Anhang 4-G: Ergänzende Unterlagen

Präambel

Dieses Dokument beinhaltet weitere Analysen, 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.

Inhaltsverzeichnis Seite

Table of Contents

Table of Contents

Table of Contents

Table of Contents

Table of Contents

Table of Contents

Table of Contents

Table of Contents

Table of Contents

Table of Contents

Table of Contents

Table of Contents

Table of Contents

Table of Contents

Page

Table of Contents

Table of Contents

Table of Contents

Table of Contents

Table of Contents

Table of Contents

Table of Contents

Table of Contents

Table of Contents

Table of Contents

Table of Contents

Table of Contents

Table of Contents

Table of Contents

Table of Contents

Table of Contents

Table of Contents

Table of Contents

Table of Contents

Table of Contents

Table of Contents

Table of Contents

Table of Contents

Table of Contents

Table of Contents

Table of Contents

Table of Contents

Table of Contents

Table of Contents

Table of Contents

Table of Contents

Table of Contents

Table of Contents

Table of Contents

Table of Contents

Table of Contents

Table of Contents

Table of Contents

Table of Contents

Table of Contents

Table of Contents

Table of Contents

Table of Contents

Table of Contents

Table of Contents

Table of Contents

Table of Contents

Table of Contents

Table of Contents

Table of Contents

Table of Contents

Table of Contents

Table of Contents

Table of Contents

Table of Contents

Table of Contents

Table of Contents

Table of Contents

Table of Contents

Table of Contents

Table of Contents

Table of Contents

Table of Contents

Table of Contents

Table of Contents

Table of Contents

Table of Contents

Table of Contents

Table of Contents

Table of Contents

Table of Contents

Table of Contents

R.1

R.1.1

R.1.1.1 Time to first event of adjudicated HHF or adjudicated CV death

R.1.1.1.1

Figure R.1.1.1.1: 1

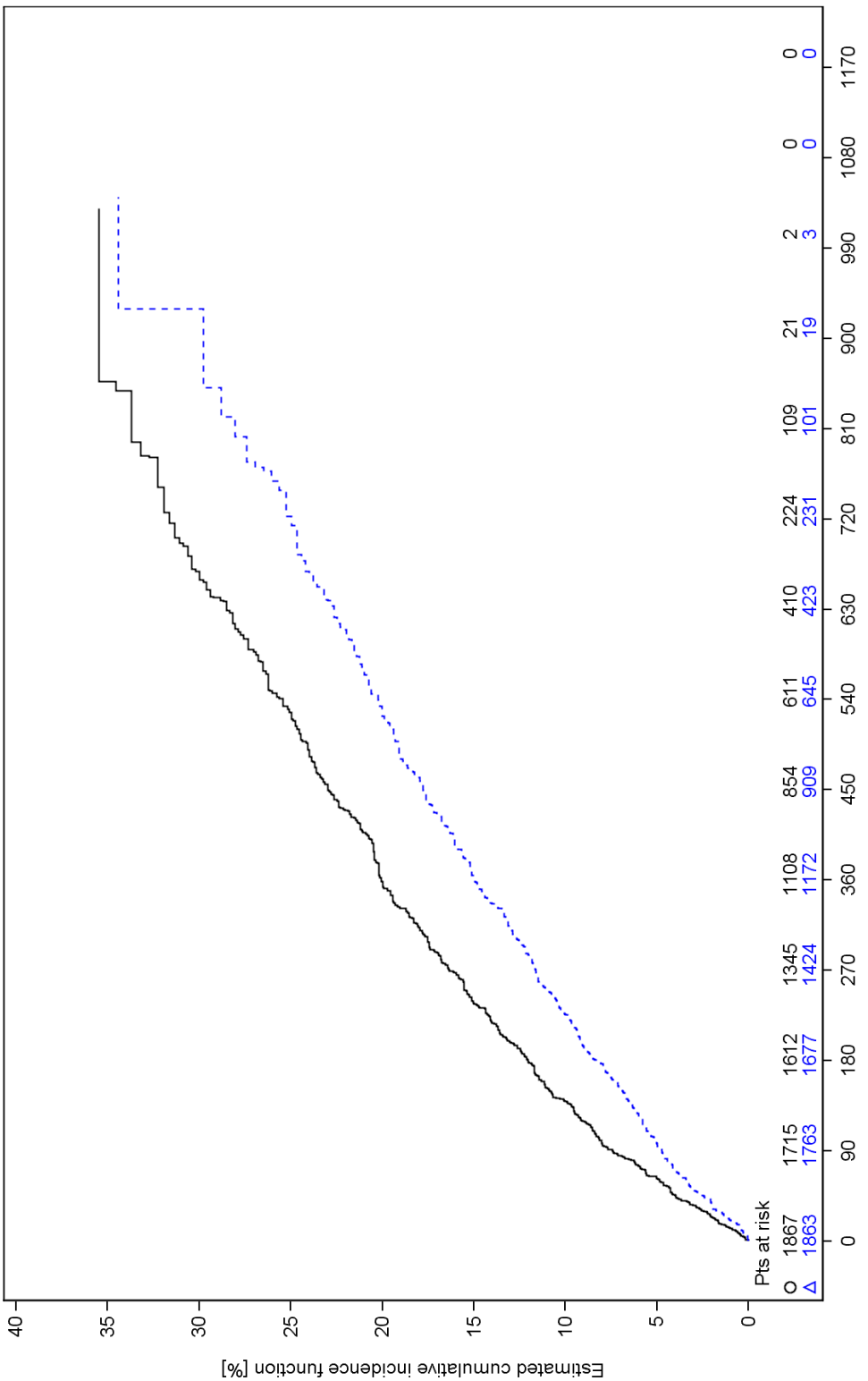

Figure R.1.1.1.1: 1 Estimated cumulative incidence function for time to first event of adjudicated HHF or adjudicated CV death (considering non-CV death as competing risk) - RS (trial 1245.121)

Table R.1.1.1.1: 1 Cox regr. for time to first event of adjudicated HHF or adjudicated CV death - RS (trial 1245.121)

	Placebo	Empa 10mg
Number of patients in analysis set	1867	1863
Number of analysed patients	1867	1863
Number of patients with event [N(%)]	462 (24.7)	361 (19.4)
Time at risk for event [years]	2199.5	2288.8
Incidence rate [patients with events per 100 patient years at risk]	21.00	15.77
95% confidence interval	(19.13, 22.96)	(14.19, 17.44)
Comparison vs Placebo*		
Hazard ratio		0.75
95% confidence interval		(0.65,0.86)
p-value		<0.0001
Time to event [days]**		
2.5% percentile	30	45
5.0% percentile	62	94
7.5% percentile	91	161
10.0% percentile	139	225
Patients with events [%]**		
1 year	20.4	15.2
2 years	32.5	25.7

* Based on a Cox regression model with terms for age (p=0.1911), baseline eGFR (CKD-EPI) (p<0.0001), sex (p=0.0522), region (p=0.0128), baseline diabetes status (3 cat.) (p=0.0008), baseline LVEF (3 cat.) (p=0.0710) and Treatment (p<0.0001).
**Based on Kaplan-Meier estimates.

R.1.1.1.2

R.1.1.1.2 Subgroup analysis by sex

Table R.1.1.1.2: 1 Cox regr. for time to first event of adjudicated HHF or adjudicated CV death by sex - RS (trial 1245.121)

Subgroup Description	Placebo	Empa 10mg
Sex: Male		
Number of patients in analysis set	1411	1426
Number of analysed patients	1411	1426
Number of patients with event [N(%)]	353 (25.0)	294 (20.6)
Time at risk for event [years]	1666.4	1739.1
Incidence rate [patients with events per 100 patient years at risk]	21.18	16.91
95% confidence interval	(19.03, 23.45)	(15.03, 18.89)
Comparison vs Placebo*		
Hazard ratio		0.80
95% confidence interval		(0.68,0.93)
p-value		0.0045
Sex: Female		
Number of patients in analysis set	456	437
Number of analysed patients	456	437
Number of patients with event [N(%)]	109 (23.9)	67 (15.3)
Time at risk for event [years]	533.1	549.7
Incidence rate [patients with events per 100 patient years at risk]	20.45	12.19
95% confidence interval	(16.79, 24.46)	(9.45, 15.27)
Comparison vs Placebo*		
Hazard ratio		0.59
95% confidence interval		(0.44,0.80)
p-value		0.0007

* Based on a Cox regression model with terms for age (p=0.1723), baseline eGFR (CKD-EPI) (p<0.0001), region (p=0.0109), baseline diabetes status (3 cat.) (p=0.0007), baseline LVEF (3 cat.) (p=0.0686), Treatment (p<0.0001), sex (p=0.0297) and Treatment by sex interaction (p=0.0837).

R.1.1.1.3

R.1.1.1.3 Subgroup analysis by age

Table R.1.1.1.3: 1 Cox regr. for time to first event of adjudicated HHF or adjudicated CV death by age (2 cat.) - RS (trial 1245.121)

Subgroup Description	Placebo	Empa 10mg
Age [years]: < 65		
Number of patients in analysis set	740	675
Number of analysed patients	740	675
Number of patients with event [N(%)]	193 (26.1)	128 (19.0)
Time at risk for event [years]	855.1	816.2
Incidence rate [patients with events per 100 patient years at risk]	22.57	15.68
95% confidence interval	(19.50, 25.86)	(13.08, 18.51)
Comparison vs Placebo*		
Hazard ratio		0.71
95% confidence interval		(0.57,0.89)
p-value		0.0025
Age [years]: >= 65		
Number of patients in analysis set	1127	1188
Number of analysed patients	1127	1188
Number of patients with event [N(%)]	269 (23.9)	233 (19.6)
Time at risk for event [years]	1344.4	1472.6
Incidence rate [patients with events per 100 patient years at risk]	20.01	15.82
95% confidence interval	(17.69, 22.47)	(13.86, 17.92)
Comparison vs Placebo*		
Hazard ratio		0.78
95% confidence interval		(0.66,0.93)
p-value		0.0062

* Based on a Cox regression model with terms for baseline eGFR (CKD-EPI) (p<0.0001), sex (p=0.0552), region (p=0.0139), baseline diabetes status (3 cat.) (p=0.0009), baseline LVEF (3 cat.) (p=0.0838), Treatment (p<0.0001), age (2 cat.) (p=0.0093) and Treatment by age (2 cat.) interaction (p=0.4909).

R.1.1.1.4 Subgroup analysis by region (North America, Latin America, Europe, Asia, Other)

Table R.1.1.1.4: 1 Cox regr. for time to first event of adjudicated HHF or adjudicated CV death by region - RS (trial 1245.121)

Subgroup Description	Placebo	Empa 10mg
Region: North America		
Number of patients in analysis set	213	212
Number of analysed patients	213	212
Number of patients with event [N(%)]	64 (30.0)	48 (22.6)
Time at risk for event [years]	242.2	275.3
Incidence rate [patients with events per 100 patient years at risk]	26.43	17.44
95% confidence interval	(20.35, 33.29)	(12.86, 22.70)
Comparison vs Placebo*		
Hazard ratio		0.69
95% confidence interval		(0.48,1.01)
p-value		0.0537
Region: Latin America		
Number of patients in analysis set	645	641
Number of analysed patients	645	641
Number of patients with event [N(%)]	151 (23.4)	115 (17.9)
Time at risk for event [years]	705.1	733.0
Incidence rate [patients with events per 100 patient years at risk]	21.41	15.69
95% confidence interval	(18.13, 24.96)	(12.95, 18.68)
Comparison vs Placebo*		
Hazard ratio		0.73
95% confidence interval		(0.58,0.94)
p-value		0.0124

* Based on a Cox regression model with terms for age (p=0.2167), baseline eGFR (CKD-EPI) (p<0.0001), sex (p=0.0600), baseline diabetes status (3 cat.) (p=0.0008), baseline LVEF (3 cat.) (p=0.0640), Treatment (p<0.0001), region (p=0.0227) and Treatment by region interaction (p=0.1004).

Table R.1.1.1.4: 1

Table R.1.1.1.4: 1 Cox regr. for time to first event of adjudicated HHF or adjudicated CV death by region - RS (trial 1245.121)

Subgroup Description	Placebo	Empa 10mg
Region: Europe		
Number of patients in analysis set	677	676
Number of analysed patients	677	676
Number of patients with event [N(%)]	149 (22.0)	140 (20.7)
Time at risk for event [years]	852.2	846.3
Incidence rate [patients with events per 100 patient years at risk]	17.48	16.54
95% confidence interval	(14.79, 20.40)	(13.92, 19.39)
Comparison vs Placebo*		
Hazard ratio		0.94
95% confidence interval		(0.74,1.18)
p-value		0.5817
Region: Asia		
Number of patients in analysis set	245	248
Number of analysed patients	245	248
Number of patients with event [N(%)]	80 (32.7)	49 (19.8)
Time at risk for event [years]	288.5	324.9
Incidence rate [patients with events per 100 patient years at risk]	27.73	15.08
95% confidence interval	(21.99, 34.13)	(11.16, 19.59)
Comparison vs Placebo*		
Hazard ratio		0.55
95% confidence interval		(0.38,0.78)
p-value		0.0009

* Based on a Cox regression model with terms for age (p=0.2167), baseline eGFR (CKD-EPI) (p<0.0001), sex (p=0.0600), baseline diabetes status (3 cat.) (p=0.0008), baseline LVEF (3 cat.) (p=0.0640), Treatment (p<0.0001), region (p=0.0227) and Treatment by region interaction (p=0.1004).

Table R.1.1.1.4: 1

Table R.1.1.1.4: 1 Cox regr. for time to first event of adjudicated HHF or adjudicated CV death by region - RS (trial 1245.121)

Subgroup Description	Placebo	Empa 10mg
Region: Other		
Number of patients in analysis set	87	86
Number of analysed patients	87	86
Number of patients with event [N(%)]	18 (20.7)	9 (10.5)
Time at risk for event [years]	111.5	109.4
Incidence rate [patients with events per 100 patient years at risk]	16.14	8.23
95% confidence interval	(9.57, 24.41)	(3.76, 14.41)
Comparison vs Placebo*		
Hazard ratio		0.50
95% confidence interval		(0.22,1.11)
p-value		0.0896

* Based on a Cox regression model with terms for age (p=0.2167), baseline eGFR (CKD-EPI) (p<0.0001), sex (p=0.0600), baseline diabetes status (3 cat.) (p=0.0008), baseline LVEF (3 cat.) (p=0.0640), Treatment (p<0.0001), region (p=0.0227) and Treatment by region interaction (p=0.1004).

R.1.1.1.5

R.1.1.1.5 Subgroup analysis by OECD member (Y/N)

Table R.1.1.1.5: 1 Cox regr. for time to first event of adjudicated HHF or adjudicated CV death by OECD member (Y/N) - RS (trial 1245.121)

Subgroup Description	Placebo	Empa 10mg
OECD member: No		
Number of patients in analysis set	741	713
Number of analysed patients	741	713
Number of patients with event [N(%)]	187 (25.2)	127 (17.8)
Time at risk for event [years]	806.7	821.8
Incidence rate [patients with events per 100 patient years at risk]	23.18	15.45
95% confidence interval	(19.98, 26.62)	(12.88, 18.26)
Comparison vs Placebo*		
Hazard ratio		0.66
95% confidence interval		(0.53,0.83)
p-value		0.0004
OECD member: Yes		
Number of patients in analysis set	1126	1150
Number of analysed patients	1126	1150
Number of patients with event [N(%)]	275 (24.4)	234 (20.3)
Time at risk for event [years]	1392.8	1467.0
Incidence rate [patients with events per 100 patient years at risk]	19.74	15.95
95% confidence interval	(17.48, 22.14)	(13.97, 18.06)
Comparison vs Placebo*		
Hazard ratio		0.81
95% confidence interval		(0.68,0.97)
p-value		0.0195

* Based on a Cox regression model with terms for age (p=0.3999), baseline eGFR (CKD-EPI) (p<0.0001), sex (p=0.0379), baseline diabetes status (3 cat.) (p=0.0010), baseline LVEF (3 cat.) (p=0.0468), Treatment (p<0.0001), OECD Member (N) (p=0.1369) and Treatment by OECD Member (N) interaction (p=0.1634).

OECD member (yes/no) countries included:
Yes: United States, Canada, Mexico, Poland, Netherlands, Hungary, Germany, Czech Republic, Italy, France, Spain, United Kingdom, Belgium, Japan, Australia, 'Korea; Republic Of South Korea';
No: Brazil, Argentina, China, India.

R.1.1.1.6 Subgroup analysis by NYHA at baseline (II, III/IV - 2 cat.)

Table R.1.1.1.6: 1 Cox regr. for time to first event of adjudicated HHF or adjudicated CV death by baseline NYHA (2 cat.) - RS (trial 1245.121)

Subgroup Description	Placebo	Empa 10mg
Baseline NYHA: II		
Number of patients in analysis set	1401	1399
Number of analysed patients	1401	1399
Number of patients with event [N(%)]	299 (21.3)	220 (15.7)
Time at risk for event [years]	1687.7	1760.4
Incidence rate [patients with events per 100 patient years at risk]	17.72	12.50
95% confidence interval	(15.77, 19.78)	(10.90, 14.20)
Comparison vs Placebo*		
Hazard ratio		0.71
95% confidence interval		(0.59,0.84)
p-value		<0.0001
Baseline NYHA: III/IV		
Number of patients in analysis set	466	464
Number of analysed patients	466	464
Number of patients with event [N(%)]	163 (35.0)	141 (30.4)
Time at risk for event [years]	511.8	528.4
Incidence rate [patients with events per 100 patient years at risk]	31.85	26.68
95% confidence interval	(27.15, 36.92)	(22.46, 31.26)
Comparison vs Placebo*		
Hazard ratio		0.83
95% confidence interval		(0.66,1.04)
p-value		0.1003

* Based on a Cox regression model with terms for age (p=0.2134), baseline eGFR (CKD-EPI) (p<0.0001), sex (p=0.0167), region (p=0.0030), baseline diabetes status (3 cat.) (p=0.0092), baseline LVEF (3 cat.) (p=0.1664), Treatment (p=0.0002), baseline NYHA (2 cat.) (p<0.0001) and Treatment by baseline NYHA (2 cat.) interaction (p=0.2716).

R.1.1.1.7

R.1.1.1.7 Subgroup analysis by diabetes at baseline

Table R.1.1.1.7: 1 Cox regr. for time to first event of adjudicated HHF or adjudicated CV death by diabetes at baseline (2 cat.) - RS (trial 1245.121)

Subgroup Description	Placebo	Empa 10mg
Baseline diabetes status: Diabetic		
Number of patients in analysis set	929	927
Number of analysed patients	929	927
Number of patients with event [N(%)]	265 (28.5)	200 (21.6)
Time at risk for event [years]	1079.4	1132.8
Incidence rate [patients with events per 100 patient years at risk]	24.55	17.66
95% confidence interval	(21.68, 27.59)	(15.29, 20.19)
Comparison vs Placebo*		
Hazard ratio		0.72
95% confidence interval		(0.60,0.87)
p-value		0.0006
Baseline diabetes status: Non-Diabetic		
Number of patients in analysis set	938	936
Number of analysed patients	938	936
Number of patients with event [N(%)]	197 (21.0)	161 (17.2)
Time at risk for event [years]	1120.2	1156.0
Incidence rate [patients with events per 100 patient years at risk]	17.59	13.93
95% confidence interval	(15.22, 20.13)	(11.86, 16.16)
Comparison vs Placebo*		
Hazard ratio		0.78
95% confidence interval		(0.64,0.97)
p-value		0.0225

* Based on a Cox regression model with terms for age (p=0.1914), baseline eGFR (CKD-EPI) (p<0.0001), sex (p=0.0533), region (p=0.0129), baseline LVEF (3 cat.) (p=0.0720), Treatment (p<0.0001), baseline diabetes status (2 cat.) (p=0.0002) and Treatment by baseline diabetes status (2 cat.) interaction (p=0.5690).

R.1.1.1.8 Subgroup analysis by BMI at baseline (<30, >=30)

Table R.1.1.1.8: 1 Cox regr. for time to first event of adjudicated HHF or adjudicated CV death by baseline BMI [kg/m2] - RS (trial 1245.121)

Subgroup Description	Placebo	Empa 10mg
Baseline BMI [kg/m²]: <30		
Number of patients in analysis set	1300	1263
Number of analysed patients	1300	1263
Number of patients with event [N(%)]	322 (24.8)	226 (17.9)
Time at risk for event [years]	1554.3	1559.8
Incidence rate [patients with events per 100 patient years at risk]	20.72	14.49
95% confidence interval	(18.52, 23.04)	(12.66, 16.44)
Comparison vs Placebo*		
Hazard ratio		0.70
95% confidence interval		(0.59,0.83)
p-value		<0.0001
Baseline BMI [kg/m²]: >=30		
Number of patients in analysis set	567	600
Number of analysed patients	567	600
Number of patients with event [N(%)]	140 (24.7)	135 (22.5)
Time at risk for event [years]	645.3	729.0
Incidence rate [patients with events per 100 patient years at risk]	21.70	18.52
95% confidence interval	(18.25, 25.44)	(15.53, 21.77)
Comparison vs Placebo*		
Hazard ratio		0.85
95% confidence interval		(0.67,1.08)
p-value		0.1945

* Based on a Cox regression model with terms for age (p=0.2803), baseline eGFR (CKD-EPI) (p<0.0001), sex (p=0.0444), region (p=0.0087), baseline diabetes status (3 cat.) (p=0.0019), baseline LVEF (3 cat.) (p=0.0645), Treatment (p=0.0005), baseline BMI (2 cat.) (p=0.1141) and Treatment by baseline BMI (2 cat.) interaction (p=0.1694).

R.1.1.1.9 Subgroup analysis by eGFR at baseline (<60, >=60)

Table R.1.1.1.9: 1 Cox regr. for time to first event of adjudicated HHF or adjudicated CV death by baseline eGFR (2 cat.) - RS (trial 1245.121)

Subgroup Description	Placebo	Empa 10mg
Baseline eGFR (CKD-EPI) [mL/min/1.73m²]: >=60		
Number of patients in analysis set	960	969
Number of analysed patients	960	969
Number of patients with event [N(%)]	224 (23.3)	159 (16.4)
Time at risk for event [years]	1134.7	1198.2
Incidence rate [patients with events per 100 patient years at risk]	19.74	13.27
95% confidence interval	(17.24, 22.41)	(11.29, 15.41)
Comparison vs Placebo*		
Hazard ratio		0.67
95% confidence interval		(0.55,0.83)
p-value		0.0001
Baseline eGFR (CKD-EPI) [mL/min/1.73m²]: <60		
Number of patients in analysis set	906	893
Number of analysed patients	906	893
Number of patients with event [N(%)]	237 (26.2)	202 (22.6)
Time at risk for event [years]	1064.0	1089.4
Incidence rate [patients with events per 100 patient years at risk]	22.28	18.54
95% confidence interval	(19.53, 25.20)	(16.07, 21.18)
Comparison vs Placebo*		
Hazard ratio		0.83
95% confidence interval		(0.69,1.00)
p-value		0.0500

* Based on a Cox regression model with terms for age (p=0.9987), sex (p=0.0743), region (p=0.0128), baseline diabetes status (3 cat.) (p=0.0004), baseline LVEF (3 cat.) (p=0.0744), Treatment (p<0.0001), baseline eGFR (CKD-EPI) (2 cat.) (p=0.0024) and Treatment by baseline eGFR (CKD-EPI) (2 cat.) interaction (p=0.1428).
2 patients were excluded as the subgroup variable was missing.

R.1.1.1.10

R.1.1.1.10 Subgroup analysis by history of HHF

Table R.1.1.1.10: 1 Cox regr. for time to first event of adjudicated HHF or adjudicated CV death by history of HHF within 12 months - RS (trial 1245.121)

Subgroup Description	Placebo	Empa 10mg
History of HHF (in the last 12 months): No		
Number of patients in analysis set	1293	1286
Number of analysed patients	1293	1286
Number of patients with event [N(%)]	285 (22.0)	208 (16.2)
Time at risk for event [years]	1594.3	1643.1
Incidence rate [patients with events per 100 patient years at risk]	17.88	12.66
95% confidence interval	(15.86, 20.01)	(11.00, 14.44)
Comparison vs Placebo*		
Hazard ratio		0.71
95% confidence interval		(0.60,0.85)
p-value		0.0002
History of HHF (in the last 12 months): Yes		
Number of patients in analysis set	574	577
Number of analysed patients	574	577
Number of patients with event [N(%)]	177 (30.8)	153 (26.5)
Time at risk for event [years]	605.2	645.7
Incidence rate [patients with events per 100 patient years at risk]	29.24	23.70
95% confidence interval	(25.09, 33.71)	(20.09, 27.59)
Comparison vs Placebo*		
Hazard ratio		0.79
95% confidence interval		(0.64,0.99)
p-value		0.0370

* Based on a Cox regression model with terms for age (p=0.4376), baseline eGFR (CKD-EPI) (p<0.0001), sex (p=0.0513), region (p=0.0252), baseline diabetes status (3 cat.) (p=0.0024), baseline LVEF (3 cat.) (p=0.1416), Treatment (p<0.0001), history of HHF (p<0.0001) and Treatment by history of HHF interaction (p=0.4498).

R.1.1.1.11

R.1.1.1.11 Subgroup analysis by cause of heart failure

Table R.1.1.1.11: 1 Cox regr. for time to first event of adjudicated HHF or adjudicated CV death by cause of heart failure - RS (trial 1245.121)

Subgroup Description	Placebo	Empa 10mg
Cause of heart failure: Ischemic		
Number of patients in analysis set	946	983
Number of analysed patients	946	983
Number of patients with event [N(%)]	236 (24.9)	207 (21.1)
Time at risk for event [years]	1143.7	1212.0
Incidence rate [patients with events per 100 patient years at risk]	20.64	17.08
95% confidence interval	(18.09, 23.35)	(14.83, 19.48)
Comparison vs Placebo*		
Hazard ratio		0.82
95% confidence interval		(0.68,0.99)
p-value		0.0411
Cause of heart failure: Non-ischemic		
Number of patients in analysis set	921	880
Number of analysed patients	921	880
Number of patients with event [N(%)]	226 (24.5)	154 (17.5)
Time at risk for event [years]	1055.8	1076.8
Incidence rate [patients with events per 100 patient years at risk]	21.41	14.30
95% confidence interval	(18.71, 24.28)	(12.13, 16.65)
Comparison vs Placebo*		
Hazard ratio		0.67
95% confidence interval		(0.55,0.82)
p-value		0.0001

* Based on a Cox regression model with terms for age (p=0.1853), baseline eGFR (CKD-EPI) (p<0.0001), sex (p=0.0531), region (p=0.0124), baseline diabetes status (3 cat.) (p=0.0010), baseline LVEF (3 cat.) (p=0.0702), Treatment (p<0.0001), cause of heart failure (2 cat.) (p=0.6290) and Treatment by cause of heart failure (2 cat.) interaction (p=0.1485).

R.1.1.1.12 Subgroup analysis by heart failure physiology (LVEF <= 30% and NTproBNP<median; LVEF <= 30% and NTproBNP>=median; LVEF > 30%)

Figure R.1.1.1.12: 1

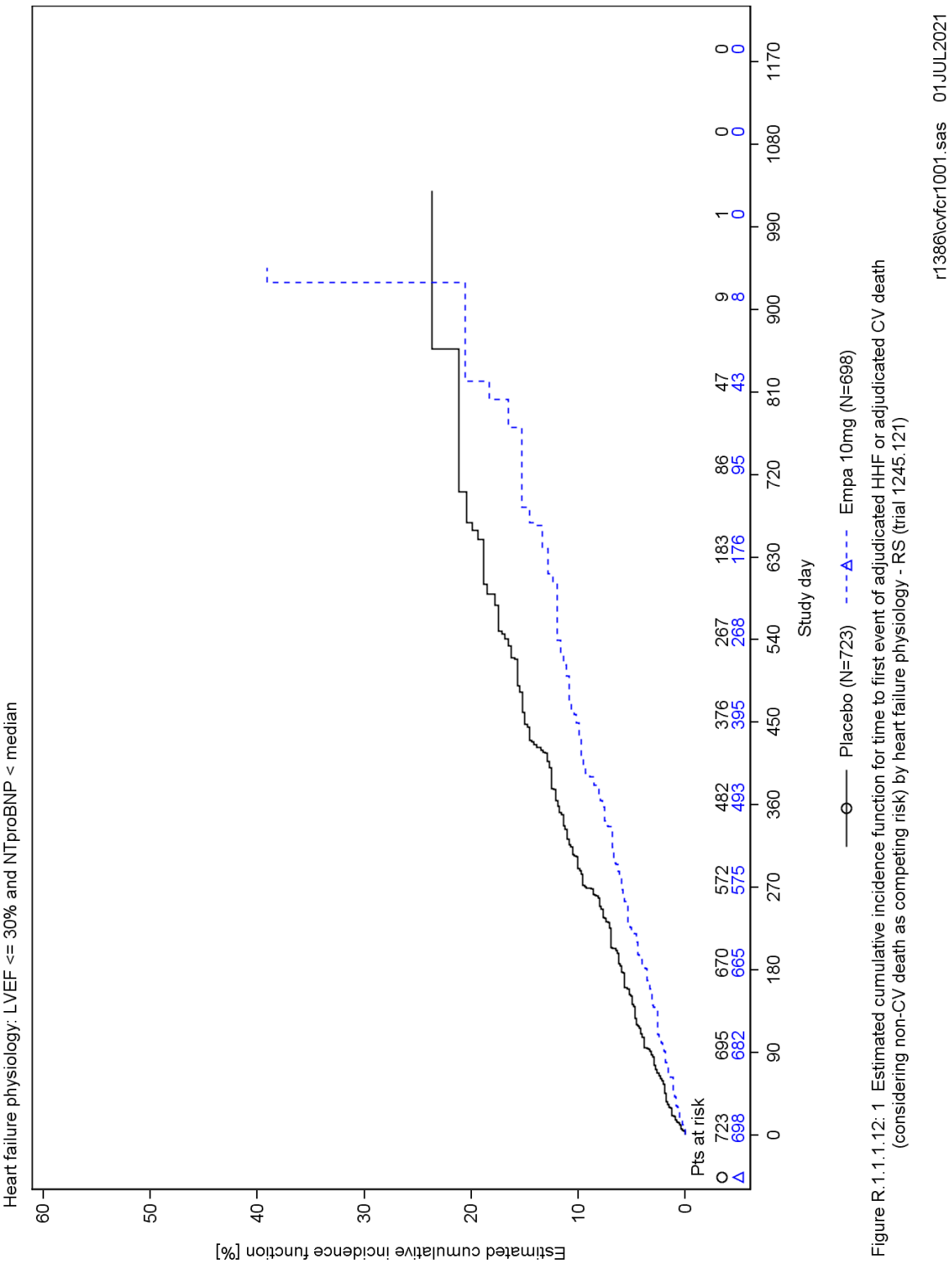

Figure R.1.1.1.12: 1 Estimated cumulative incidence function for time to first event of adjudicated HHF or adjudicated CV death (considering non-CV death as competing risk) by heart failure physiology - RS (trial 1245.121)

Figure R.1.1.1.12: 1

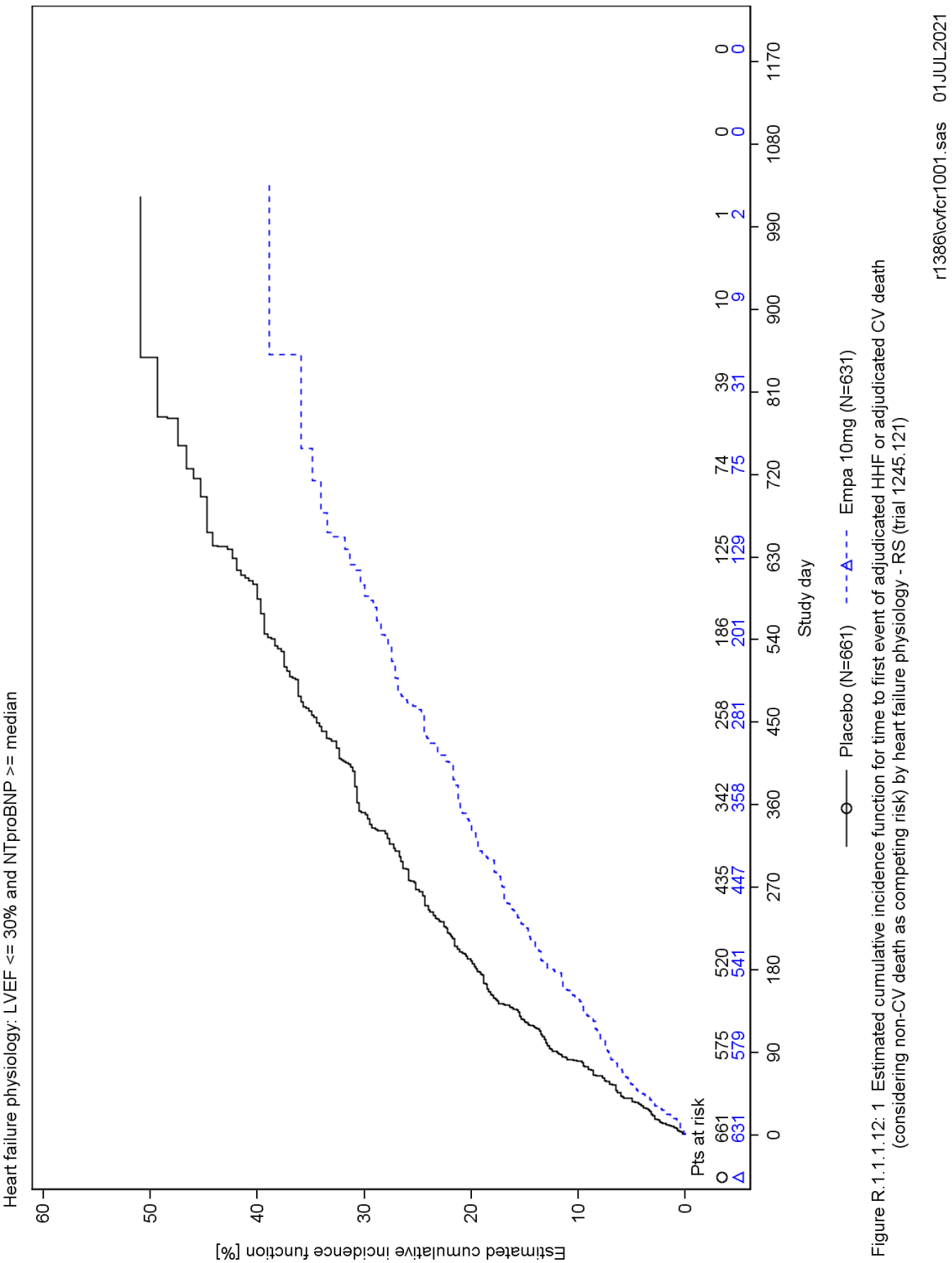

Figure R.1.1.1.12: 1 Estimated cumulative incidence function for time to first event of adjudicated HHF or adjudicated CV death (considering non-CV death as competing risk) by heart failure physiology - RS (trial 1245.121)

Figure R.1.1.1.12: 1

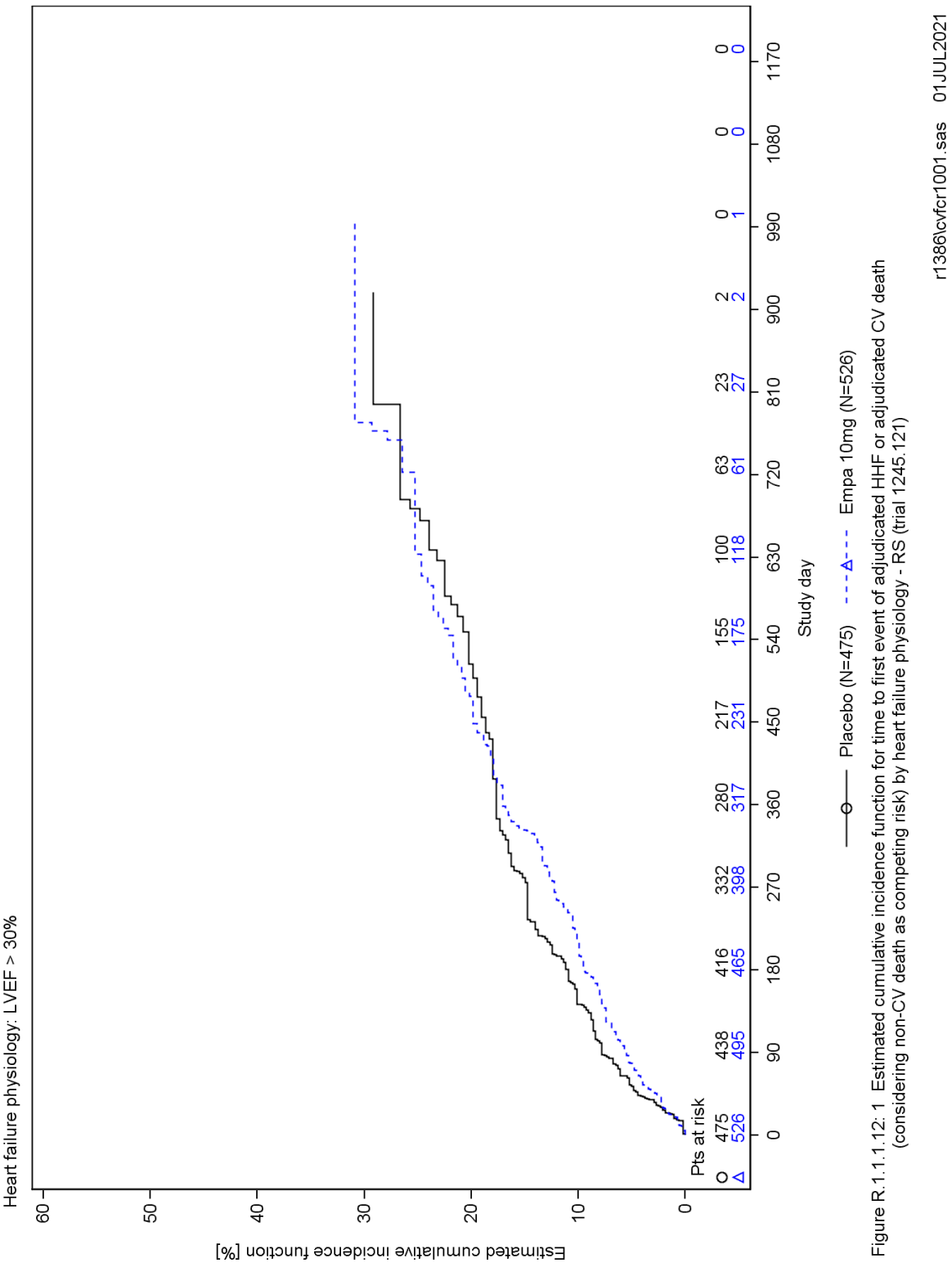

Figure R.1.1.1.12: 1 Estimated cumulative incidence function for time to first event of adjudicated HHF or adjudicated CV death (considering non-CV death as competing risk) by heart failure physiology - RS (trial 1245.121)

Table R.1.1.1.12: 1 Cox regr. for time to first event of adjudicated HHF or adjudicated CV death by heart failure physiology - RS (trial 1245.121)

Subgroup Description	Placebo	Empa 10mg
Heart failure physiology: LVEF <= 30% and NTproBNP < median		
Number of patients in analysis set	723	698
Number of analysed patients	723	698
Number of patients with event [N(%)]	114 (15.8)	80 (11.5)
Time at risk for event [years]	923.2	922.5
Incidence rate [patients with events per 100 patient years at risk]	12.35	8.67
95% confidence interval	(10.19, 14.72)	(6.88, 10.67)
Comparison vs Placebo*		
Hazard ratio		0.71
95% confidence interval		(0.53,0.94)
p-value		0.0167
Heart failure physiology: LVEF <= 30% and NTproBNP >= median		
Number of patients in analysis set	661	631
Number of analysed patients	661	631
Number of patients with event [N(%)]	249 (37.7)	169 (26.8)
Time at risk for event [years]	711.1	730.2
Incidence rate [patients with events per 100 patient years at risk]	35.01	23.15
95% confidence interval	(30.80, 39.50)	(19.79, 26.76)
Comparison vs Placebo*		
Hazard ratio		0.65
95% confidence interval		(0.53,0.79)
p-value		<0.0001

* Based on a Cox regression model with terms for age (p=0.2774), baseline eGFR (CKD-EPI) (p=0.0019), sex (p=0.0405), region (p=0.0115), baseline diabetes status (3 cat.) (p=0.0014), Treatment (p=0.0005), heart failure physiology (p<0.0001) and Treatment by heart failure physiology interaction (p=0.0430).
16 patients were excluded as the subgroup variable was missing.
The p-value for treatment by subgroup interaction trend test is 0.1865.

Table R.1.1.1.12: 1 Cox regr. for time to first event of adjudicated HHF or adjudicated CV death by heart failure physiology - RS (trial 1245.121)

Subgroup Description	Placebo	Empa 10mg
Heart failure physiology: LVEF > 30%		
Number of patients in analysis set	475	526
Number of analysed patients	475	526
Number of patients with event [N(%)]	97 (20.4)	108 (20.5)
Time at risk for event [years]	556.1	628.7
Incidence rate [patients with events per 100 patient years at risk]	17.44	17.18
95% confidence interval	(14.14, 21.08)	(14.09, 20.57)
Comparison vs Placebo*		
Hazard ratio		0.99
95% confidence interval		(0.76,1.31)
p-value		0.9712

* Based on a Cox regression model with terms for age (p=0.2774), baseline eGFR (CKD-EPI) (p=0.0019), sex (p=0.0405), region (p=0.0115), baseline diabetes status (3 cat.) (p=0.0014), Treatment (p=0.0005), heart failure physiology (p<0.0001) and Treatment by heart failure physiology interaction (p=0.0430).
16 patients were excluded as the subgroup variable was missing.
The p-value for treatment by subgroup interaction trend test is 0.1865.

R.1.1.1.13

Table R.1.1.1.13: 1 Cox regr. for time to first event of adjudicated HHF or adjudicated CV death by baseline use of MRA (Y/N) - RS (trial 1245.121)

Subgroup Description	Placebo	Empa 10mg
Baseline use of MRA: No		
Number of patients in analysis set	512	557
Number of analysed patients	512	557
Number of patients with event [N(%)]	132 (25.8)	118 (21.2)
Time at risk for event [years]	609.1	718.2
Incidence rate [patients with events per 100 patient years at risk]	21.67	16.43
95% confidence interval	(18.13, 25.52)	(13.60, 19.52)
Comparison vs Placebo*		
Hazard ratio		0.76
95% confidence interval		(0.59,0.97)
p-value		0.0277
Baseline use of MRA: Yes		
Number of patients in analysis set	1355	1306
Number of analysed patients	1355	1306
Number of patients with event [N(%)]	330 (24.4)	243 (18.6)
Time at risk for event [years]	1590.4	1570.5
Incidence rate [patients with events per 100 patient years at risk]	20.75	15.47
95% confidence interval	(18.57, 23.05)	(13.59, 17.48)
Comparison vs Placebo*		
Hazard ratio		0.75
95% confidence interval		(0.63,0.88)
p-value		0.0006

* Based on a Cox regression model with terms for age (p=0.1973), baseline eGFR (CKD-EPI) (p<0.0001), sex (p=0.0519), region (p=0.0129), baseline diabetes status (3 cat.) (p=0.0007), baseline LVEF (3 cat.) (p=0.0719), Treatment (p=0.0002), baseline use of MRA (p=0.8885) and Treatment by baseline use of MRA interaction (p=0.9345).

R.1.1.1.14

R.1.1.1.14 Subgroup analysis by baseline use of ARNi

Table R.1.1.1.14: 1

Table R.1.1.1.14: 1 Cox regr. for time to first event of adjudicated HHF or adjudicated CV death by baseline use of ARNi (Y/N) - RS (trial 1245.121)

Subgroup Description	Placebo	Empa 10mg
Baseline use of ARNi: No		
Number of patients in analysis set	1480	1523
Number of analysed patients	1480	1523
Number of patients with event [N(%)]	369 (24.9)	310 (20.4)
Time at risk for event [years]	1761.7	1897.0
Incidence rate [patients with events per 100 patient years at risk]	20.95	16.34
95% confidence interval	(18.86, 23.14)	(14.57, 18.21)
Comparison vs Placebo*		
Hazard ratio		0.77
95% confidence interval		(0.66,0.90)
p-value		0.0008
Baseline use of ARNi: Yes		
Number of patients in analysis set	387	340
Number of analysed patients	387	340
Number of patients with event [N(%)]	93 (24.0)	51 (15.0)
Time at risk for event [years]	437.8	391.8
Incidence rate [patients with events per 100 patient years at risk]	21.24	13.02
95% confidence interval	(17.14, 25.77)	(9.69, 16.83)
Comparison vs Placebo*		
Hazard ratio		0.64
95% confidence interval		(0.45,0.89)
p-value		0.0094

* Based on a Cox regression model with terms for age (p=0.1863), baseline eGFR (CKD-EPI) (p<0.0001), sex (p=0.0561), region (p=0.0128), baseline diabetes status (3 cat.) (p=0.0008), baseline LVEF (3 cat.) (p=0.0665), Treatment (p=0.0002), baseline use of ARNi (p=0.1939) and Treatment by baseline use of ARNi interaction (p=0.3101).

R.1.1.1.15 Subgroup analysis by bl. LVEF (<= 30%, >30% -<= 35% , > 35%)

Figure R.1.1.1.15: 1

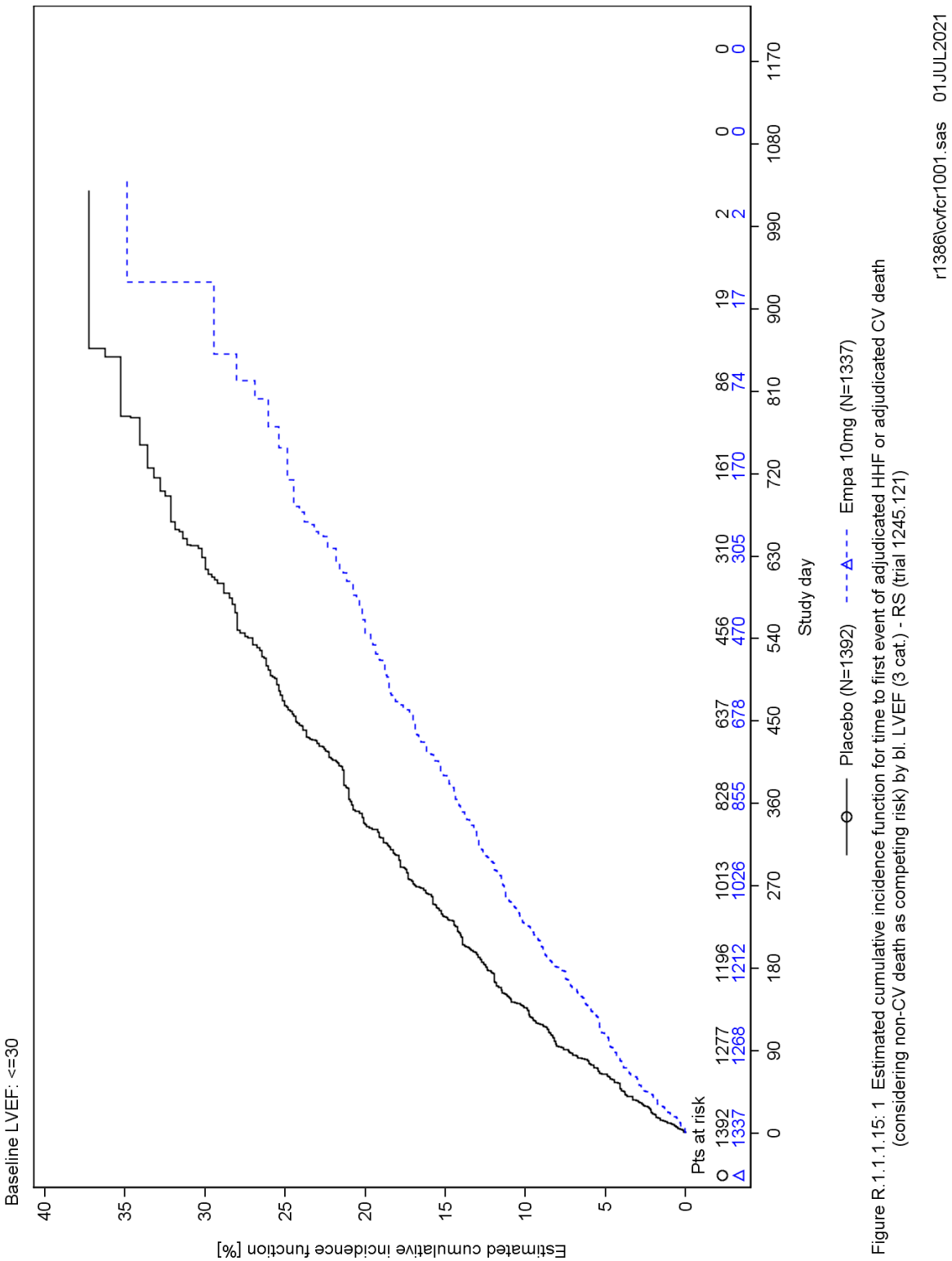

Figure R.1.1.1.15: 1 Estimated cumulative incidence function for time to first event of adjudicated HHF or adjudicated CV death (considering non-CV death as competing risk) by bl. LVEF (3 cat.) - RS (trial 1245.121)

Figure R.1.1.1.15: 1

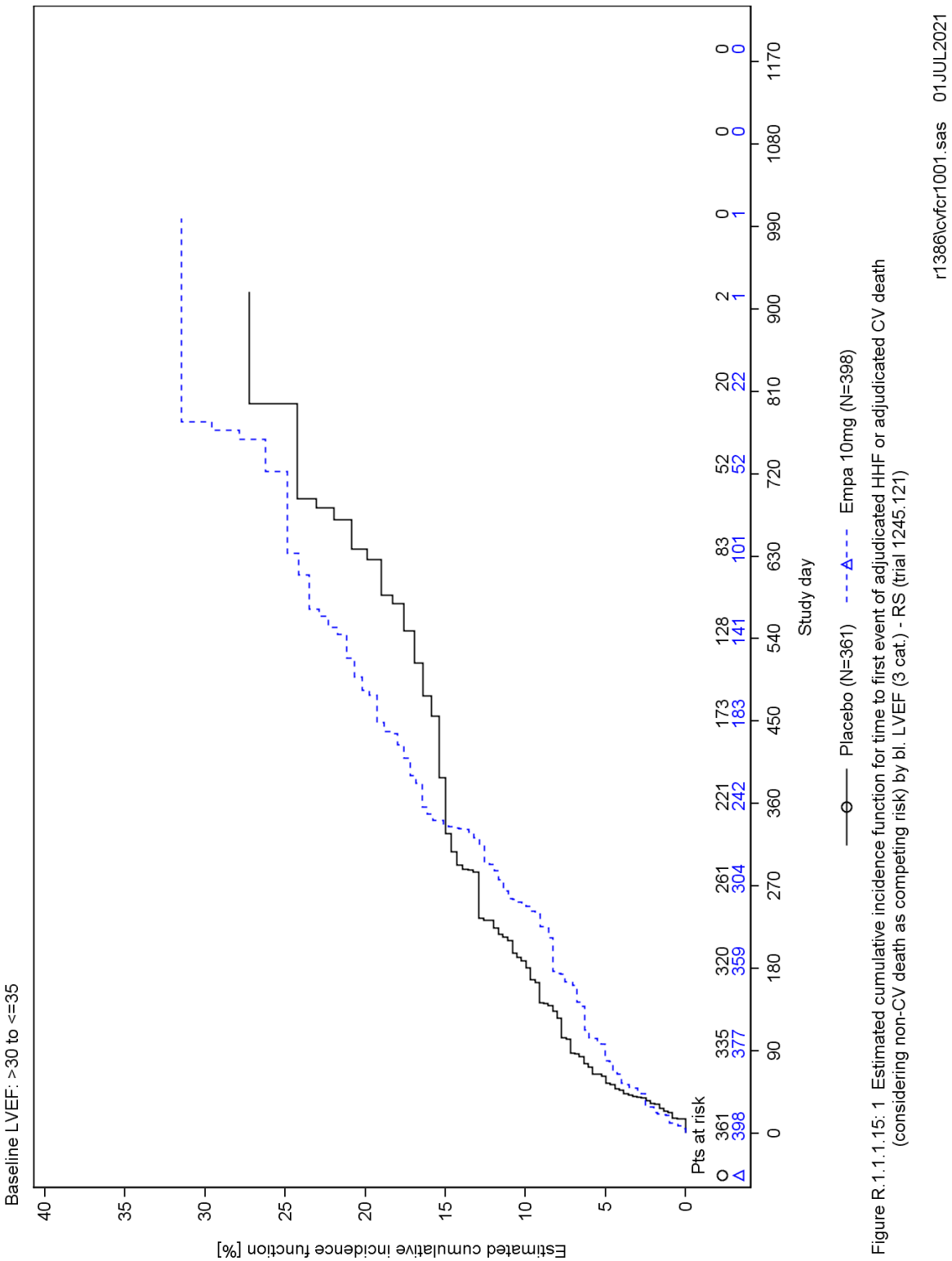

Figure R.1.1.1.15: 1 Estimated cumulative incidence function for time to first event of adjudicated HHF or adjudicated CV death (considering non-CV death as competing risk) by bl. LVEF (3 cat.) - RS (trial 1245.121)

Figure R.1.1.1.15: 1

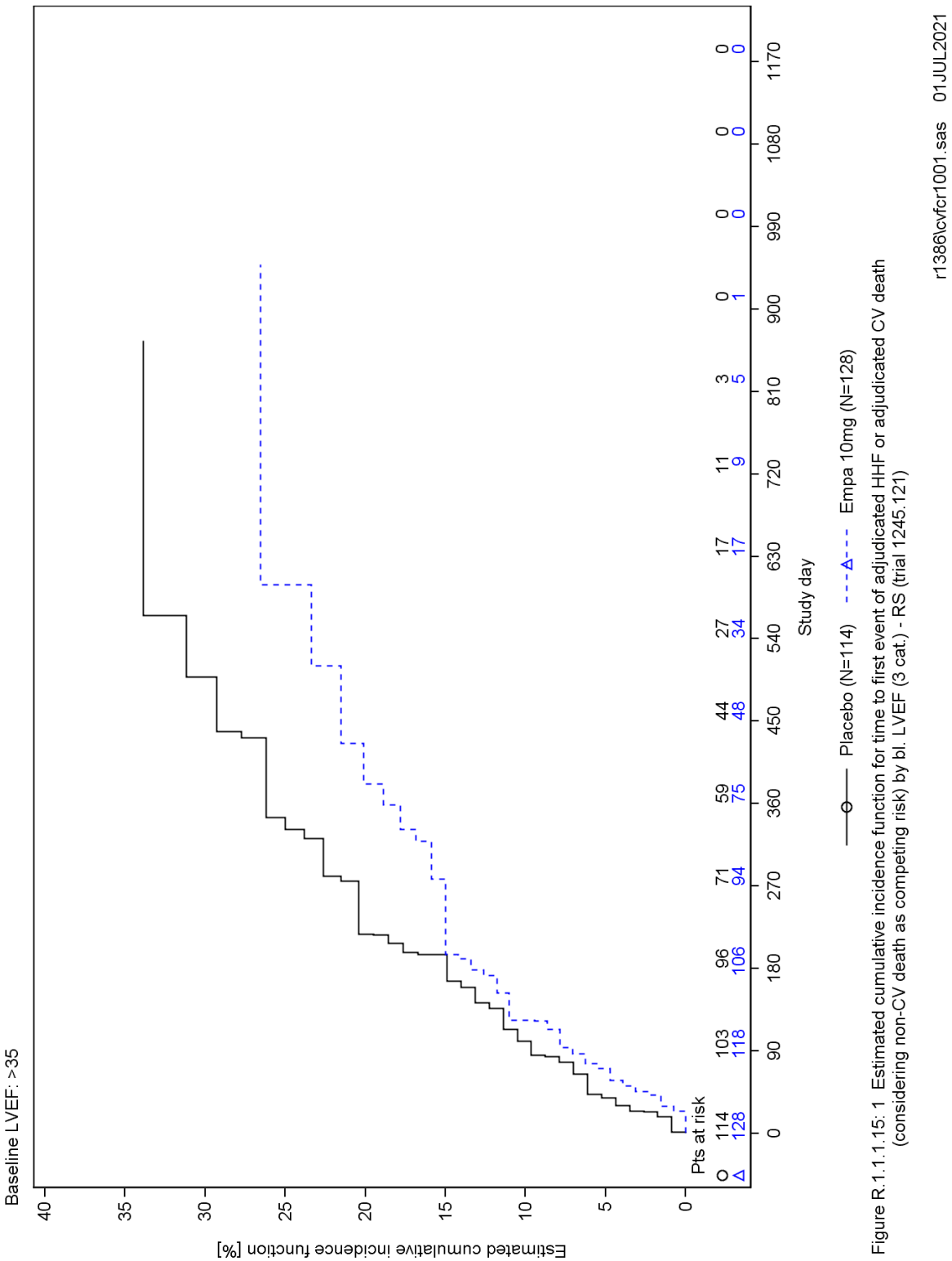

Figure R.1.1.1.15: 1 Estimated cumulative incidence function for time to first event of adjudicated HHF or adjudicated CV death (considering non-CV death as competing risk) by bl. LVEF (3 cat.) - RS (trial 1245.121)

Table R.1.1.1.15: 1 Cox regr. for time to first event of adjudicated HHF or adjudicated CV death by bl. LVEF (3 cat.) - RS (trial 1245.121)

Subgroup Description	Placebo	Empa 10mg
Baseline LVEF: <=30		
Number of patients in analysis set	1392	1337
Number of analysed patients	1392	1337
Number of patients with event [N(%)]	365 (26.2)	253 (18.9)
Time at risk for event [years]	1643.4	1660.1
Incidence rate [patients with events per 100 patient years at risk]	22.21	15.24
95% confidence interval	(19.99, 24.55)	(13.42, 17.17)
Comparison vs Placebo*		
Hazard ratio		0.68
95% confidence interval		(0.58,0.80)
p-value		<0.0001
Baseline LVEF: >30 to <=35		
Number of patients in analysis set	361	398
Number of analysed patients	361	398
Number of patients with event [N(%)]	65 (18.0)	81 (20.4)
Time at risk for event [years]	436.1	488.6
Incidence rate [patients with events per 100 patient years at risk]	14.90	16.58
95% confidence interval	(11.50, 18.74)	(13.16, 20.38)
Comparison vs Placebo*		
Hazard ratio		1.11
95% confidence interval		(0.80,1.54)
p-value		0.5204

* Based on a Cox regression model with terms for age (p=0.1976), baseline eGFR (CKD-EPI) (p<0.0001), sex (p=0.0557), region (p=0.0124), baseline diabetes status (3 cat.) (p=0.0007), Treatment (p=0.0892), baseline LVEF (3 cat.) (p=0.0761) and Treatment by baseline LVEF (3 cat.) interaction (p=0.0293).
The p-value for treatment by subgroup interaction trend test is 0.0696.

Table R.1.1.1.15: 1

Table R.1.1.1.15: 1 Cox regr. for time to first event of adjudicated HHF or adjudicated CV death by bl. LVEF (3 cat.) - RS (trial 1245.121)

Subgroup Description	Placebo	Empa 10mg
Baseline LVEF: >35		
Number of patients in analysis set	114	128
Number of analysed patients	114	128
Number of patients with event [N(%)]	32 (28.1)	27 (21.1)
Time at risk for event [years]	120.0	140.0
Incidence rate [patients with events per 100 patient years at risk]	26.67	19.28
95% confidence interval	(18.24, 36.67)	(12.71, 27.21)
Comparison vs Placebo*		
Hazard ratio		0.77
95% confidence interval		(0.46,1.28)
p-value		0.3090

* Based on a Cox regression model with terms for age (p=0.1976), baseline eGFR (CKD-EPI) (p<0.0001), sex (p=0.0557), region (p=0.0124), baseline diabetes status (3 cat.) (p=0.0007), Treatment (p=0.0892), baseline LVEF (3 cat.) (p=0.0761) and Treatment by baseline LVEF (3 cat.) interaction (p=0.0293).
The p-value for treatment by subgroup interaction trend test is 0.0696.

R.1.1.1.16 Subgroup analysis by bl. NTproBNP </>= median (median based on total patients)

Table R.1.1.1.16: 1 Cox regr. for time to first event of adjudicated HHF or adjudicated CV death by bl. NTproBNP (<median, >= median) (median based on total patients) - RS (trial 1245.121)

Subgroup Description	Placebo	Empa 10mg
Baseline NTproBNP: < median		
Number of patients in analysis set	920	942
Number of analysed patients	920	942
Number of patients with event [N(%)]	143 (15.5)	111 (11.8)
Time at risk for event [years]	1176.2	1233.5
Incidence rate [patients with events per 100 patient years at risk]	12.16	9.00
95% confidence interval	(10.25, 14.23)	(7.40, 10.75)
Comparison vs Placebo*		
Hazard ratio		0.74
95% confidence interval		(0.58,0.95)
p-value		0.0187
Baseline NTproBNP: >= median		
Number of patients in analysis set	946	920
Number of analysed patients	946	920
Number of patients with event [N(%)]	318 (33.6)	250 (27.2)
Time at risk for event [years]	1022.5	1054.1
Incidence rate [patients with events per 100 patient years at risk]	31.10	23.72
95% confidence interval	(27.78, 34.61)	(20.87, 26.75)
Comparison vs Placebo*		
Hazard ratio		0.76
95% confidence interval		(0.65,0.90)
p-value		0.0015

* Based on a Cox regression model with terms for age (p=0.1261), baseline eGFR (CKD-EPI) (p=0.0150), sex (p=0.0746), region (p=0.0144), baseline diabetes status (3 cat.) (p=0.0007), baseline LVEF (3 cat.) (p=0.0510), Treatment (p=0.0002), baseline NTproBNP (2 cat.) (p<0.0001) and Treatment by baseline NTproBNP (2 cat.) interaction (p=0.8540).
2 patients were excluded as the subgroup variable was missing.

Median: 1910 [pg/mL]

R.1.1.2

R.1.1.2 Time to adjudicated CV death

R.1.1.2.1

R.1.1.2.1 Overall analysis

Figure R.1.1.2.1: 1

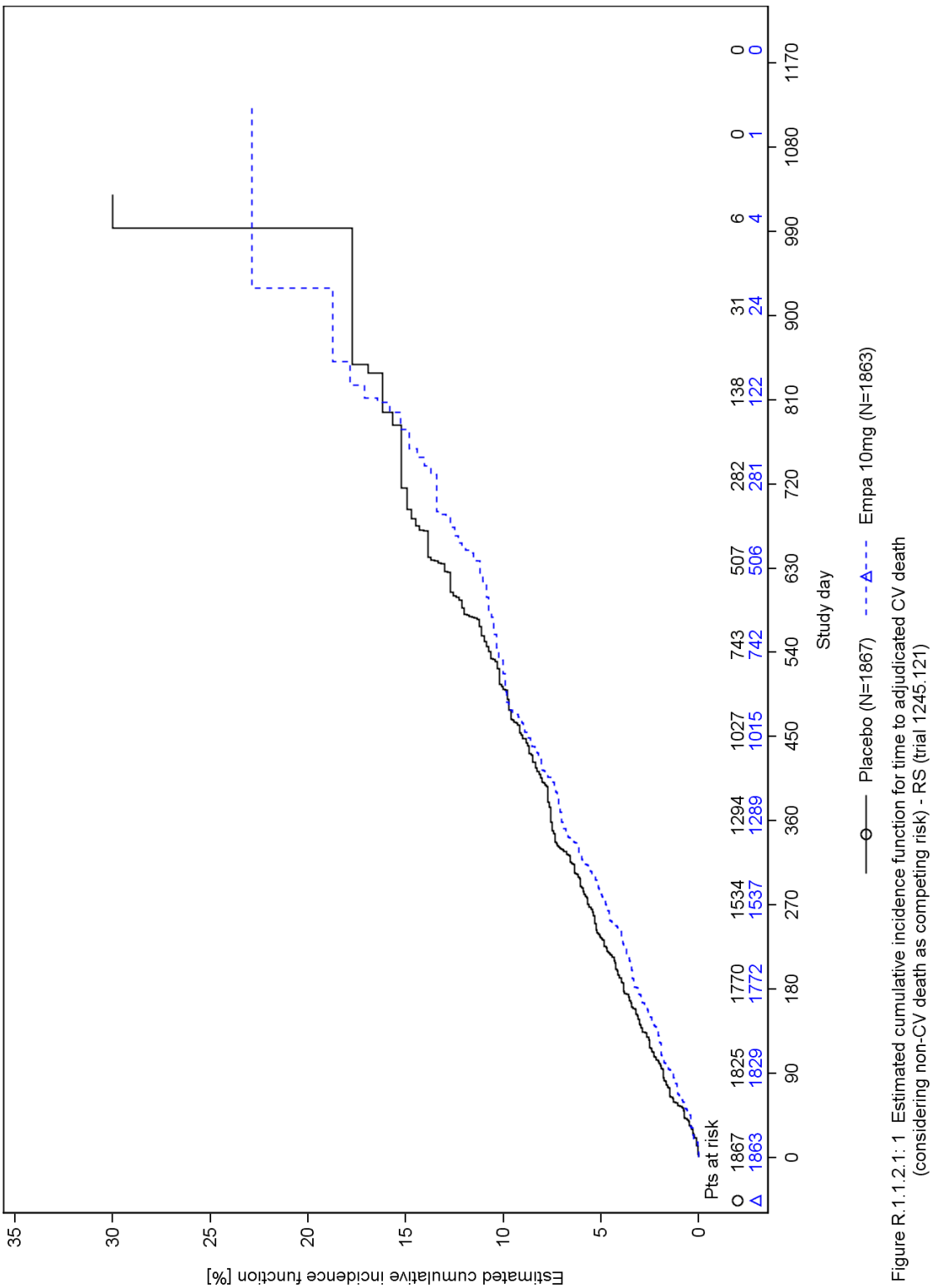

Figure R.1.1.2.1: 1 Estimated cumulative incidence function for time to adjudicated CV death (considering non-CV death as competing risk) - RS (trial 1245.121)

Table R.1.1.2.1: 1 Cox regr. for time to adjudicated CV death - RS (trial 1245.121)

	Placebo	Empa 10mg
Number of patients in analysis set	1867	1863
Number of analysed patients	1867	1863
Number of patients with event [N(%)]	202 (10.8)	187 (10.0)
Time at risk for event [years]	2483.3	2475.9
Incidence rate [patients with events per 100 patient years at risk]	8.13	7.55
95% confidence interval	(7.05, 9.29)	(6.51, 8.67)
Comparison vs Placebo*		
Hazard ratio		0.92
95% confidence interval		(0.75,1.12)
p-value		0.4133
Time to event [days]**		
2.5% percentile	117	154
5.0% percentile	234	279
7.5% percentile	346	401
10.0% percentile	499	498
Patients with events [%]**		
1 year	7.6	7.1
2 years	15.6	14.1

* Based on a Cox regression model with terms for age (p=0.1730), baseline eGFR (CKD-EPI) (p=0.0052), sex (p=0.0737), region (p=0.0096), baseline diabetes status (3 cat.) (p=0.0972), baseline LVEF (3 cat.) (p=0.9991) and Treatment (p=0.4133).
**Based on Kaplan-Meier estimates.

R.1.1.2.2

R.1.1.2.2 Subgroup analysis by sex

Table R.1.1.2.2: 1

Table R.1.1.2.2: 1 Cox regr. for time to adjudicated CV death by sex - RS (trial 1245.121)

Subgroup Description	Placebo	Empa 10mg
Sex: Male		
Number of patients in analysis set	1411	1426
Number of analysed patients	1411	1426
Number of patients with event [N(%)]	152 (10.8)	154 (10.8)
Time at risk for event [years]	1884.1	1881.6
Incidence rate [patients with events per 100 patient years at risk]	8.07	8.18
95% confidence interval	(6.84, 9.40)	(6.94, 9.53)
Comparison vs Placebo*		
Hazard ratio		1.00
95% confidence interval		(0.80,1.25)
p-value		0.9830
Sex: Female		
Number of patients in analysis set	456	437
Number of analysed patients	456	437
Number of patients with event [N(%)]	50 (11.0)	33 (7.6)
Time at risk for event [years]	599.2	594.2
Incidence rate [patients with events per 100 patient years at risk]	8.34	5.55
95% confidence interval	(6.19, 10.81)	(3.82, 7.60)
Comparison vs Placebo*		
Hazard ratio		0.68
95% confidence interval		(0.44,1.06)
p-value		0.0867

* Based on a Cox regression model with terms for age (p=0.1870), baseline eGFR (CKD-EPI) (p=0.0056), region (p=0.0113), baseline diabetes status (3 cat.) (p=0.0968), baseline LVEF (3 cat.) (p=0.9983), Treatment (p=0.1243), sex (p=0.0559) and Treatment by sex interaction (p=0.1298).

R.1.1.2.3

R.1.1.2.3 Subgroup analysis by age

Table R.1.1.2.3: 1

Table R.1.1.2.3: 1 Cox regr. for time to adjudicated CV death by age (2 cat.) - RS (trial 1245.121)

Subgroup Description	Placebo	Empa 10mg
Age [years]: < 65		
Number of patients in analysis set	740	675
Number of analysed patients	740	675
Number of patients with event [N(%)]	72 (9.7)	59 (8.7)
Time at risk for event [years]	986.0	892.1
Incidence rate [patients with events per 100 patient years at risk]	7.30	6.61
95% confidence interval	(5.71, 9.08)	(5.03, 8.40)
Comparison vs Placebo*		
Hazard ratio		0.94
95% confidence interval		(0.66,1.32)
p-value		0.7092
Age [years]: >= 65		
Number of patients in analysis set	1127	1188
Number of analysed patients	1127	1188
Number of patients with event [N(%)]	130 (11.5)	128 (10.8)
Time at risk for event [years]	1497.3	1583.8
Incidence rate [patients with events per 100 patient years at risk]	8.68	8.08
95% confidence interval	(7.25, 10.24)	(6.74, 9.54)
Comparison vs Placebo*		
Hazard ratio		0.91
95% confidence interval		(0.72,1.17)
p-value		0.4751

* Based on a Cox regression model with terms for baseline eGFR (CKD-EPI) (p=0.0008), sex (p=0.0779), region (p=0.0132), baseline diabetes status (3 cat.) (p=0.1059), baseline LVEF (3 cat.) (p=0.9994), Treatment (p=0.4726), age (2 cat.) (p=0.5070) and Treatment by age (2 cat.) interaction (p=0.9135).

R.1.1.2.4 Subgroup analysis by region (North America, Latin America, Europe, Asia, Other)

Table R.1.1.2.4: 1 Cox regr. for time to adjudicated CV death by region - RS (trial 1245.121)

Subgroup Description	Placebo	Empa 10mg
Region: North America		
Number of patients in analysis set	213	212
Number of analysed patients	213	212
Number of patients with event [N(%)]	20 (9.4)	17 (8.0)
Time at risk for event [years]	299.5	311.4
Incidence rate [patients with events per 100 patient years at risk]	6.68	5.46
95% confidence interval	(4.08, 9.91)	(3.18, 8.35)
Comparison vs Placebo*		
Hazard ratio		0.81
95% confidence interval		(0.42,1.54)
p-value		0.5170
Region: Latin America		
Number of patients in analysis set	645	641
Number of analysed patients	645	641
Number of patients with event [N(%)]	71 (11.0)	72 (11.2)
Time at risk for event [years]	778.6	766.4
Incidence rate [patients with events per 100 patient years at risk]	9.12	9.39
95% confidence interval	(7.12, 11.36)	(7.35, 11.69)
Comparison vs Placebo*		
Hazard ratio		1.01
95% confidence interval		(0.73,1.40)
p-value		0.9471

* Based on a Cox regression model with terms for age (p=0.1663), baseline eGFR (CKD-EPI) (p=0.0056), sex (p=0.0760), baseline diabetes status (3 cat.) (p=0.0953), baseline LVEF (3 cat.) (p=0.9996), Treatment (p=0.0522), region (p=0.0073) and Treatment by region interaction (p=0.4261).

Table R.1.1.2.4: 1 Cox regr. for time to adjudicated CV death by region - RS (trial 1245.121)

Subgroup Description	Placebo	Empa 10mg
Region: Europe		
Number of patients in analysis set	677	676
Number of analysed patients	677	676
Number of patients with event [N(%)]	72 (10.6)	71 (10.5)
Time at risk for event [years]	932.6	929.7
Incidence rate [patients with events per 100 patient years at risk]	7.72	7.64
95% confidence interval	(6.04, 9.60)	(5.96, 9.51)
Comparison vs Placebo*		
Hazard ratio		0.98
95% confidence interval		(0.71,1.36)
p-value		0.9082
Region: Asia		
Number of patients in analysis set	245	248
Number of analysed patients	245	248
Number of patients with event [N(%)]	27 (11.0)	23 (9.3)
Time at risk for event [years]	353.1	349.6
Incidence rate [patients with events per 100 patient years at risk]	7.65	6.58
95% confidence interval	(5.04, 10.79)	(4.17, 9.53)
Comparison vs Placebo*		
Hazard ratio		0.87
95% confidence interval		(0.50,1.52)
p-value		0.6209

* Based on a Cox regression model with terms for age (p=0.1663), baseline eGFR (CKD-EPI) (p=0.0056), sex (p=0.0760), baseline diabetes status (3 cat.) (p=0.0953), baseline LVEF (3 cat.) (p=0.9996), Treatment (p=0.0522), region (p=0.0073) and Treatment by region interaction (p=0.4261).

Table R.1.1.2.4: 1 Cox regr. for time to adjudicated CV death by region - RS (trial 1245.121)

Subgroup Description	Placebo	Empa 10mg
Region: Other		
Number of patients in analysis set	87	86
Number of analysed patients	87	86
Number of patients with event [N(%)]	12 (13.8)	4 (4.7)
Time at risk for event [years]	119.5	118.8
Incidence rate [patients with events per 100 patient years at risk]	10.05	3.37
95% confidence interval	(5.19, 16.48)	(0.92, 7.38)
Comparison vs Placebo*		
Hazard ratio		0.33
95% confidence interval		(0.11,1.02)
p-value		0.0534

* Based on a Cox regression model with terms for age (p=0.1663), baseline eGFR (CKD-EPI) (p=0.0056), sex (p=0.0760), baseline diabetes status (3 cat.) (p=0.0953), baseline LVEF (3 cat.) (p=0.9996), Treatment (p=0.0522), region (p=0.0073) and Treatment by region interaction (p=0.4261).

R.1.1.2.5

R.1.1.2.5 Subgroup analysis by OECD member (Y/N)

Table R.1.1.2.5: 1 Cox regr. for time to adjudicated CV death by OECD member (Y/N) - RS (trial 1245.121)

Subgroup Description	Placebo	Empa 10mg
OECD member: No		
Number of patients in analysis set	741	713
Number of analysed patients	741	713
Number of patients with event [N(%)]	86 (11.6)	79 (11.1)
Time at risk for event [years]	906.8	866.4
Incidence rate [patients with events per 100 patient years at risk]	9.48	9.12
95% confidence interval	(7.59, 11.59)	(7.22, 11.24)
Comparison vs Placebo*		
Hazard ratio		0.94
95% confidence interval		(0.69,1.28)
p-value		0.6855
OECD member: Yes		
Number of patients in analysis set	1126	1150
Number of analysed patients	1126	1150
Number of patients with event [N(%)]	116 (10.3)	108 (9.4)
Time at risk for event [years]	1576.6	1609.5
Incidence rate [patients with events per 100 patient years at risk]	7.36	6.71
95% confidence interval	(6.08, 8.76)	(5.50, 8.03)
Comparison vs Placebo*		
Hazard ratio		0.91
95% confidence interval		(0.70,1.18)
p-value		0.4747

* Based on a Cox regression model with terms for age (p=0.0878), baseline eGFR (CKD-EPI) (p=0.0037), sex (p=0.0645), baseline diabetes status (3 cat.) (p=0.1054), baseline LVEF (3 cat.) (p=0.9918), Treatment (p=0.4395), OECD Member (N) (p<0.0001) and Treatment by OECD Member (N) interaction (p=0.8752).

OECD member (yes/no) countries included:
Yes: United States, Canada, Mexico, Poland, Netherlands, Hungary, Germany, Czech Republic, Italy, France, Spain, United Kingdom, Belgium, Japan, Australia, 'Korea; Republic Of South Korea';
No: Brazil, Argentina, China, India.

R.1.1.2.6 Subgroup analysis by NYHA at baseline (II, III/IV - 2 cat.)

Table R.1.1.2.6: 1 Cox regr. for time to adjudicated CV death by baseline NYHA (2 cat.) - RS (trial 1245.121)

Subgroup Description	Placebo	Empa 10mg
Baseline NYHA: II		
Number of patients in analysis set	1401	1399
Number of analysed patients	1401	1399
Number of patients with event [N(%)]	121 (8.6)	121 (8.6)
Time at risk for event [years]	1877.2	1860.2
Incidence rate [patients with events per 100 patient years at risk]	6.45	6.50
95% confidence interval	(5.35, 7.64)	(5.40, 7.71)
Comparison vs Placebo*		
Hazard ratio		1.00
95% confidence interval		(0.78,1.29)
p-value		0.9848
Baseline NYHA: III/IV		
Number of patients in analysis set	466	464
Number of analysed patients	466	464
Number of patients with event [N(%)]	81 (17.4)	66 (14.2)
Time at risk for event [years]	606.1	615.7
Incidence rate [patients with events per 100 patient years at risk]	13.36	10.72
95% confidence interval	(10.61, 16.43)	(8.29, 13.46)
Comparison vs Placebo*		
Hazard ratio		0.79
95% confidence interval		(0.57,1.09)
p-value		0.1478

* Based on a Cox regression model with terms for age (p=0.1374), baseline eGFR (CKD-EPI) (p=0.0086), sex (p=0.0341), region (p=0.0035), baseline diabetes status (3 cat.) (p=0.2419), baseline LVEF (3 cat.) (p=0.9677), Treatment (p=0.2572), baseline NYHA (2 cat.) (p<0.0001) and Treatment by baseline NYHA (2 cat.) interaction (p=0.2475).

R.1.1.2.7

R.1.1.2.7 Subgroup analysis by diabetes at baseline

Table R.1.1.2.7: 1

Table R.1.1.2.7: 1 Cox regr. for time to adjudicated CV death by diabetes at baseline (2 cat.) - RS (trial 1245.121)

Subgroup Description	Placebo	Empa 10mg
Baseline diabetes status: Diabetic		
Number of patients in analysis set	929	927
Number of analysed patients	929	927
Number of patients with event [N(%)]	113 (12.2)	104 (11.2)
Time at risk for event [years]	1247.1	1235.3
Incidence rate [patients with events per 100 patient years at risk]	9.06	8.42
95% confidence interval	(7.47, 10.81)	(6.88, 10.11)
Comparison vs Placebo*		
Hazard ratio		0.92
95% confidence interval		(0.71,1.20)
p-value		0.5538
Baseline diabetes status: Non-Diabetic		
Number of patients in analysis set	938	936
Number of analysed patients	938	936
Number of patients with event [N(%)]	89 (9.5)	83 (8.9)
Time at risk for event [years]	1236.3	1240.6
Incidence rate [patients with events per 100 patient years at risk]	7.20	6.69
95% confidence interval	(5.78, 8.77)	(5.33, 8.20)
Comparison vs Placebo*		
Hazard ratio		0.92
95% confidence interval		(0.68,1.24)
p-value		0.5762

* Based on a Cox regression model with terms for age (p=0.1773), baseline eGFR (CKD-EPI) (p=0.0054), sex (p=0.0725), region (p=0.0091), baseline LVEF (3 cat.) (p=0.9991), Treatment (p=0.4175), baseline diabetes status (2 cat.) (p=0.0348) and Treatment by baseline diabetes status (2 cat.) interaction (p=0.9807).

R.1.1.2.8 Subgroup analysis by BMI at baseline (<30, >=30)

Table R.1.1.2.8: 1 Cox regr. for time to adjudicated CV death by baseline BMI [kg/m2] - RS (trial 1245.121)

Subgroup Description	Placebo	Empa 10mg
Baseline BMI [kg/m²]: <30		
Number of patients in analysis set	1300	1263
Number of analysed patients	1300	1263
Number of patients with event [N(%)]	151 (11.6)	130 (10.3)
Time at risk for event [years]	1749.4	1670.1
Incidence rate [patients with events per 100 patient years at risk]	8.63	7.78
95% confidence interval	(7.31, 10.06)	(6.50, 9.18)
Comparison vs Placebo*		
Hazard ratio		0.90
95% confidence interval		(0.71,1.14)
p-value		0.3992
Baseline BMI [kg/m²]: >=30		
Number of patients in analysis set	567	600
Number of analysed patients	567	600
Number of patients with event [N(%)]	51 (9.0)	57 (9.5)
Time at risk for event [years]	734.0	805.8
Incidence rate [patients with events per 100 patient years at risk]	6.95	7.07
95% confidence interval	(5.17, 8.98)	(5.36, 9.03)
Comparison vs Placebo*		
Hazard ratio		0.99
95% confidence interval		(0.68,1.44)
p-value		0.9462

* Based on a Cox regression model with terms for age (p=0.2566), baseline eGFR (CKD-EPI) (p=0.0045), sex (p=0.0827), region (p=0.0108), baseline diabetes status (3 cat.) (p=0.0693), baseline LVEF (3 cat.) (p=0.9987), Treatment (p=0.6159), baseline BMI (2 cat.) (p=0.1793) and Treatment by baseline BMI (2 cat.) interaction (p=0.6986).

R.1.1.2.9 Subgroup analysis by eGFR at baseline (<60, >=60)

Table R.1.1.2.9: 1 Cox regr. for time to adjudicated CV death by baseline eGFR (2 cat.) - RS (trial 1245.121)

Subgroup Description	Placebo	Empa 10mg
Baseline eGFR (CKD-EPI) [mL/min/1.73m²]: >=60		
Number of patients in analysis set	960	969
Number of analysed patients	960	969
Number of patients with event [N(%)]	88 (9.2)	91 (9.4)
Time at risk for event [years]	1280.9	1287.5
Incidence rate [patients with events per 100 patient years at risk]	6.87	7.07
95% confidence interval	(5.51, 8.38)	(5.69, 8.59)
Comparison vs Placebo*		
Hazard ratio		1.02
95% confidence interval		(0.76,1.37)
p-value		0.8807
Baseline eGFR (CKD-EPI) [mL/min/1.73m²]: <60		
Number of patients in analysis set	906	893
Number of analysed patients	906	893
Number of patients with event [N(%)]	113 (12.5)	96 (10.8)
Time at risk for event [years]	1201.5	1187.1
Incidence rate [patients with events per 100 patient years at risk]	9.40	8.09
95% confidence interval	(7.75, 11.22)	(6.55, 9.78)
Comparison vs Placebo*		
Hazard ratio		0.85
95% confidence interval		(0.65,1.12)
p-value		0.2452

* Based on a Cox regression model with terms for age (p=0.0219), sex (p=0.0812), region (p=0.0120), baseline diabetes status (3 cat.) (p=0.0879), baseline LVEF (3 cat.) (p=0.9962), Treatment (p=0.4964), baseline eGFR (CKD-EPI) (2 cat.) (p=0.1716) and Treatment by baseline eGFR (CKD-EPI) (2 cat.) interaction (p=0.3680).
2 patients were excluded as the subgroup variable was missing.

R.1.1.2.10

Table R.1.1.2.10: 1 Cox regr. for time to adjudicated CV death by history of HHF within 12 months - RS (trial 1245.121)

Subgroup Description	Placebo	Empa 10mg
History of HHF (in the last 12 months): No		
Number of patients in analysis set	1293	1286
Number of analysed patients	1293	1286
Number of patients with event [N(%)]	126 (9.7)	117 (9.1)
Time at risk for event [years]	1769.9	1744.0
Incidence rate [patients with events per 100 patient years at risk]	7.12	6.71
95% confidence interval	(5.93, 8.41)	(5.55, 7.98)
Comparison vs Placebo*		
Hazard ratio		0.94
95% confidence interval		(0.73,1.21)
p-value		0.6476
History of HHF (in the last 12 months): Yes		
Number of patients in analysis set	574	577
Number of analysed patients	574	577
Number of patients with event [N(%)]	76 (13.2)	70 (12.1)
Time at risk for event [years]	713.4	731.8
Incidence rate [patients with events per 100 patient years at risk]	10.65	9.57
95% confidence interval	(8.39, 13.18)	(7.46, 11.93)
Comparison vs Placebo*		
Hazard ratio		0.86
95% confidence interval		(0.62,1.20)
p-value		0.3815

* Based on a Cox regression model with terms for age (p=0.0942), baseline eGFR (CKD-EPI) (p=0.0075), sex (p=0.0711), region (p=0.0024), baseline diabetes status (3 cat.) (p=0.1537), baseline LVEF (3 cat.) (p=0.9010), Treatment (p=0.3311), history of HHF (p<0.0001) and Treatment by history of HHF interaction (p=0.6797).

R.1.1.2.11

R.1.1.2.11 Subgroup analysis by cause of heart failure

Table R.1.1.2.11: 1 Cox regr. for time to adjudicated CV death by cause of heart failure - RS (trial 1245.121)

Subgroup Description	Placebo	Empa 10mg
Cause of heart failure: Ischemic		
Number of patients in analysis set	946	983
Number of analysed patients	946	983
Number of patients with event [N(%)]	113 (11.9)	113 (11.5)
Time at risk for event [years]	1277.0	1315.3
Incidence rate [patients with events per 100 patient years at risk]	8.85	8.59
95% confidence interval	(7.29, 10.55)	(7.08, 10.25)
Comparison vs Placebo*		
Hazard ratio		0.96
95% confidence interval		(0.74,1.25)
p-value		0.7525
Cause of heart failure: Non-ischemic		
Number of patients in analysis set	921	880
Number of analysed patients	921	880
Number of patients with event [N(%)]	89 (9.7)	74 (8.4)
Time at risk for event [years]	1206.3	1160.5
Incidence rate [patients with events per 100 patient years at risk]	7.38	6.38
95% confidence interval	(5.92, 8.99)	(5.01, 7.91)
Comparison vs Placebo*		
Hazard ratio		0.86
95% confidence interval		(0.63,1.17)
p-value		0.3482

* Based on a Cox regression model with terms for age (p=0.2247), baseline eGFR (CKD-EPI) (p=0.0058), sex (p=0.1211), region (p=0.0051), baseline diabetes status (3 cat.) (p=0.1485), baseline LVEF (3 cat.) (p=0.9990), Treatment (p=0.3573), cause of heart failure (2 cat.) (p=0.0541) and Treatment by cause of heart failure (2 cat.) interaction (p=0.6085).

R.1.1.2.12

R.1.1.2.12 Subgroup analysis by heart failure physiology (LVEF <= 30% and NTproBNP<median; LVEF <= 30% and NTproBNP>=median; LVEF > 30%)

Table R.1.1.2.12: 1 Cox regr. for time to adjudicated CV death by heart failure physiology - RS (trial 1245.121)

Subgroup Description	Placebo	Empa 10mg
Heart failure physiology: LVEF <= 30% and NTproBNP < median		
Number of patients in analysis set	723	698
Number of analysed patients	723	698
Number of patients with event [N(%)]	44 (6.1)	49 (7.0)
Time at risk for event [years]	992.2	958.3
Incidence rate [patients with events per 100 patient years at risk]	4.43	5.11
95% confidence interval	(3.22, 5.84)	(3.78, 6.64)
Comparison vs Placebo*		
Hazard ratio		1.15
95% confidence interval		(0.77,1.73)
p-value		0.5011
Heart failure physiology: LVEF <= 30% and NTproBNP >= median		
Number of patients in analysis set	661	631
Number of analysed patients	661	631
Number of patients with event [N(%)]	110 (16.6)	76 (12.0)
Time at risk for event [years]	869.1	823.3
Incidence rate [patients with events per 100 patient years at risk]	12.66	9.23
95% confidence interval	(10.40, 15.13)	(7.27, 11.42)
Comparison vs Placebo*		
Hazard ratio		0.72
95% confidence interval		(0.53,0.96)
p-value		0.0255

* Based on a Cox regression model with terms for age (p=0.1429), baseline eGFR (CKD-EPI) (p=0.0573), sex (p=0.0728), region (p=0.0221), baseline diabetes status (3 cat.) (p=0.1625), Treatment (p=0.7682), heart failure physiology (p<0.0001) and Treatment by heart failure physiology interaction (p=0.0908).
16 patients were excluded as the subgroup variable was missing.
The p-value for treatment by subgroup interaction trend test is 0.8671.

Table R.1.1.2.12: 1 Cox regr. for time to adjudicated CV death by heart failure physiology - RS (trial 1245.121)

Subgroup Description	Placebo	Empa 10mg
Heart failure physiology: LVEF > 30%		
Number of patients in analysis set	475	526
Number of analysed patients	475	526
Number of patients with event [N(%)]	47 (9.9)	58 (11.0)
Time at risk for event [years]	611.7	686.7
Incidence rate [patients with events per 100 patient years at risk]	7.68	8.45
95% confidence interval	(5.65, 10.03)	(6.41, 10.75)
Comparison vs Placebo*		
Hazard ratio		1.10
95% confidence interval		(0.75,1.62)
p-value		0.6149

* Based on a Cox regression model with terms for age (p=0.1429), baseline eGFR (CKD-EPI) (p=0.0573), sex (p=0.0728), region (p=0.0221), baseline diabetes status (3 cat.) (p=0.1625), Treatment (p=0.7682), heart failure physiology (p<0.0001) and Treatment by heart failure physiology interaction (p=0.0908).
16 patients were excluded as the subgroup variable was missing.
The p-value for treatment by subgroup interaction trend test is 0.8671.

R.1.1.2.13

Table R.1.1.2.13: 1 Cox regr. for time to adjudicated CV death by baseline use of MRA (Y/N) - RS (trial 1245.121)

Subgroup Description	Placebo	Empa 10mg
Baseline use of MRA: No		
Number of patients in analysis set	512	557
Number of analysed patients	512	557
Number of patients with event [N(%)]	51 (10.0)	67 (12.0)
Time at risk for event [years]	704.3	780.6
Incidence rate [patients with events per 100 patient years at risk]	7.24	8.58
95% confidence interval	(5.39, 9.36)	(6.65, 10.76)
Comparison vs Placebo*		
Hazard ratio		1.19
95% confidence interval		(0.82,1.71)
p-value		0.3587
Baseline use of MRA: Yes		
Number of patients in analysis set	1355	1306
Number of analysed patients	1355	1306
Number of patients with event [N(%)]	151 (11.1)	120 (9.2)
Time at risk for event [years]	1779.0	1695.3
Incidence rate [patients with events per 100 patient years at risk]	8.49	7.08
95% confidence interval	(7.19, 9.89)	(5.87, 8.40)
Comparison vs Placebo*		
Hazard ratio		0.82
95% confidence interval		(0.65,1.05)
p-value		0.1130

* Based on a Cox regression model with terms for age (p=0.1680), baseline eGFR (CKD-EPI) (p=0.0053), sex (p=0.0739), region (p=0.0113), baseline diabetes status (3 cat.) (p=0.0957), baseline LVEF (3 cat.) (p=0.9997), Treatment (p=0.9157), baseline use of MRA (p=0.9831) and Treatment by baseline use of MRA interaction (p=0.1014).

R.1.1.2.14

Table R.1.1.2.14: 1

Table R.1.1.2.14: 1 Cox regr. for time to adjudicated CV death by baseline use of ARNi (Y/N) - RS (trial 1245.121)

Subgroup Description	Placebo	Empa 10mg
Baseline use of ARNi: No		
Number of patients in analysis set	1480	1523
Number of analysed patients	1480	1523
Number of patients with event [N(%)]	167 (11.3)	166 (10.9)
Time at risk for event [years]	1986.0	2056.1
Incidence rate [patients with events per 100 patient years at risk]	8.41	8.07
95% confidence interval	(7.18, 9.73)	(6.89, 9.35)
Comparison vs Placebo*		
Hazard ratio		0.95
95% confidence interval		(0.76,1.18)
p-value		0.6307
Baseline use of ARNi: Yes		
Number of patients in analysis set	387	340
Number of analysed patients	387	340
Number of patients with event [N(%)]	35 (9.0)	21 (6.2)
Time at risk for event [years]	497.3	419.8
Incidence rate [patients with events per 100 patient years at risk]	7.04	5.00
95% confidence interval	(4.90, 9.55)	(3.10, 7.36)
Comparison vs Placebo*		
Hazard ratio		0.73
95% confidence interval		(0.42,1.25)
p-value		0.2464

* Based on a Cox regression model with terms for age (p=0.1773), baseline eGFR (CKD-EPI) (p=0.0056), sex (p=0.0798), region (p=0.0216), baseline diabetes status (3 cat.) (p=0.1019), baseline LVEF (3 cat.) (p=0.9901), Treatment (p=0.2095), baseline use of ARNi (p=0.1013) and Treatment by baseline use of ARNi interaction (p=0.3684).

R.1.1.2.15

R.1.1.2.15 Subgroup analysis by bl. LVEF (<= 30%, >30% -<= 35% , > 35%)

Table R.1.1.2.15: 1 Cox regr. for time to adjudicated CV death by bl. LVEF (3 cat.) - RS (trial 1245.121)

Subgroup Description	Placebo	Empa 10mg
Baseline LVEF: <=30		
Number of patients in analysis set	1392	1337
Number of analysed patients	1392	1337
Number of patients with event [N(%)]	155 (11.1)	129 (9.6)
Time at risk for event [years]	1871.6	1789.2
Incidence rate [patients with events per 100 patient years at risk]	8.28	7.21
95% confidence interval	(7.03, 9.64)	(6.02, 8.51)
Comparison vs Placebo*		
Hazard ratio		0.86
95% confidence interval		(0.68,1.09)
p-value		0.2041
Baseline LVEF: >30 to <=35		
Number of patients in analysis set	361	398
Number of analysed patients	361	398
Number of patients with event [N(%)]	34 (9.4)	47 (11.8)
Time at risk for event [years]	471.5	524.5
Incidence rate [patients with events per 100 patient years at risk]	7.21	8.96
95% confidence interval	(4.99, 9.83)	(6.58, 11.70)
Comparison vs Placebo*		
Hazard ratio		1.26
95% confidence interval		(0.81,1.96)
p-value		0.3053

* Based on a Cox regression model with terms for age (p=0.1650), baseline eGFR (CKD-EPI) (p=0.0054), sex (p=0.0784), region (p=0.0081), baseline diabetes status (3 cat.) (p=0.0958), Treatment (p=0.6038), baseline LVEF (3 cat.) (p=0.9916) and Treatment by baseline LVEF (3 cat.) interaction (p=0.2681).
The p-value for treatment by subgroup interaction trend test is 0.5629.

Table R.1.1.2.15: 1

Table R.1.1.2.15: 1 Cox regr. for time to adjudicated CV death by bl. LVEF (3 cat.) - RS (trial 1245.121)

Subgroup Description	Placebo	Empa 10mg
Baseline LVEF: >35		
Number of patients in analysis set	114	128
Number of analysed patients	114	128
Number of patients with event [N(%)]	13 (11.4)	11 (8.6)
Time at risk for event [years]	140.2	162.2
Incidence rate [patients with events per 100 patient years at risk]	9.27	6.78
95% confidence interval	(4.94, 14.95)	(3.39, 11.34)
Comparison vs Placebo*		
Hazard ratio		0.72
95% confidence interval		(0.32,1.61)
p-value		0.4208

* Based on a Cox regression model with terms for age (p=0.1650), baseline eGFR (CKD-EPI) (p=0.0054), sex (p=0.0784), region (p=0.0081), baseline diabetes status (3 cat.) (p=0.0958), Treatment (p=0.6038), baseline LVEF (3 cat.) (p=0.9916) and Treatment by baseline LVEF (3 cat.) interaction (p=0.2681).
The p-value for treatment by subgroup interaction trend test is 0.5629.

R.1.1.2.16 Subgroup analysis by bl. NTproBNP </>= median (median based on total patients)

Table R.1.1.2.16: 1 Cox regr. for time to adjudicated CV death by bl. NTproBNP (<median, >= median) (median based on total patients) - RS (trial 1245.121)

Subgroup Description	Placebo	Empa 10mg
Baseline NTproBNP: < median		
Number of patients in analysis set	920	942
Number of analysed patients	920	942
Number of patients with event [N(%)]	59 (6.4)	66 (7.0)
Time at risk for event [years]	1264.5	1281.4
Incidence rate [patients with events per 100 patient years at risk]	4.67	5.15
95% confidence interval	(3.55, 5.93)	(3.98, 6.47)
Comparison vs Placebo*		
Hazard ratio		1.10
95% confidence interval		(0.77,1.56)
p-value		0.5994
Baseline NTproBNP: >= median		
Number of patients in analysis set	946	920
Number of analysed patients	946	920
Number of patients with event [N(%)]	142 (15.0)	121 (13.2)
Time at risk for event [years]	1217.9	1193.3
Incidence rate [patients with events per 100 patient years at risk]	11.66	10.14
95% confidence interval	(9.82, 13.65)	(8.41, 12.03)
Comparison vs Placebo*		
Hazard ratio		0.87
95% confidence interval		(0.68,1.10)
p-value		0.2430

* Based on a Cox regression model with terms for age (p=0.1944), baseline eGFR (CKD-EPI) (p=0.1487), sex (p=0.1001), region (p=0.0281), baseline diabetes status (3 cat.) (p=0.1093), baseline LVEF (3 cat.) (p=0.8066), Treatment (p=0.8167), baseline NTproBNP (2 cat.) (p<0.0001) and Treatment by baseline NTproBNP (2 cat.) interaction (p=0.2729).
2 patients were excluded as the subgroup variable was missing.

Median: 1910 [pg/mL]

R.1.1.3 Time to first adjudicated hospitalisation for heart failure

R.1.1.3.1

R.1.1.3.1 Overall analysis

Figure R.1.1.3.1: 1

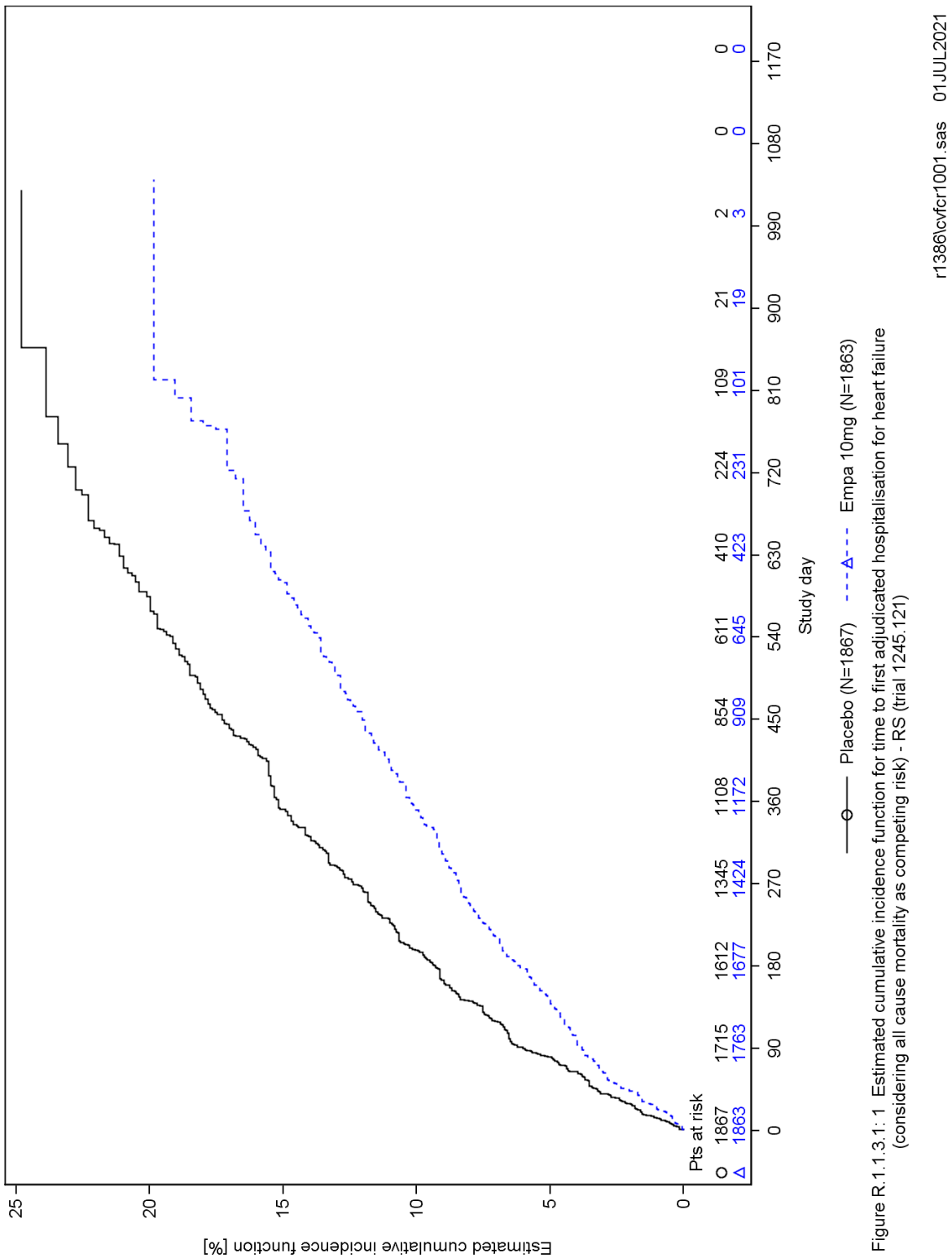

Figure R.1.1.3.1: 1 Estimated cumulative incidence function for time to first adjudicated hospitalisation for heart failure (considering all cause mortality as competing risk) - RS (trial 1245.121)

Table R.1.1.3.1: 1 Cox regr. for time to first adjudicated hospitalisation for heart failure - RS (trial 1245.121)

	Placebo	Empa 10mg
Number of patients in analysis set	1867	1863
Number of analysed patients	1867	1863
Number of patients with event [N(%)]	342 (18.3)	246 (13.2)
Time at risk for event [years]	2199.5	2288.8
Incidence rate [patients with events per 100 patient years at risk]	15.55	10.75
95% confidence interval	(13.94, 17.24)	(9.45, 12.13)
Comparison vs Placebo*		
Hazard ratio		0.69
95% confidence interval		(0.59,0.81)
p-value		<0.0001
Time to event [days]**		
2.5% percentile	35	50
5.0% percentile	80	138
7.5% percentile	127	225
10.0% percentile	195	337
Patients with events [%]**		
1 year	15.8	10.7
2 years	24.5	18.1

* Based on a Cox regression model with terms for age (p=0.0394), baseline eGFR (CKD-EPI) (p<0.0001), sex (p=0.1881), region (p<0.0001), baseline diabetes status (3 cat.) (p=0.0008), baseline LVEF (3 cat.) (p=0.0056) and Treatment (p<0.0001).
**Based on Kaplan-Meier estimates.

R.1.1.3.2

R.1.1.3.2 Subgroup analysis by sex

Table R.1.1.3.2: 1

Table R.1.1.3.2: 1 Cox regr. for time to first adjudicated hospitalisation for heart failure by sex - RS (trial 1245.121)

Subgroup Description	Placebo	Empa 10mg
Sex: Male		
Number of patients in analysis set	1411	1426
Number of analysed patients	1411	1426
Number of patients with event [N(%)]	263 (18.6)	199 (14.0)
Time at risk for event [years]	1666.4	1739.1
Incidence rate [patients with events per 100 patient years at risk]	15.78	11.44
95% confidence interval	(13.93, 17.75)	(9.91, 13.09)
Comparison vs Placebo*		
Hazard ratio		0.73
95% confidence interval		(0.61,0.88)
p-value		0.0008
Sex: Female		
Number of patients in analysis set	456	437
Number of analysed patients	456	437
Number of patients with event [N(%)]	79 (17.3)	47 (10.8)
Time at risk for event [years]	533.1	549.7
Incidence rate [patients with events per 100 patient years at risk]	14.82	8.55
95% confidence interval	(11.73, 18.26)	(6.28, 11.16)
Comparison vs Placebo*		
Hazard ratio		0.56
95% confidence interval		(0.39,0.81)
p-value		0.0019

* Based on a Cox regression model with terms for age (p=0.0362), baseline eGFR (CKD-EPI) (p<0.0001), region (p<0.0001), baseline diabetes status (3 cat.) (p=0.0007), baseline LVEF (3 cat.) (p=0.0054), Treatment (p<0.0001), sex (p=0.1290) and Treatment by sex interaction (p=0.2094).

R.1.1.3.3

R.1.1.3.3 Subgroup analysis by age

Table R.1.1.3.3: 1 Cox regr. for time to first adjudicated hospitalisation for heart failure by age (2 cat.) - RS (trial 1245.121)

Subgroup Description	Placebo	Empa 10mg
Age [years]: < 65		
Number of patients in analysis set	740	675
Number of analysed patients	740	675
Number of patients with event [N(%)]	150 (20.3)	89 (13.2)
Time at risk for event [years]	855.1	816.2
Incidence rate [patients with events per 100 patient years at risk]	17.54	10.90
95% confidence interval	(14.85, 20.46)	(8.76, 13.28)
Comparison vs Placebo*		
Hazard ratio		0.63
95% confidence interval		(0.49,0.82)
p-value		0.0006
Age [years]: >= 65		
Number of patients in analysis set	1127	1188
Number of analysed patients	1127	1188
Number of patients with event [N(%)]	192 (17.0)	157 (13.2)
Time at risk for event [years]	1344.4	1472.6
Incidence rate [patients with events per 100 patient years at risk]	14.28	10.66
95% confidence interval	(12.33, 16.37)	(9.06, 12.39)
Comparison vs Placebo*		
Hazard ratio		0.74
95% confidence interval		(0.60,0.91)
p-value		0.0053

* Based on a Cox regression model with terms for baseline eGFR (CKD-EPI) (p<0.0001), sex (p=0.1962), region (p<0.0001), baseline diabetes status (3 cat.) (p=0.0010), baseline LVEF (3 cat.) (p=0.0068), Treatment (p<0.0001), age (2 cat.) (p=0.0012) and Treatment by age (2 cat.) interaction (p=0.3550).

R.1.1.3.4 Subgroup analysis by region (North America, Latin America, Europe, Asia, Other)

Figure R.1.1.3.4: 1

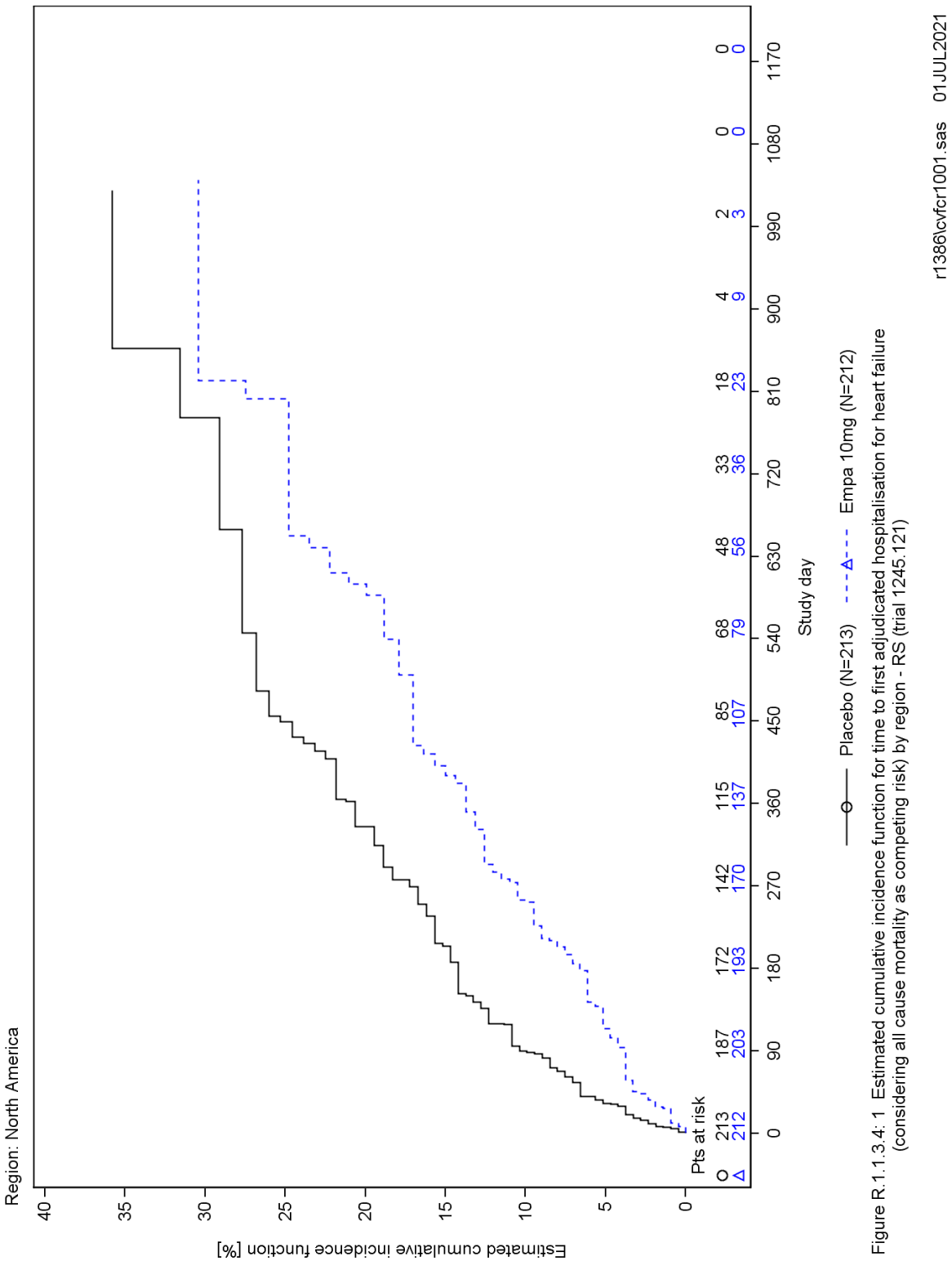

Figure R.1.1.3.4: 1 Estimated cumulative incidence function for time to first adjudicated hospitalisation for heart failure (considering all cause mortality as competing risk) by region - RS (trial 1245.121)

Figure R.1.1.3.4: 1

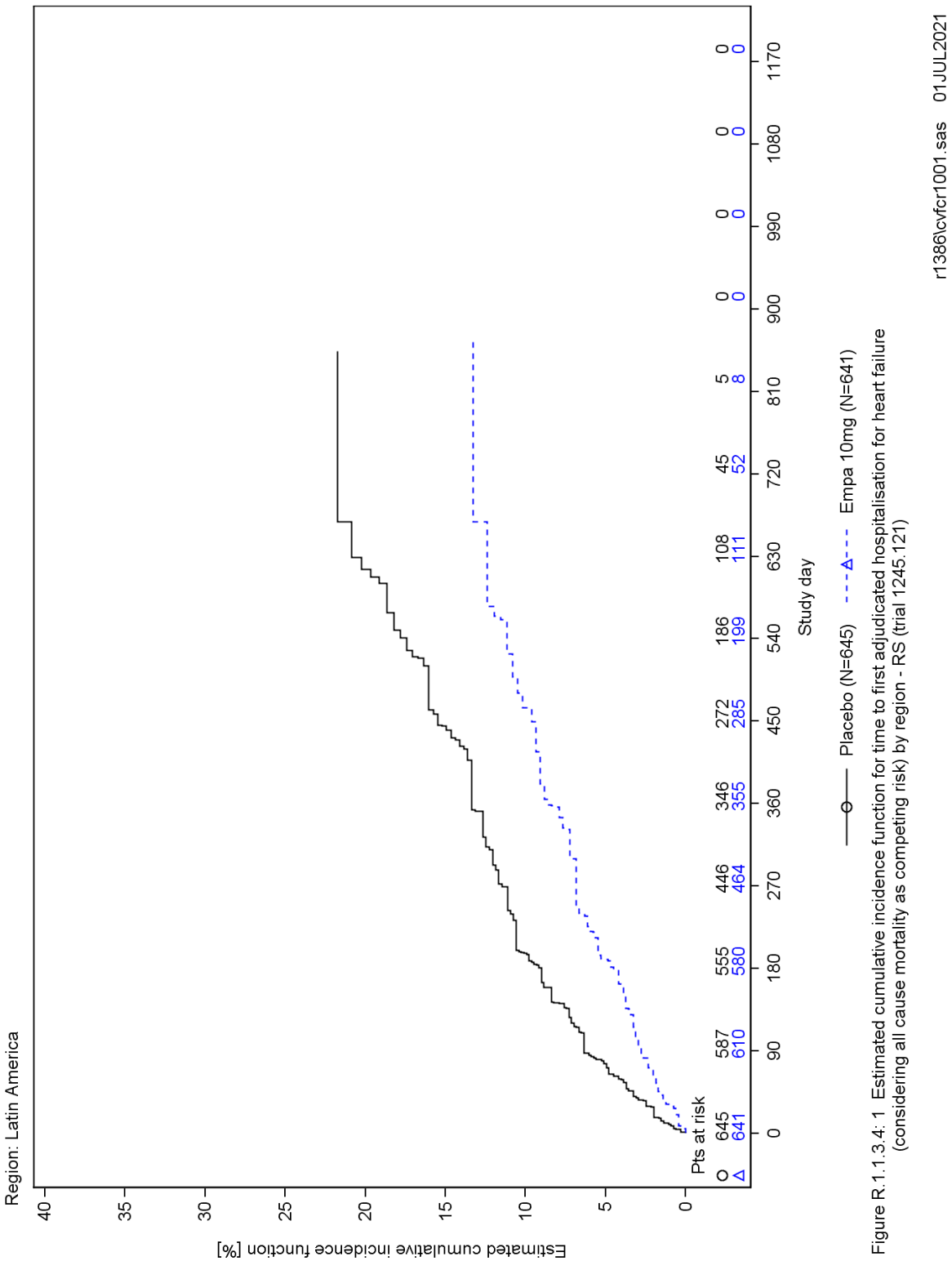

Figure R.1.1.3.4: 1 Estimated cumulative incidence function for time to first adjudicated hospitalisation for heart failure (considering all cause mortality as competing risk) by region - RS (trial 1245.121)

Figure R.1.1.3.4: 1

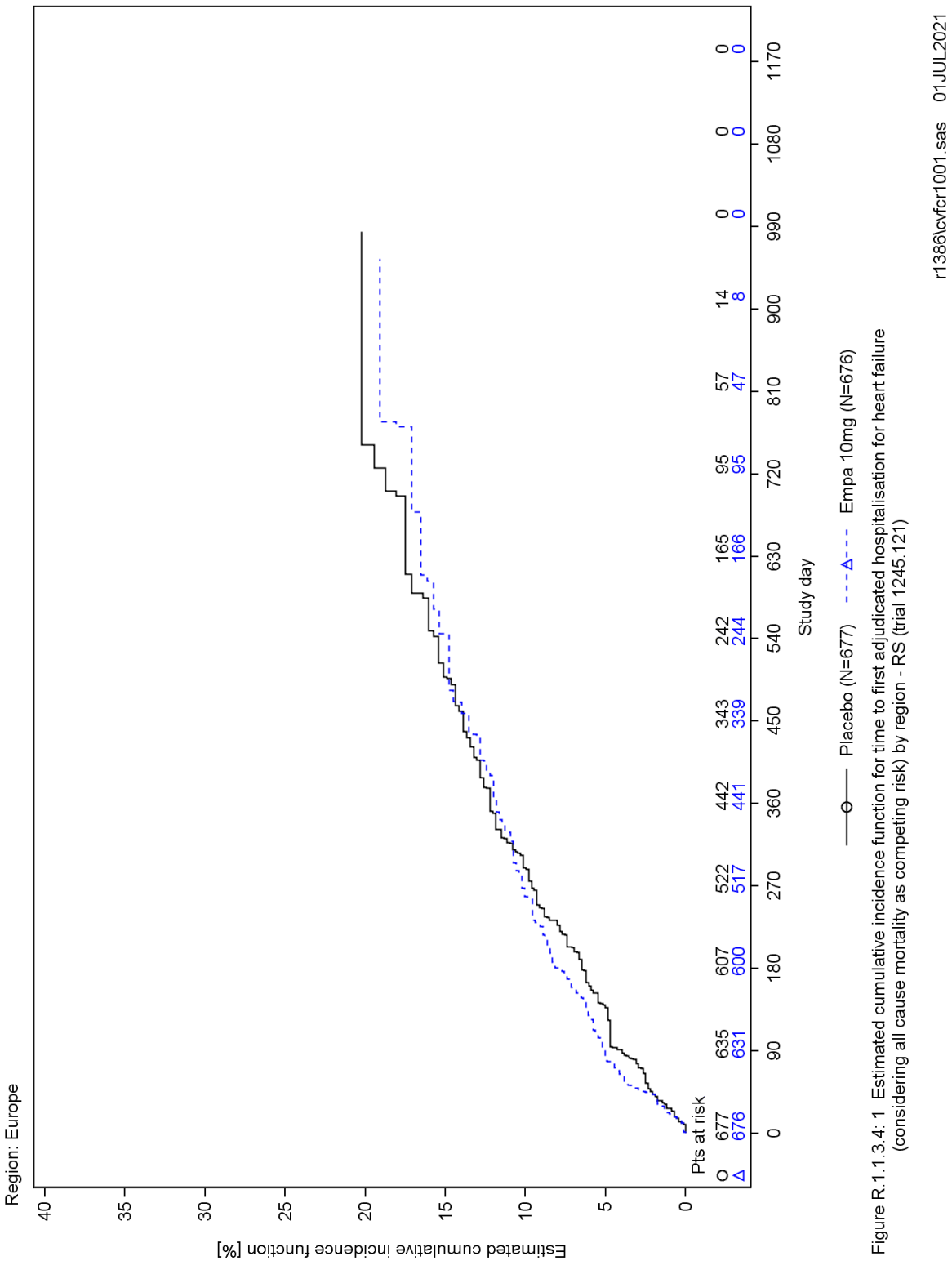

Figure R.1.1.3.4: 1 Estimated cumulative incidence function for time to first adjudicated hospitalisation for heart failure (considering all cause mortality as competing risk) by region - RS (trial 1245.121)

Figure R.1.1.3.4: 1

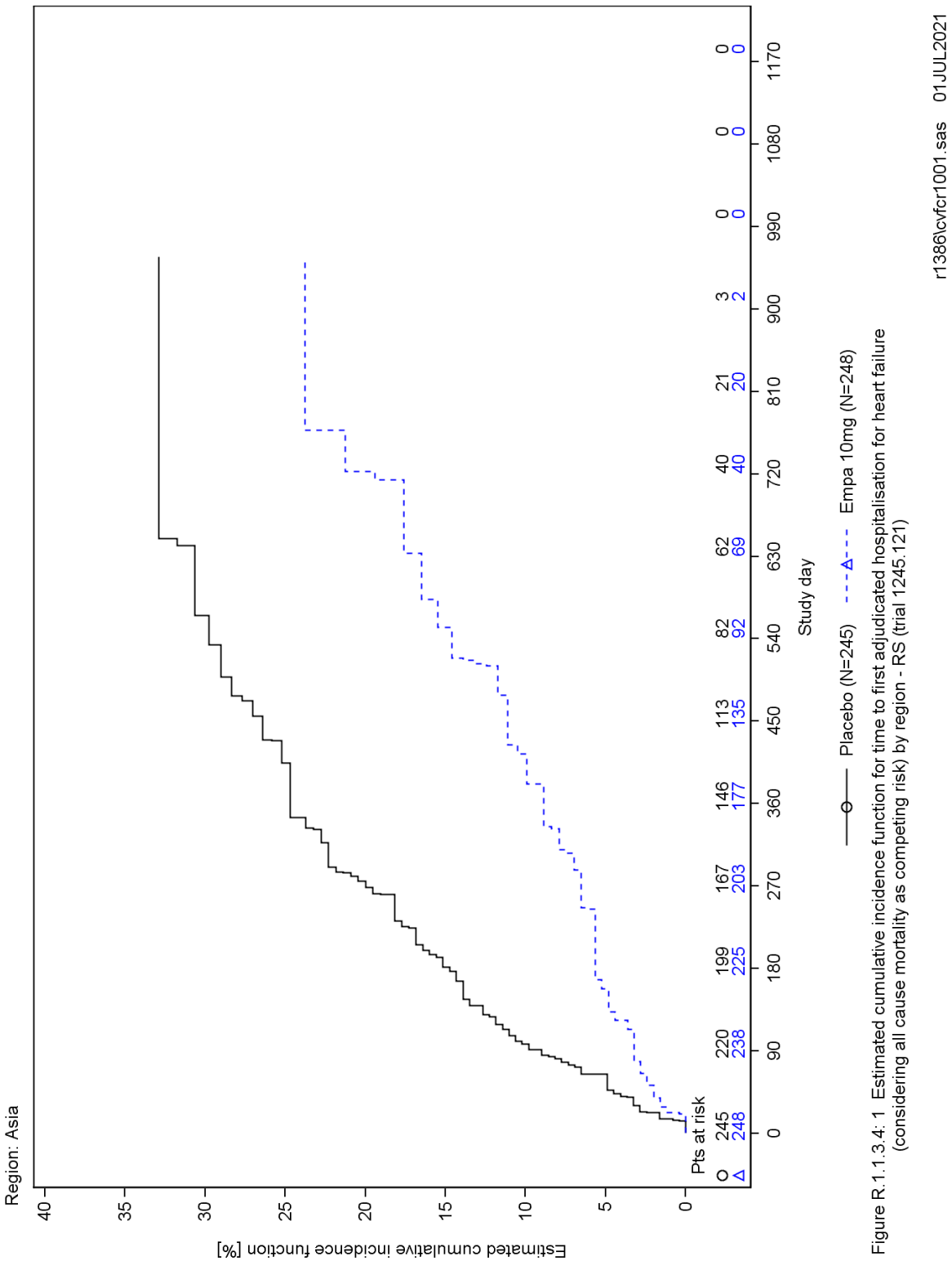

Figure R.1.1.3.4: 1 Estimated cumulative incidence function for time to first adjudicated hospitalisation for heart failure (considering all cause mortality as competing risk) by region - RS (trial 1245.121)

Figure R.1.1.3.4: 1

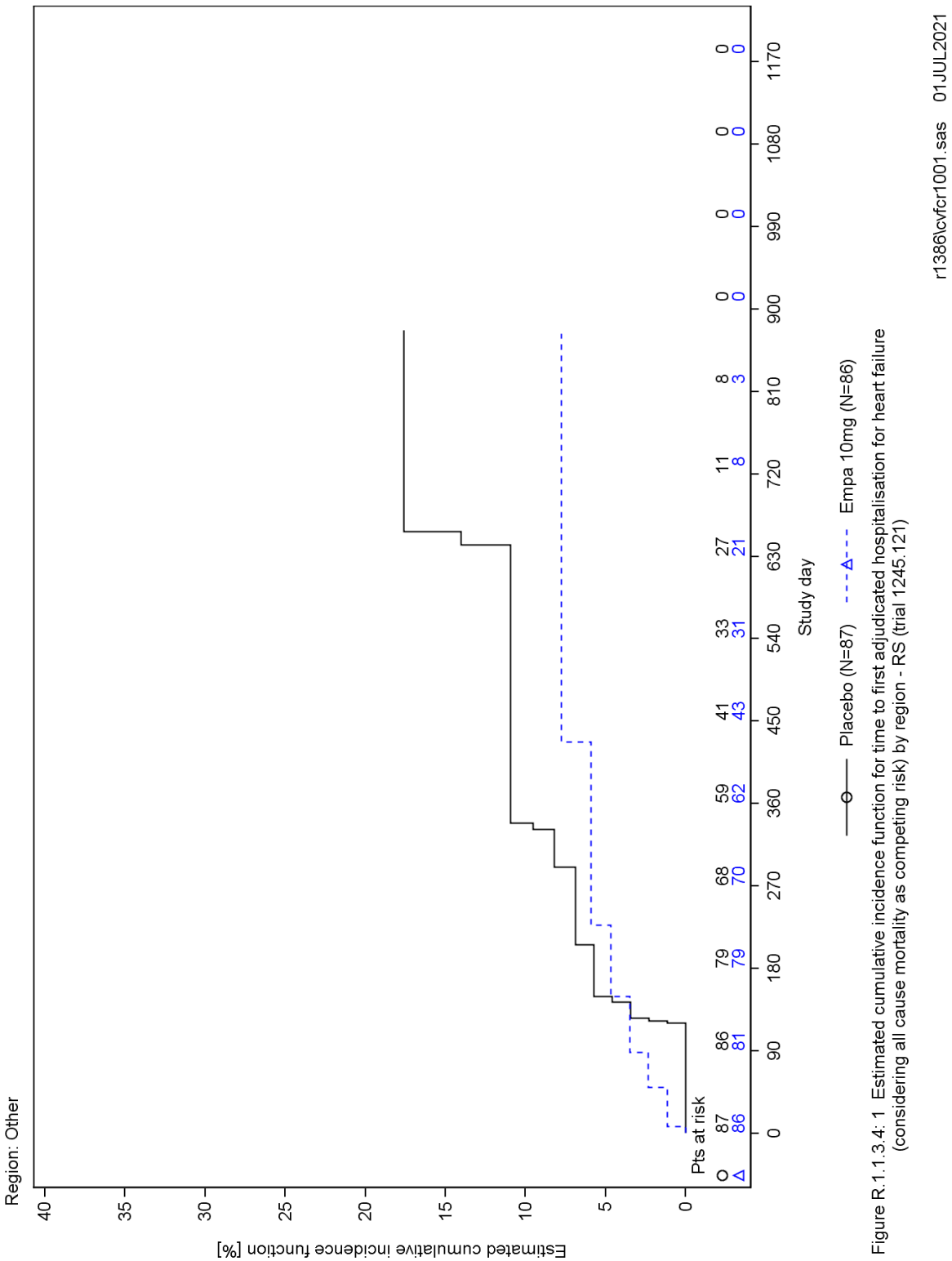

Figure R.1.1.3.4: 1 Estimated cumulative incidence function for time to first adjudicated hospitalisation for heart failure (considering all cause mortality as competing risk) by region - RS (trial 1245.121)

Table R.1.1.3.4: 1

Table R.1.1.3.4: 1 Cox regr. for time to first adjudicated hospitalisation for heart failure by region - RS (trial 1245.121)

Subgroup Description	Placebo	Empa 10mg
Region: North America		
Number of patients in analysis set	213	212
Number of analysed patients	213	212
Number of patients with event [N(%)]	55 (25.8)	42 (19.8)
Time at risk for event [years]	242.2	275.3
Incidence rate [patients with events per 100 patient years at risk]	22.71	15.26
95% confidence interval	(17.11, 29.10)	(11.00, 20.20)
Comparison vs Placebo*		
Hazard ratio		0.72
95% confidence interval		(0.48,1.08)
p-value		0.1122
Region: Latin America		
Number of patients in analysis set	645	641
Number of analysed patients	645	641
Number of patients with event [N(%)]	104 (16.1)	64 (10.0)
Time at risk for event [years]	705.1	733.0
Incidence rate [patients with events per 100 patient years at risk]	14.75	8.73
95% confidence interval	(12.05, 17.72)	(6.72, 11.00)
Comparison vs Placebo*		
Hazard ratio		0.60
95% confidence interval		(0.44,0.81)
p-value		0.0011

* Based on a Cox regression model with terms for age (p=0.0476), baseline eGFR (CKD-EPI) (p<0.0001), sex (p=0.2140), baseline diabetes status (3 cat.) (p=0.0008), baseline LVEF (3 cat.) (p=0.0042), Treatment (p=0.0003), region (p<0.0001) and Treatment by region interaction (p=0.0418).

Table R.1.1.3.4: 1 Cox regr. for time to first adjudicated hospitalisation for heart failure by region - RS (trial 1245.121)

Subgroup Description	Placebo	Empa 10mg
Region: Europe		
Number of patients in analysis set	677	676
Number of analysed patients	677	676
Number of patients with event [N(%)]	103 (15.2)	98 (14.5)
Time at risk for event [years]	852.2	846.3
Incidence rate [patients with events per 100 patient years at risk]	12.09	11.58
95% confidence interval	(9.87, 14.53)	(9.40, 13.98)
Comparison vs Placebo*		
Hazard ratio		0.95
95% confidence interval		(0.72,1.25)
p-value		0.7184
Region: Asia		
Number of patients in analysis set	245	248
Number of analysed patients	245	248
Number of patients with event [N(%)]	69 (28.2)	36 (14.5)
Time at risk for event [years]	288.5	324.9
Incidence rate [patients with events per 100 patient years at risk]	23.92	11.08
95% confidence interval	(18.61, 29.88)	(7.76, 14.98)
Comparison vs Placebo*		
Hazard ratio		0.46
95% confidence interval		(0.31,0.70)
p-value		0.0002

* Based on a Cox regression model with terms for age (p=0.0476), baseline eGFR (CKD-EPI) (p<0.0001), sex (p=0.2140), baseline diabetes status (3 cat.) (p=0.0008), baseline LVEF (3 cat.) (p=0.0042), Treatment (p=0.0003), region (p<0.0001) and Treatment by region interaction (p=0.0418).

Table R.1.1.3.4: 1 Cox regr. for time to first adjudicated hospitalisation for heart failure by region - RS (trial 1245.121)

Subgroup Description	Placebo	Empa 10mg
Region: Other		
Number of patients in analysis set	87	86
Number of analysed patients	87	86
Number of patients with event [N(%)]	11 (12.6)	6 (7.0)
Time at risk for event [years]	111.5	109.4
Incidence rate [patients with events per 100 patient years at risk]	9.86	5.49
95% confidence interval	(4.92, 16.49)	(2.01, 10.67)
Comparison vs Placebo*		
Hazard ratio		0.55
95% confidence interval		(0.20,1.48)
p-value		0.2355

* Based on a Cox regression model with terms for age (p=0.0476), baseline eGFR (CKD-EPI) (p<0.0001), sex (p=0.2140), baseline diabetes status (3 cat.) (p=0.0008), baseline LVEF (3 cat.) (p=0.0042), Treatment (p=0.0003), region (p<0.0001) and Treatment by region interaction (p=0.0418).

R.1.1.3.5

R.1.1.3.5 Subgroup analysis by OECD member (Y/N)

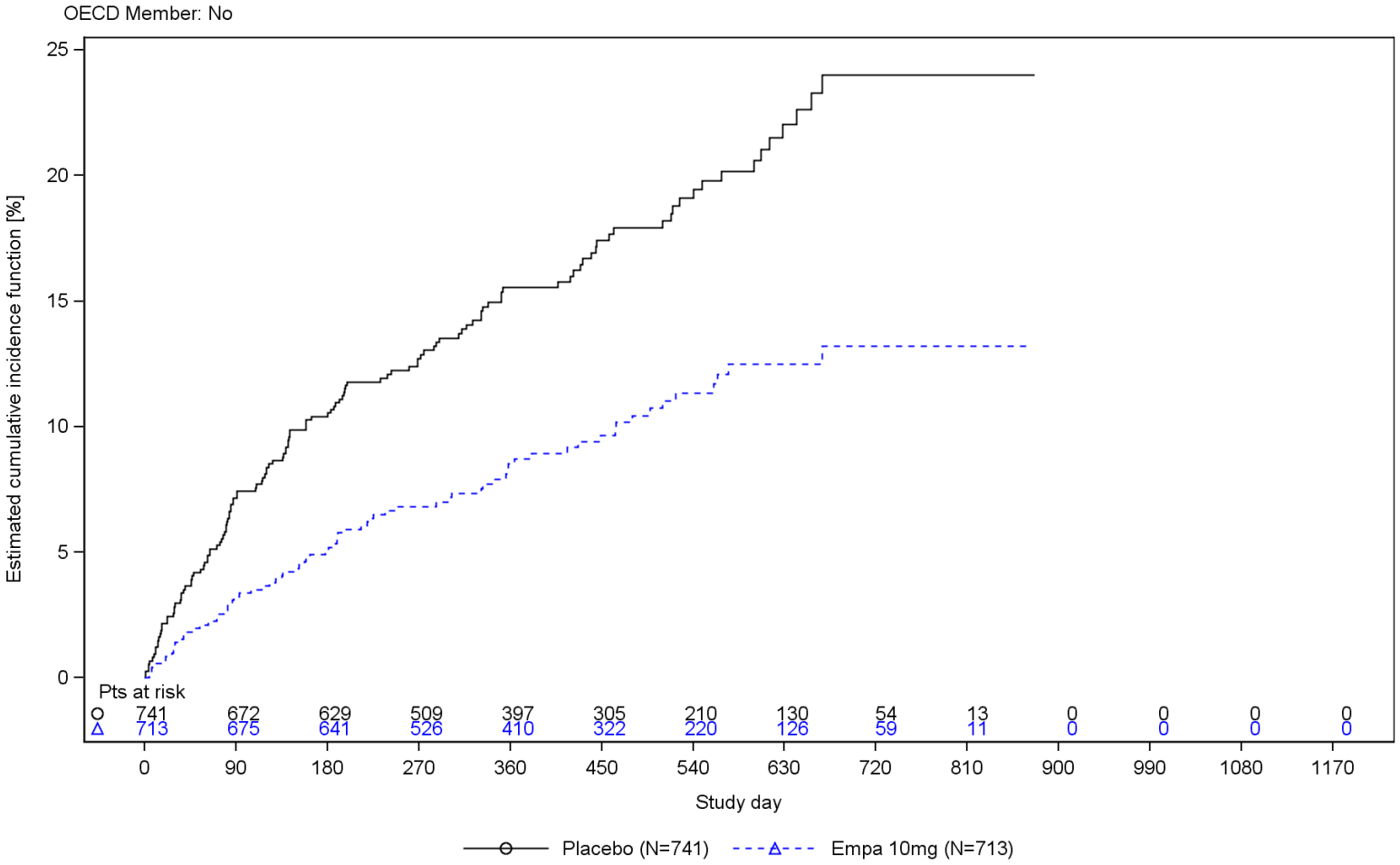

Figure R.1.1.3.5: 1 Estimated cumulative incidence function for time to first adjudicated hospitalisation for heart failure (considering all cause mortality as competing risk) by OECD member (Y/N) - RS (trial 1245.121)
OECD member (yes/no) countries included:
Yes: United States, Canada, Mexico, Poland, Netherlands, Hungary, Germany, Czech Republic, Italy, France, Spain, United Kingdom, Belgium, Japan, Australia, 'Korea; Republic Of South Korea';
No: Brazil, Argentina, China, India.

r1386\cvfcr1001.sas 01JUL2021

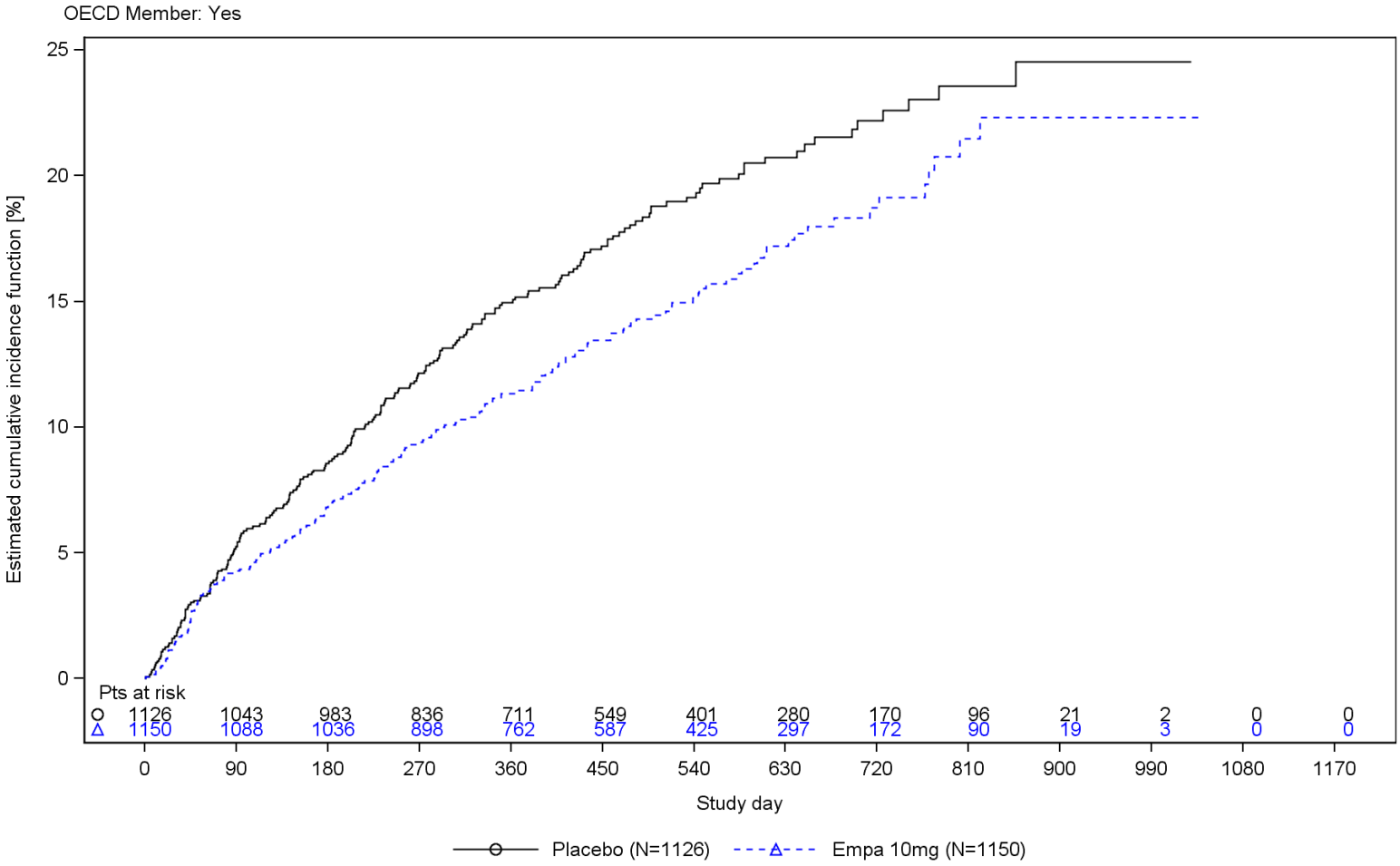

Figure R.1.1.3.5: 1 Estimated cumulative incidence function for time to first adjudicated hospitalisation for heart failure (considering all cause mortality as competing risk) by OECD member (Y/N) - RS (trial 1245.121)
OECD member (yes/no) countries included:
Yes: United States, Canada, Mexico, Poland, Netherlands, Hungary, Germany, Czech Republic, Italy, France, Spain, United Kingdom, Belgium, Japan, Australia, 'Korea; Republic Of South Korea';
No: Brazil, Argentina, China, India.

r1386\cvfcr1001.sas 01JUL2021

Table R.1.1.3.5: 1

Table R.1.1.3.5: 1 Cox regr. for time to first adjudicated hospitalisation for heart failure by OECD member (Y/N) - RS (trial 1245.121)

Subgroup Description	Placebo	Empa 10mg
OECD Member: No		
Number of patients in analysis set	741	713
Number of analysed patients	741	713
Number of patients with event [N(%)]	133 (17.9)	72 (10.1)
Time at risk for event [years]	806.7	821.8
Incidence rate [patients with events per 100 patient years at risk]	16.49	8.76
95% confidence interval	(13.80, 19.40)	(6.86, 10.90)
Comparison vs Placebo*		
Hazard ratio		0.53
95% confidence interval		(0.40,0.71)
p-value		<0.0001
OECD Member: Yes		
Number of patients in analysis set	1126	1150
Number of analysed patients	1126	1150
Number of patients with event [N(%)]	209 (18.6)	174 (15.1)
Time at risk for event [years]	1392.8	1467.0
Incidence rate [patients with events per 100 patient years at risk]	15.01	11.86
95% confidence interval	(13.04, 17.11)	(10.16, 13.69)
Comparison vs Placebo*		
Hazard ratio		0.80
95% confidence interval		(0.65,0.98)
p-value		0.0291

* Based on a Cox regression model with terms for age (p=0.0862), baseline eGFR (CKD-EPI) (p<0.0001), sex (p=0.1432), baseline diabetes status (3 cat.) (p=0.0008), baseline LVEF (3 cat.) (p=0.0024), Treatment (p<0.0001), OECD Member (p=0.3615) and Treatment by OECD Member interaction (p=0.0220).

OECD member (yes/no) countries included:
Yes: United States, Canada, Mexico, Poland, Netherlands, Hungary, Germany, Czech Republic, Italy, France, Spain, United Kingdom, Belgium, Japan, Australia, 'Korea; Republic Of South Korea';
No: Brazil, Argentina, China, India.

R.1.1.3.6 Subgroup analysis by NYHA at baseline (II, III/IV - 2 cat.)

Figure R.1.1.3.6: 1

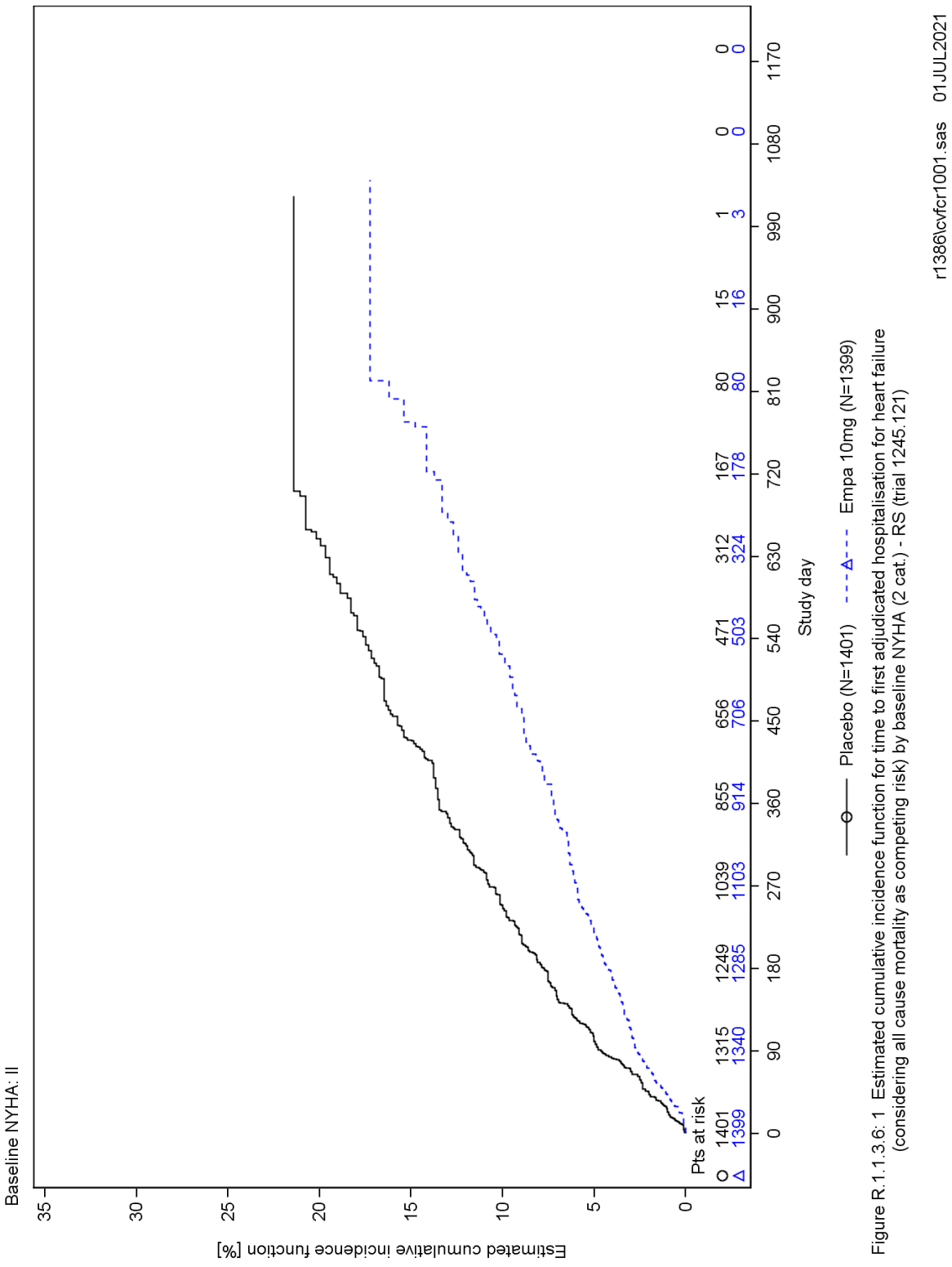

Figure R.1.1.3.6: 1 Estimated cumulative incidence function for time to first adjudicated hospitalisation for heart failure (considering all cause mortality as competing risk) by baseline NYHA (2 cat.) - RS (trial 1245.121)

Figure R.1.1.3.6: 1

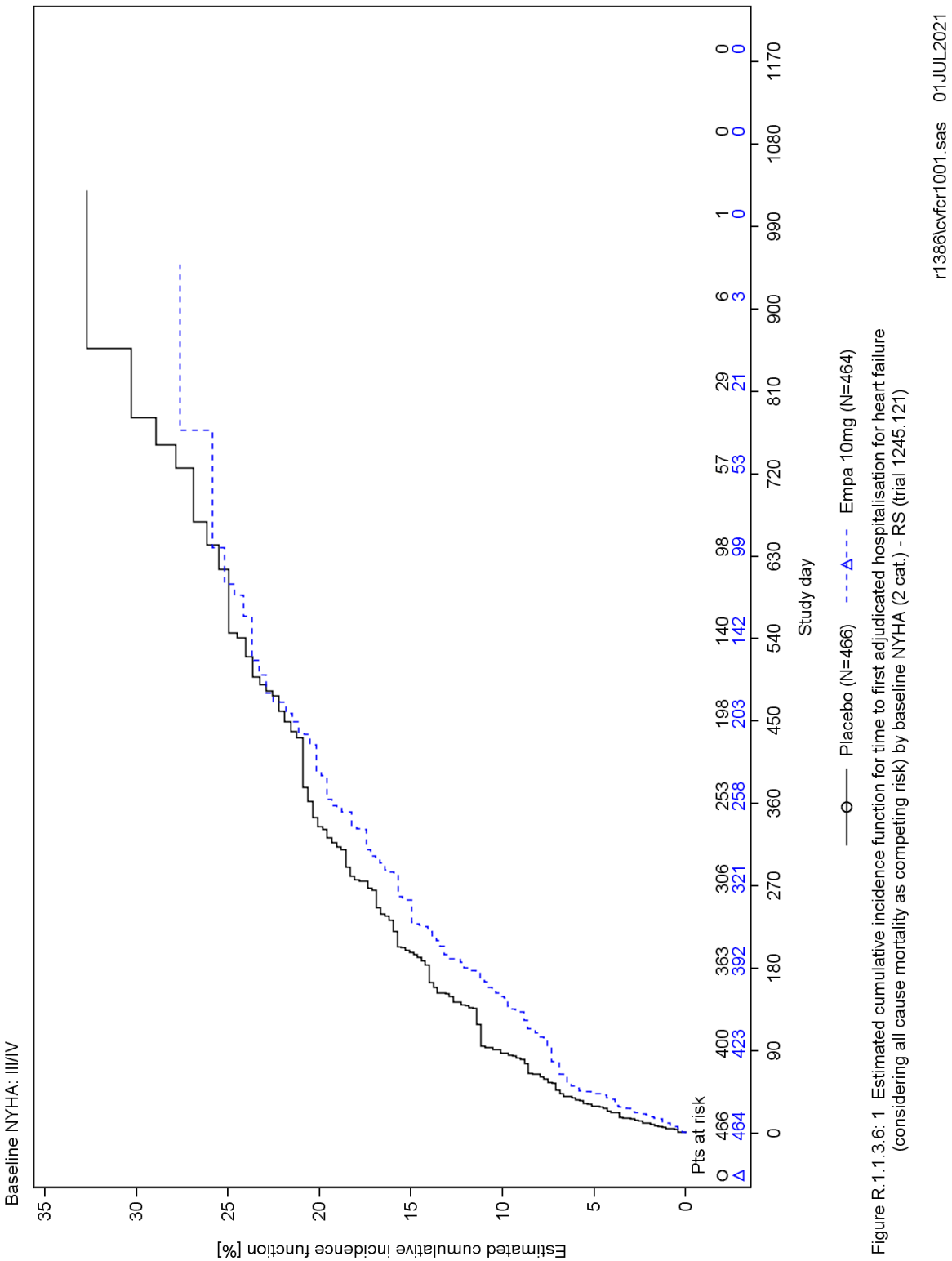

Figure R.1.1.3.6: 1 Estimated cumulative incidence function for time to first adjudicated hospitalisation for heart failure (considering all cause mortality as competing risk) by baseline NYHA (2 cat.) - RS (trial 1245.121)

Table R.1.1.3.6: 1 Cox regr. for time to first adjudicated hospitalisation for heart failure by baseline NYHA (2 cat.) - RS (trial 1245.121)

Subgroup Description	Placebo	Empa 10mg
Baseline NYHA: II		
Number of patients in analysis set	1401	1399
Number of analysed patients	1401	1399
Number of patients with event [N(%)]	230 (16.4)	142 (10.2)
Time at risk for event [years]	1687.7	1760.4
Incidence rate [patients with events per 100 patient years at risk]	13.63	8.07
95% confidence interval	(11.92, 15.44)	(6.79, 9.45)
Comparison vs Placebo*		
Hazard ratio		0.59
95% confidence interval		(0.48,0.73)
p-value		<0.0001
Baseline NYHA: III/IV		
Number of patients in analysis set	466	464
Number of analysed patients	466	464
Number of patients with event [N(%)]	112 (24.0)	104 (22.4)
Time at risk for event [years]	511.8	528.4
Incidence rate [patients with events per 100 patient years at risk]	21.88	19.68
95% confidence interval	(18.02, 26.12)	(16.08, 23.64)
Comparison vs Placebo*		
Hazard ratio		0.89
95% confidence interval		(0.68,1.16)
p-value		0.3932

* Based on a Cox regression model with terms for age (p=0.0475), baseline eGFR (CKD-EPI) (p<0.0001), sex (p=0.0947), region (p<0.0001), baseline diabetes status (3 cat.) (p=0.0057), baseline LVEF (3 cat.) (p=0.0139), Treatment (p=0.0002), baseline NYHA (2 cat.) (p<0.0001) and Treatment by baseline NYHA (2 cat.) interaction (p=0.0190).

R.1.1.3.7

R.1.1.3.7 Subgroup analysis by diabetes at baseline

Table R.1.1.3.7: 1

Table R.1.1.3.7: 1 Cox regr. for time to first adjudicated hospitalisation for heart failure by diabetes at baseline (2 cat.) - RS (trial 1245.121)

Subgroup Description	Placebo	Empa 10mg
Baseline diabetes status: Diabetic		
Number of patients in analysis set	929	927
Number of analysed patients	929	927
Number of patients with event [N(%)]	201 (21.6)	140 (15.1)
Time at risk for event [years]	1079.4	1132.8
Incidence rate [patients with events per 100 patient years at risk]	18.62	12.36
95% confidence interval	(16.14, 21.28)	(10.40, 14.49)
Comparison vs Placebo*		
Hazard ratio		0.67
95% confidence interval		(0.54,0.83)
p-value		0.0003
Baseline diabetes status: Non-Diabetic		
Number of patients in analysis set	938	936
Number of analysed patients	938	936
Number of patients with event [N(%)]	141 (15.0)	106 (11.3)
Time at risk for event [years]	1120.2	1156.0
Incidence rate [patients with events per 100 patient years at risk]	12.59	9.17
95% confidence interval	(10.60, 14.75)	(7.51, 11.00)
Comparison vs Placebo*		
Hazard ratio		0.72
95% confidence interval		(0.56,0.93)
p-value		0.0114

* Based on a Cox regression model with terms for age (p=0.0389), baseline eGFR (CKD-EPI) (p<0.0001), sex (p=0.1903), region (p<0.0001), baseline LVEF (3 cat.) (p=0.0056), Treatment (p<0.0001), baseline diabetes status (2 cat.) (p=0.0002) and Treatment by baseline diabetes status (2 cat.) interaction (p=0.6585).

R.1.1.3.8 Subgroup analysis by BMI at baseline (<30, >=30)

Figure R.1.1.3.8: 1

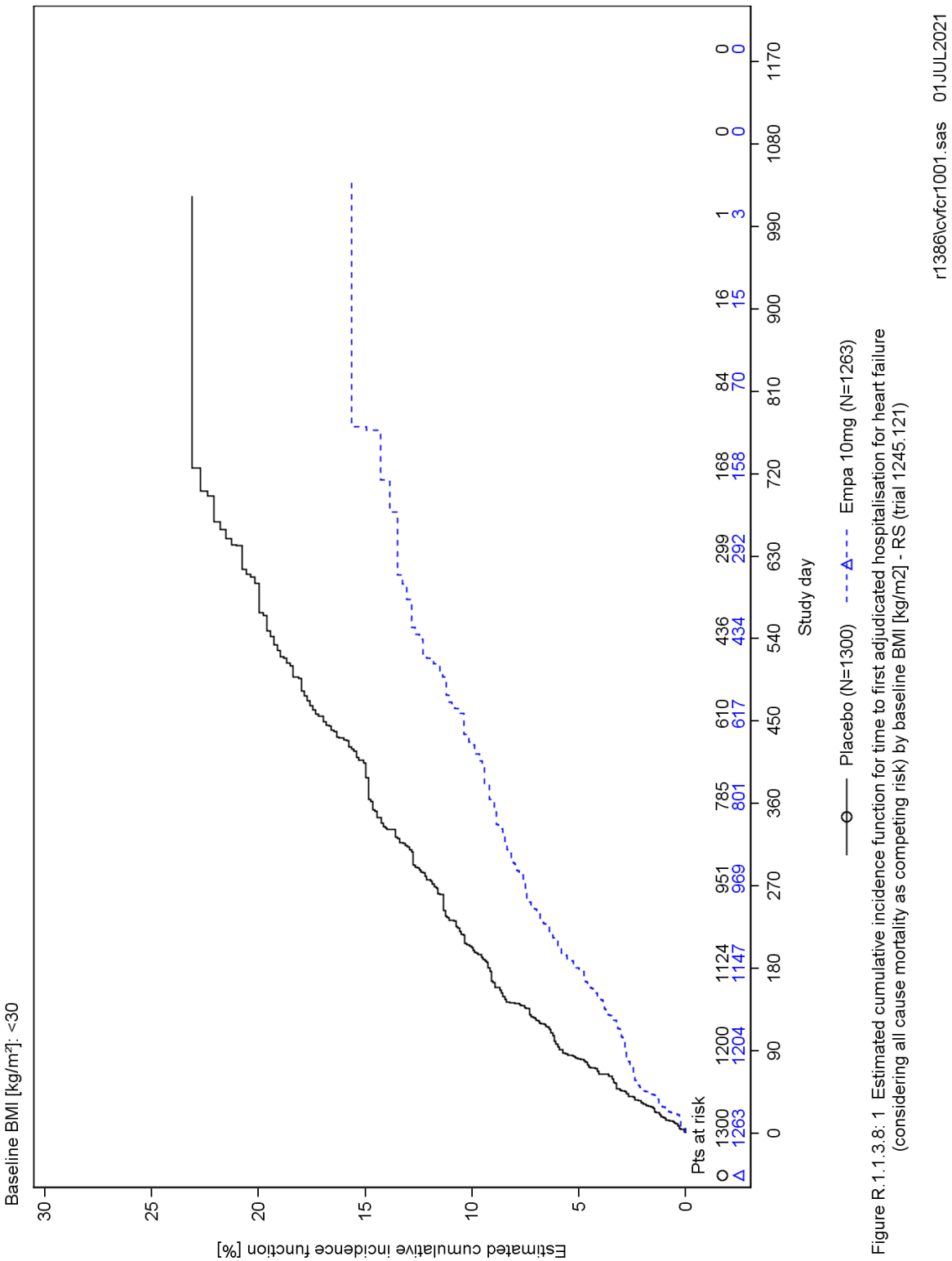

Figure R.1.1.3.8: 1 Estimated cumulative incidence function for time to first adjudicated hospitalisation for heart failure (considering all cause mortality as competing risk) by baseline BMI [kg/m2] - RS (trial 1245.121)

Figure R.1.1.3.8: 1

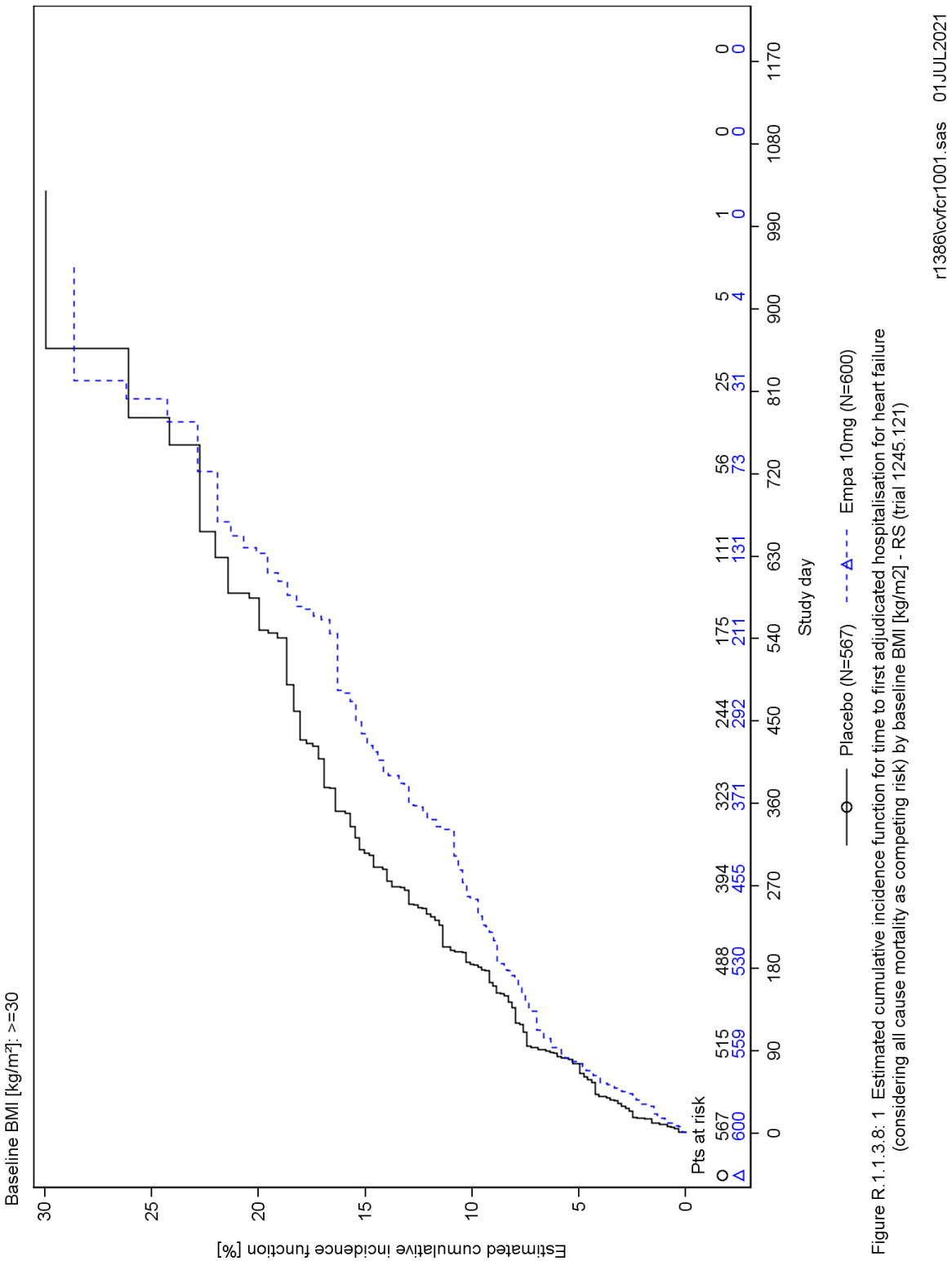

Figure R.1.1.3.8: 1 Estimated cumulative incidence function for time to first adjudicated hospitalisation for heart failure (considering all cause mortality as competing risk) by baseline BMI [kg/m2] - RS (trial 1245.121)

Table R.1.1.3.8: 1 Cox regr. for time to first adjudicated hospitalisation for heart failure by baseline BMI [kg/m2] - RS (trial 1245.121)

Subgroup Description	Placebo	Empa 10mg
Baseline BMI [kg/m²]: <30		
Number of patients in analysis set	1300	1263
Number of analysed patients	1300	1263
Number of patients with event [N(%)]	235 (18.1)	143 (11.3)
Time at risk for event [years]	1554.3	1559.8
Incidence rate [patients with events per 100 patient years at risk]	15.12	9.17
95% confidence interval	(13.25, 17.11)	(7.73, 10.73)
Comparison vs Placebo*		
Hazard ratio		0.60
95% confidence interval		(0.49,0.74)
p-value		<0.0001
Baseline BMI [kg/m²]: >=30		
Number of patients in analysis set	567	600
Number of analysed patients	567	600
Number of patients with event [N(%)]	107 (18.9)	103 (17.2)
Time at risk for event [years]	645.3	729.0
Incidence rate [patients with events per 100 patient years at risk]	16.58	14.13
95% confidence interval	(13.59, 19.87)	(11.53, 16.99)
Comparison vs Placebo*		
Hazard ratio		0.87
95% confidence interval		(0.66,1.14)
p-value		0.2972

* Based on a Cox regression model with terms for age (p=0.0964), baseline eGFR (CKD-EPI) (p<0.0001), sex (p=0.1535), region (p<0.0001), baseline diabetes status (3 cat.) (p=0.0029), baseline LVEF (3 cat.) (p=0.0044), Treatment (p=0.0002), baseline BMI (2 cat.) (p=0.0079) and Treatment by baseline BMI (2 cat.) interaction (p=0.0363).

R.1.1.3.9 Subgroup analysis by eGFR at baseline (<60, >=60)

Figure R.1.1.3.9: 1

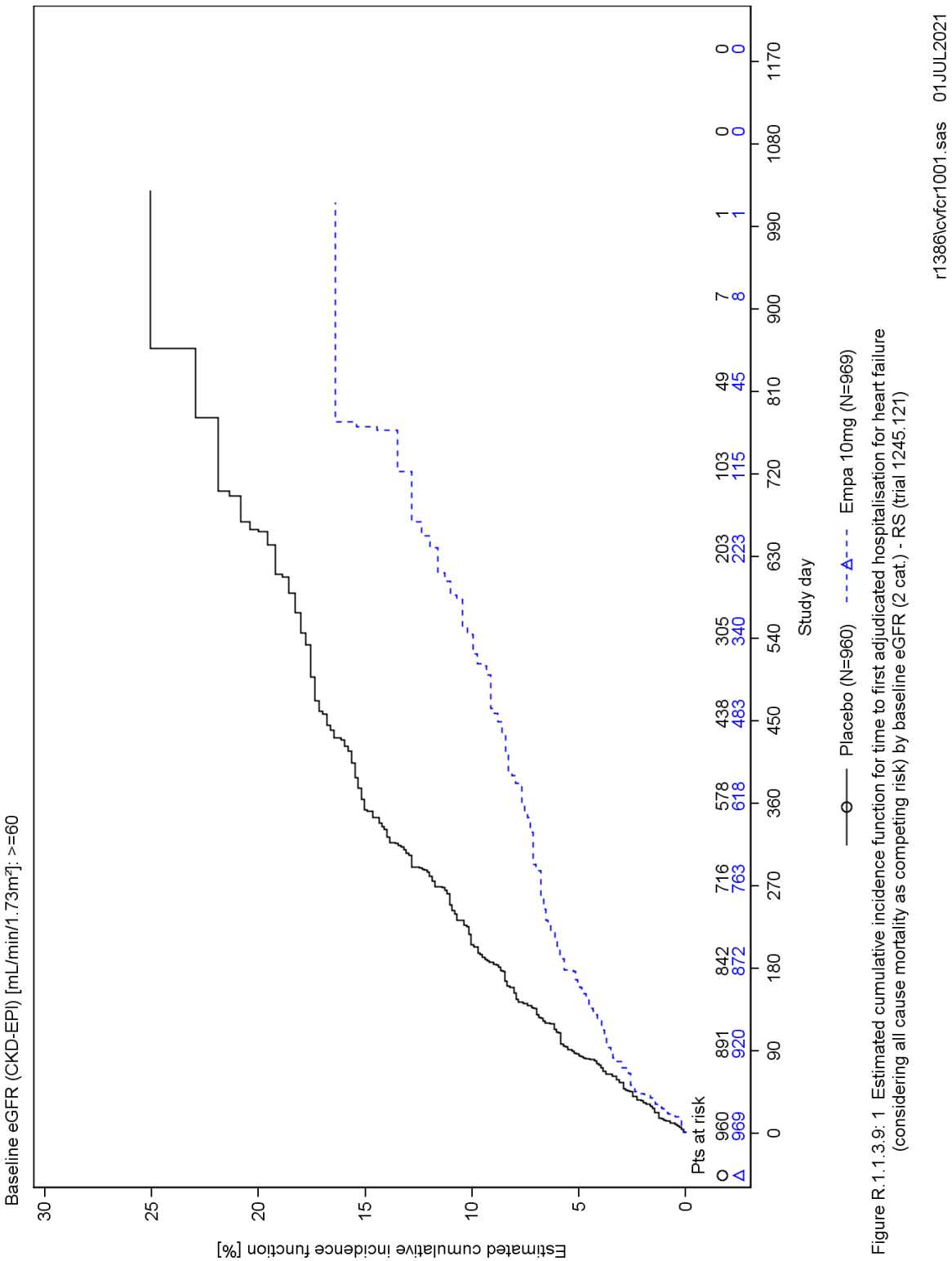

Figure R.1.1.3.9: 1 Estimated cumulative incidence function for time to first adjudicated hospitalisation for heart failure (considering all cause mortality as competing risk) by baseline eGFR (2 cat.) - RS (trial 1245.121)

Figure R.1.1.3.9: 1

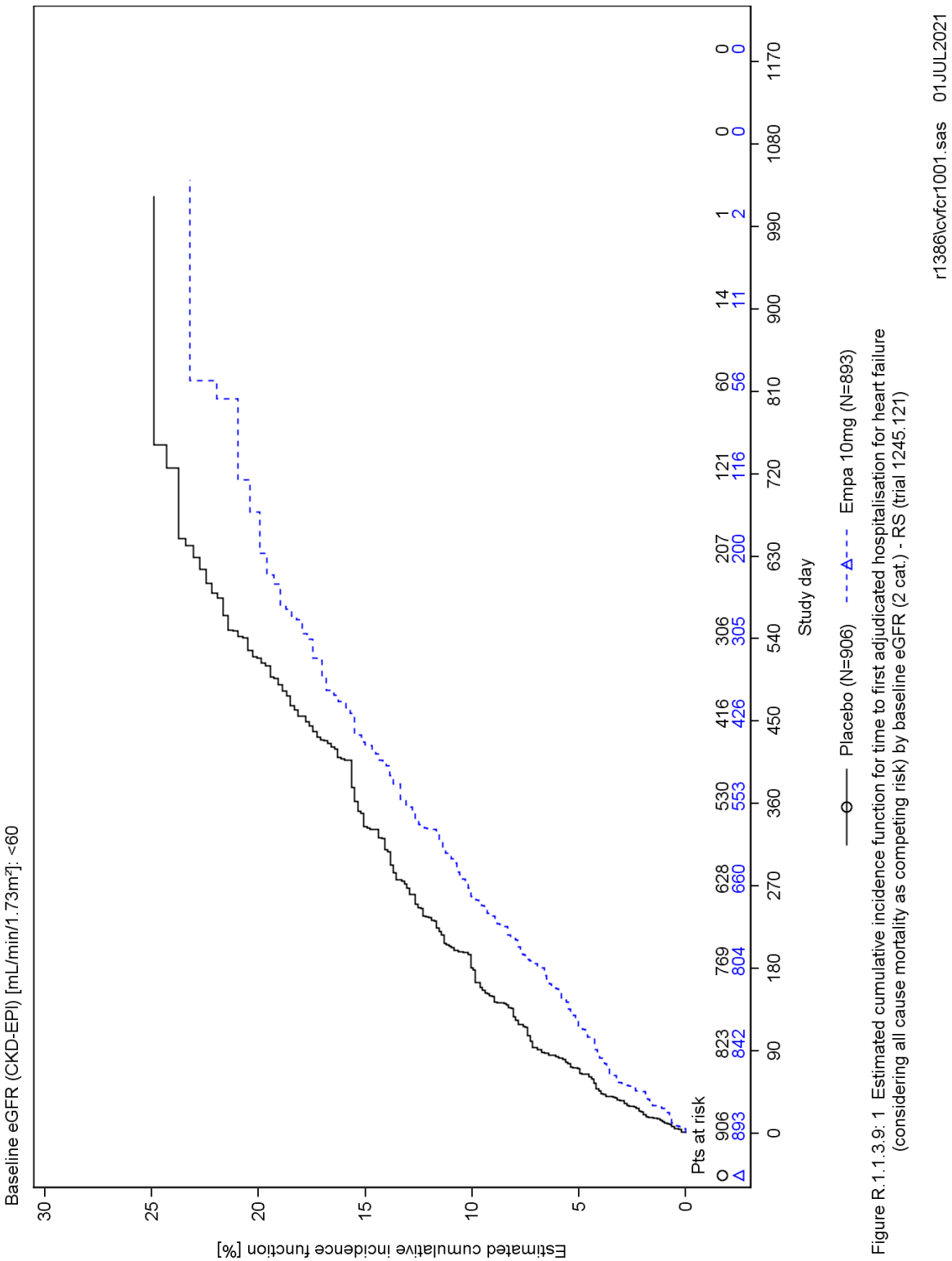

Figure R.1.1.3.9: 1 Estimated cumulative incidence function for time to first adjudicated hospitalisation for heart failure (considering all cause mortality as competing risk) by baseline eGFR (2 cat.) - RS (trial 1245.121)

Table R.1.1.3.9: 1 Cox regr. for time to first adjudicated hospitalisation for heart failure by baseline eGFR (2 cat.) - RS (trial 1245.121)

Subgroup Description	Placebo	Empa 10mg
Baseline eGFR (CKD-EPI) [mL/min/1.73m²]: >=60		
Number of patients in analysis set	960	969
Number of analysed patients	960	969
Number of patients with event [N(%)]	166 (17.3)	98 (10.1)
Time at risk for event [years]	1134.7	1198.2
Incidence rate [patients with events per 100 patient years at risk]	14.63	8.18
95% confidence interval	(12.49, 16.94)	(6.64, 9.88)
Comparison vs Placebo*		
Hazard ratio		0.56
95% confidence interval		(0.44,0.72)
p-value		<0.0001
Baseline eGFR (CKD-EPI) [mL/min/1.73m²]: <60		
Number of patients in analysis set	906	893
Number of analysed patients	906	893
Number of patients with event [N(%)]	176 (19.4)	148 (16.6)
Time at risk for event [years]	1064.0	1089.4
Incidence rate [patients with events per 100 patient years at risk]	16.54	13.59
95% confidence interval	(14.19, 19.07)	(11.48, 15.86)
Comparison vs Placebo*		
Hazard ratio		0.82
95% confidence interval		(0.66,1.02)
p-value		0.0769

* Based on a Cox regression model with terms for age (p=0.3340), sex (p=0.2448), region (p<0.0001), baseline diabetes status (3 cat.) (p=0.0004), baseline LVEF (3 cat.) (p=0.0057), Treatment (p<0.0001), baseline eGFR (CKD-EPI) (2 cat.) (p=0.0002) and Treatment by baseline eGFR (CKD-EPI) (2 cat.) interaction (p=0.0259).
2 patients were excluded as the subgroup variable was missing.

R.1.1.3.10

Table R.1.1.3.10: 1 Cox regr. for time to first adjudicated hospitalisation for heart failure by history of HHF within 12 months - RS (trial 1245.121)

Subgroup Description	Placebo	Empa 10mg
History of HHF (in the last 12 months): No		
Number of patients in analysis set	1293	1286
Number of analysed patients	1293	1286
Number of patients with event [N(%)]	205 (15.9)	132 (10.3)
Time at risk for event [years]	1594.3	1643.1
Incidence rate [patients with events per 100 patient years at risk]	12.86	8.03
95% confidence interval	(11.16, 14.68)	(6.72, 9.46)
Comparison vs Placebo*		
Hazard ratio		0.63
95% confidence interval		(0.51,0.79)
p-value		<0.0001
History of HHF (in the last 12 months): Yes		
Number of patients in analysis set	574	577
Number of analysed patients	574	577
Number of patients with event [N(%)]	137 (23.9)	114 (19.8)
Time at risk for event [years]	605.2	645.7
Incidence rate [patients with events per 100 patient years at risk]	22.64	17.66
95% confidence interval	(19.00, 26.58)	(14.56, 21.04)
Comparison vs Placebo*		
Hazard ratio		0.76
95% confidence interval		(0.59,0.98)
p-value		0.0320

* Based on a Cox regression model with terms for age (p=0.1325), baseline eGFR (CKD-EPI) (p<0.0001), sex (p=0.1826), region (p<0.0001), baseline diabetes status (3 cat.) (p=0.0023), baseline LVEF (3 cat.) (p=0.0132), Treatment (p<0.0001), history of HHF (p<0.0001) and Treatment by history of HHF interaction (p=0.2690).

R.1.1.3.11

R.1.1.3.11 Subgroup analysis by cause of heart failure

Table R.1.1.3.11: 1 Cox regr. for time to first adjudicated hospitalisation for heart failure by cause of heart failure - RS (trial 1245.121)

Subgroup Description	Placebo	Empa 10mg
Cause of heart failure: Ischemic		
Number of patients in analysis set	946	983
Number of analysed patients	946	983
Number of patients with event [N(%)]	167 (17.7)	135 (13.7)
Time at risk for event [years]	1143.7	1212.0
Incidence rate [patients with events per 100 patient years at risk]	14.60	11.14
95% confidence interval	(12.47, 16.90)	(9.34, 13.09)
Comparison vs Placebo*		
Hazard ratio		0.76
95% confidence interval		(0.61,0.96)
p-value		0.0185
Cause of heart failure: Non-ischemic		
Number of patients in analysis set	921	880
Number of analysed patients	921	880
Number of patients with event [N(%)]	175 (19.0)	111 (12.6)
Time at risk for event [years]	1055.8	1076.8
Incidence rate [patients with events per 100 patient years at risk]	16.57	10.31
95% confidence interval	(14.21, 19.12)	(8.48, 12.31)
Comparison vs Placebo*		
Hazard ratio		0.62
95% confidence interval		(0.49,0.79)
p-value		0.0001

* Based on a Cox regression model with terms for age (p=0.0488), baseline eGFR (CKD-EPI) (p<0.0001), sex (p=0.1371), region (p<0.0001), baseline diabetes status (3 cat.) (p=0.0006), baseline LVEF (3 cat.) (p=0.0056), Treatment (p<0.0001), cause of heart failure (2 cat.) (p=0.3944) and Treatment by cause of heart failure (2 cat.) interaction (p=0.2403).

R.1.1.3.12 Subgroup analysis by heart failure physiology (LVEF <= 30% and NTproBNP<median; LVEF <= 30% and NTproBNP>=median; LVEF > 30%)

Figure R.1.1.3.12: 1

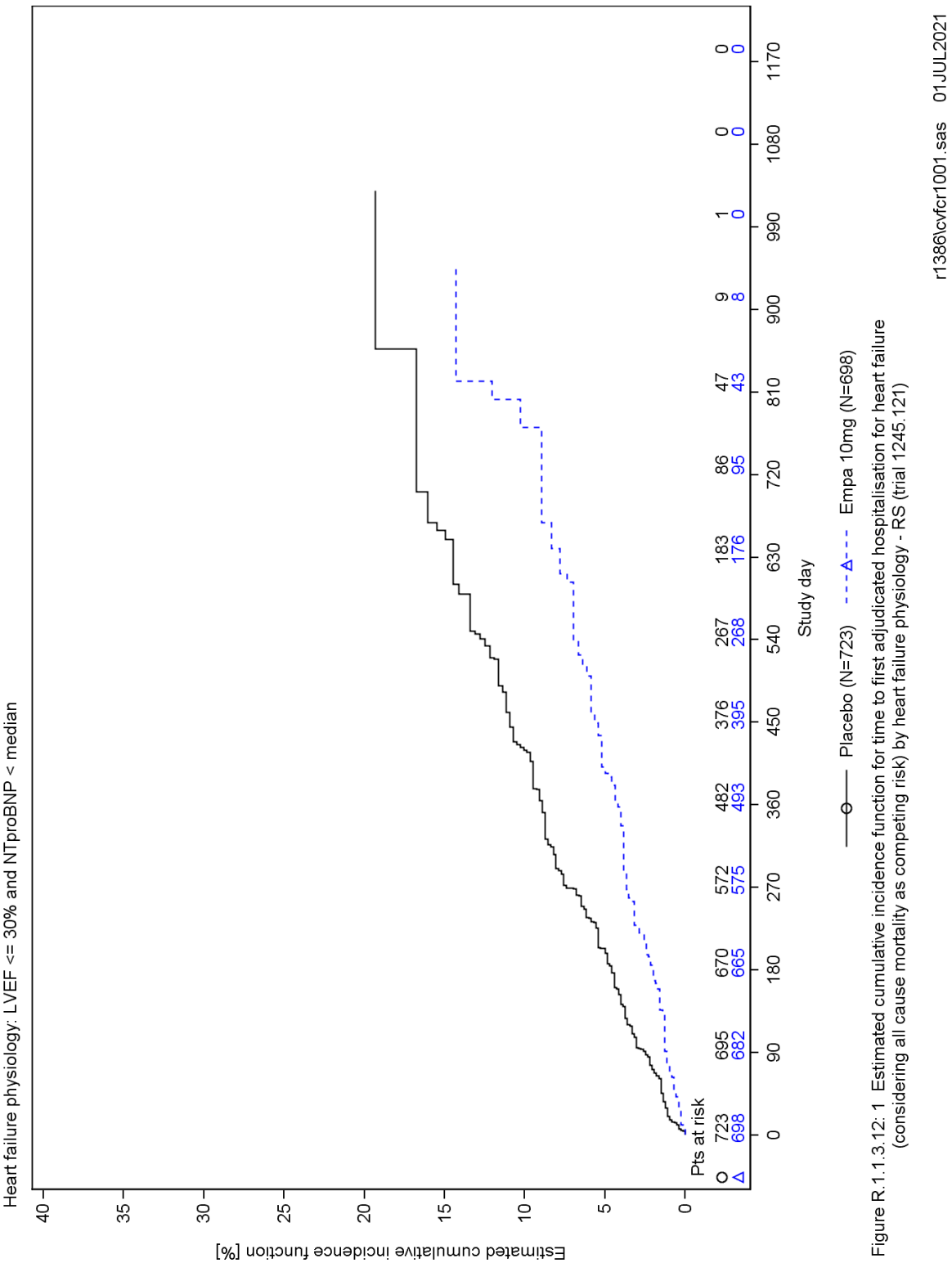

Figure R.1.1.3.12: 1 Estimated cumulative incidence function for time to first adjudicated hospitalisation for heart failure (considering all cause mortality as competing risk) by heart failure physiology - RS (trial 1245.121)

Figure R.1.1.3.12: 1

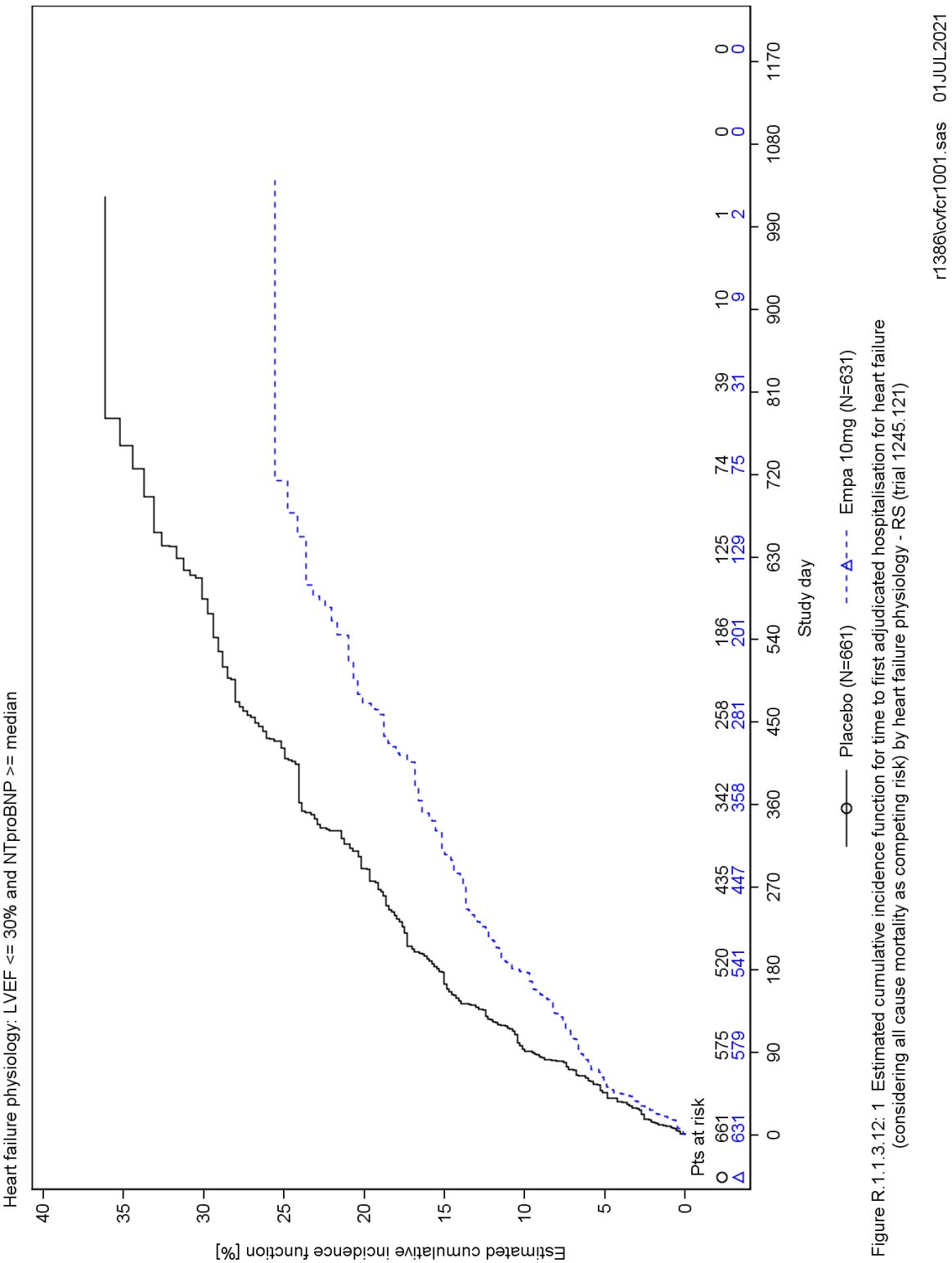

Figure R.1.1.3.12: 1 Estimated cumulative incidence function for time to first adjudicated hospitalisation for heart failure (considering all cause mortality as competing risk) by heart failure physiology - RS (trial 1245.121)

Figure R.1.1.3.12: 1

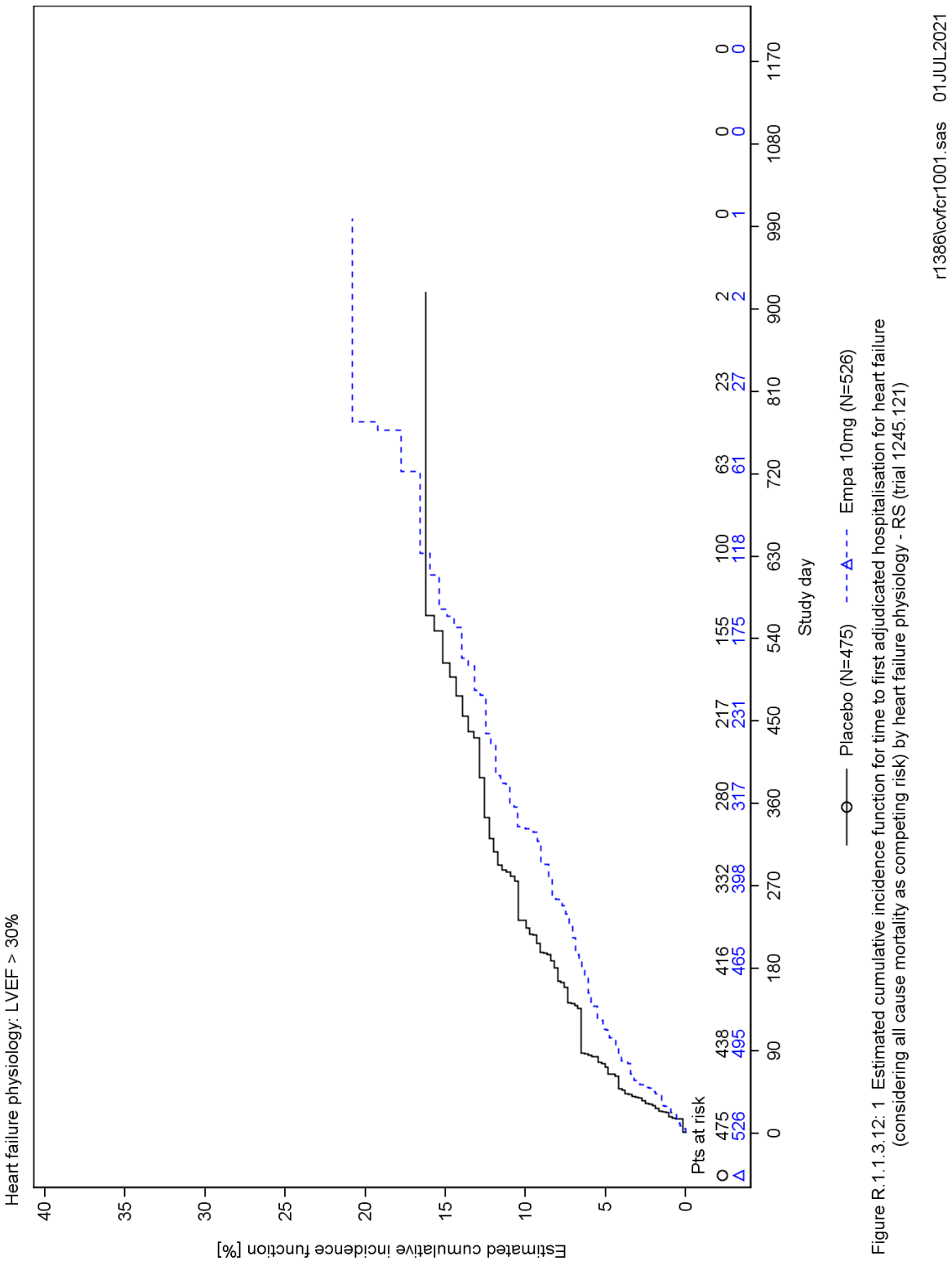

Figure R.1.1.3.12: 1 Estimated cumulative incidence function for time to first adjudicated hospitalisation for heart failure (considering all cause mortality as competing risk) by heart failure physiology - RS (trial 1245.121)

Table R.1.1.3.12: 1 Cox regr. for time to first adjudicated hospitalisation for heart failure by heart failure physiology - RS (trial 1245.121)

Subgroup Description	Placebo	Empa 10mg
Heart failure physiology: LVEF <= 30% and NTproBNP < median		
Number of patients in analysis set	723	698
Number of analysed patients	723	698
Number of patients with event [N(%)]	88 (12.2)	47 (6.7)
Time at risk for event [years]	923.2	922.5
Incidence rate [patients with events per 100 patient years at risk]	9.53	5.10
95% confidence interval	(7.64, 11.62)	(3.74, 6.65)
Comparison vs Placebo*		
Hazard ratio		0.54
95% confidence interval		(0.38,0.76)
p-value		0.0006
Heart failure physiology: LVEF <= 30% and NTproBNP >= median		
Number of patients in analysis set	661	631
Number of analysed patients	661	631
Number of patients with event [N(%)]	187 (28.3)	127 (20.1)
Time at risk for event [years]	711.1	730.2
Incidence rate [patients with events per 100 patient years at risk]	26.30	17.39
95% confidence interval	(22.66, 30.20)	(14.50, 20.55)
Comparison vs Placebo*		
Hazard ratio		0.65
95% confidence interval		(0.52,0.81)
p-value		0.0002

* Based on a Cox regression model with terms for age (p=0.0702), baseline eGFR (CKD-EPI) (p=0.0013), sex (p=0.1424), region (p<0.0001), baseline diabetes status (3 cat.) (p=0.0009), Treatment (p<0.0001), heart failure physiology (p<0.0001) and Treatment by heart failure physiology interaction (p=0.0479).
16 patients were excluded as the subgroup variable was missing.
The p-value for treatment by subgroup interaction trend test is 0.0670.

Table R.1.1.3.12: 1 Cox regr. for time to first adjudicated hospitalisation for heart failure by heart failure physiology - RS (trial 1245.121)

Subgroup Description	Placebo	Empa 10mg
Heart failure physiology: LVEF > 30%		
Number of patients in analysis set	475	526
Number of analysed patients	475	526
Number of patients with event [N(%)]	66 (13.9)	71 (13.5)
Time at risk for event [years]	556.1	628.7
Incidence rate [patients with events per 100 patient years at risk]	11.87	11.29
95% confidence interval	(9.18, 14.90)	(8.82, 14.07)
Comparison vs Placebo*		
Hazard ratio		0.96
95% confidence interval		(0.69,1.35)
p-value		0.8334

* Based on a Cox regression model with terms for age (p=0.0702), baseline eGFR (CKD-EPI) (p=0.0013), sex (p=0.1424), region (p<0.0001), baseline diabetes status (3 cat.) (p=0.0009), Treatment (p<0.0001), heart failure physiology (p<0.0001) and Treatment by heart failure physiology interaction (p=0.0479).
16 patients were excluded as the subgroup variable was missing.
The p-value for treatment by subgroup interaction trend test is 0.0670.

R.1.1.3.13

R.1.1.3.13 Subgroup analysis by baseline use of MRA

Table R.1.1.3.13: 1 Cox regr. for time to first adjudicated hospitalisation for heart failure by baseline use of MRA (Y/N) - RS (trial 1245.121)

Subgroup Description	Placebo	Empa 10mg
Baseline use of MRA: No		
Number of patients in analysis set	512	557
Number of analysed patients	512	557
Number of patients with event [N(%)]	106 (20.7)	82 (14.7)
Time at risk for event [years]	609.1	718.2
Incidence rate [patients with events per 100 patient years at risk]	17.40	11.42
95% confidence interval	(14.25, 20.87)	(9.08, 14.02)
Comparison vs Placebo*		
Hazard ratio		0.65
95% confidence interval		(0.49,0.87)
p-value		0.0040
Baseline use of MRA: Yes		
Number of patients in analysis set	1355	1306
Number of analysed patients	1355	1306
Number of patients with event [N(%)]	236 (17.4)	164 (12.6)
Time at risk for event [years]	1590.4	1570.5
Incidence rate [patients with events per 100 patient years at risk]	14.84	10.44
95% confidence interval	(13.01, 16.79)	(8.91, 12.10)
Comparison vs Placebo*		
Hazard ratio		0.71
95% confidence interval		(0.58,0.87)
p-value		0.0007

* Based on a Cox regression model with terms for age (p=0.0367), baseline eGFR (CKD-EPI) (p<0.0001), sex (p=0.1898), region (p<0.0001), baseline diabetes status (3 cat.) (p=0.0008), baseline LVEF (3 cat.) (p=0.0054), Treatment (p<0.0001), baseline use of MRA (p=0.8049) and Treatment by baseline use of MRA interaction (p=0.6568).

R.1.1.3.14

Table R.1.1.3.14: 1 Cox regr. for time to first adjudicated hospitalisation for heart failure by baseline use of ARNi (Y/N) - RS (trial 1245.121)

Subgroup Description	Placebo	Empa 10mg
Baseline use of ARNi: No		
Number of patients in analysis set	1480	1523
Number of analysed patients	1480	1523
Number of patients with event [N(%)]	266 (18.0)	206 (13.5)
Time at risk for event [years]	1761.7	1897.0
Incidence rate [patients with events per 100 patient years at risk]	15.10	10.86
95% confidence interval	(13.34, 16.97)	(9.43, 12.39)
Comparison vs Placebo*		
Hazard ratio		0.71
95% confidence interval		(0.59,0.85)
p-value		0.0002
Baseline use of ARNi: Yes		
Number of patients in analysis set	387	340
Number of analysed patients	387	340
Number of patients with event [N(%)]	76 (19.6)	40 (11.8)
Time at risk for event [years]	437.8	391.8
Incidence rate [patients with events per 100 patient years at risk]	17.36	10.21
95% confidence interval	(13.68, 21.47)	(7.29, 13.61)
Comparison vs Placebo*		
Hazard ratio		0.61
95% confidence interval		(0.42,0.90)
p-value		0.0127

* Based on a Cox regression model with terms for age (p=0.0407), baseline eGFR (CKD-EPI) (p<0.0001), sex (p=0.1899), region (p<0.0001), baseline diabetes status (3 cat.) (p=0.0008), baseline LVEF (3 cat.) (p=0.0054), Treatment (p=0.0001), baseline use of ARNi (p=0.8099) and Treatment by baseline use of ARNi interaction (p=0.5025).

R.1.1.3.15 Subgroup analysis by bl. LVEF (<= 30%, >30% -<= 35% , > 35%)

Table R.1.1.3.15: 1

Table R.1.1.3.15: 1 Cox regr. for time to first adjudicated hospitalisation for heart failure by bl. LVEF (3 cat.) - RS (trial 1245.121)

Subgroup Description	Placebo	Empa 10mg
Baseline LVEF: <=30		
Number of patients in analysis set	1392	1337
Number of analysed patients	1392	1337
Number of patients with event [N(%)]	276 (19.8)	175 (13.1)
Time at risk for event [years]	1643.4	1660.1
Incidence rate [patients with events per 100 patient years at risk]	16.79	10.54
95% confidence interval	(14.87, 18.83)	(9.04, 12.16)
Comparison vs Placebo*		
Hazard ratio		0.62
95% confidence interval		(0.51,0.75)
p-value		<0.0001
Baseline LVEF: >30 to <=35		
Number of patients in analysis set	361	398
Number of analysed patients	361	398
Number of patients with event [N(%)]	41 (11.4)	50 (12.6)
Time at risk for event [years]	436.1	488.6
Incidence rate [patients with events per 100 patient years at risk]	9.40	10.23
95% confidence interval	(6.75, 12.49)	(7.59, 13.26)
Comparison vs Placebo*		
Hazard ratio		1.08
95% confidence interval		(0.71,1.63)
p-value		0.7135

* Based on a Cox regression model with terms for age (p=0.0397), baseline eGFR (CKD-EPI) (p<0.0001), sex (p=0.1941), region (p<0.0001), baseline diabetes status (3 cat.) (p=0.0007), Treatment (p=0.0938), baseline LVEF (3 cat.) (p=0.0070) and Treatment by baseline LVEF (3 cat.) interaction (p=0.0511).
The p-value for treatment by subgroup interaction trend test is 0.0592.

Table R.1.1.3.15: 1 Cox regr. for time to first adjudicated hospitalisation for heart failure by bl. LVEF (3 cat.) - RS (trial 1245.121)

Subgroup Description	Placebo	Empa 10mg
Baseline LVEF: >35		
Number of patients in analysis set	114	128
Number of analysed patients	114	128
Number of patients with event [N(%)]	25 (21.9)	21 (16.4)
Time at risk for event [years]	120.0	140.0
Incidence rate [patients with events per 100 patient years at risk]	20.84	15.00
95% confidence interval	(13.48, 29.76)	(9.28, 22.06)
Comparison vs Placebo*		
Hazard ratio		0.79
95% confidence interval		(0.44,1.42)
p-value		0.4365

* Based on a Cox regression model with terms for age (p=0.0397), baseline eGFR (CKD-EPI) (p<0.0001), sex (p=0.1941), region (p<0.0001), baseline diabetes status (3 cat.) (p=0.0007), Treatment (p=0.0938), baseline LVEF (3 cat.) (p=0.0070) and Treatment by baseline LVEF (3 cat.) interaction (p=0.0511).
The p-value for treatment by subgroup interaction trend test is 0.0592.

R.1.1.3.16 Subgroup analysis by bl. NTproBNP </>= median (median based on total patients)

Table R.1.1.3.16: 1 Cox regr. for time to first adjudicated hospitalisation for heart failure by bl. NTproBNP (<median,>= median) (median based on total patients) - RS (trial 1245.121)

Subgroup Description	Placebo	Empa 10mg
Baseline NTproBNP: < median		
Number of patients in analysis set	920	942
Number of analysed patients	920	942
Number of patients with event [N(%)]	108 (11.7)	63 (6.7)
Time at risk for event [years]	1176.2	1233.5
Incidence rate [patients with events per 100 patient years at risk]	9.18	5.11
95% confidence interval	(7.53, 10.99)	(3.92, 6.44)
Comparison vs Placebo*		
Hazard ratio		0.56
95% confidence interval		(0.41,0.76)
p-value		0.0002
Baseline NTproBNP: >= median		
Number of patients in analysis set	946	920
Number of analysed patients	946	920
Number of patients with event [N(%)]	234 (24.7)	183 (19.9)
Time at risk for event [years]	1022.5	1054.1
Incidence rate [patients with events per 100 patient years at risk]	22.89	17.36
95% confidence interval	(20.05, 25.91)	(14.94, 19.96)
Comparison vs Placebo*		
Hazard ratio		0.76
95% confidence interval		(0.63,0.93)
p-value		0.0060

* Based on a Cox regression model with terms for age (p=0.0239), baseline eGFR (CKD-EPI) (p=0.0078), sex (p=0.2280), region (p<0.0001), baseline diabetes status (3 cat.) (p=0.0007), baseline LVEF (3 cat.) (p=0.0044), Treatment (p<0.0001), baseline NTproBNP (2 cat.) (p<0.0001) and Treatment by baseline NTproBNP (2 cat.) interaction (p=0.0975).
2 patients were excluded as the subgroup variable was missing.

Median: 1910 [pg/mL]

R.1.1.4 Time to first adjudicated HHF requiring ICU or CCU stay

R.1.1.4.1

Figure R.1.1.4.1: 1

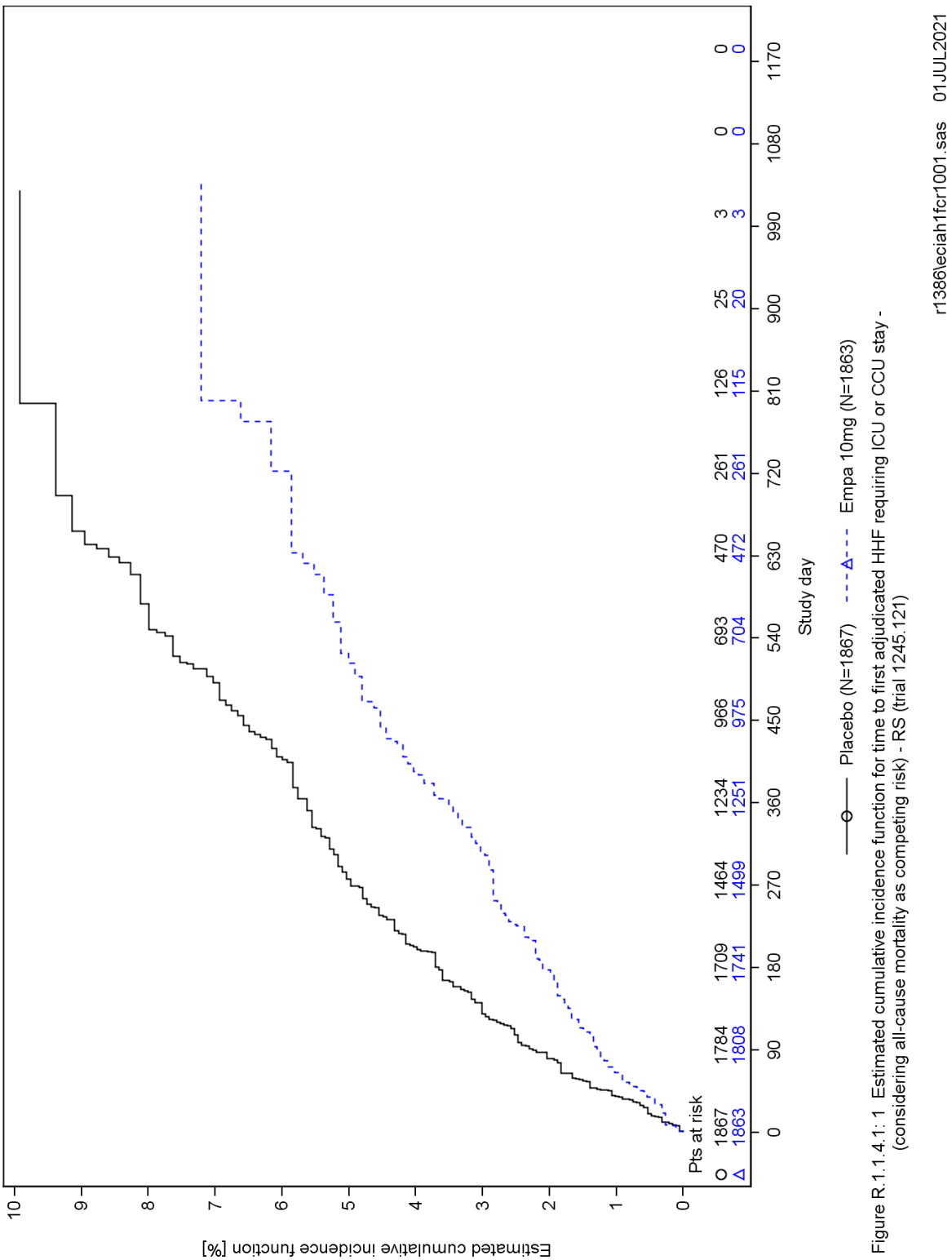

Figure R.1.1.4.1: 1 Estimated cumulative incidence function for time to first adjudicated HHF requiring ICU or CCU stay - (considering all-cause mortality as competing risk) - RS (trial 1245.121)

Table R.1.1.4.1: 1 Cox reg. for time to first adjudicated heart failure hospitalisation requiring ICU or CCU stay - RS (trial 1245.121)

	Placebo	Empa 10mg
Number of patients in analysis set	1867	1863
Number of analysed patients	1867	1863
Number of patients with event [N(%)]	136 (7.3)	89 (4.8)
Time at risk for event [years]	2379.5	2407.3
Incidence rate [patients with events per 100 patient years at risk]	5.72	3.70
95% confidence interval	(4.80, 6.72)	(2.97, 4.50)
Comparison vs Placebo*		
Hazard ratio		0.65
95% confidence interval		(0.50,0.85)
p-value		0.0017
Time to event [days]**		
2.5% percentile	106	225
5.0% percentile	269	471
7.5% percentile	506	799
10.0% percentile	695	NC.
Patients with events [%]**		
1 year	6.0	3.8
2 years	10.1	6.6

* Based on a Cox regression model with terms for age (p=0.1913), baseline eGFR (CKD-EPI) (p=0.0042), region (p=0.8066), sex (p=0.3048), baseline diabetes status (3 cat.) (p=0.0766), baseline LVEF (3 cat.) (p=0.1663) and Treatment (p=0.0017).
**Based on Kaplan-Meier estimates.
NC. = Not calculated.

R.1.1.4.2

R.1.1.4.2 Subgroup analysis by sex

Table R.1.1.4.2: 1 Cox reg. for time to first adjudicated heart failure hospitalisation requiring ICU or CCU stay by sex - RS (trial 1245.121)

Subgroup Description	Placebo	Empa 10mg
Sex: Male		
Number of patients in analysis set	1411	1426
Number of analysed patients	1411	1426
Number of patients with event [N(%)]	104 (7.4)	73 (5.1)
Time at risk for event [years]	1808.6	1828.4
Incidence rate [patients with events per 100 patient years at risk]	5.75	3.99
95% confidence interval	(4.70, 6.91)	(3.13, 4.96)
Comparison vs Placebo*		
Hazard ratio		0.70
95% confidence interval		(0.52,0.94)
p-value		0.0189
Sex: Female		
Number of patients in analysis set	456	437
Number of analysed patients	456	437
Number of patients with event [N(%)]	32 (7.0)	16 (3.7)
Time at risk for event [years]	570.9	578.9
Incidence rate [patients with events per 100 patient years at risk]	5.60	2.76
95% confidence interval	(3.83, 7.71)	(1.58, 4.27)
Comparison vs Placebo*		
Hazard ratio		0.50
95% confidence interval		(0.27,0.91)
p-value		0.0242

* Based on a Cox regression model with terms for age (p=0.1831), baseline eGFR (CKD-EPI) (p=0.0044), region (p=0.8129), baseline diabetes status (3 cat.) (p=0.0752), baseline LVEF (3 cat.) (p=0.1618), Treatment (p=0.0022), sex (p=0.2221) and Treatment by sex interaction (p=0.3331).

R.1.1.4.3

R.1.1.4.3 Subgroup analysis by age

Table R.1.1.4.3: 1 Cox reg. for time to first adjudicated heart failure hospitalisation requiring ICU or CCU stay by age (2 cat.) - RS (trial 1245.121)

Subgroup Description	Placebo	Empa 10mg
Age (2 cat.): < 65		
Number of patients in analysis set	740	675
Number of analysed patients	740	675
Number of patients with event [N(%)]	60 (8.1)	34 (5.0)
Time at risk for event [years]	939.6	863.4
Incidence rate [patients with events per 100 patient years at risk]	6.39	3.94
95% confidence interval	(4.87, 8.10)	(2.73, 5.37)
Comparison vs Placebo*		
Hazard ratio		0.64
95% confidence interval		(0.42,0.98)
p-value		0.0378
Age (2 cat.): >= 65		
Number of patients in analysis set	1127	1188
Number of analysed patients	1127	1188
Number of patients with event [N(%)]	76 (6.7)	55 (4.6)
Time at risk for event [years]	1439.9	1543.9
Incidence rate [patients with events per 100 patient years at risk]	5.28	3.56
95% confidence interval	(4.16, 6.53)	(2.68, 4.56)
Comparison vs Placebo*		
Hazard ratio		0.66
95% confidence interval		(0.47,0.94)
p-value		0.0208

* Based on a Cox regression model with terms for baseline eGFR (CKD-EPI) (p=0.0032), region (p=0.8129), sex (p=0.3007), baseline diabetes status (3 cat.) (p=0.0796), baseline LVEF (3 cat.) (p=0.1652), Treatment (p=0.0021), Age (2 cat.) (p=0.1249) and Treatment by Age (2 cat.) interaction (p=0.8946).

R.1.1.4.4 Subgroup analysis by region (North America, Latin America, Europe, Asia, Other)

Table R.1.1.4.4: 1 Cox reg. for time to first adjudicated heart failure hospitalisation requiring ICU or CCU stay by region - RS (trial 1245.121)

Subgroup Description	Placebo	Empa 10mg
Region: North America		
Number of patients in analysis set	213	212
Number of analysed patients	213	212
Number of patients with event [N(%)]	18 (8.5)	8 (3.8)
Time at risk for event [years]	277.4	302.7
Incidence rate [patients with events per 100 patient years at risk]	6.49	2.64
95% confidence interval	(3.85, 9.81)	(1.14, 4.76)
Comparison vs Placebo*		
Hazard ratio		0.43
95% confidence interval		(0.19,1.00)
p-value		0.0500
Region: Latin America		
Number of patients in analysis set	645	641
Number of analysed patients	645	641
Number of patients with event [N(%)]	48 (7.4)	30 (4.7)
Time at risk for event [years]	747.8	748.1
Incidence rate [patients with events per 100 patient years at risk]	6.42	4.01
95% confidence interval	(4.73, 8.36)	(2.71, 5.57)
Comparison vs Placebo*		
Hazard ratio		0.63
95% confidence interval		(0.40,0.99)
p-value		0.0449

* Based on a Cox regression model with terms for age (p=0.2071), baseline eGFR (CKD-EPI) (p=0.0044), sex (p=0.2970), baseline diabetes status (3 cat.) (p=0.0790), baseline LVEF (3 cat.) (p=0.1779), Treatment (p=0.0065), region (p=0.8113) and Treatment by region interaction (p=0.7116).

Table R.1.1.4.4: 1 Cox reg. for time to first adjudicated heart failure hospitalisation requiring ICU or CCU stay by region - RS (trial 1245.121)

Subgroup Description	Placebo	Empa 10mg
Region: Europe		
Number of patients in analysis set	677	676
Number of analysed patients	677	676
Number of patients with event [N(%)]	46 (6.8)	32 (4.7)
Time at risk for event [years]	902.3	905.7
Incidence rate [patients with events per 100 patient years at risk]	5.10	3.53
95% confidence interval	(3.73, 6.67)	(2.42, 4.86)
Comparison vs Placebo*		
Hazard ratio		0.69
95% confidence interval		(0.44,1.09)
p-value		0.1110
Region: Asia		
Number of patients in analysis set	245	248
Number of analysed patients	245	248
Number of patients with event [N(%)]	16 (6.5)	15 (6.0)
Time at risk for event [years]	337.7	339.8
Incidence rate [patients with events per 100 patient years at risk]	4.74	4.41
95% confidence interval	(2.71, 7.33)	(2.47, 6.91)
Comparison vs Placebo*		
Hazard ratio		0.93
95% confidence interval		(0.46,1.87)
p-value		0.8315

* Based on a Cox regression model with terms for age (p=0.2071), baseline eGFR (CKD-EPI) (p=0.0044), sex (p=0.2970), baseline diabetes status (3 cat.) (p=0.0790), baseline LVEF (3 cat.) (p=0.1779), Treatment (p=0.0065), region (p=0.8113) and Treatment by region interaction (p=0.7116).

Table R.1.1.4.4: 1 Cox reg. for time to first adjudicated heart failure hospitalisation requiring ICU or CCU stay by region - RS (trial 1245.121)

Subgroup Description	Placebo	Empa 10mg
Region: Other		
Number of patients in analysis set	87	86
Number of analysed patients	87	86
Number of patients with event [N(%)]	8 (9.2)	4 (4.7)
Time at risk for event [years]	114.3	110.9
Incidence rate [patients with events per 100 patient years at risk]	7.00	3.61
95% confidence interval	(3.02,12.62)	(0.98, 7.90)
Comparison vs Placebo*		
Hazard ratio		0.51
95% confidence interval		(0.15,1.69)
p-value		0.2677

* Based on a Cox regression model with terms for age (p=0.2071), baseline eGFR (CKD-EPI) (p=0.0044), sex (p=0.2970), baseline diabetes status (3 cat.) (p=0.0790), baseline LVEF (3 cat.) (p=0.1779), Treatment (p=0.0065), region (p=0.8113) and Treatment by region interaction (p=0.7116).

R.1.1.4.5

R.1.1.4.5 Subgroup analysis by OECD member (Y/N)

Table R.1.1.4.5: 1 Cox reg. for time to first adjudicated heart failure hospitalisation requiring ICU or CCU stay by OECD member (Y/N) - RS (trial 1245.121)

Subgroup Description	Placebo	Empa 10mg
OECD member: No		
Number of patients in analysis set	741	713
Number of analysed patients	741	713
Number of patients with event [N(%)]	58 (7.8)	35 (4.9)
Time at risk for event [years]	869.5	839.8
Incidence rate [patients with events per 100 patient years at risk]	6.67	4.17
95% confidence interval	(5.07, 8.49)	(2.90, 5.66)
Comparison vs Placebo*		
Hazard ratio		0.62
95% confidence interval		(0.41,0.94)
p-value		0.0252
OECD member: Yes		
Number of patients in analysis set	1126	1150
Number of analysed patients	1126	1150
Number of patients with event [N(%)]	78 (6.9)	54 (4.7)
Time at risk for event [years]	1510.0	1567.4
Incidence rate [patients with events per 100 patient years at risk]	5.17	3.45
95% confidence interval	(4.08, 6.37)	(2.59, 4.42)
Comparison vs Placebo*		
Hazard ratio		0.68
95% confidence interval		(0.48,0.96)
p-value		0.0282

* Based on a Cox regression model with terms for age (p=0.2355), baseline eGFR (CKD-EPI) (p=0.0042), sex (p=0.2671), baseline diabetes status (3 cat.) (p=0.0773), baseline LVEF (3 cat.) (p=0.1589), Treatment (p=0.0018), OECD member (p=0.1173) and Treatment by OECD member interaction (p=0.7410).

OECD member (yes/no) countries included:
Yes: United States, Canada, Mexico, Poland, Netherlands, Hungary, Germany, Czech Republic, Italy, France, Spain, United Kingdom, Belgium, Japan, Australia, 'Korea; Republic Of South Korea';
No: Brazil, Argentina, China, India.

R.1.1.4.6 Subgroup analysis by NYHA at baseline (II, III/IV - 2 cat.)

Table R.1.1.4.6: 1 Cox reg. for time to first adjudicated heart failure hospitalisation requiring ICU or CCU stay by NYHA (2 cat.) - RS (trial 1245.121)

Subgroup Description	Placebo	Empa 10mg
History of NYHA (2 cat.): II		
Number of patients in analysis set	1401	1399
Number of analysed patients	1401	1399
Number of patients with event [N(%)]	91 (6.5)	51 (3.6)
Time at risk for event [years]	1805.1	1822.2
Incidence rate [patients with events per 100 patient years at risk]	5.04	2.80
95% confidence interval	(4.06, 6.13)	(2.08, 3.62)
Comparison vs Placebo*		
Hazard ratio		0.56
95% confidence interval		(0.39,0.78)
p-value		0.0008
History of NYHA (2 cat.): III/IV		
Number of patients in analysis set	466	464
Number of analysed patients	466	464
Number of patients with event [N(%)]	45 (9.7)	38 (8.2)
Time at risk for event [years]	574.4	585.0
Incidence rate [patients with events per 100 patient years at risk]	7.83	6.50
95% confidence interval	(5.71,10.28)	(4.60, 8.72)
Comparison vs Placebo*		
Hazard ratio		0.85
95% confidence interval		(0.55,1.30)
p-value		0.4502

* Based on a Cox regression model with terms for age (p=0.2315), baseline eGFR (CKD-EPI) (p=0.0070), region (p=0.6415), sex (p=0.2101), baseline diabetes status (3 cat.) (p=0.0958), baseline LVEF (3 cat.) (p=0.2176), Treatment (p=0.0076), History of NYHA (2 cat.) (p<0.0001) and Treatment by History of NYHA (2 cat.) interaction (p=0.1367).

R.1.1.4.7

R.1.1.4.7 Subgroup analysis by diabetes at baseline

Table R.1.1.4.7: 1 Cox reg. for time to first adjudicated heart failure hospitalisation requiring ICU or CCU stay by diabetes at baseline (2 cat.) - RS (trial 1245.121)

Subgroup Description	Placebo	Empa 10mg
Baseline diabetes status (2 cat.): Diabetic		
Number of patients in analysis set	929	927
Number of analysed patients	929	927
Number of patients with event [N(%)]	76 (8.2)	47 (5.1)
Time at risk for event [years]	1193.0	1200.5
Incidence rate [patients with events per 100 patient years at risk]	6.37	3.92
95% confidence interval	(5.02, 7.88)	(2.88, 5.11)
Comparison vs Placebo*		
Hazard ratio		0.62
95% confidence interval		(0.43,0.89)
p-value		0.0096
Baseline diabetes status (2 cat.): Non-Diabetic		
Number of patients in analysis set	938	936
Number of analysed patients	938	936
Number of patients with event [N(%)]	60 (6.4)	42 (4.5)
Time at risk for event [years]	1186.5	1206.8
Incidence rate [patients with events per 100 patient years at risk]	5.06	3.48
95% confidence interval	(3.86, 6.41)	(2.51, 4.61)
Comparison vs Placebo*		
Hazard ratio		0.70
95% confidence interval		(0.47,1.03)
p-value		0.0711

* Based on a Cox regression model with terms for age (p=0.1556), baseline eGFR (CKD-EPI) (p=0.0047), region (p=0.8166), sex (p=0.2973), baseline LVEF (3 cat.) (p=0.1687), Treatment (p=0.0021), Baseline diabetes status (2 cat.) (p=0.2949) and Treatment by Baseline diabetes status (2 cat.) interaction (p=0.6693).

R.1.1.4.8

R.1.1.4.8 Subgroup analysis by BMI at baseline (<30, >=30)

Table R.1.1.4.8: 1 Cox reg. for time to first adjudicated heart failure hospitalisation requiring ICU or CCU stay by baseline BMI [kg/m2] - RS (trial 1245.121)

Subgroup Description	Placebo	Empa 10mg
Baseline BMI [kg/m²]: <30		
Number of patients in analysis set	1300	1263
Number of analysed patients	1300	1263
Number of patients with event [N(%)]	92 (7.1)	55 (4.4)
Time at risk for event [years]	1680.5	1625.3
Incidence rate [patients with events per 100 patient years at risk]	5.47	3.38
95% confidence interval	(4.41, 6.65)	(2.55, 4.34)
Comparison vs Placebo*		
Hazard ratio		0.62
95% confidence interval		(0.44,0.86)
p-value		0.0048
Baseline BMI [kg/m²]: >=30		
Number of patients in analysis set	567	600
Number of analysed patients	567	600
Number of patients with event [N(%)]	44 (7.8)	34 (5.7)
Time at risk for event [years]	699.0	782.0
Incidence rate [patients with events per 100 patient years at risk]	6.30	4.35
95% confidence interval	(4.57, 8.29)	(3.01, 5.93)
Comparison vs Placebo*		
Hazard ratio		0.71
95% confidence interval		(0.45,1.11)
p-value		0.1291

* Based on a Cox regression model with terms for age (p=0.2661), baseline eGFR (CKD-EPI) (p=0.0049), region (p=0.7143), sex (p=0.2811), baseline diabetes status (3 cat.) (p=0.0848), baseline LVEF (3 cat.) (p=0.1622), Treatment (p=0.0037), Baseline BMI [kg/m²] (p=0.2137) and Treatment by Baseline BMI [kg/m²] interaction (p=0.6392).

R.1.1.4.9 Subgroup analysis by eGFR at baseline (<60, >=60)

Table R.1.1.4.9: 1 Cox reg. for time to first adjudicated heart failure hospitalisation requiring ICU or CCU stay by eGFR (2 cat.) - RS (trial 1245.121)

Subgroup Description	Placebo	Empa 10mg
Baseline eGFR (2 cat.): >=60		
Number of patients in analysis set	960	969
Number of analysed patients	960	969
Number of patients with event [N(%)]	67 (7.0)	38 (3.9)
Time at risk for event [years]	1225.4	1246.4
Incidence rate [patients with events per 100 patient years at risk]	5.47	3.05
95% confidence interval	(4.24, 6.85)	(2.16, 4.09)
Comparison vs Placebo*		
Hazard ratio		0.56
95% confidence interval		(0.38,0.84)
p-value		0.0049
Baseline eGFR (2 cat.): <60		
Number of patients in analysis set	906	893
Number of analysed patients	906	893
Number of patients with event [N(%)]	69 (7.6)	51 (5.7)
Time at risk for event [years]	1153.2	1159.7
Incidence rate [patients with events per 100 patient years at risk]	5.98	4.40
95% confidence interval	(4.66, 7.48)	(3.27, 5.68)
Comparison vs Placebo*		
Hazard ratio		0.74
95% confidence interval		(0.52,1.06)
p-value		0.1032

* Based on a Cox regression model with terms for age (p=0.5433), region (p=0.8298), sex (p=0.3356), baseline diabetes status (3 cat.) (p=0.0767), baseline LVEF (3 cat.) (p=0.1782), Treatment (p=0.0015), Baseline eGFR (2 cat.) (p=0.0375) and Treatment by Baseline eGFR (2 cat.) interaction (p=0.3245).
2 patients were excluded as the subgroup variable was missing.

R.1.1.4.10

R.1.1.4.10 Subgroup analysis by history of HHF

Table R.1.1.4.10: 1 Cox reg. for time to first adjudicated heart failure hospitalisation requiring ICU or CCU stay by history of HHF within 12 months - RS (trial 1245.121)

Subgroup Description	Placebo	Empa 10mg
History of HHF (in the last 12 months): No		
Number of patients in analysis set	1293	1286
Number of analysed patients	1293	1286
Number of patients with event [N(%)]	80 (6.2)	46 (3.6)
Time at risk for event [years]	1703.1	1706.2
Incidence rate [patients with events per 100 patient years at risk]	4.70	2.70
95% confidence interval	(3.72, 5.78)	(1.97, 3.53)
Comparison vs Placebo*		
Hazard ratio		0.58
95% confidence interval		(0.40,0.83)
p-value		0.0029
History of HHF (in the last 12 months): Yes		
Number of patients in analysis set	574	577
Number of analysed patients	574	577
Number of patients with event [N(%)]	56 (9.8)	43 (7.5)
Time at risk for event [years]	676.4	701.1
Incidence rate [patients with events per 100 patient years at risk]	8.28	6.13
95% confidence interval	(6.25,10.58)	(4.44, 8.10)
Comparison vs Placebo*		
Hazard ratio		0.75
95% confidence interval		(0.50,1.12)
p-value		0.1605

* Based on a Cox regression model with terms for age (p=0.3461), baseline eGFR (CKD-EPI) (p=0.0057), region (p=0.5645), sex (p=0.2960), baseline diabetes status (3 cat.) (p=0.1006), baseline LVEF (3 cat.) (p=0.1821), Treatment (p=0.0023), History of HHF (in the last 12 months) (p<0.0001) and Treatment by History of HHF (in the last 12 months) interaction (p=0.3340).

R.1.1.4.11

R.1.1.4.11 Subgroup analysis by cause of heart failure

Table R.1.1.4.11: 1 Cox reg. for time to first adjudicated heart failure hospitalisation requiring ICU or CCU stay by cause of heart failure - RS (trial 1245.121)

Subgroup Description	Placebo	Empa 10mg
Cause of heart failure: Ischemic		
Number of patients in analysis set	946	983
Number of analysed patients	946	983
Number of patients with event [N(%)]	67 (7.1)	42 (4.3)
Time at risk for event [years]	1226.3	1282.8
Incidence rate [patients with events per 100 patient years at risk]	5.46	3.27
95% confidence interval	(4.23, 6.85)	(2.36, 4.34)
Comparison vs Placebo*		
Hazard ratio		0.60
95% confidence interval		(0.40,0.88)
p-value		0.0086
Cause of heart failure: Non-ischemic		
Number of patients in analysis set	921	880
Number of analysed patients	921	880
Number of patients with event [N(%)]	69 (7.5)	47 (5.3)
Time at risk for event [years]	1153.2	1124.4
Incidence rate [patients with events per 100 patient years at risk]	5.98	4.18
95% confidence interval	(4.66, 7.48)	(3.07, 5.46)
Comparison vs Placebo*		
Hazard ratio		0.71
95% confidence interval		(0.49,1.03)
p-value		0.0752

* Based on a Cox regression model with terms for age (p=0.2234), baseline eGFR (CKD-EPI) (p=0.0037), region (p=0.8796), sex (p=0.2545), baseline diabetes status (3 cat.) (p=0.0742), baseline LVEF (3 cat.) (p=0.1656), Treatment (p=0.0018), Cause of heart failure (p=0.2201) and Treatment by Cause of heart failure interaction (p=0.5082).

R.1.1.4.12 Subgroup analysis by heart failure physiology (LVEF <= 30% and NTproBNP<median; LVEF <= 30% and NTproBNP>=median; LVEF > 30%)

Table R.1.1.4.12: 1 Cox reg. for time to first adjudicated heart failure hospitalisation requiring ICU or CCU stay by heart failure physiology - RS (trial 1245.121)

Subgroup Description	Placebo	Empa 10mg
Heart failure physiology: LVEF <= 30% and NTproBNP < median		
Number of patients in analysis set	723	698
Number of analysed patients	723	698
Number of patients with event [N(%)]	33 (4.6)	16 (2.3)
Time at risk for event [years]	963.4	943.5
Incidence rate [patients with events per 100 patient years at risk]	3.43	1.70
95% confidence interval	(2.36, 4.69)	(0.97, 2.62)
Comparison vs Placebo*		
Hazard ratio		0.50
95% confidence interval		(0.27,0.90)
p-value		0.0214
Heart failure physiology: LVEF <= 30% and NTproBNP >= median		
Number of patients in analysis set	661	631
Number of analysed patients	661	631
Number of patients with event [N(%)]	79 (12.0)	48 (7.6)
Time at risk for event [years]	808.4	790.5
Incidence rate [patients with events per 100 patient years at risk]	9.77	6.07
95% confidence interval	(7.74, 12.04)	(4.48, 7.91)
Comparison vs Placebo*		
Hazard ratio		0.62
95% confidence interval		(0.43,0.89)
p-value		0.0098

* Based on a Cox regression model with terms for age (p=0.2185), baseline eGFR (CKD-EPI) (p=0.0668), region (p=0.9052), sex (p=0.3596), baseline diabetes status (3 cat.) (p=0.0717), Treatment (p=0.0072), Heart failure physiology (p<0.0001) and Treatment by Heart failure physiology interaction (p=0.2733).
16 patients were excluded as the subgroup variable was missing.
The p-value for treatment by subgroup interaction trend test is 0.2433.

Table R.1.1.4.12: 1 Cox reg. for time to first adjudicated heart failure hospitalisation requiring ICU or CCU stay by heart failure physiology - RS (trial 1245.121)

Subgroup Description	Placebo	Empa 10mg
Heart failure physiology: LVEF > 30%		
Number of patients in analysis set	475	526
Number of analysed patients	475	526
Number of patients with event [N(%)]	24 (5.1)	25 (4.8)
Time at risk for event [years]	597.4	665.7
Incidence rate [patients with events per 100 patient years at risk]	4.02	3.76
95% confidence interval	(2.57, 5.78)	(2.43, 5.36)
Comparison vs Placebo*		
Hazard ratio		0.95
95% confidence interval		(0.54,1.66)
p-value		0.8559

* Based on a Cox regression model with terms for age (p=0.2185), baseline eGFR (CKD-EPI) (p=0.0668), region (p=0.9052), sex (p=0.3596), baseline diabetes status (3 cat.) (p=0.0717), Treatment (p=0.0072), Heart failure physiology (p<0.0001) and Treatment by Heart failure physiology interaction (p=0.2733).
16 patients were excluded as the subgroup variable was missing.
The p-value for treatment by subgroup interaction trend test is 0.2433.

R.1.1.4.13

Table R.1.1.4.13: 1 Cox reg. for time to first adjudicated heart failure hospitalisation requiring ICU or CCU stay by baseline use of MRA (Y/N) - RS (trial 1245.121)

Subgroup Description	Placebo	Empa 10mg
Baseline use of MRA: No		
Number of patients in analysis set	512	557
Number of analysed patients	512	557
Number of patients with event [N(%)]	32 (6.3)	28 (5.0)
Time at risk for event [years]	674.2	757.2
Incidence rate [patients with events per 100 patient years at risk]	4.75	3.70
95% confidence interval	(3.25, 6.53)	(2.46, 5.19)
Comparison vs Placebo*		
Hazard ratio		0.78
95% confidence interval		(0.47,1.29)
p-value		0.3309
Baseline use of MRA: Yes		
Number of patients in analysis set	1355	1306
Number of analysed patients	1355	1306
Number of patients with event [N(%)]	104 (7.7)	61 (4.7)
Time at risk for event [years]	1705.3	1650.1
Incidence rate [patients with events per 100 patient years at risk]	6.10	3.70
95% confidence interval	(4.98, 7.33)	(2.83, 4.68)
Comparison vs Placebo*		
Hazard ratio		0.61
95% confidence interval		(0.45,0.84)
p-value		0.0024

* Based on a Cox regression model with terms for age (p=0.2239), baseline eGFR (CKD-EPI) (p=0.0036), region (p=0.8304), sex (p=0.2935), baseline diabetes status (3 cat.) (p=0.0751), baseline LVEF (3 cat.) (p=0.1882), Treatment (p=0.0150), Baseline use of MRA (p=0.4332) and Treatment by Baseline use of MRA interaction (p=0.4341).

R.1.1.4.14

Table R.1.1.4.14: 1 Cox reg. for time to first adjudicated heart failure hospitalisation requiring ICU or CCU stay by baseline use of ARNi (Y/N) - RS (trial 1245.121)

Subgroup Description	Placebo	Empa 10mg
Baseline use of ARNi: No		
Number of patients in analysis set	1480	1523
Number of analysed patients	1480	1523
Number of patients with event [N(%)]	105 (7.1)	72 (4.7)
Time at risk for event [years]	1906.2	1999.0
Incidence rate [patients with events per 100 patient years at risk]	5.51	3.60
95% confidence interval	(4.51, 6.61)	(2.82, 4.48)
Comparison vs Placebo*		
Hazard ratio		0.66
95% confidence interval		(0.49,0.89)
p-value		0.0062
Baseline use of ARNi: Yes		
Number of patients in analysis set	387	340
Number of analysed patients	387	340
Number of patients with event [N(%)]	31 (8.0)	17 (5.0)
Time at risk for event [years]	473.3	408.2
Incidence rate [patients with events per 100 patient years at risk]	6.55	4.16
95% confidence interval	(4.45, 9.05)	(2.43, 6.36)
Comparison vs Placebo*		
Hazard ratio		0.64
95% confidence interval		(0.36,1.17)
p-value		0.1460

* Based on a Cox regression model with terms for age (p=0.2037), baseline eGFR (CKD-EPI) (p=0.0044), region (p=0.7572), sex (p=0.2968), baseline diabetes status (3 cat.) (p=0.0753), baseline LVEF (3 cat.) (p=0.1772), Treatment (p=0.0113), Baseline use of ARNi (p=0.3790) and Treatment by Baseline use of ARNi interaction (p=0.9512).

