Anhang 4-G: Ergänzende Unterlagen

Präambel

Dieses Dokument beinhaltet weitere Analysen der Studie EMPEROR-Preserved, die für das Modul 4 des vorliegenden Dossiers durchgeführt wurden. Die für den medizinischen Zusatznutzen relevanten Ergebnisse sind in Modul 4 dargestellt. Weitere Analyseergebnisse werden im Folgenden ergänzend zur Gewährleistung einer transparenten Darstellung aufgeführt.

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R.1.1 Efficacy

R.1.1.1 Time to Event Analyses

R.1.1.1.1 Time to all-cause mortality

Table R.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	2991	427	14.3	6.67	2997	422	14.1	6.60	1.00	(0.87,1.15)	0.9893	
Sex												0.7776
Male	1653	267	16.2	7.53	1659	269	16.2	7.60	1.02	(0.86,1.20)	0.8554	
Female	1338	160	12.0	5.61	1338	153	11.4	5.35	0.98	(0.78,1.22)	0.8287	
Age [years]												0.9303
<70	1084	123	11.3	5.21	1066	119	11.2	5.18	0.98	(0.76,1.27)	0.9020	
>=70	1907	304	15.9	7.53	1931	303	15.7	7.39	1.00	(0.85,1.17)	0.9751	
Region												0.5378
North America	359	50	13.9	6.17	360	49	13.6	6.09	0.95	(0.64,1.41)	0.8129	
Latin America	757	138	18.2	9.12	758	132	17.4	8.70	0.98	(0.77,1.25)	0.8810	
Europe	1343	179	13.3	6.13	1346	180	13.4	6.16	1.02	(0.83,1.25)	0.8849	
Asia	343	32	9.3	4.25	343	25	7.3	3.27	0.75	(0.44,1.26)	0.2716	
Other	189	28	14.8	6.95	190	36	18.9	9.26	1.40	(0.86,2.30)	0.1781	
OECD member												0.2792
No	847	144	17.0	8.28	868	159	18.3	9.08	1.10	(0.88,1.37)	0.4212	
Yes	2144	283	13.2	6.07	2129	263	12.4	5.66	0.94	(0.79,1.11)	0.4639	
Baseline NYHA												0.0352
II^^	2452	319	13.0	6.07	2435	290	11.9	5.53	0.92	(0.78,1.07)	0.2757	
III/IV	539	108	20.0	9.42	562	132	23.5	11.46	1.26	(0.98,1.63)	0.0715	
Baseline Diabetes Status												0.4315
Diabetic	1472	226	15.4	7.14	1466	234	16.0	7.54	1.05	(0.88,1.26)	0.5861	
Non-Diabetic	1519	201	13.2	6.21	1531	188	12.3	5.71	0.94	(0.77,1.15)	0.5700	

* 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, °:Trend test, ^Incidence rate, events per 100 patient years at risk.

Analysis is based on study 1245.110.

^^ Patients with NYHA class I are counted in subgroup NYHA class II.
[1] Baseline SBP median: 132 [mmHg].
[2] Baseline NT-proBNP median for patients with history of atrial fibrillation or atrial flutter: 1354 [pg/mL].
[2] Baseline NT-proBNP median for patients without history of atrial fibrillation or atrial flutter: 614 [pg/mL].
[3] Baseline uric acid tertile cut-offs for males are T1: 5.9 T2: 7.5 [mg/dL] [rounded].
[3] Baseline uric acid tertile cut-offs for females are T1: 5.4 T2: 6.9 [mg/dL] [rounded].

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Table R.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			Interaction
Category	N	n	%	Rate^	N	n	%	Rate^	HR*	(95% CI)	p-value	p-value
Baseline Diabetes Status												0.2536°/ 0.4779
Diabetic	1472	226	15.4	7.14	1466	234	16.0	7.54	1.05	(0.88,1.26)	0.5861	
Pre-Diabetes	979	121	12.4	5.77	1001	121	12.1	5.63	1.02	(0.79,1.31)	0.9065	
Normal (no pre-diabetes)	540	80	14.8	7.01	530	67	12.6	5.84	0.84	(0.60,1.16)	0.2801	
Baseline BMI [kg/m²]												0.2008
<30	1642	256	15.6	7.40	1654	234	14.1	6.65	0.93	(0.78,1.11)	0.4106	
>=30	1349	171	12.7	5.82	1343	188	14.0	6.53	1.11	(0.90,1.36)	0.3272	
Baseline eGFR (CKD-EPI) [mL/min/1.73m²]												0.5665
>=60	1505	172	11.4	5.27	1493	161	10.8	4.96	0.95	(0.77,1.18)	0.6568	
<60	1484	254	17.1	8.11	1504	261	17.4	8.28	1.03	(0.87,1.23)	0.7173	
History of HHF (in the last 12 months)												0.5501
No	2321	308	13.3	6.24	2298	305	13.3	6.24	1.02	(0.87,1.20)	0.7854	
Yes	670	119	17.8	8.13	699	117	16.7	7.74	0.93	(0.72,1.20)	0.5931	
Baseline SBP (</>= median¹)												0.3127
< median	1474	194	13.2	6.20	1496	208	13.9	6.58	1.08	(0.89,1.31)	0.4559	
>= median	1517	233	15.4	7.12	1501	214	14.3	6.61	0.94	(0.78,1.13)	0.4951	
History of atrial fibrillation or atrial flutter												0.3891
No	1427	202	14.2	6.65	1417	187	13.2	6.18	0.94	(0.77,1.14)	0.5146	
Yes	1559	225	14.4	6.71	1576	234	14.8	6.96	1.05	(0.88,1.27)	0.5722	

* 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, °:Trend test, ^Incidence rate, events per 100 patient years at risk.

Analysis is based on study 1245.110.

^^ Patients with NYHA class I are counted in subgroup NYHA class II.
¹ Baseline SBP median: 132 [mmHg].
² Baseline NT-proBNP median for patients with history of atrial fibrillation or atrial flutter: 1354 [pg/mL].
² Baseline NT-proBNP median for patients without history of atrial fibrillation or atrial flutter: 614 [pg/mL].
³ Baseline uric acid tertile cut-offs for males are T1: 5.9 T2: 7.5 [mg/dL] [rounded].
³ Baseline uric acid tertile cut-offs for females are T1: 5.4 T2: 6.9 [mg/dL] [rounded].

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Table R.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 LVEF [%]												0.6848
< 50	988	167	16.9	7.90	995	163	16.4	7.66	0.96	(0.78,1.19)	0.7237	
>= 50	2003	260	13.0	6.06	2002	259	12.9	6.07	1.02	(0.86,1.21)	0.8354	
Baseline LVEF [%]												0.5233°/ 0.7893
<50	988	167	16.9	7.90	995	163	16.4	7.66	0.96	(0.78,1.19)	0.7234	
50 to <60	1030	148	14.4	6.66	1028	136	13.2	6.20	0.98	(0.77,1.23)	0.8436	
>=60	973	112	11.5	5.43	974	123	12.6	5.93	1.08	(0.83,1.39)	0.5769	
Baseline NT-proBNP [pg/mL] (</>=median² by atrial fibrillation/flutter status)												0.6029
< median	1508	140	9.3	4.24	1477	129	8.7	3.98	0.95	(0.74,1.20)	0.6436	
>= median	1476	285	19.3	9.24	1516	292	19.3	9.28	1.02	(0.87,1.20)	0.8062	
Baseline uric acid [mg/dL] (tertiles³)												0.8408°/ 0.6352
<T1	975	132	13.5	6.35	963	117	12.1	5.71	0.94	(0.73,1.21)	0.6390	
>=T1 and <T2	966	114	11.8	5.44	1032	132	12.8	6.00	1.11	(0.86,1.43)	0.4108	
>=T2	1018	176	17.3	8.14	970	169	17.4	8.10	0.98	(0.80,1.22)	0.8855	
Baseline use of MRA												0.9109
No	1866	257	13.8	6.39	1878	251	13.4	6.20	0.99	(0.84,1.18)	0.9450	
Yes	1125	170	15.1	7.14	1119	171	15.3	7.27	1.01	(0.82,1.25)	0.9297	
Baseline use of ACE-inhibitor, ARB or ARNi												0.4842
No	587	93	15.8	7.53	569	84	14.8	6.84	0.91	(0.68,1.22)	0.5375	
Yes	2404	334	13.9	6.47	2428	338	13.9	6.54	1.03	(0.88,1.19)	0.7407	

* 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, °:Trend test, ^Incidence rate, events per 100 patient years at risk.

Analysis is based on study 1245.110.

^^ Patients with NYHA class I are counted in subgroup NYHA class II.
¹ Baseline SBP median: 132 [mmHg].
² Baseline NT-proBNP median for patients with history of atrial fibrillation or atrial flutter: 1354 [pg/mL].
² Baseline NT-proBNP median for patients without history of atrial fibrillation or atrial flutter: 614 [pg/mL].
³ Baseline uric acid tertile cut-offs for males are T1: 5.9 T2: 7.5 [mg/dL] [rounded].
³ Baseline uric acid tertile cut-offs for females are T1: 5.4 T2: 6.9 [mg/dL] [rounded].

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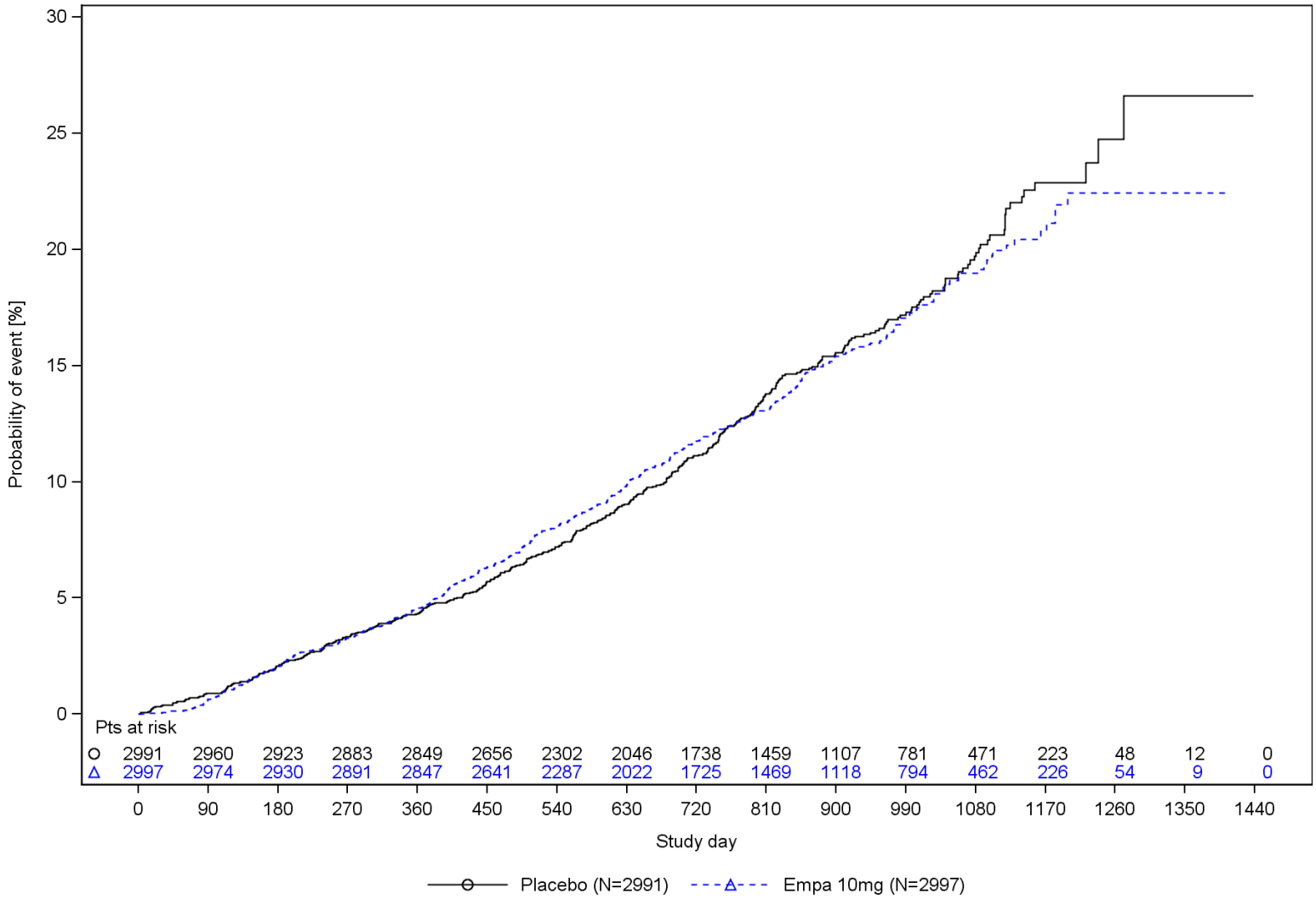

Figure R.1.1.1.1: 1 Time to all-cause mortality, Kaplan-Meier estimate - RS
Analysis is based on study 1245.110

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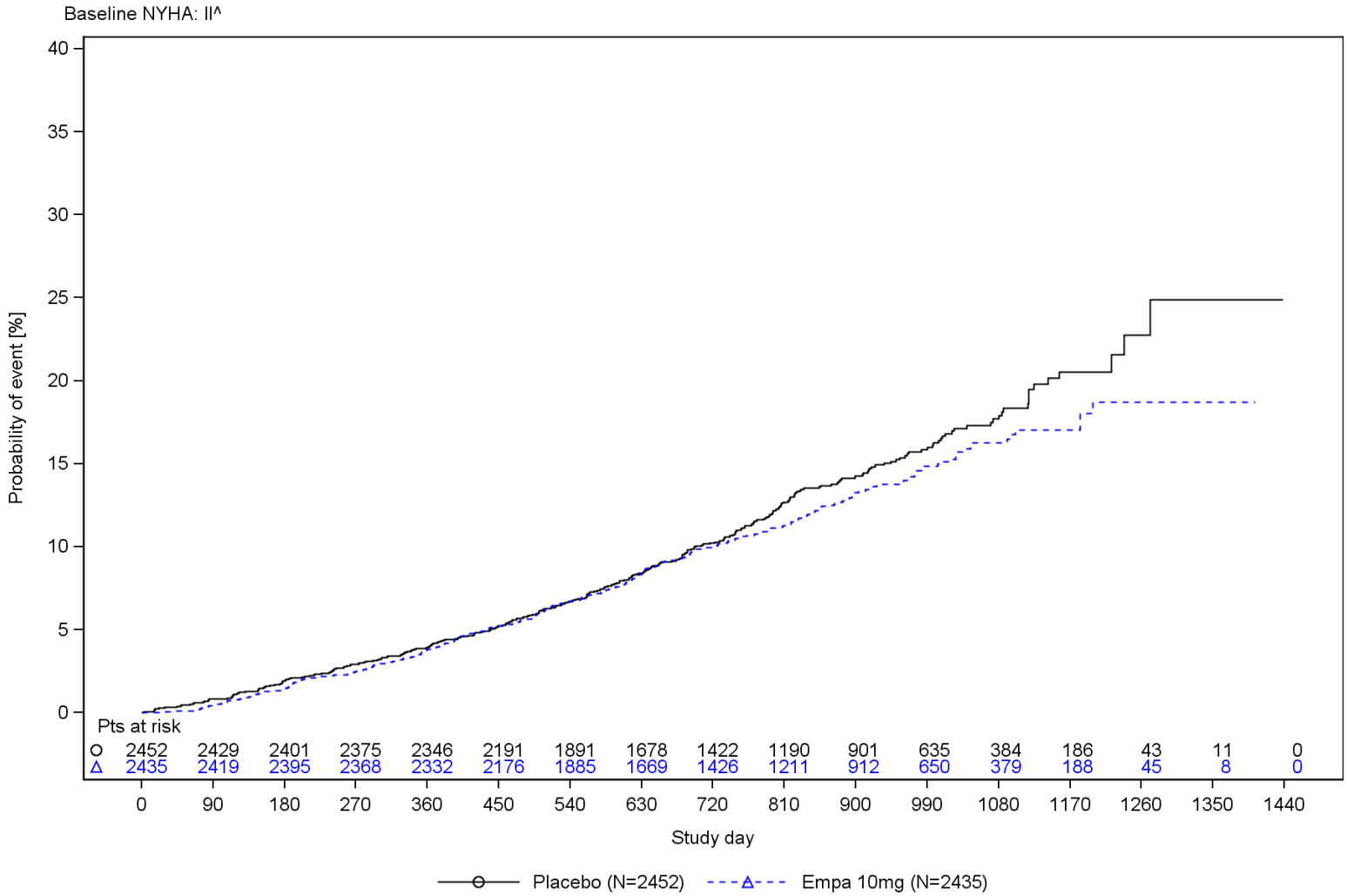

Figure R.1.1.1.1: 2 Time to all-cause mortality, Kaplan-Meier estimate by baseline NYHA - RS
Analysis is based on study 1245.110
^ Patients with NYHA class I are counted in subgroup NYHA class II.

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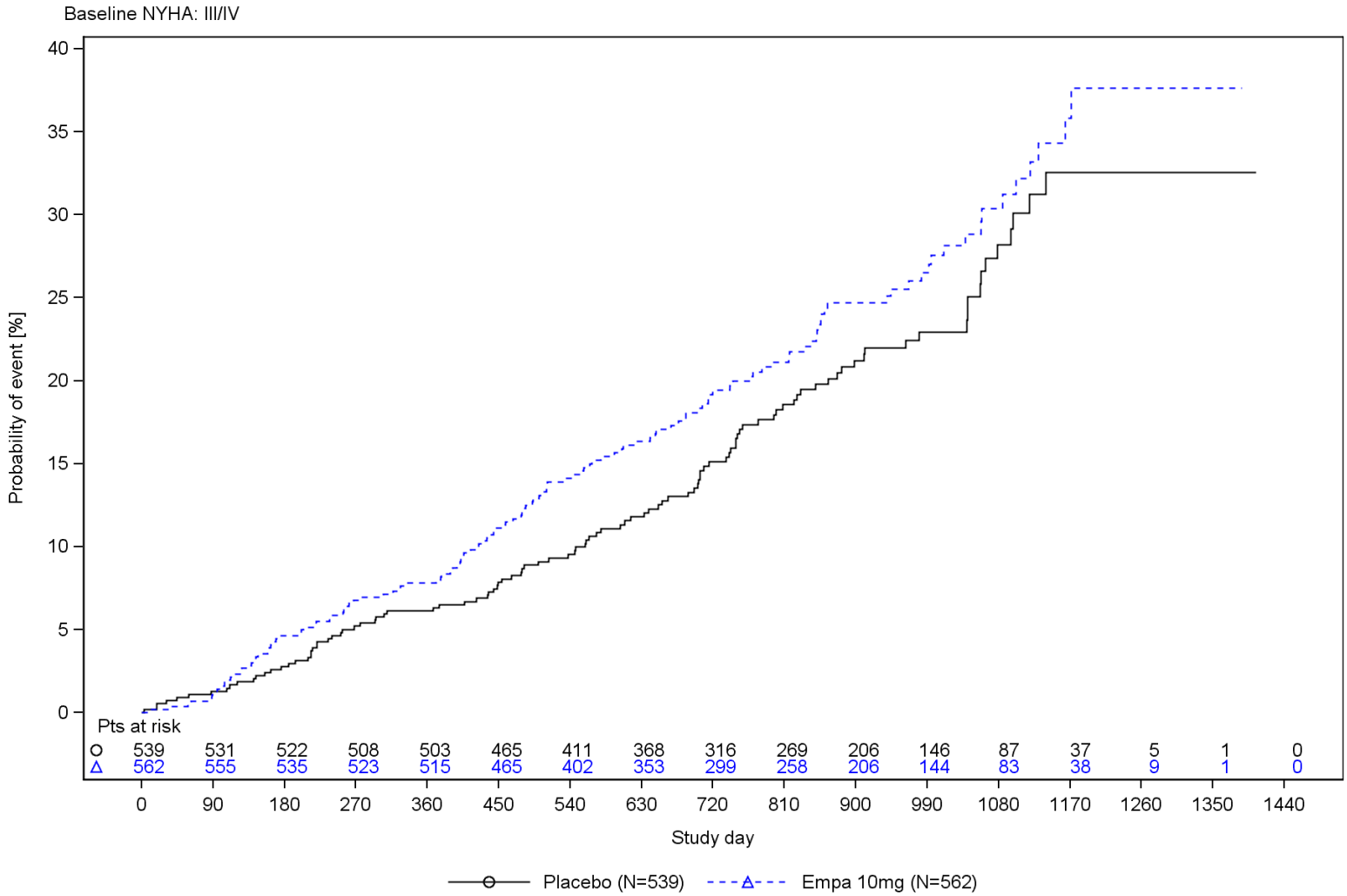

Figure R.1.1.1.1: 2 Time to all-cause mortality, Kaplan-Meier estimate by baseline NYHA - RS
Analysis is based on study 1245.110
^ Patients with NYHA class I are counted in subgroup NYHA class II.

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R.1.1.1.2 Time to adjudicated CV death

Table R.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			Interaction
Category	N	n	%	Rate^	N	n	%	Rate^	HR*	(95% CI)	p-value	p-value
Overall	2991	244	8.2	3.81	2997	219	7.3	3.42	0.91	(0.76,1.09)	0.2951	
Sex												0.6734
Male	1653	148	9.0	4.17	1659	138	8.3	3.90	0.94	(0.74,1.18)	0.5735	
Female	1338	96	7.2	3.37	1338	81	6.1	2.83	0.86	(0.64,1.16)	0.3285	
Age [years]												0.3428
<70	1084	71	6.5	3.01	1066	72	6.8	3.13	1.03	(0.74,1.43)	0.8587	
>=70	1907	173	9.1	4.28	1931	147	7.6	3.58	0.85	(0.68,1.06)	0.1505	
Region												0.3795
North America	359	27	7.5	3.33	360	26	7.2	3.23	0.95	(0.55,1.62)	0.8378	
Latin America	757	75	9.9	4.96	758	71	9.4	4.68	0.96	(0.70,1.33)	0.8230	
Europe	1343	108	8.0	3.70	1346	92	6.8	3.15	0.86	(0.65,1.14)	0.2966	
Asia	343	21	6.1	2.79	343	12	3.5	1.57	0.54	(0.27,1.11)	0.0924	
Other	189	13	6.9	3.23	190	18	9.5	4.63	1.50	(0.74,3.07)	0.2634	
OECD member												0.2259
No	847	78	9.2	4.49	868	83	9.6	4.74	1.05	(0.77,1.43)	0.7484	
Yes	2144	166	7.7	3.56	2129	136	6.4	2.93	0.83	(0.66,1.04)	0.1071	
Baseline NYHA												0.0761
II^^	2452	185	7.5	3.52	2435	151	6.2	2.88	0.82	(0.66,1.02)	0.0707	
III/IV	539	59	10.9	5.14	562	68	12.1	5.91	1.19	(0.84,1.69)	0.3315	
Baseline Diabetes Status												0.3171
Diabetic	1472	123	8.4	3.89	1466	120	8.2	3.87	0.99	(0.77,1.27)	0.9452	
Non-Diabetic	1519	121	8.0	3.74	1531	99	6.5	3.00	0.82	(0.63,1.07)	0.1491	

* 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, °:Trend test, ^Incidence rate, events per 100 patient years at risk.

Analysis is based on study 1245.110.

^^ Patients with NYHA class I are counted in subgroup NYHA class II.
[1] Baseline SBP median: 132 [mmHg].
[2] Baseline NT-proBNP median for patients with history of atrial fibrillation or atrial flutter: 1354 [pg/mL].
[2] Baseline NT-proBNP median for patients without history of atrial fibrillation or atrial flutter: 614 [pg/mL].
[3] Baseline uric acid tertile cut-offs for males are T1: 5.9 T2: 7.5 [mg/dL] [rounded].
[3] Baseline uric acid tertile cut-offs for females are T1: 5.4 T2: 6.9 [mg/dL] [rounded].

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Table R.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 Diabetes Status												0.1739°/ 0.3768
Diabetic	1472	123	8.4	3.89	1466	120	8.2	3.87	0.99	(0.77,1.27)	0.9454	
Pre-Diabetes	979	72	7.4	3.44	1001	65	6.5	3.03	0.91	(0.65,1.27)	0.5881	
Normal (no pre-diabetes)	540	49	9.1	4.29	530	34	6.4	2.96	0.69	(0.45,1.07)	0.0988	
Baseline BMI [kg/m²]												0.2894
<30	1642	146	8.9	4.22	1654	120	7.3	3.41	0.83	(0.65,1.06)	0.1385	
>=30	1349	98	7.3	3.34	1343	99	7.4	3.44	1.02	(0.77,1.35)	0.9047	
Baseline eGFR (CKD-EPI) [mL/min/1.73m²]												0.2889
>=60	1505	102	6.8	3.12	1493	81	5.4	2.50	0.80	(0.60,1.08)	0.1410	
<60	1484	141	9.5	4.50	1504	138	9.2	4.38	0.98	(0.78,1.24)	0.8906	
History of HHF (in the last 12 months)												0.6582
No	2321	174	7.5	3.52	2298	157	6.8	3.21	0.93	(0.75,1.15)	0.4915	
Yes	670	70	10.4	4.78	699	62	8.9	4.10	0.85	(0.60,1.19)	0.3385	
Baseline SBP (</>= median¹)												0.8980
< median	1474	112	7.6	3.58	1496	103	6.9	3.26	0.92	(0.70,1.20)	0.5389	
>= median	1517	132	8.7	4.04	1501	116	7.7	3.58	0.90	(0.70,1.15)	0.3969	
History of atrial fibrillation or atrial flutter												0.8753
No	1427	117	8.2	3.85	1417	103	7.3	3.40	0.89	(0.68,1.16)	0.3834	
Yes	1559	127	8.1	3.79	1576	115	7.3	3.42	0.92	(0.71,1.18)	0.4920	

* 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, °:Trend test, ^Incidence rate, events per 100 patient years at risk.

Analysis is based on study 1245.110.

^^ Patients with NYHA class I are counted in subgroup NYHA class II.
¹ Baseline SBP median: 132 [mmHg].
² Baseline NT-proBNP median for patients with history of atrial fibrillation or atrial flutter: 1354 [pg/mL].
² Baseline NT-proBNP median for patients without history of atrial fibrillation or atrial flutter: 614 [pg/mL].
³ Baseline uric acid tertile cut-offs for males are T1: 5.9 T2: 7.5 [mg/dL] [rounded].
³ Baseline uric acid tertile cut-offs for females are T1: 5.4 T2: 6.9 [mg/dL] [rounded].

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Table R.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 LVEF [%]												0.8787
< 50	988	100	10.1	4.73	995	93	9.3	4.37	0.92	(0.69,1.22)	0.5442	
>= 50	2003	144	7.2	3.36	2002	126	6.3	2.95	0.89	(0.70,1.13)	0.3409	
Baseline LVEF [%]												0.7865°/ 0.7048
<50	988	100	10.1	4.73	995	93	9.3	4.37	0.92	(0.69,1.22)	0.5440	
50 to <60	1030	85	8.3	3.82	1028	66	6.4	3.01	0.82	(0.59,1.13)	0.2145	
>=60	973	59	6.1	2.86	974	60	6.2	2.89	1.00	(0.70,1.43)	0.9974	
Baseline NT-proBNP [pg/mL] (</>=median² by atrial fibrillation/flutter status)												0.3373
< median	1508	78	5.2	2.36	1477	60	4.1	1.85	0.79	(0.56,1.10)	0.1634	
>= median	1476	164	11.1	5.32	1516	158	10.4	5.02	0.96	(0.77,1.19)	0.7015	
Baseline uric acid [mg/dL] (tertiles³)												0.5742°/ 0.2137
<T1	975	76	7.8	3.66	963	54	5.6	2.63	0.74	(0.52,1.05)	0.0957	
>=T1 and <T2	966	66	6.8	3.15	1032	78	7.6	3.55	1.13	(0.82,1.57)	0.4505	
>=T2	1018	100	9.8	4.62	970	85	8.8	4.07	0.88	(0.66,1.17)	0.3777	
Baseline use of MRA												0.6554
No	1866	149	8.0	3.71	1878	138	7.3	3.41	0.94	(0.74,1.18)	0.5825	
Yes	1125	95	8.4	3.99	1119	81	7.2	3.44	0.86	(0.64,1.16)	0.3194	
Baseline use of ACE-inhibitor, ARB or ARNi												0.7303
No	587	46	7.8	3.72	569	44	7.7	3.58	0.97	(0.64,1.46)	0.8788	
Yes	2404	198	8.2	3.83	2428	175	7.2	3.39	0.89	(0.73,1.09)	0.2753	

* 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, °:Trend test, ^Incidence rate, events per 100 patient years at risk.

Analysis is based on study 1245.110.

^^ Patients with NYHA class I are counted in subgroup NYHA class II.
¹ Baseline SBP median: 132 [mmHg].
² Baseline NT-proBNP median for patients with history of atrial fibrillation or atrial flutter: 1354 [pg/mL].
² Baseline NT-proBNP median for patients without history of atrial fibrillation or atrial flutter: 614 [pg/mL].
³ Baseline uric acid tertile cut-offs for males are T1: 5.9 T2: 7.5 [mg/dL] [rounded].
³ Baseline uric acid tertile cut-offs for females are T1: 5.4 T2: 6.9 [mg/dL] [rounded].

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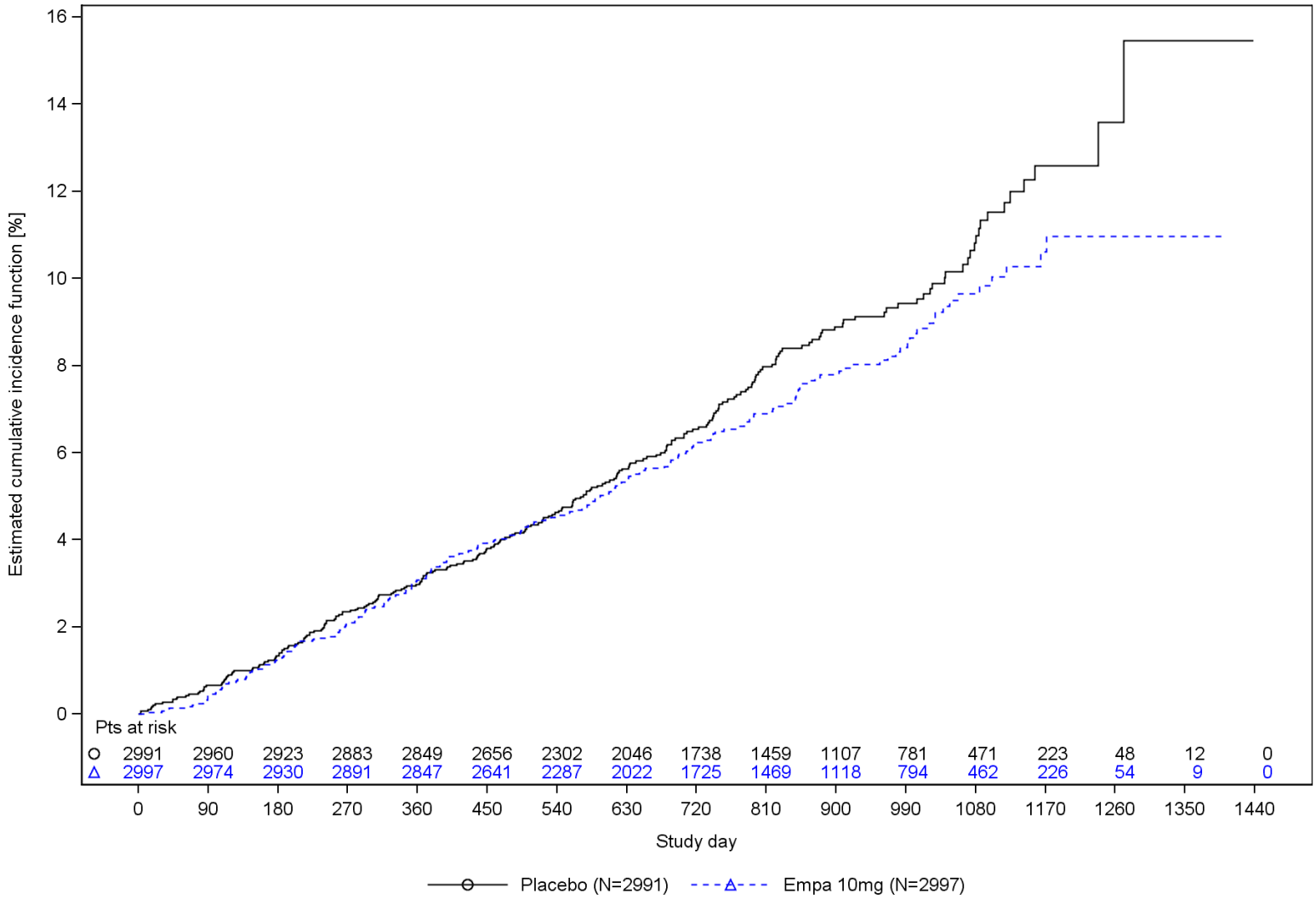

Figure R.1.1.1.2: 1 Time to adjudicated CV death, estimated cumulative incidence function (considering non-CV death as competing risk) - RS
Analysis is based on study 1245.110.

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R.1.1.1.3 Time to all-cause hospitalization

Table R.1.1.1.3: 1 Cox regression for time to first 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	2991	1340	44.8	29.18	2997	1271	42.4	26.85	0.92	(0.85,0.99)	0.0322	
Sex												0.7365
Male	1653	772	46.7	30.86	1659	739	44.5	28.52	0.91	(0.82,1.01)	0.0647	
Female	1338	568	42.5	27.17	1338	532	39.8	24.83	0.93	(0.83,1.05)	0.2569	
Age [years]												0.7808
<70	1084	423	39.0	23.94	1066	391	36.7	22.35	0.93	(0.81,1.07)	0.3180	
>=70	1907	917	48.1	32.45	1931	880	45.6	29.48	0.91	(0.83,1.00)	0.0475	
Region												0.3949
North America	359	192	53.5	38.05	360	200	55.6	39.15	1.02	(0.84,1.25)	0.8178	
Latin America	757	299	39.5	24.73	758	271	35.8	22.00	0.90	(0.76,1.06)	0.2055	
Europe	1343	583	43.4	27.66	1346	559	41.5	25.78	0.93	(0.83,1.04)	0.2176	
Asia	343	174	50.7	35.03	343	152	44.3	27.39	0.77	(0.62,0.96)	0.0193	
Other	189	92	48.7	33.59	190	89	46.8	33.22	1.00	(0.75,1.34)	0.9854	
OECD member												0.7409
No	847	352	41.6	26.47	868	330	38.0	24.22	0.90	(0.77,1.05)	0.1719	
Yes	2144	988	46.1	30.28	2129	941	44.2	27.91	0.93	(0.85,1.01)	0.0987	
Baseline NYHA												0.1799
II^^	2452	1031	42.0	26.60	2435	950	39.0	23.72	0.89	(0.82,0.97)	0.0111	
III/IV	539	309	57.3	43.12	562	321	57.1	44.01	1.01	(0.86,1.18)	0.9137	
Baseline Diabetes Status												0.7771
Diabetic	1472	702	47.7	32.14	1466	666	45.4	29.81	0.91	(0.82,1.01)	0.0801	
Non-Diabetic	1519	638	42.0	26.49	1531	605	39.5	24.20	0.93	(0.83,1.04)	0.2014	

* 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, °:Trend test, ^Incidence rate, events per 100 patient years at risk.

Analysis is based on study 1245.110.

^^ Patients with NYHA class I are counted in subgroup NYHA class II.
[1] Baseline SBP median: 132 [mmHg].
[2] Baseline NT-proBNP median for patients with history of atrial fibrillation or atrial flutter: 1354 [pg/mL].
[2] Baseline NT-proBNP median for patients without history of atrial fibrillation or atrial flutter: 614 [pg/mL].
[3] Baseline uric acid tertile cut-offs for males are T1: 5.9 T2: 7.5 [mg/dL] [rounded].
[3] Baseline uric acid tertile cut-offs for females are T1: 5.4 T2: 6.9 [mg/dL] [rounded].

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Table R.1.1.1.3: 1 Cox regression for time to first 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 Diabetes Status												0.6773°/ 0.8838
Diabetic	1472	702	47.7	32.14	1466	666	45.4	29.81	0.91	(0.82,1.01)	0.0802	
Pre-Diabetes	979	412	42.1	26.70	1001	392	39.2	24.16	0.91	(0.80,1.05)	0.2073	
Normal (no pre-diabetes)	540	226	41.9	26.12	530	213	40.2	24.28	0.96	(0.80,1.16)	0.6681	
Baseline BMI [kg/m²]												0.0072
<30	1642	753	45.9	30.44	1654	667	40.3	25.11	0.83	(0.75,0.93)	0.0007	
>=30	1349	587	43.5	27.70	1343	604	45.0	29.07	1.03	(0.92,1.16)	0.5923	
Baseline eGFR (CKD-EPI) [mL/min/1.73m²]												0.3917
>=60	1505	584	38.8	23.62	1493	523	35.0	20.63	0.88	(0.79,0.99)	0.0404	
<60	1484	755	50.9	35.66	1504	748	49.7	34.02	0.95	(0.86,1.05)	0.2826	
History of HHF (in the last 12 months)												0.9256
No	2321	968	41.7	26.26	2298	896	39.0	23.88	0.92	(0.84,1.00)	0.0592	
Yes	670	372	55.5	41.05	699	375	53.6	38.20	0.91	(0.79,1.05)	0.1918	
Baseline SBP (</>= median¹)												0.6959
< median	1474	674	45.7	30.27	1496	653	43.6	28.34	0.93	(0.84,1.04)	0.2089	
>= median	1517	666	43.9	28.15	1501	618	41.2	25.44	0.91	(0.81,1.01)	0.0744	
History of atrial fibrillation or atrial flutter												0.3970
No	1427	596	41.8	26.55	1417	538	38.0	23.06	0.89	(0.79,1.00)	0.0442	
Yes	1559	741	47.5	31.61	1576	733	46.5	30.65	0.95	(0.86,1.05)	0.3122	

* 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, °:Trend test, ^Incidence rate, events per 100 patient years at risk.

Analysis is based on study 1245.110.

^^ Patients with NYHA class I are counted in subgroup NYHA class II.
¹ Baseline SBP median: 132 [mmHg].
² Baseline NT-proBNP median for patients with history of atrial fibrillation or atrial flutter: 1354 [pg/mL].
² Baseline NT-proBNP median for patients without history of atrial fibrillation or atrial flutter: 614 [pg/mL].
³ Baseline uric acid tertile cut-offs for males are T1: 5.9 T2: 7.5 [mg/dL] [rounded].
³ Baseline uric acid tertile cut-offs for females are T1: 5.4 T2: 6.9 [mg/dL] [rounded].

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Table R.1.1.1.3: 1 Cox regression for time to first all-cause hospitalization 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 LVEF [%]												0.1270
< 50	988	447	45.2	29.31	995	401	40.3	24.90	0.84	(0.74,0.97)	0.0133	
>= 50	2003	893	44.6	29.11	2002	870	43.5	27.86	0.96	(0.87,1.05)	0.3707	
Baseline LVEF [%]												0.0284°/ 0.0721
<50	988	447	45.2	29.31	995	401	40.3	24.90	0.84	(0.74,0.97)	0.0132	
50 to <60	1030	466	45.2	29.54	1028	425	41.3	25.88	0.88	(0.78,1.01)	0.0674	
>=60	973	427	43.9	28.67	974	445	45.7	30.05	1.04	(0.91,1.19)	0.5547	
Baseline NT-proBNP [pg/mL] (</>=median² by atrial fibrillation/flutter status)												0.5665
< median	1508	600	39.8	24.16	1477	552	37.4	22.47	0.94	(0.84,1.06)	0.2997	
>= median	1476	735	49.8	34.93	1516	719	47.4	31.70	0.90	(0.81,1.00)	0.0427	
Baseline uric acid [mg/dL] (tertiles³)												0.0348°/ 0.1104
<T1	975	411	42.2	26.75	963	350	36.3	22.27	0.83	(0.72,0.96)	0.0101	
>=T1 and <T2	966	413	42.8	27.23	1032	418	40.5	24.97	0.92	(0.80,1.05)	0.2029	
>=T2	1018	501	49.2	33.53	970	491	50.6	34.14	1.01	(0.90,1.15)	0.8155	
Baseline use of MRA												0.7288
No	1866	827	44.3	28.89	1878	784	41.7	26.20	0.91	(0.83,1.00)	0.0594	
Yes	1125	513	45.6	29.66	1119	487	43.5	27.97	0.94	(0.83,1.06)	0.2968	
Baseline use of ACE-inhibitor, ARB or ARNi												0.5064
No	587	295	50.3	35.58	569	283	49.7	33.16	0.97	(0.82,1.14)	0.6845	
Yes	2404	1045	43.5	27.77	2428	988	40.7	25.46	0.91	(0.83,0.99)	0.0296	

* 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, °:Trend test, ^Incidence rate, events per 100 patient years at risk.

Analysis is based on study 1245.110.

^^ Patients with NYHA class I are counted in subgroup NYHA class II.
¹ Baseline SBP median: 132 [mmHg].
² Baseline NT-proBNP median for patients with history of atrial fibrillation or atrial flutter: 1354 [pg/mL].
² Baseline NT-proBNP median for patients without history of atrial fibrillation or atrial flutter: 614 [pg/mL].
³ Baseline uric acid tertile cut-offs for males are T1: 5.9 T2: 7.5 [mg/dL] [rounded].
³ Baseline uric acid tertile cut-offs for females are T1: 5.4 T2: 6.9 [mg/dL] [rounded].

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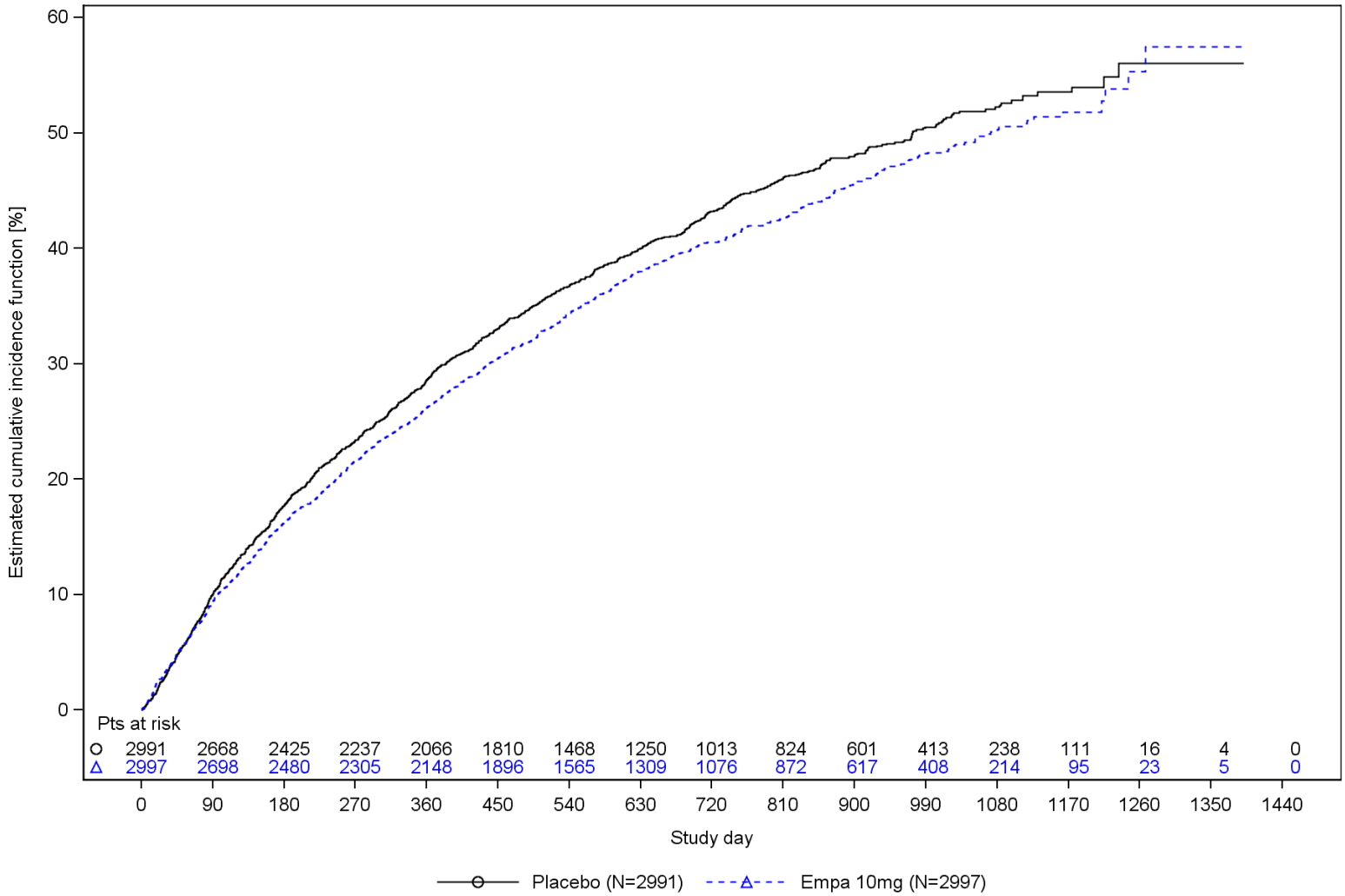

Figure R.1.1.1.3: 1 Time to the first all-cause hospitalization, estimated cumulative incidence function (considering all-cause mortality as a competing risk) - RS
Analysis is based on study 1245.110.

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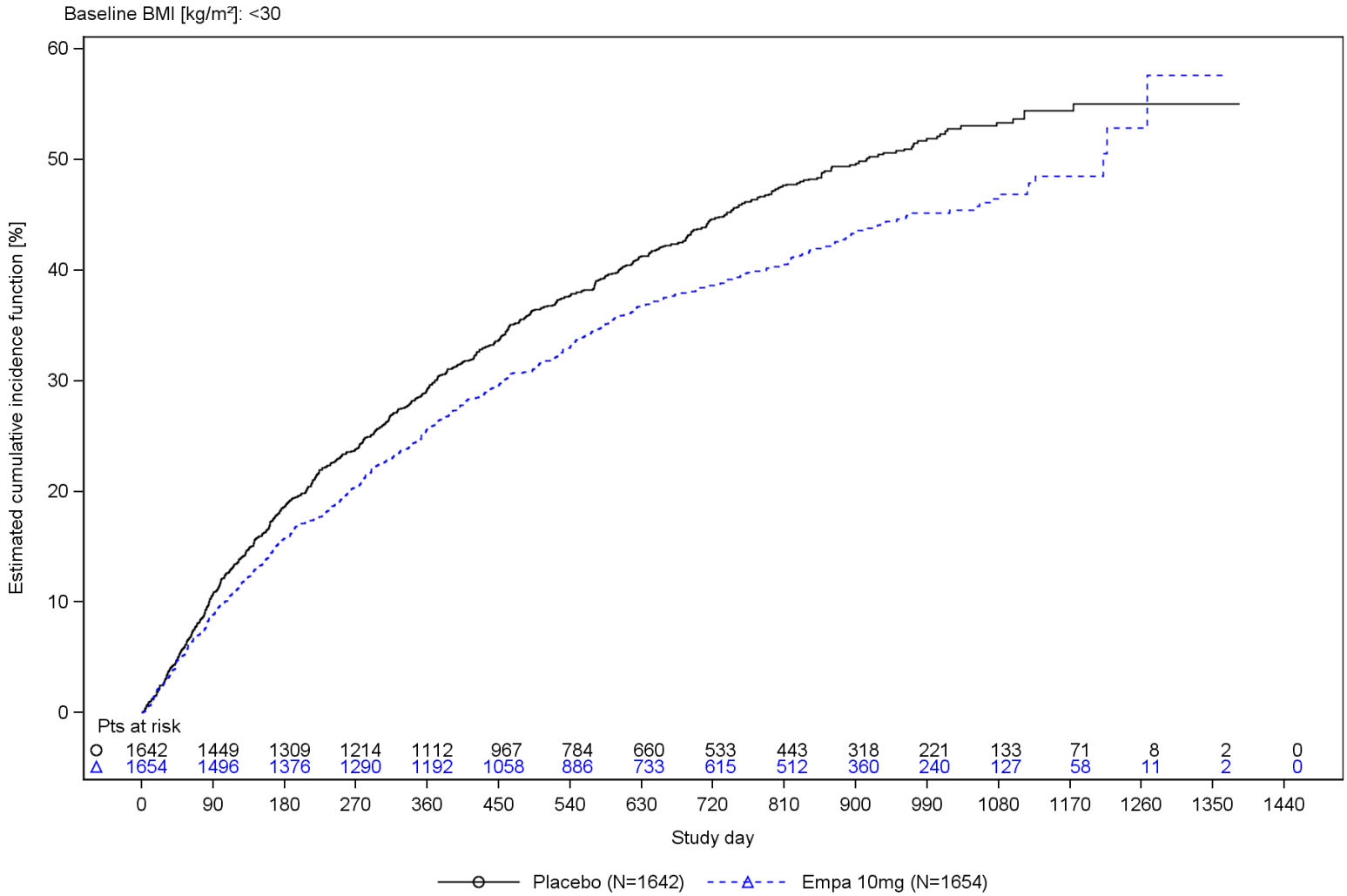

Figure R.1.1.1.3: 2 Time to the first all-cause hospitalization, estimated cumulative incidence function (considering all-cause mortality as a competing risk) by baseline BMI - RS
Analysis is based on study 1245.110.

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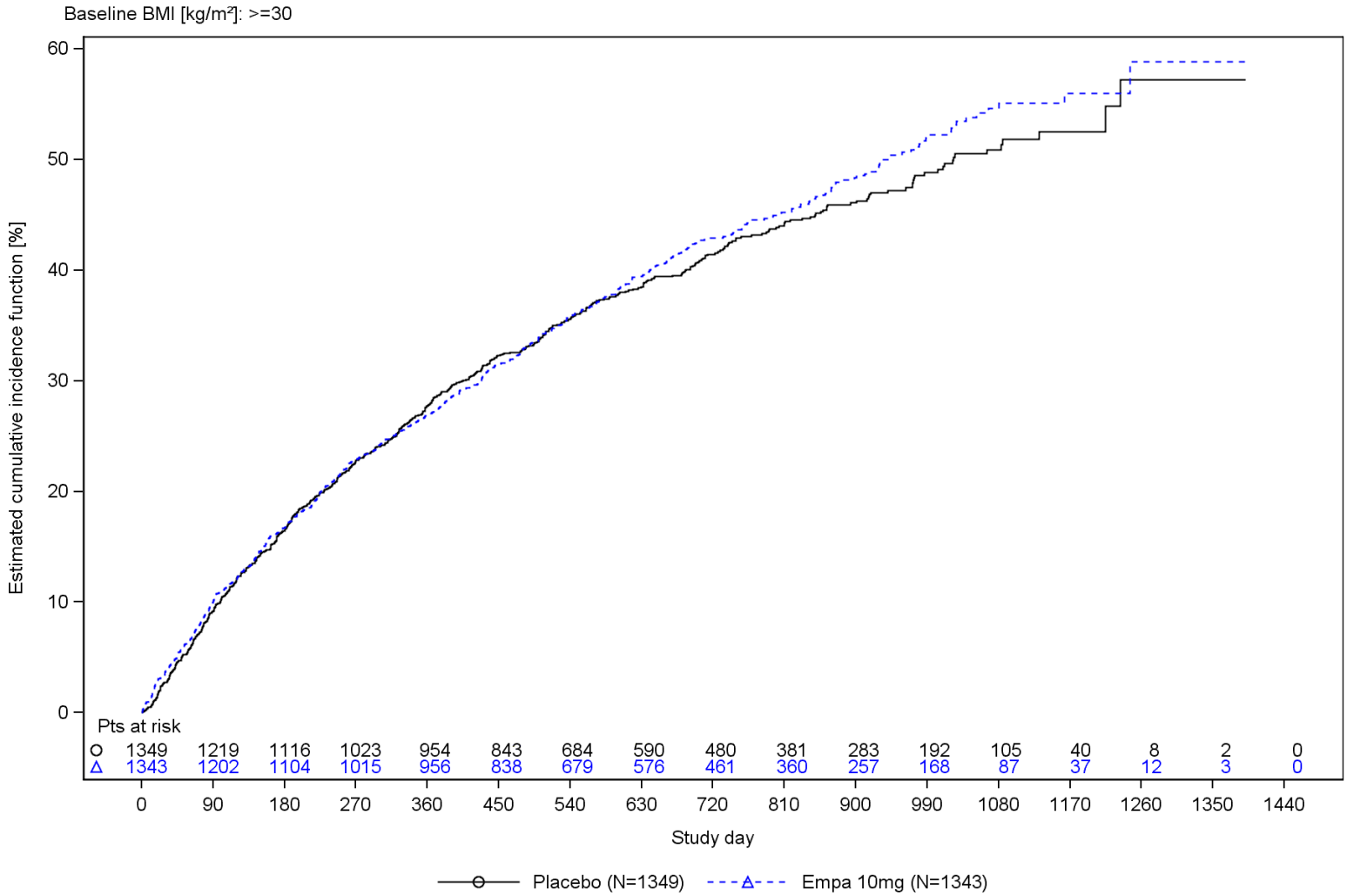

Figure R.1.1.1.3: 2 Time to the first all-cause hospitalization, estimated cumulative incidence function (considering all-cause mortality as a competing risk) by baseline BMI - RS
Analysis is based on study 1245.110.

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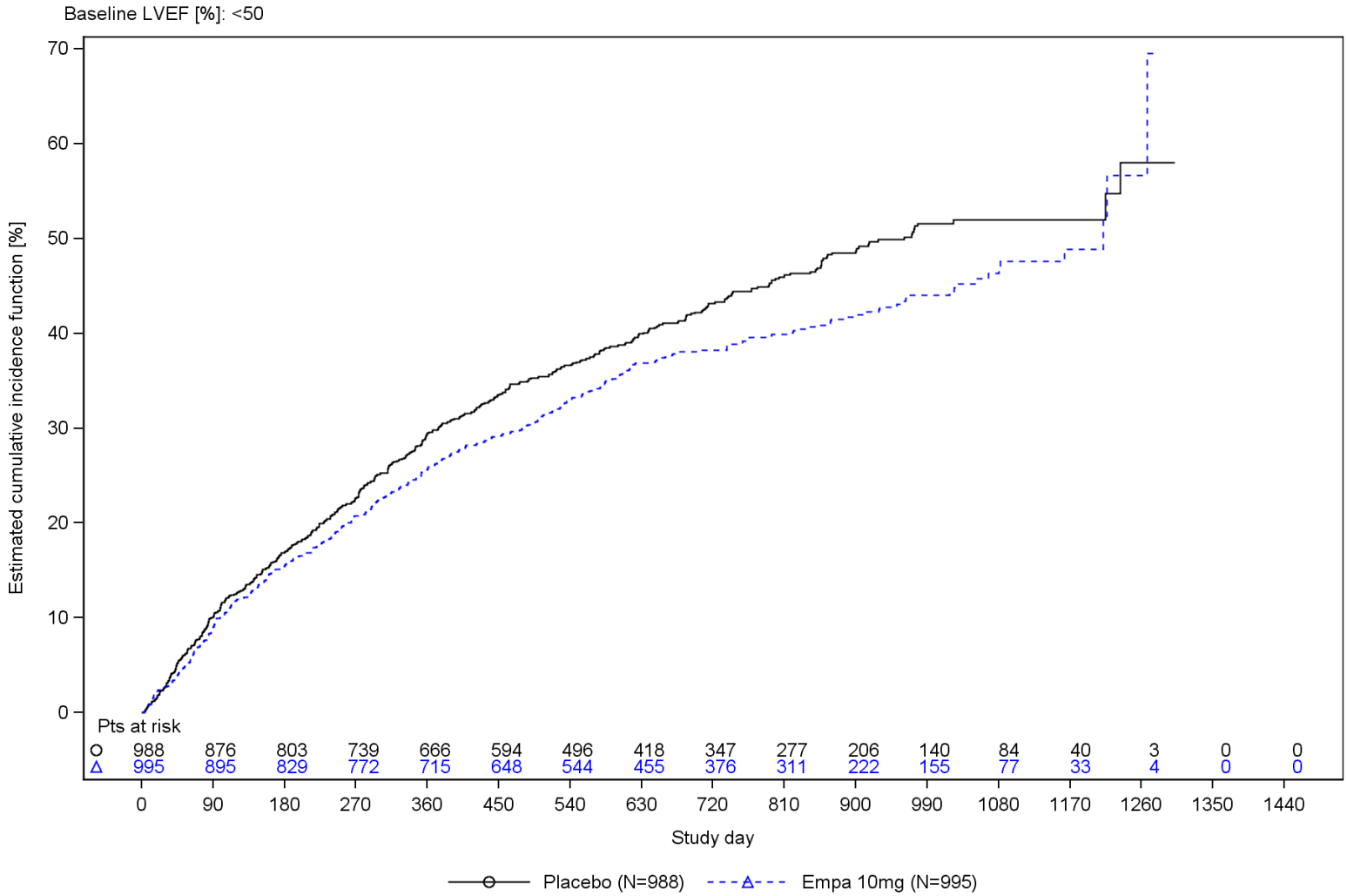

Figure R.1.1.1.3: 3 Time to the first all-cause hospitalization, estimated cumulative incidence function (considering all-cause mortality as a competing risk) by baseline LVEF - RS
Analysis is based on study 1245.110.

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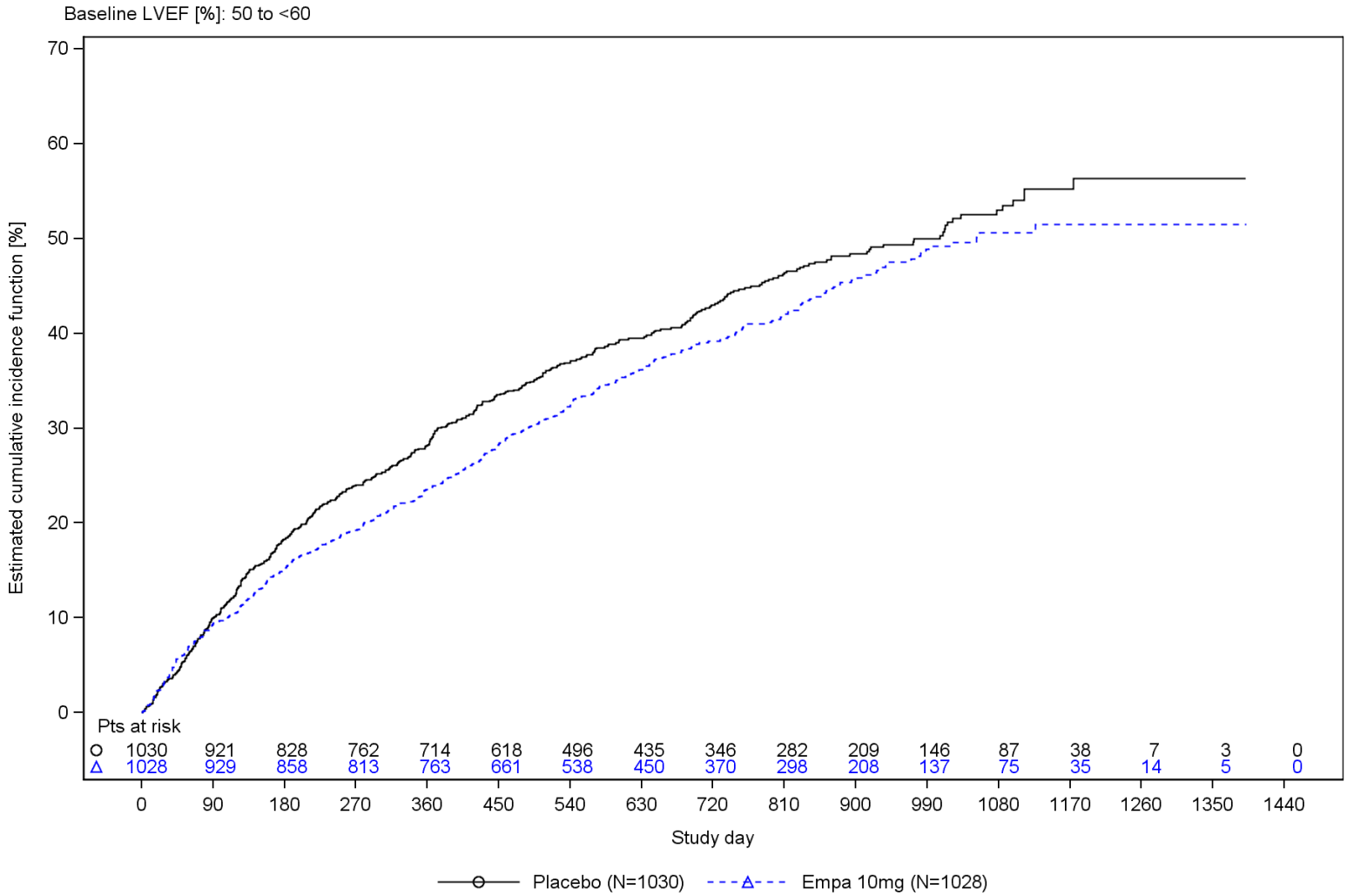

Figure R.1.1.1.3: 3 Time to the first all-cause hospitalization, estimated cumulative incidence function (considering all-cause mortality as a competing risk) by baseline LVEF - RS
Analysis is based on study 1245.110.

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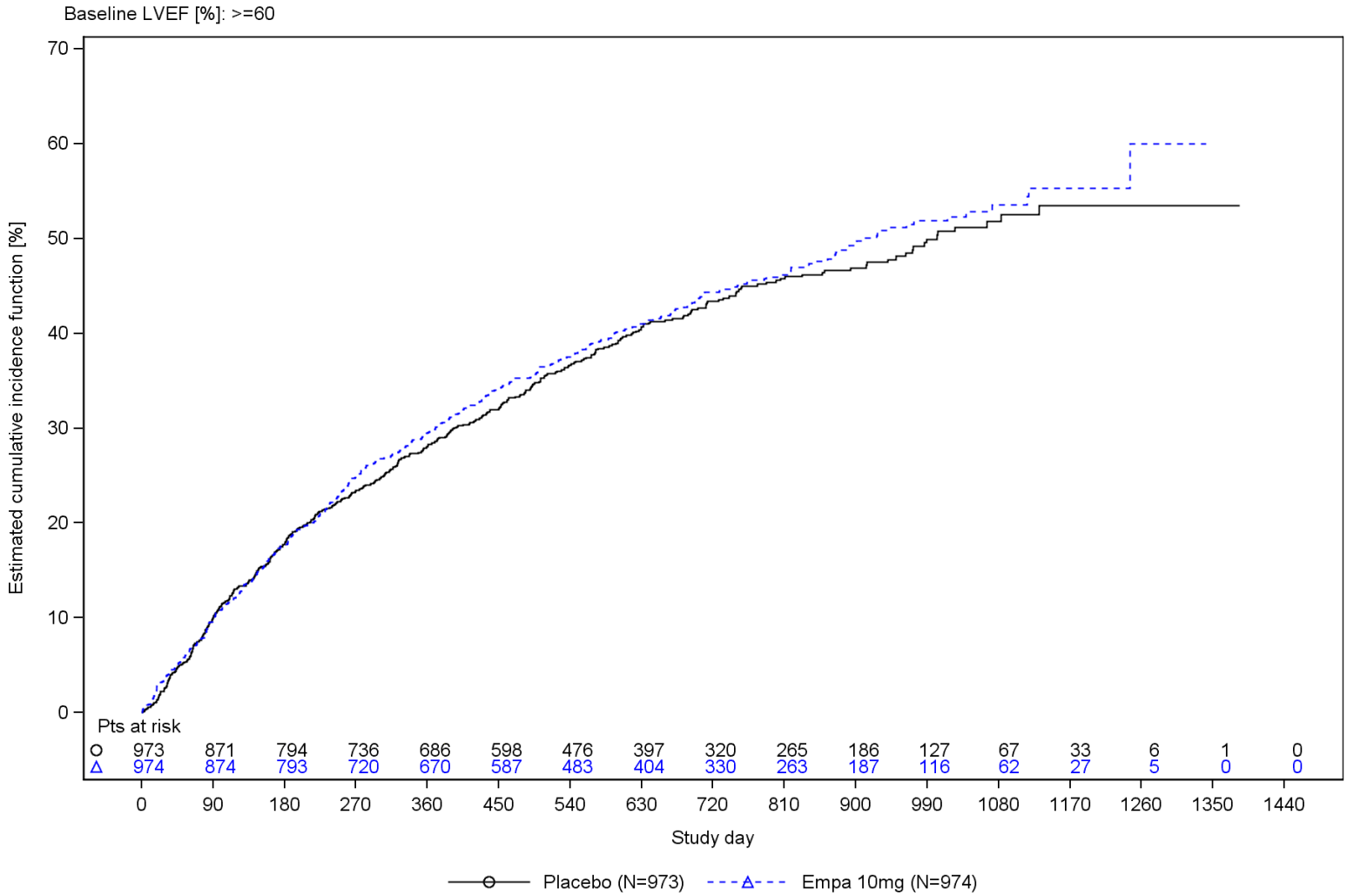

Figure R.1.1.1.3: 3 Time to the first all-cause hospitalization, estimated cumulative incidence function (considering all-cause mortality as a competing risk) by baseline LVEF - RS
Analysis is based on study 1245.110.

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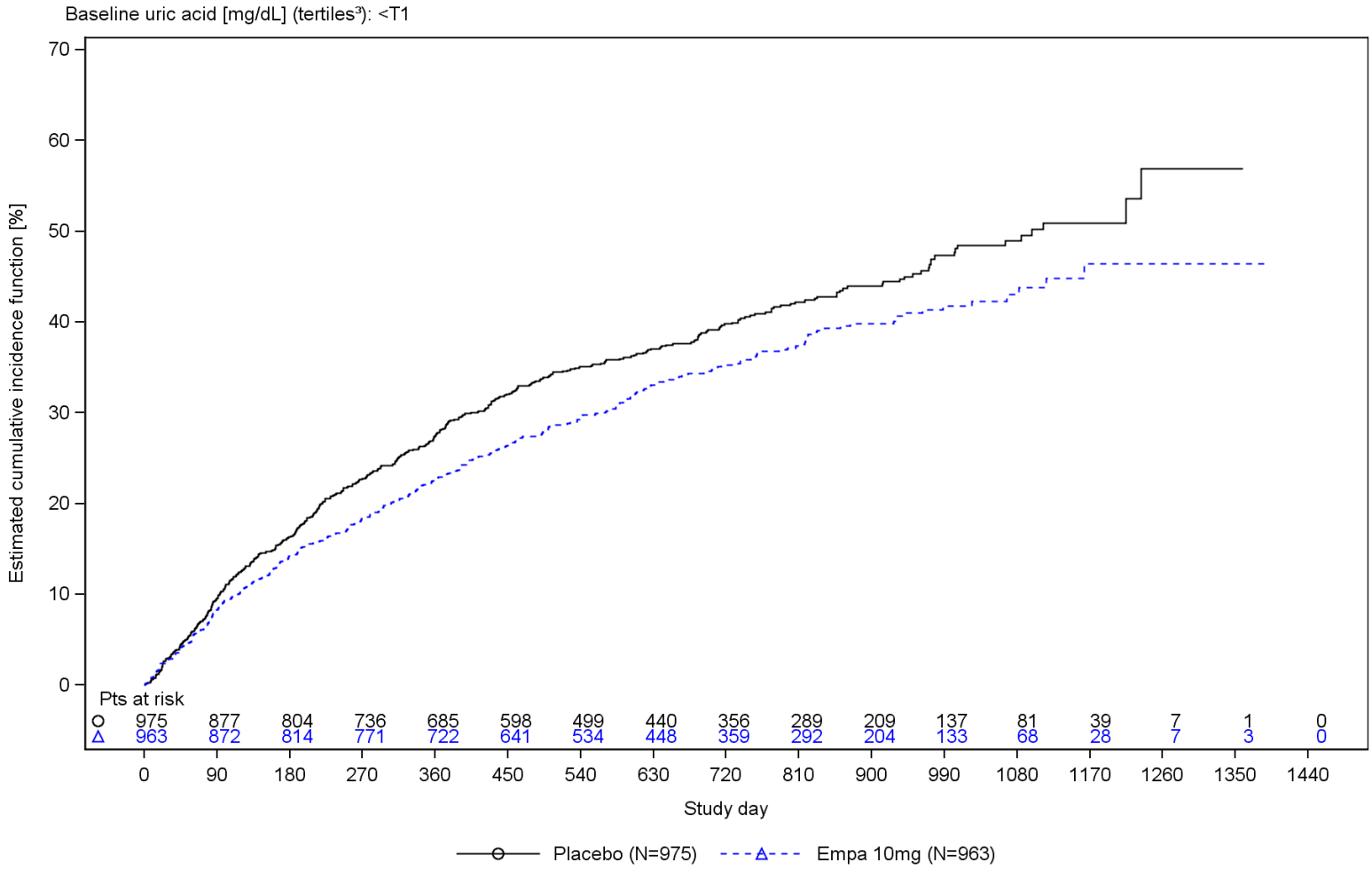

Figure R.1.1.1.3: 4 Time to the first all-cause hospitalization, estimated cumulative incidence function (considering all-cause mortality as a competing risk) by baseline uric acid - RS

Analysis is based on study 1245.110.

³ Baseline uric acid tertile cut-offs for males are T1: 5.9 T2: 7.5 [mg/dL] [rounded].

³ Baseline uric acid tertile cut-offs for females are T1: 5.4 T2: 6.9 [mg/dL] [rounded].

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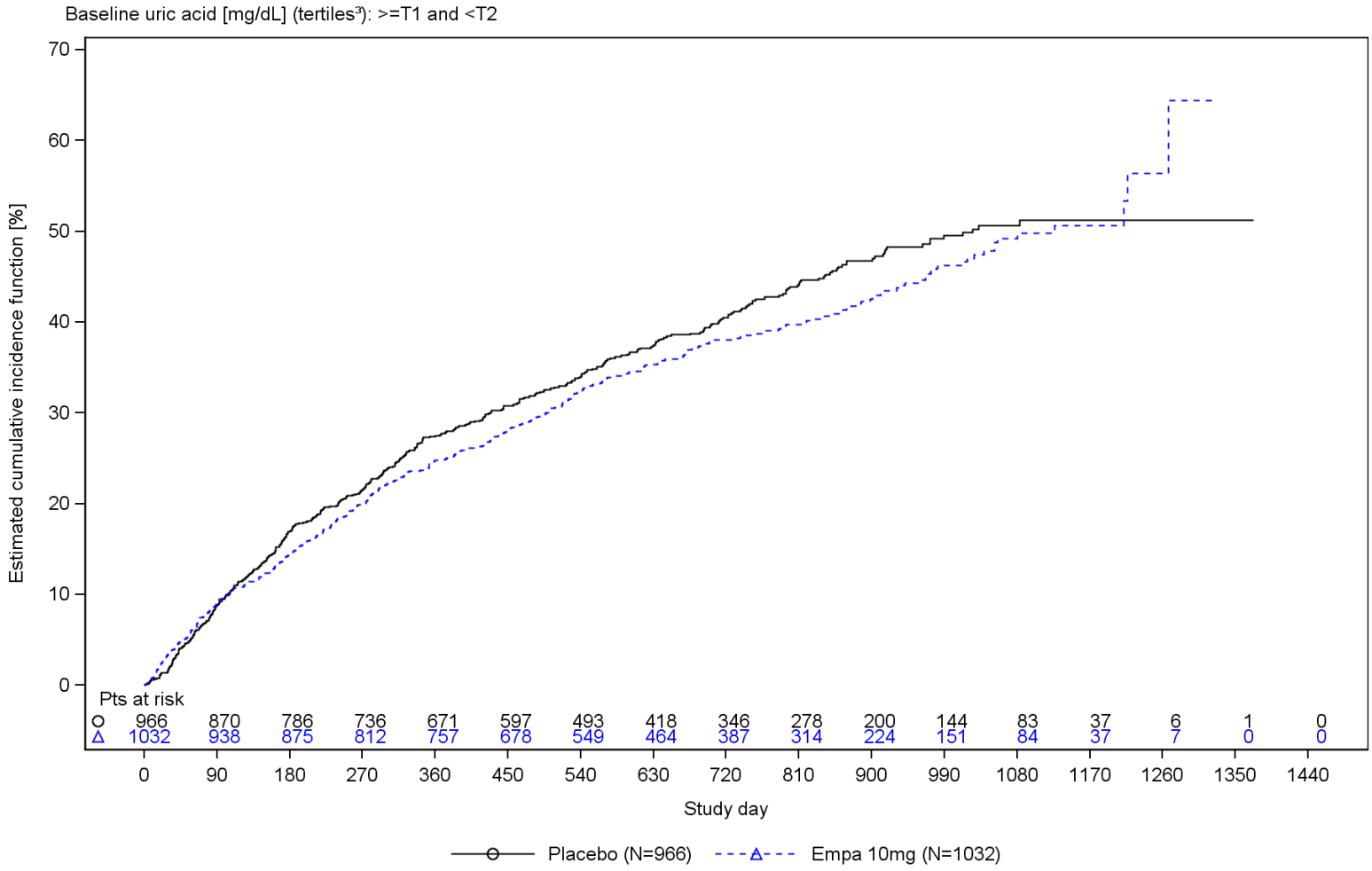

Figure R.1.1.1.3: 4 Time to the first all-cause hospitalization, estimated cumulative incidence function (considering all-cause mortality as a competing risk) by baseline uric acid - RS

Analysis is based on study 1245.110.

³ Baseline uric acid tertile cut-offs for males are T1: 5.9 T2: 7.5 [mg/dL] [rounded].

³ Baseline uric acid tertile cut-offs for females are T1: 5.4 T2: 6.9 [mg/dL] [rounded].

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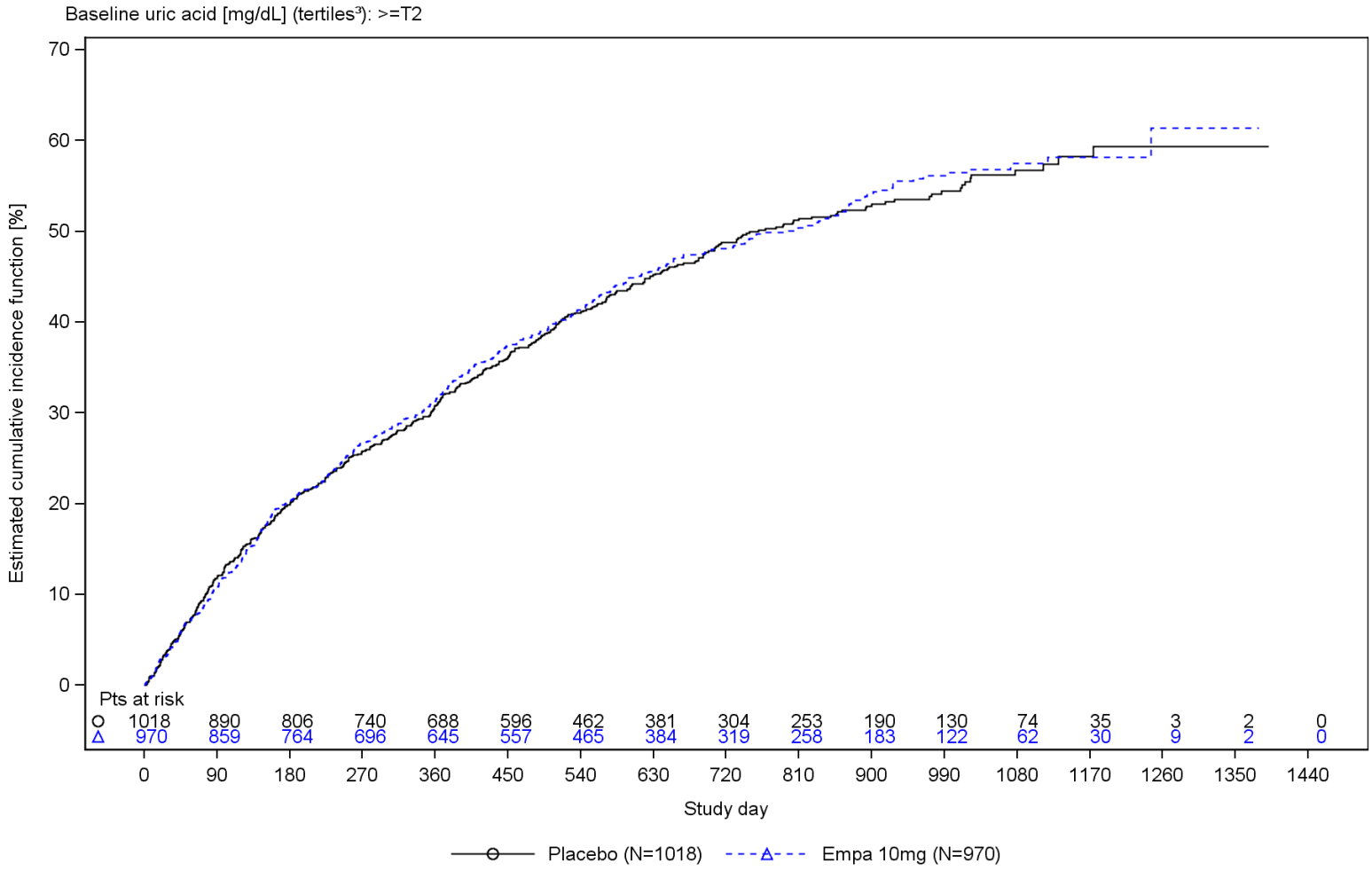

Figure R.1.1.1.3: 4 Time to the first all-cause hospitalization, estimated cumulative incidence function (considering all-cause mortality as a competing risk) by baseline uric acid - RS

Analysis is based on study 1245.110.

³ Baseline uric acid tertile cut-offs for males are T1: 5.9 T2: 7.5 [mg/dL] [rounded].

³ Baseline uric acid tertile cut-offs for females are T1: 5.4 T2: 6.9 [mg/dL] [rounded].

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R.1.1.1.4 All-cause hospitalizations (first and recurrent)

Table R.1.1.1.4: 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	2991	1340	44.8	2769	44.00	2997	1271	42.4	2566	40.70	0.93	(0.85,1.01)	0.1012	
Sex														0.5556
Male	1653	772	46.7	1609	46.18	1659	739	44.5	1534	43.94	0.95	(0.85,1.07)	0.4002	
Female	1338	568	42.5	1160	41.29	1338	532	39.8	1032	36.68	0.90	(0.79,1.03)	0.1288	
Age [years]														0.7485
<70	1084	423	39.0	853	36.78	1066	391	36.7	784	34.65	0.95	(0.81,1.10)	0.4892	
>=70	1907	917	48.1	1916	48.21	1931	880	45.6	1782	44.09	0.92	(0.83,1.02)	0.1270	
Region														0.1438
North America	359	192	53.5	478	61.31	360	200	55.6	477	60.79	1.05	(0.83,1.33)	0.6821	
Latin America	757	299	39.5	479	31.78	758	271	35.8	427	28.24	0.88	(0.73,1.07)	0.2024	
Europe	1343	583	43.4	1231	42.68	1346	559	41.5	1141	39.53	0.94	(0.83,1.07)	0.3674	
Asia	343	174	50.7	378	51.44	343	152	44.3	306	41.15	0.73	(0.57,0.94)	0.0146	
Other	189	92	48.7	203	52.39	190	89	46.8	215	56.84	1.18	(0.85,1.65)	0.3271	
OECD member														0.8305
No	847	352	41.6	650	37.94	868	330	38.0	598	34.45	0.92	(0.77,1.09)	0.3210	
Yes	2144	988	46.1	2119	46.26	2129	941	44.2	1968	43.07	0.94	(0.85,1.04)	0.2130	
Baseline NYHA														0.1621
II^^	2452	1031	42.0	2047	39.48	2435	950	39.0	1806	34.88	0.89	(0.81,0.98)	0.0187	
III/IV	539	309	57.3	722	65.14	562	321	57.1	760	67.48	1.03	(0.86,1.25)	0.7231	
Baseline Diabetes Status														0.9010
Diabetic	1472	702	47.7	1536	49.60	1466	666	45.4	1373	45.00	0.94	(0.83,1.06)	0.2912	
Non-Diabetic	1519	638	42.0	1233	38.57	1531	605	39.5	1193	36.67	0.93	(0.82,1.05)	0.2252	

* 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, °:Trend test,
^Recurrent event rate, per 100 patient years at risk.

Analysis is based on study 1245.110.

^^ Patients with NYHA class I are counted in subgroup NYHA class II.
¹ Baseline SBP median: 132 [mmHg].
² Baseline NT-proBNP median for patients with history of atrial fibrillation or atrial flutter: 1354 [pg/mL].
² Baseline NT-proBNP median for patients without history of atrial fibrillation or atrial flutter: 614 [pg/mL].
³ Baseline uric acid tertile cut-offs for males are T1: 5.9 T2: 7.5 [mg/dL] [rounded].
³ Baseline uric acid tertile cut-offs for females are T1: 5.4 T2: 6.9 [mg/dL] [rounded].

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Table R.1.1.1.4: 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 Diabetes Status														0.8780°/ 0.9875
Diabetic	1472	702	47.7	1536	49.60	1466	666	45.4	1373	45.00	0.94	(0.83,1.06)	0.2916	
Pre-Diabetes	979	412	42.1	803	38.82	1001	392	39.2	779	36.79	0.93	(0.80,1.09)	0.3701	
Normal (no pre-diabetes)	540	226	41.9	430	38.13	530	213	40.2	414	36.43	0.92	(0.74,1.13)	0.4265	
Baseline BMI [kg/m²]														0.0184
<30	1642	753	45.9	1496	44.05	1654	667	40.3	1306	37.74	0.84	(0.75,0.95)	0.0053	
>=30	1349	587	43.5	1273	43.94	1343	604	45.0	1260	44.30	1.04	(0.92,1.19)	0.5310	
Baseline eGFR (CKD-EPI) [mL/min/1.73m²]														0.2409
>=60	1505	584	38.8	1106	34.39	1493	523	35.0	960	30.12	0.88	(0.77,1.00)	0.0503	
<60	1484	755	50.9	1661	54.02	1504	748	49.7	1606	51.52	0.98	(0.87,1.10)	0.6857	
History of HHF (in the last 12 months)														0.8389
No	2321	968	41.7	1852	38.11	2298	896	39.0	1693	35.09	0.92	(0.83,1.02)	0.1119	
Yes	670	372	55.5	917	63.96	699	375	53.6	873	58.98	0.94	(0.79,1.11)	0.4723	
Baseline SBP (</>= median¹)														0.6268
< median	1474	674	45.7	1395	45.45	1496	653	43.6	1312	42.14	0.95	(0.84,1.07)	0.4093	
>= median	1517	666	43.9	1374	42.61	1501	618	41.2	1254	39.29	0.91	(0.80,1.03)	0.1311	
History of atrial fibrillation or atrial flutter														0.6707
No	1427	596	41.8	1169	39.17	1417	538	38.0	1036	34.82	0.91	(0.80,1.04)	0.1510	
Yes	1559	741	47.5	1596	48.37	1576	733	46.5	1530	46.08	0.94	(0.84,1.06)	0.3382	

* 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, °:Trend test,
^Recurrent event rate, per 100 patient years at risk.

Analysis is based on study 1245.110.

^^ Patients with NYHA class I are counted in subgroup NYHA class II.
¹ Baseline SBP median: 132 [mmHg].
² Baseline NT-proBNP median for patients with history of atrial fibrillation or atrial flutter: 1354 [pg/mL].
² Baseline NT-proBNP median for patients without history of atrial fibrillation or atrial flutter: 614 [pg/mL].
³ Baseline uric acid tertile cut-offs for males are T1: 5.9 T2: 7.5 [mg/dL] [rounded].
³ Baseline uric acid tertile cut-offs for females are T1: 5.4 T2: 6.9 [mg/dL] [rounded].

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Table R.1.1.1.4: 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 LVEF [%]														0.1599
< 50	988	447	45.2	894	43.12	995	401	40.3	775	36.91	0.85	(0.73,0.99)	0.0378	
>= 50	2003	893	44.6	1875	44.43	2002	870	43.5	1791	42.59	0.97	(0.87,1.08)	0.5918	
Baseline LVEF [%]														0.0844°/ 0.2224
<50	988	447	45.2	894	43.12	995	401	40.3	775	36.91	0.85	(0.73,0.99)	0.0378	
50 to <60	1030	466	45.2	970	44.48	1028	425	41.3	884	40.81	0.92	(0.79,1.07)	0.2735	
>=60	973	427	43.9	905	44.38	974	445	45.7	907	44.48	1.03	(0.88,1.20)	0.7270	
Baseline NT-proBNP [pg/mL] (</>=median² by atrial fibrillation/flutter status)														0.3016
< median	1508	600	39.8	1175	36.02	1477	552	37.4	1100	34.32	0.97	(0.86,1.11)	0.6909	
>= median	1476	735	49.8	1587	52.56	1516	719	47.4	1466	47.43	0.89	(0.79,1.00)	0.0548	
Baseline uric acid [mg/dL] (tertiles³)														0.0829°/ 0.1063
<T1	975	411	42.2	795	38.67	963	350	36.3	642	31.83	0.81	(0.69,0.95)	0.0093	
>=T1 and <T2	966	413	42.8	822	39.92	1032	418	40.5	825	38.00	1.00	(0.86,1.17)	0.9499	
>=T2	1018	501	49.2	1130	53.34	970	491	50.6	1081	52.57	0.98	(0.85,1.14)	0.8223	
Baseline use of MRA														0.4453
No	1866	827	44.3	1715	43.36	1878	784	41.7	1585	39.76	0.90	(0.81,1.01)	0.0766	
Yes	1125	513	45.6	1054	45.09	1119	487	43.5	981	42.32	0.97	(0.84,1.12)	0.6803	

* 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, °:Trend test,
^Recurrent event rate, per 100 patient years at risk.

Analysis is based on study 1245.110.

^^ Patients with NYHA class I are counted in subgroup NYHA class II.
¹ Baseline SBP median: 132 [mmHg].
² Baseline NT-proBNP median for patients with history of atrial fibrillation or atrial flutter: 1354 [pg/mL].
² Baseline NT-proBNP median for patients without history of atrial fibrillation or atrial flutter: 614 [pg/mL].
³ Baseline uric acid tertile cut-offs for males are T1: 5.9 T2: 7.5 [mg/dL] [rounded].
³ Baseline uric acid tertile cut-offs for females are T1: 5.4 T2: 6.9 [mg/dL] [rounded].

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Table R.1.1.1.4: 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 Category	Placebo N	Placebo n¹	Placebo %	Placebo n²	Placebo Rate^	Empa 10mg N	Empa 10mg n¹	Empa 10mg %	Empa 10mg n²	Empa 10mg Rate^	Empa 10mg vs Placebo HR*	(95% CI)	p-value	Interaction p-value
Baseline use of ACE-inhibitor, ARB or ARNi														0.5782
No	587	295	50.3	649	53.92	569	283	49.7	620	51.36	0.97	(0.80,1.18)	0.7918	
Yes	2404	1045	43.5	2120	41.65	2428	988	40.7	1946	38.17	0.92	(0.83,1.01)	0.0844	

* 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, °:Trend test,
^Recurrent event rate, per 100 patient years at risk.

Analysis is based on study 1245.110.

^^ Patients with NYHA class I are counted in subgroup NYHA class II.
¹ Baseline SBP median: 132 [mmHg].
² Baseline NT-proBNP median for patients with history of atrial fibrillation or atrial flutter: 1354 [pg/mL].
² Baseline NT-proBNP median for patients without history of atrial fibrillation or atrial flutter: 614 [pg/mL].
³ Baseline uric acid tertile cut-offs for males are T1: 5.9 T2: 7.5 [mg/dL] [rounded].
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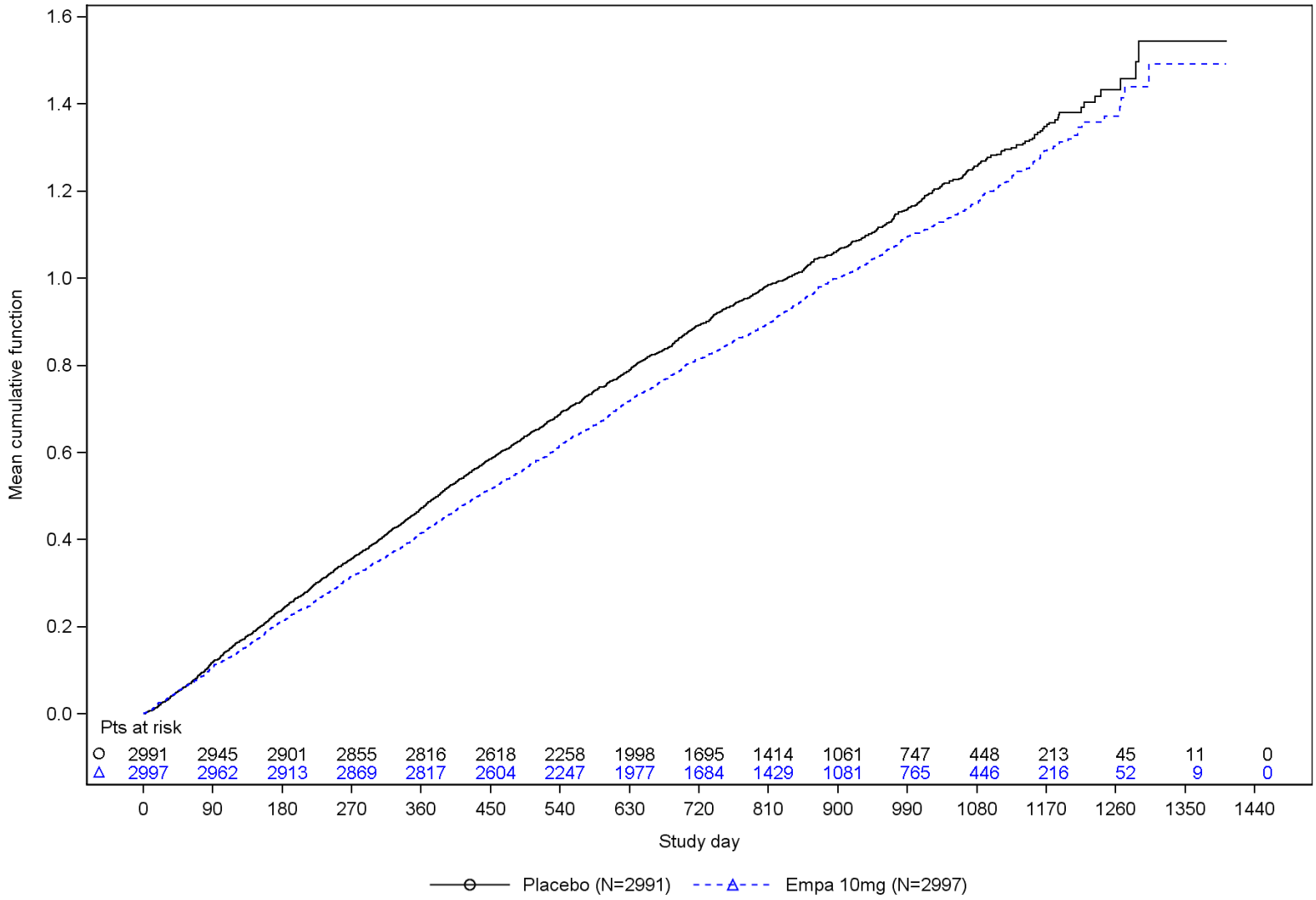

Figure R.1.1.1.4: 1 Occurrence of all-cause hospitalization (first and recurrent), mean cumulative function - RS
Analysis is based on study 1245.110.

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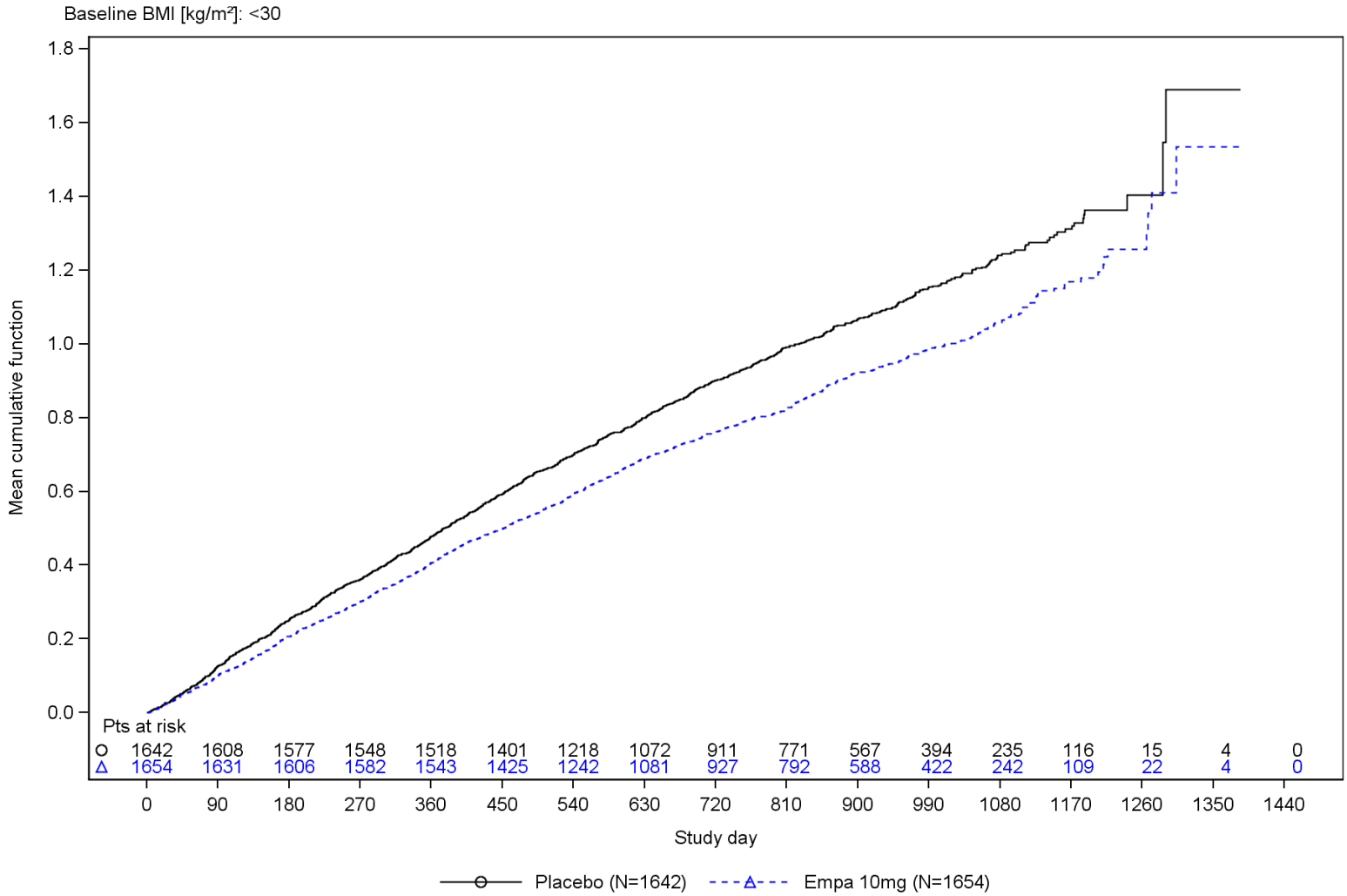

Figure R.1.1.1.4: 2 Occurrence of all-cause hospitalization (first and recurrent), mean cumulative function by baseline BMI - RS
Analysis is based on study 1245.110.

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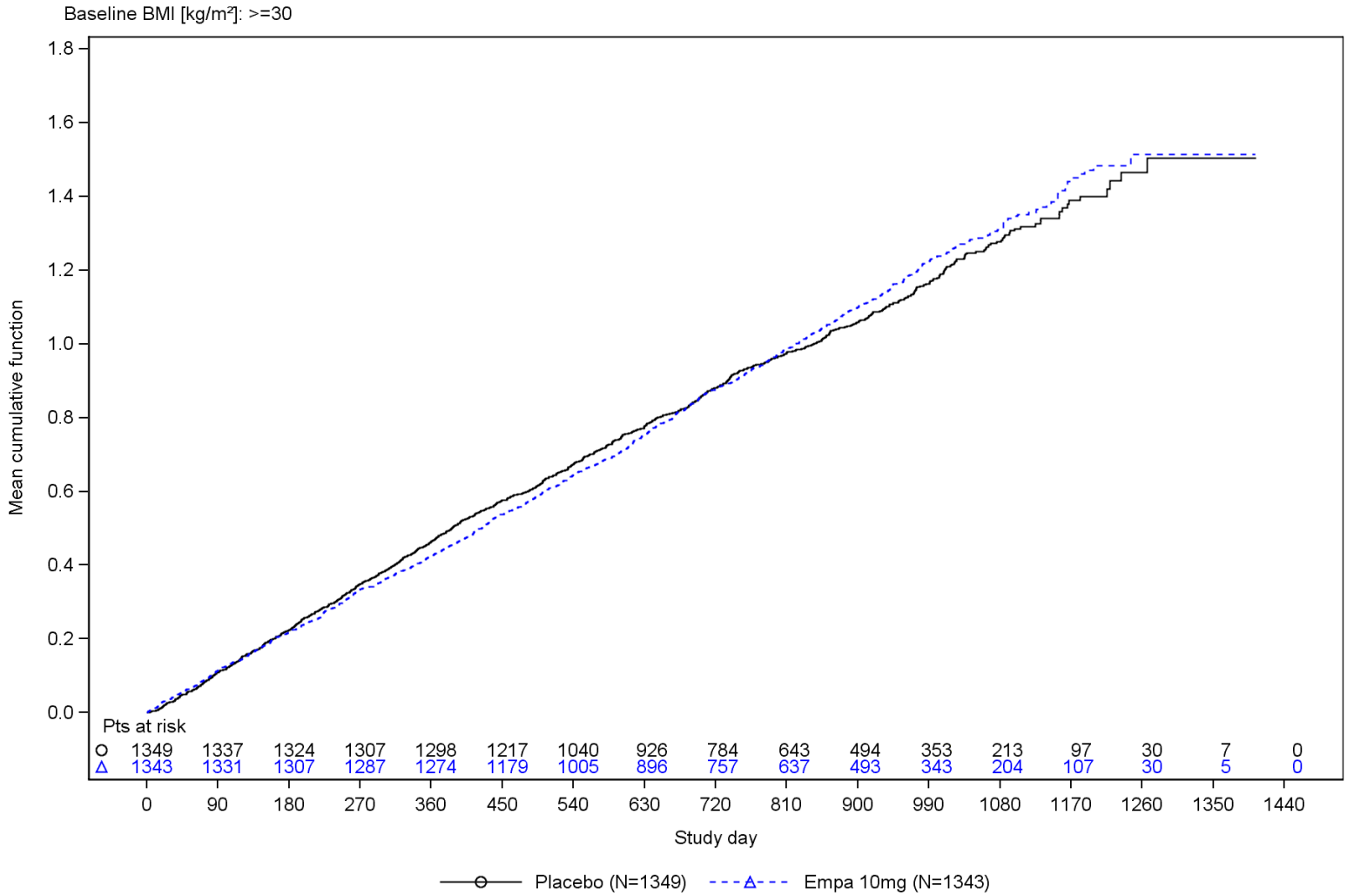

Figure R.1.1.1.4: 2 Occurrence of all-cause hospitalization (first and recurrent), mean cumulative function by baseline BMI - RS
Analysis is based on study 1245.110.

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R.1.1.1.5 Time to all-cause hospitalization or all-cause mortality

Table R.1.1.1.5: 1 Cox regression for time to first all-cause hospitalization or all-cause mortality 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
Overall	2991	1431	47.8	31.16	2997	1356	45.2	28.65	0.92	(0.85,0.99)	0.0253	
Sex												0.7983
Male	1653	827	50.0	33.06	1659	793	47.8	30.61	0.91	(0.83,1.00)	0.0614	
Female	1338	604	45.1	28.89	1338	563	42.1	26.27	0.93	(0.83,1.04)	0.2106	
Age [years]												0.8498
<70	1084	459	42.3	25.98	1066	422	39.6	24.13	0.93	(0.81,1.06)	0.2570	
>=70	1907	972	51.0	34.40	1931	934	48.4	31.29	0.91	(0.83,1.00)	0.0450	
Region												0.2745
North America	359	198	55.2	39.24	360	208	57.8	40.72	1.03	(0.85,1.25)	0.7593	
Latin America	757	329	43.5	27.21	758	300	39.6	24.35	0.90	(0.77,1.06)	0.2111	
Europe	1343	627	46.7	29.74	1346	596	44.3	27.49	0.92	(0.82,1.03)	0.1513	
Asia	343	181	52.8	36.44	343	156	45.5	28.11	0.76	(0.61,0.94)	0.0119	
Other	189	96	50.8	35.05	190	96	50.5	35.83	1.04	(0.78,1.38)	0.7963	
OECD member												0.9424
No	847	380	44.9	28.58	868	365	42.1	26.79	0.92	(0.80,1.07)	0.2763	
Yes	2144	1051	49.0	32.21	2129	991	46.5	29.39	0.92	(0.84,1.00)	0.0522	
Baseline NYHA												0.1387
II^^	2452	1105	45.1	28.51	2435	1016	41.7	25.37	0.89	(0.82,0.97)	0.0072	
III/IV	539	326	60.5	45.49	562	340	60.5	46.61	1.02	(0.87,1.18)	0.8466	
Baseline Diabetes Status												0.7726
Diabetic	1472	745	50.6	34.11	1466	706	48.2	31.60	0.91	(0.82,1.01)	0.0690	
Non-Diabetic	1519	686	45.2	28.49	1531	650	42.5	26.00	0.93	(0.83,1.03)	0.1788	

* 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, °:Trend test, ^Incidence rate, events per 100 patient years at risk.

Analysis is based on study 1245.110.

^^ Patients with NYHA class I are counted in subgroup NYHA class II.
[1] Baseline SBP median: 132 [mmHg].
[2] Baseline NT-proBNP median for patients with history of atrial fibrillation or atrial flutter: 1354 [pg/mL].
[2] Baseline NT-proBNP median for patients without history of atrial fibrillation or atrial flutter: 614 [pg/mL].
[3] Baseline uric acid tertile cut-offs for males are T1: 5.9 T2: 7.5 [mg/dL] [rounded].
[3] Baseline uric acid tertile cut-offs for females are T1: 5.4 T2: 6.9 [mg/dL] [rounded].

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Table R.1.1.1.5: 1 Cox regression for time to first all-cause hospitalization or 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 Diabetes Status												0.7436°/ 0.9402
Diabetic	1472	745	50.6	34.11	1466	706	48.2	31.60	0.91	(0.82,1.01)	0.0691	
Pre-Diabetes	979	441	45.0	28.58	1001	423	42.3	26.07	0.92	(0.81,1.05)	0.2347	
Normal (no pre-diabetes)	540	245	45.4	28.31	530	227	42.8	25.87	0.94	(0.79,1.13)	0.5218	
Baseline BMI [kg/m²]												0.0047
<30	1642	808	49.2	32.66	1654	714	43.2	26.88	0.83	(0.75,0.92)	0.0004	
>=30	1349	623	46.2	29.40	1343	642	47.8	30.90	1.03	(0.93,1.15)	0.5609	
Baseline eGFR (CKD-EPI) [mL/min/1.73m²]												0.2752
>=60	1505	632	42.0	25.56	1493	561	37.6	22.13	0.88	(0.78,0.98)	0.0218	
<60	1484	798	53.8	37.69	1504	795	52.9	36.15	0.95	(0.86,1.05)	0.3242	
History of HHF (in the last 12 months)												0.9042
No	2321	1037	44.7	28.13	2298	960	41.8	25.59	0.92	(0.84,1.00)	0.0504	
Yes	670	394	58.8	43.47	699	396	56.7	40.34	0.91	(0.79,1.04)	0.1697	
Baseline SBP (</>= median¹)												0.5692
< median	1474	705	47.8	31.66	1496	687	45.9	29.82	0.94	(0.84,1.04)	0.2379	
>= median	1517	726	47.9	30.69	1501	669	44.6	27.53	0.90	(0.81,1.00)	0.0470	
History of atrial fibrillation or atrial flutter												0.3546
No	1427	642	45.0	28.60	1417	579	40.9	24.82	0.88	(0.79,0.99)	0.0317	
Yes	1559	786	50.4	33.53	1576	776	49.2	32.45	0.95	(0.86,1.05)	0.3016	

* 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, °:Trend test, ^Incidence rate, events per 100 patient years at risk.

Analysis is based on study 1245.110.

^^ Patients with NYHA class I are counted in subgroup NYHA class II.
¹ Baseline SBP median: 132 [mmHg].
² Baseline NT-proBNP median for patients with history of atrial fibrillation or atrial flutter: 1354 [pg/mL].
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³ Baseline uric acid tertile cut-offs for males are T1: 5.9 T2: 7.5 [mg/dL] [rounded].
³ Baseline uric acid tertile cut-offs for females are T1: 5.4 T2: 6.9 [mg/dL] [rounded].

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Table R.1.1.1.5: 1 Cox regression for time to first all-cause hospitalization or 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 LVEF [%]												0.0804
< 50	988	490	49.6	32.13	995	436	43.8	27.07	0.84	(0.73,0.95)	0.0065	
>= 50	2003	941	47.0	30.68	2002	920	46.0	29.46	0.96	(0.88,1.05)	0.4089	
Baseline LVEF [%]												0.0193°/ 0.0572
<50	988	490	49.6	32.13	995	436	43.8	27.07	0.84	(0.73,0.95)	0.0065	
50 to <60	1030	496	48.2	31.44	1028	457	44.5	27.83	0.89	(0.79,1.02)	0.0846	
>=60	973	445	45.7	29.87	974	463	47.5	31.27	1.04	(0.91,1.18)	0.5531	
Baseline NT-proBNP [pg/mL] (</>=median² by atrial fibrillation/flutter status)												0.4850
< median	1508	634	42.0	25.53	1477	585	39.6	23.81	0.94	(0.84,1.06)	0.3066	
>= median	1476	792	53.7	37.64	1516	770	50.8	33.95	0.89	(0.81,0.99)	0.0270	
Baseline uric acid [mg/dL] (tertiles³)												0.0291°/ 0.0952
<T1	975	442	45.3	28.77	963	376	39.0	23.92	0.83	(0.72,0.95)	0.0078	
>=T1 and <T2	966	440	45.5	29.01	1032	445	43.1	26.58	0.92	(0.80,1.04)	0.1878	
>=T2	1018	532	52.3	35.61	970	522	53.8	36.30	1.02	(0.90,1.15)	0.8088	
Baseline use of MRA												0.9162
No	1866	879	47.1	30.70	1878	844	44.9	28.20	0.92	(0.84,1.01)	0.0922	
Yes	1125	552	49.1	31.92	1119	512	45.8	29.41	0.91	(0.81,1.03)	0.1454	
Baseline use of ACE-inhibitor, ARB or ARNi												0.7418
No	587	314	53.5	37.87	569	294	51.7	34.45	0.94	(0.80,1.10)	0.4591	
Yes	2404	1117	46.5	29.68	2428	1062	43.7	27.37	0.91	(0.84,0.99)	0.0350	

* 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, °:Trend test, ^Incidence rate, events per 100 patient years at risk.

Analysis is based on study 1245.110.

^^ Patients with NYHA class I are counted in subgroup NYHA class II.
¹ Baseline SBP median: 132 [mmHg].
² Baseline NT-proBNP median for patients with history of atrial fibrillation or atrial flutter: 1354 [pg/mL].
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³ Baseline uric acid tertile cut-offs for males are T1: 5.9 T2: 7.5 [mg/dL] [rounded].
³ Baseline uric acid tertile cut-offs for females are T1: 5.4 T2: 6.9 [mg/dL] [rounded].

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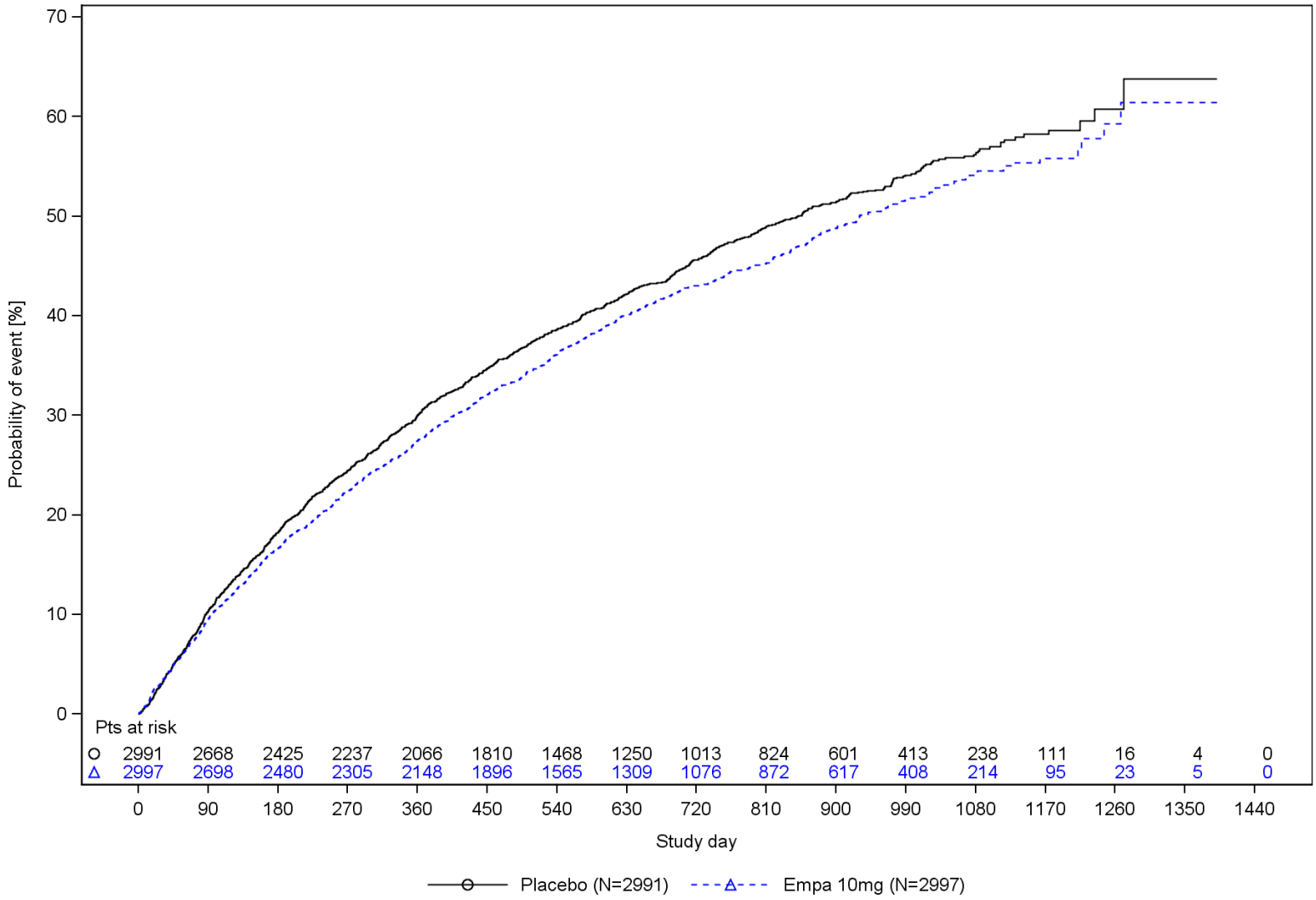

Figure R.1.1.1.5: 1 Time to first all-cause hospitalization or all-cause mortality, Kaplan-Meier estimate - RS
Analysis is based on study 1245.110

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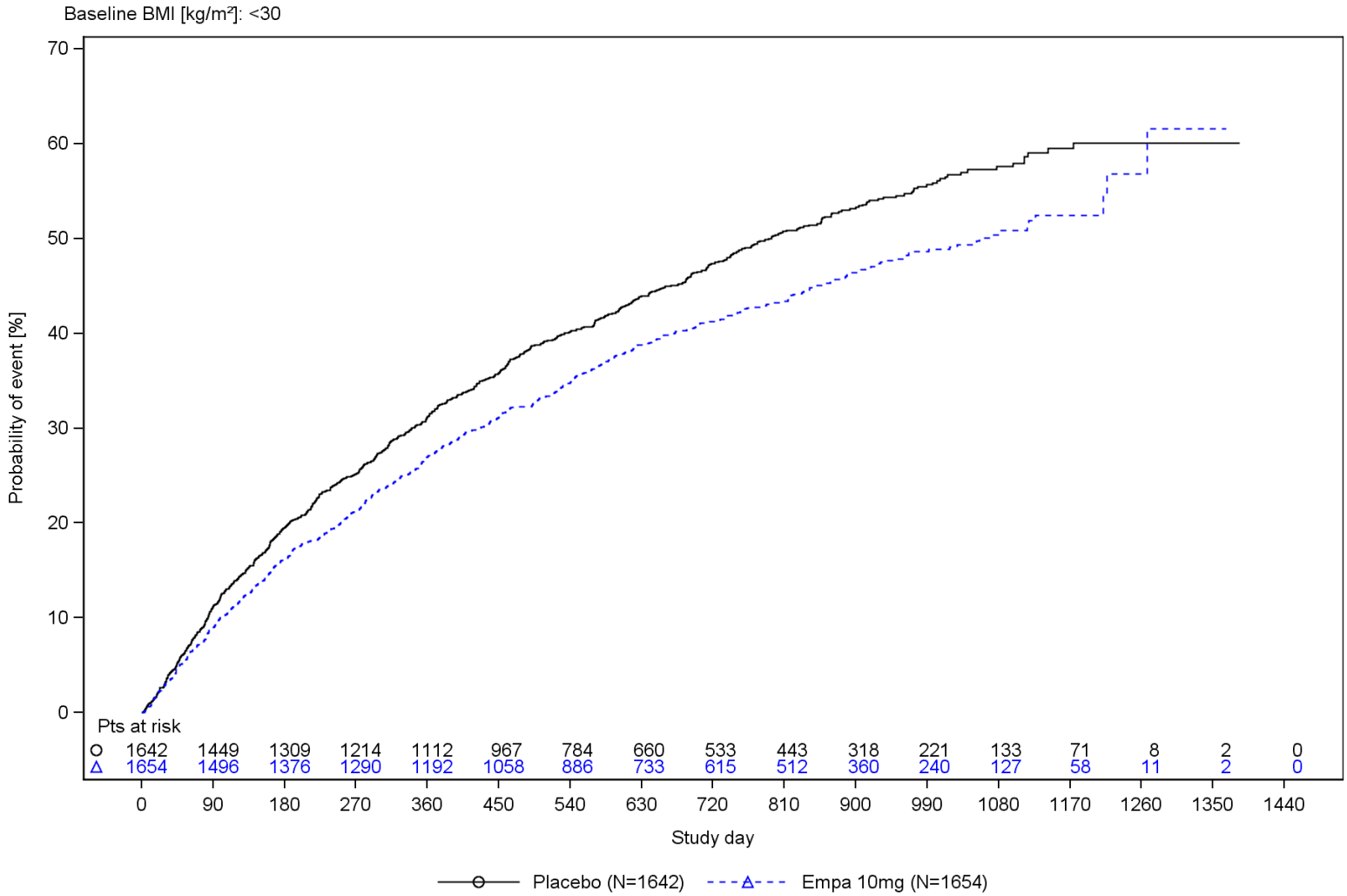

Figure R.1.1.1.5: 2 Time to first all-cause hospitalization or all-cause mortality, Kaplan-Meier estimate by baseline BMI - RS
Analysis is based on study 1245.110

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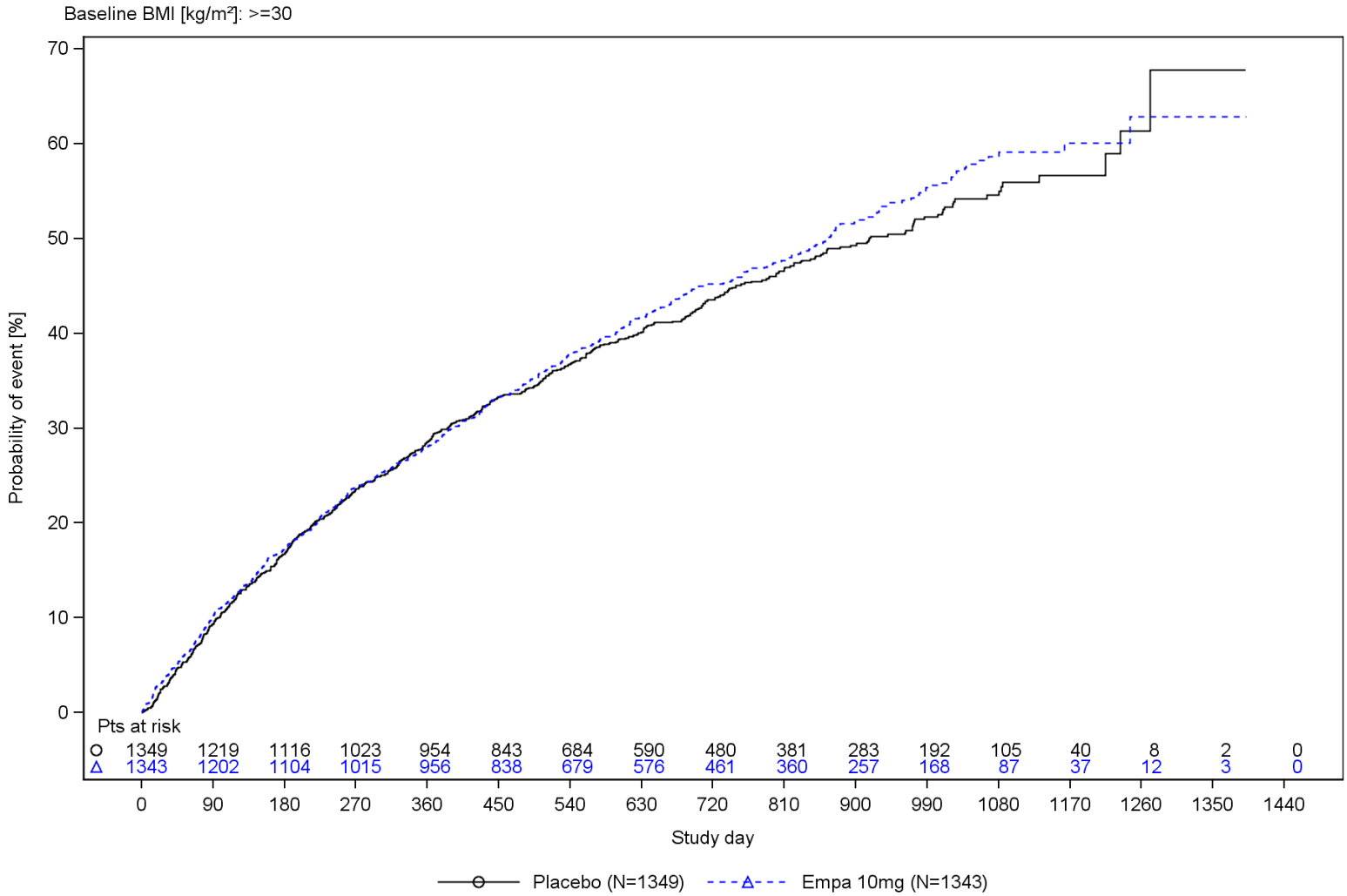

Figure R.1.1.1.5: 2 Time to first all-cause hospitalization or all-cause mortality, Kaplan-Meier estimate by baseline BMI - RS
Analysis is based on study 1245.110

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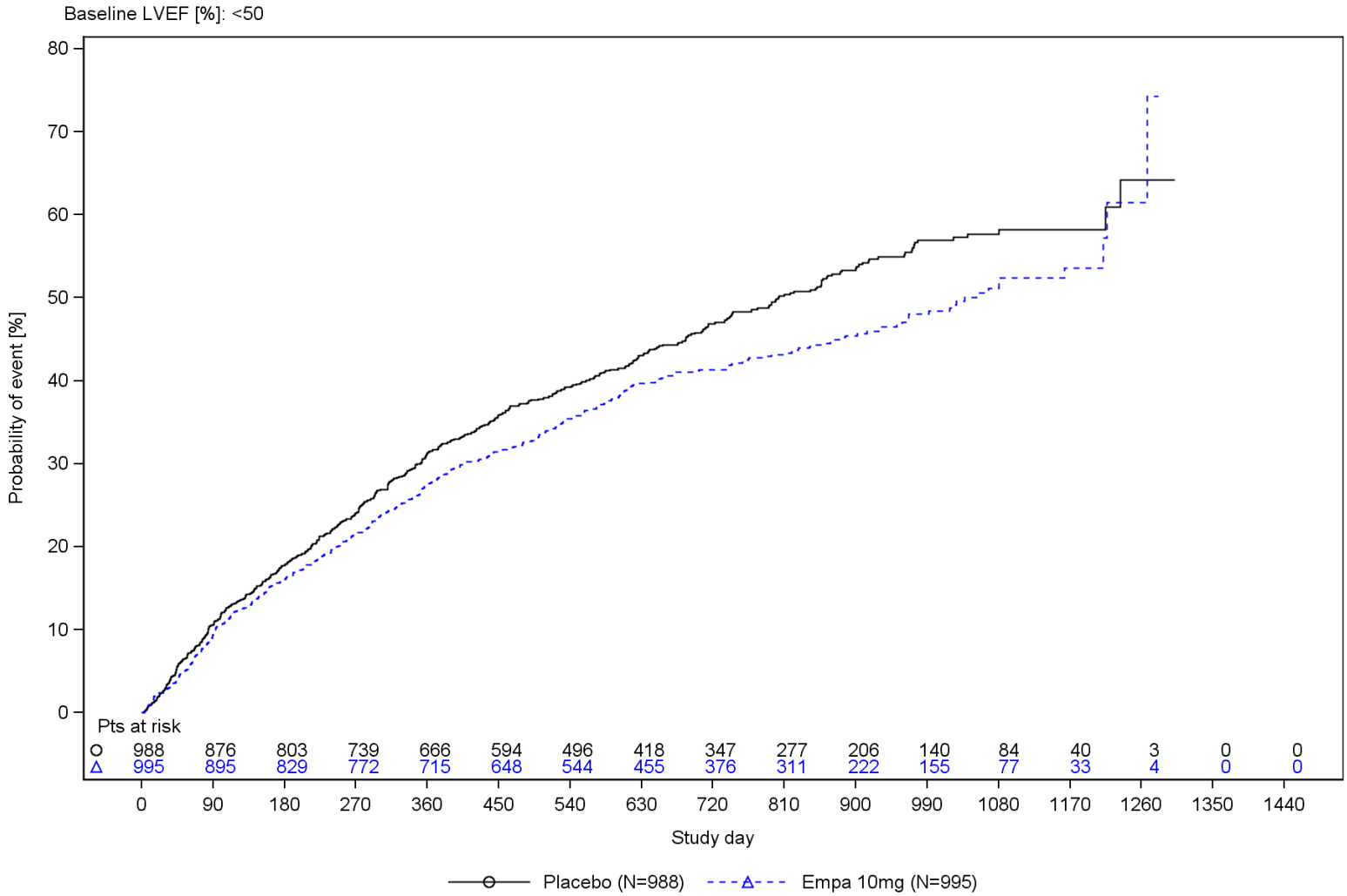

Figure R.1.1.1.5: 3 Time to first all-cause hospitalization or all-cause mortality, Kaplan-Meier estimate by baseline LVEF - RS
Analysis is based on study 1245.110

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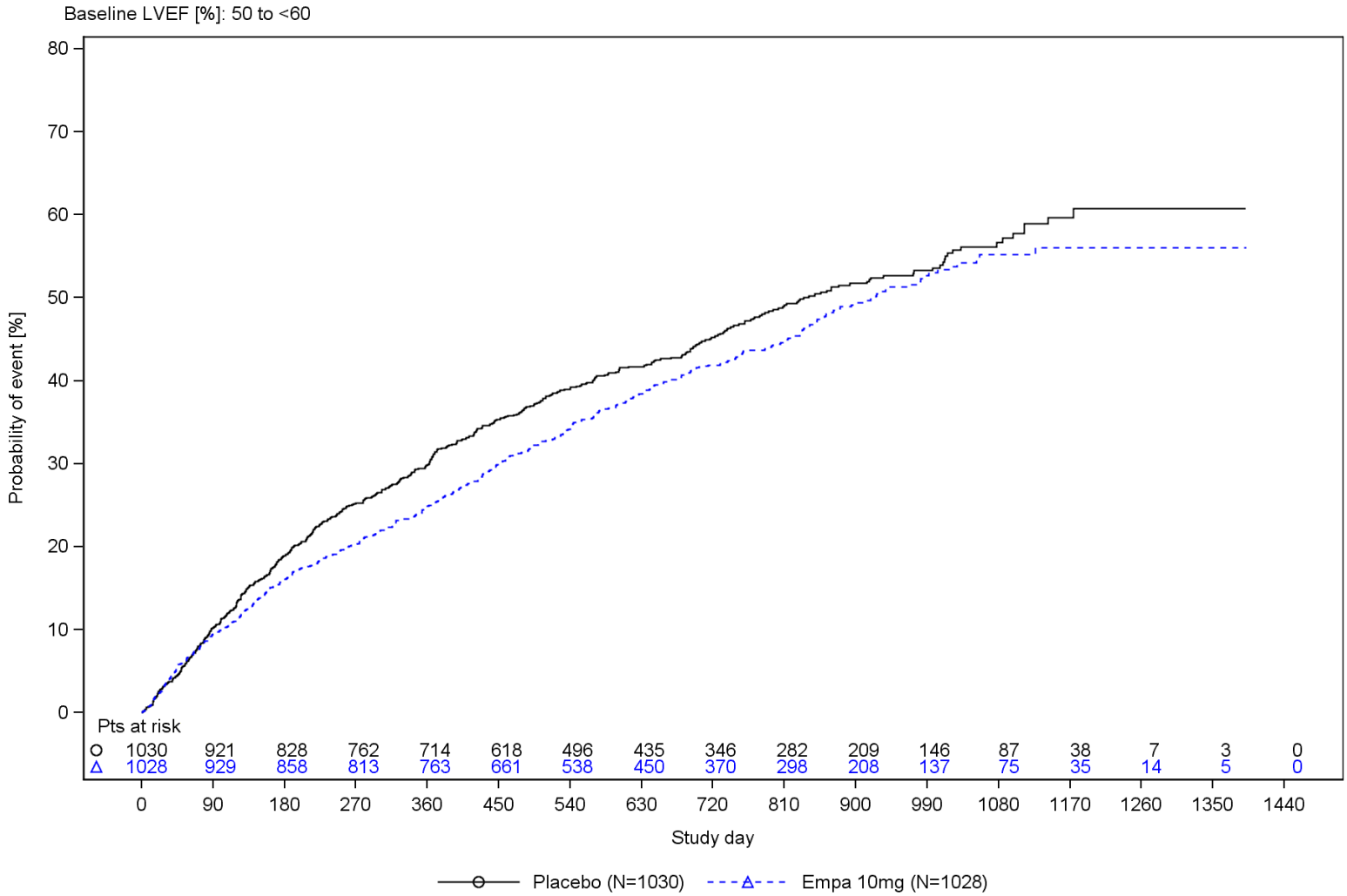

Figure R.1.1.1.5: 3 Time to first all-cause hospitalization or all-cause mortality, Kaplan-Meier estimate
by baseline LVEF - RS
Analysis is based on study 1245.110

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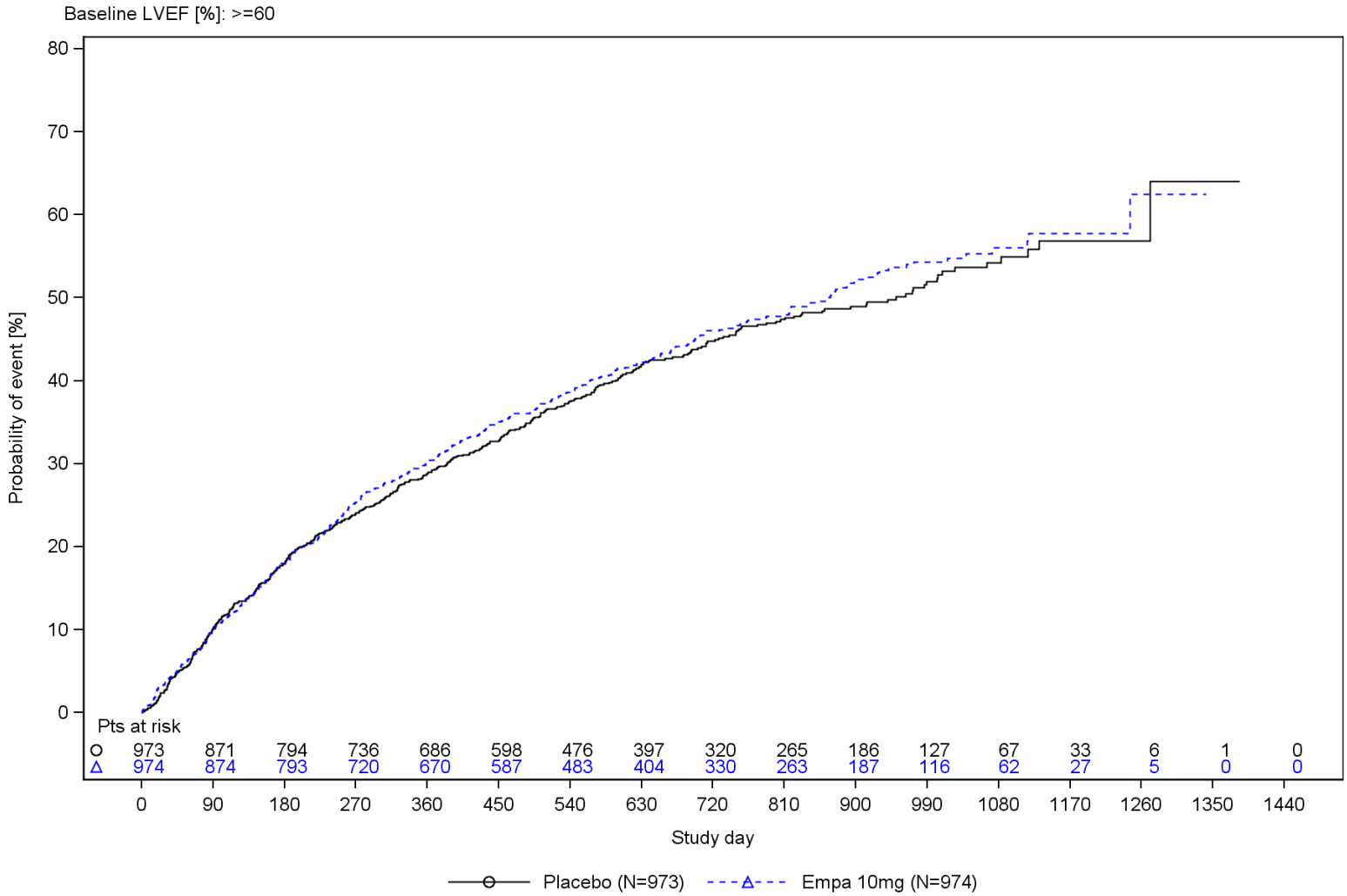

Figure R.1.1.1.5: 3 Time to first all-cause hospitalization or all-cause mortality, Kaplan-Meier estimate by baseline LVEF - RS
Analysis is based on study 1245.110

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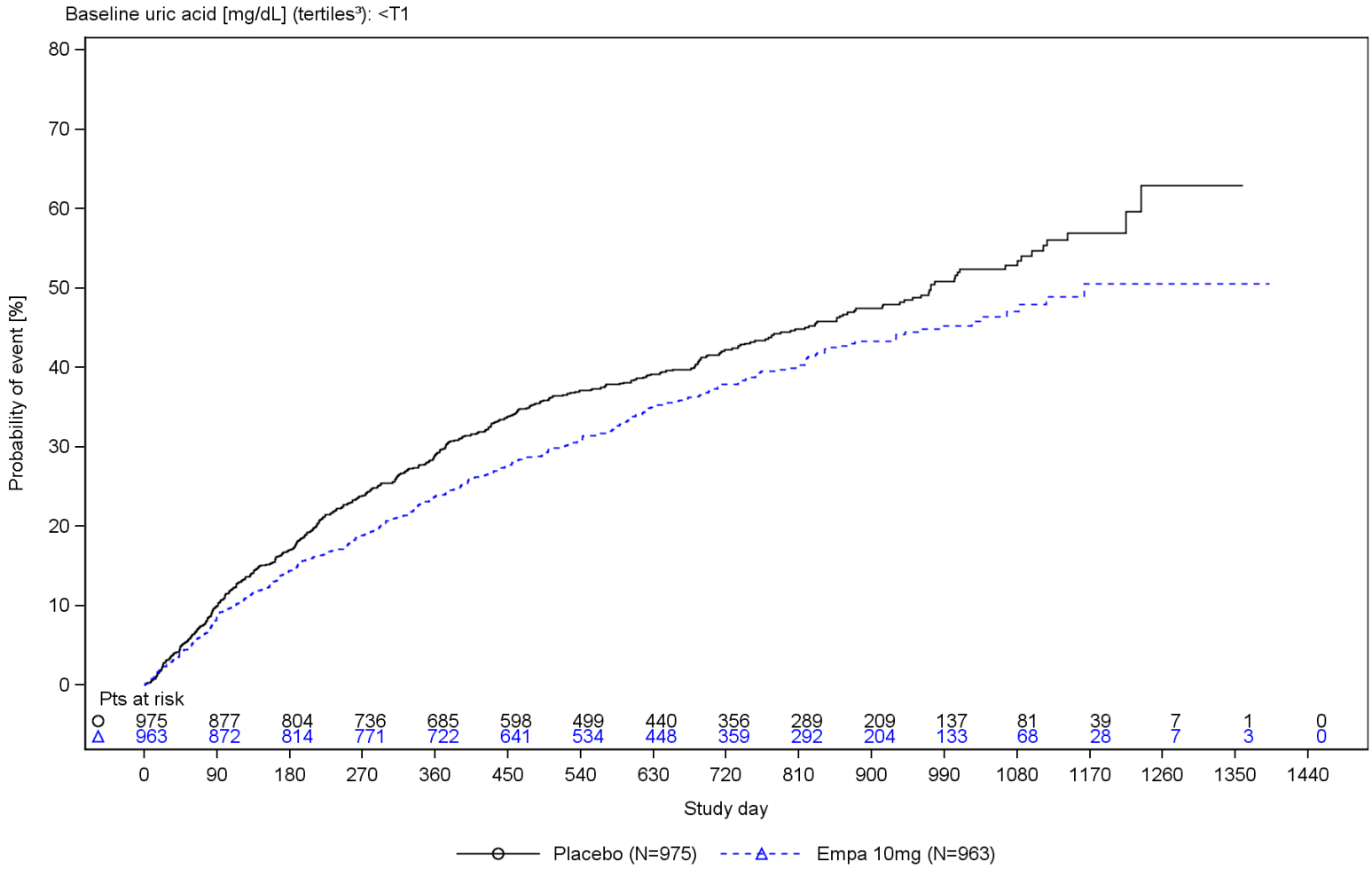

Figure R.1.1.1.5: 4 Time to first all-cause hospitalization or all-cause mortality, Kaplan-Meier estimate by baseline uric acid - RS

Analysis is based on study 1245.110

³ Baseline uric acid tertile cut-offs for males are T1: 5.9 T2: 7.5 [mg/dL] [rounded].

³ Baseline uric acid tertile cut-offs for females are T1: 5.4 T2: 6.9 [mg/dL] [rounded].

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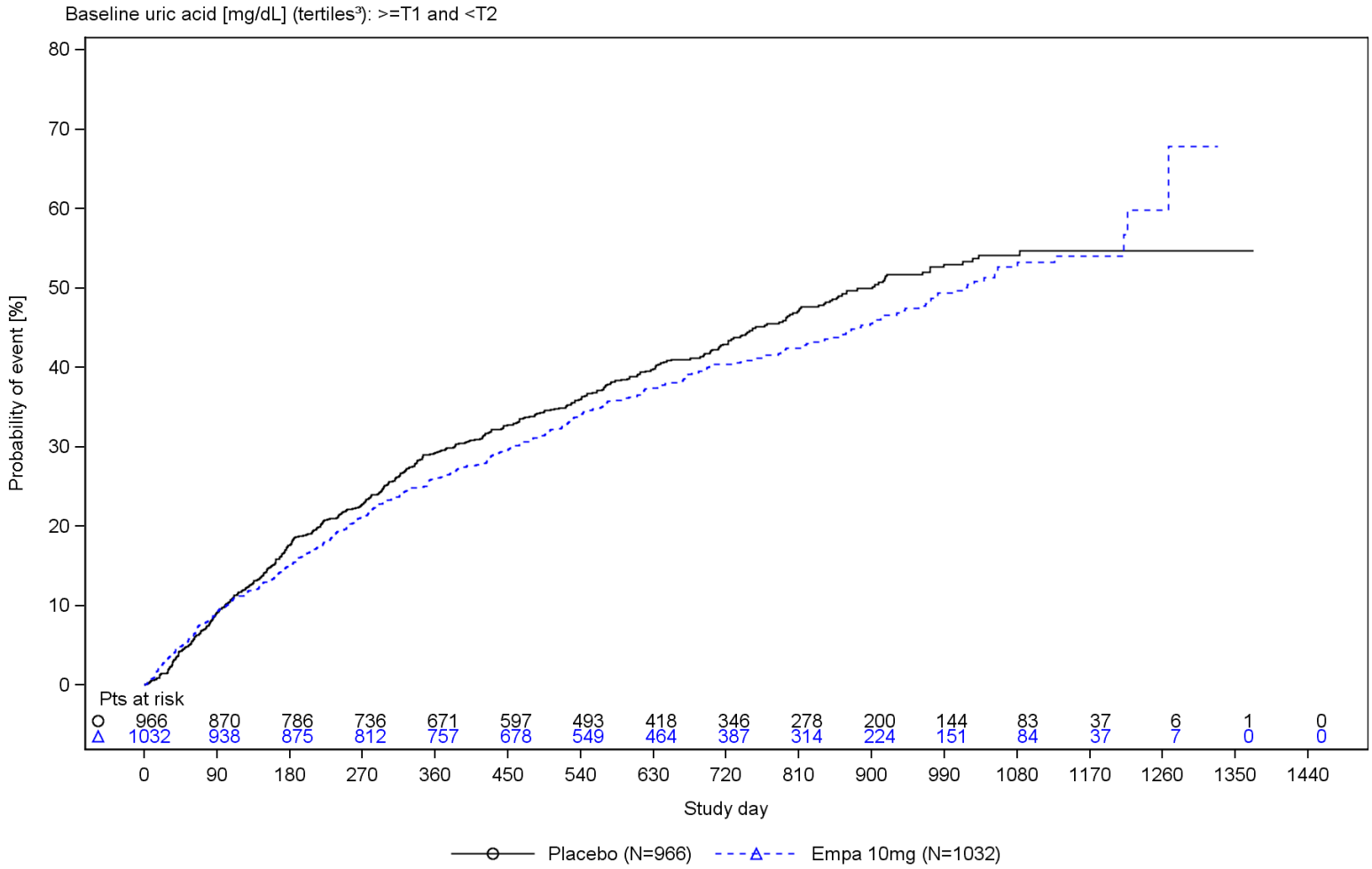

Figure R.1.1.1.5: 4 Time to first all-cause hospitalization or all-cause mortality, Kaplan-Meier estimate by baseline uric acid - RS

Analysis is based on study 1245.110

³ Baseline uric acid tertile cut-offs for males are T1: 5.9 T2: 7.5 [mg/dL] [rounded].

³ Baseline uric acid tertile cut-offs for females are T1: 5.4 T2: 6.9 [mg/dL] [rounded].

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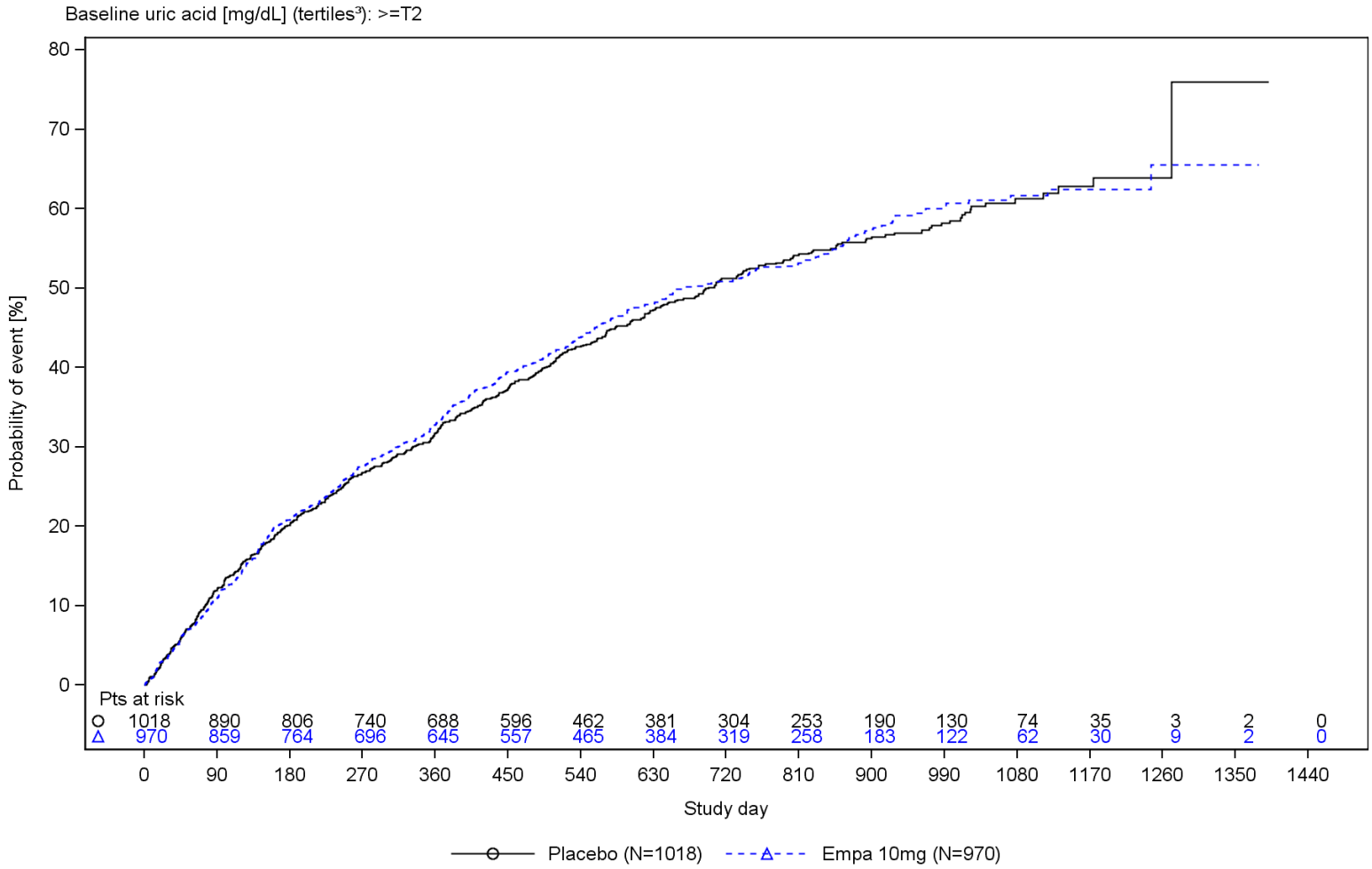

Figure R.1.1.1.5: 4 Time to first all-cause hospitalization or all-cause mortality, Kaplan-Meier estimate by baseline uric acid - RS

Analysis is based on study 1245.110

³ Baseline uric acid tertile cut-offs for males are T1: 5.9 T2: 7.5 [mg/dL] [rounded].

³ Baseline uric acid tertile cut-offs for females are T1: 5.4 T2: 6.9 [mg/dL] [rounded].

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R.1.1.1.6 Time to adjudicated HHF

Table R.1.1.1.6: 1 Cox regression for time to first 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	2991	352	11.8	5.97	2997	259	8.6	4.28	0.71	(0.60,0.83)	<0.0001	
Sex												0.8358
Male	1653	198	12.0	6.10	1659	151	9.1	4.53	0.72	(0.58,0.89)	0.0023	
Female	1338	154	11.5	5.82	1338	108	8.1	3.98	0.70	(0.54,0.89)	0.0038	
Age [years]												0.1640
<70	1084	103	9.5	4.69	1066	87	8.2	4.01	0.84	(0.63,1.12)	0.2270	
>=70	1907	249	13.1	6.74	1931	172	8.9	4.44	0.66	(0.54,0.80)	<0.0001	
Region												0.5934
North America	359	65	18.1	9.34	360	50	13.9	6.82	0.73	(0.51,1.06)	0.0996	
Latin America	757	66	8.7	4.58	758	49	6.5	3.33	0.74	(0.51,1.07)	0.1041	
Europe	1343	138	10.3	5.06	1346	98	7.3	3.52	0.69	(0.53,0.89)	0.0045	
Asia	343	58	16.9	8.70	343	37	10.8	5.28	0.58	(0.38,0.87)	0.0090	
Other	189	25	13.2	6.91	190	25	13.2	7.03	1.03	(0.59,1.79)	0.9284	
OECD member												0.8125
No	847	101	11.9	6.31	868	79	9.1	4.79	0.73	(0.55,0.98)	0.0379	
Yes	2144	251	11.7	5.85	2129	180	8.5	4.09	0.70	(0.58,0.85)	0.0003	
Baseline NYHA												0.4892
II^^	2452	236	9.6	4.80	2435	161	6.6	3.21	0.67	(0.55,0.82)	<0.0001	
III/IV	539	116	21.5	11.88	562	98	17.4	9.56	0.75	(0.57,0.99)	0.0387	
Baseline Diabetes Status												0.6552
Diabetic	1472	215	14.6	7.57	1466	155	10.6	5.38	0.69	(0.56,0.85)	0.0004	
Non-Diabetic	1519	137	9.0	4.49	1531	104	6.8	3.29	0.74	(0.57,0.96)	0.0218	

* 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, °:Trend test, ^Incidence rate, events per 100 patient years at risk.

Analysis is based on study 1245.110.

^^ Patients with NYHA class I are counted in subgroup NYHA class II.
[1] Baseline SBP median: 132 [mmHg].
[2] Baseline NT-proBNP median for patients with history of atrial fibrillation or atrial flutter: 1354 [pg/mL].
[2] Baseline NT-proBNP median for patients without history of atrial fibrillation or atrial flutter: 614 [pg/mL].
[3] Baseline uric acid tertile cut-offs for males are T1: 5.9 T2: 7.5 [mg/dL] [rounded].
[3] Baseline uric acid tertile cut-offs for females are T1: 5.4 T2: 6.9 [mg/dL] [rounded].

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Table R.1.1.1.6: 1 Cox regression for time to first 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 Diabetes Status												0.8223°/ 0.3075
Diabetic	1472	215	14.6	7.57	1466	155	10.6	5.38	0.69	(0.56,0.85)	0.0004	
Pre-Diabetes	979	87	8.9	4.41	1001	76	7.6	3.70	0.85	(0.62,1.15)	0.2850	
Normal (no pre-diabetes)	540	50	9.3	4.63	530	28	5.3	2.52	0.56	(0.35,0.89)	0.0135	
Baseline BMI [kg/m²]												0.4603
<30	1642	195	11.9	6.12	1654	135	8.2	4.05	0.67	(0.54,0.84)	0.0004	
>=30	1349	157	11.6	5.80	1343	124	9.2	4.57	0.76	(0.60,0.96)	0.0206	
Baseline eGFR (CKD-EPI) [mL/min/1.73m²]												0.2900
>=60	1505	116	7.7	3.75	1493	92	6.2	2.98	0.80	(0.61,1.05)	0.1111	
<60	1484	236	15.9	8.43	1504	167	11.1	5.65	0.67	(0.55,0.81)	<0.0001	
History of HHF (in the last 12 months)												0.6897
No	2321	194	8.4	4.17	2298	139	6.0	2.96	0.71	(0.57,0.89)	0.0024	
Yes	670	158	23.6	12.77	699	120	17.2	8.90	0.67	(0.53,0.85)	0.0009	
Baseline SBP (</>= median¹)												0.2994
< median	1474	181	12.3	6.33	1496	126	8.4	4.21	0.65	(0.52,0.82)	0.0002	
>= median	1517	171	11.3	5.64	1501	133	8.9	4.36	0.77	(0.62,0.97)	0.0253	
History of atrial fibrillation or atrial flutter												0.9743
No	1427	141	9.9	4.98	1417	98	6.9	3.41	0.71	(0.54,0.91)	0.0080	
Yes	1559	211	13.5	6.92	1576	161	10.2	5.09	0.70	(0.57,0.86)	0.0007	

* 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, °:Trend test, ^Incidence rate, events per 100 patient years at risk.

Analysis is based on study 1245.110.

^^ Patients with NYHA class I are counted in subgroup NYHA class II.
¹ Baseline SBP median: 132 [mmHg].
² Baseline NT-proBNP median for patients with history of atrial fibrillation or atrial flutter: 1354 [pg/mL].
² Baseline NT-proBNP median for patients without history of atrial fibrillation or atrial flutter: 614 [pg/mL].
³ Baseline uric acid tertile cut-offs for males are T1: 5.9 T2: 7.5 [mg/dL] [rounded].
³ Baseline uric acid tertile cut-offs for females are T1: 5.4 T2: 6.9 [mg/dL] [rounded].

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Table R.1.1.1.6: 1 Cox regression for time to first 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
Baseline LVEF [%]												0.0932
< 50	988	126	12.8	6.51	995	77	7.7	3.81	0.58	(0.44,0.77)	0.0002	
>= 50	2003	226	11.3	5.71	2002	182	9.1	4.52	0.78	(0.64,0.95)	0.0128	
Baseline LVEF [%]												0.0454°/ 0.1393
<50	988	126	12.8	6.51	995	77	7.7	3.81	0.58	(0.44,0.77)	0.0002	
50 to <60	1030	122	11.8	5.98	1028	87	8.5	4.19	0.70	(0.53,0.93)	0.0123	
>=60	973	104	10.7	5.43	974	95	9.8	4.87	0.87	(0.66,1.15)	0.3219	
Baseline NT-proBNP [pg/mL] (</>=median² by atrial fibrillation/flutter status)												0.7775
< median	1508	109	7.2	3.48	1477	71	4.8	2.27	0.67	(0.50,0.90)	0.0087	
>= median	1476	242	16.4	8.80	1516	188	12.4	6.45	0.71	(0.58,0.85)	0.0003	
Baseline uric acid [mg/dL] (tertiles³)												0.5490°/ 0.7833
<T1	975	89	9.1	4.56	963	59	6.1	3.02	0.65	(0.47,0.90)	0.0101	
>=T1 and <T2	966	84	8.7	4.26	1032	68	6.6	3.22	0.75	(0.54,1.03)	0.0772	
>=T2	1018	174	17.1	9.10	970	129	13.3	6.71	0.74	(0.59,0.93)	0.0091	
Baseline use of MRA												0.0323
No	1866	208	11.1	5.59	1878	131	7.0	3.40	0.60	(0.49,0.75)	<0.0001	
Yes	1125	144	12.8	6.63	1119	128	11.4	5.83	0.86	(0.68,1.09)	0.2195	
Baseline use of ACE-inhibitor, ARB or ARNi												0.9395
No	587	95	16.2	8.57	569	66	11.6	5.81	0.70	(0.51,0.96)	0.0288	
Yes	2404	257	10.7	5.37	2428	193	7.9	3.93	0.71	(0.59,0.86)	0.0004	

* 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, °:Trend test, ^Incidence rate, events per 100 patient years at risk.

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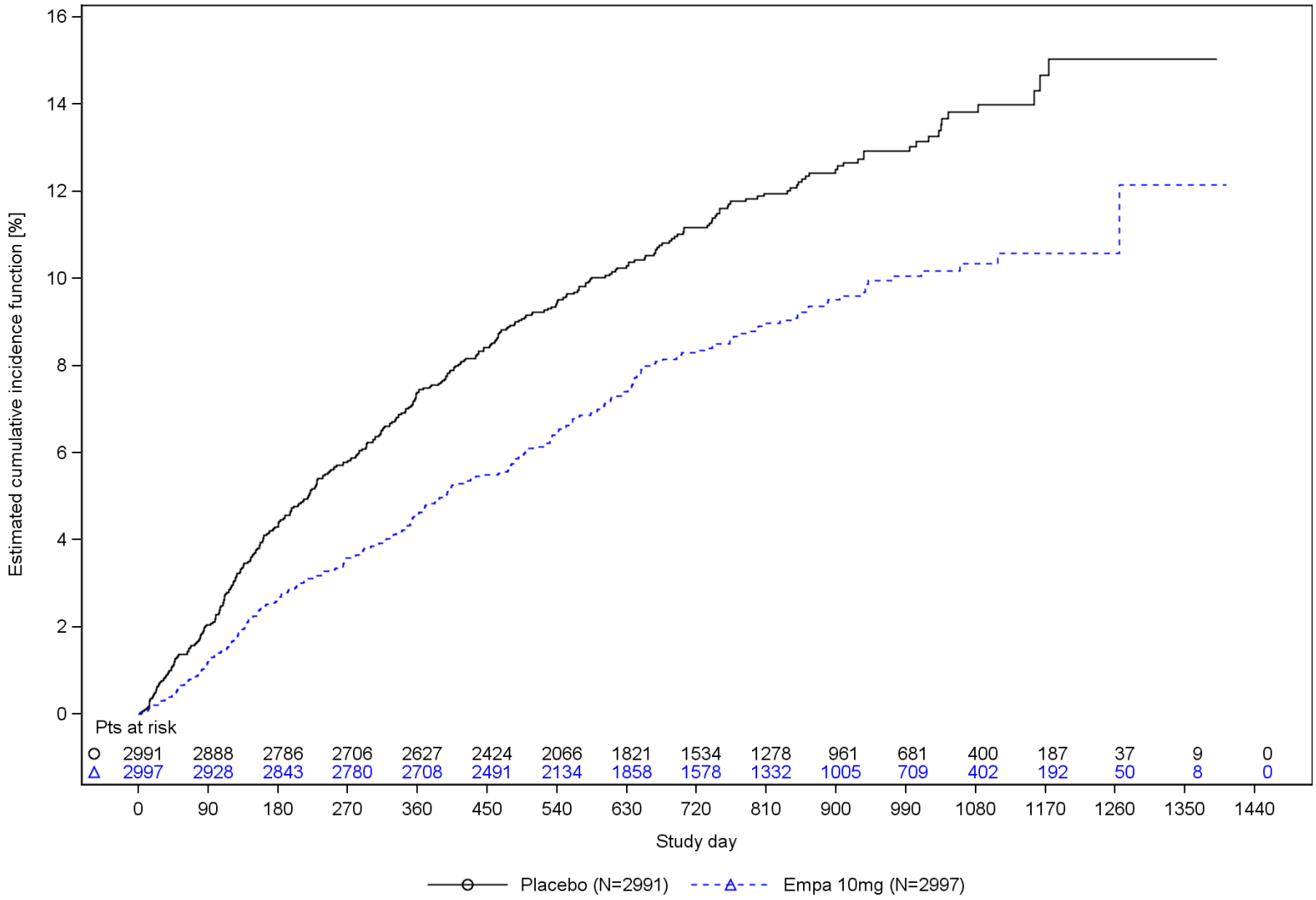

Figure R.1.1.1.6: 1 Time to first adjudicated HHF, estimated cumulative incidence function (considering all-cause mortality as a competing risk) - RS
Analysis is based on study 1245.110.

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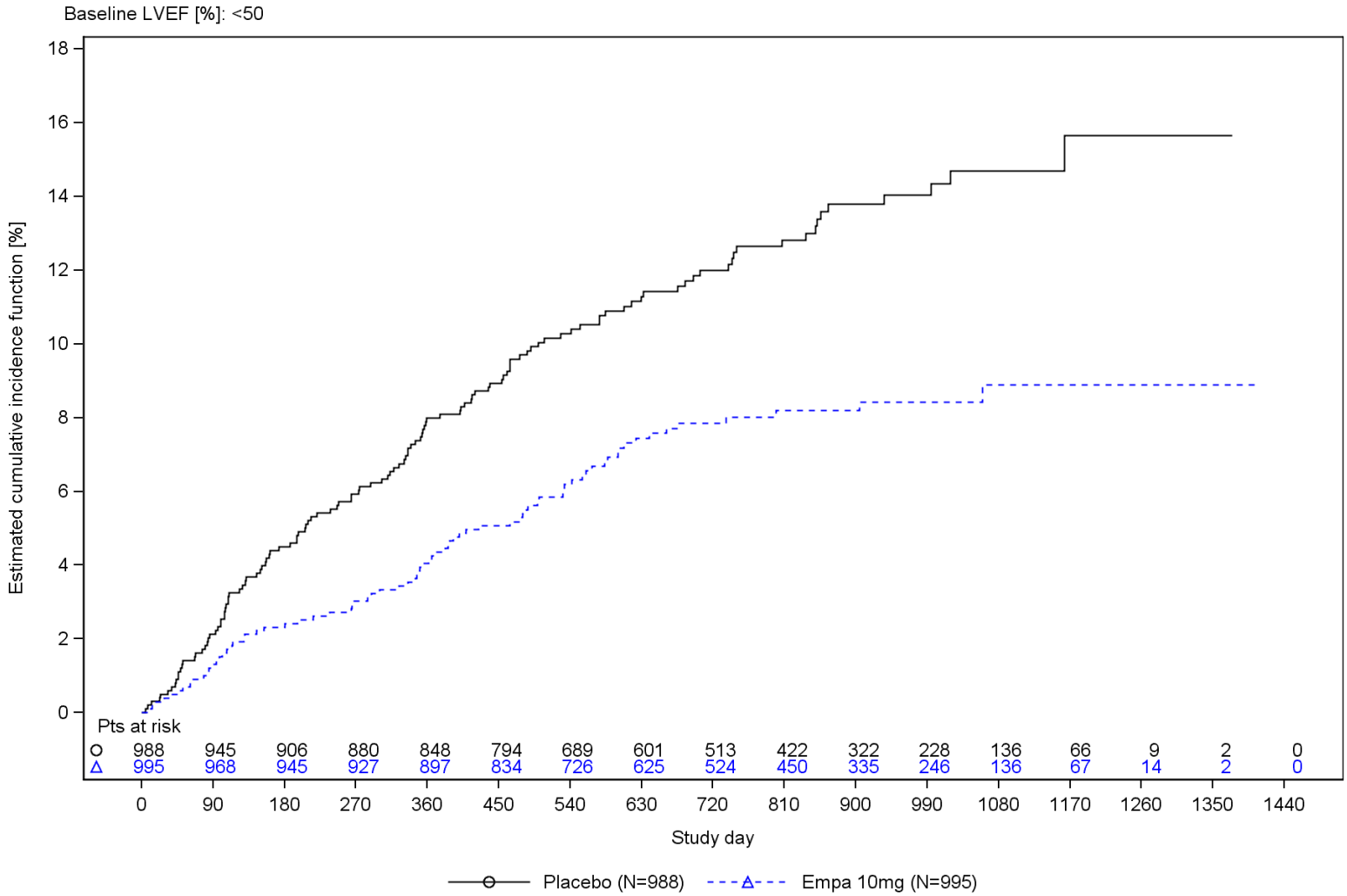

Figure R.1.1.1.6: 2 Time to first adjudicated HHF, estimated cumulative incidence function (considering all-cause mortality as a competing risk) by baseline LVEF - RS
Analysis is based on study 1245.110.

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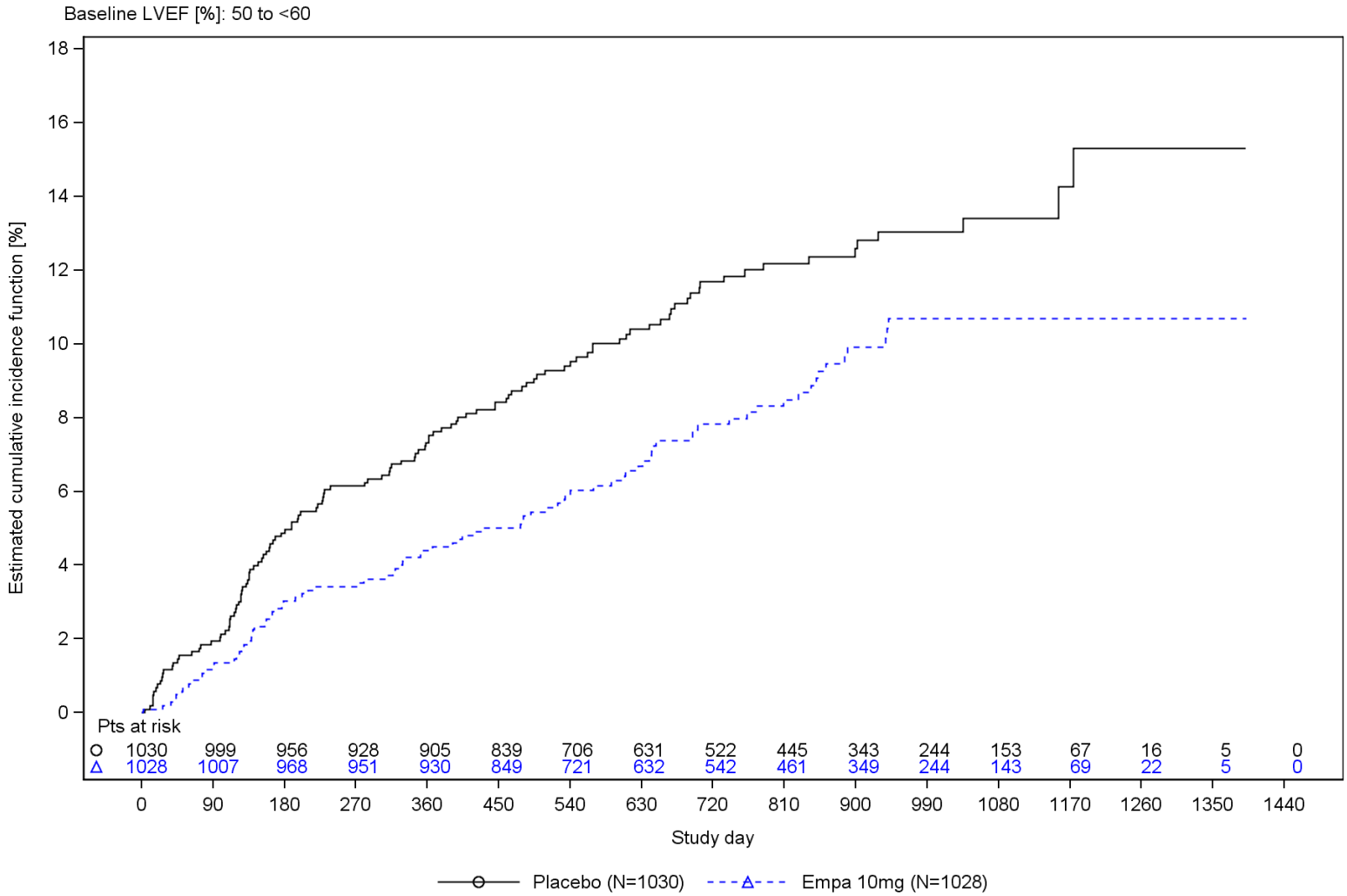

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Analysis is based on study 1245.110.

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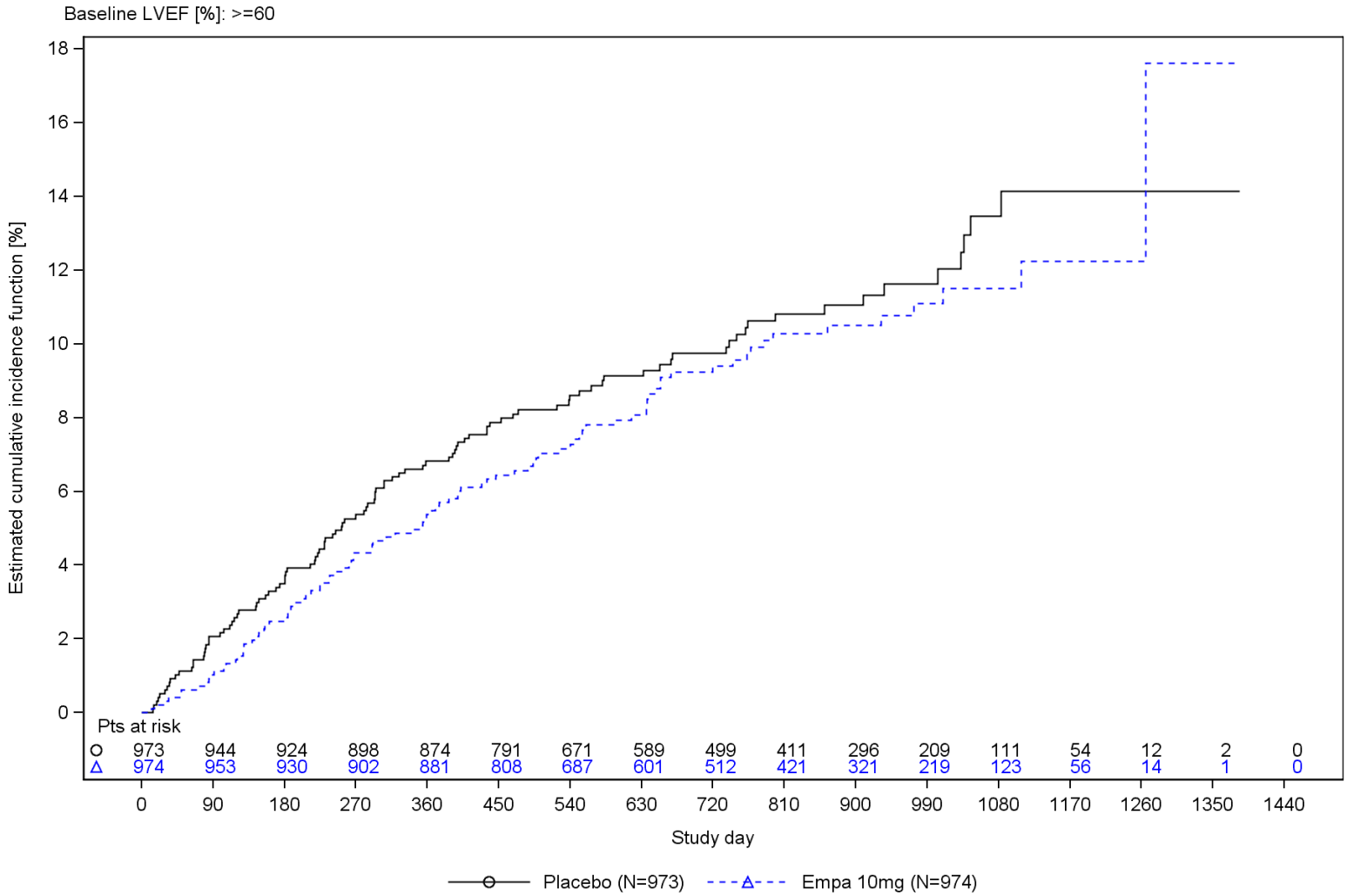

Figure R.1.1.1.6: 2 Time to first adjudicated HHF, estimated cumulative incidence function (considering all-cause mortality as a competing risk) by baseline LVEF - RS
Analysis is based on study 1245.110.

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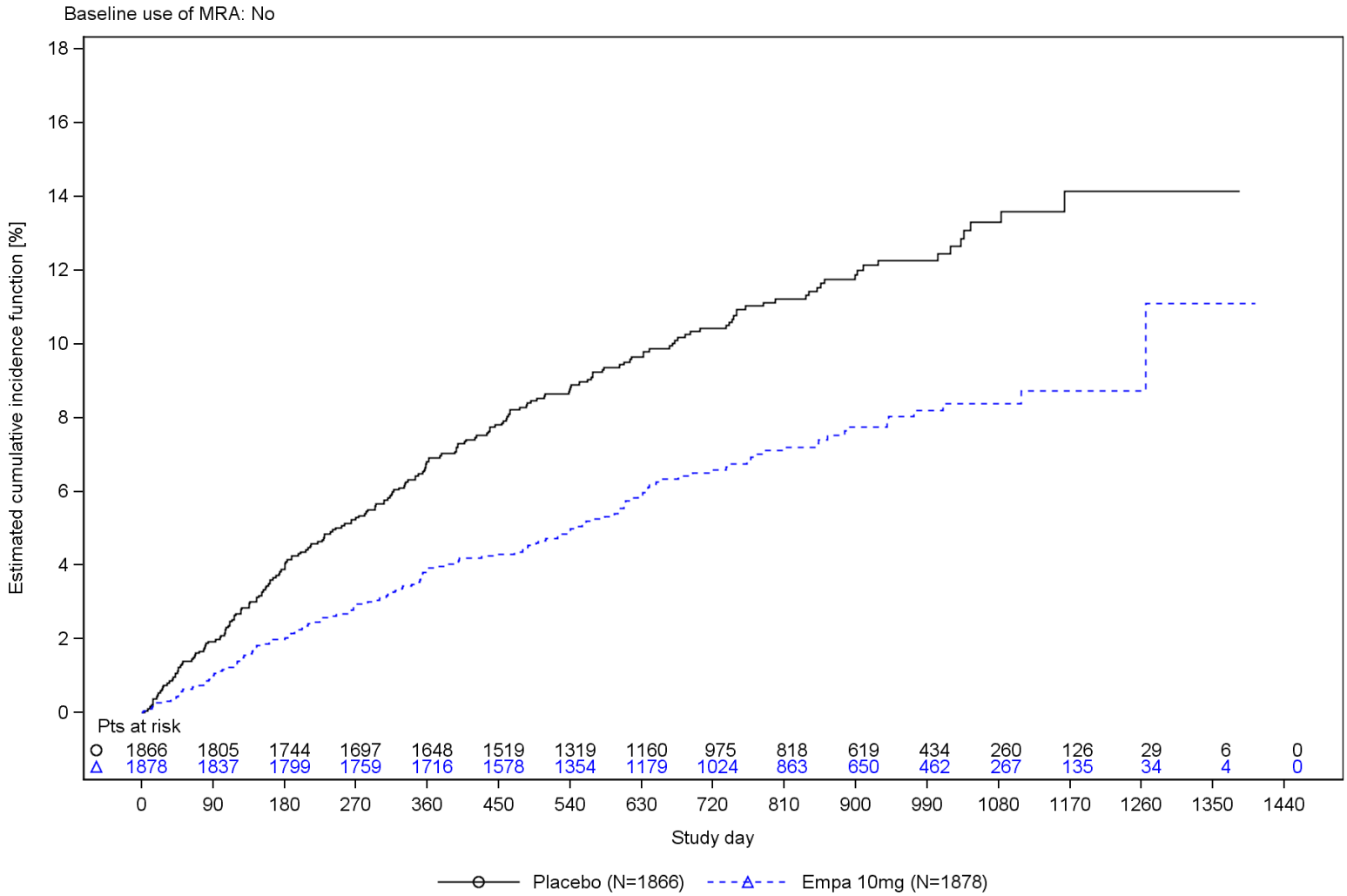

Figure R.1.1.1.6: 3 Time to first adjudicated HHF, estimated cumulative incidence function (considering all-cause mortality as a competing risk) by baseline use of MRA - RS
Analysis is based on study 1245.110.

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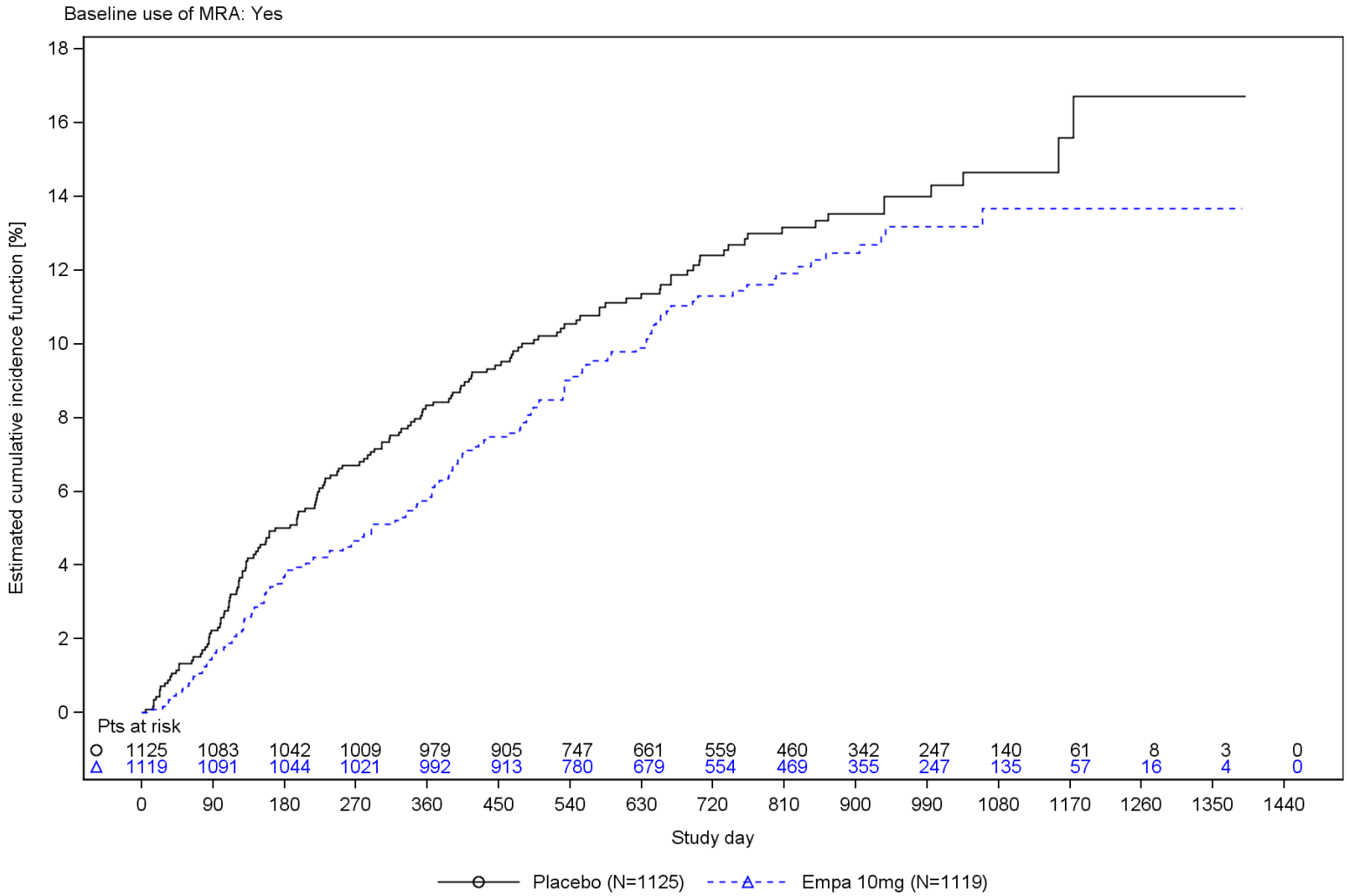

Figure R.1.1.1.6: 3 Time to first adjudicated HHF, estimated cumulative incidence function (considering all-cause mortality as a competing risk) by baseline use of MRA - RS
Analysis is based on study 1245.110.

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R.1.1.1.7 Adjudicated HHF (first and recurrent)

Table R.1.1.1.7: 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	2991	352	11.8	541	8.60	2997	259	8.6	407	6.46	0.73	(0.61,0.88)	0.0009	
Sex														0.7800
Male	1653	198	12.0	308	8.84	1659	151	9.1	253	7.25	0.75	(0.59,0.95)	0.0196	
Female	1338	154	11.5	233	8.29	1338	108	8.1	154	5.47	0.71	(0.53,0.94)	0.0171	
Age [years]														0.0832
<70	1084	103	9.5	159	6.86	1066	87	8.2	141	6.23	0.92	(0.67,1.26)	0.6073	
>=70	1907	249	13.1	382	9.61	1931	172	8.9	266	6.58	0.65	(0.52,0.82)	0.0002	
Region														0.0570
North America	359	65	18.1	88	11.29	360	50	13.9	90	11.47	1.13	(0.71,1.81)	0.6113	
Latin America	757	66	8.7	95	6.30	758	49	6.5	68	4.50	0.68	(0.45,1.02)	0.0613	
Europe	1343	138	10.3	209	7.25	1346	98	7.3	139	4.82	0.66	(0.50,0.88)	0.0048	
Asia	343	58	16.9	110	14.97	343	37	10.8	63	8.47	0.49	(0.30,0.80)	0.0044	
Other	189	25	13.2	39	10.07	190	25	13.2	47	12.43	1.28	(0.66,2.48)	0.4645	
OECD member														0.8177
No	847	101	11.9	167	9.75	868	79	9.1	128	7.37	0.75	(0.54,1.06)	0.1044	
Yes	2144	251	11.7	374	8.17	2129	180	8.5	279	6.11	0.72	(0.58,0.90)	0.0035	
Baseline NYHA														0.2899
II^^	2452	236	9.6	347	6.69	2435	161	6.6	235	4.54	0.67	(0.54,0.83)	0.0003	
III/IV	539	116	21.5	194	17.50	562	98	17.4	172	15.27	0.84	(0.59,1.19)	0.3229	
Baseline Diabetes Status														0.9697
Diabetic	1472	215	14.6	335	10.82	1466	155	10.6	250	8.19	0.73	(0.57,0.94)	0.0143	
Non-Diabetic	1519	137	9.0	206	6.44	1531	104	6.8	157	4.83	0.74	(0.56,0.97)	0.0301	

* 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, °:Trend test,
^Recurrent event rate, per 100 patient years at risk.

Analysis is based on study 1245.110.

^^ Patients with NYHA class I are counted in subgroup NYHA class II.
¹ Baseline SBP median: 132 [mmHg].
² Baseline NT-proBNP median for patients with history of atrial fibrillation or atrial flutter: 1354 [pg/mL].
² Baseline NT-proBNP median for patients without history of atrial fibrillation or atrial flutter: 614 [pg/mL].
³ Baseline uric acid tertile cut-offs for males are T1: 5.9 T2: 7.5 [mg/dL] [rounded].
³ Baseline uric acid tertile cut-offs for females are T1: 5.4 T2: 6.9 [mg/dL] [rounded].

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Table R.1.1.1.7: 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 Diabetes Status														0.6229°/ 0.5384
Diabetic	1472	215	14.6	335	10.82	1466	155	10.6	250	8.19	0.73	(0.57,0.94)	0.0145	
Pre-Diabetes	979	87	8.9	129	6.24	1001	76	7.6	110	5.20	0.83	(0.59,1.16)	0.2737	
Normal (no pre-diabetes)	540	50	9.3	77	6.83	530	28	5.3	47	4.14	0.59	(0.37,0.96)	0.0320	
Baseline BMI [kg/m²]														0.0749
<30	1642	195	11.9	312	9.19	1654	135	8.2	211	6.10	0.63	(0.49,0.81)	0.0003	
>=30	1349	157	11.6	229	7.90	1343	124	9.2	196	6.89	0.88	(0.67,1.15)	0.3504	
Baseline eGFR (CKD-EPI) [mL/min/1.73m²]														0.1369
>=60	1505	116	7.7	178	5.54	1493	92	6.2	150	4.71	0.88	(0.66,1.18)	0.3940	
<60	1484	236	15.9	363	11.81	1504	167	11.1	257	8.25	0.66	(0.52,0.85)	0.0010	
History of HHF (in the last 12 months)														0.6868
No	2321	194	8.4	271	5.58	2298	139	6.0	200	4.15	0.70	(0.56,0.88)	0.0027	
Yes	670	158	23.6	270	18.83	699	120	17.2	207	13.99	0.76	(0.56,1.04)	0.0816	
Baseline SBP (</>= median¹)														0.9094
< median	1474	181	12.3	290	9.45	1496	126	8.4	215	6.91	0.74	(0.57,0.95)	0.0204	
>= median	1517	171	11.3	251	7.78	1501	133	8.9	192	6.02	0.72	(0.55,0.94)	0.0164	
History of atrial fibrillation or atrial flutter														0.9424
No	1427	141	9.9	223	7.47	1417	98	6.9	164	5.51	0.72	(0.54,0.95)	0.0223	
Yes	1559	211	13.5	318	9.64	1576	161	10.2	243	7.32	0.73	(0.57,0.94)	0.0126	

* 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, °:Trend test,
^Recurrent event rate, per 100 patient years at risk.

Analysis is based on study 1245.110.

^^ Patients with NYHA class I are counted in subgroup NYHA class II.
¹ Baseline SBP median: 132 [mmHg].
² Baseline NT-proBNP median for patients with history of atrial fibrillation or atrial flutter: 1354 [pg/mL].
² Baseline NT-proBNP median for patients without history of atrial fibrillation or atrial flutter: 614 [pg/mL].
³ Baseline uric acid tertile cut-offs for males are T1: 5.9 T2: 7.5 [mg/dL] [rounded].
³ Baseline uric acid tertile cut-offs for females are T1: 5.4 T2: 6.9 [mg/dL] [rounded].

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Table R.1.1.1.7: 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 LVEF [%]														0.0602
< 50	988	126	12.8	209	10.08	995	77	7.7	122	5.81	0.57	(0.42,0.79)	0.0006	
>= 50	2003	226	11.3	332	7.87	2002	182	9.1	285	6.78	0.83	(0.66,1.04)	0.1132	
Baseline LVEF [%]														0.0077°/ 0.0228
<50	988	126	12.8	209	10.08	995	77	7.7	122	5.81	0.57	(0.42,0.79)	0.0006	
50 to <60	1030	122	11.8	182	8.35	1028	87	8.5	129	5.96	0.66	(0.48,0.91)	0.0122	
>=60	973	104	10.7	150	7.36	974	95	9.8	156	7.65	1.06	(0.76,1.46)	0.7445	
Baseline NT-proBNP [pg/mL] (</>=median² by atrial fibrillation/flutter status)														0.7560
< median	1508	109	7.2	152	4.66	1477	71	4.8	104	3.25	0.69	(0.51,0.94)	0.0176	
>= median	1476	242	16.4	388	12.85	1516	188	12.4	303	9.80	0.73	(0.58,0.93)	0.0091	
Baseline uric acid [mg/dL] (tertiles³)														0.6194°/ 0.7175
<T1	975	89	9.1	131	6.37	963	59	6.1	92	4.56	0.67	(0.47,0.95)	0.0259	
>=T1 and <T2	966	84	8.7	124	6.02	1032	68	6.6	99	4.56	0.82	(0.58,1.16)	0.2689	
>=T2	1018	174	17.1	281	13.26	970	129	13.3	213	10.36	0.75	(0.56,0.99)	0.0440	
Baseline use of MRA														0.0379
No	1866	208	11.1	308	7.79	1878	131	7.0	201	5.04	0.60	(0.47,0.77)	<0.0001	
Yes	1125	144	12.8	233	9.97	1119	128	11.4	206	8.89	0.90	(0.68,1.19)	0.4509	

* 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, °:Trend test,
^Recurrent event rate, per 100 patient years at risk.

Analysis is based on study 1245.110.

^^ Patients with NYHA class I are counted in subgroup NYHA class II.
¹ Baseline SBP median: 132 [mmHg].
² Baseline NT-proBNP median for patients with history of atrial fibrillation or atrial flutter: 1354 [pg/mL].
² Baseline NT-proBNP median for patients without history of atrial fibrillation or atrial flutter: 614 [pg/mL].
³ Baseline uric acid tertile cut-offs for males are T1: 5.9 T2: 7.5 [mg/dL] [rounded].
³ Baseline uric acid tertile cut-offs for females are T1: 5.4 T2: 6.9 [mg/dL] [rounded].

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Table R.1.1.1.7: 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 use of ACE-inhibitor, ARB or ARNi														0.8612
No	587	95	16.2	151	12.55	569	66	11.6	117	9.69	0.71	(0.48,1.04)	0.0777	
Yes	2404	257	10.7	390	7.66	2428	193	7.9	290	5.69	0.74	(0.60,0.91)	0.0045	

* 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, °:Trend test,
^Recurrent event rate, per 100 patient years at risk.

Analysis is based on study 1245.110.

^^ Patients with NYHA class I are counted in subgroup NYHA class II.
¹ Baseline SBP median: 132 [mmHg].
² Baseline NT-proBNP median for patients with history of atrial fibrillation or atrial flutter: 1354 [pg/mL].
² Baseline NT-proBNP median for patients without history of atrial fibrillation or atrial flutter: 614 [pg/mL].
³ Baseline uric acid tertile cut-offs for males are T1: 5.9 T2: 7.5 [mg/dL] [rounded].
³ Baseline uric acid tertile cut-offs for females are T1: 5.4 T2: 6.9 [mg/dL] [rounded].

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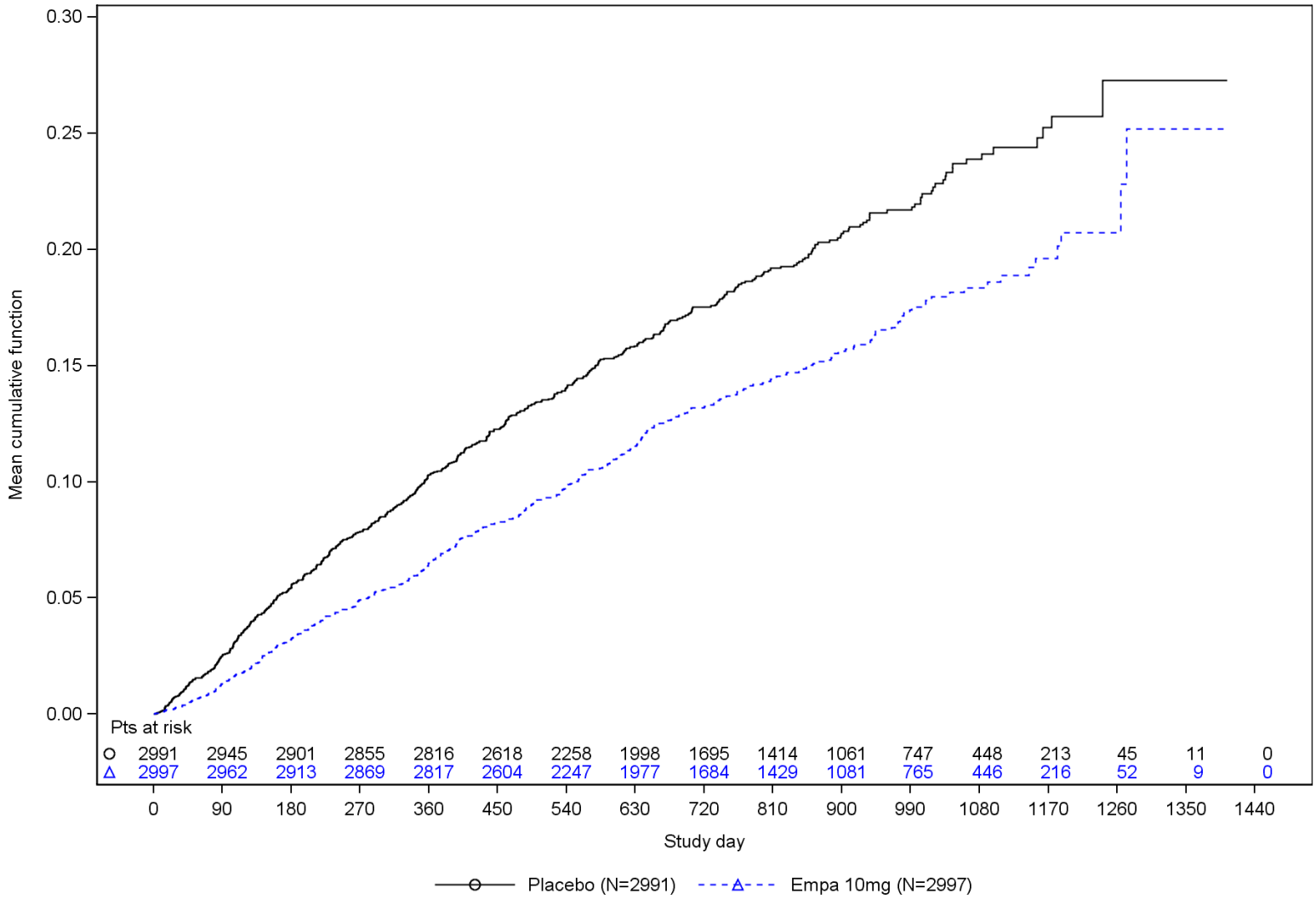

Figure R.1.1.1.7: 1 Occurrence of adjudicated HHF (first and recurrent), mean cumulative function - RS
Analysis is based on study 1245.110.

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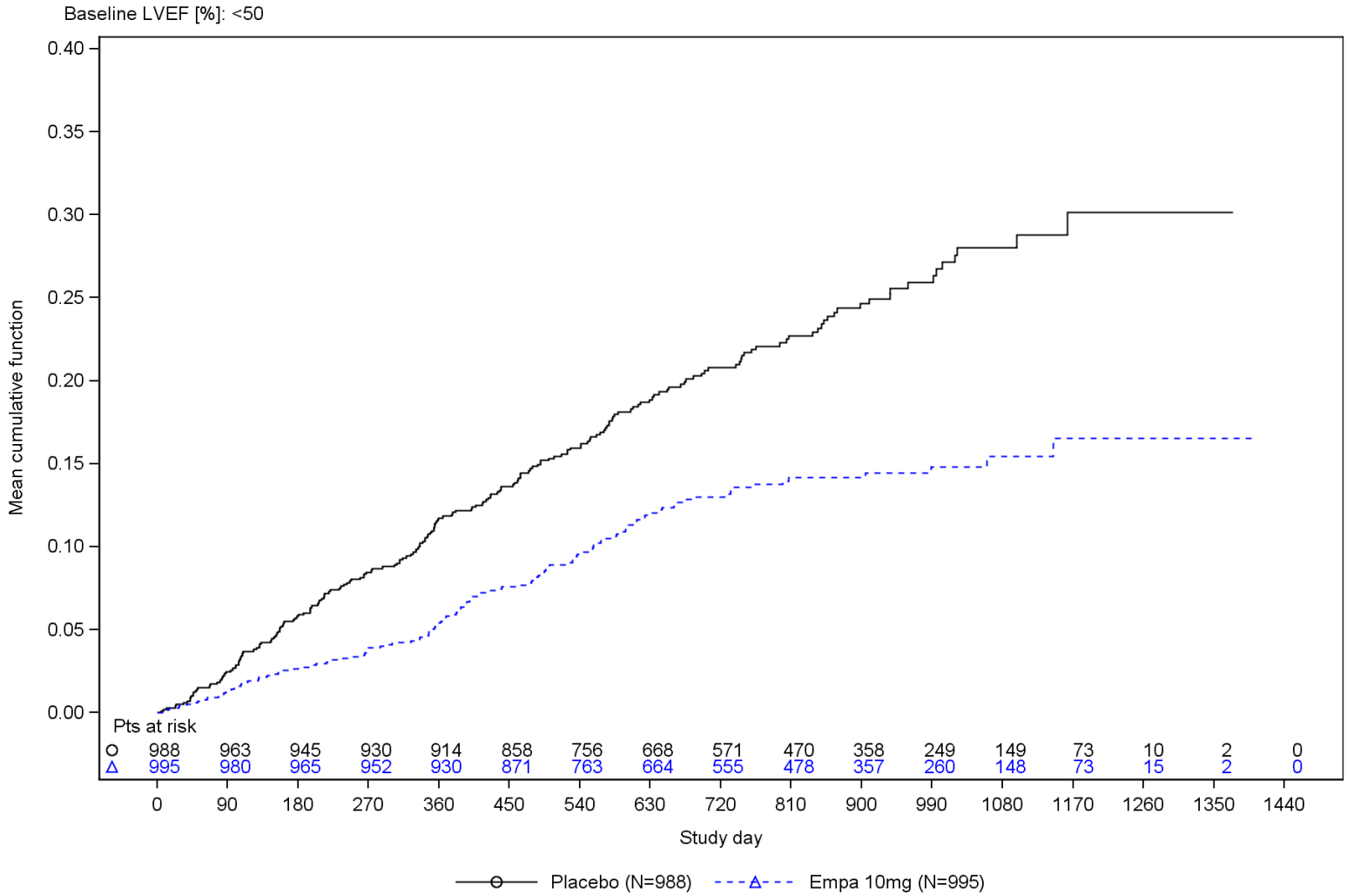

Figure R.1.1.1.7: 2 Occurrence of adjudicated HHF (first and recurrent), mean cumulative function by baseline LVEF - RS
Analysis is based on study 1245.110.

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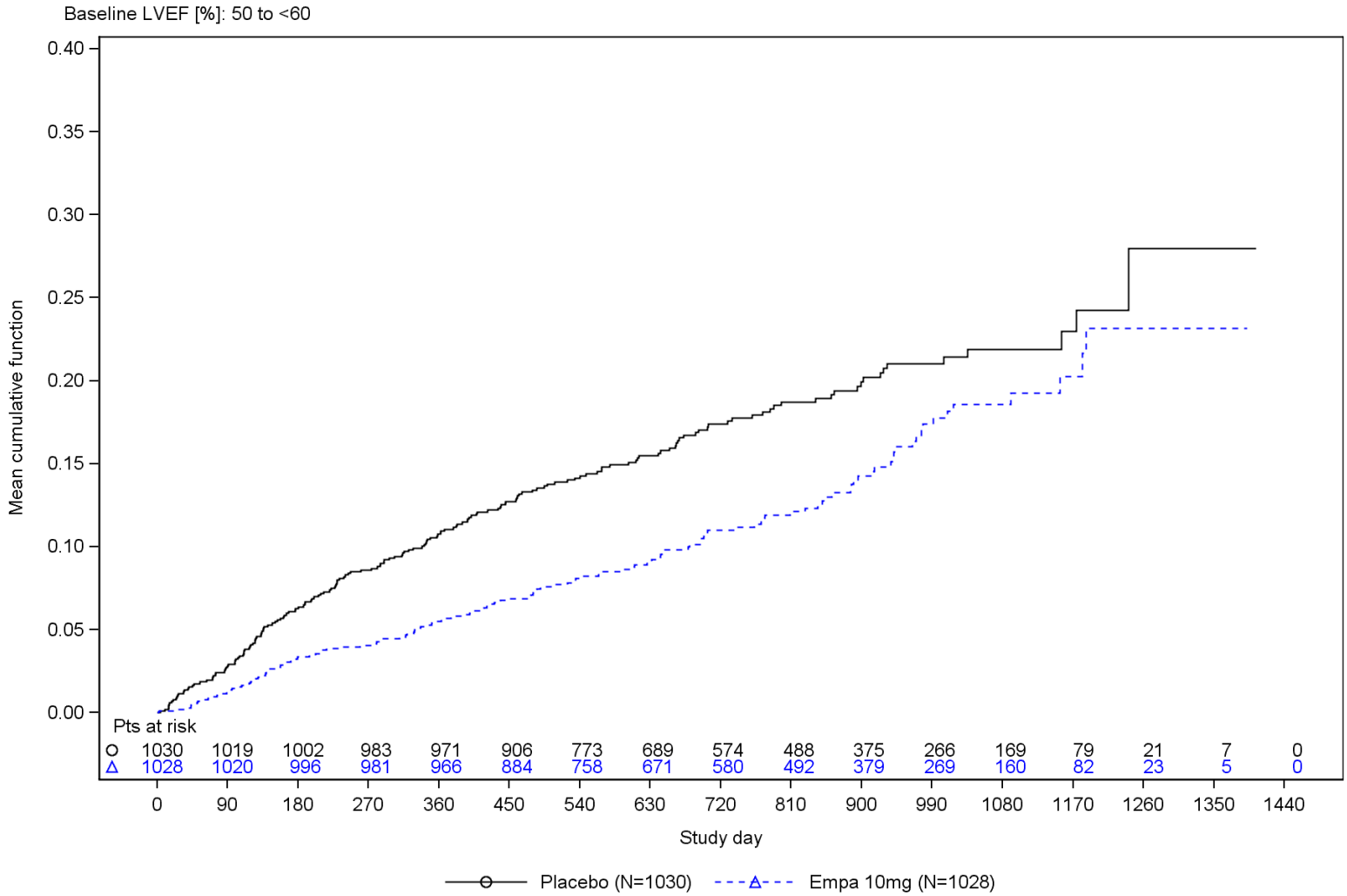

Figure R.1.1.1.7: 2 Occurrence of adjudicated HHF (first and recurrent), mean cumulative function by baseline LVEF - RS
Analysis is based on study 1245.110.

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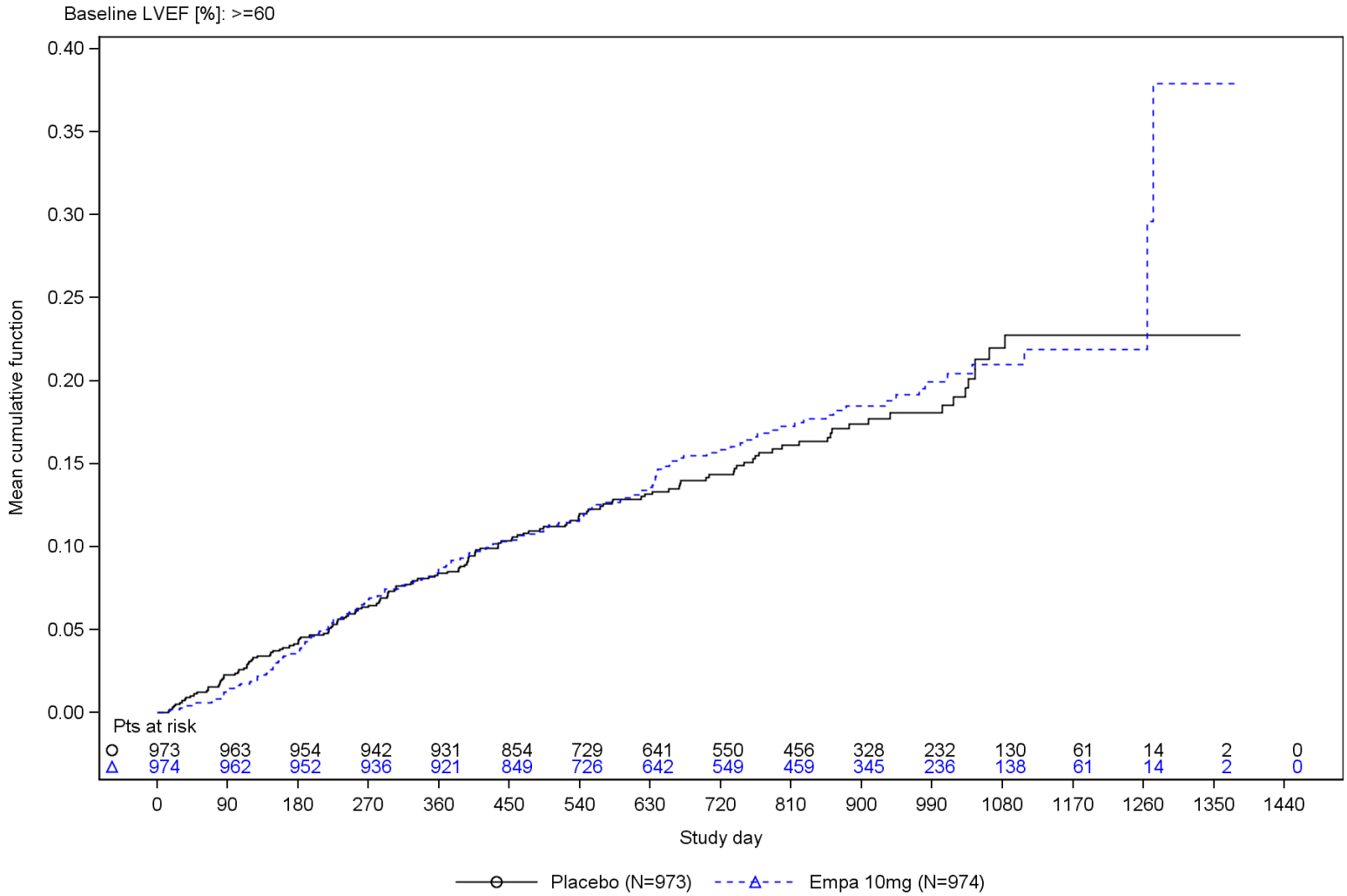

Figure R.1.1.1.7: 2 Occurrence of adjudicated HHF (first and recurrent), mean cumulative function
by baseline LVEF - RS
Analysis is based on study 1245.110.

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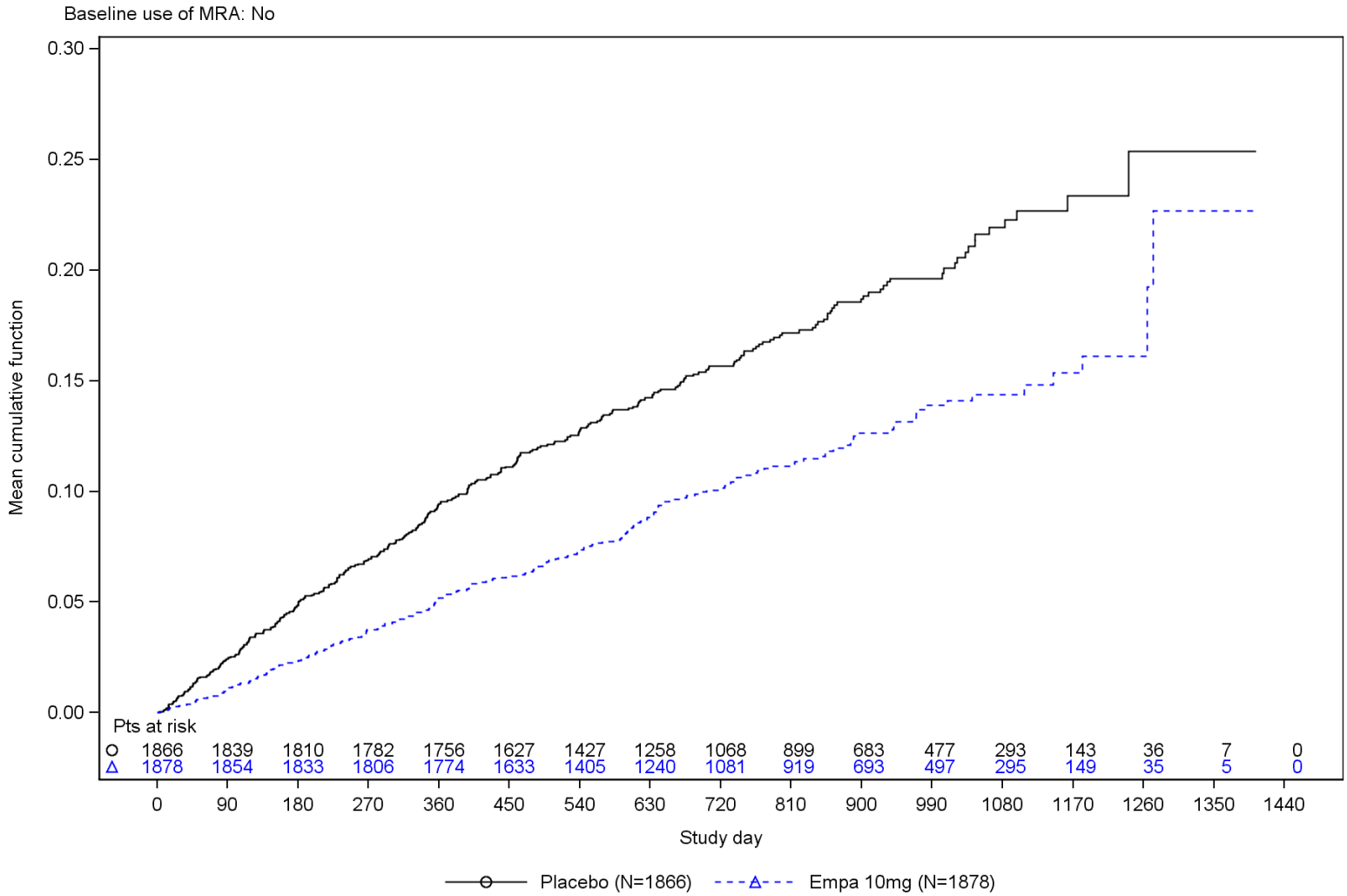

Figure R.1.1.1.7: 3 Occurrence of adjudicated HHF (first and recurrent), mean cumulative function by baseline use of MRA - RS
Analysis is based on study 1245.110.

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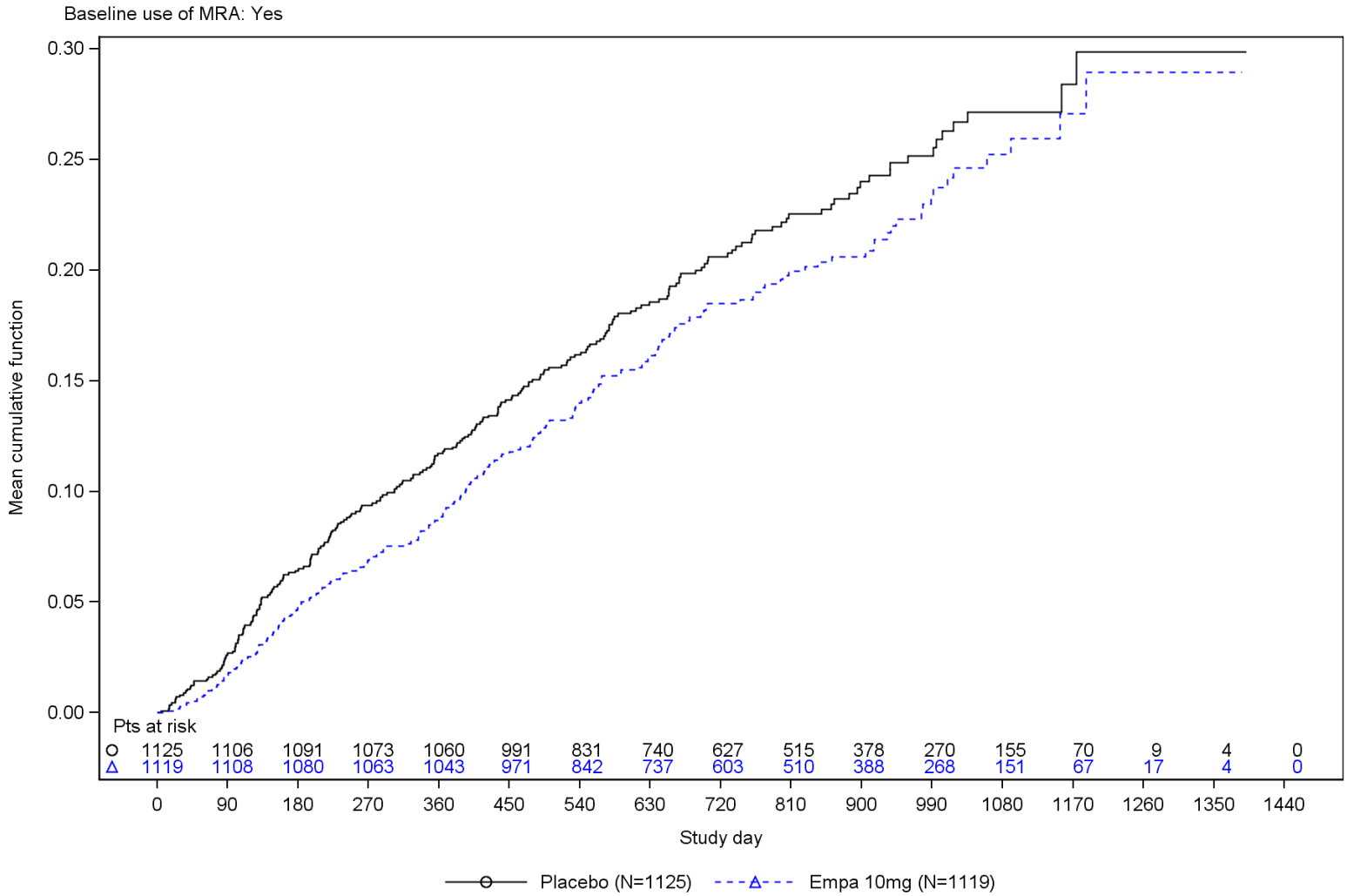

Figure R.1.1.1.7: 3 Occurrence of adjudicated HHF (first and recurrent), mean cumulative function by baseline use of MRA - RS
Analysis is based on study 1245.110.

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R.1.1.1.8 Time to adjudicated HHF requiring ICU/CCU

Table R.1.1.1.8: 1 Cox regression for time to first adjudicated HHF requiring ICU/CCU 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	2991	94	3.1	1.52	2997	68	2.3	1.09	0.71	(0.52,0.97)	0.0321	
Sex												0.4689
Male	1653	58	3.5	1.70	1659	39	2.4	1.13	0.65	(0.43,0.97)	0.0353	
Female	1338	36	2.7	1.30	1338	29	2.2	1.04	0.82	(0.50,1.33)	0.4202	
Age [years]												0.2491
<70	1084	31	2.9	1.36	1066	28	2.6	1.25	0.91	(0.54,1.51)	0.7091	
>=70	1907	63	3.3	1.61	1931	40	2.1	1.00	0.62	(0.42,0.92)	0.0182	
Region												0.3296
North America	359	16	4.5	2.12	360	11	3.1	1.42	0.68	(0.31,1.45)	0.3157	
Latin America	757	26	3.4	1.76	758	19	2.5	1.27	0.73	(0.41,1.33)	0.3061	
Europe	1343	33	2.5	1.16	1346	20	1.5	0.70	0.59	(0.34,1.03)	0.0652	
Asia	343	15	4.4	2.08	343	9	2.6	1.23	0.56	(0.24,1.28)	0.1665	
Other	189	4	2.1	1.04	190	9	4.7	2.42	2.31	(0.71,7.51)	0.1636	
OECD member												0.4190
No	847	33	3.9	1.97	868	29	3.3	1.70	0.83	(0.50,1.37)	0.4641	
Yes	2144	61	2.8	1.35	2129	39	1.8	0.86	0.64	(0.43,0.95)	0.0280	
Baseline NYHA												0.5447
II^^	2452	70	2.9	1.37	2435	46	1.9	0.90	0.66	(0.46,0.96)	0.0289	
III/IV	539	24	4.5	2.23	562	22	3.9	1.99	0.82	(0.46,1.46)	0.4952	
Baseline Diabetes Status												0.4280
Diabetic	1472	53	3.6	1.75	1466	43	2.9	1.42	0.79	(0.53,1.18)	0.2491	
Non-Diabetic	1519	41	2.7	1.30	1531	25	1.6	0.77	0.61	(0.37,1.00)	0.0508	

* 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, °:Trend test, ^Incidence rate, events per 100 patient years at risk.

Analysis is based on study 1245.110.

^^ Patients with NYHA class I are counted in subgroup NYHA class II.
[1] Baseline SBP median: 132 [mmHg].
[2] Baseline NT-proBNP median for patients with history of atrial fibrillation or atrial flutter: 1354 [pg/mL].
[2] Baseline NT-proBNP median for patients without history of atrial fibrillation or atrial flutter: 614 [pg/mL].
[3] Baseline uric acid tertile cut-offs for males are T1: 5.9 T2: 7.5 [mg/dL] [rounded].
[3] Baseline uric acid tertile cut-offs for females are T1: 5.4 T2: 6.9 [mg/dL] [rounded].

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Table R.1.1.1.8: 1 Cox regression for time to first adjudicated HHF requiring ICU/CCU 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 Diabetes Status												0.2271°/ 0.3790
Diabetic	1472	53	3.6	1.75	1466	43	2.9	1.42	0.79	(0.53,1.18)	0.2492	
Pre-Diabetes	979	27	2.8	1.32	1001	20	2.0	0.95	0.73	(0.41,1.31)	0.2953	
Normal (no pre-diabetes)	540	14	2.6	1.26	530	5	0.9	0.44	0.36	(0.13,1.01)	0.0513	
Baseline BMI [kg/m²]												0.9390
<30	1642	51	3.1	1.53	1654	36	2.2	1.05	0.70	(0.46,1.08)	0.1054	
>=30	1349	43	3.2	1.51	1343	32	2.4	1.14	0.72	(0.46,1.14)	0.1602	
Baseline eGFR (CKD-EPI) [mL/min/1.73m²]												0.9880
>=60	1505	30	2.0	0.94	1493	21	1.4	0.66	0.71	(0.41,1.24)	0.2294	
<60	1484	64	4.3	2.13	1504	47	3.1	1.52	0.71	(0.49,1.04)	0.0796	
History of HHF (in the last 12 months)												0.5251
No	2321	52	2.2	1.08	2298	33	1.4	0.69	0.64	(0.41,0.98)	0.0422	
Yes	670	42	6.3	3.04	699	35	5.0	2.43	0.78	(0.50,1.22)	0.2772	
Baseline SBP (</>= median¹)												0.8756
< median	1474	52	3.5	1.73	1496	37	2.5	1.20	0.69	(0.46,1.06)	0.0902	
>= median	1517	42	2.8	1.32	1501	31	2.1	0.98	0.73	(0.46,1.16)	0.1845	
History of atrial fibrillation or atrial flutter												0.9845
No	1427	40	2.8	1.36	1417	28	2.0	0.95	0.71	(0.44,1.15)	0.1627	
Yes	1559	54	3.5	1.67	1576	40	2.5	1.22	0.70	(0.47,1.06)	0.0933	

* 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, °:Trend test, ^Incidence rate, events per 100 patient years at risk.

Analysis is based on study 1245.110.

^^ Patients with NYHA class I are counted in subgroup NYHA class II.
¹ Baseline SBP median: 132 [mmHg].
² Baseline NT-proBNP median for patients with history of atrial fibrillation or atrial flutter: 1354 [pg/mL].
² Baseline NT-proBNP median for patients without history of atrial fibrillation or atrial flutter: 614 [pg/mL].
³ Baseline uric acid tertile cut-offs for males are T1: 5.9 T2: 7.5 [mg/dL] [rounded].
³ Baseline uric acid tertile cut-offs for females are T1: 5.4 T2: 6.9 [mg/dL] [rounded].

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Table R.1.1.1.8: 1 Cox regression for time to first adjudicated HHF requiring ICU/CCU 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 LVEF [%]												0.2894
< 50	988	38	3.8	1.87	995	22	2.2	1.06	0.57	(0.34,0.96)	0.0341	
>= 50	2003	56	2.8	1.35	2002	46	2.3	1.10	0.81	(0.55,1.19)	0.2820	
Baseline LVEF [%]												0.3623°/ 0.5688
<50	988	38	3.8	1.87	995	22	2.2	1.06	0.57	(0.34,0.96)	0.0341	
50 to <60	1030	28	2.7	1.30	1028	23	2.2	1.07	0.82	(0.47,1.43)	0.4827	
>=60	973	28	2.9	1.39	974	23	2.4	1.14	0.79	(0.46,1.38)	0.4124	
Baseline NT-proBNP [pg/mL] (</>=median[2] by atrial fibrillation/flutter status)												0.0383
< median	1508	29	1.9	0.90	1477	10	0.7	0.31	0.36	(0.17,0.73)	0.0051	
>= median	1476	65	4.4	2.21	1516	58	3.8	1.91	0.84	(0.59,1.19)	0.3215	
Baseline uric acid [mg/dL] (tertiles[3])												0.1475°/ 0.4012
<T1	975	27	2.8	1.33	963	15	1.6	0.75	0.55	(0.29,1.04)	0.0663	
>=T1 and <T2	966	19	2.0	0.93	1032	13	1.3	0.60	0.65	(0.32,1.32)	0.2384	
>=T2	1018	44	4.3	2.13	970	40	4.1	1.97	0.91	(0.59,1.40)	0.6699	
Baseline use of MRA												0.0004
No	1866	62	3.3	1.59	1878	26	1.4	0.66	0.41	(0.26,0.64)	0.0001	
Yes	1125	32	2.8	1.39	1119	42	3.8	1.84	1.32	(0.83,2.09)	0.2425	
Baseline use of ACE-inhibitor, ARB or ARNi												0.8011
No	587	25	4.3	2.13	569	19	3.3	1.59	0.76	(0.42,1.38)	0.3686	
Yes	2404	69	2.9	1.38	2428	49	2.0	0.97	0.69	(0.48,1.00)	0.0515	

* 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, °:Trend test, ^Incidence rate, events per 100 patient years at risk.

Analysis is based on study 1245.110.

^^ Patients with NYHA class I are counted in subgroup NYHA class II.
[1] Baseline SBP median: 132 [mmHg].
[2] Baseline NT-proBNP median for patients with history of atrial fibrillation or atrial flutter: 1354 [pg/mL].
[2] Baseline NT-proBNP median for patients without history of atrial fibrillation or atrial flutter: 614 [pg/mL].
[3] Baseline uric acid tertile cut-offs for males are T1: 5.9 T2: 7.5 [mg/dL] [rounded].
[3] Baseline uric acid tertile cut-offs for females are T1: 5.4 T2: 6.9 [mg/dL] [rounded].

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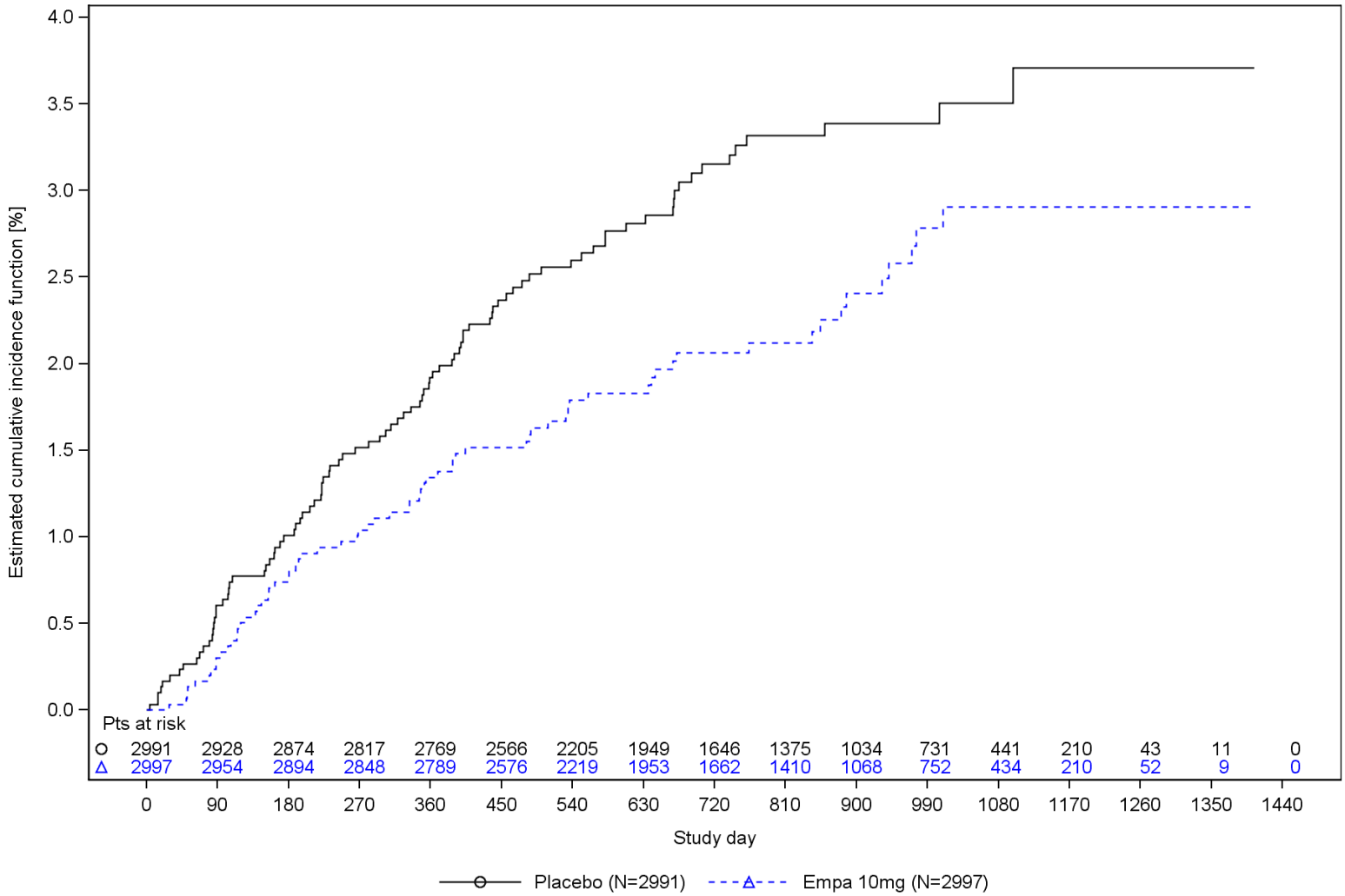

Figure R.1.1.1.8: 1 Time to the first adjudicated HHF requiring ICU/CCU, estimated cumulative incidence function (considering all-cause mortality as a competing risk) - RS
Analysis is based on study 1245.110.

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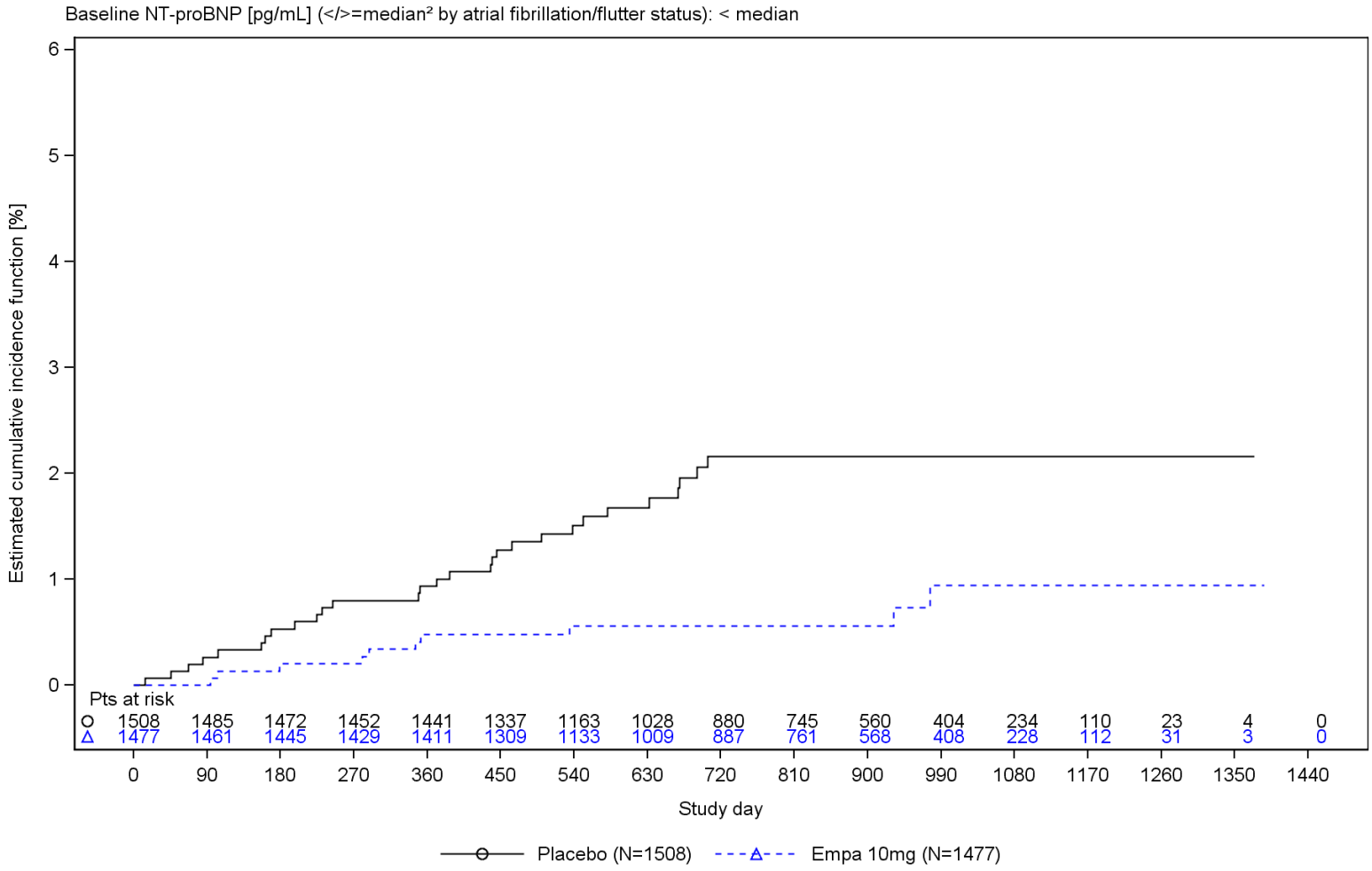

Figure R.1.1.1.8: 2 Time to the first adjudicated HHF requiring ICU/CCU, estimated cumulative incidence function (considering all-cause mortality as a competing risk) by NT-proBNP - RS

Analysis is based on study 1245.110.

² Baseline NT-proBNP median for patients with history of atrial fibrillation or atrial flutter: 1354 [pg/mL].

² Baseline NT-proBNP median for patients without history of atrial fibrillation or atrial flutter: 614 [pg/mL].

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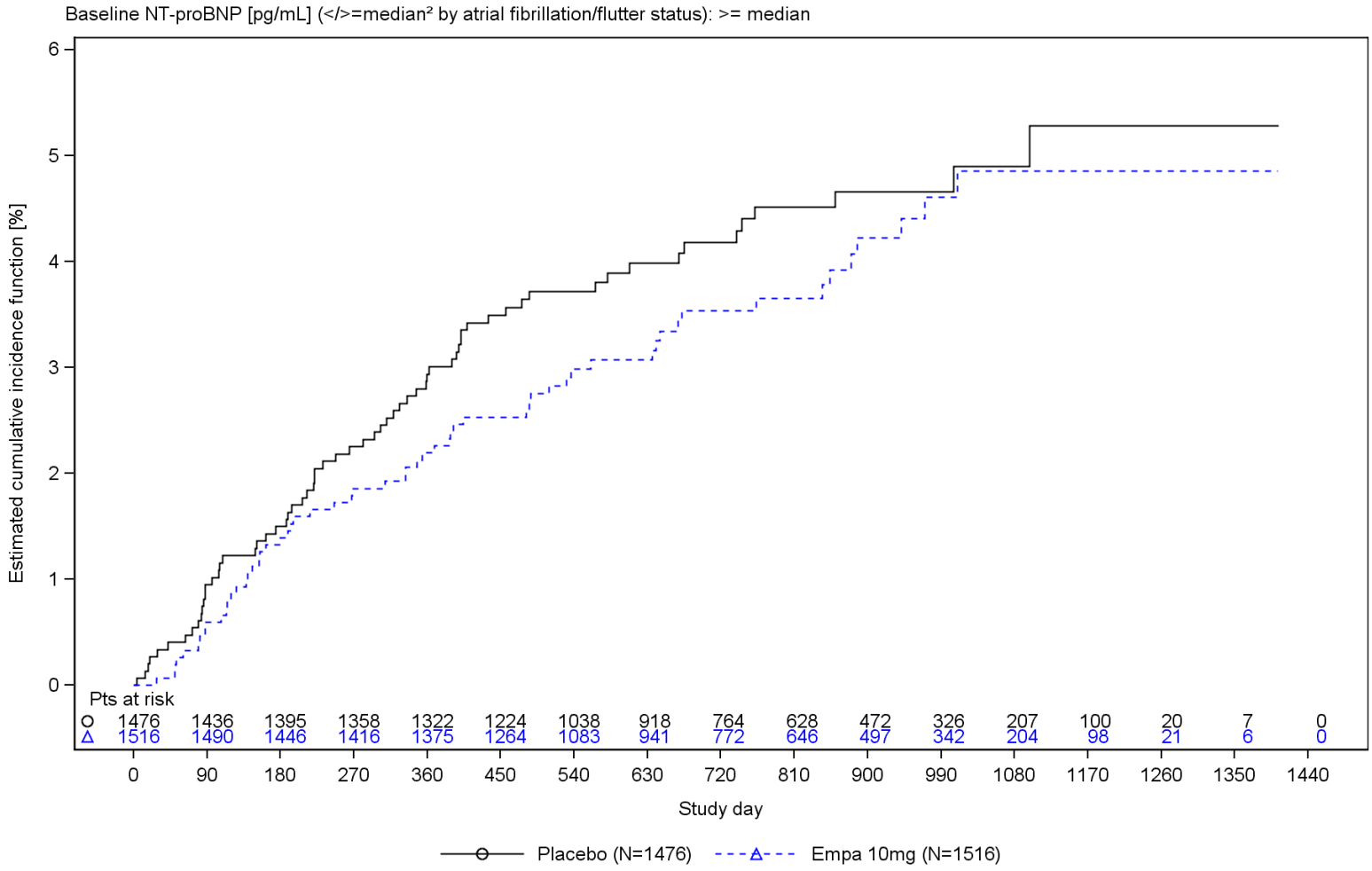

Figure R.1.1.1.8: 2 Time to the first adjudicated HHF requiring ICU/CCU, estimated cumulative incidence function (considering all-cause mortality as a competing risk) by NT-proBNP - RS

Analysis is based on study 1245.110.

² Baseline NT-proBNP median for patients with history of atrial fibrillation or atrial flutter: 1354 [pg/mL].

² Baseline NT-proBNP median for patients without history of atrial fibrillation or atrial flutter: 614 [pg/mL].

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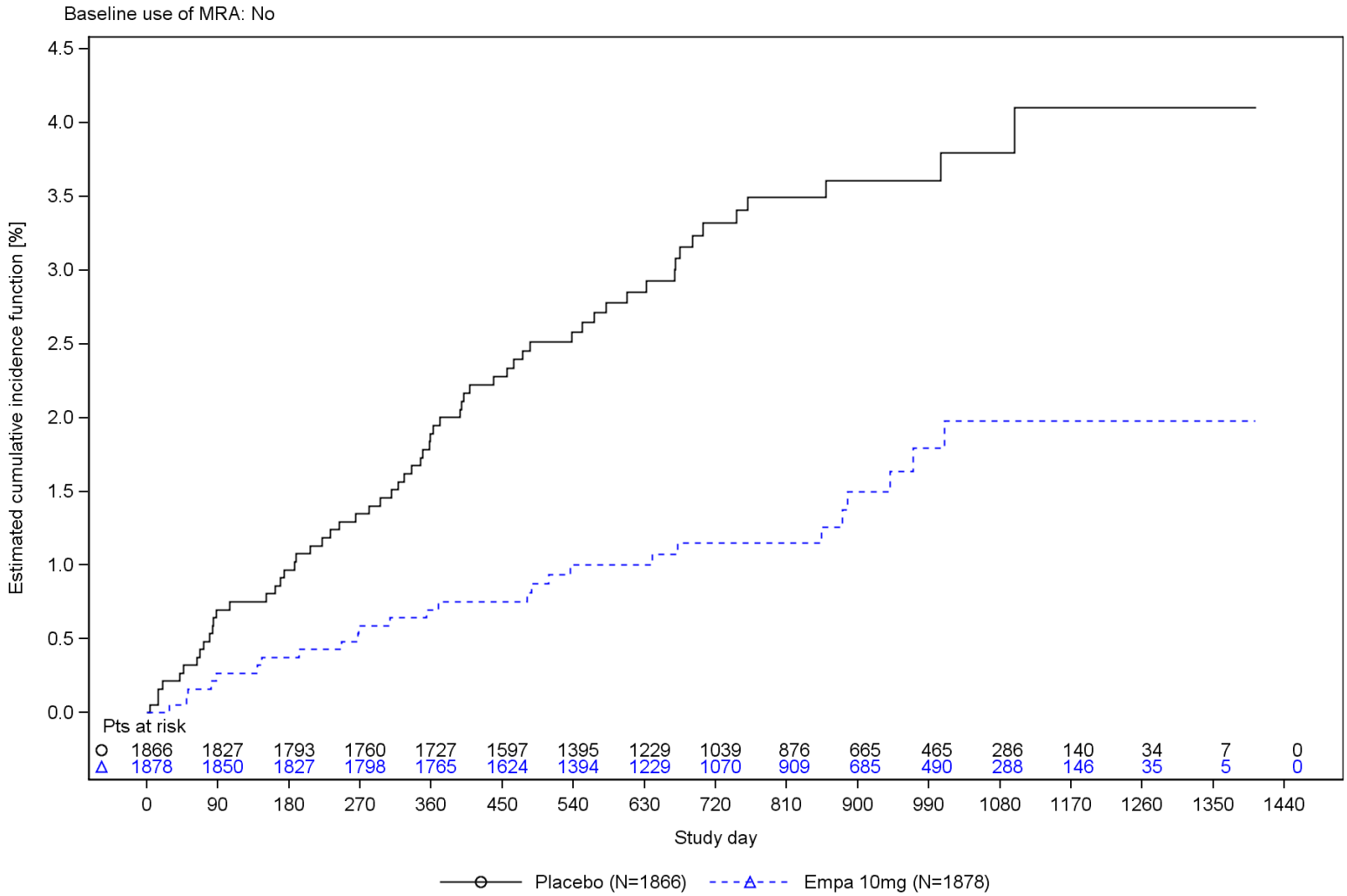

Figure R.1.1.1.8: 3 Time to the first adjudicated HHF requiring ICU/CCU, estimated cumulative incidence function (considering all-cause mortality as a competing risk) by baseline use of MRA - RS
Analysis is based on study 1245.110.

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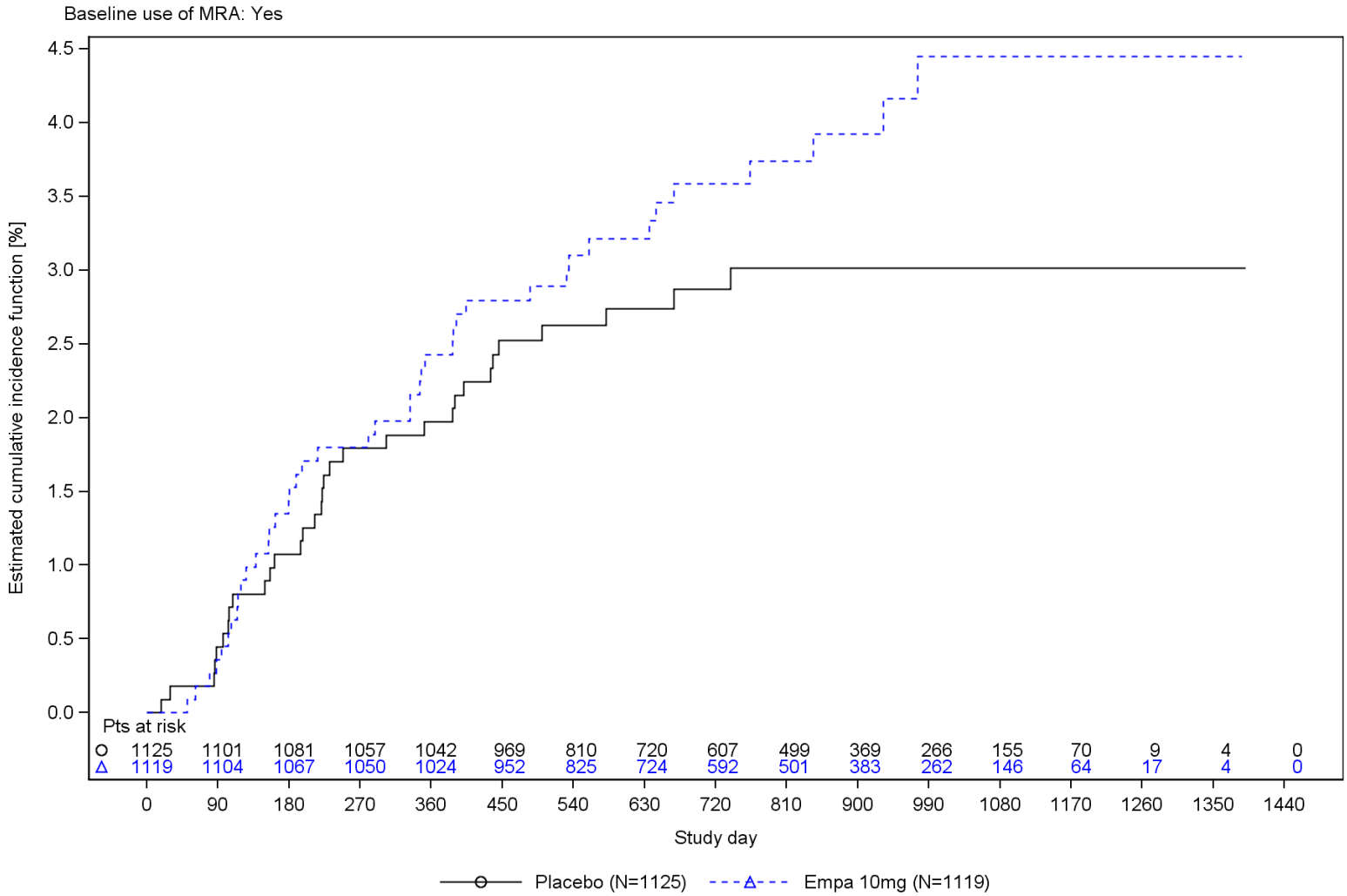

Figure R.1.1.1.8: 3 Time to the first adjudicated HHF requiring ICU/CCU, estimated cumulative incidence function (considering all-cause mortality as a competing risk) by baseline use of MRA - RS
Analysis is based on study 1245.110.

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R.1.1.1.9 Time to adjudicated HHF or adjudicated CV death

Table R.1.1.1.9: 1 Cox regression for time to first adjudicated HHF 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	2991	511	17.1	8.67	2997	415	13.8	6.86	0.79	(0.69,0.90)	0.0003	
Sex												0.5360
Male	1653	297	18.0	9.15	1659	253	15.3	7.59	0.81	(0.69,0.96)	0.0162	
Female	1338	214	16.0	8.09	1338	162	12.1	5.97	0.75	(0.61,0.92)	0.0055	
Age [years]												0.2548
<70	1084	152	14.0	6.93	1066	134	12.6	6.17	0.88	(0.70,1.11)	0.2736	
>=70	1907	359	18.8	9.71	1931	281	14.6	7.25	0.75	(0.64,0.87)	0.0002	
Region												0.3713
North America	359	83	23.1	11.92	360	64	17.8	8.73	0.72	(0.52,1.00)	0.0499	
Latin America	757	120	15.9	8.33	758	105	13.9	7.14	0.87	(0.67,1.13)	0.2920	
Europe	1343	202	15.0	7.41	1346	165	12.3	5.92	0.80	(0.65,0.98)	0.0289	
Asia	343	69	20.1	10.35	343	45	13.1	6.43	0.59	(0.41,0.86)	0.0061	
Other	189	37	19.6	10.22	190	36	18.9	10.13	1.02	(0.64,1.61)	0.9356	
OECD member												0.1737
No	847	153	18.1	9.57	868	145	16.7	8.79	0.89	(0.71,1.12)	0.3344	
Yes	2144	358	16.7	8.34	2129	270	12.7	6.14	0.74	(0.63,0.86)	0.0002	
Baseline NYHA												0.3081
II^^	2452	361	14.7	7.35	2435	275	11.3	5.48	0.75	(0.64,0.87)	0.0002	
III/IV	539	150	27.8	15.36	562	140	24.9	13.66	0.86	(0.68,1.09)	0.2064	
Baseline Diabetes Status												0.9224
Diabetic	1472	291	19.8	10.25	1466	239	16.3	8.30	0.79	(0.67,0.94)	0.0074	
Non-Diabetic	1519	220	14.5	7.21	1531	176	11.5	5.56	0.78	(0.64,0.95)	0.0146	

* 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, °:Trend test, ^Incidence rate, events per 100 patient years at risk.

Analysis is based on study 1245.110.

^^ Patients with NYHA class I are counted in subgroup NYHA class II.
¹ Baseline SBP median: 132 [mmHg].
² Baseline NT-proBNP median for patients with history of atrial fibrillation or atrial flutter: 1354 [pg/mL].
² Baseline NT-proBNP median for patients without history of atrial fibrillation or atrial flutter: 614 [pg/mL].
³ Baseline uric acid tertile cut-offs for males are T1: 5.9 T2: 7.5 [mg/dL] [rounded].
³ Baseline uric acid tertile cut-offs for females are T1: 5.4 T2: 6.9 [mg/dL] [rounded].

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Table R.1.1.1.9: 1 Cox regression for time to first adjudicated HHF 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 Diabetes Status												0.3745°/ 0.1891
Diabetic	1472	291	19.8	10.25	1466	239	16.3	8.30	0.79	(0.67,0.94)	0.0074	
Pre-Diabetes	979	138	14.1	7.00	1001	126	12.6	6.14	0.89	(0.70,1.13)	0.3422	
Normal (no pre-diabetes)	540	82	15.2	7.59	530	50	9.4	4.49	0.60	(0.42,0.85)	0.0042	
Baseline BMI [kg/m²]												0.3208
<30	1642	292	17.8	9.17	1654	223	13.5	6.70	0.74	(0.62,0.88)	0.0008	
>=30	1349	219	16.2	8.09	1343	192	14.3	7.07	0.85	(0.70,1.03)	0.0929	
Baseline eGFR (CKD-EPI) [mL/min/1.73m²]												0.7673
>=60	1505	189	12.6	6.12	1493	152	10.2	4.92	0.81	(0.65,1.00)	0.0504	
<60	1484	321	21.6	11.47	1504	263	17.5	8.90	0.78	(0.66,0.91)	0.0023	
History of HHF (in the last 12 months)												0.4441
No	2321	319	13.7	6.85	2298	258	11.2	5.49	0.81	(0.68,0.95)	0.0099	
Yes	670	192	28.7	15.52	699	157	22.5	11.64	0.73	(0.59,0.90)	0.0029	
Baseline SBP (</>= median¹)												0.5841
< median	1474	249	16.9	8.71	1496	200	13.4	6.68	0.76	(0.63,0.91)	0.0037	
>= median	1517	262	17.3	8.64	1501	215	14.3	7.04	0.82	(0.68,0.98)	0.0269	
History of atrial fibrillation or atrial flutter												0.9588
No	1427	219	15.3	7.74	1417	170	12.0	5.91	0.78	(0.64,0.95)	0.0143	
Yes	1559	292	18.7	9.57	1576	244	15.5	7.72	0.78	(0.66,0.93)	0.0050	

* 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, °:Trend test, ^Incidence rate, events per 100 patient years at risk.

Analysis is based on study 1245.110.

^^ Patients with NYHA class I are counted in subgroup NYHA class II.
¹ Baseline SBP median: 132 [mmHg].
² Baseline NT-proBNP median for patients with history of atrial fibrillation or atrial flutter: 1354 [pg/mL].
² Baseline NT-proBNP median for patients without history of atrial fibrillation or atrial flutter: 614 [pg/mL].
³ Baseline uric acid tertile cut-offs for males are T1: 5.9 T2: 7.5 [mg/dL] [rounded].
³ Baseline uric acid tertile cut-offs for females are T1: 5.4 T2: 6.9 [mg/dL] [rounded].

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Table R.1.1.1.9: 1 Cox regression for time to first adjudicated HHF or 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 LVEF [%]												0.2681
< 50	988	193	19.5	9.97	995	145	14.6	7.17	0.71	(0.57,0.88)	0.0021	
>= 50	2003	318	15.9	8.04	2002	270	13.5	6.71	0.83	(0.71,0.98)	0.0244	
Baseline LVEF [%]												0.2098°/ 0.4610
<50	988	193	19.5	9.97	995	145	14.6	7.17	0.71	(0.57,0.88)	0.0021	
50 to <60	1030	173	16.8	8.48	1028	138	13.4	6.65	0.80	(0.64,0.99)	0.0449	
>=60	973	145	14.9	7.57	974	132	13.6	6.77	0.87	(0.69,1.10)	0.2553	
Baseline NT-proBNP [pg/mL] (</>=median² by atrial fibrillation/flutter status)												0.8887
< median	1508	168	11.1	5.37	1477	126	8.5	4.04	0.76	(0.61,0.96)	0.0227	
>= median	1476	341	23.1	12.40	1516	288	19.0	9.88	0.78	(0.67,0.91)	0.0019	
Baseline uric acid [mg/dL] (tertiles³)												0.2367°/ 0.1439
<T1	975	147	15.1	7.53	963	96	10.0	4.91	0.65	(0.50,0.84)	0.0009	
>=T1 and <T2	966	132	13.7	6.69	1032	130	12.6	6.16	0.92	(0.72,1.17)	0.4905	
>=T2	1018	226	22.2	11.82	970	184	19.0	9.57	0.81	(0.67,0.98)	0.0326	
Baseline use of MRA												0.2169
No	1866	306	16.4	8.23	1878	233	12.4	6.05	0.73	(0.62,0.87)	0.0004	
Yes	1125	205	18.2	9.44	1119	182	16.3	8.29	0.87	(0.71,1.06)	0.1606	
Baseline use of ACE-inhibitor, ARB or ARNi												0.6939
No	587	121	20.6	10.91	569	90	15.8	7.93	0.75	(0.57,0.99)	0.0399	
Yes	2404	390	16.2	8.15	2428	325	13.4	6.62	0.80	(0.69,0.93)	0.0029	

* 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, °:Trend test, ^Incidence rate, events per 100 patient years at risk.

Analysis is based on study 1245.110.

^^ Patients with NYHA class I are counted in subgroup NYHA class II.
¹ Baseline SBP median: 132 [mmHg].
² Baseline NT-proBNP median for patients with history of atrial fibrillation or atrial flutter: 1354 [pg/mL].
² Baseline NT-proBNP median for patients without history of atrial fibrillation or atrial flutter: 614 [pg/mL].
³ Baseline uric acid tertile cut-offs for males are T1: 5.9 T2: 7.5 [mg/dL] [rounded].
³ Baseline uric acid tertile cut-offs for females are T1: 5.4 T2: 6.9 [mg/dL] [rounded].

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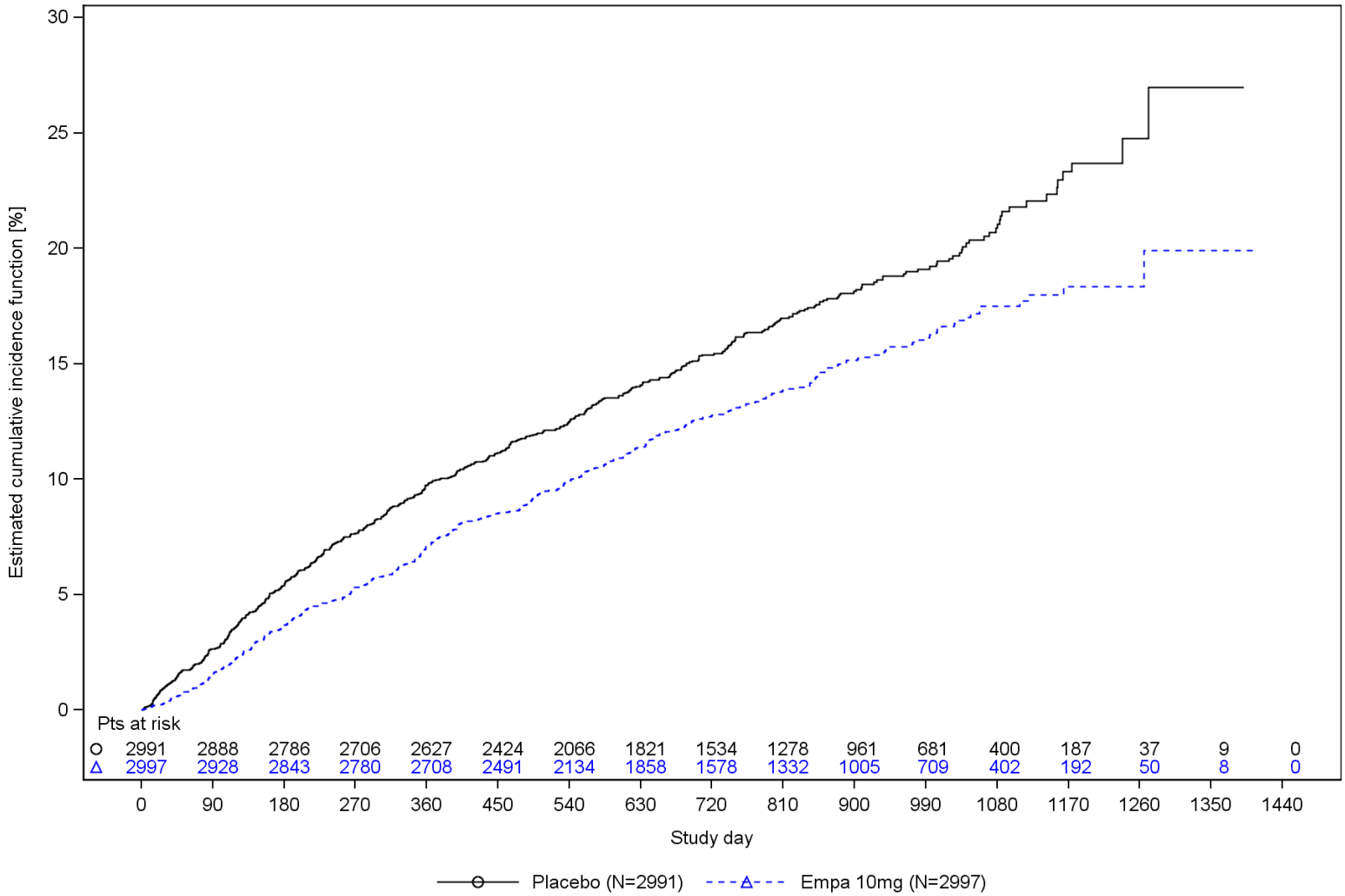

Figure R.1.1.1.9: 1 Time to the first adjudicated HHF or adjudicated CV death (considering non-CV death as a competing risk)
- RS
Analysis is based on study 1245.110.

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R.1.1.1.10 Time to first investigator defined CV hospitalization

Table R.1.1.1.10: 1 Cox regression for time to first investigator defined CV hospitalization 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
Overall	2991	765	25.6	14.31	2997	669	22.3	12.15	0.85	(0.77,0.94)	0.0020	
Sex												0.2286
Male	1653	441	26.7	15.06	1659	372	22.4	12.26	0.80	(0.70,0.92)	0.0018	
Female	1338	324	24.2	13.41	1338	297	22.2	12.02	0.91	(0.78,1.07)	0.2579	
Age [years]												0.6937
<70	1084	246	22.7	12.34	1066	216	20.3	10.86	0.87	(0.73,1.05)	0.1495	
>=70	1907	519	27.2	15.49	1931	453	23.5	12.88	0.84	(0.74,0.95)	0.0054	
Region												0.4163
North America	359	126	35.1	20.44	360	124	34.4	19.88	0.98	(0.76,1.25)	0.8472	
Latin America	757	173	22.9	12.95	758	145	19.1	10.60	0.83	(0.66,1.03)	0.0959	
Europe	1343	317	23.6	12.92	1346	287	21.3	11.34	0.87	(0.75,1.03)	0.1012	
Asia	343	98	28.6	16.16	343	72	21.0	10.96	0.66	(0.49,0.90)	0.0086	
Other	189	51	27.0	15.41	190	41	21.6	12.60	0.81	(0.54,1.22)	0.3105	
OECD member												0.5825
No	847	204	24.1	13.61	868	189	21.8	12.40	0.89	(0.73,1.08)	0.2463	
Yes	2144	561	26.2	14.59	2129	480	22.5	12.06	0.83	(0.74,0.94)	0.0034	
Baseline NYHA												0.6048
II^^	2452	566	23.1	12.65	2435	481	19.8	10.46	0.83	(0.74,0.94)	0.0028	
III/IV	539	199	36.9	22.86	562	188	33.5	20.78	0.88	(0.72,1.08)	0.2245	
Baseline Diabetes Status												0.3943
Diabetic	1472	419	28.5	16.42	1466	356	24.3	13.61	0.81	(0.71,0.94)	0.0044	
Non-Diabetic	1519	346	22.8	12.39	1531	313	20.4	10.84	0.89	(0.76,1.04)	0.1408	

* 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, °:Trend test, ^Incidence rate, events per 100 patient years at risk.

Analysis is based on study 1245.110.

^^ Patients with NYHA class I are counted in subgroup NYHA class II.
¹ Baseline SBP median: 132 [mmHg].
² Baseline NT-proBNP median for patients with history of atrial fibrillation or atrial flutter: 1354 [pg/mL].
² Baseline NT-proBNP median for patients without history of atrial fibrillation or atrial flutter: 614 [pg/mL].
³ Baseline uric acid tertile cut-offs for males are T1: 5.9 T2: 7.5 [mg/dL] [rounded].
³ Baseline uric acid tertile cut-offs for females are T1: 5.4 T2: 6.9 [mg/dL] [rounded].

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Table R.1.1.1.10: 1 Cox regression for time to first investigator defined CV 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 Diabetes Status												0.7939°/ 0.3540
Diabetic	1472	419	28.5	16.42	1466	356	24.3	13.61	0.81	(0.71,0.94)	0.0044	
Pre-Diabetes	979	221	22.6	12.28	1001	214	21.4	11.50	0.95	(0.79,1.15)	0.6021	
Normal (no pre-diabetes)	540	125	23.1	12.60	530	99	18.7	9.64	0.79	(0.60,1.02)	0.0722	
Baseline BMI [kg/m²]												0.0470
<30	1642	437	26.6	15.19	1654	352	21.3	11.53	0.77	(0.67,0.89)	0.0003	
>=30	1349	328	24.3	13.30	1343	317	23.6	12.93	0.95	(0.82,1.11)	0.5408	
Baseline eGFR (CKD-EPI) [mL/min/1.73m²]												0.6867
>=60	1505	312	20.7	11.06	1493	260	17.4	9.04	0.83	(0.70,0.97)	0.0221	
<60	1484	453	30.5	17.97	1504	409	27.2	15.56	0.86	(0.75,0.99)	0.0295	
History of HHF (in the last 12 months)												0.8489
No	2321	513	22.1	12.08	2298	437	19.0	10.13	0.85	(0.74,0.96)	0.0104	
Yes	670	252	37.6	22.99	699	232	33.2	19.47	0.83	(0.69,0.99)	0.0386	
Baseline SBP (</>= median¹)												0.6817
< median	1474	381	25.8	14.58	1496	331	22.1	12.21	0.83	(0.72,0.96)	0.0135	
>= median	1517	384	25.3	14.06	1501	338	22.5	12.10	0.87	(0.75,1.00)	0.0566	
History of atrial fibrillation or atrial flutter												0.4936
No	1427	345	24.2	13.44	1417	282	19.9	10.66	0.81	(0.69,0.95)	0.0099	
Yes	1559	420	26.9	15.17	1576	387	24.6	13.57	0.87	(0.76,1.00)	0.0572	

* 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, °:Trend test, ^Incidence rate, events per 100 patient years at risk.

Analysis is based on study 1245.110.

^^ Patients with NYHA class I are counted in subgroup NYHA class II.
¹ Baseline SBP median: 132 [mmHg].
² Baseline NT-proBNP median for patients with history of atrial fibrillation or atrial flutter: 1354 [pg/mL].
² Baseline NT-proBNP median for patients without history of atrial fibrillation or atrial flutter: 614 [pg/mL].
³ Baseline uric acid tertile cut-offs for males are T1: 5.9 T2: 7.5 [mg/dL] [rounded].
³ Baseline uric acid tertile cut-offs for females are T1: 5.4 T2: 6.9 [mg/dL] [rounded].

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Table R.1.1.1.10: 1 Cox regression for time to first investigator defined CV hospitalization 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 LVEF [%]												0.0649
< 50	988	265	26.8	15.18	995	208	20.9	11.20	0.74	(0.62,0.88)	0.0010	
>= 50	2003	500	25.0	13.89	2002	461	23.0	12.64	0.91	(0.80,1.03)	0.1381	
Baseline LVEF [%]												0.0405°/ 0.1213
<50	988	265	26.8	15.18	995	208	20.9	11.20	0.74	(0.62,0.88)	0.0010	
50 to <60	1030	268	26.0	14.52	1028	233	22.7	12.34	0.86	(0.72,1.02)	0.0911	
>=60	973	232	23.8	13.24	974	228	23.4	12.96	0.97	(0.80,1.16)	0.7075	
Baseline NT-proBNP [pg/mL] (</>=median² by atrial fibrillation/flutter status)												0.5190
< median	1508	304	20.2	10.58	1477	260	17.6	9.10	0.88	(0.74,1.03)	0.1166	
>= median	1476	460	31.2	18.69	1516	409	27.0	15.50	0.82	(0.71,0.93)	0.0029	
Baseline uric acid [mg/dL] (tertiles³)												0.5622°/ 0.7650
<T1	975	220	22.6	12.32	963	178	18.5	9.95	0.80	(0.66,0.98)	0.0275	
>=T1 and <T2	966	216	22.4	12.10	1032	207	20.1	10.67	0.88	(0.73,1.06)	0.1887	
>=T2	1018	321	31.5	18.64	970	276	28.5	16.02	0.87	(0.74,1.02)	0.0824	
Baseline use of MRA												0.4277
No	1866	478	25.6	14.27	1878	406	21.6	11.69	0.82	(0.72,0.94)	0.0036	
Yes	1125	287	25.5	14.39	1119	263	23.5	12.94	0.90	(0.76,1.06)	0.1962	
Baseline use of ACE-inhibitor, ARB or ARNi												0.1749
No	587	173	29.5	17.11	569	159	27.9	15.91	0.97	(0.78,1.20)	0.7879	
Yes	2404	592	24.6	13.66	2428	510	21.0	11.32	0.82	(0.73,0.92)	0.0009	

* 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, °:Trend test, ^Incidence rate, events per 100 patient years at risk.

Analysis is based on study 1245.110.

^^ Patients with NYHA class I are counted in subgroup NYHA class II.
¹ Baseline SBP median: 132 [mmHg].
² Baseline NT-proBNP median for patients with history of atrial fibrillation or atrial flutter: 1354 [pg/mL].
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³ Baseline uric acid tertile cut-offs for males are T1: 5.9 T2: 7.5 [mg/dL] [rounded].
³ Baseline uric acid tertile cut-offs for females are T1: 5.4 T2: 6.9 [mg/dL] [rounded].

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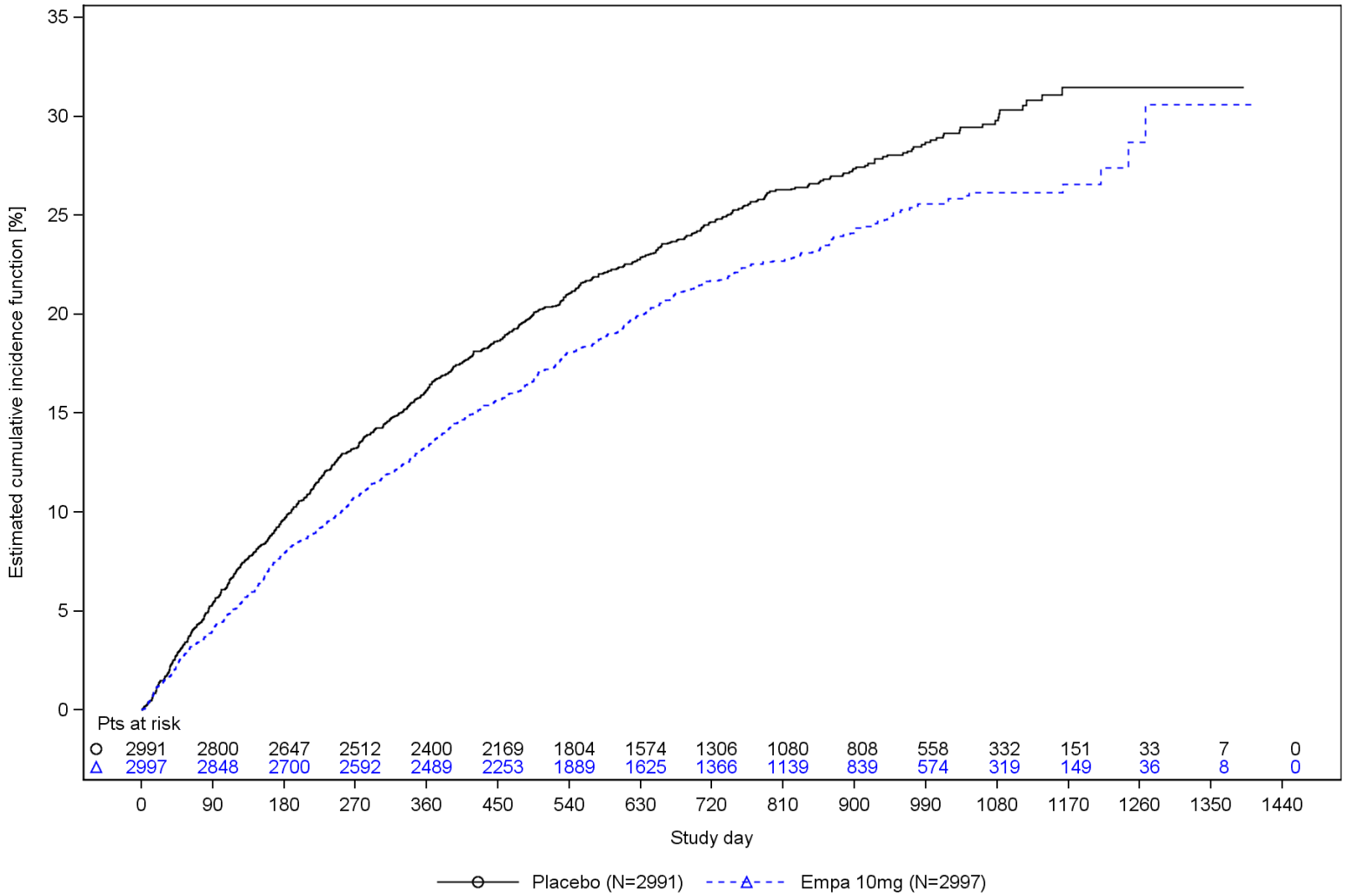

Figure R.1.1.1.10: 1 Time to the first investigator defined CV hospitalization, estimated cumulative incidence function (considering all-cause mortality as a competing risk) - RS
Analysis is based on study 1245.110.

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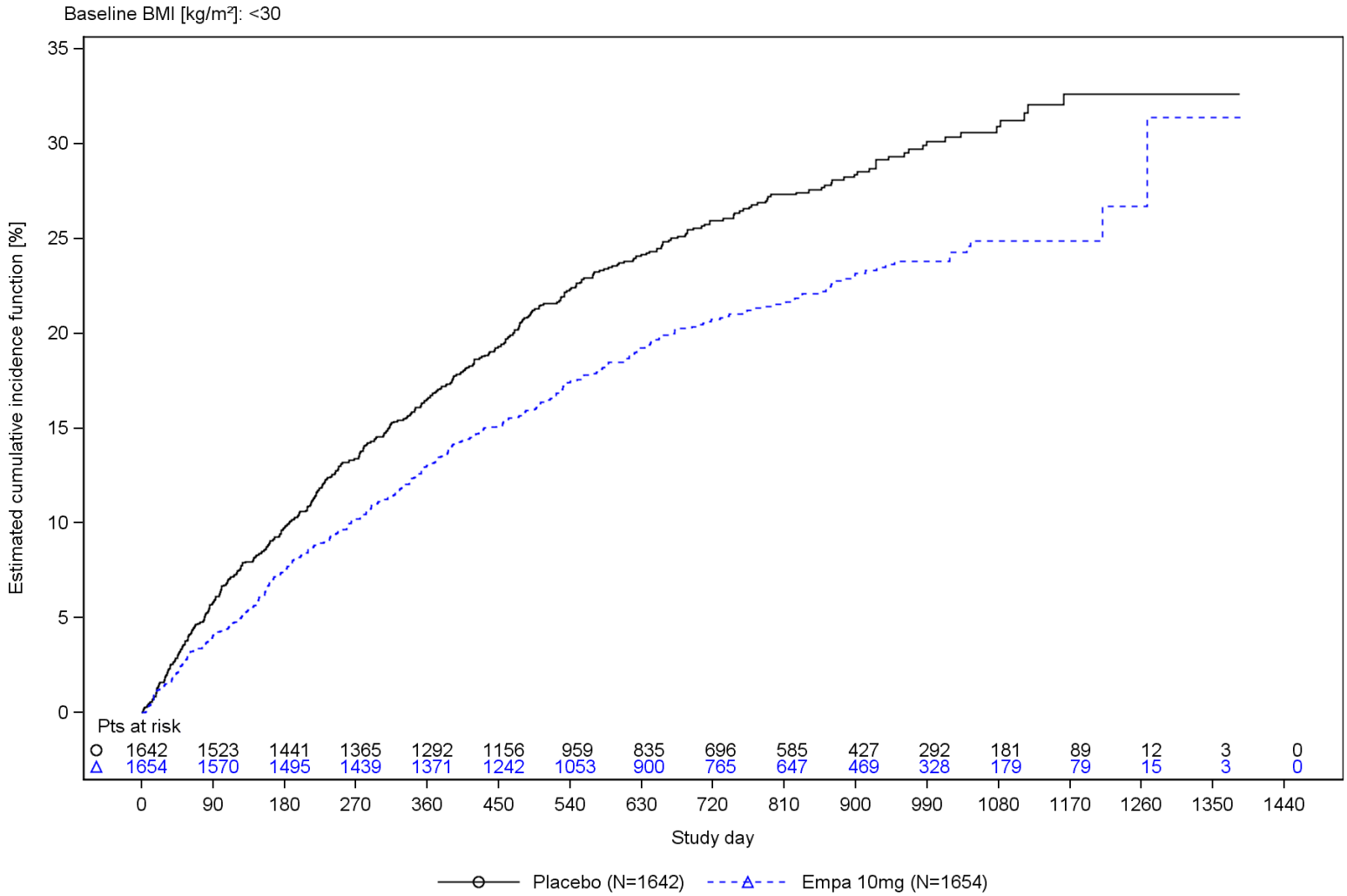

Figure R.1.1.1.10: 2 Time to the first investigator defined CV hospitalization, estimated cumulative incidence function (considering all-cause mortality as a competing risk) by baseline BMI - RS
Analysis is based on study 1245.110.

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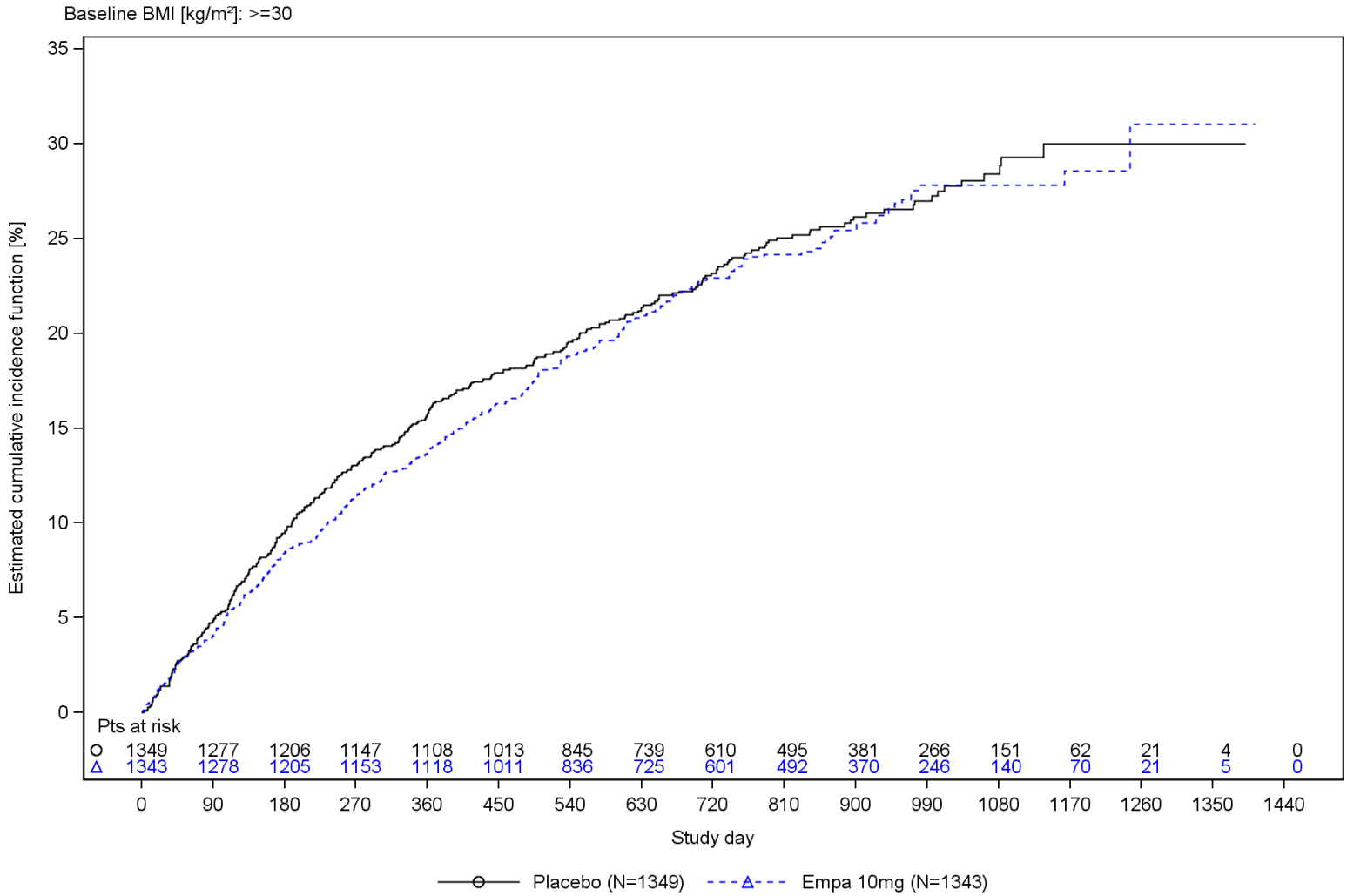

Figure R.1.1.1.10: 2 Time to the first investigator defined CV hospitalization, estimated cumulative incidence function (considering all-cause mortality as a competing risk) by baseline BMI - RS
Analysis is based on study 1245.110.

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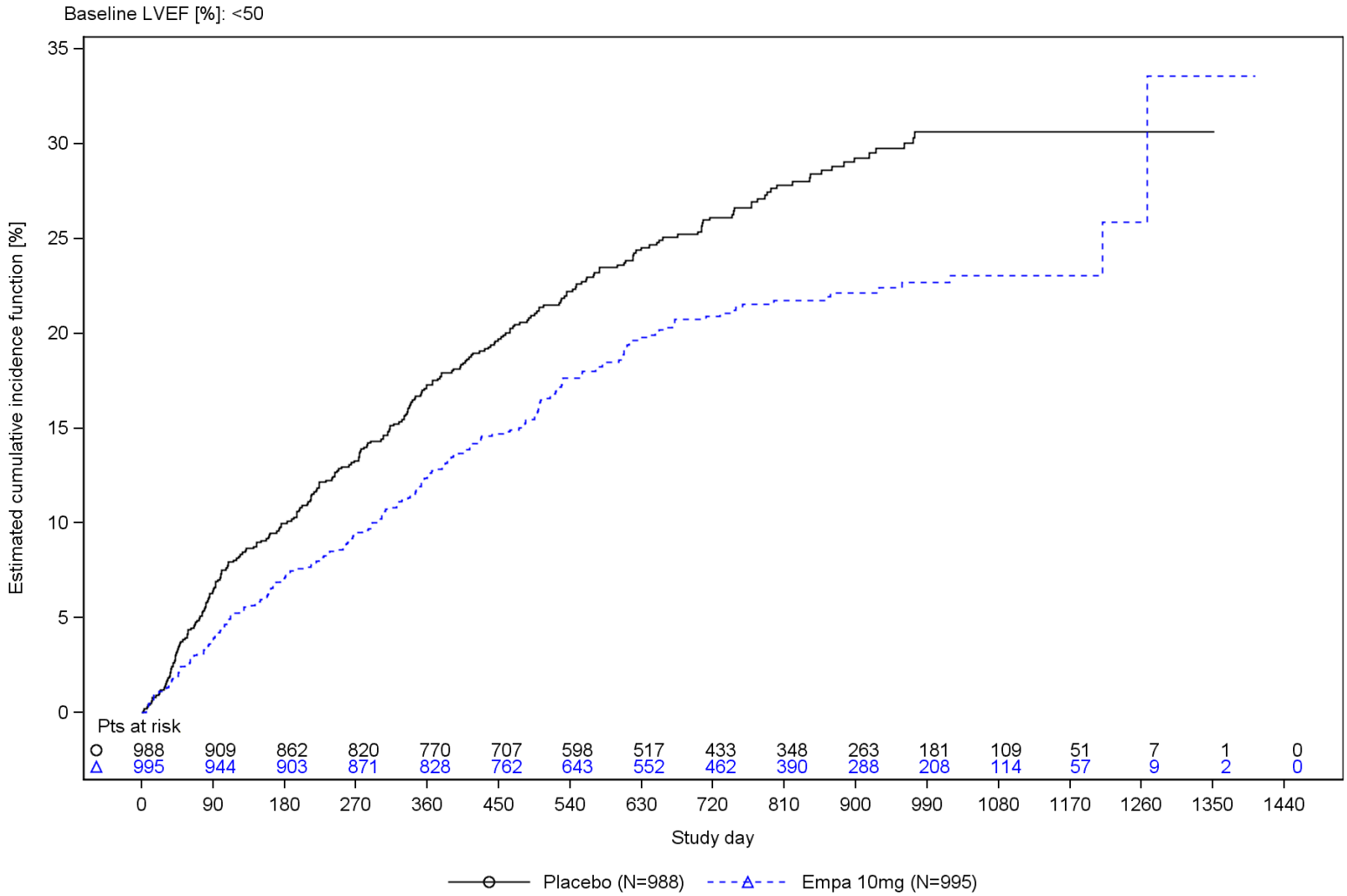

Figure R.1.1.1.10: 3 Time to the first investigator defined CV hospitalization, estimated cumulative incidence function (considering all-cause mortality as a competing risk) by baseline LVEF - RS
Analysis is based on study 1245.110.

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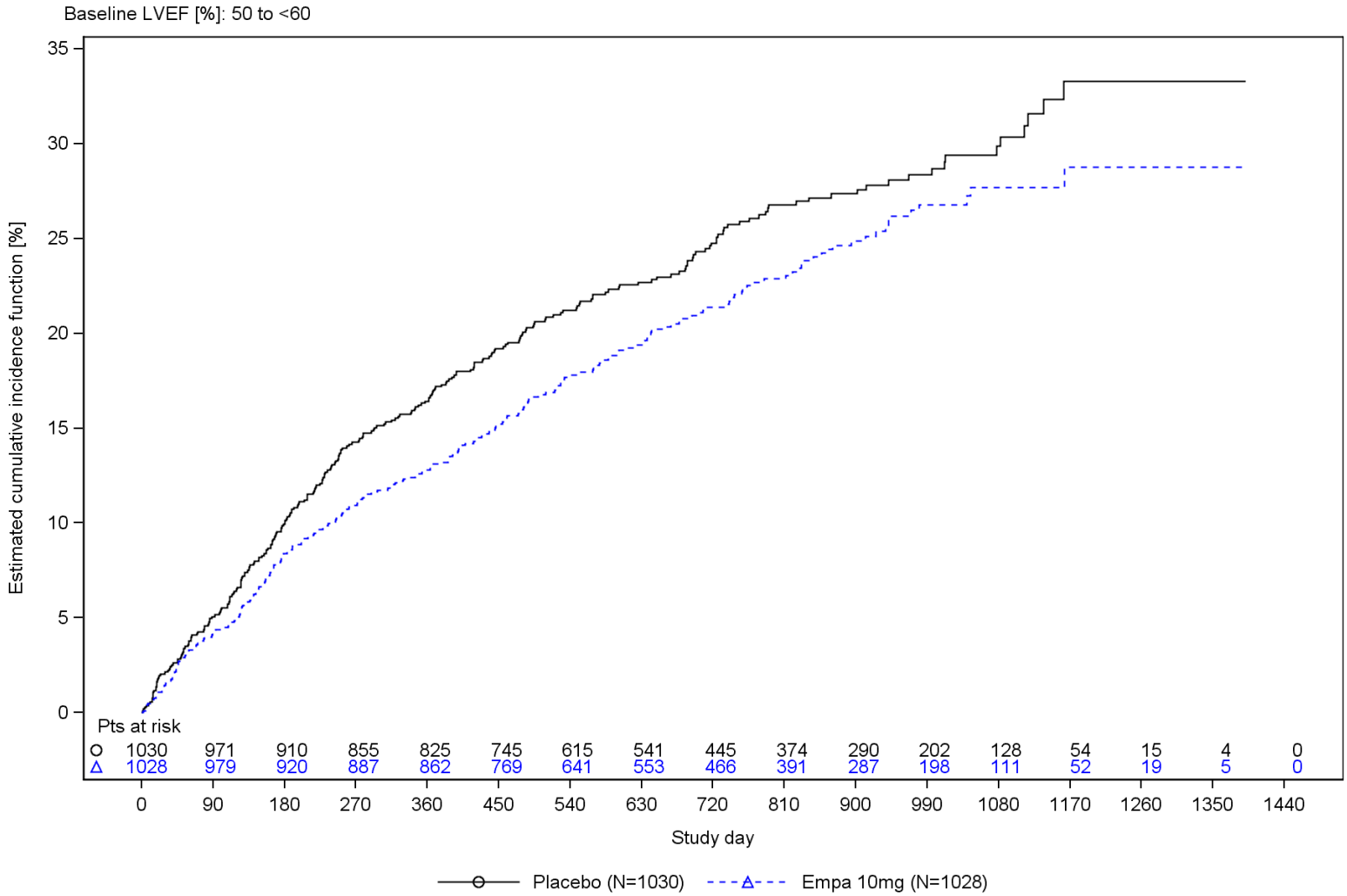

Figure R.1.1.1.10: 3 Time to the first investigator defined CV hospitalization, estimated cumulative incidence function (considering all-cause mortality as a competing risk) by baseline LVEF - RS
Analysis is based on study 1245.110.

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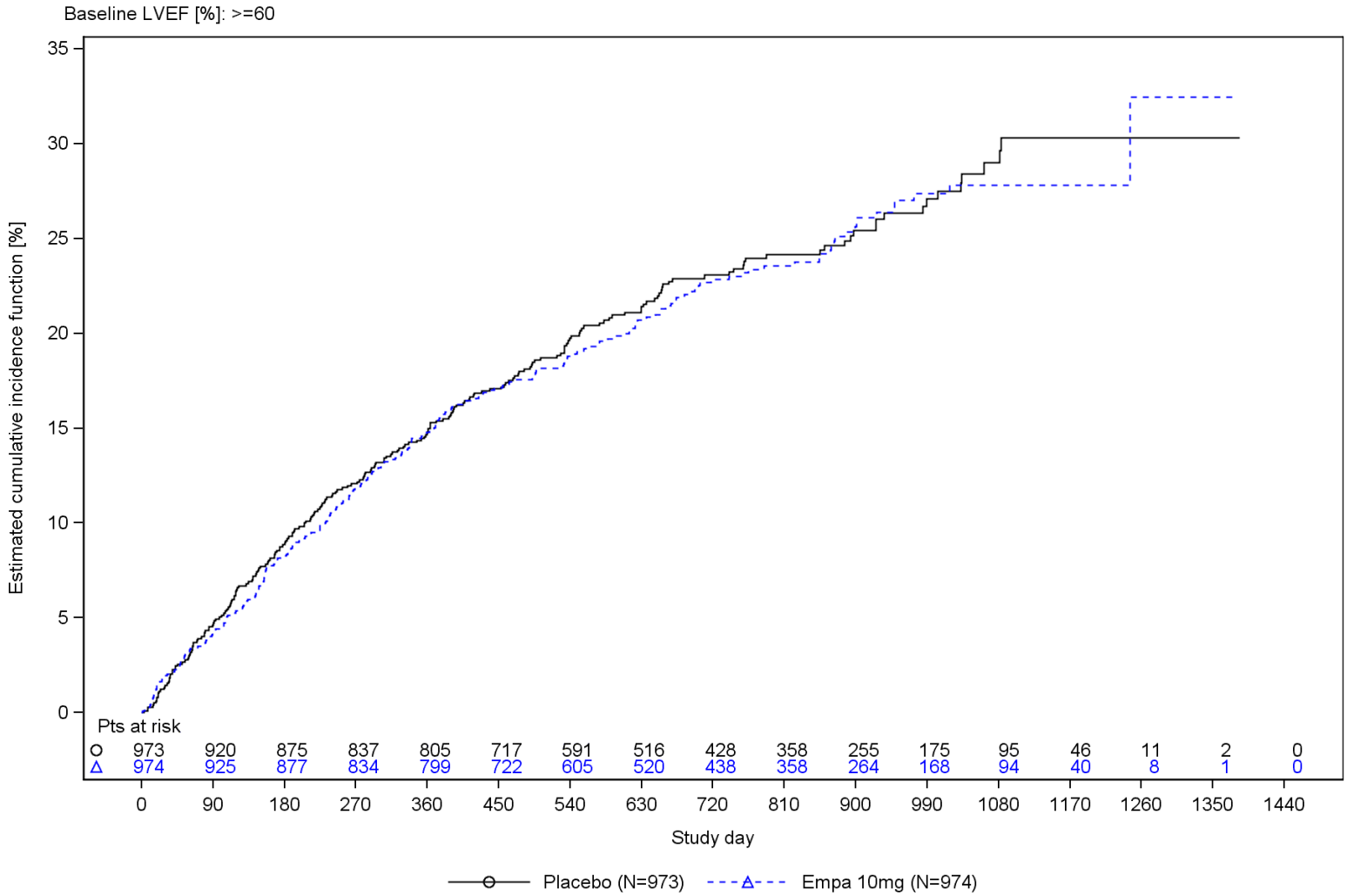

Figure R.1.1.1.10: 3 Time to the first investigator defined CV hospitalization, estimated cumulative incidence function (considering all-cause mortality as a competing risk) by baseline LVEF - RS
Analysis is based on study 1245.110.