R.1.1.4.15 Subgroup analysis by bl. LVEF (<= 30%, >30% -<= 35% , > 35%)

Table R.1.1.4.15: 1 Cox reg. for time to first adjudicated heart failure hospitalisation requiring ICU or CCU stay by bl. LVEF (3 cat.) - RS (trial 1245.121)

Subgroup Description	Placebo	Empa 10mg
baseline LVEF (3 cat.): <=30		
Number of patients in analysis set	1392	1337
Number of analysed patients	1392	1337
Number of patients with event [N(%)]	112 (8.0)	64 (4.8)
Time at risk for event [years]	1782.1	1741.6
Incidence rate [patients with events per 100 patient years at risk]	6.28	3.67
95% confidence interval	(5.17, 7.50)	(2.83, 4.63)
Comparison vs Placebo*		
Hazard ratio		0.58
95% confidence interval		(0.43,0.79)
p-value		0.0006
baseline LVEF (3 cat.): >30 to <=35		
Number of patients in analysis set	361	398
Number of analysed patients	361	398
Number of patients with event [N(%)]	16 (4.4)	18 (4.5)
Time at risk for event [years]	461.6	512.9
Incidence rate [patients with events per 100 patient years at risk]	3.47	3.51
95% confidence interval	(1.98, 5.36)	(2.08, 5.31)
Comparison vs Placebo*		
Hazard ratio		1.04
95% confidence interval		(0.53,2.03)
p-value		0.9202

* Based on a Cox regression model with terms for age (p=0.1953), baseline eGFR (CKD-EPI) (p=0.0040), region (p=0.7987), sex (p=0.3156), baseline diabetes status (3 cat.) (p=0.0754), Treatment (p=0.2421), baseline LVEF (3 cat.) (p=0.2117) and Treatment by baseline LVEF (3 cat.) interaction (p=0.2968).
The p-value for treatment by subgroup interaction trend test is 0.1945.

Table R.1.1.4.15: 1 Cox reg. for time to first adjudicated heart failure hospitalisation requiring ICU or CCU stay by bl. LVEF (3 cat.) - RS (trial 1245.121)

Subgroup Description	Placebo	Empa 10mg
baseline LVEF (3 cat.): >35		
Number of patients in analysis set	114	128
Number of analysed patients	114	128
Number of patients with event [N(%)]	8 (7.0)	7 (5.5)
Time at risk for event [years]	135.8	152.8
Incidence rate [patients with events per 100 patient years at risk]	5.89	4.58
95% confidence interval	(2.54,10.62)	(1.84, 8.55)
Comparison vs Placebo*		
Hazard ratio		0.78
95% confidence interval		(0.28,2.16)
p-value		0.6353

* Based on a Cox regression model with terms for age (p=0.1953), baseline eGFR (CKD-EPI) (p=0.0040), region (p=0.7987), sex (p=0.3156), baseline diabetes status (3 cat.) (p=0.0754), Treatment (p=0.2421), baseline LVEF (3 cat.) (p=0.2117) and Treatment by baseline LVEF (3 cat.) interaction (p=0.2968).
The p-value for treatment by subgroup interaction trend test is 0.1945.

R.1.1.4.16 Subgroup analysis by bl. NTproBNP </>= median (median based on total patients)

Table R.1.1.4.16: 1 Cox reg. for time to first adjudicated heart failure hospitalisation requiring ICU or CCU stay by bl. NTproBNP (<median,>= median) (median based on total patients) - RS (trial 1245.121)

Subgroup Description	Placebo	Empa 10mg
Baseline NTproBNP: < median		
Number of patients in analysis set	920	942
Number of analysed patients	920	942
Number of patients with event [N(%)]	44 (4.8)	21 (2.2)
Time at risk for event [years]	1225.4	1262.7
Incidence rate [patients with events per 100 patient years at risk]	3.59	1.66
95% confidence interval	(2.61, 4.73)	(1.03, 2.45)
Comparison vs Placebo*		
Hazard ratio		0.47
95% confidence interval		(0.28,0.79)
p-value		0.0041
Baseline NTproBNP: >= median		
Number of patients in analysis set	946	920
Number of analysed patients	946	920
Number of patients with event [N(%)]	92 (9.7)	68 (7.4)
Time at risk for event [years]	1153.2	1143.4
Incidence rate [patients with events per 100 patient years at risk]	7.98	5.95
95% confidence interval	(6.43, 9.69)	(4.62, 7.44)
Comparison vs Placebo*		
Hazard ratio		0.76
95% confidence interval		(0.55,1.04)
p-value		0.0860

* Based on a Cox regression model with terms for age (p=0.1781), baseline eGFR (CKD-EPI) (p=0.1224), region (p=0.9107), sex (p=0.3876), baseline diabetes status (3 cat.) (p=0.0740), baseline LVEF (3 cat.) (p=0.1015), Treatment (p=0.0008), Baseline NTproBNP (p<0.0001) and Treatment by Baseline NTproBNP interaction (p=0.1163).
2 patients were excluded as the subgroup variable was missing.

Median: 1910 [pg/mL]

R.1.1.5

R.1.1.5 Time to all-cause mortality

R.1.1.5.1

Figure R.1.1.5.1: 1

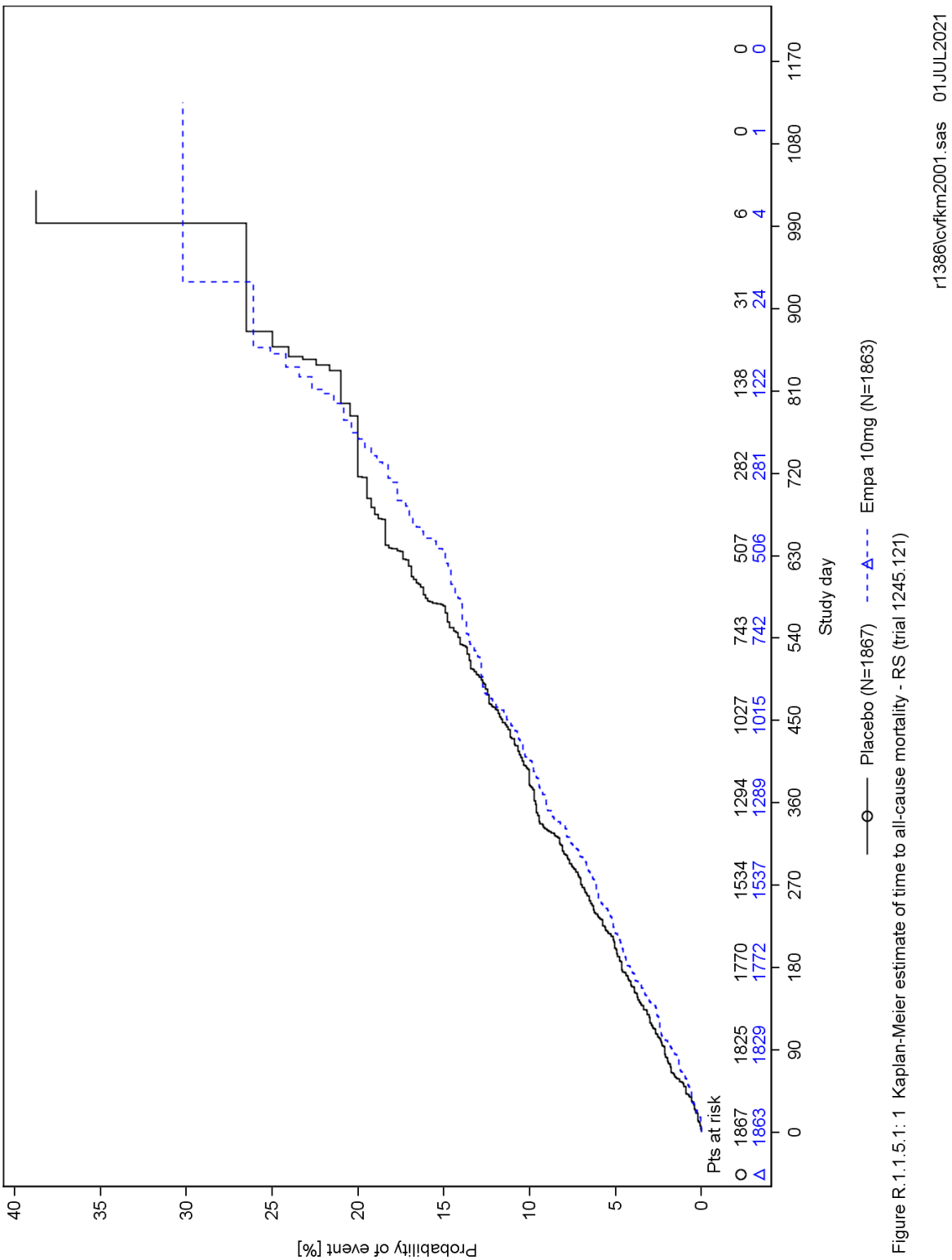

Figure R.1.1.5.1: 1 Kaplan-Meier estimate of time to all-cause mortality - RS (trial 1245.121)

Table R.1.1.5.1: 1 Cox regr. for time to all-cause mortality - RS (trial 1245.121)

	Placebo	Empa 10mg
Number of patients in analysis set	1867	1863
Number of analysed patients	1867	1863
Number of patients with event [N(%)]	266 (14.2)	249 (13.4)
Time at risk for event [years]	2483.3	2475.9
Incidence rate [patients with events per 100 patient years at risk]	10.71	10.06
95% confidence interval	(9.46, 12.04)	(8.85, 11.34)
Comparison vs Placebo*		
Hazard ratio		0.92
95% confidence interval		(0.77,1.10)
p-value		0.3536
Time to event [days]**		
2.5% percentile	104	125
5.0% percentile	201	217
7.5% percentile	289	314
10.0% percentile	379	406
Patients with events [%]**		
1 year	9.8	9.0
2 years	20.0	18.6

* Based on a Cox regression model with terms for age (p=0.0016), baseline eGFR (CKD-EPI) (p=0.0003), sex (p=0.0163), region (p=0.0002), baseline diabetes status (3 cat.) (p=0.0122), baseline LVEF (3 cat.) (p=0.9484) and Treatment (p=0.3536).
**Based on Kaplan-Meier estimates.

R.1.1.5.2

R.1.1.5.2 Subgroup analysis by sex

Table R.1.1.5.2: 1

Table R.1.1.5.2: 1 Cox regr. for time to all-cause mortality by sex - RS (trial 1245.121)

Subgroup Description	Placebo	Empa 10mg
Sex: Male		
Number of patients in analysis set	1411	1426
Number of analysed patients	1411	1426
Number of patients with event [N(%)]	206 (14.6)	201 (14.1)
Time at risk for event [years]	1884.1	1881.6
Incidence rate [patients with events per 100 patient years at risk]	10.93	10.68
95% confidence interval	(9.49, 12.48)	(9.26, 12.21)
Comparison vs Placebo*		
Hazard ratio		0.95
95% confidence interval		(0.78,1.16)
p-value		0.6115
Sex: Female		
Number of patients in analysis set	456	437
Number of analysed patients	456	437
Number of patients with event [N(%)]	60 (13.2)	48 (11.0)
Time at risk for event [years]	599.2	594.2
Incidence rate [patients with events per 100 patient years at risk]	10.01	8.08
95% confidence interval	(7.64, 12.70)	(5.96, 10.52)
Comparison vs Placebo*		
Hazard ratio		0.82
95% confidence interval		(0.56,1.20)
p-value		0.3013

* Based on a Cox regression model with terms for age (p=0.0018), baseline eGFR (CKD-EPI) (p=0.0003), region (p=0.0003), baseline diabetes status (3 cat.) (p=0.0121), baseline LVEF (3 cat.) (p=0.9461), Treatment (p=0.2490), sex (p=0.0149) and Treatment by sex interaction (p=0.4917).

R.1.1.5.3

Table R.1.1.5.3: 1

Table R.1.1.5.3: 1 Cox regr. for time to all-cause mortality by age (2 cat.) - RS (trial 1245.121)

Subgroup Description	Placebo	Empa 10mg
Age [years]: < 65		
Number of patients in analysis set	740	675
Number of analysed patients	740	675
Number of patients with event [N(%)]	83 (11.2)	71 (10.5)
Time at risk for event [years]	986.0	892.1
Incidence rate [patients with events per 100 patient years at risk]	8.42	7.96
95% confidence interval	(6.70, 10.32)	(6.22, 9.91)
Comparison vs Placebo*		
Hazard ratio		0.99
95% confidence interval		(0.72,1.36)
p-value		0.9468
Age [years]: >= 65		
Number of patients in analysis set	1127	1188
Number of analysed patients	1127	1188
Number of patients with event [N(%)]	183 (16.2)	178 (15.0)
Time at risk for event [years]	1497.3	1583.8
Incidence rate [patients with events per 100 patient years at risk]	12.22	11.24
95% confidence interval	(10.52, 14.06)	(9.65, 12.95)
Comparison vs Placebo*		
Hazard ratio		0.90
95% confidence interval		(0.73,1.10)
p-value		0.2985

* Based on a Cox regression model with terms for baseline eGFR (CKD-EPI) (p<0.0001), sex (p=0.0184), region (p=0.0004), baseline diabetes status (3 cat.) (p=0.0152), baseline LVEF (3 cat.) (p=0.9715), Treatment (p=0.5326), age (2 cat.) (p=0.0313) and Treatment by age (2 cat.) interaction (p=0.6095).

R.1.1.5.4 Subgroup analysis by region (North America, Latin America, Europe, Asia, Other)

Table R.1.1.5.4: 1

Table R.1.1.5.4: 1 Cox regr. for time to all-cause mortality by region - RS (trial 1245.121)

Subgroup Description	Placebo	Empa 10mg
Region: North America		
Number of patients in analysis set	213	212
Number of analysed patients	213	212
Number of patients with event [N(%)]	39 (18.3)	34 (16.0)
Time at risk for event [years]	299.5	311.4
Incidence rate [patients with events per 100 patient years at risk]	13.02	10.92
95% confidence interval	(9.26, 17.42)	(7.56, 14.88)
Comparison vs Placebo*		
Hazard ratio		0.81
95% confidence interval		(0.51,1.29)
p-value		0.3773
Region: Latin America		
Number of patients in analysis set	645	641
Number of analysed patients	645	641
Number of patients with event [N(%)]	89 (13.8)	99 (15.4)
Time at risk for event [years]	778.6	766.4
Incidence rate [patients with events per 100 patient years at risk]	11.43	12.92
95% confidence interval	(9.18, 13.92)	(10.50, 15.58)
Comparison vs Placebo*		
Hazard ratio		1.10
95% confidence interval		(0.82,1.46)
p-value		0.5339

* Based on a Cox regression model with terms for age (p=0.0017), baseline eGFR (CKD-EPI) (p=0.0003), sex (p=0.0180), baseline diabetes status (3 cat.) (p=0.0121), baseline LVEF (3 cat.) (p=0.9621), Treatment (p=0.0651), region (p=0.0002) and Treatment by region interaction (p=0.3812).

Table R.1.1.5.4: 1 Cox regr. for time to all-cause mortality by region - RS (trial 1245.121)

Subgroup Description	Placebo	Empa 10mg
Region: Europe		
Number of patients in analysis set	677	676
Number of analysed patients	677	676
Number of patients with event [N(%)]	96 (14.2)	84 (12.4)
Time at risk for event [years]	932.6	929.7
Incidence rate [patients with events per 100 patient years at risk]	10.29	9.04
95% confidence interval	(8.34, 12.45)	(7.21, 11.07)
Comparison vs Placebo*		
Hazard ratio		0.87
95% confidence interval		(0.65,1.17)
p-value		0.3574
Region: Asia		
Number of patients in analysis set	245	248
Number of analysed patients	245	248
Number of patients with event [N(%)]	30 (12.2)	27 (10.9)
Time at risk for event [years]	353.1	349.6
Incidence rate [patients with events per 100 patient years at risk]	8.50	7.72
95% confidence interval	(5.73, 11.79)	(5.09, 10.90)
Comparison vs Placebo*		
Hazard ratio		0.92
95% confidence interval		(0.54,1.54)
p-value		0.7425

* Based on a Cox regression model with terms for age (p=0.0017), baseline eGFR (CKD-EPI) (p=0.0003), sex (p=0.0180), baseline diabetes status (3 cat.) (p=0.0121), baseline LVEF (3 cat.) (p=0.9621), Treatment (p=0.0651), region (p=0.0002) and Treatment by region interaction (p=0.3812).

Table R.1.1.5.4: 1

Table R.1.1.5.4: 1 Cox regr. for time to all-cause mortality by region - RS (trial 1245.121)

Subgroup Description	Placebo	Empa 10mg
Region: Other		
Number of patients in analysis set	87	86
Number of analysed patients	87	86
Number of patients with event [N(%)]	12 (13.8)	5 (5.8)
Time at risk for event [years]	119.5	118.8
Incidence rate [patients with events per 100 patient years at risk]	10.05	4.21
95% confidence interval	(5.19, 16.48)	(1.37, 8.62)
Comparison vs Placebo*		
Hazard ratio		0.41
95% confidence interval		(0.14,1.15)
p-value		0.0908

* Based on a Cox regression model with terms for age (p=0.0017), baseline eGFR (CKD-EPI) (p=0.0003), sex (p=0.0180), baseline diabetes status (3 cat.) (p=0.0121), baseline LVEF (3 cat.) (p=0.9621), Treatment (p=0.0651), region (p=0.0002) and Treatment by region interaction (p=0.3812).

R.1.1.5.5

R.1.1.5.5 Subgroup analysis by OECD member (Y/N)

Table R.1.1.5.5: 1 Cox regr. for time to all-cause mortality by OECD member (Y/N) - RS (trial 1245.121)

Subgroup Description	Placebo	Empa 10mg
OECD member: No		
Number of patients in analysis set	741	713
Number of analysed patients	741	713
Number of patients with event [N(%)]	103 (13.9)	106 (14.9)
Time at risk for event [years]	906.8	866.4
Incidence rate [patients with events per 100 patient years at risk]	11.36	12.24
95% confidence interval	(9.27, 13.66)	(10.02, 14.67)
Comparison vs Placebo*		
Hazard ratio		1.04
95% confidence interval		(0.79,1.36)
p-value		0.7915
OECD member: Yes		
Number of patients in analysis set	1126	1150
Number of analysed patients	1126	1150
Number of patients with event [N(%)]	163 (14.5)	143 (12.4)
Time at risk for event [years]	1576.6	1609.5
Incidence rate [patients with events per 100 patient years at risk]	10.34	8.88
95% confidence interval	(8.81, 11.99)	(7.49, 10.40)
Comparison vs Placebo*		
Hazard ratio		0.86
95% confidence interval		(0.68,1.07)
p-value		0.1724

* Based on a Cox regression model with terms for age (p=0.0005), baseline eGFR (CKD-EPI) (p=0.0001), sex (p=0.0215), baseline diabetes status (3 cat.) (p=0.0164), baseline LVEF (3 cat.) (p=0.9246), Treatment (p=0.5057), OECD Member (N) (p<0.0001) and Treatment by OECD Member (N) interaction (p=0.2837).

OECD member (yes/no) countries included:
Yes: United States, Canada, Mexico, Poland, Netherlands, Hungary, Germany, Czech Republic, Italy, France, Spain, United Kingdom, Belgium, Japan, Australia, 'Korea; Republic Of South Korea';
No: Brazil, Argentina, China, India.

R.1.1.5.6 Subgroup analysis by NYHA at baseline (II, III/IV - 2 cat.)

Table R.1.1.5.6: 1

Table R.1.1.5.6: 1 Cox regr. for time to all-cause mortality by baseline NYHA (2 cat.) - RS (trial 1245.121)

Subgroup Description	Placebo	Empa 10mg
Baseline NYHA: II		
Number of patients in analysis set	1401	1399
Number of analysed patients	1401	1399
Number of patients with event [N(%)]	164 (11.7)	161 (11.5)
Time at risk for event [years]	1877.2	1860.2
Incidence rate [patients with events per 100 patient years at risk]	8.74	8.66
95% confidence interval	(7.45, 10.12)	(7.37, 10.04)
Comparison vs Placebo*		
Hazard ratio		0.97
95% confidence interval		(0.78,1.21)
p-value		0.7794
Baseline NYHA: III/IV		
Number of patients in analysis set	466	464
Number of analysed patients	466	464
Number of patients with event [N(%)]	102 (21.9)	88 (19.0)
Time at risk for event [years]	606.1	615.7
Incidence rate [patients with events per 100 patient years at risk]	16.83	14.29
95% confidence interval	(13.72, 20.25)	(11.46, 17.43)
Comparison vs Placebo*		
Hazard ratio		0.84
95% confidence interval		(0.63,1.11)
p-value		0.2246

* Based on a Cox regression model with terms for age (p=0.0012), baseline eGFR (CKD-EPI) (p=0.0006), sex (p=0.0064), region (p=0.0001), baseline diabetes status (3 cat.) (p=0.0485), baseline LVEF (3 cat.) (p=0.9946), Treatment (p=0.2560), baseline NYHA (2 cat.) (p<0.0001) and Treatment by baseline NYHA (2 cat.) interaction (p=0.4258).

R.1.1.5.7

R.1.1.5.7 Subgroup analysis by diabetes at baseline

Table R.1.1.5.7: 1

Table R.1.1.5.7: 1 Cox regr. for time to all-cause mortality by diabetes at baseline (2 cat.) - RS (trial 1245.121)

Subgroup Description	Placebo	Empa 10mg
Baseline diabetes status: Diabetic		
Number of patients in analysis set	929	927
Number of analysed patients	929	927
Number of patients with event [N(%)]	149 (16.0)	142 (15.3)
Time at risk for event [years]	1247.1	1235.3
Incidence rate [patients with events per 100 patient years at risk]	11.95	11.50
95% confidence interval	(10.11, 13.94)	(9.68, 13.46)
Comparison vs Placebo*		
Hazard ratio		0.95
95% confidence interval		(0.76,1.20)
p-value		0.6692
Baseline diabetes status: Non-Diabetic		
Number of patients in analysis set	938	936
Number of analysed patients	938	936
Number of patients with event [N(%)]	117 (12.5)	107 (11.4)
Time at risk for event [years]	1236.3	1240.6
Incidence rate [patients with events per 100 patient years at risk]	9.46	8.63
95% confidence interval	(7.83, 11.25)	(7.07, 10.33)
Comparison vs Placebo*		
Hazard ratio		0.89
95% confidence interval		(0.68,1.15)
p-value		0.3663

* Based on a Cox regression model with terms for age (p=0.0017), baseline eGFR (CKD-EPI) (p=0.0004), sex (p=0.0156), region (p=0.0002), baseline LVEF (3 cat.) (p=0.9453), Treatment (p=0.3368), baseline diabetes status (2 cat.) (p=0.0046) and Treatment by baseline diabetes status (2 cat.) interaction (p=0.6903).

R.1.1.5.8 Subgroup analysis by BMI at baseline (<30, >=30)

Table R.1.1.5.8: 1 Cox regr. for time to all-cause mortality by baseline BMI [kg/m2] - RS (trial 1245.121)

Subgroup Description	Placebo	Empa 10mg
Baseline BMI [kg/m²]: <30		
Number of patients in analysis set	1300	1263
Number of analysed patients	1300	1263
Number of patients with event [N(%)]	198 (15.2)	172 (13.6)
Time at risk for event [years]	1749.4	1670.1
Incidence rate [patients with events per 100 patient years at risk]	11.32	10.30
95% confidence interval	(9.80, 12.95)	(8.82, 11.89)
Comparison vs Placebo*		
Hazard ratio		0.91
95% confidence interval		(0.74,1.11)
p-value		0.3464
Baseline BMI [kg/m²]: >=30		
Number of patients in analysis set	567	600
Number of analysed patients	567	600
Number of patients with event [N(%)]	68 (12.0)	77 (12.8)
Time at risk for event [years]	734.0	805.8
Incidence rate [patients with events per 100 patient years at risk]	9.26	9.56
95% confidence interval	(7.19, 11.59)	(7.54, 11.81)
Comparison vs Placebo*		
Hazard ratio		0.98
95% confidence interval		(0.71,1.36)
p-value		0.9235

* Based on a Cox regression model with terms for age (p=0.0039), baseline eGFR (CKD-EPI) (p=0.0003), sex (p=0.0195), region (p=0.0002), baseline diabetes status (3 cat.) (p=0.0075), baseline LVEF (3 cat.) (p=0.9471), Treatment (p=0.5613), baseline BMI (2 cat.) (p=0.1368) and Treatment by baseline BMI (2 cat.) interaction (p=0.6755).

R.1.1.5.9 Subgroup analysis by eGFR at baseline (<60, >=60)

Table R.1.1.5.9: 1 Cox regr. for time to all-cause mortality by baseline eGFR (2 cat.) - RS (trial 1245.121)

Subgroup Description	Placebo	Empa 10mg
Baseline eGFR (CKD-EPI) [mL/min/1.73m²]: >=60		
Number of patients in analysis set	960	969
Number of analysed patients	960	969
Number of patients with event [N(%)]	111 (11.6)	111 (11.5)
Time at risk for event [years]	1280.9	1287.5
Incidence rate [patients with events per 100 patient years at risk]	8.67	8.62
95% confidence interval	(7.13, 10.35)	(7.09, 10.30)
Comparison vs Placebo*		
Hazard ratio		0.97
95% confidence interval		(0.75,1.27)
p-value		0.8484
Baseline eGFR (CKD-EPI) [mL/min/1.73m²]: <60		
Number of patients in analysis set	906	893
Number of analysed patients	906	893
Number of patients with event [N(%)]	154 (17.0)	138 (15.5)
Time at risk for event [years]	1201.5	1187.1
Incidence rate [patients with events per 100 patient years at risk]	12.82	11.62
95% confidence interval	(10.87, 14.92)	(9.77, 13.64)
Comparison vs Placebo*		
Hazard ratio		0.89
95% confidence interval		(0.71,1.12)
p-value		0.3358

* Based on a Cox regression model with terms for age (p<0.0001), sex (p=0.0195), region (p=0.0003), baseline diabetes status (3 cat.) (p=0.0099), baseline LVEF (3 cat.) (p=0.9494), Treatment (p=0.4373), baseline eGFR (CKD-EPI) (2 cat.) (p=0.0350) and Treatment by baseline eGFR (CKD-EPI) (2 cat.) interaction (p=0.6249).
2 patients were excluded as the subgroup variable was missing.

R.1.1.5.10

Table R.1.1.5.10: 1

Table R.1.1.5.10: 1 Cox regr. for time to all-cause mortality by history of HHF within 12 months - RS (trial 1245.121)

Subgroup Description	Placebo	Empa 10mg
History of HHF (in the last 12 months): No		
Number of patients in analysis set	1293	1286
Number of analysed patients	1293	1286
Number of patients with event [N(%)]	171 (13.2)	159 (12.4)
Time at risk for event [years]	1769.9	1744.0
Incidence rate [patients with events per 100 patient years at risk]	9.66	9.12
95% confidence interval	(8.27, 11.16)	(7.75, 10.59)
Comparison vs Placebo*		
Hazard ratio		0.94
95% confidence interval		(0.75,1.16)
p-value		0.5536
History of HHF (in the last 12 months): Yes		
Number of patients in analysis set	574	577
Number of analysed patients	574	577
Number of patients with event [N(%)]	95 (16.6)	90 (15.6)
Time at risk for event [years]	713.4	731.8
Incidence rate [patients with events per 100 patient years at risk]	13.32	12.30
95% confidence interval	(10.77, 16.12)	(9.89, 14.97)
Comparison vs Placebo*		
Hazard ratio		0.87
95% confidence interval		(0.65,1.17)
p-value		0.3622

* Based on a Cox regression model with terms for age (p=0.0005), baseline eGFR (CKD-EPI) (p=0.0005), sex (p=0.0158), region (p<0.0001), baseline diabetes status (3 cat.) (p=0.0218), baseline LVEF (3 cat.) (p=0.9230), Treatment (p=0.2783), history of HHF (p<0.0001) and Treatment by history of HHF interaction (p=0.7074).

R.1.1.5.11

R.1.1.5.11 Subgroup analysis by cause of heart failure

Table R.1.1.5.11: 1 Cox regr. for time to all-cause mortality by cause of heart failure - RS (trial 1245.121)

Subgroup Description	Placebo	Empa 10mg
Cause of heart failure: Ischemic		
Number of patients in analysis set	946	983
Number of analysed patients	946	983
Number of patients with event [N(%)]	151 (16.0)	156 (15.9)
Time at risk for event [years]	1277.0	1315.3
Incidence rate [patients with events per 100 patient years at risk]	11.82	11.86
95% confidence interval	(10.01, 13.78)	(10.07, 13.79)
Comparison vs Placebo*		
Hazard ratio		0.99
95% confidence interval		(0.79,1.24)
p-value		0.9122
Cause of heart failure: Non-ischemic		
Number of patients in analysis set	921	880
Number of analysed patients	921	880
Number of patients with event [N(%)]	115 (12.5)	93 (10.6)
Time at risk for event [years]	1206.3	1160.5
Incidence rate [patients with events per 100 patient years at risk]	9.53	8.01
95% confidence interval	(7.87, 11.35)	(6.47, 9.72)
Comparison vs Placebo*		
Hazard ratio		0.82
95% confidence interval		(0.63,1.08)
p-value		0.1669

* Based on a Cox regression model with terms for age (p=0.0031), baseline eGFR (CKD-EPI) (p=0.0004), sex (p=0.0369), region (p<0.0001), baseline diabetes status (3 cat.) (p=0.0259), baseline LVEF (3 cat.) (p=0.9471), Treatment (p=0.2542), cause of heart failure (2 cat.) (p=0.0058) and Treatment by cause of heart failure (2 cat.) interaction (p=0.3177).

R.1.1.5.12 Subgroup analysis by heart failure physiology (LVEF <= 30% and NTproBNP<median; LVEF <= 30% and NTproBNP>=median; LVEF > 30%)

Table R.1.1.5.12: 1 Cox regr. for time to all-cause mortality by heart failure physiology (3 cat.)- RS (trial 1245.121)

Subgroup Description	Placebo	Empa 10mg
Heart failure physiology: LVEF <= 30% and NTproBNP < median		
Number of patients in analysis set	723	698
Number of analysed patients	723	698
Number of patients with event [N(%)]	62 (8.6)	64 (9.2)
Time at risk for event [years]	992.2	958.3
Incidence rate [patients with events per 100 patient years at risk]	6.25	6.68
95% confidence interval	(4.79, 7.90)	(5.14, 8.41)
Comparison vs Placebo*		
Hazard ratio		1.06
95% confidence interval		(0.75,1.50)
p-value		0.7501
Heart failure physiology: LVEF <= 30% and NTproBNP >= median		
Number of patients in analysis set	661	631
Number of analysed patients	661	631
Number of patients with event [N(%)]	142 (21.5)	102 (16.2)
Time at risk for event [years]	869.1	823.3
Incidence rate [patients with events per 100 patient years at risk]	16.34	12.39
95% confidence interval	(13.76, 19.13)	(10.10, 14.91)
Comparison vs Placebo*		
Hazard ratio		0.74
95% confidence interval		(0.57,0.95)
p-value		0.0207

* Based on a Cox regression model with terms for age (p=0.0008), baseline eGFR (CKD-EPI) (p=0.0122), sex (p=0.0171), region (p=0.0004), baseline diabetes status (3 cat.) (p=0.0225), Treatment (p=0.7228), heart failure physiology (p<0.0001) and Treatment by heart failure physiology interaction (p=0.0748).
16 patients were excluded as the subgroup variable was missing.
The p-value for treatment by subgroup interaction trend test is 0.8057.

Table R.1.1.5.12: 1 Cox regr. for time to all-cause mortality by heart failure physiology (3 cat.)- RS (trial 1245.121)

Subgroup Description	Placebo	Empa 10mg
Heart failure physiology: LVEF > 30%		
Number of patients in analysis set	475	526
Number of analysed patients	475	526
Number of patients with event [N(%)]	60 (12.6)	79 (15.0)
Time at risk for event [years]	611.7	686.7
Incidence rate [patients with events per 100 patient years at risk]	9.81	11.50
95% confidence interval	(7.49, 12.44)	(9.11, 14.18)
Comparison vs Placebo*		
Hazard ratio		1.16
95% confidence interval		(0.83,1.62)
p-value		0.3974

* Based on a Cox regression model with terms for age (p=0.0008), baseline eGFR (CKD-EPI) (p=0.0122), sex (p=0.0171), region (p=0.0004), baseline diabetes status (3 cat.) (p=0.0225), Treatment (p=0.7228), heart failure physiology (p<0.0001) and Treatment by heart failure physiology interaction (p=0.0748).
16 patients were excluded as the subgroup variable was missing.
The p-value for treatment by subgroup interaction trend test is 0.8057.

R.1.1.5.13

Table R.1.1.5.13: 1

Table R.1.1.5.13: 1 Cox regr. for time to all-cause mortality by baseline use of MRA (Y/N) - RS (trial 1245.121)

Subgroup Description	Placebo	Empa 10mg
Baseline use of MRA: No		
Number of patients in analysis set	512	557
Number of analysed patients	512	557
Number of patients with event [N(%)]	68 (13.3)	87 (15.6)
Time at risk for event [years]	704.3	780.6
Incidence rate [patients with events per 100 patient years at risk]	9.65	11.15
95% confidence interval	(7.50, 12.08)	(8.93, 13.61)
Comparison vs Placebo*		
Hazard ratio		1.15
95% confidence interval		(0.84,1.59)
p-value		0.3766
Baseline use of MRA: Yes		
Number of patients in analysis set	1355	1306
Number of analysed patients	1355	1306
Number of patients with event [N(%)]	198 (14.6)	162 (12.4)
Time at risk for event [years]	1779.0	1695.3
Incidence rate [patients with events per 100 patient years at risk]	11.13	9.56
95% confidence interval	(9.63, 12.73)	(8.14, 11.08)
Comparison vs Placebo*		
Hazard ratio		0.84
95% confidence interval		(0.68,1.03)
p-value		0.0954

* Based on a Cox regression model with terms for age (p=0.0013), baseline eGFR (CKD-EPI) (p=0.0003), sex (p=0.0152), region (p=0.0003), baseline diabetes status (3 cat.) (p=0.0112), baseline LVEF (3 cat.) (p=0.9602), Treatment (p=0.8615), baseline use of MRA (p=0.3780) and Treatment by baseline use of MRA interaction (p=0.0983).

R.1.1.5.14

Table R.1.1.5.14: 1 Cox regr. for time to all-cause mortality by baseline use of ARNi (Y/N) - RS (trial 1245.121)

Subgroup Description	Placebo	Empa 10mg
Baseline use of ARNi: No		
Number of patients in analysis set	1480	1523
Number of analysed patients	1480	1523
Number of patients with event [N(%)]	213 (14.4)	217 (14.2)
Time at risk for event [years]	1986.0	2056.1
Incidence rate [patients with events per 100 patient years at risk]	10.72	10.55
95% confidence interval	(9.33, 12.21)	(9.20, 12.00)
Comparison vs Placebo*		
Hazard ratio		0.96
95% confidence interval		(0.79,1.16)
p-value		0.6750
Baseline use of ARNi: Yes		
Number of patients in analysis set	387	340
Number of analysed patients	387	340
Number of patients with event [N(%)]	53 (13.7)	32 (9.4)
Time at risk for event [years]	497.3	419.8
Incidence rate [patients with events per 100 patient years at risk]	10.66	7.62
95% confidence interval	(7.98, 13.71)	(5.21, 10.48)
Comparison vs Placebo*		
Hazard ratio		0.73
95% confidence interval		(0.47,1.13)
p-value		0.1516

* Based on a Cox regression model with terms for age (p=0.0016), baseline eGFR (CKD-EPI) (p=0.0004), sex (p=0.0175), region (p=0.0003), baseline diabetes status (3 cat.) (p=0.0125), baseline LVEF (3 cat.) (p=0.9340), Treatment (p=0.1381), baseline use of ARNi (p=0.3040) and Treatment by baseline use of ARNi interaction (p=0.2499).

R.1.1.5.15 Subgroup analysis by bl. LVEF (<= 30%, >30% -<= 35% , > 35%)

Table R.1.1.5.15: 1 Cox regr. for time to all-cause mortality by bl. LVEF (3 cat.) - RS (trial 1245.121)

Subgroup Description	Placebo	Empa 10mg
Baseline LVEF: <=30		
Number of patients in analysis set	1392	1337
Number of analysed patients	1392	1337
Number of patients with event [N(%)]	206 (14.8)	170 (12.7)
Time at risk for event [years]	1871.6	1789.2
Incidence rate [patients with events per 100 patient years at risk]	11.01	9.50
95% confidence interval	(9.55, 12.56)	(8.13, 10.98)
Comparison vs Placebo*		
Hazard ratio		0.85
95% confidence interval		(0.69,1.04)
p-value		0.1082
Baseline LVEF: >30 to <=35		
Number of patients in analysis set	361	398
Number of analysed patients	361	398
Number of patients with event [N(%)]	46 (12.7)	60 (15.1)
Time at risk for event [years]	471.5	524.5
Incidence rate [patients with events per 100 patient years at risk]	9.76	11.44
95% confidence interval	(7.14, 12.77)	(8.73, 14.51)
Comparison vs Placebo*		
Hazard ratio		1.16
95% confidence interval		(0.79,1.70)
p-value		0.4579

* Based on a Cox regression model with terms for age (p=0.0015), baseline eGFR (CKD-EPI) (p=0.0003), sex (p=0.0165), region (p=0.0002), baseline diabetes status (3 cat.) (p=0.0119), Treatment (p=0.7505), baseline LVEF (3 cat.) (p=0.9367) and Treatment by baseline LVEF (3 cat.) interaction (p=0.2925).
The p-value for treatment by subgroup interaction trend test is 0.1404.

Table R.1.1.5.15: 1 Cox regr. for time to all-cause mortality by bl. LVEF (3 cat.) - RS (trial 1245.121)

Subgroup Description	Placebo	Empa 10mg
Baseline LVEF: >35		
Number of patients in analysis set	114	128
Number of analysed patients	114	128
Number of patients with event [N(%)]	14 (12.3)	19 (14.8)
Time at risk for event [years]	140.2	162.2
Incidence rate [patients with events per 100 patient years at risk]	9.98	11.72
95% confidence interval	(5.46, 15.85)	(7.05, 17.54)
Comparison vs Placebo*		
Hazard ratio		1.17
95% confidence interval		(0.58,2.33)
p-value		0.6635

* Based on a Cox regression model with terms for age (p=0.0015), baseline eGFR (CKD-EPI) (p=0.0003), sex (p=0.0165), region (p=0.0002), baseline diabetes status (3 cat.) (p=0.0119), Treatment (p=0.7505), baseline LVEF (3 cat.) (p=0.9367) and Treatment by baseline LVEF (3 cat.) interaction (p=0.2925).
The p-value for treatment by subgroup interaction trend test is 0.1404.

R.1.1.5.16 Subgroup analysis by bl. NTproBNP </>= median (median based on total patients)

Table R.1.1.5.16: 1 Cox regr. for time to all-cause mortality by bl. NTproBNP (<median, >= median) (median based on total patients) - RS (trial 1245.121)

Subgroup Description	Placebo	Empa 10mg
Baseline NTproBNP: < median		
Number of patients in analysis set	920	942
Number of analysed patients	920	942
Number of patients with event [N(%)]	82 (8.9)	86 (9.1)
Time at risk for event [years]	1264.5	1281.4
Incidence rate [patients with events per 100 patient years at risk]	6.48	6.71
95% confidence interval	(5.16, 7.96)	(5.37, 8.20)
Comparison vs Placebo*		
Hazard ratio		1.01
95% confidence interval		(0.75,1.37)
p-value		0.9396
Baseline NTproBNP: >= median		
Number of patients in analysis set	946	920
Number of analysed patients	946	920
Number of patients with event [N(%)]	183 (19.3)	163 (17.7)
Time at risk for event [years]	1217.9	1193.3
Incidence rate [patients with events per 100 patient years at risk]	15.03	13.66
95% confidence interval	(12.93, 17.28)	(11.64, 15.84)
Comparison vs Placebo*		
Hazard ratio		0.90
95% confidence interval		(0.73,1.11)
p-value		0.3395

* Based on a Cox regression model with terms for age (p=0.0022), baseline eGFR (CKD-EPI) (p=0.0344), sex (p=0.0231), region (p=0.0005), baseline diabetes status (3 cat.) (p=0.0131), baseline LVEF (3 cat.) (p=0.7456), Treatment (p=0.6279), baseline NTproBNP (2 cat.) (p<0.0001) and Treatment by baseline NTproBNP (2 cat.) interaction (p=0.5423).
2 patients were excluded as the subgroup variable was missing.

Median: 1910 [pg/mL]

R.1.1.6

R.1.1.6 Time to composite renal endpoint

R.1.1.6.1

Figure R.1.1.6.1: 1

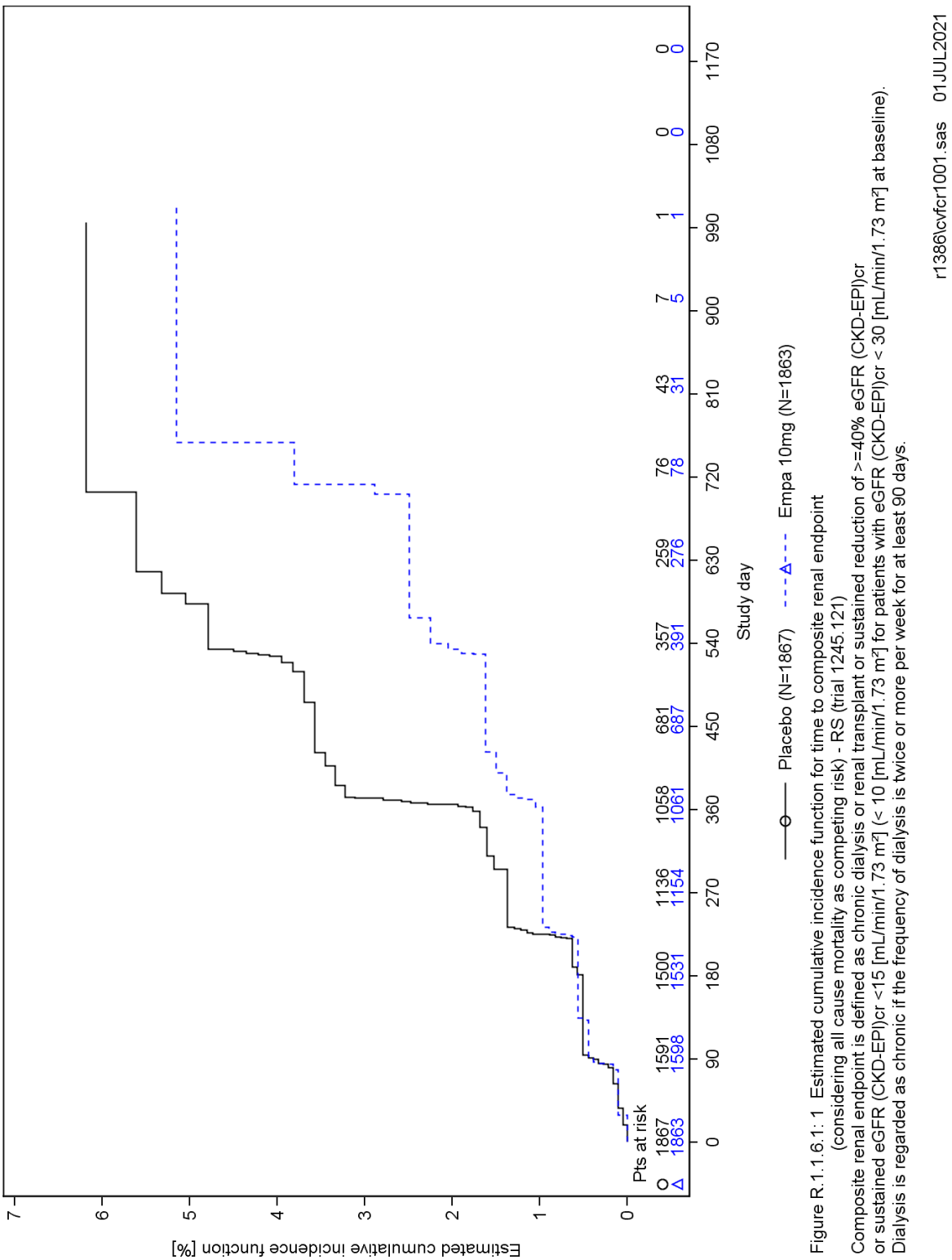

Figure R.1.1.6.1: 1 Estimated cumulative incidence function for time to composite renal endpoint (considering all cause mortality as competing risk) - RS (trial 1245.121)
Composite renal endpoint is defined as chronic dialysis or renal transplant or sustained reduction of >=40% eGFR (CKD-EPI)cr or sustained eGFR (CKD-EPI)cr <15 [mL/min/1.73 m²] (< 10 [mL/min/1.73 m²] for patients with eGFR (CKD-EPI)cr < 30 [mL/min/1.73 m²] at baseline).
Dialysis is regarded as chronic if the frequency of dialysis is twice or more per week for at least 90 days.

Table R.1.1.6.1: 1 Cox regr. for time to composite renal endpoint - RS (trial 1245.121)

	Placebo	Empa 10mg
Number of patients in analysis set	1867	1863
Number of analysed patients	1867	1863
Number of patients with event [N(%)]	58 (3.1)	30 (1.6)
Time at risk for event [years]	1889.7	1917.2
Incidence rate [patients with events per 100 patient years at risk]	3.07	1.56
95% confidence interval	(2.33, 3.91)	(1.06, 2.17)
Comparison vs Placebo*		
Hazard ratio		0.50
95% confidence interval		(0.32,0.77)
p-value		0.0019
Time to event [days]**		
2.5% percentile	367	539
5.0% percentile	531	757
7.5% percentile	NC.	NC.
10.0% percentile	NC.	NC.
Patients with events [%]**		
1 year	2.5	1.1
2 years	7.1	4.4

* Based on a Cox regression model with terms for age (p=0.8636), baseline eGFR (CKD-EPI) (p=0.1020), sex (p=0.5018), region (p=0.0549), baseline diabetes status (3 cat.) (p=0.0015), baseline LVEF (3 cat.) (p=0.0093) and Treatment (p=0.0019).
**Based on Kaplan-Meier estimates.
NC. = Not calculated.

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.

R.1.1.6.2

R.1.1.6.2 Subgroup analysis by sex

Table R.1.1.6.2: 1

Table R.1.1.6.2: 1 Cox regr. for time to composite renal endpoint by sex - RS (trial 1245.121)

Subgroup Description	Placebo	Empa 10mg
Sex: Male		
Number of patients in analysis set	1411	1426
Number of analysed patients	1411	1426
Number of patients with event [N(%)]	42 (3.0)	22 (1.5)
Time at risk for event [years]	1446.5	1475.5
Incidence rate [patients with events per 100 patient years at risk]	2.90	1.49
95% confidence interval	(2.09, 3.85)	(0.93, 2.18)
Comparison vs Placebo*		
Hazard ratio		0.51
95% confidence interval		(0.30,0.85)
p-value		0.0097
Sex: Female		
Number of patients in analysis set	456	437
Number of analysed patients	456	437
Number of patients with event [N(%)]	16 (3.5)	8 (1.8)
Time at risk for event [years]	443.2	441.8
Incidence rate [patients with events per 100 patient years at risk]	3.61	1.81
95% confidence interval	(2.06, 5.58)	(0.78, 3.26)
Comparison vs Placebo*		
Hazard ratio		0.48
95% confidence interval		(0.20,1.12)
p-value		0.0894

* Based on a Cox regression model with terms for age (p=0.8613), baseline eGFR (CKD-EPI) (p=0.1023), region (p=0.0557), baseline diabetes status (3 cat.) (p=0.0015), baseline LVEF (3 cat.) (p=0.0093), Treatment (p=0.0051), sex (p=0.5459) and Treatment by sex interaction (p=0.9136).

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.

R.1.1.6.3

Table R.1.1.6.3: 1 Cox regr. for time to composite renal endpoint by age (2 cat.) - RS (trial 1245.121)

Subgroup Description	Placebo	Empa 10mg
Age [years]: < 65		
Number of patients in analysis set	740	675
Number of analysed patients	740	675
Number of patients with event [N(%)]	25 (3.4)	11 (1.6)
Time at risk for event [years]	746.8	686.6
Incidence rate [patients with events per 100 patient years at risk]	3.35	1.60
95% confidence interval	(2.17, 4.78)	(0.80, 2.68)
Comparison vs Placebo*		
Hazard ratio		0.49
95% confidence interval		(0.24,1.00)
p-value		0.0500
Age [years]: >= 65		
Number of patients in analysis set	1127	1188
Number of analysed patients	1127	1188
Number of patients with event [N(%)]	33 (2.9)	19 (1.6)
Time at risk for event [years]	1142.9	1230.6
Incidence rate [patients with events per 100 patient years at risk]	2.89	1.54
95% confidence interval	(1.99, 3.95)	(0.93, 2.31)
Comparison vs Placebo*		
Hazard ratio		0.51
95% confidence interval		(0.29,0.89)
p-value		0.0186

* Based on a Cox regression model with terms for baseline eGFR (CKD-EPI) (p=0.0642), sex (p=0.5019), region (p=0.0629), baseline diabetes status (3 cat.) (p=0.0016), baseline LVEF (3 cat.) (p=0.0102), Treatment (p=0.0027), age (2 cat.) (p=0.5492) and Treatment by age (2 cat.) interaction (p=0.9427).

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.

R.1.1.6.4 Subgroup analysis by region (North America, Latin America, Europe, Asia, Other)

Table R.1.1.6.4: 1 Cox regr. for time to composite renal endpoint by region - RS (trial 1245.121)

Subgroup Description	Placebo	Empa 10mg
Region: North America		
Number of patients in analysis set	213	212
Number of analysed patients	213	212
Number of patients with event [N(%)]	6 (2.8)	8 (3.8)
Time at risk for event [years]	211.4	239.0
Incidence rate [patients with events per 100 patient years at risk]	2.84	3.35
95% confidence interval	(1.04, 5.52)	(1.44, 6.03)
Comparison vs Placebo*		
Hazard ratio		1.24
95% confidence interval		(0.43,3.59)
p-value		0.6949
Region: Latin America		
Number of patients in analysis set	645	641
Number of analysed patients	645	641
Number of patients with event [N(%)]	22 (3.4)	15 (2.3)
Time at risk for event [years]	598.3	591.4
Incidence rate [patients with events per 100 patient years at risk]	3.68	2.54
95% confidence interval	(2.30, 5.37)	(1.42, 3.97)
Comparison vs Placebo*		
Hazard ratio		0.67
95% confidence interval		(0.35,1.30)
p-value		0.2350

* Based on a Cox regression model with terms for age (p=0.7486), baseline eGFR (CKD-EPI) (p=0.0917), sex (p=0.5334), baseline diabetes status (3 cat.) (p=0.0012), baseline LVEF (3 cat.) (p=0.0076), Treatment (p=0.9764), region (p=0.0476) and Treatment by region interaction (p=0.1395).
NC. = Not calculated, some results could not be produced.

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.

Table R.1.1.6.4: 1 Cox regr. for time to composite renal endpoint by region - RS (trial 1245.121)

Subgroup Description	Placebo	Empa 10mg
Region: Europe		
Number of patients in analysis set	677	676
Number of analysed patients	677	676
Number of patients with event [N(%)]	23 (3.4)	5 (0.7)
Time at risk for event [years]	714.7	721.6
Incidence rate [patients with events per 100 patient years at risk]	3.22	0.69
95% confidence interval	(2.04, 4.66)	(0.22, 1.42)
Comparison vs Placebo*		
Hazard ratio		0.21
95% confidence interval		(0.08,0.54)
p-value		0.0014
Region: Asia		
Number of patients in analysis set	245	248
Number of analysed patients	245	248
Number of patients with event [N(%)]	6 (2.4)	2 (0.8)
Time at risk for event [years]	280.5	283.1
Incidence rate [patients with events per 100 patient years at risk]	2.14	0.71
95% confidence interval	(0.79, 4.16)	(0.09, 1.97)
Comparison vs Placebo*		
Hazard ratio		0.32
95% confidence interval		(0.07,1.61)
p-value		0.1673

* Based on a Cox regression model with terms for age (p=0.7486), baseline eGFR (CKD-EPI) (p=0.0917), sex (p=0.5334), baseline diabetes status (3 cat.) (p=0.0012), baseline LVEF (3 cat.) (p=0.0076), Treatment (p=0.9764), region (p=0.0476) and Treatment by region interaction (p=0.1395).
NC. = Not calculated, some results could not be produced.

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.

Table R.1.1.6.4: 1 Cox regr. for time to composite renal endpoint by region - RS (trial 1245.121)

Subgroup Description	Placebo	Empa 10mg
Region: Other		
Number of patients in analysis set	87	86
Number of analysed patients	87	86
Number of patients with event [N(%)]	1 (1.1)	0
Time at risk for event [years]	84.9	82.1
Incidence rate [patients with events per 100 patient years at risk]	1.18	0.00
95% confidence interval	(0.03, 4.34)	NC.
Comparison vs Placebo*		
Hazard ratio		NC.
95% confidence interval		NC.
p-value		NC.

* Based on a Cox regression model with terms for age (p=0.7486), baseline eGFR (CKD-EPI) (p=0.0917), sex (p=0.5334), baseline diabetes status (3 cat.) (p=0.0012), baseline LVEF (3 cat.) (p=0.0076), Treatment (p=0.9764), region (p=0.0476) and Treatment by region interaction (p=0.1395).
NC. = Not calculated, some results could not be produced.

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.

R.1.1.6.5

R.1.1.6.5 Subgroup analysis by OECD member (Y/N)

Table R.1.1.6.5: 1 Cox regr. for time to composite renal endpoint by OECD member (Y/N) - RS (trial 1245.121)

Subgroup Description	Placebo	Empa 10mg
OECD member: No		
Number of patients in analysis set	741	713
Number of analysed patients	741	713
Number of patients with event [N(%)]	22 (3.0)	15 (2.1)
Time at risk for event [years]	682.1	654.1
Incidence rate [patients with events per 100 patient years at risk]	3.23	2.29
95% confidence interval	(2.02, 4.71)	(1.28, 3.59)
Comparison vs Placebo*		
Hazard ratio		0.68
95% confidence interval		(0.35,1.32)
p-value		0.2590
OECD member: Yes		
Number of patients in analysis set	1126	1150
Number of analysed patients	1126	1150
Number of patients with event [N(%)]	36 (3.2)	15 (1.3)
Time at risk for event [years]	1207.6	1263.1
Incidence rate [patients with events per 100 patient years at risk]	2.98	1.19
95% confidence interval	(2.09, 4.03)	(0.66, 1.86)
Comparison vs Placebo*		
Hazard ratio		0.39
95% confidence interval		(0.21,0.72)
p-value		0.0023

* Based on a Cox regression model with terms for age (p=0.9324), baseline eGFR (CKD-EPI) (p=0.0725), sex (p=0.3266), baseline diabetes status (3 cat.) (p=0.0018), baseline LVEF (3 cat.) (p=0.0085), Treatment (p=0.0038), OECD Member (N) (p=0.0492) and Treatment by OECD Member (N) interaction (p=0.2217).

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.
OECD member (yes/no) countries included:
Yes: United States, Canada, Mexico, Poland, Netherlands, Hungary, Germany, Czech Republic, Italy, France, Spain, United Kingdom, Belgium, Japan, Australia, 'Korea; Republic Of South Korea';
No: Brazil, Argentina, China, India.

R.1.1.6.6

R.1.1.6.6 Subgroup analysis by NYHA at baseline (II, III/IV - 2 cat.)

Table R.1.1.6.6: 1 Cox regr. for time to composite renal endpoint by baseline NYHA (2 cat.) - RS (trial 1245.121)

Subgroup Description	Placebo	Empa 10mg
Baseline NYHA: II		
Number of patients in analysis set	1401	1399
Number of analysed patients	1401	1399
Number of patients with event [N(%)]	39 (2.8)	18 (1.3)
Time at risk for event [years]	1449.3	1454.5
Incidence rate [patients with events per 100 patient years at risk]	2.69	1.24
95% confidence interval	(1.91, 3.60)	(0.73, 1.87)
Comparison vs Placebo*		
Hazard ratio		0.45
95% confidence interval		(0.26,0.79)
p-value		0.0051
Baseline NYHA: III/IV		
Number of patients in analysis set	466	464
Number of analysed patients	466	464
Number of patients with event [N(%)]	19 (4.1)	12 (2.6)
Time at risk for event [years]	440.4	462.7
Incidence rate [patients with events per 100 patient years at risk]	4.31	2.59
95% confidence interval	(2.60, 6.46)	(1.34, 4.25)
Comparison vs Placebo*		
Hazard ratio		0.59
95% confidence interval		(0.29,1.21)
p-value		0.1500

* Based on a Cox regression model with terms for age (p=0.8928), baseline eGFR (CKD-EPI) (p=0.1106), sex (p=0.5702), region (p=0.0598), baseline diabetes status (3 cat.) (p=0.0025), baseline LVEF (3 cat.) (p=0.0112), Treatment (p=0.0044), baseline NYHA (2 cat.) (p=0.0432) and Treatment by baseline NYHA (2 cat.) interaction (p=0.5662).

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.

R.1.1.6.7

R.1.1.6.7 Subgroup analysis by diabetes at baseline

Table R.1.1.6.7: 1 Cox regr. for time to composite renal endpoint by diabetes at baseline (2 cat.) - RS (trial 1245.121)

Subgroup Description	Placebo	Empa 10mg
Baseline diabetes status: Diabetic		
Number of patients in analysis set	929	927
Number of analysed patients	929	927
Number of patients with event [N(%)]	39 (4.2)	22 (2.4)
Time at risk for event [years]	934.5	958.1
Incidence rate [patients with events per 100 patient years at risk]	4.17	2.30
95% confidence interval	(2.97, 5.58)	(1.44, 3.35)
Comparison vs Placebo*		
Hazard ratio		0.53
95% confidence interval		(0.31,0.90)
p-value		0.0179
Baseline diabetes status: Non-Diabetic		
Number of patients in analysis set	938	936
Number of analysed patients	938	936
Number of patients with event [N(%)]	19 (2.0)	8 (0.9)
Time at risk for event [years]	955.2	959.2
Incidence rate [patients with events per 100 patient years at risk]	1.99	0.83
95% confidence interval	(1.20, 2.98)	(0.36, 1.50)
Comparison vs Placebo*		
Hazard ratio		0.42
95% confidence interval		(0.19,0.97)
p-value		0.0422

* Based on a Cox regression model with terms for age (p=0.8503), baseline eGFR (CKD-EPI) (p=0.1058), sex (p=0.5212), region (p=0.0523), baseline LVEF (3 cat.) (p=0.0093), Treatment (p=0.0029), baseline diabetes status (2 cat.) (p=0.0005) and Treatment by baseline diabetes status (2 cat.) interaction (p=0.6516).

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.

R.1.1.6.8 Subgroup analysis by BMI at baseline (<30, >=30)

Table R.1.1.6.8: 1 Cox regr. for time to composite renal endpoint by baseline BMI [kg/m2] - RS (trial 1245.121)

Subgroup Description	Placebo	Empa 10mg
Baseline BMI [kg/m²]: <30		
Number of patients in analysis set	1300	1263
Number of analysed patients	1300	1263
Number of patients with event [N(%)]	33 (2.5)	16 (1.3)
Time at risk for event [years]	1344.2	1291.5
Incidence rate [patients with events per 100 patient years at risk]	2.45	1.24
95% confidence interval	(1.69, 3.36)	(0.71, 1.92)
Comparison vs Placebo*		
Hazard ratio		0.51
95% confidence interval		(0.28,0.92)
p-value		0.0261
Baseline BMI [kg/m²]: >=30		
Number of patients in analysis set	567	600
Number of analysed patients	567	600
Number of patients with event [N(%)]	25 (4.4)	14 (2.3)
Time at risk for event [years]	545.5	625.7
Incidence rate [patients with events per 100 patient years at risk]	4.58	2.24
95% confidence interval	(2.97, 6.55)	(1.22, 3.55)
Comparison vs Placebo*		
Hazard ratio		0.45
95% confidence interval		(0.24,0.88)
p-value		0.0185

* Based on a Cox regression model with terms for age (p=0.8556), baseline eGFR (CKD-EPI) (p=0.1154), sex (p=0.5709), region (p=0.0698), baseline diabetes status (3 cat.) (p=0.0038), baseline LVEF (3 cat.) (p=0.0085), Treatment (p=0.0012), baseline BMI (2 cat.) (p=0.0517) and Treatment by baseline BMI (2 cat.) interaction (p=0.8055).

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.

R.1.1.6.9 Subgroup analysis by eGFR at baseline (<60, >=60)

Table R.1.1.6.9: 1 Cox regr. for time to composite renal endpoint by baseline eGFR (2 cat.) - RS (trial 1245.121)

Subgroup Description	Placebo	Empa 10mg
Baseline eGFR (CKD-EPI) [mL/min/1.73m²]: >=60		
Number of patients in analysis set	960	969
Number of analysed patients	960	969
Number of patients with event [N(%)]	26 (2.7)	13 (1.3)
Time at risk for event [years]	974.5	995.5
Incidence rate [patients with events per 100 patient years at risk]	2.67	1.31
95% confidence interval	(1.74, 3.79)	(0.70, 2.11)
Comparison vs Placebo*		
Hazard ratio		0.47
95% confidence interval		(0.24,0.91)
p-value		0.0250
Baseline eGFR (CKD-EPI) [mL/min/1.73m²]: <60		
Number of patients in analysis set	906	893
Number of analysed patients	906	893
Number of patients with event [N(%)]	32 (3.5)	17 (1.9)
Time at risk for event [years]	915.3	921.8
Incidence rate [patients with events per 100 patient years at risk]	3.50	1.84
95% confidence interval	(2.39, 4.81)	(1.07, 2.82)
Comparison vs Placebo*		
Hazard ratio		0.53
95% confidence interval		(0.29,0.96)
p-value		0.0347

* Based on a Cox regression model with terms for age (p=0.8556), sex (p=0.4873), region (p=0.0521), baseline diabetes status (3 cat.) (p=0.0013), baseline LVEF (3 cat.) (p=0.0086), Treatment (p=0.0021), baseline eGFR (CKD-EPI) (2 cat.) (p=0.2156) and Treatment by baseline eGFR (CKD-EPI) (2 cat.) interaction (p=0.7775).
2 patients were excluded as the subgroup variable was missing.

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.

R.1.1.6.10

Table R.1.1.6.10: 1 Cox regr. for time to composite renal endpoint by history of HHF within 12 months - RS (trial 1245.121)

Subgroup Description	Placebo	Empa 10mg
History of HHF (in the last 12 months): No		
Number of patients in analysis set	1293	1286
Number of analysed patients	1293	1286
Number of patients with event [N(%)]	31 (2.4)	21 (1.6)
Time at risk for event [years]	1358.5	1367.9
Incidence rate [patients with events per 100 patient years at risk]	2.28	1.54
95% confidence interval	(1.55, 3.15)	(0.95, 2.26)
Comparison vs Placebo*		
Hazard ratio		0.66
95% confidence interval		(0.38,1.15)
p-value		0.1431
History of HHF (in the last 12 months): Yes		
Number of patients in analysis set	574	577
Number of analysed patients	574	577
Number of patients with event [N(%)]	27 (4.7)	9 (1.6)
Time at risk for event [years]	531.2	549.4
Incidence rate [patients with events per 100 patient years at risk]	5.08	1.64
95% confidence interval	(3.35, 7.17)	(0.75, 2.87)
Comparison vs Placebo*		
Hazard ratio		0.31
95% confidence interval		(0.15,0.66)
p-value		0.0023

* Based on a Cox regression model with terms for age (p=0.9236), baseline eGFR (CKD-EPI) (p=0.1117), sex (p=0.5468), region (p=0.0280), baseline diabetes status (3 cat.) (p=0.0029), baseline LVEF (3 cat.) (p=0.0174), Treatment (p=0.0009), history of HHF (p=0.0614) and Treatment by history of HHF interaction (p=0.1123).

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.

R.1.1.6.11

Table R.1.1.6.11: 1 Cox regr. for time to composite renal endpoint by cause of heart failure - RS (trial 1245.121)

Subgroup Description	Placebo	Empa 10mg
Cause of heart failure: Ischemic		
Number of patients in analysis set	946	983
Number of analysed patients	946	983
Number of patients with event [N(%)]	36 (3.8)	17 (1.7)
Time at risk for event [years]	976.6	1025.9
Incidence rate [patients with events per 100 patient years at risk]	3.69	1.66
95% confidence interval	(2.58, 4.98)	(0.97, 2.53)
Comparison vs Placebo*		
Hazard ratio		0.42
95% confidence interval		(0.24,0.75)
p-value		0.0034
Cause of heart failure: Non-ischemic		
Number of patients in analysis set	921	880
Number of analysed patients	921	880
Number of patients with event [N(%)]	22 (2.4)	13 (1.5)
Time at risk for event [years]	913.1	891.3
Incidence rate [patients with events per 100 patient years at risk]	2.41	1.46
95% confidence interval	(1.51, 3.52)	(0.78, 2.35)
Comparison vs Placebo*		
Hazard ratio		0.62
95% confidence interval		(0.31,1.23)
p-value		0.1736

* Based on a Cox regression model with terms for age (p=0.7635), baseline eGFR (CKD-EPI) (p=0.0955), sex (p=0.3641), region (p=0.0367), baseline diabetes status (3 cat.) (p=0.0031), baseline LVEF (3 cat.) (p=0.0091), Treatment (p=0.0034), cause of heart failure (2 cat.) (p=0.2165) and Treatment by cause of heart failure (2 cat.) interaction (p=0.3991).

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.

R.1.1.6.12 Subgroup analysis by heart failure physiology (LVEF <= 30% and NTproBNP<median; LVEF <= 30% and NTproBNP>=median; LVEF > 30%)

Table R.1.1.6.12: 1 Cox regr. for time to composite renal endpoint by heart failure physiology - RS (trial 1245.121)

Subgroup Description	Placebo	Empa 10mg
Heart failure physiology: LVEF <= 30% and NTproBNP < median		
Number of patients in analysis set	723	698
Number of analysed patients	723	698
Number of patients with event [N(%)]	17 (2.4)	12 (1.7)
Time at risk for event [years]	769.2	750.4
Incidence rate [patients with events per 100 patient years at risk]	2.21	1.60
95% confidence interval	(1.29, 3.38)	(0.83, 2.62)
Comparison vs Placebo*		
Hazard ratio		0.70
95% confidence interval		(0.33,1.47)
p-value		0.3455
Heart failure physiology: LVEF <= 30% and NTproBNP >= median		
Number of patients in analysis set	661	631
Number of analysed patients	661	631
Number of patients with event [N(%)]	30 (4.5)	12 (1.9)
Time at risk for event [years]	649.8	634.4
Incidence rate [patients with events per 100 patient years at risk]	4.62	1.89
95% confidence interval	(3.11, 6.41)	(0.98, 3.10)
Comparison vs Placebo*		
Hazard ratio		0.39
95% confidence interval		(0.20,0.76)
p-value		0.0058

* Based on a Cox regression model with terms for age (p=0.8036), baseline eGFR (CKD-EPI) (p=0.1600), sex (p=0.5362), region (p=0.0503), baseline diabetes status (3 cat.) (p=0.0012), Treatment (p=0.0058), heart failure physiology (p=0.0928) and Treatment by heart failure physiology interaction (p=0.5129).
16 patients were excluded as the subgroup variable was missing.
The p-value for treatment by subgroup interaction trend test is 0.5054.

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.

Table R.1.1.6.12: 1

Table R.1.1.6.12: 1 Cox regr. for time to composite renal endpoint by heart failure physiology - RS (trial 1245.121)

Subgroup Description	Placebo	Empa 10mg
Heart failure physiology: LVEF > 30%		
Number of patients in analysis set	475	526
Number of analysed patients	475	526
Number of patients with event [N(%)]	11 (2.3)	6 (1.1)
Time at risk for event [years]	465.8	528.2
Incidence rate [patients with events per 100 patient years at risk]	2.36	1.14
95% confidence interval	(1.18, 3.95)	(0.42, 2.21)
Comparison vs Placebo*		
Hazard ratio		0.51
95% confidence interval		(0.19,1.37)
p-value		0.1790

* Based on a Cox regression model with terms for age (p=0.8036), baseline eGFR (CKD-EPI) (p=0.1600), sex (p=0.5362), region (p=0.0503), baseline diabetes status (3 cat.) (p=0.0012), Treatment (p=0.0058), heart failure physiology (p=0.0928) and Treatment by heart failure physiology interaction (p=0.5129).
16 patients were excluded as the subgroup variable was missing.
The p-value for treatment by subgroup interaction trend test is 0.5054.

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.

R.1.1.6.13

R.1.1.6.13 Subgroup analysis by baseline use of MRA

Table R.1.1.6.13: 1 Cox regr. for time to composite renal endpoint by baseline use of MRA (Y/N) - RS (trial 1245.121)

Subgroup Description	Placebo	Empa 10mg
Baseline use of MRA: No		
Number of patients in analysis set	512	557
Number of analysed patients	512	557
Number of patients with event [N(%)]	12 (2.3)	11 (2.0)
Time at risk for event [years]	539.2	599.7
Incidence rate [patients with events per 100 patient years at risk]	2.23	1.83
95% confidence interval	(1.15, 3.65)	(0.92, 3.07)
Comparison vs Placebo*		
Hazard ratio		0.80
95% confidence interval		(0.35,1.82)
p-value		0.5962
Baseline use of MRA: Yes		
Number of patients in analysis set	1355	1306
Number of analysed patients	1355	1306
Number of patients with event [N(%)]	46 (3.4)	19 (1.5)
Time at risk for event [years]	1350.5	1317.6
Incidence rate [patients with events per 100 patient years at risk]	3.41	1.44
95% confidence interval	(2.49, 4.46)	(0.87, 2.16)
Comparison vs Placebo*		
Hazard ratio		0.41
95% confidence interval		(0.24,0.71)
p-value		0.0012

* Based on a Cox regression model with terms for age (p=0.9244), baseline eGFR (CKD-EPI) (p=0.0965), sex (p=0.5085), region (p=0.0607), baseline diabetes status (3 cat.) (p=0.0014), baseline LVEF (3 cat.) (p=0.0100), Treatment (p=0.0268), baseline use of MRA (p=0.6327) and Treatment by baseline use of MRA interaction (p=0.1849).

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.

R.1.1.6.14

Table R.1.1.6.14: 1 Cox regr. for time to composite renal endpoint by baseline use of ARNi (Y/N) - RS (trial 1245.121)

Subgroup Description	Placebo	Empa 10mg
Baseline use of ARNi: No		
Number of patients in analysis set	1480	1523
Number of analysed patients	1480	1523
Number of patients with event [N(%)]	49 (3.3)	27 (1.8)
Time at risk for event [years]	1524.0	1601.7
Incidence rate [patients with events per 100 patient years at risk]	3.22	1.69
95% confidence interval	(2.38, 4.18)	(1.11, 2.38)
Comparison vs Placebo*		
Hazard ratio		0.51
95% confidence interval		(0.32,0.81)
p-value		0.0049
Baseline use of ARNi: Yes		
Number of patients in analysis set	387	340
Number of analysed patients	387	340
Number of patients with event [N(%)]	9 (2.3)	3 (0.9)
Time at risk for event [years]	365.7	315.5
Incidence rate [patients with events per 100 patient years at risk]	2.46	0.95
95% confidence interval	(1.13, 4.31)	(0.20, 2.29)
Comparison vs Placebo*		
Hazard ratio		0.39
95% confidence interval		(0.11,1.45)
p-value		0.1606

* Based on a Cox regression model with terms for age (p=0.8455), baseline eGFR (CKD-EPI) (p=0.1012), sex (p=0.4717), region (p=0.0613), baseline diabetes status (3 cat.) (p=0.0016), baseline LVEF (3 cat.) (p=0.0099), Treatment (p=0.0230), baseline use of ARNi (p=0.3063) and Treatment by baseline use of ARNi interaction (p=0.7125).

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.

R.1.1.6.15 Subgroup analysis by bl. LVEF (<= 30%, >30% -<= 35% , > 35%)

Table R.1.1.6.15: 1 Cox regr. for time to composite renal endpoint by bl. LVEF (3 cat.) - RS (trial 1245.121)

Subgroup Description	Placebo	Empa 10mg
Baseline LVEF: <=30		
Number of patients in analysis set	1392	1337
Number of analysed patients	1392	1337
Number of patients with event [N(%)]	47 (3.4)	24 (1.8)
Time at risk for event [years]	1423.9	1389.0
Incidence rate [patients with events per 100 patient years at risk]	3.30	1.73
95% confidence interval	(2.43, 4.31)	(1.11, 2.48)
Comparison vs Placebo*		
Hazard ratio		0.50
95% confidence interval		(0.31,0.82)
p-value		0.0060
Baseline LVEF: >30 to <=35		
Number of patients in analysis set	361	398
Number of analysed patients	361	398
Number of patients with event [N(%)]	7 (1.9)	1 (0.3)
Time at risk for event [years]	368.0	408.6
Incidence rate [patients with events per 100 patient years at risk]	1.90	0.24
95% confidence interval	(0.76, 3.55)	(0.01, 0.90)
Comparison vs Placebo*		
Hazard ratio		0.14
95% confidence interval		(0.02,1.11)
p-value		0.0622

* Based on a Cox regression model with terms for age (p=0.8606), baseline eGFR (CKD-EPI) (p=0.0957), sex (p=0.5187), region (p=0.0546), baseline diabetes status (3 cat.) (p=0.0015), Treatment (p=0.0400), baseline LVEF (3 cat.) (p=0.0143) and Treatment by baseline LVEF (3 cat.) interaction (p=0.2651).
The p-value for treatment by subgroup interaction trend test is 0.4797.

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.

Table R.1.1.6.15: 1 Cox regr. for time to composite renal endpoint by bl. LVEF (3 cat.) - RS (trial 1245.121)

Subgroup Description	Placebo	Empa 10mg
Baseline LVEF: >35		
Number of patients in analysis set	114	128
Number of analysed patients	114	128
Number of patients with event [N(%)]	4 (3.5)	5 (3.9)
Time at risk for event [years]	97.8	119.6
Incidence rate [patients with events per 100 patient years at risk]	4.09	4.18
95% confidence interval	(1.11, 8.97)	(1.36, 8.56)
Comparison vs Placebo*		
Hazard ratio		1.04
95% confidence interval		(0.28,3.90)
p-value		0.9504

* Based on a Cox regression model with terms for age (p=0.8606), baseline eGFR (CKD-EPI) (p=0.0957), sex (p=0.5187), region (p=0.0546), baseline diabetes status (3 cat.) (p=0.0015), Treatment (p=0.0400), baseline LVEF (3 cat.) (p=0.0143) and Treatment by baseline LVEF (3 cat.) interaction (p=0.2651).
The p-value for treatment by subgroup interaction trend test is 0.4797.

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.

R.1.1.6.16 Subgroup analysis by bl. NTproBNP </>= median (median based on total patients)

Table R.1.1.6.16: 1 Cox regr. for time to composite renal endpoint by bl. NTproBNP (<median,>= median) (median based on total patients) - RS (trial 1245.121)

Subgroup Description	Placebo	Empa 10mg
Baseline NTproBNP: < median		
Number of patients in analysis set	920	942
Number of analysed patients	920	942
Number of patients with event [N(%)]	23 (2.5)	12 (1.3)
Time at risk for event [years]	972.8	1002.2
Incidence rate [patients with events per 100 patient years at risk]	2.36	1.20
95% confidence interval	(1.50, 3.42)	(0.62, 1.96)
Comparison vs Placebo*		
Hazard ratio		0.49
95% confidence interval		(0.24,0.98)
p-value		0.0446
Baseline NTproBNP: >= median		
Number of patients in analysis set	946	920
Number of analysed patients	946	920
Number of patients with event [N(%)]	35 (3.7)	18 (2.0)
Time at risk for event [years]	916.9	915.1
Incidence rate [patients with events per 100 patient years at risk]	3.82	1.97
95% confidence interval	(2.66, 5.18)	(1.17, 2.97)
Comparison vs Placebo*		
Hazard ratio		0.51
95% confidence interval		(0.29,0.91)
p-value		0.0214

* Based on a Cox regression model with terms for age (p=0.8420), baseline eGFR (CKD-EPI) (p=0.2063), sex (p=0.4488), region (p=0.0578), baseline diabetes status (3 cat.) (p=0.0013), baseline LVEF (3 cat.) (p=0.0126), Treatment (p=0.0026), baseline NTproBNP (2 cat.) (p=0.0589) and Treatment by baseline NTproBNP (2 cat.) interaction (p=0.9170).
2 patients were excluded as the subgroup variable was missing.

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.
Median: 1910 [pg/mL]

R.1.1.7

R.1.1.7 Time to renal endpoint component chronic dialysis

R.1.1.7.1

Figure R.1.1.7.1: 1

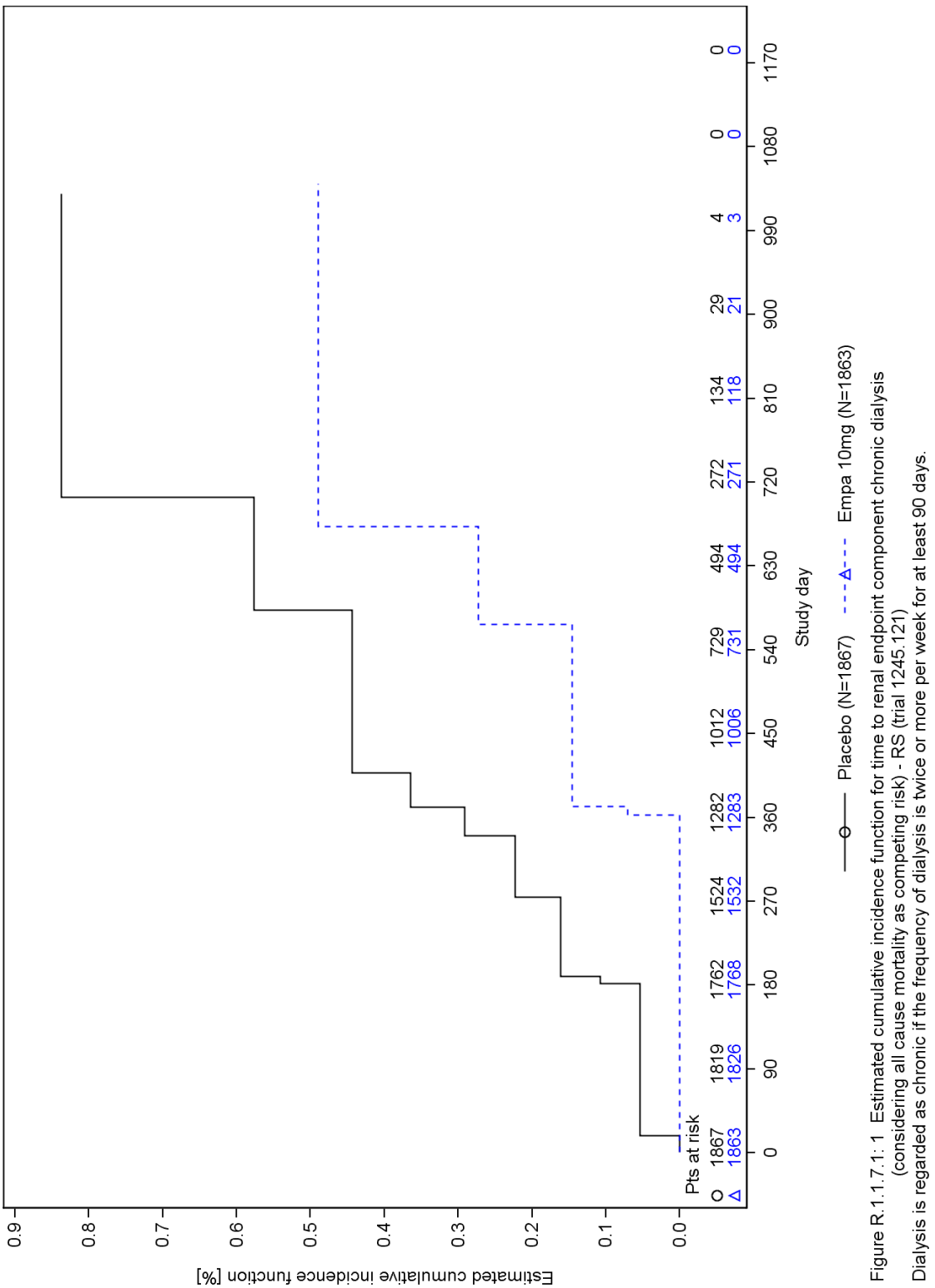

Figure R.1.1.7.1: 1 Estimated cumulative incidence function for time to renal endpoint component chronic dialysis (considering all cause mortality as competing risk) - RS (trial 1245.121)
Dialysis is regarded as chronic if the frequency of dialysis is twice or more per week for at least 90 days.

Table R.1.1.7.1: 1 Cox regr. for time to renal endpoint component chronic dialysis - RS (trial 1245.121)

	Placebo	Empa 10mg
Number of patients in analysis set	1867	1863
Number of analysed patients	1867	1863
Number of patients with event [N(%)]	9 (0.5)	4 (0.2)
Time at risk for event [years]	2459.0	2458.1
Incidence rate [patients with events per 100 patient years at risk]	0.37	0.16
95% confidence interval	(0.17, 0.64)	(0.04, 0.36)
Comparison vs Placebo*		
Hazard ratio		0.46
95% confidence interval		(0.14,1.52)
p-value		0.2054
Time to event [days]**		
2.5% percentile	NC.	NC.
5.0% percentile	NC.	NC.
7.5% percentile	NC.	NC.
10.0% percentile	NC.	NC.
Patients with events [%]**		
1 year	0.3	0.1
2 years	1.0	0.6

* Based on a Cox regression model with terms for age (p=0.0251), baseline eGFR (CKD-EPI) (p=0.0016), sex (p=0.7785), region (p=0.3098), baseline diabetes status (3 cat.) (p=0.6552), baseline LVEF (3 cat.) (p=0.7181) and Treatment (p=0.2054).
**Based on Kaplan-Meier estimates.
NC. = Not calculated.

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

R.1.1.8

R.1.1.8 Time to renal endpoint component renal transplant

R.1.1.8.1

Figure R.1.1.8.1: 1

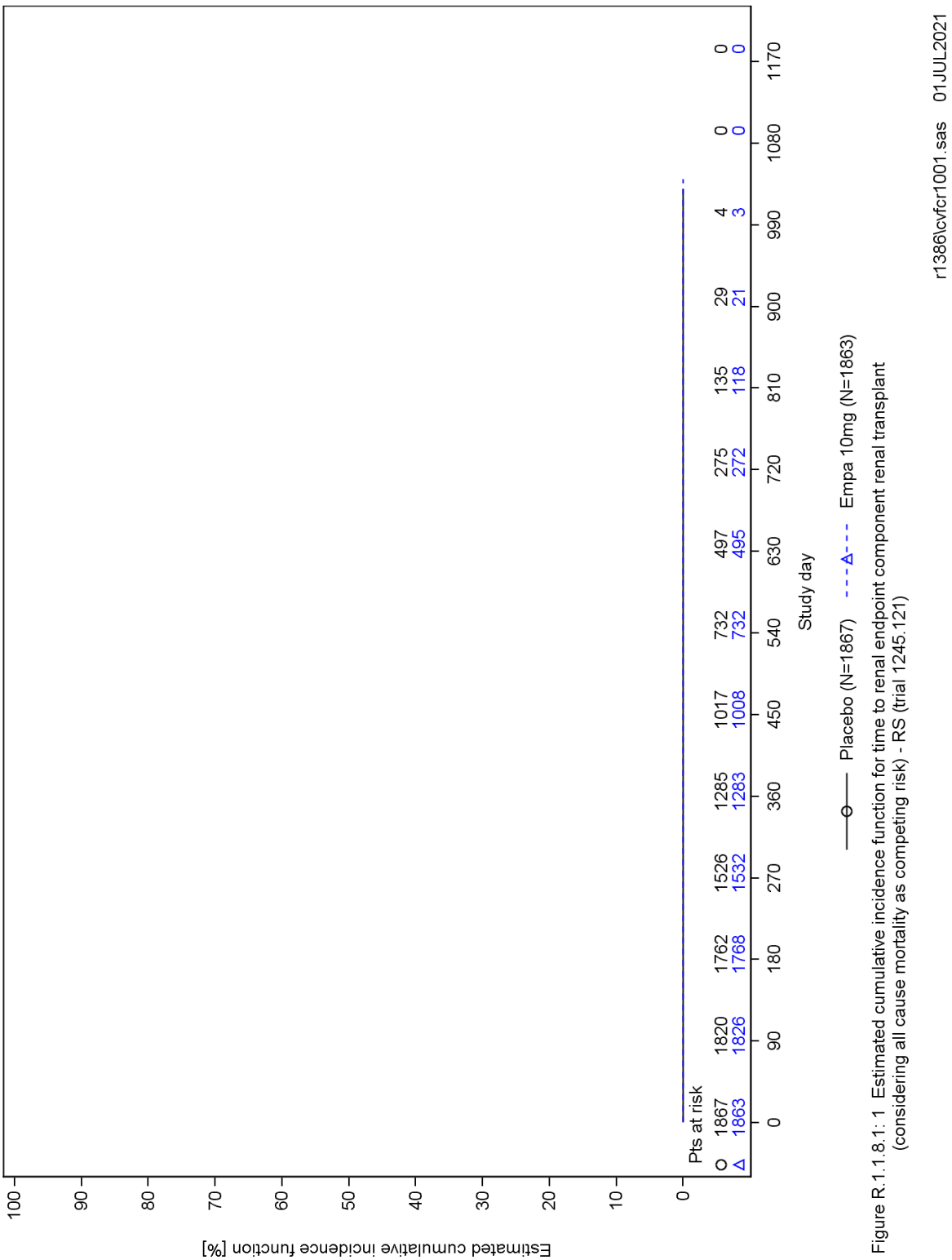

Figure R.1.1.8.1: 1 Estimated cumulative incidence function for time to renal endpoint component renal transplant (considering all cause mortality as competing risk) - RS (trial 1245.121)

Table R.1.1.8.1: 1 Cox regr. for time to renal endpoint component renal transplant - RS (trial 1245.121)

	Placebo	Empa 10mg
Number of patients in analysis set	1867	1863
Number of analysed patients	1867	1863
Number of patients with event [N(%)]	0	0
Time at risk for event [years]	2464.8	2459.8
Incidence rate [patients with events per 100 patient years at risk]	0.00	0.00
95% confidence interval	NC.	NC.
Comparison vs Placebo*		
Hazard ratio		1.00
95% confidence interval		(1.00,1.00)
p-value		NC.
Time to event [days]**		
2.5% percentile	NC.	NC.
5.0% percentile	NC.	NC.
7.5% percentile	NC.	NC.
10.0% percentile	NC.	NC.
Patients with events [%]**		
1 year	0.0	0.0
2 years	0.0	0.0

* Based on a Cox regression model with terms for age (p-value NA), baseline eGFR (CKD-EPI) (p-value NA), sex (p-value NA), region (p-value NA), baseline diabetes status (3 cat.) (p-value NA), baseline LVEF (3 cat.) (p-value NA) and Treatment (p-value NA).
**Based on Kaplan-Meier estimates.
NC. = Not calculated.

R.1.1.9 Time to renal endpoint component sustained reduction in eGFR (CKD-EPI)

R.1.1.9.1

Figure R.1.1.9.1: 1

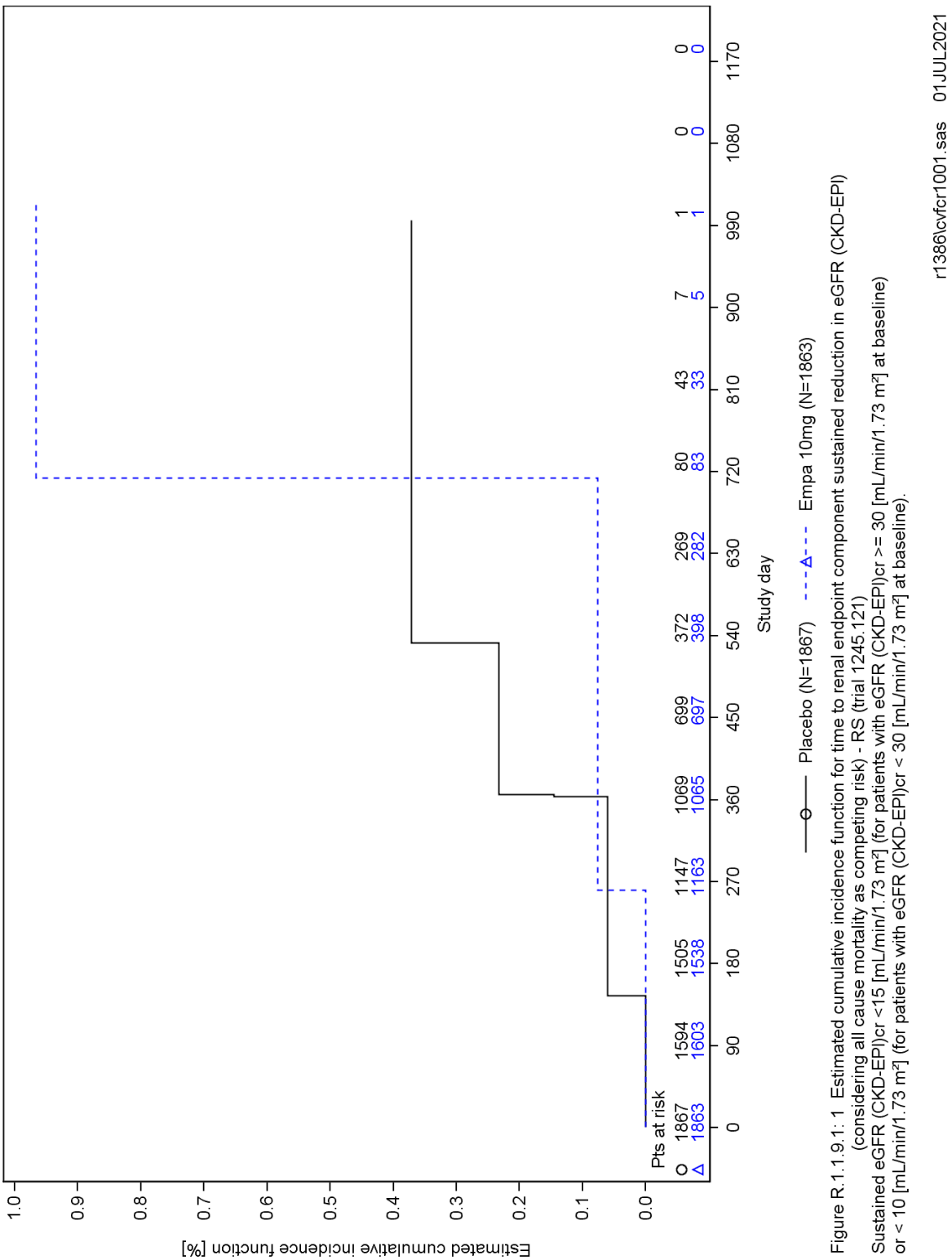

Figure R.1.1.9.1: 1 Estimated cumulative incidence function for time to renal endpoint component sustained reduction in eGFR (CKD-EPI) (considering all cause mortality as competing risk) - RS (trial 1245.121)
Sustained eGFR (CKD-EPI)cr <15 [mL/min/1.73 m²] (for patients with eGFR (CKD-EPI)cr >= 30 [mL/min/1.73 m²] at baseline) or < 10 [mL/min/1.73 m²] (for patients with eGFR (CKD-EPI)cr < 30 [mL/min/1.73 m²] at baseline).

Table R.1.1.9.1: 1 Cox regr. for time to renal endpoint component sustained reduction in eGFR (CKD-EPI) - RS (trial 1245.121)

	Placebo	Empa 10mg
Number of patients in analysis set	1867	1863
Number of analysed patients	1867	1863
Number of patients with event [N(%)]	4 (0.2)	2 (0.1)
Time at risk for event [years]	1910.3	1931.2
Incidence rate [patients with events per 100 patient years at risk]	0.21	0.10
95% confidence interval	(0.06, 0.46)	(0.01, 0.29)
Comparison vs Placebo*		
Hazard ratio		0.31
95% confidence interval		(0.05,1.87)
p-value		0.2024
Time to event [days]**		
2.5% percentile	NC.	NC.
5.0% percentile	NC.	NC.
7.5% percentile	NC.	NC.
10.0% percentile	NC.	NC.
Patients with events [%]**		
1 year	0.3	0.1
2 years	0.4	1.2

* Based on a Cox regression model with terms for age (p=0.1167), baseline eGFR (CKD-EPI) (p=0.0151), sex (p=0.4941), region (p=1.0000), baseline diabetes status (3 cat.) (p=0.9679), baseline LVEF (3 cat.) (p=0.1598) and Treatment (p=0.2024).
**Based on Kaplan-Meier estimates.
NC. = Not calculated.

Sustained eGFR (CKD-EPI)cr <15 [mL/min/1.73 m²] (for patients with eGFR (CKD-EPI)cr >= 30 [mL/min/1.73 m²] at baseline) or < 10 [mL/min/1.73 m²] (for patients with eGFR (CKD-EPI)cr < 30 [mL/min/1.73 m²] at baseline).

R.1.1.10 Time to renal endpoint component sustained eGFR (CKD-EPI) reduction >=40%

R.1.1.10.1

Figure R.1.1.10.1: 1

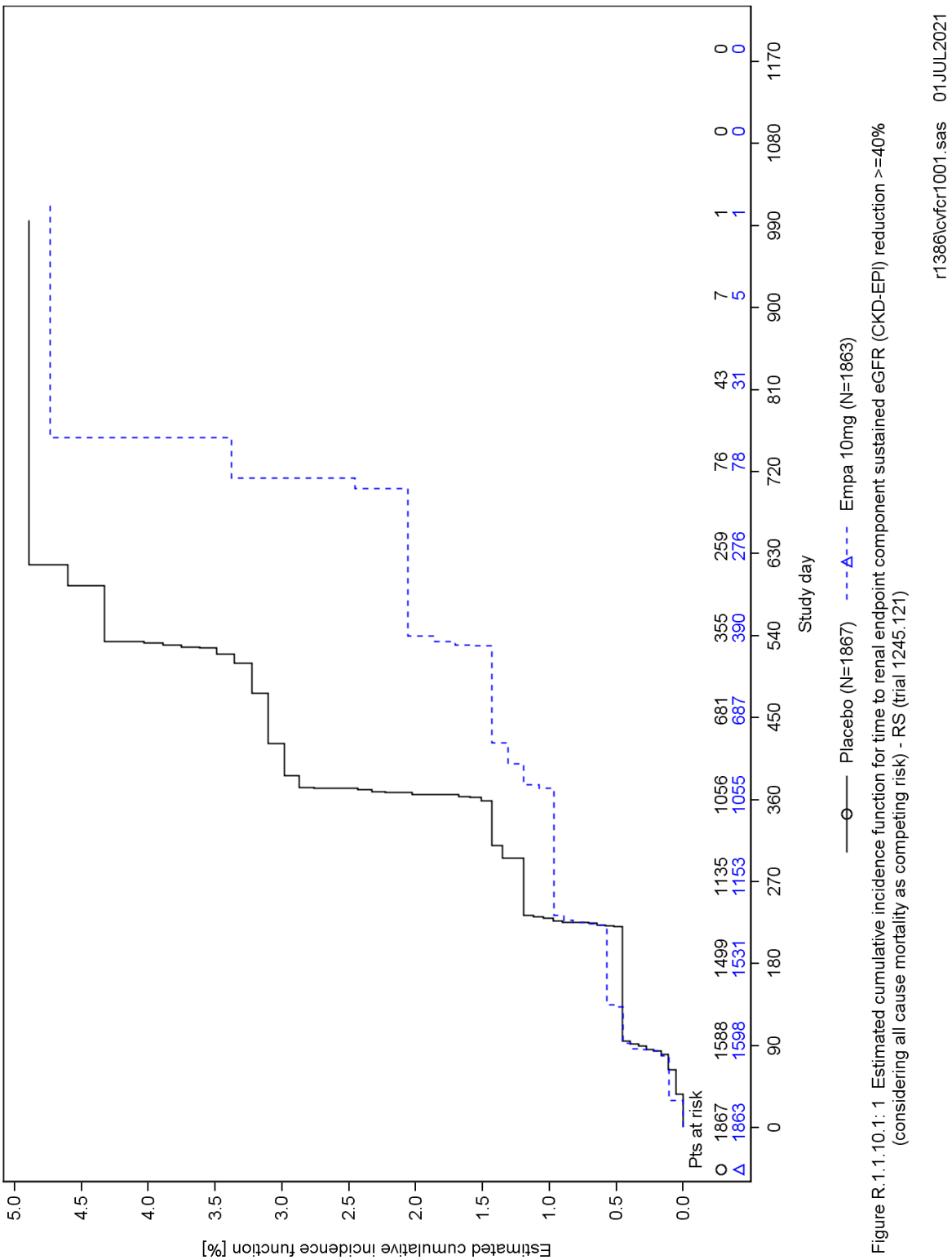

Figure R.1.1.10.1: 1 Estimated cumulative incidence function for time to renal endpoint component sustained eGFR (CKD-EPI) reduction >=40% (considering all cause mortality as competing risk) - RS (trial 1245.121)

Table R.1.1.10.1: 1 Cox regr. for time to renal endpoint component sustained eGFR (CKD-EPI) reduction >=40% - RS (trial 1245.121)

	Placebo	Empa 10mg
Number of patients in analysis set	1867	1863
Number of analysed patients	1867	1863
Number of patients with event [N(%)]	50 (2.7)	27 (1.4)
Time at risk for event [years]	1888.7	1916.2
Incidence rate [patients with events per 100 patient years at risk]	2.65	1.41
95% confidence interval	(1.96, 3.43)	(0.93, 1.99)
Comparison vs Placebo*		
Hazard ratio		0.52
95% confidence interval		(0.33,0.83)
p-value		0.0063
Time to event [days]**		
2.5% percentile	368	701
5.0% percentile	594	757
7.5% percentile	NC.	NC.
10.0% percentile	NC.	NC.
Patients with events [%]**		
1 year	2.2	1.0
2 years	5.6	4.0

* Based on a Cox regression model with terms for age (p=0.5465), baseline eGFR (CKD-EPI) (p=0.7568), sex (p=0.5217), region (p=0.0928), baseline diabetes status (3 cat.) (p=0.0026), baseline LVEF (3 cat.) (p=0.0219) and Treatment (p=0.0063).
**Based on Kaplan-Meier estimates.
NC. = Not calculated.

R.1.1.11 Time to onset of DM in patients with baseline pre-DM

R.1.1.11.1

Figure R.1.1.11.1: 1

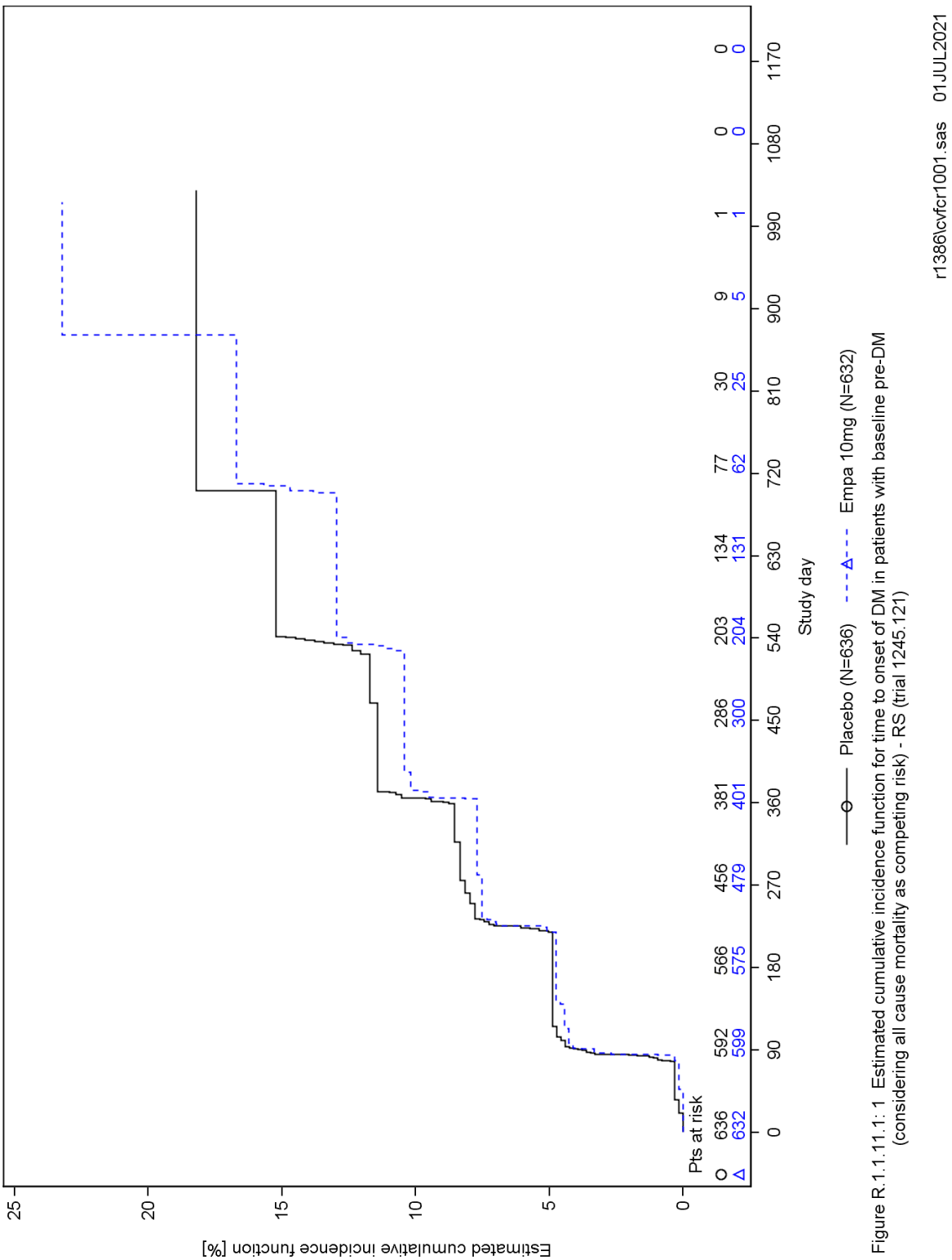

Figure R.1.1.11.1: 1 Estimated cumulative incidence function for time to onset of DM in patients with baseline pre-DM (considering all cause mortality as competing risk) - RS (trial 1245.121)

Table R.1.1.11.1: 1 Cox regr. for time to onset of DM in patients with baseline pre-DM - RS (trial 1245.121)

	Placebo	Empa 10mg
Number of patients in analysis set	636	632
Number of analysed patients	636	632
Number of patients with event [N(%)]	80 (12.6)	71 (11.2)
Time at risk for event [years]	753.3	762.4
Incidence rate [patients with events per 100 patient years at risk]	10.62	9.31
95% confidence interval	(8.42, 13.07)	(7.27, 11.60)
Comparison vs Placebo*		
Hazard ratio		0.86
95% confidence interval		(0.62,1.19)
p-value		0.3576
Time to event [days]**		
2.5% percentile	85	85
5.0% percentile	115	218
7.5% percentile	227	234
10.0% percentile	364	372
Patients with events [%]**		
1 year	11.1	9.5
2 years	20.0	18.1

* Based on a Cox regression model with terms for age (p=0.3109), baseline eGFR (CKD-EPI) (p=0.2044), sex (p=0.1253), region (p=0.7297), baseline LVEF (3 cat.) (p=0.0438) and Treatment (p=0.3576).
**Based on Kaplan-Meier estimates.

R.1.1.11.2

Table R.1.1.11.2: 1

Table R.1.1.11.2: 1 Cox regr. for time to onset of DM in patients with baseline pre-DM by sex - RS (trial 1245.121)

Subgroup Description	Placebo	Empa 10mg
Sex: Male		
Number of patients in analysis set	473	485
Number of analysed patients	473	485
Number of patients with event [N(%)]	66 (14.0)	53 (10.9)
Time at risk for event [years]	549.2	579.5
Incidence rate [patients with events per 100 patient years at risk]	12.02	9.15
95% confidence interval	(9.29, 15.08)	(6.85, 11.77)
Comparison vs Placebo*		
Hazard ratio		0.75
95% confidence interval		(0.52,1.08)
p-value		0.1224
Sex: Female		
Number of patients in analysis set	163	147
Number of analysed patients	163	147
Number of patients with event [N(%)]	14 (8.6)	18 (12.2)
Time at risk for event [years]	204.1	182.9
Incidence rate [patients with events per 100 patient years at risk]	6.86	9.84
95% confidence interval	(3.75, 10.89)	(5.83, 14.88)
Comparison vs Placebo*		
Hazard ratio		1.42
95% confidence interval		(0.71,2.86)
p-value		0.3251

* Based on a Cox regression model with terms for age (p=0.3591), baseline eGFR (CKD-EPI) (p=0.2144), region (p=0.7359), baseline LVEF (3 cat.) (p=0.0415), Treatment (p=0.8698), sex (p=0.1319) and Treatment by sex interaction (p=0.1133).

R.1.1.11.3

Figure R.1.1.11.3: 1

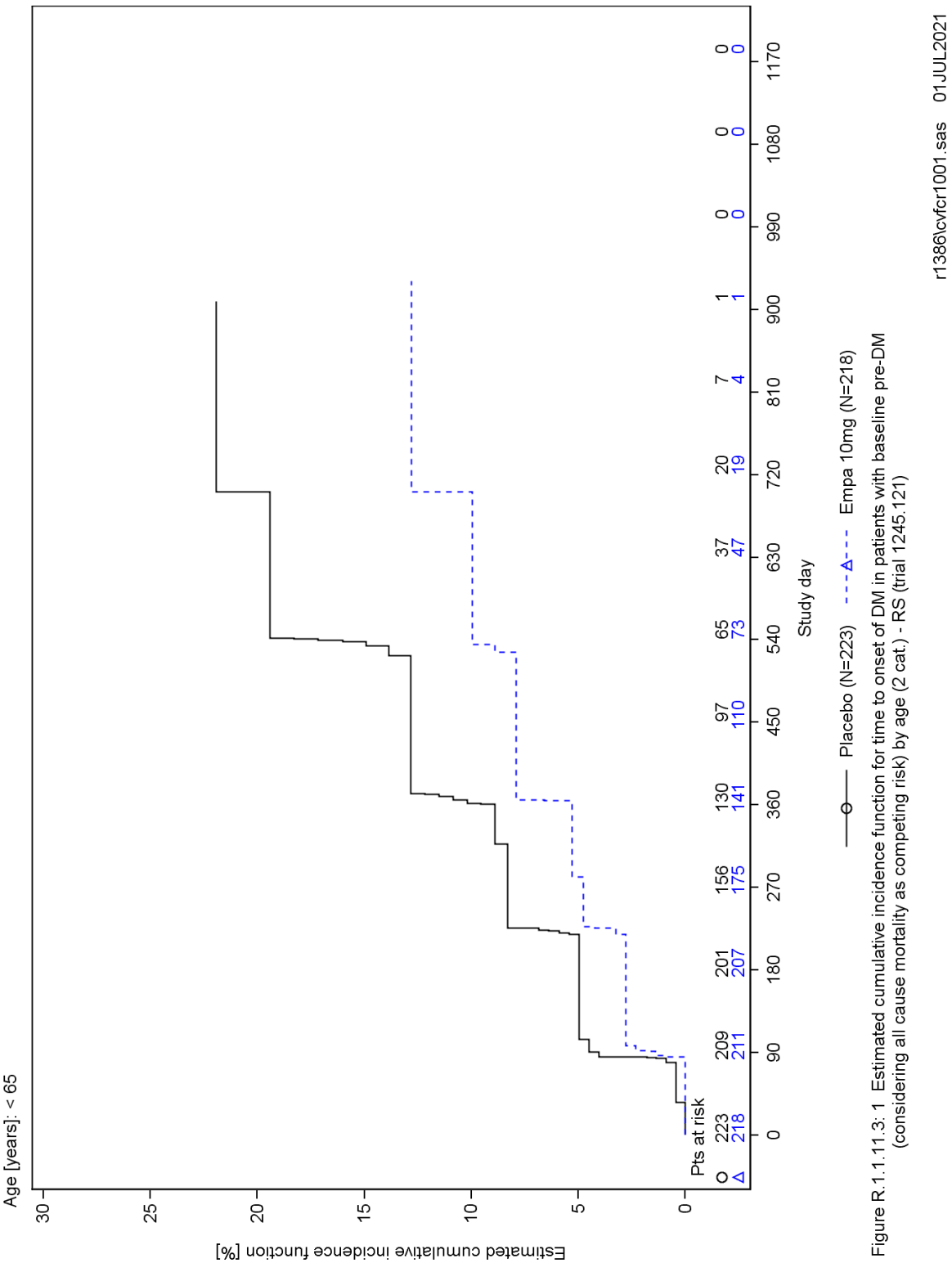

Figure R.1.1.11.3: 1 Estimated cumulative incidence function for time to onset of DM in patients with baseline pre-DM (considering all cause mortality as competing risk) by age (2 cat.) - RS (trial 1245.121)

Figure R.1.1.11.3: 1

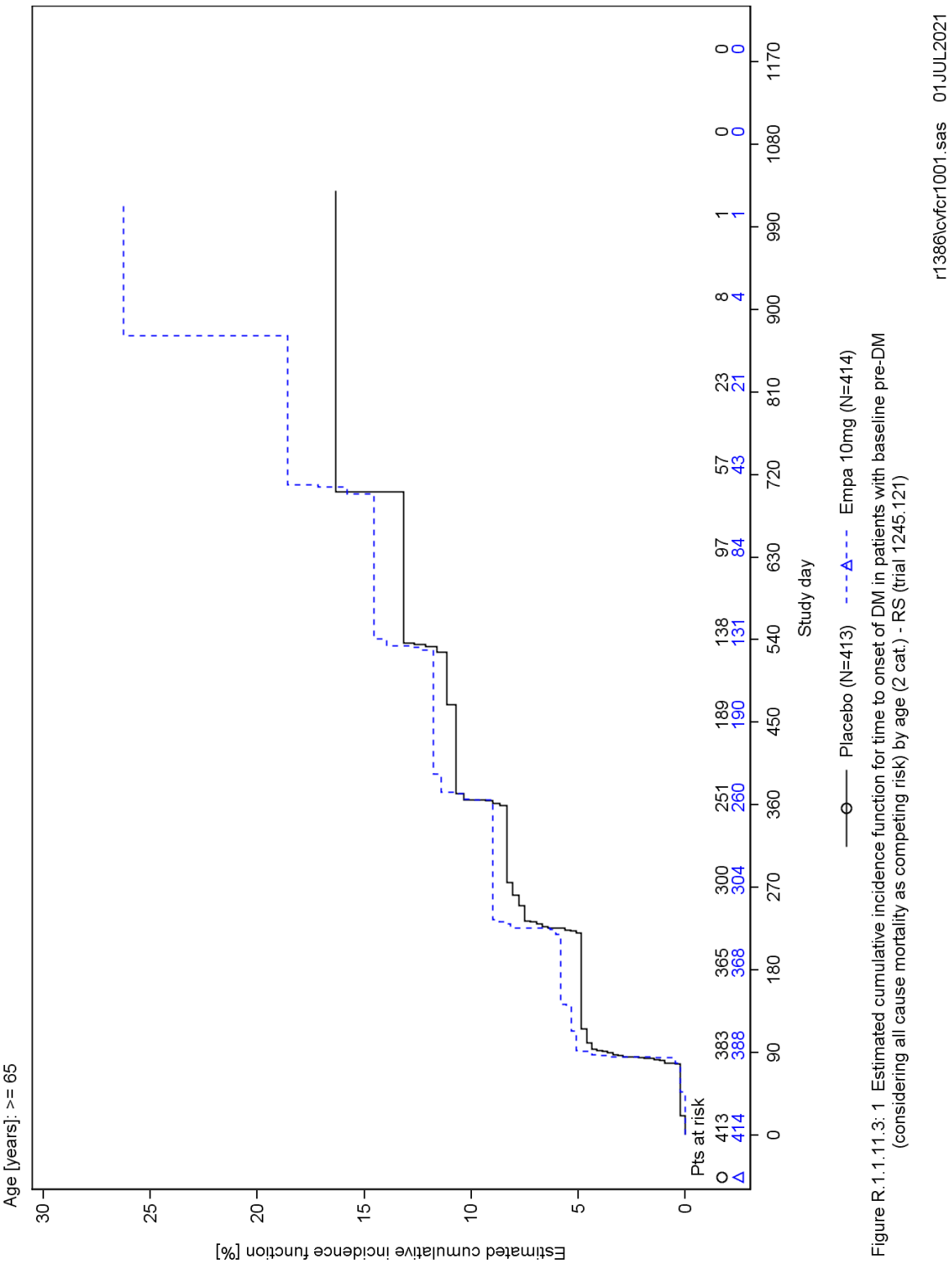

Figure R.1.1.11.3: 1 Estimated cumulative incidence function for time to onset of DM in patients with baseline pre-DM (considering all cause mortality as competing risk) by age (2 cat.) - RS (trial 1245.121)

Table R.1.1.11.3: 1 Cox regr. for time to onset of DM in patients with baseline pre-DM by age (2 cat.) - RS (trial 1245.121)

Subgroup Description	Placebo	Empa 10mg
Age [years]: < 65		
Number of patients in analysis set	223	218
Number of analysed patients	223	218
Number of patients with event [N(%)]	32 (14.3)	18 (8.3)
Time at risk for event [years]	254.9	269.1
Incidence rate [patients with events per 100 patient years at risk]	12.55	6.69
95% confidence interval	(8.59, 17.26)	(3.96, 10.11)
Comparison vs Placebo*		
Hazard ratio		0.53
95% confidence interval		(0.30,0.94)
p-value		0.0303
Age [years]: >= 65		
Number of patients in analysis set	413	414
Number of analysed patients	413	414
Number of patients with event [N(%)]	48 (11.6)	53 (12.8)
Time at risk for event [years]	498.4	493.3
Incidence rate [patients with events per 100 patient years at risk]	9.63	10.74
95% confidence interval	(7.10, 12.54)	(8.05, 13.82)
Comparison vs Placebo*		
Hazard ratio		1.09
95% confidence interval		(0.73,1.61)
p-value		0.6799

* Based on a Cox regression model with terms for baseline eGFR (CKD-EPI) (p=0.3701), sex (p=0.1662), region (p=0.6827), baseline LVEF (3 cat.) (p=0.0534), Treatment (p=0.1178), age (2 cat.) (p=0.9792) and Treatment by age (2 cat.) interaction (p=0.0432).

R.1.1.11.4 Subgroup analysis by region (North America, Latin America, Europe, Asia, Other)

Table R.1.1.11.4: 1 Cox regr. for time to onset of DM in patients with baseline pre-DM by region - RS (trial 1245.121)

Subgroup Description	Placebo	Empa 10mg
Region: North America		
Number of patients in analysis set	70	81
Number of analysed patients	70	81
Number of patients with event [N(%)]	9 (12.9)	7 (8.6)
Time at risk for event [years]	84.3	111.1
Incidence rate [patients with events per 100 patient years at risk]	10.68	6.30
95% confidence interval	(4.88, 18.71)	(2.53, 11.75)
Comparison vs Placebo*		
Hazard ratio		0.58
95% confidence interval		(0.22, 1.57)
p-value		0.2871
Region: Latin America		
Number of patients in analysis set	213	207
Number of analysed patients	213	207
Number of patients with event [N(%)]	31 (14.6)	20 (9.7)
Time at risk for event [years]	232.6	233.2
Incidence rate [patients with events per 100 patient years at risk]	13.33	8.58
95% confidence interval	(9.06, 18.42)	(5.24, 12.72)
Comparison vs Placebo*		
Hazard ratio		0.65
95% confidence interval		(0.37, 1.14)
p-value		0.1297

* Based on a Cox regression model with terms for age (p=0.3214), baseline eGFR (CKD-EPI) (p=0.2477), sex (p=0.1333), baseline LVEF (3 cat.) (p=0.0410), Treatment (p=0.7150), region (p=0.7436) and Treatment by region interaction (p=0.3506).

Table R.1.1.11.4: 1 Cox regr. for time to onset of DM in patients with baseline pre-DM by region - RS (trial 1245.121)

Subgroup Description	Placebo	Empa 10mg
Region: Europe		
Number of patients in analysis set	231	231
Number of analysed patients	231	231
Number of patients with event [N(%)]	28 (12.1)	31 (13.4)
Time at risk for event [years]	293.4	285.4
Incidence rate [patients with events per 100 patient years at risk]	9.54	10.86
95% confidence interval	(6.34, 13.39)	(7.38, 15.01)
Comparison vs Placebo*		
Hazard ratio		1.08
95% confidence interval		(0.65, 1.80)
p-value		0.7635
Region: Asia		
Number of patients in analysis set	93	90
Number of analysed patients	93	90
Number of patients with event [N(%)]	11 (11.8)	10 (11.1)
Time at risk for event [years]	107.6	108.5
Incidence rate [patients with events per 100 patient years at risk]	10.22	9.21
95% confidence interval	(5.10, 17.08)	(4.42, 15.74)
Comparison vs Placebo*		
Hazard ratio		0.89
95% confidence interval		(0.38, 2.09)
p-value		0.7843

* Based on a Cox regression model with terms for age (p=0.3214), baseline eGFR (CKD-EPI) (p=0.2477), sex (p=0.1333), baseline LVEF (3 cat.) (p=0.0410), Treatment (p=0.7150), region (p=0.7436) and Treatment by region interaction (p=0.3506).

Table R.1.1.11.4: 1 Cox regr. for time to onset of DM in patients with baseline pre-DM by region - RS (trial 1245.121)

Subgroup Description	Placebo	Empa 10mg
Region: Other		
Number of patients in analysis set	29	23
Number of analysed patients	29	23
Number of patients with event [N(%)]	1 (3.4)	3 (13.0)
Time at risk for event [years]	35.5	24.1
Incidence rate [patients with events per 100 patient years at risk]	2.82	12.42
95% confidence interval	(0.07, 10.40)	(2.56, 29.92)
Comparison vs Placebo*		
Hazard ratio		4.58
95% confidence interval		(0.47,44.34)
p-value		0.1889

* Based on a Cox regression model with terms for age (p=0.3214), baseline eGFR (CKD-EPI) (p=0.2477), sex (p=0.1333), baseline LVEF (3 cat.) (p=0.0410), Treatment (p=0.7150), region (p=0.7436) and Treatment by region interaction (p=0.3506).

R.1.1.11.5

R.1.1.11.5 Subgroup analysis by OECD member (Y/N)

Table R.1.1.11.5: 1 Cox regr. for time to onset of DM in patients with baseline pre-DM by OECD member (Y/N) - RS (trial 1245.121)

Subgroup Description	Placebo	Empa 10mg
OECD member: No		
Number of patients in analysis set	247	228
Number of analysed patients	247	228
Number of patients with event [N(%)]	29 (11.7)	23 (10.1)
Time at risk for event [years]	274.1	253.2
Incidence rate [patients with events per 100 patient years at risk]	10.58	9.08
95% confidence interval	(7.09, 14.77)	(5.76, 13.15)
Comparison vs Placebo*		
Hazard ratio		0.87
95% confidence interval		(0.50,1.50)
p-value		0.6067
OECD member: Yes		
Number of patients in analysis set	389	404
Number of analysed patients	389	404
Number of patients with event [N(%)]	51 (13.1)	48 (11.9)
Time at risk for event [years]	479.3	509.2
Incidence rate [patients with events per 100 patient years at risk]	10.64	9.43
95% confidence interval	(7.92, 13.75)	(6.95, 12.28)
Comparison vs Placebo*		
Hazard ratio		0.86
95% confidence interval		(0.58,1.27)
p-value		0.4409

* Based on a Cox regression model with terms for age (p=0.2870), baseline eGFR (CKD-EPI) (p=0.1722), sex (p=0.1654), baseline LVEF (3 cat.) (p=0.0439), Treatment (p=0.3852), OECD member (p=0.9057) and Treatment by OECD member interaction (p=0.9739).

OECD member (yes/no) countries included:
Yes: United States, Canada, Mexico, Poland, Netherlands, Hungary, Germany, Czech Republic, Italy, France, Spain, United Kingdom, Belgium, Japan, Australia, 'Korea; Republic Of South Korea';
No: Brazil, Argentina, China, India.

R.1.1.11.6

R.1.1.11.6 Subgroup analysis by NYHA at baseline (II, III/IV - 2 cat.)

Table R.1.1.11.6: 1 Cox regr. for time to onset of DM in patients with baseline pre-DM by baseline NYHA (2 cat.) - RS (trial 1245.121)

Subgroup Description	Placebo	Empa 10mg
Baseline NYHA: II		
Number of patients in analysis set	498	498
Number of analysed patients	498	498
Number of patients with event [N(%)]	62 (12.4)	53 (10.6)
Time at risk for event [years]	599.4	598.0
Incidence rate [patients with events per 100 patient years at risk]	10.34	8.86
95% confidence interval	(7.93, 13.07)	(6.64, 11.40)
Comparison vs Placebo*		
Hazard ratio		0.84
95% confidence interval		(0.58,1.22)
p-value		0.3689
Baseline NYHA: III/IV		
Number of patients in analysis set	138	134
Number of analysed patients	138	134
Number of patients with event [N(%)]	18 (13.0)	18 (13.4)
Time at risk for event [years]	153.9	164.4
Incidence rate [patients with events per 100 patient years at risk]	11.69	10.95
95% confidence interval	(6.93, 17.68)	(6.49, 16.56)
Comparison vs Placebo*		
Hazard ratio		0.90
95% confidence interval		(0.47,1.73)
p-value		0.7476

* Based on a Cox regression model with terms for age (p=0.3377), baseline eGFR (CKD-EPI) (p=0.2284), sex (p=0.1118), region (p=0.7142), baseline LVEF (3 cat.) (p=0.0388), Treatment (p=0.4708), baseline NYHA (2 cat.) (p=0.3132) and Treatment by baseline NYHA (2 cat.) interaction (p=0.8738).

R.1.1.11.7

R.1.1.1.11.7 Subgroup analysis by BMI at baseline (<30, >=30)

Table R.1.1.11.7: 1

Table R.1.1.11.7: 1 Cox regr. for time to onset of DM in patients with baseline pre-DM by baseline BMI [kg/m2] - RS (trial 1245.121)

Subgroup Description	Placebo	Empa 10mg
Baseline BMI [kg/m²]: <30		
Number of patients in analysis set	480	469
Number of analysed patients	480	469
Number of patients with event [N(%)]	61 (12.7)	49 (10.4)
Time at risk for event [years]	568.4	562.3
Incidence rate [patients with events per 100 patient years at risk]	10.73	8.71
95% confidence interval	(8.21, 13.59)	(6.45, 11.32)
Comparison vs Placebo*		
Hazard ratio		0.80
95% confidence interval		(0.55,1.16)
p-value		0.2365
Baseline BMI [kg/m²]: >=30		
Number of patients in analysis set	156	163
Number of analysed patients	156	163
Number of patients with event [N(%)]	19 (12.2)	22 (13.5)
Time at risk for event [years]	185.0	200.0
Incidence rate [patients with events per 100 patient years at risk]	10.27	11.00
95% confidence interval	(6.18, 15.38)	(6.89, 16.05)
Comparison vs Placebo*		
Hazard ratio		1.05
95% confidence interval		(0.57,1.95)
p-value		0.8748

* Based on a Cox regression model with terms for age (p=0.3538), baseline eGFR (CKD-EPI) (p=0.2149), sex (p=0.1149), region (p=0.7213), baseline LVEF (3 cat.) (p=0.0408), Treatment (p=0.6275), baseline BMI (2 cat.) (p=0.5766) and Treatment by baseline BMI (2 cat.) interaction (p=0.4519).

R.1.1.11.8

R.1.1.11.8 Subgroup analysis by eGFR at baseline (<60, >=60)

Table R.1.1.11.8: 1 Cox regr. for time to onset of DM in patients with baseline pre-DM by baseline eGFR (2 cat.) - RS (trial 1245.121)

Subgroup Description	Placebo	Empa 10mg
Baseline eGFR (CKD-EPI) [mL/min/1.73m²]: >=60		
Number of patients in analysis set	342	332
Number of analysed patients	342	332
Number of patients with event [N(%)]	47 (13.7)	32 (9.6)
Time at risk for event [years]	403.2	398.1
Incidence rate [patients with events per 100 patient years at risk]	11.66	8.04
95% confidence interval	(8.56, 15.22)	(5.50, 11.05)
Comparison vs Placebo*		
Hazard ratio		0.66
95% confidence interval		(0.42,1.04)
p-value		0.0704
Baseline eGFR (CKD-EPI) [mL/min/1.73m²]: <60		
Number of patients in analysis set	294	300
Number of analysed patients	294	300
Number of patients with event [N(%)]	33 (11.2)	39 (13.0)
Time at risk for event [years]	350.1	364.3
Incidence rate [patients with events per 100 patient years at risk]	9.43	10.71
95% confidence interval	(6.49, 12.90)	(7.61, 14.32)
Comparison vs Placebo*		
Hazard ratio		1.14
95% confidence interval		(0.72,1.82)
p-value		0.5758

* Based on a Cox regression model with terms for age (p=0.6433), sex (p=0.1403), region (p=0.6596), baseline LVEF (3 cat.) (p=0.0356), Treatment (p=0.3899), baseline eGFR (CKD-EPI) (2 cat.) (p=0.6986) and Treatment by baseline eGFR (CKD-EPI) (2 cat.) interaction (p=0.0969).

R.1.1.11.9

R.1.1.11.9 Subgroup analysis by history of HHF

Figure R.1.1.11.9: 1

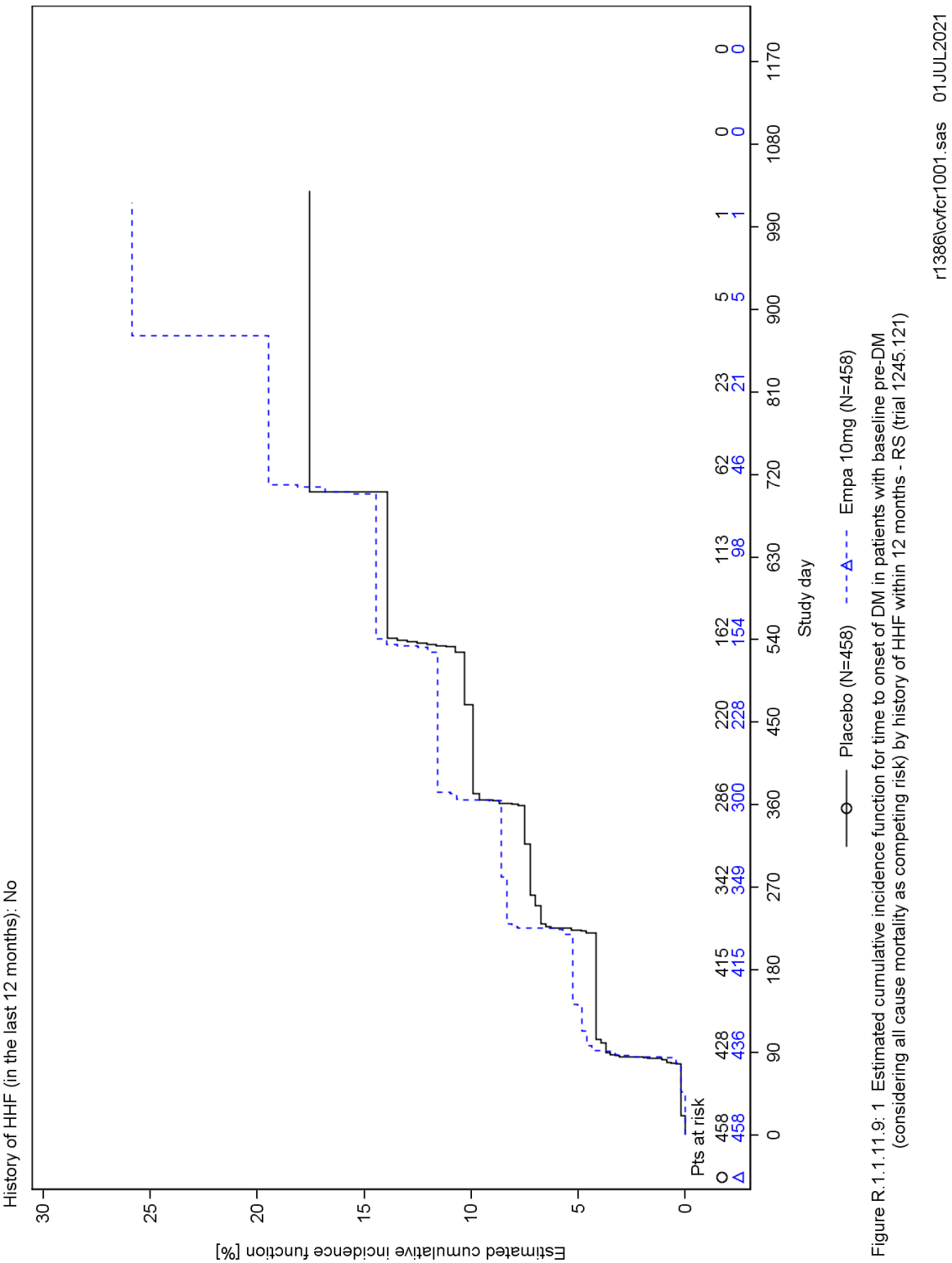

Figure R.1.1.11.9: 1 Estimated cumulative incidence function for time to onset of DM in patients with baseline pre-DM (considering all cause mortality as competing risk) by history of HHF within 12 months - RS (trial 1245.121)

Figure R.1.1.11.9: 1

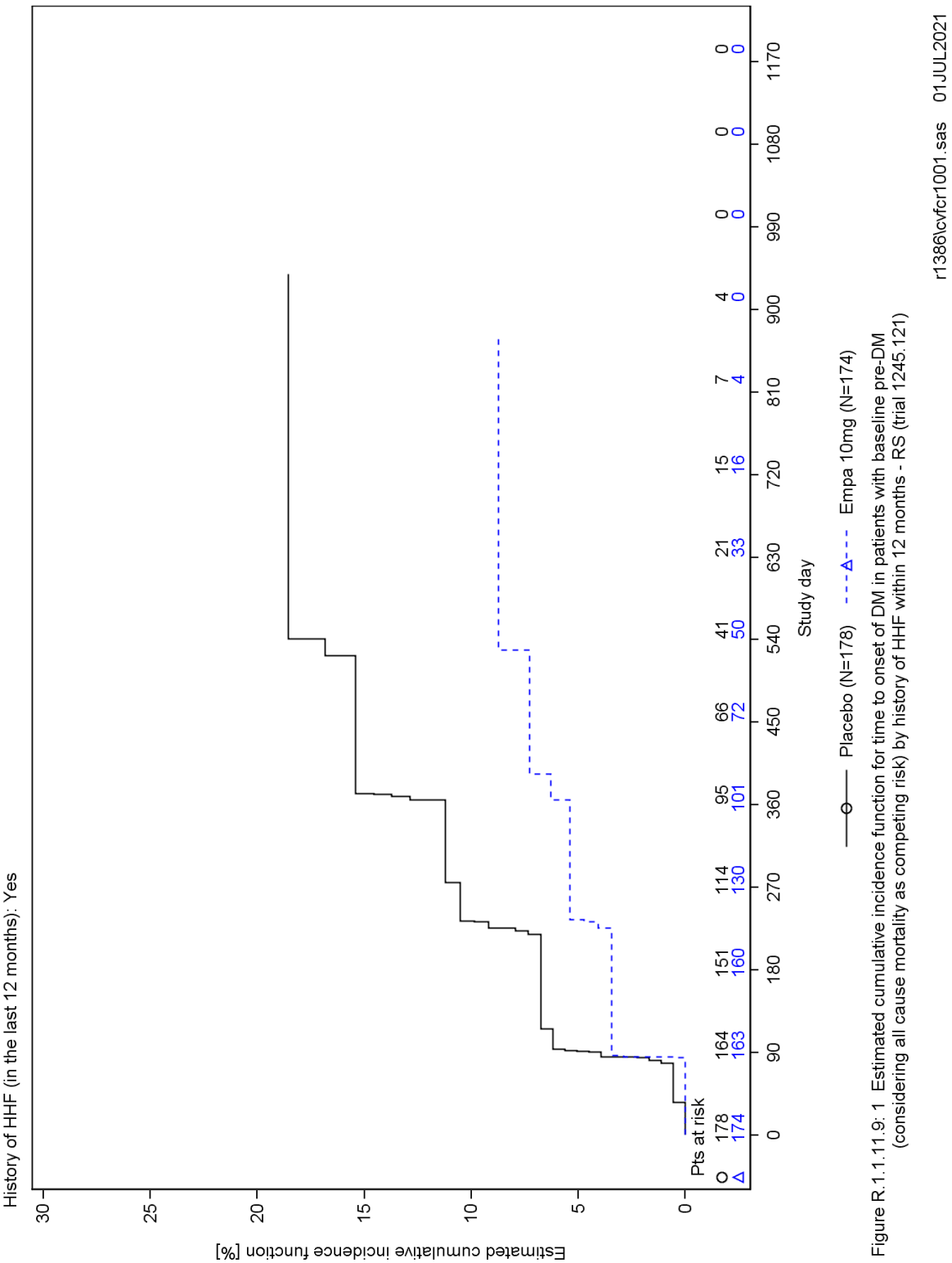

Figure R.1.1.11.9: 1 Estimated cumulative incidence function for time to onset of DM in patients with baseline pre-DM (considering all cause mortality as competing risk) by history of HHF within 12 months - RS (trial 1245.121)

Table R.1.1.11.9: 1

Table R.1.1.11.9: 1 Cox regr. for time to onset of DM in patients with baseline pre-DM by history of HHF within 12 months - RS (trial 1245.121)

Subgroup Description	Placebo	Empa 10mg
History of HHF (in the last 12 months): No		
Number of patients in analysis set	458	458
Number of analysed patients	458	458
Number of patients with event [N(%)]	54 (11.8)	59 (12.9)
Time at risk for event [years]	564.9	562.2
Incidence rate [patients with events per 100 patient years at risk]	9.56	10.50
95% confidence interval	(7.18, 12.27)	(7.99, 13.34)
Comparison vs Placebo*		
Hazard ratio		1.08
95% confidence interval		(0.75,1.56)
p-value		0.6871
History of HHF (in the last 12 months): Yes		
Number of patients in analysis set	178	174
Number of analysed patients	178	174
Number of patients with event [N(%)]	26 (14.6)	12 (6.9)
Time at risk for event [years]	188.4	200.2
Incidence rate [patients with events per 100 patient years at risk]	13.80	5.99
95% confidence interval	(9.01, 19.58)	(3.10, 9.83)
Comparison vs Placebo*		
Hazard ratio		0.42
95% confidence interval		(0.21,0.84)
p-value		0.0142

* Based on a Cox regression model with terms for age (p=0.3526), baseline eGFR (CKD-EPI) (p=0.1750), sex (p=0.1079), region (p=0.7385), baseline LVEF (3 cat.) (p=0.0473), Treatment (p=0.0491), history of HHF (p=0.5616) and Treatment by history of HHF interaction (p=0.0189).

R.1.1.11.10

Table R.1.1.11.10: 1 Cox regr. for time to onset of DM in patients with baseline pre-DM by cause of heart failure - RS (trial 1245.121)

Subgroup Description	Placebo	Empa 10mg
Cause of heart failure: Ischemic		
Number of patients in analysis set	317	303
Number of analysed patients	317	303
Number of patients with event [N(%)]	46 (14.5)	40 (13.2)
Time at risk for event [years]	382.3	371.5
Incidence rate [patients with events per 100 patient years at risk]	12.03	10.77
95% confidence interval	(8.81, 15.75)	(7.69, 14.35)
Comparison vs Placebo*		
Hazard ratio		0.90
95% confidence interval		(0.59,1.38)
p-value		0.6314
Cause of heart failure: Non-ischemic		
Number of patients in analysis set	319	329
Number of analysed patients	319	329
Number of patients with event [N(%)]	34 (10.7)	31 (9.4)
Time at risk for event [years]	371.1	390.9
Incidence rate [patients with events per 100 patient years at risk]	9.16	7.93
95% confidence interval	(6.35, 12.49)	(5.39, 10.96)
Comparison vs Placebo*		
Hazard ratio		0.83
95% confidence interval		(0.51,1.36)
p-value		0.4633

* Based on a Cox regression model with terms for age (p=0.1864), baseline eGFR (CKD-EPI) (p=0.1897), sex (p=0.2412), region (p=0.6022), baseline LVEF (3 cat.) (p=0.0424), Treatment (p=0.3851), cause of heart failure (2 cat.) (p=0.0621) and Treatment by cause of heart failure (2 cat.) interaction (p=0.8124).

R.1.1.11.11 Subgroup analysis by heart failure physiology (LVEF <= 30% and NTproBNP<median; LVEF <= 30% and NTproBNP>=median; LVEF > 30%)

Figure R.1.1.11.11: 1

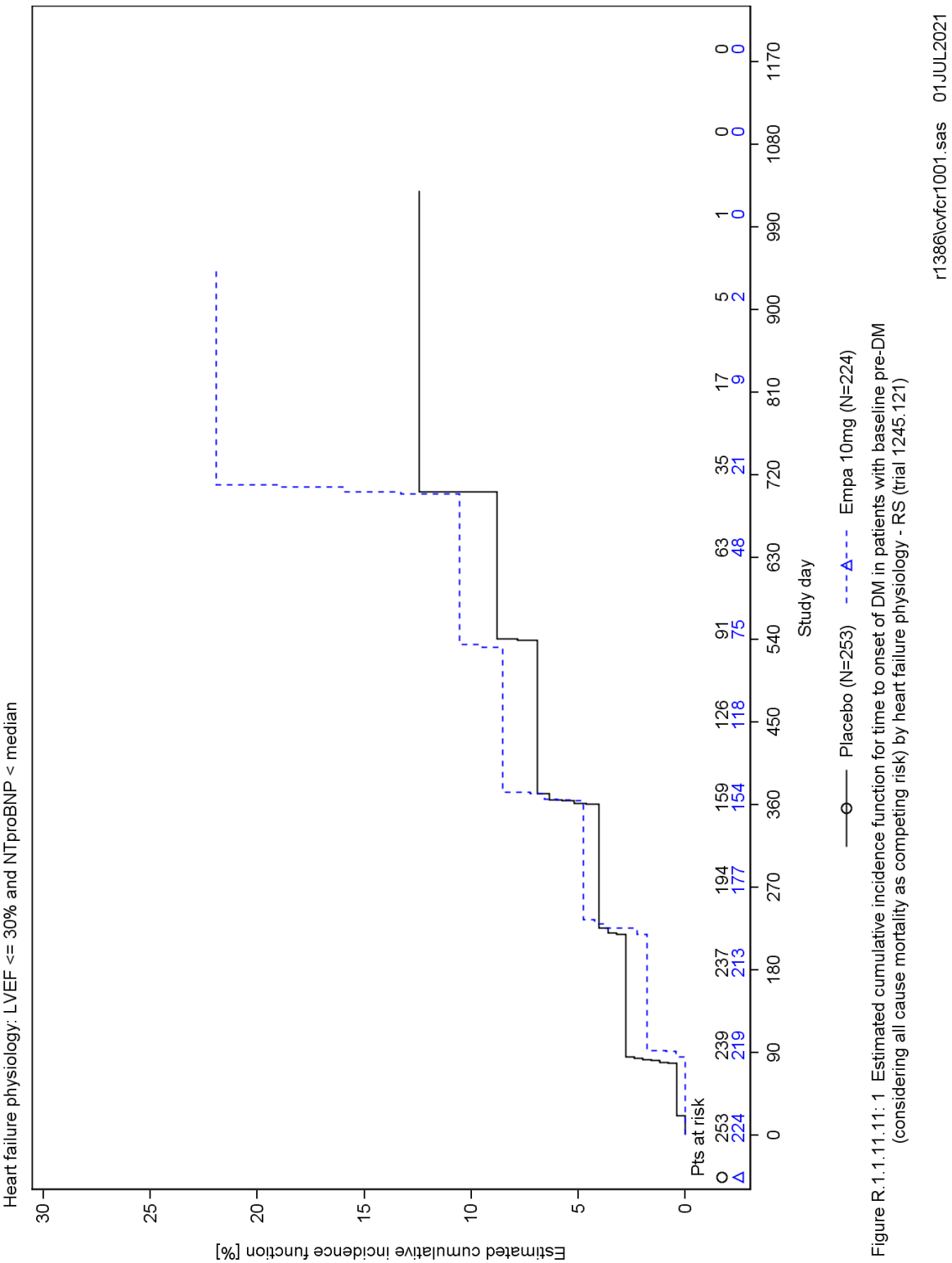

Figure R.1.1.11.11: 1 Estimated cumulative incidence function for time to onset of DM in patients with baseline pre-DM (considering all cause mortality as competing risk) by heart failure physiology - RS (trial 1245.121)

Figure R.1.1.11.11: 1

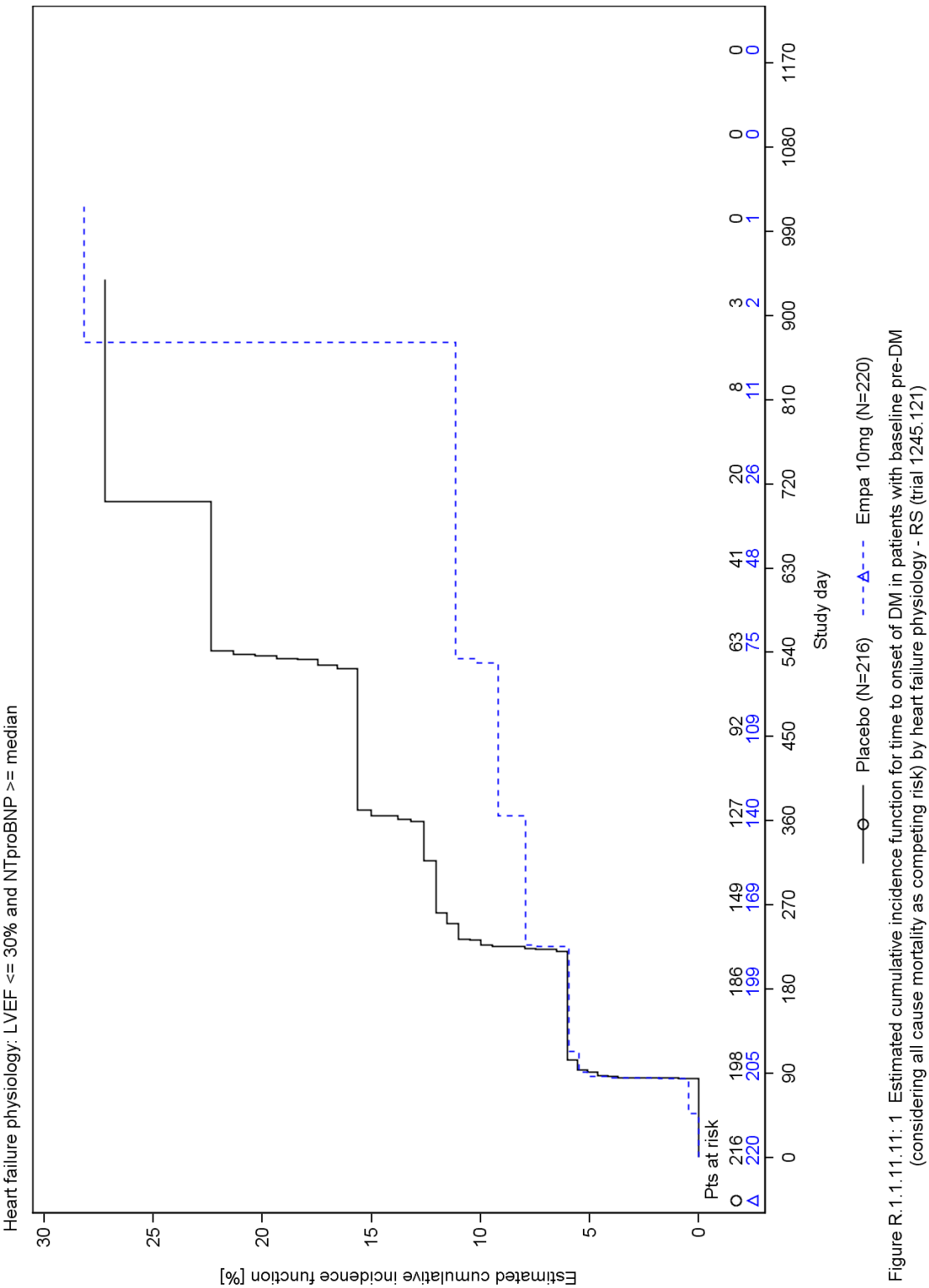

Figure R.1.1.11.11: 1 Estimated cumulative incidence function for time to onset of DM in patients with baseline pre-DM (considering all cause mortality as competing risk) by heart failure physiology - RS (trial 1245.121)

Figure R.1.1.11.11: 1

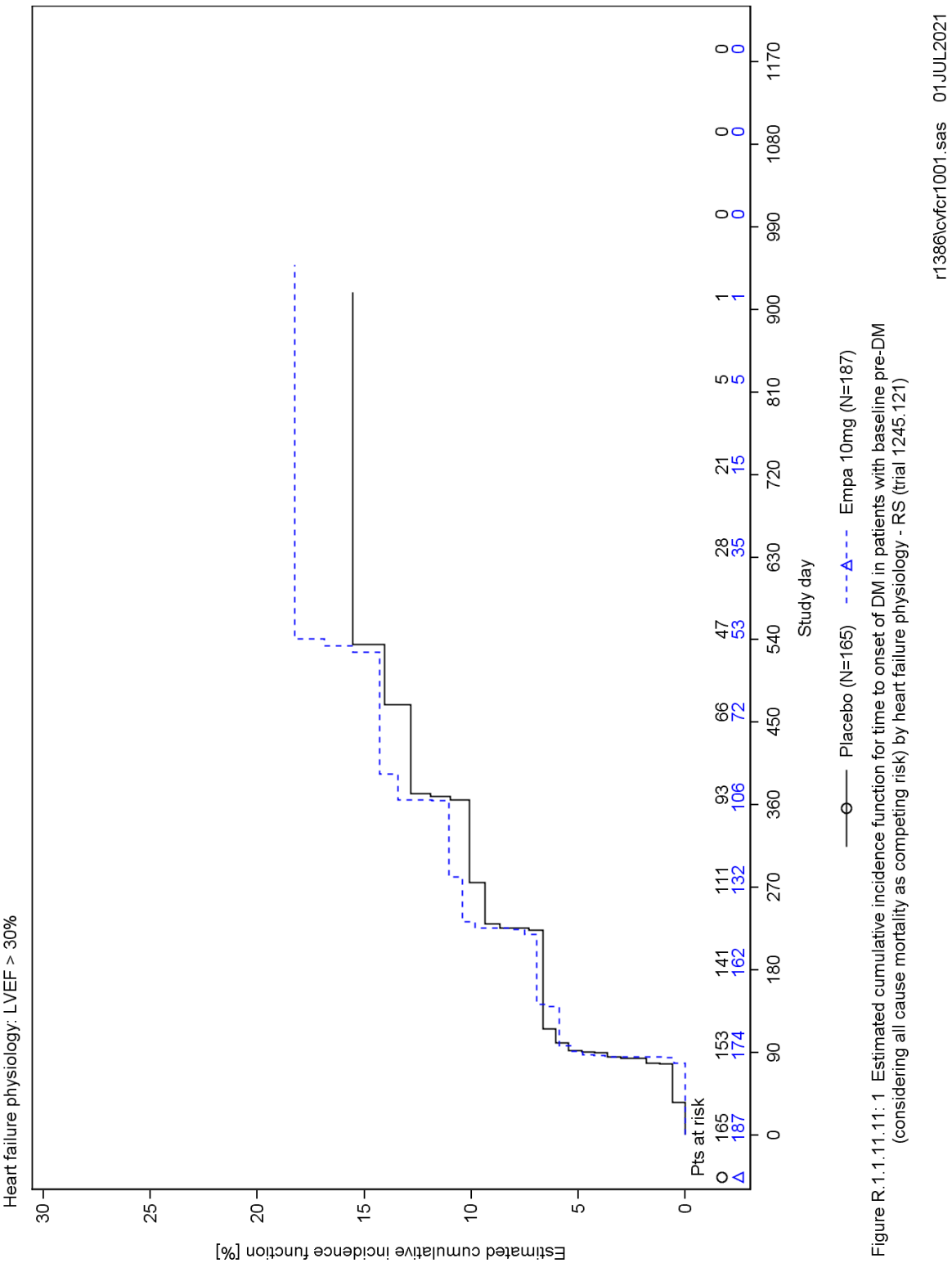

Figure R.1.1.11.11: 1 Estimated cumulative incidence function for time to onset of DM in patients with baseline pre-DM (considering all cause mortality as competing risk) by heart failure physiology - RS (trial 1245.121)

Table R.1.1.11.11: 1 Cox regr. for time to onset of DM in patients with baseline pre-DM by heart failure physiology - RS (trial 1245.121)

Subgroup Description	Placebo	Empa 10mg
Heart failure physiology: LVEF <= 30% and NTproBNP < median		
Number of patients in analysis set	253	224
Number of analysed patients	253	224
Number of patients with event [N(%)]	19 (7.5)	22 (9.8)
Time at risk for event [years]	318.6	281.1
Incidence rate [patients with events per 100 patient years at risk]	5.96	7.83
95% confidence interval	(3.59, 8.93)	(4.90, 11.42)
Comparison vs Placebo*		
Hazard ratio		1.31
95% confidence interval		(0.71,2.42)
p-value		0.3895
Heart failure physiology: LVEF <= 30% and NTproBNP >= median		
Number of patients in analysis set	216	220
Number of analysed patients	216	220
Number of patients with event [N(%)]	40 (18.5)	22 (10.0)
Time at risk for event [years]	246.4	269.3
Incidence rate [patients with events per 100 patient years at risk]	16.23	8.17
95% confidence interval	(11.60, 21.64)	(5.12, 11.92)
Comparison vs Placebo*		
Hazard ratio		0.49
95% confidence interval		(0.29,0.83)
p-value		0.0076

* Based on a Cox regression model with terms for age (p=0.3070), baseline eGFR (CKD-EPI) (p=0.2862), sex (p=0.0956), region (p=0.7599), Treatment (p=0.5378), heart failure physiology (p=0.0127) and Treatment by heart failure physiology interaction (p=0.0282).
3 patients were excluded as the subgroup variable was missing.
The p-value for treatment by subgroup interaction trend test is 0.8135.

Table R.1.1.11.11: 1 Cox regr. for time to onset of DM in patients with baseline pre-DM by heart failure physiology - RS (trial 1245.121)

Subgroup Description	Placebo	Empa 10mg
Heart failure physiology: LVEF > 30%		
Number of patients in analysis set	165	187
Number of analysed patients	165	187
Number of patients with event [N(%)]	21 (12.7)	27 (14.4)
Time at risk for event [years]	184.3	210.3
Incidence rate [patients with events per 100 patient years at risk]	11.39	12.84
95% confidence interval	(7.05, 16.76)	(8.46, 18.11)
Comparison vs Placebo*		
Hazard ratio		1.14
95% confidence interval		(0.64,2.02)
p-value		0.6500

* Based on a Cox regression model with terms for age (p=0.3070), baseline eGFR (CKD-EPI) (p=0.2862), sex (p=0.0956), region (p=0.7599), Treatment (p=0.5378), heart failure physiology (p=0.0127) and Treatment by heart failure physiology interaction (p=0.0282).
3 patients were excluded as the subgroup variable was missing.
The p-value for treatment by subgroup interaction trend test is 0.8135.

R.1.1.11.12

Table R.1.1.11.12: 1 Cox regr. for time to onset of DM in patients with baseline pre-DM by baseline use of MRA (Y/N) - RS (trial 1245.121)

Subgroup Description	Placebo	Empa 10mg
Baseline use of MRA: No		
Number of patients in analysis set	168	185
Number of analysed patients	168	185
Number of patients with event [N(%)]	20 (11.9)	22 (11.9)
Time at risk for event [years]	205.1	243.0
Incidence rate [patients with events per 100 patient years at risk]	9.75	9.05
95% confidence interval	(5.96, 14.46)	(5.67, 13.21)
Comparison vs Placebo*		
Hazard ratio		0.93
95% confidence interval		(0.51,1.71)
p-value		0.8221
Baseline use of MRA: Yes		
Number of patients in analysis set	468	447
Number of analysed patients	468	447
Number of patients with event [N(%)]	60 (12.8)	49 (11.0)
Time at risk for event [years]	548.2	519.4
Incidence rate [patients with events per 100 patient years at risk]	10.95	9.43
95% confidence interval	(8.35, 13.88)	(6.98, 12.25)
Comparison vs Placebo*		
Hazard ratio		0.83
95% confidence interval		(0.57,1.22)
p-value		0.3504

* Based on a Cox regression model with terms for age (p=0.3238), baseline eGFR (CKD-EPI) (p=0.2004), sex (p=0.1231), region (p=0.7545), baseline LVEF (3 cat.) (p=0.0437), Treatment (p=0.4934), baseline use of MRA (p=0.8620) and Treatment by baseline use of MRA interaction (p=0.7621).

R.1.1.11.13

R.1.1.11.13 Subgroup analysis by baseline use of ARNi

Table R.1.1.11.13: 1 Cox regr. for time to onset of DM in patients with baseline pre-DM by baseline use of ARNi (Y/N) - RS (trial 1245.121)

Subgroup Description	Placebo	Empa 10mg
Baseline use of ARNi: No		
Number of patients in analysis set	497	520
Number of analysed patients	497	520
Number of patients with event [N(%)]	66 (13.3)	65 (12.5)
Time at risk for event [years]	597.4	632.3
Incidence rate [patients with events per 100 patient years at risk]	11.05	10.28
95% confidence interval	(8.54, 13.87)	(7.93, 12.93)
Comparison vs Placebo*		
Hazard ratio		0.90
95% confidence interval		(0.64,1.27)
p-value		0.5458
Baseline use of ARNi: Yes		
Number of patients in analysis set	139	112
Number of analysed patients	139	112
Number of patients with event [N(%)]	14 (10.1)	6 (5.4)
Time at risk for event [years]	155.9	130.1
Incidence rate [patients with events per 100 patient years at risk]	8.98	4.61
95% confidence interval	(4.91, 14.26)	(1.69, 8.97)
Comparison vs Placebo*		
Hazard ratio		0.53
95% confidence interval		(0.20,1.38)
p-value		0.1936

* Based on a Cox regression model with terms for age (p=0.2908), baseline eGFR (CKD-EPI) (p=0.1957), sex (p=0.1094), region (p=0.8063), baseline LVEF (3 cat.) (p=0.0476), Treatment (p=0.1534), baseline use of ARNi (p=0.0511) and Treatment by baseline use of ARNi interaction (p=0.3077).

R.1.1.11.14 Subgroup analysis by bl. LVEF (<= 30%, >30% -<= 35% , > 35%)

Table R.1.1.11.14: 1 Cox regr. for time to onset of DM in patients with baseline pre-DM by bl. LVEF (3 cat.) - RS (trial 1245.121)

Subgroup Description	Placebo	Empa 10mg
Baseline LVEF: <=30		
Number of patients in analysis set	471	445
Number of analysed patients	471	445
Number of patients with event [N(%)]	59 (12.5)	44 (9.9)
Time at risk for event [years]	569.0	552.0
Incidence rate [patients with events per 100 patient years at risk]	10.37	7.97
95% confidence interval	(7.89, 13.18)	(5.79, 10.49)
Comparison vs Placebo*		
Hazard ratio		0.76
95% confidence interval		(0.51,1.12)
p-value		0.1611
Baseline LVEF: >30 to <=35		
Number of patients in analysis set	126	148
Number of analysed patients	126	148
Number of patients with event [N(%)]	17 (13.5)	25 (16.9)
Time at risk for event [years]	143.0	166.0
Incidence rate [patients with events per 100 patient years at risk]	11.89	15.06
95% confidence interval	(6.93, 18.18)	(9.75, 21.51)
Comparison vs Placebo*		
Hazard ratio		1.28
95% confidence interval		(0.69,2.38)
p-value		0.4360

* Based on a Cox regression model with terms for age (p=0.3213), baseline eGFR (CKD-EPI) (p=0.1753), sex (p=0.1318), region (p=0.7304), Treatment (p=0.4324), baseline LVEF (3 cat.) (p=0.0523) and Treatment by baseline LVEF (3 cat.) interaction (p=0.3009).
The p-value for treatment by subgroup interaction trend test is 0.4713.

Table R.1.1.11.14: 1 Cox regr. for time to onset of DM in patients with baseline pre-DM by bl. LVEF (3 cat.) - RS (trial 1245.121)

Subgroup Description	Placebo	Empa 10mg
Baseline LVEF: >35		
Number of patients in analysis set	39	39
Number of analysed patients	39	39
Number of patients with event [N(%)]	4 (10.3)	2 (5.1)
Time at risk for event [years]	41.4	44.3
Incidence rate [patients with events per 100 patient years at risk]	9.67	4.51
95% confidence interval	(2.64, 21.20)	(0.55, 12.57)
Comparison vs Placebo*		
Hazard ratio		0.49
95% confidence interval		(0.09,2.70)
p-value		0.4151

* Based on a Cox regression model with terms for age (p=0.3213), baseline eGFR (CKD-EPI) (p=0.1753), sex (p=0.1318), region (p=0.7304), Treatment (p=0.4324), baseline LVEF (3 cat.) (p=0.0523) and Treatment by baseline LVEF (3 cat.) interaction (p=0.3009).
The p-value for treatment by subgroup interaction trend test is 0.4713.

R.1.1.11.15 Subgroup analysis by bl. NTproBNP </>= median (median based on total patients)

Table R.1.1.11.15: 1 Cox regr. for time to onset of DM in patients with baseline pre-DM by bl. NTproBNP (<median,>= median) (median based on total patients) - RS (trial 1245.121)

Subgroup Description	Placebo	Empa 10mg
Baseline NTproBNP: < median		
Number of patients in analysis set	320	310
Number of analysed patients	320	310
Number of patients with event [N(%)]	30 (9.4)	33 (10.6)
Time at risk for event [years]	402.0	385.3
Incidence rate [patients with events per 100 patient years at risk]	7.46	8.56
95% confidence interval	(5.04, 10.36)	(5.90, 11.72)
Comparison vs Placebo*		
Hazard ratio		1.13
95% confidence interval		(0.68,1.85)
p-value		0.6419
Baseline NTproBNP: >= median		
Number of patients in analysis set	316	322
Number of analysed patients	316	322
Number of patients with event [N(%)]	50 (15.8)	38 (11.8)
Time at risk for event [years]	351.3	377.1
Incidence rate [patients with events per 100 patient years at risk]	14.23	10.08
95% confidence interval	(10.56, 18.44)	(7.13, 13.52)
Comparison vs Placebo*		
Hazard ratio		0.70
95% confidence interval		(0.46,1.06)
p-value		0.0927

* Based on a Cox regression model with terms for age (p=0.2547), baseline eGFR (CKD-EPI) (p=0.4046), sex (p=0.0949), region (p=0.8042), baseline LVEF (3 cat.) (p=0.0472), Treatment (p=0.4603), baseline NTproBNP (2 cat.) (p=0.0212) and Treatment by baseline NTproBNP (2 cat.) interaction (p=0.1488).

Median: 1910 [pg/mL]

R.1.1.12

R.1.1.12 Time to first all-cause hospitalisation

R.1.1.12.1

Figure R.1.1.12.1: 1

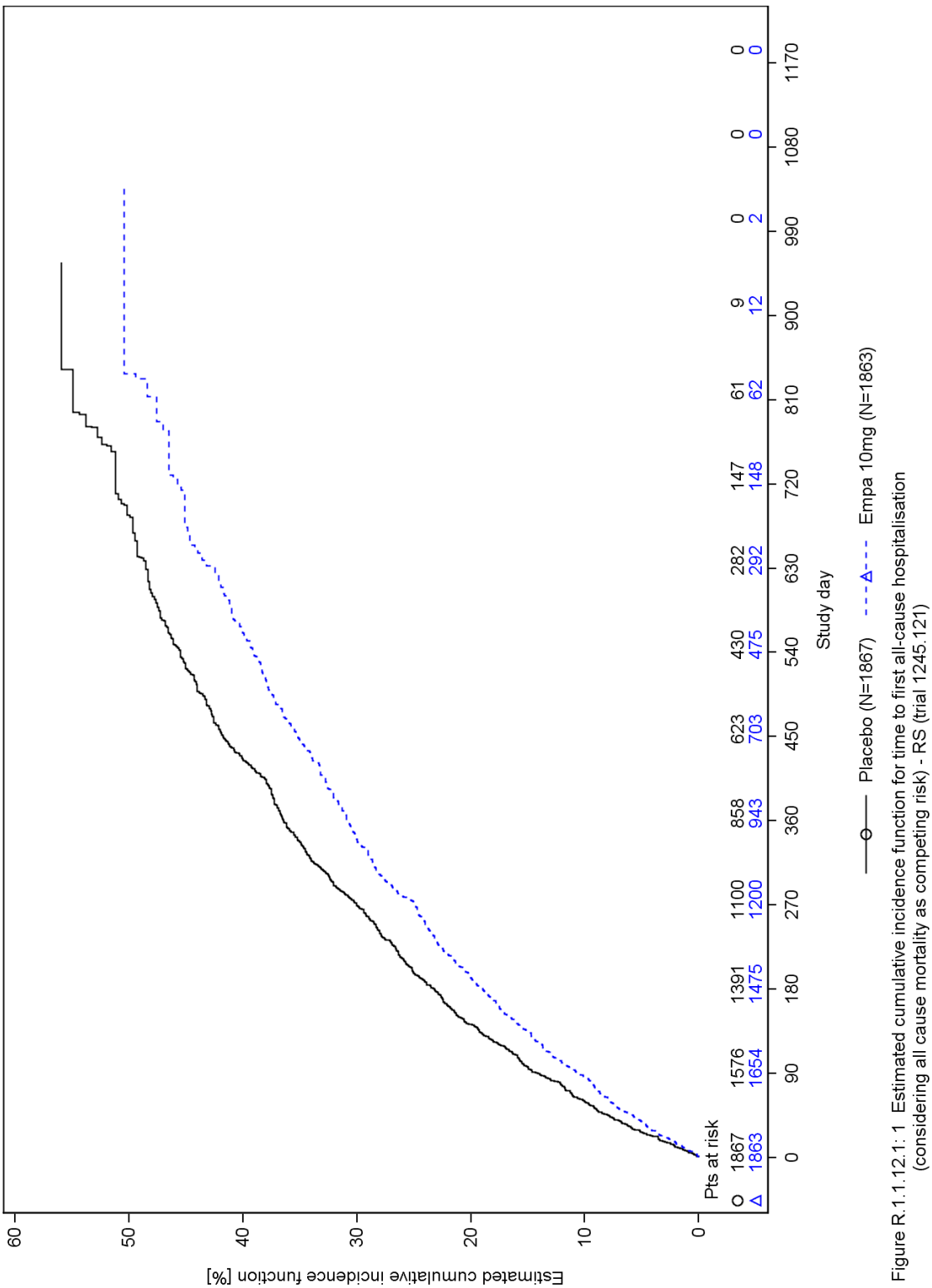

Figure R.1.1.12.1: 1 Estimated cumulative incidence function for time to first all-cause hospitalisation (considering all cause mortality as competing risk) - RS (trial 1245.121)

Table R.1.1.12.1: 1 Cox regr. for time to first all-cause hospitalisation - RS (trial 1245.121)

	Placebo	Empa 10mg
Number of patients in analysis set	1867	1863
Number of analysed patients	1867	1863
Number of patients with event [N(%)]	796 (42.6)	688 (36.9)
Time at risk for event [years]	1816.4	1933.5
Incidence rate [patients with events per 100 patient years at risk]	43.82	35.58
95% confidence interval	(40.83, 46.92)	(32.97, 38.29)
Comparison vs Placebo*		
Hazard ratio		0.82
95% confidence interval		(0.74,0.90)
p-value		<0.0001
Time to event [days]**		
2.5% percentile	15	19
5.0% percentile	27	37
7.5% percentile	41	57
10.0% percentile	59	85
Patients with events [%]**		
1 year	37.2	31.3
2 years	52.5	47.5

* Based on a Cox regression model with terms for age (p=0.5219), baseline eGFR (CKD-EPI) (p<0.0001), sex (p=0.0127), region (p<0.0001), baseline diabetes status (3 cat.) (p=0.0446), baseline LVEF (3 cat.) (p=0.1972) and Treatment (p<0.0001).
**Based on Kaplan-Meier estimates.

R.1.1.12.2

Table R.1.1.12.2: 1 Cox regr. for time to first all-cause hospitalisation by sex - RS (trial 1245.121)

Subgroup Description	Placebo	Empa 10mg
Sex: Male		
Number of patients in analysis set	1411	1426
Number of analysed patients	1411	1426
Number of patients with event [N(%)]	622 (44.1)	541 (37.9)
Time at risk for event [years]	1369.6	1455.2
Incidence rate [patients with events per 100 patient years at risk]	45.41	37.18
95% confidence interval	(41.92, 49.05)	(34.11, 40.37)
Comparison vs Placebo*		
Hazard ratio		0.82
95% confidence interval		(0.73,0.92)
p-value		0.0008
Sex: Female		
Number of patients in analysis set	456	437
Number of analysed patients	456	437
Number of patients with event [N(%)]	174 (38.2)	147 (33.6)
Time at risk for event [years]	446.8	478.2
Incidence rate [patients with events per 100 patient years at risk]	38.94	30.74
95% confidence interval	(33.37, 44.94)	(25.97, 35.90)
Comparison vs Placebo*		
Hazard ratio		0.79
95% confidence interval		(0.64,0.99)
p-value		0.0404

* Based on a Cox regression model with terms for age (p=0.5181), baseline eGFR (CKD-EPI) (p<0.0001), region (p<0.0001), baseline diabetes status (3 cat.) (p=0.0443), baseline LVEF (3 cat.) (p=0.1973), Treatment (p=0.0008), sex (p=0.0123) and Treatment by sex interaction (p=0.7955).

R.1.1.12.3

Table R.1.1.12.3: 1 Cox regr. for time to first all-cause hospitalisation by age (2 cat.) - RS (trial 1245.121)

Subgroup Description	Placebo	Empa 10mg
Age [years]: < 65		
Number of patients in analysis set	740	675
Number of analysed patients	740	675
Number of patients with event [N(%)]	306 (41.4)	224 (33.2)
Time at risk for event [years]	720.1	701.5
Incidence rate [patients with events per 100 patient years at risk]	42.49	31.93
95% confidence interval	(37.86, 47.38)	(27.89, 36.25)
Comparison vs Placebo*		
Hazard ratio		0.77
95% confidence interval		(0.65,0.91)
p-value		0.0029
Age [years]: >= 65		
Number of patients in analysis set	1127	1188
Number of analysed patients	1127	1188
Number of patients with event [N(%)]	490 (43.5)	464 (39.1)
Time at risk for event [years]	1096.3	1231.9
Incidence rate [patients with events per 100 patient years at risk]	44.70	37.66
95% confidence interval	(40.83, 48.74)	(34.31, 41.17)
Comparison vs Placebo*		
Hazard ratio		0.84
95% confidence interval		(0.74,0.96)
p-value		0.0093

* Based on a Cox regression model with terms for baseline eGFR (CKD-EPI) (p<0.0001), sex (p=0.0138), region (p<0.0001), baseline diabetes status (3 cat.) (p=0.0511), baseline LVEF (3 cat.) (p=0.2165), Treatment (p<0.0001), age (2 cat.) (p=0.1311) and Treatment by age (2 cat.) interaction (p=0.3919).

R.1.1.12.4 Subgroup analysis by region (North America, Latin America, Europe, Asia, Other)

Table R.1.1.12.4: 1 Cox regr. for time to first all-cause hospitalisation by region - RS (trial 1245.121)

Subgroup Description	Placebo	Empa 10mg
Region: North America		
Number of patients in analysis set	213	212
Number of analysed patients	213	212
Number of patients with event [N(%)]	115 (54.0)	103 (48.6)
Time at risk for event [years]	185.8	213.7
Incidence rate [patients with events per 100 patient years at risk]	61.91	48.20
95% confidence interval	(51.11, 73.72)	(39.34, 57.94)
Comparison vs Placebo*		
Hazard ratio		0.80
95% confidence interval		(0.62,1.05)
p-value		0.1062
Region: Latin America		
Number of patients in analysis set	645	641
Number of analysed patients	645	641
Number of patients with event [N(%)]	238 (36.9)	200 (31.2)
Time at risk for event [years]	607.8	649.7
Incidence rate [patients with events per 100 patient years at risk]	39.16	30.79
95% confidence interval	(34.34, 44.29)	(26.67, 35.20)
Comparison vs Placebo*		
Hazard ratio		0.79
95% confidence interval		(0.65,0.95)
p-value		0.0120

* Based on a Cox regression model with terms for age (p=0.5588), baseline eGFR (CKD-EPI) (p<0.0001), sex (p=0.0149), baseline diabetes status (3 cat.) (p=0.0441), baseline LVEF (3 cat.) (p=0.1795), Treatment (p=0.0004), region (p<0.0001) and Treatment by region interaction (p=0.1791).

Table R.1.1.12.4: 1 Cox regr. for time to first all-cause hospitalisation by region - RS (trial 1245.121)

Subgroup Description	Placebo	Empa 10mg
Region: Europe		
Number of patients in analysis set	677	676
Number of analysed patients	677	676
Number of patients with event [N(%)]	301 (44.5)	283 (41.9)
Time at risk for event [years]	679.9	686.0
Incidence rate [patients with events per 100 patient years at risk]	44.27	41.25
95% confidence interval	(39.41, 49.41)	(36.59, 46.20)
Comparison vs Placebo*		
Hazard ratio		0.93
95% confidence interval		(0.79,1.10)
p-value		0.3980
Region: Asia		
Number of patients in analysis set	245	248
Number of analysed patients	245	248
Number of patients with event [N(%)]	119 (48.6)	87 (35.1)
Time at risk for event [years]	242.5	280.5
Incidence rate [patients with events per 100 patient years at risk]	49.07	31.02
95% confidence interval	(40.65, 58.27)	(24.84, 37.87)
Comparison vs Placebo*		
Hazard ratio		0.64
95% confidence interval		(0.49,0.85)
p-value		0.0017

* Based on a Cox regression model with terms for age (p=0.5588), baseline eGFR (CKD-EPI) (p<0.0001), sex (p=0.0149), baseline diabetes status (3 cat.) (p=0.0441), baseline LVEF (3 cat.) (p=0.1795), Treatment (p=0.0004), region (p<0.0001) and Treatment by region interaction (p=0.1791).

Table R.1.1.12.4: 1 Cox regr. for time to first all-cause hospitalisation by region - RS (trial 1245.121)

Subgroup Description	Placebo	Empa 10mg
Region: Other		
Number of patients in analysis set	87	86
Number of analysed patients	87	86
Number of patients with event [N(%)]	23 (26.4)	15 (17.4)
Time at risk for event [years]	100.5	103.6
Incidence rate [patients with events per 100 patient years at risk]	22.89	14.48
95% confidence interval	(14.51, 33.15)	(8.11, 22.68)
Comparison vs Placebo*		
Hazard ratio		0.62
95% confidence interval		(0.33,1.19)
p-value		0.1544

* Based on a Cox regression model with terms for age (p=0.5588), baseline eGFR (CKD-EPI) (p<0.0001), sex (p=0.0149), baseline diabetes status (3 cat.) (p=0.0441), baseline LVEF (3 cat.) (p=0.1795), Treatment (p=0.0004), region (p<0.0001) and Treatment by region interaction (p=0.1791).

R.1.1.12.5

R.1.1.12.5 Subgroup analysis by OECD member (Y/N)

Table R.1.1.12.5: 1

Table R.1.1.12.5: 1 Cox regr. for time to first all-cause hospitalisation by OECD member (Y/N) - RS (trial 1245.121)

Subgroup Description	Placebo	Empa 10mg
OECD member: No		
Number of patients in analysis set	741	713
Number of analysed patients	741	713
Number of patients with event [N(%)]	274 (37.0)	213 (29.9)
Time at risk for event [years]	702.3	732.3
Incidence rate [patients with events per 100 patient years at risk]	39.01	29.09
95% confidence interval	(34.53, 43.77)	(25.31, 33.12)
Comparison vs Placebo*		
Hazard ratio		0.74
95% confidence interval		(0.62,0.88)
p-value		0.0010
OECD member: Yes		
Number of patients in analysis set	1126	1150
Number of analysed patients	1126	1150
Number of patients with event [N(%)]	522 (46.4)	475 (41.3)
Time at risk for event [years]	1114.1	1201.2
Incidence rate [patients with events per 100 patient years at risk]	46.85	39.54
95% confidence interval	(42.92, 50.96)	(36.07, 43.18)
Comparison vs Placebo*		
Hazard ratio		0.86
95% confidence interval		(0.76,0.97)
p-value		0.0141

* Based on a Cox regression model with terms for age (p=0.8052), baseline eGFR (CKD-EPI) (p<0.0001), sex (p=0.0145), baseline diabetes status (3 cat.) (p=0.0646), baseline LVEF (3 cat.) (p=0.1271), Treatment (p<0.0001), OECD Member (N) (p=0.0010) and Treatment by OECD Member (N) interaction (p=0.1893).

OECD member (yes/no) countries included:
Yes: United States, Canada, Mexico, Poland, Netherlands, Hungary, Germany, Czech Republic, Italy, France, Spain, United Kingdom, Belgium, Japan, Australia, 'Korea; Republic Of South Korea';
No: Brazil, Argentina, China, India.

R.1.1.12.6

R.1.1.12.6 Subgroup analysis by NYHA at baseline (II, III/IV - 2 cat.)

Figure R.1.1.12.6: 1

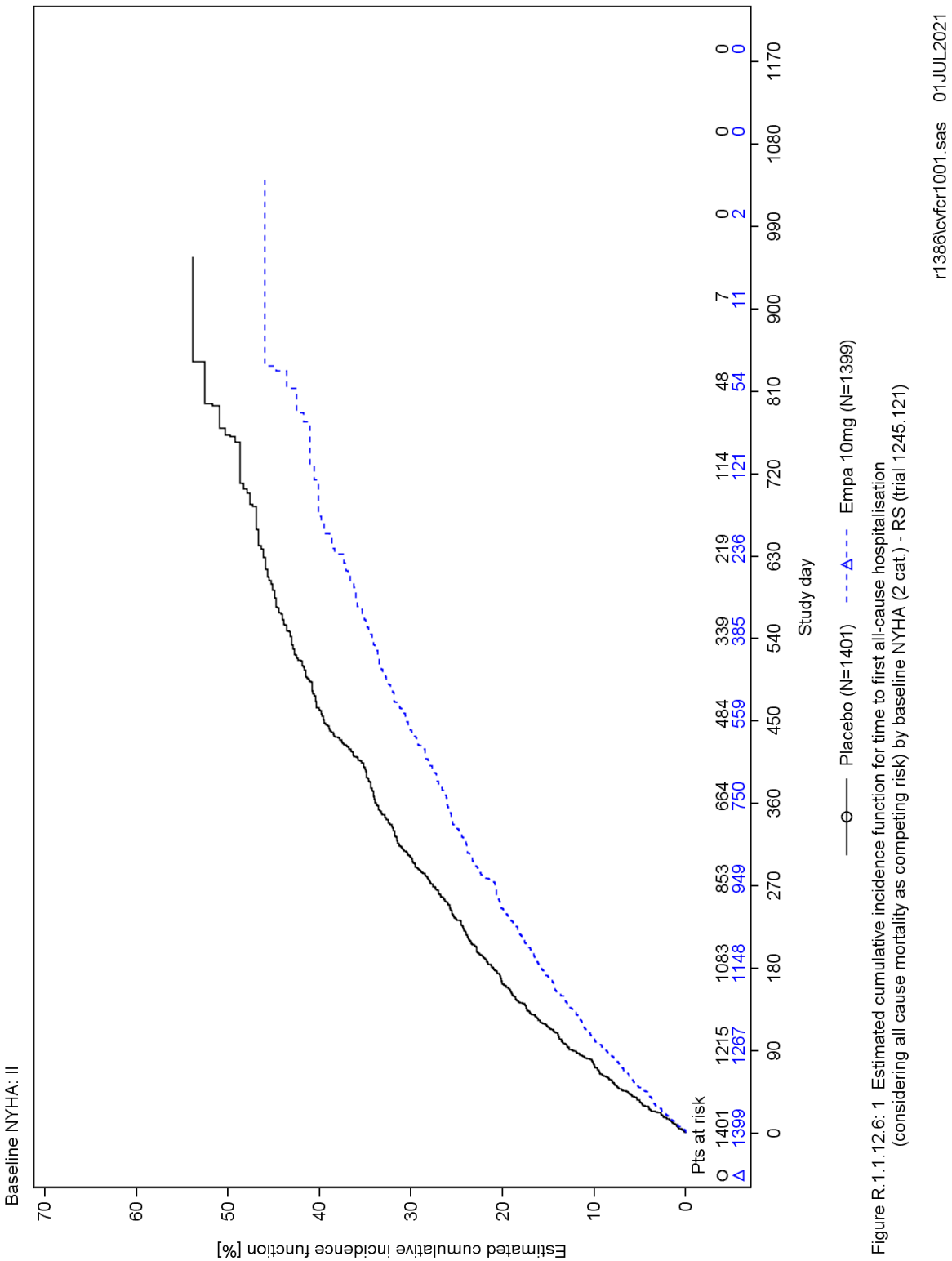

Figure R.1.1.12.6: 1 Estimated cumulative incidence function for time to first all-cause hospitalisation (considering all cause mortality as competing risk) by baseline NYHA (2 cat.) - RS (trial 1245.121)

Figure R.1.1.12.6: 1

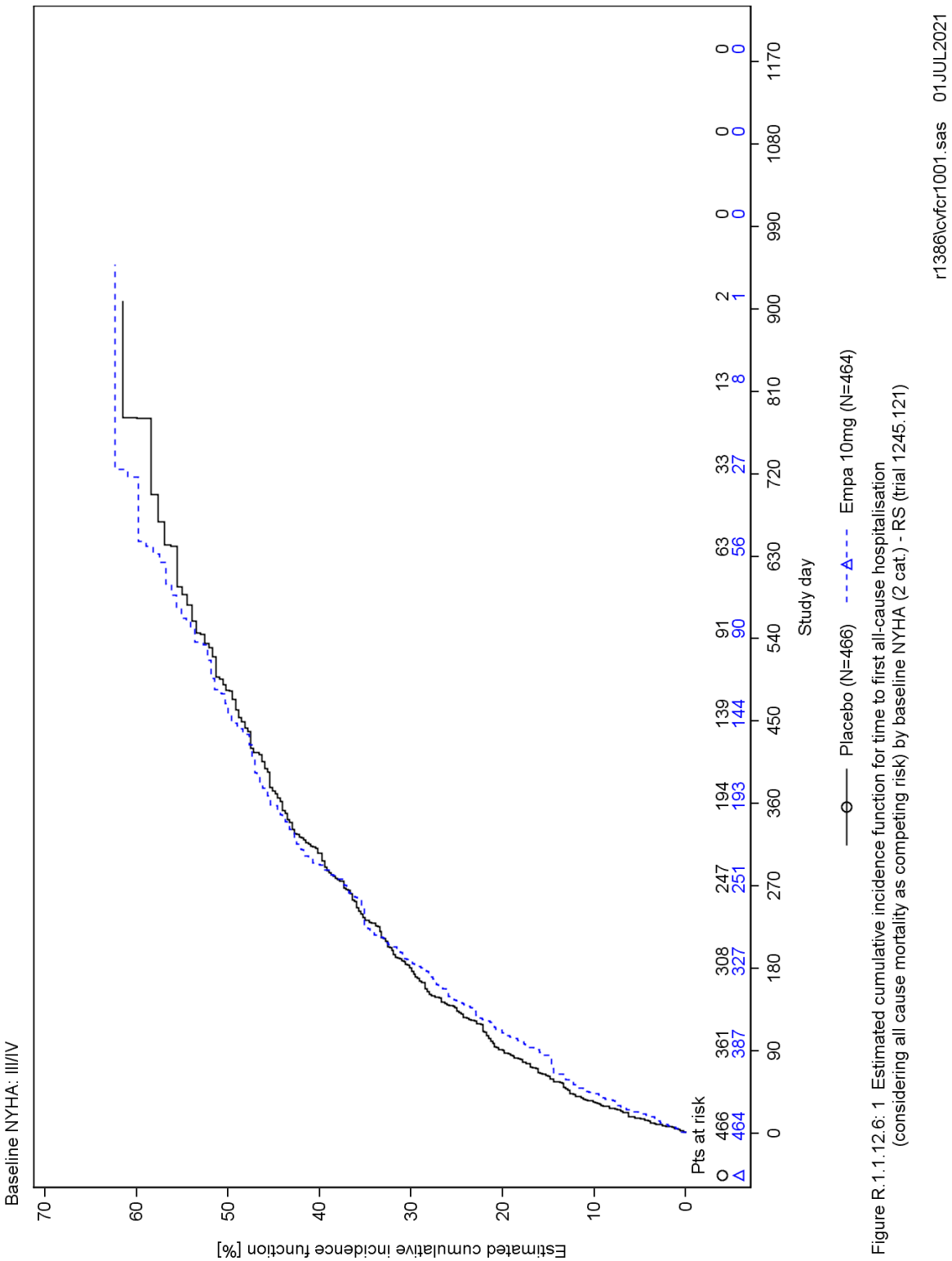

Figure R.1.1.12.6: 1 Estimated cumulative incidence function for time to first all-cause hospitalisation (considering all cause mortality as competing risk) by baseline NYHA (2 cat.) - RS (trial 1245.121)

Table R.1.1.12.6: 1

Table R.1.1.12.6: 1 Cox regr. for time to first all-cause hospitalisation by baseline NYHA (2 cat.) - RS (trial 1245.121)

Subgroup Description	Placebo	Empa 10mg
Baseline NYHA: II		
Number of patients in analysis set	1401	1399
Number of analysed patients	1401	1399
Number of patients with event [N(%)]	559 (39.9)	449 (32.1)
Time at risk for event [years]	1405.2	1515.0
Incidence rate [patients with events per 100 patient years at risk]	39.78	29.64
95% confidence interval	(36.55, 43.14)	(26.96, 32.44)
Comparison vs Placebo*		
Hazard ratio		0.75
95% confidence interval		(0.66,0.85)
p-value		<0.0001
Baseline NYHA: III/IV		
Number of patients in analysis set	466	464
Number of analysed patients	466	464
Number of patients with event [N(%)]	237 (50.9)	239 (51.5)
Time at risk for event [years]	411.2	418.4
Incidence rate [patients with events per 100 patient years at risk]	57.64	57.12
95% confidence interval	(50.53, 65.20)	(50.10, 64.58)
Comparison vs Placebo*		
Hazard ratio		0.97
95% confidence interval		(0.81,1.17)
p-value		0.7760

* Based on a Cox regression model with terms for age (p=0.6128), baseline eGFR (CKD-EPI) (p<0.0001), sex (p=0.0031), region (p<0.0001), baseline diabetes status (3 cat.) (p=0.1225), baseline LVEF (3 cat.) (p=0.2778), Treatment (p=0.0051), baseline NYHA (2 cat.) (p<0.0001) and Treatment by baseline NYHA (2 cat.) interaction (p=0.0198).

R.1.1.12.7

Table R.1.1.12.7: 1

Table R.1.1.12.7: 1 Cox regr. for time to first all-cause hospitalisation by diabetes at baseline (2 cat.) - RS (trial 1245.121)

Subgroup Description	Placebo	Empa 10mg
Baseline diabetes status: Diabetic		
Number of patients in analysis set	929	927
Number of analysed patients	929	927
Number of patients with event [N(%)]	413 (44.5)	368 (39.7)
Time at risk for event [years]	901.1	962.9
Incidence rate [patients with events per 100 patient years at risk]	45.83	38.22
95% confidence interval	(41.52, 50.36)	(34.41, 42.22)
Comparison vs Placebo*		
Hazard ratio		0.84
95% confidence interval		(0.73,0.97)
p-value		0.0157
Baseline diabetes status: Non-Diabetic		
Number of patients in analysis set	938	936
Number of analysed patients	938	936
Number of patients with event [N(%)]	383 (40.8)	320 (34.2)
Time at risk for event [years]	915.3	970.6
Incidence rate [patients with events per 100 patient years at risk]	41.84	32.97
95% confidence interval	(37.76, 46.14)	(29.46, 36.68)
Comparison vs Placebo*		
Hazard ratio		0.79
95% confidence interval		(0.68,0.91)
p-value		0.0017

* Based on a Cox regression model with terms for age (p=0.4902), baseline eGFR (CKD-EPI) (p<0.0001), sex (p=0.0122), region (p<0.0001), baseline LVEF (3 cat.) (p=0.1888), Treatment (p<0.0001), baseline diabetes status (2 cat.) (p=0.0362) and Treatment by baseline diabetes status (2 cat.) interaction (p=0.5313).

R.1.1.12.8 Subgroup analysis by BMI at baseline (<30, >=30)

Table R.1.1.12.8: 1 Cox regr. for time to first all-cause hospitalisation by baseline BMI [kg/m2] - RS (trial 1245.121)

Subgroup Description	Placebo	Empa 10mg
Baseline BMI [kg/m²]: <30		
Number of patients in analysis set	1300	1263
Number of analysed patients	1300	1263
Number of patients with event [N(%)]	548 (42.2)	436 (34.5)
Time at risk for event [years]	1297.3	1330.0
Incidence rate [patients with events per 100 patient years at risk]	42.24	32.78
95% confidence interval	(38.78, 45.85)	(29.78, 35.93)
Comparison vs Placebo*		
Hazard ratio		0.78
95% confidence interval		(0.68,0.88)
p-value		<0.0001
Baseline BMI [kg/m²]: >=30		
Number of patients in analysis set	567	600
Number of analysed patients	567	600
Number of patients with event [N(%)]	248 (43.7)	252 (42.0)
Time at risk for event [years]	519.2	603.4
Incidence rate [patients with events per 100 patient years at risk]	47.77	41.76
95% confidence interval	(42.01, 53.90)	(36.76, 47.07)
Comparison vs Placebo*		
Hazard ratio		0.88
95% confidence interval		(0.74,1.05)
p-value		0.1725

* Based on a Cox regression model with terms for age (p=0.7806), baseline eGFR (CKD-EPI) (p<0.0001), sex (p=0.0093), region (p<0.0001), baseline diabetes status (3 cat.) (p=0.0794), baseline LVEF (3 cat.) (p=0.1735), Treatment (p=0.0007), baseline BMI (2 cat.) (p=0.0199) and Treatment by baseline BMI (2 cat.) interaction (p=0.2366).

R.1.1.12.9

R.1.1.12.9 Subgroup analysis by eGFR at baseline (<60, >=60)

Figure R.1.1.12.9: 1

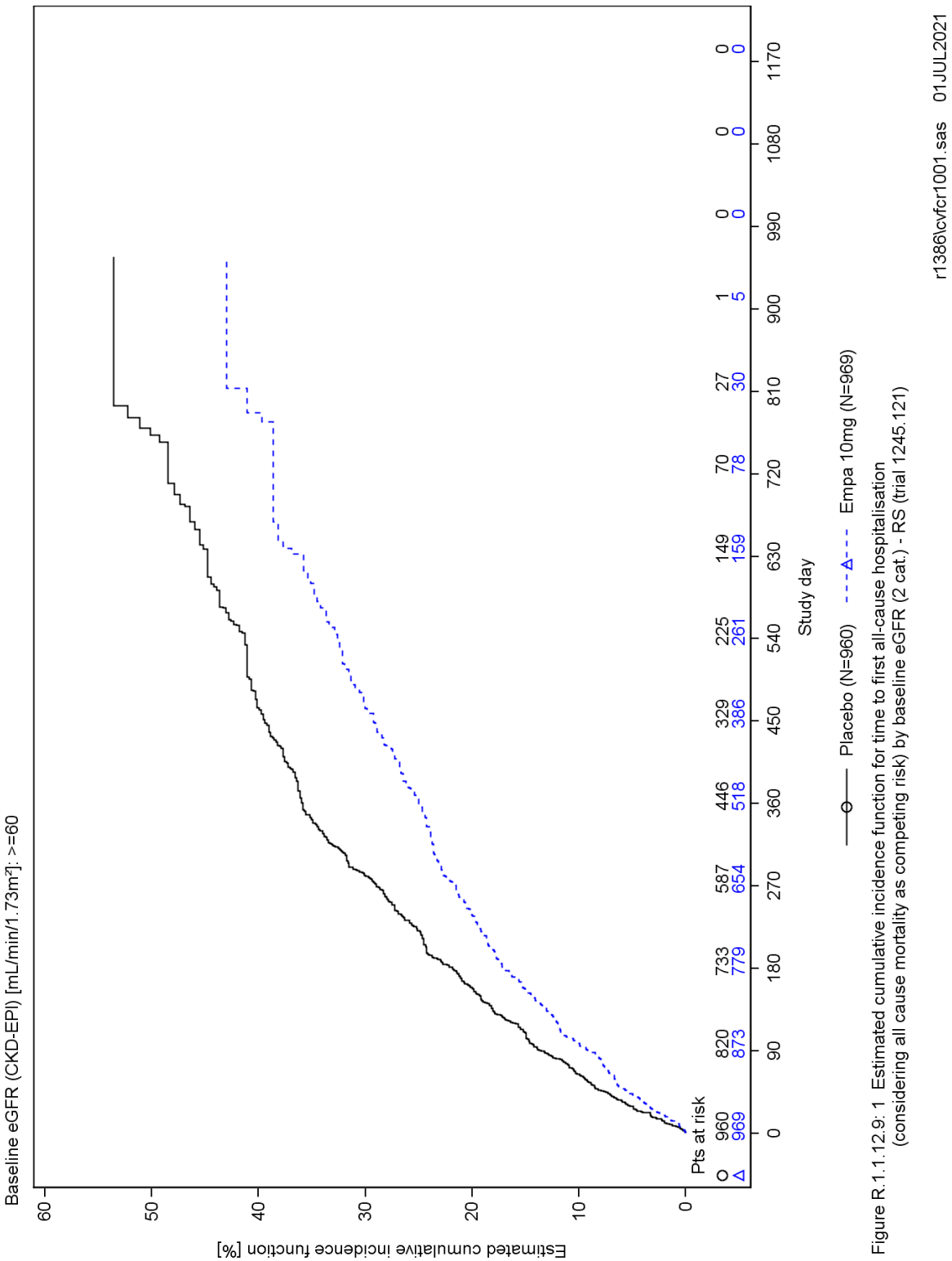

Figure R.1.1.12.9: 1 Estimated cumulative incidence function for time to first all-cause hospitalisation (considering all cause mortality as competing risk) by baseline eGFR (2 cat.) - RS (trial 1245.121)

Figure R.1.1.12.9: 1

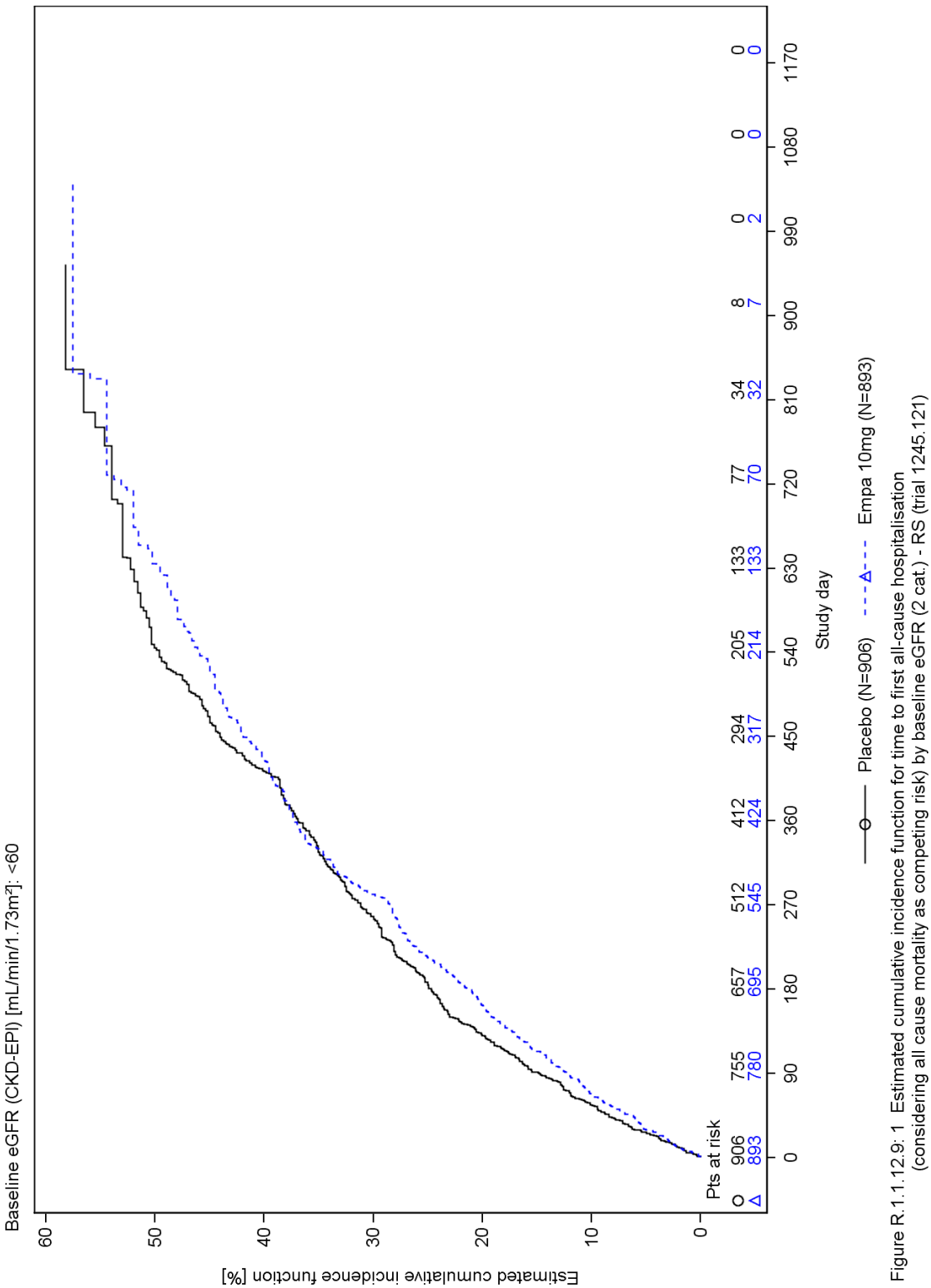

Figure R.1.1.12.9: 1 Estimated cumulative incidence function for time to first all-cause hospitalisation (considering all cause mortality as competing risk) by baseline eGFR (2 cat.) - RS (trial 1245.121)

Table R.1.1.12.9: 1 Cox regr. for time to first all-cause hospitalisation by baseline eGFR (2 cat.) - RS (trial 1245.121)

Subgroup Description	Placebo	Empa 10mg
Baseline eGFR (CKD-EPI) [mL/min/1.73m²]: >=60		
Number of patients in analysis set	960	969
Number of analysed patients	960	969
Number of patients with event [N(%)]	386 (40.2)	298 (30.8)
Time at risk for event [years]	948.3	1036.3
Incidence rate [patients with events per 100 patient years at risk]	40.70	28.75
95% confidence interval	(36.74, 44.86)	(25.58, 32.11)
Comparison vs Placebo*		
Hazard ratio		0.71
95% confidence interval		(0.61,0.82)
p-value		<0.0001
Baseline eGFR (CKD-EPI) [mL/min/1.73m²]: <60		
Number of patients in analysis set	906	893
Number of analysed patients	906	893
Number of patients with event [N(%)]	409 (45.1)	390 (43.7)
Time at risk for event [years]	867.3	895.9
Incidence rate [patients with events per 100 patient years at risk]	47.16	43.53
95% confidence interval	(42.70, 51.84)	(39.32, 47.96)
Comparison vs Placebo*		
Hazard ratio		0.93
95% confidence interval		(0.81,1.06)
p-value		0.2786

* Based on a Cox regression model with terms for age (p=0.4308), sex (p=0.0202), region (p<0.0001), baseline diabetes status (3 cat.) (p=0.0340), baseline LVEF (3 cat.) (p=0.1955), Treatment (p<0.0001), baseline eGFR (CKD-EPI) (2 cat.) (p<0.0001) and Treatment by baseline eGFR (CKD-EPI) (2 cat.) interaction (p=0.0102).
2 patients were excluded as the subgroup variable was missing.

R.1.1.12.10

Table R.1.1.12.10: 1 Cox regr. for time to first all-cause hospitalisation by history of HHF within 12 months - RS (trial 1245.121)

Subgroup Description	Placebo	Empa 10mg
History of HHF (in the last 12 months): No		
Number of patients in analysis set	1293	1286
Number of analysed patients	1293	1286
Number of patients with event [N(%)]	530 (41.0)	440 (34.2)
Time at risk for event [years]	1322.3	1400.2
Incidence rate [patients with events per 100 patient years at risk]	40.08	31.43
95% confidence interval	(36.74, 43.57)	(28.56, 34.43)
Comparison vs Placebo*		
Hazard ratio		0.79
95% confidence interval		(0.70,0.90)
p-value		0.0004
History of HHF (in the last 12 months): Yes		
Number of patients in analysis set	574	577
Number of analysed patients	574	577
Number of patients with event [N(%)]	266 (46.3)	248 (43.0)
Time at risk for event [years]	494.2	533.3
Incidence rate [patients with events per 100 patient years at risk]	53.83	46.50
95% confidence interval	(47.55, 60.49)	(40.89, 52.47)
Comparison vs Placebo*		
Hazard ratio		0.85
95% confidence interval		(0.71,1.01)
p-value		0.0633

* Based on a Cox regression model with terms for age (p=0.7701), baseline eGFR (CKD-EPI) (p<0.0001), sex (p=0.0132), region (p<0.0001), baseline diabetes status (3 cat.) (p=0.0847), baseline LVEF (3 cat.) (p=0.4273), Treatment (p=0.0003), history of HHF (p<0.0001) and Treatment by history of HHF interaction (p=0.5449).

R.1.1.12.11

Table R.1.1.12.11: 1 Cox regr. for time to first all-cause hospitalisation by cause of heart failure - RS (trial 1245.121)

Subgroup Description	Placebo	Empa 10mg
Cause of heart failure: Ischemic		
Number of patients in analysis set	946	983
Number of analysed patients	946	983
Number of patients with event [N(%)]	409 (43.2)	392 (39.9)
Time at risk for event [years]	941.7	1020.4
Incidence rate [patients with events per 100 patient years at risk]	43.43	38.42
95% confidence interval	(39.32, 47.74)	(34.71, 42.31)
Comparison vs Placebo*		
Hazard ratio		0.89
95% confidence interval		(0.78,1.02)
p-value		0.1058
Cause of heart failure: Non-ischemic		
Number of patients in analysis set	921	880
Number of analysed patients	921	880
Number of patients with event [N(%)]	387 (42.0)	296 (33.6)
Time at risk for event [years]	874.7	913.0
Incidence rate [patients with events per 100 patient years at risk]	44.24	32.42
95% confidence interval	(39.95, 48.76)	(28.83, 36.22)
Comparison vs Placebo*		
Hazard ratio		0.73
95% confidence interval		(0.63,0.85)
p-value		<0.0001

* Based on a Cox regression model with terms for age (p=0.5426), baseline eGFR (CKD-EPI) (p<0.0001), sex (p=0.0119), region (p<0.0001), baseline diabetes status (3 cat.) (p=0.0501), baseline LVEF (3 cat.) (p=0.1935), Treatment (p<0.0001), cause of heart failure (2 cat.) (p=0.8961) and Treatment by cause of heart failure (2 cat.) interaction (p=0.0620).

R.1.1.12.12 Subgroup analysis by heart failure physiology (LVEF <= 30% and NTproBNP<median; LVEF <= 30% and NTproBNP>=median; LVEF > 30%)

Table R.1.1.12.12: 1 Cox regr. for time to first all-cause hospitalisation by heart failure physiology - RS (trial 1245.121)

Subgroup Description	Placebo	Empa 10mg
Heart failure physiology: LVEF <= 30% and NTproBNP < median		
Number of patients in analysis set	723	698
Number of analysed patients	723	698
Number of patients with event [N(%)]	264 (36.5)	204 (29.2)
Time at risk for event [years]	763.6	795.3
Incidence rate [patients with events per 100 patient years at risk]	34.57	25.65
95% confidence interval	(30.53, 38.86)	(22.25, 29.29)
Comparison vs Placebo*		
Hazard ratio		0.74
95% confidence interval		(0.62,0.89)
p-value		0.0015
Heart failure physiology: LVEF <= 30% and NTproBNP >= median		
Number of patients in analysis set	661	631
Number of analysed patients	661	631
Number of patients with event [N(%)]	342 (51.7)	280 (44.4)
Time at risk for event [years]	593.6	604.6
Incidence rate [patients with events per 100 patient years at risk]	57.61	46.31
95% confidence interval	(51.67, 63.87)	(41.05, 51.89)
Comparison vs Placebo*		
Hazard ratio		0.80
95% confidence interval		(0.68,0.94)
p-value		0.0055

* Based on a Cox regression model with terms for age (p=0.5863), baseline eGFR (CKD-EPI) (p<0.0001), sex (p=0.0094), region (p<0.0001), baseline diabetes status (3 cat.) (p=0.0535), Treatment (p=0.0003), heart failure physiology (p<0.0001) and Treatment by heart failure physiology interaction (p=0.2032).
16 patients were excluded as the subgroup variable was missing.
The p-value for treatment by subgroup interaction trend test is 0.1321.

Table R.1.1.12.12: 1 Cox regr. for time to first all-cause hospitalisation by heart failure physiology - RS (trial 1245.121)

Subgroup Description	Placebo	Empa 10mg
Heart failure physiology: LVEF > 30%		
Number of patients in analysis set	475	526
Number of analysed patients	475	526
Number of patients with event [N(%)]	185 (38.9)	201 (38.2)
Time at risk for event [years]	451.5	527.2
Incidence rate [patients with events per 100 patient years at risk]	40.97	38.13
95% confidence interval	(35.28, 47.08)	(33.04, 43.58)
Comparison vs Placebo*		
Hazard ratio		0.95
95% confidence interval		(0.78,1.16)
p-value		0.5924

* Based on a Cox regression model with terms for age (p=0.5863), baseline eGFR (CKD-EPI) (p<0.0001), sex (p=0.0094), region (p<0.0001), baseline diabetes status (3 cat.) (p=0.0535), Treatment (p=0.0003), heart failure physiology (p<0.0001) and Treatment by heart failure physiology interaction (p=0.2032).
16 patients were excluded as the subgroup variable was missing.
The p-value for treatment by subgroup interaction trend test is 0.1321.

R.1.1.12.13

R.1.1.12.13 Subgroup analysis by baseline use of MRA

Table R.1.1.12.13: 1

Table R.1.1.12.13: 1 Cox regr. for time to first all-cause hospitalisation by baseline use of MRA (Y/N) - RS (trial 1245.121)

Subgroup Description	Placebo	Empa 10mg
Baseline use of MRA: No		
Number of patients in analysis set	512	557
Number of analysed patients	512	557
Number of patients with event [N(%)]	239 (46.7)	222 (39.9)
Time at risk for event [years]	490.5	599.2
Incidence rate [patients with events per 100 patient years at risk]	48.72	37.05
95% confidence interval	(42.74, 55.09)	(32.34, 42.08)
Comparison vs Placebo*		
Hazard ratio		0.78
95% confidence interval		(0.65,0.94)
p-value		0.0090
Baseline use of MRA: Yes		
Number of patients in analysis set	1355	1306
Number of analysed patients	1355	1306
Number of patients with event [N(%)]	557 (41.1)	466 (35.7)
Time at risk for event [years]	1325.9	1334.3
Incidence rate [patients with events per 100 patient years at risk]	42.01	34.93
95% confidence interval	(38.59, 45.57)	(31.83, 38.17)
Comparison vs Placebo*		
Hazard ratio		0.83
95% confidence interval		(0.73,0.94)
p-value		0.0030

* Based on a Cox regression model with terms for age (p=0.5050), baseline eGFR (CKD-EPI) (p<0.0001), sex (p=0.0131), region (p<0.0001), baseline diabetes status (3 cat.) (p=0.0456), baseline LVEF (3 cat.) (p=0.2003), Treatment (p=0.0001), baseline use of MRA (p=0.8715) and Treatment by baseline use of MRA interaction (p=0.6095).

R.1.1.12.14

R.1.1.12.14 Subgroup analysis by baseline use of ARNi

Table R.1.1.12.14: 1 Cox regr. for time to first all-cause hospitalisation by baseline use of ARNi (Y/N) - RS (trial 1245.121)

Subgroup Description	Placebo	Empa 10mg
Baseline use of ARNi: No		
Number of patients in analysis set	1480	1523
Number of analysed patients	1480	1523
Number of patients with event [N(%)]	621 (42.0)	560 (36.8)
Time at risk for event [years]	1459.0	1608.9
Incidence rate [patients with events per 100 patient years at risk]	42.56	34.81
95% confidence interval	(39.28, 45.98)	(31.98, 37.75)
Comparison vs Placebo*		
Hazard ratio		0.81
95% confidence interval		(0.72,0.91)
p-value		0.0003
Baseline use of ARNi: Yes		
Number of patients in analysis set	387	340
Number of analysed patients	387	340
Number of patients with event [N(%)]	175 (45.2)	128 (37.6)
Time at risk for event [years]	357.4	324.6
Incidence rate [patients with events per 100 patient years at risk]	48.96	39.43
95% confidence interval	(41.97, 56.48)	(32.90, 46.55)
Comparison vs Placebo*		
Hazard ratio		0.84
95% confidence interval		(0.67,1.06)
p-value		0.1352

* Based on a Cox regression model with terms for age (p=0.5346), baseline eGFR (CKD-EPI) (p<0.0001), sex (p=0.0121), region (p<0.0001), baseline diabetes status (3 cat.) (p=0.0451), baseline LVEF (3 cat.) (p=0.1951), Treatment (p=0.0033), baseline use of ARNi (p=0.3494) and Treatment by baseline use of ARNi interaction (p=0.7897).

R.1.1.12.15 Subgroup analysis by bl. LVEF (<= 30%, >30% -<= 35% , > 35%)

Table R.1.1.12.15: 1 Cox regr. for time to first all-cause hospitalisation by bl. LVEF (3 cat.) - RS (trial 1245.121)

Subgroup Description	Placebo	Empa 10mg
Baseline LVEF: <=30		
Number of patients in analysis set	1392	1337
Number of analysed patients	1392	1337
Number of patients with event [N(%)]	611 (43.9)	487 (36.4)
Time at risk for event [years]	1364.9	1406.3
Incidence rate [patients with events per 100 patient years at risk]	44.77	34.63
95% confidence interval	(41.29, 48.38)	(31.62, 37.77)
Comparison vs Placebo*		
Hazard ratio		0.77
95% confidence interval		(0.69,0.87)
p-value		<0.0001
Baseline LVEF: >30 to <=35		
Number of patients in analysis set	361	398
Number of analysed patients	361	398
Number of patients with event [N(%)]	135 (37.4)	148 (37.2)
Time at risk for event [years]	353.3	408.3
Incidence rate [patients with events per 100 patient years at risk]	38.21	36.25
95% confidence interval	(32.04, 44.92)	(30.64, 42.31)
Comparison vs Placebo*		
Hazard ratio		0.94
95% confidence interval		(0.75,1.19)
p-value		0.6332

* Based on a Cox regression model with terms for age (p=0.5120), baseline eGFR (CKD-EPI) (p<0.0001), sex (p=0.0122), region (p<0.0001), baseline diabetes status (3 cat.) (p=0.0421), Treatment (p=0.1479), baseline LVEF (3 cat.) (p=0.1950) and Treatment by baseline LVEF (3 cat.) interaction (p=0.2093).
The p-value for treatment by subgroup interaction trend test is 0.0889.

Table R.1.1.12.15: 1 Cox regr. for time to first all-cause hospitalisation by bl. LVEF (3 cat.) - RS (trial 1245.121)

Subgroup Description	Placebo	Empa 10mg
Baseline LVEF: >35		
Number of patients in analysis set	114	128
Number of analysed patients	114	128
Number of patients with event [N(%)]	50 (43.9)	53 (41.4)
Time at risk for event [years]	98.2	118.8
Incidence rate [patients with events per 100 patient years at risk]	50.90	44.60
95% confidence interval	(37.78, 65.94)	(33.40, 57.38)
Comparison vs Placebo*		
Hazard ratio		0.97
95% confidence interval		(0.66,1.43)
p-value		0.8822

* Based on a Cox regression model with terms for age (p=0.5120), baseline eGFR (CKD-EPI) (p<0.0001), sex (p=0.0122), region (p<0.0001), baseline diabetes status (3 cat.) (p=0.0421), Treatment (p=0.1479), baseline LVEF (3 cat.) (p=0.1950) and Treatment by baseline LVEF (3 cat.) interaction (p=0.2093).
The p-value for treatment by subgroup interaction trend test is 0.0889.

R.1.1.12.16 Subgroup analysis by bl. NTproBNP </>= median (median based on total patients)

Table R.1.1.12.16: 1 Cox regr. for time to first all-cause hospitalisation by bl. NTproBNP (<median,>= median) (median based on total patients) - RS (trial 1245.121)

Subgroup Description	Placebo	Empa 10mg
Baseline NTproBNP: < median		
Number of patients in analysis set	920	942
Number of analysed patients	920	942
Number of patients with event [N(%)]	330 (35.9)	283 (30.0)
Time at risk for event [years]	982.4	1058.3
Incidence rate [patients with events per 100 patient years at risk]	33.59	26.74
95% confidence interval	(30.06, 37.31)	(23.72, 29.95)
Comparison vs Placebo*		
Hazard ratio		0.80
95% confidence interval		(0.68,0.93)
p-value		0.0051
Baseline NTproBNP: >= median		
Number of patients in analysis set	946	920
Number of analysed patients	946	920
Number of patients with event [N(%)]	465 (49.2)	405 (44.0)
Time at risk for event [years]	833.2	874.0
Incidence rate [patients with events per 100 patient years at risk]	55.81	46.34
95% confidence interval	(50.85, 60.99)	(41.94, 50.96)
Comparison vs Placebo*		
Hazard ratio		0.84
95% confidence interval		(0.73,0.96)
p-value		0.0099

* Based on a Cox regression model with terms for age (p=0.4188), baseline eGFR (CKD-EPI) (p=0.0001), sex (p=0.0138), region (p<0.0001), baseline diabetes status (3 cat.) (p=0.0445), baseline LVEF (3 cat.) (p=0.3305), Treatment (p=0.0001), baseline NTproBNP (2 cat.) (p<0.0001) and Treatment by baseline NTproBNP (2 cat.) interaction (p=0.6264).
2 patients were excluded as the subgroup variable was missing.

Median: 1910 [pg/mL]

R.1.1.13 Time to first event of all-cause mortality or all-cause hospitalisation

R.1.1.13.1

Figure R.1.1.13.1: 1

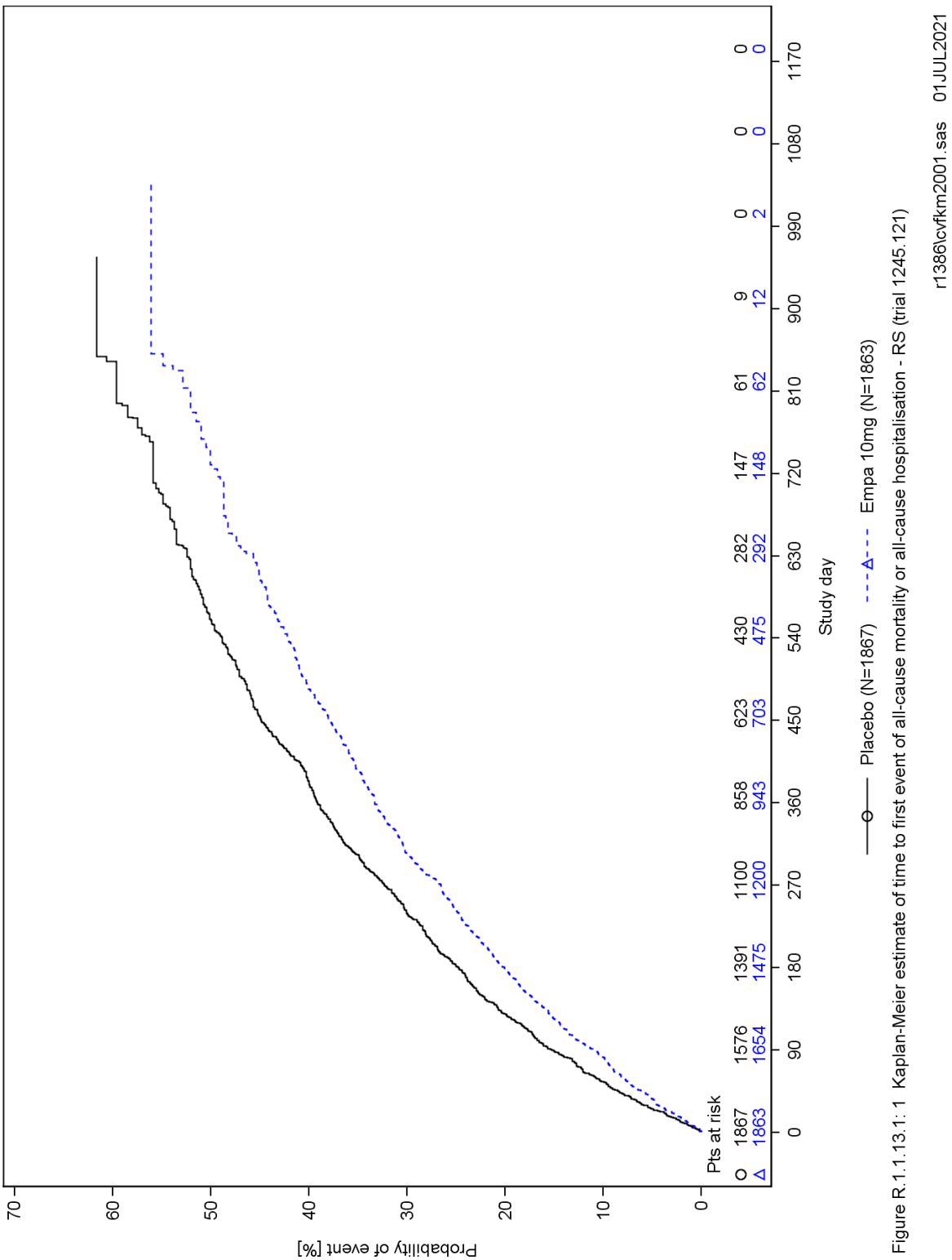

Figure R.1.1.13.1: 1 Kaplan-Meier estimate of time to first event of all-cause mortality or all-cause hospitalisation - RS (trial 1245.121)

Table R.1.1.13.1: 1 Cox regr. for time to first event of all-cause mortality or all-cause hospitalisation - RS (trial 1245.121)

	Placebo	Empa 10mg
Number of patients in analysis set	1867	1863
Number of analysed patients	1867	1863
Number of patients with event [N(%)]	860 (46.1)	743 (39.9)
Time at risk for event [years]	1816.4	1933.5
Incidence rate [patients with events per 100 patient years at risk]	47.35	38.43
95% confidence interval	(44.23, 50.56)	(35.71, 41.24)
Comparison vs Placebo*		
Hazard ratio		0.81
95% confidence interval		(0.74,0.90)
p-value		<0.0001
Time to event [days]**		
2.5% percentile	14	18
5.0% percentile	25	36
7.5% percentile	40	54
10.0% percentile	55	82
Patients with events [%]**		
1 year	39.3	33.3
2 years	55.9	50.1

* Based on a Cox regression model with terms for age (p=0.5685), baseline eGFR (CKD-EPI) (p<0.0001), sex (p=0.0027), region (p<0.0001), baseline diabetes status (3 cat.) (p=0.0702), baseline LVEF (3 cat.) (p=0.4432) and Treatment (p<0.0001).
**Based on Kaplan-Meier estimates.

R.1.1.13.2

R.1.1.13.2 Subgroup analysis by sex

Table R.1.1.13.2: 1 Cox regr. for time to first event of all-cause mortality or all-cause hospitalisation by sex - RS (trial 1245.121)

Subgroup Description	Placebo	Empa 10mg
Sex: Male		
Number of patients in analysis set	1411	1426
Number of analysed patients	1411	1426
Number of patients with event [N(%)]	674 (47.8)	587 (41.2)
Time at risk for event [years]	1369.6	1455.2
Incidence rate [patients with events per 100 patient years at risk]	49.21	40.34
95% confidence interval	(45.57, 53.00)	(37.14, 43.67)
Comparison vs Placebo*		
Hazard ratio		0.82
95% confidence interval		(0.74,0.92)
p-value		0.0005
Sex: Female		
Number of patients in analysis set	456	437
Number of analysed patients	456	437
Number of patients with event [N(%)]	186 (40.8)	156 (35.7)
Time at risk for event [years]	446.8	478.2
Incidence rate [patients with events per 100 patient years at risk]	41.63	32.62
95% confidence interval	(35.86, 47.82)	(27.70, 37.93)
Comparison vs Placebo*		
Hazard ratio		0.79
95% confidence interval		(0.64,0.98)
p-value		0.0297

* Based on a Cox regression model with terms for age (p=0.5632), baseline eGFR (CKD-EPI) (p<0.0001), region (p<0.0001), baseline diabetes status (3 cat.) (p=0.0697), baseline LVEF (3 cat.) (p=0.4433), Treatment (p=0.0004), sex (p=0.0025) and Treatment by sex interaction (p=0.7459).

R.1.1.13.3

Table R.1.1.13.3: 1 Cox regr. for time to first event of all-cause mortality or all-cause hospitalisation by age (2 cat.) - RS (trial 1245.121)

Subgroup Description	Placebo	Empa 10mg
Age [years]: < 65		
Number of patients in analysis set	740	675
Number of analysed patients	740	675
Number of patients with event [N(%)]	331 (44.7)	248 (36.7)
Time at risk for event [years]	720.1	701.5
Incidence rate [patients with events per 100 patient years at risk]	45.96	35.35
95% confidence interval	(41.14, 51.05)	(31.09, 39.89)
Comparison vs Placebo*		
Hazard ratio		0.79
95% confidence interval		(0.67,0.93)
p-value		0.0047
Age [years]: >= 65		
Number of patients in analysis set	1127	1188
Number of analysed patients	1127	1188
Number of patients with event [N(%)]	529 (46.9)	495 (41.7)
Time at risk for event [years]	1096.3	1231.9
Incidence rate [patients with events per 100 patient years at risk]	48.25	40.18
95% confidence interval	(44.23, 52.45)	(36.72, 43.80)
Comparison vs Placebo*		
Hazard ratio		0.83
95% confidence interval		(0.74,0.94)
p-value		0.0036

* Based on a Cox regression model with terms for baseline eGFR (CKD-EPI) (p<0.0001), sex (p=0.0028), region (p<0.0001), baseline diabetes status (3 cat.) (p=0.0813), baseline LVEF (3 cat.) (p=0.4746), Treatment (p<0.0001), age (2 cat.) (p=0.0827) and Treatment by age (2 cat.) interaction (p=0.5954).

R.1.1.13.4 Subgroup analysis by region (North America, Latin America, Europe, Asia, Other)

Table R.1.1.13.4: 1 Cox regr. for time to first event of all-cause mortality or all-cause hospitalisation by region - RS (trial 1245.121)

Subgroup Description	Placebo	Empa 10mg
Region: North America		
Number of patients in analysis set	213	212
Number of analysed patients	213	212
Number of patients with event [N(%)]	118 (55.4)	105 (49.5)
Time at risk for event [years]	185.8	213.7
Incidence rate [patients with events per 100 patient years at risk]	63.52	49.13
95% confidence interval	(52.58, 75.48)	(40.19, 58.97)
Comparison vs Placebo*		
Hazard ratio		0.79
95% confidence interval		(0.61,1.03)
p-value		0.0871
Region: Latin America		
Number of patients in analysis set	645	641
Number of analysed patients	645	641
Number of patients with event [N(%)]	265 (41.1)	225 (35.1)
Time at risk for event [years]	607.8	649.7
Incidence rate [patients with events per 100 patient years at risk]	43.60	34.63
95% confidence interval	(38.51, 49.01)	(30.26, 39.30)
Comparison vs Placebo*		
Hazard ratio		0.79
95% confidence interval		(0.66,0.95)
p-value		0.0109

* Based on a Cox regression model with terms for age (p=0.6066), baseline eGFR (CKD-EPI) (p<0.0001), sex (p=0.0032), baseline diabetes status (3 cat.) (p=0.0696), baseline LVEF (3 cat.) (p=0.4173), Treatment (p=0.0002), region (p<0.0001) and Treatment by region interaction (p=0.1850).

Table R.1.1.13.4: 1 Cox regr. for time to first event of all-cause mortality or all-cause hospitalisation by region - RS (trial 1245.121)

Subgroup Description	Placebo	Empa 10mg
Region: Europe		
Number of patients in analysis set	677	676
Number of analysed patients	677	676
Number of patients with event [N(%)]	322 (47.6)	301 (44.5)
Time at risk for event [years]	679.9	686.0
Incidence rate [patients with events per 100 patient years at risk]	47.36	43.88
95% confidence interval	(42.33, 52.67)	(39.06, 48.97)
Comparison vs Placebo*		
Hazard ratio		0.93
95% confidence interval		(0.79,1.08)
p-value		0.3390
Region: Asia		
Number of patients in analysis set	245	248
Number of analysed patients	245	248
Number of patients with event [N(%)]	128 (52.2)	94 (37.9)
Time at risk for event [years]	242.5	280.5
Incidence rate [patients with events per 100 patient years at risk]	52.78	33.51
95% confidence interval	(44.03, 62.31)	(27.08, 40.62)
Comparison vs Placebo*		
Hazard ratio		0.65
95% confidence interval		(0.50,0.84)
p-value		0.0014

* Based on a Cox regression model with terms for age (p=0.6066), baseline eGFR (CKD-EPI) (p<0.0001), sex (p=0.0032), baseline diabetes status (3 cat.) (p=0.0696), baseline LVEF (3 cat.) (p=0.4173), Treatment (p=0.0002), region (p<0.0001) and Treatment by region interaction (p=0.1850).

Table R.1.1.13.4: 1 Cox regr. for time to first event of all-cause mortality or all-cause hospitalisation by region - RS (trial 1245.121)

Subgroup Description	Placebo	Empa 10mg
Region: Other		
Number of patients in analysis set	87	86
Number of analysed patients	87	86
Number of patients with event [N(%)]	27 (31.0)	18 (20.9)
Time at risk for event [years]	100.5	103.6
Incidence rate [patients with events per 100 patient years at risk]	26.87	17.38
95% confidence interval	(17.71, 37.91)	(10.30, 26.28)
Comparison vs Placebo*		
Hazard ratio		0.64
95% confidence interval		(0.35,1.16)
p-value		0.1380

* Based on a Cox regression model with terms for age (p=0.6066), baseline eGFR (CKD-EPI) (p<0.0001), sex (p=0.0032), baseline diabetes status (3 cat.) (p=0.0696), baseline LVEF (3 cat.) (p=0.4173), Treatment (p=0.0002), region (p<0.0001) and Treatment by region interaction (p=0.1850).

R.1.1.13.5

R.1.1.13.5 Subgroup analysis by OECD member (Y/N)

Table R.1.1.13.5: 1

Table R.1.1.13.5: 1 Cox regr. for time to first event of all-cause mortality or all-cause hospitalisation by OECD member (Y/N) - RS (trial 1245.121)

Subgroup Description	Placebo	Empa 10mg
OECD member: No		
Number of patients in analysis set	741	713
Number of analysed patients	741	713
Number of patients with event [N(%)]	306 (41.3)	243 (34.1)
Time at risk for event [years]	702.3	732.3
Incidence rate [patients with events per 100 patient years at risk]	43.57	33.18
95% confidence interval	(38.82, 48.58)	(29.14, 37.48)
Comparison vs Placebo*		
Hazard ratio		0.75
95% confidence interval		(0.64,0.89)
p-value		0.0011
OECD member: Yes		
Number of patients in analysis set	1126	1150
Number of analysed patients	1126	1150
Number of patients with event [N(%)]	554 (49.2)	500 (43.5)
Time at risk for event [years]	1114.1	1201.2
Incidence rate [patients with events per 100 patient years at risk]	49.73	41.63
95% confidence interval	(45.67, 53.95)	(38.06, 45.35)
Comparison vs Placebo*		
Hazard ratio		0.85
95% confidence interval		(0.75,0.96)
p-value		0.0075

* Based on a Cox regression model with terms for age (p=0.9008), baseline eGFR (CKD-EPI) (p<0.0001), sex (p=0.0029), baseline diabetes status (3 cat.) (p=0.0982), baseline LVEF (3 cat.) (p=0.3372), Treatment (p<0.0001), OECD Member (N) (p=0.0305) and Treatment by OECD Member (N) interaction (p=0.2749).

OECD member (yes/no) countries included:
Yes: United States, Canada, Mexico, Poland, Netherlands, Hungary, Germany, Czech Republic, Italy, France, Spain, United Kingdom, Belgium, Japan, Australia, 'Korea; Republic Of South Korea';
No: Brazil, Argentina, China, India.

R.1.1.13.6

R.1.1.13.6 Subgroup analysis by NYHA at baseline (II, III/IV - 2 cat.)

Table R.1.1.13.6: 1 Cox regr. for time to first event of all-cause mortality or all-cause hospitalisation by baseline NYHA (2 cat.) - RS (trial 1245.121)

Subgroup Description	Placebo	Empa 10mg
Baseline NYHA: II		
Number of patients in analysis set	1401	1399
Number of analysed patients	1401	1399
Number of patients with event [N(%)]	595 (42.5)	491 (35.1)
Time at risk for event [years]	1405.2	1515.0
Incidence rate [patients with events per 100 patient years at risk]	42.34	32.41
95% confidence interval	(39.01, 45.81)	(29.61, 35.34)
Comparison vs Placebo*		
Hazard ratio		0.77
95% confidence interval		(0.68,0.87)
p-value		<0.0001
Baseline NYHA: III/IV		
Number of patients in analysis set	466	464
Number of analysed patients	466	464
Number of patients with event [N(%)]	265 (56.9)	252 (54.3)
Time at risk for event [years]	411.2	418.4
Incidence rate [patients with events per 100 patient years at risk]	64.45	60.22
95% confidence interval	(56.92, 72.43)	(53.02, 67.88)
Comparison vs Placebo*		
Hazard ratio		0.92
95% confidence interval		(0.77,1.09)
p-value		0.3331

* Based on a Cox regression model with terms for age (p=0.6558), baseline eGFR (CKD-EPI) (p<0.0001), sex (p=0.0004), region (p<0.0001), baseline diabetes status (3 cat.) (p=0.1902), baseline LVEF (3 cat.) (p=0.5496), Treatment (p=0.0013), baseline NYHA (2 cat.) (p<0.0001) and Treatment by baseline NYHA (2 cat.) interaction (p=0.1043).

R.1.1.13.7

Table R.1.1.13.7: 1 Cox regr. for time to first event of all-cause mortality or all-cause hospitalisation by diabetes at baseline (2 cat.) - RS (trial 1245.121)

Subgroup Description	Placebo	Empa 10mg
Baseline diabetes status: Diabetic		
Number of patients in analysis set	929	927
Number of analysed patients	929	927
Number of patients with event [N(%)]	447 (48.1)	392 (42.3)
Time at risk for event [years]	901.1	962.9
Incidence rate [patients with events per 100 patient years at risk]	49.61	40.71
95% confidence interval	(45.11, 54.31)	(36.78, 44.84)
Comparison vs Placebo*		
Hazard ratio		0.83
95% confidence interval		(0.72,0.95)
p-value		0.0062
Baseline diabetes status: Non-Diabetic		
Number of patients in analysis set	938	936
Number of analysed patients	938	936
Number of patients with event [N(%)]	413 (44.0)	351 (37.5)
Time at risk for event [years]	915.3	970.6
Incidence rate [patients with events per 100 patient years at risk]	45.12	36.16
95% confidence interval	(40.87, 49.58)	(32.48, 40.04)
Comparison vs Placebo*		
Hazard ratio		0.80
95% confidence interval		(0.69,0.92)
p-value		0.0023

* Based on a Cox regression model with terms for age (p=0.5343), baseline eGFR (CKD-EPI) (p<0.0001), sex (p=0.0026), region (p<0.0001), baseline LVEF (3 cat.) (p=0.4333), Treatment (p<0.0001), baseline diabetes status (2 cat.) (p=0.0530) and Treatment by baseline diabetes status (2 cat.) interaction (p=0.7483).

R.1.1.13.8 Subgroup analysis by BMI at baseline (<30, >=30)

Table R.1.1.13.8: 1 Cox regr. for time to first event of all-cause mortality or all-cause hospitalisation by baseline BMI [kg/m2] - RS (trial 1245.121)

Subgroup Description	Placebo	Empa 10mg
Baseline BMI [kg/m²]: <30		
Number of patients in analysis set	1300	1263
Number of analysed patients	1300	1263
Number of patients with event [N(%)]	595 (45.8)	483 (38.2)
Time at risk for event [years]	1297.3	1330.0
Incidence rate [patients with events per 100 patient years at risk]	45.87	36.32
95% confidence interval	(42.25, 49.62)	(33.15, 39.62)
Comparison vs Placebo*		
Hazard ratio		0.79
95% confidence interval		(0.70,0.89)
p-value		0.0002
Baseline BMI [kg/m²]: >=30		
Number of patients in analysis set	567	600
Number of analysed patients	567	600
Number of patients with event [N(%)]	265 (46.7)	260 (43.3)
Time at risk for event [years]	519.2	603.4
Incidence rate [patients with events per 100 patient years at risk]	51.04	43.09
95% confidence interval	(45.08, 57.37)	(38.01, 48.48)
Comparison vs Placebo*		
Hazard ratio		0.85
95% confidence interval		(0.72,1.01)
p-value		0.0677

* Based on a Cox regression model with terms for age (p=0.7660), baseline eGFR (CKD-EPI) (p<0.0001), sex (p=0.0021), region (p<0.0001), baseline diabetes status (3 cat.) (p=0.1068), baseline LVEF (3 cat.) (p=0.4171), Treatment (p=0.0002), baseline BMI (2 cat.) (p=0.0838) and Treatment by baseline BMI (2 cat.) interaction (p=0.4991).

R.1.1.13.9

R.1.1.13.9 Subgroup analysis by eGFR at baseline (<60, >=60)

Figure R.1.1.13.9: 1

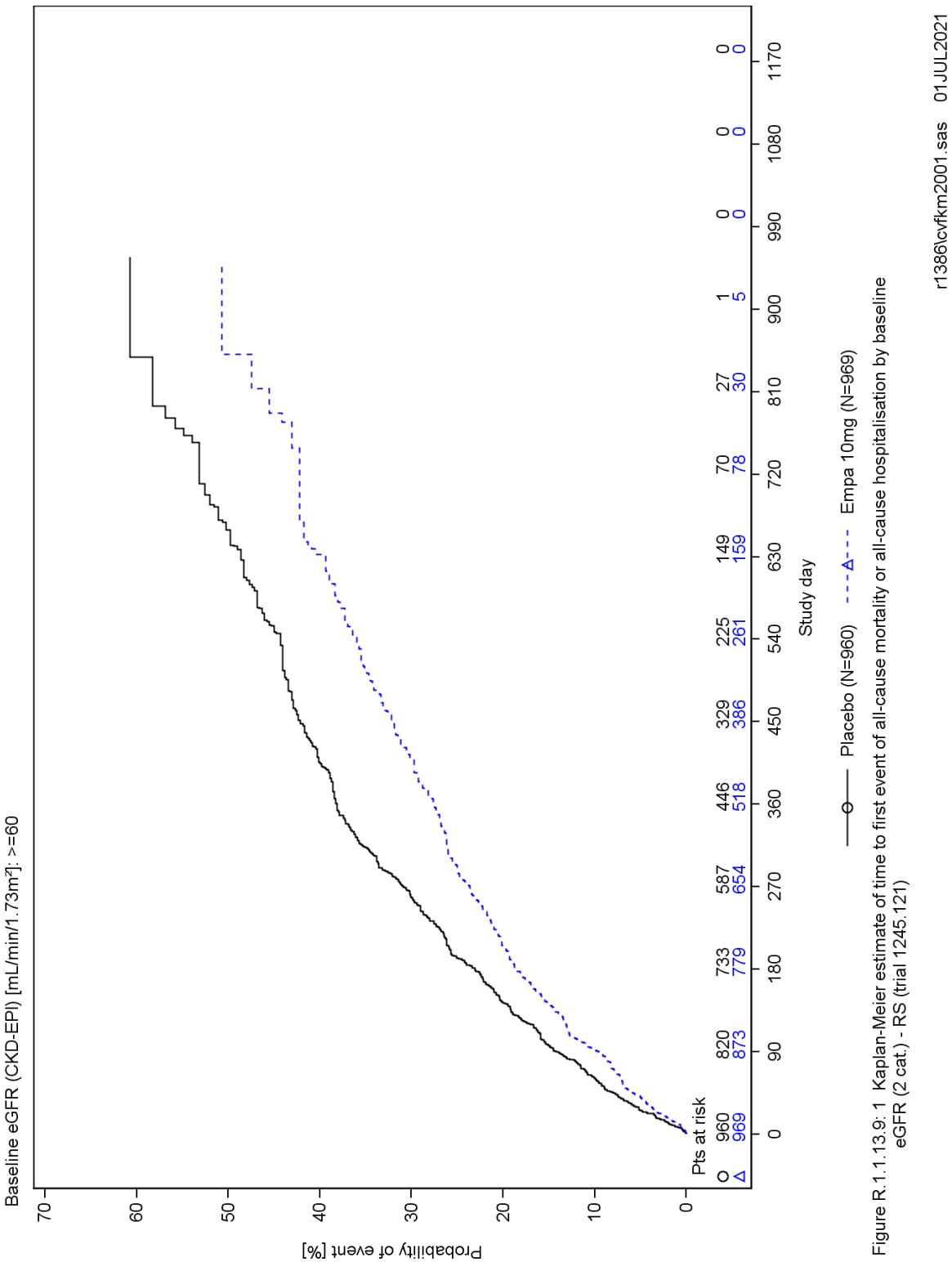

Figure R.1.1.13.9: 1 Kaplan-Meier estimate of time to first event of all-cause mortality or all-cause hospitalisation by baseline eGFR (2 cat.) - RS (trial 1245.121)

Figure R.1.1.13.9: 1

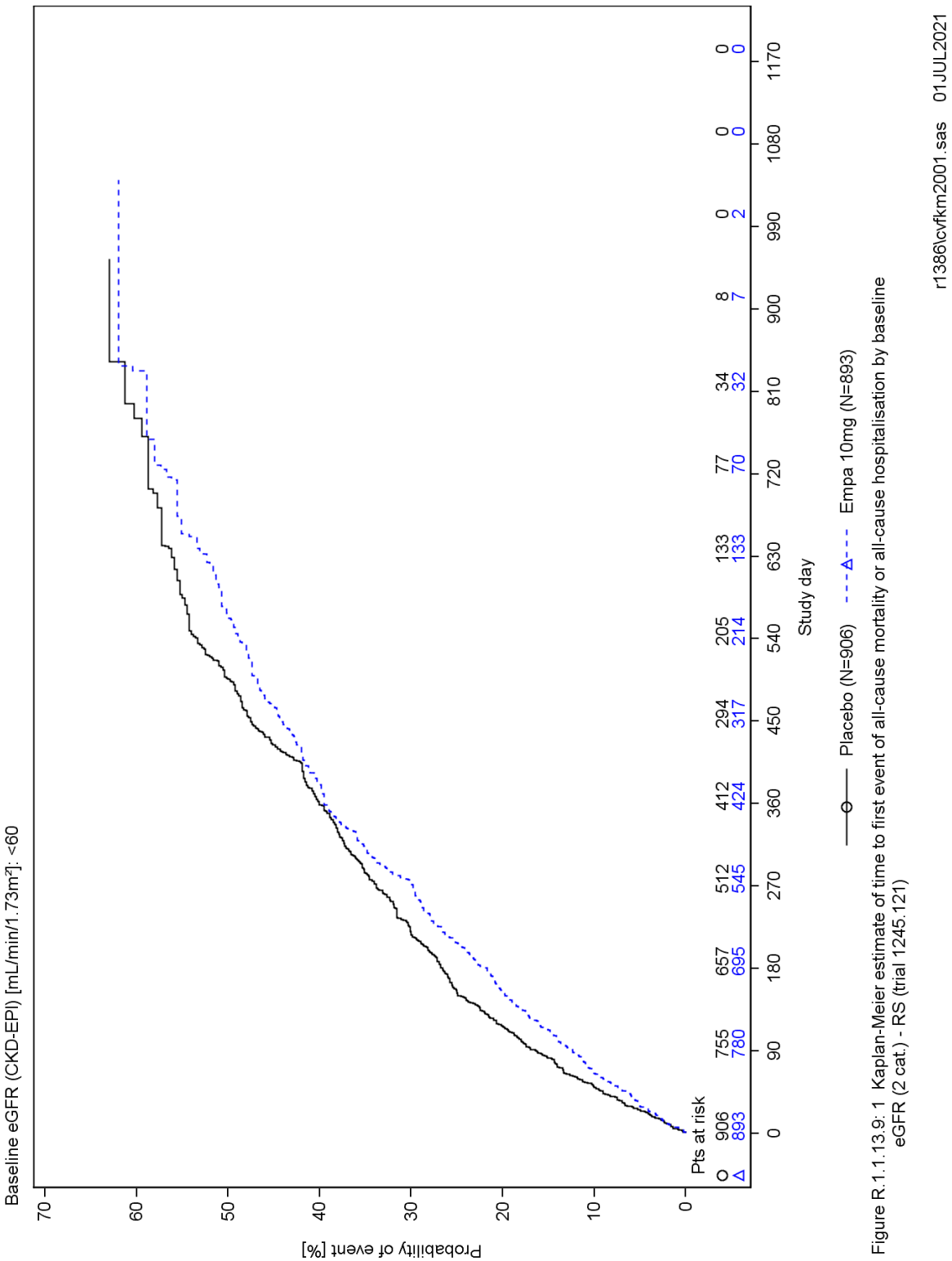

Figure R.1.1.13.9: 1 Kaplan-Meier estimate of time to first event of all-cause mortality or all-cause hospitalisation by baseline eGFR (2 cat.) - RS (trial 1245.121)

Table R.1.1.13.9: 1 Cox regr. for time to first event of all-cause mortality or all-cause hospitalisation by baseline eGFR (2 cat.) - RS (trial 1245.121)

Subgroup Description	Placebo	Empa 10mg
Baseline eGFR (CKD-EPI) [mL/min/1.73m²]: >=60		
Number of patients in analysis set	960	969
Number of analysed patients	960	969
Number of patients with event [N(%)]	417 (43.4)	329 (34.0)
Time at risk for event [years]	948.3	1036.3
Incidence rate [patients with events per 100 patient years at risk]	43.97	31.75
95% confidence interval	(39.85, 48.29)	(28.41, 35.27)
Comparison vs Placebo*		
Hazard ratio		0.72
95% confidence interval		(0.63,0.84)
p-value		<0.0001
Baseline eGFR (CKD-EPI) [mL/min/1.73m²]: <60		
Number of patients in analysis set	906	893
Number of analysed patients	906	893
Number of patients with event [N(%)]	442 (48.8)	414 (46.4)
Time at risk for event [years]	867.3	895.9
Incidence rate [patients with events per 100 patient years at risk]	50.97	46.21
95% confidence interval	(46.32, 55.82)	(41.87, 50.77)
Comparison vs Placebo*		
Hazard ratio		0.91
95% confidence interval		(0.79,1.04)
p-value		0.1593

* Based on a Cox regression model with terms for age (p=0.3625), sex (p=0.0045), region (p<0.0001), baseline diabetes status (3 cat.) (p=0.0538), baseline LVEF (3 cat.) (p=0.4346), Treatment (p<0.0001), baseline eGFR (CKD-EPI) (2 cat.) (p=0.0001) and Treatment by baseline eGFR (CKD-EPI) (2 cat.) interaction (p=0.0242).
2 patients were excluded as the subgroup variable was missing.

R.1.1.13.10

Table R.1.1.13.10: 1 Cox regr. for time to first event of all-cause mortality or all-cause hospitalisation by history of HHF within 12 months - RS (trial 1245.121)

Subgroup Description	Placebo	Empa 10mg
History of HHF (in the last 12 months): No		
Number of patients in analysis set	1293	1286
Number of analysed patients	1293	1286
Number of patients with event [N(%)]	571 (44.2)	475 (36.9)
Time at risk for event [years]	1322.3	1400.2
Incidence rate [patients with events per 100 patient years at risk]	43.18	33.92
95% confidence interval	(39.71, 46.80)	(30.94, 37.04)
Comparison vs Placebo*		
Hazard ratio		0.79
95% confidence interval		(0.70,0.90)
p-value		0.0002
History of HHF (in the last 12 months): Yes		
Number of patients in analysis set	574	577
Number of analysed patients	574	577
Number of patients with event [N(%)]	289 (50.3)	268 (46.4)
Time at risk for event [years]	494.2	533.3
Incidence rate [patients with events per 100 patient years at risk]	58.48	50.25
95% confidence interval	(51.93, 65.41)	(44.42, 56.44)
Comparison vs Placebo*		
Hazard ratio		0.85
95% confidence interval		(0.72,1.00)
p-value		0.0482

* Based on a Cox regression model with terms for age (p=0.8439), baseline eGFR (CKD-EPI) (p<0.0001), sex (p=0.0028), region (p<0.0001), baseline diabetes status (3 cat.) (p=0.1324), baseline LVEF (3 cat.) (p=0.7573), Treatment (p=0.0002), history of HHF (p<0.0001) and Treatment by history of HHF interaction (p=0.5554).

R.1.1.13.11

R.1.1.13.11 Subgroup analysis by cause of heart failure

Table R.1.1.13.11: 1 Cox regr. for time to first event of all-cause mortality or all-cause hospitalisation by cause of heart failure - RS (trial 1245.121)

Subgroup Description	Placebo	Empa 10mg
Cause of heart failure: Ischemic		
Number of patients in analysis set	946	983
Number of analysed patients	946	983
Number of patients with event [N(%)]	447 (47.3)	423 (43.0)
Time at risk for event [years]	941.7	1020.4
Incidence rate [patients with events per 100 patient years at risk]	47.47	41.45
95% confidence interval	(43.17, 51.96)	(37.60, 45.50)
Comparison vs Placebo*		
Hazard ratio		0.88
95% confidence interval		(0.77,1.00)
p-value		0.0574
Cause of heart failure: Non-ischemic		
Number of patients in analysis set	921	880
Number of analysed patients	921	880
Number of patients with event [N(%)]	413 (44.8)	320 (36.4)
Time at risk for event [years]	874.7	913.0
Incidence rate [patients with events per 100 patient years at risk]	47.22	35.05
95% confidence interval	(42.77, 51.88)	(31.31, 38.99)
Comparison vs Placebo*		
Hazard ratio		0.74
95% confidence interval		(0.64,0.86)
p-value		<0.0001

* Based on a Cox regression model with terms for age (p=0.5668), baseline eGFR (CKD-EPI) (p<0.0001), sex (p=0.0029), region (p<0.0001), baseline diabetes status (3 cat.) (p=0.0810), baseline LVEF (3 cat.) (p=0.4340), Treatment (p<0.0001), cause of heart failure (2 cat.) (p=0.6261) and Treatment by cause of heart failure (2 cat.) interaction (p=0.0977).

R.1.1.13.12 Subgroup analysis by heart failure physiology (LVEF <= 30% and NTproBNP<median; LVEF <= 30% and NTproBNP>=median; LVEF > 30%)

Table R.1.1.13.12: 1 Cox regr. for time to first event of all-cause mortality or all-cause hospitalisation by heart failure physiology - RS (trial 1245.121)

Subgroup Description	Placebo	Empa 10mg
Heart failure physiology: LVEF <= 30% and NTproBNP < median		
Number of patients in analysis set	723	698
Number of analysed patients	723	698
Number of patients with event [N(%)]	278 (38.5)	219 (31.4)
Time at risk for event [years]	763.6	795.3
Incidence rate [patients with events per 100 patient years at risk]	36.41	27.54
95% confidence interval	(32.25, 40.81)	(24.01, 31.30)
Comparison vs Placebo*		
Hazard ratio		0.76
95% confidence interval		(0.64,0.91)
p-value		0.0024
Heart failure physiology: LVEF <= 30% and NTproBNP >= median		
Number of patients in analysis set	661	631
Number of analysed patients	661	631
Number of patients with event [N(%)]	374 (56.6)	302 (47.9)
Time at risk for event [years]	593.6	604.6
Incidence rate [patients with events per 100 patient years at risk]	63.00	49.95
95% confidence interval	(56.78, 69.54)	(44.48, 55.74)
Comparison vs Placebo*		
Hazard ratio		0.79
95% confidence interval		(0.68,0.92)
p-value		0.0020

* Based on a Cox regression model with terms for age (p=0.6510), baseline eGFR (CKD-EPI) (p<0.0001), sex (p=0.0016), region (p<0.0001), baseline diabetes status (3 cat.) (p=0.0900), Treatment (p=0.0002), heart failure physiology (p<0.0001) and Treatment by heart failure physiology interaction (p=0.2484).
16 patients were excluded as the subgroup variable was missing.
The p-value for treatment by subgroup interaction trend test is 0.1911.

Table R.1.1.13.12: 1 Cox regr. for time to first event of all-cause mortality or all-cause hospitalisation by heart failure physiology - RS (trial 1245.121)

Subgroup Description	Placebo	Empa 10mg
Heart failure physiology: LVEF > 30%		
Number of patients in analysis set	475	526
Number of analysed patients	475	526
Number of patients with event [N(%)]	203 (42.7)	218 (41.4)
Time at risk for event [years]	451.5	527.2
Incidence rate [patients with events per 100 patient years at risk]	44.96	41.35
95% confidence interval	(38.99, 51.35)	(36.05, 47.02)
Comparison vs Placebo*		
Hazard ratio		0.94
95% confidence interval		(0.77,1.13)
p-value		0.4920

* Based on a Cox regression model with terms for age (p=0.6510), baseline eGFR (CKD-EPI) (p<0.0001), sex (p=0.0016), region (p<0.0001), baseline diabetes status (3 cat.) (p=0.0900), Treatment (p=0.0002), heart failure physiology (p<0.0001) and Treatment by heart failure physiology interaction (p=0.2484).
16 patients were excluded as the subgroup variable was missing.
The p-value for treatment by subgroup interaction trend test is 0.1911.

R.1.1.13.13

R.1.1.13.13 Subgroup analysis by baseline use of MRA

Table R.1.1.13.13: 1 Cox regr. for time to first event of all-cause mortality or all-cause hospitalisation by baseline use of MRA (Y/N) - RS (trial 1245.121)

Subgroup Description	Placebo	Empa 10mg
Baseline use of MRA: No		
Number of patients in analysis set	512	557
Number of analysed patients	512	557
Number of patients with event [N(%)]	253 (49.4)	243 (43.6)
Time at risk for event [years]	490.5	599.2
Incidence rate [patients with events per 100 patient years at risk]	51.57	40.56
95% confidence interval	(45.41, 58.12)	(35.62, 45.81)
Comparison vs Placebo*		
Hazard ratio		0.81
95% confidence interval		(0.68,0.96)
p-value		0.0181
Baseline use of MRA: Yes		
Number of patients in analysis set	1355	1306
Number of analysed patients	1355	1306
Number of patients with event [N(%)]	607 (44.8)	500 (38.3)
Time at risk for event [years]	1325.9	1334.3
Incidence rate [patients with events per 100 patient years at risk]	45.78	37.47
95% confidence interval	(42.21, 49.49)	(34.26, 40.83)
Comparison vs Placebo*		
Hazard ratio		0.82
95% confidence interval		(0.73,0.92)
p-value		0.0008

* Based on a Cox regression model with terms for age (p=0.5498), baseline eGFR (CKD-EPI) (p<0.0001), sex (p=0.0028), region (p<0.0001), baseline diabetes status (3 cat.) (p=0.0713), baseline LVEF (3 cat.) (p=0.4457), Treatment (p=0.0001), Baseline use of MRA (p=0.7724) and Treatment by Baseline use of MRA interaction (p=0.9239).

R.1.1.13.14

R.1.1.13.14 Subgroup analysis by baseline use of ARNi

Table R.1.1.13.14: 1 Cox regr. for time to first event of all-cause mortality or all-cause hospitalisation by baseline use of ARNi (Y/N) - RS (trial 1245.121)

Subgroup Description	Placebo	Empa 10mg
Baseline use of ARNi: No		
Number of patients in analysis set	1480	1523
Number of analysed patients	1480	1523
Number of patients with event [N(%)]	677 (45.7)	611 (40.1)
Time at risk for event [years]	1459.0	1608.9
Incidence rate [patients with events per 100 patient years at risk]	46.40	37.98
95% confidence interval	(42.97, 49.96)	(35.03, 41.05)
Comparison vs Placebo*		
Hazard ratio		0.81
95% confidence interval		(0.73,0.91)
p-value		0.0002
Baseline use of ARNi: Yes		
Number of patients in analysis set	387	340
Number of analysed patients	387	340
Number of patients with event [N(%)]	183 (47.3)	132 (38.8)
Time at risk for event [years]	357.4	324.6
Incidence rate [patients with events per 100 patient years at risk]	51.20	40.67
95% confidence interval	(44.05, 58.88)	(34.02, 47.89)
Comparison vs Placebo*		
Hazard ratio		0.83
95% confidence interval		(0.66,1.03)
p-value		0.0968

* Based on a Cox regression model with terms for age (p=0.5739), baseline eGFR (CKD-EPI) (p<0.0001), sex (p=0.0026), region (p<0.0001), baseline diabetes status (3 cat.) (p=0.0705), baseline LVEF (3 cat.) (p=0.4411), Treatment (p=0.0018), baseline use of ARNi (p=0.6748) and Treatment by baseline use of ARNi interaction (p=0.8908).

R.1.1.13.15 Subgroup analysis by bl. LVEF (<= 30%, >30% -<= 35% , > 35%)

Table R.1.1.13.15: 1 Cox regr. for time to first event of all-cause mortality or all-cause hospitalisation by bl. LVEF (3 cat.) - RS (trial 1245.121)

Subgroup Description	Placebo	Empa 10mg
Baseline LVEF: <=30		
Number of patients in analysis set	1392	1337
Number of analysed patients	1392	1337
Number of patients with event [N(%)]	657 (47.2)	525 (39.3)
Time at risk for event [years]	1364.9	1406.3
Incidence rate [patients with events per 100 patient years at risk]	48.14	37.33
95% confidence interval	(44.52, 51.89)	(34.21, 40.59)
Comparison vs Placebo*		
Hazard ratio		0.77
95% confidence interval		(0.69,0.87)
p-value		<0.0001
Baseline LVEF: >30 to <=35		
Number of patients in analysis set	361	398
Number of analysed patients	361	398
Number of patients with event [N(%)]	151 (41.8)	163 (41.0)
Time at risk for event [years]	353.3	408.3
Incidence rate [patients with events per 100 patient years at risk]	42.74	39.92
95% confidence interval	(36.20, 49.82)	(34.03, 46.28)
Comparison vs Placebo*		
Hazard ratio		0.93
95% confidence interval		(0.75,1.16)
p-value		0.5386

* Based on a Cox regression model with terms for age (p=0.5611), baseline eGFR (CKD-EPI) (p<0.0001), sex (p=0.0026), region (p<0.0001), baseline diabetes status (3 cat.) (p=0.0665), Treatment (p=0.1113), baseline LVEF (3 cat.) (p=0.4406) and Treatment by baseline LVEF (3 cat.) interaction (p=0.2353).
The p-value for treatment by subgroup interaction trend test is 0.1023.

Table R.1.1.13.15: 1 Cox regr. for time to first event of all-cause mortality or all-cause hospitalisation by bl. LVEF (3 cat.) - RS (trial 1245.121)

Subgroup Description	Placebo	Empa 10mg
Baseline LVEF: >35		
Number of patients in analysis set	114	128
Number of analysed patients	114	128
Number of patients with event [N(%)]	52 (45.6)	55 (43.0)
Time at risk for event [years]	98.2	118.8
Incidence rate [patients with events per 100 patient years at risk]	52.93	46.28
95% confidence interval	(39.53, 68.26)	(34.86, 59.28)
Comparison vs Placebo*		
Hazard ratio		0.96
95% confidence interval		(0.65,1.40)
p-value		0.8225

* Based on a Cox regression model with terms for age (p=0.5611), baseline eGFR (CKD-EPI) (p<0.0001), sex (p=0.0026), region (p<0.0001), baseline diabetes status (3 cat.) (p=0.0665), Treatment (p=0.1113), baseline LVEF (3 cat.) (p=0.4406) and Treatment by baseline LVEF (3 cat.) interaction (p=0.2353).
The p-value for treatment by subgroup interaction trend test is 0.1023.

R.1.1.13.16 Subgroup analysis by bl. NTproBNP </>= median (median based on total patients)

Table R.1.1.13.16: 1 Cox regr. for time to first event of all-cause mortality or all-cause hospitalisation by bl. NTproBNP (<median, >= median) (median based on total patients) - RS (trial 1245.121)

Subgroup Description	Placebo	Empa 10mg
Baseline NTproBNP: < median		
Number of patients in analysis set	920	942
Number of analysed patients	920	942
Number of patients with event [N(%)]	350 (38.0)	306 (32.5)
Time at risk for event [years]	982.4	1058.3
Incidence rate [patients with events per 100 patient years at risk]	35.63	28.91
95% confidence interval	(31.99, 39.46)	(25.77, 32.24)
Comparison vs Placebo*		
Hazard ratio		0.81
95% confidence interval		(0.70,0.95)
p-value		0.0085
Baseline NTproBNP: >= median		
Number of patients in analysis set	946	920
Number of analysed patients	946	920
Number of patients with event [N(%)]	509 (53.8)	437 (47.5)
Time at risk for event [years]	833.2	874.0
Incidence rate [patients with events per 100 patient years at risk]	61.09	50.00
95% confidence interval	(55.90, 66.51)	(45.42, 54.80)
Comparison vs Placebo*		
Hazard ratio		0.83
95% confidence interval		(0.73,0.94)
p-value		0.0032

* Based on a Cox regression model with terms for age (p=0.4541), baseline eGFR (CKD-EPI) (p=0.0002), sex (p=0.0029), region (p<0.0001), baseline diabetes status (3 cat.) (p=0.0718), baseline LVEF (3 cat.) (p=0.6075), Treatment (p<0.0001), baseline NTproBNP (2 cat.) (p<0.0001) and Treatment by baseline NTproBNP (2 cat.) interaction (p=0.8914).
2 patients were excluded as the subgroup variable was missing.

Median: 1910 [pg/mL]

R.1.1.14 Time to first event of 3P-MACE

R.1.1.14.1

Figure R.1.1.14.1: 1

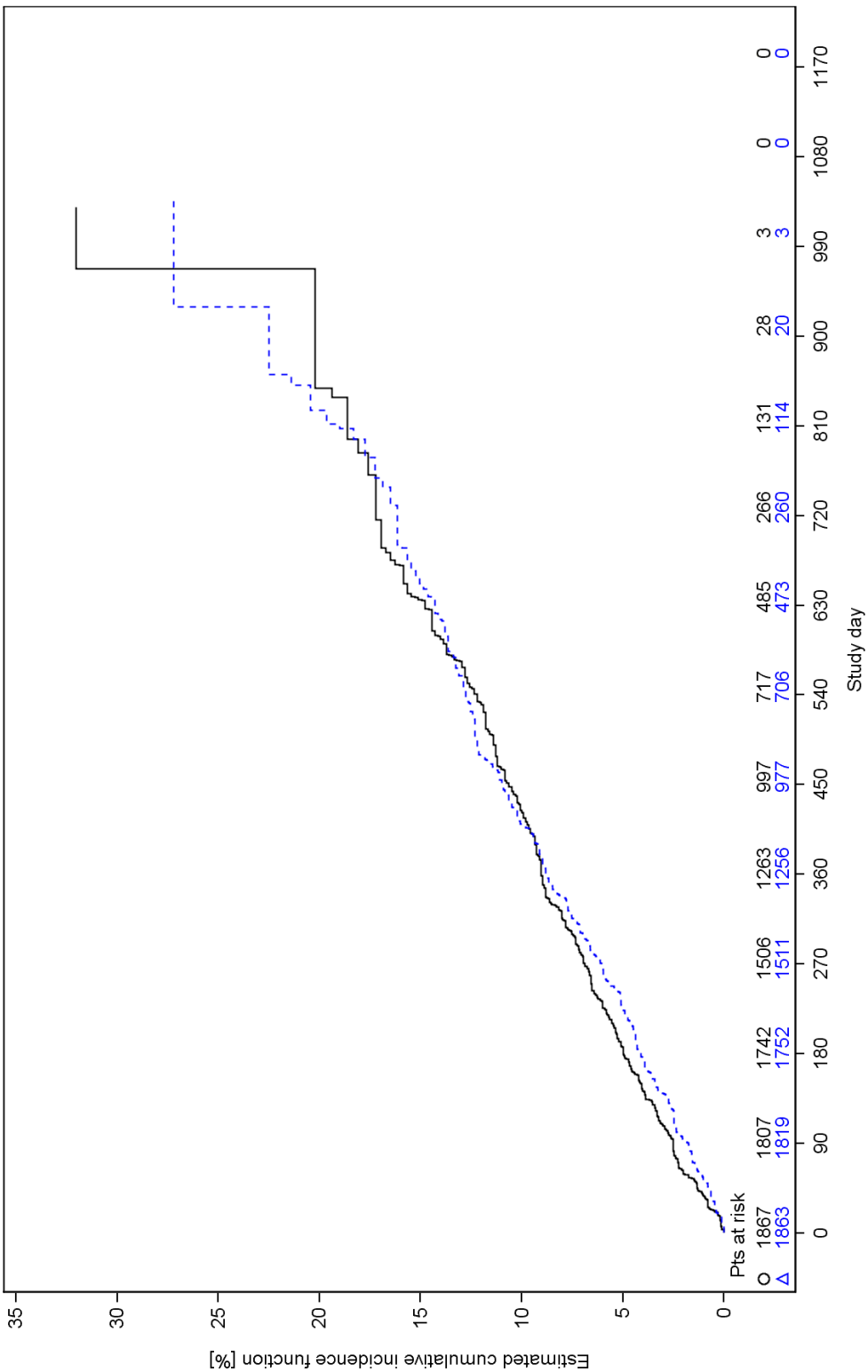

Figure R.1.1.14.1: 1 Estimated cumulative incidence function for time to first event of adjudicated CV death, adjudicated non-fatal MI or adjudicated non-fatal stroke (3-point MACE) (considering non-CV death as competing risk) - RS (trial 1245.121)

MIs were counted excluding silent MIs.

Table R.1.1.14.1: 1 Cox regr. for time to first event of adjudicated CV death, adjudicated non-fatal MI or adjudicated non-fatal stroke (3-point MACE) - RS (trial 1245.121)

	Placebo	Empa 10mg
Number of patients in analysis set	1867	1863
Number of analysed patients	1867	1863
Number of patients with event [N(%)]	232 (12.4)	228 (12.2)
Time at risk for event [years]	2430.0	2418.0
Incidence rate [patients with events per 100 patient years at risk]	9.55	9.43
95% confidence interval	(8.36, 10.81)	(8.24, 10.69)
Comparison vs Placebo*		
Hazard ratio		0.98
95% confidence interval		(0.82,1.18)
p-value		0.8296
Time to event [days]**		
2.5% percentile	82	122
5.0% percentile	179	223
7.5% percentile	298	314
10.0% percentile	416	408
Patients with events [%]**		
1 year	9.1	8.9
2 years	17.6	16.8

* Based on a Cox regression model with terms for age (p=0.1830), baseline eGFR (CKD-EPI) (p=0.0119), sex (p=0.1158), region (p=0.0737), baseline diabetes status (3 cat.) (p=0.1811), baseline LVEF (3 cat.) (p=0.9918) and Treatment (p=0.8296).
**Based on Kaplan-Meier estimates.

MIs were counted excluding silent MIs.

R.1.1.14.2

R.1.1.14.2 Subgroup analysis by sex

Table R.1.1.14.2: 1 Cox regr. for time to first event of adjudicated CV death, adjudicated non-fatal MI or adjudicated non-fatal stroke (3-point MACE) by sex - RS (trial 1245.121)

Subgroup Description	Placebo	Empa 10mg
Sex: Male		
Number of patients in analysis set	1411	1426
Number of analysed patients	1411	1426
Number of patients with event [N(%)]	175 (12.4)	185 (13.0)
Time at risk for event [years]	1847.3	1842.1
Incidence rate [patients with events per 100 patient years at risk]	9.47	10.04
95% confidence interval	(8.12, 10.93)	(8.65, 11.54)
Comparison vs Placebo*		
Hazard ratio		1.05
95% confidence interval		(0.85,1.29)
p-value		0.6712
Sex: Female		
Number of patients in analysis set	456	437
Number of analysed patients	456	437
Number of patients with event [N(%)]	57 (12.5)	43 (9.8)
Time at risk for event [years]	582.7	575.9
Incidence rate [patients with events per 100 patient years at risk]	9.78	7.47
95% confidence interval	(7.41, 12.48)	(5.40, 9.86)
Comparison vs Placebo*		
Hazard ratio		0.78
95% confidence interval		(0.52,1.15)
p-value		0.2082

* Based on a Cox regression model with terms for age (p=0.1936), baseline eGFR (CKD-EPI) (p=0.0125), region (p=0.0821), baseline diabetes status (3 cat.) (p=0.1806), baseline LVEF (3 cat.) (p=0.9902), Treatment (p=0.3578), sex (p=0.1028) and Treatment by sex interaction (p=0.1899).

MIs were counted excluding silent MIs.

R.1.1.14.3

Table R.1.1.14.3: 1 Cox regr. for time to first event of adjudicated CV death, adjudicated non-fatal MI or adjudicated non-fatal stroke (3-point MACE) by age (2 cat.) - RS (trial 1245.121)

Subgroup Description	Placebo	Empa 10mg
Age [years]: < 65		
Number of patients in analysis set	740	675
Number of analysed patients	740	675
Number of patients with event [N(%)]	80 (10.8)	75 (11.1)
Time at risk for event [years]	968.2	869.8
Incidence rate [patients with events per 100 patient years at risk]	8.26	8.62
95% confidence interval	(6.55, 10.17)	(6.78, 10.68)
Comparison vs Placebo*		
Hazard ratio		1.07
95% confidence interval		(0.78,1.46)
p-value		0.6887
Age [years]: >= 65		
Number of patients in analysis set	1127	1188
Number of analysed patients	1127	1188
Number of patients with event [N(%)]	152 (13.5)	153 (12.9)
Time at risk for event [years]	1461.8	1548.2
Incidence rate [patients with events per 100 patient years at risk]	10.40	9.88
95% confidence interval	(8.81, 12.12)	(8.38, 11.51)
Comparison vs Placebo*		
Hazard ratio		0.94
95% confidence interval		(0.75,1.18)
p-value		0.5920

* Based on a Cox regression model with terms for baseline eGFR (CKD-EPI) (p=0.0027), sex (p=0.1159), region (p=0.0842), baseline diabetes status (3 cat.) (p=0.1894), baseline LVEF (3 cat.) (p=0.9879), Treatment (p=0.9878), age (2 cat.) (p=0.4228) and Treatment by age (2 cat.) interaction (p=0.5245).

MIs were counted excluding silent MIs.

R.1.1.14.4 Subgroup analysis by region (North America, Latin America, Europe, Asia, Other)

Table R.1.1.14.4: 1 Cox regr. for time to first event of adjudicated CV death, adjudicated non-fatal MI or adjudicated non-fatal stroke (3-point MACE) by region - RS (trial 1245.121)

Subgroup Description	Placebo	Empa 10mg
Region: North America		
Number of patients in analysis set	213	212
Number of analysed patients	213	212
Number of patients with event [N(%)]	26 (12.2)	25 (11.8)
Time at risk for event [years]	282.1	296.8
Incidence rate [patients with events per 100 patient years at risk]	9.22	8.42
95% confidence interval	(6.02, 13.08)	(5.45, 12.03)
Comparison vs Placebo*		
Hazard ratio		0.90
95% confidence interval		(0.52,1.56)
p-value		0.7053
Region: Latin America		
Number of patients in analysis set	645	641
Number of analysed patients	645	641
Number of patients with event [N(%)]	77 (11.9)	87 (13.6)
Time at risk for event [years]	771.5	752.0
Incidence rate [patients with events per 100 patient years at risk]	9.98	11.57
95% confidence interval	(7.88, 12.33)	(9.27, 14.12)
Comparison vs Placebo*		
Hazard ratio		1.14
95% confidence interval		(0.84,1.55)
p-value		0.3922

* Based on a Cox regression model with terms for age (p=0.1837), baseline eGFR (CKD-EPI) (p=0.0117), sex (p=0.1155), baseline diabetes status (3 cat.) (p=0.1752), baseline LVEF (3 cat.) (p=0.9911), Treatment (p=0.1053), region (p=0.0535) and Treatment by region interaction (p=0.2482).

MIs were counted excluding silent MIs.

Table R.1.1.14.4: 1 Cox regr. for time to first event of adjudicated CV death, adjudicated non-fatal MI or adjudicated non-fatal stroke (3-point MACE) by region - RS (trial 1245.121)

Subgroup Description	Placebo	Empa 10mg
Region: Europe		
Number of patients in analysis set	677	676
Number of analysed patients	677	676
Number of patients with event [N(%)]	87 (12.9)	82 (12.1)
Time at risk for event [years]	912.5	912.9
Incidence rate [patients with events per 100 patient years at risk]	9.53	8.98
95% confidence interval	(7.64, 11.64)	(7.14, 11.03)
Comparison vs Placebo*		
Hazard ratio		0.94
95% confidence interval		(0.69,1.27)
p-value		0.6757
Region: Asia		
Number of patients in analysis set	245	248
Number of analysed patients	245	248
Number of patients with event [N(%)]	29 (11.8)	30 (12.1)
Time at risk for event [years]	348.8	343.1
Incidence rate [patients with events per 100 patient years at risk]	8.31	8.74
95% confidence interval	(5.57, 11.60)	(5.90, 12.14)
Comparison vs Placebo*		
Hazard ratio		1.06
95% confidence interval		(0.63,1.76)
p-value		0.8337

* Based on a Cox regression model with terms for age (p=0.1837), baseline eGFR (CKD-EPI) (p=0.0117), sex (p=0.1155), baseline diabetes status (3 cat.) (p=0.1752), baseline LVEF (3 cat.) (p=0.9911), Treatment (p=0.1053), region (p=0.0535) and Treatment by region interaction (p=0.2482).

MIs were counted excluding silent MIs.

Table R.1.1.14.4: 1 Cox regr. for time to first event of adjudicated CV death, adjudicated non-fatal MI or adjudicated non-fatal stroke (3-point MACE) by region - RS (trial 1245.121)

Subgroup Description	Placebo	Empa 10mg
Region: Other		
Number of patients in analysis set	87	86
Number of analysed patients	87	86
Number of patients with event [N(%)]	13 (14.9)	4 (4.7)
Time at risk for event [years]	115.1	113.1
Incidence rate [patients with events per 100 patient years at risk]	11.29	3.54
95% confidence interval	(6.01, 18.20)	(0.96, 7.75)
Comparison vs Placebo*		
Hazard ratio		0.30
95% confidence interval		(0.10,0.93)
p-value		0.0376

* Based on a Cox regression model with terms for age (p=0.1837), baseline eGFR (CKD-EPI) (p=0.0117), sex (p=0.1155), baseline diabetes status (3 cat.) (p=0.1752), baseline LVEF (3 cat.) (p=0.9911), Treatment (p=0.1053), region (p=0.0535) and Treatment by region interaction (p=0.2482).

MIs were counted excluding silent MIs.

R.1.1.14.5

R.1.1.14.5 Subgroup analysis by OECD member (Y/N)

Table R.1.1.14.5: 1 Cox regr. for time to first event of adjudicated CV death, adjudicated non-fatal MI or adjudicated non-fatal stroke (3-point MACE) by OECD member (Y/N) - RS (trial 1245.121)

Subgroup Description	Placebo	Empa 10mg
OECD member: No		
Number of patients in analysis set	741	713
Number of analysed patients	741	713
Number of patients with event [N(%)]	92 (12.4)	94 (13.2)
Time at risk for event [years]	896.2	846.7
Incidence rate [patients with events per 100 patient years at risk]	10.27	11.10
95% confidence interval	(8.28, 12.47)	(8.97, 13.46)
Comparison vs Placebo*		
Hazard ratio		1.06
95% confidence interval		(0.80,1.42)
p-value		0.6768
OECD member: Yes		
Number of patients in analysis set	1126	1150
Number of analysed patients	1126	1150
Number of patients with event [N(%)]	140 (12.4)	134 (11.7)
Time at risk for event [years]	1533.8	1571.3
Incidence rate [patients with events per 100 patient years at risk]	9.13	8.53
95% confidence interval	(7.68, 10.70)	(7.15, 10.03)
Comparison vs Placebo*		
Hazard ratio		0.93
95% confidence interval		(0.73,1.18)
p-value		0.5520

* Based on a Cox regression model with terms for age (p=0.1075), baseline eGFR (CKD-EPI) (p=0.0079), sex (p=0.1212), baseline diabetes status (3 cat.) (p=0.2016), baseline LVEF (3 cat.) (p=0.9990), Treatment (p=0.9555), OECD Member (N) (p=0.0011) and Treatment by OECD Member (N) interaction (p=0.4845).

MIs were counted excluding silent MIs.
OECD member (yes/no) countries included:
Yes: United States, Canada, Mexico, Poland, Netherlands, Hungary, Germany, Czech Republic, Italy, France, Spain, United Kingdom, Belgium, Japan, Australia, 'Korea; Republic Of South Korea';
No: Brazil, Argentina, China, India.

R.1.1.14.6

R.1.1.14.6 Subgroup analysis by NYHA at baseline (II, III/IV - 2 cat.)

Table R.1.1.14.6: 1 Cox regr. for time to first event of adjudicated CV death, adjudicated non-fatal MI or adjudicated non-fatal stroke (3-point MACE) by baseline NYHA (2 cat.) - RS (trial 1245.121)

Subgroup Description	Placebo	Empa 10mg
Baseline NYHA: II		
Number of patients in analysis set	1401	1399
Number of analysed patients	1401	1399
Number of patients with event [N(%)]	145 (10.3)	148 (10.6)
Time at risk for event [years]	1838.2	1825.1
Incidence rate [patients with events per 100 patient years at risk]	7.89	8.11
95% confidence interval	(6.66, 9.22)	(6.86, 9.47)
Comparison vs Placebo*		
Hazard ratio		1.02
95% confidence interval		(0.81,1.28)
p-value		0.8599
Baseline NYHA: III/IV		
Number of patients in analysis set	466	464
Number of analysed patients	466	464
Number of patients with event [N(%)]	87 (18.7)	80 (17.2)
Time at risk for event [years]	591.8	592.9
Incidence rate [patients with events per 100 patient years at risk]	14.70	13.49
95% confidence interval	(11.77, 17.95)	(10.70, 16.61)
Comparison vs Placebo*		
Hazard ratio		0.91
95% confidence interval		(0.67,1.23)
p-value		0.5254

* Based on a Cox regression model with terms for age (p=0.1535), baseline eGFR (CKD-EPI) (p=0.0188), sex (p=0.0630), region (p=0.0412), baseline diabetes status (3 cat.) (p=0.4006), baseline LVEF (3 cat.) (p=0.9624), Treatment (p=0.6884), baseline NYHA (2 cat.) (p<0.0001) and Treatment by baseline NYHA (2 cat.) interaction (p=0.5395).

MIs were counted excluding silent MIs.

R.1.1.14.7

R.1.1.14.7 Subgroup analysis by diabetes at baseline

Table R.1.1.14.7: 1 Cox regr. for time to first event of adjudicated CV death, adjudicated non-fatal MI or adjudicated non-fatal stroke (3-point MACE) by diabetes at baseline (2 cat.) - RS (trial 1245.121)

Subgroup Description	Placebo	Empa 10mg
Baseline diabetes status: Diabetic		
Number of patients in analysis set	929	927
Number of analysed patients	929	927
Number of patients with event [N(%)]	126 (13.6)	126 (13.6)
Time at risk for event [years]	1226.1	1209.0
Incidence rate [patients with events per 100 patient years at risk]	10.28	10.42
95% confidence interval	(8.56, 12.15)	(8.68, 12.32)
Comparison vs Placebo*		
Hazard ratio		1.01
95% confidence interval		(0.79,1.29)
p-value		0.9437
Baseline diabetes status: Non-Diabetic		
Number of patients in analysis set	938	936
Number of analysed patients	938	936
Number of patients with event [N(%)]	106 (11.3)	102 (10.9)
Time at risk for event [years]	1203.9	1209.0
Incidence rate [patients with events per 100 patient years at risk]	8.80	8.44
95% confidence interval	(7.21, 10.56)	(6.88, 10.15)
Comparison vs Placebo*		
Hazard ratio		0.95
95% confidence interval		(0.72,1.24)
p-value		0.6905

* Based on a Cox regression model with terms for age (p=0.1804), baseline eGFR (CKD-EPI) (p=0.0120), sex (p=0.1155), region (p=0.0730), baseline LVEF (3 cat.) (p=0.9914), Treatment (p=0.8047), baseline diabetes status (2 cat.) (p=0.0640) and Treatment by baseline diabetes status (2 cat.) interaction (p=0.7320).

MIs were counted excluding silent MIs.

R.1.1.14.8

R.1.1.14.8 Subgroup analysis by BMI at baseline (<30, >=30)

Table R.1.1.14.8: 1 Cox regr. for time to first event of adjudicated CV death, adjudicated non-fatal MI or adjudicated non-fatal stroke (3-point MACE) by baseline BMI [kg/m2] - RS (trial 1245.121)

Subgroup Description	Placebo	Empa 10mg
Baseline BMI [kg/m²]: <30		
Number of patients in analysis set	1300	1263
Number of analysed patients	1300	1263
Number of patients with event [N(%)]	168 (12.9)	151 (12.0)
Time at risk for event [years]	1714.9	1636.8
Incidence rate [patients with events per 100 patient years at risk]	9.80	9.23
95% confidence interval	(8.37, 11.33)	(7.81, 10.75)
Comparison vs Placebo*		
Hazard ratio		0.94
95% confidence interval		(0.76,1.18)
p-value		0.6051
Baseline BMI [kg/m²]: >=30		
Number of patients in analysis set	567	600
Number of analysed patients	567	600
Number of patients with event [N(%)]	64 (11.3)	77 (12.8)
Time at risk for event [years]	715.1	781.2
Incidence rate [patients with events per 100 patient years at risk]	8.95	9.86
95% confidence interval	(6.89, 11.27)	(7.78, 12.18)
Comparison vs Placebo*		
Hazard ratio		1.07
95% confidence interval		(0.77,1.49)
p-value		0.6878

* Based on a Cox regression model with terms for age (p=0.1996), baseline eGFR (CKD-EPI) (p=0.0119), sex (p=0.1159), region (p=0.0754), baseline diabetes status (3 cat.) (p=0.1835), baseline LVEF (3 cat.) (p=0.9910), Treatment (p=0.9607), baseline BMI (2 cat.) (p=0.8770) and Treatment by baseline BMI (2 cat.) interaction (p=0.5347).

MIs were counted excluding silent MIs.

R.1.1.14.9

R.1.1.14.9 Subgroup analysis by eGFR at baseline (<60, >=60)

Table R.1.1.14.9: 1 Cox regr. for time to first event of adjudicated CV death, adjudicated non-fatal MI or adjudicated non-fatal stroke (3-point MACE) by baseline eGFR (2 cat.) - RS (trial 1245.121)

Subgroup Description	Placebo	Empa 10mg
Baseline eGFR (CKD-EPI) [mL/min/1.73m²]: >=60		
Number of patients in analysis set	960	969
Number of analysed patients	960	969
Number of patients with event [N(%)]	104 (10.8)	113 (11.7)
Time at risk for event [years]	1253.0	1256.1
Incidence rate [patients with events per 100 patient years at risk]	8.30	9.00
95% confidence interval	(6.78, 9.97)	(7.41, 10.73)
Comparison vs Placebo*		
Hazard ratio		1.08
95% confidence interval		(0.82,1.40)
p-value		0.5929
Baseline eGFR (CKD-EPI) [mL/min/1.73m²]: <60		
Number of patients in analysis set	906	893
Number of analysed patients	906	893
Number of patients with event [N(%)]	127 (14.0)	115 (12.9)
Time at risk for event [years]	1176.2	1160.7
Incidence rate [patients with events per 100 patient years at risk]	10.80	9.91
95% confidence interval	(9.00, 12.75)	(8.18, 11.80)
Comparison vs Placebo*		
Hazard ratio		0.91
95% confidence interval		(0.71,1.17)
p-value		0.4732

* Based on a Cox regression model with terms for age (p=0.0243), sex (p=0.1271), region (p=0.0845), baseline diabetes status (3 cat.) (p=0.1608), baseline LVEF (3 cat.) (p=0.9782), Treatment (p=0.9166), baseline eGFR (CKD-EPI) (2 cat.) (p=0.3052) and Treatment by baseline eGFR (CKD-EPI) (2 cat.) interaction (p=0.3780).
2 patients were excluded as the subgroup variable was missing.

MIs were counted excluding silent MIs.

R.1.1.14.10

Table R.1.1.14.10: 1 Cox regr. for time to first event of adjudicated CV death, adjudicated non-fatal MI or adjudicated non-fatal stroke (3-point MACE) by history of HHF within 12 months - RS (trial 1245.121)

Subgroup Description	Placebo	Empa 10mg
History of HHF (in the last 12 months): No		
Number of patients in analysis set	1293	1286
Number of analysed patients	1293	1286
Number of patients with event [N(%)]	147 (11.4)	146 (11.4)
Time at risk for event [years]	1732.4	1706.2
Incidence rate [patients with events per 100 patient years at risk]	8.49	8.56
95% confidence interval	(7.17, 9.91)	(7.23, 10.00)
Comparison vs Placebo*		
Hazard ratio		1.01
95% confidence interval		(0.80,1.27)
p-value		0.9329
History of HHF (in the last 12 months): Yes		
Number of patients in analysis set	574	577
Number of analysed patients	574	577
Number of patients with event [N(%)]	85 (14.8)	82 (14.2)
Time at risk for event [years]	697.6	711.8
Incidence rate [patients with events per 100 patient years at risk]	12.18	11.52
95% confidence interval	(9.73, 14.91)	(9.16, 14.14)
Comparison vs Placebo*		
Hazard ratio		0.91
95% confidence interval		(0.67,1.24)
p-value		0.5629

* Based on a Cox regression model with terms for age (p=0.1063), baseline eGFR (CKD-EPI) (p=0.0155), sex (p=0.1158), region (p=0.0273), baseline diabetes status (3 cat.) (p=0.2618), baseline LVEF (3 cat.) (p=0.9523), Treatment (p=0.6808), history of HHF (p=0.0002) and Treatment by history of HHF interaction (p=0.6080).

MIs were counted excluding silent MIs.

R.1.1.14.11

R.1.1.14.11 Subgroup analysis by cause of heart failure

Table R.1.1.14.11: 1 Cox regr. for time to first event of adjudicated CV death, adjudicated non-fatal MI or adjudicated non-fatal stroke (3-point MACE) by cause of heart failure - RS (trial 1245.121)

Subgroup Description	Placebo	Empa 10mg
Cause of heart failure: Ischemic		
Number of patients in analysis set	946	983
Number of analysed patients	946	983
Number of patients with event [N(%)]	131 (13.8)	136 (13.8)
Time at risk for event [years]	1248.5	1287.4
Incidence rate [patients with events per 100 patient years at risk]	10.49	10.56
95% confidence interval	(8.77, 12.36)	(8.86, 12.41)
Comparison vs Placebo*		
Hazard ratio		1.00
95% confidence interval		(0.78,1.27)
p-value		0.9864
Cause of heart failure: Non-ischemic		
Number of patients in analysis set	921	880
Number of analysed patients	921	880
Number of patients with event [N(%)]	101 (11.0)	92 (10.5)
Time at risk for event [years]	1181.5	1130.6
Incidence rate [patients with events per 100 patient years at risk]	8.55	8.14
95% confidence interval	(6.96, 10.29)	(6.56, 9.88)
Comparison vs Placebo*		
Hazard ratio		0.95
95% confidence interval		(0.71,1.26)
p-value		0.7153

* Based on a Cox regression model with terms for age (p=0.2492), baseline eGFR (CKD-EPI) (p=0.0129), sex (p=0.1905), region (p=0.0395), baseline diabetes status (3 cat.) (p=0.2821), baseline LVEF (3 cat.) (p=0.9901), Treatment (p=0.7725), cause of heart failure (2 cat.) (p=0.0370) and Treatment by cause of heart failure (2 cat.) interaction (p=0.7897).

MIs were counted excluding silent MIs.

R.1.1.14.12 Subgroup analysis by heart failure physiology (LVEF <= 30% and NTproBNP<median; LVEF <= 30% and NTproBNP>=median; LVEF > 30%)

Table R.1.1.14.12: 1 Cox regr. for time to first event of adjudicated CV death, adjudicated non-fatal MI or adjudicated non-fatal stroke (3-point MACE) by heart failure physiology - RS (trial 1245.121)

Subgroup Description	Placebo	Empa 10mg
Heart failure physiology: LVEF <= 30% and NTproBNP < median		
Number of patients in analysis set	723	698
Number of analysed patients	723	698
Number of patients with event [N(%)]	57 (7.9)	62 (8.9)
Time at risk for event [years]	969.5	935.5
Incidence rate [patients with events per 100 patient years at risk]	5.88	6.63
95% confidence interval	(4.45, 7.50)	(5.08, 8.38)
Comparison vs Placebo*		
Hazard ratio		1.13
95% confidence interval		(0.79,1.62)
p-value		0.5147
Heart failure physiology: LVEF <= 30% and NTproBNP >= median		
Number of patients in analysis set	661	631
Number of analysed patients	661	631
Number of patients with event [N(%)]	118 (17.9)	93 (14.7)
Time at risk for event [years]	852.4	805.0
Incidence rate [patients with events per 100 patient years at risk]	13.84	11.55
95% confidence interval	(11.46, 16.45)	(9.32, 14.02)
Comparison vs Placebo*		
Hazard ratio		0.82
95% confidence interval		(0.63,1.08)
p-value		0.1620

* Based on a Cox regression model with terms for age (p=0.1558), baseline eGFR (CKD-EPI) (p=0.0942), sex (p=0.0986), region (p=0.1140), baseline diabetes status (3 cat.) (p=0.2626), Treatment (p=0.8986), heart failure physiology (p<0.0001) and Treatment by heart failure physiology interaction (p=0.2625).
16 patients were excluded as the subgroup variable was missing.
The p-value for treatment by subgroup interaction trend test is 0.8984.

MIs were counted excluding silent MIs.

Table R.1.1.14.12: 1 Cox regr. for time to first event of adjudicated CV death, adjudicated non-fatal MI or adjudicated non-fatal stroke (3-point MACE) by heart failure physiology - RS (trial 1245.121)

Subgroup Description	Placebo	Empa 10mg
Heart failure physiology: LVEF > 30%		
Number of patients in analysis set	475	526
Number of analysed patients	475	526
Number of patients with event [N(%)]	55 (11.6)	69 (13.1)
Time at risk for event [years]	598.8	670.0
Incidence rate [patients with events per 100 patient years at risk]	9.18	10.30
95% confidence interval	(6.92, 11.77)	(8.01, 12.87)
Comparison vs Placebo*		
Hazard ratio		1.12
95% confidence interval		(0.78,1.59)
p-value		0.5364

* Based on a Cox regression model with terms for age (p=0.1558), baseline eGFR (CKD-EPI) (p=0.0942), sex (p=0.0986), region (p=0.1140), baseline diabetes status (3 cat.) (p=0.2626), Treatment (p=0.8986), heart failure physiology (p<0.0001) and Treatment by heart failure physiology interaction (p=0.2625).
16 patients were excluded as the subgroup variable was missing.
The p-value for treatment by subgroup interaction trend test is 0.8984.

MIs were counted excluding silent MIs.

R.1.1.14.13

R.1.1.14.13 Subgroup analysis by baseline use of MRA

Figure R.1.1.14.13: 1

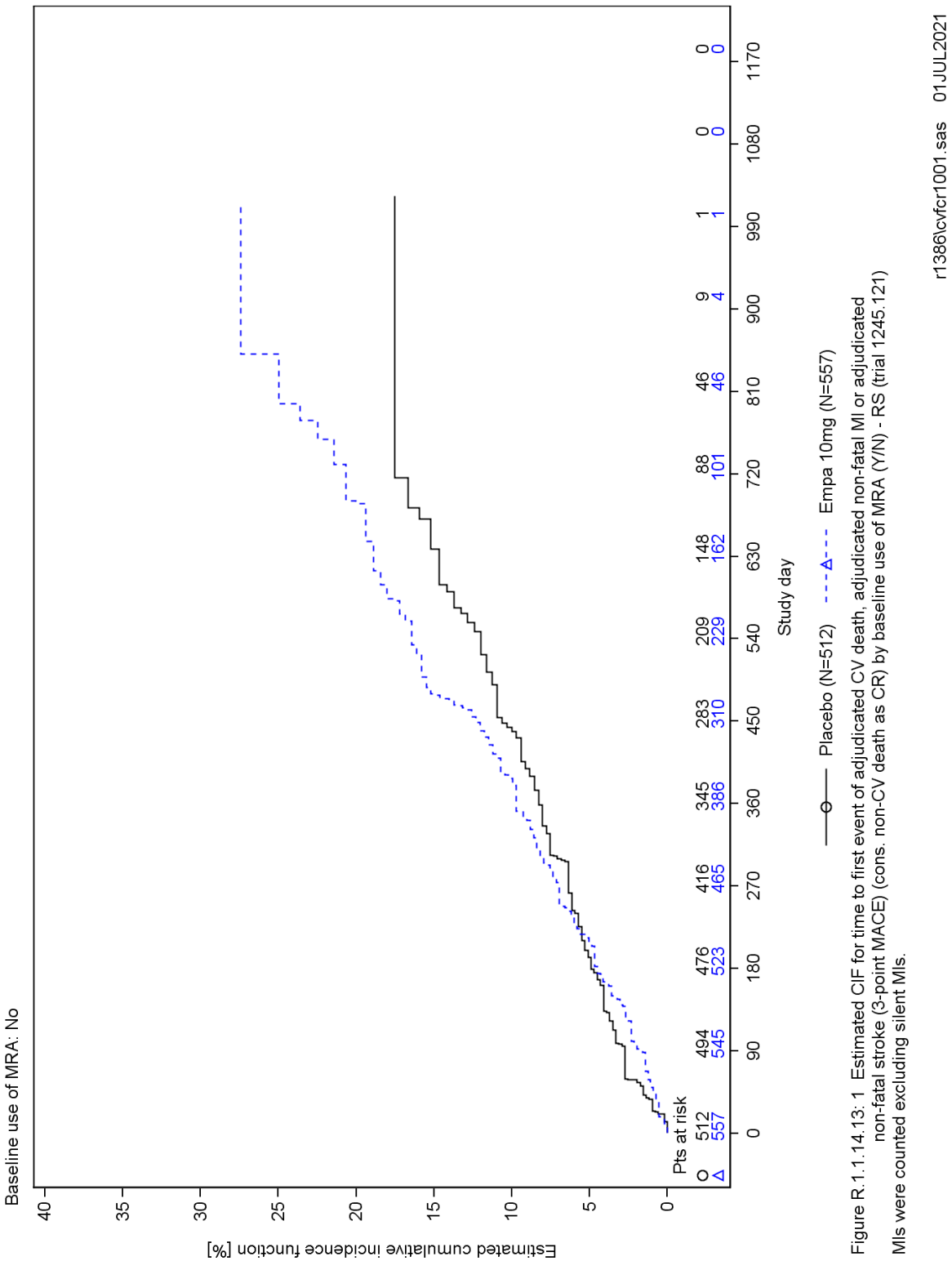

Figure R.1.1.14.13: 1 Estimated CIF for time to first event of adjudicated CV death, adjudicated non-fatal MI or adjudicated non-fatal stroke (3-point MACE) (cons. non-CV death as CR) by baseline use of MRA (Y/N) - RS (trial 1245.121)

MIs were counted excluding silent MIs.

Figure R.1.1.14.13: 1

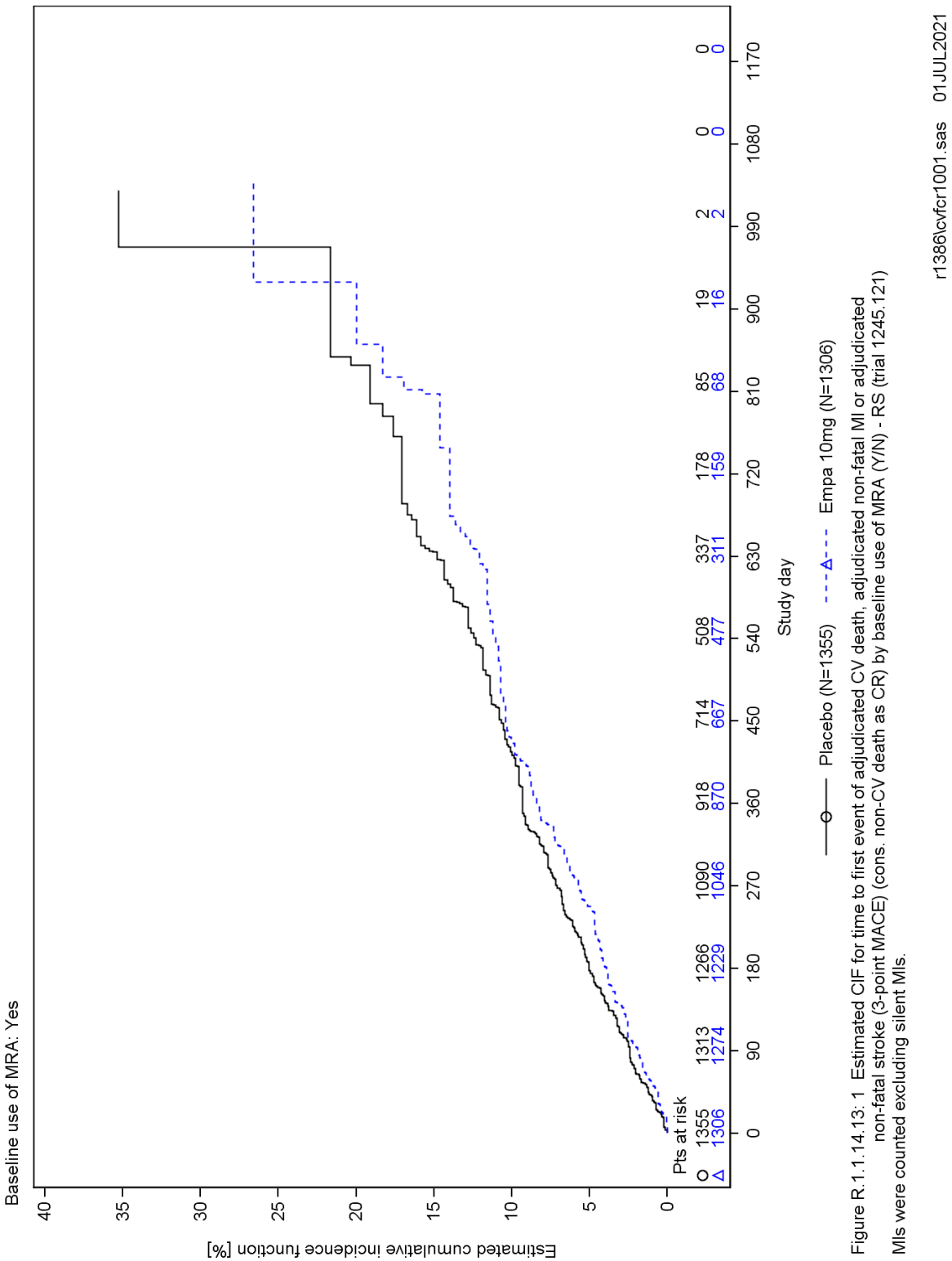

Figure R.1.1.14.13: 1 Estimated CIF for time to first event of adjudicated CV death, adjudicated non-fatal MI or adjudicated non-fatal stroke (3-point MACE) (cons. non-CV death as CR) by baseline use of MRA (Y/N) - RS (trial 1245.121)

MIs were counted excluding silent MIs.

Table R.1.1.14.13: 1 Cox regr. for time to first event of adjudicated CV death, adjudicated non-fatal MI or adjudicated non-fatal stroke (3-point MACE) by baseline use of MRA (Y/N) - RS (trial 1245.121)

Subgroup Description	Placebo	Empa 10mg
Baseline use of MRA: No		
Number of patients in analysis set	512	557
Number of analysed patients	512	557
Number of patients with event [N(%)]	62 (12.1)	89 (16.0)
Time at risk for event [years]	680.9	748.8
Incidence rate [patients with events per 100 patient years at risk]	9.11	11.89
95% confidence interval	(6.98, 11.51)	(9.55, 14.48)
Comparison vs Placebo*		
Hazard ratio		1.31
95% confidence interval		(0.95,1.82)
p-value		0.0991
Baseline use of MRA: Yes		
Number of patients in analysis set	1355	1306
Number of analysed patients	1355	1306
Number of patients with event [N(%)]	170 (12.5)	139 (10.6)
Time at risk for event [years]	1749.1	1669.3
Incidence rate [patients with events per 100 patient years at risk]	9.72	8.33
95% confidence interval	(8.31, 11.23)	(7.00, 9.77)
Comparison vs Placebo*		
Hazard ratio		0.85
95% confidence interval		(0.68,1.06)
p-value		0.1470

* Based on a Cox regression model with terms for age (p=0.2080), baseline eGFR (CKD-EPI) (p=0.0145), sex (p=0.1259), region (p=0.0521), baseline diabetes status (3 cat.) (p=0.1886), baseline LVEF (3 cat.) (p=0.9927), Treatment (p=0.5955), baseline use of MRA (p=0.2347) and Treatment by baseline use of MRA interaction (p=0.0292).

MIs were counted excluding silent MIs.

R.1.1.14.14

R.1.1.14.14 Subgroup analysis by baseline use of ARNi

Table R.1.1.14.14: 1 Cox regr. for time to first event of adjudicated CV death, adjudicated non-fatal MI or adjudicated non-fatal stroke (3-point MACE) by baseline use of ARNi (Y/N) - RS (trial 1245.121)

Subgroup Description	Placebo	Empa 10mg
Baseline use of ARNi: No		
Number of patients in analysis set	1480	1523
Number of analysed patients	1480	1523
Number of patients with event [N(%)]	188 (12.7)	202 (13.3)
Time at risk for event [years]	1950.9	2008.6
Incidence rate [patients with events per 100 patient years at risk]	9.64	10.06
95% confidence interval	(8.31, 11.06)	(8.72, 11.49)
Comparison vs Placebo*		
Hazard ratio		1.03
95% confidence interval		(0.85,1.26)
p-value		0.7627
Baseline use of ARNi: Yes		
Number of patients in analysis set	387	340
Number of analysed patients	387	340
Number of patients with event [N(%)]	44 (11.4)	26 (7.6)
Time at risk for event [years]	479.1	409.4
Incidence rate [patients with events per 100 patient years at risk]	9.18	6.35
95% confidence interval	(6.67, 12.09)	(4.15, 9.02)
Comparison vs Placebo*		
Hazard ratio		0.71
95% confidence interval		(0.43,1.15)
p-value		0.1589

* Based on a Cox regression model with terms for age (p=0.1828), baseline eGFR (CKD-EPI) (p=0.0135), sex (p=0.1253), region (p=0.1094), baseline diabetes status (3 cat.) (p=0.1926), baseline LVEF (3 cat.) (p=0.9944), Treatment (p=0.2343), baseline use of ARNi (p=0.1253) and Treatment by baseline use of ARNi interaction (p=0.1563).

MIs were counted excluding silent MIs.

R.1.1.14.15 Subgroup analysis by bl. LVEF (<= 30%, >30% -<= 35% , > 35%)

Table R.1.1.14.15: 1 Cox regr. for time to first event of adjudicated CV death, adjudicated non-fatal MI or adjudicated non-fatal stroke (3-point MACE) by bl. LVEF (3 cat.) - RS (trial 1245.121)

Subgroup Description	Placebo	Empa 10mg
Baseline LVEF: <=30		
Number of patients in analysis set	1392	1337
Number of analysed patients	1392	1337
Number of patients with event [N(%)]	177 (12.7)	159 (11.9)
Time at risk for event [years]	1831.2	1748.0
Incidence rate [patients with events per 100 patient years at risk]	9.67	9.10
95% confidence interval	(8.29, 11.14)	(7.74, 10.56)
Comparison vs Placebo*		
Hazard ratio		0.93
95% confidence interval		(0.75,1.16)
p-value		0.5246
Baseline LVEF: >30 to <=35		
Number of patients in analysis set	361	398
Number of analysed patients	361	398
Number of patients with event [N(%)]	39 (10.8)	56 (14.1)
Time at risk for event [years]	462.1	512.0
Incidence rate [patients with events per 100 patient years at risk]	8.44	10.94
95% confidence interval	(6.00, 11.29)	(8.26, 13.98)
Comparison vs Placebo*		
Hazard ratio		1.29
95% confidence interval		(0.86,1.95)
p-value		0.2161

* Based on a Cox regression model with terms for age (p=0.1741), baseline eGFR (CKD-EPI) (p=0.0123), sex (p=0.1227), region (p=0.0670), baseline diabetes status (3 cat.) (p=0.1826), Treatment (p=0.7187), baseline LVEF (3 cat.) (p=0.9828) and Treatment by baseline LVEF (3 cat.) interaction (p=0.2529).
The p-value for treatment by subgroup interaction trend test is 0.7768.

MIs were counted excluding silent MIs.

Table R.1.1.14.15: 1 Cox regr. for time to first event of adjudicated CV death, adjudicated non-fatal MI or adjudicated non-fatal stroke (3-point MACE) by bl. LVEF (3 cat.) - RS (trial 1245.121)

Subgroup Description	Placebo	Empa 10mg
Baseline LVEF: >35		
Number of patients in analysis set	114	128
Number of analysed patients	114	128
Number of patients with event [N(%)]	16 (14.0)	13 (10.2)
Time at risk for event [years]	136.7	158.0
Incidence rate [patients with events per 100 patient years at risk]	11.70	8.23
95% confidence interval	(6.69, 18.09)	(4.38, 13.27)
Comparison vs Placebo*		
Hazard ratio		0.71
95% confidence interval		(0.34,1.47)
p-value		0.3520

* Based on a Cox regression model with terms for age (p=0.1741), baseline eGFR (CKD-EPI) (p=0.0123), sex (p=0.1227), region (p=0.0670), baseline diabetes status (3 cat.) (p=0.1826), Treatment (p=0.7187), baseline LVEF (3 cat.) (p=0.9828) and Treatment by baseline LVEF (3 cat.) interaction (p=0.2529).
The p-value for treatment by subgroup interaction trend test is 0.7768.

MIs were counted excluding silent MIs.

R.1.1.14.16 Subgroup analysis by bl. NTproBNP </>= median (median based on total patients)

Table R.1.1.14.16: 1 Cox regr. for time to first event of adjudicated CV death, adjudicated non-fatal MI or adjudicated non-fatal stroke (3-point MACE) by bl. NTproBNP (<median,>= median) (median based on total patients) - RS (trial 1245.121)

Subgroup Description	Placebo	Empa 10mg
Baseline NTproBNP: < median		
Number of patients in analysis set	920	942
Number of analysed patients	920	942
Number of patients with event [N(%)]	73 (7.9)	84 (8.9)
Time at risk for event [years]	1239.0	1257.2
Incidence rate [patients with events per 100 patient years at risk]	5.89	6.68
95% confidence interval	(4.62, 7.32)	(5.33, 8.18)
Comparison vs Placebo*		
Hazard ratio		1.13
95% confidence interval		(0.82,1.54)
p-value		0.4552
Baseline NTproBNP: >= median		
Number of patients in analysis set	946	920
Number of analysed patients	946	920
Number of patients with event [N(%)]	158 (16.7)	144 (15.7)
Time at risk for event [years]	1190.2	1159.6
Incidence rate [patients with events per 100 patient years at risk]	13.28	12.42
95% confidence interval	(11.29, 15.42)	(10.47, 14.53)
Comparison vs Placebo*		
Hazard ratio		0.93
95% confidence interval		(0.74,1.17)
p-value		0.5470

* Based on a Cox regression model with terms for age (p=0.2097), baseline eGFR (CKD-EPI) (p=0.2360), sex (p=0.1518), region (p=0.1396), baseline diabetes status (3 cat.) (p=0.2085), baseline LVEF (3 cat.) (p=0.8781), Treatment (p=0.7997), baseline NTproBNP (2 cat.) (p<0.0001) and Treatment by baseline NTproBNP (2 cat.) interaction (p=0.3379).
2 patients were excluded as the subgroup variable was missing.

MIs were counted excluding silent MIs.
Median: 1910 [pg/mL]

R.1.1.15

R.1.1.15 Time to adjudicated MI (fatal or non-fatal)

R.1.1.15.1

Figure R.1.1.15.1: 1

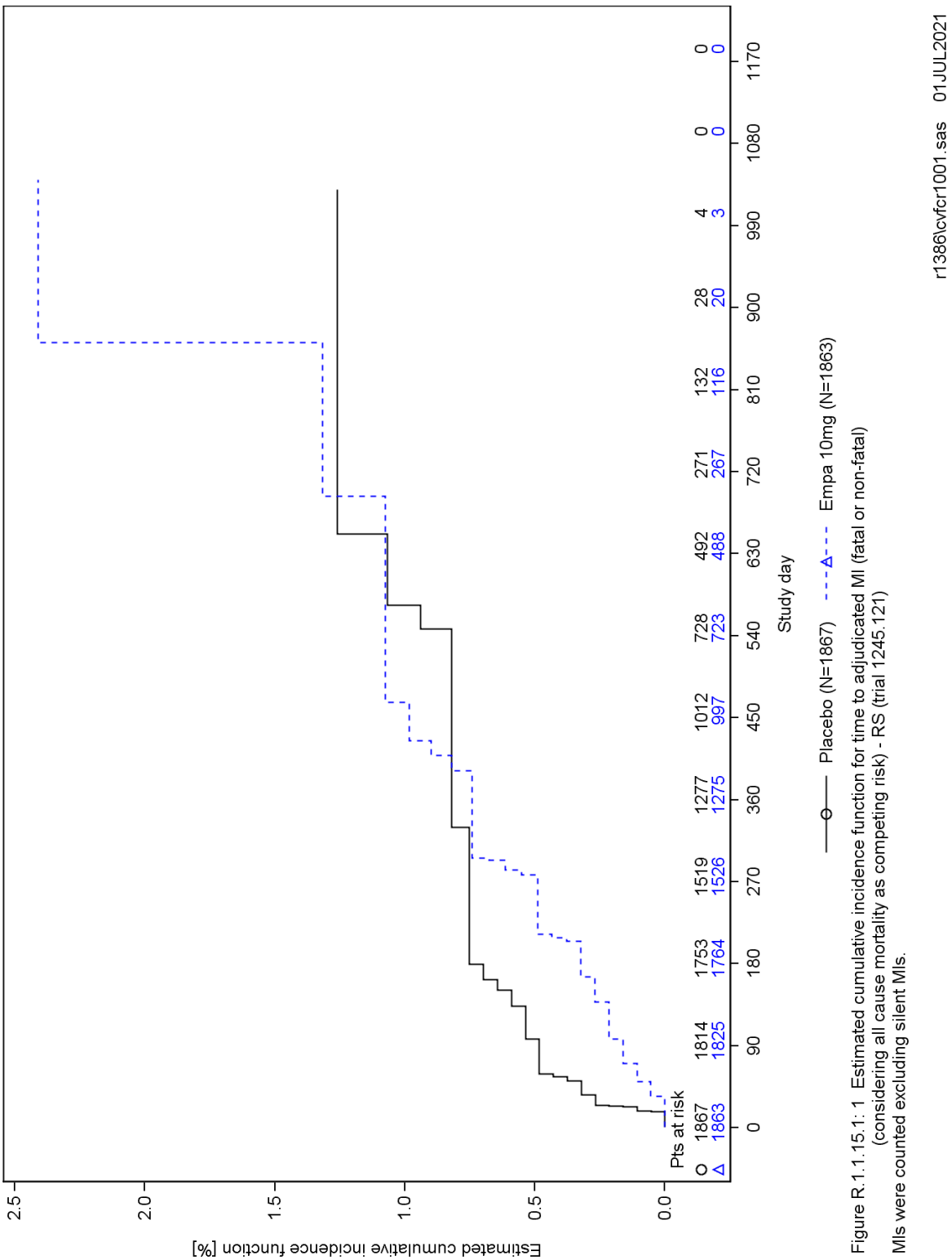

Figure R.1.1.15.1: 1 Estimated cumulative incidence function for time to adjudicated MI (fatal or non-fatal) (considering all cause mortality as competing risk) - RS (trial 1245.121)

MIs were counted excluding silent MIs.

Table R.1.1.15.1: 1 Cox regr. for time to adjudicated MI (fatal or non-fatal) - RS (trial 1245.121)

	Placebo	Empa 10mg
Number of patients in analysis set	1867	1863
Number of analysed patients	1867	1863
Number of patients with event [N(%)]	18 (1.0)	19 (1.0)
Time at risk for event [years]	2451.3	2446.2
Incidence rate [patients with events per 100 patient years at risk]	0.73	0.78
95% confidence interval	(0.44, 1.11)	(0.47, 1.16)
Comparison vs Placebo*		
Hazard ratio		1.04
95% confidence interval		(0.54,1.98)
p-value		0.9169
Time to event [days]**		
2.5% percentile	NC.	861
5.0% percentile	NC.	NC.
7.5% percentile	NC.	NC.
10.0% percentile	NC.	NC.
Patients with events [%]**		
1 year	0.8	0.8
2 years	1.4	1.4

* Based on a Cox regression model with terms for age (p=0.1859), baseline eGFR (CKD-EPI) (p=0.7721), sex (p=0.0724), region (p=0.0403), baseline diabetes status (3 cat.) (p=0.1384), baseline LVEF (3 cat.) (p=0.6987) and Treatment (p=0.9169).
**Based on Kaplan-Meier estimates.
NC. = Not calculated.

MIs were counted excluding silent MIs.

R.1.1.15.2

Table R.1.1.15.2: 1 Cox regr. for time to adjudicated MI (fatal or non-fatal) by sex - RS (trial 1245.121)

Subgroup Description	Placebo	Empa 10mg
Sex: Male		
Number of patients in analysis set	1411	1426
Number of analysed patients	1411	1426
Number of patients with event [N(%)]	11 (0.8)	13 (0.9)
Time at risk for event [years]	1863.8	1863.7
Incidence rate [patients with events per 100 patient years at risk]	0.59	0.70
95% confidence interval	(0.29, 0.99)	(0.37, 1.12)
Comparison vs Placebo*		
Hazard ratio		1.15
95% confidence interval		(0.51,2.57)
p-value		0.7315
Sex: Female		
Number of patients in analysis set	456	437
Number of analysed patients	456	437
Number of patients with event [N(%)]	7 (1.5)	6 (1.4)
Time at risk for event [years]	587.5	582.5
Incidence rate [patients with events per 100 patient years at risk]	1.19	1.03
95% confidence interval	(0.48, 2.22)	(0.38, 2.00)
Comparison vs Placebo*		
Hazard ratio		0.85
95% confidence interval		(0.28,2.54)
p-value		0.7711

* Based on a Cox regression model with terms for age (p=0.1897), baseline eGFR (CKD-EPI) (p=0.7716), region (p=0.0402), baseline diabetes status (3 cat.) (p=0.1408), baseline LVEF (3 cat.) (p=0.6997), Treatment (p=0.9751), sex (p=0.0733) and Treatment by sex interaction (p=0.6616).

MIs were counted excluding silent MIs.

R.1.1.15.3

Table R.1.1.15.3: 1 Cox regr. for time to adjudicated MI (fatal or non-fatal) by age (2 cat.) - RS (trial 1245.121)

Subgroup Description	Placebo	Empa 10mg
Age [years]: < 65		
Number of patients in analysis set	740	675
Number of analysed patients	740	675
Number of patients with event [N(%)]	4 (0.5)	5 (0.7)
Time at risk for event [years]	975.5	880.7
Incidence rate [patients with events per 100 patient years at risk]	0.41	0.57
95% confidence interval	(0.11, 0.90)	(0.18, 1.16)
Comparison vs Placebo*		
Hazard ratio		1.37
95% confidence interval		(0.37,5.12)
p-value		0.6372
Age [years]: >= 65		
Number of patients in analysis set	1127	1188
Number of analysed patients	1127	1188
Number of patients with event [N(%)]	14 (1.2)	14 (1.2)
Time at risk for event [years]	1475.8	1565.5
Incidence rate [patients with events per 100 patient years at risk]	0.95	0.89
95% confidence interval	(0.52, 1.51)	(0.49, 1.42)
Comparison vs Placebo*		
Hazard ratio		0.95
95% confidence interval		(0.45,2.00)
p-value		0.8977

* Based on a Cox regression model with terms for baseline eGFR (CKD-EPI) (p=0.8411), sex (p=0.0714), region (p=0.0356), baseline diabetes status (3 cat.) (p=0.1296), baseline LVEF (3 cat.) (p=0.6952), Treatment (p=0.7280), age (2 cat.) (p=0.1609) and Treatment by age (2 cat.) interaction (p=0.6357).

MIs were counted excluding silent MIs.

R.1.1.15.4 Subgroup analysis by region (North America, Latin America, Europe, Asia, Other)

Table R.1.1.15.4: 1 Cox regr. for time to adjudicated MI (fatal or non-fatal) by region - RS (trial 1245.121)

Subgroup Description	Placebo	Empa 10mg
Region: North America		
Number of patients in analysis set	213	212
Number of analysed patients	213	212
Number of patients with event [N(%)]	6 (2.8)	4 (1.9)
Time at risk for event [years]	284.0	302.3
Incidence rate [patients with events per 100 patient years at risk]	2.11	1.32
95% confidence interval	(0.78, 4.11)	(0.36, 2.90)
Comparison vs Placebo*		
Hazard ratio		0.62
95% confidence interval		(0.17, 2.21)
p-value		0.4607
Region: Latin America		
Number of patients in analysis set	645	641
Number of analysed patients	645	641
Number of patients with event [N(%)]	1 (0.2)	6 (0.9)
Time at risk for event [years]	778.0	760.9
Incidence rate [patients with events per 100 patient years at risk]	0.13	0.79
95% confidence interval	(0.00, 0.47)	(0.29, 1.53)
Comparison vs Placebo*		
Hazard ratio		5.84
95% confidence interval		(0.70,48.55)
p-value		0.1025

* Based on a Cox regression model with terms for age (p=0.1959), baseline eGFR (CKD-EPI) (p=0.7998), sex (p=0.0652), baseline diabetes status (3 cat.) (p=0.1541), baseline LVEF (3 cat.) (p=0.7474), Treatment (p=0.9862), region (p=0.0417) and Treatment by region interaction (p=0.4700).
NC. = Not calculated, some results could not be produced.

MIs were counted excluding silent MIs.

Table R.1.1.15.4: 1 Cox regr. for time to adjudicated MI (fatal or non-fatal) by region - RS (trial 1245.121)

Subgroup Description	Placebo	Empa 10mg
Region: Europe		
Number of patients in analysis set	677	676
Number of analysed patients	677	676
Number of patients with event [N(%)]	10 (1.5)	7 (1.0)
Time at risk for event [years]	923.2	921.5
Incidence rate [patients with events per 100 patient years at risk]	1.08	0.76
95% confidence interval	(0.52, 1.85)	(0.31, 1.42)
Comparison vs Placebo*		
Hazard ratio		0.71
95% confidence interval		(0.27, 1.86)
p-value		0.4845
Region: Asia		
Number of patients in analysis set	245	248
Number of analysed patients	245	248
Number of patients with event [N(%)]	1 (0.4)	1 (0.4)
Time at risk for event [years]	349.7	348.3
Incidence rate [patients with events per 100 patient years at risk]	0.29	0.29
95% confidence interval	(0.01, 1.06)	(0.01, 1.06)
Comparison vs Placebo*		
Hazard ratio		0.94
95% confidence interval		(0.06,14.98)
p-value		0.9623

* Based on a Cox regression model with terms for age (p=0.1959), baseline eGFR (CKD-EPI) (p=0.7998), sex (p=0.0652), baseline diabetes status (3 cat.) (p=0.1541), baseline LVEF (3 cat.) (p=0.7474), Treatment (p=0.9862), region (p=0.0417) and Treatment by region interaction (p=0.4700).
NC. = Not calculated, some results could not be produced.

MIs were counted excluding silent MIs.

Table R.1.1.15.4: 1 Cox regr. for time to adjudicated MI (fatal or non-fatal) by region - RS (trial 1245.121)

Subgroup Description	Placebo	Empa 10mg
Region: Other		
Number of patients in analysis set	87	86
Number of analysed patients	87	86
Number of patients with event [N(%)]	0	1 (1.2)
Time at risk for event [years]	116.4	113.1
Incidence rate [patients with events per 100 patient years at risk]	0.00	0.88
95% confidence interval	NC.	(0.02, 3.26)
Comparison vs Placebo*		
Hazard ratio		NC.
95% confidence interval		NC.
p-value		NC.

* Based on a Cox regression model with terms for age (p=0.1959), baseline eGFR (CKD-EPI) (p=0.7998), sex (p=0.0652), baseline diabetes status (3 cat.) (p=0.1541), baseline LVEF (3 cat.) (p=0.7474), Treatment (p=0.9862), region (p=0.0417) and Treatment by region interaction (p=0.4700).
NC. = Not calculated, some results could not be produced.

MIs were counted excluding silent MIs.

R.1.1.15.5

R.1.1.15.5 Subgroup analysis by OECD member (Y/N)

Figure R.1.1.15.5: 1

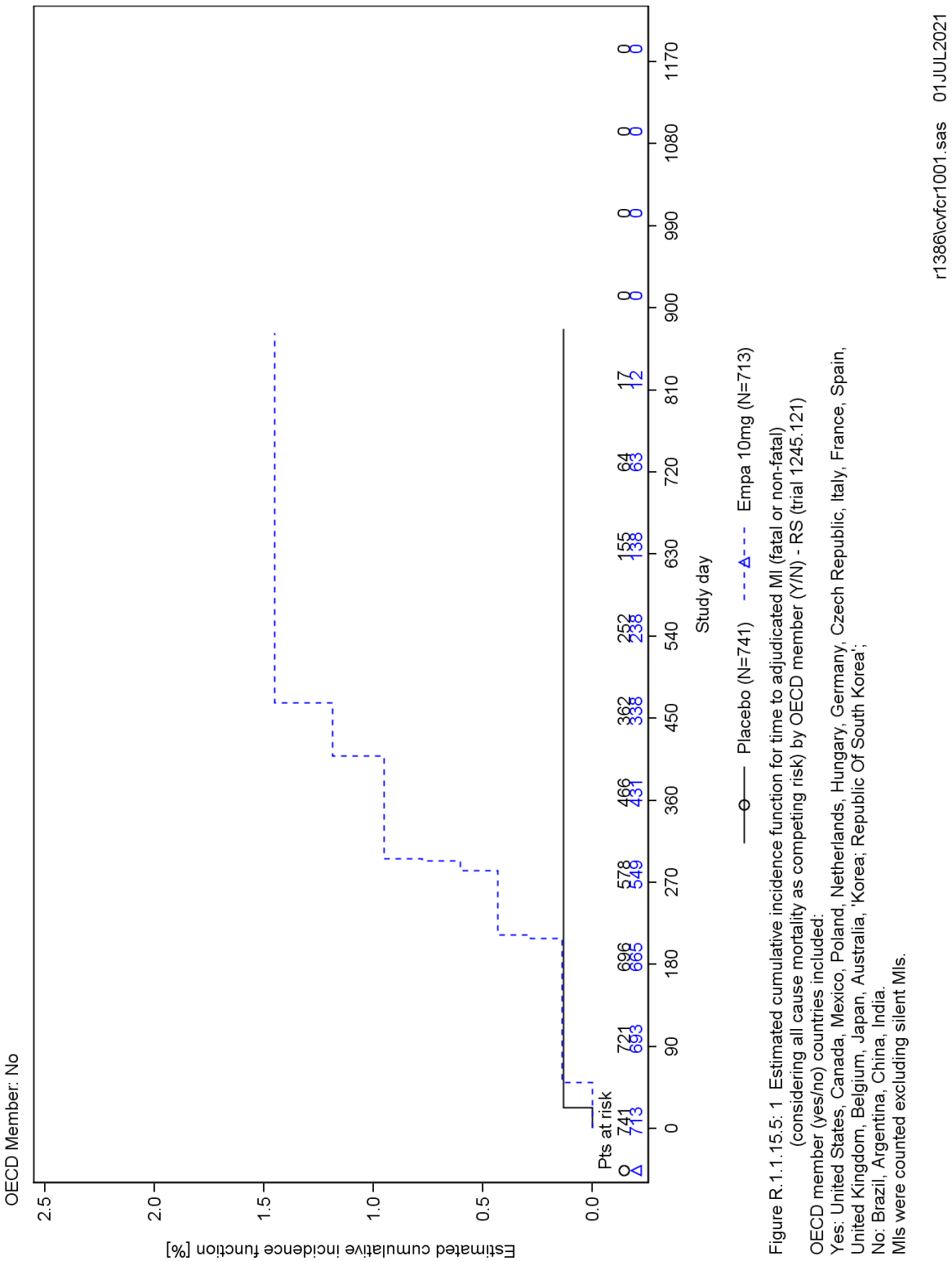

Figure R.1.1.15.5: 1 Estimated cumulative incidence function for time to adjudicated MI (fatal or non-fatal) (considering all cause mortality as competing risk) by OECD member (Y/N) - RS (trial 1245.121)
OECD member (yes/no) countries included:
Yes: United States, Canada, Mexico, Poland, Netherlands, Hungary, Germany, Czech Republic, Italy, France, Spain, United Kingdom, Belgium, Japan, Australia, 'Korea; Republic Of South Korea';
No: Brazil, Argentina, China, India.
MIs were counted excluding silent MIs.

Figure R.1.1.15.5: 1

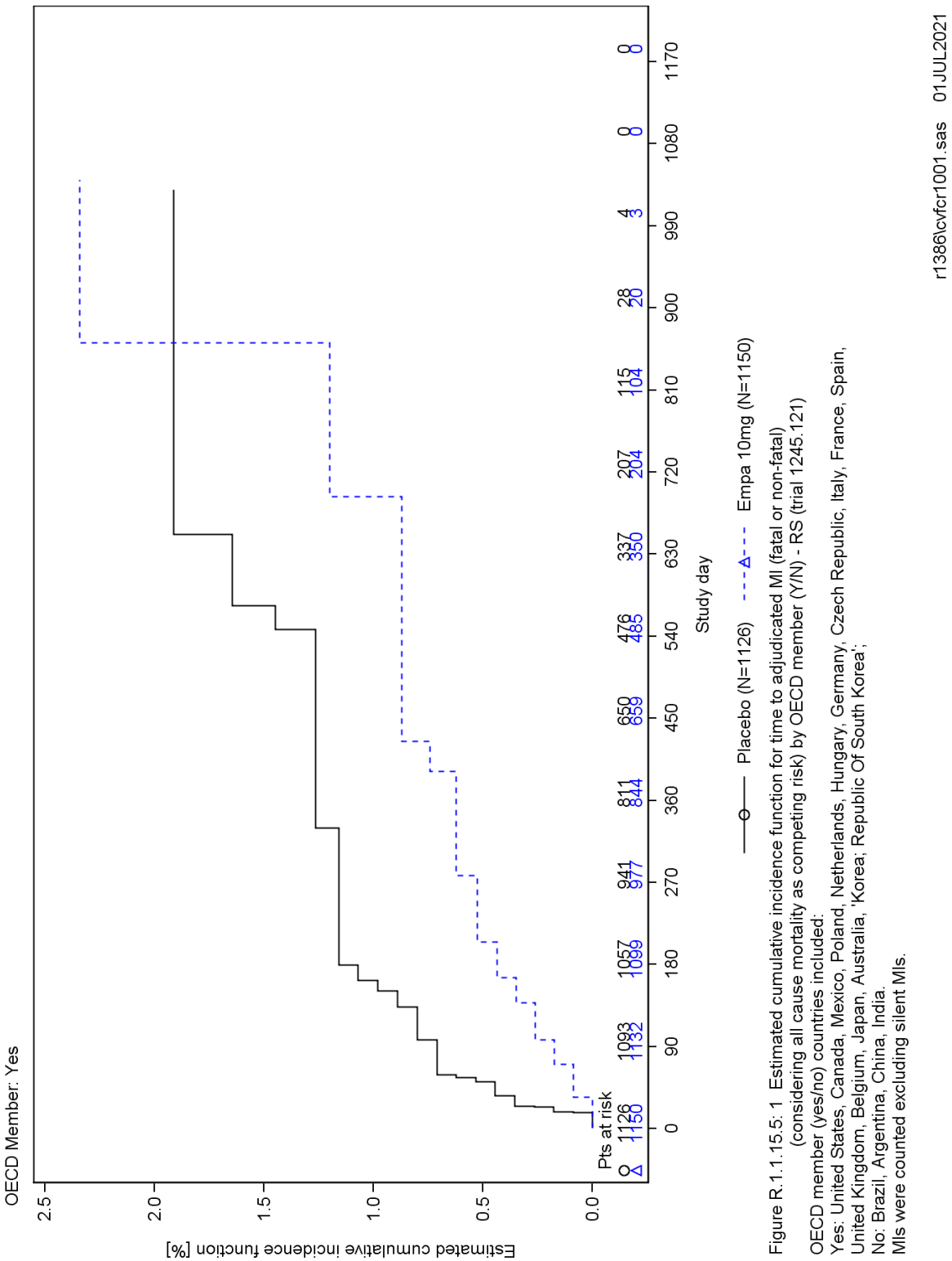

Figure R.1.1.15.5: 1 Estimated cumulative incidence function for time to adjudicated MI (fatal or non-fatal) (considering all cause mortality as competing risk) by OECD member (Y/N) - RS (trial 1245.121)
OECD member (yes/no) countries included:
Yes: United States, Canada, Mexico, Poland, Netherlands, Hungary, Germany, Czech Republic, Italy, France, Spain, United Kingdom, Belgium, Japan, Australia, 'Korea; Republic Of South Korea';
No: Brazil, Argentina, China, India.
MIs were counted excluding silent MIs.

Table R.1.1.15.5: 1 Cox regr. for time to adjudicated MI (fatal or non-fatal) by OECD member (Y/N) - RS (trial 1245.121)

Subgroup Description	Placebo	Empa 10mg
OECD member: No		
Number of patients in analysis set	741	713
Number of analysed patients	741	713
Number of patients with event [N(%)]	1 (0.1)	8 (1.1)
Time at risk for event [years]	903.0	855.5
Incidence rate [patients with events per 100 patient years at risk]	0.11	0.94
95% confidence interval	(0.00, 0.41)	(0.40, 1.69)
Comparison vs Placebo*		
Hazard ratio		8.02
95% confidence interval		(1.00,64.19)
p-value		0.0497
OECD member: Yes		
Number of patients in analysis set	1126	1150
Number of analysed patients	1126	1150
Number of patients with event [N(%)]	17 (1.5)	11 (1.0)
Time at risk for event [years]	1548.3	1590.7
Incidence rate [patients with events per 100 patient years at risk]	1.10	0.69
95% confidence interval	(0.64, 1.68)	(0.35, 1.16)
Comparison vs Placebo*		
Hazard ratio		0.63
95% confidence interval		(0.29, 1.34)
p-value		0.2314

* Based on a Cox regression model with terms for age (p=0.2053), baseline eGFR (CKD-EPI) (p=0.9101), sex (p=0.0635), baseline diabetes status (3 cat.) (p=0.1760), baseline LVEF (3 cat.) (p=0.7168), Treatment (p=0.1519), OECD Member (N) (p=0.0860) and Treatment by OECD Member (N) interaction (p=0.0242).

MIs were counted excluding silent MIs.
OECD member (yes/no) countries included:
Yes: United States, Canada, Mexico, Poland, Netherlands, Hungary, Germany, Czech Republic, Italy, France, Spain, United Kingdom, Belgium, Japan, Australia, 'Korea; Republic Of South Korea';
No: Brazil, Argentina, China, India.

R.1.1.15.6

R.1.1.15.6 Subgroup analysis by NYHA at baseline (II, III/IV - 2 cat.)

Table R.1.1.15.6: 1 Cox regr. for time to adjudicated MI (fatal or non-fatal) by baseline NYHA (2 cat.) - RS (trial 1245.121)

Subgroup Description	Placebo	Empa 10mg
Baseline NYHA: II		
Number of patients in analysis set	1401	1399
Number of analysed patients	1401	1399
Number of patients with event [N(%)]	14 (1.0)	9 (0.6)
Time at risk for event [years]	1853.9	1844.3
Incidence rate [patients with events per 100 patient years at risk]	0.76	0.49
95% confidence interval	(0.41, 1.20)	(0.22, 0.85)
Comparison vs Placebo*		
Hazard ratio		0.62
95% confidence interval		(0.27,1.45)
p-value		0.2723
Baseline NYHA: III/IV		
Number of patients in analysis set	466	464
Number of analysed patients	466	464
Number of patients with event [N(%)]	4 (0.9)	10 (2.2)
Time at risk for event [years]	597.3	601.9
Incidence rate [patients with events per 100 patient years at risk]	0.67	1.66
95% confidence interval	(0.18, 1.47)	(0.80, 2.84)
Comparison vs Placebo*		
Hazard ratio		2.50
95% confidence interval		(0.78,7.99)
p-value		0.1218

* Based on a Cox regression model with terms for age (p=0.1656), baseline eGFR (CKD-EPI) (p=0.6845), sex (p=0.0963), region (p=0.0487), baseline diabetes status (3 cat.) (p=0.1208), baseline LVEF (3 cat.) (p=0.6972), Treatment (p=0.5412), baseline NYHA (2 cat.) (p=0.1889) and Treatment by baseline NYHA (2 cat.) interaction (p=0.0577).

MIs were counted excluding silent MIs.

R.1.1.15.7

Table R.1.1.15.7: 1

Table R.1.1.15.7: 1 Cox regr. for time to adjudicated MI (fatal or non-fatal) by diabetes at baseline (2 cat.) - RS (trial 1245.121)

Subgroup Description	Placebo	Empa 10mg
Baseline diabetes status: Diabetic		
Number of patients in analysis set	929	927
Number of analysed patients	929	927
Number of patients with event [N(%)]	7 (0.8)	7 (0.8)
Time at risk for event [years]	1233.5	1222.6
Incidence rate [patients with events per 100 patient years at risk]	0.57	0.57
95% confidence interval	(0.23, 1.06)	(0.23, 1.07)
Comparison vs Placebo*		
Hazard ratio		0.99
95% confidence interval		(0.35,2.83)
p-value		0.9856
Baseline diabetes status: Non-Diabetic		
Number of patients in analysis set	938	936
Number of analysed patients	938	936
Number of patients with event [N(%)]	11 (1.2)	12 (1.3)
Time at risk for event [years]	1217.7	1223.6
Incidence rate [patients with events per 100 patient years at risk]	0.90	0.98
95% confidence interval	(0.45, 1.51)	(0.51, 1.61)
Comparison vs Placebo*		
Hazard ratio		1.07
95% confidence interval		(0.47,2.43)
p-value		0.8732

* Based on a Cox regression model with terms for age (p=0.2058), baseline eGFR (CKD-EPI) (p=0.7270), sex (p=0.0719), region (p=0.0442), baseline LVEF (3 cat.) (p=0.6874), Treatment (p=0.9330), baseline diabetes status (2 cat.) (p=0.1484) and Treatment by baseline diabetes status (2 cat.) interaction (p=0.9103).

MIs were counted excluding silent MIs.

R.1.1.15.8

R.1.1.15.8 Subgroup analysis by BMI at baseline (<30, >=30)

Table R.1.1.15.8: 1 Cox regr. for time to adjudicated MI (fatal or non-fatal) by baseline BMI [kg/m2] - RS (trial 1245.121)

Subgroup Description	Placebo	Empa 10mg
Baseline BMI [kg/m²]: <30		
Number of patients in analysis set	1300	1263
Number of analysed patients	1300	1263
Number of patients with event [N(%)]	13 (1.0)	12 (1.0)
Time at risk for event [years]	1725.7	1650.8
Incidence rate [patients with events per 100 patient years at risk]	0.75	0.73
95% confidence interval	(0.40, 1.21)	(0.38, 1.19)
Comparison vs Placebo*		
Hazard ratio		0.93
95% confidence interval		(0.42,2.05)
p-value		0.8618
Baseline BMI [kg/m²]: >=30		
Number of patients in analysis set	567	600
Number of analysed patients	567	600
Number of patients with event [N(%)]	5 (0.9)	7 (1.2)
Time at risk for event [years]	725.6	795.4
Incidence rate [patients with events per 100 patient years at risk]	0.69	0.88
95% confidence interval	(0.22, 1.41)	(0.35, 1.64)
Comparison vs Placebo*		
Hazard ratio		1.29
95% confidence interval		(0.41,4.08)
p-value		0.6630

* Based on a Cox regression model with terms for age (p=0.1924), baseline eGFR (CKD-EPI) (p=0.7638), sex (p=0.0741), region (p=0.0431), baseline diabetes status (3 cat.) (p=0.1406), baseline LVEF (3 cat.) (p=0.6912), Treatment (p=0.7939), baseline BMI (2 cat.) (p=0.9499) and Treatment by baseline BMI (2 cat.) interaction (p=0.6467).

MIs were counted excluding silent MIs.

R.1.1.15.9

R.1.1.15.9 Subgroup analysis by eGFR at baseline (<60, >=60)

Table R.1.1.15.9: 1 Cox regr. for time to adjudicated MI (fatal or non-fatal) by baseline eGFR (2 cat.) - RS (trial 1245.121)

Subgroup Description	Placebo	Empa 10mg
Baseline eGFR (CKD-EPI) [mL/min/1.73m²]: >=60		
Number of patients in analysis set	960	969
Number of analysed patients	960	969
Number of patients with event [N(%)]	10 (1.0)	10 (1.0)
Time at risk for event [years]	1264.8	1268.0
Incidence rate [patients with events per 100 patient years at risk]	0.79	0.79
95% confidence interval	(0.38, 1.35)	(0.38, 1.35)
Comparison vs Placebo*		
Hazard ratio		0.95
95% confidence interval		(0.39,2.29)
p-value		0.9101
Baseline eGFR (CKD-EPI) [mL/min/1.73m²]: <60		
Number of patients in analysis set	906	893
Number of analysed patients	906	893
Number of patients with event [N(%)]	8 (0.9)	9 (1.0)
Time at risk for event [years]	1185.6	1177.0
Incidence rate [patients with events per 100 patient years at risk]	0.67	0.76
95% confidence interval	(0.29, 1.22)	(0.35, 1.34)
Comparison vs Placebo*		
Hazard ratio		1.12
95% confidence interval		(0.43,2.90)
p-value		0.8197

* Based on a Cox regression model with terms for age (p=0.1008), sex (p=0.0641), region (p=0.0359), baseline diabetes status (3 cat.) (p=0.1507), baseline LVEF (3 cat.) (p=0.7079), Treatment (p=0.9275), baseline eGFR (CKD-EPI) (2 cat.) (p=0.2316) and Treatment by baseline eGFR (CKD-EPI) (2 cat.) interaction (p=0.8069).
2 patients were excluded as the subgroup variable was missing.

MIs were counted excluding silent MIs.

R.1.1.15.10

Table R.1.1.15.10: 1 Cox regr. for time to adjudicated MI (fatal or non-fatal) by history of HHF within 12 months - RS (trial 1245.121)

Subgroup Description	Placebo	Empa 10mg
History of HHF (in the last 12 months): No		
Number of patients in analysis set	1293	1286
Number of analysed patients	1293	1286
Number of patients with event [N(%)]	13 (1.0)	14 (1.1)
Time at risk for event [years]	1747.9	1722.5
Incidence rate [patients with events per 100 patient years at risk]	0.74	0.81
95% confidence interval	(0.40, 1.20)	(0.44, 1.29)
Comparison vs Placebo*		
Hazard ratio		1.08
95% confidence interval		(0.51,2.31)
p-value		0.8330
History of HHF (in the last 12 months): Yes		
Number of patients in analysis set	574	577
Number of analysed patients	574	577
Number of patients with event [N(%)]	5 (0.9)	5 (0.9)
Time at risk for event [years]	703.4	723.8
Incidence rate [patients with events per 100 patient years at risk]	0.71	0.69
95% confidence interval	(0.23, 1.46)	(0.22, 1.42)
Comparison vs Placebo*		
Hazard ratio		0.91
95% confidence interval		(0.26,3.16)
p-value		0.8862

* Based on a Cox regression model with terms for age (p=0.1890), baseline eGFR (CKD-EPI) (p=0.7792), sex (p=0.0724), region (p=0.0406), baseline diabetes status (3 cat.) (p=0.1403), baseline LVEF (3 cat.) (p=0.6976), Treatment (p=0.9900), history of HHF (p=0.9526) and Treatment by history of HHF interaction (p=0.8165).

MIs were counted excluding silent MIs.

R.1.1.15.11

R.1.1.15.11 Subgroup analysis by cause of heart failure

Table R.1.1.15.11: 1 Cox regr. for time to adjudicated MI (fatal or non-fatal) by cause of heart failure - RS (trial 1245.121)

Subgroup Description	Placebo	Empa 10mg
Cause of heart failure: Ischemic		
Number of patients in analysis set	946	983
Number of analysed patients	946	983
Number of patients with event [N(%)]	12 (1.3)	14 (1.4)
Time at risk for event [years]	1259.9	1299.0
Incidence rate [patients with events per 100 patient years at risk]	0.95	1.08
95% confidence interval	(0.49, 1.56)	(0.59, 1.71)
Comparison vs Placebo*		
Hazard ratio		1.13
95% confidence interval		(0.52,2.45)
p-value		0.7544
Cause of heart failure: Non-ischemic		
Number of patients in analysis set	921	880
Number of analysed patients	921	880
Number of patients with event [N(%)]	6 (0.7)	5 (0.6)
Time at risk for event [years]	1191.4	1147.3
Incidence rate [patients with events per 100 patient years at risk]	0.50	0.44
95% confidence interval	(0.18, 0.98)	(0.14, 0.89)
Comparison vs Placebo*		
Hazard ratio		0.83
95% confidence interval		(0.25,2.72)
p-value		0.7545

* Based on a Cox regression model with terms for age (p=0.2512), baseline eGFR (CKD-EPI) (p=0.7721), sex (p=0.0384), region (p=0.0585), baseline diabetes status (3 cat.) (p=0.0724), baseline LVEF (3 cat.) (p=0.6880), Treatment (p=0.9268), cause of heart failure (2 cat.) (p=0.0302) and Treatment by cause of heart failure (2 cat.) interaction (p=0.6653).

MIs were counted excluding silent MIs.

R.1.1.15.12 Subgroup analysis by heart failure physiology (LVEF <= 30% and NTproBNP<median; LVEF <= 30% and NTproBNP>=median; LVEF > 30%)

Table R.1.1.15.12: 1 Cox regr. for time to adjudicated MI (fatal or non-fatal) by heart failure physiology - RS (trial 1245.121)

Subgroup Description	Placebo	Empa 10mg
Heart failure physiology: LVEF <= 30% and NTproBNP < median		
Number of patients in analysis set	723	698
Number of analysed patients	723	698
Number of patients with event [N(%)]	6 (0.8)	6 (0.9)
Time at risk for event [years]	979.0	945.2
Incidence rate [patients with events per 100 patient years at risk]	0.61	0.63
95% confidence interval	(0.22, 1.19)	(0.23, 1.23)
Comparison vs Placebo*		
Hazard ratio		1.07
95% confidence interval		(0.34,3.32)
p-value		0.9096
Heart failure physiology: LVEF <= 30% and NTproBNP >= median		
Number of patients in analysis set	661	631
Number of analysed patients	661	631
Number of patients with event [N(%)]	7 (1.1)	9 (1.4)
Time at risk for event [years]	855.7	815.3
Incidence rate [patients with events per 100 patient years at risk]	0.82	1.10
95% confidence interval	(0.33, 1.53)	(0.50, 1.93)
Comparison vs Placebo*		
Hazard ratio		1.33
95% confidence interval		(0.50,3.59)
p-value		0.5692

* Based on a Cox regression model with terms for age (p=0.1753), baseline eGFR (CKD-EPI) (p=0.5894), sex (p=0.0623), region (p=0.0321), baseline diabetes status (3 cat.) (p=0.1321), Treatment (p=0.9021), heart failure physiology (p=0.4283) and Treatment by heart failure physiology interaction (p=0.6590).
16 patients were excluded as the subgroup variable was missing.
The p-value for treatment by subgroup interaction trend test is 0.5798.

MIs were counted excluding silent MIs.

Table R.1.1.15.12: 1 Cox regr. for time to adjudicated MI (fatal or non-fatal) by heart failure physiology - RS (trial 1245.121)

Subgroup Description	Placebo	Empa 10mg
Heart failure physiology: LVEF > 30%		
Number of patients in analysis set	475	526
Number of analysed patients	475	526
Number of patients with event [N(%)]	5 (1.1)	4 (0.8)
Time at risk for event [years]	606.2	678.2
Incidence rate [patients with events per 100 patient years at risk]	0.82	0.59
95% confidence interval	(0.27, 1.69)	(0.16, 1.29)
Comparison vs Placebo*		
Hazard ratio		0.62
95% confidence interval		(0.17,2.32)
p-value		0.4773

* Based on a Cox regression model with terms for age (p=0.1753), baseline eGFR (CKD-EPI) (p=0.5894), sex (p=0.0623), region (p=0.0321), baseline diabetes status (3 cat.) (p=0.1321), Treatment (p=0.9021), heart failure physiology (p=0.4283) and Treatment by heart failure physiology interaction (p=0.6590).
16 patients were excluded as the subgroup variable was missing.
The p-value for treatment by subgroup interaction trend test is 0.5798.

MIs were counted excluding silent MIs.

R.1.1.15.13

R.1.1.15.13 Subgroup analysis by baseline use of MRA

Table R.1.1.15.13: 1 Cox regr. for time to adjudicated MI (fatal or non-fatal) by baseline use of MRA (Y/N) - RS (trial 1245.121)

Subgroup Description	Placebo	Empa 10mg
Baseline use of MRA: No		
Number of patients in analysis set	512	557
Number of analysed patients	512	557
Number of patients with event [N(%)]	9 (1.8)	10 (1.8)
Time at risk for event [years]	687.2	763.3
Incidence rate [patients with events per 100 patient years at risk]	1.31	1.31
95% confidence interval	(0.60, 2.29)	(0.63, 2.24)
Comparison vs Placebo*		
Hazard ratio		1.01
95% confidence interval		(0.41,2.48)
p-value		0.9883
Baseline use of MRA: Yes		
Number of patients in analysis set	1355	1306
Number of analysed patients	1355	1306
Number of patients with event [N(%)]	9 (0.7)	9 (0.7)
Time at risk for event [years]	1764.1	1683.0
Incidence rate [patients with events per 100 patient years at risk]	0.51	0.53
95% confidence interval	(0.23, 0.89)	(0.24, 0.94)
Comparison vs Placebo*		
Hazard ratio		1.03
95% confidence interval		(0.41,2.61)
p-value		0.9429

* Based on a Cox regression model with terms for age (p=0.2836), baseline eGFR (CKD-EPI) (p=0.7328), sex (p=0.0650), region (p=0.1129), baseline diabetes status (3 cat.) (p=0.1379), baseline LVEF (3 cat.) (p=0.6842), Treatment (p=0.9510), baseline use of MRA (p=0.0232) and Treatment by baseline use of MRA interaction (p=0.9673).

MIs were counted excluding silent MIs.

R.1.1.15.14

R.1.1.15.14 Subgroup analysis by baseline use of ARNi

Table R.1.1.15.14: 1 Cox regr. for time to adjudicated MI (fatal or non-fatal) by baseline use of ARNi (Y/N) - RS (trial 1245.121)

Subgroup Description	Placebo	Empa 10mg
Baseline use of ARNi: No		
Number of patients in analysis set	1480	1523
Number of analysed patients	1480	1523
Number of patients with event [N(%)]	14 (0.9)	17 (1.1)
Time at risk for event [years]	1965.9	2032.1
Incidence rate [patients with events per 100 patient years at risk]	0.71	0.84
95% confidence interval	(0.39, 1.13)	(0.49, 1.28)
Comparison vs Placebo*		
Hazard ratio		1.15
95% confidence interval		(0.57,2.34)
p-value		0.6974
Baseline use of ARNi: Yes		
Number of patients in analysis set	387	340
Number of analysed patients	387	340
Number of patients with event [N(%)]	4 (1.0)	2 (0.6)
Time at risk for event [years]	485.4	414.1
Incidence rate [patients with events per 100 patient years at risk]	0.82	0.48
95% confidence interval	(0.22, 1.81)	(0.06, 1.35)
Comparison vs Placebo*		
Hazard ratio		0.55
95% confidence interval		(0.10,3.03)
p-value		0.4945

* Based on a Cox regression model with terms for age (p=0.1936), baseline eGFR (CKD-EPI) (p=0.7714), sex (p=0.0727), region (p=0.0276), baseline diabetes status (3 cat.) (p=0.1223), baseline LVEF (3 cat.) (p=0.6705), Treatment (p=0.6309), baseline use of ARNi (p=0.2884) and Treatment by baseline use of ARNi interaction (p=0.4355).

MIs were counted excluding silent MIs.

R.1.1.15.15 Subgroup analysis by bl. LVEF (<= 30%, >30% -<= 35% , > 35%)

Table R.1.1.15.15: 1 Cox regr. for time to adjudicated MI (fatal or non-fatal) by bl. LVEF (3 cat.) - RS (trial 1245.121)

Subgroup Description	Placebo	Empa 10mg
Baseline LVEF: <=30		
Number of patients in analysis set	1392	1337
Number of analysed patients	1392	1337
Number of patients with event [N(%)]	13 (0.9)	15 (1.1)
Time at risk for event [years]	1845.0	1768.0
Incidence rate [patients with events per 100 patient years at risk]	0.70	0.85
95% confidence interval	(0.38, 1.14)	(0.47, 1.33)
Comparison vs Placebo*		
Hazard ratio		1.22
95% confidence interval		(0.58,2.56)
p-value		0.6042
Baseline LVEF: >30 to <=35		
Number of patients in analysis set	361	398
Number of analysed patients	361	398
Number of patients with event [N(%)]	2 (0.6)	4 (1.0)
Time at risk for event [years]	467.8	517.7
Incidence rate [patients with events per 100 patient years at risk]	0.43	0.77
95% confidence interval	(0.05, 1.19)	(0.21, 1.69)
Comparison vs Placebo*		
Hazard ratio		1.56
95% confidence interval		(0.29,8.57)
p-value		0.6063

* Based on a Cox regression model with terms for age (p=0.1538), baseline eGFR (CKD-EPI) (p=0.7251), sex (p=0.0612), region (p=0.0440), baseline diabetes status (3 cat.) (p=0.1190), Treatment (p=0.9822), baseline LVEF (3 cat.) (p=0.7246) and Treatment by baseline LVEF (3 cat.) interaction (p=0.9654).
The p-value for treatment by subgroup interaction trend test is 0.1196.
NC. = Not calculated, some results could not be produced.

MIs were counted excluding silent MIs.

Table R.1.1.15.15: 1 Cox regr. for time to adjudicated MI (fatal or non-fatal) by bl. LVEF (3 cat.) - RS (trial 1245.121)

Subgroup Description	Placebo	Empa 10mg
Baseline LVEF: >35		
Number of patients in analysis set	114	128
Number of analysed patients	114	128
Number of patients with event [N(%)]	3 (2.6)	0
Time at risk for event [years]	138.4	160.6
Incidence rate [patients with events per 100 patient years at risk]	2.17	0.00
95% confidence interval	(0.45, 5.22)	NC.
Comparison vs Placebo*		
Hazard ratio		NC.
95% confidence interval		NC.
p-value		NC.

* Based on a Cox regression model with terms for age (p=0.1538), baseline eGFR (CKD-EPI) (p=0.7251), sex (p=0.0612), region (p=0.0440), baseline diabetes status (3 cat.) (p=0.1190), Treatment (p=0.9822), baseline LVEF (3 cat.) (p=0.7246) and Treatment by baseline LVEF (3 cat.) interaction (p=0.9654).
The p-value for treatment by subgroup interaction trend test is 0.1196.
NC. = Not calculated, some results could not be produced.

MIs were counted excluding silent MIs.

R.1.1.15.16 Subgroup analysis by bl. NTproBNP </>= median (median based on total patients)

Table R.1.1.15.16: 1 Cox regr. for time to adjudicated MI (fatal or non-fatal) by bl. NTproBNP (< median,>= median) (median based on total patients) - RS (trial 1245.121)

Subgroup Description	Placebo	Empa 10mg
Baseline NTproBNP: < median		
Number of patients in analysis set	920	942
Number of analysed patients	920	942
Number of patients with event [N(%)]	6 (0.7)	10 (1.1)
Time at risk for event [years]	1250.6	1265.6
Incidence rate [patients with events per 100 patient years at risk]	0.48	0.79
95% confidence interval	(0.18, 0.93)	(0.38, 1.35)
Comparison vs Placebo*		
Hazard ratio		1.65
95% confidence interval		(0.60,4.56)
p-value		0.3309
Baseline NTproBNP: >= median		
Number of patients in analysis set	946	920
Number of analysed patients	946	920
Number of patients with event [N(%)]	12 (1.3)	9 (1.0)
Time at risk for event [years]	1199.8	1179.5
Incidence rate [patients with events per 100 patient years at risk]	1.00	0.76
95% confidence interval	(0.52, 1.64)	(0.35, 1.34)
Comparison vs Placebo*		
Hazard ratio		0.73
95% confidence interval		(0.31,1.74)
p-value		0.4797

* Based on a Cox regression model with terms for age (p=0.1889), baseline eGFR (CKD-EPI) (p=0.6214), sex (p=0.0649), region (p=0.0315), baseline diabetes status (3 cat.) (p=0.1287), baseline LVEF (3 cat.) (p=0.7028), Treatment (p=0.7807), baseline NTproBNP (2 cat.) (p=0.2812) and Treatment by baseline NTproBNP (2 cat.) interaction (p=0.2309).
2 patients were excluded as the subgroup variable was missing.

MIs were counted excluding silent MIs.
Median: 1910 [pg/mL]

R.1.1.16

R.1.1.16 Time to adjudicated fatal MI

R.1.1.16.1

Figure R.1.1.16.1: 1

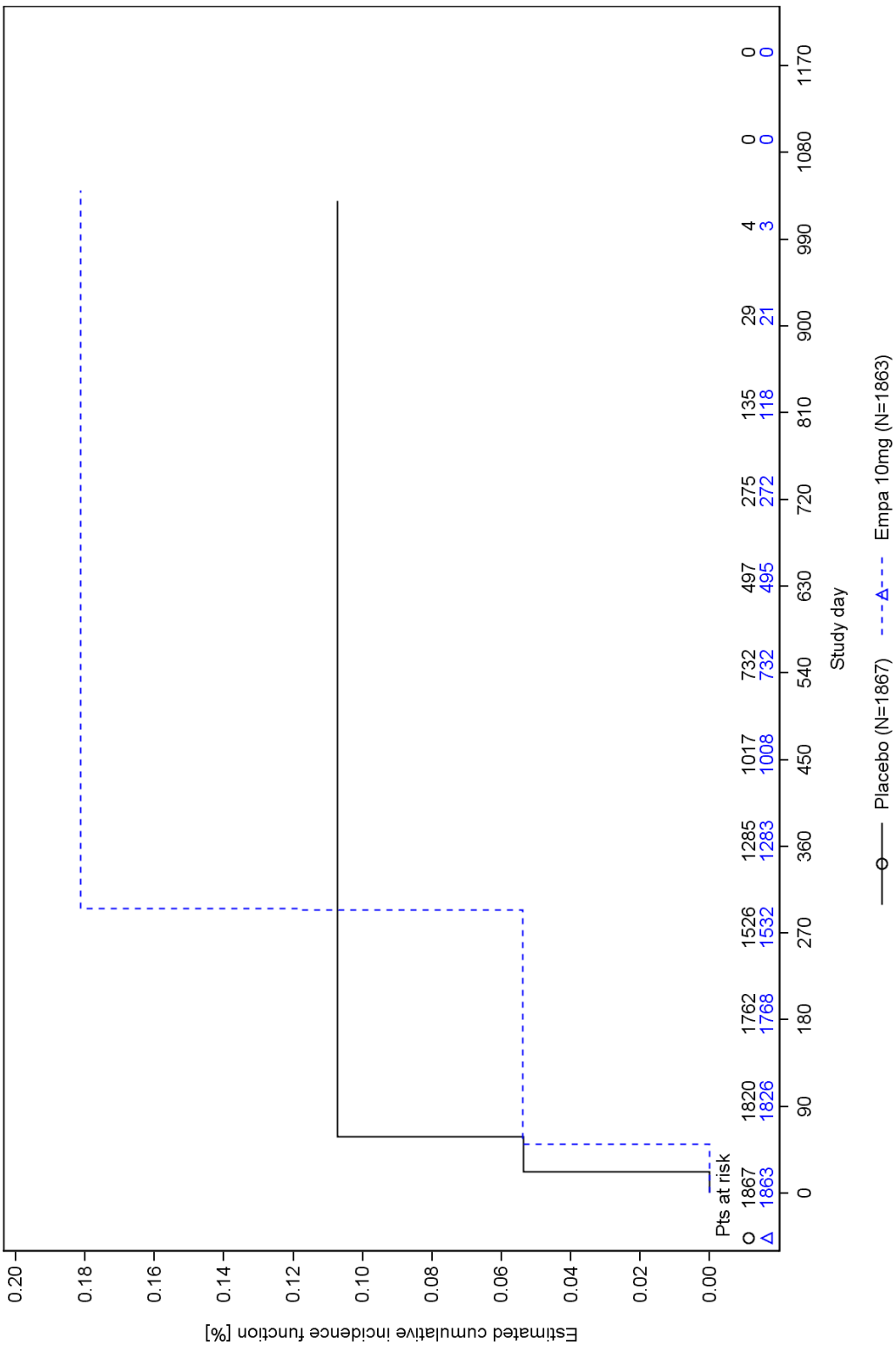

Figure R.1.1.16.1: 1 Estimated cumulative incidence function for time to adjudicated fatal MI (considering all cause mortality as competing risk) - RS (trial 1245.121)

MIs were counted excluding silent MIs.

Table R.1.1.16.1: 1 Cox regr. for time to adjudicated fatal MI - RS (trial 1245.121)

	Placebo	Empa 10mg
Number of patients in analysis set	1867	1863
Number of analysed patients	1867	1863
Number of patients with event [N(%)]	2 (0.1)	3 (0.2)
Time at risk for event [years]	2464.7	2459.7
Incidence rate [patients with events per 100 patient years at risk]	0.08	0.12
95% confidence interval	(0.01, 0.23)	(0.03, 0.29)
Comparison vs Placebo*		
Hazard ratio		1.51
95% confidence interval		(0.25,9.10)
p-value		0.6504
Time to event [days]**		
2.5% percentile	NC.	NC.
5.0% percentile	NC.	NC.
7.5% percentile	NC.	NC.
10.0% percentile	NC.	NC.
Patients with events [%]**		
1 year	0.1	0.2
2 years	0.1	0.2

* Based on a Cox regression model with terms for age (p=0.9667), baseline eGFR (CKD-EPI) (p=0.8684), sex (p=0.7784), region (p=0.8616), baseline diabetes status (3 cat.) (p=0.3252), baseline LVEF (3 cat.) (p=0.9947) and Treatment (p=0.6504).
**Based on Kaplan-Meier estimates.
NC. = Not calculated.

MIs were counted excluding silent MIs.

R.1.1.17

R.1.1.17 Time to adjudicated non-fatal MI

R.1.1.17.1

Figure R.1.1.17.1: 1

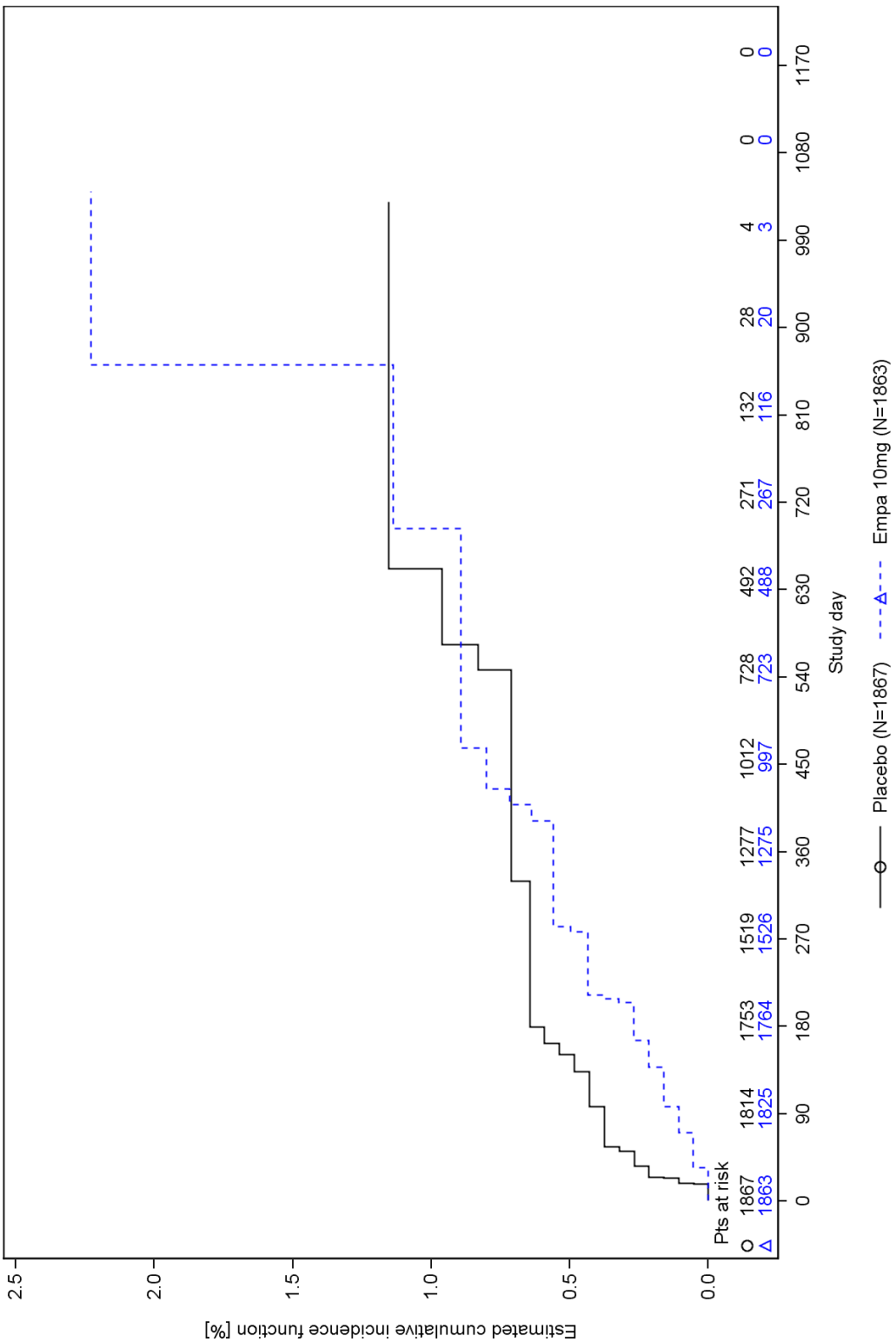

Figure R.1.1.17.1: 1 Estimated cumulative incidence function for time to adjudicated non-fatal MI (considering all cause mortality as competing risk) - RS (trial 1245.121)

MIs were counted excluding silent MIs.

Table R.1.1.17.1: 1 Cox regr. for time to adjudicated non-fatal MI - RS (trial 1245.121)

	Placebo	Empa 10mg
Number of patients in analysis set	1867	1863
Number of analysed patients	1867	1863
Number of patients with event [N(%)]	16 (0.9)	16 (0.9)
Time at risk for event [years]	2451.4	2446.3
Incidence rate [patients with events per 100 patient years at risk]	0.65	0.65
95% confidence interval	(0.37, 1.01)	(0.37, 1.01)
Comparison vs Placebo*		
Hazard ratio		0.98
95% confidence interval		(0.49,1.96)
p-value		0.9451
Time to event [days]**		
2.5% percentile	NC.	861
5.0% percentile	NC.	NC.
7.5% percentile	NC.	NC.
10.0% percentile	NC.	NC.
Patients with events [%]**		
1 year	0.7	0.6
2 years	1.3	1.3

* Based on a Cox regression model with terms for age (p=0.1444), baseline eGFR (CKD-EPI) (p=0.6961), sex (p=0.0435), region (p=0.0295), baseline diabetes status (3 cat.) (p=0.2800), baseline LVEF (3 cat.) (p=0.5946) and Treatment (p=0.9451).
**Based on Kaplan-Meier estimates.
NC. = Not calculated.

MIs were counted excluding silent MIs.

R.1.1.18

R.1.1.18 Time to adjudicated stroke (fatal or non-fatal)

R.1.1.18.1

Figure R.1.1.18.1: 1

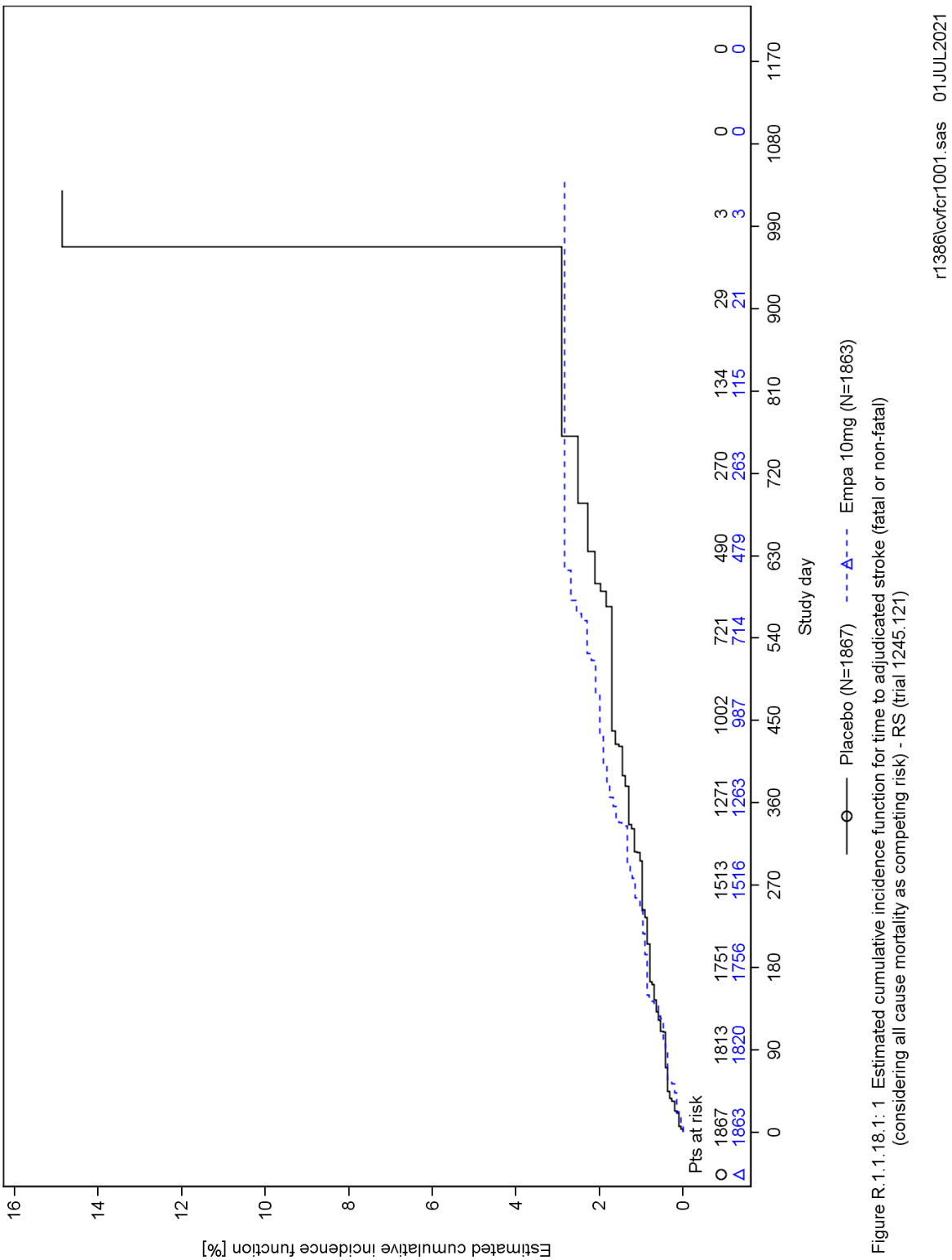

Figure R.1.1.18.1: 1 Estimated cumulative incidence function for time to adjudicated stroke (fatal or non-fatal) (considering all cause mortality as competing risk) - RS (trial 1245.121)

Table R.1.1.18.1: 1 Cox regr. for time to adjudicated stroke (fatal or non-fatal) - RS (trial 1245.121)

	Placebo	Empa 10mg
Number of patients in analysis set	1867	1863
Number of analysed patients	1867	1863
Number of patients with event [N(%)]	35 (1.9)	40 (2.1)
Time at risk for event [years]	2443.5	2429.6
Incidence rate [patients with events per 100 patient years at risk]	1.43	1.65
95% confidence interval	(1.00, 1.94)	(1.18, 2.19)
Comparison vs Placebo*		
Hazard ratio		1.13
95% confidence interval		(0.72,1.78)
p-value		0.5913
Time to event [days]**		
2.5% percentile	687	559
5.0% percentile	967	NC.
7.5% percentile	967	NC.
10.0% percentile	967	NC.
Patients with events [%]**		
1 year	1.4	1.8
2 years	2.8	3.1

* Based on a Cox regression model with terms for age (p=0.4388), baseline eGFR (CKD-EPI) (p=0.9356), sex (p=0.3388), region (p=0.7096), baseline diabetes status (3 cat.) (p=0.5029), baseline LVEF (3 cat.) (p=0.7014) and Treatment (p=0.5913).
**Based on Kaplan-Meier estimates.
NC. = Not calculated.

R.1.1.18.2

R.1.1.18.2 Subgroup analysis by sex

Table R.1.1.18.2: 1 Cox regr. for time to adjudicated stroke (fatal or non-fatal) by sex - RS (trial 1245.121)

Subgroup Description	Placebo	Empa 10mg
Sex: Male		
Number of patients in analysis set	1411	1426
Number of analysed patients	1411	1426
Number of patients with event [N(%)]	26 (1.8)	34 (2.4)
Time at risk for event [years]	1854.2	1850.1
Incidence rate [patients with events per 100 patient years at risk]	1.40	1.84
95% confidence interval	(0.92, 1.99)	(1.27, 2.51)
Comparison vs Placebo*		
Hazard ratio		1.30
95% confidence interval		(0.78,2.16)
p-value		0.3226
Sex: Female		
Number of patients in analysis set	456	437
Number of analysed patients	456	437
Number of patients with event [N(%)]	9 (2.0)	6 (1.4)
Time at risk for event [years]	589.3	579.5
Incidence rate [patients with events per 100 patient years at risk]	1.53	1.04
95% confidence interval	(0.70, 2.67)	(0.38, 2.01)
Comparison vs Placebo*		
Hazard ratio		0.66
95% confidence interval		(0.24,1.87)
p-value		0.4391

* Based on a Cox regression model with terms for age (p=0.4523), baseline eGFR (CKD-EPI) (p=0.9453), region (p=0.7013), baseline diabetes status (3 cat.) (p=0.5124), baseline LVEF (3 cat.) (p=0.6923), Treatment (p=0.7988), sex (p=0.3303) and Treatment by sex interaction (p=0.2580).

R.1.1.18.3

Table R.1.1.18.3: 1 Cox regr. for time to adjudicated stroke (fatal or non-fatal) by age (2 cat.) - RS (trial 1245.121)

Subgroup Description	Placebo	Empa 10mg
Age [years]: < 65		
Number of patients in analysis set	740	675
Number of analysed patients	740	675
Number of patients with event [N(%)]	12 (1.6)	12 (1.8)
Time at risk for event [years]	970.6	872.7
Incidence rate [patients with events per 100 patient years at risk]	1.24	1.38
95% confidence interval	(0.64, 2.03)	(0.71, 2.26)
Comparison vs Placebo*		
Hazard ratio		1.11
95% confidence interval		(0.50,2.48)
p-value		0.7918
Age [years]: >= 65		
Number of patients in analysis set	1127	1188
Number of analysed patients	1127	1188
Number of patients with event [N(%)]	23 (2.0)	28 (2.4)
Time at risk for event [years]	1473.0	1556.9
Incidence rate [patients with events per 100 patient years at risk]	1.56	1.80
95% confidence interval	(0.99, 2.26)	(1.20, 2.52)
Comparison vs Placebo*		
Hazard ratio		1.14
95% confidence interval		(0.66,1.99)
p-value		0.6312

* Based on a Cox regression model with terms for baseline eGFR (CKD-EPI) (p=0.8168), sex (p=0.3482), region (p=0.7043), baseline diabetes status (3 cat.) (p=0.4951), baseline LVEF (3 cat.) (p=0.6853), Treatment (p=0.6241), age (2 cat.) (p=0.5399) and Treatment by age (2 cat.) interaction (p=0.9560).

R.1.1.18.4 Subgroup analysis by region (North America, Latin America, Europe, Asia, Other)

Table R.1.1.18.4: 1 Cox regr. for time to adjudicated stroke (fatal or non-fatal) by region - RS (trial 1245.121)

Subgroup Description	Placebo	Empa 10mg
Region: North America		
Number of patients in analysis set	213	212
Number of analysed patients	213	212
Number of patients with event [N(%)]	6 (2.8)	6 (2.8)
Time at risk for event [years]	286.8	299.2
Incidence rate [patients with events per 100 patient years at risk]	2.09	2.01
95% confidence interval	(0.77, 4.07)	(0.74, 3.90)
Comparison vs Placebo*		
Hazard ratio		0.94
95% confidence interval		(0.30, 2.94)
p-value		0.9193
Region: Latin America		
Number of patients in analysis set	645	641
Number of analysed patients	645	641
Number of patients with event [N(%)]	10 (1.6)	14 (2.2)
Time at risk for event [years]	771.5	755.8
Incidence rate [patients with events per 100 patient years at risk]	1.30	1.85
95% confidence interval	(0.62, 2.21)	(1.01, 2.94)
Comparison vs Placebo*		
Hazard ratio		1.39
95% confidence interval		(0.62, 3.14)
p-value		0.4239

* Based on a Cox regression model with terms for age (p=0.4479), baseline eGFR (CKD-EPI) (p=0.9202), sex (p=0.3279), baseline diabetes status (3 cat.) (p=0.4984), baseline LVEF (3 cat.) (p=0.6853), Treatment (p=0.9823), region (p=0.9335) and Treatment by region interaction (p=0.5898).
NC. = Not calculated, some results could not be produced.

Table R.1.1.18.4: 1 Cox regr. for time to adjudicated stroke (fatal or non-fatal) by region - RS (trial 1245.121)

Subgroup Description	Placebo	Empa 10mg
Region: Europe		
Number of patients in analysis set	677	676
Number of analysed patients	677	676
Number of patients with event [N(%)]	15 (2.2)	12 (1.8)
Time at risk for event [years]	920.5	918.3
Incidence rate [patients with events per 100 patient years at risk]	1.63	1.31
95% confidence interval	(0.91, 2.55)	(0.68, 2.14)
Comparison vs Placebo*		
Hazard ratio		0.80
95% confidence interval		(0.37, 1.71)
p-value		0.5616
Region: Asia		
Number of patients in analysis set	245	248
Number of analysed patients	245	248
Number of patients with event [N(%)]	3 (1.2)	8 (3.2)
Time at risk for event [years]	349.5	343.2
Incidence rate [patients with events per 100 patient years at risk]	0.86	2.33
95% confidence interval	(0.18, 2.07)	(1.01, 4.20)
Comparison vs Placebo*		
Hazard ratio		2.71
95% confidence interval		(0.72,10.21)
p-value		0.1414

* Based on a Cox regression model with terms for age (p=0.4479), baseline eGFR (CKD-EPI) (p=0.9202), sex (p=0.3279), baseline diabetes status (3 cat.) (p=0.4984), baseline LVEF (3 cat.) (p=0.6853), Treatment (p=0.9823), region (p=0.9335) and Treatment by region interaction (p=0.5898).
NC. = Not calculated, some results could not be produced.

Table R.1.1.18.4: 1

Table R.1.1.18.4: 1 Cox regr. for time to adjudicated stroke (fatal or non-fatal) by region - RS (trial 1245.121)

Subgroup Description	Placebo	Empa 10mg
Region: Other		
Number of patients in analysis set	87	86
Number of analysed patients	87	86
Number of patients with event [N(%)]	1 (1.1)	0
Time at risk for event [years]	115.1	113.1
Incidence rate [patients with events per 100 patient years at risk]	0.87	0.00
95% confidence interval	(0.02, 3.20)	NC.
Comparison vs Placebo*		
Hazard ratio		NC.
95% confidence interval		NC.
p-value		NC.

* Based on a Cox regression model with terms for age (p=0.4479), baseline eGFR (CKD-EPI) (p=0.9202), sex (p=0.3279), baseline diabetes status (3 cat.) (p=0.4984), baseline LVEF (3 cat.) (p=0.6853), Treatment (p=0.9823), region (p=0.9335) and Treatment by region interaction (p=0.5898).
NC. = Not calculated, some results could not be produced.

R.1.1.18.5

R.1.1.18.5 Subgroup analysis by OECD member (Y/N)

Table R.1.1.18.5: 1 Cox regr. for time to adjudicated stroke (fatal or non-fatal) by OECD member (Y/N) - RS (trial 1245.121)

Subgroup Description	Placebo	Empa 10mg
OECD member: No		
Number of patients in analysis set	741	713
Number of analysed patients	741	713
Number of patients with event [N(%)]	11 (1.5)	15 (2.1)
Time at risk for event [years]	896.2	850.5
Incidence rate [patients with events per 100 patient years at risk]	1.23	1.76
95% confidence interval	(0.61, 2.05)	(0.99, 2.76)
Comparison vs Placebo*		
Hazard ratio		1.40
95% confidence interval		(0.64,3.06)
p-value		0.3981
OECD member: Yes		
Number of patients in analysis set	1126	1150
Number of analysed patients	1126	1150
Number of patients with event [N(%)]	24 (2.1)	25 (2.2)
Time at risk for event [years]	1547.3	1579.1
Incidence rate [patients with events per 100 patient years at risk]	1.55	1.58
95% confidence interval	(0.99, 2.23)	(1.02, 2.26)
Comparison vs Placebo*		
Hazard ratio		1.01
95% confidence interval		(0.58,1.78)
p-value		0.9612

* Based on a Cox regression model with terms for age (p=0.3741), baseline eGFR (CKD-EPI) (p=0.8786), sex (p=0.3829), baseline diabetes status (3 cat.) (p=0.4908), baseline LVEF (3 cat.) (p=0.6861), Treatment (p=0.4745), OECD Member (N) (p=0.8620) and Treatment by OECD Member (N) interaction (p=0.5112).

OECD member (yes/no) countries included:
Yes: United States, Canada, Mexico, Poland, Netherlands, Hungary, Germany, Czech Republic, Italy, France, Spain, United Kingdom, Belgium, Japan, Australia, 'Korea; Republic Of South Korea';
No: Brazil, Argentina, China, India.

R.1.1.18.6

R.1.1.18.6 Subgroup analysis by NYHA at baseline (II, III/IV - 2 cat.)

Table R.1.1.18.6: 1

Table R.1.1.18.6: 1 Cox regr. for time to adjudicated stroke (fatal or non-fatal) by baseline NYHA (2 cat.) - RS (trial 1245.121)

Subgroup Description	Placebo	Empa 10mg
Baseline NYHA: II		
Number of patients in analysis set	1401	1399
Number of analysed patients	1401	1399
Number of patients with event [N(%)]	23 (1.6)	28 (2.0)
Time at risk for event [years]	1847.8	1828.7
Incidence rate [patients with events per 100 patient years at risk]	1.24	1.53
95% confidence interval	(0.79, 1.80)	(1.02, 2.15)
Comparison vs Placebo*		
Hazard ratio		1.20
95% confidence interval		(0.69,2.09)
p-value		0.5112
Baseline NYHA: III/IV		
Number of patients in analysis set	466	464
Number of analysed patients	466	464
Number of patients with event [N(%)]	12 (2.6)	12 (2.6)
Time at risk for event [years]	595.7	600.9
Incidence rate [patients with events per 100 patient years at risk]	2.01	2.00
95% confidence interval	(1.04, 3.30)	(1.03, 3.28)
Comparison vs Placebo*		
Hazard ratio		0.99
95% confidence interval		(0.45,2.22)
p-value		0.9892

* Based on a Cox regression model with terms for age (p=0.4274), baseline eGFR (CKD-EPI) (p=0.9649), sex (p=0.3044), region (p=0.7090), baseline diabetes status (3 cat.) (p=0.4850), baseline LVEF (3 cat.) (p=0.6711), Treatment (p=0.7180), baseline NYHA (2 cat.) (p=0.1128) and Treatment by baseline NYHA (2 cat.) interaction (p=0.7016).

R.1.1.18.7

Table R.1.1.18.7: 1

Table R.1.1.18.7: 1 Cox regr. for time to adjudicated stroke (fatal or non-fatal) by diabetes at baseline (2 cat.) - RS (trial 1245.121)

Subgroup Description	Placebo	Empa 10mg
Baseline diabetes status: Diabetic		
Number of patients in analysis set	929	927
Number of analysed patients	929	927
Number of patients with event [N(%)]	16 (1.7)	21 (2.3)
Time at risk for event [years]	1232.5	1213.5
Incidence rate [patients with events per 100 patient years at risk]	1.30	1.73
95% confidence interval	(0.74, 2.01)	(1.07, 2.55)
Comparison vs Placebo*		
Hazard ratio		1.33
95% confidence interval		(0.69,2.55)
p-value		0.3897
Baseline diabetes status: Non-Diabetic		
Number of patients in analysis set	938	936
Number of analysed patients	938	936
Number of patients with event [N(%)]	19 (2.0)	19 (2.0)
Time at risk for event [years]	1211.0	1216.1
Incidence rate [patients with events per 100 patient years at risk]	1.57	1.56
95% confidence interval	(0.94, 2.35)	(0.94, 2.34)
Comparison vs Placebo*		
Hazard ratio		0.97
95% confidence interval		(0.51,1.83)
p-value		0.9152

* Based on a Cox regression model with terms for age (p=0.4039), baseline eGFR (CKD-EPI) (p=0.9250), sex (p=0.3379), region (p=0.7027), baseline LVEF (3 cat.) (p=0.7095), Treatment (p=0.5894), baseline diabetes status (2 cat.) (p=0.8805) and Treatment by baseline diabetes status (2 cat.) interaction (p=0.4905).

R.1.1.18.8 Subgroup analysis by BMI at baseline (<30, >=30)

Table R.1.1.18.8: 1 Cox regr. for time to adjudicated stroke (fatal or non-fatal) by baseline BMI [kg/m2] - RS (trial 1245.121)

Subgroup Description	Placebo	Empa 10mg
Baseline BMI [kg/m²]: <30		
Number of patients in analysis set	1300	1263
Number of analysed patients	1300	1263
Number of patients with event [N(%)]	22 (1.7)	25 (2.0)
Time at risk for event [years]	1724.1	1640.7
Incidence rate [patients with events per 100 patient years at risk]	1.28	1.52
95% confidence interval	(0.80, 1.86)	(0.99, 2.18)
Comparison vs Placebo*		
Hazard ratio		1.16
95% confidence interval		(0.66,2.07)
p-value		0.6024
Baseline BMI [kg/m²]: >=30		
Number of patients in analysis set	567	600
Number of analysed patients	567	600
Number of patients with event [N(%)]	13 (2.3)	15 (2.5)
Time at risk for event [years]	719.4	788.9
Incidence rate [patients with events per 100 patient years at risk]	1.81	1.90
95% confidence interval	(0.96, 2.91)	(1.06, 2.98)
Comparison vs Placebo*		
Hazard ratio		1.05
95% confidence interval		(0.50,2.21)
p-value		0.8994

* Based on a Cox regression model with terms for age (p=0.3330), baseline eGFR (CKD-EPI) (p=0.9563), sex (p=0.3195), region (p=0.7333), baseline diabetes status (3 cat.) (p=0.4916), baseline LVEF (3 cat.) (p=0.6985), Treatment (p=0.6760), baseline BMI (2 cat.) (p=0.2059) and Treatment by baseline BMI (2 cat.) interaction (p=0.8277).

R.1.1.18.9

R.1.1.18.9 Subgroup analysis by eGFR at baseline (<60, >=60)

Table R.1.1.18.9: 1 Cox regr. for time to adjudicated stroke (fatal or non-fatal) by baseline eGFR (2 cat.) - RS (trial 1245.121)

Subgroup Description	Placebo	Empa 10mg
Baseline eGFR (CKD-EPI) [mL/min/1.73m²]: >=60		
Number of patients in analysis set	960	969
Number of analysed patients	960	969
Number of patients with event [N(%)]	17 (1.8)	21 (2.2)
Time at risk for event [years]	1257.2	1260.8
Incidence rate [patients with events per 100 patient years at risk]	1.35	1.67
95% confidence interval	(0.79, 2.07)	(1.03, 2.45)
Comparison vs Placebo*		
Hazard ratio		1.22
95% confidence interval		(0.64,2.33)
p-value		0.5365
Baseline eGFR (CKD-EPI) [mL/min/1.73m²]: <60		
Number of patients in analysis set	906	893
Number of analysed patients	906	893
Number of patients with event [N(%)]	17 (1.9)	19 (2.1)
Time at risk for event [years]	1185.4	1167.6
Incidence rate [patients with events per 100 patient years at risk]	1.43	1.63
95% confidence interval	(0.84, 2.19)	(0.98, 2.44)
Comparison vs Placebo*		
Hazard ratio		1.10
95% confidence interval		(0.57,2.12)
p-value		0.7718

* Based on a Cox regression model with terms for age (p=0.3089), sex (p=0.3847), region (p=0.7321), baseline diabetes status (3 cat.) (p=0.4989), baseline LVEF (3 cat.) (p=0.6593), Treatment (p=0.5223), baseline eGFR (CKD-EPI) (2 cat.) (p=0.7147) and Treatment by baseline eGFR (CKD-EPI) (2 cat.) interaction (p=0.8217).
2 patients were excluded as the subgroup variable was missing.

R.1.1.18.10

Table R.1.1.18.10: 1 Cox regr. for time to adjudicated stroke (fatal or non-fatal) by history of HHF within 12 months - RS (trial 1245.121)

Subgroup Description	Placebo	Empa 10mg
History of HHF (in the last 12 months): No		
Number of patients in analysis set	1293	1286
Number of analysed patients	1293	1286
Number of patients with event [N(%)]	24 (1.9)	25 (1.9)
Time at risk for event [years]	1741.2	1715.9
Incidence rate [patients with events per 100 patient years at risk]	1.38	1.46
95% confidence interval	(0.88, 1.98)	(0.94, 2.08)
Comparison vs Placebo*		
Hazard ratio		1.05
95% confidence interval		(0.60,1.85)
p-value		0.8571
History of HHF (in the last 12 months): Yes		
Number of patients in analysis set	574	577
Number of analysed patients	574	577
Number of patients with event [N(%)]	11 (1.9)	15 (2.6)
Time at risk for event [years]	702.3	713.7
Incidence rate [patients with events per 100 patient years at risk]	1.57	2.10
95% confidence interval	(0.78, 2.62)	(1.18, 3.29)
Comparison vs Placebo*		
Hazard ratio		1.28
95% confidence interval		(0.59,2.80)
p-value		0.5293

* Based on a Cox regression model with terms for age (p=0.3976), baseline eGFR (CKD-EPI) (p=0.9578), sex (p=0.3445), region (p=0.7026), baseline diabetes status (3 cat.) (p=0.4867), baseline LVEF (3 cat.) (p=0.7570), Treatment (p=0.5381), history of HHF (p=0.2990) and Treatment by history of HHF interaction (p=0.6850).

R.1.1.18.11 Subgroup analysis by cause of heart failure

Table R.1.1.18.11: 1 Cox regr. for time to adjudicated stroke (fatal or non-fatal) by cause of heart failure - RS (trial 1245.121)

Subgroup Description	Placebo	Empa 10mg
Cause of heart failure: Ischemic		
Number of patients in analysis set	946	983
Number of analysed patients	946	983
Number of patients with event [N(%)]	19 (2.0)	18 (1.8)
Time at risk for event [years]	1256.6	1295.1
Incidence rate [patients with events per 100 patient years at risk]	1.51	1.39
95% confidence interval	(0.91, 2.26)	(0.82, 2.10)
Comparison vs Placebo*		
Hazard ratio		0.93
95% confidence interval		(0.49,1.77)
p-value		0.8154
Cause of heart failure: Non-ischemic		
Number of patients in analysis set	921	880
Number of analysed patients	921	880
Number of patients with event [N(%)]	16 (1.7)	22 (2.5)
Time at risk for event [years]	1187.0	1134.5
Incidence rate [patients with events per 100 patient years at risk]	1.35	1.94
95% confidence interval	(0.77, 2.08)	(1.22, 2.83)
Comparison vs Placebo*		
Hazard ratio		1.38
95% confidence interval		(0.73,2.64)
p-value		0.3253

* Based on a Cox regression model with terms for age (p=0.4043), baseline eGFR (CKD-EPI) (p=0.9255), sex (p=0.3067), region (p=0.7420), baseline diabetes status (3 cat.) (p=0.4879), baseline LVEF (3 cat.) (p=0.6969), Treatment (p=0.5960), cause of heart failure (2 cat.) (p=0.4816) and Treatment by cause of heart failure (2 cat.) interaction (p=0.3900).

R.1.1.18.12 Subgroup analysis by heart failure physiology (LVEF <= 30% and NTproBNP<median; LVEF <= 30% and NTproBNP>=median; LVEF > 30%)

Table R.1.1.18.12: 1 Cox regr. for time to adjudicated stroke (fatal or non-fatal) by heart failure physiology - RS (trial 1245.121)

Subgroup Description	Placebo	Empa 10mg
Heart failure physiology: LVEF <= 30% and NTproBNP < median		
Number of patients in analysis set	723	698
Number of analysed patients	723	698
Number of patients with event [N(%)]	13 (1.8)	13 (1.9)
Time at risk for event [years]	975.0	939.2
Incidence rate [patients with events per 100 patient years at risk]	1.33	1.38
95% confidence interval	(0.71, 2.15)	(0.74, 2.23)
Comparison vs Placebo*		
Hazard ratio		1.06
95% confidence interval		(0.49,2.29)
p-value		0.8843
Heart failure physiology: LVEF <= 30% and NTproBNP >= median		
Number of patients in analysis set	661	631
Number of analysed patients	661	631
Number of patients with event [N(%)]	11 (1.7)	12 (1.9)
Time at risk for event [years]	856.3	810.2
Incidence rate [patients with events per 100 patient years at risk]	1.28	1.48
95% confidence interval	(0.64, 2.15)	(0.77, 2.43)
Comparison vs Placebo*		
Hazard ratio		1.12
95% confidence interval		(0.49,2.53)
p-value		0.7930

* Based on a Cox regression model with terms for age (p=0.5129), baseline eGFR (CKD-EPI) (p=0.8470), sex (p=0.3033), region (p=0.7102), baseline diabetes status (3 cat.) (p=0.5605), Treatment (p=0.4968), heart failure physiology (p=0.6751) and Treatment by heart failure physiology interaction (p=0.8952).
16 patients were excluded as the subgroup variable was missing.
The p-value for treatment by subgroup interaction trend test is 0.6366.

Table R.1.1.18.12: 1 Cox regr. for time to adjudicated stroke (fatal or non-fatal) by heart failure physiology - RS (trial 1245.121)

Subgroup Description	Placebo	Empa 10mg
Heart failure physiology: LVEF > 30%		
Number of patients in analysis set	475	526
Number of analysed patients	475	526
Number of patients with event [N(%)]	9 (1.9)	14 (2.7)
Time at risk for event [years]	602.9	672.6
Incidence rate [patients with events per 100 patient years at risk]	1.49	2.08
95% confidence interval	(0.68, 2.61)	(1.14, 3.31)
Comparison vs Placebo*		
Hazard ratio		1.38
95% confidence interval		(0.60,3.18)
p-value		0.4553

* Based on a Cox regression model with terms for age (p=0.5129), baseline eGFR (CKD-EPI) (p=0.8470), sex (p=0.3033), region (p=0.7102), baseline diabetes status (3 cat.) (p=0.5605), Treatment (p=0.4968), heart failure physiology (p=0.6751) and Treatment by heart failure physiology interaction (p=0.8952).
16 patients were excluded as the subgroup variable was missing.
The p-value for treatment by subgroup interaction trend test is 0.6366.

R.1.1.18.13

R.1.1.18.13 Subgroup analysis by baseline use of MRA

Table R.1.1.18.13: 1 Cox regr. for time to adjudicated stroke (fatal or non-fatal) by baseline use of MRA (Y/N) - RS (trial 1245.121)

Subgroup Description	Placebo	Empa 10mg
Baseline use of MRA: No		
Number of patients in analysis set	512	557
Number of analysed patients	512	557
Number of patients with event [N(%)]	9 (1.8)	18 (3.2)
Time at risk for event [years]	688.6	754.1
Incidence rate [patients with events per 100 patient years at risk]	1.31	2.39
95% confidence interval	(0.60, 2.29)	(1.41, 3.61)
Comparison vs Placebo*		
Hazard ratio		1.80
95% confidence interval		(0.81,4.01)
p-value		0.1499
Baseline use of MRA: Yes		
Number of patients in analysis set	1355	1306
Number of analysed patients	1355	1306
Number of patients with event [N(%)]	26 (1.9)	22 (1.7)
Time at risk for event [years]	1754.9	1675.5
Incidence rate [patients with events per 100 patient years at risk]	1.48	1.31
95% confidence interval	(0.97, 2.10)	(0.82, 1.92)
Comparison vs Placebo*		
Hazard ratio		0.88
95% confidence interval		(0.50,1.55)
p-value		0.6527

* Based on a Cox regression model with terms for age (p=0.4900), baseline eGFR (CKD-EPI) (p=0.9374), sex (p=0.3508), region (p=0.7428), baseline diabetes status (3 cat.) (p=0.5165), baseline LVEF (3 cat.) (p=0.7199), Treatment (p=0.3609), baseline use of MRA (p=0.5137) and Treatment by baseline use of MRA interaction (p=0.1515).

R.1.1.18.14

Table R.1.1.18.14: 1 Cox regr. for time to adjudicated stroke (fatal or non-fatal) by baseline use of ARNi (Y/N) - RS (trial 1245.121)

Subgroup Description	Placebo	Empa 10mg
Baseline use of ARNi: No		
Number of patients in analysis set	1480	1523
Number of analysed patients	1480	1523
Number of patients with event [N(%)]	25 (1.7)	35 (2.3)
Time at risk for event [years]	1958.1	2018.4
Incidence rate [patients with events per 100 patient years at risk]	1.28	1.73
95% confidence interval	(0.83, 1.82)	(1.21, 2.35)
Comparison vs Placebo*		
Hazard ratio		1.32
95% confidence interval		(0.79,2.21)
p-value		0.2899
Baseline use of ARNi: Yes		
Number of patients in analysis set	387	340
Number of analysed patients	387	340
Number of patients with event [N(%)]	10 (2.6)	5 (1.5)
Time at risk for event [years]	485.4	411.2
Incidence rate [patients with events per 100 patient years at risk]	2.06	1.22
95% confidence interval	(0.99, 3.52)	(0.39, 2.49)
Comparison vs Placebo*		
Hazard ratio		0.62
95% confidence interval		(0.21,1.82)
p-value		0.3819

* Based on a Cox regression model with terms for age (p=0.4190), baseline eGFR (CKD-EPI) (p=0.9717), sex (p=0.3467), region (p=0.7236), baseline diabetes status (3 cat.) (p=0.5097), baseline LVEF (3 cat.) (p=0.7028), Treatment (p=0.7391), baseline use of ARNi (p=0.8215) and Treatment by baseline use of ARNi interaction (p=0.2131).

R.1.1.18.15 Subgroup analysis by bl. LVEF (<= 30%, >30% -<= 35% , > 35%)

Table R.1.1.18.15: 1 Cox regr. for time to adjudicated stroke (fatal or non-fatal) by bl. LVEF (3 cat.) - RS (trial 1245.121)

Subgroup Description	Placebo	Empa 10mg
Baseline LVEF: <=30		
Number of patients in analysis set	1392	1337
Number of analysed patients	1392	1337
Number of patients with event [N(%)]	26 (1.9)	26 (1.9)
Time at risk for event [years]	1840.6	1757.0
Incidence rate [patients with events per 100 patient years at risk]	1.41	1.48
95% confidence interval	(0.92, 2.01)	(0.97, 2.10)
Comparison vs Placebo*		
Hazard ratio		1.04
95% confidence interval		(0.60,1.79)
p-value		0.8857
Baseline LVEF: >30 to <=35		
Number of patients in analysis set	361	398
Number of analysed patients	361	398
Number of patients with event [N(%)]	5 (1.4)	12 (3.0)
Time at risk for event [years]	464.4	514.6
Incidence rate [patients with events per 100 patient years at risk]	1.08	2.33
95% confidence interval	(0.35, 2.21)	(1.20, 3.82)
Comparison vs Placebo*		
Hazard ratio		2.10
95% confidence interval		(0.74,5.98)
p-value		0.1630

* Based on a Cox regression model with terms for age (p=0.4244), baseline eGFR (CKD-EPI) (p=0.9442), sex (p=0.3529), region (p=0.7222), baseline diabetes status (3 cat.) (p=0.5218), Treatment (p=0.9981), baseline LVEF (3 cat.) (p=0.8436) and Treatment by baseline LVEF (3 cat.) interaction (p=0.2824).
The p-value for treatment by subgroup interaction trend test is 0.9360.

Table R.1.1.18.15: 1 Cox regr. for time to adjudicated stroke (fatal or non-fatal) by bl. LVEF (3 cat.) - RS (trial 1245.121)

Subgroup Description	Placebo	Empa 10mg
Baseline LVEF: >35		
Number of patients in analysis set	114	128
Number of analysed patients	114	128
Number of patients with event [N(%)]	4 (3.5)	2 (1.6)
Time at risk for event [years]	138.5	158.0
Incidence rate [patients with events per 100 patient years at risk]	2.89	1.27
95% confidence interval	(0.79, 6.33)	(0.15, 3.53)
Comparison vs Placebo*		
Hazard ratio		0.46
95% confidence interval		(0.08,2.51)
p-value		0.3678

* Based on a Cox regression model with terms for age (p=0.4244), baseline eGFR (CKD-EPI) (p=0.9442), sex (p=0.3529), region (p=0.7222), baseline diabetes status (3 cat.) (p=0.5218), Treatment (p=0.9981), baseline LVEF (3 cat.) (p=0.8436) and Treatment by baseline LVEF (3 cat.) interaction (p=0.2824).
The p-value for treatment by subgroup interaction trend test is 0.9360.

R.1.1.18.16 Subgroup analysis by bl. NTproBNP </>= median (median based on total patients)

Table R.1.1.18.16: 1 Cox regr. for time to adjudicated stroke (fatal or non-fatal) by bl. NTproBNP (<median,>= median) (median based on total patients) - RS (trial 1245.121)

Subgroup Description	Placebo	Empa 10mg
Baseline NTproBNP: < median		
Number of patients in analysis set	920	942
Number of analysed patients	920	942
Number of patients with event [N(%)]	16 (1.7)	17 (1.8)
Time at risk for event [years]	1243.9	1263.0
Incidence rate [patients with events per 100 patient years at risk]	1.29	1.35
95% confidence interval	(0.74, 1.99)	(0.78, 2.06)
Comparison vs Placebo*		
Hazard ratio		1.04
95% confidence interval		(0.53,2.07)
p-value		0.9012
Baseline NTproBNP: >= median		
Number of patients in analysis set	946	920
Number of analysed patients	946	920
Number of patients with event [N(%)]	18 (1.9)	23 (2.5)
Time at risk for event [years]	1198.8	1165.4
Incidence rate [patients with events per 100 patient years at risk]	1.50	1.97
95% confidence interval	(0.89, 2.27)	(1.25, 2.86)
Comparison vs Placebo*		
Hazard ratio		1.28
95% confidence interval		(0.69,2.37)
p-value		0.4379

* Based on a Cox regression model with terms for age (p=0.4124), baseline eGFR (CKD-EPI) (p=0.8704), sex (p=0.3838), region (p=0.7241), baseline diabetes status (3 cat.) (p=0.4998), baseline LVEF (3 cat.) (p=0.7222), Treatment (p=0.5406), baseline NTproBNP (2 cat.) (p=0.3607) and Treatment by baseline NTproBNP (2 cat.) interaction (p=0.6685).
2 patients were excluded as the subgroup variable was missing.

Median: 1910 [pg/mL]

R.1.1.19

R.1.1.19 Time to adjudicated fatal stroke

R.1.1.19.1

Figure R.1.1.19.1: 1

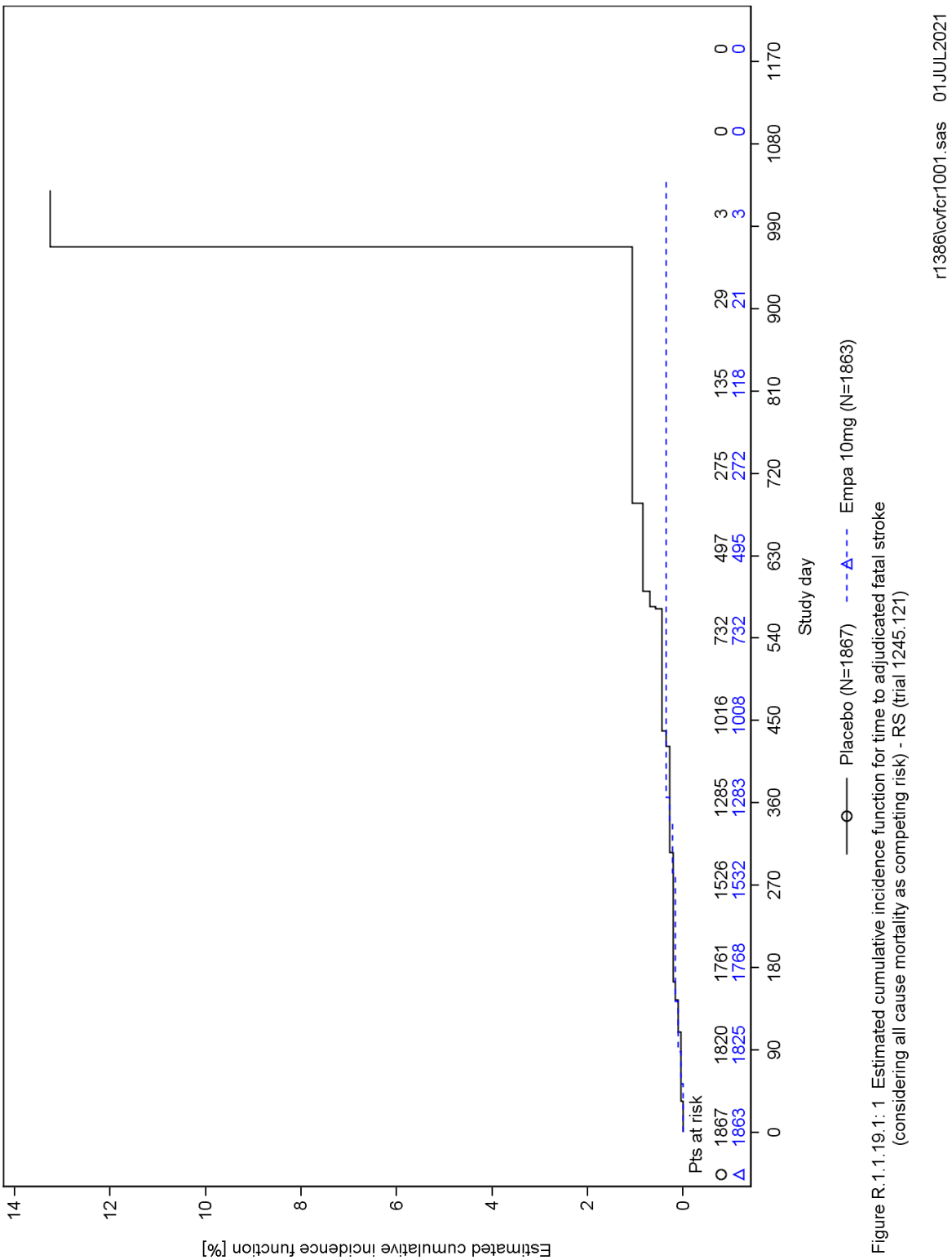

Figure R.1.1.19.1: 1 Estimated cumulative incidence function for time to adjudicated fatal stroke (considering all cause mortality as competing risk) - RS (trial 1245.121)

Table R.1.1.19.1: 1 Cox regr. for time to adjudicated fatal stroke - RS (trial 1245.121)

	Placebo	Empa 10mg
Number of patients in analysis set	1867	1863
Number of analysed patients	1867	1863
Number of patients with event [N(%)]	12 (0.6)	6 (0.3)
Time at risk for event [years]	2464.3	2459.4
Incidence rate [patients with events per 100 patient years at risk]	0.49	0.24
95% confidence interval	(0.25, 0.80)	(0.09, 0.47)
Comparison vs Placebo*		
Hazard ratio		0.50
95% confidence interval		(0.19,1.35)
p-value		0.1722
Time to event [days]**		
2.5% percentile	967	NC.
5.0% percentile	967	NC.
7.5% percentile	967	NC.
10.0% percentile	967	NC.
Patients with events [%]**		
1 year	0.3	0.3
2 years	1.2	0.4

* Based on a Cox regression model with terms for age (p=0.4019), baseline eGFR (CKD-EPI) (p=0.9164), sex (p=0.1836), region (p=0.8859), baseline diabetes status (3 cat.) (p=0.4561), baseline LVEF (3 cat.) (p=0.5168) and Treatment (p=0.1722).
**Based on Kaplan-Meier estimates.
NC. = Not calculated.

R.1.1.20

R.1.1.20 Time to adjudicated non-fatal stroke

R.1.1.20.1

Figure R.1.1.20.1: 1

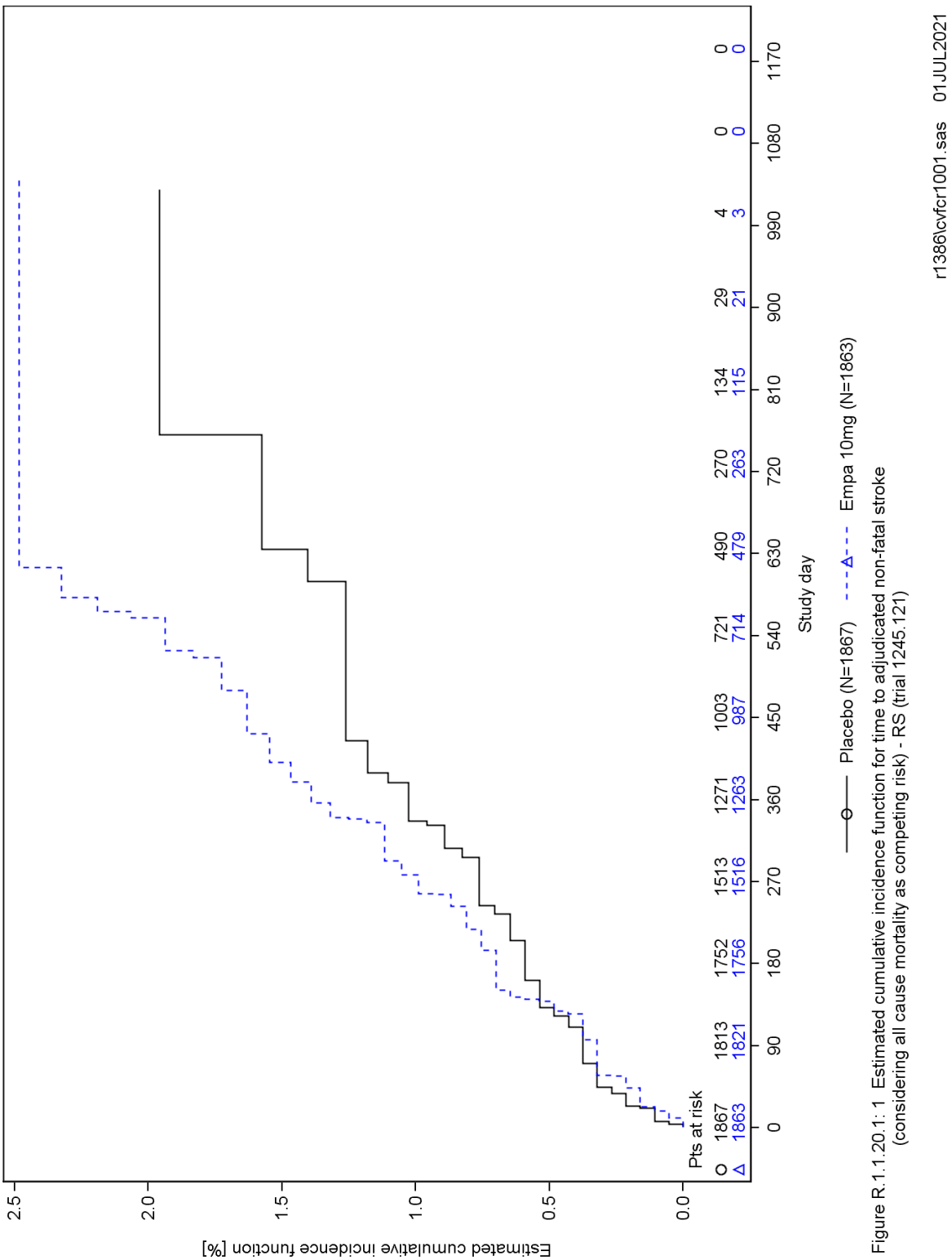

Figure R.1.1.20.1: 1 Estimated cumulative incidence function for time to adjudicated non-fatal stroke (considering all cause mortality as competing risk) - RS (trial 1245.121)

Table R.1.1.20.1: 1 Cox regr. for time to adjudicated non-fatal stroke - RS (trial 1245.121)

	Placebo	Empa 10mg
Number of patients in analysis set	1867	1863
Number of analysed patients	1867	1863
Number of patients with event [N(%)]	24 (1.3)	34 (1.8)
Time at risk for event [years]	2444.0	2429.9
Incidence rate [patients with events per 100 patient years at risk]	0.98	1.40
95% confidence interval	(0.63, 1.41)	(0.97, 1.91)
Comparison vs Placebo*		
Hazard ratio		1.40
95% confidence interval		(0.83,2.37)
p-value		0.2056
Time to event [days]**		
2.5% percentile	NC.	581
5.0% percentile	NC.	NC.
7.5% percentile	NC.	NC.
10.0% percentile	NC.	NC.
Patients with events [%]**		
1 year	1.1	1.5
2 years	1.7	2.7

* Based on a Cox regression model with terms for age (p=0.7391), baseline eGFR (CKD-EPI) (p=0.7174), sex (p=0.6924), region (p=0.6130), baseline diabetes status (3 cat.) (p=0.6274), baseline LVEF (3 cat.) (p=0.9441) and Treatment (p=0.2056).
**Based on Kaplan-Meier estimates.
NC. = Not calculated.

R.1.1.21

R.1.1.21 Time to first TIA

R.1.1.21.1

Figure R.1.1.21.1: 1

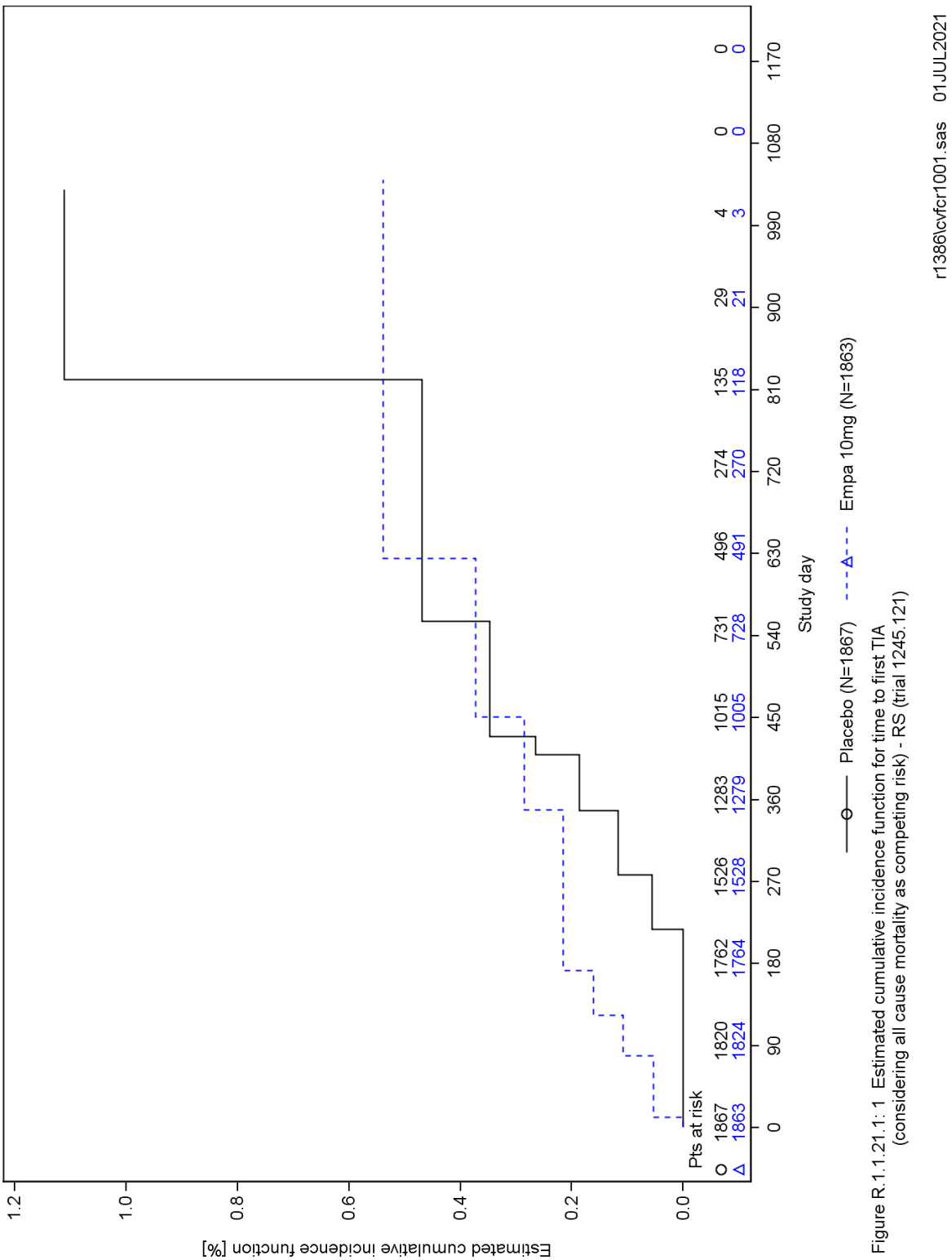

Figure R.1.1.21.1: 1 Estimated cumulative incidence function for time to first TIA
(considering all cause mortality as competing risk) - RS (trial 1245.121)

Table R.1.1.21.1: 1 Cox regr. for time to first TIA - RS (trial 1245.121)

	Placebo	Empa 10mg
Number of patients in analysis set	1867	1863
Number of analysed patients	1867	1863
Number of patients with event [N(%)]	7 (0.4)	7 (0.4)
Time at risk for event [years]	2462.8	2453.1
Incidence rate [patients with events per 100 patient years at risk]	0.28	0.29
95% confidence interval	(0.11, 0.53)	(0.11, 0.53)
Comparison vs Placebo*		
Hazard ratio		0.98
95% confidence interval		(0.34,2.81)
p-value		0.9725
Time to event [days]**		
2.5% percentile	NC.	NC.
5.0% percentile	NC.	NC.
7.5% percentile	NC.	NC.
10.0% percentile	NC.	NC.
Patients with events [%]**		
1 year	0.2	0.3
2 years	0.5	0.6

* Based on a Cox regression model with terms for age (p=0.3538), baseline eGFR (CKD-EPI) (p=0.1223), sex (p=0.4662), region (p=0.8769), baseline diabetes status (3 cat.) (p=0.1039), baseline LVEF (3 cat.) (p=0.7790) and Treatment (p=0.9725).
**Based on Kaplan-Meier estimates.
NC. = Not calculated.

R.1.1.21.2 Subgroup analysis by sex

Note: No analyses are performed, because all subgroup categories have less than 10 events.

R.1.1.21.3 Subgroup analysis by age

Note: No analyses are performed, because all subgroup categories have less than 10 events.

R.1.1.21.4 Subgroup analysis by region (North America, Latin America, Europe, Asia, Other)

Note: No analyses are performed, because all subgroup categories have less than 10 events.

R.1.1.21.5 Subgroup analysis by OECD member (Y/N)

Note: No analyses are performed, because all subgroup categories have less than 10 events.

R.1.1.21.6

R.1.1.21.6 Subgroup analysis by NYHA at baseline (II, III/IV - 2 cat.)

Table R.1.1.21.6: 1 Cox regr. for time to first TIA by baseline NYHA (2 cat.) - RS (trial 1245.121)

Subgroup Description	Placebo	Empa 10mg
Baseline NYHA: II		
Number of patients in analysis set	1401	1399
Number of analysed patients	1401	1399
Number of patients with event [N(%)]	7 (0.5)	5 (0.4)
Time at risk for event [years]	1861.6	1842.6
Incidence rate [patients with events per 100 patient years at risk]	0.38	0.27
95% confidence interval	(0.15, 0.70)	(0.09, 0.56)
Comparison vs Placebo*		
Hazard ratio		0.72
95% confidence interval		(0.23,2.27)
p-value		0.5716
Baseline NYHA: III/IV		
Number of patients in analysis set	466	464
Number of analysed patients	466	464
Number of patients with event [N(%)]	0	2 (0.4)
Time at risk for event [years]	601.2	610.5
Incidence rate [patients with events per 100 patient years at risk]	0.00	0.33
95% confidence interval	NC.	(0.04, 0.91)
Comparison vs Placebo*		
Hazard ratio		NC.
95% confidence interval		NC.
p-value		NC.

* Based on a Cox regression model with terms for age (p=0.3597), baseline eGFR (CKD-EPI) (p=0.1240), sex (p=0.4437), region (p=0.8550), baseline diabetes status (3 cat.) (p=0.1210), baseline LVEF (3 cat.) (p=0.7908), Treatment (p=0.9917), baseline NYHA (2 cat.) (p=0.9916) and Treatment by baseline NYHA (2 cat.) interaction (p=0.9914).
NC. = Not calculated, some results could not be produced.

R.1.1.21.7

Table R.1.1.21.7: 1 Cox regr. for time to first TIA by diabetes at baseline (2 cat.) - RS (trial 1245.121)

Subgroup Description	Placebo	Empa 10mg
Baseline diabetes status: Diabetic		
Number of patients in analysis set	929	927
Number of analysed patients	929	927
Number of patients with event [N(%)]	1 (0.1)	2 (0.2)
Time at risk for event [years]	1239.9	1225.5
Incidence rate [patients with events per 100 patient years at risk]	0.08	0.16
95% confidence interval	(0.00, 0.30)	(0.02, 0.45)
Comparison vs Placebo*		
Hazard ratio		1.97
95% confidence interval		(0.18,21.74)
p-value		0.5805
Baseline diabetes status: Non-Diabetic		
Number of patients in analysis set	938	936
Number of analysed patients	938	936
Number of patients with event [N(%)]	6 (0.6)	5 (0.5)
Time at risk for event [years]	1222.9	1227.6
Incidence rate [patients with events per 100 patient years at risk]	0.49	0.41
95% confidence interval	(0.18, 0.95)	(0.13, 0.83)
Comparison vs Placebo*		
Hazard ratio		0.82
95% confidence interval		(0.25, 2.69)
p-value		0.7393

* Based on a Cox regression model with terms for age (p=0.3726), baseline eGFR (CKD-EPI) (p=0.1227), sex (p=0.4631), region (p=0.8701), baseline LVEF (3 cat.) (p=0.7847), Treatment (p=0.7283), baseline diabetes status (2 cat.) (p=0.0388) and Treatment by baseline diabetes status (2 cat.) interaction (p=0.5200).

R.1.1.21.8 Subgroup analysis by BMI at baseline (<30, >=30)

Table R.1.1.21.8: 1 Cox regr. for time to first TIA by baseline BMI [kg/m2] - RS (trial 1245.121)

Subgroup Description	Placebo	Empa 10mg
Baseline BMI [kg/m²]: <30		
Number of patients in analysis set	1300	1263
Number of analysed patients	1300	1263
Number of patients with event [N(%)]	6 (0.5)	4 (0.3)
Time at risk for event [years]	1733.0	1652.2
Incidence rate [patients with events per 100 patient years at risk]	0.35	0.24
95% confidence interval	(0.13, 0.67)	(0.07, 0.53)
Comparison vs Placebo*		
Hazard ratio		0.69
95% confidence interval		(0.19, 2.45)
p-value		0.5674
Baseline BMI [kg/m²]: >=30		
Number of patients in analysis set	567	600
Number of analysed patients	567	600
Number of patients with event [N(%)]	1 (0.2)	3 (0.5)
Time at risk for event [years]	729.8	800.9
Incidence rate [patients with events per 100 patient years at risk]	0.14	0.37
95% confidence interval	(0.00, 0.51)	(0.08, 0.90)
Comparison vs Placebo*		
Hazard ratio		2.60
95% confidence interval		(0.27,25.13)
p-value		0.4089

* Based on a Cox regression model with terms for age (p=0.3545), baseline eGFR (CKD-EPI) (p=0.1310), sex (p=0.4681), region (p=0.8738), baseline diabetes status (3 cat.) (p=0.1068), baseline LVEF (3 cat.) (p=0.7850), Treatment (p=0.6586), baseline BMI (2 cat.) (p=0.8005) and Treatment by baseline BMI (2 cat.) interaction (p=0.3171).

R.1.1.21.9 Subgroup analysis by eGFR at baseline (<60, >=60)

Note: No analyses are performed, because all subgroup categories have less than 10 events.

R.1.1.21.10

Table R.1.1.21.10: 1 Cox regr. for time to first TIA by history of HHF within 12 months - RS (trial 1245.121)

Subgroup Description	Placebo	Empa 10mg
History of HHF (in the last 12 months): No		
Number of patients in analysis set	1293	1286
Number of analysed patients	1293	1286
Number of patients with event [N(%)]	7 (0.5)	5 (0.4)
Time at risk for event [years]	1754.7	1729.0
Incidence rate [patients with events per 100 patient years at risk]	0.40	0.29
95% confidence interval	(0.16, 0.74)	(0.09, 0.59)
Comparison vs Placebo*		
Hazard ratio		0.71
95% confidence interval		(0.23,2.25)
p-value		0.5622
History of HHF (in the last 12 months): Yes		
Number of patients in analysis set	574	577
Number of analysed patients	574	577
Number of patients with event [N(%)]	0	2 (0.3)
Time at risk for event [years]	708.1	724.1
Incidence rate [patients with events per 100 patient years at risk]	0.00	0.28
95% confidence interval	NC.	(0.03, 0.77)
Comparison vs Placebo*		
Hazard ratio		NC.
95% confidence interval		NC.
p-value		NC.

* Based on a Cox regression model with terms for age (p=0.2931), baseline eGFR (CKD-EPI) (p=0.1153), sex (p=0.5159), region (p=0.8591), baseline diabetes status (3 cat.) (p=0.1217), baseline LVEF (3 cat.) (p=0.7565), Treatment (p=0.9913), history of HHF (p=0.9909) and Treatment by history of HHF interaction (p=0.9909).
NC. = Not calculated, some results could not be produced.

R.1.1.21.11

Table R.1.1.21.11: 1 Cox regr. for time to first TIA by cause of heart failure - RS (trial 1245.121)

Subgroup Description	Placebo	Empa 10mg
Cause of heart failure: Ischemic		
Number of patients in analysis set	946	983
Number of analysed patients	946	983
Number of patients with event [N(%)]	1 (0.1)	2 (0.2)
Time at risk for event [years]	1267.7	1307.0
Incidence rate [patients with events per 100 patient years at risk]	0.08	0.15
95% confidence interval	(0.00, 0.29)	(0.02, 0.43)
Comparison vs Placebo*		
Hazard ratio		1.94
95% confidence interval		(0.18,21.42)
p-value		0.5895
Cause of heart failure: Non-ischemic		
Number of patients in analysis set	921	880
Number of analysed patients	921	880
Number of patients with event [N(%)]	6 (0.7)	5 (0.6)
Time at risk for event [years]	1195.1	1146.1
Incidence rate [patients with events per 100 patient years at risk]	0.50	0.44
95% confidence interval	(0.18, 0.98)	(0.14, 0.89)
Comparison vs Placebo*		
Hazard ratio		0.82
95% confidence interval		(0.25, 2.70)
p-value		0.7405

* Based on a Cox regression model with terms for age (p=0.5002), baseline eGFR (CKD-EPI) (p=0.1351), sex (p=0.6912), region (p=0.9412), baseline diabetes status (3 cat.) (p=0.1531), baseline LVEF (3 cat.) (p=0.7793), Treatment (p=0.7368), cause of heart failure (2 cat.) (p=0.0688) and Treatment by cause of heart failure (2 cat.) interaction (p=0.5285).

R.1.1.21.12 Subgroup analysis by heart failure physiology (LVEF <= 30% and NTproBNP<median; LVEF <= 30% and NTproBNP>=median; LVEF > 30%)

Note: No analyses are performed, because all subgroup categories have less than 10 events.

R.1.1.21.13 Subgroup analysis by baseline use of MRA

Note: No analyses are performed, because all subgroup categories have less than 10 events.

R.1.1.21.14

R.1.1.21.14 Subgroup analysis by baseline use of ARNi

Table R.1.1.21.14: 1 Cox regr. for time to first TIA by baseline use of ARNi (Y/N) - RS (trial 1245.121)

Subgroup Description	Placebo	Empa 10mg
Baseline use of ARNi: No		
Number of patients in analysis set	1480	1523
Number of analysed patients	1480	1523
Number of patients with event [N(%)]	6 (0.4)	5 (0.3)
Time at risk for event [years]	1971.2	2038.2
Incidence rate [patients with events per 100 patient years at risk]	0.30	0.25
95% confidence interval	(0.11, 0.59)	(0.08, 0.50)
Comparison vs Placebo*		
Hazard ratio		0.76
95% confidence interval		(0.23, 2.50)
p-value		0.6518
Baseline use of ARNi: Yes		
Number of patients in analysis set	387	340
Number of analysed patients	387	340
Number of patients with event [N(%)]	1 (0.3)	2 (0.6)
Time at risk for event [years]	491.6	414.9
Incidence rate [patients with events per 100 patient years at risk]	0.20	0.48
95% confidence interval	(0.01, 0.75)	(0.06, 1.34)
Comparison vs Placebo*		
Hazard ratio		2.73
95% confidence interval		(0.25,30.42)
p-value		0.4135

* Based on a Cox regression model with terms for age (p=0.3440), baseline eGFR (CKD-EPI) (p=0.1080), sex (p=0.4729), region (p=0.8868), baseline diabetes status (3 cat.) (p=0.1018), baseline LVEF (3 cat.) (p=0.7364), Treatment (p=0.5936), baseline use of ARNi (p=0.8146) and Treatment by baseline use of ARNi interaction (p=0.3512).

R.1.1.21.15 Subgroup analysis by bl. LVEF (<= 30%, >30% -<= 35% , > 35%)

Note: No analyses are performed, because all subgroup categories have less than 10 events.

R.1.1.21.16 Subgroup analysis by bl. NTproBNP </>= median (median based on total patients)

Note: No analyses are performed, because all subgroup categories have less than 10 events.

R.1.1.22

R.1.1.22 Time to new onset of atrial fibrillation

R.1.1.22.1

Figure R.1.1.22.1: 1

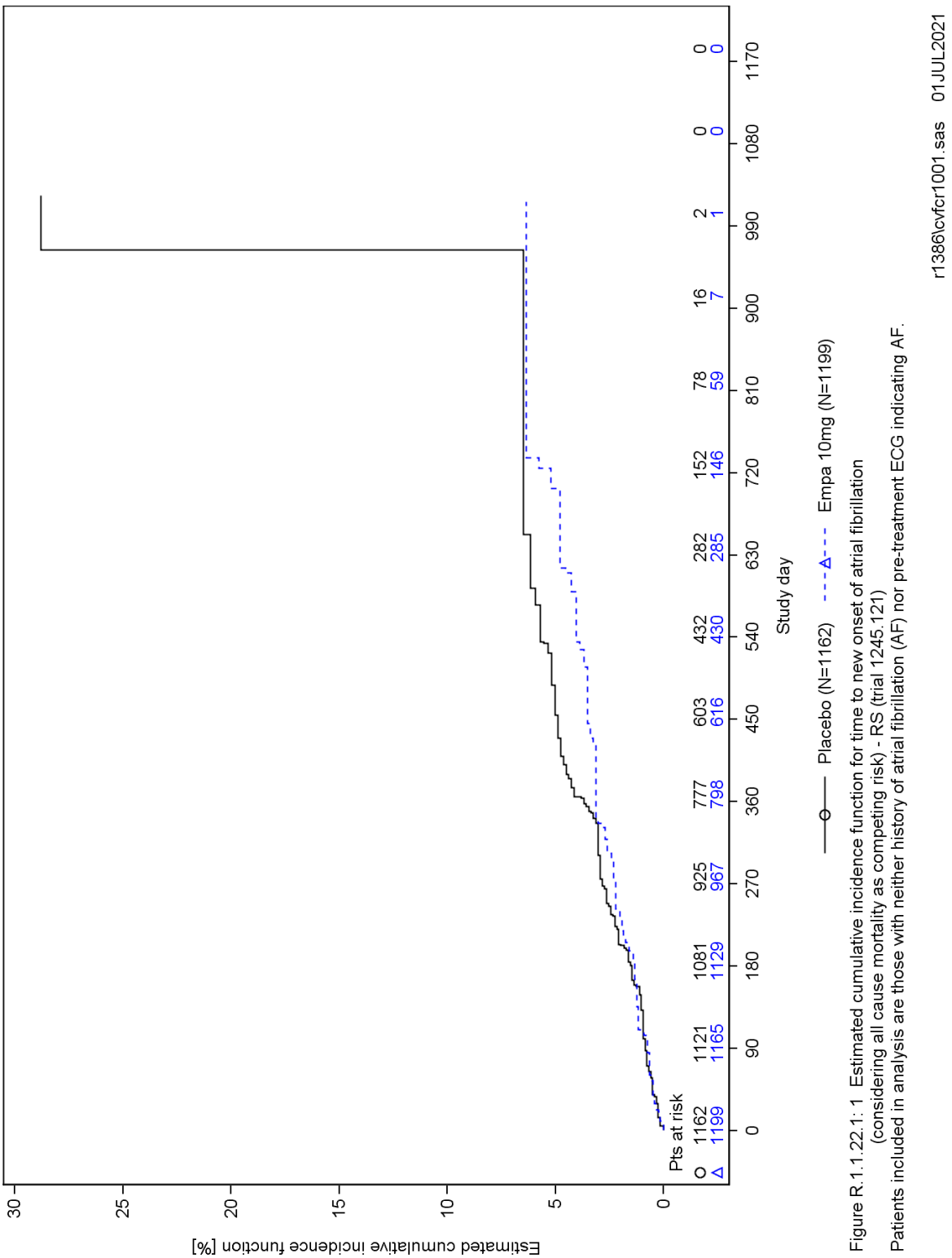

Figure R.1.1.22.1: 1 Estimated cumulative incidence function for time to new onset of atrial fibrillation (considering all cause mortality as competing risk) - RS (trial 1245.121)
Patients included in analysis are those with neither history of atrial fibrillation (AF) nor pre-treatment ECG indicating AF.

Table R.1.1.22.1: 1 Cox regr. for time to new onset of atrial fibrillation - RS (trial 1245.121)

	Placebo	Empa 10mg
Number of patients in analysis set	1867	1863
Number of analysed patients	1162	1199
Number of patients with event [N(%)]	59 (5.1)	47 (3.9)
Time at risk for event [years]	1489.9	1529.0
Incidence rate [patients with events per 100 patient years at risk]	3.96	3.07
95% confidence interval	(3.01, 5.03)	(2.26, 4.01)
Comparison vs Placebo*		
Hazard ratio		0.73
95% confidence interval		(0.50,1.07)
p-value		0.1105
Time to event [days]**		
2.5% percentile	236	303
5.0% percentile	409	615
7.5% percentile	963	NC.
10.0% percentile	963	NC.
Patients with events [%]**		
1 year	4.4	3.3
2 years	7.1	6.3

* Based on a Cox regression model with terms for age (p=0.0039), baseline eGFR (CKD-EPI) (p=0.5091), sex (p=0.5861), region (p=0.0013), baseline diabetes status (3 cat.) (p=0.4422), baseline LVEF (3 cat.) (p=0.6896) and Treatment (p=0.1105).
**Based on Kaplan-Meier estimates.
NC. = Not calculated.

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

R.1.1.22.2

R.1.1.22.2 Subgroup analysis by sex

Table R.1.1.22.2: 1 Cox regr. for time to new onset of atrial fibrillation by sex - RS (trial 1245.121)

Subgroup Description	Placebo	Empa 10mg
Sex: Male		
Number of patients in analysis set	1411	1426
Number of analysed patients	848	888
Number of patients with event [N(%)]	45 (5.3)	37 (4.2)
Time at risk for event [years]	1085.3	1128.6
Incidence rate [patients with events per 100 patient years at risk]	4.15	3.28
95% confidence interval	(3.02, 5.44)	(2.31, 4.42)
Comparison vs Placebo*		
Hazard ratio		0.74
95% confidence interval		(0.48,1.14)
p-value		0.1747
Sex: Female		
Number of patients in analysis set	456	437
Number of analysed patients	314	311
Number of patients with event [N(%)]	14 (4.5)	10 (3.2)
Time at risk for event [years]	404.6	400.5
Incidence rate [patients with events per 100 patient years at risk]	3.46	2.50
95% confidence interval	(1.89, 5.49)	(1.20, 4.27)
Comparison vs Placebo*		
Hazard ratio		0.71
95% confidence interval		(0.31,1.59)
p-value		0.4007

* Based on a Cox regression model with terms for age (p=0.0040), baseline eGFR (CKD-EPI) (p=0.5076), region (p=0.0013), baseline diabetes status (3 cat.) (p=0.4407), baseline LVEF (3 cat.) (p=0.6899), Treatment (p=0.1663), sex (p=0.5809) and Treatment by sex interaction (p=0.9220).

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

R.1.1.22.3

Table R.1.1.22.3: 1 Cox regr. for time to new onset of atrial fibrillation by age (2 cat.) - RS (trial 1245.121)

Subgroup Description	Placebo	Empa 10mg
Age [years]: < 65		
Number of patients in analysis set	740	675
Number of analysed patients	563	519
Number of patients with event [N(%)]	19 (3.4)	17 (3.3)
Time at risk for event [years]	739.1	662.6
Incidence rate [patients with events per 100 patient years at risk]	2.57	2.57
95% confidence interval	(1.55, 3.85)	(1.49, 3.92)
Comparison vs Placebo*		
Hazard ratio		0.99
95% confidence interval		(0.51,1.90)
p-value		0.9686
Age [years]: >= 65		
Number of patients in analysis set	1127	1188
Number of analysed patients	599	680
Number of patients with event [N(%)]	40 (6.7)	30 (4.4)
Time at risk for event [years]	750.8	866.4
Incidence rate [patients with events per 100 patient years at risk]	5.33	3.46
95% confidence interval	(3.81, 7.10)	(2.34, 4.81)
Comparison vs Placebo*		
Hazard ratio		0.64
95% confidence interval		(0.40,1.03)
p-value		0.0663

* Based on a Cox regression model with terms for baseline eGFR (CKD-EPI) (p=0.9981), sex (p=0.5645), region (p=0.0007), baseline diabetes status (3 cat.) (p=0.4670), baseline LVEF (3 cat.) (p=0.7657), Treatment (p=0.2678), age (2 cat.) (p=0.0839) and Treatment by age (2 cat.) interaction (p=0.2968).

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

R.1.1.22.4 Subgroup analysis by region (North America, Latin America, Europe, Asia, Other)

Table R.1.1.22.4: 1 Cox regr. for time to new onset of atrial fibrillation by region - RS (trial 1245.121)

Subgroup Description	Placebo	Empa 10mg
Region: North America		
Number of patients in analysis set	213	212
Number of analysed patients	120	118
Number of patients with event [N(%)]	14 (11.7)	7 (5.9)
Time at risk for event [years]	151.5	170.9
Incidence rate [patients with events per 100 patient years at risk]	9.24	4.10
95% confidence interval	(5.05, 14.67)	(1.65, 7.64)
Comparison vs Placebo*		
Hazard ratio		0.42
95% confidence interval		(0.17,1.04)
p-value		0.0613
Region: Latin America		
Number of patients in analysis set	645	641
Number of analysed patients	478	480
Number of patients with event [N(%)]	12 (2.5)	12 (2.5)
Time at risk for event [years]	583.7	562.8
Incidence rate [patients with events per 100 patient years at risk]	2.06	2.13
95% confidence interval	(1.06, 3.37)	(1.10, 3.50)
Comparison vs Placebo*		
Hazard ratio		1.00
95% confidence interval		(0.45,2.23)
p-value		0.9966

* Based on a Cox regression model with terms for age (p=0.0031), baseline eGFR (CKD-EPI) (p=0.5093), sex (p=0.6142), baseline diabetes status (3 cat.) (p=0.4727), baseline LVEF (3 cat.) (p=0.6730), Treatment (p=0.0857), region (p=0.0022) and Treatment by region interaction (p=0.4316).

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

Table R.1.1.22.4: 1 Cox regr. for time to new onset of atrial fibrillation by region - RS (trial 1245.121)

Subgroup Description	Placebo	Empa 10mg
Region: Europe		
Number of patients in analysis set	677	676
Number of analysed patients	329	366
Number of patients with event [N(%)]	23 (7.0)	24 (6.6)
Time at risk for event [years]	427.5	476.3
Incidence rate [patients with events per 100 patient years at risk]	5.38	5.04
95% confidence interval	(3.41, 7.79)	(3.23, 7.25)
Comparison vs Placebo*		
Hazard ratio		0.93
95% confidence interval		(0.53,1.65)
p-value		0.8093
Region: Asia		
Number of patients in analysis set	245	248
Number of analysed patients	157	157
Number of patients with event [N(%)]	8 (5.1)	3 (1.9)
Time at risk for event [years]	219.8	213.7
Incidence rate [patients with events per 100 patient years at risk]	3.64	1.40
95% confidence interval	(1.57, 6.56)	(0.29, 3.38)
Comparison vs Placebo*		
Hazard ratio		0.38
95% confidence interval		(0.10,1.42)
p-value		0.1491

* Based on a Cox regression model with terms for age (p=0.0031), baseline eGFR (CKD-EPI) (p=0.5093), sex (p=0.6142), baseline diabetes status (3 cat.) (p=0.4727), baseline LVEF (3 cat.) (p=0.6730), Treatment (p=0.0857), region (p=0.0022) and Treatment by region interaction (p=0.4316).

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

Table R.1.1.22.4: 1 Cox regr. for time to new onset of atrial fibrillation by region - RS (trial 1245.121)

Subgroup Description	Placebo	Empa 10mg
Region: Other		
Number of patients in analysis set	87	86
Number of analysed patients	78	78
Number of patients with event [N(%)]	2 (2.6)	1 (1.3)
Time at risk for event [years]	107.2	105.4
Incidence rate [patients with events per 100 patient years at risk]	1.86	0.95
95% confidence interval	(0.23, 5.20)	(0.02, 3.50)
Comparison vs Placebo*		
Hazard ratio		0.47
95% confidence interval		(0.04,5.15)
p-value		0.5334

* Based on a Cox regression model with terms for age (p=0.0031), baseline eGFR (CKD-EPI) (p=0.5093), sex (p=0.6142), baseline diabetes status (3 cat.) (p=0.4727), baseline LVEF (3 cat.) (p=0.6730), Treatment (p=0.0857), region (p=0.0022) and Treatment by region interaction (p=0.4316).

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

R.1.1.22.5

R.1.1.22.5 Subgroup analysis by OECD member (Y/N)

Table R.1.1.22.5: 1 Cox regr. for time to new onset of atrial fibrillation by OECD member (Y/N) - RS (trial 1245.121)

Subgroup Description	Placebo	Empa 10mg
OECD member: No		
Number of patients in analysis set	741	713
Number of analysed patients	557	538
Number of patients with event [N(%)]	13 (2.3)	12 (2.2)
Time at risk for event [years]	690.9	640.0
Incidence rate [patients with events per 100 patient years at risk]	1.88	1.87
95% confidence interval	(1.00, 3.03)	(0.97, 3.08)
Comparison vs Placebo*		
Hazard ratio		0.96
95% confidence interval		(0.44,2.10)
p-value		0.9135
OECD member: Yes		
Number of patients in analysis set	1126	1150
Number of analysed patients	605	661
Number of patients with event [N(%)]	46 (7.6)	35 (5.3)
Time at risk for event [years]	799.0	889.0
Incidence rate [patients with events per 100 patient years at risk]	5.76	3.94
95% confidence interval	(4.22, 7.54)	(2.74, 5.34)
Comparison vs Placebo*		
Hazard ratio		0.67
95% confidence interval		(0.43,1.05)
p-value		0.0792

* Based on a Cox regression model with terms for age (p=0.0050), baseline eGFR (CKD-EPI) (p=0.6585), sex (p=0.6365), baseline diabetes status (3 cat.) (p=0.4593), baseline LVEF (3 cat.) (p=0.6398), Treatment (p=0.3408), OECD Member (N) (p=0.0008) and Treatment by OECD Member (N) interaction (p=0.4460).

Patients included in analysis are those with neither history of atrial fibrillation (AF) nor pre-treatment ECG indicating AF.
OECD member (yes/no) countries included:
Yes: United States, Canada, Mexico, Poland, Netherlands, Hungary, Germany, Czech Republic, Italy, France, Spain, United Kingdom, Belgium, Japan, Australia, 'Korea; Republic Of South Korea';
No: Brazil, Argentina, China, India.

R.1.1.22.6

R.1.1.22.6 Subgroup analysis by NYHA at baseline (II, III/IV - 2 cat.)

Table R.1.1.22.6: 1 Cox regr. for time to new onset of atrial fibrillation by baseline NYHA (2 cat.) - RS (trial 1245.121)

Subgroup Description	Placebo	Empa 10mg
Baseline NYHA: II		
Number of patients in analysis set	1401	1399
Number of analysed patients	900	926
Number of patients with event [N(%)]	47 (5.2)	38 (4.1)
Time at risk for event [years]	1161.7	1172.8
Incidence rate [patients with events per 100 patient years at risk]	4.05	3.24
95% confidence interval	(2.97, 5.28)	(2.29, 4.35)
Comparison vs Placebo*		
Hazard ratio		0.75
95% confidence interval		(0.49,1.15)
p-value		0.1919
Baseline NYHA: III/IV		
Number of patients in analysis set	466	464
Number of analysed patients	262	273
Number of patients with event [N(%)]	12 (4.6)	9 (3.3)
Time at risk for event [years]	328.2	356.2
Incidence rate [patients with events per 100 patient years at risk]	3.66	2.53
95% confidence interval	(1.89, 6.00)	(1.16, 4.43)
Comparison vs Placebo*		
Hazard ratio		0.66
95% confidence interval		(0.28,1.57)
p-value		0.3516

* Based on a Cox regression model with terms for age (p=0.0041), baseline eGFR (CKD-EPI) (p=0.5389), sex (p=0.6008), region (p=0.0012), baseline diabetes status (3 cat.) (p=0.3888), baseline LVEF (3 cat.) (p=0.6673), Treatment (p=0.1576), baseline NYHA (2 cat.) (p=0.3278) and Treatment by baseline NYHA (2 cat.) interaction (p=0.7986).

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

R.1.1.22.7

Table R.1.1.22.7: 1 Cox regr. for time to new onset of atrial fibrillation by diabetes at baseline (2 cat.) - RS (trial 1245.121)

Subgroup Description	Placebo	Empa 10mg
Baseline diabetes status: Diabetic		
Number of patients in analysis set	929	927
Number of analysed patients	606	617
Number of patients with event [N(%)]	35 (5.8)	27 (4.4)
Time at risk for event [years]	788.0	786.8
Incidence rate [patients with events per 100 patient years at risk]	4.44	3.43
95% confidence interval	(3.09, 6.03)	(2.26, 4.84)
Comparison vs Placebo*		
Hazard ratio		0.74
95% confidence interval		(0.45,1.22)
p-value		0.2374
Baseline diabetes status: Non-Diabetic		
Number of patients in analysis set	938	936
Number of analysed patients	556	582
Number of patients with event [N(%)]	24 (4.3)	20 (3.4)
Time at risk for event [years]	701.8	742.2
Incidence rate [patients with events per 100 patient years at risk]	3.42	2.69
95% confidence interval	(2.19, 4.92)	(1.65, 4.00)
Comparison vs Placebo*		
Hazard ratio		0.72
95% confidence interval		(0.40,1.31)
p-value		0.2838

* Based on a Cox regression model with terms for age (p=0.0039), baseline eGFR (CKD-EPI) (p=0.5086), sex (p=0.5851), region (p=0.0013), baseline LVEF (3 cat.) (p=0.6911), Treatment (p=0.1133), baseline diabetes status (2 cat.) (p=0.2019) and Treatment by baseline diabetes status (2 cat.) interaction (p=0.9550).

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

R.1.1.22.8 Subgroup analysis by BMI at baseline (<30, >=30)

Figure R.1.1.22.8: 1

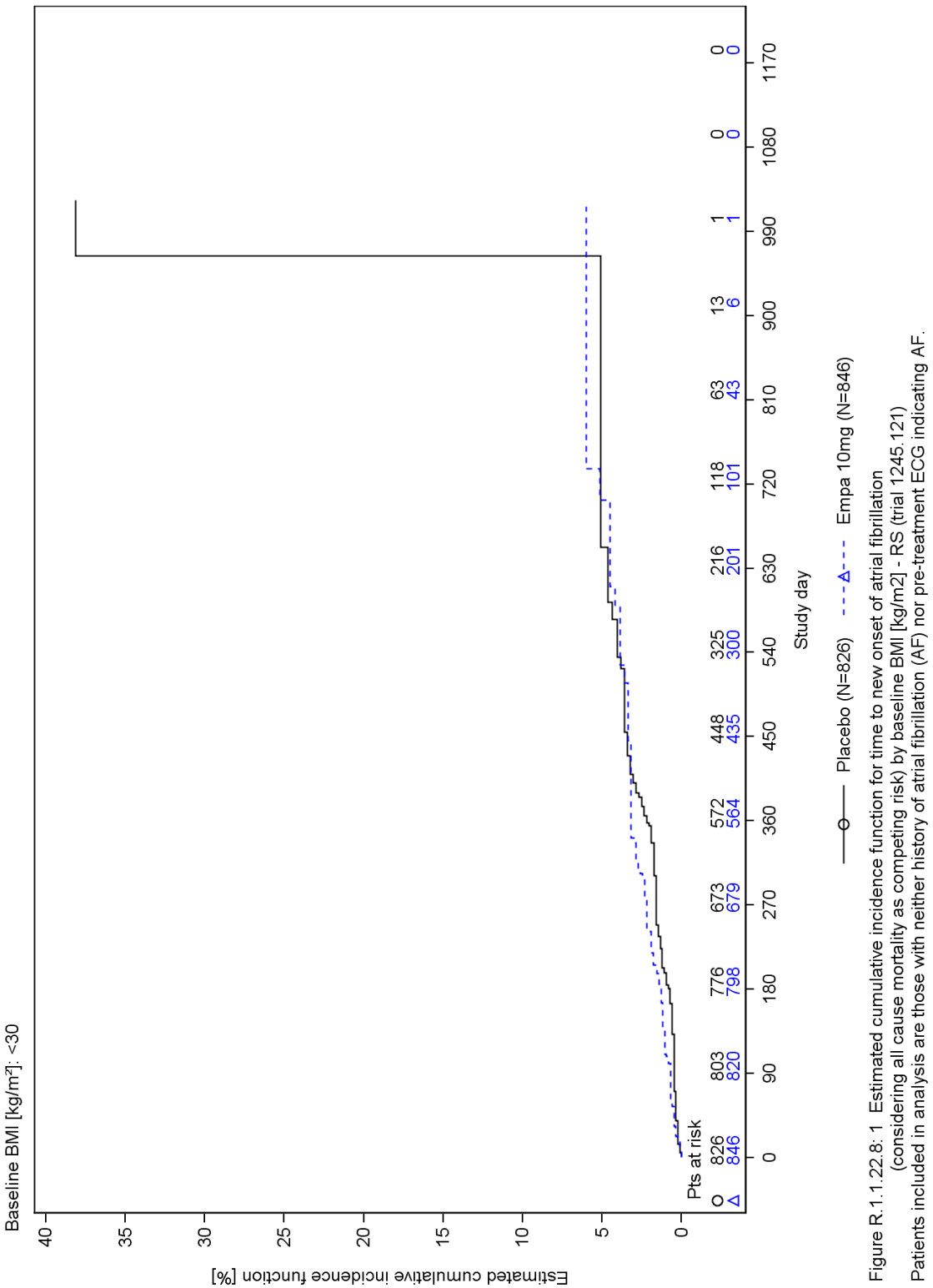

Figure R.1.1.22.8: 1 Estimated cumulative incidence function for time to new onset of atrial fibrillation (considering all cause mortality as competing risk) by baseline BMI [kg/m2] - RS (trial 1245.121)
Patients included in analysis are those with neither history of atrial fibrillation (AF) nor pre-treatment ECG indicating AF.

Figure R.1.1.22.8: 1

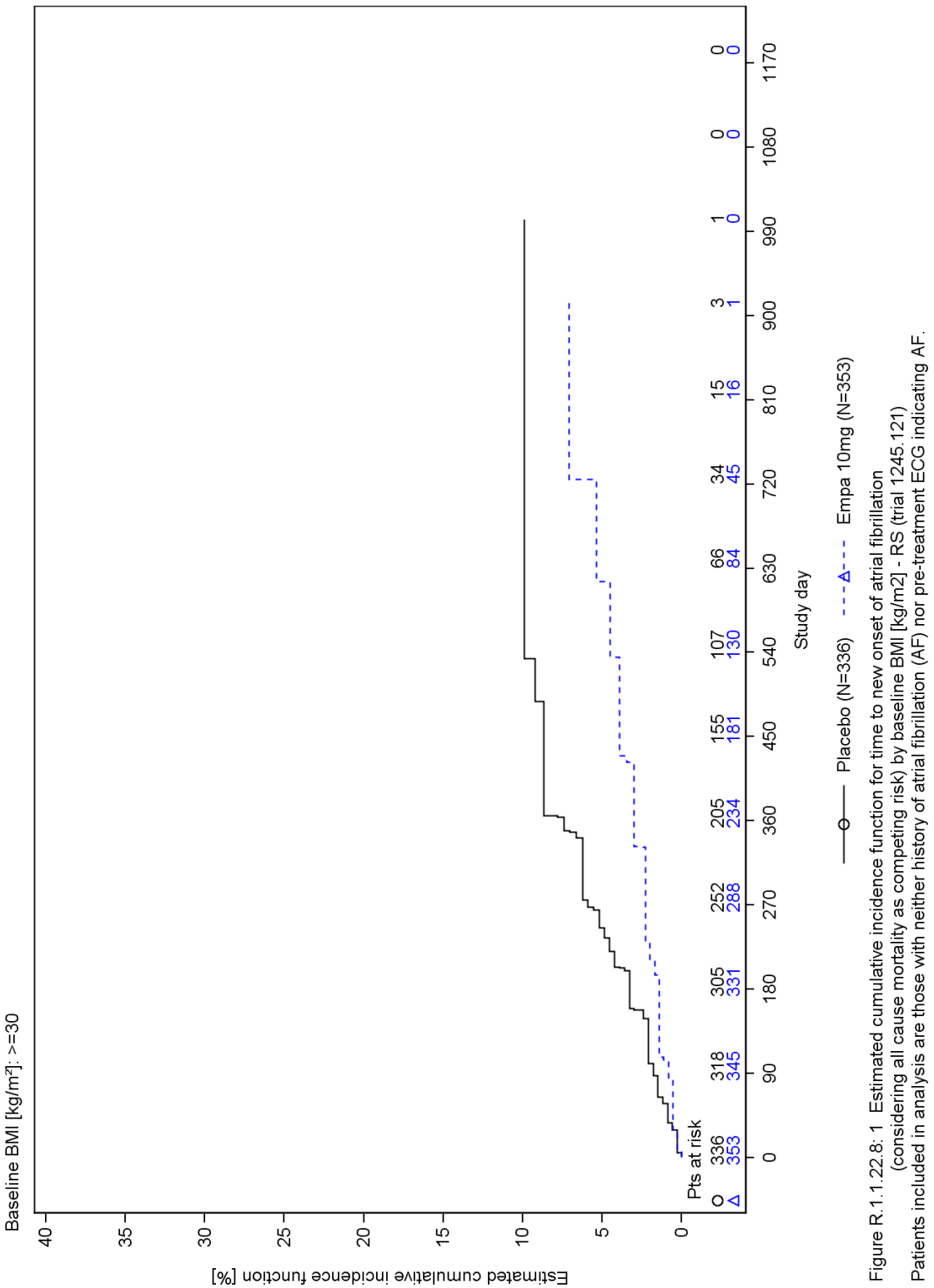

Figure R.1.1.22.8: 1 Estimated cumulative incidence function for time to new onset of atrial fibrillation (considering all cause mortality as competing risk) by baseline BMI [kg/m2] - RS (trial 1245.121)
Patients included in analysis are those with neither history of atrial fibrillation (AF) nor pre-treatment ECG indicating AF.

Table R.1.1.22.8: 1 Cox regr. for time to new onset of atrial fibrillation by baseline BMI [kg/m2] - RS (trial 1245.121)

Subgroup Description	Placebo	Empa 10mg
Baseline BMI [kg/m²]: <30		
Number of patients in analysis set	1300	1263
Number of analysed patients	826	846
Number of patients with event [N(%)]	31 (3.8)	32 (3.8)
Time at risk for event [years]	1087.0	1077.5
Incidence rate [patients with events per 100 patient years at risk]	2.85	2.97
95% confidence interval	(1.94, 3.94)	(2.03, 4.08)
Comparison vs Placebo*		
Hazard ratio		0.99
95% confidence interval		(0.60,1.62)
p-value		0.9595
Baseline BMI [kg/m²]: >=30		
Number of patients in analysis set	567	600
Number of analysed patients	336	353
Number of patients with event [N(%)]	28 (8.3)	15 (4.2)
Time at risk for event [years]	402.8	451.6
Incidence rate [patients with events per 100 patient years at risk]	6.95	3.32
95% confidence interval	(4.62, 9.75)	(1.86, 5.20)
Comparison vs Placebo*		
Hazard ratio		0.44
95% confidence interval		(0.23,0.83)
p-value		0.0106

* Based on a Cox regression model with terms for age (p=0.0010), baseline eGFR (CKD-EPI) (p=0.4193), sex (p=0.4982), region (p=0.0093), baseline diabetes status (3 cat.) (p=0.6444), baseline LVEF (3 cat.) (p=0.6265), Treatment (p=0.0415), baseline BMI (2 cat.) (p=0.0346) and Treatment by baseline BMI (2 cat.) interaction (p=0.0478).

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

R.1.1.22.9

R.1.1.22.9 Subgroup analysis by eGFR at baseline (<60, >=60)

Table R.1.1.22.9: 1 Cox regr. for time to new onset of atrial fibrillation by baseline eGFR (2 cat.) - RS (trial 1245.121)

Subgroup Description	Placebo	Empa 10mg
Baseline eGFR (CKD-EPI) [mL/min/1.73m²]: >=60		
Number of patients in analysis set	960	969
Number of analysed patients	673	703
Number of patients with event [N(%)]	28 (4.2)	28 (4.0)
Time at risk for event [years]	867.9	898.0
Incidence rate [patients with events per 100 patient years at risk]	3.23	3.12
95% confidence interval	(2.14, 4.53)	(2.07, 4.37)
Comparison vs Placebo*		
Hazard ratio		0.89
95% confidence interval		(0.52,1.50)
p-value		0.6588
Baseline eGFR (CKD-EPI) [mL/min/1.73m²]: <60		
Number of patients in analysis set	906	893
Number of analysed patients	488	495
Number of patients with event [N(%)]	31 (6.4)	19 (3.8)
Time at risk for event [years]	621.1	629.9
Incidence rate [patients with events per 100 patient years at risk]	4.99	3.02
95% confidence interval	(3.39, 6.90)	(1.82, 4.52)
Comparison vs Placebo*		
Hazard ratio		0.59
95% confidence interval		(0.33,1.04)
p-value		0.0677

* Based on a Cox regression model with terms for age (p=0.0051), sex (p=0.5260), region (p=0.0015), baseline diabetes status (3 cat.) (p=0.4716), baseline LVEF (3 cat.) (p=0.6910), Treatment (p=0.1000), baseline eGFR (CKD-EPI) (2 cat.) (p=0.7123) and Treatment by baseline eGFR (CKD-EPI) (2 cat.) interaction (p=0.2948).
2 patients were excluded as the subgroup variable was missing.

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

R.1.1.22.10

Table R.1.1.22.10: 1 Cox regr. for time to new onset of atrial fibrillation by history of HHF within 12 months - RS (trial 1245.121)

Subgroup Description	Placebo	Empa 10mg
History of HHF (in the last 12 months): No		
Number of patients in analysis set	1293	1286
Number of analysed patients	826	853
Number of patients with event [N(%)]	49 (5.9)	32 (3.8)
Time at risk for event [years]	1078.8	1107.2
Incidence rate [patients with events per 100 patient years at risk]	4.54	2.89
95% confidence interval	(3.36, 5.90)	(1.98, 3.97)
Comparison vs Placebo*		
Hazard ratio		0.62
95% confidence interval		(0.40,0.97)
p-value		0.0383
History of HHF (in the last 12 months): Yes		
Number of patients in analysis set	574	577
Number of analysed patients	336	346
Number of patients with event [N(%)]	10 (3.0)	15 (4.3)
Time at risk for event [years]	411.0	421.9
Incidence rate [patients with events per 100 patient years at risk]	2.43	3.56
95% confidence interval	(1.17, 4.16)	(1.99, 5.57)
Comparison vs Placebo*		
Hazard ratio		1.25
95% confidence interval		(0.56,2.79)
p-value		0.5874

* Based on a Cox regression model with terms for age (p=0.0072), baseline eGFR (CKD-EPI) (p=0.4839), sex (p=0.5771), region (p=0.0011), baseline diabetes status (3 cat.) (p=0.4233), baseline LVEF (3 cat.) (p=0.7526), Treatment (p=0.5942), history of HHF (p=0.3457) and Treatment by history of HHF interaction (p=0.1386).

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

R.1.1.22.11

Table R.1.1.22.11: 1 Cox regr. for time to new onset of atrial fibrillation by cause of heart failure - RS (trial 1245.121)

Subgroup Description	Placebo	Empa 10mg
Cause of heart failure: Ischemic		
Number of patients in analysis set	946	983
Number of analysed patients	626	657
Number of patients with event [N(%)]	33 (5.3)	29 (4.4)
Time at risk for event [years]	809.2	847.1
Incidence rate [patients with events per 100 patient years at risk]	4.08	3.42
95% confidence interval	(2.81, 5.58)	(2.29, 4.78)
Comparison vs Placebo*		
Hazard ratio		0.83
95% confidence interval		(0.50,1.37)
p-value		0.4647
Cause of heart failure: Non-ischemic		
Number of patients in analysis set	921	880
Number of analysed patients	536	542
Number of patients with event [N(%)]	26 (4.9)	18 (3.3)
Time at risk for event [years]	680.6	681.9
Incidence rate [patients with events per 100 patient years at risk]	3.82	2.64
95% confidence interval	(2.50, 5.42)	(1.56, 3.99)
Comparison vs Placebo*		
Hazard ratio		0.60
95% confidence interval		(0.33,1.11)
p-value		0.1037

* Based on a Cox regression model with terms for age (p=0.0031), baseline eGFR (CKD-EPI) (p=0.5270), sex (p=0.5084), region (p=0.0011), baseline diabetes status (3 cat.) (p=0.4196), baseline LVEF (3 cat.) (p=0.6967), Treatment (p=0.0848), cause of heart failure (2 cat.) (p=0.5677) and Treatment by cause of heart failure (2 cat.) interaction (p=0.4307).

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

R.1.1.22.12 Subgroup analysis by heart failure physiology (LVEF <= 30% and NTproBNP<median; LVEF <= 30% and NTproBNP>=median; LVEF > 30%)

Table R.1.1.22.12: 1 Cox regr. for time to new onset of atrial fibrillation by heart failure physiology - RS (trial 1245.121)

Subgroup Description	Placebo	Empa 10mg
Heart failure physiology: LVEF <= 30% and NTproBNP < median		
Number of patients in analysis set	723	698
Number of analysed patients	458	460
Number of patients with event [N(%)]	17 (3.7)	19 (4.1)
Time at risk for event [years]	607.1	618.3
Incidence rate [patients with events per 100 patient years at risk]	2.80	3.07
95% confidence interval	(1.63, 4.28)	(1.85, 4.60)
Comparison vs Placebo*		
Hazard ratio		1.03
95% confidence interval		(0.54,1.99)
p-value		0.9195
Heart failure physiology: LVEF <= 30% and NTproBNP >= median		
Number of patients in analysis set	661	631
Number of analysed patients	412	405
Number of patients with event [N(%)]	28 (6.8)	18 (4.4)
Time at risk for event [years]	511.2	498.9
Incidence rate [patients with events per 100 patient years at risk]	5.48	3.61
95% confidence interval	(3.64, 7.68)	(2.14, 5.46)
Comparison vs Placebo*		
Hazard ratio		0.62
95% confidence interval		(0.34,1.13)
p-value		0.1175

* Based on a Cox regression model with terms for age (p=0.0044), baseline eGFR (CKD-EPI) (p=0.4000), sex (p=0.5992), region (p=0.0009), baseline diabetes status (3 cat.) (p=0.5140), Treatment (p=0.1054), heart failure physiology (p=0.1478) and Treatment by heart failure physiology interaction (p=0.4300).
16 patients were excluded as the subgroup variable was missing.
The p-value for treatment by subgroup interaction trend test is 0.2538.

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

Table R.1.1.22.12: 1 Cox regr. for time to new onset of atrial fibrillation by heart failure physiology - RS (trial 1245.121)

Subgroup Description	Placebo	Empa 10mg
Heart failure physiology: LVEF > 30%		
Number of patients in analysis set	475	526
Number of analysed patients	284	328
Number of patients with event [N(%)]	14 (4.9)	10 (3.0)
Time at risk for event [years]	361.2	407.3
Incidence rate [patients with events per 100 patient years at risk]	3.88	2.46
95% confidence interval	(2.12, 6.15)	(1.18, 4.20)
Comparison vs Placebo*		
Hazard ratio		0.58
95% confidence interval		(0.26,1.30)
p-value		0.1838

* Based on a Cox regression model with terms for age (p=0.0044), baseline eGFR (CKD-EPI) (p=0.4000), sex (p=0.5992), region (p=0.0009), baseline diabetes status (3 cat.) (p=0.5140), Treatment (p=0.1054), heart failure physiology (p=0.1478) and Treatment by heart failure physiology interaction (p=0.4300).
16 patients were excluded as the subgroup variable was missing.
The p-value for treatment by subgroup interaction trend test is 0.2538.

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

R.1.1.22.13

R.1.1.22.13 Subgroup analysis by baseline use of MRA

Figure R.1.1.22.13: 1

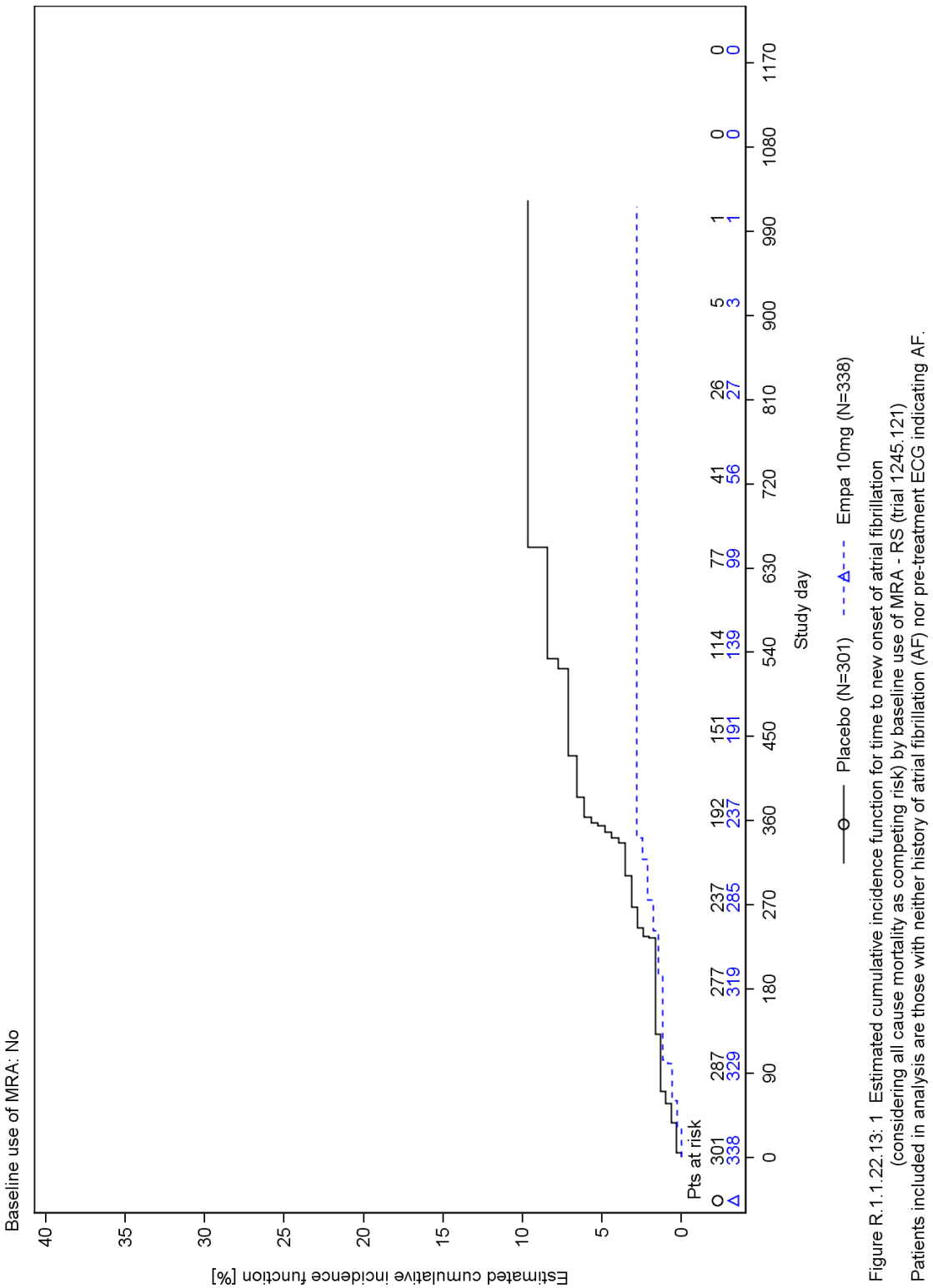

Figure R.1.1.22.13: 1 Estimated cumulative incidence function for time to new onset of atrial fibrillation (considering all cause mortality as competing risk) by baseline use of MRA - RS (trial 1245.121)
Patients included in analysis are those with neither history of atrial fibrillation (AF) nor pre-treatment ECG indicating AF.