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R.1.1.1.1.11 Time to 3P-MACE

Table R.1.1.1.11: 1 Cox regression for time to first 3P-MACE event 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
Overall	2991	330	11.0	5.36	2997	319	10.6	5.17	0.97	(0.83,1.13)	0.7073	
Sex												0.3640
Male	1653	202	12.2	5.95	1659	187	11.3	5.47	0.92	(0.75,1.12)	0.3869	
Female	1338	128	9.6	4.64	1338	132	9.9	4.81	1.06	(0.83,1.35)	0.6416	
Age [years]												0.6849
<70	1084	100	9.2	4.41	1066	100	9.4	4.50	1.01	(0.77,1.34)	0.9233	
>=70	1907	230	12.1	5.92	1931	219	11.3	5.55	0.95	(0.79,1.14)	0.5575	
Region												0.6125
North America	359	51	14.2	6.86	360	41	11.4	5.38	0.77	(0.51,1.15)	0.2023	
Latin America	757	92	12.2	6.20	758	101	13.3	6.86	1.13	(0.85,1.50)	0.4004	
Europe	1343	135	10.1	4.76	1346	126	9.4	4.44	0.94	(0.74,1.20)	0.6445	
Asia	343	32	9.3	4.49	343	30	8.7	4.14	0.90	(0.54,1.48)	0.6667	
Other	189	20	10.6	5.30	190	21	11.1	5.66	1.10	(0.59,2.02)	0.7674	
OECD member												0.0342
No	847	94	11.1	5.56	868	117	13.5	6.94	1.23	(0.94,1.62)	0.1314	
Yes	2144	236	11.0	5.29	2129	202	9.5	4.51	0.86	(0.71,1.04)	0.1229	
Baseline NYHA												0.1415
II^^	2452	254	10.4	5.00	2435	229	9.4	4.51	0.91	(0.76,1.08)	0.2797	
III/IV	539	76	14.1	7.05	562	90	16.0	8.26	1.18	(0.87,1.60)	0.2839	
Baseline Diabetes Status												0.9637
Diabetic	1472	176	12.0	5.85	1466	171	11.7	5.76	0.97	(0.79,1.20)	0.8076	
Non-Diabetic	1519	154	10.1	4.89	1531	148	9.7	4.63	0.97	(0.77,1.21)	0.7723	

* 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, °:Trend test, ^Incidence rate, events per 100 patient years at risk.

Analysis is based on study 1245.110.
MIs were counted excluding silent MIs.
^^ Patients with NYHA class I are counted in subgroup NYHA class II.
[1] Baseline SBP median: 132 [mmHg].
[2] Baseline NT-proBNP median for patients with history of atrial fibrillation or atrial flutter: 1354 [pg/mL].
[2] Baseline NT-proBNP median for patients without history of atrial fibrillation or atrial flutter: 614 [pg/mL].
[3] Baseline uric acid tertile cut-offs for males are T1: 5.9 T2: 7.5 [mg/dL] [rounded].
[3] Baseline uric acid tertile cut-offs for females are T1: 5.4 T2: 6.9 [mg/dL] [rounded].

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Table R.1.1.1.11: 1 Cox regression for time to first 3P-MACE event 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 Diabetes Status												0.4739°/ 0.3097
Diabetic	1472	176	12.0	5.85	1466	171	11.7	5.76	0.97	(0.79,1.20)	0.8074	
Pre-Diabetes	979	95	9.7	4.67	1001	103	10.3	4.98	1.10	(0.83,1.45)	0.5054	
Normal (no pre-diabetes)	540	59	10.9	5.30	530	45	8.5	4.00	0.76	(0.51,1.12)	0.1597	
Baseline BMI [kg/m²]												0.0780
<30	1642	200	12.2	6.04	1654	172	10.4	5.08	0.86	(0.70,1.06)	0.1502	
>=30	1349	130	9.6	4.57	1343	147	10.9	5.28	1.14	(0.90,1.44)	0.2774	
Baseline eGFR (CKD-EPI) [mL/min/1.73m²]												0.1209
>=60	1505	142	9.4	4.51	1493	118	7.9	3.76	0.84	(0.66,1.07)	0.1525	
<60	1484	187	12.6	6.22	1504	201	13.4	6.63	1.07	(0.88,1.31)	0.4839	
History of HHF (in the last 12 months)												0.9327
No	2321	240	10.3	5.05	2298	228	9.9	4.82	0.96	(0.80,1.16)	0.7000	
Yes	670	90	13.4	6.42	699	91	13.0	6.33	0.98	(0.73,1.31)	0.8885	
Baseline SBP (</>= median¹)												0.6102
< median	1474	154	10.4	5.12	1496	146	9.8	4.78	0.93	(0.74,1.17)	0.5383	
>= median	1517	176	11.6	5.59	1501	173	11.5	5.56	1.01	(0.82,1.25)	0.9310	
History of atrial fibrillation or atrial flutter												0.4117
No	1427	158	11.1	5.43	1417	141	10.0	4.83	0.90	(0.72,1.13)	0.3739	
Yes	1559	172	11.0	5.32	1576	177	11.2	5.47	1.03	(0.83,1.27)	0.8041	

* 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, °:Trend test, ^Incidence rate, events per 100 patient years at risk.

Analysis is based on study 1245.110.
MIs were counted excluding silent MIs.
^^ Patients with NYHA class I are counted in subgroup NYHA class II.
¹ Baseline SBP median: 132 [mmHg].
² Baseline NT-proBNP median for patients with history of atrial fibrillation or atrial flutter: 1354 [pg/mL].
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³ Baseline uric acid tertile cut-offs for males are T1: 5.9 T2: 7.5 [mg/dL] [rounded].
³ Baseline uric acid tertile cut-offs for females are T1: 5.4 T2: 6.9 [mg/dL] [rounded].

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Table R.1.1.1.11: 1 Cox regression for time to first 3P-MACE 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 LVEF [%]												0.9217
< 50	988	128	13.0	6.32	995	125	12.6	6.08	0.96	(0.75,1.23)	0.7295	
>= 50	2003	202	10.1	4.89	2002	194	9.7	4.72	0.97	(0.80,1.18)	0.7833	
Baseline LVEF [%]												0.6407°/ 0.7395
<50	988	128	13.0	6.32	995	125	12.6	6.08	0.96	(0.75,1.23)	0.7301	
50 to <60	1030	117	11.4	5.49	1028	103	10.0	4.86	0.91	(0.70,1.19)	0.4810	
>=60	973	85	8.7	4.25	974	91	9.3	4.57	1.06	(0.79,1.43)	0.6877	
Baseline NT-proBNP [pg/mL] (</>=median² by atrial fibrillation/flutter status)												0.2255
< median	1508	115	7.6	3.59	1477	94	6.4	2.98	0.84	(0.64,1.10)	0.2090	
>= median	1476	213	14.4	7.25	1516	224	14.8	7.45	1.03	(0.85,1.24)	0.7537	
Baseline uric acid [mg/dL] (tertiles³)												0.2985°/ 0.1929
<T1	975	100	10.3	4.98	963	76	7.9	3.83	0.78	(0.58,1.05)	0.1043	
>=T1 and <T2	966	97	10.0	4.81	1032	115	11.1	5.43	1.13	(0.86,1.48)	0.3714	
>=T2	1018	131	12.9	6.32	970	125	12.9	6.24	0.99	(0.77,1.26)	0.9244	
Baseline use of MRA												0.9285
No	1866	216	11.6	5.62	1878	208	11.1	5.36	0.97	(0.80,1.17)	0.7221	
Yes	1125	114	10.1	4.93	1119	111	9.9	4.86	0.98	(0.75,1.27)	0.8823	
Baseline use of ACE-inhibitor, ARB or ARNi												0.4296
No	587	64	10.9	5.44	569	69	12.1	5.89	1.10	(0.78,1.54)	0.5919	
Yes	2404	266	11.1	5.34	2428	250	10.3	5.01	0.94	(0.79,1.12)	0.4907	

* 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, °:Trend test, ^Incidence rate, events per 100 patient years at risk.

Analysis is based on study 1245.110.
MIs were counted excluding silent MIs.
^^ Patients with NYHA class I are counted in subgroup NYHA class II.
¹ Baseline SBP median: 132 [mmHg].
² Baseline NT-proBNP median for patients with history of atrial fibrillation or atrial flutter: 1354 [pg/mL].
² Baseline NT-proBNP median for patients without history of atrial fibrillation or atrial flutter: 614 [pg/mL].
³ Baseline uric acid tertile cut-offs for males are T1: 5.9 T2: 7.5 [mg/dL] [rounded].
³ Baseline uric acid tertile cut-offs for females are T1: 5.4 T2: 6.9 [mg/dL] [rounded].

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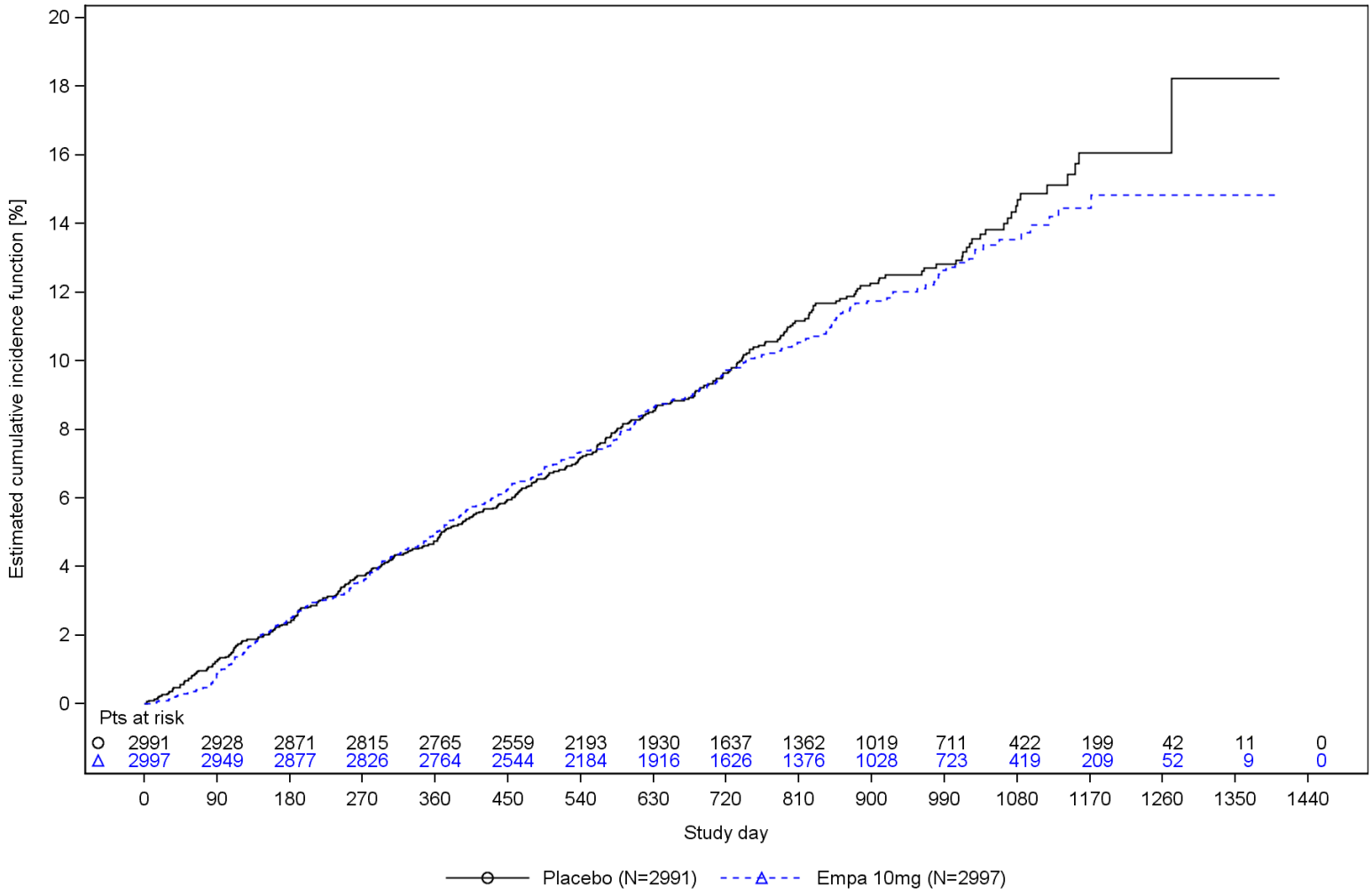

Figure R.1.1.1.11: 1 Time to the first 3P-MACE event, estimated cumulative incidence function (considering non-CV death as a competing risk) - RS

Analysis is based on study 1245.110.

MIs were counted excluding silent MIs.

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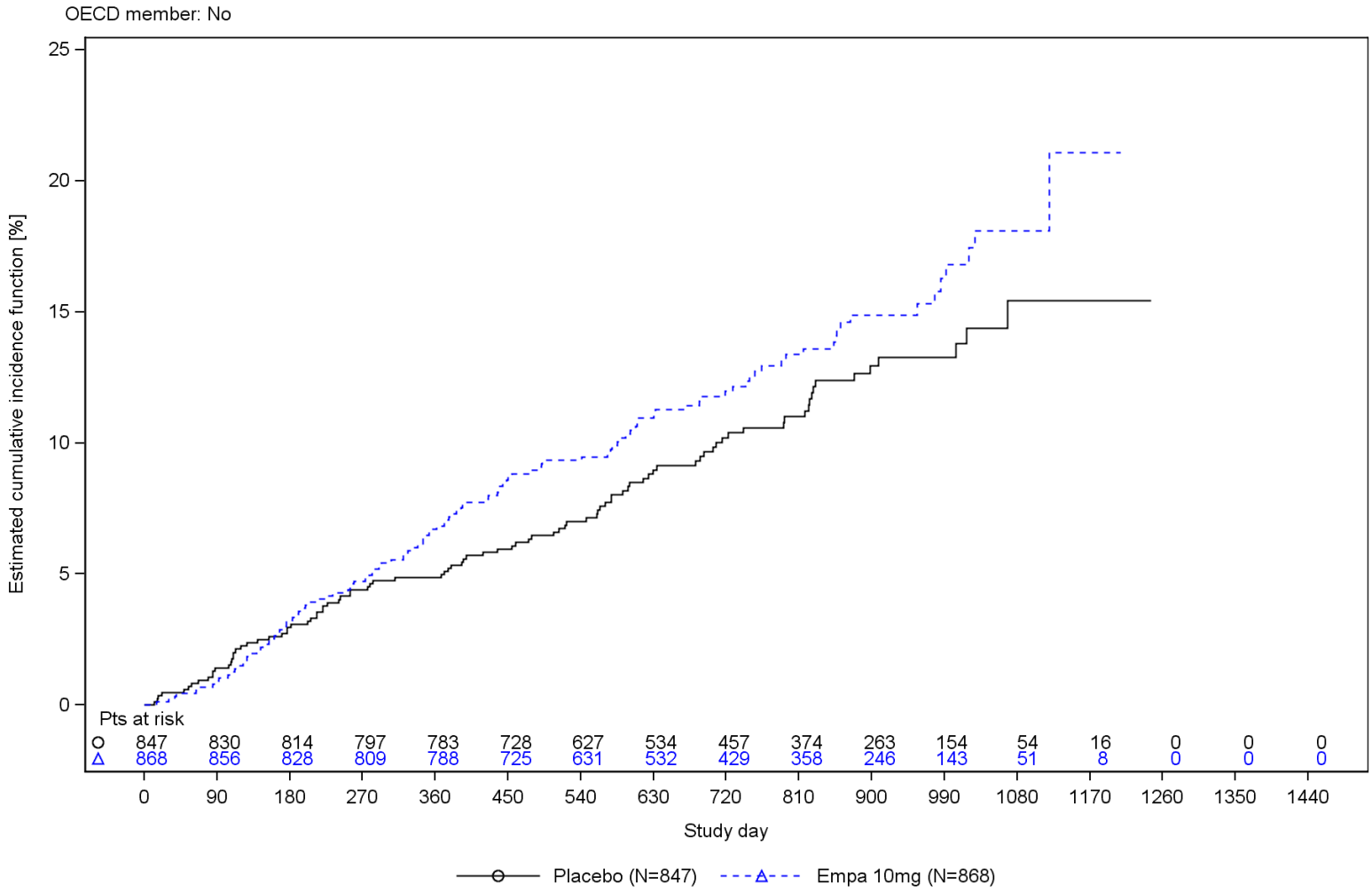

Figure R.1.1.1.11: 2 Time to the first 3P-MACE event, estimated cumulative incidence function (considering non CV-death as a competing risk) by OECD member - RS
Analysis is based on study 1245.110.
MIs were counted excluding silent MIs.

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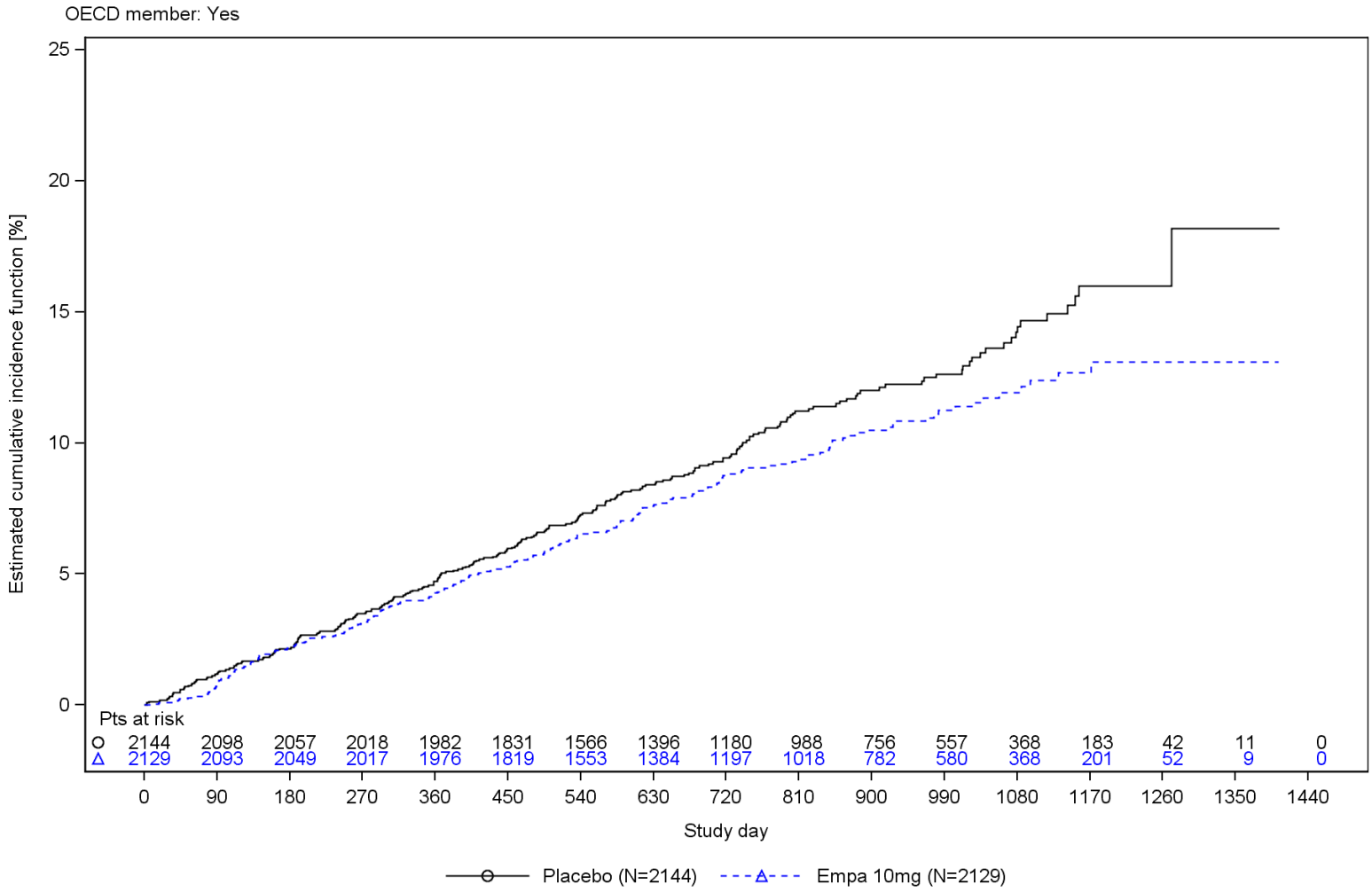

Figure R.1.1.1.11: 2 Time to the first 3P-MACE event, estimated cumulative incidence function (considering non CV-death as a competing risk) by OECD member - RS
Analysis is based on study 1245.110.
MIs were counted excluding silent MIs.

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R.1.1.1.12 Time to first adjudicated MI (fatal or non-fatal)

Table R.1.1.1.12: 1 Cox regression for time to first adjudicated MI (fatal or non-fatal) 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	2991	38	1.3	0.61	2997	47	1.6	0.75	1.24	(0.81, 1.90)	0.3230	
Sex												0.0444
Male	1653	26	1.6	0.76	1659	23	1.4	0.66	0.85	(0.48, 1.49)	0.5712	
Female	1338	12	0.9	0.43	1338	24	1.8	0.86	2.13	(1.06, 4.26)	0.0331	
Age [years]												0.3967
<70	1084	14	1.3	0.61	1066	13	1.2	0.58	0.95	(0.44, 2.01)	0.8869	
>=70	1907	24	1.3	0.61	1931	34	1.8	0.85	1.41	(0.83, 2.38)	0.1993	
Region												0.1303
North America	359	13	3.6	1.71	360	11	3.1	1.43	0.83	(0.37, 1.86)	0.6540	
Latin America	757	3	0.4	0.20	758	15	2.0	1.00	5.07	(1.47,17.51)	0.0103	
Europe	1343	15	1.1	0.52	1346	19	1.4	0.66	1.29	(0.66, 2.54)	0.4612	
Asia	343	4	1.2	0.55	343	2	0.6	0.27	0.48	(0.09, 2.63)	0.3980	
Other	189	3	1.6	0.78	190	0	0	0.00	<0.01		0.9771	
OECD member												0.0648
No	847	5	0.6	0.29	868	15	1.7	0.87	2.86	(1.04, 7.88)	0.0416	
Yes	2144	33	1.5	0.73	2129	32	1.5	0.71	0.99	(0.61, 1.62)	0.9792	
Baseline NYHA												0.0920
II^^	2452	32	1.3	0.62	2435	31	1.3	0.60	0.99	(0.60, 1.62)	0.9709	
III/IV	539	6	1.1	0.55	562	16	2.8	1.45	2.47	(0.97, 6.32)	0.0593	
Baseline Diabetes Status												0.1978
Diabetic	1472	30	2.0	0.98	1466	31	2.1	1.03	1.04	(0.63, 1.72)	0.8798	
Non-Diabetic	1519	8	0.5	0.25	1531	16	1.0	0.49	1.99	(0.85, 4.65)	0.1126	

* 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, °:Trend test, ^Incidence rate, events per 100 patient years at risk.

Analysis is based on study 1245.110.
MIs were counted excluding silent MIs.
^^ Patients with NYHA class I are counted in subgroup NYHA class II.
[1] Baseline SBP median: 132 [mmHg].
[2] Baseline NT-proBNP median for patients with history of atrial fibrillation or atrial flutter: 1354 [pg/mL].
[2] Baseline NT-proBNP median for patients without history of atrial fibrillation or atrial flutter: 614 [pg/mL].
[3] Baseline uric acid tertile cut-offs for males are T1: 5.9 T2: 7.5 [mg/dL] [rounded].
[3] Baseline uric acid tertile cut-offs for females are T1: 5.4 T2: 6.9 [mg/dL] [rounded].

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Table R.1.1.1.12: 1 Cox regression for time to first adjudicated MI (fatal or non-fatal) 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 Diabetes Status												0.3855°/ 0.2831
Diabetic	1472	30	2.0	0.98	1466	31	2.1	1.03	1.04	(0.63, 1.72)	0.8806	
Pre-Diabetes	979	5	0.5	0.24	1001	13	1.3	0.62	2.60	(0.93, 7.29)	0.0696	
Normal (no pre-diabetes)	540	3	0.6	0.27	530	3	0.6	0.26	0.98	(0.20, 4.87)	0.9829	
Baseline BMI [kg/m²]												0.0941
<30	1642	25	1.5	0.74	1654	22	1.3	0.64	0.90	(0.50, 1.59)	0.7074	
>=30	1349	13	1.0	0.45	1343	25	1.9	0.89	1.90	(0.97, 3.72)	0.0596	
Baseline eGFR (CKD-EPI) [mL/min/1.73m²]												0.3174
>=60	1505	18	1.2	0.57	1493	17	1.1	0.54	0.96	(0.49, 1.85)	0.8922	
<60	1484	20	1.3	0.66	1504	30	2.0	0.97	1.49	(0.85, 2.63)	0.1672	
History of HHF (in the last 12 months)												0.3171
No	2321	29	1.2	0.60	2298	31	1.3	0.65	1.08	(0.65, 1.79)	0.7737	
Yes	670	9	1.3	0.63	699	16	2.3	1.10	1.76	(0.78, 3.99)	0.1752	
Baseline SBP (</>= median¹)												0.6894
< median	1474	16	1.1	0.53	1496	23	1.5	0.74	1.37	(0.72, 2.60)	0.3337	
>= median	1517	22	1.5	0.69	1501	24	1.6	0.76	1.15	(0.64, 2.05)	0.6379	
History of atrial fibrillation or atrial flutter												0.9227
No	1427	24	1.7	0.81	1417	28	2.0	0.95	1.24	(0.72, 2.14)	0.4412	
Yes	1559	14	0.9	0.43	1576	19	1.2	0.58	1.29	(0.65, 2.58)	0.4636	

* 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, °:Trend test, ^Incidence rate, events per 100 patient years at risk.

Analysis is based on study 1245.110.
MIs were counted excluding silent MIs.
^^ Patients with NYHA class I are counted in subgroup NYHA class II.
¹ Baseline SBP median: 132 [mmHg].
² Baseline NT-proBNP median for patients with history of atrial fibrillation or atrial flutter: 1354 [pg/mL].
² Baseline NT-proBNP median for patients without history of atrial fibrillation or atrial flutter: 614 [pg/mL].
³ Baseline uric acid tertile cut-offs for males are T1: 5.9 T2: 7.5 [mg/dL] [rounded].
³ Baseline uric acid tertile cut-offs for females are T1: 5.4 T2: 6.9 [mg/dL] [rounded].

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Table R.1.1.1.12: 1 Cox regression for time to first adjudicated MI (fatal or non-fatal) 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 LVEF [%]												0.7582
< 50	988	14	1.4	0.68	995	16	1.6	0.77	1.13	(0.55, 2.31)	0.7424	
>= 50	2003	24	1.2	0.57	2002	31	1.5	0.74	1.30	(0.76, 2.21)	0.3374	
Baseline LVEF [%]												0.7839°/ 0.9517
<50	988	14	1.4	0.68	995	16	1.6	0.77	1.13	(0.55, 2.31)	0.7402	
50 to <60	1030	15	1.5	0.70	1028	19	1.8	0.89	1.29	(0.66, 2.54)	0.4580	
>=60	973	9	0.9	0.44	974	12	1.2	0.59	1.32	(0.56, 3.13)	0.5307	
Baseline NT-proBNP [pg/mL] (</>=median² by atrial fibrillation/flutter status)												0.6236
< median	1508	15	1.0	0.46	1477	15	1.0	0.47	1.06	(0.52, 2.16)	0.8792	
>= median	1476	23	1.6	0.77	1516	32	2.1	1.05	1.32	(0.77, 2.26)	0.3069	
Baseline uric acid [mg/dL] (tertiles³)												0.5000°/ 0.7582
<T1	975	8	0.8	0.39	963	12	1.2	0.60	1.45	(0.59, 3.55)	0.4154	
>=T1 and <T2	966	12	1.2	0.59	1032	17	1.6	0.79	1.37	(0.66, 2.88)	0.3991	
>=T2	1018	18	1.8	0.86	970	17	1.8	0.84	1.01	(0.52, 1.96)	0.9756	
Baseline use of MRA												0.7327
No	1866	28	1.5	0.72	1878	33	1.8	0.84	1.19	(0.72, 1.96)	0.5073	
Yes	1125	10	0.9	0.43	1119	14	1.3	0.61	1.40	(0.62, 3.16)	0.4159	
Baseline use of ACE-inhibitor, ARB or ARNi												0.5245
No	587	7	1.2	0.59	569	11	1.9	0.92	1.63	(0.63, 4.21)	0.3113	
Yes	2404	31	1.3	0.61	2428	36	1.5	0.71	1.16	(0.71, 1.87)	0.5553	

* 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, °:Trend test, ^Incidence rate, events per 100 patient years at risk.

Analysis is based on study 1245.110.
MIs were counted excluding silent MIs.
^^ Patients with NYHA class I are counted in subgroup NYHA class II.
¹ Baseline SBP median: 132 [mmHg].
² Baseline NT-proBNP median for patients with history of atrial fibrillation or atrial flutter: 1354 [pg/mL].
² Baseline NT-proBNP median for patients without history of atrial fibrillation or atrial flutter: 614 [pg/mL].
³ Baseline uric acid tertile cut-offs for males are T1: 5.9 T2: 7.5 [mg/dL] [rounded].
³ Baseline uric acid tertile cut-offs for females are T1: 5.4 T2: 6.9 [mg/dL] [rounded].

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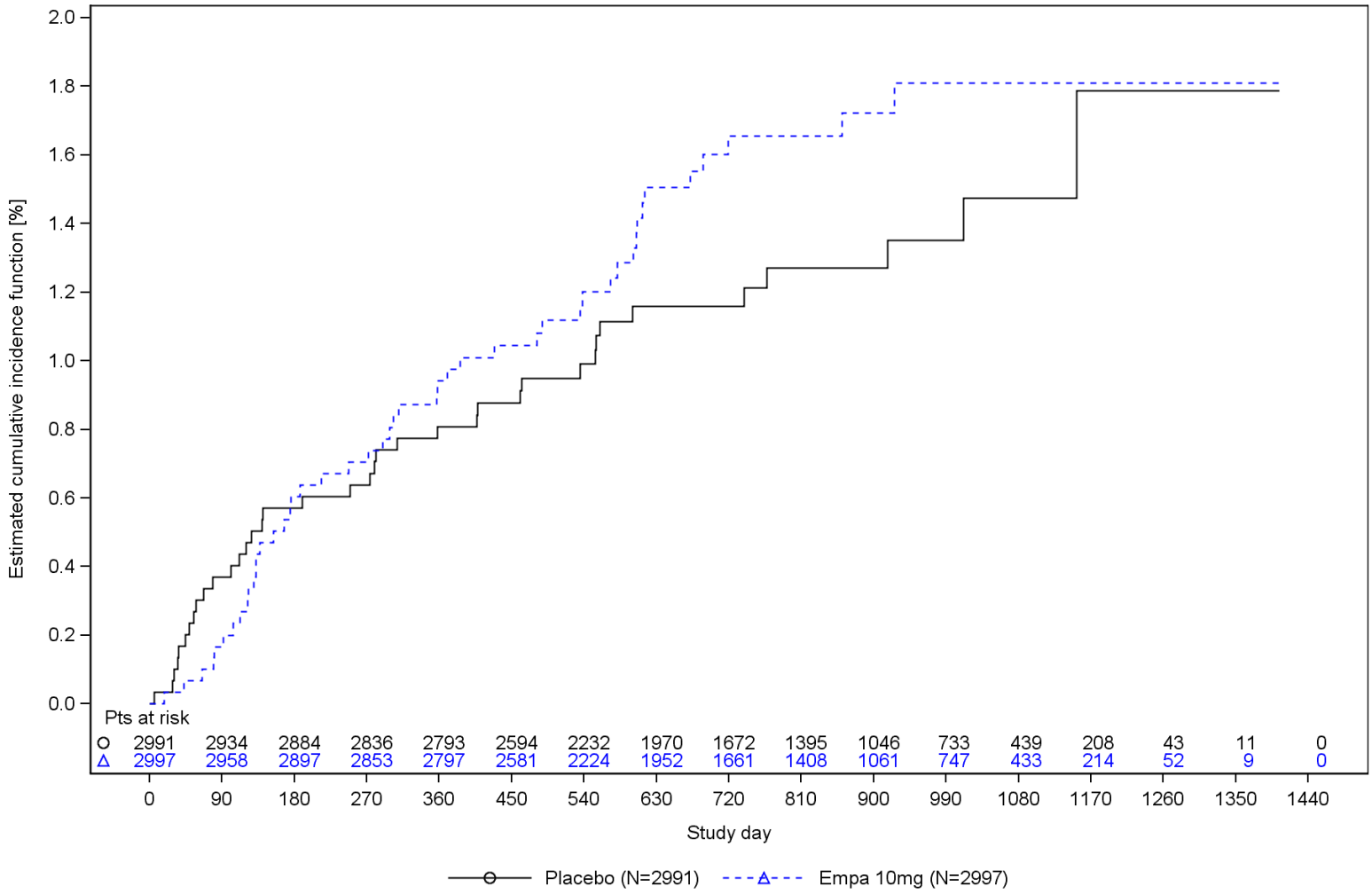

Figure R.1.1.1.12: 1 Time to the first adjudicated MI (fatal or non-fatal), estimated cumulative incidence function (considering non-MI death as a competing risk) - RS
Analysis is based on study 1245.110.
MIs were counted excluding silent MIs.

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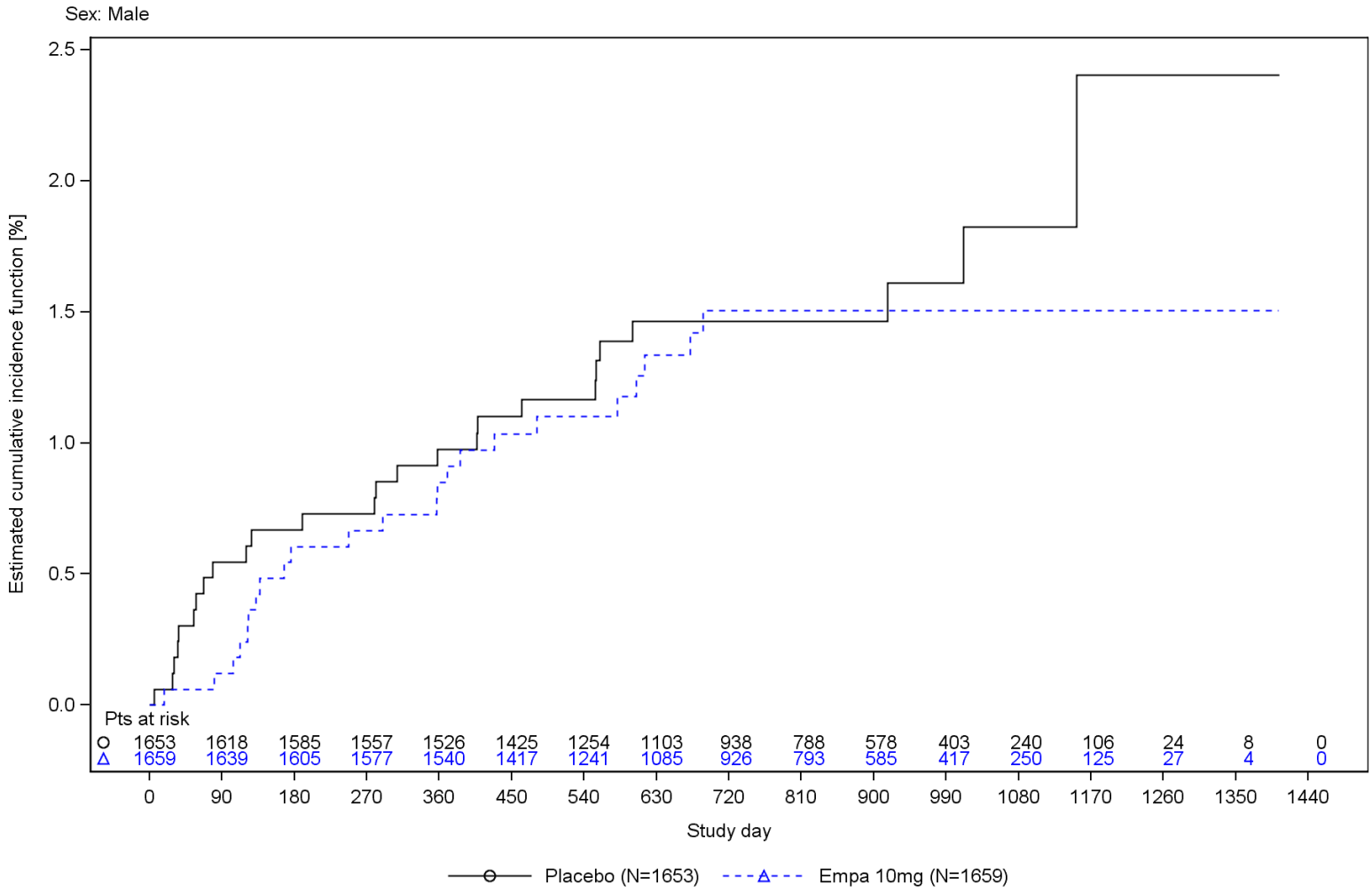

Figure R.1.1.1.12: 2 Time to the first adjudicated MI (fatal or non-fatal), estimated cumulative incidence function (considering non-MI death as a competing risk) by sex - RS
Analysis is based on study 1245.110.
MIs were counted excluding silent MIs.

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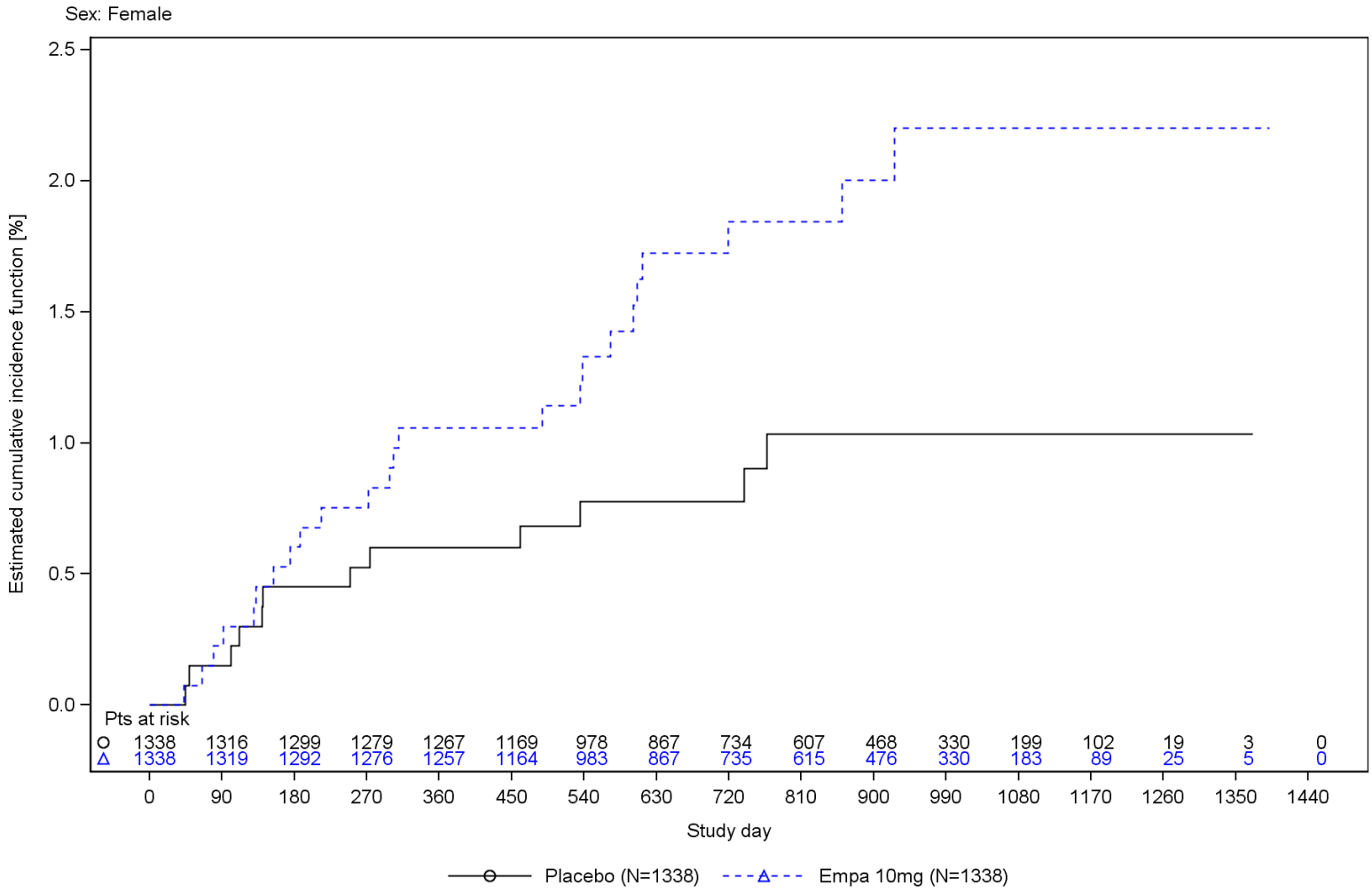

Figure R.1.1.1.12: 2 Time to the first adjudicated MI (fatal or non-fatal), estimated cumulative incidence function (considering non-MI death as a competing risk) by sex - RS
Analysis is based on study 1245.110.
MIs were counted excluding silent MIs.

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R.1.1.1.13 Time to first adjudicated fatal MI

Table R.1.1.1.13: 1 Cox regression for time to adjudicated fatal MI - 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	2991	3	0.1	0.05	2997	5	0.2	0.08	1.71	(0.41,7.16)	0.4631	

* 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.

Analysis is based on study 1245.110.
MIs were counted excluding silent MIs.

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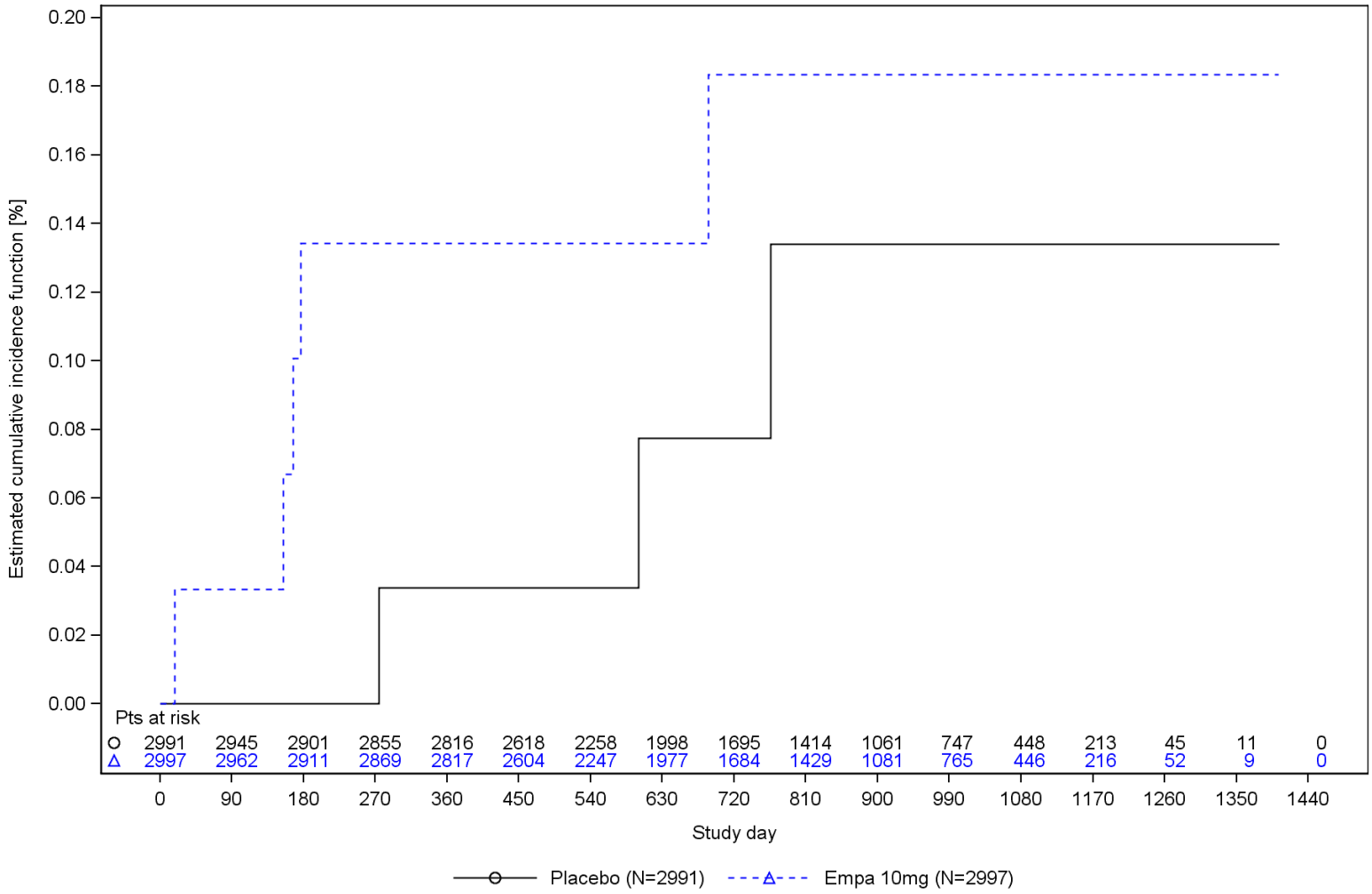

Figure R.1.1.1.13: 1 Time to the first adjudicated fatal MI, estimated cumulative incidence function (considering non-MI death as a competing risk) - RS
Analysis is based on study 1245.110.
MIs were counted excluding silent MIs.

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R.1.1.1.14 Time to first adjudicated non-fatal MI

Table R.1.1.1.14: 1 Cox regression for time to first adjudicated non-fatal MI - 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	2991	36	1.2	0.58	2997	42	1.4	0.67	1.17	(0.75,1.83)	0.4869	

* 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.

Analysis is based on study 1245.110.
MIs were counted excluding silent MIs.

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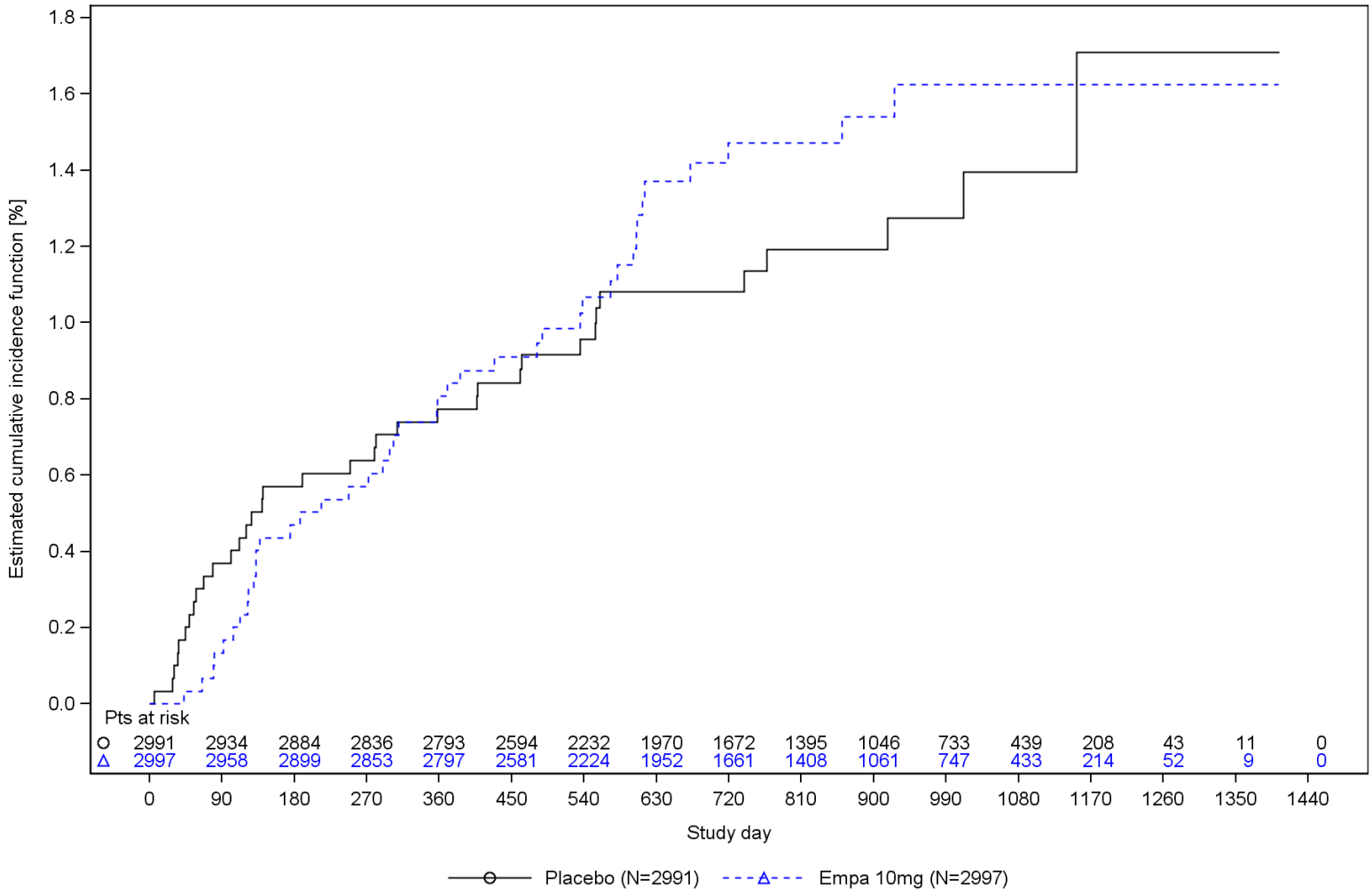

Figure R.1.1.1.14: 1 Time to the first adjudicated non-fatal MI, estimated cumulative incidence function (considering all cause mortality as a competing risk) - RS
Analysis is based on study 1245.110.
MIs were counted excluding silent MIs.

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R.1.1.1.15 Time to first adjudicated stroke (fatal or non-fatal)

Table R.1.1.1.15: 1 Cox regression for time to first adjudicated stroke (fatal or non-fatal) 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	2991	84	2.8	1.35	2997	92	3.1	1.48	1.10	(0.82,1.47)	0.5393	
Sex												0.8064
Male	1653	46	2.8	1.34	1659	52	3.1	1.51	1.13	(0.76,1.69)	0.5348	
Female	1338	38	2.8	1.37	1338	40	3.0	1.44	1.05	(0.67,1.64)	0.8214	
Age [years]												0.9587
<70	1084	22	2.0	0.96	1066	23	2.2	1.03	1.07	(0.60,1.93)	0.8115	
>=70	1907	62	3.3	1.58	1931	69	3.6	1.73	1.09	(0.78,1.54)	0.6110	
Region												0.3124
North America	359	19	5.3	2.49	360	11	3.1	1.41	0.56	(0.27,1.19)	0.1312	
Latin America	757	22	2.9	1.48	758	27	3.6	1.82	1.24	(0.71,2.18)	0.4497	
Europe	1343	25	1.9	0.87	1346	32	2.4	1.12	1.29	(0.77,2.18)	0.3359	
Asia	343	12	3.5	1.67	343	18	5.2	2.48	1.47	(0.71,3.06)	0.2986	
Other	189	6	3.2	1.57	190	4	2.1	1.08	0.70	(0.20,2.47)	0.5742	
OECD member												0.2031
No	847	23	2.7	1.36	868	34	3.9	2.00	1.46	(0.86,2.47)	0.1645	
Yes	2144	61	2.8	1.35	2129	58	2.7	1.28	0.96	(0.67,1.38)	0.8267	
Baseline NYHA												0.4081
II^^	2452	64	2.6	1.25	2435	74	3.0	1.45	1.17	(0.84,1.63)	0.3600	
III/IV	539	20	3.7	1.84	562	18	3.2	1.62	0.86	(0.46,1.63)	0.6497	
Baseline Diabetes Status												0.6573
Diabetic	1472	45	3.1	1.47	1466	46	3.1	1.53	1.03	(0.68,1.55)	0.8936	
Non-Diabetic	1519	39	2.6	1.23	1531	46	3.0	1.43	1.18	(0.77,1.80)	0.4562	

* 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, °:Trend test, ^Incidence rate, events per 100 patient years at risk.

Analysis is based on study 1245.110.

^^ Patients with NYHA class I are counted in subgroup NYHA class II.
[1] Baseline SBP median: 132 [mmHg].
[2] Baseline NT-proBNP median for patients with history of atrial fibrillation or atrial flutter: 1354 [pg/mL].
[2] Baseline NT-proBNP median for patients without history of atrial fibrillation or atrial flutter: 614 [pg/mL].
[3] Baseline uric acid tertile cut-offs for males are T1: 5.9 T2: 7.5 [mg/dL] [rounded].
[3] Baseline uric acid tertile cut-offs for females are T1: 5.4 T2: 6.9 [mg/dL] [rounded].

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Table R.1.1.1.15: 1 Cox regression for time to first adjudicated stroke (fatal or non-fatal) 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 Diabetes Status												0.6661°/ 0.1512
Diabetic	1472	45	3.1	1.47	1466	46	3.1	1.53	1.03	(0.68,1.55)	0.8933	
Pre-Diabetes	979	24	2.5	1.17	1001	37	3.7	1.78	1.53	(0.92,2.57)	0.1023	
Normal (no pre-diabetes)	540	15	2.8	1.34	530	9	1.7	0.80	0.60	(0.26,1.37)	0.2260	
Baseline BMI [kg/m²]												0.4535
<30	1642	51	3.1	1.53	1654	51	3.1	1.50	1.00	(0.68,1.47)	0.9846	
>=30	1349	33	2.4	1.15	1343	41	3.1	1.46	1.25	(0.79,1.98)	0.3339	
Baseline eGFR (CKD-EPI) [mL/min/1.73m²]												0.6405
>=60	1505	38	2.5	1.20	1493	38	2.5	1.21	1.01	(0.64,1.59)	0.9615	
<60	1484	46	3.1	1.52	1504	54	3.6	1.76	1.17	(0.79,1.73)	0.4444	
History of HHF (in the last 12 months)												0.7210
No	2321	63	2.7	1.31	2298	70	3.0	1.47	1.13	(0.80,1.59)	0.4802	
Yes	670	21	3.1	1.48	699	22	3.1	1.51	1.00	(0.55,1.81)	0.9925	
Baseline SBP (</>= median¹)												0.6467
< median	1474	39	2.6	1.29	1496	41	2.7	1.33	1.02	(0.66,1.58)	0.9307	
>= median	1517	45	3.0	1.41	1501	51	3.4	1.62	1.17	(0.78,1.75)	0.4386	
History of atrial fibrillation or atrial flutter												0.1147
No	1427	38	2.7	1.29	1417	30	2.1	1.02	0.81	(0.50,1.30)	0.3817	
Yes	1559	46	3.0	1.41	1576	62	3.9	1.90	1.32	(0.90,1.94)	0.1513	

* 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, °:Trend test, ^Incidence rate, events per 100 patient years at risk.

Analysis is based on study 1245.110.

^^ Patients with NYHA class I are counted in subgroup NYHA class II.
¹ Baseline SBP median: 132 [mmHg].
² Baseline NT-proBNP median for patients with history of atrial fibrillation or atrial flutter: 1354 [pg/mL].
² Baseline NT-proBNP median for patients without history of atrial fibrillation or atrial flutter: 614 [pg/mL].
³ Baseline uric acid tertile cut-offs for males are T1: 5.9 T2: 7.5 [mg/dL] [rounded].
³ Baseline uric acid tertile cut-offs for females are T1: 5.4 T2: 6.9 [mg/dL] [rounded].

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Table R.1.1.1.15: 1 Cox regression for time to first adjudicated stroke (fatal or non-fatal) 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 LVEF [%]												0.3592
< 50	988	25	2.5	1.22	995	34	3.4	1.64	1.33	(0.80,2.24)	0.2733	
>= 50	2003	59	2.9	1.42	2002	58	2.9	1.40	0.99	(0.69,1.43)	0.9716	
Baseline LVEF [%]												0.2082°/ 0.4413
<50	988	25	2.5	1.22	995	34	3.4	1.64	1.33	(0.80,2.24)	0.2732	
50 to <60	1030	26	2.5	1.21	1028	30	2.9	1.40	1.18	(0.70,2.00)	0.5358	
>=60	973	33	3.4	1.64	974	28	2.9	1.39	0.85	(0.51,1.40)	0.5195	
Baseline NT-proBNP [pg/mL] (</>=median² by atrial fibrillation/flutter status)												0.4620
< median	1508	35	2.3	1.08	1477	32	2.2	1.01	0.95	(0.58,1.53)	0.8173	
>= median	1476	49	3.3	1.65	1516	60	4.0	1.97	1.19	(0.81,1.73)	0.3702	
Baseline uric acid [mg/dL] (tertiles³)												0.0640°/ 0.1702
<T1	975	31	3.2	1.53	963	22	2.3	1.10	0.73	(0.42,1.26)	0.2605	
>=T1 and <T2	966	28	2.9	1.38	1032	33	3.2	1.54	1.10	(0.67,1.83)	0.7009	
>=T2	1018	25	2.5	1.19	970	36	3.7	1.78	1.50	(0.90,2.49)	0.1212	
Baseline use of MRA												0.2017
No	1866	65	3.5	1.67	1878	63	3.4	1.61	0.98	(0.69,1.38)	0.8909	
Yes	1125	19	1.7	0.82	1119	29	2.6	1.26	1.51	(0.85,2.70)	0.1596	
Baseline use of ACE-inhibitor, ARB or ARNi												0.7410
No	587	16	2.7	1.35	569	19	3.3	1.61	1.21	(0.62,2.36)	0.5702	
Yes	2404	68	2.8	1.35	2428	73	3.0	1.45	1.07	(0.77,1.49)	0.6892	

* 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, °:Trend test, ^Incidence rate, events per 100 patient years at risk.

Analysis is based on study 1245.110.

^^ Patients with NYHA class I are counted in subgroup NYHA class II.
¹ Baseline SBP median: 132 [mmHg].
² Baseline NT-proBNP median for patients with history of atrial fibrillation or atrial flutter: 1354 [pg/mL].
² Baseline NT-proBNP median for patients without history of atrial fibrillation or atrial flutter: 614 [pg/mL].
³ Baseline uric acid tertile cut-offs for males are T1: 5.9 T2: 7.5 [mg/dL] [rounded].
³ Baseline uric acid tertile cut-offs for females are T1: 5.4 T2: 6.9 [mg/dL] [rounded].

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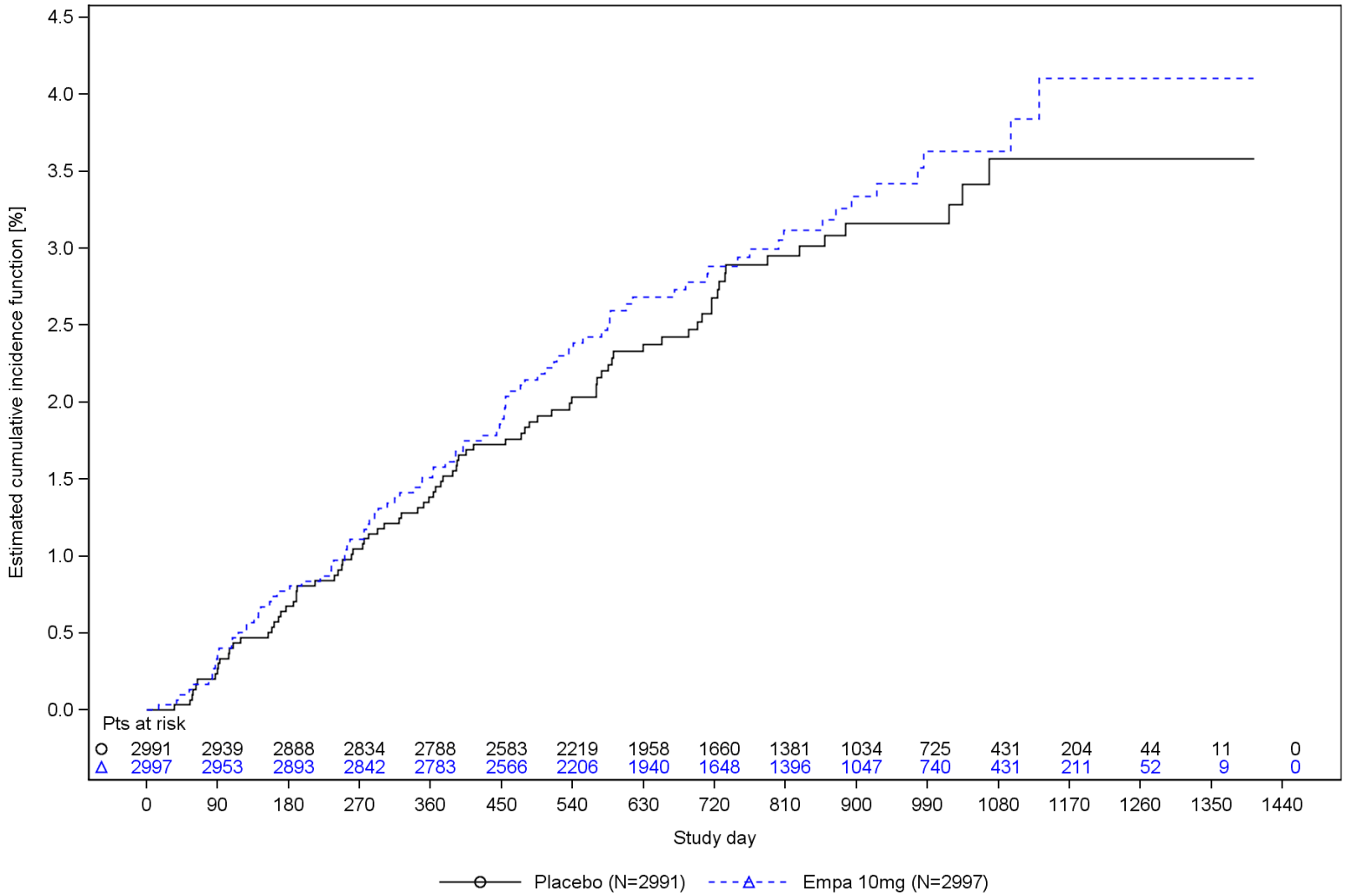

Figure R.1.1.1.15: 1 Time to the first adjudicated stroke (fatal or non-fatal), estimated cumulative incidence function (considering non-stroke death as a competing risk) - RS
Analysis is based on study 1245.110.

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R.1.1.1.16 Time to first adjudicated fatal stroke

Table R.1.1.1.16: 1 Cox regression for time to adjudicated fatal stroke - 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	2991	17	0.6	0.27	2997	16	0.5	0.25	0.95	(0.48,1.89)	0.8925	

* 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.

Analysis is based on study 1245.110.

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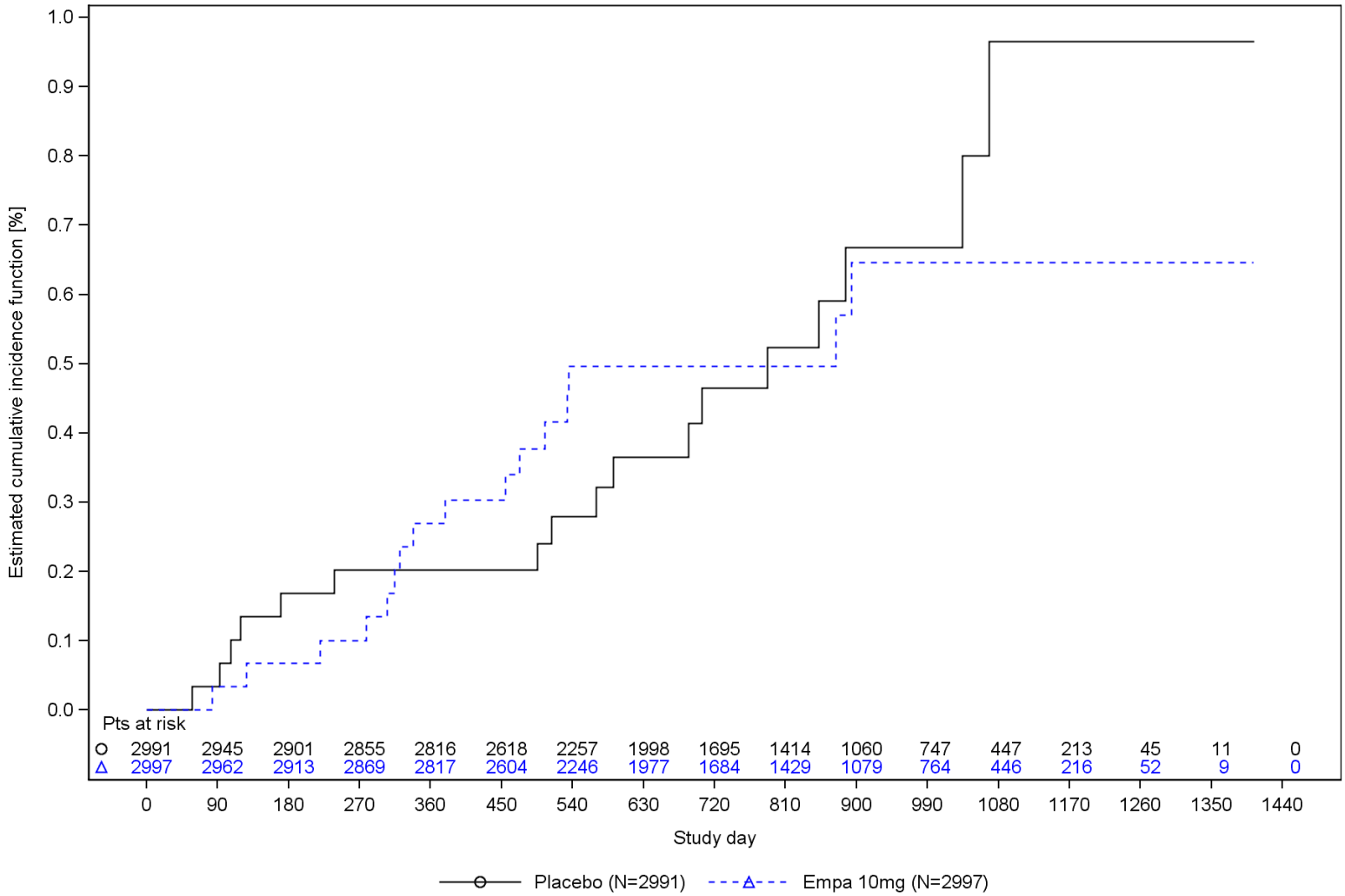

Figure R.1.1.1.16: 1 Time to the first adjudicated fatal stroke, estimated cumulative incidence function (considering non-stroke death as a competing risk) - RS
Analysis is based on study 1245.110.

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R.1.1.1.17 Time to first adjudicated non-fatal stroke

Table R.1.1.1.17: 1 Cox regression for time to first adjudicated non-fatal stroke - 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	2991	69	2.3	1.11	2997	78	2.6	1.25	1.13	(0.82,1.56)	0.4630	

* 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.

Analysis is based on study 1245.110.

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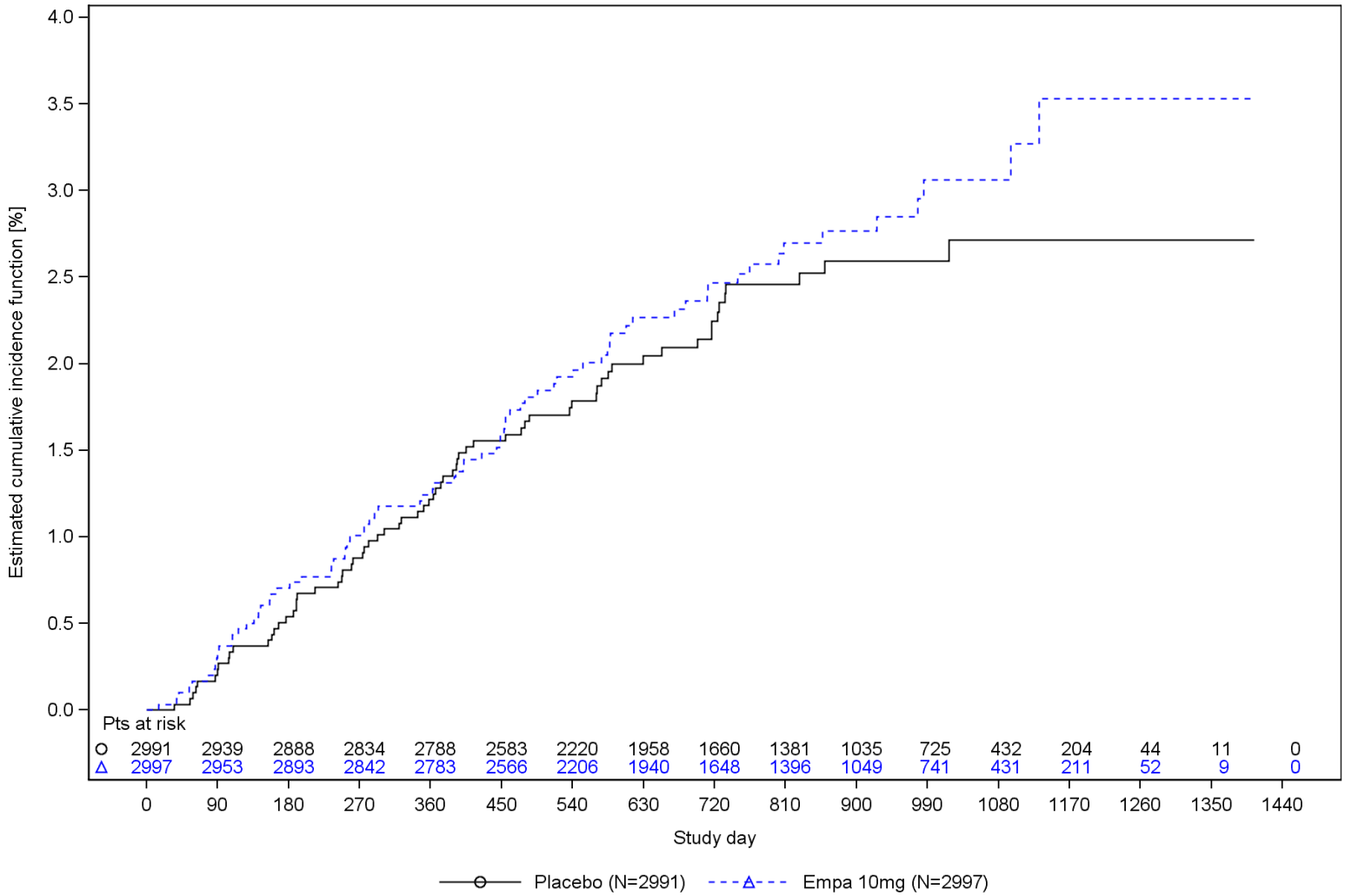

Figure R.1.1.1.17: 1 Time to the first adjudicated non-fatal stroke, estimated cumulative incidence function (considering all cause mortality as a competing risk) - RS
Analysis is based on study 1245.110.

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R.1.1.1.18 Time to first adjudicated TIA

Table R.1.1.1.18: 1 Cox regression for time to first adjudicated TIA 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	2991	27	0.9	0.43	2997	20	0.7	0.32	0.74	(0.41,1.32)	0.3050	
Sex												0.7552
Male	1653	15	0.9	0.43	1659	12	0.7	0.34	0.80	(0.37,1.71)	0.5635	
Female	1338	12	0.9	0.43	1338	8	0.6	0.28	0.66	(0.27,1.62)	0.3686	
Age [years]												0.6466
<70	1084	10	0.9	0.43	1066	6	0.6	0.27	0.61	(0.22,1.67)	0.3363	
>=70	1907	17	0.9	0.43	1931	14	0.7	0.35	0.81	(0.40,1.65)	0.5651	
Region												0.8356
North America	359	7	1.9	0.91	360	6	1.7	0.77	0.85	(0.28,2.52)	0.7646	
Latin America	757	6	0.8	0.40	758	2	0.3	0.13	0.33	(0.07,1.64)	0.1766	
Europe	1343	10	0.7	0.35	1346	10	0.7	0.35	1.00	(0.42,2.40)	0.9994	
Asia	343	1	0.3	0.14	343	0	0	0.00	<0.01		0.9859	
Other	189	3	1.6	0.78	190	2	1.1	0.53	0.68	(0.11,4.08)	0.6749	
OECD member												0.9181
No	847	7	0.8	0.41	868	5	0.6	0.29	0.70	(0.22,2.21)	0.5424	
Yes	2144	20	0.9	0.44	2129	15	0.7	0.33	0.75	(0.38,1.47)	0.4010	
Baseline NYHA												0.7797
II^^	2452	22	0.9	0.43	2435	17	0.7	0.33	0.77	(0.41,1.44)	0.4105	
III/IV	539	5	0.9	0.45	562	3	0.5	0.27	0.61	(0.15,2.57)	0.5031	
Baseline Diabetes Status												0.5362
Diabetic	1472	12	0.8	0.39	1466	7	0.5	0.23	0.59	(0.23,1.49)	0.2649	
Non-Diabetic	1519	15	1.0	0.47	1531	13	0.8	0.40	0.86	(0.41,1.80)	0.6846	

* 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, °:Trend test, ^Incidence rate, events per 100 patient years at risk.

Analysis is based on study 1245.110.

^^ Patients with NYHA class I are counted in subgroup NYHA class II.
[1] Baseline SBP median: 132 [mmHg].
[2] Baseline NT-proBNP median for patients with history of atrial fibrillation or atrial flutter: 1354 [pg/mL].
[2] Baseline NT-proBNP median for patients without history of atrial fibrillation or atrial flutter: 614 [pg/mL].
[3] Baseline uric acid tertile cut-offs for males are T1: 5.9 T2: 7.5 [mg/dL] [rounded].
[3] Baseline uric acid tertile cut-offs for females are T1: 5.4 T2: 6.9 [mg/dL] [rounded].

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Table R.1.1.1.18: 1 Cox regression for time to first adjudicated TIA 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 Diabetes Status												0.6757°/ 0.8087
Diabetic	1472	12	0.8	0.39	1466	7	0.5	0.23	0.59	(0.23,1.49)	0.2649	
Pre-Diabetes	979	10	1.0	0.49	1001	9	0.9	0.43	0.90	(0.37,2.23)	0.8261	
Normal (no pre-diabetes)	540	5	0.9	0.45	530	4	0.8	0.35	0.77	(0.21,2.86)	0.6944	
Baseline BMI [kg/m²]												0.6457
<30	1642	15	0.9	0.44	1654	10	0.6	0.29	0.65	(0.29,1.45)	0.2905	
>=30	1349	12	0.9	0.42	1343	10	0.7	0.35	0.85	(0.37,1.97)	0.7094	
Baseline eGFR (CKD-EPI) [mL/min/1.73m²]												0.8555
>=60	1505	13	0.9	0.41	1493	9	0.6	0.28	0.70	(0.30,1.63)	0.4053	
<60	1484	14	0.9	0.46	1504	11	0.7	0.35	0.78	(0.35,1.71)	0.5300	
History of HHF (in the last 12 months)												0.2394
No	2321	23	1.0	0.48	2298	14	0.6	0.29	0.61	(0.32,1.19)	0.1493	
Yes	670	4	0.6	0.28	699	6	0.9	0.41	1.45	(0.41,5.14)	0.5670	
Baseline SBP (</>= median¹)												0.8783
< median	1474	15	1.0	0.49	1496	11	0.7	0.35	0.71	(0.32,1.54)	0.3827	
>= median	1517	12	0.8	0.37	1501	9	0.6	0.28	0.77	(0.33,1.84)	0.5621	
History of atrial fibrillation or atrial flutter												0.3086
No	1427	15	1.1	0.51	1417	8	0.6	0.27	0.54	(0.23,1.27)	0.1558	
Yes	1559	12	0.8	0.37	1576	12	0.8	0.36	0.99	(0.44,2.20)	0.9770	

* 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, °:Trend test, ^Incidence rate, events per 100 patient years at risk.

Analysis is based on study 1245.110.

^^ Patients with NYHA class I are counted in subgroup NYHA class II.
¹ Baseline SBP median: 132 [mmHg].
² Baseline NT-proBNP median for patients with history of atrial fibrillation or atrial flutter: 1354 [pg/mL].
² Baseline NT-proBNP median for patients without history of atrial fibrillation or atrial flutter: 614 [pg/mL].
³ Baseline uric acid tertile cut-offs for males are T1: 5.9 T2: 7.5 [mg/dL] [rounded].
³ Baseline uric acid tertile cut-offs for females are T1: 5.4 T2: 6.9 [mg/dL] [rounded].

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Table R.1.1.1.18: 1 Cox regression for time to first adjudicated TIA 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 LVEF [%]												0.7650
< 50	988	9	0.9	0.44	995	6	0.6	0.29	0.65	(0.23,1.82)	0.4117	
>= 50	2003	18	0.9	0.43	2002	14	0.7	0.33	0.78	(0.39,1.58)	0.4962	
Baseline LVEF [%]												0.9541°/ 0.7954
<50	988	9	0.9	0.44	995	6	0.6	0.29	0.65	(0.23,1.82)	0.4116	
50 to <60	1030	11	1.1	0.51	1028	10	1.0	0.46	0.92	(0.39,2.16)	0.8415	
>=60	973	7	0.7	0.34	974	4	0.4	0.20	0.58	(0.17,1.97)	0.3804	
Baseline NT-proBNP [pg/mL] (</>=median² by atrial fibrillation/flutter status)												0.6277
< median	1508	13	0.9	0.40	1477	11	0.7	0.34	0.85	(0.38,1.89)	0.6872	
>= median	1476	14	0.9	0.47	1516	9	0.6	0.29	0.64	(0.28,1.47)	0.2900	
Baseline uric acid [mg/dL] (tertiles³)												0.7283°/ 0.9416
<T1	975	9	0.9	0.44	963	6	0.6	0.30	0.64	(0.23,1.81)	0.4026	
>=T1 and <T2	966	8	0.8	0.39	1032	6	0.6	0.28	0.72	(0.25,2.08)	0.5469	
>=T2	1018	9	0.9	0.43	970	7	0.7	0.34	0.83	(0.31,2.22)	0.7078	
Baseline use of MRA												0.8252
No	1866	18	1.0	0.46	1878	13	0.7	0.33	0.70	(0.35,1.44)	0.3363	
Yes	1125	9	0.8	0.39	1119	7	0.6	0.30	0.81	(0.30,2.17)	0.6732	
Baseline use of ACE-inhibitor, ARB or ARNi												0.0880
No	587	4	0.7	0.33	569	7	1.2	0.58	1.88	(0.55,6.42)	0.3148	
Yes	2404	23	1.0	0.45	2428	13	0.5	0.26	0.55	(0.28,1.09)	0.0876	

* 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, °:Trend test, ^Incidence rate, events per 100 patient years at risk.

Analysis is based on study 1245.110.

^^ Patients with NYHA class I are counted in subgroup NYHA class II.
¹ Baseline SBP median: 132 [mmHg].
² Baseline NT-proBNP median for patients with history of atrial fibrillation or atrial flutter: 1354 [pg/mL].
² Baseline NT-proBNP median for patients without history of atrial fibrillation or atrial flutter: 614 [pg/mL].
³ Baseline uric acid tertile cut-offs for males are T1: 5.9 T2: 7.5 [mg/dL] [rounded].
³ Baseline uric acid tertile cut-offs for females are T1: 5.4 T2: 6.9 [mg/dL] [rounded].

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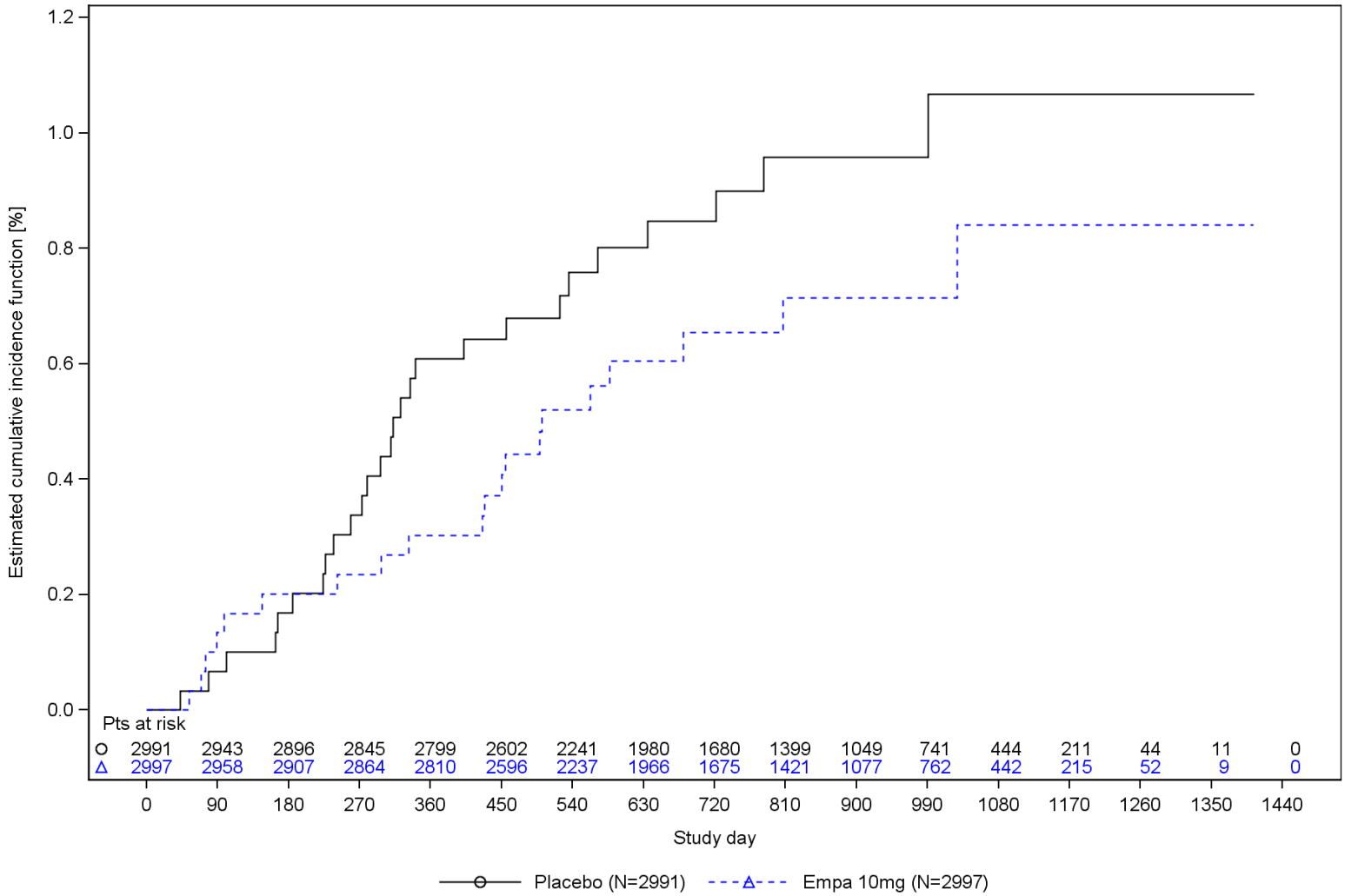

Figure R.1.1.1.18: 1 Time to the first adjudicated TIA, estimated cumulative incidence function (considering all cause mortality as a competing risk) - RS
Analysis is based on study 1245.110.

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R.1.1.1.19 Time to new onset of atrial fibrillation

Table R.1.1.1.19: 1 Cox regression for time to new onset of atrial fibrillation 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	1477	119	8.1	4.04	1454	116	8.0	3.95	1.00	(0.77,1.29)	0.9790	
Sex												0.9522
Male	811	68	8.4	4.21	815	68	8.3	4.15	1.00	(0.72,1.40)	0.9850	
Female	666	51	7.7	3.83	639	48	7.5	3.69	0.99	(0.67,1.47)	0.9500	
Age [years]												0.9107
<70	670	34	5.1	2.48	682	34	5.0	2.41	1.01	(0.63,1.62)	0.9795	
>=70	807	85	10.5	5.40	772	82	10.6	5.37	0.97	(0.72,1.32)	0.8665	
Region												0.1082
North America	161	9	5.6	2.66	153	15	9.8	4.75	1.77	(0.77,4.05)	0.1755	
Latin America	529	17	3.2	1.65	546	26	4.8	2.42	1.44	(0.78,2.66)	0.2412	
Europe	526	71	13.5	6.76	527	60	11.4	5.49	0.83	(0.59,1.18)	0.2987	
Asia	152	13	8.6	4.21	126	13	10.3	4.98	1.27	(0.59,2.75)	0.5398	
Other	109	9	8.3	4.12	102	2	2.0	1.04	0.26	(0.06,1.22)	0.0874	
OECD member												0.2453
No	557	30	5.4	2.74	565	23	4.1	2.08	0.75	(0.44,1.29)	0.3022	
Yes	920	89	9.7	4.80	889	93	10.5	5.07	1.08	(0.81,1.45)	0.5919	
Baseline NYHA												0.6457
II^^	1250	95	7.6	3.80	1208	89	7.4	3.59	0.96	(0.72,1.29)	0.7904	
III/IV	227	24	10.6	5.40	246	27	11.0	5.85	1.11	(0.64,1.93)	0.7035	
Baseline Diabetes Status												0.9813
Diabetic	805	59	7.3	3.64	791	56	7.1	3.52	0.99	(0.69,1.43)	0.9630	
Non-Diabetic	672	60	8.9	4.52	663	60	9.0	4.45	1.00	(0.70,1.43)	0.9889	

* 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, °:Trend test, ^Incidence rate, events per 100 patient years at risk.

Analysis is based on study 1245.110.
Patients included in analysis are those with neither history of atrial fibrillation (AF) nor pre-treatment ECG indicating AF.
^^ Patients with NYHA class I are counted in subgroup NYHA class II.
[1] Baseline SBP median: 132 [mmHg].
[2] Baseline NT-proBNP median for patients with history of atrial fibrillation or atrial flutter: 1354 [pg/mL].
[2] Baseline NT-proBNP median for patients without history of atrial fibrillation or atrial flutter: 614 [pg/mL].
[3] Baseline uric acid tertile cut-offs for males are T1: 5.9 T2: 7.5 [mg/dL] [rounded].
[3] Baseline uric acid tertile cut-offs for females are T1: 5.4 T2: 6.9 [mg/dL] [rounded].

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Table R.1.1.1.19: 1 Cox regression for time to new onset of atrial fibrillation 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 Diabetes Status												0.8798°/ 0.9665
Diabetic	805	59	7.3	3.64	791	56	7.1	3.52	0.99	(0.69,1.43)	0.9658	
Pre-Diabetes	431	35	8.1	4.07	414	34	8.2	3.99	0.96	(0.60,1.54)	0.8693	
Normal (no pre-diabetes)	241	25	10.4	5.36	249	26	10.4	5.23	1.06	(0.61,1.83)	0.8420	
Baseline BMI [kg/m²]												0.9964
<30	832	61	7.3	3.67	826	60	7.3	3.59	1.00	(0.70,1.43)	0.9913	
>=30	645	58	9.0	4.52	628	56	8.9	4.41	1.00	(0.69,1.45)	0.9965	
Baseline eGFR (CKD-EPI) [mL/min/1.73m²]												0.5364
>=60	801	57	7.1	3.52	810	53	6.5	3.16	0.91	(0.63,1.32)	0.6202	
<60	674	62	9.2	4.69	644	63	9.8	4.99	1.07	(0.75,1.52)	0.7071	
History of HHF (in the last 12 months)												0.4370
No	1166	93	8.0	4.02	1172	87	7.4	3.67	0.94	(0.70,1.26)	0.6938	
Yes	311	26	8.4	4.12	282	29	10.3	5.08	1.20	(0.71,2.04)	0.5024	
Baseline SBP (</>= median¹)												0.3831
< median	685	46	6.7	3.37	688	54	7.8	3.94	1.14	(0.77,1.69)	0.5162	
>= median	792	73	9.2	4.61	766	62	8.1	3.95	0.90	(0.64,1.27)	0.5598	
History of atrial fibrillation or atrial flutter												0.4863
No	1427	106	7.4	3.69	1417	108	7.6	3.77	1.04	(0.80,1.36)	0.7680	
Yes	45	12	26.7	17.71	33	8	24.2	12.78	0.75	(0.30,1.84)	0.5231	

* 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, °:Trend test, ^Incidence rate, events per 100 patient years at risk.

Analysis is based on study 1245.110.
Patients included in analysis are those with neither history of atrial fibrillation (AF) nor pre-treatment ECG indicating AF.
^^ Patients with NYHA class I are counted in subgroup NYHA class II.
¹ Baseline SBP median: 132 [mmHg].
² Baseline NT-proBNP median for patients with history of atrial fibrillation or atrial flutter: 1354 [pg/mL].
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³ Baseline uric acid tertile cut-offs for males are T1: 5.9 T2: 7.5 [mg/dL] [rounded].
³ Baseline uric acid tertile cut-offs for females are T1: 5.4 T2: 6.9 [mg/dL] [rounded].

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Table R.1.1.1.19: 1 Cox regression for time to new onset of atrial fibrillation 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 LVEF [%]												0.1183
< 50	549	38	6.9	3.40	548	28	5.1	2.47	0.72	(0.44,1.18)	0.1899	
>= 50	928	81	8.7	4.43	906	88	9.7	4.87	1.14	(0.84,1.54)	0.3958	
Baseline LVEF [%]												0.1672°/ 0.2966
<50	549	38	6.9	3.40	548	28	5.1	2.47	0.72	(0.44,1.17)	0.1854	
50 to <60	455	34	7.5	3.73	462	36	7.8	3.86	1.13	(0.71,1.81)	0.6141	
>=60	473	47	9.9	5.13	444	52	11.7	5.95	1.14	(0.77,1.69)	0.5164	
Baseline NT-proBNP [pg/mL] (</>=median² by atrial fibrillation/flutter status)												0.5526
< median	759	50	6.6	3.16	714	50	7.0	3.29	1.08	(0.73,1.60)	0.6968	
>= median	711	68	9.6	5.03	736	66	9.0	4.68	0.92	(0.66,1.30)	0.6473	
Baseline uric acid [mg/dL] (tertiles³)												0.3826°/ 0.2118
<T1	516	41	7.9	3.96	521	40	7.7	3.80	0.99	(0.64,1.54)	0.9813	
>=T1 and <T2	491	43	8.8	4.37	494	34	6.9	3.37	0.75	(0.48,1.17)	0.2068	
>=T2	453	35	7.7	3.91	418	41	9.8	4.88	1.33	(0.84,2.09)	0.2191	
Baseline use of MRA												0.6123
No	926	83	9.0	4.44	935	86	9.2	4.54	1.04	(0.77,1.40)	0.8228	
Yes	551	36	6.5	3.34	519	30	5.8	2.87	0.89	(0.55,1.45)	0.6472	
Baseline use of ACE-inhibitor, ARB or ARNi												0.4018
No	232	20	8.6	4.48	206	22	10.7	5.34	1.26	(0.69,2.32)	0.4503	
Yes	1245	99	8.0	3.96	1248	94	7.5	3.72	0.95	(0.72,1.26)	0.7157	

* 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, °:Trend test, ^Incidence rate, events per 100 patient years at risk.

Analysis is based on study 1245.110.
Patients included in analysis are those with neither history of atrial fibrillation (AF) nor pre-treatment ECG indicating AF.
^^ Patients with NYHA class I are counted in subgroup NYHA class II.
¹ Baseline SBP median: 132 [mmHg].
² Baseline NT-proBNP median for patients with history of atrial fibrillation or atrial flutter: 1354 [pg/mL].
² Baseline NT-proBNP median for patients without history of atrial fibrillation or atrial flutter: 614 [pg/mL].
³ Baseline uric acid tertile cut-offs for males are T1: 5.9 T2: 7.5 [mg/dL] [rounded].
³ Baseline uric acid tertile cut-offs for females are T1: 5.4 T2: 6.9 [mg/dL] [rounded].

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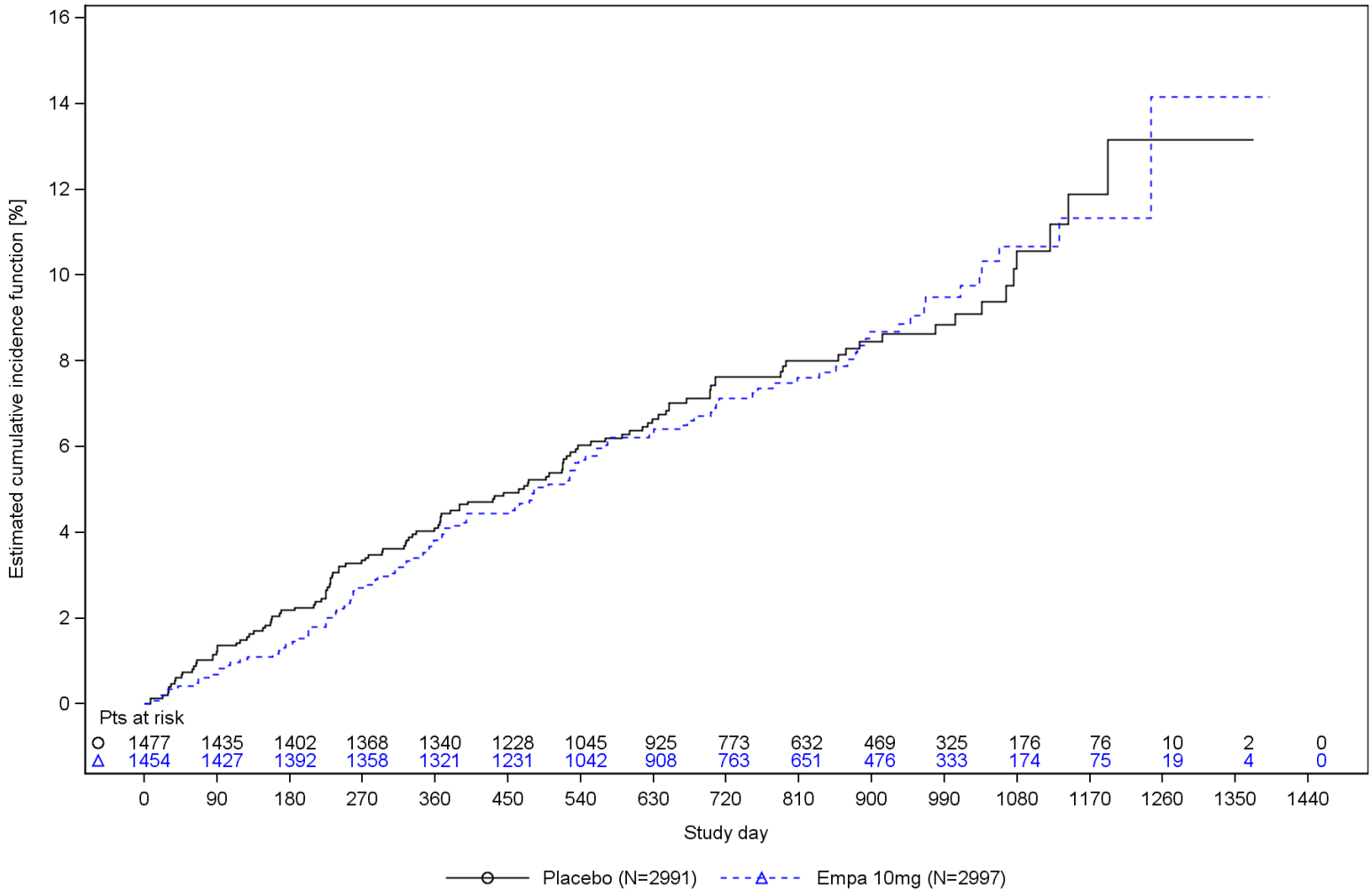

Figure R.1.1.1.19: 1 Time to new onset of atrial fibrillation until the end of planned treatment period, estimated cumulative incidence function (considering all cause mortality as a competing risk) - RS

Analysis is based on study 1245.110.

Patients included in analysis are those with neither history of atrial fibrillation (AF) nor pre-treatment ECG indicating AF.

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R.1.1.1.20 Time to composite renal endpoint

Table R.1.1.1.20: 1 Cox regression for time to first composite renal 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	2991	112	3.7	2.23	2997	108	3.6	2.13	0.95	(0.73,1.24)	0.7243	
Sex												0.2695
Male	1653	51	3.1	1.82	1659	57	3.4	2.01	1.11	(0.76,1.62)	0.5880	
Female	1338	61	4.6	2.76	1338	51	3.8	2.27	0.82	(0.57,1.19)	0.3057	
Age [years]												0.5287
<70	1084	42	3.9	2.25	1066	43	4.0	2.37	1.07	(0.70,1.63)	0.7682	
>=70	1907	70	3.7	2.22	1931	65	3.4	1.99	0.90	(0.64,1.25)	0.5207	
Region												0.3468
North America	359	17	4.7	2.97	360	11	3.1	1.83	0.60	(0.28,1.28)	0.1857	
Latin America	757	30	4.0	2.57	758	38	5.0	3.21	1.25	(0.77,2.01)	0.3658	
Europe	1343	35	2.6	1.48	1346	25	1.9	1.05	0.71	(0.43,1.19)	0.1964	
Asia	343	17	5.0	2.74	343	21	6.1	3.37	1.19	(0.63,2.26)	0.5900	
Other	189	13	6.9	4.36	190	13	6.8	4.51	1.09	(0.50,2.35)	0.8276	
OECD member												0.3691
No	847	37	4.4	2.82	868	43	5.0	3.21	1.11	(0.71,1.72)	0.6489	
Yes	2144	75	3.5	2.02	2129	65	3.1	1.74	0.86	(0.62,1.20)	0.3749	
Baseline NYHA												0.2576
II^^	2452	88	3.6	2.12	2435	76	3.1	1.80	0.87	(0.64,1.18)	0.3646	
III/IV	539	24	4.5	2.76	562	32	5.7	3.75	1.24	(0.73,2.10)	0.4333	
Baseline Diabetes Status												0.6238
Diabetic	1472	74	5.0	3.04	1466	75	5.1	3.09	1.00	(0.72,1.38)	0.9900	
Non-Diabetic	1519	38	2.5	1.47	1531	33	2.2	1.24	0.87	(0.54,1.38)	0.5456	

* 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, °:Trend test, ^Incidence rate, events per 100 patient years at risk.

Analysis is based on study 1245.110.
Composite renal endpoint is defined as chronic dialysis or renal transplant or sustained reduction of >=40% eGFR (CKD-EPI)cr or sustained eGFR (CKD-EPI)cr <15 [mL/min/1.73m²] (< 10 [mL/min/1.73m²] for patients with eGFR (CKD-EPI)cr < 30 [mL/min/1.73m²] at baseline).
Dialysis is regarded as chronic if the frequency of dialysis is twice or more per week for at least 90 days.
^^ Patients with NYHA class I are counted in subgroup NYHA class II.
[1] Baseline SBP median: 132 [mmHg].
[2] Baseline NT-proBNP median for patients with history of atrial fibrillation or atrial flutter: 1354, median for patients without history: 614 [pg/mL].
[3] Baseline uric acid tertile cut-offs for males are T1: 5.9 T2: 7.5, tertile cut-offs for females are T1: 5.4 T2: 6.9 [mg/dL] [rounded].

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Table R.1.1.1.20: 1 Cox regression for time to first composite renal event 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 Diabetes Status												0.6538°/ 0.8870
Diabetic	1472	74	5.0	3.04	1466	75	5.1	3.09	1.00	(0.72,1.38)	0.9908	
Pre-Diabetes	979	30	3.1	1.78	1001	26	2.6	1.51	0.87	(0.51,1.46)	0.5896	
Normal (no pre-diabetes)	540	8	1.5	0.89	530	7	1.3	0.75	0.87	(0.32,2.40)	0.7880	
Baseline BMI [kg/m²]												0.5308
<30	1642	58	3.5	2.14	1654	51	3.1	1.82	0.88	(0.60,1.28)	0.4881	
>=30	1349	54	4.0	2.34	1343	57	4.2	2.51	1.04	(0.71,1.51)	0.8486	
Baseline eGFR (CKD-EPI) [mL/min/1.73m²]												0.8272
>=60	1505	45	3.0	1.73	1493	41	2.7	1.58	0.92	(0.60,1.41)	0.7082	
<60	1484	67	4.5	2.78	1504	67	4.5	2.70	0.98	(0.70,1.38)	0.9059	
History of HHF (in the last 12 months)												0.3831
No	2321	80	3.4	2.05	2298	82	3.6	2.09	1.02	(0.75,1.39)	0.8881	
Yes	670	32	4.8	2.87	699	26	3.7	2.25	0.78	(0.46,1.31)	0.3516	
Baseline SBP (</>= median¹)												0.5990
< median	1474	46	3.1	1.86	1496	39	2.6	1.55	0.87	(0.56,1.33)	0.5078	
>= median	1517	66	4.4	2.59	1501	69	4.6	2.69	1.00	(0.71,1.40)	0.9912	
History of atrial fibrillation or atrial flutter												0.5997
No	1427	60	4.2	2.56	1417	61	4.3	2.55	1.03	(0.72,1.47)	0.8834	
Yes	1559	51	3.3	1.91	1576	47	3.0	1.75	0.89	(0.60,1.32)	0.5655	

* 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, °:Trend test, ^Incidence rate, events per 100 patient years at risk.

Analysis is based on study 1245.110.
Composite renal endpoint is defined as chronic dialysis or renal transplant or sustained reduction of >=40% eGFR (CKD-EPI)cr or sustained eGFR (CKD-EPI)cr <15 [mL/min/1.73m²] (< 10 [mL/min/1.73m²] for patients with eGFR (CKD-EPI)cr < 30 [mL/min/1.73m²] at baseline).
Dialysis is regarded as chronic if the frequency of dialysis is twice or more per week for at least 90 days.
^^ Patients with NYHA class I are counted in subgroup NYHA class II.
¹ Baseline SBP median: 132 [mmHg].
² Baseline NT-proBNP median for patients with history of atrial fibrillation or atrial flutter: 1354, median for patients without history: 614 [pg/mL].
³ Baseline uric acid tertile cut-offs for males are T1: 5.9 T2: 7.5, tertile cut-offs for females are T1: 5.4 T2: 6.9 [mg/dL] [rounded].

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Table R.1.1.1.20: 1 Cox regression for time to first composite renal event 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 LVEF [%]												0.6573
< 50	988	35	3.5	2.11	995	30	3.0	1.79	0.87	(0.53,1.42)	0.5735	
>= 50	2003	77	3.8	2.29	2002	78	3.9	2.29	0.99	(0.72,1.36)	0.9573	
Baseline LVEF [%]												0.8073°/ 0.8782
<50	988	35	3.5	2.11	995	30	3.0	1.79	0.87	(0.53,1.42)	0.5730	
50 to <60	1030	39	3.8	2.25	1028	39	3.8	2.23	1.03	(0.66,1.61)	0.8899	
>=60	973	38	3.9	2.33	974	39	4.0	2.36	0.95	(0.61,1.49)	0.8395	
Baseline NT-proBNP [pg/mL] (</>=median² by atrial fibrillation/flutter status)												0.8080
< median	1508	41	2.7	1.54	1477	38	2.6	1.45	0.99	(0.63,1.53)	0.9520	
>= median	1476	70	4.7	2.98	1516	70	4.6	2.86	0.92	(0.66,1.28)	0.6278	
Baseline uric acid [mg/dL] (tertiles³)												0.8907°/ 0.9816
<T1	975	34	3.5	2.08	963	31	3.2	1.87	0.92	(0.56,1.49)	0.7275	
>=T1 and <T2	966	32	3.3	1.92	1032	32	3.1	1.84	0.98	(0.60,1.60)	0.9320	
>=T2	1018	45	4.4	2.68	970	44	4.5	2.69	0.96	(0.63,1.46)	0.8539	
Baseline use of MRA												0.9521
No	1866	64	3.4	2.04	1878	64	3.4	1.98	0.96	(0.68,1.36)	0.8285	
Yes	1125	48	4.3	2.55	1119	44	3.9	2.38	0.95	(0.63,1.43)	0.7933	
Baseline use of ACE-inhibitor, ARB or ARNi												0.9699
No	587	19	3.2	2.05	569	20	3.5	2.07	0.97	(0.52,1.81)	0.9152	
Yes	2404	93	3.9	2.27	2428	88	3.6	2.14	0.95	(0.71,1.28)	0.7497	

* 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, °:Trend test, ^Incidence rate, events per 100 patient years at risk.

Analysis is based on study 1245.110.
Composite renal endpoint is defined as chronic dialysis or renal transplant or sustained reduction of >=40% eGFR (CKD-EPI)cr or sustained eGFR (CKD-EPI)cr <15 [mL/min/1.73m²] (< 10 [mL/min/1.73m²] for patients with eGFR (CKD-EPI)cr < 30 [mL/min/1.73m²] at baseline).
Dialysis is regarded as chronic if the frequency of dialysis is twice or more per week for at least 90 days.
^^ Patients with NYHA class I are counted in subgroup NYHA class II.
¹ Baseline SBP median: 132 [mmHg].
² Baseline NT-proBNP median for patients with history of atrial fibrillation or atrial flutter: 1354, median for patients without history: 614 [pg/mL].
³ Baseline uric acid tertile cut-offs for males are T1: 5.9 T2: 7.5, tertile cut-offs for females are T1: 5.4 T2: 6.9 [mg/dL] [rounded].

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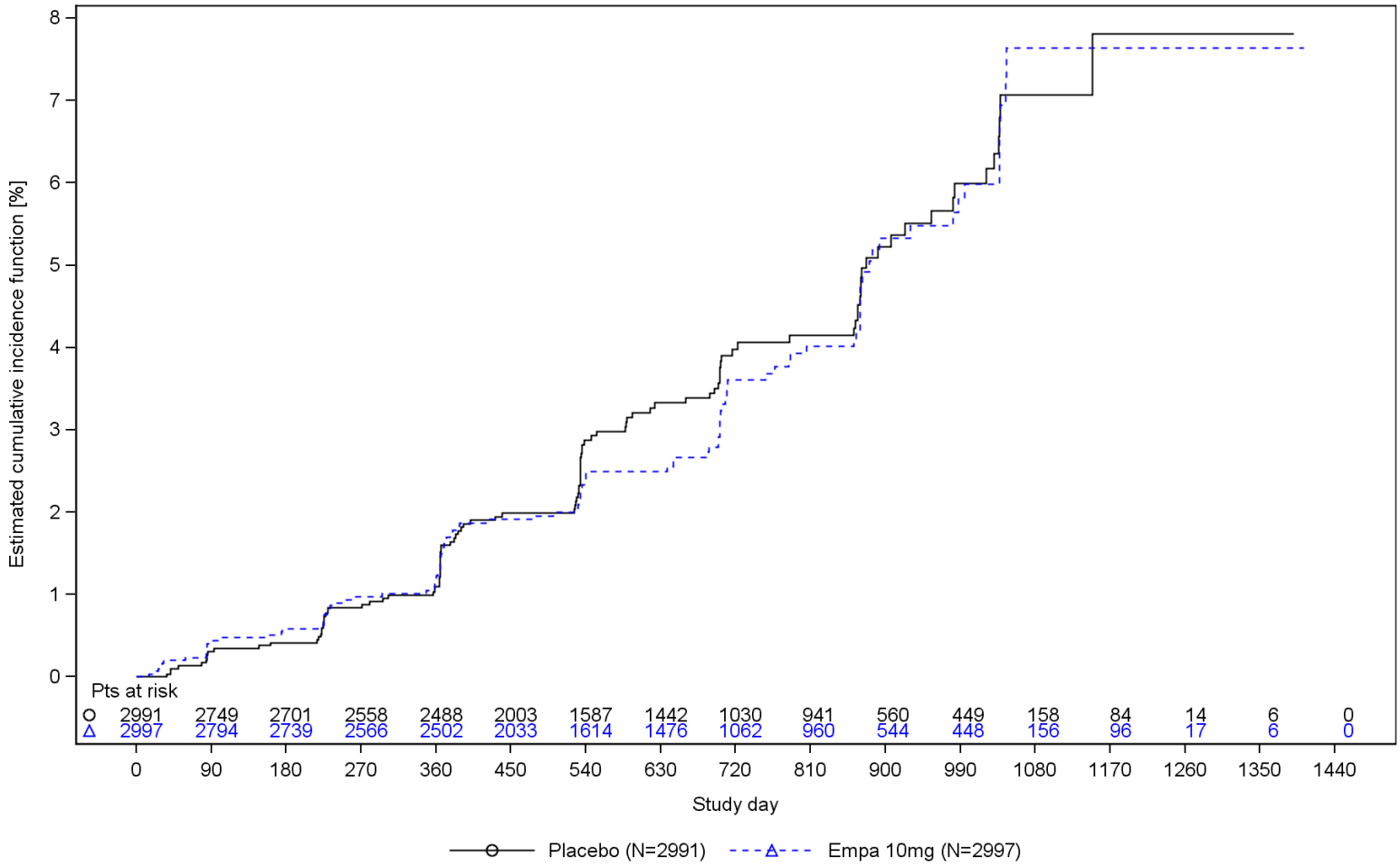

Figure R.1.1.1.20: 1 Time to first composite renal endpoint, estimated cumulative incidence function (considering all cause mortality as a competing risk) - RS

Analysis is based on study 1245.110.

Composite renal endpoint is defined as chronic dialysis or renal transplant or sustained reduction of >=40% eGFR (CKD-EPI)cr or sustained eGFR (CKD-EPI)cr <15 [mL/min/1.73m²] (< 10 [mL/min/1.73m²] for patients with eGFR (CKD-EPI)cr < 30 [mL/min/1.73m²] at baseline).

Dialysis is regarded as chronic if the frequency of dialysis is twice or more per week for at least 90 days.

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R.1.1.1.21 Time to first renal endpoint component chronic dialysis

Table R.1.1.1.21: 1 Cox regression for time to first renal endpoint component chronic dialysis - 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	2991	11	0.4	0.18	2997	11	0.4	0.17	0.92	(0.40,2.13)	0.8487	

* 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.

Analysis is based on study 1245.110.

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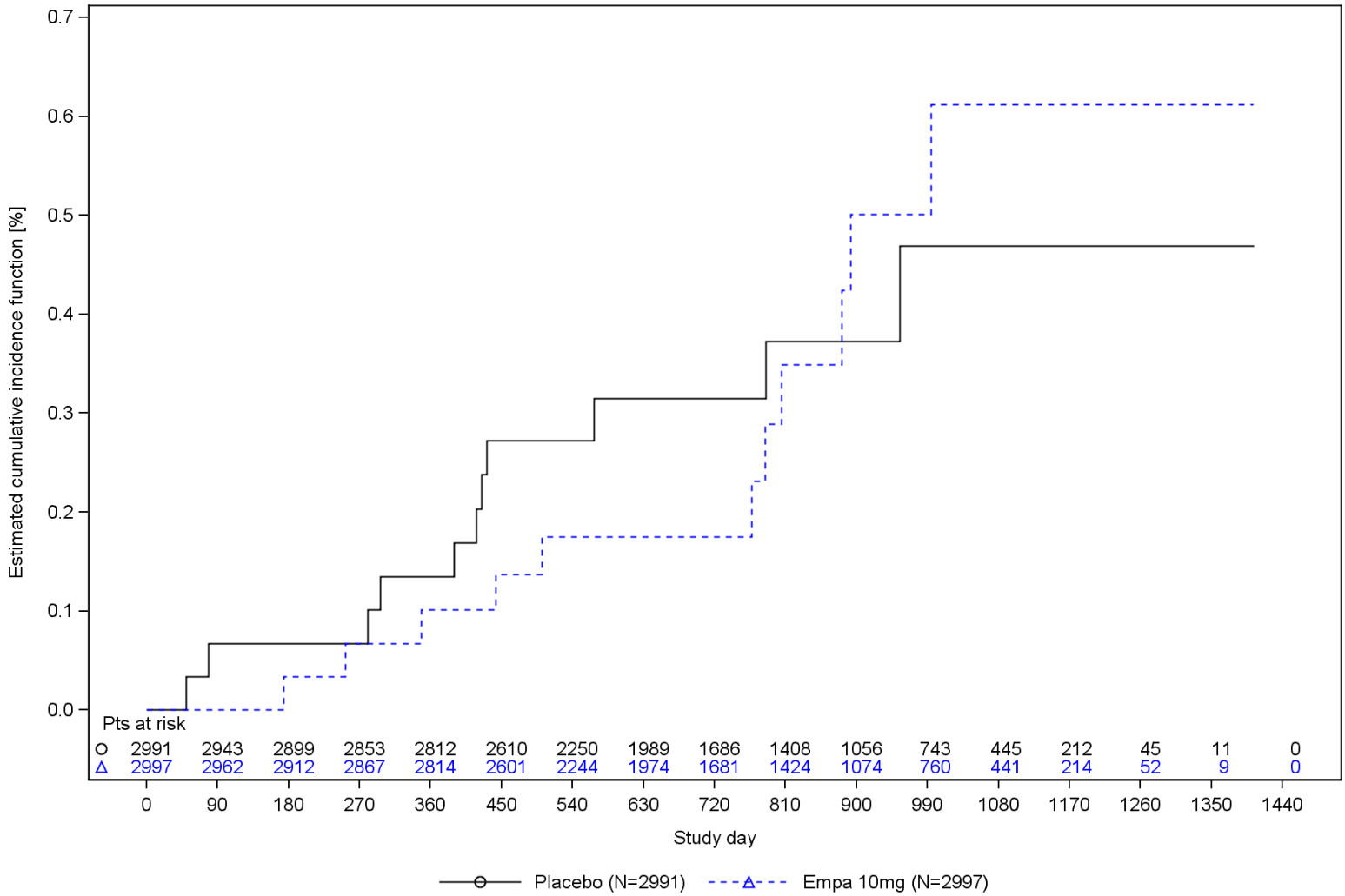

Figure R.1.1.1.21: 1 Time to first renal endpoint component chronic dialysis, estimated cumulative incidence function (considering all cause mortality as a competing risk) - RS
Analysis is based on study 1245.110.

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R.1.1.1.22 Time to first renal endpoint component renal transplant

Table R.1.1.1.22: 1 Cox regression for time to first renal endpoint component renal transplant - 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	2991	0	0	0.00	2997	0	0	0.00	1.00	(1.00,1.00)		

* 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.

Analysis is based on study 1245.110.

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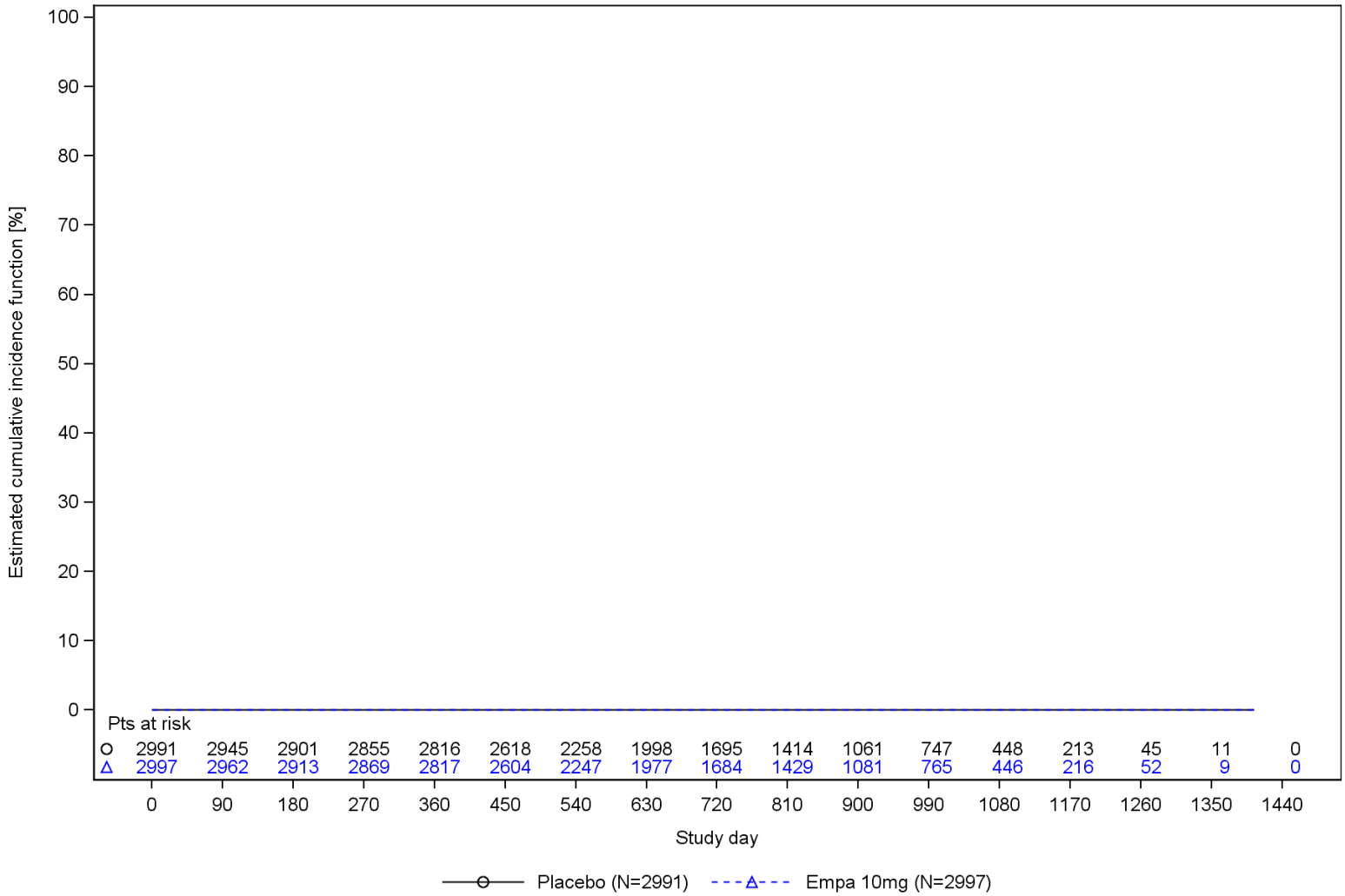

Figure R.1.1.1.22: 1 Time to first renal endpoint component renal transplant, estimated cumulative incidence function (considering all cause mortality as a competing risk) - RS
Analysis is based on study 1245.110.

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R.1.1.1.23 Time to first renal endpoint component sustained eGFR reduction >=40%

Table R.1.1.1.23: 1 Cox regression for time to first renal endpoint component sustained eGFR reduction >=40% - 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	2991	107	3.6	2.13	2997	99	3.3	1.95	0.92	(0.70,1.21)	0.5467	

* 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.

Analysis is based on study 1245.110.

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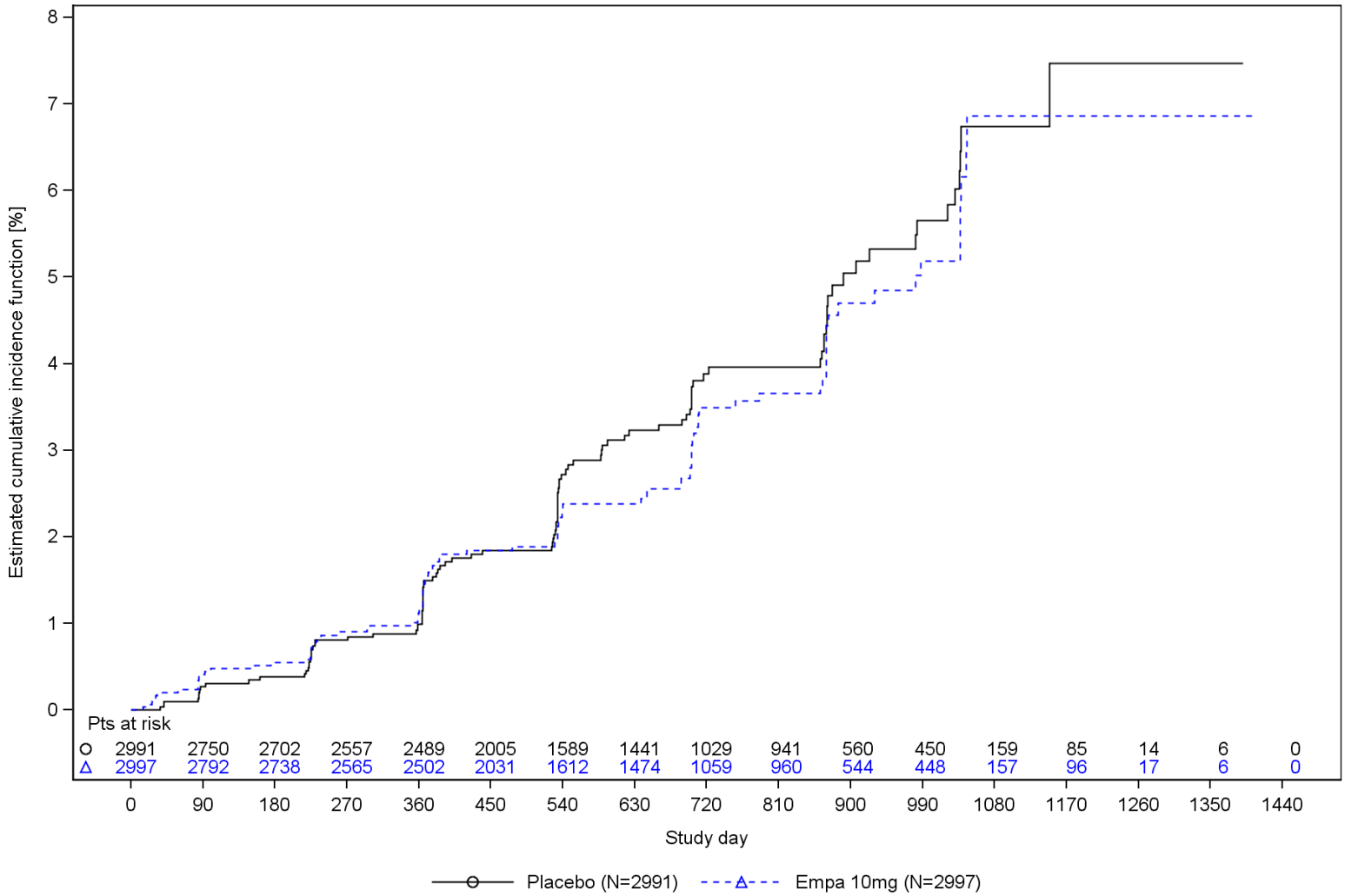

Figure R.1.1.1.23: 1 Time to first renal endpoint component sustained eGFR reduction >=40%, estimated cumulative incidence function (considering all cause mortality as a competing risk) - RS
Analysis is based on study 1245.110.

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R.1.1.1.24 Time to first renal endpoint component sustained eGFR <15 (if baseline eGFR >=30) / eGFR <10 (if baseline eGFR <30)

Table R.1.1.1.24: 1 Cox regression for time to first renal endpoint component sustained eGFR <15 (if baseline eGFR >=30) / eGFR <10 (if baseline eGFR <30) - 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	2991	8	0.3	0.16	2997	10	0.3	0.19	1.01	(0.39,2.61)	0.9901	

* 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.

Analysis is based on study 1245.110.

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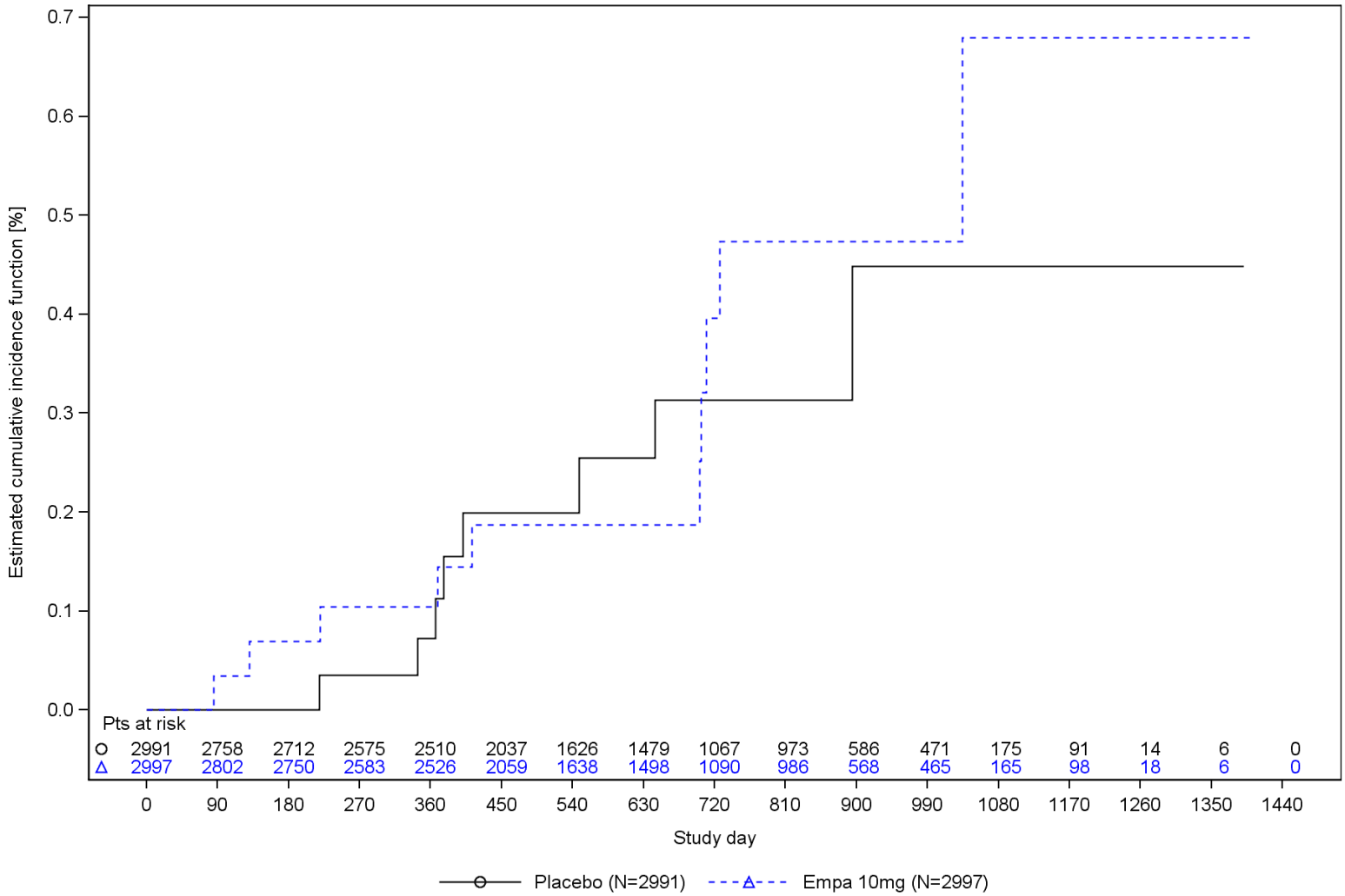

Figure R.1.1.1.24: 1 Time to first renal endpoint component sustained eGFR <15 (if baseline eGFR >=30) / eGFR <10 (if baseline eGFR < 30), estimated cumulative incidence function (considering all cause mortality as a competing risk) - RS
Analysis is based on study 1245.110.

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R.1.1.1.25 Time to first acute kidney injury

Table R.1.1.1.25: 1 Cox regression for time to first 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	2991	131	4.4	2.12	2997	97	3.2	1.56	0.73	(0.56,0.95)	0.0193	
Sex												0.4960
Male	1653	71	4.3	2.08	1659	50	3.0	1.45	0.67	(0.47,0.96)	0.0306	
Female	1338	60	4.5	2.18	1338	47	3.5	1.69	0.81	(0.55,1.18)	0.2669	
Age [years]												0.6165
<70	1084	44	4.1	1.93	1066	29	2.7	1.30	0.66	(0.41,1.06)	0.0849	
>=70	1907	87	4.6	2.23	1931	68	3.5	1.70	0.77	(0.56,1.05)	0.0987	
Region												0.7139
North America	359	49	13.6	6.82	360	39	10.8	5.23	0.77	(0.51,1.18)	0.2268	
Latin America	757	23	3.0	1.55	758	20	2.6	1.33	0.87	(0.48,1.58)	0.6367	
Europe	1343	36	2.7	1.26	1346	22	1.6	0.77	0.60	(0.35,1.03)	0.0621	
Asia	343	9	2.6	1.23	343	4	1.2	0.54	0.41	(0.13,1.33)	0.1386	
Other	189	14	7.4	3.67	190	12	6.3	3.27	0.92	(0.42,1.98)	0.8244	
OECD member												0.9119
No	847	32	3.8	1.90	868	26	3.0	1.51	0.74	(0.44,1.25)	0.2591	
Yes	2144	99	4.6	2.21	2129	71	3.3	1.58	0.72	(0.53,0.97)	0.0329	
Baseline NYHA												0.6154
II^^	2452	91	3.7	1.78	2435	61	2.5	1.19	0.68	(0.49,0.95)	0.0214	
III/IV	539	40	7.4	3.76	562	36	6.4	3.29	0.79	(0.50,1.24)	0.3019	
Baseline Diabetes Status												0.6230
Diabetic	1472	84	5.7	2.78	1466	60	4.1	2.00	0.69	(0.50,0.97)	0.0315	
Non-Diabetic	1519	47	3.1	1.49	1531	37	2.4	1.15	0.80	(0.52,1.23)	0.3010	

* 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, °:Trend test, ^Incidence rate, events per 100 patient years at risk.

Analysis is based on study 1245.110.

^^ Patients with NYHA class I are counted in subgroup NYHA class II.
¹ Baseline SBP median: 132 [mmHg].
² Baseline NT-proBNP median for patients with history of atrial fibrillation or atrial flutter: 1354 [pg/mL].
² Baseline NT-proBNP median for patients without history of atrial fibrillation or atrial flutter: 614 [pg/mL].
³ Baseline uric acid tertile cut-offs for males are T1: 5.9 T2: 7.5 [mg/dL] [rounded].
³ Baseline uric acid tertile cut-offs for females are T1: 5.4 T2: 6.9 [mg/dL] [rounded].

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Table R.1.1.1.25: 1 Cox regression for time to first 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 Diabetes Status												0.7795°/ 0.8103
Diabetic	1472	84	5.7	2.78	1466	60	4.1	2.00	0.69	(0.50,0.97)	0.0315	
Pre-Diabetes	979	35	3.6	1.72	1001	29	2.9	1.39	0.84	(0.51,1.37)	0.4841	
Normal (no pre-diabetes)	540	12	2.2	1.07	530	8	1.5	0.71	0.67	(0.27,1.65)	0.3856	
Baseline BMI [kg/m²]												0.2941
<30	1642	59	3.6	1.76	1654	37	2.2	1.08	0.62	(0.41,0.93)	0.0220	
>=30	1349	72	5.3	2.55	1343	60	4.5	2.15	0.82	(0.58,1.16)	0.2678	
Baseline eGFR (CKD-EPI) [mL/min/1.73m²]												0.6462
>=60	1505	38	2.5	1.19	1493	25	1.7	0.79	0.66	(0.40,1.09)	0.1062	
<60	1484	93	6.3	3.11	1504	72	4.8	2.36	0.76	(0.56,1.03)	0.0772	
History of HHF (in the last 12 months)												0.9881
No	2321	90	3.9	1.88	2298	63	2.7	1.32	0.72	(0.52,0.99)	0.0465	
Yes	670	41	6.1	2.96	699	34	4.9	2.35	0.72	(0.46,1.14)	0.1649	
Baseline SBP (</>= median¹)												0.6579
< median	1474	70	4.7	2.32	1496	56	3.7	1.83	0.77	(0.54,1.09)	0.1419	
>= median	1517	61	4.0	1.93	1501	41	2.7	1.30	0.68	(0.46,1.01)	0.0577	
History of atrial fibrillation or atrial flutter												0.9207
No	1427	58	4.1	1.98	1417	41	2.9	1.39	0.74	(0.49,1.10)	0.1353	
Yes	1559	73	4.7	2.26	1576	56	3.6	1.71	0.72	(0.51,1.02)	0.0618	

* 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, °:Trend test, ^Incidence rate, events per 100 patient years at risk.

Analysis is based on study 1245.110.

^^ Patients with NYHA class I are counted in subgroup NYHA class II.
¹ Baseline SBP median: 132 [mmHg].
² Baseline NT-proBNP median for patients with history of atrial fibrillation or atrial flutter: 1354 [pg/mL].
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³ Baseline uric acid tertile cut-offs for males are T1: 5.9 T2: 7.5 [mg/dL] [rounded].
³ Baseline uric acid tertile cut-offs for females are T1: 5.4 T2: 6.9 [mg/dL] [rounded].

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Table R.1.1.1.25: 1 Cox regression for time to first acute kidney injury 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 LVEF [%]												0.3545
< 50	988	37	3.7	1.81	995	22	2.2	1.05	0.59	(0.35,1.00)	0.0498	
>= 50	2003	94	4.7	2.28	2002	75	3.7	1.81	0.79	(0.58,1.06)	0.1203	
Baseline LVEF [%]												0.1802°/ 0.3608
<50	988	37	3.7	1.81	995	22	2.2	1.05	0.59	(0.35,1.00)	0.0498	
50 to <60	1030	52	5.0	2.44	1028	35	3.4	1.64	0.67	(0.43,1.02)	0.0638	
>=60	973	42	4.3	2.10	974	40	4.1	2.00	0.93	(0.61,1.44)	0.7566	
Baseline NT-proBNP [pg/mL] (</>=median[2] by atrial fibrillation/flutter status)												0.8682
< median	1508	44	2.9	1.37	1477	29	2.0	0.91	0.69	(0.43,1.11)	0.1259	
>= median	1476	87	5.9	2.96	1516	68	4.5	2.24	0.73	(0.53,1.00)	0.0498	
Baseline uric acid [mg/dL] (tertiles[3])												0.2198°/ 0.1116
<T1	975	29	3.0	1.43	963	22	2.3	1.10	0.71	(0.41,1.25)	0.2357	
>=T1 and <T2	966	36	3.7	1.78	1032	17	1.6	0.79	0.46	(0.26,0.81)	0.0075	
>=T2	1018	63	6.2	3.06	970	57	5.9	2.84	0.94	(0.65,1.34)	0.7226	
Baseline use of MRA												0.8178
No	1866	85	4.6	2.19	1878	61	3.2	1.55	0.71	(0.51,0.99)	0.0442	
Yes	1125	46	4.1	2.00	1119	36	3.2	1.57	0.76	(0.49,1.18)	0.2197	
Baseline use of ACE-inhibitor, ARB or ARNi												0.9749
No	587	31	5.3	2.64	569	21	3.7	1.76	0.72	(0.42,1.26)	0.2522	
Yes	2404	100	4.2	2.00	2428	76	3.1	1.51	0.73	(0.54,0.98)	0.0394	

* 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, °:Trend test, ^Incidence rate, events per 100 patient years at risk.

Analysis is based on study 1245.110.

^^ Patients with NYHA class I are counted in subgroup NYHA class II.
[1] Baseline SBP median: 132 [mmHg].
[2] Baseline NT-proBNP median for patients with history of atrial fibrillation or atrial flutter: 1354 [pg/mL].
[2] Baseline NT-proBNP median for patients without history of atrial fibrillation or atrial flutter: 614 [pg/mL].
[3] Baseline uric acid tertile cut-offs for males are T1: 5.9 T2: 7.5 [mg/dL] [rounded].
[3] Baseline uric acid tertile cut-offs for females are T1: 5.4 T2: 6.9 [mg/dL] [rounded].

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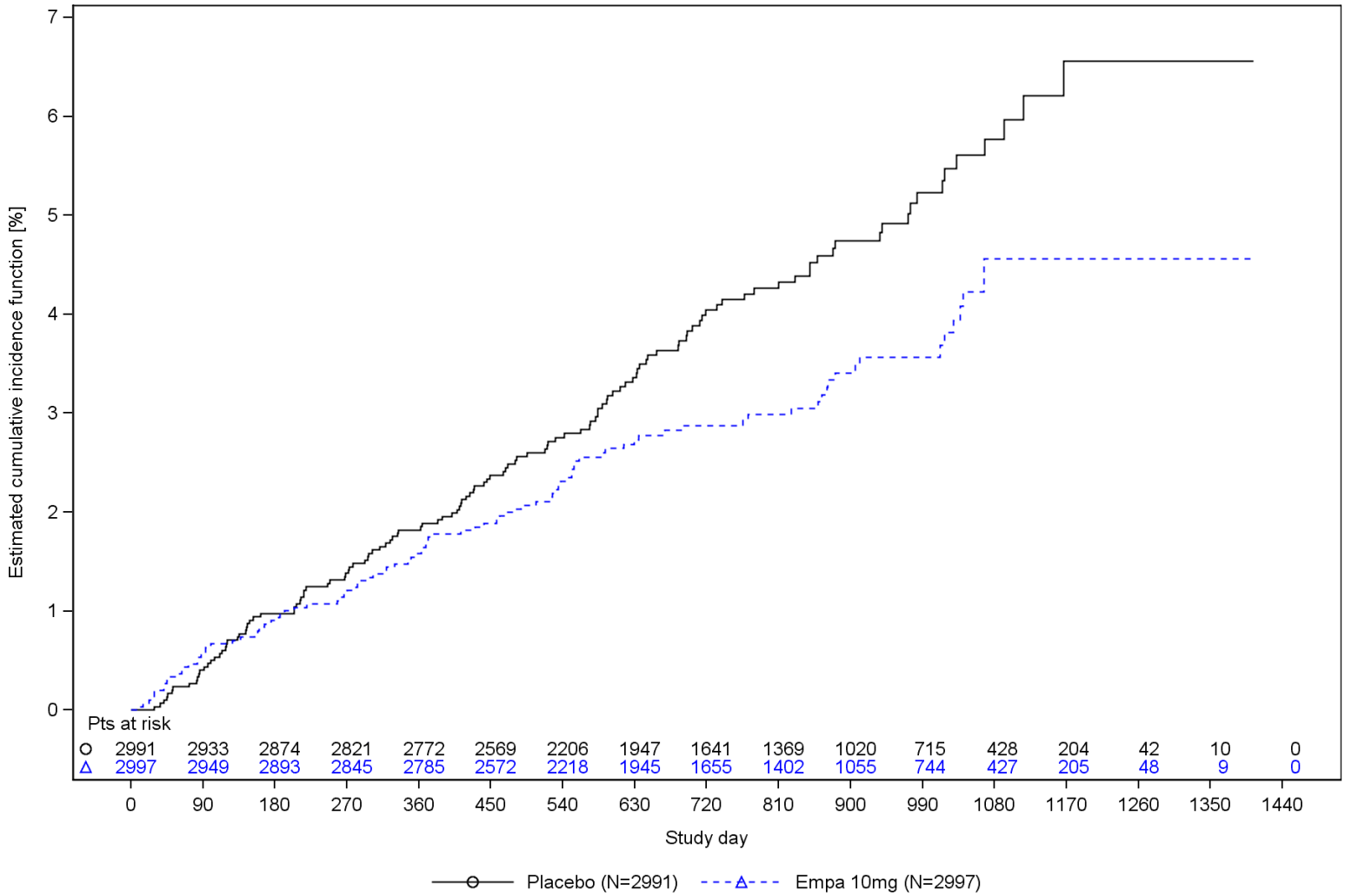

Figure R.1.1.1.25: 1 Time to the first acute kidney injury, estimated cumulative incidence function (considering all-cause mortality as a competing risk) - RS
Analysis is based on study 1245.110.

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R.1.1.1.26 Time to onset of diabetes mellitus in patients with baseline pre-diabetes

Table R.1.1.1.26: 1 Cox regression for time to onset of diabetes mellitus in patients with baseline pre-diabetes 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
Overall	979	137	14.0	7.39	1001	120	12.0	6.12	0.84	(0.65,1.07)	0.1539	
Sex												0.8685
Male	519	77	14.8	7.90	496	65	13.1	6.72	0.85	(0.61,1.19)	0.3432	
Female	460	60	13.0	6.82	505	55	10.9	5.53	0.82	(0.57,1.18)	0.2810	
Age [years]												0.5807
<70	299	39	13.0	6.68	286	35	12.2	6.13	0.93	(0.59,1.47)	0.7619	
>=70	680	98	14.4	7.72	715	85	11.9	6.11	0.80	(0.60,1.07)	0.1325	
Region												0.9753
North America	119	14	11.8	5.74	115	10	8.7	4.13	0.72	(0.32,1.63)	0.4367	
Latin America	214	31	14.5	8.09	222	24	10.8	5.91	0.74	(0.43,1.26)	0.2651	
Europe	468	63	13.5	7.06	478	59	12.3	6.19	0.88	(0.62,1.26)	0.4911	
Asia	119	16	13.4	7.24	126	16	12.7	6.46	0.91	(0.45,1.81)	0.7782	
Other	59	13	22.0	11.52	60	11	18.3	9.82	0.88	(0.39,1.96)	0.7503	
OECD member												0.4527
No	230	44	19.1	10.74	252	35	13.9	7.75	0.72	(0.46,1.13)	0.1511	
Yes	749	93	12.4	6.44	749	85	11.3	5.63	0.89	(0.66,1.19)	0.4198	
Baseline NYHA												0.6894
II^^	806	111	13.8	7.20	835	97	11.6	5.84	0.82	(0.62,1.08)	0.1510	
III/IV	173	26	15.0	8.32	166	23	13.9	7.66	0.93	(0.53,1.63)	0.8015	
Baseline BMI [kg/m²]												0.3091
<30	591	84	14.2	7.63	630	70	11.1	5.63	0.76	(0.55,1.04)	0.0854	
>=30	388	53	13.7	7.05	371	50	13.5	6.97	0.98	(0.67,1.44)	0.9237	

* Based on a Cox regression model with terms age, baseline eGFR (CKD-EPI), baseline LVEF, region, 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, °:Trend test, ^Incidence rate, events per 100 patient years at risk.

Analysis is based on study 1245.110.

^^ Patients with NYHA class I are counted in subgroup NYHA class II.
¹ Baseline SBP median: 132 [mmHg].
² Baseline NT-proBNP median for patients with history of atrial fibrillation or atrial flutter: 1354 [pg/mL].
² Baseline NT-proBNP median for patients without history of atrial fibrillation or atrial flutter: 614 [pg/mL].
³ Baseline uric acid tertile cut-offs for males are T1: 5.9 T2: 7.5 [mg/dL] [rounded].
³ Baseline uric acid tertile cut-offs for females are T1: 5.4 T2: 6.9 [mg/dL] [rounded].

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Table R.1.1.1.26: 1 Cox regression for time to onset of diabetes mellitus in patients with baseline pre-diabetes 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]												0.8558
>=60	474	59	12.4	6.38	488	53	10.9	5.42	0.86	(0.59,1.24)	0.4128	
<60	505	78	15.4	8.40	513	67	13.1	6.81	0.82	(0.59,1.13)	0.2278	
History of HHF (in the last 12 months)												0.7515
No	780	99	12.7	6.71	776	86	11.1	5.67	0.85	(0.64,1.14)	0.2752	
Yes	199	38	19.1	10.06	225	34	15.1	7.64	0.78	(0.49,1.24)	0.2925	
Baseline SBP (</>= median¹)												0.1743
< median	513	77	15.0	8.17	543	60	11.0	5.64	0.71	(0.51,1.00)	0.0498	
>= median	466	60	12.9	6.59	458	60	13.1	6.68	1.00	(0.70,1.44)	0.9858	
History of atrial fibrillation or atrial flutter												0.5273
No	414	55	13.3	7.00	404	51	12.6	6.33	0.92	(0.63,1.35)	0.6866	
Yes	562	81	14.4	7.61	596	69	11.6	5.99	0.79	(0.57,1.09)	0.1441	
Baseline LVEF [%]												0.0082
< 50	310	56	18.1	9.87	317	31	9.8	4.98	0.52	(0.33,0.80)	0.0032	
>= 50	669	81	12.1	6.30	684	89	13.0	6.65	1.06	(0.78,1.43)	0.7062	
Baseline LVEF [%]												0.0187°/ 0.0285
<50	310	56	18.1	9.87	317	31	9.8	4.98	0.52	(0.33,0.80)	0.0032	
50 to <60	340	46	13.5	7.05	335	47	14.0	7.24	1.04	(0.69,1.56)	0.8489	
>=60	329	35	10.6	5.53	349	42	12.0	6.09	1.09	(0.70,1.72)	0.6919	

* Based on a Cox regression model with terms age, baseline eGFR (CKD-EPI), baseline LVEF, region, 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, °:Trend test, ^Incidence rate, events per 100 patient years at risk.

Analysis is based on study 1245.110.

^^ Patients with NYHA class I are counted in subgroup NYHA class II.
¹ Baseline SBP median: 132 [mmHg].
² Baseline NT-proBNP median for patients with history of atrial fibrillation or atrial flutter: 1354 [pg/mL].
² Baseline NT-proBNP median for patients without history of atrial fibrillation or atrial flutter: 614 [pg/mL].
³ Baseline uric acid tertile cut-offs for males are T1: 5.9 T2: 7.5 [mg/dL] [rounded].
³ Baseline uric acid tertile cut-offs for females are T1: 5.4 T2: 6.9 [mg/dL] [rounded].

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Table R.1.1.1.26: 1 Cox regression for time to onset of diabetes mellitus in patients with baseline pre-diabetes 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 NT-proBNP [pg/mL] (</>=median² by atrial fibrillation/flutter status)												0.1817
< median	464	72	15.5	8.11	480	56	11.7	5.74	0.71	(0.50,1.01)	0.0547	
>= median	512	64	12.5	6.65	520	64	12.3	6.51	0.99	(0.70,1.41)	0.9699	
Baseline uric acid [mg/dL] (tertiles³)												0.8448°/ 0.3119
<T1	308	32	10.4	5.31	319	35	11.0	5.48	1.04	(0.64,1.68)	0.8725	
>=T1 and <T2	327	50	15.3	8.14	354	36	10.2	5.22	0.65	(0.42,1.00)	0.0502	
>=T2	334	53	15.9	8.50	323	49	15.2	7.85	0.92	(0.63,1.36)	0.6882	
Baseline use of MRA												0.6730
No	613	75	12.2	6.41	637	70	11.0	5.54	0.88	(0.63,1.22)	0.4378	
Yes	366	62	16.9	9.06	364	50	13.7	7.16	0.79	(0.54,1.15)	0.2152	
Baseline use of ACE-inhibitor, ARB or ARNi												0.6176
No	201	23	11.4	5.83	220	25	11.4	5.56	0.96	(0.54,1.69)	0.8804	
Yes	778	114	14.7	7.81	781	95	12.2	6.28	0.82	(0.62,1.07)	0.1414	

* Based on a Cox regression model with terms age, baseline eGFR (CKD-EPI), baseline LVEF, region, 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, °:Trend test, ^Incidence rate, events per 100 patient years at risk.

Analysis is based on study 1245.110.

^^ Patients with NYHA class I are counted in subgroup NYHA class II.
¹ Baseline SBP median: 132 [mmHg].
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³ Baseline uric acid tertile cut-offs for females are T1: 5.4 T2: 6.9 [mg/dL] [rounded].

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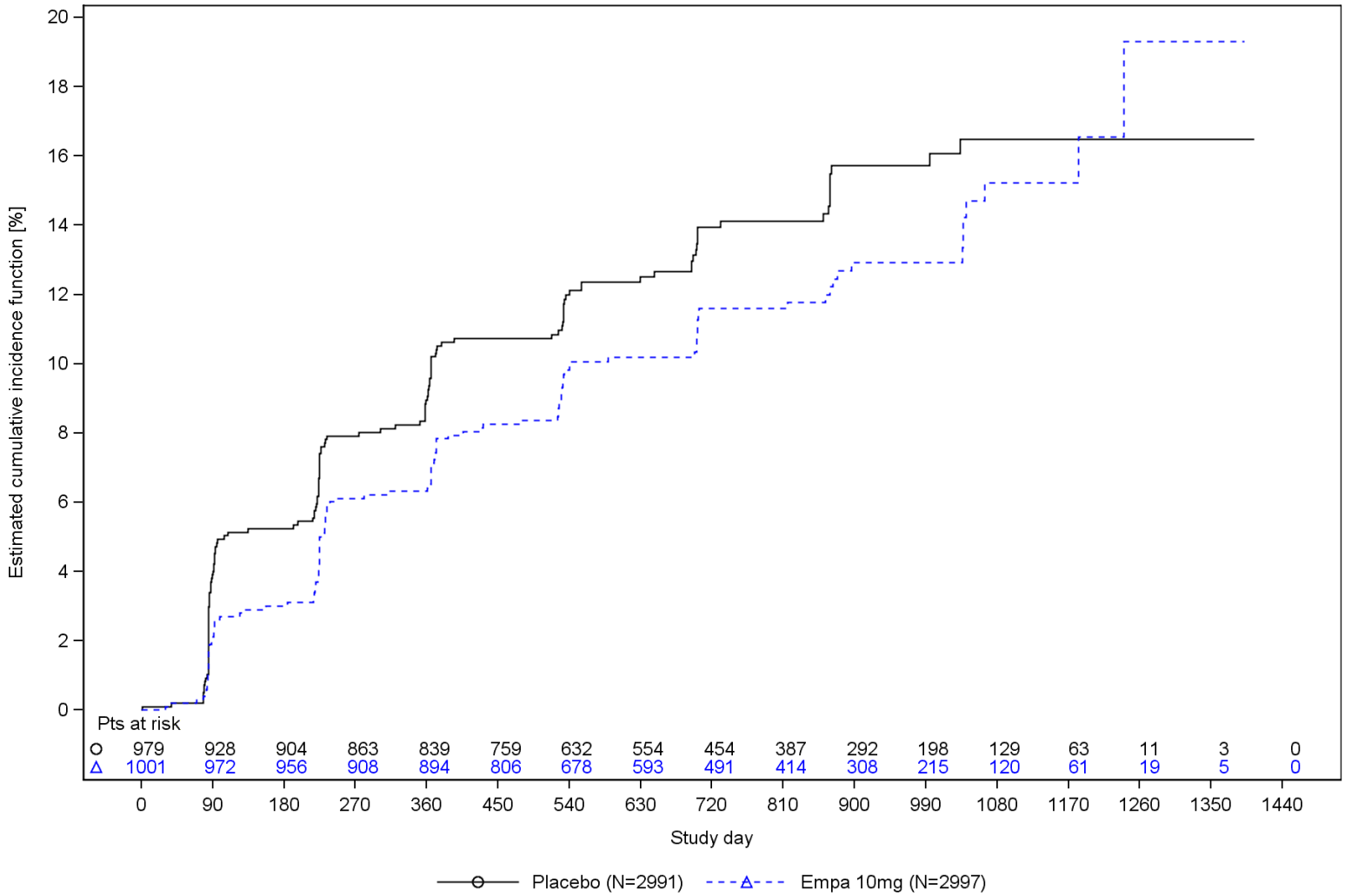

Figure R.1.1.1.26: 1 Time to the onset of diabetes mellitus in patients with baseline pre-diabetes, estimated cumulative incidence function (considering all-cause mortality as a competing risk) - RS
Analysis is based on study 1245.110.

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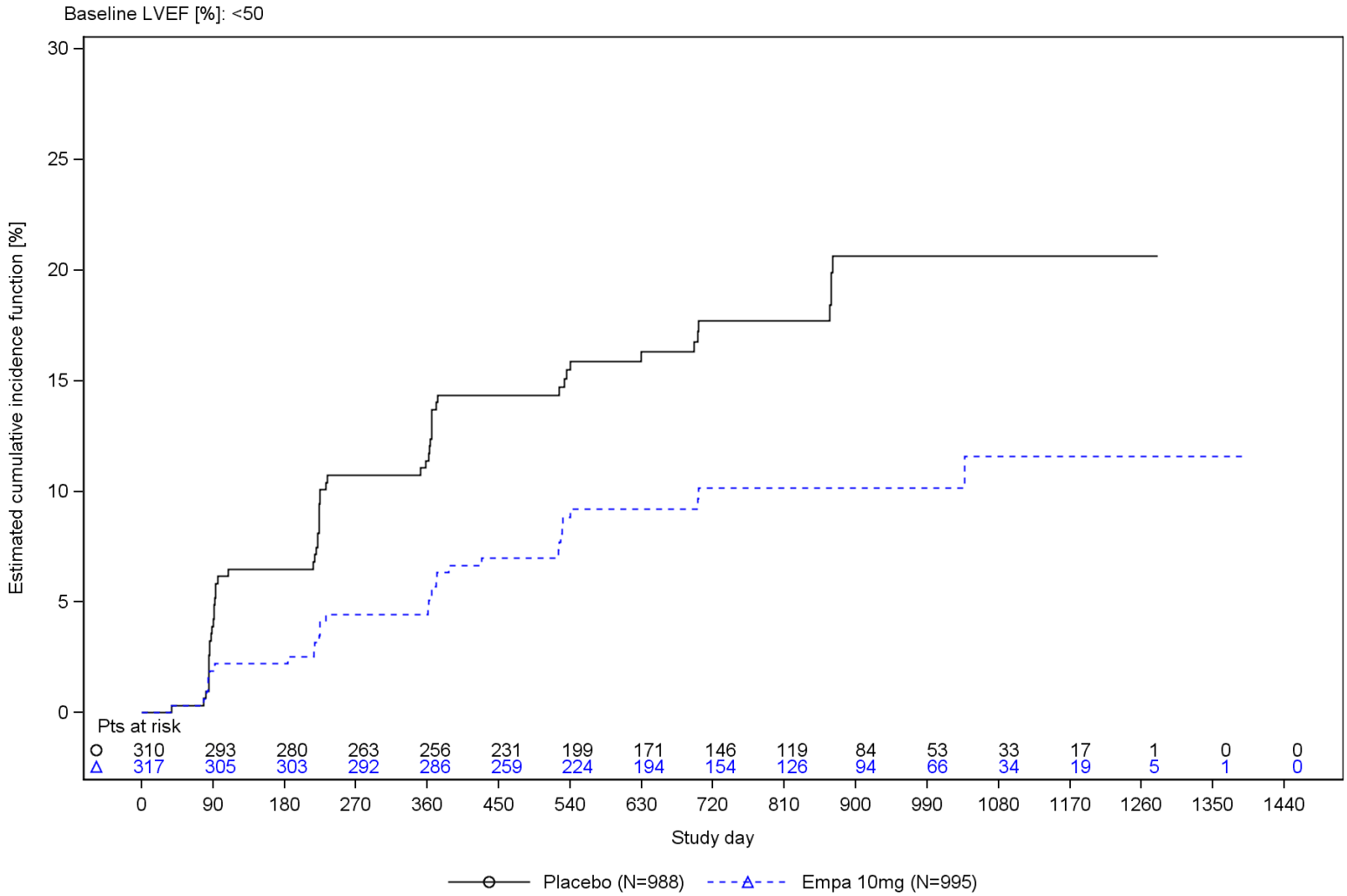

Figure R.1.1.1.26: 2 Time to the onset of diabetes mellitus in patients with baseline pre-diabetes, estimated cumulative incidence function (considering all-cause mortality as a competing risk) by baseline LVEF - RS
Analysis is based on study 1245.110.

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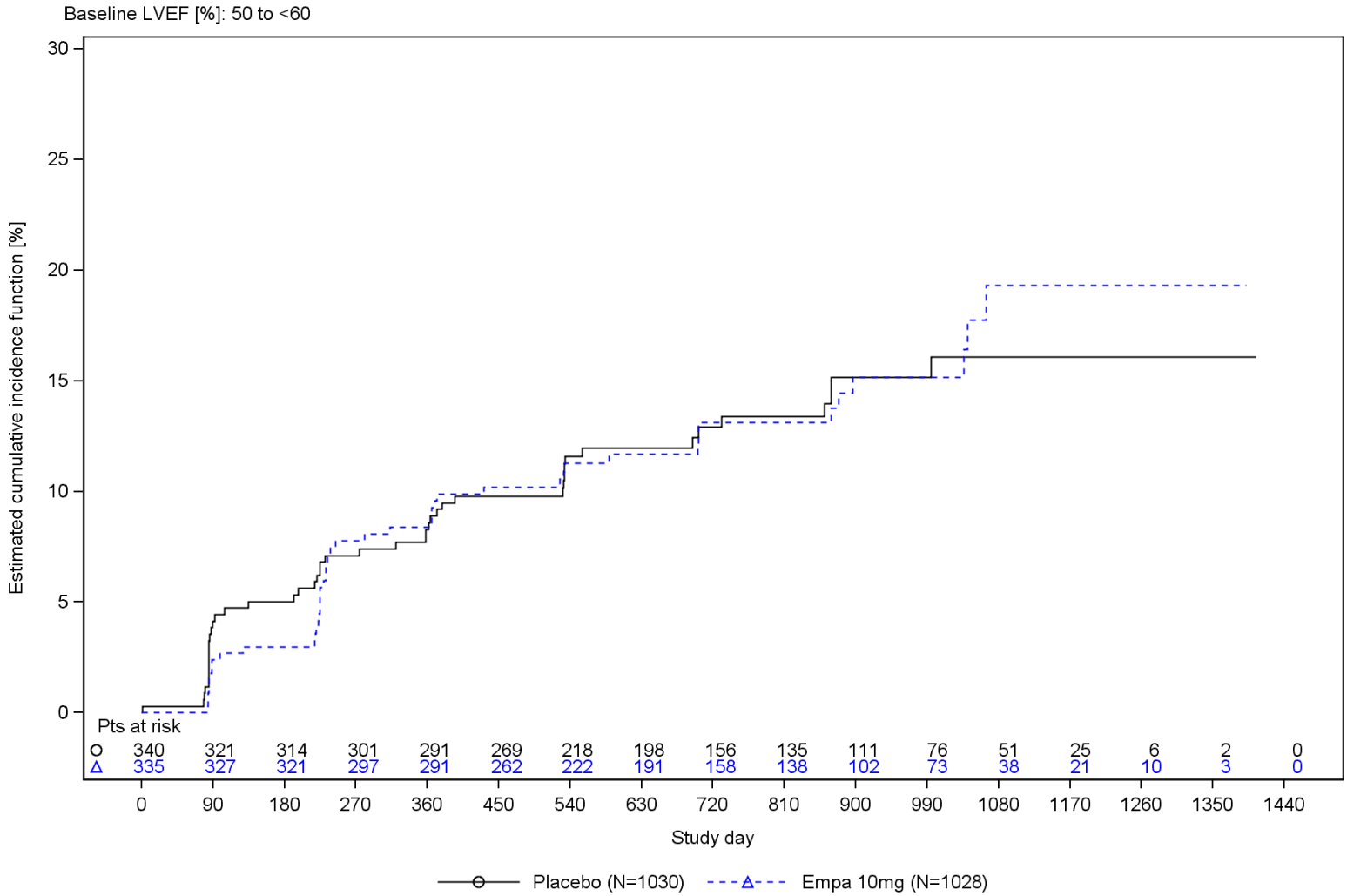

Figure R.1.1.1.26: 2 Time to the onset of diabetes mellitus in patients with baseline pre-diabetes, estimated cumulative incidence function (considering all-cause mortality as a competing risk) by baseline LVEF - RS
Analysis is based on study 1245.110.

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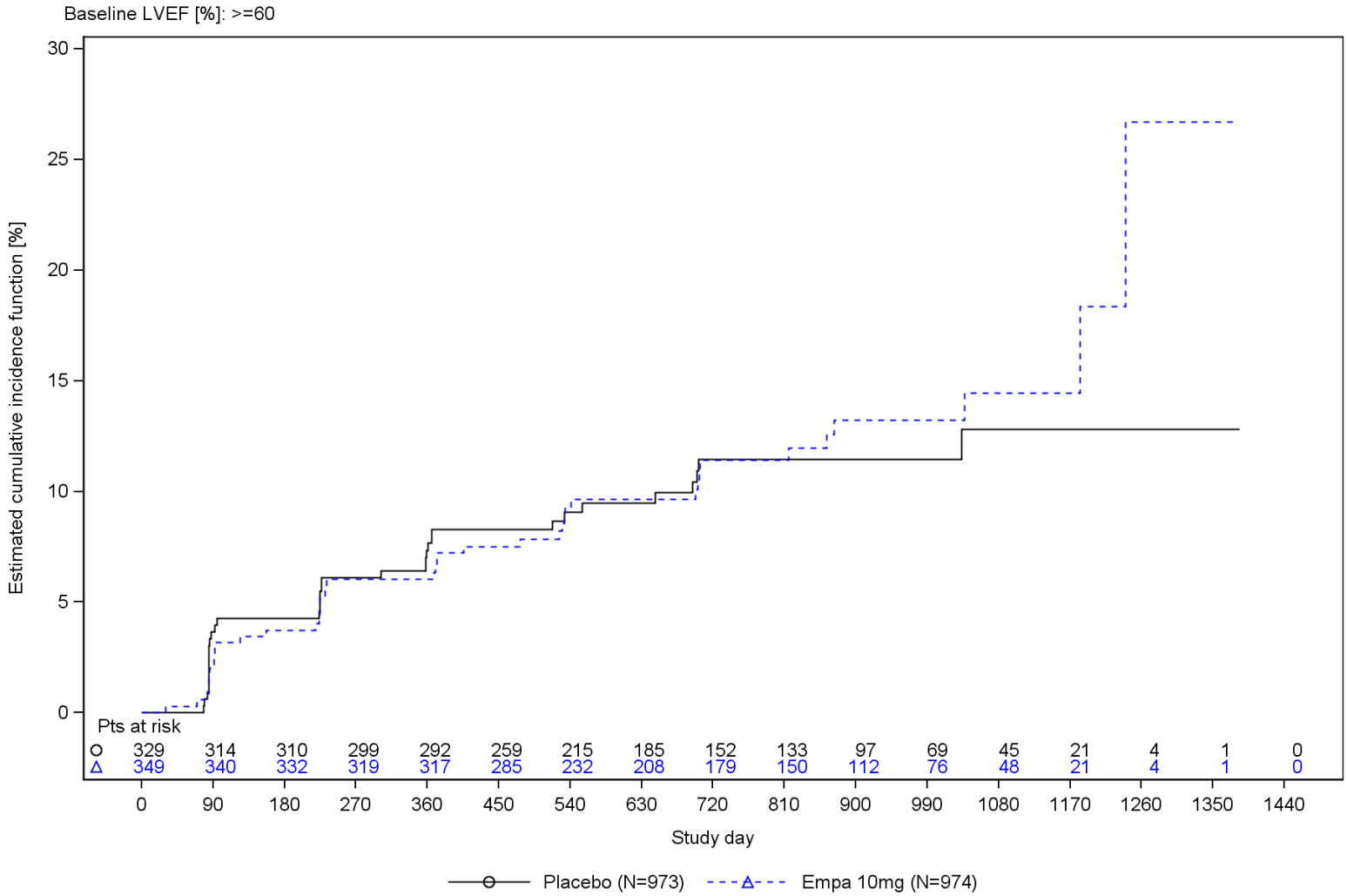

Figure R.1.1.1.26: 2 Time to the onset of diabetes mellitus in patients with baseline pre-diabetes, estimated cumulative incidence function (considering all-cause mortality as a competing risk) by baseline LVEF - RS
Analysis is based on study 1245.110.

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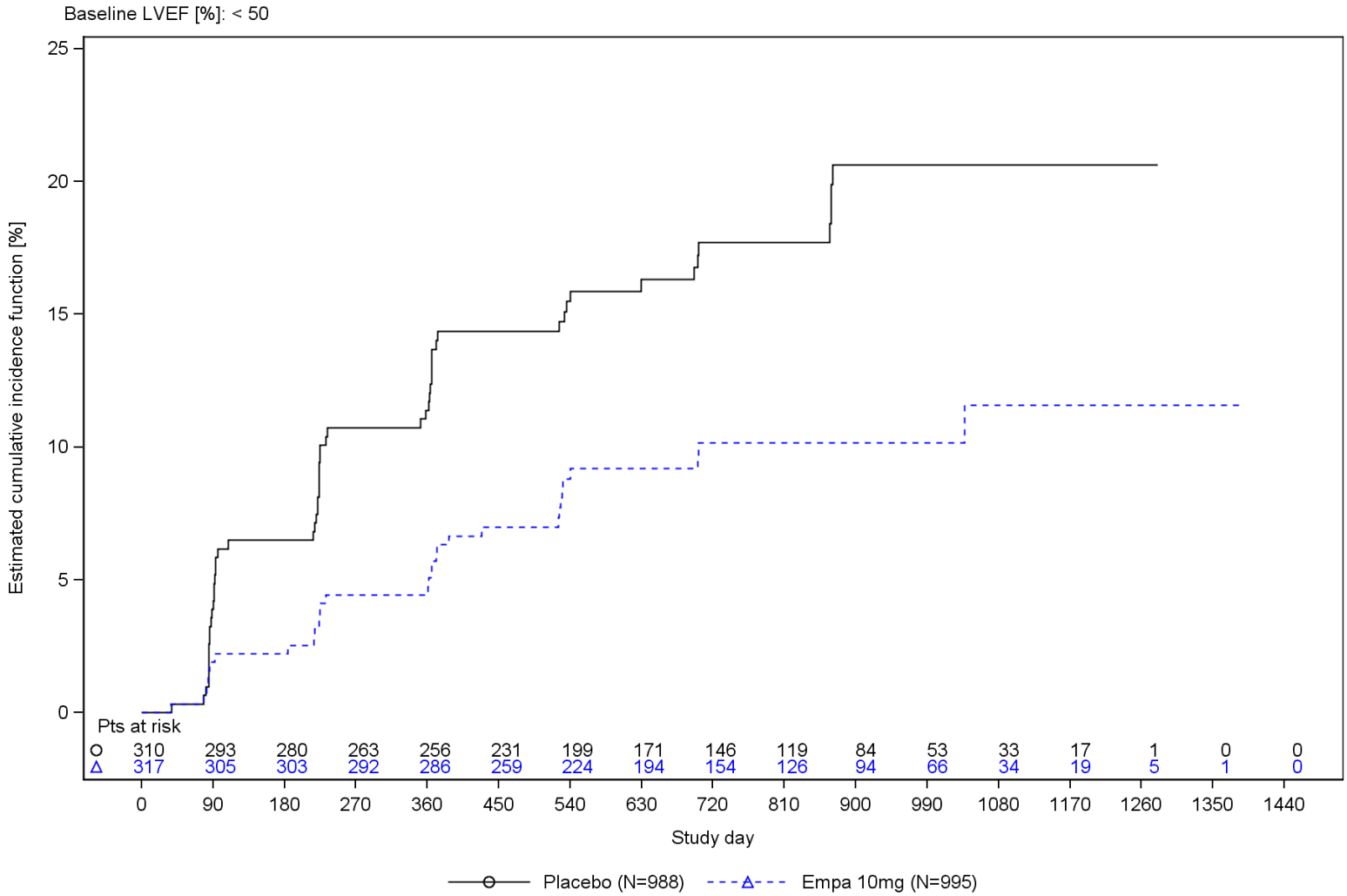

Figure 11.1.1 Time to the onset of diabetes mellitus in patients with baseline pre-diabetes, estimated cumulative incidence function (considering all-cause mortality as a competing risk) by baseline LVEF (<50/>=50) - RS
Analysis is based on study 1245.110.

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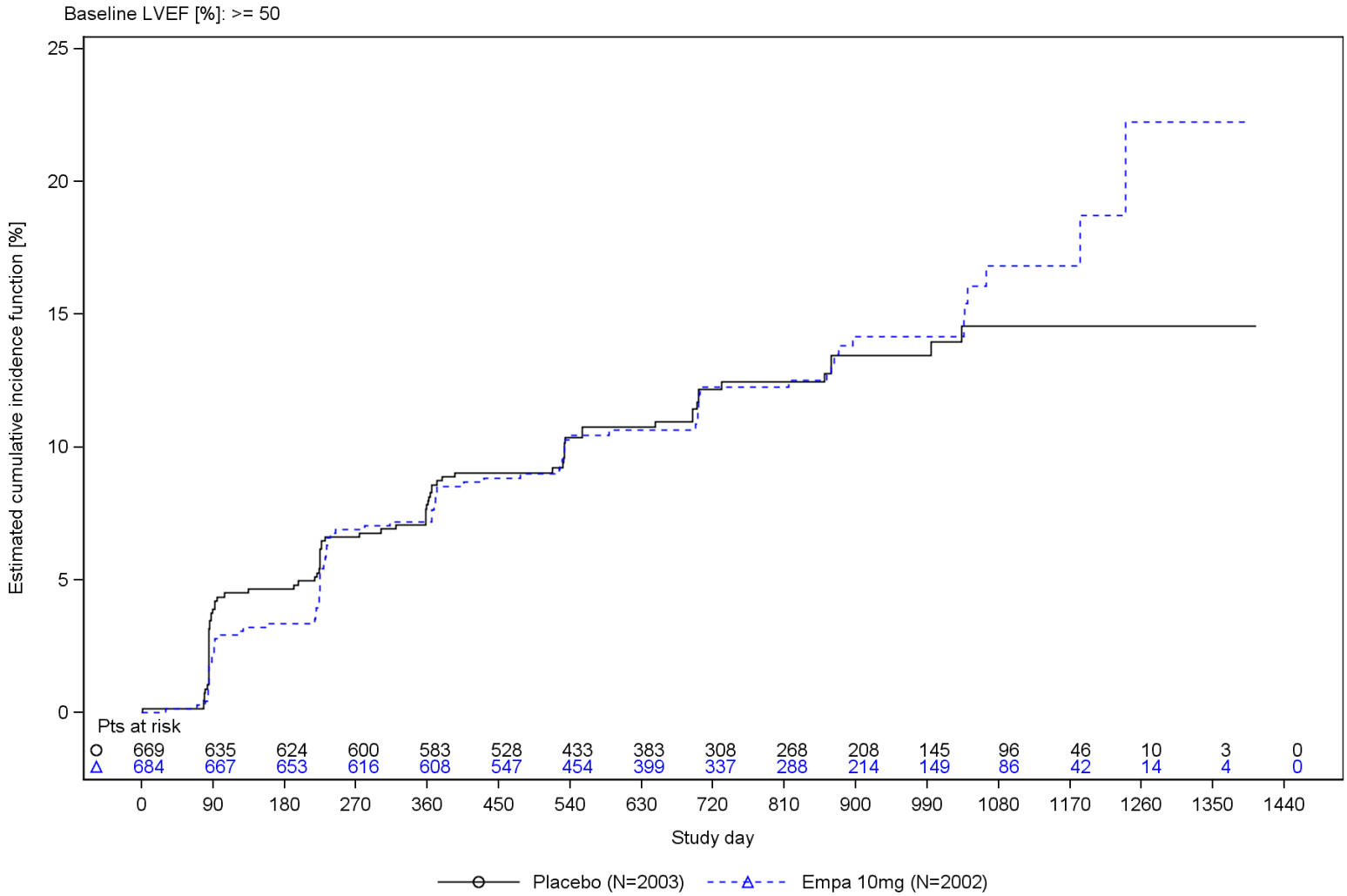

Figure 11.1.1 Time to the onset of diabetes mellitus in patients with baseline pre-diabetes, estimated cumulative incidence function (considering all-cause mortality as a competing risk) by baseline LVEF (<50/>=50) - RS
Analysis is based on study 1245.110.

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R.1.1.1.27 Time to first visit reporting intensification of diuretic therapy since last visit

Table R.1.1.1.27: 1 Cox regr. for time to first visit reporting intensification of diuretic therapy since last visit until 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	2991	610	20.4	11.12	2997	482	16.1	8.45	0.76	(0.67,0.86)	<0.0001	
Sex												0.9348
Male	1653	324	19.6	10.60	1659	258	15.6	8.09	0.76	(0.64,0.89)	0.0008	
Female	1338	286	21.4	11.77	1338	224	16.7	8.92	0.76	(0.64,0.91)	0.0025	
Age [years]												0.4300
<70	1084	200	18.5	9.77	1066	144	13.5	6.87	0.71	(0.57,0.88)	0.0015	
>=70	1907	410	21.5	11.92	1931	338	17.5	9.37	0.78	(0.68,0.91)	0.0009	
Region												0.5826
North America	359	98	27.3	15.34	360	85	23.6	12.72	0.84	(0.63,1.12)	0.2325	
Latin America	757	123	16.2	9.06	758	84	11.1	5.98	0.67	(0.50,0.88)	0.0040	
Europe	1343	245	18.2	9.56	1346	187	13.9	7.02	0.73	(0.61,0.89)	0.0013	
Asia	343	105	30.6	17.87	343	99	28.9	15.87	0.89	(0.67,1.17)	0.3891	
Other	189	39	20.6	11.46	190	27	14.2	7.86	0.68	(0.42,1.11)	0.1246	
OECD member												0.5577
No	847	142	16.8	9.22	868	107	12.3	6.68	0.71	(0.55,0.92)	0.0081	
Yes	2144	468	21.8	11.86	2129	375	17.6	9.14	0.78	(0.68,0.89)	0.0003	
Baseline NYHA												0.6194
II^^	2452	462	18.8	10.09	2435	352	14.5	7.42	0.74	(0.65,0.85)	<0.0001	
III/IV	539	148	27.5	16.33	562	130	23.1	13.58	0.79	(0.63,1.01)	0.0562	
Baseline Diabetes Status												0.2329
Diabetic	1472	316	21.5	11.81	1466	234	16.0	8.47	0.71	(0.60,0.84)	<0.0001	
Non-Diabetic	1519	294	19.4	10.46	1531	248	16.2	8.44	0.82	(0.69,0.97)	0.0192	

* 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, °:Trend test, ^Incidence rate, events per 100 patient years at risk.

Analysis is based on study 1245.110.

^^ Patients with NYHA class I are counted in subgroup NYHA class II.
¹ Baseline SBP median: 132 [mmHg].
² Baseline NT-proBNP median for patients with history of atrial fibrillation or atrial flutter: 1354 [pg/mL].
² Baseline NT-proBNP median for patients without history of atrial fibrillation or atrial flutter: 614 [pg/mL].
³ Baseline uric acid tertile cut-offs for males are T1: 5.9 T2: 7.5 [mg/dL] [rounded].
³ Baseline uric acid tertile cut-offs for females are T1: 5.4 T2: 6.9 [mg/dL] [rounded].

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Table R.1.1.1.27: 1 Cox regr. for time to first visit reporting intensification of diuretic therapy since last visit until 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 Diabetes Status												0.3095°/ 0.4889
Diabetic	1472	316	21.5	11.81	1466	234	16.0	8.47	0.71	(0.60,0.84)	<0.0001	
Pre-Diabetes	979	195	19.9	10.75	1001	167	16.7	8.80	0.82	(0.67,1.01)	0.0639	
Normal (no pre-diabetes)	540	99	18.3	9.95	530	81	15.3	7.78	0.81	(0.60,1.08)	0.1494	
Baseline BMI [kg/m²]												0.8983
<30	1642	326	19.9	10.93	1654	260	15.7	8.27	0.77	(0.65,0.90)	0.0013	
>=30	1349	284	21.1	11.34	1343	222	16.5	8.68	0.75	(0.63,0.90)	0.0016	
Baseline eGFR (CKD-EPI) [mL/min/1.73m²]												0.4547
>=60	1505	254	16.9	8.81	1493	186	12.5	6.29	0.72	(0.59,0.87)	0.0006	
<60	1484	356	24.0	13.68	1504	296	19.7	10.77	0.79	(0.67,0.92)	0.0023	
History of HHF (in the last 12 months)												0.2645
No	2321	421	18.1	9.73	2298	334	14.5	7.58	0.79	(0.68,0.91)	0.0011	
Yes	670	189	28.2	16.29	699	148	21.2	11.41	0.68	(0.55,0.84)	0.0004	
Baseline SBP (</>= median¹)												0.3041
< median	1474	312	21.2	11.69	1496	239	16.0	8.42	0.71	(0.60,0.84)	<0.0001	
>= median	1517	298	19.6	10.58	1501	243	16.2	8.48	0.81	(0.68,0.96)	0.0140	
History of atrial fibrillation or atrial flutter												0.1028
No	1427	238	16.7	8.95	1417	202	14.3	7.40	0.86	(0.71,1.03)	0.1029	
Yes	1559	370	23.7	13.11	1576	280	17.8	9.45	0.70	(0.60,0.82)	<0.0001	

* 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, °:Trend test, ^Incidence rate, events per 100 patient years at risk.

Analysis is based on study 1245.110.

^^ Patients with NYHA class I are counted in subgroup NYHA class II.
¹ Baseline SBP median: 132 [mmHg].
² Baseline NT-proBNP median for patients with history of atrial fibrillation or atrial flutter: 1354 [pg/mL].
² Baseline NT-proBNP median for patients without history of atrial fibrillation or atrial flutter: 614 [pg/mL].
³ Baseline uric acid tertile cut-offs for males are T1: 5.9 T2: 7.5 [mg/dL] [rounded].
³ Baseline uric acid tertile cut-offs for females are T1: 5.4 T2: 6.9 [mg/dL] [rounded].

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Table R.1.1.1.27: 1 Cox regr. for time to first visit reporting intensification of diuretic therapy since last visit until 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 LVEF [%]												0.3158
< 50	988	177	17.9	9.64	995	130	13.1	6.67	0.69	(0.55,0.86)	0.0013	
>= 50	2003	433	21.6	11.86	2002	352	17.6	9.37	0.79	(0.69,0.91)	0.0010	
Baseline LVEF [%]												0.0924°/ 0.1670
<50	988	177	17.9	9.64	995	130	13.1	6.67	0.69	(0.55,0.86)	0.0013	
50 to <60	1030	228	22.1	12.11	1028	165	16.1	8.44	0.70	(0.58,0.86)	0.0006	
>=60	973	205	21.1	11.61	974	187	19.2	10.39	0.89	(0.73,1.08)	0.2297	
Baseline NT-proBNP [pg/mL] (</>=median² by atrial fibrillation/flutter status)												0.2632
< median	1508	262	17.4	8.96	1477	184	12.5	6.18	0.70	(0.58,0.84)	0.0002	
>= median	1476	345	23.4	13.49	1516	298	19.7	10.96	0.80	(0.69,0.94)	0.0054	
Baseline uric acid [mg/dL] (tertiles³)												0.9837°/ 0.9990
<T1	975	165	16.9	9.00	963	129	13.4	6.96	0.78	(0.62,0.98)	0.0308	
>=T1 and <T2	966	169	17.5	9.21	1032	144	14.0	7.20	0.77	(0.62,0.96)	0.0213	
>=T2	1018	266	26.1	15.03	970	206	21.2	11.50	0.77	(0.64,0.93)	0.0053	
Baseline use of MRA												0.2547
No	1866	388	20.8	11.29	1878	292	15.5	8.09	0.72	(0.62,0.84)	<0.0001	
Yes	1125	222	19.7	10.83	1119	190	17.0	9.07	0.83	(0.68,1.01)	0.0599	
Baseline use of ACE-inhibitor, ARB or ARNi												0.6937
No	587	141	24.0	13.93	569	115	20.2	10.84	0.79	(0.62,1.02)	0.0658	
Yes	2404	469	19.5	10.48	2428	367	15.1	7.91	0.75	(0.65,0.86)	<0.0001	

* 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, °:Trend test, ^Incidence rate, events per 100 patient years at risk.

Analysis is based on study 1245.110.

^^ Patients with NYHA class I are counted in subgroup NYHA class II.
¹ Baseline SBP median: 132 [mmHg].
² Baseline NT-proBNP median for patients with history of atrial fibrillation or atrial flutter: 1354 [pg/mL].
² Baseline NT-proBNP median for patients without history of atrial fibrillation or atrial flutter: 614 [pg/mL].
³ Baseline uric acid tertile cut-offs for males are T1: 5.9 T2: 7.5 [mg/dL] [rounded].
³ Baseline uric acid tertile cut-offs for females are T1: 5.4 T2: 6.9 [mg/dL] [rounded].

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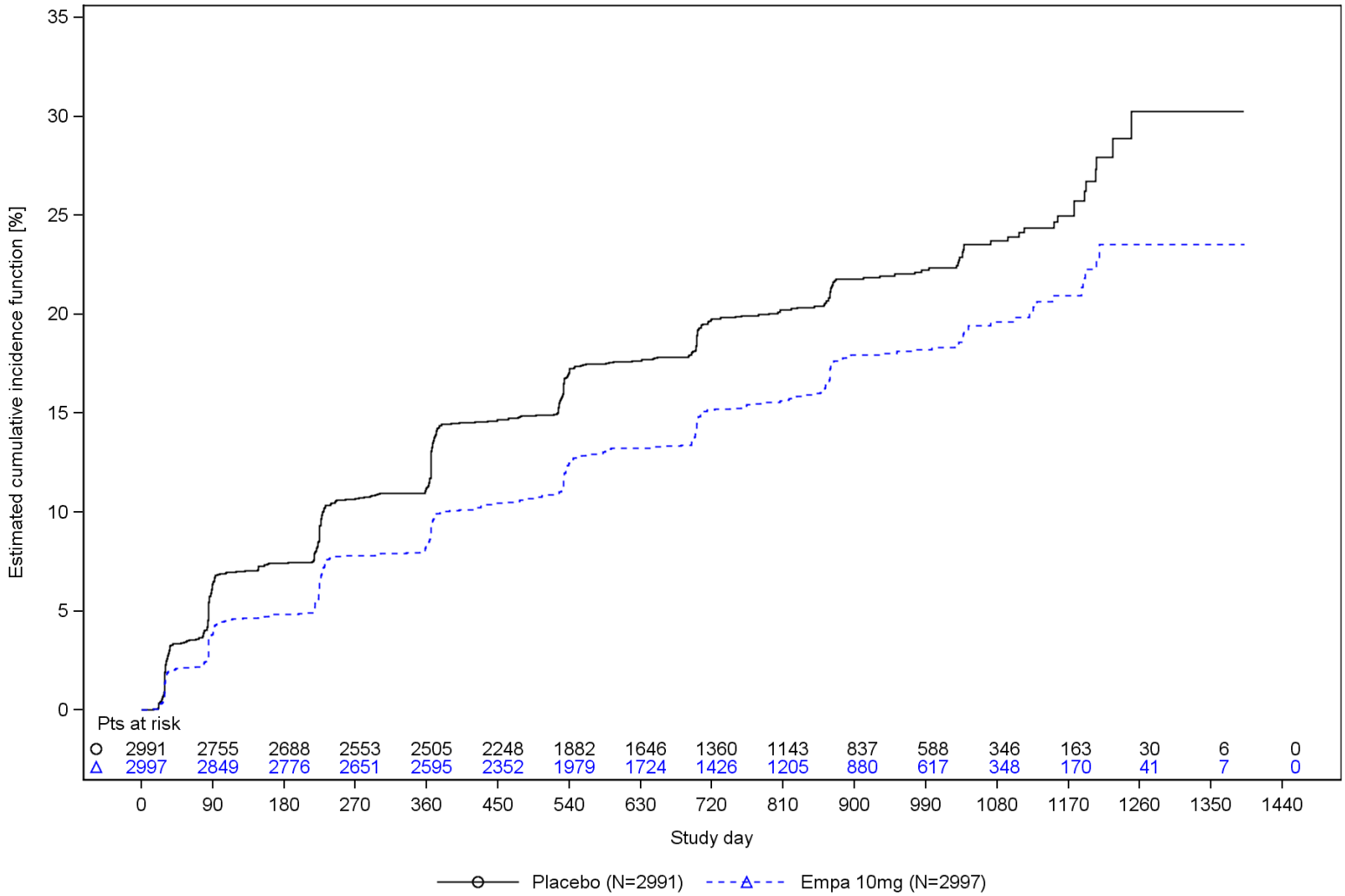

Figure R.1.1.1.27: 1 Time to the first visit reporting intensification of diuretic therapy since last visit until the end of planned treatment period (considering all-cause mortality as a competing risk) - RS

Analysis is based on study 1245.110.

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R.1.1.1.28 Visit reporting Intensification of diuretic therapy since last visit

Table R.1.1.1.28: 1 Visit rep. Intens. of diuretic therapy since last visit - Results from Joint Frailty Model for visit rep. Intens. of diuretic therapy and adj. CV death (terminal event) until the end of planned trt. 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	2991	610	20.4	838	13.30	2997	482	16.1	626	9.92	0.73	(0.65,0.82)	<0.0001	
Sex														0.9106
Male	1653	324	19.6	451	12.93	1659	258	15.6	336	9.62	0.73	(0.61,0.86)	0.0001	
Female	1338	286	21.4	387	13.76	1338	224	16.7	290	10.30	0.74	(0.61,0.88)	0.0008	
Age [years]														0.6079
<70	1084	200	18.5	268	11.55	1066	144	13.5	182	8.04	0.70	(0.56,0.86)	0.0010	
>=70	1907	410	21.5	570	14.33	1931	338	17.5	444	10.98	0.74	(0.64,0.86)	<0.0001	
Region														0.6986
North America	359	98	27.3	140	17.95	360	85	23.6	119	15.15	0.84	(0.63,1.14)	0.2681	
Latin America	757	123	16.2	144	9.54	758	84	11.1	95	6.28	0.65	(0.49,0.86)	0.0029	
Europe	1343	245	18.2	323	11.19	1346	187	13.9	227	7.86	0.70	(0.58,0.85)	0.0003	
Asia	343	105	30.6	180	24.48	343	99	28.9	151	20.29	0.79	(0.60,1.05)	0.1052	
Other	189	39	20.6	51	13.15	190	27	14.2	34	8.98	0.68	(0.42,1.12)	0.1312	
OECD member														0.5982
No	847	142	16.8	168	9.80	868	107	12.3	122	7.02	0.69	(0.53,0.90)	0.0060	
Yes	2144	468	21.8	670	14.62	2129	375	17.6	504	11.02	0.75	(0.65,0.86)	<0.0001	
Baseline NYHA														0.4446
II^^	2452	462	18.8	620	11.95	2435	352	14.5	449	8.66	0.71	(0.62,0.81)	<0.0001	
III/IV	539	148	27.5	218	19.65	562	130	23.1	177	15.70	0.79	(0.62,1.01)	0.0568	
Baseline Diabetes Status														0.1325
Diabetic	1472	316	21.5	441	14.23	1466	234	16.0	298	9.76	0.66	(0.56,0.79)	<0.0001	
Non-Diabetic	1519	294	19.4	397	12.41	1531	248	16.2	328	10.07	0.80	(0.68,0.95)	0.0108	

* 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, °:Trend test,
^Recurrent event rate, per 100 patient years at risk.

Analysis is based on study 1245.110.

^^ Patients with NYHA class I are counted in subgroup NYHA class II.
¹ Baseline SBP median: 132 [mmHg].
² Baseline NT-proBNP median for patients with history of atrial fibrillation or atrial flutter: 1354 [pg/mL].
² Baseline NT-proBNP median for patients without history of atrial fibrillation or atrial flutter: 614 [pg/mL].
³ Baseline uric acid tertile cut-offs for males are T1: 5.9 T2: 7.5 [mg/dL] [rounded].
³ Baseline uric acid tertile cut-offs for females are T1: 5.4 T2: 6.9 [mg/dL] [rounded].

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Table R.1.1.1.28: 1 Visit rep. Intens. of diuretic therapy since last visit - Results from Joint Frailty Model for visit rep. Intens. of diuretic therapy and adj. CV death (terminal event) until the end of planned trt. 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 Diabetes Status														0.3069°/ 0.2506
Diabetic	1472	316	21.5	441	14.23	1466	234	16.0	298	9.76	0.66	(0.56,0.79)	<0.0001	
Pre-Diabetes	979	195	19.9	256	12.36	1001	167	16.7	223	10.52	0.84	(0.68,1.03)	0.0977	
Normal (no pre-diabetes)	540	99	18.3	141	12.49	530	81	15.3	105	9.23	0.73	(0.55,0.99)	0.0397	
Baseline BMI [kg/m²]														0.8649
<30	1642	326	19.9	464	13.65	1654	260	15.7	354	10.22	0.74	(0.63,0.87)	0.0003	
>=30	1349	284	21.1	374	12.90	1343	222	16.5	272	9.56	0.72	(0.60,0.87)	0.0004	
Baseline eGFR (CKD-EPI) [mL/min/1.73m²]														0.6757
>=60	1505	254	16.9	331	10.28	1493	186	12.5	237	7.43	0.71	(0.59,0.86)	0.0005	
<60	1484	356	24.0	507	16.48	1504	296	19.7	389	12.47	0.75	(0.64,0.88)	0.0004	
History of HHF (in the last 12 months)														0.3035
No	2321	421	18.1	559	11.49	2298	334	14.5	428	8.86	0.76	(0.66,0.88)	0.0002	
Yes	670	189	28.2	279	19.45	699	148	21.2	198	13.37	0.66	(0.53,0.83)	0.0003	
Baseline SBP (</>= median¹)														0.7084
< median	1474	312	21.2	429	13.96	1496	239	16.0	316	10.14	0.71	(0.60,0.85)	0.0001	
>= median	1517	298	19.6	409	12.67	1501	243	16.2	310	9.71	0.75	(0.63,0.89)	0.0009	
History of atrial fibrillation or atrial flutter														0.1552
No	1427	238	16.7	314	10.51	1417	202	14.3	250	8.39	0.81	(0.67,0.98)	0.0329	
Yes	1559	370	23.7	521	15.78	1576	280	17.8	376	11.31	0.68	(0.58,0.80)	<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, 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, °:Trend test,
^Recurrent event rate, per 100 patient years at risk.

Analysis is based on study 1245.110.

^^ Patients with NYHA class I are counted in subgroup NYHA class II.
¹ Baseline SBP median: 132 [mmHg].
² Baseline NT-proBNP median for patients with history of atrial fibrillation or atrial flutter: 1354 [pg/mL].
² Baseline NT-proBNP median for patients without history of atrial fibrillation or atrial flutter: 614 [pg/mL].
³ Baseline uric acid tertile cut-offs for males are T1: 5.9 T2: 7.5 [mg/dL] [rounded].
³ Baseline uric acid tertile cut-offs for females are T1: 5.4 T2: 6.9 [mg/dL] [rounded].

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Table R.1.1.1.28: 1 Visit rep. Intens. of diuretic therapy since last visit - Results from Joint Frailty Model for visit rep. Intens. of diuretic therapy and adj. CV death (terminal event) until the end of planned trt. 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 LVEF [%]														0.6836
< 50	988	177	17.9	225	10.84	995	130	13.1	160	7.61	0.70	(0.56,0.88)	0.0025	
>= 50	2003	433	21.6	613	14.51	2002	352	17.6	466	11.07	0.74	(0.64,0.86)	<0.0001	
Baseline LVEF [%]														0.2214°/ 0.2184
<50	988	177	17.9	225	10.84	995	130	13.1	160	7.61	0.70	(0.56,0.88)	0.0025	
50 to <60	1030	228	22.1	317	14.52	1028	165	16.1	215	9.92	0.66	(0.53,0.80)	<0.0001	
>=60	973	205	21.1	296	14.50	974	187	19.2	251	12.30	0.84	(0.69,1.03)	0.0868	
Baseline NT-proBNP [pg/mL] (</>=median² by atrial fibrillation/flutter status)														0.2472
< median	1508	262	17.4	333	10.20	1477	184	12.5	222	6.92	0.67	(0.55,0.81)	<0.0001	
>= median	1476	345	23.4	501	16.58	1516	298	19.7	404	13.06	0.77	(0.66,0.90)	0.0013	
Baseline uric acid [mg/dL] (tertiles³)														0.9907°/ 0.8129
<T1	975	165	16.9	229	11.13	963	129	13.4	163	8.07	0.72	(0.57,0.91)	0.0052	
>=T1 and <T2	966	169	17.5	225	10.92	1032	144	14.0	191	8.79	0.79	(0.63,0.98)	0.0358	
>=T2	1018	266	26.1	373	17.59	970	206	21.2	269	13.07	0.73	(0.60,0.88)	0.0009	
Baseline use of MRA														0.3457
No	1866	388	20.8	522	13.18	1878	292	15.5	370	9.27	0.70	(0.60,0.81)	<0.0001	
Yes	1125	222	19.7	316	13.50	1119	190	17.0	256	11.03	0.78	(0.65,0.95)	0.0144	

* 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, °:Trend test,
^Recurrent event rate, per 100 patient years at risk.

Analysis is based on study 1245.110.

^^ Patients with NYHA class I are counted in subgroup NYHA class II.
¹ Baseline SBP median: 132 [mmHg].
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² Baseline NT-proBNP median for patients without history of atrial fibrillation or atrial flutter: 614 [pg/mL].
³ Baseline uric acid tertile cut-offs for males are T1: 5.9 T2: 7.5 [mg/dL] [rounded].
³ Baseline uric acid tertile cut-offs for females are T1: 5.4 T2: 6.9 [mg/dL] [rounded].

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Table R.1.1.1.28: 1 Visit rep. Intens. of diuretic therapy since last visit - Results from Joint Frailty Model for visit rep. Intens. of diuretic therapy and adj. CV death (terminal event) until the end of planned trt. 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 use of ACE-inhibitor, ARB or ARNi														0.8842
No	587	141	24.0	212	17.60	569	115	20.2	163	13.49	0.74	(0.58,0.95)	0.0189	
Yes	2404	469	19.5	626	12.29	2428	367	15.1	463	9.07	0.73	(0.63,0.84)	<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, 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, °:Trend test,
^Recurrent event rate, per 100 patient years at risk.

Analysis is based on study 1245.110.

^^ Patients with NYHA class I are counted in subgroup NYHA class II.
¹ Baseline SBP median: 132 [mmHg].
² Baseline NT-proBNP median for patients with history of atrial fibrillation or atrial flutter: 1354 [pg/mL].
² Baseline NT-proBNP median for patients without history of atrial fibrillation or atrial flutter: 614 [pg/mL].
³ Baseline uric acid tertile cut-offs for males are T1: 5.9 T2: 7.5 [mg/dL] [rounded].
³ Baseline uric acid tertile cut-offs for females are T1: 5.4 T2: 6.9 [mg/dL] [rounded].

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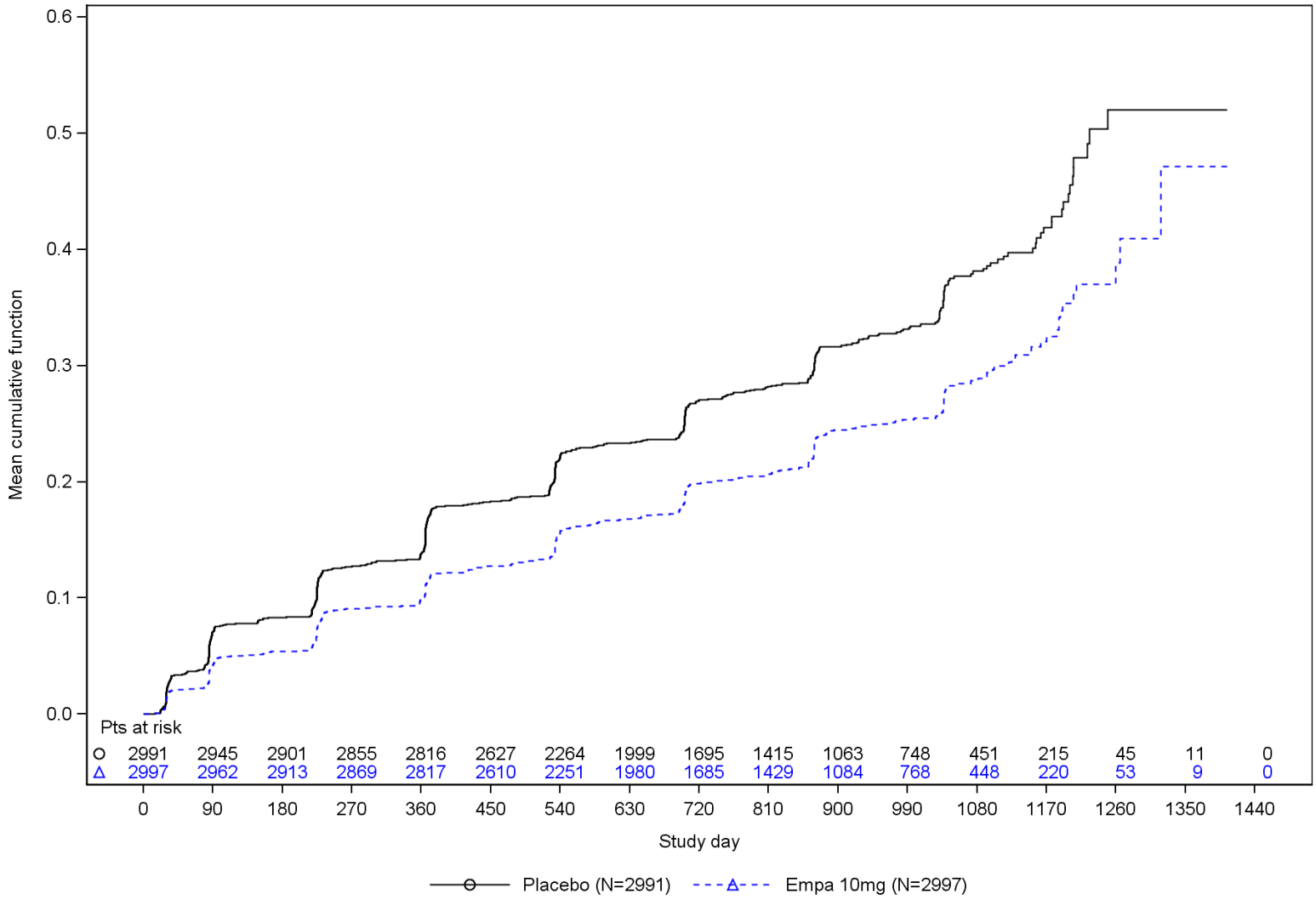

Figure R.1.1.1.28: 1 Occurrence of Visit rep. Intens. of diuretic therapy since last visit (first and recurrent), mean cumulative function - RS
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R.1.1.2 Random intercept random coefficient model

R.1.1.2.1 EGFR (CKD-EP)cr [mL/min/1.73m2] change from baseline

R.1.1.2.1.1 Overall

Table R.1.1.2.1.1: 1 EGFR (CKD-EP)cr [mL/min/1.73m2] change from baseline slope from random intercept random coefficients model - TS

Factor Comparison	N analysed	Estimate	Standard error	99.9% CI LL	99.9% CI UL	95% CI LL	95% CI UL	p-value
Intercept								
Placebo intercept	2911	-0.180	0.135	-0.624	0.264	-0.445	0.084	0.1815
Empa 10mg intercept	2925	-3.016	0.135	-3.459	-2.573	-3.280	-2.752	<0.0001
Time								
Placebo slope* [/year]		-2.616	0.108	-2.971	-2.261	-2.827	-2.405	<0.0001
Empa 10mg slope* [/year]		-1.253	0.108	-1.609	-0.897	-1.465	-1.041	<0.0001
Treatment by time interaction								
Empa 10mg vs Placebo slope [/year]		1.363	0.152	0.861	1.865	1.064	1.662	<0.0001

Model includes age (p<0.0001), baseline eGFR (CKD-EPI) (p<0.0001), baseline LVEF (p=0.3409) as linear covariate(s) and region (p=0.3574), baseline diabetes status (p<0.0001), sex (p=0.0806), baseline eGFR by Time interaction (p<0.0001), Time by Treatment interaction (p<0.0001), Treatment (p<0.0001) as fixed effect(s). Intercept and slope allowed to vary randomly between patients.
* Slope measured at baseline eGFR = 60.63
The following covariance structure has been used to fit the mixed model: Unstructured

R.1.1.2.1.2 Subgroup analysis by sex (male/female)

Table R.1.1.2.1.2: 1 EGFR (CKD-EP)cr [mL/min/1.73m2] change from baseline slope from random intercept random coefficients model by sex (male/female) - TS

Subgroup Factor Comparison	N analysed	Estimate	Standard error	95% CI LL	95% CI UL	p-value
Sex: Male						
Intercept						
Placebo intercept*	1608	-0.177	0.180	-0.529	0.176	0.3257
Empa 10mg intercept*	1624	-3.009	0.179	-3.360	-2.659	<0.0001
Time						
Placebo slope* [/year]		-2.366	0.143	-2.647	-2.086	<0.0001
Empa 10mg slope* [/year]		-1.078	0.144	-1.361	-0.796	<0.0001
Treatment by time interaction						
Empa 10mg vs Placebo slope [/year]		1.288	0.203	0.890	1.686	<0.0001
Sex: Female						
Intercept						
Placebo intercept*	1303	-0.070	0.202	-0.466	0.326	0.7294
Empa 10mg intercept*	1301	-2.910	0.202	-3.306	-2.513	<0.0001
Time						
Placebo slope* [/year]		-2.937	0.163	-3.256	-2.618	<0.0001
Empa 10mg slope* [/year]		-1.474	0.163	-1.793	-1.155	<0.0001
Treatment by time interaction						
Empa 10mg vs Placebo slope [/year]		1.463	0.230	1.012	1.914	<0.0001
p-value for heterogeneity across subgroups						
Empa 10mg vs Placebo						0.5684

Model includes age (p<0.0001), baseline eGFR (CKD-EPI) (p<0.0001), baseline LVEF (p=0.3419) as linear covariate(s) and region (p=0.3537), baseline diabetes status (p<0.0001), baseline eGFR by Time interaction (p<0.0001), Treatment by Sex interaction (p<0.0001), Time by Treatment by Sex interaction (p<0.0001) as fixed effect(s). Intercept and slope allowed to vary randomly between patients.
* All covariate effects are set equal to their mean values within subgroup for the calculation of slope and intercept.
The following covariance structure has been used to fit the mixed model: Unstructured

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R.1.1.2.1.3 Subgroup analysis by age (<70/>=70 years)

Table R.1.1.2.1.3: 1 EGFR (CKD-EP)cr [mL/min/1.73m2] change from baseline slope from random intercept random coefficients model by age (<70/>=70 years) - TS

Subgroup Factor Comparison	N analysed	Estimate	Standard error	95% CI LL	95% CI UL	p-value
Age [years]: <70						
Intercept						
Placebo intercept*	1056	0.170	0.224	-0.268	0.608	0.4470
Empa 10mg intercept*	1043	-3.071	0.226	-3.514	-2.627	<0.0001
Time						
Placebo slope* [/year]		-2.864	0.176	-3.210	-2.519	<0.0001
Empa 10mg slope* [/year]		-1.575	0.180	-1.929	-1.222	<0.0001
Treatment by time interaction						
Empa 10mg vs Placebo slope [/year]		1.289	0.252	0.795	1.783	<0.0001
Age [years]: >=70						
Intercept						
Placebo intercept*	1855	-0.312	0.169	-0.643	0.019	0.0644
Empa 10mg intercept*	1882	-2.900	0.167	-3.227	-2.573	<0.0001
Time						
Placebo slope* [/year]		-2.478	0.136	-2.745	-2.211	<0.0001
Empa 10mg slope* [/year]		-1.070	0.135	-1.335	-0.805	<0.0001
Treatment by time interaction						
Empa 10mg vs Placebo slope [/year]		1.408	0.192	1.032	1.784	<0.0001
p-value for heterogeneity across subgroups						
Empa 10mg vs Placebo						0.7076

Model includes baseline eGFR (CKD-EPI) (p<0.0001), baseline LVEF (p=0.2742) as linear covariate(s) and region (p=0.3563), baseline diabetes status (p<0.0001), sex (p=0.0855), baseline eGFR by Time interaction (p<0.0001), Treatment by age [years] interaction (p<0.0001), Time by Treatment by age [years] interaction (p<0.0001) as fixed effect(s). Intercept and slope allowed to vary randomly between patients.
* All covariate effects are set equal to their mean values within subgroup for the calculation of slope and intercept.
The following covariance structure has been used to fit the mixed model: Unstructured

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R.1.1.2.1.4 Subgroup analysis by region (North America, Latin America, Europe, Asia, Other)

Table R.1.1.2.1.4: 1 EGFR (CKD-EP)cr [mL/min/1.73m2] change from baseline slope from random intercept random coefficients model by region (North America, Latin America, Europe, Asia, Other) - TS

Subgroup Factor Comparison	N analysed	Estimate	Standard error	95% CI LL	95% CI UL	p-value
Region: North America						
Intercept						
Placebo intercept*	348	0.120	0.392	-0.648	0.887	0.7602
Empa 10mg intercept*	348	-2.938	0.393	-3.709	-2.167	<0.0001
Time						
Placebo slope* [/year]		-3.408	0.336	-4.066	-2.750	<0.0001
Empa 10mg slope* [/year]		-1.295	0.337	-1.956	-0.635	0.0001
Treatment by time interaction						
Empa 10mg vs Placebo slope [/year]		2.113	0.476	1.181	3.046	<0.0001
Region: Latin America						
Intercept						
Placebo intercept*	739	0.311	0.268	-0.214	0.836	0.2456
Empa 10mg intercept*	743	-2.878	0.267	-3.402	-2.354	<0.0001
Time						
Placebo slope* [/year]		-3.303	0.220	-3.734	-2.871	<0.0001
Empa 10mg slope* [/year]		-1.955	0.219	-2.384	-1.525	<0.0001
Treatment by time interaction						
Empa 10mg vs Placebo slope [/year]		1.348	0.311	0.739	1.957	<0.0001
Region: Europe						
Intercept						
Placebo intercept*	1306	-0.649	0.201	-1.042	-0.255	0.0012
Empa 10mg intercept*	1311	-3.252	0.200	-3.644	-2.861	<0.0001
Time						
Placebo slope* [/year]		-1.843	0.158	-2.152	-1.534	<0.0001
Empa 10mg slope* [/year]		-0.557	0.158	-0.867	-0.247	0.0004
Treatment by time interaction						
Empa 10mg vs Placebo slope [/year]		1.286	0.223	0.849	1.723	<0.0001

Model includes age (p<0.0001), baseline eGFR (CKD-EPI) (p<0.0001), baseline LVEF (p=0.3139) as linear covariate(s) and baseline diabetes status (p<0.0001), sex (p=0.0863), baseline eGFR by Time interaction (p<0.0001), Treatment by region interaction (p<0.0001), Time by Treatment by region interaction (p<0.0001) as fixed effect(s). Intercept and slope allowed to vary randomly between patients.
* All covariate effects are set equal to their mean values within subgroup for the calculation of slope and intercept.
The following covariance structure has been used to fit the mixed model: Unstructured

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Table R.1.1.2.1.4: 1 EGFR (CKD-EP)cr [mL/min/1.73m2] change from baseline slope from random intercept random coefficients model by region (North America, Latin America, Europe, Asia, Other) - TS

Subgroup Factor Comparison	N analysed	Estimate	Standard error	95% CI LL	95% CI UL	p-value
Region: Asia						
Intercept						
Placebo intercept*	337	0.280	0.366	-0.438	0.998	0.4442
Empa 10mg intercept*	337	-2.855	0.365	-3.570	-2.140	<0.0001
Time						
Placebo slope* [/year]		-3.120	0.278	-3.665	-2.575	<0.0001
Empa 10mg slope* [/year]		-2.017	0.277	-2.560	-1.474	<0.0001
Treatment by time interaction						
Empa 10mg vs Placebo slope [/year]		1.103	0.392	0.334	1.873	0.0049
Region: Other						
Intercept						
Placebo intercept*	181	-0.139	0.540	-1.197	0.919	0.7969
Empa 10mg intercept*	186	-2.247	0.537	-3.301	-1.194	<0.0001
Time						
Placebo slope* [/year]		-3.337	0.440	-4.200	-2.474	<0.0001
Empa 10mg slope* [/year]		-2.057	0.462	-2.963	-1.152	<0.0001
Treatment by time interaction						
Empa 10mg vs Placebo slope [/year]		1.280	0.638	0.029	2.531	0.0449
p-value for heterogeneity across subgroups						
Empa 10mg vs Placebo						0.5477

Model includes age (p<0.0001), baseline eGFR (CKD-EPI) (p<0.0001), baseline LVEF (p=0.3139) as linear covariate(s) and baseline diabetes status (p<0.0001), sex (p=0.0863), baseline eGFR by Time interaction (p<0.0001), Treatment by region interaction (p<0.0001), Time by Treatment by region interaction (p<0.0001) as fixed effect(s). Intercept and slope allowed to vary randomly between patients.
* All covariate effects are set equal to their mean values within subgroup for the calculation of slope and intercept.
The following covariance structure has been used to fit the mixed model: Unstructured

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R.1.1.2.1.5 Subgroup analysis by OECD member (Y/N)

Table R.1.1.2.1.5: 1 EGFR (CKD-EP)cr [mL/min/1.73m2] change from baseline slope from random intercept random coefficients model by OECD member (Y/N) - TS

Subgroup Factor Comparison	N analysed	Estimate	Standard error	95% CI LL	95% CI UL	p-value
OECD member: N						
Intercept						
Placebo intercept*	820	-0.254	0.295	-0.832	0.324	0.3886
Empa 10mg intercept*	847	-3.294	0.295	-3.871	-2.716	<0.0001
Time						
Placebo slope* [/year]		-2.685	0.210	-3.096	-2.274	<0.0001
Empa 10mg slope* [/year]		-1.493	0.209	-1.902	-1.084	<0.0001
Treatment by time interaction						
Empa 10mg vs Placebo slope [/year]		1.192	0.296	0.613	1.772	<0.0001
OECD member: Y						
Intercept						
Placebo intercept*	2091	-0.085	0.166	-0.411	0.241	0.6092
Empa 10mg intercept*	2078	-2.834	0.168	-3.163	-2.505	<0.0001
Time						
Placebo slope* [/year]		-2.588	0.126	-2.834	-2.341	<0.0001
Empa 10mg slope* [/year]		-1.161	0.126	-1.409	-0.914	<0.0001
Treatment by time interaction						
Empa 10mg vs Placebo slope [/year]		1.427	0.178	1.077	1.776	<0.0001
p-value for heterogeneity across subgroups						
Empa 10mg vs Placebo						0.4974

Model includes age (p<0.0001), baseline eGFR (CKD-EPI) (p<0.0001), baseline LVEF (p=0.2917) as linear covariate(s) and region (p=0.1871), baseline diabetes status (p<0.0001), sex (p=0.0896), baseline eGFR by Time interaction (p<0.0001), Treatment by OECD member interaction (p<0.0001), Time by Treatment by OECD member interaction (p<0.0001) as fixed effect(s). Intercept and slope allowed to vary randomly between patients.
* All covariate effects are set equal to their mean values within subgroup for the calculation of slope and intercept.
The following covariance structure has been used to fit the mixed model: Unstructured

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R.1.1.2.1.6 Subgroup analysis by NYHA class at baseline (II/III or IV)

Table R.1.1.2.1.6: 1 EGFR (CKD-EP)cr [mL/min/1.73m2] change from baseline slope from random intercept random coefficients model by NYHA class at baseline (II/III or IV) - TS

Subgroup Factor Comparison	N analysed	Estimate	Standard error	95% CI LL	95% CI UL	p-value
Baseline NYHA: II^						
Intercept						
Placebo intercept*	2390	-0.102	0.148	-0.392	0.188	0.4903
Empa 10mg intercept*	2386	-2.905	0.148	-3.195	-2.615	<0.0001
Time						
Placebo slope* [/year]		-2.608	0.118	-2.839	-2.377	<0.0001
Empa 10mg slope* [/year]		-1.246	0.118	-1.477	-1.015	<0.0001
Treatment by time interaction						
Empa 10mg vs Placebo slope [/year]		1.362	0.167	1.035	1.688	<0.0001
Baseline NYHA: III/IV						
Intercept						
Placebo intercept*	521	-0.280	0.322	-0.912	0.351	0.3840
Empa 10mg intercept*	539	-3.243	0.318	-3.867	-2.619	<0.0001
Time						
Placebo slope* [/year]		-2.688	0.267	-3.212	-2.165	<0.0001
Empa 10mg slope* [/year]		-1.327	0.271	-1.857	-0.796	<0.0001
Treatment by time interaction						
Empa 10mg vs Placebo slope [/year]		1.362	0.380	0.616	2.107	0.0003
p-value for heterogeneity across subgroups						
Empa 10mg vs Placebo						1.0000

Model includes age (p<0.0001), baseline eGFR (CKD-EPI) (p<0.0001), baseline LVEF (p=0.3303) as linear covariate(s) and region (p=0.4541), baseline diabetes status (p<0.0001), sex (p=0.1432), baseline eGFR by Time interaction (p<0.0001), Treatment by baseline NYHA interaction (p<0.0001), Time by Treatment by baseline NYHA interaction (p<0.0001) as fixed effect(s). Intercept and slope allowed to vary randomly between patients.
* All covariate effects are set equal to their mean values within subgroup for the calculation of slope and intercept.
The following covariance structure has been used to fit the mixed model: Unstructured

Analysis is based on study 1245.110
^ Patients with NYHA class I are counted in subgroup NYHA class II.

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R.1.1.2.1.7 Subgroup analysis by diabetes at baseline (diabetic/non-diabetic)

Table R.1.1.2.1.7: 1 EGFR (CKD-EP)cr [mL/min/1.73m2] change from baseline slope from random intercept random coefficients model by diabetes at baseline (diabetic/non-diabetic) - TS

Subgroup Factor Comparison	N analysed	Estimate	Standard error	95% CI LL	95% CI UL	p-value
Baseline diabetes status: Diabetic						
Intercept						
Placebo intercept*	1430	-0.141	0.193	-0.519	0.236	0.4633
Empa 10mg intercept*	1429	-3.459	0.193	-3.836	-3.081	<0.0001
Time						
Placebo slope* [/year]		-3.013	0.155	-3.316	-2.710	<0.0001
Empa 10mg slope* [/year]		-1.248	0.156	-1.553	-0.943	<0.0001
Treatment by time interaction						
Empa 10mg vs Placebo slope [/year]		1.766	0.219	1.336	2.195	<0.0001
Baseline diabetes status: Non-Diabetic						
Intercept						
Placebo intercept*	1481	-0.127	0.187	-0.494	0.240	0.4964
Empa 10mg intercept*	1496	-2.513	0.186	-2.878	-2.147	<0.0001
Time						
Placebo slope* [/year]		-2.243	0.150	-2.537	-1.949	<0.0001
Empa 10mg slope* [/year]		-1.260	0.150	-1.554	-0.966	<0.0001
Treatment by time interaction						
Empa 10mg vs Placebo slope [/year]		0.983	0.212	0.567	1.398	<0.0001
p-value for heterogeneity across subgroups						
Empa 10mg vs Placebo						0.0103

Model includes age (p<0.0001), baseline eGFR (CKD-EPI) (p<0.0001), baseline LVEF (p=0.3695) as linear covariate(s) and region (p=0.3518), sex (p=0.0640), baseline eGFR by Time interaction (p<0.0001),
Treatment by baseline diabetes status interaction (p<0.0001),
Time by Treatment by baseline diabetes status interaction (p<0.0001) as fixed effect(s). Intercept and slope allowed to vary randomly between patients.
* All covariate effects are set equal to their mean values within subgroup for the calculation of slope and intercept.
The following covariance structure has been used to fit the mixed model: Unstructured

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R.1.1.2.1.8 Subgroup analysis by diabetes at baseline (diabetic/pre-diabetic/non-diabetic)

Table R.1.1.2.1.8: 1 EGFR (CKD-EP)cr [mL/min/1.73m2] change from baseline slope from random intercept random coefficients model by diabetes at baseline (diabetic/pre-diabetic/non-diabetic) - TS

Subgroup Factor Comparison	N analysed	Estimate	Standard error	95% CI LL	95% CI UL	p-value
Baseline diabetes status: Diabetic						
Intercept						
Placebo intercept*	1430	-0.141	0.193	-0.518	0.237	0.4643
Empa 10mg intercept*	1429	-3.458	0.193	-3.836	-3.081	<0.0001
Time						
Placebo slope* [/year]		-3.013	0.155	-3.316	-2.710	<0.0001
Empa 10mg slope* [/year]		-1.248	0.156	-1.553	-0.943	<0.0001
Treatment by time interaction						
Empa 10mg vs Placebo slope [/year]		1.766	0.219	1.336	2.195	<0.0001
Baseline diabetes status: Pre-Diabetes						
Intercept						
Placebo intercept*	954	-0.204	0.233	-0.661	0.252	0.3802
Empa 10mg intercept*	979	-2.630	0.230	-3.082	-2.178	<0.0001
Time						
Placebo slope* [/year]		-2.107	0.186	-2.471	-1.742	<0.0001
Empa 10mg slope* [/year]		-1.183	0.186	-1.549	-0.818	<0.0001
Treatment by time interaction						
Empa 10mg vs Placebo slope [/year]		0.923	0.263	0.407	1.439	0.0005

Model includes age (p<0.0001), baseline eGFR (CKD-EPI) (p<0.0001), baseline LVEF (p=0.3626) as linear covariate(s) and region (p=0.3526), sex (p=0.0734), baseline eGFR by Time interaction (p<0.0001),
Treatment by baseline diabetes status interaction (p<0.0001),
Time by Treatment by baseline diabetes status interaction (p<0.0001) as fixed effect(s). Intercept and slope allowed to vary randomly between patients.
* All covariate effects are set equal to their mean values within subgroup for the calculation of slope and intercept.
The following covariance structure has been used to fit the mixed model: Unstructured
The p-value for treatment by subgroup interaction trend test for slope is 0.0338.

Analysis is based on study 1245.110

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Table R.1.1.2.1.8: 1 EGFR (CKD-EP)cr [mL/min/1.73m2] change from baseline slope from random intercept random coefficients model by diabetes at baseline (diabetic/pre-diabetic/non-diabetic) - TS

Subgroup Factor Comparison	N analysed	Estimate	Standard error	95% CI LL	95% CI UL	p-value
Baseline diabetes status: Normal (no pre-diabetes)						
Intercept						
Placebo intercept*	527	0.011	0.313	-0.603	0.624	0.9731
Empa 10mg intercept*	517	-2.290	0.315	-2.908	-1.672	<0.0001
Time						
Placebo slope* [/year]		-2.496	0.254	-2.994	-1.998	<0.0001
Empa 10mg slope* [/year]		-1.402	0.251	-1.895	-0.909	<0.0001
Treatment by time interaction						
Empa 10mg vs Placebo slope [/year]		1.095	0.357	0.394	1.795	0.0022
p-value for heterogeneity across subgroups						
Empa 10mg vs Placebo						0.0347

Model includes age (p<0.0001), baseline eGFR (CKD-EPI) (p<0.0001), baseline LVEF (p=0.3626) as linear covariate(s) and region (p=0.3526), sex (p=0.0734), baseline eGFR by Time interaction (p<0.0001),
Treatment by baseline diabetes status interaction (p<0.0001),
Time by Treatment by baseline diabetes status interaction (p<0.0001) as fixed effect(s). Intercept and slope allowed to vary randomly between patients.
* All covariate effects are set equal to their mean values within subgroup for the calculation of slope and intercept.
The following covariance structure has been used to fit the mixed model: Unstructured
The p-value for treatment by subgroup interaction trend test for slope is 0.0338.

Analysis is based on study 1245.110

R.1.1.2.1.9 Subgroup analysis by BMI at baseline (<30/>=30)

Table R.1.1.2.1.9: 1 EGFR (CKD-EP)cr [mL/min/1.73m2] change from baseline slope from random intercept random coefficients model by BMI at baseline (<30/>=30) - TS

Subgroup Factor Comparison	N analysed	Estimate	Standard error	95% CI LL	95% CI UL	p-value
Baseline BMI [kg/m2]: <30						
Intercept						
Placebo intercept*	1594	-0.248	0.180	-0.601	0.105	0.1685
Empa 10mg intercept*	1607	-2.829	0.179	-3.181	-2.478	<0.0001
Time						
Placebo slope* [/year]		-2.743	0.145	-3.028	-2.457	<0.0001
Empa 10mg slope* [/year]		-1.331	0.145	-1.615	-1.048	<0.0001
Treatment by time interaction						
Empa 10mg vs Placebo slope [/year]		1.411	0.205	1.009	1.813	<0.0001
Baseline BMI [kg/m2]: >=30						
Intercept						
Placebo intercept*	1317	-0.005	0.207	-0.412	0.401	0.9795
Empa 10mg intercept*	1318	-3.156	0.207	-3.562	-2.751	<0.0001
Time						
Placebo slope* [/year]		-2.464	0.160	-2.779	-2.150	<0.0001
Empa 10mg slope* [/year]		-1.154	0.162	-1.472	-0.835	<0.0001
Treatment by time interaction						
Empa 10mg vs Placebo slope [/year]		1.311	0.228	0.864	1.758	<0.0001
p-value for heterogeneity across subgroups						
Empa 10mg vs Placebo						0.7437

Model includes age (p<0.0001), baseline eGFR (CKD-EPI) (p<0.0001), baseline LVEF (p=0.3875) as linear covariate(s) and region (p=0.6318), baseline diabetes status (p<0.0001), sex (p=0.1009), baseline eGFR by Time interaction (p<0.0001), Treatment by baseline BMI [kg/m2] interaction (p<0.0001), Time by Treatment by baseline BMI [kg/m2] interaction (p<0.0001) as fixed effect(s). Intercept and slope allowed to vary randomly between patients.
* All covariate effects are set equal to their mean values within subgroup for the calculation of slope and intercept.
The following covariance structure has been used to fit the mixed model: Unstructured

Analysis is based on study 1245.110

R.1.1.2.1.10 Subgroup analysis by eGFR at baseline (<60/>=60)

Table R.1.1.2.1.10: 1 EGFR (CKD-EP)cr [mL/min/1.73m2] change from baseline slope from random intercept random coefficients model by eGFR at baseline (<60/>=60) - TS

Subgroup Factor Comparison	N analysed	Estimate	Standard error	95% CI LL	95% CI UL	p-value
Baseline eGFR (CKD-EPI) [mL/min/1.73m2]:						
>=60						
Intercept						
Placebo intercept*	1468	-0.902	0.189	-1.272	-0.532	<0.0001
Empa 10mg intercept*	1454	-4.136	0.189	-4.507	-3.766	<0.0001
Time						
Placebo slope* [/year]		-3.364	0.149	-3.656	-3.072	<0.0001
Empa 10mg slope* [/year]		-1.975	0.150	-2.268	-1.681	<0.0001
Treatment by time interaction						
Empa 10mg vs Placebo slope [/year]		1.390	0.211	0.976	1.803	<0.0001
Baseline eGFR (CKD-EPI) [mL/min/1.73m2]:						
<60						
Intercept						
Placebo intercept*	1443	0.645	0.192	0.269	1.021	0.0008
Empa 10mg intercept*	1471	-1.785	0.190	-2.158	-1.413	<0.0001
Time						
Placebo slope* [/year]		-1.866	0.156	-2.172	-1.559	<0.0001
Empa 10mg slope* [/year]		-0.531	0.156	-0.837	-0.224	0.0007
Treatment by time interaction						
Empa 10mg vs Placebo slope [/year]		1.335	0.221	0.902	1.768	<0.0001
p-value for heterogeneity across subgroups						
Empa 10mg vs Placebo						0.8586

Model includes age (p<0.0001), baseline eGFR (CKD-EPI) (p<0.0001), baseline LVEF (p=0.3094) as linear covariate(s) and region (p=0.3483), baseline diabetes status (p<0.0001), sex (p=0.0885), baseline by Time interaction (p<0.0001), Treatment by baseline eGFR (CKD-EPI) (2 cat.) interaction (p<0.0001), Time by Treatment by baseline eGFR (CKD-EPI) (2 cat.) interaction (p<0.0001) as fixed effect(s). Intercept and slope allowed to vary randomly between patients.
* All covariate effects are set equal to their mean values within subgroup for the calculation of slope and intercept.
The following covariance structure has been used to fit the mixed model: Unstructured
2 patients were excluded as the subgroup variable was missing.

Analysis is based on study 1245.110

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R.1.1.2.1.11 Subgroup analysis by history of HHF (Y/N)

Table R.1.1.2.1.11: 1 EGFR (CKD-EP)cr [mL/min/1.73m2] change from baseline slope from random intercept random coefficients model by history of HHF (Y/N) - TS

Subgroup Factor Comparison	N analysed	Estimate	Standard error	95% CI LL	95% CI UL	p-value
History of HHF (in the last 12 months): No						
Intercept						
Placebo intercept*	2264	-0.064	0.153	-0.365	0.237	0.6770
Empa 10mg intercept*	2245	-3.097	0.154	-3.398	-2.796	<0.0001
Time						
Placebo slope* [/year]		-2.661	0.122	-2.900	-2.422	<0.0001
Empa 10mg slope* [/year]		-1.301	0.123	-1.542	-1.061	<0.0001
Treatment by time interaction						
Empa 10mg vs Placebo slope [/year]		1.360	0.173	1.021	1.698	<0.0001
History of HHF (in the last 12 months): Yes						
Intercept						
Placebo intercept*	647	-0.354	0.285	-0.911	0.204	0.2140
Empa 10mg intercept*	680	-2.509	0.278	-3.054	-1.965	<0.0001
Time						
Placebo slope* [/year]		-2.462	0.232	-2.917	-2.007	<0.0001
Empa 10mg slope* [/year]		-1.085	0.229	-1.533	-0.637	<0.0001
Treatment by time interaction						
Empa 10mg vs Placebo slope [/year]		1.377	0.326	0.739	2.015	<0.0001
p-value for heterogeneity across subgroups						
Empa 10mg vs Placebo						0.9622

Model includes age (p<0.0001), baseline eGFR (CKD-EPI) (p<0.0001), baseline LVEF (p=0.3209) as linear covariate(s) and region (p=0.3330), baseline diabetes status (p<0.0001), sex (p=0.0820), baseline eGFR by Time interaction (p<0.0001), Treatment by history of HHF (in the last 12 months) interaction (p<0.0001), Time by Treatment by history of HHF (in the last 12 months) interaction (p<0.0001) as fixed effect(s). Intercept and slope allowed to vary randomly between patients.
* All covariate effects are set equal to their mean values within subgroup for the calculation of slope and intercept.
The following covariance structure has been used to fit the mixed model: Unstructured

Analysis is based on study 1245.110

R.1.1.2.1.12 Subgroup analysis by SBP at baseline (<median/>=median)

Table R.1.1.2.1.12: 1 EGFR (CKD-EP)cr [mL/min/1.73m2] change from baseline slope from random intercept random coefficients model by SBP at baseline (<median/>=median) - TS

Subgroup Factor Comparison	N analysed	Estimate	Standard error	95% CI LL	95% CI UL	p-value
Baseline SBP (</>= median): < median						
Intercept						
Placebo intercept*	1438	0.287	0.190	-0.086	0.660	0.1314
Empa 10mg intercept*	1465	-2.577	0.189	-2.948	-2.206	<0.0001
Time						
Placebo slope* [/year]		-2.384	0.152	-2.682	-2.085	<0.0001
Empa 10mg slope* [/year]		-0.971	0.153	-1.272	-0.670	<0.0001
Treatment by time interaction						
Empa 10mg vs Placebo slope [/year]		1.413	0.216	0.989	1.837	<0.0001
Baseline SBP (</>= median): >= median						
Intercept						
Placebo intercept*	1473	-0.543	0.189	-0.914	-0.172	0.0041
Empa 10mg intercept*	1460	-3.360	0.190	-3.732	-2.988	<0.0001
Time						
Placebo slope* [/year]		-2.849	0.152	-3.147	-2.550	<0.0001
Empa 10mg slope* [/year]		-1.530	0.152	-1.828	-1.232	<0.0001
Treatment by time interaction						
Empa 10mg vs Placebo slope [/year]		1.319	0.215	0.897	1.740	<0.0001
p-value for heterogeneity across subgroups						
Empa 10mg vs Placebo						0.7579

Model includes age (p<0.0001), baseline eGFR (CKD-EPI) (p<0.0001), baseline LVEF (p=0.5083) as linear covariate(s) and region (p=0.3916), baseline diabetes status (p<0.0001), sex (p=0.0805), baseline eGFR by Time interaction (p<0.0001), Treatment by baseline SBP (</>= median) interaction (p<0.0001), Time by Treatment by baseline SBP (</>= median) interaction (p<0.0001) as fixed effect(s). Intercept and slope allowed to vary randomly between patients.
* All covariate effects are set equal to their mean values within subgroup for the calculation of slope and intercept.
The following covariance structure has been used to fit the mixed model: Unstructured

Analysis is based on study 1245.110
Baseline SBP median: 132 [mmHg]

R.1.1.2.1.13 Subgroup analysis by history of atrial fibrillation or atrial flutter (Y/N)

Table R.1.1.2.1.13: 1 EGFR (CKD-EP)cr [mL/min/1.73m2] change from baseline slope from random intercept random coefficients model by history of atrial fibrillation or atrial flutter (Y/N) - TS

Subgroup Factor Comparison	N analysed	Estimate	Standard error	95% CI LL	95% CI UL	p-value
History of Atrial Fibrillation or A. Flutter: No						
Intercept						
Placebo intercept*	1384	0.056	0.197	-0.330	0.442	0.7759
Empa 10mg intercept*	1381	-3.047	0.197	-3.434	-2.660	<0.0001
Time						
Placebo slope* [/year]		-2.802	0.157	-3.109	-2.495	<0.0001
Empa 10mg slope* [/year]		-1.430	0.155	-1.735	-1.126	<0.0001
Treatment by time interaction						
Empa 10mg vs Placebo slope [/year]		1.372	0.220	0.940	1.804	<0.0001
History of Atrial Fibrillation or A. Flutter: Yes						
Intercept						
Placebo intercept*	1523	-0.289	0.186	-0.654	0.076	0.1203
Empa 10mg intercept*	1540	-2.923	0.185	-3.286	-2.561	<0.0001
Time						
Placebo slope* [/year]		-2.433	0.148	-2.723	-2.142	<0.0001
Empa 10mg slope* [/year]		-1.065	0.150	-1.359	-0.771	<0.0001
Treatment by time interaction						
Empa 10mg vs Placebo slope [/year]		1.368	0.211	0.955	1.780	<0.0001
p-value for heterogeneity across subgroups						
Empa 10mg vs Placebo						0.9887

Model includes age (p<0.0001), baseline eGFR (CKD-EPI) (p<0.0001), baseline LVEF (p=0.2912) as linear covariate(s) and region (p=0.3739), baseline diabetes status (p<0.0001), sex (p=0.0685), baseline eGFR by Time interaction (p<0.0001), Treatment by history of atrial fibrillation/flutter interaction (p<0.0001), Time by Treatment by history of atrial fibrillation/flutter interaction (p<0.0001) as fixed effect(s). Intercept and slope allowed to vary randomly between patients.
* All covariate effects are set equal to their mean values within subgroup for the calculation of slope and intercept.
The following covariance structure has been used to fit the mixed model: Unstructured
9 patients were excluded as the subgroup variable was missing.

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R.1.1.2.1.14 Subgroup analysis by LVEF at baseline (<50/>=50)

Table R.1.1.2.1.14: 1 EGFR (CKD-EP)cr [mL/min/1.73m2] change from baseline slope from random intercept random coefficients model by LVEF at baseline (<50/>=50) - TS

Subgroup Factor Comparison	N analysed	Estimate	Standard error	95% CI LL	95% CI UL	p-value
Baseline LVEF [%]: < 50						
Intercept						
Placebo intercept*	954	-0.402	0.236	-0.865	0.061	0.0891
Empa 10mg intercept*	973	-2.952	0.235	-3.411	-2.492	<0.0001
Time						
Placebo slope* [/year]		-2.613	0.187	-2.980	-2.246	<0.0001
Empa 10mg slope* [/year]		-1.002	0.188	-1.370	-0.634	<0.0001
Treatment by time interaction						
Empa 10mg vs Placebo slope [/year]		1.611	0.265	1.092	2.130	<0.0001
Baseline LVEF [%]: >= 50						
Intercept						
Placebo intercept*	1957	0.001	0.164	-0.320	0.322	0.9949
Empa 10mg intercept*	1952	-2.974	0.164	-3.296	-2.653	<0.0001
Time						
Placebo slope* [/year]		-2.616	0.132	-2.875	-2.358	<0.0001
Empa 10mg slope* [/year]		-1.377	0.132	-1.636	-1.118	<0.0001
Treatment by time interaction						
Empa 10mg vs Placebo slope [/year]		1.239	0.186	0.874	1.605	<0.0001
p-value for heterogeneity across subgroups						
Empa 10mg vs Placebo						0.2512

Model includes age (p<0.0001), baseline eGFR (CKD-EPI) (p<0.0001) as linear covariate(s) and region (p=0.3961), baseline diabetes status (p<0.0001), sex (p=0.0555), baseline eGFR by Time interaction (p<0.0001), Treatment by baseline LVEF [%] interaction (p<0.0001), Time by Treatment by baseline LVEF [%] interaction (p<0.0001) as fixed effect(s). Intercept and slope allowed to vary randomly between patients.
* All covariate effects are set equal to their mean values within subgroup for the calculation of slope and intercept.
The following covariance structure has been used to fit the mixed model: Unstructured

Analysis is based on study 1245.110

R.1.1.2.1.15 Subgroup analysis by LVEF at baseline (<50/50 to <60/>=60)

Table R.1.1.2.1.15: 1 EGFR (CKD-EP)cr [mL/min/1.73m2] change from baseline slope from random intercept random coefficients model by LVEF at baseline (<50/50 to <60/>=60) - TS

Subgroup Factor Comparison	N analysed	Estimate	Standard error	95% CI LL	95% CI UL	p-value
Baseline LVEF [%]: <50						
Intercept						
Placebo intercept*	954	-0.395	0.236	-0.859	0.068	0.0945
Empa 10mg intercept*	973	-2.945	0.235	-3.405	-2.485	<0.0001
Time						
Placebo slope* [/year]		-2.613	0.187	-2.980	-2.246	<0.0001
Empa 10mg slope* [/year]		-1.002	0.188	-1.370	-0.634	<0.0001
Treatment by time interaction						
Empa 10mg vs Placebo slope [/year]		1.611	0.265	1.092	2.130	<0.0001
Baseline LVEF [%]: 50 to <60						
Intercept						
Placebo intercept*	1002	0.200	0.229	-0.250	0.650	0.3832
Empa 10mg intercept*	1001	-2.846	0.229	-3.295	-2.398	<0.0001
Time						
Placebo slope* [/year]		-2.663	0.185	-3.026	-2.299	<0.0001
Empa 10mg slope* [/year]		-1.227	0.185	-1.588	-0.865	<0.0001
Treatment by time interaction						
Empa 10mg vs Placebo slope [/year]		1.436	0.261	0.924	1.949	<0.0001

Model includes age (p<0.0001), baseline eGFR (CKD-EPI) (p<0.0001) as linear covariate(s) and region (p=0.3539), baseline diabetes status (p<0.0001), sex (p=0.0826), baseline eGFR by Time interaction (p<0.0001), Treatment by baseline LVEF [%] interaction (p<0.0001), Time by Treatment by baseline LVEF [%] interaction (p<0.0001) as fixed effect(s). Intercept and slope allowed to vary randomly between patients.
* All covariate effects are set equal to their mean values within subgroup for the calculation of slope and intercept.
The following covariance structure has been used to fit the mixed model: Unstructured
The p-value for treatment by subgroup interaction trend test for slope is 0.1238.

Analysis is based on study 1245.110

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Table R.1.1.2.1.15: 1 EGFR (CKD-EP)cr [mL/min/1.73m2] change from baseline slope from random intercept random coefficients model by LVEF at baseline (<50/50 to <60/>=60) - TS

Subgroup Factor Comparison	N analysed	Estimate	Standard error	95% CI LL	95% CI UL	p-value
Baseline LVEF [%]: >=60						
Intercept						
Placebo intercept*	955	-0.206	0.233	-0.663	0.252	0.3778
Empa 10mg intercept*	951	-3.109	0.234	-3.568	-2.651	<0.0001
Time						
Placebo slope* [/year]		-2.568	0.187	-2.935	-2.201	<0.0001
Empa 10mg slope* [/year]		-1.534	0.189	-1.905	-1.164	<0.0001
Treatment by time interaction						
Empa 10mg vs Placebo slope [/year]		1.034	0.266	0.512	1.555	0.0001
p-value for heterogeneity across subgroups						
Empa 10mg vs Placebo						0.2880

Model includes age (p<0.0001), baseline eGFR (CKD-EPI) (p<0.0001) as linear covariate(s) and region (p=0.3539), baseline diabetes status (p<0.0001), sex (p=0.0826), baseline eGFR by Time interaction (p<0.0001), Treatment by baseline LVEF [%] interaction (p<0.0001), Time by Treatment by baseline LVEF [%] interaction (p<0.0001) as fixed effect(s). Intercept and slope allowed to vary randomly between patients.
* All covariate effects are set equal to their mean values within subgroup for the calculation of slope and intercept.
The following covariance structure has been used to fit the mixed model: Unstructured
The p-value for treatment by subgroup interaction trend test for slope is 0.1238.

Analysis is based on study 1245.110

R.1.1.2.1.16 Subgroup analysis by NTproBNP at baseline (<median/>=median)

Table R.1.1.2.1.16: 1 EGFR (CKD-EP)cr [mL/min/1.73m2] change from baseline slope from random intercept random coefficients model by NTproBNP at baseline (<median/>=median) - TS

Subgroup Factor Comparison	N analysed	Estimate	Standard error	95% CI LL	95% CI UL	p-value
Baseline NT-proBNP [pg/mL] (</>=median by atrial fibrillation/flutter status): < median						
Intercept						
Placebo intercept*	1477	0.090	0.188	-0.278	0.457	0.6322
Empa 10mg intercept*	1440	-2.915	0.190	-3.289	-2.542	<0.0001
Time						
Placebo slope* [/year]		-2.609	0.147	-2.897	-2.321	<0.0001
Empa 10mg slope* [/year]		-1.188	0.149	-1.480	-0.895	<0.0001
Treatment by time interaction						
Empa 10mg vs Placebo slope [/year]		1.421	0.209	1.011	1.832	<0.0001
Baseline NT-proBNP [pg/mL] (</>=median by atrial fibrillation/flutter status): >= median						
Intercept						
Placebo intercept*	1429	-0.339	0.191	-0.714	0.036	0.0762
Empa 10mg intercept*	1481	-3.020	0.187	-3.388	-2.653	<0.0001
Time						
Placebo slope* [/year]		-2.625	0.158	-2.934	-2.315	<0.0001
Empa 10mg slope* [/year]		-1.306	0.156	-1.611	-1.001	<0.0001
Treatment by time interaction						
Empa 10mg vs Placebo slope [/year]		1.319	0.222	0.884	1.753	<0.0001
p-value for heterogeneity across subgroups						
Empa 10mg vs Placebo						0.7361

Model includes age (p<0.0001), baseline eGFR (CKD-EPI) (p<0.0001), baseline LVEF (p=0.1175) as linear covariate(s) and region (p=0.2069), baseline diabetes status (p<0.0001), sex (p=0.0660), baseline eGFR by Time interaction (p<0.0001), Treatment by baseline NT-proBNP (</>=median by atrial fib./flutter) interaction (p<0.0001), Time by Treatment by baseline NT-proBNP (</>=median by atrial fib./flutter) interaction (p<0.0001) as fixed effect(s). Intercept and slope allowed to vary randomly between patients.
* All covariate effects are set equal to their mean values within subgroup for the calculation of slope and intercept.
The following covariance structure has been used to fit the mixed model: Unstructured
11 patients were excluded as the subgroup variable was missing.

Analysis is based on study 1245.110
Baseline NT-proBNP median for patients with history of atrial fibrillation or atrial flutter: 1354 [pg/mL]
Baseline NT-proBNP median for patients without history of atrial fibrillation or atrial flutter: 614 [pg/mL]

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R.1.1.2.1.17 Subgroup analysis by uric acid at baseline (tertiles)

Table R.1.1.2.1.17: 1 EGFR (CKD-EP)cr [mL/min/1.73m2] change from baseline slope from random intercept random coefficients model by uric acid at baseline (tertiles) - TS

Subgroup Factor Comparison	N analysed	Estimate	Standard error	95% CI LL	95% CI UL	p-value
Baseline uric acid [mg/dL] (tertiles): <T1						
Intercept						
Placebo intercept*	952	-0.642	0.234	-1.101	-0.183	0.0061
Empa 10mg intercept*	941	-2.950	0.235	-3.410	-2.489	<0.0001
Time						
Placebo slope* [/year]		-3.043	0.188	-3.412	-2.675	<0.0001
Empa 10mg slope* [/year]		-1.744	0.189	-2.115	-1.373	<0.0001
Treatment by time interaction						
Empa 10mg vs Placebo slope [/year]		1.299	0.267	0.777	1.822	<0.0001
Baseline uric acid [mg/dL] (tertiles): >=T1 and <T2						
Intercept						
Placebo intercept*	942	-0.225	0.234	-0.683	0.233	0.3360
Empa 10mg intercept*	1004	-3.414	0.226	-3.858	-2.970	<0.0001
Time						
Placebo slope* [/year]		-2.602	0.187	-2.969	-2.235	<0.0001
Empa 10mg slope* [/year]		-1.301	0.183	-1.660	-0.943	<0.0001
Treatment by time interaction						
Empa 10mg vs Placebo slope [/year]		1.301	0.261	0.788	1.813	<0.0001

Model includes age (p<0.0001), baseline eGFR (CKD-EPI) (p<0.0001), baseline LVEF (p=0.3078) as linear covariate(s) and region (p=0.3170), baseline diabetes status (p<0.0001), sex (p=0.0764), baseline eGFR by Time interaction (p<0.0001), Treatment by baseline uric acid (tertiles) interaction (p<0.0001), Time by Treatment by baseline uric acid (tertiles) interaction (p<0.0001) as fixed effect(s). Intercept and slope allowed to vary randomly between patients.
* All covariate effects are set equal to their mean values within subgroup for the calculation of slope and intercept.
The following covariance structure has been used to fit the mixed model: Unstructured
63 patients were excluded as the subgroup variable was missing.
The p-value for treatment by subgroup interaction trend test for slope is 0.7248.

Analysis is based on study 1245.110
Baseline uric acid tertile cut-offs for males are T1: 5.9 T2: 7.5 [mg/dL] [rounded]
Baseline uric acid tertile cut-offs for females are T1: 5.4 T2: 6.9 [mg/dL] [rounded]

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Table R.1.1.2.1.17: 1 EGFR (CKD-EP)cr [mL/min/1.73m2] change from baseline slope from random intercept random coefficients model by uric acid at baseline (tertiles) - TS

Subgroup Factor Comparison	N analysed	Estimate	Standard error	95% CI LL	95% CI UL	p-value
Baseline uric acid [mg/dL] (tertiles):						
>=T2						
Intercept						
Placebo intercept*	988	0.461	0.231	0.008	0.913	0.0460
Empa 10mg intercept*	951	-2.537	0.236	-2.999	-2.075	<0.0001
Time						
Placebo slope* [/year]		-2.206	0.188	-2.575	-1.837	<0.0001
Empa 10mg slope* [/year]		-0.772	0.193	-1.151	-0.394	<0.0001
Treatment by time interaction						
Empa 10mg vs Placebo slope [/year]		1.434	0.269	0.906	1.962	<0.0001
p-value for heterogeneity across subgroups						
Empa 10mg vs Placebo						0.9201

Model includes age (p<0.0001), baseline eGFR (CKD-EPI) (p<0.0001), baseline LVEF (p=0.3078) as linear covariate(s) and region (p=0.3170), baseline diabetes status (p<0.0001), sex (p=0.0764), baseline eGFR by Time interaction (p<0.0001), Treatment by baseline uric acid (tertiles) interaction (p<0.0001), Time by Treatment by baseline uric acid (tertiles) interaction (p<0.0001) as fixed effect(s). Intercept and slope allowed to vary randomly between patients.
* All covariate effects are set equal to their mean values within subgroup for the calculation of slope and intercept.
The following covariance structure has been used to fit the mixed model: Unstructured
63 patients were excluded as the subgroup variable was missing.
The p-value for treatment by subgroup interaction trend test for slope is 0.7248.

Analysis is based on study 1245.110
Baseline uric acid tertile cut-offs for males are T1: 5.9 T2: 7.5 [mg/dL] [rounded]
Baseline uric acid tertile cut-offs for females are T1: 5.4 T2: 6.9 [mg/dL] [rounded]

R.1.1.2.1.18 Subgroup analysis by baseline use of MRA (Y/N)

Table R.1.1.2.1.18: 1 EGFR (CKD-EP)cr [mL/min/1.73m2] change from baseline slope from random intercept random coefficients model by baseline use of MRA (Y/N) - TS

Subgroup Factor Comparison	N analysed	Estimate	Standard error	95% CI LL	95% CI UL	p-value
Baseline use of MRA: No						
Intercept						
Placebo intercept*	1807	0.098	0.171	-0.236	0.433	0.5649
Empa 10mg intercept*	1836	-2.890	0.169	-3.222	-2.558	<0.0001
Time						
Placebo slope* [/year]		-2.748	0.137	-3.016	-2.480	<0.0001
Empa 10mg slope* [/year]		-1.244	0.136	-1.510	-0.978	<0.0001
Treatment by time interaction						
Empa 10mg vs Placebo slope [/year]		1.504	0.193	1.127	1.882	<0.0001
Baseline use of MRA: Yes						
Intercept						
Placebo intercept*	1104	-0.491	0.218	-0.918	-0.064	0.0243
Empa 10mg intercept*	1089	-3.082	0.219	-3.512	-2.653	<0.0001
Time						
Placebo slope* [/year]		-2.397	0.175	-2.740	-2.054	<0.0001
Empa 10mg slope* [/year]		-1.269	0.178	-1.619	-0.920	<0.0001
Treatment by time interaction						
Empa 10mg vs Placebo slope [/year]		1.127	0.250	0.638	1.617	<0.0001
p-value for heterogeneity across subgroups						
Empa 10mg vs Placebo						0.2322

Model includes age (p<0.0001), baseline eGFR (CKD-EPI) (p<0.0001), baseline LVEF (p=0.2028) as linear covariate(s) and region (p=0.2558), baseline diabetes status (p<0.0001), sex (p=0.1034), baseline eGFR by Time interaction (p<0.0001), Treatment by baseline use of MRA interaction (p<0.0001), Time by Treatment by baseline use of MRA interaction (p<0.0001) as fixed effect(s). Intercept and slope allowed to vary randomly between patients.
* All covariate effects are set equal to their mean values within subgroup for the calculation of slope and intercept.
The following covariance structure has been used to fit the mixed model: Unstructured

Analysis is based on study 1245.110

R.1.1.2.1.19 Subgroup analysis by baseline use of ACE-inhibitors, ARB or ARNi (Y/N)

Table R.1.1.2.1.19: 1 EGFR (CKD-EP)cr [mL/min/1.73m2] change from baseline slope from random intercept random coefficients model by baseline use of ACE-inhibitors, ARB or ARNi (Y/N) - TS

Subgroup Factor Comparison	N analysed	Estimate	Standard error	95% CI LL	95% CI UL	p-value
Baseline use of ACE-inhibitor, ARB or ARNi: No						
Intercept						
Placebo intercept*	567	0.324	0.305	-0.274	0.922	0.2884
Empa 10mg intercept*	558	-1.805	0.305	-2.403	-1.207	<0.0001
Time						
Placebo slope* [/year]		-2.897	0.256	-3.400	-2.394	<0.0001
Empa 10mg slope* [/year]		-1.264	0.249	-1.753	-0.775	<0.0001
Treatment by time interaction						
Empa 10mg vs Placebo slope [/year]		1.633	0.358	0.932	2.334	<0.0001
Baseline use of ACE-inhibitor, ARB or ARNi: Yes						
Intercept						
Placebo intercept*	2344	-0.241	0.151	-0.536	0.054	0.1098
Empa 10mg intercept*	2367	-3.245	0.150	-3.539	-2.951	<0.0001
Time						
Placebo slope* [/year]		-2.559	0.119	-2.792	-2.326	<0.0001
Empa 10mg slope* [/year]		-1.249	0.120	-1.484	-1.014	<0.0001
Treatment by time interaction						
Empa 10mg vs Placebo slope [/year]		1.310	0.169	0.979	1.641	<0.0001
p-value for heterogeneity across subgroups						
Empa 10mg vs Placebo						0.4137

Model includes age (p<0.0001), baseline eGFR (CKD-EPI) (p<0.0001), baseline LVEF (p=0.2582) as linear covariate(s) and region (p=0.3940), baseline diabetes status (p<0.0001), sex (p=0.0898), baseline eGFR by Time interaction (p<0.0001), Treatment by baseline use of ACE-inhibitor, ARB or ARNi interaction (p<0.0001), Time by Treatment by baseline use of ACE-inhibitor, ARB or ARNi interaction (p<0.0001) as fixed effect(s). Intercept and slope allowed to vary randomly between patients.
* All covariate effects are set equal to their mean values within subgroup for the calculation of slope and intercept.
The following covariance structure has been used to fit the mixed model: Unstructured

Analysis is based on study 1245.110

R.1.1.3 Responder analyses

R.1.1.3.1.1 LOCF analyses

R.1.1.3.1.1.1 EQ-VAS responder analysis (7 points)

Table R.1.1.3.1.1.1: 1 Responder analysis for EQ-VAS change from baseline at week 52 <= -7 points (deterioration) overall and by subgroup - RS (LOCF-AD)

Subgroup	Placebo			Empa 10mg			Empa 10mg vs Placebo					
Category	N	n	%	N	n	%	Risk ratio *	(95% CI)	p-value	Odds ratio ***	(95% CI)	p-value **
Overall	2868	823	28.7	2886	773	26.8	0.92	(0.84,0.99)	0.0372	0.92	(0.81,1.04)	
Sex												0.5271
Male	1588	451	28.4	1597	421	26.4	0.89	(0.80,1.00)	0.0520	0.92	(0.78,1.09)	
Female	1280	372	29.1	1289	352	27.3	0.94	(0.84,1.06)	0.3396	0.91	(0.76,1.09)	
Age [years]												0.6336
<70	1035	263	25.4	1029	232	22.5	0.89	(0.76,1.03)	0.1213	0.92	(0.74,1.13)	
>=70	1833	560	30.6	1857	541	29.1	0.93	(0.84,1.02)	0.1285	0.91	(0.79,1.06)	
Region												0.1497
North America	344	102	29.7	341	103	30.2	1.02	(0.81,1.28)	0.8727	1.00	(0.71,1.41)	
Latin America	722	172	23.8	730	187	25.6	1.06	(0.88,1.26)	0.5395	1.13	(0.88,1.46)	
Europe	1301	407	31.3	1309	353	27.0	0.83	(0.73,0.94)	0.0024	0.81	(0.68,0.97)	
Asia	333	99	29.7	330	95	28.8	0.98	(0.78,1.23)	0.8567	1.03	(0.73,1.47)	
Other	168	43	25.6	176	35	19.9	0.79	(0.54,1.16)	0.2308	0.71	(0.42,1.21)	
OECD member												0.9595
No	790	194	24.6	822	188	22.9	0.92	(0.77,1.09)	0.3478	0.95	(0.74,1.20)	
Yes	2078	629	30.3	2064	585	28.3	0.92	(0.83,1.01)	0.0677	0.91	(0.79,1.05)	
Baseline NYHA												0.9319
II^^	2360	676	28.6	2358	633	26.8	0.91	(0.83,1.00)	0.0541	0.93	(0.81,1.06)	
III/IV	508	147	28.9	528	140	26.5	0.92	(0.76,1.12)	0.4120	0.87	(0.65,1.17)	
Baseline Diabetes status												0.8766
Diabetic	1409	395	28.0	1403	371	26.4	0.91	(0.81,1.03)	0.1280	0.95	(0.79,1.13)	
Non-Diabetic	1459	428	29.3	1483	402	27.1	0.92	(0.82,1.03)	0.1612	0.89	(0.75,1.06)	

* 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, °:Trend test.
^ 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.

Analysis is based on study 1245.110.
LOCF: For a missing value at week 52 the last available post-baseline value before week 52 is imputed.
^^ Patients with NYHA class I are counted in subgroup NYHA class II. [1] Baseline SBP median: 132 [mmHg].
[2] Baseline NT-proBNP median for patients with history of atrial fibrillation or atrial flutter: 1354 [pg/mL].
[2] Baseline NT-proBNP median for patients without history of atrial fibrillation or atrial flutter: 614 [pg/mL].
[3] Baseline uric acid tertile cut-offs for males are T1: 5.9 T2: 7.5 [mg/dL] [rounded].
[3] Baseline uric acid tertile cut-offs for females are T1: 5.4 T2: 6.9 [mg/dL] [rounded].

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Table R.1.1.3.1.1.1: 1 Responder analysis for EQ-VAS change from baseline at week 52 <= -7 points (deterioration) overall and by subgroup - RS (LOCF-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 Diabetes status												0.8430°/ 0.9808
Diabetic	1409	395	28.0	1403	371	26.4	0.91	(0.81,1.03)	0.1282	0.95	(0.79,1.13)	
Pre-Diabetes	938	281	30.0	972	269	27.7	0.92	(0.80,1.05)	0.2211	0.89	(0.72,1.09)	
Normal (no pre-diabetes)	521	147	28.2	511	133	26.0	0.93	(0.77,1.13)	0.4744	0.90	(0.68,1.21)	
Baseline BMI [kg/m²]												0.4219
<30	1567	459	29.3	1592	454	28.5	0.94	(0.85,1.05)	0.2951	0.96	(0.82,1.13)	
>=30	1301	364	28.0	1294	319	24.7	0.88	(0.77,1.00)	0.0498	0.87	(0.72,1.04)	
Baseline eGFR (CKD-EPI) [mL/min/1.73m²]												0.6478
>=60	1447	395	27.3	1444	368	25.5	0.90	(0.79,1.01)	0.0822	0.95	(0.80,1.13)	
<60	1421	428	30.1	1442	405	28.1	0.93	(0.83,1.04)	0.2210	0.89	(0.75,1.05)	
History of HHF (in the last 12 months)												0.4345
No	2231	635	28.5	2226	591	26.5	0.93	(0.85,1.02)	0.1455	0.91	(0.79,1.05)	
Yes	637	188	29.5	660	182	27.6	0.86	(0.72,1.03)	0.0993	0.94	(0.73,1.21)	
Baseline SBP (</>= median¹)												0.9441
< median	1414	397	28.1	1445	372	25.7	0.92	(0.82,1.03)	0.1624	0.90	(0.75,1.07)	
>= median	1454	426	29.3	1441	401	27.8	0.91	(0.81,1.02)	0.1230	0.94	(0.79,1.11)	
History of atrial fibrillation or atrial flutter												0.5878
No	1365	378	27.7	1363	353	25.9	0.94	(0.83,1.06)	0.3038	0.93	(0.77,1.11)	
Yes	1500	445	29.7	1520	419	27.6	0.90	(0.80,1.00)	0.0569	0.91	(0.77,1.07)	

* 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, °:Trend test.
^ 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.

Analysis is based on study 1245.110.
LOCF: For a missing value at week 52 the last available post-baseline value before week 52 is imputed.
^^ Patients with NYHA class I are counted in subgroup NYHA class II. ¹ Baseline SBP median: 132 [mmHg].
² Baseline NT-proBNP median for patients with history of atrial fibrillation or atrial flutter: 1354 [pg/mL].
² Baseline NT-proBNP median for patients without history of atrial fibrillation or atrial flutter: 614 [pg/mL].
³ Baseline uric acid tertile cut-offs for males are T1: 5.9 T2: 7.5 [mg/dL] [rounded].
³ Baseline uric acid tertile cut-offs for females are T1: 5.4 T2: 6.9 [mg/dL] [rounded].

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Table R.1.1.3.1.1.1: 1 Responder analysis for EQ-VAS change from baseline at week 52 <= -7 points (deterioration) overall and by subgroup - RS (LOCF-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 LVEF [%]												0.9115
< 50	928	246	26.5	957	232	24.2	0.92	(0.79,1.07)	0.2988	0.93	(0.75,1.16)	
>= 50	1940	577	29.7	1929	541	28.0	0.91	(0.83,1.01)	0.0718	0.91	(0.79,1.06)	
Baseline LVEF [%]												0.9799°/ 0.9853
<50	928	246	26.5	957	232	24.2	0.92	(0.79,1.07)	0.2988	0.93	(0.75,1.16)	
50 to <60	991	292	29.5	989	281	28.4	0.91	(0.79,1.04)	0.1742	0.94	(0.77,1.16)	
>=60	949	285	30.0	940	260	27.7	0.92	(0.80,1.06)	0.2363	0.88	(0.71,1.09)	
Baseline NT-proBNP [pg/mL] (</>=median[2] by atrial fibrillation/flutter status)												0.4112
< median	1463	423	28.9	1429	377	26.4	0.88	(0.78,0.99)	0.0394	0.90	(0.76,1.07)	
>= median	1401	400	28.6	1454	395	27.2	0.95	(0.84,1.06)	0.3585	0.93	(0.78,1.10)	
Baseline uric acid [mg/dL] (tertiles[3])												0.7996°/ 0.7886
<T1	934	268	28.7	930	242	26.0	0.91	(0.79,1.06)	0.2299	0.87	(0.71,1.08)	
>=T1 and <T2	932	248	26.6	997	273	27.4	0.96	(0.83,1.11)	0.5770	1.06	(0.85,1.31)	
>=T2	972	296	30.5	933	252	27.0	0.89	(0.78,1.03)	0.1134	0.86	(0.69,1.06)	
Baseline use of MRA												0.4055
No	1787	516	28.9	1813	492	27.1	0.94	(0.85,1.04)	0.2479	0.93	(0.80,1.08)	
Yes	1081	307	28.4	1073	281	26.2	0.87	(0.76,1.00)	0.0581	0.90	(0.74,1.10)	
Baseline use of ACE-inhibitor, ARB or ARNi												0.7886
No	557	162	29.1	545	142	26.1	0.89	(0.74,1.08)	0.2466	0.81	(0.62,1.08)	
Yes	2311	661	28.6	2341	631	27.0	0.92	(0.84,1.01)	0.0794	0.94	(0.82,1.08)	

* 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, °:Trend test.
^ 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.

Analysis is based on study 1245.110.
LOCF: For a missing value at week 52 the last available post-baseline value before week 52 is imputed.
^^ Patients with NYHA class I are counted in subgroup NYHA class II. [1] Baseline SBP median: 132 [mmHg].
[2] Baseline NT-proBNP median for patients with history of atrial fibrillation or atrial flutter: 1354 [pg/mL].
[2] Baseline NT-proBNP median for patients without history of atrial fibrillation or atrial flutter: 614 [pg/mL].
[3] Baseline uric acid tertile cut-offs for males are T1: 5.9 T2: 7.5 [mg/dL] [rounded].
[3] Baseline uric acid tertile cut-offs for females are T1: 5.4 T2: 6.9 [mg/dL] [rounded].

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Table R.1.1.3.1.1.1: 2 Responder analysis for EQ-VAS change from baseline at week 52 >= 7 points (improvement) overall and by subgroup - RS (LOCF-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	2868	985	34.3	2886	1068	37.0	1.05	(0.98,1.12)	0.1454	1.12	(0.99,1.27)	
Sex												0.5531
Male	1588	515	32.4	1597	549	34.4	1.03	(0.94,1.13)	0.5345	1.06	(0.90,1.26)	
Female	1280	470	36.7	1289	519	40.3	1.07	(0.98,1.17)	0.1386	1.19	(0.99,1.43)	
Age [years]												0.7390
<70	1035	376	36.3	1029	429	41.7	1.06	(0.96,1.18)	0.2210	1.17	(0.95,1.43)	
>=70	1833	609	33.2	1857	639	34.4	1.04	(0.96,1.13)	0.3534	1.10	(0.94,1.28)	
Region												0.3771
North America	344	106	30.8	341	118	34.6	1.12	(0.92,1.36)	0.2696	1.28	(0.89,1.84)	
Latin America	722	321	44.5	730	324	44.4	0.98	(0.88,1.09)	0.6801	0.97	(0.77,1.23)	
Europe	1301	401	30.8	1309	447	34.1	1.10	(0.99,1.22)	0.0810	1.19	(0.99,1.43)	
Asia	333	102	30.6	330	105	31.8	0.95	(0.78,1.17)	0.6468	0.93	(0.65,1.35)	
Other	168	55	32.7	176	74	42.0	1.16	(0.91,1.50)	0.2352	1.46	(0.89,2.39)	
OECD member												0.4259
No	790	321	40.6	822	356	43.3	1.01	(0.91,1.12)	0.8412	1.05	(0.84,1.31)	
Yes	2078	664	32.0	2064	712	34.5	1.07	(0.98,1.16)	0.1123	1.14	(0.99,1.32)	
Baseline NYHA												0.6365
II^^	2360	794	33.6	2358	844	35.8	1.04	(0.97,1.12)	0.2717	1.09	(0.95,1.25)	
III/IV	508	191	37.6	528	224	42.4	1.08	(0.94,1.25)	0.2734	1.28	(0.96,1.70)	
Baseline Diabetes status												0.9062
Diabetic	1409	513	36.4	1403	552	39.3	1.05	(0.96,1.15)	0.2519	1.13	(0.95,1.34)	
Non-Diabetic	1459	472	32.4	1483	516	34.8	1.04	(0.95,1.15)	0.3673	1.11	(0.93,1.32)	

* 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, °:Trend test.
^ 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.

Analysis is based on study 1245.110.
LOCF: For a missing value at week 52 the last available post-baseline value before week 52 is imputed.
^^ Patients with NYHA class I are counted in subgroup NYHA class II. [1] Baseline SBP median: 132 [mmHg].
[2] Baseline NT-proBNP median for patients with history of atrial fibrillation or atrial flutter: 1354 [pg/mL].
[2] Baseline NT-proBNP median for patients without history of atrial fibrillation or atrial flutter: 614 [pg/mL].
[3] Baseline uric acid tertile cut-offs for males are T1: 5.9 T2: 7.5 [mg/dL] [rounded].
[3] Baseline uric acid tertile cut-offs for females are T1: 5.4 T2: 6.9 [mg/dL] [rounded].

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Table R.1.1.3.1.1.1: 2 Responder analysis for EQ-VAS change from baseline at week 52 >= 7 points (improvement) overall and by subgroup - RS (LOCF-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 Diabetes status												0.5198°/ 0.2423
Diabetic	1409	513	36.4	1403	552	39.3	1.05	(0.96,1.15)	0.2520	1.13	(0.95,1.34)	
Pre-Diabetes	938	309	32.9	972	328	33.7	0.98	(0.88,1.10)	0.7800	1.00	(0.81,1.24)	
Normal (no pre-diabetes)	521	163	31.3	511	188	36.8	1.17	(0.99,1.37)	0.0623	1.35	(1.01,1.80)	
Baseline BMI [kg/m²]												0.2094
<30	1567	527	33.6	1592	533	33.5	1.01	(0.92,1.10)	0.8687	1.01	(0.85,1.19)	
>=30	1301	458	35.2	1294	535	41.3	1.09	(1.00,1.20)	0.0556	1.27	(1.06,1.52)	
Baseline eGFR (CKD-EPI) [mL/min/1.73m²]												0.7147
>=60	1447	502	34.7	1444	543	37.6	1.04	(0.95,1.13)	0.4339	1.08	(0.91,1.28)	
<60	1421	483	34.0	1442	525	36.4	1.06	(0.97,1.16)	0.2071	1.16	(0.98,1.38)	
History of HHF (in the last 12 months)												0.0914
No	2231	760	34.1	2226	836	37.6	1.08	(1.00,1.16)	0.0395	1.19	(1.03,1.36)	
Yes	637	225	35.3	660	232	35.2	0.95	(0.83,1.08)	0.4268	0.92	(0.71,1.19)	
Baseline SBP (</>= median¹)												0.8563
< median	1414	495	35.0	1445	542	37.5	1.04	(0.95,1.14)	0.3680	1.10	(0.92,1.31)	
>= median	1454	490	33.7	1441	526	36.5	1.06	(0.96,1.16)	0.2458	1.14	(0.96,1.36)	
History of atrial fibrillation or atrial flutter												0.8182
No	1365	486	35.6	1363	522	38.3	1.04	(0.95,1.14)	0.3712	1.11	(0.93,1.32)	
Yes	1500	496	33.1	1520	544	35.8	1.06	(0.97,1.16)	0.2278	1.14	(0.96,1.35)	

* 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, °:Trend test.
^ 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.

Analysis is based on study 1245.110.
LOCF: For a missing value at week 52 the last available post-baseline value before week 52 is imputed.
^^ Patients with NYHA class I are counted in subgroup NYHA class II. ¹ Baseline SBP median: 132 [mmHg].
² Baseline NT-proBNP median for patients with history of atrial fibrillation or atrial flutter: 1354 [pg/mL].
² Baseline NT-proBNP median for patients without history of atrial fibrillation or atrial flutter: 614 [pg/mL].
³ Baseline uric acid tertile cut-offs for males are T1: 5.9 T2: 7.5 [mg/dL] [rounded].
³ Baseline uric acid tertile cut-offs for females are T1: 5.4 T2: 6.9 [mg/dL] [rounded].

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Table R.1.1.3.1.1.1: 2 Responder analysis for EQ-VAS change from baseline at week 52 >= 7 points (improvement) overall and by subgroup - RS (LOCF-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 LVEF [%]												0.0538
< 50	928	342	36.9	957	352	36.8	0.96	(0.86,1.07)	0.4713	0.92	(0.75,1.14)	
>= 50	1940	643	33.1	1929	716	37.1	1.10	(1.01,1.19)	0.0231	1.23	(1.06,1.43)	
Baseline LVEF [%]												0.2747°/ 0.0850
<50	928	342	36.9	957	352	36.8	0.96	(0.86,1.07)	0.4719	0.92	(0.75,1.14)	
50 to <60	991	315	31.8	989	368	37.2	1.15	(1.02,1.29)	0.0174	1.35	(1.10,1.67)	
>=60	949	328	34.6	940	348	37.0	1.05	(0.94,1.17)	0.4141	1.12	(0.90,1.39)	
Baseline NT-proBNP [pg/mL] (</>=median² by atrial fibrillation/flutter status)												0.8734
< median	1463	491	33.6	1429	526	36.8	1.04	(0.95,1.15)	0.3548	1.12	(0.94,1.33)	
>= median	1401	491	35.0	1454	540	37.1	1.06	(0.96,1.16)	0.2420	1.13	(0.95,1.34)	
Baseline uric acid [mg/dL] (tertiles³)												0.9999°/ 0.9649
<T1	934	327	35.0	930	336	36.1	1.04	(0.93,1.16)	0.5163	1.09	(0.88,1.35)	
>=T1 and <T2	932	325	34.9	997	378	37.9	1.06	(0.95,1.18)	0.3142	1.12	(0.90,1.38)	
>=T2	972	324	33.3	933	343	36.8	1.04	(0.93,1.16)	0.5200	1.13	(0.91,1.40)	
Baseline use of MRA												0.2458
No	1787	617	34.5	1813	664	36.6	1.02	(0.94,1.11)	0.6664	1.07	(0.92,1.25)	
Yes	1081	368	34.0	1073	404	37.7	1.10	(0.99,1.22)	0.0692	1.20	(0.98,1.47)	
Baseline use of ACE-inhibitor, ARB or ARNi												0.5489
No	557	194	34.8	545	206	37.8	1.09	(0.94,1.26)	0.2412	1.22	(0.92,1.62)	
Yes	2311	791	34.2	2341	862	36.8	1.04	(0.97,1.12)	0.2998	1.10	(0.96,1.26)	

* 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, °:Trend test.
^ 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.

Analysis is based on study 1245.110.
LOCF: For a missing value at week 52 the last available post-baseline value before week 52 is imputed.
^^ Patients with NYHA class I are counted in subgroup NYHA class II. ¹ Baseline SBP median: 132 [mmHg].
² Baseline NT-proBNP median for patients with history of atrial fibrillation or atrial flutter: 1354 [pg/mL].
² Baseline NT-proBNP median for patients without history of atrial fibrillation or atrial flutter: 614 [pg/mL].
³ Baseline uric acid tertile cut-offs for males are T1: 5.9 T2: 7.5 [mg/dL] [rounded].
³ Baseline uric acid tertile cut-offs for females are T1: 5.4 T2: 6.9 [mg/dL] [rounded].

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R.1.1.3.1.1.2 EQ-VAS responder analysis (10 points)

Table R.1.1.3.1.1.2: 1 Responder analysis for EQ-VAS change from baseline at week 52 <= -10 points (deterioration) overall and by subgroup - RS (LOCF-AD)

Subgroup	Placebo			Empa 10mg			Empa 10mg vs Placebo					
Category	N	n	%	N	n	%	Risk ratio *	(95% CI)	p-value	Odds ratio ***	(95% CI)	p-value **
Overall	2868	809	28.2	2886	761	26.4	0.92	(0.84,1.00)	0.0439	0.92	(0.81,1.04)	
Sex												0.5309
Male	1588	444	28.0	1597	415	26.0	0.90	(0.80,1.00)	0.0585	0.93	(0.79,1.09)	
Female	1280	365	28.5	1289	346	26.8	0.94	(0.84,1.07)	0.3627	0.91	(0.76,1.10)	
Age [years]												0.7796
<70	1035	257	24.8	1029	230	22.4	0.90	(0.77,1.05)	0.1761	0.93	(0.75,1.16)	
>=70	1833	552	30.1	1857	531	28.6	0.92	(0.83,1.02)	0.1149	0.91	(0.78,1.05)	
Region												0.1380
North America	344	100	29.1	341	101	29.6	1.02	(0.81,1.28)	0.8736	1.00	(0.70,1.41)	
Latin America	722	170	23.5	730	185	25.3	1.06	(0.88,1.27)	0.5319	1.13	(0.88,1.46)	
Europe	1301	401	30.8	1309	346	26.4	0.82	(0.73,0.93)	0.0021	0.80	(0.67,0.96)	
Asia	333	96	28.8	330	94	28.5	1.00	(0.79,1.26)	0.9917	1.06	(0.75,1.51)	
Other	168	42	25.0	176	35	19.9	0.81	(0.55,1.19)	0.2842	0.74	(0.43,1.25)	
OECD member												0.9089
No	790	191	24.2	822	183	22.3	0.91	(0.76,1.09)	0.2948	0.93	(0.73,1.19)	
Yes	2078	618	29.7	2064	578	28.0	0.92	(0.84,1.01)	0.0919	0.92	(0.80,1.06)	
Baseline NYHA												0.7841
II^^	2360	665	28.2	2358	628	26.6	0.92	(0.84,1.01)	0.0864	0.94	(0.82,1.07)	
III/IV	508	144	28.3	528	133	25.2	0.89	(0.73,1.09)	0.2703	0.83	(0.62,1.12)	
Baseline Diabetes status												0.8343
Diabetic	1409	389	27.6	1403	365	26.0	0.91	(0.80,1.03)	0.1293	0.95	(0.79,1.13)	
Non-Diabetic	1459	420	28.8	1483	396	26.7	0.93	(0.83,1.04)	0.1886	0.90	(0.76,1.07)	

* 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, °:Trend test.
^ 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.

Analysis is based on study 1245.110.
LOCF: For a missing value at week 52 the last available post-baseline value before week 52 is imputed.
^^ Patients with NYHA class I are counted in subgroup NYHA class II. [1] Baseline SBP median: 132 [mmHg].
[2] Baseline NT-proBNP median for patients with history of atrial fibrillation or atrial flutter: 1354 [pg/mL].
[2] Baseline NT-proBNP median for patients without history of atrial fibrillation or atrial flutter: 614 [pg/mL].
[3] Baseline uric acid tertile cut-offs for males are T1: 5.9 T2: 7.5 [mg/dL] [rounded].
[3] Baseline uric acid tertile cut-offs for females are T1: 5.4 T2: 6.9 [mg/dL] [rounded].

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Table R.1.1.3.1.1.2: 1 Responder analysis for EQ-VAS change from baseline at week 52 <= -10 points (deterioration) overall and by subgroup - RS (LOCF-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 Diabetes status												0.7362°/ 0.9272
Diabetic	1409	389	27.6	1403	365	26.0	0.91	(0.80,1.03)	0.1292	0.95	(0.79,1.13)	
Pre-Diabetes	938	276	29.4	972	263	27.1	0.91	(0.79,1.05)	0.2057	0.88	(0.71,1.09)	
Normal (no pre-diabetes)	521	144	27.6	511	133	26.0	0.95	(0.78,1.16)	0.6142	0.93	(0.70,1.24)	
Baseline BMI [kg/m²]												0.3507
<30	1567	449	28.7	1592	447	28.1	0.95	(0.85,1.06)	0.3650	0.97	(0.82,1.14)	
>=30	1301	360	27.7	1294	314	24.3	0.88	(0.77,1.00)	0.0437	0.86	(0.71,1.04)	
Baseline eGFR (CKD-EPI) [mL/min/1.73m²]												0.7360
>=60	1447	385	26.6	1444	361	25.0	0.90	(0.80,1.02)	0.1089	0.96	(0.80,1.14)	
<60	1421	424	29.8	1442	400	27.7	0.93	(0.83,1.04)	0.2057	0.88	(0.74,1.05)	
History of HHF (in the last 12 months)												0.3149
No	2231	623	27.9	2226	584	26.2	0.94	(0.85,1.03)	0.1978	0.92	(0.80,1.06)	
Yes	637	186	29.2	660	177	26.8	0.85	(0.71,1.01)	0.0701	0.91	(0.71,1.18)	
Baseline SBP (</>= median¹)												0.8938
< median	1414	391	27.7	1445	368	25.5	0.92	(0.82,1.04)	0.1905	0.90	(0.76,1.08)	
>= median	1454	418	28.7	1441	393	27.3	0.91	(0.81,1.03)	0.1248	0.94	(0.79,1.11)	
History of atrial fibrillation or atrial flutter												0.5545
No	1365	371	27.2	1363	348	25.5	0.94	(0.83,1.07)	0.3438	0.93	(0.78,1.12)	
Yes	1500	438	29.2	1520	412	27.1	0.90	(0.80,1.00)	0.0590	0.91	(0.77,1.07)	

* 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, °:Trend test.
^ 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.

Analysis is based on study 1245.110.
LOCF: For a missing value at week 52 the last available post-baseline value before week 52 is imputed.
^^ Patients with NYHA class I are counted in subgroup NYHA class II. ¹ Baseline SBP median: 132 [mmHg].
² Baseline NT-proBNP median for patients with history of atrial fibrillation or atrial flutter: 1354 [pg/mL].
² Baseline NT-proBNP median for patients without history of atrial fibrillation or atrial flutter: 614 [pg/mL].
³ Baseline uric acid tertile cut-offs for males are T1: 5.9 T2: 7.5 [mg/dL] [rounded].
³ Baseline uric acid tertile cut-offs for females are T1: 5.4 T2: 6.9 [mg/dL] [rounded].

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Table R.1.1.3.1.1.2: 1 Responder analysis for EQ-VAS change from baseline at week 52 <= -10 points (deterioration) overall and by subgroup - RS (LOCF-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 LVEF [%]												0.8963
< 50	928	244	26.3	957	227	23.7	0.91	(0.78,1.06)	0.2289	0.91	(0.73,1.13)	
>= 50	1940	565	29.1	1929	534	27.7	0.92	(0.83,1.02)	0.1076	0.93	(0.80,1.07)	
Baseline LVEF [%]												0.8438°/ 0.9785
<50	928	244	26.3	957	227	23.7	0.91	(0.78,1.06)	0.2290	0.91	(0.73,1.13)	
50 to <60	991	285	28.8	989	276	27.9	0.91	(0.79,1.05)	0.2146	0.96	(0.78,1.17)	
>=60	949	280	29.5	940	258	27.4	0.93	(0.81,1.07)	0.3026	0.90	(0.72,1.11)	
Baseline NT-proBNP [pg/mL] (</>=median² by atrial fibrillation/flutter status)												0.4800
< median	1463	417	28.5	1429	374	26.2	0.89	(0.79,1.00)	0.0533	0.91	(0.77,1.08)	
>= median	1401	392	28.0	1454	386	26.5	0.94	(0.84,1.06)	0.3453	0.92	(0.78,1.10)	
Baseline uric acid [mg/dL] (tertiles³)												0.7943°/ 0.7195
<T1	934	263	28.2	930	237	25.5	0.91	(0.79,1.06)	0.2280	0.87	(0.70,1.08)	
>=T1 and <T2	932	243	26.1	997	270	27.1	0.97	(0.83,1.12)	0.6773	1.07	(0.86,1.32)	
>=T2	972	292	30.0	933	248	26.6	0.89	(0.77,1.03)	0.1098	0.85	(0.69,1.05)	
Baseline use of MRA												0.4120
No	1787	509	28.5	1813	486	26.8	0.94	(0.85,1.05)	0.2652	0.93	(0.80,1.09)	
Yes	1081	300	27.8	1073	275	25.6	0.88	(0.76,1.01)	0.0655	0.90	(0.74,1.10)	
Baseline use of ACE-inhibitor, ARB or ARNi												0.6428
No	557	160	28.7	545	138	25.3	0.88	(0.73,1.07)	0.1930	0.80	(0.60,1.06)	
Yes	2311	649	28.1	2341	623	26.6	0.93	(0.84,1.02)	0.1075	0.95	(0.83,1.09)	

* 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, °:Trend test.
^ 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.

Analysis is based on study 1245.110.
LOCF: For a missing value at week 52 the last available post-baseline value before week 52 is imputed.
^^ Patients with NYHA class I are counted in subgroup NYHA class II. ¹ Baseline SBP median: 132 [mmHg].
² Baseline NT-proBNP median for patients with history of atrial fibrillation or atrial flutter: 1354 [pg/mL].
² Baseline NT-proBNP median for patients without history of atrial fibrillation or atrial flutter: 614 [pg/mL].
³ Baseline uric acid tertile cut-offs for males are T1: 5.9 T2: 7.5 [mg/dL] [rounded].
³ Baseline uric acid tertile cut-offs for females are T1: 5.4 T2: 6.9 [mg/dL] [rounded].

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Table R.1.1.3.1.1.2: 2 Responder analysis for EQ-VAS change from baseline at week 52 >= 10 points (improvement) overall and by subgroup - RS (LOCF-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	2868	968	33.8	2886	1047	36.3	1.04	(0.98,1.12)	0.1868	1.11	(0.98,1.26)	
Sex												0.5562
Male	1588	506	31.9	1597	538	33.7	1.03	(0.93,1.13)	0.5969	1.06	(0.89,1.25)	
Female	1280	462	36.1	1289	509	39.5	1.07	(0.97,1.17)	0.1675	1.18	(0.99,1.42)	
Age [years]												0.9255
<70	1035	373	36.0	1029	421	40.9	1.05	(0.95,1.16)	0.3436	1.14	(0.93,1.39)	
>=70	1833	595	32.5	1857	626	33.7	1.04	(0.96,1.14)	0.3336	1.10	(0.94,1.29)	
Region												0.3271
North America	344	103	29.9	341	117	34.3	1.14	(0.93,1.39)	0.2011	1.33	(0.93,1.92)	
Latin America	722	317	43.9	730	319	43.7	0.97	(0.87,1.09)	0.6308	0.96	(0.76,1.22)	
Europe	1301	393	30.2	1309	435	33.2	1.09	(0.98,1.21)	0.1148	1.17	(0.97,1.41)	
Asia	333	102	30.6	330	104	31.5	0.94	(0.77,1.15)	0.5580	0.91	(0.63,1.32)	
Other	168	53	31.5	176	72	40.9	1.17	(0.90,1.52)	0.2304	1.47	(0.89,2.42)	
OECD member												0.3623
No	790	317	40.1	822	349	42.5	1.00	(0.90,1.12)	0.9803	1.03	(0.82,1.29)	
Yes	2078	651	31.3	2064	698	33.8	1.07	(0.98,1.16)	0.1219	1.14	(0.99,1.32)	
Baseline NYHA												0.7020
II^^	2360	780	33.1	2358	828	35.1	1.04	(0.97,1.12)	0.3081	1.08	(0.95,1.24)	
III/IV	508	188	37.0	528	219	41.5	1.07	(0.93,1.24)	0.3404	1.26	(0.94,1.68)	
Baseline Diabetes status												0.9074
Diabetic	1409	506	35.9	1403	539	38.4	1.04	(0.95,1.14)	0.3776	1.10	(0.93,1.32)	
Non-Diabetic	1459	462	31.7	1483	508	34.3	1.05	(0.95,1.15)	0.3291	1.12	(0.94,1.33)	

* 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, °:Trend test.
^ 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.

Analysis is based on study 1245.110.
LOCF: For a missing value at week 52 the last available post-baseline value before week 52 is imputed.
^^ Patients with NYHA class I are counted in subgroup NYHA class II. [1] Baseline SBP median: 132 [mmHg].
[2] Baseline NT-proBNP median for patients with history of atrial fibrillation or atrial flutter: 1354 [pg/mL].
[2] Baseline NT-proBNP median for patients without history of atrial fibrillation or atrial flutter: 614 [pg/mL].
[3] Baseline uric acid tertile cut-offs for males are T1: 5.9 T2: 7.5 [mg/dL] [rounded].
[3] Baseline uric acid tertile cut-offs for females are T1: 5.4 T2: 6.9 [mg/dL] [rounded].

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Table R.1.1.3.1.1.2: 2 Responder analysis for EQ-VAS change from baseline at week 52 >= 10 points (improvement) overall and by subgroup - RS (LOCF-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 Diabetes status												0.3622°/ 0.1936
Diabetic	1409	506	35.9	1403	539	38.4	1.04	(0.95,1.14)	0.3777	1.11	(0.93,1.32)	
Pre-Diabetes	938	304	32.4	972	323	33.2	0.98	(0.87,1.10)	0.7637	1.00	(0.81,1.24)	
Normal (no pre-diabetes)	521	158	30.3	511	185	36.2	1.18	(1.00,1.40)	0.0446	1.39	(1.04,1.86)	
Baseline BMI [kg/m²]												0.2643
<30	1567	520	33.2	1592	526	33.0	1.01	(0.92,1.10)	0.8627	1.01	(0.85,1.19)	
>=30	1301	448	34.4	1294	521	40.3	1.09	(0.99,1.19)	0.0849	1.25	(1.04,1.50)	
Baseline eGFR (CKD-EPI) [mL/min/1.73m²]												0.8537
>=60	1447	491	33.9	1444	533	36.9	1.04	(0.95,1.14)	0.4172	1.09	(0.91,1.29)	
<60	1421	477	33.6	1442	514	35.6	1.05	(0.96,1.15)	0.2983	1.14	(0.96,1.36)	
History of HHF (in the last 12 months)												0.0870
No	2231	745	33.4	2226	818	36.7	1.08	(1.00,1.16)	0.0514	1.18	(1.03,1.36)	
Yes	637	223	35.0	660	229	34.7	0.94	(0.82,1.08)	0.3799	0.91	(0.70,1.18)	
Baseline SBP (</>= median¹)												0.9030
< median	1414	488	34.5	1445	534	37.0	1.04	(0.95,1.14)	0.3971	1.10	(0.92,1.30)	
>= median	1454	480	33.0	1441	513	35.6	1.05	(0.96,1.15)	0.3076	1.13	(0.95,1.35)	
History of atrial fibrillation or atrial flutter												0.8676
No	1365	478	35.0	1363	513	37.6	1.04	(0.95,1.14)	0.3985	1.10	(0.92,1.32)	
Yes	1500	487	32.5	1520	532	35.0	1.05	(0.96,1.15)	0.2862	1.13	(0.95,1.34)	

* 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, °:Trend test.
^ 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.

Analysis is based on study 1245.110.
LOCF: For a missing value at week 52 the last available post-baseline value before week 52 is imputed.
^^ Patients with NYHA class I are counted in subgroup NYHA class II. ¹ Baseline SBP median: 132 [mmHg].
² Baseline NT-proBNP median for patients with history of atrial fibrillation or atrial flutter: 1354 [pg/mL].
² Baseline NT-proBNP median for patients without history of atrial fibrillation or atrial flutter: 614 [pg/mL].
³ Baseline uric acid tertile cut-offs for males are T1: 5.9 T2: 7.5 [mg/dL] [rounded].
³ Baseline uric acid tertile cut-offs for females are T1: 5.4 T2: 6.9 [mg/dL] [rounded].

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Table R.1.1.3.1.1.2: 2 Responder analysis for EQ-VAS change from baseline at week 52 >= 10 points (improvement) overall and by subgroup - RS (LOCF-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 LVEF [%]												0.0497
< 50	928	336	36.2	957	344	35.9	0.95	(0.86,1.07)	0.4057	0.91	(0.73,1.13)	
>= 50	1940	632	32.6	1929	703	36.4	1.09	(1.01,1.19)	0.0294	1.23	(1.06,1.43)	
Baseline LVEF [%]												0.2332°/ 0.0920
<50	928	336	36.2	957	344	35.9	0.95	(0.86,1.07)	0.4063	0.91	(0.73,1.13)	
50 to <60	991	310	31.3	989	360	36.4	1.14	(1.02,1.28)	0.0268	1.34	(1.08,1.65)	
>=60	949	322	33.9	940	343	36.5	1.05	(0.94,1.18)	0.3940	1.13	(0.91,1.40)	
Baseline NT-proBNP [pg/mL] (</>=median² by atrial fibrillation/flutter status)												0.7987
< median	1463	483	33.0	1429	515	36.0	1.04	(0.94,1.14)	0.4450	1.10	(0.92,1.31)	
>= median	1401	482	34.4	1454	530	36.5	1.05	(0.96,1.16)	0.2543	1.13	(0.95,1.34)	
Baseline uric acid [mg/dL] (tertiles³)												0.8309°/ 0.9729
<T1	934	322	34.5	930	328	35.3	1.03	(0.92,1.15)	0.6207	1.07	(0.86,1.33)	
>=T1 and <T2	932	321	34.4	997	369	37.0	1.04	(0.94,1.17)	0.4390	1.09	(0.88,1.35)	
>=T2	972	316	32.5	933	339	36.3	1.05	(0.93,1.18)	0.4277	1.16	(0.93,1.44)	
Baseline use of MRA												0.3171
No	1787	603	33.7	1813	650	35.9	1.02	(0.94,1.11)	0.6729	1.07	(0.92,1.26)	
Yes	1081	365	33.8	1073	397	37.0	1.09	(0.98,1.21)	0.1072	1.18	(0.97,1.44)	
Baseline use of ACE-inhibitor, ARB or ARNi												0.6127
No	557	193	34.6	545	203	37.2	1.08	(0.93,1.25)	0.3028	1.20	(0.91,1.60)	
Yes	2311	775	33.5	2341	844	36.1	1.04	(0.96,1.11)	0.3384	1.09	(0.95,1.25)	

* 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, °:Trend test.
^ 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.

Analysis is based on study 1245.110.
LOCF: For a missing value at week 52 the last available post-baseline value before week 52 is imputed.
^^ Patients with NYHA class I are counted in subgroup NYHA class II. ¹ Baseline SBP median: 132 [mmHg].
² Baseline NT-proBNP median for patients with history of atrial fibrillation or atrial flutter: 1354 [pg/mL].
² Baseline NT-proBNP median for patients without history of atrial fibrillation or atrial flutter: 614 [pg/mL].
³ Baseline uric acid tertile cut-offs for males are T1: 5.9 T2: 7.5 [mg/dL] [rounded].
³ Baseline uric acid tertile cut-offs for females are T1: 5.4 T2: 6.9 [mg/dL] [rounded].

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R.1.1.3.1.1.3 EQ-VAS responder analysis (15 points)

Table R.1.1.3.1.1.3: 1 Responder analysis for EQ-VAS change from baseline at week 52 <= -15 points (deterioration) overall and by subgroup - RS (LOCF-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	2868	491	17.1	2886	458	15.9	0.91	(0.81,1.02)	0.0941	0.92	(0.80,1.06)	
Sex												0.6191
Male	1588	266	16.8	1597	247	15.5	0.88	(0.75,1.03)	0.1214	0.93	(0.76,1.13)	
Female	1280	225	17.6	1289	211	16.4	0.93	(0.79,1.11)	0.4325	0.91	(0.74,1.13)	
Age [years]												0.5407
<70	1035	151	14.6	1029	144	14.0	0.95	(0.77,1.18)	0.6599	1.02	(0.79,1.32)	
>=70	1833	340	18.5	1857	314	16.9	0.88	(0.77,1.01)	0.0777	0.87	(0.73,1.04)	
Region												0.6068
North America	344	68	19.8	341	68	19.9	1.01	(0.75,1.36)	0.9606	0.98	(0.66,1.44)	
Latin America	722	102	14.1	730	101	13.8	0.96	(0.75,1.24)	0.7584	0.99	(0.73,1.34)	
Europe	1301	246	18.9	1309	218	16.7	0.84	(0.71,0.99)	0.0430	0.86	(0.70,1.06)	
Asia	333	49	14.7	330	51	15.5	1.06	(0.74,1.52)	0.7467	1.14	(0.74,1.77)	
Other	168	26	15.5	176	20	11.4	0.74	(0.44,1.28)	0.2832	0.69	(0.36,1.31)	
OECD member												0.4310
No	790	116	14.7	822	102	12.4	0.83	(0.65,1.06)	0.1425	0.85	(0.63,1.14)	
Yes	2078	375	18.0	2064	356	17.2	0.93	(0.82,1.06)	0.2882	0.95	(0.80,1.12)	
Baseline NYHA												0.7505
II^^	2360	393	16.7	2358	363	15.4	0.90	(0.79,1.02)	0.0988	0.92	(0.78,1.08)	
III/IV	508	98	19.3	528	95	18.0	0.94	(0.73,1.20)	0.6126	0.91	(0.65,1.26)	
Baseline Diabetes status												0.5044
Diabetic	1409	241	17.1	1403	218	15.5	0.87	(0.73,1.03)	0.1046	0.91	(0.74,1.12)	
Non-Diabetic	1459	250	17.1	1483	240	16.2	0.94	(0.80,1.10)	0.4554	0.93	(0.76,1.14)	

* 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, °:Trend test.
^ 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.

Analysis is based on study 1245.110.
LOCF: For a missing value at week 52 the last available post-baseline value before week 52 is imputed.
^^ Patients with NYHA class I are counted in subgroup NYHA class II. [1] Baseline SBP median: 132 [mmHg].
[2] Baseline NT-proBNP median for patients with history of atrial fibrillation or atrial flutter: 1354 [pg/mL].
[2] Baseline NT-proBNP median for patients without history of atrial fibrillation or atrial flutter: 614 [pg/mL].
[3] Baseline uric acid tertile cut-offs for males are T1: 5.9 T2: 7.5 [mg/dL] [rounded].
[3] Baseline uric acid tertile cut-offs for females are T1: 5.4 T2: 6.9 [mg/dL] [rounded].

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Table R.1.1.3.1.1.3: 1 Responder analysis for EQ-VAS change from baseline at week 52 <= -15 points (deterioration) overall and by subgroup - RS (LOCF-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 Diabetes status												0.3693°/ 0.6420
Diabetic	1409	241	17.1	1403	218	15.5	0.87	(0.73,1.03)	0.1044	0.91	(0.74,1.12)	
Pre-Diabetes	938	167	17.8	972	158	16.3	0.90	(0.74,1.10)	0.3180	0.89	(0.69,1.14)	
Normal (no pre-diabetes)	521	83	15.9	511	82	16.0	1.01	(0.77,1.34)	0.9173	1.02	(0.73,1.45)	
Baseline BMI [kg/m²]												0.8294
<30	1567	266	17.0	1592	258	16.2	0.92	(0.78,1.07)	0.2759	0.94	(0.77,1.14)	
>=30	1301	225	17.3	1294	200	15.5	0.89	(0.75,1.06)	0.1967	0.90	(0.73,1.12)	
Baseline eGFR (CKD-EPI) [mL/min/1.73m²]												0.8462
>=60	1447	226	15.6	1444	212	14.7	0.89	(0.75,1.06)	0.2079	0.97	(0.78,1.19)	
<60	1421	265	18.6	1442	246	17.1	0.91	(0.78,1.07)	0.2569	0.88	(0.72,1.07)	
History of HHF (in the last 12 months)												0.8066
No	2231	380	17.0	2226	346	15.5	0.91	(0.80,1.04)	0.1738	0.90	(0.76,1.06)	
Yes	637	111	17.4	660	112	17.0	0.88	(0.69,1.13)	0.3178	0.99	(0.74,1.34)	
Baseline SBP (</>= median¹)												0.9917
< median	1414	235	16.6	1445	217	15.0	0.91	(0.77,1.07)	0.2434	0.90	(0.73,1.11)	
>= median	1454	256	17.6	1441	241	16.7	0.91	(0.77,1.07)	0.2324	0.94	(0.77,1.15)	
History of atrial fibrillation or atrial flutter												0.9886
No	1365	235	17.2	1363	212	15.6	0.91	(0.77,1.07)	0.2455	0.89	(0.72,1.10)	
Yes	1500	256	17.1	1520	246	16.2	0.91	(0.77,1.07)	0.2361	0.95	(0.78,1.16)	

* 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, °:Trend test.
^ 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.

Analysis is based on study 1245.110.
LOCF: For a missing value at week 52 the last available post-baseline value before week 52 is imputed.
^^ Patients with NYHA class I are counted in subgroup NYHA class II. ¹ Baseline SBP median: 132 [mmHg].
² Baseline NT-proBNP median for patients with history of atrial fibrillation or atrial flutter: 1354 [pg/mL].
² Baseline NT-proBNP median for patients without history of atrial fibrillation or atrial flutter: 614 [pg/mL].
³ Baseline uric acid tertile cut-offs for males are T1: 5.9 T2: 7.5 [mg/dL] [rounded].
³ Baseline uric acid tertile cut-offs for females are T1: 5.4 T2: 6.9 [mg/dL] [rounded].

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Table R.1.1.3.1.1.3: 1 Responder analysis for EQ-VAS change from baseline at week 52 <= -15 points (deterioration) overall and by subgroup - RS (LOCF-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 LVEF [%]												0.0291
< 50	928	160	17.2	957	121	12.6	0.74	(0.60,0.92)	0.0065	0.72	(0.55,0.94)	
>= 50	1940	331	17.1	1929	337	17.5	0.99	(0.86,1.13)	0.8461	1.03	(0.86,1.22)	
Baseline LVEF [%]												0.0035°/ 0.0124
<50	928	160	17.2	957	121	12.6	0.74	(0.60,0.92)	0.0065	0.72	(0.55,0.94)	
50 to <60	991	182	18.4	989	168	17.0	0.86	(0.71,1.05)	0.1300	0.90	(0.70,1.14)	
>=60	949	149	15.7	940	169	18.0	1.14	(0.94,1.39)	0.1930	1.19	(0.93,1.53)	
Baseline NT-proBNP [pg/mL] (</>=median² by atrial fibrillation/flutter status)												0.4389
< median	1463	244	16.7	1429	214	15.0	0.86	(0.73,1.02)	0.0860	0.90	(0.73,1.11)	
>= median	1401	247	17.6	1454	244	16.8	0.94	(0.81,1.11)	0.4805	0.93	(0.76,1.14)	
Baseline uric acid [mg/dL] (tertiles³)												0.8297°/ 0.2690
<T1	934	158	16.9	930	131	14.1	0.84	(0.68,1.03)	0.0968	0.80	(0.62,1.04)	
>=T1 and <T2	932	140	15.0	997	170	17.1	1.05	(0.85,1.29)	0.6403	1.18	(0.92,1.52)	
>=T2	972	184	18.9	933	153	16.4	0.87	(0.72,1.06)	0.1651	0.85	(0.67,1.09)	
Baseline use of MRA												0.6644
No	1787	307	17.2	1813	288	15.9	0.92	(0.80,1.07)	0.2839	0.92	(0.76,1.10)	
Yes	1081	184	17.0	1073	170	15.8	0.88	(0.72,1.06)	0.1786	0.93	(0.73,1.18)	
Baseline use of ACE-inhibitor, ARB or ARNi												0.8584
No	557	93	16.7	545	84	15.4	0.93	(0.71,1.21)	0.5680	0.88	(0.63,1.23)	
Yes	2311	398	17.2	2341	374	16.0	0.90	(0.79,1.03)	0.1128	0.93	(0.79,1.09)	

* 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, °:Trend test.
^ 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.

Analysis is based on study 1245.110.
LOCF: For a missing value at week 52 the last available post-baseline value before week 52 is imputed.
^^ Patients with NYHA class I are counted in subgroup NYHA class II. ¹ Baseline SBP median: 132 [mmHg].
² Baseline NT-proBNP median for patients with history of atrial fibrillation or atrial flutter: 1354 [pg/mL].
² Baseline NT-proBNP median for patients without history of atrial fibrillation or atrial flutter: 614 [pg/mL].
³ Baseline uric acid tertile cut-offs for males are T1: 5.9 T2: 7.5 [mg/dL] [rounded].
³ Baseline uric acid tertile cut-offs for females are T1: 5.4 T2: 6.9 [mg/dL] [rounded].

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Table R.1.1.3.1.1.3: 2 Responder analysis for EQ-VAS change from baseline at week 52 >= 15 points (improvement) overall and by subgroup - RS (LOCF-AD)

Subgroup	Placebo			Empa 10mg			Empa 10mg vs Placebo					
Category	N	n	%	N	n	%	Risk ratio *	(95% CI)	p-value	Odds ratio ***	(95% CI)	p-value **
Overall	2868	604	21.1	2886	668	23.1	1.05	(0.96,1.15)	0.2699	1.12	(0.97,1.29)	
Sex												0.9408
Male	1588	303	19.1	1597	336	21.0	1.06	(0.93,1.21)	0.4116	1.11	(0.91,1.36)	
Female	1280	301	23.5	1289	332	25.8	1.05	(0.92,1.19)	0.4597	1.13	(0.92,1.39)	
Age [years]												0.4183
<70	1035	239	23.1	1029	268	26.0	1.01	(0.87,1.16)	0.9368	1.06	(0.84,1.33)	
>=70	1833	365	19.9	1857	400	21.5	1.09	(0.96,1.22)	0.1858	1.16	(0.97,1.39)	
Region												0.0986
North America	344	71	20.6	341	69	20.2	0.96	(0.73,1.27)	0.7970	0.99	(0.64,1.51)	
Latin America	722	216	29.9	730	210	28.8	0.93	(0.80,1.09)	0.3668	0.90	(0.69,1.18)	
Europe	1301	221	17.0	1309	278	21.2	1.23	(1.06,1.43)	0.0067	1.39	(1.11,1.73)	
Asia	333	61	18.3	330	64	19.4	0.92	(0.69,1.23)	0.5871	0.92	(0.59,1.43)	
Other	168	35	20.8	176	47	26.7	1.10	(0.78,1.56)	0.5775	1.26	(0.71,2.23)	
OECD member												0.2685
No	790	212	26.8	822	233	28.3	0.98	(0.84,1.14)	0.8145	0.99	(0.77,1.28)	
Yes	2078	392	18.9	2064	435	21.1	1.09	(0.97,1.23)	0.1284	1.18	(0.99,1.40)	
Baseline NYHA												0.7039
II^^	2360	477	20.2	2358	524	22.2	1.06	(0.96,1.18)	0.2480	1.12	(0.95,1.31)	
III/IV	508	127	25.0	528	144	27.3	1.02	(0.84,1.24)	0.8522	1.14	(0.83,1.58)	
Baseline Diabetes status												0.4777
Diabetic	1409	311	22.1	1403	351	25.0	1.09	(0.96,1.23)	0.1981	1.20	(0.98,1.47)	
Non-Diabetic	1459	293	20.1	1483	317	21.4	1.02	(0.89,1.16)	0.8080	1.04	(0.85,1.28)	

* 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, °:Trend test.
^ 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.

Analysis is based on study 1245.110.
LOCF: For a missing value at week 52 the last available post-baseline value before week 52 is imputed.
^^ Patients with NYHA class I are counted in subgroup NYHA class II. [1] Baseline SBP median: 132 [mmHg].
[2] Baseline NT-proBNP median for patients with history of atrial fibrillation or atrial flutter: 1354 [pg/mL].
[2] Baseline NT-proBNP median for patients without history of atrial fibrillation or atrial flutter: 614 [pg/mL].
[3] Baseline uric acid tertile cut-offs for males are T1: 5.9 T2: 7.5 [mg/dL] [rounded].
[3] Baseline uric acid tertile cut-offs for females are T1: 5.4 T2: 6.9 [mg/dL] [rounded].

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Table R.1.1.3.1.1.3: 2 Responder analysis for EQ-VAS change from baseline at week 52 >= 15 points (improvement) overall and by subgroup - RS (LOCF-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 Diabetes status												0.7152°/ 0.0599
Diabetic	1409	311	22.1	1403	351	25.0	1.09	(0.96,1.23)	0.1988	1.20	(0.98,1.47)	
Pre-Diabetes	938	195	20.8	972	196	20.2	0.91	(0.77,1.07)	0.2364	0.87	(0.68,1.12)	
Normal (no pre-diabetes)	521	98	18.8	511	121	23.7	1.25	(0.99,1.58)	0.0576	1.44	(1.02,2.03)	
Baseline BMI [kg/m²]												0.6586
<30	1567	326	20.8	1592	335	21.0	1.03	(0.91,1.17)	0.6241	1.05	(0.86,1.28)	
>=30	1301	278	21.4	1294	333	25.7	1.08	(0.94,1.23)	0.2772	1.21	(0.98,1.49)	
Baseline eGFR (CKD-EPI) [mL/min/1.73m²]												0.2980
>=60	1447	317	21.9	1444	340	23.5	1.00	(0.88,1.14)	0.9605	1.03	(0.84,1.26)	
<60	1421	287	20.2	1442	328	22.7	1.11	(0.97,1.26)	0.1387	1.23	(1.00,1.50)	
History of HHF (in the last 12 months)												0.6150
No	2231	470	21.1	2226	516	23.2	1.07	(0.96,1.18)	0.2342	1.14	(0.97,1.34)	
Yes	637	134	21.0	660	152	23.0	1.01	(0.84,1.22)	0.9280	1.06	(0.79,1.43)	
Baseline SBP (</>= median¹)												0.5007
< median	1414	302	21.4	1445	328	22.7	1.02	(0.89,1.16)	0.7659	1.05	(0.85,1.28)	
>= median	1454	302	20.8	1441	340	23.6	1.09	(0.96,1.23)	0.2039	1.20	(0.98,1.47)	
History of atrial fibrillation or atrial flutter												0.3034
No	1365	307	22.5	1363	322	23.6	1.00	(0.88,1.14)	0.9595	1.02	(0.83,1.26)	
Yes	1500	295	19.7	1520	344	22.6	1.11	(0.97,1.26)	0.1323	1.22	(1.00,1.49)	

* 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, °:Trend test.
^ 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.

Analysis is based on study 1245.110.
LOCF: For a missing value at week 52 the last available post-baseline value before week 52 is imputed.
^^ Patients with NYHA class I are counted in subgroup NYHA class II. ¹ Baseline SBP median: 132 [mmHg].
² Baseline NT-proBNP median for patients with history of atrial fibrillation or atrial flutter: 1354 [pg/mL].
² Baseline NT-proBNP median for patients without history of atrial fibrillation or atrial flutter: 614 [pg/mL].
³ Baseline uric acid tertile cut-offs for males are T1: 5.9 T2: 7.5 [mg/dL] [rounded].
³ Baseline uric acid tertile cut-offs for females are T1: 5.4 T2: 6.9 [mg/dL] [rounded].

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Table R.1.1.3.1.1.3: 2 Responder analysis for EQ-VAS change from baseline at week 52 >= 15 points (improvement) overall and by subgroup - RS (LOCF-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 LVEF [%]												0.8953
< 50	928	203	21.9	957	235	24.6	1.06	(0.91,1.24)	0.4419	1.11	(0.87,1.42)	
>= 50	1940	401	20.7	1929	433	22.4	1.05	(0.93,1.18)	0.4195	1.12	(0.94,1.34)	
Baseline LVEF [%]												0.7991°/ 0.9640
<50	928	203	21.9	957	235	24.6	1.06	(0.91,1.24)	0.4406	1.11	(0.87,1.42)	
50 to <60	991	192	19.4	989	212	21.4	1.06	(0.90,1.26)	0.4664	1.16	(0.90,1.49)	
>=60	949	209	22.0	940	221	23.5	1.03	(0.88,1.21)	0.6742	1.08	(0.85,1.39)	
Baseline NT-proBNP [pg/mL] (</>=median[2] by atrial fibrillation/flutter status)												0.7264
< median	1463	297	20.3	1429	325	22.7	1.04	(0.91,1.18)	0.5966	1.10	(0.90,1.35)	
>= median	1401	305	21.8	1454	341	23.5	1.07	(0.94,1.22)	0.3033	1.14	(0.93,1.39)	
Baseline uric acid [mg/dL] (tertiles[3])												0.8031°/ 0.6769
<T1	934	205	21.9	930	221	23.8	1.09	(0.93,1.28)	0.2788	1.20	(0.94,1.55)	
>=T1 and <T2	932	203	21.8	997	225	22.6	0.99	(0.85,1.16)	0.8997	0.97	(0.76,1.24)	
>=T2	972	191	19.7	933	214	22.9	1.06	(0.90,1.25)	0.4693	1.17	(0.91,1.50)	
Baseline use of MRA												0.0735
No	1787	382	21.4	1813	408	22.5	0.99	(0.88,1.11)	0.8169	1.02	(0.85,1.22)	
Yes	1081	222	20.5	1073	260	24.2	1.17	(1.01,1.36)	0.0369	1.31	(1.04,1.66)	
Baseline use of ACE-inhibitor, ARB or ARNi												0.2503
No	557	119	21.4	545	135	24.8	1.17	(0.95,1.44)	0.1310	1.34	(0.97,1.86)	
Yes	2311	485	21.0	2341	533	22.8	1.02	(0.92,1.13)	0.6432	1.07	(0.92,1.26)	

* 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, °:Trend test.
^ 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.

Analysis is based on study 1245.110.
LOCF: For a missing value at week 52 the last available post-baseline value before week 52 is imputed.
^^ Patients with NYHA class I are counted in subgroup NYHA class II. [1] Baseline SBP median: 132 [mmHg].
[2] Baseline NT-proBNP median for patients with history of atrial fibrillation or atrial flutter: 1354 [pg/mL].
[2] Baseline NT-proBNP median for patients without history of atrial fibrillation or atrial flutter: 614 [pg/mL].
[3] Baseline uric acid tertile cut-offs for males are T1: 5.9 T2: 7.5 [mg/dL] [rounded].
[3] Baseline uric acid tertile cut-offs for females are T1: 5.4 T2: 6.9 [mg/dL] [rounded].

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R.1.1.3.1.1.4 KCCQ Clinical Summary Score responder analysis (5 points)

Table R.1.1.3.1.1.4: 1 Responder analysis for KCCQ-CSS change from baseline at week 52 <= -5 points (deterioration) overall and by subgroup - RS (LOCF-AD)

Subgroup	Placebo			Empa 10mg			Empa 10mg vs Placebo					
Category	N	n	%	N	n	%	Risk ratio *	(95% CI)	p-value	Odds ratio ***	(95% CI)	p-value **
Overall	2867	809	28.2	2884	696	24.1	0.86	(0.79,0.94)	0.0005	0.81	(0.72,0.91)	
Sex												0.3233
Male	1587	440	27.7	1596	395	24.7	0.89	(0.79,1.00)	0.0534	0.85	(0.73,1.00)	
Female	1280	369	28.8	1288	301	23.4	0.82	(0.72,0.93)	0.0020	0.76	(0.63,0.91)	
Age [years]												0.4132
<70	1036	257	24.8	1030	228	22.1	0.90	(0.77,1.05)	0.1906	0.87	(0.71,1.07)	
>=70	1831	552	30.1	1854	468	25.2	0.84	(0.75,0.93)	0.0006	0.77	(0.67,0.90)	
Region												0.3810
North America	344	96	27.9	344	97	28.2	0.99	(0.78,1.24)	0.8998	0.98	(0.70,1.37)	
Latin America	724	165	22.8	729	143	19.6	0.88	(0.72,1.07)	0.1981	0.85	(0.65,1.09)	
Europe	1301	418	32.1	1309	333	25.4	0.79	(0.70,0.90)	0.0002	0.72	(0.60,0.85)	
Asia	330	83	25.2	328	82	25.0	0.99	(0.76,1.29)	0.9554	0.99	(0.69,1.41)	
Other	168	47	28.0	174	41	23.6	0.86	(0.61,1.23)	0.4129	0.82	(0.50,1.34)	
OECD member												0.5242
No	789	197	25.0	818	163	19.9	0.82	(0.68,0.98)	0.0277	0.77	(0.60,0.97)	
Yes	2078	612	29.5	2066	533	25.8	0.87	(0.79,0.96)	0.0067	0.83	(0.72,0.95)	
Baseline NYHA												0.3272
II^^	2358	662	28.1	2354	578	24.6	0.87	(0.80,0.96)	0.0056	0.83	(0.73,0.95)	
III/IV	509	147	28.9	530	118	22.3	0.78	(0.64,0.96)	0.0166	0.71	(0.53,0.95)	
Baseline Diabetes status												0.3023
Diabetic	1406	398	28.3	1399	325	23.2	0.82	(0.72,0.93)	0.0016	0.76	(0.64,0.90)	
Non-Diabetic	1461	411	28.1	1485	371	25.0	0.90	(0.80,1.01)	0.0735	0.86	(0.73,1.01)	

* 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, °:Trend test.
^ Models contain terms age, baseline eGFR (CKD-EPI), baseline LVEF, Baseline KCCQ-CSS, 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.

Analysis is based on study 1245.110.
LOCF: For a missing value at week 52 the last available post-baseline value before week 52 is imputed.
^^ Patients with NYHA class I are counted in subgroup NYHA class II. [1] Baseline SBP median: 132 [mmHg].
[2] Baseline NT-proBNP median for patients with history of atrial fibrillation or atrial flutter: 1354 [pg/mL].
[2] Baseline NT-proBNP median for patients without history of atrial fibrillation or atrial flutter: 614 [pg/mL].
[3] Baseline uric acid tertile cut-offs for males are T1: 5.9 T2: 7.5 [mg/dL] [rounded].
[3] Baseline uric acid tertile cut-offs for females are T1: 5.4 T2: 6.9 [mg/dL] [rounded].

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Table R.1.1.3.1.1.4: 1 Responder analysis for KCCQ-CSS change from baseline at week 52 <= -5 points (deterioration) overall and by subgroup - RS (LOCF-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 Diabetes status												0.7077°/ 0.2968
Diabetic	1406	398	28.3	1399	325	23.2	0.82	(0.72,0.93)	0.0016	0.76	(0.64,0.90)	
Pre-Diabetes	939	267	28.4	973	259	26.6	0.94	(0.82,1.09)	0.4118	0.92	(0.75,1.13)	
Normal (no pre-diabetes)	522	144	27.6	512	112	21.9	0.81	(0.65,1.00)	0.0481	0.75	(0.56,1.00)	
Baseline BMI [kg/m²]												0.2008
<30	1563	429	27.4	1590	394	24.8	0.90	(0.81,1.02)	0.0878	0.87	(0.74,1.02)	
>=30	1304	380	29.1	1294	302	23.3	0.81	(0.71,0.92)	0.0011	0.74	(0.62,0.88)	
Baseline eGFR (CKD-EPI) [mL/min/1.73m²]												0.6463
>=60	1448	384	26.5	1445	316	21.9	0.84	(0.74,0.95)	0.0074	0.79	(0.66,0.94)	
<60	1419	425	30.0	1439	380	26.4	0.87	(0.78,0.98)	0.0219	0.83	(0.70,0.98)	
History of HHF (in the last 12 months)												0.5785
No	2232	613	27.5	2226	527	23.7	0.87	(0.79,0.96)	0.0055	0.82	(0.72,0.94)	
Yes	635	196	30.9	658	169	25.7	0.82	(0.69,0.97)	0.0244	0.76	(0.59,0.97)	
Baseline SBP (</>= median¹)												0.0043
< median	1414	384	27.2	1444	384	26.6	0.97	(0.86,1.09)	0.6032	0.96	(0.81,1.14)	
>= median	1453	425	29.2	1440	312	21.7	0.75	(0.67,0.85)	<0.0001	0.68	(0.57,0.80)	
History of atrial fibrillation or atrial flutter												0.8725
No	1363	361	26.5	1363	308	22.6	0.87	(0.76,0.99)	0.0295	0.82	(0.69,0.98)	
Yes	1501	446	29.7	1518	387	25.5	0.85	(0.76,0.96)	0.0067	0.80	(0.68,0.94)	

* 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, °:Trend test.
^ Models contain terms age, baseline eGFR (CKD-EPI), baseline LVEF, Baseline KCCQ-CSS, 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.

Analysis is based on study 1245.110.
LOCF: For a missing value at week 52 the last available post-baseline value before week 52 is imputed.
^^ Patients with NYHA class I are counted in subgroup NYHA class II. ¹ Baseline SBP median: 132 [mmHg].
² Baseline NT-proBNP median for patients with history of atrial fibrillation or atrial flutter: 1354 [pg/mL].
² Baseline NT-proBNP median for patients without history of atrial fibrillation or atrial flutter: 614 [pg/mL].
³ Baseline uric acid tertile cut-offs for males are T1: 5.9 T2: 7.5 [mg/dL] [rounded].
³ Baseline uric acid tertile cut-offs for females are T1: 5.4 T2: 6.9 [mg/dL] [rounded].

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Table R.1.1.3.1.1.4: 1 Responder analysis for KCCQ-CSS change from baseline at week 52 <= -5 points (deterioration) overall and by subgroup - RS (LOCF-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 LVEF [%]												0.4469
< 50	929	245	26.4	957	199	20.8	0.82	(0.69,0.96)	0.0127	0.76	(0.61,0.95)	
>= 50	1938	564	29.1	1927	497	25.8	0.88	(0.79,0.97)	0.0114	0.83	(0.72,0.96)	
Baseline LVEF [%]												0.1529°/ 0.2401
<50	929	245	26.4	957	199	20.8	0.82	(0.69,0.96)	0.0127	0.76	(0.61,0.95)	
50 to <60	990	304	30.7	988	249	25.2	0.81	(0.71,0.94)	0.0040	0.74	(0.61,0.91)	
>=60	948	260	27.4	939	248	26.4	0.95	(0.82,1.10)	0.5072	0.93	(0.76,1.15)	
Baseline NT-proBNP [pg/mL] (</>=median[2] by atrial fibrillation/flutter status)												0.1259
< median	1463	402	27.5	1430	312	21.8	0.80	(0.70,0.91)	0.0005	0.74	(0.62,0.88)	
>= median	1400	404	28.9	1451	383	26.4	0.91	(0.81,1.03)	0.1344	0.88	(0.75,1.04)	
Baseline uric acid [mg/dL] (tertiles[3])												0.9096°/ 0.9547
<T1	937	248	26.5	930	207	22.3	0.85	(0.73,1.00)	0.0482	0.81	(0.65,1.00)	
>=T1 and <T2	931	258	27.7	996	242	24.3	0.88	(0.76,1.02)	0.0963	0.84	(0.68,1.03)	
>=T2	969	291	30.0	932	243	26.1	0.86	(0.75,1.00)	0.0447	0.81	(0.66,1.00)	
Baseline use of MRA												0.5124
No	1786	501	28.1	1813	445	24.5	0.88	(0.79,0.98)	0.0179	0.83	(0.72,0.97)	
Yes	1081	308	28.5	1071	251	23.4	0.83	(0.72,0.95)	0.0082	0.77	(0.63,0.94)	
Baseline use of ACE-inhibitor, ARB or ARNi												0.0713
No	557	180	32.3	543	132	24.3	0.74	(0.61,0.89)	0.0014	0.64	(0.49,0.84)	
Yes	2310	629	27.2	2341	564	24.1	0.89	(0.81,0.98)	0.0221	0.86	(0.75,0.98)	

* 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, °:Trend test.
^ Models contain terms age, baseline eGFR (CKD-EPI), baseline LVEF, Baseline KCCQ-CSS, 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.

Analysis is based on study 1245.110.
LOCF: For a missing value at week 52 the last available post-baseline value before week 52 is imputed.
^^ Patients with NYHA class I are counted in subgroup NYHA class II. [1] Baseline SBP median: 132 [mmHg].
[2] Baseline NT-proBNP median for patients with history of atrial fibrillation or atrial flutter: 1354 [pg/mL].
[2] Baseline NT-proBNP median for patients without history of atrial fibrillation or atrial flutter: 614 [pg/mL].
[3] Baseline uric acid tertile cut-offs for males are T1: 5.9 T2: 7.5 [mg/dL] [rounded].
[3] Baseline uric acid tertile cut-offs for females are T1: 5.4 T2: 6.9 [mg/dL] [rounded].

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Table R.1.1.3.1.1.4: 2 Responder analysis for KCCQ-CSS change from baseline at week 52 >= 5 points (improvement) overall and by subgroup - RS (LOCF-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	2867	1186	41.4	2884	1312	45.5	1.08	(1.02,1.14)	0.0072	1.20	(1.07,1.34)	
Sex												0.2197
Male	1587	598	37.7	1596	670	42.0	1.12	(1.03,1.21)	0.0072	1.23	(1.06,1.44)	
Female	1280	588	45.9	1288	642	49.8	1.04	(0.97,1.12)	0.2961	1.15	(0.97,1.37)	
Age [years]												0.3287
<70	1036	457	44.1	1030	492	47.8	1.04	(0.95,1.14)	0.3558	1.13	(0.93,1.37)	
>=70	1831	729	39.8	1854	820	44.2	1.10	(1.03,1.18)	0.0074	1.24	(1.07,1.43)	
Region												0.1852
North America	344	154	44.8	344	139	40.4	0.94	(0.80,1.11)	0.4554	0.89	(0.64,1.24)	
Latin America	724	360	49.7	729	403	55.3	1.07	(0.98,1.17)	0.1480	1.22	(0.97,1.54)	
Europe	1301	498	38.3	1309	570	43.5	1.12	(1.02,1.22)	0.0130	1.26	(1.07,1.50)	
Asia	330	106	32.1	328	106	32.3	0.99	(0.81,1.22)	0.9575	1.00	(0.71,1.42)	
Other	168	68	40.5	174	94	54.0	1.27	(1.03,1.57)	0.0287	1.81	(1.13,2.89)	
OECD member												0.9517
No	789	386	48.9	818	453	55.4	1.08	(0.98,1.18)	0.1113	1.24	(1.00,1.54)	
Yes	2078	800	38.5	2066	859	41.6	1.08	(1.01,1.16)	0.0333	1.18	(1.03,1.35)	
Baseline NYHA												0.4010
II^^	2358	929	39.4	2354	1026	43.6	1.09	(1.03,1.16)	0.0064	1.22	(1.07,1.38)	
III/IV	509	257	50.5	530	286	54.0	1.03	(0.92,1.16)	0.5660	1.13	(0.86,1.48)	
Baseline Diabetes status												0.4910
Diabetic	1406	604	43.0	1399	667	47.7	1.10	(1.02,1.19)	0.0154	1.24	(1.06,1.47)	
Non-Diabetic	1461	582	39.8	1485	645	43.4	1.06	(0.98,1.15)	0.1685	1.15	(0.98,1.35)	

* 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, °:Trend test.
^ Models contain terms age, baseline eGFR (CKD-EPI), baseline LVEF, Baseline KCCQ-CSS, 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.

Analysis is based on study 1245.110.
LOCF: For a missing value at week 52 the last available post-baseline value before week 52 is imputed.
^^ Patients with NYHA class I are counted in subgroup NYHA class II. [1] Baseline SBP median: 132 [mmHg].
[2] Baseline NT-proBNP median for patients with history of atrial fibrillation or atrial flutter: 1354 [pg/mL].
[2] Baseline NT-proBNP median for patients without history of atrial fibrillation or atrial flutter: 614 [pg/mL].
[3] Baseline uric acid tertile cut-offs for males are T1: 5.9 T2: 7.5 [mg/dL] [rounded].
[3] Baseline uric acid tertile cut-offs for females are T1: 5.4 T2: 6.9 [mg/dL] [rounded].

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Table R.1.1.3.1.1.4: 2 Responder analysis for KCCQ-CSS change from baseline at week 52 >= 5 points (improvement) overall and by subgroup - RS (LOCF-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 Diabetes status												0.8355°/ 0.5212
Diabetic	1406	604	43.0	1399	667	47.7	1.10	(1.02,1.19)	0.0154	1.24	(1.06,1.47)	
Pre-Diabetes	939	382	40.7	973	416	42.8	1.03	(0.93,1.14)	0.5659	1.08	(0.88,1.31)	
Normal (no pre-diabetes)	522	200	38.3	512	229	44.7	1.11	(0.97,1.27)	0.1209	1.31	(1.00,1.71)	
Baseline BMI [kg/m²]												0.4175
<30	1563	617	39.5	1590	675	42.5	1.05	(0.98,1.14)	0.1783	1.13	(0.97,1.32)	
>=30	1304	569	43.6	1294	637	49.2	1.10	(1.02,1.19)	0.0136	1.29	(1.08,1.52)	
Baseline eGFR (CKD-EPI) [mL/min/1.73m²]												0.4783
>=60	1448	596	41.2	1445	677	46.9	1.10	(1.02,1.19)	0.0141	1.25	(1.06,1.47)	
<60	1419	590	41.6	1439	635	44.1	1.06	(0.98,1.15)	0.1694	1.15	(0.97,1.35)	
History of HHF (in the last 12 months)												0.6902
No	2232	927	41.5	2226	1023	46.0	1.09	(1.02,1.16)	0.0097	1.21	(1.06,1.38)	
Yes	635	259	40.8	658	289	43.9	1.06	(0.94,1.19)	0.3740	1.15	(0.90,1.46)	
Baseline SBP (</>= median¹)												0.3051
< median	1414	585	41.4	1444	630	43.6	1.05	(0.97,1.13)	0.2542	1.13	(0.96,1.33)	
>= median	1453	601	41.4	1440	682	47.4	1.11	(1.03,1.20)	0.0084	1.27	(1.08,1.49)	
History of atrial fibrillation or atrial flutter												0.4140
No	1363	606	44.5	1363	652	47.8	1.05	(0.98,1.14)	0.1716	1.14	(0.96,1.34)	
Yes	1501	579	38.6	1518	659	43.4	1.10	(1.02,1.20)	0.0163	1.26	(1.07,1.47)	

* 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, °:Trend test.
^ Models contain terms age, baseline eGFR (CKD-EPI), baseline LVEF, Baseline KCCQ-CSS, 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.

Analysis is based on study 1245.110.
LOCF: For a missing value at week 52 the last available post-baseline value before week 52 is imputed.
^^ Patients with NYHA class I are counted in subgroup NYHA class II. ¹ Baseline SBP median: 132 [mmHg].
² Baseline NT-proBNP median for patients with history of atrial fibrillation or atrial flutter: 1354 [pg/mL].
² Baseline NT-proBNP median for patients without history of atrial fibrillation or atrial flutter: 614 [pg/mL].
³ Baseline uric acid tertile cut-offs for males are T1: 5.9 T2: 7.5 [mg/dL] [rounded].
³ Baseline uric acid tertile cut-offs for females are T1: 5.4 T2: 6.9 [mg/dL] [rounded].

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Table R.1.1.3.1.1.4: 2 Responder analysis for KCCQ-CSS change from baseline at week 52 >= 5 points (improvement) overall and by subgroup - RS (LOCF-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 LVEF [%]												0.7661
< 50	929	384	41.3	957	448	46.8	1.07	(0.97,1.17)	0.1908	1.16	(0.95,1.42)	
>= 50	1938	802	41.4	1927	864	44.8	1.08	(1.01,1.16)	0.0198	1.21	(1.05,1.40)	
Baseline LVEF [%]												0.3567°/ 0.0687
<50	929	384	41.3	957	448	46.8	1.07	(0.97,1.17)	0.1916	1.16	(0.95,1.42)	
50 to <60	990	395	39.9	988	455	46.1	1.17	(1.07,1.29)	0.0011	1.42	(1.17,1.73)	
>=60	948	407	42.9	939	409	43.6	1.00	(0.91,1.10)	0.9940	1.03	(0.84,1.26)	
Baseline NT-proBNP [pg/mL] (</>=median² by atrial fibrillation/flutter status)												0.4450
< median	1463	590	40.3	1430	652	45.6	1.10	(1.02,1.19)	0.0152	1.25	(1.06,1.47)	
>= median	1400	595	42.5	1451	659	45.4	1.05	(0.98,1.14)	0.1797	1.14	(0.97,1.34)	
Baseline uric acid [mg/dL] (tertiles³)												0.7596°/ 0.6654
<T1	937	405	43.2	930	429	46.1	1.05	(0.95,1.15)	0.3563	1.11	(0.91,1.36)	
>=T1 and <T2	931	360	38.7	996	441	44.3	1.11	(1.01,1.23)	0.0350	1.25	(1.03,1.53)	
>=T2	969	411	42.4	932	430	46.1	1.07	(0.97,1.18)	0.1806	1.20	(0.99,1.47)	
Baseline use of MRA												0.0437
No	1786	753	42.2	1813	806	44.5	1.03	(0.96,1.11)	0.3824	1.09	(0.95,1.26)	
Yes	1081	433	40.1	1071	506	47.2	1.16	(1.06,1.27)	0.0013	1.39	(1.15,1.68)	
Baseline use of ACE-inhibitor, ARB or ARNi												0.9407
No	557	226	40.6	543	236	43.5	1.08	(0.95,1.23)	0.2299	1.22	(0.94,1.59)	
Yes	2310	960	41.6	2341	1076	46.0	1.08	(1.01,1.14)	0.0172	1.19	(1.05,1.35)	

* 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, °:Trend test.
^ Models contain terms age, baseline eGFR (CKD-EPI), baseline LVEF, Baseline KCCQ-CSS, 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.

Analysis is based on study 1245.110.
LOCF: For a missing value at week 52 the last available post-baseline value before week 52 is imputed.
^^ Patients with NYHA class I are counted in subgroup NYHA class II. ¹ Baseline SBP median: 132 [mmHg].
² Baseline NT-proBNP median for patients with history of atrial fibrillation or atrial flutter: 1354 [pg/mL].
² Baseline NT-proBNP median for patients without history of atrial fibrillation or atrial flutter: 614 [pg/mL].
³ Baseline uric acid tertile cut-offs for males are T1: 5.9 T2: 7.5 [mg/dL] [rounded].
³ Baseline uric acid tertile cut-offs for females are T1: 5.4 T2: 6.9 [mg/dL] [rounded].

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R.1.1.3.1.1.5 KCCQ Clinical Summary Score responder analysis (15 points)

Table R.1.1.3.1.1.5: 1 Responder analysis for KCCQ-CSS change from baseline at week 52 <= -15 points (deterioration) overall and by subgroup - RS (LOCF-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	2867	374	13.0	2884	298	10.3	0.80	(0.69,0.92)	0.0015	0.77	(0.65,0.90)	
Sex												0.1657
Male	1587	189	11.9	1596	166	10.4	0.87	(0.72,1.06)	0.1776	0.86	(0.69,1.07)	
Female	1280	185	14.5	1288	132	10.2	0.71	(0.58,0.88)	0.0014	0.68	(0.53,0.86)	
Age [years]												0.0342
<70	1036	99	9.6	1030	98	9.5	1.01	(0.77,1.31)	0.9645	1.01	(0.75,1.36)	
>=70	1831	275	15.0	1854	200	10.8	0.72	(0.61,0.85)	0.0001	0.68	(0.56,0.83)	
Region												0.3669
North America	344	54	15.7	344	39	11.3	0.70	(0.48,1.03)	0.0673	0.66	(0.42,1.03)	
Latin America	724	78	10.8	729	62	8.5	0.81	(0.59,1.11)	0.1930	0.79	(0.55,1.13)	
Europe	1301	181	13.9	1309	147	11.2	0.81	(0.66,0.99)	0.0380	0.78	(0.62,0.99)	
Asia	330	35	10.6	328	37	11.3	1.06	(0.69,1.64)	0.7903	1.07	(0.65,1.75)	
Other	168	26	15.5	174	13	7.5	0.50	(0.27,0.93)	0.0287	0.45	(0.22,0.91)	
OECD member												0.9036
No	789	92	11.7	818	75	9.2	0.81	(0.61,1.08)	0.1457	0.79	(0.57,1.09)	
Yes	2078	282	13.6	2066	223	10.8	0.79	(0.67,0.93)	0.0053	0.76	(0.63,0.92)	
Baseline NYHA												0.4598
II^^	2358	299	12.7	2354	243	10.3	0.81	(0.70,0.95)	0.0110	0.79	(0.66,0.95)	
III/IV	509	75	14.7	530	55	10.4	0.71	(0.52,0.98)	0.0354	0.67	(0.46,0.98)	
Baseline Diabetes status												0.5171
Diabetic	1406	174	12.4	1399	145	10.4	0.84	(0.68,1.03)	0.0867	0.81	(0.64,1.03)	
Non-Diabetic	1461	200	13.7	1485	153	10.3	0.76	(0.63,0.93)	0.0064	0.73	(0.58,0.91)	

* 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, °:Trend test.
^ Models contain terms age, baseline eGFR (CKD-EPI), baseline LVEF, Baseline KCCQ-CSS, 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.

Analysis is based on study 1245.110.
LOCF: For a missing value at week 52 the last available post-baseline value before week 52 is imputed.
^^ Patients with NYHA class I are counted in subgroup NYHA class II. [1] Baseline SBP median: 132 [mmHg].
[2] Baseline NT-proBNP median for patients with history of atrial fibrillation or atrial flutter: 1354 [pg/mL].
[2] Baseline NT-proBNP median for patients without history of atrial fibrillation or atrial flutter: 614 [pg/mL].
[3] Baseline uric acid tertile cut-offs for males are T1: 5.9 T2: 7.5 [mg/dL] [rounded].
[3] Baseline uric acid tertile cut-offs for females are T1: 5.4 T2: 6.9 [mg/dL] [rounded].

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Table R.1.1.3.1.1.5: 1 Responder analysis for KCCQ-CSS change from baseline at week 52 <= -15 points (deterioration) overall and by subgroup - RS (LOCF-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 Diabetes status												0.1764°/ 0.2018
Diabetic	1406	174	12.4	1399	145	10.4	0.84	(0.68,1.03)	0.0866	0.81	(0.64,1.03)	
Pre-Diabetes	939	126	13.4	973	111	11.4	0.85	(0.67,1.08)	0.1931	0.83	(0.63,1.10)	
Normal (no pre-diabetes)	522	74	14.2	512	42	8.2	0.59	(0.42,0.85)	0.0039	0.55	(0.37,0.82)	
Baseline BMI [kg/m²]												0.5434
<30	1563	191	12.2	1590	161	10.1	0.83	(0.68,1.01)	0.0646	0.81	(0.65,1.01)	
>=30	1304	183	14.0	1294	137	10.6	0.76	(0.62,0.93)	0.0089	0.73	(0.57,0.92)	
Baseline eGFR (CKD-EPI) [mL/min/1.73m²]												0.9345
>=60	1448	164	11.3	1445	128	8.9	0.80	(0.64,0.99)	0.0441	0.78	(0.61,0.99)	
<60	1419	210	14.8	1439	170	11.8	0.79	(0.66,0.95)	0.0131	0.76	(0.61,0.94)	
History of HHF (in the last 12 months)												0.5864
No	2232	284	12.7	2226	217	9.7	0.78	(0.66,0.91)	0.0025	0.75	(0.62,0.90)	
Yes	635	90	14.2	658	81	12.3	0.85	(0.64,1.12)	0.2399	0.82	(0.59,1.14)	
Baseline SBP (</>= median¹)												0.1106
< median	1414	178	12.6	1444	164	11.4	0.89	(0.73,1.08)	0.2440	0.87	(0.70,1.10)	
>= median	1453	196	13.5	1440	134	9.3	0.71	(0.57,0.87)	0.0008	0.67	(0.53,0.85)	
History of atrial fibrillation or atrial flutter												0.8250
No	1363	160	11.7	1363	127	9.3	0.81	(0.65,1.01)	0.0576	0.79	(0.61,1.01)	
Yes	1501	214	14.3	1518	171	11.3	0.78	(0.65,0.94)	0.0102	0.75	(0.61,0.94)	

* 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, °:Trend test.
^ Models contain terms age, baseline eGFR (CKD-EPI), baseline LVEF, Baseline KCCQ-CSS, 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.

Analysis is based on study 1245.110.
LOCF: For a missing value at week 52 the last available post-baseline value before week 52 is imputed.
^^ Patients with NYHA class I are counted in subgroup NYHA class II. ¹ Baseline SBP median: 132 [mmHg].
² Baseline NT-proBNP median for patients with history of atrial fibrillation or atrial flutter: 1354 [pg/mL].
² Baseline NT-proBNP median for patients without history of atrial fibrillation or atrial flutter: 614 [pg/mL].
³ Baseline uric acid tertile cut-offs for males are T1: 5.9 T2: 7.5 [mg/dL] [rounded].
³ Baseline uric acid tertile cut-offs for females are T1: 5.4 T2: 6.9 [mg/dL] [rounded].

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Table R.1.1.3.1.1.5: 1 Responder analysis for KCCQ-CSS change from baseline at week 52 <= -15 points (deterioration) overall and by subgroup - RS (LOCF-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 LVEF [%]												0.9735
< 50	929	106	11.4	957	83	8.7	0.79	(0.61,1.04)	0.0906	0.77	(0.57,1.05)	
>= 50	1938	268	13.8	1927	215	11.2	0.80	(0.68,0.94)	0.0074	0.77	(0.63,0.93)	
Baseline LVEF [%]												0.8673°/ 0.9633
<50	929	106	11.4	957	83	8.7	0.79	(0.61,1.04)	0.0906	0.77	(0.57,1.05)	
50 to <60	990	138	13.9	988	108	10.9	0.78	(0.62,0.98)	0.0349	0.75	(0.57,0.98)	
>=60	948	130	13.7	939	107	11.4	0.82	(0.64,1.04)	0.0936	0.79	(0.60,1.04)	
Baseline NT-proBNP [pg/mL] (</>=median[2] by atrial fibrillation/flutter status)												0.4122
< median	1463	189	12.9	1430	137	9.6	0.75	(0.61,0.92)	0.0054	0.72	(0.56,0.91)	
>= median	1400	185	13.2	1451	161	11.1	0.84	(0.69,1.02)	0.0822	0.82	(0.65,1.03)	
Baseline uric acid [mg/dL] (tertiles[3])												0.9528°/ 0.9748
<T1	937	103	11.0	930	80	8.6	0.80	(0.61,1.05)	0.1098	0.78	(0.57,1.06)	
>=T1 and <T2	931	118	12.7	996	104	10.4	0.82	(0.64,1.05)	0.1217	0.80	(0.60,1.06)	
>=T2	969	146	15.1	932	112	12.0	0.79	(0.63,0.99)	0.0449	0.76	(0.58,0.99)	
Baseline use of MRA												0.0965
No	1786	243	13.6	1813	178	9.8	0.72	(0.61,0.87)	0.0005	0.69	(0.56,0.85)	
Yes	1081	131	12.1	1071	120	11.2	0.93	(0.74,1.17)	0.5244	0.92	(0.70,1.20)	
Baseline use of ACE-inhibitor, ARB or ARNi												0.1058
No	557	87	15.6	543	55	10.1	0.63	(0.46,0.86)	0.0040	0.58	(0.41,0.84)	
Yes	2310	287	12.4	2341	243	10.4	0.84	(0.72,0.99)	0.0375	0.82	(0.69,0.99)	

* 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, °:Trend test.
^ Models contain terms age, baseline eGFR (CKD-EPI), baseline LVEF, Baseline KCCQ-CSS, 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.

Analysis is based on study 1245.110.
LOCF: For a missing value at week 52 the last available post-baseline value before week 52 is imputed.
^^ Patients with NYHA class I are counted in subgroup NYHA class II. [1] Baseline SBP median: 132 [mmHg].
[2] Baseline NT-proBNP median for patients with history of atrial fibrillation or atrial flutter: 1354 [pg/mL].
[2] Baseline NT-proBNP median for patients without history of atrial fibrillation or atrial flutter: 614 [pg/mL].
[3] Baseline uric acid tertile cut-offs for males are T1: 5.9 T2: 7.5 [mg/dL] [rounded].
[3] Baseline uric acid tertile cut-offs for females are T1: 5.4 T2: 6.9 [mg/dL] [rounded].

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Table R.1.1.3.1.1.5: 2 Responder analysis for KCCQ-CSS change from baseline at week 52 >= 15 points (improvement) overall and by subgroup - RS (LOCF-AD)

Subgroup	Placebo			Empa 10mg			Empa 10mg vs Placebo					
Category	N	n	%	N	n	%	Risk ratio *	(95% CI)	p-value	Odds ratio ***	(95% CI)	p-value **
Overall	2867	600	20.9	2884	652	22.6	1.03	(0.94,1.12)	0.5808	1.07	(0.93,1.24)	
Sex												0.0294
Male	1587	276	17.4	1596	316	19.8	1.14	(1.00,1.31)	0.0546	1.21	(0.99,1.48)	
Female	1280	324	25.3	1288	336	26.1	0.93	(0.82,1.05)	0.2589	0.95	(0.77,1.16)	
Age [years]												0.4259
<70	1036	236	22.8	1030	252	24.5	0.98	(0.85,1.13)	0.7829	1.01	(0.80,1.28)	
>=70	1831	364	19.9	1854	400	21.6	1.06	(0.94,1.19)	0.3539	1.11	(0.93,1.33)	
Region												0.4420
North America	344	76	22.1	344	57	16.6	0.81	(0.60,1.08)	0.1506	0.72	(0.47,1.11)	
Latin America	724	213	29.4	729	246	33.7	1.06	(0.92,1.23)	0.4078	1.18	(0.91,1.53)	
Europe	1301	234	18.0	1309	260	19.9	1.06	(0.91,1.23)	0.4747	1.10	(0.88,1.37)	
Asia	330	36	10.9	328	34	10.4	0.91	(0.61,1.35)	0.6269	0.87	(0.51,1.48)	
Other	168	41	24.4	174	55	31.6	1.13	(0.83,1.54)	0.4247	1.41	(0.82,2.43)	
OECD member												0.3054
No	789	220	27.9	818	276	33.7	1.09	(0.94,1.25)	0.2529	1.24	(0.97,1.58)	
Yes	2078	380	18.3	2066	376	18.2	0.99	(0.87,1.11)	0.8132	0.99	(0.83,1.18)	
Baseline NYHA												0.8317
II^^	2358	440	18.7	2354	470	20.0	1.03	(0.93,1.15)	0.5592	1.06	(0.90,1.25)	
III/IV	509	160	31.4	530	182	34.3	1.01	(0.85,1.20)	0.9125	1.10	(0.82,1.49)	
Baseline Diabetes status												0.0928
Diabetic	1406	308	21.9	1399	349	24.9	1.11	(0.98,1.25)	0.1172	1.21	(0.99,1.48)	
Non-Diabetic	1461	292	20.0	1485	303	20.4	0.95	(0.83,1.08)	0.4059	0.95	(0.77,1.16)	

* 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, °:Trend test.
^ Models contain terms age, baseline eGFR (CKD-EPI), baseline LVEF, Baseline KCCQ-CSS, 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.

Analysis is based on study 1245.110.
LOCF: For a missing value at week 52 the last available post-baseline value before week 52 is imputed.
^^ Patients with NYHA class I are counted in subgroup NYHA class II. [1] Baseline SBP median: 132 [mmHg].
[2] Baseline NT-proBNP median for patients with history of atrial fibrillation or atrial flutter: 1354 [pg/mL].
[2] Baseline NT-proBNP median for patients without history of atrial fibrillation or atrial flutter: 614 [pg/mL].
[3] Baseline uric acid tertile cut-offs for males are T1: 5.9 T2: 7.5 [mg/dL] [rounded].
[3] Baseline uric acid tertile cut-offs for females are T1: 5.4 T2: 6.9 [mg/dL] [rounded].

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Table R.1.1.3.1.1.5: 2 Responder analysis for KCCQ-CSS change from baseline at week 52 >= 15 points (improvement) overall and by subgroup - RS (LOCF-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 Diabetes status												0.0505°/ 0.1448
Diabetic	1406	308	21.9	1399	349	24.9	1.11	(0.97,1.25)	0.1177	1.21	(0.99,1.48)	
Pre-Diabetes	939	185	19.7	973	200	20.6	0.99	(0.84,1.17)	0.9386	1.00	(0.78,1.29)	
Normal (no pre-diabetes)	522	107	20.5	512	103	20.1	0.86	(0.69,1.08)	0.1894	0.86	(0.61,1.21)	
Baseline BMI [kg/m²]												0.0707
<30	1563	294	18.8	1590	294	18.5	0.94	(0.82,1.07)	0.3483	0.91	(0.74,1.11)	
>=30	1304	306	23.5	1294	358	27.7	1.11	(0.98,1.26)	0.1025	1.27	(1.04,1.56)	
Baseline eGFR (CKD-EPI) [mL/min/1.73m²]												0.4055
>=60	1448	290	20.0	1445	334	23.1	1.07	(0.94,1.21)	0.3247	1.15	(0.94,1.41)	
<60	1419	310	21.8	1439	318	22.1	0.99	(0.87,1.12)	0.8489	1.00	(0.82,1.22)	
History of HHF (in the last 12 months)												0.7761
No	2232	470	21.1	2226	509	22.9	1.03	(0.93,1.15)	0.5265	1.08	(0.92,1.27)	
Yes	635	130	20.5	658	143	21.7	1.00	(0.82,1.22)	0.9926	1.04	(0.77,1.41)	
Baseline SBP (</>= median¹)												0.0583
< median	1414	312	22.1	1444	307	21.3	0.94	(0.82,1.07)	0.3387	0.92	(0.75,1.13)	
>= median	1453	288	19.8	1440	345	24.0	1.12	(0.98,1.27)	0.0848	1.24	(1.01,1.52)	
History of atrial fibrillation or atrial flutter												0.3010
No	1363	314	23.0	1363	321	23.6	0.98	(0.86,1.11)	0.7062	0.97	(0.79,1.19)	
Yes	1501	286	19.1	1518	330	21.7	1.07	(0.94,1.23)	0.2819	1.17	(0.96,1.43)	

* 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, °:Trend test.
^ Models contain terms age, baseline eGFR (CKD-EPI), baseline LVEF, Baseline KCCQ-CSS, 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.

Analysis is based on study 1245.110.
LOCF: For a missing value at week 52 the last available post-baseline value before week 52 is imputed.
^^ Patients with NYHA class I are counted in subgroup NYHA class II. ¹ Baseline SBP median: 132 [mmHg].
² Baseline NT-proBNP median for patients with history of atrial fibrillation or atrial flutter: 1354 [pg/mL].
² Baseline NT-proBNP median for patients without history of atrial fibrillation or atrial flutter: 614 [pg/mL].
³ Baseline uric acid tertile cut-offs for males are T1: 5.9 T2: 7.5 [mg/dL] [rounded].
³ Baseline uric acid tertile cut-offs for females are T1: 5.4 T2: 6.9 [mg/dL] [rounded].

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Table R.1.1.3.1.1.5: 2 Responder analysis for KCCQ-CSS change from baseline at week 52 >= 15 points (improvement) overall and by subgroup - RS (LOCF-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 LVEF [%]												0.4469
< 50	929	188	20.2	957	237	24.8	1.08	(0.92,1.25)	0.3524	1.15	(0.90,1.47)	
>= 50	1938	412	21.3	1927	415	21.5	1.00	(0.89,1.12)	0.9848	1.03	(0.87,1.23)	
Baseline LVEF [%]												0.1914°/ 0.3379
<50	929	188	20.2	957	237	24.8	1.08	(0.92,1.25)	0.3539	1.15	(0.90,1.47)	
50 to <60	990	209	21.1	988	219	22.2	1.07	(0.92,1.26)	0.3810	1.17	(0.91,1.49)	
>=60	948	203	21.4	939	196	20.9	0.93	(0.79,1.09)	0.3595	0.91	(0.71,1.17)	
Baseline NT-proBNP [pg/mL] (</>=median[2] by atrial fibrillation/flutter status)												0.9688
< median	1463	288	19.7	1430	308	21.5	1.02	(0.90,1.17)	0.7252	1.08	(0.88,1.32)	
>= median	1400	312	22.3	1451	343	23.6	1.02	(0.90,1.16)	0.7516	1.06	(0.87,1.29)	
Baseline uric acid [mg/dL] (tertiles[3])												0.5317°/ 0.5346
<T1	937	188	20.1	930	200	21.5	1.02	(0.87,1.20)	0.7781	1.05	(0.81,1.35)	
>=T1 and <T2	931	184	19.8	996	228	22.9	1.09	(0.93,1.28)	0.3117	1.16	(0.91,1.49)	
>=T2	969	221	22.8	932	217	23.3	0.96	(0.82,1.12)	0.5718	0.98	(0.77,1.25)	
Baseline use of MRA												0.0040
No	1786	377	21.1	1813	375	20.7	0.92	(0.82,1.03)	0.1630	0.91	(0.76,1.09)	
Yes	1081	223	20.6	1071	277	25.9	1.21	(1.05,1.40)	0.0098	1.40	(1.11,1.76)	
Baseline use of ACE-inhibitor, ARB or ARNi												0.7835
No	557	120	21.5	543	124	22.8	1.05	(0.86,1.28)	0.6144	1.14	(0.83,1.58)	
Yes	2310	480	20.8	2341	528	22.6	1.02	(0.92,1.13)	0.7055	1.06	(0.90,1.24)	

* 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, °:Trend test.
^ Models contain terms age, baseline eGFR (CKD-EPI), baseline LVEF, Baseline KCCQ-CSS, 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.

Analysis is based on study 1245.110.
LOCF: For a missing value at week 52 the last available post-baseline value before week 52 is imputed.
^^ Patients with NYHA class I are counted in subgroup NYHA class II. [1] Baseline SBP median: 132 [mmHg].
[2] Baseline NT-proBNP median for patients with history of atrial fibrillation or atrial flutter: 1354 [pg/mL].
[2] Baseline NT-proBNP median for patients without history of atrial fibrillation or atrial flutter: 614 [pg/mL].
[3] Baseline uric acid tertile cut-offs for males are T1: 5.9 T2: 7.5 [mg/dL] [rounded].
[3] Baseline uric acid tertile cut-offs for females are T1: 5.4 T2: 6.9 [mg/dL] [rounded].

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R.1.1.3.1.1.6 KCCQ Total Symptoms Score responder analysis (5 points)

Table R.1.1.3.1.1.6: 1 Responder analysis for KCCQ-TSS change from baseline at week 52 <= -5 points (deterioration) overall and by subgroup - RS (LOCF-AD)

Subgroup	Placebo			Empa 10mg			Empa 10mg vs Placebo					
Category	N	n	%	N	n	%	Risk ratio *	(95% CI)	p-value	Odds ratio ***	(95% CI)	p-value **
Overall	2867	820	28.6	2884	666	23.1	0.82	(0.75,0.89)	<0.0001	0.76	(0.67,0.85)	
Sex												0.9294
Male	1587	450	28.4	1596	368	23.1	0.82	(0.73,0.93)	0.0011	0.76	(0.65,0.89)	
Female	1280	370	28.9	1288	298	23.1	0.82	(0.72,0.93)	0.0018	0.75	(0.63,0.90)	
Age [years]												0.5829
<70	1036	260	25.1	1030	213	20.7	0.85	(0.73,0.99)	0.0407	0.80	(0.65,0.99)	
>=70	1831	560	30.6	1854	453	24.4	0.81	(0.73,0.89)	<0.0001	0.73	(0.63,0.85)	
Region												0.4458
North America	344	94	27.3	344	86	25.0	0.92	(0.72,1.18)	0.4967	0.88	(0.62,1.25)	
Latin America	724	168	23.2	729	140	19.2	0.84	(0.70,1.02)	0.0869	0.80	(0.62,1.04)	
Europe	1301	408	31.4	1309	319	24.4	0.79	(0.70,0.89)	0.0002	0.71	(0.60,0.85)	
Asia	330	94	28.5	328	85	25.9	0.91	(0.71,1.17)	0.4609	0.88	(0.62,1.24)	
Other	168	56	33.3	174	36	20.7	0.64	(0.45,0.92)	0.0152	0.53	(0.32,0.88)	
OECD member												0.3716
No	789	209	26.5	818	162	19.8	0.77	(0.64,0.91)	0.0028	0.70	(0.55,0.88)	
Yes	2078	611	29.4	2066	504	24.4	0.84	(0.76,0.93)	0.0005	0.78	(0.68,0.90)	
Baseline NYHA												0.2199
II^^	2358	673	28.5	2354	557	23.7	0.84	(0.76,0.92)	0.0003	0.78	(0.68,0.89)	
III/IV	509	147	28.9	530	109	20.6	0.73	(0.59,0.90)	0.0027	0.64	(0.48,0.86)	
Baseline Diabetes status												0.5071
Diabetic	1406	402	28.6	1399	313	22.4	0.80	(0.70,0.90)	0.0003	0.73	(0.61,0.87)	
Non-Diabetic	1461	418	28.6	1485	353	23.8	0.84	(0.75,0.95)	0.0057	0.79	(0.67,0.93)	

* 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, °:Trend test.
^ Models contain terms age, baseline eGFR (CKD-EPI), baseline LVEF, Baseline KCCQ-TSS, 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.

Analysis is based on study 1245.110.
LOCF: For a missing value at week 52 the last available post-baseline value before week 52 is imputed.
^^ Patients with NYHA class I are counted in subgroup NYHA class II. [1] Baseline SBP median: 132 [mmHg].
[2] Baseline NT-proBNP median for patients with history of atrial fibrillation or atrial flutter: 1354 [pg/mL].
[2] Baseline NT-proBNP median for patients without history of atrial fibrillation or atrial flutter: 614 [pg/mL].
[3] Baseline uric acid tertile cut-offs for males are T1: 5.9 T2: 7.5 [mg/dL] [rounded].
[3] Baseline uric acid tertile cut-offs for females are T1: 5.4 T2: 6.9 [mg/dL] [rounded].

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Table R.1.1.3.1.1.6: 1 Responder analysis for KCCQ-TSS change from baseline at week 52 <= -5 points (deterioration) overall and by subgroup - RS (LOCF-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 Diabetes status												0.6680°/ 0.7723
Diabetic	1406	402	28.6	1399	313	22.4	0.80	(0.70,0.90)	0.0003	0.73	(0.61,0.87)	
Pre-Diabetes	939	277	29.5	973	244	25.1	0.85	(0.74,0.99)	0.0322	0.80	(0.65,0.98)	
Normal (no pre-diabetes)	522	141	27.0	512	109	21.3	0.82	(0.66,1.02)	0.0682	0.76	(0.57,1.02)	
Baseline BMI [kg/m²]												0.2062
<30	1563	445	28.5	1590	389	24.5	0.86	(0.77,0.97)	0.0111	0.81	(0.69,0.96)	
>=30	1304	375	28.8	1294	277	21.4	0.77	(0.68,0.88)	0.0001	0.69	(0.58,0.83)	
Baseline eGFR (CKD-EPI) [mL/min/1.73m²]												0.7800
>=60	1448	394	27.2	1445	309	21.4	0.81	(0.71,0.92)	0.0012	0.75	(0.63,0.89)	
<60	1419	426	30.0	1439	357	24.8	0.83	(0.74,0.93)	0.0017	0.76	(0.65,0.91)	
History of HHF (in the last 12 months)												0.4215
No	2232	611	27.4	2226	500	22.5	0.84	(0.76,0.92)	0.0005	0.78	(0.68,0.90)	
Yes	635	209	32.9	658	166	25.2	0.77	(0.65,0.91)	0.0026	0.68	(0.53,0.87)	
Baseline SBP (</>= median¹)												0.3945
< median	1414	402	28.4	1444	348	24.1	0.85	(0.75,0.96)	0.0085	0.80	(0.67,0.95)	
>= median	1453	418	28.8	1440	318	22.1	0.79	(0.70,0.89)	0.0002	0.72	(0.60,0.85)	
History of atrial fibrillation or atrial flutter												0.0139
No	1363	351	25.8	1363	318	23.3	0.92	(0.81,1.05)	0.2339	0.90	(0.75,1.07)	
Yes	1501	467	31.1	1518	347	22.9	0.74	(0.66,0.84)	<0.0001	0.66	(0.56,0.78)	

* 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, °:Trend test.
^ Models contain terms age, baseline eGFR (CKD-EPI), baseline LVEF, Baseline KCCQ-TSS, 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.

Analysis is based on study 1245.110.
LOCF: For a missing value at week 52 the last available post-baseline value before week 52 is imputed.
^^ Patients with NYHA class I are counted in subgroup NYHA class II. ¹ Baseline SBP median: 132 [mmHg].
² Baseline NT-proBNP median for patients with history of atrial fibrillation or atrial flutter: 1354 [pg/mL].
² Baseline NT-proBNP median for patients without history of atrial fibrillation or atrial flutter: 614 [pg/mL].
³ Baseline uric acid tertile cut-offs for males are T1: 5.9 T2: 7.5 [mg/dL] [rounded].
³ Baseline uric acid tertile cut-offs for females are T1: 5.4 T2: 6.9 [mg/dL] [rounded].

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Table R.1.1.3.1.1.6: 1 Responder analysis for KCCQ-TSS change from baseline at week 52 <= -5 points (deterioration) overall and by subgroup - RS (LOCF-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 LVEF [%]												0.7255
< 50	929	244	26.3	957	203	21.2	0.84	(0.72,0.98)	0.0317	0.79	(0.64,0.98)	
>= 50	1938	576	29.7	1927	463	24.0	0.81	(0.73,0.90)	<0.0001	0.74	(0.64,0.86)	
Baseline LVEF [%]												0.7688°/ 0.4870
<50	929	244	26.3	957	203	21.2	0.84	(0.72,0.98)	0.0316	0.79	(0.64,0.98)	
50 to <60	990	309	31.2	988	236	23.9	0.77	(0.67,0.88)	0.0002	0.68	(0.56,0.83)	
>=60	948	267	28.2	939	227	24.2	0.86	(0.74,1.00)	0.0557	0.81	(0.66,1.01)	
Baseline NT-proBNP [pg/mL] (</>=median[2] by atrial fibrillation/flutter status)												0.1488
< median	1463	419	28.6	1430	307	21.5	0.77	(0.68,0.87)	<0.0001	0.69	(0.58,0.82)	
>= median	1400	398	28.4	1451	358	24.7	0.87	(0.77,0.98)	0.0260	0.83	(0.70,0.98)	
Baseline uric acid [mg/dL] (tertiles[3])												0.9801°/ 0.9170
<T1	937	258	27.5	930	203	21.8	0.81	(0.69,0.95)	0.0088	0.75	(0.60,0.93)	
>=T1 and <T2	931	259	27.8	996	230	23.1	0.84	(0.73,0.98)	0.0261	0.79	(0.64,0.97)	
>=T2	969	295	30.4	932	227	24.4	0.81	(0.70,0.94)	0.0046	0.74	(0.60,0.91)	
Baseline use of MRA												0.9547
No	1786	507	28.4	1813	416	22.9	0.82	(0.74,0.92)	0.0005	0.76	(0.65,0.89)	
Yes	1081	313	29.0	1071	250	23.3	0.82	(0.71,0.94)	0.0048	0.75	(0.62,0.92)	
Baseline use of ACE-inhibitor, ARB or ARNi												0.3543
No	557	171	30.7	543	127	23.4	0.76	(0.62,0.92)	0.0044	0.67	(0.51,0.88)	
Yes	2310	649	28.1	2341	539	23.0	0.84	(0.76,0.92)	0.0003	0.78	(0.68,0.89)	

* 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, °:Trend test.
^ Models contain terms age, baseline eGFR (CKD-EPI), baseline LVEF, Baseline KCCQ-TSS, 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.

Analysis is based on study 1245.110.
LOCF: For a missing value at week 52 the last available post-baseline value before week 52 is imputed.
^^ Patients with NYHA class I are counted in subgroup NYHA class II. [1] Baseline SBP median: 132 [mmHg].
[2] Baseline NT-proBNP median for patients with history of atrial fibrillation or atrial flutter: 1354 [pg/mL].
[2] Baseline NT-proBNP median for patients without history of atrial fibrillation or atrial flutter: 614 [pg/mL].
[3] Baseline uric acid tertile cut-offs for males are T1: 5.9 T2: 7.5 [mg/dL] [rounded].
[3] Baseline uric acid tertile cut-offs for females are T1: 5.4 T2: 6.9 [mg/dL] [rounded].

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Table R.1.1.3.1.1.6: 2 Responder analysis for KCCQ-TSS change from baseline at week 52 >= 5 points (improvement) overall and by subgroup - RS (LOCF-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	2867	1186	41.4	2884	1351	46.8	1.10	(1.04,1.16)	0.0008	1.25	(1.12,1.41)	
Sex												0.1718
Male	1587	607	38.2	1596	696	43.6	1.14	(1.05,1.23)	0.0011	1.27	(1.09,1.49)	
Female	1280	579	45.2	1288	655	50.9	1.05	(0.98,1.14)	0.1684	1.23	(1.03,1.47)	
Age [years]												0.6365
<70	1036	450	43.4	1030	506	49.1	1.08	(0.99,1.18)	0.0896	1.23	(1.01,1.50)	
>=70	1831	736	40.2	1854	845	45.6	1.11	(1.03,1.19)	0.0037	1.27	(1.10,1.47)	
Region												0.2275
North America	344	155	45.1	344	146	42.4	0.95	(0.81,1.11)	0.5306	0.88	(0.62,1.23)	
Latin America	724	353	48.8	729	393	53.9	1.06	(0.97,1.16)	0.2135	1.22	(0.97,1.55)	
Europe	1301	516	39.7	1309	607	46.4	1.13	(1.04,1.23)	0.0034	1.32	(1.11,1.57)	
Asia	330	96	29.1	328	114	34.8	1.17	(0.95,1.43)	0.1321	1.33	(0.93,1.89)	
Other	168	66	39.3	174	91	52.3	1.23	(0.99,1.54)	0.0624	1.76	(1.09,2.86)	
OECD member												0.7248
No	789	363	46.0	818	442	54.0	1.11	(1.01,1.22)	0.0228	1.38	(1.11,1.73)	
Yes	2078	823	39.6	2066	909	44.0	1.09	(1.02,1.16)	0.0126	1.21	(1.05,1.38)	
Baseline NYHA												0.1460
II^^	2358	917	38.9	2354	1051	44.6	1.12	(1.05,1.19)	0.0004	1.29	(1.13,1.46)	
III/IV	509	269	52.8	530	300	56.6	1.02	(0.92,1.14)	0.7213	1.12	(0.85,1.48)	
Baseline Diabetes status												0.0053
Diabetic	1406	581	41.3	1399	703	50.3	1.18	(1.10,1.27)	<0.0001	1.49	(1.26,1.77)	
Non-Diabetic	1461	605	41.4	1485	648	43.6	1.01	(0.94,1.10)	0.7168	1.07	(0.90,1.25)	

* 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, °:Trend test.
^ Models contain terms age, baseline eGFR (CKD-EPI), baseline LVEF, Baseline KCCQ-TSS, 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.

Analysis is based on study 1245.110.
LOCF: For a missing value at week 52 the last available post-baseline value before week 52 is imputed.
^^ Patients with NYHA class I are counted in subgroup NYHA class II. [1] Baseline SBP median: 132 [mmHg].
[2] Baseline NT-proBNP median for patients with history of atrial fibrillation or atrial flutter: 1354 [pg/mL].
[2] Baseline NT-proBNP median for patients without history of atrial fibrillation or atrial flutter: 614 [pg/mL].
[3] Baseline uric acid tertile cut-offs for males are T1: 5.9 T2: 7.5 [mg/dL] [rounded].
[3] Baseline uric acid tertile cut-offs for females are T1: 5.4 T2: 6.9 [mg/dL] [rounded].

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Table R.1.1.3.1.1.6: 2 Responder analysis for KCCQ-TSS change from baseline at week 52 >= 5 points (improvement) overall and by subgroup - RS (LOCF-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 Diabetes status												0.0155°/ 0.0206
Diabetic	1406	581	41.3	1399	703	50.3	1.18	(1.10,1.27)	<0.0001	1.49	(1.26,1.77)	
Pre-Diabetes	939	392	41.7	973	421	43.3	1.01	(0.92,1.11)	0.8311	1.05	(0.86,1.29)	
Normal (no pre-diabetes)	522	213	40.8	512	227	44.3	1.02	(0.90,1.17)	0.7433	1.09	(0.83,1.44)	
Baseline BMI [kg/m²]												0.0658
<30	1563	610	39.0	1590	659	41.4	1.04	(0.96,1.13)	0.2938	1.10	(0.94,1.29)	
>=30	1304	576	44.2	1294	692	53.5	1.15	(1.07,1.24)	0.0002	1.47	(1.24,1.76)	
Baseline eGFR (CKD-EPI) [mL/min/1.73m²]												0.9897
>=60	1448	598	41.3	1445	685	47.4	1.10	(1.02,1.18)	0.0160	1.26	(1.07,1.48)	
<60	1419	588	41.4	1439	666	46.3	1.10	(1.02,1.18)	0.0192	1.25	(1.06,1.48)	
History of HHF (in the last 12 months)												0.9795
No	2232	924	41.4	2226	1043	46.9	1.10	(1.03,1.17)	0.0029	1.25	(1.09,1.43)	
Yes	635	262	41.3	658	308	46.8	1.09	(0.97,1.23)	0.1261	1.27	(0.99,1.63)	
Baseline SBP (</>= median¹)												0.0768
< median	1414	600	42.4	1444	654	45.3	1.04	(0.97,1.13)	0.2772	1.13	(0.95,1.33)	
>= median	1453	586	40.3	1440	697	48.4	1.15	(1.07,1.24)	0.0003	1.40	(1.18,1.65)	
History of atrial fibrillation or atrial flutter												0.3364
No	1363	571	41.9	1363	657	48.2	1.13	(1.04,1.21)	0.0025	1.33	(1.12,1.58)	
Yes	1501	614	40.9	1518	692	45.6	1.07	(0.99,1.15)	0.0908	1.19	(1.01,1.40)	

* 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, °:Trend test.
^ Models contain terms age, baseline eGFR (CKD-EPI), baseline LVEF, Baseline KCCQ-TSS, 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.

Analysis is based on study 1245.110.
LOCF: For a missing value at week 52 the last available post-baseline value before week 52 is imputed.
^^ Patients with NYHA class I are counted in subgroup NYHA class II. ¹ Baseline SBP median: 132 [mmHg].
² Baseline NT-proBNP median for patients with history of atrial fibrillation or atrial flutter: 1354 [pg/mL].
² Baseline NT-proBNP median for patients without history of atrial fibrillation or atrial flutter: 614 [pg/mL].
³ Baseline uric acid tertile cut-offs for males are T1: 5.9 T2: 7.5 [mg/dL] [rounded].
³ Baseline uric acid tertile cut-offs for females are T1: 5.4 T2: 6.9 [mg/dL] [rounded].

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Table R.1.1.3.1.1.6: 2 Responder analysis for KCCQ-TSS change from baseline at week 52 >= 5 points (improvement) overall and by subgroup - RS (LOCF-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 LVEF [%]												0.6657
< 50	929	396	42.6	957	469	49.0	1.08	(0.98,1.18)	0.1093	1.22	(0.99,1.49)	
>= 50	1938	790	40.8	1927	882	45.8	1.10	(1.03,1.18)	0.0039	1.27	(1.10,1.47)	
Baseline LVEF [%]												0.7536°/ 0.3813
<50	929	396	42.6	957	469	49.0	1.08	(0.98,1.18)	0.1096	1.22	(0.99,1.49)	
50 to <60	990	394	39.8	988	450	45.5	1.15	(1.05,1.27)	0.0028	1.38	(1.13,1.69)	
>=60	948	396	41.8	939	432	46.0	1.05	(0.96,1.16)	0.2773	1.17	(0.95,1.44)	
Baseline NT-proBNP [pg/mL] (</>=median[2] by atrial fibrillation/flutter status)												0.5539
< median	1463	584	39.9	1430	665	46.5	1.11	(1.03,1.20)	0.0068	1.29	(1.10,1.53)	
>= median	1400	601	42.9	1451	684	47.1	1.08	(1.00,1.16)	0.0523	1.21	(1.02,1.43)	
Baseline uric acid [mg/dL] (tertiles[3])												0.6158°/ 0.8826
<T1	937	394	42.0	930	430	46.2	1.07	(0.98,1.18)	0.1434	1.17	(0.95,1.44)	
>=T1 and <T2	931	375	40.3	996	462	46.4	1.09	(0.99,1.20)	0.0692	1.26	(1.03,1.54)	
>=T2	969	409	42.2	932	449	48.2	1.11	(1.01,1.22)	0.0285	1.31	(1.06,1.61)	
Baseline use of MRA												0.0316
No	1786	743	41.6	1813	816	45.0	1.05	(0.98,1.12)	0.1982	1.12	(0.97,1.30)	
Yes	1081	443	41.0	1071	535	50.0	1.18	(1.08,1.29)	0.0002	1.52	(1.25,1.84)	
Baseline use of ACE-inhibitor, ARB or ARNi												0.7241
No	557	231	41.5	543	254	46.8	1.12	(0.99,1.26)	0.0741	1.34	(1.02,1.76)	
Yes	2310	955	41.3	2341	1097	46.9	1.09	(1.03,1.16)	0.0045	1.23	(1.08,1.41)	

* 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, °:Trend test.
^ Models contain terms age, baseline eGFR (CKD-EPI), baseline LVEF, Baseline KCCQ-TSS, 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.

Analysis is based on study 1245.110.
LOCF: For a missing value at week 52 the last available post-baseline value before week 52 is imputed.
^^ Patients with NYHA class I are counted in subgroup NYHA class II. [1] Baseline SBP median: 132 [mmHg].
[2] Baseline NT-proBNP median for patients with history of atrial fibrillation or atrial flutter: 1354 [pg/mL].
[2] Baseline NT-proBNP median for patients without history of atrial fibrillation or atrial flutter: 614 [pg/mL].
[3] Baseline uric acid tertile cut-offs for males are T1: 5.9 T2: 7.5 [mg/dL] [rounded].
[3] Baseline uric acid tertile cut-offs for females are T1: 5.4 T2: 6.9 [mg/dL] [rounded].

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R.1.1.3.1.1.7 KCCQ Total Symptoms Score responder analysis (15 points)

Table R.1.1.3.1.1.7: 1 Responder analysis for KCCQ-TSS change from baseline at week 52 <= -15 points (deterioration) overall and by subgroup - RS (LOCF-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	2867	401	14.0	2884	298	10.3	0.75	(0.65,0.86)	<0.0001	0.72	(0.61,0.84)	
Sex												0.8750
Male	1587	210	13.2	1596	155	9.7	0.74	(0.61,0.90)	0.0028	0.71	(0.57,0.89)	
Female	1280	191	14.9	1288	143	11.1	0.76	(0.62,0.93)	0.0071	0.73	(0.57,0.92)	
Age [years]												0.6995
<70	1036	114	11.0	1030	79	7.7	0.72	(0.55,0.94)	0.0165	0.69	(0.51,0.93)	
>=70	1831	287	15.7	1854	219	11.8	0.76	(0.65,0.90)	0.0010	0.73	(0.60,0.88)	
Region												0.2858
North America	344	51	14.8	344	39	11.3	0.77	(0.52,1.13)	0.1870	0.73	(0.47,1.15)	
Latin America	724	79	10.9	729	57	7.8	0.74	(0.54,1.01)	0.0595	0.71	(0.49,1.02)	
Europe	1301	210	16.1	1309	151	11.5	0.73	(0.60,0.88)	0.0011	0.69	(0.55,0.86)	
Asia	330	33	10.0	328	37	11.3	1.13	(0.73,1.75)	0.5969	1.15	(0.69,1.89)	
Other	168	28	16.7	174	14	8.0	0.51	(0.28,0.93)	0.0276	0.45	(0.23,0.90)	
OECD member												0.1729
No	789	102	12.9	818	65	7.9	0.63	(0.47,0.84)	0.0018	0.59	(0.42,0.82)	
Yes	2078	299	14.4	2066	233	11.3	0.79	(0.68,0.93)	0.0045	0.76	(0.63,0.92)	
Baseline NYHA												0.3373
II^^	2358	316	13.4	2354	241	10.2	0.78	(0.67,0.91)	0.0015	0.75	(0.62,0.89)	
III/IV	509	85	16.7	530	57	10.8	0.66	(0.49,0.89)	0.0065	0.60	(0.42,0.87)	
Baseline Diabetes status												0.8233
Diabetic	1406	197	14.0	1399	143	10.2	0.74	(0.61,0.90)	0.0030	0.70	(0.56,0.89)	
Non-Diabetic	1461	204	14.0	1485	155	10.4	0.76	(0.63,0.93)	0.0066	0.73	(0.58,0.91)	

* 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, °:Trend test.
^ Models contain terms age, baseline eGFR (CKD-EPI), baseline LVEF, Baseline KCCQ-TSS, 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.

Analysis is based on study 1245.110.
LOCF: For a missing value at week 52 the last available post-baseline value before week 52 is imputed.
^^ Patients with NYHA class I are counted in subgroup NYHA class II. [1] Baseline SBP median: 132 [mmHg].
[2] Baseline NT-proBNP median for patients with history of atrial fibrillation or atrial flutter: 1354 [pg/mL].
[2] Baseline NT-proBNP median for patients without history of atrial fibrillation or atrial flutter: 614 [pg/mL].
[3] Baseline uric acid tertile cut-offs for males are T1: 5.9 T2: 7.5 [mg/dL] [rounded].
[3] Baseline uric acid tertile cut-offs for females are T1: 5.4 T2: 6.9 [mg/dL] [rounded].

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Table R.1.1.3.1.1.7: 1 Responder analysis for KCCQ-TSS change from baseline at week 52 <= -15 points (deterioration) overall and by subgroup - RS (LOCF-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 Diabetes status												0.5475°/ 0.2186
Diabetic	1406	197	14.0	1399	143	10.2	0.74	(0.61,0.90)	0.0030	0.70	(0.56,0.89)	
Pre-Diabetes	939	125	13.3	973	111	11.4	0.86	(0.68,1.09)	0.2254	0.84	(0.64,1.11)	
Normal (no pre-diabetes)	522	79	15.1	512	44	8.6	0.60	(0.42,0.84)	0.0033	0.55	(0.37,0.82)	
Baseline BMI [kg/m²]												0.1270
<30	1563	202	12.9	1590	170	10.7	0.83	(0.69,1.01)	0.0601	0.81	(0.65,1.01)	
>=30	1304	199	15.3	1294	128	9.9	0.67	(0.55,0.82)	0.0001	0.62	(0.49,0.79)	
Baseline eGFR (CKD-EPI) [mL/min/1.73m²]												0.8897
>=60	1448	171	11.8	1445	125	8.7	0.76	(0.61,0.94)	0.0133	0.73	(0.57,0.94)	
<60	1419	230	16.2	1439	173	12.0	0.75	(0.62,0.89)	0.0014	0.70	(0.57,0.87)	
History of HHF (in the last 12 months)												0.7268
No	2232	294	13.2	2226	218	9.8	0.76	(0.65,0.90)	0.0010	0.73	(0.60,0.88)	
Yes	635	107	16.9	658	80	12.2	0.72	(0.55,0.94)	0.0150	0.67	(0.49,0.93)	
Baseline SBP (</>= median¹)												0.3474
< median	1414	202	14.3	1444	164	11.4	0.80	(0.66,0.97)	0.0210	0.77	(0.61,0.96)	
>= median	1453	199	13.7	1440	134	9.3	0.70	(0.57,0.86)	0.0006	0.66	(0.52,0.84)	
History of atrial fibrillation or atrial flutter												0.9231
No	1363	168	12.3	1363	124	9.1	0.76	(0.61,0.94)	0.0118	0.73	(0.57,0.93)	
Yes	1501	233	15.5	1518	174	11.5	0.75	(0.62,0.90)	0.0016	0.71	(0.57,0.88)	

* 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, °:Trend test.
^ Models contain terms age, baseline eGFR (CKD-EPI), baseline LVEF, Baseline KCCQ-TSS, 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.

Analysis is based on study 1245.110.
LOCF: For a missing value at week 52 the last available post-baseline value before week 52 is imputed.
^^ Patients with NYHA class I are counted in subgroup NYHA class II. ¹ Baseline SBP median: 132 [mmHg].
² Baseline NT-proBNP median for patients with history of atrial fibrillation or atrial flutter: 1354 [pg/mL].
² Baseline NT-proBNP median for patients without history of atrial fibrillation or atrial flutter: 614 [pg/mL].
³ Baseline uric acid tertile cut-offs for males are T1: 5.9 T2: 7.5 [mg/dL] [rounded].
³ Baseline uric acid tertile cut-offs for females are T1: 5.4 T2: 6.9 [mg/dL] [rounded].

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Table R.1.1.3.1.1.7: 1 Responder analysis for KCCQ-TSS change from baseline at week 52 <= -15 points (deterioration) overall and by subgroup - RS (LOCF-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 LVEF [%]												0.9922
< 50	929	114	12.3	957	84	8.8	0.75	(0.58,0.98)	0.0355	0.72	(0.54,0.98)	
>= 50	1938	287	14.8	1927	214	11.1	0.75	(0.64,0.89)	0.0006	0.71	(0.59,0.87)	
Baseline LVEF [%]												0.7114°/ 0.7690
<50	929	114	12.3	957	84	8.8	0.75	(0.58,0.98)	0.0355	0.72	(0.54,0.98)	
50 to <60	990	159	16.1	988	112	11.3	0.71	(0.57,0.89)	0.0026	0.67	(0.51,0.87)	
>=60	948	128	13.5	939	102	10.9	0.80	(0.63,1.02)	0.0724	0.77	(0.58,1.03)	
Baseline NT-proBNP [pg/mL] (</>=median[2] by atrial fibrillation/flutter status)												0.6051
< median	1463	199	13.6	1430	137	9.6	0.72	(0.59,0.89)	0.0018	0.69	(0.54,0.87)	
>= median	1400	201	14.4	1451	161	11.1	0.78	(0.64,0.94)	0.0108	0.75	(0.60,0.94)	
Baseline uric acid [mg/dL] (tertiles[3])												0.8725°/ 0.9115
<T1	937	109	11.6	930	76	8.2	0.73	(0.55,0.96)	0.0229	0.70	(0.51,0.95)	
>=T1 and <T2	931	133	14.3	996	111	11.1	0.79	(0.62,0.99)	0.0439	0.76	(0.57,0.99)	
>=T2	969	154	15.9	932	110	11.8	0.75	(0.60,0.94)	0.0139	0.71	(0.55,0.93)	
Baseline use of MRA												0.2507
No	1786	256	14.3	1813	180	9.9	0.71	(0.59,0.84)	0.0001	0.67	(0.54,0.82)	
Yes	1081	145	13.4	1071	118	11.0	0.83	(0.67,1.04)	0.1144	0.81	(0.62,1.05)	
Baseline use of ACE-inhibitor, ARB or ARNi												0.4151
No	557	87	15.6	543	57	10.5	0.67	(0.49,0.91)	0.0109	0.62	(0.43,0.90)	
Yes	2310	314	13.6	2341	241	10.3	0.77	(0.66,0.91)	0.0013	0.74	(0.62,0.89)	

* 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, °:Trend test.
^ Models contain terms age, baseline eGFR (CKD-EPI), baseline LVEF, Baseline KCCQ-TSS, 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.

Analysis is based on study 1245.110.
LOCF: For a missing value at week 52 the last available post-baseline value before week 52 is imputed.
^^ Patients with NYHA class I are counted in subgroup NYHA class II. [1] Baseline SBP median: 132 [mmHg].
[2] Baseline NT-proBNP median for patients with history of atrial fibrillation or atrial flutter: 1354 [pg/mL].
[2] Baseline NT-proBNP median for patients without history of atrial fibrillation or atrial flutter: 614 [pg/mL].
[3] Baseline uric acid tertile cut-offs for males are T1: 5.9 T2: 7.5 [mg/dL] [rounded].
[3] Baseline uric acid tertile cut-offs for females are T1: 5.4 T2: 6.9 [mg/dL] [rounded].

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Table R.1.1.3.1.1.7: 2 Responder analysis for KCCQ-TSS change from baseline at week 52 >= 15 points (improvement) overall and by subgroup - RS (LOCF-AD)

Subgroup	Placebo			Empa 10mg			Empa 10mg vs Placebo					
Category	N	n	%	N	n	%	Risk ratio *	(95% CI)	p-value	Odds ratio ***	(95% CI)	p-value **
Overall	2867	648	22.6	2884	754	26.1	1.08	(0.99,1.18)	0.0655	1.19	(1.03,1.37)	
Sex												0.1026
Male	1587	315	19.8	1596	366	22.9	1.16	(1.03,1.31)	0.0147	1.24	(1.02,1.52)	
Female	1280	333	26.0	1288	388	30.1	1.01	(0.90,1.14)	0.8600	1.13	(0.92,1.39)	
Age [years]												0.1618
<70	1036	261	25.2	1030	286	27.8	1.00	(0.88,1.15)	0.9573	1.07	(0.84,1.35)	
>=70	1831	387	21.1	1854	468	25.2	1.14	(1.02,1.26)	0.0193	1.27	(1.06,1.51)	
Region												0.7455
North America	344	84	24.4	344	78	22.7	0.96	(0.75,1.23)	0.7578	0.90	(0.60,1.36)	
Latin America	724	218	30.1	729	248	34.0	1.04	(0.90,1.20)	0.5900	1.17	(0.89,1.53)	
Europe	1301	260	20.0	1309	319	24.4	1.15	(1.00,1.31)	0.0448	1.26	(1.02,1.56)	
Asia	330	42	12.7	328	50	15.2	1.13	(0.82,1.56)	0.4572	1.18	(0.72,1.93)	
Other	168	44	26.2	174	59	33.9	1.09	(0.80,1.49)	0.5913	1.36	(0.79,2.36)	
OECD member												0.8750
No	789	235	29.8	818	292	35.7	1.07	(0.94,1.23)	0.3147	1.28	(0.99,1.64)	
Yes	2078	413	19.9	2066	462	22.4	1.09	(0.98,1.21)	0.1277	1.14	(0.96,1.36)	
Baseline NYHA												0.2935
II^^	2358	473	20.1	2354	551	23.4	1.11	(1.01,1.23)	0.0327	1.21	(1.03,1.43)	
III/IV	509	175	34.4	530	203	38.3	1.00	(0.85,1.18)	0.9525	1.10	(0.82,1.49)	
Baseline Diabetes status												0.0087
Diabetic	1406	325	23.1	1399	411	29.4	1.21	(1.07,1.35)	0.0015	1.44	(1.18,1.76)	
Non-Diabetic	1461	323	22.1	1485	343	23.1	0.96	(0.85,1.09)	0.5349	0.98	(0.80,1.19)	

* 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, °:Trend test.
^ Models contain terms age, baseline eGFR (CKD-EPI), baseline LVEF, Baseline KCCQ-TSS, 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.

Analysis is based on study 1245.110.
LOCF: For a missing value at week 52 the last available post-baseline value before week 52 is imputed.
^^ Patients with NYHA class I are counted in subgroup NYHA class II. [1] Baseline SBP median: 132 [mmHg].
[2] Baseline NT-proBNP median for patients with history of atrial fibrillation or atrial flutter: 1354 [pg/mL].
[2] Baseline NT-proBNP median for patients without history of atrial fibrillation or atrial flutter: 614 [pg/mL].
[3] Baseline uric acid tertile cut-offs for males are T1: 5.9 T2: 7.5 [mg/dL] [rounded].
[3] Baseline uric acid tertile cut-offs for females are T1: 5.4 T2: 6.9 [mg/dL] [rounded].

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Table R.1.1.3.1.1.7: 2 Responder analysis for KCCQ-TSS change from baseline at week 52 >= 15 points (improvement) overall and by subgroup - RS (LOCF-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 Diabetes status												0.0155°/ 0.0315
Diabetic	1406	325	23.1	1399	411	29.4	1.21	(1.07,1.35)	0.0015	1.44	(1.18,1.76)	
Pre-Diabetes	939	213	22.7	973	226	23.2	0.97	(0.83,1.13)	0.6773	0.97	(0.75,1.24)	
Normal (no pre-diabetes)	522	110	21.1	512	117	22.9	0.95	(0.77,1.17)	0.6243	0.99	(0.71,1.40)	
Baseline BMI [kg/m²]												0.4856
<30	1563	325	20.8	1590	361	22.7	1.05	(0.93,1.18)	0.4170	1.09	(0.89,1.33)	
>=30	1304	323	24.8	1294	393	30.4	1.11	(0.99,1.26)	0.0760	1.30	(1.06,1.60)	
Baseline eGFR (CKD-EPI) [mL/min/1.73m²]												0.6138
>=60	1448	320	22.1	1445	370	25.6	1.06	(0.94,1.19)	0.3486	1.15	(0.94,1.41)	
<60	1419	328	23.1	1439	384	26.7	1.11	(0.98,1.24)	0.0957	1.22	(1.00,1.50)	
History of HHF (in the last 12 months)												0.8450
No	2232	491	22.0	2226	567	25.5	1.09	(0.99,1.20)	0.0898	1.18	(1.01,1.39)	
Yes	635	157	24.7	658	187	28.4	1.07	(0.90,1.27)	0.4669	1.20	(0.89,1.60)	
Baseline SBP (</>= median¹)												0.0252
< median	1414	337	23.8	1444	354	24.5	0.98	(0.87,1.11)	0.7691	0.99	(0.81,1.21)	
>= median	1453	311	21.4	1440	400	27.8	1.19	(1.06,1.34)	0.0038	1.42	(1.16,1.74)	
History of atrial fibrillation or atrial flutter												0.3821
No	1363	329	24.1	1363	356	26.1	1.04	(0.92,1.17)	0.5082	1.10	(0.89,1.35)	
Yes	1501	318	21.2	1518	397	26.2	1.12	(1.00,1.26)	0.0572	1.27	(1.04,1.55)	

* 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, °:Trend test.
^ Models contain terms age, baseline eGFR (CKD-EPI), baseline LVEF, Baseline KCCQ-TSS, 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.

Analysis is based on study 1245.110.
LOCF: For a missing value at week 52 the last available post-baseline value before week 52 is imputed.
^^ Patients with NYHA class I are counted in subgroup NYHA class II. ¹ Baseline SBP median: 132 [mmHg].
² Baseline NT-proBNP median for patients with history of atrial fibrillation or atrial flutter: 1354 [pg/mL].
² Baseline NT-proBNP median for patients without history of atrial fibrillation or atrial flutter: 614 [pg/mL].
³ Baseline uric acid tertile cut-offs for males are T1: 5.9 T2: 7.5 [mg/dL] [rounded].
³ Baseline uric acid tertile cut-offs for females are T1: 5.4 T2: 6.9 [mg/dL] [rounded].

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Table R.1.1.3.1.1.7: 2 Responder analysis for KCCQ-TSS change from baseline at week 52 >= 15 points (improvement) overall and by subgroup - RS (LOCF-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 LVEF [%]												0.8273
< 50	929	210	22.6	957	261	27.3	1.07	(0.92,1.23)	0.3807	1.14	(0.89,1.46)	
>= 50	1938	438	22.6	1927	493	25.6	1.09	(0.98,1.21)	0.1175	1.21	(1.01,1.44)	
Baseline LVEF [%]												0.9958°/ 0.9184
<50	929	210	22.6	957	261	27.3	1.07	(0.92,1.23)	0.3818	1.14	(0.89,1.46)	
50 to <60	990	227	22.9	988	248	25.1	1.11	(0.96,1.28)	0.1673	1.25	(0.97,1.59)	
>=60	948	211	22.3	939	245	26.1	1.07	(0.92,1.24)	0.3966	1.17	(0.91,1.50)	
Baseline NT-proBNP [pg/mL] (</>=median[2] by atrial fibrillation/flutter status)												0.4404
< median	1463	321	21.9	1430	359	25.1	1.04	(0.93,1.18)	0.4774	1.12	(0.91,1.38)	
>= median	1400	326	23.3	1451	394	27.2	1.12	(0.99,1.26)	0.0647	1.25	(1.02,1.53)	
Baseline uric acid [mg/dL] (tertiles[3])												0.3811°/ 0.5865
<T1	937	209	22.3	930	219	23.5	1.01	(0.87,1.17)	0.9173	1.01	(0.79,1.31)	
>=T1 and <T2	931	190	20.4	996	252	25.3	1.11	(0.95,1.29)	0.1730	1.27	(0.99,1.63)	
>=T2	969	243	25.1	932	276	29.6	1.11	(0.96,1.27)	0.1504	1.26	(0.99,1.60)	
Baseline use of MRA												0.1076
No	1786	401	22.5	1813	447	24.7	1.02	(0.92,1.14)	0.6728	1.07	(0.89,1.28)	
Yes	1081	247	22.8	1071	307	28.7	1.18	(1.03,1.35)	0.0167	1.40	(1.11,1.76)	
Baseline use of ACE-inhibitor, ARB or ARNi												0.2226
No	557	125	22.4	543	151	27.8	1.20	(1.00,1.45)	0.0530	1.48	(1.07,2.05)	
Yes	2310	523	22.6	2341	603	25.8	1.06	(0.96,1.16)	0.2644	1.13	(0.96,1.32)	

* 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, °:Trend test.
^ Models contain terms age, baseline eGFR (CKD-EPI), baseline LVEF, Baseline KCCQ-TSS, 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.

Analysis is based on study 1245.110.
LOCF: For a missing value at week 52 the last available post-baseline value before week 52 is imputed.
^^ Patients with NYHA class I are counted in subgroup NYHA class II. [1] Baseline SBP median: 132 [mmHg].
[2] Baseline NT-proBNP median for patients with history of atrial fibrillation or atrial flutter: 1354 [pg/mL].
[2] Baseline NT-proBNP median for patients without history of atrial fibrillation or atrial flutter: 614 [pg/mL].
[3] Baseline uric acid tertile cut-offs for males are T1: 5.9 T2: 7.5 [mg/dL] [rounded].
[3] Baseline uric acid tertile cut-offs for females are T1: 5.4 T2: 6.9 [mg/dL] [rounded].

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R.1.1.3.1.1.8 KCCQ Overall Summary Score responder analysis (5 points)

Table R.1.1.3.1.1.8: 1 Responder analysis for KCCQ-OSS change from baseline at week 52 <= -5 points (deterioration) overall and by subgroup - RS (LOCF-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	2867	796	27.8	2884	640	22.2	0.81	(0.74,0.88)	<0.0001	0.74	(0.66,0.84)	
Sex												0.1395
Male	1587	426	26.8	1596	365	22.9	0.85	(0.76,0.96)	0.0101	0.81	(0.68,0.95)	
Female	1280	370	28.9	1288	275	21.4	0.75	(0.65,0.85)	<0.0001	0.67	(0.56,0.80)	
Age [years]												0.5198
<70	1036	248	23.9	1030	203	19.7	0.84	(0.71,0.99)	0.0334	0.79	(0.64,0.98)	
>=70	1831	548	29.9	1854	437	23.6	0.79	(0.71,0.88)	<0.0001	0.71	(0.62,0.83)	
Region												0.5050
North America	344	88	25.6	344	87	25.3	0.97	(0.76,1.26)	0.8437	0.96	(0.68,1.37)	
Latin America	724	158	21.8	729	127	17.4	0.81	(0.66,1.00)	0.0482	0.77	(0.59,1.00)	
Europe	1301	407	31.3	1309	313	23.9	0.77	(0.68,0.87)	<0.0001	0.69	(0.58,0.82)	
Asia	330	93	28.2	328	77	23.5	0.84	(0.65,1.08)	0.1769	0.78	(0.55,1.12)	
Other	168	50	29.8	174	36	20.7	0.71	(0.49,1.01)	0.0586	0.62	(0.37,1.03)	
OECD member												0.7128
No	789	191	24.2	818	151	18.5	0.78	(0.65,0.94)	0.0089	0.72	(0.57,0.93)	
Yes	2078	605	29.1	2066	489	23.7	0.81	(0.74,0.90)	<0.0001	0.75	(0.65,0.86)	
Baseline NYHA												0.5641
II^^	2358	647	27.4	2354	524	22.3	0.81	(0.74,0.90)	<0.0001	0.75	(0.66,0.86)	
III/IV	509	149	29.3	530	116	21.9	0.76	(0.62,0.93)	0.0087	0.68	(0.51,0.91)	
Baseline Diabetes status												0.5520
Diabetic	1406	384	27.3	1399	299	21.4	0.78	(0.69,0.89)	0.0002	0.72	(0.60,0.85)	
Non-Diabetic	1461	412	28.2	1485	341	23.0	0.83	(0.73,0.93)	0.0022	0.77	(0.65,0.91)	

* 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, °:Trend test.
^ Models contain terms age, baseline eGFR (CKD-EPI), baseline LVEF, Baseline KCCQ-OSS, 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.

Analysis is based on study 1245.110.
LOCF: For a missing value at week 52 the last available post-baseline value before week 52 is imputed.
^^ Patients with NYHA class I are counted in subgroup NYHA class II. [1] Baseline SBP median: 132 [mmHg].
[2] Baseline NT-proBNP median for patients with history of atrial fibrillation or atrial flutter: 1354 [pg/mL].
[2] Baseline NT-proBNP median for patients without history of atrial fibrillation or atrial flutter: 614 [pg/mL].
[3] Baseline uric acid tertile cut-offs for males are T1: 5.9 T2: 7.5 [mg/dL] [rounded].
[3] Baseline uric acid tertile cut-offs for females are T1: 5.4 T2: 6.9 [mg/dL] [rounded].

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Table R.1.1.3.1.1.8: 1 Responder analysis for KCCQ-OSS change from baseline at week 52 <= -5 points (deterioration) overall and by subgroup - RS (LOCF-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 Diabetes status												0.9951°/ 0.4277
Diabetic	1406	384	27.3	1399	299	21.4	0.78	(0.69,0.89)	0.0002	0.72	(0.60,0.85)	
Pre-Diabetes	939	268	28.5	973	238	24.5	0.87	(0.75,1.01)	0.0600	0.82	(0.67,1.01)	
Normal (no pre-diabetes)	522	144	27.6	512	103	20.1	0.74	(0.60,0.92)	0.0078	0.67	(0.50,0.90)	
Baseline BMI [kg/m²]												0.3695
<30	1563	431	27.6	1590	365	23.0	0.84	(0.74,0.94)	0.0029	0.78	(0.66,0.92)	
>=30	1304	365	28.0	1294	275	21.3	0.77	(0.67,0.88)	0.0001	0.70	(0.58,0.84)	
Baseline eGFR (CKD-EPI) [mL/min/1.73m²]												0.7559
>=60	1448	365	25.2	1445	283	19.6	0.79	(0.69,0.91)	0.0007	0.73	(0.61,0.88)	
<60	1419	431	30.4	1439	357	24.8	0.81	(0.72,0.92)	0.0006	0.75	(0.63,0.88)	
History of HHF (in the last 12 months)												0.5239
No	2232	608	27.2	2226	490	22.0	0.82	(0.74,0.90)	0.0001	0.76	(0.66,0.87)	
Yes	635	188	29.6	658	150	22.8	0.76	(0.64,0.91)	0.0033	0.69	(0.53,0.88)	
Baseline SBP (</>= median¹)												0.0045
< median	1414	365	25.8	1444	344	23.8	0.92	(0.81,1.04)	0.1703	0.89	(0.75,1.06)	
>= median	1453	431	29.7	1440	296	20.6	0.71	(0.62,0.80)	<0.0001	0.62	(0.52,0.74)	
History of atrial fibrillation or atrial flutter												0.4674
No	1363	347	25.5	1363	284	20.8	0.84	(0.73,0.96)	0.0092	0.78	(0.65,0.94)	
Yes	1501	447	29.8	1518	355	23.4	0.78	(0.70,0.88)	<0.0001	0.71	(0.60,0.84)	

* 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, °:Trend test.
^ Models contain terms age, baseline eGFR (CKD-EPI), baseline LVEF, Baseline KCCQ-OSS, 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.

Analysis is based on study 1245.110.
LOCF: For a missing value at week 52 the last available post-baseline value before week 52 is imputed.
^^ Patients with NYHA class I are counted in subgroup NYHA class II. ¹ Baseline SBP median: 132 [mmHg].
² Baseline NT-proBNP median for patients with history of atrial fibrillation or atrial flutter: 1354 [pg/mL].
² Baseline NT-proBNP median for patients without history of atrial fibrillation or atrial flutter: 614 [pg/mL].
³ Baseline uric acid tertile cut-offs for males are T1: 5.9 T2: 7.5 [mg/dL] [rounded].
³ Baseline uric acid tertile cut-offs for females are T1: 5.4 T2: 6.9 [mg/dL] [rounded].

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Table R.1.1.3.1.1.8: 1 Responder analysis for KCCQ-OSS change from baseline at week 52 <= -5 points (deterioration) overall and by subgroup - RS (LOCF-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 LVEF [%]												0.4535
< 50	929	248	26.7	957	190	19.9	0.76	(0.65,0.90)	0.0012	0.70	(0.56,0.87)	
>= 50	1938	548	28.3	1927	450	23.4	0.82	(0.74,0.92)	0.0003	0.76	(0.66,0.88)	
Baseline LVEF [%]												0.3520°/ 0.6455
<50	929	248	26.7	957	190	19.9	0.76	(0.65,0.90)	0.0012	0.70	(0.56,0.87)	
50 to <60	990	287	29.0	988	229	23.2	0.80	(0.69,0.93)	0.0028	0.73	(0.59,0.90)	
>=60	948	261	27.5	939	221	23.5	0.85	(0.73,0.99)	0.0365	0.80	(0.65,0.99)	
Baseline NT-proBNP [pg/mL] (</>=median² by atrial fibrillation/flutter status)												0.0645
< median	1463	401	27.4	1430	286	20.0	0.74	(0.65,0.84)	<0.0001	0.66	(0.55,0.79)	
>= median	1400	393	28.1	1451	353	24.3	0.87	(0.77,0.98)	0.0256	0.82	(0.69,0.98)	
Baseline uric acid [mg/dL] (tertiles³)												0.4523°/ 0.7261
<T1	937	242	25.8	930	203	21.8	0.86	(0.73,1.01)	0.0665	0.82	(0.66,1.02)	
>=T1 and <T2	931	253	27.2	996	216	21.7	0.80	(0.69,0.94)	0.0055	0.74	(0.60,0.92)	
>=T2	969	288	29.7	932	219	23.5	0.79	(0.68,0.92)	0.0018	0.72	(0.58,0.88)	
Baseline use of MRA												0.6268
No	1786	489	27.4	1813	404	22.3	0.82	(0.73,0.92)	0.0005	0.76	(0.65,0.89)	
Yes	1081	307	28.4	1071	236	22.0	0.78	(0.68,0.90)	0.0009	0.71	(0.58,0.87)	
Baseline use of ACE-inhibitor, ARB or ARNi												0.3120
No	557	168	30.2	543	122	22.5	0.74	(0.60,0.90)	0.0022	0.65	(0.49,0.85)	
Yes	2310	628	27.2	2341	518	22.1	0.82	(0.75,0.91)	0.0001	0.77	(0.67,0.88)	

* 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, °:Trend test.
^ Models contain terms age, baseline eGFR (CKD-EPI), baseline LVEF, Baseline KCCQ-OSS, 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.

Analysis is based on study 1245.110.
LOCF: For a missing value at week 52 the last available post-baseline value before week 52 is imputed.
^^ Patients with NYHA class I are counted in subgroup NYHA class II. ¹ Baseline SBP median: 132 [mmHg].
² Baseline NT-proBNP median for patients with history of atrial fibrillation or atrial flutter: 1354 [pg/mL].
² Baseline NT-proBNP median for patients without history of atrial fibrillation or atrial flutter: 614 [pg/mL].
³ Baseline uric acid tertile cut-offs for males are T1: 5.9 T2: 7.5 [mg/dL] [rounded].
³ Baseline uric acid tertile cut-offs for females are T1: 5.4 T2: 6.9 [mg/dL] [rounded].

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Table R.1.1.3.1.1.8: 2 Responder analysis for KCCQ-OSS change from baseline at week 52 >= 5 points (improvement) overall and by subgroup - RS (LOCF-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	2867	1234	43.0	2884	1358	47.1	1.07	(1.02,1.13)	0.0121	1.18	(1.05,1.32)	
Sex												0.4074
Male	1587	643	40.5	1596	713	44.7	1.09	(1.01,1.18)	0.0196	1.20	(1.03,1.40)	
Female	1280	591	46.2	1288	645	50.1	1.05	(0.97,1.13)	0.2446	1.15	(0.97,1.36)	
Age [years]												0.0583
<70	1036	499	48.2	1030	518	50.3	1.01	(0.93,1.09)	0.8975	1.04	(0.86,1.26)	
>=70	1831	735	40.1	1854	840	45.3	1.12	(1.04,1.20)	0.0021	1.27	(1.10,1.47)	
Region												0.1373
North America	344	154	44.8	344	141	41.0	0.94	(0.80,1.11)	0.4935	0.89	(0.64,1.24)	
Latin America	724	381	52.6	729	409	56.1	1.03	(0.95,1.13)	0.4628	1.12	(0.90,1.41)	
Europe	1301	509	39.1	1309	606	46.3	1.16	(1.06,1.26)	0.0009	1.36	(1.15,1.61)	
Asia	330	116	35.2	328	114	34.8	0.97	(0.80,1.18)	0.7532	0.95	(0.67,1.33)	
Other	168	74	44.0	174	88	50.6	1.10	(0.90,1.35)	0.3598	1.28	(0.80,2.03)	
OECD member												0.4592
No	789	398	50.4	818	451	55.1	1.04	(0.95,1.14)	0.3666	1.14	(0.92,1.41)	
Yes	2078	836	40.2	2066	907	43.9	1.09	(1.01,1.16)	0.0178	1.19	(1.04,1.36)	
Baseline NYHA												0.8862
II^^	2358	973	41.3	2354	1060	45.0	1.07	(1.01,1.14)	0.0239	1.17	(1.04,1.33)	
III/IV	509	261	51.3	530	298	56.2	1.06	(0.95,1.19)	0.2680	1.21	(0.93,1.59)	
Baseline Diabetes status												0.0905
Diabetic	1406	611	43.5	1399	691	49.4	1.12	(1.04,1.21)	0.0028	1.30	(1.11,1.54)	
Non-Diabetic	1461	623	42.6	1485	667	44.9	1.02	(0.95,1.10)	0.5717	1.07	(0.92,1.26)	

* 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, °:Trend test.
^ Models contain terms age, baseline eGFR (CKD-EPI), baseline LVEF, Baseline KCCQ-OSS, 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.

Analysis is based on study 1245.110.
LOCF: For a missing value at week 52 the last available post-baseline value before week 52 is imputed.
^^ Patients with NYHA class I are counted in subgroup NYHA class II. [1] Baseline SBP median: 132 [mmHg].
[2] Baseline NT-proBNP median for patients with history of atrial fibrillation or atrial flutter: 1354 [pg/mL].
[2] Baseline NT-proBNP median for patients without history of atrial fibrillation or atrial flutter: 614 [pg/mL].
[3] Baseline uric acid tertile cut-offs for males are T1: 5.9 T2: 7.5 [mg/dL] [rounded].
[3] Baseline uric acid tertile cut-offs for females are T1: 5.4 T2: 6.9 [mg/dL] [rounded].

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Table R.1.1.3.1.1.8: 2 Responder analysis for KCCQ-OSS change from baseline at week 52 >= 5 points (improvement) overall and by subgroup - RS (LOCF-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 Diabetes status												0.1708°/ 0.2286
Diabetic	1406	611	43.5	1399	691	49.4	1.12	(1.04,1.21)	0.0028	1.30	(1.11,1.54)	
Pre-Diabetes	939	401	42.7	973	433	44.5	1.01	(0.92,1.11)	0.7792	1.04	(0.85,1.27)	
Normal (no pre-diabetes)	522	222	42.5	512	234	45.7	1.04	(0.91,1.18)	0.5621	1.13	(0.87,1.48)	
Baseline BMI [kg/m²]												0.0482
<30	1563	657	42.0	1590	691	43.5	1.02	(0.94,1.10)	0.6625	1.05	(0.90,1.22)	
>=30	1304	577	44.2	1294	667	51.5	1.13	(1.05,1.22)	0.0013	1.36	(1.15,1.61)	
Baseline eGFR (CKD-EPI) [mL/min/1.73m²]												0.9578
>=60	1448	641	44.3	1445	709	49.1	1.07	(0.99,1.15)	0.0689	1.19	(1.01,1.39)	
<60	1419	593	41.8	1439	649	45.1	1.07	(0.99,1.16)	0.0788	1.18	(1.00,1.38)	
History of HHF (in the last 12 months)												0.5904
No	2232	950	42.6	2226	1047	47.0	1.08	(1.02,1.15)	0.0137	1.20	(1.06,1.37)	
Yes	635	284	44.7	658	311	47.3	1.04	(0.93,1.17)	0.4668	1.11	(0.87,1.41)	
Baseline SBP (</>= median¹)												0.0112
< median	1414	640	45.3	1444	658	45.6	1.00	(0.93,1.08)	0.9889	1.03	(0.87,1.20)	
>= median	1453	594	40.9	1440	700	48.6	1.15	(1.06,1.24)	0.0004	1.36	(1.15,1.59)	
History of atrial fibrillation or atrial flutter												0.3014
No	1363	618	45.3	1363	661	48.5	1.04	(0.96,1.12)	0.3050	1.11	(0.94,1.31)	
Yes	1501	615	41.0	1518	695	45.8	1.10	(1.02,1.19)	0.0148	1.24	(1.06,1.46)	

* 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, °:Trend test.
^ Models contain terms age, baseline eGFR (CKD-EPI), baseline LVEF, Baseline KCCQ-OSS, 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.

Analysis is based on study 1245.110.
LOCF: For a missing value at week 52 the last available post-baseline value before week 52 is imputed.
^^ Patients with NYHA class I are counted in subgroup NYHA class II. ¹ Baseline SBP median: 132 [mmHg].
² Baseline NT-proBNP median for patients with history of atrial fibrillation or atrial flutter: 1354 [pg/mL].
² Baseline NT-proBNP median for patients without history of atrial fibrillation or atrial flutter: 614 [pg/mL].
³ Baseline uric acid tertile cut-offs for males are T1: 5.9 T2: 7.5 [mg/dL] [rounded].
³ Baseline uric acid tertile cut-offs for females are T1: 5.4 T2: 6.9 [mg/dL] [rounded].

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Table R.1.1.3.1.1.8: 2 Responder analysis for KCCQ-OSS change from baseline at week 52 >= 5 points (improvement) overall and by subgroup - RS (LOCF-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 LVEF [%]												0.8276
< 50	929	396	42.6	957	461	48.2	1.08	(0.98,1.18)	0.1027	1.19	(0.98,1.45)	
>= 50	1938	838	43.2	1927	897	46.5	1.07	(1.00,1.14)	0.0551	1.17	(1.02,1.35)	
Baseline LVEF [%]												0.1153°/ 0.0232
<50	929	396	42.6	957	461	48.2	1.08	(0.98,1.18)	0.1035	1.19	(0.98,1.45)	
50 to <60	990	418	42.2	988	483	48.9	1.17	(1.06,1.28)	0.0010	1.41	(1.16,1.71)	
>=60	948	420	44.3	939	414	44.1	0.97	(0.88,1.07)	0.5238	0.96	(0.79,1.17)	
Baseline NT-proBNP [pg/mL] (</>=median[2] by atrial fibrillation/flutter status)												0.6711
< median	1463	621	42.4	1430	676	47.3	1.08	(1.00,1.17)	0.0404	1.21	(1.03,1.42)	
>= median	1400	612	43.7	1451	680	46.9	1.06	(0.98,1.14)	0.1517	1.15	(0.98,1.35)	
Baseline uric acid [mg/dL] (tertiles[3])												0.8594°/ 0.7470
<T1	937	417	44.5	930	446	48.0	1.05	(0.96,1.15)	0.2696	1.12	(0.92,1.37)	
>=T1 and <T2	931	377	40.5	996	453	45.5	1.09	(0.99,1.20)	0.0638	1.22	(1.00,1.48)	
>=T2	969	432	44.6	932	442	47.4	1.04	(0.95,1.14)	0.3959	1.14	(0.93,1.39)	
Baseline use of MRA												0.0620
No	1786	779	43.6	1813	833	45.9	1.03	(0.96,1.10)	0.4098	1.09	(0.94,1.25)	
Yes	1081	455	42.1	1071	525	49.0	1.14	(1.05,1.25)	0.0027	1.35	(1.12,1.63)	
Baseline use of ACE-inhibitor, ARB or ARNi												0.6954
No	557	239	42.9	543	255	47.0	1.10	(0.97,1.24)	0.1479	1.25	(0.97,1.63)	
Yes	2310	995	43.1	2341	1103	47.1	1.07	(1.00,1.13)	0.0367	1.16	(1.03,1.32)	

* 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, °:Trend test.
^ Models contain terms age, baseline eGFR (CKD-EPI), baseline LVEF, Baseline KCCQ-OSS, 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.

Analysis is based on study 1245.110.
LOCF: For a missing value at week 52 the last available post-baseline value before week 52 is imputed.
^^ Patients with NYHA class I are counted in subgroup NYHA class II. [1] Baseline SBP median: 132 [mmHg].
[2] Baseline NT-proBNP median for patients with history of atrial fibrillation or atrial flutter: 1354 [pg/mL].
[2] Baseline NT-proBNP median for patients without history of atrial fibrillation or atrial flutter: 614 [pg/mL].
[3] Baseline uric acid tertile cut-offs for males are T1: 5.9 T2: 7.5 [mg/dL] [rounded].
[3] Baseline uric acid tertile cut-offs for females are T1: 5.4 T2: 6.9 [mg/dL] [rounded].

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R.1.1.3.1.1.9 KCCQ Overall Summary Score responder analysis (15 points)

Table R.1.1.3.1.1.9: 1 Responder analysis for KCCQ-OSS change from baseline at week 52 <= -15 points (deterioration) overall and by subgroup - RS (LOCF-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	2867	348	12.1	2884	261	9.0	0.75	(0.65,0.87)	0.0002	0.72	(0.61,0.86)	
Sex												0.7070
Male	1587	200	12.6	1596	147	9.2	0.73	(0.60,0.90)	0.0024	0.70	(0.56,0.88)	
Female	1280	148	11.6	1288	114	8.9	0.78	(0.62,0.98)	0.0307	0.75	(0.58,0.98)	
Age [years]												0.9583
<70	1036	103	9.9	1030	76	7.4	0.75	(0.57,1.00)	0.0486	0.73	(0.53,1.00)	
>=70	1831	245	13.4	1854	185	10.0	0.75	(0.63,0.89)	0.0013	0.71	(0.58,0.88)	
Region												0.9904
North America	344	48	14.0	344	36	10.5	0.74	(0.49,1.10)	0.1377	0.70	(0.44,1.11)	
Latin America	724	71	9.8	729	53	7.3	0.76	(0.54,1.07)	0.1136	0.74	(0.51,1.08)	
Europe	1301	161	12.4	1309	125	9.5	0.78	(0.62,0.97)	0.0231	0.75	(0.58,0.96)	
Asia	330	45	13.6	328	31	9.5	0.70	(0.46,1.08)	0.1045	0.66	(0.41,1.09)	
Other	168	23	13.7	174	16	9.2	0.69	(0.38,1.24)	0.2110	0.65	(0.33,1.29)	
OECD member												0.3750
No	789	96	12.2	818	64	7.8	0.67	(0.50,0.90)	0.0084	0.64	(0.45,0.89)	
Yes	2078	252	12.1	2066	197	9.5	0.79	(0.66,0.93)	0.0065	0.76	(0.62,0.93)	
Baseline NYHA												0.5559
II^^	2358	284	12.0	2354	216	9.2	0.77	(0.65,0.91)	0.0017	0.74	(0.61,0.89)	
III/IV	509	64	12.6	530	45	8.5	0.68	(0.48,0.97)	0.0340	0.64	(0.43,0.97)	
Baseline Diabetes status												0.5455
Diabetic	1406	177	12.6	1399	127	9.1	0.72	(0.58,0.89)	0.0022	0.68	(0.54,0.87)	
Non-Diabetic	1461	171	11.7	1485	134	9.0	0.79	(0.64,0.97)	0.0277	0.76	(0.60,0.97)	

* 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, °:Trend test.
^ Models contain terms age, baseline eGFR (CKD-EPI), baseline LVEF, Baseline KCCQ-OSS, 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.

Analysis is based on study 1245.110.
LOCF: For a missing value at week 52 the last available post-baseline value before week 52 is imputed.
^^ Patients with NYHA class I are counted in subgroup NYHA class II. [1] Baseline SBP median: 132 [mmHg].
[2] Baseline NT-proBNP median for patients with history of atrial fibrillation or atrial flutter: 1354 [pg/mL].
[2] Baseline NT-proBNP median for patients without history of atrial fibrillation or atrial flutter: 614 [pg/mL].
[3] Baseline uric acid tertile cut-offs for males are T1: 5.9 T2: 7.5 [mg/dL] [rounded].
[3] Baseline uric acid tertile cut-offs for females are T1: 5.4 T2: 6.9 [mg/dL] [rounded].

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Table R.1.1.3.1.1.9: 1 Responder analysis for KCCQ-OSS change from baseline at week 52 <= -15 points (deterioration) overall and by subgroup - RS (LOCF-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 Diabetes status												0.8444°/ 0.2251
Diabetic	1406	177	12.6	1399	127	9.1	0.72	(0.58,0.89)	0.0022	0.68	(0.54,0.87)	
Pre-Diabetes	939	102	10.9	973	93	9.6	0.90	(0.69,1.17)	0.4246	0.88	(0.66,1.19)	
Normal (no pre-diabetes)	522	69	13.2	512	41	8.0	0.62	(0.43,0.89)	0.0102	0.58	(0.38,0.87)	
Baseline BMI [kg/m²]												0.3792
<30	1563	188	12.0	1590	152	9.6	0.80	(0.65,0.98)	0.0283	0.77	(0.62,0.97)	
>=30	1304	160	12.3	1294	109	8.4	0.70	(0.56,0.88)	0.0020	0.66	(0.51,0.86)	
Baseline eGFR (CKD-EPI) [mL/min/1.73m²]												0.2785
>=60	1448	160	11.0	1445	106	7.3	0.68	(0.54,0.86)	0.0013	0.65	(0.50,0.85)	
<60	1419	188	13.2	1439	155	10.8	0.81	(0.66,0.98)	0.0341	0.78	(0.62,0.98)	
History of HHF (in the last 12 months)												0.2012
No	2232	270	12.1	2226	188	8.4	0.71	(0.60,0.85)	0.0001	0.68	(0.55,0.83)	
Yes	635	78	12.3	658	73	11.1	0.89	(0.66,1.19)	0.4256	0.87	(0.62,1.23)	
Baseline SBP (</>= median¹)												0.3083
< median	1414	175	12.4	1444	146	10.1	0.81	(0.66,0.99)	0.0414	0.78	(0.62,0.99)	
>= median	1453	173	11.9	1440	115	8.0	0.69	(0.55,0.86)	0.0010	0.66	(0.51,0.84)	
History of atrial fibrillation or atrial flutter												0.8531
No	1363	157	11.5	1363	113	8.3	0.74	(0.59,0.93)	0.0094	0.71	(0.55,0.92)	
Yes	1501	191	12.7	1518	148	9.7	0.76	(0.62,0.93)	0.0078	0.73	(0.58,0.92)	

* 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, °:Trend test.
^ Models contain terms age, baseline eGFR (CKD-EPI), baseline LVEF, Baseline KCCQ-OSS, 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.

Analysis is based on study 1245.110.
LOCF: For a missing value at week 52 the last available post-baseline value before week 52 is imputed.
^^ Patients with NYHA class I are counted in subgroup NYHA class II. ¹ Baseline SBP median: 132 [mmHg].
² Baseline NT-proBNP median for patients with history of atrial fibrillation or atrial flutter: 1354 [pg/mL].
² Baseline NT-proBNP median for patients without history of atrial fibrillation or atrial flutter: 614 [pg/mL].
³ Baseline uric acid tertile cut-offs for males are T1: 5.9 T2: 7.5 [mg/dL] [rounded].
³ Baseline uric acid tertile cut-offs for females are T1: 5.4 T2: 6.9 [mg/dL] [rounded].

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Table R.1.1.3.1.1.9: 1 Responder analysis for KCCQ-OSS change from baseline at week 52 <= -15 points (deterioration) overall and by subgroup - RS (LOCF-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 LVEF [%]												0.4344
< 50	929	104	11.2	957	71	7.4	0.68	(0.52,0.91)	0.0091	0.65	(0.47,0.90)	
>= 50	1938	244	12.6	1927	190	9.9	0.78	(0.66,0.93)	0.0065	0.75	(0.61,0.92)	
Baseline LVEF [%]												0.2496°/ 0.4801
<50	929	104	11.2	957	71	7.4	0.69	(0.52,0.91)	0.0091	0.65	(0.47,0.90)	
50 to <60	990	132	13.3	988	95	9.6	0.72	(0.57,0.92)	0.0097	0.69	(0.52,0.91)	
>=60	948	112	11.8	939	95	10.1	0.85	(0.66,1.10)	0.2215	0.83	(0.62,1.12)	
Baseline NT-proBNP [pg/mL] (</>=median[2] by atrial fibrillation/flutter status)												0.3440
< median	1463	173	11.8	1430	116	8.1	0.70	(0.56,0.87)	0.0012	0.66	(0.52,0.85)	
>= median	1400	175	12.5	1451	145	10.0	0.80	(0.66,0.99)	0.0370	0.78	(0.61,0.98)	
Baseline uric acid [mg/dL] (tertiles[3])												0.4306°/ 0.7270
<T1	937	102	10.9	930	68	7.3	0.69	(0.52,0.93)	0.0130	0.66	(0.48,0.92)	
>=T1 and <T2	931	113	12.1	996	92	9.2	0.77	(0.59,0.99)	0.0411	0.74	(0.55,0.99)	
>=T2	969	127	13.1	932	99	10.6	0.81	(0.63,1.03)	0.0859	0.78	(0.59,1.03)	
Baseline use of MRA												0.3229
No	1786	226	12.7	1813	161	8.9	0.71	(0.59,0.86)	0.0004	0.68	(0.54,0.84)	
Yes	1081	122	11.3	1071	100	9.3	0.83	(0.65,1.06)	0.1434	0.81	(0.61,1.08)	
Baseline use of ACE-inhibitor, ARB or ARNi												0.3960
No	557	77	13.8	543	50	9.2	0.66	(0.48,0.92)	0.0145	0.62	(0.42,0.91)	
Yes	2310	271	11.7	2341	211	9.0	0.78	(0.66,0.92)	0.0036	0.75	(0.62,0.91)	

* 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, °:Trend test.
^ Models contain terms age, baseline eGFR (CKD-EPI), baseline LVEF, Baseline KCCQ-OSS, 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.

Analysis is based on study 1245.110.
LOCF: For a missing value at week 52 the last available post-baseline value before week 52 is imputed.
^^ Patients with NYHA class I are counted in subgroup NYHA class II. [1] Baseline SBP median: 132 [mmHg].
[2] Baseline NT-proBNP median for patients with history of atrial fibrillation or atrial flutter: 1354 [pg/mL].
[2] Baseline NT-proBNP median for patients without history of atrial fibrillation or atrial flutter: 614 [pg/mL].
[3] Baseline uric acid tertile cut-offs for males are T1: 5.9 T2: 7.5 [mg/dL] [rounded].
[3] Baseline uric acid tertile cut-offs for females are T1: 5.4 T2: 6.9 [mg/dL] [rounded].

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Table R.1.1.3.1.1.9: 2 Responder analysis for KCCQ-OSS change from baseline at week 52 >= 15 points (improvement) overall and by subgroup - RS (LOCF-AD)

Subgroup	Placebo			Empa 10mg			Empa 10mg vs Placebo					
Category	N	n	%	N	n	%	Risk ratio *	(95% CI)	p-value	Odds ratio ***	(95% CI)	p-value **
Overall	2867	576	20.1	2884	642	22.3	1.05	(0.96,1.15)	0.2962	1.11	(0.96,1.28)	
Sex												0.0558
Male	1587	271	17.1	1596	319	20.0	1.16	(1.01,1.32)	0.0393	1.24	(1.01,1.51)	
Female	1280	305	23.8	1288	323	25.1	0.96	(0.85,1.09)	0.5513	0.98	(0.80,1.21)	
Age [years]												0.6538
<70	1036	233	22.5	1030	259	25.1	1.02	(0.88,1.19)	0.7484	1.08	(0.86,1.37)	
>=70	1831	343	18.7	1854	383	20.7	1.07	(0.95,1.21)	0.2743	1.12	(0.94,1.34)	
Region												0.9021
North America	344	67	19.5	344	63	18.3	0.99	(0.74,1.33)	0.9667	1.00	(0.65,1.52)	
Latin America	724	221	30.5	729	250	34.3	1.05	(0.91,1.22)	0.4973	1.16	(0.90,1.49)	
Europe	1301	209	16.1	1309	235	18.0	1.05	(0.90,1.24)	0.5174	1.09	(0.87,1.36)	
Asia	330	41	12.4	328	42	12.8	0.97	(0.67,1.40)	0.8707	0.95	(0.58,1.55)	
Other	168	38	22.6	174	52	29.9	1.21	(0.88,1.66)	0.2473	1.41	(0.82,2.44)	
OECD member												0.2727
No	789	217	27.5	818	278	34.0	1.11	(0.97,1.28)	0.1360	1.28	(1.00,1.63)	
Yes	2078	359	17.3	2066	364	17.6	1.00	(0.88,1.14)	0.9718	1.02	(0.85,1.21)	
Baseline NYHA												0.7622
II^^	2358	431	18.3	2354	476	20.2	1.06	(0.95,1.18)	0.2907	1.11	(0.94,1.31)	
III/IV	509	145	28.5	530	166	31.3	1.03	(0.85,1.24)	0.7927	1.09	(0.81,1.48)	
Baseline Diabetes status												0.0560
Diabetic	1406	290	20.6	1399	343	24.5	1.15	(1.01,1.31)	0.0383	1.26	(1.03,1.54)	
Non-Diabetic	1461	286	19.6	1485	299	20.1	0.96	(0.84,1.09)	0.5120	0.97	(0.79,1.18)	

* 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, °:Trend test.
^ Models contain terms age, baseline eGFR (CKD-EPI), baseline LVEF, Baseline KCCQ-OSS, 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.

Analysis is based on study 1245.110.
LOCF: For a missing value at week 52 the last available post-baseline value before week 52 is imputed.
^^ Patients with NYHA class I are counted in subgroup NYHA class II. [1] Baseline SBP median: 132 [mmHg].
[2] Baseline NT-proBNP median for patients with history of atrial fibrillation or atrial flutter: 1354 [pg/mL].
[2] Baseline NT-proBNP median for patients without history of atrial fibrillation or atrial flutter: 614 [pg/mL].
[3] Baseline uric acid tertile cut-offs for males are T1: 5.9 T2: 7.5 [mg/dL] [rounded].
[3] Baseline uric acid tertile cut-offs for females are T1: 5.4 T2: 6.9 [mg/dL] [rounded].

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Table R.1.1.3.1.1.9: 2 Responder analysis for KCCQ-OSS change from baseline at week 52 >= 15 points (improvement) overall and by subgroup - RS (LOCF-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 Diabetes status												0.0609°/ 0.1518
Diabetic	1406	290	20.6	1399	343	24.5	1.15	(1.01,1.31)	0.0383	1.26	(1.03,1.54)	
Pre-Diabetes	939	183	19.5	973	196	20.1	0.97	(0.83,1.15)	0.7642	0.97	(0.76,1.25)	
Normal (no pre-diabetes)	522	103	19.7	512	103	20.1	0.92	(0.73,1.16)	0.4899	0.96	(0.68,1.35)	
Baseline BMI [kg/m²]												0.0823
<30	1563	295	18.9	1590	302	19.0	0.97	(0.85,1.10)	0.6115	0.96	(0.78,1.17)	
>=30	1304	281	21.5	1294	340	26.3	1.14	(1.00,1.30)	0.0519	1.29	(1.05,1.59)	
Baseline eGFR (CKD-EPI) [mL/min/1.73m²]												0.4940
>=60	1448	293	20.2	1445	344	23.8	1.08	(0.95,1.23)	0.2127	1.17	(0.96,1.43)	
<60	1419	283	19.9	1439	298	20.7	1.02	(0.89,1.17)	0.8199	1.04	(0.85,1.28)	
History of HHF (in the last 12 months)												0.6624
No	2232	445	19.9	2226	500	22.5	1.06	(0.96,1.18)	0.2581	1.13	(0.96,1.33)	
Yes	635	131	20.6	658	142	21.6	1.01	(0.83,1.23)	0.9136	1.02	(0.76,1.38)	
Baseline SBP (</>= median¹)												0.0047
< median	1414	313	22.1	1444	304	21.1	0.92	(0.81,1.05)	0.2157	0.91	(0.74,1.11)	
>= median	1453	263	18.1	1440	338	23.5	1.21	(1.06,1.38)	0.0061	1.36	(1.11,1.66)	
History of atrial fibrillation or atrial flutter												0.8874
No	1363	295	21.6	1363	326	23.9	1.04	(0.92,1.19)	0.5222	1.09	(0.89,1.34)	
Yes	1501	281	18.7	1518	316	20.8	1.06	(0.92,1.21)	0.4177	1.12	(0.92,1.37)	

* 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, °:Trend test.
^ Models contain terms age, baseline eGFR (CKD-EPI), baseline LVEF, Baseline KCCQ-OSS, 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.

Analysis is based on study 1245.110.
LOCF: For a missing value at week 52 the last available post-baseline value before week 52 is imputed.
^^ Patients with NYHA class I are counted in subgroup NYHA class II. ¹ Baseline SBP median: 132 [mmHg].
² Baseline NT-proBNP median for patients with history of atrial fibrillation or atrial flutter: 1354 [pg/mL].
² Baseline NT-proBNP median for patients without history of atrial fibrillation or atrial flutter: 614 [pg/mL].
³ Baseline uric acid tertile cut-offs for males are T1: 5.9 T2: 7.5 [mg/dL] [rounded].
³ Baseline uric acid tertile cut-offs for females are T1: 5.4 T2: 6.9 [mg/dL] [rounded].

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Table R.1.1.3.1.1.9: 2 Responder analysis for KCCQ-OSS change from baseline at week 52 >= 15 points (improvement) overall and by subgroup - RS (LOCF-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 LVEF [%]												0.6456
< 50	929	188	20.2	957	218	22.8	1.02	(0.87,1.19)	0.8192	1.04	(0.81,1.33)	
>= 50	1938	388	20.0	1927	424	22.0	1.07	(0.95,1.20)	0.2747	1.14	(0.96,1.36)	
Baseline LVEF [%]												0.8124°/ 0.4113
<50	929	188	20.2	957	218	22.8	1.02	(0.87,1.19)	0.8220	1.03	(0.81,1.33)	
50 to <60	990	198	20.0	988	224	22.7	1.15	(0.98,1.35)	0.0973	1.28	(1.00,1.63)	
>=60	948	190	20.0	939	200	21.3	0.99	(0.84,1.17)	0.8944	1.01	(0.79,1.30)	
Baseline NT-proBNP [pg/mL] (</>=median[2] by atrial fibrillation/flutter status)												0.7022
< median	1463	278	19.0	1430	298	20.8	1.03	(0.90,1.18)	0.6819	1.06	(0.86,1.30)	
>= median	1400	298	21.3	1451	344	23.7	1.07	(0.94,1.21)	0.3187	1.15	(0.94,1.40)	
Baseline uric acid [mg/dL] (tertiles[3])												0.8699°/ 0.9813
<T1	937	197	21.0	930	213	22.9	1.05	(0.90,1.22)	0.5590	1.07	(0.84,1.38)	
>=T1 and <T2	931	179	19.2	996	210	21.1	1.03	(0.87,1.21)	0.7545	1.06	(0.82,1.36)	
>=T2	969	196	20.2	932	208	22.3	1.03	(0.87,1.21)	0.7527	1.09	(0.85,1.40)	
Baseline use of MRA												0.2646
No	1786	355	19.9	1813	386	21.3	1.01	(0.89,1.14)	0.9096	1.04	(0.87,1.25)	
Yes	1081	221	20.4	1071	256	23.9	1.12	(0.97,1.31)	0.1287	1.22	(0.97,1.54)	
Baseline use of ACE-inhibitor, ARB or ARNi												0.6284
No	557	109	19.6	543	120	22.1	1.10	(0.89,1.37)	0.3773	1.22	(0.88,1.69)	
Yes	2310	467	20.2	2341	522	22.3	1.04	(0.94,1.15)	0.4665	1.08	(0.92,1.27)	

* 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, °:Trend test.
^ Models contain terms age, baseline eGFR (CKD-EPI), baseline LVEF, Baseline KCCQ-OSS, 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.

Analysis is based on study 1245.110.
LOCF: For a missing value at week 52 the last available post-baseline value before week 52 is imputed.
^^ Patients with NYHA class I are counted in subgroup NYHA class II. [1] Baseline SBP median: 132 [mmHg].
[2] Baseline NT-proBNP median for patients with history of atrial fibrillation or atrial flutter: 1354 [pg/mL].
[2] Baseline NT-proBNP median for patients without history of atrial fibrillation or atrial flutter: 614 [pg/mL].
[3] Baseline uric acid tertile cut-offs for males are T1: 5.9 T2: 7.5 [mg/dL] [rounded].
[3] Baseline uric acid tertile cut-offs for females are T1: 5.4 T2: 6.9 [mg/dL] [rounded].

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R.1.1.3.1.2 LOCF analyses with ceiling correction

R.1.1.3.1.2.1 EQ-VAS responder analysis (15 points)

Table R.1.1.3.1.2.1: 1 Responder analysis for EQ-VAS change from baseline at week 52 >= 15 points (improvement) overall and by subgroup - RS (LOCF with ceiling correction)

Subgroup	Placebo			Empa 10mg			Empa 10mg vs Placebo					
Category	N	n	%	N	n	%	Risk ratio *	(95% CI)	p-value	Odds ratio ***	(95% CI)	p-value **
Overall	2868	870	30.3	2886	937	32.5	1.06	(0.99,1.14)	0.1139	1.10	(0.98,1.23)	
Sex												0.7354
Male	1588	471	29.7	1597	499	31.2	1.05	(0.95,1.16)	0.3607	1.07	(0.92,1.25)	
Female	1280	399	31.2	1289	438	34.0	1.08	(0.97,1.20)	0.1778	1.13	(0.95,1.33)	
Age [years]												0.5250
<70	1035	357	34.5	1029	376	36.5	1.03	(0.92,1.16)	0.5852	1.06	(0.88,1.27)	
>=70	1833	513	28.0	1857	561	30.2	1.08	(0.98,1.20)	0.1098	1.12	(0.97,1.30)	
Region												0.0783
North America	344	102	29.7	341	115	33.7	1.13	(0.91,1.41)	0.2535	1.21	(0.88,1.68)	
Latin America	722	292	40.4	730	285	39.0	0.96	(0.85,1.09)	0.5110	0.93	(0.75,1.16)	
Europe	1301	301	23.1	1309	357	27.3	1.17	(1.03,1.34)	0.0158	1.24	(1.04,1.49)	
Asia	333	122	36.6	330	111	33.6	0.90	(0.73,1.11)	0.3308	0.85	(0.62,1.18)	
Other	168	53	31.5	176	69	39.2	1.21	(0.91,1.60)	0.1880	1.37	(0.87,2.14)	
OECD member												0.6849
No	790	285	36.1	822	311	37.8	1.04	(0.92,1.18)	0.5457	1.07	(0.87,1.31)	
Yes	2078	585	28.2	2064	626	30.3	1.07	(0.98,1.18)	0.1410	1.11	(0.97,1.27)	
Baseline NYHA												0.7085
II^^	2360	723	30.6	2358	766	32.5	1.06	(0.97,1.15)	0.1972	1.09	(0.96,1.23)	
III/IV	508	147	28.9	528	171	32.4	1.10	(0.92,1.31)	0.3106	1.15	(0.88,1.51)	
Baseline Diabetes status												0.7984
Diabetic	1409	441	31.3	1403	464	33.1	1.05	(0.95,1.17)	0.3502	1.08	(0.92,1.27)	
Non-Diabetic	1459	429	29.4	1483	473	31.9	1.07	(0.96,1.19)	0.1998	1.11	(0.95,1.31)	

* 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, °:Trend test.
^ 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.

Analysis is based on study 1245.110. LOCF: For a missing value at week 52 the last available post-baseline value before week 52 is imputed.
Subjects with a baseline score > 85 are considered as improved if the score remains stable > 85 points at week 52 (LOCF).
^^ Patients with NYHA class I are counted in subgroup NYHA class II. [1] Baseline SBP median: 132 [mmHg].
[2] Baseline NT-proBNP median for patients with history of atrial fibrillation or atrial flutter: 1354 [pg/mL].
[2] Baseline NT-proBNP median for patients without history of atrial fibrillation or atrial flutter: 614 [pg/mL].
[3] Baseline uric acid tertile cut-offs for males are T1: 5.9 T2: 7.5 [mg/dL] [rounded].
[3] Baseline uric acid tertile cut-offs for females are T1: 5.4 T2: 6.9 [mg/dL] [rounded].

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Table R.1.1.3.1.2.1: 1 Responder analysis for EQ-VAS change from baseline at week 52 >= 15 points (improvement) overall and by subgroup - RS (LOCF with ceiling correction)

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 Diabetes status												0.4977°/ 0.5877
Diabetic	1409	441	31.3	1403	464	33.1	1.05	(0.95,1.17)	0.3505	1.08	(0.92,1.27)	
Pre-Diabetes	938	272	29.0	972	294	30.2	1.03	(0.90,1.18)	0.6720	1.05	(0.86,1.28)	
Normal (no pre-diabetes)	521	157	30.1	511	179	35.0	1.15	(0.97,1.37)	0.1131	1.25	(0.95,1.63)	
Baseline BMI [kg/m²]												0.0920
<30	1567	500	31.9	1592	509	32.0	1.00	(0.91,1.11)	0.9522	1.00	(0.86,1.17)	
>=30	1301	370	28.4	1294	428	33.1	1.14	(1.02,1.28)	0.0213	1.23	(1.03,1.45)	
Baseline eGFR (CKD-EPI) [mL/min/1.73m²]												0.3933
>=60	1447	476	32.9	1444	497	34.4	1.03	(0.93,1.14)	0.5605	1.05	(0.90,1.23)	
<60	1421	394	27.7	1442	440	30.5	1.10	(0.98,1.23)	0.0945	1.15	(0.98,1.36)	
History of HHF (in the last 12 months)												0.7220
No	2231	673	30.2	2226	724	32.5	1.07	(0.98,1.16)	0.1201	1.11	(0.98,1.26)	
Yes	637	197	30.9	660	213	32.3	1.04	(0.89,1.21)	0.6607	1.05	(0.83,1.34)	
Baseline SBP (</>= median¹)												0.6405
< median	1414	431	30.5	1445	465	32.2	1.04	(0.94,1.16)	0.4303	1.07	(0.91,1.25)	
>= median	1454	439	30.2	1441	472	32.8	1.08	(0.97,1.20)	0.1460	1.13	(0.96,1.33)	
History of atrial fibrillation or atrial flutter												0.1907
No	1365	452	33.1	1363	462	33.9	1.01	(0.91,1.12)	0.8312	1.02	(0.87,1.20)	
Yes	1500	416	27.7	1520	473	31.1	1.12	(1.00,1.25)	0.0442	1.18	(1.00,1.38)	

* 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, °:Trend test.
^ 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.

Analysis is based on study 1245.110. LOCF: For a missing value at week 52 the last available post-baseline value before week 52 is imputed.
Subjects with a baseline score > 85 are considered as improved if the score remains stable > 85 points at week 52 (LOCF).
^^ Patients with NYHA class I are counted in subgroup NYHA class II. ¹ Baseline SBP median: 132 [mmHg].
² Baseline NT-proBNP median for patients with history of atrial fibrillation or atrial flutter: 1354 [pg/mL].
² Baseline NT-proBNP median for patients without history of atrial fibrillation or atrial flutter: 614 [pg/mL].
³ Baseline uric acid tertile cut-offs for males are T1: 5.9 T2: 7.5 [mg/dL] [rounded].
³ Baseline uric acid tertile cut-offs for females are T1: 5.4 T2: 6.9 [mg/dL] [rounded].

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Table R.1.1.3.1.2.1: 1 Responder analysis for EQ-VAS change from baseline at week 52 >= 15 points (improvement) overall and by subgroup - RS (LOCF with ceiling correction)

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 LVEF [%]												0.3504
< 50	928	306	33.0	957	325	34.0	1.01	(0.89,1.14)	0.8589	1.02	(0.84,1.24)	
>= 50	1940	564	29.1	1929	612	31.7	1.09	(0.99,1.20)	0.0747	1.14	(0.99,1.31)	
Baseline LVEF [%]												0.3678°/ 0.6276
<50	928	306	33.0	957	325	34.0	1.01	(0.89,1.14)	0.8568	1.02	(0.84,1.24)	
50 to <60	991	269	27.1	989	292	29.5	1.08	(0.94,1.24)	0.2856	1.12	(0.91,1.36)	
>=60	949	295	31.1	940	320	34.0	1.10	(0.97,1.25)	0.1432	1.16	(0.95,1.41)	
Baseline NT-proBNP [pg/mL] (</>=median² by atrial fibrillation/flutter status)												0.4657
< median	1463	437	29.9	1429	472	33.0	1.09	(0.98,1.21)	0.1028	1.14	(0.97,1.34)	
>= median	1401	431	30.8	1454	463	31.8	1.03	(0.93,1.15)	0.5535	1.05	(0.89,1.24)	
Baseline uric acid [mg/dL] (tertiles³)												0.5866°/ 0.3409
<T1	934	296	31.7	930	314	33.8	1.07	(0.94,1.21)	0.3160	1.11	(0.91,1.35)	
>=T1 and <T2	932	301	32.3	997	319	32.0	0.98	(0.87,1.11)	0.7801	0.97	(0.80,1.18)	
>=T2	972	267	27.5	933	294	31.5	1.13	(0.98,1.29)	0.0864	1.19	(0.98,1.46)	
Baseline use of MRA												0.4511
No	1787	542	30.3	1813	577	31.8	1.04	(0.94,1.14)	0.4351	1.06	(0.92,1.23)	
Yes	1081	328	30.3	1073	360	33.6	1.10	(0.98,1.24)	0.1161	1.16	(0.96,1.39)	
Baseline use of ACE-inhibitor, ARB or ARNi												0.1927
No	557	165	29.6	545	188	34.5	1.17	(0.99,1.39)	0.0604	1.28	(0.99,1.66)	
Yes	2311	705	30.5	2341	749	32.0	1.04	(0.95,1.13)	0.3967	1.06	(0.93,1.20)	

* 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, °:Trend test.
^ 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.

Analysis is based on study 1245.110. LOCF: For a missing value at week 52 the last available post-baseline value before week 52 is imputed.
Subjects with a baseline score > 85 are considered as improved if the score remains stable > 85 points at week 52 (LOCF).
^^ Patients with NYHA class I are counted in subgroup NYHA class II. ¹ Baseline SBP median: 132 [mmHg].
² Baseline NT-proBNP median for patients with history of atrial fibrillation or atrial flutter: 1354 [pg/mL].
² Baseline NT-proBNP median for patients without history of atrial fibrillation or atrial flutter: 614 [pg/mL].
³ Baseline uric acid tertile cut-offs for males are T1: 5.9 T2: 7.5 [mg/dL] [rounded].
³ Baseline uric acid tertile cut-offs for females are T1: 5.4 T2: 6.9 [mg/dL] [rounded].

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R.1.1.3.1.2.2 KCCQ Clinical Summary Score responder analysis (15 points)

Table R.1.1.3.1.2.2: 1 Responder analysis for KCCQ-CSS change from baseline at week 52 >= 15 points (improvement) overall and by subgroup - RS (LOCF with ceiling correction)

Subgroup	Placebo			Empa 10mg			Empa 10mg vs Placebo					
Category	N	n	%	N	n	%	Risk ratio *	(95% CI)	p-value	Odds ratio ***	(95% CI)	p-value **
Overall	2867	1253	43.7	2884	1315	45.6	1.05	(0.99,1.11)	0.1176	1.09	(0.98,1.21)	
Sex												0.5819
Male	1587	744	46.9	1596	789	49.4	1.06	(0.99,1.14)	0.1034	1.12	(0.97,1.29)	
Female	1280	509	39.8	1288	526	40.8	1.03	(0.93,1.12)	0.5963	1.04	(0.89,1.23)	
Age [years]												0.2579
<70	1036	515	49.7	1030	509	49.4	1.01	(0.93,1.10)	0.8764	1.01	(0.85,1.21)	
>=70	1831	738	40.3	1854	806	43.5	1.07	(1.00,1.16)	0.0583	1.14	(1.00,1.30)	
Region												0.1221
North America	344	126	36.6	344	112	32.6	0.87	(0.71,1.07)	0.2007	0.81	(0.59,1.11)	
Latin America	724	376	51.9	729	408	56.0	1.09	(0.99,1.19)	0.0811	1.20	(0.97,1.48)	
Europe	1301	486	37.4	1309	506	38.7	1.04	(0.94,1.14)	0.4780	1.06	(0.90,1.24)	
Asia	330	202	61.2	328	203	61.9	1.01	(0.90,1.14)	0.8267	1.03	(0.75,1.42)	
Other	168	63	37.5	174	86	49.4	1.32	(1.03,1.68)	0.0281	1.65	(1.07,2.56)	
OECD member												0.0397
No	789	376	47.7	818	435	53.2	1.14	(1.03,1.25)	0.0092	1.31	(1.07,1.60)	
Yes	2078	877	42.2	2066	880	42.6	1.00	(0.94,1.08)	0.9107	1.01	(0.89,1.14)	
Baseline NYHA												0.5621
II^^	2358	1068	45.3	2354	1103	46.9	1.04	(0.98,1.10)	0.2235	1.07	(0.95,1.21)	
III/IV	509	185	36.3	530	212	40.0	1.09	(0.93,1.27)	0.2761	1.16	(0.90,1.50)	
Baseline Diabetes status												0.7582
Diabetic	1406	606	43.1	1399	632	45.2	1.06	(0.97,1.14)	0.1962	1.10	(0.94,1.28)	
Non-Diabetic	1461	647	44.3	1485	683	46.0	1.04	(0.96,1.12)	0.3562	1.08	(0.93,1.25)	

* 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, °:Trend test.
^ Models contain terms age, baseline eGFR (CKD-EPI), baseline LVEF, Baseline KCCQ-CSS, 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.

Analysis is based on study 1245.110. LOCF: For a missing value at week 52 the last available post-baseline value before week 52 is imputed.
Subjects with a baseline score > 85 are considered as improved if the score remains stable > 85 points at week 52 (LOCF).
^^ Patients with NYHA class I are counted in subgroup NYHA class II. [1] Baseline SBP median: 132 [mmHg].
[2] Baseline NT-proBNP median for patients with history of atrial fibrillation or atrial flutter: 1354 [pg/mL].
[2] Baseline NT-proBNP median for patients without history of atrial fibrillation or atrial flutter: 614 [pg/mL].
[3] Baseline uric acid tertile cut-offs for males are T1: 5.9 T2: 7.5 [mg/dL] [rounded].
[3] Baseline uric acid tertile cut-offs for females are T1: 5.4 T2: 6.9 [mg/dL] [rounded].

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Table R.1.1.3.1.2.2: 1 Responder analysis for KCCQ-CSS change from baseline at week 52 >= 15 points (improvement) overall and by subgroup - RS (LOCF with ceiling correction)

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 Diabetes status												0.9056°/ 0.8987
Diabetic	1406	606	43.1	1399	632	45.2	1.06	(0.97,1.14)	0.1961	1.10	(0.94,1.28)	
Pre-Diabetes	939	413	44.0	973	439	45.1	1.03	(0.93,1.13)	0.6009	1.05	(0.87,1.27)	
Normal (no pre-diabetes)	522	234	44.8	512	244	47.7	1.06	(0.93,1.20)	0.3961	1.12	(0.87,1.44)	
Baseline BMI [kg/m²]												0.5241
<30	1563	732	46.8	1590	764	48.1	1.03	(0.96,1.10)	0.4230	1.06	(0.92,1.22)	
>=30	1304	521	40.0	1294	551	42.6	1.07	(0.98,1.17)	0.1527	1.12	(0.96,1.32)	
Baseline eGFR (CKD-EPI) [mL/min/1.73m²]												0.4835
>=60	1448	688	47.5	1445	729	50.4	1.06	(0.99,1.14)	0.0869	1.14	(0.98,1.32)	
<60	1419	565	39.8	1439	586	40.7	1.02	(0.94,1.12)	0.6145	1.04	(0.89,1.21)	
History of HHF (in the last 12 months)												0.9903
No	2232	990	44.4	2226	1033	46.4	1.05	(0.98,1.11)	0.1615	1.09	(0.96,1.23)	
Yes	635	263	41.4	658	282	42.9	1.05	(0.92,1.18)	0.4715	1.09	(0.87,1.37)	
Baseline SBP (</>= median¹)												0.0255
< median	1414	636	45.0	1444	637	44.1	0.98	(0.91,1.06)	0.6339	0.96	(0.82,1.12)	
>= median	1453	617	42.5	1440	678	47.1	1.11	(1.03,1.20)	0.0068	1.23	(1.06,1.43)	
History of atrial fibrillation or atrial flutter												0.1858
No	1363	639	46.9	1363	643	47.2	1.01	(0.93,1.09)	0.8753	1.01	(0.86,1.18)	
Yes	1501	614	40.9	1518	671	44.2	1.08	(1.00,1.18)	0.0473	1.16	(1.00,1.35)	

* 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, °:Trend test.
^ Models contain terms age, baseline eGFR (CKD-EPI), baseline LVEF, Baseline KCCQ-CSS, 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.

Analysis is based on study 1245.110. LOCF: For a missing value at week 52 the last available post-baseline value before week 52 is imputed.
Subjects with a baseline score > 85 are considered as improved if the score remains stable > 85 points at week 52 (LOCF).
^^ Patients with NYHA class I are counted in subgroup NYHA class II. ¹ Baseline SBP median: 132 [mmHg].
² Baseline NT-proBNP median for patients with history of atrial fibrillation or atrial flutter: 1354 [pg/mL].
² Baseline NT-proBNP median for patients without history of atrial fibrillation or atrial flutter: 614 [pg/mL].
³ Baseline uric acid tertile cut-offs for males are T1: 5.9 T2: 7.5 [mg/dL] [rounded].
³ Baseline uric acid tertile cut-offs for females are T1: 5.4 T2: 6.9 [mg/dL] [rounded].

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Table R.1.1.3.1.2.2: 1 Responder analysis for KCCQ-CSS change from baseline at week 52 >= 15 points (improvement) overall and by subgroup - RS (LOCF with ceiling correction)

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 LVEF [%]												0.0879
< 50	929	434	46.7	957	494	51.6	1.11	(1.02,1.22)	0.0177	1.25	(1.04,1.51)	
>= 50	1938	819	42.3	1927	821	42.6	1.01	(0.94,1.08)	0.8170	1.01	(0.89,1.15)	
Baseline LVEF [%]												0.1623°/ 0.2293
<50	929	434	46.7	957	494	51.6	1.11	(1.02,1.22)	0.0178	1.25	(1.04,1.51)	
50 to <60	990	421	42.5	988	424	42.9	1.00	(0.91,1.11)	0.9580	1.00	(0.83,1.20)	
>=60	948	398	42.0	939	397	42.3	1.01	(0.92,1.12)	0.7851	1.03	(0.85,1.24)	
Baseline NT-proBNP [pg/mL] (</>=median² by atrial fibrillation/flutter status)												0.7457
< median	1463	664	45.4	1430	680	47.6	1.06	(0.98,1.14)	0.1654	1.11	(0.95,1.29)	
>= median	1400	589	42.1	1451	634	43.7	1.04	(0.95,1.12)	0.4035	1.07	(0.92,1.24)	
Baseline uric acid [mg/dL] (tertiles³)												0.8129°/ 0.9656
<T1	937	429	45.8	930	440	47.3	1.03	(0.94,1.13)	0.5014	1.06	(0.88,1.28)	
>=T1 and <T2	931	423	45.4	996	469	47.1	1.05	(0.95,1.15)	0.3208	1.10	(0.91,1.32)	
>=T2	969	389	40.1	932	393	42.2	1.05	(0.94,1.17)	0.3740	1.09	(0.90,1.31)	
Baseline use of MRA												0.0474
No	1786	792	44.3	1813	801	44.2	1.00	(0.93,1.07)	0.9927	1.00	(0.87,1.14)	
Yes	1081	461	42.6	1071	514	48.0	1.12	(1.03,1.23)	0.0114	1.25	(1.05,1.49)	
Baseline use of ACE-inhibitor, ARB or ARNi												0.2374
No	557	225	40.4	543	250	46.0	1.12	(0.98,1.28)	0.0852	1.24	(0.97,1.59)	
Yes	2310	1028	44.5	2341	1065	45.5	1.03	(0.97,1.09)	0.3683	1.05	(0.94,1.19)	

* 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, °:Trend test.
^ Models contain terms age, baseline eGFR (CKD-EPI), baseline LVEF, Baseline KCCQ-CSS, 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.

Analysis is based on study 1245.110. LOCF: For a missing value at week 52 the last available post-baseline value before week 52 is imputed.
Subjects with a baseline score > 85 are considered as improved if the score remains stable > 85 points at week 52 (LOCF).
^^ Patients with NYHA class I are counted in subgroup NYHA class II. ¹ Baseline SBP median: 132 [mmHg].
² Baseline NT-proBNP median for patients with history of atrial fibrillation or atrial flutter: 1354 [pg/mL].
² Baseline NT-proBNP median for patients without history of atrial fibrillation or atrial flutter: 614 [pg/mL].
³ Baseline uric acid tertile cut-offs for males are T1: 5.9 T2: 7.5 [mg/dL] [rounded].
³ Baseline uric acid tertile cut-offs for females are T1: 5.4 T2: 6.9 [mg/dL] [rounded].

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R.1.1.3.1.2.3 KCCQ Total Symptoms Score responder analysis (15 points)

Table R.1.1.3.1.2.3: 1 Responder analysis for KCCQ-TSS change from baseline at week 52 >= 15 points (improvement) overall and by subgroup - RS (LOCF with ceiling correction)

Subgroup	Placebo			Empa 10mg			Empa 10mg vs Placebo					
Category	N	n	%	N	n	%	Risk ratio *	(95% CI)	p-value	Odds ratio ***	(95% CI)	p-value **
Overall	2867	1479	51.6	2884	1620	56.2	1.09	(1.04,1.15)	0.0002	1.23	(1.10,1.36)	
Sex												0.7649
Male	1587	875	55.1	1596	952	59.6	1.09	(1.03,1.15)	0.0047	1.23	(1.06,1.42)	
Female	1280	604	47.2	1288	668	51.9	1.10	(1.02,1.19)	0.0126	1.23	(1.05,1.44)	
Age [years]												0.0378
<70	1036	609	58.8	1030	618	60.0	1.03	(0.96,1.11)	0.3782	1.08	(0.90,1.29)	
>=70	1831	870	47.5	1854	1002	54.0	1.14	(1.07,1.21)	<0.0001	1.32	(1.16,1.51)	
Region												0.1000
North America	344	155	45.1	344	152	44.2	0.98	(0.83,1.15)	0.7698	0.95	(0.70,1.29)	
Latin America	724	445	61.5	729	464	63.6	1.04	(0.96,1.13)	0.2908	1.12	(0.90,1.39)	
Europe	1301	596	45.8	1309	675	51.6	1.13	(1.05,1.22)	0.0018	1.28	(1.10,1.50)	
Asia	330	207	62.7	328	224	68.3	1.09	(0.98,1.22)	0.1146	1.30	(0.94,1.80)	
Other	168	76	45.2	174	105	60.3	1.34	(1.09,1.64)	0.0047	1.90	(1.23,2.94)	
OECD member												0.7751
No	789	451	57.2	818	509	62.2	1.10	(1.02,1.20)	0.0150	1.29	(1.05,1.58)	
Yes	2078	1028	49.5	2066	1111	53.8	1.09	(1.03,1.15)	0.0040	1.20	(1.06,1.35)	
Baseline NYHA												0.6899
II^^	2358	1261	53.5	2354	1365	58.0	1.09	(1.04,1.14)	0.0007	1.22	(1.09,1.37)	
III/IV	509	218	42.8	530	255	48.1	1.12	(0.98,1.28)	0.0931	1.25	(0.97,1.60)	
Baseline Diabetes status												0.7119
Diabetic	1406	718	51.1	1399	782	55.9	1.10	(1.03,1.18)	0.0042	1.24	(1.07,1.45)	
Non-Diabetic	1461	761	52.1	1485	838	56.4	1.08	(1.02,1.16)	0.0136	1.21	(1.04,1.40)	

* 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, °:Trend test.
^ Models contain terms age, baseline eGFR (CKD-EPI), baseline LVEF, Baseline KCCQ-TSS, 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.

Analysis is based on study 1245.110. LOCF: For a missing value at week 52 the last available post-baseline value before week 52 is imputed.
Subjects with a baseline score > 85 are considered as improved if the score remains stable > 85 points at week 52 (LOCF).
^^ Patients with NYHA class I are counted in subgroup NYHA class II. [1] Baseline SBP median: 132 [mmHg].
[2] Baseline NT-proBNP median for patients with history of atrial fibrillation or atrial flutter: 1354 [pg/mL].
[2] Baseline NT-proBNP median for patients without history of atrial fibrillation or atrial flutter: 614 [pg/mL].
[3] Baseline uric acid tertile cut-offs for males are T1: 5.9 T2: 7.5 [mg/dL] [rounded].
[3] Baseline uric acid tertile cut-offs for females are T1: 5.4 T2: 6.9 [mg/dL] [rounded].

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Table R.1.1.3.1.2.3: 1 Responder analysis for KCCQ-TSS change from baseline at week 52 >= 15 points (improvement) overall and by subgroup - RS (LOCF with ceiling correction)

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 Diabetes status												0.7689°/ 0.9324
Diabetic	1406	718	51.1	1399	782	55.9	1.10	(1.03,1.18)	0.0042	1.24	(1.07,1.45)	
Pre-Diabetes	939	482	51.3	973	540	55.5	1.08	(1.00,1.17)	0.0574	1.20	(1.00,1.44)	
Normal (no pre-diabetes)	522	279	53.4	512	298	58.2	1.09	(0.98,1.21)	0.1124	1.23	(0.96,1.59)	
Baseline BMI [kg/m²]												0.5390
<30	1563	860	55.0	1590	942	59.2	1.08	(1.02,1.14)	0.0108	1.21	(1.04,1.39)	
>=30	1304	619	47.5	1294	678	52.4	1.11	(1.03,1.20)	0.0059	1.25	(1.07,1.46)	
Baseline eGFR (CKD-EPI) [mL/min/1.73m²]												0.7983
>=60	1448	799	55.2	1445	873	60.4	1.10	(1.04,1.17)	0.0020	1.27	(1.09,1.47)	
<60	1419	680	47.9	1439	747	51.9	1.09	(1.01,1.17)	0.0238	1.19	(1.02,1.38)	
History of HHF (in the last 12 months)												0.7932
No	2232	1145	51.3	2226	1250	56.2	1.10	(1.04,1.16)	0.0006	1.23	(1.09,1.39)	
Yes	635	334	52.6	658	370	56.2	1.08	(0.98,1.19)	0.1212	1.20	(0.96,1.51)	
Baseline SBP (</>= median¹)												0.1251
< median	1414	732	51.8	1444	786	54.4	1.05	(0.99,1.13)	0.1251	1.13	(0.97,1.31)	
>= median	1453	747	51.4	1440	834	57.9	1.13	(1.06,1.21)	0.0001	1.34	(1.15,1.56)	
History of atrial fibrillation or atrial flutter												0.0154
No	1363	765	56.1	1363	791	58.0	1.03	(0.97,1.10)	0.3268	1.08	(0.92,1.26)	
Yes	1501	713	47.5	1518	827	54.5	1.16	(1.08,1.24)	<0.0001	1.37	(1.18,1.59)	

* 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, °:Trend test.
^ Models contain terms age, baseline eGFR (CKD-EPI), baseline LVEF, Baseline KCCQ-TSS, 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.

Analysis is based on study 1245.110. LOCF: For a missing value at week 52 the last available post-baseline value before week 52 is imputed.
Subjects with a baseline score > 85 are considered as improved if the score remains stable > 85 points at week 52 (LOCF).
^^ Patients with NYHA class I are counted in subgroup NYHA class II. ¹ Baseline SBP median: 132 [mmHg].
² Baseline NT-proBNP median for patients with history of atrial fibrillation or atrial flutter: 1354 [pg/mL].
² Baseline NT-proBNP median for patients without history of atrial fibrillation or atrial flutter: 614 [pg/mL].
³ Baseline uric acid tertile cut-offs for males are T1: 5.9 T2: 7.5 [mg/dL] [rounded].
³ Baseline uric acid tertile cut-offs for females are T1: 5.4 T2: 6.9 [mg/dL] [rounded].

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Table R.1.1.3.1.2.3: 1 Responder analysis for KCCQ-TSS change from baseline at week 52 >= 15 points (improvement) overall and by subgroup - RS (LOCF with ceiling correction)

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 LVEF [%]												0.7541
< 50	929	524	56.4	957	580	60.6	1.08	(1.01,1.17)	0.0350	1.22	(1.02,1.48)	
>= 50	1938	955	49.3	1927	1040	54.0	1.10	(1.04,1.17)	0.0018	1.23	(1.08,1.40)	
Baseline LVEF [%]												0.4941°/ 0.6812
<50	929	524	56.4	957	580	60.6	1.08	(1.01,1.17)	0.0351	1.22	(1.02,1.48)	
50 to <60	990	502	50.7	988	540	54.7	1.07	(0.99,1.16)	0.0905	1.16	(0.97,1.39)	
>=60	948	453	47.8	939	500	53.2	1.13	(1.03,1.23)	0.0066	1.30	(1.08,1.56)	
Baseline NT-proBNP [pg/mL] (</>=median² by atrial fibrillation/flutter status)												0.6994
< median	1463	775	53.0	1430	829	58.0	1.10	(1.04,1.18)	0.0023	1.26	(1.08,1.47)	
>= median	1400	703	50.2	1451	789	54.4	1.08	(1.01,1.16)	0.0226	1.19	(1.03,1.39)	
Baseline uric acid [mg/dL] (tertiles³)												0.0754°/ 0.2019
<T1	937	528	56.4	930	544	58.5	1.04	(0.96,1.12)	0.3393	1.09	(0.91,1.32)	
>=T1 and <T2	931	480	51.6	996	555	55.7	1.10	(1.01,1.19)	0.0278	1.23	(1.02,1.48)	
>=T2	969	457	47.2	932	505	54.2	1.15	(1.06,1.26)	0.0015	1.35	(1.12,1.62)	
Baseline use of MRA												0.2104
No	1786	932	52.2	1813	1005	55.4	1.07	(1.01,1.13)	0.0273	1.16	(1.02,1.33)	
Yes	1081	547	50.6	1071	615	57.4	1.14	(1.05,1.23)	0.0010	1.34	(1.13,1.60)	
Baseline use of ACE-inhibitor, ARB or ARNi												0.0984
No	557	259	46.5	543	303	55.8	1.19	(1.06,1.34)	0.0025	1.46	(1.14,1.86)	
Yes	2310	1220	52.8	2341	1317	56.3	1.07	(1.02,1.13)	0.0069	1.18	(1.04,1.32)	

* 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, °:Trend test.
^ Models contain terms age, baseline eGFR (CKD-EPI), baseline LVEF, Baseline KCCQ-TSS, 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.

Analysis is based on study 1245.110. LOCF: For a missing value at week 52 the last available post-baseline value before week 52 is imputed.
Subjects with a baseline score > 85 are considered as improved if the score remains stable > 85 points at week 52 (LOCF).
^^ Patients with NYHA class I are counted in subgroup NYHA class II. ¹ Baseline SBP median: 132 [mmHg].
² Baseline NT-proBNP median for patients with history of atrial fibrillation or atrial flutter: 1354 [pg/mL].
² Baseline NT-proBNP median for patients without history of atrial fibrillation or atrial flutter: 614 [pg/mL].
³ Baseline uric acid tertile cut-offs for males are T1: 5.9 T2: 7.5 [mg/dL] [rounded].
³ Baseline uric acid tertile cut-offs for females are T1: 5.4 T2: 6.9 [mg/dL] [rounded].

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R.1.1.3.1.2.4 KCCQ Overall Summary Score responder analysis (15 points)

Table R.1.1.3.1.2.4: 1 Responder analysis for KCCQ-OSS change from baseline at week 52 >= 15 points (improvement) overall and by subgroup - RS (LOCF with ceiling correction)

Subgroup	Placebo			Empa 10mg			Empa 10mg vs Placebo					
Category	N	n	%	N	n	%	Risk ratio *	(95% CI)	p-value	Odds ratio ***	(95% CI)	p-value **
Overall	2867	1136	39.6	2884	1255	43.5	1.10	(1.04,1.17)	0.0016	1.19	(1.07,1.32)	
Sex												0.7893
Male	1587	668	42.1	1596	740	46.4	1.11	(1.03,1.20)	0.0075	1.21	(1.05,1.40)	
Female	1280	468	36.6	1288	515	40.0	1.09	(0.99,1.20)	0.0806	1.16	(0.98,1.36)	
Age [years]												0.3454
<70	1036	461	44.5	1030	483	46.9	1.06	(0.97,1.17)	0.1889	1.12	(0.94,1.34)	
>=70	1831	675	36.9	1854	772	41.6	1.13	(1.04,1.22)	0.0026	1.23	(1.08,1.41)	
Region												0.1463
North America	344	125	36.3	344	123	35.8	0.97	(0.80,1.18)	0.7647	0.95	(0.69,1.30)	
Latin America	724	359	49.6	729	402	55.1	1.12	(1.02,1.24)	0.0237	1.27	(1.03,1.57)	
Europe	1301	433	33.3	1309	479	36.6	1.10	(0.99,1.22)	0.0649	1.16	(0.99,1.37)	
Asia	330	162	49.1	328	165	50.3	1.03	(0.89,1.20)	0.6695	1.07	(0.78,1.45)	
Other	168	57	33.9	174	86	49.4	1.46	(1.12,1.89)	0.0047	1.93	(1.24,3.00)	
OECD member												0.0386
No	789	337	42.7	818	414	50.6	1.21	(1.09,1.34)	0.0005	1.44	(1.18,1.76)	
Yes	2078	799	38.5	2066	841	40.7	1.05	(0.98,1.13)	0.1587	1.09	(0.96,1.24)	
Baseline NYHA												0.7465
II^^	2358	965	40.9	2354	1062	45.1	1.11	(1.04,1.18)	0.0020	1.20	(1.07,1.35)	
III/IV	509	171	33.6	530	193	36.4	1.07	(0.91,1.27)	0.3926	1.12	(0.87,1.46)	
Baseline Diabetes status												0.8241
Diabetic	1406	545	38.8	1399	598	42.7	1.11	(1.02,1.21)	0.0199	1.20	(1.03,1.40)	
Non-Diabetic	1461	591	40.5	1485	657	44.2	1.09	(1.01,1.19)	0.0317	1.18	(1.02,1.37)	

* 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, °:Trend test.
^ Models contain terms age, baseline eGFR (CKD-EPI), baseline LVEF, Baseline KCCQ-OSS, 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.

Analysis is based on study 1245.110. LOCF: For a missing value at week 52 the last available post-baseline value before week 52 is imputed.
Subjects with a baseline score > 85 are considered as improved if the score remains stable > 85 points at week 52 (LOCF).
^^ Patients with NYHA class I are counted in subgroup NYHA class II. [1] Baseline SBP median: 132 [mmHg].
[2] Baseline NT-proBNP median for patients with history of atrial fibrillation or atrial flutter: 1354 [pg/mL].
[2] Baseline NT-proBNP median for patients without history of atrial fibrillation or atrial flutter: 614 [pg/mL].
[3] Baseline uric acid tertile cut-offs for males are T1: 5.9 T2: 7.5 [mg/dL] [rounded].
[3] Baseline uric acid tertile cut-offs for females are T1: 5.4 T2: 6.9 [mg/dL] [rounded].

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Table R.1.1.3.1.2.4: 1 Responder analysis for KCCQ-OSS change from baseline at week 52 >= 15 points (improvement) overall and by subgroup - RS (LOCF with ceiling correction)

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 Diabetes status												0.7273°/ 0.4717
Diabetic	1406	545	38.8	1399	598	42.7	1.11	(1.02,1.21)	0.0199	1.20	(1.03,1.40)	
Pre-Diabetes	939	385	41.0	973	419	43.1	1.05	(0.95,1.17)	0.3183	1.10	(0.91,1.32)	
Normal (no pre-diabetes)	522	206	39.5	512	238	46.5	1.17	(1.02,1.34)	0.0238	1.34	(1.04,1.73)	
Baseline BMI [kg/m²]												0.4906
<30	1563	649	41.5	1590	713	44.8	1.08	(1.00,1.17)	0.0494	1.15	(1.00,1.33)	
>=30	1304	487	37.3	1294	542	41.9	1.13	(1.03,1.24)	0.0113	1.23	(1.05,1.45)	
Baseline eGFR (CKD-EPI) [mL/min/1.73m²]												0.3159
>=60	1448	629	43.4	1445	708	49.0	1.13	(1.05,1.22)	0.0015	1.27	(1.10,1.48)	
<60	1419	507	35.7	1439	547	38.0	1.06	(0.97,1.17)	0.1955	1.11	(0.95,1.29)	
History of HHF (in the last 12 months)												0.4284
No	2232	896	40.1	2226	995	44.7	1.12	(1.04,1.19)	0.0013	1.22	(1.08,1.38)	
Yes	635	240	37.8	658	260	39.5	1.05	(0.92,1.20)	0.4780	1.09	(0.87,1.37)	
Baseline SBP (</>= median¹)												0.0153
< median	1414	579	40.9	1444	607	42.0	1.02	(0.94,1.11)	0.6094	1.04	(0.89,1.21)	
>= median	1453	557	38.3	1440	648	45.0	1.19	(1.09,1.29)	<0.0001	1.36	(1.17,1.58)	
History of atrial fibrillation or atrial flutter												0.2371
No	1363	580	42.6	1363	617	45.3	1.06	(0.98,1.15)	0.1523	1.12	(0.96,1.30)	
Yes	1501	556	37.0	1518	638	42.0	1.14	(1.05,1.25)	0.0026	1.26	(1.08,1.46)	

* 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, °:Trend test.
^ Models contain terms age, baseline eGFR (CKD-EPI), baseline LVEF, Baseline KCCQ-OSS, 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.

Analysis is based on study 1245.110. LOCF: For a missing value at week 52 the last available post-baseline value before week 52 is imputed.
Subjects with a baseline score > 85 are considered as improved if the score remains stable > 85 points at week 52 (LOCF).
^^ Patients with NYHA class I are counted in subgroup NYHA class II. ¹ Baseline SBP median: 132 [mmHg].
² Baseline NT-proBNP median for patients with history of atrial fibrillation or atrial flutter: 1354 [pg/mL].
² Baseline NT-proBNP median for patients without history of atrial fibrillation or atrial flutter: 614 [pg/mL].
³ Baseline uric acid tertile cut-offs for males are T1: 5.9 T2: 7.5 [mg/dL] [rounded].
³ Baseline uric acid tertile cut-offs for females are T1: 5.4 T2: 6.9 [mg/dL] [rounded].

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Table R.1.1.3.1.2.4: 1 Responder analysis for KCCQ-OSS change from baseline at week 52 >= 15 points (improvement) overall and by subgroup - RS (LOCF with ceiling correction)

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 LVEF [%]												0.9548
< 50	929	394	42.4	957	445	46.5	1.10	(1.00,1.22)	0.0504	1.21	(1.00,1.45)	
>= 50	1938	742	38.3	1927	810	42.0	1.10	(1.02,1.19)	0.0131	1.18	(1.03,1.34)	
Baseline LVEF [%]												0.9049°/ 0.9418
<50	929	394	42.4	957	445	46.5	1.10	(1.00,1.22)	0.0504	1.21	(1.00,1.45)	
50 to <60	990	378	38.2	988	413	41.8	1.09	(0.98,1.21)	0.1262	1.15	(0.96,1.38)	
>=60	948	364	38.4	939	397	42.3	1.11	(1.00,1.24)	0.0475	1.21	(1.00,1.46)	
Baseline NT-proBNP [pg/mL] (</>=median² by atrial fibrillation/flutter status)												0.4821
< median	1463	594	40.6	1430	650	45.5	1.13	(1.04,1.22)	0.0049	1.24	(1.07,1.44)	
>= median	1400	542	38.7	1451	605	41.7	1.08	(0.99,1.18)	0.0947	1.14	(0.98,1.33)	
Baseline uric acid [mg/dL] (tertiles³)												0.8005°/ 0.6962
<T1	937	398	42.5	930	435	46.8	1.10	(1.00,1.21)	0.0557	1.20	(0.99,1.45)	
>=T1 and <T2	931	388	41.7	996	433	43.5	1.06	(0.95,1.17)	0.2958	1.10	(0.92,1.33)	
>=T2	969	341	35.2	932	370	39.7	1.13	(1.00,1.26)	0.0444	1.22	(1.00,1.47)	
Baseline use of MRA												0.4825
No	1786	720	40.3	1813	788	43.5	1.08	(1.00,1.17)	0.0368	1.15	(1.01,1.32)	
Yes	1081	416	38.5	1071	467	43.6	1.13	(1.03,1.25)	0.0144	1.25	(1.05,1.49)	
Baseline use of ACE-inhibitor, ARB or ARNi												0.4875
No	557	202	36.3	543	230	42.4	1.15	(1.00,1.33)	0.0527	1.28	(1.00,1.64)	
Yes	2310	934	40.4	2341	1025	43.8	1.09	(1.02,1.16)	0.0102	1.17	(1.04,1.32)	

* 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, °:Trend test.
^ Models contain terms age, baseline eGFR (CKD-EPI), baseline LVEF, Baseline KCCQ-OSS, 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.

Analysis is based on study 1245.110. LOCF: For a missing value at week 52 the last available post-baseline value before week 52 is imputed.
Subjects with a baseline score > 85 are considered as improved if the score remains stable > 85 points at week 52 (LOCF).
^^ Patients with NYHA class I are counted in subgroup NYHA class II. ¹ Baseline SBP median: 132 [mmHg].
² Baseline NT-proBNP median for patients with history of atrial fibrillation or atrial flutter: 1354 [pg/mL].
² Baseline NT-proBNP median for patients without history of atrial fibrillation or atrial flutter: 614 [pg/mL].
³ Baseline uric acid tertile cut-offs for males are T1: 5.9 T2: 7.5 [mg/dL] [rounded].
³ Baseline uric acid tertile cut-offs for females are T1: 5.4 T2: 6.9 [mg/dL] [rounded].

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R.1.1.3.2 Responder analyses based on last value during the planned treatment period

R.1.1.3.2.1 Observed cases analyses

R.1.1.3.2.1.1 EQ-VAS responder analysis (7 points)

Table R.1.1.3.2.1.1: 1 Responder analysis for EQ-VAS change from baseline to last value during planned treatment period <= -7 points (deterioration) overall and by subgroup - RS (OC-AD)

Subgroup	Placebo			Empa 10mg			Empa 10mg vs Placebo					
Category	N	n	%	N	n	%	Risk ratio *	(95% CI)	p-value	Odds ratio ***	(95% CI)	p-value **
Overall	2870	845	29.4	2889	779	27.0	0.90	(0.83,0.98)	0.0126	0.89	(0.79,1.01)	
Sex												0.8550
Male	1589	470	29.6	1600	444	27.8	0.91	(0.81,1.01)	0.0809	0.93	(0.79,1.10)	
Female	1281	375	29.3	1289	335	26.0	0.89	(0.79,1.01)	0.0731	0.84	(0.70,1.01)	
Age [years]												0.5187
<70	1036	246	23.7	1030	229	22.2	0.94	(0.80,1.10)	0.4162	0.98	(0.79,1.22)	
>=70	1834	599	32.7	1859	550	29.6	0.88	(0.80,0.97)	0.0099	0.84	(0.73,0.97)	
Region												0.5670
North America	345	98	28.4	342	102	29.8	1.05	(0.83,1.32)	0.6907	1.04	(0.74,1.47)	
Latin America	723	165	22.8	731	159	21.8	0.94	(0.78,1.14)	0.5437	0.95	(0.73,1.23)	
Europe	1301	440	33.8	1310	392	29.9	0.86	(0.77,0.96)	0.0071	0.84	(0.70,1.00)	
Asia	333	102	30.6	330	86	26.1	0.86	(0.68,1.09)	0.2110	0.84	(0.59,1.20)	
Other	168	40	23.8	176	40	22.7	0.97	(0.67,1.42)	0.8906	0.96	(0.57,1.62)	
OECD member												0.5966
No	790	196	24.8	822	178	21.7	0.87	(0.73,1.03)	0.1101	0.86	(0.67,1.10)	
Yes	2080	649	31.2	2067	601	29.1	0.91	(0.83,1.00)	0.0578	0.90	(0.79,1.04)	
Baseline NYHA												0.8227
II^^	2361	697	29.5	2360	640	27.1	0.90	(0.82,0.98)	0.0182	0.89	(0.78,1.02)	
III/IV	509	148	29.1	529	139	26.3	0.92	(0.76,1.12)	0.3946	0.87	(0.65,1.16)	
Baseline Diabetes status												0.0896
Diabetic	1409	417	29.6	1403	360	25.7	0.84	(0.74,0.94)	0.0035	0.83	(0.70,0.99)	
Non-Diabetic	1461	428	29.3	1486	419	28.2	0.96	(0.86,1.08)	0.5198	0.95	(0.81,1.13)	

* 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, °:Trend test.
^ 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.

Analysis is based on study 1245.110.
For discontinued subjects, last available value was used. For completing subjects, last value up to last treatment intake + 7 days was used.
^^ Patients with NYHA class I are counted in subgroup NYHA class II. [1] Baseline SBP median: 132 [mmHg].
[2] Baseline NT-proBNP median for patients with history of atrial fibrillation or atrial flutter: 1354 [pg/mL].
[2] Baseline NT-proBNP median for patients without history of atrial fibrillation or atrial flutter: 614 [pg/mL].
[3] Baseline uric acid tertile cut-offs for males are T1: 5.9 T2: 7.5 [mg/dL] [rounded].
[3] Baseline uric acid tertile cut-offs for females are T1: 5.4 T2: 6.9 [mg/dL] [rounded].

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Table R.1.1.3.2.1.1: 1 Responder analysis for EQ-VAS change from baseline to last value during planned treatment period <= -7 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 Diabetes status												0.0717°/ 0.1916
Diabetic	1409	417	29.6	1403	360	25.7	0.84	(0.74,0.94)	0.0035	0.83	(0.70,0.99)	
Pre-Diabetes	940	276	29.4	975	270	27.7	0.94	(0.82,1.08)	0.3912	0.92	(0.75,1.13)	
Normal (no pre-diabetes)	521	152	29.2	511	149	29.2	1.01	(0.84,1.21)	0.9176	1.02	(0.77,1.35)	
Baseline BMI [kg/m²]												0.1210
<30	1568	455	29.0	1594	454	28.5	0.96	(0.86,1.07)	0.4096	0.98	(0.83,1.15)	
>=30	1302	390	30.0	1295	325	25.1	0.84	(0.74,0.95)	0.0051	0.79	(0.66,0.95)	
Baseline eGFR (CKD-EPI) [mL/min/1.73m²]												0.7319
>=60	1448	396	27.3	1445	363	25.1	0.89	(0.78,1.00)	0.0547	0.93	(0.78,1.10)	
<60	1422	449	31.6	1444	416	28.8	0.91	(0.82,1.02)	0.1012	0.86	(0.72,1.01)	
History of HHF (in the last 12 months)												0.0092
No	2233	634	28.4	2229	605	27.1	0.96	(0.87,1.05)	0.3598	0.95	(0.82,1.09)	
Yes	637	211	33.1	660	174	26.4	0.74	(0.62,0.88)	0.0006	0.73	(0.57,0.94)	
Baseline SBP (</>= median¹)												0.9045
< median	1414	407	28.8	1445	371	25.7	0.90	(0.80,1.01)	0.0701	0.86	(0.73,1.03)	
>= median	1456	438	30.1	1444	408	28.3	0.91	(0.81,1.01)	0.0866	0.92	(0.78,1.09)	
History of atrial fibrillation or atrial flutter												0.7904
No	1366	382	28.0	1364	346	25.4	0.91	(0.81,1.03)	0.1415	0.88	(0.74,1.06)	
Yes	1501	462	30.8	1522	432	28.4	0.89	(0.80,1.00)	0.0435	0.90	(0.76,1.06)	

* 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, °:Trend test.
^ 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.

Analysis is based on study 1245.110.
For discontinued subjects, last available value was used. For completing subjects, last value up to last treatment intake + 7 days was used.
^^ Patients with NYHA class I are counted in subgroup NYHA class II. ¹ Baseline SBP median: 132 [mmHg].
² Baseline NT-proBNP median for patients with history of atrial fibrillation or atrial flutter: 1354 [pg/mL].
² Baseline NT-proBNP median for patients without history of atrial fibrillation or atrial flutter: 614 [pg/mL].
³ Baseline uric acid tertile cut-offs for males are T1: 5.9 T2: 7.5 [mg/dL] [rounded].
³ Baseline uric acid tertile cut-offs for females are T1: 5.4 T2: 6.9 [mg/dL] [rounded].

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Table R.1.1.3.2.1.1: 1 Responder analysis for EQ-VAS change from baseline to last value during planned treatment period <= -7 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 LVEF [%]												0.4597
< 50	928	259	27.9	959	250	26.1	0.94	(0.82,1.09)	0.4322	0.95	(0.77,1.18)	
>= 50	1942	586	30.2	1930	529	27.4	0.88	(0.80,0.97)	0.0130	0.86	(0.74,1.00)	
Baseline LVEF [%]												0.5815°/ 0.7497
<50	928	259	27.9	959	250	26.1	0.94	(0.82,1.09)	0.4321	0.95	(0.77,1.18)	
50 to <60	993	294	29.6	990	271	27.4	0.87	(0.76,1.01)	0.0624	0.89	(0.72,1.09)	
>=60	949	292	30.8	940	258	27.4	0.89	(0.78,1.02)	0.0999	0.84	(0.68,1.03)	
Baseline NT-proBNP [pg/mL] (</>=median² by atrial fibrillation/flutter status)												0.7485
< median	1464	407	27.8	1431	375	26.2	0.91	(0.81,1.03)	0.1352	0.95	(0.80,1.13)	
>= median	1402	437	31.2	1455	403	27.7	0.89	(0.79,0.99)	0.0370	0.83	(0.70,0.99)	
Baseline uric acid [mg/dL] (tertiles³)												0.0670°/ 0.1638
<T1	935	255	27.3	931	247	26.5	0.98	(0.85,1.14)	0.8200	0.98	(0.79,1.21)	
>=T1 and <T2	932	251	26.9	999	271	27.1	0.94	(0.81,1.09)	0.4401	1.02	(0.83,1.26)	
>=T2	973	329	33.8	933	256	27.4	0.82	(0.72,0.94)	0.0038	0.74	(0.60,0.91)	
Baseline use of MRA												0.6107
No	1789	526	29.4	1815	487	26.8	0.92	(0.83,1.02)	0.0950	0.89	(0.76,1.03)	
Yes	1081	319	29.5	1074	292	27.2	0.88	(0.77,1.00)	0.0571	0.90	(0.74,1.09)	
Baseline use of ACE-inhibitor, ARB or ARNi												0.6969
No	557	181	32.5	545	164	30.1	0.93	(0.78,1.10)	0.4011	0.86	(0.66,1.13)	
Yes	2313	664	28.7	2344	615	26.2	0.89	(0.82,0.98)	0.0183	0.90	(0.78,1.03)	

* 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, °:Trend test.
^ 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.

Analysis is based on study 1245.110.
For discontinued subjects, last available value was used. For completing subjects, last value up to last treatment intake + 7 days was used.
^^ Patients with NYHA class I are counted in subgroup NYHA class II. ¹ Baseline SBP median: 132 [mmHg].
² Baseline NT-proBNP median for patients with history of atrial fibrillation or atrial flutter: 1354 [pg/mL].
² Baseline NT-proBNP median for patients without history of atrial fibrillation or atrial flutter: 614 [pg/mL].
³ Baseline uric acid tertile cut-offs for males are T1: 5.9 T2: 7.5 [mg/dL] [rounded].
³ Baseline uric acid tertile cut-offs for females are T1: 5.4 T2: 6.9 [mg/dL] [rounded].

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Table R.1.1.3.2.1.1: 2 Responder analysis for EQ-VAS change from baseline to last value during planned treatment period >= 7 points (improvement) overall and by subgroup - RS (OC-AD)

Subgroup	Placebo			Empa 10mg			Empa 10mg vs Placebo					
Category	N	n	%	N	n	%	Risk ratio *	(95% CI)	p-value	Odds ratio ***	(95% CI)	p-value **
Overall	2870	991	34.5	2889	1053	36.4	1.03	(0.96,1.10)	0.4085	1.07	(0.95,1.21)	
Sex												0.3489
Male	1589	530	33.4	1600	548	34.3	1.00	(0.91,1.09)	0.9672	1.01	(0.85,1.19)	
Female	1281	461	36.0	1289	505	39.2	1.06	(0.97,1.16)	0.2017	1.16	(0.97,1.39)	
Age [years]												0.1830
<70	1036	387	37.4	1030	448	43.5	1.08	(0.98,1.20)	0.1074	1.22	(1.00,1.49)	
>=70	1834	604	32.9	1859	605	32.5	0.99	(0.91,1.08)	0.8550	1.00	(0.86,1.17)	
Region												0.7211
North America	345	109	31.6	342	112	32.7	1.04	(0.86,1.27)	0.6661	1.12	(0.78,1.60)	
Latin America	723	309	42.7	731	349	47.7	1.09	(0.98,1.22)	0.1086	1.27	(1.00,1.60)	
Europe	1301	406	31.2	1310	413	31.5	1.00	(0.90,1.11)	0.9661	1.00	(0.83,1.20)	
Asia	333	104	31.2	330	109	33.0	0.97	(0.80,1.19)	0.7951	0.97	(0.68,1.39)	
Other	168	63	37.5	176	70	39.8	0.97	(0.76,1.23)	0.7754	0.99	(0.61,1.62)	
OECD member												0.2961
No	790	316	40.0	822	373	45.4	1.08	(0.97,1.20)	0.1678	1.21	(0.97,1.51)	
Yes	2080	675	32.5	2067	680	32.9	1.00	(0.92,1.09)	0.9445	1.01	(0.88,1.17)	
Baseline NYHA												0.6281
II^^	2361	798	33.8	2360	832	35.3	1.02	(0.95,1.10)	0.5956	1.05	(0.91,1.20)	
III/IV	509	193	37.9	529	221	41.8	1.06	(0.92,1.22)	0.4069	1.21	(0.91,1.61)	
Baseline Diabetes status												0.0064
Diabetic	1409	485	34.4	1403	557	39.7	1.12	(1.03,1.23)	0.0108	1.28	(1.08,1.53)	
Non-Diabetic	1461	506	34.6	1486	496	33.4	0.94	(0.85,1.03)	0.1805	0.90	(0.76,1.07)	

* 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, °:Trend test.
^ 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.

Analysis is based on study 1245.110.
For discontinued subjects, last available value was used. For completing subjects, last value up to last treatment intake + 7 days was used.
^^ Patients with NYHA class I are counted in subgroup NYHA class II. [1] Baseline SBP median: 132 [mmHg].
[2] Baseline NT-proBNP median for patients with history of atrial fibrillation or atrial flutter: 1354 [pg/mL].
[2] Baseline NT-proBNP median for patients without history of atrial fibrillation or atrial flutter: 614 [pg/mL].
[3] Baseline uric acid tertile cut-offs for males are T1: 5.9 T2: 7.5 [mg/dL] [rounded].
[3] Baseline uric acid tertile cut-offs for females are T1: 5.4 T2: 6.9 [mg/dL] [rounded].

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Table R.1.1.3.2.1.1: 2 Responder analysis for EQ-VAS change from baseline to last value during planned treatment period >= 7 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 Diabetes status												0.0366°/ 0.0176
Diabetic	1409	485	34.4	1403	557	39.7	1.12	(1.03,1.23)	0.0108	1.28	(1.08,1.53)	
Pre-Diabetes	940	333	35.4	975	328	33.6	0.92	(0.82,1.03)	0.1293	0.87	(0.71,1.08)	
Normal (no pre-diabetes)	521	173	33.2	511	168	32.9	0.98	(0.83,1.16)	0.8011	0.97	(0.73,1.30)	
Baseline BMI [kg/m²]												0.1133
<30	1568	547	34.9	1594	540	33.9	0.98	(0.90,1.07)	0.6415	0.95	(0.81,1.12)	
>=30	1302	444	34.1	1295	513	39.6	1.09	(0.99,1.19)	0.0812	1.24	(1.04,1.49)	
Baseline eGFR (CKD-EPI) [mL/min/1.73m²]												0.9519
>=60	1448	508	35.1	1445	542	37.5	1.03	(0.94,1.12)	0.5825	1.06	(0.89,1.25)	
<60	1422	483	34.0	1444	511	35.4	1.03	(0.94,1.13)	0.5437	1.09	(0.92,1.30)	
History of HHF (in the last 12 months)												0.7444
No	2233	784	35.1	2229	817	36.7	1.02	(0.95,1.10)	0.5561	1.06	(0.93,1.22)	
Yes	637	207	32.5	660	236	35.8	1.05	(0.91,1.20)	0.4944	1.11	(0.86,1.44)	
Baseline SBP (</>= median¹)												0.4437
< median	1414	504	35.6	1445	531	36.7	1.00	(0.92,1.10)	0.9602	1.02	(0.85,1.21)	
>= median	1456	487	33.4	1444	522	36.1	1.05	(0.96,1.16)	0.2600	1.14	(0.96,1.35)	
History of atrial fibrillation or atrial flutter												0.9458
No	1366	500	36.6	1364	528	38.7	1.02	(0.94,1.12)	0.5938	1.07	(0.90,1.28)	
Yes	1501	490	32.6	1522	523	34.4	1.03	(0.94,1.13)	0.5454	1.07	(0.91,1.27)	

* 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, °:Trend test.
^ 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.

Analysis is based on study 1245.110.
For discontinued subjects, last available value was used. For completing subjects, last value up to last treatment intake + 7 days was used.
^^ Patients with NYHA class I are counted in subgroup NYHA class II. ¹ Baseline SBP median: 132 [mmHg].
² Baseline NT-proBNP median for patients with history of atrial fibrillation or atrial flutter: 1354 [pg/mL].
² Baseline NT-proBNP median for patients without history of atrial fibrillation or atrial flutter: 614 [pg/mL].
³ Baseline uric acid tertile cut-offs for males are T1: 5.9 T2: 7.5 [mg/dL] [rounded].
³ Baseline uric acid tertile cut-offs for females are T1: 5.4 T2: 6.9 [mg/dL] [rounded].

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Table R.1.1.3.2.1.1: 2 Responder analysis for EQ-VAS change from baseline to last value during planned treatment period >= 7 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 LVEF [%]												0.4065
< 50	928	326	35.1	959	346	36.1	0.99	(0.88,1.11)	0.8407	0.98	(0.79,1.21)	
>= 50	1942	665	34.2	1930	707	36.6	1.05	(0.97,1.13)	0.2482	1.13	(0.97,1.31)	
Baseline LVEF [%]												0.5915°/ 0.6662
<50	928	326	35.1	959	346	36.1	0.99	(0.88,1.11)	0.8408	0.98	(0.79,1.21)	
50 to <60	993	336	33.8	990	362	36.6	1.06	(0.95,1.19)	0.2844	1.16	(0.95,1.43)	
>=60	949	329	34.7	940	345	36.7	1.03	(0.92,1.16)	0.5768	1.09	(0.88,1.35)	
Baseline NT-proBNP [pg/mL] (</>=median² by atrial fibrillation/flutter status)												0.9770
< median	1464	505	34.5	1431	531	37.1	1.03	(0.94,1.12)	0.5857	1.07	(0.90,1.28)	
>= median	1402	485	34.6	1455	520	35.7	1.03	(0.94,1.13)	0.5639	1.07	(0.90,1.27)	
Baseline uric acid [mg/dL] (tertiles³)												0.1543°/ 0.2554
<T1	935	339	36.3	931	331	35.6	0.98	(0.88,1.10)	0.7643	0.97	(0.79,1.21)	
>=T1 and <T2	932	335	35.9	999	361	36.1	0.98	(0.88,1.10)	0.7652	0.96	(0.78,1.19)	
>=T2	973	310	31.9	933	350	37.5	1.11	(0.99,1.24)	0.0867	1.28	(1.03,1.59)	
Baseline use of MRA												0.1217
No	1789	626	35.0	1815	653	36.0	0.99	(0.91,1.07)	0.7666	1.01	(0.86,1.18)	
Yes	1081	365	33.8	1074	400	37.2	1.10	(0.99,1.22)	0.0820	1.19	(0.98,1.46)	
Baseline use of ACE-inhibitor, ARB or ARNi												0.5402
No	557	175	31.4	545	183	33.6	1.07	(0.92,1.26)	0.3871	1.17	(0.88,1.56)	
Yes	2313	816	35.3	2344	870	37.1	1.02	(0.95,1.09)	0.6618	1.05	(0.92,1.20)	

* 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, °:Trend test.
^ 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.

Analysis is based on study 1245.110.
For discontinued subjects, last available value was used. For completing subjects, last value up to last treatment intake + 7 days was used.
^^ Patients with NYHA class I are counted in subgroup NYHA class II. ¹ Baseline SBP median: 132 [mmHg].
² Baseline NT-proBNP median for patients with history of atrial fibrillation or atrial flutter: 1354 [pg/mL].
² Baseline NT-proBNP median for patients without history of atrial fibrillation or atrial flutter: 614 [pg/mL].
³ Baseline uric acid tertile cut-offs for males are T1: 5.9 T2: 7.5 [mg/dL] [rounded].
³ Baseline uric acid tertile cut-offs for females are T1: 5.4 T2: 6.9 [mg/dL] [rounded].

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R.1.1.3.2.1.2 EQ-VAS responder analysis (10 points)

Table R.1.1.3.2.1.2: 1 Responder analysis for EQ-VAS change from baseline to last value during planned treatment period <= -10 points (deterioration) overall and by subgroup - RS (OC-AD)

Subgroup	Placebo			Empa 10mg			Empa 10mg vs Placebo					
Category	N	n	%	N	n	%	Risk ratio *	(95% CI)	p-value	Odds ratio ***	(95% CI)	p-value **
Overall	2870	830	28.9	2889	766	26.5	0.90	(0.83,0.98)	0.0152	0.89	(0.79,1.01)	
Sex												0.9924
Male	1589	461	29.0	1600	433	27.1	0.90	(0.81,1.01)	0.0696	0.92	(0.79,1.09)	
Female	1281	369	28.8	1289	333	25.8	0.90	(0.80,1.02)	0.1074	0.86	(0.71,1.03)	
Age [years]												0.4697
<70	1036	241	23.3	1030	226	21.9	0.94	(0.81,1.11)	0.4755	0.99	(0.80,1.23)	
>=70	1834	589	32.1	1859	540	29.0	0.88	(0.80,0.97)	0.0105	0.84	(0.73,0.98)	
Region												0.5358
North America	345	95	27.5	342	100	29.2	1.06	(0.84,1.34)	0.6303	1.06	(0.75,1.50)	
Latin America	723	164	22.7	731	158	21.6	0.94	(0.78,1.14)	0.5485	0.95	(0.73,1.23)	
Europe	1301	432	33.2	1310	383	29.2	0.85	(0.76,0.96)	0.0064	0.83	(0.70,0.99)	
Asia	333	99	29.7	330	85	25.8	0.87	(0.69,1.11)	0.2789	0.87	(0.61,1.24)	
Other	168	40	23.8	176	40	22.7	0.97	(0.67,1.42)	0.8893	0.96	(0.57,1.62)	
OECD member												0.5376
No	790	195	24.7	822	176	21.4	0.86	(0.72,1.03)	0.0988	0.85	(0.67,1.09)	
Yes	2080	635	30.5	2067	590	28.5	0.92	(0.84,1.01)	0.0735	0.91	(0.79,1.05)	
Baseline NYHA												0.8281
II^^	2361	682	28.9	2360	632	26.8	0.91	(0.83,0.99)	0.0347	0.91	(0.79,1.04)	
III/IV	509	148	29.1	529	134	25.3	0.89	(0.73,1.08)	0.2225	0.82	(0.62,1.10)	
Baseline Diabetes status												0.0543
Diabetic	1409	413	29.3	1403	353	25.2	0.83	(0.73,0.94)	0.0024	0.82	(0.69,0.97)	
Non-Diabetic	1461	417	28.5	1486	413	27.8	0.98	(0.87,1.09)	0.6653	0.97	(0.82,1.15)	

* 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, °:Trend test.
^ 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.

Analysis is based on study 1245.110.
For discontinued subjects, last available value was used. For completing subjects, last value up to last treatment intake + 7 days was used.
^^ Patients with NYHA class I are counted in subgroup NYHA class II. [1] Baseline SBP median: 132 [mmHg].
[2] Baseline NT-proBNP median for patients with history of atrial fibrillation or atrial flutter: 1354 [pg/mL].
[2] Baseline NT-proBNP median for patients without history of atrial fibrillation or atrial flutter: 614 [pg/mL].
[3] Baseline uric acid tertile cut-offs for males are T1: 5.9 T2: 7.5 [mg/dL] [rounded].
[3] Baseline uric acid tertile cut-offs for females are T1: 5.4 T2: 6.9 [mg/dL] [rounded].

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Table R.1.1.3.2.1.2: 1 Responder analysis for EQ-VAS change from baseline to last value during planned treatment period <= -10 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 Diabetes status												0.0436°/ 0.1231
Diabetic	1409	413	29.3	1403	353	25.2	0.83	(0.73,0.94)	0.0023	0.82	(0.69,0.97)	
Pre-Diabetes	940	267	28.4	975	264	27.1	0.95	(0.82,1.10)	0.4858	0.94	(0.76,1.15)	
Normal (no pre-diabetes)	521	150	28.8	511	149	29.2	1.02	(0.85,1.23)	0.8034	1.04	(0.78,1.38)	
Baseline BMI [kg/m²]												0.1318
<30	1568	446	28.4	1594	445	27.9	0.96	(0.86,1.07)	0.4250	0.98	(0.83,1.15)	
>=30	1302	384	29.5	1295	321	24.8	0.84	(0.74,0.95)	0.0064	0.80	(0.67,0.96)	
Baseline eGFR (CKD-EPI) [mL/min/1.73m²]												0.9210
>=60	1448	384	26.5	1445	356	24.6	0.90	(0.79,1.02)	0.0903	0.94	(0.79,1.12)	
<60	1422	446	31.4	1444	410	28.4	0.91	(0.81,1.01)	0.0773	0.85	(0.72,1.00)	
History of HHF (in the last 12 months)												0.0069
No	2233	623	27.9	2229	597	26.8	0.96	(0.88,1.06)	0.4160	0.95	(0.83,1.09)	
Yes	637	207	32.5	660	169	25.6	0.73	(0.61,0.87)	0.0005	0.72	(0.56,0.93)	
Baseline SBP (</>= median¹)												0.5460
< median	1414	403	28.5	1445	360	24.9	0.88	(0.78,0.99)	0.0353	0.84	(0.71,1.00)	
>= median	1456	427	29.3	1444	406	28.1	0.93	(0.83,1.04)	0.1838	0.95	(0.80,1.12)	
History of atrial fibrillation or atrial flutter												0.5788
No	1366	373	27.3	1364	343	25.1	0.93	(0.82,1.05)	0.2260	0.91	(0.76,1.08)	
Yes	1501	456	30.4	1522	422	27.7	0.88	(0.79,0.99)	0.0306	0.88	(0.75,1.04)	

* 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, °:Trend test.
^ 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.

Analysis is based on study 1245.110.
For discontinued subjects, last available value was used. For completing subjects, last value up to last treatment intake + 7 days was used.
^^ Patients with NYHA class I are counted in subgroup NYHA class II. ¹ Baseline SBP median: 132 [mmHg].
² Baseline NT-proBNP median for patients with history of atrial fibrillation or atrial flutter: 1354 [pg/mL].
² Baseline NT-proBNP median for patients without history of atrial fibrillation or atrial flutter: 614 [pg/mL].
³ Baseline uric acid tertile cut-offs for males are T1: 5.9 T2: 7.5 [mg/dL] [rounded].
³ Baseline uric acid tertile cut-offs for females are T1: 5.4 T2: 6.9 [mg/dL] [rounded].

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Table R.1.1.3.2.1.2: 1 Responder analysis for EQ-VAS change from baseline to last value during planned treatment period <= -10 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 LVEF [%]												0.4918
< 50	928	253	27.3	959	244	25.4	0.94	(0.81,1.09)	0.4348	0.95	(0.77,1.18)	
>= 50	1942	577	29.7	1930	522	27.0	0.89	(0.80,0.98)	0.0163	0.87	(0.75,1.00)	
Baseline LVEF [%]												0.7133°/ 0.7158
<50	928	253	27.3	959	244	25.4	0.94	(0.81,1.09)	0.4348	0.95	(0.77,1.18)	
50 to <60	993	291	29.3	990	265	26.8	0.87	(0.75,1.00)	0.0462	0.87	(0.71,1.07)	
>=60	949	286	30.1	940	257	27.3	0.91	(0.79,1.04)	0.1634	0.86	(0.70,1.06)	
Baseline NT-proBNP [pg/mL] (</>=median[2] by atrial fibrillation/flutter status)												0.8381
< median	1464	401	27.4	1431	368	25.7	0.91	(0.81,1.03)	0.1259	0.94	(0.79,1.12)	
>= median	1402	428	30.5	1455	397	27.3	0.89	(0.80,1.00)	0.0511	0.84	(0.71,1.00)	
Baseline uric acid [mg/dL] (tertiles[3])												0.0433°/ 0.1023
<T1	935	248	26.5	931	242	26.0	0.99	(0.85,1.15)	0.9085	0.99	(0.80,1.23)	
>=T1 and <T2	932	243	26.1	999	266	26.6	0.96	(0.82,1.11)	0.5694	1.04	(0.84,1.29)	
>=T2	973	329	33.8	933	253	27.1	0.81	(0.71,0.93)	0.0022	0.73	(0.59,0.89)	
Baseline use of MRA												0.4678
No	1789	515	28.8	1815	481	26.5	0.92	(0.83,1.03)	0.1385	0.90	(0.77,1.05)	
Yes	1081	315	29.1	1074	285	26.5	0.87	(0.76,0.99)	0.0422	0.88	(0.72,1.08)	
Baseline use of ACE-inhibitor, ARB or ARNi												0.9763
No	557	178	32.0	545	157	28.8	0.91	(0.76,1.08)	0.2648	0.83	(0.63,1.09)	
Yes	2313	652	28.2	2344	609	26.0	0.90	(0.82,0.99)	0.0320	0.91	(0.79,1.04)	

* 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, °:Trend test.
^ 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.

Analysis is based on study 1245.110.
For discontinued subjects, last available value was used. For completing subjects, last value up to last treatment intake + 7 days was used.
^^ Patients with NYHA class I are counted in subgroup NYHA class II. [1] Baseline SBP median: 132 [mmHg].
[2] Baseline NT-proBNP median for patients with history of atrial fibrillation or atrial flutter: 1354 [pg/mL].
[2] Baseline NT-proBNP median for patients without history of atrial fibrillation or atrial flutter: 614 [pg/mL].
[3] Baseline uric acid tertile cut-offs for males are T1: 5.9 T2: 7.5 [mg/dL] [rounded].
[3] Baseline uric acid tertile cut-offs for females are T1: 5.4 T2: 6.9 [mg/dL] [rounded].

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Table R.1.1.3.2.1.2: 2 Responder analysis for EQ-VAS change from baseline to last value during planned treatment period >= 10 points (improvement) overall and by subgroup - RS (OC-AD)

Subgroup	Placebo			Empa 10mg			Empa 10mg vs Placebo					
Category	N	n	%	N	n	%	Risk ratio *	(95% CI)	p-value	Odds ratio ***	(95% CI)	p-value **
Overall	2870	973	33.9	2889	1027	35.5	1.02	(0.95,1.09)	0.5649	1.06	(0.94,1.20)	
Sex												0.2899
Male	1589	521	32.8	1600	533	33.3	0.99	(0.90,1.08)	0.7623	0.98	(0.83,1.16)	
Female	1281	452	35.3	1289	494	38.3	1.06	(0.96,1.16)	0.2343	1.16	(0.96,1.39)	
Age [years]												0.3342
<70	1036	380	36.7	1030	432	41.9	1.06	(0.96,1.17)	0.2486	1.16	(0.95,1.42)	
>=70	1834	593	32.3	1859	595	32.0	0.99	(0.91,1.08)	0.8840	1.01	(0.86,1.17)	
Region												0.8122
North America	345	106	30.7	342	106	31.0	1.02	(0.83,1.25)	0.8713	1.06	(0.74,1.53)	
Latin America	723	307	42.5	731	343	46.9	1.08	(0.97,1.21)	0.1711	1.24	(0.98,1.57)	
Europe	1301	399	30.7	1310	403	30.8	0.99	(0.89,1.10)	0.8577	0.98	(0.82,1.19)	
Asia	333	100	30.0	330	106	32.1	0.98	(0.80,1.20)	0.8416	0.98	(0.68,1.42)	
Other	168	61	36.3	176	69	39.2	0.98	(0.76,1.25)	0.8633	1.02	(0.63,1.68)	
OECD member												0.2286
No	790	312	39.5	822	369	44.9	1.08	(0.97,1.20)	0.1769	1.21	(0.97,1.52)	
Yes	2080	661	31.8	2067	658	31.8	0.99	(0.91,1.08)	0.8213	0.99	(0.86,1.15)	
Baseline NYHA												0.6574
II^^	2361	782	33.1	2360	810	34.3	1.01	(0.94,1.09)	0.7445	1.03	(0.90,1.18)	
III/IV	509	191	37.5	529	217	41.0	1.05	(0.91,1.21)	0.4985	1.19	(0.90,1.59)	
Baseline Diabetes status												0.0111
Diabetic	1409	481	34.1	1403	546	38.9	1.11	(1.01,1.21)	0.0258	1.25	(1.05,1.50)	
Non-Diabetic	1461	492	33.7	1486	481	32.4	0.93	(0.85,1.03)	0.1647	0.90	(0.76,1.07)	

* 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, °:Trend test.
^ 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.

Analysis is based on study 1245.110.
For discontinued subjects, last available value was used. For completing subjects, last value up to last treatment intake + 7 days was used.
^^ Patients with NYHA class I are counted in subgroup NYHA class II. [1] Baseline SBP median: 132 [mmHg].
[2] Baseline NT-proBNP median for patients with history of atrial fibrillation or atrial flutter: 1354 [pg/mL].
[2] Baseline NT-proBNP median for patients without history of atrial fibrillation or atrial flutter: 614 [pg/mL].
[3] Baseline uric acid tertile cut-offs for males are T1: 5.9 T2: 7.5 [mg/dL] [rounded].
[3] Baseline uric acid tertile cut-offs for females are T1: 5.4 T2: 6.9 [mg/dL] [rounded].

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Table R.1.1.3.2.1.2: 2 Responder analysis for EQ-VAS change from baseline to last value during planned treatment period >= 10 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 Diabetes status												0.0659°/ 0.0242
Diabetic	1409	481	34.1	1403	546	38.9	1.11	(1.01,1.21)	0.0258	1.25	(1.05,1.50)	
Pre-Diabetes	940	325	34.6	975	317	32.5	0.91	(0.81,1.02)	0.0918	0.85	(0.69,1.06)	
Normal (no pre-diabetes)	521	167	32.1	511	164	32.1	0.99	(0.83,1.18)	0.9086	0.99	(0.74,1.33)	
Baseline BMI [kg/m²]												0.1292
<30	1568	537	34.2	1594	526	33.0	0.97	(0.89,1.07)	0.5474	0.94	(0.79,1.11)	
>=30	1302	436	33.5	1295	501	38.7	1.08	(0.98,1.18)	0.1279	1.22	(1.02,1.46)	
Baseline eGFR (CKD-EPI) [mL/min/1.73m²]												0.9581
>=60	1448	496	34.3	1445	526	36.4	1.02	(0.93,1.11)	0.7099	1.04	(0.87,1.24)	
<60	1422	477	33.5	1444	501	34.7	1.02	(0.93,1.12)	0.6681	1.08	(0.91,1.29)	
History of HHF (in the last 12 months)												0.7834
No	2233	768	34.4	2229	795	35.7	1.01	(0.94,1.09)	0.6988	1.05	(0.91,1.21)	
Yes	637	205	32.2	660	232	35.2	1.04	(0.90,1.19)	0.6028	1.10	(0.85,1.42)	
Baseline SBP (</>= median¹)												0.4630
< median	1414	493	34.9	1445	516	35.7	0.99	(0.91,1.09)	0.9146	1.00	(0.84,1.19)	
>= median	1456	480	33.0	1444	511	35.4	1.05	(0.95,1.15)	0.3533	1.12	(0.94,1.33)	
History of atrial fibrillation or atrial flutter												0.9823
No	1366	492	36.0	1364	517	37.9	1.02	(0.93,1.12)	0.7003	1.06	(0.89,1.26)	
Yes	1501	480	32.0	1522	508	33.4	1.02	(0.93,1.12)	0.6896	1.06	(0.89,1.25)	

* 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, °:Trend test.
^ 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.

Analysis is based on study 1245.110.
For discontinued subjects, last available value was used. For completing subjects, last value up to last treatment intake + 7 days was used.
^^ Patients with NYHA class I are counted in subgroup NYHA class II. ¹ Baseline SBP median: 132 [mmHg].
² Baseline NT-proBNP median for patients with history of atrial fibrillation or atrial flutter: 1354 [pg/mL].
² Baseline NT-proBNP median for patients without history of atrial fibrillation or atrial flutter: 614 [pg/mL].
³ Baseline uric acid tertile cut-offs for males are T1: 5.9 T2: 7.5 [mg/dL] [rounded].
³ Baseline uric acid tertile cut-offs for females are T1: 5.4 T2: 6.9 [mg/dL] [rounded].

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Table R.1.1.3.2.1.2: 2 Responder analysis for EQ-VAS change from baseline to last value during planned treatment period >= 10 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 LVEF [%]												0.2649
< 50	928	324	34.9	959	337	35.1	0.97	(0.86,1.08)	0.5637	0.93	(0.75,1.16)	
>= 50	1942	649	33.4	1930	690	35.8	1.05	(0.97,1.13)	0.2658	1.13	(0.97,1.31)	
Baseline LVEF [%]												0.4931°/ 0.4637
<50	928	324	34.9	959	337	35.1	0.97	(0.86,1.08)	0.5637	0.93	(0.75,1.16)	
50 to <60	993	327	32.9	990	355	35.9	1.07	(0.96,1.20)	0.2405	1.18	(0.96,1.46)	
>=60	949	322	33.9	940	335	35.6	1.02	(0.91,1.15)	0.6946	1.07	(0.86,1.33)	
Baseline NT-proBNP [pg/mL] (</>=median² by atrial fibrillation/flutter status)												0.9670
< median	1464	495	33.8	1431	517	36.1	1.02	(0.93,1.12)	0.7211	1.06	(0.89,1.26)	
>= median	1402	477	34.0	1455	508	34.9	1.02	(0.93,1.12)	0.6820	1.06	(0.89,1.26)	
Baseline uric acid [mg/dL] (tertiles³)												0.2183°/ 0.2806
<T1	935	332	35.5	931	325	34.9	0.99	(0.88,1.11)	0.8186	0.98	(0.79,1.22)	
>=T1 and <T2	932	327	35.1	999	347	34.7	0.97	(0.86,1.08)	0.5536	0.93	(0.75,1.15)	
>=T2	973	307	31.6	933	344	36.9	1.09	(0.97,1.23)	0.1308	1.26	(1.02,1.57)	
Baseline use of MRA												0.0907
No	1789	615	34.4	1815	635	35.0	0.98	(0.90,1.06)	0.5617	0.99	(0.84,1.15)	
Yes	1081	358	33.1	1074	392	36.5	1.10	(0.99,1.22)	0.0889	1.19	(0.97,1.46)	
Baseline use of ACE-inhibitor, ARB or ARNi												0.6317
No	557	172	30.9	545	177	32.5	1.05	(0.90,1.24)	0.5212	1.14	(0.85,1.52)	
Yes	2313	801	34.6	2344	850	36.3	1.01	(0.94,1.08)	0.7916	1.04	(0.91,1.19)	

* 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, °:Trend test.
^ 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.

Analysis is based on study 1245.110.
For discontinued subjects, last available value was used. For completing subjects, last value up to last treatment intake + 7 days was used.
^^ Patients with NYHA class I are counted in subgroup NYHA class II. ¹ Baseline SBP median: 132 [mmHg].
² Baseline NT-proBNP median for patients with history of atrial fibrillation or atrial flutter: 1354 [pg/mL].
² Baseline NT-proBNP median for patients without history of atrial fibrillation or atrial flutter: 614 [pg/mL].
³ Baseline uric acid tertile cut-offs for males are T1: 5.9 T2: 7.5 [mg/dL] [rounded].
³ Baseline uric acid tertile cut-offs for females are T1: 5.4 T2: 6.9 [mg/dL] [rounded].

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R.1.1.3.2.1.3 EQ-VAS responder analysis (15 points)

Table R.1.1.3.2.1.3: 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	Placebo			Empa 10mg			Empa 10mg vs Placebo					
Category	N	n	%	N	n	%	Risk ratio *	(95% CI)	p-value	Odds ratio ***	(95% CI)	p-value **
Overall	2870	503	17.5	2889	486	16.8	0.94	(0.84,1.05)	0.2956	0.96	(0.84,1.11)	
Sex												0.6701
Male	1589	281	17.7	1600	283	17.7	0.96	(0.83,1.12)	0.6135	1.03	(0.85,1.24)	
Female	1281	222	17.3	1289	203	15.7	0.92	(0.77,1.09)	0.3125	0.89	(0.71,1.10)	
Age [years]												0.8651
<70	1036	144	13.9	1030	133	12.9	0.92	(0.74,1.15)	0.4679	0.97	(0.75,1.27)	
>=70	1834	359	19.6	1859	353	19.0	0.94	(0.83,1.08)	0.3876	0.95	(0.80,1.13)	
Region												0.2653
North America	345	63	18.3	342	76	22.2	1.21	(0.90,1.63)	0.1972	1.25	(0.85,1.85)	
Latin America	723	107	14.8	731	93	12.7	0.85	(0.66,1.10)	0.2214	0.84	(0.62,1.15)	
Europe	1301	261	20.1	1310	245	18.7	0.90	(0.76,1.05)	0.1684	0.93	(0.76,1.14)	
Asia	333	45	13.5	330	50	15.2	1.13	(0.78,1.64)	0.5036	1.24	(0.79,1.93)	
Other	168	27	16.1	176	22	12.5	0.79	(0.48,1.33)	0.3812	0.74	(0.40,1.39)	
OECD member												0.0705
No	790	119	15.1	822	96	11.7	0.77	(0.60,0.99)	0.0410	0.76	(0.57,1.03)	
Yes	2080	384	18.5	2067	390	18.9	1.00	(0.88,1.13)	0.9814	1.04	(0.88,1.22)	
Baseline NYHA												0.6866
II^^	2361	404	17.1	2360	395	16.7	0.95	(0.84,1.08)	0.4388	0.99	(0.84,1.16)	
III/IV	509	99	19.4	529	91	17.2	0.90	(0.70,1.16)	0.4031	0.85	(0.61,1.19)	
Baseline Diabetes status												0.1102
Diabetic	1409	254	18.0	1403	227	16.2	0.85	(0.72,1.01)	0.0608	0.89	(0.72,1.09)	
Non-Diabetic	1461	249	17.0	1486	259	17.4	1.03	(0.88,1.20)	0.7306	1.04	(0.85,1.27)	

* 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, °:Trend test.
^ 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.

Analysis is based on study 1245.110.
For discontinued subjects, last available value was used. For completing subjects, last value up to last treatment intake + 7 days was used.
^^ Patients with NYHA class I are counted in subgroup NYHA class II. [1] Baseline SBP median: 132 [mmHg].
[2] Baseline NT-proBNP median for patients with history of atrial fibrillation or atrial flutter: 1354 [pg/mL].
[2] Baseline NT-proBNP median for patients without history of atrial fibrillation or atrial flutter: 614 [pg/mL].
[3] Baseline uric acid tertile cut-offs for males are T1: 5.9 T2: 7.5 [mg/dL] [rounded].
[3] Baseline uric acid tertile cut-offs for females are T1: 5.4 T2: 6.9 [mg/dL] [rounded].

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Table R.1.1.3.2.1.3: 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 Diabetes status												0.0285°/ 0.0648
Diabetic	1409	254	18.0	1403	227	16.2	0.85	(0.72,1.01)	0.0601	0.89	(0.72,1.09)	
Pre-Diabetes	940	161	17.1	975	155	15.9	0.93	(0.76,1.13)	0.4704	0.91	(0.71,1.17)	
Normal (no pre-diabetes)	521	88	16.9	511	104	20.4	1.22	(0.95,1.57)	0.1196	1.31	(0.94,1.81)	
Baseline BMI [kg/m²]												0.5064
<30	1568	256	16.3	1594	264	16.6	0.98	(0.84,1.14)	0.7795	1.03	(0.84,1.25)	
>=30	1302	247	19.0	1295	222	17.1	0.91	(0.77,1.06)	0.2307	0.91	(0.74,1.12)	
Baseline eGFR (CKD-EPI) [mL/min/1.73m²]												0.7900
>=60	1448	226	15.6	1445	225	15.6	0.96	(0.81,1.14)	0.6124	1.05	(0.85,1.29)	
<60	1422	277	19.5	1444	261	18.1	0.93	(0.80,1.08)	0.3257	0.89	(0.73,1.09)	
History of HHF (in the last 12 months)												0.0426
No	2233	380	17.0	2229	379	17.0	1.00	(0.88,1.14)	0.9541	1.01	(0.86,1.19)	
Yes	637	123	19.3	660	107	16.2	0.75	(0.59,0.96)	0.0241	0.82	(0.61,1.10)	
Baseline SBP (</>= median¹)												0.4923
< median	1414	243	17.2	1445	223	15.4	0.90	(0.77,1.06)	0.2256	0.89	(0.73,1.10)	
>= median	1456	260	17.9	1444	263	18.2	0.98	(0.84,1.14)	0.7810	1.04	(0.85,1.26)	
History of atrial fibrillation or atrial flutter												0.4086
No	1366	228	16.7	1364	225	16.5	0.99	(0.84,1.17)	0.9409	1.00	(0.81,1.23)	
Yes	1501	274	18.3	1522	261	17.1	0.90	(0.77,1.05)	0.1978	0.94	(0.77,1.14)	

* 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, °:Trend test.
^ 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.

Analysis is based on study 1245.110.
For discontinued subjects, last available value was used. For completing subjects, last value up to last treatment intake + 7 days was used.
^^ Patients with NYHA class I are counted in subgroup NYHA class II. ¹ Baseline SBP median: 132 [mmHg].
² Baseline NT-proBNP median for patients with history of atrial fibrillation or atrial flutter: 1354 [pg/mL].
² Baseline NT-proBNP median for patients without history of atrial fibrillation or atrial flutter: 614 [pg/mL].
³ Baseline uric acid tertile cut-offs for males are T1: 5.9 T2: 7.5 [mg/dL] [rounded].
³ Baseline uric acid tertile cut-offs for females are T1: 5.4 T2: 6.9 [mg/dL] [rounded].

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Table R.1.1.3.2.1.3: 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 LVEF [%]												0.8965
< 50	928	150	16.2	959	143	14.9	0.93	(0.76,1.15)	0.5023	0.95	(0.74,1.23)	
>= 50	1942	353	18.2	1930	343	17.8	0.95	(0.83,1.08)	0.4259	0.97	(0.82,1.15)	
Baseline LVEF [%]												0.2425°/ 0.1246
<50	928	150	16.2	959	143	14.9	0.93	(0.76,1.15)	0.5023	0.95	(0.74,1.23)	
50 to <60	993	189	19.0	990	166	16.8	0.82	(0.68,1.00)	0.0472	0.84	(0.66,1.07)	
>=60	949	164	17.3	940	177	18.8	1.09	(0.90,1.32)	0.3750	1.12	(0.88,1.43)	
Baseline NT-proBNP [pg/mL] (</>=median² by atrial fibrillation/flutter status)												0.2330
< median	1464	233	15.9	1431	240	16.8	1.01	(0.86,1.20)	0.8869	1.10	(0.90,1.35)	
>= median	1402	269	19.2	1455	246	16.9	0.88	(0.76,1.03)	0.1091	0.85	(0.69,1.03)	
Baseline uric acid [mg/dL] (tertiles³)												0.0939°/ 0.1934
<T1	935	150	16.0	931	154	16.5	1.05	(0.85,1.28)	0.6689	1.07	(0.83,1.38)	
>=T1 and <T2	932	135	14.5	999	161	16.1	1.03	(0.83,1.27)	0.8200	1.15	(0.89,1.49)	
>=T2	973	210	21.6	933	167	17.9	0.84	(0.70,1.00)	0.0504	0.79	(0.63,1.01)	
Baseline use of MRA												0.4022
No	1789	319	17.8	1815	314	17.3	0.98	(0.85,1.12)	0.7318	0.98	(0.82,1.17)	
Yes	1081	184	17.0	1074	172	16.0	0.88	(0.73,1.07)	0.2006	0.94	(0.74,1.19)	
Baseline use of ACE-inhibitor, ARB or ARNi												0.4991
No	557	101	18.1	545	99	18.2	1.02	(0.79,1.30)	0.8989	1.00	(0.72,1.37)	
Yes	2313	402	17.4	2344	387	16.5	0.92	(0.81,1.05)	0.2200	0.96	(0.82,1.12)	

* 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, °:Trend test.
^ 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.

Analysis is based on study 1245.110.
For discontinued subjects, last available value was used. For completing subjects, last value up to last treatment intake + 7 days was used.
^^ Patients with NYHA class I are counted in subgroup NYHA class II. ¹ Baseline SBP median: 132 [mmHg].
² Baseline NT-proBNP median for patients with history of atrial fibrillation or atrial flutter: 1354 [pg/mL].
² Baseline NT-proBNP median for patients without history of atrial fibrillation or atrial flutter: 614 [pg/mL].
³ Baseline uric acid tertile cut-offs for males are T1: 5.9 T2: 7.5 [mg/dL] [rounded].
³ Baseline uric acid tertile cut-offs for females are T1: 5.4 T2: 6.9 [mg/dL] [rounded].

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Table R.1.1.3.2.1.3: 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	Placebo			Empa 10mg			Empa 10mg vs Placebo					
Category	N	n	%	N	n	%	Risk ratio *	(95% CI)	p-value	Odds ratio ***	(95% CI)	p-value **
Overall	2870	597	20.8	2889	654	22.6	1.04	(0.95,1.14)	0.3787	1.10	(0.95,1.27)	
Sex												0.9620
Male	1589	304	19.1	1600	334	20.9	1.04	(0.92,1.19)	0.5139	1.09	(0.89,1.33)	
Female	1281	293	22.9	1289	320	24.8	1.04	(0.91,1.18)	0.5545	1.11	(0.90,1.37)	
Age [years]												0.1432
<70	1036	231	22.3	1030	290	28.2	1.13	(0.98,1.30)	0.0855	1.30	(1.03,1.64)	
>=70	1834	366	20.0	1859	364	19.6	0.98	(0.87,1.11)	0.7989	0.99	(0.82,1.19)	
Region												0.7630
North America	345	73	21.2	342	67	19.6	0.92	(0.70,1.21)	0.5747	0.91	(0.59,1.41)	
Latin America	723	202	27.9	731	232	31.7	1.10	(0.94,1.28)	0.2364	1.25	(0.96,1.63)	
Europe	1301	229	17.6	1310	244	18.6	1.04	(0.89,1.21)	0.6207	1.07	(0.85,1.33)	
Asia	333	52	15.6	330	65	19.7	1.10	(0.82,1.49)	0.5281	1.20	(0.76,1.89)	
Other	168	41	24.4	176	46	26.1	0.92	(0.66,1.28)	0.6167	0.92	(0.53,1.62)	
OECD member												0.4790
No	790	210	26.6	822	256	31.1	1.09	(0.94,1.26)	0.2699	1.21	(0.94,1.55)	
Yes	2080	387	18.6	2067	398	19.3	1.01	(0.90,1.14)	0.8075	1.04	(0.87,1.24)	
Baseline NYHA												0.8461
II^^	2361	474	20.1	2360	509	21.6	1.04	(0.93,1.15)	0.4875	1.07	(0.91,1.26)	
III/IV	509	123	24.2	529	145	27.4	1.06	(0.88,1.29)	0.5453	1.23	(0.89,1.70)	
Baseline Diabetes status												0.0048
Diabetic	1409	301	21.4	1403	370	26.4	1.18	(1.04,1.34)	0.0096	1.40	(1.14,1.71)	
Non-Diabetic	1461	296	20.3	1486	284	19.1	0.90	(0.79,1.04)	0.1467	0.86	(0.70,1.05)	

* 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, °:Trend test.
^ 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.

Analysis is based on study 1245.110.
For discontinued subjects, last available value was used. For completing subjects, last value up to last treatment intake + 7 days was used.
^^ Patients with NYHA class I are counted in subgroup NYHA class II. [1] Baseline SBP median: 132 [mmHg].
[2] Baseline NT-proBNP median for patients with history of atrial fibrillation or atrial flutter: 1354 [pg/mL].
[2] Baseline NT-proBNP median for patients without history of atrial fibrillation or atrial flutter: 614 [pg/mL].
[3] Baseline uric acid tertile cut-offs for males are T1: 5.9 T2: 7.5 [mg/dL] [rounded].
[3] Baseline uric acid tertile cut-offs for females are T1: 5.4 T2: 6.9 [mg/dL] [rounded].

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Table R.1.1.3.2.1.3: 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 Diabetes status												0.0209°/ 0.0158
Diabetic	1409	301	21.4	1403	370	26.4	1.18	(1.04,1.34)	0.0096	1.40	(1.14,1.71)	
Pre-Diabetes	940	193	20.5	975	188	19.3	0.89	(0.75,1.04)	0.1455	0.83	(0.65,1.08)	
Normal (no pre-diabetes)	521	103	19.8	511	96	18.8	0.94	(0.73,1.20)	0.6094	0.90	(0.63,1.28)	
Baseline BMI [kg/m²]												0.5551
<30	1568	321	20.5	1594	325	20.4	1.02	(0.89,1.15)	0.8188	1.02	(0.83,1.24)	
>=30	1302	276	21.2	1295	329	25.4	1.07	(0.94,1.23)	0.2955	1.20	(0.98,1.49)	
Baseline eGFR (CKD-EPI) [mL/min/1.73m²]												0.3737
>=60	1448	321	22.2	1445	342	23.7	1.00	(0.88,1.14)	0.9898	1.02	(0.83,1.25)	
<60	1422	276	19.4	1444	312	21.6	1.09	(0.95,1.25)	0.2197	1.20	(0.97,1.47)	
History of HHF (in the last 12 months)												0.7593
No	2233	469	21.0	2229	500	22.4	1.03	(0.93,1.15)	0.5328	1.08	(0.92,1.27)	
Yes	637	128	20.1	660	154	23.3	1.07	(0.89,1.29)	0.4848	1.17	(0.86,1.59)	
Baseline SBP (</>= median¹)												0.2475
< median	1414	299	21.1	1445	315	21.8	0.99	(0.86,1.13)	0.8386	0.99	(0.81,1.22)	
>= median	1456	298	20.5	1444	339	23.5	1.10	(0.97,1.25)	0.1467	1.22	(1.00,1.50)	
History of atrial fibrillation or atrial flutter												0.3319
No	1366	300	22.0	1364	342	25.1	1.09	(0.96,1.24)	0.1930	1.18	(0.96,1.45)	
Yes	1501	296	19.7	1522	310	20.4	0.99	(0.87,1.14)	0.9216	1.02	(0.83,1.25)	

* 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, °:Trend test.
^ 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.

Analysis is based on study 1245.110.
For discontinued subjects, last available value was used. For completing subjects, last value up to last treatment intake + 7 days was used.
^^ Patients with NYHA class I are counted in subgroup NYHA class II. ¹ Baseline SBP median: 132 [mmHg].
² Baseline NT-proBNP median for patients with history of atrial fibrillation or atrial flutter: 1354 [pg/mL].
² Baseline NT-proBNP median for patients without history of atrial fibrillation or atrial flutter: 614 [pg/mL].
³ Baseline uric acid tertile cut-offs for males are T1: 5.9 T2: 7.5 [mg/dL] [rounded].
³ Baseline uric acid tertile cut-offs for females are T1: 5.4 T2: 6.9 [mg/dL] [rounded].

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Table R.1.1.3.2.1.3: 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 LVEF [%]												0.7016
< 50	928	196	21.1	959	218	22.7	1.02	(0.87,1.19)	0.8364	1.03	(0.80,1.33)	
>= 50	1942	401	20.6	1930	436	22.6	1.06	(0.94,1.18)	0.3432	1.14	(0.95,1.36)	
Baseline LVEF [%]												0.9564°/ 0.6960
<50	928	196	21.1	959	218	22.7	1.02	(0.87,1.19)	0.8367	1.03	(0.80,1.33)	
50 to <60	993	201	20.2	990	228	23.0	1.10	(0.94,1.29)	0.2246	1.23	(0.96,1.58)	
>=60	949	200	21.1	940	208	22.1	1.01	(0.86,1.19)	0.9059	1.04	(0.81,1.35)	
Baseline NT-proBNP [pg/mL] (</>=median² by atrial fibrillation/flutter status)												0.9316
< median	1464	298	20.4	1431	325	22.7	1.04	(0.91,1.18)	0.5910	1.10	(0.90,1.35)	
>= median	1402	298	21.3	1455	327	22.5	1.04	(0.92,1.19)	0.5110	1.10	(0.90,1.34)	
Baseline uric acid [mg/dL] (tertiles³)												0.4821°/ 0.6676
<T1	935	210	22.5	931	204	21.9	0.98	(0.83,1.15)	0.7969	1.00	(0.77,1.28)	
>=T1 and <T2	932	189	20.3	999	227	22.7	1.08	(0.92,1.27)	0.3593	1.11	(0.87,1.43)	
>=T2	973	193	19.8	933	217	23.3	1.06	(0.90,1.25)	0.4609	1.18	(0.92,1.52)	
Baseline use of MRA												0.5871
No	1789	366	20.5	1815	406	22.4	1.02	(0.91,1.15)	0.7171	1.08	(0.90,1.30)	
Yes	1081	231	21.4	1074	248	23.1	1.08	(0.93,1.25)	0.3230	1.13	(0.90,1.43)	
Baseline use of ACE-inhibitor, ARB or ARNi												0.7807
No	557	116	20.8	545	121	22.2	1.07	(0.86,1.33)	0.5368	1.15	(0.82,1.60)	
Yes	2313	481	20.8	2344	533	22.7	1.03	(0.93,1.15)	0.5189	1.09	(0.93,1.28)	

* 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, °:Trend test.
^ 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.

Analysis is based on study 1245.110.
For discontinued subjects, last available value was used. For completing subjects, last value up to last treatment intake + 7 days was used.
^^ Patients with NYHA class I are counted in subgroup NYHA class II. ¹ Baseline SBP median: 132 [mmHg].
² Baseline NT-proBNP median for patients with history of atrial fibrillation or atrial flutter: 1354 [pg/mL].
² Baseline NT-proBNP median for patients without history of atrial fibrillation or atrial flutter: 614 [pg/mL].
³ Baseline uric acid tertile cut-offs for males are T1: 5.9 T2: 7.5 [mg/dL] [rounded].
³ Baseline uric acid tertile cut-offs for females are T1: 5.4 T2: 6.9 [mg/dL] [rounded].

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R.1.1.3.2.1.4 KCCQ Clinical Summary Score responder analysis (5 points)

Table R.1.1.3.2.1.4: 1 Responder analysis for KCCQ-CSS change from baseline to last value during planned treatment period <= -5 points (deterioration) overall and by subgroup - RS (OC-AD)

Subgroup	Placebo			Empa 10mg			Empa 10mg vs Placebo					
Category	N	n	%	N	n	%	Risk ratio *	(95% CI)	p-value	Odds ratio ***	(95% CI)	p-value **
Overall	2869	879	30.6	2886	762	26.4	0.87	(0.80,0.94)	0.0004	0.81	(0.72,0.91)	
Sex												0.6747
Male	1588	503	31.7	1597	445	27.9	0.88	(0.79,0.98)	0.0155	0.82	(0.70,0.96)	
Female	1281	376	29.4	1289	317	24.6	0.85	(0.75,0.96)	0.0092	0.79	(0.66,0.95)	
Age [years]												0.1414
<70	1038	256	24.7	1030	238	23.1	0.95	(0.81,1.10)	0.4717	0.93	(0.76,1.14)	
>=70	1831	623	34.0	1856	524	28.2	0.83	(0.75,0.91)	<0.0001	0.75	(0.65,0.87)	
Region												0.1645
North America	346	105	30.3	344	111	32.3	1.03	(0.83,1.28)	0.7812	1.05	(0.75,1.46)	
Latin America	724	174	24.0	730	147	20.1	0.86	(0.71,1.04)	0.1165	0.82	(0.63,1.06)	
Europe	1301	429	33.0	1309	382	29.2	0.89	(0.79,0.99)	0.0368	0.84	(0.71,0.99)	
Asia	330	112	33.9	328	79	24.1	0.71	(0.56,0.91)	0.0057	0.61	(0.43,0.86)	
Other	168	59	35.1	175	43	24.6	0.72	(0.52,0.99)	0.0452	0.61	(0.38,0.99)	
OECD member												0.2020
No	789	202	25.6	818	159	19.4	0.78	(0.66,0.94)	0.0073	0.72	(0.57,0.92)	
Yes	2080	677	32.5	2068	603	29.2	0.89	(0.82,0.98)	0.0129	0.84	(0.74,0.97)	
Baseline NYHA												0.2021
II^^	2359	727	30.8	2355	642	27.3	0.89	(0.81,0.97)	0.0065	0.84	(0.73,0.95)	
III/IV	510	152	29.8	531	120	22.6	0.77	(0.63,0.94)	0.0094	0.69	(0.51,0.92)	
Baseline Diabetes status												0.6028
Diabetic	1407	442	31.4	1400	374	26.7	0.85	(0.76,0.95)	0.0041	0.78	(0.66,0.93)	
Non-Diabetic	1462	437	29.9	1486	388	26.1	0.88	(0.79,0.99)	0.0339	0.84	(0.71,0.99)	

* 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, °:Trend test.
^ Models contain terms age, baseline eGFR (CKD-EPI), baseline LVEF, Baseline KCCQ-CSS, 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.

Analysis is based on study 1245.110.
For discontinued subjects, last available value was used. For completing subjects, last value up to last treatment intake + 7 days was used.
^^ Patients with NYHA class I are counted in subgroup NYHA class II. [1] Baseline SBP median: 132 [mmHg].
[2] Baseline NT-proBNP median for patients with history of atrial fibrillation or atrial flutter: 1354 [pg/mL].
[2] Baseline NT-proBNP median for patients without history of atrial fibrillation or atrial flutter: 614 [pg/mL].
[3] Baseline uric acid tertile cut-offs for males are T1: 5.9 T2: 7.5 [mg/dL] [rounded].
[3] Baseline uric acid tertile cut-offs for females are T1: 5.4 T2: 6.9 [mg/dL] [rounded].

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Table R.1.1.3.2.1.4: 1 Responder analysis for KCCQ-CSS 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 Diabetes status												0.7748°/ 0.8183
Diabetic	1407	442	31.4	1400	374	26.7	0.85	(0.76,0.95)	0.0041	0.78	(0.66,0.93)	
Pre-Diabetes	940	282	30.0	974	260	26.7	0.90	(0.78,1.03)	0.1302	0.85	(0.70,1.05)	
Normal (no pre-diabetes)	522	155	29.7	512	128	25.0	0.86	(0.71,1.04)	0.1236	0.80	(0.60,1.06)	
Baseline BMI [kg/m²]												0.3410
<30	1563	482	30.8	1591	409	25.7	0.84	(0.75,0.93)	0.0014	0.77	(0.66,0.91)	
>=30	1306	397	30.4	1295	353	27.3	0.90	(0.80,1.02)	0.0932	0.86	(0.72,1.02)	
Baseline eGFR (CKD-EPI) [mL/min/1.73m²]												0.4427
>=60	1449	419	28.9	1445	342	23.7	0.84	(0.74,0.94)	0.0034	0.78	(0.65,0.92)	
<60	1420	460	32.4	1441	420	29.1	0.89	(0.80,0.99)	0.0349	0.84	(0.71,0.99)	
History of HHF (in the last 12 months)												0.1404
No	2233	656	29.4	2228	580	26.0	0.89	(0.82,0.98)	0.0186	0.85	(0.74,0.97)	
Yes	636	223	35.1	658	182	27.7	0.78	(0.67,0.91)	0.0019	0.69	(0.54,0.87)	
Baseline SBP (</>= median¹)												0.7255
< median	1414	434	30.7	1444	393	27.2	0.88	(0.78,0.98)	0.0225	0.83	(0.70,0.98)	
>= median	1455	445	30.6	1442	369	25.6	0.85	(0.76,0.96)	0.0061	0.79	(0.67,0.94)	
History of atrial fibrillation or atrial flutter												0.2304
No	1364	376	27.6	1364	337	24.7	0.91	(0.81,1.03)	0.1469	0.88	(0.74,1.05)	
Yes	1502	503	33.5	1519	423	27.8	0.83	(0.74,0.92)	0.0004	0.75	(0.64,0.88)	

* 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, °:Trend test.
^ Models contain terms age, baseline eGFR (CKD-EPI), baseline LVEF, Baseline KCCQ-CSS, 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.

Analysis is based on study 1245.110.
For discontinued subjects, last available value was used. For completing subjects, last value up to last treatment intake + 7 days was used.
^^ Patients with NYHA class I are counted in subgroup NYHA class II. ¹ Baseline SBP median: 132 [mmHg].
² Baseline NT-proBNP median for patients with history of atrial fibrillation or atrial flutter: 1354 [pg/mL].
² Baseline NT-proBNP median for patients without history of atrial fibrillation or atrial flutter: 614 [pg/mL].
³ Baseline uric acid tertile cut-offs for males are T1: 5.9 T2: 7.5 [mg/dL] [rounded].
³ Baseline uric acid tertile cut-offs for females are T1: 5.4 T2: 6.9 [mg/dL] [rounded].

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Table R.1.1.3.2.1.4: 1 Responder analysis for KCCQ-CSS 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 LVEF [%]												0.1695
< 50	929	285	30.7	958	226	23.6	0.80	(0.69,0.92)	0.0022	0.72	(0.59,0.89)	
>= 50	1940	594	30.6	1928	536	27.8	0.90	(0.82,0.99)	0.0304	0.85	(0.74,0.99)	
Baseline LVEF [%]												0.0177°/ 0.0252
<50	929	285	30.7	958	226	23.6	0.80	(0.69,0.92)	0.0022	0.72	(0.59,0.89)	
50 to <60	992	323	32.6	988	261	26.4	0.81	(0.70,0.92)	0.0014	0.72	(0.59,0.88)	
>=60	948	271	28.6	940	275	29.3	1.01	(0.88,1.16)	0.8577	1.02	(0.83,1.25)	
Baseline NT-proBNP [pg/mL] (</>=median² by atrial fibrillation/flutter status)												0.6121
< median	1464	427	29.2	1430	364	25.5	0.88	(0.78,0.99)	0.0335	0.83	(0.70,0.99)	
>= median	1401	451	32.2	1453	396	27.3	0.85	(0.76,0.94)	0.0028	0.78	(0.66,0.92)	
Baseline uric acid [mg/dL] (tertiles³)												0.4615°/ 0.6019
<T1	937	272	29.0	930	236	25.4	0.89	(0.77,1.03)	0.1105	0.84	(0.68,1.04)	
>=T1 and <T2	931	271	29.1	997	262	26.3	0.91	(0.79,1.05)	0.1916	0.88	(0.71,1.08)	
>=T2	971	320	33.0	933	256	27.4	0.83	(0.72,0.95)	0.0056	0.75	(0.61,0.92)	
Baseline use of MRA												0.9567
No	1788	548	30.6	1814	480	26.5	0.87	(0.78,0.96)	0.0058	0.81	(0.70,0.94)	
Yes	1081	331	30.6	1072	282	26.3	0.86	(0.76,0.98)	0.0279	0.81	(0.67,0.98)	
Baseline use of ACE-inhibitor, ARB or ARNi												0.3743
No	558	189	33.9	543	151	27.8	0.81	(0.68,0.96)	0.0157	0.72	(0.55,0.94)	
Yes	2311	690	29.9	2343	611	26.1	0.88	(0.81,0.97)	0.0063	0.83	(0.73,0.95)	

* 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, °:Trend test.
^ Models contain terms age, baseline eGFR (CKD-EPI), baseline LVEF, Baseline KCCQ-CSS, 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.

Analysis is based on study 1245.110.
For discontinued subjects, last available value was used. For completing subjects, last value up to last treatment intake + 7 days was used.
^^ Patients with NYHA class I are counted in subgroup NYHA class II. ¹ Baseline SBP median: 132 [mmHg].
² Baseline NT-proBNP median for patients with history of atrial fibrillation or atrial flutter: 1354 [pg/mL].
² Baseline NT-proBNP median for patients without history of atrial fibrillation or atrial flutter: 614 [pg/mL].
³ Baseline uric acid tertile cut-offs for males are T1: 5.9 T2: 7.5 [mg/dL] [rounded].
³ Baseline uric acid tertile cut-offs for females are T1: 5.4 T2: 6.9 [mg/dL] [rounded].

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Table R.1.1.3.2.1.4: 2 Responder analysis for KCCQ-CSS change from baseline to last value during planned treatment period >= 5 points (improvement) overall and by subgroup - RS (OC-AD)

Subgroup	Placebo			Empa 10mg			Empa 10mg vs Placebo					
Category	N	n	%	N	n	%	Risk ratio *	(95% CI)	p-value	Odds ratio ***	(95% CI)	p-value **
Overall	2869	1144	39.9	2886	1267	43.9	1.08	(1.02,1.14)	0.0085	1.19	(1.06,1.34)	
Sex												0.2834
Male	1588	581	36.6	1597	649	40.6	1.11	(1.03,1.21)	0.0098	1.22	(1.05,1.43)	
Female	1281	563	44.0	1289	618	47.9	1.05	(0.97,1.13)	0.2737	1.16	(0.97,1.37)	
Age [years]												0.3931
<70	1038	451	43.4	1030	487	47.3	1.05	(0.96,1.14)	0.3044	1.14	(0.94,1.38)	
>=70	1831	693	37.8	1856	780	42.0	1.10	(1.02,1.19)	0.0110	1.23	(1.06,1.42)	
Region												0.8066
North America	346	144	41.6	344	139	40.4	1.02	(0.86,1.21)	0.8455	1.04	(0.75,1.45)	
Latin America	724	345	47.7	730	407	55.8	1.13	(1.02,1.24)	0.0138	1.38	(1.10,1.74)	
Europe	1301	492	37.8	1309	533	40.7	1.06	(0.97,1.16)	0.2329	1.13	(0.95,1.33)	
Asia	330	90	27.3	328	102	31.1	1.13	(0.90,1.41)	0.2965	1.21	(0.85,1.72)	
Other	168	73	43.5	175	86	49.1	1.07	(0.87,1.33)	0.5177	1.22	(0.77,1.94)	
OECD member												0.3182
No	789	372	47.1	818	455	55.6	1.12	(1.02,1.23)	0.0140	1.37	(1.11,1.70)	
Yes	2080	772	37.1	2068	812	39.3	1.06	(0.98,1.14)	0.1380	1.12	(0.98,1.29)	
Baseline NYHA												0.7931
II^^	2359	900	38.2	2355	988	42.0	1.08	(1.02,1.16)	0.0154	1.19	(1.05,1.35)	
III/IV	510	244	47.8	531	279	52.5	1.06	(0.95,1.20)	0.2898	1.20	(0.92,1.57)	
Baseline Diabetes status												0.1998
Diabetic	1407	562	39.9	1400	633	45.2	1.12	(1.03,1.22)	0.0059	1.28	(1.08,1.51)	
Non-Diabetic	1462	582	39.8	1486	634	42.7	1.04	(0.96,1.13)	0.3346	1.11	(0.95,1.31)	

* 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, °:Trend test.
^ Models contain terms age, baseline eGFR (CKD-EPI), baseline LVEF, Baseline KCCQ-CSS, 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.

Analysis is based on study 1245.110.
For discontinued subjects, last available value was used. For completing subjects, last value up to last treatment intake + 7 days was used.
^^ Patients with NYHA class I are counted in subgroup NYHA class II. [1] Baseline SBP median: 132 [mmHg].
[2] Baseline NT-proBNP median for patients with history of atrial fibrillation or atrial flutter: 1354 [pg/mL].
[2] Baseline NT-proBNP median for patients without history of atrial fibrillation or atrial flutter: 614 [pg/mL].
[3] Baseline uric acid tertile cut-offs for males are T1: 5.9 T2: 7.5 [mg/dL] [rounded].
[3] Baseline uric acid tertile cut-offs for females are T1: 5.4 T2: 6.9 [mg/dL] [rounded].

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Table R.1.1.3.2.1.4: 2 Responder analysis for KCCQ-CSS 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 Diabetes status												0.4841°/ 0.2715
Diabetic	1407	562	39.9	1400	633	45.2	1.12	(1.03,1.22)	0.0059	1.28	(1.08,1.51)	
Pre-Diabetes	940	377	40.1	974	402	41.3	1.01	(0.91,1.12)	0.8604	1.03	(0.85,1.26)	
Normal (no pre-diabetes)	522	205	39.3	512	232	45.3	1.10	(0.96,1.25)	0.1581	1.28	(0.98,1.68)	
Baseline BMI [kg/m²]												0.3385
<30	1563	597	38.2	1591	652	41.0	1.05	(0.97,1.14)	0.2265	1.12	(0.96,1.30)	
>=30	1306	547	41.9	1295	615	47.5	1.11	(1.02,1.21)	0.0116	1.29	(1.09,1.52)	
Baseline eGFR (CKD-EPI) [mL/min/1.73m²]												0.3089
>=60	1449	571	39.4	1445	655	45.3	1.11	(1.03,1.20)	0.0086	1.27	(1.08,1.49)	
<60	1420	573	40.4	1441	612	42.5	1.05	(0.97,1.14)	0.2621	1.12	(0.95,1.32)	
History of HHF (in the last 12 months)												0.5600
No	2233	900	40.3	2228	980	44.0	1.07	(1.00,1.14)	0.0391	1.17	(1.03,1.33)	
Yes	636	244	38.4	658	287	43.6	1.12	(0.99,1.26)	0.0833	1.27	(1.00,1.62)	
Baseline SBP (</>= median¹)												0.5419
< median	1414	570	40.3	1444	622	43.1	1.06	(0.98,1.15)	0.1553	1.16	(0.98,1.36)	
>= median	1455	574	39.5	1442	645	44.7	1.10	(1.01,1.19)	0.0218	1.23	(1.05,1.44)	
History of atrial fibrillation or atrial flutter												0.8567
No	1364	585	42.9	1364	643	47.1	1.07	(0.99,1.16)	0.0706	1.18	(1.00,1.40)	
Yes	1502	557	37.1	1519	623	41.0	1.09	(1.00,1.18)	0.0518	1.20	(1.03,1.41)	

* 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, °:Trend test.
^ Models contain terms age, baseline eGFR (CKD-EPI), baseline LVEF, Baseline KCCQ-CSS, 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.

Analysis is based on study 1245.110.
For discontinued subjects, last available value was used. For completing subjects, last value up to last treatment intake + 7 days was used.
^^ Patients with NYHA class I are counted in subgroup NYHA class II. ¹ Baseline SBP median: 132 [mmHg].
² Baseline NT-proBNP median for patients with history of atrial fibrillation or atrial flutter: 1354 [pg/mL].
² Baseline NT-proBNP median for patients without history of atrial fibrillation or atrial flutter: 614 [pg/mL].
³ Baseline uric acid tertile cut-offs for males are T1: 5.9 T2: 7.5 [mg/dL] [rounded].
³ Baseline uric acid tertile cut-offs for females are T1: 5.4 T2: 6.9 [mg/dL] [rounded].

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Table R.1.1.3.2.1.4: 2 Responder analysis for KCCQ-CSS 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 LVEF [%]												0.3054
< 50	929	358	38.5	958	442	46.1	1.13	(1.02,1.24)	0.0186	1.29	(1.06,1.58)	
>= 50	1940	786	40.5	1928	825	42.8	1.06	(0.99,1.13)	0.1222	1.14	(0.99,1.32)	
Baseline LVEF [%]												0.0240°/ 0.0155
<50	929	358	38.5	958	442	46.1	1.13	(1.02,1.24)	0.0188	1.29	(1.06,1.58)	
50 to <60	992	385	38.8	988	439	44.4	1.16	(1.05,1.28)	0.0026	1.38	(1.13,1.68)	
>=60	948	401	42.3	940	386	41.1	0.96	(0.87,1.06)	0.3954	0.94	(0.77,1.15)	
Baseline NT-proBNP [pg/mL] (</>=median[2] by atrial fibrillation/flutter status)												0.4643
< median	1464	583	39.8	1430	620	43.4	1.06	(0.98,1.15)	0.1758	1.14	(0.97,1.35)	
>= median	1401	559	39.9	1453	646	44.5	1.10	(1.02,1.20)	0.0179	1.24	(1.06,1.46)	
Baseline uric acid [mg/dL] (tertiles[3])												0.3053°/ 0.5649
<T1	937	374	39.9	930	390	41.9	1.03	(0.93,1.14)	0.6046	1.06	(0.87,1.30)	
>=T1 and <T2	931	360	38.7	997	432	43.3	1.09	(0.98,1.20)	0.1049	1.19	(0.98,1.46)	
>=T2	971	400	41.2	933	432	46.3	1.11	(1.00,1.22)	0.0429	1.29	(1.06,1.57)	
Baseline use of MRA												0.5067
No	1788	713	39.9	1814	786	43.3	1.06	(0.99,1.14)	0.0961	1.16	(1.00,1.34)	
Yes	1081	431	39.9	1072	481	44.9	1.11	(1.01,1.22)	0.0335	1.25	(1.04,1.51)	
Baseline use of ACE-inhibitor, ARB or ARNi												0.5991
No	558	215	38.5	543	230	42.4	1.11	(0.97,1.28)	0.1144	1.29	(0.99,1.67)	
Yes	2311	929	40.2	2343	1037	44.3	1.07	(1.01,1.14)	0.0328	1.17	(1.03,1.33)	

* 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, °:Trend test.
^ Models contain terms age, baseline eGFR (CKD-EPI), baseline LVEF, Baseline KCCQ-CSS, 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.

Analysis is based on study 1245.110.
For discontinued subjects, last available value was used. For completing subjects, last value up to last treatment intake + 7 days was used.
^^ Patients with NYHA class I are counted in subgroup NYHA class II. [1] Baseline SBP median: 132 [mmHg].
[2] Baseline NT-proBNP median for patients with history of atrial fibrillation or atrial flutter: 1354 [pg/mL].
[2] Baseline NT-proBNP median for patients without history of atrial fibrillation or atrial flutter: 614 [pg/mL].
[3] Baseline uric acid tertile cut-offs for males are T1: 5.9 T2: 7.5 [mg/dL] [rounded].
[3] Baseline uric acid tertile cut-offs for females are T1: 5.4 T2: 6.9 [mg/dL] [rounded].

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R.1.1.3.2.1.5 KCCQ Clinical Summary Score responder analysis (15 points)

Table R.1.1.3.2.1.5: 1 Responder analysis for KCCQ-CSS change from baseline to last value during planned treatment period <= -15 points (deterioration) overall and by subgroup - RS (OC-AD)

Subgroup	Placebo			Empa 10mg			Empa 10mg vs Placebo					
Category	N	n	%	N	n	%	Risk ratio *	(95% CI)	p-value	Odds ratio ***	(95% CI)	p-value **
Overall	2869	446	15.5	2886	348	12.1	0.78	(0.68,0.88)	0.0001	0.74	(0.63,0.86)	
Sex												0.3933
Male	1588	248	15.6	1597	204	12.8	0.82	(0.69,0.97)	0.0191	0.78	(0.64,0.96)	
Female	1281	198	15.5	1289	144	11.2	0.73	(0.60,0.89)	0.0015	0.69	(0.54,0.87)	
Age [years]												0.2807
<70	1038	123	11.8	1030	105	10.2	0.87	(0.68,1.10)	0.2462	0.85	(0.64,1.12)	
>=70	1831	323	17.6	1856	243	13.1	0.74	(0.64,0.86)	<0.0001	0.69	(0.58,0.83)	
Region												0.2245
North America	346	52	15.0	344	50	14.5	0.93	(0.65,1.33)	0.6923	0.92	(0.60,1.41)	
Latin America	724	86	11.9	730	60	8.2	0.72	(0.53,0.98)	0.0343	0.68	(0.48,0.97)	
Europe	1301	222	17.1	1309	185	14.1	0.83	(0.69,0.99)	0.0341	0.79	(0.64,0.99)	
Asia	330	46	13.9	328	34	10.4	0.74	(0.49,1.12)	0.1603	0.71	(0.44,1.14)	
Other	168	40	23.8	175	19	10.9	0.47	(0.29,0.77)	0.0029	0.39	(0.21,0.72)	
OECD member												0.0311
No	789	113	14.3	818	67	8.2	0.59	(0.45,0.79)	0.0003	0.55	(0.40,0.76)	
Yes	2080	333	16.0	2068	281	13.6	0.84	(0.73,0.97)	0.0206	0.81	(0.68,0.97)	
Baseline NYHA												0.0853
II^^	2359	356	15.1	2355	291	12.4	0.82	(0.71,0.94)	0.0056	0.79	(0.66,0.93)	
III/IV	510	90	17.6	531	57	10.7	0.61	(0.46,0.83)	0.0013	0.55	(0.38,0.80)	
Baseline Diabetes status												0.6966
Diabetic	1407	223	15.8	1400	179	12.8	0.80	(0.67,0.95)	0.0127	0.76	(0.61,0.95)	
Non-Diabetic	1462	223	15.3	1486	169	11.4	0.76	(0.63,0.91)	0.0032	0.72	(0.58,0.89)	

* 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, °:Trend test.
^ Models contain terms age, baseline eGFR (CKD-EPI), baseline LVEF, Baseline KCCQ-CSS, 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.

Analysis is based on study 1245.110.
For discontinued subjects, last available value was used. For completing subjects, last value up to last treatment intake + 7 days was used.
^^ Patients with NYHA class I are counted in subgroup NYHA class II. [1] Baseline SBP median: 132 [mmHg].
[2] Baseline NT-proBNP median for patients with history of atrial fibrillation or atrial flutter: 1354 [pg/mL].
[2] Baseline NT-proBNP median for patients without history of atrial fibrillation or atrial flutter: 614 [pg/mL].
[3] Baseline uric acid tertile cut-offs for males are T1: 5.9 T2: 7.5 [mg/dL] [rounded].
[3] Baseline uric acid tertile cut-offs for females are T1: 5.4 T2: 6.9 [mg/dL] [rounded].

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Table R.1.1.3.2.1.5: 1 Responder analysis for KCCQ-CSS 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 Diabetes status												0.3983°/ 0.5230
Diabetic	1407	223	15.8	1400	179	12.8	0.80	(0.67,0.95)	0.0127	0.76	(0.61,0.95)	
Pre-Diabetes	940	140	14.9	974	117	12.0	0.81	(0.65,1.02)	0.0757	0.78	(0.60,1.02)	
Normal (no pre-diabetes)	522	83	15.9	512	52	10.2	0.66	(0.48,0.91)	0.0102	0.61	(0.42,0.89)	
Baseline BMI [kg/m²]												0.7498
<30	1563	230	14.7	1591	179	11.3	0.76	(0.64,0.92)	0.0035	0.73	(0.59,0.90)	
>=30	1306	216	16.5	1295	169	13.1	0.80	(0.67,0.96)	0.0145	0.76	(0.61,0.95)	
Baseline eGFR (CKD-EPI) [mL/min/1.73m²]												0.4385
>=60	1449	200	13.8	1445	142	9.8	0.73	(0.60,0.89)	0.0022	0.70	(0.55,0.88)	
<60	1420	246	17.3	1441	206	14.3	0.81	(0.69,0.96)	0.0142	0.77	(0.63,0.95)	
History of HHF (in the last 12 months)												0.5607
No	2233	331	14.8	2228	259	11.6	0.79	(0.68,0.92)	0.0023	0.76	(0.64,0.91)	
Yes	636	115	18.1	658	89	13.5	0.73	(0.57,0.93)	0.0119	0.68	(0.50,0.92)	
Baseline SBP (</>= median¹)												0.5474
< median	1414	205	14.5	1444	172	11.9	0.81	(0.67,0.98)	0.0273	0.78	(0.62,0.97)	
>= median	1455	241	16.6	1442	176	12.2	0.75	(0.63,0.89)	0.0014	0.71	(0.57,0.87)	
History of atrial fibrillation or atrial flutter												0.8550
No	1364	194	14.2	1364	145	10.6	0.76	(0.63,0.93)	0.0080	0.73	(0.58,0.92)	
Yes	1502	252	16.8	1519	202	13.3	0.78	(0.66,0.93)	0.0042	0.74	(0.61,0.91)	

* 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, °:Trend test.
^ Models contain terms age, baseline eGFR (CKD-EPI), baseline LVEF, Baseline KCCQ-CSS, 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.

Analysis is based on study 1245.110.
For discontinued subjects, last available value was used. For completing subjects, last value up to last treatment intake + 7 days was used.
^^ Patients with NYHA class I are counted in subgroup NYHA class II. ¹ Baseline SBP median: 132 [mmHg].
² Baseline NT-proBNP median for patients with history of atrial fibrillation or atrial flutter: 1354 [pg/mL].
² Baseline NT-proBNP median for patients without history of atrial fibrillation or atrial flutter: 614 [pg/mL].
³ Baseline uric acid tertile cut-offs for males are T1: 5.9 T2: 7.5 [mg/dL] [rounded].
³ Baseline uric acid tertile cut-offs for females are T1: 5.4 T2: 6.9 [mg/dL] [rounded].

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Table R.1.1.3.2.1.5: 1 Responder analysis for KCCQ-CSS 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 LVEF [%]												0.3752
< 50	929	134	14.4	958	94	9.8	0.71	(0.56,0.91)	0.0060	0.67	(0.50,0.89)	
>= 50	1940	312	16.1	1928	254	13.2	0.81	(0.70,0.94)	0.0054	0.77	(0.64,0.93)	
Baseline LVEF [%]												0.1472°/ 0.2761
<50	929	134	14.4	958	94	9.8	0.71	(0.56,0.91)	0.0060	0.67	(0.50,0.89)	
50 to <60	992	168	16.9	988	123	12.4	0.73	(0.59,0.90)	0.0034	0.68	(0.53,0.88)	
>=60	948	144	15.2	940	131	13.9	0.90	(0.72,1.11)	0.3261	0.88	(0.68,1.14)	
Baseline NT-proBNP [pg/mL] (</>=median² by atrial fibrillation/flutter status)												0.6414
< median	1464	221	15.1	1430	171	12.0	0.80	(0.67,0.96)	0.0162	0.76	(0.61,0.95)	
>= median	1401	225	16.1	1453	176	12.1	0.75	(0.63,0.90)	0.0018	0.71	(0.57,0.88)	
Baseline uric acid [mg/dL] (tertiles³)												0.7739°/ 0.4398
<T1	937	144	15.4	930	101	10.9	0.72	(0.57,0.91)	0.0067	0.68	(0.52,0.90)	
>=T1 and <T2	931	130	14.0	997	123	12.3	0.89	(0.71,1.11)	0.2956	0.87	(0.66,1.14)	
>=T2	971	164	16.9	933	122	13.1	0.76	(0.62,0.94)	0.0125	0.72	(0.55,0.93)	
Baseline use of MRA												0.6411
No	1788	279	15.6	1814	225	12.4	0.80	(0.68,0.93)	0.0054	0.76	(0.63,0.92)	
Yes	1081	167	15.4	1072	123	11.5	0.75	(0.60,0.92)	0.0070	0.71	(0.55,0.91)	
Baseline use of ACE-inhibitor, ARB or ARNi												0.0421
No	558	103	18.5	543	61	11.2	0.60	(0.45,0.80)	0.0004	0.53	(0.37,0.75)	
Yes	2311	343	14.8	2343	287	12.2	0.83	(0.72,0.96)	0.0119	0.80	(0.68,0.95)	

* 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, °:Trend test.
^ Models contain terms age, baseline eGFR (CKD-EPI), baseline LVEF, Baseline KCCQ-CSS, 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.

Analysis is based on study 1245.110.
For discontinued subjects, last available value was used. For completing subjects, last value up to last treatment intake + 7 days was used.
^^ Patients with NYHA class I are counted in subgroup NYHA class II. ¹ Baseline SBP median: 132 [mmHg].
² Baseline NT-proBNP median for patients with history of atrial fibrillation or atrial flutter: 1354 [pg/mL].
² Baseline NT-proBNP median for patients without history of atrial fibrillation or atrial flutter: 614 [pg/mL].
³ Baseline uric acid tertile cut-offs for males are T1: 5.9 T2: 7.5 [mg/dL] [rounded].
³ Baseline uric acid tertile cut-offs for females are T1: 5.4 T2: 6.9 [mg/dL] [rounded].

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Table R.1.1.3.2.1.5: 2 Responder analysis for KCCQ-CSS change from baseline to last value during planned treatment period >= 15 points (improvement) overall and by subgroup - RS (OC-AD)

Subgroup	Placebo			Empa 10mg			Empa 10mg vs Placebo					
Category	N	n	%	N	n	%	Risk ratio *	(95% CI)	p-value	Odds ratio ***	(95% CI)	p-value **
Overall	2869	569	19.8	2886	669	23.2	1.11	(1.01,1.22)	0.0269	1.22	(1.06,1.41)	
Sex												0.6770
Male	1588	274	17.3	1597	311	19.5	1.13	(0.99,1.30)	0.0703	1.19	(0.98,1.46)	
Female	1281	295	23.0	1289	358	27.8	1.09	(0.96,1.24)	0.1867	1.25	(1.01,1.53)	
Age [years]												0.9167
<70	1038	222	21.4	1030	266	25.8	1.10	(0.95,1.28)	0.1889	1.25	(0.99,1.58)	
>=70	1831	347	19.0	1856	403	21.7	1.11	(0.99,1.25)	0.0737	1.20	(1.00,1.44)	
Region												0.5798
North America	346	65	18.8	344	55	16.0	0.93	(0.68,1.26)	0.6219	0.90	(0.58,1.40)	
Latin America	724	208	28.7	730	256	35.1	1.13	(0.98,1.31)	0.0980	1.34	(1.03,1.73)	
Europe	1301	231	17.8	1309	264	20.2	1.08	(0.93,1.26)	0.2850	1.14	(0.92,1.42)	
Asia	330	31	9.4	328	43	13.1	1.33	(0.89,1.99)	0.1659	1.43	(0.85,2.41)	
Other	168	34	20.2	175	51	29.1	1.26	(0.90,1.77)	0.1696	1.63	(0.93,2.88)	
OECD member												0.0518
No	789	201	25.5	818	288	35.2	1.24	(1.08,1.43)	0.0031	1.58	(1.24,2.03)	
Yes	2080	368	17.7	2068	381	18.4	1.03	(0.91,1.16)	0.6126	1.06	(0.89,1.27)	
Baseline NYHA												0.3336
II^^	2359	414	17.5	2355	489	20.8	1.14	(1.02,1.27)	0.0177	1.24	(1.05,1.46)	
III/IV	510	155	30.4	531	180	33.9	1.03	(0.87,1.23)	0.7326	1.15	(0.85,1.55)	
Baseline Diabetes status												0.2430
Diabetic	1407	295	21.0	1400	353	25.2	1.17	(1.03,1.33)	0.0168	1.33	(1.08,1.62)	
Non-Diabetic	1462	274	18.7	1486	316	21.3	1.05	(0.92,1.20)	0.4917	1.12	(0.91,1.37)	

* 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, °:Trend test.
^ Models contain terms age, baseline eGFR (CKD-EPI), baseline LVEF, Baseline KCCQ-CSS, 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.

Analysis is based on study 1245.110.
For discontinued subjects, last available value was used. For completing subjects, last value up to last treatment intake + 7 days was used.
^^ Patients with NYHA class I are counted in subgroup NYHA class II. [1] Baseline SBP median: 132 [mmHg].
[2] Baseline NT-proBNP median for patients with history of atrial fibrillation or atrial flutter: 1354 [pg/mL].
[2] Baseline NT-proBNP median for patients without history of atrial fibrillation or atrial flutter: 614 [pg/mL].
[3] Baseline uric acid tertile cut-offs for males are T1: 5.9 T2: 7.5 [mg/dL] [rounded].
[3] Baseline uric acid tertile cut-offs for females are T1: 5.4 T2: 6.9 [mg/dL] [rounded].

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Table R.1.1.3.2.1.5: 2 Responder analysis for KCCQ-CSS 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 Diabetes status												0.4713°/ 0.3775
Diabetic	1407	295	21.0	1400	353	25.2	1.17	(1.03,1.33)	0.0167	1.33	(1.08,1.62)	
Pre-Diabetes	940	185	19.7	974	204	20.9	1.01	(0.86,1.19)	0.9022	1.03	(0.80,1.32)	
Normal (no pre-diabetes)	522	89	17.0	512	112	21.9	1.12	(0.89,1.41)	0.3166	1.31	(0.92,1.85)	
Baseline BMI [kg/m²]												0.2489
<30	1563	290	18.6	1591	325	20.4	1.05	(0.92,1.19)	0.4569	1.08	(0.89,1.32)	
>=30	1306	279	21.4	1295	344	26.6	1.17	(1.03,1.33)	0.0188	1.38	(1.12,1.70)	
Baseline eGFR (CKD-EPI) [mL/min/1.73m²]												0.1359
>=60	1449	271	18.7	1445	348	24.1	1.19	(1.05,1.35)	0.0081	1.37	(1.12,1.68)	
<60	1420	298	21.0	1441	321	22.3	1.04	(0.91,1.18)	0.6013	1.08	(0.88,1.33)	
History of HHF (in the last 12 months)												0.9510
No	2233	442	19.8	2228	514	23.1	1.11	(1.00,1.23)	0.0536	1.21	(1.03,1.43)	
Yes	636	127	20.0	658	155	23.6	1.12	(0.92,1.36)	0.2771	1.25	(0.92,1.69)	
Baseline SBP (</>= median¹)												0.0665
< median	1414	299	21.1	1444	320	22.2	1.02	(0.90,1.16)	0.7827	1.06	(0.86,1.30)	
>= median	1455	270	18.6	1442	349	24.2	1.21	(1.06,1.38)	0.0045	1.40	(1.14,1.72)	
History of atrial fibrillation or atrial flutter												0.4033
No	1364	301	22.1	1364	337	24.7	1.07	(0.94,1.21)	0.3169	1.14	(0.93,1.40)	
Yes	1502	268	17.8	1519	332	21.9	1.15	(1.01,1.32)	0.0348	1.30	(1.06,1.59)	

* 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, °:Trend test.
^ Models contain terms age, baseline eGFR (CKD-EPI), baseline LVEF, Baseline KCCQ-CSS, 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.