Figure R.1.1.22.13: 1

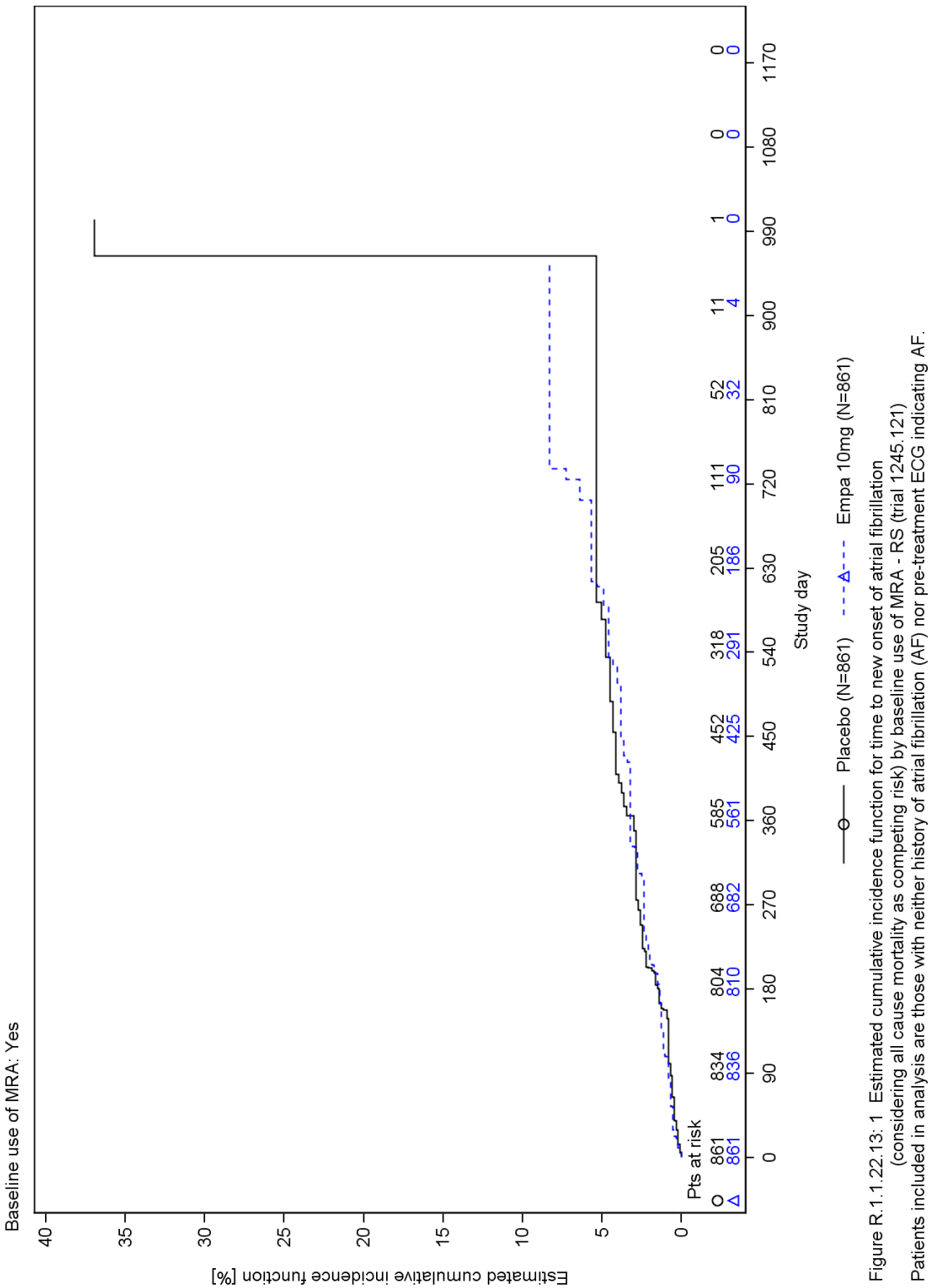

Figure R.1.1.22.13: 1 Estimated cumulative incidence function for time to new onset of atrial fibrillation (considering all cause mortality as competing risk) by baseline use of MRA - RS (trial 1245.121)
Patients included in analysis are those with neither history of atrial fibrillation (AF) nor pre-treatment ECG indicating AF.

Table R.1.1.22.13: 1 Cox regr. for time to new onset of atrial fibrillation by baseline use of MRA - RS (trial 1245.121)

Subgroup Description	Placebo	Empa 10mg
Baseline use of MRA: No		
Number of patients in analysis set	512	557
Number of analysed patients	301	338
Number of patients with event [N(%)]	21 (7.0)	9 (2.7)
Time at risk for event [years]	383.3	457.3
Incidence rate [patients with events per 100 patient years at risk]	5.48	1.97
95% confidence interval	(3.39, 8.06)	(0.90, 3.45)
Comparison vs Placebo*		
Hazard ratio		0.35
95% confidence interval		(0.16,0.76)
p-value		0.0079
Baseline use of MRA: Yes		
Number of patients in analysis set	1355	1306
Number of analysed patients	861	861
Number of patients with event [N(%)]	38 (4.4)	38 (4.4)
Time at risk for event [years]	1106.5	1071.7
Incidence rate [patients with events per 100 patient years at risk]	3.43	3.55
95% confidence interval	(2.43, 4.61)	(2.51, 4.76)
Comparison vs Placebo*		
Hazard ratio		0.97
95% confidence interval		(0.62,1.53)
p-value		0.9102

* Based on a Cox regression model with terms for age (p=0.0032), baseline eGFR (CKD-EPI) (p=0.5235), sex (p=0.6052), region (p=0.0010), baseline diabetes status (3 cat.) (p=0.4262), baseline LVEF (3 cat.) (p=0.6969), Treatment (p=0.0183), baseline use of MRA (p=0.2214) and Treatment by baseline use of MRA interaction (p=0.0249).

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

R.1.1.22.14

Table R.1.1.22.14: 1 Cox regr. for time to new onset of atrial fibrillation by baseline use of ARNi - RS (trial 1245.121)

Subgroup Description	Placebo	Empa 10mg
Baseline use of ARNi: No		
Number of patients in analysis set	1480	1523
Number of analysed patients	931	985
Number of patients with event [N(%)]	49 (5.3)	38 (3.9)
Time at risk for event [years]	1210.1	1264.1
Incidence rate [patients with events per 100 patient years at risk]	4.05	3.01
95% confidence interval	(3.00, 5.26)	(2.13, 4.03)
Comparison vs Placebo*		
Hazard ratio		0.68
95% confidence interval		(0.45,1.05)
p-value		0.0797
Baseline use of ARNi: Yes		
Number of patients in analysis set	387	340
Number of analysed patients	231	214
Number of patients with event [N(%)]	10 (4.3)	9 (4.2)
Time at risk for event [years]	279.7	265.0
Incidence rate [patients with events per 100 patient years at risk]	3.57	3.40
95% confidence interval	(1.71, 6.11)	(1.55, 5.95)
Comparison vs Placebo*		
Hazard ratio		0.96
95% confidence interval		(0.39,2.37)
p-value		0.9275

* Based on a Cox regression model with terms for age (p=0.0042), baseline eGFR (CKD-EPI) (p=0.5113), sex (p=0.6092), region (p=0.0009), baseline diabetes status (3 cat.) (p=0.4302), baseline LVEF (3 cat.) (p=0.6670), Treatment (p=0.4086), baseline use of ARNi (p=0.4571) and Treatment by baseline use of ARNi interaction (p=0.5077).

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

R.1.1.22.15 Subgroup analysis by bl. LVEF (<= 30%, >30% -<= 35% , > 35%)

Table R.1.1.22.15: 1 Cox regr. for time to new onset of atrial fibrillation by bl. LVEF (3 cat.) - RS (trial 1245.121)

Subgroup Description	Placebo	Empa 10mg
Baseline LVEF: <=30		
Number of patients in analysis set	1392	1337
Number of analysed patients	878	871
Number of patients with event [N(%)]	45 (5.1)	37 (4.2)
Time at risk for event [years]	1128.7	1121.8
Incidence rate [patients with events per 100 patient years at risk]	3.99	3.30
95% confidence interval	(2.91, 5.23)	(2.32, 4.44)
Comparison vs Placebo*		
Hazard ratio		0.78
95% confidence interval		(0.51, 1.21)
p-value		0.2691
Baseline LVEF: >30 to <=35		
Number of patients in analysis set	361	398
Number of analysed patients	215	243
Number of patients with event [N(%)]	13 (6.0)	6 (2.5)
Time at risk for event [years]	276.4	301.5
Incidence rate [patients with events per 100 patient years at risk]	4.70	1.99
95% confidence interval	(2.50, 7.58)	(0.73, 3.87)
Comparison vs Placebo*		
Hazard ratio		0.38
95% confidence interval		(0.15, 1.01)
p-value		0.0531

* Based on a Cox regression model with terms for age (p=0.0049), baseline eGFR (CKD-EPI) (p=0.5119), sex (p=0.5703), region (p=0.0010), baseline diabetes status (3 cat.) (p=0.4606), Treatment (p=0.9227), baseline LVEF (3 cat.) (p=0.4861) and Treatment by baseline LVEF (3 cat.) interaction (p=0.1882).
The p-value for treatment by subgroup interaction trend test is 0.9610.

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

Table R.1.1.22.15: 1 Cox regr. for time to new onset of atrial fibrillation by bl. LVEF (3 cat.) - RS (trial 1245.121)

Subgroup Description	Placebo	Empa 10mg
Baseline LVEF: >35		
Number of patients in analysis set	114	128
Number of analysed patients	69	85
Number of patients with event [N(%)]	1 (1.4)	4 (4.7)
Time at risk for event [years]	84.8	105.8
Incidence rate [patients with events per 100 patient years at risk]	1.18	3.78
95% confidence interval	(0.03, 4.35)	(1.03, 8.29)
Comparison vs Placebo*		
Hazard ratio		2.95
95% confidence interval		(0.33,26.43)
p-value		0.3333

* Based on a Cox regression model with terms for age (p=0.0049), baseline eGFR (CKD-EPI) (p=0.5119), sex (p=0.5703), region (p=0.0010), baseline diabetes status (3 cat.) (p=0.4606), Treatment (p=0.9227), baseline LVEF (3 cat.) (p=0.4861) and Treatment by baseline LVEF (3 cat.) interaction (p=0.1882).
The p-value for treatment by subgroup interaction trend test is 0.9610.

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

R.1.1.22.16 Subgroup analysis by bl. NTproBNP </>= median (median based on total patients)

Table R.1.1.22.16: 1 Cox regr. for time to new onset of atrial fibrillation by bl. NTproBNP (<median,>= median) (median based on total patients) - RS (trial 1245.121)

Subgroup Description	Placebo	Empa 10mg
Baseline NTproBNP: < median		
Number of patients in analysis set	920	942
Number of analysed patients	643	667
Number of patients with event [N(%)]	30 (4.7)	25 (3.7)
Time at risk for event [years]	855.6	879.0
Incidence rate [patients with events per 100 patient years at risk]	3.51	2.84
95% confidence interval	(2.37, 4.87)	(1.84, 4.06)
Comparison vs Placebo*		
Hazard ratio		0.77
95% confidence interval		(0.45,1.31)
p-value		0.3328
Baseline NTproBNP: >= median		
Number of patients in analysis set	946	920
Number of analysed patients	518	531
Number of patients with event [N(%)]	29 (5.6)	22 (4.1)
Time at risk for event [years]	633.4	648.8
Incidence rate [patients with events per 100 patient years at risk]	4.58	3.39
95% confidence interval	(3.07, 6.39)	(2.12, 4.95)
Comparison vs Placebo*		
Hazard ratio		0.69
95% confidence interval		(0.40,1.21)
p-value		0.1954

* Based on a Cox regression model with terms for age (p=0.0042), baseline eGFR (CKD-EPI) (p=0.3998), sex (p=0.5851), region (p=0.0009), baseline diabetes status (3 cat.) (p=0.4536), baseline LVEF (3 cat.) (p=0.6412), Treatment (p=0.1086), baseline NTproBNP (2 cat.) (p=0.2006) and Treatment by baseline NTproBNP (2 cat.) interaction (p=0.7878).
2 patients were excluded as the subgroup variable was missing.

Patients included in analysis are those with neither history of atrial fibrillation (AF) nor pre-treatment ECG indicating AF.
Median: 1910 [pg/mL]

R.1.1.23 Time to first acute kidney injury (based on MedDRA preferred term)

R.1.1.23.1

Figure R.1.1.23.1: 1

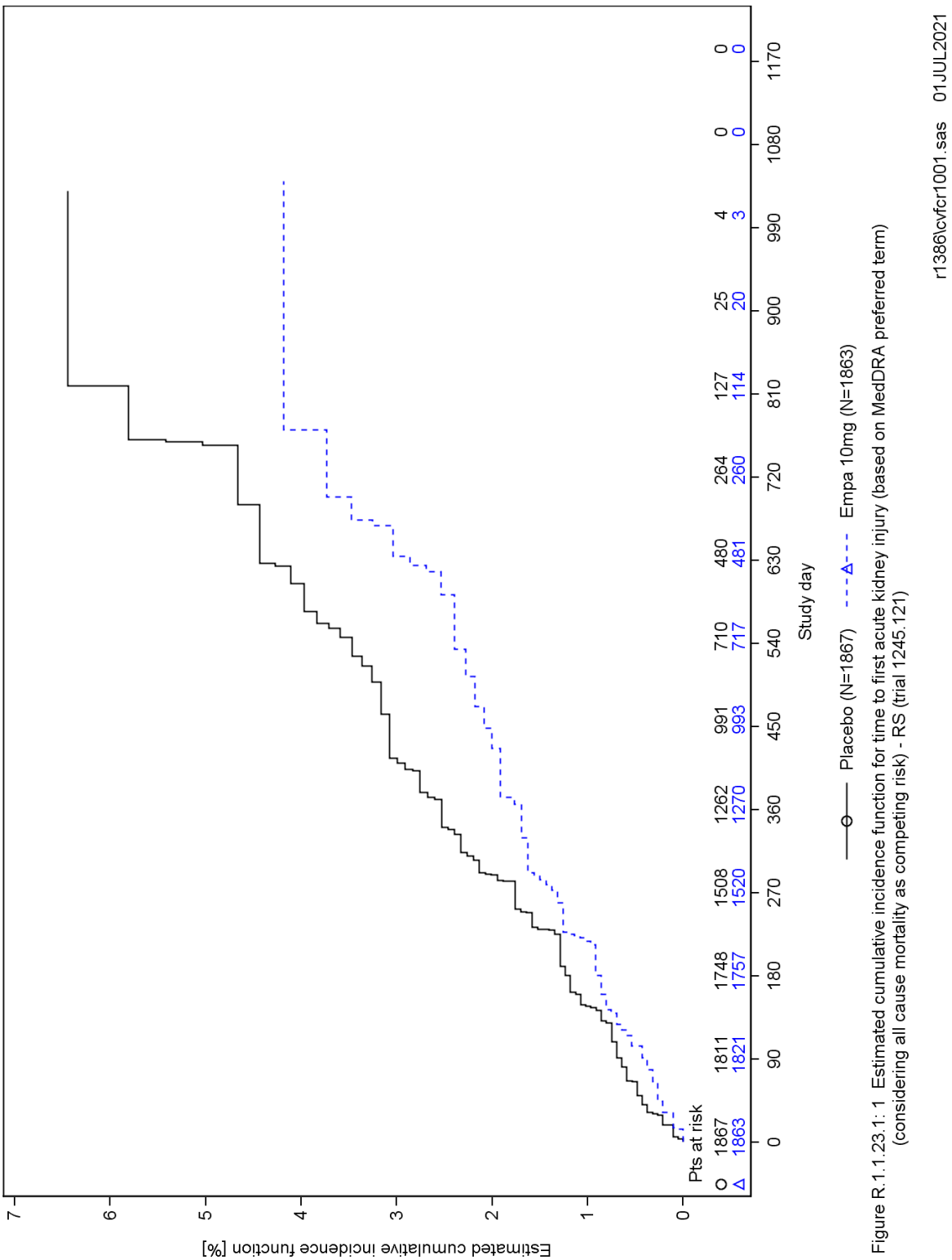

Figure R.1.1.23.1: 1 Estimated cumulative incidence function for time to first acute kidney injury (based on MedDRA preferred term) (considering all cause mortality as competing risk) - RS (trial 1245.121)

Table R.1.1.23.1: 1 Cox regr. for time to first acute kidney injury (based on MedDRA preferred term) - RS (trial 1245.121)

	Placebo	Empa 10mg
Number of patients in analysis set	1867	1863
Number of analysed patients	1867	1863
Number of patients with event [N(%)]	67 (3.6)	46 (2.5)
Time at risk for event [years]	2426.3	2433.8
Incidence rate [patients with events per 100 patient years at risk]	2.76	1.89
95% confidence interval	(2.14, 3.46)	(1.38, 2.47)
Comparison vs Placebo*		
Hazard ratio		0.66
95% confidence interval		(0.45,0.96)
p-value		0.0315
Time to event [days]**		
2.5% percentile	333	533
5.0% percentile	690	NC.
7.5% percentile	NC.	NC.
10.0% percentile	NC.	NC.
Patients with events [%]**		
1 year	2.6	1.8
2 years	5.1	4.1

* Based on a Cox regression model with terms for age (p=0.4232), baseline eGFR (CKD-EPI) (p=0.0003), sex (p=0.7355), region (p<0.0001), baseline diabetes status (3 cat.) (p=0.6928), baseline LVEF (3 cat.) (p=0.9937) and Treatment (p=0.0315).
**Based on Kaplan-Meier estimates.
NC. = Not calculated.

R.1.1.23.2

R.1.1.23.2 Subgroup analysis by sex

Table R.1.1.23.2: 1

Table R.1.1.23.2: 1 Cox regr. for time to first acute kidney injury (based on MedDRA preferred term) by sex - RS (trial 1245.121)

Subgroup Description	Placebo	Empa 10mg
Sex: Male		
Number of patients in analysis set	1411	1426
Number of analysed patients	1411	1426
Number of patients with event [N(%)]	52 (3.7)	34 (2.4)
Time at risk for event [years]	1839.8	1855.2
Incidence rate [patients with events per 100 patient years at risk]	2.83	1.83
95% confidence interval	(2.11, 3.64)	(1.27, 2.50)
Comparison vs Placebo*		
Hazard ratio		0.63
95% confidence interval		(0.41,0.97)
p-value		0.0374
Sex: Female		
Number of patients in analysis set	456	437
Number of analysed patients	456	437
Number of patients with event [N(%)]	15 (3.3)	12 (2.7)
Time at risk for event [years]	586.5	578.6
Incidence rate [patients with events per 100 patient years at risk]	2.56	2.07
95% confidence interval	(1.43, 4.01)	(1.07, 3.40)
Comparison vs Placebo*		
Hazard ratio		0.77
95% confidence interval		(0.36,1.64)
p-value		0.4948

* Based on a Cox regression model with terms for age (p=0.4307), baseline eGFR (CKD-EPI) (p=0.0003), region (p<0.0001), baseline diabetes status (3 cat.) (p=0.6947), baseline LVEF (3 cat.) (p=0.9922), Treatment (p=0.1044), sex (p=0.7903) and Treatment by sex interaction (p=0.6614).

R.1.1.23.3

Table R.1.1.23.3: 1 Cox regr. for time to first acute kidney injury (based on MedDRA preferred term) by age (2 cat.) - RS (trial 1245.121)

Subgroup Description	Placebo	Empa 10mg
Age [years]: < 65		
Number of patients in analysis set	740	675
Number of analysed patients	740	675
Number of patients with event [N(%)]	26 (3.5)	18 (2.7)
Time at risk for event [years]	964.5	871.1
Incidence rate [patients with events per 100 patient years at risk]	2.70	2.07
95% confidence interval	(1.76, 3.83)	(1.22, 3.12)
Comparison vs Placebo*		
Hazard ratio		0.77
95% confidence interval		(0.42,1.40)
p-value		0.3853
Age [years]: >= 65		
Number of patients in analysis set	1127	1188
Number of analysed patients	1127	1188
Number of patients with event [N(%)]	41 (3.6)	28 (2.4)
Time at risk for event [years]	1461.8	1562.7
Incidence rate [patients with events per 100 patient years at risk]	2.80	1.79
95% confidence interval	(2.01, 3.73)	(1.19, 2.51)
Comparison vs Placebo*		
Hazard ratio		0.61
95% confidence interval		(0.38,0.99)
p-value		0.0445

* Based on a Cox regression model with terms for baseline eGFR (CKD-EPI) (p<0.0001), sex (p=0.7031), region (p<0.0001), baseline diabetes status (3 cat.) (p=0.6763), baseline LVEF (3 cat.) (p=0.9914), Treatment (p=0.0533), age (2 cat.) (p=0.0332) and Treatment by age (2 cat.) interaction (p=0.5662).

R.1.1.23.4 Subgroup analysis by region (North America, Latin America, Europe, Asia, Other)

Table R.1.1.23.4: 1 Cox regr. for time to first acute kidney injury (based on MedDRA preferred term) by region - RS (trial 1245.121)

Subgroup Description	Placebo	Empa 10mg
Region: North America		
Number of patients in analysis set	213	212
Number of analysed patients	213	212
Number of patients with event [N(%)]	22 (10.3)	19 (9.0)
Time at risk for event [years]	274.8	297.5
Incidence rate [patients with events per 100 patient years at risk]	8.00	6.39
95% confidence interval	(5.02, 11.68)	(3.85, 9.56)
Comparison vs Placebo*		
Hazard ratio		0.78
95% confidence interval		(0.42, 1.45)
p-value		0.4376
Region: Latin America		
Number of patients in analysis set	645	641
Number of analysed patients	645	641
Number of patients with event [N(%)]	20 (3.1)	12 (1.9)
Time at risk for event [years]	764.0	758.2
Incidence rate [patients with events per 100 patient years at risk]	2.62	1.58
95% confidence interval	(1.60, 3.88)	(0.82, 2.60)
Comparison vs Placebo*		
Hazard ratio		0.61
95% confidence interval		(0.30, 1.25)
p-value		0.1750

* Based on a Cox regression model with terms for age (p=0.4125), baseline eGFR (CKD-EPI) (p=0.0003), sex (p=0.7045), baseline diabetes status (3 cat.) (p=0.7007), baseline LVEF (3 cat.) (p=0.9968), Treatment (p=0.9796), region (p<0.0001) and Treatment by region interaction (p=0.9793).
NC. = Not calculated, some results could not be produced.

Table R.1.1.23.4: 1 Cox regr. for time to first acute kidney injury (based on MedDRA preferred term) by region - RS (trial 1245.121)

Subgroup Description	Placebo	Empa 10mg
Region: Europe		
Number of patients in analysis set	677	676
Number of analysed patients	677	676
Number of patients with event [N(%)]	22 (3.2)	14 (2.1)
Time at risk for event [years]	922.4	918.5
Incidence rate [patients with events per 100 patient years at risk]	2.39	1.52
95% confidence interval	(1.49, 3.48)	(0.83, 2.42)
Comparison vs Placebo*		
Hazard ratio		0.62
95% confidence interval		(0.32, 1.22)
p-value		0.1685
Region: Asia		
Number of patients in analysis set	245	248
Number of analysed patients	245	248
Number of patients with event [N(%)]	1 (0.4)	1 (0.4)
Time at risk for event [years]	349.4	346.4
Incidence rate [patients with events per 100 patient years at risk]	0.29	0.29
95% confidence interval	(0.01, 1.06)	(0.01, 1.06)
Comparison vs Placebo*		
Hazard ratio		1.02
95% confidence interval		(0.06,16.35)
p-value		0.9873

* Based on a Cox regression model with terms for age (p=0.4125), baseline eGFR (CKD-EPI) (p=0.0003), sex (p=0.7045), baseline diabetes status (3 cat.) (p=0.7007), baseline LVEF (3 cat.) (p=0.9968), Treatment (p=0.9796), region (p<0.0001) and Treatment by region interaction (p=0.9793).
NC. = Not calculated, some results could not be produced.

Table R.1.1.23.4: 1 Cox regr. for time to first acute kidney injury (based on MedDRA preferred term) by region - RS (trial 1245.121)

Subgroup Description	Placebo	Empa 10mg
Region: Other		
Number of patients in analysis set	87	86
Number of analysed patients	87	86
Number of patients with event [N(%)]	2 (2.3)	0
Time at risk for event [years]	115.6	113.1
Incidence rate [patients with events per 100 patient years at risk]	1.73	0.00
95% confidence interval	(0.21, 4.82)	NC.
Comparison vs Placebo*		
Hazard ratio		NC.
95% confidence interval		NC.
p-value		NC.

* Based on a Cox regression model with terms for age (p=0.4125), baseline eGFR (CKD-EPI) (p=0.0003), sex (p=0.7045), baseline diabetes status (3 cat.) (p=0.7007), baseline LVEF (3 cat.) (p=0.9968), Treatment (p=0.9796), region (p<0.0001) and Treatment by region interaction (p=0.9793).
NC. = Not calculated, some results could not be produced.

R.1.1.23.5

R.1.1.23.5 Subgroup analysis by OECD member (Y/N)

Table R.1.1.23.5: 1 Cox regr. for time to first acute kidney injury (based on MedDRA preferred term) by OECD member (Y/N) - RS (trial 1245.121)

Subgroup Description	Placebo	Empa 10mg
OECD member: No		
Number of patients in analysis set	741	713
Number of analysed patients	741	713
Number of patients with event [N(%)]	18 (2.4)	11 (1.5)
Time at risk for event [years]	891.0	853.4
Incidence rate [patients with events per 100 patient years at risk]	2.02	1.29
95% confidence interval	(1.20, 3.05)	(0.64, 2.16)
Comparison vs Placebo*		
Hazard ratio		0.65
95% confidence interval		(0.31,1.38)
p-value		0.2603
OECD member: Yes		
Number of patients in analysis set	1126	1150
Number of analysed patients	1126	1150
Number of patients with event [N(%)]	49 (4.4)	35 (3.0)
Time at risk for event [years]	1535.2	1580.4
Incidence rate [patients with events per 100 patient years at risk]	3.19	2.21
95% confidence interval	(2.36, 4.15)	(1.54, 3.01)
Comparison vs Placebo*		
Hazard ratio		0.68
95% confidence interval		(0.44,1.06)
p-value		0.0858

* Based on a Cox regression model with terms for age (p=0.2913), baseline eGFR (CKD-EPI) (p<0.0001), sex (p=0.9590), baseline diabetes status (3 cat.) (p=0.6521), baseline LVEF (3 cat.) (p=0.9302), Treatment (p=0.0664), OECD Member (N) (p=0.0794) and Treatment by OECD Member (N) interaction (p=0.9089).

OECD member (yes/no) countries included:
Yes: United States, Canada, Mexico, Poland, Netherlands, Hungary, Germany, Czech Republic, Italy, France, Spain, United Kingdom, Belgium, Japan, Australia, 'Korea; Republic Of South Korea';
No: Brazil, Argentina, China, India.

R.1.1.23.6

R.1.1.23.6 Subgroup analysis by NYHA at baseline (II, III/IV - 2 cat.)

Table R.1.1.23.6: 1 Cox regr. for time to first acute kidney injury (based on MedDRA preferred term) by baseline NYHA (2 cat.) - RS (trial 1245.121)

Subgroup Description	Placebo	Empa 10mg
Baseline NYHA: II		
Number of patients in analysis set	1401	1399
Number of analysed patients	1401	1399
Number of patients with event [N(%)]	41 (2.9)	32 (2.3)
Time at risk for event [years]	1841.4	1829.2
Incidence rate [patients with events per 100 patient years at risk]	2.23	1.75
95% confidence interval	(1.60, 2.96)	(1.20, 2.41)
Comparison vs Placebo*		
Hazard ratio		0.76
95% confidence interval		(0.48,1.20)
p-value		0.2393
Baseline NYHA: III/IV		
Number of patients in analysis set	466	464
Number of analysed patients	466	464
Number of patients with event [N(%)]	26 (5.6)	14 (3.0)
Time at risk for event [years]	584.8	604.6
Incidence rate [patients with events per 100 patient years at risk]	4.45	2.32
95% confidence interval	(2.90, 6.31)	(1.27, 3.68)
Comparison vs Placebo*		
Hazard ratio		0.51
95% confidence interval		(0.27,0.98)
p-value		0.0424

* Based on a Cox regression model with terms for age (p=0.4031), baseline eGFR (CKD-EPI) (p=0.0004), sex (p=0.6867), region (p<0.0001), baseline diabetes status (3 cat.) (p=0.6621), baseline LVEF (3 cat.) (p=0.9903), Treatment (p=0.0195), baseline NYHA (2 cat.) (p=0.0921) and Treatment by baseline NYHA (2 cat.) interaction (p=0.3318).

R.1.1.23.7

R.1.1.23.7 Subgroup analysis by diabetes at baseline

Table R.1.1.23.7: 1 Cox regr. for time to first acute kidney injury (based on MedDRA preferred term) by diabetes at baseline (2 cat.) - RS (trial 1245.121)

Subgroup Description	Placebo	Empa 10mg
Baseline diabetes status: Diabetic		
Number of patients in analysis set	929	927
Number of analysed patients	929	927
Number of patients with event [N(%)]	33 (3.6)	26 (2.8)
Time at risk for event [years]	1219.2	1215.7
Incidence rate [patients with events per 100 patient years at risk]	2.71	2.14
95% confidence interval	(1.86, 3.71)	(1.40, 3.04)
Comparison vs Placebo*		
Hazard ratio		0.77
95% confidence interval		(0.46,1.28)
p-value		0.3122
Baseline diabetes status: Non-Diabetic		
Number of patients in analysis set	938	936
Number of analysed patients	938	936
Number of patients with event [N(%)]	34 (3.6)	20 (2.1)
Time at risk for event [years]	1207.1	1218.0
Incidence rate [patients with events per 100 patient years at risk]	2.82	1.64
95% confidence interval	(1.95, 3.84)	(1.00, 2.44)
Comparison vs Placebo*		
Hazard ratio		0.56
95% confidence interval		(0.32,0.98)
p-value		0.0410

* Based on a Cox regression model with terms for age (p=0.4663), baseline eGFR (CKD-EPI) (p=0.0003), sex (p=0.7198), region (p<0.0001), baseline LVEF (3 cat.) (p=0.9926), Treatment (p=0.0291), baseline diabetes status (2 cat.) (p=0.7194) and Treatment by baseline diabetes status (2 cat.) interaction (p=0.4184).

R.1.1.23.8 Subgroup analysis by BMI at baseline (<30, >=30)

Table R.1.1.23.8: 1 Cox regr. for time to first acute kidney injury (based on MedDRA preferred term) by baseline BMI [kg/m2] - RS (trial 1245.121)

Subgroup Description	Placebo	Empa 10mg
Baseline BMI [kg/m²]: <30		
Number of patients in analysis set	1300	1263
Number of analysed patients	1300	1263
Number of patients with event [N(%)]	40 (3.1)	27 (2.1)
Time at risk for event [years]	1711.2	1641.3
Incidence rate [patients with events per 100 patient years at risk]	2.34	1.65
95% confidence interval	(1.67, 3.12)	(1.08, 2.32)
Comparison vs Placebo*		
Hazard ratio		0.70
95% confidence interval		(0.43,1.14)
p-value		0.1473
Baseline BMI [kg/m²]: >=30		
Number of patients in analysis set	567	600
Number of analysed patients	567	600
Number of patients with event [N(%)]	27 (4.8)	19 (3.2)
Time at risk for event [years]	715.0	792.4
Incidence rate [patients with events per 100 patient years at risk]	3.78	2.40
95% confidence interval	(2.49, 5.33)	(1.44, 3.59)
Comparison vs Placebo*		
Hazard ratio		0.60
95% confidence interval		(0.33,1.08)
p-value		0.0860

* Based on a Cox regression model with terms for age (p=0.5486), baseline eGFR (CKD-EPI) (p=0.0003), sex (p=0.6886), region (p<0.0001), baseline diabetes status (3 cat.) (p=0.7131), baseline LVEF (3 cat.) (p=0.9970), Treatment (p=0.0249), baseline BMI (2 cat.) (p=0.3195) and Treatment by baseline BMI (2 cat.) interaction (p=0.6923).

R.1.1.23.9

R.1.1.23.9 Subgroup analysis by eGFR at baseline (<60, >=60)

Table R.1.1.23.9: 1 Cox regr. for time to first acute kidney injury (based on MedDRA preferred term) by baseline eGFR (2 cat.) - RS (trial 1245.121)

Subgroup Description	Placebo	Empa 10mg
Baseline eGFR (CKD-EPI) [mL/min/1.73m²]: >=60		
Number of patients in analysis set	960	969
Number of analysed patients	960	969
Number of patients with event [N(%)]	26 (2.7)	17 (1.8)
Time at risk for event [years]	1251.9	1263.4
Incidence rate [patients with events per 100 patient years at risk]	2.08	1.35
95% confidence interval	(1.36, 2.95)	(0.78, 2.06)
Comparison vs Placebo*		
Hazard ratio		0.63
95% confidence interval		(0.34,1.16)
p-value		0.1374
Baseline eGFR (CKD-EPI) [mL/min/1.73m²]: <60		
Number of patients in analysis set	906	893
Number of analysed patients	906	893
Number of patients with event [N(%)]	41 (4.5)	29 (3.2)
Time at risk for event [years]	1173.5	1169.2
Incidence rate [patients with events per 100 patient years at risk]	3.49	2.48
95% confidence interval	(2.51, 4.64)	(1.66, 3.46)
Comparison vs Placebo*		
Hazard ratio		0.70
95% confidence interval		(0.43,1.12)
p-value		0.1382

* Based on a Cox regression model with terms for age (p=0.9452), sex (p=0.7948), region (p<0.0001), baseline diabetes status (3 cat.) (p=0.6125), baseline LVEF (3 cat.) (p=0.9978), Treatment (p=0.0375), baseline eGFR (CKD-EPI) (2 cat.) (p=0.0327) and Treatment by baseline eGFR (CKD-EPI) (2 cat.) interaction (p=0.7932).
2 patients were excluded as the subgroup variable was missing.

R.1.1.23.10

Table R.1.1.23.10: 1 Cox regr. for time to first acute kidney injury (based on MedDRA preferred term) by history of HHF within 12 months - RS (trial 1245.121)

Subgroup Description	Placebo	Empa 10mg
History of HHF (in the last 12 months): No		
Number of patients in analysis set	1293	1286
Number of analysed patients	1293	1286
Number of patients with event [N(%)]	42 (3.2)	32 (2.5)
Time at risk for event [years]	1732.4	1714.1
Incidence rate [patients with events per 100 patient years at risk]	2.42	1.87
95% confidence interval	(1.75, 3.21)	(1.28, 2.57)
Comparison vs Placebo*		
Hazard ratio		0.75
95% confidence interval		(0.47,1.19)
p-value		0.2173
History of HHF (in the last 12 months): Yes		
Number of patients in analysis set	574	577
Number of analysed patients	574	577
Number of patients with event [N(%)]	25 (4.4)	14 (2.4)
Time at risk for event [years]	693.9	719.6
Incidence rate [patients with events per 100 patient years at risk]	3.60	1.95
95% confidence interval	(2.33, 5.15)	(1.06, 3.09)
Comparison vs Placebo*		
Hazard ratio		0.51
95% confidence interval		(0.26,0.98)
p-value		0.0431

* Based on a Cox regression model with terms for age (p=0.5641), baseline eGFR (CKD-EPI) (p=0.0003), sex (p=0.7718), region (p<0.0001), baseline diabetes status (3 cat.) (p=0.7188), baseline LVEF (3 cat.) (p=0.9617), Treatment (p=0.0182), history of HHF (p=0.1467) and Treatment by history of HHF interaction (p=0.3420).

R.1.1.23.11

Table R.1.1.23.11: 1 Cox regr. for time to first acute kidney injury (based on MedDRA preferred term) by cause of heart failure - RS (trial 1245.121)

Subgroup Description	Placebo	Empa 10mg
Cause of heart failure: Ischemic		
Number of patients in analysis set	946	983
Number of analysed patients	946	983
Number of patients with event [N(%)]	35 (3.7)	29 (3.0)
Time at risk for event [years]	1249.6	1292.3
Incidence rate [patients with events per 100 patient years at risk]	2.80	2.24
95% confidence interval	(1.95, 3.80)	(1.50, 3.13)
Comparison vs Placebo*		
Hazard ratio		0.78
95% confidence interval		(0.48,1.28)
p-value		0.3268
Cause of heart failure: Non-ischemic		
Number of patients in analysis set	921	880
Number of analysed patients	921	880
Number of patients with event [N(%)]	32 (3.5)	17 (1.9)
Time at risk for event [years]	1176.6	1141.4
Incidence rate [patients with events per 100 patient years at risk]	2.72	1.49
95% confidence interval	(1.86, 3.74)	(0.87, 2.28)
Comparison vs Placebo*		
Hazard ratio		0.53
95% confidence interval		(0.29,0.95)
p-value		0.0326

* Based on a Cox regression model with terms for age (p=0.4050), baseline eGFR (CKD-EPI) (p=0.0003), sex (p=0.7720), region (p<0.0001), baseline diabetes status (3 cat.) (p=0.7307), baseline LVEF (3 cat.) (p=0.9915), Treatment (p=0.0233), cause of heart failure (2 cat.) (p=0.3855) and Treatment by cause of heart failure (2 cat.) interaction (p=0.3123).

R.1.1.23.12 Subgroup analysis by heart failure physiology (LVEF <= 30% and NTproBNP<median; LVEF <= 30% and NTproBNP>=median; LVEF > 30%)

Table R.1.1.23.12: 1 Cox regr. for time to first acute kidney injury (based on MedDRA preferred term) by heart failure physiology - RS (trial 1245.121)

Subgroup Description	Placebo	Empa 10mg
Heart failure physiology: LVEF <= 30% and NTproBNP < median		
Number of patients in analysis set	723	698
Number of analysed patients	723	698
Number of patients with event [N(%)]	15 (2.1)	13 (1.9)
Time at risk for event [years]	974.2	941.7
Incidence rate [patients with events per 100 patient years at risk]	1.54	1.38
95% confidence interval	(0.86, 2.41)	(0.74, 2.23)
Comparison vs Placebo*		
Hazard ratio		0.91
95% confidence interval		(0.43,1.92)
p-value		0.8141
Heart failure physiology: LVEF <= 30% and NTproBNP >= median		
Number of patients in analysis set	661	631
Number of analysed patients	661	631
Number of patients with event [N(%)]	36 (5.4)	20 (3.2)
Time at risk for event [years]	839.8	811.5
Incidence rate [patients with events per 100 patient years at risk]	4.29	2.46
95% confidence interval	(3.00, 5.80)	(1.51, 3.66)
Comparison vs Placebo*		
Hazard ratio		0.54
95% confidence interval		(0.31,0.94)
p-value		0.0281

* Based on a Cox regression model with terms for age (p=0.4294), baseline eGFR (CKD-EPI) (p=0.0017), sex (p=0.7861), region (p<0.0001), baseline diabetes status (3 cat.) (p=0.6688), Treatment (p=0.0674), heart failure physiology (p=0.0125) and Treatment by heart failure physiology interaction (p=0.5357).
16 patients were excluded as the subgroup variable was missing.
The p-value for treatment by subgroup interaction trend test is 0.5464.

Table R.1.1.23.12: 1 Cox regr. for time to first acute kidney injury (based on MedDRA preferred term) by heart failure physiology - RS (trial 1245.121)

Subgroup Description	Placebo	Empa 10mg
Heart failure physiology: LVEF > 30%		
Number of patients in analysis set	475	526
Number of analysed patients	475	526
Number of patients with event [N(%)]	16 (3.4)	13 (2.5)
Time at risk for event [years]	601.9	673.0
Incidence rate [patients with events per 100 patient years at risk]	2.66	1.93
95% confidence interval	(1.52, 4.11)	(1.03, 3.11)
Comparison vs Placebo*		
Hazard ratio		0.67
95% confidence interval		(0.32,1.40)
p-value		0.2890

* Based on a Cox regression model with terms for age (p=0.4294), baseline eGFR (CKD-EPI) (p=0.0017), sex (p=0.7861), region (p<0.0001), baseline diabetes status (3 cat.) (p=0.6688), Treatment (p=0.0674), heart failure physiology (p=0.0125) and Treatment by heart failure physiology interaction (p=0.5357).
16 patients were excluded as the subgroup variable was missing.
The p-value for treatment by subgroup interaction trend test is 0.5464.

R.1.1.23.13

R.1.1.23.13 Subgroup analysis by baseline use of MRA

Table R.1.1.23.13: 1 Cox regr. for time to first acute kidney injury (based on MedDRA preferred term) by baseline use of MRA - RS (trial 1245.121)

Subgroup Description	Placebo	Empa 10mg
Baseline use of MRA: No		
Number of patients in analysis set	512	557
Number of analysed patients	512	557
Number of patients with event [N(%)]	21 (4.1)	18 (3.2)
Time at risk for event [years]	680.7	760.7
Incidence rate [patients with events per 100 patient years at risk]	3.09	2.37
95% confidence interval	(1.91, 4.54)	(1.40, 3.58)
Comparison vs Placebo*		
Hazard ratio		0.76
95% confidence interval		(0.40,1.43)
p-value		0.3939
Baseline use of MRA: Yes		
Number of patients in analysis set	1355	1306
Number of analysed patients	1355	1306
Number of patients with event [N(%)]	46 (3.4)	28 (2.1)
Time at risk for event [years]	1745.6	1673.1
Incidence rate [patients with events per 100 patient years at risk]	2.64	1.67
95% confidence interval	(1.93, 3.45)	(1.11, 2.35)
Comparison vs Placebo*		
Hazard ratio		0.61
95% confidence interval		(0.38,0.98)
p-value		0.0422

* Based on a Cox regression model with terms for age (p=0.4379), baseline eGFR (CKD-EPI) (p=0.0003), sex (p=0.7274), region (p<0.0001), baseline diabetes status (3 cat.) (p=0.6864), baseline LVEF (3 cat.) (p=0.9961), Treatment (p=0.0576), baseline use of MRA (p=0.8915) and Treatment by baseline use of MRA interaction (p=0.5930).

R.1.1.23.14

Table R.1.1.23.14: 1 Cox regr. for time to first acute kidney injury (based on MedDRA preferred term) by baseline use of ARNi - RS (trial 1245.121)

Subgroup Description	Placebo	Empa 10mg
Baseline use of ARNi: No		
Number of patients in analysis set	1480	1523
Number of analysed patients	1480	1523
Number of patients with event [N(%)]	44 (3.0)	33 (2.2)
Time at risk for event [years]	1945.3	2025.0
Incidence rate [patients with events per 100 patient years at risk]	2.26	1.63
95% confidence interval	(1.64, 2.98)	(1.12, 2.23)
Comparison vs Placebo*		
Hazard ratio		0.67
95% confidence interval		(0.43,1.06)
p-value		0.0848
Baseline use of ARNi: Yes		
Number of patients in analysis set	387	340
Number of analysed patients	387	340
Number of patients with event [N(%)]	23 (5.9)	13 (3.8)
Time at risk for event [years]	480.9	408.8
Incidence rate [patients with events per 100 patient years at risk]	4.78	3.18
95% confidence interval	(3.03, 6.93)	(1.69, 5.13)
Comparison vs Placebo*		
Hazard ratio		0.71
95% confidence interval		(0.36,1.41)
p-value		0.3264

* Based on a Cox regression model with terms for age (p=0.4411), baseline eGFR (CKD-EPI) (p=0.0003), sex (p=0.7033), region (p<0.0001), baseline diabetes status (3 cat.) (p=0.6399), baseline LVEF (3 cat.) (p=0.9970), Treatment (p=0.0764), baseline use of ARNi (p=0.0253) and Treatment by baseline use of ARNi interaction (p=0.8921).

R.1.1.23.15 Subgroup analysis by bl. LVEF (<= 30%, >30% -<= 35% , > 35%)

Table R.1.1.23.15: 1 Cox regr. for time to first acute kidney injury (based on MedDRA preferred term) by bl. LVEF (3 cat.) - RS (trial 1245.121)

Subgroup Description	Placebo	Empa 10mg
Baseline LVEF: <=30		
Number of patients in analysis set	1392	1337
Number of analysed patients	1392	1337
Number of patients with event [N(%)]	51 (3.7)	33 (2.5)
Time at risk for event [years]	1824.3	1760.8
Incidence rate [patients with events per 100 patient years at risk]	2.80	1.87
95% confidence interval	(2.08, 3.61)	(1.29, 2.57)
Comparison vs Placebo*		
Hazard ratio		0.66
95% confidence interval		(0.42,1.02)
p-value		0.0614
Baseline LVEF: >30 to <=35		
Number of patients in analysis set	361	398
Number of analysed patients	361	398
Number of patients with event [N(%)]	13 (3.6)	9 (2.3)
Time at risk for event [years]	463.2	515.5
Incidence rate [patients with events per 100 patient years at risk]	2.81	1.75
95% confidence interval	(1.49, 4.53)	(0.80, 3.06)
Comparison vs Placebo*		
Hazard ratio		0.53
95% confidence interval		(0.23,1.24)
p-value		0.1445

* Based on a Cox regression model with terms for age (p=0.4005), baseline eGFR (CKD-EPI) (p=0.0003), sex (p=0.7073), region (p<0.0001), baseline diabetes status (3 cat.) (p=0.6788), Treatment (p=0.4318), baseline LVEF (3 cat.) (p=0.9951) and Treatment by baseline LVEF (3 cat.) interaction (p=0.5428).
The p-value for treatment by subgroup interaction trend test is 0.6449.

Table R.1.1.23.15: 1 Cox regr. for time to first acute kidney injury (based on MedDRA preferred term) by bl. LVEF (3 cat.) - RS (trial 1245.121)

Subgroup Description	Placebo	Empa 10mg
Baseline LVEF: >35		
Number of patients in analysis set	114	128
Number of analysed patients	114	128
Number of patients with event [N(%)]	3 (2.6)	4 (3.1)
Time at risk for event [years]	138.8	157.5
Incidence rate [patients with events per 100 patient years at risk]	2.16	2.54
95% confidence interval	(0.45, 5.21)	(0.69, 5.57)
Comparison vs Placebo*		
Hazard ratio		1.40
95% confidence interval		(0.31,6.30)
p-value		0.6576

* Based on a Cox regression model with terms for age (p=0.4005), baseline eGFR (CKD-EPI) (p=0.0003), sex (p=0.7073), region (p<0.0001), baseline diabetes status (3 cat.) (p=0.6788), Treatment (p=0.4318), baseline LVEF (3 cat.) (p=0.9951) and Treatment by baseline LVEF (3 cat.) interaction (p=0.5428).
The p-value for treatment by subgroup interaction trend test is 0.6449.

R.1.1.23.16 Subgroup analysis by bl. NTproBNP </>= median (median based on total patients)

Table R.1.1.23.16: 1 Cox regr. for time to first acute kidney injury (based on MedDRA preferred term) by bl. NTproBNP (<median,>= median) (median based on total patients) - RS (trial 1245.121)

Subgroup Description	Placebo	Empa 10mg
Baseline NTproBNP: < median		
Number of patients in analysis set	920	942
Number of analysed patients	920	942
Number of patients with event [N(%)]	20 (2.2)	17 (1.8)
Time at risk for event [years]	1243.8	1262.4
Incidence rate [patients with events per 100 patient years at risk]	1.61	1.35
95% confidence interval	(0.98, 2.39)	(0.78, 2.06)
Comparison vs Placebo*		
Hazard ratio		0.81
95% confidence interval		(0.42,1.55)
p-value		0.5219
Baseline NTproBNP: >= median		
Number of patients in analysis set	946	920
Number of analysed patients	946	920
Number of patients with event [N(%)]	47 (5.0)	29 (3.2)
Time at risk for event [years]	1181.5	1170.1
Incidence rate [patients with events per 100 patient years at risk]	3.98	2.48
95% confidence interval	(2.92, 5.19)	(1.66, 3.46)
Comparison vs Placebo*		
Hazard ratio		0.61
95% confidence interval		(0.38,0.96)
p-value		0.0347

* Based on a Cox regression model with terms for age (p=0.3653), baseline eGFR (CKD-EPI) (p=0.0034), sex (p=0.7552), region (p<0.0001), baseline diabetes status (3 cat.) (p=0.6608), baseline LVEF (3 cat.) (p=0.8970), Treatment (p=0.0802), baseline NTproBNP (2 cat.) (p=0.0006) and Treatment by baseline NTproBNP (2 cat.) interaction (p=0.4774).
2 patients were excluded as the subgroup variable was missing.

Median: 1910 [pg/mL]

R.1.1.24

R.1.1.24 Adjudicated hospitalisation for heart failure (first and recurrent)

R.1.1.24.1

Figure R.1.1.24.1: 1

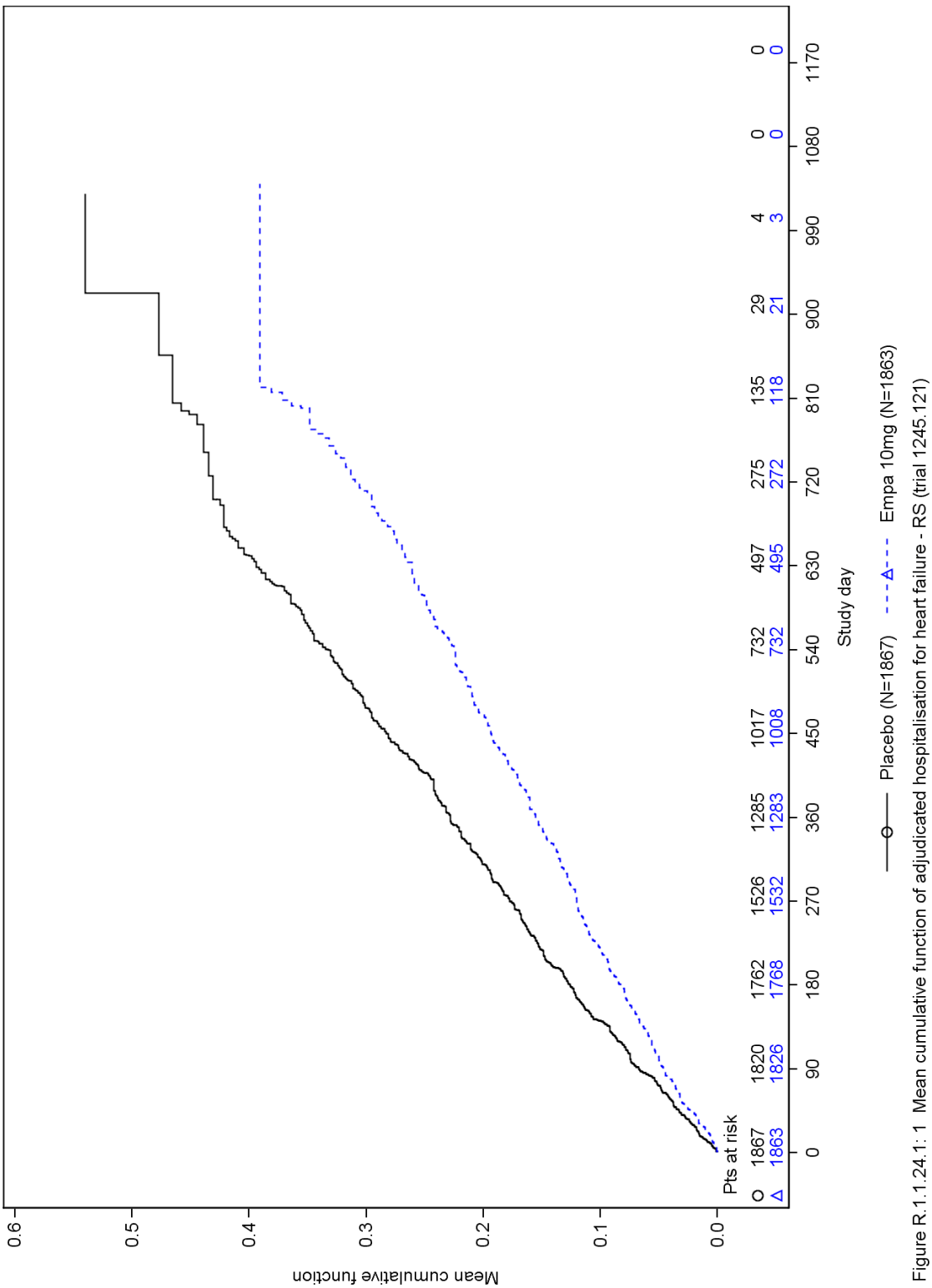

Figure R.1.1.24.1: 1 Mean cumulative function of adjudicated hospitalisation for heart failure - RS (trial 1245.121)

Table R.1.1.24.1: 1 Joint frailty model of adjudicated hospitalisation for heart failure and adjudicated CV death - RS (trial 1245.121)

	Placebo	Empa 10mg
Number of patients in analysis set	1867	1863
Number of analysed patients	1867	1863
Total number of adjudicated hosp. for HF	553	388
Number of patients with adjudicated hosp. for HF then adjudicated CV death [N(%)]	82 (4.4)	72 (3.9)
Number of patients with adjudicated hosp. for HF only [N(%)]	260 (13.9)	174 (9.3)
Number of patients with adjudicated CV death only [N(%)]	120 (6.4)	115 (6.2)
Comparison vs Placebo*		
Hazard ratio of adjudicated hosp. for HF		0.70
95% confidence interval		(0.58,0.85)
95.04% confidence interval		(0.58,0.85)
p-value		0.0003
Hazard ratio of adjudicated CV death		0.90
95% confidence interval		(0.70,1.15)

* Based on an analysis of recurrent events accounting for terminal events using a joint frailty model with terms for age (prec=0.1769/pterm=0.2194), baseline eGFR (CKD-EPI) (prec<0.0001/pterm=0.0107), treatment (prec=0.0003/pterm=0.3967), region (prec<0.0001/pterm=0.0044), baseline diabetes status (prec=0.0015/pterm=0.1465), sex (prec=0.3115/pterm=0.1215), baseline LVEF (prec=0.1036/pterm=0.8475), estimated dependence between adjudicated hosp. for HF and adjudicated CV death (alpha) (1.09) and variance of frailty (omega) (3.71).
pterm=p-value in terminal event model. prec=p-value in recurrent event model.

R.1.1.24.2

R.1.1.24.2 Subgroup analysis by sex

Table R.1.1.24.2: 1 Joint frailty model of adjudicated hospitalisation for heart failure and adjudicated CV death by sex - RS (trial 1245.121)

Subgroup Description	Placebo	Empa 10mg
Sex: Male		
Number of patients in analysis set	1411	1426
Number of analysed patients	1411	1426
Total number of adjudicated hosp. for HF	433	299
Number of patients with adjudicated hosp. for HF then adjudicated CV death [N(%)]	62 (4.4)	59 (4.1)
Number of patients with adjudicated hosp. for HF only [N(%)]	201 (14.2)	140 (9.8)
Number of patients with adjudicated CV death only [N(%)]	90 (6.4)	95 (6.7)
Comparison vs Placebo*		
Hazard ratio of adjudicated hosp. for HF		0.74
95% confidence interval		(0.59,0.92)
p-value		0.0059
Hazard ratio of adjudicated CV death		1.04
95% confidence interval		(0.78,1.38)
Sex: Female		
Number of patients in analysis set	456	437
Number of analysed patients	456	437
Total number of adjudicated hosp. for HF	120	89
Number of patients with adjudicated hosp. for HF then adjudicated CV death [N(%)]	20 (4.4)	13 (3.0)
Number of patients with adjudicated hosp. for HF only [N(%)]	59 (12.9)	34 (7.8)
Number of patients with adjudicated CV death only [N(%)]	30 (6.6)	20 (4.6)
Comparison vs Placebo*		
Hazard ratio of adjudicated hosp. for HF		0.60
95% confidence interval		(0.40,0.89)
p-value		0.0114
Hazard ratio of adjudicated CV death		0.53
95% confidence interval		(0.31,0.93)

* Based on an analysis of recurrent events accounting for terminal events using a joint frailty model with terms for age (prec=0.1794/pterm=0.2080), baseline eGFR (CKD-EPI) (prec<0.0001/pterm=0.0163), sex (prec=0.9158/pterm=0.7589), Treatment (prec=0.0059/pterm=0.8063), Treatment by sex interaction (prec=0.3679/pterm=0.0368), region (prec<0.0001/pterm=0.0051), baseline diabetes status (3 cat.) (prec=0.0014/pterm=0.1438), baseline LVEF (3 cat.) (prec=0.1011/pterm=0.8739), estimated dependence between adjudicated hosp. for HF and adjudicated CV death (alpha) (1.11) and variance of frailty (omega) (3.71).
pterm=p-value in terminal event model. prec=p-value in recurrent event model.

R.1.1.24.3

Table R.1.1.24.3: 1

Table R.1.1.24.3: 1 Joint frailty model of adjudicated hospitalisation for heart failure and adjudicated CV death by age - RS (trial 1245.121)

Subgroup Description	Placebo	Empa 10mg
Age (2 cat.): < 65		
Number of patients in analysis set	740	675
Number of analysed patients	740	675
Total number of adjudicated hosp. for HF	251	137
Number of patients with adjudicated hosp. for HF then adjudicated CV death [N(%)]	29 (3.9)	20 (3.0)
Number of patients with adjudicated hosp. for HF only [N(%)]	121 (16.4)	69 (10.2)
Number of patients with adjudicated CV death only [N(%)]	43 (5.8)	39 (5.8)
Comparison vs Placebo*		
Hazard ratio of adjudicated hosp. for HF		0.62
95% confidence interval		(0.45,0.84)
p-value		0.0020
Hazard ratio of adjudicated CV death		0.93
95% confidence interval		(0.61,1.43)
Age (2 cat.): >= 65		
Number of patients in analysis set	1127	1188
Number of analysed patients	1127	1188
Total number of adjudicated hosp. for HF	302	251
Number of patients with adjudicated hosp. for HF then adjudicated CV death [N(%)]	53 (4.7)	52 (4.4)
Number of patients with adjudicated hosp. for HF only [N(%)]	139 (12.3)	105 (8.8)
Number of patients with adjudicated CV death only [N(%)]	77 (6.8)	76 (6.4)
Comparison vs Placebo*		
Hazard ratio of adjudicated hosp. for HF		0.77
95% confidence interval		(0.60,0.98)
p-value		0.0328
Hazard ratio of adjudicated CV death		0.88
95% confidence interval		(0.64,1.21)

* Based on an analysis of recurrent events accounting for terminal events using a joint frailty model with terms for baseline eGFR (CKD-EPI) (prec<0.0001/pterm=0.0033), Age (2 cat.) (prec=0.0073/pterm=0.3996), Treatment (prec=0.0328/pterm=0.4328), Treatment by Age (2 cat.) interaction (prec=0.2804/pterm=0.8347), region (prec<0.0001/pterm=0.0054), sex (prec=0.3160/pterm=0.1276), baseline diabetes status (3 cat.) (prec=0.0019/pterm=0.1493), baseline LVEF (3 cat.) (prec=0.1100/pterm=0.8260), estimated dependence between adjudicated hosp. for HF and adjudicated CV death (alpha) (1.12) and variance of frailty (omega) (3.67). pterm=p-value in terminal event model. prec=p-value in recurrent event model.

R.1.1.24.4 Subgroup analysis by region (North America, Latin America, Europe, Asia, Other)

Table R.1.1.24.4: 1 Joint frailty model of adjudicated hospitalisation for heart failure and adjudicated CV death by region - RS (trial 1245.121)

Subgroup Description	Placebo	Empa 10mg
Region: North America		
Number of patients in analysis set	213	212
Number of analysed patients	213	212
Total number of adjudicated hosp. for HF	92	84
Number of patients with adjudicated hosp. for HF then adjudicated CV death [N(%)]	11 (5.2)	11 (5.2)
Number of patients with adjudicated hosp. for HF only [N(%)]	44 (20.7)	31 (14.6)
Number of patients with adjudicated CV death only [N(%)]	9 (4.2)	6 (2.8)
Comparison vs Placebo*		
Hazard ratio of adjudicated hosp. for HF		0.71
95% confidence interval		(0.43,1.18)
p-value		0.1876
Hazard ratio of adjudicated CV death		0.61
95% confidence interval		(0.28,1.36)
Region: Latin America		
Number of patients in analysis set	645	641
Number of analysed patients	645	641
Total number of adjudicated hosp. for HF	147	91
Number of patients with adjudicated hosp. for HF then adjudicated CV death [N(%)]	24 (3.7)	21 (3.3)
Number of patients with adjudicated hosp. for HF only [N(%)]	80 (12.4)	43 (6.7)
Number of patients with adjudicated CV death only [N(%)]	47 (7.3)	51 (8.0)
Comparison vs Placebo*		
Hazard ratio of adjudicated hosp. for HF		0.65
95% confidence interval		(0.46,0.93)
p-value		0.0180
Hazard ratio of adjudicated CV death		1.04
95% confidence interval		(0.68,1.59)

* Based on an analysis of recurrent events accounting for terminal events using a joint frailty model with terms for age (prec=0.1985/pterm=0.2165), baseline eGFR (CKD-EPI) (prec<0.0001/pterm=0.0112), region (prec<0.0001/pterm=0.1566), Treatment (prec=0.8278/pterm=0.9536), Treatment by region interaction (prec=0.0553/pterm=0.4237), sex (prec=0.3121/pterm=0.1189), baseline diabetes status (3 cat.) (prec=0.0013/pterm=0.1305), baseline LVEF (3 cat.) (prec=0.0915/pterm=0.8549), estimated dependence between adjudicated hosp. for HF and adjudicated CV death (alpha) (1.11) and variance of frailty (omega) (3.65). pterm=p-value in terminal event model. prec=p-value in recurrent event model.

Table R.1.1.24.4: 1 Joint frailty model of adjudicated hospitalisation for heart failure and adjudicated CV death by region - RS (trial 1245.121)

Subgroup Description	Placebo	Empa 10mg
Region: Europe		
Number of patients in analysis set	677	676
Number of analysed patients	677	676
Total number of adjudicated hosp. for HF	152	144
Number of patients with adjudicated hosp. for HF then adjudicated CV death [N(%)]	26 (3.8)	29 (4.3)
Number of patients with adjudicated hosp. for HF only [N(%)]	77 (11.4)	69 (10.2)
Number of patients with adjudicated CV death only [N(%)]	46 (6.8)	42 (6.2)
Comparison vs Placebo*		
Hazard ratio of adjudicated hosp. for HF		0.96
95% confidence interval		(0.70,1.33)
p-value		0.8278
Hazard ratio of adjudicated CV death		0.99
95% confidence interval		(0.65,1.50)
Region: Asia		
Number of patients in analysis set	245	248
Number of analysed patients	245	248
Total number of adjudicated hosp. for HF	145	61
Number of patients with adjudicated hosp. for HF then adjudicated CV death [N(%)]	16 (6.5)	10 (4.0)
Number of patients with adjudicated hosp. for HF only [N(%)]	53 (21.6)	26 (10.5)
Number of patients with adjudicated CV death only [N(%)]	11 (4.5)	13 (5.2)
Comparison vs Placebo*		
Hazard ratio of adjudicated hosp. for HF		0.41
95% confidence interval		(0.26,0.66)
p-value		0.0003
Hazard ratio of adjudicated CV death		0.81
95% confidence interval		(0.40,1.61)

* Based on an analysis of recurrent events accounting for terminal events using a joint frailty model with terms for age (prec=0.1985/pterm=0.2165), baseline eGFR (CKD-EPI) (prec<0.0001/pterm=0.0112), region (prec<0.0001/pterm=0.1566), Treatment (prec=0.8278/pterm=0.9536), Treatment by region interaction (prec=0.0553/pterm=0.4237), sex (prec=0.3121/pterm=0.1189), baseline diabetes status (3 cat.) (prec=0.0013/pterm=0.1305), baseline LVEF (3 cat.) (prec=0.0915/pterm=0.8549), estimated dependence between adjudicated hosp. for HF and adjudicated CV death (alpha) (1.11) and variance of frailty (omega) (3.65). pterm=p-value in terminal event model. prec=p-value in recurrent event model.

Table R.1.1.24.4: 1 Joint frailty model of adjudicated hospitalisation for heart failure and adjudicated CV death by region - RS (trial 1245.121)

Subgroup Description	Placebo	Empa 10mg
Region: Other		
Number of patients in analysis set	87	86
Number of analysed patients	87	86
Total number of adjudicated hosp. for HF	17	8
Number of patients with adjudicated hosp. for HF then adjudicated CV death [N(%)]	5 (5.7)	1 (1.2)
Number of patients with adjudicated hosp. for HF only [N(%)]	6 (6.9)	5 (5.8)
Number of patients with adjudicated CV death only [N(%)]	7 (8.0)	3 (3.5)
Comparison vs Placebo*		
Hazard ratio of adjudicated hosp. for HF		0.48
95% confidence interval		(0.16,1.40)
p-value		0.1785
Hazard ratio of adjudicated CV death		0.32
95% confidence interval		(0.08,1.25)

* Based on an analysis of recurrent events accounting for terminal events using a joint frailty model with terms for age (prec=0.1985/pterm=0.2165), baseline eGFR (CKD-EPI) (prec<0.0001/pterm=0.0112), region (prec<0.0001/pterm=0.1566), Treatment (prec=0.8278/pterm=0.9536), Treatment by region interaction (prec=0.0553/pterm=0.4237), sex (prec=0.3121/pterm=0.1189), baseline diabetes status (3 cat.) (prec=0.0013/pterm=0.1305), baseline LVEF (3 cat.) (prec=0.0915/pterm=0.8549), estimated dependence between adjudicated hosp. for HF and adjudicated CV death (alpha) (1.11) and variance of frailty (omega) (3.65).
pterm=p-value in terminal event model. prec=p-value in recurrent event model.

R.1.1.24.5

R.1.1.24.5 Subgroup analysis by OECD member (Y/N)

Table R.1.1.24.5: 1 Joint frailty model of adjudicated hospitalisation for heart failure and adjudicated CV death by OECD member - RS (trial 1245.121)

Subgroup Description	Placebo	Empa 10mg
OECD member: No		
Number of patients in analysis set	741	713
Number of analysed patients	741	713
Total number of adjudicated hosp. for HF	216	103
Number of patients with adjudicated hosp. for HF then adjudicated CV death [N(%)]	32 (4.3)	24 (3.4)
Number of patients with adjudicated hosp. for HF only [N(%)]	101 (13.6)	48 (6.7)
Number of patients with adjudicated CV death only [N(%)]	54 (7.3)	55 (7.7)
Comparison vs Placebo*		
Hazard ratio of adjudicated hosp. for HF		0.55
95% confidence interval		(0.39,0.76)
p-value		0.0003
Hazard ratio of adjudicated CV death		1.02
95% confidence interval		(0.69,1.49)

* Based on an analysis of recurrent events accounting for terminal events using a joint frailty model with terms for age (prec=0.2757/pterm=0.1219), baseline eGFR (CKD-EPI) (prec<0.0001/pterm=0.0058), OECD member (prec=0.0766/pterm=0.0032), Treatment (prec=0.0446/pterm=0.3119), Treatment by OECD member interaction (prec=0.0832/pterm=0.4716), sex (prec=0.2380/pterm=0.1089), baseline diabetes status (3 cat.) (prec=0.0011/pterm=0.1505), baseline LVEF (3 cat.) (prec=0.0711/pterm=0.8225), estimated dependence between adjudicated hosp. for HF and adjudicated CV death (alpha) (0.97) and variance of frailty (omega) (3.94).
pterm=p-value in terminal event model. prec=p-value in recurrent event model.

OECD member (yes/no) countries included:
Yes: United States, Canada, Mexico, Poland, Netherlands, Hungary, Germany, Czech Republic, Italy, France, Spain, United Kingdom, Belgium, Japan, Australia, 'Korea; Republic Of South Korea';
No: Brazil, Argentina, China, India.

Table R.1.1.24.5: 1 Joint frailty model of adjudicated hospitalisation for heart failure and adjudicated CV death by OECD member - RS (trial 1245.121)

Subgroup Description	Placebo	Empa 10mg
OECD member: Yes		
Number of patients in analysis set	1126	1150
Number of analysed patients	1126	1150
Total number of adjudicated hosp. for HF	337	285
Number of patients with adjudicated hosp. for HF then adjudicated CV death [N(%)]	50 (4.4)	48 (4.2)
Number of patients with adjudicated hosp. for HF only [N(%)]	159 (14.1)	126 (11.0)
Number of patients with adjudicated CV death only [N(%)]	66 (5.9)	60 (5.2)
Comparison vs Placebo*		
Hazard ratio of adjudicated hosp. for HF		0.78
95% confidence interval		(0.62,0.99)
p-value		0.0446
Hazard ratio of adjudicated CV death		0.85
95% confidence interval		(0.62,1.17)

* Based on an analysis of recurrent events accounting for terminal events using a joint frailty model with terms for age (prec=0.2757/pterm=0.1219), baseline eGFR (CKD-EPI) (prec<0.0001/pterm=0.0058), OECD member (prec=0.0766/pterm=0.0032), Treatment (prec=0.0446/pterm=0.3119), Treatment by OECD member interaction (prec=0.0832/pterm=0.4716), sex (prec=0.2380/pterm=0.1089), baseline diabetes status (3 cat.) (prec=0.0011/pterm=0.1505), baseline LVEF (3 cat.) (prec=0.0711/pterm=0.8225), estimated dependence between adjudicated hosp. for HF and adjudicated CV death (alpha) (0.97) and variance of frailty (omega) (3.94).
pterm=p-value in terminal event model. prec=p-value in recurrent event model.

OECD member (yes/no) countries included:
Yes: United States, Canada, Mexico, Poland, Netherlands, Hungary, Germany, Czech Republic, Italy, France, Spain, United Kingdom, Belgium, Japan, Australia, 'Korea; Republic Of South Korea';
No: Brazil, Argentina, China, India.

R.1.1.24.6

R.1.1.24.6 Subgroup analysis by NYHA at baseline (II, III/IV - 2 cat.)

Table R.1.1.24.6: 1 Joint frailty model of adjudicated hospitalisation for heart failure and adjudicated CV death by NYHA at baseline (2 cat.) - RS (trial 1245.121)

Subgroup Description	Placebo	Empa 10mg
History of NYHA (2 cat.): II		
Number of patients in analysis set	1401	1399
Number of analysed patients	1401	1399
Total number of adjudicated hosp. for HF	353	226
Number of patients with adjudicated hosp. for HF then adjudicated CV death [N(%)]	52 (3.7)	43 (3.1)
Number of patients with adjudicated hosp. for HF only [N(%)]	178 (12.7)	99 (7.1)
Number of patients with adjudicated CV death only [N(%)]	69 (4.9)	78 (5.6)
Comparison vs Placebo*		
Hazard ratio of adjudicated hosp. for HF		0.65
95% confidence interval		(0.51,0.81)
p-value		0.0002
Hazard ratio of adjudicated CV death		1.01
95% confidence interval		(0.74,1.37)
History of NYHA (2 cat.): III/IV		
Number of patients in analysis set	466	464
Number of analysed patients	466	464
Total number of adjudicated hosp. for HF	200	162
Number of patients with adjudicated hosp. for HF then adjudicated CV death [N(%)]	30 (6.4)	29 (6.3)
Number of patients with adjudicated hosp. for HF only [N(%)]	82 (17.6)	75 (16.2)
Number of patients with adjudicated CV death only [N(%)]	51 (10.9)	37 (8.0)
Comparison vs Placebo*		
Hazard ratio of adjudicated hosp. for HF		0.77
95% confidence interval		(0.55,1.09)
p-value		0.1371
Hazard ratio of adjudicated CV death		0.71
95% confidence interval		(0.45,1.11)

* Based on an analysis of recurrent events accounting for terminal events using a joint frailty model with terms for age (prec=0.2769/pterm=0.1478), baseline eGFR (CKD-EPI) (prec<0.0001/pterm=0.0178), History of NYHA (2 cat.) (prec<0.0001/pterm<0.0001), Treatment (prec=0.0002/pterm=0.9600), Treatment by History of NYHA (2 cat.) interaction (prec=0.4006/pterm=0.1989), region (prec<0.0001/pterm=0.0016), sex (prec=0.1929/pterm=0.0568), baseline diabetes status (3 cat.) (prec=0.0086/pterm=0.3008), baseline LVEF (3 cat.) (prec=0.0458/pterm=0.9397), estimated dependence between adjudicated hosp. for HF and adjudicated CV death (alpha) (1.12) and variance of frailty (omega) (3.46).
pterm=p-value in terminal event model. prec=p-value in recurrent event model.

R.1.1.24.7

Table R.1.1.24.7: 1 Joint frailty model of adjudicated hospitalisation for heart failure and adjudicated CV death by diabetes at baseline - RS (trial 1245.121)

Subgroup Description	Placebo	Empa 10mg
Baseline diabetes status (2 cat.): Diabetic		
Number of patients in analysis set	929	927
Number of analysed patients	929	927
Total number of adjudicated hosp. for HF	337	221
Number of patients with adjudicated hosp. for HF then adjudicated CV death [N(%)]	49 (5.3)	44 (4.7)
Number of patients with adjudicated hosp. for HF only [N(%)]	152 (16.4)	96 (10.4)
Number of patients with adjudicated CV death only [N(%)]	64 (6.9)	60 (6.5)
Comparison vs Placebo*		
Hazard ratio of adjudicated hosp. for HF		0.65
95% confidence interval		(0.50,0.85)
p-value		0.0015
Hazard ratio of adjudicated CV death		0.95
95% confidence interval		(0.68,1.35)
Baseline diabetes status (2 cat.): Non-Diabetic		
Number of patients in analysis set	938	936
Number of analysed patients	938	936
Total number of adjudicated hosp. for HF	216	167
Number of patients with adjudicated hosp. for HF then adjudicated CV death [N(%)]	33 (3.5)	28 (3.0)
Number of patients with adjudicated hosp. for HF only [N(%)]	108 (11.5)	78 (8.3)
Number of patients with adjudicated CV death only [N(%)]	56 (6.0)	55 (5.9)
Comparison vs Placebo*		
Hazard ratio of adjudicated hosp. for HF		0.76
95% confidence interval		(0.57,1.01)
p-value		0.0605
Hazard ratio of adjudicated CV death		0.82
95% confidence interval		(0.57,1.20)

* Based on an analysis of recurrent events accounting for terminal events using a joint frailty model with terms for age (prec=0.1681/pterm=0.2080), baseline eGFR (CKD-EPI) (prec<0.0001/pterm=0.0117), Baseline diabetes status (2 cat.) (prec=0.0017/pterm=0.3107), Treatment (prec=0.0015/pterm=0.7920), Treatment by Baseline diabetes status (2 cat.) interaction (prec=0.4428/pterm=0.5699), region (prec<0.0001/pterm=0.0041), sex (prec=0.3173/pterm=0.1220), baseline LVEF (3 cat.) (prec=0.0936/pterm=0.8342), estimated dependence between adjudicated hosp. for HF and adjudicated CV death (alpha) (1.10) and variance of frailty (omega) (3.71).
pterm=p-value in terminal event model. prec=p-value in recurrent event model.

R.1.1.24.8

R.1.1.24.8 Subgroup analysis by BMI at baseline (<30, >=30)

Table R.1.1.24.8: 1 Joint frailty model of adjudicated hospitalisation for heart failure and adjudicated CV death by baseline BMI [kg/m2] - RS (trial 1245.121)

Subgroup Description	Placebo	Empa 10mg
Baseline BMI [kg/m²]: <30		
Number of patients in analysis set	1300	1263
Number of analysed patients	1300	1263
Total number of adjudicated hosp. for HF	371	232
Number of patients with adjudicated hosp. for HF then adjudicated CV death [N(%)]	64 (4.9)	47 (3.7)
Number of patients with adjudicated hosp. for HF only [N(%)]	171 (13.2)	96 (7.6)
Number of patients with adjudicated CV death only [N(%)]	87 (6.7)	83 (6.6)
Comparison vs Placebo*		
Hazard ratio of adjudicated hosp. for HF		0.66
95% confidence interval		(0.52,0.83)
p-value		0.0005
Hazard ratio of adjudicated CV death		0.87
95% confidence interval		(0.64,1.18)
Baseline BMI [kg/m²]: >=30		
Number of patients in analysis set	567	600
Number of analysed patients	567	600
Total number of adjudicated hosp. for HF	182	156
Number of patients with adjudicated hosp. for HF then adjudicated CV death [N(%)]	18 (3.2)	25 (4.2)
Number of patients with adjudicated hosp. for HF only [N(%)]	89 (15.7)	78 (13.0)
Number of patients with adjudicated CV death only [N(%)]	33 (5.8)	32 (5.3)
Comparison vs Placebo*		
Hazard ratio of adjudicated hosp. for HF		0.76
95% confidence interval		(0.55,1.06)
p-value		0.1099
Hazard ratio of adjudicated CV death		0.99
95% confidence interval		(0.62,1.58)

* Based on an analysis of recurrent events accounting for terminal events using a joint frailty model with terms for age (prec=0.3556/pterm=0.2858), baseline eGFR (CKD-EPI) (prec<0.0001/pterm=0.0108), Baseline BMI [kg/m²] (prec=0.1683/pterm=0.3017), Treatment (prec=0.0005/pterm=0.3611), Treatment by Baseline BMI [kg/m²] interaction (prec=0.4681/pterm=0.6563), region (prec<0.0001/pterm=0.0062), sex (prec=0.2194/pterm=0.1360), baseline diabetes status (3 cat.) (prec=0.0056/pterm=0.1225), baseline LVEF (3 cat.) (prec=0.0861/pterm=0.8430), estimated dependence between adjudicated hosp. for HF and adjudicated CV death (alpha) (1.11) and variance of frailty (omega) (3.68).
pterm=p-value in terminal event model. prec=p-value in recurrent event model.

R.1.1.24.9

R.1.1.24.9 Subgroup analysis by eGFR at baseline (<60, >=60)

Table R.1.1.24.9: 1 Joint frailty model of adjudicated hospitalisation for heart failure and adjudicated CV death by baseline eGFR (2 cat.) - RS (trial 1245.121)

Subgroup Description	Placebo	Empa 10mg
Baseline eGFR (2 cat.): >=60		
Number of patients in analysis set	960	969
Number of analysed patients	960	969
Total number of adjudicated hosp. for HF	267	157
Number of patients with adjudicated hosp. for HF then adjudicated CV death [N(%)]	30 (3.1)	30 (3.1)
Number of patients with adjudicated hosp. for HF only [N(%)]	136 (14.2)	68 (7.0)
Number of patients with adjudicated CV death only [N(%)]	58 (6.0)	61 (6.3)
Comparison vs Placebo*		
Hazard ratio of adjudicated hosp. for HF		0.60
95% confidence interval		(0.45,0.79)
p-value		0.0003
Hazard ratio of adjudicated CV death		1.06
95% confidence interval		(0.74,1.53)

* Based on an analysis of recurrent events accounting for terminal events using a joint frailty model with terms for age (prec=0.9588/pterm=0.0355), Baseline eGFR (2 cat.) (prec=0.1281/pterm=0.0552), Treatment (prec=0.0003/pterm=0.7455), Treatment by Baseline eGFR (2 cat.) interaction (prec=0.1233/pterm=0.2570), region (prec<0.0001/pterm=0.0045), sex (prec=0.4014/pterm=0.1032), baseline diabetes status (3 cat.) (prec=0.0015/pterm=0.1491), baseline LVEF (3 cat.) (prec=0.0920/pterm=0.8142), estimated dependence between adjudicated hosp. for HF and adjudicated CV death (alpha) (1.10) and variance of frailty (omega) (3.78).
pterm=p-value in terminal event model. prec=p-value in recurrent event model.
2 patients were excluded as the subgroup variable was missing.

Table R.1.1.24.9: 1 Joint frailty model of adjudicated hospitalisation for heart failure and adjudicated CV death by baseline eGFR (2 cat.) - RS (trial 1245.121)

Subgroup Description	Placebo	Empa 10mg
Baseline eGFR (2 cat.): <60		
Number of patients in analysis set	906	893
Number of analysed patients	906	893
Total number of adjudicated hosp. for HF	286	231
Number of patients with adjudicated hosp. for HF then adjudicated CV death [N(%)]	52 (5.7)	42 (4.7)
Number of patients with adjudicated hosp. for HF only [N(%)]	124 (13.7)	106 (11.9)
Number of patients with adjudicated CV death only [N(%)]	61 (6.7)	54 (6.0)
Comparison vs Placebo*		
Hazard ratio of adjudicated hosp. for HF		0.81
95% confidence interval		(0.62,1.06)
p-value		0.1268
Hazard ratio of adjudicated CV death		0.79
95% confidence interval		(0.56,1.13)

* Based on an analysis of recurrent events accounting for terminal events using a joint frailty model with terms for age (prec=0.9588/pterm=0.0355), Baseline eGFR (2 cat.) (prec=0.1281/pterm=0.0552), Treatment (prec=0.0003/pterm=0.7455), Treatment by Baseline eGFR (2 cat.) interaction (prec=0.1233/pterm=0.2570), region (prec<0.0001/pterm=0.0045), sex (prec=0.4014/pterm=0.1032), baseline diabetes status (3 cat.) (prec=0.0015/pterm=0.1491), baseline LVEF (3 cat.) (prec=0.0920/pterm=0.8142), estimated dependence between adjudicated hosp. for HF and adjudicated CV death (alpha) (1.10) and variance of frailty (omega) (3.78).
pterm=p-value in terminal event model. prec=p-value in recurrent event model.
2 patients were excluded as the subgroup variable was missing.

R.1.1.24.10

Table R.1.1.24.10: 1 Joint frailty model of adjudicated hospitalisation for heart failure and adjudicated CV death by history of HHF within 12 months - RS (trial 1245.121)

Subgroup Description	Placebo	Empa 10mg
History of HHF (in the last 12 months): No		
Number of patients in analysis set	1293	1286
Number of analysed patients	1293	1286
Total number of adjudicated hosp. for HF	309	198
Number of patients with adjudicated hosp. for HF then adjudicated CV death [N(%)]	46 (3.6)	41 (3.2)
Number of patients with adjudicated hosp. for HF only [N(%)]	159 (12.3)	91 (7.1)
Number of patients with adjudicated CV death only [N(%)]	80 (6.2)	76 (5.9)
Comparison vs Placebo*		
Hazard ratio of adjudicated hosp. for HF		0.65
95% confidence interval		(0.51,0.82)
p-value		0.0004
Hazard ratio of adjudicated CV death		0.93
95% confidence interval		(0.68,1.28)
History of HHF (in the last 12 months): Yes		
Number of patients in analysis set	574	577
Number of analysed patients	574	577
Total number of adjudicated hosp. for HF	244	190
Number of patients with adjudicated hosp. for HF then adjudicated CV death [N(%)]	36 (6.3)	31 (5.4)
Number of patients with adjudicated hosp. for HF only [N(%)]	101 (17.6)	83 (14.4)
Number of patients with adjudicated CV death only [N(%)]	40 (7.0)	39 (6.8)
Comparison vs Placebo*		
Hazard ratio of adjudicated hosp. for HF		0.73
95% confidence interval		(0.53,0.99)
p-value		0.0447
Hazard ratio of adjudicated CV death		0.79
95% confidence interval		(0.51,1.21)

* Based on an analysis of recurrent events accounting for terminal events using a joint frailty model with terms for age (prec=0.5063/pterm=0.1143), baseline eGFR (CKD-EPI) (prec<0.0001/pterm=0.0155), History of HHF (in the last 12 months) (prec<0.0001/pterm=0.0003), Treatment (prec=0.0004/pterm=0.6689), Treatment by History of HHF (in the last 12 months) interaction (prec=0.5561/pterm=0.5241), region (prec<0.0001/pterm=0.0008), sex (prec=0.1860/pterm=0.0881), baseline diabetes status (3 cat.) (prec=0.0129/pterm=0.2873), baseline LVEF (3 cat.) (prec=0.1646/pterm=0.7368), estimated dependence between adjudicated hosp. for HF and adjudicated CV death (alpha) (1.14) and variance of frailty (omega) (3.49).
pterm=p-value in terminal event model. prec=p-value in recurrent event model.

R.1.1.24.11

Table R.1.1.24.11: 1 Joint frailty model of adjudicated hospitalisation for heart failure and adjudicated CV death by cause of heart failure - RS (trial 1245.121)

Subgroup Description	Placebo	Empa 10mg
Cause of heart failure: Ischemic		
Number of patients in analysis set	946	983
Number of analysed patients	946	983
Total number of adjudicated hosp. for HF	281	221
Number of patients with adjudicated hosp. for HF then adjudicated CV death [N(%)]	44 (4.7)	41 (4.2)
Number of patients with adjudicated hosp. for HF only [N(%)]	123 (13.0)	94 (9.6)
Number of patients with adjudicated CV death only [N(%)]	69 (7.3)	72 (7.3)
Comparison vs Placebo*		
Hazard ratio of adjudicated hosp. for HF		0.73
95% confidence interval		(0.56,0.95)
p-value		0.0211
Hazard ratio of adjudicated CV death		0.94
95% confidence interval		(0.67,1.32)
Cause of heart failure: Non-ischemic		
Number of patients in analysis set	921	880
Number of analysed patients	921	880
Total number of adjudicated hosp. for HF	272	167
Number of patients with adjudicated hosp. for HF then adjudicated CV death [N(%)]	38 (4.1)	31 (3.5)
Number of patients with adjudicated hosp. for HF only [N(%)]	137 (14.9)	80 (9.1)
Number of patients with adjudicated CV death only [N(%)]	51 (5.5)	43 (4.9)
Comparison vs Placebo*		
Hazard ratio of adjudicated hosp. for HF		0.66
95% confidence interval		(0.50,0.88)
p-value		0.0042
Hazard ratio of adjudicated CV death		0.83
95% confidence interval		(0.57,1.22)

* Based on an analysis of recurrent events accounting for terminal events using a joint frailty model with terms for age (prec=0.1648/pterm=0.3131), baseline eGFR (CKD-EPI) (prec<0.0001/pterm=0.0101), Cause of heart failure (prec=0.9480/pterm=0.2833), Treatment (prec=0.0211/pterm=0.7391), Treatment by Cause of heart failure interaction (prec=0.6195/pterm=0.6299), region (prec<0.0001/pterm=0.0019), sex (prec=0.3426/pterm=0.1833), baseline diabetes status (3 cat.) (prec=0.0023/pterm=0.2488), baseline LVEF (3 cat.) (prec=0.1035/pterm=0.8691), estimated dependence between adjudicated hosp. for HF and adjudicated CV death (alpha) (1.08) and variance of frailty (omega) (3.72).
pterm=p-value in terminal event model. prec=p-value in recurrent event model.

R.1.1.24.12 Subgroup analysis by heart failure physiology (LVEF <= 30% and NTproBNP<median; LVEF <= 30% and NTproBNP>=median; LVEF > 30%)

Table R.1.1.24.12: 1 Joint frailty model of adjudicated hospitalisation for heart failure and adjudicated CV death by heart failure physiology - RS (trial 1245.121)

Subgroup Description	Placebo	Empa 10mg
Heart failure physiology: LVEF <= 30% and NTproBNP < median		
Number of patients in analysis set	723	698
Number of analysed patients	723	698
Total number of adjudicated hosp. for HF	122	69
Number of patients with adjudicated hosp. for HF then adjudicated CV death [N(%)]	18 (2.5)	16 (2.3)
Number of patients with adjudicated hosp. for HF only [N(%)]	70 (9.7)	31 (4.4)
Number of patients with adjudicated CV death only [N(%)]	26 (3.6)	33 (4.7)
Comparison vs Placebo*		
Hazard ratio of adjudicated hosp. for HF		0.59
95% confidence interval		(0.41,0.86)
p-value		0.0051
Hazard ratio of adjudicated CV death		1.18
95% confidence interval		(0.73,1.89)

* Based on an analysis of recurrent events accounting for terminal events using a joint frailty model with terms for age (prec=0.2156/pterm=0.2184), baseline eGFR (CKD-EPI) (prec=0.0012/pterm=0.1005), Heart failure physiology (prec<0.0001/pterm<0.0001), Treatment (prec=0.0042/pterm=0.0423), Treatment by Heart failure physiology interaction (prec=0.3837/pterm=0.1445), region (prec<0.0001/pterm=0.0157), sex (prec=0.4835/pterm=0.1521), baseline diabetes status (3 cat.) (prec=0.0018/pterm=0.2109), estimated dependence between adjudicated hosp. for HF and adjudicated CV death (alpha) (1.12) and variance of frailty (omega) (3.26).
pterm=p-value in terminal event model. prec=p-value in recurrent event model.
16 patients were excluded as the subgroup variable was missing.

Table R.1.1.24.12: 1 Joint frailty model of adjudicated hospitalisation for heart failure and adjudicated CV death by heart failure physiology - RS (trial 1245.121)

Subgroup Description	Placebo	Empa 10mg
Heart failure physiology: LVEF <= 30% and NTproBNP >= median		
Number of patients in analysis set	661	631
Number of analysed patients	661	631
Total number of adjudicated hosp. for HF	309	206
Number of patients with adjudicated hosp. for HF then adjudicated CV death [N(%)]	48 (7.3)	34 (5.4)
Number of patients with adjudicated hosp. for HF only [N(%)]	139 (21.0)	93 (14.7)
Number of patients with adjudicated CV death only [N(%)]	62 (9.4)	42 (6.7)
Comparison vs Placebo*		
Hazard ratio of adjudicated hosp. for HF		0.66
95% confidence interval		(0.50,0.88)
p-value		0.0042
Hazard ratio of adjudicated CV death		0.67
95% confidence interval		(0.46,0.99)

* Based on an analysis of recurrent events accounting for terminal events using a joint frailty model with terms for age (prec=0.2156/pterm=0.2184), baseline eGFR (CKD-EPI) (prec=0.0012/pterm=0.1005), Heart failure physiology (prec<0.0001/pterm<0.0001), Treatment (prec=0.0042/pterm=0.0423), Treatment by Heart failure physiology interaction (prec=0.3837/pterm=0.1445), region (prec<0.0001/pterm=0.0157), sex (prec=0.4835/pterm=0.1521), baseline diabetes status (3 cat.) (prec=0.0018/pterm=0.2109), estimated dependence between adjudicated hosp. for HF and adjudicated CV death (alpha) (1.12) and variance of frailty (omega) (3.26).
pterm=p-value in terminal event model. prec=p-value in recurrent event model.
16 patients were excluded as the subgroup variable was missing.

Table R.1.1.24.12: 1 Joint frailty model of adjudicated hospitalisation for heart failure and adjudicated CV death by heart failure physiology - RS (trial 1245.121)

Subgroup Description	Placebo	Empa 10mg
Heart failure physiology: LVEF > 30%		
Number of patients in analysis set	475	526
Number of analysed patients	475	526
Total number of adjudicated hosp. for HF	118	112
Number of patients with adjudicated hosp. for HF then adjudicated CV death [N(%)]	16 (3.4)	21 (4.0)
Number of patients with adjudicated hosp. for HF only [N(%)]	50 (10.5)	50 (9.5)
Number of patients with adjudicated CV death only [N(%)]	31 (6.5)	37 (7.0)
Comparison vs Placebo*		
Hazard ratio of adjudicated hosp. for HF		0.84
95% confidence interval		(0.59,1.22)
p-value		0.3651
Hazard ratio of adjudicated CV death		1.05
95% confidence interval		(0.65,1.69)

* Based on an analysis of recurrent events accounting for terminal events using a joint frailty model with terms for age (prec=0.2156/pterm=0.2184), baseline eGFR (CKD-EPI) (prec=0.0012/pterm=0.1005), Heart failure physiology (prec<0.0001/pterm<0.0001), Treatment (prec=0.0042/pterm=0.0423), Treatment by Heart failure physiology interaction (prec=0.3837/pterm=0.1445), region (prec<0.0001/pterm=0.0157), sex (prec=0.4835/pterm=0.1521), baseline diabetes status (3 cat.) (prec=0.0018/pterm=0.2109), estimated dependence between adjudicated hosp. for HF and adjudicated CV death (alpha) (1.12) and variance of frailty (omega) (3.26).
pterm=p-value in terminal event model. prec=p-value in recurrent event model.
16 patients were excluded as the subgroup variable was missing.

R.1.1.24.13

R.1.1.24.13 Subgroup analysis by baseline use of MRA

Table R.1.1.24.13: 1 Joint frailty model of adjudicated hospitalisation for heart failure and adjudicated CV death by baseline use of MRA - RS (trial 1245.121)

Subgroup Description	Placebo	Empa 10mg
Baseline use of MRA: No		
Number of patients in analysis set	512	557
Number of analysed patients	512	557
Total number of adjudicated hosp. for HF	165	126
Number of patients with adjudicated hosp. for HF then adjudicated CV death [N(%)]	25 (4.9)	31 (5.6)
Number of patients with adjudicated hosp. for HF only [N(%)]	81 (15.8)	51 (9.2)
Number of patients with adjudicated CV death only [N(%)]	26 (5.1)	36 (6.5)
Comparison vs Placebo*		
Hazard ratio of adjudicated hosp. for HF		0.69
95% confidence interval		(0.48,0.97)
p-value		0.0353
Hazard ratio of adjudicated CV death		1.16
95% confidence interval		(0.73,1.84)
Baseline use of MRA: Yes		
Number of patients in analysis set	1355	1306
Number of analysed patients	1355	1306
Total number of adjudicated hosp. for HF	388	262
Number of patients with adjudicated hosp. for HF then adjudicated CV death [N(%)]	57 (4.2)	41 (3.1)
Number of patients with adjudicated hosp. for HF only [N(%)]	179 (13.2)	123 (9.4)
Number of patients with adjudicated CV death only [N(%)]	94 (6.9)	79 (6.0)
Comparison vs Placebo*		
Hazard ratio of adjudicated hosp. for HF		0.71
95% confidence interval		(0.56,0.89)
p-value		0.0035
Hazard ratio of adjudicated CV death		0.80
95% confidence interval		(0.59,1.09)

* Based on an analysis of recurrent events accounting for terminal events using a joint frailty model with terms for age (prec=0.2143/pterm=0.2201), baseline eGFR (CKD-EPI) (prec<0.0001/pterm=0.0102), Baseline use of MRA (prec=0.4301/pterm=0.2807), Treatment (prec=0.0035/pterm=0.1596), Treatment by Baseline use of MRA interaction (prec=0.8782/pterm=0.1975), region (prec<0.0001/pterm=0.0056), sex (prec=0.3031/pterm=0.1193), baseline diabetes status (3 cat.) (prec=0.0015/pterm=0.1634), baseline LVEF (3 cat.) (prec=0.1063/pterm=0.8580), estimated dependence between adjudicated hosp. for HF and adjudicated CV death (alpha) (1.09) and variance of frailty (omega) (3.71).
pterm=p-value in terminal event model. prec=p-value in recurrent event model.

R.1.1.24.14

Table R.1.1.24.14: 1 Joint frailty model of adjudicated hospitalisation for heart failure and adjudicated CV death by baseline use of ARNi - RS (trial 1245.121)

Subgroup Description	Placebo	Empa 10mg
Baseline use of ARNi: No		
Number of patients in analysis set	1480	1523
Number of analysed patients	1480	1523
Total number of adjudicated hosp. for HF	432	318
Number of patients with adjudicated hosp. for HF then adjudicated CV death [N(%)]	64 (4.3)	62 (4.1)
Number of patients with adjudicated hosp. for HF only [N(%)]	202 (13.6)	144 (9.5)
Number of patients with adjudicated CV death only [N(%)]	103 (7.0)	104 (6.8)
Comparison vs Placebo*		
Hazard ratio of adjudicated hosp. for HF		0.71
95% confidence interval		(0.58,0.88)
p-value		0.0020
Hazard ratio of adjudicated CV death		0.94
95% confidence interval		(0.71,1.24)
Baseline use of ARNi: Yes		
Number of patients in analysis set	387	340
Number of analysed patients	387	340
Total number of adjudicated hosp. for HF	121	70
Number of patients with adjudicated hosp. for HF then adjudicated CV death [N(%)]	18 (4.7)	10 (2.9)
Number of patients with adjudicated hosp. for HF only [N(%)]	58 (15.0)	30 (8.8)
Number of patients with adjudicated CV death only [N(%)]	17 (4.4)	11 (3.2)
Comparison vs Placebo*		
Hazard ratio of adjudicated hosp. for HF		0.65
95% confidence interval		(0.42,1.00)
p-value		0.0523
Hazard ratio of adjudicated CV death		0.65
95% confidence interval		(0.34,1.24)

* Based on an analysis of recurrent events accounting for terminal events using a joint frailty model with terms for age (prec=0.1804/pterm=0.2352), baseline eGFR (CKD-EPI) (prec<0.0001/pterm=0.0124), Baseline use of ARNi (prec=0.6798/pterm=0.6180), Treatment (prec=0.0020/pterm=0.6629), Treatment by Baseline use of ARNi interaction (prec=0.7159/pterm=0.3026), region (prec<0.0001/pterm=0.0092), sex (prec=0.3068/pterm=0.1679), baseline diabetes status (3 cat.) (prec=0.0015/pterm=0.1528), baseline LVEF (3 cat.) (prec=0.1049/pterm=0.8683), estimated dependence between adjudicated hosp. for HF and adjudicated CV death (alpha) (1.10) and variance of frailty (omega) (3.71).
pterm=p-value in terminal event model. prec=p-value in recurrent event model.

R.1.1.24.15 Subgroup analysis by bl. LVEF (<= 30%, >30% -<= 35% , > 35%)

Table R.1.1.24.15: 1 Joint frailty model of adjudicated hospitalisation for heart failure and adjudicated CV death by bl. LVEF (3 cat.) - RS (trial 1245.121)

Subgroup Description	Placebo	Empa 10mg
baseline LVEF (3 cat.): <=30		
Number of patients in analysis set	1392	1337
Number of analysed patients	1392	1337
Total number of adjudicated hosp. for HF	435	276
Number of patients with adjudicated hosp. for HF then adjudicated CV death [N(%)]	66 (4.7)	51 (3.8)
Number of patients with adjudicated hosp. for HF only [N(%)]	210 (15.1)	124 (9.3)
Number of patients with adjudicated CV death only [N(%)]	89 (6.4)	78 (5.8)
Comparison vs Placebo*		
Hazard ratio of adjudicated hosp. for HF		0.65
95% confidence interval		(0.52,0.82)
p-value		0.0002
Hazard ratio of adjudicated CV death		0.85
95% confidence interval		(0.63,1.14)
baseline LVEF (3 cat.): >30 to <=35		
Number of patients in analysis set	361	398
Number of analysed patients	361	398
Total number of adjudicated hosp. for HF	71	74
Number of patients with adjudicated hosp. for HF then adjudicated CV death [N(%)]	10 (2.8)	16 (4.0)
Number of patients with adjudicated hosp. for HF only [N(%)]	31 (8.6)	34 (8.5)
Number of patients with adjudicated CV death only [N(%)]	24 (6.6)	31 (7.8)
Comparison vs Placebo*		
Hazard ratio of adjudicated hosp. for HF		1.01
95% confidence interval		(0.64,1.58)
p-value		0.9826
Hazard ratio of adjudicated CV death		1.28
95% confidence interval		(0.73,2.25)

* Based on an analysis of recurrent events accounting for terminal events using a joint frailty model with terms for age (prec=0.1753/pterm=0.2214), baseline eGFR (CKD-EPI) (prec<0.0001/pterm=0.0114), baseline LVEF (3 cat.) (prec=0.0236/pterm=0.7449), Treatment (prec=0.0002/pterm=0.2742), Treatment by baseline LVEF (3 cat.) interaction (prec=0.2103/pterm=0.2935), region (prec<0.0001/pterm=0.0043), sex (prec=0.3308/pterm=0.1324), baseline diabetes status (3 cat.) (prec=0.0012/pterm=0.1226), estimated dependence between adjudicated hosp. for HF and adjudicated CV death (alpha) (1.09) and variance of frailty (omega) (3.70). pterm=p-value in terminal event model. prec=p-value in recurrent event model.

Table R.1.1.24.15: 1 Joint frailty model of adjudicated hospitalisation for heart failure and adjudicated CV death by bl. LVEF (3 cat.) - RS (trial 1245.121)

Subgroup Description	Placebo	Empa 10mg
baseline LVEF (3 cat.): >35		
Number of patients in analysis set	114	128
Number of analysed patients	114	128
Total number of adjudicated hosp. for HF	47	38
Number of patients with adjudicated hosp. for HF then adjudicated CV death [N(%)]	6 (5.3)	5 (3.9)
Number of patients with adjudicated hosp. for HF only [N(%)]	19 (16.7)	16 (12.5)
Number of patients with adjudicated CV death only [N(%)]	7 (6.1)	6 (4.7)
Comparison vs Placebo*		
Hazard ratio of adjudicated hosp. for HF		0.57
95% confidence interval		(0.29,1.15)
p-value		0.1165
Hazard ratio of adjudicated CV death		0.57
95% confidence interval		(0.21,1.55)

* Based on an analysis of recurrent events accounting for terminal events using a joint frailty model with terms for age (prec=0.1753/pterm=0.2214), baseline eGFR (CKD-EPI) (prec<0.0001/pterm=0.0114), baseline LVEF (3 cat.) (prec=0.0236/pterm=0.7449), Treatment (prec=0.0002/pterm=0.2742), Treatment by baseline LVEF (3 cat.) interaction (prec=0.2103/pterm=0.2935), region (prec<0.0001/pterm=0.0043), sex (prec=0.3308/pterm=0.1324), baseline diabetes status (3 cat.) (prec=0.0012/pterm=0.1226), estimated dependence between adjudicated hosp. for HF and adjudicated CV death (alpha) (1.09) and variance of frailty (omega) (3.70).
pterm=p-value in terminal event model. prec=p-value in recurrent event model.

R.1.1.24.16 Subgroup analysis by bl. NTproBNP </>= median (median based on total patients)

Table R.1.1.24.16: 1 Joint frailty model of adjudicated hospitalisation for heart failure and adjudicated CV death by bl. NTproBNP (<median,>= median) (median based on total patients) - RS (trial 1245.121)

Subgroup Description	Placebo	Empa 10mg
Baseline NTproBNP: < median		
Number of patients in analysis set	920	942
Number of analysed patients	920	942
Total number of adjudicated hosp. for HF	169	92
Number of patients with adjudicated hosp. for HF then adjudicated CV death [N(%)]	24 (2.6)	18 (1.9)
Number of patients with adjudicated hosp. for HF only [N(%)]	84 (9.1)	45 (4.8)
Number of patients with adjudicated CV death only [N(%)]	35 (3.8)	48 (5.1)
Comparison vs Placebo*		
Hazard ratio of adjudicated hosp. for HF		0.56
95% confidence interval		(0.41,0.77)
p-value		0.0003
Hazard ratio of adjudicated CV death		1.16
95% confidence interval		(0.77,1.75)

* Based on an analysis of recurrent events accounting for terminal events using a joint frailty model with terms for age (prec=0.1100/pterm=0.2786), baseline eGFR (CKD-EPI) (prec=0.0088/pterm=0.2677), Baseline NTproBNP (prec<0.0001/pterm<0.0001), Treatment (prec=0.0265/pterm=0.1779), Treatment by Baseline NTproBNP interaction (prec=0.1287/pterm=0.1666), region (prec<0.0001/pterm=0.0131), sex (prec=0.4495/pterm=0.1719), baseline diabetes status (3 cat.) (prec=0.0003/pterm=0.0769), baseline LVEF (3 cat.) (prec=0.1429/pterm=0.6947), estimated dependence between adjudicated hosp. for HF and adjudicated CV death (alpha) (1.16) and variance of frailty (omega) (3.22).
pterm=p-value in terminal event model. prec=p-value in recurrent event model.
2 patients were excluded as the subgroup variable was missing.

Median: 1910 [pg/mL]

Table R.1.1.24.16: 1 Joint frailty model of adjudicated hospitalisation for heart failure and adjudicated CV death by bl. NTproBNP (<median,>= median) (median based on total patients) - RS (trial 1245.121)

Subgroup Description	Placebo	Empa 10mg
Baseline NTproBNP: >= median		
Number of patients in analysis set	946	920
Number of analysed patients	946	920
Total number of adjudicated hosp. for HF	384	296
Number of patients with adjudicated hosp. for HF then adjudicated CV death [N(%)]	58 (6.1)	54 (5.9)
Number of patients with adjudicated hosp. for HF only [N(%)]	176 (18.6)	129 (14.0)
Number of patients with adjudicated CV death only [N(%)]	84 (8.9)	67 (7.3)
Comparison vs Placebo*		
Hazard ratio of adjudicated hosp. for HF		0.76
95% confidence interval		(0.60,0.97)
p-value		0.0265
Hazard ratio of adjudicated CV death		0.80
95% confidence interval		(0.58,1.11)

* Based on an analysis of recurrent events accounting for terminal events using a joint frailty model with terms for age (prec=0.1100/pterm=0.2786), baseline eGFR (CKD-EPI) (prec=0.0088/pterm=0.2677), Baseline NTproBNP (prec<0.0001/pterm<0.0001), Treatment (prec=0.0265/pterm=0.1779), Treatment by Baseline NTproBNP interaction (prec=0.1287/pterm=0.1666), region (prec<0.0001/pterm=0.0131), sex (prec=0.4495/pterm=0.1719), baseline diabetes status (3 cat.) (prec=0.0003/pterm=0.0769), baseline LVEF (3 cat.) (prec=0.1429/pterm=0.6947), estimated dependence between adjudicated hosp. for HF and adjudicated CV death (alpha) (1.16) and variance of frailty (omega) (3.22).
pterm=p-value in terminal event model. prec=p-value in recurrent event model.
2 patients were excluded as the subgroup variable was missing.

Median: 1910 [pg/mL]

R.1.1.25 All-cause hospitalisation (first and recurrent)

R.1.1.25.1

Figure R.1.1.25.1: 1

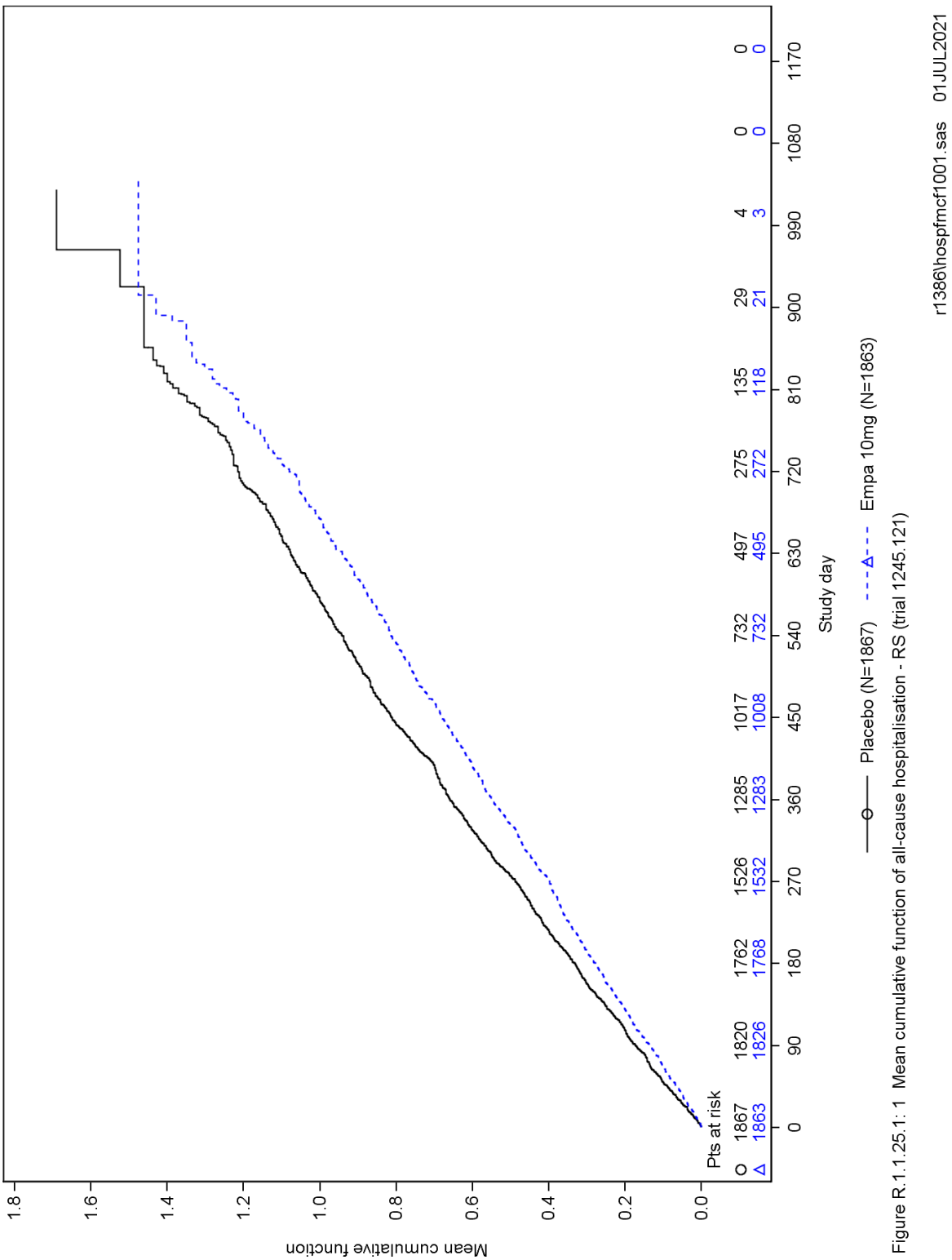

Figure R.1.1.25.1: 1 Mean cumulative function of all-cause hospitalisation - RS (trial 1245.121)

Table R.1.1.25.1: 1 Joint frailty model of all-cause hospitalisation and all-cause mortality - RS (trial 1245.121)

	Placebo	Empa 10mg
Number of patients in analysis set	1867	1863
Number of analysed patients	1867	1863
Total number of all-cause hospital	1570	1364
Number of patients with all-cause hospital then all-cause mortality [N(%)]	202 (10.8)	194 (10.4)
Number of patients with all-cause hospital only [N(%)]	594 (31.8)	494 (26.5)
Number of patients with all-cause mortality only [N(%)]	64 (3.4)	55 (3.0)
Comparison vs Placebo*		
Hazard ratio of all-cause hospital		0.85
95% confidence interval		(0.75,0.95)
p-value		0.0065
Hazard ratio of all-cause mortality		0.83
95% confidence interval		(0.62,1.10)

* Based on an analysis of recurrent events accounting for terminal events using a joint frailty model with terms for age (prec=0.3313/pterm=0.0028), baseline eGFR (CKD-EPI) (prec<0.0001/pterm=0.0016), treatment (prec=0.0065/pterm=0.1907), region (prec<0.0001/pterm=0.0002), baseline diabetes status (prec=0.0058/pterm=0.0552), sex (prec=0.1165/pterm=0.0216), baseline LVEF (prec=0.4177/pterm=0.9876), estimated dependence between all-cause hospital and all-cause mortality (alpha) (2.22) and variance of frailty (omega) (1.89).
pterm=p-value in terminal event model. prec=p-value in recurrent event model.

R.1.1.25.2

Table R.1.1.25.2: 1 Joint frailty model of all-cause hospitalisation and all-cause mortality by sex - RS (trial 1245.121)

Subgroup Description	Placebo	Empa 10mg
Sex: Male		
Number of patients in analysis set	1411	1426
Number of analysed patients	1411	1426
Total number of all-cause hospitalisation	1231	1052
Number of patients with all-cause hospitalisation then all-cause mortality [N(%)]	154 (10.9)	155 (10.9)
Number of patients with all-cause hospitalisation only [N(%)]	468 (33.2)	386 (27.1)
Number of patients with all-cause mortality only [N(%)]	52 (3.7)	46 (3.2)
Comparison vs Placebo*		
Hazard ratio of all-cause hospitalisation		0.86
95% confidence interval		(0.75,0.99)
p-value		0.0344
Hazard ratio of all-cause mortality		0.92
95% confidence interval		(0.67,1.27)
Sex: Female		
Number of patients in analysis set	456	437
Number of analysed patients	456	437
Total number of all-cause hospitalisation	339	312
Number of patients with all-cause hospitalisation then all-cause mortality [N(%)]	48 (10.5)	39 (8.9)
Number of patients with all-cause hospitalisation only [N(%)]	126 (27.6)	108 (24.7)
Number of patients with all-cause mortality only [N(%)]	12 (2.6)	9 (2.1)
Comparison vs Placebo*		
Hazard ratio of all-cause hospitalisation		0.80
95% confidence interval		(0.62,1.02)
p-value		0.0756
Hazard ratio of all-cause mortality		0.57
95% confidence interval		(0.31,1.03)

* Based on an analysis of recurrent events accounting for terminal events using a joint frailty model with terms for age (prec=0.3253/pterm=0.0028), baseline eGFR (CKD-EPI) (prec<0.0001/pterm=0.0020), sex (prec=0.4501/pterm=0.4755), Treatment (prec=0.0344/pterm=0.6196), Treatment by sex interaction (prec=0.5907/pterm=0.1581), region (prec<0.0001/pterm=0.0002), baseline diabetes status (3 cat.) (prec=0.0058/pterm=0.0534), baseline LVEF (3 cat.) (prec=0.4192/pterm=0.9947), estimated dependence between all-cause hospitalisation and all-cause mortality (alpha) (2.23) and variance of frailty (omega) (1.89).
pterm=p-value in terminal event model. prec=p-value in recurrent event model.

R.1.1.25.3

Table R.1.1.25.3: 1 Joint frailty model of all-cause hospitalisation and all-cause mortality by age - RS (trial 1245.121)

Subgroup Description	Placebo	Empa 10mg
Age (2 cat.): < 65		
Number of patients in analysis set	740	675
Number of analysed patients	740	675
Total number of all-cause hospitalisation	629	474
Number of patients with all-cause hospitalisation then all-cause mortality [N(%)]	58 (7.8)	47 (7.0)
Number of patients with all-cause hospitalisation only [N(%)]	248 (33.5)	177 (26.2)
Number of patients with all-cause mortality only [N(%)]	25 (3.4)	24 (3.6)
Comparison vs Placebo*		
Hazard ratio of all-cause hospitalisation		0.80
95% confidence interval		(0.66,0.98)
p-value		0.0278
Hazard ratio of all-cause mortality		0.89
95% confidence interval		(0.55,1.44)
Age (2 cat.): >= 65		
Number of patients in analysis set	1127	1188
Number of analysed patients	1127	1188
Total number of all-cause hospitalisation	941	890
Number of patients with all-cause hospitalisation then all-cause mortality [N(%)]	144 (12.8)	147 (12.4)
Number of patients with all-cause hospitalisation only [N(%)]	346 (30.7)	317 (26.7)
Number of patients with all-cause mortality only [N(%)]	39 (3.5)	31 (2.6)
Comparison vs Placebo*		
Hazard ratio of all-cause hospitalisation		0.87
95% confidence interval		(0.75,1.02)
p-value		0.0843
Hazard ratio of all-cause mortality		0.80
95% confidence interval		(0.57,1.14)

* Based on an analysis of recurrent events accounting for terminal events using a joint frailty model with terms for baseline eGFR (CKD-EPI) (prec<0.0001/pterm=0.0002), Age (2 cat.) (prec=0.1193/pterm=0.0285), Treatment (prec=0.0843/pterm=0.2208), Treatment by Age (2 cat.) interaction (prec=0.4969/pterm=0.7400), region (prec<0.0001/pterm=0.0003), sex (prec=0.1207/pterm=0.0247), baseline diabetes status (3 cat.) (prec=0.0068/pterm=0.0599), baseline LVEF (3 cat.) (prec=0.4201/pterm=0.9927), estimated dependence between all-cause hospitalisation and all-cause mortality (alpha) (2.24) and variance of frailty (omega) (1.89).
pterm=p-value in terminal event model. prec=p-value in recurrent event model.

R.1.1.25.4 Subgroup analysis by region (North America, Latin America, Europe, Asia, Other)

Table R.1.1.25.4: 1 Joint frailty model of all-cause hospitalisation and all-cause mortality by region - RS (trial 1245.121)

Subgroup Description	Placebo	Empa 10mg
Region: North America		
Number of patients in analysis set	213	212
Number of analysed patients	213	212
Total number of all-cause hospitalisation	271	274
Number of patients with all-cause hospitalisation then all-cause mortality [N(%)]	36 (16.9)	32 (15.1)
Number of patients with all-cause hospitalisation only [N(%)]	79 (37.1)	71 (33.5)
Number of patients with all-cause mortality only [N(%)]	3 (1.4)	2 (0.9)
Comparison vs Placebo*		
Hazard ratio of all-cause hospitalisation		0.85
95% confidence interval		(0.61,1.17)
p-value		0.3192
Hazard ratio of all-cause mortality		0.52
95% confidence interval		(0.24,1.16)
Region: Latin America		
Number of patients in analysis set	645	641
Number of analysed patients	645	641
Total number of all-cause hospitalisation	384	301
Number of patients with all-cause hospitalisation then all-cause mortality [N(%)]	62 (9.6)	74 (11.5)
Number of patients with all-cause hospitalisation only [N(%)]	176 (27.3)	126 (19.7)
Number of patients with all-cause mortality only [N(%)]	27 (4.2)	25 (3.9)
Comparison vs Placebo*		
Hazard ratio of all-cause hospitalisation		0.82
95% confidence interval		(0.66,1.02)
p-value		0.0789
Hazard ratio of all-cause mortality		1.13
95% confidence interval		(0.70,1.81)

* Based on an analysis of recurrent events accounting for terminal events using a joint frailty model with terms for age (prec=0.3637/pterm=0.0033), baseline eGFR (CKD-EPI) (prec<0.0001/pterm=0.0014), region (prec<0.0001/pterm=0.0852), Treatment (prec=0.9044/pterm=0.4769), Treatment by region interaction (prec=0.0772/pterm=0.4067), sex (prec=0.1034/pterm=0.0194), baseline diabetes status (3 cat.) (prec=0.0048/pterm=0.0563), baseline LVEF (3 cat.) (prec=0.4010/pterm=0.9971), estimated dependence between all-cause hospitalisation and all-cause mortality (alpha) (2.24) and variance of frailty (omega) (1.88).
pterm=p-value in terminal event model. prec=p-value in recurrent event model.

Table R.1.1.25.4: 1 Joint frailty model of all-cause hospitalisation and all-cause mortality by region - RS (trial 1245.121)

Subgroup Description	Placebo	Empa 10mg
Region: Europe		
Number of patients in analysis set	677	676
Number of analysed patients	677	676
Total number of all-cause hospitalisation	595	588
Number of patients with all-cause hospitalisation then all-cause mortality [N(%)]	75 (11.1)	66 (9.8)
Number of patients with all-cause hospitalisation only [N(%)]	226 (33.4)	217 (32.1)
Number of patients with all-cause mortality only [N(%)]	21 (3.1)	18 (2.7)
Comparison vs Placebo*		
Hazard ratio of all-cause hospitalisation		0.99
95% confidence interval		(0.81,1.20)
p-value		0.9044
Hazard ratio of all-cause mortality		0.84
95% confidence interval		(0.53,1.35)
Region: Asia		
Number of patients in analysis set	245	248
Number of analysed patients	245	248
Total number of all-cause hospitalisation	279	179
Number of patients with all-cause hospitalisation then all-cause mortality [N(%)]	21 (8.6)	20 (8.1)
Number of patients with all-cause hospitalisation only [N(%)]	98 (40.0)	67 (27.0)
Number of patients with all-cause mortality only [N(%)]	9 (3.7)	7 (2.8)
Comparison vs Placebo*		
Hazard ratio of all-cause hospitalisation		0.60
95% confidence interval		(0.44,0.83)
p-value		0.0018
Hazard ratio of all-cause mortality		0.69
95% confidence interval		(0.31,1.55)

* Based on an analysis of recurrent events accounting for terminal events using a joint frailty model with terms for age (prec=0.3637/pterm=0.0033), baseline eGFR (CKD-EPI) (prec<0.0001/pterm=0.0014), region (prec<0.0001/pterm=0.0852), Treatment (prec=0.9044/pterm=0.4769), Treatment by region interaction (prec=0.0772/pterm=0.4067), sex (prec=0.1034/pterm=0.0194), baseline diabetes status (3 cat.) (prec=0.0048/pterm=0.0563), baseline LVEF (3 cat.) (prec=0.4010/pterm=0.9971), estimated dependence between all-cause hospitalisation and all-cause mortality (alpha) (2.24) and variance of frailty (omega) (1.88).
pterm=p-value in terminal event model. prec=p-value in recurrent event model.

Table R.1.1.25.4: 1 Joint frailty model of all-cause hospitalisation and all-cause mortality by region - RS (trial 1245.121)

Subgroup Description	Placebo	Empa 10mg
Region: Other		
Number of patients in analysis set	87	86
Number of analysed patients	87	86
Total number of all-cause hospitalisation	41	22
Number of patients with all-cause hospitalisation then all-cause mortality [N(%)]	8 (9.2)	2 (2.3)
Number of patients with all-cause hospitalisation only [N(%)]	15 (17.2)	13 (15.1)
Number of patients with all-cause mortality only [N(%)]	4 (4.6)	3 (3.5)
Comparison vs Placebo*		
Hazard ratio of all-cause hospitalisation		0.55
95% confidence interval		(0.27,1.09)
p-value		0.0865
Hazard ratio of all-cause mortality		0.40
95% confidence interval		(0.09,1.80)

* Based on an analysis of recurrent events accounting for terminal events using a joint frailty model with terms for age (prec=0.3637/pterm=0.0033), baseline eGFR (CKD-EPI) (prec<0.0001/pterm=0.0014), region (prec<0.0001/pterm=0.0852), Treatment (prec=0.9044/pterm=0.4769), Treatment by region interaction (prec=0.0772/pterm=0.4067), sex (prec=0.1034/pterm=0.0194), baseline diabetes status (3 cat.) (prec=0.0048/pterm=0.0563), baseline LVEF (3 cat.) (prec=0.4010/pterm=0.9971), estimated dependence between all-cause hospitalisation and all-cause mortality (alpha) (2.24) and variance of frailty (omega) (1.88).
pterm=p-value in terminal event model. prec=p-value in recurrent event model.

R.1.1.25.5

R.1.1.25.5 Subgroup analysis by OECD member (Y/N)

Table R.1.1.25.5: 1 Joint frailty model of all-cause hospitalisation and all-cause mortality by OECD member - RS (trial 1245.121)

Subgroup Description	Placebo	Empa 10mg
OECD member: No		
Number of patients in analysis set	741	713
Number of analysed patients	741	713
Total number of all-cause hospitalisation	480	321
Number of patients with all-cause hospitalisation then all-cause mortality [N(%)]	71 (9.6)	76 (10.7)
Number of patients with all-cause hospitalisation only [N(%)]	203 (27.4)	137 (19.2)
Number of patients with all-cause mortality only [N(%)]	32 (4.3)	30 (4.2)
Comparison vs Placebo*		
Hazard ratio of all-cause hospitalisation		0.74
95% confidence interval		(0.60,0.91)
p-value		0.0047
Hazard ratio of all-cause mortality		1.12
95% confidence interval		(0.72,1.74)

* Based on an analysis of recurrent events accounting for terminal events using a joint frailty model with terms for age (prec=0.4293/pterm=0.0018), baseline eGFR (CKD-EPI) (prec<0.0001/pterm=0.0003), OECD member (prec=0.0949/pterm=0.0130), Treatment (prec=0.1102/pterm=0.0590), Treatment by OECD member interaction (prec=0.1650/pterm=0.1131), sex (prec=0.1590/pterm=0.0318), baseline diabetes status (3 cat.) (prec=0.0050/pterm=0.0533), baseline LVEF (3 cat.) (prec=0.3196/pterm=0.8952), estimated dependence between all-cause hospitalisation and all-cause mortality (alpha) (2.15) and variance of frailty (omega) (1.95).
pterm=p-value in terminal event model. prec=p-value in recurrent event model.

OECD member (yes/no) countries included:
Yes: United States, Canada, Mexico, Poland, Netherlands, Hungary, Germany, Czech Republic, Italy, France, Spain, United Kingdom, Belgium, Japan, Australia, 'Korea; Republic Of South Korea';
No: Brazil, Argentina, China, India.

Table R.1.1.25.5: 1 Joint frailty model of all-cause hospitalisation and all-cause mortality by OECD member - RS (trial 1245.121)

Subgroup Description	Placebo	Empa 10mg
OECD member: Yes		
Number of patients in analysis set	1126	1150
Number of analysed patients	1126	1150
Total number of all-cause hospitalisation	1090	1043
Number of patients with all-cause hospitalisation then all-cause mortality [N(%)]	131 (11.6)	118 (10.3)
Number of patients with all-cause hospitalisation only [N(%)]	391 (34.7)	357 (31.0)
Number of patients with all-cause mortality only [N(%)]	32 (2.8)	25 (2.2)
Comparison vs Placebo*		
Hazard ratio of all-cause hospitalisation		0.89
95% confidence interval		(0.76,1.03)
p-value		0.1102
Hazard ratio of all-cause mortality		0.71
95% confidence interval		(0.49,1.01)

* Based on an analysis of recurrent events accounting for terminal events using a joint frailty model with terms for age (prec=0.4293/pterm=0.0018), baseline eGFR (CKD-EPI) (prec<0.0001/pterm=0.0003), OECD member (prec=0.0949/pterm=0.0130), Treatment (prec=0.1102/pterm=0.0590), Treatment by OECD member interaction (prec=0.1650/pterm=0.1131), sex (prec=0.1590/pterm=0.0318), baseline diabetes status (3 cat.) (prec=0.0050/pterm=0.0533), baseline LVEF (3 cat.) (prec=0.3196/pterm=0.8952), estimated dependence between all-cause hospitalisation and all-cause mortality (alpha) (2.15) and variance of frailty (omega) (1.95). pterm=p-value in terminal event model. prec=p-value in recurrent event model.

OECD member (yes/no) countries included:
Yes: United States, Canada, Mexico, Poland, Netherlands, Hungary, Germany, Czech Republic, Italy, France, Spain, United Kingdom, Belgium, Japan, Australia, 'Korea; Republic Of South Korea';
No: Brazil, Argentina, China, India.

R.1.1.25.6

R.1.1.25.6 Subgroup analysis by NYHA at baseline (II, III/IV - 2 cat.)

Table R.1.1.25.6: 1 Joint frailty model of all-cause hospitalisation and all-cause mortality by NYHA at baseline (2 cat.) - RS (trial 1245.121)

Subgroup Description	Placebo	Empa 10mg
History of NYHA (2 cat.): II		
Number of patients in analysis set	1401	1399
Number of analysed patients	1401	1399
Total number of all-cause hospitalisation	1066	855
Number of patients with all-cause hospitalisation then all-cause mortality [N(%)]	128 (9.1)	119 (8.5)
Number of patients with all-cause hospitalisation only [N(%)]	431 (30.8)	330 (23.6)
Number of patients with all-cause mortality only [N(%)]	36 (2.6)	42 (3.0)
Comparison vs Placebo*		
Hazard ratio of all-cause hospitalisation		0.81
95% confidence interval		(0.70,0.93)
p-value		0.0031
Hazard ratio of all-cause mortality		0.93
95% confidence interval		(0.67,1.30)
History of NYHA (2 cat.): III/IV		
Number of patients in analysis set	466	464
Number of analysed patients	466	464
Total number of all-cause hospitalisation	504	509
Number of patients with all-cause hospitalisation then all-cause mortality [N(%)]	74 (15.9)	75 (16.2)
Number of patients with all-cause hospitalisation only [N(%)]	163 (35.0)	164 (35.3)
Number of patients with all-cause mortality only [N(%)]	28 (6.0)	13 (2.8)
Comparison vs Placebo*		
Hazard ratio of all-cause hospitalisation		0.90
95% confidence interval		(0.72,1.13)
p-value		0.3684
Hazard ratio of all-cause mortality		0.66
95% confidence interval		(0.39,1.10)

* Based on an analysis of recurrent events accounting for terminal events using a joint frailty model with terms for age (prec=0.3517/pterm=0.0021), baseline eGFR (CKD-EPI) (prec<0.0001/pterm=0.0033), History of NYHA (2 cat.) (prec<0.0001/pterm<0.0001), Treatment (prec=0.0031/pterm=0.6802), Treatment by History of NYHA (2 cat.) interaction (prec=0.4191/pterm=0.2600), region (prec<0.0001/pterm=0.0002), sex (prec=0.0520/pterm=0.0080), baseline diabetes status (3 cat.) (prec=0.0377/pterm=0.1732), baseline LVEF (3 cat.) (prec=0.3852/pterm=0.9864), estimated dependence between all-cause hospitalisation and all-cause mortality (alpha) (2.24) and variance of frailty (omega) (1.80).
pterm=p-value in terminal event model. prec=p-value in recurrent event model.

R.1.1.25.7

Table R.1.1.25.7: 1 Joint frailty model of all-cause hospitalisation and all-cause mortality by diabetes at baseline - RS (trial 1245.121)

Subgroup Description	Placebo	Empa 10mg
Baseline diabetes status (2 cat.): Diabetic		
Number of patients in analysis set	929	927
Number of analysed patients	929	927
Total number of all-cause hospitalisation	877	732
Number of patients with all-cause hospitalisation then all-cause mortality [N(%)]	115 (12.4)	118 (12.7)
Number of patients with all-cause hospitalisation only [N(%)]	298 (32.1)	250 (27.0)
Number of patients with all-cause mortality only [N(%)]	34 (3.7)	24 (2.6)
Comparison vs Placebo*		
Hazard ratio of all-cause hospitalisation		0.87
95% confidence interval		(0.73,1.03)
p-value		0.0989
Hazard ratio of all-cause mortality		0.99
95% confidence interval		(0.67,1.45)
Baseline diabetes status (2 cat.): Non-Diabetic		
Number of patients in analysis set	938	936
Number of analysed patients	938	936
Total number of all-cause hospitalisation	693	632
Number of patients with all-cause hospitalisation then all-cause mortality [N(%)]	87 (9.3)	76 (8.1)
Number of patients with all-cause hospitalisation only [N(%)]	296 (31.6)	244 (26.1)
Number of patients with all-cause mortality only [N(%)]	30 (3.2)	31 (3.3)
Comparison vs Placebo*		
Hazard ratio of all-cause hospitalisation		0.83
95% confidence interval		(0.69,0.98)
p-value		0.0313
Hazard ratio of all-cause mortality		0.68
95% confidence interval		(0.45,1.02)

* Based on an analysis of recurrent events accounting for terminal events using a joint frailty model with terms for age (prec=0.3341/pterm=0.0025), baseline eGFR (CKD-EPI) (prec<0.0001/pterm=0.0019), Baseline diabetes status (2 cat.) (prec=0.0539/pterm=0.4467), Treatment (prec=0.0989/pterm=0.9500), Treatment by Baseline diabetes status (2 cat.) interaction (prec=0.6850/pterm=0.1898), region (prec<0.0001/pterm=0.0001), sex (prec=0.1174/pterm=0.0215), baseline LVEF (3 cat.) (prec=0.4143/pterm=0.9725), estimated dependence between all-cause hospitalisation and all-cause mortality (alpha) (2.23) and variance of frailty (omega) (1.89).
pterm=p-value in terminal event model. prec=p-value in recurrent event model.

R.1.1.25.8 Subgroup analysis by BMI at baseline (<30, >=30)

Table R.1.1.25.8: 1 Joint frailty model of all-cause hospitalisation and all-cause mortality by baseline BMI [kg/m2] - RS (trial 1245.121)

Subgroup Description	Placebo	Empa 10mg
Baseline BMI [kg/m²]: <30		
Number of patients in analysis set	1300	1263
Number of analysed patients	1300	1263
Total number of all-cause hospitalisation	1034	867
Number of patients with all-cause hospitalisation then all-cause mortality [N(%)]	151 (11.6)	125 (9.9)
Number of patients with all-cause hospitalisation only [N(%)]	397 (30.5)	311 (24.6)
Number of patients with all-cause mortality only [N(%)]	47 (3.6)	47 (3.7)
Comparison vs Placebo*		
Hazard ratio of all-cause hospitalisation		0.84
95% confidence interval		(0.73,0.97)
p-value		0.0214
Hazard ratio of all-cause mortality		0.78
95% confidence interval		(0.55,1.10)
Baseline BMI [kg/m²]: >=30		
Number of patients in analysis set	567	600
Number of analysed patients	567	600
Total number of all-cause hospitalisation	536	497
Number of patients with all-cause hospitalisation then all-cause mortality [N(%)]	51 (9.0)	69 (11.5)
Number of patients with all-cause hospitalisation only [N(%)]	197 (34.7)	183 (30.5)
Number of patients with all-cause mortality only [N(%)]	17 (3.0)	8 (1.3)
Comparison vs Placebo*		
Hazard ratio of all-cause hospitalisation		0.85
95% confidence interval		(0.69,1.05)
p-value		0.1337
Hazard ratio of all-cause mortality		0.96
95% confidence interval		(0.58,1.62)

* Based on an analysis of recurrent events accounting for terminal events using a joint frailty model with terms for age (prec=0.5133/pterm=0.0057), baseline eGFR (CKD-EPI) (prec<0.0001/pterm=0.0014), Baseline BMI [kg/m²] (prec=0.2074/pterm=0.1869), Treatment (prec=0.0214/pterm=0.1534), Treatment by Baseline BMI [kg/m²] interaction (prec=0.9323/pterm=0.4999), region (prec<0.0001/pterm=0.0002), sex (prec=0.0955/pterm=0.0275), baseline diabetes status (3 cat.) (prec=0.0133/pterm=0.0430), baseline LVEF (3 cat.) (prec=0.4018/pterm=0.9865), estimated dependence between all-cause hospitalisation and all-cause mortality (alpha) (2.26) and variance of frailty (omega) (1.89).
pterm=p-value in terminal event model. prec=p-value in recurrent event model.

R.1.1.25.9

R.1.1.25.9 Subgroup analysis by eGFR at baseline (<60, >=60)

Table R.1.1.25.9: 1 Joint frailty model of all-cause hospitalisation and all-cause mortality by baseline eGFR (2 cat.) - RS (trial 1245.121)

Subgroup Description	Placebo	Empa 10mg
Baseline eGFR (2 cat.): >=60		
Number of patients in analysis set	960	969
Number of analysed patients	960	969
Total number of all-cause hospitalisation	751	581
Number of patients with all-cause hospitalisation then all-cause mortality [N(%)]	80 (8.3)	80 (8.3)
Number of patients with all-cause hospitalisation only [N(%)]	306 (31.9)	218 (22.5)
Number of patients with all-cause mortality only [N(%)]	31 (3.2)	31 (3.2)
Comparison vs Placebo*		
Hazard ratio of all-cause hospitalisation		0.77
95% confidence interval		(0.65,0.92)
p-value		0.0032
Hazard ratio of all-cause mortality		0.90
95% confidence interval		(0.60,1.36)

* Based on an analysis of recurrent events accounting for terminal events using a joint frailty model with terms for age (prec=0.5575/pterm<0.0001), Baseline eGFR (2 cat.) (prec=0.0605/pterm=0.0691), Treatment (prec=0.3934/pterm=0.2576), Treatment by Baseline eGFR (2 cat.) interaction (prec=0.1293/pterm=0.6684), region (prec<0.0001/pterm=0.0002), sex (prec=0.1653/pterm=0.0224), baseline diabetes status (3 cat.) (prec=0.0047/pterm=0.0569), baseline LVEF (3 cat.) (prec=0.3937/pterm=0.9998), estimated dependence between all-cause hospitalisation and all-cause mortality (alpha) (2.21) and variance of frailty (omega) (1.92).
pterm=p-value in terminal event model. prec=p-value in recurrent event model.
2 patients were excluded as the subgroup variable was missing.

Table R.1.1.25.9: 1 Joint frailty model of all-cause hospitalisation and all-cause mortality by baseline eGFR (2 cat.) - RS (trial 1245.121)

Subgroup Description	Placebo	Empa 10mg
Baseline eGFR (2 cat.): <60		
Number of patients in analysis set	906	893
Number of analysed patients	906	893
Total number of all-cause hospitalisation	818	783
Number of patients with all-cause hospitalisation then all-cause mortality [N(%)]	121 (13.4)	114 (12.8)
Number of patients with all-cause hospitalisation only [N(%)]	288 (31.8)	276 (30.9)
Number of patients with all-cause mortality only [N(%)]	33 (3.6)	24 (2.7)
Comparison vs Placebo*		
Hazard ratio of all-cause hospitalisation		0.93
95% confidence interval		(0.78,1.10)
p-value		0.3934
Hazard ratio of all-cause mortality		0.80
95% confidence interval		(0.54,1.18)

* Based on an analysis of recurrent events accounting for terminal events using a joint frailty model with terms for age (prec=0.5575/pterm<0.0001), Baseline eGFR (2 cat.) (prec=0.0605/pterm=0.0691), Treatment (prec=0.3934/pterm=0.2576), Treatment by Baseline eGFR (2 cat.) interaction (prec=0.1293/pterm=0.6684), region (prec<0.0001/pterm=0.0002), sex (prec=0.1653/pterm=0.0224), baseline diabetes status (3 cat.) (prec=0.0047/pterm=0.0569), baseline LVEF (3 cat.) (prec=0.3937/pterm=0.9998), estimated dependence between all-cause hospitalisation and all-cause mortality (alpha) (2.21) and variance of frailty (omega) (1.92).
pterm=p-value in terminal event model. prec=p-value in recurrent event model.
2 patients were excluded as the subgroup variable was missing.

R.1.1.25.10

Table R.1.1.25.10: 1 Joint frailty model of all-cause hospitalisation and all-cause mortality by history of HHF within 12 months - RS (trial 1245.121)

Subgroup Description	Placebo	Empa 10mg
History of HHF (in the last 12 months): No		
Number of patients in analysis set	1293	1286
Number of analysed patients	1293	1286
Total number of all-cause hospitalisation	992	850
Number of patients with all-cause hospitalisation then all-cause mortality [N(%)]	130 (10.1)	124 (9.6)
Number of patients with all-cause hospitalisation only [N(%)]	400 (30.9)	316 (24.6)
Number of patients with all-cause mortality only [N(%)]	41 (3.2)	35 (2.7)
Comparison vs Placebo*		
Hazard ratio of all-cause hospitalisation		0.87
95% confidence interval		(0.75,1.01)
p-value		0.0632
Hazard ratio of all-cause mortality		0.88
95% confidence interval		(0.63,1.25)
History of HHF (in the last 12 months): Yes		
Number of patients in analysis set	574	577
Number of analysed patients	574	577
Total number of all-cause hospitalisation	578	514
Number of patients with all-cause hospitalisation then all-cause mortality [N(%)]	72 (12.5)	70 (12.1)
Number of patients with all-cause hospitalisation only [N(%)]	194 (33.8)	178 (30.8)
Number of patients with all-cause mortality only [N(%)]	23 (4.0)	20 (3.5)
Comparison vs Placebo*		
Hazard ratio of all-cause hospitalisation		0.79
95% confidence interval		(0.64,0.97)
p-value		0.0237
Hazard ratio of all-cause mortality		0.71
95% confidence interval		(0.43,1.16)

* Based on an analysis of recurrent events accounting for terminal events using a joint frailty model with terms for age (prec=0.6622/pterm=0.0009), baseline eGFR (CKD-EPI) (prec<0.0001/pterm=0.0025), History of HHF (in the last 12 months) (prec<0.0001/pterm=0.0002), Treatment (prec=0.0632/pterm=0.4780), Treatment by History of HHF (in the last 12 months) interaction (prec=0.4296/pterm=0.4764), region (prec<0.0001/pterm<0.0001), sex (prec=0.0816/pterm=0.0155), baseline diabetes status (3 cat.) (prec=0.0249/pterm=0.1177), baseline LVEF (3 cat.) (prec=0.5300/pterm=0.7944), estimated dependence between all-cause hospitalisation and all-cause mortality (alpha) (2.25) and variance of frailty (omega) (1.85).
pterm=p-value in terminal event model. prec=p-value in recurrent event model.

R.1.1.25.11

Table R.1.1.25.11: 1 Joint frailty model of all-cause hospitalisation and all-cause mortality by cause of heart failure - RS (trial 1245.121)

Subgroup Description	Placebo	Empa 10mg
Cause of heart failure: Ischemic		
Number of patients in analysis set	946	983
Number of analysed patients	946	983
Total number of all-cause hospitalisation	836	798
Number of patients with all-cause hospitalisation then all-cause mortality [N(%)]	113 (11.9)	125 (12.7)
Number of patients with all-cause hospitalisation only [N(%)]	296 (31.3)	267 (27.2)
Number of patients with all-cause mortality only [N(%)]	38 (4.0)	31 (3.2)
Comparison vs Placebo*		
Hazard ratio of all-cause hospitalisation		0.91
95% confidence interval		(0.77,1.07)
p-value		0.2381
Hazard ratio of all-cause mortality		0.93
95% confidence interval		(0.64,1.36)
Cause of heart failure: Non-ischemic		
Number of patients in analysis set	921	880
Number of analysed patients	921	880
Total number of all-cause hospitalisation	734	566
Number of patients with all-cause hospitalisation then all-cause mortality [N(%)]	89 (9.7)	69 (7.8)
Number of patients with all-cause hospitalisation only [N(%)]	298 (32.4)	227 (25.8)
Number of patients with all-cause mortality only [N(%)]	26 (2.8)	24 (2.7)
Comparison vs Placebo*		
Hazard ratio of all-cause hospitalisation		0.78
95% confidence interval		(0.65,0.93)
p-value		0.0052
Hazard ratio of all-cause mortality		0.71
95% confidence interval		(0.46,1.08)

* Based on an analysis of recurrent events accounting for terminal events using a joint frailty model with terms for age (prec=0.2507/pterm=0.0066), baseline eGFR (CKD-EPI) (prec<0.0001/pterm=0.0016), Cause of heart failure (prec=0.7883/pterm=0.3588), Treatment (prec=0.2381/pterm=0.7067), Treatment by Cause of heart failure interaction (prec=0.2146/pterm=0.3439), region (prec<0.0001/pterm<0.0001), sex (prec=0.1625/pterm=0.0415), baseline diabetes status (3 cat.) (prec=0.0125/pterm=0.1155), baseline LVEF (3 cat.) (prec=0.4380/pterm=0.9768), estimated dependence between all-cause hospitalisation and all-cause mortality (alpha) (2.20) and variance of frailty (omega) (1.89).
pterm=p-value in terminal event model. prec=p-value in recurrent event model.

R.1.1.25.12 Subgroup analysis by heart failure physiology (LVEF <= 30% and NTproBNP<median; LVEF <= 30% and NTproBNP>=median; LVEF > 30%)

Table R.1.1.25.12: 1 Joint frailty model of all-cause hospitalisation and all-cause mortality by heart failure physiology - RS (trial 1245.121)

Subgroup Description	Placebo	Empa 10mg
Heart failure physiology: LVEF <= 30% and NTproBNP < median		
Number of patients in analysis set	723	698
Number of analysed patients	723	698
Total number of all-cause hospitalisation	489	379
Number of patients with all-cause hospitalisation then all-cause mortality [N(%)]	48 (6.6)	49 (7.0)
Number of patients with all-cause hospitalisation only [N(%)]	216 (29.9)	155 (22.2)
Number of patients with all-cause mortality only [N(%)]	14 (1.9)	15 (2.1)
Comparison vs Placebo*		
Hazard ratio of all-cause hospitalisation		0.83
95% confidence interval		(0.68,1.02)
p-value		0.0735
Hazard ratio of all-cause mortality		1.06
95% confidence interval		(0.65,1.73)

* Based on an analysis of recurrent events accounting for terminal events using a joint frailty model with terms for age (prec=0.3771/pterm=0.0017), baseline eGFR (CKD-EPI) (prec<0.0001/pterm=0.0477), Heart failure physiology (prec<0.0001/pterm<0.0001), Treatment (prec=0.0203/pterm=0.0194), Treatment by Heart failure physiology interaction (prec=0.5786/pterm=0.1298), region (prec<0.0001/pterm=0.0003), sex (prec=0.1882/pterm=0.0308), baseline diabetes status (3 cat.) (prec=0.0079/pterm=0.0945), estimated dependence between all-cause hospitalisation and all-cause mortality (alpha) (2.16) and variance of frailty (omega) (1.79).
pterm=p-value in terminal event model. prec=p-value in recurrent event model.
16 patients were excluded as the subgroup variable was missing.

Table R.1.1.25.12: 1 Joint frailty model of all-cause hospitalisation and all-cause mortality by heart failure physiology - RS (trial 1245.121)

Subgroup Description	Placebo	Empa 10mg
Heart failure physiology: LVEF <= 30% and NTproBNP >= median		
Number of patients in analysis set	661	631
Number of analysed patients	661	631
Total number of all-cause hospitalisation	712	589
Number of patients with all-cause hospitalisation then all-cause mortality [N(%)]	110 (16.6)	80 (12.7)
Number of patients with all-cause hospitalisation only [N(%)]	232 (35.1)	200 (31.7)
Number of patients with all-cause mortality only [N(%)]	32 (4.8)	22 (3.5)
Comparison vs Placebo*		
Hazard ratio of all-cause hospitalisation		0.80
95% confidence interval		(0.66,0.97)
p-value		0.0203
Hazard ratio of all-cause mortality		0.59
95% confidence interval		(0.38,0.92)

* Based on an analysis of recurrent events accounting for terminal events using a joint frailty model with terms for age (prec=0.3771/pterm=0.0017), baseline eGFR (CKD-EPI) (prec<0.0001/pterm=0.0477), Heart failure physiology (prec<0.0001/pterm<0.0001), Treatment (prec=0.0203/pterm=0.0194), Treatment by Heart failure physiology interaction (prec=0.5786/pterm=0.1298), region (prec<0.0001/pterm=0.0003), sex (prec=0.1882/pterm=0.0308), baseline diabetes status (3 cat.) (prec=0.0079/pterm=0.0945), estimated dependence between all-cause hospitalisation and all-cause mortality (alpha) (2.16) and variance of frailty (omega) (1.79).
pterm=p-value in terminal event model. prec=p-value in recurrent event model.
16 patients were excluded as the subgroup variable was missing.

Table R.1.1.25.12: 1 Joint frailty model of all-cause hospitalisation and all-cause mortality by heart failure physiology - RS (trial 1245.121)

Subgroup Description	Placebo	Empa 10mg
Heart failure physiology: LVEF > 30%		
Number of patients in analysis set	475	526
Number of analysed patients	475	526
Total number of all-cause hospitalisation	357	392
Number of patients with all-cause hospitalisation then all-cause mortality [N(%)]	42 (8.8)	62 (11.8)
Number of patients with all-cause hospitalisation only [N(%)]	143 (30.1)	139 (26.4)
Number of patients with all-cause mortality only [N(%)]	18 (3.8)	17 (3.2)
Comparison vs Placebo*		
Hazard ratio of all-cause hospitalisation		0.93
95% confidence interval		(0.74,1.18)
p-value		0.5530
Hazard ratio of all-cause mortality		1.07
95% confidence interval		(0.63,1.81)

* Based on an analysis of recurrent events accounting for terminal events using a joint frailty model with terms for age (prec=0.3771/pterm=0.0017), baseline eGFR (CKD-EPI) (prec<0.0001/pterm=0.0477), Heart failure physiology (prec<0.0001/pterm<0.0001), Treatment (prec=0.0203/pterm=0.0194), Treatment by Heart failure physiology interaction (prec=0.5786/pterm=0.1298), region (prec<0.0001/pterm=0.0003), sex (prec=0.1882/pterm=0.0308), baseline diabetes status (3 cat.) (prec=0.0079/pterm=0.0945), estimated dependence between all-cause hospitalisation and all-cause mortality (alpha) (2.16) and variance of frailty (omega) (1.79).
pterm=p-value in terminal event model. prec=p-value in recurrent event model.
16 patients were excluded as the subgroup variable was missing.

R.1.1.25.13

R.1.1.25.13 Subgroup analysis by baseline use of MRA

Table R.1.1.25.13: 1 Joint frailty model of all-cause hospitalisation and all-cause mortality by baseline use of MRA - RS (trial 1245.121)

Subgroup Description	Placebo	Empa 10mg
Baseline use of MRA: No		
Number of patients in analysis set	512	557
Number of analysed patients	512	557
Total number of all-cause hospitalisation	484	450
Number of patients with all-cause hospitalisation then all-cause mortality [N(%)]	54 (10.5)	66 (11.8)
Number of patients with all-cause hospitalisation only [N(%)]	185 (36.1)	156 (28.0)
Number of patients with all-cause mortality only [N(%)]	14 (2.7)	21 (3.8)
Comparison vs Placebo*		
Hazard ratio of all-cause hospitalisation		0.82
95% confidence interval		(0.66,1.02)
p-value		0.0733
Hazard ratio of all-cause mortality		1.00
95% confidence interval		(0.60,1.68)
Baseline use of MRA: Yes		
Number of patients in analysis set	1355	1306
Number of analysed patients	1355	1306
Total number of all-cause hospitalisation	1086	914
Number of patients with all-cause hospitalisation then all-cause mortality [N(%)]	148 (10.9)	128 (9.8)
Number of patients with all-cause hospitalisation only [N(%)]	409 (30.2)	338 (25.9)
Number of patients with all-cause mortality only [N(%)]	50 (3.7)	34 (2.6)
Comparison vs Placebo*		
Hazard ratio of all-cause hospitalisation		0.86
95% confidence interval		(0.75,1.00)
p-value		0.0460
Hazard ratio of all-cause mortality		0.77
95% confidence interval		(0.55,1.08)

* Based on an analysis of recurrent events accounting for terminal events using a joint frailty model with terms for age (prec=0.3904/pterm=0.0022), baseline eGFR (CKD-EPI) (prec<0.0001/pterm=0.0011), Baseline use of MRA (prec=0.4564/pterm=0.1370), Treatment (prec=0.0460/pterm=0.1314), Treatment by Baseline use of MRA interaction (prec=0.6871/pterm=0.4107), region (prec<0.0001/pterm=0.0002), sex (prec=0.1161/pterm=0.0213), baseline diabetes status (3 cat.) (prec=0.0056/pterm=0.0572), baseline LVEF (3 cat.) (prec=0.4322/pterm=0.9963), estimated dependence between all-cause hospitalisation and all-cause mortality (alpha) (2.21) and variance of frailty (omega) (1.89).
pterm=p-value in terminal event model. prec=p-value in recurrent event model.

R.1.1.25.14

Table R.1.1.25.14: 1 Joint frailty model of all-cause hospitalisation and all-cause mortality by baseline use of ARNi - RS (trial 1245.121)

Subgroup Description	Placebo	Empa 10mg
Baseline use of ARNi: No		
Number of patients in analysis set	1480	1523
Number of analysed patients	1480	1523
Total number of all-cause hospitalisation	1236	1098
Number of patients with all-cause hospitalisation then all-cause mortality [N(%)]	157 (10.6)	166 (10.9)
Number of patients with all-cause hospitalisation only [N(%)]	464 (31.4)	394 (25.9)
Number of patients with all-cause mortality only [N(%)]	56 (3.8)	51 (3.3)
Comparison vs Placebo*		
Hazard ratio of all-cause hospitalisation		0.84
95% confidence interval		(0.73,0.96)
p-value		0.0103
Hazard ratio of all-cause mortality		0.91
95% confidence interval		(0.66,1.24)
Baseline use of ARNi: Yes		
Number of patients in analysis set	387	340
Number of analysed patients	387	340
Total number of all-cause hospitalisation	334	266
Number of patients with all-cause hospitalisation then all-cause mortality [N(%)]	45 (11.6)	28 (8.2)
Number of patients with all-cause hospitalisation only [N(%)]	130 (33.6)	100 (29.4)
Number of patients with all-cause mortality only [N(%)]	8 (2.1)	4 (1.2)
Comparison vs Placebo*		
Hazard ratio of all-cause hospitalisation		0.88
95% confidence interval		(0.67,1.15)
p-value		0.3431
Hazard ratio of all-cause mortality		0.52
95% confidence interval		(0.26,1.02)

* Based on an analysis of recurrent events accounting for terminal events using a joint frailty model with terms for age (prec=0.3463/pterm=0.0037), baseline eGFR (CKD-EPI) (prec<0.0001/pterm=0.0015), Baseline use of ARNi (prec=0.8574/pterm=0.5596), Treatment (prec=0.0103/pterm=0.5438), Treatment by Baseline use of ARNi interaction (prec=0.7677/pterm=0.1392), region (prec<0.0001/pterm=0.0002), sex (prec=0.1074/pterm=0.0302), baseline diabetes status (3 cat.) (prec=0.0056/pterm=0.0585), baseline LVEF (3 cat.) (prec=0.4182/pterm=0.9637), estimated dependence between all-cause hospitalisation and all-cause mortality (alpha) (2.24) and variance of frailty (omega) (1.89).
pterm=p-value in terminal event model. prec=p-value in recurrent event model.

R.1.1.25.15 Subgroup analysis by bl. LVEF (<= 30%, >30% -<= 35% , > 35%)

Table R.1.1.25.15: 1 Joint frailty model of all-cause hospitalisation and all-cause mortality by bl. LVEF (3 cat.) - RS (trial 1245.121)

Subgroup Description	Placebo	Empa 10mg
baseline LVEF (3 cat.): <=30		
Number of patients in analysis set	1392	1337
Number of analysed patients	1392	1337
Total number of all-cause hospitalisation	1213	972
Number of patients with all-cause hospitalisation then all-cause mortality [N(%)]	160 (11.5)	132 (9.9)
Number of patients with all-cause hospitalisation only [N(%)]	451 (32.4)	355 (26.6)
Number of patients with all-cause mortality only [N(%)]	46 (3.3)	38 (2.8)
Comparison vs Placebo*		
Hazard ratio of all-cause hospitalisation		0.82
95% confidence interval		(0.71,0.94)
p-value		0.0047
Hazard ratio of all-cause mortality		0.75
95% confidence interval		(0.54,1.05)
baseline LVEF (3 cat.): >30 to <=35		
Number of patients in analysis set	361	398
Number of analysed patients	361	398
Total number of all-cause hospitalisation	256	281
Number of patients with all-cause hospitalisation then all-cause mortality [N(%)]	30 (8.3)	45 (11.3)
Number of patients with all-cause hospitalisation only [N(%)]	105 (29.1)	103 (25.9)
Number of patients with all-cause mortality only [N(%)]	16 (4.4)	15 (3.8)
Comparison vs Placebo*		
Hazard ratio of all-cause hospitalisation		0.95
95% confidence interval		(0.72,1.24)
p-value		0.6945
Hazard ratio of all-cause mortality		1.17
95% confidence interval		(0.63,2.18)

* Based on an analysis of recurrent events accounting for terminal events using a joint frailty model with terms for age (prec=0.3267/pterm=0.0028), baseline eGFR (CKD-EPI) (prec<0.0001/pterm=0.0015), baseline LVEF (3 cat.) (prec=0.3349/pterm=0.6447), Treatment (prec=0.0047/pterm=0.0919), Treatment by baseline LVEF (3 cat.) interaction (prec=0.6258/pterm=0.4709), region (prec<0.0001/pterm=0.0002), sex (prec=0.1147/pterm=0.0222), baseline diabetes status (3 cat.) (prec=0.0060/pterm=0.0540), estimated dependence between all-cause hospitalisation and all-cause mortality (alpha) (2.22) and variance of frailty (omega) (1.89).
pterm=p-value in terminal event model. prec=p-value in recurrent event model.

Table R.1.1.25.15: 1 Joint frailty model of all-cause hospitalisation and all-cause mortality by bl. LVEF (3 cat.) - RS (trial 1245.121)

Subgroup Description	Placebo	Empa 10mg
baseline LVEF (3 cat.): >35		
Number of patients in analysis set	114	128
Number of analysed patients	114	128
Total number of all-cause hospitalisation	101	111
Number of patients with all-cause hospitalisation then all-cause mortality [N(%)]	12 (10.5)	17 (13.3)
Number of patients with all-cause hospitalisation only [N(%)]	38 (33.3)	36 (28.1)
Number of patients with all-cause mortality only [N(%)]	2 (1.8)	2 (1.6)
Comparison vs Placebo*		
Hazard ratio of all-cause hospitalisation		0.89
95% confidence interval		(0.56,1.41)
p-value		0.6081
Hazard ratio of all-cause mortality		0.82
95% confidence interval		(0.27,2.50)

* Based on an analysis of recurrent events accounting for terminal events using a joint frailty model with terms for age (prec=0.3267/pterm=0.0028), baseline eGFR (CKD-EPI) (prec<0.0001/pterm=0.0015), baseline LVEF (3 cat.) (prec=0.3349/pterm=0.6447), Treatment (prec=0.0047/pterm=0.0919), Treatment by baseline LVEF (3 cat.) interaction (prec=0.6258/pterm=0.4709), region (prec<0.0001/pterm=0.0002), sex (prec=0.1147/pterm=0.0222), baseline diabetes status (3 cat.) (prec=0.0060/pterm=0.0540), estimated dependence between all-cause hospitalisation and all-cause mortality (alpha) (2.22) and variance of frailty (omega) (1.89).
pterm=p-value in terminal event model. prec=p-value in recurrent event model.

R.1.1.25.16 Subgroup analysis by bl. NTproBNP </>= median (median based on total patients)

Table R.1.1.25.16: 1 Joint frailty model of all-cause hospitalisation and all-cause mortality by bl. NTproBNP (<median,>= median) (median based on total patients) - RS (trial 1245.121)

Subgroup Description	Placebo	Empa 10mg
Baseline NTproBNP: < median		
Number of patients in analysis set	920	942
Number of analysed patients	920	942
Total number of all-cause hospitalisation	649	522
Number of patients with all-cause hospitalisation then all-cause mortality [N(%)]	62 (6.7)	63 (6.7)
Number of patients with all-cause hospitalisation only [N(%)]	268 (29.1)	220 (23.4)
Number of patients with all-cause mortality only [N(%)]	20 (2.2)	23 (2.4)
Comparison vs Placebo*		
Hazard ratio of all-cause hospitalisation		0.83
95% confidence interval		(0.70,0.99)
p-value		0.0366
Hazard ratio of all-cause mortality		1.10
95% confidence interval		(0.72,1.71)

* Based on an analysis of recurrent events accounting for terminal events using a joint frailty model with terms for age (prec=0.1748/pterm=0.0055), baseline eGFR (CKD-EPI) (prec<0.0001/pterm=0.1241), Baseline NTproBNP (prec<0.0001/pterm<0.0001), Treatment (prec=0.0736/pterm=0.0852), Treatment by Baseline NTproBNP interaction (prec=0.7550/pterm=0.1450), region (prec<0.0001/pterm=0.0004), sex (prec=0.1935/pterm=0.0422), baseline diabetes status (3 cat.) (prec=0.0027/pterm=0.0273), baseline LVEF (3 cat.) (prec=0.5045/pterm=0.7597), estimated dependence between all-cause hospitalisation and all-cause mortality (alpha) (2.22) and variance of frailty (omega) (1.80).
pterm=p-value in terminal event model. prec=p-value in recurrent event model.
2 patients were excluded as the subgroup variable was missing.

Median: 1910 [pg/mL]

Table R.1.1.25.16: 1 Joint frailty model of all-cause hospitalisation and all-cause mortality by bl. NTproBNP (<median,>= median) (median based on total patients) - RS (trial 1245.121)

Subgroup Description	Placebo	Empa 10mg
Baseline NTproBNP: >= median		
Number of patients in analysis set	946	920
Number of analysed patients	946	920
Total number of all-cause hospitalisation	920	842
Number of patients with all-cause hospitalisation then all-cause mortality [N(%)]	139 (14.7)	131 (14.2)
Number of patients with all-cause hospitalisation only [N(%)]	326 (34.5)	274 (29.8)
Number of patients with all-cause mortality only [N(%)]	44 (4.7)	32 (3.5)
Comparison vs Placebo*		
Hazard ratio of all-cause hospitalisation		0.86
95% confidence interval		(0.73,1.01)
p-value		0.0736
Hazard ratio of all-cause mortality		0.72
95% confidence interval		(0.50,1.05)

* Based on an analysis of recurrent events accounting for terminal events using a joint frailty model with terms for age (prec=0.1748/pterm=0.0055), baseline eGFR (CKD-EPI) (prec<0.0001/pterm=0.1241), Baseline NTproBNP (prec<0.0001/pterm<0.0001), Treatment (prec=0.0736/pterm=0.0852), Treatment by Baseline NTproBNP interaction (prec=0.7550/pterm=0.1450), region (prec<0.0001/pterm=0.0004), sex (prec=0.1935/pterm=0.0422), baseline diabetes status (3 cat.) (prec=0.0027/pterm=0.0273), baseline LVEF (3 cat.) (prec=0.5045/pterm=0.7597), estimated dependence between all-cause hospitalisation and all-cause mortality (alpha) (2.22) and variance of frailty (omega) (1.80).
pterm=p-value in terminal event model. prec=p-value in recurrent event model.
2 patients were excluded as the subgroup variable was missing.

Median: 1910 [pg/mL]

R.1.1.26 EGFR (CKD-EPI)cr slope of change from baseline

R.1.1.26.1

Table R.1.1.26.1: 1 EGFR (CKD-EPI)cr [mL/min/1.73m²] change from baseline slope from random intercept random coefficient model - TS (trial 1245.121)

Factor Comparison	N analysed	Estimate	Standard error	99.9% CI LL	 UL	95% CI LL	 UL	p-value
Intercept								
Placebo intercept	1792	-0.949	0.187	-1.564	-0.335	-1.315	-0.583	<0.0001
Empa 10mg intercept	1799	-3.024	0.185	-3.633	-2.414	-3.387	-2.661	<0.0001
Time								
Placebo slope* [/year]		-2.278	0.229	-3.035	-1.522	-2.728	-1.828	<0.0001
Empa 10mg slope* [/year]		-0.546	0.227	-1.294	0.202	-0.991	-0.101	0.0163
Treatment by time interaction								
Empa 10mg vs Placebo slope [/year]		1.733	0.323	0.669	2.796	1.100	2.366	<0.0001

Model includes age (p<0.0001), baseline eGFR (CKD-EPI) (p<0.0001) as linear covariate(s) and region (p=0.0912), baseline diabetes status (p=0.0204), sex (p=0.0988), baseline LVEF (p=0.4064), baseline 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 = 62.07
The following covariance structure has been used to fit the mixed model: Unstructured

Figure R.1.1.26.1: 1

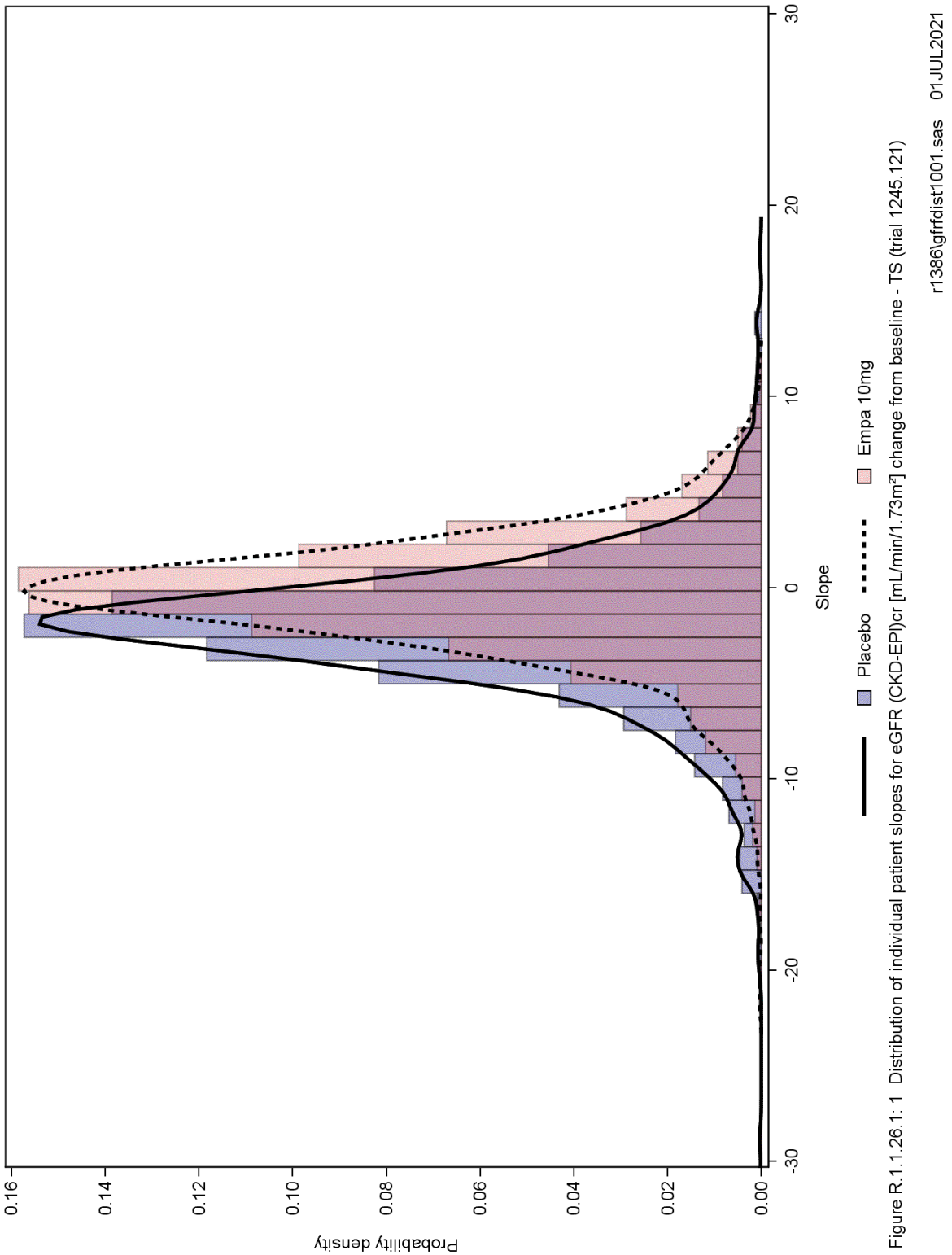

Figure R.1.1.26.1: 1 Distribution of individual patient slopes for eGFR (CKD-EPI)cr [mL/min/1.73m²] change from baseline - TS (trial 1245.121)

R.1.1.26.2

R.1.1.26.2 Subgroup analysis by sex

Table R.1.1.26.2: 1 EGFR (CKD-EPI)cr [mL/min/1.73m²] change from baseline slope from random intercept random coefficient model by sex - TS (trial 1245.121)

Subgroup Factor Comparison	N analysed	Estimate	Standard error	95% CI LL	 UL	p-value
Sex: Male						
Intercept						
Placebo intercept*	1365	-0.902	0.213	-1.320	-0.485	<0.0001
Empa 10mg intercept*	1376	-2.862	0.211	-3.276	-2.448	<0.0001
Time						
Placebo slope* [/year]		-2.271	0.262	-2.784	-1.757	<0.0001
Empa 10mg slope* [/year]		-0.630	0.260	-1.140	-0.120	0.0155
Treatment by time interaction						
Empa 10mg vs Placebo slope [/year]		1.640	0.369	0.917	2.364	<0.0001
Sex: Female						
Intercept						
Placebo intercept*	427	-1.007	0.383	-1.759	-0.255	0.0087
Empa 10mg intercept*	423	-3.455	0.382	-4.205	-2.706	<0.0001
Time						
Placebo slope* [/year]		-2.305	0.477	-3.241	-1.369	<0.0001
Empa 10mg slope* [/year]		-0.272	0.466	-1.187	0.642	0.5593
Treatment by time interaction						
Empa 10mg vs Placebo slope [/year]		2.033	0.667	0.724	3.341	0.0023
p-value for heterogeneity across subgroups						
Empa 10mg vs Placebo						0.6071

Model includes Age (p<0.0001), baseline eGFR (CKD-EPI) (p<0.0001) as linear covariate(s) and region (p=0.0944), baseline diabetes status (3 cat.) (p=0.0207), baseline LVEF (3 cat.) (p=0.4030), Baseline 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

R.1.1.26.3

Table R.1.1.26.3: 1 EGFR (CKD-EPI)cr [mL/min/1.73m²] change from baseline slope from random intercept random coefficient model by age - TS (trial 1245.121)

Subgroup Factor Comparison	N analysed	Estimate	Standard error	95% CI LL	95% CI UL	p-value
Age (2 cat.): < 65						
Intercept						
Placebo intercept*	714	-1.036	0.299	-1.623	-0.450	0.0005
Empa 10mg intercept*	649	-3.220	0.311	-3.831	-2.610	<0.0001
Time						
Placebo slope* [/year]		-2.318	0.364	-3.032	-1.603	<0.0001
Empa 10mg slope* [/year]		-0.622	0.380	-1.366	0.122	0.1014
Treatment by time interaction						
Empa 10mg vs Placebo slope [/year]		1.696	0.526	0.664	2.727	0.0013
Age (2 cat.): >= 65						
Intercept						
Placebo intercept*	1078	-0.847	0.241	-1.319	-0.374	0.0005
Empa 10mg intercept*	1150	-2.896	0.232	-3.350	-2.441	<0.0001
Time						
Placebo slope* [/year]		-2.262	0.295	-2.840	-1.683	<0.0001
Empa 10mg slope* [/year]		-0.463	0.283	-1.018	0.092	0.1023
Treatment by time interaction						
Empa 10mg vs Placebo slope [/year]		1.799	0.409	0.998	2.601	<0.0001
p-value for heterogeneity across subgroups						
Empa 10mg vs Placebo						0.8764

Model includes baseline eGFR (CKD-EPI) (p<0.0001) as linear covariate(s) and region (p=0.0413), sex (p=0.0812), baseline diabetes status (3 cat.) (p=0.0317), baseline LVEF (3 cat.) (p=0.2262), Baseline by Time interaction (p<0.0001), Treatment by Age (2 cat.) interaction (p<0.0001), Time by Treatment by Age (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

R.1.1.26.4 Subgroup analysis by region (North America, Latin America, Europe, Asia, Other)

Table R.1.1.26.4: 1 EGFR (CKD-EPI)cr [mL/min/1.73m²] change from baseline slope from random intercept random coefficient model by region - TS (trial 1245.121)

Subgroup Factor Comparison	N analysed	Estimate	Standard error	95% CI LL	95% CI UL	p-value
Region: North America						
Intercept						
Placebo intercept*	201	-1.082	0.561	-2.182	0.017	0.0537
Empa 10mg intercept*	207	-3.642	0.545	-4.710	-2.573	<0.0001
Time						
Placebo slope* [/year]		-1.958	0.721	-3.373	-0.543	0.0067
Empa 10mg slope* [/year]		-0.460	0.669	-1.773	0.853	0.4920
Treatment by time interaction						
Empa 10mg vs Placebo slope [/year]		1.498	0.984	-0.432	3.429	0.1281
Region: Latin America						
Intercept						
Placebo intercept*	616	-0.861	0.321	-1.491	-0.230	0.0074
Empa 10mg intercept*	619	-3.032	0.320	-3.659	-2.404	<0.0001
Time						
Placebo slope* [/year]		-3.000	0.409	-3.803	-2.198	<0.0001
Empa 10mg slope* [/year]		-1.045	0.410	-1.849	-0.241	0.0108
Treatment by time interaction						
Empa 10mg vs Placebo slope [/year]		1.955	0.579	0.819	3.091	0.0008
Region: Europe						
Intercept						
Placebo intercept*	651	-1.109	0.311	-1.719	-0.499	0.0004
Empa 10mg intercept*	649	-2.761	0.310	-3.369	-2.153	<0.0001
Time						
Placebo slope* [/year]		-1.938	0.380	-2.683	-1.193	<0.0001
Empa 10mg slope* [/year]		-0.728	0.382	-1.477	0.022	0.0571
Treatment by time interaction						
Empa 10mg vs Placebo slope [/year]		1.210	0.539	0.154	2.267	0.0248

Model includes Age (p<0.0001), baseline eGFR (CKD-EPI) (p<0.0001) as linear covariate(s) and baseline diabetes status (3 cat.) (p=0.0199), Sex (p=0.0991), baseline LVEF (3 cat.) (p=0.4069), Baseline 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

Table R.1.1.26.4: 1 EGFR (CKD-EPI)cr [mL/min/1.73m²] change from baseline slope from random intercept random coefficient model by region - TS (trial 1245.121)

Subgroup Factor Comparison	N analysed	Estimate	Standard error	95% CI LL	 UL	p-value
Region: Asia						
Intercept						
Placebo intercept*	239	-0.855	0.471	-1.778	0.068	0.0695
Empa 10mg intercept*	242	-3.203	0.462	-4.109	-2.297	<0.0001
Time						
Placebo slope* [/year]		-2.087	0.547	-3.160	-1.015	0.0001
Empa 10mg slope* [/year]		0.308	0.531	-0.734	1.350	0.5624
Treatment by time interaction						
Empa 10mg vs Placebo slope [/year]		2.395	0.762	0.900	3.890	0.0017
Region: Other						
Intercept						
Placebo intercept*	85	-0.296	0.866	-1.995	1.402	0.7322
Empa 10mg intercept*	82	-2.633	0.891	-4.379	-0.887	0.0031
Time						
Placebo slope* [/year]		-1.416	1.113	-3.598	0.767	0.2036
Empa 10mg slope* [/year]		0.597	1.113	-1.585	2.780	0.5916
Treatment by time interaction						
Empa 10mg vs Placebo slope [/year]		2.013	1.574	-1.074	5.099	0.2011
p-value for heterogeneity across subgroups						
Empa 10mg vs Placebo						0.7487

Model includes Age (p<0.0001), baseline eGFR (CKD-EPI) (p<0.0001) as linear covariate(s) and
baseline diabetes status (3 cat.) (p=0.0199), Sex (p=0.0991), baseline LVEF (3 cat.) (p=0.4069),
Baseline 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

R.1.1.26.5

R.1.1.26.5 Subgroup analysis by OECD member (Y/N)

Table R.1.1.26.5: 1 EGFR (CKD-EPI)cr [mL/min/1.73m²] change from baseline slope from random intercept random coefficient model by OECD member - TS (trial 1245.121)

Subgroup Factor Comparison	N analysed	Estimate	Standard error	95% CI LL	95% CI UL	p-value
OECD member: No						
Intercept						
Placebo intercept*	711	-0.827	0.300	-1.415	-0.239	0.0058
Empa 10mg intercept*	685	-3.121	0.305	-3.718	-2.523	<0.0001
Time						
Placebo slope* [/year]		-2.697	0.385	-3.451	-1.943	<0.0001
Empa 10mg slope* [/year]		-0.748	0.391	-1.514	0.018	0.0558
Treatment by time interaction						
Empa 10mg vs Placebo slope [/year]		1.949	0.548	0.874	3.024	0.0004
OECD member: Yes						
Intercept						
Placebo intercept*	1081	-1.023	0.236	-1.486	-0.560	<0.0001
Empa 10mg intercept*	1114	-2.971	0.231	-3.424	-2.519	<0.0001
Time						
Placebo slope* [/year]		-2.040	0.286	-2.602	-1.479	<0.0001
Empa 10mg slope* [/year]		-0.420	0.279	-0.967	0.128	0.1328
Treatment by time interaction						
Empa 10mg vs Placebo slope [/year]		1.621	0.400	0.836	2.405	<0.0001
p-value for heterogeneity across subgroups						
Empa 10mg vs Placebo						0.6281

Model includes Age (p<0.0001), baseline eGFR (CKD-EPI) (p<0.0001) as linear covariate(s) and baseline diabetes status (3 cat.) (p=0.0235), Sex (p=0.0701), baseline LVEF (3 cat.) (p=0.4254), Baseline 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

OECD member (yes/no) countries included:
Yes: United States, Canada, Mexico, Poland, Netherlands, Hungary, Germany, Czech Republic, Italy, France, Spain, United Kingdom, Belgium, Japan, Australia, 'Korea; Republic Of South Korea';
No: Brazil, Argentina, China, India.

R.1.1.26.6

R.1.1.26.6 Subgroup analysis by NYHA at baseline (II, III/IV - 2 cat.)

Table R.1.1.26.6: 1 EGFR (CKD-EPI)cr [mL/min/1.73m²] change from baseline slope from random intercept random coefficient model by NYHA at baseline (2 cat.) - TS (trial 1245.121)

Subgroup Factor Comparison	N analysed	Estimate	Standard error	95% CI LL	 UL	p-value
History of NYHA (2 cat.): II						
Intercept						
Placebo intercept*	1351	-0.968	0.213	-1.386	-0.550	<0.0001
Empa 10mg intercept*	1353	-3.083	0.212	-3.499	-2.667	<0.0001
Time						
Placebo slope* [/year]		-2.541	0.261	-3.053	-2.028	<0.0001
Empa 10mg slope* [/year]		-0.491	0.259	-0.998	0.017	0.0580
Treatment by time interaction						
Empa 10mg vs Placebo slope [/year]		2.050	0.368	1.329	2.771	<0.0001
History of NYHA (2 cat.): III/IV						
Intercept						
Placebo intercept*	441	-0.792	0.380	-1.538	-0.047	0.0373
Empa 10mg intercept*	446	-2.727	0.375	-3.463	-1.991	<0.0001
Time						
Placebo slope* [/year]		-1.402	0.479	-2.342	-0.461	0.0035
Empa 10mg slope* [/year]		-0.739	0.474	-1.669	0.191	0.1193
Treatment by time interaction						
Empa 10mg vs Placebo slope [/year]		0.662	0.675	-0.660	1.985	0.3262
p-value for heterogeneity across subgroups						
Empa 10mg vs Placebo						0.0710

Model includes Age (p<0.0001), baseline eGFR (CKD-EPI) (p<0.0001) as linear covariate(s) and region (p=0.0896), Sex (p=0.0930), baseline diabetes status (3 cat.) (p=0.0187), baseline LVEF (3 cat.) (p=0.4255), Baseline by Time interaction (p<0.0001), Treatment by History of NYHA (2 cat.) interaction (p<0.0001), Time by Treatment by History of NYHA (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

R.1.1.26.7

Table R.1.1.26.7: 1 EGFR (CKD-EPI)cr [mL/min/1.73m²] change from baseline slope from random intercept random coefficient model by diabetes at baseline - TS (trial 1245.121)

Subgroup Factor Comparison	N analysed	Estimate	Standard error	95% CI LL	 UL	p-value
Baseline diabetes status (2 cat.): Diabetic						
Intercept						
Placebo intercept*	896	-0.949	0.263	-1.466	-0.433	0.0003
Empa 10mg intercept*	893	-3.224	0.261	-3.736	-2.711	<0.0001
Time						
Placebo slope* [/year]		-2.807	0.325	-3.445	-2.169	<0.0001
Empa 10mg slope* [/year]		-0.601	0.321	-1.230	0.028	0.0611
Treatment by time interaction						
Empa 10mg vs Placebo slope [/year]		2.206	0.457	1.311	3.102	<0.0001
Baseline diabetes status (2 cat.): Non-Diabetic						
Intercept						
Placebo intercept*	896	-0.896	0.262	-1.410	-0.383	0.0006
Empa 10mg intercept*	906	-2.772	0.260	-3.283	-2.262	<0.0001
Time						
Placebo slope* [/year]		-1.760	0.323	-2.392	-1.127	<0.0001
Empa 10mg slope* [/year]		-0.492	0.320	-1.120	0.137	0.1250
Treatment by time interaction						
Empa 10mg vs Placebo slope [/year]		1.268	0.455	0.376	2.160	0.0053
p-value for heterogeneity across subgroups						
Empa 10mg vs Placebo						0.1455

Model includes Age (p<0.0001), baseline eGFR (CKD-EPI) (p<0.0001) as linear covariate(s) and region (p=0.0831), Sex (p=0.0978), baseline LVEF (3 cat.) (p=0.4114), Baseline by Time interaction (p<0.0001), Treatment by Baseline diabetes status (2 cat.) interaction (p<0.0001), Time by Treatment by Baseline diabetes status (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

R.1.1.26.8 Subgroup analysis by BMI at baseline (<30, >=30)

Table R.1.1.26.8: 1 EGFR (CKD-EPI)cr [mL/min/1.73m²] change from baseline slope from random intercept random coefficient model by baseline BMI [kg/m2] - TS (trial 1245.121)

Subgroup Factor Comparison	N analysed	Estimate	Standard error	95% CI LL	95% CI UL	p-value
Baseline BMI [kg/m2]: <30						
Intercept						
Placebo intercept*	1251	-0.923	0.221	-1.356	-0.490	<0.0001
Empa 10mg intercept*	1218	-3.023	0.223	-3.461	-2.586	<0.0001
Time						
Placebo slope* [/year]		-1.980	0.271	-2.511	-1.449	<0.0001
Empa 10mg slope* [/year]		-0.402	0.275	-0.942	0.137	0.1435
Treatment by time interaction						
Empa 10mg vs Placebo slope [/year]		1.578	0.386	0.821	2.335	<0.0001
Baseline BMI [kg/m2]: >=30						
Intercept						
Placebo intercept*	541	-0.949	0.349	-1.633	-0.265	0.0065
Empa 10mg intercept*	581	-2.953	0.335	-3.610	-2.297	<0.0001
Time						
Placebo slope* [/year]		-3.034	0.431	-3.878	-2.189	<0.0001
Empa 10mg slope* [/year]		-0.851	0.401	-1.638	-0.065	0.0339
Treatment by time interaction						
Empa 10mg vs Placebo slope [/year]		2.182	0.589	1.027	3.337	0.0002
p-value for heterogeneity across subgroups						
Empa 10mg vs Placebo						0.3909

Model includes Age (p<0.0001), baseline eGFR (CKD-EPI) (p<0.0001) as linear covariate(s) and region (p=0.2160), baseline diabetes status (3 cat.) (p=0.0375), Sex (p=0.1095), baseline LVEF (3 cat.) (p=0.4040), Baseline 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

R.1.1.26.9

R.1.1.26.9 Subgroup analysis by eGFR at baseline (<60, >=60)

Table R.1.1.26.9: 1 EGFR (CKD-EPI)cr [mL/min/1.73m²] change from baseline slope from random intercept random coefficient model by baseline eGFR (2 cat.) - TS (trial 1245.121)

Subgroup Factor Comparison	N analysed	Estimate	Standard error	95% CI LL	 UL	p-value
Baseline eGFR (CKD-EPI) [mL/min/1.73m2]: >=60						
Intercept						
Placebo intercept*	923	-1.821	0.262	-2.335	-1.307	<0.0001
Empa 10mg intercept*	934	-4.035	0.259	-4.543	-3.527	<0.0001
Time						
Placebo slope* [/year]		-3.431	0.318	-4.055	-2.806	<0.0001
Empa 10mg slope* [/year]		-1.070	0.314	-1.686	-0.454	0.0007
Treatment by time interaction						
Empa 10mg vs Placebo slope [/year]		2.361	0.447	1.484	3.238	<0.0001
Baseline eGFR (CKD-EPI) [mL/min/1.73m2]: <60						
Intercept						
Placebo intercept*	869	0.004	0.271	-0.526	0.535	0.9874
Empa 10mg intercept*	865	-1.875	0.269	-2.403	-1.347	<0.0001
Time						
Placebo slope* [/year]		-0.993	0.333	-1.645	-0.340	0.0029
Empa 10mg slope* [/year]		-0.019	0.330	-0.667	0.628	0.9533
Treatment by time interaction						
Empa 10mg vs Placebo slope [/year]		0.973	0.469	0.054	1.893	0.0379
p-value for heterogeneity across subgroups						
Empa 10mg vs Placebo						0.0323

Model includes Age (p<0.0001) as linear covariate(s) and region (p=0.2528), baseline diabetes status (3 cat.) (p=0.0222), Sex (p=0.1230), baseline LVEF (3 cat.) (p=0.4729), Baseline by Time interaction (p<0.0001), Treatment by Baseline eGFR (CKD-EPI) [mL/min/1.73m2] interaction (p<0.0001), Time by Treatment by Baseline eGFR (CKD-EPI) [mL/min/1.73m2] 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.

R.1.1.26.10

Table R.1.1.26.10: 1 EGFR (CKD-EPI)cr [mL/min/1.73m²] change from baseline slope from random intercept random coefficient model by history of HHF within 12 months - TS (trial 1245.121)

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*	1247	-0.868	0.224	-1.308	-0.428	0.0001
Empa 10mg intercept*	1243	-3.151	0.224	-3.590	-2.712	<0.0001
Time						
Placebo slope* [/year]		-2.181	0.271	-2.714	-1.649	<0.0001
Empa 10mg slope* [/year]		-0.389	0.270	-0.918	0.139	0.1489
Treatment by time interaction						
Empa 10mg vs Placebo slope [/year]		1.792	0.382	1.042	2.542	<0.0001
History of HHF (in the last 12 months): Yes						
Intercept						
Placebo intercept*	545	-1.045	0.338	-1.708	-0.382	0.0020
Empa 10mg intercept*	556	-2.646	0.333	-3.299	-1.993	<0.0001
Time						
Placebo slope* [/year]		-2.523	0.430	-3.367	-1.679	<0.0001
Empa 10mg slope* [/year]		-0.925	0.421	-1.751	-0.099	0.0282
Treatment by time interaction						
Empa 10mg vs Placebo slope [/year]		1.598	0.602	0.417	2.779	0.0080
p-value for heterogeneity across subgroups						
Empa 10mg vs Placebo						0.7858

Model includes Age (p<0.0001), baseline eGFR (CKD-EPI) (p<0.0001) as linear covariate(s) and region (p=0.0866), Sex (p=0.0982), baseline diabetes status (3 cat.) (p=0.0212), baseline LVEF (3 cat.) (p=0.4123), Baseline 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

R.1.1.26.11

Table R.1.1.26.11: 1 EGFR (CKD-EPI)cr [mL/min/1.73m²] change from baseline slope from random intercept random coefficient model by cause of heart failure - TS (trial 1245.121)

Subgroup Factor Comparison	N analysed	Estimate	Standard error	95% CI LL	 UL	p-value
Cause of Heart failure: Ischemic						
Intercept						
Placebo intercept*	929	-0.954	0.262	-1.468	-0.440	0.0003
Empa 10mg intercept*	959	-3.132	0.255	-3.633	-2.632	<0.0001
Time						
Placebo slope* [/year]		-2.148	0.310	-2.755	-1.541	<0.0001
Empa 10mg slope* [/year]		-0.266	0.301	-0.857	0.325	0.3771
Treatment by time interaction						
Empa 10mg vs Placebo slope [/year]		1.882	0.432	1.035	2.729	<0.0001
Cause of Heart failure: Non-ischemic						
Intercept						
Placebo intercept*	891	-0.969	0.266	-1.492	-0.447	0.0003
Empa 10mg intercept*	864	-2.936	0.269	-3.463	-2.410	<0.0001
Time						
Placebo slope* [/year]		-2.425	0.320	-3.053	-1.798	<0.0001
Empa 10mg slope* [/year]		-0.113	0.324	-0.749	0.522	0.7264
Treatment by time interaction						
Empa 10mg vs Placebo slope [/year]		2.312	0.455	1.419	3.205	<0.0001
p-value for heterogeneity across subgroups						
Empa 10mg vs Placebo						0.4937

Model includes Age (p<0.0001), baseline eGFR (CKD-EPI) (p<0.0001) as linear covariate(s) and region (p=0.0987), baseline diabetes status (3 cat.) (p=0.0459), Sex (p=0.0724), baseline LVEF (3 cat.) (p=0.4560), Baseline by Time interaction (p<0.0001), Treatment by Cause of heart failure interaction (p<0.0001), Time by Treatment by Cause of heart failure 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

R.1.1.26.12 Subgroup analysis by heart failure physiology (LVEF <= 30% and NTproBNP<median; LVEF <= 30% and NTproBNP>=median; LVEF > 30%)

Table R.1.1.26.12: 1 EGFR (CKD-EPI)cr [mL/min/1.73m²] change from baseline slope from random intercept random coefficient model by heart failure physiology - TS (trial 1245.121)

Subgroup Factor Comparison	N analysed	Estimate	Standard error	95% CI LL	95% CI UL	p-value
Heart failure physiology: LVEF <= 30% and NTproBNP < median						
Intercept						
Placebo intercept*	711	NC.	NC.	NC.	NC.	NC.
Empa 10mg intercept*	689	NC.	NC.	NC.	NC.	NC.
Time						
Placebo slope* [/year]		-1.779	0.344	-2.454	-1.104	<0.0001
Empa 10mg slope* [/year]		-0.189	0.346	-0.868	0.490	0.5850
Treatment by time interaction						
Empa 10mg vs Placebo slope [/year]		1.590	0.488	0.633	2.548	0.0011
Heart failure physiology: LVEF <= 30% and NTproBNP >= median						
Intercept						
Placebo intercept*	638	NC.	NC.	NC.	NC.	NC.
Empa 10mg intercept*	616	NC.	NC.	NC.	NC.	NC.
Time						
Placebo slope* [/year]		-2.885	0.382	-3.634	-2.136	<0.0001
Empa 10mg slope* [/year]		-0.610	0.388	-1.371	0.150	0.1158
Treatment by time interaction						
Empa 10mg vs Placebo slope [/year]		2.274	0.545	1.206	3.342	<0.0001

Model includes Age (p<0.0001), baseline eGFR (CKD-EPI) (p<0.0001) as linear covariate(s) and region (p=0.1000), baseline diabetes status (3 cat.) (p=0.0280), Sex (p=0.0877), baseline LVEF (3 cat.) (p=0.4808), Baseline by Time interaction (p<0.0001), Treatment by Heart failure physiology interaction (p<0.0001), Time by Treatment by Heart failure physiology 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
15 patients were excluded as the subgroup variable was missing.
NC. = Not calculated.

Table R.1.1.26.12: 1 EGFR (CKD-EPI)cr [mL/min/1.73m²] change from baseline slope from random intercept random coefficient model by heart failure physiology - TS (trial 1245.121)

Subgroup Factor Comparison	N analysed	Estimate	Standard error	95% CI LL	 UL	p-value
Heart failure physiology: LVEF > 30%						
Intercept						
Placebo intercept*	465	NC.	NC.	NC.	NC.	NC.
Empa 10mg intercept*	512	NC.	NC.	NC.	NC.	NC.
Time						
Placebo slope* [/year]		-2.405	0.446	-3.280	-1.529	<0.0001
Empa 10mg slope* [/year]		0.216	0.419	-0.605	1.037	0.6061
Treatment by time interaction						
Empa 10mg vs Placebo slope [/year]		2.620	0.612	1.420	3.821	<0.0001
p-value for heterogeneity across subgroups						
Empa 10mg vs Placebo						0.3843

Model includes Age (p<0.0001), baseline eGFR (CKD-EPI) (p<0.0001) as linear covariate(s) and region (p=0.1000), baseline diabetes status (3 cat.) (p=0.0280), Sex (p=0.0877), baseline LVEF (3 cat.) (p=0.4808), Baseline by Time interaction (p<0.0001), Treatment by Heart failure physiology interaction (p<0.0001), Time by Treatment by Heart failure physiology 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
15 patients were excluded as the subgroup variable was missing.
NC. = Not calculated.

R.1.1.26.13

R.1.1.26.13 Subgroup analysis by baseline use of MRA

Table R.1.1.26.13: 1 EGFR (CKD-EPI)cr [mL/min/1.73m²] change from baseline slope from random intercept random coefficient model by baseline use of MRA - TS (trial 1245.121)

Subgroup Factor Comparison	N analysed	Estimate	Standard error	95% CI LL	 UL	p-value
Baseline use of MRA: No						
Intercept						
Placebo intercept*	491	-0.187	0.354	-0.880	0.506	0.5969
Empa 10mg intercept*	535	-3.025	0.336	-3.683	-2.367	<0.0001
Time						
Placebo slope* [/year]		-2.519	0.431	-3.365	-1.674	<0.0001
Empa 10mg slope* [/year]		-0.325	0.402	-1.113	0.463	0.4188
Treatment by time interaction						
Empa 10mg vs Placebo slope [/year]		2.194	0.589	1.039	3.350	0.0002
Baseline use of MRA: Yes						
Intercept						
Placebo intercept*	1301	-1.212	0.220	-1.643	-0.780	<0.0001
Empa 10mg intercept*	1264	-2.981	0.223	-3.418	-2.544	<0.0001
Time						
Placebo slope* [/year]		-2.182	0.271	-2.713	-1.650	<0.0001
Empa 10mg slope* [/year]		-0.635	0.275	-1.175	-0.096	0.0210
Treatment by time interaction						
Empa 10mg vs Placebo slope [/year]		1.546	0.386	0.789	2.304	<0.0001
p-value for heterogeneity across subgroups						
Empa 10mg vs Placebo						0.3578

Model includes Age (p<0.0001), baseline eGFR (CKD-EPI) (p<0.0001) as linear covariate(s) and region (p=0.0902), baseline diabetes status (3 cat.) (p=0.0193), Sex (p=0.1031), baseline LVEF (3 cat.) (p=0.3836), Baseline 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

R.1.1.26.14

R.1.1.26.14 Subgroup analysis by baseline use of ARNi

Table R.1.1.26.14: 1 EGFR (CKD-EPI)cr [mL/min/1.73m²] change from baseline slope from random intercept random coefficient model by baseline use of ARNi - TS (trial 1245.121)

Subgroup Factor Comparison	N analysed	Estimate	Standard error	95% CI LL	 UL	p-value
Baseline use of ARNi: No						
Intercept						
Placebo intercept*	1422	-0.938	0.208	-1.346	-0.531	<0.0001
Empa 10mg intercept*	1470	-2.863	0.203	-3.262	-2.465	<0.0001
Time						
Placebo slope* [/year]		-2.305	0.254	-2.803	-1.807	<0.0001
Empa 10mg slope* [/year]		-0.598	0.246	-1.081	-0.115	0.0152
Treatment by time interaction						
Empa 10mg vs Placebo slope [/year]		1.707	0.354	1.013	2.401	<0.0001
Baseline use of ARNi: Yes						
Intercept						
Placebo intercept*	370	-0.881	0.421	-1.706	-0.056	0.0364
Empa 10mg intercept*	329	-3.654	0.446	-4.529	-2.778	<0.0001
Time						
Placebo slope* [/year]		-2.163	0.536	-3.215	-1.111	<0.0001
Empa 10mg slope* [/year]		-0.244	0.589	-1.400	0.911	0.6784
Treatment by time interaction						
Empa 10mg vs Placebo slope [/year]		1.919	0.797	0.356	3.482	0.0161
p-value for heterogeneity across subgroups						
Empa 10mg vs Placebo						0.8079

Model includes Age (p<0.0001), baseline eGFR (CKD-EPI) (p<0.0001) as linear covariate(s) and region (p=0.1035), baseline diabetes status (3 cat.) (p=0.0195), Sex (p=0.1087), baseline LVEF (3 cat.) (p=0.3770), Baseline by Time interaction (p<0.0001), Treatment by Baseline use of ARNi interaction (p<0.0001), Time by Treatment by Baseline use of 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

R.1.1.26.15 Subgroup analysis by bl. LVEF (<= 30%, >30% -<= 35% , > 35%)

Table R.1.1.26.15: 1 EGFR (CKD-EPI)cr [mL/min/1.73m²] change from baseline slope from random intercept random coefficient model by bl. LVEF (3 cat.) - TS (trial 1245.121)

Subgroup Factor Comparison	N analysed	Estimate	Standard error	95% CI LL	 UL	p-value
baseline LVEF (3 cat.): <=30						
Intercept						
Placebo intercept*	1337	-0.983	0.217	-1.408	-0.559	<0.0001
Empa 10mg intercept*	1292	-2.784	0.219	-3.213	-2.355	<0.0001
Time						
Placebo slope* [/year]		-2.281	0.263	-2.797	-1.764	<0.0001
Empa 10mg slope* [/year]		-0.738	0.266	-1.260	-0.216	0.0056
Treatment by time interaction						
Empa 10mg vs Placebo slope [/year]		1.542	0.374	0.808	2.277	<0.0001
baseline LVEF (3 cat.): >30 to <=35						
Intercept						
Placebo intercept*	350	-0.869	0.419	-1.690	-0.047	0.0382
Empa 10mg intercept*	386	-3.726	0.396	-4.502	-2.950	<0.0001
Time						
Placebo slope* [/year]		-1.739	0.520	-2.758	-0.719	0.0008
Empa 10mg slope* [/year]		-0.289	0.493	-1.257	0.679	0.5581
Treatment by time interaction						
Empa 10mg vs Placebo slope [/year]		1.450	0.716	0.044	2.855	0.0432
baseline LVEF (3 cat.): >35						
Intercept						
Placebo intercept*	105	-0.215	0.764	-1.713	1.283	0.7784
Empa 10mg intercept*	121	-3.004	0.705	-4.386	-1.622	<0.0001
Time						
Placebo slope* [/year]		-4.575	1.053	-6.640	-2.510	<0.0001
Empa 10mg slope* [/year]		0.798	0.903	-0.972	2.568	0.3768
Treatment by time interaction						
Empa 10mg vs Placebo slope [/year]		5.373	1.387	2.652	8.093	0.0001

Model includes Age (p<0.0001), baseline eGFR (CKD-EPI) (p<0.0001) as linear covariate(s) and region (p=0.1004), Sex (p=0.0938), baseline diabetes status (3 cat.) (p=0.0187), Baseline by Time interaction (p<0.0001), Treatment by baseline LVEF (3 cat.) interaction (p<0.0001), Time by Treatment by baseline LVEF (3 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
The p-value for treatment by subgroup interaction trend test for slope is 0.0740.

Table R.1.1.26.15: 1 EGFR (CKD-EPI)cr [mL/min/1.73m²] change from baseline slope from random intercept random coefficient model by bl. LVEF (3 cat.) - TS (trial 1245.121)

Subgroup Factor / Comparison	N analysed	Estimate	Standard error	95% CI LL	95% CI UL	p-value
p-value for heterogeneity across subgroups						
Empa 10mg vs Placebo						0.0262

Model includes Age (p<0.0001), baseline eGFR (CKD-EPI) (p<0.0001) as linear covariate(s) and region (p=0.1004), Sex (p=0.0938), baseline diabetes status (3 cat.) (p=0.0187), Baseline by Time interaction (p<0.0001), Treatment by baseline LVEF (3 cat.) interaction (p<0.0001), Time by Treatment by baseline LVEF (3 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
The p-value for treatment by subgroup interaction trend test for slope is 0.0740.

R.1.1.26.16 Subgroup analysis by bl. NTproBNP </>= median (median based on total patients)

Table R.1.1.26.16: 1 EGFR (CKD-EPI)cr [mL/min/1.73m²] change from baseline slope from random intercept random coefficient model by bl. NTproBNP (<median,>= median) (median based on total patients) - TS (trial 1245.121)

Subgroup Factor Comparison	N analysed	Estimate	Standard error	95% CI LL	95% CI UL	p-value
Baseline NTproBNP: < median						
Intercept						
Placebo intercept*	893	-1.121	0.263	-1.636	-0.606	<0.0001
Empa 10mg intercept*	915	-3.409	0.259	-3.917	-2.900	<0.0001
Time						
Placebo slope* [/year]		-2.070	0.316	-2.690	-1.450	<0.0001
Empa 10mg slope* [/year]		-0.578	0.312	-1.190	0.034	0.0640
Treatment by time interaction						
Empa 10mg vs Placebo slope [/year]		1.492	0.444	0.621	2.362	0.0008
Baseline NTproBNP: >= median						
Intercept						
Placebo intercept*	899	-0.713	0.263	-1.230	-0.197	0.0068
Empa 10mg intercept*	884	-2.575	0.264	-3.092	-2.058	<0.0001
Time						
Placebo slope* [/year]		-2.533	0.333	-3.186	-1.879	<0.0001
Empa 10mg slope* [/year]		-0.533	0.330	-1.181	0.115	0.1067
Treatment by time interaction						
Empa 10mg vs Placebo slope [/year]		1.999	0.469	1.079	2.920	<0.0001
p-value for heterogeneity across subgroups						
Empa 10mg vs Placebo						0.4321

Model includes Age (p<0.0001), baseline eGFR (CKD-EPI) (p<0.0001) as linear covariate(s) and region (p=0.0904), Sex (p=0.1014), baseline diabetes status (3 cat.) (p=0.0209), baseline LVEF (3 cat.) (p=0.4134), Baseline by Time interaction (p<0.0001), Treatment by Baseline NTproBNP interaction (p<0.0001), Time by Treatment by Baseline NTproBNP 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.

Median: 1910 [pg/mL]

R.1.2

R.1.2.1

R.1.2.1 EQ-VAS responder analysis (7 points)

R.1.2.1.1

R.1.2.1.1 Overall analysis

Table R.1.2.1.1: 1 Responder analysis (displaying odds ratio) in EQ-VAS change from baseline at week 52 of <= -7 points (deterioration) - RS (LOCF-AD) - 1245.121

	Placebo	Empa 10mg
Number of patients in analysis set	1867	1863
Number of analysed patients, N (%)	1710 (100.0)	1733 (100.0)
Number of patients with endpoint, N (%)	414 (24.2)	395 (22.8)
95% confidence interval*	(22.2, 26.3)	(20.9, 24.8)
Comparison vs Placebo**		
Odds ratio (SE)		0.913 (0.078)
95% confidence interval***		(0.772, 1.078)
p-value		0.2830

* Wilson confidence intervals.
** Logistic regression includes terms for baseline EQ-VAS score (p<0.0001), age (p=0.0155), baseline eGFR (CKD-EPI) (p=0.3098), Treatment (p=0.2830), region (5 cat.) (p<0.0001), baseline diabetes status (3 cat.) (p=0.3594), sex (p=0.0736) and baseline LVEF (3 cat.) (p=0.4013).
***Wald confidence intervals.

Data taken from study 1245.121 only.
LOCF: For a missing value at week 52 the last available post-baseline value before week 52 is imputed.

Table R.1.2.1.1: 2 Responder analysis (displaying risk ratio) in EQ-VAS change from baseline at week 52 of <= -7 points (deterioration) - RS (LOCF-AD) - 1245.121

	Placebo	Empa 10mg
Number of patients in analysis set	1867	1863
Number of analysed patients, N (%)	1710 (100.0)	1733 (100.0)
Number of patients with endpoint, N (%)	414 (24.2)	395 (22.8)
95% confidence interval*	(22.2, 26.3)	(20.9, 24.8)
Comparison vs Placebo**		
Risk ratio (SE)		0.937 (0.055)
95% confidence interval***		(0.836, 1.051)
p-value		0.2664

* Wilson confidence intervals.
** Log-linked Poisson model with robust estimate of variance includes terms for baseline EQ-VAS score (p<0.0001), age (p=0.0127), baseline eGFR (CKD-EPI) (p=0.3197), Treatment (p=0.2664), region (5 cat.) (p<0.0001), baseline diabetes status (3 cat.) (p=0.3780), sex (p=0.0872) and baseline LVEF (3 cat.) (p=0.4251).
***Wald confidence intervals.

Data taken from study 1245.121 only.
LOCF: For a missing value at week 52 the last available post-baseline value before week 52 is imputed.

Table R.1.2.1.1: 3 Responder analysis (displaying odds ratio) in EQ-VAS change from baseline at week 52 of > -7 points (stability) - RS (LOCF-AD) - 1245.121

	Placebo	Empa 10mg
Number of patients in analysis set	1867	1863
Number of analysed patients, N (%)	1710 (100.0)	1733 (100.0)
Number of patients with endpoint, N (%)	1296 (75.8)	1338 (77.2)
95% confidence interval*	(73.7, 77.8)	(75.2, 79.1)
Comparison vs Placebo**		
Odds ratio (SE)		1.096 (0.093)
95% confidence interval***		(0.927, 1.295)
p-value		0.2830

* Wilson confidence intervals.
** Logistic regression includes terms for baseline EQ-VAS score (p<0.0001), age (p=0.0155), baseline eGFR (CKD-EPI) (p=0.3098), Treatment (p=0.2830), region (5 cat.) (p<0.0001), baseline diabetes status (3 cat.) (p=0.3594), sex (p=0.0736) and baseline LVEF (3 cat.) (p=0.4013).
***Wald confidence intervals.

Data taken from study 1245.121 only.
LOCF: For a missing value at week 52 the last available post-baseline value before week 52 is imputed.

Table R.1.2.1.1: 4 Responder analysis (displaying risk ratio) in EQ-VAS change from baseline at week 52 of > -7 points (stability) - RS (LOCF-AD) - 1245.121

	Placebo	Empa 10mg
Number of patients in analysis set	1867	1863
Number of analysed patients, N (%)	1710 (100.0)	1733 (100.0)
Number of patients with endpoint, N (%)	1296 (75.8)	1338 (77.2)
95% confidence interval*	(73.7, 77.8)	(75.2, 79.1)
Comparison vs Placebo**		
Risk ratio (SE)		1.016 (0.018)
95% confidence interval***		(0.981, 1.053)
p-value		0.3832

* Wilson confidence intervals.
** Log-linked Poisson model with robust estimate of variance includes terms for baseline EQ-VAS score (p<0.0001), age (p=0.0254), baseline eGFR (CKD-EPI) (p=0.3408), Treatment (p=0.3832), region (5 cat.) (p<0.0001), baseline diabetes status (3 cat.) (p=0.2792), sex (p=0.0401) and baseline LVEF (3 cat.) (p=0.5148).
***Wald confidence intervals.

Data taken from study 1245.121 only.
LOCF: For a missing value at week 52 the last available post-baseline value before week 52 is imputed.

Table R.1.2.1.1: 5 Responder analysis (displaying odds ratio) in EQ-VAS change from baseline at week 52 of >= 7 points (improvement) - RS (LOCF-AD) - 1245.121

	Placebo	Empa 10mg
Number of patients in analysis set	1867	1863
Number of analysed patients, N (%)	1710 (100.0)	1733 (100.0)
Number of patients with endpoint, N (%)	657 (38.4)	750 (43.3)
95% confidence interval*	(36.1, 40.7)	(41.0, 45.6)
Comparison vs Placebo**		
Odds ratio (SE)		1.291 (0.103)
95% confidence interval***		(1.103, 1.511)
p-value		0.0014

* Wilson confidence intervals.
** Logistic regression includes terms for baseline EQ-VAS score (p<0.0001), age (p=0.1817), baseline eGFR (CKD-EPI) (p=0.0390), Treatment (p=0.0014), region (5 cat.) (p<0.0001), baseline diabetes status (3 cat.) (p=0.9205), sex (p=0.4633) and baseline LVEF (3 cat.) (p=0.7283).
***Wald confidence intervals.

Data taken from study 1245.121 only.
LOCF: For a missing value at week 52 the last available post-baseline value before week 52 is imputed.

Table R.1.2.1.1: 6 Responder analysis (displaying risk ratio) in EQ-VAS change from baseline at week 52 of >= 7 points (improvement) - RS (LOCF-AD) - 1245.121

	Placebo	Empa 10mg
Number of patients in analysis set	1867	1863
Number of analysed patients, N (%)	1710 (100.0)	1733 (100.0)
Number of patients with endpoint, N (%)	657 (38.4)	750 (43.3)
95% confidence interval*	(36.1, 40.7)	(41.0, 45.6)
Comparison vs Placebo**		
Risk ratio (SE)		1.110 (0.042)
95% confidence interval***		(1.031, 1.194)
p-value		0.0054

* Wilson confidence intervals.
** Log-linked Poisson model with robust estimate of variance includes terms for baseline EQ-VAS score (p<0.0001), age (p=0.1611), baseline eGFR (CKD-EPI) (p=0.0530), Treatment (p=0.0054), region (5 cat.) (p<0.0001), baseline diabetes status (3 cat.) (p=0.8658), sex (p=0.2593) and baseline LVEF (3 cat.) (p=0.7557).
***Wald confidence intervals.

Data taken from study 1245.121 only.
LOCF: For a missing value at week 52 the last available post-baseline value before week 52 is imputed.

R.1.2.1.2

R.1.2.1.2 Subgroup analysis by sex

Table R.1.2.1.2: 1 Responder analysis (displaying odds ratio) in EQ-VAS change from baseline at week 52 of <= -7 points (deterioration) by sex - RS (LOCF-AD) - 1245.121

Subgroup Description	Placebo	Empa 10mg
Sex: Male		
Number of patients in analysis set	1411	1426
Number of analysed patients, N (%)	1297 (100.0)	1328 (100.0)
Number of patients with endpoint, N (%)	309 (23.8)	294 (22.1)
95% confidence interval*	(21.6, 26.2)	(20.0, 24.5)
Comparison vs Placebo**		
Odds ratio (SE)		0.895 (0.088)
95% confidence interval***		(0.739, 1.085)
p-value		0.2592
Sex: Female		
Number of patients in analysis set	456	437
Number of analysed patients, N (%)	413 (100.0)	405 (100.0)
Number of patients with endpoint, N (%)	105 (25.4)	101 (24.9)
95% confidence interval*	(21.5, 29.8)	(21.0, 29.4)
Comparison vs Placebo**		
Odds ratio (SE)		0.968 (0.167)
95% confidence interval***		(0.691, 1.356)
p-value		0.8507

* Wilson confidence intervals.
** Logistic regression includes terms for baseline EQ-VAS score (p<0.0001), age (p=0.0150), baseline eGFR (CKD-EPI) (p=0.3086), Treatment (p=0.4699), region (5 cat.) (p<0.0001), baseline diabetes status (3 cat.) (p=0.3622), baseline LVEF (3 cat.) (p=0.4023), sex (p=0.0726) and Treatment by sex interaction (p=0.6928).
***Wald confidence intervals.

Data taken from study 1245.121 only.
LOCF: For a missing value at week 52 the last available post-baseline value before week 52 is imputed.

Table R.1.2.1.2: 2 Responder analysis (displaying risk ratio) in EQ-VAS change from baseline at week 52 of <= -7 points (deterioration) by sex - RS (LOCF-AD) - 1245.121

Subgroup Description	Placebo	Empa 10mg
Sex: Male		
Number of patients in analysis set	1411	1426
Number of analysed patients, N (%)	1297 (100.0)	1328 (100.0)
Number of patients with endpoint, N (%)	309 (23.8)	294 (22.1)
95% confidence interval*	(21.6, 26.2)	(20.0, 24.5)
Comparison vs Placebo**		
Risk ratio (SE)		0.924 (0.063)
95% confidence interval***		(0.809, 1.057)
p-value		0.2494
Sex: Female		
Number of patients in analysis set	456	437
Number of analysed patients, N (%)	413 (100.0)	405 (100.0)
Number of patients with endpoint, N (%)	105 (25.4)	101 (24.9)
95% confidence interval*	(21.5, 29.8)	(21.0, 29.4)
Comparison vs Placebo**		
Risk ratio (SE)		0.976 (0.110)
95% confidence interval***		(0.782, 1.217)
p-value		0.8278

* Wilson confidence intervals.
** Log-linked Poisson model with robust estimate of variance includes terms for baseline EQ-VAS score (p<0.0001), age (p=0.0123), baseline eGFR (CKD-EPI) (p=0.3201), Treatment (p=0.4332), region (5 cat.) (p<0.0001), baseline diabetes status (3 cat.) (p=0.3787), baseline LVEF (3 cat.) (p=0.4249), sex (p=0.0857) and Treatment by sex interaction (p=0.6823).
***Wald confidence intervals.

Data taken from study 1245.121 only.
LOCF: For a missing value at week 52 the last available post-baseline value before week 52 is imputed.

Table R.1.2.1.2: 3 Responder analysis (displaying odds ratio) in EQ-VAS change from baseline at week 52 of > -7 points (stability) by sex - RS (LOCF-AD) - 1245.121

Subgroup Description	Placebo	Empa 10mg
Sex: Male		
Number of patients in analysis set	1411	1426
Number of analysed patients, N (%)	1297 (100.0)	1328 (100.0)
Number of patients with endpoint, N (%)	988 (76.2)	1034 (77.9)
95% confidence interval*	(73.8, 78.4)	(75.5, 80.0)
Comparison vs Placebo**		
Odds ratio (SE)		1.117 (0.110)
95% confidence interval***		(0.922, 1.354)
p-value		0.2592
Sex: Female		
Number of patients in analysis set	456	437
Number of analysed patients, N (%)	413 (100.0)	405 (100.0)
Number of patients with endpoint, N (%)	308 (74.6)	304 (75.1)
95% confidence interval*	(70.2, 78.5)	(70.6, 79.0)
Comparison vs Placebo**		
Odds ratio (SE)		1.033 (0.178)
95% confidence interval***		(0.737, 1.447)
p-value		0.8507

* Wilson confidence intervals.
** Logistic regression includes terms for baseline EQ-VAS score (p<0.0001), age (p=0.0150), baseline eGFR (CKD-EPI) (p=0.3086), Treatment (p=0.4699), region (5 cat.) (p<0.0001), baseline diabetes status (3 cat.) (p=0.3622), baseline LVEF (3 cat.) (p=0.4023), sex (p=0.0726) and Treatment by sex interaction (p=0.6928).
***Wald confidence intervals.

Data taken from study 1245.121 only.
LOCF: For a missing value at week 52 the last available post-baseline value before week 52 is imputed.

Table R.1.2.1.2: 4 Responder analysis (displaying risk ratio) in EQ-VAS change from baseline at week 52 of > -7 points (stability) by sex - RS (LOCF-AD) - 1245.121

Subgroup Description	Placebo	Empa 10mg
Sex: Male		
Number of patients in analysis set	1411	1426
Number of analysed patients, N (%)	1297 (100.0)	1328 (100.0)
Number of patients with endpoint, N (%)	988 (76.2)	1034 (77.9)
95% confidence interval*	(73.8, 78.4)	(75.5, 80.0)
Comparison vs Placebo**		
Risk ratio (SE)		1.021 (0.021)
95% confidence interval***		(0.981, 1.063)
p-value		0.3066
Sex: Female		
Number of patients in analysis set	456	437
Number of analysed patients, N (%)	413 (100.0)	405 (100.0)
Number of patients with endpoint, N (%)	308 (74.6)	304 (75.1)
95% confidence interval*	(70.2, 78.5)	(70.6, 79.0)
Comparison vs Placebo**		
Risk ratio (SE)		0.999 (0.038)
95% confidence interval***		(0.926, 1.076)
p-value		0.9706

* Wilson confidence intervals.
** Log-linked Poisson model with robust estimate of variance includes terms for baseline EQ-VAS score (p<0.0001), age (p=0.0248), baseline eGFR (CKD-EPI) (p=0.3358), Treatment (p=0.6523), region (5 cat.) (p<0.0001), baseline diabetes status (3 cat.) (p=0.2817), baseline LVEF (3 cat.) (p=0.5194), sex (p=0.0404) and Treatment by sex interaction (p=0.6061).
***Wald confidence intervals.

Data taken from study 1245.121 only.
LOCF: For a missing value at week 52 the last available post-baseline value before week 52 is imputed.

Table R.1.2.1.2: 5 Responder analysis (displaying odds ratio) in EQ-VAS change from baseline at week 52 of >= 7 points (improvement) by sex - RS (LOCF-AD) - 1245.121

Subgroup Description	Placebo	Empa 10mg
Sex: Male		
Number of patients in analysis set	1411	1426
Number of analysed patients, N (%)	1297 (100.0)	1328 (100.0)
Number of patients with endpoint, N (%)	491 (37.9)	576 (43.4)
95% confidence interval*	(35.3, 40.5)	(40.7, 46.1)
Comparison vs Placebo**		
Odds ratio (SE)		1.349 (0.124)
95% confidence interval***		(1.127, 1.615)
p-value		0.0011
Sex: Female		
Number of patients in analysis set	456	437
Number of analysed patients, N (%)	413 (100.0)	405 (100.0)
Number of patients with endpoint, N (%)	166 (40.2)	174 (43.0)
95% confidence interval*	(35.6, 45.0)	(38.2, 47.8)
Comparison vs Placebo**		
Odds ratio (SE)		1.117 (0.185)
95% confidence interval***		(0.807, 1.546)
p-value		0.5054

* Wilson confidence intervals.
** Logistic regression includes terms for baseline EQ-VAS score (p<0.0001), age (p=0.1764), baseline eGFR (CKD-EPI) (p=0.0367), Treatment (p=0.0304), region (5 cat.) (p<0.0001), baseline diabetes status (3 cat.) (p=0.9181), baseline LVEF (3 cat.) (p=0.7154), sex (p=0.4610) and Treatment by sex interaction (p=0.3188).
***Wald confidence intervals.

Data taken from study 1245.121 only.
LOCF: For a missing value at week 52 the last available post-baseline value before week 52 is imputed.

Table R.1.2.1.2: 6 Responder analysis (displaying risk ratio) in EQ-VAS change from baseline at week 52 of >= 7 points (improvement) by sex - RS (LOCF-AD) - 1245.121

Subgroup Description	Placebo	Empa 10mg
Sex: Male		
Number of patients in analysis set	1411	1426
Number of analysed patients, N (%)	1297 (100.0)	1328 (100.0)
Number of patients with endpoint, N (%)	491 (37.9)	576 (43.4)
95% confidence interval*	(35.3, 40.5)	(40.7, 46.1)
Comparison vs Placebo**		
Risk ratio (SE)		1.140 (0.049)
95% confidence interval***		(1.048, 1.241)
p-value		0.0024
Sex: Female		
Number of patients in analysis set	456	437
Number of analysed patients, N (%)	413 (100.0)	405 (100.0)
Number of patients with endpoint, N (%)	166 (40.2)	174 (43.0)
95% confidence interval*	(35.6, 45.0)	(38.2, 47.8)
Comparison vs Placebo**		
Risk ratio (SE)		1.019 (0.076)
95% confidence interval***		(0.881, 1.180)
p-value		0.7980

* Wilson confidence intervals.
** Log-linked Poisson model with robust estimate of variance includes terms for baseline EQ-VAS score (p<0.0001), age (p=0.1616), baseline eGFR (CKD-EPI) (p=0.0488), Treatment (p=0.0815), region (5 cat.) (p<0.0001), baseline diabetes status (3 cat.) (p=0.8682), baseline LVEF (3 cat.) (p=0.7349), sex (p=0.2866) and Treatment by sex interaction (p=0.1932).
***Wald confidence intervals.

Data taken from study 1245.121 only.
LOCF: For a missing value at week 52 the last available post-baseline value before week 52 is imputed.

R.1.2.1.3

Table R.1.2.1.3: 1 Responder analysis (displaying odds ratio) in EQ-VAS change from baseline at week 52 of <= -7 points (deterioration) by age (2 cat.) - RS (LOCF-AD) - 1245.121

Subgroup Description	Placebo	Empa 10mg
Age [years] (2 cat.): < 65		
Number of patients in analysis set	740	675
Number of analysed patients, N (%)	675 (100.0)	632 (100.0)
Number of patients with endpoint, N (%)	147 (21.8)	122 (19.3)
95% confidence interval*	(18.8, 25.0)	(16.4, 22.6)
Comparison vs Placebo**		
Odds ratio (SE)		0.879 (0.128)
95% confidence interval***		(0.661, 1.169)
p-value		0.3757
Age [years] (2 cat.): >= 65		
Number of patients in analysis set	1127	1188
Number of analysed patients, N (%)	1035 (100.0)	1101 (100.0)
Number of patients with endpoint, N (%)	267 (25.8)	273 (24.8)
95% confidence interval*	(23.2, 28.5)	(22.3, 27.4)
Comparison vs Placebo**		
Odds ratio (SE)		0.935 (0.098)
95% confidence interval***		(0.761, 1.150)
p-value		0.5260

* Wilson confidence intervals.
** Logistic regression includes terms for baseline EQ-VAS score (p<0.0001), baseline eGFR (CKD-EPI) (p=0.0526), Treatment (p=0.2754), region (5 cat.) (p<0.0001), baseline diabetes status (3 cat.) (p=0.4024), sex (p=0.0657), baseline LVEF (3 cat.) (p=0.4893), age (2 cat.) (p=0.3437) and Treatment by age (2 cat.) interaction (p=0.7305).
***Wald confidence intervals.

Data taken from study 1245.121 only.
LOCF: For a missing value at week 52 the last available post-baseline value before week 52 is imputed.

Table R.1.2.1.3: 2 Responder analysis (displaying risk ratio) in EQ-VAS change from baseline at week 52 of <= -7 points (deterioration) by age (2 cat.) - RS (LOCF-AD) - 1245.121

Subgroup Description	Placebo	Empa 10mg
Age [years] (2 cat.): < 65		
Number of patients in analysis set	740	675
Number of analysed patients, N (%)	675 (100.0)	632 (100.0)
Number of patients with endpoint, N (%)	147 (21.8)	122 (19.3)
95% confidence interval*	(18.8, 25.0)	(16.4, 22.6)
Comparison vs Placebo**		
Risk ratio (SE)		0.907 (0.095)
95% confidence interval***		(0.739, 1.113)
p-value		0.3498
Age [years] (2 cat.): >= 65		
Number of patients in analysis set	1127	1188
Number of analysed patients, N (%)	1035 (100.0)	1101 (100.0)
Number of patients with endpoint, N (%)	267 (25.8)	273 (24.8)
95% confidence interval*	(23.2, 28.5)	(22.3, 27.4)
Comparison vs Placebo**		
Risk ratio (SE)		0.955 (0.068)
95% confidence interval***		(0.831, 1.097)
p-value		0.5143

* Wilson confidence intervals.
** Log-linked Poisson model with robust estimate of variance includes terms for baseline EQ-VAS score (p<0.0001), baseline eGFR (CKD-EPI) (p=0.0524), Treatment (p=0.2535), region (5 cat.) (p<0.0001), baseline diabetes status (3 cat.) (p=0.4207), sex (p=0.0791), baseline LVEF (3 cat.) (p=0.5154), age (2 cat.) (p=0.3185) and Treatment by age (2 cat.) interaction (p=0.6839).
***Wald confidence intervals.

Data taken from study 1245.121 only.
LOCF: For a missing value at week 52 the last available post-baseline value before week 52 is imputed.

Table R.1.2.1.3: 3 Responder analysis (displaying odds ratio) in EQ-VAS change from baseline at week 52 of > -7 points (stability) by age (2 cat.) - RS (LOCF-AD) - 1245.121

Subgroup Description	Placebo	Empa 10mg
Age [years] (2 cat.): < 65		
Number of patients in analysis set	740	675
Number of analysed patients, N (%)	675 (100.0)	632 (100.0)
Number of patients with endpoint, N (%)	528 (78.2)	510 (80.7)
95% confidence interval*	(75.0, 81.2)	(77.4, 83.6)
Comparison vs Placebo**		
Odds ratio (SE)		1.137 (0.165)
95% confidence interval***		(0.856, 1.512)
p-value		0.3757
Age [years] (2 cat.): >= 65		
Number of patients in analysis set	1127	1188
Number of analysed patients, N (%)	1035 (100.0)	1101 (100.0)
Number of patients with endpoint, N (%)	768 (74.2)	828 (75.2)
95% confidence interval*	(71.5, 76.8)	(72.6, 77.7)
Comparison vs Placebo**		
Odds ratio (SE)		1.069 (0.113)
95% confidence interval***		(0.870, 1.314)
p-value		0.5260

* Wilson confidence intervals.
** Logistic regression includes terms for baseline EQ-VAS score (p<0.0001), baseline eGFR (CKD-EPI) (p=0.0526), Treatment (p=0.2754), region (5 cat.) (p<0.0001), baseline diabetes status (3 cat.) (p=0.4024), sex (p=0.0657), baseline LVEF (3 cat.) (p=0.4893), age (2 cat.) (p=0.3437) and Treatment by age (2 cat.) interaction (p=0.7305).
***Wald confidence intervals.

Data taken from study 1245.121 only.
LOCF: For a missing value at week 52 the last available post-baseline value before week 52 is imputed.

Table R.1.2.1.3: 4 Responder analysis (displaying risk ratio) in EQ-VAS change from baseline at week 52 of > -7 points (stability) by age (2 cat.) - RS (LOCF-AD) - 1245.121

Subgroup Description	Placebo	Empa 10mg
Age [years] (2 cat.): < 65		
Number of patients in analysis set	740	675
Number of analysed patients, N (%)	675 (100.0)	632 (100.0)
Number of patients with endpoint, N (%)	528 (78.2)	510 (80.7)
95% confidence interval*	(75.0, 81.2)	(77.4, 83.6)
Comparison vs Placebo**		
Risk ratio (SE)		1.018 (0.028)
95% confidence interval***		(0.966, 1.074)
p-value		0.5026
Age [years] (2 cat.): >= 65		
Number of patients in analysis set	1127	1188
Number of analysed patients, N (%)	1035 (100.0)	1101 (100.0)
Number of patients with endpoint, N (%)	768 (74.2)	828 (75.2)
95% confidence interval*	(71.5, 76.8)	(72.6, 77.7)
Comparison vs Placebo**		
Risk ratio (SE)		1.013 (0.024)
95% confidence interval***		(0.966, 1.062)
p-value		0.5904

* Wilson confidence intervals.
** Log-linked Poisson model with robust estimate of variance includes terms for baseline EQ-VAS score (p<0.0001), baseline eGFR (CKD-EPI) (p=0.0721), Treatment (p=0.3902), region (5 cat.) (p<0.0001), baseline diabetes status (3 cat.) (p=0.3115), sex (p=0.0362), baseline LVEF (3 cat.) (p=0.6075), age (2 cat.) (p=0.3589) and Treatment by age (2 cat.) interaction (p=0.8864).
***Wald confidence intervals.

Data taken from study 1245.121 only.
LOCF: For a missing value at week 52 the last available post-baseline value before week 52 is imputed.

Table R.1.2.1.3: 5 Responder analysis (displaying odds ratio) in EQ-VAS change from baseline at week 52 of >= 7 points (improvement) by age (2 cat.) - RS (LOCF-AD) - 1245.121

Subgroup Description	Placebo	Empa 10mg
Age [years] (2 cat.): < 65		
Number of patients in analysis set	740	675
Number of analysed patients, N (%)	675 (100.0)	632 (100.0)
Number of patients with endpoint, N (%)	286 (42.4)	312 (49.4)
95% confidence interval*	(38.7, 46.1)	(45.5, 53.3)
Comparison vs Placebo**		
Odds ratio (SE)		1.327 (0.171)
95% confidence interval***		(1.031, 1.708)
p-value		0.0281
Age [years] (2 cat.): >= 65		
Number of patients in analysis set	1127	1188
Number of analysed patients, N (%)	1035 (100.0)	1101 (100.0)
Number of patients with endpoint, N (%)	371 (35.8)	438 (39.8)
95% confidence interval*	(33.0, 38.8)	(36.9, 42.7)
Comparison vs Placebo**		
Odds ratio (SE)		1.267 (0.130)
95% confidence interval***		(1.036, 1.549)
p-value		0.0210

* Wilson confidence intervals.
** Logistic regression includes terms for baseline EQ-VAS score (p<0.0001), baseline eGFR (CKD-EPI) (p=0.0115), Treatment (p=0.0016), region (5 cat.) (p<0.0001), baseline diabetes status (3 cat.) (p=0.9180), sex (p=0.4387), baseline LVEF (3 cat.) (p=0.7144), age (2 cat.) (p=0.3650) and Treatment by age (2 cat.) interaction (p=0.7794).
***Wald confidence intervals.

Data taken from study 1245.121 only.
LOCF: For a missing value at week 52 the last available post-baseline value before week 52 is imputed.

Table R.1.2.1.3: 6 Responder analysis (displaying risk ratio) in EQ-VAS change from baseline at week 52 of >= 7 points (improvement) by age (2 cat.) - RS (LOCF-AD) - 1245.121

Subgroup Description	Placebo	Empa 10mg
Age [years] (2 cat.): < 65		
Number of patients in analysis set	740	675
Number of analysed patients, N (%)	675 (100.0)	632 (100.0)
Number of patients with endpoint, N (%)	286 (42.4)	312 (49.4)
95% confidence interval*	(38.7, 46.1)	(45.5, 53.3)
Comparison vs Placebo**		
Risk ratio (SE)		1.117 (0.062)
95% confidence interval***		(1.002, 1.245)
p-value		0.0459
Age [years] (2 cat.): >= 65		
Number of patients in analysis set	1127	1188
Number of analysed patients, N (%)	1035 (100.0)	1101 (100.0)
Number of patients with endpoint, N (%)	371 (35.8)	438 (39.8)
95% confidence interval*	(33.0, 38.8)	(36.9, 42.7)
Comparison vs Placebo**		
Risk ratio (SE)		1.103 (0.056)
95% confidence interval***		(0.999, 1.218)
p-value		0.0519

* Wilson confidence intervals.
** Log-linked Poisson model with robust estimate of variance includes terms for baseline EQ-VAS score (p<0.0001), baseline eGFR (CKD-EPI) (p=0.0195), Treatment (p=0.0053), region (5 cat.) (p<0.0001), baseline diabetes status (3 cat.) (p=0.8757), sex (p=0.2424), baseline LVEF (3 cat.) (p=0.7251), age (2 cat.) (p=0.2780) and Treatment by age (2 cat.) interaction (p=0.8717).
***Wald confidence intervals.

Data taken from study 1245.121 only.
LOCF: For a missing value at week 52 the last available post-baseline value before week 52 is imputed.

R.1.2.1.4 Subgroup analysis by region (North America, Latin America, Europe, Asia, Other)

Table R.1.2.1.4: 1 Responder analysis (displaying odds ratio) in EQ-VAS change from baseline at week 52 of <= -7 points (deterioration) by region - RS (LOCF-AD) - 1245.121

Subgroup Description	Placebo	Empa 10mg
Region (5 cat.): North America		
Number of patients in analysis set	213	212
Number of analysed patients, N (%)	192 (100.0)	204 (100.0)
Number of patients with endpoint, N (%)	49 (25.5)	50 (24.5)
95% confidence interval*	(19.9, 32.1)	(19.1, 30.8)
Comparison vs Placebo**		
Odds ratio (SE)		0.965 (0.236)
95% confidence interval***		(0.597, 1.560)
p-value		0.8842
Region (5 cat.): Latin America		
Number of patients in analysis set	645	641
Number of analysed patients, N (%)	577 (100.0)	583 (100.0)
Number of patients with endpoint, N (%)	124 (21.5)	124 (21.3)
95% confidence interval*	(18.3, 25.0)	(18.1, 24.8)
Comparison vs Placebo**		
Odds ratio (SE)		0.984 (0.149)
95% confidence interval***		(0.731, 1.325)
p-value		0.9154

* Wilson confidence intervals.
** Logistic regression includes terms for baseline EQ-VAS score (p<0.0001), age (p=0.0167), baseline eGFR (CKD-EPI) (p=0.3052), Treatment (p=0.1672), baseline diabetes status (3 cat.) (p=0.3528), sex (p=0.0751), baseline LVEF (3 cat.) (p=0.4010), region (5 cat.) (p<0.0001) and Treatment by region (5 cat.) interaction (p=0.8559).
***Wald confidence intervals.

Data taken from study 1245.121 only.
LOCF: For a missing value at week 52 the last available post-baseline value before week 52 is imputed.

Table R.1.2.1.4: 1 Responder analysis (displaying odds ratio) in EQ-VAS change from baseline at week 52 of <= -7 points (deterioration) by region - RS (LOCF-AD) - 1245.121

Subgroup Description	Placebo	Empa 10mg
Region (5 cat.): Europe		
Number of patients in analysis set	677	676
Number of analysed patients, N (%)	631 (100.0)	634 (100.0)
Number of patients with endpoint, N (%)	172 (27.3)	165 (26.0)
95% confidence interval*	(23.9, 30.9)	(22.8, 29.6)
Comparison vs Placebo**		
Odds ratio (SE)		0.889 (0.120)
95% confidence interval***		(0.683, 1.157)
p-value		0.3822
Region (5 cat.): Asia		
Number of patients in analysis set	245	248
Number of analysed patients, N (%)	233 (100.0)	236 (100.0)
Number of patients with endpoint, N (%)	58 (24.9)	51 (21.6)
95% confidence interval*	(19.8, 30.8)	(16.8, 27.3)
Comparison vs Placebo**		
Odds ratio (SE)		0.868 (0.198)
95% confidence interval***		(0.556, 1.357)
p-value		0.5351

* Wilson confidence intervals.
** Logistic regression includes terms for baseline EQ-VAS score (p<0.0001), age (p=0.0167), baseline eGFR (CKD-EPI) (p=0.3052), Treatment (p=0.1672), baseline diabetes status (3 cat.) (p=0.3528), sex (p=0.0751), baseline LVEF (3 cat.) (p=0.4010), region (5 cat.) (p<0.0001) and Treatment by region (5 cat.) interaction (p=0.8559).
***Wald confidence intervals.

Data taken from study 1245.121 only.
LOCF: For a missing value at week 52 the last available post-baseline value before week 52 is imputed.

Table R.1.2.1.4: 1 Responder analysis (displaying odds ratio) in EQ-VAS change from baseline at week 52 of <= -7 points (deterioration) by region - RS (LOCF-AD) - 1245.121

Subgroup Description	Placebo	Empa 10mg
Region (5 cat.): Other		
Number of patients in analysis set	87	86
Number of analysed patients, N (%)	77 (100.0)	76 (100.0)
Number of patients with endpoint, N (%)	11 (14.3)	5 (6.6)
95% confidence interval*	(8.2, 23.8)	(2.8, 14.5)
Comparison vs Placebo**		
Odds ratio (SE)		0.518 (0.301)
95% confidence interval***		(0.166, 1.620)
p-value		0.2583

* Wilson confidence intervals.
** Logistic regression includes terms for baseline EQ-VAS score (p<0.0001), age (p=0.0167), baseline eGFR (CKD-EPI) (p=0.3052), Treatment (p=0.1672), baseline diabetes status (3 cat.) (p=0.3528), sex (p=0.0751), baseline LVEF (3 cat.) (p=0.4010), region (5 cat.) (p<0.0001) and Treatment by region (5 cat.) interaction (p=0.8559).
***Wald confidence intervals.

Data taken from study 1245.121 only.
LOCF: For a missing value at week 52 the last available post-baseline value before week 52 is imputed.

Table R.1.2.1.4: 2 Responder analysis (displaying risk ratio) in EQ-VAS change from baseline at week 52 of <= -7 points (deterioration) by region - RS (LOCF-AD) - 1245.121

Subgroup Description	Placebo	Empa 10mg
Region (5 cat.): North America		
Number of patients in analysis set	213	212
Number of analysed patients, N (%)	192 (100.0)	204 (100.0)
Number of patients with endpoint, N (%)	49 (25.5)	50 (24.5)
95% confidence interval*	(19.9, 32.1)	(19.1, 30.8)
Comparison vs Placebo**		
Risk ratio (SE)		0.987 (0.168)
95% confidence interval***		(0.707, 1.379)
p-value		0.9406
Region (5 cat.): Latin America		
Number of patients in analysis set	645	641
Number of analysed patients, N (%)	577 (100.0)	583 (100.0)
Number of patients with endpoint, N (%)	124 (21.5)	124 (21.3)
95% confidence interval*	(18.3, 25.0)	(18.1, 24.8)
Comparison vs Placebo**		
Risk ratio (SE)		0.991 (0.104)
95% confidence interval***		(0.806, 1.218)
p-value		0.9311

* Wilson confidence intervals.
** Log-linked Poisson model with robust estimate of variance includes terms for baseline EQ-VAS score (p<0.0001), age (p=0.0141), baseline eGFR (CKD-EPI) (p=0.3139), Treatment (p=0.1484), baseline diabetes status (3 cat.) (p=0.3715), sex (p=0.0873), baseline LVEF (3 cat.) (p=0.4247), region (5 cat.) (p<0.0001) and Treatment by region (5 cat.) interaction (p=0.7937).
***Wald confidence intervals.

Data taken from study 1245.121 only.
LOCF: For a missing value at week 52 the last available post-baseline value before week 52 is imputed.

Table R.1.2.1.4: 2 Responder analysis (displaying risk ratio) in EQ-VAS change from baseline at week 52 of <= -7 points (deterioration) by region - RS (LOCF-AD) - 1245.121

Subgroup Description	Placebo	Empa 10mg
Region (5 cat.): Europe		
Number of patients in analysis set	677	676
Number of analysed patients, N (%)	631 (100.0)	634 (100.0)
Number of patients with endpoint, N (%)	172 (27.3)	165 (26.0)
95% confidence interval*	(23.9, 30.9)	(22.8, 29.6)
Comparison vs Placebo**		
Risk ratio (SE)		0.919 (0.082)
95% confidence interval***		(0.771, 1.094)
p-value		0.3417
Region (5 cat.): Asia		
Number of patients in analysis set	245	248
Number of analysed patients, N (%)	233 (100.0)	236 (100.0)
Number of patients with endpoint, N (%)	58 (24.9)	51 (21.6)
95% confidence interval*	(19.8, 30.8)	(16.8, 27.3)
Comparison vs Placebo**		
Risk ratio (SE)		0.901 (0.148)
95% confidence interval***		(0.653, 1.243)
p-value		0.5243

* Wilson confidence intervals.
** Log-linked Poisson model with robust estimate of variance includes terms for baseline EQ-VAS score (p<0.0001), age (p=0.0141), baseline eGFR (CKD-EPI) (p=0.3139), Treatment (p=0.1484), baseline diabetes status (3 cat.) (p=0.3715), sex (p=0.0873), baseline LVEF (3 cat.) (p=0.4247), region (5 cat.) (p<0.0001) and Treatment by region (5 cat.) interaction (p=0.7937).
***Wald confidence intervals.

Data taken from study 1245.121 only.
LOCF: For a missing value at week 52 the last available post-baseline value before week 52 is imputed.

Table R.1.2.1.4: 2 Responder analysis (displaying risk ratio) in EQ-VAS change from baseline at week 52 of <= -7 points (deterioration) by region - RS (LOCF-AD) - 1245.121

Subgroup Description	Placebo	Empa 10mg
Region (5 cat.): Other		
Number of patients in analysis set	87	86
Number of analysed patients, N (%)	77 (100.0)	76 (100.0)
Number of patients with endpoint, N (%)	11 (14.3)	5 (6.6)
95% confidence interval*	(8.2, 23.8)	(2.8, 14.5)
Comparison vs Placebo**		
Risk ratio (SE)		0.552 (0.267)
95% confidence interval***		(0.214, 1.425)
p-value		0.2195

* Wilson confidence intervals.
** Log-linked Poisson model with robust estimate of variance includes terms for baseline EQ-VAS score (p<0.0001), age (p=0.0141), baseline eGFR (CKD-EPI) (p=0.3139), Treatment (p=0.1484), baseline diabetes status (3 cat.) (p=0.3715), sex (p=0.0873), baseline LVEF (3 cat.) (p=0.4247), region (5 cat.) (p<0.0001) and Treatment by region (5 cat.) interaction (p=0.7937).
***Wald confidence intervals.

Data taken from study 1245.121 only.
LOCF: For a missing value at week 52 the last available post-baseline value before week 52 is imputed.

Table R.1.2.1.4: 3 Responder analysis (displaying odds ratio) in EQ-VAS change from baseline at week 52 of > -7 points (stability) by region - RS (LOCF-AD) - 1245.121

Subgroup Description	Placebo	Empa 10mg
Region (5 cat.): North America		
Number of patients in analysis set	213	212
Number of analysed patients, N (%)	192 (100.0)	204 (100.0)
Number of patients with endpoint, N (%)	143 (74.5)	154 (75.5)
95% confidence interval*	(67.9, 80.1)	(69.2, 80.9)
Comparison vs Placebo**		
Odds ratio (SE)		1.036 (0.254)
95% confidence interval***		(0.641, 1.675)
p-value		0.8842
Region (5 cat.): Latin America		
Number of patients in analysis set	645	641
Number of analysed patients, N (%)	577 (100.0)	583 (100.0)
Number of patients with endpoint, N (%)	453 (78.5)	459 (78.7)
95% confidence interval*	(75.0, 81.7)	(75.2, 81.9)
Comparison vs Placebo**		
Odds ratio (SE)		1.016 (0.154)
95% confidence interval***		(0.755, 1.368)
p-value		0.9154

* Wilson confidence intervals.
** Logistic regression includes terms for baseline EQ-VAS score (p<0.0001), age (p=0.0167), baseline eGFR (CKD-EPI) (p=0.3052), Treatment (p=0.1672), baseline diabetes status (3 cat.) (p=0.3528), sex (p=0.0751), baseline LVEF (3 cat.) (p=0.4010), region (5 cat.) (p<0.0001) and Treatment by region (5 cat.) interaction (p=0.8559).
***Wald confidence intervals.

Data taken from study 1245.121 only.
LOCF: For a missing value at week 52 the last available post-baseline value before week 52 is imputed.

Table R.1.2.1.4: 3 Responder analysis (displaying odds ratio) in EQ-VAS change from baseline at week 52 of > -7 points (stability) by region - RS (LOCF-AD) - 1245.121

Subgroup Description	Placebo	Empa 10mg
Region (5 cat.): Europe		
Number of patients in analysis set	677	676
Number of analysed patients, N (%)	631 (100.0)	634 (100.0)
Number of patients with endpoint, N (%)	459 (72.7)	469 (74.0)
95% confidence interval*	(69.1, 76.1)	(70.4, 77.2)
Comparison vs Placebo**		
Odds ratio (SE)		1.125 (0.151)
95% confidence interval***		(0.864, 1.465)
p-value		0.3822
Region (5 cat.): Asia		
Number of patients in analysis set	245	248
Number of analysed patients, N (%)	233 (100.0)	236 (100.0)
Number of patients with endpoint, N (%)	175 (75.1)	185 (78.4)
95% confidence interval*	(69.2, 80.2)	(72.7, 83.2)
Comparison vs Placebo**		
Odds ratio (SE)		1.152 (0.262)
95% confidence interval***		(0.737, 1.800)
p-value		0.5351

* Wilson confidence intervals.
** Logistic regression includes terms for baseline EQ-VAS score (p<0.0001), age (p=0.0167), baseline eGFR (CKD-EPI) (p=0.3052), Treatment (p=0.1672), baseline diabetes status (3 cat.) (p=0.3528), sex (p=0.0751), baseline LVEF (3 cat.) (p=0.4010), region (5 cat.) (p<0.0001) and Treatment by region (5 cat.) interaction (p=0.8559).
***Wald confidence intervals.

Data taken from study 1245.121 only.
LOCF: For a missing value at week 52 the last available post-baseline value before week 52 is imputed.

Table R.1.2.1.4: 3 Responder analysis (displaying odds ratio) in EQ-VAS change from baseline at week 52 of > -7 points (stability) by region - RS (LOCF-AD) - 1245.121

Subgroup Description	Placebo	Empa 10mg
Region (5 cat.): Other		
Number of patients in analysis set	87	86
Number of analysed patients, N (%)	77 (100.0)	76 (100.0)
Number of patients with endpoint, N (%)	66 (85.7)	71 (93.4)
95% confidence interval*	(76.2, 91.8)	(85.5, 97.2)
Comparison vs Placebo**		
Odds ratio (SE)		1.930 (1.122)
95% confidence interval***		(0.617, 6.031)
p-value		0.2583

* Wilson confidence intervals.
** Logistic regression includes terms for baseline EQ-VAS score (p<0.0001), age (p=0.0167), baseline eGFR (CKD-EPI) (p=0.3052), Treatment (p=0.1672), baseline diabetes status (3 cat.) (p=0.3528), sex (p=0.0751), baseline LVEF (3 cat.) (p=0.4010), region (5 cat.) (p<0.0001) and Treatment by region (5 cat.) interaction (p=0.8559).
***Wald confidence intervals.

Data taken from study 1245.121 only.
LOCF: For a missing value at week 52 the last available post-baseline value before week 52 is imputed.

Table R.1.2.1.4: 4 Responder analysis (displaying risk ratio) in EQ-VAS change from baseline at week 52 of > -7 points (stability) by region - RS (LOCF-AD) - 1245.121

Subgroup Description	Placebo	Empa 10mg
Region (5 cat.): North America		
Number of patients in analysis set	213	212
Number of analysed patients, N (%)	192 (100.0)	204 (100.0)
Number of patients with endpoint, N (%)	143 (74.5)	154 (75.5)
95% confidence interval*	(67.9, 80.1)	(69.2, 80.9)
Comparison vs Placebo**		
Risk ratio (SE)		1.005 (0.057)
95% confidence interval***		(0.900, 1.123)
p-value		0.9283
Region (5 cat.): Latin America		
Number of patients in analysis set	645	641
Number of analysed patients, N (%)	577 (100.0)	583 (100.0)
Number of patients with endpoint, N (%)	453 (78.5)	459 (78.7)
95% confidence interval*	(75.0, 81.7)	(75.2, 81.9)
Comparison vs Placebo**		
Risk ratio (SE)		1.005 (0.029)
95% confidence interval***		(0.949, 1.064)
p-value		0.8684

* Wilson confidence intervals.
** Log-linked Poisson model with robust estimate of variance includes terms for baseline EQ-VAS score (p<0.0001), age (p=0.0260), baseline eGFR (CKD-EPI) (p=0.3379), Treatment (p=0.3350), baseline diabetes status (3 cat.) (p=0.2738), sex (p=0.0406), baseline LVEF (3 cat.) (p=0.5136), region (5 cat.) (p<0.0001) and Treatment by region (5 cat.) interaction (p=0.9750).
***Wald confidence intervals.

Data taken from study 1245.121 only.
LOCF: For a missing value at week 52 the last available post-baseline value before week 52 is imputed.

Table R.1.2.1.4: 4 Responder analysis (displaying risk ratio) in EQ-VAS change from baseline at week 52 of > -7 points (stability) by region - RS (LOCF-AD) - 1245.121

Subgroup Description	Placebo	Empa 10mg
Region (5 cat.): Europe		
Number of patients in analysis set	677	676
Number of analysed patients, N (%)	631 (100.0)	634 (100.0)
Number of patients with endpoint, N (%)	459 (72.7)	469 (74.0)
95% confidence interval*	(69.1, 76.1)	(70.4, 77.2)
Comparison vs Placebo**		
Risk ratio (SE)		1.023 (0.033)
95% confidence interval***		(0.960, 1.090)
p-value		0.4844
Region (5 cat.): Asia		
Number of patients in analysis set	245	248
Number of analysed patients, N (%)	233 (100.0)	236 (100.0)
Number of patients with endpoint, N (%)	175 (75.1)	185 (78.4)
95% confidence interval*	(69.2, 80.2)	(72.7, 83.2)
Comparison vs Placebo**		
Risk ratio (SE)		1.025 (0.051)
95% confidence interval***		(0.930, 1.131)
p-value		0.6178

* Wilson confidence intervals.
** Log-linked Poisson model with robust estimate of variance includes terms for baseline EQ-VAS score (p<0.0001), age (p=0.0260), baseline eGFR (CKD-EPI) (p=0.3379), Treatment (p=0.3350), baseline diabetes status (3 cat.) (p=0.2738), sex (p=0.0406), baseline LVEF (3 cat.) (p=0.5136), region (5 cat.) (p<0.0001) and Treatment by region (5 cat.) interaction (p=0.9750).
***Wald confidence intervals.

Data taken from study 1245.121 only.
LOCF: For a missing value at week 52 the last available post-baseline value before week 52 is imputed.

Table R.1.2.1.4: 4 Responder analysis (displaying risk ratio) in EQ-VAS change from baseline at week 52 of > -7 points (stability) by region - RS (LOCF-AD) - 1245.121

Subgroup Description	Placebo	Empa 10mg
Region (5 cat.): Other		
Number of patients in analysis set	87	86
Number of analysed patients, N (%)	77 (100.0)	76 (100.0)
Number of patients with endpoint, N (%)	66 (85.7)	71 (93.4)
95% confidence interval*	(76.2, 91.8)	(85.5, 97.2)
Comparison vs Placebo**		
Risk ratio (SE)		1.042 (0.055)
95% confidence interval***		(0.939, 1.156)
p-value		0.4383

* Wilson confidence intervals.
** Log-linked Poisson model with robust estimate of variance includes terms for baseline EQ-VAS score (p<0.0001), age (p=0.0260), baseline eGFR (CKD-EPI) (p=0.3379), Treatment (p=0.3350), baseline diabetes status (3 cat.) (p=0.2738), sex (p=0.0406), baseline LVEF (3 cat.) (p=0.5136), region (5 cat.) (p<0.0001) and Treatment by region (5 cat.) interaction (p=0.9750).
***Wald confidence intervals.

Data taken from study 1245.121 only.
LOCF: For a missing value at week 52 the last available post-baseline value before week 52 is imputed.

Table R.1.2.1.4: 5 Responder analysis (displaying odds ratio) in EQ-VAS change from baseline at week 52 of >= 7 points (improvement) by region - RS (LOCF-AD) - 1245.121

Subgroup Description	Placebo	Empa 10mg
Region (5 cat.): North America		
Number of patients in analysis set	213	212
Number of analysed patients, N (%)	192 (100.0)	204 (100.0)
Number of patients with endpoint, N (%)	59 (30.7)	75 (36.8)
95% confidence interval*	(24.6, 37.6)	(30.4, 43.6)
Comparison vs Placebo**		
Odds ratio (SE)		1.451 (0.356)
95% confidence interval***		(0.897, 2.347)
p-value		0.1297
Region (5 cat.): Latin America		
Number of patients in analysis set	645	641
Number of analysed patients, N (%)	577 (100.0)	583 (100.0)
Number of patients with endpoint, N (%)	257 (44.5)	291 (49.9)
95% confidence interval*	(40.5, 48.6)	(45.9, 54.0)
Comparison vs Placebo**		
Odds ratio (SE)		1.349 (0.184)
95% confidence interval***		(1.032, 1.763)
p-value		0.0284

* Wilson confidence intervals.
** Logistic regression includes terms for baseline EQ-VAS score (p<0.0001), age (p=0.1720), baseline eGFR (CKD-EPI) (p=0.0412), Treatment (p=0.0053), baseline diabetes status (3 cat.) (p=0.9186), sex (p=0.4655), baseline LVEF (3 cat.) (p=0.7387), region (5 cat.) (p<0.0001) and Treatment by region (5 cat.) interaction (p=0.9205).
***Wald confidence intervals.

Data taken from study 1245.121 only.
LOCF: For a missing value at week 52 the last available post-baseline value before week 52 is imputed.

Table R.1.2.1.4: 5 Responder analysis (displaying odds ratio) in EQ-VAS change from baseline at week 52 of >= 7 points (improvement) by region - RS (LOCF-AD) - 1245.121

Subgroup Description	Placebo	Empa 10mg
Region (5 cat.): Europe		
Number of patients in analysis set	677	676
Number of analysed patients, N (%)	631 (100.0)	634 (100.0)
Number of patients with endpoint, N (%)	219 (34.7)	233 (36.8)
95% confidence interval*	(31.1, 38.5)	(33.1, 40.6)
Comparison vs Placebo**		
Odds ratio (SE)		1.188 (0.159)
95% confidence interval***		(0.914, 1.544)
p-value		0.1980
Region (5 cat.): Asia		
Number of patients in analysis set	245	248
Number of analysed patients, N (%)	233 (100.0)	236 (100.0)
Number of patients with endpoint, N (%)	83 (35.6)	101 (42.8)
95% confidence interval*	(29.8, 42.0)	(36.6, 49.2)
Comparison vs Placebo**		
Odds ratio (SE)		1.247 (0.263)
95% confidence interval***		(0.825, 1.885)
p-value		0.2957

* Wilson confidence intervals.
** Logistic regression includes terms for baseline EQ-VAS score (p<0.0001), age (p=0.1720), baseline eGFR (CKD-EPI) (p=0.0412), Treatment (p=0.0053), baseline diabetes status (3 cat.) (p=0.9186), sex (p=0.4655), baseline LVEF (3 cat.) (p=0.7387), region (5 cat.) (p<0.0001) and Treatment by region (5 cat.) interaction (p=0.9205).
***Wald confidence intervals.

Data taken from study 1245.121 only.
LOCF: For a missing value at week 52 the last available post-baseline value before week 52 is imputed.

Table R.1.2.1.4: 5 Responder analysis (displaying odds ratio) in EQ-VAS change from baseline at week 52 of >= 7 points (improvement) by region - RS (LOCF-AD) - 1245.121

Subgroup Description	Placebo	Empa 10mg
Region (5 cat.): Other		
Number of patients in analysis set	87	86
Number of analysed patients, N (%)	77 (100.0)	76 (100.0)
Number of patients with endpoint, N (%)	39 (50.6)	50 (65.8)
95% confidence interval*	(39.7, 61.5)	(54.6, 75.5)
Comparison vs Placebo**		
Odds ratio (SE)		1.514 (0.566)
95% confidence interval***		(0.728, 3.150)
p-value		0.2673

* Wilson confidence intervals.
** Logistic regression includes terms for baseline EQ-VAS score (p<0.0001), age (p=0.1720), baseline eGFR (CKD-EPI) (p=0.0412), Treatment (p=0.0053), baseline diabetes status (3 cat.) (p=0.9186), sex (p=0.4655), baseline LVEF (3 cat.) (p=0.7387), region (5 cat.) (p<0.0001) and Treatment by region (5 cat.) interaction (p=0.9205).
***Wald confidence intervals.

Data taken from study 1245.121 only.
LOCF: For a missing value at week 52 the last available post-baseline value before week 52 is imputed.

Table R.1.2.1.4: 6 Responder analysis (displaying risk ratio) in EQ-VAS change from baseline at week 52 of >= 7 points (improvement) by region - RS (LOCF-AD) - 1245.121

Subgroup Description	Placebo	Empa 10mg
Region (5 cat.): North America		
Number of patients in analysis set	213	212
Number of analysed patients, N (%)	192 (100.0)	204 (100.0)
Number of patients with endpoint, N (%)	59 (30.7)	75 (36.8)
95% confidence interval*	(24.6, 37.6)	(30.4, 43.6)
Comparison vs Placebo**		
Risk ratio (SE)		1.139 (0.147)
95% confidence interval***		(0.884, 1.466)
p-value		0.3146
Region (5 cat.): Latin America		
Number of patients in analysis set	645	641
Number of analysed patients, N (%)	577 (100.0)	583 (100.0)
Number of patients with endpoint, N (%)	257 (44.5)	291 (49.9)
95% confidence interval*	(40.5, 48.6)	(45.9, 54.0)
Comparison vs Placebo**		
Risk ratio (SE)		1.129 (0.064)
95% confidence interval***		(1.010, 1.261)
p-value		0.0324

* Wilson confidence intervals.
** Log-linked Poisson model with robust estimate of variance includes terms for baseline EQ-VAS score (p<0.0001), age (p=0.1577), baseline eGFR (CKD-EPI) (p=0.0553), Treatment (p=0.0152), baseline diabetes status (3 cat.) (p=0.8693), sex (p=0.2536), baseline LVEF (3 cat.) (p=0.7638), region (5 cat.) (p<0.0001) and Treatment by region (5 cat.) interaction (p=0.9900).
***Wald confidence intervals.

Data taken from study 1245.121 only.
LOCF: For a missing value at week 52 the last available post-baseline value before week 52 is imputed.

Table R.1.2.1.4: 6 Responder analysis (displaying risk ratio) in EQ-VAS change from baseline at week 52 of >= 7 points (improvement) by region - RS (LOCF-AD) - 1245.121

Subgroup Description	Placebo	Empa 10mg
Region (5 cat.): Europe		
Number of patients in analysis set	677	676
Number of analysed patients, N (%)	631 (100.0)	634 (100.0)
Number of patients with endpoint, N (%)	219 (34.7)	233 (36.8)
95% confidence interval*	(31.1, 38.5)	(33.1, 40.6)
Comparison vs Placebo**		
Risk ratio (SE)		1.078 (0.076)
95% confidence interval***		(0.939, 1.239)
p-value		0.2851
Region (5 cat.): Asia		
Number of patients in analysis set	245	248
Number of analysed patients, N (%)	233 (100.0)	236 (100.0)
Number of patients with endpoint, N (%)	83 (35.6)	101 (42.8)
95% confidence interval*	(29.8, 42.0)	(36.6, 49.2)
Comparison vs Placebo**		
Risk ratio (SE)		1.107 (0.118)
95% confidence interval***		(0.899, 1.363)
p-value		0.3399

* Wilson confidence intervals.
** Log-linked Poisson model with robust estimate of variance includes terms for baseline EQ-VAS score (p<0.0001), age (p=0.1577), baseline eGFR (CKD-EPI) (p=0.0553), Treatment (p=0.0152), baseline diabetes status (3 cat.) (p=0.8693), sex (p=0.2536), baseline LVEF (3 cat.) (p=0.7638), region (5 cat.) (p<0.0001) and Treatment by region (5 cat.) interaction (p=0.9900).
***Wald confidence intervals.

Data taken from study 1245.121 only.
LOCF: For a missing value at week 52 the last available post-baseline value before week 52 is imputed.

Table R.1.2.1.4: 6 Responder analysis (displaying risk ratio) in EQ-VAS change from baseline at week 52 of >= 7 points (improvement) by region - RS (LOCF-AD) - 1245.121

Subgroup Description	Placebo	Empa 10mg
Region (5 cat.): Other		
Number of patients in analysis set	87	86
Number of analysed patients, N (%)	77 (100.0)	76 (100.0)
Number of patients with endpoint, N (%)	39 (50.6)	50 (65.8)
95% confidence interval*	(39.7, 61.5)	(54.6, 75.5)
Comparison vs Placebo**		
Risk ratio (SE)		1.120 (0.130)
95% confidence interval***		(0.891, 1.407)
p-value		0.3305

* Wilson confidence intervals.
** Log-linked Poisson model with robust estimate of variance includes terms for baseline EQ-VAS score (p<0.0001), age (p=0.1577), baseline eGFR (CKD-EPI) (p=0.0553), Treatment (p=0.0152), baseline diabetes status (3 cat.) (p=0.8693), sex (p=0.2536), baseline LVEF (3 cat.) (p=0.7638), region (5 cat.) (p<0.0001) and Treatment by region (5 cat.) interaction (p=0.9900).
***Wald confidence intervals.

Data taken from study 1245.121 only.
LOCF: For a missing value at week 52 the last available post-baseline value before week 52 is imputed.

R.1.2.1.5

R.1.2.1.5 Subgroup analysis by OECD (N/Y)

Table R.1.2.1.5: 1 Responder analysis (displaying odds ratio) in EQ-VAS change from baseline at week 52 of <= -7 points (deterioration) by OECD member (N/Y) - RS (LOCF-AD) - 1245.121

Subgroup Description	Placebo	Empa 10mg
OECD member: No		
Number of patients in analysis set	741	713
Number of analysed patients, N (%)	664 (100.0)	644 (100.0)
Number of patients with endpoint, N (%)	136 (20.5)	120 (18.6)
95% confidence interval*	(17.6, 23.7)	(15.8, 21.8)
Comparison vs Placebo**		
Odds ratio (SE)		0.901 (0.132)
95% confidence interval***		(0.675, 1.202)
p-value		0.4778
OECD member: Yes		
Number of patients in analysis set	1126	1150
Number of analysed patients, N (%)	1046 (100.0)	1089 (100.0)
Number of patients with endpoint, N (%)	278 (26.6)	275 (25.3)
95% confidence interval*	(24.0, 29.3)	(22.8, 27.9)
Comparison vs Placebo**		
Odds ratio (SE)		0.919 (0.096)
95% confidence interval***		(0.749, 1.127)
p-value		0.4153

* Wilson confidence intervals.
** Logistic regression includes terms for baseline EQ-VAS score (p<0.0001), age (p=0.0111), baseline eGFR (CKD-EPI) (p=0.2201), Treatment (p=0.2931), sex (p=0.0599), baseline diabetes status (3 cat.) (p=0.2440), baseline LVEF (3 cat.) (p=0.3367), OECD member (p=0.0021) and Treatment by OECD member interaction (p=0.9138).
***Wald confidence intervals.

Data taken from study 1245.121 only.
LOCF: For a missing value at week 52 the last available post-baseline value before week 52 is imputed.
OECD member (yes/no) countries included:
Yes: United States, Canada, Mexico, Poland, Netherlands, Hungary, Germany, Czech Republic, Italy, France, Spain, United Kingdom, Belgium, Japan, Australia, 'Korea; Republic Of South Korea';
No: Brazil, Argentina, China, India.

Table R.1.2.1.5: 2 Responder analysis (displaying risk ratio) in EQ-VAS change from baseline at week 52 of <= -7 points (deterioration) by OECD member (N/Y) - RS (LOCF-AD) - 1245.121

Subgroup Description	Placebo	Empa 10mg
OECD member: No		
Number of patients in analysis set	741	713
Number of analysed patients, N (%)	664 (100.0)	644 (100.0)
Number of patients with endpoint, N (%)	136 (20.5)	120 (18.6)
95% confidence interval*	(17.6, 23.7)	(15.8, 21.8)
Comparison vs Placebo**		
Risk ratio (SE)		0.927 (0.098)
95% confidence interval***		(0.753, 1.141)
p-value		0.4726
OECD member: Yes		
Number of patients in analysis set	1126	1150
Number of analysed patients, N (%)	1046 (100.0)	1089 (100.0)
Number of patients with endpoint, N (%)	278 (26.6)	275 (25.3)
95% confidence interval*	(24.0, 29.3)	(22.8, 27.9)
Comparison vs Placebo**		
Risk ratio (SE)		0.944 (0.067)
95% confidence interval***		(0.822, 1.084)
p-value		0.4176

* Wilson confidence intervals.
** Log-linked Poisson model with robust estimate of variance includes terms for baseline EQ-VAS score (p<0.0001), age (p=0.0098), baseline eGFR (CKD-EPI) (p=0.2125), Treatment (p=0.2939), sex (p=0.0719), baseline diabetes status (3 cat.) (p=0.2445), baseline LVEF (3 cat.) (p=0.3691), OECD member (p=0.0017) and Treatment by OECD member interaction (p=0.8817).
***Wald confidence intervals.

Data taken from study 1245.121 only.
LOCF: For a missing value at week 52 the last available post-baseline value before week 52 is imputed.
OECD member (yes/no) countries included:
Yes: United States, Canada, Mexico, Poland, Netherlands, Hungary, Germany, Czech Republic, Italy, France, Spain, United Kingdom, Belgium, Japan, Australia, 'Korea; Republic Of South Korea';
No: Brazil, Argentina, China, India.

Table R.1.2.1.5: 3 Responder analysis (displaying odds ratio) in EQ-VAS change from baseline at week 52 of > -7 points (stability) by OECD member (N/Y) - RS (LOCF-AD) - 1245.121

Subgroup Description	Placebo	Empa 10mg
OECD member: No		
Number of patients in analysis set	741	713
Number of analysed patients, N (%)	664 (100.0)	644 (100.0)
Number of patients with endpoint, N (%)	528 (79.5)	524 (81.4)
95% confidence interval*	(76.3, 82.4)	(78.2, 84.2)
Comparison vs Placebo**		
Odds ratio (SE)		1.110 (0.163)
95% confidence interval***		(0.832, 1.481)
p-value		0.4778
OECD member: Yes		
Number of patients in analysis set	1126	1150
Number of analysed patients, N (%)	1046 (100.0)	1089 (100.0)
Number of patients with endpoint, N (%)	768 (73.4)	814 (74.7)
95% confidence interval*	(70.7, 76.0)	(72.1, 77.2)
Comparison vs Placebo**		
Odds ratio (SE)		1.089 (0.113)
95% confidence interval***		(0.888, 1.335)
p-value		0.4153

* Wilson confidence intervals.
** Logistic regression includes terms for baseline EQ-VAS score (p<0.0001), age (p=0.0111), baseline eGFR (CKD-EPI) (p=0.2201), Treatment (p=0.2931), sex (p=0.0599), baseline diabetes status (3 cat.) (p=0.2440), baseline LVEF (3 cat.) (p=0.3367), OECD member (p=0.0021) and Treatment by OECD member interaction (p=0.9138).
***Wald confidence intervals.

Data taken from study 1245.121 only.
LOCF: For a missing value at week 52 the last available post-baseline value before week 52 is imputed.
OECD member (yes/no) countries included:
Yes: United States, Canada, Mexico, Poland, Netherlands, Hungary, Germany, Czech Republic, Italy, France, Spain, United Kingdom, Belgium, Japan, Australia, 'Korea; Republic Of South Korea';
No: Brazil, Argentina, China, India.

Table R.1.2.1.5: 4 Responder analysis (displaying risk ratio) in EQ-VAS change from baseline at week 52 of > -7 points (stability) by OECD member (N/Y) - RS (LOCF-AD) - 1245.121

Subgroup Description	Placebo	Empa 10mg
OECD member: No		
Number of patients in analysis set	741	713
Number of analysed patients, N (%)	664 (100.0)	644 (100.0)
Number of patients with endpoint, N (%)	528 (79.5)	524 (81.4)
95% confidence interval*	(76.3, 82.4)	(78.2, 84.2)
Comparison vs Placebo**		
Risk ratio (SE)		1.018 (0.026)
95% confidence interval***		(0.968, 1.072)
p-value		0.4819
OECD member: Yes		
Number of patients in analysis set	1126	1150
Number of analysed patients, N (%)	1046 (100.0)	1089 (100.0)
Number of patients with endpoint, N (%)	768 (73.4)	814 (74.7)
95% confidence interval*	(70.7, 76.0)	(72.1, 77.2)
Comparison vs Placebo**		
Risk ratio (SE)		1.017 (0.025)
95% confidence interval***		(0.969, 1.067)
p-value		0.4991

* Wilson confidence intervals.
** Log-linked Poisson model with robust estimate of variance includes terms for baseline EQ-VAS score (p<0.0001), age (p=0.0144), baseline eGFR (CKD-EPI) (p=0.2782), Treatment (p=0.3293), sex (p=0.0356), baseline diabetes status (3 cat.) (p=0.1915), baseline LVEF (3 cat.) (p=0.4138), OECD member (p=0.0026) and Treatment by OECD member interaction (p=0.9652).
***Wald confidence intervals.

Data taken from study 1245.121 only.
LOCF: For a missing value at week 52 the last available post-baseline value before week 52 is imputed.
OECD member (yes/no) countries included:
Yes: United States, Canada, Mexico, Poland, Netherlands, Hungary, Germany, Czech Republic, Italy, France, Spain, United Kingdom, Belgium, Japan, Australia, 'Korea; Republic Of South Korea';
No: Brazil, Argentina, China, India.

Table R.1.2.1.5: 5 Responder analysis (displaying odds ratio) in EQ-VAS change from baseline at week 52 of >= 7 points (improvement) by OECD member (N/Y) - RS (LOCF-AD) - 1245.121

Subgroup Description	Placebo	Empa 10mg
OECD member: No		
Number of patients in analysis set	741	713
Number of analysed patients, N (%)	664 (100.0)	644 (100.0)
Number of patients with endpoint, N (%)	306 (46.1)	335 (52.0)
95% confidence interval*	(42.3, 49.9)	(48.2, 55.9)
Comparison vs Placebo**		
Odds ratio (SE)		1.292 (0.164)
95% confidence interval***		(1.007, 1.657)
p-value		0.0436
OECD member: Yes		
Number of patients in analysis set	1126	1150
Number of analysed patients, N (%)	1046 (100.0)	1089 (100.0)
Number of patients with endpoint, N (%)	351 (33.6)	415 (38.1)
95% confidence interval*	(30.8, 36.5)	(35.3, 41.0)
Comparison vs Placebo**		
Odds ratio (SE)		1.308 (0.134)
95% confidence interval***		(1.069, 1.600)
p-value		0.0090

* Wilson confidence intervals.
** Logistic regression includes terms for baseline EQ-VAS score (p<0.0001), age (p=0.1059), baseline eGFR (CKD-EPI) (p=0.0248), Treatment (p=0.0013), sex (p=0.4505), baseline diabetes status (3 cat.) (p=0.7354), baseline LVEF (3 cat.) (p=0.5892), OECD member (p<0.0001) and Treatment by OECD member interaction (p=0.9402).
***Wald confidence intervals.

Data taken from study 1245.121 only.
LOCF: For a missing value at week 52 the last available post-baseline value before week 52 is imputed.
OECD member (yes/no) countries included:
Yes: United States, Canada, Mexico, Poland, Netherlands, Hungary, Germany, Czech Republic, Italy, France, Spain, United Kingdom, Belgium, Japan, Australia, 'Korea; Republic Of South Korea';
No: Brazil, Argentina, China, India.

Table R.1.2.1.5: 6 Responder analysis (displaying risk ratio) in EQ-VAS change from baseline at week 52 of >= 7 points (improvement) by OECD member (N/Y) - RS (LOCF-AD) - 1245.121

Subgroup Description	Placebo	Empa 10mg
OECD member: No		
Number of patients in analysis set	741	713
Number of analysed patients, N (%)	664 (100.0)	644 (100.0)
Number of patients with endpoint, N (%)	306 (46.1)	335 (52.0)
95% confidence interval*	(42.3, 49.9)	(48.2, 55.9)
Comparison vs Placebo**		
Risk ratio (SE)		1.109 (0.056)
95% confidence interval***		(1.004, 1.226)
p-value		0.0414
OECD member: Yes		
Number of patients in analysis set	1126	1150
Number of analysed patients, N (%)	1046 (100.0)	1089 (100.0)
Number of patients with endpoint, N (%)	351 (33.6)	415 (38.1)
95% confidence interval*	(30.8, 36.5)	(35.3, 41.0)
Comparison vs Placebo**		
Risk ratio (SE)		1.125 (0.061)
95% confidence interval***		(1.012, 1.250)
p-value		0.0294

* Wilson confidence intervals.
** Log-linked Poisson model with robust estimate of variance includes terms for baseline EQ-VAS score (p<0.0001), age (p=0.1216), baseline eGFR (CKD-EPI) (p=0.0397), Treatment (p=0.0028), sex (p=0.2634), baseline diabetes status (3 cat.) (p=0.6537), baseline LVEF (3 cat.) (p=0.6896), OECD member (p<0.0001) and Treatment by OECD member interaction (p=0.8522).
***Wald confidence intervals.

Data taken from study 1245.121 only.
LOCF: For a missing value at week 52 the last available post-baseline value before week 52 is imputed.
OECD member (yes/no) countries included:
Yes: United States, Canada, Mexico, Poland, Netherlands, Hungary, Germany, Czech Republic, Italy, France, Spain, United Kingdom, Belgium, Japan, Australia, 'Korea; Republic Of South Korea';
No: Brazil, Argentina, China, India.

R.1.2.1.6 Subgroup analysis by NYHA at baseline (II, III/IV - 2 cat.)

Table R.1.2.1.6: 1 Responder analysis (displaying odds ratio) in EQ-VAS change from baseline at week 52 of <= -7 points (deterioration) by NYHA (2 cat.) - RS (LOCF-AD) - 1245.121

Subgroup Description	Placebo	Empa 10mg
Baseline NYHA (2 cat.): II		
Number of patients in analysis set	1401	1399
Number of analysed patients, N (%)	1307 (100.0)	1303 (100.0)
Number of patients with endpoint, N (%)	309 (23.6)	296 (22.7)
95% confidence interval*	(21.4, 26.0)	(20.5, 25.1)
Comparison vs Placebo**		
Odds ratio (SE)		0.924 (0.091)
95% confidence interval***		(0.762, 1.120)
p-value		0.4196
Baseline NYHA (2 cat.): III/IV		
Number of patients in analysis set	466	464
Number of analysed patients, N (%)	403 (100.0)	430 (100.0)
Number of patients with endpoint, N (%)	105 (26.1)	99 (23.0)
95% confidence interval*	(22.0, 30.6)	(19.3, 27.2)
Comparison vs Placebo**		
Odds ratio (SE)		0.859 (0.149)
95% confidence interval***		(0.611, 1.208)
p-value		0.3819

* Wilson confidence intervals.
** Logistic regression includes terms for baseline EQ-VAS score (p<0.0001), age (p=0.0151), baseline eGFR (CKD-EPI) (p=0.4006), Treatment (p=0.2468), region (5 cat.) (p<0.0001), baseline diabetes status (3 cat.) (p=0.3903), sex (p=0.1393), baseline LVEF (3 cat.) (p=0.4976), baseline NYHA (2 cat.) (p<0.0001) and Treatment by baseline NYHA (2 cat.) interaction (p=0.7159).
***Wald confidence intervals.

Data taken from study 1245.121 only.
LOCF: For a missing value at week 52 the last available post-baseline value before week 52 is imputed.

Table R.1.2.1.6: 2 Responder analysis (displaying risk ratio) in EQ-VAS change from baseline at week 52 of <= -7 points (deterioration) by NYHA (2 cat.) - RS (LOCF-AD) - 1245.121

Subgroup Description	Placebo	Empa 10mg
Baseline NYHA (2 cat.): II		
Number of patients in analysis set	1401	1399
Number of analysed patients, N (%)	1307 (100.0)	1303 (100.0)
Number of patients with endpoint, N (%)	309 (23.6)	296 (22.7)
95% confidence interval*	(21.4, 26.0)	(20.5, 25.1)
Comparison vs Placebo**		
Risk ratio (SE)		0.945 (0.064)
95% confidence interval***		(0.827, 1.080)
p-value		0.4066
Baseline NYHA (2 cat.): III/IV		
Number of patients in analysis set	466	464
Number of analysed patients, N (%)	403 (100.0)	430 (100.0)
Number of patients with endpoint, N (%)	105 (26.1)	99 (23.0)
95% confidence interval*	(22.0, 30.6)	(19.3, 27.2)
Comparison vs Placebo**		
Risk ratio (SE)		0.905 (0.102)
95% confidence interval***		(0.726, 1.128)
p-value		0.3757

* Wilson confidence intervals.
** Log-linked Poisson model with robust estimate of variance includes terms for baseline EQ-VAS score (p<0.0001), age (p=0.0112), baseline eGFR (CKD-EPI) (p=0.3999), Treatment (p=0.2347), region (5 cat.) (p<0.0001), baseline diabetes status (3 cat.) (p=0.3824), sex (p=0.1577), baseline LVEF (3 cat.) (p=0.5110), baseline NYHA (2 cat.) (p<0.0001) and Treatment by baseline NYHA (2 cat.) interaction (p=0.7428).
***Wald confidence intervals.

Data taken from study 1245.121 only.
LOCF: For a missing value at week 52 the last available post-baseline value before week 52 is imputed.

Table R.1.2.1.6: 3 Responder analysis (displaying odds ratio) in EQ-VAS change from baseline at week 52 of > -7 points (stability) by NYHA (2 cat.) - RS (LOCF-AD) - 1245.121

Subgroup Description	Placebo	Empa 10mg
Baseline NYHA (2 cat.): II		
Number of patients in analysis set	1401	1399
Number of analysed patients, N (%)	1307 (100.0)	1303 (100.0)
Number of patients with endpoint, N (%)	998 (76.4)	1007 (77.3)
95% confidence interval*	(74.0, 78.6)	(74.9, 79.5)
Comparison vs Placebo**		
Odds ratio (SE)		1.083 (0.106)
95% confidence interval***		(0.893, 1.312)
p-value		0.4196
Baseline NYHA (2 cat.): III/IV		
Number of patients in analysis set	466	464
Number of analysed patients, N (%)	403 (100.0)	430 (100.0)
Number of patients with endpoint, N (%)	298 (73.9)	331 (77.0)
95% confidence interval*	(69.4, 78.0)	(72.8, 80.7)
Comparison vs Placebo**		
Odds ratio (SE)		1.164 (0.202)
95% confidence interval***		(0.828, 1.637)
p-value		0.3819

* Wilson confidence intervals.
** Logistic regression includes terms for baseline EQ-VAS score (p<0.0001), age (p=0.0151), baseline eGFR (CKD-EPI) (p=0.4006), Treatment (p=0.2468), region (5 cat.) (p<0.0001), baseline diabetes status (3 cat.) (p=0.3903), sex (p=0.1393), baseline LVEF (3 cat.) (p=0.4976), baseline NYHA (2 cat.) (p<0.0001) and Treatment by baseline NYHA (2 cat.) interaction (p=0.7159).
***Wald confidence intervals.

Data taken from study 1245.121 only.
LOCF: For a missing value at week 52 the last available post-baseline value before week 52 is imputed.

Table R.1.2.1.6: 4 Responder analysis (displaying risk ratio) in EQ-VAS change from baseline at week 52 of > -7 points (stability) by NYHA (2 cat.) - RS (LOCF-AD) - 1245.121

Subgroup Description	Placebo	Empa 10mg
Baseline NYHA (2 cat.): II		
Number of patients in analysis set	1401	1399
Number of analysed patients, N (%)	1307 (100.0)	1303 (100.0)
Number of patients with endpoint, N (%)	998 (76.4)	1007 (77.3)
95% confidence interval*	(74.0, 78.6)	(74.9, 79.5)
Comparison vs Placebo**		
Risk ratio (SE)		1.014 (0.021)
95% confidence interval***		(0.973, 1.055)
p-value		0.5143
Baseline NYHA (2 cat.): III/IV		
Number of patients in analysis set	466	464
Number of analysed patients, N (%)	403 (100.0)	430 (100.0)
Number of patients with endpoint, N (%)	298 (73.9)	331 (77.0)
95% confidence interval*	(69.4, 78.0)	(72.8, 80.7)
Comparison vs Placebo**		
Risk ratio (SE)		1.030 (0.038)
95% confidence interval***		(0.958, 1.107)
p-value		0.4274

* Wilson confidence intervals.
** Log-linked Poisson model with robust estimate of variance includes terms for baseline EQ-VAS score (p<0.0001), age (p=0.0306), baseline eGFR (CKD-EPI) (p=0.4110), Treatment (p=0.3126), region (5 cat.) (p<0.0001), baseline diabetes status (3 cat.) (p=0.3242), sex (p=0.0657), baseline LVEF (3 cat.) (p=0.6333), baseline NYHA (2 cat.) (p<0.0001) and Treatment by baseline NYHA (2 cat.) interaction (p=0.7074).
***Wald confidence intervals.

Data taken from study 1245.121 only.
LOCF: For a missing value at week 52 the last available post-baseline value before week 52 is imputed.

Table R.1.2.1.6: 5 Responder analysis (displaying odds ratio) in EQ-VAS change from baseline at week 52 of >= 7 points (improvement) by NYHA (2 cat.) - RS (LOCF-AD) - 1245.121

Subgroup Description	Placebo	Empa 10mg
Baseline NYHA (2 cat.): II		
Number of patients in analysis set	1401	1399
Number of analysed patients, N (%)	1307 (100.0)	1303 (100.0)
Number of patients with endpoint, N (%)	482 (36.9)	535 (41.1)
95% confidence interval*	(34.3, 39.5)	(38.4, 43.8)
Comparison vs Placebo**		
Odds ratio (SE)		1.275 (0.117)
95% confidence interval***		(1.065, 1.527)
p-value		0.0083
Baseline NYHA (2 cat.): III/IV		
Number of patients in analysis set	466	464
Number of analysed patients, N (%)	403 (100.0)	430 (100.0)
Number of patients with endpoint, N (%)	175 (43.4)	215 (50.0)
95% confidence interval*	(38.7, 48.3)	(45.3, 54.7)
Comparison vs Placebo**		
Odds ratio (SE)		1.371 (0.224)
95% confidence interval***		(0.995, 1.889)
p-value		0.0540

* Wilson confidence intervals.
** Logistic regression includes terms for baseline EQ-VAS score (p<0.0001), age (p=0.1858), baseline eGFR (CKD-EPI) (p=0.0513), Treatment (p=0.0030), region (5 cat.) (p<0.0001), baseline diabetes status (3 cat.) (p=0.8450), sex (p=0.5648), baseline LVEF (3 cat.) (p=0.6911), baseline NYHA (2 cat.) (p=0.0027) and Treatment by baseline NYHA (2 cat.) interaction (p=0.6999).
***Wald confidence intervals.

Data taken from study 1245.121 only.
LOCF: For a missing value at week 52 the last available post-baseline value before week 52 is imputed.

Table R.1.2.1.6: 6 Responder analysis (displaying risk ratio) in EQ-VAS change from baseline at week 52 of >= 7 points (improvement) by NYHA (2 cat.) - RS (LOCF-AD) - 1245.121

Subgroup Description	Placebo	Empa 10mg
Baseline NYHA (2 cat.): II		
Number of patients in analysis set	1401	1399
Number of analysed patients, N (%)	1307 (100.0)	1303 (100.0)
Number of patients with endpoint, N (%)	482 (36.9)	535 (41.1)
95% confidence interval*	(34.3, 39.5)	(38.4, 43.8)
Comparison vs Placebo**		
Risk ratio (SE)		1.113 (0.049)
95% confidence interval***		(1.020, 1.214)
p-value		0.0160
Baseline NYHA (2 cat.): III/IV		
Number of patients in analysis set	466	464
Number of analysed patients, N (%)	403 (100.0)	430 (100.0)
Number of patients with endpoint, N (%)	175 (43.4)	215 (50.0)
95% confidence interval*	(38.7, 48.3)	(45.3, 54.7)
Comparison vs Placebo**		
Risk ratio (SE)		1.110 (0.077)
95% confidence interval***		(0.968, 1.272)
p-value		0.1339

* Wilson confidence intervals.
** Log-linked Poisson model with robust estimate of variance includes terms for baseline EQ-VAS score (p<0.0001), age (p=0.1921), baseline eGFR (CKD-EPI) (p=0.0584), Treatment (p=0.0105), region (5 cat.) (p<0.0001), baseline diabetes status (3 cat.) (p=0.8237), sex (p=0.3085), baseline LVEF (3 cat.) (p=0.6858), baseline NYHA (2 cat.) (p=0.0020) and Treatment by baseline NYHA (2 cat.) interaction (p=0.9764).
***Wald confidence intervals.

Data taken from study 1245.121 only.
LOCF: For a missing value at week 52 the last available post-baseline value before week 52 is imputed.

R.1.2.1.7

R.1.2.1.7 Subgroup analysis by diabetes at baseline

Table R.1.2.1.7: 1 Responder analysis (displaying odds ratio) in EQ-VAS change from baseline at week 52 of <= -7 points (deterioration) by diabetes at baseline - RS (LOCF-AD) - 1245.121

Subgroup Description	Placebo	Empa 10mg
Diabetes at baseline (2 cat.): Diabetic		
Number of patients in analysis set	929	927
Number of analysed patients, N (%)	850 (100.0)	856 (100.0)
Number of patients with endpoint, N (%)	205 (24.1)	193 (22.5)
95% confidence interval*	(21.4, 27.1)	(19.9, 25.5)
Comparison vs Placebo**		
Odds ratio (SE)		0.907 (0.110)
95% confidence interval***		(0.715, 1.151)
p-value		0.4215
Diabetes at baseline (2 cat.): Non-Diabetic		
Number of patients in analysis set	938	936
Number of analysed patients, N (%)	860 (100.0)	877 (100.0)
Number of patients with endpoint, N (%)	209 (24.3)	202 (23.0)
95% confidence interval*	(21.6, 27.3)	(20.4, 25.9)
Comparison vs Placebo**		
Odds ratio (SE)		0.916 (0.109)
95% confidence interval***		(0.725, 1.157)
p-value		0.4609

* Wilson confidence intervals.
** Logistic regression includes terms for baseline EQ-VAS score (p<0.0001), age (p=0.0177), baseline eGFR (CKD-EPI) (p=0.3266), Treatment (p=0.2758), region (5 cat.) (p<0.0001), sex (p=0.0724), baseline LVEF (3 cat.) (p=0.3979), diabetes at baseline (2 cat.) (p=0.7064) and Treatment by diabetes at baseline (2 cat.) interaction (p=0.9550).
***Wald confidence intervals.

Data taken from study 1245.121 only.
LOCF: For a missing value at week 52 the last available post-baseline value before week 52 is imputed.

Table R.1.2.1.7: 2 Responder analysis (displaying risk ratio) in EQ-VAS change from baseline at week 52 of <= -7 points (deterioration) by diabetes at baseline - RS (LOCF-AD) - 1245.121

Subgroup Description	Placebo	Empa 10mg
Diabetes at baseline (2 cat.): Diabetic		
Number of patients in analysis set	929	927
Number of analysed patients, N (%)	850 (100.0)	856 (100.0)
Number of patients with endpoint, N (%)	205 (24.1)	193 (22.5)
95% confidence interval*	(21.4, 27.1)	(19.9, 25.5)
Comparison vs Placebo**		
Risk ratio (SE)		0.935 (0.077)
95% confidence interval***		(0.795, 1.099)
p-value		0.4127
Diabetes at baseline (2 cat.): Non-Diabetic		
Number of patients in analysis set	938	936
Number of analysed patients, N (%)	860 (100.0)	877 (100.0)
Number of patients with endpoint, N (%)	209 (24.3)	202 (23.0)
95% confidence interval*	(21.6, 27.3)	(20.4, 25.9)
Comparison vs Placebo**		
Risk ratio (SE)		0.938 (0.078)
95% confidence interval***		(0.798, 1.103)
p-value		0.4394

* Wilson confidence intervals.
** Log-linked Poisson model with robust estimate of variance includes terms for baseline EQ-VAS score (p<0.0001), age (p=0.0147), baseline eGFR (CKD-EPI) (p=0.3371), Treatment (p=0.2599), region (5 cat.) (p<0.0001), sex (p=0.0844), baseline LVEF (3 cat.) (p=0.4191), diabetes at baseline (2 cat.) (p=0.7475) and Treatment by diabetes at baseline (2 cat.) interaction (p=0.9748).
***Wald confidence intervals.

Data taken from study 1245.121 only.
LOCF: For a missing value at week 52 the last available post-baseline value before week 52 is imputed.

Table R.1.2.1.7: 3 Responder analysis (displaying odds ratio) in EQ-VAS change from baseline at week 52 of > -7 points (stability) by diabetes at baseline - RS (LOCF-AD) - 1245.121

Subgroup Description	Placebo	Empa 10mg
Diabetes at baseline (2 cat.): Diabetic		
Number of patients in analysis set	929	927
Number of analysed patients, N (%)	850 (100.0)	856 (100.0)
Number of patients with endpoint, N (%)	645 (75.9)	663 (77.5)
95% confidence interval*	(72.9, 78.6)	(74.5, 80.1)
Comparison vs Placebo**		
Odds ratio (SE)		1.103 (0.134)
95% confidence interval***		(0.869, 1.399)
p-value		0.4215
Diabetes at baseline (2 cat.): Non-Diabetic		
Number of patients in analysis set	938	936
Number of analysed patients, N (%)	860 (100.0)	877 (100.0)
Number of patients with endpoint, N (%)	651 (75.7)	675 (77.0)
95% confidence interval*	(72.7, 78.4)	(74.1, 79.6)
Comparison vs Placebo**		
Odds ratio (SE)		1.092 (0.130)
95% confidence interval***		(0.864, 1.380)
p-value		0.4609

* Wilson confidence intervals.
** Logistic regression includes terms for baseline EQ-VAS score (p<0.0001), age (p=0.0177), baseline eGFR (CKD-EPI) (p=0.3266), Treatment (p=0.2758), region (5 cat.) (p<0.0001), sex (p=0.0724), baseline LVEF (3 cat.) (p=0.3979), diabetes at baseline (2 cat.) (p=0.7064) and Treatment by diabetes at baseline (2 cat.) interaction (p=0.9550).
***Wald confidence intervals.

Data taken from study 1245.121 only.
LOCF: For a missing value at week 52 the last available post-baseline value before week 52 is imputed.

Table R.1.2.1.7: 4 Responder analysis (displaying risk ratio) in EQ-VAS change from baseline at week 52 of > -7 points (stability) by diabetes at baseline - RS (LOCF-AD) - 1245.121

Subgroup Description	Placebo	Empa 10mg
Diabetes at baseline (2 cat.): Diabetic		
Number of patients in analysis set	929	927
Number of analysed patients, N (%)	850 (100.0)	856 (100.0)
Number of patients with endpoint, N (%)	645 (75.9)	663 (77.5)
95% confidence interval*	(72.9, 78.6)	(74.5, 80.1)
Comparison vs Placebo**		
Risk ratio (SE)		1.017 (0.026)
95% confidence interval***		(0.968, 1.069)
p-value		0.5073
Diabetes at baseline (2 cat.): Non-Diabetic		
Number of patients in analysis set	938	936
Number of analysed patients, N (%)	860 (100.0)	877 (100.0)
Number of patients with endpoint, N (%)	651 (75.7)	675 (77.0)
95% confidence interval*	(72.7, 78.4)	(74.1, 79.6)
Comparison vs Placebo**		
Risk ratio (SE)		1.015 (0.026)
95% confidence interval***		(0.965, 1.067)
p-value		0.5686

* Wilson confidence intervals.
** Log-linked Poisson model with robust estimate of variance includes terms for baseline EQ-VAS score (p<0.0001), age (p=0.0292), baseline eGFR (CKD-EPI) (p=0.3678), Treatment (p=0.3841), region (5 cat.) (p<0.0001), sex (p=0.0402), baseline LVEF (3 cat.) (p=0.5083), diabetes at baseline (2 cat.) (p=0.5914) and Treatment by diabetes at baseline (2 cat.) interaction (p=0.9534).
***Wald confidence intervals.

Data taken from study 1245.121 only.
LOCF: For a missing value at week 52 the last available post-baseline value before week 52 is imputed.

Table R.1.2.1.7: 5 Responder analysis (displaying odds ratio) in EQ-VAS change from baseline at week 52 of >= 7 points (improvement) by diabetes at baseline - RS (LOCF-AD) - 1245.121

Subgroup Description	Placebo	Empa 10mg
Diabetes at baseline (2 cat.): Diabetic		
Number of patients in analysis set	929	927
Number of analysed patients, N (%)	850 (100.0)	856 (100.0)
Number of patients with endpoint, N (%)	329 (38.7)	386 (45.1)
95% confidence interval*	(35.5, 42.0)	(41.8, 48.4)
Comparison vs Placebo**		
Odds ratio (SE)		1.398 (0.159)
95% confidence interval***		(1.118, 1.748)
p-value		0.0033
Diabetes at baseline (2 cat.): Non-Diabetic		
Number of patients in analysis set	938	936
Number of analysed patients, N (%)	860 (100.0)	877 (100.0)
Number of patients with endpoint, N (%)	328 (38.1)	364 (41.5)
95% confidence interval*	(35.0, 41.4)	(38.3, 44.8)
Comparison vs Placebo**		
Odds ratio (SE)		1.195 (0.134)
95% confidence interval***		(0.959, 1.490)
p-value		0.1131

* Wilson confidence intervals.
** Logistic regression includes terms for baseline EQ-VAS score (p<0.0001), age (p=0.1881), baseline eGFR (CKD-EPI) (p=0.0392), Treatment (p=0.0014), region (5 cat.) (p<0.0001), sex (p=0.4526), baseline LVEF (3 cat.) (p=0.7273), diabetes at baseline (2 cat.) (p=0.7535) and Treatment by diabetes at baseline (2 cat.) interaction (p=0.3284).
***Wald confidence intervals.

Data taken from study 1245.121 only.
LOCF: For a missing value at week 52 the last available post-baseline value before week 52 is imputed.

Table R.1.2.1.7: 6 Responder analysis (displaying risk ratio) in EQ-VAS change from baseline at week 52 of >= 7 points (improvement) by diabetes at baseline - RS (LOCF-AD) - 1245.121

Subgroup Description	Placebo	Empa 10mg
Diabetes at baseline (2 cat.): Diabetic		
Number of patients in analysis set	929	927
Number of analysed patients, N (%)	850 (100.0)	856 (100.0)
Number of patients with endpoint, N (%)	329 (38.7)	386 (45.1)
95% confidence interval*	(35.5, 42.0)	(41.8, 48.4)
Comparison vs Placebo**		
Risk ratio (SE)		1.144 (0.059)
95% confidence interval***		(1.033, 1.266)
p-value		0.0096
Diabetes at baseline (2 cat.): Non-Diabetic		
Number of patients in analysis set	938	936
Number of analysed patients, N (%)	860 (100.0)	877 (100.0)
Number of patients with endpoint, N (%)	328 (38.1)	364 (41.5)
95% confidence interval*	(35.0, 41.4)	(38.3, 44.8)
Comparison vs Placebo**		
Risk ratio (SE)		1.075 (0.058)
95% confidence interval***		(0.967, 1.195)
p-value		0.1803

* Wilson confidence intervals.
** Log-linked Poisson model with robust estimate of variance includes terms for baseline EQ-VAS score (p<0.0001), age (p=0.1674), baseline eGFR (CKD-EPI) (p=0.0576), Treatment (p=0.0058), region (5 cat.) (p<0.0001), sex (p=0.2580), baseline LVEF (3 cat.) (p=0.7597), diabetes at baseline (2 cat.) (p=0.9409) and Treatment by diabetes at baseline (2 cat.) interaction (p=0.4074).
***Wald confidence intervals.

Data taken from study 1245.121 only.
LOCF: For a missing value at week 52 the last available post-baseline value before week 52 is imputed.

R.1.2.1.8

R.1.2.1.8 Subgroup analysis by BMI at baseline (<30, >=30)

Table R.1.2.1.8: 1 Responder analysis (displaying odds ratio) in EQ-VAS change from baseline at week 52 of <= -7 points (deterioration) by baseline BMI [kg/m2] - RS (LOCF-AD) - 1245.121

Subgroup Description	Placebo	Empa 10mg
Baseline BMI [kg/m²] (2 cat.): <30		
Number of patients in analysis set	1300	1263
Number of analysed patients, N (%)	1197 (100.0)	1179 (100.0)
Number of patients with endpoint, N (%)	291 (24.3)	259 (22.0)
95% confidence interval*	(22.0, 26.8)	(19.7, 24.4)
Comparison vs Placebo**		
Odds ratio (SE)		0.840 (0.087)
95% confidence interval***		(0.686, 1.028)
p-value		0.0905
Baseline BMI [kg/m²] (2 cat.): >=30		
Number of patients in analysis set	567	600
Number of analysed patients, N (%)	513 (100.0)	554 (100.0)
Number of patients with endpoint, N (%)	123 (24.0)	136 (24.5)
95% confidence interval*	(20.5, 27.9)	(21.1, 28.3)
Comparison vs Placebo**		
Odds ratio (SE)		1.081 (0.164)
95% confidence interval***		(0.803, 1.456)
p-value		0.6077

* Wilson confidence intervals.
** Logistic regression includes terms for baseline EQ-VAS score (p<0.0001), age (p=0.0065), baseline eGFR (CKD-EPI) (p=0.3397), Treatment (p=0.5984), region (5 cat.) (p<0.0001), baseline diabetes status (3 cat.) (p=0.3564), sex (p=0.0959), baseline LVEF (3 cat.) (p=0.3801), baseline BMI (2 cat.) (p=0.0220) and Treatment by baseline BMI (2 cat.) interaction (p=0.1689).
***Wald confidence intervals.

Data taken from study 1245.121 only.
LOCF: For a missing value at week 52 the last available post-baseline value before week 52 is imputed.

Table R.1.2.1.8: 2 Responder analysis (displaying risk ratio) in EQ-VAS change from baseline at week 52 of <= -7 points (deterioration) by baseline BMI [kg/m2] - RS (LOCF-AD) - 1245.121

Subgroup Description	Placebo	Empa 10mg
Baseline BMI [kg/m²] (2 cat.): <30		
Number of patients in analysis set	1300	1263
Number of analysed patients, N (%)	1197 (100.0)	1179 (100.0)
Number of patients with endpoint, N (%)	291 (24.3)	259 (22.0)
95% confidence interval*	(22.0, 26.8)	(19.7, 24.4)
Comparison vs Placebo**		
Risk ratio (SE)		0.885 (0.063)
95% confidence interval***		(0.770, 1.017)
p-value		0.0859
Baseline BMI [kg/m²] (2 cat.): >=30		
Number of patients in analysis set	567	600
Number of analysed patients, N (%)	513 (100.0)	554 (100.0)
Number of patients with endpoint, N (%)	123 (24.0)	136 (24.5)
95% confidence interval*	(20.5, 27.9)	(21.1, 28.3)
Comparison vs Placebo**		
Risk ratio (SE)		1.052 (0.108)
95% confidence interval***		(0.860, 1.287)
p-value		0.6224

* Wilson confidence intervals.
** Log-linked Poisson model with robust estimate of variance includes terms for baseline EQ-VAS score (p<0.0001), age (p=0.0054), baseline eGFR (CKD-EPI) (p=0.3457), Treatment (p=0.5677), region (5 cat.) (p<0.0001), baseline diabetes status (3 cat.) (p=0.3572), sex (p=0.1153), baseline LVEF (3 cat.) (p=0.3972), baseline BMI (2 cat.) (p=0.0159) and Treatment by baseline BMI (2 cat.) interaction (p=0.1672).
***Wald confidence intervals.

Data taken from study 1245.121 only.
LOCF: For a missing value at week 52 the last available post-baseline value before week 52 is imputed.

Table R.1.2.1.8: 3 Responder analysis (displaying odds ratio) in EQ-VAS change from baseline at week 52 of > -7 points (stability) by baseline BMI [kg/m2] - RS (LOCF-AD) - 1245.121

Subgroup Description	Placebo	Empa 10mg
Baseline BMI [kg/m²] (2 cat.): <30		
Number of patients in analysis set	1300	1263
Number of analysed patients, N (%)	1197 (100.0)	1179 (100.0)
Number of patients with endpoint, N (%)	906 (75.7)	920 (78.0)
95% confidence interval*	(73.2, 78.0)	(75.6, 80.3)
Comparison vs Placebo**		
Odds ratio (SE)		1.191 (0.123)
95% confidence interval***		(0.973, 1.458)
p-value		0.0905
Baseline BMI [kg/m²] (2 cat.): >=30		
Number of patients in analysis set	567	600
Number of analysed patients, N (%)	513 (100.0)	554 (100.0)
Number of patients with endpoint, N (%)	390 (76.0)	418 (75.5)
95% confidence interval*	(72.1, 79.5)	(71.7, 78.9)
Comparison vs Placebo**		
Odds ratio (SE)		0.925 (0.140)
95% confidence interval***		(0.687, 1.246)
p-value		0.6077

* Wilson confidence intervals.
** Logistic regression includes terms for baseline EQ-VAS score (p<0.0001), age (p=0.0065), baseline eGFR (CKD-EPI) (p=0.3397), Treatment (p=0.5984), region (5 cat.) (p<0.0001), baseline diabetes status (3 cat.) (p=0.3564), sex (p=0.0959), baseline LVEF (3 cat.) (p=0.3801), baseline BMI (2 cat.) (p=0.0220) and Treatment by baseline BMI (2 cat.) interaction (p=0.1689).
***Wald confidence intervals.

Data taken from study 1245.121 only.
LOCF: For a missing value at week 52 the last available post-baseline value before week 52 is imputed.

Table R.1.2.1.8: 4 Responder analysis (displaying risk ratio) in EQ-VAS change from baseline at week 52 of > -7 points (stability) by baseline BMI [kg/m2] - RS (LOCF-AD) - 1245.121

Subgroup Description	Placebo	Empa 10mg
Baseline BMI [kg/m²] (2 cat.): <30		
Number of patients in analysis set	1300	1263
Number of analysed patients, N (%)	1197 (100.0)	1179 (100.0)
Number of patients with endpoint, N (%)	906 (75.7)	920 (78.0)
95% confidence interval*	(73.2, 78.0)	(75.6, 80.3)
Comparison vs Placebo**		
Risk ratio (SE)		1.034 (0.022)
95% confidence interval***		(0.991, 1.078)
p-value		0.1263
Baseline BMI [kg/m²] (2 cat.): >=30		
Number of patients in analysis set	567	600
Number of analysed patients, N (%)	513 (100.0)	554 (100.0)
Number of patients with endpoint, N (%)	390 (76.0)	418 (75.5)
95% confidence interval*	(72.1, 79.5)	(71.7, 78.9)
Comparison vs Placebo**		
Risk ratio (SE)		0.980 (0.032)
95% confidence interval***		(0.919, 1.046)
p-value		0.5505

* Wilson confidence intervals.
** Log-linked Poisson model with robust estimate of variance includes terms for baseline EQ-VAS score (p<0.0001), age (p=0.0131), baseline eGFR (CKD-EPI) (p=0.3753), Treatment (p=0.7366), region (5 cat.) (p<0.0001), baseline diabetes status (3 cat.) (p=0.3062), sex (p=0.0514), baseline LVEF (3 cat.) (p=0.4999), baseline BMI (2 cat.) (p=0.0625) and Treatment by baseline BMI (2 cat.) interaction (p=0.1812).
***Wald confidence intervals.

Data taken from study 1245.121 only.
LOCF: For a missing value at week 52 the last available post-baseline value before week 52 is imputed.

Table R.1.2.1.8: 5 Responder analysis (displaying odds ratio) in EQ-VAS change from baseline at week 52 of >= 7 points (improvement) by baseline BMI [kg/m2] - RS (LOCF-AD) - 1245.121

Subgroup Description	Placebo	Empa 10mg
Baseline BMI [kg/m²] (2 cat.): <30		
Number of patients in analysis set	1300	1263
Number of analysed patients, N (%)	1197 (100.0)	1179 (100.0)
Number of patients with endpoint, N (%)	458 (38.3)	512 (43.4)
95% confidence interval*	(35.6, 41.0)	(40.6, 46.3)
Comparison vs Placebo**		
Odds ratio (SE)		1.369 (0.132)
95% confidence interval***		(1.132, 1.654)
p-value		0.0012
Baseline BMI [kg/m²] (2 cat.): >=30		
Number of patients in analysis set	567	600
Number of analysed patients, N (%)	513 (100.0)	554 (100.0)
Number of patients with endpoint, N (%)	199 (38.8)	238 (43.0)
95% confidence interval*	(34.7, 43.1)	(38.9, 47.1)
Comparison vs Placebo**		
Odds ratio (SE)		1.153 (0.166)
95% confidence interval***		(0.869, 1.530)
p-value		0.3224

* Wilson confidence intervals.
** Logistic regression includes terms for baseline EQ-VAS score (p<0.0001), age (p=0.0993), baseline eGFR (CKD-EPI) (p=0.0464), Treatment (p=0.0085), region (5 cat.) (p<0.0001), baseline diabetes status (3 cat.) (p=0.7918), sex (p=0.5398), baseline LVEF (3 cat.) (p=0.7516), baseline BMI (2 cat.) (p=0.0265) and Treatment by baseline BMI (2 cat.) interaction (p=0.3239).
***Wald confidence intervals.

Data taken from study 1245.121 only.
LOCF: For a missing value at week 52 the last available post-baseline value before week 52 is imputed.

Table R.1.2.1.8: 6 Responder analysis (displaying risk ratio) in EQ-VAS change from baseline at week 52 of >= 7 points (improvement) by baseline BMI [kg/m2] - RS (LOCF-AD) - 1245.121

Subgroup Description	Placebo	Empa 10mg
Baseline BMI [kg/m²] (2 cat.): <30		
Number of patients in analysis set	1300	1263
Number of analysed patients, N (%)	1197 (100.0)	1179 (100.0)
Number of patients with endpoint, N (%)	458 (38.3)	512 (43.4)
95% confidence interval*	(35.6, 41.0)	(40.6, 46.3)
Comparison vs Placebo**		
Risk ratio (SE)		1.142 (0.051)
95% confidence interval***		(1.046, 1.248)
p-value		0.0032
Baseline BMI [kg/m²] (2 cat.): >=30		
Number of patients in analysis set	567	600
Number of analysed patients, N (%)	513 (100.0)	554 (100.0)
Number of patients with endpoint, N (%)	199 (38.8)	238 (43.0)
95% confidence interval*	(34.7, 43.1)	(38.9, 47.1)
Comparison vs Placebo**		
Risk ratio (SE)		1.050 (0.071)
95% confidence interval***		(0.920, 1.198)
p-value		0.4684

* Wilson confidence intervals.
** Log-linked Poisson model with robust estimate of variance includes terms for baseline EQ-VAS score (p<0.0001), age (p=0.1051), baseline eGFR (CKD-EPI) (p=0.0624), Treatment (p=0.0249), region (5 cat.) (p<0.0001), baseline diabetes status (3 cat.) (p=0.8053), sex (p=0.2941), baseline LVEF (3 cat.) (p=0.7753), baseline BMI (2 cat.) (p=0.1205) and Treatment by baseline BMI (2 cat.) interaction (p=0.2982).
***Wald confidence intervals.

Data taken from study 1245.121 only.
LOCF: For a missing value at week 52 the last available post-baseline value before week 52 is imputed.

R.1.2.1.9 Subgroup analysis by eGFR at baseline (<60, >=60)

Table R.1.2.1.9: 1 Responder analysis (displaying odds ratio) in EQ-VAS change from baseline at week 52 of <= -7 points (deterioration) by baseline eGFR (2 cat.) - RS (LOCF-AD) - 1245.121

Subgroup Description	Placebo	Empa 10mg
Baseline eGFR (CKD-EPI) [mL/min/1.73m²] (2 cat.): >=60		
Number of patients in analysis set	960	969
Number of analysed patients, N (%)	875 (100.0)	900 (100.0)
Number of patients with endpoint, N (%)	192 (21.9)	191 (21.2)
95% confidence interval*	(19.3, 24.8)	(18.7, 24.0)
Comparison vs Placebo**		
Odds ratio (SE)		0.920 (0.112)
95% confidence interval***		(0.724, 1.169)
p-value		0.4948
Baseline eGFR (CKD-EPI) [mL/min/1.73m²] (2 cat.): <60		
Number of patients in analysis set	906	893
Number of analysed patients, N (%)	835 (100.0)	833 (100.0)
Number of patients with endpoint, N (%)	222 (26.6)	204 (24.5)
95% confidence interval*	(23.7, 29.7)	(21.7, 27.5)
Comparison vs Placebo**		
Odds ratio (SE)		0.909 (0.108)
95% confidence interval***		(0.720, 1.148)
p-value		0.4228

* Wilson confidence intervals.
** Logistic regression includes terms for baseline EQ-VAS score (p<0.0001), age (p=0.0097), Treatment (p=0.2944), region (5 cat.) (p<0.0001), baseline diabetes status (3 cat.) (p=0.3773), sex (p=0.0782), baseline LVEF (3 cat.) (p=0.4071), baseline eGFR (CKD-EPI) (2 cat.) (p=0.1578) and Treatment by baseline eGFR (CKD-EPI) (2 cat.) interaction (p=0.9437).
***Wald confidence intervals.
2 patients were excluded as the subgroup variable was missing.

Data taken from study 1245.121 only.
LOCF: For a missing value at week 52 the last available post-baseline value before week 52 is imputed.

Table R.1.2.1.9: 2 Responder analysis (displaying risk ratio) in EQ-VAS change from baseline at week 52 of <= -7 points (deterioration) by baseline eGFR (2 cat.) - RS (LOCF-AD) - 1245.121

Subgroup Description	Placebo	Empa 10mg
Baseline eGFR (CKD-EPI) [mL/min/1.73m²] (2 cat.): >=60		
Number of patients in analysis set	960	969
Number of analysed patients, N (%)	875 (100.0)	900 (100.0)
Number of patients with endpoint, N (%)	192 (21.9)	191 (21.2)
95% confidence interval*	(19.3, 24.8)	(18.7, 24.0)
Comparison vs Placebo**		
Risk ratio (SE)		0.940 (0.081)
95% confidence interval***		(0.793, 1.114)
p-value		0.4737
Baseline eGFR (CKD-EPI) [mL/min/1.73m²] (2 cat.): <60		
Number of patients in analysis set	906	893
Number of analysed patients, N (%)	835 (100.0)	833 (100.0)
Number of patients with endpoint, N (%)	222 (26.6)	204 (24.5)
95% confidence interval*	(23.7, 29.7)	(21.7, 27.5)
Comparison vs Placebo**		
Risk ratio (SE)		0.938 (0.074)
95% confidence interval***		(0.803, 1.096)
p-value		0.4197

* Wilson confidence intervals.
** Log-linked Poisson model with robust estimate of variance includes terms for baseline EQ-VAS score (p<0.0001), age (p=0.0081), Treatment (p=0.2821), region (5 cat.) (p<0.0001), baseline diabetes status (3 cat.) (p=0.3903), sex (p=0.0913), baseline LVEF (3 cat.) (p=0.4320), baseline eGFR (CKD-EPI) (2 cat.) (p=0.1581) and Treatment by baseline eGFR (CKD-EPI) (2 cat.) interaction (p=0.9871).
***Wald confidence intervals.
2 patients were excluded as the subgroup variable was missing.

Data taken from study 1245.121 only.
LOCF: For a missing value at week 52 the last available post-baseline value before week 52 is imputed.

Table R.1.2.1.9: 3 Responder analysis (displaying odds ratio) in EQ-VAS change from baseline at week 52 of > -7 points (stability) by baseline eGFR (2 cat.) - RS (LOCF-AD) - 1245.121

Subgroup Description	Placebo	Empa 10mg
Baseline eGFR (CKD-EPI) [mL/min/1.73m²] (2 cat.): >=60		
Number of patients in analysis set	960	969
Number of analysed patients, N (%)	875 (100.0)	900 (100.0)
Number of patients with endpoint, N (%)	683 (78.1)	709 (78.8)
95% confidence interval*	(75.2, 80.7)	(76.0, 81.3)
Comparison vs Placebo**		
Odds ratio (SE)		1.087 (0.133)
95% confidence interval***		(0.856, 1.381)
p-value		0.4948
Baseline eGFR (CKD-EPI) [mL/min/1.73m²] (2 cat.): <60		
Number of patients in analysis set	906	893
Number of analysed patients, N (%)	835 (100.0)	833 (100.0)
Number of patients with endpoint, N (%)	613 (73.4)	629 (75.5)
95% confidence interval*	(70.3, 76.3)	(72.5, 78.3)
Comparison vs Placebo**		
Odds ratio (SE)		1.100 (0.131)
95% confidence interval***		(0.871, 1.389)
p-value		0.4228

* Wilson confidence intervals.
** Logistic regression includes terms for baseline EQ-VAS score (p<0.0001), age (p=0.0097), Treatment (p=0.2944), region (5 cat.) (p<0.0001), baseline diabetes status (3 cat.) (p=0.3773), sex (p=0.0782), baseline LVEF (3 cat.) (p=0.4071), baseline eGFR (CKD-EPI) (2 cat.) (p=0.1578) and Treatment by baseline eGFR (CKD-EPI) (2 cat.) interaction (p=0.9437).
***Wald confidence intervals.
2 patients were excluded as the subgroup variable was missing.

Data taken from study 1245.121 only.
LOCF: For a missing value at week 52 the last available post-baseline value before week 52 is imputed.

Table R.1.2.1.9: 4 Responder analysis (displaying risk ratio) in EQ-VAS change from baseline at week 52 of > -7 points (stability) by baseline eGFR (2 cat.) - RS (LOCF-AD) - 1245.121

Subgroup Description	Placebo	Empa 10mg
Baseline eGFR (CKD-EPI) [mL/min/1.73m²] (2 cat.): >=60		
Number of patients in analysis set	960	969
Number of analysed patients, N (%)	875 (100.0)	900 (100.0)
Number of patients with endpoint, N (%)	683 (78.1)	709 (78.8)
95% confidence interval*	(75.2, 80.7)	(76.0, 81.3)
Comparison vs Placebo**		
Risk ratio (SE)		1.008 (0.024)
95% confidence interval***		(0.962, 1.057)
p-value		0.7346
Baseline eGFR (CKD-EPI) [mL/min/1.73m²] (2 cat.): <60		
Number of patients in analysis set	906	893
Number of analysed patients, N (%)	835 (100.0)	833 (100.0)
Number of patients with endpoint, N (%)	613 (73.4)	629 (75.5)
95% confidence interval*	(70.3, 76.3)	(72.5, 78.3)
Comparison vs Placebo**		
Risk ratio (SE)		1.024 (0.028)
95% confidence interval***		(0.971, 1.080)
p-value		0.3861

* Wilson confidence intervals.
** Log-linked Poisson model with robust estimate of variance includes terms for baseline EQ-VAS score (p<0.0001), age (p=0.0172), Treatment (p=0.3810), region (5 cat.) (p<0.0001), baseline diabetes status (3 cat.) (p=0.3006), sex (p=0.0448), baseline LVEF (3 cat.) (p=0.5107), baseline eGFR (CKD-EPI) (2 cat.) (p=0.1458) and Treatment by baseline eGFR (CKD-EPI) (2 cat.) interaction (p=0.6686).
***Wald confidence intervals.
2 patients were excluded as the subgroup variable was missing.

Data taken from study 1245.121 only.
LOCF: For a missing value at week 52 the last available post-baseline value before week 52 is imputed.

Table R.1.2.1.9: 5 Responder analysis (displaying odds ratio) in EQ-VAS change from baseline at week 52 of >= 7 points (improvement) by baseline eGFR (2 cat.) - RS (LOCF-AD) - 1245.121

Subgroup Description	Placebo	Empa 10mg
Baseline eGFR (CKD-EPI) [mL/min/1.73m²] (2 cat.): >=60		
Number of patients in analysis set	960	969
Number of analysed patients, N (%)	875 (100.0)	900 (100.0)
Number of patients with endpoint, N (%)	365 (41.7)	416 (46.2)
95% confidence interval*	(38.5, 45.0)	(43.0, 49.5)
Comparison vs Placebo**		
Odds ratio (SE)		1.270 (0.141)
95% confidence interval***		(1.022, 1.577)
p-value		0.0309
Baseline eGFR (CKD-EPI) [mL/min/1.73m²] (2 cat.): <60		
Number of patients in analysis set	906	893
Number of analysed patients, N (%)	835 (100.0)	833 (100.0)
Number of patients with endpoint, N (%)	292 (35.0)	334 (40.1)
95% confidence interval*	(31.8, 38.3)	(36.8, 43.5)
Comparison vs Placebo**		
Odds ratio (SE)		1.313 (0.153)
95% confidence interval***		(1.045, 1.650)
p-value		0.0192

* Wilson confidence intervals.
** Logistic regression includes terms for baseline EQ-VAS score (p<0.0001), age (p=0.1253), Treatment (p=0.0015), region (5 cat.) (p<0.0001), baseline diabetes status (3 cat.) (p=0.9162), sex (p=0.5008), baseline LVEF (3 cat.) (p=0.7251), baseline eGFR (CKD-EPI) (2 cat.) (p=0.0058) and Treatment by baseline eGFR (CKD-EPI) (2 cat.) interaction (p=0.8334).
***Wald confidence intervals.
2 patients were excluded as the subgroup variable was missing.

Data taken from study 1245.121 only.
LOCF: For a missing value at week 52 the last available post-baseline value before week 52 is imputed.

Table R.1.2.1.9: 6 Responder analysis (displaying risk ratio) in EQ-VAS change from baseline at week 52 of >= 7 points (improvement) by baseline eGFR (2 cat.) - RS (LOCF-AD) - 1245.121

Subgroup Description	Placebo	Empa 10mg
Baseline eGFR (CKD-EPI) [mL/min/1.73m²] (2 cat.): >=60		
Number of patients in analysis set	960	969
Number of analysed patients, N (%)	875 (100.0)	900 (100.0)
Number of patients with endpoint, N (%)	365 (41.7)	416 (46.2)
95% confidence interval*	(38.5, 45.0)	(43.0, 49.5)
Comparison vs Placebo**		
Risk ratio (SE)		1.083 (0.053)
95% confidence interval***		(0.983, 1.193)
p-value		0.1054
Baseline eGFR (CKD-EPI) [mL/min/1.73m²] (2 cat.): <60		
Number of patients in analysis set	906	893
Number of analysed patients, N (%)	835 (100.0)	833 (100.0)
Number of patients with endpoint, N (%)	292 (35.0)	334 (40.1)
95% confidence interval*	(31.8, 38.3)	(36.8, 43.5)
Comparison vs Placebo**		
Risk ratio (SE)		1.142 (0.065)
95% confidence interval***		(1.020, 1.277)
p-value		0.0210

* Wilson confidence intervals.
** Log-linked Poisson model with robust estimate of variance includes terms for baseline EQ-VAS score (p<0.0001), age (p=0.1171), Treatment (p=0.0050), region (5 cat.) (p<0.0001), baseline diabetes status (3 cat.) (p=0.8878), sex (p=0.2910), baseline LVEF (3 cat.) (p=0.7698), baseline eGFR (CKD-EPI) (2 cat.) (p=0.0084) and Treatment by baseline eGFR (CKD-EPI) (2 cat.) interaction (p=0.4869).
***Wald confidence intervals.
2 patients were excluded as the subgroup variable was missing.

Data taken from study 1245.121 only.
LOCF: For a missing value at week 52 the last available post-baseline value before week 52 is imputed.

R.1.2.1.10

Table R.1.2.1.10: 1 Responder analysis (displaying odds ratio) in EQ-VAS change from baseline at week 52 of <= -7 points (deterioration) by history of HHF - RS (LOCF-AD) - 1245.121

Subgroup Description	Placebo	Empa 10mg
History of HHF (in the last 12 months): No		
Number of patients in analysis set	1293	1286
Number of analysed patients, N (%)	1193 (100.0)	1209 (100.0)
Number of patients with endpoint, N (%)	289 (24.2)	280 (23.2)
95% confidence interval*	(21.9, 26.7)	(20.9, 25.6)
Comparison vs Placebo**		
Odds ratio (SE)		0.951 (0.097)
95% confidence interval***		(0.779, 1.160)
p-value		0.6184
History of HHF (in the last 12 months): Yes		
Number of patients in analysis set	574	577
Number of analysed patients, N (%)	517 (100.0)	524 (100.0)
Number of patients with endpoint, N (%)	125 (24.2)	115 (21.9)
95% confidence interval*	(20.7, 28.1)	(18.6, 25.7)
Comparison vs Placebo**		
Odds ratio (SE)		0.830 (0.129)
95% confidence interval***		(0.612, 1.126)
p-value		0.2308

* Wilson confidence intervals.
** Logistic regression includes terms for baseline EQ-VAS score (p<0.0001), age (p=0.0149), baseline eGFR (CKD-EPI) (p=0.3090), Treatment (p=0.2021), region (5 cat.) (p<0.0001), baseline diabetes status (3 cat.) (p=0.3530), sex (p=0.0722), baseline LVEF (3 cat.) (p=0.3982), history of HHF (in the last 12 months) (p=0.9723) and Treatment by history of HHF (in the last 12 months) interaction (p=0.4655).
***Wald confidence intervals.

Data taken from study 1245.121 only.
LOCF: For a missing value at week 52 the last available post-baseline value before week 52 is imputed.

Table R.1.2.1.10: 2 Responder analysis (displaying risk ratio) in EQ-VAS change from baseline at week 52 of <= -7 points (deterioration) by history of HHF - RS (LOCF-AD) - 1245.121

Subgroup Description	Placebo	Empa 10mg
History of HHF (in the last 12 months): No		
Number of patients in analysis set	1293	1286
Number of analysed patients, N (%)	1193 (100.0)	1209 (100.0)
Number of patients with endpoint, N (%)	289 (24.2)	280 (23.2)
95% confidence interval*	(21.9, 26.7)	(20.9, 25.6)
Comparison vs Placebo**		
Risk ratio (SE)		0.966 (0.067)
95% confidence interval***		(0.844, 1.106)
p-value		0.6203
History of HHF (in the last 12 months): Yes		
Number of patients in analysis set	574	577
Number of analysed patients, N (%)	517 (100.0)	524 (100.0)
Number of patients with endpoint, N (%)	125 (24.2)	115 (21.9)
95% confidence interval*	(20.7, 28.1)	(18.6, 25.7)
Comparison vs Placebo**		
Risk ratio (SE)		0.871 (0.096)
95% confidence interval***		(0.703, 1.080)
p-value		0.2084

* Wilson confidence intervals.
** Log-linked Poisson model with robust estimate of variance includes terms for baseline EQ-VAS score (p<0.0001), age (p=0.0121), baseline eGFR (CKD-EPI) (p=0.3176), Treatment (p=0.1836), region (5 cat.) (p<0.0001), baseline diabetes status (3 cat.) (p=0.3689), sex (p=0.0844), baseline LVEF (3 cat.) (p=0.4208), history of HHF (in the last 12 months) (p=0.9861) and Treatment by history of HHF (in the last 12 months) interaction (p=0.4235).
***Wald confidence intervals.

Data taken from study 1245.121 only.
LOCF: For a missing value at week 52 the last available post-baseline value before week 52 is imputed.

Table R.1.2.1.10: 3 Responder analysis (displaying odds ratio) in EQ-VAS change from baseline at week 52 of > -7 points (stability) by history of HHF - RS (LOCF-AD) - 1245.121

Subgroup Description	Placebo	Empa 10mg
History of HHF (in the last 12 months): No		
Number of patients in analysis set	1293	1286
Number of analysed patients, N (%)	1193 (100.0)	1209 (100.0)
Number of patients with endpoint, N (%)	904 (75.8)	929 (76.8)
95% confidence interval*	(73.3, 78.1)	(74.4, 79.1)
Comparison vs Placebo**		
Odds ratio (SE)		1.052 (0.107)
95% confidence interval***		(0.862, 1.284)
p-value		0.6184
History of HHF (in the last 12 months): Yes		
Number of patients in analysis set	574	577
Number of analysed patients, N (%)	517 (100.0)	524 (100.0)
Number of patients with endpoint, N (%)	392 (75.8)	409 (78.1)
95% confidence interval*	(71.9, 79.3)	(74.3, 81.4)
Comparison vs Placebo**		
Odds ratio (SE)		1.205 (0.187)
95% confidence interval***		(0.888, 1.634)
p-value		0.2308

* Wilson confidence intervals.
** Logistic regression includes terms for baseline EQ-VAS score (p<0.0001), age (p=0.0149), baseline eGFR (CKD-EPI) (p=0.3090), Treatment (p=0.2021), region (5 cat.) (p<0.0001), baseline diabetes status (3 cat.) (p=0.3530), sex (p=0.0722), baseline LVEF (3 cat.) (p=0.3982), history of HHF (in the last 12 months) (p=0.9723) and Treatment by history of HHF (in the last 12 months) interaction (p=0.4655).
***Wald confidence intervals.

Data taken from study 1245.121 only.
LOCF: For a missing value at week 52 the last available post-baseline value before week 52 is imputed.

Table R.1.2.1.10: 4 Responder analysis (displaying risk ratio) in EQ-VAS change from baseline at week 52 of > -7 points (stability) by history of HHF - RS (LOCF-AD) - 1245.121

Subgroup Description	Placebo	Empa 10mg
History of HHF (in the last 12 months): No		
Number of patients in analysis set	1293	1286
Number of analysed patients, N (%)	1193 (100.0)	1209 (100.0)
Number of patients with endpoint, N (%)	904 (75.8)	929 (76.8)
95% confidence interval*	(73.3, 78.1)	(74.4, 79.1)
Comparison vs Placebo**		
Risk ratio (SE)		1.010 (0.022)
95% confidence interval***		(0.968, 1.054)
p-value		0.6394
History of HHF (in the last 12 months): Yes		
Number of patients in analysis set	574	577
Number of analysed patients, N (%)	517 (100.0)	524 (100.0)
Number of patients with endpoint, N (%)	392 (75.8)	409 (78.1)
95% confidence interval*	(71.9, 79.3)	(74.3, 81.4)
Comparison vs Placebo**		
Risk ratio (SE)		1.029 (0.034)
95% confidence interval***		(0.965, 1.098)
p-value		0.3834

* Wilson confidence intervals.
** Log-linked Poisson model with robust estimate of variance includes terms for baseline EQ-VAS score (p<0.0001), age (p=0.0258), baseline eGFR (CKD-EPI) (p=0.3388), Treatment (p=0.3243), region (5 cat.) (p<0.0001), baseline diabetes status (3 cat.) (p=0.2750), sex (p=0.0401), baseline LVEF (3 cat.) (p=0.5125), history of HHF (in the last 12 months) (p=0.8058) and Treatment by history of HHF (in the last 12 months) interaction (p=0.6375).
***Wald confidence intervals.

Data taken from study 1245.121 only.
LOCF: For a missing value at week 52 the last available post-baseline value before week 52 is imputed.

Table R.1.2.1.10: 5 Responder analysis (displaying odds ratio) in EQ-VAS change from baseline at week 52 of >= 7 points (improvement) by history of HHF - RS (LOCF-AD) - 1245.121

Subgroup Description	Placebo	Empa 10mg
History of HHF (in the last 12 months): No		
Number of patients in analysis set	1293	1286
Number of analysed patients, N (%)	1193 (100.0)	1209 (100.0)
Number of patients with endpoint, N (%)	465 (39.0)	519 (42.9)
95% confidence interval*	(36.2, 41.8)	(40.2, 45.7)
Comparison vs Placebo**		
Odds ratio (SE)		1.235 (0.119)
95% confidence interval***		(1.023, 1.491)
p-value		0.0282
History of HHF (in the last 12 months): Yes		
Number of patients in analysis set	574	577
Number of analysed patients, N (%)	517 (100.0)	524 (100.0)
Number of patients with endpoint, N (%)	192 (37.1)	231 (44.1)
95% confidence interval*	(33.1, 41.4)	(39.9, 48.4)
Comparison vs Placebo**		
Odds ratio (SE)		1.427 (0.207)
95% confidence interval***		(1.074, 1.895)
p-value		0.0141

* Wilson confidence intervals.
** Logistic regression includes terms for baseline EQ-VAS score (p<0.0001), age (p=0.1713), baseline eGFR (CKD-EPI) (p=0.0396), Treatment (p=0.0011), region (5 cat.) (p<0.0001), baseline diabetes status (3 cat.) (p=0.9182), sex (p=0.4596), baseline LVEF (3 cat.) (p=0.7217), history of HHF (in the last 12 months) (p=0.8980) and Treatment by history of HHF (in the last 12 months) interaction (p=0.4067).
***Wald confidence intervals.

Data taken from study 1245.121 only.
LOCF: For a missing value at week 52 the last available post-baseline value before week 52 is imputed.

Table R.1.2.1.10: 6 Responder analysis (displaying risk ratio) in EQ-VAS change from baseline at week 52 of >= 7 points (improvement) by history of HHF - RS (LOCF-AD) - 1245.121

Subgroup Description	Placebo	Empa 10mg
History of HHF (in the last 12 months): No		
Number of patients in analysis set	1293	1286
Number of analysed patients, N (%)	1193 (100.0)	1209 (100.0)
Number of patients with endpoint, N (%)	465 (39.0)	519 (42.9)
95% confidence interval*	(36.2, 41.8)	(40.2, 45.7)
Comparison vs Placebo**		
Risk ratio (SE)		1.092 (0.049)
95% confidence interval***		(1.001, 1.192)
p-value		0.0475
History of HHF (in the last 12 months): Yes		
Number of patients in analysis set	574	577
Number of analysed patients, N (%)	517 (100.0)	524 (100.0)
Number of patients with endpoint, N (%)	192 (37.1)	231 (44.1)
95% confidence interval*	(33.1, 41.4)	(39.9, 48.4)
Comparison vs Placebo**		
Risk ratio (SE)		1.152 (0.080)
95% confidence interval***		(1.006, 1.319)
p-value		0.0406

* Wilson confidence intervals.
** Log-linked Poisson model with robust estimate of variance includes terms for baseline EQ-VAS score (p<0.0001), age (p=0.1550), baseline eGFR (CKD-EPI) (p=0.0539), Treatment (p=0.0052), region (5 cat.) (p<0.0001), baseline diabetes status (3 cat.) (p=0.8664), sex (p=0.2618), baseline LVEF (3 cat.) (p=0.7630), history of HHF (in the last 12 months) (p=0.9818) and Treatment by history of HHF (in the last 12 months) interaction (p=0.5178).
***Wald confidence intervals.

Data taken from study 1245.121 only.
LOCF: For a missing value at week 52 the last available post-baseline value before week 52 is imputed.

R.1.2.1.11

R.1.2.1.11 Subgroup analysis by cause of heart failure

Table R.1.2.1.11: 1 Responder analysis (displaying odds ratio) in EQ-VAS change from baseline at week 52 of <= -7 points (deterioration) by cause of heart failure - RS (LOCF-AD) - 1245.121

Subgroup Description	Placebo	Empa 10mg
Cause of heart failure: Ischemic		
Number of patients in analysis set	946	983
Number of analysed patients, N (%)	874 (100.0)	918 (100.0)
Number of patients with endpoint, N (%)	211 (24.1)	221 (24.1)
95% confidence interval*	(21.4, 27.1)	(21.4, 26.9)
Comparison vs Placebo**		
Odds ratio (SE)		1.002 (0.117)
95% confidence interval***		(0.797, 1.261)
p-value		0.9844
Cause of heart failure: Non-ischemic		
Number of patients in analysis set	921	880
Number of analysed patients, N (%)	836 (100.0)	815 (100.0)
Number of patients with endpoint, N (%)	203 (24.3)	174 (21.3)
95% confidence interval*	(21.5, 27.3)	(18.7, 24.3)
Comparison vs Placebo**		
Odds ratio (SE)		0.820 (0.102)
95% confidence interval***		(0.642, 1.046)
p-value		0.1105

* Wilson confidence intervals.
** Logistic regression includes terms for baseline EQ-VAS score (p<0.0001), age (p=0.0174), baseline eGFR (CKD-EPI) (p=0.3181), Treatment (p=0.2505), region (5 cat.) (p<0.0001), baseline diabetes status (3 cat.) (p=0.3620), sex (p=0.0690), baseline LVEF (3 cat.) (p=0.3947), cause of heart failure (p=0.5236) and Treatment by cause of heart failure interaction (p=0.2401).
***Wald confidence intervals.

Data taken from study 1245.121 only.
LOCF: For a missing value at week 52 the last available post-baseline value before week 52 is imputed.

Table R.1.2.1.11: 2 Responder analysis (displaying risk ratio) in EQ-VAS change from baseline at week 52 of <= -7 points (deterioration) by cause of heart failure - RS (LOCF-AD) - 1245.121

Subgroup Description	Placebo	Empa 10mg
Cause of heart failure: Ischemic		
Number of patients in analysis set	946	983
Number of analysed patients, N (%)	874 (100.0)	918 (100.0)
Number of patients with endpoint, N (%)	211 (24.1)	221 (24.1)
95% confidence interval*	(21.4, 27.1)	(21.4, 26.9)
Comparison vs Placebo**		
Risk ratio (SE)		1.000 (0.079)
95% confidence interval***		(0.856, 1.168)
p-value		0.9987
Cause of heart failure: Non-ischemic		
Number of patients in analysis set	921	880
Number of analysed patients, N (%)	836 (100.0)	815 (100.0)
Number of patients with endpoint, N (%)	203 (24.3)	174 (21.3)
95% confidence interval*	(21.5, 27.3)	(18.7, 24.3)
Comparison vs Placebo**		
Risk ratio (SE)		0.869 (0.075)
95% confidence interval***		(0.733, 1.029)
p-value		0.1041

* Wilson confidence intervals.
** Log-linked Poisson model with robust estimate of variance includes terms for baseline EQ-VAS score (p<0.0001), age (p=0.0145), baseline eGFR (CKD-EPI) (p=0.3200), Treatment (p=0.2313), region (5 cat.) (p<0.0001), baseline diabetes status (3 cat.) (p=0.3777), sex (p=0.0847), baseline LVEF (3 cat.) (p=0.4233), cause of heart failure (p=0.5315) and Treatment by cause of heart failure interaction (p=0.2309).
***Wald confidence intervals.

Data taken from study 1245.121 only.
LOCF: For a missing value at week 52 the last available post-baseline value before week 52 is imputed.

Table R.1.2.1.11: 3 Responder analysis (displaying odds ratio) in EQ-VAS change from baseline at week 52 of > -7 points (stability) by cause of heart failure - RS (LOCF-AD) - 1245.121

Subgroup Description	Placebo	Empa 10mg
Cause of heart failure: Ischemic		
Number of patients in analysis set	946	983
Number of analysed patients, N (%)	874 (100.0)	918 (100.0)
Number of patients with endpoint, N (%)	663 (75.9)	697 (75.9)
95% confidence interval*	(72.9, 78.6)	(73.1, 78.6)
Comparison vs Placebo**		
Odds ratio (SE)		0.998 (0.117)
95% confidence interval***		(0.793, 1.255)
p-value		0.9844
Cause of heart failure: Non-ischemic		
Number of patients in analysis set	921	880
Number of analysed patients, N (%)	836 (100.0)	815 (100.0)
Number of patients with endpoint, N (%)	633 (75.7)	641 (78.7)
95% confidence interval*	(72.7, 78.5)	(75.7, 81.3)
Comparison vs Placebo**		
Odds ratio (SE)		1.220 (0.152)
95% confidence interval***		(0.956, 1.556)
p-value		0.1105

* Wilson confidence intervals.
** Logistic regression includes terms for baseline EQ-VAS score (p<0.0001), age (p=0.0174), baseline eGFR (CKD-EPI) (p=0.3181), Treatment (p=0.2505), region (5 cat.) (p<0.0001), baseline diabetes status (3 cat.) (p=0.3620), sex (p=0.0690), baseline LVEF (3 cat.) (p=0.3947), cause of heart failure (p=0.5236) and Treatment by cause of heart failure interaction (p=0.2401).
***Wald confidence intervals.

Data taken from study 1245.121 only.
LOCF: For a missing value at week 52 the last available post-baseline value before week 52 is imputed.

Table R.1.2.1.11: 4 Responder analysis (displaying risk ratio) in EQ-VAS change from baseline at week 52 of > -7 points (stability) by cause of heart failure - RS (LOCF-AD) - 1245.121

Subgroup Description	Placebo	Empa 10mg
Cause of heart failure: Ischemic		
Number of patients in analysis set	946	983
Number of analysed patients, N (%)	874 (100.0)	918 (100.0)
Number of patients with endpoint, N (%)	663 (75.9)	697 (75.9)
95% confidence interval*	(72.9, 78.6)	(73.1, 78.6)
Comparison vs Placebo**		
Risk ratio (SE)		0.997 (0.025)
95% confidence interval***		(0.949, 1.048)
p-value		0.9123
Cause of heart failure: Non-ischemic		
Number of patients in analysis set	921	880
Number of analysed patients, N (%)	836 (100.0)	815 (100.0)
Number of patients with endpoint, N (%)	633 (75.7)	641 (78.7)
95% confidence interval*	(72.7, 78.5)	(75.7, 81.3)
Comparison vs Placebo**		
Risk ratio (SE)		1.037 (0.027)
95% confidence interval***		(0.986, 1.090)
p-value		0.1614

* Wilson confidence intervals.
** Log-linked Poisson model with robust estimate of variance includes terms for baseline EQ-VAS score (p<0.0001), age (p=0.0307), baseline eGFR (CKD-EPI) (p=0.3544), Treatment (p=0.3594), region (5 cat.) (p<0.0001), baseline diabetes status (3 cat.) (p=0.2899), sex (p=0.0373), baseline LVEF (3 cat.) (p=0.5064), cause of heart failure (p=0.5529) and Treatment by cause of heart failure interaction (p=0.2832).
***Wald confidence intervals.

Data taken from study 1245.121 only.
LOCF: For a missing value at week 52 the last available post-baseline value before week 52 is imputed.

Table R.1.2.1.11: 5 Responder analysis (displaying odds ratio) in EQ-VAS change from baseline at week 52 of >= 7 points (improvement) by cause of heart failure - RS (LOCF-AD) - 1245.121

Subgroup Description	Placebo	Empa 10mg
Cause of heart failure: Ischemic		
Number of patients in analysis set	946	983
Number of analysed patients, N (%)	874 (100.0)	918 (100.0)
Number of patients with endpoint, N (%)	314 (35.9)	392 (42.7)
95% confidence interval*	(32.8, 39.2)	(39.5, 45.9)
Comparison vs Placebo**		
Odds ratio (SE)		1.430 (0.160)
95% confidence interval***		(1.148, 1.781)
p-value		0.0014
Cause of heart failure: Non-ischemic		
Number of patients in analysis set	921	880
Number of analysed patients, N (%)	836 (100.0)	815 (100.0)
Number of patients with endpoint, N (%)	343 (41.0)	358 (43.9)
95% confidence interval*	(37.7, 44.4)	(40.6, 47.4)
Comparison vs Placebo**		
Odds ratio (SE)		1.164 (0.134)
95% confidence interval***		(0.929, 1.458)
p-value		0.1867

* Wilson confidence intervals.
** Logistic regression includes terms for baseline EQ-VAS score (p<0.0001), age (p=0.2324), baseline eGFR (CKD-EPI) (p=0.0422), Treatment (p=0.0015), region (5 cat.) (p<0.0001), baseline diabetes status (3 cat.) (p=0.8442), sex (p=0.3519), baseline LVEF (3 cat.) (p=0.7547), cause of heart failure (p=0.1510) and Treatment by cause of heart failure interaction (p=0.1995).
***Wald confidence intervals.

Data taken from study 1245.121 only.
LOCF: For a missing value at week 52 the last available post-baseline value before week 52 is imputed.

Table R.1.2.1.11: 6 Responder analysis (displaying risk ratio) in EQ-VAS change from baseline at week 52 of >= 7 points (improvement) by cause of heart failure - RS (LOCF-AD) - 1245.121

Subgroup Description	Placebo	Empa 10mg
Cause of heart failure: Ischemic		
Number of patients in analysis set	946	983
Number of analysed patients, N (%)	874 (100.0)	918 (100.0)
Number of patients with endpoint, N (%)	314 (35.9)	392 (42.7)
95% confidence interval*	(32.8, 39.2)	(39.5, 45.9)
Comparison vs Placebo**		
Risk ratio (SE)		1.170 (0.064)
95% confidence interval***		(1.052, 1.302)
p-value		0.0038
Cause of heart failure: Non-ischemic		
Number of patients in analysis set	921	880
Number of analysed patients, N (%)	836 (100.0)	815 (100.0)
Number of patients with endpoint, N (%)	343 (41.0)	358 (43.9)
95% confidence interval*	(37.7, 44.4)	(40.6, 47.4)
Comparison vs Placebo**		
Risk ratio (SE)		1.054 (0.055)
95% confidence interval***		(0.953, 1.167)
p-value		0.3048

* Wilson confidence intervals.
** Log-linked Poisson model with robust estimate of variance includes terms for baseline EQ-VAS score (p<0.0001), age (p=0.2168), baseline eGFR (CKD-EPI) (p=0.0529), Treatment (p=0.0050), region (5 cat.) (p<0.0001), baseline diabetes status (3 cat.) (p=0.8085), sex (p=0.1884), baseline LVEF (3 cat.) (p=0.7403), cause of heart failure (p=0.1682) and Treatment by cause of heart failure interaction (p=0.1644).
***Wald confidence intervals.

Data taken from study 1245.121 only.
LOCF: For a missing value at week 52 the last available post-baseline value before week 52 is imputed.

R.1.2.1.12 Subgroup analysis by heart failure physiology (LVEF <= 30% and NTproBNP<median; LVEF <= 30% and NTproBNP>=median; LVEF > 30%)

Table R.1.2.1.12: 1 Responder analysis (displaying odds ratio) in EQ-VAS change from baseline at week 52 of <= -7 points (deterioration) by heart failure physiology - RS (LOCF-AD) - 1245.121

Subgroup Description	Placebo	Empa 10mg
Heart failure physiology: LVEF <= 30% and NTproBNP < median		
Number of patients in analysis set	723	698
Number of analysed patients, N (%)	679 (100.0)	655 (100.0)
Number of patients with endpoint, N (%)	154 (22.7)	144 (22.0)
95% confidence interval*	(19.7, 26.0)	(19.0, 25.3)
Comparison vs Placebo**		
Odds ratio (SE)		0.944 (0.131)
95% confidence interval***		(0.719, 1.238)
p-value		0.6753
Heart failure physiology: LVEF <= 30% and NTproBNP >= median		
Number of patients in analysis set	661	631
Number of analysed patients, N (%)	588 (100.0)	581 (100.0)
Number of patients with endpoint, N (%)	156 (26.5)	141 (24.3)
95% confidence interval*	(23.1, 30.2)	(21.0, 27.9)
Comparison vs Placebo**		
Odds ratio (SE)		0.835 (0.120)
95% confidence interval***		(0.630, 1.107)
p-value		0.2107

* Wilson confidence intervals.
** Logistic regression includes terms for baseline EQ-VAS score (p<0.0001), age (p=0.0154), baseline eGFR (CKD-EPI) (p=0.5757), Treatment (p=0.2891), region (5 cat.) (p<0.0001), baseline diabetes status (3 cat.) (p=0.3393), sex (p=0.0962), heart failure physiology (p=0.0099) and Treatment by heart failure physiology interaction (p=0.7626).
***Wald confidence intervals.
16 patients were excluded as the subgroup variable was missing.

Data taken from study 1245.121 only.
LOCF: For a missing value at week 52 the last available post-baseline value before week 52 is imputed.
NTproBNP median [pg/mL]: with a. fibrillation/flutter at baseline: 2265; without a. fibrillation/flutter at baseline: 1671.

Table R.1.2.1.12: 1 Responder analysis (displaying odds ratio) in EQ-VAS change from baseline at week 52 of <= -7 points (deterioration) by heart failure physiology - RS (LOCF-AD) - 1245.121

Subgroup Description	Placebo	Empa 10mg
Heart failure physiology: LVEF > 30%		
Number of patients in analysis set	475	526
Number of analysed patients, N (%)	438 (100.0)	493 (100.0)
Number of patients with endpoint, N (%)	103 (23.5)	109 (22.1)
95% confidence interval*	(19.8, 27.7)	(18.7, 26.0)
Comparison vs Placebo**		
Odds ratio (SE)		0.964 (0.159)
95% confidence interval***		(0.697, 1.333)
p-value		0.8238

* Wilson confidence intervals.
** Logistic regression includes terms for baseline EQ-VAS score (p<0.0001), age (p=0.0154), baseline eGFR (CKD-EPI) (p=0.5757), Treatment (p=0.2891), region (5 cat.) (p<0.0001), baseline diabetes status (3 cat.) (p=0.3393), sex (p=0.0962), heart failure physiology (p=0.0099) and Treatment by heart failure physiology interaction (p=0.7626).
***Wald confidence intervals.
16 patients were excluded as the subgroup variable was missing.

Data taken from study 1245.121 only.
LOCF: For a missing value at week 52 the last available post-baseline value before week 52 is imputed.
NTproBNP median [pg/mL]: with a. fibrillation/flutter at baseline: 2265; without a. fibrillation/flutter at baseline: 1671.

Table R.1.2.1.12: 2 Responder analysis (displaying risk ratio) in EQ-VAS change from baseline at week 52 of <= -7 points (deterioration) by heart failure physiology - RS (LOCF-AD) - 1245.121

Subgroup Description	Placebo	Empa 10mg
Heart failure physiology: LVEF <= 30% and NTproBNP < median		
Number of patients in analysis set	723	698
Number of analysed patients, N (%)	679 (100.0)	655 (100.0)
Number of patients with endpoint, N (%)	154 (22.7)	144 (22.0)
95% confidence interval*	(19.7, 26.0)	(19.0, 25.3)
Comparison vs Placebo**		
Risk ratio (SE)		0.961 (0.094)
95% confidence interval***		(0.793, 1.163)
p-value		0.6804
Heart failure physiology: LVEF <= 30% and NTproBNP >= median		
Number of patients in analysis set	661	631
Number of analysed patients, N (%)	588 (100.0)	581 (100.0)
Number of patients with endpoint, N (%)	156 (26.5)	141 (24.3)
95% confidence interval*	(23.1, 30.2)	(21.0, 27.9)
Comparison vs Placebo**		
Risk ratio (SE)		0.880 (0.083)
95% confidence interval***		(0.732, 1.059)
p-value		0.1758

* Wilson confidence intervals.
** Log-linked Poisson model with robust estimate of variance includes terms for baseline EQ-VAS score (p<0.0001), age (p=0.0126), baseline eGFR (CKD-EPI) (p=0.5884), Treatment (p=0.2774), region (5 cat.) (p<0.0001), baseline diabetes status (3 cat.) (p=0.3716), sex (p=0.1127), heart failure physiology (p=0.0106) and Treatment by heart failure physiology interaction (p=0.7378).
***Wald confidence intervals.
16 patients were excluded as the subgroup variable was missing.

Data taken from study 1245.121 only.
LOCF: For a missing value at week 52 the last available post-baseline value before week 52 is imputed.
NTproBNP median [pg/mL]: with a. fibrillation/flutter at baseline: 2265; without a. fibrillation/flutter at baseline: 1671.

Table R.1.2.1.12: 2 Responder analysis (displaying risk ratio) in EQ-VAS change from baseline at week 52 of <= -7 points (deterioration) by heart failure physiology - RS (LOCF-AD) - 1245.121

Subgroup Description	Placebo	Empa 10mg
Heart failure physiology: LVEF > 30%		
Number of patients in analysis set	475	526
Number of analysed patients, N (%)	438 (100.0)	493 (100.0)
Number of patients with endpoint, N (%)	103 (23.5)	109 (22.1)
95% confidence interval*	(19.8, 27.7)	(18.7, 26.0)
Comparison vs Placebo**		
Risk ratio (SE)		0.975 (0.112)
95% confidence interval***		(0.777, 1.222)
p-value		0.8244

* Wilson confidence intervals.
** Log-linked Poisson model with robust estimate of variance includes terms for baseline EQ-VAS score (p<0.0001), age (p=0.0126), baseline eGFR (CKD-EPI) (p=0.5884), Treatment (p=0.2774), region (5 cat.) (p<0.0001), baseline diabetes status (3 cat.) (p=0.3716), sex (p=0.1127), heart failure physiology (p=0.0106) and Treatment by heart failure physiology interaction (p=0.7378).
***Wald confidence intervals.
16 patients were excluded as the subgroup variable was missing.

Data taken from study 1245.121 only.
LOCF: For a missing value at week 52 the last available post-baseline value before week 52 is imputed.
NTproBNP median [pg/mL]: with a. fibrillation/flutter at baseline: 2265; without a. fibrillation/flutter at baseline: 1671.

Table R.1.2.1.12: 3 Responder analysis (displaying odds ratio) in EQ-VAS change from baseline at week 52 of > -7 points (stability) by heart failure physiology - RS (LOCF-AD) - 1245.121

Subgroup Description	Placebo	Empa 10mg
Heart failure physiology: LVEF <= 30% and NTproBNP < median		
Number of patients in analysis set	723	698
Number of analysed patients, N (%)	679 (100.0)	655 (100.0)
Number of patients with endpoint, N (%)	525 (77.3)	511 (78.0)
95% confidence interval*	(74.0, 80.3)	(74.7, 81.0)
Comparison vs Placebo**		
Odds ratio (SE)		1.060 (0.147)
95% confidence interval***		(0.808, 1.391)
p-value		0.6753
Heart failure physiology: LVEF <= 30% and NTproBNP >= median		
Number of patients in analysis set	661	631
Number of analysed patients, N (%)	588 (100.0)	581 (100.0)
Number of patients with endpoint, N (%)	432 (73.5)	440 (75.7)
95% confidence interval*	(69.8, 76.9)	(72.1, 79.0)
Comparison vs Placebo**		
Odds ratio (SE)		1.197 (0.172)
95% confidence interval***		(0.903, 1.587)
p-value		0.2107

* Wilson confidence intervals.
** Logistic regression includes terms for baseline EQ-VAS score (p<0.0001), age (p=0.0154), baseline eGFR (CKD-EPI) (p=0.5757), Treatment (p=0.2891), region (5 cat.) (p<0.0001), baseline diabetes status (3 cat.) (p=0.3393), sex (p=0.0962), heart failure physiology (p=0.0099) and Treatment by heart failure physiology interaction (p=0.7626).
***Wald confidence intervals.
16 patients were excluded as the subgroup variable was missing.

Data taken from study 1245.121 only.
LOCF: For a missing value at week 52 the last available post-baseline value before week 52 is imputed.
NTproBNP median [pg/mL]: with a. fibrillation/flutter at baseline: 2265; without a. fibrillation/flutter at baseline: 1671.

Table R.1.2.1.12: 3 Responder analysis (displaying odds ratio) in EQ-VAS change from baseline at week 52 of > -7 points (stability) by heart failure physiology - RS (LOCF-AD) - 1245.121

Subgroup Description	Placebo	Empa 10mg
Heart failure physiology: LVEF > 30%		
Number of patients in analysis set	475	526
Number of analysed patients, N (%)	438 (100.0)	493 (100.0)
Number of patients with endpoint, N (%)	335 (76.5)	384 (77.9)
95% confidence interval*	(72.3, 80.2)	(74.0, 81.3)
Comparison vs Placebo**		
Odds ratio (SE)		1.038 (0.172)
95% confidence interval***		(0.750, 1.435)
p-value		0.8238

* Wilson confidence intervals.
** Logistic regression includes terms for baseline EQ-VAS score (p<0.0001), age (p=0.0154), baseline eGFR (CKD-EPI) (p=0.5757), Treatment (p=0.2891), region (5 cat.) (p<0.0001), baseline diabetes status (3 cat.) (p=0.3393), sex (p=0.0962), heart failure physiology (p=0.0099) and Treatment by heart failure physiology interaction (p=0.7626).
***Wald confidence intervals.
16 patients were excluded as the subgroup variable was missing.

Data taken from study 1245.121 only.
LOCF: For a missing value at week 52 the last available post-baseline value before week 52 is imputed.
NTproBNP median [pg/mL]: with a. fibrillation/flutter at baseline: 2265; without a. fibrillation/flutter at baseline: 1671.

Table R.1.2.1.12: 4 Responder analysis (displaying risk ratio) in EQ-VAS change from baseline at week 52 of > -7 points (stability) by heart failure physiology - RS (LOCF-AD) - 1245.121

Subgroup Description	Placebo	Empa 10mg
Heart failure physiology: LVEF <= 30% and NTproBNP < median		
Number of patients in analysis set	723	698
Number of analysed patients, N (%)	679 (100.0)	655 (100.0)
Number of patients with endpoint, N (%)	525 (77.3)	511 (78.0)
95% confidence interval*	(74.0, 80.3)	(74.7, 81.0)
Comparison vs Placebo**		
Risk ratio (SE)		1.014 (0.029)
95% confidence interval***		(0.959, 1.071)
p-value		0.6326
Heart failure physiology: LVEF <= 30% and NTproBNP >= median		
Number of patients in analysis set	661	631
Number of analysed patients, N (%)	588 (100.0)	581 (100.0)
Number of patients with endpoint, N (%)	432 (73.5)	440 (75.7)
95% confidence interval*	(69.8, 76.9)	(72.1, 79.0)
Comparison vs Placebo**		
Risk ratio (SE)		1.032 (0.033)
95% confidence interval***		(0.968, 1.099)
p-value		0.3359

* Wilson confidence intervals.
** Log-linked Poisson model with robust estimate of variance includes terms for baseline EQ-VAS score (p<0.0001), age (p=0.0219), baseline eGFR (CKD-EPI) (p=0.6433), Treatment (p=0.3991), region (5 cat.) (p<0.0001), baseline diabetes status (3 cat.) (p=0.2545), sex (p=0.0489), heart failure physiology (p=0.0087) and Treatment by heart failure physiology interaction (p=0.8166).
***Wald confidence intervals.
16 patients were excluded as the subgroup variable was missing.

Data taken from study 1245.121 only.
LOCF: For a missing value at week 52 the last available post-baseline value before week 52 is imputed.
NTproBNP median [pg/mL]: with a. fibrillation/flutter at baseline: 2265; without a. fibrillation/flutter at baseline: 1671.

Table R.1.2.1.12: 4 Responder analysis (displaying risk ratio) in EQ-VAS change from baseline at week 52 of > -7 points (stability) by heart failure physiology - RS (LOCF-AD) - 1245.121

Subgroup Description	Placebo	Empa 10mg
Heart failure physiology: LVEF > 30%		
Number of patients in analysis set	475	526
Number of analysed patients, N (%)	438 (100.0)	493 (100.0)
Number of patients with endpoint, N (%)	335 (76.5)	384 (77.9)
95% confidence interval*	(72.3, 80.2)	(74.0, 81.3)
Comparison vs Placebo**		
Risk ratio (SE)		1.002 (0.034)
95% confidence interval***		(0.937, 1.071)
p-value		0.9624

* Wilson confidence intervals.
** Log-linked Poisson model with robust estimate of variance includes terms for baseline EQ-VAS score (p<0.0001), age (p=0.0219), baseline eGFR (CKD-EPI) (p=0.6433), Treatment (p=0.3991), region (5 cat.) (p<0.0001), baseline diabetes status (3 cat.) (p=0.2545), sex (p=0.0489), heart failure physiology (p=0.0087) and Treatment by heart failure physiology interaction (p=0.8166).
***Wald confidence intervals.
16 patients were excluded as the subgroup variable was missing.

Data taken from study 1245.121 only.
LOCF: For a missing value at week 52 the last available post-baseline value before week 52 is imputed.
NTproBNP median [pg/mL]: with a. fibrillation/flutter at baseline: 2265; without a. fibrillation/flutter at baseline: 1671.

Table R.1.2.1.12: 5 Responder analysis (displaying odds ratio) in EQ-VAS change from baseline at week 52 of >= 7 points (improvement) by heart failure physiology - RS (LOCF-AD) - 1245.121

Subgroup Description	Placebo	Empa 10mg
Heart failure physiology: LVEF <= 30% and NTproBNP < median		
Number of patients in analysis set	723	698
Number of analysed patients, N (%)	679 (100.0)	655 (100.0)
Number of patients with endpoint, N (%)	268 (39.5)	271 (41.4)
95% confidence interval*	(35.9, 43.2)	(37.7, 45.2)
Comparison vs Placebo**		
Odds ratio (SE)		1.103 (0.141)
95% confidence interval***		(0.858, 1.417)
p-value		0.4432
Heart failure physiology: LVEF <= 30% and NTproBNP >= median		
Number of patients in analysis set	661	631
Number of analysed patients, N (%)	588 (100.0)	581 (100.0)
Number of patients with endpoint, N (%)	227 (38.6)	262 (45.1)
95% confidence interval*	(34.8, 42.6)	(41.1, 49.2)
Comparison vs Placebo**		
Odds ratio (SE)		1.503 (0.207)
95% confidence interval***		(1.147, 1.970)
p-value		0.0031

* Wilson confidence intervals.
** Logistic regression includes terms for baseline EQ-VAS score (p<0.0001), age (p=0.2072), baseline eGFR (CKD-EPI) (p=0.0557), Treatment (p=0.0009), region (5 cat.) (p<0.0001), baseline diabetes status (3 cat.) (p=0.9277), sex (p=0.4480), heart failure physiology (p=0.7008) and Treatment by heart failure physiology interaction (p=0.2442).
***Wald confidence intervals.
16 patients were excluded as the subgroup variable was missing.

Data taken from study 1245.121 only.
LOCF: For a missing value at week 52 the last available post-baseline value before week 52 is imputed.
NTproBNP median [pg/mL]: with a. fibrillation/flutter at baseline: 2265; without a. fibrillation/flutter at baseline: 1671.

Table R.1.2.1.12: 5 Responder analysis (displaying odds ratio) in EQ-VAS change from baseline at week 52 of >= 7 points (improvement) by heart failure physiology - RS (LOCF-AD) - 1245.121

Subgroup Description	Placebo	Empa 10mg
Heart failure physiology: LVEF > 30%		
Number of patients in analysis set	475	526
Number of analysed patients, N (%)	438 (100.0)	493 (100.0)
Number of patients with endpoint, N (%)	159 (36.3)	215 (43.6)
95% confidence interval*	(31.9, 40.9)	(39.3, 48.0)
Comparison vs Placebo**		
Odds ratio (SE)		1.353 (0.211)
95% confidence interval***		(0.997, 1.835)
p-value		0.0522

* Wilson confidence intervals.
** Logistic regression includes terms for baseline EQ-VAS score (p<0.0001), age (p=0.2072), baseline eGFR (CKD-EPI) (p=0.0557), Treatment (p=0.0009), region (5 cat.) (p<0.0001), baseline diabetes status (3 cat.) (p=0.9277), sex (p=0.4480), heart failure physiology (p=0.7008) and Treatment by heart failure physiology interaction (p=0.2442).
***Wald confidence intervals.
16 patients were excluded as the subgroup variable was missing.

Data taken from study 1245.121 only.
LOCF: For a missing value at week 52 the last available post-baseline value before week 52 is imputed.
NTproBNP median [pg/mL]: with a. fibrillation/flutter at baseline: 2265; without a. fibrillation/flutter at baseline: 1671.

Table R.1.2.1.12: 6 Responder analysis (displaying risk ratio) in EQ-VAS change from baseline at week 52 of >= 7 points (improvement) by heart failure physiology - RS (LOCF-AD) - 1245.121

Subgroup Description	Placebo	Empa 10mg
Heart failure physiology: LVEF <= 30% and NTproBNP < median		
Number of patients in analysis set	723	698
Number of analysed patients, N (%)	679 (100.0)	655 (100.0)
Number of patients with endpoint, N (%)	268 (39.5)	271 (41.4)
95% confidence interval*	(35.9, 43.2)	(37.7, 45.2)
Comparison vs Placebo**		
Risk ratio (SE)		1.063 (0.064)
95% confidence interval***		(0.945, 1.195)
p-value		0.3125
Heart failure physiology: LVEF <= 30% and NTproBNP >= median		
Number of patients in analysis set	661	631
Number of analysed patients, N (%)	588 (100.0)	581 (100.0)
Number of patients with endpoint, N (%)	227 (38.6)	262 (45.1)
95% confidence interval*	(34.8, 42.6)	(41.1, 49.2)
Comparison vs Placebo**		
Risk ratio (SE)		1.157 (0.074)
95% confidence interval***		(1.020, 1.312)
p-value		0.0230

* Wilson confidence intervals.
** Log-linked Poisson model with robust estimate of variance includes terms for baseline EQ-VAS score (p<0.0001), age (p=0.1595), baseline eGFR (CKD-EPI) (p=0.0873), Treatment (p=0.0045), region (5 cat.) (p<0.0001), baseline diabetes status (3 cat.) (p=0.8745), sex (p=0.2596), heart failure physiology (p=0.4823) and Treatment by heart failure physiology interaction (p=0.6142).
***Wald confidence intervals.
16 patients were excluded as the subgroup variable was missing.

Data taken from study 1245.121 only.
LOCF: For a missing value at week 52 the last available post-baseline value before week 52 is imputed.
NTproBNP median [pg/mL]: with a. fibrillation/flutter at baseline: 2265; without a. fibrillation/flutter at baseline: 1671.

Table R.1.2.1.12: 6 Responder analysis (displaying risk ratio) in EQ-VAS change from baseline at week 52 of >= 7 points (improvement) by heart failure physiology - RS (LOCF-AD) - 1245.121

Subgroup Description	Placebo	Empa 10mg
Heart failure physiology: LVEF > 30%		
Number of patients in analysis set	475	526
Number of analysed patients, N (%)	438 (100.0)	493 (100.0)
Number of patients with endpoint, N (%)	159 (36.3)	215 (43.6)
95% confidence interval*	(31.9, 40.9)	(39.3, 48.0)
Comparison vs Placebo**		
Risk ratio (SE)		1.124 (0.081)
95% confidence interval***		(0.975, 1.295)
p-value		0.1067

* Wilson confidence intervals.
** Log-linked Poisson model with robust estimate of variance includes terms for baseline EQ-VAS score (p<0.0001), age (p=0.1595), baseline eGFR (CKD-EPI) (p=0.0873), Treatment (p=0.0045), region (5 cat.) (p<0.0001), baseline diabetes status (3 cat.) (p=0.8745), sex (p=0.2596), heart failure physiology (p=0.4823) and Treatment by heart failure physiology interaction (p=0.6142).
***Wald confidence intervals.
16 patients were excluded as the subgroup variable was missing.

Data taken from study 1245.121 only.
LOCF: For a missing value at week 52 the last available post-baseline value before week 52 is imputed.
NTproBNP median [pg/mL]: with a. fibrillation/flutter at baseline: 2265; without a. fibrillation/flutter at baseline: 1671.

R.1.2.1.13

R.1.2.1.13 Subgroup analysis by baseline use of MRA

Table R.1.2.1.13: 1 Responder analysis (displaying odds ratio) in EQ-VAS change from baseline at week 52 of <= -7 points (deterioration) by baseline use of MRA (Y/N) - RS (LOCF-AD) - 1245.121

Subgroup Description	Placebo	Empa 10mg
Baseline use of MRA: No		
Number of patients in analysis set	512	557
Number of analysed patients, N (%)	474 (100.0)	521 (100.0)
Number of patients with endpoint, N (%)	120 (25.3)	119 (22.8)
95% confidence interval*	(21.6, 29.4)	(19.4, 26.6)
Comparison vs Placebo**		
Odds ratio (SE)		0.866 (0.136)
95% confidence interval***		(0.637, 1.178)
p-value		0.3605
Baseline use of MRA: Yes		
Number of patients in analysis set	1355	1306
Number of analysed patients, N (%)	1236 (100.0)	1212 (100.0)
Number of patients with endpoint, N (%)	294 (23.8)	276 (22.8)
95% confidence interval*	(21.5, 26.2)	(20.5, 25.2)
Comparison vs Placebo**		
Odds ratio (SE)		0.933 (0.095)
95% confidence interval***		(0.765, 1.138)
p-value		0.4944

* Wilson confidence intervals.
** Logistic regression includes terms for baseline EQ-VAS score (p<0.0001), age (p=0.0156), baseline eGFR (CKD-EPI) (p=0.3057), Treatment (p=0.2547), region (5 cat.) (p<0.0001), baseline diabetes status (3 cat.) (p=0.3581), sex (p=0.0742), baseline LVEF (3 cat.) (p=0.4052), baseline use of MRA (p=0.8835) and Treatment by baseline use of MRA interaction (p=0.6917).
***Wald confidence intervals.

Data taken from study 1245.121 only.
LOCF: For a missing value at week 52 the last available post-baseline value before week 52 is imputed.

Table R.1.2.1.13: 2 Responder analysis (displaying risk ratio) in EQ-VAS change from baseline at week 52 of <= -7 points (deterioration) by baseline use of MRA (Y/N) - RS (LOCF-AD) - 1245.121

Subgroup Description	Placebo	Empa 10mg
Baseline use of MRA: No		
Number of patients in analysis set	512	557
Number of analysed patients, N (%)	474 (100.0)	521 (100.0)
Number of patients with endpoint, N (%)	120 (25.3)	119 (22.8)
95% confidence interval*	(21.6, 29.4)	(19.4, 26.6)
Comparison vs Placebo**		
Risk ratio (SE)		0.907 (0.098)
95% confidence interval***		(0.734, 1.121)
p-value		0.3676
Baseline use of MRA: Yes		
Number of patients in analysis set	1355	1306
Number of analysed patients, N (%)	1236 (100.0)	1212 (100.0)
Number of patients with endpoint, N (%)	294 (23.8)	276 (22.8)
95% confidence interval*	(21.5, 26.2)	(20.5, 25.2)
Comparison vs Placebo**		
Risk ratio (SE)		0.950 (0.066)
95% confidence interval***		(0.829, 1.089)
p-value		0.4623

* Wilson confidence intervals.
** Log-linked Poisson model with robust estimate of variance includes terms for baseline EQ-VAS score (p<0.0001), age (p=0.0128), baseline eGFR (CKD-EPI) (p=0.3166), Treatment (p=0.2476), region (5 cat.) (p<0.0001), baseline diabetes status (3 cat.) (p=0.3765), sex (p=0.0877), baseline LVEF (3 cat.) (p=0.4266), baseline use of MRA (p=0.9025) and Treatment by baseline use of MRA interaction (p=0.7188).
***Wald confidence intervals.

Data taken from study 1245.121 only.
LOCF: For a missing value at week 52 the last available post-baseline value before week 52 is imputed.

Table R.1.2.1.13: 3 Responder analysis (displaying odds ratio) in EQ-VAS change from baseline at week 52 of > -7 points (stability) by baseline use of MRA (Y/N) - RS (LOCF-AD) - 1245.121

Subgroup Description	Placebo	Empa 10mg
Baseline use of MRA: No		
Number of patients in analysis set	512	557
Number of analysed patients, N (%)	474 (100.0)	521 (100.0)
Number of patients with endpoint, N (%)	354 (74.7)	402 (77.2)
95% confidence interval*	(70.6, 78.4)	(73.4, 80.6)
Comparison vs Placebo**		
Odds ratio (SE)		1.154 (0.181)
95% confidence interval***		(0.849, 1.569)
p-value		0.3605
Baseline use of MRA: Yes		
Number of patients in analysis set	1355	1306
Number of analysed patients, N (%)	1236 (100.0)	1212 (100.0)
Number of patients with endpoint, N (%)	942 (76.2)	936 (77.2)
95% confidence interval*	(73.8, 78.5)	(74.8, 79.5)
Comparison vs Placebo**		
Odds ratio (SE)		1.072 (0.109)
95% confidence interval***		(0.879, 1.308)
p-value		0.4944

* Wilson confidence intervals.
** Logistic regression includes terms for baseline EQ-VAS score (p<0.0001), age (p=0.0156), baseline eGFR (CKD-EPI) (p=0.3057), Treatment (p=0.2547), region (5 cat.) (p<0.0001), baseline diabetes status (3 cat.) (p=0.3581), sex (p=0.0742), baseline LVEF (3 cat.) (p=0.4052), baseline use of MRA (p=0.8835) and Treatment by baseline use of MRA interaction (p=0.6917).
***Wald confidence intervals.

Data taken from study 1245.121 only.
LOCF: For a missing value at week 52 the last available post-baseline value before week 52 is imputed.

Table R.1.2.1.13: 4 Responder analysis (displaying risk ratio) in EQ-VAS change from baseline at week 52 of > -7 points (stability) by baseline use of MRA (Y/N) - RS (LOCF-AD) - 1245.121

Subgroup Description	Placebo	Empa 10mg
Baseline use of MRA: No		
Number of patients in analysis set	512	557
Number of analysed patients, N (%)	474 (100.0)	521 (100.0)
Number of patients with endpoint, N (%)	354 (74.7)	402 (77.2)
95% confidence interval*	(70.6, 78.4)	(73.4, 80.6)
Comparison vs Placebo**		
Risk ratio (SE)		1.024 (0.035)
95% confidence interval***		(0.957, 1.095)
p-value		0.4909
Baseline use of MRA: Yes		
Number of patients in analysis set	1355	1306
Number of analysed patients, N (%)	1236 (100.0)	1212 (100.0)
Number of patients with endpoint, N (%)	942 (76.2)	936 (77.2)
95% confidence interval*	(73.8, 78.5)	(74.8, 79.5)
Comparison vs Placebo**		
Risk ratio (SE)		1.013 (0.022)
95% confidence interval***		(0.971, 1.056)
p-value		0.5576

* Wilson confidence intervals.
** Log-linked Poisson model with robust estimate of variance includes terms for baseline EQ-VAS score (p<0.0001), age (p=0.0248), baseline eGFR (CKD-EPI) (p=0.3344), Treatment (p=0.3709), region (5 cat.) (p<0.0001), baseline diabetes status (3 cat.) (p=0.2786), sex (p=0.0404), baseline LVEF (3 cat.) (p=0.5191), baseline use of MRA (p=0.8539) and Treatment by baseline use of MRA interaction (p=0.7816).
***Wald confidence intervals.

Data taken from study 1245.121 only.
LOCF: For a missing value at week 52 the last available post-baseline value before week 52 is imputed.

Table R.1.2.1.13: 5 Responder analysis (displaying odds ratio) in EQ-VAS change from baseline at week 52 of >= 7 points (improvement) by baseline use of MRA (Y/N) - RS (LOCF-AD) - 1245.121

Subgroup Description	Placebo	Empa 10mg
Baseline use of MRA: No		
Number of patients in analysis set	512	557
Number of analysed patients, N (%)	474 (100.0)	521 (100.0)
Number of patients with endpoint, N (%)	161 (34.0)	214 (41.1)
95% confidence interval*	(29.8, 38.3)	(36.9, 45.3)
Comparison vs Placebo**		
Odds ratio (SE)		1.438 (0.217)
95% confidence interval***		(1.070, 1.934)
p-value		0.0162
Baseline use of MRA: Yes		
Number of patients in analysis set	1355	1306
Number of analysed patients, N (%)	1236 (100.0)	1212 (100.0)
Number of patients with endpoint, N (%)	496 (40.1)	536 (44.2)
95% confidence interval*	(37.4, 42.9)	(41.5, 47.0)
Comparison vs Placebo**		
Odds ratio (SE)		1.239 (0.117)
95% confidence interval***		(1.030, 1.492)
p-value		0.0232

* Wilson confidence intervals.
** Logistic regression includes terms for baseline EQ-VAS score (p<0.0001), age (p=0.2222), baseline eGFR (CKD-EPI) (p=0.0460), Treatment (p=0.0012), region (5 cat.) (p<0.0001), baseline diabetes status (3 cat.) (p=0.9173), sex (p=0.4452), baseline LVEF (3 cat.) (p=0.7072), baseline use of MRA (p=0.2418) and Treatment by baseline use of MRA interaction (p=0.4036).
***Wald confidence intervals.

Data taken from study 1245.121 only.
LOCF: For a missing value at week 52 the last available post-baseline value before week 52 is imputed.

Table R.1.2.1.13: 6 Responder analysis (displaying risk ratio) in EQ-VAS change from baseline at week 52 of >= 7 points (improvement) by baseline use of MRA (Y/N) - RS (LOCF-AD) - 1245.121

Subgroup Description	Placebo	Empa 10mg
Baseline use of MRA: No		
Number of patients in analysis set	512	557
Number of analysed patients, N (%)	474 (100.0)	521 (100.0)
Number of patients with endpoint, N (%)	161 (34.0)	214 (41.1)
95% confidence interval*	(29.8, 38.3)	(36.9, 45.3)
Comparison vs Placebo**		
Risk ratio (SE)		1.150 (0.087)
95% confidence interval***		(0.992, 1.333)
p-value		0.0632
Baseline use of MRA: Yes		
Number of patients in analysis set	1355	1306
Number of analysed patients, N (%)	1236 (100.0)	1212 (100.0)
Number of patients with endpoint, N (%)	496 (40.1)	536 (44.2)
95% confidence interval*	(37.4, 42.9)	(41.5, 47.0)
Comparison vs Placebo**		
Risk ratio (SE)		1.098 (0.047)
95% confidence interval***		(1.009, 1.194)
p-value		0.0310

* Wilson confidence intervals.
** Log-linked Poisson model with robust estimate of variance includes terms for baseline EQ-VAS score (p<0.0001), age (p=0.2030), baseline eGFR (CKD-EPI) (p=0.0643), Treatment (p=0.0072), region (5 cat.) (p<0.0001), baseline diabetes status (3 cat.) (p=0.8691), sex (p=0.2500), baseline LVEF (3 cat.) (p=0.7585), baseline use of MRA (p=0.1796) and Treatment by baseline use of MRA interaction (p=0.5909).
***Wald confidence intervals.

Data taken from study 1245.121 only.
LOCF: For a missing value at week 52 the last available post-baseline value before week 52 is imputed.

R.1.2.1.14 Subgroup analysis by baseline use of ARNi

Table R.1.2.1.14: 1 Responder analysis (displaying odds ratio) in EQ-VAS change from baseline at week 52 of <= -7 points (deterioration) by baseline use of ARNi (Y/N) - RS (LOCF-AD) - 1245.121

Subgroup Description	Placebo	Empa 10mg
Baseline use of ARNi: No		
Number of patients in analysis set	1480	1523
Number of analysed patients, N (%)	1352 (100.0)	1412 (100.0)
Number of patients with endpoint, N (%)	333 (24.6)	322 (22.8)
95% confidence interval*	(22.4, 27.0)	(20.7, 25.1)
Comparison vs Placebo**		
Odds ratio (SE)		0.886 (0.084)
95% confidence interval***		(0.736, 1.067)
p-value		0.2016
Baseline use of ARNi: Yes		
Number of patients in analysis set	387	340
Number of analysed patients, N (%)	358 (100.0)	321 (100.0)
Number of patients with endpoint, N (%)	81 (22.6)	73 (22.7)
95% confidence interval*	(18.6, 27.2)	(18.5, 27.6)
Comparison vs Placebo**		
Odds ratio (SE)		1.015 (0.197)
95% confidence interval***		(0.694, 1.486)
p-value		0.9381

* Wilson confidence intervals.
** Logistic regression includes terms for baseline EQ-VAS score (p<0.0001), age (p=0.0182), baseline eGFR (CKD-EPI) (p=0.2939), Treatment (p=0.6238), region (5 cat.) (p<0.0001), baseline diabetes status (3 cat.) (p=0.3645), sex (p=0.0728), baseline LVEF (3 cat.) (p=0.3713), baseline use of ARNi (p=0.2216) and Treatment by baseline use of ARNi interaction (p=0.5287).
***Wald confidence intervals.

Data taken from study 1245.121 only.
LOCF: For a missing value at week 52 the last available post-baseline value before week 52 is imputed.

Table R.1.2.1.14: 2 Responder analysis (displaying risk ratio) in EQ-VAS change from baseline at week 52 of <= -7 points (deterioration) by baseline use of ARNi (Y/N) - RS (LOCF-AD) - 1245.121

Subgroup Description	Placebo	Empa 10mg
Baseline use of ARNi: No		
Number of patients in analysis set	1480	1523
Number of analysed patients, N (%)	1352 (100.0)	1412 (100.0)
Number of patients with endpoint, N (%)	333 (24.6)	322 (22.8)
95% confidence interval*	(22.4, 27.0)	(20.7, 25.1)
Comparison vs Placebo**		
Risk ratio (SE)		0.918 (0.059)
95% confidence interval***		(0.809, 1.043)
p-value		0.1888
Baseline use of ARNi: Yes		
Number of patients in analysis set	387	340
Number of analysed patients, N (%)	358 (100.0)	321 (100.0)
Number of patients with endpoint, N (%)	81 (22.6)	73 (22.7)
95% confidence interval*	(18.6, 27.2)	(18.5, 27.6)
Comparison vs Placebo**		
Risk ratio (SE)		1.009 (0.137)
95% confidence interval***		(0.774, 1.316)
p-value		0.9478

* Wilson confidence intervals.
** Log-linked Poisson model with robust estimate of variance includes terms for baseline EQ-VAS score (p<0.0001), age (p=0.0145), baseline eGFR (CKD-EPI) (p=0.3005), Treatment (p=0.6112), region (5 cat.) (p<0.0001), baseline diabetes status (3 cat.) (p=0.3819), sex (p=0.0857), baseline LVEF (3 cat.) (p=0.3921), baseline use of ARNi (p=0.2257) and Treatment by baseline use of ARNi interaction (p=0.5319).
***Wald confidence intervals.

Data taken from study 1245.121 only.
LOCF: For a missing value at week 52 the last available post-baseline value before week 52 is imputed.

Table R.1.2.1.14: 3 Responder analysis (displaying odds ratio) in EQ-VAS change from baseline at week 52 of > -7 points (stability) by baseline use of ARNi (Y/N) - RS (LOCF-AD) - 1245.121

Subgroup Description	Placebo	Empa 10mg
Baseline use of ARNi: No		
Number of patients in analysis set	1480	1523
Number of analysed patients, N (%)	1352 (100.0)	1412 (100.0)
Number of patients with endpoint, N (%)	1019 (75.4)	1090 (77.2)
95% confidence interval*	(73.0, 77.6)	(74.9, 79.3)
Comparison vs Placebo**		
Odds ratio (SE)		1.129 (0.107)
95% confidence interval***		(0.937, 1.359)
p-value		0.2016
Baseline use of ARNi: Yes		
Number of patients in analysis set	387	340
Number of analysed patients, N (%)	358 (100.0)	321 (100.0)
Number of patients with endpoint, N (%)	277 (77.4)	248 (77.3)
95% confidence interval*	(72.8, 81.4)	(72.4, 81.5)
Comparison vs Placebo**		
Odds ratio (SE)		0.985 (0.191)
95% confidence interval***		(0.673, 1.441)
p-value		0.9381

* Wilson confidence intervals.
** Logistic regression includes terms for baseline EQ-VAS score (p<0.0001), age (p=0.0182), baseline eGFR (CKD-EPI) (p=0.2939), Treatment (p=0.6238), region (5 cat.) (p<0.0001), baseline diabetes status (3 cat.) (p=0.3645), sex (p=0.0728), baseline LVEF (3 cat.) (p=0.3713), baseline use of ARNi (p=0.2216) and Treatment by baseline use of ARNi interaction (p=0.5287).
***Wald confidence intervals.

Data taken from study 1245.121 only.
LOCF: For a missing value at week 52 the last available post-baseline value before week 52 is imputed.

Table R.1.2.1.14: 4 Responder analysis (displaying risk ratio) in EQ-VAS change from baseline at week 52 of > -7 points (stability) by baseline use of ARNi (Y/N) - RS (LOCF-AD) - 1245.121

Subgroup Description	Placebo	Empa 10mg
Baseline use of ARNi: No		
Number of patients in analysis set	1480	1523
Number of analysed patients, N (%)	1352 (100.0)	1412 (100.0)
Number of patients with endpoint, N (%)	1019 (75.4)	1090 (77.2)
95% confidence interval*	(73.0, 77.6)	(74.9, 79.3)
Comparison vs Placebo**		
Risk ratio (SE)		1.022 (0.021)
95% confidence interval***		(0.982, 1.063)
p-value		0.2842
Baseline use of ARNi: Yes		
Number of patients in analysis set	387	340
Number of analysed patients, N (%)	358 (100.0)	321 (100.0)
Number of patients with endpoint, N (%)	277 (77.4)	248 (77.3)
95% confidence interval*	(72.8, 81.4)	(72.4, 81.5)
Comparison vs Placebo**		
Risk ratio (SE)		0.995 (0.040)
95% confidence interval***		(0.919, 1.077)
p-value		0.8966

* Wilson confidence intervals.
** Log-linked Poisson model with robust estimate of variance includes terms for baseline EQ-VAS score (p<0.0001), age (p=0.0296), baseline eGFR (CKD-EPI) (p=0.3221), Treatment (p=0.7162), region (5 cat.) (p<0.0001), baseline diabetes status (3 cat.) (p=0.2848), sex (p=0.0388), baseline LVEF (3 cat.) (p=0.4862), baseline use of ARNi (p=0.2838) and Treatment by baseline use of ARNi interaction (p=0.5515).
***Wald confidence intervals.

Data taken from study 1245.121 only.
LOCF: For a missing value at week 52 the last available post-baseline value before week 52 is imputed.

Table R.1.2.1.14: 5 Responder analysis (displaying odds ratio) in EQ-VAS change from baseline at week 52 of >= 7 points (improvement) by baseline use of ARNi (Y/N) - RS (LOCF-AD) - 1245.121

Subgroup Description	Placebo	Empa 10mg
Baseline use of ARNi: No		
Number of patients in analysis set	1480	1523
Number of analysed patients, N (%)	1352 (100.0)	1412 (100.0)
Number of patients with endpoint, N (%)	530 (39.2)	616 (43.6)
95% confidence interval*	(36.6, 41.8)	(41.1, 46.2)
Comparison vs Placebo**		
Odds ratio (SE)		1.278 (0.114)
95% confidence interval***		(1.073, 1.522)
p-value		0.0059
Baseline use of ARNi: Yes		
Number of patients in analysis set	387	340
Number of analysed patients, N (%)	358 (100.0)	321 (100.0)
Number of patients with endpoint, N (%)	127 (35.5)	134 (41.7)
95% confidence interval*	(30.7, 40.6)	(36.5, 47.2)
Comparison vs Placebo**		
Odds ratio (SE)		1.344 (0.247)
95% confidence interval***		(0.937, 1.928)
p-value		0.1079

* Wilson confidence intervals.
** Logistic regression includes terms for baseline EQ-VAS score (p<0.0001), age (p=0.1767), baseline eGFR (CKD-EPI) (p=0.0407), Treatment (p=0.0081), region (5 cat.) (p<0.0001), baseline diabetes status (3 cat.) (p=0.9198), sex (p=0.4639), baseline LVEF (3 cat.) (p=0.7297), baseline use of ARNi (p=0.8370) and Treatment by baseline use of ARNi interaction (p=0.8054).
***Wald confidence intervals.

Data taken from study 1245.121 only.
LOCF: For a missing value at week 52 the last available post-baseline value before week 52 is imputed.

Table R.1.2.1.14: 6 Responder analysis (displaying risk ratio) in EQ-VAS change from baseline at week 52 of >= 7 points (improvement) by baseline use of ARNi (Y/N) - RS (LOCF-AD) - 1245.121

Subgroup Description	Placebo	Empa 10mg
Baseline use of ARNi: No		
Number of patients in analysis set	1480	1523
Number of analysed patients, N (%)	1352 (100.0)	1412 (100.0)
Number of patients with endpoint, N (%)	530 (39.2)	616 (43.6)
95% confidence interval*	(36.6, 41.8)	(41.1, 46.2)
Comparison vs Placebo**		
Risk ratio (SE)		1.100 (0.045)
95% confidence interval***		(1.014, 1.193)
p-value		0.0210
Baseline use of ARNi: Yes		
Number of patients in analysis set	387	340
Number of analysed patients, N (%)	358 (100.0)	321 (100.0)
Number of patients with endpoint, N (%)	127 (35.5)	134 (41.7)
95% confidence interval*	(30.7, 40.6)	(36.5, 47.2)
Comparison vs Placebo**		
Risk ratio (SE)		1.150 (0.101)
95% confidence interval***		(0.968, 1.367)
p-value		0.1127

* Wilson confidence intervals.
** Log-linked Poisson model with robust estimate of variance includes terms for baseline EQ-VAS score (p<0.0001), age (p=0.1504), baseline eGFR (CKD-EPI) (p=0.0576), Treatment (p=0.0157), region (5 cat.) (p<0.0001), baseline diabetes status (3 cat.) (p=0.8616), sex (p=0.2636), baseline LVEF (3 cat.) (p=0.7468), baseline use of ARNi (p=0.5765) and Treatment by baseline use of ARNi interaction (p=0.6473).
***Wald confidence intervals.

Data taken from study 1245.121 only.
LOCF: For a missing value at week 52 the last available post-baseline value before week 52 is imputed.

R.1.2.1.15

R.1.2.1.15 Subgroup analysis by bl. LVEF (<= 30%, >30% -<= 35% , > 35%)

Table R.1.2.1.15: 1 Responder analysis (displaying odds ratio) in EQ-VAS change from baseline at week 52 of <= -7 points (deterioration) by baseline LVEF (3 cat.) - RS (LOCF-AD) - 1245.121

Subgroup Description	Placebo	Empa 10mg
Baseline LVEF (3 cat.): <=30		
Number of patients in analysis set	1392	1337
Number of analysed patients, N (%)	1272 (100.0)	1240 (100.0)
Number of patients with endpoint, N (%)	311 (24.4)	286 (23.1)
95% confidence interval*	(22.2, 26.9)	(20.8, 25.5)
Comparison vs Placebo**		
Odds ratio (SE)		0.894 (0.089)
95% confidence interval***		(0.735, 1.086)
p-value		0.2579
Baseline LVEF (3 cat.): >30 to <=35		
Number of patients in analysis set	361	398
Number of analysed patients, N (%)	334 (100.0)	373 (100.0)
Number of patients with endpoint, N (%)	78 (23.4)	85 (22.8)
95% confidence interval*	(19.1, 28.2)	(18.8, 27.3)
Comparison vs Placebo**		
Odds ratio (SE)		1.016 (0.192)
95% confidence interval***		(0.702, 1.472)
p-value		0.9315

* Wilson confidence intervals.
** Logistic regression includes terms for baseline EQ-VAS score (p<0.0001), age (p=0.0149), baseline eGFR (CKD-EPI) (p=0.3103), Treatment (p=0.4682), region (5 cat.) (p<0.0001), baseline diabetes status (3 cat.) (p=0.3531), sex (p=0.0722), baseline LVEF (3 cat.) (p=0.3913) and Treatment by baseline LVEF (3 cat.) interaction (p=0.7932).
***Wald confidence intervals.

Data taken from study 1245.121 only.
LOCF: For a missing value at week 52 the last available post-baseline value before week 52 is imputed.

Table R.1.2.1.15: 1 Responder analysis (displaying odds ratio) in EQ-VAS change from baseline at week 52 of <= -7 points (deterioration) by baseline LVEF (3 cat.) - RS (LOCF-AD) - 1245.121

Subgroup Description	Placebo	Empa 10mg
Baseline LVEF (3 cat.): >35		
Number of patients in analysis set	114	128
Number of analysed patients, N (%)	104 (100.0)	120 (100.0)
Number of patients with endpoint, N (%)	25 (24.0)	24 (20.0)
95% confidence interval*	(16.8, 33.1)	(13.8, 28.0)
Comparison vs Placebo**		
Odds ratio (SE)		0.822 (0.281)
95% confidence interval***		(0.420, 1.607)
p-value		0.5662

* Wilson confidence intervals.
** Logistic regression includes terms for baseline EQ-VAS score (p<0.0001), age (p=0.0149), baseline eGFR (CKD-EPI) (p=0.3103), Treatment (p=0.4682), region (5 cat.) (p<0.0001), baseline diabetes status (3 cat.) (p=0.3531), sex (p=0.0722), baseline LVEF (3 cat.) (p=0.3913) and Treatment by baseline LVEF (3 cat.) interaction (p=0.7932).
***Wald confidence intervals.

Data taken from study 1245.121 only.
LOCF: For a missing value at week 52 the last available post-baseline value before week 52 is imputed.

Table R.1.2.1.15: 2 Responder analysis (displaying risk ratio) in EQ-VAS change from baseline at week 52 of <= -7 points (deterioration) by baseline LVEF (3 cat.) - RS (LOCF-AD) - 1245.121

Subgroup Description	Placebo	Empa 10mg
Baseline LVEF (3 cat.): <=30		
Number of patients in analysis set	1392	1337
Number of analysed patients, N (%)	1272 (100.0)	1240 (100.0)
Number of patients with endpoint, N (%)	311 (24.4)	286 (23.1)
95% confidence interval*	(22.2, 26.9)	(20.8, 25.5)
Comparison vs Placebo**		
Risk ratio (SE)		0.924 (0.063)
95% confidence interval***		(0.809, 1.055)
p-value		0.2405
Baseline LVEF (3 cat.): >30 to <=35		
Number of patients in analysis set	361	398
Number of analysed patients, N (%)	334 (100.0)	373 (100.0)
Number of patients with endpoint, N (%)	78 (23.4)	85 (22.8)
95% confidence interval*	(19.1, 28.2)	(18.8, 27.3)
Comparison vs Placebo**		
Risk ratio (SE)		1.016 (0.135)
95% confidence interval***		(0.783, 1.318)
p-value		0.9054

* Wilson confidence intervals.
** Log-linked Poisson model with robust estimate of variance includes terms for baseline EQ-VAS score (p<0.0001), age (p=0.0119), baseline eGFR (CKD-EPI) (p=0.3203), Treatment (p=0.4289), region (5 cat.) (p<0.0001), baseline diabetes status (3 cat.) (p=0.3671), sex (p=0.0859), baseline LVEF (3 cat.) (p=0.4195) and Treatment by baseline LVEF (3 cat.) interaction (p=0.7537).
***Wald confidence intervals.

Data taken from study 1245.121 only.
LOCF: For a missing value at week 52 the last available post-baseline value before week 52 is imputed.

Table R.1.2.1.15: 2 Responder analysis (displaying risk ratio) in EQ-VAS change from baseline at week 52 of <= -7 points (deterioration) by baseline LVEF (3 cat.) - RS (LOCF-AD) - 1245.121

Subgroup Description	Placebo	Empa 10mg
Baseline LVEF (3 cat.): >35		
Number of patients in analysis set	114	128
Number of analysed patients, N (%)	104 (100.0)	120 (100.0)
Number of patients with endpoint, N (%)	25 (24.0)	24 (20.0)
95% confidence interval*	(16.8, 33.1)	(13.8, 28.0)
Comparison vs Placebo**		
Risk ratio (SE)		0.857 (0.199)
95% confidence interval***		(0.544, 1.350)
p-value		0.5058

* Wilson confidence intervals.
** Log-linked Poisson model with robust estimate of variance includes terms for baseline EQ-VAS score (p<0.0001), age (p=0.0119), baseline eGFR (CKD-EPI) (p=0.3203), Treatment (p=0.4289), region (5 cat.) (p<0.0001), baseline diabetes status (3 cat.) (p=0.3671), sex (p=0.0859), baseline LVEF (3 cat.) (p=0.4195) and Treatment by baseline LVEF (3 cat.) interaction (p=0.7537).
***Wald confidence intervals.

Data taken from study 1245.121 only.
LOCF: For a missing value at week 52 the last available post-baseline value before week 52 is imputed.

Table R.1.2.1.15: 3 Responder analysis (displaying odds ratio) in EQ-VAS change from baseline at week 52 of > -7 points (stability) by baseline LVEF (3 cat.) - RS (LOCF-AD) - 1245.121

Subgroup Description	Placebo	Empa 10mg
Baseline LVEF (3 cat.): <=30		
Number of patients in analysis set	1392	1337
Number of analysed patients, N (%)	1272 (100.0)	1240 (100.0)
Number of patients with endpoint, N (%)	961 (75.6)	954 (76.9)
95% confidence interval*	(73.1, 77.8)	(74.5, 79.2)
Comparison vs Placebo**		
Odds ratio (SE)		1.119 (0.111)
95% confidence interval***		(0.921, 1.360)
p-value		0.2579
Baseline LVEF (3 cat.): >30 to <=35		
Number of patients in analysis set	361	398
Number of analysed patients, N (%)	334 (100.0)	373 (100.0)
Number of patients with endpoint, N (%)	256 (76.6)	288 (77.2)
95% confidence interval*	(71.8, 80.9)	(72.7, 81.2)
Comparison vs Placebo**		
Odds ratio (SE)		0.984 (0.186)
95% confidence interval***		(0.680, 1.425)
p-value		0.9315

* Wilson confidence intervals.
** Logistic regression includes terms for baseline EQ-VAS score (p<0.0001), age (p=0.0149), baseline eGFR (CKD-EPI) (p=0.3103), Treatment (p=0.4682), region (5 cat.) (p<0.0001), baseline diabetes status (3 cat.) (p=0.3531), sex (p=0.0722), baseline LVEF (3 cat.) (p=0.3913) and Treatment by baseline LVEF (3 cat.) interaction (p=0.7932).
***Wald confidence intervals.

Data taken from study 1245.121 only.
LOCF: For a missing value at week 52 the last available post-baseline value before week 52 is imputed.

Table R.1.2.1.15: 3 Responder analysis (displaying odds ratio) in EQ-VAS change from baseline at week 52 of > -7 points (stability) by baseline LVEF (3 cat.) - RS (LOCF-AD) - 1245.121

Subgroup Description	Placebo	Empa 10mg
Baseline LVEF (3 cat.): >35		
Number of patients in analysis set	114	128
Number of analysed patients, N (%)	104 (100.0)	120 (100.0)
Number of patients with endpoint, N (%)	79 (76.0)	96 (80.0)
95% confidence interval*	(66.9, 83.2)	(72.0, 86.2)
Comparison vs Placebo**		
Odds ratio (SE)		1.217 (0.416)
95% confidence interval***		(0.622, 2.379)
p-value		0.5662

* Wilson confidence intervals.
** Logistic regression includes terms for baseline EQ-VAS score (p<0.0001), age (p=0.0149), baseline eGFR (CKD-EPI) (p=0.3103), Treatment (p=0.4682), region (5 cat.) (p<0.0001), baseline diabetes status (3 cat.) (p=0.3531), sex (p=0.0722), baseline LVEF (3 cat.) (p=0.3913) and Treatment by baseline LVEF (3 cat.) interaction (p=0.7932).
***Wald confidence intervals.

Data taken from study 1245.121 only.
LOCF: For a missing value at week 52 the last available post-baseline value before week 52 is imputed.

Table R.1.2.1.15: 4 Responder analysis (displaying risk ratio) in EQ-VAS change from baseline at week 52 of > -7 points (stability) by baseline LVEF (3 cat.) - RS (LOCF-AD) - 1245.121

Subgroup Description	Placebo	Empa 10mg
Baseline LVEF (3 cat.): <=30		
Number of patients in analysis set	1392	1337
Number of analysed patients, N (%)	1272 (100.0)	1240 (100.0)
Number of patients with endpoint, N (%)	961 (75.6)	954 (76.9)
95% confidence interval*	(73.1, 77.8)	(74.5, 79.2)
Comparison vs Placebo**		
Risk ratio (SE)		1.021 (0.022)
95% confidence interval***		(0.980, 1.065)
p-value		0.3201
Baseline LVEF (3 cat.): >30 to <=35		
Number of patients in analysis set	361	398
Number of analysed patients, N (%)	334 (100.0)	373 (100.0)
Number of patients with endpoint, N (%)	256 (76.6)	288 (77.2)
95% confidence interval*	(71.8, 80.9)	(72.7, 81.2)
Comparison vs Placebo**		
Risk ratio (SE)		0.997 (0.040)
95% confidence interval***		(0.922, 1.077)
p-value		0.9317

* Wilson confidence intervals.
** Log-linked Poisson model with robust estimate of variance includes terms for baseline EQ-VAS score (p<0.0001), age (p=0.0250), baseline eGFR (CKD-EPI) (p=0.3353), Treatment (p=0.6756), region (5 cat.) (p<0.0001), baseline diabetes status (3 cat.) (p=0.2769), sex (p=0.0391), baseline LVEF (3 cat.) (p=0.4998) and Treatment by baseline LVEF (3 cat.) interaction (p=0.8623).
***Wald confidence intervals.

Data taken from study 1245.121 only.
LOCF: For a missing value at week 52 the last available post-baseline value before week 52 is imputed.

Table R.1.2.1.15: 4 Responder analysis (displaying risk ratio) in EQ-VAS change from baseline at week 52 of > -7 points (stability) by baseline LVEF (3 cat.) - RS (LOCF-AD) - 1245.121

Subgroup Description	Placebo	Empa 10mg
Baseline LVEF (3 cat.): >35		
Number of patients in analysis set	114	128
Number of analysed patients, N (%)	104 (100.0)	120 (100.0)
Number of patients with endpoint, N (%)	79 (76.0)	96 (80.0)
95% confidence interval*	(66.9, 83.2)	(72.0, 86.2)
Comparison vs Placebo**		
Risk ratio (SE)		1.016 (0.068)
95% confidence interval***		(0.892, 1.158)
p-value		0.8112

* Wilson confidence intervals.
** Log-linked Poisson model with robust estimate of variance includes terms for baseline EQ-VAS score (p<0.0001), age (p=0.0250), baseline eGFR (CKD-EPI) (p=0.3353), Treatment (p=0.6756), region (5 cat.) (p<0.0001), baseline diabetes status (3 cat.) (p=0.2769), sex (p=0.0391), baseline LVEF (3 cat.) (p=0.4998) and Treatment by baseline LVEF (3 cat.) interaction (p=0.8623).
***Wald confidence intervals.

Data taken from study 1245.121 only.
LOCF: For a missing value at week 52 the last available post-baseline value before week 52 is imputed.

Table R.1.2.1.15: 5 Responder analysis (displaying odds ratio) in EQ-VAS change from baseline at week 52 of >= 7 points (improvement) by baseline LVEF (3 cat.) - RS (LOCF-AD) - 1245.121

Subgroup Description	Placebo	Empa 10mg
Baseline LVEF (3 cat.): <=30		
Number of patients in analysis set	1392	1337
Number of analysed patients, N (%)	1272 (100.0)	1240 (100.0)
Number of patients with endpoint, N (%)	498 (39.2)	535 (43.1)
95% confidence interval*	(36.5, 41.9)	(40.4, 45.9)
Comparison vs Placebo**		
Odds ratio (SE)		1.269 (0.119)
95% confidence interval***		(1.057, 1.525)
p-value		0.0108
Baseline LVEF (3 cat.): >30 to <=35		
Number of patients in analysis set	361	398
Number of analysed patients, N (%)	334 (100.0)	373 (100.0)
Number of patients with endpoint, N (%)	119 (35.6)	155 (41.6)
95% confidence interval*	(30.7, 40.9)	(36.7, 46.6)
Comparison vs Placebo**		
Odds ratio (SE)		1.338 (0.240)
95% confidence interval***		(0.942, 1.901)
p-value		0.1044

* Wilson confidence intervals.
** Logistic regression includes terms for baseline EQ-VAS score (p<0.0001), age (p=0.1815), baseline eGFR (CKD-EPI) (p=0.0398), Treatment (p=0.0204), region (5 cat.) (p<0.0001), baseline diabetes status (3 cat.) (p=0.9201), sex (p=0.4648), baseline LVEF (3 cat.) (p=0.7313) and Treatment by baseline LVEF (3 cat.) interaction (p=0.9323).
***Wald confidence intervals.

Data taken from study 1245.121 only.
LOCF: For a missing value at week 52 the last available post-baseline value before week 52 is imputed.

Table R.1.2.1.15: 5 Responder analysis (displaying odds ratio) in EQ-VAS change from baseline at week 52 of >= 7 points (improvement) by baseline LVEF (3 cat.) - RS (LOCF-AD) - 1245.121

Subgroup Description	Placebo	Empa 10mg
Baseline LVEF (3 cat.): >35		
Number of patients in analysis set	114	128
Number of analysed patients, N (%)	104 (100.0)	120 (100.0)
Number of patients with endpoint, N (%)	40 (38.5)	60 (50.0)
95% confidence interval*	(29.7, 48.1)	(41.2, 58.8)
Comparison vs Placebo**		
Odds ratio (SE)		1.401 (0.441)
95% confidence interval***		(0.756, 2.596)
p-value		0.2837

* Wilson confidence intervals.
** Logistic regression includes terms for baseline EQ-VAS score (p<0.0001), age (p=0.1815), baseline eGFR (CKD-EPI) (p=0.0398), Treatment (p=0.0204), region (5 cat.) (p<0.0001), baseline diabetes status (3 cat.) (p=0.9201), sex (p=0.4648), baseline LVEF (3 cat.) (p=0.7313) and Treatment by baseline LVEF (3 cat.) interaction (p=0.9323).
***Wald confidence intervals.

Data taken from study 1245.121 only.
LOCF: For a missing value at week 52 the last available post-baseline value before week 52 is imputed.

Table R.1.2.1.15: 6 Responder analysis (displaying risk ratio) in EQ-VAS change from baseline at week 52 of >= 7 points (improvement) by baseline LVEF (3 cat.) - RS (LOCF-AD) - 1245.121

Subgroup Description	Placebo	Empa 10mg
Baseline LVEF (3 cat.): <=30		
Number of patients in analysis set	1392	1337
Number of analysed patients, N (%)	1272 (100.0)	1240 (100.0)
Number of patients with endpoint, N (%)	498 (39.2)	535 (43.1)
95% confidence interval*	(36.5, 41.9)	(40.4, 45.9)
Comparison vs Placebo**		
Risk ratio (SE)		1.106 (0.048)
95% confidence interval***		(1.015, 1.204)
p-value		0.0216
Baseline LVEF (3 cat.): >30 to <=35		
Number of patients in analysis set	361	398
Number of analysed patients, N (%)	334 (100.0)	373 (100.0)
Number of patients with endpoint, N (%)	119 (35.6)	155 (41.6)
95% confidence interval*	(30.7, 40.9)	(36.7, 46.6)
Comparison vs Placebo**		
Risk ratio (SE)		1.130 (0.096)
95% confidence interval***		(0.957, 1.335)
p-value		0.1496

* Wilson confidence intervals.
** Log-linked Poisson model with robust estimate of variance includes terms for baseline EQ-VAS score (p<0.0001), age (p=0.1616), baseline eGFR (CKD-EPI) (p=0.0537), Treatment (p=0.0593), region (5 cat.) (p<0.0001), baseline diabetes status (3 cat.) (p=0.8667), sex (p=0.2626), baseline LVEF (3 cat.) (p=0.7414) and Treatment by baseline LVEF (3 cat.) interaction (p=0.9709).
***Wald confidence intervals.

Data taken from study 1245.121 only.
LOCF: For a missing value at week 52 the last available post-baseline value before week 52 is imputed.

Table R.1.2.1.15: 6 Responder analysis (displaying risk ratio) in EQ-VAS change from baseline at week 52 of >= 7 points (improvement) by baseline LVEF (3 cat.) - RS (LOCF-AD) - 1245.121

Subgroup Description	Placebo	Empa 10mg
Baseline LVEF (3 cat.): >35		
Number of patients in analysis set	114	128
Number of analysed patients, N (%)	104 (100.0)	120 (100.0)
Number of patients with endpoint, N (%)	40 (38.5)	60 (50.0)
95% confidence interval*	(29.7, 48.1)	(41.2, 58.8)
Comparison vs Placebo**		
Risk ratio (SE)		1.098 (0.151)
95% confidence interval***		(0.839, 1.438)
p-value		0.4959

* Wilson confidence intervals.
** Log-linked Poisson model with robust estimate of variance includes terms for baseline EQ-VAS score (p<0.0001), age (p=0.1616), baseline eGFR (CKD-EPI) (p=0.0537), Treatment (p=0.0593), region (5 cat.) (p<0.0001), baseline diabetes status (3 cat.) (p=0.8667), sex (p=0.2626), baseline LVEF (3 cat.) (p=0.7414) and Treatment by baseline LVEF (3 cat.) interaction (p=0.9709).
***Wald confidence intervals.

Data taken from study 1245.121 only.
LOCF: For a missing value at week 52 the last available post-baseline value before week 52 is imputed.

R.1.2.1.16 Subgroup analysis by bl. NTproBNP </>= median (median based on total patients)

Table R.1.2.1.16: 1 Responder analysis (displaying odds ratio) in EQ-VAS change from baseline at week 52 of <= -7 points (deterioration) by bl. NTproBNP (<median, >= median) (median based on total patients) - RS (LOCF-AD) - 1245.121

Subgroup Description	Placebo	Empa 10mg
Baseline NTproBNP (<median, >= median): < median		
Number of patients in analysis set	920	942
Number of analysed patients, N (%)	866 (100.0)	884 (100.0)
Number of patients with endpoint, N (%)	207 (23.9)	188 (21.3)
95% confidence interval*	(21.2, 26.9)	(18.7, 24.1)
Comparison vs Placebo**		
Odds ratio (SE)		0.858 (0.104)
95% confidence interval***		(0.677, 1.087)
p-value		0.2049
Baseline NTproBNP (<median, >= median): >= median		
Number of patients in analysis set	946	920
Number of analysed patients, N (%)	844 (100.0)	849 (100.0)
Number of patients with endpoint, N (%)	207 (24.5)	207 (24.4)
95% confidence interval*	(21.7, 27.5)	(21.6, 27.4)
Comparison vs Placebo**		
Odds ratio (SE)		0.972 (0.117)
95% confidence interval***		(0.767, 1.230)
p-value		0.8106

* Wilson confidence intervals.
** Logistic regression includes terms for baseline EQ-VAS score (p<0.0001), age (p=0.0178), baseline eGFR (CKD-EPI) (p=0.5970), Treatment (p=0.2858), region (5 cat.) (p<0.0001), baseline diabetes status (3 cat.) (p=0.3523), sex (p=0.0733), baseline LVEF (3 cat.) (p=0.3384), baseline NTproBNP (<median, >= median) (p=0.0151) and Treatment by baseline NTproBNP (<median, >= median) interaction (p=0.4658).
***Wald confidence intervals.
2 patients were excluded as the subgroup variable was missing.

Data taken from study 1245.121 only.
LOCF: For a missing value at week 52 the last available post-baseline value before week 52 is imputed.
Median: 1910 [pg/mL]

Table R.1.2.1.16: 2 Responder analysis (displaying risk ratio) in EQ-VAS change from baseline at week 52 of <= -7 points (deterioration) by bl. NTproBNP (<median, >= median) (median based on total patients) - RS (LOCF-AD) - 1245.121

Subgroup Description	Placebo	Empa 10mg
Baseline NTproBNP (<median, >= median): < median		
Number of patients in analysis set	920	942
Number of analysed patients, N (%)	866 (100.0)	884 (100.0)
Number of patients with endpoint, N (%)	207 (23.9)	188 (21.3)
95% confidence interval*	(21.2, 26.9)	(18.7, 24.1)
Comparison vs Placebo**		
Risk ratio (SE)		0.899 (0.076)
95% confidence interval***		(0.762, 1.062)
p-value		0.2106
Baseline NTproBNP (<median, >= median): >= median		
Number of patients in analysis set	946	920
Number of analysed patients, N (%)	844 (100.0)	849 (100.0)
Number of patients with endpoint, N (%)	207 (24.5)	207 (24.4)
95% confidence interval*	(21.7, 27.5)	(21.6, 27.4)
Comparison vs Placebo**		
Risk ratio (SE)		0.974 (0.078)
95% confidence interval***		(0.832, 1.140)
p-value		0.7423

* Wilson confidence intervals.
** Log-linked Poisson model with robust estimate of variance includes terms for baseline EQ-VAS score (p<0.0001), age (p=0.0142), baseline eGFR (CKD-EPI) (p=0.6184), Treatment (p=0.2565), region (5 cat.) (p<0.0001), baseline diabetes status (3 cat.) (p=0.3829), sex (p=0.0891), baseline LVEF (3 cat.) (p=0.3602), baseline NTproBNP (<median, >= median) (p=0.0152) and Treatment by baseline NTproBNP (<median, >= median) interaction (p=0.4961).
***Wald confidence intervals.
2 patients were excluded as the subgroup variable was missing.

Data taken from study 1245.121 only.
LOCF: For a missing value at week 52 the last available post-baseline value before week 52 is imputed.
Median: 1910 [pg/mL]

Table R.1.2.1.16: 3 Responder analysis (displaying odds ratio) in EQ-VAS change from baseline at week 52 of > -7 points (stability) by bl. NTproBNP (<median, >= median) (median based on total patients) - RS (LOCF-AD) - 1245.121

Subgroup Description	Placebo	Empa 10mg
Baseline NTproBNP (<median, >= median): < median		
Number of patients in analysis set	920	942
Number of analysed patients, N (%)	866 (100.0)	884 (100.0)
Number of patients with endpoint, N (%)	659 (76.1)	696 (78.7)
95% confidence interval*	(73.1, 78.8)	(75.9, 81.3)
Comparison vs Placebo**		
Odds ratio (SE)		1.166 (0.141)
95% confidence interval***		(0.920, 1.477)
p-value		0.2049
Baseline NTproBNP (<median, >= median): >= median		
Number of patients in analysis set	946	920
Number of analysed patients, N (%)	844 (100.0)	849 (100.0)
Number of patients with endpoint, N (%)	637 (75.5)	642 (75.6)
95% confidence interval*	(72.5, 78.3)	(72.6, 78.4)
Comparison vs Placebo**		
Odds ratio (SE)		1.029 (0.124)
95% confidence interval***		(0.813, 1.303)
p-value		0.8106

* Wilson confidence intervals.
** Logistic regression includes terms for baseline EQ-VAS score (p<0.0001), age (p=0.0178), baseline eGFR (CKD-EPI) (p=0.5970), Treatment (p=0.2858), region (5 cat.) (p<0.0001), baseline diabetes status (3 cat.) (p=0.3523), sex (p=0.0733), baseline LVEF (3 cat.) (p=0.3384), baseline NTproBNP (<median, >= median) (p=0.0151) and Treatment by baseline NTproBNP (<median, >= median) interaction (p=0.4658).
***Wald confidence intervals.
2 patients were excluded as the subgroup variable was missing.

Data taken from study 1245.121 only.
LOCF: For a missing value at week 52 the last available post-baseline value before week 52 is imputed.
Median: 1910 [pg/mL]

Table R.1.2.1.16: 4 Responder analysis (displaying risk ratio) in EQ-VAS change from baseline at week 52 of > -7 points (stability) by bl. NTproBNP (<median, >= median) (median based on total patients) - RS (LOCF-AD) - 1245.121

Subgroup Description	Placebo	Empa 10mg
Baseline NTproBNP (<median, >= median): < median		
Number of patients in analysis set	920	942
Number of analysed patients, N (%)	866 (100.0)	884 (100.0)
Number of patients with endpoint, N (%)	659 (76.1)	696 (78.7)
95% confidence interval*	(73.1, 78.8)	(75.9, 81.3)
Comparison vs Placebo**		
Risk ratio (SE)		1.031 (0.026)
95% confidence interval***		(0.982, 1.082)
p-value		0.2247
Baseline NTproBNP (<median, >= median): >= median		
Number of patients in analysis set	946	920
Number of analysed patients, N (%)	844 (100.0)	849 (100.0)
Number of patients with endpoint, N (%)	637 (75.5)	642 (75.6)
95% confidence interval*	(72.5, 78.3)	(72.6, 78.4)
Comparison vs Placebo**		
Risk ratio (SE)		1.000 (0.026)
95% confidence interval***		(0.949, 1.053)
p-value		0.9868

* Wilson confidence intervals.
** Log-linked Poisson model with robust estimate of variance includes terms for baseline EQ-VAS score (p<0.0001), age (p=0.0301), baseline eGFR (CKD-EPI) (p=0.6829), Treatment (p=0.4126), region (5 cat.) (p<0.0001), baseline diabetes status (3 cat.) (p=0.2775), sex (p=0.0349), baseline LVEF (3 cat.) (p=0.4398), baseline NTproBNP (<median, >= median) (p=0.0076) and Treatment by baseline NTproBNP (<median, >= median) interaction (p=0.3984).
***Wald confidence intervals.
2 patients were excluded as the subgroup variable was missing.

Data taken from study 1245.121 only.
LOCF: For a missing value at week 52 the last available post-baseline value before week 52 is imputed.
Median: 1910 [pg/mL]

Table R.1.2.1.16: 5 Responder analysis (displaying odds ratio) in EQ-VAS change from baseline at week 52 of >= 7 points (improvement) by bl. NTproBNP (<median, >= median) (median based on total patients) - RS (LOCF-AD) - 1245.121

Subgroup Description	Placebo	Empa 10mg
Baseline NTproBNP (<median, >= median): < median		
Number of patients in analysis set	920	942
Number of analysed patients, N (%)	866 (100.0)	884 (100.0)
Number of patients with endpoint, N (%)	320 (37.0)	371 (42.0)
95% confidence interval*	(33.8, 40.2)	(38.8, 45.2)
Comparison vs Placebo**		
Odds ratio (SE)		1.266 (0.142)
95% confidence interval***		(1.016, 1.578)
p-value		0.0355
Baseline NTproBNP (<median, >= median): >= median		
Number of patients in analysis set	946	920
Number of analysed patients, N (%)	844 (100.0)	849 (100.0)
Number of patients with endpoint, N (%)	337 (39.9)	379 (44.6)
95% confidence interval*	(36.7, 43.3)	(41.3, 48.0)
Comparison vs Placebo**		
Odds ratio (SE)		1.317 (0.151)
95% confidence interval***		(1.052, 1.647)
p-value		0.0162

* Wilson confidence intervals.
** Logistic regression includes terms for baseline EQ-VAS score (p<0.0001), age (p=0.1848), baseline eGFR (CKD-EPI) (p=0.0449), Treatment (p=0.0014), region (5 cat.) (p<0.0001), baseline diabetes status (3 cat.) (p=0.9207), sex (p=0.4655), baseline LVEF (3 cat.) (p=0.7231), baseline NTproBNP (<median, >= median) (p=0.8858) and Treatment by baseline NTproBNP (<median, >= median) interaction (p=0.8085).
***Wald confidence intervals.
2 patients were excluded as the subgroup variable was missing.

Data taken from study 1245.121 only.
LOCF: For a missing value at week 52 the last available post-baseline value before week 52 is imputed.
Median: 1910 [pg/mL]

Table R.1.2.1.16: 6 Responder analysis (displaying risk ratio) in EQ-VAS change from baseline at week 52 of >= 7 points (improvement) by bl. NTproBNP (<median, >= median) (median based on total patients) - RS (LOCF-AD) - 1245.121

Subgroup Description	Placebo	Empa 10mg
Baseline NTproBNP (<median, >= median): < median		
Number of patients in analysis set	920	942
Number of analysed patients, N (%)	866 (100.0)	884 (100.0)
Number of patients with endpoint, N (%)	320 (37.0)	371 (42.0)
95% confidence interval*	(33.8, 40.2)	(38.8, 45.2)
Comparison vs Placebo**		
Risk ratio (SE)		1.119 (0.059)
95% confidence interval***		(1.009, 1.241)
p-value		0.0331
Baseline NTproBNP (<median, >= median): >= median		
Number of patients in analysis set	946	920
Number of analysed patients, N (%)	844 (100.0)	849 (100.0)
Number of patients with endpoint, N (%)	337 (39.9)	379 (44.6)
95% confidence interval*	(36.7, 43.3)	(41.3, 48.0)
Comparison vs Placebo**		
Risk ratio (SE)		1.100 (0.058)
95% confidence interval***		(0.992, 1.220)
p-value		0.0719

* Wilson confidence intervals.
** Log-linked Poisson model with robust estimate of variance includes terms for baseline EQ-VAS score (p<0.0001), age (p=0.1688), baseline eGFR (CKD-EPI) (p=0.0768), Treatment (p=0.0055), region (5 cat.) (p<0.0001), baseline diabetes status (3 cat.) (p=0.8681), sex (p=0.2466), baseline LVEF (3 cat.) (p=0.7462), baseline NTproBNP (<median, >= median) (p=0.4811) and Treatment by baseline NTproBNP (<median, >= median) interaction (p=0.8175).
***Wald confidence intervals.
2 patients were excluded as the subgroup variable was missing.

Data taken from study 1245.121 only.
LOCF: For a missing value at week 52 the last available post-baseline value before week 52 is imputed.
Median: 1910 [pg/mL]

R.1.2.2

R.1.2.2 EQ-VAS responder analysis (10 points)

R.1.2.2.1

R.1.2.2.1 Overall analysis

Table R.1.2.2.1: 1 Responder analysis (displaying odds ratio) in EQ-VAS change from baseline at week 52 of <= -10 points (deterioration) - RS (LOCF-AD) - 1245.121

	Placebo	Empa 10mg
Number of patients in analysis set	1867	1863
Number of analysed patients, N (%)	1710 (100.0)	1733 (100.0)
Number of patients with endpoint, N (%)	409 (23.9)	386 (22.3)
95% confidence interval*	(22.0, 26.0)	(20.4, 24.3)
Comparison vs Placebo**		
Odds ratio (SE)		0.899 (0.077)
95% confidence interval***		(0.760, 1.063)
p-value		0.2126

* Wilson confidence intervals.
** Logistic regression includes terms for baseline EQ-VAS score (p<0.0001), age (p=0.0257), baseline eGFR (CKD-EPI) (p=0.2331), Treatment (p=0.2126), region (5 cat.) (p<0.0001), baseline diabetes status (3 cat.) (p=0.4751), sex (p=0.0453) and baseline LVEF (3 cat.) (p=0.3150).
***Wald confidence intervals.

Data taken from study 1245.121 only.
LOCF: For a missing value at week 52 the last available post-baseline value before week 52 is imputed.

Table R.1.2.2.1: 2 Responder analysis (displaying risk ratio) in EQ-VAS change from baseline at week 52 of <= -10 points (deterioration) - RS (LOCF-AD) - 1245.121

	Placebo	Empa 10mg
Number of patients in analysis set	1867	1863
Number of analysed patients, N (%)	1710 (100.0)	1733 (100.0)
Number of patients with endpoint, N (%)	409 (23.9)	386 (22.3)
95% confidence interval*	(22.0, 26.0)	(20.4, 24.3)
Comparison vs Placebo**		
Risk ratio (SE)		0.927 (0.055)
95% confidence interval***		(0.825, 1.041)
p-value		0.1996

* Wilson confidence intervals.
** Log-linked Poisson model with robust estimate of variance includes terms for baseline EQ-VAS score (p<0.0001), age (p=0.0216), baseline eGFR (CKD-EPI) (p=0.2415), Treatment (p=0.1996), region (5 cat.) (p<0.0001), baseline diabetes status (3 cat.) (p=0.5006), sex (p=0.0529) and baseline LVEF (3 cat.) (p=0.3398).
***Wald confidence intervals.

Data taken from study 1245.121 only.
LOCF: For a missing value at week 52 the last available post-baseline value before week 52 is imputed.

Table R.1.2.2.1: 3 Responder analysis (displaying odds ratio) in EQ-VAS change from baseline at week 52 of > -10 points (stability) - RS (LOCF-AD) - 1245.121

	Placebo	Empa 10mg
Number of patients in analysis set	1867	1863
Number of analysed patients, N (%)	1710 (100.0)	1733 (100.0)
Number of patients with endpoint, N (%)	1301 (76.1)	1347 (77.7)
95% confidence interval*	(74.0, 78.0)	(75.7, 79.6)
Comparison vs Placebo**		
Odds ratio (SE)		1.112 (0.095)
95% confidence interval***		(0.941, 1.315)
p-value		0.2126

* Wilson confidence intervals.
** Logistic regression includes terms for baseline EQ-VAS score (p<0.0001), age (p=0.0257), baseline eGFR (CKD-EPI) (p=0.2331), Treatment (p=0.2126), region (5 cat.) (p<0.0001), baseline diabetes status (3 cat.) (p=0.4751), sex (p=0.0453) and baseline LVEF (3 cat.) (p=0.3150).
***Wald confidence intervals.

Data taken from study 1245.121 only.
LOCF: For a missing value at week 52 the last available post-baseline value before week 52 is imputed.

Table R.1.2.2.1: 4 Responder analysis (displaying risk ratio) in EQ-VAS change from baseline at week 52 of > -10 points (stability) - RS (LOCF-AD) - 1245.121

	Placebo	Empa 10mg
Number of patients in analysis set	1867	1863
Number of analysed patients, N (%)	1710 (100.0)	1733 (100.0)
Number of patients with endpoint, N (%)	1301 (76.1)	1347 (77.7)
95% confidence interval*	(74.0, 78.0)	(75.7, 79.6)
Comparison vs Placebo**		
Risk ratio (SE)		1.019 (0.018)
95% confidence interval***		(0.984, 1.055)
p-value		0.3001

* Wilson confidence intervals.
** Log-linked Poisson model with robust estimate of variance includes terms for baseline EQ-VAS score (p<0.0001), age (p=0.0406), baseline eGFR (CKD-EPI) (p=0.2596), Treatment (p=0.3001), region (5 cat.) (p<0.0001), baseline diabetes status (3 cat.) (p=0.3685), sex (p=0.0250) and baseline LVEF (3 cat.) (p=0.4074).
***Wald confidence intervals.

Data taken from study 1245.121 only.
LOCF: For a missing value at week 52 the last available post-baseline value before week 52 is imputed.

Table R.1.2.2.1: 5 Responder analysis (displaying odds ratio) in EQ-VAS change from baseline at week 52 of >= 10 points (improvement) - RS (LOCF-AD) - 1245.121

	Placebo	Empa 10mg
Number of patients in analysis set	1867	1863
Number of analysed patients, N (%)	1710 (100.0)	1733 (100.0)
Number of patients with endpoint, N (%)	643 (37.6)	734 (42.4)
95% confidence interval*	(35.3, 39.9)	(40.0, 44.7)
Comparison vs Placebo**		
Odds ratio (SE)		1.289 (0.104)
95% confidence interval***		(1.100, 1.510)
p-value		0.0017

* Wilson confidence intervals.
** Logistic regression includes terms for baseline EQ-VAS score (p<0.0001), age (p=0.1745), baseline eGFR (CKD-EPI) (p=0.0384), Treatment (p=0.0017), region (5 cat.) (p<0.0001), baseline diabetes status (3 cat.) (p=0.7999), sex (p=0.8263) and baseline LVEF (3 cat.) (p=0.6244).
***Wald confidence intervals.

Data taken from study 1245.121 only.
LOCF: For a missing value at week 52 the last available post-baseline value before week 52 is imputed.

Table R.1.2.2.1: 6 Responder analysis (displaying risk ratio) in EQ-VAS change from baseline at week 52 of >= 10 points (improvement) - RS (LOCF-AD) - 1245.121

	Placebo	Empa 10mg
Number of patients in analysis set	1867	1863
Number of analysed patients, N (%)	1710 (100.0)	1733 (100.0)
Number of patients with endpoint, N (%)	643 (37.6)	734 (42.4)
95% confidence interval*	(35.3, 39.9)	(40.0, 44.7)
Comparison vs Placebo**		
Risk ratio (SE)		1.109 (0.042)
95% confidence interval***		(1.029, 1.195)
p-value		0.0067

* Wilson confidence intervals.
** Log-linked Poisson model with robust estimate of variance includes terms for baseline EQ-VAS score (p<0.0001), age (p=0.1513), baseline eGFR (CKD-EPI) (p=0.0529), Treatment (p=0.0067), region (5 cat.) (p<0.0001), baseline diabetes status (3 cat.) (p=0.8069), sex (p=0.5146) and baseline LVEF (3 cat.) (p=0.6842).
***Wald confidence intervals.

Data taken from study 1245.121 only.
LOCF: For a missing value at week 52 the last available post-baseline value before week 52 is imputed.

R.1.2.2.2

R.1.2.2.2 Subgroup analysis by sex

Table R.1.2.2.2: 1 Responder analysis (displaying odds ratio) in EQ-VAS change from baseline at week 52 of <= -10 points (deterioration) by sex - RS (LOCF-AD) - 1245.121

Subgroup Description	Placebo	Empa 10mg
Sex: Male		
Number of patients in analysis set	1411	1426
Number of analysed patients, N (%)	1297 (100.0)	1328 (100.0)
Number of patients with endpoint, N (%)	305 (23.5)	285 (21.5)
95% confidence interval*	(21.3, 25.9)	(19.3, 23.7)
Comparison vs Placebo**		
Odds ratio (SE)		0.873 (0.086)
95% confidence interval***		(0.720, 1.060)
p-value		0.1697
Sex: Female		
Number of patients in analysis set	456	437
Number of analysed patients, N (%)	413 (100.0)	405 (100.0)
Number of patients with endpoint, N (%)	104 (25.2)	101 (24.9)
95% confidence interval*	(21.2, 29.6)	(21.0, 29.4)
Comparison vs Placebo**		
Odds ratio (SE)		0.981 (0.169)
95% confidence interval***		(0.701, 1.374)
p-value		0.9122

* Wilson confidence intervals.
** Logistic regression includes terms for baseline EQ-VAS score (p<0.0001), age (p=0.0246), baseline eGFR (CKD-EPI) (p=0.2316), Treatment (p=0.4358), region (5 cat.) (p<0.0001), baseline diabetes status (3 cat.) (p=0.4796), baseline LVEF (3 cat.) (p=0.3166), sex (p=0.0443) and Treatment by sex interaction (p=0.5569).
***Wald confidence intervals.

Data taken from study 1245.121 only.
LOCF: For a missing value at week 52 the last available post-baseline value before week 52 is imputed.

Table R.1.2.2.2: 2 Responder analysis (displaying risk ratio) in EQ-VAS change from baseline at week 52 of <= -10 points (deterioration) by sex - RS (LOCF-AD) - 1245.121

Subgroup Description	Placebo	Empa 10mg
Sex: Male		
Number of patients in analysis set	1411	1426
Number of analysed patients, N (%)	1297 (100.0)	1328 (100.0)
Number of patients with endpoint, N (%)	305 (23.5)	285 (21.5)
95% confidence interval*	(21.3, 25.9)	(19.3, 23.7)
Comparison vs Placebo**		
Risk ratio (SE)		0.908 (0.063)
95% confidence interval***		(0.792, 1.040)
p-value		0.1637
Sex: Female		
Number of patients in analysis set	456	437
Number of analysed patients, N (%)	413 (100.0)	405 (100.0)
Number of patients with endpoint, N (%)	104 (25.2)	101 (24.9)
95% confidence interval*	(21.2, 29.6)	(21.0, 29.4)
Comparison vs Placebo**		
Risk ratio (SE)		0.984 (0.111)
95% confidence interval***		(0.788, 1.229)
p-value		0.8884

* Wilson confidence intervals.
** Log-linked Poisson model with robust estimate of variance includes terms for baseline EQ-VAS score (p<0.0001), age (p=0.0204), baseline eGFR (CKD-EPI) (p=0.2421), Treatment (p=0.3954), region (5 cat.) (p<0.0001), baseline diabetes status (3 cat.) (p=0.5014), baseline LVEF (3 cat.) (p=0.3399), sex (p=0.0513) and Treatment by sex interaction (p=0.5432).
***Wald confidence intervals.

Data taken from study 1245.121 only.
LOCF: For a missing value at week 52 the last available post-baseline value before week 52 is imputed.

Table R.1.2.2.2: 3 Responder analysis (displaying odds ratio) in EQ-VAS change from baseline at week 52 of > -10 points (stability) by sex - RS (LOCF-AD) - 1245.121

Subgroup Description	Placebo	Empa 10mg
Sex: Male		
Number of patients in analysis set	1411	1426
Number of analysed patients, N (%)	1297 (100.0)	1328 (100.0)
Number of patients with endpoint, N (%)	992 (76.5)	1043 (78.5)
95% confidence interval*	(74.1, 78.7)	(76.3, 80.7)
Comparison vs Placebo**		
Odds ratio (SE)		1.145 (0.113)
95% confidence interval***		(0.944, 1.389)
p-value		0.1697
Sex: Female		
Number of patients in analysis set	456	437
Number of analysed patients, N (%)	413 (100.0)	405 (100.0)
Number of patients with endpoint, N (%)	309 (74.8)	304 (75.1)
95% confidence interval*	(70.4, 78.8)	(70.6, 79.0)
Comparison vs Placebo**		
Odds ratio (SE)		1.019 (0.175)
95% confidence interval***		(0.728, 1.427)
p-value		0.9122

* Wilson confidence intervals.
** Logistic regression includes terms for baseline EQ-VAS score (p<0.0001), age (p=0.0246), baseline eGFR (CKD-EPI) (p=0.2316), Treatment (p=0.4358), region (5 cat.) (p<0.0001), baseline diabetes status (3 cat.) (p=0.4796), baseline LVEF (3 cat.) (p=0.3166), sex (p=0.0443) and Treatment by sex interaction (p=0.5569).
***Wald confidence intervals.

Data taken from study 1245.121 only.
LOCF: For a missing value at week 52 the last available post-baseline value before week 52 is imputed.

Table R.1.2.2.2: 4 Responder analysis (displaying risk ratio) in EQ-VAS change from baseline at week 52 of > -10 points (stability) by sex - RS (LOCF-AD) - 1245.121

Subgroup Description	Placebo	Empa 10mg
Sex: Male		
Number of patients in analysis set	1411	1426
Number of analysed patients, N (%)	1297 (100.0)	1328 (100.0)
Number of patients with endpoint, N (%)	992 (76.5)	1043 (78.5)
95% confidence interval*	(74.1, 78.7)	(76.3, 80.7)
Comparison vs Placebo**		
Risk ratio (SE)		1.026 (0.021)
95% confidence interval***		(0.986, 1.067)
p-value		0.2098
Sex: Female		
Number of patients in analysis set	456	437
Number of analysed patients, N (%)	413 (100.0)	405 (100.0)
Number of patients with endpoint, N (%)	309 (74.8)	304 (75.1)
95% confidence interval*	(70.4, 78.8)	(70.6, 79.0)
Comparison vs Placebo**		
Risk ratio (SE)		0.996 (0.038)
95% confidence interval***		(0.924, 1.073)
p-value		0.9117

* Wilson confidence intervals.
** Log-linked Poisson model with robust estimate of variance includes terms for baseline EQ-VAS score (p<0.0001), age (p=0.0394), baseline eGFR (CKD-EPI) (p=0.2540), Treatment (p=0.6235), region (5 cat.) (p<0.0001), baseline diabetes status (3 cat.) (p=0.3728), baseline LVEF (3 cat.) (p=0.4140), sex (p=0.0253) and Treatment by sex interaction (p=0.4922).
***Wald confidence intervals.

Data taken from study 1245.121 only.
LOCF: For a missing value at week 52 the last available post-baseline value before week 52 is imputed.

Table R.1.2.2.2: 5 Responder analysis (displaying odds ratio) in EQ-VAS change from baseline at week 52 of >= 10 points (improvement) by sex - RS (LOCF-AD) - 1245.121

Subgroup Description	Placebo	Empa 10mg
Sex: Male		
Number of patients in analysis set	1411	1426
Number of analysed patients, N (%)	1297 (100.0)	1328 (100.0)
Number of patients with endpoint, N (%)	479 (36.9)	560 (42.2)
95% confidence interval*	(34.3, 39.6)	(39.5, 44.8)
Comparison vs Placebo**		
Odds ratio (SE)		1.336 (0.124)
95% confidence interval***		(1.115, 1.601)
p-value		0.0017
Sex: Female		
Number of patients in analysis set	456	437
Number of analysed patients, N (%)	413 (100.0)	405 (100.0)
Number of patients with endpoint, N (%)	164 (39.7)	174 (43.0)
95% confidence interval*	(35.1, 44.5)	(38.2, 47.8)
Comparison vs Placebo**		
Odds ratio (SE)		1.146 (0.191)
95% confidence interval***		(0.827, 1.590)
p-value		0.4127

* Wilson confidence intervals.
** Logistic regression includes terms for baseline EQ-VAS score (p<0.0001), age (p=0.1706), baseline eGFR (CKD-EPI) (p=0.0366), Treatment (p=0.0253), region (5 cat.) (p<0.0001), baseline diabetes status (3 cat.) (p=0.7941), baseline LVEF (3 cat.) (p=0.6137), sex (p=0.8246) and Treatment by sex interaction (p=0.4229).
***Wald confidence intervals.

Data taken from study 1245.121 only.
LOCF: For a missing value at week 52 the last available post-baseline value before week 52 is imputed.

Table R.1.2.2.2: 6 Responder analysis (displaying risk ratio) in EQ-VAS change from baseline at week 52 of >= 10 points (improvement) by sex - RS (LOCF-AD) - 1245.121

Subgroup Description	Placebo	Empa 10mg
Sex: Male		
Number of patients in analysis set	1411	1426
Number of analysed patients, N (%)	1297 (100.0)	1328 (100.0)
Number of patients with endpoint, N (%)	479 (36.9)	560 (42.2)
95% confidence interval*	(34.3, 39.6)	(39.5, 44.8)
Comparison vs Placebo**		
Risk ratio (SE)		1.136 (0.050)
95% confidence interval***		(1.042, 1.239)
p-value		0.0038
Sex: Female		
Number of patients in analysis set	456	437
Number of analysed patients, N (%)	413 (100.0)	405 (100.0)
Number of patients with endpoint, N (%)	164 (39.7)	174 (43.0)
95% confidence interval*	(35.1, 44.5)	(38.2, 47.8)
Comparison vs Placebo**		
Risk ratio (SE)		1.029 (0.078)
95% confidence interval***		(0.888, 1.193)
p-value		0.7045

* Wilson confidence intervals.
** Log-linked Poisson model with robust estimate of variance includes terms for baseline EQ-VAS score (p<0.0001), age (p=0.1521), baseline eGFR (CKD-EPI) (p=0.0491), Treatment (p=0.0740), region (5 cat.) (p<0.0001), baseline diabetes status (3 cat.) (p=0.8073), baseline LVEF (3 cat.) (p=0.6648), sex (p=0.5524) and Treatment by sex interaction (p=0.2568).
***Wald confidence intervals.

Data taken from study 1245.121 only.
LOCF: For a missing value at week 52 the last available post-baseline value before week 52 is imputed.

R.1.2.2.3

Table R.1.2.2.3: 1 Responder analysis (displaying odds ratio) in EQ-VAS change from baseline at week 52 of <= -10 points (deterioration) by age (2 cat.) - RS (LOCF-AD) - 1245.121

Subgroup Description	Placebo	Empa 10mg
Age [years] (2 cat.): < 65		
Number of patients in analysis set	740	675
Number of analysed patients, N (%)	675 (100.0)	632 (100.0)
Number of patients with endpoint, N (%)	146 (21.6)	120 (19.0)
95% confidence interval*	(18.7, 24.9)	(16.1, 22.2)
Comparison vs Placebo**		
Odds ratio (SE)		0.865 (0.126)
95% confidence interval***		(0.651, 1.151)
p-value		0.3211
Age [years] (2 cat.): >= 65		
Number of patients in analysis set	1127	1188
Number of analysed patients, N (%)	1035 (100.0)	1101 (100.0)
Number of patients with endpoint, N (%)	263 (25.4)	266 (24.2)
95% confidence interval*	(22.9, 28.2)	(21.7, 26.8)
Comparison vs Placebo**		
Odds ratio (SE)		0.922 (0.098)
95% confidence interval***		(0.749, 1.135)
p-value		0.4435

* Wilson confidence intervals.
** Logistic regression includes terms for baseline EQ-VAS score (p<0.0001), baseline eGFR (CKD-EPI) (p=0.0345), Treatment (p=0.2096), region (5 cat.) (p<0.0001), baseline diabetes status (3 cat.) (p=0.5273), sex (p=0.0404), baseline LVEF (3 cat.) (p=0.3926), age (2 cat.) (p=0.4736) and Treatment by age (2 cat.) interaction (p=0.7249).
***Wald confidence intervals.

Data taken from study 1245.121 only.
LOCF: For a missing value at week 52 the last available post-baseline value before week 52 is imputed.

Table R.1.2.2.3: 2 Responder analysis (displaying risk ratio) in EQ-VAS change from baseline at week 52 of <= -10 points (deterioration) by age (2 cat.) - RS (LOCF-AD) - 1245.121

Subgroup Description	Placebo	Empa 10mg
Age [years] (2 cat.): < 65		
Number of patients in analysis set	740	675
Number of analysed patients, N (%)	675 (100.0)	632 (100.0)
Number of patients with endpoint, N (%)	146 (21.6)	120 (19.0)
95% confidence interval*	(18.7, 24.9)	(16.1, 22.2)
Comparison vs Placebo**		
Risk ratio (SE)		0.896 (0.094)
95% confidence interval***		(0.730, 1.101)
p-value		0.2980
Age [years] (2 cat.): >= 65		
Number of patients in analysis set	1127	1188
Number of analysed patients, N (%)	1035 (100.0)	1101 (100.0)
Number of patients with endpoint, N (%)	263 (25.4)	266 (24.2)
95% confidence interval*	(22.9, 28.2)	(21.7, 26.8)
Comparison vs Placebo**		
Risk ratio (SE)		0.945 (0.068)
95% confidence interval***		(0.821, 1.088)
p-value		0.4334

* Wilson confidence intervals.
** Log-linked Poisson model with robust estimate of variance includes terms for baseline EQ-VAS score (p<0.0001), baseline eGFR (CKD-EPI) (p=0.0343), Treatment (p=0.1922), region (5 cat.) (p<0.0001), baseline diabetes status (3 cat.) (p=0.5512), sex (p=0.0478), baseline LVEF (3 cat.) (p=0.4208), age (2 cat.) (p=0.4461) and Treatment by age (2 cat.) interaction (p=0.6785).
***Wald confidence intervals.

Data taken from study 1245.121 only.
LOCF: For a missing value at week 52 the last available post-baseline value before week 52 is imputed.

Table R.1.2.2.3: 3 Responder analysis (displaying odds ratio) in EQ-VAS change from baseline at week 52 of > -10 points (stability) by age (2 cat.) - RS (LOCF-AD) - 1245.121

Subgroup Description	Placebo	Empa 10mg
Age [years] (2 cat.): < 65		
Number of patients in analysis set	740	675
Number of analysed patients, N (%)	675 (100.0)	632 (100.0)
Number of patients with endpoint, N (%)	529 (78.4)	512 (81.0)
95% confidence interval*	(75.1, 81.3)	(77.8, 83.9)
Comparison vs Placebo**		
Odds ratio (SE)		1.155 (0.168)
95% confidence interval***		(0.869, 1.537)
p-value		0.3211
Age [years] (2 cat.): >= 65		
Number of patients in analysis set	1127	1188
Number of analysed patients, N (%)	1035 (100.0)	1101 (100.0)
Number of patients with endpoint, N (%)	772 (74.6)	835 (75.8)
95% confidence interval*	(71.8, 77.1)	(73.2, 78.3)
Comparison vs Placebo**		
Odds ratio (SE)		1.084 (0.115)
95% confidence interval***		(0.881, 1.334)
p-value		0.4435

* Wilson confidence intervals.
** Logistic regression includes terms for baseline EQ-VAS score (p<0.0001), baseline eGFR (CKD-EPI) (p=0.0345), Treatment (p=0.2096), region (5 cat.) (p<0.0001), baseline diabetes status (3 cat.) (p=0.5273), sex (p=0.0404), baseline LVEF (3 cat.) (p=0.3926), age (2 cat.) (p=0.4736) and Treatment by age (2 cat.) interaction (p=0.7249).
***Wald confidence intervals.

Data taken from study 1245.121 only.
LOCF: For a missing value at week 52 the last available post-baseline value before week 52 is imputed.

Table R.1.2.2.3: 4 Responder analysis (displaying risk ratio) in EQ-VAS change from baseline at week 52 of > -10 points (stability) by age (2 cat.) - RS (LOCF-AD) - 1245.121

Subgroup Description	Placebo	Empa 10mg
Age [years] (2 cat.): < 65		
Number of patients in analysis set	740	675
Number of analysed patients, N (%)	675 (100.0)	632 (100.0)
Number of patients with endpoint, N (%)	529 (78.4)	512 (81.0)
95% confidence interval*	(75.1, 81.3)	(77.8, 83.9)
Comparison vs Placebo**		
Risk ratio (SE)		1.021 (0.027)
95% confidence interval***		(0.969, 1.076)
p-value		0.4392
Age [years] (2 cat.): >= 65		
Number of patients in analysis set	1127	1188
Number of analysed patients, N (%)	1035 (100.0)	1101 (100.0)
Number of patients with endpoint, N (%)	772 (74.6)	835 (75.8)
95% confidence interval*	(71.8, 77.1)	(73.2, 78.3)
Comparison vs Placebo**		
Risk ratio (SE)		1.016 (0.024)
95% confidence interval***		(0.970, 1.065)
p-value		0.5059

* Wilson confidence intervals.
** Log-linked Poisson model with robust estimate of variance includes terms for baseline EQ-VAS score (p<0.0001), baseline eGFR (CKD-EPI) (p=0.0477), Treatment (p=0.3075), region (5 cat.) (p<0.0001), baseline diabetes status (3 cat.) (p=0.4082), sex (p=0.0227), baseline LVEF (3 cat.) (p=0.4912), age (2 cat.) (p=0.4955) and Treatment by age (2 cat.) interaction (p=0.8909).
***Wald confidence intervals.

Data taken from study 1245.121 only.
LOCF: For a missing value at week 52 the last available post-baseline value before week 52 is imputed.

Table R.1.2.2.3: 5 Responder analysis (displaying odds ratio) in EQ-VAS change from baseline at week 52 of >= 10 points (improvement) by age (2 cat.) - RS (LOCF-AD) - 1245.121

Subgroup Description	Placebo	Empa 10mg
Age [years] (2 cat.): < 65		
Number of patients in analysis set	740	675
Number of analysed patients, N (%)	675 (100.0)	632 (100.0)
Number of patients with endpoint, N (%)	278 (41.2)	309 (48.9)
95% confidence interval*	(37.5, 44.9)	(45.0, 52.8)
Comparison vs Placebo**		
Odds ratio (SE)		1.378 (0.179)
95% confidence interval***		(1.069, 1.777)
p-value		0.0133
Age [years] (2 cat.): >= 65		
Number of patients in analysis set	1127	1188
Number of analysed patients, N (%)	1035 (100.0)	1101 (100.0)
Number of patients with endpoint, N (%)	365 (35.3)	425 (38.6)
95% confidence interval*	(32.4, 38.2)	(35.8, 41.5)
Comparison vs Placebo**		
Odds ratio (SE)		1.234 (0.128)
95% confidence interval***		(1.007, 1.511)
p-value		0.0423

* Wilson confidence intervals.
** Logistic regression includes terms for baseline EQ-VAS score (p<0.0001), baseline eGFR (CKD-EPI) (p=0.0123), Treatment (p=0.0014), region (5 cat.) (p<0.0001), baseline diabetes status (3 cat.) (p=0.7931), sex (p=0.7759), baseline LVEF (3 cat.) (p=0.6097), age (2 cat.) (p=0.3117) and Treatment by age (2 cat.) interaction (p=0.5043).
***Wald confidence intervals.

Data taken from study 1245.121 only.
LOCF: For a missing value at week 52 the last available post-baseline value before week 52 is imputed.

Table R.1.2.2.3: 6 Responder analysis (displaying risk ratio) in EQ-VAS change from baseline at week 52 of >= 10 points (improvement) by age (2 cat.) - RS (LOCF-AD) - 1245.121

Subgroup Description	Placebo	Empa 10mg
Age [years] (2 cat.): < 65		
Number of patients in analysis set	740	675
Number of analysed patients, N (%)	675 (100.0)	632 (100.0)
Number of patients with endpoint, N (%)	278 (41.2)	309 (48.9)
95% confidence interval*	(37.5, 44.9)	(45.0, 52.8)
Comparison vs Placebo**		
Risk ratio (SE)		1.135 (0.064)
95% confidence interval***		(1.016, 1.268)
p-value		0.0253
Age [years] (2 cat.): >= 65		
Number of patients in analysis set	1127	1188
Number of analysed patients, N (%)	1035 (100.0)	1101 (100.0)
Number of patients with endpoint, N (%)	365 (35.3)	425 (38.6)
95% confidence interval*	(32.4, 38.2)	(35.8, 41.5)
Comparison vs Placebo**		
Risk ratio (SE)		1.089 (0.056)
95% confidence interval***		(0.984, 1.204)
p-value		0.0983

* Wilson confidence intervals.
** Log-linked Poisson model with robust estimate of variance includes terms for baseline EQ-VAS score (p<0.0001), baseline eGFR (CKD-EPI) (p=0.0208), Treatment (p=0.0056), region (5 cat.) (p<0.0001), baseline diabetes status (3 cat.) (p=0.8201), sex (p=0.4748), baseline LVEF (3 cat.) (p=0.6544), age (2 cat.) (p=0.2416) and Treatment by age (2 cat.) interaction (p=0.5878).
***Wald confidence intervals.

Data taken from study 1245.121 only.
LOCF: For a missing value at week 52 the last available post-baseline value before week 52 is imputed.

R.1.2.2.4 Subgroup analysis by region (North America, Latin America, Europe, Asia, Other)

Table R.1.2.2.4: 1 Responder analysis (displaying odds ratio) in EQ-VAS change from baseline at week 52 of <= -10 points (deterioration) by region - RS (LOCF-AD) - 1245.121

Subgroup Description	Placebo	Empa 10mg
Region (5 cat.): North America		
Number of patients in analysis set	213	212
Number of analysed patients, N (%)	192 (100.0)	204 (100.0)
Number of patients with endpoint, N (%)	48 (25.0)	50 (24.5)
95% confidence interval*	(19.4, 31.6)	(19.1, 30.8)
Comparison vs Placebo**		
Odds ratio (SE)		0.998 (0.245)
95% confidence interval***		(0.617, 1.614)
p-value		0.9937
Region (5 cat.): Latin America		
Number of patients in analysis set	645	641
Number of analysed patients, N (%)	577 (100.0)	583 (100.0)
Number of patients with endpoint, N (%)	123 (21.3)	123 (21.1)
95% confidence interval*	(18.2, 24.8)	(18.0, 24.6)
Comparison vs Placebo**		
Odds ratio (SE)		0.986 (0.150)
95% confidence interval***		(0.732, 1.327)
p-value		0.9252

* Wilson confidence intervals.
** Logistic regression includes terms for baseline EQ-VAS score (p<0.0001), age (p=0.0277), baseline eGFR (CKD-EPI) (p=0.2293), Treatment (p=0.0446), baseline diabetes status (3 cat.) (p=0.4594), sex (p=0.0472), baseline LVEF (3 cat.) (p=0.3086), region (5 cat.) (p<0.0001) and Treatment by region (5 cat.) interaction (p=0.4710).
***Wald confidence intervals.

Data taken from study 1245.121 only.
LOCF: For a missing value at week 52 the last available post-baseline value before week 52 is imputed.

Table R.1.2.2.4: 1 Responder analysis (displaying odds ratio) in EQ-VAS change from baseline at week 52 of <= -10 points (deterioration) by region - RS (LOCF-AD) - 1245.121

Subgroup Description	Placebo	Empa 10mg
Region (5 cat.): Europe		
Number of patients in analysis set	677	676
Number of analysed patients, N (%)	631 (100.0)	634 (100.0)
Number of patients with endpoint, N (%)	169 (26.8)	163 (25.7)
95% confidence interval*	(23.5, 30.4)	(22.5, 29.3)
Comparison vs Placebo**		
Odds ratio (SE)		0.897 (0.121)
95% confidence interval***		(0.689, 1.169)
p-value		0.4226
Region (5 cat.): Asia		
Number of patients in analysis set	245	248
Number of analysed patients, N (%)	233 (100.0)	236 (100.0)
Number of patients with endpoint, N (%)	58 (24.9)	47 (19.9)
95% confidence interval*	(19.8, 30.8)	(15.3, 25.5)
Comparison vs Placebo**		
Odds ratio (SE)		0.775 (0.179)
95% confidence interval***		(0.493, 1.219)
p-value		0.2707

* Wilson confidence intervals.
** Logistic regression includes terms for baseline EQ-VAS score (p<0.0001), age (p=0.0277), baseline eGFR (CKD-EPI) (p=0.2293), Treatment (p=0.0446), baseline diabetes status (3 cat.) (p=0.4594), sex (p=0.0472), baseline LVEF (3 cat.) (p=0.3086), region (5 cat.) (p<0.0001) and Treatment by region (5 cat.) interaction (p=0.4710).
***Wald confidence intervals.

Data taken from study 1245.121 only.
LOCF: For a missing value at week 52 the last available post-baseline value before week 52 is imputed.

Table R.1.2.2.4: 1 Responder analysis (displaying odds ratio) in EQ-VAS change from baseline at week 52 of <= -10 points (deterioration) by region - RS (LOCF-AD) - 1245.121

Subgroup Description	Placebo	Empa 10mg
Region (5 cat.): Other		
Number of patients in analysis set	87	86
Number of analysed patients, N (%)	77 (100.0)	76 (100.0)
Number of patients with endpoint, N (%)	11 (14.3)	3 (3.9)
95% confidence interval*	(8.2, 23.8)	(1.4, 11.0)
Comparison vs Placebo**		
Odds ratio (SE)		0.299 (0.205)
95% confidence interval***		(0.078, 1.144)
p-value		0.0779

* Wilson confidence intervals.
** Logistic regression includes terms for baseline EQ-VAS score (p<0.0001), age (p=0.0277), baseline eGFR (CKD-EPI) (p=0.2293), Treatment (p=0.0446), baseline diabetes status (3 cat.) (p=0.4594), sex (p=0.0472), baseline LVEF (3 cat.) (p=0.3086), region (5 cat.) (p<0.0001) and Treatment by region (5 cat.) interaction (p=0.4710).
***Wald confidence intervals.

Data taken from study 1245.121 only.
LOCF: For a missing value at week 52 the last available post-baseline value before week 52 is imputed.

Table R.1.2.2.4: 2 Responder analysis (displaying risk ratio) in EQ-VAS change from baseline at week 52 of <= -10 points (deterioration) by region - RS (LOCF-AD) - 1245.121

Subgroup Description	Placebo	Empa 10mg
Region (5 cat.): North America		
Number of patients in analysis set	213	212
Number of analysed patients, N (%)	192 (100.0)	204 (100.0)
Number of patients with endpoint, N (%)	48 (25.0)	50 (24.5)
95% confidence interval*	(19.4, 31.6)	(19.1, 30.8)
Comparison vs Placebo**		
Risk ratio (SE)		1.010 (0.173)
95% confidence interval***		(0.722, 1.413)
p-value		0.9555
Region (5 cat.): Latin America		
Number of patients in analysis set	645	641
Number of analysed patients, N (%)	577 (100.0)	583 (100.0)
Number of patients with endpoint, N (%)	123 (21.3)	123 (21.1)
95% confidence interval*	(18.2, 24.8)	(18.0, 24.6)
Comparison vs Placebo**		
Risk ratio (SE)		0.992 (0.105)
95% confidence interval***		(0.806, 1.222)
p-value		0.9433

* Wilson confidence intervals.
** Log-linked Poisson model with robust estimate of variance includes terms for baseline EQ-VAS score (p<0.0001), age (p=0.0238), baseline eGFR (CKD-EPI) (p=0.2354), Treatment (p=0.0433), baseline diabetes status (3 cat.) (p=0.4856), sex (p=0.0539), baseline LVEF (3 cat.) (p=0.3327), region (5 cat.) (p<0.0001) and Treatment by region (5 cat.) interaction (p=0.4217).
***Wald confidence intervals.

Data taken from study 1245.121 only.
LOCF: For a missing value at week 52 the last available post-baseline value before week 52 is imputed.

Table R.1.2.2.4: 2 Responder analysis (displaying risk ratio) in EQ-VAS change from baseline at week 52 of <= -10 points (deterioration) by region - RS (LOCF-AD) - 1245.121

Subgroup Description	Placebo	Empa 10mg
Region (5 cat.): Europe		
Number of patients in analysis set	677	676
Number of analysed patients, N (%)	631 (100.0)	634 (100.0)
Number of patients with endpoint, N (%)	169 (26.8)	163 (25.7)
95% confidence interval*	(23.5, 30.4)	(22.5, 29.3)
Comparison vs Placebo**		
Risk ratio (SE)		0.924 (0.084)
95% confidence interval***		(0.773, 1.103)
p-value		0.3801
Region (5 cat.): Asia		
Number of patients in analysis set	245	248
Number of analysed patients, N (%)	233 (100.0)	236 (100.0)
Number of patients with endpoint, N (%)	58 (24.9)	47 (19.9)
95% confidence interval*	(19.8, 30.8)	(15.3, 25.5)
Comparison vs Placebo**		
Risk ratio (SE)		0.829 (0.140)
95% confidence interval***		(0.595, 1.153)
p-value		0.2653

* Wilson confidence intervals.
** Log-linked Poisson model with robust estimate of variance includes terms for baseline EQ-VAS score (p<0.0001), age (p=0.0238), baseline eGFR (CKD-EPI) (p=0.2354), Treatment (p=0.0433), baseline diabetes status (3 cat.) (p=0.4856), sex (p=0.0539), baseline LVEF (3 cat.) (p=0.3327), region (5 cat.) (p<0.0001) and Treatment by region (5 cat.) interaction (p=0.4217).
***Wald confidence intervals.

Data taken from study 1245.121 only.
LOCF: For a missing value at week 52 the last available post-baseline value before week 52 is imputed.

Table R.1.2.2.4: 2 Responder analysis (displaying risk ratio) in EQ-VAS change from baseline at week 52 of <= -10 points (deterioration) by region - RS (LOCF-AD) - 1245.121

Subgroup Description	Placebo	Empa 10mg
Region (5 cat.): Other		
Number of patients in analysis set	87	86
Number of analysed patients, N (%)	77 (100.0)	76 (100.0)
Number of patients with endpoint, N (%)	11 (14.3)	3 (3.9)
95% confidence interval*	(8.2, 23.8)	(1.4, 11.0)
Comparison vs Placebo**		
Risk ratio (SE)		0.332 (0.204)
95% confidence interval***		(0.099, 1.110)
p-value		0.0733

* Wilson confidence intervals.
** Log-linked Poisson model with robust estimate of variance includes terms for baseline EQ-VAS score (p<0.0001), age (p=0.0238), baseline eGFR (CKD-EPI) (p=0.2354), Treatment (p=0.0433), baseline diabetes status (3 cat.) (p=0.4856), sex (p=0.0539), baseline LVEF (3 cat.) (p=0.3327), region (5 cat.) (p<0.0001) and Treatment by region (5 cat.) interaction (p=0.4217).
***Wald confidence intervals.

Data taken from study 1245.121 only.
LOCF: For a missing value at week 52 the last available post-baseline value before week 52 is imputed.

Table R.1.2.2.4: 3 Responder analysis (displaying odds ratio) in EQ-VAS change from baseline at week 52 of > -10 points (stability) by region - RS (LOCF-AD) - 1245.121

Subgroup Description	Placebo	Empa 10mg
Region (5 cat.): North America		
Number of patients in analysis set	213	212
Number of analysed patients, N (%)	192 (100.0)	204 (100.0)
Number of patients with endpoint, N (%)	144 (75.0)	154 (75.5)
95% confidence interval*	(68.4, 80.6)	(69.2, 80.9)
Comparison vs Placebo**		
Odds ratio (SE)		1.002 (0.246)
95% confidence interval***		(0.620, 1.620)
p-value		0.9937
Region (5 cat.): Latin America		
Number of patients in analysis set	645	641
Number of analysed patients, N (%)	577 (100.0)	583 (100.0)
Number of patients with endpoint, N (%)	454 (78.7)	460 (78.9)
95% confidence interval*	(75.2, 81.8)	(75.4, 82.0)
Comparison vs Placebo**		
Odds ratio (SE)		1.014 (0.154)
95% confidence interval***		(0.753, 1.366)
p-value		0.9252

* Wilson confidence intervals.
** Logistic regression includes terms for baseline EQ-VAS score (p<0.0001), age (p=0.0277), baseline eGFR (CKD-EPI) (p=0.2293), Treatment (p=0.0446), baseline diabetes status (3 cat.) (p=0.4594), sex (p=0.0472), baseline LVEF (3 cat.) (p=0.3086), region (5 cat.) (p<0.0001) and Treatment by region (5 cat.) interaction (p=0.4710).
***Wald confidence intervals.

Data taken from study 1245.121 only.
LOCF: For a missing value at week 52 the last available post-baseline value before week 52 is imputed.

Table R.1.2.2.4: 3 Responder analysis (displaying odds ratio) in EQ-VAS change from baseline at week 52 of > -10 points (stability) by region - RS (LOCF-AD) - 1245.121

Subgroup Description	Placebo	Empa 10mg
Region (5 cat.): Europe		
Number of patients in analysis set	677	676
Number of analysed patients, N (%)	631 (100.0)	634 (100.0)
Number of patients with endpoint, N (%)	462 (73.2)	471 (74.3)
95% confidence interval*	(69.6, 76.5)	(70.7, 77.5)
Comparison vs Placebo**		
Odds ratio (SE)		1.114 (0.150)
95% confidence interval***		(0.855, 1.451)
p-value		0.4226
Region (5 cat.): Asia		
Number of patients in analysis set	245	248
Number of analysed patients, N (%)	233 (100.0)	236 (100.0)
Number of patients with endpoint, N (%)	175 (75.1)	189 (80.1)
95% confidence interval*	(69.2, 80.2)	(74.5, 84.7)
Comparison vs Placebo**		
Odds ratio (SE)		1.289 (0.298)
95% confidence interval***		(0.820, 2.027)
p-value		0.2707

* Wilson confidence intervals.
** Logistic regression includes terms for baseline EQ-VAS score (p<0.0001), age (p=0.0277), baseline eGFR (CKD-EPI) (p=0.2293), Treatment (p=0.0446), baseline diabetes status (3 cat.) (p=0.4594), sex (p=0.0472), baseline LVEF (3 cat.) (p=0.3086), region (5 cat.) (p<0.0001) and Treatment by region (5 cat.) interaction (p=0.4710).
***Wald confidence intervals.

Data taken from study 1245.121 only.
LOCF: For a missing value at week 52 the last available post-baseline value before week 52 is imputed.

Table R.1.2.2.4: 3 Responder analysis (displaying odds ratio) in EQ-VAS change from baseline at week 52 of > -10 points (stability) by region - RS (LOCF-AD) - 1245.121

Subgroup Description	Placebo	Empa 10mg
Region (5 cat.): Other		
Number of patients in analysis set	87	86
Number of analysed patients, N (%)	77 (100.0)	76 (100.0)
Number of patients with endpoint, N (%)	66 (85.7)	73 (96.1)
95% confidence interval*	(76.2, 91.8)	(89.0, 98.6)
Comparison vs Placebo**		
Odds ratio (SE)		3.348 (2.294)
95% confidence interval***		(0.874,12.825)
p-value		0.0779

* Wilson confidence intervals.
** Logistic regression includes terms for baseline EQ-VAS score (p<0.0001), age (p=0.0277), baseline eGFR (CKD-EPI) (p=0.2293), Treatment (p=0.0446), baseline diabetes status (3 cat.) (p=0.4594), sex (p=0.0472), baseline LVEF (3 cat.) (p=0.3086), region (5 cat.) (p<0.0001) and Treatment by region (5 cat.) interaction (p=0.4710).
***Wald confidence intervals.

Data taken from study 1245.121 only.
LOCF: For a missing value at week 52 the last available post-baseline value before week 52 is imputed.

Table R.1.2.2.4: 4 Responder analysis (displaying risk ratio) in EQ-VAS change from baseline at week 52 of > -10 points (stability) by region - RS (LOCF-AD) - 1245.121

Subgroup Description	Placebo	Empa 10mg
Region (5 cat.): North America		
Number of patients in analysis set	213	212
Number of analysed patients, N (%)	192 (100.0)	204 (100.0)
Number of patients with endpoint, N (%)	144 (75.0)	154 (75.5)
95% confidence interval*	(68.4, 80.6)	(69.2, 80.9)
Comparison vs Placebo**		
Risk ratio (SE)		0.998 (0.056)
95% confidence interval***		(0.895, 1.114)
p-value		0.9768
Region (5 cat.): Latin America		
Number of patients in analysis set	645	641
Number of analysed patients, N (%)	577 (100.0)	583 (100.0)
Number of patients with endpoint, N (%)	454 (78.7)	460 (78.9)
95% confidence interval*	(75.2, 81.8)	(75.4, 82.0)
Comparison vs Placebo**		
Risk ratio (SE)		1.005 (0.029)
95% confidence interval***		(0.949, 1.063)
p-value		0.8759

* Wilson confidence intervals.
** Log-linked Poisson model with robust estimate of variance includes terms for baseline EQ-VAS score (p<0.0001), age (p=0.0411), baseline eGFR (CKD-EPI) (p=0.2610), Treatment (p=0.1633), baseline diabetes status (3 cat.) (p=0.3555), sex (p=0.0255), baseline LVEF (3 cat.) (p=0.3999), region (5 cat.) (p<0.0001) and Treatment by region (5 cat.) interaction (p=0.7917).
***Wald confidence intervals.

Data taken from study 1245.121 only.
LOCF: For a missing value at week 52 the last available post-baseline value before week 52 is imputed.

Table R.1.2.2.4: 4 Responder analysis (displaying risk ratio) in EQ-VAS change from baseline at week 52 of > -10 points (stability) by region - RS (LOCF-AD) - 1245.121

Subgroup Description	Placebo	Empa 10mg
Region (5 cat.): Europe		
Number of patients in analysis set	677	676
Number of analysed patients, N (%)	631 (100.0)	634 (100.0)
Number of patients with endpoint, N (%)	462 (73.2)	471 (74.3)
95% confidence interval*	(69.6, 76.5)	(70.7, 77.5)
Comparison vs Placebo**		
Risk ratio (SE)		1.020 (0.033)
95% confidence interval***		(0.958, 1.087)
p-value		0.5339
Region (5 cat.): Asia		
Number of patients in analysis set	245	248
Number of analysed patients, N (%)	233 (100.0)	236 (100.0)
Number of patients with endpoint, N (%)	175 (75.1)	189 (80.1)
95% confidence interval*	(69.2, 80.2)	(74.5, 84.7)
Comparison vs Placebo**		
Risk ratio (SE)		1.048 (0.051)
95% confidence interval***		(0.953, 1.154)
p-value		0.3342

* Wilson confidence intervals.
** Log-linked Poisson model with robust estimate of variance includes terms for baseline EQ-VAS score (p<0.0001), age (p=0.0411), baseline eGFR (CKD-EPI) (p=0.2610), Treatment (p=0.1633), baseline diabetes status (3 cat.) (p=0.3555), sex (p=0.0255), baseline LVEF (3 cat.) (p=0.3999), region (5 cat.) (p<0.0001) and Treatment by region (5 cat.) interaction (p=0.7917).
***Wald confidence intervals.