Analysis is based on study 1245.110.
For discontinued subjects, last available value was used. For completing subjects, last value up to last treatment intake + 7 days was used.
^^ Patients with NYHA class I are counted in subgroup NYHA class II. ¹ Baseline SBP median: 132 [mmHg].
² Baseline NT-proBNP median for patients with history of atrial fibrillation or atrial flutter: 1354 [pg/mL].
² Baseline NT-proBNP median for patients without history of atrial fibrillation or atrial flutter: 614 [pg/mL].
³ Baseline uric acid tertile cut-offs for males are T1: 5.9 T2: 7.5 [mg/dL] [rounded].
³ Baseline uric acid tertile cut-offs for females are T1: 5.4 T2: 6.9 [mg/dL] [rounded].

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Table R.1.1.3.2.1.5: 2 Responder analysis for KCCQ-CSS 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 LVEF [%]												0.3423
< 50	929	180	19.4	958	248	25.9	1.18	(1.01,1.37)	0.0383	1.33	(1.04,1.71)	
>= 50	1940	389	20.1	1928	421	21.8	1.07	(0.96,1.20)	0.2297	1.16	(0.97,1.39)	
Baseline LVEF [%]												0.1200°/ 0.2224
<50	929	180	19.4	958	248	25.9	1.18	(1.01,1.37)	0.0388	1.33	(1.04,1.71)	
50 to <60	992	199	20.1	988	226	22.9	1.17	(1.00,1.36)	0.0562	1.34	(1.05,1.72)	
>=60	948	190	20.0	940	195	20.7	0.98	(0.83,1.16)	0.8244	1.00	(0.77,1.29)	
Baseline NT-proBNP [pg/mL] (</>=median[2] by atrial fibrillation/flutter status)												0.1767
< median	1464	278	19.0	1430	342	23.9	1.18	(1.04,1.34)	0.0126	1.37	(1.11,1.68)	
>= median	1401	291	20.8	1453	327	22.5	1.04	(0.91,1.18)	0.5486	1.09	(0.89,1.33)	
Baseline uric acid [mg/dL] (tertiles[3])												0.7267°/ 0.9344
<T1	937	177	18.9	930	208	22.4	1.13	(0.96,1.33)	0.1388	1.23	(0.95,1.58)	
>=T1 and <T2	931	179	19.2	997	225	22.6	1.10	(0.93,1.29)	0.2630	1.18	(0.92,1.51)	
>=T2	971	206	21.2	933	229	24.5	1.09	(0.93,1.27)	0.3094	1.22	(0.96,1.56)	
Baseline use of MRA												0.5685
No	1788	342	19.1	1814	402	22.2	1.09	(0.96,1.22)	0.1734	1.19	(0.99,1.43)	
Yes	1081	227	21.0	1072	267	24.9	1.15	(0.99,1.33)	0.0669	1.26	(1.00,1.59)	
Baseline use of ACE-inhibitor, ARB or ARNi												0.3742
No	558	109	19.5	543	130	23.9	1.21	(0.98,1.49)	0.0751	1.44	(1.04,2.00)	
Yes	2311	460	19.9	2343	539	23.0	1.09	(0.98,1.20)	0.1090	1.17	(1.00,1.38)	

* 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, °:Trend test.
^ Models contain terms age, baseline eGFR (CKD-EPI), baseline LVEF, Baseline KCCQ-CSS, 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.

Analysis is based on study 1245.110.
For discontinued subjects, last available value was used. For completing subjects, last value up to last treatment intake + 7 days was used.
^^ Patients with NYHA class I are counted in subgroup NYHA class II. [1] Baseline SBP median: 132 [mmHg].
[2] Baseline NT-proBNP median for patients with history of atrial fibrillation or atrial flutter: 1354 [pg/mL].
[2] Baseline NT-proBNP median for patients without history of atrial fibrillation or atrial flutter: 614 [pg/mL].
[3] Baseline uric acid tertile cut-offs for males are T1: 5.9 T2: 7.5 [mg/dL] [rounded].
[3] Baseline uric acid tertile cut-offs for females are T1: 5.4 T2: 6.9 [mg/dL] [rounded].

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R.1.1.3.2.1.6 KCCQ Total Symptoms Score responder analysis (5 points)

Table R.1.1.3.2.1.6: 1 Responder analysis for KCCQ-TSS change from baseline to last value during planned treatment period <= -5 points (deterioration) overall and by subgroup - RS (OC-AD)

Subgroup	Placebo			Empa 10mg			Empa 10mg vs Placebo					
Category	N	n	%	N	n	%	Risk ratio *	(95% CI)	p-value	Odds ratio ***	(95% CI)	p-value **
Overall	2869	850	29.6	2886	703	24.4	0.84	(0.77,0.91)	<0.0001	0.77	(0.69,0.87)	
Sex												0.7412
Male	1588	477	30.0	1597	401	25.1	0.85	(0.76,0.95)	0.0033	0.78	(0.67,0.92)	
Female	1281	373	29.1	1289	302	23.4	0.82	(0.73,0.93)	0.0026	0.76	(0.63,0.91)	
Age [years]												0.0283
<70	1038	255	24.6	1030	236	22.9	0.96	(0.82,1.12)	0.5860	0.94	(0.77,1.16)	
>=70	1831	595	32.5	1856	467	25.2	0.78	(0.71,0.86)	<0.0001	0.70	(0.60,0.81)	
Region												0.3016
North America	346	103	29.8	344	102	29.7	1.00	(0.80,1.25)	0.9835	0.99	(0.71,1.39)	
Latin America	724	165	22.8	730	138	18.9	0.85	(0.70,1.03)	0.0993	0.81	(0.62,1.05)	
Europe	1301	419	32.2	1309	338	25.8	0.82	(0.73,0.92)	0.0008	0.74	(0.62,0.88)	
Asia	330	101	30.6	328	85	25.9	0.85	(0.67,1.08)	0.1887	0.79	(0.56,1.12)	
Other	168	62	36.9	175	40	22.9	0.64	(0.46,0.90)	0.0103	0.51	(0.32,0.84)	
OECD member												0.1453
No	789	204	25.9	818	153	18.7	0.75	(0.62,0.89)	0.0014	0.67	(0.53,0.86)	
Yes	2080	646	31.1	2068	550	26.6	0.87	(0.79,0.95)	0.0028	0.81	(0.71,0.93)	
Baseline NYHA												0.2860
II^^	2359	697	29.5	2355	585	24.8	0.85	(0.78,0.94)	0.0007	0.80	(0.70,0.91)	
III/IV	510	153	30.0	531	118	22.2	0.76	(0.62,0.93)	0.0064	0.67	(0.50,0.90)	
Baseline Diabetes status												0.9863
Diabetic	1407	421	29.9	1400	345	24.6	0.84	(0.74,0.94)	0.0034	0.77	(0.65,0.92)	
Non-Diabetic	1462	429	29.3	1486	358	24.1	0.84	(0.74,0.94)	0.0029	0.77	(0.65,0.92)	

* 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, °:Trend test.
^ Models contain terms age, baseline eGFR (CKD-EPI), baseline LVEF, Baseline KCCQ-TSS, 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.

Analysis is based on study 1245.110.
For discontinued subjects, last available value was used. For completing subjects, last value up to last treatment intake + 7 days was used.
^^ Patients with NYHA class I are counted in subgroup NYHA class II. [1] Baseline SBP median: 132 [mmHg].
[2] Baseline NT-proBNP median for patients with history of atrial fibrillation or atrial flutter: 1354 [pg/mL].
[2] Baseline NT-proBNP median for patients without history of atrial fibrillation or atrial flutter: 614 [pg/mL].
[3] Baseline uric acid tertile cut-offs for males are T1: 5.9 T2: 7.5 [mg/dL] [rounded].
[3] Baseline uric acid tertile cut-offs for females are T1: 5.4 T2: 6.9 [mg/dL] [rounded].

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Table R.1.1.3.2.1.6: 1 Responder analysis for KCCQ-TSS 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 Diabetes status												0.7710°/ 0.8458
Diabetic	1407	421	29.9	1400	345	24.6	0.84	(0.74,0.94)	0.0034	0.77	(0.65,0.92)	
Pre-Diabetes	940	277	29.5	974	244	25.1	0.86	(0.74,0.99)	0.0347	0.80	(0.65,0.98)	
Normal (no pre-diabetes)	522	152	29.1	512	114	22.3	0.80	(0.65,0.98)	0.0284	0.72	(0.54,0.96)	
Baseline BMI [kg/m²]												0.5153
<30	1563	462	29.6	1591	402	25.3	0.86	(0.77,0.96)	0.0075	0.80	(0.68,0.95)	
>=30	1306	388	29.7	1295	301	23.2	0.81	(0.72,0.92)	0.0012	0.74	(0.61,0.88)	
Baseline eGFR (CKD-EPI) [mL/min/1.73m²]												0.4824
>=60	1449	421	29.1	1445	329	22.8	0.81	(0.72,0.92)	0.0007	0.74	(0.62,0.88)	
<60	1420	429	30.2	1441	374	26.0	0.86	(0.77,0.97)	0.0106	0.80	(0.68,0.95)	
History of HHF (in the last 12 months)												0.2616
No	2233	633	28.3	2228	531	23.8	0.86	(0.78,0.95)	0.0021	0.80	(0.70,0.92)	
Yes	636	217	34.1	658	172	26.1	0.77	(0.66,0.91)	0.0017	0.67	(0.53,0.86)	
Baseline SBP (</>= median¹)												0.9752
< median	1414	407	28.8	1444	346	24.0	0.84	(0.74,0.94)	0.0036	0.77	(0.65,0.92)	
>= median	1455	443	30.4	1442	357	24.8	0.84	(0.75,0.94)	0.0027	0.77	(0.65,0.91)	
History of atrial fibrillation or atrial flutter												0.3742
No	1364	378	27.7	1364	322	23.6	0.87	(0.77,0.99)	0.0328	0.82	(0.69,0.98)	
Yes	1502	472	31.4	1519	381	25.1	0.81	(0.72,0.90)	0.0002	0.73	(0.62,0.86)	

* 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, °:Trend test.
^ Models contain terms age, baseline eGFR (CKD-EPI), baseline LVEF, Baseline KCCQ-TSS, 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.

Analysis is based on study 1245.110.
For discontinued subjects, last available value was used. For completing subjects, last value up to last treatment intake + 7 days was used.
^^ Patients with NYHA class I are counted in subgroup NYHA class II. ¹ Baseline SBP median: 132 [mmHg].
² Baseline NT-proBNP median for patients with history of atrial fibrillation or atrial flutter: 1354 [pg/mL].
² Baseline NT-proBNP median for patients without history of atrial fibrillation or atrial flutter: 614 [pg/mL].
³ Baseline uric acid tertile cut-offs for males are T1: 5.9 T2: 7.5 [mg/dL] [rounded].
³ Baseline uric acid tertile cut-offs for females are T1: 5.4 T2: 6.9 [mg/dL] [rounded].

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Table R.1.1.3.2.1.6: 1 Responder analysis for KCCQ-TSS 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 LVEF [%]												0.1192
< 50	929	264	28.4	958	197	20.6	0.75	(0.65,0.88)	0.0004	0.68	(0.55,0.84)	
>= 50	1940	586	30.2	1928	506	26.2	0.87	(0.79,0.96)	0.0073	0.82	(0.71,0.95)	
Baseline LVEF [%]												0.0278°/ 0.0728
<50	929	264	28.4	958	197	20.6	0.75	(0.65,0.88)	0.0004	0.68	(0.55,0.84)	
50 to <60	992	318	32.1	988	255	25.8	0.81	(0.71,0.92)	0.0018	0.72	(0.59,0.89)	
>=60	948	268	28.3	940	251	26.7	0.96	(0.83,1.10)	0.5302	0.94	(0.76,1.15)	
Baseline NT-proBNP [pg/mL] (</>=median[2] by atrial fibrillation/flutter status)												0.9286
< median	1464	430	29.4	1430	343	24.0	0.84	(0.75,0.95)	0.0039	0.78	(0.66,0.92)	
>= median	1401	419	29.9	1453	360	24.8	0.83	(0.74,0.94)	0.0023	0.77	(0.65,0.91)	
Baseline uric acid [mg/dL] (tertiles[3])												0.8734°/ 0.9855
<T1	937	283	30.2	930	232	24.9	0.85	(0.74,0.98)	0.0255	0.79	(0.64,0.97)	
>=T1 and <T2	931	267	28.7	997	238	23.9	0.85	(0.73,0.98)	0.0271	0.79	(0.64,0.98)	
>=T2	971	290	29.9	933	230	24.7	0.84	(0.72,0.96)	0.0144	0.77	(0.62,0.95)	
Baseline use of MRA												0.0481
No	1788	524	29.3	1814	465	25.6	0.89	(0.80,0.99)	0.0304	0.85	(0.73,0.98)	
Yes	1081	326	30.2	1072	238	22.2	0.75	(0.65,0.86)	<0.0001	0.66	(0.54,0.81)	
Baseline use of ACE-inhibitor, ARB or ARNi												0.0470
No	558	181	32.4	543	124	22.8	0.70	(0.58,0.85)	0.0003	0.60	(0.45,0.78)	
Yes	2311	669	28.9	2343	579	24.7	0.87	(0.80,0.96)	0.0039	0.82	(0.72,0.94)	

* 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, °:Trend test.
^ Models contain terms age, baseline eGFR (CKD-EPI), baseline LVEF, Baseline KCCQ-TSS, 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.

Analysis is based on study 1245.110.
For discontinued subjects, last available value was used. For completing subjects, last value up to last treatment intake + 7 days was used.
^^ Patients with NYHA class I are counted in subgroup NYHA class II. [1] Baseline SBP median: 132 [mmHg].
[2] Baseline NT-proBNP median for patients with history of atrial fibrillation or atrial flutter: 1354 [pg/mL].
[2] Baseline NT-proBNP median for patients without history of atrial fibrillation or atrial flutter: 614 [pg/mL].
[3] Baseline uric acid tertile cut-offs for males are T1: 5.9 T2: 7.5 [mg/dL] [rounded].
[3] Baseline uric acid tertile cut-offs for females are T1: 5.4 T2: 6.9 [mg/dL] [rounded].

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Table R.1.1.3.2.1.6: 2 Responder analysis for KCCQ-TSS 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	2869	1198	41.8	2886	1360	47.1	1.09	(1.04,1.15)	0.0012	1.25	(1.11,1.41)	
Sex												0.0432
Male	1588	605	38.1	1597	704	44.1	1.15	(1.07,1.24)	0.0002	1.32	(1.12,1.54)	
Female	1281	593	46.3	1289	656	50.9	1.03	(0.96,1.11)	0.4051	1.18	(0.98,1.40)	
Age [years]												0.0613
<70	1038	468	45.1	1030	499	48.4	1.02	(0.94,1.11)	0.5871	1.09	(0.90,1.33)	
>=70	1831	730	39.9	1856	861	46.4	1.14	(1.06,1.22)	0.0002	1.35	(1.16,1.56)	
Region												0.1919
North America	346	149	43.1	344	135	39.2	0.93	(0.79,1.09)	0.3691	0.83	(0.59,1.17)	
Latin America	724	353	48.8	730	408	55.9	1.10	(1.00,1.20)	0.0447	1.36	(1.07,1.73)	
Europe	1301	544	41.8	1309	618	47.2	1.09	(1.01,1.18)	0.0286	1.23	(1.04,1.47)	
Asia	330	88	26.7	328	112	34.1	1.25	(1.01,1.55)	0.0377	1.48	(1.03,2.13)	
Other	168	64	38.1	175	87	49.7	1.20	(0.96,1.51)	0.1110	1.63	(1.00,2.66)	
OECD member												0.4778
No	789	367	46.5	818	452	55.3	1.12	(1.03,1.23)	0.0114	1.45	(1.15,1.81)	
Yes	2080	831	40.0	2068	908	43.9	1.08	(1.01,1.15)	0.0254	1.18	(1.03,1.36)	
Baseline NYHA												0.2715
II^^	2359	932	39.5	2355	1060	45.0	1.11	(1.04,1.18)	0.0008	1.27	(1.11,1.45)	
III/IV	510	266	52.2	531	300	56.5	1.03	(0.93,1.15)	0.5462	1.17	(0.88,1.54)	
Baseline Diabetes status												0.0072
Diabetic	1407	585	41.6	1400	703	50.2	1.17	(1.09,1.26)	<0.0001	1.48	(1.25,1.75)	
Non-Diabetic	1462	613	41.9	1486	657	44.2	1.01	(0.94,1.09)	0.7027	1.07	(0.91,1.26)	

* 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, °:Trend test.
^ Models contain terms age, baseline eGFR (CKD-EPI), baseline LVEF, Baseline KCCQ-TSS, 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.

Analysis is based on study 1245.110.
For discontinued subjects, last available value was used. For completing subjects, last value up to last treatment intake + 7 days was used.
^^ Patients with NYHA class I are counted in subgroup NYHA class II. [1] Baseline SBP median: 132 [mmHg].
[2] Baseline NT-proBNP median for patients with history of atrial fibrillation or atrial flutter: 1354 [pg/mL].
[2] Baseline NT-proBNP median for patients without history of atrial fibrillation or atrial flutter: 614 [pg/mL].
[3] Baseline uric acid tertile cut-offs for males are T1: 5.9 T2: 7.5 [mg/dL] [rounded].
[3] Baseline uric acid tertile cut-offs for females are T1: 5.4 T2: 6.9 [mg/dL] [rounded].

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Table R.1.1.3.2.1.6: 2 Responder analysis for KCCQ-TSS 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 Diabetes status												0.0187°/ 0.0273
Diabetic	1407	585	41.6	1400	703	50.2	1.17	(1.09,1.26)	<0.0001	1.48	(1.25,1.75)	
Pre-Diabetes	940	391	41.6	974	421	43.2	1.01	(0.92,1.11)	0.8032	1.06	(0.86,1.30)	
Normal (no pre-diabetes)	522	222	42.5	512	236	46.1	1.02	(0.90,1.16)	0.7502	1.10	(0.83,1.45)	
Baseline BMI [kg/m²]												0.1826
<30	1563	614	39.3	1591	671	42.2	1.05	(0.98,1.14)	0.1810	1.13	(0.96,1.32)	
>=30	1306	584	44.7	1295	689	53.2	1.13	(1.05,1.22)	0.0010	1.42	(1.19,1.69)	
Baseline eGFR (CKD-EPI) [mL/min/1.73m²]												0.9585
>=60	1449	603	41.6	1445	688	47.6	1.09	(1.02,1.18)	0.0172	1.26	(1.06,1.48)	
<60	1420	595	41.9	1441	672	46.6	1.09	(1.01,1.18)	0.0247	1.25	(1.05,1.48)	
History of HHF (in the last 12 months)												0.4055
No	2233	946	42.4	2228	1052	47.2	1.08	(1.02,1.15)	0.0121	1.21	(1.06,1.39)	
Yes	636	252	39.6	658	308	46.8	1.14	(1.01,1.28)	0.0277	1.40	(1.09,1.81)	
Baseline SBP (</>= median¹)												0.2327
< median	1414	609	43.1	1444	672	46.5	1.06	(0.98,1.14)	0.1434	1.17	(0.99,1.38)	
>= median	1455	589	40.5	1442	688	47.7	1.13	(1.05,1.22)	0.0018	1.34	(1.13,1.59)	
History of atrial fibrillation or atrial flutter												0.8916
No	1364	586	43.0	1364	654	47.9	1.09	(1.01,1.17)	0.0285	1.24	(1.04,1.47)	
Yes	1502	611	40.7	1519	705	46.4	1.10	(1.02,1.18)	0.0165	1.26	(1.07,1.48)	

* 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, °:Trend test.
^ Models contain terms age, baseline eGFR (CKD-EPI), baseline LVEF, Baseline KCCQ-TSS, 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.

Analysis is based on study 1245.110.
For discontinued subjects, last available value was used. For completing subjects, last value up to last treatment intake + 7 days was used.
^^ Patients with NYHA class I are counted in subgroup NYHA class II. ¹ Baseline SBP median: 132 [mmHg].
² Baseline NT-proBNP median for patients with history of atrial fibrillation or atrial flutter: 1354 [pg/mL].
² Baseline NT-proBNP median for patients without history of atrial fibrillation or atrial flutter: 614 [pg/mL].
³ Baseline uric acid tertile cut-offs for males are T1: 5.9 T2: 7.5 [mg/dL] [rounded].
³ Baseline uric acid tertile cut-offs for females are T1: 5.4 T2: 6.9 [mg/dL] [rounded].

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Table R.1.1.3.2.1.6: 2 Responder analysis for KCCQ-TSS 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 LVEF [%]												0.9774
< 50	929	387	41.7	958	466	48.6	1.09	(1.00,1.20)	0.0591	1.25	(1.02,1.54)	
>= 50	1940	811	41.8	1928	894	46.4	1.09	(1.02,1.16)	0.0092	1.25	(1.08,1.44)	
Baseline LVEF [%]												0.6526°/ 0.7201
<50	929	387	41.7	958	466	48.6	1.09	(1.00,1.20)	0.0592	1.25	(1.02,1.54)	
50 to <60	992	410	41.3	988	453	45.9	1.12	(1.02,1.23)	0.0156	1.30	(1.06,1.60)	
>=60	948	401	42.3	940	441	46.9	1.06	(0.97,1.16)	0.2110	1.19	(0.97,1.47)	
Baseline NT-proBNP [pg/mL] (</>=median² by atrial fibrillation/flutter status)												0.7331
< median	1464	610	41.7	1430	676	47.3	1.08	(1.00,1.17)	0.0400	1.23	(1.04,1.45)	
>= median	1401	587	41.9	1453	683	47.0	1.10	(1.02,1.19)	0.0115	1.28	(1.08,1.51)	
Baseline uric acid [mg/dL] (tertiles³)												0.4106°/ 0.5252
<T1	937	387	41.3	930	423	45.5	1.07	(0.98,1.18)	0.1391	1.17	(0.95,1.44)	
>=T1 and <T2	931	390	41.9	997	467	46.8	1.05	(0.96,1.16)	0.2520	1.18	(0.97,1.45)	
>=T2	971	412	42.4	933	460	49.3	1.13	(1.03,1.24)	0.0070	1.38	(1.12,1.70)	
Baseline use of MRA												0.2333
No	1788	743	41.6	1814	830	45.8	1.06	(1.00,1.14)	0.0686	1.17	(1.01,1.36)	
Yes	1081	455	42.1	1072	530	49.4	1.14	(1.04,1.24)	0.0034	1.40	(1.15,1.70)	
Baseline use of ACE-inhibitor, ARB or ARNi												0.1942
No	558	220	39.4	543	254	46.8	1.18	(1.04,1.33)	0.0105	1.51	(1.15,1.99)	
Yes	2311	978	42.3	2343	1106	47.2	1.07	(1.01,1.14)	0.0183	1.20	(1.05,1.36)	

* 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, °:Trend test.
^ Models contain terms age, baseline eGFR (CKD-EPI), baseline LVEF, Baseline KCCQ-TSS, 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.

Analysis is based on study 1245.110.
For discontinued subjects, last available value was used. For completing subjects, last value up to last treatment intake + 7 days was used.
^^ Patients with NYHA class I are counted in subgroup NYHA class II. ¹ Baseline SBP median: 132 [mmHg].
² Baseline NT-proBNP median for patients with history of atrial fibrillation or atrial flutter: 1354 [pg/mL].
² Baseline NT-proBNP median for patients without history of atrial fibrillation or atrial flutter: 614 [pg/mL].
³ Baseline uric acid tertile cut-offs for males are T1: 5.9 T2: 7.5 [mg/dL] [rounded].
³ Baseline uric acid tertile cut-offs for females are T1: 5.4 T2: 6.9 [mg/dL] [rounded].

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R.1.1.3.2.1.7 KCCQ Total Symptoms Score responder analysis (15 points)

Table R.1.1.3.2.1.7: 1 Responder analysis for KCCQ-TSS change from baseline to last value during planned treatment period <= -15 points (deterioration) overall and by subgroup - RS (OC-AD)

Subgroup	Placebo			Empa 10mg			Empa 10mg vs Placebo					
Category	N	n	%	N	n	%	Risk ratio *	(95% CI)	p-value	Odds ratio ***	(95% CI)	p-value **
Overall	2869	457	15.9	2886	337	11.7	0.75	(0.66,0.85)	<0.0001	0.71	(0.60,0.82)	
Sex												0.8107
Male	1588	252	15.9	1597	189	11.8	0.76	(0.64,0.90)	0.0017	0.72	(0.58,0.88)	
Female	1281	205	16.0	1289	148	11.5	0.73	(0.61,0.89)	0.0017	0.69	(0.55,0.87)	
Age [years]												0.5222
<70	1038	125	12.0	1030	96	9.3	0.80	(0.62,1.02)	0.0729	0.77	(0.58,1.02)	
>=70	1831	332	18.1	1856	241	13.0	0.72	(0.62,0.84)	<0.0001	0.67	(0.56,0.81)	
Region												0.3883
North America	346	56	16.2	344	55	16.0	0.99	(0.71,1.40)	0.9739	0.99	(0.65,1.50)	
Latin America	724	85	11.7	730	59	8.1	0.71	(0.52,0.97)	0.0290	0.67	(0.47,0.96)	
Europe	1301	226	17.4	1309	163	12.5	0.73	(0.61,0.88)	0.0008	0.69	(0.55,0.86)	
Asia	330	54	16.4	328	40	12.2	0.75	(0.51,1.08)	0.1246	0.70	(0.45,1.10)	
Other	168	36	21.4	175	20	11.4	0.56	(0.34,0.92)	0.0227	0.49	(0.27,0.90)	
OECD member												0.1374
No	789	109	13.8	818	68	8.3	0.62	(0.47,0.82)	0.0009	0.58	(0.42,0.80)	
Yes	2080	348	16.7	2068	269	13.0	0.79	(0.68,0.91)	0.0013	0.75	(0.63,0.89)	
Baseline NYHA												0.2581
II^^	2359	372	15.8	2355	282	12.0	0.77	(0.67,0.89)	0.0004	0.73	(0.62,0.87)	
III/IV	510	85	16.7	531	55	10.4	0.64	(0.47,0.86)	0.0037	0.58	(0.40,0.84)	
Baseline Diabetes status												0.7038
Diabetic	1407	225	16.0	1400	169	12.1	0.77	(0.64,0.92)	0.0042	0.73	(0.58,0.91)	
Non-Diabetic	1462	232	15.9	1486	168	11.3	0.73	(0.61,0.88)	0.0008	0.69	(0.55,0.85)	

* 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, °:Trend test.
^ Models contain terms age, baseline eGFR (CKD-EPI), baseline LVEF, Baseline KCCQ-TSS, 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.

Analysis is based on study 1245.110.
For discontinued subjects, last available value was used. For completing subjects, last value up to last treatment intake + 7 days was used.
^^ Patients with NYHA class I are counted in subgroup NYHA class II. [1] Baseline SBP median: 132 [mmHg].
[2] Baseline NT-proBNP median for patients with history of atrial fibrillation or atrial flutter: 1354 [pg/mL].
[2] Baseline NT-proBNP median for patients without history of atrial fibrillation or atrial flutter: 614 [pg/mL].
[3] Baseline uric acid tertile cut-offs for males are T1: 5.9 T2: 7.5 [mg/dL] [rounded].
[3] Baseline uric acid tertile cut-offs for females are T1: 5.4 T2: 6.9 [mg/dL] [rounded].

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Table R.1.1.3.2.1.7: 1 Responder analysis for KCCQ-TSS 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 Diabetes status												0.3433°/ 0.3956
Diabetic	1407	225	16.0	1400	169	12.1	0.77	(0.64,0.92)	0.0042	0.73	(0.58,0.91)	
Pre-Diabetes	940	149	15.9	974	121	12.4	0.79	(0.64,0.99)	0.0384	0.76	(0.58,0.98)	
Normal (no pre-diabetes)	522	83	15.9	512	47	9.2	0.61	(0.44,0.85)	0.0032	0.56	(0.38,0.82)	
Baseline BMI [kg/m²]												0.9913
<30	1563	247	15.8	1591	187	11.8	0.75	(0.63,0.89)	0.0011	0.71	(0.58,0.87)	
>=30	1306	210	16.1	1295	150	11.6	0.75	(0.62,0.91)	0.0033	0.70	(0.56,0.89)	
Baseline eGFR (CKD-EPI) [mL/min/1.73m²]												0.9840
>=60	1449	207	14.3	1445	148	10.2	0.75	(0.61,0.91)	0.0033	0.71	(0.56,0.89)	
<60	1420	250	17.6	1441	189	13.1	0.75	(0.63,0.89)	0.0009	0.70	(0.57,0.87)	
History of HHF (in the last 12 months)												0.2913
No	2233	328	14.7	2228	248	11.1	0.78	(0.67,0.90)	0.0012	0.74	(0.62,0.89)	
Yes	636	129	20.3	658	89	13.5	0.67	(0.52,0.85)	0.0010	0.60	(0.44,0.81)	
Baseline SBP (</>= median¹)												0.4187
< median	1414	214	15.1	1444	172	11.9	0.79	(0.66,0.95)	0.0115	0.75	(0.61,0.94)	
>= median	1455	243	16.7	1442	165	11.4	0.71	(0.59,0.85)	0.0002	0.66	(0.53,0.82)	
History of atrial fibrillation or atrial flutter												0.9359
No	1364	199	14.6	1364	143	10.5	0.74	(0.61,0.91)	0.0033	0.70	(0.56,0.89)	
Yes	1502	258	17.2	1519	194	12.8	0.75	(0.63,0.89)	0.0009	0.71	(0.58,0.87)	

* 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, °:Trend test.
^ Models contain terms age, baseline eGFR (CKD-EPI), baseline LVEF, Baseline KCCQ-TSS, 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.

Analysis is based on study 1245.110.
For discontinued subjects, last available value was used. For completing subjects, last value up to last treatment intake + 7 days was used.
^^ Patients with NYHA class I are counted in subgroup NYHA class II. ¹ Baseline SBP median: 132 [mmHg].
² Baseline NT-proBNP median for patients with history of atrial fibrillation or atrial flutter: 1354 [pg/mL].
² Baseline NT-proBNP median for patients without history of atrial fibrillation or atrial flutter: 614 [pg/mL].
³ Baseline uric acid tertile cut-offs for males are T1: 5.9 T2: 7.5 [mg/dL] [rounded].
³ Baseline uric acid tertile cut-offs for females are T1: 5.4 T2: 6.9 [mg/dL] [rounded].

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Table R.1.1.3.2.1.7: 1 Responder analysis for KCCQ-TSS 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 LVEF [%]												0.7223
< 50	929	133	14.3	958	94	9.8	0.72	(0.56,0.92)	0.0087	0.68	(0.51,0.91)	
>= 50	1940	324	16.7	1928	243	12.6	0.76	(0.65,0.88)	0.0003	0.71	(0.60,0.86)	
Baseline LVEF [%]												0.1820°/ 0.1360
<50	929	133	14.3	958	94	9.8	0.72	(0.56,0.92)	0.0087	0.68	(0.51,0.91)	
50 to <60	992	186	18.8	988	121	12.2	0.66	(0.54,0.81)	<0.0001	0.60	(0.46,0.77)	
>=60	948	138	14.6	940	122	13.0	0.89	(0.72,1.12)	0.3194	0.87	(0.67,1.14)	
Baseline NT-proBNP [pg/mL] (</>=median² by atrial fibrillation/flutter status)												0.9072
< median	1464	217	14.8	1430	152	10.6	0.74	(0.61,0.90)	0.0021	0.70	(0.56,0.88)	
>= median	1401	239	17.1	1453	185	12.7	0.75	(0.63,0.89)	0.0013	0.71	(0.57,0.87)	
Baseline uric acid [mg/dL] (tertiles³)												0.7191°/ 0.9353
<T1	937	140	14.9	930	99	10.6	0.74	(0.58,0.94)	0.0119	0.70	(0.53,0.92)	
>=T1 and <T2	931	143	15.4	997	116	11.6	0.77	(0.61,0.96)	0.0205	0.73	(0.56,0.96)	
>=T2	971	165	17.0	933	122	13.1	0.78	(0.63,0.97)	0.0235	0.74	(0.57,0.96)	
Baseline use of MRA												0.4673
No	1788	286	16.0	1814	220	12.1	0.77	(0.66,0.91)	0.0019	0.74	(0.61,0.89)	
Yes	1081	171	15.8	1072	117	10.9	0.70	(0.57,0.87)	0.0012	0.65	(0.51,0.85)	
Baseline use of ACE-inhibitor, ARB or ARNi												0.1226
No	558	106	19.0	543	63	11.6	0.61	(0.46,0.81)	0.0007	0.55	(0.39,0.77)	
Yes	2311	351	15.2	2343	274	11.7	0.79	(0.68,0.91)	0.0012	0.75	(0.63,0.89)	

* 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, °:Trend test.
^ Models contain terms age, baseline eGFR (CKD-EPI), baseline LVEF, Baseline KCCQ-TSS, 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.

Analysis is based on study 1245.110.
For discontinued subjects, last available value was used. For completing subjects, last value up to last treatment intake + 7 days was used.
^^ Patients with NYHA class I are counted in subgroup NYHA class II. ¹ Baseline SBP median: 132 [mmHg].
² Baseline NT-proBNP median for patients with history of atrial fibrillation or atrial flutter: 1354 [pg/mL].
² Baseline NT-proBNP median for patients without history of atrial fibrillation or atrial flutter: 614 [pg/mL].
³ Baseline uric acid tertile cut-offs for males are T1: 5.9 T2: 7.5 [mg/dL] [rounded].
³ Baseline uric acid tertile cut-offs for females are T1: 5.4 T2: 6.9 [mg/dL] [rounded].

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Table R.1.1.3.2.1.7: 2 Responder analysis for KCCQ-TSS change from baseline to last value during planned treatment period >= 15 points (improvement) overall and by subgroup - RS (OC-AD)

Subgroup	Placebo			Empa 10mg			Empa 10mg vs Placebo					
Category	N	n	%	N	n	%	Risk ratio *	(95% CI)	p-value	Odds ratio ***	(95% CI)	p-value **
Overall	2869	681	23.7	2886	790	27.4	1.08	(1.00,1.17)	0.0617	1.20	(1.04,1.38)	
Sex												0.0494
Male	1588	322	20.3	1597	378	23.7	1.18	(1.05,1.32)	0.0069	1.27	(1.05,1.55)	
Female	1281	359	28.0	1289	412	32.0	1.00	(0.89,1.12)	0.9888	1.12	(0.91,1.37)	
Age [years]												0.2494
<70	1038	264	25.4	1030	292	28.3	1.02	(0.89,1.16)	0.8161	1.10	(0.87,1.40)	
>=70	1831	417	22.8	1856	498	26.8	1.12	(1.01,1.24)	0.0274	1.25	(1.05,1.49)	
Region												0.6362
North America	346	82	23.7	344	83	24.1	1.06	(0.84,1.35)	0.6153	1.08	(0.71,1.64)	
Latin America	724	226	31.2	730	269	36.8	1.09	(0.95,1.24)	0.2419	1.31	(1.00,1.71)	
Europe	1301	294	22.6	1309	328	25.1	1.04	(0.92,1.18)	0.5198	1.09	(0.88,1.34)	
Asia	330	38	11.5	328	56	17.1	1.39	(1.00,1.93)	0.0527	1.62	(0.98,2.68)	
Other	168	41	24.4	175	54	30.9	1.07	(0.78,1.47)	0.6671	1.29	(0.73,2.28)	
OECD member												0.5908
No	789	231	29.3	818	298	36.4	1.11	(0.97,1.27)	0.1183	1.40	(1.08,1.81)	
Yes	2080	450	21.6	2068	492	23.8	1.06	(0.96,1.18)	0.2421	1.11	(0.94,1.31)	
Baseline NYHA												0.7494
II^^	2359	501	21.2	2355	572	24.3	1.09	(0.99,1.20)	0.0766	1.18	(1.00,1.39)	
III/IV	510	180	35.3	531	218	41.1	1.06	(0.91,1.23)	0.4835	1.25	(0.93,1.69)	
Baseline Diabetes status												0.0047
Diabetic	1407	340	24.2	1400	430	30.7	1.21	(1.08,1.35)	0.0011	1.48	(1.21,1.81)	
Non-Diabetic	1462	341	23.3	1486	360	24.2	0.96	(0.85,1.07)	0.4520	0.96	(0.79,1.18)	

* 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, °:Trend test.
^ Models contain terms age, baseline eGFR (CKD-EPI), baseline LVEF, Baseline KCCQ-TSS, 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.

Analysis is based on study 1245.110.
For discontinued subjects, last available value was used. For completing subjects, last value up to last treatment intake + 7 days was used.
^^ Patients with NYHA class I are counted in subgroup NYHA class II. [1] Baseline SBP median: 132 [mmHg].
[2] Baseline NT-proBNP median for patients with history of atrial fibrillation or atrial flutter: 1354 [pg/mL].
[2] Baseline NT-proBNP median for patients without history of atrial fibrillation or atrial flutter: 614 [pg/mL].
[3] Baseline uric acid tertile cut-offs for males are T1: 5.9 T2: 7.5 [mg/dL] [rounded].
[3] Baseline uric acid tertile cut-offs for females are T1: 5.4 T2: 6.9 [mg/dL] [rounded].

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Table R.1.1.3.2.1.7: 2 Responder analysis for KCCQ-TSS 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 Diabetes status												0.0202°/ 0.0162
Diabetic	1407	340	24.2	1400	430	30.7	1.21	(1.08,1.35)	0.0011	1.48	(1.21,1.81)	
Pre-Diabetes	940	232	24.7	974	239	24.5	0.94	(0.82,1.08)	0.3819	0.91	(0.71,1.17)	
Normal (no pre-diabetes)	522	109	20.9	512	121	23.6	0.99	(0.81,1.22)	0.9398	1.07	(0.76,1.51)	
Baseline BMI [kg/m²]												0.4828
<30	1563	333	21.3	1591	370	23.3	1.05	(0.93,1.18)	0.4248	1.09	(0.89,1.33)	
>=30	1306	348	26.6	1295	420	32.4	1.11	(0.99,1.24)	0.0695	1.32	(1.07,1.62)	
Baseline eGFR (CKD-EPI) [mL/min/1.73m²]												0.4802
>=60	1449	339	23.4	1445	387	26.8	1.05	(0.94,1.18)	0.3984	1.14	(0.93,1.39)	
<60	1420	342	24.1	1441	403	28.0	1.11	(0.99,1.25)	0.0684	1.25	(1.03,1.53)	
History of HHF (in the last 12 months)												0.8070
No	2233	523	23.4	2228	602	27.0	1.09	(0.99,1.19)	0.0767	1.19	(1.01,1.40)	
Yes	636	158	24.8	658	188	28.6	1.06	(0.89,1.26)	0.5052	1.21	(0.90,1.62)	
Baseline SBP (</>= median¹)												0.2887
< median	1414	341	24.1	1444	378	26.2	1.03	(0.92,1.16)	0.5789	1.09	(0.89,1.34)	
>= median	1455	340	23.4	1442	412	28.6	1.13	(1.01,1.26)	0.0379	1.31	(1.07,1.60)	
History of atrial fibrillation or atrial flutter												0.5044
No	1364	345	25.3	1364	377	27.6	1.05	(0.94,1.18)	0.4001	1.14	(0.93,1.40)	
Yes	1502	335	22.3	1519	412	27.1	1.11	(0.99,1.24)	0.0756	1.25	(1.03,1.52)	

* 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, °:Trend test.
^ Models contain terms age, baseline eGFR (CKD-EPI), baseline LVEF, Baseline KCCQ-TSS, 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.

Analysis is based on study 1245.110.
For discontinued subjects, last available value was used. For completing subjects, last value up to last treatment intake + 7 days was used.
^^ Patients with NYHA class I are counted in subgroup NYHA class II. ¹ Baseline SBP median: 132 [mmHg].
² Baseline NT-proBNP median for patients with history of atrial fibrillation or atrial flutter: 1354 [pg/mL].
² Baseline NT-proBNP median for patients without history of atrial fibrillation or atrial flutter: 614 [pg/mL].
³ Baseline uric acid tertile cut-offs for males are T1: 5.9 T2: 7.5 [mg/dL] [rounded].
³ Baseline uric acid tertile cut-offs for females are T1: 5.4 T2: 6.9 [mg/dL] [rounded].

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Table R.1.1.3.2.1.7: 2 Responder analysis for KCCQ-TSS 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 LVEF [%]												0.5343
< 50	929	208	22.4	958	273	28.5	1.12	(0.97,1.29)	0.1152	1.26	(0.99,1.62)	
>= 50	1940	473	24.4	1928	517	26.8	1.06	(0.96,1.17)	0.2525	1.16	(0.98,1.38)	
Baseline LVEF [%]												0.2030°/ 0.3043
<50	929	208	22.4	958	273	28.5	1.12	(0.97,1.29)	0.1157	1.26	(0.99,1.62)	
50 to <60	992	236	23.8	988	263	26.6	1.14	(0.99,1.31)	0.0698	1.32	(1.04,1.69)	
>=60	948	237	25.0	940	254	27.0	0.99	(0.86,1.14)	0.8428	1.02	(0.80,1.30)	
Baseline NT-proBNP [pg/mL] (</>=median² by atrial fibrillation/flutter status)												0.2891
< median	1464	362	24.7	1430	399	27.9	1.04	(0.93,1.16)	0.5406	1.11	(0.91,1.36)	
>= median	1401	318	22.7	1453	390	26.8	1.13	(1.01,1.27)	0.0400	1.29	(1.05,1.58)	
Baseline uric acid [mg/dL] (tertiles³)												0.2128°/ 0.2871
<T1	937	214	22.8	930	229	24.6	1.04	(0.90,1.20)	0.6334	1.06	(0.82,1.37)	
>=T1 and <T2	931	211	22.7	997	257	25.8	1.01	(0.87,1.16)	0.9142	1.09	(0.85,1.39)	
>=T2	971	249	25.6	933	296	31.7	1.17	(1.02,1.33)	0.0223	1.43	(1.12,1.82)	
Baseline use of MRA												0.6917
No	1788	407	22.8	1814	483	26.6	1.09	(0.99,1.21)	0.0851	1.22	(1.02,1.46)	
Yes	1081	274	25.3	1072	307	28.6	1.06	(0.93,1.20)	0.3888	1.16	(0.92,1.46)	
Baseline use of ACE-inhibitor, ARB or ARNi												0.5925
No	558	128	22.9	543	146	26.9	1.13	(0.94,1.36)	0.1934	1.33	(0.96,1.85)	
Yes	2311	553	23.9	2343	644	27.5	1.07	(0.98,1.17)	0.1501	1.16	(0.99,1.36)	

* 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, °:Trend test.
^ Models contain terms age, baseline eGFR (CKD-EPI), baseline LVEF, Baseline KCCQ-TSS, 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.

Analysis is based on study 1245.110.
For discontinued subjects, last available value was used. For completing subjects, last value up to last treatment intake + 7 days was used.
^^ Patients with NYHA class I are counted in subgroup NYHA class II. ¹ Baseline SBP median: 132 [mmHg].
² Baseline NT-proBNP median for patients with history of atrial fibrillation or atrial flutter: 1354 [pg/mL].
² Baseline NT-proBNP median for patients without history of atrial fibrillation or atrial flutter: 614 [pg/mL].
³ Baseline uric acid tertile cut-offs for males are T1: 5.9 T2: 7.5 [mg/dL] [rounded].
³ Baseline uric acid tertile cut-offs for females are T1: 5.4 T2: 6.9 [mg/dL] [rounded].

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R.1.1.3.2.1.8 KCCQ Overall Summary Score responder analysis (5 points)

Table R.1.1.3.2.1.8: 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	2869	854	29.8	2886	719	24.9	0.84	(0.78,0.92)	<0.0001	0.78	(0.70,0.88)	
Sex												0.7666
Male	1588	482	30.4	1597	412	25.8	0.85	(0.76,0.95)	0.0044	0.79	(0.68,0.93)	
Female	1281	372	29.0	1289	307	23.8	0.83	(0.73,0.94)	0.0043	0.77	(0.64,0.92)	
Age [years]												0.2928
<70	1038	257	24.8	1030	226	21.9	0.90	(0.77,1.05)	0.1796	0.87	(0.70,1.07)	
>=70	1831	597	32.6	1856	493	26.6	0.82	(0.74,0.90)	<0.0001	0.74	(0.64,0.86)	
Region												0.5441
North America	346	100	28.9	344	99	28.8	0.98	(0.78,1.23)	0.8570	0.97	(0.69,1.35)	
Latin America	724	175	24.2	730	139	19.0	0.80	(0.66,0.97)	0.0259	0.75	(0.58,0.97)	
Europe	1301	417	32.1	1309	357	27.3	0.86	(0.76,0.96)	0.0099	0.80	(0.67,0.95)	
Asia	330	106	32.1	328	77	23.5	0.74	(0.58,0.94)	0.0155	0.65	(0.46,0.92)	
Other	168	56	33.3	175	47	26.9	0.82	(0.60,1.12)	0.2197	0.75	(0.47,1.20)	
OECD member												0.3328
No	789	203	25.7	818	160	19.6	0.78	(0.65,0.94)	0.0070	0.72	(0.57,0.92)	
Yes	2080	651	31.3	2068	559	27.0	0.86	(0.79,0.95)	0.0023	0.81	(0.71,0.93)	
Baseline NYHA												0.2959
II^^	2359	697	29.5	2355	596	25.3	0.86	(0.79,0.94)	0.0013	0.81	(0.71,0.92)	
III/IV	510	157	30.8	531	123	23.2	0.77	(0.63,0.93)	0.0079	0.68	(0.51,0.91)	
Baseline Diabetes status												0.3664
Diabetic	1407	424	30.1	1400	342	24.4	0.81	(0.72,0.91)	0.0005	0.74	(0.63,0.88)	
Non-Diabetic	1462	430	29.4	1486	377	25.4	0.88	(0.78,0.98)	0.0246	0.83	(0.70,0.98)	

* 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, °:Trend test.
^ Models contain terms age, baseline eGFR (CKD-EPI), baseline LVEF, Baseline KCCQ-OSS, 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.

Analysis is based on study 1245.110.
For discontinued subjects, last available value was used. For completing subjects, last value up to last treatment intake + 7 days was used.
^^ Patients with NYHA class I are counted in subgroup NYHA class II. [1] Baseline SBP median: 132 [mmHg].
[2] Baseline NT-proBNP median for patients with history of atrial fibrillation or atrial flutter: 1354 [pg/mL].
[2] Baseline NT-proBNP median for patients without history of atrial fibrillation or atrial flutter: 614 [pg/mL].
[3] Baseline uric acid tertile cut-offs for males are T1: 5.9 T2: 7.5 [mg/dL] [rounded].
[3] Baseline uric acid tertile cut-offs for females are T1: 5.4 T2: 6.9 [mg/dL] [rounded].

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Table R.1.1.3.2.1.8: 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 Diabetes status												0.7399°/ 0.3910
Diabetic	1407	424	30.1	1400	342	24.4	0.81	(0.72,0.91)	0.0005	0.74	(0.63,0.88)	
Pre-Diabetes	940	273	29.0	974	255	26.2	0.92	(0.79,1.06)	0.2242	0.88	(0.72,1.08)	
Normal (no pre-diabetes)	522	157	30.1	512	122	23.8	0.80	(0.66,0.98)	0.0311	0.73	(0.55,0.97)	
Baseline BMI [kg/m²]												0.6529
<30	1563	462	29.6	1591	402	25.3	0.86	(0.77,0.96)	0.0077	0.81	(0.69,0.95)	
>=30	1306	392	30.0	1295	317	24.5	0.83	(0.73,0.94)	0.0026	0.76	(0.64,0.91)	
Baseline eGFR (CKD-EPI) [mL/min/1.73m²]												0.1353
>=60	1449	406	28.0	1445	312	21.6	0.79	(0.69,0.89)	0.0002	0.72	(0.60,0.85)	
<60	1420	448	31.5	1441	407	28.2	0.89	(0.80,1.00)	0.0427	0.85	(0.72,1.00)	
History of HHF (in the last 12 months)												0.3980
No	2233	651	29.2	2228	552	24.8	0.86	(0.78,0.95)	0.0019	0.81	(0.70,0.92)	
Yes	636	203	31.9	658	167	25.4	0.79	(0.67,0.94)	0.0062	0.71	(0.55,0.91)	
Baseline SBP (</>= median¹)												0.0665
< median	1414	399	28.2	1444	374	25.9	0.91	(0.81,1.03)	0.1296	0.88	(0.74,1.04)	
>= median	1455	455	31.3	1442	345	23.9	0.78	(0.70,0.88)	<0.0001	0.70	(0.59,0.83)	
History of atrial fibrillation or atrial flutter												0.3242
No	1364	368	27.0	1364	319	23.4	0.88	(0.78,1.00)	0.0575	0.84	(0.70,1.00)	
Yes	1502	485	32.3	1519	399	26.3	0.81	(0.73,0.91)	0.0002	0.74	(0.63,0.87)	

* 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, °:Trend test.
^ Models contain terms age, baseline eGFR (CKD-EPI), baseline LVEF, Baseline KCCQ-OSS, 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.

Analysis is based on study 1245.110.
For discontinued subjects, last available value was used. For completing subjects, last value up to last treatment intake + 7 days was used.
^^ Patients with NYHA class I are counted in subgroup NYHA class II. ¹ Baseline SBP median: 132 [mmHg].
² Baseline NT-proBNP median for patients with history of atrial fibrillation or atrial flutter: 1354 [pg/mL].
² Baseline NT-proBNP median for patients without history of atrial fibrillation or atrial flutter: 614 [pg/mL].
³ Baseline uric acid tertile cut-offs for males are T1: 5.9 T2: 7.5 [mg/dL] [rounded].
³ Baseline uric acid tertile cut-offs for females are T1: 5.4 T2: 6.9 [mg/dL] [rounded].

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Table R.1.1.3.2.1.8: 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 LVEF [%]												0.8722
< 50	929	267	28.7	958	224	23.4	0.84	(0.72,0.97)	0.0187	0.78	(0.63,0.96)	
>= 50	1940	587	30.3	1928	495	25.7	0.85	(0.77,0.94)	0.0011	0.79	(0.68,0.91)	
Baseline LVEF [%]												0.9089°/ 0.9862
<50	929	267	28.7	958	224	23.4	0.84	(0.72,0.97)	0.0187	0.78	(0.63,0.96)	
50 to <60	992	306	30.8	988	259	26.2	0.85	(0.74,0.97)	0.0186	0.79	(0.64,0.96)	
>=60	948	281	29.6	940	236	25.1	0.85	(0.73,0.98)	0.0241	0.79	(0.64,0.97)	
Baseline NT-proBNP [pg/mL] (</>=median² by atrial fibrillation/flutter status)												0.4180
< median	1464	424	29.0	1430	333	23.3	0.81	(0.72,0.92)	0.0008	0.75	(0.63,0.89)	
>= median	1401	429	30.6	1453	385	26.5	0.87	(0.78,0.97)	0.0165	0.82	(0.69,0.96)	
Baseline uric acid [mg/dL] (tertiles³)												0.2280°/ 0.4834
<T1	937	258	27.5	930	228	24.5	0.91	(0.78,1.05)	0.2064	0.87	(0.71,1.08)	
>=T1 and <T2	931	269	28.9	997	245	24.6	0.86	(0.74,0.99)	0.0377	0.81	(0.66,0.99)	
>=T2	971	312	32.1	933	240	25.7	0.80	(0.70,0.92)	0.0017	0.72	(0.59,0.88)	
Baseline use of MRA												0.4177
No	1788	526	29.4	1814	459	25.3	0.87	(0.78,0.96)	0.0073	0.81	(0.70,0.95)	
Yes	1081	328	30.3	1072	260	24.3	0.81	(0.70,0.92)	0.0020	0.74	(0.61,0.90)	
Baseline use of ACE-inhibitor, ARB or ARNi												0.6723
No	558	180	32.3	543	154	28.4	0.87	(0.73,1.04)	0.1282	0.82	(0.63,1.06)	
Yes	2311	674	29.2	2343	565	24.1	0.84	(0.76,0.92)	0.0002	0.78	(0.68,0.89)	

* 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, °:Trend test.
^ Models contain terms age, baseline eGFR (CKD-EPI), baseline LVEF, Baseline KCCQ-OSS, 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.

Analysis is based on study 1245.110.
For discontinued subjects, last available value was used. For completing subjects, last value up to last treatment intake + 7 days was used.
^^ Patients with NYHA class I are counted in subgroup NYHA class II. ¹ Baseline SBP median: 132 [mmHg].
² Baseline NT-proBNP median for patients with history of atrial fibrillation or atrial flutter: 1354 [pg/mL].
² Baseline NT-proBNP median for patients without history of atrial fibrillation or atrial flutter: 614 [pg/mL].
³ Baseline uric acid tertile cut-offs for males are T1: 5.9 T2: 7.5 [mg/dL] [rounded].
³ Baseline uric acid tertile cut-offs for females are T1: 5.4 T2: 6.9 [mg/dL] [rounded].

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Table R.1.1.3.2.1.8: 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	2869	1156	40.3	2886	1336	46.3	1.12	(1.06,1.19)	<0.0001	1.30	(1.16,1.45)	
Sex												0.2541
Male	1588	598	37.7	1597	702	44.0	1.16	(1.07,1.25)	0.0002	1.34	(1.15,1.56)	
Female	1281	558	43.6	1289	634	49.2	1.09	(1.00,1.18)	0.0379	1.25	(1.05,1.48)	
Age [years]												0.0456
<70	1038	479	46.1	1030	518	50.3	1.05	(0.97,1.14)	0.2508	1.15	(0.95,1.39)	
>=70	1831	677	37.0	1856	818	44.1	1.18	(1.09,1.27)	<0.0001	1.40	(1.21,1.61)	
Region												0.7739
North America	346	138	39.9	344	145	42.2	1.10	(0.93,1.30)	0.2770	1.21	(0.87,1.69)	
Latin America	724	360	49.7	730	418	57.3	1.12	(1.02,1.22)	0.0189	1.37	(1.09,1.72)	
Europe	1301	488	37.5	1309	561	42.9	1.11	(1.02,1.22)	0.0172	1.25	(1.05,1.48)	
Asia	330	98	29.7	328	127	38.7	1.28	(1.04,1.56)	0.0172	1.51	(1.07,2.12)	
Other	168	72	42.9	175	85	48.6	1.08	(0.87,1.34)	0.4694	1.22	(0.77,1.94)	
OECD member												0.9418
No	789	381	48.3	818	465	56.8	1.12	(1.03,1.22)	0.0121	1.37	(1.11,1.70)	
Yes	2080	775	37.3	2068	871	42.1	1.13	(1.05,1.21)	0.0011	1.26	(1.11,1.45)	
Baseline NYHA												0.4510
II^^	2359	909	38.5	2355	1049	44.5	1.14	(1.07,1.21)	<0.0001	1.31	(1.16,1.49)	
III/IV	510	247	48.4	531	287	54.0	1.08	(0.96,1.21)	0.1844	1.25	(0.95,1.63)	
Baseline Diabetes status												0.1992
Diabetic	1407	567	40.3	1400	667	47.6	1.17	(1.08,1.26)	0.0001	1.40	(1.19,1.65)	
Non-Diabetic	1462	589	40.3	1486	669	45.0	1.08	(1.00,1.17)	0.0428	1.21	(1.03,1.42)	

* 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, °:Trend test.
^ Models contain terms age, baseline eGFR (CKD-EPI), baseline LVEF, Baseline KCCQ-OSS, 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.

Analysis is based on study 1245.110.
For discontinued subjects, last available value was used. For completing subjects, last value up to last treatment intake + 7 days was used.
^^ Patients with NYHA class I are counted in subgroup NYHA class II. [1] Baseline SBP median: 132 [mmHg].
[2] Baseline NT-proBNP median for patients with history of atrial fibrillation or atrial flutter: 1354 [pg/mL].
[2] Baseline NT-proBNP median for patients without history of atrial fibrillation or atrial flutter: 614 [pg/mL].
[3] Baseline uric acid tertile cut-offs for males are T1: 5.9 T2: 7.5 [mg/dL] [rounded].
[3] Baseline uric acid tertile cut-offs for females are T1: 5.4 T2: 6.9 [mg/dL] [rounded].

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Table R.1.1.3.2.1.8: 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 Diabetes status												0.4325°/ 0.3226
Diabetic	1407	567	40.3	1400	667	47.6	1.17	(1.08,1.26)	0.0001	1.40	(1.19,1.65)	
Pre-Diabetes	940	381	40.5	974	430	44.1	1.06	(0.96,1.17)	0.2466	1.14	(0.93,1.38)	
Normal (no pre-diabetes)	522	208	39.8	512	239	46.7	1.13	(0.99,1.29)	0.0633	1.35	(1.03,1.77)	
Baseline BMI [kg/m²]												0.0308
<30	1563	626	40.1	1591	688	43.2	1.06	(0.98,1.15)	0.1328	1.14	(0.98,1.33)	
>=30	1306	530	40.6	1295	648	50.0	1.20	(1.11,1.30)	<0.0001	1.52	(1.28,1.80)	
Baseline eGFR (CKD-EPI) [mL/min/1.73m²]												0.1695
>=60	1449	582	40.2	1445	703	48.7	1.17	(1.08,1.26)	<0.0001	1.42	(1.21,1.66)	
<60	1420	574	40.4	1441	633	43.9	1.08	(1.00,1.17)	0.0603	1.19	(1.01,1.40)	
History of HHF (in the last 12 months)												0.1095
No	2233	900	40.3	2228	1009	45.3	1.10	(1.03,1.17)	0.0045	1.23	(1.08,1.40)	
Yes	636	256	40.3	658	327	49.7	1.22	(1.09,1.37)	0.0006	1.55	(1.22,1.97)	
Baseline SBP (</>= median¹)												0.0515
< median	1414	591	41.8	1444	647	44.8	1.06	(0.98,1.15)	0.1241	1.17	(0.99,1.37)	
>= median	1455	565	38.8	1442	689	47.8	1.19	(1.10,1.29)	<0.0001	1.44	(1.23,1.69)	
History of atrial fibrillation or atrial flutter												0.2911
No	1364	591	43.3	1364	663	48.6	1.09	(1.01,1.18)	0.0246	1.23	(1.04,1.45)	
Yes	1502	564	37.5	1519	672	44.2	1.16	(1.07,1.26)	0.0004	1.36	(1.16,1.60)	

* 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, °:Trend test.
^ Models contain terms age, baseline eGFR (CKD-EPI), baseline LVEF, Baseline KCCQ-OSS, 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.

Analysis is based on study 1245.110.
For discontinued subjects, last available value was used. For completing subjects, last value up to last treatment intake + 7 days was used.
^^ Patients with NYHA class I are counted in subgroup NYHA class II. ¹ Baseline SBP median: 132 [mmHg].
² Baseline NT-proBNP median for patients with history of atrial fibrillation or atrial flutter: 1354 [pg/mL].
² Baseline NT-proBNP median for patients without history of atrial fibrillation or atrial flutter: 614 [pg/mL].
³ Baseline uric acid tertile cut-offs for males are T1: 5.9 T2: 7.5 [mg/dL] [rounded].
³ Baseline uric acid tertile cut-offs for females are T1: 5.4 T2: 6.9 [mg/dL] [rounded].

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Table R.1.1.3.2.1.8: 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 LVEF [%]												0.5187
< 50	929	365	39.3	958	455	47.5	1.15	(1.05,1.27)	0.0036	1.36	(1.11,1.65)	
>= 50	1940	791	40.8	1928	881	45.7	1.11	(1.04,1.19)	0.0027	1.27	(1.11,1.46)	
Baseline LVEF [%]												0.0108°/ 0.0004
<50	929	365	39.3	958	455	47.5	1.15	(1.05,1.27)	0.0036	1.36	(1.11,1.65)	
50 to <60	992	382	38.5	988	479	48.5	1.27	(1.15,1.40)	<0.0001	1.67	(1.37,2.03)	
>=60	948	409	43.1	940	402	42.8	0.96	(0.87,1.06)	0.4703	0.95	(0.78,1.16)	
Baseline NT-proBNP [pg/mL] (</>=median² by atrial fibrillation/flutter status)												0.9491
< median	1464	579	39.5	1430	654	45.7	1.12	(1.04,1.21)	0.0045	1.29	(1.10,1.52)	
>= median	1401	576	41.1	1453	681	46.9	1.13	(1.04,1.22)	0.0030	1.30	(1.11,1.53)	
Baseline uric acid [mg/dL] (tertiles³)												0.6572°/ 0.7802
<T1	937	380	40.6	930	420	45.2	1.09	(0.98,1.20)	0.0983	1.19	(0.97,1.45)	
>=T1 and <T2	931	369	39.6	997	463	46.4	1.14	(1.04,1.26)	0.0070	1.33	(1.09,1.62)	
>=T2	971	399	41.1	933	439	47.1	1.12	(1.02,1.23)	0.0207	1.32	(1.08,1.61)	
Baseline use of MRA												0.3436
No	1788	712	39.8	1814	814	44.9	1.10	(1.03,1.18)	0.0083	1.24	(1.07,1.43)	
Yes	1081	444	41.1	1072	522	48.7	1.16	(1.06,1.27)	0.0009	1.40	(1.16,1.68)	
Baseline use of ACE-inhibitor, ARB or ARNi												0.9915
No	558	216	38.7	543	235	43.3	1.12	(0.98,1.28)	0.0913	1.29	(0.99,1.68)	
Yes	2311	940	40.7	2343	1101	47.0	1.12	(1.06,1.19)	0.0002	1.30	(1.14,1.47)	

* 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, °:Trend test.
^ Models contain terms age, baseline eGFR (CKD-EPI), baseline LVEF, Baseline KCCQ-OSS, 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.

Analysis is based on study 1245.110.
For discontinued subjects, last available value was used. For completing subjects, last value up to last treatment intake + 7 days was used.
^^ Patients with NYHA class I are counted in subgroup NYHA class II. ¹ Baseline SBP median: 132 [mmHg].
² Baseline NT-proBNP median for patients with history of atrial fibrillation or atrial flutter: 1354 [pg/mL].
² Baseline NT-proBNP median for patients without history of atrial fibrillation or atrial flutter: 614 [pg/mL].
³ Baseline uric acid tertile cut-offs for males are T1: 5.9 T2: 7.5 [mg/dL] [rounded].
³ Baseline uric acid tertile cut-offs for females are T1: 5.4 T2: 6.9 [mg/dL] [rounded].

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R.1.1.3.2.1.9 KCCQ Overall Summary Score responder analysis (15 points)

Table R.1.1.3.2.1.9: 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	Placebo			Empa 10mg			Empa 10mg vs Placebo					
Category	N	n	%	N	n	%	Risk ratio *	(95% CI)	p-value	Odds ratio ***	(95% CI)	p-value **
Overall	2869	399	13.9	2886	348	12.1	0.87	(0.77,1.00)	0.0455	0.85	(0.73,1.00)	
Sex												0.9549
Male	1588	228	14.4	1597	199	12.5	0.87	(0.73,1.04)	0.1218	0.85	(0.69,1.04)	
Female	1281	171	13.3	1289	149	11.6	0.88	(0.72,1.07)	0.2062	0.86	(0.68,1.09)	
Age [years]												0.2761
<70	1038	111	10.7	1030	106	10.3	0.98	(0.76,1.25)	0.8532	0.97	(0.73,1.30)	
>=70	1831	288	15.7	1856	242	13.0	0.83	(0.71,0.97)	0.0187	0.80	(0.66,0.96)	
Region												0.0662
North America	346	54	15.6	344	48	14.0	0.88	(0.61,1.25)	0.4661	0.85	(0.55,1.30)	
Latin America	724	82	11.3	730	61	8.4	0.76	(0.56,1.03)	0.0808	0.73	(0.51,1.04)	
Europe	1301	178	13.7	1309	186	14.2	1.05	(0.87,1.26)	0.6425	1.06	(0.84,1.32)	
Asia	330	49	14.8	328	28	8.5	0.58	(0.38,0.90)	0.0146	0.54	(0.33,0.88)	
Other	168	36	21.4	175	25	14.3	0.68	(0.43,1.07)	0.0986	0.62	(0.35,1.10)	
OECD member												0.1696
No	789	103	13.1	818	76	9.3	0.74	(0.56,0.98)	0.0324	0.71	(0.51,0.97)	
Yes	2080	296	14.2	2068	272	13.2	0.92	(0.79,1.07)	0.2995	0.91	(0.76,1.09)	
Baseline NYHA												0.8101
II^^	2359	331	14.0	2355	289	12.3	0.88	(0.76,1.02)	0.0830	0.86	(0.72,1.02)	
III/IV	510	68	13.3	531	59	11.1	0.84	(0.61,1.16)	0.2921	0.82	(0.56,1.20)	
Baseline Diabetes status												0.7273
Diabetic	1407	204	14.5	1400	174	12.4	0.85	(0.71,1.03)	0.0944	0.83	(0.66,1.03)	
Non-Diabetic	1462	195	13.3	1486	174	11.7	0.90	(0.74,1.08)	0.2507	0.88	(0.70,1.10)	

* 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, °:Trend test.
^ Models contain terms age, baseline eGFR (CKD-EPI), baseline LVEF, Baseline KCCQ-OSS, 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.

Analysis is based on study 1245.110.
For discontinued subjects, last available value was used. For completing subjects, last value up to last treatment intake + 7 days was used.
^^ Patients with NYHA class I are counted in subgroup NYHA class II. [1] Baseline SBP median: 132 [mmHg].
[2] Baseline NT-proBNP median for patients with history of atrial fibrillation or atrial flutter: 1354 [pg/mL].
[2] Baseline NT-proBNP median for patients without history of atrial fibrillation or atrial flutter: 614 [pg/mL].
[3] Baseline uric acid tertile cut-offs for males are T1: 5.9 T2: 7.5 [mg/dL] [rounded].
[3] Baseline uric acid tertile cut-offs for females are T1: 5.4 T2: 6.9 [mg/dL] [rounded].

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Table R.1.1.3.2.1.9: 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 Diabetes status												0.5303°/ 0.1111
Diabetic	1407	204	14.5	1400	174	12.4	0.85	(0.71,1.03)	0.0944	0.83	(0.66,1.03)	
Pre-Diabetes	940	118	12.6	974	124	12.7	1.03	(0.82,1.30)	0.7798	1.04	(0.79,1.37)	
Normal (no pre-diabetes)	522	77	14.8	512	50	9.8	0.68	(0.49,0.94)	0.0200	0.63	(0.43,0.93)	
Baseline BMI [kg/m²]												0.5221
<30	1563	204	13.1	1591	189	11.9	0.91	(0.76,1.10)	0.3267	0.90	(0.72,1.11)	
>=30	1306	195	14.9	1295	159	12.3	0.84	(0.69,1.01)	0.0696	0.81	(0.64,1.02)	
Baseline eGFR (CKD-EPI) [mL/min/1.73m²]												0.4811
>=60	1449	170	11.7	1445	152	10.5	0.92	(0.75,1.13)	0.4293	0.91	(0.72,1.15)	
<60	1420	229	16.1	1441	196	13.6	0.84	(0.70,0.99)	0.0431	0.81	(0.65,0.99)	
History of HHF (in the last 12 months)												0.4843
No	2233	299	13.4	2228	263	11.8	0.90	(0.77,1.04)	0.1590	0.88	(0.73,1.05)	
Yes	636	100	15.7	658	85	12.9	0.80	(0.62,1.04)	0.1024	0.77	(0.56,1.06)	
Baseline SBP (</>= median¹)												0.9153
< median	1414	188	13.3	1444	171	11.8	0.88	(0.73,1.07)	0.1941	0.86	(0.69,1.08)	
>= median	1455	211	14.5	1442	177	12.3	0.87	(0.72,1.04)	0.1300	0.85	(0.68,1.05)	
History of atrial fibrillation or atrial flutter												0.1705
No	1364	158	11.6	1364	150	11.0	0.97	(0.79,1.20)	0.8068	0.97	(0.76,1.23)	
Yes	1502	241	16.0	1519	198	13.0	0.81	(0.68,0.96)	0.0137	0.77	(0.63,0.95)	

* 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, °:Trend test.
^ Models contain terms age, baseline eGFR (CKD-EPI), baseline LVEF, Baseline KCCQ-OSS, 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.

Analysis is based on study 1245.110.
For discontinued subjects, last available value was used. For completing subjects, last value up to last treatment intake + 7 days was used.
^^ Patients with NYHA class I are counted in subgroup NYHA class II. ¹ Baseline SBP median: 132 [mmHg].
² Baseline NT-proBNP median for patients with history of atrial fibrillation or atrial flutter: 1354 [pg/mL].
² Baseline NT-proBNP median for patients without history of atrial fibrillation or atrial flutter: 614 [pg/mL].
³ Baseline uric acid tertile cut-offs for males are T1: 5.9 T2: 7.5 [mg/dL] [rounded].
³ Baseline uric acid tertile cut-offs for females are T1: 5.4 T2: 6.9 [mg/dL] [rounded].

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Table R.1.1.3.2.1.9: 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 LVEF [%]												0.2544
< 50	929	129	13.9	958	100	10.4	0.78	(0.61,0.99)	0.0420	0.75	(0.56,0.99)	
>= 50	1940	270	13.9	1928	248	12.9	0.92	(0.79,1.08)	0.3039	0.91	(0.75,1.09)	
Baseline LVEF [%]												0.3786°/ 0.5133
<50	929	129	13.9	958	100	10.4	0.78	(0.61,0.99)	0.0420	0.75	(0.56,0.99)	
50 to <60	992	138	13.9	988	128	13.0	0.93	(0.75,1.16)	0.5420	0.92	(0.71,1.20)	
>=60	948	132	13.9	940	120	12.8	0.91	(0.72,1.14)	0.3972	0.89	(0.68,1.17)	
Baseline NT-proBNP [pg/mL] (</>=median² by atrial fibrillation/flutter status)												0.9004
< median	1464	195	13.3	1430	166	11.6	0.88	(0.73,1.07)	0.1904	0.86	(0.69,1.08)	
>= median	1401	204	14.6	1453	182	12.5	0.87	(0.72,1.04)	0.1205	0.84	(0.68,1.05)	
Baseline uric acid [mg/dL] (tertiles³)												0.8458°/ 0.2853
<T1	937	125	13.3	930	96	10.3	0.79	(0.62,1.02)	0.0656	0.76	(0.57,1.02)	
>=T1 and <T2	931	122	13.1	997	132	13.2	1.02	(0.81,1.28)	0.8790	1.02	(0.78,1.34)	
>=T2	971	147	15.1	933	118	12.6	0.83	(0.67,1.04)	0.1016	0.80	(0.61,1.04)	
Baseline use of MRA												0.3986
No	1788	249	13.9	1814	229	12.6	0.91	(0.77,1.08)	0.2739	0.90	(0.74,1.09)	
Yes	1081	150	13.9	1072	119	11.1	0.81	(0.65,1.01)	0.0617	0.78	(0.60,1.01)	
Baseline use of ACE-inhibitor, ARB or ARNi												0.0302
No	558	100	17.9	543	65	12.0	0.66	(0.50,0.88)	0.0044	0.60	(0.43,0.85)	
Yes	2311	299	12.9	2343	283	12.1	0.94	(0.81,1.10)	0.4560	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, °:Trend test.
^ Models contain terms age, baseline eGFR (CKD-EPI), baseline LVEF, Baseline KCCQ-OSS, 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.

Analysis is based on study 1245.110.
For discontinued subjects, last available value was used. For completing subjects, last value up to last treatment intake + 7 days was used.
^^ Patients with NYHA class I are counted in subgroup NYHA class II. ¹ Baseline SBP median: 132 [mmHg].
² Baseline NT-proBNP median for patients with history of atrial fibrillation or atrial flutter: 1354 [pg/mL].
² Baseline NT-proBNP median for patients without history of atrial fibrillation or atrial flutter: 614 [pg/mL].
³ Baseline uric acid tertile cut-offs for males are T1: 5.9 T2: 7.5 [mg/dL] [rounded].
³ Baseline uric acid tertile cut-offs for females are T1: 5.4 T2: 6.9 [mg/dL] [rounded].

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Table R.1.1.3.2.1.9: 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	Placebo			Empa 10mg			Empa 10mg vs Placebo					
Category	N	n	%	N	n	%	Risk ratio *	(95% CI)	p-value	Odds ratio ***	(95% CI)	p-value **
Overall	2869	586	20.4	2886	667	23.1	1.07	(0.98,1.17)	0.1353	1.15	(1.00,1.32)	
Sex												0.3068
Male	1588	281	17.7	1597	323	20.2	1.13	(0.99,1.29)	0.0777	1.20	(0.98,1.46)	
Female	1281	305	23.8	1289	344	26.7	1.02	(0.90,1.16)	0.7168	1.10	(0.90,1.35)	
Age [years]												0.7996
<70	1038	244	23.5	1030	278	27.0	1.06	(0.92,1.22)	0.4328	1.16	(0.92,1.45)	
>=70	1831	342	18.7	1856	389	21.0	1.08	(0.96,1.22)	0.1951	1.15	(0.96,1.37)	
Region												0.5669
North America	346	67	19.4	344	64	18.6	1.03	(0.77,1.38)	0.8282	1.07	(0.70,1.63)	
Latin America	724	217	30.0	730	251	34.4	1.07	(0.93,1.23)	0.3638	1.21	(0.93,1.56)	
Europe	1301	220	16.9	1309	242	18.5	1.03	(0.88,1.20)	0.7275	1.05	(0.85,1.32)	
Asia	330	42	12.7	328	62	18.9	1.41	(1.01,1.96)	0.0435	1.60	(1.01,2.53)	
Other	168	40	23.8	175	48	27.4	1.05	(0.76,1.44)	0.7715	1.10	(0.63,1.91)	
OECD member												0.2189
No	789	215	27.2	818	284	34.7	1.15	(1.00,1.32)	0.0540	1.36	(1.07,1.74)	
Yes	2080	371	17.8	2068	383	18.5	1.02	(0.91,1.15)	0.7220	1.05	(0.88,1.25)	
Baseline NYHA												0.7771
II^^	2359	437	18.5	2355	492	20.9	1.08	(0.97,1.20)	0.1518	1.15	(0.98,1.35)	
III/IV	510	149	29.2	531	175	33.0	1.05	(0.88,1.26)	0.6084	1.15	(0.85,1.56)	
Baseline Diabetes status												0.1662
Diabetic	1407	296	21.0	1400	347	24.8	1.14	(1.00,1.30)	0.0432	1.25	(1.02,1.53)	
Non-Diabetic	1462	290	19.8	1486	320	21.5	1.00	(0.88,1.14)	0.9590	1.05	(0.86,1.29)	

* 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, °:Trend test.
^ Models contain terms age, baseline eGFR (CKD-EPI), baseline LVEF, Baseline KCCQ-OSS, 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.

Analysis is based on study 1245.110.
For discontinued subjects, last available value was used. For completing subjects, last value up to last treatment intake + 7 days was used.
^^ Patients with NYHA class I are counted in subgroup NYHA class II. [1] Baseline SBP median: 132 [mmHg].
[2] Baseline NT-proBNP median for patients with history of atrial fibrillation or atrial flutter: 1354 [pg/mL].
[2] Baseline NT-proBNP median for patients without history of atrial fibrillation or atrial flutter: 614 [pg/mL].
[3] Baseline uric acid tertile cut-offs for males are T1: 5.9 T2: 7.5 [mg/dL] [rounded].
[3] Baseline uric acid tertile cut-offs for females are T1: 5.4 T2: 6.9 [mg/dL] [rounded].

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Table R.1.1.3.2.1.9: 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 Diabetes status												0.4495°/ 0.2094
Diabetic	1407	296	21.0	1400	347	24.8	1.14	(1.00,1.30)	0.0432	1.25	(1.02,1.53)	
Pre-Diabetes	940	191	20.3	974	201	20.6	0.95	(0.81,1.12)	0.5458	0.94	(0.73,1.21)	
Normal (no pre-diabetes)	522	99	19.0	512	119	23.2	1.10	(0.88,1.38)	0.3949	1.29	(0.92,1.81)	
Baseline BMI [kg/m²]												0.2903
<30	1563	306	19.6	1591	332	20.9	1.02	(0.90,1.16)	0.7423	1.04	(0.86,1.27)	
>=30	1306	280	21.4	1295	335	25.9	1.13	(0.99,1.29)	0.0744	1.28	(1.04,1.57)	
Baseline eGFR (CKD-EPI) [mL/min/1.73m²]												0.1805
>=60	1449	296	20.4	1445	365	25.3	1.14	(1.01,1.29)	0.0394	1.28	(1.05,1.56)	
<60	1420	290	20.4	1441	302	21.0	1.00	(0.88,1.15)	0.9491	1.02	(0.83,1.25)	
History of HHF (in the last 12 months)												0.5375
No	2233	453	20.3	2228	507	22.8	1.05	(0.95,1.17)	0.3107	1.12	(0.96,1.32)	
Yes	636	133	20.9	658	160	24.3	1.13	(0.93,1.37)	0.2141	1.23	(0.92,1.66)	
Baseline SBP (</>= median¹)												0.0123
< median	1414	311	22.0	1444	314	21.7	0.95	(0.84,1.09)	0.4745	0.97	(0.79,1.18)	
>= median	1455	275	18.9	1442	353	24.5	1.21	(1.06,1.37)	0.0049	1.36	(1.11,1.67)	
History of atrial fibrillation or atrial flutter												0.2254
No	1364	312	22.9	1364	335	24.6	1.01	(0.90,1.15)	0.8212	1.05	(0.85,1.28)	
Yes	1502	274	18.2	1519	332	21.9	1.14	(0.99,1.30)	0.0648	1.25	(1.03,1.53)	

* 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, °:Trend test.
^ Models contain terms age, baseline eGFR (CKD-EPI), baseline LVEF, Baseline KCCQ-OSS, 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.

Analysis is based on study 1245.110.
For discontinued subjects, last available value was used. For completing subjects, last value up to last treatment intake + 7 days was used.
^^ Patients with NYHA class I are counted in subgroup NYHA class II. ¹ Baseline SBP median: 132 [mmHg].
² Baseline NT-proBNP median for patients with history of atrial fibrillation or atrial flutter: 1354 [pg/mL].
² Baseline NT-proBNP median for patients without history of atrial fibrillation or atrial flutter: 614 [pg/mL].
³ Baseline uric acid tertile cut-offs for males are T1: 5.9 T2: 7.5 [mg/dL] [rounded].
³ Baseline uric acid tertile cut-offs for females are T1: 5.4 T2: 6.9 [mg/dL] [rounded].

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Table R.1.1.3.2.1.9: 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 LVEF [%]												0.8874
< 50	929	185	19.9	958	224	23.4	1.06	(0.91,1.24)	0.4571	1.10	(0.86,1.41)	
>= 50	1940	401	20.7	1928	443	23.0	1.08	(0.96,1.20)	0.1986	1.17	(0.98,1.39)	
Baseline LVEF [%]												0.2979°/ 0.0803
<50	929	185	19.9	958	224	23.4	1.06	(0.91,1.24)	0.4587	1.10	(0.86,1.41)	
50 to <60	992	191	19.3	988	231	23.4	1.22	(1.04,1.43)	0.0126	1.44	(1.13,1.84)	
>=60	948	210	22.2	940	212	22.6	0.95	(0.81,1.11)	0.4937	0.95	(0.74,1.22)	
Baseline NT-proBNP [pg/mL] (</>=median² by atrial fibrillation/flutter status)												0.7495
< median	1464	285	19.5	1430	324	22.7	1.09	(0.95,1.24)	0.2142	1.17	(0.95,1.43)	
>= median	1401	301	21.5	1453	343	23.6	1.06	(0.93,1.20)	0.4059	1.13	(0.92,1.37)	
Baseline uric acid [mg/dL] (tertiles³)												0.9750°/ 0.9353
<T1	937	191	20.4	930	211	22.7	1.07	(0.91,1.25)	0.4138	1.11	(0.87,1.43)	
>=T1 and <T2	931	179	19.2	997	212	21.3	1.03	(0.87,1.21)	0.7243	1.07	(0.83,1.38)	
>=T2	971	212	21.8	933	233	25.0	1.07	(0.91,1.25)	0.3969	1.18	(0.93,1.51)	
Baseline use of MRA												0.3774
No	1788	359	20.1	1814	401	22.1	1.04	(0.92,1.17)	0.5423	1.10	(0.91,1.31)	
Yes	1081	227	21.0	1072	266	24.8	1.13	(0.97,1.31)	0.1064	1.24	(0.98,1.56)	
Baseline use of ACE-inhibitor, ARB or ARNi												0.4820
No	558	107	19.2	543	121	22.3	1.15	(0.92,1.44)	0.2183	1.29	(0.93,1.80)	
Yes	2311	479	20.7	2343	546	23.3	1.05	(0.95,1.16)	0.3015	1.12	(0.95,1.31)	

* 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, °:Trend test.
^ Models contain terms age, baseline eGFR (CKD-EPI), baseline LVEF, Baseline KCCQ-OSS, 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.

Analysis is based on study 1245.110.
For discontinued subjects, last available value was used. For completing subjects, last value up to last treatment intake + 7 days was used.
^^ Patients with NYHA class I are counted in subgroup NYHA class II. ¹ Baseline SBP median: 132 [mmHg].
² Baseline NT-proBNP median for patients with history of atrial fibrillation or atrial flutter: 1354 [pg/mL].
² Baseline NT-proBNP median for patients without history of atrial fibrillation or atrial flutter: 614 [pg/mL].
³ Baseline uric acid tertile cut-offs for males are T1: 5.9 T2: 7.5 [mg/dL] [rounded].
³ Baseline uric acid tertile cut-offs for females are T1: 5.4 T2: 6.9 [mg/dL] [rounded].

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R.1.1.3.2.2 Observed cases analyses with ceiling correction

R.1.1.3.2.2.1 EQ-VAS responder analysis (15 points)

Table R.1.1.3.2.2.1: 1 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 with ceiling correction)

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	2870	875	30.5	2889	923	31.9	1.04	(0.96,1.12)	0.3091	1.06	(0.95,1.19)	
Sex												0.7955
Male	1589	472	29.7	1600	491	30.7	1.03	(0.93,1.14)	0.5750	1.04	(0.89,1.22)	
Female	1281	403	31.5	1289	432	33.5	1.05	(0.94,1.17)	0.3707	1.09	(0.92,1.29)	
Age [years]												0.4387
<70	1036	361	34.8	1030	396	38.4	1.08	(0.96,1.20)	0.1918	1.14	(0.95,1.37)	
>=70	1834	514	28.0	1859	527	28.3	1.01	(0.92,1.12)	0.7722	1.02	(0.88,1.18)	
Region												0.7660
North America	345	110	31.9	342	105	30.7	0.96	(0.77,1.20)	0.7342	0.95	(0.68,1.32)	
Latin America	723	282	39.0	731	317	43.4	1.11	(0.98,1.25)	0.1032	1.19	(0.97,1.48)	
Europe	1301	303	23.3	1310	316	24.1	1.03	(0.90,1.18)	0.6497	1.04	(0.87,1.25)	
Asia	333	118	35.4	330	116	35.2	0.98	(0.79,1.20)	0.8177	0.96	(0.70,1.33)	
Other	168	62	36.9	176	69	39.2	1.03	(0.79,1.34)	0.8188	1.06	(0.68,1.66)	
OECD member												0.2342
No	790	287	36.3	822	333	40.5	1.10	(0.98,1.25)	0.1051	1.18	(0.97,1.45)	
Yes	2080	588	28.3	2067	590	28.5	1.01	(0.91,1.11)	0.8999	1.01	(0.88,1.16)	
Baseline NYHA												0.4355
II^^	2361	731	31.0	2360	752	31.9	1.03	(0.95,1.11)	0.5381	1.04	(0.92,1.18)	
III/IV	509	144	28.3	529	171	32.3	1.11	(0.93,1.32)	0.2514	1.18	(0.90,1.55)	
Baseline Diabetes status												0.0918
Diabetic	1409	438	31.1	1403	485	34.6	1.11	(1.00,1.23)	0.0547	1.17	(1.00,1.38)	
Non-Diabetic	1461	437	29.9	1486	438	29.5	0.97	(0.87,1.08)	0.6195	0.96	(0.82,1.13)	

* 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, °:Trend test.
^ 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.

Analysis is based on study 1245.110.
For discontinued subjects, last available value was used. For completing subjects, last value up to last treatment intake + 7 days was used.
Subjects with a baseline score > 85 are considered as improved if the score remains stable > 85 points at last observation.
^^ Patients with NYHA class I are counted in subgroup NYHA class II. [1] Baseline SBP median: 132 [mmHg].
[2] Baseline NT-proBNP median for patients with history of atrial fibrillation or atrial flutter: 1354 [pg/mL].
[2] Baseline NT-proBNP median for patients without history of atrial fibrillation or atrial flutter: 614 [pg/mL].
[3] Baseline uric acid tertile cut-offs are: For males T1: 5.9 T2: 7.5 [mg/dL] [rounded], for females T1: 5.4 T2: 6.9 [mg/dL] [rounded].

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Table R.1.1.3.2.2.1: 1 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 with ceiling correction)

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 Diabetes status												0.0904°/ 0.2241
Diabetic	1409	438	31.1	1403	485	34.6	1.11	(1.00,1.23)	0.0547	1.17	(1.00,1.38)	
Pre-Diabetes	940	274	29.1	975	285	29.2	0.99	(0.87,1.13)	0.8840	0.99	(0.81,1.21)	
Normal (no pre-diabetes)	521	163	31.3	511	153	29.9	0.94	(0.79,1.13)	0.5348	0.92	(0.70,1.21)	
Baseline BMI [kg/m²]												0.1265
<30	1568	502	32.0	1594	504	31.6	0.99	(0.89,1.09)	0.7956	0.98	(0.84,1.14)	
>=30	1302	373	28.6	1295	419	32.4	1.11	(0.99,1.24)	0.0713	1.18	(0.99,1.40)	
Baseline eGFR (CKD-EPI) [mL/min/1.73m²]												0.4655
>=60	1448	487	33.6	1445	500	34.6	1.01	(0.92,1.12)	0.7899	1.02	(0.87,1.20)	
<60	1422	388	27.3	1444	423	29.3	1.07	(0.96,1.20)	0.2306	1.11	(0.94,1.31)	
History of HHF (in the last 12 months)												0.8515
No	2233	680	30.5	2229	709	31.8	1.04	(0.95,1.13)	0.4234	1.06	(0.93,1.20)	
Yes	637	195	30.6	660	214	32.4	1.05	(0.90,1.23)	0.5154	1.08	(0.85,1.37)	
Baseline SBP (</>= median¹)												0.2404
< median	1414	440	31.1	1445	452	31.3	0.99	(0.89,1.10)	0.9120	0.99	(0.84,1.17)	
>= median	1456	435	29.9	1444	471	32.6	1.09	(0.98,1.21)	0.1201	1.14	(0.97,1.34)	
History of atrial fibrillation or atrial flutter												0.5456
No	1366	451	33.0	1364	484	35.5	1.06	(0.96,1.17)	0.2448	1.10	(0.94,1.30)	
Yes	1501	423	28.2	1522	437	28.7	1.01	(0.91,1.13)	0.8062	1.02	(0.87,1.20)	

* 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, °:Trend test.
^ 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.

Analysis is based on study 1245.110.
For discontinued subjects, last available value was used. For completing subjects, last value up to last treatment intake + 7 days was used.
Subjects with a baseline score > 85 are considered as improved if the score remains stable > 85 points at last observation.
^^ Patients with NYHA class I are counted in subgroup NYHA class II. ¹ Baseline SBP median: 132 [mmHg].
² Baseline NT-proBNP median for patients with history of atrial fibrillation or atrial flutter: 1354 [pg/mL].
² Baseline NT-proBNP median for patients without history of atrial fibrillation or atrial flutter: 614 [pg/mL].
³ Baseline uric acid tertile cut-offs are: For males T1: 5.9 T2: 7.5 [mg/dL] [rounded], for females T1: 5.4 T2: 6.9 [mg/dL] [rounded].

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Table R.1.1.3.2.2.1: 1 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 with ceiling correction)

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 LVEF [%]												0.1084
< 50	928	304	32.8	959	305	31.8	0.95	(0.84,1.08)	0.4740	0.93	(0.76,1.13)	
>= 50	1942	571	29.4	1930	618	32.0	1.09	(0.99,1.19)	0.0804	1.14	(0.99,1.31)	
Baseline LVEF [%]												0.2317°/ 0.2568
<50	928	304	32.8	959	305	31.8	0.95	(0.84,1.08)	0.4741	0.93	(0.76,1.13)	
50 to <60	993	283	28.5	990	314	31.7	1.11	(0.97,1.26)	0.1330	1.16	(0.96,1.42)	
>=60	949	288	30.3	940	304	32.3	1.07	(0.94,1.21)	0.3341	1.11	(0.91,1.35)	
Baseline NT-proBNP [pg/mL] (</>=median² by atrial fibrillation/flutter status)												0.6115
< median	1464	448	30.6	1431	468	32.7	1.06	(0.95,1.18)	0.2872	1.09	(0.93,1.28)	
>= median	1402	426	30.4	1455	453	31.1	1.02	(0.92,1.13)	0.7393	1.03	(0.87,1.21)	
Baseline uric acid [mg/dL] (tertiles³)												0.0760°/ 0.2017
<T1	935	310	33.2	931	293	31.5	0.95	(0.83,1.08)	0.4084	0.92	(0.75,1.12)	
>=T1 and <T2	932	284	30.5	999	321	32.1	1.05	(0.92,1.19)	0.4624	1.08	(0.88,1.31)	
>=T2	973	275	28.3	933	301	32.3	1.12	(0.98,1.28)	0.0974	1.19	(0.97,1.45)	
Baseline use of MRA												0.5880
No	1789	528	29.5	1815	573	31.6	1.06	(0.96,1.16)	0.2575	1.09	(0.94,1.26)	
Yes	1081	347	32.1	1074	350	32.6	1.01	(0.90,1.14)	0.8269	1.02	(0.84,1.22)	
Baseline use of ACE-inhibitor, ARB or ARNi												0.8812
No	557	161	28.9	545	165	30.3	1.05	(0.88,1.25)	0.5747	1.08	(0.83,1.41)	
Yes	2313	714	30.9	2344	758	32.3	1.04	(0.95,1.12)	0.4001	1.06	(0.93,1.20)	

* 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, °:Trend test.
^ 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.

Analysis is based on study 1245.110.
For discontinued subjects, last available value was used. For completing subjects, last value up to last treatment intake + 7 days was used.
Subjects with a baseline score > 85 are considered as improved if the score remains stable > 85 points at last observation.
^^ Patients with NYHA class I are counted in subgroup NYHA class II. ¹ Baseline SBP median: 132 [mmHg].
² Baseline NT-proBNP median for patients with history of atrial fibrillation or atrial flutter: 1354 [pg/mL].
² Baseline NT-proBNP median for patients without history of atrial fibrillation or atrial flutter: 614 [pg/mL].
³ Baseline uric acid tertile cut-offs are: For males T1: 5.9 T2: 7.5 [mg/dL] [rounded], for females T1: 5.4 T2: 6.9 [mg/dL] [rounded].

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R.1.1.3.2.2.2 KCCQ Clinical Summary Score responder analysis (15 points)

Table R.1.1.3.2.2.2: 1 Responder analysis for KCCQ-CSS change from baseline to last value during planned treatment period >= 15 points (improvement) overall and by subgroup - RS (OC-AD with ceiling correction)

Subgroup	Placebo			Empa 10mg			Empa 10mg vs Placebo					
Category	N	n	%	N	n	%	Risk ratio *	(95% CI)	p-value	Odds ratio ***	(95% CI)	p-value **
Overall	2869	1183	41.2	2886	1315	45.6	1.11	(1.04,1.17)	0.0005	1.21	(1.08,1.34)	
Sex												0.6166
Male	1588	707	44.5	1597	773	48.4	1.09	(1.02,1.17)	0.0149	1.19	(1.03,1.37)	
Female	1281	476	37.2	1289	542	42.0	1.13	(1.03,1.24)	0.0134	1.23	(1.05,1.45)	
Age [years]												0.6008
<70	1038	495	47.7	1030	528	51.3	1.09	(1.00,1.18)	0.0499	1.19	(1.00,1.42)	
>=70	1831	688	37.6	1856	787	42.4	1.12	(1.04,1.21)	0.0034	1.22	(1.07,1.40)	
Region												0.2178
North America	346	114	32.9	344	113	32.8	0.98	(0.79,1.21)	0.8623	0.97	(0.70,1.33)	
Latin America	724	367	50.7	730	409	56.0	1.11	(1.01,1.22)	0.0284	1.26	(1.02,1.56)	
Europe	1301	458	35.2	1309	497	38.0	1.08	(0.98,1.19)	0.1385	1.13	(0.96,1.33)	
Asia	330	191	57.9	328	215	65.5	1.14	(1.01,1.28)	0.0333	1.40	(1.02,1.92)	
Other	168	53	31.5	175	81	46.3	1.47	(1.12,1.92)	0.0060	1.90	(1.22,2.97)	
OECD member												0.0025
No	789	347	44.0	818	445	54.4	1.26	(1.14,1.39)	<0.0001	1.60	(1.31,1.95)	
Yes	2080	836	40.2	2068	870	42.1	1.04	(0.97,1.12)	0.2673	1.07	(0.94,1.21)	
Baseline NYHA												0.7950
II^^	2359	1005	42.6	2355	1103	46.8	1.10	(1.04,1.17)	0.0018	1.20	(1.07,1.35)	
III/IV	510	178	34.9	531	212	39.9	1.13	(0.96,1.32)	0.1350	1.23	(0.95,1.59)	
Baseline Diabetes status												0.5701
Diabetic	1407	571	40.6	1400	635	45.4	1.13	(1.04,1.22)	0.0052	1.24	(1.06,1.45)	
Non-Diabetic	1462	612	41.9	1486	680	45.8	1.09	(1.01,1.18)	0.0335	1.18	(1.01,1.37)	

* 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, °:Trend test.
^ Models contain terms age, baseline eGFR (CKD-EPI), baseline LVEF, Baseline KCCQ-CSS, 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.

Analysis is based on study 1245.110.
For discontinued subjects, last available value was used. For completing subjects, last value up to last treatment intake + 7 days was used.
Subjects with a baseline score > 85 are considered as improved if the score remains stable > 85 points at last observation.
^^ Patients with NYHA class I are counted in subgroup NYHA class II. [1] Baseline SBP median: 132 [mmHg].
[2] Baseline NT-proBNP median for patients with history of atrial fibrillation or atrial flutter: 1354 [pg/mL].
[2] Baseline NT-proBNP median for patients without history of atrial fibrillation or atrial flutter: 614 [pg/mL].
[3] Baseline uric acid tertile cut-offs are: For males T1: 5.9 T2: 7.5 [mg/dL] [rounded], for females T1: 5.4 T2: 6.9 [mg/dL] [rounded].

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Table R.1.1.3.2.2.2: 1 Responder analysis for KCCQ-CSS change from baseline to last value during planned treatment period >= 15 points (improvement) overall and by subgroup - RS (OC-AD with ceiling correction)

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 Diabetes status												0.6233°/ 0.0719
Diabetic	1407	571	40.6	1400	635	45.4	1.13	(1.04,1.22)	0.0052	1.24	(1.06,1.45)	
Pre-Diabetes	940	409	43.5	974	433	44.5	1.02	(0.92,1.12)	0.6943	1.04	(0.86,1.25)	
Normal (no pre-diabetes)	522	203	38.9	512	247	48.2	1.23	(1.08,1.41)	0.0024	1.49	(1.15,1.92)	
Baseline BMI [kg/m²]												0.9947
<30	1563	705	45.1	1591	792	49.8	1.11	(1.03,1.19)	0.0053	1.22	(1.06,1.42)	
>=30	1306	478	36.6	1295	523	40.4	1.11	(1.00,1.22)	0.0407	1.18	(1.00,1.39)	
Baseline eGFR (CKD-EPI) [mL/min/1.73m²]												0.3947
>=60	1449	650	44.9	1445	733	50.7	1.13	(1.05,1.22)	0.0010	1.28	(1.10,1.49)	
<60	1420	533	37.5	1441	582	40.4	1.08	(0.98,1.18)	0.1090	1.13	(0.97,1.32)	
History of HHF (in the last 12 months)												0.2826
No	2233	933	41.8	2228	1015	45.6	1.09	(1.02,1.16)	0.0103	1.17	(1.03,1.32)	
Yes	636	250	39.3	658	300	45.6	1.17	(1.04,1.33)	0.0107	1.35	(1.08,1.70)	
Baseline SBP (</>= median¹)												0.1826
< median	1414	596	42.1	1444	648	44.9	1.06	(0.98,1.15)	0.1319	1.12	(0.96,1.31)	
>= median	1455	587	40.3	1442	667	46.3	1.15	(1.06,1.25)	0.0007	1.30	(1.12,1.51)	
History of atrial fibrillation or atrial flutter												0.0510
No	1364	623	45.7	1364	652	47.8	1.05	(0.97,1.13)	0.2507	1.09	(0.93,1.27)	
Yes	1502	560	37.3	1519	663	43.6	1.17	(1.08,1.28)	0.0002	1.33	(1.14,1.54)	

* 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, °:Trend test.
^ Models contain terms age, baseline eGFR (CKD-EPI), baseline LVEF, Baseline KCCQ-CSS, 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.

Analysis is based on study 1245.110.
For discontinued subjects, last available value was used. For completing subjects, last value up to last treatment intake + 7 days was used.
Subjects with a baseline score > 85 are considered as improved if the score remains stable > 85 points at last observation.
^^ Patients with NYHA class I are counted in subgroup NYHA class II. ¹ Baseline SBP median: 132 [mmHg].
² Baseline NT-proBNP median for patients with history of atrial fibrillation or atrial flutter: 1354 [pg/mL].
² Baseline NT-proBNP median for patients without history of atrial fibrillation or atrial flutter: 614 [pg/mL].
³ Baseline uric acid tertile cut-offs are: For males T1: 5.9 T2: 7.5 [mg/dL] [rounded], for females T1: 5.4 T2: 6.9 [mg/dL] [rounded].

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Table R.1.1.3.2.2.2: 1 Responder analysis for KCCQ-CSS change from baseline to last value during planned treatment period >= 15 points (improvement) overall and by subgroup - RS (OC-AD with ceiling correction)

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 LVEF [%]												0.1854
< 50	929	411	44.2	958	490	51.1	1.16	(1.06,1.28)	0.0013	1.36	(1.13,1.64)	
>= 50	1940	772	39.8	1928	825	42.8	1.08	(1.00,1.16)	0.0511	1.14	(1.00,1.30)	
Baseline LVEF [%]												0.0930°/ 0.2363
<50	929	411	44.2	958	490	51.1	1.16	(1.06,1.28)	0.0013	1.36	(1.13,1.64)	
50 to <60	992	392	39.5	988	439	44.4	1.12	(1.01,1.24)	0.0312	1.21	(1.01,1.46)	
>=60	948	380	40.1	940	386	41.1	1.03	(0.93,1.15)	0.5672	1.06	(0.88,1.28)	
Baseline NT-proBNP [pg/mL] (</>=median[2] by atrial fibrillation/flutter status)												0.1078
< median	1464	626	42.8	1430	703	49.2	1.16	(1.07,1.25)	0.0002	1.33	(1.14,1.55)	
>= median	1401	557	39.8	1453	612	42.1	1.05	(0.97,1.15)	0.2265	1.10	(0.94,1.28)	
Baseline uric acid [mg/dL] (tertiles[3])												0.7053°/ 0.8197
<T1	937	402	42.9	930	441	47.4	1.10	(1.00,1.21)	0.0457	1.20	(1.00,1.45)	
>=T1 and <T2	931	401	43.1	997	460	46.1	1.08	(0.98,1.19)	0.1097	1.17	(0.97,1.40)	
>=T2	971	368	37.9	933	401	43.0	1.13	(1.02,1.26)	0.0217	1.25	(1.03,1.51)	
Baseline use of MRA												0.7406
No	1788	733	41.0	1814	814	44.9	1.10	(1.02,1.18)	0.0119	1.19	(1.04,1.36)	
Yes	1081	450	41.6	1072	501	46.7	1.12	(1.02,1.23)	0.0161	1.24	(1.04,1.48)	
Baseline use of ACE-inhibitor, ARB or ARNi												0.2944
No	558	210	37.6	543	246	45.3	1.18	(1.03,1.36)	0.0170	1.36	(1.06,1.74)	
Yes	2311	973	42.1	2343	1069	45.6	1.09	(1.02,1.16)	0.0071	1.17	(1.04,1.32)	

* 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, °:Trend test.
^ Models contain terms age, baseline eGFR (CKD-EPI), baseline LVEF, Baseline KCCQ-CSS, 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.

Analysis is based on study 1245.110.
For discontinued subjects, last available value was used. For completing subjects, last value up to last treatment intake + 7 days was used.
Subjects with a baseline score > 85 are considered as improved if the score remains stable > 85 points at last observation.
^^ Patients with NYHA class I are counted in subgroup NYHA class II. [1] Baseline SBP median: 132 [mmHg].
[2] Baseline NT-proBNP median for patients with history of atrial fibrillation or atrial flutter: 1354 [pg/mL].
[2] Baseline NT-proBNP median for patients without history of atrial fibrillation or atrial flutter: 614 [pg/mL].
[3] Baseline uric acid tertile cut-offs are: For males T1: 5.9 T2: 7.5 [mg/dL] [rounded], for females T1: 5.4 T2: 6.9 [mg/dL] [rounded].

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R.1.1.3.2.2.3 KCCQ Total Symptoms Score responder analysis (15 points)

Table R.1.1.3.2.2.3: 1 Responder analysis for KCCQ-TSS change from baseline to last value during planned treatment period >= 15 points (improvement) overall and by subgroup - RS (OC-AD with ceiling correction)

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	2869	1478	51.5	2886	1646	57.0	1.11	(1.06,1.16)	<0.0001	1.27	(1.14,1.41)	
Sex												0.9599
Male	1588	853	53.7	1597	949	59.4	1.11	(1.05,1.18)	0.0005	1.29	(1.11,1.48)	
Female	1281	625	48.8	1289	697	54.1	1.11	(1.03,1.19)	0.0066	1.25	(1.07,1.46)	
Age [years]												0.0112
<70	1038	606	58.4	1030	616	59.8	1.03	(0.96,1.11)	0.3751	1.08	(0.90,1.29)	
>=70	1831	872	47.6	1856	1030	55.5	1.16	(1.10,1.24)	<0.0001	1.39	(1.22,1.58)	
Region												0.5170
North America	346	144	41.6	344	155	45.1	1.08	(0.91,1.28)	0.3916	1.14	(0.84,1.55)	
Latin America	724	451	62.3	730	492	67.4	1.09	(1.01,1.17)	0.0312	1.27	(1.02,1.58)	
Europe	1301	612	47.0	1309	672	51.3	1.09	(1.01,1.18)	0.0218	1.20	(1.03,1.40)	
Asia	330	196	59.4	328	227	69.2	1.17	(1.04,1.31)	0.0067	1.56	(1.13,2.15)	
Other	168	75	44.6	175	100	57.1	1.28	(1.04,1.58)	0.0185	1.69	(1.10,2.60)	
OECD member												0.2714
No	789	443	56.1	818	524	64.1	1.15	(1.06,1.25)	0.0005	1.44	(1.18,1.77)	
Yes	2080	1035	49.8	2068	1122	54.3	1.09	(1.03,1.16)	0.0032	1.20	(1.06,1.36)	
Baseline NYHA												0.2259
II^^	2359	1260	53.4	2355	1374	58.3	1.10	(1.04,1.15)	0.0003	1.24	(1.10,1.39)	
III/IV	510	218	42.7	531	272	51.2	1.19	(1.05,1.36)	0.0075	1.42	(1.10,1.82)	
Baseline Diabetes status												0.4220
Diabetic	1407	716	50.9	1400	801	57.2	1.13	(1.06,1.21)	0.0003	1.32	(1.14,1.54)	
Non-Diabetic	1462	762	52.1	1486	845	56.9	1.09	(1.02,1.16)	0.0091	1.22	(1.05,1.42)	

* 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, °:Trend test.
^ Models contain terms age, baseline eGFR (CKD-EPI), baseline LVEF, Baseline KCCQ-TSS, 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.

Analysis is based on study 1245.110.
For discontinued subjects, last available value was used. For completing subjects, last value up to last treatment intake + 7 days was used.
Subjects with a baseline score > 85 are considered as improved if the score remains stable > 85 points at last observation.
^^ Patients with NYHA class I are counted in subgroup NYHA class II. [1] Baseline SBP median: 132 [mmHg].
[2] Baseline NT-proBNP median for patients with history of atrial fibrillation or atrial flutter: 1354 [pg/mL].
[2] Baseline NT-proBNP median for patients without history of atrial fibrillation or atrial flutter: 614 [pg/mL].
[3] Baseline uric acid tertile cut-offs are: For males T1: 5.9 T2: 7.5 [mg/dL] [rounded], for females T1: 5.4 T2: 6.9 [mg/dL] [rounded].

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Table R.1.1.3.2.2.3: 1 Responder analysis for KCCQ-TSS change from baseline to last value during planned treatment period >= 15 points (improvement) overall and by subgroup - RS (OC-AD with ceiling correction)

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 Diabetes status												0.8806°/ 0.3273
Diabetic	1407	716	50.9	1400	801	57.2	1.13	(1.06,1.21)	0.0003	1.32	(1.14,1.54)	
Pre-Diabetes	940	496	52.8	974	544	55.9	1.06	(0.97,1.15)	0.1810	1.14	(0.94,1.37)	
Normal (no pre-diabetes)	522	266	51.0	512	301	58.8	1.15	(1.03,1.28)	0.0099	1.39	(1.08,1.79)	
Baseline BMI [kg/m²]												0.8486
<30	1563	842	53.9	1591	953	59.9	1.11	(1.05,1.18)	0.0004	1.30	(1.12,1.50)	
>=30	1306	636	48.7	1295	693	53.5	1.10	(1.02,1.19)	0.0092	1.23	(1.05,1.44)	
Baseline eGFR (CKD-EPI) [mL/min/1.73m²]												0.4672
>=60	1449	802	55.3	1445	872	60.3	1.09	(1.03,1.16)	0.0044	1.24	(1.07,1.45)	
<60	1420	676	47.6	1441	774	53.7	1.13	(1.05,1.22)	0.0007	1.29	(1.11,1.50)	
History of HHF (in the last 12 months)												0.6103
No	2233	1161	52.0	2228	1277	57.3	1.10	(1.05,1.16)	0.0002	1.25	(1.11,1.41)	
Yes	636	317	49.8	658	369	56.1	1.14	(1.03,1.26)	0.0136	1.33	(1.06,1.67)	
Baseline SBP (</>= median¹)												0.8505
< median	1414	726	51.3	1444	819	56.7	1.11	(1.03,1.18)	0.0032	1.26	(1.08,1.46)	
>= median	1455	752	51.7	1442	827	57.4	1.12	(1.05,1.19)	0.0010	1.28	(1.10,1.49)	
History of atrial fibrillation or atrial flutter												0.0210
No	1364	771	56.5	1364	813	59.6	1.05	(0.99,1.12)	0.1171	1.13	(0.97,1.32)	
Yes	1502	706	47.0	1519	831	54.7	1.17	(1.09,1.26)	<0.0001	1.40	(1.21,1.62)	

* 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, °:Trend test.
^ Models contain terms age, baseline eGFR (CKD-EPI), baseline LVEF, Baseline KCCQ-TSS, 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.

Analysis is based on study 1245.110.
For discontinued subjects, last available value was used. For completing subjects, last value up to last treatment intake + 7 days was used.
Subjects with a baseline score > 85 are considered as improved if the score remains stable > 85 points at last observation.
^^ Patients with NYHA class I are counted in subgroup NYHA class II. ¹ Baseline SBP median: 132 [mmHg].
² Baseline NT-proBNP median for patients with history of atrial fibrillation or atrial flutter: 1354 [pg/mL].
² Baseline NT-proBNP median for patients without history of atrial fibrillation or atrial flutter: 614 [pg/mL].
³ Baseline uric acid tertile cut-offs are: For males T1: 5.9 T2: 7.5 [mg/dL] [rounded], for females T1: 5.4 T2: 6.9 [mg/dL] [rounded].

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Table R.1.1.3.2.2.3: 1 Responder analysis for KCCQ-TSS change from baseline to last value during planned treatment period >= 15 points (improvement) overall and by subgroup - RS (OC-AD with ceiling correction)

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 LVEF [%]												0.5922
< 50	929	511	55.0	958	592	61.8	1.13	(1.05,1.22)	0.0016	1.36	(1.12,1.64)	
>= 50	1940	967	49.8	1928	1054	54.7	1.10	(1.04,1.17)	0.0016	1.23	(1.08,1.40)	
Baseline LVEF [%]												0.5400°/ 0.8305
<50	929	511	55.0	958	592	61.8	1.13	(1.05,1.22)	0.0016	1.36	(1.12,1.64)	
50 to <60	992	493	49.7	988	547	55.4	1.11	(1.02,1.20)	0.0134	1.25	(1.04,1.49)	
>=60	948	474	50.0	940	507	53.9	1.09	(1.00,1.19)	0.0477	1.21	(1.00,1.45)	
Baseline NT-proBNP [pg/mL] (</>=median² by atrial fibrillation/flutter status)												0.9674
< median	1464	796	54.4	1430	860	60.1	1.11	(1.05,1.18)	0.0008	1.29	(1.11,1.50)	
>= median	1401	681	48.6	1453	784	54.0	1.11	(1.03,1.19)	0.0036	1.25	(1.08,1.45)	
Baseline uric acid [mg/dL] (tertiles³)												0.0364°/ 0.0822
<T1	937	514	54.9	930	540	58.1	1.06	(0.98,1.14)	0.1516	1.14	(0.95,1.38)	
>=T1 and <T2	931	492	52.8	997	563	56.5	1.08	(0.99,1.17)	0.0685	1.19	(0.99,1.43)	
>=T2	971	458	47.2	933	526	56.4	1.20	(1.10,1.31)	<0.0001	1.48	(1.23,1.77)	
Baseline use of MRA												0.3773
No	1788	920	51.5	1814	1015	56.0	1.09	(1.03,1.16)	0.0037	1.22	(1.07,1.39)	
Yes	1081	558	51.6	1072	631	58.9	1.14	(1.06,1.23)	0.0006	1.36	(1.14,1.62)	
Baseline use of ACE-inhibitor, ARB or ARNi												0.1773
No	558	259	46.4	543	303	55.8	1.19	(1.06,1.34)	0.0027	1.45	(1.14,1.85)	
Yes	2311	1219	52.7	2343	1343	57.3	1.09	(1.04,1.15)	0.0006	1.23	(1.09,1.38)	

* 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, °:Trend test.
^ Models contain terms age, baseline eGFR (CKD-EPI), baseline LVEF, Baseline KCCQ-TSS, 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.

Analysis is based on study 1245.110.
For discontinued subjects, last available value was used. For completing subjects, last value up to last treatment intake + 7 days was used.
Subjects with a baseline score > 85 are considered as improved if the score remains stable > 85 points at last observation.
^^ Patients with NYHA class I are counted in subgroup NYHA class II. ¹ Baseline SBP median: 132 [mmHg].
² Baseline NT-proBNP median for patients with history of atrial fibrillation or atrial flutter: 1354 [pg/mL].
² Baseline NT-proBNP median for patients without history of atrial fibrillation or atrial flutter: 614 [pg/mL].
³ Baseline uric acid tertile cut-offs are: For males T1: 5.9 T2: 7.5 [mg/dL] [rounded], for females T1: 5.4 T2: 6.9 [mg/dL] [rounded].

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R.1.1.3.2.2.4 KCCQ Overall Summary Score responder analysis (15 points)

Table R.1.1.3.2.2.4: 1 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 with ceiling correction)

Subgroup	Placebo			Empa 10mg			Empa 10mg vs Placebo					
Category	N	n	%	N	n	%	Risk ratio *	(95% CI)	p-value	Odds ratio ***	(95% CI)	p-value **
Overall	2869	1134	39.5	2886	1253	43.4	1.10	(1.04,1.17)	0.0018	1.19	(1.06,1.32)	
Sex												0.6996
Male	1588	667	42.0	1597	726	45.5	1.09	(1.01,1.18)	0.0286	1.17	(1.01,1.35)	
Female	1281	467	36.5	1289	527	40.9	1.12	(1.01,1.23)	0.0258	1.20	(1.02,1.42)	
Age [years]												0.7043
<70	1038	467	45.0	1030	499	48.4	1.09	(0.99,1.19)	0.0727	1.17	(0.98,1.40)	
>=70	1831	667	36.4	1856	754	40.6	1.11	(1.03,1.20)	0.0090	1.20	(1.05,1.37)	
Region												0.1144
North America	346	121	35.0	344	116	33.7	0.95	(0.78,1.17)	0.6415	0.93	(0.67,1.27)	
Latin America	724	361	49.9	730	398	54.5	1.10	(1.00,1.21)	0.0600	1.22	(0.99,1.50)	
Europe	1301	436	33.5	1309	464	35.4	1.06	(0.95,1.17)	0.2895	1.09	(0.93,1.28)	
Asia	330	159	48.2	328	196	59.8	1.25	(1.09,1.44)	0.0018	1.63	(1.20,2.23)	
Other	168	57	33.9	175	79	45.1	1.33	(1.01,1.73)	0.0400	1.61	(1.03,2.50)	
OECD member												0.0327
No	789	342	43.3	818	421	51.5	1.21	(1.09,1.34)	0.0004	1.44	(1.18,1.76)	
Yes	2080	792	38.1	2068	832	40.2	1.05	(0.98,1.13)	0.1882	1.09	(0.96,1.23)	
Baseline NYHA												0.7110
II^^	2359	963	40.8	2355	1049	44.5	1.09	(1.03,1.17)	0.0060	1.18	(1.05,1.33)	
III/IV	510	171	33.5	531	204	38.4	1.13	(0.96,1.33)	0.1342	1.22	(0.94,1.59)	
Baseline Diabetes status												0.4013
Diabetic	1407	532	37.8	1400	595	42.5	1.13	(1.03,1.24)	0.0065	1.24	(1.06,1.44)	
Non-Diabetic	1462	602	41.2	1486	658	44.3	1.07	(0.99,1.17)	0.0870	1.14	(0.98,1.32)	

* 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, °:Trend test.
^ Models contain terms age, baseline eGFR (CKD-EPI), baseline LVEF, Baseline KCCQ-OSS, 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.

Analysis is based on study 1245.110.
For discontinued subjects, last available value was used. For completing subjects, last value up to last treatment intake + 7 days was used.
Subjects with a baseline score > 85 are considered as improved if the score remains stable > 85 points at last observation.
^^ Patients with NYHA class I are counted in subgroup NYHA class II. [1] Baseline SBP median: 132 [mmHg].
[2] Baseline NT-proBNP median for patients with history of atrial fibrillation or atrial flutter: 1354 [pg/mL].
[2] Baseline NT-proBNP median for patients without history of atrial fibrillation or atrial flutter: 614 [pg/mL].
[3] Baseline uric acid tertile cut-offs are: For males T1: 5.9 T2: 7.5 [mg/dL] [rounded], for females T1: 5.4 T2: 6.9 [mg/dL] [rounded].

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Table R.1.1.3.2.2.4: 1 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 with ceiling correction)

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 Diabetes status												0.8660°/ 0.0923
Diabetic	1407	532	37.8	1400	595	42.5	1.13	(1.03,1.24)	0.0065	1.24	(1.06,1.44)	
Pre-Diabetes	940	396	42.1	974	414	42.5	1.01	(0.91,1.12)	0.8697	1.02	(0.84,1.22)	
Normal (no pre-diabetes)	522	206	39.5	512	244	47.7	1.20	(1.05,1.38)	0.0075	1.41	(1.10,1.82)	
Baseline BMI [kg/m²]												0.8528
<30	1563	656	42.0	1591	731	45.9	1.09	(1.01,1.18)	0.0217	1.18	(1.02,1.37)	
>=30	1306	478	36.6	1295	522	40.3	1.11	(1.01,1.22)	0.0370	1.19	(1.01,1.39)	
Baseline eGFR (CKD-EPI) [mL/min/1.73m²]												0.1226
>=60	1449	625	43.1	1445	714	49.4	1.15	(1.06,1.24)	0.0004	1.31	(1.12,1.52)	
<60	1420	509	35.8	1441	539	37.4	1.04	(0.95,1.15)	0.3837	1.07	(0.92,1.25)	
History of HHF (in the last 12 months)												0.4986
No	2233	899	40.3	2228	976	43.8	1.09	(1.02,1.16)	0.0136	1.16	(1.03,1.31)	
Yes	636	235	36.9	658	277	42.1	1.15	(1.00,1.31)	0.0451	1.27	(1.01,1.60)	
Baseline SBP (</>= median¹)												0.1177
< median	1414	562	39.7	1444	603	41.8	1.05	(0.96,1.14)	0.2872	1.09	(0.93,1.27)	
>= median	1455	572	39.3	1442	650	45.1	1.15	(1.06,1.25)	0.0008	1.29	(1.11,1.50)	
History of atrial fibrillation or atrial flutter												0.0181
No	1364	597	43.8	1364	612	44.9	1.02	(0.94,1.11)	0.5631	1.04	(0.89,1.22)	
Yes	1502	537	35.8	1519	641	42.2	1.18	(1.08,1.29)	0.0002	1.34	(1.15,1.55)	

* 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, °:Trend test.
^ Models contain terms age, baseline eGFR (CKD-EPI), baseline LVEF, Baseline KCCQ-OSS, 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.

Analysis is based on study 1245.110.
For discontinued subjects, last available value was used. For completing subjects, last value up to last treatment intake + 7 days was used.
Subjects with a baseline score > 85 are considered as improved if the score remains stable > 85 points at last observation.
^^ Patients with NYHA class I are counted in subgroup NYHA class II. ¹ Baseline SBP median: 132 [mmHg].
² Baseline NT-proBNP median for patients with history of atrial fibrillation or atrial flutter: 1354 [pg/mL].
² Baseline NT-proBNP median for patients without history of atrial fibrillation or atrial flutter: 614 [pg/mL].
³ Baseline uric acid tertile cut-offs are: For males T1: 5.9 T2: 7.5 [mg/dL] [rounded], for females T1: 5.4 T2: 6.9 [mg/dL] [rounded].

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Table R.1.1.3.2.2.4: 1 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 with ceiling correction)

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 LVEF [%]												0.7523
< 50	929	391	42.1	958	436	45.5	1.09	(0.98,1.20)	0.1085	1.17	(0.97,1.41)	
>= 50	1940	743	38.3	1928	817	42.4	1.11	(1.03,1.19)	0.0074	1.19	(1.05,1.36)	
Baseline LVEF [%]												0.9606°/ 0.7769
<50	929	391	42.1	958	436	45.5	1.09	(0.98,1.20)	0.1082	1.17	(0.97,1.40)	
50 to <60	992	360	36.3	988	411	41.6	1.14	(1.02,1.27)	0.0204	1.24	(1.03,1.49)	
>=60	948	383	40.4	940	406	43.2	1.08	(0.97,1.20)	0.1398	1.15	(0.96,1.39)	
Baseline NT-proBNP [pg/mL] (</>=median² by atrial fibrillation/flutter status)												0.2338
< median	1464	595	40.6	1430	660	46.2	1.14	(1.05,1.24)	0.0016	1.27	(1.09,1.48)	
>= median	1401	539	38.5	1453	593	40.8	1.06	(0.97,1.16)	0.2002	1.11	(0.95,1.29)	
Baseline uric acid [mg/dL] (tertiles³)												0.5780°/ 0.3528
<T1	937	383	40.9	930	420	45.2	1.10	(1.00,1.22)	0.0566	1.20	(0.99,1.45)	
>=T1 and <T2	931	387	41.6	997	425	42.6	1.03	(0.93,1.14)	0.5182	1.06	(0.88,1.28)	
>=T2	971	354	36.5	933	393	42.1	1.15	(1.03,1.29)	0.0115	1.27	(1.05,1.54)	
Baseline use of MRA												0.4703
No	1788	716	40.0	1814	783	43.2	1.08	(1.00,1.17)	0.0424	1.15	(1.00,1.32)	
Yes	1081	418	38.7	1072	470	43.8	1.13	(1.03,1.25)	0.0138	1.25	(1.04,1.49)	
Baseline use of ACE-inhibitor, ARB or ARNi												0.6779
No	558	200	35.8	543	223	41.1	1.13	(0.98,1.31)	0.0977	1.23	(0.96,1.58)	
Yes	2311	934	40.4	2343	1030	44.0	1.09	(1.02,1.17)	0.0079	1.17	(1.04,1.32)	

* 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, °:Trend test.
^ Models contain terms age, baseline eGFR (CKD-EPI), baseline LVEF, Baseline KCCQ-OSS, 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.

Analysis is based on study 1245.110.
For discontinued subjects, last available value was used. For completing subjects, last value up to last treatment intake + 7 days was used.
Subjects with a baseline score > 85 are considered as improved if the score remains stable > 85 points at last observation.
^^ Patients with NYHA class I are counted in subgroup NYHA class II. ¹ Baseline SBP median: 132 [mmHg].
² Baseline NT-proBNP median for patients with history of atrial fibrillation or atrial flutter: 1354 [pg/mL].
² Baseline NT-proBNP median for patients without history of atrial fibrillation or atrial flutter: 614 [pg/mL].
³ Baseline uric acid tertile cut-offs are: For males T1: 5.9 T2: 7.5 [mg/dL] [rounded], for females T1: 5.4 T2: 6.9 [mg/dL] [rounded].

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R.1.2 Safety

R.1.2.1 Adverse events overall

Table R.1.2.1: 1 Proportion of patients with any adverse event 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	2989	2585	86.5	2996	2574	85.9	0.5232	0.99	(0.97,1.01)	0.95	(0.82,1.10)	-0.01	(-0.02,0.01)	
Sex														0.7018
Male	1653	1412	85.4	1658	1412	85.2	0.8343	1.00	(0.97,1.03)	0.98	(0.81,1.19)	0.00	(-0.03,0.02)	
Female	1336	1173	87.8	1338	1162	86.8	0.4588	0.99	(0.96,1.02)	0.92	(0.73,1.15)	-0.01	(-0.03,0.02)	
Age [years]														0.6881
<70	1084	909	83.9	1066	893	83.8	0.9573	1.00	(0.96,1.04)	0.99	(0.79,1.25)	0.00	(-0.03,0.03)	
>=70	1905	1676	88.0	1930	1681	87.1	0.4091	0.99	(0.97,1.01)	0.92	(0.76,1.12)	-0.01	(-0.03,0.01)	
Region														0.3493
North America	359	330	91.9	359	332	92.5	0.7808	1.01	(0.96,1.05)	1.08	(0.63,1.87)	0.01	(-0.03,0.04)	
Latin America	757	653	86.3	758	655	86.4	0.9322	1.00	(0.96,1.04)	1.01	(0.76,1.36)	0.00	(-0.03,0.04)	
Europe	1341	1127	84.0	1346	1103	81.9	0.1483	0.98	(0.94,1.01)	0.86	(0.70,1.05)	-0.02	(-0.05,0.01)	
Asia	343	316	92.1	343	314	91.5	0.7803	0.99	(0.95,1.04)	0.93	(0.54,1.60)	-0.01	(-0.05,0.04)	
Other	189	159	84.1	190	170	89.5	0.1241	1.06	(0.98,1.15)	1.60	(0.88,2.94)	0.05	(-0.01,0.12)	
OECD member														0.1693
No	847	717	84.7	868	747	86.1	0.4094	1.02	(0.98,1.06)	1.12	(0.86,1.46)	0.01	(-0.02,0.05)	
Yes	2142	1868	87.2	2128	1827	85.9	0.1953	0.98	(0.96,1.01)	0.89	(0.75,1.06)	-0.01	(-0.03,0.01)	
Baseline NYHA														0.9578
II^	2450	2091	85.3	2435	2063	84.7	0.5409	0.99	(0.97,1.02)	0.95	(0.81,1.11)	-0.01	(-0.03,0.01)	
III/IV	539	494	91.7	561	511	91.1	0.7393	0.99	(0.96,1.03)	0.93	(0.61,1.42)	-0.01	(-0.04,0.03)	
Baseline Diabetes Status														0.8464
Diabetic	1471	1283	87.2	1465	1272	86.8	0.7510	1.00	(0.97,1.02)	0.97	(0.78,1.20)	0.00	(-0.03,0.02)	
Non-Diabetic	1518	1302	85.8	1531	1302	85.0	0.5690	0.99	(0.96,1.02)	0.94	(0.77,1.15)	-0.01	(-0.03,0.02)	
Baseline Diabetes Status														0.6423
Diabetic	1471	1283	87.2	1465	1272	86.8	0.7510	1.00	(0.97,1.02)	0.97	(0.78,1.20)	0.00	(-0.03,0.02)	
Pre-Diabetes	979	845	86.3	1001	848	84.7	0.3128	0.98	(0.95,1.02)	0.88	(0.68,1.13)	-0.02	(-0.05,0.02)	
Normal (no pre-diabetes)	539	457	84.8	530	454	85.7	0.6874	1.01	(0.96,1.06)	1.07	(0.76,1.50)	0.01	(-0.03,0.05)	

Analysis is based on study 1245.110.
^ Patients with NYHA class I are counted in subgroup NYHA class II.
Risk ratios and odds ratios with confidence intervals (CIs) are estimated by Cochran-Mantel-Haenszel method. For risk differences standard Wald asymptotic confidence limits are calculated. A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied in case of any zero cells in contingency table.
Only treatment emergent AEs are displayed (onset between first dose until treatment stop +7 days).
Subgroups will only be analysed if at least 10 events occurred in at least one category (both treatments combined).
MedDRA version: 23.1. * Chi-square test for treatment effect ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction).

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Table R.1.2.1: 1 Proportion of patients with any adverse event 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 BMI [kg/m²]														0.8084
<30	1641	1429	87.1	1654	1434	86.7	0.7452	1.00	(0.97,1.02)	0.97	(0.79,1.18)	0.00	(-0.03,0.02)	
>=30	1348	1156	85.8	1342	1140	84.9	0.5530	0.99	(0.96,1.02)	0.94	(0.76,1.16)	-0.01	(-0.03,0.02)	
Baseline eGFR (CKD-EPI) [mL/min/1.73m²]														0.6040
>=60	1505	1263	83.9	1493	1237	82.9	0.4326	0.99	(0.96,1.02)	0.93	(0.76,1.12)	-0.01	(-0.04,0.02)	
<60	1482	1321	89.1	1503	1337	89.0	0.8743	1.00	(0.97,1.02)	0.98	(0.78,1.24)	0.00	(-0.02,0.02)	
History of HHF (in the last 12 months)														0.1265
No	2320	2011	86.7	2297	1961	85.4	0.1996	0.98	(0.96,1.01)	0.90	(0.76,1.06)	-0.01	(-0.03,0.01)	
Yes	669	574	85.8	699	613	87.7	0.3006	1.02	(0.98,1.07)	1.18	(0.86,1.61)	0.02	(-0.02,0.05)	
Baseline SBP (</>= median)														0.0663
< median	1474	1268	86.0	1496	1303	87.1	0.3906	1.01	(0.98,1.04)	1.10	(0.89,1.35)	0.01	(-0.01,0.04)	
>= median	1515	1317	86.9	1500	1271	84.7	0.0836	0.97	(0.95,1.00)	0.83	(0.68,1.02)	-0.02	(-0.05,0.00)	
History of atrial fibrillation or atrial flutter														0.5361
No	1426	1224	85.8	1417	1200	84.7	0.3877	0.99	(0.96,1.02)	0.91	(0.74,1.12)	-0.01	(-0.04,0.01)	
Yes	1558	1356	87.0	1575	1370	87.0	0.9664	1.00	(0.97,1.03)	1.00	(0.81,1.23)	0.00	(-0.02,0.02)	
Baseline LVEF [%]														0.2958
< 50	988	826	83.6	995	840	84.4	0.6188	1.01	(0.97,1.05)	1.06	(0.84,1.35)	0.01	(-0.02,0.04)	
>= 50	2001	1759	87.9	2001	1734	86.7	0.2356	0.99	(0.96,1.01)	0.89	(0.74,1.08)	-0.01	(-0.03,0.01)	
Baseline LVEF [%]														0.5355
<50	988	826	83.6	995	840	84.4	0.6188	1.01	(0.97,1.05)	1.06	(0.84,1.35)	0.01	(-0.02,0.04)	
50 to <60	1030	899	87.3	1028	880	85.6	0.2661	0.98	(0.95,1.01)	0.87	(0.67,1.12)	-0.02	(-0.05,0.01)	
>=60	971	860	88.6	973	854	87.8	0.5856	0.99	(0.96,1.02)	0.93	(0.70,1.22)	-0.01	(-0.04,0.02)	

Analysis is based on study 1245.110.
^ Patients with NYHA class I are counted in subgroup NYHA class II.
Risk ratios and odds ratios with confidence intervals (CIs) are estimated by Cochran-Mantel-Haenszel method. For risk differences standard Wald asymptotic confidence limits are calculated. A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied in case of any zero cells in contingency table.
Only treatment emergent AEs are displayed (onset between first dose until treatment stop +7 days).
Subgroups will only be analysed if at least 10 events occurred in at least one category (both treatments combined).
MedDRA version: 23.1. * Chi-square test for treatment effect ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction).

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Table R.1.2.1: 1 Proportion of patients with any adverse event 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 NT-proBNP [pg/mL] (</>=median by atrial fibrillation/flutter status)														0.2145
< median	1507	1288	85.5	1476	1236	83.7	0.1910	0.98	(0.95,1.01)	0.88	(0.72,1.07)	-0.02	(-0.04,0.01)	
>= median	1475	1291	87.5	1516	1334	88.0	0.6954	1.01	(0.98,1.03)	1.04	(0.84,1.30)	0.00	(-0.02,0.03)	
Baseline uric acid [mg/dL] (tertiles)														0.3563
<T1	975	834	85.5	963	806	83.7	0.2611	0.98	(0.94,1.02)	0.87	(0.68,1.11)	-0.02	(-0.05,0.01)	
>=T1 and <T2	966	823	85.2	1032	874	84.7	0.7517	0.99	(0.96,1.03)	0.96	(0.75,1.23)	-0.01	(-0.04,0.03)	
>=T2	1016	899	88.5	970	870	89.7	0.3890	1.01	(0.98,1.05)	1.13	(0.85,1.50)	0.01	(-0.02,0.04)	
Baseline use of MRA														0.1763
No	1865	1602	85.9	1878	1620	86.3	0.7478	1.00	(0.98,1.03)	1.03	(0.86,1.24)	0.00	(-0.02,0.03)	
Yes	1124	983	87.5	1118	954	85.3	0.1423	0.98	(0.94,1.01)	0.83	(0.65,1.06)	-0.02	(-0.05,0.01)	
Baseline use of ACE-inhibitor, ARB or ARNi														0.6220
No	586	512	87.4	568	498	87.7	0.8758	1.00	(0.96,1.05)	1.03	(0.73,1.46)	0.00	(-0.04,0.04)	
Yes	2403	2073	86.3	2428	2076	85.5	0.4453	0.99	(0.97,1.01)	0.94	(0.80,1.10)	-0.01	(-0.03,0.01)	

Analysis is based on study 1245.110.
^ Patients with NYHA class I are counted in subgroup NYHA class II.
Risk ratios and odds ratios with confidence intervals (CIs) are estimated by Cochran-Mantel-Haenszel method. For risk differences standard Wald asymptotic confidence limits are calculated. A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied in case of any zero cells in contingency table.
Only treatment emergent AEs are displayed (onset between first dose until treatment stop +7 days).
Subgroups will only be analysed if at least 10 events occurred in at least one category (both treatments combined).
MedDRA version: 23.1. * Chi-square test for treatment effect ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction).

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Table R.1.2.1: 2 Proportion of patients with any adverse event (excluding disease-related events) 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	2989	2507	83.9	2996	2512	83.8	0.9756	1.00	(0.98,1.02)	1.00	(0.87,1.15)	0.00	(-0.02,0.02)	
Sex														0.3805
Male	1653	1360	82.3	1658	1376	83.0	0.5861	1.01	(0.98,1.04)	1.05	(0.88,1.26)	0.01	(-0.02,0.03)	
Female	1336	1147	85.9	1338	1136	84.9	0.4867	0.99	(0.96,1.02)	0.93	(0.75,1.15)	-0.01	(-0.04,0.02)	
Age [years]														0.6070
<70	1084	878	81.0	1066	870	81.6	0.7136	1.01	(0.97,1.05)	1.04	(0.84,1.29)	0.01	(-0.03,0.04)	
>=70	1905	1629	85.5	1930	1642	85.1	0.7043	0.99	(0.97,1.02)	0.97	(0.81,1.16)	0.00	(-0.03,0.02)	
Region														0.4883
North America	359	325	90.5	359	327	91.1	0.7961	1.01	(0.96,1.05)	1.07	(0.64,1.77)	0.01	(-0.04,0.05)	
Latin America	757	627	82.8	758	634	83.6	0.6714	1.01	(0.97,1.06)	1.06	(0.81,1.39)	0.01	(-0.03,0.05)	
Europe	1341	1087	81.1	1346	1071	79.6	0.3315	0.98	(0.95,1.02)	0.91	(0.75,1.10)	-0.01	(-0.04,0.02)	
Asia	343	310	90.4	343	311	90.7	0.8963	1.00	(0.96,1.05)	1.03	(0.62,1.72)	0.00	(-0.04,0.05)	
Other	189	158	83.6	190	169	88.9	0.1302	1.06	(0.98,1.15)	1.58	(0.87,2.86)	0.05	(-0.02,0.12)	
OECD member														0.1750
No	847	690	81.5	868	725	83.5	0.2613	1.03	(0.98,1.07)	1.15	(0.90,1.48)	0.02	(-0.02,0.06)	
Yes	2142	1817	84.8	2128	1787	84.0	0.4431	0.99	(0.96,1.02)	0.94	(0.79,1.11)	-0.01	(-0.03,0.01)	
Baseline NYHA														0.4795
II^	2450	2027	82.7	2435	2020	83.0	0.8368	1.00	(0.98,1.03)	1.02	(0.88,1.18)	0.00	(-0.02,0.02)	
III/IV	539	480	89.1	561	492	87.7	0.4841	0.98	(0.94,1.03)	0.88	(0.61,1.27)	-0.01	(-0.05,0.02)	
Baseline Diabetes Status														0.8639
Diabetic	1471	1244	84.6	1465	1241	84.7	0.9153	1.00	(0.97,1.03)	1.01	(0.83,1.24)	0.00	(-0.02,0.03)	
Non-Diabetic	1518	1263	83.2	1531	1271	83.0	0.8922	1.00	(0.97,1.03)	0.99	(0.82,1.19)	0.00	(-0.03,0.02)	
Baseline Diabetes Status														0.5644
Diabetic	1471	1244	84.6	1465	1241	84.7	0.9153	1.00	(0.97,1.03)	1.01	(0.83,1.24)	0.00	(-0.02,0.03)	
Pre-Diabetes	979	823	84.1	1001	829	82.8	0.4551	0.99	(0.95,1.02)	0.91	(0.72,1.16)	-0.01	(-0.05,0.02)	
Normal (no pre-diabetes)	539	440	81.6	530	442	83.4	0.4479	1.02	(0.97,1.08)	1.13	(0.82,1.55)	0.02	(-0.03,0.06)	

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^ Patients with NYHA class I are counted in subgroup NYHA class II.
Risk ratios and odds ratios with confidence intervals (CIs) are estimated by Cochran-Mantel-Haenszel method. For risk differences standard Wald asymptotic confidence limits are calculated. A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
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Subgroups will only be analysed if at least 10 events occurred in at least one category (both treatments combined).
MedDRA version: 23.1. * Chi-square test for treatment effect ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction).

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Table R.1.2.1: 2 Proportion of patients with any adverse event (excluding disease-related events) 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 BMI [kg/m²]														0.4573
<30	1641	1383	84.3	1654	1404	84.9	0.6294	1.01	(0.98,1.04)	1.05	(0.87,1.27)	0.01	(-0.02,0.03)	
>=30	1348	1124	83.4	1342	1108	82.6	0.5718	0.99	(0.96,1.02)	0.94	(0.77,1.15)	-0.01	(-0.04,0.02)	
Baseline eGFR (CKD-EPI) [mL/min/1.73m²]														0.7294
>=60	1505	1216	80.8	1493	1210	81.0	0.8631	1.00	(0.97,1.04)	1.02	(0.85,1.22)	0.00	(-0.03,0.03)	
<60	1482	1290	87.0	1503	1302	86.6	0.7357	1.00	(0.97,1.02)	0.96	(0.78,1.19)	0.00	(-0.03,0.02)	
History of HHF (in the last 12 months)														0.0939
No	2320	1955	84.3	2297	1915	83.4	0.4076	0.99	(0.96,1.01)	0.94	(0.80,1.09)	-0.01	(-0.03,0.01)	
Yes	669	552	82.5	699	597	85.4	0.1442	1.04	(0.99,1.08)	1.24	(0.93,1.66)	0.03	(-0.01,0.07)	
Baseline SBP (</>= median)														0.2332
< median	1474	1235	83.8	1496	1270	84.9	0.4063	1.01	(0.98,1.05)	1.09	(0.89,1.33)	0.01	(-0.02,0.04)	
>= median	1515	1272	84.0	1500	1242	82.8	0.3921	0.99	(0.96,1.02)	0.92	(0.76,1.11)	-0.01	(-0.04,0.01)	
History of atrial fibrillation or atrial flutter														0.6787
No	1426	1181	82.8	1417	1179	83.2	0.7847	1.00	(0.97,1.04)	1.03	(0.84,1.25)	0.00	(-0.02,0.03)	
Yes	1558	1321	84.8	1575	1329	84.4	0.7523	1.00	(0.97,1.03)	0.97	(0.80,1.18)	0.00	(-0.03,0.02)	
Baseline LVEF [%]														0.1045
< 50	988	789	79.9	995	817	82.1	0.2013	1.03	(0.99,1.07)	1.16	(0.92,1.45)	0.02	(-0.01,0.06)	
>= 50	2001	1718	85.9	2001	1695	84.7	0.3048	0.99	(0.96,1.01)	0.91	(0.77,1.09)	-0.01	(-0.03,0.01)	
Baseline LVEF [%]														0.2202
<50	988	789	79.9	995	817	82.1	0.2013	1.03	(0.99,1.07)	1.16	(0.92,1.45)	0.02	(-0.01,0.06)	
50 to <60	1030	878	85.2	1028	857	83.4	0.2418	0.98	(0.94,1.02)	0.87	(0.68,1.10)	-0.02	(-0.05,0.01)	
>=60	971	840	86.5	973	838	86.1	0.8057	1.00	(0.96,1.03)	0.97	(0.75,1.25)	0.00	(-0.03,0.03)	

Analysis is based on study 1245.110.
^ Patients with NYHA class I are counted in subgroup NYHA class II.
Risk ratios and odds ratios with confidence intervals (CIs) are estimated by Cochran-Mantel-Haenszel method. For risk differences standard Wald asymptotic confidence limits are calculated. A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied in case of any zero cells in contingency table.
Only treatment emergent AEs are displayed (onset between first dose until treatment stop +7 days).
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MedDRA version: 23.1. * Chi-square test for treatment effect ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction).

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Table R.1.2.1: 2 Proportion of patients with any adverse event (excluding disease-related events) 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 NT-proBNP [pg/mL] (</>=median by atrial fibrillation/flutter status)														0.2527
< median	1507	1258	83.5	1476	1215	82.3	0.4001	0.99	(0.95,1.02)	0.92	(0.76,1.11)	-0.01	(-0.04,0.02)	
>= median	1475	1243	84.3	1516	1293	85.3	0.4378	1.01	(0.98,1.04)	1.08	(0.89,1.32)	0.01	(-0.02,0.04)	
Baseline uric acid [mg/dL] (tertiles)														0.6782
<T1	975	804	82.5	963	786	81.6	0.6294	0.99	(0.95,1.03)	0.94	(0.75,1.19)	-0.01	(-0.04,0.03)	
>=T1 and <T2	966	798	82.6	1032	854	82.8	0.9326	1.00	(0.96,1.04)	1.01	(0.80,1.27)	0.00	(-0.03,0.03)	
>=T2	1016	876	86.2	970	848	87.4	0.4287	1.01	(0.98,1.05)	1.11	(0.86,1.44)	0.01	(-0.02,0.04)	
Baseline use of MRA														0.0445
No	1865	1548	83.0	1878	1586	84.5	0.2298	1.02	(0.99,1.05)	1.11	(0.93,1.32)	0.01	(-0.01,0.04)	
Yes	1124	959	85.3	1118	926	82.8	0.1066	0.97	(0.94,1.01)	0.83	(0.66,1.04)	-0.02	(-0.06,0.01)	
Baseline use of ACE-inhibitor, ARB or ARNi														0.4976
No	586	495	84.5	568	487	85.7	0.5453	1.02	(0.97,1.07)	1.11	(0.80,1.53)	0.01	(-0.03,0.05)	
Yes	2403	2012	83.7	2428	2025	83.4	0.7593	1.00	(0.97,1.02)	0.98	(0.84,1.14)	0.00	(-0.02,0.02)	

Analysis is based on study 1245.110.
^ Patients with NYHA class I are counted in subgroup NYHA class II.
Risk ratios and odds ratios with confidence intervals (CIs) are estimated by Cochran-Mantel-Haenszel method. For risk differences standard Wald asymptotic confidence limits are calculated. A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied in case of any zero cells in contingency table.
Only treatment emergent AEs are displayed (onset between first dose until treatment stop +7 days).
Subgroups will only be analysed if at least 10 events occurred in at least one category (both treatments combined).
MedDRA version: 23.1. * Chi-square test for treatment effect ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction).

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Table R.1.2.1: 3 Proportion of patients with serious adverse events 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	2989	1543	51.6	2996	1436	47.9	0.0043	0.93	(0.88,0.98)	0.86	(0.78,0.95)	-0.04	(-0.06,-0.01)	
Sex														0.9212
Male	1653	885	53.5	1658	826	49.8	0.0322	0.93	(0.87,0.99)	0.86	(0.75,0.99)	-0.04	(-0.07, 0.00)	
Female	1336	658	49.3	1338	610	45.6	0.0580	0.93	(0.85,1.00)	0.86	(0.74,1.01)	-0.04	(-0.07, 0.00)	
Age [years]														0.6534
<70	1084	500	46.1	1066	464	43.5	0.2258	0.94	(0.86,1.04)	0.90	(0.76,1.07)	-0.03	(-0.07, 0.02)	
>=70	1905	1043	54.8	1930	972	50.4	0.0065	0.92	(0.87,0.98)	0.84	(0.74,0.95)	-0.04	(-0.08,-0.01)	
Region														0.7555
North America	359	215	59.9	359	212	59.1	0.8196	0.99	(0.87,1.11)	0.97	(0.72,1.30)	-0.01	(-0.08, 0.06)	
Latin America	757	392	51.8	758	369	48.7	0.2272	0.94	(0.85,1.04)	0.88	(0.72,1.08)	-0.03	(-0.08, 0.02)	
Europe	1341	651	48.5	1346	601	44.7	0.0430	0.92	(0.85,1.00)	0.86	(0.73,1.00)	-0.04	(-0.08, 0.00)	
Asia	343	188	54.8	343	163	47.5	0.0562	0.87	(0.75,1.00)	0.75	(0.55,1.01)	-0.07	(-0.15, 0.00)	
Other	189	97	51.3	190	91	47.9	0.5045	0.93	(0.76,1.14)	0.87	(0.58,1.30)	-0.03	(-0.13, 0.07)	
OECD member														0.6769
No	847	435	51.4	868	421	48.5	0.2370	0.94	(0.86,1.04)	0.89	(0.74,1.08)	-0.03	(-0.08, 0.02)	
Yes	2142	1108	51.7	2128	1015	47.7	0.0085	0.92	(0.87,0.98)	0.85	(0.75,0.96)	-0.04	(-0.07,-0.01)	
Baseline NYHA														0.4691
II^	2450	1195	48.8	2435	1090	44.8	0.0050	0.92	(0.86,0.97)	0.85	(0.76,0.95)	-0.04	(-0.07,-0.01)	
III/IV	539	348	64.6	561	346	61.7	0.3210	0.96	(0.87,1.05)	0.88	(0.69,1.13)	-0.03	(-0.09, 0.03)	
Baseline Diabetes Status														0.7423
Diabetic	1471	798	54.2	1465	732	50.0	0.0202	0.92	(0.86,0.99)	0.84	(0.73,0.97)	-0.04	(-0.08,-0.01)	
Non-Diabetic	1518	745	49.1	1531	704	46.0	0.0871	0.94	(0.87,1.01)	0.88	(0.77,1.02)	-0.03	(-0.07, 0.00)	
Baseline Diabetes Status														0.8173
Diabetic	1471	798	54.2	1465	732	50.0	0.0202	0.92	(0.86,0.99)	0.84	(0.73,0.97)	-0.04	(-0.08,-0.01)	
Pre-Diabetes	979	480	49.0	1001	453	45.3	0.0925	0.92	(0.84,1.01)	0.86	(0.72,1.03)	-0.04	(-0.08, 0.01)	
Normal (no pre-diabetes)	539	265	49.2	530	251	47.4	0.5545	0.96	(0.85,1.09)	0.93	(0.73,1.18)	-0.02	(-0.08, 0.04)	

Analysis is based on study 1245.110.
^ Patients with NYHA class I are counted in subgroup NYHA class II.
Risk ratios and odds ratios with confidence intervals (CIs) are estimated by Cochran-Mantel-Haenszel method. For risk differences standard Wald asymptotic confidence limits are calculated. A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
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Table R.1.2.1: 3 Proportion of patients with serious adverse events 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 BMI [kg/m²]														0.0008
<30	1641	870	53.0	1654	752	45.5	<0.0001	0.86	(0.80,0.92)	0.74	(0.64,0.85)	-0.08	(-0.11,-0.04)	
>=30	1348	673	49.9	1342	684	51.0	0.5886	1.02	(0.95,1.10)	1.04	(0.90,1.21)	0.01	(-0.03, 0.05)	
Baseline eGFR (CKD-EPI) [mL/min/1.73m²]														0.6941
>=60	1505	676	44.9	1493	614	41.1	0.0360	0.92	(0.84,0.99)	0.86	(0.74,0.99)	-0.04	(-0.07, 0.00)	
<60	1482	867	58.5	1503	822	54.7	0.0357	0.93	(0.88,1.00)	0.86	(0.74,0.99)	-0.04	(-0.07, 0.00)	
History of HHF (in the last 12 months)														0.5091
No	2320	1149	49.5	2297	1044	45.5	0.0056	0.92	(0.86,0.98)	0.85	(0.76,0.95)	-0.04	(-0.07,-0.01)	
Yes	669	394	58.9	699	392	56.1	0.2927	0.95	(0.87,1.04)	0.89	(0.72,1.10)	-0.03	(-0.08, 0.02)	
Baseline SBP (</>= median)														0.9784
< median	1474	770	52.2	1496	726	48.5	0.0432	0.93	(0.86,1.00)	0.86	(0.75,1.00)	-0.04	(-0.07, 0.00)	
>= median	1515	773	51.0	1500	710	47.3	0.0427	0.93	(0.86,1.00)	0.86	(0.75,1.00)	-0.04	(-0.07, 0.00)	
History of atrial fibrillation or atrial flutter														0.5137
No	1426	694	48.7	1417	628	44.3	0.0201	0.91	(0.84,0.99)	0.84	(0.72,0.97)	-0.04	(-0.08,-0.01)	
Yes	1558	847	54.4	1575	807	51.2	0.0797	0.94	(0.88,1.01)	0.88	(0.77,1.01)	-0.03	(-0.07, 0.00)	
Baseline LVEF [%]														0.8136
< 50	988	506	51.2	995	469	47.1	0.0693	0.92	(0.84,1.01)	0.85	(0.71,1.01)	-0.04	(-0.08, 0.00)	
>= 50	2001	1037	51.8	2001	967	48.3	0.0269	0.93	(0.88,0.99)	0.87	(0.77,0.98)	-0.03	(-0.07, 0.00)	
Baseline LVEF [%]														0.1775
<50	988	506	51.2	995	469	47.1	0.0693	0.92	(0.84,1.01)	0.85	(0.71,1.01)	-0.04	(-0.08, 0.00)	
50 to <60	1030	546	53.0	1028	480	46.7	0.0042	0.88	(0.81,0.96)	0.78	(0.65,0.92)	-0.06	(-0.11,-0.02)	
>=60	971	491	50.6	973	487	50.1	0.8204	0.99	(0.91,1.08)	0.98	(0.82,1.17)	-0.01	(-0.05, 0.04)	

Analysis is based on study 1245.110.
^ Patients with NYHA class I are counted in subgroup NYHA class II.
Risk ratios and odds ratios with confidence intervals (CIs) are estimated by Cochran-Mantel-Haenszel method. For risk differences standard Wald asymptotic confidence limits are calculated. A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied in case of any zero cells in contingency table.
Only treatment emergent AEs are displayed (onset between first dose until treatment stop +7 days).
Subgroups will only be analysed if at least 10 events occurred in at least one category (both treatments combined).
MedDRA version: 23.1. * Chi-square test for treatment effect ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction).

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Table R.1.2.1: 3 Proportion of patients with serious adverse events 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 NT-proBNP [pg/mL] (</>=median by atrial fibrillation/flutter status)														0.6610
< median	1507	700	46.4	1476	627	42.5	0.0291	0.91	(0.84,0.99)	0.85	(0.74,0.98)	-0.04	(-0.08, 0.00)	
>= median	1475	840	56.9	1516	808	53.3	0.0447	0.94	(0.88,1.00)	0.86	(0.75,1.00)	-0.04	(-0.07, 0.00)	
Baseline uric acid [mg/dL] (tertiles)														0.0129
<T1	975	493	50.6	963	406	42.2	0.0002	0.83	(0.76,0.92)	0.71	(0.60,0.85)	-0.08	(-0.13,-0.04)	
>=T1 and <T2	966	458	47.4	1032	469	45.4	0.3785	0.96	(0.87,1.05)	0.92	(0.77,1.10)	-0.02	(-0.06, 0.02)	
>=T2	1016	574	56.5	970	549	56.6	0.9635	1.00	(0.93,1.08)	1.00	(0.84,1.20)	0.00	(-0.04, 0.04)	
Baseline use of MRA														0.0993
No	1865	937	50.2	1878	906	48.2	0.2214	0.96	(0.90,1.02)	0.92	(0.81,1.05)	-0.02	(-0.05, 0.01)	
Yes	1124	606	53.9	1118	530	47.4	0.0021	0.88	(0.81,0.95)	0.77	(0.65,0.91)	-0.07	(-0.11,-0.02)	
Baseline use of ACE-inhibitor, ARB or ARNi														0.1629
No	586	324	55.3	568	312	54.9	0.9020	0.99	(0.90,1.10)	0.99	(0.78,1.24)	0.00	(-0.06, 0.05)	
Yes	2403	1219	50.7	2428	1124	46.3	0.0020	0.91	(0.86,0.97)	0.84	(0.75,0.94)	-0.04	(-0.07,-0.02)	

Analysis is based on study 1245.110.
^ Patients with NYHA class I are counted in subgroup NYHA class II.
Risk ratios and odds ratios with confidence intervals (CIs) are estimated by Cochran-Mantel-Haenszel method. For risk differences standard Wald asymptotic confidence limits are calculated. A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied in case of any zero cells in contingency table.
Only treatment emergent AEs are displayed (onset between first dose until treatment stop +7 days).
Subgroups will only be analysed if at least 10 events occurred in at least one category (both treatments combined).
MedDRA version: 23.1. * Chi-square test for treatment effect ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction).

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Table R.1.2.1: 4 Proportion of patients with serious adverse events (excluding disease-related events) 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	2989	1243	41.6	2996	1157	38.6	0.0192	0.93	(0.87,0.99)	0.88	(0.80,0.98)	-0.03	(-0.05, 0.00)	
Sex														0.2922
Male	1653	702	42.5	1658	673	40.6	0.2731	0.96	(0.88,1.04)	0.93	(0.81,1.06)	-0.02	(-0.05, 0.01)	
Female	1336	541	40.5	1338	484	36.2	0.0216	0.89	(0.81,0.98)	0.83	(0.71,0.97)	-0.04	(-0.08,-0.01)	
Age [years]														0.2171
<70	1084	376	34.7	1066	364	34.1	0.7922	0.98	(0.88,1.11)	0.98	(0.82,1.17)	-0.01	(-0.05, 0.03)	
>=70	1905	867	45.5	1930	793	41.1	0.0057	0.90	(0.84,0.97)	0.84	(0.73,0.95)	-0.04	(-0.08,-0.01)	
Region														0.9848
North America	359	191	53.2	359	184	51.3	0.6010	0.96	(0.84,1.11)	0.92	(0.69,1.24)	-0.02	(-0.09, 0.05)	
Latin America	757	304	40.2	758	280	36.9	0.1980	0.92	(0.81,1.04)	0.87	(0.71,1.07)	-0.03	(-0.08, 0.02)	
Europe	1341	525	39.1	1346	484	36.0	0.0876	0.92	(0.83,1.01)	0.87	(0.75,1.02)	-0.03	(-0.07, 0.00)	
Asia	343	144	42.0	343	136	39.7	0.5343	0.94	(0.79,1.13)	0.91	(0.67,1.23)	-0.02	(-0.10, 0.05)	
Other	189	79	41.8	190	73	38.4	0.5023	0.92	(0.72,1.18)	0.87	(0.58,1.31)	-0.03	(-0.13, 0.06)	
OECD member														0.8930
No	847	330	39.0	868	312	35.9	0.1969	0.92	(0.82,1.04)	0.88	(0.72,1.07)	-0.03	(-0.08, 0.02)	
Yes	2142	913	42.6	2128	845	39.7	0.0530	0.93	(0.87,1.00)	0.89	(0.78,1.00)	-0.03	(-0.06, 0.00)	
Baseline NYHA														0.4214
II^	2450	967	39.5	2435	879	36.1	0.0151	0.91	(0.85,0.98)	0.87	(0.77,0.97)	-0.03	(-0.06,-0.01)	
III/IV	539	276	51.2	561	278	49.6	0.5839	0.97	(0.86,1.09)	0.94	(0.74,1.19)	-0.02	(-0.08, 0.04)	
Baseline Diabetes Status														0.5717
Diabetic	1471	636	43.2	1465	578	39.5	0.0375	0.91	(0.84,0.99)	0.86	(0.74,0.99)	-0.04	(-0.07, 0.00)	
Non-Diabetic	1518	607	40.0	1531	579	37.8	0.2195	0.95	(0.87,1.03)	0.91	(0.79,1.06)	-0.02	(-0.06, 0.01)	
Baseline Diabetes Status														0.4891
Diabetic	1471	636	43.2	1465	578	39.5	0.0375	0.91	(0.84,0.99)	0.86	(0.74,0.99)	-0.04	(-0.07, 0.00)	
Pre-Diabetes	979	392	40.0	1001	366	36.6	0.1115	0.91	(0.82,1.02)	0.86	(0.72,1.03)	-0.03	(-0.08, 0.01)	
Normal (no pre-diabetes)	539	215	39.9	530	213	40.2	0.9203	1.01	(0.87,1.17)	1.01	(0.79,1.29)	0.00	(-0.06, 0.06)	

Analysis is based on study 1245.110.
^ Patients with NYHA class I are counted in subgroup NYHA class II.
Risk ratios and odds ratios with confidence intervals (CIs) are estimated by Cochran-Mantel-Haenszel method. For risk differences standard Wald asymptotic confidence limits are calculated. A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied in case of any zero cells in contingency table.
Only treatment emergent AEs are displayed (onset between first dose until treatment stop +7 days).
Subgroups will only be analysed if at least 10 events occurred in at least one category (both treatments combined).
MedDRA version: 23.1. * Chi-square test for treatment effect ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction).

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Table R.1.2.1: 4 Proportion of patients with serious adverse events (excluding disease-related events) 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 BMI [kg/m²]														0.0129
<30	1641	697	42.5	1654	607	36.7	0.0007	0.86	(0.79,0.94)	0.79	(0.68,0.90)	-0.06	(-0.09,-0.02)	
>=30	1348	546	40.5	1342	550	41.0	0.8004	1.01	(0.92,1.11)	1.02	(0.87,1.19)	0.00	(-0.03, 0.04)	
Baseline eGFR (CKD-EPI) [mL/min/1.73m²]														0.7905
>=60	1505	529	35.1	1493	491	32.9	0.1911	0.94	(0.85,1.03)	0.90	(0.78,1.05)	-0.02	(-0.06, 0.01)	
<60	1482	714	48.2	1503	666	44.3	0.0341	0.92	(0.85,0.99)	0.86	(0.74,0.99)	-0.04	(-0.07, 0.00)	
History of HHF (in the last 12 months)														0.0321
No	2320	954	41.1	2297	843	36.7	0.0021	0.89	(0.83,0.96)	0.83	(0.74,0.93)	-0.04	(-0.07,-0.02)	
Yes	669	289	43.2	699	314	44.9	0.5212	1.04	(0.92,1.17)	1.07	(0.87,1.33)	0.02	(-0.04, 0.07)	
Baseline SBP (</>= median)														0.6421
< median	1474	631	42.8	1496	586	39.2	0.0439	0.92	(0.84,1.00)	0.86	(0.74,1.00)	-0.04	(-0.07, 0.00)	
>= median	1515	612	40.4	1500	571	38.1	0.1903	0.94	(0.86,1.03)	0.91	(0.78,1.05)	-0.02	(-0.06, 0.01)	
History of atrial fibrillation or atrial flutter														0.7863
No	1426	549	38.5	1417	502	35.4	0.0897	0.92	(0.84,1.01)	0.88	(0.75,1.02)	-0.03	(-0.07, 0.00)	
Yes	1558	692	44.4	1575	655	41.6	0.1098	0.94	(0.86,1.02)	0.89	(0.77,1.03)	-0.03	(-0.06, 0.01)	
Baseline LVEF [%]														0.6310
< 50	988	375	38.0	995	359	36.1	0.3872	0.95	(0.85,1.07)	0.92	(0.77,1.11)	-0.02	(-0.06, 0.02)	
>= 50	2001	868	43.4	2001	798	39.9	0.0248	0.92	(0.85,0.99)	0.87	(0.76,0.98)	-0.03	(-0.07, 0.00)	
Baseline LVEF [%]														0.0888
<50	988	375	38.0	995	359	36.1	0.3872	0.95	(0.85,1.07)	0.92	(0.77,1.11)	-0.02	(-0.06, 0.02)	
50 to <60	1030	459	44.6	1028	389	37.8	0.0019	0.85	(0.77,0.94)	0.76	(0.64,0.90)	-0.07	(-0.11,-0.02)	
>=60	971	409	42.1	973	409	42.0	0.9692	1.00	(0.90,1.11)	1.00	(0.83,1.19)	0.00	(-0.04, 0.04)	

Analysis is based on study 1245.110.
^ Patients with NYHA class I are counted in subgroup NYHA class II.
Risk ratios and odds ratios with confidence intervals (CIs) are estimated by Cochran-Mantel-Haenszel method. For risk differences standard Wald asymptotic confidence limits are calculated. A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied in case of any zero cells in contingency table.
Only treatment emergent AEs are displayed (onset between first dose until treatment stop +7 days).
Subgroups will only be analysed if at least 10 events occurred in at least one category (both treatments combined).
MedDRA version: 23.1. * Chi-square test for treatment effect ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction).

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Table R.1.2.1: 4 Proportion of patients with serious adverse events (excluding disease-related events) 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 NT-proBNP [pg/mL] (</>=median by atrial fibrillation/flutter status)														0.8735
< median	1507	577	38.3	1476	527	35.7	0.1440	0.93	(0.85,1.02)	0.90	(0.77,1.04)	-0.03	(-0.06, 0.01)	
>= median	1475	664	45.0	1516	630	41.6	0.0562	0.92	(0.85,1.00)	0.87	(0.75,1.00)	-0.03	(-0.07, 0.00)	
Baseline uric acid [mg/dL] (tertiles)														0.0419
<T1	975	395	40.5	963	322	33.4	0.0013	0.83	(0.73,0.93)	0.74	(0.61,0.89)	-0.07	(-0.11,-0.03)	
>=T1 and <T2	966	369	38.2	1032	393	38.1	0.9570	1.00	(0.89,1.11)	1.00	(0.83,1.19)	0.00	(-0.04, 0.04)	
>=T2	1016	465	45.8	970	433	44.6	0.6135	0.98	(0.89,1.07)	0.96	(0.80,1.14)	-0.01	(-0.06, 0.03)	
Baseline use of MRA														0.0391
No	1865	751	40.3	1878	739	39.4	0.5663	0.98	(0.90,1.06)	0.96	(0.84,1.10)	-0.01	(-0.04, 0.02)	
Yes	1124	492	43.8	1118	418	37.4	0.0021	0.85	(0.77,0.94)	0.77	(0.65,0.91)	-0.06	(-0.10,-0.02)	
Baseline use of ACE-inhibitor, ARB or ARNi														0.1652
No	586	262	44.7	568	256	45.1	0.9020	1.01	(0.89,1.15)	1.01	(0.80,1.28)	0.00	(-0.05, 0.06)	
Yes	2403	981	40.8	2428	901	37.1	0.0081	0.91	(0.85,0.98)	0.86	(0.76,0.96)	-0.04	(-0.06,-0.01)	

Analysis is based on study 1245.110.
^ Patients with NYHA class I are counted in subgroup NYHA class II.
Risk ratios and odds ratios with confidence intervals (CIs) are estimated by Cochran-Mantel-Haenszel method. For risk differences standard Wald asymptotic confidence limits are calculated. A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied in case of any zero cells in contingency table.
Only treatment emergent AEs are displayed (onset between first dose until treatment stop +7 days).
Subgroups will only be analysed if at least 10 events occurred in at least one category (both treatments combined).
MedDRA version: 23.1. * Chi-square test for treatment effect ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction).

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Table R.1.2.1: 5 Proportion of patients with severe adverse events 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	2989	851	28.5	2996	786	26.2	0.0523	0.92	(0.85,1.00)	0.89	(0.80,1.00)	-0.02	(-0.04, 0.00)	
Sex														0.9539
Male	1653	502	30.4	1658	463	27.9	0.1218	0.92	(0.83,1.02)	0.89	(0.76,1.03)	-0.02	(-0.06, 0.01)	
Female	1336	349	26.1	1338	323	24.1	0.2374	0.92	(0.81,1.05)	0.90	(0.76,1.07)	-0.02	(-0.05, 0.01)	
Age [years]														0.9556
<70	1084	284	26.2	1066	258	24.2	0.2864	0.92	(0.80,1.07)	0.90	(0.74,1.09)	-0.02	(-0.06, 0.02)	
>=70	1905	567	29.8	1930	528	27.4	0.0990	0.92	(0.83,1.02)	0.89	(0.77,1.02)	-0.02	(-0.05, 0.00)	
Region														0.3485
North America	359	125	34.8	359	120	33.4	0.6939	0.96	(0.78,1.18)	0.94	(0.69,1.28)	-0.01	(-0.08, 0.06)	
Latin America	757	248	32.8	758	218	28.8	0.0916	0.88	(0.75,1.02)	0.83	(0.67,1.03)	-0.04	(-0.09, 0.01)	
Europe	1341	326	24.3	1346	315	23.4	0.5810	0.96	(0.84,1.10)	0.95	(0.80,1.14)	-0.01	(-0.04, 0.02)	
Asia	343	94	27.4	343	70	20.4	0.0317	0.74	(0.57,0.98)	0.68	(0.48,0.97)	-0.07	(-0.13,-0.01)	
Other	189	58	30.7	190	63	33.2	0.6060	1.08	(0.80,1.45)	1.12	(0.73,1.73)	0.02	(-0.07, 0.12)	
OECD member														0.6437
No	847	267	31.5	868	259	29.8	0.4495	0.95	(0.82,1.09)	0.92	(0.75,1.13)	-0.02	(-0.06, 0.03)	
Yes	2142	584	27.3	2128	527	24.8	0.0627	0.91	(0.82,1.01)	0.88	(0.77,1.01)	-0.02	(-0.05, 0.00)	
Baseline NYHA														0.4839
II^	2450	631	25.8	2435	566	23.2	0.0414	0.90	(0.82,1.00)	0.87	(0.77,0.99)	-0.03	(-0.05, 0.00)	
III/IV	539	220	40.8	561	220	39.2	0.5880	0.96	(0.83,1.11)	0.94	(0.73,1.19)	-0.02	(-0.07, 0.04)	
Baseline Diabetes Status														0.5306
Diabetic	1471	444	30.2	1465	418	28.5	0.3260	0.95	(0.84,1.06)	0.92	(0.79,1.08)	-0.02	(-0.05, 0.02)	
Non-Diabetic	1518	407	26.8	1531	368	24.0	0.0785	0.90	(0.79,1.01)	0.86	(0.73,1.02)	-0.03	(-0.06, 0.00)	
Baseline Diabetes Status														0.7229
Diabetic	1471	444	30.2	1465	418	28.5	0.3260	0.95	(0.84,1.06)	0.92	(0.79,1.08)	-0.02	(-0.05, 0.02)	
Pre-Diabetes	979	259	26.5	1001	243	24.3	0.2650	0.92	(0.79,1.07)	0.89	(0.73,1.09)	-0.02	(-0.06, 0.02)	
Normal (no pre-diabetes)	539	148	27.5	530	125	23.6	0.1465	0.86	(0.70,1.06)	0.82	(0.62,1.07)	-0.04	(-0.09, 0.01)	

Analysis is based on study 1245.110.
^ Patients with NYHA class I are counted in subgroup NYHA class II.
Risk ratios and odds ratios with confidence intervals (CIs) are estimated by Cochran-Mantel-Haenszel method. For risk differences standard Wald asymptotic confidence limits are calculated. A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied in case of any zero cells in contingency table.
Only treatment emergent AEs are displayed (onset between first dose until treatment stop +7 days).
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MedDRA version: 23.1. * Chi-square test for treatment effect ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction).

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Table R.1.2.1: 5 Proportion of patients with severe adverse events 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 BMI [kg/m²]														0.0183
<30	1641	477	29.1	1654	404	24.4	0.0026	0.84	(0.75,0.94)	0.79	(0.68,0.92)	-0.05	(-0.08,-0.02)	
>=30	1348	374	27.7	1342	382	28.5	0.6778	1.03	(0.91,1.16)	1.04	(0.88,1.23)	0.01	(-0.03, 0.04)	
Baseline eGFR (CKD-EPI) [mL/min/1.73m²]														0.8734
>=60	1505	346	23.0	1493	318	21.3	0.2650	0.93	(0.81,1.06)	0.91	(0.76,1.08)	-0.02	(-0.05, 0.01)	
<60	1482	505	34.1	1503	468	31.1	0.0869	0.91	(0.82,1.01)	0.87	(0.75,1.02)	-0.03	(-0.06, 0.00)	
History of HHF (in the last 12 months)														0.4912
No	2320	607	26.2	2297	562	24.5	0.1849	0.94	(0.85,1.03)	0.91	(0.80,1.04)	-0.02	(-0.04, 0.01)	
Yes	669	244	36.5	699	224	32.0	0.0845	0.88	(0.76,1.02)	0.82	(0.66,1.03)	-0.04	(-0.09, 0.01)	
Baseline SBP (</>= median)														0.9233
< median	1474	425	28.8	1496	399	26.7	0.1883	0.93	(0.82,1.04)	0.90	(0.76,1.05)	-0.02	(-0.05, 0.01)	
>= median	1515	426	28.1	1500	387	25.8	0.1514	0.92	(0.82,1.03)	0.89	(0.76,1.04)	-0.02	(-0.05, 0.01)	
History of atrial fibrillation or atrial flutter														0.2008
No	1426	394	27.6	1417	339	23.9	0.0239	0.87	(0.76,0.98)	0.82	(0.70,0.97)	-0.04	(-0.07, 0.00)	
Yes	1558	457	29.3	1575	446	28.3	0.5306	0.97	(0.86,1.08)	0.95	(0.82,1.11)	-0.01	(-0.04, 0.02)	
Baseline LVEF [%]														0.8595
< 50	988	302	30.6	995	283	28.4	0.2996	0.93	(0.81,1.07)	0.90	(0.74,1.10)	-0.02	(-0.06, 0.02)	
>= 50	2001	549	27.4	2001	503	25.1	0.0986	0.92	(0.83,1.02)	0.89	(0.77,1.02)	-0.02	(-0.05, 0.00)	
Baseline LVEF [%]														0.5177
<50	988	302	30.6	995	283	28.4	0.2996	0.93	(0.81,1.07)	0.90	(0.74,1.10)	-0.02	(-0.06, 0.02)	
50 to <60	1030	291	28.3	1028	251	24.4	0.0482	0.86	(0.75,1.00)	0.82	(0.67,1.00)	-0.04	(-0.08, 0.00)	
>=60	971	258	26.6	973	252	25.9	0.7366	0.97	(0.84,1.13)	0.97	(0.79,1.18)	-0.01	(-0.05, 0.03)	

Analysis is based on study 1245.110.
^ Patients with NYHA class I are counted in subgroup NYHA class II.
Risk ratios and odds ratios with confidence intervals (CIs) are estimated by Cochran-Mantel-Haenszel method. For risk differences standard Wald asymptotic confidence limits are calculated. A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied in case of any zero cells in contingency table.
Only treatment emergent AEs are displayed (onset between first dose until treatment stop +7 days).
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MedDRA version: 23.1. * Chi-square test for treatment effect ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction).

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Table R.1.2.1: 5 Proportion of patients with severe adverse events 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 NT-proBNP [pg/mL] (</>=median by atrial fibrillation/flutter status)														0.4775
< median	1507	352	23.4	1476	304	20.6	0.0687	0.88	(0.77,1.01)	0.85	(0.72,1.01)	-0.03	(-0.06, 0.00)	
>= median	1475	499	33.8	1516	481	31.7	0.2207	0.94	(0.85,1.04)	0.91	(0.78,1.06)	-0.02	(-0.05, 0.01)	
Baseline uric acid [mg/dL] (tertiles)														0.6740
<T1	975	255	26.2	963	219	22.7	0.0806	0.87	(0.74,1.02)	0.83	(0.68,1.02)	-0.03	(-0.07, 0.00)	
>=T1 and <T2	966	253	26.2	1032	256	24.8	0.4779	0.95	(0.82,1.10)	0.93	(0.76,1.14)	-0.01	(-0.05, 0.02)	
>=T2	1016	335	33.0	970	302	31.1	0.3803	0.94	(0.83,1.07)	0.92	(0.76,1.11)	-0.02	(-0.06, 0.02)	
Baseline use of MRA														0.9976
No	1865	514	27.6	1878	477	25.4	0.1341	0.92	(0.83,1.03)	0.89	(0.77,1.03)	-0.02	(-0.05, 0.01)	
Yes	1124	337	30.0	1118	309	27.6	0.2205	0.92	(0.81,1.05)	0.89	(0.74,1.07)	-0.02	(-0.06, 0.01)	
Baseline use of ACE-inhibitor, ARB or ARNi														0.1746
No	586	179	30.5	568	178	31.3	0.7711	1.03	(0.86,1.22)	1.04	(0.81,1.33)	0.01	(-0.05, 0.06)	
Yes	2403	672	28.0	2428	608	25.0	0.0213	0.90	(0.82,0.98)	0.86	(0.76,0.98)	-0.03	(-0.05, 0.00)	

Analysis is based on study 1245.110.
^ Patients with NYHA class I are counted in subgroup NYHA class II.
Risk ratios and odds ratios with confidence intervals (CIs) are estimated by Cochran-Mantel-Haenszel method. For risk differences standard Wald asymptotic confidence limits are calculated. A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied in case of any zero cells in contingency table.
Only treatment emergent AEs are displayed (onset between first dose until treatment stop +7 days).
Subgroups will only be analysed if at least 10 events occurred in at least one category (both treatments combined).
MedDRA version: 23.1. * Chi-square test for treatment effect ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction).

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Table R.1.2.1: 6 Proportion of patients with severe adverse events (excluding disease-related events) 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	2989	530	17.7	2996	536	17.9	0.8724	1.01	(0.90,1.12)	1.01	(0.89,1.15)	0.00	(-0.02,0.02)	
Sex														0.7629
Male	1653	295	17.8	1658	303	18.3	0.7485	1.02	(0.89,1.18)	1.03	(0.86,1.23)	0.00	(-0.02,0.03)	
Female	1336	235	17.6	1338	233	17.4	0.9048	0.99	(0.84,1.17)	0.99	(0.81,1.21)	0.00	(-0.03,0.03)	
Age [years]														0.6905
<70	1084	169	15.6	1066	173	16.2	0.6857	1.04	(0.86,1.26)	1.05	(0.83,1.32)	0.01	(-0.02,0.04)	
>=70	1905	361	19.0	1930	363	18.8	0.9106	0.99	(0.87,1.13)	0.99	(0.84,1.16)	0.00	(-0.03,0.02)	
Region														0.6599
North America	359	93	25.9	359	95	26.5	0.8652	1.02	(0.80,1.31)	1.03	(0.74,1.44)	0.01	(-0.06,0.07)	
Latin America	757	156	20.6	758	143	18.9	0.3943	0.92	(0.75,1.12)	0.90	(0.70,1.15)	-0.02	(-0.06,0.02)	
Europe	1341	190	14.2	1346	202	15.0	0.5379	1.06	(0.88,1.27)	1.07	(0.86,1.33)	0.01	(-0.02,0.04)	
Asia	343	51	14.9	343	47	13.7	0.6625	0.92	(0.64,1.33)	0.91	(0.59,1.39)	-0.01	(-0.06,0.04)	
Other	189	40	21.2	190	49	25.8	0.2882	1.22	(0.85,1.76)	1.29	(0.80,2.09)	0.05	(-0.04,0.13)	
OECD member														0.9172
No	847	164	19.4	868	168	19.4	0.9968	1.00	(0.82,1.21)	1.00	(0.79,1.27)	0.00	(-0.04,0.04)	
Yes	2142	366	17.1	2128	368	17.3	0.8581	1.01	(0.89,1.15)	1.01	(0.87,1.19)	0.00	(-0.02,0.02)	
Baseline NYHA														0.5435
II^	2450	397	16.2	2435	389	16.0	0.8278	0.99	(0.87,1.12)	0.98	(0.84,1.15)	0.00	(-0.02,0.02)	
III/IV	539	133	24.7	561	147	26.2	0.5609	1.06	(0.87,1.30)	1.08	(0.83,1.42)	0.02	(-0.04,0.07)	
Baseline Diabetes Status														0.2930
Diabetic	1471	269	18.3	1465	286	19.5	0.3927	1.07	(0.92,1.24)	1.08	(0.90,1.30)	0.01	(-0.02,0.04)	
Non-Diabetic	1518	261	17.2	1531	250	16.3	0.5228	0.95	(0.81,1.11)	0.94	(0.78,1.14)	-0.01	(-0.04,0.02)	
Baseline Diabetes Status														0.5764
Diabetic	1471	269	18.3	1465	286	19.5	0.3927	1.07	(0.92,1.24)	1.08	(0.90,1.30)	0.01	(-0.02,0.04)	
Pre-Diabetes	979	167	17.1	1001	162	16.2	0.6012	0.95	(0.78,1.16)	0.94	(0.74,1.19)	-0.01	(-0.04,0.02)	
Normal (no pre-diabetes)	539	94	17.4	530	88	16.6	0.7162	0.95	(0.73,1.24)	0.94	(0.69,1.30)	-0.01	(-0.05,0.04)	

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^ Patients with NYHA class I are counted in subgroup NYHA class II.
Risk ratios and odds ratios with confidence intervals (CIs) are estimated by Cochran-Mantel-Haenszel method. For risk differences standard Wald asymptotic confidence limits are calculated. A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
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Only treatment emergent AEs are displayed (onset between first dose until treatment stop +7 days).
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MedDRA version: 23.1. * Chi-square test for treatment effect ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction).

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Table R.1.2.1: 6 Proportion of patients with severe adverse events (excluding disease-related events) 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 BMI [kg/m²]														0.2064
<30	1641	277	16.9	1654	263	15.9	0.4478	0.94	(0.81,1.10)	0.93	(0.77,1.12)	-0.01	(-0.04,0.02)	
>=30	1348	253	18.8	1342	273	20.3	0.3033	1.08	(0.93,1.26)	1.11	(0.91,1.34)	0.02	(-0.01,0.05)	
Baseline eGFR (CKD-EPI) [mL/min/1.73m²]														0.7592
>=60	1505	207	13.8	1493	211	14.1	0.7648	1.03	(0.86,1.23)	1.03	(0.84,1.27)	0.00	(-0.02,0.03)	
<60	1482	323	21.8	1503	325	21.6	0.9096	0.99	(0.87,1.14)	0.99	(0.83,1.18)	0.00	(-0.03,0.03)	
History of HHF (in the last 12 months)														0.8362
No	2320	390	16.8	2297	386	16.8	0.9958	1.00	(0.88,1.14)	1.00	(0.86,1.17)	0.00	(-0.02,0.02)	
Yes	669	140	20.9	699	150	21.5	0.8097	1.03	(0.84,1.26)	1.03	(0.80,1.34)	0.01	(-0.04,0.05)	
Baseline SBP (</>= median)														0.9800
< median	1474	270	18.3	1496	276	18.4	0.9262	1.01	(0.87,1.17)	1.01	(0.84,1.21)	0.00	(-0.03,0.03)	
>= median	1515	260	17.2	1500	260	17.3	0.9007	1.01	(0.86,1.18)	1.01	(0.84,1.22)	0.00	(-0.03,0.03)	
History of atrial fibrillation or atrial flutter														0.1658
No	1426	249	17.5	1417	229	16.2	0.3539	0.93	(0.79,1.09)	0.91	(0.75,1.11)	-0.01	(-0.04,0.01)	
Yes	1558	281	18.0	1575	307	19.5	0.2966	1.08	(0.93,1.25)	1.10	(0.92,1.32)	0.01	(-0.01,0.04)	
Baseline LVEF [%]														0.4594
< 50	988	165	16.7	995	178	17.9	0.4839	1.07	(0.88,1.30)	1.09	(0.86,1.37)	0.01	(-0.02,0.05)	
>= 50	2001	365	18.2	2001	358	17.9	0.7736	0.98	(0.86,1.12)	0.98	(0.83,1.15)	0.00	(-0.03,0.02)	
Baseline LVEF [%]														0.3500
<50	988	165	16.7	995	178	17.9	0.4839	1.07	(0.88,1.30)	1.09	(0.86,1.37)	0.01	(-0.02,0.05)	
50 to <60	1030	186	18.1	1028	167	16.2	0.2753	0.90	(0.74,1.09)	0.88	(0.70,1.11)	-0.02	(-0.05,0.01)	
>=60	971	179	18.4	973	191	19.6	0.5020	1.06	(0.89,1.28)	1.08	(0.86,1.36)	0.01	(-0.02,0.05)	

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MedDRA version: 23.1. * Chi-square test for treatment effect ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction).

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Table R.1.2.1: 6 Proportion of patients with severe adverse events (excluding disease-related events) 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 NT-proBNP [pg/mL] (</>=median by atrial fibrillation/flutter status)														0.4029
< median	1507	237	15.7	1476	221	15.0	0.5681	0.95	(0.80,1.13)	0.94	(0.77,1.15)	-0.01	(-0.03,0.02)	
>= median	1475	293	19.9	1516	315	20.8	0.5346	1.05	(0.91,1.21)	1.06	(0.89,1.26)	0.01	(-0.02,0.04)	
Baseline uric acid [mg/dL] (tertiles)														0.8853
<T1	975	155	15.9	963	152	15.8	0.9455	0.99	(0.81,1.22)	0.99	(0.78,1.27)	0.00	(-0.03,0.03)	
>=T1 and <T2	966	161	16.7	1032	170	16.5	0.9073	0.99	(0.81,1.20)	0.99	(0.78,1.25)	0.00	(-0.03,0.03)	
>=T2	1016	208	20.5	970	208	21.4	0.5951	1.05	(0.88,1.24)	1.06	(0.85,1.32)	0.01	(-0.03,0.05)	
Baseline use of MRA														0.6372
No	1865	315	16.9	1878	327	17.4	0.6718	1.03	(0.90,1.19)	1.04	(0.88,1.23)	0.01	(-0.02,0.03)	
Yes	1124	215	19.1	1118	209	18.7	0.7930	0.98	(0.82,1.16)	0.97	(0.79,1.20)	0.00	(-0.04,0.03)	
Baseline use of ACE-inhibitor, ARB or ARNi														0.1806
No	586	120	20.5	568	134	23.6	0.2018	1.15	(0.93,1.43)	1.20	(0.91,1.58)	0.03	(-0.02,0.08)	
Yes	2403	410	17.1	2428	402	16.6	0.6387	0.97	(0.86,1.10)	0.96	(0.83,1.12)	-0.01	(-0.03,0.02)	

Analysis is based on study 1245.110.
^ Patients with NYHA class I are counted in subgroup NYHA class II.
Risk ratios and odds ratios with confidence intervals (CIs) are estimated by Cochran-Mantel-Haenszel method. For risk differences standard Wald asymptotic confidence limits are calculated. A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied in case of any zero cells in contingency table.
Only treatment emergent AEs are displayed (onset between first dose until treatment stop +7 days).
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MedDRA version: 23.1. * Chi-square test for treatment effect ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction).

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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 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	2989	551	18.4	2996	571	19.1	0.5360	1.03	(0.93,1.15)	1.04	(0.91,1.19)	0.01	(-0.01,0.03)	
Sex														0.4955
Male	1653	315	19.1	1658	337	20.3	0.3584	1.07	(0.93,1.22)	1.08	(0.91,1.29)	0.01	(-0.01,0.04)	
Female	1336	236	17.7	1338	234	17.5	0.9049	0.99	(0.84,1.17)	0.99	(0.81,1.21)	0.00	(-0.03,0.03)	
Age [years]														0.7453
<70	1084	172	15.9	1066	170	15.9	0.9594	1.01	(0.83,1.22)	1.01	(0.80,1.27)	0.00	(-0.03,0.03)	
>=70	1905	379	19.9	1930	401	20.8	0.4974	1.04	(0.92,1.18)	1.06	(0.90,1.24)	0.01	(-0.02,0.03)	
Region														0.6347
North America	359	75	20.9	359	85	23.7	0.3698	1.13	(0.86,1.49)	1.17	(0.83,1.67)	0.03	(-0.03,0.09)	
Latin America	757	159	21.0	758	149	19.7	0.5148	0.94	(0.77,1.14)	0.92	(0.72,1.18)	-0.01	(-0.05,0.03)	
Europe	1341	242	18.0	1346	247	18.4	0.8380	1.02	(0.87,1.19)	1.02	(0.84,1.24)	0.00	(-0.03,0.03)	
Asia	343	37	10.8	343	43	12.5	0.4754	1.16	(0.77,1.76)	1.19	(0.74,1.89)	0.02	(-0.03,0.07)	
Other	189	38	20.1	190	47	24.7	0.2798	1.23	(0.84,1.79)	1.31	(0.80,2.12)	0.05	(-0.04,0.13)	
OECD member														0.7749
No	847	172	20.3	868	178	20.5	0.9182	1.01	(0.84,1.22)	1.01	(0.80,1.28)	0.00	(-0.04,0.04)	
Yes	2142	379	17.7	2128	393	18.5	0.5110	1.04	(0.92,1.19)	1.05	(0.90,1.23)	0.01	(-0.02,0.03)	
Baseline NYHA														0.4130
II^	2450	411	16.8	2435	410	16.8	0.9536	1.00	(0.89,1.14)	1.00	(0.86,1.17)	0.00	(-0.02,0.02)	
III/IV	539	140	26.0	561	161	28.7	0.3109	1.10	(0.91,1.34)	1.15	(0.88,1.50)	0.03	(-0.03,0.08)	
Baseline Diabetes Status														0.6649
Diabetic	1471	288	19.6	1465	290	19.8	0.8826	1.01	(0.87,1.17)	1.01	(0.85,1.22)	0.00	(-0.03,0.03)	
Non-Diabetic	1518	263	17.3	1531	281	18.4	0.4583	1.06	(0.91,1.23)	1.07	(0.89,1.29)	0.01	(-0.02,0.04)	
Baseline Diabetes Status														0.5658
Diabetic	1471	288	19.6	1465	290	19.8	0.8826	1.01	(0.87,1.17)	1.01	(0.85,1.22)	0.00	(-0.03,0.03)	
Pre-Diabetes	979	166	17.0	1001	190	19.0	0.2408	1.12	(0.93,1.35)	1.15	(0.91,1.44)	0.02	(-0.01,0.05)	
Normal (no pre-diabetes)	539	97	18.0	530	91	17.2	0.7227	0.95	(0.74,1.24)	0.94	(0.69,1.29)	-0.01	(-0.05,0.04)	

Analysis is based on study 1245.110.
^ Patients with NYHA class I are counted in subgroup NYHA class II.
Risk ratios and odds ratios with confidence intervals (CIs) are estimated by Cochran-Mantel-Haenszel method. For risk differences standard Wald asymptotic confidence limits are calculated. A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied in case of any zero cells in contingency table.
Only treatment emergent AEs are displayed (onset between first dose until treatment stop +7 days).
Subgroups will only be analysed if at least 10 events occurred in at least one category (both treatments combined).
MedDRA version: 23.1. * Chi-square test for treatment effect ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction).

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Table R.1.2.2: 1 Proportion of patients with any adverse event leading to treatment discontinuation 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 BMI [kg/m²]														0.4719
<30	1641	310	18.9	1654	312	18.9	0.9839	1.00	(0.87,1.15)	1.00	(0.84,1.19)	0.00	(-0.03,0.03)	
>=30	1348	241	17.9	1342	259	19.3	0.3434	1.08	(0.92,1.26)	1.10	(0.90,1.33)	0.01	(-0.02,0.04)	
Baseline eGFR (CKD-EPI) [mL/min/1.73m²]														0.7964
>=60	1505	224	14.9	1493	233	15.6	0.5822	1.05	(0.89,1.24)	1.06	(0.87,1.29)	0.01	(-0.02,0.03)	
<60	1482	327	22.1	1503	338	22.5	0.7810	1.02	(0.89,1.17)	1.02	(0.86,1.22)	0.00	(-0.03,0.03)	
History of HHF (in the last 12 months)														0.8213
No	2320	410	17.7	2297	422	18.4	0.5365	1.04	(0.92,1.18)	1.05	(0.90,1.22)	0.01	(-0.02,0.03)	
Yes	669	141	21.1	699	149	21.3	0.9136	1.01	(0.82,1.24)	1.01	(0.78,1.31)	0.00	(-0.04,0.05)	
Baseline SBP (</>= median)														0.1245
< median	1474	245	16.6	1496	281	18.8	0.1228	1.13	(0.97,1.32)	1.16	(0.96,1.40)	0.02	(-0.01,0.05)	
>= median	1515	306	20.2	1500	290	19.3	0.5511	0.96	(0.83,1.11)	0.95	(0.79,1.13)	-0.01	(-0.04,0.02)	
History of atrial fibrillation or atrial flutter														0.0346
No	1426	270	18.9	1417	245	17.3	0.2551	0.91	(0.78,1.07)	0.90	(0.74,1.08)	-0.02	(-0.04,0.01)	
Yes	1558	280	18.0	1575	325	20.6	0.0590	1.15	(0.99,1.33)	1.19	(0.99,1.42)	0.03	(0.00,0.05)	
Baseline LVEF [%]														0.5753
< 50	988	201	20.3	995	201	20.2	0.9368	0.99	(0.83,1.18)	0.99	(0.80,1.23)	0.00	(-0.04,0.03)	
>= 50	2001	350	17.5	2001	370	18.5	0.4105	1.06	(0.93,1.21)	1.07	(0.91,1.26)	0.01	(-0.01,0.03)	
Baseline LVEF [%]														0.7978
<50	988	201	20.3	995	201	20.2	0.9368	0.99	(0.83,1.18)	0.99	(0.80,1.23)	0.00	(-0.04,0.03)	
50 to <60	1030	193	18.7	1028	199	19.4	0.7202	1.03	(0.86,1.23)	1.04	(0.84,1.30)	0.01	(-0.03,0.04)	
>=60	971	157	16.2	973	171	17.6	0.4080	1.09	(0.89,1.32)	1.11	(0.87,1.40)	0.01	(-0.02,0.05)	

Analysis is based on study 1245.110.
^ Patients with NYHA class I are counted in subgroup NYHA class II.
Risk ratios and odds ratios with confidence intervals (CIs) are estimated by Cochran-Mantel-Haenszel method. For risk differences standard Wald asymptotic confidence limits are calculated. A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied in case of any zero cells in contingency table.
Only treatment emergent AEs are displayed (onset between first dose until treatment stop +7 days).
Subgroups will only be analysed if at least 10 events occurred in at least one category (both treatments combined).
MedDRA version: 23.1. * Chi-square test for treatment effect ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction).

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Table R.1.2.2: 1 Proportion of patients with any adverse event leading to treatment discontinuation 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 NT-proBNP [pg/mL] (</>=median by atrial fibrillation/flutter status)														0.7299
< median	1507	207	13.7	1476	203	13.8	0.9889	1.00	(0.84,1.20)	1.00	(0.81,1.23)	0.00	(-0.02,0.02)	
>= median	1475	343	23.3	1516	367	24.2	0.5397	1.04	(0.92,1.18)	1.05	(0.89,1.25)	0.01	(-0.02,0.04)	
Baseline uric acid [mg/dL] (tertiles)														0.8420
<T1	975	173	17.7	963	169	17.5	0.9107	0.99	(0.82,1.20)	0.99	(0.78,1.25)	0.00	(-0.04,0.03)	
>=T1 and <T2	966	155	16.0	1032	176	17.1	0.5445	1.06	(0.87,1.29)	1.08	(0.85,1.36)	0.01	(-0.02,0.04)	
>=T2	1016	220	21.7	970	222	22.9	0.5090	1.06	(0.90,1.25)	1.07	(0.87,1.33)	0.01	(-0.02,0.05)	
Baseline use of MRA														0.2434
No	1865	327	17.5	1878	358	19.1	0.2263	1.09	(0.95,1.25)	1.11	(0.94,1.31)	0.02	(-0.01,0.04)	
Yes	1124	224	19.9	1118	213	19.1	0.6002	0.96	(0.81,1.13)	0.95	(0.77,1.17)	-0.01	(-0.04,0.02)	
Baseline use of ACE-inhibitor, ARB or ARNi														0.8475
No	586	121	20.6	568	119	21.0	0.8994	1.01	(0.81,1.27)	1.02	(0.77,1.35)	0.00	(-0.04,0.05)	
Yes	2403	430	17.9	2428	452	18.6	0.5161	1.04	(0.92,1.17)	1.05	(0.91,1.21)	0.01	(-0.01,0.03)	

Analysis is based on study 1245.110.
^ Patients with NYHA class I are counted in subgroup NYHA class II.
Risk ratios and odds ratios with confidence intervals (CIs) are estimated by Cochran-Mantel-Haenszel method. For risk differences standard Wald asymptotic confidence limits are calculated. A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied in case of any zero cells in contingency table.
Only treatment emergent AEs are displayed (onset between first dose until treatment stop +7 days).
Subgroups will only be analysed if at least 10 events occurred in at least one category (both treatments combined).
MedDRA version: 23.1. * Chi-square test for treatment effect ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction).

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R.1.2.3 AESI and specific Aes

Table R.1.2.3: 1 Proportion of patients with adverse events of special interest and other specific AEs by user-defined category overall and by subgroup - TS
User-defined AE category: Hepatic Injury (narrow SMQs)

Subgroup	Placebo			Empa 10mg			Empa 10mg vs Placebo						
Category	N	n	%	N	n	%	p-value *	Risk ratio (95% CI)	Odds ratio (95% CI)	Risk diff. (95% CI)	p-value **
Overall	2989	155	5.2	2996	115	3.8	0.0120	0.74 (0.58, 0.94)	0.73 (0.57, 0.93)	-0.01 (-0.02, 0.00)	
Sex											0.6792
Male	1653	86	5.2	1658	61	3.7	0.0333	0.71 (0.51, 0.97)	0.70 (0.50, 0.97)	-0.02 (-0.03, 0.00)	
Female	1336	69	5.2	1338	54	4.0	0.1636	0.78 (0.55, 1.11)	0.77 (0.54, 1.11)	-0.01 (-0.03, 0.00)	
Age [years]											0.1185
<70	1084	53	4.9	1066	49	4.6	0.7496	0.94 (0.64, 1.37)	0.94 (0.63, 1.40)	0.00 (-0.02, 0.02)	
>=70	1905	102	5.4	1930	66	3.4	0.0034	0.64 (0.47, 0.86)	0.63 (0.46, 0.86)	-0.02 (-0.03,-0.01)	
Region											0.1333
North America	359	21	5.8	359	11	3.1	0.0705	0.52 (0.26, 1.07)	0.51 (0.24, 1.07)	-0.03 (-0.06, 0.00)	
Latin America	757	35	4.6	758	30	4.0	0.5226	0.86 (0.53, 1.38)	0.85 (0.52, 1.40)	-0.01 (-0.03, 0.01)	
Europe	1341	57	4.3	1346	40	3.0	0.0756	0.70 (0.47, 1.04)	0.69 (0.46, 1.04)	-0.01 (-0.03, 0.00)	
Asia	343	36	10.5	343	21	6.1	0.0380	0.58 (0.35, 0.98)	0.56 (0.32, 0.97)	-0.04 (-0.08, 0.00)	
Other	189	6	3.2	190	13	6.8	0.1019	2.16 (0.84, 5.55)	2.24 (0.83, 6.02)	0.04 (-0.01, 0.08)	
OECD member											0.0397
No	847	38	4.5	868	42	4.8	0.7294	1.08 (0.70, 1.66)	1.08 (0.69, 1.70)	0.00 (-0.02, 0.02)	
Yes	2142	117	5.5	2128	73	3.4	0.0013	0.63 (0.47, 0.84)	0.61 (0.46, 0.83)	-0.02 (-0.03,-0.01)	
Baseline NYHA											0.2145
II^	2450	123	5.0	2435	83	3.4	0.0051	0.68 (0.52, 0.89)	0.67 (0.50, 0.89)	-0.02 (-0.03, 0.00)	
III/IV	539	32	5.9	561	32	5.7	0.8690	0.96 (0.60, 1.55)	0.96 (0.58, 1.59)	0.00 (-0.03, 0.03)	
Baseline Diabetes Status											0.9100
Diabetic	1471	83	5.6	1465	62	4.2	0.0778	0.75 (0.54, 1.03)	0.74 (0.53, 1.04)	-0.01 (-0.03, 0.00)	
Non-Diabetic	1518	72	4.7	1531	53	3.5	0.0744	0.73 (0.52, 1.03)	0.72 (0.50, 1.03)	-0.01 (-0.03, 0.00)	

Analysis is based on study 1245.110.
^ Patients with NYHA class I are counted in subgroup NYHA class II.
*** Confirmed hypoglycaemic AEs are defined by a glucose concentration <=70 mg/dL (3.9 mmol/L) or requiring assistance.
Risk ratios and odds ratios with confidence intervals (CIs) are estimated by Cochran-Mantel-Haenszel method. For risk differences standard Wald asymptotic confidence limits are calculated. A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied in case of any zero cells in contingency table.
Only treatment emergent AEs are displayed (onset between first dose until treatment stop +7 days).
MedDRA version: 23.1. * Chi-square test for treatment effect ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction).

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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 overall and by subgroup - TS
User-defined AE category: Hepatic Injury (narrow SMQs)

Subgroup	Placebo			Empa 10mg			Empa 10mg vs Placebo				
Category	N	n	%	N	n	%	p-value *	Risk ratio (95% CI)	Odds ratio (95% CI)	Risk diff. (95% CI)	p-value **
Baseline Diabetes Status											0.7894
Diabetic	1471	83	5.6	1465	62	4.2	0.0778	0.75 (0.54, 1.03)	0.74 (0.53, 1.04)	-0.01 (-0.03, 0.00)	
Pre-Diabetes	979	47	4.8	1001	32	3.2	0.0683	0.67 (0.43, 1.03)	0.65 (0.41, 1.04)	-0.02 (-0.03, 0.00)	
Normal (no pre-diabetes)	539	25	4.6	530	21	4.0	0.5861	0.85 (0.48, 1.51)	0.85 (0.47, 1.53)	-0.01 (-0.03, 0.02)	
Baseline BMI [kg/m²]											0.1200
<30	1641	100	6.1	1654	64	3.9	0.0033	0.63 (0.47, 0.86)	0.62 (0.45, 0.86)	-0.02 (-0.04,-0.01)	
>=30	1348	55	4.1	1342	51	3.8	0.7092	0.93 (0.64, 1.35)	0.93 (0.63, 1.37)	0.00 (-0.02, 0.01)	
Baseline eGFR (CKD-EPI) [mL/min/1.73m²]											0.2973
>=60	1505	72	4.8	1493	60	4.0	0.3071	0.84 (0.60, 1.17)	0.83 (0.59, 1.18)	-0.01 (-0.02, 0.01)	
<60	1482	83	5.6	1503	55	3.7	0.0116	0.65 (0.47, 0.91)	0.64 (0.45, 0.91)	-0.02 (-0.03, 0.00)	
History of HHF (in the last 12 months)											0.3975
No	2320	119	5.1	2297	82	3.6	0.0094	0.70 (0.53, 0.92)	0.68 (0.51, 0.91)	-0.02 (-0.03, 0.00)	
Yes	669	36	5.4	699	33	4.7	0.5771	0.88 (0.55, 1.39)	0.87 (0.54, 1.41)	-0.01 (-0.03, 0.02)	
Baseline SBP (</>= median)											0.6873
< median	1474	87	5.9	1496	68	4.5	0.0964	0.77 (0.57, 1.05)	0.76 (0.55, 1.05)	-0.01 (-0.03, 0.00)	
>= median	1515	68	4.5	1500	47	3.1	0.0521	0.70 (0.48, 1.01)	0.69 (0.47, 1.01)	-0.01 (-0.03, 0.00)	
History of atrial fibrillation or atrial flutter											0.9100
No	1426	67	4.7	1417	50	3.5	0.1164	0.75 (0.52, 1.08)	0.74 (0.51, 1.08)	-0.01 (-0.03, 0.00)	
Yes	1558	88	5.6	1575	65	4.1	0.0482	0.73 (0.53, 1.00)	0.72 (0.52, 1.00)	-0.02 (-0.03, 0.00)	

Analysis is based on study 1245.110.
^ Patients with NYHA class I are counted in subgroup NYHA class II.
*** Confirmed hypoglycaemic AEs are defined by a glucose concentration <=70 mg/dL (3.9 mmol/L) or requiring assistance.
Risk ratios and odds ratios with confidence intervals (CIs) are estimated by Cochran-Mantel-Haenszel method. For risk differences standard Wald asymptotic confidence limits are calculated. A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied in case of any zero cells in contingency table.
Only treatment emergent AEs are displayed (onset between first dose until treatment stop +7 days).
MedDRA version: 23.1. * Chi-square test for treatment effect ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction).

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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 overall and by subgroup - TS
User-defined AE category: Hepatic Injury (narrow SMQs)

Subgroup	Placebo			Empa 10mg			Empa 10mg vs Placebo						
Category	N	n	%	N	n	%	p-value *	Risk ratio (95% CI)	Odds ratio (95% CI)	Risk diff. (95% CI)	p-value **
Baseline LVEF [%]											0.2381
< 50	988	46	4.7	995	27	2.7	0.0216	0.58 (0.37, 0.93)	0.57 (0.35, 0.93)	-0.02 (-0.04, 0.00)	
>= 50	2001	109	5.4	2001	88	4.4	0.1249	0.81 (0.61, 1.06)	0.80 (0.60, 1.06)	-0.01 (-0.02, 0.00)	
Baseline LVEF [%]											0.4447
<50	988	46	4.7	995	27	2.7	0.0216	0.58 (0.37, 0.93)	0.57 (0.35, 0.93)	-0.02 (-0.04, 0.00)	
50 to <60	1030	57	5.5	1028	43	4.2	0.1541	0.76 (0.51, 1.11)	0.75 (0.50, 1.12)	-0.01 (-0.03, 0.01)	
>=60	971	52	5.4	973	45	4.6	0.4596	0.86 (0.59, 1.27)	0.86 (0.57, 1.29)	-0.01 (-0.03, 0.01)	
Baseline NT-proBNP [pg/mL] (</>=median by atrial fibrillation/flutter status)											0.1244
< median	1507	67	4.4	1476	38	2.6	0.0056	0.58 (0.39, 0.86)	0.57 (0.38, 0.85)	-0.02 (-0.03,-0.01)	
>= median	1475	88	6.0	1516	77	5.1	0.2881	0.85 (0.63, 1.15)	0.84 (0.62, 1.16)	-0.01 (-0.03, 0.01)	
Baseline uric acid [mg/dL] (tertiles)											0.6508
<T1	975	47	4.8	963	30	3.1	0.0547	0.65 (0.41, 1.01)	0.63 (0.40, 1.01)	-0.02 (-0.03, 0.00)	
>=T1 and <T2	966	50	5.2	1032	38	3.7	0.1039	0.71 (0.47, 1.07)	0.70 (0.46, 1.08)	-0.01 (-0.03, 0.00)	
>=T2	1016	57	5.6	970	46	4.7	0.3832	0.85 (0.58, 1.23)	0.84 (0.56, 1.25)	-0.01 (-0.03, 0.01)	
Baseline use of MRA											0.5974
No	1865	92	4.9	1878	65	3.5	0.0247	0.70 (0.51, 0.96)	0.69 (0.50, 0.96)	-0.01 (-0.03, 0.00)	
Yes	1124	63	5.6	1118	50	4.5	0.2203	0.80 (0.56, 1.15)	0.79 (0.54, 1.15)	-0.01 (-0.03, 0.01)	
Baseline use of ACE-inhibitor, ARB or ARNi											0.7422
No	586	39	6.7	568	30	5.3	0.3252	0.79 (0.50, 1.26)	0.78 (0.48, 1.28)	-0.01 (-0.04, 0.01)	
Yes	2403	116	4.8	2428	85	3.5	0.0210	0.73 (0.55, 0.95)	0.72 (0.54, 0.95)	-0.01 (-0.02, 0.00)	

Analysis is based on study 1245.110.
^ Patients with NYHA class I are counted in subgroup NYHA class II.
*** Confirmed hypoglycaemic AEs are defined by a glucose concentration <=70 mg/dL (3.9 mmol/L) or requiring assistance.
Risk ratios and odds ratios with confidence intervals (CIs) are estimated by Cochran-Mantel-Haenszel method. For risk differences standard Wald asymptotic confidence limits are calculated. A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied in case of any zero cells in contingency table.
Only treatment emergent AEs are displayed (onset between first dose until treatment stop +7 days).
MedDRA version: 23.1. * Chi-square test for treatment effect ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction).

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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 overall and by subgroup - TS
User-defined AE category: Acute renal failure (narrow 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	2989	384	12.8	2996	363	12.1	0.3923	0.94 (0.82, 1.08)	0.94 (0.80, 1.09)	-0.01 (-0.02, 0.01)	
Sex											0.3888
Male	1653	198	12.0	1658	198	11.9	0.9745	1.00 (0.83, 1.20)	1.00 (0.81, 1.23)	0.00 (-0.02, 0.02)	
Female	1336	186	13.9	1338	165	12.3	0.2234	0.89 (0.73, 1.08)	0.87 (0.69, 1.09)	-0.02 (-0.04, 0.01)	
Age [years]											0.7746
<70	1084	132	12.2	1066	119	11.2	0.4642	0.92 (0.73, 1.16)	0.91 (0.70, 1.18)	-0.01 (-0.04, 0.02)	
>=70	1905	252	13.2	1930	244	12.6	0.5888	0.96 (0.81, 1.13)	0.95 (0.79, 1.15)	-0.01 (-0.03, 0.02)	
Region											0.6951
North America	359	68	18.9	359	57	15.9	0.2790	0.84 (0.61, 1.15)	0.81 (0.55, 1.19)	-0.03 (-0.09, 0.02)	
Latin America	757	97	12.8	758	106	14.0	0.5037	1.09 (0.84, 1.41)	1.11 (0.82, 1.49)	0.01 (-0.02, 0.05)	
Europe	1341	155	11.6	1346	138	10.3	0.2775	0.89 (0.71, 1.10)	0.87 (0.69, 1.11)	-0.01 (-0.04, 0.01)	
Asia	343	36	10.5	343	33	9.6	0.7033	0.92 (0.59, 1.43)	0.91 (0.55, 1.49)	-0.01 (-0.05, 0.04)	
Other	189	28	14.8	190	29	15.3	0.9028	1.03 (0.64, 1.66)	1.04 (0.59, 1.82)	0.00 (-0.07, 0.08)	
OECD member											0.1733
No	847	112	13.2	868	124	14.3	0.5231	1.08 (0.85, 1.37)	1.09 (0.83, 1.44)	0.01 (-0.02, 0.04)	
Yes	2142	272	12.7	2128	239	11.2	0.1397	0.88 (0.75, 1.04)	0.87 (0.72, 1.05)	-0.01 (-0.03, 0.00)	
Baseline NYHA											0.6964
II^	2450	282	11.5	2435	259	10.6	0.3306	0.92 (0.79, 1.08)	0.92 (0.77, 1.09)	-0.01 (-0.03, 0.01)	
III/IV	539	102	18.9	561	104	18.5	0.8698	0.98 (0.77, 1.25)	0.97 (0.72, 1.32)	0.00 (-0.05, 0.04)	
Baseline Diabetes Status											0.0819
Diabetic	1471	222	15.1	1465	230	15.7	0.6482	1.04 (0.88, 1.23)	1.05 (0.86, 1.28)	0.01 (-0.02, 0.03)	
Non-Diabetic	1518	162	10.7	1531	133	8.7	0.0638	0.81 (0.65, 1.01)	0.80 (0.63, 1.01)	-0.02 (-0.04, 0.00)	

Analysis is based on study 1245.110.
^ Patients with NYHA class I are counted in subgroup NYHA class II.
*** Confirmed hypoglycaemic AEs are defined by a glucose concentration <=70 mg/dL (3.9 mmol/L) or requiring assistance.
Risk ratios and odds ratios with confidence intervals (CIs) are estimated by Cochran-Mantel-Haenszel method. For risk differences standard Wald asymptotic confidence limits are calculated. A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied in case of any zero cells in contingency table.
Only treatment emergent AEs are displayed (onset between first dose until treatment stop +7 days).
MedDRA version: 23.1. * Chi-square test for treatment effect ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction).

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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 overall and by subgroup - TS
User-defined AE category: Acute renal failure (narrow 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 Diabetes Status											0.1932
Diabetic	1471	222	15.1	1465	230	15.7	0.6482	1.04 (0.88, 1.23)	1.05 (0.86, 1.28)	0.01 (-0.02, 0.03)	
Pre-Diabetes	979	113	11.5	1001	97	9.7	0.1808	0.84 (0.65, 1.09)	0.82 (0.62, 1.10)	-0.02 (-0.05, 0.01)	
Normal (no pre-diabetes)	539	49	9.1	530	36	6.8	0.1649	0.75 (0.49, 1.13)	0.73 (0.47, 1.14)	-0.02 (-0.06, 0.01)	
Baseline BMI [kg/m²]											0.0105
<30	1641	206	12.6	1654	164	9.9	0.0165	0.79 (0.65, 0.96)	0.77 (0.62, 0.95)	-0.03 (-0.05, 0.00)	
>=30	1348	178	13.2	1342	199	14.8	0.2251	1.12 (0.93, 1.35)	1.14 (0.92, 1.42)	0.02 (-0.01, 0.04)	
Baseline eGFR (CKD-EPI) [mL/min/1.73m²]											0.5584
>=60	1505	120	8.0	1493	105	7.0	0.3284	0.88 (0.69, 1.13)	0.87 (0.66, 1.15)	-0.01 (-0.03, 0.01)	
<60	1482	264	17.8	1503	258	17.2	0.6412	0.96 (0.82, 1.13)	0.96 (0.79, 1.15)	-0.01 (-0.03, 0.02)	
History of HHF (in the last 12 months)											0.6772
No	2320	266	11.5	2297	252	11.0	0.5944	0.96 (0.81, 1.13)	0.95 (0.79, 1.14)	0.00 (-0.02, 0.01)	
Yes	669	118	17.6	699	111	15.9	0.3838	0.90 (0.71, 1.14)	0.88 (0.66, 1.17)	-0.02 (-0.06, 0.02)	
Baseline SBP (</>= median)											0.7631
< median	1474	192	13.0	1496	180	12.0	0.4134	0.92 (0.76, 1.12)	0.91 (0.73, 1.14)	-0.01 (-0.03, 0.01)	
>= median	1515	192	12.7	1500	183	12.2	0.6938	0.96 (0.80, 1.16)	0.96 (0.77, 1.19)	0.00 (-0.03, 0.02)	
History of atrial fibrillation or atrial flutter											0.8218
No	1426	177	12.4	1417	169	11.9	0.6920	0.96 (0.79, 1.17)	0.96 (0.76, 1.20)	0.00 (-0.03, 0.02)	
Yes	1558	206	13.2	1575	194	12.3	0.4481	0.93 (0.78, 1.12)	0.92 (0.75, 1.14)	-0.01 (-0.03, 0.01)	

Analysis is based on study 1245.110.
^ Patients with NYHA class I are counted in subgroup NYHA class II.
*** Confirmed hypoglycaemic AEs are defined by a glucose concentration <=70 mg/dL (3.9 mmol/L) or requiring assistance.
Risk ratios and odds ratios with confidence intervals (CIs) are estimated by Cochran-Mantel-Haenszel method. For risk differences standard Wald asymptotic confidence limits are calculated. A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
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Only treatment emergent AEs are displayed (onset between first dose until treatment stop +7 days).
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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 overall and by subgroup - TS
User-defined AE category: Acute renal failure (narrow 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 LVEF [%]											0.4076
< 50	988	127	12.9	995	111	11.2	0.2446	0.87 (0.68, 1.10)	0.85 (0.65, 1.12)	-0.02 (-0.05, 0.01)	
>= 50	2001	257	12.8	2001	252	12.6	0.8125	0.98 (0.83, 1.15)	0.98 (0.81, 1.18)	0.00 (-0.02, 0.02)	
Baseline LVEF [%]											0.0794
<50	988	127	12.9	995	111	11.2	0.2446	0.87 (0.68, 1.10)	0.85 (0.65, 1.12)	-0.02 (-0.05, 0.01)	
50 to <60	1030	148	14.4	1028	123	12.0	0.1068	0.83 (0.67, 1.04)	0.81 (0.63, 1.05)	-0.02 (-0.05, 0.01)	
>=60	971	109	11.2	973	129	13.3	0.1716	1.18 (0.93, 1.50)	1.21 (0.92, 1.59)	0.02 (-0.01, 0.05)	
Baseline NT-proBNP [pg/mL] (</>=median by atrial fibrillation/flutter status)											0.8713
< median	1507	151	10.0	1476	137	9.3	0.4950	0.93 (0.74, 1.15)	0.92 (0.72, 1.17)	-0.01 (-0.03, 0.01)	
>= median	1475	232	15.7	1516	226	14.9	0.5330	0.95 (0.80, 1.12)	0.94 (0.77, 1.15)	-0.01 (-0.03, 0.02)	
Baseline uric acid [mg/dL] (tertiles)											0.0491
<T1	975	97	9.9	963	90	9.3	0.6531	0.94 (0.72, 1.23)	0.93 (0.69, 1.26)	-0.01 (-0.03, 0.02)	
>=T1 and <T2	966	115	11.9	1032	91	8.8	0.0234	0.74 (0.57, 0.96)	0.72 (0.54, 0.96)	-0.03 (-0.06, 0.00)	
>=T2	1016	168	16.5	970	178	18.4	0.2864	1.11 (0.92, 1.34)	1.13 (0.90, 1.43)	0.02 (-0.02, 0.05)	
Baseline use of MRA											0.7405
No	1865	220	11.8	1878	205	10.9	0.3960	0.93 (0.77, 1.11)	0.92 (0.75, 1.12)	-0.01 (-0.03, 0.01)	
Yes	1124	164	14.6	1118	158	14.1	0.7570	0.97 (0.79, 1.19)	0.96 (0.76, 1.22)	0.00 (-0.03, 0.02)	
Baseline use of ACE-inhibitor, ARB or ARNi											0.4195
No	586	74	12.6	568	60	10.6	0.2737	0.84 (0.61, 1.15)	0.82 (0.57, 1.17)	-0.02 (-0.06, 0.02)	
Yes	2403	310	12.9	2428	303	12.5	0.6602	0.97 (0.83, 1.12)	0.96 (0.81, 1.14)	0.00 (-0.02, 0.01)	

Analysis is based on study 1245.110.
^ Patients with NYHA class I are counted in subgroup NYHA class II.
*** Confirmed hypoglycaemic AEs are defined by a glucose concentration <=70 mg/dL (3.9 mmol/L) or requiring assistance.
Risk ratios and odds ratios with confidence intervals (CIs) are estimated by Cochran-Mantel-Haenszel method. For risk differences standard Wald asymptotic confidence limits are calculated. A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
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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 overall and by subgroup - TS
User-defined AE category: Ketoacidosis (broad 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	2989	50	1.7	2996	44	1.5	0.5253	0.88 (0.59, 1.31)	0.88 (0.58, 1.32)	0.00 (-0.01, 0.00)	
Sex											0.8689
Male	1653	23	1.4	1658	21	1.3	0.7538	0.91 (0.51, 1.64)	0.91 (0.50, 1.65)	0.00 (-0.01, 0.01)	
Female	1336	27	2.0	1338	23	1.7	0.5644	0.85 (0.49, 1.48)	0.85 (0.48, 1.49)	0.00 (-0.01, 0.01)	
Age [years]											0.9421
<70	1084	25	2.3	1066	22	2.1	0.7007	0.89 (0.51, 1.58)	0.89 (0.50, 1.59)	0.00 (-0.01, 0.01)	
>=70	1905	25	1.3	1930	22	1.1	0.6275	0.87 (0.49, 1.54)	0.87 (0.49, 1.54)	0.00 (-0.01, 0.01)	
Region											0.9276
North America	359	4	1.1	359	4	1.1	1.0000	1.00 (0.25, 3.97)	1.00 (0.25, 4.03)	0.00 (-0.02, 0.02)	
Latin America	757	25	3.3	758	21	2.8	0.5462	0.84 (0.47, 1.49)	0.83 (0.46, 1.50)	-0.01 (-0.02, 0.01)	
Europe	1341	11	0.8	1346	8	0.6	0.4847	0.72 (0.29, 1.80)	0.72 (0.29, 1.80)	0.00 (-0.01, 0.00)	
Asia	343	4	1.2	343	3	0.9	0.7040	0.75 (0.17, 3.33)	0.75 (0.17, 3.37)	0.00 (-0.02, 0.01)	
Other	189	6	3.2	190	8	4.2	0.5929	1.33 (0.47, 3.75)	1.34 (0.46, 3.94)	0.01 (-0.03, 0.05)	
OECD member											0.7946
No	847	29	3.4	868	27	3.1	0.7152	0.91 (0.54, 1.52)	0.91 (0.53, 1.54)	0.00 (-0.02, 0.01)	
Yes	2142	21	1.0	2128	17	0.8	0.5277	0.81 (0.43, 1.54)	0.81 (0.43, 1.55)	0.00 (-0.01, 0.00)	
Baseline NYHA											0.8569
II^	2450	36	1.5	2435	32	1.3	0.6434	0.89 (0.56, 1.44)	0.89 (0.55, 1.44)	0.00 (-0.01, 0.01)	
III/IV	539	14	2.6	561	12	2.1	0.6169	0.82 (0.38, 1.76)	0.82 (0.38, 1.79)	0.00 (-0.02, 0.01)	
Baseline Diabetes Status											0.8900
Diabetic	1471	37	2.5	1465	33	2.3	0.6408	0.90 (0.56, 1.42)	0.89 (0.56, 1.44)	0.00 (-0.01, 0.01)	
Non-Diabetic	1518	13	0.9	1531	11	0.7	0.6666	0.84 (0.38, 1.87)	0.84 (0.37, 1.88)	0.00 (-0.01, 0.00)	

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^ Patients with NYHA class I are counted in subgroup NYHA class II.
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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 overall and by subgroup - TS
User-defined AE category: Ketoacidosis (broad 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 Diabetes Status											0.1201
Diabetic	1471	37	2.5	1465	33	2.3	0.6408	0.90 (0.56, 1.42)	0.89 (0.56, 1.44)	0.00 (-0.01, 0.01)	
Pre-Diabetes	979	6	0.6	1001	10	1.0	0.3373	1.63 (0.59, 4.47)	1.64 (0.59, 4.52)	0.00 (0.00, 0.01)	
Normal (no pre-diabetes)	539	7	1.3	530	1	0.2	0.0352	0.15 (0.02, 1.18)	0.14 (0.02, 1.17)	-0.01 (-0.02, 0.00)	
Baseline BMI [kg/m²]											0.0021
<30	1641	33	2.0	1654	15	0.9	0.0082	0.45 (0.25, 0.83)	0.45 (0.24, 0.82)	-0.01 (-0.02, 0.00)	
>=30	1348	17	1.3	1342	29	2.2	0.0719	1.71 (0.95, 3.10)	1.73 (0.95, 3.16)	0.01 (0.00, 0.02)	
Baseline eGFR (CKD-EPI) [mL/min/1.73m²]											0.5868
>=60	1505	20	1.3	1493	15	1.0	0.4086	0.76 (0.39, 1.47)	0.75 (0.38, 1.48)	0.00 (-0.01, 0.00)	
<60	1482	30	2.0	1503	29	1.9	0.8524	0.95 (0.58, 1.58)	0.95 (0.57, 1.59)	0.00 (-0.01, 0.01)	
History of HHF (in the last 12 months)											0.8149
No	2320	39	1.7	2297	33	1.4	0.5028	0.85 (0.54, 1.35)	0.85 (0.53, 1.36)	0.00 (-0.01, 0.00)	
Yes	669	11	1.6	699	11	1.6	0.9174	0.96 (0.42, 2.19)	0.96 (0.41, 2.22)	0.00 (-0.01, 0.01)	
Baseline SBP (</>= median)											0.5554
< median	1474	22	1.5	1496	17	1.1	0.3939	0.76 (0.41, 1.43)	0.76 (0.40, 1.43)	0.00 (-0.01, 0.00)	
>= median	1515	28	1.8	1500	27	1.8	0.9213	0.97 (0.58, 1.64)	0.97 (0.57, 1.66)	0.00 (-0.01, 0.01)	
History of atrial fibrillation or atrial flutter											0.3646
No	1426	31	2.2	1417	31	2.2	0.9799	1.01 (0.62, 1.65)	1.01 (0.61, 1.66)	0.00 (-0.01, 0.01)	
Yes	1558	19	1.2	1575	13	0.8	0.2726	0.68 (0.34, 1.37)	0.67 (0.33, 1.37)	0.00 (-0.01, 0.00)	

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User-defined AE category: Ketoacidosis (broad 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 LVEF [%]																0.0093
< 50	988	19	1.9	995	6	0.6	0.0084	0.31	(0.13,	0.78)	0.31	(0.12,	0.78)	-0.01	(-0.02, 0.00)	
>= 50	2001	31	1.5	2001	38	1.9	0.3953	1.23	(0.77,	1.96)	1.23	(0.76,	1.98)	0.00	(0.00, 0.01)	
Baseline LVEF [%]																0.0138
<50	988	19	1.9	995	6	0.6	0.0084	0.31	(0.13,	0.78)	0.31	(0.12,	0.78)	-0.01	(-0.02, 0.00)	
50 to <60	1030	12	1.2	1028	21	2.0	0.1130	1.75	(0.87,	3.54)	1.77	(0.87,	3.61)	0.01	(0.00, 0.02)	
>=60	971	19	2.0	973	17	1.7	0.7318	0.89	(0.47,	1.71)	0.89	(0.46,	1.72)	0.00	(-0.01, 0.01)	
Baseline NT-proBNP [pg/mL] (</>=median by atrial fibrillation/flutter status)																0.9712
< median	1507	22	1.5	1476	19	1.3	0.6856	0.88	(0.48,	1.62)	0.88	(0.47,	1.63)	0.00	(-0.01, 0.01)	
>= median	1475	28	1.9	1516	25	1.6	0.6055	0.87	(0.51,	1.48)	0.87	(0.50,	1.49)	0.00	(-0.01, 0.01)	
Baseline uric acid [mg/dL] (tertiles)																0.2880
<T1	975	14	1.4	963	8	0.8	0.2086	0.58	(0.24,	1.37)	0.58	(0.24,	1.38)	-0.01	(-0.02, 0.00)	
>=T1 and <T2	966	13	1.3	1032	19	1.8	0.3781	1.37	(0.68,	2.75)	1.37	(0.68,	2.80)	0.00	(-0.01, 0.02)	
>=T2	1016	22	2.2	970	17	1.8	0.5075	0.81	(0.43,	1.51)	0.81	(0.43,	1.53)	0.00	(-0.02, 0.01)	
Baseline use of MRA																0.7131
No	1865	31	1.7	1878	29	1.5	0.7738	0.93	(0.56,	1.54)	0.93	(0.56,	1.55)	0.00	(-0.01, 0.01)	
Yes	1124	19	1.7	1118	15	1.3	0.4993	0.79	(0.41,	1.55)	0.79	(0.40,	1.56)	0.00	(-0.01, 0.01)	
Baseline use of ACE-inhibitor, ARB or ARNi																0.6600
No	586	10	1.7	568	7	1.2	0.5039	0.72	(0.28,	1.88)	0.72	(0.27,	1.90)	0.00	(-0.02, 0.01)	
Yes	2403	40	1.7	2428	37	1.5	0.6962	0.92	(0.59,	1.43)	0.91	(0.58,	1.43)	0.00	(-0.01, 0.01)	

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*** Confirmed hypoglycaemic AEs are defined by a glucose concentration <=70 mg/dL (3.9 mmol/L) or requiring assistance.
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User-defined AE category: Ketoacidosis (narrow 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	2989	5	0.2	2996	4	0.1	0.7360	0.80 (0.21, 2.97)	0.80 (0.21, 2.97)	0.00 (0.00, 0.00)	
Sex											
Male	1653	2	0.1	1658	3	0.2					
Female	1336	3	0.2	1338	1	0.1					
Age [years]											
<70	1084	5	0.5	1066	2	0.2					
>=70	1905	0	0	1930	2	0.1					
Region											
North America	359	1	0.3	359	1	0.3					
Latin America	757	1	0.1	758	0	0					
Europe	1341	0	0	1346	1	0.1					
Asia	343	1	0.3	343	0	0					
Other	189	2	1.1	190	2	1.1					
OECD member											
No	847	4	0.5	868	1	0.1					
Yes	2142	1	<0.1	2128	3	0.1					
Baseline NYHA											
II^	2450	3	0.1	2435	3	0.1					
III/IV	539	2	0.4	561	1	0.2					
Baseline Diabetes Status											
Diabetic	1471	5	0.3	1465	4	0.3					
Non-Diabetic	1518	0	0	1531	0	0					

Analysis is based on study 1245.110.
^ Patients with NYHA class I are counted in subgroup NYHA class II.
*** Confirmed hypoglycaemic AEs are defined by a glucose concentration <=70 mg/dL (3.9 mmol/L) or requiring assistance.
Risk ratios and odds ratios with confidence intervals (CIs) are estimated by Cochran-Mantel-Haenszel method. For risk differences standard Wald asymptotic confidence limits are calculated. A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied in case of any zero cells in contingency table.
Only treatment emergent AEs are displayed (onset between first dose until treatment stop +7 days).
MedDRA version: 23.1. * Chi-square test for treatment effect ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction).

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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 overall and by subgroup - TS
User-defined AE category: Ketoacidosis (narrow 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 Diabetes Status											
Diabetic	1471	5	0.3	1465	4	0.3					
Pre-Diabetes	979	0	0	1001	0	0					
Normal (no pre-diabetes)	539	0	0	530	0	0					
Baseline BMI [kg/m²]											
<30	1641	2	0.1	1654	1	0.1					
>=30	1348	3	0.2	1342	3	0.2					
Baseline eGFR (CKD-EPI) [mL/min/1.73m²]											
>=60	1505	0	0	1493	2	0.1					
<60	1482	5	0.3	1503	2	0.1					
History of HHF (in the last 12 months)											
No	2320	2	0.1	2297	2	0.1					
Yes	669	3	0.4	699	2	0.3					
Baseline SBP (</>= median)											
< median	1474	2	0.1	1496	2	0.1					
>= median	1515	3	0.2	1500	2	0.1					
History of atrial fibrillation or atrial flutter											
No	1426	3	0.2	1417	4	0.3					
Yes	1558	2	0.1	1575	0	0					

Analysis is based on study 1245.110.
^ Patients with NYHA class I are counted in subgroup NYHA class II.
*** Confirmed hypoglycaemic AEs are defined by a glucose concentration <=70 mg/dL (3.9 mmol/L) or requiring assistance.
Risk ratios and odds ratios with confidence intervals (CIs) are estimated by Cochran-Mantel-Haenszel method. For risk differences standard Wald asymptotic confidence limits are calculated. A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied in case of any zero cells in contingency table.
Only treatment emergent AEs are displayed (onset between first dose until treatment stop +7 days).
MedDRA version: 23.1. * Chi-square test for treatment effect ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction).

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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 overall and by subgroup - TS
User-defined AE category: Ketoacidosis (narrow 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 LVEF [%]											
< 50	988	3	0.3	995	0	0					
>= 50	2001	2	0.1	2001	4	0.2					
Baseline LVEF [%]											
<50	988	3	0.3	995	0	0					
50 to <60	1030	1	0.1	1028	1	0.1					
>=60	971	1	0.1	973	3	0.3					
Baseline NT-proBNP [pg/mL] (</>=median by atrial fibrillation/flutter status)											
< median	1507	2	0.1	1476	2	0.1					
>= median	1475	3	0.2	1516	2	0.1					
Baseline uric acid [mg/dL] (tertiles)											
<T1	975	0	0	963	0	0					
>=T1 and <T2	966	2	0.2	1032	3	0.3					
>=T2	1016	3	0.3	970	1	0.1					
Baseline use of MRA											
No	1865	2	0.1	1878	2	0.1					
Yes	1124	3	0.3	1118	2	0.2					
Baseline use of ACE-inhibitor, ARB or ARNi											
No	586	2	0.3	568	0	0					
Yes	2403	3	0.1	2428	4	0.2					

Analysis is based on study 1245.110.
^ Patients with NYHA class I are counted in subgroup NYHA class II.
*** Confirmed hypoglycaemic AEs are defined by a glucose concentration <=70 mg/dL (3.9 mmol/L) or requiring assistance.
Risk ratios and odds ratios with confidence intervals (CIs) are estimated by Cochran-Mantel-Haenszel method. For risk differences standard Wald asymptotic confidence limits are calculated. A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied in case of any zero cells in contingency table.
Only treatment emergent AEs are displayed (onset between first dose until treatment stop +7 days).
MedDRA version: 23.1. * Chi-square test for treatment effect ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction).

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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 overall and by subgroup - TS
User-defined AE category: AE 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	2989	17	0.6	2996	12	0.4	0.3487	0.70 (0.34, 1.47)	0.70 (0.34, 1.47)	0.00 (-0.01, 0.00)	
Sex											0.3060
Male	1653	13	0.8	1658	11	0.7	0.6766	0.84 (0.38, 1.88)	0.84 (0.38, 1.89)	0.00 (-0.01, 0.00)	
Female	1336	4	0.3	1338	1	0.1	0.1788	0.25 (0.03, 2.23)	0.25 (0.03, 2.23)	0.00 (-0.01, 0.00)	
Age [years]											0.4378
<70	1084	9	0.8	1066	8	0.8	0.8346	0.90 (0.35, 2.33)	0.90 (0.35, 2.35)	0.00 (-0.01, 0.01)	
>=70	1905	8	0.4	1930	4	0.2	0.2383	0.49 (0.15, 1.64)	0.49 (0.15, 1.64)	0.00 (-0.01, 0.00)	
Region											0.7611
North America	359	5	1.4	359	3	0.8	0.4770	0.60 (0.14, 2.49)	0.60 (0.14, 2.52)	-0.01 (-0.02, 0.01)	
Latin America	757	5	0.7	758	2	0.3	0.2550	0.40 (0.08, 2.05)	0.40 (0.08, 2.06)	0.00 (-0.01, 0.00)	
Europe	1341	6	0.4	1346	6	0.4	0.9948	1.00 (0.32, 3.08)	1.00 (0.32, 3.10)	0.00 (-0.01, 0.01)	
Asia	343	1	0.3	343	0	0	0.4789	0.33 (0.01, 8.15)	0.33 (0.01, 8.19)	0.00 (-0.01, 0.01)	
Other	189	0	0	190	1	0.5	0.4807	2.98 (0.12, 72.80)	3.00 (0.12, 74.11)	0.01 (-0.01, 0.02)	
OECD member											0.6308
No	847	4	0.5	868	2	0.2	0.3964	0.49 (0.09, 2.66)	0.49 (0.09, 2.66)	0.00 (-0.01, 0.00)	
Yes	2142	13	0.6	2128	10	0.5	0.5409	0.77 (0.34, 1.76)	0.77 (0.34, 1.77)	0.00 (-0.01, 0.00)	
Baseline NYHA											0.5190
II^	2450	11	0.4	2435	9	0.4	0.6640	0.82 (0.34, 1.98)	0.82 (0.34, 1.99)	0.00 (0.00, 0.00)	
III/IV	539	6	1.1	561	3	0.5	0.2871	0.48 (0.12, 1.91)	0.48 (0.12, 1.92)	-0.01 (-0.02, 0.00)	
Baseline Diabetes Status											0.7584
Diabetic	1471	15	1.0	1465	11	0.8	0.4369	0.74 (0.34, 1.60)	0.73 (0.34, 1.60)	0.00 (-0.01, 0.00)	
Non-Diabetic	1518	2	0.1	1531	1	0.1	0.5585	0.50 (0.05, 5.46)	0.50 (0.04, 5.47)	0.00 (0.00, 0.00)	

Analysis is based on study 1245.110.
^ Patients with NYHA class I are counted in subgroup NYHA class II.
*** Confirmed hypoglycaemic AEs are defined by a glucose concentration <=70 mg/dL (3.9 mmol/L) or requiring assistance.
Risk ratios and odds ratios with confidence intervals (CIs) are estimated by Cochran-Mantel-Haenszel method. For risk differences standard Wald asymptotic confidence limits are calculated. A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied in case of any zero cells in contingency table.
Only treatment emergent AEs are displayed (onset between first dose until treatment stop +7 days).
MedDRA version: 23.1. * Chi-square test for treatment effect ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction).

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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 overall and by subgroup - TS
User-defined AE category: AE 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 Diabetes Status											0.8614
Diabetic	1471	15	1.0	1465	11	0.8	0.4369	0.74 (0.34, 1.60)	0.73 (0.34, 1.60)	0.00 (-0.01, 0.00)	
Pre-Diabetes	979	1	0.1	1001	0	0	0.4695	0.33 (0.01, 7.99)	0.33 (0.01, 8.00)	0.00 (0.00, 0.00)	
Normal (no pre-diabetes)	539	1	0.2	530	1	0.2	0.9905	1.02 (0.06, 16.22)	1.02 (0.06, 16.30)	0.00 (-0.01, 0.01)	
Baseline BMI [kg/m²]											0.5461
<30	1641	6	0.4	1654	3	0.2	0.3110	0.50 (0.12, 1.98)	0.50 (0.12, 1.98)	0.00 (-0.01, 0.00)	
>=30	1348	11	0.8	1342	9	0.7	0.6608	0.82 (0.34, 1.98)	0.82 (0.34, 1.99)	0.00 (-0.01, 0.01)	
Baseline eGFR (CKD-EPI) [mL/min/1.73m²]											0.4774
>=60	1505	5	0.3	1493	5	0.3	0.9899	1.01 (0.29, 3.47)	1.01 (0.29, 3.49)	0.00 (0.00, 0.00)	
<60	1482	12	0.8	1503	7	0.5	0.2374	0.58 (0.23, 1.46)	0.57 (0.23, 1.46)	0.00 (-0.01, 0.00)	
History of HHF (in the last 12 months)											0.5386
No	2320	12	0.5	2297	7	0.3	0.2594	0.59 (0.23, 1.49)	0.59 (0.23, 1.50)	0.00 (-0.01, 0.00)	
Yes	669	5	0.7	699	5	0.7	0.9445	0.96 (0.28, 3.29)	0.96 (0.28, 3.32)	0.00 (-0.01, 0.01)	
Baseline SBP (</>= median)											0.4417
< median	1474	8	0.5	1496	4	0.3	0.2369	0.49 (0.15, 1.63)	0.49 (0.15, 1.64)	0.00 (-0.01, 0.00)	
>= median	1515	9	0.6	1500	8	0.5	0.8238	0.90 (0.35, 2.32)	0.90 (0.35, 2.33)	0.00 (-0.01, 0.00)	
History of atrial fibrillation or atrial flutter											0.1062
No	1426	11	0.8	1417	4	0.3	0.0719	0.37 (0.12, 1.15)	0.36 (0.12, 1.15)	0.00 (-0.01, 0.00)	
Yes	1558	6	0.4	1575	8	0.5	0.6063	1.32 (0.46, 3.79)	1.32 (0.46, 3.81)	0.00 (0.00, 0.01)	

Analysis is based on study 1245.110.
^ Patients with NYHA class I are counted in subgroup NYHA class II.
*** Confirmed hypoglycaemic AEs are defined by a glucose concentration <=70 mg/dL (3.9 mmol/L) or requiring assistance.
Risk ratios and odds ratios with confidence intervals (CIs) are estimated by Cochran-Mantel-Haenszel method. For risk differences standard Wald asymptotic confidence limits are calculated. A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied in case of any zero cells in contingency table.
Only treatment emergent AEs are displayed (onset between first dose until treatment stop +7 days).
MedDRA version: 23.1. * Chi-square test for treatment effect ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction).

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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 overall and by subgroup - TS
User-defined AE category: AE 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 LVEF [%]													0.8286
< 50	988	5	0.5	995	4	0.4	0.7303	0.79 (0.21,	2.95)	0.79 (0.21,	2.96)	0.00 (-0.01, 0.00)	
>= 50	2001	12	0.6	2001	8	0.4	0.3699	0.67 (0.27,	1.63)	0.67 (0.27,	1.63)	0.00 (-0.01, 0.00)	
Baseline LVEF [%]													0.9765
<50	988	5	0.5	995	4	0.4	0.7303	0.79 (0.21,	2.95)	0.79 (0.21,	2.96)	0.00 (-0.01, 0.00)	
50 to <60	1030	3	0.3	1028	2	0.2	0.6559	0.67 (0.11,	3.99)	0.67 (0.11,	4.00)	0.00 (-0.01, 0.00)	
>=60	971	9	0.9	973	6	0.6	0.4344	0.67 (0.24,	1.86)	0.66 (0.24,	1.87)	0.00 (-0.01, 0.00)	
Baseline NT-proBNP [pg/mL] (</>=median by atrial fibrillation/flutter status)													0.5080
< median	1507	8	0.5	1476	7	0.5	0.8270	0.89 (0.32,	2.46)	0.89 (0.32,	2.47)	0.00 (-0.01, 0.00)	
>= median	1475	9	0.6	1516	5	0.3	0.2614	0.54 (0.18,	1.61)	0.54 (0.18,	1.61)	0.00 (-0.01, 0.00)	
Baseline uric acid [mg/dL] (tertiles)													0.1715
<T1	975	5	0.5	963	0	0	0.0424	0.09 (<0.01,	1.66)	0.09 (<0.01,	1.66)	-0.01 (-0.01, 0.00)	
>=T1 and <T2	966	3	0.3	1032	6	0.6	0.3663	1.87 (0.47,	7.46)	1.88 (0.47,	7.53)	0.00 (0.00, 0.01)	
>=T2	1016	8	0.8	970	6	0.6	0.6530	0.79 (0.27,	2.26)	0.78 (0.27,	2.27)	0.00 (-0.01, 0.01)	
Baseline use of MRA													0.4200
No	1865	11	0.6	1878	6	0.3	0.2188	0.54 (0.20,	1.46)	0.54 (0.20,	1.46)	0.00 (-0.01, 0.00)	
Yes	1124	6	0.5	1118	6	0.5	0.9926	1.01 (0.33,	3.11)	1.01 (0.32,	3.13)	0.00 (-0.01, 0.01)	
Baseline use of ACE-inhibitor, ARB or ARNi													0.6784
No	586	2	0.3	568	2	0.4	0.9751	1.03 (0.15,	7.30)	1.03 (0.14,	7.35)	0.00 (-0.01, 0.01)	
Yes	2403	15	0.6	2428	10	0.4	0.3037	0.66 (0.30,	1.47)	0.66 (0.30,	1.47)	0.00 (-0.01, 0.00)	

Analysis is based on study 1245.110.
^ Patients with NYHA class I are counted in subgroup NYHA class II.
*** Confirmed hypoglycaemic AEs are defined by a glucose concentration <=70 mg/dL (3.9 mmol/L) or requiring assistance.
Risk ratios and odds ratios with confidence intervals (CIs) are estimated by Cochran-Mantel-Haenszel method. For risk differences standard Wald asymptotic confidence limits are calculated. A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied in case of any zero cells in contingency table.
Only treatment emergent AEs are displayed (onset between first dose until treatment stop +7 days).
MedDRA version: 23.1. * Chi-square test for treatment effect ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction).

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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 overall and by subgroup - TS
User-defined AE category: Confirmed 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	2989	78	2.6	2996	73	2.4	0.6696	0.93 (0.68, 1.28)	0.93 (0.67, 1.29)	0.00 (-0.01, 0.01)	
Sex											0.6565
Male	1653	41	2.5	1658	41	2.5	0.9890	1.00 (0.65, 1.53)	1.00 (0.64, 1.55)	0.00 (-0.01, 0.01)	
Female	1336	37	2.8	1338	32	2.4	0.5378	0.86 (0.54, 1.38)	0.86 (0.53, 1.39)	0.00 (-0.02, 0.01)	
Age [years]											0.4673
<70	1084	24	2.2	1066	26	2.4	0.7293	1.10 (0.64, 1.91)	1.10 (0.63, 1.94)	0.00 (-0.01, 0.01)	
>=70	1905	54	2.8	1930	47	2.4	0.4399	0.86 (0.58, 1.26)	0.86 (0.58, 1.27)	0.00 (-0.01, 0.01)	
Region											0.8855
North America	359	14	3.9	359	18	5.0	0.4694	1.29 (0.65, 2.55)	1.30 (0.64, 2.66)	0.01 (-0.02, 0.04)	
Latin America	757	28	3.7	758	23	3.0	0.4734	0.82 (0.48, 1.41)	0.81 (0.46, 1.43)	-0.01 (-0.02, 0.01)	
Europe	1341	24	1.8	1346	21	1.6	0.6429	0.87 (0.49, 1.56)	0.87 (0.48, 1.57)	0.00 (-0.01, 0.01)	
Asia	343	5	1.5	343	5	1.5	1.0000	1.00 (0.29, 3.42)	1.00 (0.29, 3.49)	0.00 (-0.02, 0.02)	
Other	189	7	3.7	190	6	3.2	0.7704	0.85 (0.29, 2.49)	0.85 (0.28, 2.57)	-0.01 (-0.04, 0.03)	
OECD member											0.4136
No	847	30	3.5	868	24	2.8	0.3570	0.78 (0.46, 1.32)	0.77 (0.45, 1.34)	-0.01 (-0.02, 0.01)	
Yes	2142	48	2.2	2128	49	2.3	0.8923	1.03 (0.69, 1.52)	1.03 (0.69, 1.54)	0.00 (-0.01, 0.01)	
Baseline NYHA											0.7996
II^	2450	57	2.3	2435	54	2.2	0.7985	0.95 (0.66, 1.38)	0.95 (0.65, 1.39)	0.00 (-0.01, 0.01)	
III/IV	539	21	3.9	561	19	3.4	0.6519	0.87 (0.47, 1.60)	0.86 (0.46, 1.63)	-0.01 (-0.03, 0.02)	
Baseline Diabetes Status											0.7470
Diabetic	1471	66	4.5	1465	63	4.3	0.8054	0.96 (0.68, 1.34)	0.96 (0.67, 1.36)	0.00 (-0.02, 0.01)	
Non-Diabetic	1518	12	0.8	1531	10	0.7	0.6541	0.83 (0.36, 1.91)	0.83 (0.36, 1.92)	0.00 (-0.01, 0.00)	

Analysis is based on study 1245.110.
^ Patients with NYHA class I are counted in subgroup NYHA class II.
*** Confirmed hypoglycaemic AEs are defined by a glucose concentration <=70 mg/dL (3.9 mmol/L) or requiring assistance.
Risk ratios and odds ratios with confidence intervals (CIs) are estimated by Cochran-Mantel-Haenszel method. For risk differences standard Wald asymptotic confidence limits are calculated. A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied in case of any zero cells in contingency table.
Only treatment emergent AEs are displayed (onset between first dose until treatment stop +7 days).
MedDRA version: 23.1. * Chi-square test for treatment effect ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction).

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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 overall and by subgroup - TS
User-defined AE category: Confirmed 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 **
Baseline Diabetes Status											0.6401
Diabetic	1471	66	4.5	1465	63	4.3	0.8054	0.96 (0.68, 1.34)	0.96 (0.67, 1.36)	0.00 (-0.02, 0.01)	
Pre-Diabetes	979	7	0.7	1001	4	0.4	0.3451	0.56 (0.16, 1.90)	0.56 (0.16, 1.91)	0.00 (-0.01, 0.00)	
Normal (no pre-diabetes)	539	5	0.9	530	6	1.1	0.7405	1.22 (0.37, 3.97)	1.22 (0.37, 4.03)	0.00 (-0.01, 0.01)	
Baseline BMI [kg/m²]											0.2039
<30	1641	43	2.6	1654	33	2.0	0.2320	0.76 (0.49, 1.19)	0.76 (0.48, 1.20)	-0.01 (-0.02, 0.00)	
>=30	1348	35	2.6	1342	40	3.0	0.5451	1.15 (0.73, 1.80)	1.15 (0.73, 1.83)	0.00 (-0.01, 0.02)	
Baseline eGFR (CKD-EPI) [mL/min/1.73m²]											0.1080
>=60	1505	29	1.9	1493	18	1.2	0.1119	0.63 (0.35, 1.12)	0.62 (0.34, 1.12)	-0.01 (-0.02, 0.00)	
<60	1482	49	3.3	1503	55	3.7	0.5990	1.11 (0.76, 1.62)	1.11 (0.75, 1.64)	0.00 (-0.01, 0.02)	
History of HHF (in the last 12 months)											0.3077
No	2320	55	2.4	2297	56	2.4	0.8814	1.03 (0.71, 1.49)	1.03 (0.71, 1.50)	0.00 (-0.01, 0.01)	
Yes	669	23	3.4	699	17	2.4	0.2696	0.71 (0.38, 1.31)	0.70 (0.37, 1.32)	-0.01 (-0.03, 0.01)	
Baseline SBP (</>= median)											0.5359
< median	1474	32	2.2	1496	34	2.3	0.8508	1.05 (0.65, 1.69)	1.05 (0.64, 1.71)	0.00 (-0.01, 0.01)	
>= median	1515	46	3.0	1500	39	2.6	0.4693	0.86 (0.56, 1.30)	0.85 (0.55, 1.31)	0.00 (-0.02, 0.01)	
History of atrial fibrillation or atrial flutter											0.6098
No	1426	42	2.9	1417	36	2.5	0.5089	0.86 (0.56, 1.34)	0.86 (0.55, 1.35)	0.00 (-0.02, 0.01)	
Yes	1558	36	2.3	1575	37	2.3	0.9430	1.02 (0.65, 1.60)	1.02 (0.64, 1.62)	0.00 (-0.01, 0.01)	

Analysis is based on study 1245.110.
^ Patients with NYHA class I are counted in subgroup NYHA class II.
*** Confirmed hypoglycaemic AEs are defined by a glucose concentration <=70 mg/dL (3.9 mmol/L) or requiring assistance.
Risk ratios and odds ratios with confidence intervals (CIs) are estimated by Cochran-Mantel-Haenszel method. For risk differences standard Wald asymptotic confidence limits are calculated. A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied in case of any zero cells in contingency table.
Only treatment emergent AEs are displayed (onset between first dose until treatment stop +7 days).
MedDRA version: 23.1. * Chi-square test for treatment effect ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction).

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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 overall and by subgroup - TS
User-defined AE category: Confirmed 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 **
Baseline LVEF [%]																0.2765
< 50	988	31	3.1	995	23	2.3	0.2584	0.74	(0.43,	1.25)	0.73	(0.42,	1.26)	-0.01	(-0.02, 0.01)	
>= 50	2001	47	2.3	2001	50	2.5	0.7578	1.06	(0.72,	1.58)	1.07	(0.71,	1.59)	0.00	(-0.01, 0.01)	
Baseline LVEF [%]																0.4869
<50	988	31	3.1	995	23	2.3	0.2584	0.74	(0.43,	1.25)	0.73	(0.42,	1.26)	-0.01	(-0.02, 0.01)	
50 to <60	1030	25	2.4	1028	24	2.3	0.8905	0.96	(0.55,	1.67)	0.96	(0.55,	1.69)	0.00	(-0.01, 0.01)	
>=60	971	22	2.3	973	26	2.7	0.5637	1.18	(0.67,	2.07)	1.18	(0.67,	2.10)	0.00	(-0.01, 0.02)	
Baseline NT-proBNP [pg/mL] (</>=median by atrial fibrillation/flutter status)																0.6073
< median	1507	34	2.3	1476	28	1.9	0.4918	0.84	(0.51,	1.38)	0.84	(0.51,	1.39)	0.00	(-0.01, 0.01)	
>= median	1475	44	3.0	1516	45	3.0	0.9811	1.00	(0.66,	1.50)	0.99	(0.65,	1.52)	0.00	(-0.01, 0.01)	
Baseline uric acid [mg/dL] (tertiles)																0.1883
<T1	975	33	3.4	963	20	2.1	0.0776	0.61	(0.35,	1.06)	0.61	(0.34,	1.06)	-0.01	(-0.03, 0.00)	
>=T1 and <T2	966	20	2.1	1032	24	2.3	0.6977	1.12	(0.62,	2.02)	1.13	(0.62,	2.05)	0.00	(-0.01, 0.02)	
>=T2	1016	25	2.5	970	28	2.9	0.5560	1.17	(0.69,	2.00)	1.18	(0.68,	2.04)	0.00	(-0.01, 0.02)	
Baseline use of MRA																0.1480
No	1865	49	2.6	1878	54	2.9	0.6428	1.09	(0.75,	1.60)	1.10	(0.74,	1.62)	0.00	(-0.01, 0.01)	
Yes	1124	29	2.6	1118	19	1.7	0.1498	0.66	(0.37,	1.17)	0.65	(0.36,	1.17)	-0.01	(-0.02, 0.00)	
Baseline use of ACE-inhibitor, ARB or ARNi																0.2543
No	586	12	2.0	568	16	2.8	0.3959	1.38	(0.66,	2.88)	1.39	(0.65,	2.96)	0.01	(-0.01, 0.03)	
Yes	2403	66	2.7	2428	57	2.3	0.3788	0.85	(0.60,	1.21)	0.85	(0.59,	1.22)	0.00	(-0.01, 0.00)	

Analysis is based on study 1245.110.
^ Patients with NYHA class I are counted in subgroup NYHA class II.
*** Confirmed hypoglycaemic AEs are defined by a glucose concentration <=70 mg/dL (3.9 mmol/L) or requiring assistance.
Risk ratios and odds ratios with confidence intervals (CIs) are estimated by Cochran-Mantel-Haenszel method. For risk differences standard Wald asymptotic confidence limits are calculated. A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied in case of any zero cells in contingency table.
Only treatment emergent AEs are displayed (onset between first dose until treatment stop +7 days).
MedDRA version: 23.1. * Chi-square test for treatment effect ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction).

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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 overall and by subgroup - TS
User-defined AE category: Urinary Tract Infection (narrow Sub 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	2989	243	8.1	2996	297	9.9	0.0160	1.22 (1.04, 1.43)	1.24 (1.04, 1.49)	0.02 (0.00, 0.03)	
Sex											0.8396
Male	1653	79	4.8	1658	99	6.0	0.1284	1.25 (0.94, 1.67)	1.27 (0.93, 1.71)	0.01 (0.00, 0.03)	
Female	1336	164	12.3	1338	198	14.8	0.0566	1.21 (0.99, 1.46)	1.24 (0.99, 1.55)	0.03 (0.00, 0.05)	
Age [years]											0.2772
<70	1084	62	5.7	1066	86	8.1	0.0316	1.41 (1.03, 1.93)	1.45 (1.03, 2.03)	0.02 (0.00, 0.04)	
>=70	1905	181	9.5	1930	211	10.9	0.1435	1.15 (0.95, 1.39)	1.17 (0.95, 1.44)	0.01 (0.00, 0.03)	
Region											0.8433
North America	359	38	10.6	359	42	11.7	0.6352	1.11 (0.73, 1.67)	1.12 (0.70, 1.78)	0.01 (-0.03, 0.06)	
Latin America	757	63	8.3	758	83	10.9	0.0831	1.32 (0.96, 1.80)	1.35 (0.96, 1.91)	0.03 (0.00, 0.06)	
Europe	1341	105	7.8	1346	125	9.3	0.1771	1.19 (0.93, 1.52)	1.21 (0.92, 1.58)	0.01 (-0.01, 0.04)	
Asia	343	17	5.0	343	17	5.0	1.0000	1.00 (0.52, 1.93)	1.00 (0.50, 1.99)	0.00 (-0.03, 0.03)	
Other	189	20	10.6	190	30	15.8	0.1342	1.49 (0.88, 2.53)	1.58 (0.86, 2.90)	0.05 (-0.02, 0.12)	
OECD member											0.0512
No	847	60	7.1	868	97	11.2	0.0033	1.58 (1.16, 2.15)	1.65 (1.18, 2.31)	0.04 (0.01, 0.07)	
Yes	2142	183	8.5	2128	200	9.4	0.3282	1.10 (0.91, 1.33)	1.11 (0.90, 1.37)	0.01 (-0.01, 0.03)	
Baseline NYHA											0.8803
II^	2450	185	7.6	2435	222	9.1	0.0477	1.21 (1.00, 1.46)	1.23 (1.00, 1.51)	0.02 (0.00, 0.03)	
III/IV	539	58	10.8	561	75	13.4	0.1847	1.24 (0.90, 1.71)	1.28 (0.89, 1.84)	0.03 (-0.01, 0.06)	
Baseline Diabetes Status											0.3618
Diabetic	1471	131	8.9	1465	148	10.1	0.2688	1.13 (0.91, 1.42)	1.15 (0.90, 1.47)	0.01 (-0.01, 0.03)	
Non-Diabetic	1518	112	7.4	1531	149	9.7	0.0202	1.32 (1.04, 1.67)	1.35 (1.05, 1.75)	0.02 (0.00, 0.04)	

Analysis is based on study 1245.110.
^ Patients with NYHA class I are counted in subgroup NYHA class II.
*** Confirmed hypoglycaemic AEs are defined by a glucose concentration <=70 mg/dL (3.9 mmol/L) or requiring assistance.
Risk ratios and odds ratios with confidence intervals (CIs) are estimated by Cochran-Mantel-Haenszel method. For risk differences standard Wald asymptotic confidence limits are calculated. A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied in case of any zero cells in contingency table.
Only treatment emergent AEs are displayed (onset between first dose until treatment stop +7 days).
MedDRA version: 23.1. * Chi-square test for treatment effect ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction).

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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 overall and by subgroup - TS
User-defined AE category: Urinary Tract Infection (narrow Sub 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 Diabetes Status											0.3305
Diabetic	1471	131	8.9	1465	148	10.1	0.2688	1.13 (0.91, 1.42)	1.15 (0.90, 1.47)	0.01 (-0.01, 0.03)	
Pre-Diabetes	979	78	8.0	1001	95	9.5	0.2301	1.19 (0.89, 1.59)	1.21 (0.89, 1.66)	0.02 (-0.01, 0.04)	
Normal (no pre-diabetes)	539	34	6.3	530	54	10.2	0.0210	1.62 (1.07, 2.44)	1.68 (1.08, 2.63)	0.04 (0.01, 0.07)	
Baseline BMI [kg/m²]											0.3132
<30	1641	128	7.8	1654	145	8.8	0.3143	1.12 (0.90, 1.41)	1.14 (0.89, 1.46)	0.01 (-0.01, 0.03)	
>=30	1348	115	8.5	1342	152	11.3	0.0153	1.33 (1.05, 1.67)	1.37 (1.06, 1.77)	0.03 (0.01, 0.05)	
Baseline eGFR (CKD-EPI) [mL/min/1.73m²]											0.2490
>=60	1505	93	6.2	1493	126	8.4	0.0174	1.37 (1.05, 1.77)	1.40 (1.06, 1.85)	0.02 (0.00, 0.04)	
<60	1482	150	10.1	1503	171	11.4	0.2682	1.12 (0.91, 1.38)	1.14 (0.90, 1.44)	0.01 (-0.01, 0.03)	
History of HHF (in the last 12 months)											0.4466
No	2320	192	8.3	2297	224	9.8	0.0799	1.18 (0.98, 1.42)	1.20 (0.98, 1.47)	0.01 (0.00, 0.03)	
Yes	669	51	7.6	699	73	10.4	0.0693	1.37 (0.97, 1.93)	1.41 (0.97, 2.06)	0.03 (0.00, 0.06)	
Baseline SBP (</>= median)											0.3257
< median	1474	113	7.7	1496	152	10.2	0.0171	1.33 (1.05, 1.67)	1.36 (1.06, 1.76)	0.02 (0.00, 0.05)	
>= median	1515	130	8.6	1500	145	9.7	0.3005	1.13 (0.90, 1.41)	1.14 (0.89, 1.46)	0.01 (-0.01, 0.03)	
History of atrial fibrillation or atrial flutter											0.4052
No	1426	104	7.3	1417	136	9.6	0.0271	1.32 (1.03, 1.68)	1.35 (1.03, 1.76)	0.02 (0.00, 0.04)	
Yes	1558	139	8.9	1575	161	10.2	0.2161	1.15 (0.92, 1.42)	1.16 (0.92, 1.48)	0.01 (-0.01, 0.03)	

Analysis is based on study 1245.110.
^ Patients with NYHA class I are counted in subgroup NYHA class II.
*** Confirmed hypoglycaemic AEs are defined by a glucose concentration <=70 mg/dL (3.9 mmol/L) or requiring assistance.
Risk ratios and odds ratios with confidence intervals (CIs) are estimated by Cochran-Mantel-Haenszel method. For risk differences standard Wald asymptotic confidence limits are calculated. A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied in case of any zero cells in contingency table.
Only treatment emergent AEs are displayed (onset between first dose until treatment stop +7 days).
MedDRA version: 23.1. * Chi-square test for treatment effect ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction).

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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 overall and by subgroup - TS
User-defined AE category: Urinary Tract Infection (narrow Sub 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 LVEF [%]											0.3908
< 50	988	56	5.7	995	78	7.8	0.0541	1.38 (0.99, 1.93)	1.42 (0.99, 2.02)	0.02 (0.00, 0.04)	
>= 50	2001	187	9.3	2001	219	10.9	0.0939	1.17 (0.97, 1.41)	1.19 (0.97, 1.46)	0.02 (0.00, 0.03)	
Baseline LVEF [%]											0.2165
<50	988	56	5.7	995	78	7.8	0.0541	1.38 (0.99, 1.93)	1.42 (0.99, 2.02)	0.02 (0.00, 0.04)	
50 to <60	1030	87	8.4	1028	86	8.4	0.9473	0.99 (0.74, 1.32)	0.99 (0.72, 1.35)	0.00 (-0.02, 0.02)	
>=60	971	100	10.3	973	133	13.7	0.0222	1.33 (1.04, 1.69)	1.38 (1.05, 1.82)	0.03 (0.00, 0.06)	
Baseline NT-proBNP [pg/mL] (</>=median by atrial fibrillation/flutter status)											0.1913
< median	1507	115	7.6	1476	153	10.4	0.0090	1.36 (1.08, 1.71)	1.40 (1.09, 1.80)	0.03 (0.01, 0.05)	
>= median	1475	128	8.7	1516	144	9.5	0.4351	1.09 (0.87, 1.37)	1.10 (0.86, 1.42)	0.01 (-0.01, 0.03)	
Baseline uric acid [mg/dL] (tertiles)											0.3875
<T1	975	83	8.5	963	85	8.8	0.8061	1.04 (0.78, 1.38)	1.04 (0.76, 1.43)	0.00 (-0.02, 0.03)	
>=T1 and <T2	966	74	7.7	1032	106	10.3	0.0417	1.34 (1.01, 1.78)	1.38 (1.01, 1.88)	0.03 (0.00, 0.05)	
>=T2	1016	84	8.3	970	105	10.8	0.0522	1.31 (1.00, 1.72)	1.35 (1.00, 1.82)	0.03 (0.00, 0.05)	
Baseline use of MRA											0.3682
No	1865	146	7.8	1878	190	10.1	0.0143	1.29 (1.05, 1.59)	1.33 (1.06, 1.66)	0.02 (0.00, 0.04)	
Yes	1124	97	8.6	1118	107	9.6	0.4387	1.11 (0.85, 1.44)	1.12 (0.84, 1.49)	0.01 (-0.01, 0.03)	
Baseline use of ACE-inhibitor, ARB or ARNi											0.1065
No	586	48	8.2	568	73	12.9	0.0098	1.57 (1.11, 2.22)	1.65 (1.13, 2.43)	0.05 (0.01, 0.08)	
Yes	2403	195	8.1	2428	224	9.2	0.1702	1.14 (0.95, 1.37)	1.15 (0.94, 1.41)	0.01 (0.00, 0.03)	

Analysis is based on study 1245.110.
^ Patients with NYHA class I are counted in subgroup NYHA class II.
*** Confirmed hypoglycaemic AEs are defined by a glucose concentration <=70 mg/dL (3.9 mmol/L) or requiring assistance.
Risk ratios and odds ratios with confidence intervals (CIs) are estimated by Cochran-Mantel-Haenszel method. For risk differences standard Wald asymptotic confidence limits are calculated. A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied in case of any zero cells in contingency table.
Only treatment emergent AEs are displayed (onset between first dose until treatment stop +7 days).
MedDRA version: 23.1. * Chi-square test for treatment effect ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction).

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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 overall and by subgroup - TS
User-defined AE category: Complicated urinary tract infection (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	2989	45	1.5	2996	57	1.9	0.2354	1.26 (0.86, 1.86)	1.27 (0.86, 1.88)	0.00 (0.00, 0.01)	
Sex											0.0048
Male	1653	26	1.6	1658	17	1.0	0.1641	0.65 (0.36, 1.20)	0.65 (0.35, 1.20)	-0.01 (-0.01, 0.00)	
Female	1336	19	1.4	1338	40	3.0	0.0058	2.10 (1.22, 3.61)	2.14 (1.23, 3.71)	0.02 (0.00, 0.03)	
Age [years]											0.0566
<70	1084	7	0.6	1066	18	1.7	0.0241	2.61 (1.10, 6.23)	2.64 (1.10, 6.35)	0.01 (0.00, 0.02)	
>=70	1905	38	2.0	1930	39	2.0	0.9543	1.01 (0.65, 1.58)	1.01 (0.65, 1.59)	0.00 (-0.01, 0.01)	
Region											0.7677
North America	359	9	2.5	359	9	2.5	1.0000	1.00 (0.40, 2.49)	1.00 (0.39, 2.55)	0.00 (-0.02, 0.02)	
Latin America	757	12	1.6	758	17	2.2	0.3504	1.41 (0.68, 2.94)	1.42 (0.68, 3.00)	0.01 (-0.01, 0.02)	
Europe	1341	17	1.3	1346	19	1.4	0.7457	1.11 (0.58, 2.13)	1.12 (0.58, 2.15)	0.00 (-0.01, 0.01)	
Asia	343	4	1.2	343	4	1.2	1.0000	1.00 (0.25, 3.97)	1.00 (0.25, 4.03)	0.00 (-0.02, 0.02)	
Other	189	3	1.6	190	8	4.2	0.1282	2.65 (0.71, 9.85)	2.73 (0.71, 10.43)	0.03 (-0.01, 0.06)	
OECD member											0.9742
No	847	13	1.5	868	17	2.0	0.5034	1.28 (0.62, 2.61)	1.28 (0.62, 2.66)	0.00 (-0.01, 0.02)	
Yes	2142	32	1.5	2128	40	1.9	0.3276	1.26 (0.79, 2.00)	1.26 (0.79, 2.02)	0.00 (0.00, 0.01)	
Baseline NYHA											0.1365
II^	2450	37	1.5	2435	39	1.6	0.7963	1.06 (0.68, 1.66)	1.06 (0.67, 1.67)	0.00 (-0.01, 0.01)	
III/IV	539	8	1.5	561	18	3.2	0.0598	2.16 (0.95, 4.93)	2.20 (0.95, 5.10)	0.02 (0.00, 0.04)	
Baseline Diabetes Status											0.6585
Diabetic	1471	25	1.7	1465	29	2.0	0.5724	1.16 (0.69, 1.98)	1.17 (0.68, 2.00)	0.00 (-0.01, 0.01)	
Non-Diabetic	1518	20	1.3	1531	28	1.8	0.2567	1.39 (0.79, 2.45)	1.40 (0.78, 2.49)	0.01 (0.00, 0.01)	

Analysis is based on study 1245.110.
^ Patients with NYHA class I are counted in subgroup NYHA class II.
*** Confirmed hypoglycaemic AEs are defined by a glucose concentration <=70 mg/dL (3.9 mmol/L) or requiring assistance.
Risk ratios and odds ratios with confidence intervals (CIs) are estimated by Cochran-Mantel-Haenszel method. For risk differences standard Wald asymptotic confidence limits are calculated. A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied in case of any zero cells in contingency table.
Only treatment emergent AEs are displayed (onset between first dose until treatment stop +7 days).
MedDRA version: 23.1. * Chi-square test for treatment effect ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction).

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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 overall and by subgroup - TS
User-defined AE category: Complicated urinary tract infection (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 Diabetes Status											0.8614
Diabetic	1471	25	1.7	1465	29	2.0	0.5724	1.16 (0.69, 1.98)	1.17 (0.68, 2.00)	0.00 (-0.01, 0.01)	
Pre-Diabetes	979	15	1.5	1001	20	2.0	0.4316	1.30 (0.67, 2.53)	1.31 (0.67, 2.57)	0.00 (-0.01, 0.02)	
Normal (no pre-diabetes)	539	5	0.9	530	8	1.5	0.3855	1.63 (0.54, 4.94)	1.64 (0.53, 5.04)	0.01 (-0.01, 0.02)	
Baseline BMI [kg/m²]											0.3229
<30	1641	24	1.5	1654	25	1.5	0.9076	1.03 (0.59, 1.80)	1.03 (0.59, 1.82)	0.00 (-0.01, 0.01)	
>=30	1348	21	1.6	1342	32	2.4	0.1230	1.53 (0.89, 2.64)	1.54 (0.89, 2.69)	0.01 (0.00, 0.02)	
Baseline eGFR (CKD-EPI) [mL/min/1.73m²]											0.6431
>=60	1505	11	0.7	1493	16	1.1	0.3234	1.47 (0.68, 3.15)	1.47 (0.68, 3.18)	0.00 (0.00, 0.01)	
<60	1482	34	2.3	1503	41	2.7	0.4491	1.19 (0.76, 1.86)	1.19 (0.75, 1.89)	0.00 (-0.01, 0.02)	
History of HHF (in the last 12 months)											0.5374
No	2320	32	1.4	2297	43	1.9	0.1855	1.36 (0.86, 2.14)	1.36 (0.86, 2.16)	0.00 (0.00, 0.01)	
Yes	669	13	1.9	699	14	2.0	0.9368	1.03 (0.49, 2.18)	1.03 (0.48, 2.21)	0.00 (-0.01, 0.02)	
Baseline SBP (</>= median)											0.6451
< median	1474	19	1.3	1496	27	1.8	0.2550	1.40 (0.78, 2.51)	1.41 (0.78, 2.54)	0.01 (0.00, 0.01)	
>= median	1515	26	1.7	1500	30	2.0	0.5638	1.17 (0.69, 1.96)	1.17 (0.69, 1.99)	0.00 (-0.01, 0.01)	
History of atrial fibrillation or atrial flutter											0.0525
No	1426	16	1.1	1417	31	2.2	0.0259	1.95 (1.07, 3.55)	1.97 (1.07, 3.62)	0.01 (0.00, 0.02)	
Yes	1558	29	1.9	1575	26	1.7	0.6536	0.89 (0.52, 1.50)	0.88 (0.52, 1.51)	0.00 (-0.01, 0.01)	

Analysis is based on study 1245.110.
^ Patients with NYHA class I are counted in subgroup NYHA class II.
*** Confirmed hypoglycaemic AEs are defined by a glucose concentration <=70 mg/dL (3.9 mmol/L) or requiring assistance.
Risk ratios and odds ratios with confidence intervals (CIs) are estimated by Cochran-Mantel-Haenszel method. For risk differences standard Wald asymptotic confidence limits are calculated. A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied in case of any zero cells in contingency table.
Only treatment emergent AEs are displayed (onset between first dose until treatment stop +7 days).
MedDRA version: 23.1. * Chi-square test for treatment effect ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction).

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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 overall and by subgroup - TS
User-defined AE category: Complicated urinary tract infection (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 LVEF [%]											0.3531
< 50	988	9	0.9	995	16	1.6	0.1642	1.77 (0.78, 3.98)	1.78 (0.78, 4.04)	0.01 (0.00, 0.02)	
>= 50	2001	36	1.8	2001	41	2.0	0.5650	1.14 (0.73, 1.77)	1.14 (0.73, 1.79)	0.00 (-0.01, 0.01)	
Baseline LVEF [%]											0.2421
<50	988	9	0.9	995	16	1.6	0.1642	1.77 (0.78, 3.98)	1.78 (0.78, 4.04)	0.01 (0.00, 0.02)	
50 to <60	1030	18	1.7	1028	14	1.4	0.4795	0.78 (0.39, 1.56)	0.78 (0.38, 1.57)	0.00 (-0.01, 0.01)	
>=60	971	18	1.9	973	27	2.8	0.1769	1.50 (0.83, 2.70)	1.51 (0.83, 2.76)	0.01 (0.00, 0.02)	
Baseline NT-proBNP [pg/mL] (</>=median by atrial fibrillation/flutter status)											0.1481
< median	1507	17	1.1	1476	29	2.0	0.0637	1.74 (0.96, 3.16)	1.76 (0.96, 3.21)	0.01 (0.00, 0.02)	
>= median	1475	28	1.9	1516	28	1.8	0.9175	0.97 (0.58, 1.63)	0.97 (0.57, 1.65)	0.00 (-0.01, 0.01)	
Baseline uric acid [mg/dL] (tertiles)											0.6270
<T1	975	14	1.4	963	14	1.5	0.9737	1.01 (0.49, 2.11)	1.01 (0.48, 2.14)	0.00 (-0.01, 0.01)	
>=T1 and <T2	966	13	1.3	1032	16	1.6	0.7023	1.15 (0.56, 2.38)	1.15 (0.55, 2.41)	0.00 (-0.01, 0.01)	
>=T2	1016	18	1.8	970	27	2.8	0.1299	1.57 (0.87, 2.83)	1.59 (0.87, 2.90)	0.01 (0.00, 0.02)	
Baseline use of MRA											0.6886
No	1865	30	1.6	1878	36	1.9	0.4736	1.19 (0.74, 1.93)	1.20 (0.73, 1.95)	0.00 (-0.01, 0.01)	
Yes	1124	15	1.3	1118	21	1.9	0.3057	1.41 (0.73, 2.72)	1.42 (0.73, 2.76)	0.01 (0.00, 0.02)	
Baseline use of ACE-inhibitor, ARB or ARNi											0.3009
No	586	9	1.5	568	16	2.8	0.1351	1.83 (0.82, 4.12)	1.86 (0.81, 4.24)	0.01 (0.00, 0.03)	
Yes	2403	36	1.5	2428	41	1.7	0.5971	1.13 (0.72, 1.76)	1.13 (0.72, 1.77)	0.00 (-0.01, 0.01)	

Analysis is based on study 1245.110.
^ Patients with NYHA class I are counted in subgroup NYHA class II.
*** Confirmed hypoglycaemic AEs are defined by a glucose concentration <=70 mg/dL (3.9 mmol/L) or requiring assistance.
Risk ratios and odds ratios with confidence intervals (CIs) are estimated by Cochran-Mantel-Haenszel method. For risk differences standard Wald asymptotic confidence limits are calculated. A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied in case of any zero cells in contingency table.
Only treatment emergent AEs are displayed (onset between first dose until treatment stop +7 days).
MedDRA version: 23.1. * Chi-square test for treatment effect ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction).

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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 overall and by subgroup - TS
User-defined AE category: Genital Infection (narrow 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	2989	22	0.7	2996	67	2.2	<0.0001	3.04 (1.88, 4.90)	3.08 (1.90, 5.01)	0.02 (0.01, 0.02)	
Sex											0.5764
Male	1653	9	0.5	1658	32	1.9	0.0003	3.54 (1.70, 7.40)	3.59 (1.71, 7.55)	0.01 (0.01, 0.02)	
Female	1336	13	1.0	1338	35	2.6	0.0014	2.69 (1.43, 5.06)	2.73 (1.44, 5.19)	0.02 (0.01, 0.03)	
Age [years]											0.6217
<70	1084	10	0.9	1066	26	2.4	0.0061	2.64 (1.28, 5.46)	2.69 (1.29, 5.60)	0.02 (0.00, 0.03)	
>=70	1905	12	0.6	1930	41	2.1	<0.0001	3.37 (1.78, 6.40)	3.42 (1.79, 6.54)	0.01 (0.01, 0.02)	
Region											0.0671
North America	359	8	2.2	359	16	4.5	0.0967	2.00 (0.87, 4.61)	2.05 (0.86, 4.84)	0.02 (0.00, 0.05)	
Latin America	757	4	0.5	758	17	2.2	0.0043	4.24 (1.43, 12.56)	4.32 (1.45, 12.90)	0.02 (0.01, 0.03)	
Europe	1341	4	0.3	1346	29	2.2	<0.0001	7.22 (2.55, 20.49)	7.36 (2.58, 20.99)	0.02 (0.01, 0.03)	
Asia	343	2	0.6	343	0	0	0.2472	0.20 (<0.01, 4.15)	0.20 (<0.01, 4.16)	-0.01 (-0.02, 0.00)	
Other	189	4	2.1	190	5	2.6	0.7419	1.24 (0.34, 4.56)	1.25 (0.33, 4.73)	0.01 (-0.03, 0.04)	
OECD member											0.1537
No	847	7	0.8	868	12	1.4	0.2714	1.67 (0.66, 4.23)	1.68 (0.66, 4.29)	0.01 (0.00, 0.02)	
Yes	2142	15	0.7	2128	55	2.6	<0.0001	3.69 (2.09, 6.51)	3.76 (2.12, 6.68)	0.02 (0.01, 0.03)	
Baseline NYHA											0.4554
II^	2450	17	0.7	2435	56	2.3	<0.0001	3.31 (1.93, 5.69)	3.37 (1.95, 5.81)	0.02 (0.01, 0.02)	
III/IV	539	5	0.9	561	11	2.0	0.1525	2.11 (0.74, 6.04)	2.14 (0.74, 6.19)	0.01 (0.00, 0.02)	
Baseline Diabetes Status											0.5034
Diabetic	1471	14	1.0	1465	37	2.5	0.0011	2.65 (1.44, 4.89)	2.70 (1.45, 5.01)	0.02 (0.01, 0.03)	
Non-Diabetic	1518	8	0.5	1531	30	2.0	0.0004	3.72 (1.71, 8.08)	3.77 (1.72, 8.26)	0.01 (0.01, 0.02)	

Analysis is based on study 1245.110.
^ Patients with NYHA class I are counted in subgroup NYHA class II.
*** Confirmed hypoglycaemic AEs are defined by a glucose concentration <=70 mg/dL (3.9 mmol/L) or requiring assistance.
Risk ratios and odds ratios with confidence intervals (CIs) are estimated by Cochran-Mantel-Haenszel method. For risk differences standard Wald asymptotic confidence limits are calculated. A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied in case of any zero cells in contingency table.
Only treatment emergent AEs are displayed (onset between first dose until treatment stop +7 days).
MedDRA version: 23.1. * Chi-square test for treatment effect ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction).

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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 overall and by subgroup - TS
User-defined AE category: Genital Infection (narrow 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 Diabetes Status											0.4237
Diabetic	1471	14	1.0	1465	37	2.5	0.0011	2.65 (1.44, 4.89)	2.70 (1.45, 5.01)	0.02 (0.01, 0.03)	
Pre-Diabetes	979	4	0.4	1001	22	2.2	0.0005	5.38 (1.86, 15.55)	5.48 (1.88, 15.95)	0.02 (0.01, 0.03)	
Normal (no pre-diabetes)	539	4	0.7	530	8	1.5	0.2338	2.03 (0.62, 6.71)	2.05 (0.61, 6.85)	0.01 (0.00, 0.02)	
Baseline BMI [kg/m²]											0.3540
<30	1641	7	0.4	1654	29	1.8	0.0002	4.11 (1.81, 9.36)	4.17 (1.82, 9.54)	0.01 (0.01, 0.02)	
>=30	1348	15	1.1	1342	38	2.8	0.0013	2.54 (1.41, 4.60)	2.59 (1.42, 4.73)	0.02 (0.01, 0.03)	
Baseline eGFR (CKD-EPI) [mL/min/1.73m²]											0.5506
>=60	1505	11	0.7	1493	38	2.5	<0.0001	3.48 (1.79, 6.79)	3.55 (1.81, 6.97)	0.02 (0.01, 0.03)	
<60	1482	11	0.7	1503	29	1.9	0.0048	2.60 (1.30, 5.18)	2.63 (1.31, 5.29)	0.01 (0.00, 0.02)	
History of HHF (in the last 12 months)											0.3802
No	2320	16	0.7	2297	54	2.4	<0.0001	3.41 (1.96, 5.94)	3.47 (1.98, 6.07)	0.02 (0.01, 0.02)	
Yes	669	6	0.9	699	13	1.9	0.1282	2.07 (0.79, 5.42)	2.09 (0.79, 5.54)	0.01 (0.00, 0.02)	
Baseline SBP (</>= median)											0.8107
< median	1474	12	0.8	1496	35	2.3	0.0009	2.87 (1.50, 5.51)	2.92 (1.51, 5.65)	0.02 (0.01, 0.02)	
>= median	1515	10	0.7	1500	32	2.1	0.0006	3.23 (1.59, 6.55)	3.28 (1.61, 6.70)	0.01 (0.01, 0.02)	
History of atrial fibrillation or atrial flutter											0.1057
No	1426	13	0.9	1417	26	1.8	0.0343	2.01 (1.04, 3.90)	2.03 (1.04, 3.97)	0.01 (0.00, 0.02)	
Yes	1558	9	0.6	1575	41	2.6	<0.0001	4.51 (2.20, 9.24)	4.60 (2.23, 9.50)	0.02 (0.01, 0.03)	

Analysis is based on study 1245.110.
^ Patients with NYHA class I are counted in subgroup NYHA class II.
*** Confirmed hypoglycaemic AEs are defined by a glucose concentration <=70 mg/dL (3.9 mmol/L) or requiring assistance.
Risk ratios and odds ratios with confidence intervals (CIs) are estimated by Cochran-Mantel-Haenszel method. For risk differences standard Wald asymptotic confidence limits are calculated. A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
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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 overall and by subgroup - TS
User-defined AE category: Genital Infection (narrow 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 LVEF [%]											0.8268
< 50	988	6	0.6	995	20	2.0	0.0060	3.31 (1.33, 8.21)	3.36 (1.34, 8.40)	0.01 (0.00, 0.02)	
>= 50	2001	16	0.8	2001	47	2.3	<0.0001	2.94 (1.67, 5.16)	2.98 (1.69, 5.28)	0.02 (0.01, 0.02)	
Baseline LVEF [%]											0.3705
<50	988	6	0.6	995	20	2.0	0.0060	3.31 (1.33, 8.21)	3.36 (1.34, 8.40)	0.01 (0.00, 0.02)	
50 to <60	1030	6	0.6	1028	27	2.6	0.0002	4.51 (1.87, 10.87)	4.60 (1.89, 11.20)	0.02 (0.01, 0.03)	
>=60	971	10	1.0	973	20	2.1	0.0666	2.00 (0.94, 4.24)	2.02 (0.94, 4.33)	0.01 (0.00, 0.02)	
Baseline NT-proBNP [pg/mL] (</>=median by atrial fibrillation/flutter status)											0.4389
< median	1507	11	0.7	1476	39	2.6	<0.0001	3.62 (1.86, 7.04)	3.69 (1.88, 7.23)	0.02 (0.01, 0.03)	
>= median	1475	11	0.7	1516	28	1.8	0.0080	2.48 (1.24, 4.96)	2.50 (1.24, 5.05)	0.01 (0.00, 0.02)	
Baseline uric acid [mg/dL] (tertiles)											0.8723
<T1	975	8	0.8	963	20	2.1	0.0205	2.53 (1.12, 5.72)	2.56 (1.12, 5.85)	0.01 (0.00, 0.02)	
>=T1 and <T2	966	8	0.8	1032	26	2.5	0.0035	3.04 (1.38, 6.69)	3.09 (1.39, 6.87)	0.02 (0.01, 0.03)	
>=T2	1016	6	0.6	970	20	2.1	0.0039	3.49 (1.41, 8.66)	3.54 (1.42, 8.86)	0.01 (0.00, 0.02)	
Baseline use of MRA											0.6790
No	1865	14	0.8	1878	46	2.4	<0.0001	3.26 (1.80, 5.91)	3.32 (1.82, 6.06)	0.02 (0.01, 0.03)	
Yes	1124	8	0.7	1118	21	1.9	0.0145	2.64 (1.17, 5.93)	2.67 (1.18, 6.05)	0.01 (0.00, 0.02)	
Baseline use of ACE-inhibitor, ARB or ARNi											0.1415
No	586	7	1.2	568	11	1.9	0.3091	1.62 (0.63, 4.15)	1.63 (0.63, 4.24)	0.01 (-0.01, 0.02)	
Yes	2403	15	0.6	2428	56	2.3	<0.0001	3.69 (2.10, 6.51)	3.76 (2.12, 6.66)	0.02 (0.01, 0.02)	

Analysis is based on study 1245.110.
^ Patients with NYHA class I are counted in subgroup NYHA class II.
*** Confirmed hypoglycaemic AEs are defined by a glucose concentration <=70 mg/dL (3.9 mmol/L) or requiring assistance.
Risk ratios and odds ratios with confidence intervals (CIs) are estimated by Cochran-Mantel-Haenszel method. For risk differences standard Wald asymptotic confidence limits are calculated. A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
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MedDRA version: 23.1. * Chi-square test for treatment effect ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction).