Data taken from study 1245.121 only.
LOCF: For a missing value at week 52 the last available post-baseline value before week 52 is imputed.

Table R.1.2.2.4: 4 Responder analysis (displaying risk ratio) in EQ-VAS change from baseline at week 52 of > -10 points (stability) by region - RS (LOCF-AD) - 1245.121

Subgroup Description	Placebo	Empa 10mg
Region (5 cat.): Other		
Number of patients in analysis set	87	86
Number of analysed patients, N (%)	77 (100.0)	76 (100.0)
Number of patients with endpoint, N (%)	66 (85.7)	73 (96.1)
95% confidence interval*	(76.2, 91.8)	(89.0, 98.6)
Comparison vs Placebo**		
Risk ratio (SE)		1.072 (0.054)
95% confidence interval***		(0.970, 1.184)
p-value		0.1708

* Wilson confidence intervals.
** Log-linked Poisson model with robust estimate of variance includes terms for baseline EQ-VAS score (p<0.0001), age (p=0.0411), baseline eGFR (CKD-EPI) (p=0.2610), Treatment (p=0.1633), baseline diabetes status (3 cat.) (p=0.3555), sex (p=0.0255), baseline LVEF (3 cat.) (p=0.3999), region (5 cat.) (p<0.0001) and Treatment by region (5 cat.) interaction (p=0.7917).
***Wald confidence intervals.

Data taken from study 1245.121 only.
LOCF: For a missing value at week 52 the last available post-baseline value before week 52 is imputed.

Table R.1.2.2.4: 5 Responder analysis (displaying odds ratio) in EQ-VAS change from baseline at week 52 of >= 10 points (improvement) by region - RS (LOCF-AD) - 1245.121

Subgroup Description	Placebo	Empa 10mg
Region (5 cat.): North America		
Number of patients in analysis set	213	212
Number of analysed patients, N (%)	192 (100.0)	204 (100.0)
Number of patients with endpoint, N (%)	57 (29.7)	74 (36.3)
95% confidence interval*	(23.7, 36.5)	(30.0, 43.1)
Comparison vs Placebo**		
Odds ratio (SE)		1.517 (0.377)
95% confidence interval***		(0.932, 2.468)
p-value		0.0937
Region (5 cat.): Latin America		
Number of patients in analysis set	645	641
Number of analysed patients, N (%)	577 (100.0)	583 (100.0)
Number of patients with endpoint, N (%)	251 (43.5)	282 (48.4)
95% confidence interval*	(39.5, 47.6)	(44.3, 52.4)
Comparison vs Placebo**		
Odds ratio (SE)		1.320 (0.182)
95% confidence interval***		(1.008, 1.728)
p-value		0.0439

* Wilson confidence intervals.
** Logistic regression includes terms for baseline EQ-VAS score (p<0.0001), age (p=0.1659), baseline eGFR (CKD-EPI) (p=0.0398), Treatment (p=0.0053), baseline diabetes status (3 cat.) (p=0.7961), sex (p=0.8297), baseline LVEF (3 cat.) (p=0.6288), region (5 cat.) (p<0.0001) and Treatment by region (5 cat.) interaction (p=0.9160).
***Wald confidence intervals.

Data taken from study 1245.121 only.
LOCF: For a missing value at week 52 the last available post-baseline value before week 52 is imputed.

Table R.1.2.2.4: 5 Responder analysis (displaying odds ratio) in EQ-VAS change from baseline at week 52 of >= 10 points (improvement) by region - RS (LOCF-AD) - 1245.121

Subgroup Description	Placebo	Empa 10mg
Region (5 cat.): Europe		
Number of patients in analysis set	677	676
Number of analysed patients, N (%)	631 (100.0)	634 (100.0)
Number of patients with endpoint, N (%)	215 (34.1)	230 (36.3)
95% confidence interval*	(30.5, 37.9)	(32.6, 40.1)
Comparison vs Placebo**		
Odds ratio (SE)		1.204 (0.162)
95% confidence interval***		(0.925, 1.569)
p-value		0.1677
Region (5 cat.): Asia		
Number of patients in analysis set	245	248
Number of analysed patients, N (%)	233 (100.0)	236 (100.0)
Number of patients with endpoint, N (%)	82 (35.2)	99 (41.9)
95% confidence interval*	(29.3, 41.5)	(35.8, 48.3)
Comparison vs Placebo**		
Odds ratio (SE)		1.217 (0.258)
95% confidence interval***		(0.803, 1.845)
p-value		0.3546

* Wilson confidence intervals.
** Logistic regression includes terms for baseline EQ-VAS score (p<0.0001), age (p=0.1659), baseline eGFR (CKD-EPI) (p=0.0398), Treatment (p=0.0053), baseline diabetes status (3 cat.) (p=0.7961), sex (p=0.8297), baseline LVEF (3 cat.) (p=0.6288), region (5 cat.) (p<0.0001) and Treatment by region (5 cat.) interaction (p=0.9160).
***Wald confidence intervals.

Data taken from study 1245.121 only.
LOCF: For a missing value at week 52 the last available post-baseline value before week 52 is imputed.

Table R.1.2.2.4: 5 Responder analysis (displaying odds ratio) in EQ-VAS change from baseline at week 52 of >= 10 points (improvement) by region - RS (LOCF-AD) - 1245.121

Subgroup Description	Placebo	Empa 10mg
Region (5 cat.): Other		
Number of patients in analysis set	87	86
Number of analysed patients, N (%)	77 (100.0)	76 (100.0)
Number of patients with endpoint, N (%)	38 (49.4)	49 (64.5)
95% confidence interval*	(38.5, 60.3)	(53.3, 74.3)
Comparison vs Placebo**		
Odds ratio (SE)		1.507 (0.564)
95% confidence interval***		(0.724, 3.138)
p-value		0.2733

* Wilson confidence intervals.
** Logistic regression includes terms for baseline EQ-VAS score (p<0.0001), age (p=0.1659), baseline eGFR (CKD-EPI) (p=0.0398), Treatment (p=0.0053), baseline diabetes status (3 cat.) (p=0.7961), sex (p=0.8297), baseline LVEF (3 cat.) (p=0.6288), region (5 cat.) (p<0.0001) and Treatment by region (5 cat.) interaction (p=0.9160).
***Wald confidence intervals.

Data taken from study 1245.121 only.
LOCF: For a missing value at week 52 the last available post-baseline value before week 52 is imputed.

Table R.1.2.2.4: 6 Responder analysis (displaying risk ratio) in EQ-VAS change from baseline at week 52 of >= 10 points (improvement) by region - RS (LOCF-AD) - 1245.121

Subgroup Description	Placebo	Empa 10mg
Region (5 cat.): North America		
Number of patients in analysis set	213	212
Number of analysed patients, N (%)	192 (100.0)	204 (100.0)
Number of patients with endpoint, N (%)	57 (29.7)	74 (36.3)
95% confidence interval*	(23.7, 36.5)	(30.0, 43.1)
Comparison vs Placebo**		
Risk ratio (SE)		1.158 (0.154)
95% confidence interval***		(0.892, 1.504)
p-value		0.2710
Region (5 cat.): Latin America		
Number of patients in analysis set	645	641
Number of analysed patients, N (%)	577 (100.0)	583 (100.0)
Number of patients with endpoint, N (%)	251 (43.5)	282 (48.4)
95% confidence interval*	(39.5, 47.6)	(44.3, 52.4)
Comparison vs Placebo**		
Risk ratio (SE)		1.120 (0.065)
95% confidence interval***		(1.000, 1.255)
p-value		0.0503

* Wilson confidence intervals.
** Log-linked Poisson model with robust estimate of variance includes terms for baseline EQ-VAS score (p<0.0001), age (p=0.1493), baseline eGFR (CKD-EPI) (p=0.0541), Treatment (p=0.0165), baseline diabetes status (3 cat.) (p=0.8115), sex (p=0.5068), baseline LVEF (3 cat.) (p=0.6880), region (5 cat.) (p<0.0001) and Treatment by region (5 cat.) interaction (p=0.9930).
***Wald confidence intervals.

Data taken from study 1245.121 only.
LOCF: For a missing value at week 52 the last available post-baseline value before week 52 is imputed.

Table R.1.2.2.4: 6 Responder analysis (displaying risk ratio) in EQ-VAS change from baseline at week 52 of >= 10 points (improvement) by region - RS (LOCF-AD) - 1245.121

Subgroup Description	Placebo	Empa 10mg
Region (5 cat.): Europe		
Number of patients in analysis set	677	676
Number of analysed patients, N (%)	631 (100.0)	634 (100.0)
Number of patients with endpoint, N (%)	215 (34.1)	230 (36.3)
95% confidence interval*	(30.5, 37.9)	(32.6, 40.1)
Comparison vs Placebo**		
Risk ratio (SE)		1.086 (0.077)
95% confidence interval***		(0.944, 1.249)
p-value		0.2484
Region (5 cat.): Asia		
Number of patients in analysis set	245	248
Number of analysed patients, N (%)	233 (100.0)	236 (100.0)
Number of patients with endpoint, N (%)	82 (35.2)	99 (41.9)
95% confidence interval*	(29.3, 41.5)	(35.8, 48.3)
Comparison vs Placebo**		
Risk ratio (SE)		1.093 (0.118)
95% confidence interval***		(0.885, 1.350)
p-value		0.4087

* Wilson confidence intervals.
** Log-linked Poisson model with robust estimate of variance includes terms for baseline EQ-VAS score (p<0.0001), age (p=0.1493), baseline eGFR (CKD-EPI) (p=0.0541), Treatment (p=0.0165), baseline diabetes status (3 cat.) (p=0.8115), sex (p=0.5068), baseline LVEF (3 cat.) (p=0.6880), region (5 cat.) (p<0.0001) and Treatment by region (5 cat.) interaction (p=0.9930).
***Wald confidence intervals.

Data taken from study 1245.121 only.
LOCF: For a missing value at week 52 the last available post-baseline value before week 52 is imputed.

Table R.1.2.2.4: 6 Responder analysis (displaying risk ratio) in EQ-VAS change from baseline at week 52 of >= 10 points (improvement) by region - RS (LOCF-AD) - 1245.121

Subgroup Description	Placebo	Empa 10mg
Region (5 cat.): Other		
Number of patients in analysis set	87	86
Number of analysed patients, N (%)	77 (100.0)	76 (100.0)
Number of patients with endpoint, N (%)	38 (49.4)	49 (64.5)
95% confidence interval*	(38.5, 60.3)	(53.3, 74.3)
Comparison vs Placebo**		
Risk ratio (SE)		1.121 (0.133)
95% confidence interval***		(0.889, 1.413)
p-value		0.3346

* Wilson confidence intervals.
** Log-linked Poisson model with robust estimate of variance includes terms for baseline EQ-VAS score (p<0.0001), age (p=0.1493), baseline eGFR (CKD-EPI) (p=0.0541), Treatment (p=0.0165), baseline diabetes status (3 cat.) (p=0.8115), sex (p=0.5068), baseline LVEF (3 cat.) (p=0.6880), region (5 cat.) (p<0.0001) and Treatment by region (5 cat.) interaction (p=0.9930).
***Wald confidence intervals.

Data taken from study 1245.121 only.
LOCF: For a missing value at week 52 the last available post-baseline value before week 52 is imputed.

R.1.2.2.5 Subgroup analysis by OECD (N/Y)

Table R.1.2.2.5: 1 Responder analysis (displaying odds ratio) in EQ-VAS change from baseline at week 52 of <= -10 points (deterioration) by OECD member (N/Y) - RS (LOCF-AD) - 1245.121

Subgroup Description	Placebo	Empa 10mg
OECD member: No		
Number of patients in analysis set	741	713
Number of analysed patients, N (%)	664 (100.0)	644 (100.0)
Number of patients with endpoint, N (%)	135 (20.3)	118 (18.3)
95% confidence interval*	(17.4, 23.6)	(15.5, 21.5)
Comparison vs Placebo**		
Odds ratio (SE)		0.893 (0.132)
95% confidence interval***		(0.669, 1.192)
p-value		0.4409
OECD member: Yes		
Number of patients in analysis set	1126	1150
Number of analysed patients, N (%)	1046 (100.0)	1089 (100.0)
Number of patients with endpoint, N (%)	274 (26.2)	268 (24.6)
95% confidence interval*	(23.6, 28.9)	(22.1, 27.3)
Comparison vs Placebo**		
Odds ratio (SE)		0.904 (0.095)
95% confidence interval***		(0.736, 1.109)
p-value		0.3339

* Wilson confidence intervals.
** Logistic regression includes terms for baseline EQ-VAS score (p<0.0001), age (p=0.0172), baseline eGFR (CKD-EPI) (p=0.1524), Treatment (p=0.2344), sex (p=0.0349), baseline diabetes status (3 cat.) (p=0.3607), baseline LVEF (3 cat.) (p=0.2710), OECD member (p=0.0034) and Treatment by OECD member interaction (p=0.9447).
***Wald confidence intervals.

Data taken from study 1245.121 only.
LOCF: For a missing value at week 52 the last available post-baseline value before week 52 is imputed.
OECD member (yes/no) countries included:
Yes: United States, Canada, Mexico, Poland, Netherlands, Hungary, Germany, Czech Republic, Italy, France, Spain, United Kingdom, Belgium, Japan, Australia, 'Korea; Republic Of South Korea';
No: Brazil, Argentina, China, India.

Table R.1.2.2.5: 2 Responder analysis (displaying risk ratio) in EQ-VAS change from baseline at week 52 of <= -10 points (deterioration) by OECD member (N/Y) - RS (LOCF-AD) - 1245.121

Subgroup Description	Placebo	Empa 10mg
OECD member: No		
Number of patients in analysis set	741	713
Number of analysed patients, N (%)	664 (100.0)	644 (100.0)
Number of patients with endpoint, N (%)	135 (20.3)	118 (18.3)
95% confidence interval*	(17.4, 23.6)	(15.5, 21.5)
Comparison vs Placebo**		
Risk ratio (SE)		0.920 (0.099)
95% confidence interval***		(0.746, 1.135)
p-value		0.4372
OECD member: Yes		
Number of patients in analysis set	1126	1150
Number of analysed patients, N (%)	1046 (100.0)	1089 (100.0)
Number of patients with endpoint, N (%)	274 (26.2)	268 (24.6)
95% confidence interval*	(23.6, 28.9)	(22.1, 27.3)
Comparison vs Placebo**		
Risk ratio (SE)		0.933 (0.067)
95% confidence interval***		(0.811, 1.074)
p-value		0.3353

* Wilson confidence intervals.
** Log-linked Poisson model with robust estimate of variance includes terms for baseline EQ-VAS score (p<0.0001), age (p=0.0154), baseline eGFR (CKD-EPI) (p=0.1475), Treatment (p=0.2363), sex (p=0.0412), baseline diabetes status (3 cat.) (p=0.3695), baseline LVEF (3 cat.) (p=0.3050), OECD member (p=0.0027) and Treatment by OECD member interaction (p=0.9123).
***Wald confidence intervals.

Data taken from study 1245.121 only.
LOCF: For a missing value at week 52 the last available post-baseline value before week 52 is imputed.
OECD member (yes/no) countries included:
Yes: United States, Canada, Mexico, Poland, Netherlands, Hungary, Germany, Czech Republic, Italy, France, Spain, United Kingdom, Belgium, Japan, Australia, 'Korea; Republic Of South Korea';
No: Brazil, Argentina, China, India.

Table R.1.2.2.5: 3 Responder analysis (displaying odds ratio) in EQ-VAS change from baseline at week 52 of > -10 points (stability) by OECD member (N/Y) - RS (LOCF-AD) - 1245.121

Subgroup Description	Placebo	Empa 10mg
OECD member: No		
Number of patients in analysis set	741	713
Number of analysed patients, N (%)	664 (100.0)	644 (100.0)
Number of patients with endpoint, N (%)	529 (79.7)	526 (81.7)
95% confidence interval*	(76.4, 82.6)	(78.5, 84.5)
Comparison vs Placebo**		
Odds ratio (SE)		1.120 (0.165)
95% confidence interval***		(0.839, 1.495)
p-value		0.4409
OECD member: Yes		
Number of patients in analysis set	1126	1150
Number of analysed patients, N (%)	1046 (100.0)	1089 (100.0)
Number of patients with endpoint, N (%)	772 (73.8)	821 (75.4)
95% confidence interval*	(71.1, 76.4)	(72.7, 77.9)
Comparison vs Placebo**		
Odds ratio (SE)		1.106 (0.116)
95% confidence interval***		(0.901, 1.358)
p-value		0.3339

* Wilson confidence intervals.
** Logistic regression includes terms for baseline EQ-VAS score (p<0.0001), age (p=0.0172), baseline eGFR (CKD-EPI) (p=0.1524), Treatment (p=0.2344), sex (p=0.0349), baseline diabetes status (3 cat.) (p=0.3607), baseline LVEF (3 cat.) (p=0.2710), OECD member (p=0.0034) and Treatment by OECD member interaction (p=0.9447).
***Wald confidence intervals.

Data taken from study 1245.121 only.
LOCF: For a missing value at week 52 the last available post-baseline value before week 52 is imputed.
OECD member (yes/no) countries included:
Yes: United States, Canada, Mexico, Poland, Netherlands, Hungary, Germany, Czech Republic, Italy, France, Spain, United Kingdom, Belgium, Japan, Australia, 'Korea; Republic Of South Korea';
No: Brazil, Argentina, China, India.

Table R.1.2.2.5: 4 Responder analysis (displaying risk ratio) in EQ-VAS change from baseline at week 52 of > -10 points (stability) by OECD member (N/Y) - RS (LOCF-AD) - 1245.121

Subgroup Description	Placebo	Empa 10mg
OECD member: No		
Number of patients in analysis set	741	713
Number of analysed patients, N (%)	664 (100.0)	644 (100.0)
Number of patients with endpoint, N (%)	529 (79.7)	526 (81.7)
95% confidence interval*	(76.4, 82.6)	(78.5, 84.5)
Comparison vs Placebo**		
Risk ratio (SE)		1.020 (0.026)
95% confidence interval***		(0.970, 1.073)
p-value		0.4402
OECD member: Yes		
Number of patients in analysis set	1126	1150
Number of analysed patients, N (%)	1046 (100.0)	1089 (100.0)
Number of patients with endpoint, N (%)	772 (73.8)	821 (75.4)
95% confidence interval*	(71.1, 76.4)	(72.7, 77.9)
Comparison vs Placebo**		
Risk ratio (SE)		1.020 (0.025)
95% confidence interval***		(0.973, 1.070)
p-value		0.4095

* Wilson confidence intervals.
** Log-linked Poisson model with robust estimate of variance includes terms for baseline EQ-VAS score (p<0.0001), age (p=0.0217), baseline eGFR (CKD-EPI) (p=0.1959), Treatment (p=0.2596), sex (p=0.0213), baseline diabetes status (3 cat.) (p=0.2782), baseline LVEF (3 cat.) (p=0.3304), OECD member (p=0.0041) and Treatment by OECD member interaction (p=0.9951).
***Wald confidence intervals.

Data taken from study 1245.121 only.
LOCF: For a missing value at week 52 the last available post-baseline value before week 52 is imputed.
OECD member (yes/no) countries included:
Yes: United States, Canada, Mexico, Poland, Netherlands, Hungary, Germany, Czech Republic, Italy, France, Spain, United Kingdom, Belgium, Japan, Australia, 'Korea; Republic Of South Korea';
No: Brazil, Argentina, China, India.

Table R.1.2.2.5: 5 Responder analysis (displaying odds ratio) in EQ-VAS change from baseline at week 52 of >= 10 points (improvement) by OECD member (N/Y) - RS (LOCF-AD) - 1245.121

Subgroup Description	Placebo	Empa 10mg
OECD member: No		
Number of patients in analysis set	741	713
Number of analysed patients, N (%)	664 (100.0)	644 (100.0)
Number of patients with endpoint, N (%)	299 (45.0)	326 (50.6)
95% confidence interval*	(41.3, 48.8)	(46.8, 54.5)
Comparison vs Placebo**		
Odds ratio (SE)		1.273 (0.163)
95% confidence interval***		(0.991, 1.635)
p-value		0.0588
OECD member: Yes		
Number of patients in analysis set	1126	1150
Number of analysed patients, N (%)	1046 (100.0)	1089 (100.0)
Number of patients with endpoint, N (%)	344 (32.9)	408 (37.5)
95% confidence interval*	(30.1, 35.8)	(34.6, 40.4)
Comparison vs Placebo**		
Odds ratio (SE)		1.316 (0.137)
95% confidence interval***		(1.074, 1.613)
p-value		0.0081

* Wilson confidence intervals.
** Logistic regression includes terms for baseline EQ-VAS score (p<0.0001), age (p=0.1025), baseline eGFR (CKD-EPI) (p=0.0232), Treatment (p=0.0017), sex (p=0.8023), baseline diabetes status (3 cat.) (p=0.6122), baseline LVEF (3 cat.) (p=0.4804), OECD member (p<0.0001) and Treatment by OECD member interaction (p=0.8388).
***Wald confidence intervals.

Data taken from study 1245.121 only.
LOCF: For a missing value at week 52 the last available post-baseline value before week 52 is imputed.
OECD member (yes/no) countries included:
Yes: United States, Canada, Mexico, Poland, Netherlands, Hungary, Germany, Czech Republic, Italy, France, Spain, United Kingdom, Belgium, Japan, Australia, 'Korea; Republic Of South Korea';
No: Brazil, Argentina, China, India.

Table R.1.2.2.5: 6 Responder analysis (displaying risk ratio) in EQ-VAS change from baseline at week 52 of >= 10 points (improvement) by OECD member (N/Y) - RS (LOCF-AD) - 1245.121

Subgroup Description	Placebo	Empa 10mg
OECD member: No		
Number of patients in analysis set	741	713
Number of analysed patients, N (%)	664 (100.0)	644 (100.0)
Number of patients with endpoint, N (%)	299 (45.0)	326 (50.6)
95% confidence interval*	(41.3, 48.8)	(46.8, 54.5)
Comparison vs Placebo**		
Risk ratio (SE)		1.104 (0.057)
95% confidence interval***		(0.997, 1.223)
p-value		0.0564
OECD member: Yes		
Number of patients in analysis set	1126	1150
Number of analysed patients, N (%)	1046 (100.0)	1089 (100.0)
Number of patients with endpoint, N (%)	344 (32.9)	408 (37.5)
95% confidence interval*	(30.1, 35.8)	(34.6, 40.4)
Comparison vs Placebo**		
Risk ratio (SE)		1.127 (0.062)
95% confidence interval***		(1.013, 1.255)
p-value		0.0286

* Wilson confidence intervals.
** Log-linked Poisson model with robust estimate of variance includes terms for baseline EQ-VAS score (p<0.0001), age (p=0.1170), baseline eGFR (CKD-EPI) (p=0.0386), Treatment (p=0.0037), sex (p=0.5162), baseline diabetes status (3 cat.) (p=0.5785), baseline LVEF (3 cat.) (p=0.5948), OECD member (p<0.0001) and Treatment by OECD member interaction (p=0.7840).
***Wald confidence intervals.

Data taken from study 1245.121 only.
LOCF: For a missing value at week 52 the last available post-baseline value before week 52 is imputed.
OECD member (yes/no) countries included:
Yes: United States, Canada, Mexico, Poland, Netherlands, Hungary, Germany, Czech Republic, Italy, France, Spain, United Kingdom, Belgium, Japan, Australia, 'Korea; Republic Of South Korea';
No: Brazil, Argentina, China, India.

R.1.2.2.6 Subgroup analysis by NYHA at baseline (II, III/IV - 2 cat.)

Table R.1.2.2.6: 1 Responder analysis (displaying odds ratio) in EQ-VAS change from baseline at week 52 of <= -10 points (deterioration) by NYHA (2 cat.) - RS (LOCF-AD) - 1245.121

Subgroup Description	Placebo	Empa 10mg
Baseline NYHA (2 cat.): II		
Number of patients in analysis set	1401	1399
Number of analysed patients, N (%)	1307 (100.0)	1303 (100.0)
Number of patients with endpoint, N (%)	304 (23.3)	288 (22.1)
95% confidence interval*	(21.0, 25.6)	(19.9, 24.4)
Comparison vs Placebo**		
Odds ratio (SE)		0.910 (0.090)
95% confidence interval***		(0.749, 1.104)
p-value		0.3372
Baseline NYHA (2 cat.): III/IV		
Number of patients in analysis set	466	464
Number of analysed patients, N (%)	403 (100.0)	430 (100.0)
Number of patients with endpoint, N (%)	105 (26.1)	98 (22.8)
95% confidence interval*	(22.0, 30.6)	(19.1, 27.0)
Comparison vs Placebo**		
Odds ratio (SE)		0.847 (0.147)
95% confidence interval***		(0.602, 1.190)
p-value		0.3385

* Wilson confidence intervals.
** Logistic regression includes terms for baseline EQ-VAS score (p<0.0001), age (p=0.0250), baseline eGFR (CKD-EPI) (p=0.3107), Treatment (p=0.1915), region (5 cat.) (p<0.0001), baseline diabetes status (3 cat.) (p=0.5530), sex (p=0.0919), baseline LVEF (3 cat.) (p=0.4023), baseline NYHA (2 cat.) (p<0.0001) and Treatment by baseline NYHA (2 cat.) interaction (p=0.7207).
***Wald confidence intervals.

Data taken from study 1245.121 only.
LOCF: For a missing value at week 52 the last available post-baseline value before week 52 is imputed.

Table R.1.2.2.6: 2 Responder analysis (displaying risk ratio) in EQ-VAS change from baseline at week 52 of <= -10 points (deterioration) by NYHA (2 cat.) - RS (LOCF-AD) - 1245.121

Subgroup Description	Placebo	Empa 10mg
Baseline NYHA (2 cat.): II		
Number of patients in analysis set	1401	1399
Number of analysed patients, N (%)	1307 (100.0)	1303 (100.0)
Number of patients with endpoint, N (%)	304 (23.3)	288 (22.1)
95% confidence interval*	(21.0, 25.6)	(19.9, 24.4)
Comparison vs Placebo**		
Risk ratio (SE)		0.935 (0.065)
95% confidence interval***		(0.816, 1.070)
p-value		0.3275
Baseline NYHA (2 cat.): III/IV		
Number of patients in analysis set	466	464
Number of analysed patients, N (%)	403 (100.0)	430 (100.0)
Number of patients with endpoint, N (%)	105 (26.1)	98 (22.8)
95% confidence interval*	(22.0, 30.6)	(19.1, 27.0)
Comparison vs Placebo**		
Risk ratio (SE)		0.896 (0.101)
95% confidence interval***		(0.719, 1.117)
p-value		0.3306

* Wilson confidence intervals.
** Log-linked Poisson model with robust estimate of variance includes terms for baseline EQ-VAS score (p<0.0001), age (p=0.0191), baseline eGFR (CKD-EPI) (p=0.3107), Treatment (p=0.1794), region (5 cat.) (p<0.0001), baseline diabetes status (3 cat.) (p=0.5536), sex (p=0.1027), baseline LVEF (3 cat.) (p=0.4175), baseline NYHA (2 cat.) (p<0.0001) and Treatment by baseline NYHA (2 cat.) interaction (p=0.7519).
***Wald confidence intervals.

Data taken from study 1245.121 only.
LOCF: For a missing value at week 52 the last available post-baseline value before week 52 is imputed.

Table R.1.2.2.6: 3 Responder analysis (displaying odds ratio) in EQ-VAS change from baseline at week 52 of > -10 points (stability) by NYHA (2 cat.) - RS (LOCF-AD) - 1245.121

Subgroup Description	Placebo	Empa 10mg
Baseline NYHA (2 cat.): II		
Number of patients in analysis set	1401	1399
Number of analysed patients, N (%)	1307 (100.0)	1303 (100.0)
Number of patients with endpoint, N (%)	1003 (76.7)	1015 (77.9)
95% confidence interval*	(74.4, 79.0)	(75.6, 80.1)
Comparison vs Placebo**		
Odds ratio (SE)		1.099 (0.109)
95% confidence interval***		(0.906, 1.334)
p-value		0.3372
Baseline NYHA (2 cat.): III/IV		
Number of patients in analysis set	466	464
Number of analysed patients, N (%)	403 (100.0)	430 (100.0)
Number of patients with endpoint, N (%)	298 (73.9)	332 (77.2)
95% confidence interval*	(69.4, 78.0)	(73.0, 80.9)
Comparison vs Placebo**		
Odds ratio (SE)		1.181 (0.205)
95% confidence interval***		(0.840, 1.660)
p-value		0.3385

* Wilson confidence intervals.
** Logistic regression includes terms for baseline EQ-VAS score (p<0.0001), age (p=0.0250), baseline eGFR (CKD-EPI) (p=0.3107), Treatment (p=0.1915), region (5 cat.) (p<0.0001), baseline diabetes status (3 cat.) (p=0.5530), sex (p=0.0919), baseline LVEF (3 cat.) (p=0.4023), baseline NYHA (2 cat.) (p<0.0001) and Treatment by baseline NYHA (2 cat.) interaction (p=0.7207).
***Wald confidence intervals.

Data taken from study 1245.121 only.
LOCF: For a missing value at week 52 the last available post-baseline value before week 52 is imputed.

Table R.1.2.2.6: 4 Responder analysis (displaying risk ratio) in EQ-VAS change from baseline at week 52 of > -10 points (stability) by NYHA (2 cat.) - RS (LOCF-AD) - 1245.121

Subgroup Description	Placebo	Empa 10mg
Baseline NYHA (2 cat.): II		
Number of patients in analysis set	1401	1399
Number of analysed patients, N (%)	1307 (100.0)	1303 (100.0)
Number of patients with endpoint, N (%)	1003 (76.7)	1015 (77.9)
95% confidence interval*	(74.4, 79.0)	(75.6, 80.1)
Comparison vs Placebo**		
Risk ratio (SE)		1.016 (0.021)
95% confidence interval***		(0.976, 1.058)
p-value		0.4275
Baseline NYHA (2 cat.): III/IV		
Number of patients in analysis set	466	464
Number of analysed patients, N (%)	403 (100.0)	430 (100.0)
Number of patients with endpoint, N (%)	298 (73.9)	332 (77.2)
95% confidence interval*	(69.4, 78.0)	(73.0, 80.9)
Comparison vs Placebo**		
Risk ratio (SE)		1.033 (0.038)
95% confidence interval***		(0.961, 1.110)
p-value		0.3793

* Wilson confidence intervals.
** Log-linked Poisson model with robust estimate of variance includes terms for baseline EQ-VAS score (p<0.0001), age (p=0.0484), baseline eGFR (CKD-EPI) (p=0.3195), Treatment (p=0.2492), region (5 cat.) (p<0.0001), baseline diabetes status (3 cat.) (p=0.4488), sex (p=0.0427), baseline LVEF (3 cat.) (p=0.5243), baseline NYHA (2 cat.) (p<0.0001) and Treatment by baseline NYHA (2 cat.) interaction (p=0.6999).
***Wald confidence intervals.

Data taken from study 1245.121 only.
LOCF: For a missing value at week 52 the last available post-baseline value before week 52 is imputed.

Table R.1.2.2.6: 5 Responder analysis (displaying odds ratio) in EQ-VAS change from baseline at week 52 of >= 10 points (improvement) by NYHA (2 cat.) - RS (LOCF-AD) - 1245.121

Subgroup Description	Placebo	Empa 10mg
Baseline NYHA (2 cat.): II		
Number of patients in analysis set	1401	1399
Number of analysed patients, N (%)	1307 (100.0)	1303 (100.0)
Number of patients with endpoint, N (%)	473 (36.2)	522 (40.1)
95% confidence interval*	(33.6, 38.8)	(37.4, 42.7)
Comparison vs Placebo**		
Odds ratio (SE)		1.258 (0.117)
95% confidence interval***		(1.049, 1.510)
p-value		0.0133
Baseline NYHA (2 cat.): III/IV		
Number of patients in analysis set	466	464
Number of analysed patients, N (%)	403 (100.0)	430 (100.0)
Number of patients with endpoint, N (%)	170 (42.2)	212 (49.3)
95% confidence interval*	(37.5, 47.1)	(44.6, 54.0)
Comparison vs Placebo**		
Odds ratio (SE)		1.422 (0.235)
95% confidence interval***		(1.030, 1.965)
p-value		0.0326

* Wilson confidence intervals.
** Logistic regression includes terms for baseline EQ-VAS score (p<0.0001), age (p=0.1795), baseline eGFR (CKD-EPI) (p=0.0517), Treatment (p=0.0021), region (5 cat.) (p<0.0001), baseline diabetes status (3 cat.) (p=0.6801), sex (p=0.9661), baseline LVEF (3 cat.) (p=0.5778), baseline NYHA (2 cat.) (p=0.0010) and Treatment by baseline NYHA (2 cat.) interaction (p=0.5173).
***Wald confidence intervals.

Data taken from study 1245.121 only.
LOCF: For a missing value at week 52 the last available post-baseline value before week 52 is imputed.

Table R.1.2.2.6: 6 Responder analysis (displaying risk ratio) in EQ-VAS change from baseline at week 52 of >= 10 points (improvement) by NYHA (2 cat.) - RS (LOCF-AD) - 1245.121

Subgroup Description	Placebo	Empa 10mg
Baseline NYHA (2 cat.): II		
Number of patients in analysis set	1401	1399
Number of analysed patients, N (%)	1307 (100.0)	1303 (100.0)
Number of patients with endpoint, N (%)	473 (36.2)	522 (40.1)
95% confidence interval*	(33.6, 38.8)	(37.4, 42.7)
Comparison vs Placebo**		
Risk ratio (SE)		1.106 (0.050)
95% confidence interval***		(1.013, 1.209)
p-value		0.0249
Baseline NYHA (2 cat.): III/IV		
Number of patients in analysis set	466	464
Number of analysed patients, N (%)	403 (100.0)	430 (100.0)
Number of patients with endpoint, N (%)	170 (42.2)	212 (49.3)
95% confidence interval*	(37.5, 47.1)	(44.6, 54.0)
Comparison vs Placebo**		
Risk ratio (SE)		1.124 (0.080)
95% confidence interval***		(0.978, 1.292)
p-value		0.0997

* Wilson confidence intervals.
** Log-linked Poisson model with robust estimate of variance includes terms for baseline EQ-VAS score (p<0.0001), age (p=0.1852), baseline eGFR (CKD-EPI) (p=0.0581), Treatment (p=0.0095), region (5 cat.) (p<0.0001), baseline diabetes status (3 cat.) (p=0.7282), sex (p=0.5927), baseline LVEF (3 cat.) (p=0.6038), baseline NYHA (2 cat.) (p=0.0009) and Treatment by baseline NYHA (2 cat.) interaction (p=0.8510).
***Wald confidence intervals.

Data taken from study 1245.121 only.
LOCF: For a missing value at week 52 the last available post-baseline value before week 52 is imputed.

R.1.2.2.7

R.1.2.2.7 Subgroup analysis by diabetes at baseline

Table R.1.2.2.7: 1 Responder analysis (displaying odds ratio) in EQ-VAS change from baseline at week 52 of <= -10 points (deterioration) by diabetes at baseline - RS (LOCF-AD) - 1245.121

Subgroup Description	Placebo	Empa 10mg
Diabetes at baseline (2 cat.): Diabetic		
Number of patients in analysis set	929	927
Number of analysed patients, N (%)	850 (100.0)	856 (100.0)
Number of patients with endpoint, N (%)	201 (23.6)	192 (22.4)
95% confidence interval*	(20.9, 26.6)	(19.8, 25.3)
Comparison vs Placebo**		
Odds ratio (SE)		0.926 (0.113)
95% confidence interval***		(0.730, 1.176)
p-value		0.5302
Diabetes at baseline (2 cat.): Non-Diabetic		
Number of patients in analysis set	938	936
Number of analysed patients, N (%)	860 (100.0)	877 (100.0)
Number of patients with endpoint, N (%)	208 (24.2)	194 (22.1)
95% confidence interval*	(21.4, 27.2)	(19.5, 25.0)
Comparison vs Placebo**		
Odds ratio (SE)		0.871 (0.105)
95% confidence interval***		(0.689, 1.102)
p-value		0.2505

* Wilson confidence intervals.
** Logistic regression includes terms for baseline EQ-VAS score (p<0.0001), age (p=0.0275), baseline eGFR (CKD-EPI) (p=0.2455), Treatment (p=0.2100), region (5 cat.) (p<0.0001), sex (p=0.0451), baseline LVEF (3 cat.) (p=0.3116), diabetes at baseline (2 cat.) (p=0.5900) and Treatment by diabetes at baseline (2 cat.) interaction (p=0.7188).
***Wald confidence intervals.

Data taken from study 1245.121 only.
LOCF: For a missing value at week 52 the last available post-baseline value before week 52 is imputed.

Table R.1.2.2.7: 2 Responder analysis (displaying risk ratio) in EQ-VAS change from baseline at week 52 of <= -10 points (deterioration) by diabetes at baseline - RS (LOCF-AD) - 1245.121

Subgroup Description	Placebo	Empa 10mg
Diabetes at baseline (2 cat.): Diabetic		
Number of patients in analysis set	929	927
Number of analysed patients, N (%)	850 (100.0)	856 (100.0)
Number of patients with endpoint, N (%)	201 (23.6)	192 (22.4)
95% confidence interval*	(20.9, 26.6)	(19.8, 25.3)
Comparison vs Placebo**		
Risk ratio (SE)		0.948 (0.079)
95% confidence interval***		(0.805, 1.116)
p-value		0.5200
Diabetes at baseline (2 cat.): Non-Diabetic		
Number of patients in analysis set	938	936
Number of analysed patients, N (%)	860 (100.0)	877 (100.0)
Number of patients with endpoint, N (%)	208 (24.2)	194 (22.1)
95% confidence interval*	(21.4, 27.2)	(19.5, 25.0)
Comparison vs Placebo**		
Risk ratio (SE)		0.906 (0.076)
95% confidence interval***		(0.768, 1.068)
p-value		0.2390

* Wilson confidence intervals.
** Log-linked Poisson model with robust estimate of variance includes terms for baseline EQ-VAS score (p<0.0001), age (p=0.0232), baseline eGFR (CKD-EPI) (p=0.2541), Treatment (p=0.1969), region (5 cat.) (p<0.0001), sex (p=0.0515), baseline LVEF (3 cat.) (p=0.3355), diabetes at baseline (2 cat.) (p=0.6237) and Treatment by diabetes at baseline (2 cat.) interaction (p=0.7013).
***Wald confidence intervals.

Data taken from study 1245.121 only.
LOCF: For a missing value at week 52 the last available post-baseline value before week 52 is imputed.

Table R.1.2.2.7: 3 Responder analysis (displaying odds ratio) in EQ-VAS change from baseline at week 52 of > -10 points (stability) by diabetes at baseline - RS (LOCF-AD) - 1245.121

Subgroup Description	Placebo	Empa 10mg
Diabetes at baseline (2 cat.): Diabetic		
Number of patients in analysis set	929	927
Number of analysed patients, N (%)	850 (100.0)	856 (100.0)
Number of patients with endpoint, N (%)	649 (76.4)	664 (77.6)
95% confidence interval*	(73.4, 79.1)	(74.7, 80.2)
Comparison vs Placebo**		
Odds ratio (SE)		1.079 (0.131)
95% confidence interval***		(0.850, 1.370)
p-value		0.5302
Diabetes at baseline (2 cat.): Non-Diabetic		
Number of patients in analysis set	938	936
Number of analysed patients, N (%)	860 (100.0)	877 (100.0)
Number of patients with endpoint, N (%)	652 (75.8)	683 (77.9)
95% confidence interval*	(72.8, 78.6)	(75.0, 80.5)
Comparison vs Placebo**		
Odds ratio (SE)		1.148 (0.138)
95% confidence interval***		(0.907, 1.452)
p-value		0.2505

* Wilson confidence intervals.
** Logistic regression includes terms for baseline EQ-VAS score (p<0.0001), age (p=0.0275), baseline eGFR (CKD-EPI) (p=0.2455), Treatment (p=0.2100), region (5 cat.) (p<0.0001), sex (p=0.0451), baseline LVEF (3 cat.) (p=0.3116), diabetes at baseline (2 cat.) (p=0.5900) and Treatment by diabetes at baseline (2 cat.) interaction (p=0.7188).
***Wald confidence intervals.

Data taken from study 1245.121 only.
LOCF: For a missing value at week 52 the last available post-baseline value before week 52 is imputed.

Table R.1.2.2.7: 4 Responder analysis (displaying risk ratio) in EQ-VAS change from baseline at week 52 of > -10 points (stability) by diabetes at baseline - RS (LOCF-AD) - 1245.121

Subgroup Description	Placebo	Empa 10mg
Diabetes at baseline (2 cat.): Diabetic		
Number of patients in analysis set	929	927
Number of analysed patients, N (%)	850 (100.0)	856 (100.0)
Number of patients with endpoint, N (%)	649 (76.4)	664 (77.6)
95% confidence interval*	(73.4, 79.1)	(74.7, 80.2)
Comparison vs Placebo**		
Risk ratio (SE)		1.012 (0.025)
95% confidence interval***		(0.963, 1.063)
p-value		0.6309
Diabetes at baseline (2 cat.): Non-Diabetic		
Number of patients in analysis set	938	936
Number of analysed patients, N (%)	860 (100.0)	877 (100.0)
Number of patients with endpoint, N (%)	652 (75.8)	683 (77.9)
95% confidence interval*	(72.8, 78.6)	(75.0, 80.5)
Comparison vs Placebo**		
Risk ratio (SE)		1.025 (0.026)
95% confidence interval***		(0.975, 1.078)
p-value		0.3282

* Wilson confidence intervals.
** Log-linked Poisson model with robust estimate of variance includes terms for baseline EQ-VAS score (p<0.0001), age (p=0.0445), baseline eGFR (CKD-EPI) (p=0.2774), Treatment (p=0.3020), region (5 cat.) (p<0.0001), sex (p=0.0254), baseline LVEF (3 cat.) (p=0.4008), diabetes at baseline (2 cat.) (p=0.4973) and Treatment by diabetes at baseline (2 cat.) interaction (p=0.7203).
***Wald confidence intervals.

Data taken from study 1245.121 only.
LOCF: For a missing value at week 52 the last available post-baseline value before week 52 is imputed.

Table R.1.2.2.7: 5 Responder analysis (displaying odds ratio) in EQ-VAS change from baseline at week 52 of >= 10 points (improvement) by diabetes at baseline - RS (LOCF-AD) - 1245.121

Subgroup Description	Placebo	Empa 10mg
Diabetes at baseline (2 cat.): Diabetic		
Number of patients in analysis set	929	927
Number of analysed patients, N (%)	850 (100.0)	856 (100.0)
Number of patients with endpoint, N (%)	323 (38.0)	381 (44.5)
95% confidence interval*	(34.8, 41.3)	(41.2, 47.9)
Comparison vs Placebo**		
Odds ratio (SE)		1.413 (0.162)
95% confidence interval***		(1.128, 1.769)
p-value		0.0026
Diabetes at baseline (2 cat.): Non-Diabetic		
Number of patients in analysis set	938	936
Number of analysed patients, N (%)	860 (100.0)	877 (100.0)
Number of patients with endpoint, N (%)	320 (37.2)	353 (40.3)
95% confidence interval*	(34.0, 40.5)	(37.1, 43.5)
Comparison vs Placebo**		
Odds ratio (SE)		1.178 (0.134)
95% confidence interval***		(0.943, 1.472)
p-value		0.1482

* Wilson confidence intervals.
** Logistic regression includes terms for baseline EQ-VAS score (p<0.0001), age (p=0.1808), baseline eGFR (CKD-EPI) (p=0.0385), Treatment (p=0.0016), region (5 cat.) (p<0.0001), sex (p=0.8101), baseline LVEF (3 cat.) (p=0.6223), diabetes at baseline (2 cat.) (p=0.5416) and Treatment by diabetes at baseline (2 cat.) interaction (p=0.2610).
***Wald confidence intervals.

Data taken from study 1245.121 only.
LOCF: For a missing value at week 52 the last available post-baseline value before week 52 is imputed.

Table R.1.2.2.7: 6 Responder analysis (displaying risk ratio) in EQ-VAS change from baseline at week 52 of >= 10 points (improvement) by diabetes at baseline - RS (LOCF-AD) - 1245.121

Subgroup Description	Placebo	Empa 10mg
Diabetes at baseline (2 cat.): Diabetic		
Number of patients in analysis set	929	927
Number of analysed patients, N (%)	850 (100.0)	856 (100.0)
Number of patients with endpoint, N (%)	323 (38.0)	381 (44.5)
95% confidence interval*	(34.8, 41.3)	(41.2, 47.9)
Comparison vs Placebo**		
Risk ratio (SE)		1.149 (0.060)
95% confidence interval***		(1.036, 1.274)
p-value		0.0084
Diabetes at baseline (2 cat.): Non-Diabetic		
Number of patients in analysis set	938	936
Number of analysed patients, N (%)	860 (100.0)	877 (100.0)
Number of patients with endpoint, N (%)	320 (37.2)	353 (40.3)
95% confidence interval*	(34.0, 40.5)	(37.1, 43.5)
Comparison vs Placebo**		
Risk ratio (SE)		1.068 (0.059)
95% confidence interval***		(0.958, 1.189)
p-value		0.2344

* Wilson confidence intervals.
** Log-linked Poisson model with robust estimate of variance includes terms for baseline EQ-VAS score (p<0.0001), age (p=0.1573), baseline eGFR (CKD-EPI) (p=0.0578), Treatment (p=0.0074), region (5 cat.) (p<0.0001), sex (p=0.5121), baseline LVEF (3 cat.) (p=0.6884), diabetes at baseline (2 cat.) (p=0.7252) and Treatment by diabetes at baseline (2 cat.) interaction (p=0.3368).
***Wald confidence intervals.

Data taken from study 1245.121 only.
LOCF: For a missing value at week 52 the last available post-baseline value before week 52 is imputed.

R.1.2.2.8 Subgroup analysis by BMI at baseline (<30, >=30)

Table R.1.2.2.8: 1 Responder analysis (displaying odds ratio) in EQ-VAS change from baseline at week 52 of <= -10 points (deterioration) by baseline BMI [kg/m2] - RS (LOCF-AD) - 1245.121

Subgroup Description	Placebo	Empa 10mg
Baseline BMI [kg/m²] (2 cat.): <30		
Number of patients in analysis set	1300	1263
Number of analysed patients, N (%)	1197 (100.0)	1179 (100.0)
Number of patients with endpoint, N (%)	288 (24.1)	250 (21.2)
95% confidence interval*	(21.7, 26.6)	(19.0, 23.6)
Comparison vs Placebo**		
Odds ratio (SE)		0.812 (0.084)
95% confidence interval***		(0.662, 0.995)
p-value		0.0445
Baseline BMI [kg/m²] (2 cat.): >=30		
Number of patients in analysis set	567	600
Number of analysed patients, N (%)	513 (100.0)	554 (100.0)
Number of patients with endpoint, N (%)	121 (23.6)	136 (24.5)
95% confidence interval*	(20.1, 27.4)	(21.1, 28.3)
Comparison vs Placebo**		
Odds ratio (SE)		1.106 (0.168)
95% confidence interval***		(0.821, 1.490)
p-value		0.5065

* Wilson confidence intervals.
** Logistic regression includes terms for baseline EQ-VAS score (p<0.0001), age (p=0.0113), baseline eGFR (CKD-EPI) (p=0.2575), Treatment (p=0.5584), region (5 cat.) (p<0.0001), baseline diabetes status (3 cat.) (p=0.5019), sex (p=0.0618), baseline LVEF (3 cat.) (p=0.2917), baseline BMI (2 cat.) (p=0.0197) and Treatment by baseline BMI (2 cat.) interaction (p=0.0926).
***Wald confidence intervals.

Data taken from study 1245.121 only.
LOCF: For a missing value at week 52 the last available post-baseline value before week 52 is imputed.

Table R.1.2.2.8: 2 Responder analysis (displaying risk ratio) in EQ-VAS change from baseline at week 52 of <= -10 points (deterioration) by baseline BMI [kg/m2] - RS (LOCF-AD) - 1245.121

Subgroup Description	Placebo	Empa 10mg
Baseline BMI [kg/m²] (2 cat.): <30		
Number of patients in analysis set	1300	1263
Number of analysed patients, N (%)	1197 (100.0)	1179 (100.0)
Number of patients with endpoint, N (%)	288 (24.1)	250 (21.2)
95% confidence interval*	(21.7, 26.6)	(19.0, 23.6)
Comparison vs Placebo**		
Risk ratio (SE)		0.863 (0.063)
95% confidence interval***		(0.749, 0.995)
p-value		0.0425
Baseline BMI [kg/m²] (2 cat.): >=30		
Number of patients in analysis set	567	600
Number of analysed patients, N (%)	513 (100.0)	554 (100.0)
Number of patients with endpoint, N (%)	121 (23.6)	136 (24.5)
95% confidence interval*	(20.1, 27.4)	(21.1, 28.3)
Comparison vs Placebo**		
Risk ratio (SE)		1.069 (0.110)
95% confidence interval***		(0.873, 1.309)
p-value		0.5204

* Wilson confidence intervals.
** Log-linked Poisson model with robust estimate of variance includes terms for baseline EQ-VAS score (p<0.0001), age (p=0.0095), baseline eGFR (CKD-EPI) (p=0.2620), Treatment (p=0.5236), region (5 cat.) (p<0.0001), baseline diabetes status (3 cat.) (p=0.5102), sex (p=0.0740), baseline LVEF (3 cat.) (p=0.3115), baseline BMI (2 cat.) (p=0.0142) and Treatment by baseline BMI (2 cat.) interaction (p=0.0911).
***Wald confidence intervals.

Data taken from study 1245.121 only.
LOCF: For a missing value at week 52 the last available post-baseline value before week 52 is imputed.

Table R.1.2.2.8: 3 Responder analysis (displaying odds ratio) in EQ-VAS change from baseline at week 52 of > -10 points (stability) by baseline BMI [kg/m2] - RS (LOCF-AD) - 1245.121

Subgroup Description	Placebo	Empa 10mg
Baseline BMI [kg/m²] (2 cat.): <30		
Number of patients in analysis set	1300	1263
Number of analysed patients, N (%)	1197 (100.0)	1179 (100.0)
Number of patients with endpoint, N (%)	909 (75.9)	929 (78.8)
95% confidence interval*	(73.4, 78.3)	(76.4, 81.0)
Comparison vs Placebo**		
Odds ratio (SE)		1.232 (0.128)
95% confidence interval***		(1.005, 1.510)
p-value		0.0445
Baseline BMI [kg/m²] (2 cat.): >=30		
Number of patients in analysis set	567	600
Number of analysed patients, N (%)	513 (100.0)	554 (100.0)
Number of patients with endpoint, N (%)	392 (76.4)	418 (75.5)
95% confidence interval*	(72.6, 79.9)	(71.7, 78.9)
Comparison vs Placebo**		
Odds ratio (SE)		0.904 (0.137)
95% confidence interval***		(0.671, 1.218)
p-value		0.5065

* Wilson confidence intervals.
** Logistic regression includes terms for baseline EQ-VAS score (p<0.0001), age (p=0.0113), baseline eGFR (CKD-EPI) (p=0.2575), Treatment (p=0.5584), region (5 cat.) (p<0.0001), baseline diabetes status (3 cat.) (p=0.5019), sex (p=0.0618), baseline LVEF (3 cat.) (p=0.2917), baseline BMI (2 cat.) (p=0.0197) and Treatment by baseline BMI (2 cat.) interaction (p=0.0926).
***Wald confidence intervals.

Data taken from study 1245.121 only.
LOCF: For a missing value at week 52 the last available post-baseline value before week 52 is imputed.

Table R.1.2.2.8: 4 Responder analysis (displaying risk ratio) in EQ-VAS change from baseline at week 52 of > -10 points (stability) by baseline BMI [kg/m2] - RS (LOCF-AD) - 1245.121

Subgroup Description	Placebo	Empa 10mg
Baseline BMI [kg/m²] (2 cat.): <30		
Number of patients in analysis set	1300	1263
Number of analysed patients, N (%)	1197 (100.0)	1179 (100.0)
Number of patients with endpoint, N (%)	909 (75.9)	929 (78.8)
95% confidence interval*	(73.4, 78.3)	(76.4, 81.0)
Comparison vs Placebo**		
Risk ratio (SE)		1.040 (0.022)
95% confidence interval***		(0.997, 1.084)
p-value		0.0669
Baseline BMI [kg/m²] (2 cat.): >=30		
Number of patients in analysis set	567	600
Number of analysed patients, N (%)	513 (100.0)	554 (100.0)
Number of patients with endpoint, N (%)	392 (76.4)	418 (75.5)
95% confidence interval*	(72.6, 79.9)	(71.7, 78.9)
Comparison vs Placebo**		
Risk ratio (SE)		0.976 (0.032)
95% confidence interval***		(0.915, 1.041)
p-value		0.4546

* Wilson confidence intervals.
** Log-linked Poisson model with robust estimate of variance includes terms for baseline EQ-VAS score (p<0.0001), age (p=0.0215), baseline eGFR (CKD-EPI) (p=0.2906), Treatment (p=0.7106), region (5 cat.) (p<0.0001), baseline diabetes status (3 cat.) (p=0.4219), sex (p=0.0334), baseline LVEF (3 cat.) (p=0.3872), baseline BMI (2 cat.) (p=0.0568) and Treatment by baseline BMI (2 cat.) interaction (p=0.1038).
***Wald confidence intervals.

Data taken from study 1245.121 only.
LOCF: For a missing value at week 52 the last available post-baseline value before week 52 is imputed.

Table R.1.2.2.8: 5 Responder analysis (displaying odds ratio) in EQ-VAS change from baseline at week 52 of >= 10 points (improvement) by baseline BMI [kg/m2] - RS (LOCF-AD) - 1245.121

Subgroup Description	Placebo	Empa 10mg
Baseline BMI [kg/m²] (2 cat.): <30		
Number of patients in analysis set	1300	1263
Number of analysed patients, N (%)	1197 (100.0)	1179 (100.0)
Number of patients with endpoint, N (%)	451 (37.7)	498 (42.2)
95% confidence interval*	(35.0, 40.5)	(39.4, 45.1)
Comparison vs Placebo**		
Odds ratio (SE)		1.331 (0.130)
95% confidence interval***		(1.100, 1.611)
p-value		0.0033
Baseline BMI [kg/m²] (2 cat.): >=30		
Number of patients in analysis set	567	600
Number of analysed patients, N (%)	513 (100.0)	554 (100.0)
Number of patients with endpoint, N (%)	192 (37.4)	236 (42.6)
95% confidence interval*	(33.3, 41.7)	(38.5, 46.8)
Comparison vs Placebo**		
Odds ratio (SE)		1.222 (0.178)
95% confidence interval***		(0.919, 1.625)
p-value		0.1682

* Wilson confidence intervals.
** Logistic regression includes terms for baseline EQ-VAS score (p<0.0001), age (p=0.0907), baseline eGFR (CKD-EPI) (p=0.0456), Treatment (p=0.0054), region (5 cat.) (p<0.0001), baseline diabetes status (3 cat.) (p=0.6261), sex (p=0.9147), baseline LVEF (3 cat.) (p=0.6453), baseline BMI (2 cat.) (p=0.0202) and Treatment by baseline BMI (2 cat.) interaction (p=0.6239).
***Wald confidence intervals.

Data taken from study 1245.121 only.
LOCF: For a missing value at week 52 the last available post-baseline value before week 52 is imputed.

Table R.1.2.2.8: 6 Responder analysis (displaying risk ratio) in EQ-VAS change from baseline at week 52 of >= 10 points (improvement) by baseline BMI [kg/m2] - RS (LOCF-AD) - 1245.121

Subgroup Description	Placebo	Empa 10mg
Baseline BMI [kg/m²] (2 cat.): <30		
Number of patients in analysis set	1300	1263
Number of analysed patients, N (%)	1197 (100.0)	1179 (100.0)
Number of patients with endpoint, N (%)	451 (37.7)	498 (42.2)
95% confidence interval*	(35.0, 40.5)	(39.4, 45.1)
Comparison vs Placebo**		
Risk ratio (SE)		1.128 (0.052)
95% confidence interval***		(1.031, 1.234)
p-value		0.0085
Baseline BMI [kg/m²] (2 cat.): >=30		
Number of patients in analysis set	567	600
Number of analysed patients, N (%)	513 (100.0)	554 (100.0)
Number of patients with endpoint, N (%)	192 (37.4)	236 (42.6)
95% confidence interval*	(33.3, 41.7)	(38.5, 46.8)
Comparison vs Placebo**		
Risk ratio (SE)		1.077 (0.074)
95% confidence interval***		(0.942, 1.232)
p-value		0.2789

* Wilson confidence intervals.
** Log-linked Poisson model with robust estimate of variance includes terms for baseline EQ-VAS score (p<0.0001), age (p=0.0946), baseline eGFR (CKD-EPI) (p=0.0618), Treatment (p=0.0183), region (5 cat.) (p<0.0001), baseline diabetes status (3 cat.) (p=0.6993), sex (p=0.5627), baseline LVEF (3 cat.) (p=0.6985), baseline BMI (2 cat.) (p=0.0959) and Treatment by baseline BMI (2 cat.) interaction (p=0.5748).
***Wald confidence intervals.

Data taken from study 1245.121 only.
LOCF: For a missing value at week 52 the last available post-baseline value before week 52 is imputed.

R.1.2.2.9 Subgroup analysis by eGFR at baseline (<60, >=60)

Table R.1.2.2.9: 1 Responder analysis (displaying odds ratio) in EQ-VAS change from baseline at week 52 of <= -10 points (deterioration) by baseline eGFR (2 cat.) - RS (LOCF-AD) - 1245.121

Subgroup Description	Placebo	Empa 10mg
Baseline eGFR (CKD-EPI) [mL/min/1.73m²] (2 cat.): >=60		
Number of patients in analysis set	960	969
Number of analysed patients, N (%)	875 (100.0)	900 (100.0)
Number of patients with endpoint, N (%)	190 (21.7)	186 (20.7)
95% confidence interval*	(19.1, 24.6)	(18.1, 23.4)
Comparison vs Placebo**		
Odds ratio (SE)		0.899 (0.110)
95% confidence interval***		(0.707, 1.144)
p-value		0.3875
Baseline eGFR (CKD-EPI) [mL/min/1.73m²] (2 cat.): <60		
Number of patients in analysis set	906	893
Number of analysed patients, N (%)	835 (100.0)	833 (100.0)
Number of patients with endpoint, N (%)	219 (26.2)	200 (24.0)
95% confidence interval*	(23.4, 29.3)	(21.2, 27.0)
Comparison vs Placebo**		
Odds ratio (SE)		0.901 (0.108)
95% confidence interval***		(0.713, 1.139)
p-value		0.3850

* Wilson confidence intervals.
** Logistic regression includes terms for baseline EQ-VAS score (p<0.0001), age (p=0.0131), Treatment (p=0.2205), region (5 cat.) (p<0.0001), baseline diabetes status (3 cat.) (p=0.4985), sex (p=0.0474), baseline LVEF (3 cat.) (p=0.3240), baseline eGFR (CKD-EPI) (2 cat.) (p=0.1628) and Treatment by baseline eGFR (CKD-EPI) (2 cat.) interaction (p=0.9895).
***Wald confidence intervals.
2 patients were excluded as the subgroup variable was missing.

Data taken from study 1245.121 only.
LOCF: For a missing value at week 52 the last available post-baseline value before week 52 is imputed.

Table R.1.2.2.9: 2 Responder analysis (displaying risk ratio) in EQ-VAS change from baseline at week 52 of <= -10 points (deterioration) by baseline eGFR (2 cat.) - RS (LOCF-AD) - 1245.121

Subgroup Description	Placebo	Empa 10mg
Baseline eGFR (CKD-EPI) [mL/min/1.73m²] (2 cat.): >=60		
Number of patients in analysis set	960	969
Number of analysed patients, N (%)	875 (100.0)	900 (100.0)
Number of patients with endpoint, N (%)	190 (21.7)	186 (20.7)
95% confidence interval*	(19.1, 24.6)	(18.1, 23.4)
Comparison vs Placebo**		
Risk ratio (SE)		0.924 (0.081)
95% confidence interval***		(0.778, 1.098)
p-value		0.3701
Baseline eGFR (CKD-EPI) [mL/min/1.73m²] (2 cat.): <60		
Number of patients in analysis set	906	893
Number of analysed patients, N (%)	835 (100.0)	833 (100.0)
Number of patients with endpoint, N (%)	219 (26.2)	200 (24.0)
95% confidence interval*	(23.4, 29.3)	(21.2, 27.0)
Comparison vs Placebo**		
Risk ratio (SE)		0.932 (0.075)
95% confidence interval***		(0.796, 1.091)
p-value		0.3821

* Wilson confidence intervals.
** Log-linked Poisson model with robust estimate of variance includes terms for baseline EQ-VAS score (p<0.0001), age (p=0.0110), Treatment (p=0.2097), region (5 cat.) (p<0.0001), baseline diabetes status (3 cat.) (p=0.5191), sex (p=0.0546), baseline LVEF (3 cat.) (p=0.3506), baseline eGFR (CKD-EPI) (2 cat.) (p=0.1645) and Treatment by baseline eGFR (CKD-EPI) (2 cat.) interaction (p=0.9455).
***Wald confidence intervals.
2 patients were excluded as the subgroup variable was missing.

Data taken from study 1245.121 only.
LOCF: For a missing value at week 52 the last available post-baseline value before week 52 is imputed.

Table R.1.2.2.9: 3 Responder analysis (displaying odds ratio) in EQ-VAS change from baseline at week 52 of > -10 points (stability) by baseline eGFR (2 cat.) - RS (LOCF-AD) - 1245.121

Subgroup Description	Placebo	Empa 10mg
Baseline eGFR (CKD-EPI) [mL/min/1.73m²] (2 cat.): >=60		
Number of patients in analysis set	960	969
Number of analysed patients, N (%)	875 (100.0)	900 (100.0)
Number of patients with endpoint, N (%)	685 (78.3)	714 (79.3)
95% confidence interval*	(75.4, 80.9)	(76.6, 81.9)
Comparison vs Placebo**		
Odds ratio (SE)		1.112 (0.136)
95% confidence interval***		(0.874, 1.414)
p-value		0.3875
Baseline eGFR (CKD-EPI) [mL/min/1.73m²] (2 cat.): <60		
Number of patients in analysis set	906	893
Number of analysed patients, N (%)	835 (100.0)	833 (100.0)
Number of patients with endpoint, N (%)	616 (73.8)	633 (76.0)
95% confidence interval*	(70.7, 76.6)	(73.0, 78.8)
Comparison vs Placebo**		
Odds ratio (SE)		1.109 (0.132)
95% confidence interval***		(0.878, 1.402)
p-value		0.3850

* Wilson confidence intervals.
** Logistic regression includes terms for baseline EQ-VAS score (p<0.0001), age (p=0.0131), Treatment (p=0.2205), region (5 cat.) (p<0.0001), baseline diabetes status (3 cat.) (p=0.4985), sex (p=0.0474), baseline LVEF (3 cat.) (p=0.3240), baseline eGFR (CKD-EPI) (2 cat.) (p=0.1628) and Treatment by baseline eGFR (CKD-EPI) (2 cat.) interaction (p=0.9895).
***Wald confidence intervals.
2 patients were excluded as the subgroup variable was missing.

Data taken from study 1245.121 only.
LOCF: For a missing value at week 52 the last available post-baseline value before week 52 is imputed.

Table R.1.2.2.9: 4 Responder analysis (displaying risk ratio) in EQ-VAS change from baseline at week 52 of > -10 points (stability) by baseline eGFR (2 cat.) - RS (LOCF-AD) - 1245.121

Subgroup Description	Placebo	Empa 10mg
Baseline eGFR (CKD-EPI) [mL/min/1.73m²] (2 cat.): >=60		
Number of patients in analysis set	960	969
Number of analysed patients, N (%)	875 (100.0)	900 (100.0)
Number of patients with endpoint, N (%)	685 (78.3)	714 (79.3)
95% confidence interval*	(75.4, 80.9)	(76.6, 81.9)
Comparison vs Placebo**		
Risk ratio (SE)		1.012 (0.024)
95% confidence interval***		(0.966, 1.061)
p-value		0.6029
Baseline eGFR (CKD-EPI) [mL/min/1.73m²] (2 cat.): <60		
Number of patients in analysis set	906	893
Number of analysed patients, N (%)	835 (100.0)	833 (100.0)
Number of patients with endpoint, N (%)	616 (73.8)	633 (76.0)
95% confidence interval*	(70.7, 76.6)	(73.0, 78.8)
Comparison vs Placebo**		
Risk ratio (SE)		1.025 (0.028)
95% confidence interval***		(0.972, 1.081)
p-value		0.3562

* Wilson confidence intervals.
** Log-linked Poisson model with robust estimate of variance includes terms for baseline EQ-VAS score (p<0.0001), age (p=0.0225), Treatment (p=0.2994), region (5 cat.) (p<0.0001), baseline diabetes status (3 cat.) (p=0.3951), sex (p=0.0277), baseline LVEF (3 cat.) (p=0.4078), baseline eGFR (CKD-EPI) (2 cat.) (p=0.1487) and Treatment by baseline eGFR (CKD-EPI) (2 cat.) interaction (p=0.7252).
***Wald confidence intervals.
2 patients were excluded as the subgroup variable was missing.

Data taken from study 1245.121 only.
LOCF: For a missing value at week 52 the last available post-baseline value before week 52 is imputed.

Table R.1.2.2.9: 5 Responder analysis (displaying odds ratio) in EQ-VAS change from baseline at week 52 of >= 10 points (improvement) by baseline eGFR (2 cat.) - RS (LOCF-AD) - 1245.121

Subgroup Description	Placebo	Empa 10mg
Baseline eGFR (CKD-EPI) [mL/min/1.73m²] (2 cat.): >=60		
Number of patients in analysis set	960	969
Number of analysed patients, N (%)	875 (100.0)	900 (100.0)
Number of patients with endpoint, N (%)	355 (40.6)	407 (45.2)
95% confidence interval*	(37.4, 43.9)	(42.0, 48.5)
Comparison vs Placebo**		
Odds ratio (SE)		1.281 (0.143)
95% confidence interval***		(1.030, 1.594)
p-value		0.0264
Baseline eGFR (CKD-EPI) [mL/min/1.73m²] (2 cat.): <60		
Number of patients in analysis set	906	893
Number of analysed patients, N (%)	835 (100.0)	833 (100.0)
Number of patients with endpoint, N (%)	288 (34.5)	327 (39.3)
95% confidence interval*	(31.3, 37.8)	(36.0, 42.6)
Comparison vs Placebo**		
Odds ratio (SE)		1.296 (0.152)
95% confidence interval***		(1.030, 1.631)
p-value		0.0270

* Wilson confidence intervals.
** Logistic regression includes terms for baseline EQ-VAS score (p<0.0001), age (p=0.1018), Treatment (p=0.0017), region (5 cat.) (p<0.0001), baseline diabetes status (3 cat.) (p=0.7914), sex (p=0.8625), baseline LVEF (3 cat.) (p=0.6235), baseline eGFR (CKD-EPI) (2 cat.) (p=0.0106) and Treatment by baseline eGFR (CKD-EPI) (2 cat.) interaction (p=0.9417).
***Wald confidence intervals.
2 patients were excluded as the subgroup variable was missing.

Data taken from study 1245.121 only.
LOCF: For a missing value at week 52 the last available post-baseline value before week 52 is imputed.

Table R.1.2.2.9: 6 Responder analysis (displaying risk ratio) in EQ-VAS change from baseline at week 52 of >= 10 points (improvement) by baseline eGFR (2 cat.) - RS (LOCF-AD) - 1245.121

Subgroup Description	Placebo	Empa 10mg
Baseline eGFR (CKD-EPI) [mL/min/1.73m²] (2 cat.): >=60		
Number of patients in analysis set	960	969
Number of analysed patients, N (%)	875 (100.0)	900 (100.0)
Number of patients with endpoint, N (%)	355 (40.6)	407 (45.2)
95% confidence interval*	(37.4, 43.9)	(42.0, 48.5)
Comparison vs Placebo**		
Risk ratio (SE)		1.087 (0.055)
95% confidence interval***		(0.985, 1.199)
p-value		0.0965
Baseline eGFR (CKD-EPI) [mL/min/1.73m²] (2 cat.): <60		
Number of patients in analysis set	906	893
Number of analysed patients, N (%)	835 (100.0)	833 (100.0)
Number of patients with endpoint, N (%)	288 (34.5)	327 (39.3)
95% confidence interval*	(31.3, 37.8)	(36.0, 42.6)
Comparison vs Placebo**		
Risk ratio (SE)		1.134 (0.066)
95% confidence interval***		(1.012, 1.272)
p-value		0.0307

* Wilson confidence intervals.
** Log-linked Poisson model with robust estimate of variance includes terms for baseline EQ-VAS score (p<0.0001), age (p=0.0917), Treatment (p=0.0065), region (5 cat.) (p<0.0001), baseline diabetes status (3 cat.) (p=0.8202), sex (p=0.5529), baseline LVEF (3 cat.) (p=0.6972), baseline eGFR (CKD-EPI) (2 cat.) (p=0.0155) and Treatment by baseline eGFR (CKD-EPI) (2 cat.) interaction (p=0.5804).
***Wald confidence intervals.
2 patients were excluded as the subgroup variable was missing.

Data taken from study 1245.121 only.
LOCF: For a missing value at week 52 the last available post-baseline value before week 52 is imputed.

R.1.2.2.10

Table R.1.2.2.10: 1 Responder analysis (displaying odds ratio) in EQ-VAS change from baseline at week 52 of <= -10 points (deterioration) by history of HHF - RS (LOCF-AD) - 1245.121

Subgroup Description	Placebo	Empa 10mg
History of HHF (in the last 12 months): No		
Number of patients in analysis set	1293	1286
Number of analysed patients, N (%)	1193 (100.0)	1209 (100.0)
Number of patients with endpoint, N (%)	285 (23.9)	271 (22.4)
95% confidence interval*	(21.6, 26.4)	(20.2, 24.9)
Comparison vs Placebo**		
Odds ratio (SE)		0.926 (0.095)
95% confidence interval***		(0.758, 1.132)
p-value		0.4536
History of HHF (in the last 12 months): Yes		
Number of patients in analysis set	574	577
Number of analysed patients, N (%)	517 (100.0)	524 (100.0)
Number of patients with endpoint, N (%)	124 (24.0)	115 (21.9)
95% confidence interval*	(20.5, 27.8)	(18.6, 25.7)
Comparison vs Placebo**		
Odds ratio (SE)		0.839 (0.130)
95% confidence interval***		(0.618, 1.138)
p-value		0.2579

* Wilson confidence intervals.
** Logistic regression includes terms for baseline EQ-VAS score (p<0.0001), age (p=0.0234), baseline eGFR (CKD-EPI) (p=0.2332), Treatment (p=0.1748), region (5 cat.) (p<0.0001), baseline diabetes status (3 cat.) (p=0.4766), sex (p=0.0443), baseline LVEF (3 cat.) (p=0.3122), history of HHF (in the last 12 months) (p=0.7783) and Treatment by history of HHF (in the last 12 months) interaction (p=0.5942).
***Wald confidence intervals.

Data taken from study 1245.121 only.
LOCF: For a missing value at week 52 the last available post-baseline value before week 52 is imputed.

Table R.1.2.2.10: 2 Responder analysis (displaying risk ratio) in EQ-VAS change from baseline at week 52 of <= -10 points (deterioration) by history of HHF - RS (LOCF-AD) - 1245.121

Subgroup Description	Placebo	Empa 10mg
History of HHF (in the last 12 months): No		
Number of patients in analysis set	1293	1286
Number of analysed patients, N (%)	1193 (100.0)	1209 (100.0)
Number of patients with endpoint, N (%)	285 (23.9)	271 (22.4)
95% confidence interval*	(21.6, 26.4)	(20.2, 24.9)
Comparison vs Placebo**		
Risk ratio (SE)		0.949 (0.067)
95% confidence interval***		(0.827, 1.089)
p-value		0.4562
History of HHF (in the last 12 months): Yes		
Number of patients in analysis set	574	577
Number of analysed patients, N (%)	517 (100.0)	524 (100.0)
Number of patients with endpoint, N (%)	124 (24.0)	115 (21.9)
95% confidence interval*	(20.5, 27.8)	(18.6, 25.7)
Comparison vs Placebo**		
Risk ratio (SE)		0.877 (0.096)
95% confidence interval***		(0.707, 1.087)
p-value		0.2303

* Wilson confidence intervals.
** Log-linked Poisson model with robust estimate of variance includes terms for baseline EQ-VAS score (p<0.0001), age (p=0.0195), baseline eGFR (CKD-EPI) (p=0.2417), Treatment (p=0.1574), region (5 cat.) (p<0.0001), baseline diabetes status (3 cat.) (p=0.5011), sex (p=0.0512), baseline LVEF (3 cat.) (p=0.3341), history of HHF (in the last 12 months) (p=0.7449) and Treatment by history of HHF (in the last 12 months) interaction (p=0.5437).
***Wald confidence intervals.

Data taken from study 1245.121 only.
LOCF: For a missing value at week 52 the last available post-baseline value before week 52 is imputed.

Table R.1.2.2.10: 3 Responder analysis (displaying odds ratio) in EQ-VAS change from baseline at week 52 of > -10 points (stability) by history of HHF - RS (LOCF-AD) - 1245.121

Subgroup Description	Placebo	Empa 10mg
History of HHF (in the last 12 months): No		
Number of patients in analysis set	1293	1286
Number of analysed patients, N (%)	1193 (100.0)	1209 (100.0)
Number of patients with endpoint, N (%)	908 (76.1)	938 (77.6)
95% confidence interval*	(73.6, 78.4)	(75.1, 79.8)
Comparison vs Placebo**		
Odds ratio (SE)		1.080 (0.111)
95% confidence interval***		(0.883, 1.320)
p-value		0.4536
History of HHF (in the last 12 months): Yes		
Number of patients in analysis set	574	577
Number of analysed patients, N (%)	517 (100.0)	524 (100.0)
Number of patients with endpoint, N (%)	393 (76.0)	409 (78.1)
95% confidence interval*	(72.2, 79.5)	(74.3, 81.4)
Comparison vs Placebo**		
Odds ratio (SE)		1.192 (0.185)
95% confidence interval***		(0.879, 1.617)
p-value		0.2579

* Wilson confidence intervals.
** Logistic regression includes terms for baseline EQ-VAS score (p<0.0001), age (p=0.0234), baseline eGFR (CKD-EPI) (p=0.2332), Treatment (p=0.1748), region (5 cat.) (p<0.0001), baseline diabetes status (3 cat.) (p=0.4766), sex (p=0.0443), baseline LVEF (3 cat.) (p=0.3122), history of HHF (in the last 12 months) (p=0.7783) and Treatment by history of HHF (in the last 12 months) interaction (p=0.5942).
***Wald confidence intervals.

Data taken from study 1245.121 only.
LOCF: For a missing value at week 52 the last available post-baseline value before week 52 is imputed.

Table R.1.2.2.10: 4 Responder analysis (displaying risk ratio) in EQ-VAS change from baseline at week 52 of > -10 points (stability) by history of HHF - RS (LOCF-AD) - 1245.121

Subgroup Description	Placebo	Empa 10mg
History of HHF (in the last 12 months): No		
Number of patients in analysis set	1293	1286
Number of analysed patients, N (%)	1193 (100.0)	1209 (100.0)
Number of patients with endpoint, N (%)	908 (76.1)	938 (77.6)
95% confidence interval*	(73.6, 78.4)	(75.1, 79.8)
Comparison vs Placebo**		
Risk ratio (SE)		1.015 (0.022)
95% confidence interval***		(0.974, 1.059)
p-value		0.4792
History of HHF (in the last 12 months): Yes		
Number of patients in analysis set	574	577
Number of analysed patients, N (%)	517 (100.0)	524 (100.0)
Number of patients with endpoint, N (%)	393 (76.0)	409 (78.1)
95% confidence interval*	(72.2, 79.5)	(74.3, 81.4)
Comparison vs Placebo**		
Risk ratio (SE)		1.027 (0.034)
95% confidence interval***		(0.963, 1.095)
p-value		0.4198

* Wilson confidence intervals.
** Log-linked Poisson model with robust estimate of variance includes terms for baseline EQ-VAS score (p<0.0001), age (p=0.0398), baseline eGFR (CKD-EPI) (p=0.2604), Treatment (p=0.2881), region (5 cat.) (p<0.0001), baseline diabetes status (3 cat.) (p=0.3679), sex (p=0.0250), baseline LVEF (3 cat.) (p=0.4052), history of HHF (in the last 12 months) (p=0.9613) and Treatment by history of HHF (in the last 12 months) interaction (p=0.7720).
***Wald confidence intervals.

Data taken from study 1245.121 only.
LOCF: For a missing value at week 52 the last available post-baseline value before week 52 is imputed.

Table R.1.2.2.10: 5 Responder analysis (displaying odds ratio) in EQ-VAS change from baseline at week 52 of >= 10 points (improvement) by history of HHF - RS (LOCF-AD) - 1245.121

Subgroup Description	Placebo	Empa 10mg
History of HHF (in the last 12 months): No		
Number of patients in analysis set	1293	1286
Number of analysed patients, N (%)	1193 (100.0)	1209 (100.0)
Number of patients with endpoint, N (%)	457 (38.3)	509 (42.1)
95% confidence interval*	(35.6, 41.1)	(39.3, 44.9)
Comparison vs Placebo**		
Odds ratio (SE)		1.230 (0.119)
95% confidence interval***		(1.017, 1.487)
p-value		0.0327
History of HHF (in the last 12 months): Yes		
Number of patients in analysis set	574	577
Number of analysed patients, N (%)	517 (100.0)	524 (100.0)
Number of patients with endpoint, N (%)	186 (36.0)	225 (42.9)
95% confidence interval*	(32.0, 40.2)	(38.8, 47.2)
Comparison vs Placebo**		
Odds ratio (SE)		1.432 (0.209)
95% confidence interval***		(1.075, 1.907)
p-value		0.0140

* Wilson confidence intervals.
** Logistic regression includes terms for baseline EQ-VAS score (p<0.0001), age (p=0.1578), baseline eGFR (CKD-EPI) (p=0.0393), Treatment (p=0.0013), region (5 cat.) (p<0.0001), baseline diabetes status (3 cat.) (p=0.7863), sex (p=0.8184), baseline LVEF (3 cat.) (p=0.5947), history of HHF (in the last 12 months) (p=0.6449) and Treatment by history of HHF (in the last 12 months) interaction (p=0.3851).
***Wald confidence intervals.

Data taken from study 1245.121 only.
LOCF: For a missing value at week 52 the last available post-baseline value before week 52 is imputed.

Table R.1.2.2.10: 6 Responder analysis (displaying risk ratio) in EQ-VAS change from baseline at week 52 of >= 10 points (improvement) by history of HHF - RS (LOCF-AD) - 1245.121

Subgroup Description	Placebo	Empa 10mg
History of HHF (in the last 12 months): No		
Number of patients in analysis set	1293	1286
Number of analysed patients, N (%)	1193 (100.0)	1209 (100.0)
Number of patients with endpoint, N (%)	457 (38.3)	509 (42.1)
95% confidence interval*	(35.6, 41.1)	(39.3, 44.9)
Comparison vs Placebo**		
Risk ratio (SE)		1.090 (0.049)
95% confidence interval***		(0.997, 1.191)
p-value		0.0571
History of HHF (in the last 12 months): Yes		
Number of patients in analysis set	574	577
Number of analysed patients, N (%)	517 (100.0)	524 (100.0)
Number of patients with endpoint, N (%)	186 (36.0)	225 (42.9)
95% confidence interval*	(32.0, 40.2)	(38.8, 47.2)
Comparison vs Placebo**		
Risk ratio (SE)		1.155 (0.082)
95% confidence interval***		(1.005, 1.327)
p-value		0.0418

* Wilson confidence intervals.
** Log-linked Poisson model with robust estimate of variance includes terms for baseline EQ-VAS score (p<0.0001), age (p=0.1400), baseline eGFR (CKD-EPI) (p=0.0555), Treatment (p=0.0061), region (5 cat.) (p<0.0001), baseline diabetes status (3 cat.) (p=0.7992), sex (p=0.5197), baseline LVEF (3 cat.) (p=0.6758), history of HHF (in the last 12 months) (p=0.7099) and Treatment by history of HHF (in the last 12 months) interaction (p=0.4884).
***Wald confidence intervals.

Data taken from study 1245.121 only.
LOCF: For a missing value at week 52 the last available post-baseline value before week 52 is imputed.

R.1.2.2.11

R.1.2.2.11 Subgroup analysis by cause of heart failure

Table R.1.2.2.11: 1 Responder analysis (displaying odds ratio) in EQ-VAS change from baseline at week 52 of <= -10 points (deterioration) by cause of heart failure - RS (LOCF-AD) - 1245.121

Subgroup Description	Placebo	Empa 10mg
Cause of heart failure: Ischemic		
Number of patients in analysis set	946	983
Number of analysed patients, N (%)	874 (100.0)	918 (100.0)
Number of patients with endpoint, N (%)	207 (23.7)	216 (23.5)
95% confidence interval*	(21.0, 26.6)	(20.9, 26.4)
Comparison vs Placebo**		
Odds ratio (SE)		0.997 (0.117)
95% confidence interval***		(0.791, 1.255)
p-value		0.9768
Cause of heart failure: Non-ischemic		
Number of patients in analysis set	921	880
Number of analysed patients, N (%)	836 (100.0)	815 (100.0)
Number of patients with endpoint, N (%)	202 (24.2)	170 (20.9)
95% confidence interval*	(21.4, 27.2)	(18.2, 23.8)
Comparison vs Placebo**		
Odds ratio (SE)		0.800 (0.100)
95% confidence interval***		(0.626, 1.021)
p-value		0.0734

* Wilson confidence intervals.
** Logistic regression includes terms for baseline EQ-VAS score (p<0.0001), age (p=0.0277), baseline eGFR (CKD-EPI) (p=0.2382), Treatment (p=0.1858), region (5 cat.) (p<0.0001), baseline diabetes status (3 cat.) (p=0.4901), sex (p=0.0444), baseline LVEF (3 cat.) (p=0.3096), cause of heart failure (p=0.6131) and Treatment by cause of heart failure interaction (p=0.1999).
***Wald confidence intervals.

Data taken from study 1245.121 only.
LOCF: For a missing value at week 52 the last available post-baseline value before week 52 is imputed.

Table R.1.2.2.11: 2 Responder analysis (displaying risk ratio) in EQ-VAS change from baseline at week 52 of <= -10 points (deterioration) by cause of heart failure - RS (LOCF-AD) - 1245.121

Subgroup Description	Placebo	Empa 10mg
Cause of heart failure: Ischemic		
Number of patients in analysis set	946	983
Number of analysed patients, N (%)	874 (100.0)	918 (100.0)
Number of patients with endpoint, N (%)	207 (23.7)	216 (23.5)
95% confidence interval*	(21.0, 26.6)	(20.9, 26.4)
Comparison vs Placebo**		
Risk ratio (SE)		0.996 (0.080)
95% confidence interval***		(0.850, 1.167)
p-value		0.9613
Cause of heart failure: Non-ischemic		
Number of patients in analysis set	921	880
Number of analysed patients, N (%)	836 (100.0)	815 (100.0)
Number of patients with endpoint, N (%)	202 (24.2)	170 (20.9)
95% confidence interval*	(21.4, 27.2)	(18.2, 23.8)
Comparison vs Placebo**		
Risk ratio (SE)		0.853 (0.075)
95% confidence interval***		(0.718, 1.013)
p-value		0.0695

* Wilson confidence intervals.
** Log-linked Poisson model with robust estimate of variance includes terms for baseline EQ-VAS score (p<0.0001), age (p=0.0237), baseline eGFR (CKD-EPI) (p=0.2401), Treatment (p=0.1710), region (5 cat.) (p<0.0001), baseline diabetes status (3 cat.) (p=0.5128), sex (p=0.0541), baseline LVEF (3 cat.) (p=0.3398), cause of heart failure (p=0.6188) and Treatment by cause of heart failure interaction (p=0.1931).
***Wald confidence intervals.

Data taken from study 1245.121 only.
LOCF: For a missing value at week 52 the last available post-baseline value before week 52 is imputed.

Table R.1.2.2.11: 3 Responder analysis (displaying odds ratio) in EQ-VAS change from baseline at week 52 of > -10 points (stability) by cause of heart failure - RS (LOCF-AD) - 1245.121

Subgroup Description	Placebo	Empa 10mg
Cause of heart failure: Ischemic		
Number of patients in analysis set	946	983
Number of analysed patients, N (%)	874 (100.0)	918 (100.0)
Number of patients with endpoint, N (%)	667 (76.3)	702 (76.5)
95% confidence interval*	(73.4, 79.0)	(73.6, 79.1)
Comparison vs Placebo**		
Odds ratio (SE)		1.003 (0.118)
95% confidence interval***		(0.797, 1.264)
p-value		0.9768
Cause of heart failure: Non-ischemic		
Number of patients in analysis set	921	880
Number of analysed patients, N (%)	836 (100.0)	815 (100.0)
Number of patients with endpoint, N (%)	634 (75.8)	645 (79.1)
95% confidence interval*	(72.8, 78.6)	(76.2, 81.8)
Comparison vs Placebo**		
Odds ratio (SE)		1.250 (0.156)
95% confidence interval***		(0.979, 1.597)
p-value		0.0734

* Wilson confidence intervals.
** Logistic regression includes terms for baseline EQ-VAS score (p<0.0001), age (p=0.0277), baseline eGFR (CKD-EPI) (p=0.2382), Treatment (p=0.1858), region (5 cat.) (p<0.0001), baseline diabetes status (3 cat.) (p=0.4901), sex (p=0.0444), baseline LVEF (3 cat.) (p=0.3096), cause of heart failure (p=0.6131) and Treatment by cause of heart failure interaction (p=0.1999).
***Wald confidence intervals.

Data taken from study 1245.121 only.
LOCF: For a missing value at week 52 the last available post-baseline value before week 52 is imputed.

Table R.1.2.2.11: 4 Responder analysis (displaying risk ratio) in EQ-VAS change from baseline at week 52 of > -10 points (stability) by cause of heart failure - RS (LOCF-AD) - 1245.121

Subgroup Description	Placebo	Empa 10mg
Cause of heart failure: Ischemic		
Number of patients in analysis set	946	983
Number of analysed patients, N (%)	874 (100.0)	918 (100.0)
Number of patients with endpoint, N (%)	667 (76.3)	702 (76.5)
95% confidence interval*	(73.4, 79.0)	(73.6, 79.1)
Comparison vs Placebo**		
Risk ratio (SE)		0.998 (0.025)
95% confidence interval***		(0.950, 1.049)
p-value		0.9472
Cause of heart failure: Non-ischemic		
Number of patients in analysis set	921	880
Number of analysed patients, N (%)	836 (100.0)	815 (100.0)
Number of patients with endpoint, N (%)	634 (75.8)	645 (79.1)
95% confidence interval*	(72.8, 78.6)	(76.2, 81.8)
Comparison vs Placebo**		
Risk ratio (SE)		1.041 (0.027)
95% confidence interval***		(0.991, 1.095)
p-value		0.1124

* Wilson confidence intervals.
** Log-linked Poisson model with robust estimate of variance includes terms for baseline EQ-VAS score (p<0.0001), age (p=0.0467), baseline eGFR (CKD-EPI) (p=0.2699), Treatment (p=0.2787), region (5 cat.) (p<0.0001), baseline diabetes status (3 cat.) (p=0.3895), sex (p=0.0245), baseline LVEF (3 cat.) (p=0.3986), cause of heart failure (p=0.6498) and Treatment by cause of heart failure interaction (p=0.2387).
***Wald confidence intervals.

Data taken from study 1245.121 only.
LOCF: For a missing value at week 52 the last available post-baseline value before week 52 is imputed.

Table R.1.2.2.11: 5 Responder analysis (displaying odds ratio) in EQ-VAS change from baseline at week 52 of >= 10 points (improvement) by cause of heart failure - RS (LOCF-AD) - 1245.121

Subgroup Description	Placebo	Empa 10mg
Cause of heart failure: Ischemic		
Number of patients in analysis set	946	983
Number of analysed patients, N (%)	874 (100.0)	918 (100.0)
Number of patients with endpoint, N (%)	304 (34.8)	383 (41.7)
95% confidence interval*	(31.7, 38.0)	(38.6, 44.9)
Comparison vs Placebo**		
Odds ratio (SE)		1.455 (0.165)
95% confidence interval***		(1.165, 1.816)
p-value		0.0009
Cause of heart failure: Non-ischemic		
Number of patients in analysis set	921	880
Number of analysed patients, N (%)	836 (100.0)	815 (100.0)
Number of patients with endpoint, N (%)	339 (40.6)	351 (43.1)
95% confidence interval*	(37.3, 43.9)	(39.7, 46.5)
Comparison vs Placebo**		
Odds ratio (SE)		1.142 (0.132)
95% confidence interval***		(0.910, 1.432)
p-value		0.2522

* Wilson confidence intervals.
** Logistic regression includes terms for baseline EQ-VAS score (p<0.0001), age (p=0.2370), baseline eGFR (CKD-EPI) (p=0.0424), Treatment (p=0.0017), region (5 cat.) (p<0.0001), baseline diabetes status (3 cat.) (p=0.6776), sex (p=0.6366), baseline LVEF (3 cat.) (p=0.6577), cause of heart failure (p=0.0716) and Treatment by cause of heart failure interaction (p=0.1344).
***Wald confidence intervals.

Data taken from study 1245.121 only.
LOCF: For a missing value at week 52 the last available post-baseline value before week 52 is imputed.

Table R.1.2.2.11: 6 Responder analysis (displaying risk ratio) in EQ-VAS change from baseline at week 52 of >= 10 points (improvement) by cause of heart failure - RS (LOCF-AD) - 1245.121

Subgroup Description	Placebo	Empa 10mg
Cause of heart failure: Ischemic		
Number of patients in analysis set	946	983
Number of analysed patients, N (%)	874 (100.0)	918 (100.0)
Number of patients with endpoint, N (%)	304 (34.8)	383 (41.7)
95% confidence interval*	(31.7, 38.0)	(38.6, 44.9)
Comparison vs Placebo**		
Risk ratio (SE)		1.180 (0.065)
95% confidence interval***		(1.059, 1.315)
p-value		0.0027
Cause of heart failure: Non-ischemic		
Number of patients in analysis set	921	880
Number of analysed patients, N (%)	836 (100.0)	815 (100.0)
Number of patients with endpoint, N (%)	339 (40.6)	351 (43.1)
95% confidence interval*	(37.3, 43.9)	(39.7, 46.5)
Comparison vs Placebo**		
Risk ratio (SE)		1.045 (0.055)
95% confidence interval***		(0.943, 1.159)
p-value		0.4005

* Wilson confidence intervals.
** Log-linked Poisson model with robust estimate of variance includes terms for baseline EQ-VAS score (p<0.0001), age (p=0.2191), baseline eGFR (CKD-EPI) (p=0.0529), Treatment (p=0.0059), region (5 cat.) (p<0.0001), baseline diabetes status (3 cat.) (p=0.7157), sex (p=0.3730), baseline LVEF (3 cat.) (p=0.6677), cause of heart failure (p=0.0845) and Treatment by cause of heart failure interaction (p=0.1117).
***Wald confidence intervals.

Data taken from study 1245.121 only.
LOCF: For a missing value at week 52 the last available post-baseline value before week 52 is imputed.

R.1.2.2.12 Subgroup analysis by heart failure physiology (LVEF <= 30% and NTproBNP<median; LVEF <= 30% and NTproBNP>=median; LVEF > 30%)

Table R.1.2.2.12: 1 Responder analysis (displaying odds ratio) in EQ-VAS change from baseline at week 52 of <= -10 points (deterioration) by heart failure physiology - RS (LOCF-AD) - 1245.121

Subgroup Description	Placebo	Empa 10mg
Heart failure physiology: LVEF <= 30% and NTproBNP < median		
Number of patients in analysis set	723	698
Number of analysed patients, N (%)	679 (100.0)	655 (100.0)
Number of patients with endpoint, N (%)	149 (21.9)	142 (21.7)
95% confidence interval*	(19.0, 25.2)	(18.7, 25.0)
Comparison vs Placebo**		
Odds ratio (SE)		0.970 (0.135)
95% confidence interval***		(0.738, 1.275)
p-value		0.8245
Heart failure physiology: LVEF <= 30% and NTproBNP >= median		
Number of patients in analysis set	661	631
Number of analysed patients, N (%)	588 (100.0)	581 (100.0)
Number of patients with endpoint, N (%)	156 (26.5)	139 (23.9)
95% confidence interval*	(23.1, 30.2)	(20.6, 27.6)
Comparison vs Placebo**		
Odds ratio (SE)		0.819 (0.118)
95% confidence interval***		(0.618, 1.085)
p-value		0.1642

* Wilson confidence intervals.
** Logistic regression includes terms for baseline EQ-VAS score (p<0.0001), age (p=0.0263), baseline eGFR (CKD-EPI) (p=0.4784), Treatment (p=0.1972), region (5 cat.) (p<0.0001), baseline diabetes status (3 cat.) (p=0.4568), sex (p=0.0623), heart failure physiology (p=0.0052) and Treatment by heart failure physiology interaction (p=0.7002).
***Wald confidence intervals.
16 patients were excluded as the subgroup variable was missing.

Data taken from study 1245.121 only.
LOCF: For a missing value at week 52 the last available post-baseline value before week 52 is imputed.
NTproBNP median [pg/mL]: with a. fibrillation/flutter at baseline: 2265; without a. fibrillation/flutter at baseline: 1671.

Table R.1.2.2.12: 1 Responder analysis (displaying odds ratio) in EQ-VAS change from baseline at week 52 of <= -10 points (deterioration) by heart failure physiology - RS (LOCF-AD) - 1245.121

Subgroup Description	Placebo	Empa 10mg
Heart failure physiology: LVEF > 30%		
Number of patients in analysis set	475	526
Number of analysed patients, N (%)	438 (100.0)	493 (100.0)
Number of patients with endpoint, N (%)	103 (23.5)	104 (21.1)
95% confidence interval*	(19.8, 27.7)	(17.7, 24.9)
Comparison vs Placebo**		
Odds ratio (SE)		0.901 (0.150)
95% confidence interval***		(0.650, 1.248)
p-value		0.5291

* Wilson confidence intervals.
** Logistic regression includes terms for baseline EQ-VAS score (p<0.0001), age (p=0.0263), baseline eGFR (CKD-EPI) (p=0.4784), Treatment (p=0.1972), region (5 cat.) (p<0.0001), baseline diabetes status (3 cat.) (p=0.4568), sex (p=0.0623), heart failure physiology (p=0.0052) and Treatment by heart failure physiology interaction (p=0.7002).
***Wald confidence intervals.
16 patients were excluded as the subgroup variable was missing.

Data taken from study 1245.121 only.
LOCF: For a missing value at week 52 the last available post-baseline value before week 52 is imputed.
NTproBNP median [pg/mL]: with a. fibrillation/flutter at baseline: 2265; without a. fibrillation/flutter at baseline: 1671.

Table R.1.2.2.12: 2 Responder analysis (displaying risk ratio) in EQ-VAS change from baseline at week 52 of <= -10 points (deterioration) by heart failure physiology - RS (LOCF-AD) - 1245.121

Subgroup Description	Placebo	Empa 10mg
Heart failure physiology: LVEF <= 30% and NTproBNP < median		
Number of patients in analysis set	723	698
Number of analysed patients, N (%)	679 (100.0)	655 (100.0)
Number of patients with endpoint, N (%)	149 (21.9)	142 (21.7)
95% confidence interval*	(19.0, 25.2)	(18.7, 25.0)
Comparison vs Placebo**		
Risk ratio (SE)		0.979 (0.097)
95% confidence interval***		(0.805, 1.189)
p-value		0.8285
Heart failure physiology: LVEF <= 30% and NTproBNP >= median		
Number of patients in analysis set	661	631
Number of analysed patients, N (%)	588 (100.0)	581 (100.0)
Number of patients with endpoint, N (%)	156 (26.5)	139 (23.9)
95% confidence interval*	(23.1, 30.2)	(20.6, 27.6)
Comparison vs Placebo**		
Risk ratio (SE)		0.868 (0.082)
95% confidence interval***		(0.721, 1.046)
p-value		0.1371

* Wilson confidence intervals.
** Log-linked Poisson model with robust estimate of variance includes terms for baseline EQ-VAS score (p<0.0001), age (p=0.0219), baseline eGFR (CKD-EPI) (p=0.4918), Treatment (p=0.1906), region (5 cat.) (p<0.0001), baseline diabetes status (3 cat.) (p=0.4981), sex (p=0.0716), heart failure physiology (p=0.0055) and Treatment by heart failure physiology interaction (p=0.6838).
***Wald confidence intervals.
16 patients were excluded as the subgroup variable was missing.

Data taken from study 1245.121 only.
LOCF: For a missing value at week 52 the last available post-baseline value before week 52 is imputed.
NTproBNP median [pg/mL]: with a. fibrillation/flutter at baseline: 2265; without a. fibrillation/flutter at baseline: 1671.

Table R.1.2.2.12: 2 Responder analysis (displaying risk ratio) in EQ-VAS change from baseline at week 52 of <= -10 points (deterioration) by heart failure physiology - RS (LOCF-AD) - 1245.121

Subgroup Description	Placebo	Empa 10mg
Heart failure physiology: LVEF > 30%		
Number of patients in analysis set	475	526
Number of analysed patients, N (%)	438 (100.0)	493 (100.0)
Number of patients with endpoint, N (%)	103 (23.5)	104 (21.1)
95% confidence interval*	(19.8, 27.7)	(17.7, 24.9)
Comparison vs Placebo**		
Risk ratio (SE)		0.929 (0.109)
95% confidence interval***		(0.738, 1.169)
p-value		0.5309

* Wilson confidence intervals.
** Log-linked Poisson model with robust estimate of variance includes terms for baseline EQ-VAS score (p<0.0001), age (p=0.0219), baseline eGFR (CKD-EPI) (p=0.4918), Treatment (p=0.1906), region (5 cat.) (p<0.0001), baseline diabetes status (3 cat.) (p=0.4981), sex (p=0.0716), heart failure physiology (p=0.0055) and Treatment by heart failure physiology interaction (p=0.6838).
***Wald confidence intervals.
16 patients were excluded as the subgroup variable was missing.

Data taken from study 1245.121 only.
LOCF: For a missing value at week 52 the last available post-baseline value before week 52 is imputed.
NTproBNP median [pg/mL]: with a. fibrillation/flutter at baseline: 2265; without a. fibrillation/flutter at baseline: 1671.

Table R.1.2.2.12: 3 Responder analysis (displaying odds ratio) in EQ-VAS change from baseline at week 52 of > -10 points (stability) by heart failure physiology - RS (LOCF-AD) - 1245.121

Subgroup Description	Placebo	Empa 10mg
Heart failure physiology: LVEF <= 30% and NTproBNP < median		
Number of patients in analysis set	723	698
Number of analysed patients, N (%)	679 (100.0)	655 (100.0)
Number of patients with endpoint, N (%)	530 (78.1)	513 (78.3)
95% confidence interval*	(74.8, 81.0)	(75.0, 81.3)
Comparison vs Placebo**		
Odds ratio (SE)		1.031 (0.144)
95% confidence interval***		(0.785, 1.356)
p-value		0.8245
Heart failure physiology: LVEF <= 30% and NTproBNP >= median		
Number of patients in analysis set	661	631
Number of analysed patients, N (%)	588 (100.0)	581 (100.0)
Number of patients with endpoint, N (%)	432 (73.5)	442 (76.1)
95% confidence interval*	(69.8, 76.9)	(72.4, 79.4)
Comparison vs Placebo**		
Odds ratio (SE)		1.221 (0.176)
95% confidence interval***		(0.921, 1.619)
p-value		0.1642

* Wilson confidence intervals.
** Logistic regression includes terms for baseline EQ-VAS score (p<0.0001), age (p=0.0263), baseline eGFR (CKD-EPI) (p=0.4784), Treatment (p=0.1972), region (5 cat.) (p<0.0001), baseline diabetes status (3 cat.) (p=0.4568), sex (p=0.0623), heart failure physiology (p=0.0052) and Treatment by heart failure physiology interaction (p=0.7002).
***Wald confidence intervals.
16 patients were excluded as the subgroup variable was missing.

Data taken from study 1245.121 only.
LOCF: For a missing value at week 52 the last available post-baseline value before week 52 is imputed.
NTproBNP median [pg/mL]: with a. fibrillation/flutter at baseline: 2265; without a. fibrillation/flutter at baseline: 1671.

Table R.1.2.2.12: 3 Responder analysis (displaying odds ratio) in EQ-VAS change from baseline at week 52 of > -10 points (stability) by heart failure physiology - RS (LOCF-AD) - 1245.121

Subgroup Description	Placebo	Empa 10mg
Heart failure physiology: LVEF > 30%		
Number of patients in analysis set	475	526
Number of analysed patients, N (%)	438 (100.0)	493 (100.0)
Number of patients with endpoint, N (%)	335 (76.5)	389 (78.9)
95% confidence interval*	(72.3, 80.2)	(75.1, 82.3)
Comparison vs Placebo**		
Odds ratio (SE)		1.110 (0.185)
95% confidence interval***		(0.801, 1.538)
p-value		0.5291

* Wilson confidence intervals.
** Logistic regression includes terms for baseline EQ-VAS score (p<0.0001), age (p=0.0263), baseline eGFR (CKD-EPI) (p=0.4784), Treatment (p=0.1972), region (5 cat.) (p<0.0001), baseline diabetes status (3 cat.) (p=0.4568), sex (p=0.0623), heart failure physiology (p=0.0052) and Treatment by heart failure physiology interaction (p=0.7002).
***Wald confidence intervals.
16 patients were excluded as the subgroup variable was missing.

Data taken from study 1245.121 only.
LOCF: For a missing value at week 52 the last available post-baseline value before week 52 is imputed.
NTproBNP median [pg/mL]: with a. fibrillation/flutter at baseline: 2265; without a. fibrillation/flutter at baseline: 1671.

Table R.1.2.2.12: 4 Responder analysis (displaying risk ratio) in EQ-VAS change from baseline at week 52 of > -10 points (stability) by heart failure physiology - RS (LOCF-AD) - 1245.121

Subgroup Description	Placebo	Empa 10mg
Heart failure physiology: LVEF <= 30% and NTproBNP < median		
Number of patients in analysis set	723	698
Number of analysed patients, N (%)	679 (100.0)	655 (100.0)
Number of patients with endpoint, N (%)	530 (78.1)	513 (78.3)
95% confidence interval*	(74.8, 81.0)	(75.0, 81.3)
Comparison vs Placebo**		
Risk ratio (SE)		1.008 (0.028)
95% confidence interval***		(0.954, 1.064)
p-value		0.7870
Heart failure physiology: LVEF <= 30% and NTproBNP >= median		
Number of patients in analysis set	661	631
Number of analysed patients, N (%)	588 (100.0)	581 (100.0)
Number of patients with endpoint, N (%)	432 (73.5)	442 (76.1)
95% confidence interval*	(69.8, 76.9)	(72.4, 79.4)
Comparison vs Placebo**		
Risk ratio (SE)		1.036 (0.034)
95% confidence interval***		(0.973, 1.104)
p-value		0.2683

* Wilson confidence intervals.
** Log-linked Poisson model with robust estimate of variance includes terms for baseline EQ-VAS score (p<0.0001), age (p=0.0365), baseline eGFR (CKD-EPI) (p=0.5419), Treatment (p=0.2837), region (5 cat.) (p<0.0001), baseline diabetes status (3 cat.) (p=0.3440), sex (p=0.0319), heart failure physiology (p=0.0048) and Treatment by heart failure physiology interaction (p=0.7974).
***Wald confidence intervals.
16 patients were excluded as the subgroup variable was missing.

Data taken from study 1245.121 only.
LOCF: For a missing value at week 52 the last available post-baseline value before week 52 is imputed.
NTproBNP median [pg/mL]: with a. fibrillation/flutter at baseline: 2265; without a. fibrillation/flutter at baseline: 1671.

Table R.1.2.2.12: 4 Responder analysis (displaying risk ratio) in EQ-VAS change from baseline at week 52 of > -10 points (stability) by heart failure physiology - RS (LOCF-AD) - 1245.121

Subgroup Description	Placebo	Empa 10mg
Heart failure physiology: LVEF > 30%		
Number of patients in analysis set	475	526
Number of analysed patients, N (%)	438 (100.0)	493 (100.0)
Number of patients with endpoint, N (%)	335 (76.5)	389 (78.9)
95% confidence interval*	(72.3, 80.2)	(75.1, 82.3)
Comparison vs Placebo**		
Risk ratio (SE)		1.015 (0.034)
95% confidence interval***		(0.950, 1.085)
p-value		0.6569

* Wilson confidence intervals.
** Log-linked Poisson model with robust estimate of variance includes terms for baseline EQ-VAS score (p<0.0001), age (p=0.0365), baseline eGFR (CKD-EPI) (p=0.5419), Treatment (p=0.2837), region (5 cat.) (p<0.0001), baseline diabetes status (3 cat.) (p=0.3440), sex (p=0.0319), heart failure physiology (p=0.0048) and Treatment by heart failure physiology interaction (p=0.7974).
***Wald confidence intervals.
16 patients were excluded as the subgroup variable was missing.

Data taken from study 1245.121 only.
LOCF: For a missing value at week 52 the last available post-baseline value before week 52 is imputed.
NTproBNP median [pg/mL]: with a. fibrillation/flutter at baseline: 2265; without a. fibrillation/flutter at baseline: 1671.

Table R.1.2.2.12: 5 Responder analysis (displaying odds ratio) in EQ-VAS change from baseline at week 52 of >= 10 points (improvement) by heart failure physiology - RS (LOCF-AD) - 1245.121

Subgroup Description	Placebo	Empa 10mg
Heart failure physiology: LVEF <= 30% and NTproBNP < median		
Number of patients in analysis set	723	698
Number of analysed patients, N (%)	679 (100.0)	655 (100.0)
Number of patients with endpoint, N (%)	262 (38.6)	263 (40.2)
95% confidence interval*	(35.0, 42.3)	(36.5, 44.0)
Comparison vs Placebo**		
Odds ratio (SE)		1.082 (0.140)
95% confidence interval***		(0.840, 1.393)
p-value		0.5409
Heart failure physiology: LVEF <= 30% and NTproBNP >= median		
Number of patients in analysis set	661	631
Number of analysed patients, N (%)	588 (100.0)	581 (100.0)
Number of patients with endpoint, N (%)	224 (38.1)	257 (44.2)
95% confidence interval*	(34.3, 42.1)	(40.2, 48.3)
Comparison vs Placebo**		
Odds ratio (SE)		1.488 (0.207)
95% confidence interval***		(1.134, 1.953)
p-value		0.0042

* Wilson confidence intervals.
** Logistic regression includes terms for baseline EQ-VAS score (p<0.0001), age (p=0.1986), baseline eGFR (CKD-EPI) (p=0.0520), Treatment (p=0.0010), region (5 cat.) (p<0.0001), baseline diabetes status (3 cat.) (p=0.8052), sex (p=0.8071), heart failure physiology (p=0.8049) and Treatment by heart failure physiology interaction (p=0.2039).
***Wald confidence intervals.
16 patients were excluded as the subgroup variable was missing.

Data taken from study 1245.121 only.
LOCF: For a missing value at week 52 the last available post-baseline value before week 52 is imputed.
NTproBNP median [pg/mL]: with a. fibrillation/flutter at baseline: 2265; without a. fibrillation/flutter at baseline: 1671.

Table R.1.2.2.12: 5 Responder analysis (displaying odds ratio) in EQ-VAS change from baseline at week 52 of >= 10 points (improvement) by heart failure physiology - RS (LOCF-AD) - 1245.121

Subgroup Description	Placebo	Empa 10mg
Heart failure physiology: LVEF > 30%		
Number of patients in analysis set	475	526
Number of analysed patients, N (%)	438 (100.0)	493 (100.0)
Number of patients with endpoint, N (%)	154 (35.2)	212 (43.0)
95% confidence interval*	(30.8, 39.7)	(38.7, 47.4)
Comparison vs Placebo**		
Odds ratio (SE)		1.400 (0.220)
95% confidence interval***		(1.029, 1.905)
p-value		0.0320

* Wilson confidence intervals.
** Logistic regression includes terms for baseline EQ-VAS score (p<0.0001), age (p=0.1986), baseline eGFR (CKD-EPI) (p=0.0520), Treatment (p=0.0010), region (5 cat.) (p<0.0001), baseline diabetes status (3 cat.) (p=0.8052), sex (p=0.8071), heart failure physiology (p=0.8049) and Treatment by heart failure physiology interaction (p=0.2039).
***Wald confidence intervals.
16 patients were excluded as the subgroup variable was missing.

Data taken from study 1245.121 only.
LOCF: For a missing value at week 52 the last available post-baseline value before week 52 is imputed.
NTproBNP median [pg/mL]: with a. fibrillation/flutter at baseline: 2265; without a. fibrillation/flutter at baseline: 1671.

Table R.1.2.2.12: 6 Responder analysis (displaying risk ratio) in EQ-VAS change from baseline at week 52 of >= 10 points (improvement) by heart failure physiology - RS (LOCF-AD) - 1245.121

Subgroup Description	Placebo	Empa 10mg
Heart failure physiology: LVEF <= 30% and NTproBNP < median		
Number of patients in analysis set	723	698
Number of analysed patients, N (%)	679 (100.0)	655 (100.0)
Number of patients with endpoint, N (%)	262 (38.6)	263 (40.2)
95% confidence interval*	(35.0, 42.3)	(36.5, 44.0)
Comparison vs Placebo**		
Risk ratio (SE)		1.055 (0.064)
95% confidence interval***		(0.936, 1.189)
p-value		0.3814
Heart failure physiology: LVEF <= 30% and NTproBNP >= median		
Number of patients in analysis set	661	631
Number of analysed patients, N (%)	588 (100.0)	581 (100.0)
Number of patients with endpoint, N (%)	224 (38.1)	257 (44.2)
95% confidence interval*	(34.3, 42.1)	(40.2, 48.3)
Comparison vs Placebo**		
Risk ratio (SE)		1.149 (0.075)
95% confidence interval***		(1.011, 1.305)
p-value		0.0338

* Wilson confidence intervals.
** Log-linked Poisson model with robust estimate of variance includes terms for baseline EQ-VAS score (p<0.0001), age (p=0.1479), baseline eGFR (CKD-EPI) (p=0.0841), Treatment (p=0.0051), region (5 cat.) (p<0.0001), baseline diabetes status (3 cat.) (p=0.8203), sex (p=0.5228), heart failure physiology (p=0.5680) and Treatment by heart failure physiology interaction (p=0.5721).
***Wald confidence intervals.
16 patients were excluded as the subgroup variable was missing.

Data taken from study 1245.121 only.
LOCF: For a missing value at week 52 the last available post-baseline value before week 52 is imputed.
NTproBNP median [pg/mL]: with a. fibrillation/flutter at baseline: 2265; without a. fibrillation/flutter at baseline: 1671.

Table R.1.2.2.12: 6 Responder analysis (displaying risk ratio) in EQ-VAS change from baseline at week 52 of >= 10 points (improvement) by heart failure physiology - RS (LOCF-AD) - 1245.121

Subgroup Description	Placebo	Empa 10mg
Heart failure physiology: LVEF > 30%		
Number of patients in analysis set	475	526
Number of analysed patients, N (%)	438 (100.0)	493 (100.0)
Number of patients with endpoint, N (%)	154 (35.2)	212 (43.0)
95% confidence interval*	(30.8, 39.7)	(38.7, 47.4)
Comparison vs Placebo**		
Risk ratio (SE)		1.142 (0.084)
95% confidence interval***		(0.988, 1.320)
p-value		0.0720

* Wilson confidence intervals.
** Log-linked Poisson model with robust estimate of variance includes terms for baseline EQ-VAS score (p<0.0001), age (p=0.1479), baseline eGFR (CKD-EPI) (p=0.0841), Treatment (p=0.0051), region (5 cat.) (p<0.0001), baseline diabetes status (3 cat.) (p=0.8203), sex (p=0.5228), heart failure physiology (p=0.5680) and Treatment by heart failure physiology interaction (p=0.5721).
***Wald confidence intervals.
16 patients were excluded as the subgroup variable was missing.

Data taken from study 1245.121 only.
LOCF: For a missing value at week 52 the last available post-baseline value before week 52 is imputed.
NTproBNP median [pg/mL]: with a. fibrillation/flutter at baseline: 2265; without a. fibrillation/flutter at baseline: 1671.

R.1.2.2.13

R.1.2.2.13 Subgroup analysis by baseline use of MRA

Table R.1.2.2.13: 1 Responder analysis (displaying odds ratio) in EQ-VAS change from baseline at week 52 of <= -10 points (deterioration) by baseline use of MRA (Y/N) - RS (LOCF-AD) - 1245.121

Subgroup Description	Placebo	Empa 10mg
Baseline use of MRA: No		
Number of patients in analysis set	512	557
Number of analysed patients, N (%)	474 (100.0)	521 (100.0)
Number of patients with endpoint, N (%)	118 (24.9)	115 (22.1)
95% confidence interval*	(21.2, 29.0)	(18.7, 25.8)
Comparison vs Placebo**		
Odds ratio (SE)		0.846 (0.134)
95% confidence interval***		(0.621, 1.153)
p-value		0.2893
Baseline use of MRA: Yes		
Number of patients in analysis set	1355	1306
Number of analysed patients, N (%)	1236 (100.0)	1212 (100.0)
Number of patients with endpoint, N (%)	291 (23.5)	271 (22.4)
95% confidence interval*	(21.3, 26.0)	(20.1, 24.8)
Comparison vs Placebo**		
Odds ratio (SE)		0.923 (0.094)
95% confidence interval***		(0.756, 1.126)
p-value		0.4281

* Wilson confidence intervals.
** Logistic regression includes terms for baseline EQ-VAS score (p<0.0001), age (p=0.0250), baseline eGFR (CKD-EPI) (p=0.2264), Treatment (p=0.1868), region (5 cat.) (p<0.0001), baseline diabetes status (3 cat.) (p=0.4719), sex (p=0.0461), baseline LVEF (3 cat.) (p=0.3223), baseline use of MRA (p=0.7711) and Treatment by baseline use of MRA interaction (p=0.6444).
***Wald confidence intervals.

Data taken from study 1245.121 only.
LOCF: For a missing value at week 52 the last available post-baseline value before week 52 is imputed.

Table R.1.2.2.13: 2 Responder analysis (displaying risk ratio) in EQ-VAS change from baseline at week 52 of <= -10 points (deterioration) by baseline use of MRA (Y/N) - RS (LOCF-AD) - 1245.121

Subgroup Description	Placebo	Empa 10mg
Baseline use of MRA: No		
Number of patients in analysis set	512	557
Number of analysed patients, N (%)	474 (100.0)	521 (100.0)
Number of patients with endpoint, N (%)	118 (24.9)	115 (22.1)
95% confidence interval*	(21.2, 29.0)	(18.7, 25.8)
Comparison vs Placebo**		
Risk ratio (SE)		0.891 (0.098)
95% confidence interval***		(0.718, 1.106)
p-value		0.2947
Baseline use of MRA: Yes		
Number of patients in analysis set	1355	1306
Number of analysed patients, N (%)	1236 (100.0)	1212 (100.0)
Number of patients with endpoint, N (%)	291 (23.5)	271 (22.4)
95% confidence interval*	(21.3, 26.0)	(20.1, 24.8)
Comparison vs Placebo**		
Risk ratio (SE)		0.943 (0.066)
95% confidence interval***		(0.821, 1.082)
p-value		0.4005

* Wilson confidence intervals.
** Log-linked Poisson model with robust estimate of variance includes terms for baseline EQ-VAS score (p<0.0001), age (p=0.0211), baseline eGFR (CKD-EPI) (p=0.2357), Treatment (p=0.1813), region (5 cat.) (p<0.0001), baseline diabetes status (3 cat.) (p=0.4973), sex (p=0.0537), baseline LVEF (3 cat.) (p=0.3451), baseline use of MRA (p=0.7851) and Treatment by baseline use of MRA interaction (p=0.6668).
***Wald confidence intervals.

Data taken from study 1245.121 only.
LOCF: For a missing value at week 52 the last available post-baseline value before week 52 is imputed.

Table R.1.2.2.13: 3 Responder analysis (displaying odds ratio) in EQ-VAS change from baseline at week 52 of > -10 points (stability) by baseline use of MRA (Y/N) - RS (LOCF-AD) - 1245.121

Subgroup Description	Placebo	Empa 10mg
Baseline use of MRA: No		
Number of patients in analysis set	512	557
Number of analysed patients, N (%)	474 (100.0)	521 (100.0)
Number of patients with endpoint, N (%)	356 (75.1)	406 (77.9)
95% confidence interval*	(71.0, 78.8)	(74.2, 81.3)
Comparison vs Placebo**		
Odds ratio (SE)		1.182 (0.187)
95% confidence interval***		(0.868, 1.611)
p-value		0.2893
Baseline use of MRA: Yes		
Number of patients in analysis set	1355	1306
Number of analysed patients, N (%)	1236 (100.0)	1212 (100.0)
Number of patients with endpoint, N (%)	945 (76.5)	941 (77.6)
95% confidence interval*	(74.0, 78.7)	(75.2, 79.9)
Comparison vs Placebo**		
Odds ratio (SE)		1.084 (0.110)
95% confidence interval***		(0.888, 1.323)
p-value		0.4281

* Wilson confidence intervals.
** Logistic regression includes terms for baseline EQ-VAS score (p<0.0001), age (p=0.0250), baseline eGFR (CKD-EPI) (p=0.2264), Treatment (p=0.1868), region (5 cat.) (p<0.0001), baseline diabetes status (3 cat.) (p=0.4719), sex (p=0.0461), baseline LVEF (3 cat.) (p=0.3223), baseline use of MRA (p=0.7711) and Treatment by baseline use of MRA interaction (p=0.6444).
***Wald confidence intervals.

Data taken from study 1245.121 only.
LOCF: For a missing value at week 52 the last available post-baseline value before week 52 is imputed.

Table R.1.2.2.13: 4 Responder analysis (displaying risk ratio) in EQ-VAS change from baseline at week 52 of > -10 points (stability) by baseline use of MRA (Y/N) - RS (LOCF-AD) - 1245.121

Subgroup Description	Placebo	Empa 10mg
Baseline use of MRA: No		
Number of patients in analysis set	512	557
Number of analysed patients, N (%)	474 (100.0)	521 (100.0)
Number of patients with endpoint, N (%)	356 (75.1)	406 (77.9)
95% confidence interval*	(71.0, 78.8)	(74.2, 81.3)
Comparison vs Placebo**		
Risk ratio (SE)		1.029 (0.035)
95% confidence interval***		(0.963, 1.099)
p-value		0.4031
Baseline use of MRA: Yes		
Number of patients in analysis set	1355	1306
Number of analysed patients, N (%)	1236 (100.0)	1212 (100.0)
Number of patients with endpoint, N (%)	945 (76.5)	941 (77.6)
95% confidence interval*	(74.0, 78.7)	(75.2, 79.9)
Comparison vs Placebo**		
Risk ratio (SE)		1.015 (0.021)
95% confidence interval***		(0.973, 1.057)
p-value		0.4944

* Wilson confidence intervals.
** Log-linked Poisson model with robust estimate of variance includes terms for baseline EQ-VAS score (p<0.0001), age (p=0.0386), baseline eGFR (CKD-EPI) (p=0.2501), Treatment (p=0.2840), region (5 cat.) (p<0.0001), baseline diabetes status (3 cat.) (p=0.3663), sex (p=0.0254), baseline LVEF (3 cat.) (p=0.4139), baseline use of MRA (p=0.7388) and Treatment by baseline use of MRA interaction (p=0.7275).
***Wald confidence intervals.

Data taken from study 1245.121 only.
LOCF: For a missing value at week 52 the last available post-baseline value before week 52 is imputed.

Table R.1.2.2.13: 5 Responder analysis (displaying odds ratio) in EQ-VAS change from baseline at week 52 of >= 10 points (improvement) by baseline use of MRA (Y/N) - RS (LOCF-AD) - 1245.121

Subgroup Description	Placebo	Empa 10mg
Baseline use of MRA: No		
Number of patients in analysis set	512	557
Number of analysed patients, N (%)	474 (100.0)	521 (100.0)
Number of patients with endpoint, N (%)	159 (33.5)	208 (39.9)
95% confidence interval*	(29.4, 37.9)	(35.8, 44.2)
Comparison vs Placebo**		
Odds ratio (SE)		1.389 (0.212)
95% confidence interval***		(1.030, 1.872)
p-value		0.0311
Baseline use of MRA: Yes		
Number of patients in analysis set	1355	1306
Number of analysed patients, N (%)	1236 (100.0)	1212 (100.0)
Number of patients with endpoint, N (%)	484 (39.2)	526 (43.4)
95% confidence interval*	(36.5, 41.9)	(40.6, 46.2)
Comparison vs Placebo**		
Odds ratio (SE)		1.254 (0.120)
95% confidence interval***		(1.040, 1.511)
p-value		0.0177

* Wilson confidence intervals.
** Logistic regression includes terms for baseline EQ-VAS score (p<0.0001), age (p=0.2123), baseline eGFR (CKD-EPI) (p=0.0456), Treatment (p=0.0020), region (5 cat.) (p<0.0001), baseline diabetes status (3 cat.) (p=0.7922), sex (p=0.8037), baseline LVEF (3 cat.) (p=0.6056), baseline use of MRA (p=0.2494) and Treatment by baseline use of MRA interaction (p=0.5691).
***Wald confidence intervals.

Data taken from study 1245.121 only.
LOCF: For a missing value at week 52 the last available post-baseline value before week 52 is imputed.

Table R.1.2.2.13: 6 Responder analysis (displaying risk ratio) in EQ-VAS change from baseline at week 52 of >= 10 points (improvement) by baseline use of MRA (Y/N) - RS (LOCF-AD) - 1245.121

Subgroup Description	Placebo	Empa 10mg
Baseline use of MRA: No		
Number of patients in analysis set	512	557
Number of analysed patients, N (%)	474 (100.0)	521 (100.0)
Number of patients with endpoint, N (%)	159 (33.5)	208 (39.9)
95% confidence interval*	(29.4, 37.9)	(35.8, 44.2)
Comparison vs Placebo**		
Risk ratio (SE)		1.129 (0.086)
95% confidence interval***		(0.972, 1.311)
p-value		0.1121
Baseline use of MRA: Yes		
Number of patients in analysis set	1355	1306
Number of analysed patients, N (%)	1236 (100.0)	1212 (100.0)
Number of patients with endpoint, N (%)	484 (39.2)	526 (43.4)
95% confidence interval*	(36.5, 41.9)	(40.6, 46.2)
Comparison vs Placebo**		
Risk ratio (SE)		1.104 (0.048)
95% confidence interval***		(1.012, 1.203)
p-value		0.0249

* Wilson confidence intervals.
** Log-linked Poisson model with robust estimate of variance includes terms for baseline EQ-VAS score (p<0.0001), age (p=0.1904), baseline eGFR (CKD-EPI) (p=0.0643), Treatment (p=0.0126), region (5 cat.) (p<0.0001), baseline diabetes status (3 cat.) (p=0.8051), sex (p=0.5032), baseline LVEF (3 cat.) (p=0.6775), baseline use of MRA (p=0.1880) and Treatment by baseline use of MRA interaction (p=0.7951).
***Wald confidence intervals.

Data taken from study 1245.121 only.
LOCF: For a missing value at week 52 the last available post-baseline value before week 52 is imputed.

R.1.2.2.14

Table R.1.2.2.14: 1 Responder analysis (displaying odds ratio) in EQ-VAS change from baseline at week 52 of <= -10 points (deterioration) by baseline use of ARNi (Y/N) - RS (LOCF-AD) - 1245.121

Subgroup Description	Placebo	Empa 10mg
Baseline use of ARNi: No		
Number of patients in analysis set	1480	1523
Number of analysed patients, N (%)	1352 (100.0)	1412 (100.0)
Number of patients with endpoint, N (%)	329 (24.3)	314 (22.2)
95% confidence interval*	(22.1, 26.7)	(20.1, 24.5)
Comparison vs Placebo**		
Odds ratio (SE)		0.870 (0.083)
95% confidence interval***		(0.722, 1.048)
p-value		0.1434
Baseline use of ARNi: Yes		
Number of patients in analysis set	387	340
Number of analysed patients, N (%)	358 (100.0)	321 (100.0)
Number of patients with endpoint, N (%)	80 (22.3)	72 (22.4)
95% confidence interval*	(18.3, 26.9)	(18.2, 27.3)
Comparison vs Placebo**		
Odds ratio (SE)		1.014 (0.198)
95% confidence interval***		(0.692, 1.485)
p-value		0.9436

* Wilson confidence intervals.
** Logistic regression includes terms for baseline EQ-VAS score (p<0.0001), age (p=0.0296), baseline eGFR (CKD-EPI) (p=0.2195), Treatment (p=0.5626), region (5 cat.) (p<0.0001), baseline diabetes status (3 cat.) (p=0.4819), sex (p=0.0450), baseline LVEF (3 cat.) (p=0.2939), baseline use of ARNi (p=0.2590) and Treatment by baseline use of ARNi interaction (p=0.4802).
***Wald confidence intervals.

Data taken from study 1245.121 only.
LOCF: For a missing value at week 52 the last available post-baseline value before week 52 is imputed.

Table R.1.2.2.14: 2 Responder analysis (displaying risk ratio) in EQ-VAS change from baseline at week 52 of <= -10 points (deterioration) by baseline use of ARNi (Y/N) - RS (LOCF-AD) - 1245.121

Subgroup Description	Placebo	Empa 10mg
Baseline use of ARNi: No		
Number of patients in analysis set	1480	1523
Number of analysed patients, N (%)	1352 (100.0)	1412 (100.0)
Number of patients with endpoint, N (%)	329 (24.3)	314 (22.2)
95% confidence interval*	(22.1, 26.7)	(20.1, 24.5)
Comparison vs Placebo**		
Risk ratio (SE)		0.906 (0.059)
95% confidence interval***		(0.797, 1.031)
p-value		0.1337
Baseline use of ARNi: Yes		
Number of patients in analysis set	387	340
Number of analysed patients, N (%)	358 (100.0)	321 (100.0)
Number of patients with endpoint, N (%)	80 (22.3)	72 (22.4)
95% confidence interval*	(18.3, 26.9)	(18.2, 27.3)
Comparison vs Placebo**		
Risk ratio (SE)		1.008 (0.138)
95% confidence interval***		(0.770, 1.319)
p-value		0.9546

* Wilson confidence intervals.
** Log-linked Poisson model with robust estimate of variance includes terms for baseline EQ-VAS score (p<0.0001), age (p=0.0242), baseline eGFR (CKD-EPI) (p=0.2259), Treatment (p=0.5514), region (5 cat.) (p<0.0001), baseline diabetes status (3 cat.) (p=0.5056), sex (p=0.0521), baseline LVEF (3 cat.) (p=0.3157), baseline use of ARNi (p=0.2632) and Treatment by baseline use of ARNi interaction (p=0.4858).
***Wald confidence intervals.

Data taken from study 1245.121 only.
LOCF: For a missing value at week 52 the last available post-baseline value before week 52 is imputed.

Table R.1.2.2.14: 3 Responder analysis (displaying odds ratio) in EQ-VAS change from baseline at week 52 of > -10 points (stability) by baseline use of ARNi (Y/N) - RS (LOCF-AD) - 1245.121

Subgroup Description	Placebo	Empa 10mg
Baseline use of ARNi: No		
Number of patients in analysis set	1480	1523
Number of analysed patients, N (%)	1352 (100.0)	1412 (100.0)
Number of patients with endpoint, N (%)	1023 (75.7)	1098 (77.8)
95% confidence interval*	(73.3, 77.9)	(75.5, 79.9)
Comparison vs Placebo**		
Odds ratio (SE)		1.150 (0.109)
95% confidence interval***		(0.954, 1.385)
p-value		0.1434
Baseline use of ARNi: Yes		
Number of patients in analysis set	387	340
Number of analysed patients, N (%)	358 (100.0)	321 (100.0)
Number of patients with endpoint, N (%)	278 (77.7)	249 (77.6)
95% confidence interval*	(73.1, 81.7)	(72.7, 81.8)
Comparison vs Placebo**		
Odds ratio (SE)		0.986 (0.192)
95% confidence interval***		(0.673, 1.445)
p-value		0.9436

* Wilson confidence intervals.
** Logistic regression includes terms for baseline EQ-VAS score (p<0.0001), age (p=0.0296), baseline eGFR (CKD-EPI) (p=0.2195), Treatment (p=0.5626), region (5 cat.) (p<0.0001), baseline diabetes status (3 cat.) (p=0.4819), sex (p=0.0450), baseline LVEF (3 cat.) (p=0.2939), baseline use of ARNi (p=0.2590) and Treatment by baseline use of ARNi interaction (p=0.4802).
***Wald confidence intervals.

Data taken from study 1245.121 only.
LOCF: For a missing value at week 52 the last available post-baseline value before week 52 is imputed.

Table R.1.2.2.14: 4 Responder analysis (displaying risk ratio) in EQ-VAS change from baseline at week 52 of > -10 points (stability) by baseline use of ARNi (Y/N) - RS (LOCF-AD) - 1245.121

Subgroup Description	Placebo	Empa 10mg
Baseline use of ARNi: No		
Number of patients in analysis set	1480	1523
Number of analysed patients, N (%)	1352 (100.0)	1412 (100.0)
Number of patients with endpoint, N (%)	1023 (75.7)	1098 (77.8)
95% confidence interval*	(73.3, 77.9)	(75.5, 79.9)
Comparison vs Placebo**		
Risk ratio (SE)		1.025 (0.021)
95% confidence interval***		(0.986, 1.067)
p-value		0.2090
Baseline use of ARNi: Yes		
Number of patients in analysis set	387	340
Number of analysed patients, N (%)	358 (100.0)	321 (100.0)
Number of patients with endpoint, N (%)	278 (77.7)	249 (77.6)
95% confidence interval*	(73.1, 81.7)	(72.7, 81.8)
Comparison vs Placebo**		
Risk ratio (SE)		0.994 (0.040)
95% confidence interval***		(0.919, 1.076)
p-value		0.8898

* Wilson confidence intervals.
** Log-linked Poisson model with robust estimate of variance includes terms for baseline EQ-VAS score (p<0.0001), age (p=0.0467), baseline eGFR (CKD-EPI) (p=0.2428), Treatment (p=0.6623), region (5 cat.) (p<0.0001), baseline diabetes status (3 cat.) (p=0.3764), sex (p=0.0244), baseline LVEF (3 cat.) (p=0.3858), baseline use of ARNi (p=0.3229) and Treatment by baseline use of ARNi interaction (p=0.4937).
***Wald confidence intervals.

Data taken from study 1245.121 only.
LOCF: For a missing value at week 52 the last available post-baseline value before week 52 is imputed.

Table R.1.2.2.14: 5 Responder analysis (displaying odds ratio) in EQ-VAS change from baseline at week 52 of >= 10 points (improvement) by baseline use of ARNi (Y/N) - RS (LOCF-AD) - 1245.121

Subgroup Description	Placebo	Empa 10mg
Baseline use of ARNi: No		
Number of patients in analysis set	1480	1523
Number of analysed patients, N (%)	1352 (100.0)	1412 (100.0)
Number of patients with endpoint, N (%)	518 (38.3)	603 (42.7)
95% confidence interval*	(35.8, 40.9)	(40.1, 45.3)
Comparison vs Placebo**		
Odds ratio (SE)		1.280 (0.115)
95% confidence interval***		(1.074, 1.527)
p-value		0.0060
Baseline use of ARNi: Yes		
Number of patients in analysis set	387	340
Number of analysed patients, N (%)	358 (100.0)	321 (100.0)
Number of patients with endpoint, N (%)	125 (34.9)	131 (40.8)
95% confidence interval*	(30.2, 40.0)	(35.6, 46.3)
Comparison vs Placebo**		
Odds ratio (SE)		1.324 (0.246)
95% confidence interval***		(0.920, 1.905)
p-value		0.1302

* Wilson confidence intervals.
** Logistic regression includes terms for baseline EQ-VAS score (p<0.0001), age (p=0.1714), baseline eGFR (CKD-EPI) (p=0.0396), Treatment (p=0.0104), region (5 cat.) (p<0.0001), baseline diabetes status (3 cat.) (p=0.7994), sex (p=0.8268), baseline LVEF (3 cat.) (p=0.6254), baseline use of ARNi (p=0.8846) and Treatment by baseline use of ARNi interaction (p=0.8705).
***Wald confidence intervals.

Data taken from study 1245.121 only.
LOCF: For a missing value at week 52 the last available post-baseline value before week 52 is imputed.

Table R.1.2.2.14: 6 Responder analysis (displaying risk ratio) in EQ-VAS change from baseline at week 52 of >= 10 points (improvement) by baseline use of ARNi (Y/N) - RS (LOCF-AD) - 1245.121

Subgroup Description	Placebo	Empa 10mg
Baseline use of ARNi: No		
Number of patients in analysis set	1480	1523
Number of analysed patients, N (%)	1352 (100.0)	1412 (100.0)
Number of patients with endpoint, N (%)	518 (38.3)	603 (42.7)
95% confidence interval*	(35.8, 40.9)	(40.1, 45.3)
Comparison vs Placebo**		
Risk ratio (SE)		1.101 (0.046)
95% confidence interval***		(1.014, 1.195)
p-value		0.0226
Baseline use of ARNi: Yes		
Number of patients in analysis set	387	340
Number of analysed patients, N (%)	358 (100.0)	321 (100.0)
Number of patients with endpoint, N (%)	125 (34.9)	131 (40.8)
95% confidence interval*	(30.2, 40.0)	(35.6, 46.3)
Comparison vs Placebo**		
Risk ratio (SE)		1.142 (0.102)
95% confidence interval***		(0.958, 1.360)
p-value		0.1387

* Wilson confidence intervals.
** Log-linked Poisson model with robust estimate of variance includes terms for baseline EQ-VAS score (p<0.0001), age (p=0.1426), baseline eGFR (CKD-EPI) (p=0.0569), Treatment (p=0.0208), region (5 cat.) (p<0.0001), baseline diabetes status (3 cat.) (p=0.8075), sex (p=0.5215), baseline LVEF (3 cat.) (p=0.6766), baseline use of ARNi (p=0.6105) and Treatment by baseline use of ARNi interaction (p=0.7119).
***Wald confidence intervals.

Data taken from study 1245.121 only.
LOCF: For a missing value at week 52 the last available post-baseline value before week 52 is imputed.

R.1.2.2.15

R.1.2.2.15 Subgroup analysis by bl. LVEF (<= 30%, >30% -<= 35% , > 35%)

Table R.1.2.2.15: 1 Responder analysis (displaying odds ratio) in EQ-VAS change from baseline at week 52 of <= -10 points (deterioration) by baseline LVEF (3 cat.) - RS (LOCF-AD) - 1245.121

Subgroup Description	Placebo	Empa 10mg
Baseline LVEF (3 cat.): <=30		
Number of patients in analysis set	1392	1337
Number of analysed patients, N (%)	1272 (100.0)	1240 (100.0)
Number of patients with endpoint, N (%)	306 (24.1)	282 (22.7)
95% confidence interval*	(21.8, 26.5)	(20.5, 25.2)
Comparison vs Placebo**		
Odds ratio (SE)		0.897 (0.089)
95% confidence interval***		(0.738, 1.091)
p-value		0.2761
Baseline LVEF (3 cat.): >30 to <=35		
Number of patients in analysis set	361	398
Number of analysed patients, N (%)	334 (100.0)	373 (100.0)
Number of patients with endpoint, N (%)	78 (23.4)	80 (21.4)
95% confidence interval*	(19.1, 28.2)	(17.6, 25.9)
Comparison vs Placebo**		
Odds ratio (SE)		0.931 (0.177)
95% confidence interval***		(0.641, 1.351)
p-value		0.7057

* Wilson confidence intervals.
** Logistic regression includes terms for baseline EQ-VAS score (p<0.0001), age (p=0.0251), baseline eGFR (CKD-EPI) (p=0.2357), Treatment (p=0.3527), region (5 cat.) (p<0.0001), baseline diabetes status (3 cat.) (p=0.4706), sex (p=0.0450), baseline LVEF (3 cat.) (p=0.3126) and Treatment by baseline LVEF (3 cat.) interaction (p=0.9513).
***Wald confidence intervals.

Data taken from study 1245.121 only.
LOCF: For a missing value at week 52 the last available post-baseline value before week 52 is imputed.

Table R.1.2.2.15: 1 Responder analysis (displaying odds ratio) in EQ-VAS change from baseline at week 52 of <= -10 points (deterioration) by baseline LVEF (3 cat.) - RS (LOCF-AD) - 1245.121

Subgroup Description	Placebo	Empa 10mg
Baseline LVEF (3 cat.): >35		
Number of patients in analysis set	114	128
Number of analysed patients, N (%)	104 (100.0)	120 (100.0)
Number of patients with endpoint, N (%)	25 (24.0)	24 (20.0)
95% confidence interval*	(16.8, 33.1)	(13.8, 28.0)
Comparison vs Placebo**		
Odds ratio (SE)		0.823 (0.281)
95% confidence interval***		(0.422, 1.608)
p-value		0.5691

* Wilson confidence intervals.
** Logistic regression includes terms for baseline EQ-VAS score (p<0.0001), age (p=0.0251), baseline eGFR (CKD-EPI) (p=0.2357), Treatment (p=0.3527), region (5 cat.) (p<0.0001), baseline diabetes status (3 cat.) (p=0.4706), sex (p=0.0450), baseline LVEF (3 cat.) (p=0.3126) and Treatment by baseline LVEF (3 cat.) interaction (p=0.9513).
***Wald confidence intervals.

Data taken from study 1245.121 only.
LOCF: For a missing value at week 52 the last available post-baseline value before week 52 is imputed.

Table R.1.2.2.15: 2 Responder analysis (displaying risk ratio) in EQ-VAS change from baseline at week 52 of <= -10 points (deterioration) by baseline LVEF (3 cat.) - RS (LOCF-AD) - 1245.121

Subgroup Description	Placebo	Empa 10mg
Baseline LVEF (3 cat.): <=30		
Number of patients in analysis set	1392	1337
Number of analysed patients, N (%)	1272 (100.0)	1240 (100.0)
Number of patients with endpoint, N (%)	306 (24.1)	282 (22.7)
95% confidence interval*	(21.8, 26.5)	(20.5, 25.2)
Comparison vs Placebo**		
Risk ratio (SE)		0.925 (0.064)
95% confidence interval***		(0.809, 1.059)
p-value		0.2594
Baseline LVEF (3 cat.): >30 to <=35		
Number of patients in analysis set	361	398
Number of analysed patients, N (%)	334 (100.0)	373 (100.0)
Number of patients with endpoint, N (%)	78 (23.4)	80 (21.4)
95% confidence interval*	(19.1, 28.2)	(17.6, 25.9)
Comparison vs Placebo**		
Risk ratio (SE)		0.955 (0.129)
95% confidence interval***		(0.732, 1.245)
p-value		0.7321

* Wilson confidence intervals.
** Log-linked Poisson model with robust estimate of variance includes terms for baseline EQ-VAS score (p<0.0001), age (p=0.0207), baseline eGFR (CKD-EPI) (p=0.2452), Treatment (p=0.3175), region (5 cat.) (p<0.0001), baseline diabetes status (3 cat.) (p=0.4929), sex (p=0.0524), baseline LVEF (3 cat.) (p=0.3387) and Treatment by baseline LVEF (3 cat.) interaction (p=0.9237).
***Wald confidence intervals.

Data taken from study 1245.121 only.
LOCF: For a missing value at week 52 the last available post-baseline value before week 52 is imputed.

Table R.1.2.2.15: 2 Responder analysis (displaying risk ratio) in EQ-VAS change from baseline at week 52 of <= -10 points (deterioration) by baseline LVEF (3 cat.) - RS (LOCF-AD) - 1245.121

Subgroup Description	Placebo	Empa 10mg
Baseline LVEF (3 cat.): >35		
Number of patients in analysis set	114	128
Number of analysed patients, N (%)	104 (100.0)	120 (100.0)
Number of patients with endpoint, N (%)	25 (24.0)	24 (20.0)
95% confidence interval*	(16.8, 33.1)	(13.8, 28.0)
Comparison vs Placebo**		
Risk ratio (SE)		0.858 (0.199)
95% confidence interval***		(0.545, 1.351)
p-value		0.5090

* Wilson confidence intervals.
** Log-linked Poisson model with robust estimate of variance includes terms for baseline EQ-VAS score (p<0.0001), age (p=0.0207), baseline eGFR (CKD-EPI) (p=0.2452), Treatment (p=0.3175), region (5 cat.) (p<0.0001), baseline diabetes status (3 cat.) (p=0.4929), sex (p=0.0524), baseline LVEF (3 cat.) (p=0.3387) and Treatment by baseline LVEF (3 cat.) interaction (p=0.9237).
***Wald confidence intervals.

Data taken from study 1245.121 only.
LOCF: For a missing value at week 52 the last available post-baseline value before week 52 is imputed.

Table R.1.2.2.15: 3 Responder analysis (displaying odds ratio) in EQ-VAS change from baseline at week 52 of > -10 points (stability) by baseline LVEF (3 cat.) - RS (LOCF-AD) - 1245.121

Subgroup Description	Placebo	Empa 10mg
Baseline LVEF (3 cat.): <=30		
Number of patients in analysis set	1392	1337
Number of analysed patients, N (%)	1272 (100.0)	1240 (100.0)
Number of patients with endpoint, N (%)	966 (75.9)	958 (77.3)
95% confidence interval*	(73.5, 78.2)	(74.8, 79.5)
Comparison vs Placebo**		
Odds ratio (SE)		1.115 (0.111)
95% confidence interval***		(0.917, 1.355)
p-value		0.2761
Baseline LVEF (3 cat.): >30 to <=35		
Number of patients in analysis set	361	398
Number of analysed patients, N (%)	334 (100.0)	373 (100.0)
Number of patients with endpoint, N (%)	256 (76.6)	293 (78.6)
95% confidence interval*	(71.8, 80.9)	(74.1, 82.4)
Comparison vs Placebo**		
Odds ratio (SE)		1.075 (0.204)
95% confidence interval***		(0.740, 1.560)
p-value		0.7057

* Wilson confidence intervals.
** Logistic regression includes terms for baseline EQ-VAS score (p<0.0001), age (p=0.0251), baseline eGFR (CKD-EPI) (p=0.2357), Treatment (p=0.3527), region (5 cat.) (p<0.0001), baseline diabetes status (3 cat.) (p=0.4706), sex (p=0.0450), baseline LVEF (3 cat.) (p=0.3126) and Treatment by baseline LVEF (3 cat.) interaction (p=0.9513).
***Wald confidence intervals.

Data taken from study 1245.121 only.
LOCF: For a missing value at week 52 the last available post-baseline value before week 52 is imputed.

Table R.1.2.2.15: 3 Responder analysis (displaying odds ratio) in EQ-VAS change from baseline at week 52 of > -10 points (stability) by baseline LVEF (3 cat.) - RS (LOCF-AD) - 1245.121

Subgroup Description	Placebo	Empa 10mg
Baseline LVEF (3 cat.): >35		
Number of patients in analysis set	114	128
Number of analysed patients, N (%)	104 (100.0)	120 (100.0)
Number of patients with endpoint, N (%)	79 (76.0)	96 (80.0)
95% confidence interval*	(66.9, 83.2)	(72.0, 86.2)
Comparison vs Placebo**		
Odds ratio (SE)		1.215 (0.415)
95% confidence interval***		(0.622, 2.372)
p-value		0.5691

* Wilson confidence intervals.
** Logistic regression includes terms for baseline EQ-VAS score (p<0.0001), age (p=0.0251), baseline eGFR (CKD-EPI) (p=0.2357), Treatment (p=0.3527), region (5 cat.) (p<0.0001), baseline diabetes status (3 cat.) (p=0.4706), sex (p=0.0450), baseline LVEF (3 cat.) (p=0.3126) and Treatment by baseline LVEF (3 cat.) interaction (p=0.9513).
***Wald confidence intervals.

Data taken from study 1245.121 only.
LOCF: For a missing value at week 52 the last available post-baseline value before week 52 is imputed.

Table R.1.2.2.15: 4 Responder analysis (displaying risk ratio) in EQ-VAS change from baseline at week 52 of > -10 points (stability) by baseline LVEF (3 cat.) - RS (LOCF-AD) - 1245.121

Subgroup Description	Placebo	Empa 10mg
Baseline LVEF (3 cat.): <=30		
Number of patients in analysis set	1392	1337
Number of analysed patients, N (%)	1272 (100.0)	1240 (100.0)
Number of patients with endpoint, N (%)	966 (75.9)	958 (77.3)
95% confidence interval*	(73.5, 78.2)	(74.8, 79.5)
Comparison vs Placebo**		
Risk ratio (SE)		1.020 (0.022)
95% confidence interval***		(0.979, 1.063)
p-value		0.3441
Baseline LVEF (3 cat.): >30 to <=35		
Number of patients in analysis set	361	398
Number of analysed patients, N (%)	334 (100.0)	373 (100.0)
Number of patients with endpoint, N (%)	256 (76.6)	293 (78.6)
95% confidence interval*	(71.8, 80.9)	(74.1, 82.4)
Comparison vs Placebo**		
Risk ratio (SE)		1.014 (0.040)
95% confidence interval***		(0.939, 1.095)
p-value		0.7185

* Wilson confidence intervals.
** Log-linked Poisson model with robust estimate of variance includes terms for baseline EQ-VAS score (p<0.0001), age (p=0.0404), baseline eGFR (CKD-EPI) (p=0.2586), Treatment (p=0.5256), region (5 cat.) (p<0.0001), baseline diabetes status (3 cat.) (p=0.3679), sex (p=0.0250), baseline LVEF (3 cat.) (p=0.4069) and Treatment by baseline LVEF (3 cat.) interaction (p=0.9910).
***Wald confidence intervals.

Data taken from study 1245.121 only.
LOCF: For a missing value at week 52 the last available post-baseline value before week 52 is imputed.

Table R.1.2.2.15: 4 Responder analysis (displaying risk ratio) in EQ-VAS change from baseline at week 52 of > -10 points (stability) by baseline LVEF (3 cat.) - RS (LOCF-AD) - 1245.121

Subgroup Description	Placebo	Empa 10mg
Baseline LVEF (3 cat.): >35		
Number of patients in analysis set	114	128
Number of analysed patients, N (%)	104 (100.0)	120 (100.0)
Number of patients with endpoint, N (%)	79 (76.0)	96 (80.0)
95% confidence interval*	(66.9, 83.2)	(72.0, 86.2)
Comparison vs Placebo**		
Risk ratio (SE)		1.017 (0.068)
95% confidence interval***		(0.892, 1.159)
p-value		0.8017

* Wilson confidence intervals.
** Log-linked Poisson model with robust estimate of variance includes terms for baseline EQ-VAS score (p<0.0001), age (p=0.0404), baseline eGFR (CKD-EPI) (p=0.2586), Treatment (p=0.5256), region (5 cat.) (p<0.0001), baseline diabetes status (3 cat.) (p=0.3679), sex (p=0.0250), baseline LVEF (3 cat.) (p=0.4069) and Treatment by baseline LVEF (3 cat.) interaction (p=0.9910).
***Wald confidence intervals.

Data taken from study 1245.121 only.
LOCF: For a missing value at week 52 the last available post-baseline value before week 52 is imputed.

Table R.1.2.2.15: 5 Responder analysis (displaying odds ratio) in EQ-VAS change from baseline at week 52 of >= 10 points (improvement) by baseline LVEF (3 cat.) - RS (LOCF-AD) - 1245.121

Subgroup Description	Placebo	Empa 10mg
Baseline LVEF (3 cat.): <=30		
Number of patients in analysis set	1392	1337
Number of analysed patients, N (%)	1272 (100.0)	1240 (100.0)
Number of patients with endpoint, N (%)	489 (38.4)	522 (42.1)
95% confidence interval*	(35.8, 41.1)	(39.4, 44.9)
Comparison vs Placebo**		
Odds ratio (SE)		1.251 (0.118)
95% confidence interval***		(1.040, 1.504)
p-value		0.0176
Baseline LVEF (3 cat.): >30 to <=35		
Number of patients in analysis set	361	398
Number of analysed patients, N (%)	334 (100.0)	373 (100.0)
Number of patients with endpoint, N (%)	114 (34.1)	153 (41.0)
95% confidence interval*	(29.3, 39.4)	(36.1, 46.1)
Comparison vs Placebo**		
Odds ratio (SE)		1.422 (0.257)
95% confidence interval***		(0.997, 2.027)
p-value		0.0520

* Wilson confidence intervals.
** Logistic regression includes terms for baseline EQ-VAS score (p<0.0001), age (p=0.1760), baseline eGFR (CKD-EPI) (p=0.0394), Treatment (p=0.0210), region (5 cat.) (p<0.0001), baseline diabetes status (3 cat.) (p=0.8003), sex (p=0.8360), baseline LVEF (3 cat.) (p=0.6138) and Treatment by baseline LVEF (3 cat.) interaction (p=0.8145).
***Wald confidence intervals.

Data taken from study 1245.121 only.
LOCF: For a missing value at week 52 the last available post-baseline value before week 52 is imputed.

Table R.1.2.2.15: 5 Responder analysis (displaying odds ratio) in EQ-VAS change from baseline at week 52 of >= 10 points (improvement) by baseline LVEF (3 cat.) - RS (LOCF-AD) - 1245.121

Subgroup Description	Placebo	Empa 10mg
Baseline LVEF (3 cat.): >35		
Number of patients in analysis set	114	128
Number of analysed patients, N (%)	104 (100.0)	120 (100.0)
Number of patients with endpoint, N (%)	40 (38.5)	59 (49.2)
95% confidence interval*	(29.7, 48.1)	(40.4, 58.0)
Comparison vs Placebo**		
Odds ratio (SE)		1.340 (0.424)
95% confidence interval***		(0.721, 2.490)
p-value		0.3549

* Wilson confidence intervals.
** Logistic regression includes terms for baseline EQ-VAS score (p<0.0001), age (p=0.1760), baseline eGFR (CKD-EPI) (p=0.0394), Treatment (p=0.0210), region (5 cat.) (p<0.0001), baseline diabetes status (3 cat.) (p=0.8003), sex (p=0.8360), baseline LVEF (3 cat.) (p=0.6138) and Treatment by baseline LVEF (3 cat.) interaction (p=0.8145).
***Wald confidence intervals.

Data taken from study 1245.121 only.
LOCF: For a missing value at week 52 the last available post-baseline value before week 52 is imputed.

Table R.1.2.2.15: 6 Responder analysis (displaying risk ratio) in EQ-VAS change from baseline at week 52 of >= 10 points (improvement) by baseline LVEF (3 cat.) - RS (LOCF-AD) - 1245.121

Subgroup Description	Placebo	Empa 10mg
Baseline LVEF (3 cat.): <=30		
Number of patients in analysis set	1392	1337
Number of analysed patients, N (%)	1272 (100.0)	1240 (100.0)
Number of patients with endpoint, N (%)	489 (38.4)	522 (42.1)
95% confidence interval*	(35.8, 41.1)	(39.4, 44.9)
Comparison vs Placebo**		
Risk ratio (SE)		1.098 (0.049)
95% confidence interval***		(1.007, 1.198)
p-value		0.0352
Baseline LVEF (3 cat.): >30 to <=35		
Number of patients in analysis set	361	398
Number of analysed patients, N (%)	334 (100.0)	373 (100.0)
Number of patients with endpoint, N (%)	114 (34.1)	153 (41.0)
95% confidence interval*	(29.3, 39.4)	(36.1, 46.1)
Comparison vs Placebo**		
Risk ratio (SE)		1.164 (0.101)
95% confidence interval***		(0.981, 1.380)
p-value		0.0811

* Wilson confidence intervals.
** Log-linked Poisson model with robust estimate of variance includes terms for baseline EQ-VAS score (p<0.0001), age (p=0.1528), baseline eGFR (CKD-EPI) (p=0.0542), Treatment (p=0.0619), region (5 cat.) (p<0.0001), baseline diabetes status (3 cat.) (p=0.8093), sex (p=0.5268), baseline LVEF (3 cat.) (p=0.6374) and Treatment by baseline LVEF (3 cat.) interaction (p=0.8162).
***Wald confidence intervals.

Data taken from study 1245.121 only.
LOCF: For a missing value at week 52 the last available post-baseline value before week 52 is imputed.

Table R.1.2.2.15: 6 Responder analysis (displaying risk ratio) in EQ-VAS change from baseline at week 52 of >= 10 points (improvement) by baseline LVEF (3 cat.) - RS (LOCF-AD) - 1245.121

Subgroup Description	Placebo	Empa 10mg
Baseline LVEF (3 cat.): >35		
Number of patients in analysis set	114	128
Number of analysed patients, N (%)	104 (100.0)	120 (100.0)
Number of patients with endpoint, N (%)	40 (38.5)	59 (49.2)
95% confidence interval*	(29.7, 48.1)	(40.4, 58.0)
Comparison vs Placebo**		
Risk ratio (SE)		1.075 (0.150)
95% confidence interval***		(0.819, 1.412)
p-value		0.6022

* Wilson confidence intervals.
** Log-linked Poisson model with robust estimate of variance includes terms for baseline EQ-VAS score (p<0.0001), age (p=0.1528), baseline eGFR (CKD-EPI) (p=0.0542), Treatment (p=0.0619), region (5 cat.) (p<0.0001), baseline diabetes status (3 cat.) (p=0.8093), sex (p=0.5268), baseline LVEF (3 cat.) (p=0.6374) and Treatment by baseline LVEF (3 cat.) interaction (p=0.8162).
***Wald confidence intervals.

Data taken from study 1245.121 only.
LOCF: For a missing value at week 52 the last available post-baseline value before week 52 is imputed.

R.1.2.2.16 Subgroup analysis by bl. NTproBNP </>= median (median based on total patients)

Table R.1.2.2.16: 1 Responder analysis (displaying odds ratio) in EQ-VAS change from baseline at week 52 of <= -10 points (deterioration) by bl. NTproBNP (<median, >= median) (median based on total patients) - RS (LOCF-AD) - 1245.121

Subgroup Description	Placebo	Empa 10mg
Baseline NTproBNP (<median, >= median): < median		
Number of patients in analysis set	920	942
Number of analysed patients, N (%)	866 (100.0)	884 (100.0)
Number of patients with endpoint, N (%)	203 (23.4)	183 (20.7)
95% confidence interval*	(20.7, 26.4)	(18.2, 23.5)
Comparison vs Placebo**		
Odds ratio (SE)		0.850 (0.103)
95% confidence interval***		(0.670, 1.079)
p-value		0.1811
Baseline NTproBNP (<median, >= median): >= median		
Number of patients in analysis set	946	920
Number of analysed patients, N (%)	844 (100.0)	849 (100.0)
Number of patients with endpoint, N (%)	206 (24.4)	203 (23.9)
95% confidence interval*	(21.6, 27.4)	(21.2, 26.9)
Comparison vs Placebo**		
Odds ratio (SE)		0.951 (0.115)
95% confidence interval***		(0.751, 1.205)
p-value		0.6771

* Wilson confidence intervals.
** Logistic regression includes terms for baseline EQ-VAS score (p<0.0001), age (p=0.0295), baseline eGFR (CKD-EPI) (p=0.4936), Treatment (p=0.2140), region (5 cat.) (p<0.0001), baseline diabetes status (3 cat.) (p=0.4625), sex (p=0.0452), baseline LVEF (3 cat.) (p=0.2691), baseline NTproBNP (<median, >= median) (p=0.0112) and Treatment by baseline NTproBNP (<median, >= median) interaction (p=0.5115).
***Wald confidence intervals.
2 patients were excluded as the subgroup variable was missing.

Data taken from study 1245.121 only.
LOCF: For a missing value at week 52 the last available post-baseline value before week 52 is imputed.
Median: 1910 [pg/mL]

Table R.1.2.2.16: 2 Responder analysis (displaying risk ratio) in EQ-VAS change from baseline at week 52 of <= -10 points (deterioration) by bl. NTproBNP (<median, >= median) (median based on total patients) - RS (LOCF-AD) - 1245.121

Subgroup Description	Placebo	Empa 10mg
Baseline NTproBNP (<median, >= median): < median		
Number of patients in analysis set	920	942
Number of analysed patients, N (%)	866 (100.0)	884 (100.0)
Number of patients with endpoint, N (%)	203 (23.4)	183 (20.7)
95% confidence interval*	(20.7, 26.4)	(18.2, 23.5)
Comparison vs Placebo**		
Risk ratio (SE)		0.892 (0.077)
95% confidence interval***		(0.754, 1.056)
p-value		0.1847
Baseline NTproBNP (<median, >= median): >= median		
Number of patients in analysis set	946	920
Number of analysed patients, N (%)	844 (100.0)	849 (100.0)
Number of patients with endpoint, N (%)	206 (24.4)	203 (23.9)
95% confidence interval*	(21.6, 27.4)	(21.2, 26.9)
Comparison vs Placebo**		
Risk ratio (SE)		0.960 (0.078)
95% confidence interval***		(0.818, 1.126)
p-value		0.6177

* Wilson confidence intervals.
** Log-linked Poisson model with robust estimate of variance includes terms for baseline EQ-VAS score (p<0.0001), age (p=0.0242), baseline eGFR (CKD-EPI) (p=0.5138), Treatment (p=0.1911), region (5 cat.) (p<0.0001), baseline diabetes status (3 cat.) (p=0.4998), sex (p=0.0542), baseline LVEF (3 cat.) (p=0.2925), baseline NTproBNP (<median, >= median) (p=0.0113) and Treatment by baseline NTproBNP (<median, >= median) interaction (p=0.5354).
***Wald confidence intervals.
2 patients were excluded as the subgroup variable was missing.

Data taken from study 1245.121 only.
LOCF: For a missing value at week 52 the last available post-baseline value before week 52 is imputed.
Median: 1910 [pg/mL]

Table R.1.2.2.16: 3 Responder analysis (displaying odds ratio) in EQ-VAS change from baseline at week 52 of > -10 points (stability) by bl. NTproBNP (<median, >= median) (median based on total patients) - RS (LOCF-AD) - 1245.121

Subgroup Description	Placebo	Empa 10mg
Baseline NTproBNP (<median, >= median): < median		
Number of patients in analysis set	920	942
Number of analysed patients, N (%)	866 (100.0)	884 (100.0)
Number of patients with endpoint, N (%)	663 (76.6)	701 (79.3)
95% confidence interval*	(73.6, 79.3)	(76.5, 81.8)
Comparison vs Placebo**		
Odds ratio (SE)		1.177 (0.143)
95% confidence interval***		(0.927, 1.493)
p-value		0.1811
Baseline NTproBNP (<median, >= median): >= median		
Number of patients in analysis set	946	920
Number of analysed patients, N (%)	844 (100.0)	849 (100.0)
Number of patients with endpoint, N (%)	638 (75.6)	646 (76.1)
95% confidence interval*	(72.6, 78.4)	(73.1, 78.8)
Comparison vs Placebo**		
Odds ratio (SE)		1.051 (0.127)
95% confidence interval***		(0.830, 1.332)
p-value		0.6771

* Wilson confidence intervals.
** Logistic regression includes terms for baseline EQ-VAS score (p<0.0001), age (p=0.0295), baseline eGFR (CKD-EPI) (p=0.4936), Treatment (p=0.2140), region (5 cat.) (p<0.0001), baseline diabetes status (3 cat.) (p=0.4625), sex (p=0.0452), baseline LVEF (3 cat.) (p=0.2691), baseline NTproBNP (<median, >= median) (p=0.0112) and Treatment by baseline NTproBNP (<median, >= median) interaction (p=0.5115).
***Wald confidence intervals.
2 patients were excluded as the subgroup variable was missing.

Data taken from study 1245.121 only.
LOCF: For a missing value at week 52 the last available post-baseline value before week 52 is imputed.
Median: 1910 [pg/mL]

Table R.1.2.2.16: 4 Responder analysis (displaying risk ratio) in EQ-VAS change from baseline at week 52 of > -10 points (stability) by bl. NTproBNP (<median, >= median) (median based on total patients) - RS (LOCF-AD) - 1245.121

Subgroup Description	Placebo	Empa 10mg
Baseline NTproBNP (<median, >= median): < median		
Number of patients in analysis set	920	942
Number of analysed patients, N (%)	866 (100.0)	884 (100.0)
Number of patients with endpoint, N (%)	663 (76.6)	701 (79.3)
95% confidence interval*	(73.6, 79.3)	(76.5, 81.8)
Comparison vs Placebo**		
Risk ratio (SE)		1.031 (0.025)
95% confidence interval***		(0.983, 1.082)
p-value		0.2049
Baseline NTproBNP (<median, >= median): >= median		
Number of patients in analysis set	946	920
Number of analysed patients, N (%)	844 (100.0)	849 (100.0)
Number of patients with endpoint, N (%)	638 (75.6)	646 (76.1)
95% confidence interval*	(72.6, 78.4)	(73.1, 78.8)
Comparison vs Placebo**		
Risk ratio (SE)		1.004 (0.026)
95% confidence interval***		(0.954, 1.057)
p-value		0.8706

* Wilson confidence intervals.
** Log-linked Poisson model with robust estimate of variance includes terms for baseline EQ-VAS score (p<0.0001), age (p=0.0478), baseline eGFR (CKD-EPI) (p=0.5735), Treatment (p=0.3252), region (5 cat.) (p<0.0001), baseline diabetes status (3 cat.) (p=0.3661), sex (p=0.0217), baseline LVEF (3 cat.) (p=0.3571), baseline NTproBNP (<median, >= median) (p=0.0056) and Treatment by baseline NTproBNP (<median, >= median) interaction (p=0.4551).
***Wald confidence intervals.
2 patients were excluded as the subgroup variable was missing.

Data taken from study 1245.121 only.
LOCF: For a missing value at week 52 the last available post-baseline value before week 52 is imputed.
Median: 1910 [pg/mL]

Table R.1.2.2.16: 5 Responder analysis (displaying odds ratio) in EQ-VAS change from baseline at week 52 of >= 10 points (improvement) by bl. NTproBNP (<median, >= median) (median based on total patients) - RS (LOCF-AD) - 1245.121

Subgroup Description	Placebo	Empa 10mg
Baseline NTproBNP (<median, >= median): < median		
Number of patients in analysis set	920	942
Number of analysed patients, N (%)	866 (100.0)	884 (100.0)
Number of patients with endpoint, N (%)	312 (36.0)	363 (41.1)
95% confidence interval*	(32.9, 39.3)	(37.9, 44.3)
Comparison vs Placebo**		
Odds ratio (SE)		1.271 (0.144)
95% confidence interval***		(1.018, 1.587)
p-value		0.0344
Baseline NTproBNP (<median, >= median): >= median		
Number of patients in analysis set	946	920
Number of analysed patients, N (%)	844 (100.0)	849 (100.0)
Number of patients with endpoint, N (%)	331 (39.2)	371 (43.7)
95% confidence interval*	(36.0, 42.6)	(40.4, 47.1)
Comparison vs Placebo**		
Odds ratio (SE)		1.308 (0.151)
95% confidence interval***		(1.043, 1.639)
p-value		0.0199

* Wilson confidence intervals.
** Logistic regression includes terms for baseline EQ-VAS score (p<0.0001), age (p=0.1769), baseline eGFR (CKD-EPI) (p=0.0441), Treatment (p=0.0017), region (5 cat.) (p<0.0001), baseline diabetes status (3 cat.) (p=0.7996), sex (p=0.8282), baseline LVEF (3 cat.) (p=0.6203), baseline NTproBNP (<median, >= median) (p=0.9028) and Treatment by baseline NTproBNP (<median, >= median) interaction (p=0.8591).
***Wald confidence intervals.
2 patients were excluded as the subgroup variable was missing.

Data taken from study 1245.121 only.
LOCF: For a missing value at week 52 the last available post-baseline value before week 52 is imputed.
Median: 1910 [pg/mL]

Table R.1.2.2.16: 6 Responder analysis (displaying risk ratio) in EQ-VAS change from baseline at week 52 of >= 10 points (improvement) by bl. NTproBNP (<median, >= median) (median based on total patients) - RS (LOCF-AD) - 1245.121

Subgroup Description	Placebo	Empa 10mg
Baseline NTproBNP (<median, >= median): < median		
Number of patients in analysis set	920	942
Number of analysed patients, N (%)	866 (100.0)	884 (100.0)
Number of patients with endpoint, N (%)	312 (36.0)	363 (41.1)
95% confidence interval*	(32.9, 39.3)	(37.9, 44.3)
Comparison vs Placebo**		
Risk ratio (SE)		1.123 (0.060)
95% confidence interval***		(1.011, 1.247)
p-value		0.0309
Baseline NTproBNP (<median, >= median): >= median		
Number of patients in analysis set	946	920
Number of analysed patients, N (%)	844 (100.0)	849 (100.0)
Number of patients with endpoint, N (%)	331 (39.2)	371 (43.7)
95% confidence interval*	(36.0, 42.6)	(40.4, 47.1)
Comparison vs Placebo**		
Risk ratio (SE)		1.095 (0.059)
95% confidence interval***		(0.985, 1.217)
p-value		0.0939

* Wilson confidence intervals.
** Log-linked Poisson model with robust estimate of variance includes terms for baseline EQ-VAS score (p<0.0001), age (p=0.1589), baseline eGFR (CKD-EPI) (p=0.0763), Treatment (p=0.0068), region (5 cat.) (p<0.0001), baseline diabetes status (3 cat.) (p=0.8070), sex (p=0.4932), baseline LVEF (3 cat.) (p=0.6695), baseline NTproBNP (<median, >= median) (p=0.4859) and Treatment by baseline NTproBNP (<median, >= median) interaction (p=0.7393).
***Wald confidence intervals.
2 patients were excluded as the subgroup variable was missing.

Data taken from study 1245.121 only.
LOCF: For a missing value at week 52 the last available post-baseline value before week 52 is imputed.
Median: 1910 [pg/mL]

R.1.2.3

R.1.2.3 EQ-VAS responder analysis (15 points)

R.1.2.3.1

Table R.1.2.3.1: 1 Responder analysis (displaying odds ratio) in EQ-VAS change from baseline at week 52 of <= -15 points (deterioration) - RS (LOCF-AD) - 1245.121

	Placebo	Empa 10mg
Number of patients in analysis set	1867	1863
Number of analysed patients, N (%)	1710 (100.0)	1733 (100.0)
Number of patients with endpoint, N (%)	246 (14.4)	229 (13.2)
95% confidence interval*	(12.8, 16.1)	(11.7, 14.9)
Comparison vs Placebo**		
Odds ratio (SE)		0.896 (0.092)
95% confidence interval***		(0.732, 1.096)
p-value		0.2846

* Wilson confidence intervals.
** Logistic regression includes terms for baseline EQ-VAS score (p<0.0001), age (p=0.0466), baseline eGFR (CKD-EPI) (p=0.0224), Treatment (p=0.2846), region (5 cat.) (p<0.0001), baseline diabetes status (3 cat.) (p=0.7052), sex (p=0.0436) and baseline LVEF (3 cat.) (p=0.3953).
***Wald confidence intervals.

Data taken from study 1245.121 only.
LOCF: For a missing value at week 52 the last available post-baseline value before week 52 is imputed.

Table R.1.2.3.1: 2 Responder analysis (displaying risk ratio) in EQ-VAS change from baseline at week 52 of <= -15 points (deterioration) - RS (LOCF-AD) - 1245.121

	Placebo	Empa 10mg
Number of patients in analysis set	1867	1863
Number of analysed patients, N (%)	1710 (100.0)	1733 (100.0)
Number of patients with endpoint, N (%)	246 (14.4)	229 (13.2)
95% confidence interval*	(12.8, 16.1)	(11.7, 14.9)
Comparison vs Placebo**		
Risk ratio (SE)		0.914 (0.075)
95% confidence interval***		(0.777, 1.074)
p-value		0.2736

* Wilson confidence intervals.
** Log-linked Poisson model with robust estimate of variance includes terms for baseline EQ-VAS score (p<0.0001), age (p=0.0618), baseline eGFR (CKD-EPI) (p=0.0277), Treatment (p=0.2736), region (5 cat.) (p<0.0001), baseline diabetes status (3 cat.) (p=0.7182), sex (p=0.0479) and baseline LVEF (3 cat.) (p=0.4236).
***Wald confidence intervals.

Data taken from study 1245.121 only.
LOCF: For a missing value at week 52 the last available post-baseline value before week 52 is imputed.

Table R.1.2.3.1: 3 Responder analysis (displaying odds ratio) in EQ-VAS change from baseline at week 52 of > -15 points (stability) - RS (LOCF-AD) - 1245.121

	Placebo	Empa 10mg
Number of patients in analysis set	1867	1863
Number of analysed patients, N (%)	1710 (100.0)	1733 (100.0)
Number of patients with endpoint, N (%)	1464 (85.6)	1504 (86.8)
95% confidence interval*	(83.9, 87.2)	(85.1, 88.3)
Comparison vs Placebo**		
Odds ratio (SE)		1.116 (0.115)
95% confidence interval***		(0.913, 1.366)
p-value		0.2846

* Wilson confidence intervals.
** Logistic regression includes terms for baseline EQ-VAS score (p<0.0001), age (p=0.0466), baseline eGFR (CKD-EPI) (p=0.0224), Treatment (p=0.2846), region (5 cat.) (p<0.0001), baseline diabetes status (3 cat.) (p=0.7052), sex (p=0.0436) and baseline LVEF (3 cat.) (p=0.3953).
***Wald confidence intervals.

Data taken from study 1245.121 only.
LOCF: For a missing value at week 52 the last available post-baseline value before week 52 is imputed.

Table R.1.2.3.1: 4 Responder analysis (displaying risk ratio) in EQ-VAS change from baseline at week 52 of > -15 points (stability) - RS (LOCF-AD) - 1245.121

	Placebo	Empa 10mg
Number of patients in analysis set	1867	1863
Number of analysed patients, N (%)	1710 (100.0)	1733 (100.0)
Number of patients with endpoint, N (%)	1464 (85.6)	1504 (86.8)
95% confidence interval*	(83.9, 87.2)	(85.1, 88.3)
Comparison vs Placebo**		
Risk ratio (SE)		1.012 (0.013)
95% confidence interval***		(0.986, 1.039)
p-value		0.3546

* Wilson confidence intervals.
** Log-linked Poisson model with robust estimate of variance includes terms for baseline EQ-VAS score (p<0.0001), age (p=0.1074), baseline eGFR (CKD-EPI) (p=0.0286), Treatment (p=0.3546), region (5 cat.) (p=0.0010), baseline diabetes status (3 cat.) (p=0.6185), sex (p=0.0303) and baseline LVEF (3 cat.) (p=0.4417).
***Wald confidence intervals.

Data taken from study 1245.121 only.
LOCF: For a missing value at week 52 the last available post-baseline value before week 52 is imputed.

Table R.1.2.3.1: 5 Responder analysis (displaying odds ratio) in EQ-VAS change from baseline at week 52 of >= 15 points (improvement) - RS (LOCF-AD) - 1245.121

	Placebo	Empa 10mg
Number of patients in analysis set	1867	1863
Number of analysed patients, N (%)	1710 (100.0)	1733 (100.0)
Number of patients with endpoint, N (%)	420 (24.6)	495 (28.6)
95% confidence interval*	(22.6, 26.7)	(26.5, 30.7)
Comparison vs Placebo**		
Odds ratio (SE)		1.283 (0.116)
95% confidence interval***		(1.074, 1.532)
p-value		0.0060

* Wilson confidence intervals.
** Logistic regression includes terms for baseline EQ-VAS score (p<0.0001), age (p=0.1141), baseline eGFR (CKD-EPI) (p=0.1381), Treatment (p=0.0060), region (5 cat.) (p<0.0001), baseline diabetes status (3 cat.) (p=0.6758), sex (p=0.4540) and baseline LVEF (3 cat.) (p=0.0589).
***Wald confidence intervals.

Data taken from study 1245.121 only.
LOCF: For a missing value at week 52 the last available post-baseline value before week 52 is imputed.

Table R.1.2.3.1: 6 Responder analysis (displaying risk ratio) in EQ-VAS change from baseline at week 52 of >= 15 points (improvement) - RS (LOCF-AD) - 1245.121

	Placebo	Empa 10mg
Number of patients in analysis set	1867	1863
Number of analysed patients, N (%)	1710 (100.0)	1733 (100.0)
Number of patients with endpoint, N (%)	420 (24.6)	495 (28.6)
95% confidence interval*	(22.6, 26.7)	(26.5, 30.7)
Comparison vs Placebo**		
Risk ratio (SE)		1.128 (0.059)
95% confidence interval***		(1.018, 1.249)
p-value		0.0209

* Wilson confidence intervals.
** Log-linked Poisson model with robust estimate of variance includes terms for baseline EQ-VAS score (p<0.0001), age (p=0.0931), baseline eGFR (CKD-EPI) (p=0.1446), Treatment (p=0.0209), region (5 cat.) (p<0.0001), baseline diabetes status (3 cat.) (p=0.5624), sex (p=0.2276) and baseline LVEF (3 cat.) (p=0.1228).
***Wald confidence intervals.

Data taken from study 1245.121 only.
LOCF: For a missing value at week 52 the last available post-baseline value before week 52 is imputed.

R.1.2.3.2

R.1.2.3.2 Subgroup analysis by sex

Table R.1.2.3.2: 1 Responder analysis (displaying odds ratio) in EQ-VAS change from baseline at week 52 of <= -15 points (deterioration) by sex - RS (LOCF-AD) - 1245.121

Subgroup Description	Placebo	Empa 10mg
Sex: Male		
Number of patients in analysis set	1411	1426
Number of analysed patients, N (%)	1297 (100.0)	1328 (100.0)
Number of patients with endpoint, N (%)	181 (14.0)	168 (12.7)
95% confidence interval*	(12.2, 15.9)	(11.0, 14.5)
Comparison vs Placebo**		
Odds ratio (SE)		0.881 (0.105)
95% confidence interval***		(0.698, 1.114)
p-value		0.2898
Sex: Female		
Number of patients in analysis set	456	437
Number of analysed patients, N (%)	413 (100.0)	405 (100.0)
Number of patients with endpoint, N (%)	65 (15.7)	61 (15.1)
95% confidence interval*	(12.5, 19.6)	(11.9, 18.9)
Comparison vs Placebo**		
Odds ratio (SE)		0.939 (0.191)
95% confidence interval***		(0.631, 1.398)
p-value		0.7565

* Wilson confidence intervals.
** Logistic regression includes terms for baseline EQ-VAS score (p<0.0001), age (p=0.0458), baseline eGFR (CKD-EPI) (p=0.0224), Treatment (p=0.4213), region (5 cat.) (p<0.0001), baseline diabetes status (3 cat.) (p=0.7064), baseline LVEF (3 cat.) (p=0.3961), sex (p=0.0429) and Treatment by sex interaction (p=0.7878).
***Wald confidence intervals.

Data taken from study 1245.121 only.
LOCF: For a missing value at week 52 the last available post-baseline value before week 52 is imputed.

Table R.1.2.3.2: 2 Responder analysis (displaying risk ratio) in EQ-VAS change from baseline at week 52 of <= -15 points (deterioration) by sex - RS (LOCF-AD) - 1245.121

Subgroup Description	Placebo	Empa 10mg
Sex: Male		
Number of patients in analysis set	1411	1426
Number of analysed patients, N (%)	1297 (100.0)	1328 (100.0)
Number of patients with endpoint, N (%)	181 (14.0)	168 (12.7)
95% confidence interval*	(12.2, 15.9)	(11.0, 14.5)
Comparison vs Placebo**		
Risk ratio (SE)		0.902 (0.087)
95% confidence interval***		(0.746, 1.091)
p-value		0.2879
Sex: Female		
Number of patients in analysis set	456	437
Number of analysed patients, N (%)	413 (100.0)	405 (100.0)
Number of patients with endpoint, N (%)	65 (15.7)	61 (15.1)
95% confidence interval*	(12.5, 19.6)	(11.9, 18.9)
Comparison vs Placebo**		
Risk ratio (SE)		0.946 (0.149)
95% confidence interval***		(0.694, 1.289)
p-value		0.7245

* Wilson confidence intervals.
** Log-linked Poisson model with robust estimate of variance includes terms for baseline EQ-VAS score (p<0.0001), age (p=0.0608), baseline eGFR (CKD-EPI) (p=0.0278), Treatment (p=0.3919), region (5 cat.) (p<0.0001), baseline diabetes status (3 cat.) (p=0.7182), baseline LVEF (3 cat.) (p=0.4243), sex (p=0.0471) and Treatment by sex interaction (p=0.7988).
***Wald confidence intervals.

Data taken from study 1245.121 only.
LOCF: For a missing value at week 52 the last available post-baseline value before week 52 is imputed.

Table R.1.2.3.2: 3 Responder analysis (displaying odds ratio) in EQ-VAS change from baseline at week 52 of > -15 points (stability) by sex - RS (LOCF-AD) - 1245.121

Subgroup Description	Placebo	Empa 10mg
Sex: Male		
Number of patients in analysis set	1411	1426
Number of analysed patients, N (%)	1297 (100.0)	1328 (100.0)
Number of patients with endpoint, N (%)	1116 (86.0)	1160 (87.3)
95% confidence interval*	(84.1, 87.8)	(85.5, 89.0)
Comparison vs Placebo**		
Odds ratio (SE)		1.135 (0.135)
95% confidence interval***		(0.898, 1.434)
p-value		0.2898
Sex: Female		
Number of patients in analysis set	456	437
Number of analysed patients, N (%)	413 (100.0)	405 (100.0)
Number of patients with endpoint, N (%)	348 (84.3)	344 (84.9)
95% confidence interval*	(80.4, 87.5)	(81.1, 88.1)
Comparison vs Placebo**		
Odds ratio (SE)		1.065 (0.216)
95% confidence interval***		(0.715, 1.585)
p-value		0.7565

* Wilson confidence intervals.
** Logistic regression includes terms for baseline EQ-VAS score (p<0.0001), age (p=0.0458), baseline eGFR (CKD-EPI) (p=0.0224), Treatment (p=0.4213), region (5 cat.) (p<0.0001), baseline diabetes status (3 cat.) (p=0.7064), baseline LVEF (3 cat.) (p=0.3961), sex (p=0.0429) and Treatment by sex interaction (p=0.7878).
***Wald confidence intervals.

Data taken from study 1245.121 only.
LOCF: For a missing value at week 52 the last available post-baseline value before week 52 is imputed.

Table R.1.2.3.2: 4 Responder analysis (displaying risk ratio) in EQ-VAS change from baseline at week 52 of > -15 points (stability) by sex - RS (LOCF-AD) - 1245.121

Subgroup Description	Placebo	Empa 10mg
Sex: Male		
Number of patients in analysis set	1411	1426
Number of analysed patients, N (%)	1297 (100.0)	1328 (100.0)
Number of patients with endpoint, N (%)	1116 (86.0)	1160 (87.3)
95% confidence interval*	(84.1, 87.8)	(85.5, 89.0)
Comparison vs Placebo**		
Risk ratio (SE)		1.015 (0.015)
95% confidence interval***		(0.986, 1.045)
p-value		0.3110
Sex: Female		
Number of patients in analysis set	456	437
Number of analysed patients, N (%)	413 (100.0)	405 (100.0)
Number of patients with endpoint, N (%)	348 (84.3)	344 (84.9)
95% confidence interval*	(80.4, 87.5)	(81.1, 88.1)
Comparison vs Placebo**		
Risk ratio (SE)		1.003 (0.029)
95% confidence interval***		(0.948, 1.061)
p-value		0.9174

* Wilson confidence intervals.
** Log-linked Poisson model with robust estimate of variance includes terms for baseline EQ-VAS score (p<0.0001), age (p=0.1059), baseline eGFR (CKD-EPI) (p=0.0280), Treatment (p=0.5765), region (5 cat.) (p=0.0010), baseline diabetes status (3 cat.) (p=0.6216), baseline LVEF (3 cat.) (p=0.4468), sex (p=0.0305) and Treatment by sex interaction (p=0.7077).
***Wald confidence intervals.

Data taken from study 1245.121 only.
LOCF: For a missing value at week 52 the last available post-baseline value before week 52 is imputed.

Table R.1.2.3.2: 5 Responder analysis (displaying odds ratio) in EQ-VAS change from baseline at week 52 of >= 15 points (improvement) by sex - RS (LOCF-AD) - 1245.121

Subgroup Description	Placebo	Empa 10mg
Sex: Male		
Number of patients in analysis set	1411	1426
Number of analysed patients, N (%)	1297 (100.0)	1328 (100.0)
Number of patients with endpoint, N (%)	312 (24.1)	378 (28.5)
95% confidence interval*	(21.8, 26.5)	(26.1, 31.0)
Comparison vs Placebo**		
Odds ratio (SE)		1.345 (0.140)
95% confidence interval***		(1.097, 1.648)
p-value		0.0043
Sex: Female		
Number of patients in analysis set	456	437
Number of analysed patients, N (%)	413 (100.0)	405 (100.0)
Number of patients with endpoint, N (%)	108 (26.2)	117 (28.9)
95% confidence interval*	(22.1, 30.6)	(24.7, 33.5)
Comparison vs Placebo**		
Odds ratio (SE)		1.102 (0.205)
95% confidence interval***		(0.765, 1.586)
p-value		0.6031

* Wilson confidence intervals.
** Logistic regression includes terms for baseline EQ-VAS score (p<0.0001), age (p=0.1133), baseline eGFR (CKD-EPI) (p=0.1304), Treatment (p=0.0650), region (5 cat.) (p<0.0001), baseline diabetes status (3 cat.) (p=0.6780), baseline LVEF (3 cat.) (p=0.0557), sex (p=0.4623) and Treatment by sex interaction (p=0.3496).
***Wald confidence intervals.

Data taken from study 1245.121 only.
LOCF: For a missing value at week 52 the last available post-baseline value before week 52 is imputed.

Table R.1.2.3.2: 6 Responder analysis (displaying risk ratio) in EQ-VAS change from baseline at week 52 of >= 15 points (improvement) by sex - RS (LOCF-AD) - 1245.121

Subgroup Description	Placebo	Empa 10mg
Sex: Male		
Number of patients in analysis set	1411	1426
Number of analysed patients, N (%)	1297 (100.0)	1328 (100.0)
Number of patients with endpoint, N (%)	312 (24.1)	378 (28.5)
95% confidence interval*	(21.8, 26.5)	(26.1, 31.0)
Comparison vs Placebo**		
Risk ratio (SE)		1.170 (0.071)
95% confidence interval***		(1.039, 1.317)
p-value		0.0095
Sex: Female		
Number of patients in analysis set	456	437
Number of analysed patients, N (%)	413 (100.0)	405 (100.0)
Number of patients with endpoint, N (%)	108 (26.2)	117 (28.9)
95% confidence interval*	(22.1, 30.6)	(24.7, 33.5)
Comparison vs Placebo**		
Risk ratio (SE)		1.008 (0.104)
95% confidence interval***		(0.824, 1.233)
p-value		0.9359

* Wilson confidence intervals.
** Log-linked Poisson model with robust estimate of variance includes terms for baseline EQ-VAS score (p<0.0001), age (p=0.0961), baseline eGFR (CKD-EPI) (p=0.1338), Treatment (p=0.1663), region (5 cat.) (p<0.0001), baseline diabetes status (3 cat.) (p=0.5649), baseline LVEF (3 cat.) (p=0.1129), sex (p=0.2593) and Treatment by sex interaction (p=0.2122).
***Wald confidence intervals.

Data taken from study 1245.121 only.
LOCF: For a missing value at week 52 the last available post-baseline value before week 52 is imputed.

R.1.2.3.3

R.1.2.3.3 Subgroup analysis by age

Table R.1.2.3.3: 1 Responder analysis (displaying odds ratio) in EQ-VAS change from baseline at week 52 of <= -15 points (deterioration) by age (2 cat.) - RS (LOCF-AD) - 1245.121

Subgroup Description	Placebo	Empa 10mg
Age [years] (2 cat.): < 65		
Number of patients in analysis set	740	675
Number of analysed patients, N (%)	675 (100.0)	632 (100.0)
Number of patients with endpoint, N (%)	79 (11.7)	69 (10.9)
95% confidence interval*	(9.5, 14.3)	(8.7, 13.6)
Comparison vs Placebo**		
Odds ratio (SE)		0.949 (0.172)
95% confidence interval***		(0.665, 1.354)
p-value		0.7708
Age [years] (2 cat.): >= 65		
Number of patients in analysis set	1127	1188
Number of analysed patients, N (%)	1035 (100.0)	1101 (100.0)
Number of patients with endpoint, N (%)	167 (16.1)	160 (14.5)
95% confidence interval*	(14.0, 18.5)	(12.6, 16.7)
Comparison vs Placebo**		
Odds ratio (SE)		0.875 (0.109)
95% confidence interval***		(0.685, 1.117)
p-value		0.2842

* Wilson confidence intervals.
** Logistic regression includes terms for baseline EQ-VAS score (p<0.0001), baseline eGFR (CKD-EPI) (p=0.0020), Treatment (p=0.3964), region (5 cat.) (p<0.0001), baseline diabetes status (3 cat.) (p=0.7317), sex (p=0.0427), baseline LVEF (3 cat.) (p=0.4420), age (2 cat.) (p=0.4277) and Treatment by age (2 cat.) interaction (p=0.7138).
***Wald confidence intervals.

Data taken from study 1245.121 only.
LOCF: For a missing value at week 52 the last available post-baseline value before week 52 is imputed.

Table R.1.2.3.3: 2 Responder analysis (displaying risk ratio) in EQ-VAS change from baseline at week 52 of <= -15 points (deterioration) by age (2 cat.) - RS (LOCF-AD) - 1245.121

Subgroup Description	Placebo	Empa 10mg
Age [years] (2 cat.): < 65		
Number of patients in analysis set	740	675
Number of analysed patients, N (%)	675 (100.0)	632 (100.0)
Number of patients with endpoint, N (%)	79 (11.7)	69 (10.9)
95% confidence interval*	(9.5, 14.3)	(8.7, 13.6)
Comparison vs Placebo**		
Risk ratio (SE)		0.953 (0.145)
95% confidence interval***		(0.708, 1.284)
p-value		0.7525
Age [years] (2 cat.): >= 65		
Number of patients in analysis set	1127	1188
Number of analysed patients, N (%)	1035 (100.0)	1101 (100.0)
Number of patients with endpoint, N (%)	167 (16.1)	160 (14.5)
95% confidence interval*	(14.0, 18.5)	(12.6, 16.7)
Comparison vs Placebo**		
Risk ratio (SE)		0.898 (0.088)
95% confidence interval***		(0.740, 1.089)
p-value		0.2747

* Wilson confidence intervals.
** Log-linked Poisson model with robust estimate of variance includes terms for baseline EQ-VAS score (p<0.0001), baseline eGFR (CKD-EPI) (p=0.0024), Treatment (p=0.3897), region (5 cat.) (p<0.0001), baseline diabetes status (3 cat.) (p=0.7424), sex (p=0.0465), baseline LVEF (3 cat.) (p=0.4682), age (2 cat.) (p=0.4144) and Treatment by age (2 cat.) interaction (p=0.7423).
***Wald confidence intervals.

Data taken from study 1245.121 only.
LOCF: For a missing value at week 52 the last available post-baseline value before week 52 is imputed.

Table R.1.2.3.3: 3 Responder analysis (displaying odds ratio) in EQ-VAS change from baseline at week 52 of > -15 points (stability) by age (2 cat.) - RS (LOCF-AD) - 1245.121

Subgroup Description	Placebo	Empa 10mg
Age [years] (2 cat.): < 65		
Number of patients in analysis set	740	675
Number of analysed patients, N (%)	675 (100.0)	632 (100.0)
Number of patients with endpoint, N (%)	596 (88.3)	563 (89.1)
95% confidence interval*	(85.7, 90.5)	(86.4, 91.3)
Comparison vs Placebo**		
Odds ratio (SE)		1.054 (0.191)
95% confidence interval***		(0.739, 1.504)
p-value		0.7708
Age [years] (2 cat.): >= 65		
Number of patients in analysis set	1127	1188
Number of analysed patients, N (%)	1035 (100.0)	1101 (100.0)
Number of patients with endpoint, N (%)	868 (83.9)	941 (85.5)
95% confidence interval*	(81.5, 86.0)	(83.3, 87.4)
Comparison vs Placebo**		
Odds ratio (SE)		1.143 (0.143)
95% confidence interval***		(0.895, 1.460)
p-value		0.2842

* Wilson confidence intervals.
** Logistic regression includes terms for baseline EQ-VAS score (p<0.0001), baseline eGFR (CKD-EPI) (p=0.0020), Treatment (p=0.3964), region (5 cat.) (p<0.0001), baseline diabetes status (3 cat.) (p=0.7317), sex (p=0.0427), baseline LVEF (3 cat.) (p=0.4420), age (2 cat.) (p=0.4277) and Treatment by age (2 cat.) interaction (p=0.7138).
***Wald confidence intervals.

Data taken from study 1245.121 only.
LOCF: For a missing value at week 52 the last available post-baseline value before week 52 is imputed.

Table R.1.2.3.3: 4 Responder analysis (displaying risk ratio) in EQ-VAS change from baseline at week 52 of > -15 points (stability) by age (2 cat.) - RS (LOCF-AD) - 1245.121

Subgroup Description	Placebo	Empa 10mg
Age [years] (2 cat.): < 65		
Number of patients in analysis set	740	675
Number of analysed patients, N (%)	675 (100.0)	632 (100.0)
Number of patients with endpoint, N (%)	596 (88.3)	563 (89.1)
95% confidence interval*	(85.7, 90.5)	(86.4, 91.3)
Comparison vs Placebo**		
Risk ratio (SE)		1.003 (0.019)
95% confidence interval***		(0.965, 1.041)
p-value		0.8936
Age [years] (2 cat.): >= 65		
Number of patients in analysis set	1127	1188
Number of analysed patients, N (%)	1035 (100.0)	1101 (100.0)
Number of patients with endpoint, N (%)	868 (83.9)	941 (85.5)
95% confidence interval*	(81.5, 86.0)	(83.3, 87.4)
Comparison vs Placebo**		
Risk ratio (SE)		1.018 (0.018)
95% confidence interval***		(0.983, 1.054)
p-value		0.3195

* Wilson confidence intervals.
** Log-linked Poisson model with robust estimate of variance includes terms for baseline EQ-VAS score (p<0.0001), baseline eGFR (CKD-EPI) (p=0.0033), Treatment (p=0.4380), region (5 cat.) (p=0.0005), baseline diabetes status (3 cat.) (p=0.6401), sex (p=0.0305), baseline LVEF (3 cat.) (p=0.4888), age (2 cat.) (p=0.4706) and Treatment by age (2 cat.) interaction (p=0.5631).
***Wald confidence intervals.

Data taken from study 1245.121 only.
LOCF: For a missing value at week 52 the last available post-baseline value before week 52 is imputed.

Table R.1.2.3.3: 5 Responder analysis (displaying odds ratio) in EQ-VAS change from baseline at week 52 of >= 15 points (improvement) by age (2 cat.) - RS (LOCF-AD) - 1245.121

Subgroup Description	Placebo	Empa 10mg
Age [years] (2 cat.): < 65		
Number of patients in analysis set	740	675
Number of analysed patients, N (%)	675 (100.0)	632 (100.0)
Number of patients with endpoint, N (%)	189 (28.0)	212 (33.5)
95% confidence interval*	(24.7, 31.5)	(30.0, 37.3)
Comparison vs Placebo**		
Odds ratio (SE)		1.254 (0.178)
95% confidence interval***		(0.950, 1.655)
p-value		0.1098
Age [years] (2 cat.): >= 65		
Number of patients in analysis set	1127	1188
Number of analysed patients, N (%)	1035 (100.0)	1101 (100.0)
Number of patients with endpoint, N (%)	231 (22.3)	283 (25.7)
95% confidence interval*	(19.9, 25.0)	(23.2, 28.4)
Comparison vs Placebo**		
Odds ratio (SE)		1.296 (0.153)
95% confidence interval***		(1.029, 1.633)
p-value		0.0277

* Wilson confidence intervals.
** Logistic regression includes terms for baseline EQ-VAS score (p<0.0001), baseline eGFR (CKD-EPI) (p=0.0310), Treatment (p=0.0083), region (5 cat.) (p<0.0001), baseline diabetes status (3 cat.) (p=0.6932), sex (p=0.4414), baseline LVEF (3 cat.) (p=0.0591), age (2 cat.) (p=0.5461) and Treatment by age (2 cat.) interaction (p=0.8581).
***Wald confidence intervals.

Data taken from study 1245.121 only.
LOCF: For a missing value at week 52 the last available post-baseline value before week 52 is imputed.

Table R.1.2.3.3: 6 Responder analysis (displaying risk ratio) in EQ-VAS change from baseline at week 52 of >= 15 points (improvement) by age (2 cat.) - RS (LOCF-AD) - 1245.121

Subgroup Description	Placebo	Empa 10mg
Age [years] (2 cat.): < 65		
Number of patients in analysis set	740	675
Number of analysed patients, N (%)	675 (100.0)	632 (100.0)
Number of patients with endpoint, N (%)	189 (28.0)	212 (33.5)
95% confidence interval*	(24.7, 31.5)	(30.0, 37.3)
Comparison vs Placebo**		
Risk ratio (SE)		1.119 (0.085)
95% confidence interval***		(0.965, 1.299)
p-value		0.1373
Age [years] (2 cat.): >= 65		
Number of patients in analysis set	1127	1188
Number of analysed patients, N (%)	1035 (100.0)	1101 (100.0)
Number of patients with endpoint, N (%)	231 (22.3)	283 (25.7)
95% confidence interval*	(19.9, 25.0)	(23.2, 28.4)
Comparison vs Placebo**		
Risk ratio (SE)		1.130 (0.081)
95% confidence interval***		(0.982, 1.301)
p-value		0.0876

* Wilson confidence intervals.
** Log-linked Poisson model with robust estimate of variance includes terms for baseline EQ-VAS score (p<0.0001), baseline eGFR (CKD-EPI) (p=0.0376), Treatment (p=0.0239), region (5 cat.) (p<0.0001), baseline diabetes status (3 cat.) (p=0.5762), sex (p=0.2172), baseline LVEF (3 cat.) (p=0.1198), age (2 cat.) (p=0.3824) and Treatment by age (2 cat.) interaction (p=0.9249).
***Wald confidence intervals.

Data taken from study 1245.121 only.
LOCF: For a missing value at week 52 the last available post-baseline value before week 52 is imputed.

R.1.2.3.4 Subgroup analysis by region (North America, Latin America, Europe, Asia, Other)

Table R.1.2.3.4: 1 Responder analysis (displaying odds ratio) in EQ-VAS change from baseline at week 52 of <= -15 points (deterioration) by region - RS (LOCF-AD) - 1245.121

Subgroup Description	Placebo	Empa 10mg
Region (5 cat.): North America		
Number of patients in analysis set	213	212
Number of analysed patients, N (%)	192 (100.0)	204 (100.0)
Number of patients with endpoint, N (%)	29 (15.1)	28 (13.7)
95% confidence interval*	(10.7, 20.9)	(9.7, 19.1)
Comparison vs Placebo**		
Odds ratio (SE)		0.912 (0.270)
95% confidence interval***		(0.510, 1.630)
p-value		0.7550
Region (5 cat.): Latin America		
Number of patients in analysis set	645	641
Number of analysed patients, N (%)	577 (100.0)	583 (100.0)
Number of patients with endpoint, N (%)	59 (10.2)	71 (12.2)
95% confidence interval*	(8.0, 13.0)	(9.8, 15.1)
Comparison vs Placebo**		
Odds ratio (SE)		1.247 (0.242)
95% confidence interval***		(0.853, 1.823)
p-value		0.2544

* Wilson confidence intervals.
** Logistic regression includes terms for baseline EQ-VAS score (p<0.0001), age (p=0.0494), baseline eGFR (CKD-EPI) (p=0.0203), Treatment (p=0.0807), baseline diabetes status (3 cat.) (p=0.6957), sex (p=0.0384), baseline LVEF (3 cat.) (p=0.3924), region (5 cat.) (p<0.0001) and Treatment by region (5 cat.) interaction (p=0.1686).
***Wald confidence intervals.

Data taken from study 1245.121 only.
LOCF: For a missing value at week 52 the last available post-baseline value before week 52 is imputed.

Table R.1.2.3.4: 1 Responder analysis (displaying odds ratio) in EQ-VAS change from baseline at week 52 of <= -15 points (deterioration) by region - RS (LOCF-AD) - 1245.121

Subgroup Description	Placebo	Empa 10mg
Region (5 cat.): Europe		
Number of patients in analysis set	677	676
Number of analysed patients, N (%)	631 (100.0)	634 (100.0)
Number of patients with endpoint, N (%)	109 (17.3)	101 (15.9)
95% confidence interval*	(14.5, 20.4)	(13.3, 19.0)
Comparison vs Placebo**		
Odds ratio (SE)		0.854 (0.135)
95% confidence interval***		(0.627, 1.163)
p-value		0.3179
Region (5 cat.): Asia		
Number of patients in analysis set	245	248
Number of analysed patients, N (%)	233 (100.0)	236 (100.0)
Number of patients with endpoint, N (%)	40 (17.2)	26 (11.0)
95% confidence interval*	(12.9, 22.5)	(7.6, 15.7)
Comparison vs Placebo**		
Odds ratio (SE)		0.605 (0.168)
95% confidence interval***		(0.351, 1.043)
p-value		0.0707

* Wilson confidence intervals.
** Logistic regression includes terms for baseline EQ-VAS score (p<0.0001), age (p=0.0494), baseline eGFR (CKD-EPI) (p=0.0203), Treatment (p=0.0807), baseline diabetes status (3 cat.) (p=0.6957), sex (p=0.0384), baseline LVEF (3 cat.) (p=0.3924), region (5 cat.) (p<0.0001) and Treatment by region (5 cat.) interaction (p=0.1686).
***Wald confidence intervals.

Data taken from study 1245.121 only.
LOCF: For a missing value at week 52 the last available post-baseline value before week 52 is imputed.

Table R.1.2.3.4: 1 Responder analysis (displaying odds ratio) in EQ-VAS change from baseline at week 52 of <= -15 points (deterioration) by region - RS (LOCF-AD) - 1245.121

Subgroup Description	Placebo	Empa 10mg
Region (5 cat.): Other		
Number of patients in analysis set	87	86
Number of analysed patients, N (%)	77 (100.0)	76 (100.0)
Number of patients with endpoint, N (%)	9 (11.7)	3 (3.9)
95% confidence interval*	(6.3, 20.7)	(1.4, 11.0)
Comparison vs Placebo**		
Odds ratio (SE)		0.387 (0.271)
95% confidence interval***		(0.098, 1.528)
p-value		0.1756

* Wilson confidence intervals.
** Logistic regression includes terms for baseline EQ-VAS score (p<0.0001), age (p=0.0494), baseline eGFR (CKD-EPI) (p=0.0203), Treatment (p=0.0807), baseline diabetes status (3 cat.) (p=0.6957), sex (p=0.0384), baseline LVEF (3 cat.) (p=0.3924), region (5 cat.) (p<0.0001) and Treatment by region (5 cat.) interaction (p=0.1686).
***Wald confidence intervals.

Data taken from study 1245.121 only.
LOCF: For a missing value at week 52 the last available post-baseline value before week 52 is imputed.

Table R.1.2.3.4: 2 Responder analysis (displaying risk ratio) in EQ-VAS change from baseline at week 52 of <= -15 points (deterioration) by region - RS (LOCF-AD) - 1245.121

Subgroup Description	Placebo	Empa 10mg
Region (5 cat.): North America		
Number of patients in analysis set	213	212
Number of analysed patients, N (%)	192 (100.0)	204 (100.0)
Number of patients with endpoint, N (%)	29 (15.1)	28 (13.7)
95% confidence interval*	(10.7, 20.9)	(9.7, 19.1)
Comparison vs Placebo**		
Risk ratio (SE)		0.935 (0.226)
95% confidence interval***		(0.582, 1.502)
p-value		0.7797
Region (5 cat.): Latin America		
Number of patients in analysis set	645	641
Number of analysed patients, N (%)	577 (100.0)	583 (100.0)
Number of patients with endpoint, N (%)	59 (10.2)	71 (12.2)
95% confidence interval*	(8.0, 13.0)	(9.8, 15.1)
Comparison vs Placebo**		
Risk ratio (SE)		1.203 (0.194)
95% confidence interval***		(0.878, 1.649)
p-value		0.2506

* Wilson confidence intervals.
** Log-linked Poisson model with robust estimate of variance includes terms for baseline EQ-VAS score (p<0.0001), age (p=0.0659), baseline eGFR (CKD-EPI) (p=0.0246), Treatment (p=0.0846), baseline diabetes status (3 cat.) (p=0.7101), sex (p=0.0409), baseline LVEF (3 cat.) (p=0.4191), region (5 cat.) (p<0.0001) and Treatment by region (5 cat.) interaction (p=0.1595).
***Wald confidence intervals.

Data taken from study 1245.121 only.
LOCF: For a missing value at week 52 the last available post-baseline value before week 52 is imputed.

Table R.1.2.3.4: 2 Responder analysis (displaying risk ratio) in EQ-VAS change from baseline at week 52 of <= -15 points (deterioration) by region - RS (LOCF-AD) - 1245.121

Subgroup Description	Placebo	Empa 10mg
Region (5 cat.): Europe		
Number of patients in analysis set	677	676
Number of analysed patients, N (%)	631 (100.0)	634 (100.0)
Number of patients with endpoint, N (%)	109 (17.3)	101 (15.9)
95% confidence interval*	(14.5, 20.4)	(13.3, 19.0)
Comparison vs Placebo**		
Risk ratio (SE)		0.881 (0.108)
95% confidence interval***		(0.692, 1.121)
p-value		0.3011
Region (5 cat.): Asia		
Number of patients in analysis set	245	248
Number of analysed patients, N (%)	233 (100.0)	236 (100.0)
Number of patients with endpoint, N (%)	40 (17.2)	26 (11.0)
95% confidence interval*	(12.9, 22.5)	(7.6, 15.7)
Comparison vs Placebo**		
Risk ratio (SE)		0.660 (0.150)
95% confidence interval***		(0.423, 1.029)
p-value		0.0666

* Wilson confidence intervals.
** Log-linked Poisson model with robust estimate of variance includes terms for baseline EQ-VAS score (p<0.0001), age (p=0.0659), baseline eGFR (CKD-EPI) (p=0.0246), Treatment (p=0.0846), baseline diabetes status (3 cat.) (p=0.7101), sex (p=0.0409), baseline LVEF (3 cat.) (p=0.4191), region (5 cat.) (p<0.0001) and Treatment by region (5 cat.) interaction (p=0.1595).
***Wald confidence intervals.

Data taken from study 1245.121 only.
LOCF: For a missing value at week 52 the last available post-baseline value before week 52 is imputed.

Table R.1.2.3.4: 2 Responder analysis (displaying risk ratio) in EQ-VAS change from baseline at week 52 of <= -15 points (deterioration) by region - RS (LOCF-AD) - 1245.121

Subgroup Description	Placebo	Empa 10mg
Region (5 cat.): Other		
Number of patients in analysis set	87	86
Number of analysed patients, N (%)	77 (100.0)	76 (100.0)
Number of patients with endpoint, N (%)	9 (11.7)	3 (3.9)
95% confidence interval*	(6.3, 20.7)	(1.4, 11.0)
Comparison vs Placebo**		
Risk ratio (SE)		0.422 (0.268)
95% confidence interval***		(0.121, 1.468)
p-value		0.1748

* Wilson confidence intervals.
** Log-linked Poisson model with robust estimate of variance includes terms for baseline EQ-VAS score (p<0.0001), age (p=0.0659), baseline eGFR (CKD-EPI) (p=0.0246), Treatment (p=0.0846), baseline diabetes status (3 cat.) (p=0.7101), sex (p=0.0409), baseline LVEF (3 cat.) (p=0.4191), region (5 cat.) (p<0.0001) and Treatment by region (5 cat.) interaction (p=0.1595).
***Wald confidence intervals.

Data taken from study 1245.121 only.
LOCF: For a missing value at week 52 the last available post-baseline value before week 52 is imputed.

Table R.1.2.3.4: 3 Responder analysis (displaying odds ratio) in EQ-VAS change from baseline at week 52 of > -15 points (stability) by region - RS (LOCF-AD) - 1245.121

Subgroup Description	Placebo	Empa 10mg
Region (5 cat.): North America		
Number of patients in analysis set	213	212
Number of analysed patients, N (%)	192 (100.0)	204 (100.0)
Number of patients with endpoint, N (%)	163 (84.9)	176 (86.3)
95% confidence interval*	(79.1, 89.3)	(80.9, 90.3)
Comparison vs Placebo**		
Odds ratio (SE)		1.097 (0.325)
95% confidence interval***		(0.613, 1.962)
p-value		0.7550
Region (5 cat.): Latin America		
Number of patients in analysis set	645	641
Number of analysed patients, N (%)	577 (100.0)	583 (100.0)
Number of patients with endpoint, N (%)	518 (89.8)	512 (87.8)
95% confidence interval*	(87.0, 92.0)	(84.9, 90.2)
Comparison vs Placebo**		
Odds ratio (SE)		0.802 (0.155)
95% confidence interval***		(0.548, 1.172)
p-value		0.2544

* Wilson confidence intervals.
** Logistic regression includes terms for baseline EQ-VAS score (p<0.0001), age (p=0.0494), baseline eGFR (CKD-EPI) (p=0.0203), Treatment (p=0.0807), baseline diabetes status (3 cat.) (p=0.6957), sex (p=0.0384), baseline LVEF (3 cat.) (p=0.3924), region (5 cat.) (p<0.0001) and Treatment by region (5 cat.) interaction (p=0.1686).
***Wald confidence intervals.

Data taken from study 1245.121 only.
LOCF: For a missing value at week 52 the last available post-baseline value before week 52 is imputed.

Table R.1.2.3.4: 3 Responder analysis (displaying odds ratio) in EQ-VAS change from baseline at week 52 of > -15 points (stability) by region - RS (LOCF-AD) - 1245.121

Subgroup Description	Placebo	Empa 10mg
Region (5 cat.): Europe		
Number of patients in analysis set	677	676
Number of analysed patients, N (%)	631 (100.0)	634 (100.0)
Number of patients with endpoint, N (%)	522 (82.7)	533 (84.1)
95% confidence interval*	(79.6, 85.5)	(81.0, 86.7)
Comparison vs Placebo**		
Odds ratio (SE)		1.170 (0.184)
95% confidence interval***		(0.859, 1.594)
p-value		0.3179
Region (5 cat.): Asia		
Number of patients in analysis set	245	248
Number of analysed patients, N (%)	233 (100.0)	236 (100.0)
Number of patients with endpoint, N (%)	193 (82.8)	210 (89.0)
95% confidence interval*	(77.5, 87.1)	(84.3, 92.4)
Comparison vs Placebo**		
Odds ratio (SE)		1.654 (0.460)
95% confidence interval***		(0.958, 2.853)
p-value		0.0707

* Wilson confidence intervals.
** Logistic regression includes terms for baseline EQ-VAS score (p<0.0001), age (p=0.0494), baseline eGFR (CKD-EPI) (p=0.0203), Treatment (p=0.0807), baseline diabetes status (3 cat.) (p=0.6957), sex (p=0.0384), baseline LVEF (3 cat.) (p=0.3924), region (5 cat.) (p<0.0001) and Treatment by region (5 cat.) interaction (p=0.1686).
***Wald confidence intervals.

Data taken from study 1245.121 only.
LOCF: For a missing value at week 52 the last available post-baseline value before week 52 is imputed.

Table R.1.2.3.4: 3 Responder analysis (displaying odds ratio) in EQ-VAS change from baseline at week 52 of > -15 points (stability) by region - RS (LOCF-AD) - 1245.121

Subgroup Description	Placebo	Empa 10mg
Region (5 cat.): Other		
Number of patients in analysis set	87	86
Number of analysed patients, N (%)	77 (100.0)	76 (100.0)
Number of patients with endpoint, N (%)	68 (88.3)	73 (96.1)
95% confidence interval*	(79.3, 93.7)	(89.0, 98.6)
Comparison vs Placebo**		
Odds ratio (SE)		2.583 (1.809)
95% confidence interval***		(0.654,10.196)
p-value		0.1756

* Wilson confidence intervals.
** Logistic regression includes terms for baseline EQ-VAS score (p<0.0001), age (p=0.0494), baseline eGFR (CKD-EPI) (p=0.0203), Treatment (p=0.0807), baseline diabetes status (3 cat.) (p=0.6957), sex (p=0.0384), baseline LVEF (3 cat.) (p=0.3924), region (5 cat.) (p<0.0001) and Treatment by region (5 cat.) interaction (p=0.1686).
***Wald confidence intervals.

Data taken from study 1245.121 only.
LOCF: For a missing value at week 52 the last available post-baseline value before week 52 is imputed.

Table R.1.2.3.4: 4 Responder analysis (displaying risk ratio) in EQ-VAS change from baseline at week 52 of > -15 points (stability) by region - RS (LOCF-AD) - 1245.121

Subgroup Description	Placebo	Empa 10mg
Region (5 cat.): North America		
Number of patients in analysis set	213	212
Number of analysed patients, N (%)	192 (100.0)	204 (100.0)
Number of patients with endpoint, N (%)	163 (84.9)	176 (86.3)
95% confidence interval*	(79.1, 89.3)	(80.9, 90.3)
Comparison vs Placebo**		
Risk ratio (SE)		1.013 (0.041)
95% confidence interval***		(0.936, 1.097)
p-value		0.7437
Region (5 cat.): Latin America		
Number of patients in analysis set	645	641
Number of analysed patients, N (%)	577 (100.0)	583 (100.0)
Number of patients with endpoint, N (%)	518 (89.8)	512 (87.8)
95% confidence interval*	(87.0, 92.0)	(84.9, 90.2)
Comparison vs Placebo**		
Risk ratio (SE)		0.979 (0.020)
95% confidence interval***		(0.941, 1.019)
p-value		0.2921

* Wilson confidence intervals.
** Log-linked Poisson model with robust estimate of variance includes terms for baseline EQ-VAS score (p<0.0001), age (p=0.1122), baseline eGFR (CKD-EPI) (p=0.0265), Treatment (p=0.0976), baseline diabetes status (3 cat.) (p=0.6051), sex (p=0.0294), baseline LVEF (3 cat.) (p=0.4426), region (5 cat.) (p=0.0010) and Treatment by region (5 cat.) interaction (p=0.2303).
***Wald confidence intervals.

Data taken from study 1245.121 only.
LOCF: For a missing value at week 52 the last available post-baseline value before week 52 is imputed.

Table R.1.2.3.4: 4 Responder analysis (displaying risk ratio) in EQ-VAS change from baseline at week 52 of > -15 points (stability) by region - RS (LOCF-AD) - 1245.121

Subgroup Description	Placebo	Empa 10mg
Region (5 cat.): Europe		
Number of patients in analysis set	677	676
Number of analysed patients, N (%)	631 (100.0)	634 (100.0)
Number of patients with endpoint, N (%)	522 (82.7)	533 (84.1)
95% confidence interval*	(79.6, 85.5)	(81.0, 86.7)
Comparison vs Placebo**		
Risk ratio (SE)		1.020 (0.025)
95% confidence interval***		(0.972, 1.070)
p-value		0.4170
Region (5 cat.): Asia		
Number of patients in analysis set	245	248
Number of analysed patients, N (%)	233 (100.0)	236 (100.0)
Number of patients with endpoint, N (%)	193 (82.8)	210 (89.0)
95% confidence interval*	(77.5, 87.1)	(84.3, 92.4)
Comparison vs Placebo**		
Risk ratio (SE)		1.064 (0.039)
95% confidence interval***		(0.990, 1.144)
p-value		0.0904

* Wilson confidence intervals.
** Log-linked Poisson model with robust estimate of variance includes terms for baseline EQ-VAS score (p<0.0001), age (p=0.1122), baseline eGFR (CKD-EPI) (p=0.0265), Treatment (p=0.0976), baseline diabetes status (3 cat.) (p=0.6051), sex (p=0.0294), baseline LVEF (3 cat.) (p=0.4426), region (5 cat.) (p=0.0010) and Treatment by region (5 cat.) interaction (p=0.2303).
***Wald confidence intervals.

Data taken from study 1245.121 only.
LOCF: For a missing value at week 52 the last available post-baseline value before week 52 is imputed.

Table R.1.2.3.4: 4 Responder analysis (displaying risk ratio) in EQ-VAS change from baseline at week 52 of > -15 points (stability) by region - RS (LOCF-AD) - 1245.121

Subgroup Description	Placebo	Empa 10mg
Region (5 cat.): Other		
Number of patients in analysis set	87	86
Number of analysed patients, N (%)	77 (100.0)	76 (100.0)
Number of patients with endpoint, N (%)	68 (88.3)	73 (96.1)
95% confidence interval*	(79.3, 93.7)	(89.0, 98.6)
Comparison vs Placebo**		
Risk ratio (SE)		1.058 (0.049)
95% confidence interval***		(0.966, 1.159)
p-value		0.2244

* Wilson confidence intervals.
** Log-linked Poisson model with robust estimate of variance includes terms for baseline EQ-VAS score (p<0.0001), age (p=0.1122), baseline eGFR (CKD-EPI) (p=0.0265), Treatment (p=0.0976), baseline diabetes status (3 cat.) (p=0.6051), sex (p=0.0294), baseline LVEF (3 cat.) (p=0.4426), region (5 cat.) (p=0.0010) and Treatment by region (5 cat.) interaction (p=0.2303).
***Wald confidence intervals.

Data taken from study 1245.121 only.
LOCF: For a missing value at week 52 the last available post-baseline value before week 52 is imputed.

Table R.1.2.3.4: 5 Responder analysis (displaying odds ratio) in EQ-VAS change from baseline at week 52 of >= 15 points (improvement) by region - RS (LOCF-AD) - 1245.121

Subgroup Description	Placebo	Empa 10mg
Region (5 cat.): North America		
Number of patients in analysis set	213	212
Number of analysed patients, N (%)	192 (100.0)	204 (100.0)
Number of patients with endpoint, N (%)	35 (18.2)	55 (27.0)
95% confidence interval*	(13.4, 24.3)	(21.3, 33.4)
Comparison vs Placebo**		
Odds ratio (SE)		1.993 (0.570)
95% confidence interval***		(1.138, 3.490)
p-value		0.0159
Region (5 cat.): Latin America		
Number of patients in analysis set	645	641
Number of analysed patients, N (%)	577 (100.0)	583 (100.0)
Number of patients with endpoint, N (%)	175 (30.3)	199 (34.1)
95% confidence interval*	(26.7, 34.2)	(30.4, 38.1)
Comparison vs Placebo**		
Odds ratio (SE)		1.286 (0.191)
95% confidence interval***		(0.961, 1.722)
p-value		0.0905

* Wilson confidence intervals.
** Logistic regression includes terms for baseline EQ-VAS score (p<0.0001), age (p=0.1110), baseline eGFR (CKD-EPI) (p=0.1317), Treatment (p=0.0096), baseline diabetes status (3 cat.) (p=0.7037), sex (p=0.4454), baseline LVEF (3 cat.) (p=0.0578), region (5 cat.) (p<0.0001) and Treatment by region (5 cat.) interaction (p=0.5317).
***Wald confidence intervals.

Data taken from study 1245.121 only.
LOCF: For a missing value at week 52 the last available post-baseline value before week 52 is imputed.

Table R.1.2.3.4: 5 Responder analysis (displaying odds ratio) in EQ-VAS change from baseline at week 52 of >= 15 points (improvement) by region - RS (LOCF-AD) - 1245.121

Subgroup Description	Placebo	Empa 10mg
Region (5 cat.): Europe		
Number of patients in analysis set	677	676
Number of analysed patients, N (%)	631 (100.0)	634 (100.0)
Number of patients with endpoint, N (%)	130 (20.6)	141 (22.2)
95% confidence interval*	(17.6, 23.9)	(19.2, 25.6)
Comparison vs Placebo**		
Odds ratio (SE)		1.193 (0.187)
95% confidence interval***		(0.877, 1.623)
p-value		0.2605
Region (5 cat.): Asia		
Number of patients in analysis set	245	248
Number of analysed patients, N (%)	233 (100.0)	236 (100.0)
Number of patients with endpoint, N (%)	51 (21.9)	61 (25.8)
95% confidence interval*	(17.1, 27.6)	(20.7, 31.8)
Comparison vs Placebo**		
Odds ratio (SE)		1.070 (0.262)
95% confidence interval***		(0.662, 1.729)
p-value		0.7837

* Wilson confidence intervals.
** Logistic regression includes terms for baseline EQ-VAS score (p<0.0001), age (p=0.1110), baseline eGFR (CKD-EPI) (p=0.1317), Treatment (p=0.0096), baseline diabetes status (3 cat.) (p=0.7037), sex (p=0.4454), baseline LVEF (3 cat.) (p=0.0578), region (5 cat.) (p<0.0001) and Treatment by region (5 cat.) interaction (p=0.5317).
***Wald confidence intervals.

Data taken from study 1245.121 only.
LOCF: For a missing value at week 52 the last available post-baseline value before week 52 is imputed.

Table R.1.2.3.4: 5 Responder analysis (displaying odds ratio) in EQ-VAS change from baseline at week 52 of >= 15 points (improvement) by region - RS (LOCF-AD) - 1245.121

Subgroup Description	Placebo	Empa 10mg
Region (5 cat.): Other		
Number of patients in analysis set	87	86
Number of analysed patients, N (%)	77 (100.0)	76 (100.0)
Number of patients with endpoint, N (%)	29 (37.7)	39 (51.3)
95% confidence interval*	(27.7, 48.8)	(40.3, 62.2)
Comparison vs Placebo**		
Odds ratio (SE)		1.352 (0.508)
95% confidence interval***		(0.647, 2.824)
p-value		0.4226

* Wilson confidence intervals.
** Logistic regression includes terms for baseline EQ-VAS score (p<0.0001), age (p=0.1110), baseline eGFR (CKD-EPI) (p=0.1317), Treatment (p=0.0096), baseline diabetes status (3 cat.) (p=0.7037), sex (p=0.4454), baseline LVEF (3 cat.) (p=0.0578), region (5 cat.) (p<0.0001) and Treatment by region (5 cat.) interaction (p=0.5317).
***Wald confidence intervals.

Data taken from study 1245.121 only.
LOCF: For a missing value at week 52 the last available post-baseline value before week 52 is imputed.

Table R.1.2.3.4: 6 Responder analysis (displaying risk ratio) in EQ-VAS change from baseline at week 52 of >= 15 points (improvement) by region - RS (LOCF-AD) - 1245.121

Subgroup Description	Placebo	Empa 10mg
Region (5 cat.): North America		
Number of patients in analysis set	213	212
Number of analysed patients, N (%)	192 (100.0)	204 (100.0)
Number of patients with endpoint, N (%)	35 (18.2)	55 (27.0)
95% confidence interval*	(13.4, 24.3)	(21.3, 33.4)
Comparison vs Placebo**		
Risk ratio (SE)		1.332 (0.235)
95% confidence interval***		(0.942, 1.882)
p-value		0.1045
Region (5 cat.): Latin America		
Number of patients in analysis set	645	641
Number of analysed patients, N (%)	577 (100.0)	583 (100.0)
Number of patients with endpoint, N (%)	175 (30.3)	199 (34.1)
95% confidence interval*	(26.7, 34.2)	(30.4, 38.1)
Comparison vs Placebo**		
Risk ratio (SE)		1.133 (0.089)
95% confidence interval***		(0.971, 1.321)
p-value		0.1126

* Wilson confidence intervals.
** Log-linked Poisson model with robust estimate of variance includes terms for baseline EQ-VAS score (p<0.0001), age (p=0.0970), baseline eGFR (CKD-EPI) (p=0.1390), Treatment (p=0.0345), baseline diabetes status (3 cat.) (p=0.5928), sex (p=0.2185), baseline LVEF (3 cat.) (p=0.1177), region (5 cat.) (p<0.0001) and Treatment by region (5 cat.) interaction (p=0.8665).
***Wald confidence intervals.

Data taken from study 1245.121 only.
LOCF: For a missing value at week 52 the last available post-baseline value before week 52 is imputed.

Table R.1.2.3.4: 6 Responder analysis (displaying risk ratio) in EQ-VAS change from baseline at week 52 of >= 15 points (improvement) by region - RS (LOCF-AD) - 1245.121

Subgroup Description	Placebo	Empa 10mg
Region (5 cat.): Europe		
Number of patients in analysis set	677	676
Number of analysed patients, N (%)	631 (100.0)	634 (100.0)
Number of patients with endpoint, N (%)	130 (20.6)	141 (22.2)
95% confidence interval*	(17.6, 23.9)	(19.2, 25.6)
Comparison vs Placebo**		
Risk ratio (SE)		1.106 (0.113)
95% confidence interval***		(0.906, 1.351)
p-value		0.3214
Region (5 cat.): Asia		
Number of patients in analysis set	245	248
Number of analysed patients, N (%)	233 (100.0)	236 (100.0)
Number of patients with endpoint, N (%)	51 (21.9)	61 (25.8)
95% confidence interval*	(17.1, 27.6)	(20.7, 31.8)
Comparison vs Placebo**		
Risk ratio (SE)		1.032 (0.158)
95% confidence interval***		(0.764, 1.393)
p-value		0.8379

* Wilson confidence intervals.
** Log-linked Poisson model with robust estimate of variance includes terms for baseline EQ-VAS score (p<0.0001), age (p=0.0970), baseline eGFR (CKD-EPI) (p=0.1390), Treatment (p=0.0345), baseline diabetes status (3 cat.) (p=0.5928), sex (p=0.2185), baseline LVEF (3 cat.) (p=0.1177), region (5 cat.) (p<0.0001) and Treatment by region (5 cat.) interaction (p=0.8665).
***Wald confidence intervals.

Data taken from study 1245.121 only.
LOCF: For a missing value at week 52 the last available post-baseline value before week 52 is imputed.

Table R.1.2.3.4: 6 Responder analysis (displaying risk ratio) in EQ-VAS change from baseline at week 52 of >= 15 points (improvement) by region - RS (LOCF-AD) - 1245.121

Subgroup Description	Placebo	Empa 10mg
Region (5 cat.): Other		
Number of patients in analysis set	87	86
Number of analysed patients, N (%)	77 (100.0)	76 (100.0)
Number of patients with endpoint, N (%)	29 (37.7)	39 (51.3)
95% confidence interval*	(27.7, 48.8)	(40.3, 62.2)
Comparison vs Placebo**		
Risk ratio (SE)		1.112 (0.170)
95% confidence interval***		(0.824, 1.501)
p-value		0.4893

* Wilson confidence intervals.
** Log-linked Poisson model with robust estimate of variance includes terms for baseline EQ-VAS score (p<0.0001), age (p=0.0970), baseline eGFR (CKD-EPI) (p=0.1390), Treatment (p=0.0345), baseline diabetes status (3 cat.) (p=0.5928), sex (p=0.2185), baseline LVEF (3 cat.) (p=0.1177), region (5 cat.) (p<0.0001) and Treatment by region (5 cat.) interaction (p=0.8665).
***Wald confidence intervals.

Data taken from study 1245.121 only.
LOCF: For a missing value at week 52 the last available post-baseline value before week 52 is imputed.

R.1.2.3.5

R.1.2.3.5 Subgroup analysis by OECD (N/Y)

Table R.1.2.3.5: 1 Responder analysis (displaying odds ratio) in EQ-VAS change from baseline at week 52 of <= -15 points (deterioration) by OECD member (N/Y) - RS (LOCF-AD) - 1245.121

Subgroup Description	Placebo	Empa 10mg
OECD member: No		
Number of patients in analysis set	741	713
Number of analysed patients, N (%)	664 (100.0)	644 (100.0)
Number of patients with endpoint, N (%)	75 (11.3)	67 (10.4)
95% confidence interval*	(9.1, 13.9)	(8.3, 13.0)
Comparison vs Placebo**		
Odds ratio (SE)		0.935 (0.172)
95% confidence interval***		(0.651, 1.341)
p-value		0.7136
OECD member: Yes		
Number of patients in analysis set	1126	1150
Number of analysed patients, N (%)	1046 (100.0)	1089 (100.0)
Number of patients with endpoint, N (%)	171 (16.3)	162 (14.9)
95% confidence interval*	(14.2, 18.7)	(12.9, 17.1)
Comparison vs Placebo**		
Odds ratio (SE)		0.877 (0.108)
95% confidence interval***		(0.688, 1.117)
p-value		0.2864

* Wilson confidence intervals.
** Logistic regression includes terms for baseline EQ-VAS score (p<0.0001), age (p=0.0386), baseline eGFR (CKD-EPI) (p=0.0146), Treatment (p=0.3680), sex (p=0.0521), baseline diabetes status (3 cat.) (p=0.6340), baseline LVEF (3 cat.) (p=0.4232), OECD member (p=0.0051) and Treatment by OECD member interaction (p=0.7725).
***Wald confidence intervals.

Data taken from study 1245.121 only.
LOCF: For a missing value at week 52 the last available post-baseline value before week 52 is imputed.
OECD member (yes/no) countries included:
Yes: United States, Canada, Mexico, Poland, Netherlands, Hungary, Germany, Czech Republic, Italy, France, Spain, United Kingdom, Belgium, Japan, Australia, 'Korea; Republic Of South Korea';
No: Brazil, Argentina, China, India.

Table R.1.2.3.5: 2 Responder analysis (displaying risk ratio) in EQ-VAS change from baseline at week 52 of <= -15 points (deterioration) by OECD member (N/Y) - RS (LOCF-AD) - 1245.121

Subgroup Description	Placebo	Empa 10mg
OECD member: No		
Number of patients in analysis set	741	713
Number of analysed patients, N (%)	664 (100.0)	644 (100.0)
Number of patients with endpoint, N (%)	75 (11.3)	67 (10.4)
95% confidence interval*	(9.1, 13.9)	(8.3, 13.0)
Comparison vs Placebo**		
Risk ratio (SE)		0.945 (0.146)
95% confidence interval***		(0.699, 1.279)
p-value		0.7154
OECD member: Yes		
Number of patients in analysis set	1126	1150
Number of analysed patients, N (%)	1046 (100.0)	1089 (100.0)
Number of patients with endpoint, N (%)	171 (16.3)	162 (14.9)
95% confidence interval*	(14.2, 18.7)	(12.9, 17.1)
Comparison vs Placebo**		
Risk ratio (SE)		0.901 (0.089)
95% confidence interval***		(0.742, 1.093)
p-value		0.2882

* Wilson confidence intervals.
** Log-linked Poisson model with robust estimate of variance includes terms for baseline EQ-VAS score (p<0.0001), age (p=0.0535), baseline eGFR (CKD-EPI) (p=0.0163), Treatment (p=0.3780), sex (p=0.0568), baseline diabetes status (3 cat.) (p=0.6327), baseline LVEF (3 cat.) (p=0.4611), OECD member (p=0.0044) and Treatment by OECD member interaction (p=0.7919).
***Wald confidence intervals.

Data taken from study 1245.121 only.
LOCF: For a missing value at week 52 the last available post-baseline value before week 52 is imputed.
OECD member (yes/no) countries included:
Yes: United States, Canada, Mexico, Poland, Netherlands, Hungary, Germany, Czech Republic, Italy, France, Spain, United Kingdom, Belgium, Japan, Australia, 'Korea; Republic Of South Korea';
No: Brazil, Argentina, China, India.

Table R.1.2.3.5: 3 Responder analysis (displaying odds ratio) in EQ-VAS change from baseline at week 52 of > -15 points (stability) by OECD member (N/Y) - RS (LOCF-AD) - 1245.121

Subgroup Description	Placebo	Empa 10mg
OECD member: No		
Number of patients in analysis set	741	713
Number of analysed patients, N (%)	664 (100.0)	644 (100.0)
Number of patients with endpoint, N (%)	589 (88.7)	577 (89.6)
95% confidence interval*	(86.1, 90.9)	(87.0, 91.7)
Comparison vs Placebo**		
Odds ratio (SE)		1.070 (0.197)
95% confidence interval***		(0.746, 1.535)
p-value		0.7136
OECD member: Yes		
Number of patients in analysis set	1126	1150
Number of analysed patients, N (%)	1046 (100.0)	1089 (100.0)
Number of patients with endpoint, N (%)	875 (83.7)	927 (85.1)
95% confidence interval*	(81.3, 85.8)	(82.9, 87.1)
Comparison vs Placebo**		
Odds ratio (SE)		1.141 (0.141)
95% confidence interval***		(0.895, 1.454)
p-value		0.2864

* Wilson confidence intervals.
** Logistic regression includes terms for baseline EQ-VAS score (p<0.0001), age (p=0.0386), baseline eGFR (CKD-EPI) (p=0.0146), Treatment (p=0.3680), sex (p=0.0521), baseline diabetes status (3 cat.) (p=0.6340), baseline LVEF (3 cat.) (p=0.4232), OECD member (p=0.0051) and Treatment by OECD member interaction (p=0.7725).
***Wald confidence intervals.

Data taken from study 1245.121 only.
LOCF: For a missing value at week 52 the last available post-baseline value before week 52 is imputed.
OECD member (yes/no) countries included:
Yes: United States, Canada, Mexico, Poland, Netherlands, Hungary, Germany, Czech Republic, Italy, France, Spain, United Kingdom, Belgium, Japan, Australia, 'Korea; Republic Of South Korea';
No: Brazil, Argentina, China, India.