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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 overall and by subgroup - TS
User-defined AE category: Complicated Genital Infection (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	2989	8	0.3	2996	8	0.3	0.9963	1.00 (0.37, 2.65)	1.00 (0.37, 2.66)	0.00 (0.00, 0.00)	
Sex											0.4723
Male	1653	7	0.4	1658	8	0.5	0.8003	1.14 (0.41, 3.13)	1.14 (0.41, 3.15)	0.00 (0.00, 0.01)	
Female	1336	1	0.1	1338	0	0	0.4787	0.33 (0.01, 8.16)	0.33 (0.01, 8.17)	0.00 (0.00, 0.00)	
Age [years]											0.5141
<70	1084	1	0.1	1066	2	0.2	0.5537	2.03 (0.18, 22.40)	2.04 (0.18, 22.48)	0.00 (0.00, 0.00)	
>=70	1905	7	0.4	1930	6	0.3	0.7631	0.85 (0.28, 2.51)	0.85 (0.28, 2.52)	0.00 (0.00, 0.00)	
Region											
North America	359	2	0.6	359	1	0.3					
Latin America	757	1	0.1	758	2	0.3					
Europe	1341	3	0.2	1346	5	0.4					
Asia	343	2	0.6	343	0	0					
Other	189	0	0	190	0	0					
OECD member											0.4606
No	847	1	0.1	868	0	0	0.4685	0.33 (0.01, 7.97)	0.32 (0.01, 7.99)	0.00 (0.00, 0.00)	
Yes	2142	7	0.3	2128	8	0.4	0.7861	1.15 (0.42, 3.17)	1.15 (0.42, 3.18)	0.00 (0.00, 0.00)	
Baseline NYHA											0.2827
II^	2450	7	0.3	2435	5	0.2	0.5704	0.72 (0.23, 2.26)	0.72 (0.23, 2.27)	0.00 (0.00, 0.00)	
III/IV	539	1	0.2	561	3	0.5	0.3361	2.88 (0.30, 27.62)	2.89 (0.30, 27.89)	0.00 (0.00, 0.01)	
Baseline Diabetes Status											
Diabetic	1471	6	0.4	1465	3	0.2					
Non-Diabetic	1518	2	0.1	1531	5	0.3					

Analysis is based on study 1245.110.
^ Patients with NYHA class I are counted in subgroup NYHA class II.
*** Confirmed hypoglycaemic AEs are defined by a glucose concentration <=70 mg/dL (3.9 mmol/L) or requiring assistance.
Risk ratios and odds ratios with confidence intervals (CIs) are estimated by Cochran-Mantel-Haenszel method. For risk differences standard Wald asymptotic confidence limits are calculated. A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied in case of any zero cells in contingency table.
Only treatment emergent AEs are displayed (onset between first dose until treatment stop +7 days).
MedDRA version: 23.1. * Chi-square test for treatment effect ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction).

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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 overall and by subgroup - TS
User-defined AE category: Complicated Genital Infection (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 Diabetes Status											
Diabetic	1471	6	0.4	1465	3	0.2					
Pre-Diabetes	979	0	0	1001	3	0.3					
Normal (no pre-diabetes)	539	2	0.4	530	2	0.4					
Baseline BMI [kg/m²]											
<30	1641	4	0.2	1654	5	0.3					
>=30	1348	4	0.3	1342	3	0.2					
Baseline eGFR (CKD-EPI) [mL/min/1.73m²]											0.9829
>=60	1505	3	0.2	1493	3	0.2	0.9922	1.01 (0.20, 4.99)	1.01 (0.20, 5.00)	0.00 (0.00, 0.00)	
<60	1482	5	0.3	1503	5	0.3	0.9822	0.99 (0.29, 3.40)	0.99 (0.28, 3.41)	0.00 (0.00, 0.00)	
History of HHF (in the last 12 months)											0.2496
No	2320	5	0.2	2297	7	0.3	0.5516	1.41 (0.45, 4.45)	1.42 (0.45, 4.47)	0.00 (0.00, 0.00)	
Yes	669	3	0.4	699	1	0.1	0.2957	0.32 (0.03, 3.06)	0.32 (0.03, 3.07)	0.00 (-0.01, 0.00)	
Baseline SBP (</>= median)											
< median	1474	5	0.3	1496	2	0.1					
>= median	1515	3	0.2	1500	6	0.4					
History of atrial fibrillation or atrial flutter											0.3162
No	1426	4	0.3	1417	2	0.1	0.4182	0.50 (0.09, 2.74)	0.50 (0.09, 2.75)	0.00 (0.00, 0.00)	
Yes	1558	4	0.3	1575	6	0.4	0.5377	1.48 (0.42, 5.25)	1.49 (0.42, 5.27)	0.00 (0.00, 0.01)	

Analysis is based on study 1245.110.
^ Patients with NYHA class I are counted in subgroup NYHA class II.
*** Confirmed hypoglycaemic AEs are defined by a glucose concentration <=70 mg/dL (3.9 mmol/L) or requiring assistance.
Risk ratios and odds ratios with confidence intervals (CIs) are estimated by Cochran-Mantel-Haenszel method. For risk differences standard Wald asymptotic confidence limits are calculated. A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied in case of any zero cells in contingency table.
Only treatment emergent AEs are displayed (onset between first dose until treatment stop +7 days).
MedDRA version: 23.1. * Chi-square test for treatment effect ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction).

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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 overall and by subgroup - TS
User-defined AE category: Complicated Genital Infection (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 LVEF [%]											0.2696
< 50	988	1	0.1	995	3	0.3	0.3202	2.98 (0.31, 28.59)	2.98 (0.31, 28.74)	0.00 (0.00, 0.01)	
>= 50	2001	7	0.3	2001	5	0.2	0.5631	0.71 (0.23, 2.25)	0.71 (0.23, 2.25)	0.00 (0.00, 0.00)	
Baseline LVEF [%]											
<50	988	1	0.1	995	3	0.3					
50 to <60	1030	3	0.3	1028	3	0.3					
>=60	971	4	0.4	973	2	0.2					
Baseline NT-proBNP [pg/mL] (</>=median by atrial fibrillation/flutter status)											
< median	1507	4	0.3	1476	3	0.2					
>= median	1475	4	0.3	1516	5	0.3					
Baseline uric acid [mg/dL] (tertiles)											
<T1	975	4	0.4	963	2	0.2					
>=T1 and <T2	966	2	0.2	1032	3	0.3					
>=T2	1016	2	0.2	970	3	0.3					
Baseline use of MRA											
No	1865	5	0.3	1878	4	0.2					
Yes	1124	3	0.3	1118	4	0.4					
Baseline use of ACE-inhibitor, ARB or ARNi											0.1414
No	586	3	0.5	568	0	0	0.1411	0.15 (<0.01, 2.85)	0.15 (<0.01, 2.85)	-0.01 (-0.01, 0.00)	
Yes	2403	5	0.2	2428	8	0.3	0.4154	1.58 (0.52, 4.83)	1.59 (0.52, 4.85)	0.00 (0.00, 0.00)	

Analysis is based on study 1245.110.
^ Patients with NYHA class I are counted in subgroup NYHA class II.
*** Confirmed hypoglycaemic AEs are defined by a glucose concentration <=70 mg/dL (3.9 mmol/L) or requiring assistance.
Risk ratios and odds ratios with confidence intervals (CIs) are estimated by Cochran-Mantel-Haenszel method. For risk differences standard Wald asymptotic confidence limits are calculated. A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied in case of any zero cells in contingency table.
Only treatment emergent AEs are displayed (onset between first dose until treatment stop +7 days).
MedDRA version: 23.1. * Chi-square test for treatment effect ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction).

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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 overall and by subgroup - TS
User-defined AE category: Acute pyelonephritis (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	2989	5	0.2	2996	13	0.4	0.0596	2.59 (0.93, 7.27)	2.60 (0.93, 7.30)	0.00 (0.00, 0.01)	
Sex											0.1519
Male	1653	3	0.2	1658	3	0.2	0.9970	1.00 (0.20, 4.93)	1.00 (0.20, 4.95)	0.00 (0.00, 0.00)	
Female	1336	2	0.1	1338	10	0.7	0.0208	4.99 (1.10, 22.74)	5.02 (1.10, 22.97)	0.01 (0.00, 0.01)	
Age [years]											0.1058
<70	1084	0	0	1066	7	0.7	0.0123	15.25 (0.87,266.73)	15.35 (0.88,269.17)	0.01 (0.00, 0.01)	
>=70	1905	5	0.3	1930	6	0.3	0.7792	1.18 (0.36, 3.87)	1.19 (0.36, 3.89)	0.00 (0.00, 0.00)	
Region											
North America	359	2	0.6	359	2	0.6					
Latin America	757	1	0.1	758	3	0.4					
Europe	1341	0	0	1346	4	0.3					
Asia	343	1	0.3	343	2	0.6					
Other	189	1	0.5	190	2	1.1					
OECD member											0.6677
No	847	1	0.1	868	4	0.5	0.1881	3.90 (0.44, 34.85)	3.92 (0.44, 35.11)	0.00 (0.00, 0.01)	
Yes	2142	4	0.2	2128	9	0.4	0.1613	2.26 (0.70, 7.34)	2.27 (0.70, 7.38)	0.00 (0.00, 0.01)	
Baseline NYHA											0.3256
II^	2450	5	0.2	2435	9	0.4	0.2792	1.81 (0.61, 5.40)	1.81 (0.61, 5.42)	0.00 (0.00, 0.00)	
III/IV	539	0	0	561	4	0.7	0.0804	8.65 (0.47,160.24)	8.71 (0.47,162.15)	0.01 (0.00, 0.01)	
Baseline Diabetes Status											0.3284
Diabetic	1471	4	0.3	1465	7	0.5	0.3612	1.76 (0.52, 5.99)	1.76 (0.51, 6.03)	0.00 (0.00, 0.01)	
Non-Diabetic	1518	1	0.1	1531	6	0.4	0.0600	5.95 (0.72, 49.36)	5.97 (0.72, 49.63)	0.00 (0.00, 0.01)	

Analysis is based on study 1245.110.
^ Patients with NYHA class I are counted in subgroup NYHA class II.
*** Confirmed hypoglycaemic AEs are defined by a glucose concentration <=70 mg/dL (3.9 mmol/L) or requiring assistance.
Risk ratios and odds ratios with confidence intervals (CIs) are estimated by Cochran-Mantel-Haenszel method. For risk differences standard Wald asymptotic confidence limits are calculated. A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied in case of any zero cells in contingency table.
Only treatment emergent AEs are displayed (onset between first dose until treatment stop +7 days).
MedDRA version: 23.1. * Chi-square test for treatment effect ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction).

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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 overall and by subgroup - TS
User-defined AE category: Acute pyelonephritis (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 Diabetes Status											0.6740
Diabetic	1471	4	0.3	1465	7	0.5	0.3612	1.76 (0.52, 5.99)	1.76 (0.51, 6.03)	0.00 (0.00, 0.01)	
Pre-Diabetes	979	1	0.1	1001	3	0.3	0.3277	2.93 (0.31, 28.16)	2.94 (0.31, 28.31)	0.00 (0.00, 0.01)	
Normal (no pre-diabetes)	539	0	0	530	3	0.6	0.1286	7.12 (0.37,137.48)	7.16 (0.37,138.94)	0.01 (0.00, 0.01)	
Baseline BMI [kg/m²]											0.1559
<30	1641	5	0.3	1654	7	0.4	0.5723	1.39 (0.44, 4.37)	1.39 (0.44, 4.39)	0.00 (0.00, 0.01)	
>=30	1348	0	0	1342	6	0.4	0.0228	13.06 (0.74,231.56)	13.12 (0.74,233.07)	0.00 (0.00, 0.01)	
Baseline eGFR (CKD-EPI) [mL/min/1.73m²]											0.8747
>=60	1505	1	0.1	1493	3	0.2	0.3131	3.02 (0.31, 29.04)	3.03 (0.31, 29.14)	0.00 (0.00, 0.00)	
<60	1482	4	0.3	1503	10	0.7	0.1139	2.47 (0.77, 7.84)	2.47 (0.77, 7.91)	0.00 (0.00, 0.01)	
History of HHF (in the last 12 months)											0.9210
No	2320	4	0.2	2297	10	0.4	0.1042	2.53 (0.79, 8.04)	2.53 (0.79, 8.08)	0.00 (0.00, 0.01)	
Yes	669	1	0.1	699	3	0.4	0.3382	2.87 (0.30, 27.53)	2.88 (0.30, 27.75)	0.00 (0.00, 0.01)	
Baseline SBP (</>= median)											
< median	1474	5	0.3	1496	4	0.3					
>= median	1515	0	0	1500	9	0.6					
History of atrial fibrillation or atrial flutter											0.9649
No	1426	2	0.1	1417	5	0.4	0.2528	2.52 (0.49, 12.95)	2.52 (0.49, 13.02)	0.00 (0.00, 0.01)	
Yes	1558	3	0.2	1575	8	0.5	0.1356	2.64 (0.70, 9.92)	2.65 (0.70, 9.99)	0.00 (0.00, 0.01)	

Analysis is based on study 1245.110.
^ Patients with NYHA class I are counted in subgroup NYHA class II.
*** Confirmed hypoglycaemic AEs are defined by a glucose concentration <=70 mg/dL (3.9 mmol/L) or requiring assistance.
Risk ratios and odds ratios with confidence intervals (CIs) are estimated by Cochran-Mantel-Haenszel method. For risk differences standard Wald asymptotic confidence limits are calculated. A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied in case of any zero cells in contingency table.
Only treatment emergent AEs are displayed (onset between first dose until treatment stop +7 days).
MedDRA version: 23.1. * Chi-square test for treatment effect ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction).

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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 overall and by subgroup - TS
User-defined AE category: Acute pyelonephritis (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 LVEF [%]											0.1315
< 50	988	2	0.2	995	1	0.1	0.5593	0.50 (0.05, 5.47)	0.50 (0.04, 5.48)	0.00 (0.00, 0.00)	
>= 50	2001	3	0.1	2001	12	0.6	0.0199	4.00 (1.13, 14.15)	4.02 (1.13, 14.26)	0.00 (0.00, 0.01)	
Baseline LVEF [%]											0.2932
<50	988	2	0.2	995	1	0.1	0.5593	0.50 (0.05, 5.47)	0.50 (0.04, 5.48)	0.00 (0.00, 0.00)	
50 to <60	1030	0	0	1028	4	0.4	0.0729	9.02 (0.49,167.27)	9.05 (0.49,168.36)	0.00 (0.00, 0.01)	
>=60	971	3	0.3	973	8	0.8	0.1314	2.66 (0.71, 10.00)	2.67 (0.71, 10.11)	0.01 (0.00, 0.01)	
Baseline NT-proBNP [pg/mL] (</>=median by atrial fibrillation/flutter status)											0.6777
< median	1507	3	0.2	1476	9	0.6	0.0764	3.06 (0.83, 11.29)	3.08 (0.83, 11.38)	0.00 (0.00, 0.01)	
>= median	1475	2	0.1	1516	4	0.3	0.4332	1.95 (0.36, 10.61)	1.95 (0.36, 10.65)	0.00 (0.00, 0.00)	
Baseline uric acid [mg/dL] (tertiles)											
<T1	975	3	0.3	963	5	0.5					
>=T1 and <T2	966	0	0	1032	4	0.4					
>=T2	1016	2	0.2	970	4	0.4					
Baseline use of MRA											0.7187
No	1865	3	0.2	1878	9	0.5	0.0849	2.98 (0.81, 10.99)	2.99 (0.81, 11.06)	0.00 (0.00, 0.01)	
Yes	1124	2	0.2	1118	4	0.4	0.4098	2.01 (0.37, 10.96)	2.01 (0.37, 11.02)	0.00 (0.00, 0.01)	
Baseline use of ACE-inhibitor, ARB or ARNi											0.8628
No	586	1	0.2	568	3	0.5	0.3016	3.10 (0.32, 29.67)	3.11 (0.32, 29.95)	0.00 (0.00, 0.01)	
Yes	2403	4	0.2	2428	10	0.4	0.1126	2.47 (0.78, 7.88)	2.48 (0.78, 7.92)	0.00 (0.00, 0.01)	

Analysis is based on study 1245.110.
^ Patients with NYHA class I are counted in subgroup NYHA class II.
*** Confirmed hypoglycaemic AEs are defined by a glucose concentration <=70 mg/dL (3.9 mmol/L) or requiring assistance.
Risk ratios and odds ratios with confidence intervals (CIs) are estimated by Cochran-Mantel-Haenszel method. For risk differences standard Wald asymptotic confidence limits are calculated. A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied in case of any zero cells in contingency table.
Only treatment emergent AEs are displayed (onset between first dose until treatment stop +7 days).
MedDRA version: 23.1. * Chi-square test for treatment effect ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction).

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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 overall and by subgroup - TS
User-defined AE category: Urosepsis (PT) or pyelonephritis (narrow Sub 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	2989	17	0.6	2996	24	0.8	0.2759	1.41 (0.76, 2.62)	1.41 (0.76, 2.63)	0.00 (0.00, 0.01)	
Sex											0.0505
Male	1653	11	0.7	1658	8	0.5	0.4859	0.73 (0.29, 1.80)	0.72 (0.29, 1.80)	0.00 (-0.01, 0.00)	
Female	1336	6	0.4	1338	16	1.2	0.0326	2.66 (1.05, 6.78)	2.68 (1.05, 6.88)	0.01 (0.00, 0.01)	
Age [years]											0.1189
<70	1084	2	0.2	1066	8	0.8	0.0538	4.07 (0.87, 19.11)	4.09 (0.87, 19.31)	0.01 (0.00, 0.01)	
>=70	1905	15	0.8	1930	16	0.8	0.8856	1.05 (0.52, 2.12)	1.05 (0.52, 2.14)	0.00 (-0.01, 0.01)	
Region											0.9702
North America	359	2	0.6	359	4	1.1	0.4123	2.00 (0.37, 10.85)	2.01 (0.37, 11.05)	0.01 (-0.01, 0.02)	
Latin America	757	4	0.5	758	5	0.7	0.7396	1.25 (0.34, 4.63)	1.25 (0.33, 4.67)	0.00 (-0.01, 0.01)	
Europe	1341	7	0.5	1346	8	0.6	0.8013	1.14 (0.41, 3.13)	1.14 (0.41, 3.15)	0.00 (0.00, 0.01)	
Asia	343	2	0.6	343	3	0.9	0.6535	1.50 (0.25, 8.92)	1.50 (0.25, 9.06)	0.00 (-0.01, 0.02)	
Other	189	2	1.1	190	4	2.1	0.4142	1.99 (0.37, 10.73)	2.01 (0.36, 11.11)	0.01 (-0.01, 0.04)	
OECD member											0.9471
No	847	4	0.5	868	6	0.7	0.5515	1.46 (0.41, 5.17)	1.47 (0.41, 5.22)	0.00 (-0.01, 0.01)	
Yes	2142	13	0.6	2128	18	0.8	0.3578	1.39 (0.68, 2.84)	1.40 (0.68, 2.86)	0.00 (0.00, 0.01)	
Baseline NYHA											0.2160
II^	2450	15	0.6	2435	17	0.7	0.7098	1.14 (0.57, 2.28)	1.14 (0.57, 2.29)	0.00 (0.00, 0.01)	
III/IV	539	2	0.4	561	7	1.2	0.1066	3.36 (0.70, 16.12)	3.39 (0.70, 16.40)	0.01 (0.00, 0.02)	
Baseline Diabetes Status											0.7817
Diabetic	1471	10	0.7	1465	13	0.9	0.5236	1.31 (0.57, 2.97)	1.31 (0.57, 2.99)	0.00 (0.00, 0.01)	
Non-Diabetic	1518	7	0.5	1531	11	0.7	0.3537	1.56 (0.61, 4.01)	1.56 (0.60, 4.04)	0.00 (0.00, 0.01)	

Analysis is based on study 1245.110.
^ Patients with NYHA class I are counted in subgroup NYHA class II.
*** Confirmed hypoglycaemic AEs are defined by a glucose concentration <=70 mg/dL (3.9 mmol/L) or requiring assistance.
Risk ratios and odds ratios with confidence intervals (CIs) are estimated by Cochran-Mantel-Haenszel method. For risk differences standard Wald asymptotic confidence limits are calculated. A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied in case of any zero cells in contingency table.
Only treatment emergent AEs are displayed (onset between first dose until treatment stop +7 days).
MedDRA version: 23.1. * Chi-square test for treatment effect ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction).

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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 overall and by subgroup - TS
User-defined AE category: Urosepsis (PT) or pyelonephritis (narrow Sub 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 Diabetes Status											0.8975
Diabetic	1471	10	0.7	1465	13	0.9	0.5236	1.31 (0.57, 2.97)	1.31 (0.57, 2.99)	0.00 (0.00, 0.01)	
Pre-Diabetes	979	5	0.5	1001	7	0.7	0.5888	1.37 (0.44, 4.30)	1.37 (0.43, 4.34)	0.00 (0.00, 0.01)	
Normal (no pre-diabetes)	539	2	0.4	530	4	0.8	0.4012	2.03 (0.37, 11.06)	2.04 (0.37, 11.20)	0.00 (-0.01, 0.01)	
Baseline BMI [kg/m²]											0.0686
<30	1641	12	0.7	1654	10	0.6	0.6553	0.83 (0.36, 1.91)	0.83 (0.36, 1.92)	0.00 (-0.01, 0.00)	
>=30	1348	5	0.4	1342	14	1.0	0.0374	2.81 (1.02, 7.79)	2.83 (1.02, 7.88)	0.01 (0.00, 0.01)	
Baseline eGFR (CKD-EPI) [mL/min/1.73m²]											0.5491
>=60	1505	5	0.3	1493	5	0.3	0.9899	1.01 (0.29, 3.47)	1.01 (0.29, 3.49)	0.00 (0.00, 0.00)	
<60	1482	12	0.8	1503	19	1.3	0.2208	1.56 (0.76, 3.20)	1.57 (0.76, 3.24)	0.00 (0.00, 0.01)	
History of HHF (in the last 12 months)											0.2714
No	2320	11	0.5	2297	19	0.8	0.1355	1.74 (0.83, 3.66)	1.75 (0.83, 3.69)	0.00 (0.00, 0.01)	
Yes	669	6	0.9	699	5	0.7	0.7070	0.80 (0.24, 2.60)	0.80 (0.24, 2.62)	0.00 (-0.01, 0.01)	
Baseline SBP (</>= median)											0.3083
< median	1474	9	0.6	1496	9	0.6	0.9749	0.99 (0.39, 2.48)	0.99 (0.39, 2.49)	0.00 (-0.01, 0.01)	
>= median	1515	8	0.5	1500	15	1.0	0.1364	1.89 (0.81, 4.45)	1.90 (0.80, 4.50)	0.00 (0.00, 0.01)	
History of atrial fibrillation or atrial flutter											0.4081
No	1426	5	0.4	1417	10	0.7	0.1913	2.01 (0.69, 5.87)	2.02 (0.69, 5.92)	0.00 (0.00, 0.01)	
Yes	1558	12	0.8	1575	14	0.9	0.7143	1.15 (0.54, 2.49)	1.16 (0.53, 2.51)	0.00 (-0.01, 0.01)	

Analysis is based on study 1245.110.
^ Patients with NYHA class I are counted in subgroup NYHA class II.
*** Confirmed hypoglycaemic AEs are defined by a glucose concentration <=70 mg/dL (3.9 mmol/L) or requiring assistance.
Risk ratios and odds ratios with confidence intervals (CIs) are estimated by Cochran-Mantel-Haenszel method. For risk differences standard Wald asymptotic confidence limits are calculated. A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied in case of any zero cells in contingency table.
Only treatment emergent AEs are displayed (onset between first dose until treatment stop +7 days).
MedDRA version: 23.1. * Chi-square test for treatment effect ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction).

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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 overall and by subgroup - TS
User-defined AE category: Urosepsis (PT) or pyelonephritis (narrow Sub 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 LVEF [%]											0.3564
< 50	988	4	0.4	995	3	0.3	0.6980	0.74 (0.17, 3.32)	0.74 (0.17, 3.33)	0.00 (-0.01, 0.00)	
>= 50	2001	13	0.6	2001	21	1.0	0.1682	1.62 (0.81, 3.22)	1.62 (0.81, 3.25)	0.00 (0.00, 0.01)	
Baseline LVEF [%]											0.2344
<50	988	4	0.4	995	3	0.3	0.6980	0.74 (0.17, 3.32)	0.74 (0.17, 3.33)	0.00 (-0.01, 0.00)	
50 to <60	1030	7	0.7	1028	6	0.6	0.7835	0.86 (0.29, 2.55)	0.86 (0.29, 2.56)	0.00 (-0.01, 0.01)	
>=60	971	6	0.6	973	15	1.5	0.0488	2.49 (0.97, 6.40)	2.52 (0.97, 6.52)	0.01 (0.00, 0.02)	
Baseline NT-proBNP [pg/mL] (</>=median by atrial fibrillation/flutter status)											0.1034
< median	1507	5	0.3	1476	13	0.9	0.0529	2.65 (0.95, 7.43)	2.67 (0.95, 7.51)	0.01 (0.00, 0.01)	
>= median	1475	12	0.8	1516	11	0.7	0.7831	0.89 (0.39, 2.01)	0.89 (0.39, 2.03)	0.00 (-0.01, 0.01)	
Baseline uric acid [mg/dL] (tertiles)											0.5856
<T1	975	3	0.3	963	7	0.7	0.1978	2.36 (0.61, 9.11)	2.37 (0.61, 9.20)	0.00 (0.00, 0.01)	
>=T1 and <T2	966	6	0.6	1032	6	0.6	0.9086	0.94 (0.30, 2.89)	0.94 (0.30, 2.91)	0.00 (-0.01, 0.01)	
>=T2	1016	8	0.8	970	11	1.1	0.4276	1.44 (0.58, 3.57)	1.45 (0.58, 3.61)	0.00 (-0.01, 0.01)	
Baseline use of MRA											0.9596
No	1865	10	0.5	1878	14	0.7	0.4225	1.39 (0.62, 3.12)	1.39 (0.62, 3.14)	0.00 (0.00, 0.01)	
Yes	1124	7	0.6	1118	10	0.9	0.4584	1.44 (0.55, 3.76)	1.44 (0.55, 3.80)	0.00 (0.00, 0.01)	
Baseline use of ACE-inhibitor, ARB or ARNi											0.4242
No	586	2	0.3	568	5	0.9	0.2384	2.58 (0.50, 13.24)	2.59 (0.50, 13.42)	0.01 (0.00, 0.01)	
Yes	2403	15	0.6	2428	19	0.8	0.5104	1.25 (0.64, 2.46)	1.26 (0.64, 2.48)	0.00 (0.00, 0.01)	

Analysis is based on study 1245.110.
^ Patients with NYHA class I are counted in subgroup NYHA class II.
*** Confirmed hypoglycaemic AEs are defined by a glucose concentration <=70 mg/dL (3.9 mmol/L) or requiring assistance.
Risk ratios and odds ratios with confidence intervals (CIs) are estimated by Cochran-Mantel-Haenszel method. For risk differences standard Wald asymptotic confidence limits are calculated. A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied in case of any zero cells in contingency table.
Only treatment emergent AEs are displayed (onset between first dose until treatment stop +7 days).
MedDRA version: 23.1. * Chi-square test for treatment effect ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction).

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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 overall and by subgroup - TS
User-defined AE category: Sepsis (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	2989	59	2.0	2996	67	2.2	0.4795	1.13 (0.80, 1.60)	1.14 (0.80, 1.62)	0.00 (0.00, 0.01)	
Sex											0.1967
Male	1653	40	2.4	1658	38	2.3	0.8083	0.95 (0.61, 1.47)	0.95 (0.60, 1.48)	0.00 (-0.01, 0.01)	
Female	1336	19	1.4	1338	29	2.2	0.1467	1.52 (0.86, 2.70)	1.54 (0.86, 2.75)	0.01 (0.00, 0.02)	
Age [years]											0.3275
<70	1084	20	1.8	1066	17	1.6	0.6555	0.86 (0.46, 1.64)	0.86 (0.45, 1.66)	0.00 (-0.01, 0.01)	
>=70	1905	39	2.0	1930	50	2.6	0.2638	1.27 (0.84, 1.91)	1.27 (0.83, 1.94)	0.01 (0.00, 0.01)	
Region											0.6134
North America	359	10	2.8	359	19	5.3	0.0880	1.90 (0.90, 4.03)	1.95 (0.89, 4.26)	0.03 (0.00, 0.05)	
Latin America	757	15	2.0	758	17	2.2	0.7237	1.13 (0.57, 2.25)	1.13 (0.56, 2.29)	0.00 (-0.01, 0.02)	
Europe	1341	24	1.8	1346	22	1.6	0.7564	0.91 (0.51, 1.62)	0.91 (0.51, 1.63)	0.00 (-0.01, 0.01)	
Asia	343	5	1.5	343	4	1.2	0.7372	0.80 (0.22, 2.95)	0.80 (0.21, 3.00)	0.00 (-0.02, 0.01)	
Other	189	5	2.6	190	5	2.6	0.9933	0.99 (0.29, 3.38)	0.99 (0.28, 3.49)	0.00 (-0.03, 0.03)	
OECD member											0.9610
No	847	17	2.0	868	20	2.3	0.6720	1.15 (0.61, 2.18)	1.15 (0.60, 2.21)	0.00 (-0.01, 0.02)	
Yes	2142	42	2.0	2128	47	2.2	0.5708	1.13 (0.75, 1.70)	1.13 (0.74, 1.72)	0.00 (-0.01, 0.01)	
Baseline NYHA											0.0545
II^	2450	46	1.9	2435	41	1.7	0.6087	0.90 (0.59, 1.36)	0.90 (0.59, 1.37)	0.00 (-0.01, 0.01)	
III/IV	539	13	2.4	561	26	4.6	0.0463	1.92 (1.00, 3.70)	1.97 (1.00, 3.87)	0.02 (0.00, 0.04)	
Baseline Diabetes Status											0.2249
Diabetic	1471	30	2.0	1465	41	2.8	0.1806	1.37 (0.86, 2.19)	1.38 (0.86, 2.23)	0.01 (0.00, 0.02)	
Non-Diabetic	1518	29	1.9	1531	26	1.7	0.6598	0.89 (0.53, 1.50)	0.89 (0.52, 1.51)	0.00 (-0.01, 0.01)	

Analysis is based on study 1245.110.
^ Patients with NYHA class I are counted in subgroup NYHA class II.
*** Confirmed hypoglycaemic AEs are defined by a glucose concentration <=70 mg/dL (3.9 mmol/L) or requiring assistance.
Risk ratios and odds ratios with confidence intervals (CIs) are estimated by Cochran-Mantel-Haenszel method. For risk differences standard Wald asymptotic confidence limits are calculated. A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied in case of any zero cells in contingency table.
Only treatment emergent AEs are displayed (onset between first dose until treatment stop +7 days).
MedDRA version: 23.1. * Chi-square test for treatment effect ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction).

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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 overall and by subgroup - TS
User-defined AE category: Sepsis (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 Diabetes Status											0.0191
Diabetic	1471	30	2.0	1465	41	2.8	0.1806	1.37 (0.86, 2.19)	1.38 (0.86, 2.23)	0.01 (0.00, 0.02)	
Pre-Diabetes	979	14	1.4	1001	22	2.2	0.2011	1.54 (0.79, 2.99)	1.55 (0.79, 3.05)	0.01 (0.00, 0.02)	
Normal (no pre-diabetes)	539	15	2.8	530	4	0.8	0.0121	0.27 (0.09, 0.81)	0.27 (0.09, 0.81)	-0.02 (-0.04, 0.00)	
Baseline BMI [kg/m²]											0.0229
<30	1641	31	1.9	1654	22	1.3	0.2022	0.70 (0.41, 1.21)	0.70 (0.40, 1.21)	-0.01 (-0.01, 0.00)	
>=30	1348	28	2.1	1342	45	3.4	0.0417	1.61 (1.01, 2.57)	1.64 (1.01, 2.64)	0.01 (0.00, 0.03)	
Baseline eGFR (CKD-EPI) [mL/min/1.73m²]											0.8312
>=60	1505	23	1.5	1493	27	1.8	0.5492	1.18 (0.68, 2.05)	1.19 (0.68, 2.08)	0.00 (-0.01, 0.01)	
<60	1482	36	2.4	1503	40	2.7	0.6872	1.10 (0.70, 1.71)	1.10 (0.70, 1.73)	0.00 (-0.01, 0.01)	
History of HHF (in the last 12 months)											0.3376
No	2320	44	1.9	2297	44	1.9	0.9624	1.01 (0.67, 1.53)	1.01 (0.66, 1.54)	0.00 (-0.01, 0.01)	
Yes	669	15	2.2	699	23	3.3	0.2383	1.47 (0.77, 2.79)	1.48 (0.77, 2.87)	0.01 (-0.01, 0.03)	
Baseline SBP (</>= median)											0.0901
< median	1474	26	1.8	1496	40	2.7	0.0926	1.52 (0.93, 2.47)	1.53 (0.93, 2.52)	0.01 (0.00, 0.02)	
>= median	1515	33	2.2	1500	27	1.8	0.4572	0.83 (0.50, 1.37)	0.82 (0.49, 1.38)	0.00 (-0.01, 0.01)	
History of atrial fibrillation or atrial flutter											0.4652
No	1426	26	1.8	1417	25	1.8	0.9057	0.97 (0.56, 1.67)	0.97 (0.56, 1.68)	0.00 (-0.01, 0.01)	
Yes	1558	33	2.1	1575	42	2.7	0.3152	1.26 (0.80, 1.98)	1.27 (0.80, 2.01)	0.01 (-0.01, 0.02)	

Analysis is based on study 1245.110.
^ Patients with NYHA class I are counted in subgroup NYHA class II.
*** Confirmed hypoglycaemic AEs are defined by a glucose concentration <=70 mg/dL (3.9 mmol/L) or requiring assistance.
Risk ratios and odds ratios with confidence intervals (CIs) are estimated by Cochran-Mantel-Haenszel method. For risk differences standard Wald asymptotic confidence limits are calculated. A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied in case of any zero cells in contingency table.
Only treatment emergent AEs are displayed (onset between first dose until treatment stop +7 days).
MedDRA version: 23.1. * Chi-square test for treatment effect ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction).

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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 overall and by subgroup - TS
User-defined AE category: Sepsis (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 LVEF [%]											0.2998
< 50	988	16	1.6	995	24	2.4	0.2094	1.49 (0.80, 2.79)	1.50 (0.79, 2.84)	0.01 (0.00, 0.02)	
>= 50	2001	43	2.1	2001	43	2.1	1.0000	1.00 (0.66, 1.52)	1.00 (0.65, 1.53)	0.00 (-0.01, 0.01)	
Baseline LVEF [%]											0.4751
<50	988	16	1.6	995	24	2.4	0.2094	1.49 (0.80, 2.79)	1.50 (0.79, 2.84)	0.01 (0.00, 0.02)	
50 to <60	1030	22	2.1	1028	19	1.8	0.6405	0.87 (0.47, 1.59)	0.86 (0.46, 1.60)	0.00 (-0.01, 0.01)	
>=60	971	21	2.2	973	24	2.5	0.6560	1.14 (0.64, 2.03)	1.14 (0.63, 2.07)	0.00 (-0.01, 0.02)	
Baseline NT-proBNP [pg/mL] (</>=median by atrial fibrillation/flutter status)											0.5417
< median	1507	24	1.6	1476	23	1.6	0.9400	0.98 (0.55, 1.73)	0.98 (0.55, 1.74)	0.00 (-0.01, 0.01)	
>= median	1475	35	2.4	1516	44	2.9	0.3666	1.22 (0.79, 1.90)	1.23 (0.78, 1.93)	0.01 (-0.01, 0.02)	
Baseline uric acid [mg/dL] (tertiles)											0.4972
<T1	975	15	1.5	963	16	1.7	0.8291	1.08 (0.54, 2.17)	1.08 (0.53, 2.20)	0.00 (-0.01, 0.01)	
>=T1 and <T2	966	16	1.7	1032	26	2.5	0.1790	1.52 (0.82, 2.82)	1.53 (0.82, 2.88)	0.01 (0.00, 0.02)	
>=T2	1016	27	2.7	970	24	2.5	0.7963	0.93 (0.54, 1.60)	0.93 (0.53, 1.62)	0.00 (-0.02, 0.01)	
Baseline use of MRA											0.0982
No	1865	40	2.1	1878	36	1.9	0.6212	0.89 (0.57, 1.40)	0.89 (0.57, 1.41)	0.00 (-0.01, 0.01)	
Yes	1124	19	1.7	1118	31	2.8	0.0827	1.64 (0.93, 2.89)	1.66 (0.93, 2.95)	0.01 (0.00, 0.02)	
Baseline use of ACE-inhibitor, ARB or ARNi											0.7282
No	586	13	2.2	568	16	2.8	0.5161	1.27 (0.62, 2.62)	1.28 (0.61, 2.68)	0.01 (-0.01, 0.02)	
Yes	2403	46	1.9	2428	51	2.1	0.6445	1.10 (0.74, 1.63)	1.10 (0.74, 1.64)	0.00 (-0.01, 0.01)	

Analysis is based on study 1245.110.
^ Patients with NYHA class I are counted in subgroup NYHA class II.
*** Confirmed hypoglycaemic AEs are defined by a glucose concentration <=70 mg/dL (3.9 mmol/L) or requiring assistance.
Risk ratios and odds ratios with confidence intervals (CIs) are estimated by Cochran-Mantel-Haenszel method. For risk differences standard Wald asymptotic confidence limits are calculated. A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied in case of any zero cells in contingency table.
Only treatment emergent AEs are displayed (onset between first dose until treatment stop +7 days).
MedDRA version: 23.1. * Chi-square test for treatment effect ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction).

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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 overall and by subgroup - TS
User-defined AE category: Sepsis (investigator-defined) with source of infection UTI

Subgroup	Placebo			Empa 10mg			Empa 10mg vs Placebo				
Category	N	n	%	N	n	%	p-value *	Risk ratio (95% CI)	Odds ratio (95% CI)	Risk diff. (95% CI)	p-value **
Overall	2989	15	0.5	2996	18	0.6	0.6052	1.20 (0.60, 2.37)	1.20 (0.60, 2.38)	0.00 (0.00, 0.00)	
Sex											0.2285
Male	1653	9	0.5	1658	7	0.4	0.6120	0.78 (0.29, 2.08)	0.77 (0.29, 2.08)	0.00 (-0.01, 0.00)	
Female	1336	6	0.4	1338	11	0.8	0.2250	1.83 (0.68, 4.94)	1.84 (0.68, 4.98)	0.00 (0.00, 0.01)	
Age [years]											0.8303
<70	1084	3	0.3	1066	3	0.3	0.9836	1.02 (0.21, 5.03)	1.02 (0.20, 5.05)	0.00 (0.00, 0.00)	
>=70	1905	12	0.6	1930	15	0.8	0.5855	1.23 (0.58, 2.63)	1.24 (0.58, 2.65)	0.00 (0.00, 0.01)	
Region											0.5114
North America	359	0	0	359	5	1.4	0.0404	11.00 (0.61,198.20)	11.16 (0.61,202.49)	0.01 (0.00, 0.03)	
Latin America	757	4	0.5	758	2	0.3	0.4124	0.50 (0.09, 2.72)	0.50 (0.09, 2.73)	0.00 (-0.01, 0.00)	
Europe	1341	8	0.6	1346	8	0.6	0.9940	1.00 (0.38, 2.65)	1.00 (0.37, 2.66)	0.00 (-0.01, 0.01)	
Asia	343	1	0.3	343	1	0.3	1.0000	1.00 (0.06, 15.92)	1.00 (0.06, 16.05)	0.00 (-0.01, 0.01)	
Other	189	2	1.1	190	2	1.1	0.9958	0.99 (0.14, 6.99)	0.99 (0.14, 7.14)	0.00 (-0.02, 0.02)	
OECD member											0.2564
No	847	5	0.6	868	3	0.3	0.4572	0.59 (0.14, 2.44)	0.58 (0.14, 2.45)	0.00 (-0.01, 0.00)	
Yes	2142	10	0.5	2128	15	0.7	0.3080	1.51 (0.68, 3.35)	1.51 (0.68, 3.38)	0.00 (0.00, 0.01)	
Baseline NYHA											0.4266
II^	2450	12	0.5	2435	12	0.5	0.9880	1.01 (0.45, 2.24)	1.01 (0.45, 2.24)	0.00 (0.00, 0.00)	
III/IV	539	3	0.6	561	6	1.1	0.3451	1.92 (0.48, 7.64)	1.93 (0.48, 7.76)	0.01 (-0.01, 0.02)	
Baseline Diabetes Status											0.8625
Diabetic	1471	8	0.5	1465	9	0.6	0.8013	1.13 (0.44, 2.92)	1.13 (0.43, 2.94)	0.00 (0.00, 0.01)	
Non-Diabetic	1518	7	0.5	1531	9	0.6	0.6282	1.27 (0.48, 3.41)	1.28 (0.47, 3.44)	0.00 (0.00, 0.01)	

Analysis is based on study 1245.110.
^ Patients with NYHA class I are counted in subgroup NYHA class II.
*** Confirmed hypoglycaemic AEs are defined by a glucose concentration <=70 mg/dL (3.9 mmol/L) or requiring assistance.
Risk ratios and odds ratios with confidence intervals (CIs) are estimated by Cochran-Mantel-Haenszel method. For risk differences standard Wald asymptotic confidence limits are calculated. A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied in case of any zero cells in contingency table.
Only treatment emergent AEs are displayed (onset between first dose until treatment stop +7 days).
MedDRA version: 23.1. * Chi-square test for treatment effect ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction).

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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 overall and by subgroup - TS
User-defined AE category: Sepsis (investigator-defined) with source of infection UTI

Subgroup	Placebo			Empa 10mg			Empa 10mg vs Placebo				
Category	N	n	%	N	n	%	p-value *	Risk ratio (95% CI)	Odds ratio (95% CI)	Risk diff. (95% CI)	p-value **
Baseline Diabetes Status											0.9541
Diabetic	1471	8	0.5	1465	9	0.6	0.8013	1.13 (0.44, 2.92)	1.13 (0.43, 2.94)	0.00 (0.00, 0.01)	
Pre-Diabetes	979	5	0.5	1001	7	0.7	0.5888	1.37 (0.44, 4.30)	1.37 (0.43, 4.34)	0.00 (0.00, 0.01)	
Normal (no pre-diabetes)	539	2	0.4	530	2	0.4	0.9865	1.02 (0.14, 7.19)	1.02 (0.14, 7.25)	0.00 (-0.01, 0.01)	
Baseline BMI [kg/m²]											0.1347
<30	1641	8	0.5	1654	5	0.3	0.3965	0.62 (0.20, 1.89)	0.62 (0.20, 1.90)	0.00 (-0.01, 0.00)	
>=30	1348	7	0.5	1342	13	1.0	0.1749	1.87 (0.75, 4.66)	1.87 (0.75, 4.71)	0.00 (0.00, 0.01)	
Baseline eGFR (CKD-EPI) [mL/min/1.73m²]											0.7874
>=60	1505	4	0.3	1493	4	0.3	0.9910	1.01 (0.25, 4.02)	1.01 (0.25, 4.04)	0.00 (0.00, 0.00)	
<60	1482	11	0.7	1503	14	0.9	0.5706	1.25 (0.57, 2.76)	1.26 (0.57, 2.78)	0.00 (0.00, 0.01)	
History of HHF (in the last 12 months)											0.8880
No	2320	9	0.4	2297	11	0.5	0.6380	1.23 (0.51, 2.97)	1.24 (0.51, 2.99)	0.00 (0.00, 0.00)	
Yes	669	6	0.9	699	7	1.0	0.8420	1.12 (0.38, 3.31)	1.12 (0.37, 3.34)	0.00 (-0.01, 0.01)	
Baseline SBP (</>= median)											0.8702
< median	1474	7	0.5	1496	8	0.5	0.8180	1.13 (0.41, 3.10)	1.13 (0.41, 3.12)	0.00 (0.00, 0.01)	
>= median	1515	8	0.5	1500	10	0.7	0.6213	1.26 (0.50, 3.19)	1.26 (0.50, 3.21)	0.00 (0.00, 0.01)	
History of atrial fibrillation or atrial flutter											0.3834
No	1426	3	0.2	1417	6	0.4	0.3120	2.01 (0.50, 8.03)	2.02 (0.50, 8.08)	0.00 (0.00, 0.01)	
Yes	1558	12	0.8	1575	12	0.8	0.9787	0.99 (0.45, 2.20)	0.99 (0.44, 2.21)	0.00 (-0.01, 0.01)	

Analysis is based on study 1245.110.
^ Patients with NYHA class I are counted in subgroup NYHA class II.
*** Confirmed hypoglycaemic AEs are defined by a glucose concentration <=70 mg/dL (3.9 mmol/L) or requiring assistance.
Risk ratios and odds ratios with confidence intervals (CIs) are estimated by Cochran-Mantel-Haenszel method. For risk differences standard Wald asymptotic confidence limits are calculated. A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied in case of any zero cells in contingency table.
Only treatment emergent AEs are displayed (onset between first dose until treatment stop +7 days).
MedDRA version: 23.1. * Chi-square test for treatment effect ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction).

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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 overall and by subgroup - TS
User-defined AE category: Sepsis (investigator-defined) with source of infection UTI

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 LVEF [%]											0.3997
< 50	988	3	0.3	995	6	0.6	0.3214	1.99 (0.50, 7.92)	1.99 (0.50, 7.99)	0.00 (0.00, 0.01)	
>= 50	2001	12	0.6	2001	12	0.6	1.0000	1.00 (0.45, 2.22)	1.00 (0.45, 2.23)	0.00 (0.00, 0.00)	
Baseline LVEF [%]											0.1959
<50	988	3	0.3	995	6	0.6	0.3214	1.99 (0.50, 7.92)	1.99 (0.50, 7.99)	0.00 (0.00, 0.01)	
50 to <60	1030	7	0.7	1028	3	0.3	0.2059	0.43 (0.11, 1.66)	0.43 (0.11, 1.66)	0.00 (-0.01, 0.00)	
>=60	971	5	0.5	973	9	0.9	0.2850	1.80 (0.60, 5.34)	1.80 (0.60, 5.40)	0.00 (0.00, 0.01)	
Baseline NT-proBNP [pg/mL] (</>=median by atrial fibrillation/flutter status)											0.0721
< median	1507	3	0.2	1476	9	0.6	0.0764	3.06 (0.83, 11.29)	3.08 (0.83, 11.38)	0.00 (0.00, 0.01)	
>= median	1475	12	0.8	1516	9	0.6	0.4715	0.73 (0.31, 1.73)	0.73 (0.31, 1.73)	0.00 (-0.01, 0.00)	
Baseline uric acid [mg/dL] (tertiles)											0.5421
<T1	975	1	0.1	963	3	0.3	0.3108	3.04 (0.32, 29.15)	3.04 (0.32, 29.31)	0.00 (0.00, 0.01)	
>=T1 and <T2	966	7	0.7	1032	6	0.6	0.6907	0.80 (0.27, 2.38)	0.80 (0.27, 2.39)	0.00 (-0.01, 0.01)	
>=T2	1016	7	0.7	970	9	0.9	0.5517	1.35 (0.50, 3.60)	1.35 (0.50, 3.64)	0.00 (-0.01, 0.01)	
Baseline use of MRA											0.1988
No	1865	10	0.5	1878	8	0.4	0.6260	0.79 (0.31, 2.01)	0.79 (0.31, 2.02)	0.00 (-0.01, 0.00)	
Yes	1124	5	0.4	1118	10	0.9	0.1916	2.01 (0.69, 5.86)	2.02 (0.69, 5.93)	0.00 (0.00, 0.01)	
Baseline use of ACE-inhibitor, ARB or ARNi											0.5694
No	586	3	0.5	568	5	0.9	0.4509	1.72 (0.41, 7.16)	1.73 (0.41, 7.26)	0.00 (-0.01, 0.01)	
Yes	2403	12	0.5	2428	13	0.5	0.8614	1.07 (0.49, 2.34)	1.07 (0.49, 2.36)	0.00 (0.00, 0.00)	

Analysis is based on study 1245.110.
^ Patients with NYHA class I are counted in subgroup NYHA class II.
*** Confirmed hypoglycaemic AEs are defined by a glucose concentration <=70 mg/dL (3.9 mmol/L) or requiring assistance.
Risk ratios and odds ratios with confidence intervals (CIs) are estimated by Cochran-Mantel-Haenszel method. For risk differences standard Wald asymptotic confidence limits are calculated. A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied in case of any zero cells in contingency table.
Only treatment emergent AEs are displayed (onset between first dose until treatment stop +7 days).
MedDRA version: 23.1. * Chi-square test for treatment effect ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction).

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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 overall and by subgroup - TS
User-defined AE category: Sepsis (investigator-defined) with source of infection non-UTI or missing

Subgroup	Placebo			Empa 10mg			Empa 10mg vs Placebo					
Category	N	n	%	N	n	%	p-value *	Risk ratio (95% CI)	Odds ratio (95% CI)	Risk diff. (95% CI)	p-value **
Overall	2989	44	1.5	2996	49	1.6	0.6092	1.11 (0.74, 1.66)	1.11 (0.74, 1.68)	0.00 (0.00, 0.01)	
Sex											0.4582
Male	1653	31	1.9	1658	31	1.9	0.9904	1.00 (0.61, 1.63)	1.00 (0.60, 1.65)	0.00 (-0.01, 0.01)	
Female	1336	13	1.0	1338	18	1.3	0.3686	1.38 (0.68, 2.81)	1.39 (0.68, 2.84)	0.00 (0.00, 0.01)	
Age [years]											0.3346
<70	1084	17	1.6	1066	14	1.3	0.6200	0.84 (0.41, 1.69)	0.84 (0.41, 1.70)	0.00 (-0.01, 0.01)	
>=70	1905	27	1.4	1930	35	1.8	0.3308	1.28 (0.78, 2.11)	1.28 (0.77, 2.13)	0.00 (0.00, 0.01)	
Region											0.8580
North America	359	10	2.8	359	14	3.9	0.4063	1.40 (0.63, 3.11)	1.42 (0.62, 3.23)	0.01 (-0.02, 0.04)	
Latin America	757	11	1.5	758	15	2.0	0.4308	1.36 (0.63, 2.95)	1.37 (0.62, 3.00)	0.01 (-0.01, 0.02)	
Europe	1341	16	1.2	1346	14	1.0	0.7058	0.87 (0.43, 1.78)	0.87 (0.42, 1.79)	0.00 (-0.01, 0.01)	
Asia	343	4	1.2	343	3	0.9	0.7040	0.75 (0.17, 3.33)	0.75 (0.17, 3.37)	0.00 (-0.02, 0.01)	
Other	189	3	1.6	190	3	1.6	0.9948	0.99 (0.20, 4.87)	0.99 (0.20, 4.99)	0.00 (-0.03, 0.03)	
OECD member											0.4796
No	847	12	1.4	868	17	2.0	0.3843	1.38 (0.66, 2.88)	1.39 (0.66, 2.93)	0.01 (-0.01, 0.02)	
Yes	2142	32	1.5	2128	32	1.5	0.9789	1.01 (0.62, 1.64)	1.01 (0.61, 1.65)	0.00 (-0.01, 0.01)	
Baseline NYHA											0.0782
II^	2450	34	1.4	2435	29	1.2	0.5422	0.86 (0.52, 1.40)	0.86 (0.52, 1.41)	0.00 (-0.01, 0.00)	
III/IV	539	10	1.9	561	20	3.6	0.0818	1.92 (0.91, 4.07)	1.96 (0.91, 4.22)	0.02 (0.00, 0.04)	
Baseline Diabetes Status											0.1266
Diabetic	1471	22	1.5	1465	32	2.2	0.1649	1.46 (0.85, 2.50)	1.47 (0.85, 2.54)	0.01 (0.00, 0.02)	
Non-Diabetic	1518	22	1.4	1531	17	1.1	0.4051	0.77 (0.41, 1.44)	0.76 (0.40, 1.44)	0.00 (-0.01, 0.00)	

Analysis is based on study 1245.110.
^ Patients with NYHA class I are counted in subgroup NYHA class II.
*** Confirmed hypoglycaemic AEs are defined by a glucose concentration <=70 mg/dL (3.9 mmol/L) or requiring assistance.
Risk ratios and odds ratios with confidence intervals (CIs) are estimated by Cochran-Mantel-Haenszel method. For risk differences standard Wald asymptotic confidence limits are calculated. A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied in case of any zero cells in contingency table.
Only treatment emergent AEs are displayed (onset between first dose until treatment stop +7 days).
MedDRA version: 23.1. * Chi-square test for treatment effect ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction).

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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 overall and by subgroup - TS
User-defined AE category: Sepsis (investigator-defined) with source of infection non-UTI or missing

Subgroup	Placebo			Empa 10mg			Empa 10mg vs Placebo				
Category	N	n	%	N	n	%	p-value *	Risk ratio (95% CI)	Odds ratio (95% CI)	Risk diff. (95% CI)	p-value **
Baseline Diabetes Status											0.0161
Diabetic	1471	22	1.5	1465	32	2.2	0.1649	1.46 (0.85, 2.50)	1.47 (0.85, 2.54)	0.01 (0.00, 0.02)	
Pre-Diabetes	979	9	0.9	1001	15	1.5	0.2390	1.63 (0.72, 3.71)	1.64 (0.71, 3.76)	0.01 (0.00, 0.02)	
Normal (no pre-diabetes)	539	13	2.4	530	2	0.4	0.0047	0.16 (0.04, 0.69)	0.15 (0.03, 0.68)	-0.02 (-0.03,-0.01)	
Baseline BMI [kg/m²]											0.0815
<30	1641	23	1.4	1654	17	1.0	0.3273	0.73 (0.39, 1.37)	0.73 (0.39, 1.37)	0.00 (-0.01, 0.00)	
>=30	1348	21	1.6	1342	32	2.4	0.1230	1.53 (0.89, 2.64)	1.54 (0.89, 2.69)	0.01 (0.00, 0.02)	
Baseline eGFR (CKD-EPI) [mL/min/1.73m²]											0.6749
>=60	1505	19	1.3	1493	23	1.5	0.5172	1.22 (0.67, 2.23)	1.22 (0.66, 2.26)	0.00 (-0.01, 0.01)	
<60	1482	25	1.7	1503	26	1.7	0.9278	1.03 (0.60, 1.77)	1.03 (0.59, 1.78)	0.00 (-0.01, 0.01)	
History of HHF (in the last 12 months)											0.2249
No	2320	35	1.5	2297	33	1.4	0.8392	0.95 (0.59, 1.53)	0.95 (0.59, 1.54)	0.00 (-0.01, 0.01)	
Yes	669	9	1.3	699	16	2.3	0.1927	1.70 (0.76, 3.82)	1.72 (0.75, 3.91)	0.01 (0.00, 0.02)	
Baseline SBP (</>= median)											0.0376
< median	1474	19	1.3	1496	32	2.1	0.0746	1.66 (0.94, 2.91)	1.67 (0.94, 2.97)	0.01 (0.00, 0.02)	
>= median	1515	25	1.7	1500	17	1.1	0.2260	0.69 (0.37, 1.27)	0.68 (0.37, 1.27)	-0.01 (-0.01, 0.00)	
History of atrial fibrillation or atrial flutter											0.2039
No	1426	23	1.6	1417	19	1.3	0.5477	0.83 (0.45, 1.52)	0.83 (0.45, 1.53)	0.00 (-0.01, 0.01)	
Yes	1558	21	1.3	1575	30	1.9	0.2181	1.41 (0.81, 2.46)	1.42 (0.81, 2.49)	0.01 (0.00, 0.01)	

Analysis is based on study 1245.110.
^ Patients with NYHA class I are counted in subgroup NYHA class II.
*** Confirmed hypoglycaemic AEs are defined by a glucose concentration <=70 mg/dL (3.9 mmol/L) or requiring assistance.
Risk ratios and odds ratios with confidence intervals (CIs) are estimated by Cochran-Mantel-Haenszel method. For risk differences standard Wald asymptotic confidence limits are calculated. A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied in case of any zero cells in contingency table.
Only treatment emergent AEs are displayed (onset between first dose until treatment stop +7 days).
MedDRA version: 23.1. * Chi-square test for treatment effect ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction).

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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 overall and by subgroup - TS
User-defined AE category: Sepsis (investigator-defined) with source of infection non-UTI or missing

Subgroup	Placebo			Empa 10mg			Empa 10mg vs Placebo						
Category	N	n	%	N	n	%	p-value *	Risk ratio (95% CI)	Odds ratio (95% CI)	Risk diff. (95% CI)	p-value **
Baseline LVEF [%]											0.4698
< 50	988	13	1.3	995	18	1.8	0.3760	1.37 (0.68, 2.79)	1.38 (0.67, 2.84)	0.00 (-0.01, 0.02)	
>= 50	2001	31	1.5	2001	31	1.5	1.0000	1.00 (0.61, 1.64)	1.00 (0.61, 1.65)	0.00 (-0.01, 0.01)	
Baseline LVEF [%]											0.7437
<50	988	13	1.3	995	18	1.8	0.3760	1.37 (0.68, 2.79)	1.38 (0.67, 2.84)	0.00 (-0.01, 0.02)	
50 to <60	1030	15	1.5	1028	16	1.6	0.8521	1.07 (0.53, 2.15)	1.07 (0.53, 2.18)	0.00 (-0.01, 0.01)	
>=60	971	16	1.6	973	15	1.5	0.8518	0.94 (0.47, 1.88)	0.93 (0.46, 1.90)	0.00 (-0.01, 0.01)	
Baseline NT-proBNP [pg/mL] (</>=median by atrial fibrillation/flutter status)											0.0734
< median	1507	21	1.4	1476	14	0.9	0.2591	0.68 (0.35, 1.33)	0.68 (0.34, 1.34)	0.00 (-0.01, 0.00)	
>= median	1475	23	1.6	1516	35	2.3	0.1373	1.48 (0.88, 2.49)	1.49 (0.88, 2.54)	0.01 (0.00, 0.02)	
Baseline uric acid [mg/dL] (tertiles)											0.1566
<T1	975	14	1.4	963	13	1.3	0.8718	0.94 (0.44, 1.99)	0.94 (0.44, 2.01)	0.00 (-0.01, 0.01)	
>=T1 and <T2	966	9	0.9	1032	20	1.9	0.0602	2.08 (0.95, 4.55)	2.10 (0.95, 4.64)	0.01 (0.00, 0.02)	
>=T2	1016	20	2.0	970	15	1.5	0.4748	0.79 (0.40, 1.53)	0.78 (0.40, 1.54)	0.00 (-0.02, 0.01)	
Baseline use of MRA											0.2581
No	1865	30	1.6	1878	28	1.5	0.7708	0.93 (0.56, 1.55)	0.93 (0.55, 1.56)	0.00 (-0.01, 0.01)	
Yes	1124	14	1.2	1118	21	1.9	0.2268	1.51 (0.77, 2.95)	1.52 (0.77, 3.00)	0.01 (0.00, 0.02)	
Baseline use of ACE-inhibitor, ARB or ARNi											0.9585
No	586	10	1.7	568	11	1.9	0.7700	1.13 (0.49, 2.65)	1.14 (0.48, 2.70)	0.00 (-0.01, 0.02)	
Yes	2403	34	1.4	2428	38	1.6	0.6667	1.11 (0.70, 1.75)	1.11 (0.70, 1.77)	0.00 (-0.01, 0.01)	

Analysis is based on study 1245.110.
^ Patients with NYHA class I are counted in subgroup NYHA class II.
*** Confirmed hypoglycaemic AEs are defined by a glucose concentration <=70 mg/dL (3.9 mmol/L) or requiring assistance.
Risk ratios and odds ratios with confidence intervals (CIs) are estimated by Cochran-Mantel-Haenszel method. For risk differences standard Wald asymptotic confidence limits are calculated. A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied in case of any zero cells in contingency table.
Only treatment emergent AEs are displayed (onset between first dose until treatment stop +7 days).
MedDRA version: 23.1. * Chi-square test for treatment effect ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction).

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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 overall and by subgroup - TS
User-defined AE category: Bone fracture (narrow 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	2989	126	4.2	2996	134	4.5	0.6256	1.06 (0.84, 1.35)	1.06 (0.83, 1.36)	0.00 (-0.01, 0.01)	
Sex											0.9839
Male	1653	49	3.0	1658	52	3.1	0.7735	1.06 (0.72, 1.55)	1.06 (0.71, 1.58)	0.00 (-0.01, 0.01)	
Female	1336	77	5.8	1338	82	6.1	0.6898	1.06 (0.79, 1.44)	1.07 (0.77, 1.47)	0.00 (-0.01, 0.02)	
Age [years]											0.9889
<70	1084	28	2.6	1066	29	2.7	0.8428	1.05 (0.63, 1.76)	1.05 (0.62, 1.79)	0.00 (-0.01, 0.01)	
>=70	1905	98	5.1	1930	105	5.4	0.6822	1.06 (0.81, 1.38)	1.06 (0.80, 1.41)	0.00 (-0.01, 0.02)	
Region											0.2048
North America	359	22	6.1	359	17	4.7	0.4103	0.77 (0.42, 1.43)	0.76 (0.40, 1.46)	-0.01 (-0.05, 0.02)	
Latin America	757	24	3.2	758	21	2.8	0.6466	0.87 (0.49, 1.56)	0.87 (0.48, 1.58)	0.00 (-0.02, 0.01)	
Europe	1341	51	3.8	1346	49	3.6	0.8237	0.96 (0.65, 1.41)	0.96 (0.64, 1.42)	0.00 (-0.02, 0.01)	
Asia	343	21	6.1	343	38	11.1	0.0206	1.81 (1.08, 3.02)	1.91 (1.10, 3.33)	0.05 (0.01, 0.09)	
Other	189	8	4.2	190	9	4.7	0.8126	1.12 (0.44, 2.84)	1.13 (0.42, 2.98)	0.01 (-0.04, 0.05)	
OECD member											0.7289
No	847	25	3.0	868	25	2.9	0.9300	0.98 (0.57, 1.68)	0.98 (0.56, 1.71)	0.00 (-0.02, 0.02)	
Yes	2142	101	4.7	2128	109	5.1	0.5386	1.09 (0.83, 1.41)	1.09 (0.83, 1.44)	0.00 (-0.01, 0.02)	
Baseline NYHA											0.6659
II^	2450	97	4.0	2435	105	4.3	0.5356	1.09 (0.83, 1.43)	1.09 (0.82, 1.45)	0.00 (-0.01, 0.01)	
III/IV	539	29	5.4	561	29	5.2	0.8756	0.96 (0.58, 1.59)	0.96 (0.56, 1.63)	0.00 (-0.03, 0.02)	
Baseline Diabetes Status											0.1355
Diabetic	1471	52	3.5	1465	67	4.6	0.1537	1.29 (0.91, 1.84)	1.31 (0.90, 1.89)	0.01 (0.00, 0.02)	
Non-Diabetic	1518	74	4.9	1531	67	4.4	0.5122	0.90 (0.65, 1.24)	0.89 (0.64, 1.25)	0.00 (-0.02, 0.01)	

Analysis is based on study 1245.110.
^ Patients with NYHA class I are counted in subgroup NYHA class II.
*** Confirmed hypoglycaemic AEs are defined by a glucose concentration <=70 mg/dL (3.9 mmol/L) or requiring assistance.
Risk ratios and odds ratios with confidence intervals (CIs) are estimated by Cochran-Mantel-Haenszel method. For risk differences standard Wald asymptotic confidence limits are calculated. A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied in case of any zero cells in contingency table.
Only treatment emergent AEs are displayed (onset between first dose until treatment stop +7 days).
MedDRA version: 23.1. * Chi-square test for treatment effect ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction).

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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 overall and by subgroup - TS
User-defined AE category: Bone fracture (narrow 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 Diabetes Status											0.3067
Diabetic	1471	52	3.5	1465	67	4.6	0.1537	1.29 (0.91, 1.84)	1.31 (0.90, 1.89)	0.01 (0.00, 0.02)	
Pre-Diabetes	979	50	5.1	1001	44	4.4	0.4566	0.86 (0.58, 1.28)	0.85 (0.56, 1.29)	-0.01 (-0.03, 0.01)	
Normal (no pre-diabetes)	539	24	4.5	530	23	4.3	0.9282	0.97 (0.56, 1.70)	0.97 (0.54, 1.75)	0.00 (-0.03, 0.02)	
Baseline BMI [kg/m²]											0.4835
<30	1641	81	4.9	1654	81	4.9	0.9589	0.99 (0.73, 1.34)	0.99 (0.72, 1.36)	0.00 (-0.02, 0.01)	
>=30	1348	45	3.3	1342	53	3.9	0.3977	1.18 (0.80, 1.75)	1.19 (0.79, 1.78)	0.01 (-0.01, 0.02)	
Baseline eGFR (CKD-EPI) [mL/min/1.73m²]											0.2886
>=60	1505	50	3.3	1493	61	4.1	0.2683	1.23 (0.85, 1.78)	1.24 (0.85, 1.81)	0.01 (-0.01, 0.02)	
<60	1482	76	5.1	1503	73	4.9	0.7337	0.95 (0.69, 1.30)	0.94 (0.68, 1.31)	0.00 (-0.02, 0.01)	
History of HHF (in the last 12 months)											0.9950
No	2320	98	4.2	2297	103	4.5	0.6651	1.06 (0.81, 1.39)	1.06 (0.80, 1.41)	0.00 (-0.01, 0.01)	
Yes	669	28	4.2	699	31	4.4	0.8203	1.06 (0.64, 1.75)	1.06 (0.63, 1.79)	0.00 (-0.02, 0.02)	
Baseline SBP (</>= median)											0.7103
< median	1474	66	4.5	1496	68	4.5	0.9290	1.02 (0.73, 1.41)	1.02 (0.72, 1.44)	0.00 (-0.01, 0.02)	
>= median	1515	60	4.0	1500	66	4.4	0.5464	1.11 (0.79, 1.56)	1.12 (0.78, 1.60)	0.00 (-0.01, 0.02)	
History of atrial fibrillation or atrial flutter											0.0785
No	1426	55	3.9	1417	44	3.1	0.2743	0.81 (0.55, 1.19)	0.80 (0.53, 1.20)	-0.01 (-0.02, 0.01)	
Yes	1558	71	4.6	1575	90	5.7	0.1424	1.25 (0.93, 1.70)	1.27 (0.92, 1.75)	0.01 (0.00, 0.03)	

Analysis is based on study 1245.110.
^ Patients with NYHA class I are counted in subgroup NYHA class II.
*** Confirmed hypoglycaemic AEs are defined by a glucose concentration <=70 mg/dL (3.9 mmol/L) or requiring assistance.
Risk ratios and odds ratios with confidence intervals (CIs) are estimated by Cochran-Mantel-Haenszel method. For risk differences standard Wald asymptotic confidence limits are calculated. A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied in case of any zero cells in contingency table.
Only treatment emergent AEs are displayed (onset between first dose until treatment stop +7 days).
MedDRA version: 23.1. * Chi-square test for treatment effect ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction).

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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 overall and by subgroup - TS
User-defined AE category: Bone fracture (narrow 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 LVEF [%]											0.8773
< 50	988	28	2.8	995	31	3.1	0.7121	1.10 (0.66, 1.82)	1.10 (0.66, 1.85)	0.00 (-0.01, 0.02)	
>= 50	2001	98	4.9	2001	103	5.1	0.7174	1.05 (0.80, 1.38)	1.05 (0.79, 1.40)	0.00 (-0.01, 0.02)	
Baseline LVEF [%]											0.9309
<50	988	28	2.8	995	31	3.1	0.7121	1.10 (0.66, 1.82)	1.10 (0.66, 1.85)	0.00 (-0.01, 0.02)	
50 to <60	1030	50	4.9	1028	50	4.9	0.9921	1.00 (0.68, 1.47)	1.00 (0.67, 1.50)	0.00 (-0.02, 0.02)	
>=60	971	48	4.9	973	53	5.4	0.6168	1.10 (0.75, 1.61)	1.11 (0.74, 1.65)	0.01 (-0.01, 0.02)	
Baseline NT-proBNP [pg/mL] (</>=median by atrial fibrillation/flutter status)											0.9966
< median	1507	56	3.7	1476	58	3.9	0.7610	1.06 (0.74, 1.52)	1.06 (0.73, 1.54)	0.00 (-0.01, 0.02)	
>= median	1475	70	4.7	1516	76	5.0	0.7343	1.06 (0.77, 1.45)	1.06 (0.76, 1.48)	0.00 (-0.01, 0.02)	
Baseline uric acid [mg/dL] (tertiles)											0.7779
<T1	975	45	4.6	963	43	4.5	0.8739	0.97 (0.64, 1.46)	0.97 (0.63, 1.48)	0.00 (-0.02, 0.02)	
>=T1 and <T2	966	37	3.8	1032	47	4.6	0.4203	1.19 (0.78, 1.81)	1.20 (0.77, 1.86)	0.01 (-0.01, 0.02)	
>=T2	1016	44	4.3	970	43	4.4	0.9114	1.02 (0.68, 1.54)	1.02 (0.67, 1.57)	0.00 (-0.02, 0.02)	
Baseline use of MRA											0.7296
No	1865	77	4.1	1878	85	4.5	0.5502	1.10 (0.81, 1.48)	1.10 (0.80, 1.51)	0.00 (-0.01, 0.02)	
Yes	1124	49	4.4	1118	49	4.4	0.9784	1.01 (0.68, 1.48)	1.01 (0.67, 1.51)	0.00 (-0.02, 0.02)	
Baseline use of ACE-inhibitor, ARB or ARNi											0.1475
No	586	28	4.8	568	39	6.9	0.1294	1.44 (0.90, 2.30)	1.47 (0.89, 2.42)	0.02 (-0.01, 0.05)	
Yes	2403	98	4.1	2428	95	3.9	0.7689	0.96 (0.73, 1.26)	0.96 (0.72, 1.28)	0.00 (-0.01, 0.01)	

Analysis is based on study 1245.110.
^ Patients with NYHA class I are counted in subgroup NYHA class II.
*** Confirmed hypoglycaemic AEs are defined by a glucose concentration <=70 mg/dL (3.9 mmol/L) or requiring assistance.
Risk ratios and odds ratios with confidence intervals (CIs) are estimated by Cochran-Mantel-Haenszel method. For risk differences standard Wald asymptotic confidence limits are calculated. A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied in case of any zero cells in contingency table.
Only treatment emergent AEs are displayed (onset between first dose until treatment stop +7 days).
MedDRA version: 23.1. * Chi-square test for treatment effect ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction).

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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 overall and by subgroup - TS
User-defined AE category: Urinary tract malignancies (broad Sub BIcMQs)

Subgroup	Placebo			Empa 10mg			Empa 10mg vs Placebo				
Category	N	n	%	N	n	%	p-value *	Risk ratio (95% CI)	Odds ratio (95% CI)	Risk diff. (95% CI)	p-value **
Overall	2989	10	0.3	2996	16	0.5	0.2407	1.60 (0.73, 3.51)	1.60 (0.72, 3.53)	0.00 (0.00, 0.01)	
Sex											0.6496
Male	1653	6	0.4	1658	11	0.7	0.2264	1.83 (0.68, 4.93)	1.83 (0.68, 4.97)	0.00 (0.00, 0.01)	
Female	1336	4	0.3	1338	5	0.4	0.7402	1.25 (0.34, 4.64)	1.25 (0.33, 4.66)	0.00 (0.00, 0.01)	
Age [years]											0.4428
<70	1084	4	0.4	1066	4	0.4	0.9811	1.02 (0.25, 4.06)	1.02 (0.25, 4.08)	0.00 (-0.01, 0.01)	
>=70	1905	6	0.3	1930	12	0.6	0.1646	1.97 (0.74, 5.25)	1.98 (0.74, 5.29)	0.00 (0.00, 0.01)	
Region											0.8092
North America	359	0	0	359	1	0.3	0.4789	3.00 (0.12, 73.40)	3.01 (0.12, 74.09)	0.00 (0.00, 0.01)	
Latin America	757	1	0.1	758	3	0.4	0.3173	3.00 (0.31, 28.74)	3.00 (0.31, 28.94)	0.00 (0.00, 0.01)	
Europe	1341	6	0.4	1346	7	0.5	0.7862	1.16 (0.39, 3.45)	1.16 (0.39, 3.47)	0.00 (0.00, 0.01)	
Asia	343	3	0.9	343	3	0.9	1.0000	1.00 (0.20, 4.92)	1.00 (0.20, 4.99)	0.00 (-0.01, 0.01)	
Other	189	0	0	190	2	1.1	0.2482	4.97 (0.24,102.91)	5.03 (0.24,105.40)	0.01 (-0.01, 0.03)	
OECD member											0.3739
No	847	1	0.1	868	4	0.5	0.1881	3.90 (0.44, 34.85)	3.92 (0.44, 35.11)	0.00 (0.00, 0.01)	
Yes	2142	9	0.4	2128	12	0.6	0.5020	1.34 (0.57, 3.18)	1.34 (0.57, 3.20)	0.00 (0.00, 0.01)	
Baseline NYHA											0.2963
II^	2450	10	0.4	2435	13	0.5	0.5210	1.31 (0.57, 2.98)	1.31 (0.57, 2.99)	0.00 (0.00, 0.01)	
III/IV	539	0	0	561	3	0.5	0.1435	6.73 (0.35,129.91)	6.76 (0.35,131.22)	0.01 (0.00, 0.01)	
Baseline Diabetes Status											0.6297
Diabetic	1471	6	0.4	1465	8	0.5	0.5868	1.34 (0.47, 3.85)	1.34 (0.46, 3.87)	0.00 (0.00, 0.01)	
Non-Diabetic	1518	4	0.3	1531	8	0.5	0.2534	1.98 (0.60, 6.57)	1.99 (0.60, 6.62)	0.00 (0.00, 0.01)	

Analysis is based on study 1245.110.
^ Patients with NYHA class I are counted in subgroup NYHA class II.
*** Confirmed hypoglycaemic AEs are defined by a glucose concentration <=70 mg/dL (3.9 mmol/L) or requiring assistance.
Risk ratios and odds ratios with confidence intervals (CIs) are estimated by Cochran-Mantel-Haenszel method. For risk differences standard Wald asymptotic confidence limits are calculated. A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied in case of any zero cells in contingency table.
Only treatment emergent AEs are displayed (onset between first dose until treatment stop +7 days).
MedDRA version: 23.1. * Chi-square test for treatment effect ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction).

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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 overall and by subgroup - TS
User-defined AE category: Urinary tract malignancies (broad Sub BIcMQs)

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 Diabetes Status											0.8098
Diabetic	1471	6	0.4	1465	8	0.5	0.5868	1.34 (0.47, 3.85)	1.34 (0.46, 3.87)	0.00 (0.00, 0.01)	
Pre-Diabetes	979	3	0.3	1001	5	0.5	0.4983	1.63 (0.39, 6.80)	1.63 (0.39, 6.85)	0.00 (0.00, 0.01)	
Normal (no pre-diabetes)	539	1	0.2	530	3	0.6	0.3083	3.05 (0.32, 29.24)	3.06 (0.32, 29.54)	0.00 (0.00, 0.01)	
Baseline BMI [kg/m²]											0.6295
<30	1641	4	0.2	1654	8	0.5	0.2530	1.98 (0.60, 6.58)	1.99 (0.60, 6.62)	0.00 (0.00, 0.01)	
>=30	1348	6	0.4	1342	8	0.6	0.5862	1.34 (0.47, 3.85)	1.34 (0.46, 3.88)	0.00 (0.00, 0.01)	
Baseline eGFR (CKD-EPI) [mL/min/1.73m²]											0.4687
>=60	1505	3	0.2	1493	7	0.5	0.2006	2.35 (0.61, 9.08)	2.36 (0.61, 9.14)	0.00 (0.00, 0.01)	
<60	1482	7	0.5	1503	9	0.6	0.6361	1.27 (0.47, 3.40)	1.27 (0.47, 3.42)	0.00 (0.00, 0.01)	
History of HHF (in the last 12 months)											0.2057
No	2320	10	0.4	2297	12	0.5	0.6521	1.21 (0.52, 2.80)	1.21 (0.52, 2.81)	0.00 (0.00, 0.00)	
Yes	669	0	0	699	4	0.6	0.0812	8.61 (0.46,159.69)	8.66 (0.47,161.22)	0.01 (0.00, 0.01)	
Baseline SBP (</>= median)											0.7323
< median	1474	5	0.3	1496	7	0.5	0.5804	1.38 (0.44, 4.34)	1.38 (0.44, 4.36)	0.00 (0.00, 0.01)	
>= median	1515	5	0.3	1500	9	0.6	0.2756	1.82 (0.61, 5.41)	1.82 (0.61, 5.45)	0.00 (0.00, 0.01)	
History of atrial fibrillation or atrial flutter											0.2503
No	1426	4	0.3	1417	3	0.2	0.7113	0.75 (0.17, 3.37)	0.75 (0.17, 3.38)	0.00 (0.00, 0.00)	
Yes	1558	6	0.4	1575	13	0.8	0.1125	2.14 (0.82, 5.62)	2.15 (0.82, 5.68)	0.00 (0.00, 0.01)	

Analysis is based on study 1245.110.
^ Patients with NYHA class I are counted in subgroup NYHA class II.
*** Confirmed hypoglycaemic AEs are defined by a glucose concentration <=70 mg/dL (3.9 mmol/L) or requiring assistance.
Risk ratios and odds ratios with confidence intervals (CIs) are estimated by Cochran-Mantel-Haenszel method. For risk differences standard Wald asymptotic confidence limits are calculated. A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied in case of any zero cells in contingency table.
Only treatment emergent AEs are displayed (onset between first dose until treatment stop +7 days).
MedDRA version: 23.1. * Chi-square test for treatment effect ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction).

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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 overall and by subgroup - TS
User-defined AE category: Urinary tract malignancies (broad Sub BIcMQs)

Subgroup	Placebo			Empa 10mg			Empa 10mg vs Placebo				
Category	N	n	%	N	n	%	p-value *	Risk ratio (95% CI)	Odds ratio (95% CI)	Risk diff. (95% CI)	p-value **
Baseline LVEF [%]											0.7017
< 50	988	3	0.3	995	6	0.6	0.3214	1.99 (0.50, 7.92)	1.99 (0.50, 7.99)	0.00 (0.00, 0.01)	
>= 50	2001	7	0.3	2001	10	0.5	0.4659	1.43 (0.54, 3.75)	1.43 (0.54, 3.77)	0.00 (0.00, 0.01)	
Baseline LVEF [%]											0.9230
<50	988	3	0.3	995	6	0.6	0.3214	1.99 (0.50, 7.92)	1.99 (0.50, 7.99)	0.00 (0.00, 0.01)	
50 to <60	1030	3	0.3	1028	4	0.4	0.7031	1.34 (0.30, 5.95)	1.34 (0.30, 5.99)	0.00 (0.00, 0.01)	
>=60	971	4	0.4	973	6	0.6	0.5282	1.50 (0.42, 5.29)	1.50 (0.42, 5.33)	0.00 (0.00, 0.01)	
Baseline NT-proBNP [pg/mL] (</>=median by atrial fibrillation/flutter status)											0.4927
< median	1507	5	0.3	1476	10	0.7	0.1820	2.04 (0.70, 5.96)	2.05 (0.70, 6.01)	0.00 (0.00, 0.01)	
>= median	1475	5	0.3	1516	6	0.4	0.7975	1.17 (0.36, 3.82)	1.17 (0.36, 3.84)	0.00 (0.00, 0.00)	
Baseline uric acid [mg/dL] (tertiles)											0.4166
<T1	975	5	0.5	963	8	0.8	0.3913	1.62 (0.53, 4.93)	1.63 (0.53, 4.99)	0.00 (0.00, 0.01)	
>=T1 and <T2	966	3	0.3	1032	2	0.2	0.6017	0.62 (0.10, 3.73)	0.62 (0.10, 3.74)	0.00 (-0.01, 0.00)	
>=T2	1016	2	0.2	970	6	0.6	0.1380	3.14 (0.64, 15.53)	3.16 (0.64, 15.67)	0.00 (0.00, 0.01)	
Baseline use of MRA											0.6081
No	1865	6	0.3	1878	8	0.4	0.6013	1.32 (0.46, 3.81)	1.33 (0.46, 3.83)	0.00 (0.00, 0.00)	
Yes	1124	4	0.4	1118	8	0.7	0.2432	2.01 (0.61, 6.66)	2.02 (0.61, 6.72)	0.00 (0.00, 0.01)	
Baseline use of ACE-inhibitor, ARB or ARNi											0.5031
No	586	2	0.3	568	5	0.9	0.2384	2.58 (0.50, 13.24)	2.59 (0.50, 13.42)	0.01 (0.00, 0.01)	
Yes	2403	8	0.3	2428	11	0.5	0.5048	1.36 (0.55, 3.38)	1.36 (0.55, 3.39)	0.00 (0.00, 0.00)	

Analysis is based on study 1245.110.
^ Patients with NYHA class I are counted in subgroup NYHA class II.
*** Confirmed hypoglycaemic AEs are defined by a glucose concentration <=70 mg/dL (3.9 mmol/L) or requiring assistance.
Risk ratios and odds ratios with confidence intervals (CIs) are estimated by Cochran-Mantel-Haenszel method. For risk differences standard Wald asymptotic confidence limits are calculated. A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied in case of any zero cells in contingency table.
Only treatment emergent AEs are displayed (onset between first dose until treatment stop +7 days).
MedDRA version: 23.1. * Chi-square test for treatment effect ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction).

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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 overall and by subgroup - TS
User-defined AE category: Volume depletion (narrow 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	2989	286	9.6	2996	356	11.9	0.0038	1.24 (1.07, 1.44)	1.27 (1.08, 1.50)	0.02 (0.01, 0.04)	
Sex											0.4733
Male	1653	161	9.7	1658	191	11.5	0.0966	1.18 (0.97, 1.44)	1.21 (0.97, 1.51)	0.02 (0.00, 0.04)	
Female	1336	125	9.4	1338	165	12.3	0.0134	1.32 (1.06, 1.64)	1.36 (1.07, 1.74)	0.03 (0.01, 0.05)	
Age [years]											0.1282
<70	1084	69	6.4	1066	102	9.6	0.0061	1.50 (1.12, 2.02)	1.56 (1.13, 2.14)	0.03 (0.01, 0.05)	
>=70	1905	217	11.4	1930	254	13.2	0.0951	1.16 (0.97, 1.37)	1.18 (0.97, 1.43)	0.02 (0.00, 0.04)	
Region											0.3950
North America	359	46	12.8	359	64	17.8	0.0622	1.39 (0.98, 1.97)	1.48 (0.98, 2.23)	0.05 (0.00, 0.10)	
Latin America	757	60	7.9	758	70	9.2	0.3631	1.17 (0.84, 1.62)	1.18 (0.82, 1.70)	0.01 (-0.02, 0.04)	
Europe	1341	129	9.6	1346	142	10.5	0.4234	1.10 (0.87, 1.37)	1.11 (0.86, 1.42)	0.01 (-0.01, 0.03)	
Asia	343	33	9.6	343	47	13.7	0.0958	1.42 (0.94, 2.17)	1.49 (0.93, 2.39)	0.04 (-0.01, 0.09)	
Other	189	18	9.5	190	33	17.4	0.0252	1.82 (1.07, 3.12)	2.00 (1.08, 3.69)	0.08 (0.01, 0.15)	
OECD member											0.4374
No	847	62	7.3	868	88	10.1	0.0389	1.39 (1.01, 1.89)	1.43 (1.02, 2.01)	0.03 (0.00, 0.05)	
Yes	2142	224	10.5	2128	268	12.6	0.0288	1.20 (1.02, 1.42)	1.23 (1.02, 1.49)	0.02 (0.00, 0.04)	
Baseline NYHA											0.2122
II^	2450	222	9.1	2435	259	10.6	0.0646	1.17 (0.99, 1.39)	1.19 (0.99, 1.44)	0.02 (0.00, 0.03)	
III/IV	539	64	11.9	561	97	17.3	0.0111	1.46 (1.09, 1.95)	1.55 (1.10, 2.18)	0.05 (0.01, 0.10)	
Baseline Diabetes Status											0.5281
Diabetic	1471	137	9.3	1465	161	11.0	0.1326	1.18 (0.95, 1.46)	1.20 (0.95, 1.53)	0.02 (-0.01, 0.04)	
Non-Diabetic	1518	149	9.8	1531	195	12.7	0.0108	1.30 (1.06, 1.59)	1.34 (1.07, 1.68)	0.03 (0.01, 0.05)	

Analysis is based on study 1245.110.
^ Patients with NYHA class I are counted in subgroup NYHA class II.
*** Confirmed hypoglycaemic AEs are defined by a glucose concentration <=70 mg/dL (3.9 mmol/L) or requiring assistance.
Risk ratios and odds ratios with confidence intervals (CIs) are estimated by Cochran-Mantel-Haenszel method. For risk differences standard Wald asymptotic confidence limits are calculated. A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied in case of any zero cells in contingency table.
Only treatment emergent AEs are displayed (onset between first dose until treatment stop +7 days).
MedDRA version: 23.1. * Chi-square test for treatment effect ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction).

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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 overall and by subgroup - TS
User-defined AE category: Volume depletion (narrow 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 Diabetes Status											0.7467
Diabetic	1471	137	9.3	1465	161	11.0	0.1326	1.18 (0.95, 1.46)	1.20 (0.95, 1.53)	0.02 (-0.01, 0.04)	
Pre-Diabetes	979	91	9.3	1001	125	12.5	0.0227	1.34 (1.04, 1.73)	1.39 (1.05, 1.85)	0.03 (0.00, 0.06)	
Normal (no pre-diabetes)	539	58	10.8	530	70	13.2	0.2179	1.23 (0.89, 1.70)	1.26 (0.87, 1.83)	0.02 (-0.01, 0.06)	
Baseline BMI [kg/m²]											0.7764
<30	1641	154	9.4	1654	189	11.4	0.0549	1.22 (1.00, 1.49)	1.25 (1.00, 1.56)	0.02 (0.00, 0.04)	
>=30	1348	132	9.8	1342	167	12.4	0.0287	1.27 (1.02, 1.58)	1.31 (1.03, 1.67)	0.03 (0.00, 0.05)	
Baseline eGFR (CKD-EPI) [mL/min/1.73m²]											0.1230
>=60	1505	123	8.2	1493	131	8.8	0.5543	1.07 (0.85, 1.36)	1.08 (0.84, 1.40)	0.01 (-0.01, 0.03)	
<60	1482	163	11.0	1503	225	15.0	0.0013	1.36 (1.13, 1.64)	1.42 (1.15, 1.77)	0.04 (0.02, 0.06)	
History of HHF (in the last 12 months)											0.8358
No	2320	220	9.5	2297	268	11.7	0.0158	1.23 (1.04, 1.46)	1.26 (1.04, 1.52)	0.02 (0.00, 0.04)	
Yes	669	66	9.9	699	88	12.6	0.1111	1.28 (0.94, 1.72)	1.32 (0.94, 1.85)	0.03 (-0.01, 0.06)	
Baseline SBP (</>= median)											0.9887
< median	1474	162	11.0	1496	204	13.6	0.0283	1.24 (1.02, 1.51)	1.28 (1.03, 1.59)	0.03 (0.00, 0.05)	
>= median	1515	124	8.2	1500	152	10.1	0.0636	1.24 (0.99, 1.55)	1.26 (0.99, 1.62)	0.02 (0.00, 0.04)	
History of atrial fibrillation or atrial flutter											0.0625
No	1426	97	6.8	1417	144	10.2	0.0013	1.49 (1.17, 1.91)	1.55 (1.18, 2.03)	0.03 (0.01, 0.05)	
Yes	1558	188	12.1	1575	212	13.5	0.2425	1.12 (0.93, 1.34)	1.13 (0.92, 1.40)	0.01 (-0.01, 0.04)	

Analysis is based on study 1245.110.
^ Patients with NYHA class I are counted in subgroup NYHA class II.
*** Confirmed hypoglycaemic AEs are defined by a glucose concentration <=70 mg/dL (3.9 mmol/L) or requiring assistance.
Risk ratios and odds ratios with confidence intervals (CIs) are estimated by Cochran-Mantel-Haenszel method. For risk differences standard Wald asymptotic confidence limits are calculated. A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied in case of any zero cells in contingency table.
Only treatment emergent AEs are displayed (onset between first dose until treatment stop +7 days).
MedDRA version: 23.1. * Chi-square test for treatment effect ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction).

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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 overall and by subgroup - TS
User-defined AE category: Volume depletion (narrow 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 LVEF [%]											0.1203
< 50	988	69	7.0	995	105	10.6	0.0050	1.51 (1.13, 2.02)	1.57 (1.14, 2.16)	0.04 (0.01, 0.06)	
>= 50	2001	217	10.8	2001	251	12.5	0.0944	1.16 (0.98, 1.37)	1.18 (0.97, 1.43)	0.02 (0.00, 0.04)	
Baseline LVEF [%]											0.0176
<50	988	69	7.0	995	105	10.6	0.0050	1.51 (1.13, 2.02)	1.57 (1.14, 2.16)	0.04 (0.01, 0.06)	
50 to <60	1030	123	11.9	1028	116	11.3	0.6415	0.94 (0.74, 1.20)	0.94 (0.72, 1.23)	-0.01 (-0.03, 0.02)	
>=60	971	94	9.7	973	135	13.9	0.0041	1.43 (1.12, 1.84)	1.50 (1.14, 1.99)	0.04 (0.01, 0.07)	
Baseline NT-proBNP [pg/mL] (</>=median by atrial fibrillation/flutter status)											0.8164
< median	1507	138	9.2	1476	165	11.2	0.0676	1.22 (0.99, 1.51)	1.25 (0.98, 1.58)	0.02 (0.00, 0.04)	
>= median	1475	147	10.0	1516	191	12.6	0.0230	1.26 (1.03, 1.55)	1.30 (1.04, 1.64)	0.03 (0.00, 0.05)	
Baseline uric acid [mg/dL] (tertiles)											0.8841
<T1	975	75	7.7	963	91	9.4	0.1669	1.23 (0.92, 1.65)	1.25 (0.91, 1.72)	0.02 (-0.01, 0.04)	
>=T1 and <T2	966	86	8.9	1032	122	11.8	0.0328	1.33 (1.02, 1.72)	1.37 (1.03, 1.84)	0.03 (0.00, 0.06)	
>=T2	1016	119	11.7	970	139	14.3	0.0829	1.22 (0.97, 1.54)	1.26 (0.97, 1.64)	0.03 (0.00, 0.06)	
Baseline use of MRA											0.0095
No	1865	155	8.3	1878	228	12.1	0.0001	1.46 (1.20, 1.77)	1.52 (1.23, 1.89)	0.04 (0.02, 0.06)	
Yes	1124	131	11.7	1118	128	11.4	0.8789	0.98 (0.78, 1.24)	0.98 (0.76, 1.27)	0.00 (-0.03, 0.02)	
Baseline use of ACE-inhibitor, ARB or ARNi											0.5303
No	586	56	9.6	568	61	10.7	0.5056	1.12 (0.80, 1.59)	1.14 (0.78, 1.67)	0.01 (-0.02, 0.05)	
Yes	2403	230	9.6	2428	295	12.1	0.0040	1.27 (1.08, 1.49)	1.31 (1.09, 1.57)	0.03 (0.01, 0.04)	

Analysis is based on study 1245.110.
^ Patients with NYHA class I are counted in subgroup NYHA class II.
*** Confirmed hypoglycaemic AEs are defined by a glucose concentration <=70 mg/dL (3.9 mmol/L) or requiring assistance.
Risk ratios and odds ratios with confidence intervals (CIs) are estimated by Cochran-Mantel-Haenszel method. For risk differences standard Wald asymptotic confidence limits are calculated. A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied in case of any zero cells in contingency table.
Only treatment emergent AEs are displayed (onset between first dose until treatment stop +7 days).
MedDRA version: 23.1. * Chi-square test for treatment effect ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction).

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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 overall and by subgroup - TS
User-defined AE category: Hypotension (BIcMQ based)

Subgroup	Placebo			Empa 10mg			Empa 10mg vs Placebo						
Category	N	n	%	N	n	%	p-value *	Risk ratio (95% CI)	Odds ratio (95% CI)	Risk diff. (95% CI)	p-value **
Overall	2989	257	8.6	2996	311	10.4	0.0187	1.21 (1.03, 1.41)	1.23 (1.04, 1.46)	0.02 (0.00, 0.03)	
Sex											0.3164
Male	1653	149	9.0	1658	168	10.1	0.2740	1.12 (0.91, 1.39)	1.14 (0.90, 1.44)	0.01 (-0.01, 0.03)	
Female	1336	108	8.1	1338	143	10.7	0.0210	1.32 (1.04, 1.68)	1.36 (1.05, 1.77)	0.03 (0.00, 0.05)	
Age [years]											0.2399
<70	1084	65	6.0	1066	90	8.4	0.0283	1.41 (1.04, 1.92)	1.45 (1.04, 2.01)	0.02 (0.00, 0.05)	
>=70	1905	192	10.1	1930	221	11.5	0.1705	1.14 (0.95, 1.36)	1.15 (0.94, 1.42)	0.01 (-0.01, 0.03)	
Region											0.3882
North America	359	45	12.5	359	60	16.7	0.1131	1.33 (0.93, 1.91)	1.40 (0.92, 2.13)	0.04 (-0.01, 0.09)	
Latin America	757	54	7.1	758	68	9.0	0.1888	1.26 (0.89, 1.77)	1.28 (0.88, 1.86)	0.02 (-0.01, 0.05)	
Europe	1341	120	8.9	1346	126	9.4	0.7108	1.05 (0.82, 1.33)	1.05 (0.81, 1.37)	0.00 (-0.02, 0.03)	
Asia	343	23	6.7	343	28	8.2	0.4668	1.22 (0.72, 2.07)	1.24 (0.70, 2.19)	0.01 (-0.02, 0.05)	
Other	189	15	7.9	190	29	15.3	0.0260	1.92 (1.07, 3.47)	2.09 (1.08, 4.04)	0.07 (0.01, 0.14)	
OECD member											0.1908
No	847	57	6.7	868	85	9.8	0.0214	1.46 (1.05, 2.01)	1.50 (1.06, 2.13)	0.03 (0.00, 0.06)	
Yes	2142	200	9.3	2128	226	10.6	0.1618	1.14 (0.95, 1.36)	1.15 (0.94, 1.41)	0.01 (-0.01, 0.03)	
Baseline NYHA											0.2217
II^	2450	199	8.1	2435	225	9.2	0.1653	1.14 (0.95, 1.37)	1.15 (0.94, 1.41)	0.01 (0.00, 0.03)	
III/IV	539	58	10.8	561	86	15.3	0.0247	1.42 (1.04, 1.94)	1.50 (1.05, 2.14)	0.05 (0.01, 0.09)	
Baseline Diabetes Status											0.4372
Diabetic	1471	122	8.3	1465	137	9.4	0.3122	1.13 (0.89, 1.42)	1.14 (0.88, 1.47)	0.01 (-0.01, 0.03)	
Non-Diabetic	1518	135	8.9	1531	174	11.4	0.0237	1.28 (1.03, 1.58)	1.31 (1.04, 1.66)	0.02 (0.00, 0.05)	

Analysis is based on study 1245.110.
^ Patients with NYHA class I are counted in subgroup NYHA class II.
*** Confirmed hypoglycaemic AEs are defined by a glucose concentration <=70 mg/dL (3.9 mmol/L) or requiring assistance.
Risk ratios and odds ratios with confidence intervals (CIs) are estimated by Cochran-Mantel-Haenszel method. For risk differences standard Wald asymptotic confidence limits are calculated. A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied in case of any zero cells in contingency table.
Only treatment emergent AEs are displayed (onset between first dose until treatment stop +7 days).
MedDRA version: 23.1. * Chi-square test for treatment effect ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction).

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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 overall and by subgroup - TS
User-defined AE category: Hypotension (BIcMQ based)

Subgroup	Placebo			Empa 10mg			Empa 10mg vs Placebo						
Category	N	n	%	N	n	%	p-value *	Risk ratio (95% CI)		Odds ratio (95% CI)		Risk diff. (95% CI)	p-value **
Baseline Diabetes Status													0.6519
Diabetic	1471	122	8.3	1465	137	9.4	0.3122	1.13 (0.89,	1.42)	1.14 (0.88,	1.47)	0.01 (-0.01, 0.03)	
Pre-Diabetes	979	79	8.1	1001	108	10.8	0.0385	1.34 (1.01,	1.76)	1.38 (1.02,	1.87)	0.03 (0.00, 0.05)	
Normal (no pre-diabetes)	539	56	10.4	530	66	12.5	0.2888	1.20 (0.86,	1.68)	1.23 (0.84,	1.79)	0.02 (-0.02, 0.06)	
Baseline BMI [kg/m²]													0.8653
<30	1641	134	8.2	1654	161	9.7	0.1149	1.19 (0.96,	1.48)	1.21 (0.95,	1.54)	0.02 (0.00, 0.04)	
>=30	1348	123	9.1	1342	150	11.2	0.0779	1.22 (0.98,	1.54)	1.25 (0.97,	1.61)	0.02 (0.00, 0.04)	
Baseline eGFR (CKD-EPI) [mL/min/1.73m²]													0.1960
>=60	1505	112	7.4	1493	118	7.9	0.6348	1.06 (0.83,	1.36)	1.07 (0.82,	1.40)	0.00 (-0.01, 0.02)	
<60	1482	145	9.8	1503	193	12.8	0.0084	1.31 (1.07,	1.61)	1.36 (1.08,	1.71)	0.03 (0.01, 0.05)	
History of HHF (in the last 12 months)													0.4948
No	2320	201	8.7	2297	233	10.1	0.0849	1.17 (0.98,	1.40)	1.19 (0.98,	1.45)	0.01 (0.00, 0.03)	
Yes	669	56	8.4	699	78	11.2	0.0829	1.33 (0.96,	1.85)	1.37 (0.96,	1.97)	0.03 (0.00, 0.06)	
Baseline SBP (</>= median)													0.9769
< median	1474	145	9.8	1496	177	11.8	0.0805	1.20 (0.98,	1.48)	1.23 (0.97,	1.55)	0.02 (0.00, 0.04)	
>= median	1515	112	7.4	1500	134	8.9	0.1223	1.21 (0.95,	1.54)	1.23 (0.95,	1.60)	0.02 (0.00, 0.03)	
History of atrial fibrillation or atrial flutter													0.0344
No	1426	86	6.0	1417	129	9.1	0.0019	1.51 (1.16,	1.96)	1.56 (1.18,	2.07)	0.03 (0.01, 0.05)	
Yes	1558	170	10.9	1575	182	11.6	0.5681	1.06 (0.87,	1.29)	1.07 (0.85,	1.33)	0.01 (-0.02, 0.03)	

Analysis is based on study 1245.110.
^ Patients with NYHA class I are counted in subgroup NYHA class II.
*** Confirmed hypoglycaemic AEs are defined by a glucose concentration <=70 mg/dL (3.9 mmol/L) or requiring assistance.
Risk ratios and odds ratios with confidence intervals (CIs) are estimated by Cochran-Mantel-Haenszel method. For risk differences standard Wald asymptotic confidence limits are calculated. A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied in case of any zero cells in contingency table.
Only treatment emergent AEs are displayed (onset between first dose until treatment stop +7 days).
MedDRA version: 23.1. * Chi-square test for treatment effect ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction).

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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 overall and by subgroup - TS
User-defined AE category: Hypotension (BIcMQ based)

Subgroup	Placebo			Empa 10mg			Empa 10mg vs Placebo						
Category	N	n	%	N	n	%	p-value *	Risk ratio (95% CI)	Odds ratio (95% CI)	Risk diff. (95% CI)	p-value **
Baseline LVEF [%]											0.2986
< 50	988	66	6.7	995	92	9.2	0.0349	1.38 (1.02, 1.88)	1.42 (1.02, 1.98)	0.03 (0.00, 0.05)	
>= 50	2001	191	9.5	2001	219	10.9	0.1444	1.15 (0.95, 1.38)	1.16 (0.95, 1.43)	0.01 (0.00, 0.03)	
Baseline LVEF [%]											0.0276
<50	988	66	6.7	995	92	9.2	0.0349	1.38 (1.02, 1.88)	1.42 (1.02, 1.98)	0.03 (0.00, 0.05)	
50 to <60	1030	113	11.0	1028	104	10.1	0.5282	0.92 (0.72, 1.19)	0.91 (0.69, 1.21)	-0.01 (-0.04, 0.02)	
>=60	971	78	8.0	973	115	11.8	0.0053	1.47 (1.12, 1.93)	1.53 (1.13, 2.08)	0.04 (0.01, 0.06)	
Baseline NT-proBNP [pg/mL] (</>=median by atrial fibrillation/flutter status)											0.6118
< median	1507	126	8.4	1476	143	9.7	0.2057	1.16 (0.92, 1.46)	1.18 (0.91, 1.51)	0.01 (-0.01, 0.03)	
>= median	1475	130	8.8	1516	168	11.1	0.0384	1.26 (1.01, 1.56)	1.29 (1.01, 1.64)	0.02 (0.00, 0.04)	
Baseline uric acid [mg/dL] (tertiles)											0.9886
<T1	975	67	6.9	963	79	8.2	0.2667	1.19 (0.87, 1.63)	1.21 (0.86, 1.70)	0.01 (-0.01, 0.04)	
>=T1 and <T2	966	80	8.3	1032	105	10.2	0.1447	1.23 (0.93, 1.62)	1.25 (0.92, 1.70)	0.02 (-0.01, 0.04)	
>=T2	1016	105	10.3	970	123	12.7	0.1012	1.23 (0.96, 1.57)	1.26 (0.96, 1.66)	0.02 (0.00, 0.05)	
Baseline use of MRA											0.0186
No	1865	139	7.5	1878	198	10.5	0.0010	1.41 (1.15, 1.74)	1.46 (1.17, 1.84)	0.03 (0.01, 0.05)	
Yes	1124	118	10.5	1118	113	10.1	0.7608	0.96 (0.75, 1.23)	0.96 (0.73, 1.26)	0.00 (-0.03, 0.02)	
Baseline use of ACE-inhibitor, ARB or ARNi											0.4117
No	586	52	8.9	568	53	9.3	0.7871	1.05 (0.73, 1.51)	1.06 (0.71, 1.58)	0.00 (-0.03, 0.04)	
Yes	2403	205	8.5	2428	258	10.6	0.0134	1.25 (1.05, 1.48)	1.27 (1.05, 1.55)	0.02 (0.00, 0.04)	

Analysis is based on study 1245.110.
^ Patients with NYHA class I are counted in subgroup NYHA class II.
*** Confirmed hypoglycaemic AEs are defined by a glucose concentration <=70 mg/dL (3.9 mmol/L) or requiring assistance.
Risk ratios and odds ratios with confidence intervals (CIs) are estimated by Cochran-Mantel-Haenszel method. For risk differences standard Wald asymptotic confidence limits are calculated. A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied in case of any zero cells in contingency table.
Only treatment emergent AEs are displayed (onset between first dose until treatment stop +7 days).
MedDRA version: 23.1. * Chi-square test for treatment effect ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction).

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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 overall and by subgroup - TS
User-defined AE category: Symptomatic hypotension (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	2989	156	5.2	2996	197	6.6	0.0260	1.26 (1.03, 1.54)	1.28 (1.03, 1.59)	0.01 (0.00, 0.03)	
Sex											0.5734
Male	1653	90	5.4	1658	108	6.5	0.1945	1.20 (0.91, 1.57)	1.21 (0.91, 1.61)	0.01 (-0.01, 0.03)	
Female	1336	66	4.9	1338	89	6.7	0.0583	1.35 (0.99, 1.83)	1.37 (0.99, 1.90)	0.02 (0.00, 0.03)	
Age [years]											0.4492
<70	1084	39	3.6	1066	55	5.2	0.0766	1.43 (0.96, 2.14)	1.46 (0.96, 2.22)	0.02 (0.00, 0.03)	
>=70	1905	117	6.1	1930	142	7.4	0.1336	1.20 (0.95, 1.52)	1.21 (0.94, 1.56)	0.01 (0.00, 0.03)	
Region											0.2052
North America	359	24	6.7	359	35	9.7	0.1350	1.46 (0.89, 2.40)	1.51 (0.88, 2.59)	0.03 (-0.01, 0.07)	
Latin America	757	35	4.6	758	50	6.6	0.0952	1.43 (0.94, 2.17)	1.46 (0.93, 2.27)	0.02 (0.00, 0.04)	
Europe	1341	78	5.8	1346	78	5.8	0.9809	1.00 (0.73, 1.35)	1.00 (0.72, 1.38)	0.00 (-0.02, 0.02)	
Asia	343	10	2.9	343	12	3.5	0.6647	1.20 (0.53, 2.74)	1.21 (0.51, 2.83)	0.01 (-0.02, 0.03)	
Other	189	9	4.8	190	22	11.6	0.0155	2.43 (1.15, 5.14)	2.62 (1.17, 5.85)	0.07 (0.01, 0.12)	
OECD member											0.1096
No	847	35	4.1	868	60	6.9	0.0119	1.67 (1.11, 2.51)	1.72 (1.12, 2.64)	0.03 (0.01, 0.05)	
Yes	2142	121	5.6	2128	137	6.4	0.2793	1.14 (0.90, 1.44)	1.15 (0.89, 1.48)	0.01 (-0.01, 0.02)	
Baseline NYHA											0.2346
II^	2450	117	4.8	2435	135	5.5	0.2246	1.16 (0.91, 1.48)	1.17 (0.91, 1.51)	0.01 (0.00, 0.02)	
III/IV	539	39	7.2	561	62	11.1	0.0285	1.53 (1.04, 2.24)	1.59 (1.05, 2.42)	0.04 (0.00, 0.07)	
Baseline Diabetes Status											0.2875
Diabetic	1471	78	5.3	1465	87	5.9	0.4543	1.12 (0.83, 1.51)	1.13 (0.82, 1.54)	0.01 (-0.01, 0.02)	
Non-Diabetic	1518	78	5.1	1531	110	7.2	0.0188	1.40 (1.06, 1.85)	1.43 (1.06, 1.93)	0.02 (0.00, 0.04)	

Analysis is based on study 1245.110.
^ Patients with NYHA class I are counted in subgroup NYHA class II.
*** Confirmed hypoglycaemic AEs are defined by a glucose concentration <=70 mg/dL (3.9 mmol/L) or requiring assistance.
Risk ratios and odds ratios with confidence intervals (CIs) are estimated by Cochran-Mantel-Haenszel method. For risk differences standard Wald asymptotic confidence limits are calculated. A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied in case of any zero cells in contingency table.
Only treatment emergent AEs are displayed (onset between first dose until treatment stop +7 days).
MedDRA version: 23.1. * Chi-square test for treatment effect ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction).

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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 overall and by subgroup - TS
User-defined AE category: Symptomatic hypotension (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 Diabetes Status											0.5557
Diabetic	1471	78	5.3	1465	87	5.9	0.4543	1.12 (0.83, 1.51)	1.13 (0.82, 1.54)	0.01 (-0.01, 0.02)	
Pre-Diabetes	979	50	5.1	1001	70	7.0	0.0787	1.37 (0.96, 1.95)	1.40 (0.96, 2.03)	0.02 (0.00, 0.04)	
Normal (no pre-diabetes)	539	28	5.2	530	40	7.5	0.1151	1.45 (0.91, 2.32)	1.49 (0.90, 2.45)	0.02 (-0.01, 0.05)	
Baseline BMI [kg/m²]											0.5996
<30	1641	80	4.9	1654	107	6.5	0.0480	1.33 (1.00, 1.76)	1.35 (1.00, 1.82)	0.02 (0.00, 0.03)	
>=30	1348	76	5.6	1342	90	6.7	0.2495	1.19 (0.88, 1.60)	1.20 (0.88, 1.65)	0.01 (-0.01, 0.03)	
Baseline eGFR (CKD-EPI) [mL/min/1.73m²]											0.0402
>=60	1505	71	4.7	1493	68	4.6	0.8319	0.97 (0.70, 1.34)	0.96 (0.69, 1.35)	0.00 (-0.02, 0.01)	
<60	1482	85	5.7	1503	129	8.6	0.0026	1.50 (1.15, 1.95)	1.54 (1.16, 2.05)	0.03 (0.01, 0.05)	
History of HHF (in the last 12 months)											0.2974
No	2320	125	5.4	2297	147	6.4	0.1444	1.19 (0.94, 1.50)	1.20 (0.94, 1.54)	0.01 (0.00, 0.02)	
Yes	669	31	4.6	699	50	7.2	0.0484	1.54 (1.00, 2.39)	1.59 (1.00, 2.51)	0.03 (0.00, 0.05)	
Baseline SBP (</>= median)											0.6794
< median	1474	86	5.8	1496	114	7.6	0.0522	1.31 (1.00, 1.71)	1.33 (1.00, 1.78)	0.02 (0.00, 0.04)	
>= median	1515	70	4.6	1500	83	5.5	0.2535	1.20 (0.88, 1.63)	1.21 (0.87, 1.68)	0.01 (-0.01, 0.02)	
History of atrial fibrillation or atrial flutter											0.0330
No	1426	48	3.4	1417	81	5.7	0.0026	1.70 (1.20, 2.41)	1.74 (1.21, 2.51)	0.02 (0.01, 0.04)	
Yes	1558	108	6.9	1575	116	7.4	0.6380	1.06 (0.83, 1.37)	1.07 (0.81, 1.40)	0.00 (-0.01, 0.02)	

Analysis is based on study 1245.110.
^ Patients with NYHA class I are counted in subgroup NYHA class II.
*** Confirmed hypoglycaemic AEs are defined by a glucose concentration <=70 mg/dL (3.9 mmol/L) or requiring assistance.
Risk ratios and odds ratios with confidence intervals (CIs) are estimated by Cochran-Mantel-Haenszel method. For risk differences standard Wald asymptotic confidence limits are calculated. A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied in case of any zero cells in contingency table.
Only treatment emergent AEs are displayed (onset between first dose until treatment stop +7 days).
MedDRA version: 23.1. * Chi-square test for treatment effect ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction).

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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 overall and by subgroup - TS
User-defined AE category: Symptomatic hypotension (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 LVEF [%]											0.3896
< 50	988	44	4.5	995	64	6.4	0.0522	1.44 (0.99, 2.10)	1.47 (0.99, 2.19)	0.02 (0.00, 0.04)	
>= 50	2001	112	5.6	2001	133	6.6	0.1661	1.19 (0.93, 1.52)	1.20 (0.93, 1.56)	0.01 (0.00, 0.03)	
Baseline LVEF [%]											0.1597
<50	988	44	4.5	995	64	6.4	0.0522	1.44 (0.99, 2.10)	1.47 (0.99, 2.19)	0.02 (0.00, 0.04)	
50 to <60	1030	70	6.8	1028	69	6.7	0.9394	0.99 (0.72, 1.36)	0.99 (0.70, 1.39)	0.00 (-0.02, 0.02)	
>=60	971	42	4.3	973	64	6.6	0.0288	1.52 (1.04, 2.22)	1.56 (1.04, 2.32)	0.02 (0.00, 0.04)	
Baseline NT-proBNP [pg/mL] (</>=median by atrial fibrillation/flutter status)											0.5325
< median	1507	79	5.2	1476	91	6.2	0.2769	1.18 (0.88, 1.58)	1.19 (0.87, 1.62)	0.01 (-0.01, 0.03)	
>= median	1475	77	5.2	1516	106	7.0	0.0432	1.34 (1.01, 1.78)	1.36 (1.01, 1.85)	0.02 (0.00, 0.03)	
Baseline uric acid [mg/dL] (tertiles)											0.9038
<T1	975	34	3.5	963	47	4.9	0.1254	1.40 (0.91, 2.16)	1.42 (0.90, 2.23)	0.01 (0.00, 0.03)	
>=T1 and <T2	966	50	5.2	1032	67	6.5	0.2105	1.25 (0.88, 1.79)	1.27 (0.87, 1.85)	0.01 (-0.01, 0.03)	
>=T2	1016	68	6.7	970	81	8.4	0.1610	1.25 (0.91, 1.70)	1.27 (0.91, 1.78)	0.02 (-0.01, 0.04)	
Baseline use of MRA											0.3972
No	1865	87	4.7	1878	119	6.3	0.0249	1.36 (1.04, 1.78)	1.38 (1.04, 1.84)	0.02 (0.00, 0.03)	
Yes	1124	69	6.1	1118	78	7.0	0.4229	1.14 (0.83, 1.55)	1.15 (0.82, 1.60)	0.01 (-0.01, 0.03)	
Baseline use of ACE-inhibitor, ARB or ARNi											0.2458
No	586	31	5.3	568	29	5.1	0.8878	0.97 (0.59, 1.58)	0.96 (0.57, 1.62)	0.00 (-0.03, 0.02)	
Yes	2403	125	5.2	2428	168	6.9	0.0124	1.33 (1.06, 1.67)	1.35 (1.07, 1.72)	0.02 (0.00, 0.03)	

Analysis is based on study 1245.110.
^ Patients with NYHA class I are counted in subgroup NYHA class II.
*** Confirmed hypoglycaemic AEs are defined by a glucose concentration <=70 mg/dL (3.9 mmol/L) or requiring assistance.
Risk ratios and odds ratios with confidence intervals (CIs) are estimated by Cochran-Mantel-Haenszel method. For risk differences standard Wald asymptotic confidence limits are calculated. A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied in case of any zero cells in contingency table.
Only treatment emergent AEs are displayed (onset between first dose until treatment stop +7 days).
MedDRA version: 23.1. * Chi-square test for treatment effect ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction).

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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 overall and by subgroup - TS
User-defined AE category: Allergic skin reactions (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	2989	54	1.8	2996	78	2.6	0.0358	1.44 (1.02, 2.03)	1.45 (1.02, 2.06)	0.01 (0.00, 0.02)	
Sex											0.2818
Male	1653	30	1.8	1658	36	2.2	0.4632	1.20 (0.74, 1.93)	1.20 (0.74, 1.96)	0.00 (-0.01, 0.01)	
Female	1336	24	1.8	1338	42	3.1	0.0253	1.75 (1.06, 2.87)	1.77 (1.07, 2.94)	0.01 (0.00, 0.03)	
Age [years]											0.5436
<70	1084	15	1.4	1066	25	2.3	0.0990	1.69 (0.90, 3.20)	1.71 (0.90, 3.26)	0.01 (0.00, 0.02)	
>=70	1905	39	2.0	1930	53	2.7	0.1573	1.34 (0.89, 2.02)	1.35 (0.89, 2.05)	0.01 (0.00, 0.02)	
Region											0.5613
North America	359	12	3.3	359	14	3.9	0.6895	1.17 (0.55, 2.49)	1.17 (0.54, 2.57)	0.01 (-0.02, 0.03)	
Latin America	757	7	0.9	758	13	1.7	0.1778	1.85 (0.74, 4.62)	1.87 (0.74, 4.71)	0.01 (0.00, 0.02)	
Europe	1341	14	1.0	1346	29	2.2	0.0218	2.06 (1.10, 3.89)	2.09 (1.10, 3.97)	0.01 (0.00, 0.02)	
Asia	343	16	4.7	343	17	5.0	0.8584	1.06 (0.55, 2.07)	1.07 (0.53, 2.15)	0.00 (-0.03, 0.03)	
Other	189	5	2.6	190	5	2.6	0.9933	0.99 (0.29, 3.38)	0.99 (0.28, 3.49)	0.00 (-0.03, 0.03)	
OECD member											0.9592
No	847	11	1.3	868	16	1.8	0.3650	1.42 (0.66, 3.04)	1.43 (0.66, 3.09)	0.01 (-0.01, 0.02)	
Yes	2142	43	2.0	2128	62	2.9	0.0559	1.45 (0.99, 2.13)	1.46 (0.99, 2.17)	0.01 (0.00, 0.02)	
Baseline NYHA											0.7907
II^	2450	43	1.8	2435	60	2.5	0.0846	1.40 (0.95, 2.07)	1.41 (0.95, 2.10)	0.01 (0.00, 0.02)	
III/IV	539	11	2.0	561	18	3.2	0.2269	1.57 (0.75, 3.30)	1.59 (0.74, 3.40)	0.01 (-0.01, 0.03)	
Baseline Diabetes Status											0.3426
Diabetic	1471	22	1.5	1465	38	2.6	0.0355	1.73 (1.03, 2.92)	1.75 (1.03, 2.98)	0.01 (0.00, 0.02)	
Non-Diabetic	1518	32	2.1	1531	40	2.6	0.3589	1.24 (0.78, 1.96)	1.25 (0.78, 1.99)	0.01 (-0.01, 0.02)	

Analysis is based on study 1245.110.
^ Patients with NYHA class I are counted in subgroup NYHA class II.
*** Confirmed hypoglycaemic AEs are defined by a glucose concentration <=70 mg/dL (3.9 mmol/L) or requiring assistance.
Risk ratios and odds ratios with confidence intervals (CIs) are estimated by Cochran-Mantel-Haenszel method. For risk differences standard Wald asymptotic confidence limits are calculated. A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied in case of any zero cells in contingency table.
Only treatment emergent AEs are displayed (onset between first dose until treatment stop +7 days).
MedDRA version: 23.1. * Chi-square test for treatment effect ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction).

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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 overall and by subgroup - TS
User-defined AE category: Allergic skin reactions (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 Diabetes Status											0.6317
Diabetic	1471	22	1.5	1465	38	2.6	0.0355	1.73 (1.03, 2.92)	1.75 (1.03, 2.98)	0.01 (0.00, 0.02)	
Pre-Diabetes	979	20	2.0	1001	26	2.6	0.4128	1.27 (0.71, 2.26)	1.28 (0.71, 2.31)	0.01 (-0.01, 0.02)	
Normal (no pre-diabetes)	539	12	2.2	530	14	2.6	0.6595	1.19 (0.55, 2.54)	1.19 (0.55, 2.60)	0.00 (-0.01, 0.02)	
Baseline BMI [kg/m²]											0.1124
<30	1641	35	2.1	1654	40	2.4	0.5827	1.13 (0.72, 1.78)	1.14 (0.72, 1.80)	0.00 (-0.01, 0.01)	
>=30	1348	19	1.4	1342	38	2.8	0.0104	2.01 (1.16, 3.47)	2.04 (1.17, 3.55)	0.01 (0.00, 0.03)	
Baseline eGFR (CKD-EPI) [mL/min/1.73m²]											0.8688
>=60	1505	26	1.7	1493	36	2.4	0.1884	1.40 (0.85, 2.30)	1.41 (0.84, 2.34)	0.01 (0.00, 0.02)	
<60	1482	28	1.9	1503	42	2.8	0.1023	1.48 (0.92, 2.37)	1.49 (0.92, 2.42)	0.01 (0.00, 0.02)	
History of HHF (in the last 12 months)											0.5169
No	2320	42	1.8	2297	56	2.4	0.1391	1.35 (0.91, 2.00)	1.36 (0.90, 2.03)	0.01 (0.00, 0.01)	
Yes	669	12	1.8	699	22	3.1	0.1079	1.75 (0.88, 3.52)	1.78 (0.87, 3.62)	0.01 (0.00, 0.03)	
Baseline SBP (</>= median)											0.3742
< median	1474	26	1.8	1496	32	2.1	0.4601	1.21 (0.73, 2.02)	1.22 (0.72, 2.05)	0.00 (-0.01, 0.01)	
>= median	1515	28	1.8	1500	46	3.1	0.0306	1.66 (1.04, 2.64)	1.68 (1.04, 2.70)	0.01 (0.00, 0.02)	
History of atrial fibrillation or atrial flutter											0.1748
No	1426	23	1.6	1417	24	1.7	0.8658	1.05 (0.60, 1.85)	1.05 (0.59, 1.87)	0.00 (-0.01, 0.01)	
Yes	1558	31	2.0	1575	54	3.4	0.0132	1.72 (1.11, 2.67)	1.75 (1.12, 2.74)	0.01 (0.00, 0.03)	

Analysis is based on study 1245.110.
^ Patients with NYHA class I are counted in subgroup NYHA class II.
*** Confirmed hypoglycaemic AEs are defined by a glucose concentration <=70 mg/dL (3.9 mmol/L) or requiring assistance.
Risk ratios and odds ratios with confidence intervals (CIs) are estimated by Cochran-Mantel-Haenszel method. For risk differences standard Wald asymptotic confidence limits are calculated. A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied in case of any zero cells in contingency table.
Only treatment emergent AEs are displayed (onset between first dose until treatment stop +7 days).
MedDRA version: 23.1. * Chi-square test for treatment effect ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction).

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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 overall and by subgroup - TS
User-defined AE category: Allergic skin reactions (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 LVEF [%]											0.8986
< 50	988	15	1.5	995	21	2.1	0.3232	1.39 (0.72, 2.68)	1.40 (0.72, 2.73)	0.01 (-0.01, 0.02)	
>= 50	2001	39	1.9	2001	57	2.8	0.0629	1.46 (0.98, 2.19)	1.48 (0.98, 2.23)	0.01 (0.00, 0.02)	
Baseline LVEF [%]											0.9904
<50	988	15	1.5	995	21	2.1	0.3232	1.39 (0.72, 2.68)	1.40 (0.72, 2.73)	0.01 (-0.01, 0.02)	
50 to <60	1030	16	1.6	1028	23	2.2	0.2552	1.44 (0.77, 2.71)	1.45 (0.76, 2.76)	0.01 (0.00, 0.02)	
>=60	971	23	2.4	973	34	3.5	0.1413	1.48 (0.88, 2.49)	1.49 (0.87, 2.55)	0.01 (0.00, 0.03)	
Baseline NT-proBNP [pg/mL] (</>=median by atrial fibrillation/flutter status)											0.8891
< median	1507	29	1.9	1476	40	2.7	0.1535	1.41 (0.88, 2.26)	1.42 (0.88, 2.30)	0.01 (0.00, 0.02)	
>= median	1475	25	1.7	1516	38	2.5	0.1222	1.48 (0.90, 2.44)	1.49 (0.90, 2.48)	0.01 (0.00, 0.02)	
Baseline uric acid [mg/dL] (tertiles)											0.1851
<T1	975	19	1.9	963	17	1.8	0.7650	0.91 (0.47, 1.73)	0.90 (0.47, 1.75)	0.00 (-0.01, 0.01)	
>=T1 and <T2	966	17	1.8	1032	28	2.7	0.1512	1.54 (0.85, 2.80)	1.56 (0.85, 2.86)	0.01 (0.00, 0.02)	
>=T2	1016	17	1.7	970	33	3.4	0.0140	2.03 (1.14, 3.63)	2.07 (1.15, 3.74)	0.02 (0.00, 0.03)	
Baseline use of MRA											0.0770
No	1865	41	2.2	1878	48	2.6	0.4729	1.16 (0.77, 1.76)	1.17 (0.77, 1.78)	0.00 (-0.01, 0.01)	
Yes	1124	13	1.2	1118	30	2.7	0.0084	2.32 (1.22, 4.42)	2.36 (1.22, 4.54)	0.02 (0.00, 0.03)	
Baseline use of ACE-inhibitor, ARB or ARNi											0.0480
No	586	10	1.7	568	26	4.6	0.0050	2.68 (1.31, 5.51)	2.76 (1.32, 5.78)	0.03 (0.01, 0.05)	
Yes	2403	44	1.8	2428	52	2.1	0.4392	1.17 (0.79, 1.74)	1.17 (0.78, 1.76)	0.00 (0.00, 0.01)	

Analysis is based on study 1245.110.
^ Patients with NYHA class I are counted in subgroup NYHA class II.
*** Confirmed hypoglycaemic AEs are defined by a glucose concentration <=70 mg/dL (3.9 mmol/L) or requiring assistance.
Risk ratios and odds ratios with confidence intervals (CIs) are estimated by Cochran-Mantel-Haenszel method. For risk differences standard Wald asymptotic confidence limits are calculated. A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied in case of any zero cells in contingency table.
Only treatment emergent AEs are displayed (onset between first dose until treatment stop +7 days).
MedDRA version: 23.1. * Chi-square test for treatment effect ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction).

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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 overall and by subgroup - TS
User-defined AE category: Increased urination (project-defined PTs)

Subgroup	Placebo			Empa 10mg			Empa 10mg vs Placebo					
Category	N	n	%	N	n	%	p-value *	Risk ratio (95% CI)	Odds ratio (95% CI)	Risk diff. (95% CI)	p-value **
Overall	2989	19	0.6	2996	29	1.0	0.1496	1.52 (0.86, 2.71)	1.53 (0.85, 2.73)	0.00 (0.00, 0.01)	
Sex											0.2990
Male	1653	11	0.7	1658	21	1.3	0.0771	1.90 (0.92, 3.93)	1.91 (0.92, 3.98)	0.01 (0.00, 0.01)	
Female	1336	8	0.6	1338	8	0.6	0.9976	1.00 (0.38, 2.65)	1.00 (0.37, 2.67)	0.00 (-0.01, 0.01)	
Age [years]											0.3690
<70	1084	7	0.6	1066	7	0.7	0.9749	1.02 (0.36, 2.89)	1.02 (0.36, 2.91)	0.00 (-0.01, 0.01)	
>=70	1905	12	0.6	1930	22	1.1	0.0921	1.81 (0.90, 3.65)	1.82 (0.90, 3.69)	0.01 (0.00, 0.01)	
Region											0.8074
North America	359	4	1.1	359	3	0.8	0.7041	0.75 (0.17, 3.33)	0.75 (0.17, 3.37)	0.00 (-0.02, 0.01)	
Latin America	757	2	0.3	758	2	0.3	0.9989	1.00 (0.14, 7.07)	1.00 (0.14, 7.11)	0.00 (-0.01, 0.01)	
Europe	1341	8	0.6	1346	15	1.1	0.1451	1.87 (0.79, 4.39)	1.88 (0.79, 4.44)	0.01 (0.00, 0.01)	
Asia	343	4	1.2	343	6	1.7	0.5240	1.50 (0.43, 5.27)	1.51 (0.42, 5.40)	0.01 (-0.01, 0.02)	
Other	189	1	0.5	190	3	1.6	0.3173	2.98 (0.31, 28.43)	3.02 (0.31, 29.26)	0.01 (-0.01, 0.03)	
OECD member											0.1467
No	847	5	0.6	868	3	0.3	0.4572	0.59 (0.14, 2.44)	0.58 (0.14, 2.45)	0.00 (-0.01, 0.00)	
Yes	2142	14	0.7	2128	26	1.2	0.0540	1.87 (0.98, 3.57)	1.88 (0.98, 3.61)	0.01 (0.00, 0.01)	
Baseline NYHA											0.6556
II^	2450	15	0.6	2435	21	0.9	0.3067	1.41 (0.73, 2.73)	1.41 (0.73, 2.75)	0.00 (0.00, 0.01)	
III/IV	539	4	0.7	561	8	1.4	0.2750	1.92 (0.58, 6.34)	1.93 (0.58, 6.46)	0.01 (-0.01, 0.02)	
Baseline Diabetes Status											0.6660
Diabetic	1471	10	0.7	1465	17	1.2	0.1725	1.71 (0.78, 3.72)	1.72 (0.78, 3.76)	0.00 (0.00, 0.01)	
Non-Diabetic	1518	9	0.6	1531	12	0.8	0.5239	1.32 (0.56, 3.13)	1.32 (0.56, 3.15)	0.00 (0.00, 0.01)	

Analysis is based on study 1245.110.
^ Patients with NYHA class I are counted in subgroup NYHA class II.
*** Confirmed hypoglycaemic AEs are defined by a glucose concentration <=70 mg/dL (3.9 mmol/L) or requiring assistance.
Risk ratios and odds ratios with confidence intervals (CIs) are estimated by Cochran-Mantel-Haenszel method. For risk differences standard Wald asymptotic confidence limits are calculated. A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied in case of any zero cells in contingency table.
Only treatment emergent AEs are displayed (onset between first dose until treatment stop +7 days).
MedDRA version: 23.1. * Chi-square test for treatment effect ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction).

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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 overall and by subgroup - TS
User-defined AE category: Increased urination (project-defined PTs)

Subgroup	Placebo			Empa 10mg			Empa 10mg vs Placebo				
Category	N	n	%	N	n	%	p-value *	Risk ratio (95% CI)	Odds ratio (95% CI)	Risk diff. (95% CI)	p-value **
Baseline Diabetes Status											0.7578
Diabetic	1471	10	0.7	1465	17	1.2	0.1725	1.71 (0.78, 3.72)	1.72 (0.78, 3.76)	0.00 (0.00, 0.01)	
Pre-Diabetes	979	7	0.7	1001	8	0.8	0.8290	1.12 (0.41, 3.07)	1.12 (0.40, 3.10)	0.00 (-0.01, 0.01)	
Normal (no pre-diabetes)	539	2	0.4	530	4	0.8	0.4012	2.03 (0.37, 11.06)	2.04 (0.37, 11.20)	0.00 (-0.01, 0.01)	
Baseline BMI [kg/m²]											0.3219
<30	1641	7	0.4	1654	15	0.9	0.0905	2.13 (0.87, 5.20)	2.14 (0.87, 5.25)	0.00 (0.00, 0.01)	
>=30	1348	12	0.9	1342	14	1.0	0.6851	1.17 (0.54, 2.52)	1.17 (0.54, 2.55)	0.00 (-0.01, 0.01)	
Baseline eGFR (CKD-EPI) [mL/min/1.73m²]											0.9959
>=60	1505	6	0.4	1493	9	0.6	0.4283	1.51 (0.54, 4.24)	1.52 (0.54, 4.27)	0.00 (0.00, 0.01)	
<60	1482	13	0.9	1503	20	1.3	0.2361	1.52 (0.76, 3.04)	1.52 (0.76, 3.07)	0.00 (0.00, 0.01)	
History of HHF (in the last 12 months)											0.6065
No	2320	14	0.6	2297	19	0.8	0.3669	1.37 (0.69, 2.73)	1.37 (0.69, 2.75)	0.00 (0.00, 0.01)	
Yes	669	5	0.7	699	10	1.4	0.2251	1.91 (0.66, 5.57)	1.93 (0.66, 5.67)	0.01 (0.00, 0.02)	
Baseline SBP (</>= median)											0.6512
< median	1474	9	0.6	1496	12	0.8	0.5333	1.31 (0.56, 3.11)	1.32 (0.55, 3.13)	0.00 (0.00, 0.01)	
>= median	1515	10	0.7	1500	17	1.1	0.1678	1.72 (0.79, 3.74)	1.73 (0.79, 3.78)	0.00 (0.00, 0.01)	
History of atrial fibrillation or atrial flutter											0.0723
No	1426	11	0.8	1417	9	0.6	0.6639	0.82 (0.34, 1.98)	0.82 (0.34, 1.99)	0.00 (-0.01, 0.00)	
Yes	1558	8	0.5	1575	20	1.3	0.0245	2.47 (1.09, 5.60)	2.49 (1.09, 5.67)	0.01 (0.00, 0.01)	

Analysis is based on study 1245.110.
^ Patients with NYHA class I are counted in subgroup NYHA class II.
*** Confirmed hypoglycaemic AEs are defined by a glucose concentration <=70 mg/dL (3.9 mmol/L) or requiring assistance.
Risk ratios and odds ratios with confidence intervals (CIs) are estimated by Cochran-Mantel-Haenszel method. For risk differences standard Wald asymptotic confidence limits are calculated. A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied in case of any zero cells in contingency table.
Only treatment emergent AEs are displayed (onset between first dose until treatment stop +7 days).
MedDRA version: 23.1. * Chi-square test for treatment effect ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction).

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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 overall and by subgroup - TS
User-defined AE category: Increased urination (project-defined PTs)

Subgroup	Placebo			Empa 10mg			Empa 10mg vs Placebo				
Category	N	n	%	N	n	%	p-value *	Risk ratio (95% CI)	Odds ratio (95% CI)	Risk diff. (95% CI)	p-value **
Baseline LVEF [%]											0.6161
< 50	988	4	0.4	995	8	0.8	0.2518	1.99 (0.60, 6.57)	1.99 (0.60, 6.64)	0.00 (0.00, 0.01)	
>= 50	2001	15	0.7	2001	21	1.0	0.3151	1.40 (0.72, 2.71)	1.40 (0.72, 2.73)	0.00 (0.00, 0.01)	
Baseline LVEF [%]											0.3886
<50	988	4	0.4	995	8	0.8	0.2518	1.99 (0.60, 6.57)	1.99 (0.60, 6.64)	0.00 (0.00, 0.01)	
50 to <60	1030	4	0.4	1028	10	1.0	0.1068	2.50 (0.79, 7.96)	2.52 (0.79, 8.06)	0.01 (0.00, 0.01)	
>=60	971	11	1.1	973	11	1.1	0.9961	1.00 (0.43, 2.29)	1.00 (0.43, 2.31)	0.00 (-0.01, 0.01)	
Baseline NT-proBNP [pg/mL] (</>=median by atrial fibrillation/flutter status)											0.8958
< median	1507	11	0.7	1476	17	1.2	0.2323	1.58 (0.74, 3.36)	1.58 (0.74, 3.39)	0.00 (0.00, 0.01)	
>= median	1475	8	0.5	1516	12	0.8	0.4032	1.46 (0.60, 3.56)	1.46 (0.60, 3.59)	0.00 (0.00, 0.01)	
Baseline uric acid [mg/dL] (tertiles)											0.6094
<T1	975	8	0.8	963	11	1.1	0.4723	1.39 (0.56, 3.45)	1.40 (0.56, 3.49)	0.00 (-0.01, 0.01)	
>=T1 and <T2	966	6	0.6	1032	7	0.7	0.8738	1.09 (0.37, 3.24)	1.09 (0.37, 3.26)	0.00 (-0.01, 0.01)	
>=T2	1016	5	0.5	970	11	1.1	0.1097	2.30 (0.80, 6.61)	2.32 (0.80, 6.70)	0.01 (0.00, 0.01)	
Baseline use of MRA											0.0044
No	1865	18	1.0	1878	13	0.7	0.3570	0.72 (0.35, 1.46)	0.72 (0.35, 1.46)	0.00 (-0.01, 0.00)	
Yes	1124	1	0.1	1118	16	1.4	0.0002	16.09 (2.14,121.09)	16.30 (2.16,123.16)	0.01 (0.01, 0.02)	
Baseline use of ACE-inhibitor, ARB or ARNi											0.2174
No	586	3	0.5	568	9	1.6	0.0725	3.10 (0.84, 11.37)	3.13 (0.84, 11.62)	0.01 (0.00, 0.02)	
Yes	2403	16	0.7	2428	20	1.0	0.5235	1.24 (0.64, 2.38)	1.24 (0.64, 2.40)	0.00 (0.00, 0.01)	

Analysis is based on study 1245.110.
^ Patients with NYHA class I are counted in subgroup NYHA class II.
*** Confirmed hypoglycaemic AEs are defined by a glucose concentration <=70 mg/dL (3.9 mmol/L) or requiring assistance.
Risk ratios and odds ratios with confidence intervals (CIs) are estimated by Cochran-Mantel-Haenszel method. For risk differences standard Wald asymptotic confidence limits are calculated. A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied in case of any zero cells in contingency table.
Only treatment emergent AEs are displayed (onset between first dose until treatment stop +7 days).
MedDRA version: 23.1. * Chi-square test for treatment effect ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction).

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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 overall and by subgroup - TS
User-defined AE category: Thirst (project-defined PTs)

Subgroup	Placebo			Empa 10mg			Empa 10mg vs Placebo				
Category	N	n	%	N	n	%	p-value *	Risk ratio (95% CI)	Odds ratio (95% CI)	Risk diff. (95% CI)	p-value **
Overall	2989	2	0.1	2996	5	0.2	0.2579	2.49 (0.48, 12.85)	2.50 (0.48, 12.88)	0.00 (0.00, 0.00)	
Sex											
Male	1653	1	0.1	1658	4	0.2					
Female	1336	1	0.1	1338	1	0.1					
Age [years]											
<70	1084	1	0.1	1066	1	0.1					
>=70	1905	1	0.1	1930	4	0.2					
Region											
North America	359	0	0	359	1	0.3					
Latin America	757	1	0.1	758	0	0					
Europe	1341	1	0.1	1346	3	0.2					
Asia	343	0	0	343	1	0.3					
Other	189	0	0	190	0	0					
OECD member											
No	847	0	0	868	0	0					
Yes	2142	2	0.1	2128	5	0.2					
Baseline NYHA											
II^	2450	2	0.1	2435	3	0.1					
III/IV	539	0	0	561	2	0.4					
Baseline Diabetes Status											
Diabetic	1471	0	0	1465	5	0.3					
Non-Diabetic	1518	2	0.1	1531	0	0					

Analysis is based on study 1245.110.
^ Patients with NYHA class I are counted in subgroup NYHA class II.
*** Confirmed hypoglycaemic AEs are defined by a glucose concentration <=70 mg/dL (3.9 mmol/L) or requiring assistance.
Risk ratios and odds ratios with confidence intervals (CIs) are estimated by Cochran-Mantel-Haenszel method. For risk differences standard Wald asymptotic confidence limits are calculated. A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied in case of any zero cells in contingency table.
Only treatment emergent AEs are displayed (onset between first dose until treatment stop +7 days).
MedDRA version: 23.1. * Chi-square test for treatment effect ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction).

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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 overall and by subgroup - TS
User-defined AE category: Thirst (project-defined PTs)

Subgroup	Placebo			Empa 10mg			Empa 10mg vs Placebo				
Category	N	n	%	N	n	%	p-value *	Risk ratio (95% CI)	Odds ratio (95% CI)	Risk diff. (95% CI)	p-value **
Baseline Diabetes Status											
Diabetic	1471	0	0	1465	5	0.3					
Pre-Diabetes	979	1	0.1	1001	0	0					
Normal (no pre-diabetes)	539	1	0.2	530	0	0					
Baseline BMI [kg/m²]											
<30	1641	1	0.1	1654	2	0.1					
>=30	1348	1	0.1	1342	3	0.2					
Baseline eGFR (CKD-EPI) [mL/min/1.73m²]											
>=60	1505	1	0.1	1493	2	0.1					
<60	1482	1	0.1	1503	3	0.2					
History of HHF (in the last 12 months)											
No	2320	2	0.1	2297	5	0.2					
Yes	669	0	0	699	0	0					
Baseline SBP (</>= median)											
< median	1474	2	0.1	1496	4	0.3					
>= median	1515	0	0	1500	1	0.1					
History of atrial fibrillation or atrial flutter											
No	1426	0	0	1417	0	0					
Yes	1558	2	0.1	1575	5	0.3					

Analysis is based on study 1245.110.
^ Patients with NYHA class I are counted in subgroup NYHA class II.
*** Confirmed hypoglycaemic AEs are defined by a glucose concentration <=70 mg/dL (3.9 mmol/L) or requiring assistance.
Risk ratios and odds ratios with confidence intervals (CIs) are estimated by Cochran-Mantel-Haenszel method. For risk differences standard Wald asymptotic confidence limits are calculated. A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied in case of any zero cells in contingency table.
Only treatment emergent AEs are displayed (onset between first dose until treatment stop +7 days).
MedDRA version: 23.1. * Chi-square test for treatment effect ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction).

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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 overall and by subgroup - TS
User-defined AE category: Thirst (project-defined PTs)

Subgroup	Placebo			Empa 10mg			Empa 10mg vs Placebo				
Category	N	n	%	N	n	%	p-value *	Risk ratio (95% CI)	Odds ratio (95% CI)	Risk diff. (95% CI)	p-value **
Baseline LVEF [%]											
< 50	988	1	0.1	995	1	0.1					
>= 50	2001	1	<0.1	2001	4	0.2					
Baseline LVEF [%]											
<50	988	1	0.1	995	1	0.1					
50 to <60	1030	1	0.1	1028	1	0.1					
>=60	971	0	0	973	3	0.3					
Baseline NT-proBNP [pg/mL] (</>=median by atrial fibrillation/flutter status)											
< median	1507	0	0	1476	1	0.1					
>= median	1475	2	0.1	1516	4	0.3					
Baseline uric acid [mg/dL] (tertiles)											
<T1	975	1	0.1	963	0	0					
>=T1 and <T2	966	0	0	1032	2	0.2					
>=T2	1016	1	0.1	970	3	0.3					
Baseline use of MRA											
No	1865	2	0.1	1878	3	0.2					
Yes	1124	0	0	1118	2	0.2					
Baseline use of ACE-inhibitor, ARB or ARNi											
No	586	1	0.2	568	2	0.4					
Yes	2403	1	<0.1	2428	3	0.1					

Analysis is based on study 1245.110.
^ Patients with NYHA class I are counted in subgroup NYHA class II.
*** Confirmed hypoglycaemic AEs are defined by a glucose concentration <=70 mg/dL (3.9 mmol/L) or requiring assistance.
Risk ratios and odds ratios with confidence intervals (CIs) are estimated by Cochran-Mantel-Haenszel method. For risk differences standard Wald asymptotic confidence limits are calculated. A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied in case of any zero cells in contingency table.
Only treatment emergent AEs are displayed (onset between first dose until treatment stop +7 days).
MedDRA version: 23.1. * Chi-square test for treatment effect ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction).

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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 overall and by subgroup - TS
User-defined AE category: Serum lipids increased (Sub 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	2989	109	3.6	2996	100	3.3	0.5151	0.92 (0.70, 1.19)	0.91 (0.69, 1.20)	0.00 (-0.01, 0.01)	
Sex											0.9118
Male	1653	58	3.5	1658	54	3.3	0.6886	0.93 (0.64, 1.34)	0.93 (0.63, 1.35)	0.00 (-0.01, 0.01)	
Female	1336	51	3.8	1338	46	3.4	0.5998	0.90 (0.61, 1.33)	0.90 (0.60, 1.35)	0.00 (-0.02, 0.01)	
Age [years]											0.0075
<70	1084	53	4.9	1066	66	6.2	0.1868	1.27 (0.89, 1.80)	1.28 (0.89, 1.86)	0.01 (-0.01, 0.03)	
>=70	1905	56	2.9	1930	34	1.8	0.0160	0.60 (0.39, 0.91)	0.59 (0.38, 0.91)	-0.01 (-0.02, 0.00)	
Region											0.4434
North America	359	1	0.3	359	6	1.7	0.0576	6.00 (0.73, 49.59)	6.08 (0.73, 50.80)	0.01 (0.00, 0.03)	
Latin America	757	47	6.2	758	45	5.9	0.8246	0.96 (0.64, 1.42)	0.95 (0.63, 1.45)	0.00 (-0.03, 0.02)	
Europe	1341	34	2.5	1346	26	1.9	0.2896	0.76 (0.46, 1.26)	0.76 (0.45, 1.27)	-0.01 (-0.02, 0.01)	
Asia	343	19	5.5	343	17	5.0	0.7320	0.89 (0.47, 1.69)	0.89 (0.45, 1.74)	-0.01 (-0.04, 0.03)	
Other	189	8	4.2	190	6	3.2	0.5791	0.75 (0.26, 2.11)	0.74 (0.25, 2.17)	-0.01 (-0.05, 0.03)	
OECD member											0.9529
No	847	53	6.3	868	49	5.6	0.5920	0.90 (0.62, 1.31)	0.90 (0.60, 1.34)	-0.01 (-0.03, 0.02)	
Yes	2142	56	2.6	2128	51	2.4	0.6490	0.92 (0.63, 1.33)	0.91 (0.62, 1.34)	0.00 (-0.01, 0.01)	
Baseline NYHA											0.5942
II^	2450	91	3.7	2435	80	3.3	0.4148	0.88 (0.66, 1.19)	0.88 (0.65, 1.20)	0.00 (-0.01, 0.01)	
III/IV	539	18	3.3	561	20	3.6	0.8378	1.07 (0.57, 2.00)	1.07 (0.56, 2.05)	0.00 (-0.02, 0.02)	
Baseline Diabetes Status											0.4509
Diabetic	1471	58	3.9	1465	58	4.0	0.9821	1.00 (0.70, 1.43)	1.00 (0.69, 1.46)	0.00 (-0.01, 0.01)	
Non-Diabetic	1518	51	3.4	1531	42	2.7	0.3224	0.82 (0.55, 1.22)	0.81 (0.54, 1.23)	-0.01 (-0.02, 0.01)	

Analysis is based on study 1245.110.
^ Patients with NYHA class I are counted in subgroup NYHA class II.
*** Confirmed hypoglycaemic AEs are defined by a glucose concentration <=70 mg/dL (3.9 mmol/L) or requiring assistance.
Risk ratios and odds ratios with confidence intervals (CIs) are estimated by Cochran-Mantel-Haenszel method. For risk differences standard Wald asymptotic confidence limits are calculated. A ratio less than one or risk difference less than 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: 23.1. * Chi-square test for treatment effect ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction).

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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 overall and by subgroup - TS
User-defined AE category: Serum lipids increased (Sub 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 Diabetes Status											0.5569
Diabetic	1471	58	3.9	1465	58	4.0	0.9821	1.00 (0.70, 1.43)	1.00 (0.69, 1.46)	0.00 (-0.01, 0.01)	
Pre-Diabetes	979	35	3.6	1001	26	2.6	0.2081	0.73 (0.44, 1.20)	0.72 (0.43, 1.20)	-0.01 (-0.03, 0.01)	
Normal (no pre-diabetes)	539	16	3.0	530	16	3.0	0.9614	1.02 (0.51, 2.01)	1.02 (0.50, 2.06)	0.00 (-0.02, 0.02)	
Baseline BMI [kg/m²]											0.5655
<30	1641	66	4.0	1654	57	3.4	0.3834	0.86 (0.61, 1.21)	0.85 (0.59, 1.22)	-0.01 (-0.02, 0.01)	
>=30	1348	43	3.2	1342	43	3.2	0.9832	1.00 (0.66, 1.52)	1.00 (0.65, 1.54)	0.00 (-0.01, 0.01)	
Baseline eGFR (CKD-EPI) [mL/min/1.73m²]											0.0667
>=60	1505	58	3.9	1493	65	4.4	0.4903	1.13 (0.80, 1.60)	1.14 (0.79, 1.63)	0.00 (-0.01, 0.02)	
<60	1482	51	3.4	1503	35	2.3	0.0692	0.68 (0.44, 1.03)	0.67 (0.43, 1.03)	-0.01 (-0.02, 0.00)	
History of HHF (in the last 12 months)											0.5980
No	2320	82	3.5	2297	71	3.1	0.3999	0.87 (0.64, 1.20)	0.87 (0.63, 1.20)	0.00 (-0.01, 0.01)	
Yes	669	27	4.0	699	29	4.1	0.9161	1.03 (0.62, 1.72)	1.03 (0.60, 1.76)	0.00 (-0.02, 0.02)	
Baseline SBP (</>= median)											0.6509
< median	1474	55	3.7	1496	48	3.2	0.4362	0.86 (0.59, 1.26)	0.86 (0.58, 1.27)	-0.01 (-0.02, 0.01)	
>= median	1515	54	3.6	1500	52	3.5	0.8842	0.97 (0.67, 1.41)	0.97 (0.66, 1.43)	0.00 (-0.01, 0.01)	
History of atrial fibrillation or atrial flutter											0.4618
No	1426	60	4.2	1417	59	4.2	0.9535	0.99 (0.70, 1.41)	0.99 (0.69, 1.43)	0.00 (-0.02, 0.01)	
Yes	1558	49	3.1	1575	40	2.5	0.3078	0.81 (0.53, 1.22)	0.80 (0.53, 1.23)	-0.01 (-0.02, 0.01)	

Analysis is based on study 1245.110.
^ Patients with NYHA class I are counted in subgroup NYHA class II.
*** Confirmed hypoglycaemic AEs are defined by a glucose concentration <=70 mg/dL (3.9 mmol/L) or requiring assistance.
Risk ratios and odds ratios with confidence intervals (CIs) are estimated by Cochran-Mantel-Haenszel method. For risk differences standard Wald asymptotic confidence limits are calculated. A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied in case of any zero cells in contingency table.
Only treatment emergent AEs are displayed (onset between first dose until treatment stop +7 days).
MedDRA version: 23.1. * Chi-square test for treatment effect ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction).

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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 overall and by subgroup - TS
User-defined AE category: Serum lipids increased (Sub 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 LVEF [%]														0.2883
< 50	988	39	3.9	995	43	4.3	0.6756	1.09	(0.72, 1.67)	1.10	(0.71, 1.71)	0.00	(-0.01, 0.02)	
>= 50	2001	70	3.5	2001	57	2.8	0.2411	0.81	(0.58, 1.15)	0.81	(0.57, 1.15)	-0.01	(-0.02, 0.00)	
Baseline LVEF [%]														0.2478
<50	988	39	3.9	995	43	4.3	0.6756	1.09	(0.72, 1.67)	1.10	(0.71, 1.71)	0.00	(-0.01, 0.02)	
50 to <60	1030	40	3.9	1028	26	2.5	0.0812	0.65	(0.40, 1.06)	0.64	(0.39, 1.06)	-0.01	(-0.03, 0.00)	
>=60	971	30	3.1	973	31	3.2	0.9030	1.03	(0.63, 1.69)	1.03	(0.62, 1.72)	0.00	(-0.01, 0.02)	
Baseline NT-proBNP [pg/mL] (</>=median by atrial fibrillation/flutter status)														0.6915
< median	1507	68	4.5	1476	58	3.9	0.4289	0.87	(0.62, 1.23)	0.87	(0.61, 1.24)	-0.01	(-0.02, 0.01)	
>= median	1475	41	2.8	1516	41	2.7	0.8998	0.97	(0.63, 1.49)	0.97	(0.63, 1.51)	0.00	(-0.01, 0.01)	
Baseline uric acid [mg/dL] (tertiles)														0.3658
<T1	975	27	2.8	963	32	3.3	0.4781	1.20	(0.72, 1.99)	1.21	(0.72, 2.03)	0.01	(-0.01, 0.02)	
>=T1 and <T2	966	32	3.3	1032	33	3.2	0.8849	0.97	(0.60, 1.56)	0.96	(0.59, 1.58)	0.00	(-0.02, 0.01)	
>=T2	1016	49	4.8	970	35	3.6	0.1788	0.75	(0.49, 1.14)	0.74	(0.47, 1.15)	-0.01	(-0.03, 0.01)	
Baseline use of MRA														0.4820
No	1865	68	3.6	1878	58	3.1	0.3442	0.85	(0.60, 1.20)	0.84	(0.59, 1.20)	-0.01	(-0.02, 0.01)	
Yes	1124	41	3.6	1118	42	3.8	0.8913	1.03	(0.68, 1.57)	1.03	(0.67, 1.60)	0.00	(-0.01, 0.02)	
Baseline use of ACE-inhibitor, ARB or ARNi														0.0219
No	586	23	3.9	568	9	1.6	0.0155	0.40	(0.19, 0.86)	0.39	(0.18, 0.86)	-0.02	(-0.04, 0.00)	
Yes	2403	86	3.6	2428	91	3.7	0.7545	1.05	(0.78, 1.40)	1.05	(0.78, 1.42)	0.00	(-0.01, 0.01)	

Analysis is based on study 1245.110.
^ Patients with NYHA class I are counted in subgroup NYHA class II.
*** Confirmed hypoglycaemic AEs are defined by a glucose concentration <=70 mg/dL (3.9 mmol/L) or requiring assistance.
Risk ratios and odds ratios with confidence intervals (CIs) are estimated by Cochran-Mantel-Haenszel method. For risk differences standard Wald asymptotic confidence limits are calculated. A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied in case of any zero cells in contingency table.
Only treatment emergent AEs are displayed (onset between first dose until treatment stop +7 days).
MedDRA version: 23.1. * Chi-square test for treatment effect ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction).

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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 overall and by subgroup - TS
User-defined AE category: Angioedema (narrow BicMQ excl. urticaria)

Subgroup	Placebo			Empa 10mg			Empa 10mg vs Placebo						
Category	N	n	%	N	n	%	p-value *	Risk ratio (95% CI)	Odds ratio (95% CI)	Risk diff. (95% CI)	p-value **
Overall	2989	12	0.4	2996	10	0.3	0.6652	0.83 (0.36, 1.92)	0.83 (0.36, 1.93)	0.00 (0.00, 0.00)	
Sex											0.9354
Male	1653	5	0.3	1658	4	0.2	0.7351	0.80 (0.21, 2.96)	0.80 (0.21, 2.97)	0.00 (0.00, 0.00)	
Female	1336	7	0.5	1338	6	0.4	0.7789	0.86 (0.29, 2.54)	0.86 (0.29, 2.55)	0.00 (-0.01, 0.00)	
Age [years]											0.1262
<70	1084	4	0.4	1066	0	0	0.0763	0.11 (<0.01, 2.10)	0.11 (<0.01, 2.09)	0.00 (-0.01, 0.00)	
>=70	1905	8	0.4	1930	10	0.5	0.6565	1.23 (0.49, 3.12)	1.24 (0.49, 3.14)	0.00 (0.00, 0.01)	
Region											
North America	359	3	0.8	359	1	0.3					
Latin America	757	1	0.1	758	0	0					
Europe	1341	3	0.2	1346	6	0.4					
Asia	343	4	1.2	343	3	0.9					
Other	189	1	0.5	190	0	0					
OECD member											0.3087
No	847	2	0.2	868	0	0	0.2392	0.20 (<0.01, 4.06)	0.19 (<0.01, 4.06)	0.00 (-0.01, 0.00)	
Yes	2142	10	0.5	2128	10	0.5	0.9883	1.01 (0.42, 2.41)	1.01 (0.42, 2.42)	0.00 (0.00, 0.00)	
Baseline NYHA											0.1840
II^	2450	9	0.4	2435	10	0.4	0.8078	1.12 (0.46, 2.75)	1.12 (0.45, 2.76)	0.00 (0.00, 0.00)	
III/IV	539	3	0.6	561	0	0	0.1228	0.14 (<0.01, 2.65)	0.14 (<0.01, 2.65)	-0.01 (-0.01, 0.00)	
Baseline Diabetes Status											0.9483
Diabetic	1471	5	0.3	1465	4	0.3	0.7431	0.80 (0.22, 2.99)	0.80 (0.22, 3.00)	0.00 (0.00, 0.00)	
Non-Diabetic	1518	7	0.5	1531	6	0.4	0.7693	0.85 (0.29, 2.52)	0.85 (0.28, 2.53)	0.00 (-0.01, 0.00)	

Analysis is based on study 1245.110.
^ Patients with NYHA class I are counted in subgroup NYHA class II.
*** Confirmed hypoglycaemic AEs are defined by a glucose concentration <=70 mg/dL (3.9 mmol/L) or requiring assistance.
Risk ratios and odds ratios with confidence intervals (CIs) are estimated by Cochran-Mantel-Haenszel method. For risk differences standard Wald asymptotic confidence limits are calculated. A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied in case of any zero cells in contingency table.
Only treatment emergent AEs are displayed (onset between first dose until treatment stop +7 days).
MedDRA version: 23.1. * Chi-square test for treatment effect ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction).

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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 overall and by subgroup - TS
User-defined AE category: Angioedema (narrow BicMQ excl. urticaria)

Subgroup	Placebo			Empa 10mg			Empa 10mg vs Placebo				
Category	N	n	%	N	n	%	p-value *	Risk ratio (95% CI)	Odds ratio (95% CI)	Risk diff. (95% CI)	p-value **
Baseline Diabetes Status											0.9881
Diabetic	1471	5	0.3	1465	4	0.3	0.7431	0.80 (0.22, 2.99)	0.80 (0.22, 3.00)	0.00 (0.00, 0.00)	
Pre-Diabetes	979	6	0.6	1001	5	0.5	0.7344	0.82 (0.25, 2.66)	0.81 (0.25, 2.68)	0.00 (-0.01, 0.01)	
Normal (no pre-diabetes)	539	1	0.2	530	1	0.2	0.9905	1.02 (0.06, 16.22)	1.02 (0.06, 16.30)	0.00 (-0.01, 0.01)	
Baseline BMI [kg/m²]											0.2910
<30	1641	7	0.4	1654	8	0.5	0.8076	1.13 (0.41, 3.12)	1.13 (0.41, 3.14)	0.00 (0.00, 0.01)	
>=30	1348	5	0.4	1342	2	0.1	0.2587	0.40 (0.08, 2.07)	0.40 (0.08, 2.07)	0.00 (-0.01, 0.00)	
Baseline eGFR (CKD-EPI) [mL/min/1.73m²]											0.3331
>=60	1505	6	0.4	1493	7	0.5	0.7700	1.18 (0.40, 3.49)	1.18 (0.39, 3.51)	0.00 (0.00, 0.01)	
<60	1482	6	0.4	1503	3	0.2	0.3065	0.49 (0.12, 1.97)	0.49 (0.12, 1.97)	0.00 (-0.01, 0.00)	
History of HHF (in the last 12 months)											0.0326
No	2320	4	0.2	2297	8	0.3	0.2406	2.02 (0.61, 6.70)	2.02 (0.61, 6.73)	0.00 (0.00, 0.00)	
Yes	669	8	1.2	699	2	0.3	0.0483	0.24 (0.05, 1.12)	0.24 (0.05, 1.12)	-0.01 (-0.02, 0.00)	
Baseline SBP (</>= median)											0.5533
< median	1474	5	0.3	1496	3	0.2	0.4660	0.59 (0.14, 2.47)	0.59 (0.14, 2.47)	0.00 (-0.01, 0.00)	
>= median	1515	7	0.5	1500	7	0.5	0.9851	1.01 (0.36, 2.87)	1.01 (0.35, 2.89)	0.00 (0.00, 0.00)	
History of atrial fibrillation or atrial flutter											0.4433
No	1426	3	0.2	1417	4	0.3	0.6989	1.34 (0.30, 5.98)	1.34 (0.30, 6.01)	0.00 (0.00, 0.00)	
Yes	1558	9	0.6	1575	6	0.4	0.4251	0.66 (0.24, 1.85)	0.66 (0.23, 1.85)	0.00 (-0.01, 0.00)	

Analysis is based on study 1245.110.
^ Patients with NYHA class I are counted in subgroup NYHA class II.
*** Confirmed hypoglycaemic AEs are defined by a glucose concentration <=70 mg/dL (3.9 mmol/L) or requiring assistance.
Risk ratios and odds ratios with confidence intervals (CIs) are estimated by Cochran-Mantel-Haenszel method. For risk differences standard Wald asymptotic confidence limits are calculated. A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied in case of any zero cells in contingency table.
Only treatment emergent AEs are displayed (onset between first dose until treatment stop +7 days).
MedDRA version: 23.1. * Chi-square test for treatment effect ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction).

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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 overall and by subgroup - TS
User-defined AE category: Angioedema (narrow BicMQ excl. urticaria)

Subgroup	Placebo			Empa 10mg			Empa 10mg vs Placebo				
Category	N	n	%	N	n	%	p-value *	Risk ratio (95% CI)	Odds ratio (95% CI)	Risk diff. (95% CI)	p-value **
Baseline LVEF [%]											0.8450
< 50	988	2	0.2	995	2	0.2	0.9944	0.99 (0.14, 7.04)	0.99 (0.14, 7.06)	0.00 (0.00, 0.00)	
>= 50	2001	10	0.5	2001	8	0.4	0.6366	0.80 (0.32, 2.02)	0.80 (0.31, 2.03)	0.00 (-0.01, 0.00)	
Baseline LVEF [%]											
<50	988	2	0.2	995	2	0.2					
50 to <60	1030	4	0.4	1028	5	0.5					
>=60	971	6	0.6	973	3	0.3					
Baseline NT-proBNP [pg/mL] (</>=median by atrial fibrillation/flutter status)											0.1180
< median	1507	10	0.7	1476	5	0.3	0.2099	0.51 (0.17, 1.49)	0.51 (0.17, 1.49)	0.00 (-0.01, 0.00)	
>= median	1475	2	0.1	1516	5	0.3	0.2718	2.43 (0.47, 12.52)	2.44 (0.47, 12.58)	0.00 (0.00, 0.01)	
Baseline uric acid [mg/dL] (tertiles)											
<T1	975	1	0.1	963	4	0.4					
>=T1 and <T2	966	5	0.5	1032	3	0.3					
>=T2	1016	6	0.6	970	3	0.3					
Baseline use of MRA											0.2213
No	1865	4	0.2	1878	6	0.3	0.5337	1.49 (0.42, 5.27)	1.49 (0.42, 5.29)	0.00 (0.00, 0.00)	
Yes	1124	8	0.7	1118	4	0.4	0.2508	0.50 (0.15, 1.66)	0.50 (0.15, 1.67)	0.00 (-0.01, 0.00)	
Baseline use of ACE-inhibitor, ARB or ARNi											0.5138
No	586	4	0.7	568	2	0.4	0.4351	0.52 (0.09, 2.81)	0.51 (0.09, 2.82)	0.00 (-0.01, 0.00)	
Yes	2403	8	0.3	2428	8	0.3	0.9835	0.99 (0.37, 2.63)	0.99 (0.37, 2.64)	0.00 (0.00, 0.00)	

Analysis is based on study 1245.110.
^ Patients with NYHA class I are counted in subgroup NYHA class II.
*** Confirmed hypoglycaemic AEs are defined by a glucose concentration <=70 mg/dL (3.9 mmol/L) or requiring assistance.
Risk ratios and odds ratios with confidence intervals (CIs) are estimated by Cochran-Mantel-Haenszel method. For risk differences standard Wald asymptotic confidence limits are calculated. A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied in case of any zero cells in contingency table.
Only treatment emergent AEs are displayed (onset between first dose until treatment stop +7 days).
MedDRA version: 23.1. * Chi-square test for treatment effect ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction).

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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 overall and by subgroup - TS
User-defined AE category: Hypersensitivity reactions (narrow 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	2989	126	4.2	2996	140	4.7	0.3906	1.11 (0.88, 1.40)	1.11 (0.87, 1.42)	0.00 (-0.01, 0.02)	
Sex											0.4788
Male	1653	62	3.8	1658	63	3.8	0.9410	1.01 (0.72, 1.43)	1.01 (0.71, 1.45)	0.00 (-0.01, 0.01)	
Female	1336	64	4.8	1338	77	5.8	0.2645	1.20 (0.87, 1.66)	1.21 (0.86, 1.71)	0.01 (-0.01, 0.03)	
Age [years]											0.1214
<70	1084	34	3.1	1066	49	4.6	0.0789	1.47 (0.95, 2.25)	1.49 (0.95, 2.32)	0.01 (0.00, 0.03)	
>=70	1905	92	4.8	1930	91	4.7	0.8681	0.98 (0.74, 1.30)	0.98 (0.72, 1.31)	0.00 (-0.01, 0.01)	
Region											0.5368
North America	359	22	6.1	359	22	6.1	1.0000	1.00 (0.56, 1.77)	1.00 (0.54, 1.84)	0.00 (-0.04, 0.04)	
Latin America	757	20	2.6	758	28	3.7	0.2425	1.40 (0.79, 2.46)	1.41 (0.79, 2.53)	0.01 (-0.01, 0.03)	
Europe	1341	39	2.9	1346	51	3.8	0.2046	1.30 (0.86, 1.96)	1.31 (0.86, 2.01)	0.01 (0.00, 0.02)	
Asia	343	37	10.8	343	34	9.9	0.7069	0.92 (0.59, 1.43)	0.91 (0.56, 1.49)	-0.01 (-0.05, 0.04)	
Other	189	8	4.2	190	5	2.6	0.3918	0.62 (0.21, 1.87)	0.61 (0.20, 1.90)	-0.02 (-0.05, 0.02)	
OECD member											0.3856
No	847	22	2.6	868	31	3.6	0.2439	1.38 (0.80, 2.36)	1.39 (0.80, 2.42)	0.01 (-0.01, 0.03)	
Yes	2142	104	4.9	2128	109	5.1	0.6887	1.05 (0.81, 1.37)	1.06 (0.80, 1.39)	0.00 (-0.01, 0.02)	
Baseline NYHA											0.2874
II^	2450	98	4.0	2435	115	4.7	0.2161	1.18 (0.91, 1.54)	1.19 (0.90, 1.57)	0.01 (0.00, 0.02)	
III/IV	539	28	5.2	561	25	4.5	0.5675	0.86 (0.51, 1.45)	0.85 (0.49, 1.48)	-0.01 (-0.03, 0.02)	
Baseline Diabetes Status											0.8016
Diabetic	1471	57	3.9	1465	65	4.4	0.4455	1.15 (0.81, 1.62)	1.15 (0.80, 1.66)	0.01 (-0.01, 0.02)	
Non-Diabetic	1518	69	4.5	1531	75	4.9	0.6456	1.08 (0.78, 1.48)	1.08 (0.77, 1.51)	0.00 (-0.01, 0.02)	

Analysis is based on study 1245.110.
^ Patients with NYHA class I are counted in subgroup NYHA class II.
*** Confirmed hypoglycaemic AEs are defined by a glucose concentration <=70 mg/dL (3.9 mmol/L) or requiring assistance.
Risk ratios and odds ratios with confidence intervals (CIs) are estimated by Cochran-Mantel-Haenszel method. For risk differences standard Wald asymptotic confidence limits are calculated. A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied in case of any zero cells in contingency table.
Only treatment emergent AEs are displayed (onset between first dose until treatment stop +7 days).
MedDRA version: 23.1. * Chi-square test for treatment effect ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction).

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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 overall and by subgroup - TS
User-defined AE category: Hypersensitivity reactions (narrow 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 Diabetes Status													0.5994
Diabetic	1471	57	3.9	1465	65	4.4	0.4455	1.15 (0.81,	1.62)	1.15 (0.80,	1.66)	0.01 (-0.01, 0.02)	
Pre-Diabetes	979	41	4.2	1001	51	5.1	0.3378	1.22 (0.81,	1.82)	1.23 (0.81,	1.87)	0.01 (-0.01, 0.03)	
Normal (no pre-diabetes)	539	28	5.2	530	24	4.5	0.6125	0.87 (0.51,	1.48)	0.87 (0.49,	1.51)	-0.01 (-0.03, 0.02)	
Baseline BMI [kg/m²]													0.1717
<30	1641	80	4.9	1654	78	4.7	0.8306	0.97 (0.71,	1.31)	0.97 (0.70,	1.33)	0.00 (-0.02, 0.01)	
>=30	1348	46	3.4	1342	62	4.6	0.1107	1.35 (0.93,	1.97)	1.37 (0.93,	2.02)	0.01 (0.00, 0.03)	
Baseline eGFR (CKD-EPI) [mL/min/1.73m²]													0.3759
>=60	1505	57	3.8	1493	70	4.7	0.2206	1.24 (0.88,	1.74)	1.25 (0.87,	1.79)	0.01 (-0.01, 0.02)	
<60	1482	69	4.7	1503	70	4.7	0.9985	1.00 (0.72,	1.38)	1.00 (0.71,	1.41)	0.00 (-0.02, 0.02)	
History of HHF (in the last 12 months)													0.8786
No	2320	93	4.0	2297	103	4.5	0.4230	1.12 (0.85,	1.47)	1.12 (0.84,	1.50)	0.00 (-0.01, 0.02)	
Yes	669	33	4.9	699	37	5.3	0.7623	1.07 (0.68,	1.70)	1.08 (0.67,	1.74)	0.00 (-0.02, 0.03)	
Baseline SBP (</>= median)													0.0843
< median	1474	69	4.7	1496	63	4.2	0.5344	0.90 (0.64,	1.26)	0.90 (0.63,	1.27)	0.00 (-0.02, 0.01)	
>= median	1515	57	3.8	1500	77	5.1	0.0678	1.36 (0.98,	1.91)	1.38 (0.98,	1.96)	0.01 (0.00, 0.03)	
History of atrial fibrillation or atrial flutter													0.9973
No	1426	50	3.5	1417	55	3.9	0.5959	1.11 (0.76,	1.61)	1.11 (0.75,	1.64)	0.00 (-0.01, 0.02)	
Yes	1558	75	4.8	1575	84	5.3	0.5077	1.11 (0.82,	1.50)	1.11 (0.81,	1.53)	0.01 (-0.01, 0.02)	

Analysis is based on study 1245.110.
^ Patients with NYHA class I are counted in subgroup NYHA class II.
*** Confirmed hypoglycaemic AEs are defined by a glucose concentration <=70 mg/dL (3.9 mmol/L) or requiring assistance.
Risk ratios and odds ratios with confidence intervals (CIs) are estimated by Cochran-Mantel-Haenszel method. For risk differences standard Wald asymptotic confidence limits are calculated. A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied in case of any zero cells in contingency table.
Only treatment emergent AEs are displayed (onset between first dose until treatment stop +7 days).
MedDRA version: 23.1. * Chi-square test for treatment effect ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction).

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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 overall and by subgroup - TS
User-defined AE category: Hypersensitivity reactions (narrow 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 LVEF [%]											0.0859
< 50	988	27	2.7	995	43	4.3	0.0552	1.58 (0.99, 2.54)	1.61 (0.99, 2.62)	0.02 (0.00, 0.03)	
>= 50	2001	99	4.9	2001	97	4.8	0.8835	0.98 (0.75, 1.29)	0.98 (0.73, 1.30)	0.00 (-0.01, 0.01)	
Baseline LVEF [%]											0.2257
<50	988	27	2.7	995	43	4.3	0.0552	1.58 (0.99, 2.54)	1.61 (0.99, 2.62)	0.02 (0.00, 0.03)	
50 to <60	1030	42	4.1	1028	42	4.1	0.9927	1.00 (0.66, 1.52)	1.00 (0.65, 1.55)	0.00 (-0.02, 0.02)	
>=60	971	57	5.9	973	55	5.7	0.8369	0.96 (0.67, 1.38)	0.96 (0.66, 1.41)	0.00 (-0.02, 0.02)	
Baseline NT-proBNP [pg/mL] (</>=median by atrial fibrillation/flutter status)											0.3510
< median	1507	75	5.0	1476	74	5.0	0.9632	1.01 (0.74, 1.38)	1.01 (0.72, 1.40)	0.00 (-0.02, 0.02)	
>= median	1475	50	3.4	1516	65	4.3	0.2017	1.26 (0.88, 1.82)	1.28 (0.88, 1.86)	0.01 (0.00, 0.02)	
Baseline uric acid [mg/dL] (tertiles)											0.9121
<T1	975	36	3.7	963	43	4.5	0.3896	1.21 (0.78, 1.87)	1.22 (0.78, 1.92)	0.01 (-0.01, 0.03)	
>=T1 and <T2	966	38	3.9	1032	45	4.4	0.6329	1.11 (0.73, 1.69)	1.11 (0.72, 1.73)	0.00 (-0.01, 0.02)	
>=T2	1016	51	5.0	970	52	5.4	0.7318	1.07 (0.73, 1.56)	1.07 (0.72, 1.59)	0.00 (-0.02, 0.02)	
Baseline use of MRA											0.6349
No	1865	79	4.2	1878	92	4.9	0.3315	1.16 (0.86, 1.55)	1.16 (0.86, 1.58)	0.01 (-0.01, 0.02)	
Yes	1124	47	4.2	1118	48	4.3	0.8954	1.03 (0.69, 1.52)	1.03 (0.68, 1.55)	0.00 (-0.02, 0.02)	
Baseline use of ACE-inhibitor, ARB or ARNi											0.5003
No	586	29	4.9	568	36	6.3	0.3061	1.28 (0.80, 2.06)	1.30 (0.79, 2.15)	0.01 (-0.01, 0.04)	
Yes	2403	97	4.0	2428	104	4.3	0.6676	1.06 (0.81, 1.39)	1.06 (0.80, 1.41)	0.00 (-0.01, 0.01)	

Analysis is based on study 1245.110.
^ Patients with NYHA class I are counted in subgroup NYHA class II.
*** Confirmed hypoglycaemic AEs are defined by a glucose concentration <=70 mg/dL (3.9 mmol/L) or requiring assistance.
Risk ratios and odds ratios with confidence intervals (CIs) are estimated by Cochran-Mantel-Haenszel method. For risk differences standard Wald asymptotic confidence limits are calculated. A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied in case of any zero cells in contingency table.
Only treatment emergent AEs are displayed (onset between first dose until treatment stop +7 days).
MedDRA version: 23.1. * Chi-square test for treatment effect ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction).

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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 overall and by subgroup - TS
User-defined AE category: Ventricular Tachyarrhythmia (narrow 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	2989	52	1.7	2996	52	1.7	0.9904	1.00 (0.68, 1.46)	1.00 (0.68, 1.47)	0.00 (-0.01, 0.01)	
Sex											0.3616
Male	1653	41	2.5	1658	37	2.2	0.6370	0.90 (0.58, 1.40)	0.90 (0.57, 1.41)	0.00 (-0.01, 0.01)	
Female	1336	11	0.8	1338	15	1.1	0.4328	1.36 (0.63, 2.95)	1.37 (0.62, 2.98)	0.00 (0.00, 0.01)	
Age [years]											0.9412
<70	1084	19	1.8	1066	19	1.8	0.9585	1.02 (0.54, 1.91)	1.02 (0.54, 1.93)	0.00 (-0.01, 0.01)	
>=70	1905	33	1.7	1930	33	1.7	0.9574	0.99 (0.61, 1.59)	0.99 (0.61, 1.61)	0.00 (-0.01, 0.01)	
Region											0.7582
North America	359	5	1.4	359	4	1.1	0.7373	0.80 (0.22, 2.95)	0.80 (0.21, 3.00)	0.00 (-0.02, 0.01)	
Latin America	757	13	1.7	758	14	1.8	0.8487	1.08 (0.51, 2.27)	1.08 (0.50, 2.31)	0.00 (-0.01, 0.01)	
Europe	1341	22	1.6	1346	18	1.3	0.5163	0.82 (0.44, 1.51)	0.81 (0.43, 1.52)	0.00 (-0.01, 0.01)	
Asia	343	9	2.6	343	14	4.1	0.2889	1.56 (0.68, 3.55)	1.58 (0.67, 3.70)	0.01 (-0.01, 0.04)	
Other	189	3	1.6	190	2	1.1	0.6483	0.66 (0.11, 3.92)	0.66 (0.11, 3.99)	-0.01 (-0.03, 0.02)	
OECD member											0.7226
No	847	15	1.8	868	17	2.0	0.7741	1.11 (0.56, 2.20)	1.11 (0.55, 2.23)	0.00 (-0.01, 0.01)	
Yes	2142	37	1.7	2128	35	1.6	0.8339	0.95 (0.60, 1.51)	0.95 (0.60, 1.52)	0.00 (-0.01, 0.01)	
Baseline NYHA											0.0919
II^	2450	41	1.7	2435	47	1.9	0.5000	1.15 (0.76, 1.75)	1.16 (0.76, 1.76)	0.00 (0.00, 0.01)	
III/IV	539	11	2.0	561	5	0.9	0.1114	0.44 (0.15, 1.25)	0.43 (0.15, 1.25)	-0.01 (-0.03, 0.00)	
Baseline Diabetes Status											0.4426
Diabetic	1471	24	1.6	1465	20	1.4	0.5526	0.84 (0.46, 1.51)	0.83 (0.46, 1.52)	0.00 (-0.01, 0.01)	
Non-Diabetic	1518	28	1.8	1531	32	2.1	0.6254	1.13 (0.69, 1.87)	1.14 (0.68, 1.90)	0.00 (-0.01, 0.01)	

Analysis is based on study 1245.110.
^ Patients with NYHA class I are counted in subgroup NYHA class II.
*** Confirmed hypoglycaemic AEs are defined by a glucose concentration <=70 mg/dL (3.9 mmol/L) or requiring assistance.
Risk ratios and odds ratios with confidence intervals (CIs) are estimated by Cochran-Mantel-Haenszel method. For risk differences standard Wald asymptotic confidence limits are calculated. A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied in case of any zero cells in contingency table.
Only treatment emergent AEs are displayed (onset between first dose until treatment stop +7 days).
MedDRA version: 23.1. * Chi-square test for treatment effect ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction).

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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 overall and by subgroup - TS
User-defined AE category: Ventricular Tachyarrhythmia (narrow 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 Diabetes Status											0.7320
Diabetic	1471	24	1.6	1465	20	1.4	0.5526	0.84 (0.46, 1.51)	0.83 (0.46, 1.52)	0.00 (-0.01, 0.01)	
Pre-Diabetes	979	16	1.6	1001	18	1.8	0.7790	1.10 (0.56, 2.15)	1.10 (0.56, 2.17)	0.00 (-0.01, 0.01)	
Normal (no pre-diabetes)	539	12	2.2	530	14	2.6	0.6595	1.19 (0.55, 2.54)	1.19 (0.55, 2.60)	0.00 (-0.01, 0.02)	
Baseline BMI [kg/m²]											0.5561
<30	1641	32	2.0	1654	35	2.1	0.7356	1.09 (0.68, 1.74)	1.09 (0.67, 1.76)	0.00 (-0.01, 0.01)	
>=30	1348	20	1.5	1342	17	1.3	0.6291	0.85 (0.45, 1.62)	0.85 (0.44, 1.63)	0.00 (-0.01, 0.01)	
Baseline eGFR (CKD-EPI) [mL/min/1.73m²]											0.3969
>=60	1505	24	1.6	1493	28	1.9	0.5561	1.18 (0.69, 2.02)	1.18 (0.68, 2.04)	0.00 (-0.01, 0.01)	
<60	1482	28	1.9	1503	24	1.6	0.5413	0.85 (0.49, 1.45)	0.84 (0.49, 1.46)	0.00 (-0.01, 0.01)	
History of HHF (in the last 12 months)											0.0312
No	2320	35	1.5	2297	44	1.9	0.2864	1.27 (0.82, 1.97)	1.27 (0.81, 2.00)	0.00 (0.00, 0.01)	
Yes	669	17	2.5	699	8	1.1	0.0539	0.45 (0.20, 1.04)	0.44 (0.19, 1.04)	-0.01 (-0.03, 0.00)	
Baseline SBP (</>= median)											0.4668
< median	1474	23	1.6	1496	27	1.8	0.6047	1.16 (0.67, 2.01)	1.16 (0.66, 2.03)	0.00 (-0.01, 0.01)	
>= median	1515	29	1.9	1500	25	1.7	0.6084	0.87 (0.51, 1.48)	0.87 (0.51, 1.49)	0.00 (-0.01, 0.01)	
History of atrial fibrillation or atrial flutter											0.7250
No	1426	28	2.0	1417	26	1.8	0.8016	0.93 (0.55, 1.59)	0.93 (0.54, 1.60)	0.00 (-0.01, 0.01)	
Yes	1558	24	1.5	1575	26	1.7	0.8053	1.07 (0.62, 1.86)	1.07 (0.61, 1.88)	0.00 (-0.01, 0.01)	

Analysis is based on study 1245.110.
^ Patients with NYHA class I are counted in subgroup NYHA class II.
*** Confirmed hypoglycaemic AEs are defined by a glucose concentration <=70 mg/dL (3.9 mmol/L) or requiring assistance.
Risk ratios and odds ratios with confidence intervals (CIs) are estimated by Cochran-Mantel-Haenszel method. For risk differences standard Wald asymptotic confidence limits are calculated. A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied in case of any zero cells in contingency table.
Only treatment emergent AEs are displayed (onset between first dose until treatment stop +7 days).
MedDRA version: 23.1. * Chi-square test for treatment effect ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction).

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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 overall and by subgroup - TS
User-defined AE category: Ventricular Tachyarrhythmia (narrow 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 LVEF [%]											0.3133
< 50	988	27	2.7	995	22	2.2	0.4543	0.81 (0.46, 1.41)	0.80 (0.46, 1.42)	-0.01 (-0.02, 0.01)	
>= 50	2001	25	1.2	2001	30	1.5	0.4972	1.20 (0.71, 2.03)	1.20 (0.70, 2.05)	0.00 (0.00, 0.01)	
Baseline LVEF [%]											0.5588
<50	988	27	2.7	995	22	2.2	0.4543	0.81 (0.46, 1.41)	0.80 (0.46, 1.42)	-0.01 (-0.02, 0.01)	
50 to <60	1030	13	1.3	1028	14	1.4	0.8424	1.08 (0.51, 2.28)	1.08 (0.51, 2.31)	0.00 (-0.01, 0.01)	
>=60	971	12	1.2	973	16	1.6	0.4497	1.33 (0.63, 2.80)	1.34 (0.63, 2.84)	0.00 (-0.01, 0.01)	
Baseline NT-proBNP [pg/mL] (</>=median by atrial fibrillation/flutter status)											0.1259
< median	1507	17	1.1	1476	24	1.6	0.2429	1.44 (0.78, 2.67)	1.45 (0.78, 2.71)	0.00 (0.00, 0.01)	
>= median	1475	35	2.4	1516	28	1.8	0.3166	0.78 (0.48, 1.27)	0.77 (0.47, 1.28)	-0.01 (-0.02, 0.01)	
Baseline uric acid [mg/dL] (tertiles)											0.4063
<T1	975	14	1.4	963	20	2.1	0.2826	1.45 (0.73, 2.85)	1.46 (0.73, 2.90)	0.01 (-0.01, 0.02)	
>=T1 and <T2	966	15	1.6	1032	12	1.2	0.4505	0.75 (0.35, 1.59)	0.75 (0.35, 1.60)	0.00 (-0.01, 0.01)	
>=T2	1016	23	2.3	970	20	2.1	0.7573	0.91 (0.50, 1.65)	0.91 (0.50, 1.67)	0.00 (-0.01, 0.01)	
Baseline use of MRA											0.9748
No	1865	28	1.5	1878	28	1.5	0.9791	0.99 (0.59, 1.67)	0.99 (0.59, 1.68)	0.00 (-0.01, 0.01)	
Yes	1124	24	2.1	1118	24	2.1	0.9850	1.01 (0.57, 1.76)	1.01 (0.57, 1.78)	0.00 (-0.01, 0.01)	
Baseline use of ACE-inhibitor, ARB or ARNi											0.4108
No	586	9	1.5	568	12	2.1	0.4636	1.38 (0.58, 3.24)	1.38 (0.58, 3.31)	0.01 (-0.01, 0.02)	
Yes	2403	43	1.8	2428	40	1.6	0.7042	0.92 (0.60, 1.41)	0.92 (0.60, 1.42)	0.00 (-0.01, 0.01)	

Analysis is based on study 1245.110.
^ Patients with NYHA class I are counted in subgroup NYHA class II.
*** Confirmed hypoglycaemic AEs are defined by a glucose concentration <=70 mg/dL (3.9 mmol/L) or requiring assistance.
Risk ratios and odds ratios with confidence intervals (CIs) are estimated by Cochran-Mantel-Haenszel method. For risk differences standard Wald asymptotic confidence limits are calculated. A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied in case of any zero cells in contingency table.
Only treatment emergent AEs are displayed (onset between first dose until treatment stop +7 days).
MedDRA version: 23.1. * Chi-square test for treatment effect ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction).

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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 overall and by subgroup - TS
User-defined AE category: Hepatic Injury (narrow SMQs)

Subgroup	Placebo			Empa 10mg			Empa 10mg vs Placebo						
Category	N	n	%	N	n	%	p-value *	Risk ratio (95% CI)	Odds ratio (95% CI)	Risk diff. (95% CI)	p-value **
Overall	2989	41	1.4	2996	32	1.1	0.2847	0.78 (0.49, 1.23)	0.78 (0.49, 1.24)	0.00 (-0.01, 0.00)	
Sex											0.4915
Male	1653	25	1.5	1658	22	1.3	0.6519	0.88 (0.50, 1.55)	0.88 (0.49, 1.56)	0.00 (-0.01, 0.01)	
Female	1336	16	1.2	1338	10	0.7	0.2355	0.62 (0.28, 1.37)	0.62 (0.28, 1.37)	0.00 (-0.01, 0.00)	
Age [years]											0.2277
<70	1084	8	0.7	1066	10	0.9	0.6107	1.27 (0.50, 3.21)	1.27 (0.50, 3.24)	0.00 (-0.01, 0.01)	
>=70	1905	33	1.7	1930	22	1.1	0.1229	0.66 (0.39, 1.12)	0.65 (0.38, 1.13)	-0.01 (-0.01, 0.00)	
Region											0.2914
North America	359	8	2.2	359	4	1.1	0.2442	0.50 (0.15, 1.65)	0.49 (0.15, 1.66)	-0.01 (-0.03, 0.01)	
Latin America	757	4	0.5	758	9	1.2	0.1644	2.25 (0.69, 7.27)	2.26 (0.69, 7.38)	0.01 (0.00, 0.02)	
Europe	1341	19	1.4	1346	11	0.8	0.1391	0.58 (0.28, 1.21)	0.57 (0.27, 1.21)	-0.01 (-0.01, 0.00)	
Asia	343	8	2.3	343	5	1.5	0.4009	0.63 (0.21, 1.89)	0.62 (0.20, 1.91)	-0.01 (-0.03, 0.01)	
Other	189	2	1.1	190	3	1.6	0.6569	1.49 (0.25, 8.83)	1.50 (0.25, 9.08)	0.01 (-0.02, 0.03)	
OECD member											0.0300
No	847	4	0.5	868	10	1.2	0.1178	2.44 (0.77, 7.75)	2.46 (0.77, 7.86)	0.01 (0.00, 0.02)	
Yes	2142	37	1.7	2128	22	1.0	0.0522	0.60 (0.35, 1.01)	0.59 (0.35, 1.01)	-0.01 (-0.01, 0.00)	
Baseline NYHA											0.8377
II^	2450	27	1.1	2435	20	0.8	0.3150	0.75 (0.42, 1.33)	0.74 (0.42, 1.33)	0.00 (-0.01, 0.00)	
III/IV	539	14	2.6	561	12	2.1	0.6169	0.82 (0.38, 1.76)	0.82 (0.38, 1.79)	0.00 (-0.02, 0.01)	
Baseline Diabetes Status											0.8197
Diabetic	1471	23	1.6	1465	17	1.2	0.3461	0.74 (0.40, 1.38)	0.74 (0.39, 1.39)	0.00 (-0.01, 0.00)	
Non-Diabetic	1518	18	1.2	1531	15	1.0	0.5825	0.83 (0.42, 1.63)	0.82 (0.41, 1.64)	0.00 (-0.01, 0.01)	

Analysis is based on study 1245.110.
^ Patients with NYHA class I are counted in subgroup NYHA class II.
*** Confirmed hypoglycaemic AEs are defined by a glucose concentration <=70 mg/dL (3.9 mmol/L) or requiring assistance.
Risk ratios and odds ratios with confidence intervals (CIs) are estimated by Cochran-Mantel-Haenszel method. For risk differences standard Wald asymptotic confidence limits are calculated. A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied in case of any zero cells in contingency table.
Only treatment emergent AEs are displayed (onset between first dose until treatment stop +7 days).
MedDRA version: 23.1. * Chi-square test for treatment effect ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction).

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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 overall and by subgroup - TS
User-defined AE category: Hepatic Injury (narrow SMQs)

Subgroup	Placebo			Empa 10mg			Empa 10mg vs Placebo				
Category	N	n	%	N	n	%	p-value *	Risk ratio (95% CI)	Odds ratio (95% CI)	Risk diff. (95% CI)	p-value **
Baseline Diabetes Status											0.9370
Diabetic	1471	23	1.6	1465	17	1.2	0.3461	0.74 (0.40, 1.38)	0.74 (0.39, 1.39)	0.00 (-0.01, 0.00)	
Pre-Diabetes	979	11	1.1	1001	10	1.0	0.7867	0.89 (0.38, 2.08)	0.89 (0.38, 2.10)	0.00 (-0.01, 0.01)	
Normal (no pre-diabetes)	539	7	1.3	530	5	0.9	0.5814	0.73 (0.23, 2.27)	0.72 (0.23, 2.29)	0.00 (-0.02, 0.01)	
Baseline BMI [kg/m²]											0.1252
<30	1641	30	1.8	1654	18	1.1	0.0763	0.60 (0.33, 1.06)	0.59 (0.33, 1.06)	-0.01 (-0.02, 0.00)	
>=30	1348	11	0.8	1342	14	1.0	0.5392	1.28 (0.58, 2.81)	1.28 (0.58, 2.83)	0.00 (0.00, 0.01)	
Baseline eGFR (CKD-EPI) [mL/min/1.73m²]											0.0856
>=60	1505	15	1.0	1493	18	1.2	0.5835	1.21 (0.61, 2.39)	1.21 (0.61, 2.41)	0.00 (-0.01, 0.01)	
<60	1482	26	1.8	1503	14	0.9	0.0506	0.53 (0.28, 1.01)	0.53 (0.27, 1.01)	-0.01 (-0.02, 0.00)	
History of HHF (in the last 12 months)											0.8817
No	2320	28	1.2	2297	22	1.0	0.4135	0.79 (0.46, 1.38)	0.79 (0.45, 1.39)	0.00 (-0.01, 0.00)	
Yes	669	13	1.9	699	10	1.4	0.4611	0.74 (0.33, 1.67)	0.73 (0.32, 1.68)	-0.01 (-0.02, 0.01)	
Baseline SBP (</>= median)											0.5335
< median	1474	27	1.8	1496	19	1.3	0.2152	0.69 (0.39, 1.24)	0.69 (0.38, 1.25)	-0.01 (-0.01, 0.00)	
>= median	1515	14	0.9	1500	13	0.9	0.8671	0.94 (0.44, 1.99)	0.94 (0.44, 2.00)	0.00 (-0.01, 0.01)	
History of atrial fibrillation or atrial flutter											0.5095
No	1426	15	1.1	1417	14	1.0	0.8654	0.94 (0.46, 1.94)	0.94 (0.45, 1.95)	0.00 (-0.01, 0.01)	
Yes	1558	26	1.7	1575	18	1.1	0.2110	0.68 (0.38, 1.24)	0.68 (0.37, 1.25)	-0.01 (-0.01, 0.00)	

Analysis is based on study 1245.110.
^ Patients with NYHA class I are counted in subgroup NYHA class II.
*** Confirmed hypoglycaemic AEs are defined by a glucose concentration <=70 mg/dL (3.9 mmol/L) or requiring assistance.
Risk ratios and odds ratios with confidence intervals (CIs) are estimated by Cochran-Mantel-Haenszel method. For risk differences standard Wald asymptotic confidence limits are calculated. A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied in case of any zero cells in contingency table.
Only treatment emergent AEs are displayed (onset between first dose until treatment stop +7 days).
MedDRA version: 23.1. * Chi-square test for treatment effect ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction).

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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 overall and by subgroup - TS
User-defined AE category: Hepatic Injury (narrow SMQs)

Subgroup	Placebo			Empa 10mg			Empa 10mg vs Placebo				
Category	N	n	%	N	n	%	p-value *	Risk ratio (95% CI)	Odds ratio (95% CI)	Risk diff. (95% CI)	p-value **
Baseline LVEF [%]											0.1428
< 50	988	14	1.4	995	6	0.6	0.0697	0.43 (0.16, 1.10)	0.42 (0.16, 1.10)	-0.01 (-0.02, 0.00)	
>= 50	2001	27	1.3	2001	26	1.3	0.8900	0.96 (0.56, 1.64)	0.96 (0.56, 1.66)	0.00 (-0.01, 0.01)	
Baseline LVEF [%]											0.0734
<50	988	14	1.4	995	6	0.6	0.0697	0.43 (0.16, 1.10)	0.42 (0.16, 1.10)	-0.01 (-0.02, 0.00)	
50 to <60	1030	19	1.8	1028	12	1.2	0.2072	0.63 (0.31, 1.30)	0.63 (0.30, 1.30)	-0.01 (-0.02, 0.00)	
>=60	971	8	0.8	973	14	1.4	0.2000	1.75 (0.74, 4.14)	1.76 (0.73, 4.21)	0.01 (0.00, 0.02)	
Baseline NT-proBNP [pg/mL] (</>=median by atrial fibrillation/flutter status)											0.9215
< median	1507	15	1.0	1476	11	0.7	0.4625	0.75 (0.35, 1.62)	0.75 (0.34, 1.63)	0.00 (-0.01, 0.00)	
>= median	1475	26	1.8	1516	21	1.4	0.4066	0.79 (0.44, 1.39)	0.78 (0.44, 1.40)	0.00 (-0.01, 0.01)	
Baseline uric acid [mg/dL] (tertiles)											0.9901
<T1	975	11	1.1	963	9	0.9	0.6732	0.83 (0.34, 1.99)	0.83 (0.34, 2.00)	0.00 (-0.01, 0.01)	
>=T1 and <T2	966	11	1.1	1032	9	0.9	0.5497	0.77 (0.32, 1.84)	0.76 (0.32, 1.85)	0.00 (-0.01, 0.01)	
>=T2	1016	19	1.9	970	14	1.4	0.4570	0.77 (0.39, 1.53)	0.77 (0.38, 1.54)	0.00 (-0.02, 0.01)	
Baseline use of MRA											0.5014
No	1865	21	1.1	1878	19	1.0	0.7338	0.90 (0.48, 1.67)	0.90 (0.48, 1.67)	0.00 (-0.01, 0.01)	
Yes	1124	20	1.8	1118	13	1.2	0.2255	0.65 (0.33, 1.31)	0.65 (0.32, 1.31)	-0.01 (-0.02, 0.00)	
Baseline use of ACE-inhibitor, ARB or ARNi											0.8388
No	586	11	1.9	568	9	1.6	0.7033	0.84 (0.35, 2.02)	0.84 (0.35, 2.05)	0.00 (-0.02, 0.01)	
Yes	2403	30	1.2	2428	23	0.9	0.3150	0.76 (0.44, 1.30)	0.76 (0.44, 1.31)	0.00 (-0.01, 0.00)	

Analysis is based on study 1245.110.
^ Patients with NYHA class I are counted in subgroup NYHA class II.
*** Confirmed hypoglycaemic AEs are defined by a glucose concentration <=70 mg/dL (3.9 mmol/L) or requiring assistance.
Risk ratios and odds ratios with confidence intervals (CIs) are estimated by Cochran-Mantel-Haenszel method. For risk differences standard Wald asymptotic confidence limits are calculated. A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied in case of any zero cells in contingency table.
Only treatment emergent AEs are displayed (onset between first dose until treatment stop +7 days).
MedDRA version: 23.1. * Chi-square test for treatment effect ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction).

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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 overall and by subgroup - TS
User-defined AE category: Acute renal failure (narrow 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	2989	161	5.4	2996	123	4.1	0.0198	0.76 (0.61, 0.96)	0.75 (0.59, 0.96)	-0.01 (-0.02, 0.00)	
Sex											0.2453
Male	1653	92	5.6	1658	62	3.7	0.0126	0.67 (0.49, 0.92)	0.66 (0.47, 0.92)	-0.02 (-0.03, 0.00)	
Female	1336	69	5.2	1338	61	4.6	0.4666	0.88 (0.63, 1.24)	0.88 (0.62, 1.25)	-0.01 (-0.02, 0.01)	
Age [years]											0.4373
<70	1084	55	5.1	1066	36	3.4	0.0507	0.67 (0.44, 1.00)	0.65 (0.43, 1.00)	-0.02 (-0.03, 0.00)	
>=70	1905	106	5.6	1930	87	4.5	0.1346	0.81 (0.61, 1.07)	0.80 (0.60, 1.07)	-0.01 (-0.02, 0.00)	
Region											0.1183
North America	359	44	12.3	359	38	10.6	0.4814	0.86 (0.57, 1.30)	0.85 (0.53, 1.34)	-0.02 (-0.06, 0.03)	
Latin America	757	36	4.8	758	38	5.0	0.8161	1.05 (0.68, 1.64)	1.06 (0.66, 1.69)	0.00 (-0.02, 0.02)	
Europe	1341	56	4.2	1346	27	2.0	0.0012	0.48 (0.31, 0.76)	0.47 (0.29, 0.75)	-0.02 (-0.03,-0.01)	
Asia	343	11	3.2	343	6	1.7	0.2195	0.55 (0.20, 1.46)	0.54 (0.20, 1.47)	-0.01 (-0.04, 0.01)	
Other	189	14	7.4	190	14	7.4	0.9884	0.99 (0.49, 2.03)	0.99 (0.46, 2.15)	0.00 (-0.05, 0.05)	
OECD member											0.1658
No	847	42	5.0	868	42	4.8	0.9084	0.98 (0.64, 1.48)	0.97 (0.63, 1.51)	0.00 (-0.02, 0.02)	
Yes	2142	119	5.6	2128	81	3.8	0.0068	0.69 (0.52, 0.90)	0.67 (0.50, 0.90)	-0.02 (-0.03, 0.00)	
Baseline NYHA											0.3920
II^	2450	115	4.7	2435	81	3.3	0.0149	0.71 (0.54, 0.94)	0.70 (0.52, 0.93)	-0.01 (-0.02, 0.00)	
III/IV	539	46	8.5	561	42	7.5	0.5220	0.88 (0.59, 1.31)	0.87 (0.56, 1.34)	-0.01 (-0.04, 0.02)	
Baseline Diabetes Status											0.9501
Diabetic	1471	102	6.9	1465	78	5.3	0.0691	0.77 (0.58, 1.02)	0.75 (0.56, 1.02)	-0.02 (-0.03, 0.00)	
Non-Diabetic	1518	59	3.9	1531	45	2.9	0.1496	0.76 (0.52, 1.11)	0.75 (0.50, 1.11)	-0.01 (-0.02, 0.00)	

Analysis is based on study 1245.110.
^ Patients with NYHA class I are counted in subgroup NYHA class II.
*** Confirmed hypoglycaemic AEs are defined by a glucose concentration <=70 mg/dL (3.9 mmol/L) or requiring assistance.
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Only treatment emergent AEs are displayed (onset between first dose until treatment stop +7 days).
MedDRA version: 23.1. * Chi-square test for treatment effect ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction).

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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 overall and by subgroup - TS
User-defined AE category: Acute renal failure (narrow 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 Diabetes Status											0.9816
Diabetic	1471	102	6.9	1465	78	5.3	0.0691	0.77 (0.58, 1.02)	0.75 (0.56, 1.02)	-0.02 (-0.03, 0.00)	
Pre-Diabetes	979	46	4.7	1001	36	3.6	0.2184	0.77 (0.50, 1.17)	0.76 (0.48, 1.18)	-0.01 (-0.03, 0.01)	
Normal (no pre-diabetes)	539	13	2.4	530	9	1.7	0.4112	0.70 (0.30, 1.63)	0.70 (0.30, 1.65)	-0.01 (-0.02, 0.01)	
Baseline BMI [kg/m²]											0.0028
<30	1641	84	5.1	1654	43	2.6	0.0002	0.51 (0.35, 0.73)	0.49 (0.34, 0.72)	-0.03 (-0.04,-0.01)	
>=30	1348	77	5.7	1342	80	6.0	0.7829	1.04 (0.77, 1.41)	1.05 (0.76, 1.44)	0.00 (-0.02, 0.02)	
Baseline eGFR (CKD-EPI) [mL/min/1.73m²]											0.0792
>=60	1505	48	3.2	1493	25	1.7	0.0071	0.53 (0.33, 0.85)	0.52 (0.32, 0.84)	-0.02 (-0.03, 0.00)	
<60	1482	113	7.6	1503	98	6.5	0.2391	0.86 (0.66, 1.11)	0.85 (0.64, 1.12)	-0.01 (-0.03, 0.01)	
History of HHF (in the last 12 months)											0.6403
No	2320	112	4.8	2297	81	3.5	0.0272	0.73 (0.55, 0.97)	0.72 (0.54, 0.96)	-0.01 (-0.02, 0.00)	
Yes	669	49	7.3	699	42	6.0	0.3289	0.82 (0.55, 1.22)	0.81 (0.53, 1.24)	-0.01 (-0.04, 0.01)	
Baseline SBP (</>= median)											0.5665
< median	1474	80	5.4	1496	66	4.4	0.2005	0.81 (0.59, 1.12)	0.80 (0.58, 1.12)	-0.01 (-0.03, 0.01)	
>= median	1515	81	5.3	1500	57	3.8	0.0422	0.71 (0.51, 0.99)	0.70 (0.49, 0.99)	-0.02 (-0.03, 0.00)	
History of atrial fibrillation or atrial flutter											0.5782
No	1426	74	5.2	1417	60	4.2	0.2296	0.82 (0.59, 1.14)	0.81 (0.57, 1.14)	-0.01 (-0.03, 0.01)	
Yes	1558	87	5.6	1575	63	4.0	0.0379	0.72 (0.52, 0.98)	0.70 (0.51, 0.98)	-0.02 (-0.03, 0.00)	

Analysis is based on study 1245.110.
^ Patients with NYHA class I are counted in subgroup NYHA class II.
*** Confirmed hypoglycaemic AEs are defined by a glucose concentration <=70 mg/dL (3.9 mmol/L) or requiring assistance.
Risk ratios and odds ratios with confidence intervals (CIs) are estimated by Cochran-Mantel-Haenszel method. For risk differences standard Wald asymptotic confidence limits are calculated. A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied in case of any zero cells in contingency table.
Only treatment emergent AEs are displayed (onset between first dose until treatment stop +7 days).
MedDRA version: 23.1. * Chi-square test for treatment effect ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction).

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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 overall and by subgroup - TS
User-defined AE category: Acute renal failure (narrow 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 LVEF [%]													0.2301
< 50	988	52	5.3	995	32	3.2	0.0236	0.61 (0.40,	0.94)	0.60 (0.38,	0.94)	-0.02 (-0.04, 0.00)	
>= 50	2001	109	5.4	2001	91	4.5	0.1916	0.83 (0.64,	1.10)	0.83 (0.62,	1.10)	-0.01 (-0.02, 0.00)	
Baseline LVEF [%]													0.3308
<50	988	52	5.3	995	32	3.2	0.0236	0.61 (0.40,	0.94)	0.60 (0.38,	0.94)	-0.02 (-0.04, 0.00)	
50 to <60	1030	63	6.1	1028	47	4.6	0.1193	0.75 (0.52,	1.08)	0.74 (0.50,	1.08)	-0.02 (-0.03, 0.00)	
>=60	971	46	4.7	973	44	4.5	0.8213	0.95 (0.64,	1.43)	0.95 (0.62,	1.45)	0.00 (-0.02, 0.02)	
Baseline NT-proBNP [pg/mL] (</>=median by atrial fibrillation/flutter status)													0.7716
< median	1507	54	3.6	1476	38	2.6	0.1111	0.72 (0.48,	1.08)	0.71 (0.47,	1.08)	-0.01 (-0.02, 0.00)	
>= median	1475	107	7.3	1516	85	5.6	0.0661	0.77 (0.59,	1.02)	0.76 (0.57,	1.02)	-0.02 (-0.03, 0.00)	
Baseline uric acid [mg/dL] (tertiles)													0.2851
<T1	975	41	4.2	963	30	3.1	0.2016	0.74 (0.47,	1.18)	0.73 (0.45,	1.18)	-0.01 (-0.03, 0.01)	
>=T1 and <T2	966	41	4.2	1032	25	2.4	0.0228	0.57 (0.35,	0.93)	0.56 (0.34,	0.93)	-0.02 (-0.03, 0.00)	
>=T2	1016	76	7.5	970	66	6.8	0.5588	0.91 (0.66,	1.25)	0.90 (0.64,	1.27)	-0.01 (-0.03, 0.02)	
Baseline use of MRA													0.5484
No	1865	98	5.3	1878	71	3.8	0.0299	0.72 (0.53,	0.97)	0.71 (0.52,	0.97)	-0.01 (-0.03, 0.00)	
Yes	1124	63	5.6	1118	52	4.7	0.3060	0.83 (0.58,	1.19)	0.82 (0.56,	1.20)	-0.01 (-0.03, 0.01)	
Baseline use of ACE-inhibitor, ARB or ARNi													0.3759
No	586	31	5.3	568	28	4.9	0.7810	0.93 (0.57,	1.53)	0.93 (0.55,	1.57)	0.00 (-0.03, 0.02)	
Yes	2403	130	5.4	2428	95	3.9	0.0135	0.72 (0.56,	0.94)	0.71 (0.54,	0.93)	-0.01 (-0.03, 0.00)	

Analysis is based on study 1245.110.
^ Patients with NYHA class I are counted in subgroup NYHA class II.
*** Confirmed hypoglycaemic AEs are defined by a glucose concentration <=70 mg/dL (3.9 mmol/L) or requiring assistance.
Risk ratios and odds ratios with confidence intervals (CIs) are estimated by Cochran-Mantel-Haenszel method. For risk differences standard Wald asymptotic confidence limits are calculated. A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied in case of any zero cells in contingency table.
Only treatment emergent AEs are displayed (onset between first dose until treatment stop +7 days).
MedDRA version: 23.1. * Chi-square test for treatment effect ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction).

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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 overall and by subgroup - TS
User-defined AE category: Ketoacidosis (broad 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	2989	34	1.1	2996	23	0.8	0.1408	0.67 (0.40, 1.14)	0.67 (0.40, 1.14)	0.00 (-0.01, 0.00)	
Sex											0.3587
Male	1653	15	0.9	1658	13	0.8	0.6983	0.86 (0.41, 1.81)	0.86 (0.41, 1.82)	0.00 (-0.01, 0.01)	
Female	1336	19	1.4	1338	10	0.7	0.0921	0.53 (0.25, 1.13)	0.52 (0.24, 1.13)	-0.01 (-0.01, 0.00)	
Age [years]											0.9180
<70	1084	19	1.8	1066	13	1.2	0.3073	0.70 (0.35, 1.40)	0.69 (0.34, 1.41)	-0.01 (-0.02, 0.00)	
>=70	1905	15	0.8	1930	10	0.5	0.3002	0.66 (0.30, 1.46)	0.66 (0.29, 1.46)	0.00 (-0.01, 0.00)	
Region											0.7017
North America	359	3	0.8	359	3	0.8	1.0000	1.00 (0.20, 4.92)	1.00 (0.20, 4.99)	0.00 (-0.01, 0.01)	
Latin America	757	18	2.4	758	10	1.3	0.1261	0.55 (0.26, 1.19)	0.55 (0.25, 1.20)	-0.01 (-0.02, 0.00)	
Europe	1341	5	0.4	1346	6	0.4	0.7673	1.20 (0.37, 3.91)	1.20 (0.36, 3.93)	0.00 (0.00, 0.01)	
Asia	343	4	1.2	343	1	0.3	0.1781	0.25 (0.03, 2.23)	0.25 (0.03, 2.23)	-0.01 (-0.02, 0.00)	
Other	189	4	2.1	190	3	1.6	0.6976	0.75 (0.17, 3.29)	0.74 (0.16, 3.36)	-0.01 (-0.03, 0.02)	
OECD member											0.1569
No	847	21	2.5	868	10	1.2	0.0391	0.46 (0.22, 0.98)	0.46 (0.21, 0.98)	-0.01 (-0.03, 0.00)	
Yes	2142	13	0.6	2128	13	0.6	0.9866	1.01 (0.47, 2.17)	1.01 (0.47, 2.18)	0.00 (0.00, 0.00)	
Baseline NYHA											0.9139
II^	2450	25	1.0	2435	17	0.7	0.2225	0.68 (0.37, 1.26)	0.68 (0.37, 1.27)	0.00 (-0.01, 0.00)	
III/IV	539	9	1.7	561	6	1.1	0.3908	0.64 (0.23, 1.79)	0.64 (0.23, 1.80)	-0.01 (-0.02, 0.01)	
Baseline Diabetes Status											0.4924
Diabetic	1471	29	2.0	1465	21	1.4	0.2599	0.73 (0.42, 1.27)	0.72 (0.41, 1.27)	-0.01 (-0.01, 0.00)	
Non-Diabetic	1518	5	0.3	1531	2	0.1	0.2516	0.40 (0.08, 2.04)	0.40 (0.08, 2.04)	0.00 (-0.01, 0.00)	

Analysis is based on study 1245.110.
^ Patients with NYHA class I are counted in subgroup NYHA class II.
*** Confirmed hypoglycaemic AEs are defined by a glucose concentration <=70 mg/dL (3.9 mmol/L) or requiring assistance.
Risk ratios and odds ratios with confidence intervals (CIs) are estimated by Cochran-Mantel-Haenszel method. For risk differences standard Wald asymptotic confidence limits are calculated. A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied in case of any zero cells in contingency table.
Only treatment emergent AEs are displayed (onset between first dose until treatment stop +7 days).
MedDRA version: 23.1. * Chi-square test for treatment effect ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction).

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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 overall and by subgroup - TS
User-defined AE category: Ketoacidosis (broad 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 Diabetes Status											0.8262
Diabetic	1471	29	2.0	1465	21	1.4	0.2599	0.73 (0.42, 1.27)	0.72 (0.41, 1.27)	-0.01 (-0.01, 0.00)	
Pre-Diabetes	979	4	0.4	1001	2	0.2	0.3981	0.49 (0.09, 2.66)	0.49 (0.09, 2.67)	0.00 (-0.01, 0.00)	
Normal (no pre-diabetes)	539	1	0.2	530	0	0	0.4865	0.34 (0.01, 8.30)	0.34 (0.01, 8.32)	0.00 (-0.01, 0.00)	
Baseline BMI [kg/m²]											0.0121
<30	1641	22	1.3	1654	7	0.4	0.0048	0.32 (0.14, 0.74)	0.31 (0.13, 0.73)	-0.01 (-0.02, 0.00)	
>=30	1348	12	0.9	1342	16	1.2	0.4403	1.34 (0.64, 2.82)	1.34 (0.63, 2.85)	0.00 (0.00, 0.01)	
Baseline eGFR (CKD-EPI) [mL/min/1.73m²]											0.5699
>=60	1505	13	0.9	1493	7	0.5	0.1841	0.54 (0.22, 1.36)	0.54 (0.22, 1.36)	0.00 (-0.01, 0.00)	
<60	1482	21	1.4	1503	16	1.1	0.3842	0.75 (0.39, 1.43)	0.75 (0.39, 1.44)	0.00 (-0.01, 0.00)	
History of HHF (in the last 12 months)											0.2710
No	2320	27	1.2	2297	15	0.7	0.0676	0.56 (0.30, 1.05)	0.56 (0.30, 1.05)	-0.01 (-0.01, 0.00)	
Yes	669	7	1.0	699	8	1.1	0.8617	1.09 (0.40, 3.00)	1.09 (0.39, 3.04)	0.00 (-0.01, 0.01)	
Baseline SBP (</>= median)											0.4527
< median	1474	15	1.0	1496	8	0.5	0.1334	0.53 (0.22, 1.24)	0.52 (0.22, 1.24)	0.00 (-0.01, 0.00)	
>= median	1515	19	1.3	1500	15	1.0	0.5088	0.80 (0.41, 1.56)	0.80 (0.40, 1.57)	0.00 (-0.01, 0.00)	
History of atrial fibrillation or atrial flutter											0.5242
No	1426	21	1.5	1417	16	1.1	0.4191	0.77 (0.40, 1.46)	0.76 (0.40, 1.47)	0.00 (-0.01, 0.00)	
Yes	1558	13	0.8	1575	7	0.4	0.1706	0.53 (0.21, 1.33)	0.53 (0.21, 1.33)	0.00 (-0.01, 0.00)	

Analysis is based on study 1245.110.
^ Patients with NYHA class I are counted in subgroup NYHA class II.
*** Confirmed hypoglycaemic AEs are defined by a glucose concentration <=70 mg/dL (3.9 mmol/L) or requiring assistance.
Risk ratios and odds ratios with confidence intervals (CIs) are estimated by Cochran-Mantel-Haenszel method. For risk differences standard Wald asymptotic confidence limits are calculated. A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied in case of any zero cells in contingency table.
Only treatment emergent AEs are displayed (onset between first dose until treatment stop +7 days).
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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 overall and by subgroup - TS
User-defined AE category: Ketoacidosis (broad 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 LVEF [%]											0.1545
< 50	988	10	1.0	995	3	0.3	0.0499	0.30 (0.08, 1.08)	0.30 (0.08, 1.08)	-0.01 (-0.01, 0.00)	
>= 50	2001	24	1.2	2001	20	1.0	0.5443	0.83 (0.46, 1.50)	0.83 (0.46, 1.51)	0.00 (-0.01, 0.00)	
Baseline LVEF [%]											0.1276
<50	988	10	1.0	995	3	0.3	0.0499	0.30 (0.08, 1.08)	0.30 (0.08, 1.08)	-0.01 (-0.01, 0.00)	
50 to <60	1030	8	0.8	1028	11	1.1	0.4866	1.38 (0.56, 3.41)	1.38 (0.55, 3.45)	0.00 (-0.01, 0.01)	
>=60	971	16	1.6	973	9	0.9	0.1573	0.56 (0.25, 1.26)	0.56 (0.25, 1.27)	-0.01 (-0.02, 0.00)	
Baseline NT-proBNP [pg/mL] (</>=median by atrial fibrillation/flutter status)											0.4179
< median	1507	13	0.9	1476	11	0.7	0.7197	0.86 (0.39, 1.92)	0.86 (0.39, 1.93)	0.00 (-0.01, 0.01)	
>= median	1475	21	1.4	1516	12	0.8	0.0980	0.56 (0.27, 1.13)	0.55 (0.27, 1.13)	-0.01 (-0.01, 0.00)	
Baseline uric acid [mg/dL] (tertiles)											0.0476
<T1	975	8	0.8	963	5	0.5	0.4165	0.63 (0.21, 1.93)	0.63 (0.21, 1.94)	0.00 (-0.01, 0.00)	
>=T1 and <T2	966	9	0.9	1032	14	1.4	0.3736	1.46 (0.63, 3.35)	1.46 (0.63, 3.39)	0.00 (-0.01, 0.01)	
>=T2	1016	16	1.6	970	4	0.4	0.0095	0.26 (0.09, 0.78)	0.26 (0.09, 0.78)	-0.01 (-0.02, 0.00)	
Baseline use of MRA											0.5176
No	1865	22	1.2	1878	13	0.7	0.1214	0.59 (0.30, 1.16)	0.58 (0.29, 1.16)	0.00 (-0.01, 0.00)	
Yes	1124	12	1.1	1118	10	0.9	0.6775	0.84 (0.36, 1.93)	0.84 (0.36, 1.94)	0.00 (-0.01, 0.01)	
Baseline use of ACE-inhibitor, ARB or ARNi											0.3581
No	586	8	1.4	568	3	0.5	0.1435	0.39 (0.10, 1.45)	0.38 (0.10, 1.45)	-0.01 (-0.02, 0.00)	
Yes	2403	26	1.1	2428	20	0.8	0.3554	0.76 (0.43, 1.36)	0.76 (0.42, 1.36)	0.00 (-0.01, 0.00)	

Analysis is based on study 1245.110.
^ Patients with NYHA class I are counted in subgroup NYHA class II.
*** Confirmed hypoglycaemic AEs are defined by a glucose concentration <=70 mg/dL (3.9 mmol/L) or requiring assistance.
Risk ratios and odds ratios with confidence intervals (CIs) are estimated by Cochran-Mantel-Haenszel method. For risk differences standard Wald asymptotic confidence limits are calculated. A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied in case of any zero cells in contingency table.
Only treatment emergent AEs are displayed (onset between first dose until treatment stop +7 days).
MedDRA version: 23.1. * Chi-square test for treatment effect ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction).

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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 overall and by subgroup - TS
User-defined AE category: Ketoacidosis (narrow 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	2989	5	0.2	2996	4	0.1	0.7360	0.80 (0.21, 2.97)	0.80 (0.21, 2.97)	0.00 (0.00, 0.00)	
Sex											
Male	1653	2	0.1	1658	3	0.2					
Female	1336	3	0.2	1338	1	0.1					
Age [years]											
<70	1084	5	0.5	1066	2	0.2					
>=70	1905	0	0	1930	2	0.1					
Region											
North America	359	1	0.3	359	1	0.3					
Latin America	757	1	0.1	758	0	0					
Europe	1341	0	0	1346	1	0.1					
Asia	343	1	0.3	343	0	0					
Other	189	2	1.1	190	2	1.1					
OECD member											
No	847	4	0.5	868	1	0.1					
Yes	2142	1	<0.1	2128	3	0.1					
Baseline NYHA											
II^	2450	3	0.1	2435	3	0.1					
III/IV	539	2	0.4	561	1	0.2					
Baseline Diabetes Status											
Diabetic	1471	5	0.3	1465	4	0.3					
Non-Diabetic	1518	0	0	1531	0	0					

Analysis is based on study 1245.110.
^ Patients with NYHA class I are counted in subgroup NYHA class II.
*** Confirmed hypoglycaemic AEs are defined by a glucose concentration <=70 mg/dL (3.9 mmol/L) or requiring assistance.
Risk ratios and odds ratios with confidence intervals (CIs) are estimated by Cochran-Mantel-Haenszel method. For risk differences standard Wald asymptotic confidence limits are calculated. A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied in case of any zero cells in contingency table.
Only treatment emergent AEs are displayed (onset between first dose until treatment stop +7 days).
MedDRA version: 23.1. * Chi-square test for treatment effect ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction).

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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 overall and by subgroup - TS
User-defined AE category: Ketoacidosis (narrow 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 Diabetes Status											
Diabetic	1471	5	0.3	1465	4	0.3					
Pre-Diabetes	979	0	0	1001	0	0					
Normal (no pre-diabetes)	539	0	0	530	0	0					
Baseline BMI [kg/m²]											
<30	1641	2	0.1	1654	1	0.1					
>=30	1348	3	0.2	1342	3	0.2					
Baseline eGFR (CKD-EPI) [mL/min/1.73m²]											
>=60	1505	0	0	1493	2	0.1					
<60	1482	5	0.3	1503	2	0.1					
History of HHF (in the last 12 months)											
No	2320	2	0.1	2297	2	0.1					
Yes	669	3	0.4	699	2	0.3					
Baseline SBP (</>= median)											
< median	1474	2	0.1	1496	2	0.1					
>= median	1515	3	0.2	1500	2	0.1					
History of atrial fibrillation or atrial flutter											
No	1426	3	0.2	1417	4	0.3					
Yes	1558	2	0.1	1575	0	0					

Analysis is based on study 1245.110.
^ Patients with NYHA class I are counted in subgroup NYHA class II.
*** Confirmed hypoglycaemic AEs are defined by a glucose concentration <=70 mg/dL (3.9 mmol/L) or requiring assistance.
Risk ratios and odds ratios with confidence intervals (CIs) are estimated by Cochran-Mantel-Haenszel method. For risk differences standard Wald asymptotic confidence limits are calculated. A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied in case of any zero cells in contingency table.
Only treatment emergent AEs are displayed (onset between first dose until treatment stop +7 days).
MedDRA version: 23.1. * Chi-square test for treatment effect ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction).

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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 overall and by subgroup - TS
User-defined AE category: Ketoacidosis (narrow 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 LVEF [%]											
< 50	988	3	0.3	995	0	0					
>= 50	2001	2	0.1	2001	4	0.2					
Baseline LVEF [%]											
<50	988	3	0.3	995	0	0					
50 to <60	1030	1	0.1	1028	1	0.1					
>=60	971	1	0.1	973	3	0.3					
Baseline NT-proBNP [pg/mL] (</>=median by atrial fibrillation/flutter status)											
< median	1507	2	0.1	1476	2	0.1					
>= median	1475	3	0.2	1516	2	0.1					
Baseline uric acid [mg/dL] (tertiles)											
<T1	975	0	0	963	0	0					
>=T1 and <T2	966	2	0.2	1032	3	0.3					
>=T2	1016	3	0.3	970	1	0.1					
Baseline use of MRA											
No	1865	2	0.1	1878	2	0.1					
Yes	1124	3	0.3	1118	2	0.2					
Baseline use of ACE-inhibitor, ARB or ARNi											
No	586	2	0.3	568	0	0					
Yes	2403	3	0.1	2428	4	0.2					

Analysis is based on study 1245.110.
^ Patients with NYHA class I are counted in subgroup NYHA class II.
*** Confirmed hypoglycaemic AEs are defined by a glucose concentration <=70 mg/dL (3.9 mmol/L) or requiring assistance.
Risk ratios and odds ratios with confidence intervals (CIs) are estimated by Cochran-Mantel-Haenszel method. For risk differences standard Wald asymptotic confidence limits are calculated. A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied in case of any zero cells in contingency table.
Only treatment emergent AEs are displayed (onset between first dose until treatment stop +7 days).
MedDRA version: 23.1. * Chi-square test for treatment effect ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction).

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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 overall and by subgroup - TS
User-defined AE category: AE 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	2989	17	0.6	2996	11	0.4	0.2531	0.65 (0.30, 1.38)	0.64 (0.30, 1.38)	0.00 (-0.01, 0.00)	
Sex											0.3470
Male	1653	13	0.8	1658	10	0.6	0.5254	0.77 (0.34, 1.74)	0.77 (0.33, 1.75)	0.00 (-0.01, 0.00)	
Female	1336	4	0.3	1338	1	0.1	0.1788	0.25 (0.03, 2.23)	0.25 (0.03, 2.23)	0.00 (-0.01, 0.00)	
Age [years]											0.2830
<70	1084	9	0.8	1066	8	0.8	0.8346	0.90 (0.35, 2.33)	0.90 (0.35, 2.35)	0.00 (-0.01, 0.01)	
>=70	1905	8	0.4	1930	3	0.2	0.1257	0.37 (0.10, 1.39)	0.37 (0.10, 1.39)	0.00 (-0.01, 0.00)	
Region											0.8168
North America	359	5	1.4	359	3	0.8	0.4770	0.60 (0.14, 2.49)	0.60 (0.14, 2.52)	-0.01 (-0.02, 0.01)	
Latin America	757	5	0.7	758	2	0.3	0.2550	0.40 (0.08, 2.05)	0.40 (0.08, 2.06)	0.00 (-0.01, 0.00)	
Europe	1341	6	0.4	1346	5	0.4	0.7578	0.83 (0.25, 2.71)	0.83 (0.25, 2.72)	0.00 (-0.01, 0.00)	
Asia	343	1	0.3	343	0	0	0.4789	0.33 (0.01, 8.15)	0.33 (0.01, 8.19)	0.00 (-0.01, 0.01)	
Other	189	0	0	190	1	0.5	0.4807	2.98 (0.12, 72.80)	3.00 (0.12, 74.11)	0.01 (-0.01, 0.02)	
OECD member											0.7124
No	847	4	0.5	868	2	0.2	0.3964	0.49 (0.09, 2.66)	0.49 (0.09, 2.66)	0.00 (-0.01, 0.00)	
Yes	2142	13	0.6	2128	9	0.4	0.4011	0.70 (0.30, 1.63)	0.70 (0.30, 1.63)	0.00 (-0.01, 0.00)	
Baseline NYHA											0.6178
II^	2450	11	0.4	2435	8	0.3	0.4989	0.73 (0.29, 1.82)	0.73 (0.29, 1.82)	0.00 (0.00, 0.00)	
III/IV	539	6	1.1	561	3	0.5	0.2871	0.48 (0.12, 1.91)	0.48 (0.12, 1.92)	-0.01 (-0.02, 0.00)	
Baseline Diabetes Status											0.8159
Diabetic	1471	15	1.0	1465	10	0.7	0.3202	0.67 (0.30, 1.49)	0.67 (0.30, 1.49)	0.00 (-0.01, 0.00)	
Non-Diabetic	1518	2	0.1	1531	1	0.1	0.5585	0.50 (0.05, 5.46)	0.50 (0.04, 5.47)	0.00 (0.00, 0.00)	

Analysis is based on study 1245.110.
^ Patients with NYHA class I are counted in subgroup NYHA class II.
*** Confirmed hypoglycaemic AEs are defined by a glucose concentration <=70 mg/dL (3.9 mmol/L) or requiring assistance.
Risk ratios and odds ratios with confidence intervals (CIs) are estimated by Cochran-Mantel-Haenszel method. For risk differences standard Wald asymptotic confidence limits are calculated. A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
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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 overall and by subgroup - TS
User-defined AE category: AE 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 Diabetes Status											0.8688
Diabetic	1471	15	1.0	1465	10	0.7	0.3202	0.67 (0.30, 1.49)	0.67 (0.30, 1.49)	0.00 (-0.01, 0.00)	
Pre-Diabetes	979	1	0.1	1001	0	0	0.4695	0.33 (0.01, 7.99)	0.33 (0.01, 8.00)	0.00 (0.00, 0.00)	
Normal (no pre-diabetes)	539	1	0.2	530	1	0.2	0.9905	1.02 (0.06, 16.22)	1.02 (0.06, 16.30)	0.00 (-0.01, 0.01)	
Baseline BMI [kg/m²]											0.6467
<30	1641	6	0.4	1654	3	0.2	0.3110	0.50 (0.12, 1.98)	0.50 (0.12, 1.98)	0.00 (-0.01, 0.00)	
>=30	1348	11	0.8	1342	8	0.6	0.4959	0.73 (0.29, 1.81)	0.73 (0.29, 1.82)	0.00 (-0.01, 0.00)	
Baseline eGFR (CKD-EPI) [mL/min/1.73m²]											0.3740
>=60	1505	5	0.3	1493	5	0.3	0.9899	1.01 (0.29, 3.47)	1.01 (0.29, 3.49)	0.00 (0.00, 0.00)	
<60	1482	12	0.8	1503	6	0.4	0.1475	0.49 (0.19, 1.31)	0.49 (0.18, 1.31)	0.00 (-0.01, 0.00)	
History of HHF (in the last 12 months)											0.4264
No	2320	12	0.5	2297	6	0.3	0.1628	0.51 (0.19, 1.34)	0.50 (0.19, 1.34)	0.00 (-0.01, 0.00)	
Yes	669	5	0.7	699	5	0.7	0.9445	0.96 (0.28, 3.29)	0.96 (0.28, 3.32)	0.00 (-0.01, 0.01)	
Baseline SBP (</>= median)											0.5555
< median	1474	8	0.5	1496	4	0.3	0.2369	0.49 (0.15, 1.63)	0.49 (0.15, 1.64)	0.00 (-0.01, 0.00)	
>= median	1515	9	0.6	1500	7	0.5	0.6302	0.79 (0.29, 2.10)	0.78 (0.29, 2.11)	0.00 (-0.01, 0.00)	
History of atrial fibrillation or atrial flutter											0.0631
No	1426	11	0.8	1417	3	0.2	0.0330	0.27 (0.08, 0.98)	0.27 (0.08, 0.98)	-0.01 (-0.01, 0.00)	
Yes	1558	6	0.4	1575	8	0.5	0.6063	1.32 (0.46, 3.79)	1.32 (0.46, 3.81)	0.00 (0.00, 0.01)	

Analysis is based on study 1245.110.
^ Patients with NYHA class I are counted in subgroup NYHA class II.
*** Confirmed hypoglycaemic AEs are defined by a glucose concentration <=70 mg/dL (3.9 mmol/L) or requiring assistance.
Risk ratios and odds ratios with confidence intervals (CIs) are estimated by Cochran-Mantel-Haenszel method. For risk differences standard Wald asymptotic confidence limits are calculated. A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied in case of any zero cells in contingency table.
Only treatment emergent AEs are displayed (onset between first dose until treatment stop +7 days).
MedDRA version: 23.1. * Chi-square test for treatment effect ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction).

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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 overall and by subgroup - TS
User-defined AE category: AE 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 LVEF [%]											0.7066
< 50	988	5	0.5	995	4	0.4	0.7303	0.79 (0.21, 2.95)	0.79 (0.21, 2.96)	0.00 (-0.01, 0.00)	
>= 50	2001	12	0.6	2001	7	0.3	0.2502	0.58 (0.23, 1.48)	0.58 (0.23, 1.48)	0.00 (-0.01, 0.00)	
Baseline LVEF [%]											0.9174
<50	988	5	0.5	995	4	0.4	0.7303	0.79 (0.21, 2.95)	0.79 (0.21, 2.96)	0.00 (-0.01, 0.00)	
50 to <60	1030	3	0.3	1028	2	0.2	0.6559	0.67 (0.11, 3.99)	0.67 (0.11, 4.00)	0.00 (-0.01, 0.00)	
>=60	971	9	0.9	973	5	0.5	0.2816	0.55 (0.19, 1.65)	0.55 (0.18, 1.65)	0.00 (-0.01, 0.00)	
Baseline NT-proBNP [pg/mL] (</>=median by atrial fibrillation/flutter status)											0.6530
< median	1507	8	0.5	1476	6	0.4	0.6193	0.77 (0.27, 2.20)	0.76 (0.26, 2.21)	0.00 (-0.01, 0.00)	
>= median	1475	9	0.6	1516	5	0.3	0.2614	0.54 (0.18, 1.61)	0.54 (0.18, 1.61)	0.00 (-0.01, 0.00)	
Baseline uric acid [mg/dL] (tertiles)											0.1557
<T1	975	5	0.5	963	0	0	0.0424	0.09 (<0.01, 1.66)	0.09 (<0.01, 1.66)	-0.01 (-0.01, 0.00)	
>=T1 and <T2	966	3	0.3	1032	6	0.6	0.3663	1.87 (0.47, 7.46)	1.88 (0.47, 7.53)	0.00 (0.00, 0.01)	
>=T2	1016	8	0.8	970	5	0.5	0.4525	0.65 (0.21, 1.99)	0.65 (0.21, 2.00)	0.00 (-0.01, 0.00)	
Baseline use of MRA											0.3097
No	1865	11	0.6	1878	5	0.3	0.1292	0.45 (0.16, 1.30)	0.45 (0.16, 1.30)	0.00 (-0.01, 0.00)	
Yes	1124	6	0.5	1118	6	0.5	0.9926	1.01 (0.33, 3.11)	1.01 (0.32, 3.13)	0.00 (-0.01, 0.01)	
Baseline use of ACE-inhibitor, ARB or ARNi											0.6101
No	586	2	0.3	568	2	0.4	0.9751	1.03 (0.15, 7.30)	1.03 (0.14, 7.35)	0.00 (-0.01, 0.01)	
Yes	2403	15	0.6	2428	9	0.4	0.2101	0.59 (0.26, 1.35)	0.59 (0.26, 1.36)	0.00 (-0.01, 0.00)	

Analysis is based on study 1245.110.
^ Patients with NYHA class I are counted in subgroup NYHA class II.
*** Confirmed hypoglycaemic AEs are defined by a glucose concentration <=70 mg/dL (3.9 mmol/L) or requiring assistance.
Risk ratios and odds ratios with confidence intervals (CIs) are estimated by Cochran-Mantel-Haenszel method. For risk differences standard Wald asymptotic confidence limits are calculated. A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied in case of any zero cells in contingency table.
Only treatment emergent AEs are displayed (onset between first dose until treatment stop +7 days).
MedDRA version: 23.1. * Chi-square test for treatment effect ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction).

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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 overall and by subgroup - TS
User-defined AE category: Confirmed 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	2989	9	0.3	2996	13	0.4	0.3959	1.44 (0.62, 3.37)	1.44 (0.62, 3.38)	0.00 (0.00, 0.00)	
Sex											0.1484
Male	1653	7	0.4	1658	6	0.4	0.7769	0.85 (0.29, 2.54)	0.85 (0.29, 2.55)	0.00 (0.00, 0.00)	
Female	1336	2	0.1	1338	7	0.5	0.0955	3.49 (0.73, 16.79)	3.51 (0.73, 16.92)	0.00 (0.00, 0.01)	
Age [years]											0.1023
<70	1084	1	0.1	1066	6	0.6	0.0555	6.10 (0.74, 50.59)	6.13 (0.74, 51.00)	0.00 (0.00, 0.01)	
>=70	1905	8	0.4	1930	7	0.4	0.7764	0.86 (0.31, 2.38)	0.86 (0.31, 2.39)	0.00 (0.00, 0.00)	
Region											
North America	359	2	0.6	359	5	1.4					
Latin America	757	3	0.4	758	3	0.4					
Europe	1341	4	0.3	1346	1	0.1					
Asia	343	0	0	343	1	0.3					
Other	189	0	0	190	3	1.6					
OECD member											0.4440
No	847	2	0.2	868	5	0.6	0.2697	2.44 (0.47, 12.54)	2.45 (0.47, 12.65)	0.00 (0.00, 0.01)	
Yes	2142	7	0.3	2128	8	0.4	0.7861	1.15 (0.42, 3.17)	1.15 (0.42, 3.18)	0.00 (0.00, 0.00)	
Baseline NYHA											0.1119
II^	2450	9	0.4	2435	8	0.3	0.8179	0.89 (0.35, 2.31)	0.89 (0.34, 2.32)	0.00 (0.00, 0.00)	
III/IV	539	0	0	561	5	0.9	0.0457	10.57 (0.59,190.68)	10.66 (0.59,193.32)	0.01 (0.00, 0.02)	
Baseline Diabetes Status											0.3456
Diabetic	1471	8	0.5	1465	13	0.9	0.2694	1.63 (0.68, 3.92)	1.64 (0.68, 3.96)	0.00 (0.00, 0.01)	
Non-Diabetic	1518	1	0.1	1531	0	0	0.4756	0.33 (0.01, 8.11)	0.33 (0.01, 8.11)	0.00 (0.00, 0.00)	

Analysis is based on study 1245.110.
^ Patients with NYHA class I are counted in subgroup NYHA class II.
*** Confirmed hypoglycaemic AEs are defined by a glucose concentration <=70 mg/dL (3.9 mmol/L) or requiring assistance.
Risk ratios and odds ratios with confidence intervals (CIs) are estimated by Cochran-Mantel-Haenszel method. For risk differences standard Wald asymptotic confidence limits are calculated. A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied in case of any zero cells in contingency table.
Only treatment emergent AEs are displayed (onset between first dose until treatment stop +7 days).
MedDRA version: 23.1. * Chi-square test for treatment effect ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction).

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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 overall and by subgroup - TS
User-defined AE category: Confirmed 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 **
Baseline Diabetes Status											0.6262
Diabetic	1471	8	0.5	1465	13	0.9	0.2694	1.63 (0.68, 3.92)	1.64 (0.68, 3.96)	0.00 (0.00, 0.01)	
Pre-Diabetes	979	1	0.1	1001	0	0	0.4695	0.33 (0.01, 7.99)	0.33 (0.01, 8.00)	0.00 (0.00, 0.00)	
Normal (no pre-diabetes)	539	0	0	530	0	0	0.9933	1.02 (0.02, 51.16)	1.02 (0.02, 51.35)	0.00 (0.00, 0.00)	
Baseline BMI [kg/m²]											0.4329
<30	1641	2	0.1	1654	5	0.3	0.2607	2.48 (0.48, 12.77)	2.48 (0.48, 12.83)	0.00 (0.00, 0.00)	
>=30	1348	7	0.5	1342	8	0.6	0.7890	1.15 (0.42, 3.16)	1.15 (0.42, 3.18)	0.00 (0.00, 0.01)	
Baseline eGFR (CKD-EPI) [mL/min/1.73m²]											0.6830
>=60	1505	5	0.3	1493	6	0.4	0.7525	1.21 (0.37, 3.96)	1.21 (0.37, 3.97)	0.00 (0.00, 0.01)	
<60	1482	4	0.3	1503	7	0.5	0.3773	1.73 (0.51, 5.88)	1.73 (0.51, 5.92)	0.00 (0.00, 0.01)	
History of HHF (in the last 12 months)											0.1648
No	2320	7	0.3	2297	6	0.3	0.7951	0.87 (0.29, 2.57)	0.87 (0.29, 2.58)	0.00 (0.00, 0.00)	
Yes	669	2	0.3	699	7	1.0	0.1082	3.35 (0.70, 16.07)	3.37 (0.70, 16.30)	0.01 (0.00, 0.02)	
Baseline SBP (</>= median)											0.4469
< median	1474	4	0.3	1496	8	0.5	0.2579	1.97 (0.59, 6.53)	1.98 (0.59, 6.58)	0.00 (0.00, 0.01)	
>= median	1515	5	0.3	1500	5	0.3	0.9874	1.01 (0.29, 3.48)	1.01 (0.29, 3.50)	0.00 (0.00, 0.00)	
History of atrial fibrillation or atrial flutter											0.3554
No	1426	6	0.4	1417	6	0.4	0.9912	1.01 (0.33, 3.11)	1.01 (0.32, 3.13)	0.00 (0.00, 0.00)	
Yes	1558	3	0.2	1575	7	0.4	0.2114	2.31 (0.60, 8.91)	2.31 (0.60, 8.96)	0.00 (0.00, 0.01)	

Analysis is based on study 1245.110.
^ Patients with NYHA class I are counted in subgroup NYHA class II.
*** Confirmed hypoglycaemic AEs are defined by a glucose concentration <=70 mg/dL (3.9 mmol/L) or requiring assistance.
Risk ratios and odds ratios with confidence intervals (CIs) are estimated by Cochran-Mantel-Haenszel method. For risk differences standard Wald asymptotic confidence limits are calculated. A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied in case of any zero cells in contingency table.
Only treatment emergent AEs are displayed (onset between first dose until treatment stop +7 days).
MedDRA version: 23.1. * Chi-square test for treatment effect ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction).

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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 overall and by subgroup - TS
User-defined AE category: Confirmed 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 **
Baseline LVEF [%]											0.0575
< 50	988	5	0.5	995	2	0.2	0.2521	0.40 (0.08, 2.04)	0.40 (0.08, 2.05)	0.00 (-0.01, 0.00)	
>= 50	2001	4	0.2	2001	11	0.5	0.0702	2.75 (0.88, 8.62)	2.76 (0.88, 8.68)	0.00 (0.00, 0.01)	
Baseline LVEF [%]											
<50	988	5	0.5	995	2	0.2					
50 to <60	1030	2	0.2	1028	4	0.4					
>=60	971	2	0.2	973	7	0.7					
Baseline NT-proBNP [pg/mL] (</>=median by atrial fibrillation/flutter status)											0.9254
< median	1507	2	0.1	1476	3	0.2	0.6377	1.53 (0.26, 9.15)	1.53 (0.26, 9.19)	0.00 (0.00, 0.00)	
>= median	1475	7	0.5	1516	10	0.7	0.5009	1.39 (0.53, 3.64)	1.39 (0.53, 3.67)	0.00 (0.00, 0.01)	
Baseline uric acid [mg/dL] (tertiles)											0.4942
<T1	975	5	0.5	963	5	0.5	0.9843	1.01 (0.29, 3.49)	1.01 (0.29, 3.51)	0.00 (-0.01, 0.01)	
>=T1 and <T2	966	2	0.2	1032	2	0.2	0.9472	0.94 (0.13, 6.63)	0.94 (0.13, 6.66)	0.00 (0.00, 0.00)	
>=T2	1016	2	0.2	970	6	0.6	0.1380	3.14 (0.64, 15.53)	3.16 (0.64, 15.67)	0.00 (0.00, 0.01)	
Baseline use of MRA											0.3020
No	1865	5	0.3	1878	10	0.5	0.2005	1.99 (0.68, 5.80)	1.99 (0.68, 5.84)	0.00 (0.00, 0.01)	
Yes	1124	4	0.4	1118	3	0.3	0.7103	0.75 (0.17, 3.36)	0.75 (0.17, 3.37)	0.00 (-0.01, 0.00)	
Baseline use of ACE-inhibitor, ARB or ARNi											0.0998
No	586	0	0	568	5	0.9	0.0371	11.35 (0.63,204.75)	11.45 (0.63,207.53)	0.01 (0.00, 0.02)	
Yes	2403	9	0.4	2428	8	0.3	0.7915	0.88 (0.34, 2.28)	0.88 (0.34, 2.28)	0.00 (0.00, 0.00)	

Analysis is based on study 1245.110.
^ Patients with NYHA class I are counted in subgroup NYHA class II.
*** Confirmed hypoglycaemic AEs are defined by a glucose concentration <=70 mg/dL (3.9 mmol/L) or requiring assistance.
Risk ratios and odds ratios with confidence intervals (CIs) are estimated by Cochran-Mantel-Haenszel method. For risk differences standard Wald asymptotic confidence limits are calculated. A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied in case of any zero cells in contingency table.
Only treatment emergent AEs are displayed (onset between first dose until treatment stop +7 days).
MedDRA version: 23.1. * Chi-square test for treatment effect ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction).

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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 overall and by subgroup - TS
User-defined AE category: Urinary Tract Infection (narrow Sub 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	2989	45	1.5	2996	54	1.8	0.3679	1.20 (0.81, 1.77)	1.20 (0.81, 1.79)	0.00 (0.00, 0.01)	
Sex											0.0051
Male	1653	26	1.6	1658	16	1.0	0.1181	0.61 (0.33, 1.14)	0.61 (0.33, 1.14)	-0.01 (-0.01, 0.00)	
Female	1336	19	1.4	1338	38	2.8	0.0111	2.00 (1.16, 3.45)	2.03 (1.16, 3.53)	0.01 (0.00, 0.03)	
Age [years]											0.0602
<70	1084	7	0.6	1066	17	1.6	0.0363	2.47 (1.03, 5.93)	2.49 (1.03, 6.04)	0.01 (0.00, 0.02)	
>=70	1905	38	2.0	1930	37	1.9	0.8622	0.96 (0.61, 1.50)	0.96 (0.61, 1.52)	0.00 (-0.01, 0.01)	
Region											0.9290
North America	359	9	2.5	359	9	2.5	1.0000	1.00 (0.40, 2.49)	1.00 (0.39, 2.55)	0.00 (-0.02, 0.02)	
Latin America	757	12	1.6	758	16	2.1	0.4476	1.33 (0.63, 2.80)	1.34 (0.63, 2.85)	0.01 (-0.01, 0.02)	
Europe	1341	17	1.3	1346	19	1.4	0.7457	1.11 (0.58, 2.13)	1.12 (0.58, 2.15)	0.00 (-0.01, 0.01)	
Asia	343	4	1.2	343	4	1.2	1.0000	1.00 (0.25, 3.97)	1.00 (0.25, 4.03)	0.00 (-0.02, 0.02)	
Other	189	3	1.6	190	6	3.2	0.3153	1.99 (0.50, 7.84)	2.02 (0.50, 8.21)	0.02 (-0.01, 0.05)	
OECD member											0.8468
No	847	13	1.5	868	15	1.7	0.7522	1.13 (0.54, 2.35)	1.13 (0.53, 2.39)	0.00 (-0.01, 0.01)	
Yes	2142	32	1.5	2128	39	1.8	0.3867	1.23 (0.77, 1.95)	1.23 (0.77, 1.97)	0.00 (0.00, 0.01)	
Baseline NYHA											0.1430
II^	2450	37	1.5	2435	37	1.5	0.9788	1.01 (0.64, 1.58)	1.01 (0.64, 1.59)	0.00 (-0.01, 0.01)	
III/IV	539	8	1.5	561	17	3.0	0.0854	2.04 (0.89, 4.69)	2.07 (0.89, 4.85)	0.02 (0.00, 0.03)	
Baseline Diabetes Status											0.6003
Diabetic	1471	25	1.7	1465	27	1.8	0.7682	1.08 (0.63, 1.86)	1.09 (0.63, 1.88)	0.00 (-0.01, 0.01)	
Non-Diabetic	1518	20	1.3	1531	27	1.8	0.3175	1.34 (0.75, 2.38)	1.34 (0.75, 2.41)	0.00 (0.00, 0.01)	

Analysis is based on study 1245.110.
^ Patients with NYHA class I are counted in subgroup NYHA class II.
*** Confirmed hypoglycaemic AEs are defined by a glucose concentration <=70 mg/dL (3.9 mmol/L) or requiring assistance.
Risk ratios and odds ratios with confidence intervals (CIs) are estimated by Cochran-Mantel-Haenszel method. For risk differences standard Wald asymptotic confidence limits are calculated. A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied in case of any zero cells in contingency table.
Only treatment emergent AEs are displayed (onset between first dose until treatment stop +7 days).
MedDRA version: 23.1. * Chi-square test for treatment effect ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction).

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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 overall and by subgroup - TS
User-defined AE category: Urinary Tract Infection (narrow Sub 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 Diabetes Status											0.8056
Diabetic	1471	25	1.7	1465	27	1.8	0.7682	1.08 (0.63, 1.86)	1.09 (0.63, 1.88)	0.00 (-0.01, 0.01)	
Pre-Diabetes	979	15	1.5	1001	19	1.9	0.5309	1.24 (0.63, 2.42)	1.24 (0.63, 2.46)	0.00 (-0.01, 0.02)	
Normal (no pre-diabetes)	539	5	0.9	530	8	1.5	0.3855	1.63 (0.54, 4.94)	1.64 (0.53, 5.04)	0.01 (-0.01, 0.02)	
Baseline BMI [kg/m²]											0.3586
<30	1641	24	1.5	1654	24	1.5	0.9780	0.99 (0.57, 1.74)	0.99 (0.56, 1.75)	0.00 (-0.01, 0.01)	
>=30	1348	21	1.6	1342	30	2.2	0.1976	1.43 (0.83, 2.49)	1.44 (0.82, 2.54)	0.01 (0.00, 0.02)	
Baseline eGFR (CKD-EPI) [mL/min/1.73m²]											0.6704
>=60	1505	11	0.7	1493	15	1.0	0.4189	1.37 (0.63, 2.98)	1.38 (0.63, 3.01)	0.00 (0.00, 0.01)	
<60	1482	34	2.3	1503	39	2.6	0.5950	1.13 (0.72, 1.78)	1.13 (0.71, 1.81)	0.00 (-0.01, 0.01)	
History of HHF (in the last 12 months)											0.6508
No	2320	32	1.4	2297	40	1.7	0.3208	1.26 (0.80, 2.00)	1.27 (0.79, 2.02)	0.00 (0.00, 0.01)	
Yes	669	13	1.9	699	14	2.0	0.9368	1.03 (0.49, 2.18)	1.03 (0.48, 2.21)	0.00 (-0.01, 0.02)	
Baseline SBP (</>= median)											0.4736
< median	1474	19	1.3	1496	27	1.8	0.2550	1.40 (0.78, 2.51)	1.41 (0.78, 2.54)	0.01 (0.00, 0.01)	
>= median	1515	26	1.7	1500	27	1.8	0.8610	1.05 (0.62, 1.79)	1.05 (0.61, 1.81)	0.00 (-0.01, 0.01)	
History of atrial fibrillation or atrial flutter											0.0424
No	1426	16	1.1	1417	30	2.1	0.0355	1.89 (1.03, 3.45)	1.91 (1.03, 3.51)	0.01 (0.00, 0.02)	
Yes	1558	29	1.9	1575	24	1.5	0.4638	0.82 (0.48, 1.40)	0.82 (0.47, 1.41)	0.00 (-0.01, 0.01)	

Analysis is based on study 1245.110.
^ Patients with NYHA class I are counted in subgroup NYHA class II.
*** Confirmed hypoglycaemic AEs are defined by a glucose concentration <=70 mg/dL (3.9 mmol/L) or requiring assistance.
Risk ratios and odds ratios with confidence intervals (CIs) are estimated by Cochran-Mantel-Haenszel method. For risk differences standard Wald asymptotic confidence limits are calculated. A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied in case of any zero cells in contingency table.
Only treatment emergent AEs are displayed (onset between first dose until treatment stop +7 days).
MedDRA version: 23.1. * Chi-square test for treatment effect ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction).

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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 overall and by subgroup - TS
User-defined AE category: Urinary Tract Infection (narrow Sub 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 LVEF [%]											0.2780
< 50	988	9	0.9	995	16	1.6	0.1642	1.77 (0.78, 3.98)	1.78 (0.78, 4.04)	0.01 (0.00, 0.02)	
>= 50	2001	36	1.8	2001	38	1.9	0.8145	1.06 (0.67, 1.66)	1.06 (0.67, 1.67)	0.00 (-0.01, 0.01)	
Baseline LVEF [%]											0.2908
<50	988	9	0.9	995	16	1.6	0.1642	1.77 (0.78, 3.98)	1.78 (0.78, 4.04)	0.01 (0.00, 0.02)	
50 to <60	1030	18	1.7	1028	14	1.4	0.4795	0.78 (0.39, 1.56)	0.78 (0.38, 1.57)	0.00 (-0.01, 0.01)	
>=60	971	18	1.9	973	24	2.5	0.3528	1.33 (0.73, 2.44)	1.34 (0.72, 2.48)	0.01 (-0.01, 0.02)	
Baseline NT-proBNP [pg/mL] (</>=median by atrial fibrillation/flutter status)											0.1792
< median	1507	17	1.1	1476	27	1.8	0.1122	1.62 (0.89, 2.96)	1.63 (0.89, 3.01)	0.01 (0.00, 0.02)	
>= median	1475	28	1.9	1516	27	1.8	0.8113	0.94 (0.56, 1.58)	0.94 (0.55, 1.60)	0.00 (-0.01, 0.01)	
Baseline uric acid [mg/dL] (tertiles)											0.7121
<T1	975	14	1.4	963	14	1.5	0.9737	1.01 (0.49, 2.11)	1.01 (0.48, 2.14)	0.00 (-0.01, 0.01)	
>=T1 and <T2	966	13	1.3	1032	15	1.5	0.8378	1.08 (0.52, 2.26)	1.08 (0.51, 2.28)	0.00 (-0.01, 0.01)	
>=T2	1016	18	1.8	970	25	2.6	0.2175	1.45 (0.80, 2.65)	1.47 (0.80, 2.71)	0.01 (0.00, 0.02)	
Baseline use of MRA											0.6774
No	1865	30	1.6	1878	34	1.8	0.6339	1.13 (0.69, 1.83)	1.13 (0.69, 1.85)	0.00 (-0.01, 0.01)	
Yes	1124	15	1.3	1118	20	1.8	0.3855	1.34 (0.69, 2.60)	1.35 (0.69, 2.64)	0.00 (-0.01, 0.01)	
Baseline use of ACE-inhibitor, ARB or ARNi											0.2337
No	586	9	1.5	568	16	2.8	0.1351	1.83 (0.82, 4.12)	1.86 (0.81, 4.24)	0.01 (0.00, 0.03)	
Yes	2403	36	1.5	2428	38	1.6	0.8497	1.04 (0.66, 1.64)	1.05 (0.66, 1.65)	0.00 (-0.01, 0.01)	

Analysis is based on study 1245.110.
^ Patients with NYHA class I are counted in subgroup NYHA class II.
*** Confirmed hypoglycaemic AEs are defined by a glucose concentration <=70 mg/dL (3.9 mmol/L) or requiring assistance.
Risk ratios and odds ratios with confidence intervals (CIs) are estimated by Cochran-Mantel-Haenszel method. For risk differences standard Wald asymptotic confidence limits are calculated. A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied in case of any zero cells in contingency table.
Only treatment emergent AEs are displayed (onset between first dose until treatment stop +7 days).
MedDRA version: 23.1. * Chi-square test for treatment effect ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction).

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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 overall and by subgroup - TS
User-defined AE category: Complicated urinary tract infection (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	2989	45	1.5	2996	54	1.8	0.3679	1.20 (0.81, 1.77)	1.20 (0.81, 1.79)	0.00 (0.00, 0.01)	
Sex											0.0051
Male	1653	26	1.6	1658	16	1.0	0.1181	0.61 (0.33, 1.14)	0.61 (0.33, 1.14)	-0.01 (-0.01, 0.00)	
Female	1336	19	1.4	1338	38	2.8	0.0111	2.00 (1.16, 3.45)	2.03 (1.16, 3.53)	0.01 (0.00, 0.03)	
Age [years]											0.0602
<70	1084	7	0.6	1066	17	1.6	0.0363	2.47 (1.03, 5.93)	2.49 (1.03, 6.04)	0.01 (0.00, 0.02)	
>=70	1905	38	2.0	1930	37	1.9	0.8622	0.96 (0.61, 1.50)	0.96 (0.61, 1.52)	0.00 (-0.01, 0.01)	
Region											0.9290
North America	359	9	2.5	359	9	2.5	1.0000	1.00 (0.40, 2.49)	1.00 (0.39, 2.55)	0.00 (-0.02, 0.02)	
Latin America	757	12	1.6	758	16	2.1	0.4476	1.33 (0.63, 2.80)	1.34 (0.63, 2.85)	0.01 (-0.01, 0.02)	
Europe	1341	17	1.3	1346	19	1.4	0.7457	1.11 (0.58, 2.13)	1.12 (0.58, 2.15)	0.00 (-0.01, 0.01)	
Asia	343	4	1.2	343	4	1.2	1.0000	1.00 (0.25, 3.97)	1.00 (0.25, 4.03)	0.00 (-0.02, 0.02)	
Other	189	3	1.6	190	6	3.2	0.3153	1.99 (0.50, 7.84)	2.02 (0.50, 8.21)	0.02 (-0.01, 0.05)	
OECD member											0.8468
No	847	13	1.5	868	15	1.7	0.7522	1.13 (0.54, 2.35)	1.13 (0.53, 2.39)	0.00 (-0.01, 0.01)	
Yes	2142	32	1.5	2128	39	1.8	0.3867	1.23 (0.77, 1.95)	1.23 (0.77, 1.97)	0.00 (0.00, 0.01)	
Baseline NYHA											0.1430
II^	2450	37	1.5	2435	37	1.5	0.9788	1.01 (0.64, 1.58)	1.01 (0.64, 1.59)	0.00 (-0.01, 0.01)	
III/IV	539	8	1.5	561	17	3.0	0.0854	2.04 (0.89, 4.69)	2.07 (0.89, 4.85)	0.02 (0.00, 0.03)	
Baseline Diabetes Status											0.6003
Diabetic	1471	25	1.7	1465	27	1.8	0.7682	1.08 (0.63, 1.86)	1.09 (0.63, 1.88)	0.00 (-0.01, 0.01)	
Non-Diabetic	1518	20	1.3	1531	27	1.8	0.3175	1.34 (0.75, 2.38)	1.34 (0.75, 2.41)	0.00 (0.00, 0.01)	

Analysis is based on study 1245.110.
^ Patients with NYHA class I are counted in subgroup NYHA class II.
*** Confirmed hypoglycaemic AEs are defined by a glucose concentration <=70 mg/dL (3.9 mmol/L) or requiring assistance.
Risk ratios and odds ratios with confidence intervals (CIs) are estimated by Cochran-Mantel-Haenszel method. For risk differences standard Wald asymptotic confidence limits are calculated. A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied in case of any zero cells in contingency table.
Only treatment emergent AEs are displayed (onset between first dose until treatment stop +7 days).
MedDRA version: 23.1. * Chi-square test for treatment effect ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction).

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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 overall and by subgroup - TS
User-defined AE category: Complicated urinary tract infection (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 Diabetes Status											0.8056
Diabetic	1471	25	1.7	1465	27	1.8	0.7682	1.08 (0.63, 1.86)	1.09 (0.63, 1.88)	0.00 (-0.01, 0.01)	
Pre-Diabetes	979	15	1.5	1001	19	1.9	0.5309	1.24 (0.63, 2.42)	1.24 (0.63, 2.46)	0.00 (-0.01, 0.02)	
Normal (no pre-diabetes)	539	5	0.9	530	8	1.5	0.3855	1.63 (0.54, 4.94)	1.64 (0.53, 5.04)	0.01 (-0.01, 0.02)	
Baseline BMI [kg/m²]											0.3586
<30	1641	24	1.5	1654	24	1.5	0.9780	0.99 (0.57, 1.74)	0.99 (0.56, 1.75)	0.00 (-0.01, 0.01)	
>=30	1348	21	1.6	1342	30	2.2	0.1976	1.43 (0.83, 2.49)	1.44 (0.82, 2.54)	0.01 (0.00, 0.02)	
Baseline eGFR (CKD-EPI) [mL/min/1.73m²]											0.6704
>=60	1505	11	0.7	1493	15	1.0	0.4189	1.37 (0.63, 2.98)	1.38 (0.63, 3.01)	0.00 (0.00, 0.01)	
<60	1482	34	2.3	1503	39	2.6	0.5950	1.13 (0.72, 1.78)	1.13 (0.71, 1.81)	0.00 (-0.01, 0.01)	
History of HHF (in the last 12 months)											0.6508
No	2320	32	1.4	2297	40	1.7	0.3208	1.26 (0.80, 2.00)	1.27 (0.79, 2.02)	0.00 (0.00, 0.01)	
Yes	669	13	1.9	699	14	2.0	0.9368	1.03 (0.49, 2.18)	1.03 (0.48, 2.21)	0.00 (-0.01, 0.02)	
Baseline SBP (</>= median)											0.4736
< median	1474	19	1.3	1496	27	1.8	0.2550	1.40 (0.78, 2.51)	1.41 (0.78, 2.54)	0.01 (0.00, 0.01)	
>= median	1515	26	1.7	1500	27	1.8	0.8610	1.05 (0.62, 1.79)	1.05 (0.61, 1.81)	0.00 (-0.01, 0.01)	
History of atrial fibrillation or atrial flutter											0.0424
No	1426	16	1.1	1417	30	2.1	0.0355	1.89 (1.03, 3.45)	1.91 (1.03, 3.51)	0.01 (0.00, 0.02)	
Yes	1558	29	1.9	1575	24	1.5	0.4638	0.82 (0.48, 1.40)	0.82 (0.47, 1.41)	0.00 (-0.01, 0.01)	

Analysis is based on study 1245.110.
^ Patients with NYHA class I are counted in subgroup NYHA class II.
*** Confirmed hypoglycaemic AEs are defined by a glucose concentration <=70 mg/dL (3.9 mmol/L) or requiring assistance.
Risk ratios and odds ratios with confidence intervals (CIs) are estimated by Cochran-Mantel-Haenszel method. For risk differences standard Wald asymptotic confidence limits are calculated. A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied in case of any zero cells in contingency table.
Only treatment emergent AEs are displayed (onset between first dose until treatment stop +7 days).
MedDRA version: 23.1. * Chi-square test for treatment effect ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction).

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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 overall and by subgroup - TS
User-defined AE category: Complicated urinary tract infection (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 LVEF [%]											0.2780
< 50	988	9	0.9	995	16	1.6	0.1642	1.77 (0.78, 3.98)	1.78 (0.78, 4.04)	0.01 (0.00, 0.02)	
>= 50	2001	36	1.8	2001	38	1.9	0.8145	1.06 (0.67, 1.66)	1.06 (0.67, 1.67)	0.00 (-0.01, 0.01)	
Baseline LVEF [%]											0.2908
<50	988	9	0.9	995	16	1.6	0.1642	1.77 (0.78, 3.98)	1.78 (0.78, 4.04)	0.01 (0.00, 0.02)	
50 to <60	1030	18	1.7	1028	14	1.4	0.4795	0.78 (0.39, 1.56)	0.78 (0.38, 1.57)	0.00 (-0.01, 0.01)	
>=60	971	18	1.9	973	24	2.5	0.3528	1.33 (0.73, 2.44)	1.34 (0.72, 2.48)	0.01 (-0.01, 0.02)	
Baseline NT-proBNP [pg/mL] (</>=median by atrial fibrillation/flutter status)											0.1792
< median	1507	17	1.1	1476	27	1.8	0.1122	1.62 (0.89, 2.96)	1.63 (0.89, 3.01)	0.01 (0.00, 0.02)	
>= median	1475	28	1.9	1516	27	1.8	0.8113	0.94 (0.56, 1.58)	0.94 (0.55, 1.60)	0.00 (-0.01, 0.01)	
Baseline uric acid [mg/dL] (tertiles)											0.7121
<T1	975	14	1.4	963	14	1.5	0.9737	1.01 (0.49, 2.11)	1.01 (0.48, 2.14)	0.00 (-0.01, 0.01)	
>=T1 and <T2	966	13	1.3	1032	15	1.5	0.8378	1.08 (0.52, 2.26)	1.08 (0.51, 2.28)	0.00 (-0.01, 0.01)	
>=T2	1016	18	1.8	970	25	2.6	0.2175	1.45 (0.80, 2.65)	1.47 (0.80, 2.71)	0.01 (0.00, 0.02)	
Baseline use of MRA											0.6774
No	1865	30	1.6	1878	34	1.8	0.6339	1.13 (0.69, 1.83)	1.13 (0.69, 1.85)	0.00 (-0.01, 0.01)	
Yes	1124	15	1.3	1118	20	1.8	0.3855	1.34 (0.69, 2.60)	1.35 (0.69, 2.64)	0.00 (-0.01, 0.01)	
Baseline use of ACE-inhibitor, ARB or ARNi											0.2337
No	586	9	1.5	568	16	2.8	0.1351	1.83 (0.82, 4.12)	1.86 (0.81, 4.24)	0.01 (0.00, 0.03)	
Yes	2403	36	1.5	2428	38	1.6	0.8497	1.04 (0.66, 1.64)	1.05 (0.66, 1.65)	0.00 (-0.01, 0.01)	

Analysis is based on study 1245.110.
^ Patients with NYHA class I are counted in subgroup NYHA class II.
*** Confirmed hypoglycaemic AEs are defined by a glucose concentration <=70 mg/dL (3.9 mmol/L) or requiring assistance.
Risk ratios and odds ratios with confidence intervals (CIs) are estimated by Cochran-Mantel-Haenszel method. For risk differences standard Wald asymptotic confidence limits are calculated. A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied in case of any zero cells in contingency table.
Only treatment emergent AEs are displayed (onset between first dose until treatment stop +7 days).
MedDRA version: 23.1. * Chi-square test for treatment effect ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction).

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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 overall and by subgroup - TS
User-defined AE category: Genital Infection (narrow 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	2989	6	0.2	2996	3	0.1	0.3153	0.50 (0.12, 1.99)	0.50 (0.12, 1.99)	0.00 (0.00, 0.00)	
Sex											
Male	1653	5	0.3	1658	3	0.2					
Female	1336	1	0.1	1338	0	0					
Age [years]											
<70	1084	1	0.1	1066	1	0.1					
>=70	1905	5	0.3	1930	2	0.1					
Region											
North America	359	1	0.3	359	0	0					
Latin America	757	1	0.1	758	0	0					
Europe	1341	2	0.1	1346	3	0.2					
Asia	343	2	0.6	343	0	0					
Other	189	0	0	190	0	0					
OECD member											
No	847	1	0.1	868	0	0					
Yes	2142	5	0.2	2128	3	0.1					
Baseline NYHA											
II^	2450	6	0.2	2435	2	0.1					
III/IV	539	0	0	561	1	0.2					
Baseline Diabetes Status											
Diabetic	1471	4	0.3	1465	1	0.1					
Non-Diabetic	1518	2	0.1	1531	2	0.1					

Analysis is based on study 1245.110.
^ Patients with NYHA class I are counted in subgroup NYHA class II.
*** Confirmed hypoglycaemic AEs are defined by a glucose concentration <=70 mg/dL (3.9 mmol/L) or requiring assistance.
Risk ratios and odds ratios with confidence intervals (CIs) are estimated by Cochran-Mantel-Haenszel method. For risk differences standard Wald asymptotic confidence limits are calculated. A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied in case of any zero cells in contingency table.
Only treatment emergent AEs are displayed (onset between first dose until treatment stop +7 days).
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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 overall and by subgroup - TS
User-defined AE category: Genital Infection (narrow 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 Diabetes Status											
Diabetic	1471	4	0.3	1465	1	0.1					
Pre-Diabetes	979	0	0	1001	2	0.2					
Normal (no pre-diabetes)	539	2	0.4	530	0	0					
Baseline BMI [kg/m²]											
<30	1641	4	0.2	1654	2	0.1					
>=30	1348	2	0.1	1342	1	0.1					
Baseline eGFR (CKD-EPI) [mL/min/1.73m²]											
>=60	1505	3	0.2	1493	2	0.1					
<60	1482	3	0.2	1503	1	0.1					
History of HHF (in the last 12 months)											
No	2320	4	0.2	2297	3	0.1					
Yes	669	2	0.3	699	0	0					
Baseline SBP (</>= median)											
< median	1474	5	0.3	1496	0	0					
>= median	1515	1	0.1	1500	3	0.2					
History of atrial fibrillation or atrial flutter											
No	1426	4	0.3	1417	1	0.1					
Yes	1558	2	0.1	1575	2	0.1					

Analysis is based on study 1245.110.
^ Patients with NYHA class I are counted in subgroup NYHA class II.
*** Confirmed hypoglycaemic AEs are defined by a glucose concentration <=70 mg/dL (3.9 mmol/L) or requiring assistance.
Risk ratios and odds ratios with confidence intervals (CIs) are estimated by Cochran-Mantel-Haenszel method. For risk differences standard Wald asymptotic confidence limits are calculated. A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied in case of any zero cells in contingency table.
Only treatment emergent AEs are displayed (onset between first dose until treatment stop +7 days).
MedDRA version: 23.1. * Chi-square test for treatment effect ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction).

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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 overall and by subgroup - TS
User-defined AE category: Genital Infection (narrow 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 LVEF [%]											
< 50	988	1	0.1	995	1	0.1					
>= 50	2001	5	0.2	2001	2	0.1					
Baseline LVEF [%]											
<50	988	1	0.1	995	1	0.1					
50 to <60	1030	3	0.3	1028	1	0.1					
>=60	971	2	0.2	973	1	0.1					
Baseline NT-proBNP [pg/mL] (</>=median by atrial fibrillation/flutter status)											
< median	1507	3	0.2	1476	1	0.1					
>= median	1475	3	0.2	1516	2	0.1					
Baseline uric acid [mg/dL] (tertiles)											
<T1	975	3	0.3	963	1	0.1					
>=T1 and <T2	966	2	0.2	1032	2	0.2					
>=T2	1016	1	0.1	970	0	0					
Baseline use of MRA											
No	1865	3	0.2	1878	2	0.1					
Yes	1124	3	0.3	1118	1	0.1					
Baseline use of ACE-inhibitor, ARB or ARNi											
No	586	3	0.5	568	0	0					
Yes	2403	3	0.1	2428	3	0.1					

Analysis is based on study 1245.110.
^ Patients with NYHA class I are counted in subgroup NYHA class II.
*** Confirmed hypoglycaemic AEs are defined by a glucose concentration <=70 mg/dL (3.9 mmol/L) or requiring assistance.
Risk ratios and odds ratios with confidence intervals (CIs) are estimated by Cochran-Mantel-Haenszel method. For risk differences standard Wald asymptotic confidence limits are calculated. A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied in case of any zero cells in contingency table.
Only treatment emergent AEs are displayed (onset between first dose until treatment stop +7 days).
MedDRA version: 23.1. * Chi-square test for treatment effect ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction).

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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 overall and by subgroup - TS
User-defined AE category: Complicated Genital Infection (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	2989	6	0.2	2996	3	0.1	0.3153	0.50 (0.12, 1.99)	0.50 (0.12, 1.99)	0.00 (0.00, 0.00)	
Sex											
Male	1653	5	0.3	1658	3	0.2					
Female	1336	1	0.1	1338	0	0					
Age [years]											
<70	1084	1	0.1	1066	1	0.1					
>=70	1905	5	0.3	1930	2	0.1					
Region											
North America	359	1	0.3	359	0	0					
Latin America	757	1	0.1	758	0	0					
Europe	1341	2	0.1	1346	3	0.2					
Asia	343	2	0.6	343	0	0					
Other	189	0	0	190	0	0					
OECD member											
No	847	1	0.1	868	0	0					
Yes	2142	5	0.2	2128	3	0.1					
Baseline NYHA											
II^	2450	6	0.2	2435	2	0.1					
III/IV	539	0	0	561	1	0.2					
Baseline Diabetes Status											
Diabetic	1471	4	0.3	1465	1	0.1					
Non-Diabetic	1518	2	0.1	1531	2	0.1					

Analysis is based on study 1245.110.
^ Patients with NYHA class I are counted in subgroup NYHA class II.
*** Confirmed hypoglycaemic AEs are defined by a glucose concentration <=70 mg/dL (3.9 mmol/L) or requiring assistance.
Risk ratios and odds ratios with confidence intervals (CIs) are estimated by Cochran-Mantel-Haenszel method. For risk differences standard Wald asymptotic confidence limits are calculated. A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied in case of any zero cells in contingency table.
Only treatment emergent AEs are displayed (onset between first dose until treatment stop +7 days).
MedDRA version: 23.1. * Chi-square test for treatment effect ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction).

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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 overall and by subgroup - TS
User-defined AE category: Complicated Genital Infection (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 Diabetes Status											
Diabetic	1471	4	0.3	1465	1	0.1					
Pre-Diabetes	979	0	0	1001	2	0.2					
Normal (no pre-diabetes)	539	2	0.4	530	0	0					
Baseline BMI [kg/m²]											
<30	1641	4	0.2	1654	2	0.1					
>=30	1348	2	0.1	1342	1	0.1					
Baseline eGFR (CKD-EPI) [mL/min/1.73m²]											
>=60	1505	3	0.2	1493	2	0.1					
<60	1482	3	0.2	1503	1	0.1					
History of HHF (in the last 12 months)											
No	2320	4	0.2	2297	3	0.1					
Yes	669	2	0.3	699	0	0					
Baseline SBP (</>= median)											
< median	1474	5	0.3	1496	0	0					
>= median	1515	1	0.1	1500	3	0.2					
History of atrial fibrillation or atrial flutter											
No	1426	4	0.3	1417	1	0.1					
Yes	1558	2	0.1	1575	2	0.1					

Analysis is based on study 1245.110.
^ Patients with NYHA class I are counted in subgroup NYHA class II.
*** Confirmed hypoglycaemic AEs are defined by a glucose concentration <=70 mg/dL (3.9 mmol/L) or requiring assistance.
Risk ratios and odds ratios with confidence intervals (CIs) are estimated by Cochran-Mantel-Haenszel method. For risk differences standard Wald asymptotic confidence limits are calculated. A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied in case of any zero cells in contingency table.
Only treatment emergent AEs are displayed (onset between first dose until treatment stop +7 days).
MedDRA version: 23.1. * Chi-square test for treatment effect ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction).

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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 overall and by subgroup - TS
User-defined AE category: Complicated Genital Infection (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 LVEF [%]											
< 50	988	1	0.1	995	1	0.1					
>= 50	2001	5	0.2	2001	2	0.1					
Baseline LVEF [%]											
<50	988	1	0.1	995	1	0.1					
50 to <60	1030	3	0.3	1028	1	0.1					
>=60	971	2	0.2	973	1	0.1					
Baseline NT-proBNP [pg/mL] (</>=median by atrial fibrillation/flutter status)											
< median	1507	3	0.2	1476	1	0.1					
>= median	1475	3	0.2	1516	2	0.1					
Baseline uric acid [mg/dL] (tertiles)											
<T1	975	3	0.3	963	1	0.1					
>=T1 and <T2	966	2	0.2	1032	2	0.2					
>=T2	1016	1	0.1	970	0	0					
Baseline use of MRA											
No	1865	3	0.2	1878	2	0.1					
Yes	1124	3	0.3	1118	1	0.1					
Baseline use of ACE-inhibitor, ARB or ARNi											
No	586	3	0.5	568	0	0					
Yes	2403	3	0.1	2428	3	0.1					

Analysis is based on study 1245.110.
^ Patients with NYHA class I are counted in subgroup NYHA class II.
*** Confirmed hypoglycaemic AEs are defined by a glucose concentration <=70 mg/dL (3.9 mmol/L) or requiring assistance.
Risk ratios and odds ratios with confidence intervals (CIs) are estimated by Cochran-Mantel-Haenszel method. For risk differences standard Wald asymptotic confidence limits are calculated. A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied in case of any zero cells in contingency table.
Only treatment emergent AEs are displayed (onset between first dose until treatment stop +7 days).
MedDRA version: 23.1. * Chi-square test for treatment effect ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction).

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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 overall and by subgroup - TS
User-defined AE category: Acute pyelonephritis (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	2989	5	0.2	2996	10	0.3	0.1977	2.00 (0.68, 5.83)	2.00 (0.68, 5.85)	0.00 (0.00, 0.00)	
Sex											
Male	1653	3	0.2	1658	3	0.2					
Female	1336	2	0.1	1338	7	0.5					
Age [years]											
<70	1084	0	0	1066	6	0.6					
>=70	1905	5	0.3	1930	4	0.2					
Region											
North America	359	2	0.6	359	2	0.6					
Latin America	757	1	0.1	758	2	0.3					
Europe	1341	0	0	1346	3	0.2					
Asia	343	1	0.3	343	2	0.6					
Other	189	1	0.5	190	1	0.5					
OECD member											0.9819
No	847	1	0.1	868	2	0.2	0.5778	1.95 (0.18, 21.48)	1.95 (0.18, 21.59)	0.00 (0.00, 0.01)	
Yes	2142	4	0.2	2128	8	0.4	0.2429	2.01 (0.61, 6.68)	2.02 (0.61, 6.71)	0.00 (0.00, 0.01)	
Baseline NYHA											0.3345
II^	2450	5	0.2	2435	7	0.3	0.5561	1.41 (0.45, 4.43)	1.41 (0.45, 4.45)	0.00 (0.00, 0.00)	
III/IV	539	0	0	561	3	0.5	0.1435	6.73 (0.35,129.91)	6.76 (0.35,131.22)	0.01 (0.00, 0.01)	
Baseline Diabetes Status											0.4529
Diabetic	1471	4	0.3	1465	6	0.4	0.5222	1.51 (0.43, 5.33)	1.51 (0.42, 5.36)	0.00 (0.00, 0.01)	
Non-Diabetic	1518	1	0.1	1531	4	0.3	0.1825	3.97 (0.44, 35.44)	3.97 (0.44, 35.59)	0.00 (0.00, 0.00)	

Analysis is based on study 1245.110.
^ Patients with NYHA class I are counted in subgroup NYHA class II.
*** Confirmed hypoglycaemic AEs are defined by a glucose concentration <=70 mg/dL (3.9 mmol/L) or requiring assistance.
Risk ratios and odds ratios with confidence intervals (CIs) are estimated by Cochran-Mantel-Haenszel method. For risk differences standard Wald asymptotic confidence limits are calculated. A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied in case of any zero cells in contingency table.
Only treatment emergent AEs are displayed (onset between first dose until treatment stop +7 days).
MedDRA version: 23.1. * Chi-square test for treatment effect ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction).

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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 overall and by subgroup - TS
User-defined AE category: Acute pyelonephritis (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 Diabetes Status											0.7672
Diabetic	1471	4	0.3	1465	6	0.4	0.5222	1.51 (0.43, 5.33)	1.51 (0.42, 5.36)	0.00 (0.00, 0.01)	
Pre-Diabetes	979	1	0.1	1001	2	0.2	0.5765	1.96 (0.18, 21.54)	1.96 (0.18, 21.63)	0.00 (0.00, 0.00)	
Normal (no pre-diabetes)	539	0	0	530	2	0.4	0.2416	5.08 (0.24,105.66)	5.10 (0.24,106.57)	0.00 (0.00, 0.01)	
Baseline BMI [kg/m²]											0.1334
<30	1641	5	0.3	1654	5	0.3	0.9900	0.99 (0.29, 3.42)	0.99 (0.29, 3.43)	0.00 (0.00, 0.00)	
>=30	1348	0	0	1342	5	0.4	0.0405	11.05 (0.61,199.62)	11.09 (0.61,200.76)	0.00 (0.00, 0.01)	
Baseline eGFR (CKD-EPI) [mL/min/1.73m²]											0.9871
>=60	1505	1	0.1	1493	2	0.1	0.5588	2.02 (0.18, 22.21)	2.02 (0.18, 22.27)	0.00 (0.00, 0.00)	
<60	1482	4	0.3	1503	8	0.5	0.2574	1.97 (0.60, 6.53)	1.98 (0.59, 6.58)	0.00 (0.00, 0.01)	
History of HHF (in the last 12 months)											0.7116
No	2320	4	0.2	2297	7	0.3	0.3564	1.77 (0.52, 6.03)	1.77 (0.52, 6.05)	0.00 (0.00, 0.00)	
Yes	669	1	0.1	699	3	0.4	0.3382	2.87 (0.30, 27.53)	2.88 (0.30, 27.75)	0.00 (0.00, 0.01)	
Baseline SBP (</>= median)											
< median	1474	5	0.3	1496	4	0.3					
>= median	1515	0	0	1500	6	0.4					
History of atrial fibrillation or atrial flutter											
No	1426	2	0.1	1417	4	0.3					
Yes	1558	3	0.2	1575	6	0.4					

Analysis is based on study 1245.110.
^ Patients with NYHA class I are counted in subgroup NYHA class II.
*** Confirmed hypoglycaemic AEs are defined by a glucose concentration <=70 mg/dL (3.9 mmol/L) or requiring assistance.
Risk ratios and odds ratios with confidence intervals (CIs) are estimated by Cochran-Mantel-Haenszel method. For risk differences standard Wald asymptotic confidence limits are calculated. A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied in case of any zero cells in contingency table.
Only treatment emergent AEs are displayed (onset between first dose until treatment stop +7 days).
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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 overall and by subgroup - TS
User-defined AE category: Acute pyelonephritis (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 LVEF [%]											0.1967
< 50	988	2	0.2	995	1	0.1	0.5593	0.50 (0.05, 5.47)	0.50 (0.04, 5.48)	0.00 (0.00, 0.00)	
>= 50	2001	3	0.1	2001	9	0.4	0.0828	3.00 (0.81, 11.06)	3.01 (0.81, 11.13)	0.00 (0.00, 0.01)	
Baseline LVEF [%]											
<50	988	2	0.2	995	1	0.1					
50 to <60	1030	0	0	1028	4	0.4					
>=60	971	3	0.3	973	5	0.5					
Baseline NT-proBNP [pg/mL] (</>=median by atrial fibrillation/flutter status)											
< median	1507	3	0.2	1476	6	0.4					
>= median	1475	2	0.1	1516	4	0.3					
Baseline uric acid [mg/dL] (tertiles)											
<T1	975	3	0.3	963	5	0.5					
>=T1 and <T2	966	0	0	1032	2	0.2					
>=T2	1016	2	0.2	970	3	0.3					
Baseline use of MRA											0.4221
No	1865	3	0.2	1878	8	0.4	0.1341	2.65 (0.70, 9.97)	2.66 (0.70, 10.02)	0.00 (0.00, 0.01)	
Yes	1124	2	0.2	1118	2	0.2	0.9957	1.01 (0.14, 7.12)	1.01 (0.14, 7.15)	0.00 (0.00, 0.00)	
Baseline use of ACE-inhibitor, ARB or ARNi											0.9758
No	586	1	0.2	568	2	0.4	0.5450	2.06 (0.19, 22.69)	2.07 (0.19, 22.86)	0.00 (0.00, 0.01)	
Yes	2403	4	0.2	2428	8	0.3	0.2550	1.98 (0.60, 6.56)	1.98 (0.60, 6.59)	0.00 (0.00, 0.00)	

Analysis is based on study 1245.110.
^ Patients with NYHA class I are counted in subgroup NYHA class II.
*** Confirmed hypoglycaemic AEs are defined by a glucose concentration <=70 mg/dL (3.9 mmol/L) or requiring assistance.
Risk ratios and odds ratios with confidence intervals (CIs) are estimated by Cochran-Mantel-Haenszel method. For risk differences standard Wald asymptotic confidence limits are calculated. A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied in case of any zero cells in contingency table.
Only treatment emergent AEs are displayed (onset between first dose until treatment stop +7 days).
MedDRA version: 23.1. * Chi-square test for treatment effect ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction).

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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 overall and by subgroup - TS
User-defined AE category: Urosepsis (PT) or pyelonephritis (narrow Sub 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	2989	17	0.6	2996	21	0.7	0.5198	1.23 (0.65, 2.33)	1.23 (0.65, 2.34)	0.00 (0.00, 0.01)	
Sex											0.0575
Male	1653	11	0.7	1658	7	0.4	0.3412	0.63 (0.25, 1.63)	0.63 (0.24, 1.64)	0.00 (-0.01, 0.00)	
Female	1336	6	0.4	1338	14	1.0	0.0731	2.33 (0.90, 6.04)	2.34 (0.90, 6.12)	0.01 (0.00, 0.01)	
Age [years]											0.1255
<70	1084	2	0.2	1066	7	0.7	0.0900	3.56 (0.74, 17.09)	3.58 (0.74, 17.25)	0.00 (0.00, 0.01)	
>=70	1905	15	0.8	1930	14	0.7	0.8246	0.92 (0.45, 1.90)	0.92 (0.44, 1.91)	0.00 (-0.01, 0.00)	
Region											0.9715
North America	359	2	0.6	359	4	1.1	0.4123	2.00 (0.37, 10.85)	2.01 (0.37, 11.05)	0.01 (-0.01, 0.02)	
Latin America	757	4	0.5	758	4	0.5	0.9985	1.00 (0.25, 3.98)	1.00 (0.25, 4.01)	0.00 (-0.01, 0.01)	
Europe	1341	7	0.5	1346	8	0.6	0.8013	1.14 (0.41, 3.13)	1.14 (0.41, 3.15)	0.00 (0.00, 0.01)	
Asia	343	2	0.6	343	3	0.9	0.6535	1.50 (0.25, 8.92)	1.50 (0.25, 9.06)	0.00 (-0.01, 0.02)	
Other	189	2	1.1	190	2	1.1	0.9958	0.99 (0.14, 6.99)	0.99 (0.14, 7.14)	0.00 (-0.02, 0.02)	
OECD member											0.7067
No	847	4	0.5	868	4	0.5	0.9723	0.98 (0.24, 3.89)	0.98 (0.24, 3.91)	0.00 (-0.01, 0.01)	
Yes	2142	13	0.6	2128	17	0.8	0.4527	1.32 (0.64, 2.70)	1.32 (0.64, 2.72)	0.00 (0.00, 0.01)	
Baseline NYHA											0.2380
II^	2450	15	0.6	2435	15	0.6	0.9865	1.01 (0.49, 2.05)	1.01 (0.49, 2.06)	0.00 (0.00, 0.00)	
III/IV	539	2	0.4	561	6	1.1	0.1729	2.88 (0.58, 14.22)	2.90 (0.58, 14.44)	0.01 (0.00, 0.02)	
Baseline Diabetes Status											0.7048
Diabetic	1471	10	0.7	1465	11	0.8	0.8193	1.10 (0.47, 2.59)	1.11 (0.47, 2.61)	0.00 (-0.01, 0.01)	
Non-Diabetic	1518	7	0.5	1531	10	0.7	0.4765	1.42 (0.54, 3.71)	1.42 (0.54, 3.74)	0.00 (0.00, 0.01)	

Analysis is based on study 1245.110.
^ Patients with NYHA class I are counted in subgroup NYHA class II.
*** Confirmed hypoglycaemic AEs are defined by a glucose concentration <=70 mg/dL (3.9 mmol/L) or requiring assistance.
Risk ratios and odds ratios with confidence intervals (CIs) are estimated by Cochran-Mantel-Haenszel method. For risk differences standard Wald asymptotic confidence limits are calculated. A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied in case of any zero cells in contingency table.
Only treatment emergent AEs are displayed (onset between first dose until treatment stop +7 days).
MedDRA version: 23.1. * Chi-square test for treatment effect ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction).