Table R.1.2.3.5: 4 Responder analysis (displaying risk ratio) in EQ-VAS change from baseline at week 52 of > -15 points (stability) by OECD member (N/Y) - RS (LOCF-AD) - 1245.121

Subgroup Description	Placebo	Empa 10mg
OECD member: No		
Number of patients in analysis set	741	713
Number of analysed patients, N (%)	664 (100.0)	644 (100.0)
Number of patients with endpoint, N (%)	589 (88.7)	577 (89.6)
95% confidence interval*	(86.1, 90.9)	(87.0, 91.7)
Comparison vs Placebo**		
Risk ratio (SE)		1.007 (0.019)
95% confidence interval***		(0.970, 1.045)
p-value		0.7178
OECD member: Yes		
Number of patients in analysis set	1126	1150
Number of analysed patients, N (%)	1046 (100.0)	1089 (100.0)
Number of patients with endpoint, N (%)	875 (83.7)	927 (85.1)
95% confidence interval*	(81.3, 85.8)	(82.9, 87.1)
Comparison vs Placebo**		
Risk ratio (SE)		1.018 (0.019)
95% confidence interval***		(0.982, 1.055)
p-value		0.3388

* Wilson confidence intervals.
** Log-linked Poisson model with robust estimate of variance includes terms for baseline EQ-VAS score (p<0.0001), age (p=0.0716), baseline eGFR (CKD-EPI) (p=0.0235), Treatment (p=0.3550), sex (p=0.0389), baseline diabetes status (3 cat.) (p=0.5439), baseline LVEF (3 cat.) (p=0.4450), OECD member (p=0.0058) and Treatment by OECD member interaction (p=0.6846).
***Wald confidence intervals.

Data taken from study 1245.121 only.
LOCF: For a missing value at week 52 the last available post-baseline value before week 52 is imputed.
OECD member (yes/no) countries included:
Yes: United States, Canada, Mexico, Poland, Netherlands, Hungary, Germany, Czech Republic, Italy, France, Spain, United Kingdom, Belgium, Japan, Australia, 'Korea; Republic Of South Korea';
No: Brazil, Argentina, China, India.

Table R.1.2.3.5: 5 Responder analysis (displaying odds ratio) in EQ-VAS change from baseline at week 52 of >= 15 points (improvement) by OECD member (N/Y) - RS (LOCF-AD) - 1245.121

Subgroup Description	Placebo	Empa 10mg
OECD member: No		
Number of patients in analysis set	741	713
Number of analysed patients, N (%)	664 (100.0)	644 (100.0)
Number of patients with endpoint, N (%)	212 (31.9)	231 (35.9)
95% confidence interval*	(28.5, 35.6)	(32.3, 39.6)
Comparison vs Placebo**		
Odds ratio (SE)		1.186 (0.162)
95% confidence interval***		(0.908, 1.549)
p-value		0.2112
OECD member: Yes		
Number of patients in analysis set	1126	1150
Number of analysed patients, N (%)	1046 (100.0)	1089 (100.0)
Number of patients with endpoint, N (%)	208 (19.9)	264 (24.2)
95% confidence interval*	(17.6, 22.4)	(21.8, 26.9)
Comparison vs Placebo**		
Odds ratio (SE)		1.392 (0.167)
95% confidence interval***		(1.100, 1.761)
p-value		0.0059

* Wilson confidence intervals.
** Logistic regression includes terms for baseline EQ-VAS score (p<0.0001), age (p=0.0581), baseline eGFR (CKD-EPI) (p=0.1030), Treatment (p=0.0058), sex (p=0.4652), baseline diabetes status (3 cat.) (p=0.4267), baseline LVEF (3 cat.) (p=0.0282), OECD member (p<0.0001) and Treatment by OECD member interaction (p=0.3789).
***Wald confidence intervals.

Data taken from study 1245.121 only.
LOCF: For a missing value at week 52 the last available post-baseline value before week 52 is imputed.
OECD member (yes/no) countries included:
Yes: United States, Canada, Mexico, Poland, Netherlands, Hungary, Germany, Czech Republic, Italy, France, Spain, United Kingdom, Belgium, Japan, Australia, 'Korea; Republic Of South Korea';
No: Brazil, Argentina, China, India.

Table R.1.2.3.5: 6 Responder analysis (displaying risk ratio) in EQ-VAS change from baseline at week 52 of >= 15 points (improvement) by OECD member (N/Y) - RS (LOCF-AD) - 1245.121

Subgroup Description	Placebo	Empa 10mg
OECD member: No		
Number of patients in analysis set	741	713
Number of analysed patients, N (%)	664 (100.0)	644 (100.0)
Number of patients with endpoint, N (%)	212 (31.9)	231 (35.9)
95% confidence interval*	(28.5, 35.6)	(32.3, 39.6)
Comparison vs Placebo**		
Risk ratio (SE)		1.095 (0.077)
95% confidence interval***		(0.955, 1.257)
p-value		0.1938
OECD member: Yes		
Number of patients in analysis set	1126	1150
Number of analysed patients, N (%)	1046 (100.0)	1089 (100.0)
Number of patients with endpoint, N (%)	208 (19.9)	264 (24.2)
95% confidence interval*	(17.6, 22.4)	(21.8, 26.9)
Comparison vs Placebo**		
Risk ratio (SE)		1.191 (0.092)
95% confidence interval***		(1.025, 1.385)
p-value		0.0229

* Wilson confidence intervals.
** Log-linked Poisson model with robust estimate of variance includes terms for baseline EQ-VAS score (p<0.0001), age (p=0.0571), baseline eGFR (CKD-EPI) (p=0.1349), Treatment (p=0.0105), sex (p=0.2641), baseline diabetes status (3 cat.) (p=0.3327), baseline LVEF (3 cat.) (p=0.0539), OECD member (p<0.0001) and Treatment by OECD member interaction (p=0.4196).
***Wald confidence intervals.

Data taken from study 1245.121 only.
LOCF: For a missing value at week 52 the last available post-baseline value before week 52 is imputed.
OECD member (yes/no) countries included:
Yes: United States, Canada, Mexico, Poland, Netherlands, Hungary, Germany, Czech Republic, Italy, France, Spain, United Kingdom, Belgium, Japan, Australia, 'Korea; Republic Of South Korea';
No: Brazil, Argentina, China, India.

R.1.2.3.6 Subgroup analysis by NYHA at baseline (II, III/IV - 2 cat.)

Table R.1.2.3.6: 1 Responder analysis (displaying odds ratio) in EQ-VAS change from baseline at week 52 of <= -15 points (deterioration) by NYHA (2 cat.) - RS (LOCF-AD) - 1245.121

Subgroup Description	Placebo	Empa 10mg
Baseline NYHA (2 cat.): II		
Number of patients in analysis set	1401	1399
Number of analysed patients, N (%)	1307 (100.0)	1303 (100.0)
Number of patients with endpoint, N (%)	178 (13.6)	167 (12.8)
95% confidence interval*	(11.9, 15.6)	(11.1, 14.7)
Comparison vs Placebo**		
Odds ratio (SE)		0.909 (0.109)
95% confidence interval***		(0.718, 1.151)
p-value		0.4288
Baseline NYHA (2 cat.): III/IV		
Number of patients in analysis set	466	464
Number of analysed patients, N (%)	403 (100.0)	430 (100.0)
Number of patients with endpoint, N (%)	68 (16.9)	62 (14.4)
95% confidence interval*	(13.5, 20.8)	(11.4, 18.1)
Comparison vs Placebo**		
Odds ratio (SE)		0.841 (0.170)
95% confidence interval***		(0.566, 1.249)
p-value		0.3907

* Wilson confidence intervals.
** Logistic regression includes terms for baseline EQ-VAS score (p<0.0001), age (p=0.0447), baseline eGFR (CKD-EPI) (p=0.0335), Treatment (p=0.2534), region (5 cat.) (p=0.0002), baseline diabetes status (3 cat.) (p=0.7395), sex (p=0.0844), baseline LVEF (3 cat.) (p=0.4619), baseline NYHA (2 cat.) (p<0.0001) and Treatment by baseline NYHA (2 cat.) interaction (p=0.7392).
***Wald confidence intervals.

Data taken from study 1245.121 only.
LOCF: For a missing value at week 52 the last available post-baseline value before week 52 is imputed.

Table R.1.2.3.6: 2 Responder analysis (displaying risk ratio) in EQ-VAS change from baseline at week 52 of <= -15 points (deterioration) by NYHA (2 cat.) - RS (LOCF-AD) - 1245.121

Subgroup Description	Placebo	Empa 10mg
Baseline NYHA (2 cat.): II		
Number of patients in analysis set	1401	1399
Number of analysed patients, N (%)	1307 (100.0)	1303 (100.0)
Number of patients with endpoint, N (%)	178 (13.6)	167 (12.8)
95% confidence interval*	(11.9, 15.6)	(11.1, 14.7)
Comparison vs Placebo**		
Risk ratio (SE)		0.925 (0.090)
95% confidence interval***		(0.764, 1.119)
p-value		0.4214
Baseline NYHA (2 cat.): III/IV		
Number of patients in analysis set	466	464
Number of analysed patients, N (%)	403 (100.0)	430 (100.0)
Number of patients with endpoint, N (%)	68 (16.9)	62 (14.4)
95% confidence interval*	(13.5, 20.8)	(11.4, 18.1)
Comparison vs Placebo**		
Risk ratio (SE)		0.876 (0.133)
95% confidence interval***		(0.650, 1.181)
p-value		0.3840

* Wilson confidence intervals.
** Log-linked Poisson model with robust estimate of variance includes terms for baseline EQ-VAS score (p<0.0001), age (p=0.0551), baseline eGFR (CKD-EPI) (p=0.0383), Treatment (p=0.2431), region (5 cat.) (p<0.0001), baseline diabetes status (3 cat.) (p=0.7228), sex (p=0.0891), baseline LVEF (3 cat.) (p=0.4724), baseline NYHA (2 cat.) (p<0.0001) and Treatment by baseline NYHA (2 cat.) interaction (p=0.7646).
***Wald confidence intervals.

Data taken from study 1245.121 only.
LOCF: For a missing value at week 52 the last available post-baseline value before week 52 is imputed.

Table R.1.2.3.6: 3 Responder analysis (displaying odds ratio) in EQ-VAS change from baseline at week 52 of > -15 points (stability) by NYHA (2 cat.) - RS (LOCF-AD) - 1245.121

Subgroup Description	Placebo	Empa 10mg
Baseline NYHA (2 cat.): II		
Number of patients in analysis set	1401	1399
Number of analysed patients, N (%)	1307 (100.0)	1303 (100.0)
Number of patients with endpoint, N (%)	1129 (86.4)	1136 (87.2)
95% confidence interval*	(84.4, 88.1)	(85.3, 88.9)
Comparison vs Placebo**		
Odds ratio (SE)		1.100 (0.132)
95% confidence interval***		(0.869, 1.392)
p-value		0.4288
Baseline NYHA (2 cat.): III/IV		
Number of patients in analysis set	466	464
Number of analysed patients, N (%)	403 (100.0)	430 (100.0)
Number of patients with endpoint, N (%)	335 (83.1)	368 (85.6)
95% confidence interval*	(79.2, 86.5)	(81.9, 88.6)
Comparison vs Placebo**		
Odds ratio (SE)		1.189 (0.240)
95% confidence interval***		(0.800, 1.767)
p-value		0.3907

* Wilson confidence intervals.
** Logistic regression includes terms for baseline EQ-VAS score (p<0.0001), age (p=0.0447), baseline eGFR (CKD-EPI) (p=0.0335), Treatment (p=0.2534), region (5 cat.) (p=0.0002), baseline diabetes status (3 cat.) (p=0.7395), sex (p=0.0844), baseline LVEF (3 cat.) (p=0.4619), baseline NYHA (2 cat.) (p<0.0001) and Treatment by baseline NYHA (2 cat.) interaction (p=0.7392).
***Wald confidence intervals.

Data taken from study 1245.121 only.
LOCF: For a missing value at week 52 the last available post-baseline value before week 52 is imputed.

Table R.1.2.3.6: 4 Responder analysis (displaying risk ratio) in EQ-VAS change from baseline at week 52 of > -15 points (stability) by NYHA (2 cat.) - RS (LOCF-AD) - 1245.121

Subgroup Description	Placebo	Empa 10mg
Baseline NYHA (2 cat.): II		
Number of patients in analysis set	1401	1399
Number of analysed patients, N (%)	1307 (100.0)	1303 (100.0)
Number of patients with endpoint, N (%)	1129 (86.4)	1136 (87.2)
95% confidence interval*	(84.4, 88.1)	(85.3, 88.9)
Comparison vs Placebo**		
Risk ratio (SE)		1.010 (0.015)
95% confidence interval***		(0.981, 1.040)
p-value		0.4989
Baseline NYHA (2 cat.): III/IV		
Number of patients in analysis set	466	464
Number of analysed patients, N (%)	403 (100.0)	430 (100.0)
Number of patients with endpoint, N (%)	335 (83.1)	368 (85.6)
95% confidence interval*	(79.2, 86.5)	(81.9, 88.6)
Comparison vs Placebo**		
Risk ratio (SE)		1.024 (0.029)
95% confidence interval***		(0.968, 1.083)
p-value		0.4069

* Wilson confidence intervals.
** Log-linked Poisson model with robust estimate of variance includes terms for baseline EQ-VAS score (p<0.0001), age (p=0.1200), baseline eGFR (CKD-EPI) (p=0.0389), Treatment (p=0.2949), region (5 cat.) (p=0.0015), baseline diabetes status (3 cat.) (p=0.6843), sex (p=0.0507), baseline LVEF (3 cat.) (p=0.5407), baseline NYHA (2 cat.) (p<0.0001) and Treatment by baseline NYHA (2 cat.) interaction (p=0.6733).
***Wald confidence intervals.

Data taken from study 1245.121 only.
LOCF: For a missing value at week 52 the last available post-baseline value before week 52 is imputed.

Table R.1.2.3.6: 5 Responder analysis (displaying odds ratio) in EQ-VAS change from baseline at week 52 of >= 15 points (improvement) by NYHA (2 cat.) - RS (LOCF-AD) - 1245.121

Subgroup Description	Placebo	Empa 10mg
Baseline NYHA (2 cat.): II		
Number of patients in analysis set	1401	1399
Number of analysed patients, N (%)	1307 (100.0)	1303 (100.0)
Number of patients with endpoint, N (%)	303 (23.2)	346 (26.6)
95% confidence interval*	(21.0, 25.5)	(24.2, 29.0)
Comparison vs Placebo**		
Odds ratio (SE)		1.268 (0.133)
95% confidence interval***		(1.032, 1.559)
p-value		0.0240
Baseline NYHA (2 cat.): III/IV		
Number of patients in analysis set	466	464
Number of analysed patients, N (%)	403 (100.0)	430 (100.0)
Number of patients with endpoint, N (%)	117 (29.0)	149 (34.7)
95% confidence interval*	(24.8, 33.6)	(30.3, 39.3)
Comparison vs Placebo**		
Odds ratio (SE)		1.361 (0.244)
95% confidence interval***		(0.958, 1.933)
p-value		0.0850

* Wilson confidence intervals.
** Logistic regression includes terms for baseline EQ-VAS score (p<0.0001), age (p=0.1193), baseline eGFR (CKD-EPI) (p=0.1774), Treatment (p=0.0086), region (5 cat.) (p<0.0001), baseline diabetes status (3 cat.) (p=0.6553), sex (p=0.5434), baseline LVEF (3 cat.) (p=0.0540), baseline NYHA (2 cat.) (p=0.0006) and Treatment by baseline NYHA (2 cat.) interaction (p=0.7334).
***Wald confidence intervals.

Data taken from study 1245.121 only.
LOCF: For a missing value at week 52 the last available post-baseline value before week 52 is imputed.

Table R.1.2.3.6: 6 Responder analysis (displaying risk ratio) in EQ-VAS change from baseline at week 52 of >= 15 points (improvement) by NYHA (2 cat.) - RS (LOCF-AD) - 1245.121

Subgroup Description	Placebo	Empa 10mg
Baseline NYHA (2 cat.): II		
Number of patients in analysis set	1401	1399
Number of analysed patients, N (%)	1307 (100.0)	1303 (100.0)
Number of patients with endpoint, N (%)	303 (23.2)	346 (26.6)
95% confidence interval*	(21.0, 25.5)	(24.2, 29.0)
Comparison vs Placebo**		
Risk ratio (SE)		1.136 (0.070)
95% confidence interval***		(1.007, 1.281)
p-value		0.0382
Baseline NYHA (2 cat.): III/IV		
Number of patients in analysis set	466	464
Number of analysed patients, N (%)	403 (100.0)	430 (100.0)
Number of patients with endpoint, N (%)	117 (29.0)	149 (34.7)
95% confidence interval*	(24.8, 33.6)	(30.3, 39.3)
Comparison vs Placebo**		
Risk ratio (SE)		1.121 (0.110)
95% confidence interval***		(0.925, 1.358)
p-value		0.2430

* Wilson confidence intervals.
** Log-linked Poisson model with robust estimate of variance includes terms for baseline EQ-VAS score (p<0.0001), age (p=0.1265), baseline eGFR (CKD-EPI) (p=0.1423), Treatment (p=0.0367), region (5 cat.) (p<0.0001), baseline diabetes status (3 cat.) (p=0.5157), sex (p=0.2684), baseline LVEF (3 cat.) (p=0.0959), baseline NYHA (2 cat.) (p=0.0009) and Treatment by baseline NYHA (2 cat.) interaction (p=0.9088).
***Wald confidence intervals.

Data taken from study 1245.121 only.
LOCF: For a missing value at week 52 the last available post-baseline value before week 52 is imputed.

R.1.2.3.7 Subgroup analysis by diabetes at baseline

Table R.1.2.3.7: 1 Responder analysis (displaying odds ratio) in EQ-VAS change from baseline at week 52 of <= -15 points (deterioration) by diabetes at baseline - RS (LOCF-AD) - 1245.121

Subgroup Description	Placebo	Empa 10mg
Diabetes at baseline (2 cat.): Diabetic		
Number of patients in analysis set	929	927
Number of analysed patients, N (%)	850 (100.0)	856 (100.0)
Number of patients with endpoint, N (%)	122 (14.4)	113 (13.2)
95% confidence interval*	(12.2, 16.9)	(11.1, 15.6)
Comparison vs Placebo**		
Odds ratio (SE)		0.900 (0.132)
95% confidence interval***		(0.676, 1.199)
p-value		0.4730
Diabetes at baseline (2 cat.): Non-Diabetic		
Number of patients in analysis set	938	936
Number of analysed patients, N (%)	860 (100.0)	877 (100.0)
Number of patients with endpoint, N (%)	124 (14.4)	116 (13.2)
95% confidence interval*	(12.2, 16.9)	(11.1, 15.6)
Comparison vs Placebo**		
Odds ratio (SE)		0.890 (0.129)
95% confidence interval***		(0.671, 1.182)
p-value		0.4204

* Wilson confidence intervals.
** Logistic regression includes terms for baseline EQ-VAS score (p<0.0001), age (p=0.0492), baseline eGFR (CKD-EPI) (p=0.0236), Treatment (p=0.2816), region (5 cat.) (p<0.0001), sex (p=0.0432), baseline LVEF (3 cat.) (p=0.3913), diabetes at baseline (2 cat.) (p=0.7417) and Treatment by diabetes at baseline (2 cat.) interaction (p=0.9554).
***Wald confidence intervals.

Data taken from study 1245.121 only.
LOCF: For a missing value at week 52 the last available post-baseline value before week 52 is imputed.

Table R.1.2.3.7: 2 Responder analysis (displaying risk ratio) in EQ-VAS change from baseline at week 52 of <= -15 points (deterioration) by diabetes at baseline - RS (LOCF-AD) - 1245.121

Subgroup Description	Placebo	Empa 10mg
Diabetes at baseline (2 cat.): Diabetic		
Number of patients in analysis set	929	927
Number of analysed patients, N (%)	850 (100.0)	856 (100.0)
Number of patients with endpoint, N (%)	122 (14.4)	113 (13.2)
95% confidence interval*	(12.2, 16.9)	(11.1, 15.6)
Comparison vs Placebo**		
Risk ratio (SE)		0.919 (0.107)
95% confidence interval***		(0.731, 1.155)
p-value		0.4668
Diabetes at baseline (2 cat.): Non-Diabetic		
Number of patients in analysis set	938	936
Number of analysed patients, N (%)	860 (100.0)	877 (100.0)
Number of patients with endpoint, N (%)	124 (14.4)	116 (13.2)
95% confidence interval*	(12.2, 16.9)	(11.1, 15.6)
Comparison vs Placebo**		
Risk ratio (SE)		0.908 (0.106)
95% confidence interval***		(0.722, 1.142)
p-value		0.4083

* Wilson confidence intervals.
** Log-linked Poisson model with robust estimate of variance includes terms for baseline EQ-VAS score (p<0.0001), age (p=0.0653), baseline eGFR (CKD-EPI) (p=0.0291), Treatment (p=0.2708), region (5 cat.) (p<0.0001), sex (p=0.0474), baseline LVEF (3 cat.) (p=0.4197), diabetes at baseline (2 cat.) (p=0.7654) and Treatment by diabetes at baseline (2 cat.) interaction (p=0.9431).
***Wald confidence intervals.

Data taken from study 1245.121 only.
LOCF: For a missing value at week 52 the last available post-baseline value before week 52 is imputed.

Table R.1.2.3.7: 3 Responder analysis (displaying odds ratio) in EQ-VAS change from baseline at week 52 of > -15 points (stability) by diabetes at baseline - RS (LOCF-AD) - 1245.121

Subgroup Description	Placebo	Empa 10mg
Diabetes at baseline (2 cat.): Diabetic		
Number of patients in analysis set	929	927
Number of analysed patients, N (%)	850 (100.0)	856 (100.0)
Number of patients with endpoint, N (%)	728 (85.6)	743 (86.8)
95% confidence interval*	(83.1, 87.8)	(84.4, 88.9)
Comparison vs Placebo**		
Odds ratio (SE)		1.111 (0.162)
95% confidence interval***		(0.834, 1.479)
p-value		0.4730
Diabetes at baseline (2 cat.): Non-Diabetic		
Number of patients in analysis set	938	936
Number of analysed patients, N (%)	860 (100.0)	877 (100.0)
Number of patients with endpoint, N (%)	736 (85.6)	761 (86.8)
95% confidence interval*	(83.1, 87.8)	(84.4, 88.9)
Comparison vs Placebo**		
Odds ratio (SE)		1.123 (0.162)
95% confidence interval***		(0.846, 1.491)
p-value		0.4204

* Wilson confidence intervals.
** Logistic regression includes terms for baseline EQ-VAS score (p<0.0001), age (p=0.0492), baseline eGFR (CKD-EPI) (p=0.0236), Treatment (p=0.2816), region (5 cat.) (p<0.0001), sex (p=0.0432), baseline LVEF (3 cat.) (p=0.3913), diabetes at baseline (2 cat.) (p=0.7417) and Treatment by diabetes at baseline (2 cat.) interaction (p=0.9554).
***Wald confidence intervals.

Data taken from study 1245.121 only.
LOCF: For a missing value at week 52 the last available post-baseline value before week 52 is imputed.

Table R.1.2.3.7: 4 Responder analysis (displaying risk ratio) in EQ-VAS change from baseline at week 52 of > -15 points (stability) by diabetes at baseline - RS (LOCF-AD) - 1245.121

Subgroup Description	Placebo	Empa 10mg
Diabetes at baseline (2 cat.): Diabetic		
Number of patients in analysis set	929	927
Number of analysed patients, N (%)	850 (100.0)	856 (100.0)
Number of patients with endpoint, N (%)	728 (85.6)	743 (86.8)
95% confidence interval*	(83.1, 87.8)	(84.4, 88.9)
Comparison vs Placebo**		
Risk ratio (SE)		1.012 (0.019)
95% confidence interval***		(0.975, 1.049)
p-value		0.5343
Diabetes at baseline (2 cat.): Non-Diabetic		
Number of patients in analysis set	938	936
Number of analysed patients, N (%)	860 (100.0)	877 (100.0)
Number of patients with endpoint, N (%)	736 (85.6)	761 (86.8)
95% confidence interval*	(83.1, 87.8)	(84.4, 88.9)
Comparison vs Placebo**		
Risk ratio (SE)		1.013 (0.019)
95% confidence interval***		(0.976, 1.051)
p-value		0.4904

* Wilson confidence intervals.
** Log-linked Poisson model with robust estimate of variance includes terms for baseline EQ-VAS score (p<0.0001), age (p=0.1138), baseline eGFR (CKD-EPI) (p=0.0306), Treatment (p=0.3544), region (5 cat.) (p=0.0009), sex (p=0.0304), baseline LVEF (3 cat.) (p=0.4333), diabetes at baseline (2 cat.) (p=0.6710) and Treatment by diabetes at baseline (2 cat.) interaction (p=0.9598).
***Wald confidence intervals.

Data taken from study 1245.121 only.
LOCF: For a missing value at week 52 the last available post-baseline value before week 52 is imputed.

Table R.1.2.3.7: 5 Responder analysis (displaying odds ratio) in EQ-VAS change from baseline at week 52 of >= 15 points (improvement) by diabetes at baseline - RS (LOCF-AD) - 1245.121

Subgroup Description	Placebo	Empa 10mg
Diabetes at baseline (2 cat.): Diabetic		
Number of patients in analysis set	929	927
Number of analysed patients, N (%)	850 (100.0)	856 (100.0)
Number of patients with endpoint, N (%)	218 (25.6)	253 (29.6)
95% confidence interval*	(22.8, 28.7)	(26.6, 32.7)
Comparison vs Placebo**		
Odds ratio (SE)		1.266 (0.162)
95% confidence interval***		(0.986, 1.627)
p-value		0.0648
Diabetes at baseline (2 cat.): Non-Diabetic		
Number of patients in analysis set	938	936
Number of analysed patients, N (%)	860 (100.0)	877 (100.0)
Number of patients with endpoint, N (%)	202 (23.5)	242 (27.6)
95% confidence interval*	(20.8, 26.4)	(24.7, 30.6)
Comparison vs Placebo**		
Odds ratio (SE)		1.298 (0.166)
95% confidence interval***		(1.010, 1.669)
p-value		0.0415

* Wilson confidence intervals.
** Logistic regression includes terms for baseline EQ-VAS score (p<0.0001), age (p=0.1216), baseline eGFR (CKD-EPI) (p=0.1466), Treatment (p=0.0060), region (5 cat.) (p<0.0001), sex (p=0.4563), baseline LVEF (3 cat.) (p=0.0625), diabetes at baseline (2 cat.) (p=0.8605) and Treatment by diabetes at baseline (2 cat.) interaction (p=0.8904).
***Wald confidence intervals.

Data taken from study 1245.121 only.
LOCF: For a missing value at week 52 the last available post-baseline value before week 52 is imputed.

Table R.1.2.3.7: 6 Responder analysis (displaying risk ratio) in EQ-VAS change from baseline at week 52 of >= 15 points (improvement) by diabetes at baseline - RS (LOCF-AD) - 1245.121

Subgroup Description	Placebo	Empa 10mg
Diabetes at baseline (2 cat.): Diabetic		
Number of patients in analysis set	929	927
Number of analysed patients, N (%)	850 (100.0)	856 (100.0)
Number of patients with endpoint, N (%)	218 (25.6)	253 (29.6)
95% confidence interval*	(22.8, 28.7)	(26.6, 32.7)
Comparison vs Placebo**		
Risk ratio (SE)		1.111 (0.080)
95% confidence interval***		(0.965, 1.280)
p-value		0.1430
Diabetes at baseline (2 cat.): Non-Diabetic		
Number of patients in analysis set	938	936
Number of analysed patients, N (%)	860 (100.0)	877 (100.0)
Number of patients with endpoint, N (%)	202 (23.5)	242 (27.6)
95% confidence interval*	(20.8, 26.4)	(24.7, 30.6)
Comparison vs Placebo**		
Risk ratio (SE)		1.142 (0.086)
95% confidence interval***		(0.985, 1.325)
p-value		0.0785

* Wilson confidence intervals.
** Log-linked Poisson model with robust estimate of variance includes terms for baseline EQ-VAS score (p<0.0001), age (p=0.0980), baseline eGFR (CKD-EPI) (p=0.1574), Treatment (p=0.0223), region (5 cat.) (p<0.0001), sex (p=0.2322), baseline LVEF (3 cat.) (p=0.1284), diabetes at baseline (2 cat.) (p=0.9307) and Treatment by diabetes at baseline (2 cat.) interaction (p=0.7919).
***Wald confidence intervals.

Data taken from study 1245.121 only.
LOCF: For a missing value at week 52 the last available post-baseline value before week 52 is imputed.

R.1.2.3.8 Subgroup analysis by BMI at baseline (<30, >=30)

Table R.1.2.3.8: 1 Responder analysis (displaying odds ratio) in EQ-VAS change from baseline at week 52 of <= -15 points (deterioration) by baseline BMI [kg/m2] - RS (LOCF-AD) - 1245.121

Subgroup Description	Placebo	Empa 10mg
Baseline BMI [kg/m²] (2 cat.): <30		
Number of patients in analysis set	1300	1263
Number of analysed patients, N (%)	1197 (100.0)	1179 (100.0)
Number of patients with endpoint, N (%)	175 (14.6)	152 (12.9)
95% confidence interval*	(12.7, 16.7)	(11.1, 14.9)
Comparison vs Placebo**		
Odds ratio (SE)		0.835 (0.104)
95% confidence interval***		(0.655, 1.065)
p-value		0.1473
Baseline BMI [kg/m²] (2 cat.): >=30		
Number of patients in analysis set	567	600
Number of analysed patients, N (%)	513 (100.0)	554 (100.0)
Number of patients with endpoint, N (%)	71 (13.8)	77 (13.9)
95% confidence interval*	(11.1, 17.1)	(11.3, 17.0)
Comparison vs Placebo**		
Odds ratio (SE)		1.038 (0.192)
95% confidence interval***		(0.723, 1.491)
p-value		0.8402

* Wilson confidence intervals.
** Logistic regression includes terms for baseline EQ-VAS score (p<0.0001), age (p=0.0297), baseline eGFR (CKD-EPI) (p=0.0246), Treatment (p=0.5215), region (5 cat.) (p=0.0001), baseline diabetes status (3 cat.) (p=0.7160), sex (p=0.0527), baseline LVEF (3 cat.) (p=0.3746), baseline BMI (2 cat.) (p=0.1397) and Treatment by baseline BMI (2 cat.) interaction (p=0.3293).
***Wald confidence intervals.

Data taken from study 1245.121 only.
LOCF: For a missing value at week 52 the last available post-baseline value before week 52 is imputed.

Table R.1.2.3.8: 2 Responder analysis (displaying risk ratio) in EQ-VAS change from baseline at week 52 of <= -15 points (deterioration) by baseline BMI [kg/m2] - RS (LOCF-AD) - 1245.121

Subgroup Description	Placebo	Empa 10mg
Baseline BMI [kg/m²] (2 cat.): <30		
Number of patients in analysis set	1300	1263
Number of analysed patients, N (%)	1197 (100.0)	1179 (100.0)
Number of patients with endpoint, N (%)	175 (14.6)	152 (12.9)
95% confidence interval*	(12.7, 16.7)	(11.1, 14.9)
Comparison vs Placebo**		
Risk ratio (SE)		0.864 (0.086)
95% confidence interval***		(0.711, 1.051)
p-value		0.1435
Baseline BMI [kg/m²] (2 cat.): >=30		
Number of patients in analysis set	567	600
Number of analysed patients, N (%)	513 (100.0)	554 (100.0)
Number of patients with endpoint, N (%)	71 (13.8)	77 (13.9)
95% confidence interval*	(11.1, 17.1)	(11.3, 17.0)
Comparison vs Placebo**		
Risk ratio (SE)		1.027 (0.152)
95% confidence interval***		(0.769, 1.372)
p-value		0.8557

* Wilson confidence intervals.
** Log-linked Poisson model with robust estimate of variance includes terms for baseline EQ-VAS score (p<0.0001), age (p=0.0418), baseline eGFR (CKD-EPI) (p=0.0302), Treatment (p=0.5037), region (5 cat.) (p<0.0001), baseline diabetes status (3 cat.) (p=0.7189), sex (p=0.0587), baseline LVEF (3 cat.) (p=0.3992), baseline BMI (2 cat.) (p=0.1245) and Treatment by baseline BMI (2 cat.) interaction (p=0.3328).
***Wald confidence intervals.

Data taken from study 1245.121 only.
LOCF: For a missing value at week 52 the last available post-baseline value before week 52 is imputed.

Table R.1.2.3.8: 3 Responder analysis (displaying odds ratio) in EQ-VAS change from baseline at week 52 of > -15 points (stability) by baseline BMI [kg/m2] - RS (LOCF-AD) - 1245.121

Subgroup Description	Placebo	Empa 10mg
Baseline BMI [kg/m²] (2 cat.): <30		
Number of patients in analysis set	1300	1263
Number of analysed patients, N (%)	1197 (100.0)	1179 (100.0)
Number of patients with endpoint, N (%)	1022 (85.4)	1027 (87.1)
95% confidence interval*	(83.3, 87.3)	(85.1, 88.9)
Comparison vs Placebo**		
Odds ratio (SE)		1.197 (0.149)
95% confidence interval***		(0.939, 1.527)
p-value		0.1473
Baseline BMI [kg/m²] (2 cat.): >=30		
Number of patients in analysis set	567	600
Number of analysed patients, N (%)	513 (100.0)	554 (100.0)
Number of patients with endpoint, N (%)	442 (86.2)	477 (86.1)
95% confidence interval*	(82.9, 88.9)	(83.0, 88.7)
Comparison vs Placebo**		
Odds ratio (SE)		0.963 (0.178)
95% confidence interval***		(0.671, 1.384)
p-value		0.8402

* Wilson confidence intervals.
** Logistic regression includes terms for baseline EQ-VAS score (p<0.0001), age (p=0.0297), baseline eGFR (CKD-EPI) (p=0.0246), Treatment (p=0.5215), region (5 cat.) (p=0.0001), baseline diabetes status (3 cat.) (p=0.7160), sex (p=0.0527), baseline LVEF (3 cat.) (p=0.3746), baseline BMI (2 cat.) (p=0.1397) and Treatment by baseline BMI (2 cat.) interaction (p=0.3293).
***Wald confidence intervals.

Data taken from study 1245.121 only.
LOCF: For a missing value at week 52 the last available post-baseline value before week 52 is imputed.

Table R.1.2.3.8: 4 Responder analysis (displaying risk ratio) in EQ-VAS change from baseline at week 52 of > -15 points (stability) by baseline BMI [kg/m2] - RS (LOCF-AD) - 1245.121

Subgroup Description	Placebo	Empa 10mg
Baseline BMI [kg/m²] (2 cat.): <30		
Number of patients in analysis set	1300	1263
Number of analysed patients, N (%)	1197 (100.0)	1179 (100.0)
Number of patients with endpoint, N (%)	1022 (85.4)	1027 (87.1)
95% confidence interval*	(83.3, 87.3)	(85.1, 88.9)
Comparison vs Placebo**		
Risk ratio (SE)		1.022 (0.016)
95% confidence interval***		(0.990, 1.054)
p-value		0.1818
Baseline BMI [kg/m²] (2 cat.): >=30		
Number of patients in analysis set	567	600
Number of analysed patients, N (%)	513 (100.0)	554 (100.0)
Number of patients with endpoint, N (%)	442 (86.2)	477 (86.1)
95% confidence interval*	(82.9, 88.9)	(83.0, 88.7)
Comparison vs Placebo**		
Risk ratio (SE)		0.993 (0.024)
95% confidence interval***		(0.948, 1.041)
p-value		0.7835

* Wilson confidence intervals.
** Log-linked Poisson model with robust estimate of variance includes terms for baseline EQ-VAS score (p<0.0001), age (p=0.0814), baseline eGFR (CKD-EPI) (p=0.0314), Treatment (p=0.6062), region (5 cat.) (p=0.0016), baseline diabetes status (3 cat.) (p=0.6472), sex (p=0.0360), baseline LVEF (3 cat.) (p=0.4256), baseline BMI (2 cat.) (p=0.2689) and Treatment by baseline BMI (2 cat.) interaction (p=0.3311).
***Wald confidence intervals.

Data taken from study 1245.121 only.
LOCF: For a missing value at week 52 the last available post-baseline value before week 52 is imputed.

Table R.1.2.3.8: 5 Responder analysis (displaying odds ratio) in EQ-VAS change from baseline at week 52 of >= 15 points (improvement) by baseline BMI [kg/m2] - RS (LOCF-AD) - 1245.121

Subgroup Description	Placebo	Empa 10mg
Baseline BMI [kg/m²] (2 cat.): <30		
Number of patients in analysis set	1300	1263
Number of analysed patients, N (%)	1197 (100.0)	1179 (100.0)
Number of patients with endpoint, N (%)	300 (25.1)	328 (27.8)
95% confidence interval*	(22.7, 27.6)	(25.3, 30.4)
Comparison vs Placebo**		
Odds ratio (SE)		1.237 (0.135)
95% confidence interval***		(0.998, 1.532)
p-value		0.0518
Baseline BMI [kg/m²] (2 cat.): >=30		
Number of patients in analysis set	567	600
Number of analysed patients, N (%)	513 (100.0)	554 (100.0)
Number of patients with endpoint, N (%)	120 (23.4)	167 (30.1)
95% confidence interval*	(19.9, 27.2)	(26.5, 34.1)
Comparison vs Placebo**		
Odds ratio (SE)		1.421 (0.231)
95% confidence interval***		(1.033, 1.955)
p-value		0.0308

* Wilson confidence intervals.
** Logistic regression includes terms for baseline EQ-VAS score (p<0.0001), age (p=0.0638), baseline eGFR (CKD-EPI) (p=0.1510), Treatment (p=0.0040), region (5 cat.) (p<0.0001), baseline diabetes status (3 cat.) (p=0.6363), sex (p=0.4926), baseline LVEF (3 cat.) (p=0.0594), baseline BMI (2 cat.) (p=0.0530) and Treatment by baseline BMI (2 cat.) interaction (p=0.4778).
***Wald confidence intervals.

Data taken from study 1245.121 only.
LOCF: For a missing value at week 52 the last available post-baseline value before week 52 is imputed.

Table R.1.2.3.8: 6 Responder analysis (displaying risk ratio) in EQ-VAS change from baseline at week 52 of >= 15 points (improvement) by baseline BMI [kg/m2] - RS (LOCF-AD) - 1245.121

Subgroup Description	Placebo	Empa 10mg
Baseline BMI [kg/m²] (2 cat.): <30		
Number of patients in analysis set	1300	1263
Number of analysed patients, N (%)	1197 (100.0)	1179 (100.0)
Number of patients with endpoint, N (%)	300 (25.1)	328 (27.8)
95% confidence interval*	(22.7, 27.6)	(25.3, 30.4)
Comparison vs Placebo**		
Risk ratio (SE)		1.111 (0.070)
95% confidence interval***		(0.981, 1.257)
p-value		0.0964
Baseline BMI [kg/m²] (2 cat.): >=30		
Number of patients in analysis set	567	600
Number of analysed patients, N (%)	513 (100.0)	554 (100.0)
Number of patients with endpoint, N (%)	120 (23.4)	167 (30.1)
95% confidence interval*	(19.9, 27.2)	(26.5, 34.1)
Comparison vs Placebo**		
Risk ratio (SE)		1.183 (0.111)
95% confidence interval***		(0.985, 1.421)
p-value		0.0721

* Wilson confidence intervals.
** Log-linked Poisson model with robust estimate of variance includes terms for baseline EQ-VAS score (p<0.0001), age (p=0.0598), baseline eGFR (CKD-EPI) (p=0.1552), Treatment (p=0.0155), region (5 cat.) (p<0.0001), baseline diabetes status (3 cat.) (p=0.5354), sex (p=0.2443), baseline LVEF (3 cat.) (p=0.1212), baseline BMI (2 cat.) (p=0.1463) and Treatment by baseline BMI (2 cat.) interaction (p=0.5756).
***Wald confidence intervals.

Data taken from study 1245.121 only.
LOCF: For a missing value at week 52 the last available post-baseline value before week 52 is imputed.

R.1.2.3.9

R.1.2.3.9 Subgroup analysis by eGFR at baseline (<60, >=60)

Table R.1.2.3.9: 1 Responder analysis (displaying odds ratio) in EQ-VAS change from baseline at week 52 of <= -15 points (deterioration) by baseline eGFR (2 cat.) - RS (LOCF-AD) - 1245.121

Subgroup Description	Placebo	Empa 10mg
Baseline eGFR (CKD-EPI) [mL/min/1.73m²] (2 cat.): >=60		
Number of patients in analysis set	960	969
Number of analysed patients, N (%)	875 (100.0)	900 (100.0)
Number of patients with endpoint, N (%)	112 (12.8)	100 (11.1)
95% confidence interval*	(10.7, 15.2)	(9.2, 13.3)
Comparison vs Placebo**		
Odds ratio (SE)		0.809 (0.123)
95% confidence interval***		(0.601, 1.090)
p-value		0.1641
Baseline eGFR (CKD-EPI) [mL/min/1.73m²] (2 cat.): <60		
Number of patients in analysis set	906	893
Number of analysed patients, N (%)	835 (100.0)	833 (100.0)
Number of patients with endpoint, N (%)	134 (16.0)	129 (15.5)
95% confidence interval*	(13.7, 18.7)	(13.2, 18.1)
Comparison vs Placebo**		
Odds ratio (SE)		0.981 (0.137)
95% confidence interval***		(0.746, 1.290)
p-value		0.8916

* Wilson confidence intervals.
** Logistic regression includes terms for baseline EQ-VAS score (p<0.0001), age (p=0.0086), Treatment (p=0.2641), region (5 cat.) (p<0.0001), baseline diabetes status (3 cat.) (p=0.7208), sex (p=0.0412), baseline LVEF (3 cat.) (p=0.4218), baseline eGFR (CKD-EPI) (2 cat.) (p=0.0683) and Treatment by baseline eGFR (CKD-EPI) (2 cat.) interaction (p=0.3517).
***Wald confidence intervals.
2 patients were excluded as the subgroup variable was missing.

Data taken from study 1245.121 only.
LOCF: For a missing value at week 52 the last available post-baseline value before week 52 is imputed.

Table R.1.2.3.9: 2 Responder analysis (displaying risk ratio) in EQ-VAS change from baseline at week 52 of <= -15 points (deterioration) by baseline eGFR (2 cat.) - RS (LOCF-AD) - 1245.121

Subgroup Description	Placebo	Empa 10mg
Baseline eGFR (CKD-EPI) [mL/min/1.73m²] (2 cat.): >=60		
Number of patients in analysis set	960	969
Number of analysed patients, N (%)	875 (100.0)	900 (100.0)
Number of patients with endpoint, N (%)	112 (12.8)	100 (11.1)
95% confidence interval*	(10.7, 15.2)	(9.2, 13.3)
Comparison vs Placebo**		
Risk ratio (SE)		0.839 (0.106)
95% confidence interval***		(0.656, 1.074)
p-value		0.1638
Baseline eGFR (CKD-EPI) [mL/min/1.73m²] (2 cat.): <60		
Number of patients in analysis set	906	893
Number of analysed patients, N (%)	835 (100.0)	833 (100.0)
Number of patients with endpoint, N (%)	134 (16.0)	129 (15.5)
95% confidence interval*	(13.7, 18.7)	(13.2, 18.1)
Comparison vs Placebo**		
Risk ratio (SE)		0.982 (0.108)
95% confidence interval***		(0.792, 1.219)
p-value		0.8721

* Wilson confidence intervals.
** Log-linked Poisson model with robust estimate of variance includes terms for baseline EQ-VAS score (p<0.0001), age (p=0.0133), Treatment (p=0.2474), region (5 cat.) (p<0.0001), baseline diabetes status (3 cat.) (p=0.7277), sex (p=0.0458), baseline LVEF (3 cat.) (p=0.4501), baseline eGFR (CKD-EPI) (2 cat.) (p=0.0727) and Treatment by baseline eGFR (CKD-EPI) (2 cat.) interaction (p=0.3466).
***Wald confidence intervals.
2 patients were excluded as the subgroup variable was missing.

Data taken from study 1245.121 only.
LOCF: For a missing value at week 52 the last available post-baseline value before week 52 is imputed.

Table R.1.2.3.9: 3 Responder analysis (displaying odds ratio) in EQ-VAS change from baseline at week 52 of > -15 points (stability) by baseline eGFR (2 cat.) - RS (LOCF-AD) - 1245.121

Subgroup Description	Placebo	Empa 10mg
Baseline eGFR (CKD-EPI) [mL/min/1.73m²] (2 cat.): >=60		
Number of patients in analysis set	960	969
Number of analysed patients, N (%)	875 (100.0)	900 (100.0)
Number of patients with endpoint, N (%)	763 (87.2)	800 (88.9)
95% confidence interval*	(84.8, 89.3)	(86.7, 90.8)
Comparison vs Placebo**		
Odds ratio (SE)		1.235 (0.188)
95% confidence interval***		(0.917, 1.664)
p-value		0.1641
Baseline eGFR (CKD-EPI) [mL/min/1.73m²] (2 cat.): <60		
Number of patients in analysis set	906	893
Number of analysed patients, N (%)	835 (100.0)	833 (100.0)
Number of patients with endpoint, N (%)	701 (84.0)	704 (84.5)
95% confidence interval*	(81.3, 86.3)	(81.9, 86.8)
Comparison vs Placebo**		
Odds ratio (SE)		1.019 (0.142)
95% confidence interval***		(0.775, 1.340)
p-value		0.8916

* Wilson confidence intervals.
** Logistic regression includes terms for baseline EQ-VAS score (p<0.0001), age (p=0.0086), Treatment (p=0.2641), region (5 cat.) (p<0.0001), baseline diabetes status (3 cat.) (p=0.7208), sex (p=0.0412), baseline LVEF (3 cat.) (p=0.4218), baseline eGFR (CKD-EPI) (2 cat.) (p=0.0683) and Treatment by baseline eGFR (CKD-EPI) (2 cat.) interaction (p=0.3517).
***Wald confidence intervals.
2 patients were excluded as the subgroup variable was missing.

Data taken from study 1245.121 only.
LOCF: For a missing value at week 52 the last available post-baseline value before week 52 is imputed.

Table R.1.2.3.9: 4 Responder analysis (displaying risk ratio) in EQ-VAS change from baseline at week 52 of > -15 points (stability) by baseline eGFR (2 cat.) - RS (LOCF-AD) - 1245.121

Subgroup Description	Placebo	Empa 10mg
Baseline eGFR (CKD-EPI) [mL/min/1.73m²] (2 cat.): >=60		
Number of patients in analysis set	960	969
Number of analysed patients, N (%)	875 (100.0)	900 (100.0)
Number of patients with endpoint, N (%)	763 (87.2)	800 (88.9)
95% confidence interval*	(84.8, 89.3)	(86.7, 90.8)
Comparison vs Placebo**		
Risk ratio (SE)		1.020 (0.017)
95% confidence interval***		(0.986, 1.055)
p-value		0.2492
Baseline eGFR (CKD-EPI) [mL/min/1.73m²] (2 cat.): <60		
Number of patients in analysis set	906	893
Number of analysed patients, N (%)	835 (100.0)	833 (100.0)
Number of patients with endpoint, N (%)	701 (84.0)	704 (84.5)
95% confidence interval*	(81.3, 86.3)	(81.9, 86.8)
Comparison vs Placebo**		
Risk ratio (SE)		1.004 (0.021)
95% confidence interval***		(0.964, 1.045)
p-value		0.8513

* Wilson confidence intervals.
** Log-linked Poisson model with robust estimate of variance includes terms for baseline EQ-VAS score (p<0.0001), age (p=0.0229), Treatment (p=0.3782), region (5 cat.) (p=0.0009), baseline diabetes status (3 cat.) (p=0.6474), sex (p=0.0297), baseline LVEF (3 cat.) (p=0.4506), baseline eGFR (CKD-EPI) (2 cat.) (p=0.0686) and Treatment by baseline eGFR (CKD-EPI) (2 cat.) interaction (p=0.5528).
***Wald confidence intervals.
2 patients were excluded as the subgroup variable was missing.

Data taken from study 1245.121 only.
LOCF: For a missing value at week 52 the last available post-baseline value before week 52 is imputed.

Table R.1.2.3.9: 5 Responder analysis (displaying odds ratio) in EQ-VAS change from baseline at week 52 of >= 15 points (improvement) by baseline eGFR (2 cat.) - RS (LOCF-AD) - 1245.121

Subgroup Description	Placebo	Empa 10mg
Baseline eGFR (CKD-EPI) [mL/min/1.73m²] (2 cat.): >=60		
Number of patients in analysis set	960	969
Number of analysed patients, N (%)	875 (100.0)	900 (100.0)
Number of patients with endpoint, N (%)	226 (25.8)	287 (31.9)
95% confidence interval*	(23.0, 28.8)	(28.9, 35.0)
Comparison vs Placebo**		
Odds ratio (SE)		1.428 (0.176)
95% confidence interval***		(1.121, 1.819)
p-value		0.0039
Baseline eGFR (CKD-EPI) [mL/min/1.73m²] (2 cat.): <60		
Number of patients in analysis set	906	893
Number of analysed patients, N (%)	835 (100.0)	833 (100.0)
Number of patients with endpoint, N (%)	194 (23.2)	208 (25.0)
95% confidence interval*	(20.5, 26.2)	(22.2, 28.0)
Comparison vs Placebo**		
Odds ratio (SE)		1.130 (0.151)
95% confidence interval***		(0.870, 1.468)
p-value		0.3586

* Wilson confidence intervals.
** Logistic regression includes terms for baseline EQ-VAS score (p<0.0001), age (p=0.0698), Treatment (p=0.0085), region (5 cat.) (p<0.0001), baseline diabetes status (3 cat.) (p=0.7000), sex (p=0.4309), baseline LVEF (3 cat.) (p=0.0605), baseline eGFR (CKD-EPI) (2 cat.) (p=0.0567) and Treatment by baseline eGFR (CKD-EPI) (2 cat.) interaction (p=0.1988).
***Wald confidence intervals.
2 patients were excluded as the subgroup variable was missing.

Data taken from study 1245.121 only.
LOCF: For a missing value at week 52 the last available post-baseline value before week 52 is imputed.

Table R.1.2.3.9: 6 Responder analysis (displaying risk ratio) in EQ-VAS change from baseline at week 52 of >= 15 points (improvement) by baseline eGFR (2 cat.) - RS (LOCF-AD) - 1245.121

Subgroup Description	Placebo	Empa 10mg
Baseline eGFR (CKD-EPI) [mL/min/1.73m²] (2 cat.): >=60		
Number of patients in analysis set	960	969
Number of analysed patients, N (%)	875 (100.0)	900 (100.0)
Number of patients with endpoint, N (%)	226 (25.8)	287 (31.9)
95% confidence interval*	(23.0, 28.8)	(28.9, 35.0)
Comparison vs Placebo**		
Risk ratio (SE)		1.178 (0.083)
95% confidence interval***		(1.027, 1.351)
p-value		0.0194
Baseline eGFR (CKD-EPI) [mL/min/1.73m²] (2 cat.): <60		
Number of patients in analysis set	906	893
Number of analysed patients, N (%)	835 (100.0)	833 (100.0)
Number of patients with endpoint, N (%)	194 (23.2)	208 (25.0)
95% confidence interval*	(20.5, 26.2)	(22.2, 28.0)
Comparison vs Placebo**		
Risk ratio (SE)		1.066 (0.084)
95% confidence interval***		(0.914, 1.243)
p-value		0.4128

* Wilson confidence intervals.
** Log-linked Poisson model with robust estimate of variance includes terms for baseline EQ-VAS score (p<0.0001), age (p=0.0556), Treatment (p=0.0302), region (5 cat.) (p<0.0001), baseline diabetes status (3 cat.) (p=0.5868), sex (p=0.2181), baseline LVEF (3 cat.) (p=0.1331), baseline eGFR (CKD-EPI) (2 cat.) (p=0.0797) and Treatment by baseline eGFR (CKD-EPI) (2 cat.) interaction (p=0.3437).
***Wald confidence intervals.
2 patients were excluded as the subgroup variable was missing.

Data taken from study 1245.121 only.
LOCF: For a missing value at week 52 the last available post-baseline value before week 52 is imputed.

R.1.2.3.10

R.1.2.3.10 Subgroup analysis by history of HHF

Table R.1.2.3.10: 1 Responder analysis (displaying odds ratio) in EQ-VAS change from baseline at week 52 of <= -15 points (deterioration) by history of HHF - RS (LOCF-AD) - 1245.121

Subgroup Description	Placebo	Empa 10mg
History of HHF (in the last 12 months): No		
Number of patients in analysis set	1293	1286
Number of analysed patients, N (%)	1193 (100.0)	1209 (100.0)
Number of patients with endpoint, N (%)	163 (13.7)	157 (13.0)
95% confidence interval*	(11.8, 15.7)	(11.2, 15.0)
Comparison vs Placebo**		
Odds ratio (SE)		0.956 (0.119)
95% confidence interval***		(0.749, 1.222)
p-value		0.7210
History of HHF (in the last 12 months): Yes		
Number of patients in analysis set	574	577
Number of analysed patients, N (%)	517 (100.0)	524 (100.0)
Number of patients with endpoint, N (%)	83 (16.1)	72 (13.7)
95% confidence interval*	(13.1, 19.5)	(11.1, 17.0)
Comparison vs Placebo**		
Odds ratio (SE)		0.776 (0.141)
95% confidence interval***		(0.543, 1.108)
p-value		0.1627

* Wilson confidence intervals.
** Logistic regression includes terms for baseline EQ-VAS score (p<0.0001), age (p=0.0312), baseline eGFR (CKD-EPI) (p=0.0227), Treatment (p=0.1759), region (5 cat.) (p<0.0001), baseline diabetes status (3 cat.) (p=0.7240), sex (p=0.0412), baseline LVEF (3 cat.) (p=0.4175), history of HHF (in the last 12 months) (p=0.1348) and Treatment by history of HHF (in the last 12 months) interaction (p=0.3428).
***Wald confidence intervals.

Data taken from study 1245.121 only.
LOCF: For a missing value at week 52 the last available post-baseline value before week 52 is imputed.

Table R.1.2.3.10: 2 Responder analysis (displaying risk ratio) in EQ-VAS change from baseline at week 52 of <= -15 points (deterioration) by history of HHF - RS (LOCF-AD) - 1245.121

Subgroup Description	Placebo	Empa 10mg
History of HHF (in the last 12 months): No		
Number of patients in analysis set	1293	1286
Number of analysed patients, N (%)	1193 (100.0)	1209 (100.0)
Number of patients with endpoint, N (%)	163 (13.7)	157 (13.0)
95% confidence interval*	(11.8, 15.7)	(11.2, 15.0)
Comparison vs Placebo**		
Risk ratio (SE)		0.965 (0.097)
95% confidence interval***		(0.792, 1.175)
p-value		0.7210
History of HHF (in the last 12 months): Yes		
Number of patients in analysis set	574	577
Number of analysed patients, N (%)	517 (100.0)	524 (100.0)
Number of patients with endpoint, N (%)	83 (16.1)	72 (13.7)
95% confidence interval*	(13.1, 19.5)	(11.1, 17.0)
Comparison vs Placebo**		
Risk ratio (SE)		0.810 (0.118)
95% confidence interval***		(0.610, 1.077)
p-value		0.1472

* Wilson confidence intervals.
** Log-linked Poisson model with robust estimate of variance includes terms for baseline EQ-VAS score (p<0.0001), age (p=0.0431), baseline eGFR (CKD-EPI) (p=0.0288), Treatment (p=0.1625), region (5 cat.) (p<0.0001), baseline diabetes status (3 cat.) (p=0.7348), sex (p=0.0460), baseline LVEF (3 cat.) (p=0.4397), history of HHF (in the last 12 months) (p=0.1381) and Treatment by history of HHF (in the last 12 months) interaction (p=0.3236).
***Wald confidence intervals.

Data taken from study 1245.121 only.
LOCF: For a missing value at week 52 the last available post-baseline value before week 52 is imputed.

Table R.1.2.3.10: 3 Responder analysis (displaying odds ratio) in EQ-VAS change from baseline at week 52 of > -15 points (stability) by history of HHF - RS (LOCF-AD) - 1245.121

Subgroup Description	Placebo	Empa 10mg
History of HHF (in the last 12 months): No		
Number of patients in analysis set	1293	1286
Number of analysed patients, N (%)	1193 (100.0)	1209 (100.0)
Number of patients with endpoint, N (%)	1030 (86.3)	1052 (87.0)
95% confidence interval*	(84.3, 88.2)	(85.0, 88.8)
Comparison vs Placebo**		
Odds ratio (SE)		1.046 (0.131)
95% confidence interval***		(0.819, 1.335)
p-value		0.7210
History of HHF (in the last 12 months): Yes		
Number of patients in analysis set	574	577
Number of analysed patients, N (%)	517 (100.0)	524 (100.0)
Number of patients with endpoint, N (%)	434 (83.9)	452 (86.3)
95% confidence interval*	(80.5, 86.9)	(83.0, 88.9)
Comparison vs Placebo**		
Odds ratio (SE)		1.289 (0.235)
95% confidence interval***		(0.902, 1.841)
p-value		0.1627

* Wilson confidence intervals.
** Logistic regression includes terms for baseline EQ-VAS score (p<0.0001), age (p=0.0312), baseline eGFR (CKD-EPI) (p=0.0227), Treatment (p=0.1759), region (5 cat.) (p<0.0001), baseline diabetes status (3 cat.) (p=0.7240), sex (p=0.0412), baseline LVEF (3 cat.) (p=0.4175), history of HHF (in the last 12 months) (p=0.1348) and Treatment by history of HHF (in the last 12 months) interaction (p=0.3428).
***Wald confidence intervals.

Data taken from study 1245.121 only.
LOCF: For a missing value at week 52 the last available post-baseline value before week 52 is imputed.

Table R.1.2.3.10: 4 Responder analysis (displaying risk ratio) in EQ-VAS change from baseline at week 52 of > -15 points (stability) by history of HHF - RS (LOCF-AD) - 1245.121

Subgroup Description	Placebo	Empa 10mg
History of HHF (in the last 12 months): No		
Number of patients in analysis set	1293	1286
Number of analysed patients, N (%)	1193 (100.0)	1209 (100.0)
Number of patients with endpoint, N (%)	1030 (86.3)	1052 (87.0)
95% confidence interval*	(84.3, 88.2)	(85.0, 88.8)
Comparison vs Placebo**		
Risk ratio (SE)		1.006 (0.016)
95% confidence interval***		(0.975, 1.037)
p-value		0.7176
History of HHF (in the last 12 months): Yes		
Number of patients in analysis set	574	577
Number of analysed patients, N (%)	517 (100.0)	524 (100.0)
Number of patients with endpoint, N (%)	434 (83.9)	452 (86.3)
95% confidence interval*	(80.5, 86.9)	(83.0, 88.9)
Comparison vs Placebo**		
Risk ratio (SE)		1.028 (0.026)
95% confidence interval***		(0.979, 1.081)
p-value		0.2702

* Wilson confidence intervals.
** Log-linked Poisson model with robust estimate of variance includes terms for baseline EQ-VAS score (p<0.0001), age (p=0.0859), baseline eGFR (CKD-EPI) (p=0.0302), Treatment (p=0.2592), region (5 cat.) (p=0.0011), baseline diabetes status (3 cat.) (p=0.6323), sex (p=0.0295), baseline LVEF (3 cat.) (p=0.4723), history of HHF (in the last 12 months) (p=0.2210) and Treatment by history of HHF (in the last 12 months) interaction (p=0.4524).
***Wald confidence intervals.

Data taken from study 1245.121 only.
LOCF: For a missing value at week 52 the last available post-baseline value before week 52 is imputed.

Table R.1.2.3.10: 5 Responder analysis (displaying odds ratio) in EQ-VAS change from baseline at week 52 of >= 15 points (improvement) by history of HHF - RS (LOCF-AD) - 1245.121

Subgroup Description	Placebo	Empa 10mg
History of HHF (in the last 12 months): No		
Number of patients in analysis set	1293	1286
Number of analysed patients, N (%)	1193 (100.0)	1209 (100.0)
Number of patients with endpoint, N (%)	294 (24.6)	345 (28.5)
95% confidence interval*	(22.3, 27.2)	(26.1, 31.1)
Comparison vs Placebo**		
Odds ratio (SE)		1.291 (0.140)
95% confidence interval***		(1.043, 1.597)
p-value		0.0188
History of HHF (in the last 12 months): Yes		
Number of patients in analysis set	574	577
Number of analysed patients, N (%)	517 (100.0)	524 (100.0)
Number of patients with endpoint, N (%)	126 (24.4)	150 (28.6)
95% confidence interval*	(20.9, 28.3)	(24.9, 32.6)
Comparison vs Placebo**		
Odds ratio (SE)		1.264 (0.207)
95% confidence interval***		(0.917, 1.743)
p-value		0.1529

* Wilson confidence intervals.
** Logistic regression includes terms for baseline EQ-VAS score (p<0.0001), age (p=0.1160), baseline eGFR (CKD-EPI) (p=0.1377), Treatment (p=0.0128), region (5 cat.) (p<0.0001), baseline diabetes status (3 cat.) (p=0.6763), sex (p=0.4544), baseline LVEF (3 cat.) (p=0.0632), history of HHF (in the last 12 months) (p=0.9632) and Treatment by history of HHF (in the last 12 months) interaction (p=0.9153).
***Wald confidence intervals.

Data taken from study 1245.121 only.
LOCF: For a missing value at week 52 the last available post-baseline value before week 52 is imputed.

Table R.1.2.3.10: 6 Responder analysis (displaying risk ratio) in EQ-VAS change from baseline at week 52 of >= 15 points (improvement) by history of HHF - RS (LOCF-AD) - 1245.121

Subgroup Description	Placebo	Empa 10mg
History of HHF (in the last 12 months): No		
Number of patients in analysis set	1293	1286
Number of analysed patients, N (%)	1193 (100.0)	1209 (100.0)
Number of patients with endpoint, N (%)	294 (24.6)	345 (28.5)
95% confidence interval*	(22.3, 27.2)	(26.1, 31.1)
Comparison vs Placebo**		
Risk ratio (SE)		1.136 (0.070)
95% confidence interval***		(1.006, 1.282)
p-value		0.0404
History of HHF (in the last 12 months): Yes		
Number of patients in analysis set	574	577
Number of analysed patients, N (%)	517 (100.0)	524 (100.0)
Number of patients with endpoint, N (%)	126 (24.4)	150 (28.6)
95% confidence interval*	(20.9, 28.3)	(24.9, 32.6)
Comparison vs Placebo**		
Risk ratio (SE)		1.111 (0.107)
95% confidence interval***		(0.920, 1.341)
p-value		0.2745

* Wilson confidence intervals.
** Log-linked Poisson model with robust estimate of variance includes terms for baseline EQ-VAS score (p<0.0001), age (p=0.0950), baseline eGFR (CKD-EPI) (p=0.1457), Treatment (p=0.0426), region (5 cat.) (p<0.0001), baseline diabetes status (3 cat.) (p=0.5621), sex (p=0.2263), baseline LVEF (3 cat.) (p=0.1308), history of HHF (in the last 12 months) (p=0.9754) and Treatment by history of HHF (in the last 12 months) interaction (p=0.8470).
***Wald confidence intervals.

Data taken from study 1245.121 only.
LOCF: For a missing value at week 52 the last available post-baseline value before week 52 is imputed.

R.1.2.3.11

R.1.2.3.11 Subgroup analysis by cause of heart failure

Table R.1.2.3.11: 1 Responder analysis (displaying odds ratio) in EQ-VAS change from baseline at week 52 of <= -15 points (deterioration) by cause of heart failure - RS (LOCF-AD) - 1245.121

Subgroup Description	Placebo	Empa 10mg
Cause of heart failure: Ischemic		
Number of patients in analysis set	946	983
Number of analysed patients, N (%)	874 (100.0)	918 (100.0)
Number of patients with endpoint, N (%)	129 (14.8)	142 (15.5)
95% confidence interval*	(12.6, 17.3)	(13.3, 18.0)
Comparison vs Placebo**		
Odds ratio (SE)		1.068 (0.147)
95% confidence interval***		(0.816, 1.399)
p-value		0.6308
Cause of heart failure: Non-ischemic		
Number of patients in analysis set	921	880
Number of analysed patients, N (%)	836 (100.0)	815 (100.0)
Number of patients with endpoint, N (%)	117 (14.0)	87 (10.7)
95% confidence interval*	(11.8, 16.5)	(8.7, 13.0)
Comparison vs Placebo**		
Odds ratio (SE)		0.710 (0.111)
95% confidence interval***		(0.522, 0.965)
p-value		0.0287

* Wilson confidence intervals.
** Logistic regression includes terms for baseline EQ-VAS score (p<0.0001), age (p=0.0613), baseline eGFR (CKD-EPI) (p=0.0248), Treatment (p=0.1839), region (5 cat.) (p=0.0003), baseline diabetes status (3 cat.) (p=0.6855), sex (p=0.0300), baseline LVEF (3 cat.) (p=0.3896), cause of heart failure (p=0.0497) and Treatment by cause of heart failure interaction (p=0.0500).
***Wald confidence intervals.

Data taken from study 1245.121 only.
LOCF: For a missing value at week 52 the last available post-baseline value before week 52 is imputed.

Table R.1.2.3.11: 2 Responder analysis (displaying risk ratio) in EQ-VAS change from baseline at week 52 of <= -15 points (deterioration) by cause of heart failure - RS (LOCF-AD) - 1245.121

Subgroup Description	Placebo	Empa 10mg
Cause of heart failure: Ischemic		
Number of patients in analysis set	946	983
Number of analysed patients, N (%)	874 (100.0)	918 (100.0)
Number of patients with endpoint, N (%)	129 (14.8)	142 (15.5)
95% confidence interval*	(12.6, 17.3)	(13.3, 18.0)
Comparison vs Placebo**		
Risk ratio (SE)		1.052 (0.113)
95% confidence interval***		(0.852, 1.298)
p-value		0.6389
Cause of heart failure: Non-ischemic		
Number of patients in analysis set	921	880
Number of analysed patients, N (%)	836 (100.0)	815 (100.0)
Number of patients with endpoint, N (%)	117 (14.0)	87 (10.7)
95% confidence interval*	(11.8, 16.5)	(8.7, 13.0)
Comparison vs Placebo**		
Risk ratio (SE)		0.753 (0.098)
95% confidence interval***		(0.583, 0.973)
p-value		0.0299

* Wilson confidence intervals.
** Log-linked Poisson model with robust estimate of variance includes terms for baseline EQ-VAS score (p<0.0001), age (p=0.0792), baseline eGFR (CKD-EPI) (p=0.0288), Treatment (p=0.1671), region (5 cat.) (p=0.0002), baseline diabetes status (3 cat.) (p=0.6904), sex (p=0.0347), baseline LVEF (3 cat.) (p=0.4262), cause of heart failure (p=0.0509) and Treatment by cause of heart failure interaction (p=0.0484).
***Wald confidence intervals.

Data taken from study 1245.121 only.
LOCF: For a missing value at week 52 the last available post-baseline value before week 52 is imputed.

Table R.1.2.3.11: 3 Responder analysis (displaying odds ratio) in EQ-VAS change from baseline at week 52 of > -15 points (stability) by cause of heart failure - RS (LOCF-AD) - 1245.121

Subgroup Description	Placebo	Empa 10mg
Cause of heart failure: Ischemic		
Number of patients in analysis set	946	983
Number of analysed patients, N (%)	874 (100.0)	918 (100.0)
Number of patients with endpoint, N (%)	745 (85.2)	776 (84.5)
95% confidence interval*	(82.7, 87.4)	(82.0, 86.7)
Comparison vs Placebo**		
Odds ratio (SE)		0.936 (0.129)
95% confidence interval***		(0.715, 1.226)
p-value		0.6308
Cause of heart failure: Non-ischemic		
Number of patients in analysis set	921	880
Number of analysed patients, N (%)	836 (100.0)	815 (100.0)
Number of patients with endpoint, N (%)	719 (86.0)	728 (89.3)
95% confidence interval*	(83.5, 88.2)	(87.0, 91.3)
Comparison vs Placebo**		
Odds ratio (SE)		1.409 (0.221)
95% confidence interval***		(1.036, 1.916)
p-value		0.0287

* Wilson confidence intervals.
** Logistic regression includes terms for baseline EQ-VAS score (p<0.0001), age (p=0.0613), baseline eGFR (CKD-EPI) (p=0.0248), Treatment (p=0.1839), region (5 cat.) (p=0.0003), baseline diabetes status (3 cat.) (p=0.6855), sex (p=0.0300), baseline LVEF (3 cat.) (p=0.3896), cause of heart failure (p=0.0497) and Treatment by cause of heart failure interaction (p=0.0500).
***Wald confidence intervals.

Data taken from study 1245.121 only.
LOCF: For a missing value at week 52 the last available post-baseline value before week 52 is imputed.

Table R.1.2.3.11: 4 Responder analysis (displaying risk ratio) in EQ-VAS change from baseline at week 52 of > -15 points (stability) by cause of heart failure - RS (LOCF-AD) - 1245.121

Subgroup Description	Placebo	Empa 10mg
Cause of heart failure: Ischemic		
Number of patients in analysis set	946	983
Number of analysed patients, N (%)	874 (100.0)	918 (100.0)
Number of patients with endpoint, N (%)	745 (85.2)	776 (84.5)
95% confidence interval*	(82.7, 87.4)	(82.0, 86.7)
Comparison vs Placebo**		
Risk ratio (SE)		0.990 (0.019)
95% confidence interval***		(0.953, 1.028)
p-value		0.5935
Cause of heart failure: Non-ischemic		
Number of patients in analysis set	921	880
Number of analysed patients, N (%)	836 (100.0)	815 (100.0)
Number of patients with endpoint, N (%)	719 (86.0)	728 (89.3)
95% confidence interval*	(83.5, 88.2)	(87.0, 91.3)
Comparison vs Placebo**		
Risk ratio (SE)		1.037 (0.019)
95% confidence interval***		(1.001, 1.075)
p-value		0.0424

* Wilson confidence intervals.
** Log-linked Poisson model with robust estimate of variance includes terms for baseline EQ-VAS score (p<0.0001), age (p=0.1505), baseline eGFR (CKD-EPI) (p=0.0334), Treatment (p=0.3165), region (5 cat.) (p=0.0031), baseline diabetes status (3 cat.) (p=0.6324), sex (p=0.0203), baseline LVEF (3 cat.) (p=0.4245), cause of heart failure (p=0.0661) and Treatment by cause of heart failure interaction (p=0.0747).
***Wald confidence intervals.

Data taken from study 1245.121 only.
LOCF: For a missing value at week 52 the last available post-baseline value before week 52 is imputed.

Table R.1.2.3.11: 5 Responder analysis (displaying odds ratio) in EQ-VAS change from baseline at week 52 of >= 15 points (improvement) by cause of heart failure - RS (LOCF-AD) - 1245.121

Subgroup Description	Placebo	Empa 10mg
Cause of heart failure: Ischemic		
Number of patients in analysis set	946	983
Number of analysed patients, N (%)	874 (100.0)	918 (100.0)
Number of patients with endpoint, N (%)	196 (22.4)	265 (28.9)
95% confidence interval*	(19.8, 25.3)	(26.0, 31.9)
Comparison vs Placebo**		
Odds ratio (SE)		1.516 (0.193)
95% confidence interval***		(1.181, 1.946)
p-value		0.0011
Cause of heart failure: Non-ischemic		
Number of patients in analysis set	921	880
Number of analysed patients, N (%)	836 (100.0)	815 (100.0)
Number of patients with endpoint, N (%)	224 (26.8)	230 (28.2)
95% confidence interval*	(23.9, 29.9)	(25.2, 31.4)
Comparison vs Placebo**		
Odds ratio (SE)		1.080 (0.140)
95% confidence interval***		(0.838, 1.392)
p-value		0.5515

* Wilson confidence intervals.
** Logistic regression includes terms for baseline EQ-VAS score (p<0.0001), age (p=0.1334), baseline eGFR (CKD-EPI) (p=0.1355), Treatment (p=0.0065), region (5 cat.) (p<0.0001), baseline diabetes status (3 cat.) (p=0.6318), sex (p=0.3935), baseline LVEF (3 cat.) (p=0.0631), cause of heart failure (p=0.4845) and Treatment by cause of heart failure interaction (p=0.0617).
***Wald confidence intervals.

Data taken from study 1245.121 only.
LOCF: For a missing value at week 52 the last available post-baseline value before week 52 is imputed.

Table R.1.2.3.11: 6 Responder analysis (displaying risk ratio) in EQ-VAS change from baseline at week 52 of >= 15 points (improvement) by cause of heart failure - RS (LOCF-AD) - 1245.121

Subgroup Description	Placebo	Empa 10mg
Cause of heart failure: Ischemic		
Number of patients in analysis set	946	983
Number of analysed patients, N (%)	874 (100.0)	918 (100.0)
Number of patients with endpoint, N (%)	196 (22.4)	265 (28.9)
95% confidence interval*	(19.8, 25.3)	(26.0, 31.9)
Comparison vs Placebo**		
Risk ratio (SE)		1.247 (0.095)
95% confidence interval***		(1.074, 1.449)
p-value		0.0038
Cause of heart failure: Non-ischemic		
Number of patients in analysis set	921	880
Number of analysed patients, N (%)	836 (100.0)	815 (100.0)
Number of patients with endpoint, N (%)	224 (26.8)	230 (28.2)
95% confidence interval*	(23.9, 29.9)	(25.2, 31.4)
Comparison vs Placebo**		
Risk ratio (SE)		1.022 (0.073)
95% confidence interval***		(0.888, 1.176)
p-value		0.7651

* Wilson confidence intervals.
** Log-linked Poisson model with robust estimate of variance includes terms for baseline EQ-VAS score (p<0.0001), age (p=0.1113), baseline eGFR (CKD-EPI) (p=0.1359), Treatment (p=0.0206), region (5 cat.) (p<0.0001), baseline diabetes status (3 cat.) (p=0.5250), sex (p=0.1913), baseline LVEF (3 cat.) (p=0.1230), cause of heart failure (p=0.5149) and Treatment by cause of heart failure interaction (p=0.0568).
***Wald confidence intervals.

Data taken from study 1245.121 only.
LOCF: For a missing value at week 52 the last available post-baseline value before week 52 is imputed.

R.1.2.3.12 Subgroup analysis by heart failure physiology (LVEF <= 30% and NTproBNP<median; LVEF <= 30% and NTproBNP>=median; LVEF > 30%)

Table R.1.2.3.12: 1 Responder analysis (displaying odds ratio) in EQ-VAS change from baseline at week 52 of <= -15 points (deterioration) by heart failure physiology - RS (LOCF-AD) - 1245.121

Subgroup Description	Placebo	Empa 10mg
Heart failure physiology: LVEF <= 30% and NTproBNP < median		
Number of patients in analysis set	723	698
Number of analysed patients, N (%)	679 (100.0)	655 (100.0)
Number of patients with endpoint, N (%)	87 (12.8)	78 (11.9)
95% confidence interval*	(10.5, 15.5)	(9.6, 14.6)
Comparison vs Placebo**		
Odds ratio (SE)		0.906 (0.156)
95% confidence interval***		(0.646, 1.270)
p-value		0.5669
Heart failure physiology: LVEF <= 30% and NTproBNP >= median		
Number of patients in analysis set	661	631
Number of analysed patients, N (%)	588 (100.0)	581 (100.0)
Number of patients with endpoint, N (%)	92 (15.6)	91 (15.7)
95% confidence interval*	(12.9, 18.8)	(12.9, 18.8)
Comparison vs Placebo**		
Odds ratio (SE)		0.951 (0.161)
95% confidence interval***		(0.683, 1.324)
p-value		0.7680

* Wilson confidence intervals.
** Logistic regression includes terms for baseline EQ-VAS score (p<0.0001), age (p=0.0453), baseline eGFR (CKD-EPI) (p=0.0772), Treatment (p=0.2538), region (5 cat.) (p<0.0001), baseline diabetes status (3 cat.) (p=0.6544), sex (p=0.0548), heart failure physiology (p=0.0120) and Treatment by heart failure physiology interaction (p=0.8291).
***Wald confidence intervals.
16 patients were excluded as the subgroup variable was missing.

Data taken from study 1245.121 only.
LOCF: For a missing value at week 52 the last available post-baseline value before week 52 is imputed.
NTproBNP median [pg/mL]: with a. fibrillation/flutter at baseline: 2265; without a. fibrillation/flutter at baseline: 1671.

Table R.1.2.3.12: 1 Responder analysis (displaying odds ratio) in EQ-VAS change from baseline at week 52 of <= -15 points (deterioration) by heart failure physiology - RS (LOCF-AD) - 1245.121

Subgroup Description	Placebo	Empa 10mg
Heart failure physiology: LVEF > 30%		
Number of patients in analysis set	475	526
Number of analysed patients, N (%)	438 (100.0)	493 (100.0)
Number of patients with endpoint, N (%)	66 (15.1)	60 (12.2)
95% confidence interval*	(12.0, 18.7)	(9.6, 15.4)
Comparison vs Placebo**		
Odds ratio (SE)		0.812 (0.162)
95% confidence interval***		(0.550, 1.200)
p-value		0.2955

* Wilson confidence intervals.
** Logistic regression includes terms for baseline EQ-VAS score (p<0.0001), age (p=0.0453), baseline eGFR (CKD-EPI) (p=0.0772), Treatment (p=0.2538), region (5 cat.) (p<0.0001), baseline diabetes status (3 cat.) (p=0.6544), sex (p=0.0548), heart failure physiology (p=0.0120) and Treatment by heart failure physiology interaction (p=0.8291).
***Wald confidence intervals.
16 patients were excluded as the subgroup variable was missing.

Data taken from study 1245.121 only.
LOCF: For a missing value at week 52 the last available post-baseline value before week 52 is imputed.
NTproBNP median [pg/mL]: with a. fibrillation/flutter at baseline: 2265; without a. fibrillation/flutter at baseline: 1671.

Table R.1.2.3.12: 2 Responder analysis (displaying risk ratio) in EQ-VAS change from baseline at week 52 of <= -15 points (deterioration) by heart failure physiology - RS (LOCF-AD) - 1245.121

Subgroup Description	Placebo	Empa 10mg
Heart failure physiology: LVEF <= 30% and NTproBNP < median		
Number of patients in analysis set	723	698
Number of analysed patients, N (%)	679 (100.0)	655 (100.0)
Number of patients with endpoint, N (%)	87 (12.8)	78 (11.9)
95% confidence interval*	(10.5, 15.5)	(9.6, 14.6)
Comparison vs Placebo**		
Risk ratio (SE)		0.924 (0.132)
95% confidence interval***		(0.699, 1.221)
p-value		0.5787
Heart failure physiology: LVEF <= 30% and NTproBNP >= median		
Number of patients in analysis set	661	631
Number of analysed patients, N (%)	588 (100.0)	581 (100.0)
Number of patients with endpoint, N (%)	92 (15.6)	91 (15.7)
95% confidence interval*	(12.9, 18.8)	(12.9, 18.8)
Comparison vs Placebo**		
Risk ratio (SE)		0.953 (0.124)
95% confidence interval***		(0.738, 1.229)
p-value		0.7103

* Wilson confidence intervals.
** Log-linked Poisson model with robust estimate of variance includes terms for baseline EQ-VAS score (p<0.0001), age (p=0.0586), baseline eGFR (CKD-EPI) (p=0.0880), Treatment (p=0.2390), region (5 cat.) (p<0.0001), baseline diabetes status (3 cat.) (p=0.6854), sex (p=0.0585), heart failure physiology (p=0.0119) and Treatment by heart failure physiology interaction (p=0.8425).
***Wald confidence intervals.
16 patients were excluded as the subgroup variable was missing.

Data taken from study 1245.121 only.
LOCF: For a missing value at week 52 the last available post-baseline value before week 52 is imputed.
NTproBNP median [pg/mL]: with a. fibrillation/flutter at baseline: 2265; without a. fibrillation/flutter at baseline: 1671.

Table R.1.2.3.12: 2 Responder analysis (displaying risk ratio) in EQ-VAS change from baseline at week 52 of <= -15 points (deterioration) by heart failure physiology - RS (LOCF-AD) - 1245.121

Subgroup Description	Placebo	Empa 10mg
Heart failure physiology: LVEF > 30%		
Number of patients in analysis set	475	526
Number of analysed patients, N (%)	438 (100.0)	493 (100.0)
Number of patients with endpoint, N (%)	66 (15.1)	60 (12.2)
95% confidence interval*	(12.0, 18.7)	(9.6, 15.4)
Comparison vs Placebo**		
Risk ratio (SE)		0.845 (0.137)
95% confidence interval***		(0.615, 1.160)
p-value		0.2976

* Wilson confidence intervals.
** Log-linked Poisson model with robust estimate of variance includes terms for baseline EQ-VAS score (p<0.0001), age (p=0.0586), baseline eGFR (CKD-EPI) (p=0.0880), Treatment (p=0.2390), region (5 cat.) (p<0.0001), baseline diabetes status (3 cat.) (p=0.6854), sex (p=0.0585), heart failure physiology (p=0.0119) and Treatment by heart failure physiology interaction (p=0.8425).
***Wald confidence intervals.
16 patients were excluded as the subgroup variable was missing.

Data taken from study 1245.121 only.
LOCF: For a missing value at week 52 the last available post-baseline value before week 52 is imputed.
NTproBNP median [pg/mL]: with a. fibrillation/flutter at baseline: 2265; without a. fibrillation/flutter at baseline: 1671.

Table R.1.2.3.12: 3 Responder analysis (displaying odds ratio) in EQ-VAS change from baseline at week 52 of > -15 points (stability) by heart failure physiology - RS (LOCF-AD) - 1245.121

Subgroup Description	Placebo	Empa 10mg
Heart failure physiology: LVEF <= 30% and NTproBNP < median		
Number of patients in analysis set	723	698
Number of analysed patients, N (%)	679 (100.0)	655 (100.0)
Number of patients with endpoint, N (%)	592 (87.2)	577 (88.1)
95% confidence interval*	(84.5, 89.5)	(85.4, 90.4)
Comparison vs Placebo**		
Odds ratio (SE)		1.104 (0.190)
95% confidence interval***		(0.787, 1.547)
p-value		0.5669
Heart failure physiology: LVEF <= 30% and NTproBNP >= median		
Number of patients in analysis set	661	631
Number of analysed patients, N (%)	588 (100.0)	581 (100.0)
Number of patients with endpoint, N (%)	496 (84.4)	490 (84.3)
95% confidence interval*	(81.2, 87.1)	(81.2, 87.1)
Comparison vs Placebo**		
Odds ratio (SE)		1.051 (0.177)
95% confidence interval***		(0.755, 1.463)
p-value		0.7680

* Wilson confidence intervals.
** Logistic regression includes terms for baseline EQ-VAS score (p<0.0001), age (p=0.0453), baseline eGFR (CKD-EPI) (p=0.0772), Treatment (p=0.2538), region (5 cat.) (p<0.0001), baseline diabetes status (3 cat.) (p=0.6544), sex (p=0.0548), heart failure physiology (p=0.0120) and Treatment by heart failure physiology interaction (p=0.8291).
***Wald confidence intervals.
16 patients were excluded as the subgroup variable was missing.

Data taken from study 1245.121 only.
LOCF: For a missing value at week 52 the last available post-baseline value before week 52 is imputed.
NTproBNP median [pg/mL]: with a. fibrillation/flutter at baseline: 2265; without a. fibrillation/flutter at baseline: 1671.

Table R.1.2.3.12: 3 Responder analysis (displaying odds ratio) in EQ-VAS change from baseline at week 52 of > -15 points (stability) by heart failure physiology - RS (LOCF-AD) - 1245.121

Subgroup Description	Placebo	Empa 10mg
Heart failure physiology: LVEF > 30%		
Number of patients in analysis set	475	526
Number of analysed patients, N (%)	438 (100.0)	493 (100.0)
Number of patients with endpoint, N (%)	372 (84.9)	433 (87.8)
95% confidence interval*	(81.3, 88.0)	(84.6, 90.4)
Comparison vs Placebo**		
Odds ratio (SE)		1.232 (0.245)
95% confidence interval***		(0.834, 1.819)
p-value		0.2955

* Wilson confidence intervals.
** Logistic regression includes terms for baseline EQ-VAS score (p<0.0001), age (p=0.0453), baseline eGFR (CKD-EPI) (p=0.0772), Treatment (p=0.2538), region (5 cat.) (p<0.0001), baseline diabetes status (3 cat.) (p=0.6544), sex (p=0.0548), heart failure physiology (p=0.0120) and Treatment by heart failure physiology interaction (p=0.8291).
***Wald confidence intervals.
16 patients were excluded as the subgroup variable was missing.

Data taken from study 1245.121 only.
LOCF: For a missing value at week 52 the last available post-baseline value before week 52 is imputed.
NTproBNP median [pg/mL]: with a. fibrillation/flutter at baseline: 2265; without a. fibrillation/flutter at baseline: 1671.

Table R.1.2.3.12: 4 Responder analysis (displaying risk ratio) in EQ-VAS change from baseline at week 52 of > -15 points (stability) by heart failure physiology - RS (LOCF-AD) - 1245.121

Subgroup Description	Placebo	Empa 10mg
Heart failure physiology: LVEF <= 30% and NTproBNP < median		
Number of patients in analysis set	723	698
Number of analysed patients, N (%)	679 (100.0)	655 (100.0)
Number of patients with endpoint, N (%)	592 (87.2)	577 (88.1)
95% confidence interval*	(84.5, 89.5)	(85.4, 90.4)
Comparison vs Placebo**		
Risk ratio (SE)		1.013 (0.020)
95% confidence interval***		(0.974, 1.054)
p-value		0.5177
Heart failure physiology: LVEF <= 30% and NTproBNP >= median		
Number of patients in analysis set	661	631
Number of analysed patients, N (%)	588 (100.0)	581 (100.0)
Number of patients with endpoint, N (%)	496 (84.4)	490 (84.3)
95% confidence interval*	(81.2, 87.1)	(81.2, 87.1)
Comparison vs Placebo**		
Risk ratio (SE)		1.001 (0.024)
95% confidence interval***		(0.955, 1.050)
p-value		0.9517

* Wilson confidence intervals.
** Log-linked Poisson model with robust estimate of variance includes terms for baseline EQ-VAS score (p<0.0001), age (p=0.0992), baseline eGFR (CKD-EPI) (p=0.0880), Treatment (p=0.3558), region (5 cat.) (p=0.0006), baseline diabetes status (3 cat.) (p=0.5493), sex (p=0.0344), heart failure physiology (p=0.0102) and Treatment by heart failure physiology interaction (p=0.8284).
***Wald confidence intervals.
16 patients were excluded as the subgroup variable was missing.

Data taken from study 1245.121 only.
LOCF: For a missing value at week 52 the last available post-baseline value before week 52 is imputed.
NTproBNP median [pg/mL]: with a. fibrillation/flutter at baseline: 2265; without a. fibrillation/flutter at baseline: 1671.

Table R.1.2.3.12: 4 Responder analysis (displaying risk ratio) in EQ-VAS change from baseline at week 52 of > -15 points (stability) by heart failure physiology - RS (LOCF-AD) - 1245.121

Subgroup Description	Placebo	Empa 10mg
Heart failure physiology: LVEF > 30%		
Number of patients in analysis set	475	526
Number of analysed patients, N (%)	438 (100.0)	493 (100.0)
Number of patients with endpoint, N (%)	372 (84.9)	433 (87.8)
95% confidence interval*	(81.3, 88.0)	(84.6, 90.4)
Comparison vs Placebo**		
Risk ratio (SE)		1.023 (0.026)
95% confidence interval***		(0.973, 1.076)
p-value		0.3671

* Wilson confidence intervals.
** Log-linked Poisson model with robust estimate of variance includes terms for baseline EQ-VAS score (p<0.0001), age (p=0.0992), baseline eGFR (CKD-EPI) (p=0.0880), Treatment (p=0.3558), region (5 cat.) (p=0.0006), baseline diabetes status (3 cat.) (p=0.5493), sex (p=0.0344), heart failure physiology (p=0.0102) and Treatment by heart failure physiology interaction (p=0.8284).
***Wald confidence intervals.
16 patients were excluded as the subgroup variable was missing.

Data taken from study 1245.121 only.
LOCF: For a missing value at week 52 the last available post-baseline value before week 52 is imputed.
NTproBNP median [pg/mL]: with a. fibrillation/flutter at baseline: 2265; without a. fibrillation/flutter at baseline: 1671.

Table R.1.2.3.12: 5 Responder analysis (displaying odds ratio) in EQ-VAS change from baseline at week 52 of >= 15 points (improvement) by heart failure physiology - RS (LOCF-AD) - 1245.121

Subgroup Description	Placebo	Empa 10mg
Heart failure physiology: LVEF <= 30% and NTproBNP < median		
Number of patients in analysis set	723	698
Number of analysed patients, N (%)	679 (100.0)	655 (100.0)
Number of patients with endpoint, N (%)	166 (24.4)	177 (27.0)
95% confidence interval*	(21.4, 27.8)	(23.8, 30.6)
Comparison vs Placebo**		
Odds ratio (SE)		1.200 (0.174)
95% confidence interval***		(0.903, 1.595)
p-value		0.2098
Heart failure physiology: LVEF <= 30% and NTproBNP >= median		
Number of patients in analysis set	661	631
Number of analysed patients, N (%)	588 (100.0)	581 (100.0)
Number of patients with endpoint, N (%)	145 (24.7)	173 (29.8)
95% confidence interval*	(21.3, 28.3)	(26.2, 33.6)
Comparison vs Placebo**		
Odds ratio (SE)		1.461 (0.226)
95% confidence interval***		(1.078, 1.979)
p-value		0.0144

* Wilson confidence intervals.
** Logistic regression includes terms for baseline EQ-VAS score (p<0.0001), age (p=0.1220), baseline eGFR (CKD-EPI) (p=0.1724), Treatment (p=0.0079), region (5 cat.) (p<0.0001), baseline diabetes status (3 cat.) (p=0.6995), sex (p=0.3679), heart failure physiology (p=0.5019) and Treatment by heart failure physiology interaction (p=0.5695).
***Wald confidence intervals.
16 patients were excluded as the subgroup variable was missing.

Data taken from study 1245.121 only.
LOCF: For a missing value at week 52 the last available post-baseline value before week 52 is imputed.
NTproBNP median [pg/mL]: with a. fibrillation/flutter at baseline: 2265; without a. fibrillation/flutter at baseline: 1671.

Table R.1.2.3.12: 5 Responder analysis (displaying odds ratio) in EQ-VAS change from baseline at week 52 of >= 15 points (improvement) by heart failure physiology - RS (LOCF-AD) - 1245.121

Subgroup Description	Placebo	Empa 10mg
Heart failure physiology: LVEF > 30%		
Number of patients in analysis set	475	526
Number of analysed patients, N (%)	438 (100.0)	493 (100.0)
Number of patients with endpoint, N (%)	107 (24.4)	143 (29.0)
95% confidence interval*	(20.6, 28.7)	(25.2, 33.2)
Comparison vs Placebo**		
Odds ratio (SE)		1.184 (0.207)
95% confidence interval***		(0.840, 1.669)
p-value		0.3345

* Wilson confidence intervals.
** Logistic regression includes terms for baseline EQ-VAS score (p<0.0001), age (p=0.1220), baseline eGFR (CKD-EPI) (p=0.1724), Treatment (p=0.0079), region (5 cat.) (p<0.0001), baseline diabetes status (3 cat.) (p=0.6995), sex (p=0.3679), heart failure physiology (p=0.5019) and Treatment by heart failure physiology interaction (p=0.5695).
***Wald confidence intervals.
16 patients were excluded as the subgroup variable was missing.

Data taken from study 1245.121 only.
LOCF: For a missing value at week 52 the last available post-baseline value before week 52 is imputed.
NTproBNP median [pg/mL]: with a. fibrillation/flutter at baseline: 2265; without a. fibrillation/flutter at baseline: 1671.

Table R.1.2.3.12: 6 Responder analysis (displaying risk ratio) in EQ-VAS change from baseline at week 52 of >= 15 points (improvement) by heart failure physiology - RS (LOCF-AD) - 1245.121

Subgroup Description	Placebo	Empa 10mg
Heart failure physiology: LVEF <= 30% and NTproBNP < median		
Number of patients in analysis set	723	698
Number of analysed patients, N (%)	679 (100.0)	655 (100.0)
Number of patients with endpoint, N (%)	166 (24.4)	177 (27.0)
95% confidence interval*	(21.4, 27.8)	(23.8, 30.6)
Comparison vs Placebo**		
Risk ratio (SE)		1.143 (0.099)
95% confidence interval***		(0.965, 1.353)
p-value		0.1210
Heart failure physiology: LVEF <= 30% and NTproBNP >= median		
Number of patients in analysis set	661	631
Number of analysed patients, N (%)	588 (100.0)	581 (100.0)
Number of patients with endpoint, N (%)	145 (24.7)	173 (29.8)
95% confidence interval*	(21.3, 28.3)	(26.2, 33.6)
Comparison vs Placebo**		
Risk ratio (SE)		1.164 (0.103)
95% confidence interval***		(0.978, 1.385)
p-value		0.0866

* Wilson confidence intervals.
** Log-linked Poisson model with robust estimate of variance includes terms for baseline EQ-VAS score (p<0.0001), age (p=0.0835), baseline eGFR (CKD-EPI) (p=0.1857), Treatment (p=0.0253), region (5 cat.) (p<0.0001), baseline diabetes status (3 cat.) (p=0.5553), sex (p=0.1949), heart failure physiology (p=0.4690) and Treatment by heart failure physiology interaction (p=0.7885).
***Wald confidence intervals.
16 patients were excluded as the subgroup variable was missing.

Data taken from study 1245.121 only.
LOCF: For a missing value at week 52 the last available post-baseline value before week 52 is imputed.
NTproBNP median [pg/mL]: with a. fibrillation/flutter at baseline: 2265; without a. fibrillation/flutter at baseline: 1671.

Table R.1.2.3.12: 6 Responder analysis (displaying risk ratio) in EQ-VAS change from baseline at week 52 of >= 15 points (improvement) by heart failure physiology - RS (LOCF-AD) - 1245.121

Subgroup Description	Placebo	Empa 10mg
Heart failure physiology: LVEF > 30%		
Number of patients in analysis set	475	526
Number of analysed patients, N (%)	438 (100.0)	493 (100.0)
Number of patients with endpoint, N (%)	107 (24.4)	143 (29.0)
95% confidence interval*	(20.6, 28.7)	(25.2, 33.2)
Comparison vs Placebo**		
Risk ratio (SE)		1.068 (0.103)
95% confidence interval***		(0.884, 1.290)
p-value		0.4964

* Wilson confidence intervals.
** Log-linked Poisson model with robust estimate of variance includes terms for baseline EQ-VAS score (p<0.0001), age (p=0.0835), baseline eGFR (CKD-EPI) (p=0.1857), Treatment (p=0.0253), region (5 cat.) (p<0.0001), baseline diabetes status (3 cat.) (p=0.5553), sex (p=0.1949), heart failure physiology (p=0.4690) and Treatment by heart failure physiology interaction (p=0.7885).
***Wald confidence intervals.
16 patients were excluded as the subgroup variable was missing.

Data taken from study 1245.121 only.
LOCF: For a missing value at week 52 the last available post-baseline value before week 52 is imputed.
NTproBNP median [pg/mL]: with a. fibrillation/flutter at baseline: 2265; without a. fibrillation/flutter at baseline: 1671.

R.1.2.3.13

R.1.2.3.13 Subgroup analysis by baseline use of MRA

Table R.1.2.3.13: 1 Responder analysis (displaying odds ratio) in EQ-VAS change from baseline at week 52 of <= -15 points (deterioration) by baseline use of MRA (Y/N) - RS (LOCF-AD) - 1245.121

Subgroup Description	Placebo	Empa 10mg
Baseline use of MRA: No		
Number of patients in analysis set	512	557
Number of analysed patients, N (%)	474 (100.0)	521 (100.0)
Number of patients with endpoint, N (%)	74 (15.6)	62 (11.9)
95% confidence interval*	(12.6, 19.2)	(9.4, 15.0)
Comparison vs Placebo**		
Odds ratio (SE)		0.725 (0.139)
95% confidence interval***		(0.497, 1.056)
p-value		0.0934
Baseline use of MRA: Yes		
Number of patients in analysis set	1355	1306
Number of analysed patients, N (%)	1236 (100.0)	1212 (100.0)
Number of patients with endpoint, N (%)	172 (13.9)	167 (13.8)
95% confidence interval*	(12.1, 16.0)	(12.0, 15.8)
Comparison vs Placebo**		
Odds ratio (SE)		0.979 (0.119)
95% confidence interval***		(0.771, 1.243)
p-value		0.8620

* Wilson confidence intervals.
** Logistic regression includes terms for baseline EQ-VAS score (p<0.0001), age (p=0.0399), baseline eGFR (CKD-EPI) (p=0.0188), Treatment (p=0.1312), region (5 cat.) (p<0.0001), baseline diabetes status (3 cat.) (p=0.6929), sex (p=0.0456), baseline LVEF (3 cat.) (p=0.4142), baseline use of MRA (p=0.2834) and Treatment by baseline use of MRA interaction (p=0.1858).
***Wald confidence intervals.

Data taken from study 1245.121 only.
LOCF: For a missing value at week 52 the last available post-baseline value before week 52 is imputed.

Table R.1.2.3.13: 2 Responder analysis (displaying risk ratio) in EQ-VAS change from baseline at week 52 of <= -15 points (deterioration) by baseline use of MRA (Y/N) - RS (LOCF-AD) - 1245.121

Subgroup Description	Placebo	Empa 10mg
Baseline use of MRA: No		
Number of patients in analysis set	512	557
Number of analysed patients, N (%)	474 (100.0)	521 (100.0)
Number of patients with endpoint, N (%)	74 (15.6)	62 (11.9)
95% confidence interval*	(12.6, 19.2)	(9.4, 15.0)
Comparison vs Placebo**		
Risk ratio (SE)		0.771 (0.120)
95% confidence interval***		(0.568, 1.046)
p-value		0.0944
Baseline use of MRA: Yes		
Number of patients in analysis set	1355	1306
Number of analysed patients, N (%)	1236 (100.0)	1212 (100.0)
Number of patients with endpoint, N (%)	172 (13.9)	167 (13.8)
95% confidence interval*	(12.1, 16.0)	(12.0, 15.8)
Comparison vs Placebo**		
Risk ratio (SE)		0.980 (0.095)
95% confidence interval***		(0.810, 1.186)
p-value		0.8364

* Wilson confidence intervals.
** Log-linked Poisson model with robust estimate of variance includes terms for baseline EQ-VAS score (p<0.0001), age (p=0.0533), baseline eGFR (CKD-EPI) (p=0.0245), Treatment (p=0.1267), region (5 cat.) (p<0.0001), baseline diabetes status (3 cat.) (p=0.7052), sex (p=0.0500), baseline LVEF (3 cat.) (p=0.4368), baseline use of MRA (p=0.2795) and Treatment by baseline use of MRA interaction (p=0.1909).
***Wald confidence intervals.

Data taken from study 1245.121 only.
LOCF: For a missing value at week 52 the last available post-baseline value before week 52 is imputed.

Table R.1.2.3.13: 3 Responder analysis (displaying odds ratio) in EQ-VAS change from baseline at week 52 of > -15 points (stability) by baseline use of MRA (Y/N) - RS (LOCF-AD) - 1245.121

Subgroup Description	Placebo	Empa 10mg
Baseline use of MRA: No		
Number of patients in analysis set	512	557
Number of analysed patients, N (%)	474 (100.0)	521 (100.0)
Number of patients with endpoint, N (%)	400 (84.4)	459 (88.1)
95% confidence interval*	(80.8, 87.4)	(85.0, 90.6)
Comparison vs Placebo**		
Odds ratio (SE)		1.380 (0.265)
95% confidence interval***		(0.947, 2.010)
p-value		0.0934
Baseline use of MRA: Yes		
Number of patients in analysis set	1355	1306
Number of analysed patients, N (%)	1236 (100.0)	1212 (100.0)
Number of patients with endpoint, N (%)	1064 (86.1)	1045 (86.2)
95% confidence interval*	(84.0, 87.9)	(84.2, 88.0)
Comparison vs Placebo**		
Odds ratio (SE)		1.021 (0.125)
95% confidence interval***		(0.804, 1.297)
p-value		0.8620

* Wilson confidence intervals.
** Logistic regression includes terms for baseline EQ-VAS score (p<0.0001), age (p=0.0399), baseline eGFR (CKD-EPI) (p=0.0188), Treatment (p=0.1312), region (5 cat.) (p<0.0001), baseline diabetes status (3 cat.) (p=0.6929), sex (p=0.0456), baseline LVEF (3 cat.) (p=0.4142), baseline use of MRA (p=0.2834) and Treatment by baseline use of MRA interaction (p=0.1858).
***Wald confidence intervals.

Data taken from study 1245.121 only.
LOCF: For a missing value at week 52 the last available post-baseline value before week 52 is imputed.

Table R.1.2.3.13: 4 Responder analysis (displaying risk ratio) in EQ-VAS change from baseline at week 52 of > -15 points (stability) by baseline use of MRA (Y/N) - RS (LOCF-AD) - 1245.121

Subgroup Description	Placebo	Empa 10mg
Baseline use of MRA: No		
Number of patients in analysis set	512	557
Number of analysed patients, N (%)	474 (100.0)	521 (100.0)
Number of patients with endpoint, N (%)	400 (84.4)	459 (88.1)
95% confidence interval*	(80.8, 87.4)	(85.0, 90.6)
Comparison vs Placebo**		
Risk ratio (SE)		1.038 (0.026)
95% confidence interval***		(0.989, 1.090)
p-value		0.1309
Baseline use of MRA: Yes		
Number of patients in analysis set	1355	1306
Number of analysed patients, N (%)	1236 (100.0)	1212 (100.0)
Number of patients with endpoint, N (%)	1064 (86.1)	1045 (86.2)
95% confidence interval*	(84.0, 87.9)	(84.2, 88.0)
Comparison vs Placebo**		
Risk ratio (SE)		1.002 (0.016)
95% confidence interval***		(0.971, 1.033)
p-value		0.9150

* Wilson confidence intervals.
** Log-linked Poisson model with robust estimate of variance includes terms for baseline EQ-VAS score (p<0.0001), age (p=0.0919), baseline eGFR (CKD-EPI) (p=0.0243), Treatment (p=0.1833), region (5 cat.) (p=0.0011), baseline diabetes status (3 cat.) (p=0.6111), sex (p=0.0315), baseline LVEF (3 cat.) (p=0.4481), baseline use of MRA (p=0.3147) and Treatment by baseline use of MRA interaction (p=0.2228).
***Wald confidence intervals.

Data taken from study 1245.121 only.
LOCF: For a missing value at week 52 the last available post-baseline value before week 52 is imputed.

Table R.1.2.3.13: 5 Responder analysis (displaying odds ratio) in EQ-VAS change from baseline at week 52 of >= 15 points (improvement) by baseline use of MRA (Y/N) - RS (LOCF-AD) - 1245.121

Subgroup Description	Placebo	Empa 10mg
Baseline use of MRA: No		
Number of patients in analysis set	512	557
Number of analysed patients, N (%)	474 (100.0)	521 (100.0)
Number of patients with endpoint, N (%)	100 (21.1)	138 (26.5)
95% confidence interval*	(17.7, 25.0)	(22.9, 30.4)
Comparison vs Placebo**		
Odds ratio (SE)		1.364 (0.238)
95% confidence interval***		(0.970, 1.920)
p-value		0.0747
Baseline use of MRA: Yes		
Number of patients in analysis set	1355	1306
Number of analysed patients, N (%)	1236 (100.0)	1212 (100.0)
Number of patients with endpoint, N (%)	320 (25.9)	357 (29.5)
95% confidence interval*	(23.5, 28.4)	(27.0, 32.1)
Comparison vs Placebo**		
Odds ratio (SE)		1.256 (0.133)
95% confidence interval***		(1.020, 1.546)
p-value		0.0318

* Wilson confidence intervals.
** Logistic regression includes terms for baseline EQ-VAS score (p<0.0001), age (p=0.1440), baseline eGFR (CKD-EPI) (p=0.1622), Treatment (p=0.0083), region (5 cat.) (p<0.0001), baseline diabetes status (3 cat.) (p=0.6894), sex (p=0.4354), baseline LVEF (3 cat.) (p=0.0491), baseline use of MRA (p=0.1838) and Treatment by baseline use of MRA interaction (p=0.6838).
***Wald confidence intervals.

Data taken from study 1245.121 only.
LOCF: For a missing value at week 52 the last available post-baseline value before week 52 is imputed.

Table R.1.2.3.13: 6 Responder analysis (displaying risk ratio) in EQ-VAS change from baseline at week 52 of >= 15 points (improvement) by baseline use of MRA (Y/N) - RS (LOCF-AD) - 1245.121

Subgroup Description	Placebo	Empa 10mg
Baseline use of MRA: No		
Number of patients in analysis set	512	557
Number of analysed patients, N (%)	474 (100.0)	521 (100.0)
Number of patients with endpoint, N (%)	100 (21.1)	138 (26.5)
95% confidence interval*	(17.7, 25.0)	(22.9, 30.4)
Comparison vs Placebo**		
Risk ratio (SE)		1.142 (0.120)
95% confidence interval***		(0.930, 1.402)
p-value		0.2050
Baseline use of MRA: Yes		
Number of patients in analysis set	1355	1306
Number of analysed patients, N (%)	1236 (100.0)	1212 (100.0)
Number of patients with endpoint, N (%)	320 (25.9)	357 (29.5)
95% confidence interval*	(23.5, 28.4)	(27.0, 32.1)
Comparison vs Placebo**		
Risk ratio (SE)		1.127 (0.068)
95% confidence interval***		(1.001, 1.269)
p-value		0.0477

* Wilson confidence intervals.
** Log-linked Poisson model with robust estimate of variance includes terms for baseline EQ-VAS score (p<0.0001), age (p=0.1250), baseline eGFR (CKD-EPI) (p=0.1752), Treatment (p=0.0365), region (5 cat.) (p<0.0001), baseline diabetes status (3 cat.) (p=0.5586), sex (p=0.2248), baseline LVEF (3 cat.) (p=0.0909), baseline use of MRA (p=0.1292) and Treatment by baseline use of MRA interaction (p=0.9135).
***Wald confidence intervals.

Data taken from study 1245.121 only.
LOCF: For a missing value at week 52 the last available post-baseline value before week 52 is imputed.

R.1.2.3.14 Subgroup analysis by baseline use of ARNi

Table R.1.2.3.14: 1 Responder analysis (displaying odds ratio) in EQ-VAS change from baseline at week 52 of <= -15 points (deterioration) by baseline use of ARNi (Y/N) - RS (LOCF-AD) - 1245.121

Subgroup Description	Placebo	Empa 10mg
Baseline use of ARNi: No		
Number of patients in analysis set	1480	1523
Number of analysed patients, N (%)	1352 (100.0)	1412 (100.0)
Number of patients with endpoint, N (%)	193 (14.3)	184 (13.0)
95% confidence interval*	(12.5, 16.2)	(11.4, 14.9)
Comparison vs Placebo**		
Odds ratio (SE)		0.881 (0.102)
95% confidence interval***		(0.703, 1.104)
p-value		0.2719
Baseline use of ARNi: Yes		
Number of patients in analysis set	387	340
Number of analysed patients, N (%)	358 (100.0)	321 (100.0)
Number of patients with endpoint, N (%)	53 (14.8)	45 (14.0)
95% confidence interval*	(11.5, 18.9)	(10.6, 18.2)
Comparison vs Placebo**		
Odds ratio (SE)		0.955 (0.218)
95% confidence interval***		(0.611, 1.493)
p-value		0.8397

* Wilson confidence intervals.
** Logistic regression includes terms for baseline EQ-VAS score (p<0.0001), age (p=0.0473), baseline eGFR (CKD-EPI) (p=0.0219), Treatment (p=0.4991), region (5 cat.) (p<0.0001), baseline diabetes status (3 cat.) (p=0.7090), sex (p=0.0438), baseline LVEF (3 cat.) (p=0.3962), baseline use of ARNi (p=0.9624) and Treatment by baseline use of ARNi interaction (p=0.7529).
***Wald confidence intervals.

Data taken from study 1245.121 only.
LOCF: For a missing value at week 52 the last available post-baseline value before week 52 is imputed.

Table R.1.2.3.14: 2 Responder analysis (displaying risk ratio) in EQ-VAS change from baseline at week 52 of <= -15 points (deterioration) by baseline use of ARNi (Y/N) - RS (LOCF-AD) - 1245.121

Subgroup Description	Placebo	Empa 10mg
Baseline use of ARNi: No		
Number of patients in analysis set	1480	1523
Number of analysed patients, N (%)	1352 (100.0)	1412 (100.0)
Number of patients with endpoint, N (%)	193 (14.3)	184 (13.0)
95% confidence interval*	(12.5, 16.2)	(11.4, 14.9)
Comparison vs Placebo**		
Risk ratio (SE)		0.901 (0.084)
95% confidence interval***		(0.751, 1.081)
p-value		0.2619
Baseline use of ARNi: Yes		
Number of patients in analysis set	387	340
Number of analysed patients, N (%)	358 (100.0)	321 (100.0)
Number of patients with endpoint, N (%)	53 (14.8)	45 (14.0)
95% confidence interval*	(11.5, 18.9)	(10.6, 18.2)
Comparison vs Placebo**		
Risk ratio (SE)		0.962 (0.175)
95% confidence interval***		(0.674, 1.374)
p-value		0.8331

* Wilson confidence intervals.
** Log-linked Poisson model with robust estimate of variance includes terms for baseline EQ-VAS score (p<0.0001), age (p=0.0618), baseline eGFR (CKD-EPI) (p=0.0270), Treatment (p=0.4844), region (5 cat.) (p<0.0001), baseline diabetes status (3 cat.) (p=0.7217), sex (p=0.0480), baseline LVEF (3 cat.) (p=0.4242), baseline use of ARNi (p=0.9442) and Treatment by baseline use of ARNi interaction (p=0.7467).
***Wald confidence intervals.

Data taken from study 1245.121 only.
LOCF: For a missing value at week 52 the last available post-baseline value before week 52 is imputed.

Table R.1.2.3.14: 3 Responder analysis (displaying odds ratio) in EQ-VAS change from baseline at week 52 of > -15 points (stability) by baseline use of ARNi (Y/N) - RS (LOCF-AD) - 1245.121

Subgroup Description	Placebo	Empa 10mg
Baseline use of ARNi: No		
Number of patients in analysis set	1480	1523
Number of analysed patients, N (%)	1352 (100.0)	1412 (100.0)
Number of patients with endpoint, N (%)	1159 (85.7)	1228 (87.0)
95% confidence interval*	(83.8, 87.5)	(85.1, 88.6)
Comparison vs Placebo**		
Odds ratio (SE)		1.135 (0.131)
95% confidence interval***		(0.906, 1.423)
p-value		0.2719
Baseline use of ARNi: Yes		
Number of patients in analysis set	387	340
Number of analysed patients, N (%)	358 (100.0)	321 (100.0)
Number of patients with endpoint, N (%)	305 (85.2)	276 (86.0)
95% confidence interval*	(81.1, 88.5)	(81.8, 89.4)
Comparison vs Placebo**		
Odds ratio (SE)		1.047 (0.239)
95% confidence interval***		(0.670, 1.638)
p-value		0.8397

* Wilson confidence intervals.
** Logistic regression includes terms for baseline EQ-VAS score (p<0.0001), age (p=0.0473), baseline eGFR (CKD-EPI) (p=0.0219), Treatment (p=0.4991), region (5 cat.) (p<0.0001), baseline diabetes status (3 cat.) (p=0.7090), sex (p=0.0438), baseline LVEF (3 cat.) (p=0.3962), baseline use of ARNi (p=0.9624) and Treatment by baseline use of ARNi interaction (p=0.7529).
***Wald confidence intervals.

Data taken from study 1245.121 only.
LOCF: For a missing value at week 52 the last available post-baseline value before week 52 is imputed.

Table R.1.2.3.14: 4 Responder analysis (displaying risk ratio) in EQ-VAS change from baseline at week 52 of > -15 points (stability) by baseline use of ARNi (Y/N) - RS (LOCF-AD) - 1245.121

Subgroup Description	Placebo	Empa 10mg
Baseline use of ARNi: No		
Number of patients in analysis set	1480	1523
Number of analysed patients, N (%)	1352 (100.0)	1412 (100.0)
Number of patients with endpoint, N (%)	1159 (85.7)	1228 (87.0)
95% confidence interval*	(83.8, 87.5)	(85.1, 88.6)
Comparison vs Placebo**		
Risk ratio (SE)		1.014 (0.015)
95% confidence interval***		(0.985, 1.044)
p-value		0.3403
Baseline use of ARNi: Yes		
Number of patients in analysis set	387	340
Number of analysed patients, N (%)	358 (100.0)	321 (100.0)
Number of patients with endpoint, N (%)	305 (85.2)	276 (86.0)
95% confidence interval*	(81.1, 88.5)	(81.8, 89.4)
Comparison vs Placebo**		
Risk ratio (SE)		1.005 (0.031)
95% confidence interval***		(0.946, 1.067)
p-value		0.8724

* Wilson confidence intervals.
** Log-linked Poisson model with robust estimate of variance includes terms for baseline EQ-VAS score (p<0.0001), age (p=0.1077), baseline eGFR (CKD-EPI) (p=0.0281), Treatment (p=0.5774), region (5 cat.) (p=0.0010), baseline diabetes status (3 cat.) (p=0.6215), sex (p=0.0309), baseline LVEF (3 cat.) (p=0.4434), baseline use of ARNi (p=0.9280) and Treatment by baseline use of ARNi interaction (p=0.7887).
***Wald confidence intervals.

Data taken from study 1245.121 only.
LOCF: For a missing value at week 52 the last available post-baseline value before week 52 is imputed.

Table R.1.2.3.14: 5 Responder analysis (displaying odds ratio) in EQ-VAS change from baseline at week 52 of >= 15 points (improvement) by baseline use of ARNi (Y/N) - RS (LOCF-AD) - 1245.121

Subgroup Description	Placebo	Empa 10mg
Baseline use of ARNi: No		
Number of patients in analysis set	1480	1523
Number of analysed patients, N (%)	1352 (100.0)	1412 (100.0)
Number of patients with endpoint, N (%)	336 (24.9)	401 (28.4)
95% confidence interval*	(22.6, 27.2)	(26.1, 30.8)
Comparison vs Placebo**		
Odds ratio (SE)		1.256 (0.127)
95% confidence interval***		(1.031, 1.531)
p-value		0.0234
Baseline use of ARNi: Yes		
Number of patients in analysis set	387	340
Number of analysed patients, N (%)	358 (100.0)	321 (100.0)
Number of patients with endpoint, N (%)	84 (23.5)	94 (29.3)
95% confidence interval*	(19.4, 28.1)	(24.6, 34.5)
Comparison vs Placebo**		
Odds ratio (SE)		1.410 (0.293)
95% confidence interval***		(0.939, 2.118)
p-value		0.0980

* Wilson confidence intervals.
** Logistic regression includes terms for baseline EQ-VAS score (p<0.0001), age (p=0.1165), baseline eGFR (CKD-EPI) (p=0.1470), Treatment (p=0.0132), region (5 cat.) (p<0.0001), baseline diabetes status (3 cat.) (p=0.6595), sex (p=0.4356), baseline LVEF (3 cat.) (p=0.0559), baseline use of ARNi (p=0.4176) and Treatment by baseline use of ARNi interaction (p=0.6176).
***Wald confidence intervals.

Data taken from study 1245.121 only.
LOCF: For a missing value at week 52 the last available post-baseline value before week 52 is imputed.

Table R.1.2.3.14: 6 Responder analysis (displaying risk ratio) in EQ-VAS change from baseline at week 52 of >= 15 points (improvement) by baseline use of ARNi (Y/N) - RS (LOCF-AD) - 1245.121

Subgroup Description	Placebo	Empa 10mg
Baseline use of ARNi: No		
Number of patients in analysis set	1480	1523
Number of analysed patients, N (%)	1352 (100.0)	1412 (100.0)
Number of patients with endpoint, N (%)	336 (24.9)	401 (28.4)
95% confidence interval*	(22.6, 27.2)	(26.1, 30.8)
Comparison vs Placebo**		
Risk ratio (SE)		1.109 (0.065)
95% confidence interval***		(0.990, 1.243)
p-value		0.0750
Baseline use of ARNi: Yes		
Number of patients in analysis set	387	340
Number of analysed patients, N (%)	358 (100.0)	321 (100.0)
Number of patients with endpoint, N (%)	84 (23.5)	94 (29.3)
95% confidence interval*	(19.4, 28.1)	(24.6, 34.5)
Comparison vs Placebo**		
Risk ratio (SE)		1.214 (0.143)
95% confidence interval***		(0.964, 1.529)
p-value		0.0985

* Wilson confidence intervals.
** Log-linked Poisson model with robust estimate of variance includes terms for baseline EQ-VAS score (p<0.0001), age (p=0.0927), baseline eGFR (CKD-EPI) (p=0.1541), Treatment (p=0.0232), region (5 cat.) (p<0.0001), baseline diabetes status (3 cat.) (p=0.5440), sex (p=0.2102), baseline LVEF (3 cat.) (p=0.1148), baseline use of ARNi (p=0.6541) and Treatment by baseline use of ARNi interaction (p=0.4897).
***Wald confidence intervals.

Data taken from study 1245.121 only.
LOCF: For a missing value at week 52 the last available post-baseline value before week 52 is imputed.

R.1.2.3.15 Subgroup analysis by bl. LVEF (<= 30%, >30% -<= 35% , > 35%)

Table R.1.2.3.15: 1 Responder analysis (displaying odds ratio) in EQ-VAS change from baseline at week 52 of <= -15 points (deterioration) by baseline LVEF (3 cat.) - RS (LOCF-AD) - 1245.121

Subgroup Description	Placebo	Empa 10mg
Baseline LVEF (3 cat.): <=30		
Number of patients in analysis set	1392	1337
Number of analysed patients, N (%)	1272 (100.0)	1240 (100.0)
Number of patients with endpoint, N (%)	180 (14.2)	169 (13.6)
95% confidence interval*	(12.3, 16.2)	(11.8, 15.7)
Comparison vs Placebo**		
Odds ratio (SE)		0.927 (0.111)
95% confidence interval***		(0.733, 1.173)
p-value		0.5293
Baseline LVEF (3 cat.): >30 to <=35		
Number of patients in analysis set	361	398
Number of analysed patients, N (%)	334 (100.0)	373 (100.0)
Number of patients with endpoint, N (%)	50 (15.0)	44 (11.8)
95% confidence interval*	(11.5, 19.2)	(8.9, 15.5)
Comparison vs Placebo**		
Odds ratio (SE)		0.790 (0.182)
95% confidence interval***		(0.503, 1.240)
p-value		0.3053

* Wilson confidence intervals.
** Logistic regression includes terms for baseline EQ-VAS score (p<0.0001), age (p=0.0474), baseline eGFR (CKD-EPI) (p=0.0233), Treatment (p=0.3737), region (5 cat.) (p<0.0001), baseline diabetes status (3 cat.) (p=0.7090), sex (p=0.0440), baseline LVEF (3 cat.) (p=0.3913) and Treatment by baseline LVEF (3 cat.) interaction (p=0.8264).
***Wald confidence intervals.

Data taken from study 1245.121 only.
LOCF: For a missing value at week 52 the last available post-baseline value before week 52 is imputed.

Table R.1.2.3.15: 1 Responder analysis (displaying odds ratio) in EQ-VAS change from baseline at week 52 of <= -15 points (deterioration) by baseline LVEF (3 cat.) - RS (LOCF-AD) - 1245.121

Subgroup Description	Placebo	Empa 10mg
Baseline LVEF (3 cat.): >35		
Number of patients in analysis set	114	128
Number of analysed patients, N (%)	104 (100.0)	120 (100.0)
Number of patients with endpoint, N (%)	16 (15.4)	16 (13.3)
95% confidence interval*	(9.7, 23.5)	(8.4, 20.6)
Comparison vs Placebo**		
Odds ratio (SE)		0.895 (0.356)
95% confidence interval***		(0.410, 1.951)
p-value		0.7799

* Wilson confidence intervals.
** Logistic regression includes terms for baseline EQ-VAS score (p<0.0001), age (p=0.0474), baseline eGFR (CKD-EPI) (p=0.0233), Treatment (p=0.3737), region (5 cat.) (p<0.0001), baseline diabetes status (3 cat.) (p=0.7090), sex (p=0.0440), baseline LVEF (3 cat.) (p=0.3913) and Treatment by baseline LVEF (3 cat.) interaction (p=0.8264).
***Wald confidence intervals.

Data taken from study 1245.121 only.
LOCF: For a missing value at week 52 the last available post-baseline value before week 52 is imputed.

Table R.1.2.3.15: 2 Responder analysis (displaying risk ratio) in EQ-VAS change from baseline at week 52 of <= -15 points (deterioration) by baseline LVEF (3 cat.) - RS (LOCF-AD) - 1245.121

Subgroup Description	Placebo	Empa 10mg
Baseline LVEF (3 cat.): <=30		
Number of patients in analysis set	1392	1337
Number of analysed patients, N (%)	1272 (100.0)	1240 (100.0)
Number of patients with endpoint, N (%)	180 (14.2)	169 (13.6)
95% confidence interval*	(12.3, 16.2)	(11.8, 15.7)
Comparison vs Placebo**		
Risk ratio (SE)		0.939 (0.090)
95% confidence interval***		(0.778, 1.134)
p-value		0.5145
Baseline LVEF (3 cat.): >30 to <=35		
Number of patients in analysis set	361	398
Number of analysed patients, N (%)	334 (100.0)	373 (100.0)
Number of patients with endpoint, N (%)	50 (15.0)	44 (11.8)
95% confidence interval*	(11.5, 19.2)	(8.9, 15.5)
Comparison vs Placebo**		
Risk ratio (SE)		0.828 (0.157)
95% confidence interval***		(0.571, 1.201)
p-value		0.3194

* Wilson confidence intervals.
** Log-linked Poisson model with robust estimate of variance includes terms for baseline EQ-VAS score (p<0.0001), age (p=0.0625), baseline eGFR (CKD-EPI) (p=0.0296), Treatment (p=0.3420), region (5 cat.) (p<0.0001), baseline diabetes status (3 cat.) (p=0.7228), sex (p=0.0479), baseline LVEF (3 cat.) (p=0.4145) and Treatment by baseline LVEF (3 cat.) interaction (p=0.8378).
***Wald confidence intervals.

Data taken from study 1245.121 only.
LOCF: For a missing value at week 52 the last available post-baseline value before week 52 is imputed.

Table R.1.2.3.15: 2 Responder analysis (displaying risk ratio) in EQ-VAS change from baseline at week 52 of <= -15 points (deterioration) by baseline LVEF (3 cat.) - RS (LOCF-AD) - 1245.121

Subgroup Description	Placebo	Empa 10mg
Baseline LVEF (3 cat.): >35		
Number of patients in analysis set	114	128
Number of analysed patients, N (%)	104 (100.0)	120 (100.0)
Number of patients with endpoint, N (%)	16 (15.4)	16 (13.3)
95% confidence interval*	(9.7, 23.5)	(8.4, 20.6)
Comparison vs Placebo**		
Risk ratio (SE)		0.902 (0.277)
95% confidence interval***		(0.494, 1.646)
p-value		0.7359

* Wilson confidence intervals.
** Log-linked Poisson model with robust estimate of variance includes terms for baseline EQ-VAS score (p<0.0001), age (p=0.0625), baseline eGFR (CKD-EPI) (p=0.0296), Treatment (p=0.3420), region (5 cat.) (p<0.0001), baseline diabetes status (3 cat.) (p=0.7228), sex (p=0.0479), baseline LVEF (3 cat.) (p=0.4145) and Treatment by baseline LVEF (3 cat.) interaction (p=0.8378).
***Wald confidence intervals.

Data taken from study 1245.121 only.
LOCF: For a missing value at week 52 the last available post-baseline value before week 52 is imputed.

Table R.1.2.3.15: 3 Responder analysis (displaying odds ratio) in EQ-VAS change from baseline at week 52 of > -15 points (stability) by baseline LVEF (3 cat.) - RS (LOCF-AD) - 1245.121

Subgroup Description	Placebo	Empa 10mg
Baseline LVEF (3 cat.): <=30		
Number of patients in analysis set	1392	1337
Number of analysed patients, N (%)	1272 (100.0)	1240 (100.0)
Number of patients with endpoint, N (%)	1092 (85.8)	1071 (86.4)
95% confidence interval*	(83.8, 87.7)	(84.3, 88.2)
Comparison vs Placebo**		
Odds ratio (SE)		1.078 (0.129)
95% confidence interval***		(0.852, 1.365)
p-value		0.5293
Baseline LVEF (3 cat.): >30 to <=35		
Number of patients in analysis set	361	398
Number of analysed patients, N (%)	334 (100.0)	373 (100.0)
Number of patients with endpoint, N (%)	284 (85.0)	329 (88.2)
95% confidence interval*	(80.8, 88.5)	(84.5, 91.1)
Comparison vs Placebo**		
Odds ratio (SE)		1.266 (0.291)
95% confidence interval***		(0.806, 1.987)
p-value		0.3053

* Wilson confidence intervals.
** Logistic regression includes terms for baseline EQ-VAS score (p<0.0001), age (p=0.0474), baseline eGFR (CKD-EPI) (p=0.0233), Treatment (p=0.3737), region (5 cat.) (p<0.0001), baseline diabetes status (3 cat.) (p=0.7090), sex (p=0.0440), baseline LVEF (3 cat.) (p=0.3913) and Treatment by baseline LVEF (3 cat.) interaction (p=0.8264).
***Wald confidence intervals.

Data taken from study 1245.121 only.
LOCF: For a missing value at week 52 the last available post-baseline value before week 52 is imputed.

Table R.1.2.3.15: 3 Responder analysis (displaying odds ratio) in EQ-VAS change from baseline at week 52 of > -15 points (stability) by baseline LVEF (3 cat.) - RS (LOCF-AD) - 1245.121

Subgroup Description	Placebo	Empa 10mg
Baseline LVEF (3 cat.): >35		
Number of patients in analysis set	114	128
Number of analysed patients, N (%)	104 (100.0)	120 (100.0)
Number of patients with endpoint, N (%)	88 (84.6)	104 (86.7)
95% confidence interval*	(76.5, 90.3)	(79.4, 91.6)
Comparison vs Placebo**		
Odds ratio (SE)		1.118 (0.445)
95% confidence interval***		(0.512, 2.437)
p-value		0.7799

* Wilson confidence intervals.
** Logistic regression includes terms for baseline EQ-VAS score (p<0.0001), age (p=0.0474), baseline eGFR (CKD-EPI) (p=0.0233), Treatment (p=0.3737), region (5 cat.) (p<0.0001), baseline diabetes status (3 cat.) (p=0.7090), sex (p=0.0440), baseline LVEF (3 cat.) (p=0.3913) and Treatment by baseline LVEF (3 cat.) interaction (p=0.8264).
***Wald confidence intervals.

Data taken from study 1245.121 only.
LOCF: For a missing value at week 52 the last available post-baseline value before week 52 is imputed.

Table R.1.2.3.15: 4 Responder analysis (displaying risk ratio) in EQ-VAS change from baseline at week 52 of > -15 points (stability) by baseline LVEF (3 cat.) - RS (LOCF-AD) - 1245.121

Subgroup Description	Placebo	Empa 10mg
Baseline LVEF (3 cat.): <=30		
Number of patients in analysis set	1392	1337
Number of analysed patients, N (%)	1272 (100.0)	1240 (100.0)
Number of patients with endpoint, N (%)	1092 (85.8)	1071 (86.4)
95% confidence interval*	(83.8, 87.7)	(84.3, 88.2)
Comparison vs Placebo**		
Risk ratio (SE)		1.008 (0.016)
95% confidence interval***		(0.978, 1.040)
p-value		0.5921
Baseline LVEF (3 cat.): >30 to <=35		
Number of patients in analysis set	361	398
Number of analysed patients, N (%)	334 (100.0)	373 (100.0)
Number of patients with endpoint, N (%)	284 (85.0)	329 (88.2)
95% confidence interval*	(80.8, 88.5)	(84.5, 91.1)
Comparison vs Placebo**		
Risk ratio (SE)		1.030 (0.030)
95% confidence interval***		(0.973, 1.091)
p-value		0.3125

* Wilson confidence intervals.
** Log-linked Poisson model with robust estimate of variance includes terms for baseline EQ-VAS score (p<0.0001), age (p=0.1090), baseline eGFR (CKD-EPI) (p=0.0295), Treatment (p=0.5193), region (5 cat.) (p=0.0009), baseline diabetes status (3 cat.) (p=0.6224), sex (p=0.0317), baseline LVEF (3 cat.) (p=0.4728) and Treatment by baseline LVEF (3 cat.) interaction (p=0.7986).
***Wald confidence intervals.

Data taken from study 1245.121 only.
LOCF: For a missing value at week 52 the last available post-baseline value before week 52 is imputed.

Table R.1.2.3.15: 4 Responder analysis (displaying risk ratio) in EQ-VAS change from baseline at week 52 of > -15 points (stability) by baseline LVEF (3 cat.) - RS (LOCF-AD) - 1245.121

Subgroup Description	Placebo	Empa 10mg
Baseline LVEF (3 cat.): >35		
Number of patients in analysis set	114	128
Number of analysed patients, N (%)	104 (100.0)	120 (100.0)
Number of patients with endpoint, N (%)	88 (84.6)	104 (86.7)
95% confidence interval*	(76.5, 90.3)	(79.4, 91.6)
Comparison vs Placebo**		
Risk ratio (SE)		1.002 (0.052)
95% confidence interval***		(0.904, 1.110)
p-value		0.9686

* Wilson confidence intervals.
** Log-linked Poisson model with robust estimate of variance includes terms for baseline EQ-VAS score (p<0.0001), age (p=0.1090), baseline eGFR (CKD-EPI) (p=0.0295), Treatment (p=0.5193), region (5 cat.) (p=0.0009), baseline diabetes status (3 cat.) (p=0.6224), sex (p=0.0317), baseline LVEF (3 cat.) (p=0.4728) and Treatment by baseline LVEF (3 cat.) interaction (p=0.7986).
***Wald confidence intervals.

Data taken from study 1245.121 only.
LOCF: For a missing value at week 52 the last available post-baseline value before week 52 is imputed.

Table R.1.2.3.15: 5 Responder analysis (displaying odds ratio) in EQ-VAS change from baseline at week 52 of >= 15 points (improvement) by baseline LVEF (3 cat.) - RS (LOCF-AD) - 1245.121

Subgroup Description	Placebo	Empa 10mg
Baseline LVEF (3 cat.): <=30		
Number of patients in analysis set	1392	1337
Number of analysed patients, N (%)	1272 (100.0)	1240 (100.0)
Number of patients with endpoint, N (%)	313 (24.6)	352 (28.4)
95% confidence interval*	(22.3, 27.0)	(25.9, 31.0)
Comparison vs Placebo**		
Odds ratio (SE)		1.321 (0.140)
95% confidence interval***		(1.074, 1.625)
p-value		0.0085
Baseline LVEF (3 cat.): >30 to <=35		
Number of patients in analysis set	361	398
Number of analysed patients, N (%)	334 (100.0)	373 (100.0)
Number of patients with endpoint, N (%)	77 (23.1)	96 (25.7)
95% confidence interval*	(18.9, 27.9)	(21.6, 30.4)
Comparison vs Placebo**		
Odds ratio (SE)		1.142 (0.235)
95% confidence interval***		(0.763, 1.710)
p-value		0.5177

* Wilson confidence intervals.
** Logistic regression includes terms for baseline EQ-VAS score (p<0.0001), age (p=0.1134), baseline eGFR (CKD-EPI) (p=0.1352), Treatment (p=0.1011), region (5 cat.) (p<0.0001), baseline diabetes status (3 cat.) (p=0.6731), sex (p=0.4446), baseline LVEF (3 cat.) (p=0.0625) and Treatment by baseline LVEF (3 cat.) interaction (p=0.8207).
***Wald confidence intervals.

Data taken from study 1245.121 only.
LOCF: For a missing value at week 52 the last available post-baseline value before week 52 is imputed.

Table R.1.2.3.15: 5 Responder analysis (displaying odds ratio) in EQ-VAS change from baseline at week 52 of >= 15 points (improvement) by baseline LVEF (3 cat.) - RS (LOCF-AD) - 1245.121

Subgroup Description	Placebo	Empa 10mg
Baseline LVEF (3 cat.): >35		
Number of patients in analysis set	114	128
Number of analysed patients, N (%)	104 (100.0)	120 (100.0)
Number of patients with endpoint, N (%)	30 (28.8)	47 (39.2)
95% confidence interval*	(21.0, 38.2)	(30.9, 48.1)
Comparison vs Placebo**		
Odds ratio (SE)		1.297 (0.438)
95% confidence interval***		(0.668, 2.516)
p-value		0.4421

* Wilson confidence intervals.
** Logistic regression includes terms for baseline EQ-VAS score (p<0.0001), age (p=0.1134), baseline eGFR (CKD-EPI) (p=0.1352), Treatment (p=0.1011), region (5 cat.) (p<0.0001), baseline diabetes status (3 cat.) (p=0.6731), sex (p=0.4446), baseline LVEF (3 cat.) (p=0.0625) and Treatment by baseline LVEF (3 cat.) interaction (p=0.8207).
***Wald confidence intervals.

Data taken from study 1245.121 only.
LOCF: For a missing value at week 52 the last available post-baseline value before week 52 is imputed.

Table R.1.2.3.15: 6 Responder analysis (displaying risk ratio) in EQ-VAS change from baseline at week 52 of >= 15 points (improvement) by baseline LVEF (3 cat.) - RS (LOCF-AD) - 1245.121

Subgroup Description	Placebo	Empa 10mg
Baseline LVEF (3 cat.): <=30		
Number of patients in analysis set	1392	1337
Number of analysed patients, N (%)	1272 (100.0)	1240 (100.0)
Number of patients with endpoint, N (%)	313 (24.6)	352 (28.4)
95% confidence interval*	(22.3, 27.0)	(25.9, 31.0)
Comparison vs Placebo**		
Risk ratio (SE)		1.155 (0.071)
95% confidence interval***		(1.023, 1.303)
p-value		0.0195
Baseline LVEF (3 cat.): >30 to <=35		
Number of patients in analysis set	361	398
Number of analysed patients, N (%)	334 (100.0)	373 (100.0)
Number of patients with endpoint, N (%)	77 (23.1)	96 (25.7)
95% confidence interval*	(18.9, 27.9)	(21.6, 30.4)
Comparison vs Placebo**		
Risk ratio (SE)		1.059 (0.122)
95% confidence interval***		(0.845, 1.328)
p-value		0.6195

* Wilson confidence intervals.
** Log-linked Poisson model with robust estimate of variance includes terms for baseline EQ-VAS score (p<0.0001), age (p=0.0932), baseline eGFR (CKD-EPI) (p=0.1358), Treatment (p=0.2482), region (5 cat.) (p<0.0001), baseline diabetes status (3 cat.) (p=0.5560), sex (p=0.2222), baseline LVEF (3 cat.) (p=0.1116) and Treatment by baseline LVEF (3 cat.) interaction (p=0.7426).
***Wald confidence intervals.

Data taken from study 1245.121 only.
LOCF: For a missing value at week 52 the last available post-baseline value before week 52 is imputed.

Table R.1.2.3.15: 6 Responder analysis (displaying risk ratio) in EQ-VAS change from baseline at week 52 of >= 15 points (improvement) by baseline LVEF (3 cat.) - RS (LOCF-AD) - 1245.121

Subgroup Description	Placebo	Empa 10mg
Baseline LVEF (3 cat.): >35		
Number of patients in analysis set	114	128
Number of analysed patients, N (%)	104 (100.0)	120 (100.0)
Number of patients with endpoint, N (%)	30 (28.8)	47 (39.2)
95% confidence interval*	(21.0, 38.2)	(30.9, 48.1)
Comparison vs Placebo**		
Risk ratio (SE)		1.054 (0.185)
95% confidence interval***		(0.746, 1.488)
p-value		0.7667

* Wilson confidence intervals.
** Log-linked Poisson model with robust estimate of variance includes terms for baseline EQ-VAS score (p<0.0001), age (p=0.0932), baseline eGFR (CKD-EPI) (p=0.1358), Treatment (p=0.2482), region (5 cat.) (p<0.0001), baseline diabetes status (3 cat.) (p=0.5560), sex (p=0.2222), baseline LVEF (3 cat.) (p=0.1116) and Treatment by baseline LVEF (3 cat.) interaction (p=0.7426).
***Wald confidence intervals.

Data taken from study 1245.121 only.
LOCF: For a missing value at week 52 the last available post-baseline value before week 52 is imputed.

R.1.2.3.16 Subgroup analysis by bl. NTproBNP </>= median (median based on total patients)

Table R.1.2.3.16: 1 Responder analysis (displaying odds ratio) in EQ-VAS change from baseline at week 52 of <= -15 points (deterioration) by bl. NTproBNP (<median, >= median) (median based on total patients) - RS (LOCF-AD) - 1245.121

Subgroup Description	Placebo	Empa 10mg
Baseline NTproBNP (<median, >= median): < median		
Number of patients in analysis set	920	942
Number of analysed patients, N (%)	866 (100.0)	884 (100.0)
Number of patients with endpoint, N (%)	118 (13.6)	106 (12.0)
95% confidence interval*	(11.5, 16.1)	(10.0, 14.3)
Comparison vs Placebo**		
Odds ratio (SE)		0.870 (0.129)
95% confidence interval***		(0.650, 1.163)
p-value		0.3470
Baseline NTproBNP (<median, >= median): >= median		
Number of patients in analysis set	946	920
Number of analysed patients, N (%)	844 (100.0)	849 (100.0)
Number of patients with endpoint, N (%)	128 (15.2)	123 (14.5)
95% confidence interval*	(12.9, 17.7)	(12.3, 17.0)
Comparison vs Placebo**		
Odds ratio (SE)		0.921 (0.132)
95% confidence interval***		(0.696, 1.218)
p-value		0.5632

* Wilson confidence intervals.
** Logistic regression includes terms for baseline EQ-VAS score (p<0.0001), age (p=0.0526), baseline eGFR (CKD-EPI) (p=0.0678), Treatment (p=0.2808), region (5 cat.) (p<0.0001), baseline diabetes status (3 cat.) (p=0.7005), sex (p=0.0452), baseline LVEF (3 cat.) (p=0.3840), baseline NTproBNP (<median, >= median) (p=0.0313) and Treatment by baseline NTproBNP (<median, >= median) interaction (p=0.7822).
***Wald confidence intervals.
2 patients were excluded as the subgroup variable was missing.

Data taken from study 1245.121 only.
LOCF: For a missing value at week 52 the last available post-baseline value before week 52 is imputed.
Median: 1910 [pg/mL]

Table R.1.2.3.16: 2 Responder analysis (displaying risk ratio) in EQ-VAS change from baseline at week 52 of <= -15 points (deterioration) by bl. NTproBNP (<median, >= median) (median based on total patients) - RS (LOCF-AD) - 1245.121

Subgroup Description	Placebo	Empa 10mg
Baseline NTproBNP (<median, >= median): < median		
Number of patients in analysis set	920	942
Number of analysed patients, N (%)	866 (100.0)	884 (100.0)
Number of patients with endpoint, N (%)	118 (13.6)	106 (12.0)
95% confidence interval*	(11.5, 16.1)	(10.0, 14.3)
Comparison vs Placebo**		
Risk ratio (SE)		0.894 (0.109)
95% confidence interval***		(0.704, 1.135)
p-value		0.3564
Baseline NTproBNP (<median, >= median): >= median		
Number of patients in analysis set	946	920
Number of analysed patients, N (%)	844 (100.0)	849 (100.0)
Number of patients with endpoint, N (%)	128 (15.2)	123 (14.5)
95% confidence interval*	(12.9, 17.7)	(12.3, 17.0)
Comparison vs Placebo**		
Risk ratio (SE)		0.930 (0.104)
95% confidence interval***		(0.747, 1.159)
p-value		0.5177

* Wilson confidence intervals.
** Log-linked Poisson model with robust estimate of variance includes terms for baseline EQ-VAS score (p<0.0001), age (p=0.0682), baseline eGFR (CKD-EPI) (p=0.0788), Treatment (p=0.2634), region (5 cat.) (p<0.0001), baseline diabetes status (3 cat.) (p=0.7227), sex (p=0.0511), baseline LVEF (3 cat.) (p=0.4180), baseline NTproBNP (<median, >= median) (p=0.0329) and Treatment by baseline NTproBNP (<median, >= median) interaction (p=0.8096).
***Wald confidence intervals.
2 patients were excluded as the subgroup variable was missing.

Data taken from study 1245.121 only.
LOCF: For a missing value at week 52 the last available post-baseline value before week 52 is imputed.
Median: 1910 [pg/mL]

Table R.1.2.3.16: 3 Responder analysis (displaying odds ratio) in EQ-VAS change from baseline at week 52 of > -15 points (stability) by bl. NTproBNP (<median, >= median) (median based on total patients) - RS (LOCF-AD) - 1245.121

Subgroup Description	Placebo	Empa 10mg
Baseline NTproBNP (<median, >= median): < median		
Number of patients in analysis set	920	942
Number of analysed patients, N (%)	866 (100.0)	884 (100.0)
Number of patients with endpoint, N (%)	748 (86.4)	778 (88.0)
95% confidence interval*	(83.9, 88.5)	(85.7, 90.0)
Comparison vs Placebo**		
Odds ratio (SE)		1.150 (0.171)
95% confidence interval***		(0.860, 1.538)
p-value		0.3470
Baseline NTproBNP (<median, >= median): >= median		
Number of patients in analysis set	946	920
Number of analysed patients, N (%)	844 (100.0)	849 (100.0)
Number of patients with endpoint, N (%)	716 (84.8)	726 (85.5)
95% confidence interval*	(82.3, 87.1)	(83.0, 87.7)
Comparison vs Placebo**		
Odds ratio (SE)		1.086 (0.155)
95% confidence interval***		(0.821, 1.437)
p-value		0.5632

* Wilson confidence intervals.
** Logistic regression includes terms for baseline EQ-VAS score (p<0.0001), age (p=0.0526), baseline eGFR (CKD-EPI) (p=0.0678), Treatment (p=0.2808), region (5 cat.) (p<0.0001), baseline diabetes status (3 cat.) (p=0.7005), sex (p=0.0452), baseline LVEF (3 cat.) (p=0.3840), baseline NTproBNP (<median, >= median) (p=0.0313) and Treatment by baseline NTproBNP (<median, >= median) interaction (p=0.7822).
***Wald confidence intervals.
2 patients were excluded as the subgroup variable was missing.

Data taken from study 1245.121 only.
LOCF: For a missing value at week 52 the last available post-baseline value before week 52 is imputed.
Median: 1910 [pg/mL]

Table R.1.2.3.16: 4 Responder analysis (displaying risk ratio) in EQ-VAS change from baseline at week 52 of > -15 points (stability) by bl. NTproBNP (<median, >= median) (median based on total patients) - RS (LOCF-AD) - 1245.121

Subgroup Description	Placebo	Empa 10mg
Baseline NTproBNP (<median, >= median): < median		
Number of patients in analysis set	920	942
Number of analysed patients, N (%)	866 (100.0)	884 (100.0)
Number of patients with endpoint, N (%)	748 (86.4)	778 (88.0)
95% confidence interval*	(83.9, 88.5)	(85.7, 90.0)
Comparison vs Placebo**		
Risk ratio (SE)		1.017 (0.018)
95% confidence interval***		(0.982, 1.053)
p-value		0.3566
Baseline NTproBNP (<median, >= median): >= median		
Number of patients in analysis set	946	920
Number of analysed patients, N (%)	844 (100.0)	849 (100.0)
Number of patients with endpoint, N (%)	716 (84.8)	726 (85.5)
95% confidence interval*	(82.3, 87.1)	(83.0, 87.7)
Comparison vs Placebo**		
Risk ratio (SE)		1.007 (0.020)
95% confidence interval***		(0.969, 1.047)
p-value		0.7128

* Wilson confidence intervals.
** Log-linked Poisson model with robust estimate of variance includes terms for baseline EQ-VAS score (p<0.0001), age (p=0.1201), baseline eGFR (CKD-EPI) (p=0.0859), Treatment (p=0.3727), region (5 cat.) (p=0.0005), baseline diabetes status (3 cat.) (p=0.6193), sex (p=0.0278), baseline LVEF (3 cat.) (p=0.4435), baseline NTproBNP (<median, >= median) (p=0.0186) and Treatment by baseline NTproBNP (<median, >= median) interaction (p=0.7266).
***Wald confidence intervals.
2 patients were excluded as the subgroup variable was missing.

Data taken from study 1245.121 only.
LOCF: For a missing value at week 52 the last available post-baseline value before week 52 is imputed.
Median: 1910 [pg/mL]

Table R.1.2.3.16: 5 Responder analysis (displaying odds ratio) in EQ-VAS change from baseline at week 52 of >= 15 points (improvement) by bl. NTproBNP (<median, >= median) (median based on total patients) - RS (LOCF-AD) - 1245.121

Subgroup Description	Placebo	Empa 10mg
Baseline NTproBNP (<median, >= median): < median		
Number of patients in analysis set	920	942
Number of analysed patients, N (%)	866 (100.0)	884 (100.0)
Number of patients with endpoint, N (%)	196 (22.6)	248 (28.1)
95% confidence interval*	(20.0, 25.5)	(25.2, 31.1)
Comparison vs Placebo**		
Odds ratio (SE)		1.387 (0.177)
95% confidence interval***		(1.080, 1.782)
p-value		0.0104
Baseline NTproBNP (<median, >= median): >= median		
Number of patients in analysis set	946	920
Number of analysed patients, N (%)	844 (100.0)	849 (100.0)
Number of patients with endpoint, N (%)	224 (26.5)	247 (29.1)
95% confidence interval*	(23.7, 29.6)	(26.1, 32.2)
Comparison vs Placebo**		
Odds ratio (SE)		1.182 (0.152)
95% confidence interval***		(0.919, 1.520)
p-value		0.1937

* Wilson confidence intervals.
** Logistic regression includes terms for baseline EQ-VAS score (p<0.0001), age (p=0.1152), baseline eGFR (CKD-EPI) (p=0.1915), Treatment (p=0.0064), region (5 cat.) (p<0.0001), baseline diabetes status (3 cat.) (p=0.6567), sex (p=0.4312), baseline LVEF (3 cat.) (p=0.0524), baseline NTproBNP (<median, >= median) (p=0.5286) and Treatment by baseline NTproBNP (<median, >= median) interaction (p=0.3760).
***Wald confidence intervals.
2 patients were excluded as the subgroup variable was missing.

Data taken from study 1245.121 only.
LOCF: For a missing value at week 52 the last available post-baseline value before week 52 is imputed.
Median: 1910 [pg/mL]

Table R.1.2.3.16: 6 Responder analysis (displaying risk ratio) in EQ-VAS change from baseline at week 52 of >= 15 points (improvement) by bl. NTproBNP (<median, >= median) (median based on total patients) - RS (LOCF-AD) - 1245.121

Subgroup Description	Placebo	Empa 10mg
Baseline NTproBNP (<median, >= median): < median		
Number of patients in analysis set	920	942
Number of analysed patients, N (%)	866 (100.0)	884 (100.0)
Number of patients with endpoint, N (%)	196 (22.6)	248 (28.1)
95% confidence interval*	(20.0, 25.5)	(25.2, 31.1)
Comparison vs Placebo**		
Risk ratio (SE)		1.216 (0.090)
95% confidence interval***		(1.053, 1.405)
p-value		0.0079
Baseline NTproBNP (<median, >= median): >= median		
Number of patients in analysis set	946	920
Number of analysed patients, N (%)	844 (100.0)	849 (100.0)
Number of patients with endpoint, N (%)	224 (26.5)	247 (29.1)
95% confidence interval*	(23.7, 29.6)	(26.1, 32.2)
Comparison vs Placebo**		
Risk ratio (SE)		1.049 (0.077)
95% confidence interval***		(0.908, 1.213)
p-value		0.5145

* Wilson confidence intervals.
** Log-linked Poisson model with robust estimate of variance includes terms for baseline EQ-VAS score (p<0.0001), age (p=0.1065), baseline eGFR (CKD-EPI) (p=0.2278), Treatment (p=0.0195), region (5 cat.) (p<0.0001), baseline diabetes status (3 cat.) (p=0.5697), sex (p=0.1957), baseline LVEF (3 cat.) (p=0.0827), baseline NTproBNP (<median, >= median) (p=0.2341) and Treatment by baseline NTproBNP (<median, >= median) interaction (p=0.1566).
***Wald confidence intervals.
2 patients were excluded as the subgroup variable was missing.

Data taken from study 1245.121 only.
LOCF: For a missing value at week 52 the last available post-baseline value before week 52 is imputed.
Median: 1910 [pg/mL]

R.1.2.4

R.1.2.4 KCCQ Clinical Summary Score responder analysis (5 points)

R.1.2.4.1

Table R.1.2.4.1: 1 Responder analysis (displaying odds ratio) in KCCQ-CSS change from baseline at week 52 of <= -5 points (deterioration) - RS (LOCF-AD) - 1245.121

	Placebo	Empa 10mg
Number of patients in analysis set	1867	1863
Number of analysed patients, N (%)	1709 (100.0)	1740 (100.0)
Number of patients with endpoint, N (%)	448 (26.2)	397 (22.8)
95% confidence interval*	(24.2, 28.4)	(20.9, 24.8)
Comparison vs Placebo**		
Odds ratio (SE)		0.820 (0.066)
95% confidence interval***		(0.700, 0.961)
p-value		0.0143

* Wilson confidence intervals.
** Logistic regression includes terms for baseline KCCQ - clinical summary score (p<0.0001), age (p=0.0146), baseline eGFR (CKD-EPI) (p=0.0006), Treatment (p=0.0143), region (5 cat.) (p=0.0001), baseline diabetes status (3 cat.) (p=0.9175), sex (p=0.4616) and baseline LVEF (3 cat.) (p=0.6908).
***Wald confidence intervals.

Data taken from study 1245.121 only.
LOCF: For a missing value at week 52 the last available post-baseline value before week 52 is imputed.

Table R.1.2.4.1: 2 Responder analysis (displaying risk ratio) in KCCQ-CSS change from baseline at week 52 of <= -5 points (deterioration) - RS (LOCF-AD) - 1245.121

	Placebo	Empa 10mg
Number of patients in analysis set	1867	1863
Number of analysed patients, N (%)	1709 (100.0)	1740 (100.0)
Number of patients with endpoint, N (%)	448 (26.2)	397 (22.8)
95% confidence interval*	(24.2, 28.4)	(20.9, 24.8)
Comparison vs Placebo**		
Risk ratio (SE)		0.865 (0.051)
95% confidence interval***		(0.771, 0.971)
p-value		0.0135

* Wilson confidence intervals.
** Log-linked Poisson model with robust estimate of variance includes terms for baseline KCCQ - clinical summary score (p<0.0001), age (p=0.0153), baseline eGFR (CKD-EPI) (p=0.0007), Treatment (p=0.0135), region (5 cat.) (p=0.0002), baseline diabetes status (3 cat.) (p=0.9204), sex (p=0.4425) and baseline LVEF (3 cat.) (p=0.6868).
***Wald confidence intervals.

Data taken from study 1245.121 only.
LOCF: For a missing value at week 52 the last available post-baseline value before week 52 is imputed.

Table R.1.2.4.1: 3 Responder analysis (displaying odds ratio) in KCCQ-CSS change from baseline at week 52 of > -5 points (stability) - RS (LOCF-AD) - 1245.121

	Placebo	Empa 10mg
Number of patients in analysis set	1867	1863
Number of analysed patients, N (%)	1709 (100.0)	1740 (100.0)
Number of patients with endpoint, N (%)	1261 (73.8)	1343 (77.2)
95% confidence interval*	(71.6, 75.8)	(75.2, 79.1)
Comparison vs Placebo**		
Odds ratio (SE)		1.219 (0.099)
95% confidence interval***		(1.040, 1.428)
p-value		0.0143

* Wilson confidence intervals.
** Logistic regression includes terms for baseline KCCQ - clinical summary score (p<0.0001), age (p=0.0146), baseline eGFR (CKD-EPI) (p=0.0006), Treatment (p=0.0143), region (5 cat.) (p=0.0001), baseline diabetes status (3 cat.) (p=0.9175), sex (p=0.4616) and baseline LVEF (3 cat.) (p=0.6908).
***Wald confidence intervals.

Data taken from study 1245.121 only.
LOCF: For a missing value at week 52 the last available post-baseline value before week 52 is imputed.

Table R.1.2.4.1: 4 Responder analysis (displaying risk ratio) in KCCQ-CSS change from baseline at week 52 of > -5 points (stability) - RS (LOCF-AD) - 1245.121

	Placebo	Empa 10mg
Number of patients in analysis set	1867	1863
Number of analysed patients, N (%)	1709 (100.0)	1740 (100.0)
Number of patients with endpoint, N (%)	1261 (73.8)	1343 (77.2)
95% confidence interval*	(71.6, 75.8)	(75.2, 79.1)
Comparison vs Placebo**		
Risk ratio (SE)		1.047 (0.020)
95% confidence interval***		(1.009, 1.087)
p-value		0.0162

* Wilson confidence intervals.
** Log-linked Poisson model with robust estimate of variance includes terms for baseline KCCQ - clinical summary score (p<0.0001), age (p=0.0246), baseline eGFR (CKD-EPI) (p=0.0008), Treatment (p=0.0162), region (5 cat.) (p<0.0001), baseline diabetes status (3 cat.) (p=0.9217), sex (p=0.4902) and baseline LVEF (3 cat.) (p=0.6723).
***Wald confidence intervals.

Data taken from study 1245.121 only.
LOCF: For a missing value at week 52 the last available post-baseline value before week 52 is imputed.

Table R.1.2.4.1: 5 Responder analysis (displaying odds ratio) in KCCQ-CSS change from baseline at week 52 of >= 5 points (improvement) - RS (LOCF-AD) - 1245.121

	Placebo	Empa 10mg
Number of patients in analysis set	1867	1863
Number of analysed patients, N (%)	1709 (100.0)	1740 (100.0)
Number of patients with endpoint, N (%)	717 (42.0)	806 (46.3)
95% confidence interval*	(39.6, 44.3)	(44.0, 48.7)
Comparison vs Placebo**		
Odds ratio (SE)		1.232 (0.093)
95% confidence interval***		(1.063, 1.428)
p-value		0.0055

* Wilson confidence intervals.
** Logistic regression includes terms for baseline KCCQ - clinical summary score (p<0.0001), age (p=0.0196), baseline eGFR (CKD-EPI) (p=0.7996), Treatment (p=0.0055), region (5 cat.) (p<0.0001), baseline diabetes status (3 cat.) (p=0.7834), sex (p=0.7483) and baseline LVEF (3 cat.) (p=0.2711).
***Wald confidence intervals.

Data taken from study 1245.121 only.
LOCF: For a missing value at week 52 the last available post-baseline value before week 52 is imputed.

Table R.1.2.4.1: 6 Responder analysis (displaying risk ratio) in KCCQ-CSS change from baseline at week 52 of >= 5 points (improvement) - RS (LOCF-AD) - 1245.121

	Placebo	Empa 10mg
Number of patients in analysis set	1867	1863
Number of analysed patients, N (%)	1709 (100.0)	1740 (100.0)
Number of patients with endpoint, N (%)	717 (42.0)	806 (46.3)
95% confidence interval*	(39.6, 44.3)	(44.0, 48.7)
Comparison vs Placebo**		
Risk ratio (SE)		1.095 (0.039)
95% confidence interval***		(1.021, 1.175)
p-value		0.0112

* Wilson confidence intervals.
** Log-linked Poisson model with robust estimate of variance includes terms for baseline KCCQ - clinical summary score (p<0.0001), age (p=0.0402), baseline eGFR (CKD-EPI) (p=0.8120), Treatment (p=0.0112), region (5 cat.) (p<0.0001), baseline diabetes status (3 cat.) (p=0.7353), sex (p=0.9433) and baseline LVEF (3 cat.) (p=0.2434).
***Wald confidence intervals.

Data taken from study 1245.121 only.
LOCF: For a missing value at week 52 the last available post-baseline value before week 52 is imputed.

R.1.2.4.2

R.1.2.4.2 Subgroup analysis by sex

Table R.1.2.4.2: 1 Responder analysis (displaying odds ratio) in KCCQ-CSS change from baseline at week 52 of <= -5 points (deterioration) by sex - RS (LOCF-AD) - 1245.121

Subgroup Description	Placebo	Empa 10mg
Sex: Male		
Number of patients in analysis set	1411	1426
Number of analysed patients, N (%)	1297 (100.0)	1332 (100.0)
Number of patients with endpoint, N (%)	356 (27.4)	293 (22.0)
95% confidence interval*	(25.1, 29.9)	(19.9, 24.3)
Comparison vs Placebo**		
Odds ratio (SE)		0.734 (0.068)
95% confidence interval***		(0.612, 0.880)
p-value		0.0009
Sex: Female		
Number of patients in analysis set	456	437
Number of analysed patients, N (%)	412 (100.0)	408 (100.0)
Number of patients with endpoint, N (%)	92 (22.3)	104 (25.5)
95% confidence interval*	(18.6, 26.6)	(21.5, 29.9)
Comparison vs Placebo**		
Odds ratio (SE)		1.177 (0.197)
95% confidence interval***		(0.848, 1.633)
p-value		0.3301

* Wilson confidence intervals.
** Logistic regression includes terms for baseline KCCQ - clinical summary score (p<0.0001), age (p=0.0121), baseline eGFR (CKD-EPI) (p=0.0006), Treatment (p=0.4446), region (5 cat.) (p=0.0002), baseline diabetes status (3 cat.) (p=0.9285), baseline LVEF (3 cat.) (p=0.7126), sex (p=0.4488) and Treatment by sex interaction (p=0.0136).
***Wald confidence intervals.

Data taken from study 1245.121 only.
LOCF: For a missing value at week 52 the last available post-baseline value before week 52 is imputed.

Table R.1.2.4.2: 2 Responder analysis (displaying risk ratio) in KCCQ-CSS change from baseline at week 52 of <= -5 points (deterioration) by sex - RS (LOCF-AD) - 1245.121

Subgroup Description	Placebo	Empa 10mg
Sex: Male		
Number of patients in analysis set	1411	1426
Number of analysed patients, N (%)	1297 (100.0)	1332 (100.0)
Number of patients with endpoint, N (%)	356 (27.4)	293 (22.0)
95% confidence interval*	(25.1, 29.9)	(19.9, 24.3)
Comparison vs Placebo**		
Risk ratio (SE)		0.799 (0.054)
95% confidence interval***		(0.700, 0.912)
p-value		0.0009
Sex: Female		
Number of patients in analysis set	456	437
Number of analysed patients, N (%)	412 (100.0)	408 (100.0)
Number of patients with endpoint, N (%)	92 (22.3)	104 (25.5)
95% confidence interval*	(18.6, 26.6)	(21.5, 29.9)
Comparison vs Placebo**		
Risk ratio (SE)		1.122 (0.137)
95% confidence interval***		(0.883, 1.425)
p-value		0.3452

* Wilson confidence intervals.
** Log-linked Poisson model with robust estimate of variance includes terms for baseline KCCQ - clinical summary score (p<0.0001), age (p=0.0126), baseline eGFR (CKD-EPI) (p=0.0007), Treatment (p=0.4336), region (5 cat.) (p=0.0003), baseline diabetes status (3 cat.) (p=0.9315), baseline LVEF (3 cat.) (p=0.7096), sex (p=0.4266) and Treatment by sex interaction (p=0.0151).
***Wald confidence intervals.

Data taken from study 1245.121 only.
LOCF: For a missing value at week 52 the last available post-baseline value before week 52 is imputed.

Table R.1.2.4.2: 3 Responder analysis (displaying odds ratio) in KCCQ-CSS change from baseline at week 52 of > -5 points (stability) by sex - RS (LOCF-AD) - 1245.121

Subgroup Description	Placebo	Empa 10mg
Sex: Male		
Number of patients in analysis set	1411	1426
Number of analysed patients, N (%)	1297 (100.0)	1332 (100.0)
Number of patients with endpoint, N (%)	941 (72.6)	1039 (78.0)
95% confidence interval*	(70.1, 74.9)	(75.7, 80.1)
Comparison vs Placebo**		
Odds ratio (SE)		1.362 (0.126)
95% confidence interval***		(1.136, 1.633)
p-value		0.0009
Sex: Female		
Number of patients in analysis set	456	437
Number of analysed patients, N (%)	412 (100.0)	408 (100.0)
Number of patients with endpoint, N (%)	320 (77.7)	304 (74.5)
95% confidence interval*	(73.4, 81.4)	(70.1, 78.5)
Comparison vs Placebo**		
Odds ratio (SE)		0.850 (0.142)
95% confidence interval***		(0.612, 1.179)
p-value		0.3301

* Wilson confidence intervals.
** Logistic regression includes terms for baseline KCCQ - clinical summary score (p<0.0001), age (p=0.0121), baseline eGFR (CKD-EPI) (p=0.0006), Treatment (p=0.4446), region (5 cat.) (p=0.0002), baseline diabetes status (3 cat.) (p=0.9285), baseline LVEF (3 cat.) (p=0.7126), sex (p=0.4488) and Treatment by sex interaction (p=0.0136).
***Wald confidence intervals.

Data taken from study 1245.121 only.
LOCF: For a missing value at week 52 the last available post-baseline value before week 52 is imputed.

Table R.1.2.4.2: 4 Responder analysis (displaying risk ratio) in KCCQ-CSS change from baseline at week 52 of > -5 points (stability) by sex - RS (LOCF-AD) - 1245.121

Subgroup Description	Placebo	Empa 10mg
Sex: Male		
Number of patients in analysis set	1411	1426
Number of analysed patients, N (%)	1297 (100.0)	1332 (100.0)
Number of patients with endpoint, N (%)	941 (72.6)	1039 (78.0)
95% confidence interval*	(70.1, 74.9)	(75.7, 80.1)
Comparison vs Placebo**		
Risk ratio (SE)		1.076 (0.024)
95% confidence interval***		(1.031, 1.124)
p-value		0.0009
Sex: Female		
Number of patients in analysis set	456	437
Number of analysed patients, N (%)	412 (100.0)	408 (100.0)
Number of patients with endpoint, N (%)	320 (77.7)	304 (74.5)
95% confidence interval*	(73.4, 81.4)	(70.1, 78.5)
Comparison vs Placebo**		
Risk ratio (SE)		0.960 (0.037)
95% confidence interval***		(0.890, 1.035)
p-value		0.2905

* Wilson confidence intervals.
** Log-linked Poisson model with robust estimate of variance includes terms for baseline KCCQ - clinical summary score (p<0.0001), age (p=0.0216), baseline eGFR (CKD-EPI) (p=0.0007), Treatment (p=0.4605), region (5 cat.) (p<0.0001), baseline diabetes status (3 cat.) (p=0.9320), baseline LVEF (3 cat.) (p=0.6978), sex (p=0.5097) and Treatment by sex interaction (p=0.0102).
***Wald confidence intervals.

Data taken from study 1245.121 only.
LOCF: For a missing value at week 52 the last available post-baseline value before week 52 is imputed.

Table R.1.2.4.2: 5 Responder analysis (displaying odds ratio) in KCCQ-CSS change from baseline at week 52 of >= 5 points (improvement) by sex - RS (LOCF-AD) - 1245.121

Subgroup Description	Placebo	Empa 10mg
Sex: Male		
Number of patients in analysis set	1411	1426
Number of analysed patients, N (%)	1297 (100.0)	1332 (100.0)
Number of patients with endpoint, N (%)	512 (39.5)	603 (45.3)
95% confidence interval*	(36.9, 42.2)	(42.6, 48.0)
Comparison vs Placebo**		
Odds ratio (SE)		1.293 (0.112)
95% confidence interval***		(1.091, 1.532)
p-value		0.0030
Sex: Female		
Number of patients in analysis set	456	437
Number of analysed patients, N (%)	412 (100.0)	408 (100.0)
Number of patients with endpoint, N (%)	205 (49.8)	203 (49.8)
95% confidence interval*	(45.0, 54.6)	(44.9, 54.6)
Comparison vs Placebo**		
Odds ratio (SE)		1.059 (0.163)
95% confidence interval***		(0.784, 1.431)
p-value		0.7078

* Wilson confidence intervals.
** Logistic regression includes terms for baseline KCCQ - clinical summary score (p<0.0001), age (p=0.0186), baseline eGFR (CKD-EPI) (p=0.7816), Treatment (p=0.0743), region (5 cat.) (p<0.0001), baseline diabetes status (3 cat.) (p=0.7894), baseline LVEF (3 cat.) (p=0.2789), sex (p=0.7467) and Treatment by sex interaction (p=0.2582).
***Wald confidence intervals.

Data taken from study 1245.121 only.
LOCF: For a missing value at week 52 the last available post-baseline value before week 52 is imputed.

Table R.1.2.4.2: 6 Responder analysis (displaying risk ratio) in KCCQ-CSS change from baseline at week 52 of >= 5 points (improvement) by sex - RS (LOCF-AD) - 1245.121

Subgroup Description	Placebo	Empa 10mg
Sex: Male		
Number of patients in analysis set	1411	1426
Number of analysed patients, N (%)	1297 (100.0)	1332 (100.0)
Number of patients with endpoint, N (%)	512 (39.5)	603 (45.3)
95% confidence interval*	(36.9, 42.2)	(42.6, 48.0)
Comparison vs Placebo**		
Risk ratio (SE)		1.125 (0.048)
95% confidence interval***		(1.035, 1.224)
p-value		0.0057
Sex: Female		
Number of patients in analysis set	456	437
Number of analysed patients, N (%)	412 (100.0)	408 (100.0)
Number of patients with endpoint, N (%)	205 (49.8)	203 (49.8)
95% confidence interval*	(45.0, 54.6)	(44.9, 54.6)
Comparison vs Placebo**		
Risk ratio (SE)		1.018 (0.068)
95% confidence interval***		(0.894, 1.160)
p-value		0.7870

* Wilson confidence intervals.
** Log-linked Poisson model with robust estimate of variance includes terms for baseline KCCQ - clinical summary score (p<0.0001), age (p=0.0380), baseline eGFR (CKD-EPI) (p=0.7912), Treatment (p=0.0848), region (5 cat.) (p<0.0001), baseline diabetes status (3 cat.) (p=0.7381), baseline LVEF (3 cat.) (p=0.2579), sex (p=0.9767) and Treatment by sex interaction (p=0.2057).
***Wald confidence intervals.

Data taken from study 1245.121 only.
LOCF: For a missing value at week 52 the last available post-baseline value before week 52 is imputed.

R.1.2.4.3

Table R.1.2.4.3: 1 Responder analysis (displaying odds ratio) in KCCQ-CSS change from baseline at week 52 of <= -5 points (deterioration) by age (2 cat.) - RS (LOCF-AD) - 1245.121

Subgroup Description	Placebo	Empa 10mg
Age [years] (2 cat.): < 65		
Number of patients in analysis set	740	675
Number of analysed patients, N (%)	675 (100.0)	635 (100.0)
Number of patients with endpoint, N (%)	158 (23.4)	123 (19.4)
95% confidence interval*	(20.4, 26.7)	(16.5, 22.6)
Comparison vs Placebo**		
Odds ratio (SE)		0.785 (0.108)
95% confidence interval***		(0.599, 1.029)
p-value		0.0801
Age [years] (2 cat.): >= 65		
Number of patients in analysis set	1127	1188
Number of analysed patients, N (%)	1034 (100.0)	1105 (100.0)
Number of patients with endpoint, N (%)	290 (28.0)	274 (24.8)
95% confidence interval*	(25.4, 30.9)	(22.3, 27.4)
Comparison vs Placebo**		
Odds ratio (SE)		0.845 (0.084)
95% confidence interval***		(0.695, 1.028)
p-value		0.0924

* Wilson confidence intervals.
** Logistic regression includes terms for baseline KCCQ - clinical summary score (p<0.0001), baseline eGFR (CKD-EPI) (p<0.0001), Treatment (p=0.0161), region (5 cat.) (p<0.0001), baseline diabetes status (3 cat.) (p=0.9644), sex (p=0.4226), baseline LVEF (3 cat.) (p=0.6975), age (2 cat.) (p=0.8459) and Treatment by age (2 cat.) interaction (p=0.6655).
***Wald confidence intervals.

Data taken from study 1245.121 only.
LOCF: For a missing value at week 52 the last available post-baseline value before week 52 is imputed.

Table R.1.2.4.3: 2 Responder analysis (displaying risk ratio) in KCCQ-CSS change from baseline at week 52 of <= -5 points (deterioration) by age (2 cat.) - RS (LOCF-AD) - 1245.121

Subgroup Description	Placebo	Empa 10mg
Age [years] (2 cat.): < 65		
Number of patients in analysis set	740	675
Number of analysed patients, N (%)	675 (100.0)	635 (100.0)
Number of patients with endpoint, N (%)	158 (23.4)	123 (19.4)
95% confidence interval*	(20.4, 26.7)	(16.5, 22.6)
Comparison vs Placebo**		
Risk ratio (SE)		0.832 (0.088)
95% confidence interval***		(0.676, 1.024)
p-value		0.0820
Age [years] (2 cat.): >= 65		
Number of patients in analysis set	1127	1188
Number of analysed patients, N (%)	1034 (100.0)	1105 (100.0)
Number of patients with endpoint, N (%)	290 (28.0)	274 (24.8)
95% confidence interval*	(25.4, 30.9)	(22.3, 27.4)
Comparison vs Placebo**		
Risk ratio (SE)		0.886 (0.063)
95% confidence interval***		(0.771, 1.018)
p-value		0.0886

* Wilson confidence intervals.
** Log-linked Poisson model with robust estimate of variance includes terms for baseline KCCQ - clinical summary score (p<0.0001), baseline eGFR (CKD-EPI) (p<0.0001), Treatment (p=0.0166), region (5 cat.) (p<0.0001), baseline diabetes status (3 cat.) (p=0.9676), sex (p=0.4017), baseline LVEF (3 cat.) (p=0.6998), age (2 cat.) (p=0.8035) and Treatment by age (2 cat.) interaction (p=0.6180).
***Wald confidence intervals.

Data taken from study 1245.121 only.
LOCF: For a missing value at week 52 the last available post-baseline value before week 52 is imputed.

Table R.1.2.4.3: 3 Responder analysis (displaying odds ratio) in KCCQ-CSS change from baseline at week 52 of > -5 points (stability) by age (2 cat.) - RS (LOCF-AD) - 1245.121

Subgroup Description	Placebo	Empa 10mg
Age [years] (2 cat.): < 65		
Number of patients in analysis set	740	675
Number of analysed patients, N (%)	675 (100.0)	635 (100.0)
Number of patients with endpoint, N (%)	517 (76.6)	512 (80.6)
95% confidence interval*	(73.3, 79.6)	(77.4, 83.5)
Comparison vs Placebo**		
Odds ratio (SE)		1.273 (0.176)
95% confidence interval***		(0.971, 1.669)
p-value		0.0801
Age [years] (2 cat.): >= 65		
Number of patients in analysis set	1127	1188
Number of analysed patients, N (%)	1034 (100.0)	1105 (100.0)
Number of patients with endpoint, N (%)	744 (72.0)	831 (75.2)
95% confidence interval*	(69.1, 74.6)	(72.6, 77.7)
Comparison vs Placebo**		
Odds ratio (SE)		1.183 (0.118)
95% confidence interval***		(0.973, 1.438)
p-value		0.0924

* Wilson confidence intervals.
** Logistic regression includes terms for baseline KCCQ - clinical summary score (p<0.0001), baseline eGFR (CKD-EPI) (p<0.0001), Treatment (p=0.0161), region (5 cat.) (p<0.0001), baseline diabetes status (3 cat.) (p=0.9644), sex (p=0.4226), baseline LVEF (3 cat.) (p=0.6975), age (2 cat.) (p=0.8459) and Treatment by age (2 cat.) interaction (p=0.6655).
***Wald confidence intervals.

Data taken from study 1245.121 only.
LOCF: For a missing value at week 52 the last available post-baseline value before week 52 is imputed.

Table R.1.2.4.3: 4 Responder analysis (displaying risk ratio) in KCCQ-CSS change from baseline at week 52 of > -5 points (stability) by age (2 cat.) - RS (LOCF-AD) - 1245.121

Subgroup Description	Placebo	Empa 10mg
Age [years] (2 cat.): < 65		
Number of patients in analysis set	740	675
Number of analysed patients, N (%)	675 (100.0)	635 (100.0)
Number of patients with endpoint, N (%)	517 (76.6)	512 (80.6)
95% confidence interval*	(73.3, 79.6)	(77.4, 83.5)
Comparison vs Placebo**		
Risk ratio (SE)		1.050 (0.030)
95% confidence interval***		(0.992, 1.110)
p-value		0.0905
Age [years] (2 cat.): >= 65		
Number of patients in analysis set	1127	1188
Number of analysed patients, N (%)	1034 (100.0)	1105 (100.0)
Number of patients with endpoint, N (%)	744 (72.0)	831 (75.2)
95% confidence interval*	(69.1, 74.6)	(72.6, 77.7)
Comparison vs Placebo**		
Risk ratio (SE)		1.043 (0.027)
95% confidence interval***		(0.992, 1.097)
p-value		0.0984

* Wilson confidence intervals.
** Log-linked Poisson model with robust estimate of variance includes terms for baseline KCCQ - clinical summary score (p<0.0001), baseline eGFR (CKD-EPI) (p<0.0001), Treatment (p=0.0179), region (5 cat.) (p<0.0001), baseline diabetes status (3 cat.) (p=0.9567), sex (p=0.4577), baseline LVEF (3 cat.) (p=0.6672), age (2 cat.) (p=0.9338) and Treatment by age (2 cat.) interaction (p=0.8709).
***Wald confidence intervals.

Data taken from study 1245.121 only.
LOCF: For a missing value at week 52 the last available post-baseline value before week 52 is imputed.

Table R.1.2.4.3: 5 Responder analysis (displaying odds ratio) in KCCQ-CSS change from baseline at week 52 of >= 5 points (improvement) by age (2 cat.) - RS (LOCF-AD) - 1245.121

Subgroup Description	Placebo	Empa 10mg
Age [years] (2 cat.): < 65		
Number of patients in analysis set	740	675
Number of analysed patients, N (%)	675 (100.0)	635 (100.0)
Number of patients with endpoint, N (%)	297 (44.0)	322 (50.7)
95% confidence interval*	(40.3, 47.8)	(46.8, 54.6)
Comparison vs Placebo**		
Odds ratio (SE)		1.339 (0.164)
95% confidence interval***		(1.053, 1.702)
p-value		0.0171
Age [years] (2 cat.): >= 65		
Number of patients in analysis set	1127	1188
Number of analysed patients, N (%)	1034 (100.0)	1105 (100.0)
Number of patients with endpoint, N (%)	420 (40.6)	484 (43.8)
95% confidence interval*	(37.7, 43.6)	(40.9, 46.7)
Comparison vs Placebo**		
Odds ratio (SE)		1.167 (0.111)
95% confidence interval***		(0.968, 1.408)
p-value		0.1051

* Wilson confidence intervals.
** Logistic regression includes terms for baseline KCCQ - clinical summary score (p<0.0001), baseline eGFR (CKD-EPI) (p=0.2541), Treatment (p=0.0040), region (5 cat.) (p<0.0001), baseline diabetes status (3 cat.) (p=0.8399), sex (p=0.6818), baseline LVEF (3 cat.) (p=0.3459), age (2 cat.) (p=0.4024) and Treatment by age (2 cat.) interaction (p=0.3771).
***Wald confidence intervals.

Data taken from study 1245.121 only.
LOCF: For a missing value at week 52 the last available post-baseline value before week 52 is imputed.

Table R.1.2.4.3: 6 Responder analysis (displaying risk ratio) in KCCQ-CSS change from baseline at week 52 of >= 5 points (improvement) by age (2 cat.) - RS (LOCF-AD) - 1245.121

Subgroup Description	Placebo	Empa 10mg
Age [years] (2 cat.): < 65		
Number of patients in analysis set	740	675
Number of analysed patients, N (%)	675 (100.0)	635 (100.0)
Number of patients with endpoint, N (%)	297 (44.0)	322 (50.7)
95% confidence interval*	(40.3, 47.8)	(46.8, 54.6)
Comparison vs Placebo**		
Risk ratio (SE)		1.129 (0.063)
95% confidence interval***		(1.013, 1.259)
p-value		0.0282
Age [years] (2 cat.): >= 65		
Number of patients in analysis set	1127	1188
Number of analysed patients, N (%)	1034 (100.0)	1105 (100.0)
Number of patients with endpoint, N (%)	420 (40.6)	484 (43.8)
95% confidence interval*	(37.7, 43.6)	(40.9, 46.7)
Comparison vs Placebo**		
Risk ratio (SE)		1.069 (0.050)
95% confidence interval***		(0.975, 1.173)
p-value		0.1554

* Wilson confidence intervals.
** Log-linked Poisson model with robust estimate of variance includes terms for baseline KCCQ - clinical summary score (p<0.0001), baseline eGFR (CKD-EPI) (p=0.3000), Treatment (p=0.0094), region (5 cat.) (p<0.0001), baseline diabetes status (3 cat.) (p=0.7771), sex (p=0.8627), baseline LVEF (3 cat.) (p=0.3132), age (2 cat.) (p=0.5438) and Treatment by age (2 cat.) interaction (p=0.4528).
***Wald confidence intervals.

Data taken from study 1245.121 only.
LOCF: For a missing value at week 52 the last available post-baseline value before week 52 is imputed.

R.1.2.4.4 Subgroup analysis by region (North America, Latin America, Europe, Asia, Other)

Table R.1.2.4.4: 1 Responder analysis (displaying odds ratio) in KCCQ-CSS change from baseline at week 52 of <= -5 points (deterioration) by region - RS (LOCF-AD) - 1245.121

Subgroup Description	Placebo	Empa 10mg
Region (5 cat.): North America		
Number of patients in analysis set	213	212
Number of analysed patients, N (%)	192 (100.0)	204 (100.0)
Number of patients with endpoint, N (%)	53 (27.6)	52 (25.5)
95% confidence interval*	(21.8, 34.3)	(20.0, 31.9)
Comparison vs Placebo**		
Odds ratio (SE)		0.857 (0.199)
95% confidence interval***		(0.544, 1.350)
p-value		0.5058
Region (5 cat.): Latin America		
Number of patients in analysis set	645	641
Number of analysed patients, N (%)	577 (100.0)	586 (100.0)
Number of patients with endpoint, N (%)	131 (22.7)	122 (20.8)
95% confidence interval*	(19.5, 26.3)	(17.7, 24.3)
Comparison vs Placebo**		
Odds ratio (SE)		0.898 (0.130)
95% confidence interval***		(0.676, 1.192)
p-value		0.4555

* Wilson confidence intervals.
** Logistic regression includes terms for baseline KCCQ - clinical summary score (p<0.0001), age (p=0.0149), baseline eGFR (CKD-EPI) (p=0.0006), Treatment (p=0.0022), baseline diabetes status (3 cat.) (p=0.9112), sex (p=0.4837), baseline LVEF (3 cat.) (p=0.6893), region (5 cat.) (p=0.0001) and Treatment by region (5 cat.) interaction (p=0.2298).
***Wald confidence intervals.

Data taken from study 1245.121 only.
LOCF: For a missing value at week 52 the last available post-baseline value before week 52 is imputed.

Table R.1.2.4.4: 1 Responder analysis (displaying odds ratio) in KCCQ-CSS change from baseline at week 52 of <= -5 points (deterioration) by region - RS (LOCF-AD) - 1245.121

Subgroup Description	Placebo	Empa 10mg
Region (5 cat.): Europe		
Number of patients in analysis set	677	676
Number of analysed patients, N (%)	631 (100.0)	638 (100.0)
Number of patients with endpoint, N (%)	191 (30.3)	167 (26.2)
95% confidence interval*	(26.8, 34.0)	(22.9, 29.7)
Comparison vs Placebo**		
Odds ratio (SE)		0.800 (0.101)
95% confidence interval***		(0.624, 1.026)
p-value		0.0787
Region (5 cat.): Asia		
Number of patients in analysis set	245	248
Number of analysed patients, N (%)	232 (100.0)	236 (100.0)
Number of patients with endpoint, N (%)	59 (25.4)	53 (22.5)
95% confidence interval*	(20.3, 31.4)	(17.6, 28.2)
Comparison vs Placebo**		
Odds ratio (SE)		0.864 (0.189)
95% confidence interval***		(0.562, 1.327)
p-value		0.5034

* Wilson confidence intervals.
** Logistic regression includes terms for baseline KCCQ - clinical summary score (p<0.0001), age (p=0.0149), baseline eGFR (CKD-EPI) (p=0.0006), Treatment (p=0.0022), baseline diabetes status (3 cat.) (p=0.9112), sex (p=0.4837), baseline LVEF (3 cat.) (p=0.6893), region (5 cat.) (p=0.0001) and Treatment by region (5 cat.) interaction (p=0.2298).
***Wald confidence intervals.

Data taken from study 1245.121 only.
LOCF: For a missing value at week 52 the last available post-baseline value before week 52 is imputed.

Table R.1.2.4.4: 1 Responder analysis (displaying odds ratio) in KCCQ-CSS change from baseline at week 52 of <= -5 points (deterioration) by region - RS (LOCF-AD) - 1245.121

Subgroup Description	Placebo	Empa 10mg
Region (5 cat.): Other		
Number of patients in analysis set	87	86
Number of analysed patients, N (%)	77 (100.0)	76 (100.0)
Number of patients with endpoint, N (%)	14 (18.2)	3 (3.9)
95% confidence interval*	(11.2, 28.2)	(1.4, 11.0)
Comparison vs Placebo**		
Odds ratio (SE)		0.184 (0.122)
95% confidence interval***		(0.050, 0.673)
p-value		0.0105

* Wilson confidence intervals.
** Logistic regression includes terms for baseline KCCQ - clinical summary score (p<0.0001), age (p=0.0149), baseline eGFR (CKD-EPI) (p=0.0006), Treatment (p=0.0022), baseline diabetes status (3 cat.) (p=0.9112), sex (p=0.4837), baseline LVEF (3 cat.) (p=0.6893), region (5 cat.) (p=0.0001) and Treatment by region (5 cat.) interaction (p=0.2298).
***Wald confidence intervals.

Data taken from study 1245.121 only.
LOCF: For a missing value at week 52 the last available post-baseline value before week 52 is imputed.

Table R.1.2.4.4: 2 Responder analysis (displaying risk ratio) in KCCQ-CSS change from baseline at week 52 of <= -5 points (deterioration) by region - RS (LOCF-AD) - 1245.121

Subgroup Description	Placebo	Empa 10mg
Region (5 cat.): North America		
Number of patients in analysis set	213	212
Number of analysed patients, N (%)	192 (100.0)	204 (100.0)
Number of patients with endpoint, N (%)	53 (27.6)	52 (25.5)
95% confidence interval*	(21.8, 34.3)	(20.0, 31.9)
Comparison vs Placebo**		
Risk ratio (SE)		0.896 (0.149)
95% confidence interval***		(0.647, 1.241)
p-value		0.5100
Region (5 cat.): Latin America		
Number of patients in analysis set	645	641
Number of analysed patients, N (%)	577 (100.0)	586 (100.0)
Number of patients with endpoint, N (%)	131 (22.7)	122 (20.8)
95% confidence interval*	(19.5, 26.3)	(17.7, 24.3)
Comparison vs Placebo**		
Risk ratio (SE)		0.920 (0.101)
95% confidence interval***		(0.743, 1.141)
p-value		0.4485

* Wilson confidence intervals.
** Log-linked Poisson model with robust estimate of variance includes terms for baseline KCCQ - clinical summary score (p<0.0001), age (p=0.0154), baseline eGFR (CKD-EPI) (p=0.0008), Treatment (p=0.0030), baseline diabetes status (3 cat.) (p=0.9145), sex (p=0.4639), baseline LVEF (3 cat.) (p=0.6818), region (5 cat.) (p=0.0003) and Treatment by region (5 cat.) interaction (p=0.2369).
***Wald confidence intervals.

Data taken from study 1245.121 only.
LOCF: For a missing value at week 52 the last available post-baseline value before week 52 is imputed.

Table R.1.2.4.4: 2 Responder analysis (displaying risk ratio) in KCCQ-CSS change from baseline at week 52 of <= -5 points (deterioration) by region - RS (LOCF-AD) - 1245.121

Subgroup Description	Placebo	Empa 10mg
Region (5 cat.): Europe		
Number of patients in analysis set	677	676
Number of analysed patients, N (%)	631 (100.0)	638 (100.0)
Number of patients with endpoint, N (%)	191 (30.3)	167 (26.2)
95% confidence interval*	(26.8, 34.0)	(22.9, 29.7)
Comparison vs Placebo**		
Risk ratio (SE)		0.855 (0.075)
95% confidence interval***		(0.720, 1.016)
p-value		0.0758
Region (5 cat.): Asia		
Number of patients in analysis set	245	248
Number of analysed patients, N (%)	232 (100.0)	236 (100.0)
Number of patients with endpoint, N (%)	59 (25.4)	53 (22.5)
95% confidence interval*	(20.3, 31.4)	(17.6, 28.2)
Comparison vs Placebo**		
Risk ratio (SE)		0.895 (0.148)
95% confidence interval***		(0.648, 1.237)
p-value		0.5028

* Wilson confidence intervals.
** Log-linked Poisson model with robust estimate of variance includes terms for baseline KCCQ - clinical summary score (p<0.0001), age (p=0.0154), baseline eGFR (CKD-EPI) (p=0.0008), Treatment (p=0.0030), baseline diabetes status (3 cat.) (p=0.9145), sex (p=0.4639), baseline LVEF (3 cat.) (p=0.6818), region (5 cat.) (p=0.0003) and Treatment by region (5 cat.) interaction (p=0.2369).
***Wald confidence intervals.

Data taken from study 1245.121 only.
LOCF: For a missing value at week 52 the last available post-baseline value before week 52 is imputed.

Table R.1.2.4.4: 2 Responder analysis (displaying risk ratio) in KCCQ-CSS change from baseline at week 52 of <= -5 points (deterioration) by region - RS (LOCF-AD) - 1245.121

Subgroup Description	Placebo	Empa 10mg
Region (5 cat.): Other		
Number of patients in analysis set	87	86
Number of analysed patients, N (%)	77 (100.0)	76 (100.0)
Number of patients with endpoint, N (%)	14 (18.2)	3 (3.9)
95% confidence interval*	(11.2, 28.2)	(1.4, 11.0)
Comparison vs Placebo**		
Risk ratio (SE)		0.219 (0.133)
95% confidence interval***		(0.067, 0.720)
p-value		0.0123

* Wilson confidence intervals.
** Log-linked Poisson model with robust estimate of variance includes terms for baseline KCCQ - clinical summary score (p<0.0001), age (p=0.0154), baseline eGFR (CKD-EPI) (p=0.0008), Treatment (p=0.0030), baseline diabetes status (3 cat.) (p=0.9145), sex (p=0.4639), baseline LVEF (3 cat.) (p=0.6818), region (5 cat.) (p=0.0003) and Treatment by region (5 cat.) interaction (p=0.2369).
***Wald confidence intervals.

Data taken from study 1245.121 only.
LOCF: For a missing value at week 52 the last available post-baseline value before week 52 is imputed.

Table R.1.2.4.4: 3 Responder analysis (displaying odds ratio) in KCCQ-CSS change from baseline at week 52 of > -5 points (stability) by region - RS (LOCF-AD) - 1245.121

Subgroup Description	Placebo	Empa 10mg
Region (5 cat.): North America		
Number of patients in analysis set	213	212
Number of analysed patients, N (%)	192 (100.0)	204 (100.0)
Number of patients with endpoint, N (%)	139 (72.4)	152 (74.5)
95% confidence interval*	(65.7, 78.2)	(68.1, 80.0)
Comparison vs Placebo**		
Odds ratio (SE)		1.167 (0.270)
95% confidence interval***		(0.741, 1.838)
p-value		0.5058
Region (5 cat.): Latin America		
Number of patients in analysis set	645	641
Number of analysed patients, N (%)	577 (100.0)	586 (100.0)
Number of patients with endpoint, N (%)	446 (77.3)	464 (79.2)
95% confidence interval*	(73.7, 80.5)	(75.7, 82.3)
Comparison vs Placebo**		
Odds ratio (SE)		1.114 (0.161)
95% confidence interval***		(0.839, 1.479)
p-value		0.4555

* Wilson confidence intervals.
** Logistic regression includes terms for baseline KCCQ - clinical summary score (p<0.0001), age (p=0.0149), baseline eGFR (CKD-EPI) (p=0.0006), Treatment (p=0.0022), baseline diabetes status (3 cat.) (p=0.9112), sex (p=0.4837), baseline LVEF (3 cat.) (p=0.6893), region (5 cat.) (p=0.0001) and Treatment by region (5 cat.) interaction (p=0.2298).
***Wald confidence intervals.

Data taken from study 1245.121 only.
LOCF: For a missing value at week 52 the last available post-baseline value before week 52 is imputed.

Table R.1.2.4.4: 3 Responder analysis (displaying odds ratio) in KCCQ-CSS change from baseline at week 52 of > -5 points (stability) by region - RS (LOCF-AD) - 1245.121

Subgroup Description	Placebo	Empa 10mg
Region (5 cat.): Europe		
Number of patients in analysis set	677	676
Number of analysed patients, N (%)	631 (100.0)	638 (100.0)
Number of patients with endpoint, N (%)	440 (69.7)	471 (73.8)
95% confidence interval*	(66.0, 73.2)	(70.3, 77.1)
Comparison vs Placebo**		
Odds ratio (SE)		1.250 (0.158)
95% confidence interval***		(0.975, 1.602)
p-value		0.0787
Region (5 cat.): Asia		
Number of patients in analysis set	245	248
Number of analysed patients, N (%)	232 (100.0)	236 (100.0)
Number of patients with endpoint, N (%)	173 (74.6)	183 (77.5)
95% confidence interval*	(68.6, 79.7)	(71.8, 82.4)
Comparison vs Placebo**		
Odds ratio (SE)		1.158 (0.254)
95% confidence interval***		(0.753, 1.780)
p-value		0.5034

* Wilson confidence intervals.
** Logistic regression includes terms for baseline KCCQ - clinical summary score (p<0.0001), age (p=0.0149), baseline eGFR (CKD-EPI) (p=0.0006), Treatment (p=0.0022), baseline diabetes status (3 cat.) (p=0.9112), sex (p=0.4837), baseline LVEF (3 cat.) (p=0.6893), region (5 cat.) (p=0.0001) and Treatment by region (5 cat.) interaction (p=0.2298).
***Wald confidence intervals.

Data taken from study 1245.121 only.
LOCF: For a missing value at week 52 the last available post-baseline value before week 52 is imputed.

Table R.1.2.4.4: 3 Responder analysis (displaying odds ratio) in KCCQ-CSS change from baseline at week 52 of > -5 points (stability) by region - RS (LOCF-AD) - 1245.121

Subgroup Description	Placebo	Empa 10mg
Region (5 cat.): Other		
Number of patients in analysis set	87	86
Number of analysed patients, N (%)	77 (100.0)	76 (100.0)
Number of patients with endpoint, N (%)	63 (81.8)	73 (96.1)
95% confidence interval*	(71.8, 88.8)	(89.0, 98.6)
Comparison vs Placebo**		
Odds ratio (SE)		5.438 (3.598)
95% confidence interval***		(1.487,19.890)
p-value		0.0105

* Wilson confidence intervals.
** Logistic regression includes terms for baseline KCCQ - clinical summary score (p<0.0001), age (p=0.0149), baseline eGFR (CKD-EPI) (p=0.0006), Treatment (p=0.0022), baseline diabetes status (3 cat.) (p=0.9112), sex (p=0.4837), baseline LVEF (3 cat.) (p=0.6893), region (5 cat.) (p=0.0001) and Treatment by region (5 cat.) interaction (p=0.2298).
***Wald confidence intervals.

Data taken from study 1245.121 only.
LOCF: For a missing value at week 52 the last available post-baseline value before week 52 is imputed.

Table R.1.2.4.4: 4 Responder analysis (displaying risk ratio) in KCCQ-CSS change from baseline at week 52 of > -5 points (stability) by region - RS (LOCF-AD) - 1245.121

Subgroup Description	Placebo	Empa 10mg
Region (5 cat.): North America		
Number of patients in analysis set	213	212
Number of analysed patients, N (%)	192 (100.0)	204 (100.0)
Number of patients with endpoint, N (%)	139 (72.4)	152 (74.5)
95% confidence interval*	(65.7, 78.2)	(68.1, 80.0)
Comparison vs Placebo**		
Risk ratio (SE)		1.041 (0.063)
95% confidence interval***		(0.925, 1.171)
p-value		0.5071
Region (5 cat.): Latin America		
Number of patients in analysis set	645	641
Number of analysed patients, N (%)	577 (100.0)	586 (100.0)
Number of patients with endpoint, N (%)	446 (77.3)	464 (79.2)
95% confidence interval*	(73.7, 80.5)	(75.7, 82.3)
Comparison vs Placebo**		
Risk ratio (SE)		1.022 (0.031)
95% confidence interval***		(0.962, 1.085)
p-value		0.4812

* Wilson confidence intervals.
** Log-linked Poisson model with robust estimate of variance includes terms for baseline KCCQ - clinical summary score (p<0.0001), age (p=0.0250), baseline eGFR (CKD-EPI) (p=0.0008), Treatment (p=0.0035), baseline diabetes status (3 cat.) (p=0.9106), sex (p=0.5083), baseline LVEF (3 cat.) (p=0.6783), region (5 cat.) (p<0.0001) and Treatment by region (5 cat.) interaction (p=0.2882).
***Wald confidence intervals.

Data taken from study 1245.121 only.
LOCF: For a missing value at week 52 the last available post-baseline value before week 52 is imputed.

Table R.1.2.4.4: 4 Responder analysis (displaying risk ratio) in KCCQ-CSS change from baseline at week 52 of > -5 points (stability) by region - RS (LOCF-AD) - 1245.121

Subgroup Description	Placebo	Empa 10mg
Region (5 cat.): Europe		
Number of patients in analysis set	677	676
Number of analysed patients, N (%)	631 (100.0)	638 (100.0)
Number of patients with endpoint, N (%)	440 (69.7)	471 (73.8)
95% confidence interval*	(66.0, 73.2)	(70.3, 77.1)
Comparison vs Placebo**		
Risk ratio (SE)		1.062 (0.037)
95% confidence interval***		(0.992, 1.137)
p-value		0.0819
Region (5 cat.): Asia		
Number of patients in analysis set	245	248
Number of analysed patients, N (%)	232 (100.0)	236 (100.0)
Number of patients with endpoint, N (%)	173 (74.6)	183 (77.5)
95% confidence interval*	(68.6, 79.7)	(71.8, 82.4)
Comparison vs Placebo**		
Risk ratio (SE)		1.033 (0.054)
95% confidence interval***		(0.933, 1.144)
p-value		0.5291

* Wilson confidence intervals.
** Log-linked Poisson model with robust estimate of variance includes terms for baseline KCCQ - clinical summary score (p<0.0001), age (p=0.0250), baseline eGFR (CKD-EPI) (p=0.0008), Treatment (p=0.0035), baseline diabetes status (3 cat.) (p=0.9106), sex (p=0.5083), baseline LVEF (3 cat.) (p=0.6783), region (5 cat.) (p<0.0001) and Treatment by region (5 cat.) interaction (p=0.2882).
***Wald confidence intervals.

Data taken from study 1245.121 only.
LOCF: For a missing value at week 52 the last available post-baseline value before week 52 is imputed.

Table R.1.2.4.4: 4 Responder analysis (displaying risk ratio) in KCCQ-CSS change from baseline at week 52 of > -5 points (stability) by region - RS (LOCF-AD) - 1245.121

Subgroup Description	Placebo	Empa 10mg
Region (5 cat.): Other		
Number of patients in analysis set	87	86
Number of analysed patients, N (%)	77 (100.0)	76 (100.0)
Number of patients with endpoint, N (%)	63 (81.8)	73 (96.1)
95% confidence interval*	(71.8, 88.8)	(89.0, 98.6)
Comparison vs Placebo**		
Risk ratio (SE)		1.175 (0.066)
95% confidence interval***		(1.052, 1.312)
p-value		0.0043

* Wilson confidence intervals.
** Log-linked Poisson model with robust estimate of variance includes terms for baseline KCCQ - clinical summary score (p<0.0001), age (p=0.0250), baseline eGFR (CKD-EPI) (p=0.0008), Treatment (p=0.0035), baseline diabetes status (3 cat.) (p=0.9106), sex (p=0.5083), baseline LVEF (3 cat.) (p=0.6783), region (5 cat.) (p<0.0001) and Treatment by region (5 cat.) interaction (p=0.2882).
***Wald confidence intervals.

Data taken from study 1245.121 only.
LOCF: For a missing value at week 52 the last available post-baseline value before week 52 is imputed.

Table R.1.2.4.4: 5 Responder analysis (displaying odds ratio) in KCCQ-CSS change from baseline at week 52 of >= 5 points (improvement) by region - RS (LOCF-AD) - 1245.121

Subgroup Description	Placebo	Empa 10mg
Region (5 cat.): North America		
Number of patients in analysis set	213	212
Number of analysed patients, N (%)	192 (100.0)	204 (100.0)
Number of patients with endpoint, N (%)	71 (37.0)	85 (41.7)
95% confidence interval*	(30.5, 44.0)	(35.1, 48.5)
Comparison vs Placebo**		
Odds ratio (SE)		1.291 (0.291)
95% confidence interval***		(0.830, 2.009)
p-value		0.2572
Region (5 cat.): Latin America		
Number of patients in analysis set	645	641
Number of analysed patients, N (%)	577 (100.0)	586 (100.0)
Number of patients with endpoint, N (%)	295 (51.1)	324 (55.3)
95% confidence interval*	(47.1, 55.2)	(51.2, 59.3)
Comparison vs Placebo**		
Odds ratio (SE)		1.205 (0.155)
95% confidence interval***		(0.936, 1.552)
p-value		0.1469

* Wilson confidence intervals.
** Logistic regression includes terms for baseline KCCQ - clinical summary score (p<0.0001), age (p=0.0189), baseline eGFR (CKD-EPI) (p=0.8056), Treatment (p=0.0105), baseline diabetes status (3 cat.) (p=0.7793), sex (p=0.7433), baseline LVEF (3 cat.) (p=0.2635), region (5 cat.) (p<0.0001) and Treatment by region (5 cat.) interaction (p=0.9323).
***Wald confidence intervals.

Data taken from study 1245.121 only.
LOCF: For a missing value at week 52 the last available post-baseline value before week 52 is imputed.

Table R.1.2.4.4: 5 Responder analysis (displaying odds ratio) in KCCQ-CSS change from baseline at week 52 of >= 5 points (improvement) by region - RS (LOCF-AD) - 1245.121

Subgroup Description	Placebo	Empa 10mg
Region (5 cat.): Europe		
Number of patients in analysis set	677	676
Number of analysed patients, N (%)	631 (100.0)	638 (100.0)
Number of patients with endpoint, N (%)	252 (39.9)	272 (42.6)
95% confidence interval*	(36.2, 43.8)	(38.9, 46.5)
Comparison vs Placebo**		
Odds ratio (SE)		1.165 (0.143)
95% confidence interval***		(0.916, 1.483)
p-value		0.2134
Region (5 cat.): Asia		
Number of patients in analysis set	245	248
Number of analysed patients, N (%)	232 (100.0)	236 (100.0)
Number of patients with endpoint, N (%)	60 (25.9)	81 (34.3)
95% confidence interval*	(20.7, 31.9)	(28.6, 40.6)
Comparison vs Placebo**		
Odds ratio (SE)		1.424 (0.305)
95% confidence interval***		(0.936, 2.166)
p-value		0.0989

* Wilson confidence intervals.
** Logistic regression includes terms for baseline KCCQ - clinical summary score (p<0.0001), age (p=0.0189), baseline eGFR (CKD-EPI) (p=0.8056), Treatment (p=0.0105), baseline diabetes status (3 cat.) (p=0.7793), sex (p=0.7433), baseline LVEF (3 cat.) (p=0.2635), region (5 cat.) (p<0.0001) and Treatment by region (5 cat.) interaction (p=0.9323).
***Wald confidence intervals.

Data taken from study 1245.121 only.
LOCF: For a missing value at week 52 the last available post-baseline value before week 52 is imputed.

Table R.1.2.4.4: 5 Responder analysis (displaying odds ratio) in KCCQ-CSS change from baseline at week 52 of >= 5 points (improvement) by region - RS (LOCF-AD) - 1245.121

Subgroup Description	Placebo	Empa 10mg
Region (5 cat.): Other		
Number of patients in analysis set	87	86
Number of analysed patients, N (%)	77 (100.0)	76 (100.0)
Number of patients with endpoint, N (%)	39 (50.6)	44 (57.9)
95% confidence interval*	(39.7, 61.5)	(46.7, 68.4)
Comparison vs Placebo**		
Odds ratio (SE)		1.382 (0.475)
95% confidence interval***		(0.704, 2.712)
p-value		0.3472

* Wilson confidence intervals.
** Logistic regression includes terms for baseline KCCQ - clinical summary score (p<0.0001), age (p=0.0189), baseline eGFR (CKD-EPI) (p=0.8056), Treatment (p=0.0105), baseline diabetes status (3 cat.) (p=0.7793), sex (p=0.7433), baseline LVEF (3 cat.) (p=0.2635), region (5 cat.) (p<0.0001) and Treatment by region (5 cat.) interaction (p=0.9323).
***Wald confidence intervals.

Data taken from study 1245.121 only.
LOCF: For a missing value at week 52 the last available post-baseline value before week 52 is imputed.

Table R.1.2.4.4: 6 Responder analysis (displaying risk ratio) in KCCQ-CSS change from baseline at week 52 of >= 5 points (improvement) by region - RS (LOCF-AD) - 1245.121

Subgroup Description	Placebo	Empa 10mg
Region (5 cat.): North America		
Number of patients in analysis set	213	212
Number of analysed patients, N (%)	192 (100.0)	204 (100.0)
Number of patients with endpoint, N (%)	71 (37.0)	85 (41.7)
95% confidence interval*	(30.5, 44.0)	(35.1, 48.5)
Comparison vs Placebo**		
Risk ratio (SE)		1.140 (0.136)
95% confidence interval***		(0.903, 1.440)
p-value		0.2693
Region (5 cat.): Latin America		
Number of patients in analysis set	645	641
Number of analysed patients, N (%)	577 (100.0)	586 (100.0)
Number of patients with endpoint, N (%)	295 (51.1)	324 (55.3)
95% confidence interval*	(47.1, 55.2)	(51.2, 59.3)
Comparison vs Placebo**		
Risk ratio (SE)		1.059 (0.056)
95% confidence interval***		(0.955, 1.174)
p-value		0.2781

* Wilson confidence intervals.
** Log-linked Poisson model with robust estimate of variance includes terms for baseline KCCQ - clinical summary score (p<0.0001), age (p=0.0381), baseline eGFR (CKD-EPI) (p=0.8194), Treatment (p=0.0063), baseline diabetes status (3 cat.) (p=0.7313), sex (p=0.9258), baseline LVEF (3 cat.) (p=0.2363), region (5 cat.) (p<0.0001) and Treatment by region (5 cat.) interaction (p=0.7277).
***Wald confidence intervals.

Data taken from study 1245.121 only.
LOCF: For a missing value at week 52 the last available post-baseline value before week 52 is imputed.

Table R.1.2.4.4: 6 Responder analysis (displaying risk ratio) in KCCQ-CSS change from baseline at week 52 of >= 5 points (improvement) by region - RS (LOCF-AD) - 1245.121

Subgroup Description	Placebo	Empa 10mg
Region (5 cat.): Europe		
Number of patients in analysis set	677	676
Number of analysed patients, N (%)	631 (100.0)	638 (100.0)
Number of patients with endpoint, N (%)	252 (39.9)	272 (42.6)
95% confidence interval*	(36.2, 43.8)	(38.9, 46.5)
Comparison vs Placebo**		
Risk ratio (SE)		1.073 (0.068)
95% confidence interval***		(0.947, 1.215)
p-value		0.2704
Region (5 cat.): Asia		
Number of patients in analysis set	245	248
Number of analysed patients, N (%)	232 (100.0)	236 (100.0)
Number of patients with endpoint, N (%)	60 (25.9)	81 (34.3)
95% confidence interval*	(20.7, 31.9)	(28.6, 40.6)
Comparison vs Placebo**		
Risk ratio (SE)		1.264 (0.169)
95% confidence interval***		(0.972, 1.643)
p-value		0.0803

* Wilson confidence intervals.
** Log-linked Poisson model with robust estimate of variance includes terms for baseline KCCQ - clinical summary score (p<0.0001), age (p=0.0381), baseline eGFR (CKD-EPI) (p=0.8194), Treatment (p=0.0063), baseline diabetes status (3 cat.) (p=0.7313), sex (p=0.9258), baseline LVEF (3 cat.) (p=0.2363), region (5 cat.) (p<0.0001) and Treatment by region (5 cat.) interaction (p=0.7277).
***Wald confidence intervals.

Data taken from study 1245.121 only.
LOCF: For a missing value at week 52 the last available post-baseline value before week 52 is imputed.

Table R.1.2.4.4: 6 Responder analysis (displaying risk ratio) in KCCQ-CSS change from baseline at week 52 of >= 5 points (improvement) by region - RS (LOCF-AD) - 1245.121

Subgroup Description	Placebo	Empa 10mg
Region (5 cat.): Other		
Number of patients in analysis set	87	86
Number of analysed patients, N (%)	77 (100.0)	76 (100.0)
Number of patients with endpoint, N (%)	39 (50.6)	44 (57.9)
95% confidence interval*	(39.7, 61.5)	(46.7, 68.4)
Comparison vs Placebo**		
Risk ratio (SE)		1.174 (0.158)
95% confidence interval***		(0.901, 1.529)
p-value		0.2342

* Wilson confidence intervals.
** Log-linked Poisson model with robust estimate of variance includes terms for baseline KCCQ - clinical summary score (p<0.0001), age (p=0.0381), baseline eGFR (CKD-EPI) (p=0.8194), Treatment (p=0.0063), baseline diabetes status (3 cat.) (p=0.7313), sex (p=0.9258), baseline LVEF (3 cat.) (p=0.2363), region (5 cat.) (p<0.0001) and Treatment by region (5 cat.) interaction (p=0.7277).
***Wald confidence intervals.

Data taken from study 1245.121 only.
LOCF: For a missing value at week 52 the last available post-baseline value before week 52 is imputed.

R.1.2.4.5

R.1.2.4.5 Subgroup analysis by OECD (N/Y)

Table R.1.2.4.5: 1 Responder analysis (displaying odds ratio) in KCCQ-CSS change from baseline at week 52 of <= -5 points (deterioration) by OECD member (N/Y) - RS (LOCF-AD) - 1245.121

Subgroup Description	Placebo	Empa 10mg
OECD member: No		
Number of patients in analysis set	741	713
Number of analysed patients, N (%)	663 (100.0)	647 (100.0)
Number of patients with endpoint, N (%)	147 (22.2)	121 (18.7)
95% confidence interval*	(19.2, 25.5)	(15.9, 21.9)
Comparison vs Placebo**		
Odds ratio (SE)		0.807 (0.113)
95% confidence interval***		(0.614, 1.062)
p-value		0.1259
OECD member: Yes		
Number of patients in analysis set	1126	1150
Number of analysed patients, N (%)	1046 (100.0)	1093 (100.0)
Number of patients with endpoint, N (%)	301 (28.8)	276 (25.3)
95% confidence interval*	(26.1, 31.6)	(22.8, 27.9)
Comparison vs Placebo**		
Odds ratio (SE)		0.826 (0.082)
95% confidence interval***		(0.680, 1.002)
p-value		0.0529

* Wilson confidence intervals.
** Logistic regression includes terms for baseline KCCQ - clinical summary score (p<0.0001), age (p=0.0084), baseline eGFR (CKD-EPI) (p=0.0003), Treatment (p=0.0178), sex (p=0.4397), baseline diabetes status (3 cat.) (p=0.8370), baseline LVEF (3 cat.) (p=0.7980), OECD member (p=0.0124) and Treatment by OECD member interaction (p=0.8961).
***Wald confidence intervals.

Data taken from study 1245.121 only.
LOCF: For a missing value at week 52 the last available post-baseline value before week 52 is imputed.
OECD member (yes/no) countries included:
Yes: United States, Canada, Mexico, Poland, Netherlands, Hungary, Germany, Czech Republic, Italy, France, Spain, United Kingdom, Belgium, Japan, Australia, 'Korea; Republic Of South Korea';
No: Brazil, Argentina, China, India.

Table R.1.2.4.5: 2 Responder analysis (displaying risk ratio) in KCCQ-CSS change from baseline at week 52 of <= -5 points (deterioration) by OECD member (N/Y) - RS (LOCF-AD) - 1245.121

Subgroup Description	Placebo	Empa 10mg
OECD member: No		
Number of patients in analysis set	741	713
Number of analysed patients, N (%)	663 (100.0)	647 (100.0)
Number of patients with endpoint, N (%)	147 (22.2)	121 (18.7)
95% confidence interval*	(19.2, 25.5)	(15.9, 21.9)
Comparison vs Placebo**		
Risk ratio (SE)		0.846 (0.091)
95% confidence interval***		(0.685, 1.046)
p-value		0.1229
OECD member: Yes		
Number of patients in analysis set	1126	1150
Number of analysed patients, N (%)	1046 (100.0)	1093 (100.0)
Number of patients with endpoint, N (%)	301 (28.8)	276 (25.3)
95% confidence interval*	(26.1, 31.6)	(22.8, 27.9)
Comparison vs Placebo**		
Risk ratio (SE)		0.873 (0.061)
95% confidence interval***		(0.760, 1.001)
p-value		0.0525

* Wilson confidence intervals.
** Log-linked Poisson model with robust estimate of variance includes terms for baseline KCCQ - clinical summary score (p<0.0001), age (p=0.0087), baseline eGFR (CKD-EPI) (p=0.0004), Treatment (p=0.0186), sex (p=0.4279), baseline diabetes status (3 cat.) (p=0.8367), baseline LVEF (3 cat.) (p=0.7988), OECD member (p=0.0119) and Treatment by OECD member interaction (p=0.8145).
***Wald confidence intervals.

Data taken from study 1245.121 only.
LOCF: For a missing value at week 52 the last available post-baseline value before week 52 is imputed.
OECD member (yes/no) countries included:
Yes: United States, Canada, Mexico, Poland, Netherlands, Hungary, Germany, Czech Republic, Italy, France, Spain, United Kingdom, Belgium, Japan, Australia, 'Korea; Republic Of South Korea';
No: Brazil, Argentina, China, India.

Table R.1.2.4.5: 3 Responder analysis (displaying odds ratio) in KCCQ-CSS change from baseline at week 52 of > -5 points (stability) by OECD member (N/Y) - RS (LOCF-AD) - 1245.121

Subgroup Description	Placebo	Empa 10mg
OECD member: No		
Number of patients in analysis set	741	713
Number of analysed patients, N (%)	663 (100.0)	647 (100.0)
Number of patients with endpoint, N (%)	516 (77.8)	526 (81.3)
95% confidence interval*	(74.5, 80.8)	(78.1, 84.1)
Comparison vs Placebo**		
Odds ratio (SE)		1.238 (0.173)
95% confidence interval***		(0.942, 1.629)
p-value		0.1259
OECD member: Yes		
Number of patients in analysis set	1126	1150
Number of analysed patients, N (%)	1046 (100.0)	1093 (100.0)
Number of patients with endpoint, N (%)	745 (71.2)	817 (74.7)
95% confidence interval*	(68.4, 73.9)	(72.1, 77.2)
Comparison vs Placebo**		
Odds ratio (SE)		1.211 (0.120)
95% confidence interval***		(0.998, 1.470)
p-value		0.0529

* Wilson confidence intervals.
** Logistic regression includes terms for baseline KCCQ - clinical summary score (p<0.0001), age (p=0.0084), baseline eGFR (CKD-EPI) (p=0.0003), Treatment (p=0.0178), sex (p=0.4397), baseline diabetes status (3 cat.) (p=0.8370), baseline LVEF (3 cat.) (p=0.7980), OECD member (p=0.0124) and Treatment by OECD member interaction (p=0.8961).
***Wald confidence intervals.

Data taken from study 1245.121 only.
LOCF: For a missing value at week 52 the last available post-baseline value before week 52 is imputed.
OECD member (yes/no) countries included:
Yes: United States, Canada, Mexico, Poland, Netherlands, Hungary, Germany, Czech Republic, Italy, France, Spain, United Kingdom, Belgium, Japan, Australia, 'Korea; Republic Of South Korea';
No: Brazil, Argentina, China, India.

Table R.1.2.4.5: 4 Responder analysis (displaying risk ratio) in KCCQ-CSS change from baseline at week 52 of > -5 points (stability) by OECD member (N/Y) - RS (LOCF-AD) - 1245.121

Subgroup Description	Placebo	Empa 10mg
OECD member: No		
Number of patients in analysis set	741	713
Number of analysed patients, N (%)	663 (100.0)	647 (100.0)
Number of patients with endpoint, N (%)	516 (77.8)	526 (81.3)
95% confidence interval*	(74.5, 80.8)	(78.1, 84.1)
Comparison vs Placebo**		
Risk ratio (SE)		1.042 (0.029)
95% confidence interval***		(0.987, 1.100)
p-value		0.1384
OECD member: Yes		
Number of patients in analysis set	1126	1150
Number of analysed patients, N (%)	1046 (100.0)	1093 (100.0)
Number of patients with endpoint, N (%)	745 (71.2)	817 (74.7)
95% confidence interval*	(68.4, 73.9)	(72.1, 77.2)
Comparison vs Placebo**		
Risk ratio (SE)		1.052 (0.027)
95% confidence interval***		(0.999, 1.107)
p-value		0.0523

* Wilson confidence intervals.
** Log-linked Poisson model with robust estimate of variance includes terms for baseline KCCQ - clinical summary score (p<0.0001), age (p=0.0128), baseline eGFR (CKD-EPI) (p=0.0004), Treatment (p=0.0160), sex (p=0.4507), baseline diabetes status (3 cat.) (p=0.8427), baseline LVEF (3 cat.) (p=0.7728), OECD member (p=0.0144) and Treatment by OECD member interaction (p=0.8004).
***Wald confidence intervals.

Data taken from study 1245.121 only.
LOCF: For a missing value at week 52 the last available post-baseline value before week 52 is imputed.
OECD member (yes/no) countries included:
Yes: United States, Canada, Mexico, Poland, Netherlands, Hungary, Germany, Czech Republic, Italy, France, Spain, United Kingdom, Belgium, Japan, Australia, 'Korea; Republic Of South Korea';
No: Brazil, Argentina, China, India.

Table R.1.2.4.5: 5 Responder analysis (displaying odds ratio) in KCCQ-CSS change from baseline at week 52 of >= 5 points (improvement) by OECD member (N/Y) - RS (LOCF-AD) - 1245.121

Subgroup Description	Placebo	Empa 10mg
OECD member: No		
Number of patients in analysis set	741	713
Number of analysed patients, N (%)	663 (100.0)	647 (100.0)
Number of patients with endpoint, N (%)	323 (48.7)	358 (55.3)
95% confidence interval*	(44.9, 52.5)	(51.5, 59.1)
Comparison vs Placebo**		
Odds ratio (SE)		1.345 (0.163)
95% confidence interval***		(1.060, 1.706)
p-value		0.0145
OECD member: Yes		
Number of patients in analysis set	1126	1150
Number of analysed patients, N (%)	1046 (100.0)	1093 (100.0)
Number of patients with endpoint, N (%)	394 (37.7)	448 (41.0)
95% confidence interval*	(34.8, 40.6)	(38.1, 43.9)
Comparison vs Placebo**		
Odds ratio (SE)		1.176 (0.113)
95% confidence interval***		(0.974, 1.419)
p-value		0.0914

* Wilson confidence intervals.
** Logistic regression includes terms for baseline KCCQ - clinical summary score (p<0.0001), age (p=0.0156), baseline eGFR (CKD-EPI) (p=0.8531), Treatment (p=0.0030), sex (p=0.7260), baseline diabetes status (3 cat.) (p=0.7395), baseline LVEF (3 cat.) (p=0.2595), OECD member (p<0.0001) and Treatment by OECD member interaction (p=0.3847).
***Wald confidence intervals.

Data taken from study 1245.121 only.
LOCF: For a missing value at week 52 the last available post-baseline value before week 52 is imputed.
OECD member (yes/no) countries included:
Yes: United States, Canada, Mexico, Poland, Netherlands, Hungary, Germany, Czech Republic, Italy, France, Spain, United Kingdom, Belgium, Japan, Australia, 'Korea; Republic Of South Korea';
No: Brazil, Argentina, China, India.

Table R.1.2.4.5: 6 Responder analysis (displaying risk ratio) in KCCQ-CSS change from baseline at week 52 of >= 5 points (improvement) by OECD member (N/Y) - RS (LOCF-AD) - 1245.121

Subgroup Description	Placebo	Empa 10mg
OECD member: No		
Number of patients in analysis set	741	713
Number of analysed patients, N (%)	663 (100.0)	647 (100.0)
Number of patients with endpoint, N (%)	323 (48.7)	358 (55.3)
95% confidence interval*	(44.9, 52.5)	(51.5, 59.1)
Comparison vs Placebo**		
Risk ratio (SE)		1.111 (0.056)
95% confidence interval***		(1.007, 1.227)
p-value		0.0359
OECD member: Yes		
Number of patients in analysis set	1126	1150
Number of analysed patients, N (%)	1046 (100.0)	1093 (100.0)
Number of patients with endpoint, N (%)	394 (37.7)	448 (41.0)
95% confidence interval*	(34.8, 40.6)	(38.1, 43.9)
Comparison vs Placebo**		
Risk ratio (SE)		1.085 (0.055)
95% confidence interval***		(0.982, 1.199)
p-value		0.1069

* Wilson confidence intervals.
** Log-linked Poisson model with robust estimate of variance includes terms for baseline KCCQ - clinical summary score (p<0.0001), age (p=0.0315), baseline eGFR (CKD-EPI) (p=0.8896), Treatment (p=0.0087), sex (p=0.8932), baseline diabetes status (3 cat.) (p=0.7645), baseline LVEF (3 cat.) (p=0.2874), OECD member (p<0.0001) and Treatment by OECD member interaction (p=0.7403).
***Wald confidence intervals.

Data taken from study 1245.121 only.
LOCF: For a missing value at week 52 the last available post-baseline value before week 52 is imputed.
OECD member (yes/no) countries included:
Yes: United States, Canada, Mexico, Poland, Netherlands, Hungary, Germany, Czech Republic, Italy, France, Spain, United Kingdom, Belgium, Japan, Australia, 'Korea; Republic Of South Korea';
No: Brazil, Argentina, China, India.

R.1.2.4.6 Subgroup analysis by NYHA at baseline (II, III/IV - 2 cat.)

Table R.1.2.4.6: 1 Responder analysis (displaying odds ratio) in KCCQ-CSS change from baseline at week 52 of <= -5 points (deterioration) by NYHA (2 cat.) - RS (LOCF-AD) - 1245.121

Subgroup Description	Placebo	Empa 10mg
Baseline NYHA (2 cat.): II		
Number of patients in analysis set	1401	1399
Number of analysed patients, N (%)	1306 (100.0)	1307 (100.0)
Number of patients with endpoint, N (%)	337 (25.8)	301 (23.0)
95% confidence interval*	(23.5, 28.2)	(20.8, 25.4)
Comparison vs Placebo**		
Odds ratio (SE)		0.833 (0.078)
95% confidence interval***		(0.695, 1.000)
p-value		0.0501
Baseline NYHA (2 cat.): III/IV		
Number of patients in analysis set	466	464
Number of analysed patients, N (%)	403 (100.0)	433 (100.0)
Number of patients with endpoint, N (%)	111 (27.5)	96 (22.2)
95% confidence interval*	(23.4, 32.1)	(18.5, 26.3)
Comparison vs Placebo**		
Odds ratio (SE)		0.772 (0.127)
95% confidence interval***		(0.559, 1.067)
p-value		0.1168

* Wilson confidence intervals.
** Logistic regression includes terms for baseline KCCQ - clinical summary score (p<0.0001), age (p=0.0158), baseline eGFR (CKD-EPI) (p=0.0008), Treatment (p=0.0198), region (5 cat.) (p=0.0002), baseline diabetes status (3 cat.) (p=0.9484), sex (p=0.4524), baseline LVEF (3 cat.) (p=0.6964), baseline NYHA (2 cat.) (p=0.0035) and Treatment by baseline NYHA (2 cat.) interaction (p=0.6881).
***Wald confidence intervals.

Data taken from study 1245.121 only.
LOCF: For a missing value at week 52 the last available post-baseline value before week 52 is imputed.

Table R.1.2.4.6: 2 Responder analysis (displaying risk ratio) in KCCQ-CSS change from baseline at week 52 of <= -5 points (deterioration) by NYHA (2 cat.) - RS (LOCF-AD) - 1245.121

Subgroup Description	Placebo	Empa 10mg
Baseline NYHA (2 cat.): II		
Number of patients in analysis set	1401	1399
Number of analysed patients, N (%)	1306 (100.0)	1307 (100.0)
Number of patients with endpoint, N (%)	337 (25.8)	301 (23.0)
95% confidence interval*	(23.5, 28.2)	(20.8, 25.4)
Comparison vs Placebo**		
Risk ratio (SE)		0.875 (0.059)
95% confidence interval***		(0.766, 1.000)
p-value		0.0494
Baseline NYHA (2 cat.): III/IV		
Number of patients in analysis set	466	464
Number of analysed patients, N (%)	403 (100.0)	433 (100.0)
Number of patients with endpoint, N (%)	111 (27.5)	96 (22.2)
95% confidence interval*	(23.4, 32.1)	(18.5, 26.3)
Comparison vs Placebo**		
Risk ratio (SE)		0.830 (0.098)
95% confidence interval***		(0.659, 1.045)
p-value		0.1134

* Wilson confidence intervals.
** Log-linked Poisson model with robust estimate of variance includes terms for baseline KCCQ - clinical summary score (p<0.0001), age (p=0.0170), baseline eGFR (CKD-EPI) (p=0.0010), Treatment (p=0.0185), region (5 cat.) (p=0.0003), baseline diabetes status (3 cat.) (p=0.9482), sex (p=0.4299), baseline LVEF (3 cat.) (p=0.6959), baseline NYHA (2 cat.) (p=0.0033) and Treatment by baseline NYHA (2 cat.) interaction (p=0.6969).
***Wald confidence intervals.

Data taken from study 1245.121 only.
LOCF: For a missing value at week 52 the last available post-baseline value before week 52 is imputed.

Table R.1.2.4.6: 3 Responder analysis (displaying odds ratio) in KCCQ-CSS change from baseline at week 52 of > -5 points (stability) by NYHA (2 cat.) - RS (LOCF-AD) - 1245.121

Subgroup Description	Placebo	Empa 10mg
Baseline NYHA (2 cat.): II		
Number of patients in analysis set	1401	1399
Number of analysed patients, N (%)	1306 (100.0)	1307 (100.0)
Number of patients with endpoint, N (%)	969 (74.2)	1006 (77.0)
95% confidence interval*	(71.8, 76.5)	(74.6, 79.2)
Comparison vs Placebo**		
Odds ratio (SE)		1.200 (0.112)
95% confidence interval***		(1.000, 1.440)
p-value		0.0501
Baseline NYHA (2 cat.): III/IV		
Number of patients in analysis set	466	464
Number of analysed patients, N (%)	403 (100.0)	433 (100.0)
Number of patients with endpoint, N (%)	292 (72.5)	337 (77.8)
95% confidence interval*	(67.9, 76.6)	(73.7, 81.5)
Comparison vs Placebo**		
Odds ratio (SE)		1.295 (0.213)
95% confidence interval***		(0.938, 1.787)
p-value		0.1168

* Wilson confidence intervals.
** Logistic regression includes terms for baseline KCCQ - clinical summary score (p<0.0001), age (p=0.0158), baseline eGFR (CKD-EPI) (p=0.0008), Treatment (p=0.0198), region (5 cat.) (p=0.0002), baseline diabetes status (3 cat.) (p=0.9484), sex (p=0.4524), baseline LVEF (3 cat.) (p=0.6964), baseline NYHA (2 cat.) (p=0.0035) and Treatment by baseline NYHA (2 cat.) interaction (p=0.6881).
***Wald confidence intervals.

Data taken from study 1245.121 only.
LOCF: For a missing value at week 52 the last available post-baseline value before week 52 is imputed.

Table R.1.2.4.6: 4 Responder analysis (displaying risk ratio) in KCCQ-CSS change from baseline at week 52 of > -5 points (stability) by NYHA (2 cat.) - RS (LOCF-AD) - 1245.121

Subgroup Description	Placebo	Empa 10mg
Baseline NYHA (2 cat.): II		
Number of patients in analysis set	1401	1399
Number of analysed patients, N (%)	1306 (100.0)	1307 (100.0)
Number of patients with endpoint, N (%)	969 (74.2)	1006 (77.0)
95% confidence interval*	(71.8, 76.5)	(74.6, 79.2)
Comparison vs Placebo**		
Risk ratio (SE)		1.044 (0.023)
95% confidence interval***		(1.000, 1.090)
p-value		0.0513
Baseline NYHA (2 cat.): III/IV		
Number of patients in analysis set	466	464
Number of analysed patients, N (%)	403 (100.0)	433 (100.0)
Number of patients with endpoint, N (%)	292 (72.5)	337 (77.8)
95% confidence interval*	(67.9, 76.6)	(73.7, 81.5)
Comparison vs Placebo**		
Risk ratio (SE)		1.062 (0.042)
95% confidence interval***		(0.984, 1.147)
p-value		0.1245

* Wilson confidence intervals.
** Log-linked Poisson model with robust estimate of variance includes terms for baseline KCCQ - clinical summary score (p<0.0001), age (p=0.0272), baseline eGFR (CKD-EPI) (p=0.0011), Treatment (p=0.0217), region (5 cat.) (p<0.0001), baseline diabetes status (3 cat.) (p=0.9570), sex (p=0.4898), baseline LVEF (3 cat.) (p=0.6798), baseline NYHA (2 cat.) (p=0.0048) and Treatment by baseline NYHA (2 cat.) interaction (p=0.6996).
***Wald confidence intervals.

Data taken from study 1245.121 only.
LOCF: For a missing value at week 52 the last available post-baseline value before week 52 is imputed.

Table R.1.2.4.6: 5 Responder analysis (displaying odds ratio) in KCCQ-CSS change from baseline at week 52 of >= 5 points (improvement) by NYHA (2 cat.) - RS (LOCF-AD) - 1245.121

Subgroup Description	Placebo	Empa 10mg
Baseline NYHA (2 cat.): II		
Number of patients in analysis set	1401	1399
Number of analysed patients, N (%)	1306 (100.0)	1307 (100.0)
Number of patients with endpoint, N (%)	518 (39.7)	573 (43.8)
95% confidence interval*	(37.0, 42.3)	(41.2, 46.5)
Comparison vs Placebo**		
Odds ratio (SE)		1.293 (0.112)
95% confidence interval***		(1.091, 1.532)
p-value		0.0030
Baseline NYHA (2 cat.): III/IV		
Number of patients in analysis set	466	464
Number of analysed patients, N (%)	403 (100.0)	433 (100.0)
Number of patients with endpoint, N (%)	199 (49.4)	233 (53.8)
95% confidence interval*	(44.5, 54.2)	(49.1, 58.5)
Comparison vs Placebo**		
Odds ratio (SE)		1.079 (0.166)
95% confidence interval***		(0.798, 1.459)
p-value		0.6210

* Wilson confidence intervals.
** Logistic regression includes terms for baseline KCCQ - clinical summary score (p<0.0001), age (p=0.0194), baseline eGFR (CKD-EPI) (p=0.8994), Treatment (p=0.0592), region (5 cat.) (p<0.0001), baseline diabetes status (3 cat.) (p=0.8150), sex (p=0.7333), baseline LVEF (3 cat.) (p=0.3008), baseline NYHA (2 cat.) (p=0.0009) and Treatment by baseline NYHA (2 cat.) interaction (p=0.3059).
***Wald confidence intervals.

Data taken from study 1245.121 only.
LOCF: For a missing value at week 52 the last available post-baseline value before week 52 is imputed.

Table R.1.2.4.6: 6 Responder analysis (displaying risk ratio) in KCCQ-CSS change from baseline at week 52 of >= 5 points (improvement) by NYHA (2 cat.) - RS (LOCF-AD) - 1245.121

Subgroup Description	Placebo	Empa 10mg
Baseline NYHA (2 cat.): II		
Number of patients in analysis set	1401	1399
Number of analysed patients, N (%)	1306 (100.0)	1307 (100.0)
Number of patients with endpoint, N (%)	518 (39.7)	573 (43.8)
95% confidence interval*	(37.0, 42.3)	(41.2, 46.5)
Comparison vs Placebo**		
Risk ratio (SE)		1.132 (0.048)
95% confidence interval***		(1.041, 1.231)
p-value		0.0038
Baseline NYHA (2 cat.): III/IV		
Number of patients in analysis set	466	464
Number of analysed patients, N (%)	403 (100.0)	433 (100.0)
Number of patients with endpoint, N (%)	199 (49.4)	233 (53.8)
95% confidence interval*	(44.5, 54.2)	(49.1, 58.5)
Comparison vs Placebo**		
Risk ratio (SE)		1.021 (0.067)
95% confidence interval***		(0.898, 1.161)
p-value		0.7481

* Wilson confidence intervals.
** Log-linked Poisson model with robust estimate of variance includes terms for baseline KCCQ - clinical summary score (p<0.0001), age (p=0.0473), baseline eGFR (CKD-EPI) (p=0.8809), Treatment (p=0.0641), region (5 cat.) (p<0.0001), baseline diabetes status (3 cat.) (p=0.8169), sex (p=0.9302), baseline LVEF (3 cat.) (p=0.2765), baseline NYHA (2 cat.) (p=0.0009) and Treatment by baseline NYHA (2 cat.) interaction (p=0.1889).
***Wald confidence intervals.