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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 overall and by subgroup - TS
User-defined AE category: Urosepsis (PT) or pyelonephritis (narrow Sub 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 Diabetes Status											0.8162
Diabetic	1471	10	0.7	1465	11	0.8	0.8193	1.10 (0.47, 2.59)	1.11 (0.47, 2.61)	0.00 (-0.01, 0.01)	
Pre-Diabetes	979	5	0.5	1001	6	0.6	0.7907	1.17 (0.36, 3.83)	1.17 (0.36, 3.86)	0.00 (-0.01, 0.01)	
Normal (no pre-diabetes)	539	2	0.4	530	4	0.8	0.4012	2.03 (0.37, 11.06)	2.04 (0.37, 11.20)	0.00 (-0.01, 0.01)	
Baseline BMI [kg/m²]											0.0881
<30	1641	12	0.7	1654	9	0.5	0.4997	0.74 (0.31, 1.76)	0.74 (0.31, 1.77)	0.00 (-0.01, 0.00)	
>=30	1348	5	0.4	1342	12	0.9	0.0868	2.41 (0.85, 6.82)	2.42 (0.85, 6.90)	0.01 (0.00, 0.01)	
Baseline eGFR (CKD-EPI) [mL/min/1.73m²]											0.4743
>=60	1505	5	0.3	1493	4	0.3	0.7476	0.81 (0.22, 3.00)	0.81 (0.22, 3.01)	0.00 (0.00, 0.00)	
<60	1482	12	0.8	1503	17	1.1	0.3708	1.40 (0.67, 2.91)	1.40 (0.67, 2.94)	0.00 (0.00, 0.01)	
History of HHF (in the last 12 months)											0.3953
No	2320	11	0.5	2297	16	0.7	0.3217	1.47 (0.68, 3.16)	1.47 (0.68, 3.18)	0.00 (0.00, 0.01)	
Yes	669	6	0.9	699	5	0.7	0.7070	0.80 (0.24, 2.60)	0.80 (0.24, 2.62)	0.00 (-0.01, 0.01)	
Baseline SBP (</>= median)											0.5107
< median	1474	9	0.6	1496	9	0.6	0.9749	0.99 (0.39, 2.48)	0.99 (0.39, 2.49)	0.00 (-0.01, 0.01)	
>= median	1515	8	0.5	1500	12	0.8	0.3577	1.52 (0.62, 3.70)	1.52 (0.62, 3.73)	0.00 (0.00, 0.01)	
History of atrial fibrillation or atrial flutter											0.3801
No	1426	5	0.4	1417	9	0.6	0.2786	1.81 (0.61, 5.39)	1.82 (0.61, 5.43)	0.00 (0.00, 0.01)	
Yes	1558	12	0.8	1575	12	0.8	0.9787	0.99 (0.45, 2.20)	0.99 (0.44, 2.21)	0.00 (-0.01, 0.01)	

Analysis is based on study 1245.110.
^ Patients with NYHA class I are counted in subgroup NYHA class II.
*** Confirmed hypoglycaemic AEs are defined by a glucose concentration <=70 mg/dL (3.9 mmol/L) or requiring assistance.
Risk ratios and odds ratios with confidence intervals (CIs) are estimated by Cochran-Mantel-Haenszel method. For risk differences standard Wald asymptotic confidence limits are calculated. A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied in case of any zero cells in contingency table.
Only treatment emergent AEs are displayed (onset between first dose until treatment stop +7 days).
MedDRA version: 23.1. * Chi-square test for treatment effect ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction).

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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 overall and by subgroup - TS
User-defined AE category: Urosepsis (PT) or pyelonephritis (narrow Sub 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 LVEF [%]											0.4626
< 50	988	4	0.4	995	3	0.3	0.6980	0.74 (0.17, 3.32)	0.74 (0.17, 3.33)	0.00 (-0.01, 0.00)	
>= 50	2001	13	0.6	2001	18	0.9	0.3673	1.38 (0.68, 2.82)	1.39 (0.68, 2.84)	0.00 (0.00, 0.01)	
Baseline LVEF [%]											0.4072
<50	988	4	0.4	995	3	0.3	0.6980	0.74 (0.17, 3.32)	0.74 (0.17, 3.33)	0.00 (-0.01, 0.00)	
50 to <60	1030	7	0.7	1028	6	0.6	0.7835	0.86 (0.29, 2.55)	0.86 (0.29, 2.56)	0.00 (-0.01, 0.01)	
>=60	971	6	0.6	973	12	1.2	0.1567	2.00 (0.75, 5.30)	2.01 (0.75, 5.37)	0.01 (0.00, 0.01)	
Baseline NT-proBNP [pg/mL] (</>=median by atrial fibrillation/flutter status)											0.1378
< median	1507	5	0.3	1476	11	0.7	0.1222	2.25 (0.78, 6.45)	2.26 (0.78, 6.51)	0.00 (0.00, 0.01)	
>= median	1475	12	0.8	1516	10	0.7	0.6223	0.81 (0.35, 1.87)	0.81 (0.35, 1.88)	0.00 (-0.01, 0.00)	
Baseline uric acid [mg/dL] (tertiles)											0.4784
<T1	975	3	0.3	963	7	0.7	0.1978	2.36 (0.61, 9.11)	2.37 (0.61, 9.20)	0.00 (0.00, 0.01)	
>=T1 and <T2	966	6	0.6	1032	5	0.5	0.6800	0.78 (0.24, 2.55)	0.78 (0.24, 2.56)	0.00 (-0.01, 0.01)	
>=T2	1016	8	0.8	970	9	0.9	0.7342	1.18 (0.46, 3.04)	1.18 (0.45, 3.07)	0.00 (-0.01, 0.01)	
Baseline use of MRA											0.9018
No	1865	10	0.5	1878	12	0.6	0.6808	1.19 (0.52, 2.75)	1.19 (0.51, 2.77)	0.00 (0.00, 0.01)	
Yes	1124	7	0.6	1118	9	0.8	0.6083	1.29 (0.48, 3.46)	1.29 (0.48, 3.49)	0.00 (-0.01, 0.01)	
Baseline use of ACE-inhibitor, ARB or ARNi											0.3253
No	586	2	0.3	568	5	0.9	0.2384	2.58 (0.50, 13.24)	2.59 (0.50, 13.42)	0.01 (0.00, 0.01)	
Yes	2403	15	0.6	2428	16	0.7	0.8798	1.06 (0.52, 2.13)	1.06 (0.52, 2.14)	0.00 (0.00, 0.00)	

Analysis is based on study 1245.110.
^ Patients with NYHA class I are counted in subgroup NYHA class II.
*** Confirmed hypoglycaemic AEs are defined by a glucose concentration <=70 mg/dL (3.9 mmol/L) or requiring assistance.
Risk ratios and odds ratios with confidence intervals (CIs) are estimated by Cochran-Mantel-Haenszel method. For risk differences standard Wald asymptotic confidence limits are calculated. A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied in case of any zero cells in contingency table.
Only treatment emergent AEs are displayed (onset between first dose until treatment stop +7 days).
MedDRA version: 23.1. * Chi-square test for treatment effect ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction).

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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 overall and by subgroup - TS
User-defined AE category: Sepsis (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	2989	59	2.0	2996	67	2.2	0.4795	1.13 (0.80, 1.60)	1.14 (0.80, 1.62)	0.00 (0.00, 0.01)	
Sex											0.1967
Male	1653	40	2.4	1658	38	2.3	0.8083	0.95 (0.61, 1.47)	0.95 (0.60, 1.48)	0.00 (-0.01, 0.01)	
Female	1336	19	1.4	1338	29	2.2	0.1467	1.52 (0.86, 2.70)	1.54 (0.86, 2.75)	0.01 (0.00, 0.02)	
Age [years]											0.3275
<70	1084	20	1.8	1066	17	1.6	0.6555	0.86 (0.46, 1.64)	0.86 (0.45, 1.66)	0.00 (-0.01, 0.01)	
>=70	1905	39	2.0	1930	50	2.6	0.2638	1.27 (0.84, 1.91)	1.27 (0.83, 1.94)	0.01 (0.00, 0.01)	
Region											0.6134
North America	359	10	2.8	359	19	5.3	0.0880	1.90 (0.90, 4.03)	1.95 (0.89, 4.26)	0.03 (0.00, 0.05)	
Latin America	757	15	2.0	758	17	2.2	0.7237	1.13 (0.57, 2.25)	1.13 (0.56, 2.29)	0.00 (-0.01, 0.02)	
Europe	1341	24	1.8	1346	22	1.6	0.7564	0.91 (0.51, 1.62)	0.91 (0.51, 1.63)	0.00 (-0.01, 0.01)	
Asia	343	5	1.5	343	4	1.2	0.7372	0.80 (0.22, 2.95)	0.80 (0.21, 3.00)	0.00 (-0.02, 0.01)	
Other	189	5	2.6	190	5	2.6	0.9933	0.99 (0.29, 3.38)	0.99 (0.28, 3.49)	0.00 (-0.03, 0.03)	
OECD member											0.9610
No	847	17	2.0	868	20	2.3	0.6720	1.15 (0.61, 2.18)	1.15 (0.60, 2.21)	0.00 (-0.01, 0.02)	
Yes	2142	42	2.0	2128	47	2.2	0.5708	1.13 (0.75, 1.70)	1.13 (0.74, 1.72)	0.00 (-0.01, 0.01)	
Baseline NYHA											0.0545
II^	2450	46	1.9	2435	41	1.7	0.6087	0.90 (0.59, 1.36)	0.90 (0.59, 1.37)	0.00 (-0.01, 0.01)	
III/IV	539	13	2.4	561	26	4.6	0.0463	1.92 (1.00, 3.70)	1.97 (1.00, 3.87)	0.02 (0.00, 0.04)	
Baseline Diabetes Status											0.2249
Diabetic	1471	30	2.0	1465	41	2.8	0.1806	1.37 (0.86, 2.19)	1.38 (0.86, 2.23)	0.01 (0.00, 0.02)	
Non-Diabetic	1518	29	1.9	1531	26	1.7	0.6598	0.89 (0.53, 1.50)	0.89 (0.52, 1.51)	0.00 (-0.01, 0.01)	

Analysis is based on study 1245.110.
^ Patients with NYHA class I are counted in subgroup NYHA class II.
*** Confirmed hypoglycaemic AEs are defined by a glucose concentration <=70 mg/dL (3.9 mmol/L) or requiring assistance.
Risk ratios and odds ratios with confidence intervals (CIs) are estimated by Cochran-Mantel-Haenszel method. For risk differences standard Wald asymptotic confidence limits are calculated. A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied in case of any zero cells in contingency table.
Only treatment emergent AEs are displayed (onset between first dose until treatment stop +7 days).
MedDRA version: 23.1. * Chi-square test for treatment effect ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction).

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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 overall and by subgroup - TS
User-defined AE category: Sepsis (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 Diabetes Status											0.0191
Diabetic	1471	30	2.0	1465	41	2.8	0.1806	1.37 (0.86, 2.19)	1.38 (0.86, 2.23)	0.01 (0.00, 0.02)	
Pre-Diabetes	979	14	1.4	1001	22	2.2	0.2011	1.54 (0.79, 2.99)	1.55 (0.79, 3.05)	0.01 (0.00, 0.02)	
Normal (no pre-diabetes)	539	15	2.8	530	4	0.8	0.0121	0.27 (0.09, 0.81)	0.27 (0.09, 0.81)	-0.02 (-0.04, 0.00)	
Baseline BMI [kg/m²]											0.0229
<30	1641	31	1.9	1654	22	1.3	0.2022	0.70 (0.41, 1.21)	0.70 (0.40, 1.21)	-0.01 (-0.01, 0.00)	
>=30	1348	28	2.1	1342	45	3.4	0.0417	1.61 (1.01, 2.57)	1.64 (1.01, 2.64)	0.01 (0.00, 0.03)	
Baseline eGFR (CKD-EPI) [mL/min/1.73m²]											0.8312
>=60	1505	23	1.5	1493	27	1.8	0.5492	1.18 (0.68, 2.05)	1.19 (0.68, 2.08)	0.00 (-0.01, 0.01)	
<60	1482	36	2.4	1503	40	2.7	0.6872	1.10 (0.70, 1.71)	1.10 (0.70, 1.73)	0.00 (-0.01, 0.01)	
History of HHF (in the last 12 months)											0.3376
No	2320	44	1.9	2297	44	1.9	0.9624	1.01 (0.67, 1.53)	1.01 (0.66, 1.54)	0.00 (-0.01, 0.01)	
Yes	669	15	2.2	699	23	3.3	0.2383	1.47 (0.77, 2.79)	1.48 (0.77, 2.87)	0.01 (-0.01, 0.03)	
Baseline SBP (</>= median)											0.0901
< median	1474	26	1.8	1496	40	2.7	0.0926	1.52 (0.93, 2.47)	1.53 (0.93, 2.52)	0.01 (0.00, 0.02)	
>= median	1515	33	2.2	1500	27	1.8	0.4572	0.83 (0.50, 1.37)	0.82 (0.49, 1.38)	0.00 (-0.01, 0.01)	
History of atrial fibrillation or atrial flutter											0.4652
No	1426	26	1.8	1417	25	1.8	0.9057	0.97 (0.56, 1.67)	0.97 (0.56, 1.68)	0.00 (-0.01, 0.01)	
Yes	1558	33	2.1	1575	42	2.7	0.3152	1.26 (0.80, 1.98)	1.27 (0.80, 2.01)	0.01 (-0.01, 0.02)	

Analysis is based on study 1245.110.
^ Patients with NYHA class I are counted in subgroup NYHA class II.
*** Confirmed hypoglycaemic AEs are defined by a glucose concentration <=70 mg/dL (3.9 mmol/L) or requiring assistance.
Risk ratios and odds ratios with confidence intervals (CIs) are estimated by Cochran-Mantel-Haenszel method. For risk differences standard Wald asymptotic confidence limits are calculated. A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied in case of any zero cells in contingency table.
Only treatment emergent AEs are displayed (onset between first dose until treatment stop +7 days).
MedDRA version: 23.1. * Chi-square test for treatment effect ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction).

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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 overall and by subgroup - TS
User-defined AE category: Sepsis (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 LVEF [%]													0.2998
< 50	988	16	1.6	995	24	2.4	0.2094	1.49 (0.80,	2.79)	1.50 (0.79,	2.84)	0.01 (0.00, 0.02)	
>= 50	2001	43	2.1	2001	43	2.1	1.0000	1.00 (0.66,	1.52)	1.00 (0.65,	1.53)	0.00 (-0.01, 0.01)	
Baseline LVEF [%]													0.4751
<50	988	16	1.6	995	24	2.4	0.2094	1.49 (0.80,	2.79)	1.50 (0.79,	2.84)	0.01 (0.00, 0.02)	
50 to <60	1030	22	2.1	1028	19	1.8	0.6405	0.87 (0.47,	1.59)	0.86 (0.46,	1.60)	0.00 (-0.01, 0.01)	
>=60	971	21	2.2	973	24	2.5	0.6560	1.14 (0.64,	2.03)	1.14 (0.63,	2.07)	0.00 (-0.01, 0.02)	
Baseline NT-proBNP [pg/mL] (</>=median by atrial fibrillation/flutter status)													0.5417
< median	1507	24	1.6	1476	23	1.6	0.9400	0.98 (0.55,	1.73)	0.98 (0.55,	1.74)	0.00 (-0.01, 0.01)	
>= median	1475	35	2.4	1516	44	2.9	0.3666	1.22 (0.79,	1.90)	1.23 (0.78,	1.93)	0.01 (-0.01, 0.02)	
Baseline uric acid [mg/dL] (tertiles)													0.4972
<T1	975	15	1.5	963	16	1.7	0.8291	1.08 (0.54,	2.17)	1.08 (0.53,	2.20)	0.00 (-0.01, 0.01)	
>=T1 and <T2	966	16	1.7	1032	26	2.5	0.1790	1.52 (0.82,	2.82)	1.53 (0.82,	2.88)	0.01 (0.00, 0.02)	
>=T2	1016	27	2.7	970	24	2.5	0.7963	0.93 (0.54,	1.60)	0.93 (0.53,	1.62)	0.00 (-0.02, 0.01)	
Baseline use of MRA													0.0982
No	1865	40	2.1	1878	36	1.9	0.6212	0.89 (0.57,	1.40)	0.89 (0.57,	1.41)	0.00 (-0.01, 0.01)	
Yes	1124	19	1.7	1118	31	2.8	0.0827	1.64 (0.93,	2.89)	1.66 (0.93,	2.95)	0.01 (0.00, 0.02)	
Baseline use of ACE-inhibitor, ARB or ARNi													0.7282
No	586	13	2.2	568	16	2.8	0.5161	1.27 (0.62,	2.62)	1.28 (0.61,	2.68)	0.01 (-0.01, 0.02)	
Yes	2403	46	1.9	2428	51	2.1	0.6445	1.10 (0.74,	1.63)	1.10 (0.74,	1.64)	0.00 (-0.01, 0.01)	

Analysis is based on study 1245.110.
^ Patients with NYHA class I are counted in subgroup NYHA class II.
*** Confirmed hypoglycaemic AEs are defined by a glucose concentration <=70 mg/dL (3.9 mmol/L) or requiring assistance.
Risk ratios and odds ratios with confidence intervals (CIs) are estimated by Cochran-Mantel-Haenszel method. For risk differences standard Wald asymptotic confidence limits are calculated. A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied in case of any zero cells in contingency table.
Only treatment emergent AEs are displayed (onset between first dose until treatment stop +7 days).
MedDRA version: 23.1. * Chi-square test for treatment effect ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction).

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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 overall and by subgroup - TS
User-defined AE category: Sepsis (investigator-defined) with source of infection UTI

Subgroup	Placebo			Empa 10mg			Empa 10mg vs Placebo				
Category	N	n	%	N	n	%	p-value *	Risk ratio (95% CI)	Odds ratio (95% CI)	Risk diff. (95% CI)	p-value **
Overall	2989	15	0.5	2996	18	0.6	0.6052	1.20 (0.60, 2.37)	1.20 (0.60, 2.38)	0.00 (0.00, 0.00)	
Sex											0.2285
Male	1653	9	0.5	1658	7	0.4	0.6120	0.78 (0.29, 2.08)	0.77 (0.29, 2.08)	0.00 (-0.01, 0.00)	
Female	1336	6	0.4	1338	11	0.8	0.2250	1.83 (0.68, 4.94)	1.84 (0.68, 4.98)	0.00 (0.00, 0.01)	
Age [years]											0.8303
<70	1084	3	0.3	1066	3	0.3	0.9836	1.02 (0.21, 5.03)	1.02 (0.20, 5.05)	0.00 (0.00, 0.00)	
>=70	1905	12	0.6	1930	15	0.8	0.5855	1.23 (0.58, 2.63)	1.24 (0.58, 2.65)	0.00 (0.00, 0.01)	
Region											0.5114
North America	359	0	0	359	5	1.4	0.0404	11.00 (0.61,198.20)	11.16 (0.61,202.49)	0.01 (0.00, 0.03)	
Latin America	757	4	0.5	758	2	0.3	0.4124	0.50 (0.09, 2.72)	0.50 (0.09, 2.73)	0.00 (-0.01, 0.00)	
Europe	1341	8	0.6	1346	8	0.6	0.9940	1.00 (0.38, 2.65)	1.00 (0.37, 2.66)	0.00 (-0.01, 0.01)	
Asia	343	1	0.3	343	1	0.3	1.0000	1.00 (0.06, 15.92)	1.00 (0.06, 16.05)	0.00 (-0.01, 0.01)	
Other	189	2	1.1	190	2	1.1	0.9958	0.99 (0.14, 6.99)	0.99 (0.14, 7.14)	0.00 (-0.02, 0.02)	
OECD member											0.2564
No	847	5	0.6	868	3	0.3	0.4572	0.59 (0.14, 2.44)	0.58 (0.14, 2.45)	0.00 (-0.01, 0.00)	
Yes	2142	10	0.5	2128	15	0.7	0.3080	1.51 (0.68, 3.35)	1.51 (0.68, 3.38)	0.00 (0.00, 0.01)	
Baseline NYHA											0.4266
II^	2450	12	0.5	2435	12	0.5	0.9880	1.01 (0.45, 2.24)	1.01 (0.45, 2.24)	0.00 (0.00, 0.00)	
III/IV	539	3	0.6	561	6	1.1	0.3451	1.92 (0.48, 7.64)	1.93 (0.48, 7.76)	0.01 (-0.01, 0.02)	
Baseline Diabetes Status											0.8625
Diabetic	1471	8	0.5	1465	9	0.6	0.8013	1.13 (0.44, 2.92)	1.13 (0.43, 2.94)	0.00 (0.00, 0.01)	
Non-Diabetic	1518	7	0.5	1531	9	0.6	0.6282	1.27 (0.48, 3.41)	1.28 (0.47, 3.44)	0.00 (0.00, 0.01)	

Analysis is based on study 1245.110.
^ Patients with NYHA class I are counted in subgroup NYHA class II.
*** Confirmed hypoglycaemic AEs are defined by a glucose concentration <=70 mg/dL (3.9 mmol/L) or requiring assistance.
Risk ratios and odds ratios with confidence intervals (CIs) are estimated by Cochran-Mantel-Haenszel method. For risk differences standard Wald asymptotic confidence limits are calculated. A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied in case of any zero cells in contingency table.
Only treatment emergent AEs are displayed (onset between first dose until treatment stop +7 days).
MedDRA version: 23.1. * Chi-square test for treatment effect ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction).

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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 overall and by subgroup - TS
User-defined AE category: Sepsis (investigator-defined) with source of infection UTI

Subgroup	Placebo			Empa 10mg			Empa 10mg vs Placebo				
Category	N	n	%	N	n	%	p-value *	Risk ratio (95% CI)	Odds ratio (95% CI)	Risk diff. (95% CI)	p-value **
Baseline Diabetes Status											0.9541
Diabetic	1471	8	0.5	1465	9	0.6	0.8013	1.13 (0.44, 2.92)	1.13 (0.43, 2.94)	0.00 (0.00, 0.01)	
Pre-Diabetes	979	5	0.5	1001	7	0.7	0.5888	1.37 (0.44, 4.30)	1.37 (0.43, 4.34)	0.00 (0.00, 0.01)	
Normal (no pre-diabetes)	539	2	0.4	530	2	0.4	0.9865	1.02 (0.14, 7.19)	1.02 (0.14, 7.25)	0.00 (-0.01, 0.01)	
Baseline BMI [kg/m²]											0.1347
<30	1641	8	0.5	1654	5	0.3	0.3965	0.62 (0.20, 1.89)	0.62 (0.20, 1.90)	0.00 (-0.01, 0.00)	
>=30	1348	7	0.5	1342	13	1.0	0.1749	1.87 (0.75, 4.66)	1.87 (0.75, 4.71)	0.00 (0.00, 0.01)	
Baseline eGFR (CKD-EPI) [mL/min/1.73m²]											0.7874
>=60	1505	4	0.3	1493	4	0.3	0.9910	1.01 (0.25, 4.02)	1.01 (0.25, 4.04)	0.00 (0.00, 0.00)	
<60	1482	11	0.7	1503	14	0.9	0.5706	1.25 (0.57, 2.76)	1.26 (0.57, 2.78)	0.00 (0.00, 0.01)	
History of HHF (in the last 12 months)											0.8880
No	2320	9	0.4	2297	11	0.5	0.6380	1.23 (0.51, 2.97)	1.24 (0.51, 2.99)	0.00 (0.00, 0.00)	
Yes	669	6	0.9	699	7	1.0	0.8420	1.12 (0.38, 3.31)	1.12 (0.37, 3.34)	0.00 (-0.01, 0.01)	
Baseline SBP (</>= median)											0.8702
< median	1474	7	0.5	1496	8	0.5	0.8180	1.13 (0.41, 3.10)	1.13 (0.41, 3.12)	0.00 (0.00, 0.01)	
>= median	1515	8	0.5	1500	10	0.7	0.6213	1.26 (0.50, 3.19)	1.26 (0.50, 3.21)	0.00 (0.00, 0.01)	
History of atrial fibrillation or atrial flutter											0.3834
No	1426	3	0.2	1417	6	0.4	0.3120	2.01 (0.50, 8.03)	2.02 (0.50, 8.08)	0.00 (0.00, 0.01)	
Yes	1558	12	0.8	1575	12	0.8	0.9787	0.99 (0.45, 2.20)	0.99 (0.44, 2.21)	0.00 (-0.01, 0.01)	

Analysis is based on study 1245.110.
^ Patients with NYHA class I are counted in subgroup NYHA class II.
*** Confirmed hypoglycaemic AEs are defined by a glucose concentration <=70 mg/dL (3.9 mmol/L) or requiring assistance.
Risk ratios and odds ratios with confidence intervals (CIs) are estimated by Cochran-Mantel-Haenszel method. For risk differences standard Wald asymptotic confidence limits are calculated. A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied in case of any zero cells in contingency table.
Only treatment emergent AEs are displayed (onset between first dose until treatment stop +7 days).
MedDRA version: 23.1. * Chi-square test for treatment effect ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction).

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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 overall and by subgroup - TS
User-defined AE category: Sepsis (investigator-defined) with source of infection UTI

Subgroup	Placebo			Empa 10mg			Empa 10mg vs Placebo				
Category	N	n	%	N	n	%	p-value *	Risk ratio (95% CI)	Odds ratio (95% CI)	Risk diff. (95% CI)	p-value **
Baseline LVEF [%]											0.3997
< 50	988	3	0.3	995	6	0.6	0.3214	1.99 (0.50, 7.92)	1.99 (0.50, 7.99)	0.00 (0.00, 0.01)	
>= 50	2001	12	0.6	2001	12	0.6	1.0000	1.00 (0.45, 2.22)	1.00 (0.45, 2.23)	0.00 (0.00, 0.00)	
Baseline LVEF [%]											0.1959
<50	988	3	0.3	995	6	0.6	0.3214	1.99 (0.50, 7.92)	1.99 (0.50, 7.99)	0.00 (0.00, 0.01)	
50 to <60	1030	7	0.7	1028	3	0.3	0.2059	0.43 (0.11, 1.66)	0.43 (0.11, 1.66)	0.00 (-0.01, 0.00)	
>=60	971	5	0.5	973	9	0.9	0.2850	1.80 (0.60, 5.34)	1.80 (0.60, 5.40)	0.00 (0.00, 0.01)	
Baseline NT-proBNP [pg/mL] (</>=median by atrial fibrillation/flutter status)											0.0721
< median	1507	3	0.2	1476	9	0.6	0.0764	3.06 (0.83, 11.29)	3.08 (0.83, 11.38)	0.00 (0.00, 0.01)	
>= median	1475	12	0.8	1516	9	0.6	0.4715	0.73 (0.31, 1.73)	0.73 (0.31, 1.73)	0.00 (-0.01, 0.00)	
Baseline uric acid [mg/dL] (tertiles)											0.5421
<T1	975	1	0.1	963	3	0.3	0.3108	3.04 (0.32, 29.15)	3.04 (0.32, 29.31)	0.00 (0.00, 0.01)	
>=T1 and <T2	966	7	0.7	1032	6	0.6	0.6907	0.80 (0.27, 2.38)	0.80 (0.27, 2.39)	0.00 (-0.01, 0.01)	
>=T2	1016	7	0.7	970	9	0.9	0.5517	1.35 (0.50, 3.60)	1.35 (0.50, 3.64)	0.00 (-0.01, 0.01)	
Baseline use of MRA											0.1988
No	1865	10	0.5	1878	8	0.4	0.6260	0.79 (0.31, 2.01)	0.79 (0.31, 2.02)	0.00 (-0.01, 0.00)	
Yes	1124	5	0.4	1118	10	0.9	0.1916	2.01 (0.69, 5.86)	2.02 (0.69, 5.93)	0.00 (0.00, 0.01)	
Baseline use of ACE-inhibitor, ARB or ARNi											0.5694
No	586	3	0.5	568	5	0.9	0.4509	1.72 (0.41, 7.16)	1.73 (0.41, 7.26)	0.00 (-0.01, 0.01)	
Yes	2403	12	0.5	2428	13	0.5	0.8614	1.07 (0.49, 2.34)	1.07 (0.49, 2.36)	0.00 (0.00, 0.00)	

Analysis is based on study 1245.110.
^ Patients with NYHA class I are counted in subgroup NYHA class II.
*** Confirmed hypoglycaemic AEs are defined by a glucose concentration <=70 mg/dL (3.9 mmol/L) or requiring assistance.
Risk ratios and odds ratios with confidence intervals (CIs) are estimated by Cochran-Mantel-Haenszel method. For risk differences standard Wald asymptotic confidence limits are calculated. A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied in case of any zero cells in contingency table.
Only treatment emergent AEs are displayed (onset between first dose until treatment stop +7 days).
MedDRA version: 23.1. * Chi-square test for treatment effect ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction).

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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 overall and by subgroup - TS
User-defined AE category: Sepsis (investigator-defined) with source of infection non-UTI or missing

Subgroup	Placebo			Empa 10mg			Empa 10mg vs Placebo					
Category	N	n	%	N	n	%	p-value *	Risk ratio (95% CI)	Odds ratio (95% CI)	Risk diff. (95% CI)	p-value **
Overall	2989	44	1.5	2996	49	1.6	0.6092	1.11 (0.74, 1.66)	1.11 (0.74, 1.68)	0.00 (0.00, 0.01)	
Sex											0.4582
Male	1653	31	1.9	1658	31	1.9	0.9904	1.00 (0.61, 1.63)	1.00 (0.60, 1.65)	0.00 (-0.01, 0.01)	
Female	1336	13	1.0	1338	18	1.3	0.3686	1.38 (0.68, 2.81)	1.39 (0.68, 2.84)	0.00 (0.00, 0.01)	
Age [years]											0.3346
<70	1084	17	1.6	1066	14	1.3	0.6200	0.84 (0.41, 1.69)	0.84 (0.41, 1.70)	0.00 (-0.01, 0.01)	
>=70	1905	27	1.4	1930	35	1.8	0.3308	1.28 (0.78, 2.11)	1.28 (0.77, 2.13)	0.00 (0.00, 0.01)	
Region											0.8580
North America	359	10	2.8	359	14	3.9	0.4063	1.40 (0.63, 3.11)	1.42 (0.62, 3.23)	0.01 (-0.02, 0.04)	
Latin America	757	11	1.5	758	15	2.0	0.4308	1.36 (0.63, 2.95)	1.37 (0.62, 3.00)	0.01 (-0.01, 0.02)	
Europe	1341	16	1.2	1346	14	1.0	0.7058	0.87 (0.43, 1.78)	0.87 (0.42, 1.79)	0.00 (-0.01, 0.01)	
Asia	343	4	1.2	343	3	0.9	0.7040	0.75 (0.17, 3.33)	0.75 (0.17, 3.37)	0.00 (-0.02, 0.01)	
Other	189	3	1.6	190	3	1.6	0.9948	0.99 (0.20, 4.87)	0.99 (0.20, 4.99)	0.00 (-0.03, 0.03)	
OECD member											0.4796
No	847	12	1.4	868	17	2.0	0.3843	1.38 (0.66, 2.88)	1.39 (0.66, 2.93)	0.01 (-0.01, 0.02)	
Yes	2142	32	1.5	2128	32	1.5	0.9789	1.01 (0.62, 1.64)	1.01 (0.61, 1.65)	0.00 (-0.01, 0.01)	
Baseline NYHA											0.0782
II^	2450	34	1.4	2435	29	1.2	0.5422	0.86 (0.52, 1.40)	0.86 (0.52, 1.41)	0.00 (-0.01, 0.00)	
III/IV	539	10	1.9	561	20	3.6	0.0818	1.92 (0.91, 4.07)	1.96 (0.91, 4.22)	0.02 (0.00, 0.04)	
Baseline Diabetes Status											0.1266
Diabetic	1471	22	1.5	1465	32	2.2	0.1649	1.46 (0.85, 2.50)	1.47 (0.85, 2.54)	0.01 (0.00, 0.02)	
Non-Diabetic	1518	22	1.4	1531	17	1.1	0.4051	0.77 (0.41, 1.44)	0.76 (0.40, 1.44)	0.00 (-0.01, 0.00)	

Analysis is based on study 1245.110.
^ Patients with NYHA class I are counted in subgroup NYHA class II.
*** Confirmed hypoglycaemic AEs are defined by a glucose concentration <=70 mg/dL (3.9 mmol/L) or requiring assistance.
Risk ratios and odds ratios with confidence intervals (CIs) are estimated by Cochran-Mantel-Haenszel method. For risk differences standard Wald asymptotic confidence limits are calculated. A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied in case of any zero cells in contingency table.
Only treatment emergent AEs are displayed (onset between first dose until treatment stop +7 days).
MedDRA version: 23.1. * Chi-square test for treatment effect ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction).

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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 overall and by subgroup - TS
User-defined AE category: Sepsis (investigator-defined) with source of infection non-UTI or missing

Subgroup	Placebo			Empa 10mg			Empa 10mg vs Placebo				
Category	N	n	%	N	n	%	p-value *	Risk ratio (95% CI)	Odds ratio (95% CI)	Risk diff. (95% CI)	p-value **
Baseline Diabetes Status											0.0161
Diabetic	1471	22	1.5	1465	32	2.2	0.1649	1.46 (0.85, 2.50)	1.47 (0.85, 2.54)	0.01 (0.00, 0.02)	
Pre-Diabetes	979	9	0.9	1001	15	1.5	0.2390	1.63 (0.72, 3.71)	1.64 (0.71, 3.76)	0.01 (0.00, 0.02)	
Normal (no pre-diabetes)	539	13	2.4	530	2	0.4	0.0047	0.16 (0.04, 0.69)	0.15 (0.03, 0.68)	-0.02 (-0.03,-0.01)	
Baseline BMI [kg/m²]											0.0815
<30	1641	23	1.4	1654	17	1.0	0.3273	0.73 (0.39, 1.37)	0.73 (0.39, 1.37)	0.00 (-0.01, 0.00)	
>=30	1348	21	1.6	1342	32	2.4	0.1230	1.53 (0.89, 2.64)	1.54 (0.89, 2.69)	0.01 (0.00, 0.02)	
Baseline eGFR (CKD-EPI) [mL/min/1.73m²]											0.6749
>=60	1505	19	1.3	1493	23	1.5	0.5172	1.22 (0.67, 2.23)	1.22 (0.66, 2.26)	0.00 (-0.01, 0.01)	
<60	1482	25	1.7	1503	26	1.7	0.9278	1.03 (0.60, 1.77)	1.03 (0.59, 1.78)	0.00 (-0.01, 0.01)	
History of HHF (in the last 12 months)											0.2249
No	2320	35	1.5	2297	33	1.4	0.8392	0.95 (0.59, 1.53)	0.95 (0.59, 1.54)	0.00 (-0.01, 0.01)	
Yes	669	9	1.3	699	16	2.3	0.1927	1.70 (0.76, 3.82)	1.72 (0.75, 3.91)	0.01 (0.00, 0.02)	
Baseline SBP (</>= median)											0.0376
< median	1474	19	1.3	1496	32	2.1	0.0746	1.66 (0.94, 2.91)	1.67 (0.94, 2.97)	0.01 (0.00, 0.02)	
>= median	1515	25	1.7	1500	17	1.1	0.2260	0.69 (0.37, 1.27)	0.68 (0.37, 1.27)	-0.01 (-0.01, 0.00)	
History of atrial fibrillation or atrial flutter											0.2039
No	1426	23	1.6	1417	19	1.3	0.5477	0.83 (0.45, 1.52)	0.83 (0.45, 1.53)	0.00 (-0.01, 0.01)	
Yes	1558	21	1.3	1575	30	1.9	0.2181	1.41 (0.81, 2.46)	1.42 (0.81, 2.49)	0.01 (0.00, 0.01)	

Analysis is based on study 1245.110.
^ Patients with NYHA class I are counted in subgroup NYHA class II.
*** Confirmed hypoglycaemic AEs are defined by a glucose concentration <=70 mg/dL (3.9 mmol/L) or requiring assistance.
Risk ratios and odds ratios with confidence intervals (CIs) are estimated by Cochran-Mantel-Haenszel method. For risk differences standard Wald asymptotic confidence limits are calculated. A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied in case of any zero cells in contingency table.
Only treatment emergent AEs are displayed (onset between first dose until treatment stop +7 days).
MedDRA version: 23.1. * Chi-square test for treatment effect ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction).

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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 overall and by subgroup - TS
User-defined AE category: Sepsis (investigator-defined) with source of infection non-UTI or missing

Subgroup	Placebo			Empa 10mg			Empa 10mg vs Placebo						
Category	N	n	%	N	n	%	p-value *	Risk ratio (95% CI)		Odds ratio (95% CI)		Risk diff. (95% CI)	p-value **
Baseline LVEF [%]													0.4698
< 50	988	13	1.3	995	18	1.8	0.3760	1.37 (0.68,	2.79)	1.38 (0.67,	2.84)	0.00 (-0.01, 0.02)	
>= 50	2001	31	1.5	2001	31	1.5	1.0000	1.00 (0.61,	1.64)	1.00 (0.61,	1.65)	0.00 (-0.01, 0.01)	
Baseline LVEF [%]													0.7437
<50	988	13	1.3	995	18	1.8	0.3760	1.37 (0.68,	2.79)	1.38 (0.67,	2.84)	0.00 (-0.01, 0.02)	
50 to <60	1030	15	1.5	1028	16	1.6	0.8521	1.07 (0.53,	2.15)	1.07 (0.53,	2.18)	0.00 (-0.01, 0.01)	
>=60	971	16	1.6	973	15	1.5	0.8518	0.94 (0.47,	1.88)	0.93 (0.46,	1.90)	0.00 (-0.01, 0.01)	
Baseline NT-proBNP [pg/mL] (</>=median by atrial fibrillation/flutter status)													0.0734
< median	1507	21	1.4	1476	14	0.9	0.2591	0.68 (0.35,	1.33)	0.68 (0.34,	1.34)	0.00 (-0.01, 0.00)	
>= median	1475	23	1.6	1516	35	2.3	0.1373	1.48 (0.88,	2.49)	1.49 (0.88,	2.54)	0.01 (0.00, 0.02)	
Baseline uric acid [mg/dL] (tertiles)													0.1566
<T1	975	14	1.4	963	13	1.3	0.8718	0.94 (0.44,	1.99)	0.94 (0.44,	2.01)	0.00 (-0.01, 0.01)	
>=T1 and <T2	966	9	0.9	1032	20	1.9	0.0602	2.08 (0.95,	4.55)	2.10 (0.95,	4.64)	0.01 (0.00, 0.02)	
>=T2	1016	20	2.0	970	15	1.5	0.4748	0.79 (0.40,	1.53)	0.78 (0.40,	1.54)	0.00 (-0.02, 0.01)	
Baseline use of MRA													0.2581
No	1865	30	1.6	1878	28	1.5	0.7708	0.93 (0.56,	1.55)	0.93 (0.55,	1.56)	0.00 (-0.01, 0.01)	
Yes	1124	14	1.2	1118	21	1.9	0.2268	1.51 (0.77,	2.95)	1.52 (0.77,	3.00)	0.01 (0.00, 0.02)	
Baseline use of ACE-inhibitor, ARB or ARNi													0.9585
No	586	10	1.7	568	11	1.9	0.7700	1.13 (0.49,	2.65)	1.14 (0.48,	2.70)	0.00 (-0.01, 0.02)	
Yes	2403	34	1.4	2428	38	1.6	0.6667	1.11 (0.70,	1.75)	1.11 (0.70,	1.77)	0.00 (-0.01, 0.01)	

Analysis is based on study 1245.110.
^ Patients with NYHA class I are counted in subgroup NYHA class II.
*** Confirmed hypoglycaemic AEs are defined by a glucose concentration <=70 mg/dL (3.9 mmol/L) or requiring assistance.
Risk ratios and odds ratios with confidence intervals (CIs) are estimated by Cochran-Mantel-Haenszel method. For risk differences standard Wald asymptotic confidence limits are calculated. A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied in case of any zero cells in contingency table.
Only treatment emergent AEs are displayed (onset between first dose until treatment stop +7 days).
MedDRA version: 23.1. * Chi-square test for treatment effect ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction).

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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 overall and by subgroup - TS
User-defined AE category: Bone fracture (narrow 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	2989	61	2.0	2996	65	2.2	0.7287	1.06 (0.75, 1.50)	1.06 (0.75, 1.52)	0.00 (-0.01, 0.01)	
Sex											0.6706
Male	1653	24	1.5	1658	28	1.7	0.5836	1.16 (0.68, 2.00)	1.17 (0.67, 2.02)	0.00 (-0.01, 0.01)	
Female	1336	37	2.8	1338	37	2.8	0.9948	1.00 (0.64, 1.56)	1.00 (0.63, 1.58)	0.00 (-0.01, 0.01)	
Age [years]											0.3258
<70	1084	16	1.5	1066	12	1.1	0.4738	0.76 (0.36, 1.60)	0.76 (0.36, 1.61)	0.00 (-0.01, 0.01)	
>=70	1905	45	2.4	1930	53	2.7	0.4513	1.16 (0.79, 1.72)	1.17 (0.78, 1.75)	0.00 (-0.01, 0.01)	
Region											0.4612
North America	359	13	3.6	359	9	2.5	0.3864	0.69 (0.30, 1.60)	0.68 (0.29, 1.62)	-0.01 (-0.04, 0.01)	
Latin America	757	10	1.3	758	7	0.9	0.4627	0.70 (0.27, 1.83)	0.70 (0.26, 1.84)	0.00 (-0.01, 0.01)	
Europe	1341	25	1.9	1346	27	2.0	0.7898	1.08 (0.63, 1.84)	1.08 (0.62, 1.87)	0.00 (-0.01, 0.01)	
Asia	343	10	2.9	343	16	4.7	0.2303	1.60 (0.74, 3.48)	1.63 (0.73, 3.64)	0.02 (-0.01, 0.05)	
Other	189	3	1.6	190	6	3.2	0.3153	1.99 (0.50, 7.84)	2.02 (0.50, 8.21)	0.02 (-0.01, 0.05)	
OECD member											0.1574
No	847	13	1.5	868	8	0.9	0.2483	0.60 (0.25, 1.44)	0.60 (0.25, 1.45)	-0.01 (-0.02, 0.00)	
Yes	2142	48	2.2	2128	57	2.7	0.3558	1.20 (0.82, 1.75)	1.20 (0.81, 1.77)	0.00 (0.00, 0.01)	
Baseline NYHA											0.7920
II^	2450	45	1.8	2435	46	1.9	0.8923	1.03 (0.68, 1.55)	1.03 (0.68, 1.56)	0.00 (-0.01, 0.01)	
III/IV	539	16	3.0	561	19	3.4	0.6927	1.14 (0.59, 2.20)	1.15 (0.58, 2.25)	0.00 (-0.02, 0.02)	
Baseline Diabetes Status											0.0626
Diabetic	1471	23	1.6	1465	35	2.4	0.1080	1.53 (0.91, 2.57)	1.54 (0.91, 2.62)	0.01 (0.00, 0.02)	
Non-Diabetic	1518	38	2.5	1531	30	2.0	0.3093	0.78 (0.49, 1.26)	0.78 (0.48, 1.26)	-0.01 (-0.02, 0.01)	

Analysis is based on study 1245.110.
^ Patients with NYHA class I are counted in subgroup NYHA class II.
*** Confirmed hypoglycaemic AEs are defined by a glucose concentration <=70 mg/dL (3.9 mmol/L) or requiring assistance.
Risk ratios and odds ratios with confidence intervals (CIs) are estimated by Cochran-Mantel-Haenszel method. For risk differences standard Wald asymptotic confidence limits are calculated. A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied in case of any zero cells in contingency table.
Only treatment emergent AEs are displayed (onset between first dose until treatment stop +7 days).
MedDRA version: 23.1. * Chi-square test for treatment effect ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction).

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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 overall and by subgroup - TS
User-defined AE category: Bone fracture (narrow 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 Diabetes Status											0.1748
Diabetic	1471	23	1.6	1465	35	2.4	0.1080	1.53 (0.91, 2.57)	1.54 (0.91, 2.62)	0.01 (0.00, 0.02)	
Pre-Diabetes	979	26	2.7	1001	21	2.1	0.4149	0.79 (0.45, 1.39)	0.79 (0.44, 1.41)	-0.01 (-0.02, 0.01)	
Normal (no pre-diabetes)	539	12	2.2	530	9	1.7	0.5338	0.76 (0.32, 1.80)	0.76 (0.32, 1.82)	-0.01 (-0.02, 0.01)	
Baseline BMI [kg/m²]											0.9539
<30	1641	38	2.3	1654	41	2.5	0.7595	1.07 (0.69, 1.66)	1.07 (0.69, 1.68)	0.00 (-0.01, 0.01)	
>=30	1348	23	1.7	1342	24	1.8	0.8708	1.05 (0.59, 1.85)	1.05 (0.59, 1.87)	0.00 (-0.01, 0.01)	
Baseline eGFR (CKD-EPI) [mL/min/1.73m²]											0.6328
>=60	1505	25	1.7	1493	29	1.9	0.5626	1.17 (0.69, 1.99)	1.17 (0.68, 2.01)	0.00 (-0.01, 0.01)	
<60	1482	36	2.4	1503	36	2.4	0.9518	0.99 (0.62, 1.56)	0.99 (0.62, 1.57)	0.00 (-0.01, 0.01)	
History of HHF (in the last 12 months)											0.4469
No	2320	43	1.9	2297	49	2.1	0.4964	1.15 (0.77, 1.73)	1.15 (0.76, 1.75)	0.00 (-0.01, 0.01)	
Yes	669	18	2.7	699	16	2.3	0.6334	0.85 (0.44, 1.65)	0.85 (0.43, 1.68)	0.00 (-0.02, 0.01)	
Baseline SBP (</>= median)											0.9395
< median	1474	31	2.1	1496	33	2.2	0.8471	1.05 (0.65, 1.70)	1.05 (0.64, 1.72)	0.00 (-0.01, 0.01)	
>= median	1515	30	2.0	1500	32	2.1	0.7670	1.08 (0.66, 1.76)	1.08 (0.65, 1.78)	0.00 (-0.01, 0.01)	
History of atrial fibrillation or atrial flutter											0.8414
No	1426	20	1.4	1417	20	1.4	0.9839	1.01 (0.54, 1.86)	1.01 (0.54, 1.88)	0.00 (-0.01, 0.01)	
Yes	1558	41	2.6	1575	45	2.9	0.6992	1.09 (0.72, 1.65)	1.09 (0.71, 1.67)	0.00 (-0.01, 0.01)	

Analysis is based on study 1245.110.
^ Patients with NYHA class I are counted in subgroup NYHA class II.
*** Confirmed hypoglycaemic AEs are defined by a glucose concentration <=70 mg/dL (3.9 mmol/L) or requiring assistance.
Risk ratios and odds ratios with confidence intervals (CIs) are estimated by Cochran-Mantel-Haenszel method. For risk differences standard Wald asymptotic confidence limits are calculated. A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied in case of any zero cells in contingency table.
Only treatment emergent AEs are displayed (onset between first dose until treatment stop +7 days).
MedDRA version: 23.1. * Chi-square test for treatment effect ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction).

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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 overall and by subgroup - TS
User-defined AE category: Bone fracture (narrow 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 LVEF [%]											0.9881
< 50	988	13	1.3	995	14	1.4	0.8608	1.07 (0.51, 2.26)	1.07 (0.50, 2.29)	0.00 (-0.01, 0.01)	
>= 50	2001	48	2.4	2001	51	2.5	0.7601	1.06 (0.72, 1.57)	1.06 (0.71, 1.59)	0.00 (-0.01, 0.01)	
Baseline LVEF [%]											0.1539
<50	988	13	1.3	995	14	1.4	0.8608	1.07 (0.51, 2.26)	1.07 (0.50, 2.29)	0.00 (-0.01, 0.01)	
50 to <60	1030	19	1.8	1028	30	2.9	0.1102	1.58 (0.90, 2.79)	1.60 (0.89, 2.86)	0.01 (0.00, 0.02)	
>=60	971	29	3.0	973	21	2.2	0.2487	0.72 (0.42, 1.26)	0.72 (0.41, 1.27)	-0.01 (-0.02, 0.01)	
Baseline NT-proBNP [pg/mL] (</>=median by atrial fibrillation/flutter status)											0.7076
< median	1507	25	1.7	1476	28	1.9	0.6226	1.14 (0.67, 1.95)	1.15 (0.67, 1.98)	0.00 (-0.01, 0.01)	
>= median	1475	36	2.4	1516	37	2.4	0.9999	1.00 (0.64, 1.57)	1.00 (0.63, 1.59)	0.00 (-0.01, 0.01)	
Baseline uric acid [mg/dL] (tertiles)											0.2945
<T1	975	23	2.4	963	17	1.8	0.3581	0.75 (0.40, 1.39)	0.74 (0.39, 1.40)	-0.01 (-0.02, 0.01)	
>=T1 and <T2	966	14	1.4	1032	23	2.2	0.1966	1.54 (0.80, 2.97)	1.55 (0.79, 3.03)	0.01 (0.00, 0.02)	
>=T2	1016	24	2.4	970	25	2.6	0.7574	1.09 (0.63, 1.90)	1.09 (0.62, 1.93)	0.00 (-0.01, 0.02)	
Baseline use of MRA											0.5212
No	1865	33	1.8	1878	39	2.1	0.4938	1.17 (0.74, 1.86)	1.18 (0.74, 1.88)	0.00 (-0.01, 0.01)	
Yes	1124	28	2.5	1118	26	2.3	0.7983	0.93 (0.55, 1.58)	0.93 (0.54, 1.60)	0.00 (-0.01, 0.01)	
Baseline use of ACE-inhibitor, ARB or ARNi											0.2938
No	586	16	2.7	568	22	3.9	0.2767	1.42 (0.75, 2.67)	1.44 (0.75, 2.76)	0.01 (-0.01, 0.03)	
Yes	2403	45	1.9	2428	43	1.8	0.7917	0.95 (0.63, 1.43)	0.94 (0.62, 1.44)	0.00 (-0.01, 0.01)	

Analysis is based on study 1245.110.
^ Patients with NYHA class I are counted in subgroup NYHA class II.
*** Confirmed hypoglycaemic AEs are defined by a glucose concentration <=70 mg/dL (3.9 mmol/L) or requiring assistance.
Risk ratios and odds ratios with confidence intervals (CIs) are estimated by Cochran-Mantel-Haenszel method. For risk differences standard Wald asymptotic confidence limits are calculated. A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied in case of any zero cells in contingency table.
Only treatment emergent AEs are displayed (onset between first dose until treatment stop +7 days).
MedDRA version: 23.1. * Chi-square test for treatment effect ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction).

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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 overall and by subgroup - TS
User-defined AE category: Urinary tract malignancies (broad Sub BIcMQs)

Subgroup	Placebo			Empa 10mg			Empa 10mg vs Placebo				
Category	N	n	%	N	n	%	p-value *	Risk ratio (95% CI)	Odds ratio (95% CI)	Risk diff. (95% CI)	p-value **
Overall	2989	10	0.3	2996	16	0.5	0.2407	1.60 (0.73, 3.51)	1.60 (0.72, 3.53)	0.00 (0.00, 0.01)	
Sex											0.6496
Male	1653	6	0.4	1658	11	0.7	0.2264	1.83 (0.68, 4.93)	1.83 (0.68, 4.97)	0.00 (0.00, 0.01)	
Female	1336	4	0.3	1338	5	0.4	0.7402	1.25 (0.34, 4.64)	1.25 (0.33, 4.66)	0.00 (0.00, 0.01)	
Age [years]											0.4428
<70	1084	4	0.4	1066	4	0.4	0.9811	1.02 (0.25, 4.06)	1.02 (0.25, 4.08)	0.00 (-0.01, 0.01)	
>=70	1905	6	0.3	1930	12	0.6	0.1646	1.97 (0.74, 5.25)	1.98 (0.74, 5.29)	0.00 (0.00, 0.01)	
Region											0.8092
North America	359	0	0	359	1	0.3	0.4789	3.00 (0.12, 73.40)	3.01 (0.12, 74.09)	0.00 (0.00, 0.01)	
Latin America	757	1	0.1	758	3	0.4	0.3173	3.00 (0.31, 28.74)	3.00 (0.31, 28.94)	0.00 (0.00, 0.01)	
Europe	1341	6	0.4	1346	7	0.5	0.7862	1.16 (0.39, 3.45)	1.16 (0.39, 3.47)	0.00 (0.00, 0.01)	
Asia	343	3	0.9	343	3	0.9	1.0000	1.00 (0.20, 4.92)	1.00 (0.20, 4.99)	0.00 (-0.01, 0.01)	
Other	189	0	0	190	2	1.1	0.2482	4.97 (0.24,102.91)	5.03 (0.24,105.40)	0.01 (-0.01, 0.03)	
OECD member											0.3739
No	847	1	0.1	868	4	0.5	0.1881	3.90 (0.44, 34.85)	3.92 (0.44, 35.11)	0.00 (0.00, 0.01)	
Yes	2142	9	0.4	2128	12	0.6	0.5020	1.34 (0.57, 3.18)	1.34 (0.57, 3.20)	0.00 (0.00, 0.01)	
Baseline NYHA											0.2963
II^	2450	10	0.4	2435	13	0.5	0.5210	1.31 (0.57, 2.98)	1.31 (0.57, 2.99)	0.00 (0.00, 0.01)	
III/IV	539	0	0	561	3	0.5	0.1435	6.73 (0.35,129.91)	6.76 (0.35,131.22)	0.01 (0.00, 0.01)	
Baseline Diabetes Status											0.6297
Diabetic	1471	6	0.4	1465	8	0.5	0.5868	1.34 (0.47, 3.85)	1.34 (0.46, 3.87)	0.00 (0.00, 0.01)	
Non-Diabetic	1518	4	0.3	1531	8	0.5	0.2534	1.98 (0.60, 6.57)	1.99 (0.60, 6.62)	0.00 (0.00, 0.01)	

Analysis is based on study 1245.110.
^ Patients with NYHA class I are counted in subgroup NYHA class II.
*** Confirmed hypoglycaemic AEs are defined by a glucose concentration <=70 mg/dL (3.9 mmol/L) or requiring assistance.
Risk ratios and odds ratios with confidence intervals (CIs) are estimated by Cochran-Mantel-Haenszel method. For risk differences standard Wald asymptotic confidence limits are calculated. A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied in case of any zero cells in contingency table.
Only treatment emergent AEs are displayed (onset between first dose until treatment stop +7 days).
MedDRA version: 23.1. * Chi-square test for treatment effect ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction).

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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 overall and by subgroup - TS
User-defined AE category: Urinary tract malignancies (broad Sub BIcMQs)

Subgroup	Placebo			Empa 10mg			Empa 10mg vs Placebo				
Category	N	n	%	N	n	%	p-value *	Risk ratio (95% CI)	Odds ratio (95% CI)	Risk diff. (95% CI)	p-value **
Baseline Diabetes Status											0.8098
Diabetic	1471	6	0.4	1465	8	0.5	0.5868	1.34 (0.47, 3.85)	1.34 (0.46, 3.87)	0.00 (0.00, 0.01)	
Pre-Diabetes	979	3	0.3	1001	5	0.5	0.4983	1.63 (0.39, 6.80)	1.63 (0.39, 6.85)	0.00 (0.00, 0.01)	
Normal (no pre-diabetes)	539	1	0.2	530	3	0.6	0.3083	3.05 (0.32, 29.24)	3.06 (0.32, 29.54)	0.00 (0.00, 0.01)	
Baseline BMI [kg/m²]											0.6295
<30	1641	4	0.2	1654	8	0.5	0.2530	1.98 (0.60, 6.58)	1.99 (0.60, 6.62)	0.00 (0.00, 0.01)	
>=30	1348	6	0.4	1342	8	0.6	0.5862	1.34 (0.47, 3.85)	1.34 (0.46, 3.88)	0.00 (0.00, 0.01)	
Baseline eGFR (CKD-EPI) [mL/min/1.73m²]											0.4687
>=60	1505	3	0.2	1493	7	0.5	0.2006	2.35 (0.61, 9.08)	2.36 (0.61, 9.14)	0.00 (0.00, 0.01)	
<60	1482	7	0.5	1503	9	0.6	0.6361	1.27 (0.47, 3.40)	1.27 (0.47, 3.42)	0.00 (0.00, 0.01)	
History of HHF (in the last 12 months)											0.2057
No	2320	10	0.4	2297	12	0.5	0.6521	1.21 (0.52, 2.80)	1.21 (0.52, 2.81)	0.00 (0.00, 0.00)	
Yes	669	0	0	699	4	0.6	0.0812	8.61 (0.46,159.69)	8.66 (0.47,161.22)	0.01 (0.00, 0.01)	
Baseline SBP (</>= median)											0.7323
< median	1474	5	0.3	1496	7	0.5	0.5804	1.38 (0.44, 4.34)	1.38 (0.44, 4.36)	0.00 (0.00, 0.01)	
>= median	1515	5	0.3	1500	9	0.6	0.2756	1.82 (0.61, 5.41)	1.82 (0.61, 5.45)	0.00 (0.00, 0.01)	
History of atrial fibrillation or atrial flutter											0.2503
No	1426	4	0.3	1417	3	0.2	0.7113	0.75 (0.17, 3.37)	0.75 (0.17, 3.38)	0.00 (0.00, 0.00)	
Yes	1558	6	0.4	1575	13	0.8	0.1125	2.14 (0.82, 5.62)	2.15 (0.82, 5.68)	0.00 (0.00, 0.01)	

Analysis is based on study 1245.110.
^ Patients with NYHA class I are counted in subgroup NYHA class II.
*** Confirmed hypoglycaemic AEs are defined by a glucose concentration <=70 mg/dL (3.9 mmol/L) or requiring assistance.
Risk ratios and odds ratios with confidence intervals (CIs) are estimated by Cochran-Mantel-Haenszel method. For risk differences standard Wald asymptotic confidence limits are calculated. A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied in case of any zero cells in contingency table.
Only treatment emergent AEs are displayed (onset between first dose until treatment stop +7 days).
MedDRA version: 23.1. * Chi-square test for treatment effect ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction).

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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 overall and by subgroup - TS
User-defined AE category: Urinary tract malignancies (broad Sub BIcMQs)

Subgroup	Placebo			Empa 10mg			Empa 10mg vs Placebo				
Category	N	n	%	N	n	%	p-value *	Risk ratio (95% CI)	Odds ratio (95% CI)	Risk diff. (95% CI)	p-value **
Baseline LVEF [%]											0.7017
< 50	988	3	0.3	995	6	0.6	0.3214	1.99 (0.50, 7.92)	1.99 (0.50, 7.99)	0.00 (0.00, 0.01)	
>= 50	2001	7	0.3	2001	10	0.5	0.4659	1.43 (0.54, 3.75)	1.43 (0.54, 3.77)	0.00 (0.00, 0.01)	
Baseline LVEF [%]											0.9230
<50	988	3	0.3	995	6	0.6	0.3214	1.99 (0.50, 7.92)	1.99 (0.50, 7.99)	0.00 (0.00, 0.01)	
50 to <60	1030	3	0.3	1028	4	0.4	0.7031	1.34 (0.30, 5.95)	1.34 (0.30, 5.99)	0.00 (0.00, 0.01)	
>=60	971	4	0.4	973	6	0.6	0.5282	1.50 (0.42, 5.29)	1.50 (0.42, 5.33)	0.00 (0.00, 0.01)	
Baseline NT-proBNP [pg/mL] (</>=median by atrial fibrillation/flutter status)											0.4927
< median	1507	5	0.3	1476	10	0.7	0.1820	2.04 (0.70, 5.96)	2.05 (0.70, 6.01)	0.00 (0.00, 0.01)	
>= median	1475	5	0.3	1516	6	0.4	0.7975	1.17 (0.36, 3.82)	1.17 (0.36, 3.84)	0.00 (0.00, 0.00)	
Baseline uric acid [mg/dL] (tertiles)											0.4166
<T1	975	5	0.5	963	8	0.8	0.3913	1.62 (0.53, 4.93)	1.63 (0.53, 4.99)	0.00 (0.00, 0.01)	
>=T1 and <T2	966	3	0.3	1032	2	0.2	0.6017	0.62 (0.10, 3.73)	0.62 (0.10, 3.74)	0.00 (-0.01, 0.00)	
>=T2	1016	2	0.2	970	6	0.6	0.1380	3.14 (0.64, 15.53)	3.16 (0.64, 15.67)	0.00 (0.00, 0.01)	
Baseline use of MRA											0.6081
No	1865	6	0.3	1878	8	0.4	0.6013	1.32 (0.46, 3.81)	1.33 (0.46, 3.83)	0.00 (0.00, 0.00)	
Yes	1124	4	0.4	1118	8	0.7	0.2432	2.01 (0.61, 6.66)	2.02 (0.61, 6.72)	0.00 (0.00, 0.01)	
Baseline use of ACE-inhibitor, ARB or ARNi											0.5031
No	586	2	0.3	568	5	0.9	0.2384	2.58 (0.50, 13.24)	2.59 (0.50, 13.42)	0.01 (0.00, 0.01)	
Yes	2403	8	0.3	2428	11	0.5	0.5048	1.36 (0.55, 3.38)	1.36 (0.55, 3.39)	0.00 (0.00, 0.00)	

Analysis is based on study 1245.110.
^ Patients with NYHA class I are counted in subgroup NYHA class II.
*** Confirmed hypoglycaemic AEs are defined by a glucose concentration <=70 mg/dL (3.9 mmol/L) or requiring assistance.
Risk ratios and odds ratios with confidence intervals (CIs) are estimated by Cochran-Mantel-Haenszel method. For risk differences standard Wald asymptotic confidence limits are calculated. A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied in case of any zero cells in contingency table.
Only treatment emergent AEs are displayed (onset between first dose until treatment stop +7 days).
MedDRA version: 23.1. * Chi-square test for treatment effect ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction).

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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 overall and by subgroup - TS
User-defined AE category: Volume depletion (narrow 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	2989	56	1.9	2996	67	2.2	0.3226	1.19 (0.84, 1.70)	1.20 (0.84, 1.71)	0.00 (0.00, 0.01)	
Sex											0.9075
Male	1653	32	1.9	1658	39	2.4	0.4083	1.22 (0.77, 1.93)	1.22 (0.76, 1.96)	0.00 (-0.01, 0.01)	
Female	1336	24	1.8	1338	28	2.1	0.5791	1.16 (0.68, 2.00)	1.17 (0.67, 2.03)	0.00 (-0.01, 0.01)	
Age [years]											0.6183
<70	1084	15	1.4	1066	15	1.4	0.9632	1.02 (0.50, 2.07)	1.02 (0.49, 2.09)	0.00 (-0.01, 0.01)	
>=70	1905	41	2.2	1930	52	2.7	0.2752	1.25 (0.84, 1.88)	1.26 (0.83, 1.91)	0.01 (0.00, 0.02)	
Region											0.2162
North America	359	13	3.6	359	25	7.0	0.0455	1.92 (1.00, 3.70)	1.99 (1.00, 3.96)	0.03 (0.00, 0.07)	
Latin America	757	7	0.9	758	13	1.7	0.1778	1.85 (0.74, 4.62)	1.87 (0.74, 4.71)	0.01 (0.00, 0.02)	
Europe	1341	25	1.9	1346	20	1.5	0.4447	0.80 (0.44, 1.43)	0.79 (0.44, 1.44)	0.00 (-0.01, 0.01)	
Asia	343	5	1.5	343	3	0.9	0.4769	0.60 (0.14, 2.49)	0.60 (0.14, 2.52)	-0.01 (-0.02, 0.01)	
Other	189	6	3.2	190	6	3.2	0.9926	0.99 (0.33, 3.03)	0.99 (0.31, 3.14)	0.00 (-0.04, 0.04)	
OECD member											0.5775
No	847	10	1.2	868	15	1.7	0.3443	1.46 (0.66, 3.24)	1.47 (0.66, 3.29)	0.01 (-0.01, 0.02)	
Yes	2142	46	2.1	2128	52	2.4	0.5183	1.14 (0.77, 1.68)	1.14 (0.76, 1.70)	0.00 (-0.01, 0.01)	
Baseline NYHA											0.3592
II^	2450	40	1.6	2435	42	1.7	0.8020	1.06 (0.69, 1.62)	1.06 (0.68, 1.64)	0.00 (-0.01, 0.01)	
III/IV	539	16	3.0	561	25	4.5	0.1928	1.50 (0.81, 2.78)	1.52 (0.80, 2.89)	0.01 (-0.01, 0.04)	
Baseline Diabetes Status											0.6071
Diabetic	1471	32	2.2	1465	35	2.4	0.6982	1.10 (0.68, 1.76)	1.10 (0.68, 1.79)	0.00 (-0.01, 0.01)	
Non-Diabetic	1518	24	1.6	1531	32	2.1	0.2952	1.32 (0.78, 2.23)	1.33 (0.78, 2.27)	0.01 (0.00, 0.01)	

Analysis is based on study 1245.110.
^ Patients with NYHA class I are counted in subgroup NYHA class II.
*** Confirmed hypoglycaemic AEs are defined by a glucose concentration <=70 mg/dL (3.9 mmol/L) or requiring assistance.
Risk ratios and odds ratios with confidence intervals (CIs) are estimated by Cochran-Mantel-Haenszel method. For risk differences standard Wald asymptotic confidence limits are calculated. A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied in case of any zero cells in contingency table.
Only treatment emergent AEs are displayed (onset between first dose until treatment stop +7 days).
MedDRA version: 23.1. * Chi-square test for treatment effect ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction).

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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 overall and by subgroup - TS
User-defined AE category: Volume depletion (narrow 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 Diabetes Status											0.4761
Diabetic	1471	32	2.2	1465	35	2.4	0.6982	1.10 (0.68, 1.76)	1.10 (0.68, 1.79)	0.00 (-0.01, 0.01)	
Pre-Diabetes	979	12	1.2	1001	21	2.1	0.1296	1.71 (0.85, 3.46)	1.73 (0.84, 3.53)	0.01 (0.00, 0.02)	
Normal (no pre-diabetes)	539	12	2.2	530	11	2.1	0.8650	0.93 (0.42, 2.09)	0.93 (0.41, 2.13)	0.00 (-0.02, 0.02)	
Baseline BMI [kg/m²]											0.6784
<30	1641	27	1.6	1654	35	2.1	0.3201	1.29 (0.78, 2.11)	1.29 (0.78, 2.15)	0.00 (0.00, 0.01)	
>=30	1348	29	2.2	1342	32	2.4	0.6846	1.11 (0.67, 1.82)	1.11 (0.67, 1.85)	0.00 (-0.01, 0.01)	
Baseline eGFR (CKD-EPI) [mL/min/1.73m²]											0.2042
>=60	1505	24	1.6	1493	21	1.4	0.6719	0.88 (0.49, 1.58)	0.88 (0.49, 1.59)	0.00 (-0.01, 0.01)	
<60	1482	32	2.2	1503	46	3.1	0.1227	1.42 (0.91, 2.21)	1.43 (0.91, 2.26)	0.01 (0.00, 0.02)	
History of HHF (in the last 12 months)											0.6769
No	2320	38	1.6	2297	47	2.0	0.3022	1.25 (0.82, 1.91)	1.25 (0.81, 1.93)	0.00 (0.00, 0.01)	
Yes	669	18	2.7	699	20	2.9	0.8478	1.06 (0.57, 1.99)	1.07 (0.56, 2.03)	0.00 (-0.02, 0.02)	
Baseline SBP (</>= median)											0.9887
< median	1474	28	1.9	1496	34	2.3	0.4770	1.20 (0.73, 1.96)	1.20 (0.72, 1.99)	0.00 (-0.01, 0.01)	
>= median	1515	28	1.8	1500	33	2.2	0.4927	1.19 (0.72, 1.96)	1.19 (0.72, 1.99)	0.00 (-0.01, 0.01)	
History of atrial fibrillation or atrial flutter											0.4357
No	1426	19	1.3	1417	27	1.9	0.2260	1.43 (0.80, 2.56)	1.44 (0.80, 2.60)	0.01 (0.00, 0.02)	
Yes	1558	37	2.4	1575	40	2.5	0.7657	1.07 (0.69, 1.66)	1.07 (0.68, 1.68)	0.00 (-0.01, 0.01)	

Analysis is based on study 1245.110.
^ Patients with NYHA class I are counted in subgroup NYHA class II.
*** Confirmed hypoglycaemic AEs are defined by a glucose concentration <=70 mg/dL (3.9 mmol/L) or requiring assistance.
Risk ratios and odds ratios with confidence intervals (CIs) are estimated by Cochran-Mantel-Haenszel method. For risk differences standard Wald asymptotic confidence limits are calculated. A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied in case of any zero cells in contingency table.
Only treatment emergent AEs are displayed (onset between first dose until treatment stop +7 days).
MedDRA version: 23.1. * Chi-square test for treatment effect ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction).

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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 overall and by subgroup - TS
User-defined AE category: Volume depletion (narrow 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 LVEF [%]											0.4735
< 50	988	15	1.5	995	22	2.2	0.2543	1.46 (0.76, 2.79)	1.47 (0.76, 2.84)	0.01 (0.00, 0.02)	
>= 50	2001	41	2.0	2001	45	2.2	0.6628	1.10 (0.72, 1.67)	1.10 (0.72, 1.69)	0.00 (-0.01, 0.01)	
Baseline LVEF [%]											0.3885
<50	988	15	1.5	995	22	2.2	0.2543	1.46 (0.76, 2.79)	1.47 (0.76, 2.84)	0.01 (0.00, 0.02)	
50 to <60	1030	15	1.5	1028	22	2.1	0.2431	1.47 (0.77, 2.82)	1.48 (0.76, 2.87)	0.01 (0.00, 0.02)	
>=60	971	26	2.7	973	23	2.4	0.6589	0.88 (0.51, 1.54)	0.88 (0.50, 1.55)	0.00 (-0.02, 0.01)	
Baseline NT-proBNP [pg/mL] (</>=median by atrial fibrillation/flutter status)											0.3959
< median	1507	24	1.6	1476	33	2.2	0.1995	1.40 (0.83, 2.36)	1.41 (0.83, 2.40)	0.01 (0.00, 0.02)	
>= median	1475	32	2.2	1516	34	2.2	0.8915	1.03 (0.64, 1.67)	1.03 (0.63, 1.69)	0.00 (-0.01, 0.01)	
Baseline uric acid [mg/dL] (tertiles)											0.7677
<T1	975	12	1.2	963	17	1.8	0.3325	1.43 (0.69, 2.99)	1.44 (0.69, 3.04)	0.01 (-0.01, 0.02)	
>=T1 and <T2	966	20	2.1	1032	22	2.1	0.9238	1.03 (0.57, 1.87)	1.03 (0.56, 1.90)	0.00 (-0.01, 0.01)	
>=T2	1016	22	2.2	970	27	2.8	0.3747	1.29 (0.74, 2.24)	1.29 (0.73, 2.29)	0.01 (-0.01, 0.02)	
Baseline use of MRA											0.8223
No	1865	33	1.8	1878	41	2.2	0.3633	1.23 (0.78, 1.94)	1.24 (0.78, 1.97)	0.00 (0.00, 0.01)	
Yes	1124	23	2.0	1118	26	2.3	0.6511	1.14 (0.65, 1.98)	1.14 (0.65, 2.01)	0.00 (-0.01, 0.01)	
Baseline use of ACE-inhibitor, ARB or ARNi											0.7037
No	586	13	2.2	568	17	3.0	0.4084	1.35 (0.66, 2.75)	1.36 (0.65, 2.83)	0.01 (-0.01, 0.03)	
Yes	2403	43	1.8	2428	50	2.1	0.4949	1.15 (0.77, 1.72)	1.15 (0.76, 1.74)	0.00 (-0.01, 0.01)	

Analysis is based on study 1245.110.
^ Patients with NYHA class I are counted in subgroup NYHA class II.
*** Confirmed hypoglycaemic AEs are defined by a glucose concentration <=70 mg/dL (3.9 mmol/L) or requiring assistance.
Risk ratios and odds ratios with confidence intervals (CIs) are estimated by Cochran-Mantel-Haenszel method. For risk differences standard Wald asymptotic confidence limits are calculated. A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied in case of any zero cells in contingency table.
Only treatment emergent AEs are displayed (onset between first dose until treatment stop +7 days).
MedDRA version: 23.1. * Chi-square test for treatment effect ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction).

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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 overall and by subgroup - TS
User-defined AE category: Hypotension (BIcMQ based)

Subgroup	Placebo			Empa 10mg			Empa 10mg vs Placebo						
Category	N	n	%	N	n	%	p-value *	Risk ratio (95% CI)	Odds ratio (95% CI)	Risk diff. (95% CI)	p-value **
Overall	2989	47	1.6	2996	62	2.1	0.1505	1.32 (0.90, 1.92)	1.32 (0.90, 1.94)	0.00 (0.00, 0.01)	
Sex											0.5632
Male	1653	27	1.6	1658	39	2.4	0.1390	1.44 (0.89, 2.34)	1.45 (0.88, 2.38)	0.01 (0.00, 0.02)	
Female	1336	20	1.5	1338	23	1.7	0.6482	1.15 (0.63, 2.08)	1.15 (0.63, 2.11)	0.00 (-0.01, 0.01)	
Age [years]											0.4071
<70	1084	15	1.4	1066	15	1.4	0.9632	1.02 (0.50, 2.07)	1.02 (0.49, 2.09)	0.00 (-0.01, 0.01)	
>=70	1905	32	1.7	1930	47	2.4	0.0996	1.45 (0.93, 2.26)	1.46 (0.93, 2.30)	0.01 (0.00, 0.02)	
Region											0.4828
North America	359	12	3.3	359	23	6.4	0.0566	1.92 (0.97, 3.79)	1.98 (0.97, 4.04)	0.03 (0.00, 0.06)	
Latin America	757	7	0.9	758	12	1.6	0.2495	1.71 (0.68, 4.32)	1.72 (0.67, 4.40)	0.01 (0.00, 0.02)	
Europe	1341	21	1.6	1346	18	1.3	0.6202	0.85 (0.46, 1.60)	0.85 (0.45, 1.61)	0.00 (-0.01, 0.01)	
Asia	343	3	0.9	343	3	0.9	1.0000	1.00 (0.20, 4.92)	1.00 (0.20, 4.99)	0.00 (-0.01, 0.01)	
Other	189	4	2.1	190	6	3.2	0.5271	1.49 (0.43, 5.20)	1.51 (0.42, 5.43)	0.01 (-0.02, 0.04)	
OECD member											0.5707
No	847	9	1.1	868	15	1.7	0.2408	1.63 (0.72, 3.70)	1.64 (0.71, 3.76)	0.01 (0.00, 0.02)	
Yes	2142	38	1.8	2128	47	2.2	0.3093	1.24 (0.82, 1.90)	1.25 (0.81, 1.93)	0.00 (0.00, 0.01)	
Baseline NYHA											0.2376
II^	2450	35	1.4	2435	39	1.6	0.6205	1.12 (0.71, 1.76)	1.12 (0.71, 1.78)	0.00 (-0.01, 0.01)	
III/IV	539	12	2.2	561	23	4.1	0.0768	1.84 (0.93, 3.66)	1.88 (0.92, 3.81)	0.02 (0.00, 0.04)	
Baseline Diabetes Status											0.6819
Diabetic	1471	27	1.8	1465	33	2.3	0.4245	1.23 (0.74, 2.03)	1.23 (0.74, 2.06)	0.00 (-0.01, 0.01)	
Non-Diabetic	1518	20	1.3	1531	29	1.9	0.2055	1.44 (0.82, 2.53)	1.45 (0.81, 2.57)	0.01 (0.00, 0.01)	

Analysis is based on study 1245.110.
^ Patients with NYHA class I are counted in subgroup NYHA class II.
*** Confirmed hypoglycaemic AEs are defined by a glucose concentration <=70 mg/dL (3.9 mmol/L) or requiring assistance.
Risk ratios and odds ratios with confidence intervals (CIs) are estimated by Cochran-Mantel-Haenszel method. For risk differences standard Wald asymptotic confidence limits are calculated. A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied in case of any zero cells in contingency table.
Only treatment emergent AEs are displayed (onset between first dose until treatment stop +7 days).
MedDRA version: 23.1. * Chi-square test for treatment effect ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction).

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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 overall and by subgroup - TS
User-defined AE category: Hypotension (BIcMQ based)

Subgroup	Placebo			Empa 10mg			Empa 10mg vs Placebo				
Category	N	n	%	N	n	%	p-value *	Risk ratio (95% CI)	Odds ratio (95% CI)	Risk diff. (95% CI)	p-value **
Baseline Diabetes Status											0.5481
Diabetic	1471	27	1.8	1465	33	2.3	0.4245	1.23 (0.74, 2.03)	1.23 (0.74, 2.06)	0.00 (-0.01, 0.01)	
Pre-Diabetes	979	10	1.0	1001	19	1.9	0.1045	1.86 (0.87, 3.98)	1.87 (0.87, 4.05)	0.01 (0.00, 0.02)	
Normal (no pre-diabetes)	539	10	1.9	530	10	1.9	0.9697	1.02 (0.43, 2.42)	1.02 (0.42, 2.46)	0.00 (-0.02, 0.02)	
Baseline BMI [kg/m²]											0.7635
<30	1641	22	1.3	1654	31	1.9	0.2235	1.40 (0.81, 2.40)	1.41 (0.81, 2.44)	0.01 (0.00, 0.01)	
>=30	1348	25	1.9	1342	31	2.3	0.4082	1.25 (0.74, 2.10)	1.25 (0.73, 2.13)	0.00 (-0.01, 0.02)	
Baseline eGFR (CKD-EPI) [mL/min/1.73m²]											0.1454
>=60	1505	21	1.4	1493	19	1.3	0.7696	0.91 (0.49, 1.69)	0.91 (0.49, 1.70)	0.00 (-0.01, 0.01)	
<60	1482	26	1.8	1503	43	2.9	0.0443	1.63 (1.01, 2.64)	1.65 (1.01, 2.70)	0.01 (0.00, 0.02)	
History of HHF (in the last 12 months)											0.9260
No	2320	32	1.4	2297	42	1.8	0.2243	1.33 (0.84, 2.09)	1.33 (0.84, 2.12)	0.00 (0.00, 0.01)	
Yes	669	15	2.2	699	20	2.9	0.4685	1.28 (0.66, 2.47)	1.28 (0.65, 2.53)	0.01 (-0.01, 0.02)	
Baseline SBP (</>= median)											0.7017
< median	1474	23	1.6	1496	33	2.2	0.1960	1.41 (0.83, 2.40)	1.42 (0.83, 2.44)	0.01 (0.00, 0.02)	
>= median	1515	24	1.6	1500	29	1.9	0.4657	1.22 (0.71, 2.09)	1.22 (0.71, 2.11)	0.00 (-0.01, 0.01)	
History of atrial fibrillation or atrial flutter											0.5104
No	1426	17	1.2	1417	26	1.8	0.1603	1.54 (0.84, 2.82)	1.55 (0.84, 2.87)	0.01 (0.00, 0.02)	
Yes	1558	30	1.9	1575	36	2.3	0.4827	1.19 (0.73, 1.92)	1.19 (0.73, 1.94)	0.00 (-0.01, 0.01)	

Analysis is based on study 1245.110.
^ Patients with NYHA class I are counted in subgroup NYHA class II.
*** Confirmed hypoglycaemic AEs are defined by a glucose concentration <=70 mg/dL (3.9 mmol/L) or requiring assistance.
Risk ratios and odds ratios with confidence intervals (CIs) are estimated by Cochran-Mantel-Haenszel method. For risk differences standard Wald asymptotic confidence limits are calculated. A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied in case of any zero cells in contingency table.
Only treatment emergent AEs are displayed (onset between first dose until treatment stop +7 days).
MedDRA version: 23.1. * Chi-square test for treatment effect ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction).

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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 overall and by subgroup - TS
User-defined AE category: Hypotension (BIcMQ based)

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 LVEF [%]											0.6607
< 50	988	14	1.4	995	21	2.1	0.2409	1.49 (0.76, 2.91)	1.50 (0.76, 2.97)	0.01 (0.00, 0.02)	
>= 50	2001	33	1.6	2001	41	2.0	0.3479	1.24 (0.79, 1.96)	1.25 (0.79, 1.98)	0.00 (0.00, 0.01)	
Baseline LVEF [%]											0.8539
<50	988	14	1.4	995	21	2.1	0.2409	1.49 (0.76, 2.91)	1.50 (0.76, 2.97)	0.01 (0.00, 0.02)	
50 to <60	1030	14	1.4	1028	19	1.8	0.3772	1.36 (0.69, 2.70)	1.37 (0.68, 2.74)	0.00 (-0.01, 0.02)	
>=60	971	19	2.0	973	22	2.3	0.6406	1.16 (0.63, 2.12)	1.16 (0.62, 2.16)	0.00 (-0.01, 0.02)	
Baseline NT-proBNP [pg/mL] (</>=median by atrial fibrillation/flutter status)											0.6465
< median	1507	22	1.5	1476	31	2.1	0.1856	1.44 (0.84, 2.47)	1.45 (0.83, 2.51)	0.01 (0.00, 0.02)	
>= median	1475	25	1.7	1516	31	2.0	0.4802	1.21 (0.72, 2.03)	1.21 (0.71, 2.06)	0.00 (-0.01, 0.01)	
Baseline uric acid [mg/dL] (tertiles)											0.7342
<T1	975	11	1.1	963	16	1.7	0.3166	1.47 (0.69, 3.16)	1.48 (0.68, 3.21)	0.01 (-0.01, 0.02)	
>=T1 and <T2	966	17	1.8	1032	20	1.9	0.7679	1.10 (0.58, 2.09)	1.10 (0.57, 2.12)	0.00 (-0.01, 0.01)	
>=T2	1016	17	1.7	970	25	2.6	0.1616	1.54 (0.84, 2.83)	1.55 (0.83, 2.90)	0.01 (0.00, 0.02)	
Baseline use of MRA											0.9732
No	1865	27	1.4	1878	36	1.9	0.2645	1.32 (0.81, 2.17)	1.33 (0.80, 2.20)	0.00 (0.00, 0.01)	
Yes	1124	20	1.8	1118	26	2.3	0.3617	1.31 (0.73, 2.33)	1.31 (0.73, 2.37)	0.01 (-0.01, 0.02)	
Baseline use of ACE-inhibitor, ARB or ARNi											0.9609
No	586	10	1.7	568	13	2.3	0.4792	1.34 (0.59, 3.03)	1.35 (0.59, 3.10)	0.01 (-0.01, 0.02)	
Yes	2403	37	1.5	2428	49	2.0	0.2087	1.31 (0.86, 2.00)	1.32 (0.86, 2.03)	0.00 (0.00, 0.01)	

Analysis is based on study 1245.110.
^ Patients with NYHA class I are counted in subgroup NYHA class II.
*** Confirmed hypoglycaemic AEs are defined by a glucose concentration <=70 mg/dL (3.9 mmol/L) or requiring assistance.
Risk ratios and odds ratios with confidence intervals (CIs) are estimated by Cochran-Mantel-Haenszel method. For risk differences standard Wald asymptotic confidence limits are calculated. A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied in case of any zero cells in contingency table.
Only treatment emergent AEs are displayed (onset between first dose until treatment stop +7 days).
MedDRA version: 23.1. * Chi-square test for treatment effect ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction).

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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 overall and by subgroup - TS
User-defined AE category: Symptomatic hypotension (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	2989	27	0.9	2996	29	1.0	0.7951	1.07 (0.64, 1.81)	1.07 (0.63, 1.82)	0.00 (0.00, 0.01)	
Sex											0.1905
Male	1653	15	0.9	1658	21	1.3	0.3191	1.40 (0.72, 2.70)	1.40 (0.72, 2.73)	0.00 (0.00, 0.01)	
Female	1336	12	0.9	1338	8	0.6	0.3675	0.67 (0.27, 1.62)	0.66 (0.27, 1.63)	0.00 (-0.01, 0.00)	
Age [years]											0.9051
<70	1084	8	0.7	1066	8	0.8	0.9732	1.02 (0.38, 2.70)	1.02 (0.38, 2.72)	0.00 (-0.01, 0.01)	
>=70	1905	19	1.0	1930	21	1.1	0.7822	1.09 (0.59, 2.02)	1.09 (0.59, 2.04)	0.00 (-0.01, 0.01)	
Region											0.6120
North America	359	9	2.5	359	13	3.6	0.3864	1.44 (0.63, 3.34)	1.46 (0.62, 3.46)	0.01 (-0.01, 0.04)	
Latin America	757	4	0.5	758	6	0.8	0.5271	1.50 (0.42, 5.29)	1.50 (0.42, 5.34)	0.00 (-0.01, 0.01)	
Europe	1341	12	0.9	1346	7	0.5	0.2463	0.58 (0.23, 1.47)	0.58 (0.23, 1.48)	0.00 (-0.01, 0.00)	
Asia	343	1	0.3	343	1	0.3	1.0000	1.00 (0.06, 15.92)	1.00 (0.06, 16.05)	0.00 (-0.01, 0.01)	
Other	189	1	0.5	190	2	1.1	0.5652	1.99 (0.18, 21.76)	2.00 (0.18, 22.24)	0.01 (-0.01, 0.02)	
OECD member											0.8652
No	847	5	0.6	868	5	0.6	0.9690	0.98 (0.28, 3.36)	0.98 (0.28, 3.38)	0.00 (-0.01, 0.01)	
Yes	2142	22	1.0	2128	24	1.1	0.7498	1.10 (0.62, 1.95)	1.10 (0.61, 1.97)	0.00 (-0.01, 0.01)	
Baseline NYHA											0.2743
II^	2450	19	0.8	2435	16	0.7	0.6236	0.85 (0.44, 1.64)	0.85 (0.43, 1.65)	0.00 (-0.01, 0.00)	
III/IV	539	8	1.5	561	13	2.3	0.3128	1.56 (0.65, 3.74)	1.57 (0.65, 3.83)	0.01 (-0.01, 0.02)	
Baseline Diabetes Status											0.3906
Diabetic	1471	18	1.2	1465	16	1.1	0.7391	0.89 (0.46, 1.74)	0.89 (0.45, 1.75)	0.00 (-0.01, 0.01)	
Non-Diabetic	1518	9	0.6	1531	13	0.8	0.4032	1.43 (0.61, 3.34)	1.44 (0.61, 3.37)	0.00 (0.00, 0.01)	

Analysis is based on study 1245.110.
^ Patients with NYHA class I are counted in subgroup NYHA class II.
*** Confirmed hypoglycaemic AEs are defined by a glucose concentration <=70 mg/dL (3.9 mmol/L) or requiring assistance.
Risk ratios and odds ratios with confidence intervals (CIs) are estimated by Cochran-Mantel-Haenszel method. For risk differences standard Wald asymptotic confidence limits are calculated. A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied in case of any zero cells in contingency table.
Only treatment emergent AEs are displayed (onset between first dose until treatment stop +7 days).
MedDRA version: 23.1. * Chi-square test for treatment effect ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction).

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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 overall and by subgroup - TS
User-defined AE category: Symptomatic hypotension (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 Diabetes Status											0.6537
Diabetic	1471	18	1.2	1465	16	1.1	0.7391	0.89 (0.46, 1.74)	0.89 (0.45, 1.75)	0.00 (-0.01, 0.01)	
Pre-Diabetes	979	7	0.7	1001	11	1.1	0.3682	1.54 (0.60, 3.95)	1.54 (0.60, 4.00)	0.00 (0.00, 0.01)	
Normal (no pre-diabetes)	539	2	0.4	530	2	0.4	0.9865	1.02 (0.14, 7.19)	1.02 (0.14, 7.25)	0.00 (-0.01, 0.01)	
Baseline BMI [kg/m²]											0.8240
<30	1641	10	0.6	1654	10	0.6	0.9859	0.99 (0.41, 2.38)	0.99 (0.41, 2.39)	0.00 (-0.01, 0.01)	
>=30	1348	17	1.3	1342	19	1.4	0.7270	1.12 (0.59, 2.15)	1.12 (0.58, 2.17)	0.00 (-0.01, 0.01)	
Baseline eGFR (CKD-EPI) [mL/min/1.73m²]											0.0306
>=60	1505	11	0.7	1493	4	0.3	0.0724	0.37 (0.12, 1.15)	0.36 (0.12, 1.15)	0.00 (-0.01, 0.00)	
<60	1482	16	1.1	1503	25	1.7	0.1707	1.54 (0.83, 2.87)	1.55 (0.82, 2.91)	0.01 (0.00, 0.01)	
History of HHF (in the last 12 months)											0.2604
No	2320	20	0.9	2297	17	0.7	0.6421	0.86 (0.45, 1.63)	0.86 (0.45, 1.64)	0.00 (-0.01, 0.00)	
Yes	669	7	1.0	699	12	1.7	0.2895	1.64 (0.65, 4.14)	1.65 (0.65, 4.22)	0.01 (-0.01, 0.02)	
Baseline SBP (</>= median)											0.3096
< median	1474	12	0.8	1496	17	1.1	0.3719	1.40 (0.67, 2.91)	1.40 (0.67, 2.94)	0.00 (0.00, 0.01)	
>= median	1515	15	1.0	1500	12	0.8	0.5796	0.81 (0.38, 1.72)	0.81 (0.38, 1.73)	0.00 (-0.01, 0.00)	
History of atrial fibrillation or atrial flutter											0.4500
No	1426	14	1.0	1417	12	0.8	0.7056	0.86 (0.40, 1.86)	0.86 (0.40, 1.87)	0.00 (-0.01, 0.01)	
Yes	1558	13	0.8	1575	17	1.1	0.4815	1.29 (0.63, 2.65)	1.30 (0.63, 2.68)	0.00 (0.00, 0.01)	

Analysis is based on study 1245.110.
^ Patients with NYHA class I are counted in subgroup NYHA class II.
*** Confirmed hypoglycaemic AEs are defined by a glucose concentration <=70 mg/dL (3.9 mmol/L) or requiring assistance.
Risk ratios and odds ratios with confidence intervals (CIs) are estimated by Cochran-Mantel-Haenszel method. For risk differences standard Wald asymptotic confidence limits are calculated. A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied in case of any zero cells in contingency table.
Only treatment emergent AEs are displayed (onset between first dose until treatment stop +7 days).
MedDRA version: 23.1. * Chi-square test for treatment effect ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction).

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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 overall and by subgroup - TS
User-defined AE category: Symptomatic hypotension (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 LVEF [%]											0.9183
< 50	988	8	0.8	995	9	0.9	0.8189	1.12 (0.43, 2.88)	1.12 (0.43, 2.91)	0.00 (-0.01, 0.01)	
>= 50	2001	19	0.9	2001	20	1.0	0.8722	1.05 (0.56, 1.97)	1.05 (0.56, 1.98)	0.00 (-0.01, 0.01)	
Baseline LVEF [%]											0.8767
<50	988	8	0.8	995	9	0.9	0.8189	1.12 (0.43, 2.88)	1.12 (0.43, 2.91)	0.00 (-0.01, 0.01)	
50 to <60	1030	8	0.8	1028	10	1.0	0.6329	1.25 (0.50, 3.16)	1.25 (0.49, 3.19)	0.00 (-0.01, 0.01)	
>=60	971	11	1.1	973	10	1.0	0.8226	0.91 (0.39, 2.13)	0.91 (0.38, 2.14)	0.00 (-0.01, 0.01)	
Baseline NT-proBNP [pg/mL] (</>=median by atrial fibrillation/flutter status)											0.9053
< median	1507	12	0.8	1476	13	0.9	0.8002	1.11 (0.51, 2.42)	1.11 (0.50, 2.43)	0.00 (-0.01, 0.01)	
>= median	1475	15	1.0	1516	16	1.1	0.9173	1.04 (0.51, 2.09)	1.04 (0.51, 2.11)	0.00 (-0.01, 0.01)	
Baseline uric acid [mg/dL] (tertiles)											0.3306
<T1	975	3	0.3	963	8	0.8	0.1254	2.70 (0.72, 10.15)	2.71 (0.72, 10.26)	0.01 (0.00, 0.01)	
>=T1 and <T2	966	10	1.0	1032	9	0.9	0.7074	0.84 (0.34, 2.06)	0.84 (0.34, 2.08)	0.00 (-0.01, 0.01)	
>=T2	1016	12	1.2	970	11	1.1	0.9219	0.96 (0.43, 2.17)	0.96 (0.42, 2.19)	0.00 (-0.01, 0.01)	
Baseline use of MRA											0.7215
No	1865	17	0.9	1878	17	0.9	0.9838	0.99 (0.51, 1.94)	0.99 (0.51, 1.95)	0.00 (-0.01, 0.01)	
Yes	1124	10	0.9	1118	12	1.1	0.6591	1.21 (0.52, 2.78)	1.21 (0.52, 2.81)	0.00 (-0.01, 0.01)	
Baseline use of ACE-inhibitor, ARB or ARNi											0.5270
No	586	4	0.7	568	6	1.1	0.4934	1.55 (0.44, 5.46)	1.55 (0.44, 5.53)	0.00 (-0.01, 0.01)	
Yes	2403	23	1.0	2428	23	0.9	0.9719	0.99 (0.56, 1.76)	0.99 (0.55, 1.77)	0.00 (-0.01, 0.01)	

Analysis is based on study 1245.110.
^ Patients with NYHA class I are counted in subgroup NYHA class II.
*** Confirmed hypoglycaemic AEs are defined by a glucose concentration <=70 mg/dL (3.9 mmol/L) or requiring assistance.
Risk ratios and odds ratios with confidence intervals (CIs) are estimated by Cochran-Mantel-Haenszel method. For risk differences standard Wald asymptotic confidence limits are calculated. A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied in case of any zero cells in contingency table.
Only treatment emergent AEs are displayed (onset between first dose until treatment stop +7 days).
MedDRA version: 23.1. * Chi-square test for treatment effect ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction).

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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 overall and by subgroup - TS
User-defined AE category: Allergic skin reactions (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	2989	0	0	2996	1	<0.1	0.4805	2.99 (0.12, 73.44)	2.99 (0.12, 73.52)	0.00 (0.00, 0.00)	
Sex											
Male	1653	0	0	1658	1	0.1					
Female	1336	0	0	1338	0	0					
Age [years]											
<70	1084	0	0	1066	1	0.1					
>=70	1905	0	0	1930	0	0					
Region											
North America	359	0	0	359	0	0					
Latin America	757	0	0	758	1	0.1					
Europe	1341	0	0	1346	0	0					
Asia	343	0	0	343	0	0					
Other	189	0	0	190	0	0					
OECD member											
No	847	0	0	868	1	0.1					
Yes	2142	0	0	2128	0	0					
Baseline NYHA											
II^	2450	0	0	2435	1	<0.1					
III/IV	539	0	0	561	0	0					
Baseline Diabetes Status											
Diabetic	1471	0	0	1465	1	0.1					
Non-Diabetic	1518	0	0	1531	0	0					

Analysis is based on study 1245.110.
^ Patients with NYHA class I are counted in subgroup NYHA class II.
*** Confirmed hypoglycaemic AEs are defined by a glucose concentration <=70 mg/dL (3.9 mmol/L) or requiring assistance.
Risk ratios and odds ratios with confidence intervals (CIs) are estimated by Cochran-Mantel-Haenszel method. For risk differences standard Wald asymptotic confidence limits are calculated. A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied in case of any zero cells in contingency table.
Only treatment emergent AEs are displayed (onset between first dose until treatment stop +7 days).
MedDRA version: 23.1. * Chi-square test for treatment effect ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction).

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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 overall and by subgroup - TS
User-defined AE category: Allergic skin reactions (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 Diabetes Status											
Diabetic	1471	0	0	1465	1	0.1					
Pre-Diabetes	979	0	0	1001	0	0					
Normal (no pre-diabetes)	539	0	0	530	0	0					
Baseline BMI [kg/m²]											
<30	1641	0	0	1654	0	0					
>=30	1348	0	0	1342	1	0.1					
Baseline eGFR (CKD-EPI) [mL/min/1.73m²]											
>=60	1505	0	0	1493	0	0					
<60	1482	0	0	1503	1	0.1					
History of HHF (in the last 12 months)											
No	2320	0	0	2297	0	0					
Yes	669	0	0	699	1	0.1					
Baseline SBP (</>= median)											
< median	1474	0	0	1496	1	0.1					
>= median	1515	0	0	1500	0	0					
History of atrial fibrillation or atrial flutter											
No	1426	0	0	1417	1	0.1					
Yes	1558	0	0	1575	0	0					

Analysis is based on study 1245.110.
^ Patients with NYHA class I are counted in subgroup NYHA class II.
*** Confirmed hypoglycaemic AEs are defined by a glucose concentration <=70 mg/dL (3.9 mmol/L) or requiring assistance.
Risk ratios and odds ratios with confidence intervals (CIs) are estimated by Cochran-Mantel-Haenszel method. For risk differences standard Wald asymptotic confidence limits are calculated. A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied in case of any zero cells in contingency table.
Only treatment emergent AEs are displayed (onset between first dose until treatment stop +7 days).
MedDRA version: 23.1. * Chi-square test for treatment effect ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction).

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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 overall and by subgroup - TS
User-defined AE category: Allergic skin reactions (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 LVEF [%]											
< 50	988	0	0	995	0	0					
>= 50	2001	0	0	2001	1	<0.1					
Baseline LVEF [%]											
<50	988	0	0	995	0	0					
50 to <60	1030	0	0	1028	0	0					
>=60	971	0	0	973	1	0.1					
Baseline NT-proBNP [pg/mL] (</>=median by atrial fibrillation/flutter status)											
< median	1507	0	0	1476	0	0					
>= median	1475	0	0	1516	1	0.1					
Baseline uric acid [mg/dL] (tertiles)											
<T1	975	0	0	963	0	0					
>=T1 and <T2	966	0	0	1032	0	0					
>=T2	1016	0	0	970	1	0.1					
Baseline use of MRA											
No	1865	0	0	1878	1	0.1					
Yes	1124	0	0	1118	0	0					
Baseline use of ACE-inhibitor, ARB or ARNi											
No	586	0	0	568	0	0					
Yes	2403	0	0	2428	1	<0.1					

Analysis is based on study 1245.110.
^ Patients with NYHA class I are counted in subgroup NYHA class II.
*** Confirmed hypoglycaemic AEs are defined by a glucose concentration <=70 mg/dL (3.9 mmol/L) or requiring assistance.
Risk ratios and odds ratios with confidence intervals (CIs) are estimated by Cochran-Mantel-Haenszel method. For risk differences standard Wald asymptotic confidence limits are calculated. A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied in case of any zero cells in contingency table.
Only treatment emergent AEs are displayed (onset between first dose until treatment stop +7 days).
MedDRA version: 23.1. * Chi-square test for treatment effect ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction).

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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 overall and by subgroup - TS
User-defined AE category: Increased urination (project-defined PTs)

Subgroup	Placebo			Empa 10mg			Empa 10mg vs Placebo				
Category	N	n	%	N	n	%	p-value *	Risk ratio (95% CI)	Odds ratio (95% CI)	Risk diff. (95% CI)	p-value **
Overall	2989	1	<0.1	2996	0	0	0.4784	0.33 (0.01, 8.16)	0.33 (0.01, 8.16)	0.00 (0.00, 0.00)	
Sex											
Male	1653	0	0	1658	0	0					
Female	1336	1	0.1	1338	0	0					
Age [years]											
<70	1084	0	0	1066	0	0					
>=70	1905	1	0.1	1930	0	0					
Region											
North America	359	1	0.3	359	0	0					
Latin America	757	0	0	758	0	0					
Europe	1341	0	0	1346	0	0					
Asia	343	0	0	343	0	0					
Other	189	0	0	190	0	0					
OECD member											
No	847	0	0	868	0	0					
Yes	2142	1	<0.1	2128	0	0					
Baseline NYHA											
II^	2450	1	<0.1	2435	0	0					
III/IV	539	0	0	561	0	0					
Baseline Diabetes Status											
Diabetic	1471	1	0.1	1465	0	0					
Non-Diabetic	1518	0	0	1531	0	0					

Analysis is based on study 1245.110.
^ Patients with NYHA class I are counted in subgroup NYHA class II.
*** Confirmed hypoglycaemic AEs are defined by a glucose concentration <=70 mg/dL (3.9 mmol/L) or requiring assistance.
Risk ratios and odds ratios with confidence intervals (CIs) are estimated by Cochran-Mantel-Haenszel method. For risk differences standard Wald asymptotic confidence limits are calculated. A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied in case of any zero cells in contingency table.
Only treatment emergent AEs are displayed (onset between first dose until treatment stop +7 days).
MedDRA version: 23.1. * Chi-square test for treatment effect ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction).

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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 overall and by subgroup - TS
User-defined AE category: Increased urination (project-defined PTs)

Subgroup	Placebo			Empa 10mg			Empa 10mg vs Placebo				
Category	N	n	%	N	n	%	p-value *	Risk ratio (95% CI)	Odds ratio (95% CI)	Risk diff. (95% CI)	p-value **
Baseline Diabetes Status											
Diabetic	1471	1	0.1	1465	0	0					
Pre-Diabetes	979	0	0	1001	0	0					
Normal (no pre-diabetes)	539	0	0	530	0	0					
Baseline BMI [kg/m²]											
<30	1641	0	0	1654	0	0					
>=30	1348	1	0.1	1342	0	0					
Baseline eGFR (CKD-EPI) [mL/min/1.73m²]											
>=60	1505	0	0	1493	0	0					
<60	1482	1	0.1	1503	0	0					
History of HHF (in the last 12 months)											
No	2320	1	<0.1	2297	0	0					
Yes	669	0	0	699	0	0					
Baseline SBP (</>= median)											
< median	1474	1	0.1	1496	0	0					
>= median	1515	0	0	1500	0	0					
History of atrial fibrillation or atrial flutter											
No	1426	0	0	1417	0	0					
Yes	1558	1	0.1	1575	0	0					

Analysis is based on study 1245.110.
^ Patients with NYHA class I are counted in subgroup NYHA class II.
*** Confirmed hypoglycaemic AEs are defined by a glucose concentration <=70 mg/dL (3.9 mmol/L) or requiring assistance.
Risk ratios and odds ratios with confidence intervals (CIs) are estimated by Cochran-Mantel-Haenszel method. For risk differences standard Wald asymptotic confidence limits are calculated. A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied in case of any zero cells in contingency table.
Only treatment emergent AEs are displayed (onset between first dose until treatment stop +7 days).
MedDRA version: 23.1. * Chi-square test for treatment effect ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction).

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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 overall and by subgroup - TS
User-defined AE category: Increased urination (project-defined PTs)

Subgroup	Placebo			Empa 10mg			Empa 10mg vs Placebo				
Category	N	n	%	N	n	%	p-value *	Risk ratio (95% CI)	Odds ratio (95% CI)	Risk diff. (95% CI)	p-value **
Baseline LVEF [%]											
< 50	988	0	0	995	0	0					
>= 50	2001	1	<0.1	2001	0	0					
Baseline LVEF [%]											
<50	988	0	0	995	0	0					
50 to <60	1030	0	0	1028	0	0					
>=60	971	1	0.1	973	0	0					
Baseline NT-proBNP [pg/mL] (</>=median by atrial fibrillation/flutter status)											
< median	1507	0	0	1476	0	0					
>= median	1475	1	0.1	1516	0	0					
Baseline uric acid [mg/dL] (tertiles)											
<T1	975	0	0	963	0	0					
>=T1 and <T2	966	0	0	1032	0	0					
>=T2	1016	1	0.1	970	0	0					
Baseline use of MRA											
No	1865	1	0.1	1878	0	0					
Yes	1124	0	0	1118	0	0					
Baseline use of ACE-inhibitor, ARB or ARNi											
No	586	0	0	568	0	0					
Yes	2403	1	<0.1	2428	0	0					

Analysis is based on study 1245.110.
^ Patients with NYHA class I are counted in subgroup NYHA class II.
*** Confirmed hypoglycaemic AEs are defined by a glucose concentration <=70 mg/dL (3.9 mmol/L) or requiring assistance.
Risk ratios and odds ratios with confidence intervals (CIs) are estimated by Cochran-Mantel-Haenszel method. For risk differences standard Wald asymptotic confidence limits are calculated. A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied in case of any zero cells in contingency table.
Only treatment emergent AEs are displayed (onset between first dose until treatment stop +7 days).
MedDRA version: 23.1. * Chi-square test for treatment effect ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction).

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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 overall and by subgroup - TS
User-defined AE category: Thirst (project-defined PTs)

Subgroup	Placebo			Empa 10mg			Empa 10mg vs Placebo				
Category	N	n	%	N	n	%	p-value *	Risk ratio (95% CI)	Odds ratio (95% CI)	Risk diff. (95% CI)	p-value **
Overall	2989	0	0	2996	0	0	0.9991	1.00 (0.02, 50.26)	1.00 (0.02, 50.30)	0.00 (0.00, 0.00)	
Sex											
Male	1653	0	0	1658	0	0					
Female	1336	0	0	1338	0	0					
Age [years]											
<70	1084	0	0	1066	0	0					
>=70	1905	0	0	1930	0	0					
Region											
North America	359	0	0	359	0	0					
Latin America	757	0	0	758	0	0					
Europe	1341	0	0	1346	0	0					
Asia	343	0	0	343	0	0					
Other	189	0	0	190	0	0					
OECD member											
No	847	0	0	868	0	0					
Yes	2142	0	0	2128	0	0					
Baseline NYHA											
II^	2450	0	0	2435	0	0					
III/IV	539	0	0	561	0	0					
Baseline Diabetes Status											
Diabetic	1471	0	0	1465	0	0					
Non-Diabetic	1518	0	0	1531	0	0					

Analysis is based on study 1245.110.
^ Patients with NYHA class I are counted in subgroup NYHA class II.
*** Confirmed hypoglycaemic AEs are defined by a glucose concentration <=70 mg/dL (3.9 mmol/L) or requiring assistance.
Risk ratios and odds ratios with confidence intervals (CIs) are estimated by Cochran-Mantel-Haenszel method. For risk differences standard Wald asymptotic confidence limits are calculated. A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied in case of any zero cells in contingency table.
Only treatment emergent AEs are displayed (onset between first dose until treatment stop +7 days).
MedDRA version: 23.1. * Chi-square test for treatment effect ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction).

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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 overall and by subgroup - TS
User-defined AE category: Thirst (project-defined PTs)

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 Diabetes Status											
Diabetic	1471	0	0	1465	0	0					
Pre-Diabetes	979	0	0	1001	0	0					
Normal (no pre-diabetes)	539	0	0	530	0	0					
Baseline BMI [kg/m²]											
<30	1641	0	0	1654	0	0					
>=30	1348	0	0	1342	0	0					
Baseline eGFR (CKD-EPI) [mL/min/1.73m²]											
>=60	1505	0	0	1493	0	0					
<60	1482	0	0	1503	0	0					
History of HHF (in the last 12 months)											
No	2320	0	0	2297	0	0					
Yes	669	0	0	699	0	0					
Baseline SBP (</>= median)											
< median	1474	0	0	1496	0	0					
>= median	1515	0	0	1500	0	0					
History of atrial fibrillation or atrial flutter											
No	1426	0	0	1417	0	0					
Yes	1558	0	0	1575	0	0					

Analysis is based on study 1245.110.
^ Patients with NYHA class I are counted in subgroup NYHA class II.
*** Confirmed hypoglycaemic AEs are defined by a glucose concentration <=70 mg/dL (3.9 mmol/L) or requiring assistance.
Risk ratios and odds ratios with confidence intervals (CIs) are estimated by Cochran-Mantel-Haenszel method. For risk differences standard Wald asymptotic confidence limits are calculated. A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied in case of any zero cells in contingency table.
Only treatment emergent AEs are displayed (onset between first dose until treatment stop +7 days).
MedDRA version: 23.1. * Chi-square test for treatment effect ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction).

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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 overall and by subgroup - TS
User-defined AE category: Thirst (project-defined PTs)

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 LVEF [%]											
< 50	988	0	0	995	0	0					
>= 50	2001	0	0	2001	0	0					
Baseline LVEF [%]											
<50	988	0	0	995	0	0					
50 to <60	1030	0	0	1028	0	0					
>=60	971	0	0	973	0	0					
Baseline NT-proBNP [pg/mL] (</>=median by atrial fibrillation/flutter status)											
< median	1507	0	0	1476	0	0					
>= median	1475	0	0	1516	0	0					
Baseline uric acid [mg/dL] (tertiles)											
<T1	975	0	0	963	0	0					
>=T1 and <T2	966	0	0	1032	0	0					
>=T2	1016	0	0	970	0	0					
Baseline use of MRA											
No	1865	0	0	1878	0	0					
Yes	1124	0	0	1118	0	0					
Baseline use of ACE-inhibitor, ARB or ARNi											
No	586	0	0	568	0	0					
Yes	2403	0	0	2428	0	0					

Analysis is based on study 1245.110.
^ Patients with NYHA class I are counted in subgroup NYHA class II.
*** Confirmed hypoglycaemic AEs are defined by a glucose concentration <=70 mg/dL (3.9 mmol/L) or requiring assistance.
Risk ratios and odds ratios with confidence intervals (CIs) are estimated by Cochran-Mantel-Haenszel method. For risk differences standard Wald asymptotic confidence limits are calculated. A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied in case of any zero cells in contingency table.
Only treatment emergent AEs are displayed (onset between first dose until treatment stop +7 days).
MedDRA version: 23.1. * Chi-square test for treatment effect ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction).

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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 overall and by subgroup - TS
User-defined AE category: Serum lipids increased (Sub 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	2989	0	0	2996	1	<0.1	0.4805	2.99 (0.12, 73.44)	2.99 (0.12, 73.52)	0.00 (0.00, 0.00)	
Sex											
Male	1653	0	0	1658	1	0.1					
Female	1336	0	0	1338	0	0					
Age [years]											
<70	1084	0	0	1066	1	0.1					
>=70	1905	0	0	1930	0	0					
Region											
North America	359	0	0	359	0	0					
Latin America	757	0	0	758	1	0.1					
Europe	1341	0	0	1346	0	0					
Asia	343	0	0	343	0	0					
Other	189	0	0	190	0	0					
OECD member											
No	847	0	0	868	0	0					
Yes	2142	0	0	2128	1	<0.1					
Baseline NYHA											
II^	2450	0	0	2435	1	<0.1					
III/IV	539	0	0	561	0	0					
Baseline Diabetes Status											
Diabetic	1471	0	0	1465	1	0.1					
Non-Diabetic	1518	0	0	1531	0	0					

Analysis is based on study 1245.110.
^ Patients with NYHA class I are counted in subgroup NYHA class II.
*** Confirmed hypoglycaemic AEs are defined by a glucose concentration <=70 mg/dL (3.9 mmol/L) or requiring assistance.
Risk ratios and odds ratios with confidence intervals (CIs) are estimated by Cochran-Mantel-Haenszel method. For risk differences standard Wald asymptotic confidence limits are calculated. A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied in case of any zero cells in contingency table.
Only treatment emergent AEs are displayed (onset between first dose until treatment stop +7 days).
MedDRA version: 23.1. * Chi-square test for treatment effect ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction).

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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 overall and by subgroup - TS
User-defined AE category: Serum lipids increased (Sub 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 Diabetes Status											
Diabetic	1471	0	0	1465	1	0.1					
Pre-Diabetes	979	0	0	1001	0	0					
Normal (no pre-diabetes)	539	0	0	530	0	0					
Baseline BMI [kg/m²]											
<30	1641	0	0	1654	1	0.1					
>=30	1348	0	0	1342	0	0					
Baseline eGFR (CKD-EPI) [mL/min/1.73m²]											
>=60	1505	0	0	1493	1	0.1					
<60	1482	0	0	1503	0	0					
History of HHF (in the last 12 months)											
No	2320	0	0	2297	1	<0.1					
Yes	669	0	0	699	0	0					
Baseline SBP (</>= median)											
< median	1474	0	0	1496	1	0.1					
>= median	1515	0	0	1500	0	0					
History of atrial fibrillation or atrial flutter											
No	1426	0	0	1417	1	0.1					
Yes	1558	0	0	1575	0	0					

Analysis is based on study 1245.110.
^ Patients with NYHA class I are counted in subgroup NYHA class II.
*** Confirmed hypoglycaemic AEs are defined by a glucose concentration <=70 mg/dL (3.9 mmol/L) or requiring assistance.
Risk ratios and odds ratios with confidence intervals (CIs) are estimated by Cochran-Mantel-Haenszel method. For risk differences standard Wald asymptotic confidence limits are calculated. A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied in case of any zero cells in contingency table.
Only treatment emergent AEs are displayed (onset between first dose until treatment stop +7 days).
MedDRA version: 23.1. * Chi-square test for treatment effect ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction).

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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 overall and by subgroup - TS
User-defined AE category: Serum lipids increased (Sub 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 LVEF [%]											
< 50	988	0	0	995	0	0					
>= 50	2001	0	0	2001	1	<0.1					
Baseline LVEF [%]											
<50	988	0	0	995	0	0					
50 to <60	1030	0	0	1028	0	0					
>=60	971	0	0	973	1	0.1					
Baseline NT-proBNP [pg/mL] (</>=median by atrial fibrillation/flutter status)											
< median	1507	0	0	1476	0	0					
>= median	1475	0	0	1516	1	0.1					
Baseline uric acid [mg/dL] (tertiles)											
<T1	975	0	0	963	1	0.1					
>=T1 and <T2	966	0	0	1032	0	0					
>=T2	1016	0	0	970	0	0					
Baseline use of MRA											
No	1865	0	0	1878	1	0.1					
Yes	1124	0	0	1118	0	0					
Baseline use of ACE-inhibitor, ARB or ARNi											
No	586	0	0	568	1	0.2					
Yes	2403	0	0	2428	0	0					

Analysis is based on study 1245.110.
^ Patients with NYHA class I are counted in subgroup NYHA class II.
*** Confirmed hypoglycaemic AEs are defined by a glucose concentration <=70 mg/dL (3.9 mmol/L) or requiring assistance.
Risk ratios and odds ratios with confidence intervals (CIs) are estimated by Cochran-Mantel-Haenszel method. For risk differences standard Wald asymptotic confidence limits are calculated. A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied in case of any zero cells in contingency table.
Only treatment emergent AEs are displayed (onset between first dose until treatment stop +7 days).
MedDRA version: 23.1. * Chi-square test for treatment effect ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction).

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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 overall and by subgroup - TS
User-defined AE category: Angioedema (narrow BicMQ excl. urticaria)

Subgroup	Placebo			Empa 10mg			Empa 10mg vs Placebo				
Category	N	n	%	N	n	%	p-value *	Risk ratio (95% CI)	Odds ratio (95% CI)	Risk diff. (95% CI)	p-value **
Overall	2989	3	0.1	2996	0	0	0.1329	0.14 (<0.01, 2.76)	0.14 (<0.01, 2.76)	0.00 (0.00, 0.00)	
Sex											
Male	1653	2	0.1	1658	0	0					
Female	1336	1	0.1	1338	0	0					
Age [years]											
<70	1084	0	0	1066	0	0					
>=70	1905	3	0.2	1930	0	0					
Region											
North America	359	1	0.3	359	0	0					
Latin America	757	1	0.1	758	0	0					
Europe	1341	1	0.1	1346	0	0					
Asia	343	0	0	343	0	0					
Other	189	0	0	190	0	0					
OECD member											
No	847	1	0.1	868	0	0					
Yes	2142	2	0.1	2128	0	0					
Baseline NYHA											
II^	2450	2	0.1	2435	0	0					
III/IV	539	1	0.2	561	0	0					
Baseline Diabetes Status											
Diabetic	1471	2	0.1	1465	0	0					
Non-Diabetic	1518	1	0.1	1531	0	0					

Analysis is based on study 1245.110.
^ Patients with NYHA class I are counted in subgroup NYHA class II.
*** Confirmed hypoglycaemic AEs are defined by a glucose concentration <=70 mg/dL (3.9 mmol/L) or requiring assistance.
Risk ratios and odds ratios with confidence intervals (CIs) are estimated by Cochran-Mantel-Haenszel method. For risk differences standard Wald asymptotic confidence limits are calculated. A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied in case of any zero cells in contingency table.
Only treatment emergent AEs are displayed (onset between first dose until treatment stop +7 days).
MedDRA version: 23.1. * Chi-square test for treatment effect ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction).

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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 overall and by subgroup - TS
User-defined AE category: Angioedema (narrow BicMQ excl. urticaria)

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 Diabetes Status											
Diabetic	1471	2	0.1	1465	0	0					
Pre-Diabetes	979	1	0.1	1001	0	0					
Normal (no pre-diabetes)	539	0	0	530	0	0					
Baseline BMI [kg/m²]											
<30	1641	2	0.1	1654	0	0					
>=30	1348	1	0.1	1342	0	0					
Baseline eGFR (CKD-EPI) [mL/min/1.73m²]											
>=60	1505	2	0.1	1493	0	0					
<60	1482	1	0.1	1503	0	0					
History of HHF (in the last 12 months)											
No	2320	1	<0.1	2297	0	0					
Yes	669	2	0.3	699	0	0					
Baseline SBP (</>= median)											
< median	1474	1	0.1	1496	0	0					
>= median	1515	2	0.1	1500	0	0					
History of atrial fibrillation or atrial flutter											
No	1426	3	0.2	1417	0	0					
Yes	1558	0	0	1575	0	0					

Analysis is based on study 1245.110.
^ Patients with NYHA class I are counted in subgroup NYHA class II.
*** Confirmed hypoglycaemic AEs are defined by a glucose concentration <=70 mg/dL (3.9 mmol/L) or requiring assistance.
Risk ratios and odds ratios with confidence intervals (CIs) are estimated by Cochran-Mantel-Haenszel method. For risk differences standard Wald asymptotic confidence limits are calculated. A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied in case of any zero cells in contingency table.
Only treatment emergent AEs are displayed (onset between first dose until treatment stop +7 days).
MedDRA version: 23.1. * Chi-square test for treatment effect ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction).

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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 overall and by subgroup - TS
User-defined AE category: Angioedema (narrow BicMQ excl. urticaria)

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 LVEF [%]											
< 50	988	1	0.1	995	0	0					
>= 50	2001	2	0.1	2001	0	0					
Baseline LVEF [%]											
<50	988	1	0.1	995	0	0					
50 to <60	1030	0	0	1028	0	0					
>=60	971	2	0.2	973	0	0					
Baseline NT-proBNP [pg/mL] (</>=median by atrial fibrillation/flutter status)											
< median	1507	2	0.1	1476	0	0					
>= median	1475	1	0.1	1516	0	0					
Baseline uric acid [mg/dL] (tertiles)											
<T1	975	1	0.1	963	0	0					
>=T1 and <T2	966	1	0.1	1032	0	0					
>=T2	1016	1	0.1	970	0	0					
Baseline use of MRA											
No	1865	3	0.2	1878	0	0					
Yes	1124	0	0	1118	0	0					
Baseline use of ACE-inhibitor, ARB or ARNi											
No	586	0	0	568	0	0					
Yes	2403	3	0.1	2428	0	0					

Analysis is based on study 1245.110.
^ Patients with NYHA class I are counted in subgroup NYHA class II.
*** Confirmed hypoglycaemic AEs are defined by a glucose concentration <=70 mg/dL (3.9 mmol/L) or requiring assistance.
Risk ratios and odds ratios with confidence intervals (CIs) are estimated by Cochran-Mantel-Haenszel method. For risk differences standard Wald asymptotic confidence limits are calculated. A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied in case of any zero cells in contingency table.
Only treatment emergent AEs are displayed (onset between first dose until treatment stop +7 days).
MedDRA version: 23.1. * Chi-square test for treatment effect ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction).

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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 overall and by subgroup - TS
User-defined AE category: Hypersensitivity reactions (narrow 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	2989	16	0.5	2996	8	0.3	0.1006	0.50 (0.21, 1.16)	0.50 (0.21, 1.16)	0.00 (-0.01, 0.00)	
Sex											0.2533
Male	1653	6	0.4	1658	5	0.3	0.7588	0.83 (0.25, 2.72)	0.83 (0.25, 2.73)	0.00 (0.00, 0.00)	
Female	1336	10	0.7	1338	3	0.2	0.0513	0.30 (0.08, 1.09)	0.30 (0.08, 1.09)	-0.01 (-0.01, 0.00)	
Age [years]											0.2156
<70	1084	4	0.4	1066	4	0.4	0.9811	1.02 (0.25, 4.06)	1.02 (0.25, 4.08)	0.00 (-0.01, 0.01)	
>=70	1905	12	0.6	1930	4	0.2	0.0423	0.33 (0.11, 1.02)	0.33 (0.11, 1.02)	0.00 (-0.01, 0.00)	
Region											0.7838
North America	359	3	0.8	359	0	0	0.1325	0.14 (<0.01, 2.76)	0.14 (<0.01, 2.75)	-0.01 (-0.02, 0.00)	
Latin America	757	5	0.7	758	2	0.3	0.2550	0.40 (0.08, 2.05)	0.40 (0.08, 2.06)	0.00 (-0.01, 0.00)	
Europe	1341	7	0.5	1346	6	0.4	0.7758	0.85 (0.29, 2.53)	0.85 (0.29, 2.55)	0.00 (-0.01, 0.00)	
Asia	343	0	0	343	0	0	1.0000	1.00 (0.02, 50.25)	1.00 (0.02, 50.54)	0.00 (-0.01, 0.01)	
Other	189	1	0.5	190	0	0	0.4760	0.33 (0.01, 8.09)	0.33 (0.01, 8.15)	-0.01 (-0.02, 0.01)	
OECD member											0.7452
No	847	3	0.4	868	2	0.2	0.6346	0.65 (0.11, 3.88)	0.65 (0.11, 3.90)	0.00 (-0.01, 0.00)	
Yes	2142	13	0.6	2128	6	0.3	0.1107	0.46 (0.18, 1.22)	0.46 (0.18, 1.22)	0.00 (-0.01, 0.00)	
Baseline NYHA											0.1212
II^	2450	10	0.4	2435	8	0.3	0.6461	0.80 (0.32, 2.04)	0.80 (0.32, 2.04)	0.00 (0.00, 0.00)	
III/IV	539	6	1.1	561	0	0	0.0199	0.07 (<0.01, 1.31)	0.07 (<0.01, 1.30)	-0.01 (-0.02, 0.00)	
Baseline Diabetes Status											0.5728
Diabetic	1471	8	0.5	1465	3	0.2	0.1327	0.38 (0.10, 1.42)	0.38 (0.10, 1.42)	0.00 (-0.01, 0.00)	
Non-Diabetic	1518	8	0.5	1531	5	0.3	0.3957	0.62 (0.20, 1.89)	0.62 (0.20, 1.89)	0.00 (-0.01, 0.00)	

Analysis is based on study 1245.110.
^ Patients with NYHA class I are counted in subgroup NYHA class II.
*** Confirmed hypoglycaemic AEs are defined by a glucose concentration <=70 mg/dL (3.9 mmol/L) or requiring assistance.
Risk ratios and odds ratios with confidence intervals (CIs) are estimated by Cochran-Mantel-Haenszel method. For risk differences standard Wald asymptotic confidence limits are calculated. A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied in case of any zero cells in contingency table.
Only treatment emergent AEs are displayed (onset between first dose until treatment stop +7 days).
MedDRA version: 23.1. * Chi-square test for treatment effect ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction).

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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 overall and by subgroup - TS
User-defined AE category: Hypersensitivity reactions (narrow 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 Diabetes Status											0.8455
Diabetic	1471	8	0.5	1465	3	0.2	0.1327	0.38 (0.10, 1.42)	0.38 (0.10, 1.42)	0.00 (-0.01, 0.00)	
Pre-Diabetes	979	5	0.5	1001	3	0.3	0.4593	0.59 (0.14, 2.45)	0.59 (0.14, 2.46)	0.00 (-0.01, 0.00)	
Normal (no pre-diabetes)	539	3	0.6	530	2	0.4	0.6676	0.68 (0.11, 4.04)	0.68 (0.11, 4.07)	0.00 (-0.01, 0.01)	
Baseline BMI [kg/m²]											0.1483
<30	1641	7	0.4	1654	1	0.1	0.0328	0.14 (0.02, 1.15)	0.14 (0.02, 1.15)	0.00 (-0.01, 0.00)	
>=30	1348	9	0.7	1342	7	0.5	0.6223	0.78 (0.29, 2.09)	0.78 (0.29, 2.10)	0.00 (-0.01, 0.00)	
Baseline eGFR (CKD-EPI) [mL/min/1.73m²]											0.7524
>=60	1505	7	0.5	1493	4	0.3	0.3719	0.58 (0.17, 1.96)	0.57 (0.17, 1.97)	0.00 (-0.01, 0.00)	
<60	1482	9	0.6	1503	4	0.3	0.1570	0.44 (0.14, 1.42)	0.44 (0.13, 1.42)	0.00 (-0.01, 0.00)	
History of HHF (in the last 12 months)											0.0940
No	2320	12	0.5	2297	3	0.1	0.0210	0.25 (0.07, 0.89)	0.25 (0.07, 0.89)	0.00 (-0.01, 0.00)	
Yes	669	4	0.6	699	5	0.7	0.7883	1.20 (0.32, 4.44)	1.20 (0.32, 4.48)	0.00 (-0.01, 0.01)	
Baseline SBP (</>= median)											0.4052
< median	1474	7	0.5	1496	5	0.3	0.5457	0.70 (0.22, 2.21)	0.70 (0.22, 2.22)	0.00 (-0.01, 0.00)	
>= median	1515	9	0.6	1500	3	0.2	0.0857	0.34 (0.09, 1.24)	0.34 (0.09, 1.24)	0.00 (-0.01, 0.00)	
History of atrial fibrillation or atrial flutter											0.0988
No	1426	10	0.7	1417	2	0.1	0.0213	0.20 (0.04, 0.92)	0.20 (0.04, 0.92)	-0.01 (-0.01, 0.00)	
Yes	1558	6	0.4	1575	6	0.4	0.9850	0.99 (0.32, 3.06)	0.99 (0.32, 3.07)	0.00 (0.00, 0.00)	

Analysis is based on study 1245.110.
^ Patients with NYHA class I are counted in subgroup NYHA class II.
*** Confirmed hypoglycaemic AEs are defined by a glucose concentration <=70 mg/dL (3.9 mmol/L) or requiring assistance.
Risk ratios and odds ratios with confidence intervals (CIs) are estimated by Cochran-Mantel-Haenszel method. For risk differences standard Wald asymptotic confidence limits are calculated. A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied in case of any zero cells in contingency table.
Only treatment emergent AEs are displayed (onset between first dose until treatment stop +7 days).
MedDRA version: 23.1. * Chi-square test for treatment effect ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction).

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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 overall and by subgroup - TS
User-defined AE category: Hypersensitivity reactions (narrow 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 LVEF [%]											0.4496
< 50	988	2	0.2	995	2	0.2	0.9944	0.99 (0.14, 7.04)	0.99 (0.14, 7.06)	0.00 (0.00, 0.00)	
>= 50	2001	14	0.7	2001	6	0.3	0.0729	0.43 (0.17, 1.11)	0.43 (0.16, 1.11)	0.00 (-0.01, 0.00)	
Baseline LVEF [%]											0.7514
<50	988	2	0.2	995	2	0.2	0.9944	0.99 (0.14, 7.04)	0.99 (0.14, 7.06)	0.00 (0.00, 0.00)	
50 to <60	1030	7	0.7	1028	3	0.3	0.2059	0.43 (0.11, 1.66)	0.43 (0.11, 1.66)	0.00 (-0.01, 0.00)	
>=60	971	7	0.7	973	3	0.3	0.2036	0.43 (0.11, 1.65)	0.43 (0.11, 1.65)	0.00 (-0.01, 0.00)	
Baseline NT-proBNP [pg/mL] (</>=median by atrial fibrillation/flutter status)											0.8002
< median	1507	11	0.7	1476	5	0.3	0.1436	0.46 (0.16, 1.33)	0.46 (0.16, 1.33)	0.00 (-0.01, 0.00)	
>= median	1475	5	0.3	1516	3	0.2	0.4551	0.58 (0.14, 2.44)	0.58 (0.14, 2.44)	0.00 (-0.01, 0.00)	
Baseline uric acid [mg/dL] (tertiles)											0.7133
<T1	975	4	0.4	963	2	0.2	0.4222	0.51 (0.09, 2.76)	0.51 (0.09, 2.76)	0.00 (-0.01, 0.00)	
>=T1 and <T2	966	4	0.4	1032	1	0.1	0.1562	0.23 (0.03, 2.09)	0.23 (0.03, 2.09)	0.00 (-0.01, 0.00)	
>=T2	1016	8	0.8	970	5	0.5	0.4525	0.65 (0.21, 1.99)	0.65 (0.21, 2.00)	0.00 (-0.01, 0.00)	
Baseline use of MRA											0.7610
No	1865	9	0.5	1878	4	0.2	0.1610	0.44 (0.14, 1.43)	0.44 (0.14, 1.43)	0.00 (-0.01, 0.00)	
Yes	1124	7	0.6	1118	4	0.4	0.3693	0.57 (0.17, 1.96)	0.57 (0.17, 1.96)	0.00 (-0.01, 0.00)	
Baseline use of ACE-inhibitor, ARB or ARNi											0.9747
No	586	2	0.3	568	1	0.2	0.5816	0.52 (0.05, 5.67)	0.51 (0.05, 5.70)	0.00 (-0.01, 0.00)	
Yes	2403	14	0.6	2428	7	0.3	0.1200	0.49 (0.20, 1.22)	0.49 (0.20, 1.22)	0.00 (-0.01, 0.00)	

Analysis is based on study 1245.110.
^ Patients with NYHA class I are counted in subgroup NYHA class II.
*** Confirmed hypoglycaemic AEs are defined by a glucose concentration <=70 mg/dL (3.9 mmol/L) or requiring assistance.
Risk ratios and odds ratios with confidence intervals (CIs) are estimated by Cochran-Mantel-Haenszel method. For risk differences standard Wald asymptotic confidence limits are calculated. A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied in case of any zero cells in contingency table.
Only treatment emergent AEs are displayed (onset between first dose until treatment stop +7 days).
MedDRA version: 23.1. * Chi-square test for treatment effect ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction).

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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 overall and by subgroup - TS
User-defined AE category: Ventricular Tachyarrhythmia (narrow 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	2989	29	1.0	2996	28	0.9	0.8871	0.96 (0.57, 1.62)	0.96 (0.57, 1.62)	0.00 (-0.01, 0.00)	
Sex											0.7877
Male	1653	23	1.4	1658	23	1.4	0.9918	1.00 (0.56, 1.77)	1.00 (0.56, 1.78)	0.00 (-0.01, 0.01)	
Female	1336	6	0.4	1338	5	0.4	0.7607	0.83 (0.25, 2.72)	0.83 (0.25, 2.73)	0.00 (-0.01, 0.00)	
Age [years]											0.9152
<70	1084	12	1.1	1066	11	1.0	0.8656	0.93 (0.41, 2.10)	0.93 (0.41, 2.12)	0.00 (-0.01, 0.01)	
>=70	1905	17	0.9	1930	17	0.9	0.9695	0.99 (0.51, 1.93)	0.99 (0.50, 1.94)	0.00 (-0.01, 0.01)	
Region											0.8083
North America	359	3	0.8	359	4	1.1	0.7041	1.33 (0.30, 5.91)	1.34 (0.30, 6.02)	0.00 (-0.01, 0.02)	
Latin America	757	6	0.8	758	9	1.2	0.4378	1.50 (0.54, 4.19)	1.50 (0.53, 4.25)	0.00 (-0.01, 0.01)	
Europe	1341	14	1.0	1346	10	0.7	0.4069	0.71 (0.32, 1.60)	0.71 (0.31, 1.60)	0.00 (-0.01, 0.00)	
Asia	343	3	0.9	343	3	0.9	1.0000	1.00 (0.20, 4.92)	1.00 (0.20, 4.99)	0.00 (-0.01, 0.01)	
Other	189	3	1.6	190	2	1.1	0.6483	0.66 (0.11, 3.92)	0.66 (0.11, 3.99)	-0.01 (-0.03, 0.02)	
OECD member											0.5345
No	847	7	0.8	868	9	1.0	0.6504	1.25 (0.47, 3.35)	1.26 (0.47, 3.39)	0.00 (-0.01, 0.01)	
Yes	2142	22	1.0	2128	19	0.9	0.6529	0.87 (0.47, 1.60)	0.87 (0.47, 1.61)	0.00 (-0.01, 0.00)	
Baseline NYHA											0.1980
II^	2450	21	0.9	2435	24	1.0	0.6384	1.15 (0.64, 2.06)	1.15 (0.64, 2.07)	0.00 (0.00, 0.01)	
III/IV	539	8	1.5	561	4	0.7	0.2183	0.48 (0.15, 1.59)	0.48 (0.14, 1.59)	-0.01 (-0.02, 0.00)	
Baseline Diabetes Status											0.6762
Diabetic	1471	12	0.8	1465	10	0.7	0.6757	0.84 (0.36, 1.93)	0.84 (0.36, 1.94)	0.00 (-0.01, 0.00)	
Non-Diabetic	1518	17	1.1	1531	18	1.2	0.8850	1.05 (0.54, 2.03)	1.05 (0.54, 2.05)	0.00 (-0.01, 0.01)	

Analysis is based on study 1245.110.
^ Patients with NYHA class I are counted in subgroup NYHA class II.
*** Confirmed hypoglycaemic AEs are defined by a glucose concentration <=70 mg/dL (3.9 mmol/L) or requiring assistance.
Risk ratios and odds ratios with confidence intervals (CIs) are estimated by Cochran-Mantel-Haenszel method. For risk differences standard Wald asymptotic confidence limits are calculated. A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied in case of any zero cells in contingency table.
Only treatment emergent AEs are displayed (onset between first dose until treatment stop +7 days).
MedDRA version: 23.1. * Chi-square test for treatment effect ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction).

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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 overall and by subgroup - TS
User-defined AE category: Ventricular Tachyarrhythmia (narrow 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 Diabetes Status											0.4879
Diabetic	1471	12	0.8	1465	10	0.7	0.6757	0.84 (0.36, 1.93)	0.84 (0.36, 1.94)	0.00 (-0.01, 0.00)	
Pre-Diabetes	979	9	0.9	1001	13	1.3	0.4207	1.41 (0.61, 3.29)	1.42 (0.60, 3.33)	0.00 (-0.01, 0.01)	
Normal (no pre-diabetes)	539	8	1.5	530	5	0.9	0.4199	0.64 (0.21, 1.93)	0.63 (0.21, 1.94)	-0.01 (-0.02, 0.01)	
Baseline BMI [kg/m²]											0.6758
<30	1641	17	1.0	1654	18	1.1	0.8835	1.05 (0.54, 2.03)	1.05 (0.54, 2.05)	0.00 (-0.01, 0.01)	
>=30	1348	12	0.9	1342	10	0.7	0.6762	0.84 (0.36, 1.93)	0.84 (0.36, 1.94)	0.00 (-0.01, 0.01)	
Baseline eGFR (CKD-EPI) [mL/min/1.73m²]											0.9132
>=60	1505	13	0.9	1493	12	0.8	0.8566	0.93 (0.43, 2.03)	0.93 (0.42, 2.04)	0.00 (-0.01, 0.01)	
<60	1482	16	1.1	1503	16	1.1	0.9681	0.99 (0.49, 1.96)	0.99 (0.49, 1.98)	0.00 (-0.01, 0.01)	
History of HHF (in the last 12 months)											0.1006
No	2320	21	0.9	2297	25	1.1	0.5309	1.20 (0.68, 2.14)	1.20 (0.67, 2.16)	0.00 (0.00, 0.01)	
Yes	669	8	1.2	699	3	0.4	0.1125	0.36 (0.10, 1.35)	0.36 (0.09, 1.35)	-0.01 (-0.02, 0.00)	
Baseline SBP (</>= median)											0.7295
< median	1474	13	0.9	1496	14	0.9	0.8771	1.06 (0.50, 2.25)	1.06 (0.50, 2.27)	0.00 (-0.01, 0.01)	
>= median	1515	16	1.1	1500	14	0.9	0.7342	0.88 (0.43, 1.80)	0.88 (0.43, 1.81)	0.00 (-0.01, 0.01)	
History of atrial fibrillation or atrial flutter											0.9059
No	1426	13	0.9	1417	12	0.8	0.8532	0.93 (0.43, 2.03)	0.93 (0.42, 2.04)	0.00 (-0.01, 0.01)	
Yes	1558	16	1.0	1575	16	1.0	0.9754	0.99 (0.50, 1.97)	0.99 (0.49, 1.98)	0.00 (-0.01, 0.01)	

Analysis is based on study 1245.110.
^ Patients with NYHA class I are counted in subgroup NYHA class II.
*** Confirmed hypoglycaemic AEs are defined by a glucose concentration <=70 mg/dL (3.9 mmol/L) or requiring assistance.
Risk ratios and odds ratios with confidence intervals (CIs) are estimated by Cochran-Mantel-Haenszel method. For risk differences standard Wald asymptotic confidence limits are calculated. A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied in case of any zero cells in contingency table.
Only treatment emergent AEs are displayed (onset between first dose until treatment stop +7 days).
MedDRA version: 23.1. * Chi-square test for treatment effect ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction).

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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 overall and by subgroup - TS
User-defined AE category: Ventricular Tachyarrhythmia (narrow 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 LVEF [%]											0.5095
< 50	988	14	1.4	995	16	1.6	0.7275	1.13 (0.56, 2.31)	1.14 (0.55, 2.34)	0.00 (-0.01, 0.01)	
>= 50	2001	15	0.7	2001	12	0.6	0.5624	0.80 (0.38, 1.70)	0.80 (0.37, 1.71)	0.00 (-0.01, 0.00)	
Baseline LVEF [%]											0.4830
<50	988	14	1.4	995	16	1.6	0.7275	1.13 (0.56, 2.31)	1.14 (0.55, 2.34)	0.00 (-0.01, 0.01)	
50 to <60	1030	8	0.8	1028	4	0.4	0.2482	0.50 (0.15, 1.66)	0.50 (0.15, 1.66)	0.00 (-0.01, 0.00)	
>=60	971	7	0.7	973	8	0.8	0.7986	1.14 (0.42, 3.13)	1.14 (0.41, 3.16)	0.00 (-0.01, 0.01)	
Baseline NT-proBNP [pg/mL] (</>=median by atrial fibrillation/flutter status)											0.1820
< median	1507	6	0.4	1476	10	0.7	0.2963	1.70 (0.62, 4.67)	1.71 (0.62, 4.71)	0.00 (0.00, 0.01)	
>= median	1475	23	1.6	1516	18	1.2	0.3817	0.76 (0.41, 1.41)	0.76 (0.41, 1.41)	0.00 (-0.01, 0.00)	
Baseline uric acid [mg/dL] (tertiles)											0.1779
<T1	975	6	0.6	963	10	1.0	0.3035	1.69 (0.62, 4.62)	1.69 (0.61, 4.68)	0.00 (0.00, 0.01)	
>=T1 and <T2	966	8	0.8	1032	3	0.3	0.1047	0.35 (0.09, 1.32)	0.35 (0.09, 1.32)	-0.01 (-0.01, 0.00)	
>=T2	1016	15	1.5	970	15	1.5	0.8983	1.05 (0.51, 2.13)	1.05 (0.51, 2.16)	0.00 (-0.01, 0.01)	
Baseline use of MRA											0.8846
No	1865	16	0.9	1878	15	0.8	0.8417	0.93 (0.46, 1.88)	0.93 (0.46, 1.89)	0.00 (-0.01, 0.01)	
Yes	1124	13	1.2	1118	13	1.2	0.9890	1.01 (0.47, 2.16)	1.01 (0.46, 2.18)	0.00 (-0.01, 0.01)	
Baseline use of ACE-inhibitor, ARB or ARNi											0.9035
No	586	5	0.9	568	5	0.9	0.9605	1.03 (0.30, 3.54)	1.03 (0.30, 3.58)	0.00 (-0.01, 0.01)	
Yes	2403	24	1.0	2428	23	0.9	0.8554	0.95 (0.54, 1.68)	0.95 (0.53, 1.68)	0.00 (-0.01, 0.01)	

Analysis is based on study 1245.110.
^ Patients with NYHA class I are counted in subgroup NYHA class II.
*** Confirmed hypoglycaemic AEs are defined by a glucose concentration <=70 mg/dL (3.9 mmol/L) or requiring assistance.
Risk ratios and odds ratios with confidence intervals (CIs) are estimated by Cochran-Mantel-Haenszel method. For risk differences standard Wald asymptotic confidence limits are calculated. A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied in case of any zero cells in contingency table.
Only treatment emergent AEs are displayed (onset between first dose until treatment stop +7 days).
MedDRA version: 23.1. * Chi-square test for treatment effect ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction).

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Table R.1.2.3: 3 Proportion of patients with severe adverse events of special interest and severe other specific AEs by user-defined category overall and by subgroup - TS
User-defined AE category: Hepatic Injury (narrow SMQs)

Subgroup	Placebo			Empa 10mg			Empa 10mg vs Placebo				
Category	N	n	%	N	n	%	p-value *	Risk ratio (95% CI)	Odds ratio (95% CI)	Risk diff. (95% CI)	p-value **
Overall	2989	14	0.5	2996	16	0.5	0.7191	1.14 (0.56, 2.33)	1.14 (0.56, 2.34)	0.00 (0.00,0.00)	
Sex											0.2834
Male	1653	10	0.6	1658	14	0.8	0.4168	1.40 (0.62, 3.13)	1.40 (0.62, 3.16)	0.00 (0.00,0.01)	
Female	1336	4	0.3	1338	2	0.1	0.4126	0.50 (0.09, 2.72)	0.50 (0.09, 2.73)	0.00 (-0.01,0.00)	
Age [years]											0.2073
<70	1084	1	0.1	1066	4	0.4	0.1732	4.07 (0.46, 36.33)	4.08 (0.46, 36.55)	0.00 (0.00,0.01)	
>=70	1905	13	0.7	1930	12	0.6	0.8155	0.91 (0.42, 1.99)	0.91 (0.41, 2.00)	0.00 (-0.01,0.00)	
Region											0.3126
North America	359	1	0.3	359	2	0.6	0.5629	2.00 (0.18, 21.96)	2.01 (0.18, 22.22)	0.00 (-0.01,0.01)	
Latin America	757	2	0.3	758	5	0.7	0.2565	2.50 (0.49, 12.83)	2.51 (0.48, 12.96)	0.00 (0.00,0.01)	
Europe	1341	8	0.6	1346	5	0.4	0.4005	0.62 (0.20, 1.90)	0.62 (0.20, 1.90)	0.00 (-0.01,0.00)	
Asia	343	3	0.9	343	1	0.3	0.3159	0.33 (0.03, 3.19)	0.33 (0.03, 3.20)	-0.01 (-0.02,0.01)	
Other	189	0	0	190	3	1.6	0.1329	6.96 (0.36,133.89)	7.07 (0.36,137.91)	0.02 (0.00,0.04)	
OECD member											0.4885
No	847	2	0.2	868	4	0.5	0.4307	1.95 (0.36, 10.63)	1.96 (0.36, 10.71)	0.00 (0.00,0.01)	
Yes	2142	12	0.6	2128	12	0.6	0.9871	1.01 (0.45, 2.24)	1.01 (0.45, 2.25)	0.00 (0.00,0.00)	
Baseline NYHA											0.5815
II^	2450	11	0.4	2435	11	0.5	0.9885	1.01 (0.44, 2.32)	1.01 (0.44, 2.33)	0.00 (0.00,0.00)	
III/IV	539	3	0.6	561	5	0.9	0.5137	1.60 (0.38, 6.67)	1.61 (0.38, 6.76)	0.00 (-0.01,0.01)	
Baseline Diabetes Status											0.6825
Diabetic	1471	6	0.4	1465	8	0.5	0.5868	1.34 (0.47, 3.85)	1.34 (0.46, 3.87)	0.00 (0.00,0.01)	
Non-Diabetic	1518	8	0.5	1531	8	0.5	0.9864	0.99 (0.37, 2.63)	0.99 (0.37, 2.65)	0.00 (-0.01,0.01)	

Analysis is based on study 1245.110.
^ Patients with NYHA class I are counted in subgroup NYHA class II.
*** Confirmed hypoglycaemic AEs are defined by a glucose concentration <=70 mg/dL (3.9 mmol/L) or requiring assistance.
Risk ratios and odds ratios with confidence intervals (CIs) are estimated by Cochran-Mantel-Haenszel method. For risk differences standard Wald asymptotic confidence limits are calculated. A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied in case of any zero cells in contingency table.
Only treatment emergent AEs are displayed (onset between first dose until treatment stop +7 days).
MedDRA version: 23.1. * Chi-square test for treatment effect ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction).

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Table R.1.2.3: 3 Proportion of patients with severe adverse events of special interest and severe other specific AEs by user-defined category overall and by subgroup - TS
User-defined AE category: Hepatic Injury (narrow SMQs)

Subgroup	Placebo			Empa 10mg			Empa 10mg vs Placebo				
Category	N	n	%	N	n	%	p-value *	Risk ratio (95% CI)	Odds ratio (95% CI)	Risk diff. (95% CI)	p-value **
Baseline Diabetes Status											0.8119
Diabetic	1471	6	0.4	1465	8	0.5	0.5868	1.34 (0.47, 3.85)	1.34 (0.46, 3.87)	0.00 (0.00,0.01)	
Pre-Diabetes	979	5	0.5	1001	6	0.6	0.7907	1.17 (0.36, 3.83)	1.17 (0.36, 3.86)	0.00 (-0.01,0.01)	
Normal (no pre-diabetes)	539	3	0.6	530	2	0.4	0.6676	0.68 (0.11, 4.04)	0.68 (0.11, 4.07)	0.00 (-0.01,0.01)	
Baseline BMI [kg/m²]											0.3824
<30	1641	10	0.6	1654	9	0.5	0.8047	0.89 (0.36, 2.19)	0.89 (0.36, 2.20)	0.00 (-0.01,0.00)	
>=30	1348	4	0.3	1342	7	0.5	0.3608	1.76 (0.52, 5.99)	1.76 (0.51, 6.03)	0.00 (0.00,0.01)	
Baseline eGFR (CKD-EPI) [mL/min/1.73m²]											0.4144
>=60	1505	5	0.3	1493	8	0.5	0.3963	1.61 (0.53, 4.92)	1.62 (0.53, 4.95)	0.00 (0.00,0.01)	
<60	1482	9	0.6	1503	8	0.5	0.7854	0.88 (0.34, 2.27)	0.88 (0.34, 2.28)	0.00 (-0.01,0.00)	
History of HHF (in the last 12 months)											0.1822
No	2320	12	0.5	2297	10	0.4	0.6862	0.84 (0.36, 1.94)	0.84 (0.36, 1.95)	0.00 (0.00,0.00)	
Yes	669	2	0.3	699	6	0.9	0.1749	2.87 (0.58, 14.18)	2.89 (0.58, 14.36)	0.01 (0.00,0.01)	
Baseline SBP (</>= median)											0.6300
< median	1474	9	0.6	1496	9	0.6	0.9749	0.99 (0.39, 2.48)	0.99 (0.39, 2.49)	0.00 (-0.01,0.01)	
>= median	1515	5	0.3	1500	7	0.5	0.5513	1.41 (0.45, 4.45)	1.42 (0.45, 4.47)	0.00 (0.00,0.01)	
History of atrial fibrillation or atrial flutter											0.5896
No	1426	4	0.3	1417	6	0.4	0.5198	1.51 (0.43, 5.34)	1.51 (0.43, 5.37)	0.00 (0.00,0.01)	
Yes	1558	10	0.6	1575	10	0.6	0.9806	0.99 (0.41, 2.37)	0.99 (0.41, 2.38)	0.00 (-0.01,0.01)	

Analysis is based on study 1245.110.
^ Patients with NYHA class I are counted in subgroup NYHA class II.
*** Confirmed hypoglycaemic AEs are defined by a glucose concentration <=70 mg/dL (3.9 mmol/L) or requiring assistance.
Risk ratios and odds ratios with confidence intervals (CIs) are estimated by Cochran-Mantel-Haenszel method. For risk differences standard Wald asymptotic confidence limits are calculated. A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied in case of any zero cells in contingency table.
Only treatment emergent AEs are displayed (onset between first dose until treatment stop +7 days).
MedDRA version: 23.1. * Chi-square test for treatment effect ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction).

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Table R.1.2.3: 3 Proportion of patients with severe adverse events of special interest and severe other specific AEs by user-defined category overall and by subgroup - TS
User-defined AE category: Hepatic Injury (narrow SMQs)

Subgroup	Placebo			Empa 10mg			Empa 10mg vs Placebo				
Category	N	n	%	N	n	%	p-value *	Risk ratio (95% CI)	Odds ratio (95% CI)	Risk diff. (95% CI)	p-value **
Baseline LVEF [%]											0.1455
< 50	988	5	0.5	995	2	0.2	0.2521	0.40 (0.08, 2.04)	0.40 (0.08, 2.05)	0.00 (-0.01,0.00)	
>= 50	2001	9	0.4	2001	14	0.7	0.2958	1.56 (0.67, 3.59)	1.56 (0.67, 3.61)	0.00 (0.00,0.01)	
Baseline LVEF [%]											0.1378
<50	988	5	0.5	995	2	0.2	0.2521	0.40 (0.08, 2.04)	0.40 (0.08, 2.05)	0.00 (-0.01,0.00)	
50 to <60	1030	8	0.8	1028	8	0.8	0.9969	1.00 (0.38, 2.66)	1.00 (0.37, 2.68)	0.00 (-0.01,0.01)	
>=60	971	1	0.1	973	6	0.6	0.0587	5.99 (0.72, 49.64)	6.02 (0.72, 50.09)	0.01 (0.00,0.01)	
Baseline NT-proBNP [pg/mL] (</>=median by atrial fibrillation/flutter status)											0.8689
< median	1507	5	0.3	1476	6	0.4	0.7364	1.23 (0.37, 4.01)	1.23 (0.37, 4.03)	0.00 (0.00,0.01)	
>= median	1475	9	0.6	1516	10	0.7	0.8648	1.08 (0.44, 2.65)	1.08 (0.44, 2.67)	0.00 (-0.01,0.01)	
Baseline uric acid [mg/dL] (tertiles)											0.3658
<T1	975	3	0.3	963	7	0.7	0.1978	2.36 (0.61, 9.11)	2.37 (0.61, 9.20)	0.00 (0.00,0.01)	
>=T1 and <T2	966	6	0.6	1032	4	0.4	0.4598	0.62 (0.18, 2.20)	0.62 (0.18, 2.21)	0.00 (-0.01,0.00)	
>=T2	1016	5	0.5	970	5	0.5	0.9414	1.05 (0.30, 3.61)	1.05 (0.30, 3.63)	0.00 (-0.01,0.01)	
Baseline use of MRA											0.5013
No	1865	7	0.4	1878	10	0.5	0.4747	1.42 (0.54, 3.72)	1.42 (0.54, 3.74)	0.00 (0.00,0.01)	
Yes	1124	7	0.6	1118	6	0.5	0.7883	0.86 (0.29, 2.56)	0.86 (0.29, 2.57)	0.00 (-0.01,0.01)	
Baseline use of ACE-inhibitor, ARB or ARNi											0.5459
No	586	6	1.0	568	5	0.9	0.8018	0.86 (0.26, 2.80)	0.86 (0.26, 2.83)	0.00 (-0.01,0.01)	
Yes	2403	8	0.3	2428	11	0.5	0.5048	1.36 (0.55, 3.38)	1.36 (0.55, 3.39)	0.00 (0.00,0.00)	

Analysis is based on study 1245.110.
^ Patients with NYHA class I are counted in subgroup NYHA class II.
*** Confirmed hypoglycaemic AEs are defined by a glucose concentration <=70 mg/dL (3.9 mmol/L) or requiring assistance.
Risk ratios and odds ratios with confidence intervals (CIs) are estimated by Cochran-Mantel-Haenszel method. For risk differences standard Wald asymptotic confidence limits are calculated. A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied in case of any zero cells in contingency table.
Only treatment emergent AEs are displayed (onset between first dose until treatment stop +7 days).
MedDRA version: 23.1. * Chi-square test for treatment effect ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction).

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Table R.1.2.3: 3 Proportion of patients with severe adverse events of special interest and severe other specific AEs by user-defined category overall and by subgroup - TS
User-defined AE category: Acute renal failure (narrow 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	2989	74	2.5	2996	63	2.1	0.3348	0.85 (0.61, 1.18)	0.85 (0.60, 1.19)	0.00 (-0.01,0.00)	
Sex											0.4451
Male	1653	40	2.4	1658	30	1.8	0.2221	0.75 (0.47, 1.19)	0.74 (0.46, 1.20)	-0.01 (-0.02,0.00)	
Female	1336	34	2.5	1338	33	2.5	0.8966	0.97 (0.60, 1.56)	0.97 (0.60, 1.57)	0.00 (-0.01,0.01)	
Age [years]											0.7799
<70	1084	22	2.0	1066	17	1.6	0.4501	0.79 (0.42, 1.47)	0.78 (0.41, 1.48)	0.00 (-0.02,0.01)	
>=70	1905	52	2.7	1930	46	2.4	0.4969	0.87 (0.59, 1.29)	0.87 (0.58, 1.30)	0.00 (-0.01,0.01)	
Region											0.3639
North America	359	17	4.7	359	13	3.6	0.4556	0.76 (0.38, 1.55)	0.76 (0.36, 1.58)	-0.01 (-0.04,0.02)	
Latin America	757	22	2.9	758	28	3.7	0.3908	1.27 (0.73, 2.20)	1.28 (0.73, 2.26)	0.01 (-0.01,0.03)	
Europe	1341	25	1.9	1346	13	1.0	0.0486	0.52 (0.27, 1.01)	0.51 (0.26, 1.01)	-0.01 (-0.02,0.00)	
Asia	343	4	1.2	343	4	1.2	1.0000	1.00 (0.25, 3.97)	1.00 (0.25, 4.03)	0.00 (-0.02,0.02)	
Other	189	6	3.2	190	5	2.6	0.7529	0.83 (0.26, 2.67)	0.82 (0.25, 2.75)	-0.01 (-0.04,0.03)	
OECD member											0.0848
No	847	23	2.7	868	29	3.3	0.4500	1.23 (0.72, 2.11)	1.24 (0.71, 2.16)	0.01 (-0.01,0.02)	
Yes	2142	51	2.4	2128	34	1.6	0.0669	0.67 (0.44, 1.03)	0.67 (0.43, 1.03)	-0.01 (-0.02,0.00)	
Baseline NYHA											0.9904
II^	2450	49	2.0	2435	41	1.7	0.4112	0.84 (0.56, 1.27)	0.84 (0.55, 1.28)	0.00 (-0.01,0.00)	
III/IV	539	25	4.6	561	22	3.9	0.5569	0.85 (0.48, 1.48)	0.84 (0.47, 1.51)	-0.01 (-0.03,0.02)	
Baseline Diabetes Status											0.6944
Diabetic	1471	46	3.1	1465	41	2.8	0.5997	0.89 (0.59, 1.35)	0.89 (0.58, 1.37)	0.00 (-0.02,0.01)	
Non-Diabetic	1518	28	1.8	1531	22	1.4	0.3756	0.78 (0.45, 1.36)	0.78 (0.44, 1.36)	0.00 (-0.01,0.00)	

Analysis is based on study 1245.110.
^ Patients with NYHA class I are counted in subgroup NYHA class II.
*** Confirmed hypoglycaemic AEs are defined by a glucose concentration <=70 mg/dL (3.9 mmol/L) or requiring assistance.
Risk ratios and odds ratios with confidence intervals (CIs) are estimated by Cochran-Mantel-Haenszel method. For risk differences standard Wald asymptotic confidence limits are calculated. A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied in case of any zero cells in contingency table.
Only treatment emergent AEs are displayed (onset between first dose until treatment stop +7 days).
MedDRA version: 23.1. * Chi-square test for treatment effect ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction).

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Table R.1.2.3: 3 Proportion of patients with severe adverse events of special interest and severe other specific AEs by user-defined category overall and by subgroup - TS
User-defined AE category: Acute renal failure (narrow 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 Diabetes Status											0.8951
Diabetic	1471	46	3.1	1465	41	2.8	0.5997	0.89 (0.59, 1.35)	0.89 (0.58, 1.37)	0.00 (-0.02,0.01)	
Pre-Diabetes	979	21	2.1	1001	16	1.6	0.3691	0.75 (0.39, 1.42)	0.74 (0.38, 1.43)	-0.01 (-0.02,0.01)	
Normal (no pre-diabetes)	539	7	1.3	530	6	1.1	0.8037	0.87 (0.29, 2.58)	0.87 (0.29, 2.61)	0.00 (-0.01,0.01)	
Baseline BMI [kg/m²]											0.6225
<30	1641	31	1.9	1654	24	1.5	0.3264	0.77 (0.45, 1.30)	0.76 (0.45, 1.31)	0.00 (-0.01,0.00)	
>=30	1348	43	3.2	1342	39	2.9	0.6686	0.91 (0.59, 1.40)	0.91 (0.58, 1.41)	0.00 (-0.02,0.01)	
Baseline eGFR (CKD-EPI) [mL/min/1.73m²]											0.3514
>=60	1505	18	1.2	1493	11	0.7	0.1989	0.62 (0.29, 1.30)	0.61 (0.29, 1.30)	0.00 (-0.01,0.00)	
<60	1482	56	3.8	1503	52	3.5	0.6408	0.92 (0.63, 1.33)	0.91 (0.62, 1.34)	0.00 (-0.02,0.01)	
History of HHF (in the last 12 months)											0.3015
No	2320	56	2.4	2297	42	1.8	0.1677	0.76 (0.51, 1.13)	0.75 (0.50, 1.13)	-0.01 (-0.01,0.00)	
Yes	669	18	2.7	699	21	3.0	0.7275	1.12 (0.60, 2.08)	1.12 (0.59, 2.12)	0.00 (-0.01,0.02)	
Baseline SBP (</>= median)											0.7548
< median	1474	34	2.3	1496	31	2.1	0.6624	0.90 (0.56, 1.45)	0.90 (0.55, 1.47)	0.00 (-0.01,0.01)	
>= median	1515	40	2.6	1500	32	2.1	0.3620	0.81 (0.51, 1.28)	0.80 (0.50, 1.29)	-0.01 (-0.02,0.01)	
History of atrial fibrillation or atrial flutter											0.6629
No	1426	34	2.4	1417	31	2.2	0.7259	0.92 (0.57, 1.48)	0.92 (0.56, 1.50)	0.00 (-0.01,0.01)	
Yes	1558	40	2.6	1575	32	2.0	0.3171	0.79 (0.50, 1.25)	0.79 (0.49, 1.26)	-0.01 (-0.02,0.01)	

Analysis is based on study 1245.110.
^ Patients with NYHA class I are counted in subgroup NYHA class II.
*** Confirmed hypoglycaemic AEs are defined by a glucose concentration <=70 mg/dL (3.9 mmol/L) or requiring assistance.
Risk ratios and odds ratios with confidence intervals (CIs) are estimated by Cochran-Mantel-Haenszel method. For risk differences standard Wald asymptotic confidence limits are calculated. A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied in case of any zero cells in contingency table.
Only treatment emergent AEs are displayed (onset between first dose until treatment stop +7 days).
MedDRA version: 23.1. * Chi-square test for treatment effect ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction).

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Table R.1.2.3: 3 Proportion of patients with severe adverse events of special interest and severe other specific AEs by user-defined category overall and by subgroup - TS
User-defined AE category: Acute renal failure (narrow 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 LVEF [%]											0.4717
< 50	988	24	2.4	995	17	1.7	0.2595	0.70 (0.38, 1.30)	0.70 (0.37, 1.31)	-0.01 (-0.02,0.01)	
>= 50	2001	50	2.5	2001	46	2.3	0.6794	0.92 (0.62, 1.37)	0.92 (0.61, 1.38)	0.00 (-0.01,0.01)	
Baseline LVEF [%]											0.6216
<50	988	24	2.4	995	17	1.7	0.2595	0.70 (0.38, 1.30)	0.70 (0.37, 1.31)	-0.01 (-0.02,0.01)	
50 to <60	1030	25	2.4	1028	26	2.5	0.8817	1.04 (0.61, 1.79)	1.04 (0.60, 1.82)	0.00 (-0.01,0.01)	
>=60	971	25	2.6	973	20	2.1	0.4466	0.80 (0.45, 1.43)	0.79 (0.44, 1.44)	-0.01 (-0.02,0.01)	
Baseline NT-proBNP [pg/mL] (</>=median by atrial fibrillation/flutter status)											0.5960
< median	1507	25	1.7	1476	18	1.2	0.3141	0.74 (0.40, 1.34)	0.73 (0.40, 1.35)	0.00 (-0.01,0.00)	
>= median	1475	49	3.3	1516	45	3.0	0.5794	0.89 (0.60, 1.33)	0.89 (0.59, 1.34)	0.00 (-0.02,0.01)	
Baseline uric acid [mg/dL] (tertiles)											0.1300
<T1	975	19	1.9	963	11	1.1	0.1505	0.59 (0.28, 1.23)	0.58 (0.28, 1.23)	-0.01 (-0.02,0.00)	
>=T1 and <T2	966	21	2.2	1032	13	1.3	0.1143	0.58 (0.29, 1.15)	0.57 (0.29, 1.15)	-0.01 (-0.02,0.00)	
>=T2	1016	34	3.3	970	38	3.9	0.4961	1.17 (0.74, 1.84)	1.18 (0.74, 1.89)	0.01 (-0.01,0.02)	
Baseline use of MRA											0.4075
No	1865	46	2.5	1878	35	1.9	0.2051	0.76 (0.49, 1.17)	0.75 (0.48, 1.17)	-0.01 (-0.02,0.00)	
Yes	1124	28	2.5	1118	28	2.5	0.9838	1.01 (0.60, 1.69)	1.01 (0.59, 1.71)	0.00 (-0.01,0.01)	
Baseline use of ACE-inhibitor, ARB or ARNi											0.6402
No	586	17	2.9	568	12	2.1	0.3923	0.73 (0.35, 1.51)	0.72 (0.34, 1.53)	-0.01 (-0.03,0.01)	
Yes	2403	57	2.4	2428	51	2.1	0.5233	0.89 (0.61, 1.29)	0.88 (0.60, 1.29)	0.00 (-0.01,0.01)	

Analysis is based on study 1245.110.
^ Patients with NYHA class I are counted in subgroup NYHA class II.
*** Confirmed hypoglycaemic AEs are defined by a glucose concentration <=70 mg/dL (3.9 mmol/L) or requiring assistance.
Risk ratios and odds ratios with confidence intervals (CIs) are estimated by Cochran-Mantel-Haenszel method. For risk differences standard Wald asymptotic confidence limits are calculated. A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied in case of any zero cells in contingency table.
Only treatment emergent AEs are displayed (onset between first dose until treatment stop +7 days).
MedDRA version: 23.1. * Chi-square test for treatment effect ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction).

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Table R.1.2.3: 3 Proportion of patients with severe adverse events of special interest and severe other specific AEs by user-defined category overall and by subgroup - TS
User-defined AE category: Ketoacidosis (broad 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	2989	6	0.2	2996	4	0.1	0.5243	0.67 (0.19, 2.35)	0.66 (0.19, 2.36)	0.00 (0.00,0.00)	
Sex											
Male	1653	2	0.1	1658	2	0.1					
Female	1336	4	0.3	1338	2	0.1					
Age [years]											
<70	1084	4	0.4	1066	1	0.1					
>=70	1905	2	0.1	1930	3	0.2					
Region											
North America	359	1	0.3	359	1	0.3					
Latin America	757	1	0.1	758	0	0					
Europe	1341	2	0.1	1346	1	0.1					
Asia	343	1	0.3	343	0	0					
Other	189	1	0.5	190	2	1.1					
OECD member											
No	847	2	0.2	868	0	0					
Yes	2142	4	0.2	2128	4	0.2					
Baseline NYHA											
II^	2450	4	0.2	2435	3	0.1					
III/IV	539	2	0.4	561	1	0.2					
Baseline Diabetes Status											
Diabetic	1471	4	0.3	1465	4	0.3					
Non-Diabetic	1518	2	0.1	1531	0	0					

Analysis is based on study 1245.110.
^ Patients with NYHA class I are counted in subgroup NYHA class II.
*** Confirmed hypoglycaemic AEs are defined by a glucose concentration <=70 mg/dL (3.9 mmol/L) or requiring assistance.
Risk ratios and odds ratios with confidence intervals (CIs) are estimated by Cochran-Mantel-Haenszel method. For risk differences standard Wald asymptotic confidence limits are calculated. A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied in case of any zero cells in contingency table.
Only treatment emergent AEs are displayed (onset between first dose until treatment stop +7 days).
MedDRA version: 23.1. * Chi-square test for treatment effect ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction).

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Table R.1.2.3: 3 Proportion of patients with severe adverse events of special interest and severe other specific AEs by user-defined category overall and by subgroup - TS
User-defined AE category: Ketoacidosis (broad 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 Diabetes Status											
Diabetic	1471	4	0.3	1465	4	0.3					
Pre-Diabetes	979	1	0.1	1001	0	0					
Normal (no pre-diabetes)	539	1	0.2	530	0	0					
Baseline BMI [kg/m²]											
<30	1641	4	0.2	1654	2	0.1					
>=30	1348	2	0.1	1342	2	0.1					
Baseline eGFR (CKD-EPI) [mL/min/1.73m²]											
>=60	1505	1	0.1	1493	2	0.1					
<60	1482	5	0.3	1503	2	0.1					
History of HHF (in the last 12 months)											
No	2320	3	0.1	2297	2	0.1					
Yes	669	3	0.4	699	2	0.3					
Baseline SBP (</>= median)											
< median	1474	4	0.3	1496	1	0.1					
>= median	1515	2	0.1	1500	3	0.2					
History of atrial fibrillation or atrial flutter											
No	1426	3	0.2	1417	2	0.1					
Yes	1558	3	0.2	1575	2	0.1					

Analysis is based on study 1245.110.
^ Patients with NYHA class I are counted in subgroup NYHA class II.
*** Confirmed hypoglycaemic AEs are defined by a glucose concentration <=70 mg/dL (3.9 mmol/L) or requiring assistance.
Risk ratios and odds ratios with confidence intervals (CIs) are estimated by Cochran-Mantel-Haenszel method. For risk differences standard Wald asymptotic confidence limits are calculated. A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied in case of any zero cells in contingency table.
Only treatment emergent AEs are displayed (onset between first dose until treatment stop +7 days).
MedDRA version: 23.1. * Chi-square test for treatment effect ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction).

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Table R.1.2.3: 3 Proportion of patients with severe adverse events of special interest and severe other specific AEs by user-defined category overall and by subgroup - TS
User-defined AE category: Ketoacidosis (broad 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 LVEF [%]											
< 50	988	1	0.1	995	0	0					
>= 50	2001	5	0.2	2001	4	0.2					
Baseline LVEF [%]											
<50	988	1	0.1	995	0	0					
50 to <60	1030	3	0.3	1028	3	0.3					
>=60	971	2	0.2	973	1	0.1					
Baseline NT-proBNP [pg/mL] (</>=median by atrial fibrillation/flutter status)											
< median	1507	3	0.2	1476	1	0.1					
>= median	1475	3	0.2	1516	3	0.2					
Baseline uric acid [mg/dL] (tertiles)											
<T1	975	0	0	963	0	0					
>=T1 and <T2	966	2	0.2	1032	2	0.2					
>=T2	1016	3	0.3	970	2	0.2					
Baseline use of MRA											
No	1865	5	0.3	1878	3	0.2					
Yes	1124	1	0.1	1118	1	0.1					
Baseline use of ACE-inhibitor, ARB or ARNi											
No	586	1	0.2	568	1	0.2					
Yes	2403	5	0.2	2428	3	0.1					

Analysis is based on study 1245.110.
^ Patients with NYHA class I are counted in subgroup NYHA class II.
*** Confirmed hypoglycaemic AEs are defined by a glucose concentration <=70 mg/dL (3.9 mmol/L) or requiring assistance.
Risk ratios and odds ratios with confidence intervals (CIs) are estimated by Cochran-Mantel-Haenszel method. For risk differences standard Wald asymptotic confidence limits are calculated. A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied in case of any zero cells in contingency table.
Only treatment emergent AEs are displayed (onset between first dose until treatment stop +7 days).
MedDRA version: 23.1. * Chi-square test for treatment effect ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction).

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Table R.1.2.3: 3 Proportion of patients with severe adverse events of special interest and severe other specific AEs by user-defined category overall and by subgroup - TS
User-defined AE category: Ketoacidosis (narrow 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	2989	2	0.1	2996	2	0.1	0.9981	1.00 (0.14, 7.08)	1.00 (0.14, 7.09)	0.00 (0.00,0.00)	
Sex											
Male	1653	1	0.1	1658	1	0.1					
Female	1336	1	0.1	1338	1	0.1					
Age [years]											
<70	1084	2	0.2	1066	1	0.1					
>=70	1905	0	0	1930	1	0.1					
Region											
North America	359	0	0	359	0	0					
Latin America	757	0	0	758	0	0					
Europe	1341	0	0	1346	1	0.1					
Asia	343	1	0.3	343	0	0					
Other	189	1	0.5	190	1	0.5					
OECD member											
No	847	2	0.2	868	0	0					
Yes	2142	0	0	2128	2	0.1					
Baseline NYHA											
II^	2450	2	0.1	2435	2	0.1					
III/IV	539	0	0	561	0	0					
Baseline Diabetes Status											
Diabetic	1471	2	0.1	1465	2	0.1					
Non-Diabetic	1518	0	0	1531	0	0					

Analysis is based on study 1245.110.
^ Patients with NYHA class I are counted in subgroup NYHA class II.
*** Confirmed hypoglycaemic AEs are defined by a glucose concentration <=70 mg/dL (3.9 mmol/L) or requiring assistance.
Risk ratios and odds ratios with confidence intervals (CIs) are estimated by Cochran-Mantel-Haenszel method. For risk differences standard Wald asymptotic confidence limits are calculated. A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied in case of any zero cells in contingency table.
Only treatment emergent AEs are displayed (onset between first dose until treatment stop +7 days).
MedDRA version: 23.1. * Chi-square test for treatment effect ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction).

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Table R.1.2.3: 3 Proportion of patients with severe adverse events of special interest and severe other specific AEs by user-defined category overall and by subgroup - TS
User-defined AE category: Ketoacidosis (narrow 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 Diabetes Status											
Diabetic	1471	2	0.1	1465	2	0.1					
Pre-Diabetes	979	0	0	1001	0	0					
Normal (no pre-diabetes)	539	0	0	530	0	0					
Baseline BMI [kg/m²]											
<30	1641	1	0.1	1654	0	0					
>=30	1348	1	0.1	1342	2	0.1					
Baseline eGFR (CKD-EPI) [mL/min/1.73m²]											
>=60	1505	0	0	1493	1	0.1					
<60	1482	2	0.1	1503	1	0.1					
History of HHF (in the last 12 months)											
No	2320	1	<0.1	2297	1	<0.1					
Yes	669	1	0.1	699	1	0.1					
Baseline SBP (</>= median)											
< median	1474	1	0.1	1496	1	0.1					
>= median	1515	1	0.1	1500	1	0.1					
History of atrial fibrillation or atrial flutter											
No	1426	1	0.1	1417	2	0.1					
Yes	1558	1	0.1	1575	0	0					

Analysis is based on study 1245.110.
^ Patients with NYHA class I are counted in subgroup NYHA class II.
*** Confirmed hypoglycaemic AEs are defined by a glucose concentration <=70 mg/dL (3.9 mmol/L) or requiring assistance.
Risk ratios and odds ratios with confidence intervals (CIs) are estimated by Cochran-Mantel-Haenszel method. For risk differences standard Wald asymptotic confidence limits are calculated. A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied in case of any zero cells in contingency table.
Only treatment emergent AEs are displayed (onset between first dose until treatment stop +7 days).
MedDRA version: 23.1. * Chi-square test for treatment effect ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction).

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Table R.1.2.3: 3 Proportion of patients with severe adverse events of special interest and severe other specific AEs by user-defined category overall and by subgroup - TS
User-defined AE category: Ketoacidosis (narrow 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 LVEF [%]											
< 50	988	1	0.1	995	0	0					
>= 50	2001	1	<0.1	2001	2	0.1					
Baseline LVEF [%]											
<50	988	1	0.1	995	0	0					
50 to <60	1030	0	0	1028	1	0.1					
>=60	971	1	0.1	973	1	0.1					
Baseline NT-proBNP [pg/mL] (</>=median by atrial fibrillation/flutter status)											
< median	1507	2	0.1	1476	0	0					
>= median	1475	0	0	1516	2	0.1					
Baseline uric acid [mg/dL] (tertiles)											
<T1	975	0	0	963	0	0					
>=T1 and <T2	966	1	0.1	1032	2	0.2					
>=T2	1016	1	0.1	970	0	0					
Baseline use of MRA											
No	1865	1	0.1	1878	1	0.1					
Yes	1124	1	0.1	1118	1	0.1					
Baseline use of ACE-inhibitor, ARB or ARNi											
No	586	1	0.2	568	0	0					
Yes	2403	1	<0.1	2428	2	0.1					

Analysis is based on study 1245.110.
^ Patients with NYHA class I are counted in subgroup NYHA class II.
*** Confirmed hypoglycaemic AEs are defined by a glucose concentration <=70 mg/dL (3.9 mmol/L) or requiring assistance.
Risk ratios and odds ratios with confidence intervals (CIs) are estimated by Cochran-Mantel-Haenszel method. For risk differences standard Wald asymptotic confidence limits are calculated. A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied in case of any zero cells in contingency table.
Only treatment emergent AEs are displayed (onset between first dose until treatment stop +7 days).
MedDRA version: 23.1. * Chi-square test for treatment effect ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction).

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Table R.1.2.3: 3 Proportion of patients with severe adverse events of special interest and severe other specific AEs by user-defined category overall and by subgroup - TS
User-defined AE category: AE 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	2989	12	0.4	2996	10	0.3	0.6652	0.83 (0.36, 1.92)	0.83 (0.36, 1.93)	0.00 (0.00,0.00)	
Sex											0.6538
Male	1653	10	0.6	1658	9	0.5	0.8129	0.90 (0.37, 2.20)	0.90 (0.36, 2.21)	0.00 (-0.01,0.00)	
Female	1336	2	0.1	1338	1	0.1	0.5626	0.50 (0.05, 5.50)	0.50 (0.05, 5.51)	0.00 (0.00,0.00)	
Age [years]											0.1792
<70	1084	5	0.5	1066	7	0.7	0.5431	1.42 (0.45, 4.47)	1.43 (0.45, 4.51)	0.00 (0.00,0.01)	
>=70	1905	7	0.4	1930	3	0.2	0.1980	0.42 (0.11, 1.63)	0.42 (0.11, 1.63)	0.00 (-0.01,0.00)	
Region											
North America	359	4	1.1	359	3	0.8					
Latin America	757	3	0.4	758	2	0.3					
Europe	1341	4	0.3	1346	4	0.3					
Asia	343	1	0.3	343	0	0					
Other	189	0	0	190	1	0.5					
OECD member											0.7576
No	847	3	0.4	868	2	0.2	0.6346	0.65 (0.11, 3.88)	0.65 (0.11, 3.90)	0.00 (-0.01,0.00)	
Yes	2142	9	0.4	2128	8	0.4	0.8185	0.89 (0.35, 2.31)	0.89 (0.34, 2.32)	0.00 (0.00,0.00)	
Baseline NYHA											0.8277
II^	2450	8	0.3	2435	7	0.3	0.8052	0.88 (0.32, 2.42)	0.88 (0.32, 2.43)	0.00 (0.00,0.00)	
III/IV	539	4	0.7	561	3	0.5	0.6655	0.72 (0.16, 3.20)	0.72 (0.16, 3.23)	0.00 (-0.01,0.01)	
Baseline Diabetes Status											0.6460
Diabetic	1471	10	0.7	1465	9	0.6	0.8249	0.90 (0.37, 2.22)	0.90 (0.37, 2.23)	0.00 (-0.01,0.01)	
Non-Diabetic	1518	2	0.1	1531	1	0.1	0.5585	0.50 (0.05, 5.46)	0.50 (0.04, 5.47)	0.00 (0.00,0.00)	

Analysis is based on study 1245.110.
^ Patients with NYHA class I are counted in subgroup NYHA class II.
*** Confirmed hypoglycaemic AEs are defined by a glucose concentration <=70 mg/dL (3.9 mmol/L) or requiring assistance.
Risk ratios and odds ratios with confidence intervals (CIs) are estimated by Cochran-Mantel-Haenszel method. For risk differences standard Wald asymptotic confidence limits are calculated. A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied in case of any zero cells in contingency table.
Only treatment emergent AEs are displayed (onset between first dose until treatment stop +7 days).
MedDRA version: 23.1. * Chi-square test for treatment effect ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction).

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Table R.1.2.3: 3 Proportion of patients with severe adverse events of special interest and severe other specific AEs by user-defined category overall and by subgroup - TS
User-defined AE category: AE 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 Diabetes Status											0.8276
Diabetic	1471	10	0.7	1465	9	0.6	0.8249	0.90 (0.37, 2.22)	0.90 (0.37, 2.23)	0.00 (-0.01,0.01)	
Pre-Diabetes	979	1	0.1	1001	0	0	0.4695	0.33 (0.01, 7.99)	0.33 (0.01, 8.00)	0.00 (0.00,0.00)	
Normal (no pre-diabetes)	539	1	0.2	530	1	0.2	0.9905	1.02 (0.06, 16.22)	1.02 (0.06, 16.30)	0.00 (-0.01,0.01)	
Baseline BMI [kg/m²]											0.4799
<30	1641	4	0.2	1654	2	0.1	0.4083	0.50 (0.09, 2.70)	0.50 (0.09, 2.71)	0.00 (0.00,0.00)	
>=30	1348	8	0.6	1342	8	0.6	0.9929	1.00 (0.38, 2.67)	1.00 (0.38, 2.68)	0.00 (-0.01,0.01)	
Baseline eGFR (CKD-EPI) [mL/min/1.73m²]											0.1023
>=60	1505	2	0.1	1493	5	0.3	0.2519	2.52 (0.49, 12.97)	2.53 (0.49, 13.04)	0.00 (0.00,0.01)	
<60	1482	10	0.7	1503	5	0.3	0.1863	0.49 (0.17, 1.44)	0.49 (0.17, 1.44)	0.00 (-0.01,0.00)	
History of HHF (in the last 12 months)											0.2545
No	2320	9	0.4	2297	5	0.2	0.2928	0.56 (0.19, 1.67)	0.56 (0.19, 1.67)	0.00 (0.00,0.00)	
Yes	669	3	0.4	699	5	0.7	0.5175	1.60 (0.38, 6.65)	1.60 (0.38, 6.72)	0.00 (-0.01,0.01)	
Baseline SBP (</>= median)											0.6187
< median	1474	6	0.4	1496	4	0.3	0.5112	0.66 (0.19, 2.32)	0.66 (0.18, 2.33)	0.00 (-0.01,0.00)	
>= median	1515	6	0.4	1500	6	0.4	0.9862	1.01 (0.33, 3.12)	1.01 (0.33, 3.14)	0.00 (0.00,0.00)	
History of atrial fibrillation or atrial flutter											0.1967
No	1426	7	0.5	1417	3	0.2	0.2087	0.43 (0.11, 1.66)	0.43 (0.11, 1.67)	0.00 (-0.01,0.00)	
Yes	1558	5	0.3	1575	7	0.4	0.5757	1.38 (0.44, 4.35)	1.39 (0.44, 4.38)	0.00 (0.00,0.01)	

Analysis is based on study 1245.110.
^ Patients with NYHA class I are counted in subgroup NYHA class II.
*** Confirmed hypoglycaemic AEs are defined by a glucose concentration <=70 mg/dL (3.9 mmol/L) or requiring assistance.
Risk ratios and odds ratios with confidence intervals (CIs) are estimated by Cochran-Mantel-Haenszel method. For risk differences standard Wald asymptotic confidence limits are calculated. A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied in case of any zero cells in contingency table.
Only treatment emergent AEs are displayed (onset between first dose until treatment stop +7 days).
MedDRA version: 23.1. * Chi-square test for treatment effect ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction).

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Table R.1.2.3: 3 Proportion of patients with severe adverse events of special interest and severe other specific AEs by user-defined category overall and by subgroup - TS
User-defined AE category: AE 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 LVEF [%]											0.7520
< 50	988	4	0.4	995	4	0.4	0.9920	0.99 (0.25, 3.96)	0.99 (0.25, 3.98)	0.00 (-0.01,0.01)	
>= 50	2001	8	0.4	2001	6	0.3	0.5923	0.75 (0.26, 2.16)	0.75 (0.26, 2.16)	0.00 (0.00,0.00)	
Baseline LVEF [%]											
<50	988	4	0.4	995	4	0.4					
50 to <60	1030	3	0.3	1028	2	0.2					
>=60	971	5	0.5	973	4	0.4					
Baseline NT-proBNP [pg/mL] (</>=median by atrial fibrillation/flutter status)											0.9550
< median	1507	6	0.4	1476	5	0.3	0.7890	0.85 (0.26, 2.78)	0.85 (0.26, 2.79)	0.00 (0.00,0.00)	
>= median	1475	6	0.4	1516	5	0.3	0.7281	0.81 (0.25, 2.65)	0.81 (0.25, 2.66)	0.00 (-0.01,0.00)	
Baseline uric acid [mg/dL] (tertiles)											0.3622
<T1	975	3	0.3	963	0	0	0.1364	0.14 (<0.01, 2.80)	0.14 (<0.01, 2.80)	0.00 (-0.01,0.00)	
>=T1 and <T2	966	3	0.3	1032	5	0.5	0.5384	1.56 (0.37, 6.51)	1.56 (0.37, 6.56)	0.00 (0.00,0.01)	
>=T2	1016	6	0.6	970	5	0.5	0.8217	0.87 (0.27, 2.85)	0.87 (0.27, 2.87)	0.00 (-0.01,0.01)	
Baseline use of MRA											0.3859
No	1865	7	0.4	1878	4	0.2	0.3589	0.57 (0.17, 1.94)	0.57 (0.17, 1.94)	0.00 (-0.01,0.00)	
Yes	1124	5	0.4	1118	6	0.5	0.7557	1.21 (0.37, 3.94)	1.21 (0.37, 3.97)	0.00 (0.00,0.01)	
Baseline use of ACE-inhibitor, ARB or ARNi											0.8107
No	586	2	0.3	568	2	0.4	0.9751	1.03 (0.15, 7.30)	1.03 (0.14, 7.35)	0.00 (-0.01,0.01)	
Yes	2403	10	0.4	2428	8	0.3	0.6211	0.79 (0.31, 2.00)	0.79 (0.31, 2.01)	0.00 (0.00,0.00)	

Analysis is based on study 1245.110.
^ Patients with NYHA class I are counted in subgroup NYHA class II.
*** Confirmed hypoglycaemic AEs are defined by a glucose concentration <=70 mg/dL (3.9 mmol/L) or requiring assistance.
Risk ratios and odds ratios with confidence intervals (CIs) are estimated by Cochran-Mantel-Haenszel method. For risk differences standard Wald asymptotic confidence limits are calculated. A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied in case of any zero cells in contingency table.
Only treatment emergent AEs are displayed (onset between first dose until treatment stop +7 days).
MedDRA version: 23.1. * Chi-square test for treatment effect ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction).

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Table R.1.2.3: 3 Proportion of patients with severe adverse events of special interest and severe other specific AEs by user-defined category overall and by subgroup - TS
User-defined AE category: Confirmed 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	2989	5	0.2	2996	6	0.2	0.7658	1.20 (0.37, 3.92)	1.20 (0.37, 3.93)	0.00 (0.00,0.00)	
Sex											
Male	1653	3	0.2	1658	2	0.1					
Female	1336	2	0.1	1338	4	0.3					
Age [years]											
<70	1084	1	0.1	1066	2	0.2					
>=70	1905	4	0.2	1930	4	0.2					
Region											
North America	359	0	0	359	1	0.3					
Latin America	757	2	0.3	758	1	0.1					
Europe	1341	2	0.1	1346	2	0.1					
Asia	343	0	0	343	1	0.3					
Other	189	1	0.5	190	1	0.5					
OECD member											
No	847	2	0.2	868	2	0.2					
Yes	2142	3	0.1	2128	4	0.2					
Baseline NYHA											
II^	2450	4	0.2	2435	4	0.2					
III/IV	539	1	0.2	561	2	0.4					
Baseline Diabetes Status											
Diabetic	1471	4	0.3	1465	5	0.3					
Non-Diabetic	1518	1	0.1	1531	1	0.1					

Analysis is based on study 1245.110.
^ Patients with NYHA class I are counted in subgroup NYHA class II.
*** Confirmed hypoglycaemic AEs are defined by a glucose concentration <=70 mg/dL (3.9 mmol/L) or requiring assistance.
Risk ratios and odds ratios with confidence intervals (CIs) are estimated by Cochran-Mantel-Haenszel method. For risk differences standard Wald asymptotic confidence limits are calculated. A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied in case of any zero cells in contingency table.
Only treatment emergent AEs are displayed (onset between first dose until treatment stop +7 days).
MedDRA version: 23.1. * Chi-square test for treatment effect ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction).

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Table R.1.2.3: 3 Proportion of patients with severe adverse events of special interest and severe other specific AEs by user-defined category overall and by subgroup - TS
User-defined AE category: Confirmed 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 **
Baseline Diabetes Status											
Diabetic	1471	4	0.3	1465	5	0.3					
Pre-Diabetes	979	1	0.1	1001	1	0.1					
Normal (no pre-diabetes)	539	0	0	530	0	0					
Baseline BMI [kg/m²]											
<30	1641	2	0.1	1654	2	0.1					
>=30	1348	3	0.2	1342	4	0.3					
Baseline eGFR (CKD-EPI) [mL/min/1.73m²]											
>=60	1505	3	0.2	1493	1	0.1					
<60	1482	2	0.1	1503	5	0.3					
History of HHF (in the last 12 months)											
No	2320	3	0.1	2297	4	0.2					
Yes	669	2	0.3	699	2	0.3					
Baseline SBP (</>= median)											
< median	1474	3	0.2	1496	3	0.2					
>= median	1515	2	0.1	1500	3	0.2					
History of atrial fibrillation or atrial flutter											
No	1426	3	0.2	1417	2	0.1					
Yes	1558	2	0.1	1575	4	0.3					

Analysis is based on study 1245.110.
^ Patients with NYHA class I are counted in subgroup NYHA class II.
*** Confirmed hypoglycaemic AEs are defined by a glucose concentration <=70 mg/dL (3.9 mmol/L) or requiring assistance.
Risk ratios and odds ratios with confidence intervals (CIs) are estimated by Cochran-Mantel-Haenszel method. For risk differences standard Wald asymptotic confidence limits are calculated. A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied in case of any zero cells in contingency table.
Only treatment emergent AEs are displayed (onset between first dose until treatment stop +7 days).
MedDRA version: 23.1. * Chi-square test for treatment effect ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction).

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Table R.1.2.3: 3 Proportion of patients with severe adverse events of special interest and severe other specific AEs by user-defined category overall and by subgroup - TS
User-defined AE category: Confirmed 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 **
Baseline LVEF [%]											
< 50	988	3	0.3	995	1	0.1					
>= 50	2001	2	0.1	2001	5	0.2					
Baseline LVEF [%]											
<50	988	3	0.3	995	1	0.1					
50 to <60	1030	2	0.2	1028	2	0.2					
>=60	971	0	0	973	3	0.3					
Baseline NT-proBNP [pg/mL] (</>=median by atrial fibrillation/flutter status)											
< median	1507	0	0	1476	2	0.1					
>= median	1475	5	0.3	1516	4	0.3					
Baseline uric acid [mg/dL] (tertiles)											
<T1	975	2	0.2	963	2	0.2					
>=T1 and <T2	966	2	0.2	1032	0	0					
>=T2	1016	1	0.1	970	4	0.4					
Baseline use of MRA											
No	1865	3	0.2	1878	5	0.3					
Yes	1124	2	0.2	1118	1	0.1					
Baseline use of ACE-inhibitor, ARB or ARNi											
No	586	1	0.2	568	3	0.5					
Yes	2403	4	0.2	2428	3	0.1					

Analysis is based on study 1245.110.
^ Patients with NYHA class I are counted in subgroup NYHA class II.
*** Confirmed hypoglycaemic AEs are defined by a glucose concentration <=70 mg/dL (3.9 mmol/L) or requiring assistance.
Risk ratios and odds ratios with confidence intervals (CIs) are estimated by Cochran-Mantel-Haenszel method. For risk differences standard Wald asymptotic confidence limits are calculated. A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied in case of any zero cells in contingency table.
Only treatment emergent AEs are displayed (onset between first dose until treatment stop +7 days).
MedDRA version: 23.1. * Chi-square test for treatment effect ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction).

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Table R.1.2.3: 3 Proportion of patients with severe adverse events of special interest and severe other specific AEs by user-defined category overall and by subgroup - TS
User-defined AE category: Urinary Tract Infection (narrow Sub 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	2989	18	0.6	2996	22	0.7	0.5306	1.22 (0.66, 2.27)	1.22 (0.65, 2.28)	0.00 (0.00,0.01)	
Sex											0.0921
Male	1653	13	0.8	1658	10	0.6	0.5254	0.77 (0.34, 1.74)	0.77 (0.33, 1.75)	0.00 (-0.01,0.00)	
Female	1336	5	0.4	1338	12	0.9	0.0891	2.40 (0.85, 6.78)	2.41 (0.85, 6.86)	0.01 (0.00,0.01)	
Age [years]											0.1245
<70	1084	2	0.2	1066	7	0.7	0.0900	3.56 (0.74, 17.09)	3.58 (0.74, 17.25)	0.00 (0.00,0.01)	
>=70	1905	16	0.8	1930	15	0.8	0.8284	0.93 (0.46, 1.87)	0.92 (0.46, 1.88)	0.00 (-0.01,0.01)	
Region											0.8377
North America	359	4	1.1	359	5	1.4	0.7373	1.25 (0.34, 4.62)	1.25 (0.33, 4.71)	0.00 (-0.01,0.02)	
Latin America	757	5	0.7	758	7	0.9	0.5637	1.40 (0.45, 4.39)	1.40 (0.44, 4.44)	0.00 (-0.01,0.01)	
Europe	1341	7	0.5	1346	7	0.5	0.9944	1.00 (0.35, 2.83)	1.00 (0.35, 2.85)	0.00 (-0.01,0.01)	
Asia	343	1	0.3	343	0	0	0.4789	0.33 (0.01, 8.15)	0.33 (0.01, 8.19)	0.00 (-0.01,0.01)	
Other	189	1	0.5	190	3	1.6	0.3173	2.98 (0.31, 28.43)	3.02 (0.31, 29.26)	0.01 (-0.01,0.03)	
OECD member											0.8823
No	847	6	0.7	868	7	0.8	0.8149	1.14 (0.38, 3.37)	1.14 (0.38, 3.40)	0.00 (-0.01,0.01)	
Yes	2142	12	0.6	2128	15	0.7	0.5510	1.26 (0.59, 2.68)	1.26 (0.59, 2.70)	0.00 (0.00,0.01)	
Baseline NYHA											0.5402
II^	2450	14	0.6	2435	15	0.6	0.8393	1.08 (0.52, 2.23)	1.08 (0.52, 2.24)	0.00 (0.00,0.00)	
III/IV	539	4	0.7	561	7	1.2	0.3995	1.68 (0.50, 5.71)	1.69 (0.49, 5.81)	0.01 (-0.01,0.02)	
Baseline Diabetes Status											0.5896
Diabetic	1471	10	0.7	1465	14	1.0	0.4066	1.41 (0.63, 3.15)	1.41 (0.62, 3.18)	0.00 (0.00,0.01)	
Non-Diabetic	1518	8	0.5	1531	8	0.5	0.9864	0.99 (0.37, 2.63)	0.99 (0.37, 2.65)	0.00 (-0.01,0.01)	

Analysis is based on study 1245.110.
^ Patients with NYHA class I are counted in subgroup NYHA class II.
*** Confirmed hypoglycaemic AEs are defined by a glucose concentration <=70 mg/dL (3.9 mmol/L) or requiring assistance.
Risk ratios and odds ratios with confidence intervals (CIs) are estimated by Cochran-Mantel-Haenszel method. For risk differences standard Wald asymptotic confidence limits are calculated. A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied in case of any zero cells in contingency table.
Only treatment emergent AEs are displayed (onset between first dose until treatment stop +7 days).
MedDRA version: 23.1. * Chi-square test for treatment effect ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction).

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Table R.1.2.3: 3 Proportion of patients with severe adverse events of special interest and severe other specific AEs by user-defined category overall and by subgroup - TS
User-defined AE category: Urinary Tract Infection (narrow Sub 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 Diabetes Status											0.6872
Diabetic	1471	10	0.7	1465	14	1.0	0.4066	1.41 (0.63, 3.15)	1.41 (0.62, 3.18)	0.00 (0.00,0.01)	
Pre-Diabetes	979	7	0.7	1001	6	0.6	0.7501	0.84 (0.28, 2.49)	0.84 (0.28, 2.50)	0.00 (-0.01,0.01)	
Normal (no pre-diabetes)	539	1	0.2	530	2	0.4	0.5533	2.03 (0.18, 22.36)	2.04 (0.18, 22.54)	0.00 (0.00,0.01)	
Baseline BMI [kg/m²]											0.2370
<30	1641	9	0.5	1654	7	0.4	0.6051	0.77 (0.29, 2.07)	0.77 (0.29, 2.07)	0.00 (-0.01,0.00)	
>=30	1348	9	0.7	1342	15	1.1	0.2145	1.67 (0.74, 3.81)	1.68 (0.73, 3.86)	0.00 (0.00,0.01)	
Baseline eGFR (CKD-EPI) [mL/min/1.73m²]											0.7717
>=60	1505	4	0.3	1493	4	0.3	0.9910	1.01 (0.25, 4.02)	1.01 (0.25, 4.04)	0.00 (0.00,0.00)	
<60	1482	14	0.9	1503	18	1.2	0.5023	1.27 (0.63, 2.54)	1.27 (0.63, 2.56)	0.00 (0.00,0.01)	
History of HHF (in the last 12 months)											0.3898
No	2320	11	0.5	2297	16	0.7	0.3217	1.47 (0.68, 3.16)	1.47 (0.68, 3.18)	0.00 (0.00,0.01)	
Yes	669	7	1.0	699	6	0.9	0.7202	0.82 (0.28, 2.43)	0.82 (0.27, 2.45)	0.00 (-0.01,0.01)	
Baseline SBP (</>= median)											0.4069
< median	1474	9	0.6	1496	14	0.9	0.3120	1.53 (0.67, 3.53)	1.54 (0.66, 3.56)	0.00 (0.00,0.01)	
>= median	1515	9	0.6	1500	8	0.5	0.8238	0.90 (0.35, 2.32)	0.90 (0.35, 2.33)	0.00 (-0.01,0.00)	
History of atrial fibrillation or atrial flutter											0.0727
No	1426	4	0.3	1417	11	0.8	0.0681	2.77 (0.88, 8.67)	2.78 (0.88, 8.76)	0.00 (0.00,0.01)	
Yes	1558	14	0.9	1575	11	0.7	0.5289	0.78 (0.35, 1.71)	0.78 (0.35, 1.71)	0.00 (-0.01,0.00)	

Analysis is based on study 1245.110.
^ Patients with NYHA class I are counted in subgroup NYHA class II.
*** Confirmed hypoglycaemic AEs are defined by a glucose concentration <=70 mg/dL (3.9 mmol/L) or requiring assistance.
Risk ratios and odds ratios with confidence intervals (CIs) are estimated by Cochran-Mantel-Haenszel method. For risk differences standard Wald asymptotic confidence limits are calculated. A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied in case of any zero cells in contingency table.
Only treatment emergent AEs are displayed (onset between first dose until treatment stop +7 days).
MedDRA version: 23.1. * Chi-square test for treatment effect ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction).

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Table R.1.2.3: 3 Proportion of patients with severe adverse events of special interest and severe other specific AEs by user-defined category overall and by subgroup - TS
User-defined AE category: Urinary Tract Infection (narrow Sub 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 LVEF [%]											0.1758
< 50	988	3	0.3	995	8	0.8	0.1336	2.65 (0.70, 9.95)	2.66 (0.70, 10.06)	0.01 (0.00,0.01)	
>= 50	2001	15	0.7	2001	14	0.7	0.8522	0.93 (0.45, 1.93)	0.93 (0.45, 1.94)	0.00 (-0.01,0.00)	
Baseline LVEF [%]											0.1051
<50	988	3	0.3	995	8	0.8	0.1336	2.65 (0.70, 9.95)	2.66 (0.70, 10.06)	0.01 (0.00,0.01)	
50 to <60	1030	9	0.9	1028	4	0.4	0.1652	0.45 (0.14, 1.44)	0.44 (0.14, 1.44)	0.00 (-0.01,0.00)	
>=60	971	6	0.6	973	10	1.0	0.3173	1.66 (0.61, 4.56)	1.67 (0.60, 4.61)	0.00 (0.00,0.01)	
Baseline NT-proBNP [pg/mL] (</>=median by atrial fibrillation/flutter status)											0.9755
< median	1507	6	0.4	1476	7	0.5	0.7524	1.19 (0.40, 3.54)	1.19 (0.40, 3.56)	0.00 (0.00,0.01)	
>= median	1475	12	0.8	1516	15	1.0	0.6111	1.22 (0.57, 2.59)	1.22 (0.57, 2.61)	0.00 (-0.01,0.01)	
Baseline uric acid [mg/dL] (tertiles)											0.3188
<T1	975	3	0.3	963	3	0.3	0.9879	1.01 (0.20, 5.00)	1.01 (0.20, 5.03)	0.00 (0.00,0.00)	
>=T1 and <T2	966	9	0.9	1032	7	0.7	0.5254	0.73 (0.27, 1.95)	0.73 (0.27, 1.96)	0.00 (-0.01,0.01)	
>=T2	1016	6	0.6	970	12	1.2	0.1286	2.09 (0.79, 5.56)	2.11 (0.79, 5.64)	0.01 (0.00,0.01)	
Baseline use of MRA											0.1264
No	1865	14	0.8	1878	12	0.6	0.6808	0.85 (0.39, 1.84)	0.85 (0.39, 1.84)	0.00 (-0.01,0.00)	
Yes	1124	4	0.4	1118	10	0.9	0.1055	2.51 (0.79, 7.99)	2.53 (0.79, 8.08)	0.01 (0.00,0.01)	
Baseline use of ACE-inhibitor, ARB or ARNi											0.1561
No	586	3	0.5	568	8	1.4	0.1171	2.75 (0.73, 10.32)	2.78 (0.73, 10.52)	0.01 (0.00,0.02)	
Yes	2403	15	0.6	2428	14	0.6	0.8304	0.92 (0.45, 1.91)	0.92 (0.44, 1.92)	0.00 (0.00,0.00)	

Analysis is based on study 1245.110.
^ Patients with NYHA class I are counted in subgroup NYHA class II.
*** Confirmed hypoglycaemic AEs are defined by a glucose concentration <=70 mg/dL (3.9 mmol/L) or requiring assistance.
Risk ratios and odds ratios with confidence intervals (CIs) are estimated by Cochran-Mantel-Haenszel method. For risk differences standard Wald asymptotic confidence limits are calculated. A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied in case of any zero cells in contingency table.
Only treatment emergent AEs are displayed (onset between first dose until treatment stop +7 days).
MedDRA version: 23.1. * Chi-square test for treatment effect ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction).

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Table R.1.2.3: 3 Proportion of patients with severe adverse events of special interest and severe other specific AEs by user-defined category overall and by subgroup - TS
User-defined AE category: Complicated urinary tract infection (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	2989	18	0.6	2996	19	0.6	0.8746	1.05 (0.55, 2.00)	1.05 (0.55, 2.01)	0.00 (0.00,0.00)	
Sex											0.0344
Male	1653	13	0.8	1658	7	0.4	0.1762	0.54 (0.21, 1.34)	0.53 (0.21, 1.34)	0.00 (-0.01,0.00)	
Female	1336	5	0.4	1338	12	0.9	0.0891	2.40 (0.85, 6.78)	2.41 (0.85, 6.86)	0.01 (0.00,0.01)	
Age [years]											0.1360
<70	1084	2	0.2	1066	6	0.6	0.1497	3.05 (0.62, 15.08)	3.06 (0.62, 15.21)	0.00 (0.00,0.01)	
>=70	1905	16	0.8	1930	13	0.7	0.5522	0.80 (0.39, 1.66)	0.80 (0.38, 1.67)	0.00 (-0.01,0.00)	
Region											0.8247
North America	359	4	1.1	359	4	1.1	1.0000	1.00 (0.25, 3.97)	1.00 (0.25, 4.03)	0.00 (-0.02,0.02)	
Latin America	757	5	0.7	758	6	0.8	0.7639	1.20 (0.37, 3.91)	1.20 (0.36, 3.95)	0.00 (-0.01,0.01)	
Europe	1341	7	0.5	1346	6	0.4	0.7758	0.85 (0.29, 2.53)	0.85 (0.29, 2.55)	0.00 (-0.01,0.00)	
Asia	343	1	0.3	343	0	0	0.4789	0.33 (0.01, 8.15)	0.33 (0.01, 8.19)	0.00 (-0.01,0.01)	
Other	189	1	0.5	190	3	1.6	0.3173	2.98 (0.31, 28.43)	3.02 (0.31, 29.26)	0.01 (-0.01,0.03)	
OECD member											0.8739
No	847	6	0.7	868	6	0.7	0.9660	0.98 (0.32, 3.01)	0.98 (0.31, 3.04)	0.00 (-0.01,0.01)	
Yes	2142	12	0.6	2128	13	0.6	0.8282	1.09 (0.50, 2.38)	1.09 (0.50, 2.40)	0.00 (0.00,0.01)	
Baseline NYHA											0.3650
II^	2450	14	0.6	2435	12	0.5	0.7057	0.86 (0.40, 1.86)	0.86 (0.40, 1.87)	0.00 (0.00,0.00)	
III/IV	539	4	0.7	561	7	1.2	0.3995	1.68 (0.50, 5.71)	1.69 (0.49, 5.81)	0.01 (-0.01,0.02)	
Baseline Diabetes Status											0.6238
Diabetic	1471	10	0.7	1465	12	0.8	0.6617	1.20 (0.52, 2.78)	1.21 (0.52, 2.80)	0.00 (0.00,0.01)	
Non-Diabetic	1518	8	0.5	1531	7	0.5	0.7830	0.87 (0.32, 2.39)	0.87 (0.31, 2.40)	0.00 (-0.01,0.00)	

Analysis is based on study 1245.110.
^ Patients with NYHA class I are counted in subgroup NYHA class II.
*** Confirmed hypoglycaemic AEs are defined by a glucose concentration <=70 mg/dL (3.9 mmol/L) or requiring assistance.
Risk ratios and odds ratios with confidence intervals (CIs) are estimated by Cochran-Mantel-Haenszel method. For risk differences standard Wald asymptotic confidence limits are calculated. A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied in case of any zero cells in contingency table.
Only treatment emergent AEs are displayed (onset between first dose until treatment stop +7 days).
MedDRA version: 23.1. * Chi-square test for treatment effect ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction).

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Table R.1.2.3: 3 Proportion of patients with severe adverse events of special interest and severe other specific AEs by user-defined category overall and by subgroup - TS
User-defined AE category: Complicated urinary tract infection (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 Diabetes Status											0.6429
Diabetic	1471	10	0.7	1465	12	0.8	0.6617	1.20 (0.52, 2.78)	1.21 (0.52, 2.80)	0.00 (0.00,0.01)	
Pre-Diabetes	979	7	0.7	1001	5	0.5	0.5367	0.70 (0.22, 2.19)	0.70 (0.22, 2.20)	0.00 (-0.01,0.00)	
Normal (no pre-diabetes)	539	1	0.2	530	2	0.4	0.5533	2.03 (0.18, 22.36)	2.04 (0.18, 22.54)	0.00 (0.00,0.01)	
Baseline BMI [kg/m²]											0.2484
<30	1641	9	0.5	1654	6	0.4	0.4285	0.66 (0.24, 1.85)	0.66 (0.23, 1.86)	0.00 (-0.01,0.00)	
>=30	1348	9	0.7	1342	13	1.0	0.3860	1.45 (0.62, 3.38)	1.46 (0.62, 3.42)	0.00 (0.00,0.01)	
Baseline eGFR (CKD-EPI) [mL/min/1.73m²]											0.6368
>=60	1505	4	0.3	1493	3	0.2	0.7130	0.76 (0.17, 3.37)	0.76 (0.17, 3.38)	0.00 (0.00,0.00)	
<60	1482	14	0.9	1503	16	1.1	0.7427	1.13 (0.55, 2.30)	1.13 (0.55, 2.32)	0.00 (-0.01,0.01)	
History of HHF (in the last 12 months)											0.3725
No	2320	11	0.5	2297	14	0.6	0.5309	1.29 (0.58, 2.83)	1.29 (0.58, 2.84)	0.00 (0.00,0.01)	
Yes	669	7	1.0	699	5	0.7	0.5116	0.68 (0.22, 2.14)	0.68 (0.22, 2.16)	0.00 (-0.01,0.01)	
Baseline SBP (</>= median)											0.2714
< median	1474	9	0.6	1496	13	0.9	0.4116	1.42 (0.61, 3.32)	1.43 (0.61, 3.35)	0.00 (0.00,0.01)	
>= median	1515	9	0.6	1500	6	0.4	0.4489	0.67 (0.24, 1.89)	0.67 (0.24, 1.89)	0.00 (-0.01,0.00)	
History of atrial fibrillation or atrial flutter											0.0588
No	1426	4	0.3	1417	10	0.7	0.1054	2.52 (0.79, 8.00)	2.53 (0.79, 8.07)	0.00 (0.00,0.01)	
Yes	1558	14	0.9	1575	9	0.6	0.2835	0.64 (0.28, 1.46)	0.63 (0.27, 1.47)	0.00 (-0.01,0.00)	

Analysis is based on study 1245.110.
^ Patients with NYHA class I are counted in subgroup NYHA class II.
*** Confirmed hypoglycaemic AEs are defined by a glucose concentration <=70 mg/dL (3.9 mmol/L) or requiring assistance.
Risk ratios and odds ratios with confidence intervals (CIs) are estimated by Cochran-Mantel-Haenszel method. For risk differences standard Wald asymptotic confidence limits are calculated. A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied in case of any zero cells in contingency table.
Only treatment emergent AEs are displayed (onset between first dose until treatment stop +7 days).
MedDRA version: 23.1. * Chi-square test for treatment effect ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction).

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Table R.1.2.3: 3 Proportion of patients with severe adverse events of special interest and severe other specific AEs by user-defined category overall and by subgroup - TS
User-defined AE category: Complicated urinary tract infection (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 LVEF [%]											0.1780
< 50	988	3	0.3	995	7	0.7	0.2088	2.32 (0.60, 8.93)	2.33 (0.60, 9.02)	0.00 (0.00,0.01)	
>= 50	2001	15	0.7	2001	12	0.6	0.5624	0.80 (0.38, 1.70)	0.80 (0.37, 1.71)	0.00 (-0.01,0.00)	
Baseline LVEF [%]											0.0942
<50	988	3	0.3	995	7	0.7	0.2088	2.32 (0.60, 8.93)	2.33 (0.60, 9.02)	0.00 (0.00,0.01)	
50 to <60	1030	9	0.9	1028	3	0.3	0.0830	0.33 (0.09, 1.23)	0.33 (0.09, 1.23)	-0.01 (-0.01,0.00)	
>=60	971	6	0.6	973	9	0.9	0.4392	1.50 (0.53, 4.19)	1.50 (0.53, 4.23)	0.00 (0.00,0.01)	
Baseline NT-proBNP [pg/mL] (</>=median by atrial fibrillation/flutter status)											0.9638
< median	1507	6	0.4	1476	6	0.4	0.9712	1.02 (0.33, 3.16)	1.02 (0.33, 3.17)	0.00 (0.00,0.00)	
>= median	1475	12	0.8	1516	13	0.9	0.8950	1.05 (0.48, 2.30)	1.05 (0.48, 2.32)	0.00 (-0.01,0.01)	
Baseline uric acid [mg/dL] (tertiles)											0.2668
<T1	975	3	0.3	963	2	0.2	0.6643	0.67 (0.11, 4.03)	0.67 (0.11, 4.04)	0.00 (-0.01,0.00)	
>=T1 and <T2	966	9	0.9	1032	6	0.6	0.3647	0.62 (0.22, 1.75)	0.62 (0.22, 1.75)	0.00 (-0.01,0.00)	
>=T2	1016	6	0.6	970	11	1.1	0.1888	1.92 (0.71, 5.17)	1.93 (0.71, 5.24)	0.01 (0.00,0.01)	
Baseline use of MRA											0.0597
No	1865	14	0.8	1878	9	0.5	0.2880	0.64 (0.28, 1.47)	0.64 (0.27, 1.47)	0.00 (-0.01,0.00)	
Yes	1124	4	0.4	1118	10	0.9	0.1055	2.51 (0.79, 7.99)	2.53 (0.79, 8.08)	0.01 (0.00,0.01)	
Baseline use of ACE-inhibitor, ARB or ARNi											0.2723
No	586	3	0.5	568	6	1.1	0.2932	2.06 (0.52, 8.21)	2.07 (0.52, 8.34)	0.01 (0.00,0.02)	
Yes	2403	15	0.6	2428	13	0.5	0.6844	0.86 (0.41, 1.80)	0.86 (0.41, 1.80)	0.00 (-0.01,0.00)	

Analysis is based on study 1245.110.
^ Patients with NYHA class I are counted in subgroup NYHA class II.
*** Confirmed hypoglycaemic AEs are defined by a glucose concentration <=70 mg/dL (3.9 mmol/L) or requiring assistance.
Risk ratios and odds ratios with confidence intervals (CIs) are estimated by Cochran-Mantel-Haenszel method. For risk differences standard Wald asymptotic confidence limits are calculated. A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied in case of any zero cells in contingency table.
Only treatment emergent AEs are displayed (onset between first dose until treatment stop +7 days).
MedDRA version: 23.1. * Chi-square test for treatment effect ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction).

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Table R.1.2.3: 3 Proportion of patients with severe adverse events of special interest and severe other specific AEs by user-defined category overall and by subgroup - TS
User-defined AE category: Genital Infection (narrow 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	2989	2	0.1	2996	4	0.1	0.4156	2.00 (0.37, 10.89)	2.00 (0.37, 10.91)	0.00 (0.00,0.00)	
Sex											
Male	1653	2	0.1	1658	2	0.1					
Female	1336	0	0	1338	2	0.1					
Age [years]											
<70	1084	0	0	1066	2	0.2					
>=70	1905	2	0.1	1930	2	0.1					
Region											
North America	359	0	0	359	1	0.3					
Latin America	757	0	0	758	1	0.1					
Europe	1341	2	0.1	1346	2	0.1					
Asia	343	0	0	343	0	0					
Other	189	0	0	190	0	0					
OECD member											
No	847	0	0	868	1	0.1					
Yes	2142	2	0.1	2128	3	0.1					
Baseline NYHA											
II^	2450	2	0.1	2435	3	0.1					
III/IV	539	0	0	561	1	0.2					
Baseline Diabetes Status											
Diabetic	1471	1	0.1	1465	1	0.1					
Non-Diabetic	1518	1	0.1	1531	3	0.2					

Analysis is based on study 1245.110.
^ Patients with NYHA class I are counted in subgroup NYHA class II.
*** Confirmed hypoglycaemic AEs are defined by a glucose concentration <=70 mg/dL (3.9 mmol/L) or requiring assistance.
Risk ratios and odds ratios with confidence intervals (CIs) are estimated by Cochran-Mantel-Haenszel method. For risk differences standard Wald asymptotic confidence limits are calculated. A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied in case of any zero cells in contingency table.
Only treatment emergent AEs are displayed (onset between first dose until treatment stop +7 days).
MedDRA version: 23.1. * Chi-square test for treatment effect ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction).

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Table R.1.2.3: 3 Proportion of patients with severe adverse events of special interest and severe other specific AEs by user-defined category overall and by subgroup - TS
User-defined AE category: Genital Infection (narrow 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 Diabetes Status											
Diabetic	1471	1	0.1	1465	1	0.1					
Pre-Diabetes	979	0	0	1001	3	0.3					
Normal (no pre-diabetes)	539	1	0.2	530	0	0					
Baseline BMI [kg/m²]											
<30	1641	1	0.1	1654	0	0					
>=30	1348	1	0.1	1342	4	0.3					
Baseline eGFR (CKD-EPI) [mL/min/1.73m²]											
>=60	1505	0	0	1493	3	0.2					
<60	1482	2	0.1	1503	1	0.1					
History of HHF (in the last 12 months)											
No	2320	1	<0.1	2297	3	0.1					
Yes	669	1	0.1	699	1	0.1					
Baseline SBP (</>= median)											
< median	1474	1	0.1	1496	2	0.1					
>= median	1515	1	0.1	1500	2	0.1					
History of atrial fibrillation or atrial flutter											
No	1426	1	0.1	1417	2	0.1					
Yes	1558	1	0.1	1575	2	0.1					

Analysis is based on study 1245.110.
^ Patients with NYHA class I are counted in subgroup NYHA class II.
*** Confirmed hypoglycaemic AEs are defined by a glucose concentration <=70 mg/dL (3.9 mmol/L) or requiring assistance.
Risk ratios and odds ratios with confidence intervals (CIs) are estimated by Cochran-Mantel-Haenszel method. For risk differences standard Wald asymptotic confidence limits are calculated. A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied in case of any zero cells in contingency table.
Only treatment emergent AEs are displayed (onset between first dose until treatment stop +7 days).
MedDRA version: 23.1. * Chi-square test for treatment effect ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction).

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Table R.1.2.3: 3 Proportion of patients with severe adverse events of special interest and severe other specific AEs by user-defined category overall and by subgroup - TS
User-defined AE category: Genital Infection (narrow 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 LVEF [%]											
< 50	988	0	0	995	2	0.2					
>= 50	2001	2	0.1	2001	2	0.1					
Baseline LVEF [%]											
<50	988	0	0	995	2	0.2					
50 to <60	1030	1	0.1	1028	1	0.1					
>=60	971	1	0.1	973	1	0.1					
Baseline NT-proBNP [pg/mL] (</>=median by atrial fibrillation/flutter status)											
< median	1507	1	0.1	1476	1	0.1					
>= median	1475	1	0.1	1516	3	0.2					
Baseline uric acid [mg/dL] (tertiles)											
<T1	975	1	0.1	963	0	0					
>=T1 and <T2	966	1	0.1	1032	3	0.3					
>=T2	1016	0	0	970	1	0.1					
Baseline use of MRA											
No	1865	0	0	1878	2	0.1					
Yes	1124	2	0.2	1118	2	0.2					
Baseline use of ACE-inhibitor, ARB or ARNi											
No	586	1	0.2	568	0	0					
Yes	2403	1	<0.1	2428	4	0.2					

Analysis is based on study 1245.110.
^ Patients with NYHA class I are counted in subgroup NYHA class II.
*** Confirmed hypoglycaemic AEs are defined by a glucose concentration <=70 mg/dL (3.9 mmol/L) or requiring assistance.
Risk ratios and odds ratios with confidence intervals (CIs) are estimated by Cochran-Mantel-Haenszel method. For risk differences standard Wald asymptotic confidence limits are calculated. A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied in case of any zero cells in contingency table.
Only treatment emergent AEs are displayed (onset between first dose until treatment stop +7 days).
MedDRA version: 23.1. * Chi-square test for treatment effect ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction).

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Table R.1.2.3: 3 Proportion of patients with severe adverse events of special interest and severe other specific AEs by user-defined category overall and by subgroup - TS
User-defined AE category: Complicated Genital Infection (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	2989	2	0.1	2996	1	<0.1	0.5622	0.50 (0.05, 5.50)	0.50 (0.05, 5.50)	0.00 (0.00,0.00)	
Sex											
Male	1653	2	0.1	1658	1	0.1					
Female	1336	0	0	1338	0	0					
Age [years]											
<70	1084	0	0	1066	1	0.1					
>=70	1905	2	0.1	1930	0	0					
Region											
North America	359	0	0	359	0	0					
Latin America	757	0	0	758	0	0					
Europe	1341	2	0.1	1346	1	0.1					
Asia	343	0	0	343	0	0					
Other	189	0	0	190	0	0					
OECD member											
No	847	0	0	868	0	0					
Yes	2142	2	0.1	2128	1	<0.1					
Baseline NYHA											
II^	2450	2	0.1	2435	1	<0.1					
III/IV	539	0	0	561	0	0					
Baseline Diabetes Status											
Diabetic	1471	1	0.1	1465	0	0					
Non-Diabetic	1518	1	0.1	1531	1	0.1					

Analysis is based on study 1245.110.
^ Patients with NYHA class I are counted in subgroup NYHA class II.
*** Confirmed hypoglycaemic AEs are defined by a glucose concentration <=70 mg/dL (3.9 mmol/L) or requiring assistance.
Risk ratios and odds ratios with confidence intervals (CIs) are estimated by Cochran-Mantel-Haenszel method. For risk differences standard Wald asymptotic confidence limits are calculated. A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied in case of any zero cells in contingency table.
Only treatment emergent AEs are displayed (onset between first dose until treatment stop +7 days).
MedDRA version: 23.1. * Chi-square test for treatment effect ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction).

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Table R.1.2.3: 3 Proportion of patients with severe adverse events of special interest and severe other specific AEs by user-defined category overall and by subgroup - TS
User-defined AE category: Complicated Genital Infection (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 Diabetes Status											
Diabetic	1471	1	0.1	1465	0	0					
Pre-Diabetes	979	0	0	1001	1	0.1					
Normal (no pre-diabetes)	539	1	0.2	530	0	0					
Baseline BMI [kg/m²]											
<30	1641	1	0.1	1654	0	0					
>=30	1348	1	0.1	1342	1	0.1					
Baseline eGFR (CKD-EPI) [mL/min/1.73m²]											
>=60	1505	0	0	1493	1	0.1					
<60	1482	2	0.1	1503	0	0					
History of HHF (in the last 12 months)											
No	2320	1	<0.1	2297	1	<0.1					
Yes	669	1	0.1	699	0	0					
Baseline SBP (</>= median)											
< median	1474	1	0.1	1496	0	0					
>= median	1515	1	0.1	1500	1	0.1					
History of atrial fibrillation or atrial flutter											
No	1426	1	0.1	1417	0	0					
Yes	1558	1	0.1	1575	1	0.1					

Analysis is based on study 1245.110.
^ Patients with NYHA class I are counted in subgroup NYHA class II.
*** Confirmed hypoglycaemic AEs are defined by a glucose concentration <=70 mg/dL (3.9 mmol/L) or requiring assistance.
Risk ratios and odds ratios with confidence intervals (CIs) are estimated by Cochran-Mantel-Haenszel method. For risk differences standard Wald asymptotic confidence limits are calculated. A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied in case of any zero cells in contingency table.
Only treatment emergent AEs are displayed (onset between first dose until treatment stop +7 days).
MedDRA version: 23.1. * Chi-square test for treatment effect ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction).

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Table R.1.2.3: 3 Proportion of patients with severe adverse events of special interest and severe other specific AEs by user-defined category overall and by subgroup - TS
User-defined AE category: Complicated Genital Infection (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 LVEF [%]											
< 50	988	0	0	995	1	0.1					
>= 50	2001	2	0.1	2001	0	0					
Baseline LVEF [%]											
<50	988	0	0	995	1	0.1					
50 to <60	1030	1	0.1	1028	0	0					
>=60	971	1	0.1	973	0	0					
Baseline NT-proBNP [pg/mL] (</>=median by atrial fibrillation/flutter status)											
< median	1507	1	0.1	1476	0	0					
>= median	1475	1	0.1	1516	1	0.1					
Baseline uric acid [mg/dL] (tertiles)											
<T1	975	1	0.1	963	0	0					
>=T1 and <T2	966	1	0.1	1032	1	0.1					
>=T2	1016	0	0	970	0	0					
Baseline use of MRA											
No	1865	0	0	1878	1	0.1					
Yes	1124	2	0.2	1118	0	0					
Baseline use of ACE-inhibitor, ARB or ARNi											
No	586	1	0.2	568	0	0					
Yes	2403	1	<0.1	2428	1	<0.1					

Analysis is based on study 1245.110.
^ Patients with NYHA class I are counted in subgroup NYHA class II.
*** Confirmed hypoglycaemic AEs are defined by a glucose concentration <=70 mg/dL (3.9 mmol/L) or requiring assistance.
Risk ratios and odds ratios with confidence intervals (CIs) are estimated by Cochran-Mantel-Haenszel method. For risk differences standard Wald asymptotic confidence limits are calculated. A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied in case of any zero cells in contingency table.
Only treatment emergent AEs are displayed (onset between first dose until treatment stop +7 days).
MedDRA version: 23.1. * Chi-square test for treatment effect ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction).

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Table R.1.2.3: 3 Proportion of patients with severe adverse events of special interest and severe other specific AEs by user-defined category overall and by subgroup - TS
User-defined AE category: Acute pyelonephritis (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	2989	2	0.1	2996	4	0.1	0.4156	2.00 (0.37, 10.89)	2.00 (0.37, 10.91)	0.00 (0.00,0.00)	
Sex											
Male	1653	2	0.1	1658	2	0.1					
Female	1336	0	0	1338	2	0.1					
Age [years]											
<70	1084	0	0	1066	2	0.2					
>=70	1905	2	0.1	1930	2	0.1					
Region											
North America	359	1	0.3	359	1	0.3					
Latin America	757	1	0.1	758	1	0.1					
Europe	1341	0	0	1346	1	0.1					
Asia	343	0	0	343	0	0					
Other	189	0	0	190	1	0.5					
OECD member											
No	847	1	0.1	868	1	0.1					
Yes	2142	1	<0.1	2128	3	0.1					
Baseline NYHA											
II^	2450	2	0.1	2435	2	0.1					
III/IV	539	0	0	561	2	0.4					
Baseline Diabetes Status											
Diabetic	1471	1	0.1	1465	3	0.2					
Non-Diabetic	1518	1	0.1	1531	1	0.1					

Analysis is based on study 1245.110.
^ Patients with NYHA class I are counted in subgroup NYHA class II.
*** Confirmed hypoglycaemic AEs are defined by a glucose concentration <=70 mg/dL (3.9 mmol/L) or requiring assistance.
Risk ratios and odds ratios with confidence intervals (CIs) are estimated by Cochran-Mantel-Haenszel method. For risk differences standard Wald asymptotic confidence limits are calculated. A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied in case of any zero cells in contingency table.
Only treatment emergent AEs are displayed (onset between first dose until treatment stop +7 days).
MedDRA version: 23.1. * Chi-square test for treatment effect ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction).

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Table R.1.2.3: 3 Proportion of patients with severe adverse events of special interest and severe other specific AEs by user-defined category overall and by subgroup - TS
User-defined AE category: Acute pyelonephritis (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 Diabetes Status											
Diabetic	1471	1	0.1	1465	3	0.2					
Pre-Diabetes	979	1	0.1	1001	1	0.1					
Normal (no pre-diabetes)	539	0	0	530	0	0					
Baseline BMI [kg/m²]											
<30	1641	2	0.1	1654	1	0.1					
>=30	1348	0	0	1342	3	0.2					
Baseline eGFR (CKD-EPI) [mL/min/1.73m²]											
>=60	1505	0	0	1493	0	0					
<60	1482	2	0.1	1503	4	0.3					
History of HHF (in the last 12 months)											
No	2320	1	<0.1	2297	3	0.1					
Yes	669	1	0.1	699	1	0.1					
Baseline SBP (</>= median)											
< median	1474	2	0.1	1496	3	0.2					
>= median	1515	0	0	1500	1	0.1					
History of atrial fibrillation or atrial flutter											
No	1426	1	0.1	1417	2	0.1					
Yes	1558	1	0.1	1575	2	0.1					

Analysis is based on study 1245.110.
^ Patients with NYHA class I are counted in subgroup NYHA class II.
*** Confirmed hypoglycaemic AEs are defined by a glucose concentration <=70 mg/dL (3.9 mmol/L) or requiring assistance.
Risk ratios and odds ratios with confidence intervals (CIs) are estimated by Cochran-Mantel-Haenszel method. For risk differences standard Wald asymptotic confidence limits are calculated. A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied in case of any zero cells in contingency table.
Only treatment emergent AEs are displayed (onset between first dose until treatment stop +7 days).
MedDRA version: 23.1. * Chi-square test for treatment effect ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction).

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Table R.1.2.3: 3 Proportion of patients with severe adverse events of special interest and severe other specific AEs by user-defined category overall and by subgroup - TS
User-defined AE category: Acute pyelonephritis (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 LVEF [%]											
< 50	988	0	0	995	1	0.1					
>= 50	2001	2	0.1	2001	3	0.1					
Baseline LVEF [%]											
<50	988	0	0	995	1	0.1					
50 to <60	1030	0	0	1028	1	0.1					
>=60	971	2	0.2	973	2	0.2					
Baseline NT-proBNP [pg/mL] (</>=median by atrial fibrillation/flutter status)											
< median	1507	1	0.1	1476	3	0.2					
>= median	1475	1	0.1	1516	1	0.1					
Baseline uric acid [mg/dL] (tertiles)											
<T1	975	1	0.1	963	0	0					
>=T1 and <T2	966	0	0	1032	2	0.2					
>=T2	1016	1	0.1	970	2	0.2					
Baseline use of MRA											
No	1865	2	0.1	1878	3	0.2					
Yes	1124	0	0	1118	1	0.1					
Baseline use of ACE-inhibitor, ARB or ARNi											
No	586	1	0.2	568	0	0					
Yes	2403	1	<0.1	2428	4	0.2					

Analysis is based on study 1245.110.
^ Patients with NYHA class I are counted in subgroup NYHA class II.
*** Confirmed hypoglycaemic AEs are defined by a glucose concentration <=70 mg/dL (3.9 mmol/L) or requiring assistance.
Risk ratios and odds ratios with confidence intervals (CIs) are estimated by Cochran-Mantel-Haenszel method. For risk differences standard Wald asymptotic confidence limits are calculated. A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied in case of any zero cells in contingency table.
Only treatment emergent AEs are displayed (onset between first dose until treatment stop +7 days).
MedDRA version: 23.1. * Chi-square test for treatment effect ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction).

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Table R.1.2.3: 3 Proportion of patients with severe adverse events of special interest and severe other specific AEs by user-defined category overall and by subgroup - TS
User-defined AE category: Urosepsis (PT) or pyelonephritis (narrow Sub 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	2989	10	0.3	2996	10	0.3	0.9958	1.00 (0.42, 2.39)	1.00 (0.41, 2.40)	0.00 (0.00,0.00)	
Sex											0.1837
Male	1653	7	0.4	1658	4	0.2	0.3623	0.57 (0.17, 1.94)	0.57 (0.17, 1.95)	0.00 (-0.01,0.00)	
Female	1336	3	0.2	1338	6	0.4	0.3176	2.00 (0.50, 7.97)	2.00 (0.50, 8.02)	0.00 (0.00,0.01)	
Age [years]											0.2730
<70	1084	1	0.1	1066	3	0.3	0.3088	3.05 (0.32, 29.28)	3.06 (0.32, 29.43)	0.00 (0.00,0.01)	
>=70	1905	9	0.5	1930	7	0.4	0.5981	0.77 (0.29, 2.06)	0.77 (0.29, 2.06)	0.00 (-0.01,0.00)	
Region											
North America	359	1	0.3	359	3	0.8					
Latin America	757	2	0.3	758	2	0.3					
Europe	1341	5	0.4	1346	3	0.2					
Asia	343	1	0.3	343	0	0					
Other	189	1	0.5	190	2	1.1					
OECD member											0.5864
No	847	3	0.4	868	2	0.2	0.6346	0.65 (0.11, 3.88)	0.65 (0.11, 3.90)	0.00 (-0.01,0.00)	
Yes	2142	7	0.3	2128	8	0.4	0.7861	1.15 (0.42, 3.17)	1.15 (0.42, 3.18)	0.00 (0.00,0.00)	
Baseline NYHA											0.3587
II^	2450	8	0.3	2435	6	0.2	0.6004	0.75 (0.26, 2.17)	0.75 (0.26, 2.18)	0.00 (0.00,0.00)	
III/IV	539	2	0.4	561	4	0.7	0.4414	1.92 (0.35, 10.45)	1.93 (0.35, 10.57)	0.00 (-0.01,0.01)	
Baseline Diabetes Status											0.6431
Diabetic	1471	5	0.3	1465	6	0.4	0.7574	1.20 (0.37, 3.94)	1.21 (0.37, 3.96)	0.00 (0.00,0.01)	
Non-Diabetic	1518	5	0.3	1531	4	0.3	0.7289	0.79 (0.21, 2.95)	0.79 (0.21, 2.96)	0.00 (0.00,0.00)	

Analysis is based on study 1245.110.
^ Patients with NYHA class I are counted in subgroup NYHA class II.
*** Confirmed hypoglycaemic AEs are defined by a glucose concentration <=70 mg/dL (3.9 mmol/L) or requiring assistance.
Risk ratios and odds ratios with confidence intervals (CIs) are estimated by Cochran-Mantel-Haenszel method. For risk differences standard Wald asymptotic confidence limits are calculated. A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
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Table R.1.2.3: 3 Proportion of patients with severe adverse events of special interest and severe other specific AEs by user-defined category overall and by subgroup - TS
User-defined AE category: Urosepsis (PT) or pyelonephritis (narrow Sub 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 Diabetes Status											0.8779
Diabetic	1471	5	0.3	1465	6	0.4	0.7574	1.20 (0.37, 3.94)	1.21 (0.37, 3.96)	0.00 (0.00,0.01)	
Pre-Diabetes	979	4	0.4	1001	3	0.3	0.6832	0.73 (0.16, 3.27)	0.73 (0.16, 3.28)	0.00 (-0.01,0.00)	
Normal (no pre-diabetes)	539	1	0.2	530	1	0.2	0.9905	1.02 (0.06, 16.22)	1.02 (0.06, 16.30)	0.00 (-0.01,0.01)	
Baseline BMI [kg/m²]											0.1800
<30	1641	6	0.4	1654	3	0.2	0.3110	0.50 (0.12, 1.98)	0.50 (0.12, 1.98)	0.00 (-0.01,0.00)	
>=30	1348	4	0.3	1342	7	0.5	0.3608	1.76 (0.52, 5.99)	1.76 (0.51, 6.03)	0.00 (0.00,0.01)	
Baseline eGFR (CKD-EPI) [mL/min/1.73m²]											0.5491
>=60	1505	2	0.1	1493	1	0.1	0.5682	0.50 (0.05, 5.55)	0.50 (0.05, 5.56)	0.00 (0.00,0.00)	
<60	1482	8	0.5	1503	9	0.6	0.8304	1.11 (0.43, 2.87)	1.11 (0.43, 2.88)	0.00 (0.00,0.01)	
History of HHF (in the last 12 months)											0.3347
No	2320	5	0.2	2297	7	0.3	0.5516	1.41 (0.45, 4.45)	1.42 (0.45, 4.47)	0.00 (0.00,0.00)	
Yes	669	5	0.7	699	3	0.4	0.4404	0.57 (0.14, 2.39)	0.57 (0.14, 2.40)	0.00 (-0.01,0.00)	
Baseline SBP (</>= median)											0.3788
< median	1474	5	0.3	1496	7	0.5	0.5804	1.38 (0.44, 4.34)	1.38 (0.44, 4.36)	0.00 (0.00,0.01)	
>= median	1515	5	0.3	1500	3	0.2	0.4877	0.61 (0.15, 2.53)	0.61 (0.14, 2.54)	0.00 (0.00,0.00)	
History of atrial fibrillation or atrial flutter											0.0714
No	1426	1	0.1	1417	5	0.4	0.1005	5.03 (0.59, 43.01)	5.05 (0.59, 43.25)	0.00 (0.00,0.01)	
Yes	1558	9	0.6	1575	5	0.3	0.2749	0.55 (0.18, 1.64)	0.55 (0.18, 1.64)	0.00 (-0.01,0.00)	

Analysis is based on study 1245.110.
^ Patients with NYHA class I are counted in subgroup NYHA class II.
*** Confirmed hypoglycaemic AEs are defined by a glucose concentration <=70 mg/dL (3.9 mmol/L) or requiring assistance.
Risk ratios and odds ratios with confidence intervals (CIs) are estimated by Cochran-Mantel-Haenszel method. For risk differences standard Wald asymptotic confidence limits are calculated. A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
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Table R.1.2.3: 3 Proportion of patients with severe adverse events of special interest and severe other specific AEs by user-defined category overall and by subgroup - TS
User-defined AE category: Urosepsis (PT) or pyelonephritis (narrow Sub 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 LVEF [%]											0.5414
< 50	988	1	0.1	995	2	0.2	0.5675	1.99 (0.18, 21.87)	1.99 (0.18, 21.96)	0.00 (0.00,0.00)	
>= 50	2001	9	0.4	2001	8	0.4	0.8080	0.89 (0.34, 2.30)	0.89 (0.34, 2.31)	0.00 (0.00,0.00)	
Baseline LVEF [%]											0.3865
<50	988	1	0.1	995	2	0.2	0.5675	1.99 (0.18, 21.87)	1.99 (0.18, 21.96)	0.00 (0.00,0.00)	
50 to <60	1030	5	0.5	1028	2	0.2	0.2571	0.40 (0.08, 2.06)	0.40 (0.08, 2.06)	0.00 (-0.01,0.00)	
>=60	971	4	0.4	973	6	0.6	0.5282	1.50 (0.42, 5.29)	1.50 (0.42, 5.33)	0.00 (0.00,0.01)	
Baseline NT-proBNP [pg/mL] (</>=median by atrial fibrillation/flutter status)											0.1560
< median	1507	2	0.1	1476	5	0.3	0.2449	2.55 (0.50, 13.14)	2.56 (0.50, 13.20)	0.00 (0.00,0.01)	
>= median	1475	8	0.5	1516	5	0.3	0.3770	0.61 (0.20, 1.85)	0.61 (0.20, 1.86)	0.00 (-0.01,0.00)	
Baseline uric acid [mg/dL] (tertiles)											0.5716
<T1	975	1	0.1	963	1	0.1	0.9930	1.01 (0.06, 16.16)	1.01 (0.06, 16.21)	0.00 (0.00,0.00)	
>=T1 and <T2	966	5	0.5	1032	3	0.3	0.4222	0.56 (0.13, 2.34)	0.56 (0.13, 2.35)	0.00 (-0.01,0.00)	
>=T2	1016	4	0.4	970	6	0.6	0.4791	1.57 (0.44, 5.55)	1.57 (0.44, 5.60)	0.00 (0.00,0.01)	
Baseline use of MRA											0.1666
No	1865	8	0.4	1878	5	0.3	0.3975	0.62 (0.20, 1.89)	0.62 (0.20, 1.90)	0.00 (-0.01,0.00)	
Yes	1124	2	0.2	1118	5	0.4	0.2531	2.51 (0.49, 12.93)	2.52 (0.49, 13.02)	0.00 (0.00,0.01)	
Baseline use of ACE-inhibitor, ARB or ARNi											0.9703
No	586	2	0.3	568	2	0.4	0.9751	1.03 (0.15, 7.30)	1.03 (0.14, 7.35)	0.00 (-0.01,0.01)	
Yes	2403	8	0.3	2428	8	0.3	0.9835	0.99 (0.37, 2.63)	0.99 (0.37, 2.64)	0.00 (0.00,0.00)	

Analysis is based on study 1245.110.
^ Patients with NYHA class I are counted in subgroup NYHA class II.
*** Confirmed hypoglycaemic AEs are defined by a glucose concentration <=70 mg/dL (3.9 mmol/L) or requiring assistance.
Risk ratios and odds ratios with confidence intervals (CIs) are estimated by Cochran-Mantel-Haenszel method. For risk differences standard Wald asymptotic confidence limits are calculated. A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
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Table R.1.2.3: 3 Proportion of patients with severe adverse events of special interest and severe other specific AEs by user-defined category overall and by subgroup - TS
User-defined AE category: Sepsis (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	2989	46	1.5	2996	53	1.8	0.4854	1.15 (0.78, 1.70)	1.15 (0.77, 1.72)	0.00 (0.00,0.01)	
Sex											0.1668
Male	1653	33	2.0	1658	31	1.9	0.7913	0.94 (0.58, 1.52)	0.94 (0.57, 1.53)	0.00 (-0.01,0.01)	
Female	1336	13	1.0	1338	22	1.6	0.1268	1.69 (0.85, 3.34)	1.70 (0.85, 3.39)	0.01 (0.00,0.02)	
Age [years]											0.9668
<70	1084	14	1.3	1066	16	1.5	0.6789	1.16 (0.57, 2.37)	1.16 (0.57, 2.40)	0.00 (-0.01,0.01)	
>=70	1905	32	1.7	1930	37	1.9	0.5804	1.14 (0.71, 1.82)	1.14 (0.71, 1.84)	0.00 (-0.01,0.01)	
Region											0.3475
North America	359	6	1.7	359	16	4.5	0.0304	2.67 (1.06, 6.74)	2.74 (1.06, 7.10)	0.03 (0.00,0.05)	
Latin America	757	13	1.7	758	14	1.8	0.8487	1.08 (0.51, 2.27)	1.08 (0.50, 2.31)	0.00 (-0.01,0.01)	
Europe	1341	20	1.5	1346	17	1.3	0.6114	0.85 (0.45, 1.61)	0.84 (0.44, 1.62)	0.00 (-0.01,0.01)	
Asia	343	3	0.9	343	2	0.6	0.6535	0.67 (0.11, 3.96)	0.66 (0.11, 4.00)	0.00 (-0.02,0.01)	
Other	189	4	2.1	190	4	2.1	0.9940	0.99 (0.25, 3.92)	0.99 (0.25, 4.04)	0.00 (-0.03,0.03)	
OECD member											0.7389
No	847	15	1.8	868	16	1.8	0.9105	1.04 (0.52, 2.09)	1.04 (0.51, 2.12)	0.00 (-0.01,0.01)	
Yes	2142	31	1.4	2128	37	1.7	0.4468	1.20 (0.75, 1.93)	1.20 (0.74, 1.95)	0.00 (0.00,0.01)	
Baseline NYHA											0.0535
II^	2450	35	1.4	2435	30	1.2	0.5489	0.86 (0.53, 1.40)	0.86 (0.53, 1.41)	0.00 (-0.01,0.00)	
III/IV	539	11	2.0	561	23	4.1	0.0486	2.01 (0.99, 4.08)	2.05 (0.99, 4.25)	0.02 (0.00,0.04)	
Baseline Diabetes Status											0.0907
Diabetic	1471	21	1.4	1465	33	2.3	0.0962	1.58 (0.92, 2.71)	1.59 (0.92, 2.76)	0.01 (0.00,0.02)	
Non-Diabetic	1518	25	1.6	1531	20	1.3	0.4355	0.79 (0.44, 1.42)	0.79 (0.44, 1.43)	0.00 (-0.01,0.01)	

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^ Patients with NYHA class I are counted in subgroup NYHA class II.
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Risk ratios and odds ratios with confidence intervals (CIs) are estimated by Cochran-Mantel-Haenszel method. For risk differences standard Wald asymptotic confidence limits are calculated. A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied in case of any zero cells in contingency table.
Only treatment emergent AEs are displayed (onset between first dose until treatment stop +7 days).
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Table R.1.2.3: 3 Proportion of patients with severe adverse events of special interest and severe other specific AEs by user-defined category overall and by subgroup - TS
User-defined AE category: Sepsis (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 Diabetes Status											0.0217
Diabetic	1471	21	1.4	1465	33	2.3	0.0962	1.58 (0.92, 2.71)	1.59 (0.92, 2.76)	0.01 (0.00,0.02)	
Pre-Diabetes	979	12	1.2	1001	17	1.7	0.3815	1.39 (0.67, 2.89)	1.39 (0.66, 2.93)	0.00 (-0.01,0.02)	
Normal (no pre-diabetes)	539	13	2.4	530	3	0.6	0.0130	0.23 (0.07, 0.82)	0.23 (0.07, 0.81)	-0.02 (-0.03,0.00)	
Baseline BMI [kg/m²]											0.0141
<30	1641	25	1.5	1654	16	1.0	0.1499	0.63 (0.34, 1.18)	0.63 (0.34, 1.19)	-0.01 (-0.01,0.00)	
>=30	1348	21	1.6	1342	37	2.8	0.0323	1.77 (1.04, 3.01)	1.79 (1.04, 3.08)	0.01 (0.00,0.02)	
Baseline eGFR (CKD-EPI) [mL/min/1.73m²]											0.6033
>=60	1505	17	1.1	1493	22	1.5	0.4059	1.30 (0.70, 2.45)	1.31 (0.69, 2.48)	0.00 (0.00,0.01)	
<60	1482	29	2.0	1503	31	2.1	0.8370	1.05 (0.64, 1.74)	1.06 (0.63, 1.76)	0.00 (-0.01,0.01)	
History of HHF (in the last 12 months)											0.0637
No	2320	37	1.6	2297	33	1.4	0.6601	0.90 (0.57, 1.44)	0.90 (0.56, 1.44)	0.00 (-0.01,0.01)	
Yes	669	9	1.3	699	20	2.9	0.0517	2.13 (0.98, 4.64)	2.16 (0.98, 4.78)	0.02 (0.00,0.03)	
Baseline SBP (</>= median)											0.0476
< median	1474	21	1.4	1496	35	2.3	0.0668	1.64 (0.96, 2.81)	1.66 (0.96, 2.86)	0.01 (0.00,0.02)	
>= median	1515	25	1.7	1500	18	1.2	0.2973	0.73 (0.40, 1.33)	0.72 (0.39, 1.33)	0.00 (-0.01,0.00)	
History of atrial fibrillation or atrial flutter											0.8972
No	1426	19	1.3	1417	21	1.5	0.7349	1.11 (0.60, 2.06)	1.11 (0.60, 2.08)	0.00 (-0.01,0.01)	
Yes	1558	27	1.7	1575	32	2.0	0.5385	1.17 (0.71, 1.95)	1.18 (0.70, 1.97)	0.00 (-0.01,0.01)	

Analysis is based on study 1245.110.
^ Patients with NYHA class I are counted in subgroup NYHA class II.
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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 LVEF [%]											0.2395
< 50	988	13	1.3	995	21	2.1	0.1728	1.60 (0.81, 3.19)	1.62 (0.81, 3.25)	0.01 (0.00,0.02)	
>= 50	2001	33	1.6	2001	32	1.6	0.9005	0.97 (0.60, 1.57)	0.97 (0.59, 1.58)	0.00 (-0.01,0.01)	
Baseline LVEF [%]											0.4960
<50	988	13	1.3	995	21	2.1	0.1728	1.60 (0.81, 3.19)	1.62 (0.81, 3.25)	0.01 (0.00,0.02)	
50 to <60	1030	17	1.7	1028	17	1.7	0.9954	1.00 (0.51, 1.95)	1.00 (0.51, 1.97)	0.00 (-0.01,0.01)	
>=60	971	16	1.6	973	15	1.5	0.8518	0.94 (0.47, 1.88)	0.93 (0.46, 1.90)	0.00 (-0.01,0.01)	
Baseline NT-proBNP [pg/mL] (</>=median by atrial fibrillation/flutter status)											0.6574
< median	1507	19	1.3	1476	19	1.3	0.9486	1.02 (0.54, 1.92)	1.02 (0.54, 1.94)	0.00 (-0.01,0.01)	
>= median	1475	27	1.8	1516	34	2.2	0.4252	1.23 (0.74, 2.02)	1.23 (0.74, 2.05)	0.00 (-0.01,0.01)	
Baseline uric acid [mg/dL] (tertiles)											0.6727
<T1	975	13	1.3	963	13	1.3	0.9746	1.01 (0.47, 2.17)	1.01 (0.47, 2.20)	0.00 (-0.01,0.01)	
>=T1 and <T2	966	13	1.3	1032	21	2.0	0.2340	1.51 (0.76, 3.00)	1.52 (0.76, 3.06)	0.01 (0.00,0.02)	
>=T2	1016	19	1.9	970	19	2.0	0.8853	1.05 (0.56, 1.97)	1.05 (0.55, 1.99)	0.00 (-0.01,0.01)	
Baseline use of MRA											0.1726
No	1865	32	1.7	1878	30	1.6	0.7766	0.93 (0.57, 1.53)	0.93 (0.56, 1.54)	0.00 (-0.01,0.01)	
Yes	1124	14	1.2	1118	23	2.1	0.1315	1.65 (0.85, 3.19)	1.67 (0.85, 3.25)	0.01 (0.00,0.02)	
Baseline use of ACE-inhibitor, ARB or ARNi											0.6758
No	586	10	1.7	568	13	2.3	0.4792	1.34 (0.59, 3.03)	1.35 (0.59, 3.10)	0.01 (-0.01,0.02)	
Yes	2403	36	1.5	2428	40	1.6	0.6767	1.10 (0.70, 1.72)	1.10 (0.70, 1.73)	0.00 (-0.01,0.01)	

Analysis is based on study 1245.110.
^ Patients with NYHA class I are counted in subgroup NYHA class II.
*** Confirmed hypoglycaemic AEs are defined by a glucose concentration <=70 mg/dL (3.9 mmol/L) or requiring assistance.
Risk ratios and odds ratios with confidence intervals (CIs) are estimated by Cochran-Mantel-Haenszel method. For risk differences standard Wald asymptotic confidence limits are calculated. A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied in case of any zero cells in contingency table.
Only treatment emergent AEs are displayed (onset between first dose until treatment stop +7 days).
MedDRA version: 23.1. * Chi-square test for treatment effect ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction).

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Table R.1.2.3: 3 Proportion of patients with severe adverse events of special interest and severe other specific AEs by user-defined category overall and by subgroup - TS
User-defined AE category: Sepsis (investigator-defined) with source of infection UTI

Subgroup	Placebo			Empa 10mg			Empa 10mg vs Placebo				
Category	N	n	%	N	n	%	p-value *	Risk ratio (95% CI)	Odds ratio (95% CI)	Risk diff. (95% CI)	p-value **
Overall	2989	11	0.4	2996	12	0.4	0.8389	1.09 (0.48, 2.46)	1.09 (0.48, 2.47)	0.00 (0.00,0.00)	
Sex											0.5360
Male	1653	6	0.4	1658	5	0.3	0.7588	0.83 (0.25, 2.72)	0.83 (0.25, 2.73)	0.00 (0.00,0.00)	
Female	1336	5	0.4	1338	7	0.5	0.5646	1.40 (0.44, 4.39)	1.40 (0.44, 4.42)	0.00 (0.00,0.01)	
Age [years]											0.6714
<70	1084	2	0.2	1066	3	0.3	0.6409	1.53 (0.26, 9.11)	1.53 (0.25, 9.16)	0.00 (0.00,0.01)	
>=70	1905	9	0.5	1930	9	0.5	0.9779	0.99 (0.39, 2.48)	0.99 (0.39, 2.49)	0.00 (0.00,0.00)	
Region											0.4446
North America	359	0	0	359	5	1.4	0.0404	11.00 (0.61,198.20)	11.16 (0.61,202.49)	0.01 (0.00,0.03)	
Latin America	757	2	0.3	758	1	0.1	0.5625	0.50 (0.05, 5.50)	0.50 (0.05, 5.51)	0.00 (-0.01,0.00)	
Europe	1341	6	0.4	1346	5	0.4	0.7578	0.83 (0.25, 2.71)	0.83 (0.25, 2.72)	0.00 (-0.01,0.00)	
Asia	343	1	0.3	343	0	0	0.4789	0.33 (0.01, 8.15)	0.33 (0.01, 8.19)	0.00 (-0.01,0.01)	
Other	189	2	1.1	190	1	0.5	0.5591	0.50 (0.05, 5.44)	0.49 (0.04, 5.50)	-0.01 (-0.02,0.01)	
OECD member											0.2772
No	847	4	0.5	868	2	0.2	0.3964	0.49 (0.09, 2.66)	0.49 (0.09, 2.66)	0.00 (-0.01,0.00)	
Yes	2142	7	0.3	2128	10	0.5	0.4577	1.44 (0.55, 3.77)	1.44 (0.55, 3.79)	0.00 (0.00,0.01)	
Baseline NYHA											0.7908
II^	2450	8	0.3	2435	8	0.3	0.9902	1.01 (0.38, 2.68)	1.01 (0.38, 2.69)	0.00 (0.00,0.00)	
III/IV	539	3	0.6	561	4	0.7	0.7443	1.28 (0.29, 5.70)	1.28 (0.29, 5.76)	0.00 (-0.01,0.01)	
Baseline Diabetes Status											0.8390
Diabetic	1471	6	0.4	1465	6	0.4	0.9943	1.00 (0.32, 3.11)	1.00 (0.32, 3.12)	0.00 (0.00,0.00)	
Non-Diabetic	1518	5	0.3	1531	6	0.4	0.7734	1.19 (0.36, 3.89)	1.19 (0.36, 3.91)	0.00 (0.00,0.00)	

Analysis is based on study 1245.110.
^ Patients with NYHA class I are counted in subgroup NYHA class II.
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MedDRA version: 23.1. * Chi-square test for treatment effect ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction).

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Table R.1.2.3: 3 Proportion of patients with severe adverse events of special interest and severe other specific AEs by user-defined category overall and by subgroup - TS
User-defined AE category: Sepsis (investigator-defined) with source of infection UTI

Subgroup	Placebo			Empa 10mg			Empa 10mg vs Placebo				
Category	N	n	%	N	n	%	p-value *	Risk ratio (95% CI)	Odds ratio (95% CI)	Risk diff. (95% CI)	p-value **
Baseline Diabetes Status											0.9743
Diabetic	1471	6	0.4	1465	6	0.4	0.9943	1.00 (0.32, 3.11)	1.00 (0.32, 3.12)	0.00 (0.00,0.00)	
Pre-Diabetes	979	4	0.4	1001	5	0.5	0.7636	1.22 (0.33, 4.54)	1.22 (0.33, 4.57)	0.00 (-0.01,0.01)	
Normal (no pre-diabetes)	539	1	0.2	530	1	0.2	0.9905	1.02 (0.06, 16.22)	1.02 (0.06, 16.30)	0.00 (-0.01,0.01)	
Baseline BMI [kg/m²]											0.3017
<30	1641	5	0.3	1654	3	0.2	0.4721	0.60 (0.14, 2.49)	0.59 (0.14, 2.49)	0.00 (0.00,0.00)	
>=30	1348	6	0.4	1342	9	0.7	0.4322	1.51 (0.54, 4.22)	1.51 (0.54, 4.25)	0.00 (0.00,0.01)	
Baseline eGFR (CKD-EPI) [mL/min/1.73m²]											0.6769
>=60	1505	2	0.1	1493	3	0.2	0.6480	1.51 (0.25, 9.04)	1.51 (0.25, 9.07)	0.00 (0.00,0.00)	
<60	1482	9	0.6	1503	9	0.6	0.9761	0.99 (0.39, 2.48)	0.99 (0.39, 2.49)	0.00 (-0.01,0.01)	
History of HHF (in the last 12 months)											0.8776
No	2320	6	0.3	2297	6	0.3	0.9862	1.01 (0.33, 3.13)	1.01 (0.33, 3.14)	0.00 (0.00,0.00)	
Yes	669	5	0.7	699	6	0.9	0.8183	1.15 (0.35, 3.75)	1.15 (0.35, 3.79)	0.00 (-0.01,0.01)	
Baseline SBP (</>= median)											0.8041
< median	1474	6	0.4	1496	6	0.4	0.9795	0.99 (0.32, 3.05)	0.99 (0.32, 3.06)	0.00 (0.00,0.00)	
>= median	1515	5	0.3	1500	6	0.4	0.7500	1.21 (0.37, 3.96)	1.21 (0.37, 3.98)	0.00 (0.00,0.01)	
History of atrial fibrillation or atrial flutter											0.1046
No	1426	0	0	1417	4	0.3	0.0723	9.06 (0.49,168.07)	9.08 (0.49,168.86)	0.00 (0.00,0.01)	
Yes	1558	11	0.7	1575	8	0.5	0.4752	0.72 (0.29, 1.78)	0.72 (0.29, 1.79)	0.00 (-0.01,0.00)	

Analysis is based on study 1245.110.
^ Patients with NYHA class I are counted in subgroup NYHA class II.
*** Confirmed hypoglycaemic AEs are defined by a glucose concentration <=70 mg/dL (3.9 mmol/L) or requiring assistance.
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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 LVEF [%]											0.2340
< 50	988	2	0.2	995	5	0.5	0.2599	2.48 (0.48, 12.76)	2.49 (0.48, 12.86)	0.00 (0.00,0.01)	
>= 50	2001	9	0.4	2001	7	0.3	0.6164	0.78 (0.29, 2.08)	0.78 (0.29, 2.09)	0.00 (0.00,0.00)	
Baseline LVEF [%]											
<50	988	2	0.2	995	5	0.5					
50 to <60	1030	5	0.5	1028	2	0.2					
>=60	971	4	0.4	973	5	0.5					
Baseline NT-proBNP [pg/mL] (</>=median by atrial fibrillation/flutter status)											0.2126
< median	1507	2	0.1	1476	5	0.3	0.2449	2.55 (0.50, 13.14)	2.56 (0.50, 13.20)	0.00 (0.00,0.01)	
>= median	1475	9	0.6	1516	7	0.5	0.5780	0.76 (0.28, 2.03)	0.76 (0.28, 2.03)	0.00 (-0.01,0.00)	
Baseline uric acid [mg/dL] (tertiles)											0.3039
<T1	975	1	0.1	963	2	0.2	0.5562	2.02 (0.18, 22.29)	2.03 (0.18, 22.39)	0.00 (0.00,0.00)	
>=T1 and <T2	966	6	0.6	1032	3	0.3	0.2704	0.47 (0.12, 1.87)	0.47 (0.12, 1.87)	0.00 (-0.01,0.00)	
>=T2	1016	4	0.4	970	7	0.7	0.3249	1.83 (0.54, 6.24)	1.84 (0.54, 6.30)	0.00 (0.00,0.01)	
Baseline use of MRA											0.0575
No	1865	9	0.5	1878	5	0.3	0.2783	0.55 (0.19, 1.64)	0.55 (0.18, 1.65)	0.00 (-0.01,0.00)	
Yes	1124	2	0.2	1118	7	0.6	0.0933	3.52 (0.73, 16.90)	3.53 (0.73, 17.05)	0.00 (0.00,0.01)	
Baseline use of ACE-inhibitor, ARB or ARNi											0.7177
No	586	3	0.5	568	4	0.7	0.6741	1.38 (0.31, 6.12)	1.38 (0.31, 6.19)	0.00 (-0.01,0.01)	
Yes	2403	8	0.3	2428	8	0.3	0.9835	0.99 (0.37, 2.63)	0.99 (0.37, 2.64)	0.00 (0.00,0.00)	

Analysis is based on study 1245.110.
^ Patients with NYHA class I are counted in subgroup NYHA class II.
*** Confirmed hypoglycaemic AEs are defined by a glucose concentration <=70 mg/dL (3.9 mmol/L) or requiring assistance.
Risk ratios and odds ratios with confidence intervals (CIs) are estimated by Cochran-Mantel-Haenszel method. For risk differences standard Wald asymptotic confidence limits are calculated. 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: Sepsis (investigator-defined) with source of infection non-UTI or missing

Subgroup	Placebo			Empa 10mg			Empa 10mg vs Placebo					
Category	N	n	%	N	n	%	p-value *	Risk ratio (95% CI)	Odds ratio (95% CI)	Risk diff. (95% CI)	p-value **
Overall	2989	35	1.2	2996	41	1.4	0.4950	1.17 (0.75, 1.83)	1.17 (0.74, 1.84)	0.00 (0.00,0.01)	
Sex											0.1940
Male	1653	27	1.6	1658	26	1.6	0.8811	0.96 (0.56, 1.64)	0.96 (0.56, 1.65)	0.00 (-0.01,0.01)	
Female	1336	8	0.6	1338	15	1.1	0.1437	1.87 (0.80, 4.40)	1.88 (0.80, 4.45)	0.01 (0.00,0.01)	
Age [years]											0.8582
<70	1084	12	1.1	1066	13	1.2	0.8078	1.10 (0.50, 2.40)	1.10 (0.50, 2.43)	0.00 (-0.01,0.01)	
>=70	1905	23	1.2	1930	28	1.5	0.5105	1.20 (0.69, 2.08)	1.20 (0.69, 2.10)	0.00 (0.00,0.01)	
Region											0.8188
North America	359	6	1.7	359	11	3.1	0.2197	1.83 (0.69, 4.90)	1.86 (0.68, 5.08)	0.01 (-0.01,0.04)	
Latin America	757	11	1.5	758	13	1.7	0.6831	1.18 (0.53, 2.62)	1.18 (0.53, 2.66)	0.00 (-0.01,0.02)	
Europe	1341	14	1.0	1346	12	0.9	0.6864	0.85 (0.40, 1.84)	0.85 (0.39, 1.85)	0.00 (-0.01,0.01)	
Asia	343	2	0.6	343	2	0.6	1.0000	1.00 (0.14, 7.06)	1.00 (0.14, 7.14)	0.00 (-0.01,0.01)	
Other	189	2	1.1	190	3	1.6	0.6569	1.49 (0.25, 8.83)	1.50 (0.25, 9.08)	0.01 (-0.02,0.03)	
OECD member											0.8498
No	847	11	1.3	868	14	1.6	0.5873	1.24 (0.57, 2.72)	1.25 (0.56, 2.76)	0.00 (-0.01,0.01)	
Yes	2142	24	1.1	2128	27	1.3	0.6555	1.13 (0.66, 1.96)	1.13 (0.65, 1.97)	0.00 (-0.01,0.01)	
Baseline NYHA											0.0429
II^	2450	27	1.1	2435	22	0.9	0.4862	0.82 (0.47, 1.44)	0.82 (0.46, 1.44)	0.00 (-0.01,0.00)	
III/IV	539	8	1.5	561	19	3.4	0.0415	2.28 (1.01, 5.17)	2.33 (1.01, 5.36)	0.02 (0.00,0.04)	
Baseline Diabetes Status											0.0424
Diabetic	1471	15	1.0	1465	27	1.8	0.0603	1.81 (0.97, 3.38)	1.82 (0.97, 3.44)	0.01 (0.00,0.02)	
Non-Diabetic	1518	20	1.3	1531	14	0.9	0.2892	0.69 (0.35, 1.37)	0.69 (0.35, 1.37)	0.00 (-0.01,0.00)	

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^ Patients with NYHA class I are counted in subgroup NYHA class II.
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Risk ratios and odds ratios with confidence intervals (CIs) are estimated by Cochran-Mantel-Haenszel method. For risk differences standard Wald asymptotic confidence limits are calculated. A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
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Table R.1.2.3: 3 Proportion of patients with severe adverse events of special interest and severe other specific AEs by user-defined category overall and by subgroup - TS
User-defined AE category: Sepsis (investigator-defined) with source of infection non-UTI or missing

Subgroup	Placebo			Empa 10mg			Empa 10mg vs Placebo				
Category	N	n	%	N	n	%	p-value *	Risk ratio (95% CI)	Odds ratio (95% CI)	Risk diff. (95% CI)	p-value **
Baseline Diabetes Status											0.0159
Diabetic	1471	15	1.0	1465	27	1.8	0.0603	1.81 (0.97, 3.38)	1.82 (0.97, 3.44)	0.01 (0.00,0.02)	
Pre-Diabetes	979	8	0.8	1001	12	1.2	0.3958	1.47 (0.60, 3.57)	1.47 (0.60, 3.62)	0.00 (0.00,0.01)	
Normal (no pre-diabetes)	539	12	2.2	530	2	0.4	0.0078	0.17 (0.04, 0.75)	0.17 (0.04, 0.75)	-0.02 (-0.03,0.00)	
Baseline BMI [kg/m²]											0.0250
<30	1641	20	1.2	1654	13	0.8	0.2122	0.64 (0.32, 1.29)	0.64 (0.32, 1.30)	0.00 (-0.01,0.00)	
>=30	1348	15	1.1	1342	28	2.1	0.0441	1.88 (1.01, 3.49)	1.89 (1.01, 3.56)	0.01 (0.00,0.02)	
Baseline eGFR (CKD-EPI) [mL/min/1.73m²]											0.7231
>=60	1505	15	1.0	1493	19	1.3	0.4756	1.28 (0.65, 2.50)	1.28 (0.65, 2.53)	0.00 (0.00,0.01)	
<60	1482	20	1.3	1503	22	1.5	0.7911	1.08 (0.59, 1.98)	1.09 (0.59, 2.00)	0.00 (-0.01,0.01)	
History of HHF (in the last 12 months)											0.0316
No	2320	31	1.3	2297	27	1.2	0.6239	0.88 (0.53, 1.47)	0.88 (0.52, 1.48)	0.00 (-0.01,0.00)	
Yes	669	4	0.6	699	14	2.0	0.0226	3.35 (1.11, 10.13)	3.40 (1.11, 10.38)	0.01 (0.00,0.03)	
Baseline SBP (</>= median)											0.0174
< median	1474	15	1.0	1496	29	1.9	0.0378	1.90 (1.03, 3.54)	1.92 (1.03, 3.60)	0.01 (0.00,0.02)	
>= median	1515	20	1.3	1500	12	0.8	0.1635	0.61 (0.30, 1.24)	0.60 (0.29, 1.24)	-0.01 (-0.01,0.00)	
History of atrial fibrillation or atrial flutter											0.2790
No	1426	19	1.3	1417	17	1.2	0.7517	0.90 (0.47, 1.73)	0.90 (0.47, 1.74)	0.00 (-0.01,0.01)	
Yes	1558	16	1.0	1575	24	1.5	0.2155	1.48 (0.79, 2.78)	1.49 (0.79, 2.82)	0.00 (0.00,0.01)	

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^ Patients with NYHA class I are counted in subgroup NYHA class II.
*** Confirmed hypoglycaemic AEs are defined by a glucose concentration <=70 mg/dL (3.9 mmol/L) or requiring assistance.
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User-defined AE category: Sepsis (investigator-defined) with source of infection non-UTI or missing

Subgroup	Placebo			Empa 10mg			Empa 10mg vs Placebo						
Category	N	n	%	N	n	%	p-value *	Risk ratio (95% CI)		Odds ratio (95% CI)		Risk diff. (95% CI)	p-value **
Baseline LVEF [%]													0.4975
< 50	988	11	1.1	995	16	1.6	0.3419	1.44 (0.67,	3.10)	1.45 (0.67,	3.14)	0.00 (-0.01,0.02)	
>= 50	2001	24	1.2	2001	25	1.2	0.8857	1.04 (0.60,	1.82)	1.04 (0.59,	1.83)	0.00 (-0.01,0.01)	
Baseline LVEF [%]													0.6166
<50	988	11	1.1	995	16	1.6	0.3419	1.44 (0.67,	3.10)	1.45 (0.67,	3.14)	0.00 (-0.01,0.02)	
50 to <60	1030	12	1.2	1028	15	1.5	0.5577	1.25 (0.59,	2.66)	1.26 (0.59,	2.70)	0.00 (-0.01,0.01)	
>=60	971	12	1.2	973	10	1.0	0.6645	0.83 (0.36,	1.92)	0.83 (0.36,	1.93)	0.00 (-0.01,0.01)	
Baseline NT-proBNP [pg/mL] (</>=median by atrial fibrillation/flutter status)													0.2399
< median	1507	17	1.1	1476	14	0.9	0.6287	0.84 (0.42,	1.70)	0.84 (0.41,	1.71)	0.00 (-0.01,0.01)	
>= median	1475	18	1.2	1516	27	1.8	0.2079	1.46 (0.81,	2.64)	1.47 (0.80,	2.68)	0.01 (0.00,0.01)	
Baseline uric acid [mg/dL] (tertiles)													0.1562
<T1	975	12	1.2	963	11	1.1	0.8572	0.93 (0.41,	2.09)	0.93 (0.41,	2.11)	0.00 (-0.01,0.01)	
>=T1 and <T2	966	7	0.7	1032	18	1.7	0.0405	2.41 (1.01,	5.74)	2.43 (1.01,	5.85)	0.01 (0.00,0.02)	
>=T2	1016	15	1.5	970	12	1.2	0.6453	0.84 (0.39,	1.78)	0.84 (0.39,	1.80)	0.00 (-0.01,0.01)	
Baseline use of MRA													0.6490
No	1865	23	1.2	1878	25	1.3	0.7900	1.08 (0.61,	1.89)	1.08 (0.61,	1.91)	0.00 (-0.01,0.01)	
Yes	1124	12	1.1	1118	16	1.4	0.4384	1.34 (0.64,	2.82)	1.35 (0.63,	2.86)	0.00 (-0.01,0.01)	
Baseline use of ACE-inhibitor, ARB or ARNi													0.7771
No	586	7	1.2	568	9	1.6	0.5711	1.33 (0.50,	3.54)	1.33 (0.49,	3.60)	0.00 (-0.01,0.02)	
Yes	2403	28	1.2	2428	32	1.3	0.6317	1.13 (0.68,	1.87)	1.13 (0.68,	1.89)	0.00 (0.00,0.01)	

Analysis is based on study 1245.110.
^ Patients with NYHA class I are counted in subgroup NYHA class II.
*** Confirmed hypoglycaemic AEs are defined by a glucose concentration <=70 mg/dL (3.9 mmol/L) or requiring assistance.
Risk ratios and odds ratios with confidence intervals (CIs) are estimated by Cochran-Mantel-Haenszel method. For risk differences standard Wald asymptotic confidence limits are calculated. A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied in case of any zero cells in contingency table.
Only treatment emergent AEs are displayed (onset between first dose until treatment stop +7 days).
MedDRA version: 23.1. * Chi-square test for treatment effect ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction).

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Table R.1.2.3: 3 Proportion of patients with severe adverse events of special interest and severe other specific AEs by user-defined category overall and by subgroup - TS
User-defined AE category: Bone fracture (narrow 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	2989	29	1.0	2996	32	1.1	0.7062	1.10 (0.67, 1.81)	1.10 (0.66, 1.83)	0.00 (0.00,0.01)	
Sex											0.9101
Male	1653	14	0.8	1658	15	0.9	0.8585	1.07 (0.52, 2.21)	1.07 (0.51, 2.22)	0.00 (-0.01,0.01)	
Female	1336	15	1.1	1338	17	1.3	0.7253	1.13 (0.57, 2.26)	1.13 (0.56, 2.28)	0.00 (-0.01,0.01)	
Age [years]											0.8441
<70	1084	9	0.8	1066	9	0.8	0.9715	1.02 (0.41, 2.55)	1.02 (0.40, 2.57)	0.00 (-0.01,0.01)	
>=70	1905	20	1.0	1930	23	1.2	0.6766	1.14 (0.63, 2.06)	1.14 (0.62, 2.08)	0.00 (-0.01,0.01)	
Region											0.6184
North America	359	8	2.2	359	4	1.1	0.2442	0.50 (0.15, 1.65)	0.49 (0.15, 1.66)	-0.01 (-0.03,0.01)	
Latin America	757	5	0.7	758	5	0.7	0.9983	1.00 (0.29, 3.44)	1.00 (0.29, 3.46)	0.00 (-0.01,0.01)	
Europe	1341	9	0.7	1346	12	0.9	0.5166	1.33 (0.56, 3.14)	1.33 (0.56, 3.17)	0.00 (0.00,0.01)	
Asia	343	3	0.9	343	6	1.7	0.3141	2.00 (0.50, 7.93)	2.02 (0.50, 8.13)	0.01 (-0.01,0.03)	
Other	189	4	2.1	190	5	2.6	0.7419	1.24 (0.34, 4.56)	1.25 (0.33, 4.73)	0.01 (-0.03,0.04)	
OECD member											0.2379
No	847	8	0.9	868	5	0.6	0.3791	0.61 (0.20, 1.86)	0.61 (0.20, 1.86)	0.00 (-0.01,0.00)	
Yes	2142	21	1.0	2128	27	1.3	0.3714	1.29 (0.73, 2.28)	1.30 (0.73, 2.30)	0.00 (0.00,0.01)	
Baseline NYHA											0.5559
II^	2450	22	0.9	2435	26	1.1	0.5474	1.19 (0.68, 2.09)	1.19 (0.67, 2.11)	0.00 (0.00,0.01)	
III/IV	539	7	1.3	561	6	1.1	0.7251	0.82 (0.28, 2.43)	0.82 (0.27, 2.46)	0.00 (-0.02,0.01)	
Baseline Diabetes Status											0.2245
Diabetic	1471	11	0.7	1465	17	1.2	0.2501	1.55 (0.73, 3.30)	1.56 (0.73, 3.34)	0.00 (0.00,0.01)	
Non-Diabetic	1518	18	1.2	1531	15	1.0	0.5825	0.83 (0.42, 1.63)	0.82 (0.41, 1.64)	0.00 (-0.01,0.01)	

Analysis is based on study 1245.110.
^ Patients with NYHA class I are counted in subgroup NYHA class II.
*** Confirmed hypoglycaemic AEs are defined by a glucose concentration <=70 mg/dL (3.9 mmol/L) or requiring assistance.
Risk ratios and odds ratios with confidence intervals (CIs) are estimated by Cochran-Mantel-Haenszel method. For risk differences standard Wald asymptotic confidence limits are calculated. A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied in case of any zero cells in contingency table.
Only treatment emergent AEs are displayed (onset between first dose until treatment stop +7 days).
MedDRA version: 23.1. * Chi-square test for treatment effect ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction).

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Table R.1.2.3: 3 Proportion of patients with severe adverse events of special interest and severe other specific AEs by user-defined category overall and by subgroup - TS
User-defined AE category: Bone fracture (narrow 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 Diabetes Status											0.4721
Diabetic	1471	11	0.7	1465	17	1.2	0.2501	1.55 (0.73, 3.30)	1.56 (0.73, 3.34)	0.00 (0.00,0.01)	
Pre-Diabetes	979	10	1.0	1001	9	0.9	0.7801	0.88 (0.36, 2.16)	0.88 (0.36, 2.17)	0.00 (-0.01,0.01)	
Normal (no pre-diabetes)	539	8	1.5	530	6	1.1	0.6126	0.76 (0.27, 2.18)	0.76 (0.26, 2.21)	0.00 (-0.02,0.01)	
Baseline BMI [kg/m²]											0.4439
<30	1641	19	1.2	1654	18	1.1	0.8497	0.94 (0.50, 1.78)	0.94 (0.49, 1.80)	0.00 (-0.01,0.01)	
>=30	1348	10	0.7	1342	14	1.0	0.4059	1.41 (0.63, 3.15)	1.41 (0.62, 3.19)	0.00 (0.00,0.01)	
Baseline eGFR (CKD-EPI) [mL/min/1.73m²]											0.9468
>=60	1505	14	0.9	1493	15	1.0	0.8350	1.08 (0.52, 2.23)	1.08 (0.52, 2.25)	0.00 (-0.01,0.01)	
<60	1482	15	1.0	1503	17	1.1	0.7524	1.12 (0.56, 2.23)	1.12 (0.56, 2.25)	0.00 (-0.01,0.01)	
History of HHF (in the last 12 months)											0.3640
No	2320	21	0.9	2297	26	1.1	0.4428	1.25 (0.71, 2.22)	1.25 (0.70, 2.23)	0.00 (0.00,0.01)	
Yes	669	8	1.2	699	6	0.9	0.5353	0.72 (0.25, 2.06)	0.72 (0.25, 2.07)	0.00 (-0.01,0.01)	
Baseline SBP (</>= median)											0.9706
< median	1474	16	1.1	1496	18	1.2	0.7630	1.11 (0.57, 2.17)	1.11 (0.56, 2.18)	0.00 (-0.01,0.01)	
>= median	1515	13	0.9	1500	14	0.9	0.8264	1.09 (0.51, 2.31)	1.09 (0.51, 2.32)	0.00 (-0.01,0.01)	
History of atrial fibrillation or atrial flutter											0.2246
No	1426	6	0.4	1417	11	0.8	0.2189	1.84 (0.68, 4.98)	1.85 (0.68, 5.02)	0.00 (0.00,0.01)	
Yes	1558	23	1.5	1575	21	1.3	0.7339	0.90 (0.50, 1.63)	0.90 (0.50, 1.64)	0.00 (-0.01,0.01)	

Analysis is based on study 1245.110.
^ Patients with NYHA class I are counted in subgroup NYHA class II.
*** Confirmed hypoglycaemic AEs are defined by a glucose concentration <=70 mg/dL (3.9 mmol/L) or requiring assistance.
Risk ratios and odds ratios with confidence intervals (CIs) are estimated by Cochran-Mantel-Haenszel method. For risk differences standard Wald asymptotic confidence limits are calculated. A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied in case of any zero cells in contingency table.
Only treatment emergent AEs are displayed (onset between first dose until treatment stop +7 days).
MedDRA version: 23.1. * Chi-square test for treatment effect ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction).

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Table R.1.2.3: 3 Proportion of patients with severe adverse events of special interest and severe other specific AEs by user-defined category overall and by subgroup - TS
User-defined AE category: Bone fracture (narrow 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 LVEF [%]											0.6970
< 50	988	6	0.6	995	8	0.8	0.6009	1.32 (0.46, 3.80)	1.33 (0.46, 3.84)	0.00 (-0.01,0.01)	
>= 50	2001	23	1.1	2001	24	1.2	0.8833	1.04 (0.59, 1.84)	1.04 (0.59, 1.86)	0.00 (-0.01,0.01)	
Baseline LVEF [%]											0.8282
<50	988	6	0.6	995	8	0.8	0.6009	1.32 (0.46, 3.80)	1.33 (0.46, 3.84)	0.00 (-0.01,0.01)	
50 to <60	1030	9	0.9	1028	11	1.1	0.6500	1.22 (0.51, 2.94)	1.23 (0.51, 2.97)	0.00 (-0.01,0.01)	
>=60	971	14	1.4	973	13	1.3	0.8421	0.93 (0.44, 1.96)	0.93 (0.43, 1.98)	0.00 (-0.01,0.01)	
Baseline NT-proBNP [pg/mL] (</>=median by atrial fibrillation/flutter status)											0.2818
< median	1507	10	0.7	1476	15	1.0	0.2908	1.53 (0.69, 3.40)	1.54 (0.69, 3.43)	0.00 (0.00,0.01)	
>= median	1475	19	1.3	1516	17	1.1	0.6758	0.87 (0.45, 1.67)	0.87 (0.45, 1.68)	0.00 (-0.01,0.01)	
Baseline uric acid [mg/dL] (tertiles)											0.8637
<T1	975	10	1.0	963	9	0.9	0.8388	0.91 (0.37, 2.23)	0.91 (0.37, 2.25)	0.00 (-0.01,0.01)	
>=T1 and <T2	966	8	0.8	1032	11	1.1	0.5843	1.29 (0.52, 3.19)	1.29 (0.52, 3.22)	0.00 (-0.01,0.01)	
>=T2	1016	11	1.1	970	12	1.2	0.7478	1.14 (0.51, 2.58)	1.14 (0.50, 2.61)	0.00 (-0.01,0.01)	
Baseline use of MRA											0.2844
No	1865	16	0.9	1878	22	1.2	0.3387	1.37 (0.72, 2.59)	1.37 (0.72, 2.62)	0.00 (0.00,0.01)	
Yes	1124	13	1.2	1118	10	0.9	0.5380	0.77 (0.34, 1.76)	0.77 (0.34, 1.77)	0.00 (-0.01,0.01)	
Baseline use of ACE-inhibitor, ARB or ARNi											0.5411
No	586	9	1.5	568	12	2.1	0.4636	1.38 (0.58, 3.24)	1.38 (0.58, 3.31)	0.01 (-0.01,0.02)	
Yes	2403	20	0.8	2428	20	0.8	0.9738	0.99 (0.53, 1.83)	0.99 (0.53, 1.84)	0.00 (-0.01,0.01)	

Analysis is based on study 1245.110.
^ Patients with NYHA class I are counted in subgroup NYHA class II.
*** Confirmed hypoglycaemic AEs are defined by a glucose concentration <=70 mg/dL (3.9 mmol/L) or requiring assistance.
Risk ratios and odds ratios with confidence intervals (CIs) are estimated by Cochran-Mantel-Haenszel method. For risk differences standard Wald asymptotic confidence limits are calculated. A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied in case of any zero cells in contingency table.
Only treatment emergent AEs are displayed (onset between first dose until treatment stop +7 days).
MedDRA version: 23.1. * Chi-square test for treatment effect ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction).

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Table R.1.2.3: 3 Proportion of patients with severe adverse events of special interest and severe other specific AEs by user-defined category overall and by subgroup - TS
User-defined AE category: Urinary tract malignancies (broad Sub BIcMQs)

Subgroup	Placebo			Empa 10mg			Empa 10mg vs Placebo				
Category	N	n	%	N	n	%	p-value *	Risk ratio (95% CI)	Odds ratio (95% CI)	Risk diff. (95% CI)	p-value **
Overall	2989	3	0.1	2996	7	0.2	0.2069	2.33 (0.60, 8.99)	2.33 (0.60, 9.02)	0.00 (0.00,0.00)	
Sex											
Male	1653	3	0.2	1658	5	0.3					
Female	1336	0	0	1338	2	0.1					
Age [years]											
<70	1084	1	0.1	1066	3	0.3					
>=70	1905	2	0.1	1930	4	0.2					
Region											
North America	359	0	0	359	0	0					
Latin America	757	1	0.1	758	2	0.3					
Europe	1341	2	0.1	1346	3	0.2					
Asia	343	0	0	343	2	0.6					
Other	189	0	0	190	0	0					
OECD member											
No	847	1	0.1	868	2	0.2					
Yes	2142	2	0.1	2128	5	0.2					
Baseline NYHA											0.6727
II^	2450	3	0.1	2435	7	0.3	0.2020	2.35 (0.61, 9.07)	2.35 (0.61, 9.10)	0.00 (0.00,0.00)	
III/IV	539	0	0	561	0	0	0.9841	0.96 (0.02, 48.34)	0.96 (0.02, 48.51)	0.00 (0.00,0.00)	
Baseline Diabetes Status											
Diabetic	1471	3	0.2	1465	3	0.2					
Non-Diabetic	1518	0	0	1531	4	0.3					

Analysis is based on study 1245.110.
^ Patients with NYHA class I are counted in subgroup NYHA class II.
*** Confirmed hypoglycaemic AEs are defined by a glucose concentration <=70 mg/dL (3.9 mmol/L) or requiring assistance.
Risk ratios and odds ratios with confidence intervals (CIs) are estimated by Cochran-Mantel-Haenszel method. For risk differences standard Wald asymptotic confidence limits are calculated. A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied in case of any zero cells in contingency table.
Only treatment emergent AEs are displayed (onset between first dose until treatment stop +7 days).
MedDRA version: 23.1. * Chi-square test for treatment effect ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction).

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Table R.1.2.3: 3 Proportion of patients with severe adverse events of special interest and severe other specific AEs by user-defined category overall and by subgroup - TS
User-defined AE category: Urinary tract malignancies (broad Sub BIcMQs)

Subgroup	Placebo			Empa 10mg			Empa 10mg vs Placebo				
Category	N	n	%	N	n	%	p-value *	Risk ratio (95% CI)	Odds ratio (95% CI)	Risk diff. (95% CI)	p-value **
Baseline Diabetes Status											
Diabetic	1471	3	0.2	1465	3	0.2					
Pre-Diabetes	979	0	0	1001	2	0.2					
Normal (no pre-diabetes)	539	0	0	530	2	0.4					
Baseline BMI [kg/m²]											
<30	1641	1	0.1	1654	3	0.2					
>=30	1348	2	0.1	1342	4	0.3					
Baseline eGFR (CKD-EPI) [mL/min/1.73m²]											
>=60	1505	1	0.1	1493	4	0.3					
<60	1482	2	0.1	1503	3	0.2					
History of HHF (in the last 12 months)											
No	2320	3	0.1	2297	6	0.3					
Yes	669	0	0	699	1	0.1					
Baseline SBP (</>= median)											
< median	1474	1	0.1	1496	4	0.3					
>= median	1515	2	0.1	1500	3	0.2					
History of atrial fibrillation or atrial flutter											
No	1426	1	0.1	1417	3	0.2					
Yes	1558	2	0.1	1575	4	0.3					

Analysis is based on study 1245.110.
^ Patients with NYHA class I are counted in subgroup NYHA class II.
*** Confirmed hypoglycaemic AEs are defined by a glucose concentration <=70 mg/dL (3.9 mmol/L) or requiring assistance.
Risk ratios and odds ratios with confidence intervals (CIs) are estimated by Cochran-Mantel-Haenszel method. For risk differences standard Wald asymptotic confidence limits are calculated. A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied in case of any zero cells in contingency table.
Only treatment emergent AEs are displayed (onset between first dose until treatment stop +7 days).
MedDRA version: 23.1. * Chi-square test for treatment effect ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction).

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Table R.1.2.3: 3 Proportion of patients with severe adverse events of special interest and severe other specific AEs by user-defined category overall and by subgroup - TS
User-defined AE category: Urinary tract malignancies (broad Sub BIcMQs)

Subgroup	Placebo			Empa 10mg			Empa 10mg vs Placebo				
Category	N	n	%	N	n	%	p-value *	Risk ratio (95% CI)	Odds ratio (95% CI)	Risk diff. (95% CI)	p-value **
Baseline LVEF [%]											
< 50	988	2	0.2	995	3	0.3					
>= 50	2001	1	<0.1	2001	4	0.2					
Baseline LVEF [%]											
<50	988	2	0.2	995	3	0.3					
50 to <60	1030	0	0	1028	2	0.2					
>=60	971	1	0.1	973	2	0.2					
Baseline NT-proBNP [pg/mL] (</>=median by atrial fibrillation/flutter status)											
< median	1507	2	0.1	1476	5	0.3					
>= median	1475	1	0.1	1516	2	0.1					
Baseline uric acid [mg/dL] (tertiles)											
<T1	975	1	0.1	963	4	0.4					
>=T1 and <T2	966	1	0.1	1032	1	0.1					
>=T2	1016	1	0.1	970	2	0.2					
Baseline use of MRA											
No	1865	1	0.1	1878	5	0.3					
Yes	1124	2	0.2	1118	2	0.2					
Baseline use of ACE-inhibitor, ARB or ARNi											
No	586	1	0.2	568	2	0.4					
Yes	2403	2	0.1	2428	5	0.2					

Analysis is based on study 1245.110.
^ Patients with NYHA class I are counted in subgroup NYHA class II.
*** Confirmed hypoglycaemic AEs are defined by a glucose concentration <=70 mg/dL (3.9 mmol/L) or requiring assistance.
Risk ratios and odds ratios with confidence intervals (CIs) are estimated by Cochran-Mantel-Haenszel method. For risk differences standard Wald asymptotic confidence limits are calculated. A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied in case of any zero cells in contingency table.
Only treatment emergent AEs are displayed (onset between first dose until treatment stop +7 days).
MedDRA version: 23.1. * Chi-square test for treatment effect ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction).

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Table R.1.2.3: 3 Proportion of patients with severe adverse events of special interest and severe other specific AEs by user-defined category overall and by subgroup - TS
User-defined AE category: Volume depletion (narrow 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	2989	28	0.9	2996	43	1.4	0.0749	1.53 (0.95, 2.46)	1.54 (0.95, 2.49)	0.00 (0.00,0.01)	
Sex											0.8619
Male	1653	17	1.0	1658	27	1.6	0.1317	1.58 (0.87, 2.89)	1.59 (0.87, 2.93)	0.01 (0.00,0.01)	
Female	1336	11	0.8	1338	16	1.2	0.3354	1.45 (0.68, 3.12)	1.46 (0.67, 3.15)	0.00 (0.00,0.01)	
Age [years]											0.5389
<70	1084	8	0.7	1066	15	1.4	0.1316	1.91 (0.81, 4.48)	1.92 (0.81, 4.55)	0.01 (0.00,0.02)	
>=70	1905	20	1.0	1930	28	1.5	0.2642	1.38 (0.78, 2.44)	1.39 (0.78, 2.47)	0.00 (0.00,0.01)	
Region											0.3965
North America	359	7	1.9	359	17	4.7	0.0379	2.43 (1.02, 5.78)	2.50 (1.02, 6.10)	0.03 (0.00,0.05)	
Latin America	757	4	0.5	758	8	1.1	0.2473	2.00 (0.60, 6.60)	2.01 (0.60, 6.70)	0.01 (0.00,0.01)	
Europe	1341	11	0.8	1346	11	0.8	0.9930	1.00 (0.43, 2.29)	1.00 (0.43, 2.31)	0.00 (-0.01,0.01)	
Asia	343	2	0.6	343	0	0	0.2472	0.20 (<0.01, 4.15)	0.20 (<0.01, 4.16)	-0.01 (-0.02,0.00)	
Other	189	4	2.1	190	7	3.7	0.3633	1.74 (0.52, 5.85)	1.77 (0.51, 6.15)	0.02 (-0.02,0.05)	
OECD member											0.2658
No	847	5	0.6	868	13	1.5	0.0653	2.54 (0.91, 7.09)	2.56 (0.91, 7.21)	0.01 (0.00,0.02)	
Yes	2142	23	1.1	2128	30	1.4	0.3214	1.31 (0.77, 2.25)	1.32 (0.76, 2.28)	0.00 (0.00,0.01)	
Baseline NYHA											0.1220
II^	2450	21	0.9	2435	24	1.0	0.6384	1.15 (0.64, 2.06)	1.15 (0.64, 2.07)	0.00 (0.00,0.01)	
III/IV	539	7	1.3	561	19	3.4	0.0227	2.61 (1.11, 6.15)	2.66 (1.11, 6.39)	0.02 (0.00,0.04)	
Baseline Diabetes Status											0.1213
Diabetic	1471	19	1.3	1465	21	1.4	0.7403	1.11 (0.60, 2.06)	1.11 (0.59, 2.08)	0.00 (-0.01,0.01)	
Non-Diabetic	1518	9	0.6	1531	22	1.4	0.0202	2.42 (1.12, 5.25)	2.44 (1.12, 5.33)	0.01 (0.00,0.02)	

Analysis is based on study 1245.110.
^ Patients with NYHA class I are counted in subgroup NYHA class II.
*** Confirmed hypoglycaemic AEs are defined by a glucose concentration <=70 mg/dL (3.9 mmol/L) or requiring assistance.
Risk ratios and odds ratios with confidence intervals (CIs) are estimated by Cochran-Mantel-Haenszel method. For risk differences standard Wald asymptotic confidence limits are calculated. A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied in case of any zero cells in contingency table.
Only treatment emergent AEs are displayed (onset between first dose until treatment stop +7 days).
MedDRA version: 23.1. * Chi-square test for treatment effect ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction).

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Table R.1.2.3: 3 Proportion of patients with severe adverse events of special interest and severe other specific AEs by user-defined category overall and by subgroup - TS
User-defined AE category: Volume depletion (narrow 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 Diabetes Status											0.0476
Diabetic	1471	19	1.3	1465	21	1.4	0.7403	1.11 (0.60, 2.06)	1.11 (0.59, 2.08)	0.00 (-0.01,0.01)	
Pre-Diabetes	979	3	0.3	1001	17	1.7	0.0020	5.54 (1.63, 18.85)	5.62 (1.64, 19.24)	0.01 (0.01,0.02)	
Normal (no pre-diabetes)	539	6	1.1	530	5	0.9	0.7833	0.85 (0.26, 2.76)	0.85 (0.26, 2.79)	0.00 (-0.01,0.01)	
Baseline BMI [kg/m²]											0.3800
<30	1641	10	0.6	1654	20	1.2	0.0699	1.98 (0.93, 4.23)	2.00 (0.93, 4.28)	0.01 (0.00,0.01)	
>=30	1348	18	1.3	1342	23	1.7	0.4230	1.28 (0.70, 2.37)	1.29 (0.69, 2.40)	0.00 (-0.01,0.01)	
Baseline eGFR (CKD-EPI) [mL/min/1.73m²]											0.2394
>=60	1505	11	0.7	1493	11	0.7	0.9850	1.01 (0.44, 2.32)	1.01 (0.44, 2.33)	0.00 (-0.01,0.01)	
<60	1482	17	1.1	1503	32	2.1	0.0348	1.86 (1.04, 3.33)	1.87 (1.04, 3.39)	0.01 (0.00,0.02)	
History of HHF (in the last 12 months)											0.3077
No	2320	18	0.8	2297	32	1.4	0.0427	1.80 (1.01, 3.19)	1.81 (1.01, 3.23)	0.01 (0.00,0.01)	
Yes	669	10	1.5	699	11	1.6	0.9055	1.05 (0.45, 2.46)	1.05 (0.44, 2.50)	0.00 (-0.01,0.01)	
Baseline SBP (</>= median)											0.3012
< median	1474	17	1.2	1496	21	1.4	0.5438	1.22 (0.64, 2.30)	1.22 (0.64, 2.32)	0.00 (-0.01,0.01)	
>= median	1515	11	0.7	1500	22	1.5	0.0507	2.02 (0.98, 4.15)	2.04 (0.98, 4.21)	0.01 (0.00,0.01)	
History of atrial fibrillation or atrial flutter											0.6521
No	1426	10	0.7	1417	13	0.9	0.5200	1.31 (0.58, 2.97)	1.31 (0.57, 3.00)	0.00 (0.00,0.01)	
Yes	1558	18	1.2	1575	30	1.9	0.0877	1.65 (0.92, 2.95)	1.66 (0.92, 2.99)	0.01 (0.00,0.02)	

Analysis is based on study 1245.110.
^ Patients with NYHA class I are counted in subgroup NYHA class II.
*** Confirmed hypoglycaemic AEs are defined by a glucose concentration <=70 mg/dL (3.9 mmol/L) or requiring assistance.
Risk ratios and odds ratios with confidence intervals (CIs) are estimated by Cochran-Mantel-Haenszel method. For risk differences standard Wald asymptotic confidence limits are calculated. A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied in case of any zero cells in contingency table.
Only treatment emergent AEs are displayed (onset between first dose until treatment stop +7 days).
MedDRA version: 23.1. * Chi-square test for treatment effect ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction).

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Table R.1.2.3: 3 Proportion of patients with severe adverse events of special interest and severe other specific AEs by user-defined category overall and by subgroup - TS
User-defined AE category: Volume depletion (narrow 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 LVEF [%]											0.2115
< 50	988	7	0.7	995	17	1.7	0.0417	2.41 (1.00, 5.79)	2.44 (1.01, 5.90)	0.01 (0.00,0.02)	
>= 50	2001	21	1.0	2001	26	1.3	0.4632	1.24 (0.70, 2.19)	1.24 (0.70, 2.21)	0.00 (0.00,0.01)	
Baseline LVEF [%]											0.0240
<50	988	7	0.7	995	17	1.7	0.0417	2.41 (1.00, 5.79)	2.44 (1.01, 5.90)	0.01 (0.00,0.02)	
50 to <60	1030	4	0.4	1028	14	1.4	0.0177	3.51 (1.16, 10.62)	3.54 (1.16, 10.80)	0.01 (0.00,0.02)	
>=60	971	17	1.8	973	12	1.2	0.3467	0.70 (0.34, 1.47)	0.70 (0.33, 1.48)	-0.01 (-0.02,0.01)	
Baseline NT-proBNP [pg/mL] (</>=median by atrial fibrillation/flutter status)											0.3802
< median	1507	13	0.9	1476	15	1.0	0.6635	1.18 (0.56, 2.47)	1.18 (0.56, 2.49)	0.00 (-0.01,0.01)	
>= median	1475	15	1.0	1516	28	1.8	0.0566	1.82 (0.97, 3.39)	1.83 (0.97, 3.44)	0.01 (0.00,0.02)	
Baseline uric acid [mg/dL] (tertiles)											0.1392
<T1	975	4	0.4	963	13	1.3	0.0265	3.29 (1.08, 10.06)	3.32 (1.08, 10.22)	0.01 (0.00,0.02)	
>=T1 and <T2	966	12	1.2	1032	11	1.1	0.7119	0.86 (0.38, 1.94)	0.86 (0.38, 1.95)	0.00 (-0.01,0.01)	
>=T2	1016	11	1.1	970	19	2.0	0.1096	1.81 (0.87, 3.78)	1.83 (0.86, 3.86)	0.01 (0.00,0.02)	
Baseline use of MRA											0.5128
No	1865	16	0.9	1878	28	1.5	0.0724	1.74 (0.94, 3.20)	1.75 (0.94, 3.24)	0.01 (0.00,0.01)	
Yes	1124	12	1.1	1118	15	1.3	0.5519	1.26 (0.59, 2.67)	1.26 (0.59, 2.70)	0.00 (-0.01,0.01)	
Baseline use of ACE-inhibitor, ARB or ARNi											0.7280
No	586	7	1.2	568	12	2.1	0.2204	1.77 (0.70, 4.46)	1.79 (0.70, 4.57)	0.01 (-0.01,0.02)	
Yes	2403	21	0.9	2428	31	1.3	0.1749	1.46 (0.84, 2.53)	1.47 (0.84, 2.56)	0.00 (0.00,0.01)	

Analysis is based on study 1245.110.
^ Patients with NYHA class I are counted in subgroup NYHA class II.
*** Confirmed hypoglycaemic AEs are defined by a glucose concentration <=70 mg/dL (3.9 mmol/L) or requiring assistance.
Risk ratios and odds ratios with confidence intervals (CIs) are estimated by Cochran-Mantel-Haenszel method. For risk differences standard Wald asymptotic confidence limits are calculated. A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied in case of any zero cells in contingency table.
Only treatment emergent AEs are displayed (onset between first dose until treatment stop +7 days).
MedDRA version: 23.1. * Chi-square test for treatment effect ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction).

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Table R.1.2.3: 3 Proportion of patients with severe adverse events of special interest and severe other specific AEs by user-defined category overall and by subgroup - TS
User-defined AE category: Hypotension (BIcMQ based)

Subgroup	Placebo			Empa 10mg			Empa 10mg vs Placebo				
Category	N	n	%	N	n	%	p-value *	Risk ratio (95% CI)	Odds ratio (95% CI)	Risk diff. (95% CI)	p-value **
Overall	2989	22	0.7	2996	40	1.3	0.0221	1.81 (1.08, 3.04)	1.82 (1.08, 3.08)	0.01 (0.00,0.01)	
Sex											0.7596
Male	1653	14	0.8	1658	27	1.6	0.0420	1.92 (1.01, 3.65)	1.94 (1.01, 3.71)	0.01 (0.00,0.02)	
Female	1336	8	0.6	1338	13	1.0	0.2749	1.62 (0.67, 3.90)	1.63 (0.67, 3.94)	0.00 (0.00,0.01)	
Age [years]											0.8860
<70	1084	8	0.7	1066	15	1.4	0.1316	1.91 (0.81, 4.48)	1.92 (0.81, 4.55)	0.01 (0.00,0.02)	
>=70	1905	14	0.7	1930	25	1.3	0.0837	1.76 (0.92, 3.38)	1.77 (0.92, 3.42)	0.01 (0.00,0.01)	
Region											0.3982
North America	359	6	1.7	359	16	4.5	0.0304	2.67 (1.06, 6.74)	2.74 (1.06, 7.10)	0.03 (0.00,0.05)	
Latin America	757	4	0.5	758	8	1.1	0.2473	2.00 (0.60, 6.60)	2.01 (0.60, 6.70)	0.01 (0.00,0.01)	
Europe	1341	9	0.7	1346	9	0.7	0.9937	1.00 (0.40, 2.50)	1.00 (0.39, 2.52)	0.00 (-0.01,0.01)	
Asia	343	1	0.3	343	0	0	0.4789	0.33 (0.01, 8.15)	0.33 (0.01, 8.19)	0.00 (-0.01,0.01)	
Other	189	2	1.1	190	7	3.7	0.0932	3.48 (0.73, 16.54)	3.58 (0.73, 17.44)	0.03 (0.00,0.06)	
OECD member											0.2500
No	847	4	0.5	868	13	1.5	0.0321	3.17 (1.04, 9.69)	3.20 (1.04, 9.87)	0.01 (0.00,0.02)	
Yes	2142	18	0.8	2128	27	1.3	0.1704	1.51 (0.83, 2.73)	1.52 (0.83, 2.76)	0.00 (0.00,0.01)	
Baseline NYHA											0.0688
II^	2450	18	0.7	2435	23	0.9	0.4214	1.29 (0.70, 2.38)	1.29 (0.69, 2.39)	0.00 (0.00,0.01)	
III/IV	539	4	0.7	561	17	3.0	0.0056	4.08 (1.38, 12.06)	4.18 (1.40, 12.50)	0.02 (0.01,0.04)	
Baseline Diabetes Status											0.1760
Diabetic	1471	15	1.0	1465	20	1.4	0.3885	1.34 (0.69, 2.60)	1.34 (0.69, 2.63)	0.00 (0.00,0.01)	
Non-Diabetic	1518	7	0.5	1531	20	1.3	0.0127	2.83 (1.20, 6.68)	2.86 (1.20, 6.78)	0.01 (0.00,0.02)	

Analysis is based on study 1245.110.
^ Patients with NYHA class I are counted in subgroup NYHA class II.
*** Confirmed hypoglycaemic AEs are defined by a glucose concentration <=70 mg/dL (3.9 mmol/L) or requiring assistance.
Risk ratios and odds ratios with confidence intervals (CIs) are estimated by Cochran-Mantel-Haenszel method. For risk differences standard Wald asymptotic confidence limits are calculated. A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied in case of any zero cells in contingency table.
Only treatment emergent AEs are displayed (onset between first dose until treatment stop +7 days).
MedDRA version: 23.1. * Chi-square test for treatment effect ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction).

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Table R.1.2.3: 3 Proportion of patients with severe adverse events of special interest and severe other specific AEs by user-defined category overall and by subgroup - TS
User-defined AE category: Hypotension (BIcMQ based)

Subgroup	Placebo			Empa 10mg			Empa 10mg vs Placebo				
Category	N	n	%	N	n	%	p-value *	Risk ratio (95% CI)	Odds ratio (95% CI)	Risk diff. (95% CI)	p-value **
Baseline Diabetes Status											0.0553
Diabetic	1471	15	1.0	1465	20	1.4	0.3885	1.34 (0.69, 2.60)	1.34 (0.69, 2.63)	0.00 (0.00,0.01)	
Pre-Diabetes	979	2	0.2	1001	16	1.6	0.0011	7.82 (1.80, 33.94)	7.94 (1.82, 34.60)	0.01 (0.01,0.02)	
Normal (no pre-diabetes)	539	5	0.9	530	4	0.8	0.7570	0.81 (0.22, 3.01)	0.81 (0.22, 3.04)	0.00 (-0.01,0.01)	
Baseline BMI [kg/m²]											0.6525
<30	1641	8	0.5	1654	17	1.0	0.0739	2.11 (0.91, 4.87)	2.12 (0.91, 4.93)	0.01 (0.00,0.01)	
>=30	1348	14	1.0	1342	23	1.7	0.1327	1.65 (0.85, 3.19)	1.66 (0.85, 3.24)	0.01 (0.00,0.02)	
Baseline eGFR (CKD-EPI) [mL/min/1.73m²]											0.2093
>=60	1505	9	0.6	1493	10	0.7	0.8044	1.12 (0.46, 2.75)	1.12 (0.45, 2.77)	0.00 (0.00,0.01)	
<60	1482	13	0.9	1503	30	2.0	0.0103	2.28 (1.19, 4.34)	2.30 (1.20, 4.43)	0.01 (0.00,0.02)	
History of HHF (in the last 12 months)											0.4110
No	2320	14	0.6	2297	29	1.3	0.0198	2.09 (1.11, 3.95)	2.11 (1.11, 4.00)	0.01 (0.00,0.01)	
Yes	669	8	1.2	699	11	1.6	0.5505	1.32 (0.53, 3.25)	1.32 (0.53, 3.30)	0.00 (-0.01,0.02)	
Baseline SBP (</>= median)											0.8400
< median	1474	12	0.8	1496	21	1.4	0.1253	1.72 (0.85, 3.49)	1.73 (0.85, 3.54)	0.01 (0.00,0.01)	
>= median	1515	10	0.7	1500	19	1.3	0.0880	1.92 (0.90, 4.11)	1.93 (0.89, 4.17)	0.01 (0.00,0.01)	
History of atrial fibrillation or atrial flutter											0.5271
No	1426	9	0.6	1417	13	0.9	0.3837	1.45 (0.62, 3.39)	1.46 (0.62, 3.42)	0.00 (0.00,0.01)	
Yes	1558	13	0.8	1575	27	1.7	0.0283	2.05 (1.06, 3.97)	2.07 (1.07, 4.03)	0.01 (0.00,0.02)	

Analysis is based on study 1245.110.
^ Patients with NYHA class I are counted in subgroup NYHA class II.
*** Confirmed hypoglycaemic AEs are defined by a glucose concentration <=70 mg/dL (3.9 mmol/L) or requiring assistance.
Risk ratios and odds ratios with confidence intervals (CIs) are estimated by Cochran-Mantel-Haenszel method. For risk differences standard Wald asymptotic confidence limits are calculated. A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied in case of any zero cells in contingency table.
Only treatment emergent AEs are displayed (onset between first dose until treatment stop +7 days).
MedDRA version: 23.1. * Chi-square test for treatment effect ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction).

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Table R.1.2.3: 3 Proportion of patients with severe adverse events of special interest and severe other specific AEs by user-defined category overall and by subgroup - TS
User-defined AE category: Hypotension (BIcMQ based)

Subgroup	Placebo			Empa 10mg			Empa 10mg vs Placebo				
Category	N	n	%	N	n	%	p-value *	Risk ratio (95% CI)	Odds ratio (95% CI)	Risk diff. (95% CI)	p-value **
Baseline LVEF [%]											0.5305
< 50	988	7	0.7	995	16	1.6	0.0614	2.27 (0.94, 5.49)	2.29 (0.94, 5.59)	0.01 (0.00,0.02)	
>= 50	2001	15	0.7	2001	24	1.2	0.1476	1.60 (0.84, 3.04)	1.61 (0.84, 3.07)	0.00 (0.00,0.01)	
Baseline LVEF [%]											0.0910
<50	988	7	0.7	995	16	1.6	0.0614	2.27 (0.94, 5.49)	2.29 (0.94, 5.59)	0.01 (0.00,0.02)	
50 to <60	1030	3	0.3	1028	13	1.3	0.0119	4.34 (1.24, 15.19)	4.38 (1.25, 15.43)	0.01 (0.00,0.02)	
>=60	971	12	1.2	973	11	1.1	0.8300	0.91 (0.41, 2.06)	0.91 (0.40, 2.08)	0.00 (-0.01,0.01)	
Baseline NT-proBNP [pg/mL] (</>=median by atrial fibrillation/flutter status)											0.2883
< median	1507	11	0.7	1476	14	0.9	0.5126	1.30 (0.59, 2.85)	1.30 (0.59, 2.88)	0.00 (0.00,0.01)	
>= median	1475	11	0.7	1516	26	1.7	0.0165	2.30 (1.14, 4.64)	2.32 (1.14, 4.72)	0.01 (0.00,0.02)	
Baseline uric acid [mg/dL] (tertiles)											0.1492
<T1	975	4	0.4	963	12	1.2	0.0420	3.04 (0.98, 9.38)	3.06 (0.98, 9.53)	0.01 (0.00,0.02)	
>=T1 and <T2	966	10	1.0	1032	10	1.0	0.8819	0.94 (0.39, 2.24)	0.94 (0.39, 2.26)	0.00 (-0.01,0.01)	
>=T2	1016	7	0.7	970	18	1.9	0.0197	2.69 (1.13, 6.42)	2.73 (1.13, 6.55)	0.01 (0.00,0.02)	
Baseline use of MRA											0.8087
No	1865	13	0.7	1878	25	1.3	0.0530	1.91 (0.98, 3.72)	1.92 (0.98, 3.77)	0.01 (0.00,0.01)	
Yes	1124	9	0.8	1118	15	1.3	0.2133	1.68 (0.74, 3.81)	1.68 (0.73, 3.87)	0.01 (0.00,0.01)	
Baseline use of ACE-inhibitor, ARB or ARNi											0.9639
No	586	5	0.9	568	9	1.6	0.2566	1.86 (0.63, 5.51)	1.87 (0.62, 5.62)	0.01 (-0.01,0.02)	
Yes	2403	17	0.7	2428	31	1.3	0.0461	1.80 (1.00, 3.25)	1.82 (1.00, 3.29)	0.01 (0.00,0.01)	

Analysis is based on study 1245.110.
^ Patients with NYHA class I are counted in subgroup NYHA class II.
*** Confirmed hypoglycaemic AEs are defined by a glucose concentration <=70 mg/dL (3.9 mmol/L) or requiring assistance.
Risk ratios and odds ratios with confidence intervals (CIs) are estimated by Cochran-Mantel-Haenszel method. For risk differences standard Wald asymptotic confidence limits are calculated. A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied in case of any zero cells in contingency table.
Only treatment emergent AEs are displayed (onset between first dose until treatment stop +7 days).
MedDRA version: 23.1. * Chi-square test for treatment effect ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction).

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Table R.1.2.3: 3 Proportion of patients with severe adverse events of special interest and severe other specific AEs by user-defined category overall and by subgroup - TS
User-defined AE category: Symptomatic hypotension (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	2989	15	0.5	2996	20	0.7	0.4005	1.33 (0.68, 2.59)	1.33 (0.68, 2.61)	0.00 (0.00,0.01)	
Sex											0.8348
Male	1653	10	0.6	1658	14	0.8	0.4168	1.40 (0.62, 3.13)	1.40 (0.62, 3.16)	0.00 (0.00,0.01)	
Female	1336	5	0.4	1338	6	0.4	0.7644	1.20 (0.37, 3.92)	1.20 (0.37, 3.94)	0.00 (0.00,0.01)	
Age [years]											0.7938
<70	1084	6	0.6	1066	7	0.7	0.7577	1.19 (0.40, 3.52)	1.19 (0.40, 3.55)	0.00 (-0.01,0.01)	
>=70	1905	9	0.5	1930	13	0.7	0.4096	1.43 (0.61, 3.33)	1.43 (0.61, 3.35)	0.00 (0.00,0.01)	
Region											0.4085
North America	359	5	1.4	359	10	2.8	0.1920	2.00 (0.69, 5.79)	2.03 (0.69, 6.00)	0.01 (-0.01,0.03)	
Latin America	757	2	0.3	758	5	0.7	0.2565	2.50 (0.49, 12.83)	2.51 (0.48, 12.96)	0.00 (0.00,0.01)	
Europe	1341	7	0.5	1346	3	0.2	0.2030	0.43 (0.11, 1.65)	0.43 (0.11, 1.65)	0.00 (-0.01,0.00)	
Asia	343	0	0	343	0	0	1.0000	1.00 (0.02, 50.25)	1.00 (0.02, 50.54)	0.00 (-0.01,0.01)	
Other	189	1	0.5	190	2	1.1	0.5652	1.99 (0.18, 21.76)	2.00 (0.18, 22.24)	0.01 (-0.01,0.02)	
OECD member											0.4182
No	847	2	0.2	868	5	0.6	0.2697	2.44 (0.47, 12.54)	2.45 (0.47, 12.65)	0.00 (0.00,0.01)	
Yes	2142	13	0.6	2128	15	0.7	0.6916	1.16 (0.55, 2.43)	1.16 (0.55, 2.45)	0.00 (0.00,0.01)	
Baseline NYHA											0.1120
II^	2450	11	0.4	2435	9	0.4	0.6640	0.82 (0.34, 1.98)	0.82 (0.34, 1.99)	0.00 (0.00,0.00)	
III/IV	539	4	0.7	561	11	2.0	0.0815	2.64 (0.85, 8.25)	2.68 (0.85, 8.45)	0.01 (0.00,0.03)	
Baseline Diabetes Status											0.1350
Diabetic	1471	12	0.8	1465	11	0.8	0.8419	0.92 (0.41, 2.08)	0.92 (0.40, 2.09)	0.00 (-0.01,0.01)	
Non-Diabetic	1518	3	0.2	1531	9	0.6	0.0853	2.97 (0.81, 10.97)	2.99 (0.81, 11.05)	0.00 (0.00,0.01)	

Analysis is based on study 1245.110.
^ Patients with NYHA class I are counted in subgroup NYHA class II.
*** Confirmed hypoglycaemic AEs are defined by a glucose concentration <=70 mg/dL (3.9 mmol/L) or requiring assistance.
Risk ratios and odds ratios with confidence intervals (CIs) are estimated by Cochran-Mantel-Haenszel method. For risk differences standard Wald asymptotic confidence limits are calculated. A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied in case of any zero cells in contingency table.
Only treatment emergent AEs are displayed (onset between first dose until treatment stop +7 days).
MedDRA version: 23.1. * Chi-square test for treatment effect ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction).

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Table R.1.2.3: 3 Proportion of patients with severe adverse events of special interest and severe other specific AEs by user-defined category overall and by subgroup - TS
User-defined AE category: Symptomatic hypotension (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 Diabetes Status											0.0717
Diabetic	1471	12	0.8	1465	11	0.8	0.8419	0.92 (0.41, 2.08)	0.92 (0.40, 2.09)	0.00 (-0.01,0.01)	
Pre-Diabetes	979	1	0.1	1001	9	0.9	0.0124	8.80 (1.12, 69.35)	8.87 (1.12, 70.17)	0.01 (0.00,0.01)	
Normal (no pre-diabetes)	539	2	0.4	530	0	0	0.2535	0.20 (<0.01, 4.23)	0.20 (<0.01, 4.23)	0.00 (-0.01,0.00)	
Baseline BMI [kg/m²]											0.8200
<30	1641	5	0.3	1654	6	0.4	0.7726	1.19 (0.36, 3.89)	1.19 (0.36, 3.91)	0.00 (0.00,0.00)	
>=30	1348	10	0.7	1342	14	1.0	0.4059	1.41 (0.63, 3.15)	1.41 (0.62, 3.19)	0.00 (0.00,0.01)	
Baseline eGFR (CKD-EPI) [mL/min/1.73m²]											0.0522
>=60	1505	6	0.4	1493	2	0.1	0.1601	0.34 (0.07, 1.66)	0.34 (0.07, 1.66)	0.00 (-0.01,0.00)	
<60	1482	9	0.6	1503	18	1.2	0.0885	1.97 (0.89, 4.38)	1.98 (0.89, 4.43)	0.01 (0.00,0.01)	
History of HHF (in the last 12 months)											0.4885
No	2320	9	0.4	2297	14	0.6	0.2850	1.57 (0.68, 3.62)	1.57 (0.68, 3.65)	0.00 (0.00,0.01)	
Yes	669	6	0.9	699	6	0.9	0.9392	0.96 (0.31, 2.95)	0.96 (0.31, 2.98)	0.00 (-0.01,0.01)	
Baseline SBP (</>= median)											0.7195
< median	1474	8	0.5	1496	12	0.8	0.3875	1.48 (0.61, 3.61)	1.48 (0.60, 3.64)	0.00 (0.00,0.01)	
>= median	1515	7	0.5	1500	8	0.5	0.7809	1.15 (0.42, 3.18)	1.16 (0.42, 3.19)	0.00 (0.00,0.01)	
History of atrial fibrillation or atrial flutter											0.1743
No	1426	8	0.6	1417	6	0.4	0.6003	0.75 (0.26, 2.17)	0.75 (0.26, 2.18)	0.00 (-0.01,0.00)	
Yes	1558	7	0.4	1575	14	0.9	0.1316	1.98 (0.80, 4.89)	1.99 (0.80, 4.94)	0.00 (0.00,0.01)	

Analysis is based on study 1245.110.
^ Patients with NYHA class I are counted in subgroup NYHA class II.
*** Confirmed hypoglycaemic AEs are defined by a glucose concentration <=70 mg/dL (3.9 mmol/L) or requiring assistance.
Risk ratios and odds ratios with confidence intervals (CIs) are estimated by Cochran-Mantel-Haenszel method. For risk differences standard Wald asymptotic confidence limits are calculated. A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied in case of any zero cells in contingency table.
Only treatment emergent AEs are displayed (onset between first dose until treatment stop +7 days).
MedDRA version: 23.1. * Chi-square test for treatment effect ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction).

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Table R.1.2.3: 3 Proportion of patients with severe adverse events of special interest and severe other specific AEs by user-defined category overall and by subgroup - TS
User-defined AE category: Symptomatic hypotension (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 LVEF [%]											0.7537
< 50	988	6	0.6	995	7	0.7	0.7906	1.16 (0.39, 3.43)	1.16 (0.39, 3.46)	0.00 (-0.01,0.01)	
>= 50	2001	9	0.4	2001	13	0.6	0.3925	1.44 (0.62, 3.37)	1.45 (0.62, 3.39)	0.00 (0.00,0.01)	
Baseline LVEF [%]											0.3421
<50	988	6	0.6	995	7	0.7	0.7906	1.16 (0.39, 3.43)	1.16 (0.39, 3.46)	0.00 (-0.01,0.01)	
50 to <60	1030	2	0.2	1028	7	0.7	0.0943	3.51 (0.73, 16.84)	3.52 (0.73, 17.00)	0.00 (0.00,0.01)	
>=60	971	7	0.7	973	6	0.6	0.7779	0.86 (0.29, 2.54)	0.85 (0.29, 2.55)	0.00 (-0.01,0.01)	
Baseline NT-proBNP [pg/mL] (</>=median by atrial fibrillation/flutter status)											0.3118
< median	1507	8	0.5	1476	7	0.5	0.8270	0.89 (0.32, 2.46)	0.89 (0.32, 2.47)	0.00 (-0.01,0.00)	
>= median	1475	7	0.5	1516	13	0.9	0.1989	1.81 (0.72, 4.52)	1.81 (0.72, 4.56)	0.00 (0.00,0.01)	
Baseline uric acid [mg/dL] (tertiles)											0.2979
<T1	975	1	0.1	963	5	0.5	0.0988	5.06 (0.59, 43.25)	5.08 (0.59, 43.59)	0.00 (0.00,0.01)	
>=T1 and <T2	966	7	0.7	1032	6	0.6	0.6907	0.80 (0.27, 2.38)	0.80 (0.27, 2.39)	0.00 (-0.01,0.01)	
>=T2	1016	6	0.6	970	9	0.9	0.3855	1.57 (0.56, 4.40)	1.58 (0.56, 4.45)	0.00 (0.00,0.01)	
Baseline use of MRA											0.6731
No	1865	10	0.5	1878	12	0.6	0.6808	1.19 (0.52, 2.75)	1.19 (0.51, 2.77)	0.00 (0.00,0.01)	
Yes	1124	5	0.4	1118	8	0.7	0.3986	1.61 (0.53, 4.90)	1.61 (0.53, 4.95)	0.00 (0.00,0.01)	
Baseline use of ACE-inhibitor, ARB or ARNi											0.3738
No	586	2	0.3	568	5	0.9	0.2384	2.58 (0.50, 13.24)	2.59 (0.50, 13.42)	0.01 (0.00,0.01)	
Yes	2403	13	0.5	2428	15	0.6	0.7251	1.14 (0.54, 2.39)	1.14 (0.54, 2.41)	0.00 (0.00,0.01)	

Analysis is based on study 1245.110.
^ Patients with NYHA class I are counted in subgroup NYHA class II.
*** Confirmed hypoglycaemic AEs are defined by a glucose concentration <=70 mg/dL (3.9 mmol/L) or requiring assistance.
Risk ratios and odds ratios with confidence intervals (CIs) are estimated by Cochran-Mantel-Haenszel method. For risk differences standard Wald asymptotic confidence limits are calculated. A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied in case of any zero cells in contingency table.
Only treatment emergent AEs are displayed (onset between first dose until treatment stop +7 days).
MedDRA version: 23.1. * Chi-square test for treatment effect ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction).

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Table R.1.2.3: 3 Proportion of patients with severe adverse events of special interest and severe other specific AEs by user-defined category overall and by subgroup - TS
User-defined AE category: Allergic skin reactions (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	2989	1	<0.1	2996	1	<0.1	0.9987	1.00 (0.06, 15.94)	1.00 (0.06, 15.96)	0.00 (0.00,0.00)	
Sex											
Male	1653	1	0.1	1658	0	0					
Female	1336	0	0	1338	1	0.1					
Age [years]											
<70	1084	0	0	1066	0	0					
>=70	1905	1	0.1	1930	1	0.1					
Region											
North America	359	0	0	359	0	0					
Latin America	757	0	0	758	0	0					
Europe	1341	1	0.1	1346	1	0.1					
Asia	343	0	0	343	0	0					
Other	189	0	0	190	0	0					
OECD member											
No	847	0	0	868	0	0					
Yes	2142	1	<0.1	2128	1	<0.1					
Baseline NYHA											
II^	2450	1	<0.1	2435	1	<0.1					
III/IV	539	0	0	561	0	0					
Baseline Diabetes Status											
Diabetic	1471	0	0	1465	0	0					
Non-Diabetic	1518	1	0.1	1531	1	0.1					

Analysis is based on study 1245.110.
^ Patients with NYHA class I are counted in subgroup NYHA class II.
*** Confirmed hypoglycaemic AEs are defined by a glucose concentration <=70 mg/dL (3.9 mmol/L) or requiring assistance.
Risk ratios and odds ratios with confidence intervals (CIs) are estimated by Cochran-Mantel-Haenszel method. For risk differences standard Wald asymptotic confidence limits are calculated. A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
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Table R.1.2.3: 3 Proportion of patients with severe adverse events of special interest and severe other specific AEs by user-defined category overall and by subgroup - TS
User-defined AE category: Allergic skin reactions (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 Diabetes Status											
Diabetic	1471	0	0	1465	0	0					
Pre-Diabetes	979	0	0	1001	0	0					
Normal (no pre-diabetes)	539	1	0.2	530	1	0.2					
Baseline BMI [kg/m²]											
<30	1641	1	0.1	1654	1	0.1					
>=30	1348	0	0	1342	0	0					
Baseline eGFR (CKD-EPI) [mL/min/1.73m²]											
>=60	1505	0	0	1493	0	0					
<60	1482	1	0.1	1503	1	0.1					
History of HHF (in the last 12 months)											
No	2320	0	0	2297	1	<0.1					
Yes	669	1	0.1	699	0	0					
Baseline SBP (</>= median)											
< median	1474	0	0	1496	0	0					
>= median	1515	1	0.1	1500	1	0.1					
History of atrial fibrillation or atrial flutter											
No	1426	0	0	1417	0	0					
Yes	1558	1	0.1	1575	1	0.1					

Analysis is based on study 1245.110.
^ Patients with NYHA class I are counted in subgroup NYHA class II.
*** Confirmed hypoglycaemic AEs are defined by a glucose concentration <=70 mg/dL (3.9 mmol/L) or requiring assistance.
Risk ratios and odds ratios with confidence intervals (CIs) are estimated by Cochran-Mantel-Haenszel method. For risk differences standard Wald asymptotic confidence limits are calculated. A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied in case of any zero cells in contingency table.
Only treatment emergent AEs are displayed (onset between first dose until treatment stop +7 days).
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Table R.1.2.3: 3 Proportion of patients with severe adverse events of special interest and severe other specific AEs by user-defined category overall and by subgroup - TS
User-defined AE category: Allergic skin reactions (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 LVEF [%]											
< 50	988	0	0	995	1	0.1					
>= 50	2001	1	<0.1	2001	0	0					
Baseline LVEF [%]											
<50	988	0	0	995	1	0.1					
50 to <60	1030	0	0	1028	0	0					
>=60	971	1	0.1	973	0	0					
Baseline NT-proBNP [pg/mL] (</>=median by atrial fibrillation/flutter status)											
< median	1507	1	0.1	1476	0	0					
>= median	1475	0	0	1516	1	0.1					
Baseline uric acid [mg/dL] (tertiles)											
<T1	975	1	0.1	963	0	0					
>=T1 and <T2	966	0	0	1032	1	0.1					
>=T2	1016	0	0	970	0	0					
Baseline use of MRA											
No	1865	1	0.1	1878	1	0.1					
Yes	1124	0	0	1118	0	0					
Baseline use of ACE-inhibitor, ARB or ARNi											
No	586	0	0	568	0	0					
Yes	2403	1	<0.1	2428	1	<0.1					

Analysis is based on study 1245.110.
^ Patients with NYHA class I are counted in subgroup NYHA class II.
*** Confirmed hypoglycaemic AEs are defined by a glucose concentration <=70 mg/dL (3.9 mmol/L) or requiring assistance.
Risk ratios and odds ratios with confidence intervals (CIs) are estimated by Cochran-Mantel-Haenszel method. For risk differences standard Wald asymptotic confidence limits are calculated. A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
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Table R.1.2.3: 3 Proportion of patients with severe adverse events of special interest and severe other specific AEs by user-defined category overall and by subgroup - TS
User-defined AE category: Increased urination (project-defined PTs)

Subgroup	Placebo			Empa 10mg			Empa 10mg vs Placebo				
Category	N	n	%	N	n	%	p-value *	Risk ratio (95% CI)	Odds ratio (95% CI)	Risk diff. (95% CI)	p-value **
Overall	2989	0	0	2996	0	0	0.9991	1.00 (0.02, 50.26)	1.00 (0.02, 50.30)	0.00 (0.00,0.00)	
Sex											
Male	1653	0	0	1658	0	0					
Female	1336	0	0	1338	0	0					
Age [years]											
<70	1084	0	0	1066	0	0					
>=70	1905	0	0	1930	0	0					
Region											
North America	359	0	0	359	0	0					
Latin America	757	0	0	758	0	0					
Europe	1341	0	0	1346	0	0					
Asia	343	0	0	343	0	0					
Other	189	0	0	190	0	0					
OECD member											
No	847	0	0	868	0	0					
Yes	2142	0	0	2128	0	0					
Baseline NYHA											
II^	2450	0	0	2435	0	0					
III/IV	539	0	0	561	0	0					
Baseline Diabetes Status											
Diabetic	1471	0	0	1465	0	0					
Non-Diabetic	1518	0	0	1531	0	0					

Analysis is based on study 1245.110.
^ Patients with NYHA class I are counted in subgroup NYHA class II.
*** Confirmed hypoglycaemic AEs are defined by a glucose concentration <=70 mg/dL (3.9 mmol/L) or requiring assistance.
Risk ratios and odds ratios with confidence intervals (CIs) are estimated by Cochran-Mantel-Haenszel method. For risk differences standard Wald asymptotic confidence limits are calculated. A ratio less than one or risk difference less than 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: Increased urination (project-defined PTs)

Subgroup	Placebo			Empa 10mg			Empa 10mg vs Placebo				
Category	N	n	%	N	n	%	p-value *	Risk ratio (95% CI)	Odds ratio (95% CI)	Risk diff. (95% CI)	p-value **
Baseline Diabetes Status											
Diabetic	1471	0	0	1465	0	0					
Pre-Diabetes	979	0	0	1001	0	0					
Normal (no pre-diabetes)	539	0	0	530	0	0					
Baseline BMI [kg/m²]											
<30	1641	0	0	1654	0	0					
>=30	1348	0	0	1342	0	0					
Baseline eGFR (CKD-EPI) [mL/min/1.73m²]											
>=60	1505	0	0	1493	0	0					
<60	1482	0	0	1503	0	0					
History of HHF (in the last 12 months)											
No	2320	0	0	2297	0	0					
Yes	669	0	0	699	0	0					
Baseline SBP (</>= median)											
< median	1474	0	0	1496	0	0					
>= median	1515	0	0	1500	0	0					
History of atrial fibrillation or atrial flutter											
No	1426	0	0	1417	0	0					
Yes	1558	0	0	1575	0	0					

Analysis is based on study 1245.110.
^ Patients with NYHA class I are counted in subgroup NYHA class II.
*** Confirmed hypoglycaemic AEs are defined by a glucose concentration <=70 mg/dL (3.9 mmol/L) or requiring assistance.
Risk ratios and odds ratios with confidence intervals (CIs) are estimated by Cochran-Mantel-Haenszel method. For risk differences standard Wald asymptotic confidence limits are calculated. A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied in case of any zero cells in contingency table.
Only treatment emergent AEs are displayed (onset between first dose until treatment stop +7 days).
MedDRA version: 23.1. * 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: Increased urination (project-defined PTs)

Subgroup	Placebo			Empa 10mg			Empa 10mg vs Placebo				
Category	N	n	%	N	n	%	p-value *	Risk ratio (95% CI)	Odds ratio (95% CI)	Risk diff. (95% CI)	p-value **
Baseline LVEF [%]											
< 50	988	0	0	995	0	0					
>= 50	2001	0	0	2001	0	0					
Baseline LVEF [%]											
<50	988	0	0	995	0	0					
50 to <60	1030	0	0	1028	0	0					
>=60	971	0	0	973	0	0					
Baseline NT-proBNP [pg/mL] (</>=median by atrial fibrillation/flutter status)											
< median	1507	0	0	1476	0	0					
>= median	1475	0	0	1516	0	0					
Baseline uric acid [mg/dL] (tertiles)											
<T1	975	0	0	963	0	0					
>=T1 and <T2	966	0	0	1032	0	0					
>=T2	1016	0	0	970	0	0					
Baseline use of MRA											
No	1865	0	0	1878	0	0					
Yes	1124	0	0	1118	0	0					
Baseline use of ACE-inhibitor, ARB or ARNi											
No	586	0	0	568	0	0					
Yes	2403	0	0	2428	0	0					

Analysis is based on study 1245.110.
^ Patients with NYHA class I are counted in subgroup NYHA class II.
*** Confirmed hypoglycaemic AEs are defined by a glucose concentration <=70 mg/dL (3.9 mmol/L) or requiring assistance.
Risk ratios and odds ratios with confidence intervals (CIs) are estimated by Cochran-Mantel-Haenszel method. For risk differences standard Wald asymptotic confidence limits are calculated. A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied in case of any zero cells in contingency table.
Only treatment emergent AEs are displayed (onset between first dose until treatment stop +7 days).
MedDRA version: 23.1. * Chi-square test for treatment effect ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction).

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Table R.1.2.3: 3 Proportion of patients with severe adverse events of special interest and severe other specific AEs by user-defined category overall and by subgroup - TS
User-defined AE category: Thirst (project-defined PTs)

Subgroup	Placebo			Empa 10mg			Empa 10mg vs Placebo				
Category	N	n	%	N	n	%	p-value *	Risk ratio (95% CI)	Odds ratio (95% CI)	Risk diff. (95% CI)	p-value **
Overall	2989	0	0	2996	0	0	0.9991	1.00 (0.02, 50.26)	1.00 (0.02, 50.30)	0.00 (0.00,0.00)	
Sex											
Male	1653	0	0	1658	0	0					
Female	1336	0	0	1338	0	0					
Age [years]											
<70	1084	0	0	1066	0	0					
>=70	1905	0	0	1930	0	0					
Region											
North America	359	0	0	359	0	0					
Latin America	757	0	0	758	0	0					
Europe	1341	0	0	1346	0	0					
Asia	343	0	0	343	0	0					
Other	189	0	0	190	0	0					
OECD member											
No	847	0	0	868	0	0					
Yes	2142	0	0	2128	0	0					
Baseline NYHA											
II^	2450	0	0	2435	0	0					
III/IV	539	0	0	561	0	0					
Baseline Diabetes Status											
Diabetic	1471	0	0	1465	0	0					
Non-Diabetic	1518	0	0	1531	0	0					

Analysis is based on study 1245.110.
^ Patients with NYHA class I are counted in subgroup NYHA class II.
*** Confirmed hypoglycaemic AEs are defined by a glucose concentration <=70 mg/dL (3.9 mmol/L) or requiring assistance.
Risk ratios and odds ratios with confidence intervals (CIs) are estimated by Cochran-Mantel-Haenszel method. For risk differences standard Wald asymptotic confidence limits are calculated. A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied in case of any zero cells in contingency table.
Only treatment emergent AEs are displayed (onset between first dose until treatment stop +7 days).
MedDRA version: 23.1. * Chi-square test for treatment effect ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction).

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Table R.1.2.3: 3 Proportion of patients with severe adverse events of special interest and severe other specific AEs by user-defined category overall and by subgroup - TS
User-defined AE category: Thirst (project-defined PTs)

Subgroup	Placebo			Empa 10mg			Empa 10mg vs Placebo				
Category	N	n	%	N	n	%	p-value *	Risk ratio (95% CI)	Odds ratio (95% CI)	Risk diff. (95% CI)	p-value **
Baseline Diabetes Status											
Diabetic	1471	0	0	1465	0	0					
Pre-Diabetes	979	0	0	1001	0	0					
Normal (no pre-diabetes)	539	0	0	530	0	0					
Baseline BMI [kg/m²]											
<30	1641	0	0	1654	0	0					
>=30	1348	0	0	1342	0	0					
Baseline eGFR (CKD-EPI) [mL/min/1.73m²]											
>=60	1505	0	0	1493	0	0					
<60	1482	0	0	1503	0	0					
History of HHF (in the last 12 months)											
No	2320	0	0	2297	0	0					
Yes	669	0	0	699	0	0					
Baseline SBP (</>= median)											
< median	1474	0	0	1496	0	0					
>= median	1515	0	0	1500	0	0					
History of atrial fibrillation or atrial flutter											
No	1426	0	0	1417	0	0					
Yes	1558	0	0	1575	0	0					

Analysis is based on study 1245.110.
^ Patients with NYHA class I are counted in subgroup NYHA class II.
*** Confirmed hypoglycaemic AEs are defined by a glucose concentration <=70 mg/dL (3.9 mmol/L) or requiring assistance.
Risk ratios and odds ratios with confidence intervals (CIs) are estimated by Cochran-Mantel-Haenszel method. For risk differences standard Wald asymptotic confidence limits are calculated. A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied in case of any zero cells in contingency table.
Only treatment emergent AEs are displayed (onset between first dose until treatment stop +7 days).
MedDRA version: 23.1. * Chi-square test for treatment effect ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction).

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Table R.1.2.3: 3 Proportion of patients with severe adverse events of special interest and severe other specific AEs by user-defined category overall and by subgroup - TS
User-defined AE category: Thirst (project-defined PTs)

Subgroup	Placebo			Empa 10mg			Empa 10mg vs Placebo				
Category	N	n	%	N	n	%	p-value *	Risk ratio (95% CI)	Odds ratio (95% CI)	Risk diff. (95% CI)	p-value **
Baseline LVEF [%]											
< 50	988	0	0	995	0	0					
>= 50	2001	0	0	2001	0	0					
Baseline LVEF [%]											
<50	988	0	0	995	0	0					
50 to <60	1030	0	0	1028	0	0					
>=60	971	0	0	973	0	0					
Baseline NT-proBNP [pg/mL] (</>=median by atrial fibrillation/flutter status)											
< median	1507	0	0	1476	0	0					
>= median	1475	0	0	1516	0	0					
Baseline uric acid [mg/dL] (tertiles)											
<T1	975	0	0	963	0	0					
>=T1 and <T2	966	0	0	1032	0	0					
>=T2	1016	0	0	970	0	0					
Baseline use of MRA											
No	1865	0	0	1878	0	0					
Yes	1124	0	0	1118	0	0					
Baseline use of ACE-inhibitor, ARB or ARNi											
No	586	0	0	568	0	0					
Yes	2403	0	0	2428	0	0					

Analysis is based on study 1245.110.
^ Patients with NYHA class I are counted in subgroup NYHA class II.
*** Confirmed hypoglycaemic AEs are defined by a glucose concentration <=70 mg/dL (3.9 mmol/L) or requiring assistance.
Risk ratios and odds ratios with confidence intervals (CIs) are estimated by Cochran-Mantel-Haenszel method. For risk differences standard Wald asymptotic confidence limits are calculated. A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied in case of any zero cells in contingency table.
Only treatment emergent AEs are displayed (onset between first dose until treatment stop +7 days).
MedDRA version: 23.1. * Chi-square test for treatment effect ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction).

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Table R.1.2.3: 3 Proportion of patients with severe adverse events of special interest and severe other specific AEs by user-defined category overall and by subgroup - TS
User-defined AE category: Serum lipids increased (Sub 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	2989	1	<0.1	2996	1	<0.1	0.9987	1.00 (0.06, 15.94)	1.00 (0.06, 15.96)	0.00 (0.00,0.00)	
Sex											
Male	1653	0	0	1658	0	0					
Female	1336	1	0.1	1338	1	0.1					
Age [years]											
<70	1084	1	0.1	1066	1	0.1					
>=70	1905	0	0	1930	0	0					
Region											
North America	359	0	0	359	0	0					
Latin America	757	1	0.1	758	1	0.1					
Europe	1341	0	0	1346	0	0					
Asia	343	0	0	343	0	0					
Other	189	0	0	190	0	0					
OECD member											
No	847	1	0.1	868	1	0.1					
Yes	2142	0	0	2128	0	0					
Baseline NYHA											
II^	2450	0	0	2435	1	<0.1					
III/IV	539	1	0.2	561	0	0					
Baseline Diabetes Status											
Diabetic	1471	1	0.1	1465	1	0.1					
Non-Diabetic	1518	0	0	1531	0	0					

Analysis is based on study 1245.110.
^ Patients with NYHA class I are counted in subgroup NYHA class II.
*** Confirmed hypoglycaemic AEs are defined by a glucose concentration <=70 mg/dL (3.9 mmol/L) or requiring assistance.
Risk ratios and odds ratios with confidence intervals (CIs) are estimated by Cochran-Mantel-Haenszel method. For risk differences standard Wald asymptotic confidence limits are calculated. A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied in case of any zero cells in contingency table.
Only treatment emergent AEs are displayed (onset between first dose until treatment stop +7 days).
MedDRA version: 23.1. * Chi-square test for treatment effect ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction).

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Table R.1.2.3: 3 Proportion of patients with severe adverse events of special interest and severe other specific AEs by user-defined category overall and by subgroup - TS
User-defined AE category: Serum lipids increased (Sub 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 Diabetes Status											
Diabetic	1471	1	0.1	1465	1	0.1					
Pre-Diabetes	979	0	0	1001	0	0					
Normal (no pre-diabetes)	539	0	0	530	0	0					
Baseline BMI [kg/m²]											
<30	1641	1	0.1	1654	1	0.1					
>=30	1348	0	0	1342	0	0					
Baseline eGFR (CKD-EPI) [mL/min/1.73m²]											
>=60	1505	0	0	1493	1	0.1					
<60	1482	1	0.1	1503	0	0					
History of HHF (in the last 12 months)											
No	2320	1	<0.1	2297	1	<0.1					
Yes	669	0	0	699	0	0					
Baseline SBP (</>= median)											
< median	1474	1	0.1	1496	1	0.1					
>= median	1515	0	0	1500	0	0					
History of atrial fibrillation or atrial flutter											
No	1426	1	0.1	1417	1	0.1					
Yes	1558	0	0	1575	0	0					

Analysis is based on study 1245.110.
^ Patients with NYHA class I are counted in subgroup NYHA class II.
*** Confirmed hypoglycaemic AEs are defined by a glucose concentration <=70 mg/dL (3.9 mmol/L) or requiring assistance.
Risk ratios and odds ratios with confidence intervals (CIs) are estimated by Cochran-Mantel-Haenszel method. For risk differences standard Wald asymptotic confidence limits are calculated. A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied in case of any zero cells in contingency table.
Only treatment emergent AEs are displayed (onset between first dose until treatment stop +7 days).
MedDRA version: 23.1. * Chi-square test for treatment effect ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction).

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Table R.1.2.3: 3 Proportion of patients with severe adverse events of special interest and severe other specific AEs by user-defined category overall and by subgroup - TS
User-defined AE category: Serum lipids increased (Sub 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 LVEF [%]											
< 50	988	1	0.1	995	0	0					
>= 50	2001	0	0	2001	1	<0.1					
Baseline LVEF [%]											
<50	988	1	0.1	995	0	0					
50 to <60	1030	0	0	1028	0	0					
>=60	971	0	0	973	1	0.1					
Baseline NT-proBNP [pg/mL] (</>=median by atrial fibrillation/flutter status)											
< median	1507	1	0.1	1476	1	0.1					
>= median	1475	0	0	1516	0	0					
Baseline uric acid [mg/dL] (tertiles)											
<T1	975	0	0	963	1	0.1					
>=T1 and <T2	966	0	0	1032	0	0					
>=T2	1016	1	0.1	970	0	0					
Baseline use of MRA											
No	1865	0	0	1878	0	0					
Yes	1124	1	0.1	1118	1	0.1					
Baseline use of ACE-inhibitor, ARB or ARNi											
No	586	0	0	568	0	0					
Yes	2403	1	<0.1	2428	1	<0.1					

Analysis is based on study 1245.110.
^ Patients with NYHA class I are counted in subgroup NYHA class II.
*** Confirmed hypoglycaemic AEs are defined by a glucose concentration <=70 mg/dL (3.9 mmol/L) or requiring assistance.
Risk ratios and odds ratios with confidence intervals (CIs) are estimated by Cochran-Mantel-Haenszel method. For risk differences standard Wald asymptotic confidence limits are calculated. A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied in case of any zero cells in contingency table.
Only treatment emergent AEs are displayed (onset between first dose until treatment stop +7 days).
MedDRA version: 23.1. * Chi-square test for treatment effect ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction).

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Table R.1.2.3: 3 Proportion of patients with severe adverse events of special interest and severe other specific AEs by user-defined category overall and by subgroup - TS
User-defined AE category: Angioedema (narrow BicMQ excl. urticaria)

Subgroup	Placebo			Empa 10mg			Empa 10mg vs Placebo				
Category	N	n	%	N	n	%	p-value *	Risk ratio (95% CI)	Odds ratio (95% CI)	Risk diff. (95% CI)	p-value **
Overall	2989	1	<0.1	2996	0	0	0.4784	0.33 (0.01, 8.16)	0.33 (0.01, 8.16)	0.00 (0.00,0.00)	
Sex											
Male	1653	1	0.1	1658	0	0					
Female	1336	0	0	1338	0	0					
Age [years]											
<70	1084	0	0	1066	0	0					
>=70	1905	1	0.1	1930	0	0					
Region											
North America	359	0	0	359	0	0					
Latin America	757	0	0	758	0	0					
Europe	1341	1	0.1	1346	0	0					
Asia	343	0	0	343	0	0					
Other	189	0	0	190	0	0					
OECD member											
No	847	0	0	868	0	0					
Yes	2142	1	<0.1	2128	0	0					
Baseline NYHA											
II^	2450	1	<0.1	2435	0	0					
III/IV	539	0	0	561	0	0					
Baseline Diabetes Status											
Diabetic	1471	1	0.1	1465	0	0					
Non-Diabetic	1518	0	0	1531	0	0					

Analysis is based on study 1245.110.
^ Patients with NYHA class I are counted in subgroup NYHA class II.
*** Confirmed hypoglycaemic AEs are defined by a glucose concentration <=70 mg/dL (3.9 mmol/L) or requiring assistance.
Risk ratios and odds ratios with confidence intervals (CIs) are estimated by Cochran-Mantel-Haenszel method. For risk differences standard Wald asymptotic confidence limits are calculated. A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied in case of any zero cells in contingency table.
Only treatment emergent AEs are displayed (onset between first dose until treatment stop +7 days).
MedDRA version: 23.1. * Chi-square test for treatment effect ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction).

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Table R.1.2.3: 3 Proportion of patients with severe adverse events of special interest and severe other specific AEs by user-defined category overall and by subgroup - TS
User-defined AE category: Angioedema (narrow BicMQ excl. urticaria)

Subgroup	Placebo			Empa 10mg			Empa 10mg vs Placebo				
Category	N	n	%	N	n	%	p-value *	Risk ratio (95% CI)	Odds ratio (95% CI)	Risk diff. (95% CI)	p-value **
Baseline Diabetes Status											
Diabetic	1471	1	0.1	1465	0	0					
Pre-Diabetes	979	0	0	1001	0	0					
Normal (no pre-diabetes)	539	0	0	530	0	0					
Baseline BMI [kg/m²]											
<30	1641	1	0.1	1654	0	0					
>=30	1348	0	0	1342	0	0					
Baseline eGFR (CKD-EPI) [mL/min/1.73m²]											
>=60	1505	0	0	1493	0	0					
<60	1482	1	0.1	1503	0	0					
History of HHF (in the last 12 months)											
No	2320	0	0	2297	0	0					
Yes	669	1	0.1	699	0	0					
Baseline SBP (</>= median)											
< median	1474	1	0.1	1496	0	0					
>= median	1515	0	0	1500	0	0					
History of atrial fibrillation or atrial flutter											
No	1426	1	0.1	1417	0	0					
Yes	1558	0	0	1575	0	0					

Analysis is based on study 1245.110.
^ Patients with NYHA class I are counted in subgroup NYHA class II.
*** Confirmed hypoglycaemic AEs are defined by a glucose concentration <=70 mg/dL (3.9 mmol/L) or requiring assistance.
Risk ratios and odds ratios with confidence intervals (CIs) are estimated by Cochran-Mantel-Haenszel method. For risk differences standard Wald asymptotic confidence limits are calculated. A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied in case of any zero cells in contingency table.
Only treatment emergent AEs are displayed (onset between first dose until treatment stop +7 days).
MedDRA version: 23.1. * Chi-square test for treatment effect ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction).

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Table R.1.2.3: 3 Proportion of patients with severe adverse events of special interest and severe other specific AEs by user-defined category overall and by subgroup - TS
User-defined AE category: Angioedema (narrow BicMQ excl. urticaria)

Subgroup	Placebo			Empa 10mg			Empa 10mg vs Placebo				
Category	N	n	%	N	n	%	p-value *	Risk ratio (95% CI)	Odds ratio (95% CI)	Risk diff. (95% CI)	p-value **
Baseline LVEF [%]											
< 50	988	1	0.1	995	0	0					
>= 50	2001	0	0	2001	0	0					
Baseline LVEF [%]											
<50	988	1	0.1	995	0	0					
50 to <60	1030	0	0	1028	0	0					
>=60	971	0	0	973	0	0					
Baseline NT-proBNP [pg/mL] (</>=median by atrial fibrillation/flutter status)											
< median	1507	1	0.1	1476	0	0					
>= median	1475	0	0	1516	0	0					
Baseline uric acid [mg/dL] (tertiles)											
<T1	975	0	0	963	0	0					
>=T1 and <T2	966	1	0.1	1032	0	0					
>=T2	1016	0	0	970	0	0					
Baseline use of MRA											
No	1865	1	0.1	1878	0	0					
Yes	1124	0	0	1118	0	0					
Baseline use of ACE-inhibitor, ARB or ARNi											
No	586	0	0	568	0	0					
Yes	2403	1	<0.1	2428	0	0					

Analysis is based on study 1245.110.
^ Patients with NYHA class I are counted in subgroup NYHA class II.
*** Confirmed hypoglycaemic AEs are defined by a glucose concentration <=70 mg/dL (3.9 mmol/L) or requiring assistance.
Risk ratios and odds ratios with confidence intervals (CIs) are estimated by Cochran-Mantel-Haenszel method. For risk differences standard Wald asymptotic confidence limits are calculated. A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied in case of any zero cells in contingency table.
Only treatment emergent AEs are displayed (onset between first dose until treatment stop +7 days).
MedDRA version: 23.1. * Chi-square test for treatment effect ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction).

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Table R.1.2.3: 3 Proportion of patients with severe adverse events of special interest and severe other specific AEs by user-defined category overall and by subgroup - TS
User-defined AE category: Hypersensitivity reactions (narrow 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	2989	8	0.3	2996	5	0.2	0.4025	0.62 (0.20, 1.90)	0.62 (0.20, 1.91)	0.00 (0.00,0.00)	
Sex											
Male	1653	3	0.2	1658	3	0.2					
Female	1336	5	0.4	1338	2	0.1					
Age [years]											
<70	1084	1	0.1	1066	3	0.3					
>=70	1905	7	0.4	1930	2	0.1					
Region											
North America	359	2	0.6	359	0	0					
Latin America	757	2	0.3	758	2	0.3					
Europe	1341	3	0.2	1346	3	0.2					
Asia	343	0	0	343	0	0					
Other	189	1	0.5	190	0	0					
OECD member											0.2826
No	847	1	0.1	868	2	0.2	0.5778	1.95 (0.18, 21.48)	1.95 (0.18, 21.59)	0.00 (0.00,0.01)	
Yes	2142	7	0.3	2128	3	0.1	0.2091	0.43 (0.11, 1.67)	0.43 (0.11, 1.67)	0.00 (0.00,0.00)	
Baseline NYHA											0.8092
II^	2450	6	0.2	2435	4	0.2	0.5330	0.67 (0.19, 2.37)	0.67 (0.19, 2.38)	0.00 (0.00,0.00)	
III/IV	539	2	0.4	561	1	0.2	0.5399	0.48 (0.04, 5.28)	0.48 (0.04, 5.30)	0.00 (-0.01,0.00)	
Baseline Diabetes Status											
Diabetic	1471	3	0.2	1465	2	0.1					
Non-Diabetic	1518	5	0.3	1531	3	0.2					

Analysis is based on study 1245.110.
^ Patients with NYHA class I are counted in subgroup NYHA class II.
*** Confirmed hypoglycaemic AEs are defined by a glucose concentration <=70 mg/dL (3.9 mmol/L) or requiring assistance.
Risk ratios and odds ratios with confidence intervals (CIs) are estimated by Cochran-Mantel-Haenszel method. For risk differences standard Wald asymptotic confidence limits are calculated. A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied in case of any zero cells in contingency table.
Only treatment emergent AEs are displayed (onset between first dose until treatment stop +7 days).
MedDRA version: 23.1. * Chi-square test for treatment effect ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction).

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Table R.1.2.3: 3 Proportion of patients with severe adverse events of special interest and severe other specific AEs by user-defined category overall and by subgroup - TS
User-defined AE category: Hypersensitivity reactions (narrow 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 Diabetes Status											
Diabetic	1471	3	0.2	1465	2	0.1					
Pre-Diabetes	979	2	0.2	1001	1	0.1					
Normal (no pre-diabetes)	539	3	0.6	530	2	0.4					
Baseline BMI [kg/m²]											
<30	1641	3	0.2	1654	1	0.1					
>=30	1348	5	0.4	1342	4	0.3					
Baseline eGFR (CKD-EPI) [mL/min/1.73m²]											
>=60	1505	3	0.2	1493	2	0.1					
<60	1482	5	0.3	1503	3	0.2					
History of HHF (in the last 12 months)											
No	2320	6	0.3	2297	3	0.1					
Yes	669	2	0.3	699	2	0.3					
Baseline SBP (</>= median)											
< median	1474	4	0.3	1496	3	0.2					
>= median	1515	4	0.3	1500	2	0.1					
History of atrial fibrillation or atrial flutter											
No	1426	3	0.2	1417	2	0.1					
Yes	1558	5	0.3	1575	3	0.2					

Analysis is based on study 1245.110.
^ Patients with NYHA class I are counted in subgroup NYHA class II.
*** Confirmed hypoglycaemic AEs are defined by a glucose concentration <=70 mg/dL (3.9 mmol/L) or requiring assistance.
Risk ratios and odds ratios with confidence intervals (CIs) are estimated by Cochran-Mantel-Haenszel method. For risk differences standard Wald asymptotic confidence limits are calculated. A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied in case of any zero cells in contingency table.
Only treatment emergent AEs are displayed (onset between first dose until treatment stop +7 days).
MedDRA version: 23.1. * Chi-square test for treatment effect ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction).

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Table R.1.2.3: 3 Proportion of patients with severe adverse events of special interest and severe other specific AEs by user-defined category overall and by subgroup - TS
User-defined AE category: Hypersensitivity reactions (narrow 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 LVEF [%]											
< 50	988	2	0.2	995	2	0.2					
>= 50	2001	6	0.3	2001	3	0.1					
Baseline LVEF [%]											
<50	988	2	0.2	995	2	0.2					
50 to <60	1030	3	0.3	1028	1	0.1					
>=60	971	3	0.3	973	2	0.2					
Baseline NT-proBNP [pg/mL] (</>=median by atrial fibrillation/flutter status)											
< median	1507	7	0.5	1476	2	0.1					
>= median	1475	1	0.1	1516	3	0.2					
Baseline uric acid [mg/dL] (tertiles)											
<T1	975	2	0.2	963	2	0.2					
>=T1 and <T2	966	3	0.3	1032	1	0.1					
>=T2	1016	3	0.3	970	2	0.2					
Baseline use of MRA											
No	1865	3	0.2	1878	2	0.1					
Yes	1124	5	0.4	1118	3	0.3					
Baseline use of ACE-inhibitor, ARB or ARNi											0.6973
No	586	1	0.2	568	1	0.2	0.9824	1.03 (0.06, 16.45)	1.03 (0.06, 16.53)	0.00 (0.00,0.00)	
Yes	2403	7	0.3	2428	4	0.2	0.3561	0.57 (0.17, 1.93)	0.56 (0.17, 1.93)	0.00 (0.00,0.00)	

Analysis is based on study 1245.110.
^ Patients with NYHA class I are counted in subgroup NYHA class II.
*** Confirmed hypoglycaemic AEs are defined by a glucose concentration <=70 mg/dL (3.9 mmol/L) or requiring assistance.
Risk ratios and odds ratios with confidence intervals (CIs) are estimated by Cochran-Mantel-Haenszel method. For risk differences standard Wald asymptotic confidence limits are calculated. A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied in case of any zero cells in contingency table.
Only treatment emergent AEs are displayed (onset between first dose until treatment stop +7 days).
MedDRA version: 23.1. * Chi-square test for treatment effect ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction).

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Table R.1.2.3: 3 Proportion of patients with severe adverse events of special interest and severe other specific AEs by user-defined category overall and by subgroup - TS
User-defined AE category: Ventricular Tachyarrhythmia (narrow 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	2989	11	0.4	2996	13	0.4	0.6867	1.18 (0.53, 2.63)	1.18 (0.53, 2.64)	0.00 (0.00,0.00)	
Sex											0.2258
Male	1653	8	0.5	1658	12	0.7	0.3733	1.50 (0.61, 3.65)	1.50 (0.61, 3.68)	0.00 (0.00,0.01)	
Female	1336	3	0.2	1338	1	0.1	0.3162	0.33 (0.03, 3.20)	0.33 (0.03, 3.20)	0.00 (0.00,0.00)	
Age [years]											0.3740
<70	1084	4	0.4	1066	7	0.7	0.3499	1.78 (0.52, 6.06)	1.78 (0.52, 6.11)	0.00 (0.00,0.01)	
>=70	1905	7	0.4	1930	6	0.3	0.7631	0.85 (0.28, 2.51)	0.85 (0.28, 2.52)	0.00 (0.00,0.00)	
Region											0.8220
North America	359	1	0.3	359	1	0.3	1.0000	1.00 (0.06, 15.93)	1.00 (0.06, 16.05)	0.00 (-0.01,0.01)	
Latin America	757	4	0.5	758	4	0.5	0.9985	1.00 (0.25, 3.98)	1.00 (0.25, 4.01)	0.00 (-0.01,0.01)	
Europe	1341	5	0.4	1346	6	0.4	0.7673	1.20 (0.37, 3.91)	1.20 (0.36, 3.93)	0.00 (0.00,0.01)	
Asia	343	1	0.3	343	0	0	0.4789	0.33 (0.01, 8.15)	0.33 (0.01, 8.19)	0.00 (-0.01,0.01)	
Other	189	0	0	190	2	1.1	0.2482	4.97 (0.24,102.91)	5.03 (0.24,105.40)	0.01 (-0.01,0.03)	
OECD member											0.8779
No	847	3	0.4	868	4	0.5	0.7291	1.30 (0.29, 5.80)	1.30 (0.29, 5.84)	0.00 (0.00,0.01)	
Yes	2142	8	0.4	2128	9	0.4	0.7975	1.13 (0.44, 2.93)	1.13 (0.44, 2.94)	0.00 (0.00,0.00)	
Baseline NYHA											0.4512
II^	2450	8	0.3	2435	11	0.5	0.4821	1.38 (0.56, 3.43)	1.39 (0.56, 3.45)	0.00 (0.00,0.00)	
III/IV	539	3	0.6	561	2	0.4	0.6219	0.64 (0.11, 3.82)	0.64 (0.11, 3.84)	0.00 (-0.01,0.01)	
Baseline Diabetes Status											0.6706
Diabetic	1471	5	0.3	1465	7	0.5	0.5581	1.41 (0.45, 4.42)	1.41 (0.45, 4.45)	0.00 (0.00,0.01)	
Non-Diabetic	1518	6	0.4	1531	6	0.4	0.9882	0.99 (0.32, 3.07)	0.99 (0.32, 3.08)	0.00 (0.00,0.00)	

Analysis is based on study 1245.110.
^ Patients with NYHA class I are counted in subgroup NYHA class II.
*** Confirmed hypoglycaemic AEs are defined by a glucose concentration <=70 mg/dL (3.9 mmol/L) or requiring assistance.
Risk ratios and odds ratios with confidence intervals (CIs) are estimated by Cochran-Mantel-Haenszel method. For risk differences standard Wald asymptotic confidence limits are calculated. A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied in case of any zero cells in contingency table.
Only treatment emergent AEs are displayed (onset between first dose until treatment stop +7 days).
MedDRA version: 23.1. * Chi-square test for treatment effect ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction).

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Table R.1.2.3: 3 Proportion of patients with severe adverse events of special interest and severe other specific AEs by user-defined category overall and by subgroup - TS
User-defined AE category: Ventricular Tachyarrhythmia (narrow 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 Diabetes Status											0.9127
Diabetic	1471	5	0.3	1465	7	0.5	0.5581	1.41 (0.45, 4.42)	1.41 (0.45, 4.45)	0.00 (0.00,0.01)	
Pre-Diabetes	979	4	0.4	1001	4	0.4	0.9749	0.98 (0.25, 3.90)	0.98 (0.24, 3.92)	0.00 (-0.01,0.01)	
Normal (no pre-diabetes)	539	2	0.4	530	2	0.4	0.9865	1.02 (0.14, 7.19)	1.02 (0.14, 7.25)	0.00 (-0.01,0.01)	
Baseline BMI [kg/m²]											0.3854
<30	1641	7	0.4	1654	6	0.4	0.7702	0.85 (0.29, 2.53)	0.85 (0.29, 2.53)	0.00 (0.00,0.00)	
>=30	1348	4	0.3	1342	7	0.5	0.3608	1.76 (0.52, 5.99)	1.76 (0.51, 6.03)	0.00 (0.00,0.01)	
Baseline eGFR (CKD-EPI) [mL/min/1.73m²]											0.4477
>=60	1505	6	0.4	1493	5	0.3	0.7728	0.84 (0.26, 2.75)	0.84 (0.26, 2.76)	0.00 (0.00,0.00)	
<60	1482	5	0.3	1503	8	0.5	0.4188	1.58 (0.52, 4.81)	1.58 (0.52, 4.84)	0.00 (0.00,0.01)	
History of HHF (in the last 12 months)											0.4469
No	2320	8	0.3	2297	11	0.5	0.4768	1.39 (0.56, 3.45)	1.39 (0.56, 3.46)	0.00 (0.00,0.01)	
Yes	669	3	0.4	699	2	0.3	0.6190	0.64 (0.11, 3.81)	0.64 (0.11, 3.82)	0.00 (-0.01,0.00)	
Baseline SBP (</>= median)											0.8924
< median	1474	7	0.5	1496	8	0.5	0.8180	1.13 (0.41, 3.10)	1.13 (0.41, 3.12)	0.00 (0.00,0.01)	
>= median	1515	4	0.3	1500	5	0.3	0.7273	1.26 (0.34, 4.69)	1.26 (0.34, 4.71)	0.00 (0.00,0.00)	
History of atrial fibrillation or atrial flutter											0.2312
No	1426	7	0.5	1417	5	0.4	0.5703	0.72 (0.23, 2.26)	0.72 (0.23, 2.27)	0.00 (-0.01,0.00)	
Yes	1558	4	0.3	1575	8	0.5	0.2551	1.98 (0.60, 6.56)	1.98 (0.60, 6.60)	0.00 (0.00,0.01)	

Analysis is based on study 1245.110.
^ Patients with NYHA class I are counted in subgroup NYHA class II.
*** Confirmed hypoglycaemic AEs are defined by a glucose concentration <=70 mg/dL (3.9 mmol/L) or requiring assistance.
Risk ratios and odds ratios with confidence intervals (CIs) are estimated by Cochran-Mantel-Haenszel method. For risk differences standard Wald asymptotic confidence limits are calculated. A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied in case of any zero cells in contingency table.
Only treatment emergent AEs are displayed (onset between first dose until treatment stop +7 days).
MedDRA version: 23.1. * Chi-square test for treatment effect ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction).

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Table R.1.2.3: 3 Proportion of patients with severe adverse events of special interest and severe other specific AEs by user-defined category overall and by subgroup - TS
User-defined AE category: Ventricular Tachyarrhythmia (narrow 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 LVEF [%]											0.2265
< 50	988	4	0.4	995	8	0.8	0.2518	1.99 (0.60, 6.57)	1.99 (0.60, 6.64)	0.00 (0.00,0.01)	
>= 50	2001	7	0.3	2001	5	0.2	0.5631	0.71 (0.23, 2.25)	0.71 (0.23, 2.25)	0.00 (0.00,0.00)	
Baseline LVEF [%]											0.3721
<50	988	4	0.4	995	8	0.8	0.2518	1.99 (0.60, 6.57)	1.99 (0.60, 6.64)	0.00 (0.00,0.01)	
50 to <60	1030	3	0.3	1028	1	0.1	0.3178	0.33 (0.03, 3.21)	0.33 (0.03, 3.21)	0.00 (-0.01,0.00)	
>=60	971	4	0.4	973	4	0.4	0.9977	1.00 (0.25, 3.98)	1.00 (0.25, 4.00)	0.00 (-0.01,0.01)	
Baseline NT-proBNP [pg/mL] (</>=median by atrial fibrillation/flutter status)											0.0740
< median	1507	0	0	1476	5	0.3	0.0386	11.23 (0.62,202.92)	11.27 (0.62,203.98)	0.00 (0.00,0.01)	
>= median	1475	11	0.7	1516	8	0.5	0.4530	0.71 (0.29, 1.75)	0.71 (0.28, 1.76)	0.00 (-0.01,0.00)	
Baseline uric acid [mg/dL] (tertiles)											0.8098
<T1	975	2	0.2	963	3	0.3	0.6443	1.52 (0.25, 9.07)	1.52 (0.25, 9.12)	0.00 (0.00,0.01)	
>=T1 and <T2	966	0	0	1032	1	0.1	0.5085	2.81 (0.11, 68.85)	2.81 (0.11, 69.08)	0.00 (0.00,0.00)	
>=T2	1016	9	0.9	970	9	0.9	0.9213	1.05 (0.42, 2.63)	1.05 (0.41, 2.65)	0.00 (-0.01,0.01)	
Baseline use of MRA											0.2179
No	1865	7	0.4	1878	5	0.3	0.5550	0.71 (0.23, 2.23)	0.71 (0.22, 2.24)	0.00 (0.00,0.00)	
Yes	1124	4	0.4	1118	8	0.7	0.2432	2.01 (0.61, 6.66)	2.02 (0.61, 6.72)	0.00 (0.00,0.01)	
Baseline use of ACE-inhibitor, ARB or ARNi											0.5044
No	586	3	0.5	568	2	0.4	0.6794	0.69 (0.12, 4.10)	0.69 (0.11, 4.12)	0.00 (-0.01,0.01)	
Yes	2403	8	0.3	2428	11	0.5	0.5048	1.36 (0.55, 3.38)	1.36 (0.55, 3.39)	0.00 (0.00,0.00)	

Analysis is based on study 1245.110.
^ Patients with NYHA class I are counted in subgroup NYHA class II.
*** Confirmed hypoglycaemic AEs are defined by a glucose concentration <=70 mg/dL (3.9 mmol/L) or requiring assistance.
Risk ratios and odds ratios with confidence intervals (CIs) are estimated by Cochran-Mantel-Haenszel method. For risk differences standard Wald asymptotic confidence limits are calculated. A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied in case of any zero cells in contingency table.
Only treatment emergent AEs are displayed (onset between first dose until treatment stop +7 days).
MedDRA version: 23.1. * Chi-square test for treatment effect ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction).

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R.1.2.4 Adverse events on SOC level

Table R.1.2.4: 1 Proportion of patients with any adverse event occuring in at least 1% of the patients in either treatment arm in the overall population on SOC level by SOC, 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	2989	1142	38.2	2996	1146	38.3	0.9719	1.00	(0.94, 1.07)	1.00	(0.90, 1.11)	0.00	(-0.02, 0.03)	

Analysis is based on study 1245.110.
^ Patients with NYHA class I are counted in subgroup NYHA class II.
Risk ratios and odds ratios with confidence intervals (CIs) are estimated by Cochran-Mantel-Haenszel method. For risk differences standard Wald asymptotic confidence limits are calculated. A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied in case of any zero cells in contingency table.
Only treatment emergent AEs are displayed (onset between first dose until treatment stop +7 days).
MedDRA version: 23.1. * Chi-square test for treatment effect ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction).

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Table R.1.2.4: 1 Proportion of patients with any adverse event occuring in at least 1% of the patients in either treatment arm in the overall population on SOC level by SOC, 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	2989	1082	36.2	2996	946	31.6	0.0002	0.87	(0.81,	0.94)	0.81	(0.73,	0.91)	-0.05	(-0.07,-0.02)	
Sex																0.2825
Male	1653	613	37.1	1658	518	31.2	0.0004	0.84	(0.77,	0.93)	0.77	(0.67,	0.89)	-0.06	(-0.09,-0.03)	
Female	1336	469	35.1	1338	428	32.0	0.0879	0.91	(0.82,	1.01)	0.87	(0.74,	1.02)	-0.03	(-0.07, 0.00)	
Age [years]																0.3654
<70	1084	354	32.7	1066	318	29.8	0.1576	0.91	(0.81,	1.04)	0.88	(0.73,	1.05)	-0.03	(-0.07, 0.01)	
>=70	1905	728	38.2	1930	628	32.5	0.0002	0.85	(0.78,	0.93)	0.78	(0.68,	0.89)	-0.06	(-0.09,-0.03)	
Region																0.9048
North America	359	153	42.6	359	143	39.8	0.4484	0.93	(0.78,	1.11)	0.89	(0.66,	1.20)	-0.03	(-0.10, 0.04)	
Latin America	757	259	34.2	758	223	29.4	0.0451	0.86	(0.74,	1.00)	0.80	(0.65,	1.00)	-0.05	(-0.09, 0.00)	
Europe	1341	482	35.9	1346	415	30.8	0.0050	0.86	(0.77,	0.95)	0.79	(0.68,	0.93)	-0.05	(-0.09,-0.02)	
Asia	343	127	37.0	343	115	33.5	0.3376	0.91	(0.74,	1.11)	0.86	(0.63,	1.17)	-0.03	(-0.11, 0.04)	
Other	189	61	32.3	190	50	26.3	0.2024	0.82	(0.60,	1.12)	0.75	(0.48,	1.17)	-0.06	(-0.15, 0.03)	
OECD member																0.7802
No	847	299	35.3	868	263	30.3	0.0274	0.86	(0.75,	0.98)	0.80	(0.65,	0.98)	-0.05	(-0.09,-0.01)	
Yes	2142	783	36.6	2128	683	32.1	0.0022	0.88	(0.81,	0.95)	0.82	(0.72,	0.93)	-0.04	(-0.07,-0.02)	
Baseline NYHA																0.8927
II^	2450	829	33.8	2435	715	29.4	0.0008	0.87	(0.80,	0.94)	0.81	(0.72,	0.92)	-0.04	(-0.07,-0.02)	
III/IV	539	253	46.9	561	231	41.2	0.0543	0.88	(0.77,	1.00)	0.79	(0.62,	1.00)	-0.06	(-0.12, 0.00)	
Baseline Diabetes Status																0.1119
Diabetic	1471	563	38.3	1465	462	31.5	0.0001	0.82	(0.75,	0.91)	0.74	(0.64,	0.87)	-0.07	(-0.10,-0.03)	
Non-Diabetic	1518	519	34.2	1531	484	31.6	0.1300	0.92	(0.84,	1.02)	0.89	(0.76,	1.04)	-0.03	(-0.06, 0.01)	

Analysis is based on study 1245.110.
^ Patients with NYHA class I are counted in subgroup NYHA class II.
Risk ratios and odds ratios with confidence intervals (CIs) are estimated by Cochran-Mantel-Haenszel method. For risk differences standard Wald asymptotic confidence limits are calculated. A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied in case of any zero cells in contingency table.
Only treatment emergent AEs are displayed (onset between first dose until treatment stop +7 days).
MedDRA version: 23.1. * Chi-square test for treatment effect ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction).

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Table R.1.2.4: 1 Proportion of patients with any adverse event occuring in at least 1% of the patients in either treatment arm in the overall population on SOC level by SOC, 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 Diabetes Status																0.2567
Diabetic	1471	563	38.3	1465	462	31.5	0.0001	0.82	(0.75,	0.91)	0.74	(0.64,	0.87)	-0.07	(-0.10,-0.03)	
Pre-Diabetes	979	326	33.3	1001	304	30.4	0.1617	0.91	(0.80,	1.04)	0.87	(0.72,	1.06)	-0.03	(-0.07, 0.01)	
Normal (no pre-diabetes)	539	193	35.8	530	180	34.0	0.5269	0.95	(0.81,	1.12)	0.92	(0.72,	1.19)	-0.02	(-0.08, 0.04)	
Baseline BMI [kg/m²]																0.7236
<30	1641	596	36.3	1654	530	32.0	0.0097	0.88	(0.80,	0.97)	0.83	(0.72,	0.95)	-0.04	(-0.08,-0.01)	
>=30	1348	486	36.1	1342	416	31.0	0.0055	0.86	(0.77,	0.96)	0.80	(0.68,	0.94)	-0.05	(-0.09,-0.01)	
Baseline eGFR (CKD-EPI) [mL/min/1.73m²]																0.7432
>=60	1505	473	31.4	1493	414	27.7	0.0265	0.88	(0.79,	0.99)	0.84	(0.72,	0.98)	-0.04	(-0.07, 0.00)	
<60	1482	609	41.1	1503	532	35.4	0.0014	0.86	(0.79,	0.94)	0.79	(0.68,	0.91)	-0.06	(-0.09,-0.02)	
History of HHF (in the last 12 months)																0.7367
No	2320	795	34.3	2297	680	29.6	0.0007	0.86	(0.79,	0.94)	0.81	(0.71,	0.91)	-0.05	(-0.07,-0.02)	
Yes	669	287	42.9	699	266	38.1	0.0679	0.89	(0.78,	1.01)	0.82	(0.66,	1.02)	-0.05	(-0.10, 0.00)	
Baseline SBP (</>= median)																0.6190
< median	1474	544	36.9	1496	490	32.8	0.0175	0.89	(0.80,	0.98)	0.83	(0.72,	0.97)	-0.04	(-0.08,-0.01)	
>= median	1515	538	35.5	1500	456	30.4	0.0028	0.86	(0.77,	0.95)	0.79	(0.68,	0.92)	-0.05	(-0.08,-0.02)	
History of atrial fibrillation or atrial flutter																0.6413
No	1426	472	33.1	1417	417	29.4	0.0348	0.89	(0.80,	0.99)	0.84	(0.72,	0.99)	-0.04	(-0.07, 0.00)	
Yes	1558	609	39.1	1575	529	33.6	0.0014	0.86	(0.78,	0.94)	0.79	(0.68,	0.91)	-0.06	(-0.09,-0.02)	

Analysis is based on study 1245.110.
^ Patients with NYHA class I are counted in subgroup NYHA class II.
Risk ratios and odds ratios with confidence intervals (CIs) are estimated by Cochran-Mantel-Haenszel method. For risk differences standard Wald asymptotic confidence limits are calculated. A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied in case of any zero cells in contingency table.
Only treatment emergent AEs are displayed (onset between first dose until treatment stop +7 days).
MedDRA version: 23.1. * Chi-square test for treatment effect ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction).

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Table R.1.2.4: 1 Proportion of patients with any adverse event occuring in at least 1% of the patients in either treatment arm in the overall population on SOC level by SOC, 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 LVEF [%]																0.0900
< 50	988	367	37.1	995	295	29.6	0.0004	0.80	(0.70,	0.90)	0.71	(0.59,	0.86)	-0.07	(-0.12,-0.03)	
>= 50	2001	715	35.7	2001	651	32.5	0.0329	0.91	(0.84,	0.99)	0.87	(0.76,	0.99)	-0.03	(-0.06, 0.00)	
Baseline LVEF [%]																0.0459
<50	988	367	37.1	995	295	29.6	0.0004	0.80	(0.70,	0.90)	0.71	(0.59,	0.86)	-0.07	(-0.12,-0.03)	
50 to <60	1030	384	37.3	1028	323	31.4	0.0051	0.84	(0.75,	0.95)	0.77	(0.64,	0.93)	-0.06	(-0.10,-0.02)	
>=60	971	331	34.1	973	328	33.7	0.8601	0.99	(0.87,	1.12)	0.98	(0.81,	1.19)	0.00	(-0.05, 0.04)	
Baseline NT-proBNP [pg/mL] (</>=median by atrial fibrillation/flutter status)																0.8479
< median	1507	476	31.6	1476	409	27.7	0.0205	0.88	(0.79,	0.98)	0.83	(0.71,	0.97)	-0.04	(-0.07,-0.01)	
>= median	1475	604	40.9	1516	537	35.4	0.0019	0.87	(0.79,	0.95)	0.79	(0.68,	0.92)	-0.06	(-0.09,-0.02)	
Baseline uric acid [mg/dL] (tertiles)																0.7802
<T1	975	324	33.2	963	271	28.1	0.0152	0.85	(0.74,	0.97)	0.79	(0.65,	0.95)	-0.05	(-0.09,-0.01)	
>=T1 and <T2	966	321	33.2	1032	310	30.0	0.1252	0.90	(0.79,	1.03)	0.86	(0.71,	1.04)	-0.03	(-0.07, 0.01)	
>=T2	1016	423	41.6	970	358	36.9	0.0311	0.89	(0.79,	0.99)	0.82	(0.68,	0.98)	-0.05	(-0.09, 0.00)	
Baseline use of MRA																0.1383
No	1865	648	34.7	1878	594	31.6	0.0429	0.91	(0.83,	1.00)	0.87	(0.76,	1.00)	-0.03	(-0.06, 0.00)	
Yes	1124	434	38.6	1118	352	31.5	0.0004	0.82	(0.73,	0.91)	0.73	(0.61,	0.87)	-0.07	(-0.11,-0.03)	
Baseline use of ACE-inhibitor, ARB or ARNi																0.0101
No	586	221	37.7	568	222	39.1	0.6321	1.04	(0.90,	1.20)	1.06	(0.84,	1.34)	0.01	(-0.04, 0.07)	
Yes	2403	861	35.8	2428	724	29.8	<0.0001	0.83	(0.77,	0.90)	0.76	(0.67,	0.86)	-0.06	(-0.09,-0.03)	

Analysis is based on study 1245.110.
^ Patients with NYHA class I are counted in subgroup NYHA class II.
Risk ratios and odds ratios with confidence intervals (CIs) are estimated by Cochran-Mantel-Haenszel method. For risk differences standard Wald asymptotic confidence limits are calculated. A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied in case of any zero cells in contingency table.
Only treatment emergent AEs are displayed (onset between first dose until treatment stop +7 days).
MedDRA version: 23.1. * Chi-square test for treatment effect ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction).

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Table R.1.2.4: 1 Proportion of patients with any adverse event occuring in at least 1% of the patients in either treatment arm in the overall population on SOC level by SOC, 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	2989	937	31.3	2996	807	26.9	0.0002	0.86	(0.79, 0.93)	0.81	(0.72, 0.90)	-0.04	(-0.07,-0.02)	
Sex														0.6219
Male	1653	514	31.1	1658	451	27.2	0.0137	0.87	(0.79, 0.97)	0.83	(0.71, 0.96)	-0.04	(-0.07,-0.01)	
Female	1336	423	31.7	1338	356	26.6	0.0040	0.84	(0.75, 0.95)	0.78	(0.66, 0.92)	-0.05	(-0.08,-0.02)	
Age [years]														0.2573
<70	1084	369	34.0	1066	330	31.0	0.1270	0.91	(0.80, 1.03)	0.87	(0.73, 1.04)	-0.03	(-0.07, 0.01)	
>=70	1905	568	29.8	1930	477	24.7	0.0004	0.83	(0.75, 0.92)	0.77	(0.67, 0.89)	-0.05	(-0.08,-0.02)	
Region														0.2968
North America	359	114	31.8	359	117	32.6	0.8106	1.03	(0.83, 1.27)	1.04	(0.76, 1.42)	0.01	(-0.06, 0.08)	
Latin America	757	274	36.2	758	227	29.9	0.0097	0.83	(0.72, 0.96)	0.75	(0.61, 0.93)	-0.06	(-0.11,-0.02)	
Europe	1341	364	27.1	1346	292	21.7	0.0010	0.80	(0.70, 0.91)	0.74	(0.62, 0.89)	-0.05	(-0.09,-0.02)	
Asia	343	107	31.2	343	102	29.7	0.6783	0.95	(0.76, 1.20)	0.93	(0.67, 1.29)	-0.01	(-0.08, 0.05)	
Other	189	78	41.3	190	69	36.3	0.3223	0.88	(0.68, 1.13)	0.81	(0.54, 1.23)	-0.05	(-0.15, 0.05)	
OECD member														0.8794
No	847	312	36.8	868	272	31.3	0.0163	0.85	(0.75, 0.97)	0.78	(0.64, 0.96)	-0.05	(-0.10,-0.01)	
Yes	2142	625	29.2	2128	535	25.1	0.0030	0.86	(0.78, 0.95)	0.82	(0.71, 0.93)	-0.04	(-0.07,-0.01)	
Baseline NYHA														0.8037
II^	2450	738	30.1	2435	626	25.7	0.0006	0.85	(0.78, 0.93)	0.80	(0.71, 0.91)	-0.04	(-0.07,-0.02)	
III/IV	539	199	36.9	561	181	32.3	0.1045	0.87	(0.74, 1.03)	0.81	(0.63, 1.04)	-0.05	(-0.10, 0.01)	
Baseline Diabetes Status														0.5260
Diabetic	1471	575	39.1	1465	503	34.3	0.0075	0.88	(0.80, 0.97)	0.81	(0.70, 0.95)	-0.05	(-0.08,-0.01)	
Non-Diabetic	1518	362	23.8	1531	304	19.9	0.0077	0.83	(0.73, 0.95)	0.79	(0.67, 0.94)	-0.04	(-0.07,-0.01)	

Analysis is based on study 1245.110.
^ Patients with NYHA class I are counted in subgroup NYHA class II.
Risk ratios and odds ratios with confidence intervals (CIs) are estimated by Cochran-Mantel-Haenszel method. For risk differences standard Wald asymptotic confidence limits are calculated. A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied in case of any zero cells in contingency table.
Only treatment emergent AEs are displayed (onset between first dose until treatment stop +7 days).
MedDRA version: 23.1. * Chi-square test for treatment effect ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction).

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Table R.1.2.4: 1 Proportion of patients with any adverse event occuring in at least 1% of the patients in either treatment arm in the overall population on SOC level by SOC, 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 Diabetes Status														0.7994
Diabetic	1471	575	39.1	1465	503	34.3	0.0075	0.88	(0.80, 0.97)	0.81	(0.70, 0.95)	-0.05	(-0.08,-0.01)	
Pre-Diabetes	979	243	24.8	1001	205	20.5	0.0210	0.83	(0.70, 0.97)	0.78	(0.63, 0.96)	-0.04	(-0.08,-0.01)	
Normal (no pre-diabetes)	539	119	22.1	530	99	18.7	0.1679	0.85	(0.67, 1.07)	0.81	(0.60, 1.09)	-0.03	(-0.08, 0.01)	
Baseline BMI [kg/m²]														0.8417
<30	1641	499	30.4	1654	429	25.9	0.0043	0.85	(0.76, 0.95)	0.80	(0.69, 0.93)	-0.04	(-0.08,-0.01)	
>=30	1348	438	32.5	1342	378	28.2	0.0147	0.87	(0.77, 0.97)	0.81	(0.69, 0.96)	-0.04	(-0.08,-0.01)	
Baseline eGFR (CKD-EPI) [mL/min/1.73m²]														0.2700
>=60	1505	416	27.6	1493	336	22.5	0.0012	0.81	(0.72, 0.92)	0.76	(0.64, 0.90)	-0.05	(-0.08,-0.02)	
<60	1482	521	35.2	1503	471	31.3	0.0268	0.89	(0.81, 0.99)	0.84	(0.72, 0.98)	-0.04	(-0.07, 0.00)	
History of HHF (in the last 12 months)														0.8996
No	2320	698	30.1	2297	591	25.7	0.0010	0.86	(0.78, 0.94)	0.81	(0.71, 0.92)	-0.04	(-0.07,-0.02)	
Yes	669	239	35.7	699	216	30.9	0.0584	0.86	(0.74, 1.01)	0.80	(0.64, 1.01)	-0.05	(-0.10, 0.00)	
Baseline SBP (</>= median)														0.4013
< median	1474	485	32.9	1496	409	27.3	0.0009	0.83	(0.74, 0.93)	0.77	(0.66, 0.90)	-0.06	(-0.09,-0.02)	
>= median	1515	452	29.8	1500	398	26.5	0.0439	0.89	(0.79, 1.00)	0.85	(0.72, 1.00)	-0.03	(-0.07, 0.00)	
History of atrial fibrillation or atrial flutter														0.4496
No	1426	467	32.7	1417	410	28.9	0.0277	0.88	(0.79, 0.99)	0.84	(0.71, 0.98)	-0.04	(-0.07, 0.00)	
Yes	1558	469	30.1	1575	394	25.0	0.0014	0.83	(0.74, 0.93)	0.77	(0.66, 0.91)	-0.05	(-0.08,-0.02)	

Analysis is based on study 1245.110.
^ Patients with NYHA class I are counted in subgroup NYHA class II.
Risk ratios and odds ratios with confidence intervals (CIs) are estimated by Cochran-Mantel-Haenszel method. For risk differences standard Wald asymptotic confidence limits are calculated. A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied in case of any zero cells in contingency table.
Only treatment emergent AEs are displayed (onset between first dose until treatment stop +7 days).
MedDRA version: 23.1. * Chi-square test for treatment effect ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction).

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Table R.1.2.4: 1 Proportion of patients with any adverse event occuring in at least 1% of the patients in either treatment arm in the overall population on SOC level by SOC, 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 LVEF [%]																0.8958
< 50	988	319	32.3	995	274	27.5	0.0209	0.85	(0.74,	0.98)	0.80	(0.66,	0.97)	-0.05	(-0.09,-0.01)	
>= 50	2001	618	30.9	2001	533	26.6	0.0030	0.86	(0.78,	0.95)	0.81	(0.71,	0.93)	-0.04	(-0.07,-0.01)	
Baseline LVEF [%]																0.7339
<50	988	319	32.3	995	274	27.5	0.0209	0.85	(0.74,	0.98)	0.80	(0.66,	0.97)	-0.05	(-0.09,-0.01)	
50 to <60	1030	321	31.2	1028	266	25.9	0.0079	0.83	(0.72,	0.95)	0.77	(0.64,	0.93)	-0.05	(-0.09,-0.01)	
>=60	971	297	30.6	973	267	27.4	0.1264	0.90	(0.78,	1.03)	0.86	(0.71,	1.04)	-0.03	(-0.07, 0.01)	
Baseline NT-proBNP [pg/mL] (</>=median by atrial fibrillation/flutter status)																0.5975
< median	1507	459	30.5	1476	376	25.5	0.0024	0.84	(0.74,	0.94)	0.78	(0.66,	0.92)	-0.05	(-0.08,-0.02)	
>= median	1475	477	32.3	1516	428	28.2	0.0145	0.87	(0.78,	0.97)	0.82	(0.70,	0.96)	-0.04	(-0.07,-0.01)	
Baseline uric acid [mg/dL] (tertiles)																0.7457
<T1	975	242	24.8	963	209	21.7	0.1044	0.87	(0.74,	1.03)	0.84	(0.68,	1.04)	-0.03	(-0.07, 0.01)	
>=T1 and <T2	966	265	27.4	1032	255	24.7	0.1656	0.90	(0.78,	1.04)	0.87	(0.71,	1.06)	-0.03	(-0.07, 0.01)	
>=T2	1016	422	41.5	970	338	34.8	0.0022	0.84	(0.75,	0.94)	0.75	(0.63,	0.90)	-0.07	(-0.11,-0.02)	
Baseline use of MRA																0.0134
No	1865	526	28.2	1878	495	26.4	0.2049	0.93	(0.84,	1.04)	0.91	(0.79,	1.05)	-0.02	(-0.05, 0.01)	
Yes	1124	411	36.6	1118	312	27.9	<0.0001	0.76	(0.68,	0.86)	0.67	(0.56,	0.80)	-0.09	(-0.13,-0.05)	
Baseline use of ACE-inhibitor, ARB or ARNi																0.4978
No	586	182	31.1	568	143	25.2	0.0264	0.81	(0.67,	0.98)	0.75	(0.58,	0.97)	-0.06	(-0.11,-0.01)	
Yes	2403	755	31.4	2428	664	27.3	0.0019	0.87	(0.80,	0.95)	0.82	(0.73,	0.93)	-0.04	(-0.07,-0.02)	

Analysis is based on study 1245.110.
^ Patients with NYHA class I are counted in subgroup NYHA class II.
Risk ratios and odds ratios with confidence intervals (CIs) are estimated by Cochran-Mantel-Haenszel method. For risk differences standard Wald asymptotic confidence limits are calculated. A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied in case of any zero cells in contingency table.
Only treatment emergent AEs are displayed (onset between first dose until treatment stop +7 days).
MedDRA version: 23.1. * Chi-square test for treatment effect ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction).

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Table R.1.2.4: 1 Proportion of patients with any adverse event occuring in at least 1% of the patients in either treatment arm in the overall population on SOC level by SOC, 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	2989	639	21.4	2996	589	19.7	0.0997	0.92	(0.83, 1.02)	0.90	(0.79, 1.02)	-0.02	(-0.04, 0.00)	

Analysis is based on study 1245.110.
^ Patients with NYHA class I are counted in subgroup NYHA class II.
Risk ratios and odds ratios with confidence intervals (CIs) are estimated by Cochran-Mantel-Haenszel method. For risk differences standard Wald asymptotic confidence limits are calculated. A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied in case of any zero cells in contingency table.
Only treatment emergent AEs are displayed (onset between first dose until treatment stop +7 days).
MedDRA version: 23.1. * Chi-square test for treatment effect ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction).

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Table R.1.2.4: 1 Proportion of patients with any adverse event occuring in at least 1% of the patients in either treatment arm in the overall population on SOC level by SOC, 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	2989	611	20.4	2996	625	20.9	0.6885	1.02 (0.92, 1.13)	1.03 (0.91, 1.16)	0.00 (-0.02, 0.02)	

Analysis is based on study 1245.110.
^ Patients with NYHA class I are counted in subgroup NYHA class II.
Risk ratios and odds ratios with confidence intervals (CIs) are estimated by Cochran-Mantel-Haenszel method. For risk differences standard Wald asymptotic confidence limits are calculated. A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied in case of any zero cells in contingency table.
Only treatment emergent AEs are displayed (onset between first dose until treatment stop +7 days).
MedDRA version: 23.1. * Chi-square test for treatment effect ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction).

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Table R.1.2.4: 1 Proportion of patients with any adverse event occuring in at least 1% of the patients in either treatment arm in the overall population on SOC level by SOC, 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	2989	612	20.5	2996	610	20.4	0.9124	0.99	(0.90, 1.10)	0.99	(0.88, 1.13)	0.00	(-0.02, 0.02)	

Analysis is based on study 1245.110.
^ Patients with NYHA class I are counted in subgroup NYHA class II.
Risk ratios and odds ratios with confidence intervals (CIs) are estimated by Cochran-Mantel-Haenszel method. For risk differences standard Wald asymptotic confidence limits are calculated. A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied in case of any zero cells in contingency table.
Only treatment emergent AEs are displayed (onset between first dose until treatment stop +7 days).
MedDRA version: 23.1. * Chi-square test for treatment effect ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction).

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Table R.1.2.4: 1 Proportion of patients with any adverse event occuring in at least 1% of the patients in either treatment arm in the overall population on SOC level by SOC, 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	2989	607	20.3	2996	534	17.8	0.0144	0.88	(0.79, 0.97)	0.85	(0.75, 0.97)	-0.02	(-0.04, 0.00)	
Sex														0.2494
Male	1653	306	18.5	1658	253	15.3	0.0125	0.82	(0.71, 0.96)	0.79	(0.66, 0.95)	-0.03	(-0.06,-0.01)	
Female	1336	301	22.5	1338	281	21.0	0.3382	0.93	(0.81, 1.08)	0.91	(0.76, 1.10)	-0.02	(-0.05, 0.02)	
Age [years]														0.7082
<70	1084	196	18.1	1066	164	15.4	0.0941	0.85	(0.70, 1.03)	0.82	(0.66, 1.03)	-0.03	(-0.06, 0.00)	
>=70	1905	411	21.6	1930	370	19.2	0.0646	0.89	(0.78, 1.01)	0.86	(0.74, 1.01)	-0.02	(-0.05, 0.00)	
Region														0.2494
North America	359	117	32.6	359	89	24.8	0.0209	0.76	(0.60, 0.96)	0.68	(0.49, 0.94)	-0.08	(-0.14,-0.01)	
Latin America	757	124	16.4	758	122	16.1	0.8803	0.98	(0.78, 1.24)	0.98	(0.75, 1.29)	0.00	(-0.04, 0.03)	
Europe	1341	211	15.7	1346	204	15.2	0.6782	0.96	(0.81, 1.15)	0.96	(0.78, 1.18)	-0.01	(-0.03, 0.02)	
Asia	343	117	34.1	343	87	25.4	0.0122	0.74	(0.59, 0.94)	0.66	(0.47, 0.91)	-0.09	(-0.16,-0.02)	
Other	189	38	20.1	190	32	16.8	0.4130	0.84	(0.55, 1.28)	0.80	(0.48, 1.35)	-0.03	(-0.11, 0.05)	
OECD member														0.3834
No	847	140	16.5	868	137	15.8	0.6749	0.95	(0.77, 1.18)	0.95	(0.73, 1.22)	-0.01	(-0.04, 0.03)	
Yes	2142	467	21.8	2128	397	18.7	0.0105	0.86	(0.76, 0.96)	0.82	(0.71, 0.96)	-0.03	(-0.06,-0.01)	
Baseline NYHA														0.1634
II^	2450	481	19.6	2435	435	17.9	0.1134	0.91	(0.81, 1.02)	0.89	(0.77, 1.03)	-0.02	(-0.04, 0.00)	
III/IV	539	126	23.4	561	99	17.6	0.0185	0.75	(0.60, 0.96)	0.70	(0.52, 0.94)	-0.06	(-0.10,-0.01)	
Baseline Diabetes Status														0.6373
Diabetic	1471	283	19.2	1465	254	17.3	0.1828	0.90	(0.77, 1.05)	0.88	(0.73, 1.06)	-0.02	(-0.05, 0.01)	
Non-Diabetic	1518	324	21.3	1531	280	18.3	0.0343	0.86	(0.74, 0.99)	0.82	(0.69, 0.99)	-0.03	(-0.06, 0.00)	

Analysis is based on study 1245.110.
^ Patients with NYHA class I are counted in subgroup NYHA class II.
Risk ratios and odds ratios with confidence intervals (CIs) are estimated by Cochran-Mantel-Haenszel method. For risk differences standard Wald asymptotic confidence limits are calculated. A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied in case of any zero cells in contingency table.
Only treatment emergent AEs are displayed (onset between first dose until treatment stop +7 days).
MedDRA version: 23.1. * Chi-square test for treatment effect ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction).

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Table R.1.2.4: 1 Proportion of patients with any adverse event occuring in at least 1% of the patients in either treatment arm in the overall population on SOC level by SOC, 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 Diabetes Status														0.8903
Diabetic	1471	283	19.2	1465	254	17.3	0.1828	0.90	(0.77, 1.05)	0.88	(0.73, 1.06)	-0.02	(-0.05, 0.01)	
Pre-Diabetes	979	218	22.3	1001	191	19.1	0.0799	0.86	(0.72, 1.02)	0.82	(0.66, 1.02)	-0.03	(-0.07, 0.00)	
Normal (no pre-diabetes)	539	106	19.7	530	89	16.8	0.2238	0.85	(0.66, 1.10)	0.82	(0.60, 1.13)	-0.03	(-0.07, 0.02)	
Baseline BMI [kg/m²]														0.4438
<30	1641	339	20.7	1654	289	17.5	0.0199	0.85	(0.73, 0.97)	0.81	(0.68, 0.97)	-0.03	(-0.06,-0.01)	
>=30	1348	268	19.9	1342	245	18.3	0.2834	0.92	(0.79, 1.07)	0.90	(0.74, 1.09)	-0.02	(-0.05, 0.01)	
Baseline eGFR (CKD-EPI) [mL/min/1.73m²]														0.6016
>=60	1505	288	19.1	1493	243	16.3	0.0403	0.85	(0.73, 0.99)	0.82	(0.68, 0.99)	-0.03	(-0.06, 0.00)	
<60	1482	319	21.5	1503	291	19.4	0.1427	0.90	(0.78, 1.04)	0.88	(0.73, 1.05)	-0.02	(-0.05, 0.01)	
History of HHF (in the last 12 months)														0.7203
No	2320	477	20.6	2297	419	18.2	0.0463	0.89	(0.79, 1.00)	0.86	(0.74, 1.00)	-0.02	(-0.05, 0.00)	
Yes	669	130	19.4	699	115	16.5	0.1507	0.85	(0.67, 1.06)	0.82	(0.62, 1.08)	-0.03	(-0.07, 0.01)	
Baseline SBP (</>= median)														0.7124
< median	1474	304	20.6	1496	276	18.4	0.1349	0.89	(0.77, 1.04)	0.87	(0.73, 1.04)	-0.02	(-0.05, 0.01)	
>= median	1515	303	20.0	1500	258	17.2	0.0482	0.86	(0.74, 1.00)	0.83	(0.69, 1.00)	-0.03	(-0.06, 0.00)	
History of atrial fibrillation or atrial flutter														0.3930
No	1426	286	20.1	1417	238	16.8	0.0250	0.84	(0.72, 0.98)	0.80	(0.67, 0.97)	-0.03	(-0.06, 0.00)	
Yes	1558	319	20.5	1575	296	18.8	0.2362	0.92	(0.80, 1.06)	0.90	(0.75, 1.07)	-0.02	(-0.04, 0.01)	

Analysis is based on study 1245.110.
^ Patients with NYHA class I are counted in subgroup NYHA class II.
Risk ratios and odds ratios with confidence intervals (CIs) are estimated by Cochran-Mantel-Haenszel method. For risk differences standard Wald asymptotic confidence limits are calculated. A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied in case of any zero cells in contingency table.
Only treatment emergent AEs are displayed (onset between first dose until treatment stop +7 days).
MedDRA version: 23.1. * Chi-square test for treatment effect ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction).

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Table R.1.2.4: 1 Proportion of patients with any adverse event occuring in at least 1% of the patients in either treatment arm in the overall population on SOC level by SOC, 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 LVEF [%]																0.6138
< 50	988	169	17.1	995	156	15.7	0.3908	0.92	(0.75,	1.12)	0.90	(0.71,	1.14)	-0.01	(-0.05, 0.02)	
>= 50	2001	438	21.9	2001	378	18.9	0.0186	0.86	(0.76,	0.98)	0.83	(0.71,	0.97)	-0.03	(-0.05,-0.01)	
Baseline LVEF [%]																0.7935
<50	988	169	17.1	995	156	15.7	0.3908	0.92	(0.75,	1.12)	0.90	(0.71,	1.14)	-0.01	(-0.05, 0.02)	
50 to <60	1030	213	20.7	1028	178	17.3	0.0517	0.84	(0.70,	1.00)	0.80	(0.64,	1.00)	-0.03	(-0.07, 0.00)	
>=60	971	225	23.2	973	200	20.6	0.1628	0.89	(0.75,	1.05)	0.86	(0.69,	1.06)	-0.03	(-0.06, 0.01)	
Baseline NT-proBNP [pg/mL] (</>=median by atrial fibrillation/flutter status)																0.1523
< median	1507	325	21.6	1476	260	17.6	0.0066	0.82	(0.71,	0.95)	0.78	(0.65,	0.93)	-0.04	(-0.07,-0.01)	
>= median	1475	280	19.0	1516	274	18.1	0.5222	0.95	(0.82,	1.11)	0.94	(0.78,	1.13)	-0.01	(-0.04, 0.02)	
Baseline uric acid [mg/dL] (tertiles)																0.3567
<T1	975	179	18.4	963	173	18.0	0.8219	0.98	(0.81,	1.18)	0.97	(0.77,	1.23)	0.00	(-0.04, 0.03)	
>=T1 and <T2	966	197	20.4	1032	171	16.6	0.0276	0.81	(0.68,	0.98)	0.78	(0.62,	0.97)	-0.04	(-0.07, 0.00)	
>=T2	1016	229	22.5	970	186	19.2	0.0653	0.85	(0.72,	1.01)	0.82	(0.66,	1.01)	-0.03	(-0.07, 0.00)	
Baseline use of MRA																0.1336
No	1865	368	19.7	1878	346	18.4	0.3085	0.93	(0.82,	1.07)	0.92	(0.78,	1.08)	-0.01	(-0.04, 0.01)	
Yes	1124	239	21.3	1118	188	16.8	0.0073	0.79	(0.67,	0.94)	0.75	(0.61,	0.93)	-0.04	(-0.08,-0.01)	
Baseline use of ACE-inhibitor, ARB or ARNi																0.9994
No	586	142	24.2	568	121	21.3	0.2356	0.88	(0.71,	1.09)	0.85	(0.64,	1.12)	-0.03	(-0.08, 0.02)	
Yes	2403	465	19.4	2428	413	17.0	0.0349	0.88	(0.78,	0.99)	0.85	(0.74,	0.99)	-0.02	(-0.05, 0.00)	

Analysis is based on study 1245.110.
^ Patients with NYHA class I are counted in subgroup NYHA class II.
Risk ratios and odds ratios with confidence intervals (CIs) are estimated by Cochran-Mantel-Haenszel method. For risk differences standard Wald asymptotic confidence limits are calculated. A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied in case of any zero cells in contingency table.
Only treatment emergent AEs are displayed (onset between first dose until treatment stop +7 days).
MedDRA version: 23.1. * Chi-square test for treatment effect ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction).

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Table R.1.2.4: 1 Proportion of patients with any adverse event occuring in at least 1% of the patients in either treatment arm in the overall population on SOC level by SOC, 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	2989	523	17.5	2996	553	18.5	0.3333	1.05 (0.95, 1.18)	1.07 (0.94, 1.22)	0.01 (-0.01, 0.03)	

Analysis is based on study 1245.110.
^ Patients with NYHA class I are counted in subgroup NYHA class II.
Risk ratios and odds ratios with confidence intervals (CIs) are estimated by Cochran-Mantel-Haenszel method. For risk differences standard Wald asymptotic confidence limits are calculated. A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied in case of any zero cells in contingency table.
Only treatment emergent AEs are displayed (onset between first dose until treatment stop +7 days).
MedDRA version: 23.1. * Chi-square test for treatment effect ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction).

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Table R.1.2.4: 1 Proportion of patients with any adverse event occuring in at least 1% of the patients in either treatment arm in the overall population on SOC level by SOC, 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	2989	476	15.9	2996	434	14.5	0.1211	0.91 (0.81, 1.03)	0.89 (0.78, 1.03)	-0.01 (-0.03, 0.00)	

Analysis is based on study 1245.110.
^ Patients with NYHA class I are counted in subgroup NYHA class II.
Risk ratios and odds ratios with confidence intervals (CIs) are estimated by Cochran-Mantel-Haenszel method. For risk differences standard Wald asymptotic confidence limits are calculated. A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied in case of any zero cells in contingency table.
Only treatment emergent AEs are displayed (onset between first dose until treatment stop +7 days).
MedDRA version: 23.1. * Chi-square test for treatment effect ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction).

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Table R.1.2.4: 1 Proportion of patients with any adverse event occuring in at least 1% of the patients in either treatment arm in the overall population on SOC level by SOC, 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	2989	411	13.8	2996	424	14.2	0.6538	1.03	(0.91, 1.17)	1.03	(0.89, 1.20)	0.00	(-0.01, 0.02)	

Analysis is based on study 1245.110.
^ Patients with NYHA class I are counted in subgroup NYHA class II.
Risk ratios and odds ratios with confidence intervals (CIs) are estimated by Cochran-Mantel-Haenszel method. For risk differences standard Wald asymptotic confidence limits are calculated. A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied in case of any zero cells in contingency table.
Only treatment emergent AEs are displayed (onset between first dose until treatment stop +7 days).
MedDRA version: 23.1. * Chi-square test for treatment effect ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction).

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Table R.1.2.4: 1 Proportion of patients with any adverse event occuring in at least 1% of the patients in either treatment arm in the overall population on SOC level by SOC, 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	2989	409	13.7	2996	422	14.1	0.6530	1.03	(0.91, 1.17)	1.03	(0.89, 1.20)	0.00	(-0.01, 0.02)	

Analysis is based on study 1245.110.
^ Patients with NYHA class I are counted in subgroup NYHA class II.
Risk ratios and odds ratios with confidence intervals (CIs) are estimated by Cochran-Mantel-Haenszel method. For risk differences standard Wald asymptotic confidence limits are calculated. A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied in case of any zero cells in contingency table.
Only treatment emergent AEs are displayed (onset between first dose until treatment stop +7 days).
MedDRA version: 23.1. * Chi-square test for treatment effect ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction).

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Table R.1.2.4: 1 Proportion of patients with any adverse event occuring in at least 1% of the patients in either treatment arm in the overall population on SOC level by SOC, 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	2989	357	11.9	2996	294	9.8	0.0081	0.82	(0.71, 0.95)	0.80	(0.68, 0.94)	-0.02	(-0.04,-0.01)	
Sex														0.9789
Male	1653	186	11.3	1658	153	9.2	0.0547	0.82	(0.67, 1.00)	0.80	(0.64, 1.00)	-0.02	(-0.04, 0.00)	
Female	1336	171	12.8	1338	141	10.5	0.0686	0.82	(0.67, 1.02)	0.80	(0.63, 1.02)	-0.02	(-0.05, 0.00)	
Age [years]														0.8798
<70	1084	139	12.8	1066	114	10.7	0.1256	0.83	(0.66, 1.05)	0.81	(0.63, 1.06)	-0.02	(-0.05, 0.01)	
>=70	1905	218	11.4	1930	180	9.3	0.0316	0.81	(0.68, 0.98)	0.80	(0.65, 0.98)	-0.02	(-0.04, 0.00)	
Region														0.8776
North America	359	67	18.7	359	47	13.1	0.0411	0.70	(0.50, 0.99)	0.66	(0.44, 0.98)	-0.06	(-0.11, 0.00)	
Latin America	757	75	9.9	758	66	8.7	0.4213	0.88	(0.64, 1.20)	0.87	(0.61, 1.23)	-0.01	(-0.04, 0.02)	
Europe	1341	123	9.2	1346	102	7.6	0.1358	0.83	(0.64, 1.06)	0.81	(0.62, 1.07)	-0.02	(-0.04, 0.00)	
Asia	343	57	16.6	343	47	13.7	0.2871	0.82	(0.58, 1.18)	0.80	(0.52, 1.21)	-0.03	(-0.08, 0.02)	
Other	189	35	18.5	190	32	16.8	0.6688	0.91	(0.59, 1.41)	0.89	(0.53, 1.51)	-0.02	(-0.09, 0.06)	
OECD member														0.3957
No	847	105	12.4	868	97	11.2	0.4327	0.90	(0.70, 1.17)	0.89	(0.66, 1.19)	-0.01	(-0.04, 0.02)	
Yes	2142	252	11.8	2128	197	9.3	0.0076	0.79	(0.66, 0.94)	0.77	(0.63, 0.93)	-0.03	(-0.04,-0.01)	
Baseline NYHA														0.5903
II^	2450	268	10.9	2435	213	8.7	0.0102	0.80	(0.67, 0.95)	0.78	(0.65, 0.94)	-0.02	(-0.04,-0.01)	
III/IV	539	89	16.5	561	81	14.4	0.3416	0.87	(0.66, 1.15)	0.85	(0.62, 1.18)	-0.02	(-0.06, 0.02)	
Baseline Diabetes Status														0.7155
Diabetic	1471	176	12.0	1465	148	10.1	0.1074	0.84	(0.69, 1.04)	0.83	(0.66, 1.04)	-0.02	(-0.04, 0.00)	
Non-Diabetic	1518	181	11.9	1531	146	9.5	0.0332	0.80	(0.65, 0.98)	0.78	(0.62, 0.98)	-0.02	(-0.05, 0.00)	

Analysis is based on study 1245.110.
^ Patients with NYHA class I are counted in subgroup NYHA class II.
Risk ratios and odds ratios with confidence intervals (CIs) are estimated by Cochran-Mantel-Haenszel method. For risk differences standard Wald asymptotic confidence limits are calculated. A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied in case of any zero cells in contingency table.
Only treatment emergent AEs are displayed (onset between first dose until treatment stop +7 days).
MedDRA version: 23.1. * Chi-square test for treatment effect ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction).

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Table R.1.2.4: 1 Proportion of patients with any adverse event occuring in at least 1% of the patients in either treatment arm in the overall population on SOC level by SOC, 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 **
Baseline Diabetes Status																0.8833
Diabetic	1471	176	12.0	1465	148	10.1	0.1074	0.84	(0.69,	1.04)	0.83	(0.66,	1.04)	-0.02	(-0.04, 0.00)	
Pre-Diabetes	979	113	11.5	1001	95	9.5	0.1365	0.82	(0.64,	1.06)	0.80	(0.60,	1.07)	-0.02	(-0.05, 0.01)	
Normal (no pre-diabetes)	539	68	12.6	530	51	9.6	0.1198	0.76	(0.54,	1.07)	0.74	(0.50,	1.08)	-0.03	(-0.07, 0.01)	
Baseline BMI [kg/m²]																0.0233
<30	1641	217	13.2	1654	155	9.4	0.0005	0.71	(0.58,	0.86)	0.68	(0.55,	0.84)	-0.04	(-0.06,-0.02)	
>=30	1348	140	10.4	1342	139	10.4	0.9809	1.00	(0.80,	1.25)	1.00	(0.78,	1.28)	0.00	(-0.02, 0.02)	
Baseline eGFR (CKD-EPI) [mL/min/1.73m²]																0.8231
>=60	1505	169	11.2	1493	140	9.4	0.0954	0.84	(0.68,	1.03)	0.82	(0.65,	1.04)	-0.02	(-0.04, 0.00)	
<60	1482	188	12.7	1503	154	10.2	0.0364	0.81	(0.66,	0.99)	0.79	(0.63,	0.99)	-0.02	(-0.05, 0.00)	
History of HHF (in the last 12 months)																0.5671
No	2320	262	11.3	2297	207	9.0	0.0103	0.80	(0.67,	0.95)	0.78	(0.64,	0.94)	-0.02	(-0.04,-0.01)	
Yes	669	95	14.2	699	87	12.4	0.3397	0.88	(0.67,	1.15)	0.86	(0.63,	1.17)	-0.02	(-0.05, 0.02)	
Baseline SBP (</>= median)																0.6785
< median	1474	172	11.7	1496	148	9.9	0.1186	0.85	(0.69,	1.04)	0.83	(0.66,	1.05)	-0.02	(-0.04, 0.00)	
>= median	1515	185	12.2	1500	146	9.7	0.0296	0.80	(0.65,	0.98)	0.78	(0.62,	0.98)	-0.02	(-0.05, 0.00)	
History of atrial fibrillation or atrial flutter																0.1141
No	1426	149	10.4	1417	139	9.8	0.5721	0.94	(0.75,	1.17)	0.93	(0.73,	1.19)	-0.01	(-0.03, 0.02)	
Yes	1558	207	13.3	1575	155	9.8	0.0026	0.74	(0.61,	0.90)	0.71	(0.57,	0.89)	-0.03	(-0.06,-0.01)	

Analysis is based on study 1245.110.
^ Patients with NYHA class I are counted in subgroup NYHA class II.
Risk ratios and odds ratios with confidence intervals (CIs) are estimated by Cochran-Mantel-Haenszel method. For risk differences standard Wald asymptotic confidence limits are calculated. A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied in case of any zero cells in contingency table.
Only treatment emergent AEs are displayed (onset between first dose until treatment stop +7 days).
MedDRA version: 23.1. * Chi-square test for treatment effect ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction).

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Table R.1.2.4: 1 Proportion of patients with any adverse event occuring in at least 1% of the patients in either treatment arm in the overall population on SOC level by SOC, 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 LVEF [%]														0.1675
< 50	988	121	12.2	995	86	8.6	0.0087	0.71	(0.54, 0.92)	0.68	(0.51, 0.91)	-0.04	(-0.06,-0.01)	
>= 50	2001	236	11.8	2001	208	10.4	0.1587	0.88	(0.74, 1.05)	0.87	(0.71, 1.06)	-0.01	(-0.03, 0.01)	
Baseline LVEF [%]														0.3220
<50	988	121	12.2	995	86	8.6	0.0087	0.71	(0.54, 0.92)	0.68	(0.51, 0.91)	-0.04	(-0.06,-0.01)	
50 to <60	1030	128	12.4	1028	107	10.4	0.1500	0.84	(0.66, 1.07)	0.82	(0.62, 1.08)	-0.02	(-0.05, 0.01)	
>=60	971	108	11.1	973	101	10.4	0.5973	0.93	(0.72, 1.21)	0.93	(0.69, 1.23)	-0.01	(-0.03, 0.02)	
Baseline NT-proBNP [pg/mL] (</>=median by atrial fibrillation/flutter status)														0.1295
< median	1507	172	11.4	1476	122	8.3	0.0039	0.72	(0.58, 0.90)	0.70	(0.55, 0.89)	-0.03	(-0.05,-0.01)	
>= median	1475	184	12.5	1516	172	11.3	0.3405	0.91	(0.75, 1.11)	0.90	(0.72, 1.12)	-0.01	(-0.03, 0.01)	
Baseline uric acid [mg/dL] (tertiles)														0.8799
<T1	975	98	10.1	963	80	8.3	0.1838	0.83	(0.62, 1.10)	0.81	(0.59, 1.11)	-0.02	(-0.04, 0.01)	
>=T1 and <T2	966	119	12.3	1032	100	9.7	0.0601	0.79	(0.61, 1.01)	0.76	(0.58, 1.01)	-0.03	(-0.05, 0.00)	
>=T2	1016	139	13.7	970	114	11.8	0.1976	0.86	(0.68, 1.08)	0.84	(0.64, 1.10)	-0.02	(-0.05, 0.01)	
Baseline use of MRA														0.8571
No	1865	215	11.5	1878	176	9.4	0.0310	0.81	(0.67, 0.98)	0.79	(0.64, 0.98)	-0.02	(-0.04, 0.00)	
Yes	1124	142	12.6	1118	118	10.6	0.1243	0.84	(0.66, 1.05)	0.82	(0.63, 1.06)	-0.02	(-0.05, 0.01)	
Baseline use of ACE-inhibitor, ARB or ARNi														0.7352
No	586	79	13.5	568	66	11.6	0.3402	0.86	(0.63, 1.17)	0.84	(0.59, 1.20)	-0.02	(-0.06, 0.02)	
Yes	2403	278	11.6	2428	228	9.4	0.0134	0.81	(0.69, 0.96)	0.79	(0.66, 0.95)	-0.02	(-0.04, 0.00)	

Analysis is based on study 1245.110.
^ Patients with NYHA class I are counted in subgroup NYHA class II.
Risk ratios and odds ratios with confidence intervals (CIs) are estimated by Cochran-Mantel-Haenszel method. For risk differences standard Wald asymptotic confidence limits are calculated. A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied in case of any zero cells in contingency table.
Only treatment emergent AEs are displayed (onset between first dose until treatment stop +7 days).
MedDRA version: 23.1. * Chi-square test for treatment effect ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction).

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Table R.1.2.4: 1 Proportion of patients with any adverse event occuring in at least 1% of the patients in either treatment arm in the overall population on SOC level by SOC, 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	2989	320	10.7	2996	240	8.0	0.0003	0.75	(0.64, 0.88)	0.73	(0.61, 0.87)		-0.03	(-0.04,-0.01)	
Sex															0.3852
Male	1653	195	11.8	1658	138	8.3	0.0009	0.71	(0.57, 0.87)	0.68	(0.54, 0.85)		-0.03	(-0.06,-0.01)	
Female	1336	125	9.4	1338	102	7.6	0.1079	0.81	(0.63, 1.05)	0.80	(0.61, 1.05)		-0.02	(-0.04, 0.00)	
Age [years]															0.8880
<70	1084	99	9.1	1066	74	6.9	0.0619	0.76	(0.57, 1.01)	0.74	(0.54, 1.02)		-0.02	(-0.04, 0.00)	
>=70	1905	221	11.6	1930	166	8.6	0.0020	0.74	(0.61, 0.90)	0.72	(0.58, 0.89)		-0.03	(-0.05,-0.01)	
Region															0.3621
North America	359	41	11.4	359	24	6.7	0.0270	0.59	(0.36, 0.95)	0.56	(0.33, 0.94)		-0.05	(-0.09,-0.01)	
Latin America	757	87	11.5	758	77	10.2	0.4032	0.88	(0.66, 1.18)	0.87	(0.63, 1.20)		-0.01	(-0.04, 0.02)	
Europe	1341	124	9.2	1346	80	5.9	0.0012	0.64	(0.49, 0.84)	0.62	(0.46, 0.83)		-0.03	(-0.05,-0.01)	
Asia	343	49	14.3	343	41	12.0	0.3656	0.84	(0.57, 1.23)	0.81	(0.52, 1.27)		-0.02	(-0.07, 0.03)	
Other	189	19	10.1	190	18	9.5	0.8493	0.94	(0.51, 1.74)	0.94	(0.48, 1.85)		-0.01	(-0.07, 0.05)	
OECD member															0.0903
No	847	92	10.9	868	86	9.9	0.5172	0.91	(0.69, 1.20)	0.90	(0.66, 1.23)		-0.01	(-0.04, 0.02)	
Yes	2142	228	10.6	2128	154	7.2	<0.0001	0.68	(0.56, 0.83)	0.65	(0.53, 0.81)		-0.03	(-0.05,-0.02)	
Baseline NYHA															0.3613
II^	2450	250	10.2	2435	178	7.3	0.0003	0.72	(0.60, 0.86)	0.69	(0.57, 0.85)		-0.03	(-0.04,-0.01)	
III/IV	539	70	13.0	561	62	11.1	0.3234	0.85	(0.62, 1.17)	0.83	(0.58, 1.20)		-0.02	(-0.06, 0.02)	
Baseline Diabetes Status															0.3814
Diabetic	1471	175	11.9	1465	139	9.5	0.0347	0.80	(0.65, 0.98)	0.78	(0.61, 0.98)		-0.02	(-0.05, 0.00)	
Non-Diabetic	1518	145	9.6	1531	101	6.6	0.0027	0.69	(0.54, 0.88)	0.67	(0.51, 0.87)		-0.03	(-0.05,-0.01)	

Analysis is based on study 1245.110.
^ Patients with NYHA class I are counted in subgroup NYHA class II.
Risk ratios and odds ratios with confidence intervals (CIs) are estimated by Cochran-Mantel-Haenszel method. For risk differences standard Wald asymptotic confidence limits are calculated. A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied in case of any zero cells in contingency table.
Only treatment emergent AEs are displayed (onset between first dose until treatment stop +7 days).
MedDRA version: 23.1. * Chi-square test for treatment effect ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction).

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Table R.1.2.4: 1 Proportion of patients with any adverse event occuring in at least 1% of the patients in either treatment arm in the overall population on SOC level by SOC, 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 Diabetes Status														0.6654
Diabetic	1471	175	11.9	1465	139	9.5	0.0347	0.80	(0.65, 0.98)	0.78	(0.61, 0.98)	-0.02	(-0.05, 0.00)	
Pre-Diabetes	979	93	9.5	1001	67	6.7	0.0220	0.70	(0.52, 0.95)	0.68	(0.49, 0.95)	-0.03	(-0.05, 0.00)	
Normal (no pre-diabetes)	539	52	9.6	530	34	6.4	0.0520	0.66	(0.44, 1.01)	0.64	(0.41, 1.01)	-0.03	(-0.06, 0.00)	
Baseline BMI [kg/m²]														0.3073
<30	1641	186	11.3	1654	150	9.1	0.0317	0.80	(0.65, 0.98)	0.78	(0.62, 0.98)	-0.02	(-0.04, 0.00)	
>=30	1348	134	9.9	1342	90	6.7	0.0024	0.67	(0.52, 0.87)	0.65	(0.49, 0.86)	-0.03	(-0.05,-0.01)	
Baseline eGFR (CKD-EPI) [mL/min/1.73m²]														0.9193
>=60	1505	131	8.7	1493	96	6.4	0.0186	0.74	(0.57, 0.95)	0.72	(0.55, 0.95)	-0.02	(-0.04, 0.00)	
<60	1482	189	12.8	1503	144	9.6	0.0059	0.75	(0.61, 0.92)	0.72	(0.58, 0.91)	-0.03	(-0.05,-0.01)	
History of HHF (in the last 12 months)														0.2462
No	2320	242	10.4	2297	169	7.4	0.0002	0.71	(0.58, 0.85)	0.68	(0.56, 0.84)	-0.03	(-0.05,-0.01)	
Yes	669	78	11.7	699	71	10.2	0.3728	0.87	(0.64, 1.18)	0.86	(0.61, 1.20)	-0.02	(-0.05, 0.02)	
Baseline SBP (</>= median)														0.7211
< median	1474	168	11.4	1496	124	8.3	0.0044	0.73	(0.58, 0.91)	0.70	(0.55, 0.90)	-0.03	(-0.05,-0.01)	
>= median	1515	152	10.0	1500	116	7.7	0.0265	0.77	(0.61, 0.97)	0.75	(0.58, 0.97)	-0.02	(-0.04, 0.00)	
History of atrial fibrillation or atrial flutter														0.2461
No	1426	137	9.6	1417	113	8.0	0.1243	0.83	(0.65, 1.05)	0.82	(0.63, 1.06)	-0.02	(-0.04, 0.00)	
Yes	1558	183	11.7	1575	127	8.1	0.0006	0.69	(0.55, 0.85)	0.66	(0.52, 0.84)	-0.04	(-0.06,-0.02)	

Analysis is based on study 1245.110.
^ Patients with NYHA class I are counted in subgroup NYHA class II.
Risk ratios and odds ratios with confidence intervals (CIs) are estimated by Cochran-Mantel-Haenszel method. For risk differences standard Wald asymptotic confidence limits are calculated. A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied in case of any zero cells in contingency table.
Only treatment emergent AEs are displayed (onset between first dose until treatment stop +7 days).
MedDRA version: 23.1. * Chi-square test for treatment effect ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction).

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Table R.1.2.4: 1 Proportion of patients with any adverse event occuring in at least 1% of the patients in either treatment arm in the overall population on SOC level by SOC, 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 LVEF [%]																0.2871
< 50	988	103	10.4	995	68	6.8	0.0044	0.66	(0.49,	0.88)	0.63	(0.46,	0.87)	-0.04	(-0.06,-0.01)	
>= 50	2001	217	10.8	2001	172	8.6	0.0163	0.79	(0.66,	0.96)	0.77	(0.63,	0.95)	-0.02	(-0.04, 0.00)	
Baseline LVEF [%]																0.5235
<50	988	103	10.4	995	68	6.8	0.0044	0.66	(0.49,	0.88)	0.63	(0.46,	0.87)	-0.04	(-0.06,-0.01)	
50 to <60	1030	107	10.4	1028	88	8.6	0.1568	0.82	(0.63,	1.08)	0.81	(0.60,	1.09)	-0.02	(-0.04, 0.01)	
>=60	971	110	11.3	973	84	8.6	0.0474	0.76	(0.58,	1.00)	0.74	(0.55,	1.00)	-0.03	(-0.05, 0.00)	
Baseline NT-proBNP [pg/mL] (</>=median by atrial fibrillation/flutter status)																0.4478
< median	1507	151	10.0	1476	103	7.0	0.0029	0.70	(0.55,	0.89)	0.67	(0.52,	0.87)	-0.03	(-0.05,-0.01)	
>= median	1475	169	11.5	1516	137	9.0	0.0290	0.79	(0.64,	0.98)	0.77	(0.61,	0.97)	-0.02	(-0.05, 0.00)	
Baseline uric acid [mg/dL] (tertiles)																0.8531
<T1	975	98	10.1	963	77	8.0	0.1144	0.80	(0.60,	1.06)	0.78	(0.57,	1.06)	-0.02	(-0.05, 0.00)	
>=T1 and <T2	966	94	9.7	1032	76	7.4	0.0581	0.76	(0.57,	1.01)	0.74	(0.54,	1.01)	-0.02	(-0.05, 0.00)	
>=T2	1016	125	12.3	970	85	8.8	0.0103	0.71	(0.55,	0.92)	0.68	(0.51,	0.92)	-0.04	(-0.06,-0.01)	
Baseline use of MRA																0.8723
No	1865	189	10.1	1878	144	7.7	0.0080	0.76	(0.62,	0.93)	0.74	(0.59,	0.92)	-0.02	(-0.04,-0.01)	
Yes	1124	131	11.7	1118	96	8.6	0.0160	0.74	(0.57,	0.95)	0.71	(0.54,	0.94)	-0.03	(-0.06,-0.01)	
Baseline use of ACE-inhibitor, ARB or ARNi																0.0212
No	586	59	10.1	568	61	10.7	0.7088	1.07	(0.76,	1.50)	1.07	(0.74,	1.57)	0.01	(-0.03, 0.04)	
Yes	2403	261	10.9	2428	179	7.4	<0.0001	0.68	(0.57,	0.81)	0.65	(0.54,	0.80)	-0.03	(-0.05,-0.02)	

Analysis is based on study 1245.110.
^ Patients with NYHA class I are counted in subgroup NYHA class II.
Risk ratios and odds ratios with confidence intervals (CIs) are estimated by Cochran-Mantel-Haenszel method. For risk differences standard Wald asymptotic confidence limits are calculated. A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied in case of any zero cells in contingency table.
Only treatment emergent AEs are displayed (onset between first dose until treatment stop +7 days).
MedDRA version: 23.1. * Chi-square test for treatment effect ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction).

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Table R.1.2.4: 1 Proportion of patients with any adverse event occuring in at least 1% of the patients in either treatment arm in the overall population on SOC level by SOC, 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	2989	258	8.6	2996	298	9.9	0.0797	1.15 (0.98, 1.35)	1.17 (0.98, 1.39)	0.01 (0.00, 0.03)	

Analysis is based on study 1245.110.
^ Patients with NYHA class I are counted in subgroup NYHA class II.
Risk ratios and odds ratios with confidence intervals (CIs) are estimated by Cochran-Mantel-Haenszel method. For risk differences standard Wald asymptotic confidence limits are calculated. A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied in case of any zero cells in contingency table.
Only treatment emergent AEs are displayed (onset between first dose until treatment stop +7 days).
MedDRA version: 23.1. * Chi-square test for treatment effect ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction).

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Table R.1.2.4: 1 Proportion of patients with any adverse event occuring in at least 1% of the patients in either treatment arm in the overall population on SOC level by SOC, 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	2989	211	7.1	2996	197	6.6	0.4578	0.93 (0.77, 1.12)	0.93 (0.76, 1.13)	0.00 (-0.02, 0.01)	

Analysis is based on study 1245.110.
^ Patients with NYHA class I are counted in subgroup NYHA class II.
Risk ratios and odds ratios with confidence intervals (CIs) are estimated by Cochran-Mantel-Haenszel method. For risk differences standard Wald asymptotic confidence limits are calculated. A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied in case of any zero cells in contingency table.
Only treatment emergent AEs are displayed (onset between first dose until treatment stop +7 days).
MedDRA version: 23.1. * Chi-square test for treatment effect ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction).

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Table R.1.2.4: 1 Proportion of patients with any adverse event occuring in at least 1% of the patients in either treatment arm in the overall population on SOC level by SOC, 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	2989	185	6.2	2996	201	6.7	0.4132	1.08 (0.89, 1.31)	1.09 (0.89, 1.34)	0.01 (-0.01, 0.02)	

Analysis is based on study 1245.110.
^ Patients with NYHA class I are counted in subgroup NYHA class II.
Risk ratios and odds ratios with confidence intervals (CIs) are estimated by Cochran-Mantel-Haenszel method. For risk differences standard Wald asymptotic confidence limits are calculated. A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied in case of any zero cells in contingency table.
Only treatment emergent AEs are displayed (onset between first dose until treatment stop +7 days).
MedDRA version: 23.1. * Chi-square test for treatment effect ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction).

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Table R.1.2.4: 1 Proportion of patients with any adverse event occuring in at least 1% of the patients in either treatment arm in the overall population on SOC level by SOC, 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	2989	154	5.2	2996	160	5.3	0.7440	1.04 (0.84, 1.29)	1.04 (0.83, 1.30)	0.00 (-0.01, 0.01)	

Analysis is based on study 1245.110.
^ Patients with NYHA class I are counted in subgroup NYHA class II.
Risk ratios and odds ratios with confidence intervals (CIs) are estimated by Cochran-Mantel-Haenszel method. For risk differences standard Wald asymptotic confidence limits are calculated. A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied in case of any zero cells in contingency table.
Only treatment emergent AEs are displayed (onset between first dose until treatment stop +7 days).
MedDRA version: 23.1. * Chi-square test for treatment effect ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction).

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Table R.1.2.4: 1 Proportion of patients with any adverse event occuring in at least 1% of the patients in either treatment arm in the overall population on SOC level by SOC, 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	2989	137	4.6	2996	123	4.1	0.3644	0.90	(0.71, 1.14)	0.89	(0.69, 1.14)	0.00	(-0.02, 0.01)	

Analysis is based on study 1245.110.
^ Patients with NYHA class I are counted in subgroup NYHA class II.
Risk ratios and odds ratios with confidence intervals (CIs) are estimated by Cochran-Mantel-Haenszel method. For risk differences standard Wald asymptotic confidence limits are calculated. A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied in case of any zero cells in contingency table.
Only treatment emergent AEs are displayed (onset between first dose until treatment stop +7 days).
MedDRA version: 23.1. * Chi-square test for treatment effect ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction).

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Table R.1.2.4: 1 Proportion of patients with any adverse event occuring in at least 1% of the patients in either treatment arm in the overall population on SOC level by SOC, 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	2989	117	3.9	2996	116	3.9	0.9322	0.99	(0.77, 1.27)	0.99	(0.76, 1.28)	0.00	(-0.01, 0.01)	

Analysis is based on study 1245.110.
^ Patients with NYHA class I are counted in subgroup NYHA class II.
Risk ratios and odds ratios with confidence intervals (CIs) are estimated by Cochran-Mantel-Haenszel method. For risk differences standard Wald asymptotic confidence limits are calculated. A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied in case of any zero cells in contingency table.
Only treatment emergent AEs are displayed (onset between first dose until treatment stop +7 days).
MedDRA version: 23.1. * Chi-square test for treatment effect ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction).

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Table R.1.2.4: 1 Proportion of patients with any adverse event occuring in at least 1% of the patients in either treatment arm in the overall population on SOC level by SOC, 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	2989	83	2.8	2996	108	3.6	0.0684	1.30	(0.98, 1.72)	1.31	(0.98, 1.75)	0.01	(0.00, 0.02)	

Analysis is based on study 1245.110.
^ Patients with NYHA class I are counted in subgroup NYHA class II.
Risk ratios and odds ratios with confidence intervals (CIs) are estimated by Cochran-Mantel-Haenszel method. For risk differences standard Wald asymptotic confidence limits are calculated. A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied in case of any zero cells in contingency table.
Only treatment emergent AEs are displayed (onset between first dose until treatment stop +7 days).
MedDRA version: 23.1. * Chi-square test for treatment effect ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction).

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Table R.1.2.4: 1 Proportion of patients with any adverse event occuring in at least 1% of the patients in either treatment arm in the overall population on SOC level by SOC, 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	2989	72	2.4	2996	53	1.8	0.0835	0.73	(0.52, 1.04)	0.73	(0.51, 1.04)	-0.01	(-0.01, 0.00)	

Analysis is based on study 1245.110.
^ Patients with NYHA class I are counted in subgroup NYHA class II.
Risk ratios and odds ratios with confidence intervals (CIs) are estimated by Cochran-Mantel-Haenszel method. For risk differences standard Wald asymptotic confidence limits are calculated. A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied in case of any zero cells in contingency table.
Only treatment emergent AEs are displayed (onset between first dose until treatment stop +7 days).
MedDRA version: 23.1. * Chi-square test for treatment effect ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction).

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Table R.1.2.4: 2 Proportion of patients with serious adverse events occuring in at least 1% of the patients in either treatment arm in the overall population on SOC level by SOC, 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	2989	882	29.5	2996	740	24.7	<0.0001	0.84	(0.77, 0.91)	0.78	(0.70, 0.88)	-0.05	(-0.07,-0.03)	
Sex														0.2553
Male	1653	506	30.6	1658	407	24.5	<0.0001	0.80	(0.72, 0.90)	0.74	(0.63, 0.86)	-0.06	(-0.09,-0.03)	
Female	1336	376	28.1	1338	333	24.9	0.0565	0.88	(0.78, 1.00)	0.85	(0.71, 1.00)	-0.03	(-0.07, 0.00)	
Age [years]														0.0859
<70	1084	278	25.6	1066	254	23.8	0.3286	0.93	(0.80, 1.08)	0.91	(0.75, 1.10)	-0.02	(-0.05, 0.02)	
>=70	1905	604	31.7	1930	486	25.2	<0.0001	0.79	(0.72, 0.88)	0.72	(0.63, 0.83)	-0.07	(-0.09,-0.04)	
Region														0.9419
North America	359	134	37.3	359	120	33.4	0.2745	0.90	(0.73, 1.09)	0.84	(0.62, 1.15)	-0.04	(-0.11, 0.03)	
Latin America	757	220	29.1	758	187	24.7	0.0538	0.85	(0.72, 1.00)	0.80	(0.64, 1.00)	-0.04	(-0.09, 0.00)	
Europe	1341	371	27.7	1346	307	22.8	0.0037	0.82	(0.72, 0.94)	0.77	(0.65, 0.92)	-0.05	(-0.08,-0.02)	
Asia	343	108	31.5	343	85	24.8	0.0508	0.79	(0.62, 1.00)	0.72	(0.51, 1.00)	-0.07	(-0.13, 0.00)	
Other	189	49	25.9	190	41	21.6	0.3200	0.83	(0.58, 1.20)	0.79	(0.49, 1.26)	-0.04	(-0.13, 0.04)	
OECD member														0.4168
No	847	244	28.8	868	221	25.5	0.1191	0.88	(0.76, 1.03)	0.84	(0.68, 1.04)	-0.03	(-0.08, 0.01)	
Yes	2142	638	29.8	2128	519	24.4	<0.0001	0.82	(0.74, 0.90)	0.76	(0.66, 0.87)	-0.05	(-0.08,-0.03)	
Baseline NYHA														0.6225
II^	2450	658	26.9	2435	539	22.1	0.0001	0.82	(0.75, 0.91)	0.77	(0.68, 0.88)	-0.05	(-0.07,-0.02)	
III/IV	539	224	41.6	561	201	35.8	0.0511	0.86	(0.74, 1.00)	0.79	(0.62, 1.00)	-0.06	(-0.11, 0.00)	
Baseline Diabetes Status														0.0552
Diabetic	1471	481	32.7	1465	371	25.3	<0.0001	0.77	(0.69, 0.87)	0.70	(0.59, 0.82)	-0.07	(-0.11,-0.04)	
Non-Diabetic	1518	401	26.4	1531	369	24.1	0.1414	0.91	(0.81, 1.03)	0.88	(0.75, 1.04)	-0.02	(-0.05, 0.01)	

Analysis is based on study 1245.110.
^ Patients with NYHA class I are counted in subgroup NYHA class II.
Risk ratios and odds ratios with confidence intervals (CIs) are estimated by Cochran-Mantel-Haenszel method. For risk differences standard Wald asymptotic confidence limits are calculated. A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied in case of any zero cells in contingency table.
Only treatment emergent AEs are displayed (onset between first dose until treatment stop +7 days).
MedDRA version: 23.1. * Chi-square test for treatment effect ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction).

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Table R.1.2.4: 2 Proportion of patients with serious adverse events occuring in at least 1% of the patients in either treatment arm in the overall population on SOC level by SOC, 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 Diabetes Status											0.1359
Diabetic	1471	481	32.7	1465	371	25.3	<0.0001	0.77 (0.69, 0.87)	0.70 (0.59, 0.82)	-0.07 (-0.11,-0.04)	
Pre-Diabetes	979	256	26.1	1001	245	24.5	0.3918	0.94 (0.80, 1.09)	0.92 (0.75, 1.12)	-0.02 (-0.06, 0.02)	
Normal (no pre-diabetes)	539	145	26.9	530	124	23.4	0.1867	0.87 (0.71, 1.07)	0.83 (0.63, 1.09)	-0.04 (-0.09, 0.02)	
Baseline BMI [kg/m²]											0.5865
<30	1641	489	29.8	1654	404	24.4	0.0005	0.82 (0.73, 0.92)	0.76 (0.65, 0.89)	-0.05 (-0.08,-0.02)	
>=30	1348	393	29.2	1342	336	25.0	0.0163	0.86 (0.76, 0.97)	0.81 (0.68, 0.96)	-0.04 (-0.07,-0.01)	
Baseline eGFR (CKD-EPI) [mL/min/1.73m²]											0.8790
>=60	1505	369	24.5	1493	308	20.6	0.0109	0.84 (0.74, 0.96)	0.80 (0.67, 0.95)	-0.04 (-0.07,-0.01)	
<60	1482	513	34.6	1503	432	28.7	0.0006	0.83 (0.75, 0.92)	0.76 (0.65, 0.89)	-0.06 (-0.09,-0.03)	
History of HHF (in the last 12 months)											0.1264
No	2320	636	27.4	2297	504	21.9	<0.0001	0.80 (0.72, 0.89)	0.74 (0.65, 0.85)	-0.05 (-0.08,-0.03)	
Yes	669	246	36.8	699	236	33.8	0.2442	0.92 (0.80, 1.06)	0.88 (0.70, 1.09)	-0.03 (-0.08, 0.02)	
Baseline SBP (</>= median)											0.8125
< median	1474	443	30.1	1496	380	25.4	0.0046	0.85 (0.75, 0.95)	0.79 (0.67, 0.93)	-0.05 (-0.08,-0.01)	
>= median	1515	439	29.0	1500	360	24.0	0.0020	0.83 (0.73, 0.93)	0.77 (0.66, 0.91)	-0.05 (-0.08,-0.02)	
History of atrial fibrillation or atrial flutter											0.4234
No	1426	365	25.6	1417	316	22.3	0.0395	0.87 (0.76, 0.99)	0.83 (0.70, 0.99)	-0.03 (-0.06, 0.00)	
Yes	1558	516	33.1	1575	424	26.9	0.0002	0.81 (0.73, 0.91)	0.74 (0.64, 0.87)	-0.06 (-0.09,-0.03)	

Analysis is based on study 1245.110.
^ Patients with NYHA class I are counted in subgroup NYHA class II.
Risk ratios and odds ratios with confidence intervals (CIs) are estimated by Cochran-Mantel-Haenszel method. For risk differences standard Wald asymptotic confidence limits are calculated. A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied in case of any zero cells in contingency table.
Only treatment emergent AEs are displayed (onset between first dose until treatment stop +7 days).
MedDRA version: 23.1. * Chi-square test for treatment effect ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction).

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Table R.1.2.4: 2 Proportion of patients with serious adverse events occuring in at least 1% of the patients in either treatment arm in the overall population on SOC level by SOC, 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 LVEF [%]																0.1961
< 50	988	298	30.2	995	232	23.3	0.0006	0.77	(0.67,	0.90)	0.70	(0.58,	0.86)	-0.07	(-0.11,-0.03)	
>= 50	2001	584	29.2	2001	508	25.4	0.0070	0.87	(0.79,	0.96)	0.83	(0.72,	0.95)	-0.04	(-0.07,-0.01)	
Baseline LVEF [%]																0.0495
<50	988	298	30.2	995	232	23.3	0.0006	0.77	(0.67,	0.90)	0.70	(0.58,	0.86)	-0.07	(-0.11,-0.03)	
50 to <60	1030	316	30.7	1028	247	24.0	0.0007	0.78	(0.68,	0.90)	0.71	(0.59,	0.87)	-0.07	(-0.10,-0.03)	
>=60	971	268	27.6	973	261	26.8	0.7006	0.97	(0.84,	1.12)	0.96	(0.79,	1.17)	-0.01	(-0.05, 0.03)	
Baseline NT-proBNP [pg/mL] (</>=median by atrial fibrillation/flutter status)																0.9903
< median	1507	356	23.6	1476	291	19.7	0.0096	0.83	(0.73,	0.96)	0.79	(0.67,	0.95)	-0.04	(-0.07,-0.01)	
>= median	1475	524	35.5	1516	449	29.6	0.0006	0.83	(0.75,	0.92)	0.76	(0.66,	0.89)	-0.06	(-0.09,-0.03)	
Baseline uric acid [mg/dL] (tertiles)																0.1403
<T1	975	270	27.7	963	197	20.5	0.0002	0.74	(0.63,	0.87)	0.67	(0.54,	0.83)	-0.07	(-0.11,-0.03)	
>=T1 and <T2	966	247	25.6	1032	237	23.0	0.1745	0.90	(0.77,	1.05)	0.87	(0.71,	1.06)	-0.03	(-0.06, 0.01)	
>=T2	1016	353	34.7	970	300	30.9	0.0704	0.89	(0.78,	1.01)	0.84	(0.70,	1.01)	-0.04	(-0.08, 0.00)	
Baseline use of MRA																0.5952
No	1865	530	28.4	1878	455	24.2	0.0036	0.85	(0.77,	0.95)	0.81	(0.70,	0.93)	-0.04	(-0.07,-0.01)	
Yes	1124	352	31.3	1118	285	25.5	0.0022	0.81	(0.71,	0.93)	0.75	(0.62,	0.90)	-0.06	(-0.10,-0.02)	
Baseline use of ACE-inhibitor, ARB or ARNi																0.0234
No	586	185	31.6	568	179	31.5	0.9837	1.00	(0.84,	1.18)	1.00	(0.78,	1.28)	0.00	(-0.05, 0.05)	
Yes	2403	697	29.0	2428	561	23.1	<0.0001	0.80	(0.72,	0.88)	0.74	(0.65,	0.84)	-0.06	(-0.08,-0.03)	

Analysis is based on study 1245.110.
^ Patients with NYHA class I are counted in subgroup NYHA class II.
Risk ratios and odds ratios with confidence intervals (CIs) are estimated by Cochran-Mantel-Haenszel method. For risk differences standard Wald asymptotic confidence limits are calculated. A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied in case of any zero cells in contingency table.
Only treatment emergent AEs are displayed (onset between first dose until treatment stop +7 days).
MedDRA version: 23.1. * Chi-square test for treatment effect ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction).

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Table R.1.2.4: 2 Proportion of patients with serious adverse events occuring in at least 1% of the patients in either treatment arm in the overall population on SOC level by SOC, 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	2989	355	11.9	2996	327	10.9	0.2414	0.92	(0.80, 1.06)	0.91	(0.77, 1.07)	-0.01	(-0.03, 0.01)	

Analysis is based on study 1245.110.
^ Patients with NYHA class I are counted in subgroup NYHA class II.
Risk ratios and odds ratios with confidence intervals (CIs) are estimated by Cochran-Mantel-Haenszel method. For risk differences standard Wald asymptotic confidence limits are calculated. A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied in case of any zero cells in contingency table.
Only treatment emergent AEs are displayed (onset between first dose until treatment stop +7 days).
MedDRA version: 23.1. * Chi-square test for treatment effect ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction).

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Table R.1.2.4: 2 Proportion of patients with serious adverse events occuring in at least 1% of the patients in either treatment arm in the overall population on SOC level by SOC, 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	2989	200	6.7	2996	165	5.5	0.0557	0.82	(0.67, 1.01)	0.81	(0.66, 1.01)	-0.01	(-0.02, 0.00)	

Analysis is based on study 1245.110.
^ Patients with NYHA class I are counted in subgroup NYHA class II.
Risk ratios and odds ratios with confidence intervals (CIs) are estimated by Cochran-Mantel-Haenszel method. For risk differences standard Wald asymptotic confidence limits are calculated. A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied in case of any zero cells in contingency table.
Only treatment emergent AEs are displayed (onset between first dose until treatment stop +7 days).
MedDRA version: 23.1. * Chi-square test for treatment effect ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction).

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Table R.1.2.4: 2 Proportion of patients with serious adverse events occuring in at least 1% of the patients in either treatment arm in the overall population on SOC level by SOC, 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	2989	184	6.2	2996	197	6.6	0.5063	1.07	(0.88, 1.30)	1.07	(0.87, 1.32)	0.00	(-0.01, 0.02)	

Analysis is based on study 1245.110.
^ Patients with NYHA class I are counted in subgroup NYHA class II.
Risk ratios and odds ratios with confidence intervals (CIs) are estimated by Cochran-Mantel-Haenszel method. For risk differences standard Wald asymptotic confidence limits are calculated. A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied in case of any zero cells in contingency table.
Only treatment emergent AEs are displayed (onset between first dose until treatment stop +7 days).
MedDRA version: 23.1. * Chi-square test for treatment effect ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction).

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Table R.1.2.4: 2 Proportion of patients with serious adverse events occuring in at least 1% of the patients in either treatment arm in the overall population on SOC level by SOC, 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	2989	144	4.8	2996	166	5.5	0.2069	1.15	(0.93, 1.43)	1.16	(0.92, 1.46)	0.01	(0.00, 0.02)	

Analysis is based on study 1245.110.
^ Patients with NYHA class I are counted in subgroup NYHA class II.
Risk ratios and odds ratios with confidence intervals (CIs) are estimated by Cochran-Mantel-Haenszel method. For risk differences standard Wald asymptotic confidence limits are calculated. A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied in case of any zero cells in contingency table.
Only treatment emergent AEs are displayed (onset between first dose until treatment stop +7 days).
MedDRA version: 23.1. * Chi-square test for treatment effect ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction).

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Table R.1.2.4: 2 Proportion of patients with serious adverse events occuring in at least 1% of the patients in either treatment arm in the overall population on SOC level by SOC, 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	2989	154	5.2	2996	130	4.3	0.1390	0.84	(0.67, 1.06)	0.84	(0.66, 1.06)	-0.01	(-0.02, 0.00)	

Analysis is based on study 1245.110.
^ Patients with NYHA class I are counted in subgroup NYHA class II.
Risk ratios and odds ratios with confidence intervals (CIs) are estimated by Cochran-Mantel-Haenszel method. For risk differences standard Wald asymptotic confidence limits are calculated. A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied in case of any zero cells in contingency table.
Only treatment emergent AEs are displayed (onset between first dose until treatment stop +7 days).
MedDRA version: 23.1. * Chi-square test for treatment effect ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction).

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Table R.1.2.4: 2 Proportion of patients with serious adverse events occuring in at least 1% of the patients in either treatment arm in the overall population on SOC level by SOC, 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	2989	151	5.1	2996	113	3.8	0.0159	0.75	(0.59,	0.95)	0.74	(0.57,	0.95)	-0.01	(-0.02, 0.00)	
Sex																0.3489
Male	1653	85	5.1	1658	70	4.2	0.2101	0.82	(0.60,	1.12)	0.81	(0.59,	1.12)	-0.01	(-0.02, 0.01)	
Female	1336	66	4.9	1338	43	3.2	0.0240	0.65	(0.45,	0.95)	0.64	(0.43,	0.95)	-0.02	(-0.03, 0.00)	
Age [years]																0.0082
<70	1084	42	3.9	1066	48	4.5	0.4670	1.16	(0.77,	1.74)	1.17	(0.77,	1.79)	0.01	(-0.01, 0.02)	
>=70	1905	109	5.7	1930	65	3.4	0.0005	0.59	(0.44,	0.79)	0.57	(0.42,	0.79)	-0.02	(-0.04,-0.01)	
Region																0.9270
North America	359	31	8.6	359	21	5.8	0.1499	0.68	(0.40,	1.16)	0.66	(0.37,	1.17)	-0.03	(-0.07, 0.01)	
Latin America	757	33	4.4	758	24	3.2	0.2224	0.73	(0.43,	1.22)	0.72	(0.42,	1.23)	-0.01	(-0.03, 0.01)	
Europe	1341	69	5.1	1346	52	3.9	0.1091	0.75	(0.53,	1.07)	0.74	(0.51,	1.07)	-0.01	(-0.03, 0.00)	
Asia	343	10	2.9	343	7	2.0	0.4612	0.70	(0.27,	1.82)	0.69	(0.26,	1.84)	-0.01	(-0.03, 0.01)	
Other	189	8	4.2	190	9	4.7	0.8126	1.12	(0.44,	2.84)	1.13	(0.42,	2.98)	0.01	(-0.04, 0.05)	
OECD member																0.1227
No	847	31	3.7	868	33	3.8	0.8768	1.04	(0.64,	1.68)	1.04	(0.63,	1.71)	0.00	(-0.02, 0.02)	
Yes	2142	120	5.6	2128	80	3.8	0.0044	0.67	(0.51,	0.88)	0.66	(0.49,	0.88)	-0.02	(-0.03,-0.01)	
Baseline NYHA																0.5759
II^	2450	109	4.4	2435	77	3.2	0.0188	0.71	(0.53,	0.95)	0.70	(0.52,	0.94)	-0.01	(-0.02, 0.00)	
III/IV	539	42	7.8	561	36	6.4	0.3744	0.82	(0.54,	1.26)	0.81	(0.51,	1.29)	-0.01	(-0.04, 0.02)	
Baseline Diabetes Status																0.2553
Diabetic	1471	91	6.2	1465	60	4.1	0.0103	0.66	(0.48,	0.91)	0.65	(0.46,	0.90)	-0.02	(-0.04, 0.00)	
Non-Diabetic	1518	60	4.0	1531	53	3.5	0.4732	0.88	(0.61,	1.26)	0.87	(0.60,	1.27)	0.00	(-0.02, 0.01)	

Analysis is based on study 1245.110.
^ Patients with NYHA class I are counted in subgroup NYHA class II.
Risk ratios and odds ratios with confidence intervals (CIs) are estimated by Cochran-Mantel-Haenszel method. For risk differences standard Wald asymptotic confidence limits are calculated. A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied in case of any zero cells in contingency table.
Only treatment emergent AEs are displayed (onset between first dose until treatment stop +7 days).
MedDRA version: 23.1. * Chi-square test for treatment effect ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction).

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Table R.1.2.4: 2 Proportion of patients with serious adverse events occuring in at least 1% of the patients in either treatment arm in the overall population on SOC level by SOC, 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 Diabetes Status														0.4225
Diabetic	1471	91	6.2	1465	60	4.1	0.0103	0.66	(0.48, 0.91)	0.65	(0.46, 0.90)	-0.02	(-0.04, 0.00)	
Pre-Diabetes	979	38	3.9	1001	31	3.1	0.3412	0.80	(0.50, 1.27)	0.79	(0.49, 1.28)	-0.01	(-0.02, 0.01)	
Normal (no pre-diabetes)	539	22	4.1	530	22	4.2	0.9545	1.02	(0.57, 1.81)	1.02	(0.56, 1.86)	0.00	(-0.02, 0.02)	
Baseline BMI [kg/m²]														0.3634
<30	1641	72	4.4	1654	48	2.9	0.0228	0.66	(0.46, 0.95)	0.65	(0.45, 0.94)	-0.01	(-0.03, 0.00)	
>=30	1348	79	5.9	1342	65	4.8	0.2413	0.83	(0.60, 1.14)	0.82	(0.58, 1.15)	-0.01	(-0.03, 0.01)	
Baseline eGFR (CKD-EPI) [mL/min/1.73m²]														0.4327
>=60	1505	64	4.3	1493	42	2.8	0.0329	0.66	(0.45, 0.97)	0.65	(0.44, 0.97)	-0.01	(-0.03, 0.00)	
<60	1482	87	5.9	1503	71	4.7	0.1618	0.80	(0.59, 1.09)	0.80	(0.58, 1.10)	-0.01	(-0.03, 0.00)	
History of HHF (in the last 12 months)														0.1576
No	2320	105	4.5	2297	68	3.0	0.0051	0.65	(0.48, 0.88)	0.64	(0.47, 0.88)	-0.02	(-0.03, 0.00)	
Yes	669	46	6.9	699	45	6.4	0.7451	0.94	(0.63, 1.39)	0.93	(0.61, 1.43)	0.00	(-0.03, 0.02)	
Baseline SBP (</>= median)														0.3661
< median	1474	79	5.4	1496	66	4.4	0.2307	0.82	(0.60, 1.13)	0.81	(0.58, 1.14)	-0.01	(-0.02, 0.01)	
>= median	1515	72	4.8	1500	47	3.1	0.0224	0.66	(0.46, 0.95)	0.65	(0.45, 0.94)	-0.02	(-0.03, 0.00)	
History of atrial fibrillation or atrial flutter														0.5939
No	1426	71	5.0	1417	49	3.5	0.0437	0.69	(0.49, 0.99)	0.68	(0.47, 0.99)	-0.02	(-0.03, 0.00)	
Yes	1558	80	5.1	1575	64	4.1	0.1522	0.79	(0.57, 1.09)	0.78	(0.56, 1.10)	-0.01	(-0.03, 0.00)	

Analysis is based on study 1245.110.
^ Patients with NYHA class I are counted in subgroup NYHA class II.
Risk ratios and odds ratios with confidence intervals (CIs) are estimated by Cochran-Mantel-Haenszel method. For risk differences standard Wald asymptotic confidence limits are calculated. A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied in case of any zero cells in contingency table.
Only treatment emergent AEs are displayed (onset between first dose until treatment stop +7 days).
MedDRA version: 23.1. * Chi-square test for treatment effect ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction).

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Table R.1.2.4: 2 Proportion of patients with serious adverse events occuring in at least 1% of the patients in either treatment arm in the overall population on SOC level by SOC, 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 LVEF [%]																0.5866
< 50	988	42	4.3	995	35	3.5	0.3980	0.83	(0.53,	1.28)	0.82	(0.52,	1.30)	-0.01	(-0.02, 0.01)	
>= 50	2001	109	5.4	2001	78	3.9	0.0202	0.72	(0.54,	0.95)	0.70	(0.52,	0.95)	-0.02	(-0.03, 0.00)	
Baseline LVEF [%]																0.7868
<50	988	42	4.3	995	35	3.5	0.3980	0.83	(0.53,	1.28)	0.82	(0.52,	1.30)	-0.01	(-0.02, 0.01)	
50 to <60	1030	61	5.9	1028	46	4.5	0.1391	0.76	(0.52,	1.10)	0.74	(0.50,	1.10)	-0.01	(-0.03, 0.00)	
>=60	971	48	4.9	973	32	3.3	0.0663	0.67	(0.43,	1.03)	0.65	(0.41,	1.03)	-0.02	(-0.03, 0.00)	
Baseline NT-proBNP [pg/mL] (</>=median by atrial fibrillation/flutter status)																0.2291
< median	1507	77	5.1	1476	48	3.3	0.0114	0.64	(0.45,	0.91)	0.62	(0.43,	0.90)	-0.02	(-0.03, 0.00)	
>= median	1475	74	5.0	1516	65	4.3	0.3435	0.85	(0.62,	1.18)	0.85	(0.60,	1.19)	-0.01	(-0.02, 0.01)	
Baseline uric acid [mg/dL] (tertiles)																0.2825
<T1	975	46	4.7	963	25	2.6	0.0129	0.55	(0.34,	0.89)	0.54	(0.33,	0.88)	-0.02	(-0.04, 0.00)	
>=T1 and <T2	966	41	4.2	1032	40	3.9	0.6766	0.91	(0.60,	1.40)	0.91	(0.58,	1.42)	0.00	(-0.02, 0.01)	
>=T2	1016	63	6.2	970	48	4.9	0.2246	0.80	(0.55,	1.15)	0.79	(0.54,	1.16)	-0.01	(-0.03, 0.01)	
Baseline use of MRA																0.4392
No	1865	96	5.1	1878	67	3.6	0.0179	0.69	(0.51,	0.94)	0.68	(0.50,	0.94)	-0.02	(-0.03, 0.00)	
Yes	1124	55	4.9	1118	46	4.1	0.3741	0.84	(0.57,	1.23)	0.83	(0.56,	1.25)	-0.01	(-0.02, 0.01)	
Baseline use of ACE-inhibitor, ARB or ARNi																0.2607
No	586	35	6.0	568	32	5.6	0.8056	0.94	(0.59,	1.50)	0.94	(0.57,	1.54)	0.00	(-0.03, 0.02)	
Yes	2403	116	4.8	2428	81	3.3	0.0088	0.69	(0.52,	0.91)	0.68	(0.51,	0.91)	-0.01	(-0.03, 0.00)	

Analysis is based on study 1245.110.
^ Patients with NYHA class I are counted in subgroup NYHA class II.
Risk ratios and odds ratios with confidence intervals (CIs) are estimated by Cochran-Mantel-Haenszel method. For risk differences standard Wald asymptotic confidence limits are calculated. A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied in case of any zero cells in contingency table.
Only treatment emergent AEs are displayed (onset between first dose until treatment stop +7 days).
MedDRA version: 23.1. * Chi-square test for treatment effect ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction).

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Table R.1.2.4: 2 Proportion of patients with serious adverse events occuring in at least 1% of the patients in either treatment arm in the overall population on SOC level by SOC, 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	2989	131	4.4	2996	116	3.9	0.3205	0.88	(0.69, 1.13)	0.88	(0.68, 1.13)	-0.01	(-0.02, 0.00)	

Analysis is based on study 1245.110.
^ Patients with NYHA class I are counted in subgroup NYHA class II.
Risk ratios and odds ratios with confidence intervals (CIs) are estimated by Cochran-Mantel-Haenszel method. For risk differences standard Wald asymptotic confidence limits are calculated. A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied in case of any zero cells in contingency table.
Only treatment emergent AEs are displayed (onset between first dose until treatment stop +7 days).
MedDRA version: 23.1. * Chi-square test for treatment effect ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction).

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Table R.1.2.4: 2 Proportion of patients with serious adverse events occuring in at least 1% of the patients in either treatment arm in the overall population on SOC level by SOC, 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	2989	111	3.7	2996	119	4.0	0.6032	1.07	(0.83, 1.38)	1.07	(0.82, 1.40)	0.00	(-0.01, 0.01)	

Analysis is based on study 1245.110.
^ Patients with NYHA class I are counted in subgroup NYHA class II.
Risk ratios and odds ratios with confidence intervals (CIs) are estimated by Cochran-Mantel-Haenszel method. For risk differences standard Wald asymptotic confidence limits are calculated. A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied in case of any zero cells in contingency table.
Only treatment emergent AEs are displayed (onset between first dose until treatment stop +7 days).
MedDRA version: 23.1. * Chi-square test for treatment effect ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction).

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Table R.1.2.4: 2 Proportion of patients with serious adverse events occuring in at least 1% of the patients in either treatment arm in the overall population on SOC level by SOC, 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	2989	104	3.5	2996	116	3.9	0.4199	1.11	(0.86, 1.44)	1.12	(0.85, 1.46)	0.00	(-0.01, 0.01)	

Analysis is based on study 1245.110.
^ Patients with NYHA class I are counted in subgroup NYHA class II.
Risk ratios and odds ratios with confidence intervals (CIs) are estimated by Cochran-Mantel-Haenszel method. For risk differences standard Wald asymptotic confidence limits are calculated. A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied in case of any zero cells in contingency table.
Only treatment emergent AEs are displayed (onset between first dose until treatment stop +7 days).
MedDRA version: 23.1. * Chi-square test for treatment effect ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction).

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Table R.1.2.4: 2 Proportion of patients with serious adverse events occuring in at least 1% of the patients in either treatment arm in the overall population on SOC level by SOC, 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	2989	114	3.8	2996	84	2.8	0.0289	0.74	(0.56, 0.97)	0.73	(0.55, 0.97)	-0.01	(-0.02, 0.00)	
Sex														0.8631
Male	1653	61	3.7	1658	46	2.8	0.1362	0.75	(0.52, 1.10)	0.74	(0.50, 1.10)	-0.01	(-0.02, 0.00)	
Female	1336	53	4.0	1338	38	2.8	0.1080	0.72	(0.48, 1.08)	0.71	(0.46, 1.08)	-0.01	(-0.03, 0.00)	
Age [years]														0.1387
<70	1084	42	3.9	1066	39	3.7	0.7926	0.94	(0.62, 1.45)	0.94	(0.60, 1.47)	0.00	(-0.02, 0.01)	
>=70	1905	72	3.8	1930	45	2.3	0.0091	0.62	(0.43, 0.89)	0.61	(0.42, 0.89)	-0.01	(-0.03, 0.00)	
Region														0.0243
North America	359	19	5.3	359	24	6.7	0.4316	1.26	(0.70, 2.26)	1.28	(0.69, 2.38)	0.01	(-0.02, 0.05)	
Latin America	757	36	4.8	758	28	3.7	0.3043	0.78	(0.48, 1.26)	0.77	(0.46, 1.27)	-0.01	(-0.03, 0.01)	
Europe	1341	34	2.5	1346	16	1.2	0.0098	0.47	(0.26, 0.85)	0.46	(0.25, 0.84)	-0.01	(-0.02, 0.00)	
Asia	343	16	4.7	343	4	1.2	0.0065	0.25	(0.08, 0.74)	0.24	(0.08, 0.73)	-0.03	(-0.06,-0.01)	
Other	189	9	4.8	190	12	6.3	0.5085	1.33	(0.57, 3.07)	1.35	(0.55, 3.28)	0.02	(-0.03, 0.06)	
OECD member														0.6304
No	847	45	5.3	868	31	3.6	0.0798	0.67	(0.43, 1.05)	0.66	(0.41, 1.05)	-0.02	(-0.04, 0.00)	
Yes	2142	69	3.2	2128	53	2.5	0.1519	0.77	(0.54, 1.10)	0.77	(0.53, 1.10)	-0.01	(-0.02, 0.00)	
Baseline NYHA														0.9070
II^	2450	82	3.3	2435	59	2.4	0.0538	0.72	(0.52, 1.01)	0.72	(0.51, 1.01)	-0.01	(-0.02, 0.00)	
III/IV	539	32	5.9	561	25	4.5	0.2681	0.75	(0.45, 1.25)	0.74	(0.43, 1.26)	-0.01	(-0.04, 0.01)	
Baseline Diabetes Status														0.9599
Diabetic	1471	80	5.4	1465	59	4.0	0.0718	0.74	(0.53, 1.03)	0.73	(0.52, 1.03)	-0.01	(-0.03, 0.00)	
Non-Diabetic	1518	34	2.2	1531	25	1.6	0.2239	0.73	(0.44, 1.22)	0.72	(0.43, 1.22)	-0.01	(-0.02, 0.00)	

Analysis is based on study 1245.110.
^ Patients with NYHA class I are counted in subgroup NYHA class II.
Risk ratios and odds ratios with confidence intervals (CIs) are estimated by Cochran-Mantel-Haenszel method. For risk differences standard Wald asymptotic confidence limits are calculated. A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied in case of any zero cells in contingency table.
Only treatment emergent AEs are displayed (onset between first dose until treatment stop +7 days).
MedDRA version: 23.1. * Chi-square test for treatment effect ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction).

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Table R.1.2.4: 2 Proportion of patients with serious adverse events occuring in at least 1% of the patients in either treatment arm in the overall population on SOC level by SOC, 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 Diabetes Status														0.1410
Diabetic	1471	80	5.4	1465	59	4.0	0.0718	0.74	(0.53, 1.03)	0.73	(0.52, 1.03)	-0.01	(-0.03, 0.00)	
Pre-Diabetes	979	27	2.8	1001	14	1.4	0.0337	0.51	(0.27, 0.96)	0.50	(0.26, 0.96)	-0.01	(-0.03, 0.00)	
Normal (no pre-diabetes)	539	7	1.3	530	11	2.1	0.3237	1.60	(0.62, 4.09)	1.61	(0.62, 4.19)	0.01	(-0.01, 0.02)	
Baseline BMI [kg/m²]														0.0880
<30	1641	65	4.0	1654	38	2.3	0.0061	0.58	(0.39, 0.86)	0.57	(0.38, 0.86)	-0.02	(-0.03, 0.00)	
>=30	1348	49	3.6	1342	46	3.4	0.7709	0.94	(0.64, 1.40)	0.94	(0.62, 1.42)	0.00	(-0.02, 0.01)	
Baseline eGFR (CKD-EPI) [mL/min/1.73m²]														0.9040
>=60	1505	39	2.6	1493	29	1.9	0.2328	0.75	(0.47, 1.21)	0.74	(0.46, 1.21)	-0.01	(-0.02, 0.00)	
<60	1482	75	5.1	1503	55	3.7	0.0607	0.72	(0.51, 1.02)	0.71	(0.50, 1.02)	-0.01	(-0.03, 0.00)	
History of HHF (in the last 12 months)														0.8169
No	2320	81	3.5	2297	60	2.6	0.0825	0.75	(0.54, 1.04)	0.74	(0.53, 1.04)	-0.01	(-0.02, 0.00)	
Yes	669	33	4.9	699	24	3.4	0.1654	0.70	(0.42, 1.16)	0.69	(0.40, 1.17)	-0.01	(-0.04, 0.01)	
Baseline SBP (</>= median)														0.2925
< median	1474	58	3.9	1496	37	2.5	0.0236	0.63	(0.42, 0.94)	0.62	(0.41, 0.94)	-0.01	(-0.03, 0.00)	
>= median	1515	56	3.7	1500	47	3.1	0.3948	0.85	(0.58, 1.24)	0.84	(0.57, 1.25)	-0.01	(-0.02, 0.01)	
History of atrial fibrillation or atrial flutter														0.0854
No	1426	60	4.2	1417	54	3.8	0.5898	0.91	(0.63, 1.30)	0.90	(0.62, 1.31)	0.00	(-0.02, 0.01)	
Yes	1558	54	3.5	1575	30	1.9	0.0068	0.55	(0.35, 0.85)	0.54	(0.34, 0.85)	-0.02	(-0.03, 0.00)	

Analysis is based on study 1245.110.
^ Patients with NYHA class I are counted in subgroup NYHA class II.
Risk ratios and odds ratios with confidence intervals (CIs) are estimated by Cochran-Mantel-Haenszel method. For risk differences standard Wald asymptotic confidence limits are calculated. A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied in case of any zero cells in contingency table.
Only treatment emergent AEs are displayed (onset between first dose until treatment stop +7 days).
MedDRA version: 23.1. * Chi-square test for treatment effect ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction).

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Table R.1.2.4: 2 Proportion of patients with serious adverse events occuring in at least 1% of the patients in either treatment arm in the overall population on SOC level by SOC, 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 LVEF [%]																0.0924
< 50	988	38	3.8	995	19	1.9	0.0099	0.50	(0.29,	0.86)	0.49	(0.28,	0.85)	-0.02	(-0.03, 0.00)	
>= 50	2001	76	3.8	2001	65	3.2	0.3456	0.86	(0.62,	1.18)	0.85	(0.61,	1.19)	-0.01	(-0.02, 0.01)	
Baseline LVEF [%]																0.1501
<50	988	38	3.8	995	19	1.9	0.0099	0.50	(0.29,	0.86)	0.49	(0.28,	0.85)	-0.02	(-0.03, 0.00)	
50 to <60	1030	36	3.5	1028	36	3.5	0.9933	1.00	(0.64,	1.58)	1.00	(0.63,	1.60)	0.00	(-0.02, 0.02)	
>=60	971	40	4.1	973	29	3.0	0.1748	0.72	(0.45,	1.16)	0.72	(0.44,	1.16)	-0.01	(-0.03, 0.01)	
Baseline NT-proBNP [pg/mL] (</>=median by atrial fibrillation/flutter status)																0.3394
< median	1507	51	3.4	1476	31	2.1	0.0320	0.62	(0.40,	0.96)	0.61	(0.39,	0.96)	-0.01	(-0.02, 0.00)	
>= median	1475	63	4.3	1516	53	3.5	0.2723	0.82	(0.57,	1.17)	0.81	(0.56,	1.18)	-0.01	(-0.02, 0.01)	
Baseline uric acid [mg/dL] (tertiles)																0.7147
<T1	975	21	2.2	963	19	2.0	0.7795	0.92	(0.50,	1.69)	0.91	(0.49,	1.71)	0.00	(-0.01, 0.01)	
>=T1 and <T2	966	36	3.7	1032	29	2.8	0.2485	0.75	(0.47,	1.22)	0.75	(0.45,	1.23)	-0.01	(-0.02, 0.01)	
>=T2	1016	56	5.5	970	36	3.7	0.0564	0.67	(0.45,	1.01)	0.66	(0.43,	1.01)	-0.02	(-0.04, 0.00)	
Baseline use of MRA																0.5092
No	1865	65	3.5	1878	52	2.8	0.2079	0.79	(0.55,	1.14)	0.79	(0.54,	1.14)	-0.01	(-0.02, 0.00)	
Yes	1124	49	4.4	1118	32	2.9	0.0575	0.66	(0.42,	1.02)	0.65	(0.41,	1.02)	-0.01	(-0.03, 0.00)	
Baseline use of ACE-inhibitor, ARB or ARNi																0.3085
No	586	20	3.4	568	19	3.3	0.9491	0.98	(0.53,	1.82)	0.98	(0.52,	1.86)	0.00	(-0.02, 0.02)	
Yes	2403	94	3.9	2428	65	2.7	0.0162	0.68	(0.50,	0.93)	0.68	(0.49,	0.93)	-0.01	(-0.02, 0.00)	

Analysis is based on study 1245.110.
^ Patients with NYHA class I are counted in subgroup NYHA class II.
Risk ratios and odds ratios with confidence intervals (CIs) are estimated by Cochran-Mantel-Haenszel method. For risk differences standard Wald asymptotic confidence limits are calculated. A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied in case of any zero cells in contingency table.
Only treatment emergent AEs are displayed (onset between first dose until treatment stop +7 days).
MedDRA version: 23.1. * Chi-square test for treatment effect ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction).

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Table R.1.2.4: 2 Proportion of patients with serious adverse events occuring in at least 1% of the patients in either treatment arm in the overall population on SOC level by SOC, 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	2989	76	2.5	2996	53	1.8	0.0393	0.70	(0.49,	0.98)	0.69	(0.48,	0.98)	-0.01	(-0.02, 0.00)	
Sex																0.6182
Male	1653	44	2.7	1658	33	2.0	0.1999	0.75	(0.48,	1.17)	0.74	(0.47,	1.17)	-0.01	(-0.02, 0.00)	
Female	1336	32	2.4	1338	20	1.5	0.0918	0.62	(0.36,	1.09)	0.62	(0.35,	1.09)	-0.01	(-0.02, 0.00)	
Age [years]																0.6860
<70	1084	23	2.1	1066	14	1.3	0.1495	0.62	(0.32,	1.20)	0.61	(0.31,	1.20)	-0.01	(-0.02, 0.00)	
>=70	1905	53	2.8	1930	39	2.0	0.1234	0.73	(0.48,	1.09)	0.72	(0.47,	1.10)	-0.01	(-0.02, 0.00)	
Region																0.0952
North America	359	14	3.9	359	13	3.6	0.8445	0.93	(0.44,	1.95)	0.93	(0.43,	2.00)	0.00	(-0.03, 0.03)	
Latin America	757	11	1.5	758	4	0.5	0.0689	0.36	(0.12,	1.14)	0.36	(0.11,	1.13)	-0.01	(-0.02, 0.00)	
Europe	1341	32	2.4	1346	29	2.2	0.6868	0.90	(0.55,	1.48)	0.90	(0.54,	1.50)	0.00	(-0.01, 0.01)	
Asia	343	16	4.7	343	3	0.9	0.0025	0.19	(0.06,	0.64)	0.18	(0.05,	0.62)	-0.04	(-0.06,-0.01)	
Other	189	3	1.6	190	4	2.1	0.7081	1.33	(0.30,	5.85)	1.33	(0.29,	6.04)	0.01	(-0.02, 0.03)	
OECD member																0.8642
No	847	12	1.4	868	8	0.9	0.3397	0.65	(0.27,	1.58)	0.65	(0.26,	1.59)	0.00	(-0.02, 0.01)	
Yes	2142	64	3.0	2128	45	2.1	0.0705	0.71	(0.49,	1.03)	0.70	(0.48,	1.03)	-0.01	(-0.02, 0.00)	
Baseline NYHA																0.4013
II^	2450	65	2.7	2435	42	1.7	0.0267	0.65	(0.44,	0.95)	0.64	(0.44,	0.95)	-0.01	(-0.02, 0.00)	
III/IV	539	11	2.0	561	11	2.0	0.9245	0.96	(0.42,	2.20)	0.96	(0.41,	2.23)	0.00	(-0.02, 0.02)	
Baseline Diabetes Status																0.4234
Diabetic	1471	35	2.4	1465	28	1.9	0.3815	0.80	(0.49,	1.31)	0.80	(0.48,	1.32)	0.00	(-0.02, 0.01)	
Non-Diabetic	1518	41	2.7	1531	25	1.6	0.0427	0.60	(0.37,	0.99)	0.60	(0.36,	0.99)	-0.01	(-0.02, 0.00)	

Analysis is based on study 1245.110.
^ Patients with NYHA class I are counted in subgroup NYHA class II.
Risk ratios and odds ratios with confidence intervals (CIs) are estimated by Cochran-Mantel-Haenszel method. For risk differences standard Wald asymptotic confidence limits are calculated. A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied in case of any zero cells in contingency table.
Only treatment emergent AEs are displayed (onset between first dose until treatment stop +7 days).
MedDRA version: 23.1. * Chi-square test for treatment effect ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction).

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Table R.1.2.4: 2 Proportion of patients with serious adverse events occuring in at least 1% of the patients in either treatment arm in the overall population on SOC level by SOC, 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 Diabetes Status																0.6611
Diabetic	1471	35	2.4	1465	28	1.9	0.3815	0.80	(0.49,	1.31)	0.80	(0.48,	1.32)	0.00	(-0.02, 0.01)	
Pre-Diabetes	979	28	2.9	1001	16	1.6	0.0569	0.56	(0.30,	1.03)	0.55	(0.30,	1.03)	-0.01	(-0.03, 0.00)	
Normal (no pre-diabetes)	539	13	2.4	530	9	1.7	0.4112	0.70	(0.30,	1.63)	0.70	(0.30,	1.65)	-0.01	(-0.02, 0.01)	
Baseline BMI [kg/m²]																0.4615
<30	1641	42	2.6	1654	26	1.6	0.0462	0.61	(0.38,	1.00)	0.61	(0.37,	1.00)	-0.01	(-0.02, 0.00)	
>=30	1348	34	2.5	1342	27	2.0	0.3740	0.80	(0.48,	1.31)	0.79	(0.48,	1.32)	-0.01	(-0.02, 0.01)	
Baseline eGFR (CKD-EPI) [mL/min/1.73m²]																0.2112
>=60	1505	36	2.4	1493	19	1.3	0.0224	0.53	(0.31,	0.92)	0.53	(0.30,	0.92)	-0.01	(-0.02, 0.00)	
<60	1482	40	2.7	1503	34	2.3	0.4427	0.84	(0.53,	1.32)	0.83	(0.53,	1.33)	0.00	(-0.02, 0.01)	
History of HHF (in the last 12 months)																0.9359
No	2320	53	2.3	2297	36	1.6	0.0764	0.69	(0.45,	1.04)	0.68	(0.44,	1.04)	-0.01	(-0.02, 0.00)	
Yes	669	23	3.4	699	17	2.4	0.2696	0.71	(0.38,	1.31)	0.70	(0.37,	1.32)	-0.01	(-0.03, 0.01)	
Baseline SBP (</>= median)																0.4476
< median	1474	36	2.4	1496	29	1.9	0.3481	0.79	(0.49,	1.29)	0.79	(0.48,	1.29)	-0.01	(-0.02, 0.01)	
>= median	1515	40	2.6	1500	24	1.6	0.0476	0.61	(0.37,	1.00)	0.60	(0.36,	1.00)	-0.01	(-0.02, 0.00)	
History of atrial fibrillation or atrial flutter																0.4555
No	1426	31	2.2	1417	18	1.3	0.0642	0.58	(0.33,	1.04)	0.58	(0.32,	1.04)	-0.01	(-0.02, 0.00)	
Yes	1558	45	2.9	1575	35	2.2	0.2373	0.77	(0.50,	1.19)	0.76	(0.49,	1.20)	-0.01	(-0.02, 0.00)	

Analysis is based on study 1245.110.
^ Patients with NYHA class I are counted in subgroup NYHA class II.
Risk ratios and odds ratios with confidence intervals (CIs) are estimated by Cochran-Mantel-Haenszel method. For risk differences standard Wald asymptotic confidence limits are calculated. A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
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MedDRA version: 23.1. * Chi-square test for treatment effect ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction).

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Table R.1.2.4: 2 Proportion of patients with serious adverse events occuring in at least 1% of the patients in either treatment arm in the overall population on SOC level by SOC, 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 LVEF [%]																0.3259
< 50	988	21	2.1	995	19	1.9	0.7323	0.90	(0.49,	1.66)	0.90	(0.48,	1.68)	0.00	(-0.01, 0.01)	
>= 50	2001	55	2.7	2001	34	1.7	0.0244	0.62	(0.40,	0.94)	0.61	(0.40,	0.94)	-0.01	(-0.02, 0.00)	
Baseline LVEF [%]																0.6057
<50	988	21	2.1	995	19	1.9	0.7323	0.90	(0.49,	1.66)	0.90	(0.48,	1.68)	0.00	(-0.01, 0.01)	
50 to <60	1030	28	2.7	1028	18	1.8	0.1377	0.64	(0.36,	1.16)	0.64	(0.35,	1.16)	-0.01	(-0.02, 0.00)	
>=60	971	27	2.8	973	16	1.6	0.0885	0.59	(0.32,	1.09)	0.58	(0.31,	1.09)	-0.01	(-0.02, 0.00)	
Baseline NT-proBNP [pg/mL] (</>=median by atrial fibrillation/flutter status)																0.4561
< median	1507	36	2.4	1476	21	1.4	0.0540	0.60	(0.35,	1.02)	0.59	(0.34,	1.02)	-0.01	(-0.02, 0.00)	
>= median	1475	40	2.7	1516	32	2.1	0.2836	0.78	(0.49,	1.23)	0.77	(0.48,	1.24)	-0.01	(-0.02, 0.00)	
Baseline uric acid [mg/dL] (tertiles)																0.7468
<T1	975	25	2.6	963	17	1.8	0.2272	0.69	(0.37,	1.27)	0.68	(0.37,	1.27)	-0.01	(-0.02, 0.00)	
>=T1 and <T2	966	24	2.5	1032	15	1.5	0.0960	0.59	(0.31,	1.11)	0.58	(0.30,	1.11)	-0.01	(-0.02, 0.00)	
>=T2	1016	27	2.7	970	21	2.2	0.4750	0.81	(0.46,	1.43)	0.81	(0.46,	1.44)	0.00	(-0.02, 0.01)	
Baseline use of MRA																0.7209
No	1865	48	2.6	1878	32	1.7	0.0658	0.66	(0.43,	1.03)	0.66	(0.42,	1.03)	-0.01	(-0.02, 0.00)	
Yes	1124	28	2.5	1118	21	1.9	0.3211	0.75	(0.43,	1.32)	0.75	(0.42,	1.33)	-0.01	(-0.02, 0.01)	
Baseline use of ACE-inhibitor, ARB or ARNi																0.9569
No	586	16	2.7	568	11	1.9	0.3725	0.71	(0.33,	1.52)	0.70	(0.32,	1.53)	-0.01	(-0.03, 0.01)	
Yes	2403	60	2.5	2428	42	1.7	0.0637	0.69	(0.47,	1.02)	0.69	(0.46,	1.02)	-0.01	(-0.02, 0.00)	

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^ Patients with NYHA class I are counted in subgroup NYHA class II.
Risk ratios and odds ratios with confidence intervals (CIs) are estimated by Cochran-Mantel-Haenszel method. For risk differences standard Wald asymptotic confidence limits are calculated. A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied in case of any zero cells in contingency table.
Only treatment emergent AEs are displayed (onset between first dose until treatment stop +7 days).
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Table R.1.2.4: 2 Proportion of patients with serious adverse events occuring in at least 1% of the patients in either treatment arm in the overall population on SOC level by SOC, 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	2989	60	2.0	2996	33	1.1	0.0046	0.55	(0.36,	0.84)	0.54	(0.35,	0.83)	-0.01	(-0.02, 0.00)	
Sex																0.9859
Male	1653	31	1.9	1658	17	1.0	0.0407	0.55	(0.30,	0.98)	0.54	(0.30,	0.98)	-0.01	(-0.02, 0.00)	
Female	1336	29	2.2	1338	16	1.2	0.0501	0.55	(0.30,	1.01)	0.55	(0.29,	1.01)	-0.01	(-0.02, 0.00)	
Age [years]																0.5973
<70	1084	12	1.1	1066	5	0.5	0.0949	0.42	(0.15,	1.20)	0.42	(0.15,	1.20)	-0.01	(-0.01, 0.00)	
>=70	1905	48	2.5	1930	28	1.5	0.0176	0.58	(0.36,	0.91)	0.57	(0.36,	0.91)	-0.01	(-0.02, 0.00)	
Region																0.8976
North America	359	10	2.8	359	7	1.9	0.4615	0.70	(0.27,	1.82)	0.69	(0.26,	1.84)	-0.01	(-0.03, 0.01)	
Latin America	757	8	1.1	758	4	0.5	0.2454	0.50	(0.15,	1.65)	0.50	(0.15,	1.66)	-0.01	(-0.01, 0.00)	
Europe	1341	31	2.3	1346	15	1.1	0.0167	0.48	(0.26,	0.89)	0.48	(0.26,	0.89)	-0.01	(-0.02, 0.00)	
Asia	343	6	1.7	343	5	1.5	0.7612	0.83	(0.26,	2.70)	0.83	(0.25,	2.75)	0.00	(-0.02, 0.02)	
Other	189	5	2.6	190	2	1.1	0.2495	0.40	(0.08,	2.03)	0.39	(0.08,	2.04)	-0.02	(-0.04, 0.01)	
OECD member																0.0813
No	847	6	0.7	868	8	0.9	0.6236	1.30	(0.45,	3.73)	1.30	(0.45,	3.77)	0.00	(-0.01, 0.01)	
Yes	2142	54	2.5	2128	25	1.2	0.0011	0.47	(0.29,	0.75)	0.46	(0.29,	0.74)	-0.01	(-0.02,-0.01)	
Baseline NYHA																0.0853
II^	2450	47	1.9	2435	20	0.8	0.0010	0.43	(0.25,	0.72)	0.42	(0.25,	0.72)	-0.01	(-0.02, 0.00)	
III/IV	539	13	2.4	561	13	2.3	0.9178	0.96	(0.45,	2.05)	0.96	(0.44,	2.09)	0.00	(-0.02, 0.02)	
Baseline Diabetes Status																0.6941
Diabetic	1471	30	2.0	1465	15	1.0	0.0251	0.50	(0.27,	0.93)	0.50	(0.27,	0.93)	-0.01	(-0.02, 0.00)	
Non-Diabetic	1518	30	2.0	1531	18	1.2	0.0758	0.59	(0.33,	1.06)	0.59	(0.33,	1.06)	-0.01	(-0.02, 0.00)	

Analysis is based on study 1245.110.
^ Patients with NYHA class I are counted in subgroup NYHA class II.
Risk ratios and odds ratios with confidence intervals (CIs) are estimated by Cochran-Mantel-Haenszel method. For risk differences standard Wald asymptotic confidence limits are calculated. A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied in case of any zero cells in contingency table.
Only treatment emergent AEs are displayed (onset between first dose until treatment stop +7 days).
MedDRA version: 23.1. * Chi-square test for treatment effect ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction).

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Table R.1.2.4: 2 Proportion of patients with serious adverse events occuring in at least 1% of the patients in either treatment arm in the overall population on SOC level by SOC, 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 Diabetes Status														0.4389
Diabetic	1471	30	2.0	1465	15	1.0	0.0251	0.50	(0.27, 0.93)	0.50	(0.27, 0.93)	-0.01	(-0.02, 0.00)	
Pre-Diabetes	979	20	2.0	1001	9	0.9	0.0342	0.44	(0.20, 0.96)	0.44	(0.20, 0.96)	-0.01	(-0.02, 0.00)	
Normal (no pre-diabetes)	539	10	1.9	530	9	1.7	0.8458	0.92	(0.37, 2.23)	0.91	(0.37, 2.27)	0.00	(-0.02, 0.01)	
Baseline BMI [kg/m²]														0.3581
<30	1641	34	2.1	1654	22	1.3	0.0995	0.64	(0.38, 1.09)	0.64	(0.37, 1.09)	-0.01	(-0.02, 0.00)	
>=30	1348	26	1.9	1342	11	0.8	0.0135	0.42	(0.21, 0.86)	0.42	(0.21, 0.85)	-0.01	(-0.02, 0.00)	
Baseline eGFR (CKD-EPI) [mL/min/1.73m²]														0.1834
>=60	1505	23	1.5	1493	8	0.5	0.0072	0.35	(0.16, 0.78)	0.35	(0.15, 0.78)	-0.01	(-0.02, 0.00)	
<60	1482	37	2.5	1503	25	1.7	0.1105	0.67	(0.40, 1.10)	0.66	(0.40, 1.10)	-0.01	(-0.02, 0.00)	
History of HHF (in the last 12 months)														0.4203
No	2320	42	1.8	2297	20	0.9	0.0055	0.48	(0.28, 0.82)	0.48	(0.28, 0.81)	-0.01	(-0.02, 0.00)	
Yes	669	18	2.7	699	13	1.9	0.3020	0.69	(0.34, 1.40)	0.69	(0.33, 1.41)	-0.01	(-0.02, 0.01)	
Baseline SBP (</>= median)														0.9990
< median	1474	36	2.4	1496	20	1.3	0.0268	0.55	(0.32, 0.94)	0.54	(0.31, 0.94)	-0.01	(-0.02, 0.00)	
>= median	1515	24	1.6	1500	13	0.9	0.0736	0.55	(0.28, 1.07)	0.54	(0.28, 1.07)	-0.01	(-0.02, 0.00)	
History of atrial fibrillation or atrial flutter														0.3781
No	1426	18	1.3	1417	7	0.5	0.0282	0.39	(0.16, 0.93)	0.39	(0.16, 0.93)	-0.01	(-0.01, 0.00)	
Yes	1558	42	2.7	1575	26	1.7	0.0448	0.61	(0.38, 0.99)	0.61	(0.37, 0.99)	-0.01	(-0.02, 0.00)	

Analysis is based on study 1245.110.
^ Patients with NYHA class I are counted in subgroup NYHA class II.
Risk ratios and odds ratios with confidence intervals (CIs) are estimated by Cochran-Mantel-Haenszel method. For risk differences standard Wald asymptotic confidence limits are calculated. A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied in case of any zero cells in contingency table.
Only treatment emergent AEs are displayed (onset between first dose until treatment stop +7 days).
MedDRA version: 23.1. * Chi-square test for treatment effect ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction).

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Table R.1.2.4: 2 Proportion of patients with serious adverse events occuring in at least 1% of the patients in either treatment arm in the overall population on SOC level by SOC, 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 LVEF [%]																0.3980
< 50	988	15	1.5	995	11	1.1	0.4192	0.73	(0.34,	1.58)	0.73	(0.33,	1.59)	0.00	(-0.01, 0.01)	
>= 50	2001	45	2.2	2001	22	1.1	0.0046	0.49	(0.29,	0.81)	0.48	(0.29,	0.81)	-0.01	(-0.02, 0.00)	
Baseline LVEF [%]																0.3842
<50	988	15	1.5	995	11	1.1	0.4192	0.73	(0.34,	1.58)	0.73	(0.33,	1.59)	0.00	(-0.01, 0.01)	
50 to <60	1030	27	2.6	1028	10	1.0	0.0049	0.37	(0.18,	0.76)	0.36	(0.18,	0.76)	-0.02	(-0.03,-0.01)	
>=60	971	18	1.9	973	12	1.2	0.2671	0.67	(0.32,	1.37)	0.66	(0.32,	1.38)	-0.01	(-0.02, 0.00)	
Baseline NT-proBNP [pg/mL] (</>=median by atrial fibrillation/flutter status)																0.0863
< median	1507	28	1.9	1476	9	0.6	0.0021	0.33	(0.16,	0.69)	0.32	(0.15,	0.69)	-0.01	(-0.02, 0.00)	
>= median	1475	32	2.2	1516	24	1.6	0.2369	0.73	(0.43,	1.23)	0.73	(0.43,	1.24)	-0.01	(-0.02, 0.00)	
Baseline uric acid [mg/dL] (tertiles)																0.1054
<T1	975	17	1.7	963	3	0.3	0.0018	0.18	(0.05,	0.61)	0.18	(0.05,	0.60)	-0.01	(-0.02,-0.01)	
>=T1 and <T2	966	16	1.7	1032	14	1.4	0.5820	0.82	(0.40,	1.67)	0.82	(0.40,	1.68)	0.00	(-0.01, 0.01)	
>=T2	1016	27	2.7	970	16	1.6	0.1229	0.62	(0.34,	1.14)	0.61	(0.33,	1.15)	-0.01	(-0.02, 0.00)	
Baseline use of MRA																0.1232
No	1865	28	1.5	1878	21	1.1	0.3025	0.74	(0.42,	1.31)	0.74	(0.42,	1.31)	0.00	(-0.01, 0.00)	
Yes	1124	32	2.8	1118	12	1.1	0.0025	0.38	(0.20,	0.73)	0.37	(0.19,	0.72)	-0.02	(-0.03,-0.01)	
Baseline use of ACE-inhibitor, ARB or ARNi																0.0287
No	586	13	2.2	568	14	2.5	0.7819	1.11	(0.53,	2.34)	1.11	(0.52,	2.39)	0.00	(-0.01, 0.02)	
Yes	2403	47	2.0	2428	19	0.8	0.0004	0.40	(0.24,	0.68)	0.40	(0.23,	0.68)	-0.01	(-0.02,-0.01)	

Analysis is based on study 1245.110.
^ Patients with NYHA class I are counted in subgroup NYHA class II.
Risk ratios and odds ratios with confidence intervals (CIs) are estimated by Cochran-Mantel-Haenszel method. For risk differences standard Wald asymptotic confidence limits are calculated. A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied in case of any zero cells in contingency table.
Only treatment emergent AEs are displayed (onset between first dose until treatment stop +7 days).
MedDRA version: 23.1. * Chi-square test for treatment effect ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction).

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Table R.1.2.4: 2 Proportion of patients with serious adverse events occuring in at least 1% of the patients in either treatment arm in the overall population on SOC level by SOC, 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	2989	51	1.7	2996	53	1.8	0.8526	1.04	(0.71, 1.52)	1.04	(0.70, 1.53)	0.00	(-0.01, 0.01)	

Analysis is based on study 1245.110.
^ Patients with NYHA class I are counted in subgroup NYHA class II.
Risk ratios and odds ratios with confidence intervals (CIs) are estimated by Cochran-Mantel-Haenszel method. For risk differences standard Wald asymptotic confidence limits are calculated. A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied in case of any zero cells in contingency table.
Only treatment emergent AEs are displayed (onset between first dose until treatment stop +7 days).
MedDRA version: 23.1. * Chi-square test for treatment effect ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction).

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Table R.1.2.4: 2 Proportion of patients with serious adverse events occuring in at least 1% of the patients in either treatment arm in the overall population on SOC level by SOC, 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	2989	45	1.5	2996	37	1.2	0.3680	0.82	(0.53, 1.26)	0.82	(0.53, 1.27)	0.00	(-0.01, 0.00)	

Analysis is based on study 1245.110.
^ Patients with NYHA class I are counted in subgroup NYHA class II.
Risk ratios and odds ratios with confidence intervals (CIs) are estimated by Cochran-Mantel-Haenszel method. For risk differences standard Wald asymptotic confidence limits are calculated. A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied in case of any zero cells in contingency table.
Only treatment emergent AEs are displayed (onset between first dose until treatment stop +7 days).
MedDRA version: 23.1. * Chi-square test for treatment effect ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction).

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Table R.1.2.4: 3 Proportion of patients with severe adverse events occuring in at least 1% of the patients in either treatment arm in the overall population on SOC level by SOC, 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	2989	388	13.0	2996	304	10.1	0.0006	0.78	(0.68, 0.90)	0.76	(0.65, 0.89)	-0.03	(-0.04,-0.01)	
Sex														0.6477
Male	1653	222	13.4	1658	179	10.8	0.0202	0.80	(0.67, 0.97)	0.78	(0.63, 0.96)	-0.03	(-0.05, 0.00)	
Female	1336	166	12.4	1338	125	9.3	0.0105	0.75	(0.60, 0.94)	0.73	(0.57, 0.93)	-0.03	(-0.05,-0.01)	
Age [years]														0.6238
<70	1084	125	11.5	1066	101	9.5	0.1200	0.82	(0.64, 1.05)	0.80	(0.61, 1.06)	-0.02	(-0.05, 0.01)	
>=70	1905	263	13.8	1930	203	10.5	0.0018	0.76	(0.64, 0.90)	0.73	(0.60, 0.89)	-0.03	(-0.05,-0.01)	
Region														0.8749
North America	359	62	17.3	359	47	13.1	0.1188	0.76	(0.53, 1.08)	0.72	(0.48, 1.09)	-0.04	(-0.09, 0.01)	
Latin America	757	116	15.3	758	90	11.9	0.0501	0.77	(0.60, 1.00)	0.74	(0.55, 1.00)	-0.03	(-0.07, 0.00)	
Europe	1341	144	10.7	1346	114	8.5	0.0460	0.79	(0.62, 1.00)	0.77	(0.59, 1.00)	-0.02	(-0.04, 0.00)	
Asia	343	47	13.7	343	33	9.6	0.0958	0.70	(0.46, 1.07)	0.67	(0.42, 1.08)	-0.04	(-0.09, 0.01)	
Other	189	19	10.1	190	20	10.5	0.8795	1.05	(0.58, 1.90)	1.05	(0.54, 2.04)	0.00	(-0.06, 0.07)	
OECD member														0.2875
No	847	120	14.2	868	107	12.3	0.2608	0.87	(0.68, 1.11)	0.85	(0.64, 1.13)	-0.02	(-0.05, 0.01)	
Yes	2142	268	12.5	2128	197	9.3	0.0006	0.74	(0.62, 0.88)	0.71	(0.59, 0.87)	-0.03	(-0.05,-0.01)	
Baseline NYHA														0.8372
II^	2450	268	10.9	2435	209	8.6	0.0055	0.78	(0.66, 0.93)	0.76	(0.63, 0.92)	-0.02	(-0.04,-0.01)	
III/IV	539	120	22.3	561	95	16.9	0.0259	0.76	(0.60, 0.97)	0.71	(0.53, 0.96)	-0.05	(-0.10,-0.01)	
Baseline Diabetes Status														0.2717
Diabetic	1471	222	15.1	1465	161	11.0	0.0010	0.73	(0.60, 0.88)	0.69	(0.56, 0.86)	-0.04	(-0.07,-0.02)	
Non-Diabetic	1518	166	10.9	1531	143	9.3	0.1445	0.85	(0.69, 1.06)	0.84	(0.66, 1.06)	-0.02	(-0.04, 0.01)	

Analysis is based on study 1245.110.
^ Patients with NYHA class I are counted in subgroup NYHA class II.
Risk ratios and odds ratios with confidence intervals (CIs) are estimated by Cochran-Mantel-Haenszel method. For risk differences standard Wald asymptotic confidence limits are calculated. A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied in case of any zero cells in contingency table.
Only treatment emergent AEs are displayed (onset between first dose until treatment stop +7 days).
MedDRA version: 23.1. * Chi-square test for treatment effect ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction).

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Table R.1.2.4: 3 Proportion of patients with severe adverse events occuring in at least 1% of the patients in either treatment arm in the overall population on SOC level by SOC, 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 Diabetes Status														0.4984
Diabetic	1471	222	15.1	1465	161	11.0	0.0010	0.73	(0.60, 0.88)	0.69	(0.56, 0.86)	-0.04	(-0.07,-0.02)	
Pre-Diabetes	979	109	11.1	1001	92	9.2	0.1523	0.83	(0.63, 1.07)	0.81	(0.60, 1.08)	-0.02	(-0.05, 0.01)	
Normal (no pre-diabetes)	539	57	10.6	530	51	9.6	0.6054	0.91	(0.64, 1.30)	0.90	(0.60, 1.34)	-0.01	(-0.05, 0.03)	
Baseline BMI [kg/m²]														0.8388
<30	1641	225	13.7	1654	175	10.6	0.0059	0.77	(0.64, 0.93)	0.74	(0.60, 0.92)	-0.03	(-0.05,-0.01)	
>=30	1348	163	12.1	1342	129	9.6	0.0387	0.79	(0.64, 0.99)	0.77	(0.61, 0.99)	-0.02	(-0.05, 0.00)	
Baseline eGFR (CKD-EPI) [mL/min/1.73m²]														0.9299
>=60	1505	154	10.2	1493	120	8.0	0.0370	0.79	(0.63, 0.99)	0.77	(0.60, 0.98)	-0.02	(-0.04, 0.00)	
<60	1482	234	15.8	1503	184	12.2	0.0052	0.78	(0.65, 0.93)	0.74	(0.60, 0.92)	-0.04	(-0.06,-0.01)	
History of HHF (in the last 12 months)														0.8971
No	2320	257	11.1	2297	199	8.7	0.0060	0.78	(0.66, 0.93)	0.76	(0.63, 0.93)	-0.02	(-0.04,-0.01)	
Yes	669	131	19.6	699	105	15.0	0.0257	0.77	(0.61, 0.97)	0.73	(0.55, 0.96)	-0.05	(-0.09,-0.01)	
Baseline SBP (</>= median)														0.6614
< median	1474	199	13.5	1496	153	10.2	0.0058	0.76	(0.62, 0.92)	0.73	(0.58, 0.91)	-0.03	(-0.06,-0.01)	
>= median	1515	189	12.5	1500	151	10.1	0.0366	0.81	(0.66, 0.99)	0.79	(0.63, 0.99)	-0.02	(-0.05, 0.00)	
History of atrial fibrillation or atrial flutter														0.9392
No	1426	178	12.5	1417	139	9.8	0.0236	0.79	(0.64, 0.97)	0.76	(0.60, 0.96)	-0.03	(-0.05, 0.00)	
Yes	1558	210	13.5	1575	165	10.5	0.0096	0.78	(0.64, 0.94)	0.75	(0.60, 0.93)	-0.03	(-0.05,-0.01)	

Analysis is based on study 1245.110.
^ Patients with NYHA class I are counted in subgroup NYHA class II.
Risk ratios and odds ratios with confidence intervals (CIs) are estimated by Cochran-Mantel-Haenszel method. For risk differences standard Wald asymptotic confidence limits are calculated. A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
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Only treatment emergent AEs are displayed (onset between first dose until treatment stop +7 days).
MedDRA version: 23.1. * Chi-square test for treatment effect ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction).

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Table R.1.2.4: 3 Proportion of patients with severe adverse events occuring in at least 1% of the patients in either treatment arm in the overall population on SOC level by SOC, 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 LVEF [%]																0.8048
< 50	988	139	14.1	995	112	11.3	0.0596	0.80	(0.63,	1.01)	0.77	(0.59,	1.01)	-0.03	(-0.06, 0.00)	
>= 50	2001	249	12.4	2001	192	9.6	0.0040	0.77	(0.65,	0.92)	0.75	(0.61,	0.91)	-0.03	(-0.05,-0.01)	
Baseline LVEF [%]																0.5382
<50	988	139	14.1	995	112	11.3	0.0596	0.80	(0.63,	1.01)	0.77	(0.59,	1.01)	-0.03	(-0.06, 0.00)	
50 to <60	1030	137	13.3	1028	96	9.3	0.0046	0.70	(0.55,	0.90)	0.67	(0.51,	0.89)	-0.04	(-0.07,-0.01)	
>=60	971	112	11.5	973	96	9.9	0.2342	0.86	(0.66,	1.11)	0.84	(0.63,	1.12)	-0.02	(-0.04, 0.01)	
Baseline NT-proBNP [pg/mL] (</>=median by atrial fibrillation/flutter status)																0.6091
< median	1507	140	9.3	1476	101	6.8	0.0142	0.74	(0.58,	0.94)	0.72	(0.55,	0.94)	-0.02	(-0.04, 0.00)	
>= median	1475	248	16.8	1516	203	13.4	0.0089	0.80	(0.67,	0.95)	0.76	(0.63,	0.94)	-0.03	(-0.06,-0.01)	
Baseline uric acid [mg/dL] (tertiles)																0.7424
<T1	975	108	11.1	963	78	8.1	0.0261	0.73	(0.55,	0.96)	0.71	(0.52,	0.96)	-0.03	(-0.06, 0.00)	
>=T1 and <T2	966	113	11.7	1032	102	9.9	0.1910	0.84	(0.66,	1.09)	0.83	(0.62,	1.10)	-0.02	(-0.05, 0.01)	
>=T2	1016	164	16.1	970	121	12.5	0.0198	0.77	(0.62,	0.96)	0.74	(0.57,	0.95)	-0.04	(-0.07,-0.01)	
Baseline use of MRA																0.3900
No	1865	234	12.5	1878	175	9.3	0.0015	0.74	(0.62,	0.89)	0.72	(0.58,	0.88)	-0.03	(-0.05,-0.01)	
Yes	1124	154	13.7	1118	129	11.5	0.1232	0.84	(0.68,	1.05)	0.82	(0.64,	1.06)	-0.02	(-0.05, 0.01)	
Baseline use of ACE-inhibitor, ARB or ARNi																0.4811
No	586	84	14.3	568	70	12.3	0.3153	0.86	(0.64,	1.16)	0.84	(0.60,	1.18)	-0.02	(-0.06, 0.02)	
Yes	2403	304	12.7	2428	234	9.6	0.0009	0.76	(0.65,	0.89)	0.74	(0.61,	0.88)	-0.03	(-0.05,-0.01)	

Analysis is based on study 1245.110.
^ Patients with NYHA class I are counted in subgroup NYHA class II.
Risk ratios and odds ratios with confidence intervals (CIs) are estimated by Cochran-Mantel-Haenszel method. For risk differences standard Wald asymptotic confidence limits are calculated. A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied in case of any zero cells in contingency table.
Only treatment emergent AEs are displayed (onset between first dose until treatment stop +7 days).
MedDRA version: 23.1. * Chi-square test for treatment effect ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction).

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Table R.1.2.4: 3 Proportion of patients with severe adverse events occuring in at least 1% of the patients in either treatment arm in the overall population on SOC level by SOC, 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	2989	180	6.0	2996	186	6.2	0.7637	1.03	(0.85, 1.26)	1.03	(0.84, 1.28)	0.00	(-0.01, 0.01)	

Analysis is based on study 1245.110.
^ Patients with NYHA class I are counted in subgroup NYHA class II.
Risk ratios and odds ratios with confidence intervals (CIs) are estimated by Cochran-Mantel-Haenszel method. For risk differences standard Wald asymptotic confidence limits are calculated. A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied in case of any zero cells in contingency table.
Only treatment emergent AEs are displayed (onset between first dose until treatment stop +7 days).
MedDRA version: 23.1. * Chi-square test for treatment effect ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction).

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Table R.1.2.4: 3 Proportion of patients with severe adverse events occuring in at least 1% of the patients in either treatment arm in the overall population on SOC level by SOC, 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	2989	90	3.0	2996	98	3.3	0.5642	1.09	(0.82, 1.44)	1.09	(0.81, 1.46)	0.00	(-0.01, 0.01)	

Analysis is based on study 1245.110.
^ Patients with NYHA class I are counted in subgroup NYHA class II.
Risk ratios and odds ratios with confidence intervals (CIs) are estimated by Cochran-Mantel-Haenszel method. For risk differences standard Wald asymptotic confidence limits are calculated. A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied in case of any zero cells in contingency table.
Only treatment emergent AEs are displayed (onset between first dose until treatment stop +7 days).
MedDRA version: 23.1. * Chi-square test for treatment effect ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction).

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Table R.1.2.4: 3 Proportion of patients with severe adverse events occuring in at least 1% of the patients in either treatment arm in the overall population on SOC level by SOC, 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	2989	81	2.7	2996	97	3.2	0.2295	1.19	(0.89, 1.60)	1.20	(0.89, 1.62)	0.01	(0.00, 0.01)	

Analysis is based on study 1245.110.
^ Patients with NYHA class I are counted in subgroup NYHA class II.
Risk ratios and odds ratios with confidence intervals (CIs) are estimated by Cochran-Mantel-Haenszel method. For risk differences standard Wald asymptotic confidence limits are calculated. A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied in case of any zero cells in contingency table.
Only treatment emergent AEs are displayed (onset between first dose until treatment stop +7 days).
MedDRA version: 23.1. * Chi-square test for treatment effect ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction).

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Table R.1.2.4: 3 Proportion of patients with severe adverse events occuring in at least 1% of the patients in either treatment arm in the overall population on SOC level by SOC, 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	2989	93	3.1	2996	84	2.8	0.4824	0.90	(0.67, 1.21)	0.90	(0.67, 1.21)	0.00	(-0.01, 0.01)	

Analysis is based on study 1245.110.
^ Patients with NYHA class I are counted in subgroup NYHA class II.
Risk ratios and odds ratios with confidence intervals (CIs) are estimated by Cochran-Mantel-Haenszel method. For risk differences standard Wald asymptotic confidence limits are calculated. A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied in case of any zero cells in contingency table.
Only treatment emergent AEs are displayed (onset between first dose until treatment stop +7 days).
MedDRA version: 23.1. * Chi-square test for treatment effect ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction).

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Table R.1.2.4: 3 Proportion of patients with severe adverse events occuring in at least 1% of the patients in either treatment arm in the overall population on SOC level by SOC, 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	2989	60	2.0	2996	83	2.8	0.0533	1.38	(0.99, 1.92)	1.39	(0.99, 1.95)	0.01	(0.00, 0.02)	

Analysis is based on study 1245.110.
^ Patients with NYHA class I are counted in subgroup NYHA class II.
Risk ratios and odds ratios with confidence intervals (CIs) are estimated by Cochran-Mantel-Haenszel method. For risk differences standard Wald asymptotic confidence limits are calculated. A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied in case of any zero cells in contingency table.
Only treatment emergent AEs are displayed (onset between first dose until treatment stop +7 days).
MedDRA version: 23.1. * Chi-square test for treatment effect ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction).

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Table R.1.2.4: 3 Proportion of patients with severe adverse events occuring in at least 1% of the patients in either treatment arm in the overall population on SOC level by SOC, 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	2989	81	2.7	2996	56	1.9	0.0297	0.69	(0.49, 0.97)	0.68	(0.48, 0.97)	-0.01	(-0.02, 0.00)	
Sex														0.6952
Male	1653	45	2.7	1658	33	2.0	0.1650	0.73	(0.47, 1.14)	0.73	(0.46, 1.14)	-0.01	(-0.02, 0.00)	
Female	1336	36	2.7	1338	23	1.7	0.0859	0.64	(0.38, 1.07)	0.63	(0.37, 1.07)	-0.01	(-0.02, 0.00)	
Age [years]														0.4952
<70	1084	25	2.3	1066	20	1.9	0.4861	0.81	(0.45, 1.46)	0.81	(0.45, 1.47)	0.00	(-0.02, 0.01)	
>=70	1905	56	2.9	1930	36	1.9	0.0297	0.63	(0.42, 0.96)	0.63	(0.41, 0.96)	-0.01	(-0.02, 0.00)	
Region														0.3652
North America	359	21	5.8	359	11	3.1	0.0705	0.52	(0.26, 1.07)	0.51	(0.24, 1.07)	-0.03	(-0.06, 0.00)	
Latin America	757	26	3.4	758	15	2.0	0.0808	0.58	(0.31, 1.08)	0.57	(0.30, 1.08)	-0.01	(-0.03, 0.00)	
Europe	1341	20	1.5	1346	18	1.3	0.7351	0.90	(0.48, 1.69)	0.90	(0.47, 1.70)	0.00	(-0.01, 0.01)	
Asia	343	9	2.6	343	4	1.2	0.1615	0.44	(0.14, 1.43)	0.44	(0.13, 1.44)	-0.01	(-0.03, 0.01)	
Other	189	5	2.6	190	8	4.2	0.4026	1.59	(0.53, 4.78)	1.62	(0.52, 5.04)	0.02	(-0.02, 0.05)	
OECD member														0.4644
No	847	25	3.0	868	21	2.4	0.4952	0.82	(0.46, 1.45)	0.82	(0.45, 1.47)	-0.01	(-0.02, 0.01)	
Yes	2142	56	2.6	2128	35	1.6	0.0283	0.63	(0.41, 0.96)	0.62	(0.41, 0.95)	-0.01	(-0.02, 0.00)	
Baseline NYHA														0.2154
II^	2450	62	2.5	2435	37	1.5	0.0122	0.60	(0.40, 0.90)	0.59	(0.39, 0.90)	-0.01	(-0.02, 0.00)	
III/IV	539	19	3.5	561	19	3.4	0.9001	0.96	(0.51, 1.79)	0.96	(0.50, 1.83)	0.00	(-0.02, 0.02)	
Baseline Diabetes Status														0.0912
Diabetic	1471	51	3.5	1465	27	1.8	0.0062	0.53	(0.34, 0.84)	0.52	(0.33, 0.84)	-0.02	(-0.03, 0.00)	
Non-Diabetic	1518	30	2.0	1531	29	1.9	0.8693	0.96	(0.58, 1.59)	0.96	(0.57, 1.60)	0.00	(-0.01, 0.01)	

Analysis is based on study 1245.110.
^ Patients with NYHA class I are counted in subgroup NYHA class II.
Risk ratios and odds ratios with confidence intervals (CIs) are estimated by Cochran-Mantel-Haenszel method. For risk differences standard Wald asymptotic confidence limits are calculated. A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied in case of any zero cells in contingency table.
Only treatment emergent AEs are displayed (onset between first dose until treatment stop +7 days).
MedDRA version: 23.1. * Chi-square test for treatment effect ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction).

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Table R.1.2.4: 3 Proportion of patients with severe adverse events occuring in at least 1% of the patients in either treatment arm in the overall population on SOC level by SOC, 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 Diabetes Status																0.1822
Diabetic	1471	51	3.5	1465	27	1.8	0.0062	0.53	(0.34,	0.84)	0.52	(0.33,	0.84)	-0.02	(-0.03, 0.00)	
Pre-Diabetes	979	18	1.8	1001	15	1.5	0.5545	0.82	(0.41,	1.61)	0.81	(0.41,	1.62)	0.00	(-0.01, 0.01)	
Normal (no pre-diabetes)	539	12	2.2	530	14	2.6	0.6595	1.19	(0.55,	2.54)	1.19	(0.55,	2.60)	0.00	(-0.01, 0.02)	
Baseline BMI [kg/m²]																0.1158
<30	1641	44	2.7	1654	23	1.4	0.0087	0.52	(0.31,	0.85)	0.51	(0.31,	0.85)	-0.01	(-0.02, 0.00)	
>=30	1348	37	2.7	1342	33	2.5	0.6416	0.90	(0.56,	1.42)	0.89	(0.56,	1.44)	0.00	(-0.01, 0.01)	
Baseline eGFR (CKD-EPI) [mL/min/1.73m²]																0.4952
>=60	1505	34	2.3	1493	20	1.3	0.0584	0.59	(0.34,	1.03)	0.59	(0.34,	1.03)	-0.01	(-0.02, 0.00)	
<60	1482	47	3.2	1503	36	2.4	0.1972	0.76	(0.49,	1.16)	0.75	(0.48,	1.16)	-0.01	(-0.02, 0.00)	
History of HHF (in the last 12 months)																0.1357
No	2320	52	2.2	2297	42	1.8	0.3206	0.82	(0.55,	1.22)	0.81	(0.54,	1.23)	0.00	(-0.01, 0.00)	
Yes	669	29	4.3	699	14	2.0	0.0135	0.46	(0.25,	0.87)	0.45	(0.24,	0.86)	-0.02	(-0.04, 0.00)	
Baseline SBP (</>= median)																0.7362
< median	1474	42	2.8	1496	31	2.1	0.1714	0.73	(0.46,	1.15)	0.72	(0.45,	1.15)	-0.01	(-0.02, 0.00)	
>= median	1515	39	2.6	1500	25	1.7	0.0839	0.65	(0.39,	1.06)	0.64	(0.39,	1.07)	-0.01	(-0.02, 0.00)	
History of atrial fibrillation or atrial flutter																0.5613
No	1426	42	2.9	1417	26	1.8	0.0527	0.62	(0.38,	1.01)	0.62	(0.38,	1.01)	-0.01	(-0.02, 0.00)	
Yes	1558	39	2.5	1575	30	1.9	0.2538	0.76	(0.48,	1.22)	0.76	(0.47,	1.22)	-0.01	(-0.02, 0.00)	

Analysis is based on study 1245.110.
^ Patients with NYHA class I are counted in subgroup NYHA class II.
Risk ratios and odds ratios with confidence intervals (CIs) are estimated by Cochran-Mantel-Haenszel method. For risk differences standard Wald asymptotic confidence limits are calculated. A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied in case of any zero cells in contingency table.
Only treatment emergent AEs are displayed (onset between first dose until treatment stop +7 days).
MedDRA version: 23.1. * Chi-square test for treatment effect ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction).

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Table R.1.2.4: 3 Proportion of patients with severe adverse events occuring in at least 1% of the patients in either treatment arm in the overall population on SOC level by SOC, 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 LVEF [%]																0.4027
< 50	988	30	3.0	995	17	1.7	0.0519	0.56	(0.31,	1.01)	0.56	(0.30,	1.01)	-0.01	(-0.03, 0.00)	
>= 50	2001	51	2.5	2001	39	1.9	0.2008	0.76	(0.51,	1.15)	0.76	(0.50,	1.16)	-0.01	(-0.02, 0.00)	
Baseline LVEF [%]																0.4767
<50	988	30	3.0	995	17	1.7	0.0519	0.56	(0.31,	1.01)	0.56	(0.30,	1.01)	-0.01	(-0.03, 0.00)	
50 to <60	1030	27	2.6	1028	17	1.7	0.1292	0.63	(0.35,	1.15)	0.62	(0.34,	1.15)	-0.01	(-0.02, 0.00)	
>=60	971	24	2.5	973	22	2.3	0.7600	0.91	(0.52,	1.62)	0.91	(0.51,	1.64)	0.00	(-0.02, 0.01)	
Baseline NT-proBNP [pg/mL] (</>=median by atrial fibrillation/flutter status)																0.0436
< median	1507	41	2.7	1476	18	1.2	0.0032	0.45	(0.26,	0.78)	0.44	(0.25,	0.77)	-0.02	(-0.02,-0.01)	
>= median	1475	40	2.7	1516	38	2.5	0.7247	0.92	(0.60,	1.43)	0.92	(0.59,	1.45)	0.00	(-0.01, 0.01)	
Baseline uric acid [mg/dL] (tertiles)																0.7050
<T1	975	24	2.5	963	13	1.3	0.0738	0.55	(0.28,	1.07)	0.54	(0.27,	1.07)	-0.01	(-0.02, 0.00)	
>=T1 and <T2	966	25	2.6	1032	19	1.8	0.2556	0.71	(0.39,	1.28)	0.71	(0.39,	1.29)	-0.01	(-0.02, 0.01)	
>=T2	1016	32	3.1	970	24	2.5	0.3634	0.79	(0.47,	1.32)	0.78	(0.46,	1.33)	-0.01	(-0.02, 0.01)	
Baseline use of MRA																0.7316
No	1865	51	2.7	1878	37	2.0	0.1228	0.72	(0.47,	1.09)	0.71	(0.47,	1.10)	-0.01	(-0.02, 0.00)	
Yes	1124	30	2.7	1118	19	1.7	0.1164	0.64	(0.36,	1.12)	0.63	(0.35,	1.13)	-0.01	(-0.02, 0.00)	
Baseline use of ACE-inhibitor, ARB or ARNi																0.0824
No	586	20	3.4	568	21	3.7	0.7943	1.08	(0.59,	1.98)	1.09	(0.58,	2.03)	0.00	(-0.02, 0.02)	
Yes	2403	61	2.5	2428	35	1.4	0.0063	0.57	(0.38,	0.86)	0.56	(0.37,	0.85)	-0.01	(-0.02, 0.00)	

Analysis is based on study 1245.110.
^ Patients with NYHA class I are counted in subgroup NYHA class II.
Risk ratios and odds ratios with confidence intervals (CIs) are estimated by Cochran-Mantel-Haenszel method. For risk differences standard Wald asymptotic confidence limits are calculated. A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied in case of any zero cells in contingency table.
Only treatment emergent AEs are displayed (onset between first dose until treatment stop +7 days).
MedDRA version: 23.1. * Chi-square test for treatment effect ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction).

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Table R.1.2.4: 3 Proportion of patients with severe adverse events occuring in at least 1% of the patients in either treatment arm in the overall population on SOC level by SOC, 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	2989	71	2.4	2996	65	2.2	0.5932	0.91	(0.65, 1.27)	0.91	(0.65, 1.28)	0.00	(-0.01, 0.01)	

Analysis is based on study 1245.110.
^ Patients with NYHA class I are counted in subgroup NYHA class II.
Risk ratios and odds ratios with confidence intervals (CIs) are estimated by Cochran-Mantel-Haenszel method. For risk differences standard Wald asymptotic confidence limits are calculated. A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied in case of any zero cells in contingency table.
Only treatment emergent AEs are displayed (onset between first dose until treatment stop +7 days).
MedDRA version: 23.1. * Chi-square test for treatment effect ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction).

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Table R.1.2.4: 3 Proportion of patients with severe adverse events occuring in at least 1% of the patients in either treatment arm in the overall population on SOC level by SOC, 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	2989	47	1.6	2996	62	2.1	0.1505	1.32 (0.90, 1.92)	1.32 (0.90, 1.94)	0.00 (0.00, 0.01)	

Analysis is based on study 1245.110.
^ Patients with NYHA class I are counted in subgroup NYHA class II.
Risk ratios and odds ratios with confidence intervals (CIs) are estimated by Cochran-Mantel-Haenszel method. For risk differences standard Wald asymptotic confidence limits are calculated. A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied in case of any zero cells in contingency table.
Only treatment emergent AEs are displayed (onset between first dose until treatment stop +7 days).
MedDRA version: 23.1. * Chi-square test for treatment effect ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction).

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Table R.1.2.4: 3 Proportion of patients with severe adverse events occuring in at least 1% of the patients in either treatment arm in the overall population on SOC level by SOC, 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	2989	56	1.9	2996	59	2.0	0.7873	1.05	(0.73, 1.51)	1.05	(0.73, 1.52)	0.00	(-0.01, 0.01)	

Analysis is based on study 1245.110.
^ Patients with NYHA class I are counted in subgroup NYHA class II.
Risk ratios and odds ratios with confidence intervals (CIs) are estimated by Cochran-Mantel-Haenszel method. For risk differences standard Wald asymptotic confidence limits are calculated. A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied in case of any zero cells in contingency table.
Only treatment emergent AEs are displayed (onset between first dose until treatment stop +7 days).
MedDRA version: 23.1. * Chi-square test for treatment effect ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction).

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Table R.1.2.4: 3 Proportion of patients with severe adverse events occuring in at least 1% of the patients in either treatment arm in the overall population on SOC level by SOC, 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	2989	56	1.9	2996	42	1.4	0.1505	0.75	(0.50, 1.11)	0.74	(0.50, 1.11)	0.00	(-0.01, 0.00)	

Analysis is based on study 1245.110.
^ Patients with NYHA class I are counted in subgroup NYHA class II.
Risk ratios and odds ratios with confidence intervals (CIs) are estimated by Cochran-Mantel-Haenszel method. For risk differences standard Wald asymptotic confidence limits are calculated. A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied in case of any zero cells in contingency table.
Only treatment emergent AEs are displayed (onset between first dose until treatment stop +7 days).
MedDRA version: 23.1. * Chi-square test for treatment effect ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction).

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Table R.1.2.4: 3 Proportion of patients with severe adverse events occuring in at least 1% of the patients in either treatment arm in the overall population on SOC level by SOC, 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	2989	35	1.2	2996	17	0.6	0.0119	0.48	(0.27, 0.86)	0.48	(0.27, 0.86)	-0.01	(-0.01, 0.00)	
Sex														0.9250
Male	1653	19	1.1	1658	9	0.5	0.0567	0.47	(0.21, 1.04)	0.47	(0.21, 1.04)	-0.01	(-0.01, 0.00)	
Female	1336	16	1.2	1338	8	0.6	0.1002	0.50	(0.21, 1.16)	0.50	(0.21, 1.16)	-0.01	(-0.01, 0.00)	
Age [years]														0.9334
<70	1084	6	0.6	1066	3	0.3	0.3286	0.51	(0.13, 2.03)	0.51	(0.13, 2.03)	0.00	(-0.01, 0.00)	
>=70	1905	29	1.5	1930	14	0.7	0.0191	0.48	(0.25, 0.90)	0.47	(0.25, 0.90)	-0.01	(-0.01, 0.00)	
Region														0.6446
North America	359	7	1.9	359	4	1.1	0.3620	0.57	(0.17, 1.94)	0.57	(0.16, 1.95)	-0.01	(-0.03, 0.01)	
Latin America	757	5	0.7	758	3	0.4	0.4772	0.60	(0.14, 2.50)	0.60	(0.14, 2.51)	0.00	(-0.01, 0.00)	
Europe	1341	16	1.2	1346	5	0.4	0.0156	0.31	(0.11, 0.85)	0.31	(0.11, 0.85)	-0.01	(-0.01, 0.00)	
Asia	343	2	0.6	343	3	0.9	0.6535	1.50	(0.25, 8.92)	1.50	(0.25, 9.06)	0.00	(-0.01, 0.02)	
Other	189	5	2.6	190	2	1.1	0.2495	0.40	(0.08, 2.03)	0.39	(0.08, 2.04)	-0.02	(-0.04, 0.01)	
OECD member														0.0736
No	847	6	0.7	868	7	0.8	0.8149	1.14	(0.38, 3.37)	1.14	(0.38, 3.40)	0.00	(-0.01, 0.01)	
Yes	2142	29	1.4	2128	10	0.5	0.0024	0.35	(0.17, 0.71)	0.34	(0.17, 0.71)	-0.01	(-0.01, 0.00)	
Baseline NYHA														0.1986
II^	2450	27	1.1	2435	10	0.4	0.0053	0.37	(0.18, 0.77)	0.37	(0.18, 0.77)	-0.01	(-0.01, 0.00)	
III/IV	539	8	1.5	561	7	1.2	0.7353	0.84	(0.31, 2.30)	0.84	(0.30, 2.33)	0.00	(-0.02, 0.01)	
Baseline Diabetes Status														0.0923
Diabetic	1471	12	0.8	1465	10	0.7	0.6757	0.84	(0.36, 1.93)	0.84	(0.36, 1.94)	0.00	(-0.01, 0.00)	
Non-Diabetic	1518	23	1.5	1531	7	0.5	0.0031	0.30	(0.13, 0.70)	0.30	(0.13, 0.70)	-0.01	(-0.02, 0.00)	

Analysis is based on study 1245.110.
^ Patients with NYHA class I are counted in subgroup NYHA class II.
Risk ratios and odds ratios with confidence intervals (CIs) are estimated by Cochran-Mantel-Haenszel method. For risk differences standard Wald asymptotic confidence limits are calculated. A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied in case of any zero cells in contingency table.
Only treatment emergent AEs are displayed (onset between first dose until treatment stop +7 days).
MedDRA version: 23.1. * Chi-square test for treatment effect ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction).

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Table R.1.2.4: 3 Proportion of patients with severe adverse events occuring in at least 1% of the patients in either treatment arm in the overall population on SOC level by SOC, 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 Diabetes Status																0.2425
Diabetic	1471	12	0.8	1465	10	0.7	0.6757	0.84	(0.36,	1.93)	0.84	(0.36,	1.94)	0.00	(-0.01, 0.00)	
Pre-Diabetes	979	12	1.2	1001	4	0.4	0.0401	0.33	(0.11,	1.01)	0.32	(0.10,	1.01)	-0.01	(-0.02, 0.00)	
Normal (no pre-diabetes)	539	11	2.0	530	3	0.6	0.0340	0.28	(0.08,	0.99)	0.27	(0.08,	0.99)	-0.01	(-0.03, 0.00)	
Baseline BMI [kg/m²]																0.9267
<30	1641	23	1.4	1654	11	0.7	0.0365	0.47	(0.23,	0.97)	0.47	(0.23,	0.97)	-0.01	(-0.01, 0.00)	
>=30	1348	12	0.9	1342	6	0.4	0.1587	0.50	(0.19,	1.33)	0.50	(0.19,	1.34)	0.00	(-0.01, 0.00)	
Baseline eGFR (CKD-EPI) [mL/min/1.73m²]																0.4512
>=60	1505	12	0.8	1493	4	0.3	0.0467	0.34	(0.11,	1.04)	0.33	(0.11,	1.04)	-0.01	(-0.01, 0.00)	
<60	1482	23	1.6	1503	13	0.9	0.0856	0.56	(0.28,	1.10)	0.55	(0.28,	1.10)	-0.01	(-0.01, 0.00)	
History of HHF (in the last 12 months)																0.0687
No	2320	26	1.1	2297	8	0.3	0.0021	0.31	(0.14,	0.68)	0.31	(0.14,	0.68)	-0.01	(-0.01, 0.00)	
Yes	669	9	1.3	699	9	1.3	0.9254	0.96	(0.38,	2.40)	0.96	(0.38,	2.42)	0.00	(-0.01, 0.01)	
Baseline SBP (</>= median)																0.9410
< median	1474	20	1.4	1496	10	0.7	0.0607	0.49	(0.23,	1.05)	0.49	(0.23,	1.05)	-0.01	(-0.01, 0.00)	
>= median	1515	15	1.0	1500	7	0.5	0.0913	0.47	(0.19,	1.15)	0.47	(0.19,	1.15)	-0.01	(-0.01, 0.00)	
History of atrial fibrillation or atrial flutter																0.9033
No	1426	11	0.8	1417	5	0.4	0.1358	0.46	(0.16,	1.31)	0.46	(0.16,	1.31)	0.00	(-0.01, 0.00)	
Yes	1558	24	1.5	1575	12	0.8	0.0409	0.49	(0.25,	0.99)	0.49	(0.24,	0.98)	-0.01	(-0.02, 0.00)	

Analysis is based on study 1245.110.
^ Patients with NYHA class I are counted in subgroup NYHA class II.
Risk ratios and odds ratios with confidence intervals (CIs) are estimated by Cochran-Mantel-Haenszel method. For risk differences standard Wald asymptotic confidence limits are calculated. A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied in case of any zero cells in contingency table.
Only treatment emergent AEs are displayed (onset between first dose until treatment stop +7 days).
MedDRA version: 23.1. * Chi-square test for treatment effect ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction).

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Table R.1.2.4: 3 Proportion of patients with severe adverse events occuring in at least 1% of the patients in either treatment arm in the overall population on SOC level by SOC, 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 LVEF [%]																0.7772
< 50	988	7	0.7	995	4	0.4	0.3582	0.57	(0.17,	1.93)	0.57	(0.17,	1.94)	0.00	(-0.01, 0.00)	
>= 50	2001	28	1.4	2001	13	0.6	0.0185	0.46	(0.24,	0.89)	0.46	(0.24,	0.89)	-0.01	(-0.01, 0.00)	
Baseline LVEF [%]																0.9594
<50	988	7	0.7	995	4	0.4	0.3582	0.57	(0.17,	1.93)	0.57	(0.17,	1.94)	0.00	(-0.01, 0.00)	
50 to <60	1030	17	1.7	1028	8	0.8	0.0709	0.47	(0.20,	1.09)	0.47	(0.20,	1.09)	-0.01	(-0.02, 0.00)	
>=60	971	11	1.1	973	5	0.5	0.1310	0.45	(0.16,	1.30)	0.45	(0.16,	1.30)	-0.01	(-0.01, 0.00)	
Baseline NT-proBNP [pg/mL] (</>=median by atrial fibrillation/flutter status)																0.4749
< median	1507	12	0.8	1476	4	0.3	0.0496	0.34	(0.11,	1.05)	0.34	(0.11,	1.05)	-0.01	(-0.01, 0.00)	
>= median	1475	23	1.6	1516	13	0.9	0.0785	0.55	(0.28,	1.08)	0.55	(0.28,	1.08)	-0.01	(-0.01, 0.00)	
Baseline uric acid [mg/dL] (tertiles)																0.8483
<T1	975	8	0.8	963	3	0.3	0.1359	0.38	(0.10,	1.43)	0.38	(0.10,	1.43)	-0.01	(-0.01, 0.00)	
>=T1 and <T2	966	11	1.1	1032	7	0.7	0.2764	0.60	(0.23,	1.53)	0.59	(0.23,	1.54)	0.00	(-0.01, 0.00)	
>=T2	1016	16	1.6	970	7	0.7	0.0757	0.46	(0.19,	1.11)	0.45	(0.19,	1.11)	-0.01	(-0.02, 0.00)	
Baseline use of MRA																0.6133
No	1865	21	1.1	1878	9	0.5	0.0265	0.43	(0.20,	0.93)	0.42	(0.19,	0.93)	-0.01	(-0.01, 0.00)	
Yes	1124	14	1.2	1118	8	0.7	0.2030	0.57	(0.24,	1.36)	0.57	(0.24,	1.37)	-0.01	(-0.01, 0.00)	
Baseline use of ACE-inhibitor, ARB or ARNi																0.0071
No	586	9	1.5	568	11	1.9	0.6020	1.26	(0.53,	3.02)	1.27	(0.52,	3.08)	0.00	(-0.01, 0.02)	
Yes	2403	26	1.1	2428	6	0.2	0.0003	0.23	(0.09,	0.55)	0.23	(0.09,	0.55)	-0.01	(-0.01, 0.00)	

Analysis is based on study 1245.110.
^ Patients with NYHA class I are counted in subgroup NYHA class II.
Risk ratios and odds ratios with confidence intervals (CIs) are estimated by Cochran-Mantel-Haenszel method. For risk differences standard Wald asymptotic confidence limits are calculated. A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied in case of any zero cells in contingency table.
Only treatment emergent AEs are displayed (onset between first dose until treatment stop +7 days).
MedDRA version: 23.1. * Chi-square test for treatment effect ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction).

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Table R.1.2.4: 3 Proportion of patients with severe adverse events occuring in at least 1% of the patients in either treatment arm in the overall population on SOC level by SOC, 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	2989	33	1.1	2996	27	0.9	0.4309	0.82	(0.49, 1.35)	0.81	(0.49, 1.36)	0.00	(-0.01, 0.00)	

Analysis is based on study 1245.110.
^ Patients with NYHA class I are counted in subgroup NYHA class II.
Risk ratios and odds ratios with confidence intervals (CIs) are estimated by Cochran-Mantel-Haenszel method. For risk differences standard Wald asymptotic confidence limits are calculated. A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied in case of any zero cells in contingency table.
Only treatment emergent AEs are displayed (onset between first dose until treatment stop +7 days).
MedDRA version: 23.1. * Chi-square test for treatment effect ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction).

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R.1.2.5 Adverse events on PT level

Table R.1.2.5: 1 Proportion of patients with any adverse event occuring in at least 1% of the patients in either treatment arm in the overall population on PT level by SOC and PT, 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	2989	181	6.1	2996	236	7.9	0.0056	1.30 (1.08, 1.57)	1.33 (1.09, 1.62)	0.02 (0.01, 0.03)	
Sex											0.5757
Male	1653	59	3.6	1658	83	5.0	0.0413	1.40 (1.01, 1.94)	1.42 (1.01, 2.00)	0.01 (0.00, 0.03)	
Female	1336	122	9.1	1338	153	11.4	0.0499	1.25 (1.00, 1.57)	1.28 (1.00, 1.65)	0.02 (0.00, 0.05)	
Age [years]											0.0774
<70	1084	44	4.1	1066	74	6.9	0.0033	1.71 (1.19, 2.46)	1.76 (1.20, 2.59)	0.03 (0.01, 0.05)	
>=70	1905	137	7.2	1930	162	8.4	0.1650	1.17 (0.94, 1.45)	1.18 (0.93, 1.50)	0.01 (0.00, 0.03)	
Region											0.4482
North America	359	34	9.5	359	36	10.0	0.8013	1.06 (0.68, 1.65)	1.07 (0.65, 1.74)	0.01 (-0.04, 0.05)	
Latin America	757	52	6.9	758	79	10.4	0.0139	1.52 (1.09, 2.12)	1.58 (1.09, 2.27)	0.04 (0.01, 0.06)	
Europe	1341	73	5.4	1346	87	6.5	0.2640	1.19 (0.88, 1.61)	1.20 (0.87, 1.65)	0.01 (-0.01, 0.03)	
Asia	343	9	2.6	343	9	2.6	1.0000	1.00 (0.40, 2.49)	1.00 (0.39, 2.55)	0.00 (-0.02, 0.02)	
Other	189	13	6.9	190	25	13.2	0.0418	1.91 (1.01, 3.63)	2.05 (1.02, 4.14)	0.06 (0.00, 0.12)	
OECD member											0.0243
No	847	48	5.7	868	88	10.1	0.0006	1.79 (1.27, 2.51)	1.88 (1.30, 2.71)	0.04 (0.02, 0.07)	
Yes	2142	133	6.2	2128	148	7.0	0.3258	1.12 (0.89, 1.40)	1.13 (0.89, 1.44)	0.01 (-0.01, 0.02)	
Baseline NYHA											0.5318
II^	2450	135	5.5	2435	180	7.4	0.0074	1.34 (1.08, 1.66)	1.37 (1.09, 1.72)	0.02 (0.01, 0.03)	
III/IV	539	46	8.5	561	56	10.0	0.4079	1.17 (0.81, 1.70)	1.19 (0.79, 1.79)	0.01 (-0.02, 0.05)	
Baseline Diabetes Status											0.9911
Diabetic	1471	95	6.5	1465	123	8.4	0.0452	1.30 (1.00, 1.68)	1.33 (1.01, 1.75)	0.02 (0.00, 0.04)	
Non-Diabetic	1518	86	5.7	1531	113	7.4	0.0552	1.30 (0.99, 1.71)	1.33 (0.99, 1.77)	0.02 (0.00, 0.03)	

Analysis is based on study 1245.110.
^ Patients with NYHA class I are counted in subgroup NYHA class II.
Risk ratios and odds ratios with confidence intervals (CIs) are estimated by Cochran-Mantel-Haenszel method. For risk differences standard Wald asymptotic confidence limits are calculated. A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied in case of any zero cells in contingency table.
Only treatment emergent AEs are displayed (onset between first dose until treatment stop +7 days).
MedDRA version: 23.1. * Chi-square test for treatment effect ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction).

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Table R.1.2.5: 1 Proportion of patients with any adverse event occuring in at least 1% of the patients in either treatment arm in the overall population on PT level by SOC and PT, 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 Diabetes Status											0.6813
Diabetic	1471	95	6.5	1465	123	8.4	0.0452	1.30 (1.00, 1.68)	1.33 (1.01, 1.75)	0.02 (0.00, 0.04)	
Pre-Diabetes	979	59	6.0	1001	72	7.2	0.2966	1.19 (0.86, 1.66)	1.21 (0.85, 1.73)	0.01 (-0.01, 0.03)	
Normal (no pre-diabetes)	539	27	5.0	530	41	7.7	0.0678	1.54 (0.96, 2.47)	1.59 (0.96, 2.62)	0.03 (0.00, 0.06)	
Baseline BMI [kg/m²]											0.2747
<30	1641	94	5.7	1654	111	6.7	0.2429	1.17 (0.90, 1.53)	1.18 (0.89, 1.57)	0.01 (-0.01, 0.03)	
>=30	1348	87	6.5	1342	125	9.3	0.0059	1.44 (1.11, 1.88)	1.49 (1.12, 1.98)	0.03 (0.01, 0.05)	
Baseline eGFR (CKD-EPI) [mL/min/1.73m²]											0.1351
>=60	1505	68	4.5	1493	104	7.0	0.0040	1.54 (1.15, 2.08)	1.58 (1.16, 2.17)	0.02 (0.01, 0.04)	
<60	1482	113	7.6	1503	132	8.8	0.2493	1.15 (0.91, 1.47)	1.17 (0.90, 1.52)	0.01 (-0.01, 0.03)	
History of HHF (in the last 12 months)											0.1840
No	2320	147	6.3	2297	177	7.7	0.0685	1.22 (0.98, 1.50)	1.23 (0.98, 1.55)	0.01 (0.00, 0.03)	
Yes	669	34	5.1	699	59	8.4	0.0136	1.66 (1.10, 2.50)	1.72 (1.11, 2.66)	0.03 (0.01, 0.06)	
Baseline SBP (</>= median)											0.2263
< median	1474	82	5.6	1496	122	8.2	0.0052	1.47 (1.12, 1.92)	1.51 (1.13, 2.01)	0.03 (0.01, 0.04)	
>= median	1515	99	6.5	1500	114	7.6	0.2537	1.16 (0.90, 1.51)	1.18 (0.89, 1.56)	0.01 (-0.01, 0.03)	
History of atrial fibrillation or atrial flutter											0.2852
No	1426	79	5.5	1417	114	8.0	0.0079	1.45 (1.10, 1.92)	1.49 (1.11, 2.01)	0.03 (0.01, 0.04)	
Yes	1558	102	6.5	1575	122	7.7	0.1927	1.18 (0.92, 1.52)	1.20 (0.91, 1.57)	0.01 (-0.01, 0.03)	

Analysis is based on study 1245.110.
^ Patients with NYHA class I are counted in subgroup NYHA class II.
Risk ratios and odds ratios with confidence intervals (CIs) are estimated by Cochran-Mantel-Haenszel method. For risk differences standard Wald asymptotic confidence limits are calculated. A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied in case of any zero cells in contingency table.
Only treatment emergent AEs are displayed (onset between first dose until treatment stop +7 days).
MedDRA version: 23.1. * Chi-square test for treatment effect ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction).

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Table R.1.2.5: 1 Proportion of patients with any adverse event occuring in at least 1% of the patients in either treatment arm in the overall population on PT level by SOC and PT, 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 LVEF [%]											0.3522
< 50	988	44	4.5	995	67	6.7	0.0272	1.51 (1.04, 2.19)	1.55 (1.05, 2.29)	0.02 (0.00, 0.04)	
>= 50	2001	137	6.8	2001	169	8.4	0.0570	1.23 (0.99, 1.53)	1.26 (0.99, 1.59)	0.02 (0.00, 0.03)	
Baseline LVEF [%]											0.5148
<50	988	44	4.5	995	67	6.7	0.0272	1.51 (1.04, 2.19)	1.55 (1.05, 2.29)	0.02 (0.00, 0.04)	
50 to <60	1030	62	6.0	1028	70	6.8	0.4646	1.13 (0.81, 1.57)	1.14 (0.80, 1.62)	0.01 (-0.01, 0.03)	
>=60	971	75	7.7	973	99	10.2	0.0584	1.32 (0.99, 1.75)	1.35 (0.99, 1.85)	0.02 (0.00, 0.05)	
Baseline NT-proBNP [pg/mL] (</>=median by atrial fibrillation/flutter status)											0.2337
< median	1507	87	5.8	1476	124	8.4	0.0051	1.46 (1.12, 1.90)	1.50 (1.13, 1.99)	0.03 (0.01, 0.04)	
>= median	1475	94	6.4	1516	112	7.4	0.2731	1.16 (0.89, 1.51)	1.17 (0.88, 1.56)	0.01 (-0.01, 0.03)	
Baseline uric acid [mg/dL] (tertiles)											0.4620
<T1	975	59	6.1	963	64	6.6	0.5914	1.10 (0.78, 1.55)	1.11 (0.77, 1.59)	0.01 (-0.02, 0.03)	
>=T1 and <T2	966	56	5.8	1032	82	7.9	0.0584	1.37 (0.99, 1.90)	1.40 (0.99, 1.99)	0.02 (0.00, 0.04)	
>=T2	1016	64	6.3	970	89	9.2	0.0163	1.46 (1.07, 1.98)	1.50 (1.08, 2.10)	0.03 (0.01, 0.05)	
Baseline use of MRA											0.7021
No	1865	109	5.8	1878	147	7.8	0.0163	1.34 (1.05, 1.70)	1.37 (1.06, 1.77)	0.02 (0.00, 0.04)	
Yes	1124	72	6.4	1118	89	8.0	0.1539	1.24 (0.92, 1.68)	1.26 (0.92, 1.74)	0.02 (-0.01, 0.04)	
Baseline use of ACE-inhibitor, ARB or ARNi											0.1957
No	586	35	6.0	568	56	9.9	0.0143	1.65 (1.10, 2.48)	1.72 (1.11, 2.67)	0.04 (0.01, 0.07)	
Yes	2403	146	6.1	2428	180	7.4	0.0638	1.22 (0.99, 1.51)	1.24 (0.99, 1.55)	0.01 (0.00, 0.03)	

Analysis is based on study 1245.110.
^ Patients with NYHA class I are counted in subgroup NYHA class II.
Risk ratios and odds ratios with confidence intervals (CIs) are estimated by Cochran-Mantel-Haenszel method. For risk differences standard Wald asymptotic confidence limits are calculated. A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied in case of any zero cells in contingency table.
Only treatment emergent AEs are displayed (onset between first dose until treatment stop +7 days).
MedDRA version: 23.1. * Chi-square test for treatment effect ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction).

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Table R.1.2.5: 1 Proportion of patients with any adverse event occuring in at least 1% of the patients in either treatment arm in the overall population on PT level by SOC and PT, 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	2989	187	6.3	2996	158	5.3	0.1029	0.84 (0.69, 1.04)	0.83 (0.67, 1.04)	-0.01 (-0.02, 0.00)	

Analysis is based on study 1245.110.
^ Patients with NYHA class I are counted in subgroup NYHA class II.
Risk ratios and odds ratios with confidence intervals (CIs) are estimated by Cochran-Mantel-Haenszel method. For risk differences standard Wald asymptotic confidence limits are calculated. A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied in case of any zero cells in contingency table.
Only treatment emergent AEs are displayed (onset between first dose until treatment stop +7 days).
MedDRA version: 23.1. * Chi-square test for treatment effect ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction).

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Table R.1.2.5: 1 Proportion of patients with any adverse event occuring in at least 1% of the patients in either treatment arm in the overall population on PT level by SOC and PT, 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	2989	123	4.1	2996	147	4.9	0.1402	1.19 (0.94, 1.51)	1.20 (0.94, 1.54)	0.01 (0.00, 0.02)	

Analysis is based on study 1245.110.
^ Patients with NYHA class I are counted in subgroup NYHA class II.
Risk ratios and odds ratios with confidence intervals (CIs) are estimated by Cochran-Mantel-Haenszel method. For risk differences standard Wald asymptotic confidence limits are calculated. A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied in case of any zero cells in contingency table.
Only treatment emergent AEs are displayed (onset between first dose until treatment stop +7 days).
MedDRA version: 23.1. * Chi-square test for treatment effect ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction).

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Table R.1.2.5: 1 Proportion of patients with any adverse event occuring in at least 1% of the patients in either treatment arm in the overall population on PT level by SOC and PT, 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	2989	134	4.5	2996	113	3.8	0.1665	0.84 (0.66, 1.08)	0.84 (0.65, 1.08)	-0.01 (-0.02, 0.00)	

Analysis is based on study 1245.110.
^ Patients with NYHA class I are counted in subgroup NYHA class II.
Risk ratios and odds ratios with confidence intervals (CIs) are estimated by Cochran-Mantel-Haenszel method. For risk differences standard Wald asymptotic confidence limits are calculated. A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied in case of any zero cells in contingency table.
Only treatment emergent AEs are displayed (onset between first dose until treatment stop +7 days).
MedDRA version: 23.1. * Chi-square test for treatment effect ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction).

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Table R.1.2.5: 1 Proportion of patients with any adverse event occuring in at least 1% of the patients in either treatment arm in the overall population on PT level by SOC and PT, 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	2989	132	4.4	2996	106	3.5	0.0822	0.80 (0.62, 1.03)	0.79 (0.61, 1.03)	-0.01 (-0.02, 0.00)	

Analysis is based on study 1245.110.
^ Patients with NYHA class I are counted in subgroup NYHA class II.
Risk ratios and odds ratios with confidence intervals (CIs) are estimated by Cochran-Mantel-Haenszel method. For risk differences standard Wald asymptotic confidence limits are calculated. A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied in case of any zero cells in contingency table.
Only treatment emergent AEs are displayed (onset between first dose until treatment stop +7 days).
MedDRA version: 23.1. * Chi-square test for treatment effect ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction).

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Table R.1.2.5: 1 Proportion of patients with any adverse event occuring in at least 1% of the patients in either treatment arm in the overall population on PT level by SOC and PT, 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	2989	113	3.8	2996	105	3.5	0.5690	0.93 (0.71, 1.20)	0.92 (0.71, 1.21)	0.00 (-0.01, 0.01)	

Analysis is based on study 1245.110.
^ Patients with NYHA class I are counted in subgroup NYHA class II.
Risk ratios and odds ratios with confidence intervals (CIs) are estimated by Cochran-Mantel-Haenszel method. For risk differences standard Wald asymptotic confidence limits are calculated. A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied in case of any zero cells in contingency table.
Only treatment emergent AEs are displayed (onset between first dose until treatment stop +7 days).
MedDRA version: 23.1. * Chi-square test for treatment effect ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction).

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Table R.1.2.5: 1 Proportion of patients with any adverse event occuring in at least 1% of the patients in either treatment arm in the overall population on PT level by SOC and PT, 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	2989	77	2.6	2996	63	2.1	0.2258	0.82 (0.59, 1.13)	0.81 (0.58, 1.14)	0.00 (-0.01, 0.00)	

Analysis is based on study 1245.110.
^ Patients with NYHA class I are counted in subgroup NYHA class II.
Risk ratios and odds ratios with confidence intervals (CIs) are estimated by Cochran-Mantel-Haenszel method. For risk differences standard Wald asymptotic confidence limits are calculated. A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied in case of any zero cells in contingency table.
Only treatment emergent AEs are displayed (onset between first dose until treatment stop +7 days).
MedDRA version: 23.1. * Chi-square test for treatment effect ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction).

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Table R.1.2.5: 1 Proportion of patients with any adverse event occuring in at least 1% of the patients in either treatment arm in the overall population on PT level by SOC and PT, 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	2989	52	1.7	2996	36	1.2	0.0837	0.69 (0.45, 1.05)	0.69 (0.45, 1.05)	-0.01 (-0.01, 0.00)	

Analysis is based on study 1245.110.
^ Patients with NYHA class I are counted in subgroup NYHA class II.
Risk ratios and odds ratios with confidence intervals (CIs) are estimated by Cochran-Mantel-Haenszel method. For risk differences standard Wald asymptotic confidence limits are calculated. A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied in case of any zero cells in contingency table.
Only treatment emergent AEs are displayed (onset between first dose until treatment stop +7 days).
MedDRA version: 23.1. * Chi-square test for treatment effect ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction).

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Table R.1.2.5: 1 Proportion of patients with any adverse event occuring in at least 1% of the patients in either treatment arm in the overall population on PT level by SOC and PT, 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	2989	43	1.4	2996	47	1.6	0.6791	1.09 (0.72, 1.64)	1.09 (0.72, 1.66)	0.00 (0.00, 0.01)	

Analysis is based on study 1245.110.
^ Patients with NYHA class I are counted in subgroup NYHA class II.
Risk ratios and odds ratios with confidence intervals (CIs) are estimated by Cochran-Mantel-Haenszel method. For risk differences standard Wald asymptotic confidence limits are calculated. A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied in case of any zero cells in contingency table.
Only treatment emergent AEs are displayed (onset between first dose until treatment stop +7 days).
MedDRA version: 23.1. * Chi-square test for treatment effect ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction).

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Table R.1.2.5: 1 Proportion of patients with any adverse event occuring in at least 1% of the patients in either treatment arm in the overall population on PT level by SOC and PT, 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	2989	28	0.9	2996	44	1.5	0.0591	1.57 (0.98, 2.51)	1.58 (0.98, 2.54)	0.01 (0.00, 0.01)	

Analysis is based on study 1245.110.
^ Patients with NYHA class I are counted in subgroup NYHA class II.
Risk ratios and odds ratios with confidence intervals (CIs) are estimated by Cochran-Mantel-Haenszel method. For risk differences standard Wald asymptotic confidence limits are calculated. A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied in case of any zero cells in contingency table.
Only treatment emergent AEs are displayed (onset between first dose until treatment stop +7 days).
MedDRA version: 23.1. * Chi-square test for treatment effect ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction).

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Table R.1.2.5: 1 Proportion of patients with any adverse event occuring in at least 1% of the patients in either treatment arm in the overall population on PT level by SOC and PT, 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	2989	35	1.2	2996	33	1.1	0.7998	0.94 (0.59, 1.51)	0.94 (0.58, 1.52)	0.00 (-0.01, 0.00)	

Analysis is based on study 1245.110.
^ Patients with NYHA class I are counted in subgroup NYHA class II.
Risk ratios and odds ratios with confidence intervals (CIs) are estimated by Cochran-Mantel-Haenszel method. For risk differences standard Wald asymptotic confidence limits are calculated. A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied in case of any zero cells in contingency table.
Only treatment emergent AEs are displayed (onset between first dose until treatment stop +7 days).
MedDRA version: 23.1. * Chi-square test for treatment effect ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction).

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Table R.1.2.5: 1 Proportion of patients with any adverse event occuring in at least 1% of the patients in either treatment arm in the overall population on PT level by SOC and PT, 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	2989	594	19.9	2996	449	15.0	<0.0001	0.75 (0.67,	0.84)	0.71 (0.62,	0.81)	-0.05 (-0.07,-0.03)	
Sex													0.4714
Male	1653	336	20.3	1658	245	14.8	<0.0001	0.73 (0.63,	0.84)	0.68 (0.57,	0.81)	-0.06 (-0.08,-0.03)	
Female	1336	258	19.3	1338	204	15.2	0.0054	0.79 (0.67,	0.93)	0.75 (0.61,	0.92)	-0.04 (-0.07,-0.01)	
Age [years]													0.2407
<70	1084	185	17.1	1066	151	14.2	0.0640	0.83 (0.68,	1.01)	0.80 (0.63,	1.01)	-0.03 (-0.06, 0.00)	
>=70	1905	409	21.5	1930	298	15.4	<0.0001	0.72 (0.63,	0.82)	0.67 (0.57,	0.79)	-0.06 (-0.08,-0.04)	
Region													0.6526
North America	359	51	14.2	359	44	12.3	0.4407	0.86 (0.59,	1.26)	0.84 (0.55,	1.30)	-0.02 (-0.07, 0.03)	
Latin America	757	166	21.9	758	128	16.9	0.0131	0.77 (0.63,	0.95)	0.72 (0.56,	0.93)	-0.05 (-0.09,-0.01)	
Europe	1341	272	20.3	1346	200	14.9	0.0002	0.73 (0.62,	0.86)	0.69 (0.56,	0.84)	-0.05 (-0.08,-0.03)	
Asia	343	72	21.0	343	46	13.4	0.0085	0.64 (0.46,	0.90)	0.58 (0.39,	0.87)	-0.08 (-0.13,-0.02)	
Other	189	33	17.5	190	31	16.3	0.7662	0.93 (0.60,	1.46)	0.92 (0.54,	1.58)	-0.01 (-0.09, 0.06)	
OECD member													0.5969
No	847	190	22.4	868	153	17.6	0.0129	0.79 (0.65,	0.95)	0.74 (0.58,	0.94)	-0.05 (-0.09,-0.01)	
Yes	2142	404	18.9	2128	296	13.9	<0.0001	0.74 (0.64,	0.85)	0.70 (0.59,	0.82)	-0.05 (-0.07,-0.03)	
Baseline NYHA													0.0863
II^	2450	437	17.8	2435	307	12.6	<0.0001	0.71 (0.62,	0.81)	0.66 (0.57,	0.78)	-0.05 (-0.07,-0.03)	
III/IV	539	157	29.1	561	142	25.3	0.1550	0.87 (0.72,	1.05)	0.82 (0.63,	1.08)	-0.04 (-0.09, 0.01)	
Baseline Diabetes Status													0.5052
Diabetic	1471	324	22.0	1465	235	16.0	<0.0001	0.73 (0.63,	0.85)	0.68 (0.56,	0.81)	-0.06 (-0.09,-0.03)	
Non-Diabetic	1518	270	17.8	1531	214	14.0	0.0040	0.79 (0.67,	0.93)	0.75 (0.62,	0.91)	-0.04 (-0.06,-0.01)	

Analysis is based on study 1245.110.
^ Patients with NYHA class I are counted in subgroup NYHA class II.
Risk ratios and odds ratios with confidence intervals (CIs) are estimated by Cochran-Mantel-Haenszel method. For risk differences standard Wald asymptotic confidence limits are calculated. A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
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MedDRA version: 23.1. * Chi-square test for treatment effect ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction).

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Table R.1.2.5: 1 Proportion of patients with any adverse event occuring in at least 1% of the patients in either treatment arm in the overall population on PT level by SOC and PT, 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 Diabetes Status											0.7903
Diabetic	1471	324	22.0	1465	235	16.0	<0.0001	0.73 (0.63, 0.85)	0.68 (0.56, 0.81)	-0.06 (-0.09,-0.03)	
Pre-Diabetes	979	172	17.6	1001	137	13.7	0.0173	0.78 (0.63, 0.96)	0.74 (0.58, 0.95)	-0.04 (-0.07,-0.01)	
Normal (no pre-diabetes)	539	98	18.2	530	77	14.5	0.1065	0.80 (0.61, 1.05)	0.76 (0.55, 1.06)	-0.04 (-0.08, 0.01)	
Baseline BMI [kg/m²]											0.2765
<30	1641	334	20.4	1654	240	14.5	<0.0001	0.71 (0.61, 0.83)	0.66 (0.55, 0.80)	-0.06 (-0.08,-0.03)	
>=30	1348	260	19.3	1342	209	15.6	0.0111	0.81 (0.68, 0.95)	0.77 (0.63, 0.94)	-0.04 (-0.07,-0.01)	
Baseline eGFR (CKD-EPI) [mL/min/1.73m²]											0.8705
>=60	1505	248	16.5	1493	183	12.3	0.0010	0.74 (0.62, 0.89)	0.71 (0.58, 0.87)	-0.04 (-0.07,-0.02)	
<60	1482	346	23.3	1503	266	17.7	0.0001	0.76 (0.66, 0.87)	0.71 (0.59, 0.84)	-0.06 (-0.09,-0.03)	
History of HHF (in the last 12 months)											0.2290
No	2320	417	18.0	2297	296	12.9	<0.0001	0.72 (0.62, 0.82)	0.68 (0.57, 0.79)	-0.05 (-0.07,-0.03)	
Yes	669	177	26.5	699	153	21.9	0.0483	0.83 (0.69, 1.00)	0.78 (0.61, 1.00)	-0.05 (-0.09, 0.00)	
Baseline SBP (</>= median)											0.4529
< median	1474	308	20.9	1496	226	15.1	<0.0001	0.72 (0.62, 0.84)	0.67 (0.56, 0.81)	-0.06 (-0.09,-0.03)	
>= median	1515	286	18.9	1500	223	14.9	0.0033	0.79 (0.67, 0.92)	0.75 (0.62, 0.91)	-0.04 (-0.07,-0.01)	
History of atrial fibrillation or atrial flutter											0.1581
No	1426	226	15.8	1417	187	13.2	0.0448	0.83 (0.70, 1.00)	0.81 (0.65, 1.00)	-0.03 (-0.05, 0.00)	
Yes	1558	367	23.6	1575	262	16.6	<0.0001	0.71 (0.61, 0.81)	0.65 (0.54, 0.77)	-0.07 (-0.10,-0.04)	

Analysis is based on study 1245.110.
^ Patients with NYHA class I are counted in subgroup NYHA class II.
Risk ratios and odds ratios with confidence intervals (CIs) are estimated by Cochran-Mantel-Haenszel method. For risk differences standard Wald asymptotic confidence limits are calculated. A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied in case of any zero cells in contingency table.
Only treatment emergent AEs are displayed (onset between first dose until treatment stop +7 days).
MedDRA version: 23.1. * Chi-square test for treatment effect ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction).

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Table R.1.2.5: 1 Proportion of patients with any adverse event occuring in at least 1% of the patients in either treatment arm in the overall population on PT level by SOC and PT, 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 LVEF [%]													0.4120
< 50	988	208	21.1	995	148	14.9	0.0003	0.71 (0.58,	0.86)	0.66 (0.52,	0.83)	-0.06 (-0.10,-0.03)	
>= 50	2001	386	19.3	2001	301	15.0	0.0004	0.78 (0.68,	0.89)	0.74 (0.63,	0.87)	-0.04 (-0.07,-0.02)	
Baseline LVEF [%]													0.2988
<50	988	208	21.1	995	148	14.9	0.0003	0.71 (0.58,	0.86)	0.66 (0.52,	0.83)	-0.06 (-0.10,-0.03)	
50 to <60	1030	208	20.2	1028	148	14.4	0.0005	0.71 (0.59,	0.86)	0.66 (0.53,	0.84)	-0.06 (-0.09,-0.03)	
>=60	971	178	18.3	973	153	15.7	0.1262	0.86 (0.70,	1.04)	0.83 (0.66,	1.05)	-0.03 (-0.06, 0.01)	
Baseline NT-proBNP [pg/mL] (</>=median by atrial fibrillation/flutter status)													0.2508
< median	1507	237	15.7	1476	160	10.8	<0.0001	0.69 (0.57,	0.83)	0.65 (0.53,	0.81)	-0.05 (-0.07,-0.02)	
>= median	1475	356	24.1	1516	289	19.1	0.0007	0.79 (0.69,	0.91)	0.74 (0.62,	0.88)	-0.05 (-0.08,-0.02)	
Baseline uric acid [mg/dL] (tertiles)													0.0692
<T1	975	183	18.8	963	112	11.6	<0.0001	0.62 (0.50,	0.77)	0.57 (0.44,	0.73)	-0.07 (-0.10,-0.04)	
>=T1 and <T2	966	159	16.5	1032	145	14.1	0.1340	0.85 (0.69,	1.05)	0.83 (0.65,	1.06)	-0.02 (-0.06, 0.01)	
>=T2	1016	241	23.7	970	189	19.5	0.0220	0.82 (0.69,	0.97)	0.78 (0.63,	0.96)	-0.04 (-0.08,-0.01)	
Baseline use of MRA													0.8530
No	1865	336	18.0	1878	253	13.5	0.0001	0.75 (0.64,	0.87)	0.71 (0.59,	0.85)	-0.05 (-0.07,-0.02)	
Yes	1124	258	23.0	1118	196	17.5	0.0014	0.76 (0.65,	0.90)	0.71 (0.58,	0.88)	-0.05 (-0.09,-0.02)	
Baseline use of ACE-inhibitor, ARB or ARNi													0.0263
No	586	119	20.3	568	110	19.4	0.6886	0.95 (0.76,	1.20)	0.94 (0.71,	1.26)	-0.01 (-0.06, 0.04)	
Yes	2403	475	19.8	2428	339	14.0	<0.0001	0.71 (0.62,	0.80)	0.66 (0.57,	0.77)	-0.06 (-0.08,-0.04)	

Analysis is based on study 1245.110.
^ Patients with NYHA class I are counted in subgroup NYHA class II.
Risk ratios and odds ratios with confidence intervals (CIs) are estimated by Cochran-Mantel-Haenszel method. For risk differences standard Wald asymptotic confidence limits are calculated. A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied in case of any zero cells in contingency table.
Only treatment emergent AEs are displayed (onset between first dose until treatment stop +7 days).
MedDRA version: 23.1. * Chi-square test for treatment effect ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction).

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Table R.1.2.5: 1 Proportion of patients with any adverse event occuring in at least 1% of the patients in either treatment arm in the overall population on PT level by SOC and PT, 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	2989	223	7.5	2996	210	7.0	0.5004	0.94 (0.78, 1.13)	0.93 (0.77, 1.14)	0.00 (-0.02, 0.01)	

Analysis is based on study 1245.110.
^ Patients with NYHA class I are counted in subgroup NYHA class II.
Risk ratios and odds ratios with confidence intervals (CIs) are estimated by Cochran-Mantel-Haenszel method. For risk differences standard Wald asymptotic confidence limits are calculated. A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied in case of any zero cells in contingency table.
Only treatment emergent AEs are displayed (onset between first dose until treatment stop +7 days).
MedDRA version: 23.1. * Chi-square test for treatment effect ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction).

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Table R.1.2.5: 1 Proportion of patients with any adverse event occuring in at least 1% of the patients in either treatment arm in the overall population on PT level by SOC and PT, 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	2989	72	2.4	2996	70	2.3	0.8540	0.97 (0.70, 1.34)	0.97 (0.69, 1.35)	0.00 (-0.01, 0.01)	

Analysis is based on study 1245.110.
^ Patients with NYHA class I are counted in subgroup NYHA class II.
Risk ratios and odds ratios with confidence intervals (CIs) are estimated by Cochran-Mantel-Haenszel method. For risk differences standard Wald asymptotic confidence limits are calculated. A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied in case of any zero cells in contingency table.
Only treatment emergent AEs are displayed (onset between first dose until treatment stop +7 days).
MedDRA version: 23.1. * Chi-square test for treatment effect ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction).

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Table R.1.2.5: 1 Proportion of patients with any adverse event occuring in at least 1% of the patients in either treatment arm in the overall population on PT level by SOC and PT, 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	2989	66	2.2	2996	58	1.9	0.4598	0.88 (0.62, 1.24)	0.87 (0.61, 1.25)	0.00 (-0.01, 0.00)	

Analysis is based on study 1245.110.
^ Patients with NYHA class I are counted in subgroup NYHA class II.
Risk ratios and odds ratios with confidence intervals (CIs) are estimated by Cochran-Mantel-Haenszel method. For risk differences standard Wald asymptotic confidence limits are calculated. A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied in case of any zero cells in contingency table.
Only treatment emergent AEs are displayed (onset between first dose until treatment stop +7 days).
MedDRA version: 23.1. * Chi-square test for treatment effect ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction).

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Table R.1.2.5: 1 Proportion of patients with any adverse event occuring in at least 1% of the patients in either treatment arm in the overall population on PT level by SOC and PT, 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	2989	48	1.6	2996	50	1.7	0.8477	1.04 (0.70, 1.54)	1.04 (0.70, 1.55)	0.00 (-0.01, 0.01)	

Analysis is based on study 1245.110.
^ Patients with NYHA class I are counted in subgroup NYHA class II.
Risk ratios and odds ratios with confidence intervals (CIs) are estimated by Cochran-Mantel-Haenszel method. For risk differences standard Wald asymptotic confidence limits are calculated. A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied in case of any zero cells in contingency table.
Only treatment emergent AEs are displayed (onset between first dose until treatment stop +7 days).
MedDRA version: 23.1. * Chi-square test for treatment effect ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction).

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Table R.1.2.5: 1 Proportion of patients with any adverse event occuring in at least 1% of the patients in either treatment arm in the overall population on PT level by SOC and PT, 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	2989	41	1.4	2996	31	1.0	0.2318	0.75 (0.47, 1.20)	0.75 (0.47, 1.20)	0.00 (-0.01, 0.00)	

Analysis is based on study 1245.110.
^ Patients with NYHA class I are counted in subgroup NYHA class II.
Risk ratios and odds ratios with confidence intervals (CIs) are estimated by Cochran-Mantel-Haenszel method. For risk differences standard Wald asymptotic confidence limits are calculated. A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied in case of any zero cells in contingency table.
Only treatment emergent AEs are displayed (onset between first dose until treatment stop +7 days).
MedDRA version: 23.1. * Chi-square test for treatment effect ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction).

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Table R.1.2.5: 1 Proportion of patients with any adverse event occuring in at least 1% of the patients in either treatment arm in the overall population on PT level by SOC and PT, 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	2989	39	1.3	2996	28	0.9	0.1735	0.72 (0.44, 1.16)	0.71 (0.44, 1.16)	0.00 (-0.01, 0.00)	

Analysis is based on study 1245.110.
^ Patients with NYHA class I are counted in subgroup NYHA class II.
Risk ratios and odds ratios with confidence intervals (CIs) are estimated by Cochran-Mantel-Haenszel method. For risk differences standard Wald asymptotic confidence limits are calculated. A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied in case of any zero cells in contingency table.
Only treatment emergent AEs are displayed (onset between first dose until treatment stop +7 days).
MedDRA version: 23.1. * Chi-square test for treatment effect ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction).

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Table R.1.2.5: 1 Proportion of patients with any adverse event occuring in at least 1% of the patients in either treatment arm in the overall population on PT level by SOC and PT, 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	2989	37	1.2	2996	32	1.1	0.5384	0.86 (0.54, 1.38)	0.86 (0.54, 1.39)	0.00 (-0.01, 0.00)	

Analysis is based on study 1245.110.
^ Patients with NYHA class I are counted in subgroup NYHA class II.
Risk ratios and odds ratios with confidence intervals (CIs) are estimated by Cochran-Mantel-Haenszel method. For risk differences standard Wald asymptotic confidence limits are calculated. A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied in case of any zero cells in contingency table.
Only treatment emergent AEs are displayed (onset between first dose until treatment stop +7 days).
MedDRA version: 23.1. * Chi-square test for treatment effect ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction).

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Table R.1.2.5: 1 Proportion of patients with any adverse event occuring in at least 1% of the patients in either treatment arm in the overall population on PT level by SOC and PT, 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	2989	27	0.9	2996	37	1.2	0.2123	1.37 (0.83, 2.24)	1.37 (0.83, 2.26)	0.00 (0.00, 0.01)	

Analysis is based on study 1245.110.
^ Patients with NYHA class I are counted in subgroup NYHA class II.
Risk ratios and odds ratios with confidence intervals (CIs) are estimated by Cochran-Mantel-Haenszel method. For risk differences standard Wald asymptotic confidence limits are calculated. A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied in case of any zero cells in contingency table.
Only treatment emergent AEs are displayed (onset between first dose until treatment stop +7 days).
MedDRA version: 23.1. * Chi-square test for treatment effect ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction).

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Table R.1.2.5: 1 Proportion of patients with any adverse event occuring in at least 1% of the patients in either treatment arm in the overall population on PT level by SOC and PT, 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	2989	30	1.0	2996	36	1.2	0.4635	1.20 (0.74, 1.94)	1.20 (0.74, 1.95)	0.00 (0.00, 0.01)	

Analysis is based on study 1245.110.
^ Patients with NYHA class I are counted in subgroup NYHA class II.
Risk ratios and odds ratios with confidence intervals (CIs) are estimated by Cochran-Mantel-Haenszel method. For risk differences standard Wald asymptotic confidence limits are calculated. A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied in case of any zero cells in contingency table.
Only treatment emergent AEs are displayed (onset between first dose until treatment stop +7 days).
MedDRA version: 23.1. * Chi-square test for treatment effect ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction).

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Table R.1.2.5: 1 Proportion of patients with any adverse event occuring in at least 1% of the patients in either treatment arm in the overall population on PT level by SOC and PT, 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	2989	35	1.2	2996	22	0.7	0.0820	0.63 (0.37, 1.07)	0.62 (0.37, 1.07)	0.00 (-0.01, 0.00)	

Analysis is based on study 1245.110.
^ Patients with NYHA class I are counted in subgroup NYHA class II.
Risk ratios and odds ratios with confidence intervals (CIs) are estimated by Cochran-Mantel-Haenszel method. For risk differences standard Wald asymptotic confidence limits are calculated. A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied in case of any zero cells in contingency table.
Only treatment emergent AEs are displayed (onset between first dose until treatment stop +7 days).
MedDRA version: 23.1. * Chi-square test for treatment effect ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction).

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Table R.1.2.5: 1 Proportion of patients with any adverse event occuring in at least 1% of the patients in either treatment arm in the overall population on PT level by SOC and PT, 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	2989	214	7.2	2996	144	4.8	0.0001	0.67 (0.55, 0.82)	0.65 (0.53, 0.81)	-0.02 (-0.04,-0.01)	
Sex											0.8726
Male	1653	120	7.3	1658	82	4.9	0.0054	0.68 (0.52, 0.89)	0.66 (0.50, 0.89)	-0.02 (-0.04,-0.01)	
Female	1336	94	7.0	1338	62	4.6	0.0081	0.66 (0.48, 0.90)	0.64 (0.46, 0.89)	-0.02 (-0.04,-0.01)	
Age [years]											0.0483
<70	1084	91	8.4	1066	75	7.0	0.2378	0.84 (0.62, 1.12)	0.83 (0.60, 1.14)	-0.01 (-0.04, 0.01)	
>=70	1905	123	6.5	1930	69	3.6	<0.0001	0.55 (0.42, 0.74)	0.54 (0.40, 0.73)	-0.03 (-0.04,-0.02)	
Region											0.9343
North America	359	28	7.8	359	16	4.5	0.0619	0.57 (0.31, 1.04)	0.55 (0.29, 1.04)	-0.03 (-0.07, 0.00)	
Latin America	757	60	7.9	758	39	5.1	0.0285	0.65 (0.44, 0.96)	0.63 (0.42, 0.96)	-0.03 (-0.05, 0.00)	
Europe	1341	89	6.6	1346	64	4.8	0.0353	0.72 (0.52, 0.98)	0.70 (0.50, 0.98)	-0.02 (-0.04, 0.00)	
Asia	343	18	5.2	343	14	4.1	0.4689	0.78 (0.39, 1.54)	0.77 (0.38, 1.57)	-0.01 (-0.04, 0.02)	
Other	189	19	10.1	190	11	5.8	0.1243	0.58 (0.28, 1.18)	0.55 (0.25, 1.19)	-0.04 (-0.10, 0.01)	
OECD member											0.1476
No	847	70	8.3	868	38	4.4	0.0009	0.53 (0.36, 0.78)	0.51 (0.34, 0.76)	-0.04 (-0.06,-0.02)	
Yes	2142	144	6.7	2128	106	5.0	0.0154	0.74 (0.58, 0.95)	0.73 (0.56, 0.94)	-0.02 (-0.03, 0.00)	
Baseline NYHA											0.3914
II^	2450	177	7.2	2435	113	4.6	0.0001	0.64 (0.51, 0.81)	0.62 (0.49, 0.80)	-0.03 (-0.04,-0.01)	
III/IV	539	37	6.9	561	31	5.5	0.3567	0.80 (0.51, 1.28)	0.79 (0.48, 1.30)	-0.01 (-0.04, 0.02)	
Baseline Diabetes Status											0.7007
Diabetic	1471	197	13.4	1465	134	9.1	0.0003	0.68 (0.56, 0.84)	0.65 (0.52, 0.82)	-0.04 (-0.07,-0.02)	
Non-Diabetic	1518	17	1.1	1531	10	0.7	0.1690	0.58 (0.27, 1.27)	0.58 (0.26, 1.27)	0.00 (-0.01, 0.00)	

Analysis is based on study 1245.110.
^ Patients with NYHA class I are counted in subgroup NYHA class II.
Risk ratios and odds ratios with confidence intervals (CIs) are estimated by Cochran-Mantel-Haenszel method. For risk differences standard Wald asymptotic confidence limits are calculated. A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied in case of any zero cells in contingency table.
Only treatment emergent AEs are displayed (onset between first dose until treatment stop +7 days).
MedDRA version: 23.1. * Chi-square test for treatment effect ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction).

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Table R.1.2.5: 1 Proportion of patients with any adverse event occuring in at least 1% of the patients in either treatment arm in the overall population on PT level by SOC and PT, 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 Diabetes Status											0.5002
Diabetic	1471	197	13.4	1465	134	9.1	0.0003	0.68 (0.56, 0.84)	0.65 (0.52, 0.82)	-0.04 (-0.07,-0.02)	
Pre-Diabetes	979	16	1.6	1001	8	0.8	0.0895	0.49 (0.21, 1.14)	0.48 (0.21, 1.14)	-0.01 (-0.02, 0.00)	
Normal (no pre-diabetes)	539	1	0.2	530	2	0.4	0.5533	2.03 (0.18, 22.36)	2.04 (0.18, 22.54)	0.00 (0.00, 0.01)	
Baseline BMI [kg/m²]											0.7534
<30	1641	92	5.6	1654	60	3.6	0.0068	0.65 (0.47, 0.89)	0.63 (0.45, 0.88)	-0.02 (-0.03,-0.01)	
>=30	1348	122	9.1	1342	84	6.3	0.0065	0.69 (0.53, 0.90)	0.67 (0.50, 0.90)	-0.03 (-0.05,-0.01)	
Baseline eGFR (CKD-EPI) [mL/min/1.73m²]											0.1614
>=60	1505	109	7.2	1493	62	4.2	0.0003	0.57 (0.42, 0.78)	0.55 (0.40, 0.76)	-0.03 (-0.05,-0.01)	
<60	1482	105	7.1	1503	82	5.5	0.0663	0.77 (0.58, 1.02)	0.76 (0.56, 1.02)	-0.02 (-0.03, 0.00)	
History of HHF (in the last 12 months)											0.8953
No	2320	161	6.9	2297	106	4.6	0.0007	0.66 (0.52, 0.84)	0.65 (0.50, 0.83)	-0.02 (-0.04,-0.01)	
Yes	669	53	7.9	699	38	5.4	0.0651	0.69 (0.46, 1.03)	0.67 (0.43, 1.03)	-0.02 (-0.05, 0.00)	
Baseline SBP (</>= median)											0.3155
< median	1474	108	7.3	1496	66	4.4	0.0007	0.60 (0.45, 0.81)	0.58 (0.43, 0.80)	-0.03 (-0.05,-0.01)	
>= median	1515	106	7.0	1500	78	5.2	0.0393	0.74 (0.56, 0.99)	0.73 (0.54, 0.99)	-0.02 (-0.04, 0.00)	
History of atrial fibrillation or atrial flutter											0.8902
No	1426	120	8.4	1417	78	5.5	0.0023	0.65 (0.50, 0.86)	0.63 (0.47, 0.85)	-0.03 (-0.05,-0.01)	
Yes	1558	94	6.0	1575	64	4.1	0.0118	0.67 (0.49, 0.92)	0.66 (0.48, 0.91)	-0.02 (-0.04, 0.00)	

Analysis is based on study 1245.110.
^ Patients with NYHA class I are counted in subgroup NYHA class II.
Risk ratios and odds ratios with confidence intervals (CIs) are estimated by Cochran-Mantel-Haenszel method. For risk differences standard Wald asymptotic confidence limits are calculated. A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied in case of any zero cells in contingency table.
Only treatment emergent AEs are displayed (onset between first dose until treatment stop +7 days).
MedDRA version: 23.1. * Chi-square test for treatment effect ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction).

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Table R.1.2.5: 1 Proportion of patients with any adverse event occuring in at least 1% of the patients in either treatment arm in the overall population on PT level by SOC and PT, 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 LVEF [%]											0.0780
< 50	988	84	8.5	995	44	4.4	0.0002	0.52 (0.37, 0.74)	0.50 (0.34, 0.73)	-0.04 (-0.06,-0.02)	
>= 50	2001	130	6.5	2001	100	5.0	0.0416	0.77 (0.60, 0.99)	0.76 (0.58, 0.99)	-0.01 (-0.03, 0.00)	
Baseline LVEF [%]											0.1890
<50	988	84	8.5	995	44	4.4	0.0002	0.52 (0.37, 0.74)	0.50 (0.34, 0.73)	-0.04 (-0.06,-0.02)	
50 to <60	1030	73	7.1	1028	59	5.7	0.2120	0.81 (0.58, 1.13)	0.80 (0.56, 1.14)	-0.01 (-0.03, 0.01)	
>=60	971	57	5.9	973	41	4.2	0.0951	0.72 (0.49, 1.06)	0.71 (0.47, 1.06)	-0.02 (-0.04, 0.00)	
Baseline NT-proBNP [pg/mL] (</>=median by atrial fibrillation/flutter status)											0.1559
< median	1507	121	8.0	1476	68	4.6	0.0001	0.57 (0.43, 0.77)	0.55 (0.41, 0.75)	-0.03 (-0.05,-0.02)	
>= median	1475	93	6.3	1516	74	4.9	0.0900	0.77 (0.58, 1.04)	0.76 (0.56, 1.04)	-0.01 (-0.03, 0.00)	
Baseline uric acid [mg/dL] (tertiles)											0.2976
<T1	975	64	6.6	963	51	5.3	0.2374	0.81 (0.56, 1.15)	0.80 (0.54, 1.16)	-0.01 (-0.03, 0.01)	
>=T1 and <T2	966	57	5.9	1032	44	4.3	0.0951	0.72 (0.49, 1.06)	0.71 (0.47, 1.06)	-0.02 (-0.04, 0.00)	
>=T2	1016	91	9.0	970	48	4.9	0.0005	0.55 (0.39, 0.77)	0.53 (0.37, 0.76)	-0.04 (-0.06,-0.02)	
Baseline use of MRA											0.6721
No	1865	127	6.8	1878	89	4.7	0.0066	0.70 (0.53, 0.91)	0.68 (0.52, 0.90)	-0.02 (-0.04,-0.01)	
Yes	1124	87	7.7	1118	55	4.9	0.0061	0.64 (0.46, 0.88)	0.62 (0.44, 0.87)	-0.03 (-0.05,-0.01)	
Baseline use of ACE-inhibitor, ARB or ARNi											0.4400
No	586	32	5.5	568	25	4.4	0.4064	0.81 (0.48, 1.34)	0.80 (0.47, 1.36)	-0.01 (-0.04, 0.01)	
Yes	2403	182	7.6	2428	119	4.9	0.0001	0.65 (0.52, 0.81)	0.63 (0.50, 0.80)	-0.03 (-0.04,-0.01)	

Analysis is based on study 1245.110.
^ Patients with NYHA class I are counted in subgroup NYHA class II.
Risk ratios and odds ratios with confidence intervals (CIs) are estimated by Cochran-Mantel-Haenszel method. For risk differences standard Wald asymptotic confidence limits are calculated. A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied in case of any zero cells in contingency table.
Only treatment emergent AEs are displayed (onset between first dose until treatment stop +7 days).
MedDRA version: 23.1. * Chi-square test for treatment effect ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction).

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Table R.1.2.5: 1 Proportion of patients with any adverse event occuring in at least 1% of the patients in either treatment arm in the overall population on PT level by SOC and PT, 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	2989	208	7.0	2996	179	6.0	0.1216	0.86 (0.71, 1.04)	0.85 (0.69, 1.04)	-0.01 (-0.02, 0.00)	

Analysis is based on study 1245.110.
^ Patients with NYHA class I are counted in subgroup NYHA class II.
Risk ratios and odds ratios with confidence intervals (CIs) are estimated by Cochran-Mantel-Haenszel method. For risk differences standard Wald asymptotic confidence limits are calculated. A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied in case of any zero cells in contingency table.
Only treatment emergent AEs are displayed (onset between first dose until treatment stop +7 days).
MedDRA version: 23.1. * Chi-square test for treatment effect ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction).

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Table R.1.2.5: 1 Proportion of patients with any adverse event occuring in at least 1% of the patients in either treatment arm in the overall population on PT level by SOC and PT, 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	2989	208	7.0	2996	131	4.4	<0.0001	0.63 (0.51,	0.78)	0.61 (0.49,	0.77)	-0.03 (-0.04,-0.01)		
Sex														0.8957
Male	1653	108	6.5	1658	69	4.2	0.0024	0.64 (0.47,	0.85)	0.62 (0.46,	0.85)	-0.02 (-0.04,-0.01)		
Female	1336	100	7.5	1338	62	4.6	0.0020	0.62 (0.46,	0.84)	0.60 (0.43,	0.83)	-0.03 (-0.05,-0.01)		
Age [years]														0.0219
<70	1084	90	8.3	1066	72	6.8	0.1738	0.81 (0.60,	1.10)	0.80 (0.58,	1.10)	-0.02 (-0.04, 0.01)		
>=70	1905	118	6.2	1930	59	3.1	<0.0001	0.49 (0.36,	0.67)	0.48 (0.35,	0.66)	-0.03 (-0.04,-0.02)		
Region														0.5886
North America	359	7	1.9	359	5	1.4	0.5604	0.71 (0.23,	2.23)	0.71 (0.22,	2.26)	-0.01 (-0.02, 0.01)		
Latin America	757	88	11.6	758	65	8.6	0.0489	0.74 (0.54,	1.00)	0.71 (0.51,	1.00)	-0.03 (-0.06, 0.00)		
Europe	1341	78	5.8	1346	39	2.9	0.0002	0.50 (0.34,	0.73)	0.48 (0.33,	0.72)	-0.03 (-0.04,-0.01)		
Asia	343	26	7.6	343	15	4.4	0.0764	0.58 (0.31,	1.07)	0.56 (0.29,	1.07)	-0.03 (-0.07, 0.00)		
Other	189	9	4.8	190	7	3.7	0.6019	0.77 (0.29,	2.03)	0.77 (0.28,	2.10)	-0.01 (-0.05, 0.03)		
OECD member														0.0439
No	847	98	11.6	868	77	8.9	0.0648	0.77 (0.58,	1.02)	0.74 (0.54,	1.02)	-0.03 (-0.06, 0.00)		
Yes	2142	110	5.1	2128	54	2.5	<0.0001	0.49 (0.36,	0.68)	0.48 (0.35,	0.67)	-0.03 (-0.04,-0.01)		
Baseline NYHA														0.5847
II^	2450	158	6.4	2435	95	3.9	<0.0001	0.60 (0.47,	0.78)	0.59 (0.45,	0.76)	-0.03 (-0.04,-0.01)		
III/IV	539	50	9.3	561	36	6.4	0.0774	0.69 (0.46,	1.04)	0.67 (0.43,	1.05)	-0.03 (-0.06, 0.00)		
Baseline Diabetes Status														0.0003
Diabetic	1471	101	6.9	1465	89	6.1	0.3837	0.88 (0.67,	1.17)	0.88 (0.65,	1.18)	-0.01 (-0.03, 0.01)		
Non-Diabetic	1518	107	7.0	1531	42	2.7	<0.0001	0.39 (0.27,	0.55)	0.37 (0.26,	0.54)	-0.04 (-0.06,-0.03)		

Analysis is based on study 1245.110.
^ Patients with NYHA class I are counted in subgroup NYHA class II.
Risk ratios and odds ratios with confidence intervals (CIs) are estimated by Cochran-Mantel-Haenszel method. For risk differences standard Wald asymptotic confidence limits are calculated. A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied in case of any zero cells in contingency table.
Only treatment emergent AEs are displayed (onset between first dose until treatment stop +7 days).
MedDRA version: 23.1. * Chi-square test for treatment effect ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction).

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Table R.1.2.5: 1 Proportion of patients with any adverse event occuring in at least 1% of the patients in either treatment arm in the overall population on PT level by SOC and PT, 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 Diabetes Status													0.0010
Diabetic	1471	101	6.9	1465	89	6.1	0.3837	0.88 (0.67,	1.17)	0.88 (0.65,	1.18)	-0.01 (-0.03, 0.01)	
Pre-Diabetes	979	72	7.4	1001	25	2.5	<0.0001	0.34 (0.22,	0.53)	0.32 (0.20,	0.51)	-0.05 (-0.07,-0.03)	
Normal (no pre-diabetes)	539	35	6.5	530	17	3.2	0.0125	0.49 (0.28,	0.87)	0.48 (0.26,	0.86)	-0.03 (-0.06,-0.01)	
Baseline BMI [kg/m²]													0.5234
<30	1641	105	6.4	1654	62	3.7	0.0005	0.59 (0.43,	0.80)	0.57 (0.41,	0.79)	-0.03 (-0.04,-0.01)	
>=30	1348	103	7.6	1342	69	5.1	0.0081	0.67 (0.50,	0.90)	0.66 (0.48,	0.90)	-0.02 (-0.04,-0.01)	
Baseline eGFR (CKD-EPI) [mL/min/1.73m²]													0.1154
>=60	1505	90	6.0	1493	45	3.0	<0.0001	0.50 (0.35,	0.72)	0.49 (0.34,	0.70)	-0.03 (-0.04,-0.01)	
<60	1482	118	8.0	1503	86	5.7	0.0153	0.72 (0.55,	0.94)	0.70 (0.53,	0.94)	-0.02 (-0.04, 0.00)	
History of HHF (in the last 12 months)													0.9158
No	2320	152	6.6	2297	95	4.1	0.0003	0.63 (0.49,	0.81)	0.62 (0.47,	0.80)	-0.02 (-0.04,-0.01)	
Yes	669	56	8.4	699	36	5.2	0.0174	0.62 (0.41,	0.92)	0.59 (0.39,	0.92)	-0.03 (-0.06,-0.01)	
Baseline SBP (</>= median)													0.7560
< median	1474	100	6.8	1496	66	4.4	0.0049	0.65 (0.48,	0.88)	0.63 (0.46,	0.87)	-0.02 (-0.04,-0.01)	
>= median	1515	108	7.1	1500	65	4.3	0.0010	0.61 (0.45,	0.82)	0.59 (0.43,	0.81)	-0.03 (-0.04,-0.01)	
History of atrial fibrillation or atrial flutter													0.3849
No	1426	115	8.1	1417	78	5.5	0.0067	0.68 (0.52,	0.90)	0.66 (0.49,	0.89)	-0.03 (-0.04,-0.01)	
Yes	1558	93	6.0	1575	53	3.4	0.0005	0.56 (0.41,	0.78)	0.55 (0.39,	0.77)	-0.03 (-0.04,-0.01)	

Analysis is based on study 1245.110.
^ Patients with NYHA class I are counted in subgroup NYHA class II.
Risk ratios and odds ratios with confidence intervals (CIs) are estimated by Cochran-Mantel-Haenszel method. For risk differences standard Wald asymptotic confidence limits are calculated. A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied in case of any zero cells in contingency table.
Only treatment emergent AEs are displayed (onset between first dose until treatment stop +7 days).
MedDRA version: 23.1. * Chi-square test for treatment effect ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction).

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Table R.1.2.5: 1 Proportion of patients with any adverse event occuring in at least 1% of the patients in either treatment arm in the overall population on PT level by SOC and PT, 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 LVEF [%]											0.3006
< 50	988	71	7.2	995	52	5.2	0.0704	0.73 (0.51, 1.03)	0.71 (0.49, 1.03)	-0.02 (-0.04, 0.00)	
>= 50	2001	137	6.8	2001	79	3.9	<0.0001	0.58 (0.44, 0.76)	0.56 (0.42, 0.74)	-0.03 (-0.04,-0.02)	
Baseline LVEF [%]											0.4132
<50	988	71	7.2	995	52	5.2	0.0704	0.73 (0.51, 1.03)	0.71 (0.49, 1.03)	-0.02 (-0.04, 0.00)	
50 to <60	1030	65	6.3	1028	42	4.1	0.0230	0.65 (0.44, 0.95)	0.63 (0.42, 0.94)	-0.02 (-0.04, 0.00)	
>=60	971	72	7.4	973	37	3.8	0.0005	0.51 (0.35, 0.75)	0.49 (0.33, 0.74)	-0.04 (-0.06,-0.02)	
Baseline NT-proBNP [pg/mL] (</>=median by atrial fibrillation/flutter status)											0.9411
< median	1507	97	6.4	1476	59	4.0	0.0028	0.62 (0.45, 0.85)	0.61 (0.43, 0.84)	-0.02 (-0.04,-0.01)	
>= median	1475	111	7.5	1516	72	4.7	0.0015	0.63 (0.47, 0.84)	0.61 (0.45, 0.83)	-0.03 (-0.04,-0.01)	
Baseline uric acid [mg/dL] (tertiles)											0.0877
<T1	975	24	2.5	963	8	0.8	0.0049	0.34 (0.15, 0.75)	0.33 (0.15, 0.74)	-0.02 (-0.03,-0.01)	
>=T1 and <T2	966	59	6.1	1032	33	3.2	0.0019	0.52 (0.35, 0.79)	0.51 (0.33, 0.78)	-0.03 (-0.05,-0.01)	
>=T2	1016	124	12.2	970	89	9.2	0.0292	0.75 (0.58, 0.97)	0.73 (0.54, 0.97)	-0.03 (-0.06, 0.00)	
Baseline use of MRA											0.9235
No	1865	110	5.9	1878	69	3.7	0.0014	0.62 (0.46, 0.84)	0.61 (0.45, 0.83)	-0.02 (-0.04,-0.01)	
Yes	1124	98	8.7	1118	62	5.5	0.0035	0.64 (0.47, 0.86)	0.61 (0.44, 0.85)	-0.03 (-0.05,-0.01)	
Baseline use of ACE-inhibitor, ARB or ARNi											0.1354
No	586	41	7.0	568	17	3.0	0.0019	0.43 (0.25, 0.74)	0.41 (0.23, 0.73)	-0.04 (-0.06,-0.02)	
Yes	2403	167	6.9	2428	114	4.7	0.0008	0.68 (0.54, 0.85)	0.66 (0.52, 0.84)	-0.02 (-0.04,-0.01)	

Analysis is based on study 1245.110.
^ Patients with NYHA class I are counted in subgroup NYHA class II.
Risk ratios and odds ratios with confidence intervals (CIs) are estimated by Cochran-Mantel-Haenszel method. For risk differences standard Wald asymptotic confidence limits are calculated. A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied in case of any zero cells in contingency table.
Only treatment emergent AEs are displayed (onset between first dose until treatment stop +7 days).
MedDRA version: 23.1. * Chi-square test for treatment effect ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction).

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Table R.1.2.5: 1 Proportion of patients with any adverse event occuring in at least 1% of the patients in either treatment arm in the overall population on PT level by SOC and PT, 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	2989	93	3.1	2996	83	2.8	0.4349	0.89 (0.67, 1.19)	0.89 (0.66, 1.20)	0.00 (-0.01, 0.01)	

Analysis is based on study 1245.110.
^ Patients with NYHA class I are counted in subgroup NYHA class II.
Risk ratios and odds ratios with confidence intervals (CIs) are estimated by Cochran-Mantel-Haenszel method. For risk differences standard Wald asymptotic confidence limits are calculated. A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied in case of any zero cells in contingency table.
Only treatment emergent AEs are displayed (onset between first dose until treatment stop +7 days).
MedDRA version: 23.1. * Chi-square test for treatment effect ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction).

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Table R.1.2.5: 1 Proportion of patients with any adverse event occuring in at least 1% of the patients in either treatment arm in the overall population on PT level by SOC and PT, 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	2989	89	3.0	2996	56	1.9	0.0053	0.63 (0.45, 0.87)	0.62 (0.44, 0.87)	-0.01 (-0.02, 0.00)	
Sex											0.0174
Male	1653	51	3.1	1658	43	2.6	0.3942	0.84 (0.56, 1.25)	0.84 (0.55, 1.26)	0.00 (-0.02, 0.01)	
Female	1336	38	2.8	1338	13	1.0	0.0004	0.34 (0.18, 0.64)	0.34 (0.18, 0.63)	-0.02 (-0.03,-0.01)	
Age [years]											0.2276
<70	1084	30	2.8	1066	24	2.3	0.4445	0.81 (0.48, 1.38)	0.81 (0.47, 1.39)	-0.01 (-0.02, 0.01)	
>=70	1905	59	3.1	1930	32	1.7	0.0034	0.54 (0.35, 0.82)	0.53 (0.34, 0.82)	-0.01 (-0.02, 0.00)	
Region											0.3936
North America	359	24	6.7	359	12	3.3	0.0402	0.50 (0.25, 0.98)	0.48 (0.24, 0.98)	-0.03 (-0.07, 0.00)	
Latin America	757	12	1.6	758	6	0.8	0.1540	0.50 (0.19, 1.32)	0.50 (0.18, 1.33)	-0.01 (-0.02, 0.00)	
Europe	1341	29	2.2	1346	20	1.5	0.1899	0.69 (0.39, 1.21)	0.68 (0.38, 1.21)	-0.01 (-0.02, 0.00)	
Asia	343	7	2.0	343	10	2.9	0.4612	1.43 (0.55, 3.71)	1.44 (0.54, 3.83)	0.01 (-0.01, 0.03)	
Other	189	17	9.0	190	8	4.2	0.0606	0.47 (0.21, 1.06)	0.44 (0.19, 1.06)	-0.05 (-0.10, 0.00)	
OECD member											0.2294
No	847	30	3.5	868	14	1.6	0.0115	0.46 (0.24, 0.85)	0.45 (0.24, 0.85)	-0.02 (-0.03, 0.00)	
Yes	2142	59	2.8	2128	42	2.0	0.0932	0.72 (0.48, 1.06)	0.71 (0.48, 1.06)	-0.01 (-0.02, 0.00)	
Baseline NYHA											0.4636
II^	2450	61	2.5	2435	41	1.7	0.0488	0.68 (0.46, 1.00)	0.67 (0.45, 1.00)	-0.01 (-0.02, 0.00)	
III/IV	539	28	5.2	561	15	2.7	0.0310	0.51 (0.28, 0.95)	0.50 (0.26, 0.95)	-0.03 (-0.05, 0.00)	
Baseline Diabetes Status											0.7108
Diabetic	1471	42	2.9	1465	28	1.9	0.0937	0.67 (0.42, 1.07)	0.66 (0.41, 1.08)	-0.01 (-0.02, 0.00)	
Non-Diabetic	1518	47	3.1	1531	28	1.8	0.0239	0.59 (0.37, 0.94)	0.58 (0.36, 0.94)	-0.01 (-0.02, 0.00)	

Analysis is based on study 1245.110.
^ Patients with NYHA class I are counted in subgroup NYHA class II.
Risk ratios and odds ratios with confidence intervals (CIs) are estimated by Cochran-Mantel-Haenszel method. For risk differences standard Wald asymptotic confidence limits are calculated. A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied in case of any zero cells in contingency table.
Only treatment emergent AEs are displayed (onset between first dose until treatment stop +7 days).
MedDRA version: 23.1. * Chi-square test for treatment effect ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction).

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Table R.1.2.5: 1 Proportion of patients with any adverse event occuring in at least 1% of the patients in either treatment arm in the overall population on PT level by SOC and PT, 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 Diabetes Status											0.9332
Diabetic	1471	42	2.9	1465	28	1.9	0.0937	0.67 (0.42, 1.07)	0.66 (0.41, 1.08)	-0.01 (-0.02, 0.00)	
Pre-Diabetes	979	30	3.1	1001	18	1.8	0.0670	0.59 (0.33, 1.05)	0.58 (0.32, 1.05)	-0.01 (-0.03, 0.00)	
Normal (no pre-diabetes)	539	17	3.2	530	10	1.9	0.1868	0.60 (0.28, 1.29)	0.59 (0.27, 1.30)	-0.01 (-0.03, 0.01)	
Baseline BMI [kg/m²]											0.4746
<30	1641	48	2.9	1654	27	1.6	0.0129	0.56 (0.35, 0.89)	0.55 (0.34, 0.89)	-0.01 (-0.02, 0.00)	
>=30	1348	41	3.0	1342	29	2.2	0.1515	0.71 (0.44, 1.14)	0.70 (0.43, 1.14)	-0.01 (-0.02, 0.00)	
Baseline eGFR (CKD-EPI) [mL/min/1.73m²]											0.5647
>=60	1505	22	1.5	1493	16	1.1	0.3397	0.73 (0.39, 1.39)	0.73 (0.38, 1.40)	0.00 (-0.01, 0.00)	
<60	1482	67	4.5	1503	40	2.7	0.0063	0.59 (0.40, 0.87)	0.58 (0.39, 0.86)	-0.02 (-0.03,-0.01)	
History of HHF (in the last 12 months)											0.2866
No	2320	67	2.9	2297	37	1.6	0.0035	0.56 (0.37, 0.83)	0.55 (0.37, 0.83)	-0.01 (-0.02, 0.00)	
Yes	669	22	3.3	699	19	2.7	0.5363	0.83 (0.45, 1.51)	0.82 (0.44, 1.53)	-0.01 (-0.02, 0.01)	
Baseline SBP (</>= median)											0.9231
< median	1474	48	3.3	1496	31	2.1	0.0449	0.64 (0.41, 0.99)	0.63 (0.40, 0.99)	-0.01 (-0.02, 0.00)	
>= median	1515	41	2.7	1500	25	1.7	0.0511	0.62 (0.38, 1.01)	0.61 (0.37, 1.01)	-0.01 (-0.02, 0.00)	
History of atrial fibrillation or atrial flutter											0.9710
No	1426	34	2.4	1417	21	1.5	0.0807	0.62 (0.36, 1.07)	0.62 (0.36, 1.07)	-0.01 (-0.02, 0.00)	
Yes	1558	55	3.5	1575	35	2.2	0.0284	0.63 (0.41, 0.96)	0.62 (0.40, 0.95)	-0.01 (-0.02, 0.00)	

Analysis is based on study 1245.110.
^ Patients with NYHA class I are counted in subgroup NYHA class II.
Risk ratios and odds ratios with confidence intervals (CIs) are estimated by Cochran-Mantel-Haenszel method. For risk differences standard Wald asymptotic confidence limits are calculated. A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied in case of any zero cells in contingency table.
Only treatment emergent AEs are displayed (onset between first dose until treatment stop +7 days).
MedDRA version: 23.1. * Chi-square test for treatment effect ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction).

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Table R.1.2.5: 1 Proportion of patients with any adverse event occuring in at least 1% of the patients in either treatment arm in the overall population on PT level by SOC and PT, 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 LVEF [%]											0.3373
< 50	988	27	2.7	995	13	1.3	0.0239	0.48 (0.25, 0.92)	0.47 (0.24, 0.92)	-0.01 (-0.03, 0.00)	
>= 50	2001	62	3.1	2001	43	2.1	0.0602	0.69 (0.47, 1.02)	0.69 (0.46, 1.02)	-0.01 (-0.02, 0.00)	
Baseline LVEF [%]											0.6070
<50	988	27	2.7	995	13	1.3	0.0239	0.48 (0.25, 0.92)	0.47 (0.24, 0.92)	-0.01 (-0.03, 0.00)	
50 to <60	1030	33	3.2	1028	24	2.3	0.2296	0.73 (0.43, 1.22)	0.72 (0.42, 1.23)	-0.01 (-0.02, 0.01)	
>=60	971	29	3.0	973	19	2.0	0.1419	0.65 (0.37, 1.16)	0.65 (0.36, 1.16)	-0.01 (-0.02, 0.00)	
Baseline NT-proBNP [pg/mL] (</>=median by atrial fibrillation/flutter status)											0.4449
< median	1507	32	2.1	1476	23	1.6	0.2513	0.73 (0.43, 1.25)	0.73 (0.42, 1.25)	-0.01 (-0.02, 0.00)	
>= median	1475	57	3.9	1516	33	2.2	0.0069	0.56 (0.37, 0.86)	0.55 (0.36, 0.86)	-0.02 (-0.03, 0.00)	
Baseline uric acid [mg/dL] (tertiles)											0.7193
<T1	975	4	0.4	963	2	0.2	0.4222	0.51 (0.09, 2.76)	0.51 (0.09, 2.76)	0.00 (-0.01, 0.00)	
>=T1 and <T2	966	13	1.3	1032	12	1.2	0.7131	0.86 (0.40, 1.88)	0.86 (0.39, 1.90)	0.00 (-0.01, 0.01)	
>=T2	1016	71	7.0	970	42	4.3	0.0106	0.62 (0.43, 0.90)	0.60 (0.41, 0.89)	-0.03 (-0.05,-0.01)	
Baseline use of MRA											0.7690
No	1865	50	2.7	1878	33	1.8	0.0550	0.66 (0.42, 1.01)	0.65 (0.42, 1.01)	-0.01 (-0.02, 0.00)	
Yes	1124	39	3.5	1118	23	2.1	0.0414	0.59 (0.36, 0.99)	0.58 (0.35, 0.98)	-0.01 (-0.03, 0.00)	
Baseline use of ACE-inhibitor, ARB or ARNi											0.2786
No	586	27	4.6	568	12	2.1	0.0190	0.46 (0.23, 0.90)	0.45 (0.22, 0.89)	-0.02 (-0.05, 0.00)	
Yes	2403	62	2.6	2428	44	1.8	0.0685	0.70 (0.48, 1.03)	0.70 (0.47, 1.03)	-0.01 (-0.02, 0.00)	

Analysis is based on study 1245.110.
^ Patients with NYHA class I are counted in subgroup NYHA class II.
Risk ratios and odds ratios with confidence intervals (CIs) are estimated by Cochran-Mantel-Haenszel method. For risk differences standard Wald asymptotic confidence limits are calculated. A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied in case of any zero cells in contingency table.
Only treatment emergent AEs are displayed (onset between first dose until treatment stop +7 days).
MedDRA version: 23.1. * Chi-square test for treatment effect ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction).

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Table R.1.2.5: 1 Proportion of patients with any adverse event occuring in at least 1% of the patients in either treatment arm in the overall population on PT level by SOC and PT, 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	2989	67	2.2	2996	77	2.6	0.4069	1.15 (0.83, 1.58)	1.15 (0.83, 1.60)	0.00 (0.00, 0.01)	

Analysis is based on study 1245.110.
^ Patients with NYHA class I are counted in subgroup NYHA class II.
Risk ratios and odds ratios with confidence intervals (CIs) are estimated by Cochran-Mantel-Haenszel method. For risk differences standard Wald asymptotic confidence limits are calculated. A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied in case of any zero cells in contingency table.
Only treatment emergent AEs are displayed (onset between first dose until treatment stop +7 days).
MedDRA version: 23.1. * Chi-square test for treatment effect ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction).

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Table R.1.2.5: 1 Proportion of patients with any adverse event occuring in at least 1% of the patients in either treatment arm in the overall population on PT level by SOC and PT, 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	2989	48	1.6	2996	61	2.0	0.2134	1.27 (0.87, 1.84)	1.27 (0.87, 1.87)	0.00 (0.00, 0.01)	

Analysis is based on study 1245.110.
^ Patients with NYHA class I are counted in subgroup NYHA class II.
Risk ratios and odds ratios with confidence intervals (CIs) are estimated by Cochran-Mantel-Haenszel method. For risk differences standard Wald asymptotic confidence limits are calculated. A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied in case of any zero cells in contingency table.
Only treatment emergent AEs are displayed (onset between first dose until treatment stop +7 days).
MedDRA version: 23.1. * Chi-square test for treatment effect ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction).

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Table R.1.2.5: 1 Proportion of patients with any adverse event occuring in at least 1% of the patients in either treatment arm in the overall population on PT level by SOC and PT, 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	2989	43	1.4	2996	26	0.9	0.0386	0.60	(0.37, 0.98)	0.60	(0.37, 0.98)	-0.01	(-0.01, 0.00)	
Sex														0.1820
Male	1653	21	1.3	1658	17	1.0	0.5080	0.81	(0.43, 1.52)	0.81	(0.42, 1.53)	0.00	(-0.01, 0.00)	
Female	1336	22	1.6	1338	9	0.7	0.0186	0.41	(0.19, 0.88)	0.40	(0.19, 0.88)	-0.01	(-0.02, 0.00)	
Age [years]														0.1983
<70	1084	12	1.1	1066	11	1.0	0.8656	0.93	(0.41, 2.10)	0.93	(0.41, 2.12)	0.00	(-0.01, 0.01)	
>=70	1905	31	1.6	1930	15	0.8	0.0156	0.48	(0.26, 0.88)	0.47	(0.25, 0.88)	-0.01	(-0.02, 0.00)	
Region														0.9572
North America	359	4	1.1	359	3	0.8	0.7041	0.75	(0.17, 3.33)	0.75	(0.17, 3.37)	0.00	(-0.02, 0.01)	
Latin America	757	13	1.7	758	6	0.8	0.1055	0.46	(0.18, 1.21)	0.46	(0.17, 1.21)	-0.01	(-0.02, 0.00)	
Europe	1341	21	1.6	1346	13	1.0	0.1640	0.62	(0.31, 1.23)	0.61	(0.31, 1.23)	-0.01	(-0.01, 0.00)	
Asia	343	3	0.9	343	2	0.6	0.6535	0.67	(0.11, 3.96)	0.66	(0.11, 4.00)	0.00	(-0.02, 0.01)	
Other	189	2	1.1	190	2	1.1	0.9958	0.99	(0.14, 6.99)	0.99	(0.14, 7.14)	0.00	(-0.02, 0.02)	
OECD member														0.4551
No	847	15	1.8	868	7	0.8	0.0760	0.46	(0.19, 1.11)	0.45	(0.18, 1.11)	-0.01	(-0.02, 0.00)	
Yes	2142	28	1.3	2128	19	0.9	0.1945	0.68	(0.38, 1.22)	0.68	(0.38, 1.22)	0.00	(-0.01, 0.00)	
Baseline NYHA														0.9670
II^	2450	32	1.3	2435	19	0.8	0.0706	0.60	(0.34, 1.05)	0.59	(0.34, 1.05)	-0.01	(-0.01, 0.00)	
III/IV	539	11	2.0	561	7	1.2	0.3000	0.61	(0.24, 1.57)	0.61	(0.23, 1.58)	-0.01	(-0.02, 0.01)	
Baseline Diabetes Status														0.6545
Diabetic	1471	16	1.1	1465	11	0.8	0.3391	0.69	(0.32, 1.48)	0.69	(0.32, 1.49)	0.00	(-0.01, 0.00)	
Non-Diabetic	1518	27	1.8	1531	15	1.0	0.0584	0.55	(0.29, 1.03)	0.55	(0.29, 1.03)	-0.01	(-0.02, 0.00)	

Analysis is based on study 1245.110.
^ Patients with NYHA class I are counted in subgroup NYHA class II.
Risk ratios and odds ratios with confidence intervals (CIs) are estimated by Cochran-Mantel-Haenszel method. For risk differences standard Wald asymptotic confidence limits are calculated. A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied in case of any zero cells in contingency table.
Only treatment emergent AEs are displayed (onset between first dose until treatment stop +7 days).
MedDRA version: 23.1. * Chi-square test for treatment effect ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction).

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Table R.1.2.5: 1 Proportion of patients with any adverse event occuring in at least 1% of the patients in either treatment arm in the overall population on PT level by SOC and PT, 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 Diabetes Status											0.8692
Diabetic	1471	16	1.1	1465	11	0.8	0.3391	0.69 (0.32, 1.48)	0.69 (0.32, 1.49)	0.00 (-0.01, 0.00)	
Pre-Diabetes	979	24	2.5	1001	13	1.3	0.0582	0.53 (0.27, 1.03)	0.52 (0.27, 1.03)	-0.01 (-0.02, 0.00)	
Normal (no pre-diabetes)	539	3	0.6	530	2	0.4	0.6676	0.68 (0.11, 4.04)	0.68 (0.11, 4.07)	0.00 (-0.01, 0.01)	
Baseline BMI [kg/m²]											0.6011
<30	1641	27	1.6	1654	18	1.1	0.1683	0.66 (0.37, 1.20)	0.66 (0.36, 1.20)	-0.01 (-0.01, 0.00)	
>=30	1348	16	1.2	1342	8	0.6	0.1032	0.50 (0.22, 1.17)	0.50 (0.21, 1.17)	-0.01 (-0.01, 0.00)	
Baseline eGFR (CKD-EPI) [mL/min/1.73m²]											0.5237
>=60	1505	20	1.3	1493	14	0.9	0.3118	0.71 (0.36, 1.39)	0.70 (0.35, 1.40)	0.00 (-0.01, 0.00)	
<60	1482	23	1.6	1503	12	0.8	0.0558	0.51 (0.26, 1.03)	0.51 (0.25, 1.03)	-0.01 (-0.02, 0.00)	
History of HHF (in the last 12 months)											0.7428
No	2320	32	1.4	2297	20	0.9	0.1015	0.63 (0.36, 1.10)	0.63 (0.36, 1.10)	-0.01 (-0.01, 0.00)	
Yes	669	11	1.6	699	6	0.9	0.1897	0.52 (0.19, 1.40)	0.52 (0.19, 1.41)	-0.01 (-0.02, 0.00)	
Baseline SBP (</>= median)											0.3281
< median	1474	21	1.4	1496	16	1.1	0.3829	0.75 (0.39, 1.43)	0.75 (0.39, 1.44)	0.00 (-0.01, 0.00)	
>= median	1515	22	1.5	1500	10	0.7	0.0353	0.46 (0.22, 0.97)	0.46 (0.21, 0.97)	-0.01 (-0.02, 0.00)	
History of atrial fibrillation or atrial flutter											0.9918
No	1426	15	1.1	1417	9	0.6	0.2246	0.60 (0.27, 1.38)	0.60 (0.26, 1.38)	0.00 (-0.01, 0.00)	
Yes	1558	28	1.8	1575	17	1.1	0.0913	0.60 (0.33, 1.09)	0.60 (0.33, 1.09)	-0.01 (-0.02, 0.00)	

Analysis is based on study 1245.110.
^ Patients with NYHA class I are counted in subgroup NYHA class II.
Risk ratios and odds ratios with confidence intervals (CIs) are estimated by Cochran-Mantel-Haenszel method. For risk differences standard Wald asymptotic confidence limits are calculated. A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied in case of any zero cells in contingency table.
Only treatment emergent AEs are displayed (onset between first dose until treatment stop +7 days).
MedDRA version: 23.1. * Chi-square test for treatment effect ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction).

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Table R.1.2.5: 1 Proportion of patients with any adverse event occuring in at least 1% of the patients in either treatment arm in the overall population on PT level by SOC and PT, 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 LVEF [%]											0.5392
< 50	988	18	1.8	995	9	0.9	0.0780	0.50 (0.22, 1.10)	0.49 (0.22, 1.10)	-0.01 (-0.02, 0.00)	
>= 50	2001	25	1.2	2001	17	0.8	0.2146	0.68 (0.37, 1.26)	0.68 (0.36, 1.26)	0.00 (-0.01, 0.00)	
Baseline LVEF [%]											0.0685
<50	988	18	1.8	995	9	0.9	0.0780	0.50 (0.22, 1.10)	0.49 (0.22, 1.10)	-0.01 (-0.02, 0.00)	
50 to <60	1030	19	1.8	1028	7	0.7	0.0181	0.37 (0.16, 0.87)	0.36 (0.15, 0.87)	-0.01 (-0.02, 0.00)	
>=60	971	6	0.6	973	10	1.0	0.3173	1.66 (0.61, 4.56)	1.67 (0.60, 4.61)	0.00 (0.00, 0.01)	
Baseline NT-proBNP [pg/mL] (</>=median by atrial fibrillation/flutter status)											0.3798
< median	1507	19	1.3	1476	14	0.9	0.4149	0.75 (0.38, 1.49)	0.75 (0.37, 1.50)	0.00 (-0.01, 0.00)	
>= median	1475	24	1.6	1516	12	0.8	0.0362	0.49 (0.24, 0.97)	0.48 (0.24, 0.97)	-0.01 (-0.02, 0.00)	
Baseline uric acid [mg/dL] (tertiles)											0.9999
<T1	975	10	1.0	963	6	0.6	0.3274	0.61 (0.22, 1.66)	0.61 (0.22, 1.67)	0.00 (-0.01, 0.00)	
>=T1 and <T2	966	14	1.4	1032	9	0.9	0.2268	0.60 (0.26, 1.38)	0.60 (0.26, 1.39)	-0.01 (-0.02, 0.00)	
>=T2	1016	19	1.9	970	11	1.1	0.1789	0.61 (0.29, 1.27)	0.60 (0.28, 1.27)	-0.01 (-0.02, 0.00)	
Baseline use of MRA											0.6670
No	1865	22	1.2	1878	12	0.6	0.0813	0.54 (0.27, 1.09)	0.54 (0.27, 1.09)	-0.01 (-0.01, 0.00)	
Yes	1124	21	1.9	1118	14	1.3	0.2394	0.67 (0.34, 1.31)	0.67 (0.34, 1.32)	-0.01 (-0.02, 0.00)	
Baseline use of ACE-inhibitor, ARB or ARNi											0.3383
No	586	7	1.2	568	2	0.4	0.1039	0.29 (0.06, 1.41)	0.29 (0.06, 1.41)	-0.01 (-0.02, 0.00)	
Yes	2403	36	1.5	2428	24	1.0	0.1098	0.66 (0.39, 1.10)	0.66 (0.39, 1.10)	-0.01 (-0.01, 0.00)	

Analysis is based on study 1245.110.
^ Patients with NYHA class I are counted in subgroup NYHA class II.
Risk ratios and odds ratios with confidence intervals (CIs) are estimated by Cochran-Mantel-Haenszel method. For risk differences standard Wald asymptotic confidence limits are calculated. A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied in case of any zero cells in contingency table.
Only treatment emergent AEs are displayed (onset between first dose until treatment stop +7 days).
MedDRA version: 23.1. * Chi-square test for treatment effect ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction).

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Table R.1.2.5: 1 Proportion of patients with any adverse event occuring in at least 1% of the patients in either treatment arm in the overall population on PT level by SOC and PT, 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	2989	36	1.2	2996	20	0.7	0.0310	0.55 (0.32, 0.96)	0.55 (0.32, 0.95)	-0.01 (-0.01, 0.00)	
Sex											0.7167
Male	1653	18	1.1	1658	9	0.5	0.0806	0.50 (0.22, 1.11)	0.50 (0.22, 1.11)	-0.01 (-0.01, 0.00)	
Female	1336	18	1.3	1338	11	0.8	0.1898	0.61 (0.29, 1.29)	0.61 (0.29, 1.29)	-0.01 (-0.01, 0.00)	
Age [years]											0.5421
<70	1084	8	0.7	1066	3	0.3	0.1379	0.38 (0.10, 1.43)	0.38 (0.10, 1.43)	0.00 (-0.01, 0.00)	
>=70	1905	28	1.5	1930	17	0.9	0.0904	0.60 (0.33, 1.09)	0.60 (0.32, 1.09)	-0.01 (-0.01, 0.00)	
Region											0.2587
North America	359	5	1.4	359	4	1.1	0.7373	0.80 (0.22, 2.95)	0.80 (0.21, 3.00)	0.00 (-0.02, 0.01)	
Latin America	757	7	0.9	758	3	0.4	0.2037	0.43 (0.11, 1.65)	0.43 (0.11, 1.65)	-0.01 (-0.01, 0.00)	
Europe	1341	10	0.7	1346	5	0.4	0.1930	0.50 (0.17, 1.45)	0.50 (0.17, 1.46)	0.00 (-0.01, 0.00)	
Asia	343	12	3.5	343	3	0.9	0.0188	0.25 (0.07, 0.88)	0.24 (0.07, 0.87)	-0.03 (-0.05, 0.00)	
Other	189	2	1.1	190	5	2.6	0.2553	2.49 (0.49, 12.66)	2.53 (0.48, 13.19)	0.02 (-0.01, 0.04)	
OECD member											0.2653
No	847	9	1.1	868	8	0.9	0.7684	0.87 (0.34, 2.24)	0.87 (0.33, 2.26)	0.00 (-0.01, 0.01)	
Yes	2142	27	1.3	2128	12	0.6	0.0167	0.45 (0.23, 0.88)	0.44 (0.22, 0.88)	-0.01 (-0.01, 0.00)	
Baseline NYHA											0.6361
II^	2450	31	1.3	2435	18	0.7	0.0650	0.58 (0.33, 1.04)	0.58 (0.32, 1.04)	-0.01 (-0.01, 0.00)	
III/IV	539	5	0.9	561	2	0.4	0.2337	0.38 (0.07, 1.97)	0.38 (0.07, 1.98)	-0.01 (-0.02, 0.00)	
Baseline Diabetes Status											0.5317
Diabetic	1471	15	1.0	1465	10	0.7	0.3202	0.67 (0.30, 1.49)	0.67 (0.30, 1.49)	0.00 (-0.01, 0.00)	
Non-Diabetic	1518	21	1.4	1531	10	0.7	0.0445	0.47 (0.22, 1.00)	0.47 (0.22, 1.00)	-0.01 (-0.01, 0.00)	

Analysis is based on study 1245.110.
^ Patients with NYHA class I are counted in subgroup NYHA class II.
Risk ratios and odds ratios with confidence intervals (CIs) are estimated by Cochran-Mantel-Haenszel method. For risk differences standard Wald asymptotic confidence limits are calculated. A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied in case of any zero cells in contingency table.
Only treatment emergent AEs are displayed (onset between first dose until treatment stop +7 days).
MedDRA version: 23.1. * Chi-square test for treatment effect ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction).

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Table R.1.2.5: 1 Proportion of patients with any adverse event occuring in at least 1% of the patients in either treatment arm in the overall population on PT level by SOC and PT, 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 **
Baseline Diabetes Status											0.1970
Diabetic	1471	15	1.0	1465	10	0.7	0.3202	0.67 (0.30, 1.49)	0.67 (0.30, 1.49)	0.00 (-0.01, 0.00)	
Pre-Diabetes	979	12	1.2	1001	10	1.0	0.6304	0.82 (0.35, 1.88)	0.81 (0.35, 1.89)	0.00 (-0.01, 0.01)	
Normal (no pre-diabetes)	539	9	1.7	530	0	0	0.0046	0.05 (<0.01, 0.92)	0.05 (<0.01, 0.91)	-0.02 (-0.03,-0.01)	
Baseline BMI [kg/m²]											0.4157
<30	1641	27	1.6	1654	13	0.8	0.0243	0.48 (0.25, 0.92)	0.47 (0.24, 0.92)	-0.01 (-0.02, 0.00)	
>=30	1348	9	0.7	1342	7	0.5	0.6223	0.78 (0.29, 2.09)	0.78 (0.29, 2.10)	0.00 (-0.01, 0.00)	
Baseline eGFR (CKD-EPI) [mL/min/1.73m²]											0.6289
>=60	1505	17	1.1	1493	8	0.5	0.0739	0.47 (0.21, 1.10)	0.47 (0.20, 1.10)	-0.01 (-0.01, 0.00)	
<60	1482	19	1.3	1503	12	0.8	0.1925	0.62 (0.30, 1.28)	0.62 (0.30, 1.28)	0.00 (-0.01, 0.00)	
History of HHF (in the last 12 months)											0.7286
No	2320	24	1.0	2297	14	0.6	0.1100	0.59 (0.31, 1.14)	0.59 (0.30, 1.14)	0.00 (-0.01, 0.00)	
Yes	669	12	1.8	699	6	0.9	0.1291	0.48 (0.18, 1.27)	0.47 (0.18, 1.27)	-0.01 (-0.02, 0.00)	
Baseline SBP (</>= median)											0.7395
< median	1474	23	1.6	1496	12	0.8	0.0556	0.51 (0.26, 1.03)	0.51 (0.25, 1.03)	-0.01 (-0.02, 0.00)	
>= median	1515	13	0.9	1500	8	0.5	0.2837	0.62 (0.26, 1.50)	0.62 (0.26, 1.50)	0.00 (-0.01, 0.00)	
History of atrial fibrillation or atrial flutter											0.5531
No	1426	10	0.7	1417	7	0.5	0.4736	0.70 (0.27, 1.85)	0.70 (0.27, 1.85)	0.00 (-0.01, 0.00)	
Yes	1558	26	1.7	1575	13	0.8	0.0333	0.49 (0.26, 0.96)	0.49 (0.25, 0.96)	-0.01 (-0.02, 0.00)	

Analysis is based on study 1245.110.
^ Patients with NYHA class I are counted in subgroup NYHA class II.
Risk ratios and odds ratios with confidence intervals (CIs) are estimated by Cochran-Mantel-Haenszel method. For risk differences standard Wald asymptotic confidence limits are calculated. A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied in case of any zero cells in contingency table.
Only treatment emergent AEs are displayed (onset between first dose until treatment stop +7 days).
MedDRA version: 23.1. * Chi-square test for treatment effect ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction).

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Table R.1.2.5: 1 Proportion of patients with any adverse event occuring in at least 1% of the patients in either treatment arm in the overall population on PT level by SOC and PT, 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 **
Baseline LVEF [%]											0.6345
< 50	988	7	0.7	995	5	0.5	0.5543	0.71 (0.23, 2.23)	0.71 (0.22, 2.24)	0.00 (-0.01, 0.00)	
>= 50	2001	29	1.4	2001	15	0.7	0.0338	0.52 (0.28, 0.96)	0.51 (0.27, 0.96)	-0.01 (-0.01, 0.00)	
Baseline LVEF [%]											0.8842
<50	988	7	0.7	995	5	0.5	0.5543	0.71 (0.23, 2.23)	0.71 (0.22, 2.24)	0.00 (-0.01, 0.00)	
50 to <60	1030	11	1.1	1028	6	0.6	0.2249	0.55 (0.20, 1.47)	0.54 (0.20, 1.48)	0.00 (-0.01, 0.00)	
>=60	971	18	1.9	973	9	0.9	0.0802	0.50 (0.23, 1.11)	0.49 (0.22, 1.11)	-0.01 (-0.02, 0.00)	
Baseline NT-proBNP [pg/mL] (</>=median by atrial fibrillation/flutter status)											0.1916
< median	1507	12	0.8	1476	10	0.7	0.7046	0.85 (0.37, 1.96)	0.85 (0.37, 1.97)	0.00 (-0.01, 0.00)	
>= median	1475	24	1.6	1516	10	0.7	0.0126	0.41 (0.19, 0.84)	0.40 (0.19, 0.84)	-0.01 (-0.02, 0.00)	
Baseline uric acid [mg/dL] (tertiles)											0.2115
<T1	975	5	0.5	963	5	0.5	0.9843	1.01 (0.29, 3.49)	1.01 (0.29, 3.51)	0.00 (-0.01, 0.01)	
>=T1 and <T2	966	15	1.6	1032	4	0.4	0.0073	0.25 (0.08, 0.75)	0.25 (0.08, 0.75)	-0.01 (-0.02, 0.00)	
>=T2	1016	16	1.6	970	10	1.0	0.2865	0.65 (0.30, 1.44)	0.65 (0.29, 1.44)	-0.01 (-0.02, 0.00)	
Baseline use of MRA											0.3872
No	1865	19	1.0	1878	13	0.7	0.2779	0.68 (0.34, 1.37)	0.68 (0.33, 1.38)	0.00 (-0.01, 0.00)	
Yes	1124	17	1.5	1118	7	0.6	0.0414	0.41 (0.17, 0.99)	0.41 (0.17, 0.99)	-0.01 (-0.02, 0.00)	
Baseline use of ACE-inhibitor, ARB or ARNi											0.9904
No	586	13	2.2	568	7	1.2	0.1994	0.56 (0.22, 1.38)	0.55 (0.22, 1.39)	-0.01 (-0.02, 0.01)	
Yes	2403	23	1.0	2428	13	0.5	0.0884	0.56 (0.28, 1.10)	0.56 (0.28, 1.10)	0.00 (-0.01, 0.00)	

Analysis is based on study 1245.110.
^ Patients with NYHA class I are counted in subgroup NYHA class II.
Risk ratios and odds ratios with confidence intervals (CIs) are estimated by Cochran-Mantel-Haenszel method. For risk differences standard Wald asymptotic confidence limits are calculated. A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied in case of any zero cells in contingency table.
Only treatment emergent AEs are displayed (onset between first dose until treatment stop +7 days).
MedDRA version: 23.1. * Chi-square test for treatment effect ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction).

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Table R.1.2.5: 1 Proportion of patients with any adverse event occuring in at least 1% of the patients in either treatment arm in the overall population on PT level by SOC and PT, 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	2989	36	1.2	2996	33	1.1	0.7091	0.91 (0.57, 1.46)	0.91 (0.57, 1.47)	0.00 (-0.01, 0.00)	

Analysis is based on study 1245.110.
^ Patients with NYHA class I are counted in subgroup NYHA class II.
Risk ratios and odds ratios with confidence intervals (CIs) are estimated by Cochran-Mantel-Haenszel method. For risk differences standard Wald asymptotic confidence limits are calculated. A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied in case of any zero cells in contingency table.
Only treatment emergent AEs are displayed (onset between first dose until treatment stop +7 days).
MedDRA version: 23.1. * Chi-square test for treatment effect ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction).

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Table R.1.2.5: 1 Proportion of patients with any adverse event occuring in at least 1% of the patients in either treatment arm in the overall population on PT level by SOC and PT, 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	2989	35	1.2	2996	26	0.9	0.2430	0.74 (0.45, 1.23)	0.74 (0.44, 1.23)	0.00 (-0.01, 0.00)	

Analysis is based on study 1245.110.
^ Patients with NYHA class I are counted in subgroup NYHA class II.
Risk ratios and odds ratios with confidence intervals (CIs) are estimated by Cochran-Mantel-Haenszel method. For risk differences standard Wald asymptotic confidence limits are calculated. A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied in case of any zero cells in contingency table.
Only treatment emergent AEs are displayed (onset between first dose until treatment stop +7 days).
MedDRA version: 23.1. * Chi-square test for treatment effect ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction).

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Table R.1.2.5: 1 Proportion of patients with any adverse event occuring in at least 1% of the patients in either treatment arm in the overall population on PT level by SOC and PT, 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	2989	29	1.0	2996	35	1.2	0.4565	1.20 (0.74, 1.96)	1.21 (0.74, 1.98)	0.00 (0.00, 0.01)	

Analysis is based on study 1245.110.
^ Patients with NYHA class I are counted in subgroup NYHA class II.
Risk ratios and odds ratios with confidence intervals (CIs) are estimated by Cochran-Mantel-Haenszel method. For risk differences standard Wald asymptotic confidence limits are calculated. A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied in case of any zero cells in contingency table.
Only treatment emergent AEs are displayed (onset between first dose until treatment stop +7 days).
MedDRA version: 23.1. * Chi-square test for treatment effect ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction).

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Table R.1.2.5: 1 Proportion of patients with any adverse event occuring in at least 1% of the patients in either treatment arm in the overall population on PT level by SOC and PT, 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	2989	32	1.1	2996	8	0.3	0.0001	0.25 (0.12, 0.54)	0.25 (0.11, 0.54)	-0.01 (-0.01, 0.00)	
Sex											0.5269
Male	1653	16	1.0	1658	3	0.2	0.0027	0.19 (0.05, 0.64)	0.19 (0.05, 0.64)	-0.01 (-0.01, 0.00)	
Female	1336	16	1.2	1338	5	0.4	0.0158	0.31 (0.11, 0.85)	0.31 (0.11, 0.85)	-0.01 (-0.01, 0.00)	
Age [years]											0.4595
<70	1084	8	0.7	1066	3	0.3	0.1379	0.38 (0.10, 1.43)	0.38 (0.10, 1.43)	0.00 (-0.01, 0.00)	
>=70	1905	24	1.3	1930	5	0.3	0.0003	0.21 (0.08, 0.54)	0.20 (0.08, 0.53)	-0.01 (-0.02, 0.00)	
Region											0.6449
North America	359	9	2.5	359	1	0.3	0.0108	0.11 (0.01, 0.87)	0.11 (0.01, 0.86)	-0.02 (-0.04,-0.01)	
Latin America	757	7	0.9	758	1	0.1	0.0333	0.14 (0.02, 1.16)	0.14 (0.02, 1.15)	-0.01 (-0.02, 0.00)	
Europe	1341	13	1.0	1346	4	0.3	0.0280	0.31 (0.10, 0.94)	0.30 (0.10, 0.94)	-0.01 (-0.01, 0.00)	
Asia	343	0	0	343	0	0	1.0000	1.00 (0.02, 50.25)	1.00 (0.02, 50.54)	0.00 (-0.01, 0.01)	
Other	189	3	1.6	190	2	1.1	0.6483	0.66 (0.11, 3.92)	0.66 (0.11, 3.99)	-0.01 (-0.03, 0.02)	
OECD member											0.0866
No	847	9	1.1	868	5	0.6	0.2629	0.54 (0.18, 1.61)	0.54 (0.18, 1.62)	0.00 (-0.01, 0.00)	
Yes	2142	23	1.1	2128	3	0.1	<0.0001	0.13 (0.04, 0.44)	0.13 (0.04, 0.43)	-0.01 (-0.01, 0.00)	
Baseline NYHA											0.9548
II^	2450	20	0.8	2435	5	0.2	0.0028	0.25 (0.09, 0.67)	0.25 (0.09, 0.67)	-0.01 (-0.01, 0.00)	
III/IV	539	12	2.2	561	3	0.5	0.0156	0.24 (0.07, 0.85)	0.24 (0.07, 0.84)	-0.02 (-0.03, 0.00)	
Baseline Diabetes Status											0.1844
Diabetic	1471	27	1.8	1465	5	0.3	<0.0001	0.19 (0.07, 0.48)	0.18 (0.07, 0.48)	-0.01 (-0.02,-0.01)	
Non-Diabetic	1518	5	0.3	1531	3	0.2	0.4715	0.59 (0.14, 2.48)	0.59 (0.14, 2.49)	0.00 (0.00, 0.00)	

Analysis is based on study 1245.110.
^ Patients with NYHA class I are counted in subgroup NYHA class II.
Risk ratios and odds ratios with confidence intervals (CIs) are estimated by Cochran-Mantel-Haenszel method. For risk differences standard Wald asymptotic confidence limits are calculated. A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied in case of any zero cells in contingency table.
Only treatment emergent AEs are displayed (onset between first dose until treatment stop +7 days).
MedDRA version: 23.1. * Chi-square test for treatment effect ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction).

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Table R.1.2.5: 1 Proportion of patients with any adverse event occuring in at least 1% of the patients in either treatment arm in the overall population on PT level by SOC and PT, 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 Diabetes Status											0.2025
Diabetic	1471	27	1.8	1465	5	0.3	<0.0001	0.19 (0.07, 0.48)	0.18 (0.07, 0.48)	-0.01 (-0.02,-0.01)	
Pre-Diabetes	979	1	0.1	1001	2	0.2	0.5765	1.96 (0.18, 21.54)	1.96 (0.18, 21.63)	0.00 (0.00, 0.00)	
Normal (no pre-diabetes)	539	4	0.7	530	1	0.2	0.1849	0.25 (0.03, 2.27)	0.25 (0.03, 2.27)	-0.01 (-0.01, 0.00)	
Baseline BMI [kg/m²]											0.9875
<30	1641	16	1.0	1654	4	0.2	0.0067	0.25 (0.08, 0.74)	0.25 (0.08, 0.74)	-0.01 (-0.01, 0.00)	
>=30	1348	16	1.2	1342	4	0.3	0.0073	0.25 (0.08, 0.75)	0.25 (0.08, 0.75)	-0.01 (-0.02, 0.00)	
Baseline eGFR (CKD-EPI) [mL/min/1.73m²]											0.7488
>=60	1505	10	0.7	1493	2	0.1	0.0214	0.20 (0.04, 0.92)	0.20 (0.04, 0.92)	-0.01 (-0.01, 0.00)	
<60	1482	22	1.5	1503	6	0.4	0.0021	0.27 (0.11, 0.66)	0.27 (0.11, 0.66)	-0.01 (-0.02, 0.00)	
History of HHF (in the last 12 months)											0.0566
No	2320	27	1.2	2297	4	0.2	<0.0001	0.15 (0.05, 0.43)	0.15 (0.05, 0.42)	-0.01 (-0.01,-0.01)	
Yes	669	5	0.7	699	4	0.6	0.6888	0.77 (0.21, 2.84)	0.76 (0.20, 2.86)	0.00 (-0.01, 0.01)	
Baseline SBP (</>= median)											0.6559
< median	1474	17	1.2	1496	5	0.3	0.0092	0.29 (0.11, 0.78)	0.29 (0.11, 0.78)	-0.01 (-0.01, 0.00)	
>= median	1515	15	1.0	1500	3	0.2	0.0049	0.20 (0.06, 0.70)	0.20 (0.06, 0.69)	-0.01 (-0.01, 0.00)	
History of atrial fibrillation or atrial flutter											0.5421
No	1426	16	1.1	1417	3	0.2	0.0029	0.19 (0.06, 0.65)	0.19 (0.05, 0.64)	-0.01 (-0.02, 0.00)	
Yes	1558	16	1.0	1575	5	0.3	0.0150	0.31 (0.11, 0.84)	0.31 (0.11, 0.84)	-0.01 (-0.01, 0.00)	

Analysis is based on study 1245.110.
^ Patients with NYHA class I are counted in subgroup NYHA class II.
Risk ratios and odds ratios with confidence intervals (CIs) are estimated by Cochran-Mantel-Haenszel method. For risk differences standard Wald asymptotic confidence limits are calculated. A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied in case of any zero cells in contingency table.
Only treatment emergent AEs are displayed (onset between first dose until treatment stop +7 days).
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Table R.1.2.5: 1 Proportion of patients with any adverse event occuring in at least 1% of the patients in either treatment arm in the overall population on PT level by SOC and PT, 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 LVEF [%]											0.8532
< 50	988	9	0.9	995	2	0.2	0.0333	0.22 (0.05, 1.02)	0.22 (0.05, 1.02)	-0.01 (-0.01, 0.00)	
>= 50	2001	23	1.1	2001	6	0.3	0.0015	0.26 (0.11, 0.64)	0.26 (0.11, 0.64)	-0.01 (-0.01, 0.00)	
Baseline LVEF [%]											0.8883
<50	988	9	0.9	995	2	0.2	0.0333	0.22 (0.05, 1.02)	0.22 (0.05, 1.02)	-0.01 (-0.01, 0.00)	
50 to <60	1030	10	1.0	1028	2	0.2	0.0207	0.20 (0.04, 0.91)	0.20 (0.04, 0.91)	-0.01 (-0.01, 0.00)	
>=60	971	13	1.3	973	4	0.4	0.0280	0.31 (0.10, 0.94)	0.30 (0.10, 0.94)	-0.01 (-0.02, 0.00)	
Baseline NT-proBNP [pg/mL] (</>=median by atrial fibrillation/flutter status)											0.3558
< median	1507	22	1.5	1476	4	0.3	0.0005	0.19 (0.06, 0.54)	0.18 (0.06, 0.53)	-0.01 (-0.02,-0.01)	
>= median	1475	10	0.7	1516	4	0.3	0.0971	0.39 (0.12, 1.24)	0.39 (0.12, 1.24)	0.00 (-0.01, 0.00)	
Baseline uric acid [mg/dL] (tertiles)											0.5658
<T1	975	6	0.6	963	2	0.2	0.1616	0.34 (0.07, 1.67)	0.34 (0.07, 1.67)	0.00 (-0.01, 0.00)	
>=T1 and <T2	966	14	1.4	1032	2	0.2	0.0017	0.13 (0.03, 0.59)	0.13 (0.03, 0.58)	-0.01 (-0.02, 0.00)	
>=T2	1016	12	1.2	970	4	0.4	0.0554	0.35 (0.11, 1.08)	0.35 (0.11, 1.08)	-0.01 (-0.02, 0.00)	
Baseline use of MRA											0.6448
No	1865	17	0.9	1878	5	0.3	0.0098	0.29 (0.11, 0.79)	0.29 (0.11, 0.79)	-0.01 (-0.01, 0.00)	
Yes	1124	15	1.3	1118	3	0.3	0.0047	0.20 (0.06, 0.69)	0.20 (0.06, 0.69)	-0.01 (-0.02, 0.00)	
Baseline use of ACE-inhibitor, ARB or ARNi											0.1105
No	586	7	1.2	568	4	0.7	0.3914	0.59 (0.17, 2.00)	0.59 (0.17, 2.01)	0.00 (-0.02, 0.01)	
Yes	2403	25	1.0	2428	4	0.2	<0.0001	0.16 (0.06, 0.45)	0.16 (0.05, 0.45)	-0.01 (-0.01, 0.00)	

Analysis is based on study 1245.110.
^ Patients with NYHA class I are counted in subgroup NYHA class II.
Risk ratios and odds ratios with confidence intervals (CIs) are estimated by Cochran-Mantel-Haenszel method. For risk differences standard Wald asymptotic confidence limits are calculated. A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied in case of any zero cells in contingency table.
Only treatment emergent AEs are displayed (onset between first dose until treatment stop +7 days).
MedDRA version: 23.1. * Chi-square test for treatment effect ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction).

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Table R.1.2.5: 1 Proportion of patients with any adverse event occuring in at least 1% of the patients in either treatment arm in the overall population on PT level by SOC and PT, 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	2989	256	8.6	2996	220	7.3	0.0807	0.86 (0.72, 1.02)	0.85 (0.70, 1.02)	-0.01 (-0.03, 0.00)	

Analysis is based on study 1245.110.
^ Patients with NYHA class I are counted in subgroup NYHA class II.
Risk ratios and odds ratios with confidence intervals (CIs) are estimated by Cochran-Mantel-Haenszel method. For risk differences standard Wald asymptotic confidence limits are calculated. A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied in case of any zero cells in contingency table.
Only treatment emergent AEs are displayed (onset between first dose until treatment stop +7 days).
MedDRA version: 23.1. * Chi-square test for treatment effect ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction).

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Table R.1.2.5: 1 Proportion of patients with any adverse event occuring in at least 1% of the patients in either treatment arm in the overall population on PT level by SOC and PT, 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	2989	188	6.3	2996	232	7.7	0.0277	1.23 (1.02, 1.48)	1.25 (1.02, 1.53)	0.01 (0.00, 0.03)	
Sex											0.1356
Male	1653	112	6.8	1658	122	7.4	0.5130	1.09 (0.85, 1.39)	1.09 (0.84, 1.43)	0.01 (-0.01, 0.02)	
Female	1336	76	5.7	1338	110	8.2	0.0101	1.45 (1.09, 1.92)	1.49 (1.10, 2.01)	0.03 (0.01, 0.04)	
Age [years]											0.1245
<70	1084	44	4.1	1066	68	6.4	0.0155	1.57 (1.09, 2.27)	1.61 (1.09, 2.38)	0.02 (0.00, 0.04)	
>=70	1905	144	7.6	1930	164	8.5	0.2850	1.12 (0.91, 1.39)	1.14 (0.90, 1.43)	0.01 (-0.01, 0.03)	
Region											0.1162
North America	359	30	8.4	359	45	12.5	0.0672	1.50 (0.97, 2.32)	1.57 (0.97, 2.56)	0.04 (0.00, 0.09)	
Latin America	757	41	5.4	758	53	7.0	0.2036	1.29 (0.87, 1.92)	1.31 (0.86, 2.00)	0.02 (-0.01, 0.04)	
Europe	1341	91	6.8	1346	90	6.7	0.9181	0.99 (0.74, 1.31)	0.98 (0.73, 1.33)	0.00 (-0.02, 0.02)	
Asia	343	17	5.0	343	20	5.8	0.6121	1.18 (0.63, 2.21)	1.19 (0.61, 2.31)	0.01 (-0.03, 0.04)	
Other	189	9	4.8	190	24	12.6	0.0066	2.65 (1.27, 5.56)	2.89 (1.31, 6.40)	0.08 (0.02, 0.13)	
OECD member											0.1637
No	847	43	5.1	868	68	7.8	0.0203	1.54 (1.07, 2.23)	1.59 (1.07, 2.36)	0.03 (0.00, 0.05)	
Yes	2142	145	6.8	2128	164	7.7	0.2372	1.14 (0.92, 1.41)	1.15 (0.91, 1.45)	0.01 (-0.01, 0.02)	
Baseline NYHA											0.1005
II^	2450	148	6.0	2435	165	6.8	0.2940	1.12 (0.91, 1.39)	1.13 (0.90, 1.42)	0.01 (-0.01, 0.02)	
III/IV	539	40	7.4	561	67	11.9	0.0114	1.61 (1.11, 2.34)	1.69 (1.12, 2.55)	0.05 (0.01, 0.08)	
Baseline Diabetes Status											0.2904
Diabetic	1471	91	6.2	1465	100	6.8	0.4822	1.10 (0.84, 1.45)	1.11 (0.83, 1.49)	0.01 (-0.01, 0.02)	
Non-Diabetic	1518	97	6.4	1531	132	8.6	0.0194	1.35 (1.05, 1.74)	1.38 (1.05, 1.81)	0.02 (0.00, 0.04)	

Analysis is based on study 1245.110.
^ Patients with NYHA class I are counted in subgroup NYHA class II.
Risk ratios and odds ratios with confidence intervals (CIs) are estimated by Cochran-Mantel-Haenszel method. For risk differences standard Wald asymptotic confidence limits are calculated. A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied in case of any zero cells in contingency table.
Only treatment emergent AEs are displayed (onset between first dose until treatment stop +7 days).
MedDRA version: 23.1. * Chi-square test for treatment effect ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction).

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Table R.1.2.5: 1 Proportion of patients with any adverse event occuring in at least 1% of the patients in either treatment arm in the overall population on PT level by SOC and PT, 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 Diabetes Status											0.5439
Diabetic	1471	91	6.2	1465	100	6.8	0.4822	1.10 (0.84, 1.45)	1.11 (0.83, 1.49)	0.01 (-0.01, 0.02)	
Pre-Diabetes	979	59	6.0	1001	84	8.4	0.0421	1.39 (1.01, 1.92)	1.43 (1.01, 2.02)	0.02 (0.00, 0.05)	
Normal (no pre-diabetes)	539	38	7.1	530	48	9.1	0.2278	1.28 (0.85, 1.93)	1.31 (0.84, 2.05)	0.02 (-0.01, 0.05)	
Baseline BMI [kg/m²]											0.6066
<30	1641	98	6.0	1654	116	7.0	0.2252	1.17 (0.91, 1.52)	1.19 (0.90, 1.57)	0.01 (-0.01, 0.03)	
>=30	1348	90	6.7	1342	116	8.6	0.0551	1.29 (0.99, 1.69)	1.32 (0.99, 1.76)	0.02 (0.00, 0.04)	
Baseline eGFR (CKD-EPI) [mL/min/1.73m²]											0.0312
>=60	1505	88	5.8	1493	84	5.6	0.7948	0.96 (0.72, 1.29)	0.96 (0.71, 1.31)	0.00 (-0.02, 0.01)	
<60	1482	100	6.7	1503	148	9.8	0.0022	1.46 (1.14, 1.86)	1.51 (1.16, 1.97)	0.03 (0.01, 0.05)	
History of HHF (in the last 12 months)											0.7065
No	2320	148	6.4	2297	177	7.7	0.0781	1.21 (0.98, 1.49)	1.23 (0.98, 1.54)	0.01 (0.00, 0.03)	
Yes	669	40	6.0	699	55	7.9	0.1694	1.32 (0.89, 1.95)	1.34 (0.88, 2.05)	0.02 (-0.01, 0.05)	
Baseline SBP (</>= median)											0.8063
< median	1474	111	7.5	1496	141	9.4	0.0639	1.25 (0.99, 1.59)	1.28 (0.99, 1.66)	0.02 (0.00, 0.04)	
>= median	1515	77	5.1	1500	91	6.1	0.2388	1.19 (0.89, 1.60)	1.21 (0.88, 1.65)	0.01 (-0.01, 0.03)	
History of atrial fibrillation or atrial flutter											0.0442
No	1426	60	4.2	1417	95	6.7	0.0034	1.59 (1.16, 2.18)	1.64 (1.17, 2.28)	0.02 (0.01, 0.04)	
Yes	1558	127	8.2	1575	137	8.7	0.5816	1.07 (0.85, 1.34)	1.07 (0.83, 1.38)	0.01 (-0.01, 0.02)	

Analysis is based on study 1245.110.
^ Patients with NYHA class I are counted in subgroup NYHA class II.
Risk ratios and odds ratios with confidence intervals (CIs) are estimated by Cochran-Mantel-Haenszel method. For risk differences standard Wald asymptotic confidence limits are calculated. A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied in case of any zero cells in contingency table.
Only treatment emergent AEs are displayed (onset between first dose until treatment stop +7 days).
MedDRA version: 23.1. * Chi-square test for treatment effect ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction).

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Table R.1.2.5: 1 Proportion of patients with any adverse event occuring in at least 1% of the patients in either treatment arm in the overall population on PT level by SOC and PT, 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 LVEF [%]											0.2665
< 50	988	46	4.7	995	68	6.8	0.0372	1.47 (1.02, 2.11)	1.50 (1.02, 2.21)	0.02 (0.00, 0.04)	
>= 50	2001	142	7.1	2001	164	8.2	0.1906	1.15 (0.93, 1.43)	1.17 (0.93, 1.48)	0.01 (-0.01, 0.03)	
Baseline LVEF [%]											0.0282
<50	988	46	4.7	995	68	6.8	0.0372	1.47 (1.02, 2.11)	1.50 (1.02, 2.21)	0.02 (0.00, 0.04)	
50 to <60	1030	90	8.7	1028	82	8.0	0.5327	0.91 (0.69, 1.22)	0.91 (0.66, 1.24)	-0.01 (-0.03, 0.02)	
>=60	971	52	5.4	973	82	8.4	0.0075	1.57 (1.12, 2.20)	1.63 (1.14, 2.33)	0.03 (0.01, 0.05)	
Baseline NT-proBNP [pg/mL] (</>=median by atrial fibrillation/flutter status)											0.5203
< median	1507	95	6.3	1476	108	7.3	0.2719	1.16 (0.89, 1.51)	1.17 (0.88, 1.56)	0.01 (-0.01, 0.03)	
>= median	1475	92	6.2	1516	124	8.2	0.0402	1.31 (1.01, 1.70)	1.34 (1.01, 1.77)	0.02 (0.00, 0.04)	
Baseline uric acid [mg/dL] (tertiles)											0.9483
<T1	975	43	4.4	963	56	5.8	0.1602	1.32 (0.90, 1.94)	1.34 (0.89, 2.01)	0.01 (-0.01, 0.03)	
>=T1 and <T2	966	58	6.0	1032	76	7.4	0.2245	1.23 (0.88, 1.71)	1.24 (0.87, 1.77)	0.01 (-0.01, 0.04)	
>=T2	1016	83	8.2	970	97	10.0	0.1555	1.22 (0.93, 1.62)	1.25 (0.92, 1.70)	0.02 (-0.01, 0.04)	
Baseline use of MRA											0.0781
No	1865	99	5.3	1878	142	7.6	0.0050	1.42 (1.11, 1.83)	1.46 (1.12, 1.90)	0.02 (0.01, 0.04)	
Yes	1124	89	7.9	1118	90	8.1	0.9083	1.02 (0.77, 1.35)	1.02 (0.75, 1.38)	0.00 (-0.02, 0.02)	
Baseline use of ACE-inhibitor, ARB or ARNi											0.1375
No	586	35	6.0	568	30	5.3	0.6107	0.88 (0.55, 1.42)	0.88 (0.53, 1.45)	-0.01 (-0.03, 0.02)	
Yes	2403	153	6.4	2428	202	8.3	0.0093	1.31 (1.07, 1.60)	1.33 (1.07, 1.66)	0.02 (0.00, 0.03)	

Analysis is based on study 1245.110.
^ Patients with NYHA class I are counted in subgroup NYHA class II.
Risk ratios and odds ratios with confidence intervals (CIs) are estimated by Cochran-Mantel-Haenszel method. For risk differences standard Wald asymptotic confidence limits are calculated. A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied in case of any zero cells in contingency table.
Only treatment emergent AEs are displayed (onset between first dose until treatment stop +7 days).
MedDRA version: 23.1. * Chi-square test for treatment effect ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction).

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Table R.1.2.5: 1 Proportion of patients with any adverse event occuring in at least 1% of the patients in either treatment arm in the overall population on PT level by SOC and PT, 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	2989	33	1.1	2996	35	1.2	0.8148	1.06 (0.66, 1.70)	1.06 (0.66, 1.71)	0.00 (0.00, 0.01)	

Analysis is based on study 1245.110.
^ Patients with NYHA class I are counted in subgroup NYHA class II.
Risk ratios and odds ratios with confidence intervals (CIs) are estimated by Cochran-Mantel-Haenszel method. For risk differences standard Wald asymptotic confidence limits are calculated. A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied in case of any zero cells in contingency table.
Only treatment emergent AEs are displayed (onset between first dose until treatment stop +7 days).
MedDRA version: 23.1. * Chi-square test for treatment effect ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction).

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Table R.1.2.5: 1 Proportion of patients with any adverse event occuring in at least 1% of the patients in either treatment arm in the overall population on PT level by SOC and PT, 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	2989	32	1.1	2996	13	0.4	0.0044	0.41 (0.21, 0.77)	0.40 (0.21, 0.77)	-0.01 (-0.01, 0.00)	
Sex											0.5924
Male	1653	12	0.7	1658	6	0.4	0.1543	0.50 (0.19, 1.33)	0.50 (0.19, 1.33)	0.00 (-0.01, 0.00)	
Female	1336	20	1.5	1338	7	0.5	0.0118	0.35 (0.15, 0.82)	0.35 (0.15, 0.82)	-0.01 (-0.02, 0.00)	
Age [years]											0.3233
<70	1084	10	0.9	1066	6	0.6	0.3320	0.61 (0.22, 1.67)	0.61 (0.22, 1.68)	0.00 (-0.01, 0.00)	
>=70	1905	22	1.2	1930	7	0.4	0.0046	0.31 (0.13, 0.73)	0.31 (0.13, 0.73)	-0.01 (-0.01, 0.00)	
Region											0.8915
North America	359	4	1.1	359	0	0	0.0726	0.11 (<0.01, 2.06)	0.11 (<0.01, 2.05)	-0.01 (-0.02, 0.00)	
Latin America	757	19	2.5	758	9	1.2	0.0560	0.47 (0.22, 1.04)	0.47 (0.21, 1.04)	-0.01 (-0.03, 0.00)	
Europe	1341	8	0.6	1346	4	0.3	0.2445	0.50 (0.15, 1.65)	0.50 (0.15, 1.65)	0.00 (-0.01, 0.00)	
Asia	343	1	0.3	343	0	0	0.4789	0.33 (0.01, 8.15)	0.33 (0.01, 8.19)	0.00 (-0.01, 0.01)	
Other	189	0	0	190	0	0	0.9979	0.99 (0.02, 49.88)	0.99 (0.02, 50.39)	0.00 (-0.01, 0.01)	
OECD member											0.3463
No	847	17	2.0	868	9	1.0	0.1002	0.52 (0.23, 1.15)	0.51 (0.23, 1.15)	-0.01 (-0.02, 0.00)	
Yes	2142	15	0.7	2128	4	0.2	0.0119	0.27 (0.09, 0.81)	0.27 (0.09, 0.81)	-0.01 (-0.01, 0.00)	
Baseline NYHA											0.9433
II^	2450	27	1.1	2435	11	0.5	0.0097	0.41 (0.20, 0.82)	0.41 (0.20, 0.82)	-0.01 (-0.01, 0.00)	
III/IV	539	5	0.9	561	2	0.4	0.2337	0.38 (0.07, 1.97)	0.38 (0.07, 1.98)	-0.01 (-0.02, 0.00)	
Baseline Diabetes Status											0.6041
Diabetic	1471	20	1.4	1465	7	0.5	0.0123	0.35 (0.15, 0.83)	0.35 (0.15, 0.83)	-0.01 (-0.02, 0.00)	
Non-Diabetic	1518	12	0.8	1531	6	0.4	0.1508	0.50 (0.19, 1.32)	0.49 (0.18, 1.32)	0.00 (-0.01, 0.00)	

Analysis is based on study 1245.110.
^ Patients with NYHA class I are counted in subgroup NYHA class II.
Risk ratios and odds ratios with confidence intervals (CIs) are estimated by Cochran-Mantel-Haenszel method. For risk differences standard Wald asymptotic confidence limits are calculated. A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied in case of any zero cells in contingency table.
Only treatment emergent AEs are displayed (onset between first dose until treatment stop +7 days).
MedDRA version: 23.1. * Chi-square test for treatment effect ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction).

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Table R.1.2.5: 1 Proportion of patients with any adverse event occuring in at least 1% of the patients in either treatment arm in the overall population on PT level by SOC and PT, 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 **
Baseline Diabetes Status											0.8156
Diabetic	1471	20	1.4	1465	7	0.5	0.0123	0.35 (0.15, 0.83)	0.35 (0.15, 0.83)	-0.01 (-0.02, 0.00)	
Pre-Diabetes	979	9	0.9	1001	5	0.5	0.2650	0.54 (0.18, 1.62)	0.54 (0.18, 1.62)	0.00 (-0.01, 0.00)	
Normal (no pre-diabetes)	539	3	0.6	530	1	0.2	0.3246	0.34 (0.04, 3.25)	0.34 (0.04, 3.26)	0.00 (-0.01, 0.00)	
Baseline BMI [kg/m²]											0.0720
<30	1641	17	1.0	1654	3	0.2	0.0016	0.18 (0.05, 0.60)	0.17 (0.05, 0.59)	-0.01 (-0.01, 0.00)	
>=30	1348	15	1.1	1342	10	0.7	0.3205	0.67 (0.30, 1.49)	0.67 (0.30, 1.49)	0.00 (-0.01, 0.00)	
Baseline eGFR (CKD-EPI) [mL/min/1.73m²]											0.7693
>=60	1505	14	0.9	1493	5	0.3	0.0400	0.36 (0.13, 1.00)	0.36 (0.13, 1.00)	-0.01 (-0.01, 0.00)	
<60	1482	18	1.2	1503	8	0.5	0.0449	0.44 (0.19, 1.00)	0.44 (0.19, 1.00)	-0.01 (-0.01, 0.00)	
History of HHF (in the last 12 months)											0.7427
No	2320	26	1.1	2297	11	0.5	0.0145	0.43 (0.21, 0.86)	0.42 (0.21, 0.86)	-0.01 (-0.01, 0.00)	
Yes	669	6	0.9	699	2	0.3	0.1386	0.32 (0.06, 1.58)	0.32 (0.06, 1.58)	-0.01 (-0.01, 0.00)	
Baseline SBP (</>= median)											0.1180
< median	1474	7	0.5	1496	6	0.4	0.7606	0.84 (0.28, 2.51)	0.84 (0.28, 2.52)	0.00 (-0.01, 0.00)	
>= median	1515	25	1.7	1500	7	0.5	0.0015	0.28 (0.12, 0.65)	0.28 (0.12, 0.65)	-0.01 (-0.02, 0.00)	
History of atrial fibrillation or atrial flutter											0.7115
No	1426	23	1.6	1417	10	0.7	0.0239	0.44 (0.21, 0.92)	0.43 (0.21, 0.91)	-0.01 (-0.02, 0.00)	
Yes	1558	9	0.6	1575	3	0.2	0.0794	0.33 (0.09, 1.22)	0.33 (0.09, 1.22)	0.00 (-0.01, 0.00)	

Analysis is based on study 1245.110.
^ Patients with NYHA class I are counted in subgroup NYHA class II.
Risk ratios and odds ratios with confidence intervals (CIs) are estimated by Cochran-Mantel-Haenszel method. For risk differences standard Wald asymptotic confidence limits are calculated. A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied in case of any zero cells in contingency table.
Only treatment emergent AEs are displayed (onset between first dose until treatment stop +7 days).
MedDRA version: 23.1. * Chi-square test for treatment effect ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction).

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Table R.1.2.5: 1 Proportion of patients with any adverse event occuring in at least 1% of the patients in either treatment arm in the overall population on PT level by SOC and PT, 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 **
Baseline LVEF [%]											0.3739
< 50	988	8	0.8	995	5	0.5	0.3967	0.62 (0.20, 1.89)	0.62 (0.20, 1.90)	0.00 (-0.01, 0.00)	
>= 50	2001	24	1.2	2001	8	0.4	0.0045	0.33 (0.15, 0.74)	0.33 (0.15, 0.74)	-0.01 (-0.01, 0.00)	
Baseline LVEF [%]											0.6610
<50	988	8	0.8	995	5	0.5	0.3967	0.62 (0.20, 1.89)	0.62 (0.20, 1.90)	0.00 (-0.01, 0.00)	
50 to <60	1030	10	1.0	1028	3	0.3	0.0519	0.30 (0.08, 1.09)	0.30 (0.08, 1.09)	-0.01 (-0.01, 0.00)	
>=60	971	14	1.4	973	5	0.5	0.0376	0.36 (0.13, 0.99)	0.35 (0.13, 0.98)	-0.01 (-0.02, 0.00)	
Baseline NT-proBNP [pg/mL] (</>=median by atrial fibrillation/flutter status)											0.5056
< median	1507	21	1.4	1476	7	0.5	0.0092	0.34 (0.15, 0.80)	0.34 (0.14, 0.80)	-0.01 (-0.02, 0.00)	
>= median	1475	11	0.7	1516	6	0.4	0.2030	0.53 (0.20, 1.43)	0.53 (0.20, 1.43)	0.00 (-0.01, 0.00)	
Baseline uric acid [mg/dL] (tertiles)											0.7496
<T1	975	8	0.8	963	2	0.2	0.0597	0.25 (0.05, 1.19)	0.25 (0.05, 1.19)	-0.01 (-0.01, 0.00)	
>=T1 and <T2	966	14	1.4	1032	6	0.6	0.0515	0.40 (0.15, 1.04)	0.40 (0.15, 1.04)	-0.01 (-0.02, 0.00)	
>=T2	1016	10	1.0	970	5	0.5	0.2278	0.52 (0.18, 1.53)	0.52 (0.18, 1.53)	0.00 (-0.01, 0.00)	
Baseline use of MRA											0.6286
No	1865	22	1.2	1878	8	0.4	0.0097	0.36 (0.16, 0.81)	0.36 (0.16, 0.81)	-0.01 (-0.01, 0.00)	
Yes	1124	10	0.9	1118	5	0.4	0.1988	0.50 (0.17, 1.47)	0.50 (0.17, 1.47)	0.00 (-0.01, 0.00)	
Baseline use of ACE-inhibitor, ARB or ARNi											0.8845
No	586	3	0.5	568	1	0.2	0.3317	0.34 (0.04, 3.30)	0.34 (0.04, 3.30)	0.00 (-0.01, 0.00)	
Yes	2403	29	1.2	2428	12	0.5	0.0069	0.41 (0.21, 0.80)	0.41 (0.21, 0.80)	-0.01 (-0.01, 0.00)	

Analysis is based on study 1245.110.
^ Patients with NYHA class I are counted in subgroup NYHA class II.
Risk ratios and odds ratios with confidence intervals (CIs) are estimated by Cochran-Mantel-Haenszel method. For risk differences standard Wald asymptotic confidence limits are calculated. A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied in case of any zero cells in contingency table.
Only treatment emergent AEs are displayed (onset between first dose until treatment stop +7 days).
MedDRA version: 23.1. * Chi-square test for treatment effect ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction).

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Table R.1.2.5: 1 Proportion of patients with any adverse event occuring in at least 1% of the patients in either treatment arm in the overall population on PT level by SOC and PT, 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	2989	119	4.0	2996	137	4.6	0.2582	1.15 (0.90, 1.46)	1.16 (0.90, 1.49)	0.01 (0.00, 0.02)	

Analysis is based on study 1245.110.
^ Patients with NYHA class I are counted in subgroup NYHA class II.
Risk ratios and odds ratios with confidence intervals (CIs) are estimated by Cochran-Mantel-Haenszel method. For risk differences standard Wald asymptotic confidence limits are calculated. A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied in case of any zero cells in contingency table.
Only treatment emergent AEs are displayed (onset between first dose until treatment stop +7 days).
MedDRA version: 23.1. * Chi-square test for treatment effect ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction).

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Table R.1.2.5: 1 Proportion of patients with any adverse event occuring in at least 1% of the patients in either treatment arm in the overall population on PT level by SOC and PT, 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	2989	76	2.5	2996	93	3.1	0.1898	1.22 (0.91, 1.65)	1.23 (0.90, 1.67)	0.01 (0.00, 0.01)	

Analysis is based on study 1245.110.
^ Patients with NYHA class I are counted in subgroup NYHA class II.
Risk ratios and odds ratios with confidence intervals (CIs) are estimated by Cochran-Mantel-Haenszel method. For risk differences standard Wald asymptotic confidence limits are calculated. A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied in case of any zero cells in contingency table.
Only treatment emergent AEs are displayed (onset between first dose until treatment stop +7 days).
MedDRA version: 23.1. * Chi-square test for treatment effect ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction).

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Table R.1.2.5: 1 Proportion of patients with any adverse event occuring in at least 1% of the patients in either treatment arm in the overall population on PT level by SOC and PT, 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	2989	51	1.7	2996	58	1.9	0.5065	1.13 (0.78, 1.65)	1.14 (0.78, 1.66)	0.00 (0.00, 0.01)	

Analysis is based on study 1245.110.
^ Patients with NYHA class I are counted in subgroup NYHA class II.
Risk ratios and odds ratios with confidence intervals (CIs) are estimated by Cochran-Mantel-Haenszel method. For risk differences standard Wald asymptotic confidence limits are calculated. A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied in case of any zero cells in contingency table.
Only treatment emergent AEs are displayed (onset between first dose until treatment stop +7 days).
MedDRA version: 23.1. * Chi-square test for treatment effect ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction).

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Table R.1.2.5: 1 Proportion of patients with any adverse event occuring in at least 1% of the patients in either treatment arm in the overall population on PT level by SOC and PT, 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	2989	49	1.6	2996	38	1.3	0.2305	0.77 (0.51, 1.18)	0.77 (0.50, 1.18)	0.00 (-0.01, 0.00)	

Analysis is based on study 1245.110.
^ Patients with NYHA class I are counted in subgroup NYHA class II.
Risk ratios and odds ratios with confidence intervals (CIs) are estimated by Cochran-Mantel-Haenszel method. For risk differences standard Wald asymptotic confidence limits are calculated. A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied in case of any zero cells in contingency table.
Only treatment emergent AEs are displayed (onset between first dose until treatment stop +7 days).
MedDRA version: 23.1. * Chi-square test for treatment effect ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction).

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Table R.1.2.5: 1 Proportion of patients with any adverse event occuring in at least 1% of the patients in either treatment arm in the overall population on PT level by SOC and PT, 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	2989	40	1.3	2996	40	1.3	0.9916	1.00 (0.65, 1.54)	1.00 (0.64, 1.55)	0.00 (-0.01, 0.01)	

Analysis is based on study 1245.110.
^ Patients with NYHA class I are counted in subgroup NYHA class II.
Risk ratios and odds ratios with confidence intervals (CIs) are estimated by Cochran-Mantel-Haenszel method. For risk differences standard Wald asymptotic confidence limits are calculated. A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied in case of any zero cells in contingency table.
Only treatment emergent AEs are displayed (onset between first dose until treatment stop +7 days).
MedDRA version: 23.1. * Chi-square test for treatment effect ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction).

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Table R.1.2.5: 1 Proportion of patients with any adverse event occuring in at least 1% of the patients in either treatment arm in the overall population on PT level by SOC and PT, 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	2989	25	0.8	2996	36	1.2	0.1596	1.44 (0.86, 2.39)	1.44 (0.86, 2.41)	0.00 (0.00, 0.01)	

Analysis is based on study 1245.110.
^ Patients with NYHA class I are counted in subgroup NYHA class II.
Risk ratios and odds ratios with confidence intervals (CIs) are estimated by Cochran-Mantel-Haenszel method. For risk differences standard Wald asymptotic confidence limits are calculated. A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied in case of any zero cells in contingency table.
Only treatment emergent AEs are displayed (onset between first dose until treatment stop +7 days).
MedDRA version: 23.1. * Chi-square test for treatment effect ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction).

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Table R.1.2.5: 1 Proportion of patients with any adverse event occuring in at least 1% of the patients in either treatment arm in the overall population on PT level by SOC and PT, 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	2989	32	1.1	2996	34	1.1	0.8119	1.06 (0.66, 1.71)	1.06 (0.65, 1.72)	0.00 (0.00, 0.01)	

Analysis is based on study 1245.110.
^ Patients with NYHA class I are counted in subgroup NYHA class II.
Risk ratios and odds ratios with confidence intervals (CIs) are estimated by Cochran-Mantel-Haenszel method. For risk differences standard Wald asymptotic confidence limits are calculated. A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied in case of any zero cells in contingency table.
Only treatment emergent AEs are displayed (onset between first dose until treatment stop +7 days).
MedDRA version: 23.1. * Chi-square test for treatment effect ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction).

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Table R.1.2.5: 1 Proportion of patients with any adverse event occuring in at least 1% of the patients in either treatment arm in the overall population on PT level by SOC and PT, 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	2989	31	1.0	2996	33	1.1	0.8088	1.06 (0.65, 1.73)	1.06 (0.65, 1.74)	0.00 (0.00, 0.01)	

Analysis is based on study 1245.110.
^ Patients with NYHA class I are counted in subgroup NYHA class II.
Risk ratios and odds ratios with confidence intervals (CIs) are estimated by Cochran-Mantel-Haenszel method. For risk differences standard Wald asymptotic confidence limits are calculated. A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied in case of any zero cells in contingency table.
Only treatment emergent AEs are displayed (onset between first dose until treatment stop +7 days).
MedDRA version: 23.1. * Chi-square test for treatment effect ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction).

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Table R.1.2.5: 1 Proportion of patients with any adverse event occuring in at least 1% of the patients in either treatment arm in the overall population on PT level by SOC and PT, 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	2989	25	0.8	2996	32	1.1	0.3561	1.28 (0.76, 2.15)	1.28 (0.76, 2.17)	0.00 (0.00, 0.01)	

Analysis is based on study 1245.110.
^ Patients with NYHA class I are counted in subgroup NYHA class II.
Risk ratios and odds ratios with confidence intervals (CIs) are estimated by Cochran-Mantel-Haenszel method. For risk differences standard Wald asymptotic confidence limits are calculated. A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied in case of any zero cells in contingency table.
Only treatment emergent AEs are displayed (onset between first dose until treatment stop +7 days).
MedDRA version: 23.1. * Chi-square test for treatment effect ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction).

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Table R.1.2.5: 1 Proportion of patients with any adverse event occuring in at least 1% of the patients in either treatment arm in the overall population on PT level by SOC and PT, 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	2989	216	7.2	2996	209	7.0	0.7059	0.97 (0.80, 1.16)	0.96 (0.79, 1.17)	0.00 (-0.02, 0.01)	

Analysis is based on study 1245.110.
^ Patients with NYHA class I are counted in subgroup NYHA class II.
Risk ratios and odds ratios with confidence intervals (CIs) are estimated by Cochran-Mantel-Haenszel method. For risk differences standard Wald asymptotic confidence limits are calculated. A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied in case of any zero cells in contingency table.
Only treatment emergent AEs are displayed (onset between first dose until treatment stop +7 days).
MedDRA version: 23.1. * Chi-square test for treatment effect ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction).

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Table R.1.2.5: 1 Proportion of patients with any adverse event occuring in at least 1% of the patients in either treatment arm in the overall population on PT level by SOC and PT, 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	2989	107	3.6	2996	81	2.7	0.0520	0.76 (0.57, 1.00)	0.75 (0.56, 1.00)	-0.01 (-0.02, 0.00)	

Analysis is based on study 1245.110.
^ Patients with NYHA class I are counted in subgroup NYHA class II.
Risk ratios and odds ratios with confidence intervals (CIs) are estimated by Cochran-Mantel-Haenszel method. For risk differences standard Wald asymptotic confidence limits are calculated. A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied in case of any zero cells in contingency table.
Only treatment emergent AEs are displayed (onset between first dose until treatment stop +7 days).
MedDRA version: 23.1. * Chi-square test for treatment effect ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction).

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Table R.1.2.5: 1 Proportion of patients with any adverse event occuring in at least 1% of the patients in either treatment arm in the overall population on PT level by SOC and PT, 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	2989	91	3.0	2996	86	2.9	0.6911	0.94 (0.71, 1.26)	0.94 (0.70, 1.27)	0.00 (-0.01, 0.01)	

Analysis is based on study 1245.110.
^ Patients with NYHA class I are counted in subgroup NYHA class II.
Risk ratios and odds ratios with confidence intervals (CIs) are estimated by Cochran-Mantel-Haenszel method. For risk differences standard Wald asymptotic confidence limits are calculated. A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied in case of any zero cells in contingency table.
Only treatment emergent AEs are displayed (onset between first dose until treatment stop +7 days).
MedDRA version: 23.1. * Chi-square test for treatment effect ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction).

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Table R.1.2.5: 1 Proportion of patients with any adverse event occuring in at least 1% of the patients in either treatment arm in the overall population on PT level by SOC and PT, 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	2989	73	2.4	2996	69	2.3	0.7235	0.94 (0.68, 1.31)	0.94 (0.67, 1.31)	0.00 (-0.01, 0.01)	

Analysis is based on study 1245.110.
^ Patients with NYHA class I are counted in subgroup NYHA class II.
Risk ratios and odds ratios with confidence intervals (CIs) are estimated by Cochran-Mantel-Haenszel method. For risk differences standard Wald asymptotic confidence limits are calculated. A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied in case of any zero cells in contingency table.
Only treatment emergent AEs are displayed (onset between first dose until treatment stop +7 days).
MedDRA version: 23.1. * Chi-square test for treatment effect ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction).

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Table R.1.2.5: 1 Proportion of patients with any adverse event occuring in at least 1% of the patients in either treatment arm in the overall population on PT level by SOC and PT, 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	2989	44	1.5	2996	36	1.2	0.3623	0.82 (0.53, 1.26)	0.81 (0.52, 1.27)	0.00 (-0.01, 0.00)	

Analysis is based on study 1245.110.
^ Patients with NYHA class I are counted in subgroup NYHA class II.
Risk ratios and odds ratios with confidence intervals (CIs) are estimated by Cochran-Mantel-Haenszel method. For risk differences standard Wald asymptotic confidence limits are calculated. A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied in case of any zero cells in contingency table.
Only treatment emergent AEs are displayed (onset between first dose until treatment stop +7 days).
MedDRA version: 23.1. * Chi-square test for treatment effect ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction).

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Table R.1.2.5: 1 Proportion of patients with any adverse event occuring in at least 1% of the patients in either treatment arm in the overall population on PT level by SOC and PT, 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	2989	108	3.6	2996	102	3.4	0.6608	0.94 (0.72, 1.23)	0.94 (0.71, 1.24)	0.00 (-0.01, 0.01)	

Analysis is based on study 1245.110.
^ Patients with NYHA class I are counted in subgroup NYHA class II.
Risk ratios and odds ratios with confidence intervals (CIs) are estimated by Cochran-Mantel-Haenszel method. For risk differences standard Wald asymptotic confidence limits are calculated. A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied in case of any zero cells in contingency table.
Only treatment emergent AEs are displayed (onset between first dose until treatment stop +7 days).
MedDRA version: 23.1. * Chi-square test for treatment effect ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction).

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Table R.1.2.5: 1 Proportion of patients with any adverse event occuring in at least 1% of the patients in either treatment arm in the overall population on PT level by SOC and PT, 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	2989	101	3.4	2996	103	3.4	0.9001	1.02 (0.78, 1.33)	1.02 (0.77, 1.35)	0.00 (-0.01, 0.01)	

Analysis is based on study 1245.110.
^ Patients with NYHA class I are counted in subgroup NYHA class II.
Risk ratios and odds ratios with confidence intervals (CIs) are estimated by Cochran-Mantel-Haenszel method. For risk differences standard Wald asymptotic confidence limits are calculated. A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied in case of any zero cells in contingency table.
Only treatment emergent AEs are displayed (onset between first dose until treatment stop +7 days).
MedDRA version: 23.1. * Chi-square test for treatment effect ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction).

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Table R.1.2.5: 1 Proportion of patients with any adverse event occuring in at least 1% of the patients in either treatment arm in the overall population on PT level by SOC and PT, 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	2989	88	2.9	2996	81	2.7	0.5744	0.92 (0.68, 1.24)	0.92 (0.67, 1.24)	0.00 (-0.01, 0.01)	

Analysis is based on study 1245.110.
^ Patients with NYHA class I are counted in subgroup NYHA class II.
Risk ratios and odds ratios with confidence intervals (CIs) are estimated by Cochran-Mantel-Haenszel method. For risk differences standard Wald asymptotic confidence limits are calculated. A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied in case of any zero cells in contingency table.
Only treatment emergent AEs are displayed (onset between first dose until treatment stop +7 days).
MedDRA version: 23.1. * Chi-square test for treatment effect ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction).

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Table R.1.2.5: 1 Proportion of patients with any adverse event occuring in at least 1% of the patients in either treatment arm in the overall population on PT level by SOC and PT, 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	2989	82	2.7	2996	49	1.6	0.0034	0.60	(0.42, 0.85)	0.59	(0.41, 0.84)	-0.01	(-0.02, 0.00)	
Sex														0.9124
Male	1653	41	2.5	1658	25	1.5	0.0453	0.61	(0.37, 0.99)	0.60	(0.36, 0.99)	-0.01	(-0.02, 0.00)	
Female	1336	41	3.1	1338	24	1.8	0.0323	0.58	(0.36, 0.96)	0.58	(0.35, 0.96)	-0.01	(-0.02, 0.00)	
Age [years]														0.9655
<70	1084	31	2.9	1066	18	1.7	0.0688	0.59	(0.33, 1.05)	0.58	(0.32, 1.05)	-0.01	(-0.02, 0.00)	
>=70	1905	51	2.7	1930	31	1.6	0.0219	0.60	(0.39, 0.93)	0.59	(0.38, 0.93)	-0.01	(-0.02, 0.00)	
Region														0.2307
North America	359	24	6.7	359	14	3.9	0.0955	0.58	(0.31, 1.11)	0.57	(0.29, 1.11)	-0.03	(-0.06, 0.00)	
Latin America	757	16	2.1	758	18	2.4	0.7316	1.12	(0.58, 2.19)	1.13	(0.57, 2.23)	0.00	(-0.01, 0.02)	
Europe	1341	17	1.3	1346	8	0.6	0.0691	0.47	(0.20, 1.08)	0.47	(0.20, 1.08)	-0.01	(-0.01, 0.00)	
Asia	343	18	5.2	343	7	2.0	0.0250	0.39	(0.16, 0.92)	0.38	(0.16, 0.91)	-0.03	(-0.06, 0.00)	
Other	189	7	3.7	190	2	1.1	0.0901	0.28	(0.06, 1.35)	0.28	(0.06, 1.35)	-0.03	(-0.06, 0.00)	
OECD member														0.5837
No	847	21	2.5	868	15	1.7	0.2779	0.70	(0.36, 1.34)	0.69	(0.35, 1.35)	-0.01	(-0.02, 0.01)	
Yes	2142	61	2.8	2128	34	1.6	0.0056	0.56	(0.37, 0.85)	0.55	(0.36, 0.85)	-0.01	(-0.02, 0.00)	
Baseline NYHA														0.1395
II^	2450	66	2.7	2435	44	1.8	0.0367	0.67	(0.46, 0.98)	0.66	(0.45, 0.98)	-0.01	(-0.02, 0.00)	
III/IV	539	16	3.0	561	5	0.9	0.0118	0.30	(0.11, 0.81)	0.29	(0.11, 0.81)	-0.02	(-0.04, 0.00)	
Baseline Diabetes Status														0.3004
Diabetic	1471	43	2.9	1465	21	1.4	0.0057	0.49	(0.29, 0.82)	0.48	(0.29, 0.82)	-0.01	(-0.03, 0.00)	
Non-Diabetic	1518	39	2.6	1531	28	1.8	0.1633	0.71	(0.44, 1.15)	0.71	(0.43, 1.15)	-0.01	(-0.02, 0.00)	

Analysis is based on study 1245.110.
^ Patients with NYHA class I are counted in subgroup NYHA class II.
Risk ratios and odds ratios with confidence intervals (CIs) are estimated by Cochran-Mantel-Haenszel method. For risk differences standard Wald asymptotic confidence limits are calculated. A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied in case of any zero cells in contingency table.
Only treatment emergent AEs are displayed (onset between first dose until treatment stop +7 days).
MedDRA version: 23.1. * Chi-square test for treatment effect ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction).

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Table R.1.2.5: 1 Proportion of patients with any adverse event occuring in at least 1% of the patients in either treatment arm in the overall population on PT level by SOC and PT, 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 Diabetes Status											0.0949
Diabetic	1471	43	2.9	1465	21	1.4	0.0057	0.49 (0.29, 0.82)	0.48 (0.29, 0.82)	-0.01 (-0.03, 0.00)	
Pre-Diabetes	979	28	2.9	1001	14	1.4	0.0240	0.49 (0.26, 0.92)	0.48 (0.25, 0.92)	-0.01 (-0.03, 0.00)	
Normal (no pre-diabetes)	539	11	2.0	530	14	2.6	0.5158	1.29 (0.59, 2.83)	1.30 (0.59, 2.90)	0.01 (-0.01, 0.02)	
Baseline BMI [kg/m²]											0.6378
<30	1641	50	3.0	1654	28	1.7	0.0106	0.56 (0.35, 0.88)	0.55 (0.34, 0.87)	-0.01 (-0.02, 0.00)	
>=30	1348	32	2.4	1342	21	1.6	0.1311	0.66 (0.38, 1.14)	0.65 (0.38, 1.14)	-0.01 (-0.02, 0.00)	
Baseline eGFR (CKD-EPI) [mL/min/1.73m²]											0.2469
>=60	1505	39	2.6	1493	18	1.2	0.0055	0.47 (0.27, 0.81)	0.46 (0.26, 0.81)	-0.01 (-0.02, 0.00)	
<60	1482	43	2.9	1503	31	2.1	0.1405	0.71 (0.45, 1.12)	0.70 (0.44, 1.12)	-0.01 (-0.02, 0.00)	
History of HHF (in the last 12 months)											0.2715
No	2320	69	3.0	2297	37	1.6	0.0020	0.54 (0.36, 0.80)	0.53 (0.36, 0.80)	-0.01 (-0.02,-0.01)	
Yes	669	13	1.9	699	12	1.7	0.7546	0.88 (0.41, 1.92)	0.88 (0.40, 1.95)	0.00 (-0.02, 0.01)	
Baseline SBP (</>= median)											0.4390
< median	1474	39	2.6	1496	27	1.8	0.1200	0.68 (0.42, 1.11)	0.68 (0.41, 1.11)	-0.01 (-0.02, 0.00)	
>= median	1515	43	2.8	1500	22	1.5	0.0095	0.52 (0.31, 0.86)	0.51 (0.30, 0.86)	-0.01 (-0.02, 0.00)	
History of atrial fibrillation or atrial flutter											0.3978
No	1426	36	2.5	1417	25	1.8	0.1619	0.70 (0.42, 1.16)	0.69 (0.41, 1.16)	-0.01 (-0.02, 0.00)	
Yes	1558	46	3.0	1575	24	1.5	0.0068	0.52 (0.32, 0.84)	0.51 (0.31, 0.84)	-0.01 (-0.02, 0.00)	

Analysis is based on study 1245.110.
^ Patients with NYHA class I are counted in subgroup NYHA class II.
Risk ratios and odds ratios with confidence intervals (CIs) are estimated by Cochran-Mantel-Haenszel method. For risk differences standard Wald asymptotic confidence limits are calculated. A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied in case of any zero cells in contingency table.
Only treatment emergent AEs are displayed (onset between first dose until treatment stop +7 days).
MedDRA version: 23.1. * Chi-square test for treatment effect ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction).

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Table R.1.2.5: 1 Proportion of patients with any adverse event occuring in at least 1% of the patients in either treatment arm in the overall population on PT level by SOC and PT, 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 LVEF [%]											0.1803
< 50	988	18	1.8	995	16	1.6	0.7138	0.88 (0.45, 1.72)	0.88 (0.45, 1.74)	0.00 (-0.01, 0.01)	
>= 50	2001	64	3.2	2001	33	1.6	0.0014	0.52 (0.34, 0.78)	0.51 (0.33, 0.78)	-0.02 (-0.03,-0.01)	
Baseline LVEF [%]											0.3935
<50	988	18	1.8	995	16	1.6	0.7138	0.88 (0.45, 1.72)	0.88 (0.45, 1.74)	0.00 (-0.01, 0.01)	
50 to <60	1030	31	3.0	1028	15	1.5	0.0173	0.48 (0.26, 0.89)	0.48 (0.26, 0.89)	-0.02 (-0.03, 0.00)	
>=60	971	33	3.4	973	18	1.8	0.0327	0.54 (0.31, 0.96)	0.54 (0.30, 0.96)	-0.02 (-0.03, 0.00)	
Baseline NT-proBNP [pg/mL] (</>=median by atrial fibrillation/flutter status)											0.7990
< median	1507	48	3.2	1476	27	1.8	0.0180	0.57 (0.36, 0.92)	0.57 (0.35, 0.91)	-0.01 (-0.02, 0.00)	
>= median	1475	34	2.3	1516	22	1.5	0.0850	0.63 (0.37, 1.07)	0.62 (0.36, 1.07)	-0.01 (-0.02, 0.00)	
Baseline uric acid [mg/dL] (tertiles)											0.3892
<T1	975	27	2.8	963	11	1.1	0.0098	0.41 (0.21, 0.83)	0.41 (0.20, 0.82)	-0.02 (-0.03, 0.00)	
>=T1 and <T2	966	20	2.1	1032	17	1.6	0.4833	0.80 (0.42, 1.51)	0.79 (0.41, 1.52)	0.00 (-0.02, 0.01)	
>=T2	1016	35	3.4	970	21	2.2	0.0850	0.63 (0.37, 1.07)	0.62 (0.36, 1.07)	-0.01 (-0.03, 0.00)	
Baseline use of MRA											0.8733
No	1865	59	3.2	1878	36	1.9	0.0153	0.61 (0.40, 0.91)	0.60 (0.39, 0.91)	-0.01 (-0.02, 0.00)	
Yes	1124	23	2.0	1118	13	1.2	0.0961	0.57 (0.29, 1.12)	0.56 (0.28, 1.12)	-0.01 (-0.02, 0.00)	
Baseline use of ACE-inhibitor, ARB or ARNi											0.3858
No	586	21	3.6	568	9	1.6	0.0329	0.44 (0.20, 0.96)	0.43 (0.20, 0.95)	-0.02 (-0.04, 0.00)	
Yes	2403	61	2.5	2428	40	1.6	0.0304	0.65 (0.44, 0.96)	0.64 (0.43, 0.96)	-0.01 (-0.02, 0.00)	

Analysis is based on study 1245.110.
^ Patients with NYHA class I are counted in subgroup NYHA class II.
Risk ratios and odds ratios with confidence intervals (CIs) are estimated by Cochran-Mantel-Haenszel method. For risk differences standard Wald asymptotic confidence limits are calculated. A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied in case of any zero cells in contingency table.
Only treatment emergent AEs are displayed (onset between first dose until treatment stop +7 days).
MedDRA version: 23.1. * Chi-square test for treatment effect ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction).

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Table R.1.2.5: 1 Proportion of patients with any adverse event occuring in at least 1% of the patients in either treatment arm in the overall population on PT level by SOC and PT, 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	2989	41	1.4	2996	39	1.3	0.8137	0.95 (0.61, 1.47)	0.95 (0.61, 1.47)	0.00 (-0.01, 0.01)	

Analysis is based on study 1245.110.
^ Patients with NYHA class I are counted in subgroup NYHA class II.
Risk ratios and odds ratios with confidence intervals (CIs) are estimated by Cochran-Mantel-Haenszel method. For risk differences standard Wald asymptotic confidence limits are calculated. A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied in case of any zero cells in contingency table.
Only treatment emergent AEs are displayed (onset between first dose until treatment stop +7 days).
MedDRA version: 23.1. * Chi-square test for treatment effect ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction).

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Table R.1.2.5: 1 Proportion of patients with any adverse event occuring in at least 1% of the patients in either treatment arm in the overall population on PT level by SOC and PT, 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	2989	116	3.9	2996	114	3.8	0.8787	0.98 (0.76, 1.26)	0.98 (0.75, 1.28)	0.00 (-0.01, 0.01)	

Analysis is based on study 1245.110.
^ Patients with NYHA class I are counted in subgroup NYHA class II.
Risk ratios and odds ratios with confidence intervals (CIs) are estimated by Cochran-Mantel-Haenszel method. For risk differences standard Wald asymptotic confidence limits are calculated. A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied in case of any zero cells in contingency table.
Only treatment emergent AEs are displayed (onset between first dose until treatment stop +7 days).
MedDRA version: 23.1. * Chi-square test for treatment effect ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction).

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Table R.1.2.5: 1 Proportion of patients with any adverse event occuring in at least 1% of the patients in either treatment arm in the overall population on PT level by SOC and PT, 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	2989	50	1.7	2996	63	2.1	0.2217	1.26 (0.87, 1.82)	1.26 (0.87, 1.84)	0.00 (0.00, 0.01)	

Analysis is based on study 1245.110.
^ Patients with NYHA class I are counted in subgroup NYHA class II.
Risk ratios and odds ratios with confidence intervals (CIs) are estimated by Cochran-Mantel-Haenszel method. For risk differences standard Wald asymptotic confidence limits are calculated. A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied in case of any zero cells in contingency table.
Only treatment emergent AEs are displayed (onset between first dose until treatment stop +7 days).
MedDRA version: 23.1. * Chi-square test for treatment effect ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction).

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Table R.1.2.5: 1 Proportion of patients with any adverse event occuring in at least 1% of the patients in either treatment arm in the overall population on PT level by SOC and PT, 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	2989	60	2.0	2996	62	2.1	0.8651	1.03 (0.73, 1.46)	1.03 (0.72, 1.48)	0.00 (-0.01, 0.01)	

Analysis is based on study 1245.110.
^ Patients with NYHA class I are counted in subgroup NYHA class II.
Risk ratios and odds ratios with confidence intervals (CIs) are estimated by Cochran-Mantel-Haenszel method. For risk differences standard Wald asymptotic confidence limits are calculated. A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied in case of any zero cells in contingency table.
Only treatment emergent AEs are displayed (onset between first dose until treatment stop +7 days).
MedDRA version: 23.1. * Chi-square test for treatment effect ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction).

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Table R.1.2.5: 1 Proportion of patients with any adverse event occuring in at least 1% of the patients in either treatment arm in the overall population on PT level by SOC and PT, 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	2989	35	1.2	2996	42	1.4	0.4280	1.20 (0.77, 1.87)	1.20 (0.76, 1.88)	0.00 (0.00, 0.01)	

Analysis is based on study 1245.110.
^ Patients with NYHA class I are counted in subgroup NYHA class II.
Risk ratios and odds ratios with confidence intervals (CIs) are estimated by Cochran-Mantel-Haenszel method. For risk differences standard Wald asymptotic confidence limits are calculated. A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied in case of any zero cells in contingency table.
Only treatment emergent AEs are displayed (onset between first dose until treatment stop +7 days).
MedDRA version: 23.1. * Chi-square test for treatment effect ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction).

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Table R.1.2.5: 1 Proportion of patients with any adverse event occuring in at least 1% of the patients in either treatment arm in the overall population on PT level by SOC and PT, 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	2989	96	3.2	2996	58	1.9	0.0018	0.60 (0.44, 0.83)	0.59 (0.43, 0.83)	-0.01 (-0.02, 0.00)	
Sex											0.1470
Male	1653	55	3.3	1658	40	2.4	0.1149	0.73 (0.49, 1.08)	0.72 (0.48, 1.09)	-0.01 (-0.02, 0.00)	
Female	1336	41	3.1	1338	18	1.3	0.0024	0.44 (0.25, 0.76)	0.43 (0.25, 0.75)	-0.02 (-0.03,-0.01)	
Age [years]											0.0046
<70	1084	24	2.2	1066	27	2.5	0.6272	1.14 (0.66, 1.97)	1.15 (0.66, 2.00)	0.00 (-0.01, 0.02)	
>=70	1905	72	3.8	1930	31	1.6	<0.0001	0.42 (0.28, 0.64)	0.42 (0.27, 0.64)	-0.02 (-0.03,-0.01)	
Region											0.5057
North America	359	28	7.8	359	13	3.6	0.0158	0.46 (0.24, 0.88)	0.44 (0.23, 0.87)	-0.04 (-0.08,-0.01)	
Latin America	757	17	2.2	758	10	1.3	0.1730	0.59 (0.27, 1.27)	0.58 (0.26, 1.28)	-0.01 (-0.02, 0.00)	
Europe	1341	42	3.1	1346	24	1.8	0.0239	0.57 (0.35, 0.93)	0.56 (0.34, 0.93)	-0.01 (-0.03, 0.00)	
Asia	343	4	1.2	343	4	1.2	1.0000	1.00 (0.25, 3.97)	1.00 (0.25, 4.03)	0.00 (-0.02, 0.02)	
Other	189	5	2.6	190	7	3.7	0.5637	1.39 (0.45, 4.31)	1.41 (0.44, 4.52)	0.01 (-0.02, 0.05)	
OECD member											0.1914
No	847	16	1.9	868	15	1.7	0.8025	0.91 (0.46, 1.84)	0.91 (0.45, 1.86)	0.00 (-0.01, 0.01)	
Yes	2142	80	3.7	2128	43	2.0	0.0008	0.54 (0.38, 0.78)	0.53 (0.37, 0.77)	-0.02 (-0.03,-0.01)	
Baseline NYHA											0.0848
II^	2450	67	2.7	2435	32	1.3	0.0004	0.48 (0.32, 0.73)	0.47 (0.31, 0.72)	-0.01 (-0.02,-0.01)	
III/IV	539	29	5.4	561	26	4.6	0.5705	0.86 (0.51, 1.44)	0.85 (0.50, 1.47)	-0.01 (-0.03, 0.02)	
Baseline Diabetes Status											0.3779
Diabetic	1471	53	3.6	1465	36	2.5	0.0702	0.68 (0.45, 1.03)	0.67 (0.44, 1.04)	-0.01 (-0.02, 0.00)	
Non-Diabetic	1518	43	2.8	1531	22	1.4	0.0076	0.51 (0.30, 0.84)	0.50 (0.30, 0.84)	-0.01 (-0.02, 0.00)	

Analysis is based on study 1245.110.
^ Patients with NYHA class I are counted in subgroup NYHA class II.
Risk ratios and odds ratios with confidence intervals (CIs) are estimated by Cochran-Mantel-Haenszel method. For risk differences standard Wald asymptotic confidence limits are calculated. A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied in case of any zero cells in contingency table.
Only treatment emergent AEs are displayed (onset between first dose until treatment stop +7 days).
MedDRA version: 23.1. * Chi-square test for treatment effect ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction).

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Table R.1.2.5: 1 Proportion of patients with any adverse event occuring in at least 1% of the patients in either treatment arm in the overall population on PT level by SOC and PT, 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 Diabetes Status											0.4277
Diabetic	1471	53	3.6	1465	36	2.5	0.0702	0.68 (0.45, 1.03)	0.67 (0.44, 1.04)	-0.01 (-0.02, 0.00)	
Pre-Diabetes	979	32	3.3	1001	14	1.4	0.0057	0.43 (0.23, 0.80)	0.42 (0.22, 0.79)	-0.02 (-0.03,-0.01)	
Normal (no pre-diabetes)	539	11	2.0	530	8	1.5	0.5109	0.74 (0.30, 1.82)	0.74 (0.29, 1.84)	-0.01 (-0.02, 0.01)	
Baseline BMI [kg/m²]											0.6484
<30	1641	43	2.6	1654	24	1.5	0.0174	0.55 (0.34, 0.91)	0.55 (0.33, 0.91)	-0.01 (-0.02, 0.00)	
>=30	1348	53	3.9	1342	34	2.5	0.0404	0.64 (0.42, 0.98)	0.64 (0.41, 0.98)	-0.01 (-0.03, 0.00)	
Baseline eGFR (CKD-EPI) [mL/min/1.73m²]											0.8380
>=60	1505	37	2.5	1493	23	1.5	0.0727	0.63 (0.37, 1.05)	0.62 (0.37, 1.05)	-0.01 (-0.02, 0.00)	
<60	1482	59	4.0	1503	35	2.3	0.0097	0.58 (0.39, 0.88)	0.58 (0.38, 0.88)	-0.02 (-0.03, 0.00)	
History of HHF (in the last 12 months)											0.1969
No	2320	76	3.3	2297	40	1.7	0.0009	0.53 (0.36, 0.78)	0.52 (0.36, 0.77)	-0.02 (-0.02,-0.01)	
Yes	669	20	3.0	699	18	2.6	0.6410	0.86 (0.46, 1.61)	0.86 (0.45, 1.64)	0.00 (-0.02, 0.01)	
Baseline SBP (</>= median)											0.4776
< median	1474	53	3.6	1496	29	1.9	0.0059	0.54 (0.34, 0.84)	0.53 (0.34, 0.84)	-0.02 (-0.03, 0.00)	
>= median	1515	43	2.8	1500	29	1.9	0.1037	0.68 (0.43, 1.08)	0.67 (0.42, 1.09)	-0.01 (-0.02, 0.00)	
History of atrial fibrillation or atrial flutter											0.7550
No	1426	41	2.9	1417	26	1.8	0.0675	0.64 (0.39, 1.04)	0.63 (0.38, 1.04)	-0.01 (-0.02, 0.00)	
Yes	1558	55	3.5	1575	32	2.0	0.0107	0.58 (0.37, 0.88)	0.57 (0.36, 0.88)	-0.01 (-0.03, 0.00)	

Analysis is based on study 1245.110.
^ Patients with NYHA class I are counted in subgroup NYHA class II.
Risk ratios and odds ratios with confidence intervals (CIs) are estimated by Cochran-Mantel-Haenszel method. For risk differences standard Wald asymptotic confidence limits are calculated. A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied in case of any zero cells in contingency table.
Only treatment emergent AEs are displayed (onset between first dose until treatment stop +7 days).
MedDRA version: 23.1. * Chi-square test for treatment effect ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction).

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Table R.1.2.5: 1 Proportion of patients with any adverse event occuring in at least 1% of the patients in either treatment arm in the overall population on PT level by SOC and PT, 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 LVEF [%]											0.7826
< 50	988	30	3.0	995	17	1.7	0.0519	0.56 (0.31, 1.01)	0.56 (0.30, 1.01)	-0.01 (-0.03, 0.00)	
>= 50	2001	66	3.3	2001	41	2.0	0.0143	0.62 (0.42, 0.91)	0.61 (0.41, 0.91)	-0.01 (-0.02, 0.00)	
Baseline LVEF [%]											0.4856
<50	988	30	3.0	995	17	1.7	0.0519	0.56 (0.31, 1.01)	0.56 (0.30, 1.01)	-0.01 (-0.03, 0.00)	
50 to <60	1030	35	3.4	1028	17	1.7	0.0117	0.49 (0.27, 0.86)	0.48 (0.27, 0.86)	-0.02 (-0.03, 0.00)	
>=60	971	31	3.2	973	24	2.5	0.3344	0.77 (0.46, 1.31)	0.77 (0.45, 1.32)	-0.01 (-0.02, 0.01)	
Baseline NT-proBNP [pg/mL] (</>=median by atrial fibrillation/flutter status)											0.2838
< median	1507	51	3.4	1476	25	1.7	0.0034	0.50 (0.31, 0.80)	0.49 (0.30, 0.80)	-0.02 (-0.03,-0.01)	
>= median	1475	45	3.1	1516	33	2.2	0.1337	0.71 (0.46, 1.11)	0.71 (0.45, 1.11)	-0.01 (-0.02, 0.00)	
Baseline uric acid [mg/dL] (tertiles)											0.3589
<T1	975	24	2.5	963	18	1.9	0.3705	0.76 (0.41, 1.39)	0.75 (0.41, 1.40)	-0.01 (-0.02, 0.01)	
>=T1 and <T2	966	26	2.7	1032	21	2.0	0.3332	0.76 (0.43, 1.33)	0.75 (0.42, 1.34)	-0.01 (-0.02, 0.01)	
>=T2	1016	43	4.2	970	19	2.0	0.0036	0.46 (0.27, 0.79)	0.45 (0.26, 0.78)	-0.02 (-0.04,-0.01)	
Baseline use of MRA											0.7336
No	1865	55	2.9	1878	35	1.9	0.0302	0.63 (0.42, 0.96)	0.62 (0.41, 0.96)	-0.01 (-0.02, 0.00)	
Yes	1124	41	3.6	1118	23	2.1	0.0238	0.56 (0.34, 0.93)	0.55 (0.33, 0.93)	-0.02 (-0.03, 0.00)	
Baseline use of ACE-inhibitor, ARB or ARNi											0.1792
No	586	14	2.4	568	13	2.3	0.9102	0.96 (0.45, 2.02)	0.96 (0.45, 2.05)	0.00 (-0.02, 0.02)	
Yes	2403	82	3.4	2428	45	1.9	0.0007	0.54 (0.38, 0.78)	0.53 (0.37, 0.77)	-0.02 (-0.02,-0.01)	

Analysis is based on study 1245.110.
^ Patients with NYHA class I are counted in subgroup NYHA class II.
Risk ratios and odds ratios with confidence intervals (CIs) are estimated by Cochran-Mantel-Haenszel method. For risk differences standard Wald asymptotic confidence limits are calculated. A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied in case of any zero cells in contingency table.
Only treatment emergent AEs are displayed (onset between first dose until treatment stop +7 days).
MedDRA version: 23.1. * Chi-square test for treatment effect ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction).

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Table R.1.2.5: 1 Proportion of patients with any adverse event occuring in at least 1% of the patients in either treatment arm in the overall population on PT level by SOC and PT, 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	2989	75	2.5	2996	96	3.2	0.1066	1.28 (0.95, 1.72)	1.29 (0.95, 1.75)	0.01 (0.00, 0.02)	

Analysis is based on study 1245.110.
^ Patients with NYHA class I are counted in subgroup NYHA class II.
Risk ratios and odds ratios with confidence intervals (CIs) are estimated by Cochran-Mantel-Haenszel method. For risk differences standard Wald asymptotic confidence limits are calculated. A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied in case of any zero cells in contingency table.
Only treatment emergent AEs are displayed (onset between first dose until treatment stop +7 days).
MedDRA version: 23.1. * Chi-square test for treatment effect ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction).

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Table R.1.2.5: 1 Proportion of patients with any adverse event occuring in at least 1% of the patients in either treatment arm in the overall population on PT level by SOC and PT, 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	2989	68	2.3	2996	68	2.3	0.9890	1.00 (0.72, 1.39)	1.00 (0.71, 1.40)	0.00 (-0.01, 0.01)	

Analysis is based on study 1245.110.
^ Patients with NYHA class I are counted in subgroup NYHA class II.
Risk ratios and odds ratios with confidence intervals (CIs) are estimated by Cochran-Mantel-Haenszel method. For risk differences standard Wald asymptotic confidence limits are calculated. A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied in case of any zero cells in contingency table.
Only treatment emergent AEs are displayed (onset between first dose until treatment stop +7 days).
MedDRA version: 23.1. * Chi-square test for treatment effect ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction).

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Table R.1.2.5: 1 Proportion of patients with any adverse event occuring in at least 1% of the patients in either treatment arm in the overall population on PT level by SOC and PT, 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	2989	49	1.6	2996	44	1.5	0.5934	0.90 (0.60, 1.34)	0.89 (0.59, 1.35)	0.00 (-0.01, 0.00)	

Analysis is based on study 1245.110.
^ Patients with NYHA class I are counted in subgroup NYHA class II.
Risk ratios and odds ratios with confidence intervals (CIs) are estimated by Cochran-Mantel-Haenszel method. For risk differences standard Wald asymptotic confidence limits are calculated. A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied in case of any zero cells in contingency table.
Only treatment emergent AEs are displayed (onset between first dose until treatment stop +7 days).
MedDRA version: 23.1. * Chi-square test for treatment effect ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction).

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Table R.1.2.5: 1 Proportion of patients with any adverse event occuring in at least 1% of the patients in either treatment arm in the overall population on PT level by SOC and PT, 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	2989	33	1.1	2996	19	0.6	0.0502	0.57 (0.33, 1.01)	0.57 (0.32, 1.01)	0.00 (-0.01, 0.00)	

Analysis is based on study 1245.110.
^ Patients with NYHA class I are counted in subgroup NYHA class II.
Risk ratios and odds ratios with confidence intervals (CIs) are estimated by Cochran-Mantel-Haenszel method. For risk differences standard Wald asymptotic confidence limits are calculated. A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied in case of any zero cells in contingency table.
Only treatment emergent AEs are displayed (onset between first dose until treatment stop +7 days).
MedDRA version: 23.1. * Chi-square test for treatment effect ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction).

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Table R.1.2.5: 1 Proportion of patients with any adverse event occuring in at least 1% of the patients in either treatment arm in the overall population on PT level by SOC and PT, 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	2989	88	2.9	2996	80	2.7	0.5212	0.91 (0.67, 1.22)	0.90 (0.67, 1.23)	0.00 (-0.01, 0.01)	

Analysis is based on study 1245.110.
^ Patients with NYHA class I are counted in subgroup NYHA class II.
Risk ratios and odds ratios with confidence intervals (CIs) are estimated by Cochran-Mantel-Haenszel method. For risk differences standard Wald asymptotic confidence limits are calculated. A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied in case of any zero cells in contingency table.
Only treatment emergent AEs are displayed (onset between first dose until treatment stop +7 days).
MedDRA version: 23.1. * Chi-square test for treatment effect ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction).

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Table R.1.2.5: 1 Proportion of patients with any adverse event occuring in at least 1% of the patients in either treatment arm in the overall population on PT level by SOC and PT, 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	2989	38	1.3	2996	56	1.9	0.0629	1.47 (0.98, 2.21)	1.48 (0.98, 2.24)	0.01 (0.00, 0.01)	

Analysis is based on study 1245.110.
^ Patients with NYHA class I are counted in subgroup NYHA class II.
Risk ratios and odds ratios with confidence intervals (CIs) are estimated by Cochran-Mantel-Haenszel method. For risk differences standard Wald asymptotic confidence limits are calculated. A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied in case of any zero cells in contingency table.
Only treatment emergent AEs are displayed (onset between first dose until treatment stop +7 days).
MedDRA version: 23.1. * Chi-square test for treatment effect ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction).

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Table R.1.2.5: 1 Proportion of patients with any adverse event occuring in at least 1% of the patients in either treatment arm in the overall population on PT level by SOC and PT, 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	2989	53	1.8	2996	56	1.9	0.7813	1.05 (0.73, 1.53)	1.06 (0.72, 1.54)	0.00 (-0.01, 0.01)	

Analysis is based on study 1245.110.
^ Patients with NYHA class I are counted in subgroup NYHA class II.
Risk ratios and odds ratios with confidence intervals (CIs) are estimated by Cochran-Mantel-Haenszel method. For risk differences standard Wald asymptotic confidence limits are calculated. A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied in case of any zero cells in contingency table.
Only treatment emergent AEs are displayed (onset between first dose until treatment stop +7 days).
MedDRA version: 23.1. * Chi-square test for treatment effect ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction).

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Table R.1.2.5: 1 Proportion of patients with any adverse event occuring in at least 1% of the patients in either treatment arm in the overall population on PT level by SOC and PT, 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	2989	50	1.7	2996	47	1.6	0.7499	0.94 (0.63, 1.39)	0.94 (0.63, 1.40)	0.00 (-0.01, 0.01)	

Analysis is based on study 1245.110.
^ Patients with NYHA class I are counted in subgroup NYHA class II.
Risk ratios and odds ratios with confidence intervals (CIs) are estimated by Cochran-Mantel-Haenszel method. For risk differences standard Wald asymptotic confidence limits are calculated. A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied in case of any zero cells in contingency table.
Only treatment emergent AEs are displayed (onset between first dose until treatment stop +7 days).
MedDRA version: 23.1. * Chi-square test for treatment effect ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction).

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Table R.1.2.5: 1 Proportion of patients with any adverse event occuring in at least 1% of the patients in either treatment arm in the overall population on PT level by SOC and PT, 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	2989	34	1.1	2996	37	1.2	0.7277	1.09 (0.68, 1.72)	1.09 (0.68, 1.74)	0.00 (0.00, 0.01)	

Analysis is based on study 1245.110.
^ Patients with NYHA class I are counted in subgroup NYHA class II.
Risk ratios and odds ratios with confidence intervals (CIs) are estimated by Cochran-Mantel-Haenszel method. For risk differences standard Wald asymptotic confidence limits are calculated. A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied in case of any zero cells in contingency table.
Only treatment emergent AEs are displayed (onset between first dose until treatment stop +7 days).
MedDRA version: 23.1. * Chi-square test for treatment effect ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction).

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Table R.1.2.5: 1 Proportion of patients with any adverse event occuring in at least 1% of the patients in either treatment arm in the overall population on PT level by SOC and PT, 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	2989	30	1.0	2996	31	1.0	0.9049	1.03 (0.63, 1.70)	1.03 (0.62, 1.71)	0.00 (0.00, 0.01)	

Analysis is based on study 1245.110.
^ Patients with NYHA class I are counted in subgroup NYHA class II.
Risk ratios and odds ratios with confidence intervals (CIs) are estimated by Cochran-Mantel-Haenszel method. For risk differences standard Wald asymptotic confidence limits are calculated. A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied in case of any zero cells in contingency table.
Only treatment emergent AEs are displayed (onset between first dose until treatment stop +7 days).
MedDRA version: 23.1. * Chi-square test for treatment effect ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction).

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Table R.1.2.5: 1 Proportion of patients with any adverse event occuring in at least 1% of the patients in either treatment arm in the overall population on PT level by SOC and PT, 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	2989	219	7.3	2996	213	7.1	0.7452	0.97 (0.81, 1.16)	0.97 (0.80, 1.18)	0.00 (-0.02, 0.01)	

Analysis is based on study 1245.110.
^ Patients with NYHA class I are counted in subgroup NYHA class II.
Risk ratios and odds ratios with confidence intervals (CIs) are estimated by Cochran-Mantel-Haenszel method. For risk differences standard Wald asymptotic confidence limits are calculated. A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied in case of any zero cells in contingency table.
Only treatment emergent AEs are displayed (onset between first dose until treatment stop +7 days).
MedDRA version: 23.1. * Chi-square test for treatment effect ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction).

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Table R.1.2.5: 1 Proportion of patients with any adverse event occuring in at least 1% of the patients in either treatment arm in the overall population on PT level by SOC and PT, 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	2989	51	1.7	2996	61	2.0	0.3465	1.19 (0.83, 1.72)	1.20 (0.82, 1.74)	0.00 (0.00, 0.01)	

Analysis is based on study 1245.110.
^ Patients with NYHA class I are counted in subgroup NYHA class II.
Risk ratios and odds ratios with confidence intervals (CIs) are estimated by Cochran-Mantel-Haenszel method. For risk differences standard Wald asymptotic confidence limits are calculated. A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied in case of any zero cells in contingency table.
Only treatment emergent AEs are displayed (onset between first dose until treatment stop +7 days).
MedDRA version: 23.1. * Chi-square test for treatment effect ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction).

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Table R.1.2.5: 1 Proportion of patients with any adverse event occuring in at least 1% of the patients in either treatment arm in the overall population on PT level by SOC and PT, 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	2989	31	1.0	2996	29	1.0	0.7882	0.93 (0.56, 1.54)	0.93 (0.56, 1.55)	0.00 (-0.01, 0.00)	

Analysis is based on study 1245.110.
^ Patients with NYHA class I are counted in subgroup NYHA class II.
Risk ratios and odds ratios with confidence intervals (CIs) are estimated by Cochran-Mantel-Haenszel method. For risk differences standard Wald asymptotic confidence limits are calculated. A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied in case of any zero cells in contingency table.
Only treatment emergent AEs are displayed (onset between first dose until treatment stop +7 days).
MedDRA version: 23.1. * Chi-square test for treatment effect ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction).

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Table R.1.2.5: 1 Proportion of patients with any adverse event occuring in at least 1% of the patients in either treatment arm in the overall population on PT level by SOC and PT, 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	2989	16	0.5	2996	30	1.0	0.0390	1.87 (1.02, 3.42)	1.88 (1.02, 3.46)	0.00 (0.00, 0.01)	
Sex											0.9573
Male	1653	10	0.6	1658	19	1.1	0.0948	1.89 (0.88, 4.06)	1.90 (0.88, 4.11)	0.01 (0.00, 0.01)	
Female	1336	6	0.4	1338	11	0.8	0.2250	1.83 (0.68, 4.94)	1.84 (0.68, 4.98)	0.00 (0.00, 0.01)	
Age [years]											0.8689
<70	1084	4	0.4	1066	8	0.8	0.2352	2.03 (0.61, 6.73)	2.04 (0.61, 6.80)	0.00 (0.00, 0.01)	
>=70	1905	12	0.6	1930	22	1.1	0.0921	1.81 (0.90, 3.65)	1.82 (0.90, 3.69)	0.01 (0.00, 0.01)	
Region											0.8428
North America	359	5	1.4	359	11	3.1	0.1293	2.20 (0.77, 6.27)	2.24 (0.77, 6.51)	0.02 (0.00, 0.04)	
Latin America	757	1	0.1	758	0	0	0.4786	0.33 (0.01, 8.16)	0.33 (0.01, 8.17)	0.00 (0.00, 0.00)	
Europe	1341	3	0.2	1346	5	0.4	0.4821	1.66 (0.40, 6.93)	1.66 (0.40, 6.97)	0.00 (0.00, 0.01)	
Asia	343	1	0.3	343	3	0.9	0.3159	3.00 (0.31, 28.70)	3.02 (0.31, 29.15)	0.01 (-0.01, 0.02)	
Other	189	6	3.2	190	11	5.8	0.2188	1.82 (0.69, 4.83)	1.87 (0.68, 5.18)	0.03 (-0.02, 0.07)	
OECD member											0.2513
No	847	2	0.2	868	1	0.1	0.5491	0.49 (0.04, 5.37)	0.49 (0.04, 5.38)	0.00 (-0.01, 0.00)	
Yes	2142	14	0.7	2128	29	1.4	0.0203	2.09 (1.10, 3.93)	2.10 (1.11, 3.99)	0.01 (0.00, 0.01)	
Baseline NYHA											0.6903
II^	2450	11	0.4	2435	22	0.9	0.0525	2.01 (0.98, 4.14)	2.02 (0.98, 4.18)	0.00 (0.00, 0.01)	
III/IV	539	5	0.9	561	8	1.4	0.4445	1.54 (0.51, 4.67)	1.55 (0.50, 4.75)	0.00 (-0.01, 0.02)	
Baseline Diabetes Status											0.2173
Diabetic	1471	5	0.3	1465	15	1.0	0.0243	3.01 (1.10, 8.27)	3.03 (1.10, 8.37)	0.01 (0.00, 0.01)	
Non-Diabetic	1518	11	0.7	1531	15	1.0	0.4437	1.35 (0.62, 2.93)	1.36 (0.62, 2.96)	0.00 (0.00, 0.01)	

Analysis is based on study 1245.110.
^ Patients with NYHA class I are counted in subgroup NYHA class II.
Risk ratios and odds ratios with confidence intervals (CIs) are estimated by Cochran-Mantel-Haenszel method. For risk differences standard Wald asymptotic confidence limits are calculated. A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied in case of any zero cells in contingency table.
Only treatment emergent AEs are displayed (onset between first dose until treatment stop +7 days).
MedDRA version: 23.1. * Chi-square test for treatment effect ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction).

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Table R.1.2.5: 1 Proportion of patients with any adverse event occuring in at least 1% of the patients in either treatment arm in the overall population on PT level by SOC and PT, 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 Diabetes Status											0.0612
Diabetic	1471	5	0.3	1465	15	1.0	0.0243	3.01 (1.10, 8.27)	3.03 (1.10, 8.37)	0.01 (0.00, 0.01)	
Pre-Diabetes	979	5	0.5	1001	13	1.3	0.0647	2.54 (0.91, 7.11)	2.56 (0.91, 7.22)	0.01 (0.00, 0.02)	
Normal (no pre-diabetes)	539	6	1.1	530	2	0.4	0.1628	0.34 (0.07, 1.67)	0.34 (0.07, 1.67)	-0.01 (-0.02, 0.00)	
Baseline BMI [kg/m²]											0.2630
<30	1641	8	0.5	1654	10	0.6	0.6485	1.24 (0.49, 3.13)	1.24 (0.49, 3.15)	0.00 (0.00, 0.01)	
>=30	1348	8	0.6	1342	20	1.5	0.0219	2.51 (1.11, 5.68)	2.53 (1.11, 5.77)	0.01 (0.00, 0.02)	
Baseline eGFR (CKD-EPI) [mL/min/1.73m²]											0.4044
>=60	1505	4	0.3	1493	11	0.7	0.0676	2.77 (0.88, 8.69)	2.79 (0.88, 8.77)	0.00 (0.00, 0.01)	
<60	1482	12	0.8	1503	19	1.3	0.2208	1.56 (0.76, 3.20)	1.57 (0.76, 3.24)	0.00 (0.00, 0.01)	
History of HHF (in the last 12 months)											0.2429
No	2320	13	0.6	2297	19	0.8	0.2745	1.48 (0.73, 2.98)	1.48 (0.73, 3.00)	0.00 (0.00, 0.01)	
Yes	669	3	0.4	699	11	1.6	0.0387	3.51 (0.98, 12.52)	3.55 (0.99, 12.78)	0.01 (0.00, 0.02)	
Baseline SBP (</>= median)											0.3116
< median	1474	7	0.5	1496	18	1.2	0.0298	2.53 (1.06, 6.05)	2.55 (1.06, 6.13)	0.01 (0.00, 0.01)	
>= median	1515	9	0.6	1500	12	0.8	0.4966	1.35 (0.57, 3.19)	1.35 (0.57, 3.21)	0.00 (0.00, 0.01)	
History of atrial fibrillation or atrial flutter											0.7610
No	1426	5	0.4	1417	8	0.6	0.3979	1.61 (0.53, 4.91)	1.61 (0.53, 4.94)	0.00 (0.00, 0.01)	
Yes	1558	11	0.7	1575	22	1.4	0.0583	1.98 (0.96, 4.07)	1.99 (0.96, 4.12)	0.01 (0.00, 0.01)	

Analysis is based on study 1245.110.
^ Patients with NYHA class I are counted in subgroup NYHA class II.
Risk ratios and odds ratios with confidence intervals (CIs) are estimated by Cochran-Mantel-Haenszel method. For risk differences standard Wald asymptotic confidence limits are calculated. A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied in case of any zero cells in contingency table.
Only treatment emergent AEs are displayed (onset between first dose until treatment stop +7 days).
MedDRA version: 23.1. * Chi-square test for treatment effect ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction).

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Table R.1.2.5: 1 Proportion of patients with any adverse event occuring in at least 1% of the patients in either treatment arm in the overall population on PT level by SOC and PT, 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 LVEF [%]											0.4758
< 50	988	1	0.1	995	4	0.4	0.1817	3.97 (0.44, 35.47)	3.98 (0.44, 35.71)	0.00 (0.00, 0.01)	
>= 50	2001	15	0.7	2001	26	1.3	0.0842	1.73 (0.92, 3.26)	1.74 (0.92, 3.30)	0.01 (0.00, 0.01)	
Baseline LVEF [%]											0.7503
<50	988	1	0.1	995	4	0.4	0.1817	3.97 (0.44, 35.47)	3.98 (0.44, 35.71)	0.00 (0.00, 0.01)	
50 to <60	1030	4	0.4	1028	6	0.6	0.5241	1.50 (0.43, 5.31)	1.51 (0.42, 5.35)	0.00 (0.00, 0.01)	
>=60	971	11	1.1	973	20	2.1	0.1044	1.81 (0.87, 3.77)	1.83 (0.87, 3.84)	0.01 (0.00, 0.02)	
Baseline NT-proBNP [pg/mL] (</>=median by atrial fibrillation/flutter status)											0.0833
< median	1507	6	0.4	1476	19	1.3	0.0077	3.23 (1.29, 8.07)	3.26 (1.30, 8.19)	0.01 (0.00, 0.02)	
>= median	1475	10	0.7	1516	11	0.7	0.8761	1.07 (0.46, 2.51)	1.07 (0.45, 2.53)	0.00 (-0.01, 0.01)	
Baseline uric acid [mg/dL] (tertiles)											0.2361
<T1	975	1	0.1	963	5	0.5	0.0988	5.06 (0.59, 43.25)	5.08 (0.59, 43.59)	0.00 (0.00, 0.01)	
>=T1 and <T2	966	2	0.2	1032	9	0.9	0.0447	4.21 (0.91, 19.45)	4.24 (0.91, 19.68)	0.01 (0.00, 0.01)	
>=T2	1016	13	1.3	970	16	1.6	0.4921	1.29 (0.62, 2.67)	1.29 (0.62, 2.70)	0.00 (-0.01, 0.01)	
Baseline use of MRA											0.8708
No	1865	11	0.6	1878	20	1.1	0.1088	1.81 (0.87, 3.76)	1.81 (0.87, 3.80)	0.00 (0.00, 0.01)	
Yes	1124	5	0.4	1118	10	0.9	0.1916	2.01 (0.69, 5.86)	2.02 (0.69, 5.93)	0.00 (0.00, 0.01)	
Baseline use of ACE-inhibitor, ARB or ARNi											0.5266
No	586	7	1.2	568	10	1.8	0.4249	1.47 (0.56, 3.85)	1.48 (0.56, 3.92)	0.01 (-0.01, 0.02)	
Yes	2403	9	0.4	2428	20	0.8	0.0433	2.20 (1.00, 4.82)	2.21 (1.00, 4.86)	0.00 (0.00, 0.01)	

Analysis is based on study 1245.110.
^ Patients with NYHA class I are counted in subgroup NYHA class II.
Risk ratios and odds ratios with confidence intervals (CIs) are estimated by Cochran-Mantel-Haenszel method. For risk differences standard Wald asymptotic confidence limits are calculated. A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied in case of any zero cells in contingency table.
Only treatment emergent AEs are displayed (onset between first dose until treatment stop +7 days).
MedDRA version: 23.1. * Chi-square test for treatment effect ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction).

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Table R.1.2.5: 1 Proportion of patients with any adverse event occuring in at least 1% of the patients in either treatment arm in the overall population on PT level by SOC and PT, 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	2989	25	0.8	2996	36	1.2	0.1596	1.44 (0.86, 2.39)	1.44 (0.86, 2.41)	0.00 (0.00, 0.01)	

Analysis is based on study 1245.110.
^ Patients with NYHA class I are counted in subgroup NYHA class II.
Risk ratios and odds ratios with confidence intervals (CIs) are estimated by Cochran-Mantel-Haenszel method. For risk differences standard Wald asymptotic confidence limits are calculated. A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied in case of any zero cells in contingency table.
Only treatment emergent AEs are displayed (onset between first dose until treatment stop +7 days).
MedDRA version: 23.1. * Chi-square test for treatment effect ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction).

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Table R.1.2.5: 1 Proportion of patients with any adverse event occuring in at least 1% of the patients in either treatment arm in the overall population on PT level by SOC and PT, 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	2989	187	6.3	2996	134	4.5	0.0022	0.71 (0.58,	0.89)	0.70 (0.56,	0.88)	-0.02	(-0.03,-0.01)	
Sex														0.5796
Male	1653	113	6.8	1658	77	4.6	0.0067	0.68 (0.51,	0.90)	0.66 (0.49,	0.89)	-0.02	(-0.04,-0.01)	
Female	1336	74	5.5	1338	57	4.3	0.1256	0.77 (0.55,	1.08)	0.76 (0.53,	1.08)	-0.01	(-0.03, 0.00)	
Age [years]														0.5226
<70	1084	51	4.7	1066	40	3.8	0.2728	0.80 (0.53,	1.20)	0.79 (0.52,	1.21)	-0.01	(-0.03, 0.01)	
>=70	1905	136	7.1	1930	94	4.9	0.0031	0.68 (0.53,	0.88)	0.67 (0.51,	0.87)	-0.02	(-0.04,-0.01)	
Region														0.4980
North America	359	20	5.6	359	13	3.6	0.2122	0.65 (0.33,	1.29)	0.64 (0.31,	1.30)	-0.02	(-0.05, 0.01)	
Latin America	757	52	6.9	758	41	5.4	0.2364	0.79 (0.53,	1.17)	0.78 (0.51,	1.18)	-0.01	(-0.04, 0.01)	
Europe	1341	75	5.6	1346	45	3.3	0.0048	0.60 (0.42,	0.86)	0.58 (0.40,	0.85)	-0.02	(-0.04,-0.01)	
Asia	343	25	7.3	343	26	7.6	0.8843	1.04 (0.61,	1.76)	1.04 (0.59,	1.85)	0.00	(-0.04, 0.04)	
Other	189	15	7.9	190	9	4.7	0.2010	0.60 (0.27,	1.33)	0.58 (0.25,	1.35)	-0.03	(-0.08, 0.02)	
OECD member														0.3866
No	847	56	6.6	868	47	5.4	0.2970	0.82 (0.56,	1.19)	0.81 (0.54,	1.21)	-0.01	(-0.03, 0.01)	
Yes	2142	131	6.1	2128	87	4.1	0.0026	0.67 (0.51,	0.87)	0.65 (0.50,	0.86)	-0.02	(-0.03,-0.01)	
Baseline NYHA														0.3457
II^	2450	144	5.9	2435	96	3.9	0.0018	0.67 (0.52,	0.86)	0.66 (0.50,	0.86)	-0.02	(-0.03,-0.01)	
III/IV	539	43	8.0	561	38	6.8	0.4446	0.85 (0.56,	1.29)	0.84 (0.53,	1.32)	-0.01	(-0.04, 0.02)	
Baseline Diabetes Status														0.1886
Diabetic	1471	103	7.0	1465	83	5.7	0.1372	0.81 (0.61,	1.07)	0.80 (0.59,	1.08)	-0.01	(-0.03, 0.00)	
Non-Diabetic	1518	84	5.5	1531	51	3.3	0.0031	0.60 (0.43,	0.85)	0.59 (0.41,	0.84)	-0.02	(-0.04,-0.01)	

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^ Patients with NYHA class I are counted in subgroup NYHA class II.
Risk ratios and odds ratios with confidence intervals (CIs) are estimated by Cochran-Mantel-Haenszel method. For risk differences standard Wald asymptotic confidence limits are calculated. A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied in case of any zero cells in contingency table.
Only treatment emergent AEs are displayed (onset between first dose until treatment stop +7 days).
MedDRA version: 23.1. * Chi-square test for treatment effect ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction).

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Table R.1.2.5: 1 Proportion of patients with any adverse event occuring in at least 1% of the patients in either treatment arm in the overall population on PT level by SOC and PT, 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 Diabetes Status											0.4256
Diabetic	1471	103	7.0	1465	83	5.7	0.1372	0.81 (0.61, 1.07)	0.80 (0.59, 1.08)	-0.01 (-0.03, 0.00)	
Pre-Diabetes	979	50	5.1	1001	31	3.1	0.0240	0.61 (0.39, 0.94)	0.59 (0.38, 0.94)	-0.02 (-0.04, 0.00)	
Normal (no pre-diabetes)	539	34	6.3	530	20	3.8	0.0585	0.60 (0.35, 1.03)	0.58 (0.33, 1.03)	-0.03 (-0.05, 0.00)	
Baseline BMI [kg/m²]											0.2178
<30	1641	107	6.5	1654	86	5.2	0.1064	0.80 (0.61, 1.05)	0.79 (0.59, 1.05)	-0.01 (-0.03, 0.00)	
>=30	1348	80	5.9	1342	48	3.6	0.0041	0.60 (0.42, 0.86)	0.59 (0.41, 0.85)	-0.02 (-0.04,-0.01)	
Baseline eGFR (CKD-EPI) [mL/min/1.73m²]											0.9248
>=60	1505	67	4.5	1493	48	3.2	0.0779	0.72 (0.50, 1.04)	0.71 (0.49, 1.04)	-0.01 (-0.03, 0.00)	
<60	1482	120	8.1	1503	86	5.7	0.0105	0.71 (0.54, 0.92)	0.69 (0.52, 0.92)	-0.02 (-0.04,-0.01)	
History of HHF (in the last 12 months)											0.0932
No	2320	138	5.9	2297	86	3.7	0.0005	0.63 (0.48, 0.82)	0.62 (0.47, 0.81)	-0.02 (-0.03,-0.01)	
Yes	669	49	7.3	699	48	6.9	0.7418	0.94 (0.64, 1.38)	0.93 (0.62, 1.41)	0.00 (-0.03, 0.02)	
Baseline SBP (</>= median)											0.1929
< median	1474	96	6.5	1496	60	4.0	0.0022	0.62 (0.45, 0.84)	0.60 (0.43, 0.84)	-0.03 (-0.04,-0.01)	
>= median	1515	91	6.0	1500	74	4.9	0.1951	0.82 (0.61, 1.11)	0.81 (0.59, 1.11)	-0.01 (-0.03, 0.01)	
History of atrial fibrillation or atrial flutter											0.0872
No	1426	74	5.2	1417	65	4.6	0.4566	0.88 (0.64, 1.22)	0.88 (0.62, 1.24)	-0.01 (-0.02, 0.01)	
Yes	1558	113	7.3	1575	69	4.4	0.0006	0.60 (0.45, 0.81)	0.59 (0.43, 0.80)	-0.03 (-0.05,-0.01)	

Analysis is based on study 1245.110.
^ Patients with NYHA class I are counted in subgroup NYHA class II.
Risk ratios and odds ratios with confidence intervals (CIs) are estimated by Cochran-Mantel-Haenszel method. For risk differences standard Wald asymptotic confidence limits are calculated. A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied in case of any zero cells in contingency table.
Only treatment emergent AEs are displayed (onset between first dose until treatment stop +7 days).
MedDRA version: 23.1. * Chi-square test for treatment effect ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction).

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Table R.1.2.5: 1 Proportion of patients with any adverse event occuring in at least 1% of the patients in either treatment arm in the overall population on PT level by SOC and PT, 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 LVEF [%]											0.1585
< 50	988	56	5.7	995	31	3.1	0.0055	0.55 (0.36, 0.84)	0.54 (0.34, 0.84)	-0.03 (-0.04,-0.01)	
>= 50	2001	131	6.5	2001	103	5.1	0.0592	0.79 (0.61, 1.01)	0.77 (0.59, 1.01)	-0.01 (-0.03, 0.00)	
Baseline LVEF [%]											0.3431
<50	988	56	5.7	995	31	3.1	0.0055	0.55 (0.36, 0.84)	0.54 (0.34, 0.84)	-0.03 (-0.04,-0.01)	
50 to <60	1030	63	6.1	1028	52	5.1	0.2960	0.83 (0.58, 1.18)	0.82 (0.56, 1.19)	-0.01 (-0.03, 0.01)	
>=60	971	68	7.0	973	51	5.2	0.1052	0.75 (0.53, 1.06)	0.73 (0.51, 1.07)	-0.02 (-0.04, 0.00)	
Baseline NT-proBNP [pg/mL] (</>=median by atrial fibrillation/flutter status)											0.9034
< median	1507	83	5.5	1476	57	3.9	0.0336	0.70 (0.50, 0.97)	0.69 (0.49, 0.97)	-0.02 (-0.03, 0.00)	
>= median	1475	104	7.1	1516	77	5.1	0.0238	0.72 (0.54, 0.96)	0.71 (0.52, 0.96)	-0.02 (-0.04, 0.00)	
Baseline uric acid [mg/dL] (tertiles)											0.4306
<T1	975	51	5.2	963	44	4.6	0.4999	0.87 (0.59, 1.29)	0.87 (0.57, 1.31)	-0.01 (-0.03, 0.01)	
>=T1 and <T2	966	56	5.8	1032	36	3.5	0.0139	0.60 (0.40, 0.91)	0.59 (0.38, 0.90)	-0.02 (-0.04, 0.00)	
>=T2	1016	79	7.8	970	53	5.5	0.0387	0.70 (0.50, 0.98)	0.69 (0.48, 0.98)	-0.02 (-0.04, 0.00)	
Baseline use of MRA											0.7727
No	1865	114	6.1	1878	80	4.3	0.0106	0.70 (0.53, 0.92)	0.68 (0.51, 0.92)	-0.02 (-0.03, 0.00)	
Yes	1124	73	6.5	1118	54	4.8	0.0882	0.74 (0.53, 1.05)	0.73 (0.51, 1.05)	-0.02 (-0.04, 0.00)	
Baseline use of ACE-inhibitor, ARB or ARNi											0.0968
No	586	36	6.1	568	35	6.2	0.9895	1.00 (0.64, 1.57)	1.00 (0.62, 1.62)	0.00 (-0.03, 0.03)	
Yes	2403	151	6.3	2428	99	4.1	0.0005	0.65 (0.51, 0.83)	0.63 (0.49, 0.82)	-0.02 (-0.03,-0.01)	

Analysis is based on study 1245.110.
^ Patients with NYHA class I are counted in subgroup NYHA class II.
Risk ratios and odds ratios with confidence intervals (CIs) are estimated by Cochran-Mantel-Haenszel method. For risk differences standard Wald asymptotic confidence limits are calculated. A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied in case of any zero cells in contingency table.
Only treatment emergent AEs are displayed (onset between first dose until treatment stop +7 days).
MedDRA version: 23.1. * Chi-square test for treatment effect ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction).

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Table R.1.2.5: 1 Proportion of patients with any adverse event occuring in at least 1% of the patients in either treatment arm in the overall population on PT level by SOC and PT, 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	2989	46	1.5	2996	26	0.9	0.0173	0.56 (0.35, 0.91)	0.56 (0.35, 0.91)	-0.01 (-0.01, 0.00)	
Sex											0.0217
Male	1653	29	1.8	1658	9	0.5	0.0011	0.31 (0.15, 0.65)	0.31 (0.14, 0.65)	-0.01 (-0.02, 0.00)	
Female	1336	17	1.3	1338	17	1.3	0.9965	1.00 (0.51, 1.95)	1.00 (0.51, 1.96)	0.00 (-0.01, 0.01)	
Age [years]											0.3262
<70	1084	14	1.3	1066	5	0.5	0.0416	0.36 (0.13, 1.00)	0.36 (0.13, 1.00)	-0.01 (-0.02, 0.00)	
>=70	1905	32	1.7	1930	21	1.1	0.1166	0.65 (0.37, 1.12)	0.64 (0.37, 1.12)	-0.01 (-0.01, 0.00)	
Region											0.1855
North America	359	8	2.2	359	3	0.8	0.1287	0.38 (0.10, 1.40)	0.37 (0.10, 1.41)	-0.01 (-0.03, 0.00)	
Latin America	757	10	1.3	758	2	0.3	0.0203	0.20 (0.04, 0.91)	0.20 (0.04, 0.90)	-0.01 (-0.02, 0.00)	
Europe	1341	14	1.0	1346	8	0.6	0.1959	0.57 (0.24, 1.35)	0.57 (0.24, 1.36)	0.00 (-0.01, 0.00)	
Asia	343	13	3.8	343	8	2.3	0.2678	0.62 (0.26, 1.47)	0.61 (0.25, 1.48)	-0.01 (-0.04, 0.01)	
Other	189	1	0.5	190	5	2.6	0.1011	4.97 (0.59, 42.17)	5.08 (0.59, 43.91)	0.02 (0.00, 0.05)	
OECD member											0.7614
No	847	10	1.2	868	5	0.6	0.1788	0.49 (0.17, 1.42)	0.48 (0.17, 1.42)	-0.01 (-0.01, 0.00)	
Yes	2142	36	1.7	2128	21	1.0	0.0482	0.59 (0.34, 1.00)	0.58 (0.34, 1.00)	-0.01 (-0.01, 0.00)	
Baseline NYHA											0.6756
II^	2450	36	1.5	2435	19	0.8	0.0225	0.53 (0.31, 0.92)	0.53 (0.30, 0.92)	-0.01 (-0.01, 0.00)	
III/IV	539	10	1.9	561	7	1.2	0.4142	0.67 (0.26, 1.75)	0.67 (0.25, 1.77)	-0.01 (-0.02, 0.01)	
Baseline Diabetes Status											0.3834
Diabetic	1471	28	1.9	1465	13	0.9	0.0190	0.47 (0.24, 0.90)	0.46 (0.24, 0.89)	-0.01 (-0.02, 0.00)	
Non-Diabetic	1518	18	1.2	1531	13	0.8	0.3542	0.72 (0.35, 1.46)	0.71 (0.35, 1.46)	0.00 (-0.01, 0.00)	

Analysis is based on study 1245.110.
^ Patients with NYHA class I are counted in subgroup NYHA class II.
Risk ratios and odds ratios with confidence intervals (CIs) are estimated by Cochran-Mantel-Haenszel method. For risk differences standard Wald asymptotic confidence limits are calculated. A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied in case of any zero cells in contingency table.
Only treatment emergent AEs are displayed (onset between first dose until treatment stop +7 days).
MedDRA version: 23.1. * Chi-square test for treatment effect ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction).

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Table R.1.2.5: 1 Proportion of patients with any adverse event occuring in at least 1% of the patients in either treatment arm in the overall population on PT level by SOC and PT, 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 **
Baseline Diabetes Status											0.6260
Diabetic	1471	28	1.9	1465	13	0.9	0.0190	0.47 (0.24, 0.90)	0.46 (0.24, 0.89)	-0.01 (-0.02, 0.00)	
Pre-Diabetes	979	14	1.4	1001	11	1.1	0.5094	0.77 (0.35, 1.68)	0.77 (0.35, 1.70)	0.00 (-0.01, 0.01)	
Normal (no pre-diabetes)	539	4	0.7	530	2	0.4	0.4248	0.51 (0.09, 2.76)	0.51 (0.09, 2.78)	0.00 (-0.01, 0.01)	
Baseline BMI [kg/m²]											0.2691
<30	1641	29	1.8	1654	13	0.8	0.0121	0.44 (0.23, 0.85)	0.44 (0.23, 0.85)	-0.01 (-0.02, 0.00)	
>=30	1348	17	1.3	1342	13	1.0	0.4702	0.77 (0.37, 1.58)	0.77 (0.37, 1.58)	0.00 (-0.01, 0.01)	
Baseline eGFR (CKD-EPI) [mL/min/1.73m²]											0.8640
>=60	1505	17	1.1	1493	10	0.7	0.1827	0.59 (0.27, 1.29)	0.59 (0.27, 1.29)	0.00 (-0.01, 0.00)	
<60	1482	29	2.0	1503	16	1.1	0.0455	0.54 (0.30, 1.00)	0.54 (0.29, 1.00)	-0.01 (-0.02, 0.00)	
History of HHF (in the last 12 months)											0.1894
No	2320	37	1.6	2297	17	0.7	0.0069	0.46 (0.26, 0.82)	0.46 (0.26, 0.82)	-0.01 (-0.01, 0.00)	
Yes	669	9	1.3	699	9	1.3	0.9254	0.96 (0.38, 2.40)	0.96 (0.38, 2.42)	0.00 (-0.01, 0.01)	
Baseline SBP (</>= median)											0.2986
< median	1474	24	1.6	1496	17	1.1	0.2507	0.70 (0.38, 1.29)	0.69 (0.37, 1.30)	0.00 (-0.01, 0.00)	
>= median	1515	22	1.5	1500	9	0.6	0.0204	0.41 (0.19, 0.89)	0.41 (0.19, 0.89)	-0.01 (-0.02, 0.00)	
History of atrial fibrillation or atrial flutter											0.1698
No	1426	22	1.5	1417	8	0.6	0.0107	0.37 (0.16, 0.82)	0.36 (0.16, 0.82)	-0.01 (-0.02, 0.00)	
Yes	1558	24	1.5	1575	18	1.1	0.3333	0.74 (0.40, 1.36)	0.74 (0.40, 1.37)	0.00 (-0.01, 0.00)	

Analysis is based on study 1245.110.
^ Patients with NYHA class I are counted in subgroup NYHA class II.
Risk ratios and odds ratios with confidence intervals (CIs) are estimated by Cochran-Mantel-Haenszel method. For risk differences standard Wald asymptotic confidence limits are calculated. A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied in case of any zero cells in contingency table.
Only treatment emergent AEs are displayed (onset between first dose until treatment stop +7 days).
MedDRA version: 23.1. * Chi-square test for treatment effect ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction).

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Table R.1.2.5: 1 Proportion of patients with any adverse event occuring in at least 1% of the patients in either treatment arm in the overall population on PT level by SOC and PT, 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 **
Baseline LVEF [%]											0.0389
< 50	988	16	1.6	995	3	0.3	0.0026	0.19 (0.05, 0.64)	0.18 (0.05, 0.63)	-0.01 (-0.02, 0.00)	
>= 50	2001	30	1.5	2001	23	1.1	0.3331	0.77 (0.45, 1.32)	0.76 (0.44, 1.32)	0.00 (-0.01, 0.00)	
Baseline LVEF [%]											0.0918
<50	988	16	1.6	995	3	0.3	0.0026	0.19 (0.05, 0.64)	0.18 (0.05, 0.63)	-0.01 (-0.02, 0.00)	
50 to <60	1030	16	1.6	1028	10	1.0	0.2383	0.63 (0.29, 1.37)	0.62 (0.28, 1.38)	-0.01 (-0.02, 0.00)	
>=60	971	14	1.4	973	13	1.3	0.8421	0.93 (0.44, 1.96)	0.93 (0.43, 1.98)	0.00 (-0.01, 0.01)	
Baseline NT-proBNP [pg/mL] (</>=median by atrial fibrillation/flutter status)											0.8284
< median	1507	23	1.5	1476	12	0.8	0.0705	0.53 (0.27, 1.07)	0.53 (0.26, 1.07)	-0.01 (-0.01, 0.00)	
>= median	1475	23	1.6	1516	14	0.9	0.1157	0.59 (0.31, 1.15)	0.59 (0.30, 1.15)	-0.01 (-0.01, 0.00)	
Baseline uric acid [mg/dL] (tertiles)											0.0536
<T1	975	13	1.3	963	7	0.7	0.1866	0.55 (0.22, 1.36)	0.54 (0.22, 1.36)	-0.01 (-0.02, 0.00)	
>=T1 and <T2	966	6	0.6	1032	10	1.0	0.3833	1.56 (0.57, 4.28)	1.57 (0.57, 4.32)	0.00 (0.00, 0.01)	
>=T2	1016	26	2.6	970	8	0.8	0.0029	0.32 (0.15, 0.71)	0.32 (0.14, 0.70)	-0.02 (-0.03,-0.01)	
Baseline use of MRA											0.8058
No	1865	26	1.4	1878	14	0.7	0.0536	0.53 (0.28, 1.02)	0.53 (0.28, 1.02)	-0.01 (-0.01, 0.00)	
Yes	1124	20	1.8	1118	12	1.1	0.1588	0.60 (0.30, 1.23)	0.60 (0.29, 1.23)	-0.01 (-0.02, 0.00)	
Baseline use of ACE-inhibitor, ARB or ARNi											0.1287
No	586	6	1.0	568	7	1.2	0.7372	1.20 (0.41, 3.56)	1.21 (0.40, 3.61)	0.00 (-0.01, 0.01)	
Yes	2403	40	1.7	2428	19	0.8	0.0053	0.47 (0.27, 0.81)	0.47 (0.27, 0.81)	-0.01 (-0.02, 0.00)	

Analysis is based on study 1245.110.
^ Patients with NYHA class I are counted in subgroup NYHA class II.
Risk ratios and odds ratios with confidence intervals (CIs) are estimated by Cochran-Mantel-Haenszel method. For risk differences standard Wald asymptotic confidence limits are calculated. A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied in case of any zero cells in contingency table.
Only treatment emergent AEs are displayed (onset between first dose until treatment stop +7 days).
MedDRA version: 23.1. * Chi-square test for treatment effect ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction).

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Table R.1.2.5: 1 Proportion of patients with any adverse event occuring in at least 1% of the patients in either treatment arm in the overall population on PT level by SOC and PT, 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	2989	33	1.1	2996	24	0.8	0.2276	0.73 (0.43, 1.22)	0.72 (0.43, 1.23)	0.00 (-0.01, 0.00)	

Analysis is based on study 1245.110.
^ Patients with NYHA class I are counted in subgroup NYHA class II.
Risk ratios and odds ratios with confidence intervals (CIs) are estimated by Cochran-Mantel-Haenszel method. For risk differences standard Wald asymptotic confidence limits are calculated. A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied in case of any zero cells in contingency table.
Only treatment emergent AEs are displayed (onset between first dose until treatment stop +7 days).
MedDRA version: 23.1. * Chi-square test for treatment effect ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction).

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Table R.1.2.5: 1 Proportion of patients with any adverse event occuring in at least 1% of the patients in either treatment arm in the overall population on PT level by SOC and PT, 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	2989	43	1.4	2996	57	1.9	0.1615	1.32 (0.89, 1.96)	1.33 (0.89, 1.98)	0.00 (0.00, 0.01)	

Analysis is based on study 1245.110.
^ Patients with NYHA class I are counted in subgroup NYHA class II.
Risk ratios and odds ratios with confidence intervals (CIs) are estimated by Cochran-Mantel-Haenszel method. For risk differences standard Wald asymptotic confidence limits are calculated. A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied in case of any zero cells in contingency table.
Only treatment emergent AEs are displayed (onset between first dose until treatment stop +7 days).
MedDRA version: 23.1. * Chi-square test for treatment effect ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction).

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Table R.1.2.5: 1 Proportion of patients with any adverse event occuring in at least 1% of the patients in either treatment arm in the overall population on PT level by SOC and PT, 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	2989	39	1.3	2996	31	1.0	0.3312	0.79 (0.50, 1.27)	0.79 (0.49, 1.27)	0.00 (-0.01, 0.00)	

Analysis is based on study 1245.110.
^ Patients with NYHA class I are counted in subgroup NYHA class II.
Risk ratios and odds ratios with confidence intervals (CIs) are estimated by Cochran-Mantel-Haenszel method. For risk differences standard Wald asymptotic confidence limits are calculated. A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied in case of any zero cells in contingency table.
Only treatment emergent AEs are displayed (onset between first dose until treatment stop +7 days).
MedDRA version: 23.1. * Chi-square test for treatment effect ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction).

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Table R.1.2.5: 1 Proportion of patients with any adverse event occuring in at least 1% of the patients in either treatment arm in the overall population on PT level by SOC and PT, 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	2989	63	2.1	2996	61	2.0	0.8457	0.97 (0.68, 1.37)	0.97 (0.68, 1.38)	0.00 (-0.01, 0.01)	

Analysis is based on study 1245.110.
^ Patients with NYHA class I are counted in subgroup NYHA class II.
Risk ratios and odds ratios with confidence intervals (CIs) are estimated by Cochran-Mantel-Haenszel method. For risk differences standard Wald asymptotic confidence limits are calculated. A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied in case of any zero cells in contingency table.
Only treatment emergent AEs are displayed (onset between first dose until treatment stop +7 days).
MedDRA version: 23.1. * Chi-square test for treatment effect ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction).

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Table R.1.2.5: 1 Proportion of patients with any adverse event occuring in at least 1% of the patients in either treatment arm in the overall population on PT level by SOC and PT, 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	2989	49	1.6	2996	50	1.7	0.9286	1.02 (0.69, 1.50)	1.02 (0.68, 1.52)	0.00 (-0.01, 0.01)	

Analysis is based on study 1245.110.
^ Patients with NYHA class I are counted in subgroup NYHA class II.
Risk ratios and odds ratios with confidence intervals (CIs) are estimated by Cochran-Mantel-Haenszel method. For risk differences standard Wald asymptotic confidence limits are calculated. A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied in case of any zero cells in contingency table.
Only treatment emergent AEs are displayed (onset between first dose until treatment stop +7 days).
MedDRA version: 23.1. * Chi-square test for treatment effect ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction).

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Table R.1.2.5: 1 Proportion of patients with any adverse event occuring in at least 1% of the patients in either treatment arm in the overall population on PT level by SOC and PT, 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	2989	46	1.5	2996	37	1.2	0.3146	0.80 (0.52, 1.23)	0.80 (0.52, 1.24)	0.00 (-0.01, 0.00)	

Analysis is based on study 1245.110.
^ Patients with NYHA class I are counted in subgroup NYHA class II.
Risk ratios and odds ratios with confidence intervals (CIs) are estimated by Cochran-Mantel-Haenszel method. For risk differences standard Wald asymptotic confidence limits are calculated. A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied in case of any zero cells in contingency table.
Only treatment emergent AEs are displayed (onset between first dose until treatment stop +7 days).
MedDRA version: 23.1. * Chi-square test for treatment effect ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction).

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Table R.1.2.5: 1 Proportion of patients with any adverse event occuring in at least 1% of the patients in either treatment arm in the overall population on PT level by SOC and PT, 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	2989	32	1.1	2996	17	0.6	0.0308	0.53 (0.29, 0.95)	0.53 (0.29, 0.95)	-0.01 (-0.01, 0.00)	
Sex											0.2438
Male	1653	24	1.5	1658	10	0.6	0.0154	0.42 (0.20, 0.87)	0.41 (0.20, 0.86)	-0.01 (-0.02, 0.00)	
Female	1336	8	0.6	1338	7	0.5	0.7935	0.87 (0.32, 2.40)	0.87 (0.32, 2.41)	0.00 (-0.01, 0.00)	
Age [years]											0.1873
<70	1084	7	0.6	1066	1	0.1	0.0356	0.15 (0.02, 1.18)	0.14 (0.02, 1.18)	-0.01 (-0.01, 0.00)	
>=70	1905	25	1.3	1930	16	0.8	0.1456	0.63 (0.34, 1.18)	0.63 (0.33, 1.18)	0.00 (-0.01, 0.00)	
Region											0.9550
North America	359	7	1.9	359	4	1.1	0.3620	0.57 (0.17, 1.94)	0.57 (0.16, 1.95)	-0.01 (-0.03, 0.01)	
Latin America	757	2	0.3	758	1	0.1	0.5625	0.50 (0.05, 5.50)	0.50 (0.05, 5.51)	0.00 (-0.01, 0.00)	
Europe	1341	18	1.3	1346	8	0.6	0.0477	0.44 (0.19, 1.01)	0.44 (0.19, 1.01)	-0.01 (-0.01, 0.00)	
Asia	343	0	0	343	0	0	1.0000	1.00 (0.02, 50.25)	1.00 (0.02, 50.54)	0.00 (-0.01, 0.01)	
Other	189	5	2.6	190	4	2.1	0.7298	0.80 (0.22, 2.92)	0.79 (0.21, 2.99)	-0.01 (-0.04, 0.03)	
OECD member											0.2718
No	847	1	0.1	868	2	0.2	0.5778	1.95 (0.18, 21.48)	1.95 (0.18, 21.59)	0.00 (0.00, 0.01)	
Yes	2142	31	1.4	2128	15	0.7	0.0188	0.49 (0.26, 0.90)	0.48 (0.26, 0.90)	-0.01 (-0.01, 0.00)	
Baseline NYHA											0.4336
II^	2450	26	1.1	2435	12	0.5	0.0238	0.46 (0.23, 0.92)	0.46 (0.23, 0.92)	-0.01 (-0.01, 0.00)	
III/IV	539	6	1.1	561	5	0.9	0.7116	0.80 (0.25, 2.61)	0.80 (0.24, 2.63)	0.00 (-0.01, 0.01)	
Baseline Diabetes Status											0.8784
Diabetic	1471	14	1.0	1465	7	0.5	0.1276	0.50 (0.20, 1.24)	0.50 (0.20, 1.24)	0.00 (-0.01, 0.00)	
Non-Diabetic	1518	18	1.2	1531	10	0.7	0.1232	0.55 (0.26, 1.19)	0.55 (0.25, 1.19)	-0.01 (-0.01, 0.00)	

Analysis is based on study 1245.110.
^ Patients with NYHA class I are counted in subgroup NYHA class II.
Risk ratios and odds ratios with confidence intervals (CIs) are estimated by Cochran-Mantel-Haenszel method. For risk differences standard Wald asymptotic confidence limits are calculated. A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied in case of any zero cells in contingency table.
Only treatment emergent AEs are displayed (onset between first dose until treatment stop +7 days).
MedDRA version: 23.1. * Chi-square test for treatment effect ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction).

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Table R.1.2.5: 1 Proportion of patients with any adverse event occuring in at least 1% of the patients in either treatment arm in the overall population on PT level by SOC and PT, 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 **
Baseline Diabetes Status											0.7700
Diabetic	1471	14	1.0	1465	7	0.5	0.1276	0.50 (0.20, 1.24)	0.50 (0.20, 1.24)	0.00 (-0.01, 0.00)	
Pre-Diabetes	979	12	1.2	1001	8	0.8	0.3426	0.65 (0.27, 1.59)	0.65 (0.26, 1.60)	0.00 (-0.01, 0.00)	
Normal (no pre-diabetes)	539	6	1.1	530	2	0.4	0.1628	0.34 (0.07, 1.67)	0.34 (0.07, 1.67)	-0.01 (-0.02, 0.00)	
Baseline BMI [kg/m²]											0.8279
<30	1641	16	1.0	1654	8	0.5	0.0972	0.50 (0.21, 1.16)	0.49 (0.21, 1.16)	0.00 (-0.01, 0.00)	
>=30	1348	16	1.2	1342	9	0.7	0.1629	0.57 (0.25, 1.27)	0.56 (0.25, 1.28)	-0.01 (-0.01, 0.00)	
Baseline eGFR (CKD-EPI) [mL/min/1.73m²]											0.6582
>=60	1505	15	1.0	1493	9	0.6	0.2263	0.60 (0.27, 1.38)	0.60 (0.26, 1.38)	0.00 (-0.01, 0.00)	
<60	1482	17	1.1	1503	8	0.5	0.0653	0.46 (0.20, 1.07)	0.46 (0.20, 1.07)	-0.01 (-0.01, 0.00)	
History of HHF (in the last 12 months)											0.4418
No	2320	29	1.3	2297	14	0.6	0.0235	0.49 (0.26, 0.92)	0.48 (0.26, 0.92)	-0.01 (-0.01, 0.00)	
Yes	669	3	0.4	699	3	0.4	0.9571	0.96 (0.19, 4.73)	0.96 (0.19, 4.76)	0.00 (-0.01, 0.01)	
Baseline SBP (</>= median)											0.2202
< median	1474	17	1.2	1496	6	0.4	0.0194	0.35 (0.14, 0.88)	0.35 (0.14, 0.88)	-0.01 (-0.01, 0.00)	
>= median	1515	15	1.0	1500	11	0.7	0.4458	0.74 (0.34, 1.61)	0.74 (0.34, 1.61)	0.00 (-0.01, 0.00)	
History of atrial fibrillation or atrial flutter											0.5863
No	1426	10	0.7	1417	4	0.3	0.1106	0.40 (0.13, 1.28)	0.40 (0.13, 1.28)	0.00 (-0.01, 0.00)	
Yes	1558	22	1.4	1575	13	0.8	0.1183	0.58 (0.30, 1.16)	0.58 (0.29, 1.16)	-0.01 (-0.01, 0.00)	

Analysis is based on study 1245.110.
^ Patients with NYHA class I are counted in subgroup NYHA class II.
Risk ratios and odds ratios with confidence intervals (CIs) are estimated by Cochran-Mantel-Haenszel method. For risk differences standard Wald asymptotic confidence limits are calculated. A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied in case of any zero cells in contingency table.
Only treatment emergent AEs are displayed (onset between first dose until treatment stop +7 days).
MedDRA version: 23.1. * Chi-square test for treatment effect ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction).

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Table R.1.2.5: 1 Proportion of patients with any adverse event occuring in at least 1% of the patients in either treatment arm in the overall population on PT level by SOC and PT, 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 **
Baseline LVEF [%]											0.1290
< 50	988	8	0.8	995	1	0.1	0.0188	0.12 (0.02, 0.99)	0.12 (0.02, 0.99)	-0.01 (-0.01, 0.00)	
>= 50	2001	24	1.2	2001	16	0.8	0.2036	0.67 (0.36, 1.25)	0.66 (0.35, 1.25)	0.00 (-0.01, 0.00)	
Baseline LVEF [%]											0.1130
<50	988	8	0.8	995	1	0.1	0.0188	0.12 (0.02, 0.99)	0.12 (0.02, 0.99)	-0.01 (-0.01, 0.00)	
50 to <60	1030	13	1.3	1028	5	0.5	0.0588	0.39 (0.14, 1.08)	0.38 (0.14, 1.08)	-0.01 (-0.02, 0.00)	
>=60	971	11	1.1	973	11	1.1	0.9961	1.00 (0.43, 2.29)	1.00 (0.43, 2.31)	0.00 (-0.01, 0.01)	
Baseline NT-proBNP [pg/mL] (</>=median by atrial fibrillation/flutter status)											0.5029
< median	1507	16	1.1	1476	10	0.7	0.2590	0.64 (0.29, 1.40)	0.64 (0.29, 1.41)	0.00 (-0.01, 0.00)	
>= median	1475	16	1.1	1516	7	0.5	0.0512	0.43 (0.18, 1.03)	0.42 (0.17, 1.03)	-0.01 (-0.01, 0.00)	
Baseline uric acid [mg/dL] (tertiles)											0.3933
<T1	975	9	0.9	963	7	0.7	0.6332	0.79 (0.29, 2.11)	0.79 (0.29, 2.12)	0.00 (-0.01, 0.01)	
>=T1 and <T2	966	13	1.3	1032	4	0.4	0.0198	0.29 (0.09, 0.88)	0.29 (0.09, 0.88)	-0.01 (-0.02, 0.00)	
>=T2	1016	10	1.0	970	6	0.6	0.3622	0.63 (0.23, 1.72)	0.63 (0.23, 1.73)	0.00 (-0.01, 0.00)	
Baseline use of MRA											0.8810
No	1865	25	1.3	1878	13	0.7	0.0479	0.52 (0.27, 1.01)	0.51 (0.26, 1.01)	-0.01 (-0.01, 0.00)	
Yes	1124	7	0.6	1118	4	0.4	0.3693	0.57 (0.17, 1.96)	0.57 (0.17, 1.96)	0.00 (-0.01, 0.00)	
Baseline use of ACE-inhibitor, ARB or ARNi											0.9561
No	586	8	1.4	568	4	0.7	0.2685	0.52 (0.16, 1.70)	0.51 (0.15, 1.71)	-0.01 (-0.02, 0.01)	
Yes	2403	24	1.0	2428	13	0.5	0.0648	0.54 (0.27, 1.05)	0.53 (0.27, 1.05)	0.00 (-0.01, 0.00)	

Analysis is based on study 1245.110.
^ Patients with NYHA class I are counted in subgroup NYHA class II.
Risk ratios and odds ratios with confidence intervals (CIs) are estimated by Cochran-Mantel-Haenszel method. For risk differences standard Wald asymptotic confidence limits are calculated. A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied in case of any zero cells in contingency table.
Only treatment emergent AEs are displayed (onset between first dose until treatment stop +7 days).
MedDRA version: 23.1. * Chi-square test for treatment effect ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction).

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Table R.1.2.5: 1 Proportion of patients with any adverse event occuring in at least 1% of the patients in either treatment arm in the overall population on PT level by SOC and PT, 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	2989	66	2.2	2996	78	2.6	0.3183	1.18 (0.85, 1.63)	1.18 (0.85, 1.65)	0.00 (0.00, 0.01)	

Analysis is based on study 1245.110.
^ Patients with NYHA class I are counted in subgroup NYHA class II.
Risk ratios and odds ratios with confidence intervals (CIs) are estimated by Cochran-Mantel-Haenszel method. For risk differences standard Wald asymptotic confidence limits are calculated. A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied in case of any zero cells in contingency table.
Only treatment emergent AEs are displayed (onset between first dose until treatment stop +7 days).
MedDRA version: 23.1. * Chi-square test for treatment effect ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction).

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Table R.1.2.5: 1 Proportion of patients with any adverse event occuring in at least 1% of the patients in either treatment arm in the overall population on PT level by SOC and PT, 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	2989	30	1.0	2996	26	0.9	0.5852	0.86 (0.51, 1.46)	0.86 (0.51, 1.46)	0.00 (-0.01, 0.00)	

Analysis is based on study 1245.110.
^ Patients with NYHA class I are counted in subgroup NYHA class II.
Risk ratios and odds ratios with confidence intervals (CIs) are estimated by Cochran-Mantel-Haenszel method. For risk differences standard Wald asymptotic confidence limits are calculated. A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied in case of any zero cells in contingency table.
Only treatment emergent AEs are displayed (onset between first dose until treatment stop +7 days).
MedDRA version: 23.1. * Chi-square test for treatment effect ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction).

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Table R.1.2.5: 1 Proportion of patients with any adverse event occuring in at least 1% of the patients in either treatment arm in the overall population on PT level by SOC and PT, 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	2989	42	1.4	2996	44	1.5	0.8366	1.05 (0.69, 1.59)	1.05 (0.68, 1.60)	0.00 (-0.01, 0.01)	

Analysis is based on study 1245.110.
^ Patients with NYHA class I are counted in subgroup NYHA class II.
Risk ratios and odds ratios with confidence intervals (CIs) are estimated by Cochran-Mantel-Haenszel method. For risk differences standard Wald asymptotic confidence limits are calculated. A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied in case of any zero cells in contingency table.
Only treatment emergent AEs are displayed (onset between first dose until treatment stop +7 days).
MedDRA version: 23.1. * Chi-square test for treatment effect ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction).

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Table R.1.2.5: 1 Proportion of patients with any adverse event occuring in at least 1% of the patients in either treatment arm in the overall population on PT level by SOC and PT, 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	2989	43	1.4	2996	49	1.6	0.5358	1.14 (0.76, 1.71)	1.14 (0.75, 1.72)	0.00 (0.00, 0.01)	

Analysis is based on study 1245.110.
^ Patients with NYHA class I are counted in subgroup NYHA class II.
Risk ratios and odds ratios with confidence intervals (CIs) are estimated by Cochran-Mantel-Haenszel method. For risk differences standard Wald asymptotic confidence limits are calculated. A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied in case of any zero cells in contingency table.
Only treatment emergent AEs are displayed (onset between first dose until treatment stop +7 days).
MedDRA version: 23.1. * Chi-square test for treatment effect ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction).

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Table R.1.2.5: 1 Proportion of patients with any adverse event occuring in at least 1% of the patients in either treatment arm in the overall population on PT level by SOC and PT, 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	2989	38	1.3	2996	26	0.9	0.1291	0.68 (0.42, 1.12)	0.68 (0.41, 1.12)	0.00 (-0.01, 0.00)	

Analysis is based on study 1245.110.
^ Patients with NYHA class I are counted in subgroup NYHA class II.
Risk ratios and odds ratios with confidence intervals (CIs) are estimated by Cochran-Mantel-Haenszel method. For risk differences standard Wald asymptotic confidence limits are calculated. A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied in case of any zero cells in contingency table.
Only treatment emergent AEs are displayed (onset between first dose until treatment stop +7 days).
MedDRA version: 23.1. * Chi-square test for treatment effect ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction).

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Table R.1.2.5: 2 Proportion of patients with serious adverse events occuring in at least 1% of the patients in either treatment arm in the overall population on PT level by SOC and PT, 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	2989	594	19.9	2996	448	15.0	<0.0001	0.75 (0.67,	0.84)	0.71 (0.62,	0.81)	-0.05 (-0.07,-0.03)	
Sex													0.4986
Male	1653	336	20.3	1658	245	14.8	<0.0001	0.73 (0.63,	0.84)	0.68 (0.57,	0.81)	-0.06 (-0.08,-0.03)	
Female	1336	258	19.3	1338	203	15.2	0.0046	0.79 (0.66,	0.93)	0.75 (0.61,	0.91)	-0.04 (-0.07,-0.01)	
Age [years]													0.2300
<70	1084	185	17.1	1066	151	14.2	0.0640	0.83 (0.68,	1.01)	0.80 (0.63,	1.01)	-0.03 (-0.06, 0.00)	
>=70	1905	409	21.5	1930	297	15.4	<0.0001	0.72 (0.63,	0.82)	0.67 (0.56,	0.78)	-0.06 (-0.09,-0.04)	
Region													0.6451
North America	359	51	14.2	359	44	12.3	0.4407	0.86 (0.59,	1.26)	0.84 (0.55,	1.30)	-0.02 (-0.07, 0.03)	
Latin America	757	166	21.9	758	128	16.9	0.0131	0.77 (0.63,	0.95)	0.72 (0.56,	0.93)	-0.05 (-0.09,-0.01)	
Europe	1341	272	20.3	1346	199	14.8	0.0002	0.73 (0.62,	0.86)	0.68 (0.56,	0.83)	-0.05 (-0.08,-0.03)	
Asia	343	72	21.0	343	46	13.4	0.0085	0.64 (0.46,	0.90)	0.58 (0.39,	0.87)	-0.08 (-0.13,-0.02)	
Other	189	33	17.5	190	31	16.3	0.7662	0.93 (0.60,	1.46)	0.92 (0.54,	1.58)	-0.01 (-0.09, 0.06)	
OECD member													0.5777
No	847	190	22.4	868	153	17.6	0.0129	0.79 (0.65,	0.95)	0.74 (0.58,	0.94)	-0.05 (-0.09,-0.01)	
Yes	2142	404	18.9	2128	295	13.9	<0.0001	0.74 (0.64,	0.84)	0.69 (0.59,	0.82)	-0.05 (-0.07,-0.03)	
Baseline NYHA													0.0816
II^	2450	437	17.8	2435	306	12.6	<0.0001	0.70 (0.62,	0.81)	0.66 (0.57,	0.78)	-0.05 (-0.07,-0.03)	
III/IV	539	157	29.1	561	142	25.3	0.1550	0.87 (0.72,	1.05)	0.82 (0.63,	1.08)	-0.04 (-0.09, 0.01)	
Baseline Diabetes Status													0.4820
Diabetic	1471	324	22.0	1465	234	16.0	<0.0001	0.73 (0.62,	0.84)	0.67 (0.56,	0.81)	-0.06 (-0.09,-0.03)	
Non-Diabetic	1518	270	17.8	1531	214	14.0	0.0040	0.79 (0.67,	0.93)	0.75 (0.62,	0.91)	-0.04 (-0.06,-0.01)	

Analysis is based on study 1245.110.
^ Patients with NYHA class I are counted in subgroup NYHA class II.
Risk ratios and odds ratios with confidence intervals (CIs) are estimated by Cochran-Mantel-Haenszel method. For risk differences standard Wald asymptotic confidence limits are calculated. A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied in case of any zero cells in contingency table.
Only treatment emergent AEs are displayed (onset between first dose until treatment stop +7 days).
MedDRA version: 23.1. * Chi-square test for treatment effect ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction).

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Table R.1.2.5: 2 Proportion of patients with serious adverse events occuring in at least 1% of the patients in either treatment arm in the overall population on PT level by SOC and PT, 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 Diabetes Status											0.7705
Diabetic	1471	324	22.0	1465	234	16.0	<0.0001	0.73 (0.62, 0.84)	0.67 (0.56, 0.81)	-0.06 (-0.09,-0.03)	
Pre-Diabetes	979	172	17.6	1001	137	13.7	0.0173	0.78 (0.63, 0.96)	0.74 (0.58, 0.95)	-0.04 (-0.07,-0.01)	
Normal (no pre-diabetes)	539	98	18.2	530	77	14.5	0.1065	0.80 (0.61, 1.05)	0.76 (0.55, 1.06)	-0.04 (-0.08, 0.01)	
Baseline BMI [kg/m²]											0.2959
<30	1641	334	20.4	1654	240	14.5	<0.0001	0.71 (0.61, 0.83)	0.66 (0.55, 0.80)	-0.06 (-0.08,-0.03)	
>=30	1348	260	19.3	1342	208	15.5	0.0096	0.80 (0.68, 0.95)	0.77 (0.63, 0.94)	-0.04 (-0.07,-0.01)	
Baseline eGFR (CKD-EPI) [mL/min/1.73m²]											0.8337
>=60	1505	248	16.5	1493	182	12.2	0.0008	0.74 (0.62, 0.88)	0.70 (0.57, 0.86)	-0.04 (-0.07,-0.02)	
<60	1482	346	23.3	1503	266	17.7	0.0001	0.76 (0.66, 0.87)	0.71 (0.59, 0.84)	-0.06 (-0.09,-0.03)	
History of HHF (in the last 12 months)											0.2184
No	2320	417	18.0	2297	295	12.8	<0.0001	0.71 (0.62, 0.82)	0.67 (0.57, 0.79)	-0.05 (-0.07,-0.03)	
Yes	669	177	26.5	699	153	21.9	0.0483	0.83 (0.69, 1.00)	0.78 (0.61, 1.00)	-0.05 (-0.09, 0.00)	
Baseline SBP (</>= median)											0.4773
< median	1474	308	20.9	1496	226	15.1	<0.0001	0.72 (0.62, 0.84)	0.67 (0.56, 0.81)	-0.06 (-0.09,-0.03)	
>= median	1515	286	18.9	1500	222	14.8	0.0028	0.78 (0.67, 0.92)	0.75 (0.62, 0.90)	-0.04 (-0.07,-0.01)	
History of atrial fibrillation or atrial flutter											0.1726
No	1426	226	15.8	1417	186	13.1	0.0392	0.83 (0.69, 0.99)	0.80 (0.65, 0.99)	-0.03 (-0.05, 0.00)	
Yes	1558	367	23.6	1575	262	16.6	<0.0001	0.71 (0.61, 0.81)	0.65 (0.54, 0.77)	-0.07 (-0.10,-0.04)	

Analysis is based on study 1245.110.
^ Patients with NYHA class I are counted in subgroup NYHA class II.
Risk ratios and odds ratios with confidence intervals (CIs) are estimated by Cochran-Mantel-Haenszel method. For risk differences standard Wald asymptotic confidence limits are calculated. A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied in case of any zero cells in contingency table.
Only treatment emergent AEs are displayed (onset between first dose until treatment stop +7 days).
MedDRA version: 23.1. * Chi-square test for treatment effect ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction).

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Table R.1.2.5: 2 Proportion of patients with serious adverse events occuring in at least 1% of the patients in either treatment arm in the overall population on PT level by SOC and PT, 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 LVEF [%]											0.4281
< 50	988	208	21.1	995	148	14.9	0.0003	0.71 (0.58, 0.86)	0.66 (0.52, 0.83)	-0.06 (-0.10,-0.03)	
>= 50	2001	386	19.3	2001	300	15.0	0.0003	0.78 (0.68, 0.89)	0.74 (0.63, 0.87)	-0.04 (-0.07,-0.02)	
Baseline LVEF [%]											0.2869
<50	988	208	21.1	995	148	14.9	0.0003	0.71 (0.58, 0.86)	0.66 (0.52, 0.83)	-0.06 (-0.10,-0.03)	
50 to <60	1030	208	20.2	1028	147	14.3	0.0004	0.71 (0.58, 0.86)	0.66 (0.52, 0.83)	-0.06 (-0.09,-0.03)	
>=60	971	178	18.3	973	153	15.7	0.1262	0.86 (0.70, 1.04)	0.83 (0.66, 1.05)	-0.03 (-0.06, 0.01)	
Baseline NT-proBNP [pg/mL] (</>=median by atrial fibrillation/flutter status)											0.2303
< median	1507	237	15.7	1476	159	10.8	<0.0001	0.68 (0.57, 0.83)	0.65 (0.52, 0.80)	-0.05 (-0.07,-0.03)	
>= median	1475	356	24.1	1516	289	19.1	0.0007	0.79 (0.69, 0.91)	0.74 (0.62, 0.88)	-0.05 (-0.08,-0.02)	
Baseline uric acid [mg/dL] (tertiles)											0.0597
<T1	975	183	18.8	963	111	11.5	<0.0001	0.61 (0.49, 0.76)	0.56 (0.44, 0.73)	-0.07 (-0.10,-0.04)	
>=T1 and <T2	966	159	16.5	1032	145	14.1	0.1340	0.85 (0.69, 1.05)	0.83 (0.65, 1.06)	-0.02 (-0.06, 0.01)	
>=T2	1016	241	23.7	970	189	19.5	0.0220	0.82 (0.69, 0.97)	0.78 (0.63, 0.96)	-0.04 (-0.08,-0.01)	
Baseline use of MRA											0.8260
No	1865	336	18.0	1878	252	13.4	0.0001	0.74 (0.64, 0.87)	0.71 (0.59, 0.84)	-0.05 (-0.07,-0.02)	
Yes	1124	258	23.0	1118	196	17.5	0.0014	0.76 (0.65, 0.90)	0.71 (0.58, 0.88)	-0.05 (-0.09,-0.02)	
Baseline use of ACE-inhibitor, ARB or ARNi											0.0249
No	586	119	20.3	568	110	19.4	0.6886	0.95 (0.76, 1.20)	0.94 (0.71, 1.26)	-0.01 (-0.06, 0.04)	
Yes	2403	475	19.8	2428	338	13.9	<0.0001	0.70 (0.62, 0.80)	0.66 (0.56, 0.76)	-0.06 (-0.08,-0.04)	

Analysis is based on study 1245.110.
^ Patients with NYHA class I are counted in subgroup NYHA class II.
Risk ratios and odds ratios with confidence intervals (CIs) are estimated by Cochran-Mantel-Haenszel method. For risk differences standard Wald asymptotic confidence limits are calculated. A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied in case of any zero cells in contingency table.
Only treatment emergent AEs are displayed (onset between first dose until treatment stop +7 days).
MedDRA version: 23.1. * Chi-square test for treatment effect ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction).

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Table R.1.2.5: 2 Proportion of patients with serious adverse events occuring in at least 1% of the patients in either treatment arm in the overall population on PT level by SOC and PT, 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	2989	80	2.7	2996	92	3.1	0.3613	1.15 (0.85, 1.54)	1.15 (0.85, 1.56)	0.00 (0.00, 0.01)	

Analysis is based on study 1245.110.
^ Patients with NYHA class I are counted in subgroup NYHA class II.
Risk ratios and odds ratios with confidence intervals (CIs) are estimated by Cochran-Mantel-Haenszel method. For risk differences standard Wald asymptotic confidence limits are calculated. A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied in case of any zero cells in contingency table.
Only treatment emergent AEs are displayed (onset between first dose until treatment stop +7 days).
MedDRA version: 23.1. * Chi-square test for treatment effect ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction).

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Table R.1.2.5: 2 Proportion of patients with serious adverse events occuring in at least 1% of the patients in either treatment arm in the overall population on PT level by SOC and PT, 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	2989	66	2.2	2996	57	1.9	0.4048	0.86 (0.61, 1.22)	0.86 (0.60, 1.23)	0.00 (-0.01, 0.00)	

Analysis is based on study 1245.110.
^ Patients with NYHA class I are counted in subgroup NYHA class II.
Risk ratios and odds ratios with confidence intervals (CIs) are estimated by Cochran-Mantel-Haenszel method. For risk differences standard Wald asymptotic confidence limits are calculated. A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied in case of any zero cells in contingency table.
Only treatment emergent AEs are displayed (onset between first dose until treatment stop +7 days).
MedDRA version: 23.1. * Chi-square test for treatment effect ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction).

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Table R.1.2.5: 2 Proportion of patients with serious adverse events occuring in at least 1% of the patients in either treatment arm in the overall population on PT level by SOC and PT, 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	2989	48	1.6	2996	50	1.7	0.8477	1.04 (0.70, 1.54)	1.04 (0.70, 1.55)	0.00 (-0.01, 0.01)	

Analysis is based on study 1245.110.
^ Patients with NYHA class I are counted in subgroup NYHA class II.
Risk ratios and odds ratios with confidence intervals (CIs) are estimated by Cochran-Mantel-Haenszel method. For risk differences standard Wald asymptotic confidence limits are calculated. A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied in case of any zero cells in contingency table.
Only treatment emergent AEs are displayed (onset between first dose until treatment stop +7 days).
MedDRA version: 23.1. * Chi-square test for treatment effect ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction).

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Table R.1.2.5: 2 Proportion of patients with serious adverse events occuring in at least 1% of the patients in either treatment arm in the overall population on PT level by SOC and PT, 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	2989	27	0.9	2996	37	1.2	0.2123	1.37 (0.83, 2.24)	1.37 (0.83, 2.26)	0.00 (0.00, 0.01)	

Analysis is based on study 1245.110.
^ Patients with NYHA class I are counted in subgroup NYHA class II.
Risk ratios and odds ratios with confidence intervals (CIs) are estimated by Cochran-Mantel-Haenszel method. For risk differences standard Wald asymptotic confidence limits are calculated. A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied in case of any zero cells in contingency table.
Only treatment emergent AEs are displayed (onset between first dose until treatment stop +7 days).
MedDRA version: 23.1. * Chi-square test for treatment effect ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction).

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Table R.1.2.5: 2 Proportion of patients with serious adverse events occuring in at least 1% of the patients in either treatment arm in the overall population on PT level by SOC and PT, 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	2989	32	1.1	2996	22	0.7	0.1689	0.69 (0.40, 1.18)	0.68 (0.40, 1.18)	0.00 (-0.01, 0.00)	

Analysis is based on study 1245.110.
^ Patients with NYHA class I are counted in subgroup NYHA class II.
Risk ratios and odds ratios with confidence intervals (CIs) are estimated by Cochran-Mantel-Haenszel method. For risk differences standard Wald asymptotic confidence limits are calculated. A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied in case of any zero cells in contingency table.
Only treatment emergent AEs are displayed (onset between first dose until treatment stop +7 days).
MedDRA version: 23.1. * Chi-square test for treatment effect ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction).

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Table R.1.2.5: 2 Proportion of patients with serious adverse events occuring in at least 1% of the patients in either treatment arm in the overall population on PT level by SOC and PT, 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	2989	30	1.0	2996	25	0.8	0.4927	0.83 (0.49, 1.41)	0.83 (0.49, 1.41)	0.00 (-0.01, 0.00)	

Analysis is based on study 1245.110.
^ Patients with NYHA class I are counted in subgroup NYHA class II.
Risk ratios and odds ratios with confidence intervals (CIs) are estimated by Cochran-Mantel-Haenszel method. For risk differences standard Wald asymptotic confidence limits are calculated. A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied in case of any zero cells in contingency table.
Only treatment emergent AEs are displayed (onset between first dose until treatment stop +7 days).
MedDRA version: 23.1. * Chi-square test for treatment effect ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction).

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Table R.1.2.5: 2 Proportion of patients with serious adverse events occuring in at least 1% of the patients in either treatment arm in the overall population on PT level by SOC and PT, 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	2989	119	4.0	2996	100	3.3	0.1849	0.84 (0.65, 1.09)	0.83 (0.64, 1.09)	-0.01 (-0.02, 0.00)	

Analysis is based on study 1245.110.
^ Patients with NYHA class I are counted in subgroup NYHA class II.
Risk ratios and odds ratios with confidence intervals (CIs) are estimated by Cochran-Mantel-Haenszel method. For risk differences standard Wald asymptotic confidence limits are calculated. A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied in case of any zero cells in contingency table.
Only treatment emergent AEs are displayed (onset between first dose until treatment stop +7 days).
MedDRA version: 23.1. * Chi-square test for treatment effect ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction).

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Table R.1.2.5: 2 Proportion of patients with serious adverse events occuring in at least 1% of the patients in either treatment arm in the overall population on PT level by SOC and PT, 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	2989	47	1.6	2996	49	1.6	0.8460	1.04 (0.70, 1.55)	1.04 (0.70, 1.56)	0.00 (-0.01, 0.01)	

Analysis is based on study 1245.110.
^ Patients with NYHA class I are counted in subgroup NYHA class II.
Risk ratios and odds ratios with confidence intervals (CIs) are estimated by Cochran-Mantel-Haenszel method. For risk differences standard Wald asymptotic confidence limits are calculated. A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied in case of any zero cells in contingency table.
Only treatment emergent AEs are displayed (onset between first dose until treatment stop +7 days).
MedDRA version: 23.1. * Chi-square test for treatment effect ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction).

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Table R.1.2.5: 2 Proportion of patients with serious adverse events occuring in at least 1% of the patients in either treatment arm in the overall population on PT level by SOC and PT, 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	2989	28	0.9	2996	36	1.2	0.3193	1.28 (0.78, 2.10)	1.29 (0.78, 2.11)	0.00 (0.00, 0.01)	

Analysis is based on study 1245.110.
^ Patients with NYHA class I are counted in subgroup NYHA class II.
Risk ratios and odds ratios with confidence intervals (CIs) are estimated by Cochran-Mantel-Haenszel method. For risk differences standard Wald asymptotic confidence limits are calculated. A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied in case of any zero cells in contingency table.
Only treatment emergent AEs are displayed (onset between first dose until treatment stop +7 days).
MedDRA version: 23.1. * Chi-square test for treatment effect ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction).

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Table R.1.2.5: 2 Proportion of patients with serious adverse events occuring in at least 1% of the patients in either treatment arm in the overall population on PT level by SOC and PT, 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	2989	107	3.6	2996	81	2.7	0.0520	0.76 (0.57, 1.00)	0.75 (0.56, 1.00)	-0.01 (-0.02, 0.00)	

Analysis is based on study 1245.110.
^ Patients with NYHA class I are counted in subgroup NYHA class II.
Risk ratios and odds ratios with confidence intervals (CIs) are estimated by Cochran-Mantel-Haenszel method. For risk differences standard Wald asymptotic confidence limits are calculated. A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied in case of any zero cells in contingency table.
Only treatment emergent AEs are displayed (onset between first dose until treatment stop +7 days).
MedDRA version: 23.1. * Chi-square test for treatment effect ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction).

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Table R.1.2.5: 2 Proportion of patients with serious adverse events occuring in at least 1% of the patients in either treatment arm in the overall population on PT level by SOC and PT, 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	2989	42	1.4	2996	38	1.3	0.6450	0.90 (0.58, 1.40)	0.90 (0.58, 1.40)	0.00 (-0.01, 0.00)	

Analysis is based on study 1245.110.
^ Patients with NYHA class I are counted in subgroup NYHA class II.
Risk ratios and odds ratios with confidence intervals (CIs) are estimated by Cochran-Mantel-Haenszel method. For risk differences standard Wald asymptotic confidence limits are calculated. A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied in case of any zero cells in contingency table.
Only treatment emergent AEs are displayed (onset between first dose until treatment stop +7 days).
MedDRA version: 23.1. * Chi-square test for treatment effect ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction).

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Table R.1.2.5: 2 Proportion of patients with serious adverse events occuring in at least 1% of the patients in either treatment arm in the overall population on PT level by SOC and PT, 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	2989	35	1.2	2996	42	1.4	0.4280	1.20 (0.77, 1.87)	1.20 (0.76, 1.88)	0.00 (0.00, 0.01)	

Analysis is based on study 1245.110.
^ Patients with NYHA class I are counted in subgroup NYHA class II.
Risk ratios and odds ratios with confidence intervals (CIs) are estimated by Cochran-Mantel-Haenszel method. For risk differences standard Wald asymptotic confidence limits are calculated. A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied in case of any zero cells in contingency table.
Only treatment emergent AEs are displayed (onset between first dose until treatment stop +7 days).
MedDRA version: 23.1. * Chi-square test for treatment effect ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction).

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Table R.1.2.5: 2 Proportion of patients with serious adverse events occuring in at least 1% of the patients in either treatment arm in the overall population on PT level by SOC and PT, 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	2989	32	1.1	2996	17	0.6	0.0308	0.53 (0.29, 0.95)	0.53 (0.29, 0.95)	-0.01 (-0.01, 0.00)	
Sex											0.2438
Male	1653	24	1.5	1658	10	0.6	0.0154	0.42 (0.20, 0.87)	0.41 (0.20, 0.86)	-0.01 (-0.02, 0.00)	
Female	1336	8	0.6	1338	7	0.5	0.7935	0.87 (0.32, 2.40)	0.87 (0.32, 2.41)	0.00 (-0.01, 0.00)	
Age [years]											0.1873
<70	1084	7	0.6	1066	1	0.1	0.0356	0.15 (0.02, 1.18)	0.14 (0.02, 1.18)	-0.01 (-0.01, 0.00)	
>=70	1905	25	1.3	1930	16	0.8	0.1456	0.63 (0.34, 1.18)	0.63 (0.33, 1.18)	0.00 (-0.01, 0.00)	
Region											0.9550
North America	359	7	1.9	359	4	1.1	0.3620	0.57 (0.17, 1.94)	0.57 (0.16, 1.95)	-0.01 (-0.03, 0.01)	
Latin America	757	2	0.3	758	1	0.1	0.5625	0.50 (0.05, 5.50)	0.50 (0.05, 5.51)	0.00 (-0.01, 0.00)	
Europe	1341	18	1.3	1346	8	0.6	0.0477	0.44 (0.19, 1.01)	0.44 (0.19, 1.01)	-0.01 (-0.01, 0.00)	
Asia	343	0	0	343	0	0	1.0000	1.00 (0.02, 50.25)	1.00 (0.02, 50.54)	0.00 (-0.01, 0.01)	
Other	189	5	2.6	190	4	2.1	0.7298	0.80 (0.22, 2.92)	0.79 (0.21, 2.99)	-0.01 (-0.04, 0.03)	
OECD member											0.2718
No	847	1	0.1	868	2	0.2	0.5778	1.95 (0.18, 21.48)	1.95 (0.18, 21.59)	0.00 (0.00, 0.01)	
Yes	2142	31	1.4	2128	15	0.7	0.0188	0.49 (0.26, 0.90)	0.48 (0.26, 0.90)	-0.01 (-0.01, 0.00)	
Baseline NYHA											0.4336
II^	2450	26	1.1	2435	12	0.5	0.0238	0.46 (0.23, 0.92)	0.46 (0.23, 0.92)	-0.01 (-0.01, 0.00)	
III/IV	539	6	1.1	561	5	0.9	0.7116	0.80 (0.25, 2.61)	0.80 (0.24, 2.63)	0.00 (-0.01, 0.01)	
Baseline Diabetes Status											0.8784
Diabetic	1471	14	1.0	1465	7	0.5	0.1276	0.50 (0.20, 1.24)	0.50 (0.20, 1.24)	0.00 (-0.01, 0.00)	
Non-Diabetic	1518	18	1.2	1531	10	0.7	0.1232	0.55 (0.26, 1.19)	0.55 (0.25, 1.19)	-0.01 (-0.01, 0.00)	

Analysis is based on study 1245.110.
^ Patients with NYHA class I are counted in subgroup NYHA class II.
Risk ratios and odds ratios with confidence intervals (CIs) are estimated by Cochran-Mantel-Haenszel method. For risk differences standard Wald asymptotic confidence limits are calculated. A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied in case of any zero cells in contingency table.
Only treatment emergent AEs are displayed (onset between first dose until treatment stop +7 days).
MedDRA version: 23.1. * Chi-square test for treatment effect ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction).

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Table R.1.2.5: 2 Proportion of patients with serious adverse events occuring in at least 1% of the patients in either treatment arm in the overall population on PT level by SOC and PT, 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 **
Baseline Diabetes Status											0.7700
Diabetic	1471	14	1.0	1465	7	0.5	0.1276	0.50 (0.20, 1.24)	0.50 (0.20, 1.24)	0.00 (-0.01, 0.00)	
Pre-Diabetes	979	12	1.2	1001	8	0.8	0.3426	0.65 (0.27, 1.59)	0.65 (0.26, 1.60)	0.00 (-0.01, 0.00)	
Normal (no pre-diabetes)	539	6	1.1	530	2	0.4	0.1628	0.34 (0.07, 1.67)	0.34 (0.07, 1.67)	-0.01 (-0.02, 0.00)	
Baseline BMI [kg/m²]											0.8279
<30	1641	16	1.0	1654	8	0.5	0.0972	0.50 (0.21, 1.16)	0.49 (0.21, 1.16)	0.00 (-0.01, 0.00)	
>=30	1348	16	1.2	1342	9	0.7	0.1629	0.57 (0.25, 1.27)	0.56 (0.25, 1.28)	-0.01 (-0.01, 0.00)	
Baseline eGFR (CKD-EPI) [mL/min/1.73m²]											0.6582
>=60	1505	15	1.0	1493	9	0.6	0.2263	0.60 (0.27, 1.38)	0.60 (0.26, 1.38)	0.00 (-0.01, 0.00)	
<60	1482	17	1.1	1503	8	0.5	0.0653	0.46 (0.20, 1.07)	0.46 (0.20, 1.07)	-0.01 (-0.01, 0.00)	
History of HHF (in the last 12 months)											0.4418
No	2320	29	1.3	2297	14	0.6	0.0235	0.49 (0.26, 0.92)	0.48 (0.26, 0.92)	-0.01 (-0.01, 0.00)	
Yes	669	3	0.4	699	3	0.4	0.9571	0.96 (0.19, 4.73)	0.96 (0.19, 4.76)	0.00 (-0.01, 0.01)	
Baseline SBP (</>= median)											0.2202
< median	1474	17	1.2	1496	6	0.4	0.0194	0.35 (0.14, 0.88)	0.35 (0.14, 0.88)	-0.01 (-0.01, 0.00)	
>= median	1515	15	1.0	1500	11	0.7	0.4458	0.74 (0.34, 1.61)	0.74 (0.34, 1.61)	0.00 (-0.01, 0.00)	
History of atrial fibrillation or atrial flutter											0.5863
No	1426	10	0.7	1417	4	0.3	0.1106	0.40 (0.13, 1.28)	0.40 (0.13, 1.28)	0.00 (-0.01, 0.00)	
Yes	1558	22	1.4	1575	13	0.8	0.1183	0.58 (0.30, 1.16)	0.58 (0.29, 1.16)	-0.01 (-0.01, 0.00)	

Analysis is based on study 1245.110.
^ Patients with NYHA class I are counted in subgroup NYHA class II.
Risk ratios and odds ratios with confidence intervals (CIs) are estimated by Cochran-Mantel-Haenszel method. For risk differences standard Wald asymptotic confidence limits are calculated. A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied in case of any zero cells in contingency table.
Only treatment emergent AEs are displayed (onset between first dose until treatment stop +7 days).
MedDRA version: 23.1. * Chi-square test for treatment effect ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction).

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Table R.1.2.5: 2 Proportion of patients with serious adverse events occuring in at least 1% of the patients in either treatment arm in the overall population on PT level by SOC and PT, 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 **
Baseline LVEF [%]											0.1290
< 50	988	8	0.8	995	1	0.1	0.0188	0.12 (0.02, 0.99)	0.12 (0.02, 0.99)	-0.01 (-0.01, 0.00)	
>= 50	2001	24	1.2	2001	16	0.8	0.2036	0.67 (0.36, 1.25)	0.66 (0.35, 1.25)	0.00 (-0.01, 0.00)	
Baseline LVEF [%]											0.1130
<50	988	8	0.8	995	1	0.1	0.0188	0.12 (0.02, 0.99)	0.12 (0.02, 0.99)	-0.01 (-0.01, 0.00)	
50 to <60	1030	13	1.3	1028	5	0.5	0.0588	0.39 (0.14, 1.08)	0.38 (0.14, 1.08)	-0.01 (-0.02, 0.00)	
>=60	971	11	1.1	973	11	1.1	0.9961	1.00 (0.43, 2.29)	1.00 (0.43, 2.31)	0.00 (-0.01, 0.01)	
Baseline NT-proBNP [pg/mL] (</>=median by atrial fibrillation/flutter status)											0.5029
< median	1507	16	1.1	1476	10	0.7	0.2590	0.64 (0.29, 1.40)	0.64 (0.29, 1.41)	0.00 (-0.01, 0.00)	
>= median	1475	16	1.1	1516	7	0.5	0.0512	0.43 (0.18, 1.03)	0.42 (0.17, 1.03)	-0.01 (-0.01, 0.00)	
Baseline uric acid [mg/dL] (tertiles)											0.3933
<T1	975	9	0.9	963	7	0.7	0.6332	0.79 (0.29, 2.11)	0.79 (0.29, 2.12)	0.00 (-0.01, 0.01)	
>=T1 and <T2	966	13	1.3	1032	4	0.4	0.0198	0.29 (0.09, 0.88)	0.29 (0.09, 0.88)	-0.01 (-0.02, 0.00)	
>=T2	1016	10	1.0	970	6	0.6	0.3622	0.63 (0.23, 1.72)	0.63 (0.23, 1.73)	0.00 (-0.01, 0.00)	
Baseline use of MRA											0.8810
No	1865	25	1.3	1878	13	0.7	0.0479	0.52 (0.27, 1.01)	0.51 (0.26, 1.01)	-0.01 (-0.01, 0.00)	
Yes	1124	7	0.6	1118	4	0.4	0.3693	0.57 (0.17, 1.96)	0.57 (0.17, 1.96)	0.00 (-0.01, 0.00)	
Baseline use of ACE-inhibitor, ARB or ARNi											0.9561
No	586	8	1.4	568	4	0.7	0.2685	0.52 (0.16, 1.70)	0.51 (0.15, 1.71)	-0.01 (-0.02, 0.01)	
Yes	2403	24	1.0	2428	13	0.5	0.0648	0.54 (0.27, 1.05)	0.53 (0.27, 1.05)	0.00 (-0.01, 0.00)	

Analysis is based on study 1245.110.
^ Patients with NYHA class I are counted in subgroup NYHA class II.
Risk ratios and odds ratios with confidence intervals (CIs) are estimated by Cochran-Mantel-Haenszel method. For risk differences standard Wald asymptotic confidence limits are calculated. A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied in case of any zero cells in contingency table.
Only treatment emergent AEs are displayed (onset between first dose until treatment stop +7 days).
MedDRA version: 23.1. * Chi-square test for treatment effect ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction).

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Table R.1.2.5: 2 Proportion of patients with serious adverse events occuring in at least 1% of the patients in either treatment arm in the overall population on PT level by SOC and PT, 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	2989	32	1.1	2996	13	0.4	0.0044	0.41 (0.21, 0.77)	0.40 (0.21, 0.77)	-0.01 (-0.01, 0.00)	
Sex											0.5924
Male	1653	12	0.7	1658	6	0.4	0.1543	0.50 (0.19, 1.33)	0.50 (0.19, 1.33)	0.00 (-0.01, 0.00)	
Female	1336	20	1.5	1338	7	0.5	0.0118	0.35 (0.15, 0.82)	0.35 (0.15, 0.82)	-0.01 (-0.02, 0.00)	
Age [years]											0.3233
<70	1084	10	0.9	1066	6	0.6	0.3320	0.61 (0.22, 1.67)	0.61 (0.22, 1.68)	0.00 (-0.01, 0.00)	
>=70	1905	22	1.2	1930	7	0.4	0.0046	0.31 (0.13, 0.73)	0.31 (0.13, 0.73)	-0.01 (-0.01, 0.00)	
Region											0.8915
North America	359	4	1.1	359	0	0	0.0726	0.11 (<0.01, 2.06)	0.11 (<0.01, 2.05)	-0.01 (-0.02, 0.00)	
Latin America	757	19	2.5	758	9	1.2	0.0560	0.47 (0.22, 1.04)	0.47 (0.21, 1.04)	-0.01 (-0.03, 0.00)	
Europe	1341	8	0.6	1346	4	0.3	0.2445	0.50 (0.15, 1.65)	0.50 (0.15, 1.65)	0.00 (-0.01, 0.00)	
Asia	343	1	0.3	343	0	0	0.4789	0.33 (0.01, 8.15)	0.33 (0.01, 8.19)	0.00 (-0.01, 0.01)	
Other	189	0	0	190	0	0	0.9979	0.99 (0.02, 49.88)	0.99 (0.02, 50.39)	0.00 (-0.01, 0.01)	
OECD member											0.3463
No	847	17	2.0	868	9	1.0	0.1002	0.52 (0.23, 1.15)	0.51 (0.23, 1.15)	-0.01 (-0.02, 0.00)	
Yes	2142	15	0.7	2128	4	0.2	0.0119	0.27 (0.09, 0.81)	0.27 (0.09, 0.81)	-0.01 (-0.01, 0.00)	
Baseline NYHA											0.9433
II^	2450	27	1.1	2435	11	0.5	0.0097	0.41 (0.20, 0.82)	0.41 (0.20, 0.82)	-0.01 (-0.01, 0.00)	
III/IV	539	5	0.9	561	2	0.4	0.2337	0.38 (0.07, 1.97)	0.38 (0.07, 1.98)	-0.01 (-0.02, 0.00)	
Baseline Diabetes Status											0.6041
Diabetic	1471	20	1.4	1465	7	0.5	0.0123	0.35 (0.15, 0.83)	0.35 (0.15, 0.83)	-0.01 (-0.02, 0.00)	
Non-Diabetic	1518	12	0.8	1531	6	0.4	0.1508	0.50 (0.19, 1.32)	0.49 (0.18, 1.32)	0.00 (-0.01, 0.00)	

Analysis is based on study 1245.110.
^ Patients with NYHA class I are counted in subgroup NYHA class II.
Risk ratios and odds ratios with confidence intervals (CIs) are estimated by Cochran-Mantel-Haenszel method. For risk differences standard Wald asymptotic confidence limits are calculated. A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied in case of any zero cells in contingency table.
Only treatment emergent AEs are displayed (onset between first dose until treatment stop +7 days).
MedDRA version: 23.1. * Chi-square test for treatment effect ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction).

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Table R.1.2.5: 2 Proportion of patients with serious adverse events occuring in at least 1% of the patients in either treatment arm in the overall population on PT level by SOC and PT, 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 **
Baseline Diabetes Status											0.8156
Diabetic	1471	20	1.4	1465	7	0.5	0.0123	0.35 (0.15, 0.83)	0.35 (0.15, 0.83)	-0.01 (-0.02, 0.00)	
Pre-Diabetes	979	9	0.9	1001	5	0.5	0.2650	0.54 (0.18, 1.62)	0.54 (0.18, 1.62)	0.00 (-0.01, 0.00)	
Normal (no pre-diabetes)	539	3	0.6	530	1	0.2	0.3246	0.34 (0.04, 3.25)	0.34 (0.04, 3.26)	0.00 (-0.01, 0.00)	
Baseline BMI [kg/m²]											0.0720
<30	1641	17	1.0	1654	3	0.2	0.0016	0.18 (0.05, 0.60)	0.17 (0.05, 0.59)	-0.01 (-0.01, 0.00)	
>=30	1348	15	1.1	1342	10	0.7	0.3205	0.67 (0.30, 1.49)	0.67 (0.30, 1.49)	0.00 (-0.01, 0.00)	
Baseline eGFR (CKD-EPI) [mL/min/1.73m²]											0.7693
>=60	1505	14	0.9	1493	5	0.3	0.0400	0.36 (0.13, 1.00)	0.36 (0.13, 1.00)	-0.01 (-0.01, 0.00)	
<60	1482	18	1.2	1503	8	0.5	0.0449	0.44 (0.19, 1.00)	0.44 (0.19, 1.00)	-0.01 (-0.01, 0.00)	
History of HHF (in the last 12 months)											0.7427
No	2320	26	1.1	2297	11	0.5	0.0145	0.43 (0.21, 0.86)	0.42 (0.21, 0.86)	-0.01 (-0.01, 0.00)	
Yes	669	6	0.9	699	2	0.3	0.1386	0.32 (0.06, 1.58)	0.32 (0.06, 1.58)	-0.01 (-0.01, 0.00)	
Baseline SBP (</>= median)											0.1180
< median	1474	7	0.5	1496	6	0.4	0.7606	0.84 (0.28, 2.51)	0.84 (0.28, 2.52)	0.00 (-0.01, 0.00)	
>= median	1515	25	1.7	1500	7	0.5	0.0015	0.28 (0.12, 0.65)	0.28 (0.12, 0.65)	-0.01 (-0.02, 0.00)	
History of atrial fibrillation or atrial flutter											0.7115
No	1426	23	1.6	1417	10	0.7	0.0239	0.44 (0.21, 0.92)	0.43 (0.21, 0.91)	-0.01 (-0.02, 0.00)	
Yes	1558	9	0.6	1575	3	0.2	0.0794	0.33 (0.09, 1.22)	0.33 (0.09, 1.22)	0.00 (-0.01, 0.00)	

Analysis is based on study 1245.110.
^ Patients with NYHA class I are counted in subgroup NYHA class II.
Risk ratios and odds ratios with confidence intervals (CIs) are estimated by Cochran-Mantel-Haenszel method. For risk differences standard Wald asymptotic confidence limits are calculated. A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
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Only treatment emergent AEs are displayed (onset between first dose until treatment stop +7 days).
MedDRA version: 23.1. * Chi-square test for treatment effect ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction).

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Table R.1.2.5: 2 Proportion of patients with serious adverse events occuring in at least 1% of the patients in either treatment arm in the overall population on PT level by SOC and PT, 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 **
Baseline LVEF [%]											0.3739
< 50	988	8	0.8	995	5	0.5	0.3967	0.62 (0.20, 1.89)	0.62 (0.20, 1.90)	0.00 (-0.01, 0.00)	
>= 50	2001	24	1.2	2001	8	0.4	0.0045	0.33 (0.15, 0.74)	0.33 (0.15, 0.74)	-0.01 (-0.01, 0.00)	
Baseline LVEF [%]											0.6610
<50	988	8	0.8	995	5	0.5	0.3967	0.62 (0.20, 1.89)	0.62 (0.20, 1.90)	0.00 (-0.01, 0.00)	
50 to <60	1030	10	1.0	1028	3	0.3	0.0519	0.30 (0.08, 1.09)	0.30 (0.08, 1.09)	-0.01 (-0.01, 0.00)	
>=60	971	14	1.4	973	5	0.5	0.0376	0.36 (0.13, 0.99)	0.35 (0.13, 0.98)	-0.01 (-0.02, 0.00)	
Baseline NT-proBNP [pg/mL] (</>=median by atrial fibrillation/flutter status)											0.5056
< median	1507	21	1.4	1476	7	0.5	0.0092	0.34 (0.15, 0.80)	0.34 (0.14, 0.80)	-0.01 (-0.02, 0.00)	
>= median	1475	11	0.7	1516	6	0.4	0.2030	0.53 (0.20, 1.43)	0.53 (0.20, 1.43)	0.00 (-0.01, 0.00)	
Baseline uric acid [mg/dL] (tertiles)											0.7496
<T1	975	8	0.8	963	2	0.2	0.0597	0.25 (0.05, 1.19)	0.25 (0.05, 1.19)	-0.01 (-0.01, 0.00)	
>=T1 and <T2	966	14	1.4	1032	6	0.6	0.0515	0.40 (0.15, 1.04)	0.40 (0.15, 1.04)	-0.01 (-0.02, 0.00)	
>=T2	1016	10	1.0	970	5	0.5	0.2278	0.52 (0.18, 1.53)	0.52 (0.18, 1.53)	0.00 (-0.01, 0.00)	
Baseline use of MRA											0.6286
No	1865	22	1.2	1878	8	0.4	0.0097	0.36 (0.16, 0.81)	0.36 (0.16, 0.81)	-0.01 (-0.01, 0.00)	
Yes	1124	10	0.9	1118	5	0.4	0.1988	0.50 (0.17, 1.47)	0.50 (0.17, 1.47)	0.00 (-0.01, 0.00)	
Baseline use of ACE-inhibitor, ARB or ARNi											0.8845
No	586	3	0.5	568	1	0.2	0.3317	0.34 (0.04, 3.30)	0.34 (0.04, 3.30)	0.00 (-0.01, 0.00)	
Yes	2403	29	1.2	2428	12	0.5	0.0069	0.41 (0.21, 0.80)	0.41 (0.21, 0.80)	-0.01 (-0.01, 0.00)	

Analysis is based on study 1245.110.
^ Patients with NYHA class I are counted in subgroup NYHA class II.
Risk ratios and odds ratios with confidence intervals (CIs) are estimated by Cochran-Mantel-Haenszel method. For risk differences standard Wald asymptotic confidence limits are calculated. A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied in case of any zero cells in contingency table.
Only treatment emergent AEs are displayed (onset between first dose until treatment stop +7 days).
MedDRA version: 23.1. * Chi-square test for treatment effect ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction).

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Table R.1.2.5: 2 Proportion of patients with serious adverse events occuring in at least 1% of the patients in either treatment arm in the overall population on PT level by SOC and PT, 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	2989	37	1.2	2996	23	0.8	0.0679	0.62 (0.37, 1.04)	0.62 (0.37, 1.04)	0.00 (-0.01, 0.00)	

Analysis is based on study 1245.110.
^ Patients with NYHA class I are counted in subgroup NYHA class II.
Risk ratios and odds ratios with confidence intervals (CIs) are estimated by Cochran-Mantel-Haenszel method. For risk differences standard Wald asymptotic confidence limits are calculated. A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied in case of any zero cells in contingency table.
Only treatment emergent AEs are displayed (onset between first dose until treatment stop +7 days).
MedDRA version: 23.1. * Chi-square test for treatment effect ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction).

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Table R.1.2.5: 2 Proportion of patients with serious adverse events occuring in at least 1% of the patients in either treatment arm in the overall population on PT level by SOC and PT, 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	2989	30	1.0	2996	31	1.0	0.9049	1.03 (0.63, 1.70)	1.03 (0.62, 1.71)	0.00 (0.00, 0.01)	

Analysis is based on study 1245.110.
^ Patients with NYHA class I are counted in subgroup NYHA class II.
Risk ratios and odds ratios with confidence intervals (CIs) are estimated by Cochran-Mantel-Haenszel method. For risk differences standard Wald asymptotic confidence limits are calculated. A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied in case of any zero cells in contingency table.
Only treatment emergent AEs are displayed (onset between first dose until treatment stop +7 days).
MedDRA version: 23.1. * Chi-square test for treatment effect ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction).

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Table R.1.2.5: 2 Proportion of patients with serious adverse events occuring in at least 1% of the patients in either treatment arm in the overall population on PT level by SOC and PT, 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	2989	38	1.3	2996	56	1.9	0.0629	1.47 (0.98, 2.21)	1.48 (0.98, 2.24)	0.01 (0.00, 0.01)	

Analysis is based on study 1245.110.
^ Patients with NYHA class I are counted in subgroup NYHA class II.
Risk ratios and odds ratios with confidence intervals (CIs) are estimated by Cochran-Mantel-Haenszel method. For risk differences standard Wald asymptotic confidence limits are calculated. A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied in case of any zero cells in contingency table.
Only treatment emergent AEs are displayed (onset between first dose until treatment stop +7 days).
MedDRA version: 23.1. * Chi-square test for treatment effect ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction).

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Table R.1.2.5: 2 Proportion of patients with serious adverse events occuring in at least 1% of the patients in either treatment arm in the overall population on PT level by SOC and PT, 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	2989	30	1.0	2996	19	0.6	0.1127	0.63 (0.36, 1.12)	0.63 (0.35, 1.12)	0.00 (-0.01, 0.00)	

Analysis is based on study 1245.110.
^ Patients with NYHA class I are counted in subgroup NYHA class II.
Risk ratios and odds ratios with confidence intervals (CIs) are estimated by Cochran-Mantel-Haenszel method. For risk differences standard Wald asymptotic confidence limits are calculated. A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied in case of any zero cells in contingency table.
Only treatment emergent AEs are displayed (onset between first dose until treatment stop +7 days).
MedDRA version: 23.1. * Chi-square test for treatment effect ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction).

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Table R.1.2.5: 3 Proportion of patients with severe adverse events occuring in at least 1% of the patients in either treatment arm in the overall population on PT level by SOC and PT, 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	2989	230	7.7	2996	150	5.0	<0.0001	0.65 (0.53,	0.79)	0.63 (0.51,	0.78)	-0.03 (-0.04,-0.01)	
Sex													0.3756
Male	1653	123	7.4	1658	87	5.2	0.0096	0.71 (0.54,	0.92)	0.69 (0.52,	0.91)	-0.02 (-0.04,-0.01)	
Female	1336	107	8.0	1338	63	4.7	0.0005	0.59 (0.43,	0.80)	0.57 (0.41,	0.78)	-0.03 (-0.05,-0.01)	
Age [years]													0.6650
<70	1084	78	7.2	1066	53	5.0	0.0311	0.69 (0.49,	0.97)	0.67 (0.47,	0.97)	-0.02 (-0.04, 0.00)	
>=70	1905	152	8.0	1930	97	5.0	0.0002	0.63 (0.49,	0.81)	0.61 (0.47,	0.79)	-0.03 (-0.05,-0.01)	
Region													0.3679
North America	359	13	3.6	359	11	3.1	0.6780	0.85 (0.38,	1.86)	0.84 (0.37,	1.90)	-0.01 (-0.03, 0.02)	
Latin America	757	76	10.0	758	54	7.1	0.0428	0.71 (0.51,	0.99)	0.69 (0.48,	0.99)	-0.03 (-0.06, 0.00)	
Europe	1341	99	7.4	1346	59	4.4	0.0010	0.59 (0.43,	0.81)	0.58 (0.41,	0.80)	-0.03 (-0.05,-0.01)	
Asia	343	30	8.7	343	13	3.8	0.0074	0.43 (0.23,	0.82)	0.41 (0.21,	0.80)	-0.05 (-0.09,-0.01)	
Other	189	12	6.3	190	13	6.8	0.8467	1.08 (0.50,	2.30)	1.08 (0.48,	2.44)	0.00 (-0.05, 0.05)	
OECD member													0.9467
No	847	88	10.4	868	58	6.7	0.0059	0.64 (0.47,	0.88)	0.62 (0.44,	0.87)	-0.04 (-0.06,-0.01)	
Yes	2142	142	6.6	2128	92	4.3	0.0009	0.65 (0.51,	0.84)	0.64 (0.49,	0.83)	-0.02 (-0.04,-0.01)	
Baseline NYHA													0.8474
II^	2450	146	6.0	2435	95	3.9	0.0009	0.65 (0.51,	0.84)	0.64 (0.49,	0.83)	-0.02 (-0.03,-0.01)	
III/IV	539	84	15.6	561	55	9.8	0.0039	0.63 (0.46,	0.87)	0.59 (0.41,	0.85)	-0.06 (-0.10,-0.02)	
Baseline Diabetes Status													0.7633
Diabetic	1471	133	9.0	1465	84	5.7	0.0006	0.63 (0.49,	0.83)	0.61 (0.46,	0.81)	-0.03 (-0.05,-0.01)	
Non-Diabetic	1518	97	6.4	1531	66	4.3	0.0107	0.67 (0.50,	0.91)	0.66 (0.48,	0.91)	-0.02 (-0.04, 0.00)	

Analysis is based on study 1245.110.
^ Patients with NYHA class I are counted in subgroup NYHA class II.
Risk ratios and odds ratios with confidence intervals (CIs) are estimated by Cochran-Mantel-Haenszel method. For risk differences standard Wald asymptotic confidence limits are calculated. A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied in case of any zero cells in contingency table.
Only treatment emergent AEs are displayed (onset between first dose until treatment stop +7 days).
MedDRA version: 23.1. * Chi-square test for treatment effect ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction).

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Table R.1.2.5: 3 Proportion of patients with severe adverse events occuring in at least 1% of the patients in either treatment arm in the overall population on PT level by SOC and PT, 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 Diabetes Status											0.9544
Diabetic	1471	133	9.0	1465	84	5.7	0.0006	0.63 (0.49, 0.83)	0.61 (0.46, 0.81)	-0.03 (-0.05,-0.01)	
Pre-Diabetes	979	62	6.3	1001	43	4.3	0.0431	0.68 (0.46, 0.99)	0.66 (0.45, 0.99)	-0.02 (-0.04, 0.00)	
Normal (no pre-diabetes)	539	35	6.5	530	23	4.3	0.1201	0.67 (0.40, 1.12)	0.65 (0.38, 1.12)	-0.02 (-0.05, 0.01)	
Baseline BMI [kg/m²]											0.8462
<30	1641	132	8.0	1654	88	5.3	0.0017	0.66 (0.51, 0.86)	0.64 (0.49, 0.85)	-0.03 (-0.04,-0.01)	
>=30	1348	98	7.3	1342	62	4.6	0.0037	0.64 (0.47, 0.87)	0.62 (0.45, 0.86)	-0.03 (-0.04,-0.01)	
Baseline eGFR (CKD-EPI) [mL/min/1.73m²]											0.8713
>=60	1505	92	6.1	1493	58	3.9	0.0051	0.64 (0.46, 0.88)	0.62 (0.44, 0.87)	-0.02 (-0.04,-0.01)	
<60	1482	138	9.3	1503	92	6.1	0.0011	0.66 (0.51, 0.85)	0.64 (0.48, 0.84)	-0.03 (-0.05,-0.01)	
History of HHF (in the last 12 months)											0.8621
No	2320	139	6.0	2297	90	3.9	0.0012	0.65 (0.50, 0.85)	0.64 (0.49, 0.84)	-0.02 (-0.03,-0.01)	
Yes	669	91	13.6	699	60	8.6	0.0031	0.63 (0.46, 0.86)	0.60 (0.42, 0.84)	-0.05 (-0.08,-0.02)	
Baseline SBP (</>= median)											0.0790
< median	1474	128	8.7	1496	71	4.7	<0.0001	0.55 (0.41, 0.72)	0.52 (0.39, 0.71)	-0.04 (-0.06,-0.02)	
>= median	1515	102	6.7	1500	79	5.3	0.0902	0.78 (0.59, 1.04)	0.77 (0.57, 1.04)	-0.01 (-0.03, 0.00)	
History of atrial fibrillation or atrial flutter											0.7804
No	1426	102	7.2	1417	68	4.8	0.0081	0.67 (0.50, 0.90)	0.65 (0.48, 0.90)	-0.02 (-0.04,-0.01)	
Yes	1558	128	8.2	1575	82	5.2	0.0008	0.63 (0.48, 0.83)	0.61 (0.46, 0.82)	-0.03 (-0.05,-0.01)	

Analysis is based on study 1245.110.
^ Patients with NYHA class I are counted in subgroup NYHA class II.
Risk ratios and odds ratios with confidence intervals (CIs) are estimated by Cochran-Mantel-Haenszel method. For risk differences standard Wald asymptotic confidence limits are calculated. A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied in case of any zero cells in contingency table.
Only treatment emergent AEs are displayed (onset between first dose until treatment stop +7 days).
MedDRA version: 23.1. * Chi-square test for treatment effect ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction).

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Table R.1.2.5: 3 Proportion of patients with severe adverse events occuring in at least 1% of the patients in either treatment arm in the overall population on PT level by SOC and PT, 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 LVEF [%]											0.9987
< 50	988	87	8.8	995	57	5.7	0.0083	0.65 (0.47, 0.90)	0.63 (0.45, 0.89)	-0.03 (-0.05,-0.01)	
>= 50	2001	143	7.1	2001	93	4.6	0.0008	0.65 (0.50, 0.84)	0.63 (0.48, 0.83)	-0.02 (-0.04,-0.01)	
Baseline LVEF [%]											0.3614
<50	988	87	8.8	995	57	5.7	0.0083	0.65 (0.47, 0.90)	0.63 (0.45, 0.89)	-0.03 (-0.05,-0.01)	
50 to <60	1030	81	7.9	1028	44	4.3	0.0007	0.54 (0.38, 0.78)	0.52 (0.36, 0.76)	-0.04 (-0.06,-0.02)	
>=60	971	62	6.4	973	49	5.0	0.1999	0.79 (0.55, 1.13)	0.78 (0.53, 1.14)	-0.01 (-0.03, 0.01)	
Baseline NT-proBNP [pg/mL] (</>=median by atrial fibrillation/flutter status)											0.2170
< median	1507	82	5.4	1476	43	2.9	0.0006	0.54 (0.37, 0.77)	0.52 (0.36, 0.76)	-0.03 (-0.04,-0.01)	
>= median	1475	148	10.0	1516	107	7.1	0.0036	0.70 (0.55, 0.89)	0.68 (0.53, 0.88)	-0.03 (-0.05,-0.01)	
Baseline uric acid [mg/dL] (tertiles)											0.3249
<T1	975	61	6.3	963	33	3.4	0.0037	0.55 (0.36, 0.83)	0.53 (0.34, 0.82)	-0.03 (-0.05,-0.01)	
>=T1 and <T2	966	64	6.6	1032	55	5.3	0.2213	0.80 (0.57, 1.14)	0.79 (0.55, 1.15)	-0.01 (-0.03, 0.01)	
>=T2	1016	103	10.1	970	60	6.2	0.0013	0.61 (0.45, 0.83)	0.58 (0.42, 0.81)	-0.04 (-0.06,-0.02)	
Baseline use of MRA											0.4079
No	1865	127	6.8	1878	77	4.1	0.0003	0.60 (0.46, 0.79)	0.59 (0.44, 0.78)	-0.03 (-0.04,-0.01)	
Yes	1124	103	9.2	1118	73	6.5	0.0204	0.71 (0.53, 0.95)	0.69 (0.51, 0.95)	-0.03 (-0.05, 0.00)	
Baseline use of ACE-inhibitor, ARB or ARNi											0.2350
No	586	44	7.5	568	35	6.2	0.3652	0.82 (0.53, 1.26)	0.81 (0.51, 1.28)	-0.01 (-0.04, 0.02)	
Yes	2403	186	7.7	2428	115	4.7	<0.0001	0.61 (0.49, 0.77)	0.59 (0.47, 0.75)	-0.03 (-0.04,-0.02)	

Analysis is based on study 1245.110.
^ Patients with NYHA class I are counted in subgroup NYHA class II.
Risk ratios and odds ratios with confidence intervals (CIs) are estimated by Cochran-Mantel-Haenszel method. For risk differences standard Wald asymptotic confidence limits are calculated. A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied in case of any zero cells in contingency table.
Only treatment emergent AEs are displayed (onset between first dose until treatment stop +7 days).
MedDRA version: 23.1. * Chi-square test for treatment effect ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction).

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Table R.1.2.5: 3 Proportion of patients with severe adverse events occuring in at least 1% of the patients in either treatment arm in the overall population on PT level by SOC and PT, 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	2989	30	1.0	2996	28	0.9	0.7850	0.93 (0.56, 1.55)	0.93 (0.55, 1.56)	0.00 (-0.01, 0.00)	

Analysis is based on study 1245.110.
^ Patients with NYHA class I are counted in subgroup NYHA class II.
Risk ratios and odds ratios with confidence intervals (CIs) are estimated by Cochran-Mantel-Haenszel method. For risk differences standard Wald asymptotic confidence limits are calculated. A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied in case of any zero cells in contingency table.
Only treatment emergent AEs are displayed (onset between first dose until treatment stop +7 days).
MedDRA version: 23.1. * Chi-square test for treatment effect ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction).

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Table R.1.2.5: 3 Proportion of patients with severe adverse events occuring in at least 1% of the patients in either treatment arm in the overall population on PT level by SOC and PT, 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	2989	57	1.9	2996	50	1.7	0.4870	0.88 (0.60, 1.28)	0.87 (0.60, 1.28)	0.00 (-0.01, 0.00)	

Analysis is based on study 1245.110.
^ Patients with NYHA class I are counted in subgroup NYHA class II.
Risk ratios and odds ratios with confidence intervals (CIs) are estimated by Cochran-Mantel-Haenszel method. For risk differences standard Wald asymptotic confidence limits are calculated. A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied in case of any zero cells in contingency table.
Only treatment emergent AEs are displayed (onset between first dose until treatment stop +7 days).
MedDRA version: 23.1. * Chi-square test for treatment effect ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction).

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Table R.1.2.5: 3 Proportion of patients with severe adverse events occuring in at least 1% of the patients in either treatment arm in the overall population on PT level by SOC and PT, 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	2989	30	1.0	2996	30	1.0	0.9927	1.00 (0.60, 1.65)	1.00 (0.60, 1.66)	0.00 (-0.01, 0.01)	

Analysis is based on study 1245.110.
^ Patients with NYHA class I are counted in subgroup NYHA class II.
Risk ratios and odds ratios with confidence intervals (CIs) are estimated by Cochran-Mantel-Haenszel method. For risk differences standard Wald asymptotic confidence limits are calculated. A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied in case of any zero cells in contingency table.
Only treatment emergent AEs are displayed (onset between first dose until treatment stop +7 days).
MedDRA version: 23.1. * Chi-square test for treatment effect ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction).

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Table R.1.2.5: 3 Proportion of patients with severe adverse events occuring in at least 1% of the patients in either treatment arm in the overall population on PT level by SOC and PT, 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	2989	38	1.3	2996	56	1.9	0.0629	1.47 (0.98, 2.21)	1.48 (0.98, 2.24)	0.01 (0.00, 0.01)	

Analysis is based on study 1245.110.
^ Patients with NYHA class I are counted in subgroup NYHA class II.
Risk ratios and odds ratios with confidence intervals (CIs) are estimated by Cochran-Mantel-Haenszel method. For risk differences standard Wald asymptotic confidence limits are calculated. A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied in case of any zero cells in contingency table.
Only treatment emergent AEs are displayed (onset between first dose until treatment stop +7 days).
MedDRA version: 23.1. * Chi-square test for treatment effect ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction).

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Table R.1.2.5: 3 Proportion of patients with severe adverse events occuring in at least 1% of the patients in either treatment arm in the overall population on PT level by SOC and PT, 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	2989	44	1.5	2996	34	1.1	0.2501	0.77 (0.49, 1.20)	0.77 (0.49, 1.21)	0.00 (-0.01, 0.00)	

Analysis is based on study 1245.110.
^ Patients with NYHA class I are counted in subgroup NYHA class II.
Risk ratios and odds ratios with confidence intervals (CIs) are estimated by Cochran-Mantel-Haenszel method. For risk differences standard Wald asymptotic confidence limits are calculated. A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied in case of any zero cells in contingency table.
Only treatment emergent AEs are displayed (onset between first dose until treatment stop +7 days).
MedDRA version: 23.1. * Chi-square test for treatment effect ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction).

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Table R.1.2.5: 3 Proportion of patients with severe adverse events occuring in at least 1% of the patients in either treatment arm in the overall population on PT level by SOC and PT, 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	2989	18	0.6	2996	30	1.0	0.0835	1.66 (0.93, 2.98)	1.67 (0.93, 3.00)	0.00 (0.00, 0.01)	

Analysis is based on study 1245.110.
^ Patients with NYHA class I are counted in subgroup NYHA class II.
Risk ratios and odds ratios with confidence intervals (CIs) are estimated by Cochran-Mantel-Haenszel method. For risk differences standard Wald asymptotic confidence limits are calculated. A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied in case of any zero cells in contingency table.
Only treatment emergent AEs are displayed (onset between first dose until treatment stop +7 days).
MedDRA version: 23.1. * Chi-square test for treatment effect ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction).

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R.1.2.6 Medical concepts for adverse events of special interest and other specific AEs

Listing R.1.2.6: 1 Listing of preferred terms that define adverse events of special interest and other specific AE categories

Source	Group	Group code	Scope	Preferred term code	Preferred term
BIcMQ 'Allergic skin reactions excl. angioedema and application site reactions (BIcMQ)'	Allergic skin reactions	40000014		10012431	Dermatitis
				10012434	Dermatitis allergic
				10012438	Dermatitis atopic
				10012442	Dermatitis contact
				10012470	Dermatitis infected
				10013687	Drug eruption
				10016741	Fixed eruption
				10021247	Idiopathic urticaria
				10037844	Rash
				10037855	Rash erythematous
				10037857	Rash follicular
				10037867	Rash macular
				10037868	Rash maculo-papular
				10037870	Rash morbilliform
				10037871	Rash neonatal
				10037879	Rash papulosquamous
				10037884	Rash pruritic
				10037888	Rash pustular
				10037890	Rash scarlatiniform
				10037898	Rash vesicular
				10040914	Skin reaction
				10041307	Solar urticaria
				10046735	Urticaria
				10046739	Urticaria aquagenic
				10046740	Urticaria cholinergic
				10046742	Urticaria contact
				10046750	Urticaria papular
				10046751	Urticaria physical
				10046752	Urticaria pigmentosa
				10046755	Urticaria vesiculosa
				10050004	Rash maculovesicular
				10052568	Urticaria chronic
				10056671	Mucocutaneous rash
				10057984	Rash rubelliform
				10058675	Dermatitis psoriasiform
				10058898	Hand dermatitis
				10059499	Haemorrhagic urticaria
				10063438	Pruritus allergic
				10071588	Vulvovaginal rash
				10072757	Chronic spontaneous urticaria

* AE must be serious to qualify.

MedDRA version: 23.1

Listing R.1.2.6: 1 Listing of preferred terms that define adverse events of special interest and other specific AE categories

Source	Group	Group code	Scope	Preferred term code	Preferred term
BIcMQ 'Allergic skin reactions excl. angioedema and application site reactions (BIcMQ)'	Allergic skin reactions	40000014		10075807	Nodular rash
				10078325	Symmetrical drug-related intertriginous and flexural exanthema
				10082290	Urticarial dermatitis
				10082571	Penile rash
				10082985	Erythrodermic atopic dermatitis
				10083156	Immune-mediated dermatitis
				10084122	Anal erythema
				10084123	Anal rash
BIcMQ 'Hyperlipidaemia (BIcMQ)'	Hyperlipidaemia	40000015		10002988	Apolipoprotein A-I increased
				10002994	Apolipoprotein A-II increased
				10003000	Apolipoprotein B increased
				10005425	Blood cholesterol increased
				10005839	Blood triglycerides increased
				10017349	Free fatty acids increased
				10020061	High density lipoprotein increased
				10020603	Hypercholesterolaemia
				10020869	Hypertriglyceridaemia
				10024592	Lipids increased
				10024910	Low density lipoprotein increased
				10038316	Remnant hyperlipidaemia
				10047361	Very low density lipoprotein increased
				10049030	LDL/HDL ratio increased
				10054009	Lipoprotein (a) increased
				10056645	Apolipoprotein increased
				10058108	Dyslipidaemia
				10058630	Total cholesterol/HDL ratio increased
				10062060	Hyperlipidaemia
				10063967	Non-high-density lipoprotein cholesterol increased
				10064236	Intermediate density lipoprotein increased
				10065516	Apolipoprotein B/Apolipoprotein A-1 ratio increased
				10069944	Hyper HDL cholesterolaemia
				10071236	Acquired mixed hyperlipidaemia
				10073041	Remnant-like lipoprotein particles increased
				10081354	Lipoprotein increased

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Listing R.1.2.6: 1 Listing of preferred terms that define adverse events of special interest and other specific AE categories

Source	Group	Group code	Scope	Preferred term code	Preferred term
BIcMQ 'Hyperlipidaemia (BIcMQ)'	Hyperlipidaemia	40000015		10083834	Apolipoprotein E increased
Broad BIcMQ 'Ketoacidosis (BIcMQ)'	DKA (broad)	40000009		10000410	Acetonaemia
				10000457	Acid base balance abnormal
				10000483	Acid-base balance disorder mixed
				10000486	Acidosis
				10002523	Anion gap abnormal
				10002528	Anion gap increased
				10005358	Blood bicarbonate abnormal
				10005359	Blood bicarbonate decreased
				10005705	Blood pH abnormal
				10005706	Blood pH decreased
				10012650	Diabetic coma
				10012668	Diabetic hyperglycaemic coma
				10012671	Diabetic ketoacidosis
				10012672	Diabetic ketoacidotic hyperglycaemic coma
				10012673	Diabetic ketosis
				10023379	Ketoacidosis
				10023388	Ketonuria
				10023391	Ketosis
				10023499	Kussmaul respiration
				10027417	Metabolic acidosis
				10049037	Coma acidotic
				10057593	Blood ketone body
				10057594	Blood ketone body increased
				10057597	Urine ketone body present
				10057598	Blood ketone body present
				10058938	Acetonaemic vomiting
				10059222	Urine ketone body
				10059994	Base excess decreased
				10060915	Base excess negative
				10063336	Base excess abnormal
				10067018	Diabetic encephalopathy
				10074309	Diabetic metabolic decompensation
				10079252	Alcoholic ketoacidosis
				10080061	Euglycaemic diabetic ketoacidosis
				10082528	Starvation ketoacidosis
Broad BIcMQ 'Urinary bladder and tract malignancies (BIcMQ)', Broad BIcMQ 'Renal malignancies (BIcMQ)'	Urinary tract malignancies	40000010		10004986	Bladder adenocarcinoma recurrent

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Listing R.1.2.6: 1 Listing of preferred terms that define adverse events of special interest and other specific AE categories

Source	Group	Group code	Scope	Preferred term code	Preferred term
Broad BIcMQ 'Urinary bladder and tract malignancies (BIcMQ)', Broad BIcMQ 'Renal malignancies (BIcMQ)'	Urinary tract malignancies	40000010		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
				10038394	Renal cancer stage IV

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Listing R.1.2.6: 1 Listing of preferred terms that define adverse events of special interest and other specific AE categories

Source	Group	Group code	Scope	Preferred term code	Preferred term
Broad BIcMQ 'Urinary bladder and tract malignancies (BIcMQ)', Broad BIcMQ 'Renal malignancies (BIcMQ)'	Urinary tract malignancies	40000010		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
				10067943	Hereditary papillary renal carcinoma

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Source	Group	Group code	Scope	Preferred term code	Preferred term
Broad BIcMQ 'Urinary bladder and tract malignancies (BIcMQ)', Broad BIcMQ 'Renal malignancies (BIcMQ)'	Urinary tract malignancies	40000010		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
				10080544	Chromophobe renal cell carcinoma
Narrow BIcMQ 'Angioedema excl. Urticaria (BIcMQ)'	Angioedema excl. Urticaria	40000029		10002424	Angioedema
				10010726	Conjunctival oedema
				10011033	Corneal oedema
				10015029	Epiglottic oedema
				10015967	Eye swelling
				10015993	Eyelid oedema
				10016029	Face oedema
				10018291	Gingival swelling
				10023845	Laryngeal oedema
				10023893	Laryngotracheal oedema
				10024558	Lip oedema
				10024570	Lip swelling
				10030110	Oedema mouth
				10031118	Oropharyngeal swelling
				10034545	Periorbital oedema
				10034829	Pharyngeal oedema
				10042682	Swelling face
				10042690	Swelling of eyelid
				10042727	Swollen tongue
				10043967	Tongue oedema
				10044296	Tracheal oedema
				10049305	Gingival oedema
				10052139	Eye oedema
				10052250	Circumoral oedema
				10056647	Periorbital swelling

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Source	Group	Group code	Scope	Preferred term code	Preferred term
Narrow BIcMQ 'Angioedema excl. Urticaria (BIcMQ)'	Angioedema excl. Urticaria	40000029		10056998	Palatal oedema
				10057431	Scleral oedema
				10060934	Allergic oedema
				10066837	Gleich's syndrome
				10067317	Oculorespiratory syndrome
				10070492	Limbal swelling
				10073257	Idiopathic angioedema
				10074403	Palatal swelling
				10075203	Mouth swelling
				10076229	Intestinal angioedema
				10078783	Oropharyngeal oedema
				10080955	Hereditary angioedema with C1 esterase inhibitor deficiency
				10081035	Acquired C1 inhibitor deficiency
				10081703	Circumoral swelling
				10082270	Pharyngeal swelling
Narrow BIcMQ 'Bone fractures (BIcMQ)'	Bone fracture	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

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Source	Group	Group code	Scope	Preferred term code	Preferred term
Narrow BIcMQ 'Bone fractures (BIcMQ)'	Bone fracture	40000012		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
				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

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Listing R.1.2.6: 1 Listing of preferred terms that define adverse events of special interest and other specific AE categories

Source	Group	Group code	Scope	Preferred term code	Preferred term
Narrow BIcMQ 'Bone fractures (BIcMQ)'	Bone fracture	40000012		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
				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
Narrow BIcMQ 'Genital tract infections predisposed by glucosuria (BIcMQ)'	Genital infections	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
				10030345	Oophoritis

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Source	Group	Group code	Scope	Preferred term code	Preferred term
Narrow BIcMQ 'Genital tract infections predisposed by glucosuria (BIcMQ)'	Genital infections	40000004		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
				10056628	Ovarian bacterial infection
				10057001	Seminal vesicular infection

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Listing R.1.2.6: 1 Listing of preferred terms that define adverse events of special interest and other specific AE categories

Source	Group	Group code	Scope	Preferred term code	Preferred term
Narrow BIcMQ 'Genital tract infections predisposed by glucosuria (BIcMQ)'	Genital infections	40000004		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
				10081280	Ureaplasmal vulvovaginitis
				10082162	Ureaplasma cervicitis
				10083412	Neovaginal infection
				10084348	Scrotal cellulitis

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Source	Group	Group code	Scope	Preferred term code	Preferred term
Narrow BIcMQ 'Genital tract infections predisposed by glucosuria (BIcMQ)', Narrow BIcMQ 'Complicated genital tract infections predisposed by glucosuria (BIcMQ)'	Complicated genital infections	40000005		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
				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

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Listing R.1.2.6: 1 Listing of preferred terms that define adverse events of special interest and other specific AE categories

Source	Group	Group code	Scope	Preferred term code	Preferred term
Narrow BIcMQ 'Genital tract infections predisposed by glucosuria (BIcMQ)', Narrow BIcMQ 'Complicated genital tract infections predisposed by glucosuria (BIcMQ)'	Complicated genital infections	40000005		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
				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

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Source	Group	Group code	Scope	Preferred term code	Preferred term
Narrow BIcMQ 'Genital tract infections predisposed by glucosuria (BIcMQ)', Narrow BIcMQ 'Complicated genital tract infections predisposed by glucosuria (BIcMQ)'	Complicated genital infections	40000005		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
Narrow BIcMQ 'Ketoacidosis (BIcMQ)'	DKA (narrow)	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	40000013		10023424	Kidney infection
				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

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Source	Group	Group code	Scope	Preferred term code	Preferred term
Narrow BIcMQ 'Renal infections predisposed by glucosuria (BIcMQ)', PT 'Urosepsis'	Pyelonephritis or urosepsis	40000013		10072058	Perinephritis
				10074409	Escherichia pyelonephritis
				10082040	Nephritis bacterial
				10084121	Infected urinoma
Narrow BIcMQ 'UTI predisposed by glucosuria (BIcMQ)'	Urinary tract infections	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
				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

* AE must be serious to qualify.

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Listing R.1.2.6: 1 Listing of preferred terms that define adverse events of special interest and other specific AE categories

Source	Group	Group code	Scope	Preferred term code	Preferred term
Narrow BIcMQ 'UTI predisposed by glucosuria (BIcMQ)'	Urinary tract infections	40000002		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
				10078665	Bacterial urethritis
				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 'UTI predisposed by glucosuria (BIcMQ)', BIcMQ 'Renal infections predisposed by glucosuria (BIcMQ)', PT 'Urosepsis'	Complicated urinary tract infections	40000003		10004056	Bacteriuria*
				10004058	Bacteriuria in pregnancy*

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Listing R.1.2.6: 1 Listing of preferred terms that define adverse events of special interest and other specific AE categories

Source	Group	Group code	Scope	Preferred term code	Preferred term
Narrow BIcMQ 'UTI predisposed by glucosuria (BIcMQ)', BIcMQ 'Renal infections predisposed by glucosuria (BIcMQ)', PT 'Urosepsis'	Complicated urinary tract infections	40000003		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*
				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

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Listing R.1.2.6: 1 Listing of preferred terms that define adverse events of special interest and other specific AE categories

Source	Group	Group code	Scope	Preferred term code	Preferred term
Narrow BIcMQ 'UTI predisposed by glucosuria (BIcMQ)', BIcMQ 'Renal infections predisposed by glucosuria (BIcMQ)', PT 'Urosepsis'	Complicated urinary tract infections	40000003		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*
				10078665	Bacterial urethritis*
				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	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

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Source	Group	Group code	Scope	Preferred term code	Preferred term
Narrow BIcMQ 'Volume depletion and hypotension due to dehydration (BIcMQ)'	Volume depletion	40000006		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	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
				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 injury	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 Listing of preferred terms that define adverse events of special interest and other specific AE categories

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 injury	40000011		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
				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

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Listing R.1.2.6: 1 Listing of preferred terms that define adverse events of special interest and other specific AE categories

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 injury	40000011		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
				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
				10052550	Liver induration

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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 injury	40000011		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
				10064712	Mitochondrial aspartate aminotransferase increased
				10065274	Hepatic calcification
				10066195	Hepatobiliary scan abnormal
				10066244	Hepatic sequestration

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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 injury	40000011		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
				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

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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 injury	40000011		10074151	Parenteral nutrition associated liver disease
				10074726	Portal fibrosis
				10075895	Liver palpable
				10076204	Minimal hepatic encephalopathy
				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
				10078962	Immune-mediated hepatitis
				10079446	Portal hypertensive colopathy
				10080429	Primary biliary cholangitis
				10080576	Alloimmune hepatitis
				10080679	Regenerative siderotic hepatic nodule
				10080860	Acquired hepatocerebral degeneration
				10082249	Nonalcoholic fatty liver disease
				10082443	Magnetic resonance proton density fat fraction measurement
				10082480	Cardiohepatic syndrome
				10082832	AST/ALT ratio abnormal
				10083010	Sugiura procedure
				10083123	Magnetic resonance imaging liver abnormal
				10083171	Hepatic venous pressure gradient increased
				10083172	Hepatic venous pressure gradient abnormal

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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 injury	40000011		10083406	Immune-mediated cholangitis
				10083521	Immune-mediated hepatic disorder
				10084058	Congestive hepatopathy
				10084751	Hepatic hypoperfusion
				10084797	Flood syndrome
PTs 'Pollakiuria', 'Polyuria' and 'Nocturia'	Increased urination	40000017		10029446	Nocturia
				10036018	Pollakiuria
				10036142	Polyuria
PTs 'Thirst' and 'Polydipsia'	Thirst	40000018		10036067	Polydipsia
				10043458	Thirst
SMQ 'Acute renal failure'	Renal impairment	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 'Hypersensitivity'	Hypersensitivity	20000214	Narrow	10002198	Anaphylactic reaction
				10002199	Anaphylactic shock
				10002216	Anaphylactoid reaction
				10002222	Anaphylaxis treatment

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Source	Group	Group code	Scope	Preferred term code	Preferred term
SMQ 'Hypersensitivity'	Hypersensitivity	20000214	Narrow	10002424	Angioedema
				10003036	Application site dermatitis
				10003054	Application site rash
				10003645	Atopy
				10005149	Blepharitis allergic
				10005589	Blood immunoglobulin E abnormal
				10005591	Blood immunoglobulin E increased
				10006404	Bromoderma
				10006482	Bronchospasm
				10009192	Circulatory collapse
				10010726	Conjunctival oedema
				10010744	Conjunctivitis allergic
				10010836	Contrast media reaction
				10011033	Corneal oedema
				10011686	Cutaneous vasculitis
				10012431	Dermatitis
				10012432	Dermatitis acneiform
				10012434	Dermatitis allergic
				10012438	Dermatitis atopic
				10012441	Dermatitis bullous
				10012442	Dermatitis contact
				10012455	Dermatitis exfoliative
				10012456	Dermatitis exfoliative generalised
				10012468	Dermatitis herpetiformis
				10012470	Dermatitis infected
				10013687	Drug eruption
				10013700	Drug hypersensitivity
				10014184	Eczema
				10014198	Eczema infantile
				10014201	Eczema nummular
				10014627	Encephalopathy allergic
				10014989	Epidermolysis bullosa
				10015029	Epiglottic oedema
				10015218	Erythema multiforme
				10015226	Erythema nodosum
				10015907	Eye allergy
				10015967	Eye swelling
				10015993	Eyelid oedema
				10016029	Face oedema
				10016741	Fixed eruption
				10018258	Giant papillary conjunctivitis
				10018291	Gingival swelling

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Source	Group	Group code	Scope	Preferred term code	Preferred term
SMQ 'Hypersensitivity'	Hypersensitivity	20000214	Narrow	10019617	Henoch-Schonlein purpura
				10019860	Hereditary angioedema
				10020751	Hypersensitivity
				10020764	Hypersensitivity vasculitis
				10021247	Idiopathic urticaria
				10022056	Injection site dermatitis
				10022071	Injection site hypersensitivity
				10022094	Injection site rash
				10022107	Injection site urticaria
				10023845	Laryngeal oedema
				10023891	Laryngospasm
				10023893	Laryngotracheal oedema
				10024558	Lip oedema
				10024570	Lip swelling
				10028164	Multiple allergies
				10029120	Nephritis allergic
				10029415	Nikolsky's sign
				10030081	Oculomucocutaneous syndrome
				10030110	Oedema mouth
				10031111	Oropharyngeal spasm
				10031118	Oropharyngeal swelling
				10034541	Perioral dermatitis
				10034545	Periorbital oedema
				10034829	Pharyngeal oedema
				10037789	Radioallergosorbent test positive
				10037844	Rash
				10037855	Rash erythematous
				10037857	Rash follicular
				10037867	Rash macular
				10037868	Rash maculo-papular
				10037870	Rash morbilliform
				10037871	Rash neonatal
				10037879	Rash papulosquamous
				10037884	Rash pruritic
				10037888	Rash pustular
				10037890	Rash scarlatiniform
				10037898	Rash vesicular
				10037973	Reaction to azo-dyes
				10037974	Reaction to colouring
				10037977	Reaction to food additive
				10038192	Red man syndrome
				10039085	Rhinitis allergic

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Source	Group	Group code	Scope	Preferred term code	Preferred term
SMQ 'Hypersensitivity'	Hypersensitivity	20000214	Narrow	10039755	Scrotal oedema
				10040400	Serum sickness
				10040402	Serum sickness-like reaction
				10040560	Shock
				10040581	Shock symptom
				10040893	Skin necrosis
				10040914	Skin reaction
				10040934	Skin test positive
				10041307	Solar urticaria
				10041316	Solvent sensitivity
				10042033	Stevens-Johnson syndrome
				10042682	Swelling face
				10042690	Swelling of eyelid
				10042727	Swollen tongue
				10043967	Tongue oedema
				10044223	Toxic epidermal necrolysis
				10044296	Tracheal oedema
				10045240	Type I hypersensitivity
				10046735	Urticaria
				10046740	Urticaria cholinergic
				10046742	Urticaria contact
				10046750	Urticaria papular
				10046751	Urticaria physical
				10046752	Urticaria pigmentosa
				10046755	Urticaria vesiculosa
				10046943	Vaginal ulceration
				10047111	Vasculitic rash
				10047768	Vulval ulceration
				10048799	Acute generalised exanthematous pustulosis
				10048820	Urticarial vasculitis
				10049153	Allergic sinusitis
				10049305	Gingival oedema
				10050004	Rash maculovesicular
				10050099	Application site eczema
				10050104	Application site urticaria
				10050181	Vulvovaginal ulceration
				10050639	Allergic pharyngitis
				10050894	Anti-neutrophil cytoplasmic antibody positive vasculitis
				10051126	Scleritis allergic
				10051394	Allergic cystitis

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Source	Group	Group code	Scope	Preferred term code	Preferred term
SMQ 'Hypersensitivity'	Hypersensitivity	20000214	Narrow	10051792	Infusion related reaction
				10051891	Kaposi's varicelliform eruption
				10052098	Iodine allergy
				10052139	Eye oedema
				10052250	Circumoral oedema
				10052271	Catheter site rash
				10052272	Catheter site urticaria
				10052568	Urticaria chronic
				10052613	Allergic bronchitis
				10053177	Epidermolysis
				10053613	Type IV hypersensitivity reaction
				10053614	Type III immune complex mediated reaction
				10053779	Allergic cough
				10054000	Type II hypersensitivity
				10055048	Allergy to vaccine
				10055182	Eczema weeping
				10056352	Allergy test positive
				10056387	Encephalitis allergic
				10056647	Periorbital swelling
				10056671	Mucocutaneous rash
				10056872	Palpable purpura
				10056998	Palatal oedema
				10057380	Allergic keratitis
				10057431	Scleral oedema
				10057970	Toxic skin eruption
				10057984	Rash rubelliform
				10058675	Dermatitis psoriasiform
				10058681	Eczema vesicular
				10058898	Hand dermatitis
				10059071	Stoma site rash
				10059284	Epidermal necrosis
				10059447	Allergic colitis
				10059499	Haemorrhagic urticaria
				10059830	Infusion site rash
				10060934	Allergic oedema
				10061430	Arthritis allergic
				10061557	Allergic otitis media
				10062506	Heparin-induced thrombocytopenia
				10062918	Dennie-Morgan fold
				10063119	Anaphylactoid shock
				10063438	Pruritus allergic

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Listing R.1.2.6: 1 Listing of preferred terms that define adverse events of special interest and other specific AE categories

Source	Group	Group code	Scope	Preferred term code	Preferred term
SMQ 'Hypersensitivity'	Hypersensitivity	20000214	Narrow	10063527	Allergic respiratory symptom
				10063532	Allergic respiratory disease
				10063683	Application site hypersensitivity
				10063786	Implant site rash
				10063787	Implant site urticaria
				10063855	Implant site dermatitis
				10063858	Implant site hypersensitivity
				10064059	Antiallergic therapy
				10064579	Exfoliative rash
				10064788	Reaction to preservatives
				10064866	Laryngitis allergic
				10065458	Infusion site dermatitis
				10065471	Infusion site hypersensitivity
				10065490	Infusion site urticaria
				10065514	Antiendomysial antibody positive
				10066042	Eczema vaccinatum
				10066173	Allergic transfusion reaction
				10066221	Injection site eczema
				10066273	Vulval eczema
				10066797	Injection site recall reaction
				10066837	Gleich's syndrome
				10066973	Contrast media allergy
				10067113	Anaphylactic transfusion reaction
				10067142	Immediate post-injection reaction
				10067317	Oculorespiratory syndrome
				10067510	Contact stomatitis
				10067950	Oropharyngeal blistering
				10067972	Interstitial granulomatous dermatitis
				10067995	Injection site vasculitis
				10068355	Oral allergy syndrome
				10068809	Palisaded neutrophilic granulomatous dermatitis
				10068880	Vaccination site hypersensitivity
				10069167	Kounis syndrome
				10069440	Henoch-Schonlein purpura nephritis
				10069477	Vaccination site dermatitis
				10069482	Vaccination site rash
				10069489	Vaccination site exfoliation
				10069622	Vaccination site urticaria
				10069623	Vaccination site vesicles
				10069773	Administration related reaction
				10070492	Limbal swelling

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Listing R.1.2.6: 1 Listing of preferred terms that define adverse events of special interest and other specific AE categories

Source	Group	Group code	Scope	Preferred term code	Preferred term
SMQ 'Hypersensitivity'	Hypersensitivity	20000214	Narrow	10070559	Distributive shock
				10070581	Immune tolerance induction
				10071152	Injection related reaction
				10071156	Administration site rash
				10071198	Allergic hepatitis
				10071380	Chronic hyperplastic eosinophilic sinusitis
				10071399	Chronic eosinophilic rhinosinusitis
				10071588	Vulvovaginal rash
				10072867	Device allergy
				10073168	Incision site dermatitis
				10073411	Incision site rash
				10073508	Drug reaction with eosinophilia and systemic symptoms
				10073612	Instillation site hypersensitivity
				10073622	Instillation site rash
				10073627	Instillation site urticaria
				10073992	Catheter site dermatitis
				10073995	Catheter site eczema
				10073998	Catheter site hypersensitivity
				10074014	Catheter site vasculitis
				10074079	Allergy to immunoglobulin therapy
				10074332	Pathergy reaction
				10074350	Drug provocation test
				10074403	Palatal swelling
				10074509	Stoma site hypersensitivity
				10074850	Infusion site eczema
				10074851	Infusion site vasculitis
				10075072	Allergic otitis externa
				10075084	Aspirin-exacerbated respiratory disease
				10075096	Administration site dermatitis
				10075099	Administration site eczema
				10075102	Administration site hypersensitivity
				10075109	Administration site urticaria
				10075185	Allergic eosinophilia
				10075203	Mouth swelling
				10075308	Allergic gastroenteritis
				10075479	Allergy alert test positive
				10075572	Medical device site dermatitis
				10075575	Medical device site eczema
				10075579	Medical device site hypersensitivity
				10075585	Medical device site rash

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Listing R.1.2.6: 1 Listing of preferred terms that define adverse events of special interest and other specific AE categories

Source	Group	Group code	Scope	Preferred term code	Preferred term
SMQ 'Hypersensitivity'	Hypersensitivity	20000214	Narrow	10075588	Medical device site urticaria
				10075807	Nodular rash
				10075964	Administration site recall reaction
				10075969	Administration site vasculitis
				10076024	Application site recall reaction
				10076027	Application site vasculitis
				10076085	Infusion site recall reaction
				10076140	Medical device site recall reaction
				10076161	Vaccination site eczema
				10076188	Vaccination site recall reaction
				10076191	Vaccination site vasculitis
				10076229	Intestinal angioedema
				10076470	Documented hypersensitivity to administered product
				10076606	Mast cell degranulation present
				10076665	Dialysis membrane reaction
				10077117	Vessel puncture site rash
				10077279	Allergy to surgical sutures
				10077813	Vessel puncture site vesicles
				10078117	Eosinophilic granulomatosis with polyangiitis
				10078325	Symmetrical drug-related intertriginous and flexural exanthema
				10078682	Anal eczema
				10078783	Oropharyngeal oedema
				10078853	Allergic reaction to excipient
				10079554	Allergic stomatitis
				10079645	Therapeutic product cross-reactivity
				10079925	Reaction to excipient
				10080783	Vulvovaginitis allergic
				10080894	Procedural shock
				10080955	Hereditary angioedema with C1 esterase inhibitor deficiency
				10081000	Vernal keratoconjunctivitis
				10081004	Hypersensitivity myocarditis
				10081035	Acquired C1 inhibitor deficiency
				10081492	Atopic cough
				10081703	Circumoral swelling
				10081988	Hypersensitivity pneumonitis
				10082270	Pharyngeal swelling
				10082290	Urticarial dermatitis

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Listing R.1.2.6: 1 Listing of preferred terms that define adverse events of special interest and other specific AE categories

Source	Group	Group code	Scope	Preferred term code	Preferred term
SMQ 'Hypersensitivity'	Hypersensitivity	20000214	Narrow	10082742	Infusion related hypersensitivity reaction
				10083164	SJS-TEN overlap
				10083260	Scrotal dermatitis
				10083809	Bullous haemorrhagic dermatosis
				10083842	Immune thrombocytopenia
				10084049	Nutritional supplement allergy
SMQ 'Hypoglycaemia'	Hypoglycaemia	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
SMQ 'Ventricular tachyarrhythmias'	Ventricular tachyarrhythmias	20000058	Narrow	10033929	Parasystole
				10039111	Rhythm idioventricular
				10044066	Torsade de pointes
				10047281	Ventricular arrhythmia
				10047289	Ventricular extrasystoles
				10047290	Ventricular fibrillation
				10047294	Ventricular flutter
				10047302	Ventricular tachycardia
				10049003	Accelerated idioventricular rhythm
				10049761	Ventricular pre-excitation
				10058184	Ventricular parasystole
				10061592	Cardiac fibrillation
				10065341	Ventricular tachyarrhythmia

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