Data taken from study 1245.121 only.
LOCF: For a missing value at week 52 the last available post-baseline value before week 52 is imputed.

R.1.2.4.7

R.1.2.4.7 Subgroup analysis by diabetes at baseline

Table R.1.2.4.7: 1 Responder analysis (displaying odds ratio) in KCCQ-CSS change from baseline at week 52 of <= -5 points (deterioration) by diabetes at baseline - RS (LOCF-AD) - 1245.121

Subgroup Description	Placebo	Empa 10mg
Diabetes at baseline (2 cat.): Diabetic		
Number of patients in analysis set	929	927
Number of analysed patients, N (%)	850 (100.0)	861 (100.0)
Number of patients with endpoint, N (%)	224 (26.4)	191 (22.2)
95% confidence interval*	(23.5, 29.4)	(19.5, 25.1)
Comparison vs Placebo**		
Odds ratio (SE)		0.785 (0.090)
95% confidence interval***		(0.626, 0.984)
p-value		0.0354
Diabetes at baseline (2 cat.): Non-Diabetic		
Number of patients in analysis set	938	936
Number of analysed patients, N (%)	859 (100.0)	879 (100.0)
Number of patients with endpoint, N (%)	224 (26.1)	206 (23.4)
95% confidence interval*	(23.3, 29.1)	(20.8, 26.3)
Comparison vs Placebo**		
Odds ratio (SE)		0.856 (0.097)
95% confidence interval***		(0.686, 1.069)
p-value		0.1706

* Wilson confidence intervals.
** Logistic regression includes terms for baseline KCCQ - clinical summary score (p<0.0001), age (p=0.0157), baseline eGFR (CKD-EPI) (p=0.0006), Treatment (p=0.0139), region (5 cat.) (p=0.0001), sex (p=0.4564), baseline LVEF (3 cat.) (p=0.6870), diabetes at baseline (2 cat.) (p=0.8337) and Treatment by diabetes at baseline (2 cat.) interaction (p=0.5894).
***Wald confidence intervals.

Data taken from study 1245.121 only.
LOCF: For a missing value at week 52 the last available post-baseline value before week 52 is imputed.

Table R.1.2.4.7: 2 Responder analysis (displaying risk ratio) in KCCQ-CSS change from baseline at week 52 of <= -5 points (deterioration) by diabetes at baseline - RS (LOCF-AD) - 1245.121

Subgroup Description	Placebo	Empa 10mg
Diabetes at baseline (2 cat.): Diabetic		
Number of patients in analysis set	929	927
Number of analysed patients, N (%)	850 (100.0)	861 (100.0)
Number of patients with endpoint, N (%)	224 (26.4)	191 (22.2)
95% confidence interval*	(23.5, 29.4)	(19.5, 25.1)
Comparison vs Placebo**		
Risk ratio (SE)		0.836 (0.070)
95% confidence interval***		(0.710, 0.986)
p-value		0.0333
Diabetes at baseline (2 cat.): Non-Diabetic		
Number of patients in analysis set	938	936
Number of analysed patients, N (%)	859 (100.0)	879 (100.0)
Number of patients with endpoint, N (%)	224 (26.1)	206 (23.4)
95% confidence interval*	(23.3, 29.1)	(20.8, 26.3)
Comparison vs Placebo**		
Risk ratio (SE)		0.893 (0.074)
95% confidence interval***		(0.760, 1.050)
p-value		0.1711

* Wilson confidence intervals.
** Log-linked Poisson model with robust estimate of variance includes terms for baseline KCCQ - clinical summary score (p<0.0001), age (p=0.0165), baseline eGFR (CKD-EPI) (p=0.0007), Treatment (p=0.0132), region (5 cat.) (p=0.0002), sex (p=0.4368), baseline LVEF (3 cat.) (p=0.6811), diabetes at baseline (2 cat.) (p=0.8484) and Treatment by diabetes at baseline (2 cat.) interaction (p=0.5751).
***Wald confidence intervals.

Data taken from study 1245.121 only.
LOCF: For a missing value at week 52 the last available post-baseline value before week 52 is imputed.

Table R.1.2.4.7: 3 Responder analysis (displaying odds ratio) in KCCQ-CSS change from baseline at week 52 of > -5 points (stability) by diabetes at baseline - RS (LOCF-AD) - 1245.121

Subgroup Description	Placebo	Empa 10mg
Diabetes at baseline (2 cat.): Diabetic		
Number of patients in analysis set	929	927
Number of analysed patients, N (%)	850 (100.0)	861 (100.0)
Number of patients with endpoint, N (%)	626 (73.6)	670 (77.8)
95% confidence interval*	(70.6, 76.5)	(74.9, 80.5)
Comparison vs Placebo**		
Odds ratio (SE)		1.275 (0.147)
95% confidence interval***		(1.017, 1.598)
p-value		0.0354
Diabetes at baseline (2 cat.): Non-Diabetic		
Number of patients in analysis set	938	936
Number of analysed patients, N (%)	859 (100.0)	879 (100.0)
Number of patients with endpoint, N (%)	635 (73.9)	673 (76.6)
95% confidence interval*	(70.9, 76.7)	(73.7, 79.2)
Comparison vs Placebo**		
Odds ratio (SE)		1.168 (0.132)
95% confidence interval***		(0.935, 1.459)
p-value		0.1706

* Wilson confidence intervals.
** Logistic regression includes terms for baseline KCCQ - clinical summary score (p<0.0001), age (p=0.0157), baseline eGFR (CKD-EPI) (p=0.0006), Treatment (p=0.0139), region (5 cat.) (p=0.0001), sex (p=0.4564), baseline LVEF (3 cat.) (p=0.6870), diabetes at baseline (2 cat.) (p=0.8337) and Treatment by diabetes at baseline (2 cat.) interaction (p=0.5894).
***Wald confidence intervals.

Data taken from study 1245.121 only.
LOCF: For a missing value at week 52 the last available post-baseline value before week 52 is imputed.

Table R.1.2.4.7: 4 Responder analysis (displaying risk ratio) in KCCQ-CSS change from baseline at week 52 of > -5 points (stability) by diabetes at baseline - RS (LOCF-AD) - 1245.121

Subgroup Description	Placebo	Empa 10mg
Diabetes at baseline (2 cat.): Diabetic		
Number of patients in analysis set	929	927
Number of analysed patients, N (%)	850 (100.0)	861 (100.0)
Number of patients with endpoint, N (%)	626 (73.6)	670 (77.8)
95% confidence interval*	(70.6, 76.5)	(74.9, 80.5)
Comparison vs Placebo**		
Risk ratio (SE)		1.056 (0.028)
95% confidence interval***		(1.002, 1.113)
p-value		0.0431
Diabetes at baseline (2 cat.): Non-Diabetic		
Number of patients in analysis set	938	936
Number of analysed patients, N (%)	859 (100.0)	879 (100.0)
Number of patients with endpoint, N (%)	635 (73.9)	673 (76.6)
95% confidence interval*	(70.9, 76.7)	(73.7, 79.2)
Comparison vs Placebo**		
Risk ratio (SE)		1.038 (0.028)
95% confidence interval***		(0.985, 1.095)
p-value		0.1662

* Wilson confidence intervals.
** Log-linked Poisson model with robust estimate of variance includes terms for baseline KCCQ - clinical summary score (p<0.0001), age (p=0.0256), baseline eGFR (CKD-EPI) (p=0.0009), Treatment (p=0.0161), region (5 cat.) (p<0.0001), sex (p=0.4859), baseline LVEF (3 cat.) (p=0.6685), diabetes at baseline (2 cat.) (p=0.8038) and Treatment by diabetes at baseline (2 cat.) interaction (p=0.6567).
***Wald confidence intervals.

Data taken from study 1245.121 only.
LOCF: For a missing value at week 52 the last available post-baseline value before week 52 is imputed.

Table R.1.2.4.7: 5 Responder analysis (displaying odds ratio) in KCCQ-CSS change from baseline at week 52 of >= 5 points (improvement) by diabetes at baseline - RS (LOCF-AD) - 1245.121

Subgroup Description	Placebo	Empa 10mg
Diabetes at baseline (2 cat.): Diabetic		
Number of patients in analysis set	929	927
Number of analysed patients, N (%)	850 (100.0)	861 (100.0)
Number of patients with endpoint, N (%)	367 (43.2)	406 (47.2)
95% confidence interval*	(39.9, 46.5)	(43.8, 50.5)
Comparison vs Placebo**		
Odds ratio (SE)		1.211 (0.130)
95% confidence interval***		(0.982, 1.494)
p-value		0.0732
Diabetes at baseline (2 cat.): Non-Diabetic		
Number of patients in analysis set	938	936
Number of analysed patients, N (%)	859 (100.0)	879 (100.0)
Number of patients with endpoint, N (%)	350 (40.7)	400 (45.5)
95% confidence interval*	(37.5, 44.1)	(42.2, 48.8)
Comparison vs Placebo**		
Odds ratio (SE)		1.254 (0.133)
95% confidence interval***		(1.019, 1.542)
p-value		0.0326

* Wilson confidence intervals.
** Logistic regression includes terms for baseline KCCQ - clinical summary score (p<0.0001), age (p=0.0207), baseline eGFR (CKD-EPI) (p=0.8163), Treatment (p=0.0055), region (5 cat.) (p<0.0001), sex (p=0.7489), baseline LVEF (3 cat.) (p=0.2660), diabetes at baseline (2 cat.) (p=0.8335) and Treatment by diabetes at baseline (2 cat.) interaction (p=0.8207).
***Wald confidence intervals.

Data taken from study 1245.121 only.
LOCF: For a missing value at week 52 the last available post-baseline value before week 52 is imputed.

Table R.1.2.4.7: 6 Responder analysis (displaying risk ratio) in KCCQ-CSS change from baseline at week 52 of >= 5 points (improvement) by diabetes at baseline - RS (LOCF-AD) - 1245.121

Subgroup Description	Placebo	Empa 10mg
Diabetes at baseline (2 cat.): Diabetic		
Number of patients in analysis set	929	927
Number of analysed patients, N (%)	850 (100.0)	861 (100.0)
Number of patients with endpoint, N (%)	367 (43.2)	406 (47.2)
95% confidence interval*	(39.9, 46.5)	(43.8, 50.5)
Comparison vs Placebo**		
Risk ratio (SE)		1.079 (0.054)
95% confidence interval***		(0.978, 1.191)
p-value		0.1298
Diabetes at baseline (2 cat.): Non-Diabetic		
Number of patients in analysis set	938	936
Number of analysed patients, N (%)	859 (100.0)	879 (100.0)
Number of patients with endpoint, N (%)	350 (40.7)	400 (45.5)
95% confidence interval*	(37.5, 44.1)	(42.2, 48.8)
Comparison vs Placebo**		
Risk ratio (SE)		1.112 (0.057)
95% confidence interval***		(1.006, 1.230)
p-value		0.0376

* Wilson confidence intervals.
** Log-linked Poisson model with robust estimate of variance includes terms for baseline KCCQ - clinical summary score (p<0.0001), age (p=0.0411), baseline eGFR (CKD-EPI) (p=0.8298), Treatment (p=0.0110), region (5 cat.) (p<0.0001), sex (p=0.9355), baseline LVEF (3 cat.) (p=0.2385), diabetes at baseline (2 cat.) (p=0.6658) and Treatment by diabetes at baseline (2 cat.) interaction (p=0.6725).
***Wald confidence intervals.

Data taken from study 1245.121 only.
LOCF: For a missing value at week 52 the last available post-baseline value before week 52 is imputed.

R.1.2.4.8 Subgroup analysis by BMI at baseline (<30, >=30)

Table R.1.2.4.8: 1 Responder analysis (displaying odds ratio) in KCCQ-CSS change from baseline at week 52 of <= -5 points (deterioration) by baseline BMI [kg/m2] - RS (LOCF-AD) - 1245.121

Subgroup Description	Placebo	Empa 10mg
Baseline BMI [kg/m²] (2 cat.): <30		
Number of patients in analysis set	1300	1263
Number of analysed patients, N (%)	1197 (100.0)	1181 (100.0)
Number of patients with endpoint, N (%)	303 (25.3)	260 (22.0)
95% confidence interval*	(22.9, 27.9)	(19.7, 24.5)
Comparison vs Placebo**		
Odds ratio (SE)		0.815 (0.080)
95% confidence interval***		(0.672, 0.989)
p-value		0.0381
Baseline BMI [kg/m²] (2 cat.): >=30		
Number of patients in analysis set	567	600
Number of analysed patients, N (%)	512 (100.0)	559 (100.0)
Number of patients with endpoint, N (%)	145 (28.3)	137 (24.5)
95% confidence interval*	(24.6, 32.4)	(21.1, 28.2)
Comparison vs Placebo**		
Odds ratio (SE)		0.816 (0.116)
95% confidence interval***		(0.618, 1.077)
p-value		0.1518

* Wilson confidence intervals.
** Logistic regression includes terms for baseline KCCQ - clinical summary score (p<0.0001), age (p=0.0049), baseline eGFR (CKD-EPI) (p=0.0008), Treatment (p=0.0182), region (5 cat.) (p=0.0013), baseline diabetes status (3 cat.) (p=0.9281), sex (p=0.5009), baseline LVEF (3 cat.) (p=0.6673), baseline BMI (2 cat.) (p=0.0114) and Treatment by baseline BMI (2 cat.) interaction (p=0.9935).
***Wald confidence intervals.

Data taken from study 1245.121 only.
LOCF: For a missing value at week 52 the last available post-baseline value before week 52 is imputed.

Table R.1.2.4.8: 2 Responder analysis (displaying risk ratio) in KCCQ-CSS change from baseline at week 52 of <= -5 points (deterioration) by baseline BMI [kg/m2] - RS (LOCF-AD) - 1245.121

Subgroup Description	Placebo	Empa 10mg
Baseline BMI [kg/m²] (2 cat.): <30		
Number of patients in analysis set	1300	1263
Number of analysed patients, N (%)	1197 (100.0)	1181 (100.0)
Number of patients with endpoint, N (%)	303 (25.3)	260 (22.0)
95% confidence interval*	(22.9, 27.9)	(19.7, 24.5)
Comparison vs Placebo**		
Risk ratio (SE)		0.860 (0.062)
95% confidence interval***		(0.746, 0.990)
p-value		0.0363
Baseline BMI [kg/m²] (2 cat.): >=30		
Number of patients in analysis set	567	600
Number of analysed patients, N (%)	512 (100.0)	559 (100.0)
Number of patients with endpoint, N (%)	145 (28.3)	137 (24.5)
95% confidence interval*	(24.6, 32.4)	(21.1, 28.2)
Comparison vs Placebo**		
Risk ratio (SE)		0.866 (0.087)
95% confidence interval***		(0.711, 1.054)
p-value		0.1517

* Wilson confidence intervals.
** Log-linked Poisson model with robust estimate of variance includes terms for baseline KCCQ - clinical summary score (p<0.0001), age (p=0.0054), baseline eGFR (CKD-EPI) (p=0.0010), Treatment (p=0.0171), region (5 cat.) (p=0.0018), baseline diabetes status (3 cat.) (p=0.9283), sex (p=0.4789), baseline LVEF (3 cat.) (p=0.6545), baseline BMI (2 cat.) (p=0.0094) and Treatment by baseline BMI (2 cat.) interaction (p=0.9532).
***Wald confidence intervals.

Data taken from study 1245.121 only.
LOCF: For a missing value at week 52 the last available post-baseline value before week 52 is imputed.

Table R.1.2.4.8: 3 Responder analysis (displaying odds ratio) in KCCQ-CSS change from baseline at week 52 of > -5 points (stability) by baseline BMI [kg/m2] - RS (LOCF-AD) - 1245.121

Subgroup Description	Placebo	Empa 10mg
Baseline BMI [kg/m²] (2 cat.): <30		
Number of patients in analysis set	1300	1263
Number of analysed patients, N (%)	1197 (100.0)	1181 (100.0)
Number of patients with endpoint, N (%)	894 (74.7)	921 (78.0)
95% confidence interval*	(72.1, 77.1)	(75.5, 80.3)
Comparison vs Placebo**		
Odds ratio (SE)		1.227 (0.121)
95% confidence interval***		(1.011, 1.489)
p-value		0.0381
Baseline BMI [kg/m²] (2 cat.): >=30		
Number of patients in analysis set	567	600
Number of analysed patients, N (%)	512 (100.0)	559 (100.0)
Number of patients with endpoint, N (%)	367 (71.7)	422 (75.5)
95% confidence interval*	(67.6, 75.4)	(71.8, 78.9)
Comparison vs Placebo**		
Odds ratio (SE)		1.225 (0.174)
95% confidence interval***		(0.928, 1.617)
p-value		0.1518

* Wilson confidence intervals.
** Logistic regression includes terms for baseline KCCQ - clinical summary score (p<0.0001), age (p=0.0049), baseline eGFR (CKD-EPI) (p=0.0008), Treatment (p=0.0182), region (5 cat.) (p=0.0013), baseline diabetes status (3 cat.) (p=0.9281), sex (p=0.5009), baseline LVEF (3 cat.) (p=0.6673), baseline BMI (2 cat.) (p=0.0114) and Treatment by baseline BMI (2 cat.) interaction (p=0.9935).
***Wald confidence intervals.

Data taken from study 1245.121 only.
LOCF: For a missing value at week 52 the last available post-baseline value before week 52 is imputed.

Table R.1.2.4.8: 4 Responder analysis (displaying risk ratio) in KCCQ-CSS change from baseline at week 52 of > -5 points (stability) by baseline BMI [kg/m2] - RS (LOCF-AD) - 1245.121

Subgroup Description	Placebo	Empa 10mg
Baseline BMI [kg/m²] (2 cat.): <30		
Number of patients in analysis set	1300	1263
Number of analysed patients, N (%)	1197 (100.0)	1181 (100.0)
Number of patients with endpoint, N (%)	894 (74.7)	921 (78.0)
95% confidence interval*	(72.1, 77.1)	(75.5, 80.3)
Comparison vs Placebo**		
Risk ratio (SE)		1.046 (0.023)
95% confidence interval***		(1.001, 1.093)
p-value		0.0444
Baseline BMI [kg/m²] (2 cat.): >=30		
Number of patients in analysis set	567	600
Number of analysed patients, N (%)	512 (100.0)	559 (100.0)
Number of patients with endpoint, N (%)	367 (71.7)	422 (75.5)
95% confidence interval*	(67.6, 75.4)	(71.8, 78.9)
Comparison vs Placebo**		
Risk ratio (SE)		1.054 (0.038)
95% confidence interval***		(0.982, 1.132)
p-value		0.1481

* Wilson confidence intervals.
** Log-linked Poisson model with robust estimate of variance includes terms for baseline KCCQ - clinical summary score (p<0.0001), age (p=0.0096), baseline eGFR (CKD-EPI) (p=0.0011), Treatment (p=0.0222), region (5 cat.) (p<0.0001), baseline diabetes status (3 cat.) (p=0.9394), sex (p=0.5358), baseline LVEF (3 cat.) (p=0.6602), baseline BMI (2 cat.) (p=0.0202) and Treatment by baseline BMI (2 cat.) interaction (p=0.8627).
***Wald confidence intervals.

Data taken from study 1245.121 only.
LOCF: For a missing value at week 52 the last available post-baseline value before week 52 is imputed.

Table R.1.2.4.8: 5 Responder analysis (displaying odds ratio) in KCCQ-CSS change from baseline at week 52 of >= 5 points (improvement) by baseline BMI [kg/m2] - RS (LOCF-AD) - 1245.121

Subgroup Description	Placebo	Empa 10mg
Baseline BMI [kg/m²] (2 cat.): <30		
Number of patients in analysis set	1300	1263
Number of analysed patients, N (%)	1197 (100.0)	1181 (100.0)
Number of patients with endpoint, N (%)	495 (41.4)	528 (44.7)
95% confidence interval*	(38.6, 44.2)	(41.9, 47.6)
Comparison vs Placebo**		
Odds ratio (SE)		1.211 (0.110)
95% confidence interval***		(1.013, 1.447)
p-value		0.0354
Baseline BMI [kg/m²] (2 cat.): >=30		
Number of patients in analysis set	567	600
Number of analysed patients, N (%)	512 (100.0)	559 (100.0)
Number of patients with endpoint, N (%)	222 (43.4)	278 (49.7)
95% confidence interval*	(39.1, 47.7)	(45.6, 53.9)
Comparison vs Placebo**		
Odds ratio (SE)		1.293 (0.174)
95% confidence interval***		(0.993, 1.683)
p-value		0.0562

* Wilson confidence intervals.
** Logistic regression includes terms for baseline KCCQ - clinical summary score (p<0.0001), age (p=0.0129), baseline eGFR (CKD-EPI) (p=0.8204), Treatment (p=0.0058), region (5 cat.) (p<0.0001), baseline diabetes status (3 cat.) (p=0.8002), sex (p=0.7628), baseline LVEF (3 cat.) (p=0.2700), baseline BMI (2 cat.) (p=0.2448) and Treatment by baseline BMI (2 cat.) interaction (p=0.6860).
***Wald confidence intervals.

Data taken from study 1245.121 only.
LOCF: For a missing value at week 52 the last available post-baseline value before week 52 is imputed.

Table R.1.2.4.8: 6 Responder analysis (displaying risk ratio) in KCCQ-CSS change from baseline at week 52 of >= 5 points (improvement) by baseline BMI [kg/m2] - RS (LOCF-AD) - 1245.121

Subgroup Description	Placebo	Empa 10mg
Baseline BMI [kg/m²] (2 cat.): <30		
Number of patients in analysis set	1300	1263
Number of analysed patients, N (%)	1197 (100.0)	1181 (100.0)
Number of patients with endpoint, N (%)	495 (41.4)	528 (44.7)
95% confidence interval*	(38.6, 44.2)	(41.9, 47.6)
Comparison vs Placebo**		
Risk ratio (SE)		1.086 (0.047)
95% confidence interval***		(0.998, 1.183)
p-value		0.0558
Baseline BMI [kg/m²] (2 cat.): >=30		
Number of patients in analysis set	567	600
Number of analysed patients, N (%)	512 (100.0)	559 (100.0)
Number of patients with endpoint, N (%)	222 (43.4)	278 (49.7)
95% confidence interval*	(39.1, 47.7)	(45.6, 53.9)
Comparison vs Placebo**		
Risk ratio (SE)		1.118 (0.072)
95% confidence interval***		(0.986, 1.268)
p-value		0.0821

* Wilson confidence intervals.
** Log-linked Poisson model with robust estimate of variance includes terms for baseline KCCQ - clinical summary score (p<0.0001), age (p=0.0296), baseline eGFR (CKD-EPI) (p=0.8339), Treatment (p=0.0120), region (5 cat.) (p<0.0001), baseline diabetes status (3 cat.) (p=0.7730), sex (p=0.9716), baseline LVEF (3 cat.) (p=0.2450), baseline BMI (2 cat.) (p=0.3559) and Treatment by baseline BMI (2 cat.) interaction (p=0.7102).
***Wald confidence intervals.

Data taken from study 1245.121 only.
LOCF: For a missing value at week 52 the last available post-baseline value before week 52 is imputed.

R.1.2.4.9 Subgroup analysis by eGFR at baseline (<60, >=60)

Table R.1.2.4.9: 1 Responder analysis (displaying odds ratio) in KCCQ-CSS change from baseline at week 52 of <= -5 points (deterioration) by baseline eGFR (2 cat.) - RS (LOCF-AD) - 1245.121

Subgroup Description	Placebo	Empa 10mg
Baseline eGFR (CKD-EPI) [mL/min/1.73m²] (2 cat.): >=60		
Number of patients in analysis set	960	969
Number of analysed patients, N (%)	875 (100.0)	903 (100.0)
Number of patients with endpoint, N (%)	208 (23.8)	176 (19.5)
95% confidence interval*	(21.1, 26.7)	(17.0, 22.2)
Comparison vs Placebo**		
Odds ratio (SE)		0.750 (0.088)
95% confidence interval***		(0.596, 0.945)
p-value		0.0146
Baseline eGFR (CKD-EPI) [mL/min/1.73m²] (2 cat.): <60		
Number of patients in analysis set	906	893
Number of analysed patients, N (%)	834 (100.0)	837 (100.0)
Number of patients with endpoint, N (%)	240 (28.8)	221 (26.4)
95% confidence interval*	(25.8, 31.9)	(23.5, 29.5)
Comparison vs Placebo**		
Odds ratio (SE)		0.889 (0.099)
95% confidence interval***		(0.715, 1.106)
p-value		0.2922

* Wilson confidence intervals.
** Logistic regression includes terms for baseline KCCQ - clinical summary score (p<0.0001), age (p=0.0003), Treatment (p=0.0125), region (5 cat.) (p<0.0001), baseline diabetes status (3 cat.) (p=0.9193), sex (p=0.4236), baseline LVEF (3 cat.) (p=0.6465), baseline eGFR (CKD-EPI) (2 cat.) (p=0.0322) and Treatment by baseline eGFR (CKD-EPI) (2 cat.) interaction (p=0.2935).
***Wald confidence intervals.
2 patients were excluded as the subgroup variable was missing.

Data taken from study 1245.121 only.
LOCF: For a missing value at week 52 the last available post-baseline value before week 52 is imputed.

Table R.1.2.4.9: 2 Responder analysis (displaying risk ratio) in KCCQ-CSS change from baseline at week 52 of <= -5 points (deterioration) by baseline eGFR (2 cat.) - RS (LOCF-AD) - 1245.121

Subgroup Description	Placebo	Empa 10mg
Baseline eGFR (CKD-EPI) [mL/min/1.73m²] (2 cat.): >=60		
Number of patients in analysis set	960	969
Number of analysed patients, N (%)	875 (100.0)	903 (100.0)
Number of patients with endpoint, N (%)	208 (23.8)	176 (19.5)
95% confidence interval*	(21.1, 26.7)	(17.0, 22.2)
Comparison vs Placebo**		
Risk ratio (SE)		0.802 (0.073)
95% confidence interval***		(0.672, 0.958)
p-value		0.0148
Baseline eGFR (CKD-EPI) [mL/min/1.73m²] (2 cat.): <60		
Number of patients in analysis set	906	893
Number of analysed patients, N (%)	834 (100.0)	837 (100.0)
Number of patients with endpoint, N (%)	240 (28.8)	221 (26.4)
95% confidence interval*	(25.8, 31.9)	(23.5, 29.5)
Comparison vs Placebo**		
Risk ratio (SE)		0.921 (0.071)
95% confidence interval***		(0.791, 1.072)
p-value		0.2871

* Wilson confidence intervals.
** Log-linked Poisson model with robust estimate of variance includes terms for baseline KCCQ - clinical summary score (p<0.0001), age (p=0.0004), Treatment (p=0.0109), region (5 cat.) (p=0.0002), baseline diabetes status (3 cat.) (p=0.9185), sex (p=0.4024), baseline LVEF (3 cat.) (p=0.6327), baseline eGFR (CKD-EPI) (2 cat.) (p=0.0311) and Treatment by baseline eGFR (CKD-EPI) (2 cat.) interaction (p=0.2470).
***Wald confidence intervals.
2 patients were excluded as the subgroup variable was missing.

Data taken from study 1245.121 only.
LOCF: For a missing value at week 52 the last available post-baseline value before week 52 is imputed.

Table R.1.2.4.9: 3 Responder analysis (displaying odds ratio) in KCCQ-CSS change from baseline at week 52 of > -5 points (stability) by baseline eGFR (2 cat.) - RS (LOCF-AD) - 1245.121

Subgroup Description	Placebo	Empa 10mg
Baseline eGFR (CKD-EPI) [mL/min/1.73m²] (2 cat.): >=60		
Number of patients in analysis set	960	969
Number of analysed patients, N (%)	875 (100.0)	903 (100.0)
Number of patients with endpoint, N (%)	667 (76.2)	727 (80.5)
95% confidence interval*	(73.3, 78.9)	(77.8, 83.0)
Comparison vs Placebo**		
Odds ratio (SE)		1.333 (0.157)
95% confidence interval***		(1.058, 1.678)
p-value		0.0146
Baseline eGFR (CKD-EPI) [mL/min/1.73m²] (2 cat.): <60		
Number of patients in analysis set	906	893
Number of analysed patients, N (%)	834 (100.0)	837 (100.0)
Number of patients with endpoint, N (%)	594 (71.2)	616 (73.6)
95% confidence interval*	(68.1, 74.2)	(70.5, 76.5)
Comparison vs Placebo**		
Odds ratio (SE)		1.124 (0.125)
95% confidence interval***		(0.904, 1.398)
p-value		0.2922

* Wilson confidence intervals.
** Logistic regression includes terms for baseline KCCQ - clinical summary score (p<0.0001), age (p=0.0003), Treatment (p=0.0125), region (5 cat.) (p<0.0001), baseline diabetes status (3 cat.) (p=0.9193), sex (p=0.4236), baseline LVEF (3 cat.) (p=0.6465), baseline eGFR (CKD-EPI) (2 cat.) (p=0.0322) and Treatment by baseline eGFR (CKD-EPI) (2 cat.) interaction (p=0.2935).
***Wald confidence intervals.
2 patients were excluded as the subgroup variable was missing.

Data taken from study 1245.121 only.
LOCF: For a missing value at week 52 the last available post-baseline value before week 52 is imputed.

Table R.1.2.4.9: 4 Responder analysis (displaying risk ratio) in KCCQ-CSS change from baseline at week 52 of > -5 points (stability) by baseline eGFR (2 cat.) - RS (LOCF-AD) - 1245.121

Subgroup Description	Placebo	Empa 10mg
Baseline eGFR (CKD-EPI) [mL/min/1.73m²] (2 cat.): >=60		
Number of patients in analysis set	960	969
Number of analysed patients, N (%)	875 (100.0)	903 (100.0)
Number of patients with endpoint, N (%)	667 (76.2)	727 (80.5)
95% confidence interval*	(73.3, 78.9)	(77.8, 83.0)
Comparison vs Placebo**		
Risk ratio (SE)		1.060 (0.026)
95% confidence interval***		(1.009, 1.113)
p-value		0.0194
Baseline eGFR (CKD-EPI) [mL/min/1.73m²] (2 cat.): <60		
Number of patients in analysis set	906	893
Number of analysed patients, N (%)	834 (100.0)	837 (100.0)
Number of patients with endpoint, N (%)	594 (71.2)	616 (73.6)
95% confidence interval*	(68.1, 74.2)	(70.5, 76.5)
Comparison vs Placebo**		
Risk ratio (SE)		1.033 (0.031)
95% confidence interval***		(0.974, 1.094)
p-value		0.2787

* Wilson confidence intervals.
** Log-linked Poisson model with robust estimate of variance includes terms for baseline KCCQ - clinical summary score (p<0.0001), age (p=0.0005), Treatment (p=0.0196), region (5 cat.) (p<0.0001), baseline diabetes status (3 cat.) (p=0.9329), sex (p=0.4804), baseline LVEF (3 cat.) (p=0.6486), baseline eGFR (CKD-EPI) (2 cat.) (p=0.0328) and Treatment by baseline eGFR (CKD-EPI) (2 cat.) interaction (p=0.5004).
***Wald confidence intervals.
2 patients were excluded as the subgroup variable was missing.

Data taken from study 1245.121 only.
LOCF: For a missing value at week 52 the last available post-baseline value before week 52 is imputed.

Table R.1.2.4.9: 5 Responder analysis (displaying odds ratio) in KCCQ-CSS change from baseline at week 52 of >= 5 points (improvement) by baseline eGFR (2 cat.) - RS (LOCF-AD) - 1245.121

Subgroup Description	Placebo	Empa 10mg
Baseline eGFR (CKD-EPI) [mL/min/1.73m²] (2 cat.): >=60		
Number of patients in analysis set	960	969
Number of analysed patients, N (%)	875 (100.0)	903 (100.0)
Number of patients with endpoint, N (%)	364 (41.6)	437 (48.4)
95% confidence interval*	(38.4, 44.9)	(45.1, 51.7)
Comparison vs Placebo**		
Odds ratio (SE)		1.399 (0.147)
95% confidence interval***		(1.139, 1.719)
p-value		0.0014
Baseline eGFR (CKD-EPI) [mL/min/1.73m²] (2 cat.): <60		
Number of patients in analysis set	906	893
Number of analysed patients, N (%)	834 (100.0)	837 (100.0)
Number of patients with endpoint, N (%)	353 (42.3)	369 (44.1)
95% confidence interval*	(39.0, 45.7)	(40.8, 47.5)
Comparison vs Placebo**		
Odds ratio (SE)		1.077 (0.116)
95% confidence interval***		(0.871, 1.331)
p-value		0.4935

* Wilson confidence intervals.
** Logistic regression includes terms for baseline KCCQ - clinical summary score (p<0.0001), age (p=0.0113), Treatment (p=0.0065), region (5 cat.) (p<0.0001), baseline diabetes status (3 cat.) (p=0.7756), sex (p=0.7018), baseline LVEF (3 cat.) (p=0.2723), baseline eGFR (CKD-EPI) (2 cat.) (p=0.7108) and Treatment by baseline eGFR (CKD-EPI) (2 cat.) interaction (p=0.0824).
***Wald confidence intervals.
2 patients were excluded as the subgroup variable was missing.

Data taken from study 1245.121 only.
LOCF: For a missing value at week 52 the last available post-baseline value before week 52 is imputed.

Table R.1.2.4.9: 6 Responder analysis (displaying risk ratio) in KCCQ-CSS change from baseline at week 52 of >= 5 points (improvement) by baseline eGFR (2 cat.) - RS (LOCF-AD) - 1245.121

Subgroup Description	Placebo	Empa 10mg
Baseline eGFR (CKD-EPI) [mL/min/1.73m²] (2 cat.): >=60		
Number of patients in analysis set	960	969
Number of analysed patients, N (%)	875 (100.0)	903 (100.0)
Number of patients with endpoint, N (%)	364 (41.6)	437 (48.4)
95% confidence interval*	(38.4, 44.9)	(45.1, 51.7)
Comparison vs Placebo**		
Risk ratio (SE)		1.153 (0.058)
95% confidence interval***		(1.045, 1.272)
p-value		0.0046
Baseline eGFR (CKD-EPI) [mL/min/1.73m²] (2 cat.): <60		
Number of patients in analysis set	906	893
Number of analysed patients, N (%)	834 (100.0)	837 (100.0)
Number of patients with endpoint, N (%)	353 (42.3)	369 (44.1)
95% confidence interval*	(39.0, 45.7)	(40.8, 47.5)
Comparison vs Placebo**		
Risk ratio (SE)		1.034 (0.053)
95% confidence interval***		(0.935, 1.144)
p-value		0.5100

* Wilson confidence intervals.
** Log-linked Poisson model with robust estimate of variance includes terms for baseline KCCQ - clinical summary score (p<0.0001), age (p=0.0294), Treatment (p=0.0142), region (5 cat.) (p<0.0001), baseline diabetes status (3 cat.) (p=0.7223), sex (p=0.8992), baseline LVEF (3 cat.) (p=0.2394), baseline eGFR (CKD-EPI) (2 cat.) (p=0.7252) and Treatment by baseline eGFR (CKD-EPI) (2 cat.) interaction (p=0.1311).
***Wald confidence intervals.
2 patients were excluded as the subgroup variable was missing.

Data taken from study 1245.121 only.
LOCF: For a missing value at week 52 the last available post-baseline value before week 52 is imputed.

R.1.2.4.10

Table R.1.2.4.10: 1 Responder analysis (displaying odds ratio) in KCCQ-CSS change from baseline at week 52 of <= -5 points (deterioration) by history of HHF - RS (LOCF-AD) - 1245.121

Subgroup Description	Placebo	Empa 10mg
History of HHF (in the last 12 months): No		
Number of patients in analysis set	1293	1286
Number of analysed patients, N (%)	1194 (100.0)	1212 (100.0)
Number of patients with endpoint, N (%)	311 (26.0)	283 (23.3)
95% confidence interval*	(23.6, 28.6)	(21.1, 25.8)
Comparison vs Placebo**		
Odds ratio (SE)		0.874 (0.084)
95% confidence interval***		(0.723, 1.056)
p-value		0.1619
History of HHF (in the last 12 months): Yes		
Number of patients in analysis set	574	577
Number of analysed patients, N (%)	515 (100.0)	528 (100.0)
Number of patients with endpoint, N (%)	137 (26.6)	114 (21.6)
95% confidence interval*	(23.0, 30.6)	(18.3, 25.3)
Comparison vs Placebo**		
Odds ratio (SE)		0.707 (0.105)
95% confidence interval***		(0.529, 0.946)
p-value		0.0195

* Wilson confidence intervals.
** Logistic regression includes terms for baseline KCCQ - clinical summary score (p<0.0001), age (p=0.0132), baseline eGFR (CKD-EPI) (p=0.0006), Treatment (p=0.0065), region (5 cat.) (p=0.0001), baseline diabetes status (3 cat.) (p=0.9118), sex (p=0.4550), baseline LVEF (3 cat.) (p=0.6883), history of HHF (in the last 12 months) (p=0.9238) and Treatment by history of HHF (in the last 12 months) interaction (p=0.2329).
***Wald confidence intervals.

Data taken from study 1245.121 only.
LOCF: For a missing value at week 52 the last available post-baseline value before week 52 is imputed.

Table R.1.2.4.10: 2 Responder analysis (displaying risk ratio) in KCCQ-CSS change from baseline at week 52 of <= -5 points (deterioration) by history of HHF - RS (LOCF-AD) - 1245.121

Subgroup Description	Placebo	Empa 10mg
History of HHF (in the last 12 months): No		
Number of patients in analysis set	1293	1286
Number of analysed patients, N (%)	1194 (100.0)	1212 (100.0)
Number of patients with endpoint, N (%)	311 (26.0)	283 (23.3)
95% confidence interval*	(23.6, 28.6)	(21.1, 25.8)
Comparison vs Placebo**		
Risk ratio (SE)		0.907 (0.063)
95% confidence interval***		(0.790, 1.040)
p-value		0.1614
History of HHF (in the last 12 months): Yes		
Number of patients in analysis set	574	577
Number of analysed patients, N (%)	515 (100.0)	528 (100.0)
Number of patients with endpoint, N (%)	137 (26.6)	114 (21.6)
95% confidence interval*	(23.0, 30.6)	(18.3, 25.3)
Comparison vs Placebo**		
Risk ratio (SE)		0.774 (0.084)
95% confidence interval***		(0.626, 0.957)
p-value		0.0181

* Wilson confidence intervals.
** Log-linked Poisson model with robust estimate of variance includes terms for baseline KCCQ - clinical summary score (p<0.0001), age (p=0.0135), baseline eGFR (CKD-EPI) (p=0.0007), Treatment (p=0.0060), region (5 cat.) (p=0.0002), baseline diabetes status (3 cat.) (p=0.9149), sex (p=0.4333), baseline LVEF (3 cat.) (p=0.6886), history of HHF (in the last 12 months) (p=0.9249) and Treatment by history of HHF (in the last 12 months) interaction (p=0.2202).
***Wald confidence intervals.

Data taken from study 1245.121 only.
LOCF: For a missing value at week 52 the last available post-baseline value before week 52 is imputed.

Table R.1.2.4.10: 3 Responder analysis (displaying odds ratio) in KCCQ-CSS change from baseline at week 52 of > -5 points (stability) by history of HHF - RS (LOCF-AD) - 1245.121

Subgroup Description	Placebo	Empa 10mg
History of HHF (in the last 12 months): No		
Number of patients in analysis set	1293	1286
Number of analysed patients, N (%)	1194 (100.0)	1212 (100.0)
Number of patients with endpoint, N (%)	883 (74.0)	929 (76.7)
95% confidence interval*	(71.4, 76.4)	(74.2, 78.9)
Comparison vs Placebo**		
Odds ratio (SE)		1.145 (0.110)
95% confidence interval***		(0.947, 1.383)
p-value		0.1619
History of HHF (in the last 12 months): Yes		
Number of patients in analysis set	574	577
Number of analysed patients, N (%)	515 (100.0)	528 (100.0)
Number of patients with endpoint, N (%)	378 (73.4)	414 (78.4)
95% confidence interval*	(69.4, 77.0)	(74.7, 81.7)
Comparison vs Placebo**		
Odds ratio (SE)		1.413 (0.209)
95% confidence interval***		(1.057, 1.890)
p-value		0.0195

* Wilson confidence intervals.
** Logistic regression includes terms for baseline KCCQ - clinical summary score (p<0.0001), age (p=0.0132), baseline eGFR (CKD-EPI) (p=0.0006), Treatment (p=0.0065), region (5 cat.) (p=0.0001), baseline diabetes status (3 cat.) (p=0.9118), sex (p=0.4550), baseline LVEF (3 cat.) (p=0.6883), history of HHF (in the last 12 months) (p=0.9238) and Treatment by history of HHF (in the last 12 months) interaction (p=0.2329).
***Wald confidence intervals.

Data taken from study 1245.121 only.
LOCF: For a missing value at week 52 the last available post-baseline value before week 52 is imputed.

Table R.1.2.4.10: 4 Responder analysis (displaying risk ratio) in KCCQ-CSS change from baseline at week 52 of > -5 points (stability) by history of HHF - RS (LOCF-AD) - 1245.121

Subgroup Description	Placebo	Empa 10mg
History of HHF (in the last 12 months): No		
Number of patients in analysis set	1293	1286
Number of analysed patients, N (%)	1194 (100.0)	1212 (100.0)
Number of patients with endpoint, N (%)	883 (74.0)	929 (76.7)
95% confidence interval*	(71.4, 76.4)	(74.2, 78.9)
Comparison vs Placebo**		
Risk ratio (SE)		1.032 (0.024)
95% confidence interval***		(0.987, 1.080)
p-value		0.1682
History of HHF (in the last 12 months): Yes		
Number of patients in analysis set	574	577
Number of analysed patients, N (%)	515 (100.0)	528 (100.0)
Number of patients with endpoint, N (%)	378 (73.4)	414 (78.4)
95% confidence interval*	(69.4, 77.0)	(74.7, 81.7)
Comparison vs Placebo**		
Risk ratio (SE)		1.082 (0.037)
95% confidence interval***		(1.011, 1.158)
p-value		0.0224

* Wilson confidence intervals.
** Log-linked Poisson model with robust estimate of variance includes terms for baseline KCCQ - clinical summary score (p<0.0001), age (p=0.0231), baseline eGFR (CKD-EPI) (p=0.0008), Treatment (p=0.0077), region (5 cat.) (p<0.0001), baseline diabetes status (3 cat.) (p=0.9140), sex (p=0.4858), baseline LVEF (3 cat.) (p=0.6652), history of HHF (in the last 12 months) (p=0.8655) and Treatment by history of HHF (in the last 12 months) interaction (p=0.2568).
***Wald confidence intervals.

Data taken from study 1245.121 only.
LOCF: For a missing value at week 52 the last available post-baseline value before week 52 is imputed.

Table R.1.2.4.10: 5 Responder analysis (displaying odds ratio) in KCCQ-CSS change from baseline at week 52 of >= 5 points (improvement) by history of HHF - RS (LOCF-AD) - 1245.121

Subgroup Description	Placebo	Empa 10mg
History of HHF (in the last 12 months): No		
Number of patients in analysis set	1293	1286
Number of analysed patients, N (%)	1194 (100.0)	1212 (100.0)
Number of patients with endpoint, N (%)	503 (42.1)	574 (47.4)
95% confidence interval*	(39.4, 44.9)	(44.6, 50.2)
Comparison vs Placebo**		
Odds ratio (SE)		1.266 (0.114)
95% confidence interval***		(1.061, 1.510)
p-value		0.0088
History of HHF (in the last 12 months): Yes		
Number of patients in analysis set	574	577
Number of analysed patients, N (%)	515 (100.0)	528 (100.0)
Number of patients with endpoint, N (%)	214 (41.6)	232 (43.9)
95% confidence interval*	(37.4, 45.9)	(39.8, 48.2)
Comparison vs Placebo**		
Odds ratio (SE)		1.157 (0.159)
95% confidence interval***		(0.884, 1.515)
p-value		0.2868

* Wilson confidence intervals.
** Logistic regression includes terms for baseline KCCQ - clinical summary score (p<0.0001), age (p=0.0186), baseline eGFR (CKD-EPI) (p=0.8061), Treatment (p=0.0199), region (5 cat.) (p<0.0001), baseline diabetes status (3 cat.) (p=0.7924), sex (p=0.7436), baseline LVEF (3 cat.) (p=0.2865), history of HHF (in the last 12 months) (p=0.4914) and Treatment by history of HHF (in the last 12 months) interaction (p=0.5849).
***Wald confidence intervals.

Data taken from study 1245.121 only.
LOCF: For a missing value at week 52 the last available post-baseline value before week 52 is imputed.

Table R.1.2.4.10: 6 Responder analysis (displaying risk ratio) in KCCQ-CSS change from baseline at week 52 of >= 5 points (improvement) by history of HHF - RS (LOCF-AD) - 1245.121

Subgroup Description	Placebo	Empa 10mg
History of HHF (in the last 12 months): No		
Number of patients in analysis set	1293	1286
Number of analysed patients, N (%)	1194 (100.0)	1212 (100.0)
Number of patients with endpoint, N (%)	503 (42.1)	574 (47.4)
95% confidence interval*	(39.4, 44.9)	(44.6, 50.2)
Comparison vs Placebo**		
Risk ratio (SE)		1.110 (0.047)
95% confidence interval***		(1.021, 1.205)
p-value		0.0138
History of HHF (in the last 12 months): Yes		
Number of patients in analysis set	574	577
Number of analysed patients, N (%)	515 (100.0)	528 (100.0)
Number of patients with endpoint, N (%)	214 (41.6)	232 (43.9)
95% confidence interval*	(37.4, 45.9)	(39.8, 48.2)
Comparison vs Placebo**		
Risk ratio (SE)		1.061 (0.072)
95% confidence interval***		(0.929, 1.213)
p-value		0.3818

* Wilson confidence intervals.
** Log-linked Poisson model with robust estimate of variance includes terms for baseline KCCQ - clinical summary score (p<0.0001), age (p=0.0397), baseline eGFR (CKD-EPI) (p=0.8260), Treatment (p=0.0412), region (5 cat.) (p<0.0001), baseline diabetes status (3 cat.) (p=0.7531), sex (p=0.9454), baseline LVEF (3 cat.) (p=0.2549), history of HHF (in the last 12 months) (p=0.6447) and Treatment by history of HHF (in the last 12 months) interaction (p=0.5783).
***Wald confidence intervals.

Data taken from study 1245.121 only.
LOCF: For a missing value at week 52 the last available post-baseline value before week 52 is imputed.

R.1.2.4.11

Table R.1.2.4.11: 1 Responder analysis (displaying odds ratio) in KCCQ-CSS change from baseline at week 52 of <= -5 points (deterioration) by cause of heart failure - RS (LOCF-AD) - 1245.121

Subgroup Description	Placebo	Empa 10mg
Cause of heart failure: Ischemic		
Number of patients in analysis set	946	983
Number of analysed patients, N (%)	876 (100.0)	923 (100.0)
Number of patients with endpoint, N (%)	242 (27.6)	212 (23.0)
95% confidence interval*	(24.8, 30.7)	(20.4, 25.8)
Comparison vs Placebo**		
Odds ratio (SE)		0.783 (0.087)
95% confidence interval***		(0.630, 0.973)
p-value		0.0272
Cause of heart failure: Non-ischemic		
Number of patients in analysis set	921	880
Number of analysed patients, N (%)	833 (100.0)	817 (100.0)
Number of patients with endpoint, N (%)	206 (24.7)	185 (22.6)
95% confidence interval*	(21.9, 27.8)	(19.9, 25.6)
Comparison vs Placebo**		
Odds ratio (SE)		0.865 (0.102)
95% confidence interval***		(0.686, 1.091)
p-value		0.2214

* Wilson confidence intervals.
** Logistic regression includes terms for baseline KCCQ - clinical summary score (p<0.0001), age (p=0.0144), baseline eGFR (CKD-EPI) (p=0.0006), Treatment (p=0.0163), region (5 cat.) (p=0.0002), baseline diabetes status (3 cat.) (p=0.9100), sex (p=0.4695), baseline LVEF (3 cat.) (p=0.6895), cause of heart failure (p=0.8419) and Treatment by cause of heart failure interaction (p=0.5369).
***Wald confidence intervals.

Data taken from study 1245.121 only.
LOCF: For a missing value at week 52 the last available post-baseline value before week 52 is imputed.

Table R.1.2.4.11: 2 Responder analysis (displaying risk ratio) in KCCQ-CSS change from baseline at week 52 of <= -5 points (deterioration) by cause of heart failure - RS (LOCF-AD) - 1245.121

Subgroup Description	Placebo	Empa 10mg
Cause of heart failure: Ischemic		
Number of patients in analysis set	946	983
Number of analysed patients, N (%)	876 (100.0)	923 (100.0)
Number of patients with endpoint, N (%)	242 (27.6)	212 (23.0)
95% confidence interval*	(24.8, 30.7)	(20.4, 25.8)
Comparison vs Placebo**		
Risk ratio (SE)		0.838 (0.067)
95% confidence interval***		(0.717, 0.980)
p-value		0.0268
Cause of heart failure: Non-ischemic		
Number of patients in analysis set	921	880
Number of analysed patients, N (%)	833 (100.0)	817 (100.0)
Number of patients with endpoint, N (%)	206 (24.7)	185 (22.6)
95% confidence interval*	(21.9, 27.8)	(19.9, 25.6)
Comparison vs Placebo**		
Risk ratio (SE)		0.898 (0.078)
95% confidence interval***		(0.757, 1.064)
p-value		0.2140

* Wilson confidence intervals.
** Log-linked Poisson model with robust estimate of variance includes terms for baseline KCCQ - clinical summary score (p<0.0001), age (p=0.0148), baseline eGFR (CKD-EPI) (p=0.0007), Treatment (p=0.0157), region (5 cat.) (p=0.0002), baseline diabetes status (3 cat.) (p=0.9141), sex (p=0.4520), baseline LVEF (3 cat.) (p=0.6848), cause of heart failure (p=0.8406) and Treatment by cause of heart failure interaction (p=0.5622).
***Wald confidence intervals.

Data taken from study 1245.121 only.
LOCF: For a missing value at week 52 the last available post-baseline value before week 52 is imputed.

Table R.1.2.4.11: 3 Responder analysis (displaying odds ratio) in KCCQ-CSS change from baseline at week 52 of > -5 points (stability) by cause of heart failure - RS (LOCF-AD) - 1245.121

Subgroup Description	Placebo	Empa 10mg
Cause of heart failure: Ischemic		
Number of patients in analysis set	946	983
Number of analysed patients, N (%)	876 (100.0)	923 (100.0)
Number of patients with endpoint, N (%)	634 (72.4)	711 (77.0)
95% confidence interval*	(69.3, 75.2)	(74.2, 79.6)
Comparison vs Placebo**		
Odds ratio (SE)		1.277 (0.142)
95% confidence interval***		(1.028, 1.587)
p-value		0.0272
Cause of heart failure: Non-ischemic		
Number of patients in analysis set	921	880
Number of analysed patients, N (%)	833 (100.0)	817 (100.0)
Number of patients with endpoint, N (%)	627 (75.3)	632 (77.4)
95% confidence interval*	(72.2, 78.1)	(74.4, 80.1)
Comparison vs Placebo**		
Odds ratio (SE)		1.156 (0.137)
95% confidence interval***		(0.917, 1.457)
p-value		0.2214

* Wilson confidence intervals.
** Logistic regression includes terms for baseline KCCQ - clinical summary score (p<0.0001), age (p=0.0144), baseline eGFR (CKD-EPI) (p=0.0006), Treatment (p=0.0163), region (5 cat.) (p=0.0002), baseline diabetes status (3 cat.) (p=0.9100), sex (p=0.4695), baseline LVEF (3 cat.) (p=0.6895), cause of heart failure (p=0.8419) and Treatment by cause of heart failure interaction (p=0.5369).
***Wald confidence intervals.

Data taken from study 1245.121 only.
LOCF: For a missing value at week 52 the last available post-baseline value before week 52 is imputed.

Table R.1.2.4.11: 4 Responder analysis (displaying risk ratio) in KCCQ-CSS change from baseline at week 52 of > -5 points (stability) by cause of heart failure - RS (LOCF-AD) - 1245.121

Subgroup Description	Placebo	Empa 10mg
Cause of heart failure: Ischemic		
Number of patients in analysis set	946	983
Number of analysed patients, N (%)	876 (100.0)	923 (100.0)
Number of patients with endpoint, N (%)	634 (72.4)	711 (77.0)
95% confidence interval*	(69.3, 75.2)	(74.2, 79.6)
Comparison vs Placebo**		
Risk ratio (SE)		1.063 (0.029)
95% confidence interval***		(1.008, 1.121)
p-value		0.0253
Cause of heart failure: Non-ischemic		
Number of patients in analysis set	921	880
Number of analysed patients, N (%)	833 (100.0)	817 (100.0)
Number of patients with endpoint, N (%)	627 (75.3)	632 (77.4)
95% confidence interval*	(72.2, 78.1)	(74.4, 80.1)
Comparison vs Placebo**		
Risk ratio (SE)		1.031 (0.028)
95% confidence interval***		(0.977, 1.087)
p-value		0.2629

* Wilson confidence intervals.
** Log-linked Poisson model with robust estimate of variance includes terms for baseline KCCQ - clinical summary score (p<0.0001), age (p=0.0247), baseline eGFR (CKD-EPI) (p=0.0008), Treatment (p=0.0175), region (5 cat.) (p<0.0001), baseline diabetes status (3 cat.) (p=0.9102), sex (p=0.4944), baseline LVEF (3 cat.) (p=0.6660), cause of heart failure (p=0.9005) and Treatment by cause of heart failure interaction (p=0.4293).
***Wald confidence intervals.

Data taken from study 1245.121 only.
LOCF: For a missing value at week 52 the last available post-baseline value before week 52 is imputed.

Table R.1.2.4.11: 5 Responder analysis (displaying odds ratio) in KCCQ-CSS change from baseline at week 52 of >= 5 points (improvement) by cause of heart failure - RS (LOCF-AD) - 1245.121

Subgroup Description	Placebo	Empa 10mg
Cause of heart failure: Ischemic		
Number of patients in analysis set	946	983
Number of analysed patients, N (%)	876 (100.0)	923 (100.0)
Number of patients with endpoint, N (%)	360 (41.1)	421 (45.6)
95% confidence interval*	(37.9, 44.4)	(42.4, 48.8)
Comparison vs Placebo**		
Odds ratio (SE)		1.210 (0.126)
95% confidence interval***		(0.987, 1.485)
p-value		0.0673
Cause of heart failure: Non-ischemic		
Number of patients in analysis set	921	880
Number of analysed patients, N (%)	833 (100.0)	817 (100.0)
Number of patients with endpoint, N (%)	357 (42.9)	385 (47.1)
95% confidence interval*	(39.5, 46.2)	(43.7, 50.6)
Comparison vs Placebo**		
Odds ratio (SE)		1.257 (0.137)
95% confidence interval***		(1.015, 1.556)
p-value		0.0358

* Wilson confidence intervals.
** Logistic regression includes terms for baseline KCCQ - clinical summary score (p<0.0001), age (p=0.0194), baseline eGFR (CKD-EPI) (p=0.7986), Treatment (p=0.0054), region (5 cat.) (p<0.0001), baseline diabetes status (3 cat.) (p=0.7884), sex (p=0.7671), baseline LVEF (3 cat.) (p=0.2712), cause of heart failure (p=0.8982) and Treatment by cause of heart failure interaction (p=0.8019).
***Wald confidence intervals.

Data taken from study 1245.121 only.
LOCF: For a missing value at week 52 the last available post-baseline value before week 52 is imputed.

Table R.1.2.4.11: 6 Responder analysis (displaying risk ratio) in KCCQ-CSS change from baseline at week 52 of >= 5 points (improvement) by cause of heart failure - RS (LOCF-AD) - 1245.121

Subgroup Description	Placebo	Empa 10mg
Cause of heart failure: Ischemic		
Number of patients in analysis set	946	983
Number of analysed patients, N (%)	876 (100.0)	923 (100.0)
Number of patients with endpoint, N (%)	360 (41.1)	421 (45.6)
95% confidence interval*	(37.9, 44.4)	(42.4, 48.8)
Comparison vs Placebo**		
Risk ratio (SE)		1.087 (0.056)
95% confidence interval***		(0.983, 1.202)
p-value		0.1049
Cause of heart failure: Non-ischemic		
Number of patients in analysis set	921	880
Number of analysed patients, N (%)	833 (100.0)	817 (100.0)
Number of patients with endpoint, N (%)	357 (42.9)	385 (47.1)
95% confidence interval*	(39.5, 46.2)	(43.7, 50.6)
Comparison vs Placebo**		
Risk ratio (SE)		1.104 (0.056)
95% confidence interval***		(1.001, 1.219)
p-value		0.0484

* Wilson confidence intervals.
** Log-linked Poisson model with robust estimate of variance includes terms for baseline KCCQ - clinical summary score (p<0.0001), age (p=0.0414), baseline eGFR (CKD-EPI) (p=0.8162), Treatment (p=0.0110), region (5 cat.) (p<0.0001), baseline diabetes status (3 cat.) (p=0.7426), sex (p=0.9429), baseline LVEF (3 cat.) (p=0.2428), cause of heart failure (p=0.9737) and Treatment by cause of heart failure interaction (p=0.8249).
***Wald confidence intervals.

Data taken from study 1245.121 only.
LOCF: For a missing value at week 52 the last available post-baseline value before week 52 is imputed.

R.1.2.4.12

R.1.2.4.12 Subgroup analysis by heart failure physiology (LVEF <= 30% and NTproBNP<median; LVEF <= 30% and NTproBNP>=median; LVEF > 30%)

Table R.1.2.4.12: 1 Responder analysis (displaying odds ratio) in KCCQ-CSS change from baseline at week 52 of <= -5 points (deterioration) by heart failure physiology - RS (LOCF-AD) - 1245.121

Subgroup Description	Placebo	Empa 10mg
Heart failure physiology: LVEF <= 30% and NTproBNP < median		
Number of patients in analysis set	723	698
Number of analysed patients, N (%)	679 (100.0)	655 (100.0)
Number of patients with endpoint, N (%)	163 (24.0)	127 (19.4)
95% confidence interval*	(20.9, 27.4)	(16.5, 22.6)
Comparison vs Placebo**		
Odds ratio (SE)		0.739 (0.100)
95% confidence interval***		(0.566, 0.965)
p-value		0.0261
Heart failure physiology: LVEF <= 30% and NTproBNP >= median		
Number of patients in analysis set	661	631
Number of analysed patients, N (%)	588 (100.0)	586 (100.0)
Number of patients with endpoint, N (%)	173 (29.4)	141 (24.1)
95% confidence interval*	(25.9, 33.2)	(20.8, 27.7)
Comparison vs Placebo**		
Odds ratio (SE)		0.758 (0.103)
95% confidence interval***		(0.582, 0.989)
p-value		0.0411

* Wilson confidence intervals.
** Logistic regression includes terms for baseline KCCQ - clinical summary score (p<0.0001), age (p=0.0136), baseline eGFR (CKD-EPI) (p=0.0035), Treatment (p=0.0214), region (5 cat.) (p<0.0001), baseline diabetes status (3 cat.) (p=0.9086), sex (p=0.4964), heart failure physiology (p=0.0086) and Treatment by heart failure physiology interaction (p=0.2427).
***Wald confidence intervals.
16 patients were excluded as the subgroup variable was missing.

Data taken from study 1245.121 only.
LOCF: For a missing value at week 52 the last available post-baseline value before week 52 is imputed.
NTproBNP median [pg/mL]: with a. fibrillation/flutter at baseline: 2265; without a. fibrillation/flutter at baseline: 1671.

Table R.1.2.4.12: 1 Responder analysis (displaying odds ratio) in KCCQ-CSS change from baseline at week 52 of <= -5 points (deterioration) by heart failure physiology - RS (LOCF-AD) - 1245.121

Subgroup Description	Placebo	Empa 10mg
Heart failure physiology: LVEF > 30%		
Number of patients in analysis set	475	526
Number of analysed patients, N (%)	437 (100.0)	495 (100.0)
Number of patients with endpoint, N (%)	111 (25.4)	127 (25.7)
95% confidence interval*	(21.5, 29.7)	(22.0, 29.7)
Comparison vs Placebo**		
Odds ratio (SE)		1.014 (0.156)
95% confidence interval***		(0.751, 1.370)
p-value		0.9269

* Wilson confidence intervals.
** Logistic regression includes terms for baseline KCCQ - clinical summary score (p<0.0001), age (p=0.0136), baseline eGFR (CKD-EPI) (p=0.0035), Treatment (p=0.0214), region (5 cat.) (p<0.0001), baseline diabetes status (3 cat.) (p=0.9086), sex (p=0.4964), heart failure physiology (p=0.0086) and Treatment by heart failure physiology interaction (p=0.2427).
***Wald confidence intervals.
16 patients were excluded as the subgroup variable was missing.

Data taken from study 1245.121 only.
LOCF: For a missing value at week 52 the last available post-baseline value before week 52 is imputed.
NTproBNP median [pg/mL]: with a. fibrillation/flutter at baseline: 2265; without a. fibrillation/flutter at baseline: 1671.

Table R.1.2.4.12: 2 Responder analysis (displaying risk ratio) in KCCQ-CSS change from baseline at week 52 of <= -5 points (deterioration) by heart failure physiology - RS (LOCF-AD) - 1245.121

Subgroup Description	Placebo	Empa 10mg
Heart failure physiology: LVEF <= 30% and NTproBNP < median		
Number of patients in analysis set	723	698
Number of analysed patients, N (%)	679 (100.0)	655 (100.0)
Number of patients with endpoint, N (%)	163 (24.0)	127 (19.4)
95% confidence interval*	(20.9, 27.4)	(16.5, 22.6)
Comparison vs Placebo**		
Risk ratio (SE)		0.795 (0.082)
95% confidence interval***		(0.649, 0.974)
p-value		0.0268
Heart failure physiology: LVEF <= 30% and NTproBNP >= median		
Number of patients in analysis set	661	631
Number of analysed patients, N (%)	588 (100.0)	586 (100.0)
Number of patients with endpoint, N (%)	173 (29.4)	141 (24.1)
95% confidence interval*	(25.9, 33.2)	(20.8, 27.7)
Comparison vs Placebo**		
Risk ratio (SE)		0.823 (0.078)
95% confidence interval***		(0.683, 0.992)
p-value		0.0404

* Wilson confidence intervals.
** Log-linked Poisson model with robust estimate of variance includes terms for baseline KCCQ - clinical summary score (p<0.0001), age (p=0.0143), baseline eGFR (CKD-EPI) (p=0.0037), Treatment (p=0.0197), region (5 cat.) (p=0.0001), baseline diabetes status (3 cat.) (p=0.9133), sex (p=0.4836), heart failure physiology (p=0.0091) and Treatment by heart failure physiology interaction (p=0.2324).
***Wald confidence intervals.
16 patients were excluded as the subgroup variable was missing.

Data taken from study 1245.121 only.
LOCF: For a missing value at week 52 the last available post-baseline value before week 52 is imputed.
NTproBNP median [pg/mL]: with a. fibrillation/flutter at baseline: 2265; without a. fibrillation/flutter at baseline: 1671.

Table R.1.2.4.12: 2 Responder analysis (displaying risk ratio) in KCCQ-CSS change from baseline at week 52 of <= -5 points (deterioration) by heart failure physiology - RS (LOCF-AD) - 1245.121

Subgroup Description	Placebo	Empa 10mg
Heart failure physiology: LVEF > 30%		
Number of patients in analysis set	475	526
Number of analysed patients, N (%)	437 (100.0)	495 (100.0)
Number of patients with endpoint, N (%)	111 (25.4)	127 (25.7)
95% confidence interval*	(21.5, 29.7)	(22.0, 29.7)
Comparison vs Placebo**		
Risk ratio (SE)		1.009 (0.110)
95% confidence interval***		(0.814, 1.250)
p-value		0.9350

* Wilson confidence intervals.
** Log-linked Poisson model with robust estimate of variance includes terms for baseline KCCQ - clinical summary score (p<0.0001), age (p=0.0143), baseline eGFR (CKD-EPI) (p=0.0037), Treatment (p=0.0197), region (5 cat.) (p=0.0001), baseline diabetes status (3 cat.) (p=0.9133), sex (p=0.4836), heart failure physiology (p=0.0091) and Treatment by heart failure physiology interaction (p=0.2324).
***Wald confidence intervals.
16 patients were excluded as the subgroup variable was missing.

Data taken from study 1245.121 only.
LOCF: For a missing value at week 52 the last available post-baseline value before week 52 is imputed.
NTproBNP median [pg/mL]: with a. fibrillation/flutter at baseline: 2265; without a. fibrillation/flutter at baseline: 1671.

Table R.1.2.4.12: 3 Responder analysis (displaying odds ratio) in KCCQ-CSS change from baseline at week 52 of > -5 points (stability) by heart failure physiology - RS (LOCF-AD) - 1245.121

Subgroup Description	Placebo	Empa 10mg
Heart failure physiology: LVEF <= 30% and NTproBNP < median		
Number of patients in analysis set	723	698
Number of analysed patients, N (%)	679 (100.0)	655 (100.0)
Number of patients with endpoint, N (%)	516 (76.0)	528 (80.6)
95% confidence interval*	(72.6, 79.1)	(77.4, 83.5)
Comparison vs Placebo**		
Odds ratio (SE)		1.353 (0.184)
95% confidence interval***		(1.037, 1.765)
p-value		0.0261
Heart failure physiology: LVEF <= 30% and NTproBNP >= median		
Number of patients in analysis set	661	631
Number of analysed patients, N (%)	588 (100.0)	586 (100.0)
Number of patients with endpoint, N (%)	415 (70.6)	445 (75.9)
95% confidence interval*	(66.8, 74.1)	(72.3, 79.2)
Comparison vs Placebo**		
Odds ratio (SE)		1.319 (0.178)
95% confidence interval***		(1.011, 1.719)
p-value		0.0411

* Wilson confidence intervals.
** Logistic regression includes terms for baseline KCCQ - clinical summary score (p<0.0001), age (p=0.0136), baseline eGFR (CKD-EPI) (p=0.0035), Treatment (p=0.0214), region (5 cat.) (p<0.0001), baseline diabetes status (3 cat.) (p=0.9086), sex (p=0.4964), heart failure physiology (p=0.0086) and Treatment by heart failure physiology interaction (p=0.2427).
***Wald confidence intervals.
16 patients were excluded as the subgroup variable was missing.

Data taken from study 1245.121 only.
LOCF: For a missing value at week 52 the last available post-baseline value before week 52 is imputed.
NTproBNP median [pg/mL]: with a. fibrillation/flutter at baseline: 2265; without a. fibrillation/flutter at baseline: 1671.

Table R.1.2.4.12: 3 Responder analysis (displaying odds ratio) in KCCQ-CSS change from baseline at week 52 of > -5 points (stability) by heart failure physiology - RS (LOCF-AD) - 1245.121

Subgroup Description	Placebo	Empa 10mg
Heart failure physiology: LVEF > 30%		
Number of patients in analysis set	475	526
Number of analysed patients, N (%)	437 (100.0)	495 (100.0)
Number of patients with endpoint, N (%)	326 (74.6)	368 (74.3)
95% confidence interval*	(70.3, 78.5)	(70.3, 78.0)
Comparison vs Placebo**		
Odds ratio (SE)		0.986 (0.151)
95% confidence interval***		(0.730, 1.332)
p-value		0.9269

* Wilson confidence intervals.
** Logistic regression includes terms for baseline KCCQ - clinical summary score (p<0.0001), age (p=0.0136), baseline eGFR (CKD-EPI) (p=0.0035), Treatment (p=0.0214), region (5 cat.) (p<0.0001), baseline diabetes status (3 cat.) (p=0.9086), sex (p=0.4964), heart failure physiology (p=0.0086) and Treatment by heart failure physiology interaction (p=0.2427).
***Wald confidence intervals.
16 patients were excluded as the subgroup variable was missing.

Data taken from study 1245.121 only.
LOCF: For a missing value at week 52 the last available post-baseline value before week 52 is imputed.
NTproBNP median [pg/mL]: with a. fibrillation/flutter at baseline: 2265; without a. fibrillation/flutter at baseline: 1671.

Table R.1.2.4.12: 4 Responder analysis (displaying risk ratio) in KCCQ-CSS change from baseline at week 52 of > -5 points (stability) by heart failure physiology - RS (LOCF-AD) - 1245.121

Subgroup Description	Placebo	Empa 10mg
Heart failure physiology: LVEF <= 30% and NTproBNP < median		
Number of patients in analysis set	723	698
Number of analysed patients, N (%)	679 (100.0)	655 (100.0)
Number of patients with endpoint, N (%)	516 (76.0)	528 (80.6)
95% confidence interval*	(72.6, 79.1)	(77.4, 83.5)
Comparison vs Placebo**		
Risk ratio (SE)		1.066 (0.030)
95% confidence interval***		(1.008, 1.127)
p-value		0.0254
Heart failure physiology: LVEF <= 30% and NTproBNP >= median		
Number of patients in analysis set	661	631
Number of analysed patients, N (%)	588 (100.0)	586 (100.0)
Number of patients with endpoint, N (%)	415 (70.6)	445 (75.9)
95% confidence interval*	(66.8, 74.1)	(72.3, 79.2)
Comparison vs Placebo**		
Risk ratio (SE)		1.073 (0.037)
95% confidence interval***		(1.003, 1.149)
p-value		0.0413

* Wilson confidence intervals.
** Log-linked Poisson model with robust estimate of variance includes terms for baseline KCCQ - clinical summary score (p<0.0001), age (p=0.0219), baseline eGFR (CKD-EPI) (p=0.0043), Treatment (p=0.0290), region (5 cat.) (p<0.0001), baseline diabetes status (3 cat.) (p=0.9049), sex (p=0.4893), heart failure physiology (p=0.0069) and Treatment by heart failure physiology interaction (p=0.2406).
***Wald confidence intervals.
16 patients were excluded as the subgroup variable was missing.

Data taken from study 1245.121 only.
LOCF: For a missing value at week 52 the last available post-baseline value before week 52 is imputed.
NTproBNP median [pg/mL]: with a. fibrillation/flutter at baseline: 2265; without a. fibrillation/flutter at baseline: 1671.

Table R.1.2.4.12: 4 Responder analysis (displaying risk ratio) in KCCQ-CSS change from baseline at week 52 of > -5 points (stability) by heart failure physiology - RS (LOCF-AD) - 1245.121

Subgroup Description	Placebo	Empa 10mg
Heart failure physiology: LVEF > 30%		
Number of patients in analysis set	475	526
Number of analysed patients, N (%)	437 (100.0)	495 (100.0)
Number of patients with endpoint, N (%)	326 (74.6)	368 (74.3)
95% confidence interval*	(70.3, 78.5)	(70.3, 78.0)
Comparison vs Placebo**		
Risk ratio (SE)		0.993 (0.037)
95% confidence interval***		(0.923, 1.069)
p-value		0.8608

* Wilson confidence intervals.
** Log-linked Poisson model with robust estimate of variance includes terms for baseline KCCQ - clinical summary score (p<0.0001), age (p=0.0219), baseline eGFR (CKD-EPI) (p=0.0043), Treatment (p=0.0290), region (5 cat.) (p<0.0001), baseline diabetes status (3 cat.) (p=0.9049), sex (p=0.4893), heart failure physiology (p=0.0069) and Treatment by heart failure physiology interaction (p=0.2406).
***Wald confidence intervals.
16 patients were excluded as the subgroup variable was missing.

Data taken from study 1245.121 only.
LOCF: For a missing value at week 52 the last available post-baseline value before week 52 is imputed.
NTproBNP median [pg/mL]: with a. fibrillation/flutter at baseline: 2265; without a. fibrillation/flutter at baseline: 1671.

Table R.1.2.4.12: 5 Responder analysis (displaying odds ratio) in KCCQ-CSS change from baseline at week 52 of >= 5 points (improvement) by heart failure physiology - RS (LOCF-AD) - 1245.121

Subgroup Description	Placebo	Empa 10mg
Heart failure physiology: LVEF <= 30% and NTproBNP < median		
Number of patients in analysis set	723	698
Number of analysed patients, N (%)	679 (100.0)	655 (100.0)
Number of patients with endpoint, N (%)	273 (40.2)	305 (46.6)
95% confidence interval*	(36.6, 43.9)	(42.8, 50.4)
Comparison vs Placebo**		
Odds ratio (SE)		1.411 (0.171)
95% confidence interval***		(1.113, 1.788)
p-value		0.0044
Heart failure physiology: LVEF <= 30% and NTproBNP >= median		
Number of patients in analysis set	661	631
Number of analysed patients, N (%)	588 (100.0)	586 (100.0)
Number of patients with endpoint, N (%)	248 (42.2)	277 (47.3)
95% confidence interval*	(38.2, 46.2)	(43.3, 51.3)
Comparison vs Placebo**		
Odds ratio (SE)		1.216 (0.157)
95% confidence interval***		(0.943, 1.567)
p-value		0.1315

* Wilson confidence intervals.
** Logistic regression includes terms for baseline KCCQ - clinical summary score (p<0.0001), age (p=0.0197), baseline eGFR (CKD-EPI) (p=0.9528), Treatment (p=0.0104), region (5 cat.) (p<0.0001), baseline diabetes status (3 cat.) (p=0.7367), sex (p=0.7617), heart failure physiology (p=0.1743) and Treatment by heart failure physiology interaction (p=0.2839).
***Wald confidence intervals.
16 patients were excluded as the subgroup variable was missing.

Data taken from study 1245.121 only.
LOCF: For a missing value at week 52 the last available post-baseline value before week 52 is imputed.
NTproBNP median [pg/mL]: with a. fibrillation/flutter at baseline: 2265; without a. fibrillation/flutter at baseline: 1671.

Table R.1.2.4.12: 5 Responder analysis (displaying odds ratio) in KCCQ-CSS change from baseline at week 52 of >= 5 points (improvement) by heart failure physiology - RS (LOCF-AD) - 1245.121

Subgroup Description	Placebo	Empa 10mg
Heart failure physiology: LVEF > 30%		
Number of patients in analysis set	475	526
Number of analysed patients, N (%)	437 (100.0)	495 (100.0)
Number of patients with endpoint, N (%)	192 (43.9)	222 (44.8)
95% confidence interval*	(39.4, 48.6)	(40.5, 49.3)
Comparison vs Placebo**		
Odds ratio (SE)		1.048 (0.152)
95% confidence interval***		(0.789, 1.392)
p-value		0.7480

* Wilson confidence intervals.
** Logistic regression includes terms for baseline KCCQ - clinical summary score (p<0.0001), age (p=0.0197), baseline eGFR (CKD-EPI) (p=0.9528), Treatment (p=0.0104), region (5 cat.) (p<0.0001), baseline diabetes status (3 cat.) (p=0.7367), sex (p=0.7617), heart failure physiology (p=0.1743) and Treatment by heart failure physiology interaction (p=0.2839).
***Wald confidence intervals.
16 patients were excluded as the subgroup variable was missing.

Data taken from study 1245.121 only.
LOCF: For a missing value at week 52 the last available post-baseline value before week 52 is imputed.
NTproBNP median [pg/mL]: with a. fibrillation/flutter at baseline: 2265; without a. fibrillation/flutter at baseline: 1671.

Table R.1.2.4.12: 6 Responder analysis (displaying risk ratio) in KCCQ-CSS change from baseline at week 52 of >= 5 points (improvement) by heart failure physiology - RS (LOCF-AD) - 1245.121

Subgroup Description	Placebo	Empa 10mg
Heart failure physiology: LVEF <= 30% and NTproBNP < median		
Number of patients in analysis set	723	698
Number of analysed patients, N (%)	679 (100.0)	655 (100.0)
Number of patients with endpoint, N (%)	273 (40.2)	305 (46.6)
95% confidence interval*	(36.6, 43.9)	(42.8, 50.4)
Comparison vs Placebo**		
Risk ratio (SE)		1.172 (0.069)
95% confidence interval***		(1.045, 1.316)
p-value		0.0068
Heart failure physiology: LVEF <= 30% and NTproBNP >= median		
Number of patients in analysis set	661	631
Number of analysed patients, N (%)	588 (100.0)	586 (100.0)
Number of patients with endpoint, N (%)	248 (42.2)	277 (47.3)
95% confidence interval*	(38.2, 46.2)	(43.3, 51.3)
Comparison vs Placebo**		
Risk ratio (SE)		1.099 (0.067)
95% confidence interval***		(0.976, 1.238)
p-value		0.1185

* Wilson confidence intervals.
** Log-linked Poisson model with robust estimate of variance includes terms for baseline KCCQ - clinical summary score (p<0.0001), age (p=0.0412), baseline eGFR (CKD-EPI) (p=0.9600), Treatment (p=0.0200), region (5 cat.) (p<0.0001), baseline diabetes status (3 cat.) (p=0.6854), sex (p=0.8888), heart failure physiology (p=0.1671) and Treatment by heart failure physiology interaction (p=0.2089).
***Wald confidence intervals.
16 patients were excluded as the subgroup variable was missing.

Data taken from study 1245.121 only.
LOCF: For a missing value at week 52 the last available post-baseline value before week 52 is imputed.
NTproBNP median [pg/mL]: with a. fibrillation/flutter at baseline: 2265; without a. fibrillation/flutter at baseline: 1671.

Table R.1.2.4.12: 6 Responder analysis (displaying risk ratio) in KCCQ-CSS change from baseline at week 52 of >= 5 points (improvement) by heart failure physiology - RS (LOCF-AD) - 1245.121

Subgroup Description	Placebo	Empa 10mg
Heart failure physiology: LVEF > 30%		
Number of patients in analysis set	475	526
Number of analysed patients, N (%)	437 (100.0)	495 (100.0)
Number of patients with endpoint, N (%)	192 (43.9)	222 (44.8)
95% confidence interval*	(39.4, 48.6)	(40.5, 49.3)
Comparison vs Placebo**		
Risk ratio (SE)		0.999 (0.069)
95% confidence interval***		(0.874, 1.143)
p-value		0.9907

* Wilson confidence intervals.
** Log-linked Poisson model with robust estimate of variance includes terms for baseline KCCQ - clinical summary score (p<0.0001), age (p=0.0412), baseline eGFR (CKD-EPI) (p=0.9600), Treatment (p=0.0200), region (5 cat.) (p<0.0001), baseline diabetes status (3 cat.) (p=0.6854), sex (p=0.8888), heart failure physiology (p=0.1671) and Treatment by heart failure physiology interaction (p=0.2089).
***Wald confidence intervals.
16 patients were excluded as the subgroup variable was missing.

Data taken from study 1245.121 only.
LOCF: For a missing value at week 52 the last available post-baseline value before week 52 is imputed.
NTproBNP median [pg/mL]: with a. fibrillation/flutter at baseline: 2265; without a. fibrillation/flutter at baseline: 1671.

R.1.2.4.13

Table R.1.2.4.13: 1 Responder analysis (displaying odds ratio) in KCCQ-CSS change from baseline at week 52 of <= -5 points (deterioration) by baseline use of MRA (Y/N) - RS (LOCF-AD) - 1245.121

Subgroup Description	Placebo	Empa 10mg
Baseline use of MRA: No		
Number of patients in analysis set	512	557
Number of analysed patients, N (%)	475 (100.0)	522 (100.0)
Number of patients with endpoint, N (%)	131 (27.6)	116 (22.2)
95% confidence interval*	(23.8, 31.8)	(18.9, 26.0)
Comparison vs Placebo**		
Odds ratio (SE)		0.748 (0.112)
95% confidence interval***		(0.558, 1.003)
p-value		0.0520
Baseline use of MRA: Yes		
Number of patients in analysis set	1355	1306
Number of analysed patients, N (%)	1234 (100.0)	1218 (100.0)
Number of patients with endpoint, N (%)	317 (25.7)	281 (23.1)
95% confidence interval*	(23.3, 28.2)	(20.8, 25.5)
Comparison vs Placebo**		
Odds ratio (SE)		0.854 (0.082)
95% confidence interval***		(0.707, 1.031)
p-value		0.1004

* Wilson confidence intervals.
** Logistic regression includes terms for baseline KCCQ - clinical summary score (p<0.0001), age (p=0.0118), baseline eGFR (CKD-EPI) (p=0.0005), Treatment (p=0.0116), region (5 cat.) (p=0.0002), baseline diabetes status (3 cat.) (p=0.9087), sex (p=0.4798), baseline LVEF (3 cat.) (p=0.6701), baseline use of MRA (p=0.2870) and Treatment by baseline use of MRA interaction (p=0.4554).
***Wald confidence intervals.

Data taken from study 1245.121 only.
LOCF: For a missing value at week 52 the last available post-baseline value before week 52 is imputed.

Table R.1.2.4.13: 2 Responder analysis (displaying risk ratio) in KCCQ-CSS change from baseline at week 52 of <= -5 points (deterioration) by baseline use of MRA (Y/N) - RS (LOCF-AD) - 1245.121

Subgroup Description	Placebo	Empa 10mg
Baseline use of MRA: No		
Number of patients in analysis set	512	557
Number of analysed patients, N (%)	475 (100.0)	522 (100.0)
Number of patients with endpoint, N (%)	131 (27.6)	116 (22.2)
95% confidence interval*	(23.8, 31.8)	(18.9, 26.0)
Comparison vs Placebo**		
Risk ratio (SE)		0.809 (0.087)
95% confidence interval***		(0.655, 0.999)
p-value		0.0494
Baseline use of MRA: Yes		
Number of patients in analysis set	1355	1306
Number of analysed patients, N (%)	1234 (100.0)	1218 (100.0)
Number of patients with endpoint, N (%)	317 (25.7)	281 (23.1)
95% confidence interval*	(23.3, 28.2)	(20.8, 25.5)
Comparison vs Placebo**		
Risk ratio (SE)		0.890 (0.062)
95% confidence interval***		(0.776, 1.022)
p-value		0.0977

* Wilson confidence intervals.
** Log-linked Poisson model with robust estimate of variance includes terms for baseline KCCQ - clinical summary score (p<0.0001), age (p=0.0122), baseline eGFR (CKD-EPI) (p=0.0006), Treatment (p=0.0107), region (5 cat.) (p=0.0003), baseline diabetes status (3 cat.) (p=0.9110), sex (p=0.4610), baseline LVEF (3 cat.) (p=0.6642), baseline use of MRA (p=0.2771) and Treatment by baseline use of MRA interaction (p=0.4572).
***Wald confidence intervals.

Data taken from study 1245.121 only.
LOCF: For a missing value at week 52 the last available post-baseline value before week 52 is imputed.

Table R.1.2.4.13: 3 Responder analysis (displaying odds ratio) in KCCQ-CSS change from baseline at week 52 of > -5 points (stability) by baseline use of MRA (Y/N) - RS (LOCF-AD) - 1245.121

Subgroup Description	Placebo	Empa 10mg
Baseline use of MRA: No		
Number of patients in analysis set	512	557
Number of analysed patients, N (%)	475 (100.0)	522 (100.0)
Number of patients with endpoint, N (%)	344 (72.4)	406 (77.8)
95% confidence interval*	(68.2, 76.2)	(74.0, 81.1)
Comparison vs Placebo**		
Odds ratio (SE)		1.337 (0.200)
95% confidence interval***		(0.997, 1.793)
p-value		0.0520
Baseline use of MRA: Yes		
Number of patients in analysis set	1355	1306
Number of analysed patients, N (%)	1234 (100.0)	1218 (100.0)
Number of patients with endpoint, N (%)	917 (74.3)	937 (76.9)
95% confidence interval*	(71.8, 76.7)	(74.5, 79.2)
Comparison vs Placebo**		
Odds ratio (SE)		1.171 (0.113)
95% confidence interval***		(0.970, 1.414)
p-value		0.1004

* Wilson confidence intervals.
** Logistic regression includes terms for baseline KCCQ - clinical summary score (p<0.0001), age (p=0.0118), baseline eGFR (CKD-EPI) (p=0.0005), Treatment (p=0.0116), region (5 cat.) (p=0.0002), baseline diabetes status (3 cat.) (p=0.9087), sex (p=0.4798), baseline LVEF (3 cat.) (p=0.6701), baseline use of MRA (p=0.2870) and Treatment by baseline use of MRA interaction (p=0.4554).
***Wald confidence intervals.

Data taken from study 1245.121 only.
LOCF: For a missing value at week 52 the last available post-baseline value before week 52 is imputed.

Table R.1.2.4.13: 4 Responder analysis (displaying risk ratio) in KCCQ-CSS change from baseline at week 52 of > -5 points (stability) by baseline use of MRA (Y/N) - RS (LOCF-AD) - 1245.121

Subgroup Description	Placebo	Empa 10mg
Baseline use of MRA: No		
Number of patients in analysis set	512	557
Number of analysed patients, N (%)	475 (100.0)	522 (100.0)
Number of patients with endpoint, N (%)	344 (72.4)	406 (77.8)
95% confidence interval*	(68.2, 76.2)	(74.0, 81.1)
Comparison vs Placebo**		
Risk ratio (SE)		1.071 (0.039)
95% confidence interval***		(0.998, 1.149)
p-value		0.0563
Baseline use of MRA: Yes		
Number of patients in analysis set	1355	1306
Number of analysed patients, N (%)	1234 (100.0)	1218 (100.0)
Number of patients with endpoint, N (%)	917 (74.3)	937 (76.9)
95% confidence interval*	(71.8, 76.7)	(74.5, 79.2)
Comparison vs Placebo**		
Risk ratio (SE)		1.037 (0.023)
95% confidence interval***		(0.992, 1.084)
p-value		0.1086

* Wilson confidence intervals.
** Log-linked Poisson model with robust estimate of variance includes terms for baseline KCCQ - clinical summary score (p<0.0001), age (p=0.0197), baseline eGFR (CKD-EPI) (p=0.0007), Treatment (p=0.0135), region (5 cat.) (p<0.0001), baseline diabetes status (3 cat.) (p=0.9157), sex (p=0.5002), baseline LVEF (3 cat.) (p=0.6502), baseline use of MRA (p=0.3125) and Treatment by baseline use of MRA interaction (p=0.4468).
***Wald confidence intervals.

Data taken from study 1245.121 only.
LOCF: For a missing value at week 52 the last available post-baseline value before week 52 is imputed.

Table R.1.2.4.13: 5 Responder analysis (displaying odds ratio) in KCCQ-CSS change from baseline at week 52 of >= 5 points (improvement) by baseline use of MRA (Y/N) - RS (LOCF-AD) - 1245.121

Subgroup Description	Placebo	Empa 10mg
Baseline use of MRA: No		
Number of patients in analysis set	512	557
Number of analysed patients, N (%)	475 (100.0)	522 (100.0)
Number of patients with endpoint, N (%)	194 (40.8)	248 (47.5)
95% confidence interval*	(36.5, 45.3)	(43.3, 51.8)
Comparison vs Placebo**		
Odds ratio (SE)		1.381 (0.193)
95% confidence interval***		(1.051, 1.816)
p-value		0.0207
Baseline use of MRA: Yes		
Number of patients in analysis set	1355	1306
Number of analysed patients, N (%)	1234 (100.0)	1218 (100.0)
Number of patients with endpoint, N (%)	523 (42.4)	558 (45.8)
95% confidence interval*	(39.7, 45.2)	(43.0, 48.6)
Comparison vs Placebo**		
Odds ratio (SE)		1.173 (0.105)
95% confidence interval***		(0.984, 1.398)
p-value		0.0753

* Wilson confidence intervals.
** Logistic regression includes terms for baseline KCCQ - clinical summary score (p<0.0001), age (p=0.0126), baseline eGFR (CKD-EPI) (p=0.6746), Treatment (p=0.0036), region (5 cat.) (p<0.0001), baseline diabetes status (3 cat.) (p=0.7614), sex (p=0.7839), baseline LVEF (3 cat.) (p=0.2988), baseline use of MRA (p=0.0306) and Treatment by baseline use of MRA interaction (p=0.3232).
***Wald confidence intervals.

Data taken from study 1245.121 only.
LOCF: For a missing value at week 52 the last available post-baseline value before week 52 is imputed.

Table R.1.2.4.13: 6 Responder analysis (displaying risk ratio) in KCCQ-CSS change from baseline at week 52 of >= 5 points (improvement) by baseline use of MRA (Y/N) - RS (LOCF-AD) - 1245.121

Subgroup Description	Placebo	Empa 10mg
Baseline use of MRA: No		
Number of patients in analysis set	512	557
Number of analysed patients, N (%)	475 (100.0)	522 (100.0)
Number of patients with endpoint, N (%)	194 (40.8)	248 (47.5)
95% confidence interval*	(36.5, 45.3)	(43.3, 51.8)
Comparison vs Placebo**		
Risk ratio (SE)		1.145 (0.076)
95% confidence interval***		(1.005, 1.305)
p-value		0.0421
Baseline use of MRA: Yes		
Number of patients in analysis set	1355	1306
Number of analysed patients, N (%)	1234 (100.0)	1218 (100.0)
Number of patients with endpoint, N (%)	523 (42.4)	558 (45.8)
95% confidence interval*	(39.7, 45.2)	(43.0, 48.6)
Comparison vs Placebo**		
Risk ratio (SE)		1.073 (0.046)
95% confidence interval***		(0.987, 1.167)
p-value		0.0974

* Wilson confidence intervals.
** Log-linked Poisson model with robust estimate of variance includes terms for baseline KCCQ - clinical summary score (p<0.0001), age (p=0.0272), baseline eGFR (CKD-EPI) (p=0.7001), Treatment (p=0.0091), region (5 cat.) (p<0.0001), baseline diabetes status (3 cat.) (p=0.7227), sex (p=0.9740), baseline LVEF (3 cat.) (p=0.2480), baseline use of MRA (p=0.0422) and Treatment by baseline use of MRA interaction (p=0.4131).
***Wald confidence intervals.

Data taken from study 1245.121 only.
LOCF: For a missing value at week 52 the last available post-baseline value before week 52 is imputed.

R.1.2.4.14

Table R.1.2.4.14: 1 Responder analysis (displaying odds ratio) in KCCQ-CSS change from baseline at week 52 of <= -5 points (deterioration) by baseline use of ARNi (Y/N) - RS (LOCF-AD) - 1245.121

Subgroup Description	Placebo	Empa 10mg
Baseline use of ARNi: No		
Number of patients in analysis set	1480	1523
Number of analysed patients, N (%)	1350 (100.0)	1418 (100.0)
Number of patients with endpoint, N (%)	357 (26.4)	333 (23.5)
95% confidence interval*	(24.2, 28.9)	(21.4, 25.8)
Comparison vs Placebo**		
Odds ratio (SE)		0.837 (0.075)
95% confidence interval***		(0.702, 0.997)
p-value		0.0467
Baseline use of ARNi: Yes		
Number of patients in analysis set	387	340
Number of analysed patients, N (%)	359 (100.0)	322 (100.0)
Number of patients with endpoint, N (%)	91 (25.3)	64 (19.9)
95% confidence interval*	(21.1, 30.1)	(15.9, 24.6)
Comparison vs Placebo**		
Odds ratio (SE)		0.732 (0.138)
95% confidence interval***		(0.506, 1.060)
p-value		0.0984

* Wilson confidence intervals.
** Logistic regression includes terms for baseline KCCQ - clinical summary score (p<0.0001), age (p=0.0165), baseline eGFR (CKD-EPI) (p=0.0006), Treatment (p=0.0189), region (5 cat.) (p=0.0001), baseline diabetes status (3 cat.) (p=0.9181), sex (p=0.4353), baseline LVEF (3 cat.) (p=0.7137), baseline use of ARNi (p=0.0792) and Treatment by baseline use of ARNi interaction (p=0.5225).
***Wald confidence intervals.

Data taken from study 1245.121 only.
LOCF: For a missing value at week 52 the last available post-baseline value before week 52 is imputed.

Table R.1.2.4.14: 2 Responder analysis (displaying risk ratio) in KCCQ-CSS change from baseline at week 52 of <= -5 points (deterioration) by baseline use of ARNi (Y/N) - RS (LOCF-AD) - 1245.121

Subgroup Description	Placebo	Empa 10mg
Baseline use of ARNi: No		
Number of patients in analysis set	1480	1523
Number of analysed patients, N (%)	1350 (100.0)	1418 (100.0)
Number of patients with endpoint, N (%)	357 (26.4)	333 (23.5)
95% confidence interval*	(24.2, 28.9)	(21.4, 25.8)
Comparison vs Placebo**		
Risk ratio (SE)		0.878 (0.057)
95% confidence interval***		(0.774, 0.997)
p-value		0.0444
Baseline use of ARNi: Yes		
Number of patients in analysis set	387	340
Number of analysed patients, N (%)	359 (100.0)	322 (100.0)
Number of patients with endpoint, N (%)	91 (25.3)	64 (19.9)
95% confidence interval*	(21.1, 30.1)	(15.9, 24.6)
Comparison vs Placebo**		
Risk ratio (SE)		0.792 (0.112)
95% confidence interval***		(0.600, 1.044)
p-value		0.0977

* Wilson confidence intervals.
** Log-linked Poisson model with robust estimate of variance includes terms for baseline KCCQ - clinical summary score (p<0.0001), age (p=0.0172), baseline eGFR (CKD-EPI) (p=0.0007), Treatment (p=0.0191), region (5 cat.) (p=0.0002), baseline diabetes status (3 cat.) (p=0.9223), sex (p=0.4178), baseline LVEF (3 cat.) (p=0.7159), baseline use of ARNi (p=0.0751) and Treatment by baseline use of ARNi interaction (p=0.5045).
***Wald confidence intervals.

Data taken from study 1245.121 only.
LOCF: For a missing value at week 52 the last available post-baseline value before week 52 is imputed.

Table R.1.2.4.14: 3 Responder analysis (displaying odds ratio) in KCCQ-CSS change from baseline at week 52 of > -5 points (stability) by baseline use of ARNi (Y/N) - RS (LOCF-AD) - 1245.121

Subgroup Description	Placebo	Empa 10mg
Baseline use of ARNi: No		
Number of patients in analysis set	1480	1523
Number of analysed patients, N (%)	1350 (100.0)	1418 (100.0)
Number of patients with endpoint, N (%)	993 (73.6)	1085 (76.5)
95% confidence interval*	(71.1, 75.8)	(74.2, 78.6)
Comparison vs Placebo**		
Odds ratio (SE)		1.195 (0.107)
95% confidence interval***		(1.003, 1.425)
p-value		0.0467
Baseline use of ARNi: Yes		
Number of patients in analysis set	387	340
Number of analysed patients, N (%)	359 (100.0)	322 (100.0)
Number of patients with endpoint, N (%)	268 (74.7)	258 (80.1)
95% confidence interval*	(69.9, 78.9)	(75.4, 84.1)
Comparison vs Placebo**		
Odds ratio (SE)		1.366 (0.258)
95% confidence interval***		(0.944, 1.978)
p-value		0.0984

* Wilson confidence intervals.
** Logistic regression includes terms for baseline KCCQ - clinical summary score (p<0.0001), age (p=0.0165), baseline eGFR (CKD-EPI) (p=0.0006), Treatment (p=0.0189), region (5 cat.) (p=0.0001), baseline diabetes status (3 cat.) (p=0.9181), sex (p=0.4353), baseline LVEF (3 cat.) (p=0.7137), baseline use of ARNi (p=0.0792) and Treatment by baseline use of ARNi interaction (p=0.5225).
***Wald confidence intervals.

Data taken from study 1245.121 only.
LOCF: For a missing value at week 52 the last available post-baseline value before week 52 is imputed.

Table R.1.2.4.14: 4 Responder analysis (displaying risk ratio) in KCCQ-CSS change from baseline at week 52 of > -5 points (stability) by baseline use of ARNi (Y/N) - RS (LOCF-AD) - 1245.121

Subgroup Description	Placebo	Empa 10mg
Baseline use of ARNi: No		
Number of patients in analysis set	1480	1523
Number of analysed patients, N (%)	1350 (100.0)	1418 (100.0)
Number of patients with endpoint, N (%)	993 (73.6)	1085 (76.5)
95% confidence interval*	(71.1, 75.8)	(74.2, 78.6)
Comparison vs Placebo**		
Risk ratio (SE)		1.042 (0.023)
95% confidence interval***		(0.999, 1.087)
p-value		0.0552
Baseline use of ARNi: Yes		
Number of patients in analysis set	387	340
Number of analysed patients, N (%)	359 (100.0)	322 (100.0)
Number of patients with endpoint, N (%)	268 (74.7)	258 (80.1)
95% confidence interval*	(69.9, 78.9)	(75.4, 84.1)
Comparison vs Placebo**		
Risk ratio (SE)		1.070 (0.044)
95% confidence interval***		(0.988, 1.160)
p-value		0.0969

* Wilson confidence intervals.
** Log-linked Poisson model with robust estimate of variance includes terms for baseline KCCQ - clinical summary score (p<0.0001), age (p=0.0282), baseline eGFR (CKD-EPI) (p=0.0009), Treatment (p=0.0180), region (5 cat.) (p<0.0001), baseline diabetes status (3 cat.) (p=0.9175), sex (p=0.4602), baseline LVEF (3 cat.) (p=0.6947), baseline use of ARNi (p=0.1031) and Treatment by baseline use of ARNi interaction (p=0.5673).
***Wald confidence intervals.

Data taken from study 1245.121 only.
LOCF: For a missing value at week 52 the last available post-baseline value before week 52 is imputed.

Table R.1.2.4.14: 5 Responder analysis (displaying odds ratio) in KCCQ-CSS change from baseline at week 52 of >= 5 points (improvement) by baseline use of ARNi (Y/N) - RS (LOCF-AD) - 1245.121

Subgroup Description	Placebo	Empa 10mg
Baseline use of ARNi: No		
Number of patients in analysis set	1480	1523
Number of analysed patients, N (%)	1350 (100.0)	1418 (100.0)
Number of patients with endpoint, N (%)	574 (42.5)	673 (47.5)
95% confidence interval*	(39.9, 45.2)	(44.9, 50.1)
Comparison vs Placebo**		
Odds ratio (SE)		1.261 (0.106)
95% confidence interval***		(1.070, 1.486)
p-value		0.0057
Baseline use of ARNi: Yes		
Number of patients in analysis set	387	340
Number of analysed patients, N (%)	359 (100.0)	322 (100.0)
Number of patients with endpoint, N (%)	143 (39.8)	133 (41.3)
95% confidence interval*	(34.9, 45.0)	(36.1, 46.8)
Comparison vs Placebo**		
Odds ratio (SE)		1.108 (0.191)
95% confidence interval***		(0.791, 1.553)
p-value		0.5507

* Wilson confidence intervals.
** Logistic regression includes terms for baseline KCCQ - clinical summary score (p<0.0001), age (p=0.0186), baseline eGFR (CKD-EPI) (p=0.7848), Treatment (p=0.0805), region (5 cat.) (p<0.0001), baseline diabetes status (3 cat.) (p=0.7917), sex (p=0.7790), baseline LVEF (3 cat.) (p=0.2899), baseline use of ARNi (p=0.2573) and Treatment by baseline use of ARNi interaction (p=0.5003).
***Wald confidence intervals.

Data taken from study 1245.121 only.
LOCF: For a missing value at week 52 the last available post-baseline value before week 52 is imputed.

Table R.1.2.4.14: 6 Responder analysis (displaying risk ratio) in KCCQ-CSS change from baseline at week 52 of >= 5 points (improvement) by baseline use of ARNi (Y/N) - RS (LOCF-AD) - 1245.121

Subgroup Description	Placebo	Empa 10mg
Baseline use of ARNi: No		
Number of patients in analysis set	1480	1523
Number of analysed patients, N (%)	1350 (100.0)	1418 (100.0)
Number of patients with endpoint, N (%)	574 (42.5)	673 (47.5)
95% confidence interval*	(39.9, 45.2)	(44.9, 50.1)
Comparison vs Placebo**		
Risk ratio (SE)		1.103 (0.044)
95% confidence interval***		(1.021, 1.191)
p-value		0.0133
Baseline use of ARNi: Yes		
Number of patients in analysis set	387	340
Number of analysed patients, N (%)	359 (100.0)	322 (100.0)
Number of patients with endpoint, N (%)	143 (39.8)	133 (41.3)
95% confidence interval*	(34.9, 45.0)	(36.1, 46.8)
Comparison vs Placebo**		
Risk ratio (SE)		1.053 (0.091)
95% confidence interval***		(0.889, 1.249)
p-value		0.5476

* Wilson confidence intervals.
** Log-linked Poisson model with robust estimate of variance includes terms for baseline KCCQ - clinical summary score (p<0.0001), age (p=0.0365), baseline eGFR (CKD-EPI) (p=0.8098), Treatment (p=0.1151), region (5 cat.) (p<0.0001), baseline diabetes status (3 cat.) (p=0.7407), sex (p=0.9799), baseline LVEF (3 cat.) (p=0.2629), baseline use of ARNi (p=0.1690) and Treatment by baseline use of ARNi interaction (p=0.6320).
***Wald confidence intervals.

Data taken from study 1245.121 only.
LOCF: For a missing value at week 52 the last available post-baseline value before week 52 is imputed.

R.1.2.4.15 Subgroup analysis by bl. LVEF (<= 30%, >30% -<= 35% , > 35%)

Table R.1.2.4.15: 1 Responder analysis (displaying odds ratio) in KCCQ-CSS change from baseline at week 52 of <= -5 points (deterioration) by baseline LVEF (3 cat.) - RS (LOCF-AD) - 1245.121

Subgroup Description	Placebo	Empa 10mg
Baseline LVEF (3 cat.): <=30		
Number of patients in analysis set	1392	1337
Number of analysed patients, N (%)	1272 (100.0)	1245 (100.0)
Number of patients with endpoint, N (%)	337 (26.5)	270 (21.7)
95% confidence interval*	(24.1, 29.0)	(19.5, 24.1)
Comparison vs Placebo**		
Odds ratio (SE)		0.755 (0.072)
95% confidence interval***		(0.626, 0.910)
p-value		0.0032
Baseline LVEF (3 cat.): >30 to <=35		
Number of patients in analysis set	361	398
Number of analysed patients, N (%)	333 (100.0)	375 (100.0)
Number of patients with endpoint, N (%)	77 (23.1)	101 (26.9)
95% confidence interval*	(18.9, 27.9)	(22.7, 31.6)
Comparison vs Placebo**		
Odds ratio (SE)		1.233 (0.219)
95% confidence interval***		(0.871, 1.747)
p-value		0.2376

* Wilson confidence intervals.
** Logistic regression includes terms for baseline KCCQ - clinical summary score (p<0.0001), age (p=0.0124), baseline eGFR (CKD-EPI) (p=0.0006), Treatment (p=0.0836), region (5 cat.) (p=0.0002), baseline diabetes status (3 cat.) (p=0.9000), sex (p=0.4353), baseline LVEF (3 cat.) (p=0.6696) and Treatment by baseline LVEF (3 cat.) interaction (p=0.0241).
***Wald confidence intervals.

Data taken from study 1245.121 only.
LOCF: For a missing value at week 52 the last available post-baseline value before week 52 is imputed.

Table R.1.2.4.15: 1 Responder analysis (displaying odds ratio) in KCCQ-CSS change from baseline at week 52 of <= -5 points (deterioration) by baseline LVEF (3 cat.) - RS (LOCF-AD) - 1245.121

Subgroup Description	Placebo	Empa 10mg
Baseline LVEF (3 cat.): >35		
Number of patients in analysis set	114	128
Number of analysed patients, N (%)	104 (100.0)	120 (100.0)
Number of patients with endpoint, N (%)	34 (32.7)	26 (21.7)
95% confidence interval*	(24.4, 42.2)	(15.2, 29.9)
Comparison vs Placebo**		
Odds ratio (SE)		0.566 (0.176)
95% confidence interval***		(0.308, 1.041)
p-value		0.0672

* Wilson confidence intervals.
** Logistic regression includes terms for baseline KCCQ - clinical summary score (p<0.0001), age (p=0.0124), baseline eGFR (CKD-EPI) (p=0.0006), Treatment (p=0.0836), region (5 cat.) (p=0.0002), baseline diabetes status (3 cat.) (p=0.9000), sex (p=0.4353), baseline LVEF (3 cat.) (p=0.6696) and Treatment by baseline LVEF (3 cat.) interaction (p=0.0241).
***Wald confidence intervals.

Data taken from study 1245.121 only.
LOCF: For a missing value at week 52 the last available post-baseline value before week 52 is imputed.

Table R.1.2.4.15: 2 Responder analysis (displaying risk ratio) in KCCQ-CSS change from baseline at week 52 of <= -5 points (deterioration) by baseline LVEF (3 cat.) - RS (LOCF-AD) - 1245.121

Subgroup Description	Placebo	Empa 10mg
Baseline LVEF (3 cat.): <=30		
Number of patients in analysis set	1392	1337
Number of analysed patients, N (%)	1272 (100.0)	1245 (100.0)
Number of patients with endpoint, N (%)	337 (26.5)	270 (21.7)
95% confidence interval*	(24.1, 29.0)	(19.5, 24.1)
Comparison vs Placebo**		
Risk ratio (SE)		0.813 (0.057)
95% confidence interval***		(0.709, 0.933)
p-value		0.0031
Baseline LVEF (3 cat.): >30 to <=35		
Number of patients in analysis set	361	398
Number of analysed patients, N (%)	333 (100.0)	375 (100.0)
Number of patients with endpoint, N (%)	77 (23.1)	101 (26.9)
95% confidence interval*	(18.9, 27.9)	(22.7, 31.6)
Comparison vs Placebo**		
Risk ratio (SE)		1.163 (0.149)
95% confidence interval***		(0.905, 1.495)
p-value		0.2380

* Wilson confidence intervals.
** Log-linked Poisson model with robust estimate of variance includes terms for baseline KCCQ - clinical summary score (p<0.0001), age (p=0.0129), baseline eGFR (CKD-EPI) (p=0.0007), Treatment (p=0.0817), region (5 cat.) (p=0.0003), baseline diabetes status (3 cat.) (p=0.9008), sex (p=0.4183), baseline LVEF (3 cat.) (p=0.6993) and Treatment by baseline LVEF (3 cat.) interaction (p=0.0235).
***Wald confidence intervals.

Data taken from study 1245.121 only.
LOCF: For a missing value at week 52 the last available post-baseline value before week 52 is imputed.

Table R.1.2.4.15: 2 Responder analysis (displaying risk ratio) in KCCQ-CSS change from baseline at week 52 of <= -5 points (deterioration) by baseline LVEF (3 cat.) - RS (LOCF-AD) - 1245.121

Subgroup Description	Placebo	Empa 10mg
Baseline LVEF (3 cat.): >35		
Number of patients in analysis set	114	128
Number of analysed patients, N (%)	104 (100.0)	120 (100.0)
Number of patients with endpoint, N (%)	34 (32.7)	26 (21.7)
95% confidence interval*	(24.4, 42.2)	(15.2, 29.9)
Comparison vs Placebo**		
Risk ratio (SE)		0.670 (0.146)
95% confidence interval***		(0.437, 1.026)
p-value		0.0657

* Wilson confidence intervals.
** Log-linked Poisson model with robust estimate of variance includes terms for baseline KCCQ - clinical summary score (p<0.0001), age (p=0.0129), baseline eGFR (CKD-EPI) (p=0.0007), Treatment (p=0.0817), region (5 cat.) (p=0.0003), baseline diabetes status (3 cat.) (p=0.9008), sex (p=0.4183), baseline LVEF (3 cat.) (p=0.6993) and Treatment by baseline LVEF (3 cat.) interaction (p=0.0235).
***Wald confidence intervals.

Data taken from study 1245.121 only.
LOCF: For a missing value at week 52 the last available post-baseline value before week 52 is imputed.

Table R.1.2.4.15: 3 Responder analysis (displaying odds ratio) in KCCQ-CSS change from baseline at week 52 of > -5 points (stability) by baseline LVEF (3 cat.) - RS (LOCF-AD) - 1245.121

Subgroup Description	Placebo	Empa 10mg
Baseline LVEF (3 cat.): <=30		
Number of patients in analysis set	1392	1337
Number of analysed patients, N (%)	1272 (100.0)	1245 (100.0)
Number of patients with endpoint, N (%)	935 (73.5)	975 (78.3)
95% confidence interval*	(71.0, 75.9)	(75.9, 80.5)
Comparison vs Placebo**		
Odds ratio (SE)		1.325 (0.126)
95% confidence interval***		(1.099, 1.598)
p-value		0.0032
Baseline LVEF (3 cat.): >30 to <=35		
Number of patients in analysis set	361	398
Number of analysed patients, N (%)	333 (100.0)	375 (100.0)
Number of patients with endpoint, N (%)	256 (76.9)	274 (73.1)
95% confidence interval*	(72.1, 81.1)	(68.4, 77.3)
Comparison vs Placebo**		
Odds ratio (SE)		0.811 (0.144)
95% confidence interval***		(0.572, 1.148)
p-value		0.2376

* Wilson confidence intervals.
** Logistic regression includes terms for baseline KCCQ - clinical summary score (p<0.0001), age (p=0.0124), baseline eGFR (CKD-EPI) (p=0.0006), Treatment (p=0.0836), region (5 cat.) (p=0.0002), baseline diabetes status (3 cat.) (p=0.9000), sex (p=0.4353), baseline LVEF (3 cat.) (p=0.6696) and Treatment by baseline LVEF (3 cat.) interaction (p=0.0241).
***Wald confidence intervals.

Data taken from study 1245.121 only.
LOCF: For a missing value at week 52 the last available post-baseline value before week 52 is imputed.

Table R.1.2.4.15: 3 Responder analysis (displaying odds ratio) in KCCQ-CSS change from baseline at week 52 of > -5 points (stability) by baseline LVEF (3 cat.) - RS (LOCF-AD) - 1245.121

Subgroup Description	Placebo	Empa 10mg
Baseline LVEF (3 cat.): >35		
Number of patients in analysis set	114	128
Number of analysed patients, N (%)	104 (100.0)	120 (100.0)
Number of patients with endpoint, N (%)	70 (67.3)	94 (78.3)
95% confidence interval*	(57.8, 75.6)	(70.1, 84.8)
Comparison vs Placebo**		
Odds ratio (SE)		1.767 (0.550)
95% confidence interval***		(0.961, 3.252)
p-value		0.0672

* Wilson confidence intervals.
** Logistic regression includes terms for baseline KCCQ - clinical summary score (p<0.0001), age (p=0.0124), baseline eGFR (CKD-EPI) (p=0.0006), Treatment (p=0.0836), region (5 cat.) (p=0.0002), baseline diabetes status (3 cat.) (p=0.9000), sex (p=0.4353), baseline LVEF (3 cat.) (p=0.6696) and Treatment by baseline LVEF (3 cat.) interaction (p=0.0241).
***Wald confidence intervals.

Data taken from study 1245.121 only.
LOCF: For a missing value at week 52 the last available post-baseline value before week 52 is imputed.

Table R.1.2.4.15: 4 Responder analysis (displaying risk ratio) in KCCQ-CSS change from baseline at week 52 of > -5 points (stability) by baseline LVEF (3 cat.) - RS (LOCF-AD) - 1245.121

Subgroup Description	Placebo	Empa 10mg
Baseline LVEF (3 cat.): <=30		
Number of patients in analysis set	1392	1337
Number of analysed patients, N (%)	1272 (100.0)	1245 (100.0)
Number of patients with endpoint, N (%)	935 (73.5)	975 (78.3)
95% confidence interval*	(71.0, 75.9)	(75.9, 80.5)
Comparison vs Placebo**		
Risk ratio (SE)		1.067 (0.024)
95% confidence interval***		(1.022, 1.115)
p-value		0.0033
Baseline LVEF (3 cat.): >30 to <=35		
Number of patients in analysis set	361	398
Number of analysed patients, N (%)	333 (100.0)	375 (100.0)
Number of patients with endpoint, N (%)	256 (76.9)	274 (73.1)
95% confidence interval*	(72.1, 81.1)	(68.4, 77.3)
Comparison vs Placebo**		
Risk ratio (SE)		0.948 (0.040)
95% confidence interval***		(0.872, 1.031)
p-value		0.2130

* Wilson confidence intervals.
** Log-linked Poisson model with robust estimate of variance includes terms for baseline KCCQ - clinical summary score (p<0.0001), age (p=0.0220), baseline eGFR (CKD-EPI) (p=0.0008), Treatment (p=0.1013), region (5 cat.) (p<0.0001), baseline diabetes status (3 cat.) (p=0.9094), sex (p=0.4448), baseline LVEF (3 cat.) (p=0.5787) and Treatment by baseline LVEF (3 cat.) interaction (p=0.0226).
***Wald confidence intervals.

Data taken from study 1245.121 only.
LOCF: For a missing value at week 52 the last available post-baseline value before week 52 is imputed.

Table R.1.2.4.15: 4 Responder analysis (displaying risk ratio) in KCCQ-CSS change from baseline at week 52 of > -5 points (stability) by baseline LVEF (3 cat.) - RS (LOCF-AD) - 1245.121

Subgroup Description	Placebo	Empa 10mg
Baseline LVEF (3 cat.): >35		
Number of patients in analysis set	114	128
Number of analysed patients, N (%)	104 (100.0)	120 (100.0)
Number of patients with endpoint, N (%)	70 (67.3)	94 (78.3)
95% confidence interval*	(57.8, 75.6)	(70.1, 84.8)
Comparison vs Placebo**		
Risk ratio (SE)		1.154 (0.094)
95% confidence interval***		(0.983, 1.354)
p-value		0.0796

* Wilson confidence intervals.
** Log-linked Poisson model with robust estimate of variance includes terms for baseline KCCQ - clinical summary score (p<0.0001), age (p=0.0220), baseline eGFR (CKD-EPI) (p=0.0008), Treatment (p=0.1013), region (5 cat.) (p<0.0001), baseline diabetes status (3 cat.) (p=0.9094), sex (p=0.4448), baseline LVEF (3 cat.) (p=0.5787) and Treatment by baseline LVEF (3 cat.) interaction (p=0.0226).
***Wald confidence intervals.

Data taken from study 1245.121 only.
LOCF: For a missing value at week 52 the last available post-baseline value before week 52 is imputed.

Table R.1.2.4.15: 5 Responder analysis (displaying odds ratio) in KCCQ-CSS change from baseline at week 52 of >= 5 points (improvement) by baseline LVEF (3 cat.) - RS (LOCF-AD) - 1245.121

Subgroup Description	Placebo	Empa 10mg
Baseline LVEF (3 cat.): <=30		
Number of patients in analysis set	1392	1337
Number of analysed patients, N (%)	1272 (100.0)	1245 (100.0)
Number of patients with endpoint, N (%)	525 (41.3)	584 (46.9)
95% confidence interval*	(38.6, 44.0)	(44.1, 49.7)
Comparison vs Placebo**		
Odds ratio (SE)		1.309 (0.115)
95% confidence interval***		(1.101, 1.556)
p-value		0.0023
Baseline LVEF (3 cat.): >30 to <=35		
Number of patients in analysis set	361	398
Number of analysed patients, N (%)	333 (100.0)	375 (100.0)
Number of patients with endpoint, N (%)	154 (46.2)	166 (44.3)
95% confidence interval*	(41.0, 51.6)	(39.3, 49.3)
Comparison vs Placebo**		
Odds ratio (SE)		0.911 (0.151)
95% confidence interval***		(0.659, 1.260)
p-value		0.5733

* Wilson confidence intervals.
** Logistic regression includes terms for baseline KCCQ - clinical summary score (p<0.0001), age (p=0.0181), baseline eGFR (CKD-EPI) (p=0.7826), Treatment (p=0.0540), region (5 cat.) (p<0.0001), baseline diabetes status (3 cat.) (p=0.7696), sex (p=0.7162), baseline LVEF (3 cat.) (p=0.2220) and Treatment by baseline LVEF (3 cat.) interaction (p=0.0915).
***Wald confidence intervals.

Data taken from study 1245.121 only.
LOCF: For a missing value at week 52 the last available post-baseline value before week 52 is imputed.

Table R.1.2.4.15: 5 Responder analysis (displaying odds ratio) in KCCQ-CSS change from baseline at week 52 of >= 5 points (improvement) by baseline LVEF (3 cat.) - RS (LOCF-AD) - 1245.121

Subgroup Description	Placebo	Empa 10mg
Baseline LVEF (3 cat.): >35		
Number of patients in analysis set	114	128
Number of analysed patients, N (%)	104 (100.0)	120 (100.0)
Number of patients with endpoint, N (%)	38 (36.5)	56 (46.7)
95% confidence interval*	(27.9, 46.1)	(38.0, 55.6)
Comparison vs Placebo**		
Odds ratio (SE)		1.664 (0.503)
95% confidence interval***		(0.920, 3.010)
p-value		0.0920

* Wilson confidence intervals.
** Logistic regression includes terms for baseline KCCQ - clinical summary score (p<0.0001), age (p=0.0181), baseline eGFR (CKD-EPI) (p=0.7826), Treatment (p=0.0540), region (5 cat.) (p<0.0001), baseline diabetes status (3 cat.) (p=0.7696), sex (p=0.7162), baseline LVEF (3 cat.) (p=0.2220) and Treatment by baseline LVEF (3 cat.) interaction (p=0.0915).
***Wald confidence intervals.

Data taken from study 1245.121 only.
LOCF: For a missing value at week 52 the last available post-baseline value before week 52 is imputed.

Table R.1.2.4.15: 6 Responder analysis (displaying risk ratio) in KCCQ-CSS change from baseline at week 52 of >= 5 points (improvement) by baseline LVEF (3 cat.) - RS (LOCF-AD) - 1245.121

Subgroup Description	Placebo	Empa 10mg
Baseline LVEF (3 cat.): <=30		
Number of patients in analysis set	1392	1337
Number of analysed patients, N (%)	1272 (100.0)	1245 (100.0)
Number of patients with endpoint, N (%)	525 (41.3)	584 (46.9)
95% confidence interval*	(38.6, 44.0)	(44.1, 49.7)
Comparison vs Placebo**		
Risk ratio (SE)		1.133 (0.048)
95% confidence interval***		(1.043, 1.231)
p-value		0.0030
Baseline LVEF (3 cat.): >30 to <=35		
Number of patients in analysis set	361	398
Number of analysed patients, N (%)	333 (100.0)	375 (100.0)
Number of patients with endpoint, N (%)	154 (46.2)	166 (44.3)
95% confidence interval*	(41.0, 51.6)	(39.3, 49.3)
Comparison vs Placebo**		
Risk ratio (SE)		0.937 (0.072)
95% confidence interval***		(0.807, 1.089)
p-value		0.3955

* Wilson confidence intervals.
** Log-linked Poisson model with robust estimate of variance includes terms for baseline KCCQ - clinical summary score (p<0.0001), age (p=0.0360), baseline eGFR (CKD-EPI) (p=0.8064), Treatment (p=0.1133), region (5 cat.) (p<0.0001), baseline diabetes status (3 cat.) (p=0.7337), sex (p=0.8809), baseline LVEF (3 cat.) (p=0.1691) and Treatment by baseline LVEF (3 cat.) interaction (p=0.0635).
***Wald confidence intervals.

Data taken from study 1245.121 only.
LOCF: For a missing value at week 52 the last available post-baseline value before week 52 is imputed.

Table R.1.2.4.15: 6 Responder analysis (displaying risk ratio) in KCCQ-CSS change from baseline at week 52 of >= 5 points (improvement) by baseline LVEF (3 cat.) - RS (LOCF-AD) - 1245.121

Subgroup Description	Placebo	Empa 10mg
Baseline LVEF (3 cat.): >35		
Number of patients in analysis set	114	128
Number of analysed patients, N (%)	104 (100.0)	120 (100.0)
Number of patients with endpoint, N (%)	38 (36.5)	56 (46.7)
95% confidence interval*	(27.9, 46.1)	(38.0, 55.6)
Comparison vs Placebo**		
Risk ratio (SE)		1.248 (0.194)
95% confidence interval***		(0.921, 1.693)
p-value		0.1531

* Wilson confidence intervals.
** Log-linked Poisson model with robust estimate of variance includes terms for baseline KCCQ - clinical summary score (p<0.0001), age (p=0.0360), baseline eGFR (CKD-EPI) (p=0.8064), Treatment (p=0.1133), region (5 cat.) (p<0.0001), baseline diabetes status (3 cat.) (p=0.7337), sex (p=0.8809), baseline LVEF (3 cat.) (p=0.1691) and Treatment by baseline LVEF (3 cat.) interaction (p=0.0635).
***Wald confidence intervals.

Data taken from study 1245.121 only.
LOCF: For a missing value at week 52 the last available post-baseline value before week 52 is imputed.

R.1.2.4.16 Subgroup analysis by bl. NTproBNP </>= median (median based on total patients)

Table R.1.2.4.16: 1 Responder analysis (displaying odds ratio) in KCCQ-CSS change from baseline at week 52 of <= -5 points (deterioration) by bl. NTproBNP (<median, >= median) (median based on total patients) - RS (LOCF-AD) - 1245.121

Subgroup Description	Placebo	Empa 10mg
Baseline NTproBNP (<median, >= median): < median		
Number of patients in analysis set	920	942
Number of analysed patients, N (%)	866 (100.0)	886 (100.0)
Number of patients with endpoint, N (%)	207 (23.9)	182 (20.5)
95% confidence interval*	(21.2, 26.9)	(18.0, 23.3)
Comparison vs Placebo**		
Odds ratio (SE)		0.810 (0.095)
95% confidence interval***		(0.644, 1.019)
p-value		0.0717
Baseline NTproBNP (<median, >= median): >= median		
Number of patients in analysis set	946	920
Number of analysed patients, N (%)	843 (100.0)	854 (100.0)
Number of patients with endpoint, N (%)	241 (28.6)	215 (25.2)
95% confidence interval*	(25.6, 31.7)	(22.4, 28.2)
Comparison vs Placebo**		
Odds ratio (SE)		0.832 (0.093)
95% confidence interval***		(0.668, 1.036)
p-value		0.1002

* Wilson confidence intervals.
** Logistic regression includes terms for baseline KCCQ - clinical summary score (p<0.0001), age (p=0.0183), baseline eGFR (CKD-EPI) (p=0.0056), Treatment (p=0.0148), region (5 cat.) (p<0.0001), baseline diabetes status (3 cat.) (p=0.9175), sex (p=0.4240), baseline LVEF (3 cat.) (p=0.8128), baseline NTproBNP (<median, >= median) (p=0.0022) and Treatment by baseline NTproBNP (<median, >= median) interaction (p=0.8684).
***Wald confidence intervals.
2 patients were excluded as the subgroup variable was missing.

Data taken from study 1245.121 only.
LOCF: For a missing value at week 52 the last available post-baseline value before week 52 is imputed.
Median: 1910 [pg/mL]

Table R.1.2.4.16: 2 Responder analysis (displaying risk ratio) in KCCQ-CSS change from baseline at week 52 of <= -5 points (deterioration) by bl. NTproBNP (<median, >= median) (median based on total patients) - RS (LOCF-AD) - 1245.121

Subgroup Description	Placebo	Empa 10mg
Baseline NTproBNP (<median, >= median): < median		
Number of patients in analysis set	920	942
Number of analysed patients, N (%)	866 (100.0)	886 (100.0)
Number of patients with endpoint, N (%)	207 (23.9)	182 (20.5)
95% confidence interval*	(21.2, 26.9)	(18.0, 23.3)
Comparison vs Placebo**		
Risk ratio (SE)		0.853 (0.076)
95% confidence interval***		(0.717, 1.015)
p-value		0.0727
Baseline NTproBNP (<median, >= median): >= median		
Number of patients in analysis set	946	920
Number of analysed patients, N (%)	843 (100.0)	854 (100.0)
Number of patients with endpoint, N (%)	241 (28.6)	215 (25.2)
95% confidence interval*	(25.6, 31.7)	(22.4, 28.2)
Comparison vs Placebo**		
Risk ratio (SE)		0.877 (0.069)
95% confidence interval***		(0.752, 1.023)
p-value		0.0940

* Wilson confidence intervals.
** Log-linked Poisson model with robust estimate of variance includes terms for baseline KCCQ - clinical summary score (p<0.0001), age (p=0.0192), baseline eGFR (CKD-EPI) (p=0.0058), Treatment (p=0.0140), region (5 cat.) (p<0.0001), baseline diabetes status (3 cat.) (p=0.9239), sex (p=0.4102), baseline LVEF (3 cat.) (p=0.8118), baseline NTproBNP (<median, >= median) (p=0.0022) and Treatment by baseline NTproBNP (<median, >= median) interaction (p=0.8141).
***Wald confidence intervals.
2 patients were excluded as the subgroup variable was missing.

Data taken from study 1245.121 only.
LOCF: For a missing value at week 52 the last available post-baseline value before week 52 is imputed.
Median: 1910 [pg/mL]

Table R.1.2.4.16: 3 Responder analysis (displaying odds ratio) in KCCQ-CSS change from baseline at week 52 of > -5 points (stability) by bl. NTproBNP (<median, >= median) (median based on total patients) - RS (LOCF-AD) - 1245.121

Subgroup Description	Placebo	Empa 10mg
Baseline NTproBNP (<median, >= median): < median		
Number of patients in analysis set	920	942
Number of analysed patients, N (%)	866 (100.0)	886 (100.0)
Number of patients with endpoint, N (%)	659 (76.1)	704 (79.5)
95% confidence interval*	(73.1, 78.8)	(76.7, 82.0)
Comparison vs Placebo**		
Odds ratio (SE)		1.235 (0.145)
95% confidence interval***		(0.982, 1.554)
p-value		0.0717
Baseline NTproBNP (<median, >= median): >= median		
Number of patients in analysis set	946	920
Number of analysed patients, N (%)	843 (100.0)	854 (100.0)
Number of patients with endpoint, N (%)	602 (71.4)	639 (74.8)
95% confidence interval*	(68.3, 74.4)	(71.8, 77.6)
Comparison vs Placebo**		
Odds ratio (SE)		1.202 (0.135)
95% confidence interval***		(0.965, 1.497)
p-value		0.1002

* Wilson confidence intervals.
** Logistic regression includes terms for baseline KCCQ - clinical summary score (p<0.0001), age (p=0.0183), baseline eGFR (CKD-EPI) (p=0.0056), Treatment (p=0.0148), region (5 cat.) (p<0.0001), baseline diabetes status (3 cat.) (p=0.9175), sex (p=0.4240), baseline LVEF (3 cat.) (p=0.8128), baseline NTproBNP (<median, >= median) (p=0.0022) and Treatment by baseline NTproBNP (<median, >= median) interaction (p=0.8684).
***Wald confidence intervals.
2 patients were excluded as the subgroup variable was missing.

Data taken from study 1245.121 only.
LOCF: For a missing value at week 52 the last available post-baseline value before week 52 is imputed.
Median: 1910 [pg/mL]

Table R.1.2.4.16: 4 Responder analysis (displaying risk ratio) in KCCQ-CSS change from baseline at week 52 of > -5 points (stability) by bl. NTproBNP (<median, >= median) (median based on total patients) - RS (LOCF-AD) - 1245.121

Subgroup Description	Placebo	Empa 10mg
Baseline NTproBNP (<median, >= median): < median		
Number of patients in analysis set	920	942
Number of analysed patients, N (%)	866 (100.0)	886 (100.0)
Number of patients with endpoint, N (%)	659 (76.1)	704 (79.5)
95% confidence interval*	(73.1, 78.8)	(76.7, 82.0)
Comparison vs Placebo**		
Risk ratio (SE)		1.046 (0.026)
95% confidence interval***		(0.996, 1.099)
p-value		0.0745
Baseline NTproBNP (<median, >= median): >= median		
Number of patients in analysis set	946	920
Number of analysed patients, N (%)	843 (100.0)	854 (100.0)
Number of patients with endpoint, N (%)	602 (71.4)	639 (74.8)
95% confidence interval*	(68.3, 74.4)	(71.8, 77.6)
Comparison vs Placebo**		
Risk ratio (SE)		1.047 (0.030)
95% confidence interval***		(0.989, 1.108)
p-value		0.1121

* Wilson confidence intervals.
** Log-linked Poisson model with robust estimate of variance includes terms for baseline KCCQ - clinical summary score (p<0.0001), age (p=0.0306), baseline eGFR (CKD-EPI) (p=0.0065), Treatment (p=0.0177), region (5 cat.) (p<0.0001), baseline diabetes status (3 cat.) (p=0.9184), sex (p=0.4357), baseline LVEF (3 cat.) (p=0.8039), baseline NTproBNP (<median, >= median) (p=0.0016) and Treatment by baseline NTproBNP (<median, >= median) interaction (p=0.9839).
***Wald confidence intervals.
2 patients were excluded as the subgroup variable was missing.

Data taken from study 1245.121 only.
LOCF: For a missing value at week 52 the last available post-baseline value before week 52 is imputed.
Median: 1910 [pg/mL]

Table R.1.2.4.16: 5 Responder analysis (displaying odds ratio) in KCCQ-CSS change from baseline at week 52 of >= 5 points (improvement) by bl. NTproBNP (<median, >= median) (median based on total patients) - RS (LOCF-AD) - 1245.121

Subgroup Description	Placebo	Empa 10mg
Baseline NTproBNP (<median, >= median): < median		
Number of patients in analysis set	920	942
Number of analysed patients, N (%)	866 (100.0)	886 (100.0)
Number of patients with endpoint, N (%)	358 (41.3)	407 (45.9)
95% confidence interval*	(38.1, 44.7)	(42.7, 49.2)
Comparison vs Placebo**		
Odds ratio (SE)		1.266 (0.133)
95% confidence interval***		(1.030, 1.556)
p-value		0.0249
Baseline NTproBNP (<median, >= median): >= median		
Number of patients in analysis set	946	920
Number of analysed patients, N (%)	843 (100.0)	854 (100.0)
Number of patients with endpoint, N (%)	359 (42.6)	399 (46.7)
95% confidence interval*	(39.3, 46.0)	(43.4, 50.1)
Comparison vs Placebo**		
Odds ratio (SE)		1.196 (0.129)
95% confidence interval***		(0.968, 1.477)
p-value		0.0980

* Wilson confidence intervals.
** Logistic regression includes terms for baseline KCCQ - clinical summary score (p<0.0001), age (p=0.0223), baseline eGFR (CKD-EPI) (p=0.9018), Treatment (p=0.0060), region (5 cat.) (p<0.0001), baseline diabetes status (3 cat.) (p=0.7783), sex (p=0.7083), baseline LVEF (3 cat.) (p=0.2693), baseline NTproBNP (<median, >= median) (p=0.0558) and Treatment by baseline NTproBNP (<median, >= median) interaction (p=0.7037).
***Wald confidence intervals.
2 patients were excluded as the subgroup variable was missing.

Data taken from study 1245.121 only.
LOCF: For a missing value at week 52 the last available post-baseline value before week 52 is imputed.
Median: 1910 [pg/mL]

Table R.1.2.4.16: 6 Responder analysis (displaying risk ratio) in KCCQ-CSS change from baseline at week 52 of >= 5 points (improvement) by bl. NTproBNP (<median, >= median) (median based on total patients) - RS (LOCF-AD) - 1245.121

Subgroup Description	Placebo	Empa 10mg
Baseline NTproBNP (<median, >= median): < median		
Number of patients in analysis set	920	942
Number of analysed patients, N (%)	866 (100.0)	886 (100.0)
Number of patients with endpoint, N (%)	358 (41.3)	407 (45.9)
95% confidence interval*	(38.1, 44.7)	(42.7, 49.2)
Comparison vs Placebo**		
Risk ratio (SE)		1.109 (0.057)
95% confidence interval***		(1.003, 1.226)
p-value		0.0434
Baseline NTproBNP (<median, >= median): >= median		
Number of patients in analysis set	946	920
Number of analysed patients, N (%)	843 (100.0)	854 (100.0)
Number of patients with endpoint, N (%)	359 (42.6)	399 (46.7)
95% confidence interval*	(39.3, 46.0)	(43.4, 50.1)
Comparison vs Placebo**		
Risk ratio (SE)		1.080 (0.054)
95% confidence interval***		(0.979, 1.192)
p-value		0.1243

* Wilson confidence intervals.
** Log-linked Poisson model with robust estimate of variance includes terms for baseline KCCQ - clinical summary score (p<0.0001), age (p=0.0484), baseline eGFR (CKD-EPI) (p=0.9058), Treatment (p=0.0119), region (5 cat.) (p<0.0001), baseline diabetes status (3 cat.) (p=0.7280), sex (p=0.8597), baseline LVEF (3 cat.) (p=0.2512), baseline NTproBNP (<median, >= median) (p=0.0473) and Treatment by baseline NTproBNP (<median, >= median) interaction (p=0.7164).
***Wald confidence intervals.
2 patients were excluded as the subgroup variable was missing.

Data taken from study 1245.121 only.
LOCF: For a missing value at week 52 the last available post-baseline value before week 52 is imputed.
Median: 1910 [pg/mL]

R.1.2.5

R.1.2.5 KCCQ Clinical Summary Score responder analysis (15 points)

R.1.2.5.1

Table R.1.2.5.1: 1 Responder analysis (displaying odds ratio) in KCCQ-CSS change from baseline at week 52 of <= -15 points (deterioration) - RS (LOCF-AD) - 1245.121

	Placebo	Empa 10mg
Number of patients in analysis set	1867	1863
Number of analysed patients, N (%)	1709 (100.0)	1740 (100.0)
Number of patients with endpoint, N (%)	204 (11.9)	192 (11.0)
95% confidence interval*	(10.5, 13.6)	(9.6, 12.6)
Comparison vs Placebo**		
Odds ratio (SE)		0.911 (0.098)
95% confidence interval***		(0.737, 1.125)
p-value		0.3850

* Wilson confidence intervals.
** Logistic regression includes terms for baseline KCCQ - clinical summary score (p<0.0001), age (p=0.2321), baseline eGFR (CKD-EPI) (p=0.0038), Treatment (p=0.3850), region (5 cat.) (p=0.0464), baseline diabetes status (3 cat.) (p=0.8748), sex (p=0.7358) and baseline LVEF (3 cat.) (p=0.9172).
***Wald confidence intervals.

Data taken from study 1245.121 only.
LOCF: For a missing value at week 52 the last available post-baseline value before week 52 is imputed.

Table R.1.2.5.1: 2 Responder analysis (displaying risk ratio) in KCCQ-CSS change from baseline at week 52 of <= -15 points (deterioration) - RS (LOCF-AD) - 1245.121

	Placebo	Empa 10mg
Number of patients in analysis set	1867	1863
Number of analysed patients, N (%)	1709 (100.0)	1740 (100.0)
Number of patients with endpoint, N (%)	204 (11.9)	192 (11.0)
95% confidence interval*	(10.5, 13.6)	(9.6, 12.6)
Comparison vs Placebo**		
Risk ratio (SE)		0.921 (0.086)
95% confidence interval***		(0.767, 1.107)
p-value		0.3821

* Wilson confidence intervals.
** Log-linked Poisson model with robust estimate of variance includes terms for baseline KCCQ - clinical summary score (p<0.0001), age (p=0.2581), baseline eGFR (CKD-EPI) (p=0.0042), Treatment (p=0.3821), region (5 cat.) (p=0.0581), baseline diabetes status (3 cat.) (p=0.8781), sex (p=0.7329) and baseline LVEF (3 cat.) (p=0.9165).
***Wald confidence intervals.

Data taken from study 1245.121 only.
LOCF: For a missing value at week 52 the last available post-baseline value before week 52 is imputed.

Table R.1.2.5.1: 3 Responder analysis (displaying odds ratio) in KCCQ-CSS change from baseline at week 52 of > -15 points (stability) - RS (LOCF-AD) - 1245.121

	Placebo	Empa 10mg
Number of patients in analysis set	1867	1863
Number of analysed patients, N (%)	1709 (100.0)	1740 (100.0)
Number of patients with endpoint, N (%)	1505 (88.1)	1548 (89.0)
95% confidence interval*	(86.4, 89.5)	(87.4, 90.4)
Comparison vs Placebo**		
Odds ratio (SE)		1.098 (0.118)
95% confidence interval***		(0.889, 1.357)
p-value		0.3850

* Wilson confidence intervals.
** Logistic regression includes terms for baseline KCCQ - clinical summary score (p<0.0001), age (p=0.2321), baseline eGFR (CKD-EPI) (p=0.0038), Treatment (p=0.3850), region (5 cat.) (p=0.0464), baseline diabetes status (3 cat.) (p=0.8748), sex (p=0.7358) and baseline LVEF (3 cat.) (p=0.9172).
***Wald confidence intervals.

Data taken from study 1245.121 only.
LOCF: For a missing value at week 52 the last available post-baseline value before week 52 is imputed.

Table R.1.2.5.1: 4 Responder analysis (displaying risk ratio) in KCCQ-CSS change from baseline at week 52 of > -15 points (stability) - RS (LOCF-AD) - 1245.121

	Placebo	Empa 10mg
Number of patients in analysis set	1867	1863
Number of analysed patients, N (%)	1709 (100.0)	1740 (100.0)
Number of patients with endpoint, N (%)	1505 (88.1)	1548 (89.0)
95% confidence interval*	(86.4, 89.5)	(87.4, 90.4)
Comparison vs Placebo**		
Risk ratio (SE)		1.010 (0.012)
95% confidence interval***		(0.986, 1.035)
p-value		0.3993

* Wilson confidence intervals.
** Log-linked Poisson model with robust estimate of variance includes terms for baseline KCCQ - clinical summary score (p<0.0001), age (p=0.3133), baseline eGFR (CKD-EPI) (p=0.0045), Treatment (p=0.3993), region (5 cat.) (p=0.0020), baseline diabetes status (3 cat.) (p=0.8674), sex (p=0.7450) and baseline LVEF (3 cat.) (p=0.9313).
***Wald confidence intervals.

Data taken from study 1245.121 only.
LOCF: For a missing value at week 52 the last available post-baseline value before week 52 is imputed.

Table R.1.2.5.1: 5 Responder analysis (displaying odds ratio) in KCCQ-CSS change from baseline at week 52 of >= 15 points (improvement) - RS (LOCF-AD) - 1245.121

	Placebo	Empa 10mg
Number of patients in analysis set	1867	1863
Number of analysed patients, N (%)	1709 (100.0)	1740 (100.0)
Number of patients with endpoint, N (%)	357 (20.9)	424 (24.4)
95% confidence interval*	(19.0, 22.9)	(22.4, 26.4)
Comparison vs Placebo**		
Odds ratio (SE)		1.275 (0.120)
95% confidence interval***		(1.061, 1.532)
p-value		0.0096

* Wilson confidence intervals.
** Logistic regression includes terms for baseline KCCQ - clinical summary score (p<0.0001), age (p=0.0716), baseline eGFR (CKD-EPI) (p=0.1990), Treatment (p=0.0096), region (5 cat.) (p<0.0001), baseline diabetes status (3 cat.) (p=0.9520), sex (p=0.4646) and baseline LVEF (3 cat.) (p=0.4047).
***Wald confidence intervals.

Data taken from study 1245.121 only.
LOCF: For a missing value at week 52 the last available post-baseline value before week 52 is imputed.

Table R.1.2.5.1: 6 Responder analysis (displaying risk ratio) in KCCQ-CSS change from baseline at week 52 of >= 15 points (improvement) - RS (LOCF-AD) - 1245.121

	Placebo	Empa 10mg
Number of patients in analysis set	1867	1863
Number of analysed patients, N (%)	1709 (100.0)	1740 (100.0)
Number of patients with endpoint, N (%)	357 (20.9)	424 (24.4)
95% confidence interval*	(19.0, 22.9)	(22.4, 26.4)
Comparison vs Placebo**		
Risk ratio (SE)		1.144 (0.067)
95% confidence interval***		(1.020, 1.283)
p-value		0.0219

* Wilson confidence intervals.
** Log-linked Poisson model with robust estimate of variance includes terms for baseline KCCQ - clinical summary score (p<0.0001), age (p=0.1335), baseline eGFR (CKD-EPI) (p=0.2443), Treatment (p=0.0219), region (5 cat.) (p<0.0001), baseline diabetes status (3 cat.) (p=0.8991), sex (p=0.3174) and baseline LVEF (3 cat.) (p=0.2930).
***Wald confidence intervals.

Data taken from study 1245.121 only.
LOCF: For a missing value at week 52 the last available post-baseline value before week 52 is imputed.

R.1.2.5.2

R.1.2.5.2 Subgroup analysis by sex

Table R.1.2.5.2: 1 Responder analysis (displaying odds ratio) in KCCQ-CSS change from baseline at week 52 of <= -15 points (deterioration) by sex - RS (LOCF-AD) - 1245.121

Subgroup Description	Placebo	Empa 10mg
Sex: Male		
Number of patients in analysis set	1411	1426
Number of analysed patients, N (%)	1297 (100.0)	1332 (100.0)
Number of patients with endpoint, N (%)	163 (12.6)	142 (10.7)
95% confidence interval*	(10.9, 14.5)	(9.1, 12.4)
Comparison vs Placebo**		
Odds ratio (SE)		0.827 (0.102)
95% confidence interval***		(0.649, 1.053)
p-value		0.1234
Sex: Female		
Number of patients in analysis set	456	437
Number of analysed patients, N (%)	412 (100.0)	408 (100.0)
Number of patients with endpoint, N (%)	41 (10.0)	50 (12.3)
95% confidence interval*	(7.4, 13.2)	(9.4, 15.8)
Comparison vs Placebo**		
Odds ratio (SE)		1.254 (0.283)
95% confidence interval***		(0.806, 1.952)
p-value		0.3153

* Wilson confidence intervals.
** Logistic regression includes terms for baseline KCCQ - clinical summary score (p<0.0001), age (p=0.2139), baseline eGFR (CKD-EPI) (p=0.0037), Treatment (p=0.8868), region (5 cat.) (p=0.0495), baseline diabetes status (3 cat.) (p=0.8836), baseline LVEF (3 cat.) (p=0.9110), sex (p=0.7581) and Treatment by sex interaction (p=0.1054).
***Wald confidence intervals.

Data taken from study 1245.121 only.
LOCF: For a missing value at week 52 the last available post-baseline value before week 52 is imputed.

Table R.1.2.5.2: 2 Responder analysis (displaying risk ratio) in KCCQ-CSS change from baseline at week 52 of <= -15 points (deterioration) by sex - RS (LOCF-AD) - 1245.121

Subgroup Description	Placebo	Empa 10mg
Sex: Male		
Number of patients in analysis set	1411	1426
Number of analysed patients, N (%)	1297 (100.0)	1332 (100.0)
Number of patients with endpoint, N (%)	163 (12.6)	142 (10.7)
95% confidence interval*	(10.9, 14.5)	(9.1, 12.4)
Comparison vs Placebo**		
Risk ratio (SE)		0.848 (0.091)
95% confidence interval***		(0.688, 1.046)
p-value		0.1237
Sex: Female		
Number of patients in analysis set	456	437
Number of analysed patients, N (%)	412 (100.0)	408 (100.0)
Number of patients with endpoint, N (%)	41 (10.0)	50 (12.3)
95% confidence interval*	(7.4, 13.2)	(9.4, 15.8)
Comparison vs Placebo**		
Risk ratio (SE)		1.216 (0.240)
95% confidence interval***		(0.826, 1.790)
p-value		0.3210

* Wilson confidence intervals.
** Log-linked Poisson model with robust estimate of variance includes terms for baseline KCCQ - clinical summary score (p<0.0001), age (p=0.2393), baseline eGFR (CKD-EPI) (p=0.0041), Treatment (p=0.8903), region (5 cat.) (p=0.0615), baseline diabetes status (3 cat.) (p=0.8868), baseline LVEF (3 cat.) (p=0.9109), sex (p=0.7598) and Treatment by sex interaction (p=0.1089).
***Wald confidence intervals.

Data taken from study 1245.121 only.
LOCF: For a missing value at week 52 the last available post-baseline value before week 52 is imputed.

Table R.1.2.5.2: 3 Responder analysis (displaying odds ratio) in KCCQ-CSS change from baseline at week 52 of > -15 points (stability) by sex - RS (LOCF-AD) - 1245.121

Subgroup Description	Placebo	Empa 10mg
Sex: Male		
Number of patients in analysis set	1411	1426
Number of analysed patients, N (%)	1297 (100.0)	1332 (100.0)
Number of patients with endpoint, N (%)	1134 (87.4)	1190 (89.3)
95% confidence interval*	(85.5, 89.1)	(87.6, 90.9)
Comparison vs Placebo**		
Odds ratio (SE)		1.209 (0.149)
95% confidence interval***		(0.950, 1.540)
p-value		0.1234
Sex: Female		
Number of patients in analysis set	456	437
Number of analysed patients, N (%)	412 (100.0)	408 (100.0)
Number of patients with endpoint, N (%)	371 (90.0)	358 (87.7)
95% confidence interval*	(86.8, 92.6)	(84.2, 90.6)
Comparison vs Placebo**		
Odds ratio (SE)		0.797 (0.180)
95% confidence interval***		(0.512, 1.241)
p-value		0.3153

* Wilson confidence intervals.
** Logistic regression includes terms for baseline KCCQ - clinical summary score (p<0.0001), age (p=0.2139), baseline eGFR (CKD-EPI) (p=0.0037), Treatment (p=0.8868), region (5 cat.) (p=0.0495), baseline diabetes status (3 cat.) (p=0.8836), baseline LVEF (3 cat.) (p=0.9110), sex (p=0.7581) and Treatment by sex interaction (p=0.1054).
***Wald confidence intervals.

Data taken from study 1245.121 only.
LOCF: For a missing value at week 52 the last available post-baseline value before week 52 is imputed.

Table R.1.2.5.2: 4 Responder analysis (displaying risk ratio) in KCCQ-CSS change from baseline at week 52 of > -15 points (stability) by sex - RS (LOCF-AD) - 1245.121

Subgroup Description	Placebo	Empa 10mg
Sex: Male		
Number of patients in analysis set	1411	1426
Number of analysed patients, N (%)	1297 (100.0)	1332 (100.0)
Number of patients with endpoint, N (%)	1134 (87.4)	1190 (89.3)
95% confidence interval*	(85.5, 89.1)	(87.6, 90.9)
Comparison vs Placebo**		
Risk ratio (SE)		1.022 (0.014)
95% confidence interval***		(0.994, 1.051)
p-value		0.1220
Sex: Female		
Number of patients in analysis set	456	437
Number of analysed patients, N (%)	412 (100.0)	408 (100.0)
Number of patients with endpoint, N (%)	371 (90.0)	358 (87.7)
95% confidence interval*	(86.8, 92.6)	(84.2, 90.6)
Comparison vs Placebo**		
Risk ratio (SE)		0.974 (0.024)
95% confidence interval***		(0.928, 1.022)
p-value		0.2854

* Wilson confidence intervals.
** Log-linked Poisson model with robust estimate of variance includes terms for baseline KCCQ - clinical summary score (p<0.0001), age (p=0.2982), baseline eGFR (CKD-EPI) (p=0.0042), Treatment (p=0.8739), region (5 cat.) (p=0.0023), baseline diabetes status (3 cat.) (p=0.8764), baseline LVEF (3 cat.) (p=0.9217), sex (p=0.7498) and Treatment by sex interaction (p=0.0905).
***Wald confidence intervals.

Data taken from study 1245.121 only.
LOCF: For a missing value at week 52 the last available post-baseline value before week 52 is imputed.

Table R.1.2.5.2: 5 Responder analysis (displaying odds ratio) in KCCQ-CSS change from baseline at week 52 of >= 15 points (improvement) by sex - RS (LOCF-AD) - 1245.121

Subgroup Description	Placebo	Empa 10mg
Sex: Male		
Number of patients in analysis set	1411	1426
Number of analysed patients, N (%)	1297 (100.0)	1332 (100.0)
Number of patients with endpoint, N (%)	245 (18.9)	298 (22.4)
95% confidence interval*	(16.9, 21.1)	(20.2, 24.7)
Comparison vs Placebo**		
Odds ratio (SE)		1.262 (0.139)
95% confidence interval***		(1.017, 1.567)
p-value		0.0347
Sex: Female		
Number of patients in analysis set	456	437
Number of analysed patients, N (%)	412 (100.0)	408 (100.0)
Number of patients with endpoint, N (%)	112 (27.2)	126 (30.9)
95% confidence interval*	(23.1, 31.7)	(26.6, 35.5)
Comparison vs Placebo**		
Odds ratio (SE)		1.308 (0.233)
95% confidence interval***		(0.922, 1.855)
p-value		0.1322

* Wilson confidence intervals.
** Logistic regression includes terms for baseline KCCQ - clinical summary score (p<0.0001), age (p=0.0719), baseline eGFR (CKD-EPI) (p=0.2009), Treatment (p=0.0167), region (5 cat.) (p<0.0001), baseline diabetes status (3 cat.) (p=0.9516), baseline LVEF (3 cat.) (p=0.4043), sex (p=0.4672) and Treatment by sex interaction (p=0.8664).
***Wald confidence intervals.

Data taken from study 1245.121 only.
LOCF: For a missing value at week 52 the last available post-baseline value before week 52 is imputed.

Table R.1.2.5.2: 6 Responder analysis (displaying risk ratio) in KCCQ-CSS change from baseline at week 52 of >= 15 points (improvement) by sex - RS (LOCF-AD) - 1245.121

Subgroup Description	Placebo	Empa 10mg
Sex: Male		
Number of patients in analysis set	1411	1426
Number of analysed patients, N (%)	1297 (100.0)	1332 (100.0)
Number of patients with endpoint, N (%)	245 (18.9)	298 (22.4)
95% confidence interval*	(16.9, 21.1)	(20.2, 24.7)
Comparison vs Placebo**		
Risk ratio (SE)		1.137 (0.080)
95% confidence interval***		(0.990, 1.306)
p-value		0.0690
Sex: Female		
Number of patients in analysis set	456	437
Number of analysed patients, N (%)	412 (100.0)	408 (100.0)
Number of patients with endpoint, N (%)	112 (27.2)	126 (30.9)
95% confidence interval*	(23.1, 31.7)	(26.6, 35.5)
Comparison vs Placebo**		
Risk ratio (SE)		1.160 (0.122)
95% confidence interval***		(0.944, 1.424)
p-value		0.1575

* Wilson confidence intervals.
** Log-linked Poisson model with robust estimate of variance includes terms for baseline KCCQ - clinical summary score (p<0.0001), age (p=0.1337), baseline eGFR (CKD-EPI) (p=0.2463), Treatment (p=0.0289), region (5 cat.) (p<0.0001), baseline diabetes status (3 cat.) (p=0.9003), baseline LVEF (3 cat.) (p=0.2926), sex (p=0.3245) and Treatment by sex interaction (p=0.8754).
***Wald confidence intervals.

Data taken from study 1245.121 only.
LOCF: For a missing value at week 52 the last available post-baseline value before week 52 is imputed.

R.1.2.5.3

Table R.1.2.5.3: 1 Responder analysis (displaying odds ratio) in KCCQ-CSS change from baseline at week 52 of <= -15 points (deterioration) by age (2 cat.) - RS (LOCF-AD) - 1245.121

Subgroup Description	Placebo	Empa 10mg
Age [years] (2 cat.): < 65		
Number of patients in analysis set	740	675
Number of analysed patients, N (%)	675 (100.0)	635 (100.0)
Number of patients with endpoint, N (%)	73 (10.8)	57 (9.0)
95% confidence interval*	(8.7, 13.4)	(7.0, 11.5)
Comparison vs Placebo**		
Odds ratio (SE)		0.819 (0.154)
95% confidence interval***		(0.566, 1.184)
p-value		0.2881
Age [years] (2 cat.): >= 65		
Number of patients in analysis set	1127	1188
Number of analysed patients, N (%)	1034 (100.0)	1105 (100.0)
Number of patients with endpoint, N (%)	131 (12.7)	135 (12.2)
95% confidence interval*	(10.8, 14.8)	(10.4, 14.3)
Comparison vs Placebo**		
Odds ratio (SE)		0.963 (0.127)
95% confidence interval***		(0.744, 1.248)
p-value		0.7778

* Wilson confidence intervals.
** Logistic regression includes terms for baseline KCCQ - clinical summary score (p<0.0001), baseline eGFR (CKD-EPI) (p=0.0004), Treatment (p=0.3020), region (5 cat.) (p=0.0368), baseline diabetes status (3 cat.) (p=0.9101), sex (p=0.6913), baseline LVEF (3 cat.) (p=0.9159), age (2 cat.) (p=0.8422) and Treatment by age (2 cat.) interaction (p=0.4801).
***Wald confidence intervals.

Data taken from study 1245.121 only.
LOCF: For a missing value at week 52 the last available post-baseline value before week 52 is imputed.

Table R.1.2.5.3: 2 Responder analysis (displaying risk ratio) in KCCQ-CSS change from baseline at week 52 of <= -15 points (deterioration) by age (2 cat.) - RS (LOCF-AD) - 1245.121

Subgroup Description	Placebo	Empa 10mg
Age [years] (2 cat.): < 65		
Number of patients in analysis set	740	675
Number of analysed patients, N (%)	675 (100.0)	635 (100.0)
Number of patients with endpoint, N (%)	73 (10.8)	57 (9.0)
95% confidence interval*	(8.7, 13.4)	(7.0, 11.5)
Comparison vs Placebo**		
Risk ratio (SE)		0.837 (0.140)
95% confidence interval***		(0.604, 1.161)
p-value		0.2872
Age [years] (2 cat.): >= 65		
Number of patients in analysis set	1127	1188
Number of analysed patients, N (%)	1034 (100.0)	1105 (100.0)
Number of patients with endpoint, N (%)	131 (12.7)	135 (12.2)
95% confidence interval*	(10.8, 14.8)	(10.4, 14.3)
Comparison vs Placebo**		
Risk ratio (SE)		0.968 (0.110)
95% confidence interval***		(0.774, 1.210)
p-value		0.7754

* Wilson confidence intervals.
** Log-linked Poisson model with robust estimate of variance includes terms for baseline KCCQ - clinical summary score (p<0.0001), baseline eGFR (CKD-EPI) (p=0.0003), Treatment (p=0.2979), region (5 cat.) (p=0.0482), baseline diabetes status (3 cat.) (p=0.9131), sex (p=0.6873), baseline LVEF (3 cat.) (p=0.9158), age (2 cat.) (p=0.8255) and Treatment by age (2 cat.) interaction (p=0.4740).
***Wald confidence intervals.

Data taken from study 1245.121 only.
LOCF: For a missing value at week 52 the last available post-baseline value before week 52 is imputed.

Table R.1.2.5.3: 3 Responder analysis (displaying odds ratio) in KCCQ-CSS change from baseline at week 52 of > -15 points (stability) by age (2 cat.) - RS (LOCF-AD) - 1245.121

Subgroup Description	Placebo	Empa 10mg
Age [years] (2 cat.): < 65		
Number of patients in analysis set	740	675
Number of analysed patients, N (%)	675 (100.0)	635 (100.0)
Number of patients with endpoint, N (%)	602 (89.2)	578 (91.0)
95% confidence interval*	(86.6, 91.3)	(88.5, 93.0)
Comparison vs Placebo**		
Odds ratio (SE)		1.221 (0.230)
95% confidence interval***		(0.845, 1.765)
p-value		0.2881
Age [years] (2 cat.): >= 65		
Number of patients in analysis set	1127	1188
Number of analysed patients, N (%)	1034 (100.0)	1105 (100.0)
Number of patients with endpoint, N (%)	903 (87.3)	970 (87.8)
95% confidence interval*	(85.2, 89.2)	(85.7, 89.6)
Comparison vs Placebo**		
Odds ratio (SE)		1.038 (0.137)
95% confidence interval***		(0.801, 1.345)
p-value		0.7778

* Wilson confidence intervals.
** Logistic regression includes terms for baseline KCCQ - clinical summary score (p<0.0001), baseline eGFR (CKD-EPI) (p=0.0004), Treatment (p=0.3020), region (5 cat.) (p=0.0368), baseline diabetes status (3 cat.) (p=0.9101), sex (p=0.6913), baseline LVEF (3 cat.) (p=0.9159), age (2 cat.) (p=0.8422) and Treatment by age (2 cat.) interaction (p=0.4801).
***Wald confidence intervals.

Data taken from study 1245.121 only.
LOCF: For a missing value at week 52 the last available post-baseline value before week 52 is imputed.

Table R.1.2.5.3: 4 Responder analysis (displaying risk ratio) in KCCQ-CSS change from baseline at week 52 of > -15 points (stability) by age (2 cat.) - RS (LOCF-AD) - 1245.121

Subgroup Description	Placebo	Empa 10mg
Age [years] (2 cat.): < 65		
Number of patients in analysis set	740	675
Number of analysed patients, N (%)	675 (100.0)	635 (100.0)
Number of patients with endpoint, N (%)	602 (89.2)	578 (91.0)
95% confidence interval*	(86.6, 91.3)	(88.5, 93.0)
Comparison vs Placebo**		
Risk ratio (SE)		1.019 (0.019)
95% confidence interval***		(0.983, 1.056)
p-value		0.3009
Age [years] (2 cat.): >= 65		
Number of patients in analysis set	1127	1188
Number of analysed patients, N (%)	1034 (100.0)	1105 (100.0)
Number of patients with endpoint, N (%)	903 (87.3)	970 (87.8)
95% confidence interval*	(85.2, 89.2)	(85.7, 89.6)
Comparison vs Placebo**		
Risk ratio (SE)		1.004 (0.016)
95% confidence interval***		(0.973, 1.037)
p-value		0.7905

* Wilson confidence intervals.
** Log-linked Poisson model with robust estimate of variance includes terms for baseline KCCQ - clinical summary score (p<0.0001), baseline eGFR (CKD-EPI) (p=0.0003), Treatment (p=0.3424), region (5 cat.) (p=0.0012), baseline diabetes status (3 cat.) (p=0.8949), sex (p=0.7071), baseline LVEF (3 cat.) (p=0.9305), age (2 cat.) (p=0.9270) and Treatment by age (2 cat.) interaction (p=0.5532).
***Wald confidence intervals.

Data taken from study 1245.121 only.
LOCF: For a missing value at week 52 the last available post-baseline value before week 52 is imputed.

Table R.1.2.5.3: 5 Responder analysis (displaying odds ratio) in KCCQ-CSS change from baseline at week 52 of >= 15 points (improvement) by age (2 cat.) - RS (LOCF-AD) - 1245.121

Subgroup Description	Placebo	Empa 10mg
Age [years] (2 cat.): < 65		
Number of patients in analysis set	740	675
Number of analysed patients, N (%)	675 (100.0)	635 (100.0)
Number of patients with endpoint, N (%)	158 (23.4)	179 (28.2)
95% confidence interval*	(20.4, 26.7)	(24.8, 31.8)
Comparison vs Placebo**		
Odds ratio (SE)		1.325 (0.196)
95% confidence interval***		(0.992, 1.770)
p-value		0.0571
Age [years] (2 cat.): >= 65		
Number of patients in analysis set	1127	1188
Number of analysed patients, N (%)	1034 (100.0)	1105 (100.0)
Number of patients with endpoint, N (%)	199 (19.2)	245 (22.2)
95% confidence interval*	(17.0, 21.8)	(19.8, 24.7)
Comparison vs Placebo**		
Odds ratio (SE)		1.234 (0.150)
95% confidence interval***		(0.973, 1.566)
p-value		0.0832

* Wilson confidence intervals.
** Logistic regression includes terms for baseline KCCQ - clinical summary score (p<0.0001), baseline eGFR (CKD-EPI) (p=0.0212), Treatment (p=0.0101), region (5 cat.) (p<0.0001), baseline diabetes status (3 cat.) (p=0.9760), sex (p=0.5047), baseline LVEF (3 cat.) (p=0.3353), age (2 cat.) (p=0.9424) and Treatment by age (2 cat.) interaction (p=0.7120).
***Wald confidence intervals.

Data taken from study 1245.121 only.
LOCF: For a missing value at week 52 the last available post-baseline value before week 52 is imputed.

Table R.1.2.5.3: 6 Responder analysis (displaying risk ratio) in KCCQ-CSS change from baseline at week 52 of >= 15 points (improvement) by age (2 cat.) - RS (LOCF-AD) - 1245.121

Subgroup Description	Placebo	Empa 10mg
Age [years] (2 cat.): < 65		
Number of patients in analysis set	740	675
Number of analysed patients, N (%)	675 (100.0)	635 (100.0)
Number of patients with endpoint, N (%)	158 (23.4)	179 (28.2)
95% confidence interval*	(20.4, 26.7)	(24.8, 31.8)
Comparison vs Placebo**		
Risk ratio (SE)		1.163 (0.103)
95% confidence interval***		(0.978, 1.383)
p-value		0.0866
Age [years] (2 cat.): >= 65		
Number of patients in analysis set	1127	1188
Number of analysed patients, N (%)	1034 (100.0)	1105 (100.0)
Number of patients with endpoint, N (%)	199 (19.2)	245 (22.2)
95% confidence interval*	(17.0, 21.8)	(19.8, 24.7)
Comparison vs Placebo**		
Risk ratio (SE)		1.120 (0.087)
95% confidence interval***		(0.962, 1.305)
p-value		0.1450

* Wilson confidence intervals.
** Log-linked Poisson model with robust estimate of variance includes terms for baseline KCCQ - clinical summary score (p<0.0001), baseline eGFR (CKD-EPI) (p=0.0433), Treatment (p=0.0247), region (5 cat.) (p<0.0001), baseline diabetes status (3 cat.) (p=0.9019), sex (p=0.3523), baseline LVEF (3 cat.) (p=0.2531), age (2 cat.) (p=0.9383) and Treatment by age (2 cat.) interaction (p=0.7467).
***Wald confidence intervals.

Data taken from study 1245.121 only.
LOCF: For a missing value at week 52 the last available post-baseline value before week 52 is imputed.

R.1.2.5.4 Subgroup analysis by region (North America, Latin America, Europe, Asia, Other)

Table R.1.2.5.4: 1 Responder analysis (displaying odds ratio) in KCCQ-CSS change from baseline at week 52 of <= -15 points (deterioration) by region - RS (LOCF-AD) - 1245.121

Subgroup Description	Placebo	Empa 10mg
Region (5 cat.): North America		
Number of patients in analysis set	213	212
Number of analysed patients, N (%)	192 (100.0)	204 (100.0)
Number of patients with endpoint, N (%)	18 (9.4)	25 (12.3)
95% confidence interval*	(6.0, 14.3)	(8.4, 17.5)
Comparison vs Placebo**		
Odds ratio (SE)		1.308 (0.431)
95% confidence interval***		(0.685, 2.496)
p-value		0.4156
Region (5 cat.): Latin America		
Number of patients in analysis set	645	641
Number of analysed patients, N (%)	577 (100.0)	586 (100.0)
Number of patients with endpoint, N (%)	68 (11.8)	58 (9.9)
95% confidence interval*	(9.4, 14.7)	(7.7, 12.6)
Comparison vs Placebo**		
Odds ratio (SE)		0.830 (0.159)
95% confidence interval***		(0.571, 1.207)
p-value		0.3286

* Wilson confidence intervals.
** Logistic regression includes terms for baseline KCCQ - clinical summary score (p<0.0001), age (p=0.2377), baseline eGFR (CKD-EPI) (p=0.0040), Treatment (p=0.1225), baseline diabetes status (3 cat.) (p=0.8671), sex (p=0.7726), baseline LVEF (3 cat.) (p=0.9314), region (5 cat.) (p=0.0509) and Treatment by region (5 cat.) interaction (p=0.4034).
***Wald confidence intervals.

Data taken from study 1245.121 only.
LOCF: For a missing value at week 52 the last available post-baseline value before week 52 is imputed.

Table R.1.2.5.4: 1 Responder analysis (displaying odds ratio) in KCCQ-CSS change from baseline at week 52 of <= -15 points (deterioration) by region - RS (LOCF-AD) - 1245.121

Subgroup Description	Placebo	Empa 10mg
Region (5 cat.): Europe		
Number of patients in analysis set	677	676
Number of analysed patients, N (%)	631 (100.0)	638 (100.0)
Number of patients with endpoint, N (%)	85 (13.5)	82 (12.9)
95% confidence interval*	(11.0, 16.4)	(10.5, 15.7)
Comparison vs Placebo**		
Odds ratio (SE)		0.932 (0.156)
95% confidence interval***		(0.672, 1.294)
p-value		0.6751
Region (5 cat.): Asia		
Number of patients in analysis set	245	248
Number of analysed patients, N (%)	232 (100.0)	236 (100.0)
Number of patients with endpoint, N (%)	27 (11.6)	26 (11.0)
95% confidence interval*	(8.1, 16.4)	(7.6, 15.7)
Comparison vs Placebo**		
Odds ratio (SE)		0.960 (0.282)
95% confidence interval***		(0.540, 1.706)
p-value		0.8894

* Wilson confidence intervals.
** Logistic regression includes terms for baseline KCCQ - clinical summary score (p<0.0001), age (p=0.2377), baseline eGFR (CKD-EPI) (p=0.0040), Treatment (p=0.1225), baseline diabetes status (3 cat.) (p=0.8671), sex (p=0.7726), baseline LVEF (3 cat.) (p=0.9314), region (5 cat.) (p=0.0509) and Treatment by region (5 cat.) interaction (p=0.4034).
***Wald confidence intervals.

Data taken from study 1245.121 only.
LOCF: For a missing value at week 52 the last available post-baseline value before week 52 is imputed.

Table R.1.2.5.4: 1 Responder analysis (displaying odds ratio) in KCCQ-CSS change from baseline at week 52 of <= -15 points (deterioration) by region - RS (LOCF-AD) - 1245.121

Subgroup Description	Placebo	Empa 10mg
Region (5 cat.): Other		
Number of patients in analysis set	87	86
Number of analysed patients, N (%)	77 (100.0)	76 (100.0)
Number of patients with endpoint, N (%)	6 (7.8)	1 (1.3)
95% confidence interval*	(3.6, 16.0)	(0.2, 7.1)
Comparison vs Placebo**		
Odds ratio (SE)		0.160 (0.175)
95% confidence interval***		(0.019, 1.363)
p-value		0.0936

* Wilson confidence intervals.
** Logistic regression includes terms for baseline KCCQ - clinical summary score (p<0.0001), age (p=0.2377), baseline eGFR (CKD-EPI) (p=0.0040), Treatment (p=0.1225), baseline diabetes status (3 cat.) (p=0.8671), sex (p=0.7726), baseline LVEF (3 cat.) (p=0.9314), region (5 cat.) (p=0.0509) and Treatment by region (5 cat.) interaction (p=0.4034).
***Wald confidence intervals.

Data taken from study 1245.121 only.
LOCF: For a missing value at week 52 the last available post-baseline value before week 52 is imputed.

Table R.1.2.5.4: 2 Responder analysis (displaying risk ratio) in KCCQ-CSS change from baseline at week 52 of <= -15 points (deterioration) by region - RS (LOCF-AD) - 1245.121

Subgroup Description	Placebo	Empa 10mg
Region (5 cat.): North America		
Number of patients in analysis set	213	212
Number of analysed patients, N (%)	192 (100.0)	204 (100.0)
Number of patients with endpoint, N (%)	18 (9.4)	25 (12.3)
95% confidence interval*	(6.0, 14.3)	(8.4, 17.5)
Comparison vs Placebo**		
Risk ratio (SE)		1.267 (0.372)
95% confidence interval***		(0.713, 2.251)
p-value		0.4196
Region (5 cat.): Latin America		
Number of patients in analysis set	645	641
Number of analysed patients, N (%)	577 (100.0)	586 (100.0)
Number of patients with endpoint, N (%)	68 (11.8)	58 (9.9)
95% confidence interval*	(9.4, 14.7)	(7.7, 12.6)
Comparison vs Placebo**		
Risk ratio (SE)		0.848 (0.143)
95% confidence interval***		(0.610, 1.179)
p-value		0.3279

* Wilson confidence intervals.
** Log-linked Poisson model with robust estimate of variance includes terms for baseline KCCQ - clinical summary score (p<0.0001), age (p=0.2637), baseline eGFR (CKD-EPI) (p=0.0044), Treatment (p=0.1210), baseline diabetes status (3 cat.) (p=0.8705), sex (p=0.7704), baseline LVEF (3 cat.) (p=0.9308), region (5 cat.) (p=0.0637) and Treatment by region (5 cat.) interaction (p=0.4101).
***Wald confidence intervals.

Data taken from study 1245.121 only.
LOCF: For a missing value at week 52 the last available post-baseline value before week 52 is imputed.

Table R.1.2.5.4: 2 Responder analysis (displaying risk ratio) in KCCQ-CSS change from baseline at week 52 of <= -15 points (deterioration) by region - RS (LOCF-AD) - 1245.121

Subgroup Description	Placebo	Empa 10mg
Region (5 cat.): Europe		
Number of patients in analysis set	677	676
Number of analysed patients, N (%)	631 (100.0)	638 (100.0)
Number of patients with endpoint, N (%)	85 (13.5)	82 (12.9)
95% confidence interval*	(11.0, 16.4)	(10.5, 15.7)
Comparison vs Placebo**		
Risk ratio (SE)		0.942 (0.134)
95% confidence interval***		(0.712, 1.245)
p-value		0.6730
Region (5 cat.): Asia		
Number of patients in analysis set	245	248
Number of analysed patients, N (%)	232 (100.0)	236 (100.0)
Number of patients with endpoint, N (%)	27 (11.6)	26 (11.0)
95% confidence interval*	(8.1, 16.4)	(7.6, 15.7)
Comparison vs Placebo**		
Risk ratio (SE)		0.964 (0.249)
95% confidence interval***		(0.581, 1.599)
p-value		0.8877

* Wilson confidence intervals.
** Log-linked Poisson model with robust estimate of variance includes terms for baseline KCCQ - clinical summary score (p<0.0001), age (p=0.2637), baseline eGFR (CKD-EPI) (p=0.0044), Treatment (p=0.1210), baseline diabetes status (3 cat.) (p=0.8705), sex (p=0.7704), baseline LVEF (3 cat.) (p=0.9308), region (5 cat.) (p=0.0637) and Treatment by region (5 cat.) interaction (p=0.4101).
***Wald confidence intervals.

Data taken from study 1245.121 only.
LOCF: For a missing value at week 52 the last available post-baseline value before week 52 is imputed.

Table R.1.2.5.4: 2 Responder analysis (displaying risk ratio) in KCCQ-CSS change from baseline at week 52 of <= -15 points (deterioration) by region - RS (LOCF-AD) - 1245.121

Subgroup Description	Placebo	Empa 10mg
Region (5 cat.): Other		
Number of patients in analysis set	87	86
Number of analysed patients, N (%)	77 (100.0)	76 (100.0)
Number of patients with endpoint, N (%)	6 (7.8)	1 (1.3)
95% confidence interval*	(3.6, 16.0)	(0.2, 7.1)
Comparison vs Placebo**		
Risk ratio (SE)		0.172 (0.182)
95% confidence interval***		(0.021, 1.375)
p-value		0.0969

* Wilson confidence intervals.
** Log-linked Poisson model with robust estimate of variance includes terms for baseline KCCQ - clinical summary score (p<0.0001), age (p=0.2637), baseline eGFR (CKD-EPI) (p=0.0044), Treatment (p=0.1210), baseline diabetes status (3 cat.) (p=0.8705), sex (p=0.7704), baseline LVEF (3 cat.) (p=0.9308), region (5 cat.) (p=0.0637) and Treatment by region (5 cat.) interaction (p=0.4101).
***Wald confidence intervals.

Data taken from study 1245.121 only.
LOCF: For a missing value at week 52 the last available post-baseline value before week 52 is imputed.

Table R.1.2.5.4: 3 Responder analysis (displaying odds ratio) in KCCQ-CSS change from baseline at week 52 of > -15 points (stability) by region - RS (LOCF-AD) - 1245.121

Subgroup Description	Placebo	Empa 10mg
Region (5 cat.): North America		
Number of patients in analysis set	213	212
Number of analysed patients, N (%)	192 (100.0)	204 (100.0)
Number of patients with endpoint, N (%)	174 (90.6)	179 (87.7)
95% confidence interval*	(85.7, 94.0)	(82.5, 91.6)
Comparison vs Placebo**		
Odds ratio (SE)		0.765 (0.252)
95% confidence interval***		(0.401, 1.459)
p-value		0.4156
Region (5 cat.): Latin America		
Number of patients in analysis set	645	641
Number of analysed patients, N (%)	577 (100.0)	586 (100.0)
Number of patients with endpoint, N (%)	509 (88.2)	528 (90.1)
95% confidence interval*	(85.3, 90.6)	(87.4, 92.3)
Comparison vs Placebo**		
Odds ratio (SE)		1.205 (0.230)
95% confidence interval***		(0.829, 1.752)
p-value		0.3286

* Wilson confidence intervals.
** Logistic regression includes terms for baseline KCCQ - clinical summary score (p<0.0001), age (p=0.2377), baseline eGFR (CKD-EPI) (p=0.0040), Treatment (p=0.1225), baseline diabetes status (3 cat.) (p=0.8671), sex (p=0.7726), baseline LVEF (3 cat.) (p=0.9314), region (5 cat.) (p=0.0509) and Treatment by region (5 cat.) interaction (p=0.4034).
***Wald confidence intervals.

Data taken from study 1245.121 only.
LOCF: For a missing value at week 52 the last available post-baseline value before week 52 is imputed.

Table R.1.2.5.4: 3 Responder analysis (displaying odds ratio) in KCCQ-CSS change from baseline at week 52 of > -15 points (stability) by region - RS (LOCF-AD) - 1245.121

Subgroup Description	Placebo	Empa 10mg
Region (5 cat.): Europe		
Number of patients in analysis set	677	676
Number of analysed patients, N (%)	631 (100.0)	638 (100.0)
Number of patients with endpoint, N (%)	546 (86.5)	556 (87.1)
95% confidence interval*	(83.6, 89.0)	(84.3, 89.5)
Comparison vs Placebo**		
Odds ratio (SE)		1.073 (0.180)
95% confidence interval***		(0.773, 1.489)
p-value		0.6751
Region (5 cat.): Asia		
Number of patients in analysis set	245	248
Number of analysed patients, N (%)	232 (100.0)	236 (100.0)
Number of patients with endpoint, N (%)	205 (88.4)	210 (89.0)
95% confidence interval*	(83.6, 91.9)	(84.3, 92.4)
Comparison vs Placebo**		
Odds ratio (SE)		1.042 (0.306)
95% confidence interval***		(0.586, 1.851)
p-value		0.8894

* Wilson confidence intervals.
** Logistic regression includes terms for baseline KCCQ - clinical summary score (p<0.0001), age (p=0.2377), baseline eGFR (CKD-EPI) (p=0.0040), Treatment (p=0.1225), baseline diabetes status (3 cat.) (p=0.8671), sex (p=0.7726), baseline LVEF (3 cat.) (p=0.9314), region (5 cat.) (p=0.0509) and Treatment by region (5 cat.) interaction (p=0.4034).
***Wald confidence intervals.

Data taken from study 1245.121 only.
LOCF: For a missing value at week 52 the last available post-baseline value before week 52 is imputed.

Table R.1.2.5.4: 3 Responder analysis (displaying odds ratio) in KCCQ-CSS change from baseline at week 52 of > -15 points (stability) by region - RS (LOCF-AD) - 1245.121

Subgroup Description	Placebo	Empa 10mg
Region (5 cat.): Other		
Number of patients in analysis set	87	86
Number of analysed patients, N (%)	77 (100.0)	76 (100.0)
Number of patients with endpoint, N (%)	71 (92.2)	75 (98.7)
95% confidence interval*	(84.0, 96.4)	(92.9, 99.8)
Comparison vs Placebo**		
Odds ratio (SE)		6.267 (6.858)
95% confidence interval***		(0.734,53.531)
p-value		0.0936

* Wilson confidence intervals.
** Logistic regression includes terms for baseline KCCQ - clinical summary score (p<0.0001), age (p=0.2377), baseline eGFR (CKD-EPI) (p=0.0040), Treatment (p=0.1225), baseline diabetes status (3 cat.) (p=0.8671), sex (p=0.7726), baseline LVEF (3 cat.) (p=0.9314), region (5 cat.) (p=0.0509) and Treatment by region (5 cat.) interaction (p=0.4034).
***Wald confidence intervals.

Data taken from study 1245.121 only.
LOCF: For a missing value at week 52 the last available post-baseline value before week 52 is imputed.

Table R.1.2.5.4: 4 Responder analysis (displaying risk ratio) in KCCQ-CSS change from baseline at week 52 of > -15 points (stability) by region - RS (LOCF-AD) - 1245.121

Subgroup Description	Placebo	Empa 10mg
Region (5 cat.): North America		
Number of patients in analysis set	213	212
Number of analysed patients, N (%)	192 (100.0)	204 (100.0)
Number of patients with endpoint, N (%)	174 (90.6)	179 (87.7)
95% confidence interval*	(85.7, 94.0)	(82.5, 91.6)
Comparison vs Placebo**		
Risk ratio (SE)		0.973 (0.034)
95% confidence interval***		(0.908, 1.042)
p-value		0.4279
Region (5 cat.): Latin America		
Number of patients in analysis set	645	641
Number of analysed patients, N (%)	577 (100.0)	586 (100.0)
Number of patients with endpoint, N (%)	509 (88.2)	528 (90.1)
95% confidence interval*	(85.3, 90.6)	(87.4, 92.3)
Comparison vs Placebo**		
Risk ratio (SE)		1.019 (0.021)
95% confidence interval***		(0.979, 1.061)
p-value		0.3485

* Wilson confidence intervals.
** Log-linked Poisson model with robust estimate of variance includes terms for baseline KCCQ - clinical summary score (p<0.0001), age (p=0.3160), baseline eGFR (CKD-EPI) (p=0.0049), Treatment (p=0.2841), baseline diabetes status (3 cat.) (p=0.8497), sex (p=0.7722), baseline LVEF (3 cat.) (p=0.9432), region (5 cat.) (p=0.0022) and Treatment by region (5 cat.) interaction (p=0.4154).
***Wald confidence intervals.

Data taken from study 1245.121 only.
LOCF: For a missing value at week 52 the last available post-baseline value before week 52 is imputed.

Table R.1.2.5.4: 4 Responder analysis (displaying risk ratio) in KCCQ-CSS change from baseline at week 52 of > -15 points (stability) by region - RS (LOCF-AD) - 1245.121

Subgroup Description	Placebo	Empa 10mg
Region (5 cat.): Europe		
Number of patients in analysis set	677	676
Number of analysed patients, N (%)	631 (100.0)	638 (100.0)
Number of patients with endpoint, N (%)	546 (86.5)	556 (87.1)
95% confidence interval*	(83.6, 89.0)	(84.3, 89.5)
Comparison vs Placebo**		
Risk ratio (SE)		1.009 (0.022)
95% confidence interval***		(0.967, 1.053)
p-value		0.6778
Region (5 cat.): Asia		
Number of patients in analysis set	245	248
Number of analysed patients, N (%)	232 (100.0)	236 (100.0)
Number of patients with endpoint, N (%)	205 (88.4)	210 (89.0)
95% confidence interval*	(83.6, 91.9)	(84.3, 92.4)
Comparison vs Placebo**		
Risk ratio (SE)		1.004 (0.033)
95% confidence interval***		(0.941, 1.071)
p-value		0.9090

* Wilson confidence intervals.
** Log-linked Poisson model with robust estimate of variance includes terms for baseline KCCQ - clinical summary score (p<0.0001), age (p=0.3160), baseline eGFR (CKD-EPI) (p=0.0049), Treatment (p=0.2841), baseline diabetes status (3 cat.) (p=0.8497), sex (p=0.7722), baseline LVEF (3 cat.) (p=0.9432), region (5 cat.) (p=0.0022) and Treatment by region (5 cat.) interaction (p=0.4154).
***Wald confidence intervals.

Data taken from study 1245.121 only.
LOCF: For a missing value at week 52 the last available post-baseline value before week 52 is imputed.

Table R.1.2.5.4: 4 Responder analysis (displaying risk ratio) in KCCQ-CSS change from baseline at week 52 of > -15 points (stability) by region - RS (LOCF-AD) - 1245.121

Subgroup Description	Placebo	Empa 10mg
Region (5 cat.): Other		
Number of patients in analysis set	87	86
Number of analysed patients, N (%)	77 (100.0)	76 (100.0)
Number of patients with endpoint, N (%)	71 (92.2)	75 (98.7)
95% confidence interval*	(84.0, 96.4)	(92.9, 99.8)
Comparison vs Placebo**		
Risk ratio (SE)		1.070 (0.038)
95% confidence interval***		(0.998, 1.146)
p-value		0.0558

* Wilson confidence intervals.
** Log-linked Poisson model with robust estimate of variance includes terms for baseline KCCQ - clinical summary score (p<0.0001), age (p=0.3160), baseline eGFR (CKD-EPI) (p=0.0049), Treatment (p=0.2841), baseline diabetes status (3 cat.) (p=0.8497), sex (p=0.7722), baseline LVEF (3 cat.) (p=0.9432), region (5 cat.) (p=0.0022) and Treatment by region (5 cat.) interaction (p=0.4154).
***Wald confidence intervals.

Data taken from study 1245.121 only.
LOCF: For a missing value at week 52 the last available post-baseline value before week 52 is imputed.

Table R.1.2.5.4: 5 Responder analysis (displaying odds ratio) in KCCQ-CSS change from baseline at week 52 of >= 15 points (improvement) by region - RS (LOCF-AD) - 1245.121

Subgroup Description	Placebo	Empa 10mg
Region (5 cat.): North America		
Number of patients in analysis set	213	212
Number of analysed patients, N (%)	192 (100.0)	204 (100.0)
Number of patients with endpoint, N (%)	27 (14.1)	40 (19.6)
95% confidence interval*	(9.8, 19.7)	(14.7, 25.6)
Comparison vs Placebo**		
Odds ratio (SE)		1.818 (0.560)
95% confidence interval***		(0.994, 3.323)
p-value		0.0522
Region (5 cat.): Latin America		
Number of patients in analysis set	645	641
Number of analysed patients, N (%)	577 (100.0)	586 (100.0)
Number of patients with endpoint, N (%)	167 (28.9)	198 (33.8)
95% confidence interval*	(25.4, 32.8)	(30.1, 37.7)
Comparison vs Placebo**		
Odds ratio (SE)		1.282 (0.189)
95% confidence interval***		(0.960, 1.712)
p-value		0.0925

* Wilson confidence intervals.
** Logistic regression includes terms for baseline KCCQ - clinical summary score (p<0.0001), age (p=0.0683), baseline eGFR (CKD-EPI) (p=0.1962), Treatment (p=0.0282), baseline diabetes status (3 cat.) (p=0.9684), sex (p=0.4899), baseline LVEF (3 cat.) (p=0.3947), region (5 cat.) (p<0.0001) and Treatment by region (5 cat.) interaction (p=0.7549).
***Wald confidence intervals.

Data taken from study 1245.121 only.
LOCF: For a missing value at week 52 the last available post-baseline value before week 52 is imputed.

Table R.1.2.5.4: 5 Responder analysis (displaying odds ratio) in KCCQ-CSS change from baseline at week 52 of >= 15 points (improvement) by region - RS (LOCF-AD) - 1245.121

Subgroup Description	Placebo	Empa 10mg
Region (5 cat.): Europe		
Number of patients in analysis set	677	676
Number of analysed patients, N (%)	631 (100.0)	638 (100.0)
Number of patients with endpoint, N (%)	115 (18.2)	127 (19.9)
95% confidence interval*	(15.4, 21.4)	(17.0, 23.2)
Comparison vs Placebo**		
Odds ratio (SE)		1.174 (0.186)
95% confidence interval***		(0.860, 1.601)
p-value		0.3121
Region (5 cat.): Asia		
Number of patients in analysis set	245	248
Number of analysed patients, N (%)	232 (100.0)	236 (100.0)
Number of patients with endpoint, N (%)	22 (9.5)	33 (14.0)
95% confidence interval*	(6.3, 13.9)	(10.1, 19.0)
Comparison vs Placebo**		
Odds ratio (SE)		1.352 (0.426)
95% confidence interval***		(0.729, 2.508)
p-value		0.3391

* Wilson confidence intervals.
** Logistic regression includes terms for baseline KCCQ - clinical summary score (p<0.0001), age (p=0.0683), baseline eGFR (CKD-EPI) (p=0.1962), Treatment (p=0.0282), baseline diabetes status (3 cat.) (p=0.9684), sex (p=0.4899), baseline LVEF (3 cat.) (p=0.3947), region (5 cat.) (p<0.0001) and Treatment by region (5 cat.) interaction (p=0.7549).
***Wald confidence intervals.

Data taken from study 1245.121 only.
LOCF: For a missing value at week 52 the last available post-baseline value before week 52 is imputed.

Table R.1.2.5.4: 5 Responder analysis (displaying odds ratio) in KCCQ-CSS change from baseline at week 52 of >= 15 points (improvement) by region - RS (LOCF-AD) - 1245.121

Subgroup Description	Placebo	Empa 10mg
Region (5 cat.): Other		
Number of patients in analysis set	87	86
Number of analysed patients, N (%)	77 (100.0)	76 (100.0)
Number of patients with endpoint, N (%)	26 (33.8)	26 (34.2)
95% confidence interval*	(24.2, 44.9)	(24.5, 45.4)
Comparison vs Placebo**		
Odds ratio (SE)		1.052 (0.398)
95% confidence interval***		(0.502, 2.206)
p-value		0.8924

* Wilson confidence intervals.
** Logistic regression includes terms for baseline KCCQ - clinical summary score (p<0.0001), age (p=0.0683), baseline eGFR (CKD-EPI) (p=0.1962), Treatment (p=0.0282), baseline diabetes status (3 cat.) (p=0.9684), sex (p=0.4899), baseline LVEF (3 cat.) (p=0.3947), region (5 cat.) (p<0.0001) and Treatment by region (5 cat.) interaction (p=0.7549).
***Wald confidence intervals.

Data taken from study 1245.121 only.
LOCF: For a missing value at week 52 the last available post-baseline value before week 52 is imputed.

Table R.1.2.5.4: 6 Responder analysis (displaying risk ratio) in KCCQ-CSS change from baseline at week 52 of >= 15 points (improvement) by region - RS (LOCF-AD) - 1245.121

Subgroup Description	Placebo	Empa 10mg
Region (5 cat.): North America		
Number of patients in analysis set	213	212
Number of analysed patients, N (%)	192 (100.0)	204 (100.0)
Number of patients with endpoint, N (%)	27 (14.1)	40 (19.6)
95% confidence interval*	(9.8, 19.7)	(14.7, 25.6)
Comparison vs Placebo**		
Risk ratio (SE)		1.450 (0.304)
95% confidence interval***		(0.962, 2.186)
p-value		0.0757
Region (5 cat.): Latin America		
Number of patients in analysis set	645	641
Number of analysed patients, N (%)	577 (100.0)	586 (100.0)
Number of patients with endpoint, N (%)	167 (28.9)	198 (33.8)
95% confidence interval*	(25.4, 32.8)	(30.1, 37.7)
Comparison vs Placebo**		
Risk ratio (SE)		1.108 (0.093)
95% confidence interval***		(0.941, 1.306)
p-value		0.2193

* Wilson confidence intervals.
** Log-linked Poisson model with robust estimate of variance includes terms for baseline KCCQ - clinical summary score (p<0.0001), age (p=0.1287), baseline eGFR (CKD-EPI) (p=0.2442), Treatment (p=0.0191), baseline diabetes status (3 cat.) (p=0.9125), sex (p=0.3371), baseline LVEF (3 cat.) (p=0.2972), region (5 cat.) (p<0.0001) and Treatment by region (5 cat.) interaction (p=0.7597).
***Wald confidence intervals.

Data taken from study 1245.121 only.
LOCF: For a missing value at week 52 the last available post-baseline value before week 52 is imputed.

Table R.1.2.5.4: 6 Responder analysis (displaying risk ratio) in KCCQ-CSS change from baseline at week 52 of >= 15 points (improvement) by region - RS (LOCF-AD) - 1245.121

Subgroup Description	Placebo	Empa 10mg
Region (5 cat.): Europe		
Number of patients in analysis set	677	676
Number of analysed patients, N (%)	631 (100.0)	638 (100.0)
Number of patients with endpoint, N (%)	115 (18.2)	127 (19.9)
95% confidence interval*	(15.4, 21.4)	(17.0, 23.2)
Comparison vs Placebo**		
Risk ratio (SE)		1.101 (0.119)
95% confidence interval***		(0.890, 1.361)
p-value		0.3775
Region (5 cat.): Asia		
Number of patients in analysis set	245	248
Number of analysed patients, N (%)	232 (100.0)	236 (100.0)
Number of patients with endpoint, N (%)	22 (9.5)	33 (14.0)
95% confidence interval*	(6.3, 13.9)	(10.1, 19.0)
Comparison vs Placebo**		
Risk ratio (SE)		1.295 (0.298)
95% confidence interval***		(0.825, 2.032)
p-value		0.2617

* Wilson confidence intervals.
** Log-linked Poisson model with robust estimate of variance includes terms for baseline KCCQ - clinical summary score (p<0.0001), age (p=0.1287), baseline eGFR (CKD-EPI) (p=0.2442), Treatment (p=0.0191), baseline diabetes status (3 cat.) (p=0.9125), sex (p=0.3371), baseline LVEF (3 cat.) (p=0.2972), region (5 cat.) (p<0.0001) and Treatment by region (5 cat.) interaction (p=0.7597).
***Wald confidence intervals.

Data taken from study 1245.121 only.
LOCF: For a missing value at week 52 the last available post-baseline value before week 52 is imputed.

Table R.1.2.5.4: 6 Responder analysis (displaying risk ratio) in KCCQ-CSS change from baseline at week 52 of >= 15 points (improvement) by region - RS (LOCF-AD) - 1245.121

Subgroup Description	Placebo	Empa 10mg
Region (5 cat.): Other		
Number of patients in analysis set	87	86
Number of analysed patients, N (%)	77 (100.0)	76 (100.0)
Number of patients with endpoint, N (%)	26 (33.8)	26 (34.2)
95% confidence interval*	(24.2, 44.9)	(24.5, 45.4)
Comparison vs Placebo**		
Risk ratio (SE)		1.112 (0.231)
95% confidence interval***		(0.740, 1.669)
p-value		0.6096

* Wilson confidence intervals.
** Log-linked Poisson model with robust estimate of variance includes terms for baseline KCCQ - clinical summary score (p<0.0001), age (p=0.1287), baseline eGFR (CKD-EPI) (p=0.2442), Treatment (p=0.0191), baseline diabetes status (3 cat.) (p=0.9125), sex (p=0.3371), baseline LVEF (3 cat.) (p=0.2972), region (5 cat.) (p<0.0001) and Treatment by region (5 cat.) interaction (p=0.7597).
***Wald confidence intervals.

Data taken from study 1245.121 only.
LOCF: For a missing value at week 52 the last available post-baseline value before week 52 is imputed.

R.1.2.5.5

R.1.2.5.5 Subgroup analysis by OECD (N/Y)

Table R.1.2.5.5: 1 Responder analysis (displaying odds ratio) in KCCQ-CSS change from baseline at week 52 of <= -15 points (deterioration) by OECD member (N/Y) - RS (LOCF-AD) - 1245.121

Subgroup Description	Placebo	Empa 10mg
OECD member: No		
Number of patients in analysis set	741	713
Number of analysed patients, N (%)	663 (100.0)	647 (100.0)
Number of patients with endpoint, N (%)	74 (11.2)	56 (8.7)
95% confidence interval*	(9.0, 13.8)	(6.7, 11.1)
Comparison vs Placebo**		
Odds ratio (SE)		0.761 (0.143)
95% confidence interval***		(0.526, 1.100)
p-value		0.1459
OECD member: Yes		
Number of patients in analysis set	1126	1150
Number of analysed patients, N (%)	1046 (100.0)	1093 (100.0)
Number of patients with endpoint, N (%)	130 (12.4)	136 (12.4)
95% confidence interval*	(10.6, 14.6)	(10.6, 14.5)
Comparison vs Placebo**		
Odds ratio (SE)		0.994 (0.131)
95% confidence interval***		(0.767, 1.288)
p-value		0.9648

* Wilson confidence intervals.
** Logistic regression includes terms for baseline KCCQ - clinical summary score (p<0.0001), age (p=0.1752), baseline eGFR (CKD-EPI) (p=0.0029), Treatment (p=0.2236), sex (p=0.7331), baseline diabetes status (3 cat.) (p=0.8118), baseline LVEF (3 cat.) (p=0.8570), OECD member (p=0.2912) and Treatment by OECD member interaction (p=0.2445).
***Wald confidence intervals.

Data taken from study 1245.121 only.
LOCF: For a missing value at week 52 the last available post-baseline value before week 52 is imputed.
OECD member (yes/no) countries included:
Yes: United States, Canada, Mexico, Poland, Netherlands, Hungary, Germany, Czech Republic, Italy, France, Spain, United Kingdom, Belgium, Japan, Australia, 'Korea; Republic Of South Korea';
No: Brazil, Argentina, China, India.

Table R.1.2.5.5: 2 Responder analysis (displaying risk ratio) in KCCQ-CSS change from baseline at week 52 of <= -15 points (deterioration) by OECD member (N/Y) - RS (LOCF-AD) - 1245.121

Subgroup Description	Placebo	Empa 10mg
OECD member: No		
Number of patients in analysis set	741	713
Number of analysed patients, N (%)	663 (100.0)	647 (100.0)
Number of patients with endpoint, N (%)	74 (11.2)	56 (8.7)
95% confidence interval*	(9.0, 13.8)	(6.7, 11.1)
Comparison vs Placebo**		
Risk ratio (SE)		0.783 (0.131)
95% confidence interval***		(0.565, 1.087)
p-value		0.1443
OECD member: Yes		
Number of patients in analysis set	1126	1150
Number of analysed patients, N (%)	1046 (100.0)	1093 (100.0)
Number of patients with endpoint, N (%)	130 (12.4)	136 (12.4)
95% confidence interval*	(10.6, 14.6)	(10.6, 14.5)
Comparison vs Placebo**		
Risk ratio (SE)		0.995 (0.113)
95% confidence interval***		(0.796, 1.244)
p-value		0.9649

* Wilson confidence intervals.
** Log-linked Poisson model with robust estimate of variance includes terms for baseline KCCQ - clinical summary score (p<0.0001), age (p=0.1986), baseline eGFR (CKD-EPI) (p=0.0032), Treatment (p=0.2182), sex (p=0.7310), baseline diabetes status (3 cat.) (p=0.8129), baseline LVEF (3 cat.) (p=0.8558), OECD member (p=0.2836) and Treatment by OECD member interaction (p=0.2376).
***Wald confidence intervals.

Data taken from study 1245.121 only.
LOCF: For a missing value at week 52 the last available post-baseline value before week 52 is imputed.
OECD member (yes/no) countries included:
Yes: United States, Canada, Mexico, Poland, Netherlands, Hungary, Germany, Czech Republic, Italy, France, Spain, United Kingdom, Belgium, Japan, Australia, 'Korea; Republic Of South Korea';
No: Brazil, Argentina, China, India.

Table R.1.2.5.5: 3 Responder analysis (displaying odds ratio) in KCCQ-CSS change from baseline at week 52 of > -15 points (stability) by OECD member (N/Y) - RS (LOCF-AD) - 1245.121

Subgroup Description	Placebo	Empa 10mg
OECD member: No		
Number of patients in analysis set	741	713
Number of analysed patients, N (%)	663 (100.0)	647 (100.0)
Number of patients with endpoint, N (%)	589 (88.8)	591 (91.3)
95% confidence interval*	(86.2, 91.0)	(88.9, 93.3)
Comparison vs Placebo**		
Odds ratio (SE)		1.315 (0.247)
95% confidence interval***		(0.909, 1.901)
p-value		0.1459
OECD member: Yes		
Number of patients in analysis set	1126	1150
Number of analysed patients, N (%)	1046 (100.0)	1093 (100.0)
Number of patients with endpoint, N (%)	916 (87.6)	957 (87.6)
95% confidence interval*	(85.4, 89.4)	(85.5, 89.4)
Comparison vs Placebo**		
Odds ratio (SE)		1.006 (0.133)
95% confidence interval***		(0.776, 1.303)
p-value		0.9648

* Wilson confidence intervals.
** Logistic regression includes terms for baseline KCCQ - clinical summary score (p<0.0001), age (p=0.1752), baseline eGFR (CKD-EPI) (p=0.0029), Treatment (p=0.2236), sex (p=0.7331), baseline diabetes status (3 cat.) (p=0.8118), baseline LVEF (3 cat.) (p=0.8570), OECD member (p=0.2912) and Treatment by OECD member interaction (p=0.2445).
***Wald confidence intervals.

Data taken from study 1245.121 only.
LOCF: For a missing value at week 52 the last available post-baseline value before week 52 is imputed.
OECD member (yes/no) countries included:
Yes: United States, Canada, Mexico, Poland, Netherlands, Hungary, Germany, Czech Republic, Italy, France, Spain, United Kingdom, Belgium, Japan, Australia, 'Korea; Republic Of South Korea';
No: Brazil, Argentina, China, India.

Table R.1.2.5.5: 4 Responder analysis (displaying risk ratio) in KCCQ-CSS change from baseline at week 52 of > -15 points (stability) by OECD member (N/Y) - RS (LOCF-AD) - 1245.121

Subgroup Description	Placebo	Empa 10mg
OECD member: No		
Number of patients in analysis set	741	713
Number of analysed patients, N (%)	663 (100.0)	647 (100.0)
Number of patients with endpoint, N (%)	589 (88.8)	591 (91.3)
95% confidence interval*	(86.2, 91.0)	(88.9, 93.3)
Comparison vs Placebo**		
Risk ratio (SE)		1.026 (0.019)
95% confidence interval***		(0.990, 1.063)
p-value		0.1577
OECD member: Yes		
Number of patients in analysis set	1126	1150
Number of analysed patients, N (%)	1046 (100.0)	1093 (100.0)
Number of patients with endpoint, N (%)	916 (87.6)	957 (87.6)
95% confidence interval*	(85.4, 89.4)	(85.5, 89.4)
Comparison vs Placebo**		
Risk ratio (SE)		1.001 (0.016)
95% confidence interval***		(0.970, 1.033)
p-value		0.9541

* Wilson confidence intervals.
** Log-linked Poisson model with robust estimate of variance includes terms for baseline KCCQ - clinical summary score (p<0.0001), age (p=0.2369), baseline eGFR (CKD-EPI) (p=0.0036), Treatment (p=0.2743), sex (p=0.7263), baseline diabetes status (3 cat.) (p=0.8131), baseline LVEF (3 cat.) (p=0.8788), OECD member (p=0.3488) and Treatment by OECD member interaction (p=0.3084).
***Wald confidence intervals.

Data taken from study 1245.121 only.
LOCF: For a missing value at week 52 the last available post-baseline value before week 52 is imputed.
OECD member (yes/no) countries included:
Yes: United States, Canada, Mexico, Poland, Netherlands, Hungary, Germany, Czech Republic, Italy, France, Spain, United Kingdom, Belgium, Japan, Australia, 'Korea; Republic Of South Korea';
No: Brazil, Argentina, China, India.

Table R.1.2.5.5: 5 Responder analysis (displaying odds ratio) in KCCQ-CSS change from baseline at week 52 of >= 15 points (improvement) by OECD member (N/Y) - RS (LOCF-AD) - 1245.121

Subgroup Description	Placebo	Empa 10mg
OECD member: No		
Number of patients in analysis set	741	713
Number of analysed patients, N (%)	663 (100.0)	647 (100.0)
Number of patients with endpoint, N (%)	186 (28.1)	221 (34.2)
95% confidence interval*	(24.8, 31.6)	(30.6, 37.9)
Comparison vs Placebo**		
Odds ratio (SE)		1.381 (0.191)
95% confidence interval***		(1.053, 1.812)
p-value		0.0198
OECD member: Yes		
Number of patients in analysis set	1126	1150
Number of analysed patients, N (%)	1046 (100.0)	1093 (100.0)
Number of patients with endpoint, N (%)	171 (16.3)	203 (18.6)
95% confidence interval*	(14.2, 18.7)	(16.4, 21.0)
Comparison vs Placebo**		
Odds ratio (SE)		1.213 (0.154)
95% confidence interval***		(0.946, 1.556)
p-value		0.1274

* Wilson confidence intervals.
** Logistic regression includes terms for baseline KCCQ - clinical summary score (p<0.0001), age (p=0.0656), baseline eGFR (CKD-EPI) (p=0.1975), Treatment (p=0.0060), sex (p=0.5474), baseline diabetes status (3 cat.) (p=0.8901), baseline LVEF (3 cat.) (p=0.3365), OECD member (p<0.0001) and Treatment by OECD member interaction (p=0.4908).
***Wald confidence intervals.

Data taken from study 1245.121 only.
LOCF: For a missing value at week 52 the last available post-baseline value before week 52 is imputed.
OECD member (yes/no) countries included:
Yes: United States, Canada, Mexico, Poland, Netherlands, Hungary, Germany, Czech Republic, Italy, France, Spain, United Kingdom, Belgium, Japan, Australia, 'Korea; Republic Of South Korea';
No: Brazil, Argentina, China, India.

Table R.1.2.5.5: 6 Responder analysis (displaying risk ratio) in KCCQ-CSS change from baseline at week 52 of >= 15 points (improvement) by OECD member (N/Y) - RS (LOCF-AD) - 1245.121

Subgroup Description	Placebo	Empa 10mg
OECD member: No		
Number of patients in analysis set	741	713
Number of analysed patients, N (%)	663 (100.0)	647 (100.0)
Number of patients with endpoint, N (%)	186 (28.1)	221 (34.2)
95% confidence interval*	(24.8, 31.6)	(30.6, 37.9)
Comparison vs Placebo**		
Risk ratio (SE)		1.157 (0.092)
95% confidence interval***		(0.990, 1.351)
p-value		0.0666
OECD member: Yes		
Number of patients in analysis set	1126	1150
Number of analysed patients, N (%)	1046 (100.0)	1093 (100.0)
Number of patients with endpoint, N (%)	171 (16.3)	203 (18.6)
95% confidence interval*	(14.2, 18.7)	(16.4, 21.0)
Comparison vs Placebo**		
Risk ratio (SE)		1.134 (0.099)
95% confidence interval***		(0.956, 1.345)
p-value		0.1497

* Wilson confidence intervals.
** Log-linked Poisson model with robust estimate of variance includes terms for baseline KCCQ - clinical summary score (p<0.0001), age (p=0.1117), baseline eGFR (CKD-EPI) (p=0.2665), Treatment (p=0.0216), sex (p=0.4156), baseline diabetes status (3 cat.) (p=0.9540), baseline LVEF (3 cat.) (p=0.1922), OECD member (p<0.0001) and Treatment by OECD member interaction (p=0.8650).
***Wald confidence intervals.

Data taken from study 1245.121 only.
LOCF: For a missing value at week 52 the last available post-baseline value before week 52 is imputed.
OECD member (yes/no) countries included:
Yes: United States, Canada, Mexico, Poland, Netherlands, Hungary, Germany, Czech Republic, Italy, France, Spain, United Kingdom, Belgium, Japan, Australia, 'Korea; Republic Of South Korea';
No: Brazil, Argentina, China, India.

R.1.2.5.6 Subgroup analysis by NYHA at baseline (II, III/IV - 2 cat.)

Table R.1.2.5.6: 1 Responder analysis (displaying odds ratio) in KCCQ-CSS change from baseline at week 52 of <= -15 points (deterioration) by NYHA (2 cat.) - RS (LOCF-AD) - 1245.121

Subgroup Description	Placebo	Empa 10mg
Baseline NYHA (2 cat.): II		
Number of patients in analysis set	1401	1399
Number of analysed patients, N (%)	1306 (100.0)	1307 (100.0)
Number of patients with endpoint, N (%)	153 (11.7)	140 (10.7)
95% confidence interval*	(10.1, 13.6)	(9.1, 12.5)
Comparison vs Placebo**		
Odds ratio (SE)		0.884 (0.111)
95% confidence interval***		(0.691, 1.130)
p-value		0.3243
Baseline NYHA (2 cat.): III/IV		
Number of patients in analysis set	466	464
Number of analysed patients, N (%)	403 (100.0)	433 (100.0)
Number of patients with endpoint, N (%)	51 (12.7)	52 (12.0)
95% confidence interval*	(9.8, 16.3)	(9.3, 15.4)
Comparison vs Placebo**		
Odds ratio (SE)		0.985 (0.210)
95% confidence interval***		(0.648, 1.497)
p-value		0.9428

* Wilson confidence intervals.
** Logistic regression includes terms for baseline KCCQ - clinical summary score (p<0.0001), age (p=0.2403), baseline eGFR (CKD-EPI) (p=0.0051), Treatment (p=0.5747), region (5 cat.) (p=0.0391), baseline diabetes status (3 cat.) (p=0.9187), sex (p=0.7065), baseline LVEF (3 cat.) (p=0.9184), baseline NYHA (2 cat.) (p=0.0026) and Treatment by baseline NYHA (2 cat.) interaction (p=0.6622).
***Wald confidence intervals.

Data taken from study 1245.121 only.
LOCF: For a missing value at week 52 the last available post-baseline value before week 52 is imputed.

Table R.1.2.5.6: 2 Responder analysis (displaying risk ratio) in KCCQ-CSS change from baseline at week 52 of <= -15 points (deterioration) by NYHA (2 cat.) - RS (LOCF-AD) - 1245.121

Subgroup Description	Placebo	Empa 10mg
Baseline NYHA (2 cat.): II		
Number of patients in analysis set	1401	1399
Number of analysed patients, N (%)	1306 (100.0)	1307 (100.0)
Number of patients with endpoint, N (%)	153 (11.7)	140 (10.7)
95% confidence interval*	(10.1, 13.6)	(9.1, 12.5)
Comparison vs Placebo**		
Risk ratio (SE)		0.898 (0.098)
95% confidence interval***		(0.724, 1.113)
p-value		0.3242
Baseline NYHA (2 cat.): III/IV		
Number of patients in analysis set	466	464
Number of analysed patients, N (%)	403 (100.0)	433 (100.0)
Number of patients with endpoint, N (%)	51 (12.7)	52 (12.0)
95% confidence interval*	(9.8, 16.3)	(9.3, 15.4)
Comparison vs Placebo**		
Risk ratio (SE)		0.988 (0.178)
95% confidence interval***		(0.693, 1.407)
p-value		0.9446

* Wilson confidence intervals.
** Log-linked Poisson model with robust estimate of variance includes terms for baseline KCCQ - clinical summary score (p<0.0001), age (p=0.2679), baseline eGFR (CKD-EPI) (p=0.0057), Treatment (p=0.5681), region (5 cat.) (p=0.0514), baseline diabetes status (3 cat.) (p=0.9202), sex (p=0.6991), baseline LVEF (3 cat.) (p=0.9155), baseline NYHA (2 cat.) (p=0.0029) and Treatment by baseline NYHA (2 cat.) interaction (p=0.6522).
***Wald confidence intervals.

Data taken from study 1245.121 only.
LOCF: For a missing value at week 52 the last available post-baseline value before week 52 is imputed.

Table R.1.2.5.6: 3 Responder analysis (displaying odds ratio) in KCCQ-CSS change from baseline at week 52 of > -15 points (stability) by NYHA (2 cat.) - RS (LOCF-AD) - 1245.121

Subgroup Description	Placebo	Empa 10mg
Baseline NYHA (2 cat.): II		
Number of patients in analysis set	1401	1399
Number of analysed patients, N (%)	1306 (100.0)	1307 (100.0)
Number of patients with endpoint, N (%)	1153 (88.3)	1167 (89.3)
95% confidence interval*	(86.4, 89.9)	(87.5, 90.9)
Comparison vs Placebo**		
Odds ratio (SE)		1.132 (0.142)
95% confidence interval***		(0.885, 1.447)
p-value		0.3243
Baseline NYHA (2 cat.): III/IV		
Number of patients in analysis set	466	464
Number of analysed patients, N (%)	403 (100.0)	433 (100.0)
Number of patients with endpoint, N (%)	352 (87.3)	381 (88.0)
95% confidence interval*	(83.7, 90.2)	(84.6, 90.7)
Comparison vs Placebo**		
Odds ratio (SE)		1.015 (0.217)
95% confidence interval***		(0.668, 1.543)
p-value		0.9428

* Wilson confidence intervals.
** Logistic regression includes terms for baseline KCCQ - clinical summary score (p<0.0001), age (p=0.2403), baseline eGFR (CKD-EPI) (p=0.0051), Treatment (p=0.5747), region (5 cat.) (p=0.0391), baseline diabetes status (3 cat.) (p=0.9187), sex (p=0.7065), baseline LVEF (3 cat.) (p=0.9184), baseline NYHA (2 cat.) (p=0.0026) and Treatment by baseline NYHA (2 cat.) interaction (p=0.6622).
***Wald confidence intervals.

Data taken from study 1245.121 only.
LOCF: For a missing value at week 52 the last available post-baseline value before week 52 is imputed.

Table R.1.2.5.6: 4 Responder analysis (displaying risk ratio) in KCCQ-CSS change from baseline at week 52 of > -15 points (stability) by NYHA (2 cat.) - RS (LOCF-AD) - 1245.121

Subgroup Description	Placebo	Empa 10mg
Baseline NYHA (2 cat.): II		
Number of patients in analysis set	1401	1399
Number of analysed patients, N (%)	1306 (100.0)	1307 (100.0)
Number of patients with endpoint, N (%)	1153 (88.3)	1167 (89.3)
95% confidence interval*	(86.4, 89.9)	(87.5, 90.9)
Comparison vs Placebo**		
Risk ratio (SE)		1.014 (0.014)
95% confidence interval***		(0.987, 1.042)
p-value		0.3263
Baseline NYHA (2 cat.): III/IV		
Number of patients in analysis set	466	464
Number of analysed patients, N (%)	403 (100.0)	433 (100.0)
Number of patients with endpoint, N (%)	352 (87.3)	381 (88.0)
95% confidence interval*	(83.7, 90.2)	(84.6, 90.7)
Comparison vs Placebo**		
Risk ratio (SE)		1.002 (0.026)
95% confidence interval***		(0.953, 1.054)
p-value		0.9360

* Wilson confidence intervals.
** Log-linked Poisson model with robust estimate of variance includes terms for baseline KCCQ - clinical summary score (p<0.0001), age (p=0.3270), baseline eGFR (CKD-EPI) (p=0.0059), Treatment (p=0.5901), region (5 cat.) (p=0.0013), baseline diabetes status (3 cat.) (p=0.9189), sex (p=0.7329), baseline LVEF (3 cat.) (p=0.9311), baseline NYHA (2 cat.) (p=0.0063) and Treatment by baseline NYHA (2 cat.) interaction (p=0.6919).
***Wald confidence intervals.

Data taken from study 1245.121 only.
LOCF: For a missing value at week 52 the last available post-baseline value before week 52 is imputed.

Table R.1.2.5.6: 5 Responder analysis (displaying odds ratio) in KCCQ-CSS change from baseline at week 52 of >= 15 points (improvement) by NYHA (2 cat.) - RS (LOCF-AD) - 1245.121

Subgroup Description	Placebo	Empa 10mg
Baseline NYHA (2 cat.): II		
Number of patients in analysis set	1401	1399
Number of analysed patients, N (%)	1306 (100.0)	1307 (100.0)
Number of patients with endpoint, N (%)	243 (18.6)	271 (20.7)
95% confidence interval*	(16.6, 20.8)	(18.6, 23.0)
Comparison vs Placebo**		
Odds ratio (SE)		1.282 (0.143)
95% confidence interval***		(1.029, 1.596)
p-value		0.0265
Baseline NYHA (2 cat.): III/IV		
Number of patients in analysis set	466	464
Number of analysed patients, N (%)	403 (100.0)	433 (100.0)
Number of patients with endpoint, N (%)	114 (28.3)	153 (35.3)
95% confidence interval*	(24.1, 32.9)	(31.0, 39.9)
Comparison vs Placebo**		
Odds ratio (SE)		1.287 (0.223)
95% confidence interval***		(0.916, 1.808)
p-value		0.1453

* Wilson confidence intervals.
** Logistic regression includes terms for baseline KCCQ - clinical summary score (p<0.0001), age (p=0.0736), baseline eGFR (CKD-EPI) (p=0.2311), Treatment (p=0.0152), region (5 cat.) (p<0.0001), baseline diabetes status (3 cat.) (p=0.9812), sex (p=0.4592), baseline LVEF (3 cat.) (p=0.3855), baseline NYHA (2 cat.) (p=0.0177) and Treatment by baseline NYHA (2 cat.) interaction (p=0.9828).
***Wald confidence intervals.

Data taken from study 1245.121 only.
LOCF: For a missing value at week 52 the last available post-baseline value before week 52 is imputed.

Table R.1.2.5.6: 6 Responder analysis (displaying risk ratio) in KCCQ-CSS change from baseline at week 52 of >= 15 points (improvement) by NYHA (2 cat.) - RS (LOCF-AD) - 1245.121

Subgroup Description	Placebo	Empa 10mg
Baseline NYHA (2 cat.): II		
Number of patients in analysis set	1401	1399
Number of analysed patients, N (%)	1306 (100.0)	1307 (100.0)
Number of patients with endpoint, N (%)	243 (18.6)	271 (20.7)
95% confidence interval*	(16.6, 20.8)	(18.6, 23.0)
Comparison vs Placebo**		
Risk ratio (SE)		1.169 (0.083)
95% confidence interval***		(1.017, 1.344)
p-value		0.0283
Baseline NYHA (2 cat.): III/IV		
Number of patients in analysis set	466	464
Number of analysed patients, N (%)	403 (100.0)	433 (100.0)
Number of patients with endpoint, N (%)	114 (28.3)	153 (35.3)
95% confidence interval*	(24.1, 32.9)	(31.0, 39.9)
Comparison vs Placebo**		
Risk ratio (SE)		1.119 (0.114)
95% confidence interval***		(0.916, 1.366)
p-value		0.2717

* Wilson confidence intervals.
** Log-linked Poisson model with robust estimate of variance includes terms for baseline KCCQ - clinical summary score (p<0.0001), age (p=0.1558), baseline eGFR (CKD-EPI) (p=0.2685), Treatment (p=0.0313), region (5 cat.) (p<0.0001), baseline diabetes status (3 cat.) (p=0.9635), sex (p=0.3116), baseline LVEF (3 cat.) (p=0.2889), baseline NYHA (2 cat.) (p=0.0136) and Treatment by baseline NYHA (2 cat.) interaction (p=0.7233).
***Wald confidence intervals.

Data taken from study 1245.121 only.
LOCF: For a missing value at week 52 the last available post-baseline value before week 52 is imputed.

R.1.2.5.7

R.1.2.5.7 Subgroup analysis by diabetes at baseline

Table R.1.2.5.7: 1 Responder analysis (displaying odds ratio) in KCCQ-CSS change from baseline at week 52 of <= -15 points (deterioration) by diabetes at baseline - RS (LOCF-AD) - 1245.121

Subgroup Description	Placebo	Empa 10mg
Diabetes at baseline (2 cat.): Diabetic		
Number of patients in analysis set	929	927
Number of analysed patients, N (%)	850 (100.0)	861 (100.0)
Number of patients with endpoint, N (%)	102 (12.0)	94 (10.9)
95% confidence interval*	(10.0, 14.4)	(9.0, 13.2)
Comparison vs Placebo**		
Odds ratio (SE)		0.893 (0.137)
95% confidence interval***		(0.661, 1.207)
p-value		0.4622
Diabetes at baseline (2 cat.): Non-Diabetic		
Number of patients in analysis set	938	936
Number of analysed patients, N (%)	859 (100.0)	879 (100.0)
Number of patients with endpoint, N (%)	102 (11.9)	98 (11.1)
95% confidence interval*	(9.9, 14.2)	(9.2, 13.4)
Comparison vs Placebo**		
Odds ratio (SE)		0.927 (0.141)
95% confidence interval***		(0.689, 1.249)
p-value		0.6193

* Wilson confidence intervals.
** Logistic regression includes terms for baseline KCCQ - clinical summary score (p<0.0001), age (p=0.2399), baseline eGFR (CKD-EPI) (p=0.0039), Treatment (p=0.3832), region (5 cat.) (p=0.0438), sex (p=0.7328), baseline LVEF (3 cat.) (p=0.9198), diabetes at baseline (2 cat.) (p=0.7475) and Treatment by diabetes at baseline (2 cat.) interaction (p=0.8624).
***Wald confidence intervals.

Data taken from study 1245.121 only.
LOCF: For a missing value at week 52 the last available post-baseline value before week 52 is imputed.

Table R.1.2.5.7: 2 Responder analysis (displaying risk ratio) in KCCQ-CSS change from baseline at week 52 of <= -15 points (deterioration) by diabetes at baseline - RS (LOCF-AD) - 1245.121

Subgroup Description	Placebo	Empa 10mg
Diabetes at baseline (2 cat.): Diabetic		
Number of patients in analysis set	929	927
Number of analysed patients, N (%)	850 (100.0)	861 (100.0)
Number of patients with endpoint, N (%)	102 (12.0)	94 (10.9)
95% confidence interval*	(10.0, 14.4)	(9.0, 13.2)
Comparison vs Placebo**		
Risk ratio (SE)		0.906 (0.121)
95% confidence interval***		(0.698, 1.176)
p-value		0.4582
Diabetes at baseline (2 cat.): Non-Diabetic		
Number of patients in analysis set	938	936
Number of analysed patients, N (%)	859 (100.0)	879 (100.0)
Number of patients with endpoint, N (%)	102 (11.9)	98 (11.1)
95% confidence interval*	(9.9, 14.2)	(9.2, 13.4)
Comparison vs Placebo**		
Risk ratio (SE)		0.936 (0.124)
95% confidence interval***		(0.723, 1.213)
p-value		0.6188

* Wilson confidence intervals.
** Log-linked Poisson model with robust estimate of variance includes terms for baseline KCCQ - clinical summary score (p<0.0001), age (p=0.2655), baseline eGFR (CKD-EPI) (p=0.0043), Treatment (p=0.3802), region (5 cat.) (p=0.0547), sex (p=0.7296), baseline LVEF (3 cat.) (p=0.9190), diabetes at baseline (2 cat.) (p=0.7544) and Treatment by diabetes at baseline (2 cat.) interaction (p=0.8603).
***Wald confidence intervals.

Data taken from study 1245.121 only.
LOCF: For a missing value at week 52 the last available post-baseline value before week 52 is imputed.

Table R.1.2.5.7: 3 Responder analysis (displaying odds ratio) in KCCQ-CSS change from baseline at week 52 of > -15 points (stability) by diabetes at baseline - RS (LOCF-AD) - 1245.121

Subgroup Description	Placebo	Empa 10mg
Diabetes at baseline (2 cat.): Diabetic		
Number of patients in analysis set	929	927
Number of analysed patients, N (%)	850 (100.0)	861 (100.0)
Number of patients with endpoint, N (%)	748 (88.0)	767 (89.1)
95% confidence interval*	(85.6, 90.0)	(86.8, 91.0)
Comparison vs Placebo**		
Odds ratio (SE)		1.119 (0.172)
95% confidence interval***		(0.829, 1.512)
p-value		0.4622
Diabetes at baseline (2 cat.): Non-Diabetic		
Number of patients in analysis set	938	936
Number of analysed patients, N (%)	859 (100.0)	879 (100.0)
Number of patients with endpoint, N (%)	757 (88.1)	781 (88.9)
95% confidence interval*	(85.8, 90.1)	(86.6, 90.8)
Comparison vs Placebo**		
Odds ratio (SE)		1.078 (0.164)
95% confidence interval***		(0.801, 1.452)
p-value		0.6193

* Wilson confidence intervals.
** Logistic regression includes terms for baseline KCCQ - clinical summary score (p<0.0001), age (p=0.2399), baseline eGFR (CKD-EPI) (p=0.0039), Treatment (p=0.3832), region (5 cat.) (p=0.0438), sex (p=0.7328), baseline LVEF (3 cat.) (p=0.9198), diabetes at baseline (2 cat.) (p=0.7475) and Treatment by diabetes at baseline (2 cat.) interaction (p=0.8624).
***Wald confidence intervals.

Data taken from study 1245.121 only.
LOCF: For a missing value at week 52 the last available post-baseline value before week 52 is imputed.

Table R.1.2.5.7: 4 Responder analysis (displaying risk ratio) in KCCQ-CSS change from baseline at week 52 of > -15 points (stability) by diabetes at baseline - RS (LOCF-AD) - 1245.121

Subgroup Description	Placebo	Empa 10mg
Diabetes at baseline (2 cat.): Diabetic		
Number of patients in analysis set	929	927
Number of analysed patients, N (%)	850 (100.0)	861 (100.0)
Number of patients with endpoint, N (%)	748 (88.0)	767 (89.1)
95% confidence interval*	(85.6, 90.0)	(86.8, 91.0)
Comparison vs Placebo**		
Risk ratio (SE)		1.012 (0.017)
95% confidence interval***		(0.978, 1.047)
p-value		0.4920
Diabetes at baseline (2 cat.): Non-Diabetic		
Number of patients in analysis set	938	936
Number of analysed patients, N (%)	859 (100.0)	879 (100.0)
Number of patients with endpoint, N (%)	757 (88.1)	781 (88.9)
95% confidence interval*	(85.8, 90.1)	(86.6, 90.8)
Comparison vs Placebo**		
Risk ratio (SE)		1.009 (0.017)
95% confidence interval***		(0.975, 1.043)
p-value		0.6117

* Wilson confidence intervals.
** Log-linked Poisson model with robust estimate of variance includes terms for baseline KCCQ - clinical summary score (p<0.0001), age (p=0.3198), baseline eGFR (CKD-EPI) (p=0.0047), Treatment (p=0.3982), region (5 cat.) (p=0.0017), sex (p=0.7414), baseline LVEF (3 cat.) (p=0.9336), diabetes at baseline (2 cat.) (p=0.7243) and Treatment by diabetes at baseline (2 cat.) interaction (p=0.8976).
***Wald confidence intervals.

Data taken from study 1245.121 only.
LOCF: For a missing value at week 52 the last available post-baseline value before week 52 is imputed.

Table R.1.2.5.7: 5 Responder analysis (displaying odds ratio) in KCCQ-CSS change from baseline at week 52 of >= 15 points (improvement) by diabetes at baseline - RS (LOCF-AD) - 1245.121

Subgroup Description	Placebo	Empa 10mg
Diabetes at baseline (2 cat.): Diabetic		
Number of patients in analysis set	929	927
Number of analysed patients, N (%)	850 (100.0)	861 (100.0)
Number of patients with endpoint, N (%)	184 (21.6)	224 (26.0)
95% confidence interval*	(19.0, 24.5)	(23.2, 29.0)
Comparison vs Placebo**		
Odds ratio (SE)		1.334 (0.176)
95% confidence interval***		(1.030, 1.728)
p-value		0.0292
Diabetes at baseline (2 cat.): Non-Diabetic		
Number of patients in analysis set	938	936
Number of analysed patients, N (%)	859 (100.0)	879 (100.0)
Number of patients with endpoint, N (%)	173 (20.1)	200 (22.8)
95% confidence interval*	(17.6, 23.0)	(20.1, 25.6)
Comparison vs Placebo**		
Odds ratio (SE)		1.217 (0.162)
95% confidence interval***		(0.938, 1.580)
p-value		0.1393

* Wilson confidence intervals.
** Logistic regression includes terms for baseline KCCQ - clinical summary score (p<0.0001), age (p=0.0738), baseline eGFR (CKD-EPI) (p=0.2024), Treatment (p=0.0098), region (5 cat.) (p<0.0001), sex (p=0.4663), baseline LVEF (3 cat.) (p=0.4009), diabetes at baseline (2 cat.) (p=0.8138) and Treatment by diabetes at baseline (2 cat.) interaction (p=0.6264).
***Wald confidence intervals.

Data taken from study 1245.121 only.
LOCF: For a missing value at week 52 the last available post-baseline value before week 52 is imputed.

Table R.1.2.5.7: 6 Responder analysis (displaying risk ratio) in KCCQ-CSS change from baseline at week 52 of >= 15 points (improvement) by diabetes at baseline - RS (LOCF-AD) - 1245.121

Subgroup Description	Placebo	Empa 10mg
Diabetes at baseline (2 cat.): Diabetic		
Number of patients in analysis set	929	927
Number of analysed patients, N (%)	850 (100.0)	861 (100.0)
Number of patients with endpoint, N (%)	184 (21.6)	224 (26.0)
95% confidence interval*	(19.0, 24.5)	(23.2, 29.0)
Comparison vs Placebo**		
Risk ratio (SE)		1.164 (0.096)
95% confidence interval***		(0.991, 1.367)
p-value		0.0643
Diabetes at baseline (2 cat.): Non-Diabetic		
Number of patients in analysis set	938	936
Number of analysed patients, N (%)	859 (100.0)	879 (100.0)
Number of patients with endpoint, N (%)	173 (20.1)	200 (22.8)
95% confidence interval*	(17.6, 23.0)	(20.1, 25.6)
Comparison vs Placebo**		
Risk ratio (SE)		1.122 (0.093)
95% confidence interval***		(0.953, 1.321)
p-value		0.1657

* Wilson confidence intervals.
** Log-linked Poisson model with robust estimate of variance includes terms for baseline KCCQ - clinical summary score (p<0.0001), age (p=0.1344), baseline eGFR (CKD-EPI) (p=0.2493), Treatment (p=0.0226), region (5 cat.) (p<0.0001), sex (p=0.3133), baseline LVEF (3 cat.) (p=0.2903), diabetes at baseline (2 cat.) (p=0.6393) and Treatment by diabetes at baseline (2 cat.) interaction (p=0.7533).
***Wald confidence intervals.

Data taken from study 1245.121 only.
LOCF: For a missing value at week 52 the last available post-baseline value before week 52 is imputed.

R.1.2.5.8 Subgroup analysis by BMI at baseline (<30, >=30)

Table R.1.2.5.8: 1 Responder analysis (displaying odds ratio) in KCCQ-CSS change from baseline at week 52 of <= -15 points (deterioration) by baseline BMI [kg/m2] - RS (LOCF-AD) - 1245.121

Subgroup Description	Placebo	Empa 10mg
Baseline BMI [kg/m²] (2 cat.): <30		
Number of patients in analysis set	1300	1263
Number of analysed patients, N (%)	1197 (100.0)	1181 (100.0)
Number of patients with endpoint, N (%)	137 (11.4)	124 (10.5)
95% confidence interval*	(9.8, 13.4)	(8.9, 12.4)
Comparison vs Placebo**		
Odds ratio (SE)		0.897 (0.119)
95% confidence interval***		(0.692, 1.163)
p-value		0.4110
Baseline BMI [kg/m²] (2 cat.): >=30		
Number of patients in analysis set	567	600
Number of analysed patients, N (%)	512 (100.0)	559 (100.0)
Number of patients with endpoint, N (%)	67 (13.1)	68 (12.2)
95% confidence interval*	(10.4, 16.3)	(9.7, 15.1)
Comparison vs Placebo**		
Odds ratio (SE)		0.923 (0.172)
95% confidence interval***		(0.641, 1.329)
p-value		0.6666

* Wilson confidence intervals.
** Logistic regression includes terms for baseline KCCQ - clinical summary score (p<0.0001), age (p=0.1338), baseline eGFR (CKD-EPI) (p=0.0045), Treatment (p=0.4079), region (5 cat.) (p=0.0935), baseline diabetes status (3 cat.) (p=0.9163), sex (p=0.7739), baseline LVEF (3 cat.) (p=0.9291), baseline BMI (2 cat.) (p=0.0466) and Treatment by baseline BMI (2 cat.) interaction (p=0.8998).
***Wald confidence intervals.

Data taken from study 1245.121 only.
LOCF: For a missing value at week 52 the last available post-baseline value before week 52 is imputed.

Table R.1.2.5.8: 2 Responder analysis (displaying risk ratio) in KCCQ-CSS change from baseline at week 52 of <= -15 points (deterioration) by baseline BMI [kg/m2] - RS (LOCF-AD) - 1245.121

Subgroup Description	Placebo	Empa 10mg
Baseline BMI [kg/m²] (2 cat.): <30		
Number of patients in analysis set	1300	1263
Number of analysed patients, N (%)	1197 (100.0)	1181 (100.0)
Number of patients with endpoint, N (%)	137 (11.4)	124 (10.5)
95% confidence interval*	(9.8, 13.4)	(8.9, 12.4)
Comparison vs Placebo**		
Risk ratio (SE)		0.909 (0.105)
95% confidence interval***		(0.724, 1.141)
p-value		0.4090
Baseline BMI [kg/m²] (2 cat.): >=30		
Number of patients in analysis set	567	600
Number of analysed patients, N (%)	512 (100.0)	559 (100.0)
Number of patients with endpoint, N (%)	67 (13.1)	68 (12.2)
95% confidence interval*	(10.4, 16.3)	(9.7, 15.1)
Comparison vs Placebo**		
Risk ratio (SE)		0.934 (0.148)
95% confidence interval***		(0.685, 1.274)
p-value		0.6666

* Wilson confidence intervals.
** Log-linked Poisson model with robust estimate of variance includes terms for baseline KCCQ - clinical summary score (p<0.0001), age (p=0.1589), baseline eGFR (CKD-EPI) (p=0.0050), Treatment (p=0.4031), region (5 cat.) (p=0.1089), baseline diabetes status (3 cat.) (p=0.9183), sex (p=0.7705), baseline LVEF (3 cat.) (p=0.9289), baseline BMI (2 cat.) (p=0.0469) and Treatment by baseline BMI (2 cat.) interaction (p=0.8876).
***Wald confidence intervals.

Data taken from study 1245.121 only.
LOCF: For a missing value at week 52 the last available post-baseline value before week 52 is imputed.

Table R.1.2.5.8: 3 Responder analysis (displaying odds ratio) in KCCQ-CSS change from baseline at week 52 of > -15 points (stability) by baseline BMI [kg/m2] - RS (LOCF-AD) - 1245.121

Subgroup Description	Placebo	Empa 10mg
Baseline BMI [kg/m²] (2 cat.): <30		
Number of patients in analysis set	1300	1263
Number of analysed patients, N (%)	1197 (100.0)	1181 (100.0)
Number of patients with endpoint, N (%)	1060 (88.6)	1057 (89.5)
95% confidence interval*	(86.6, 90.2)	(87.6, 91.1)
Comparison vs Placebo**		
Odds ratio (SE)		1.115 (0.148)
95% confidence interval***		(0.860, 1.446)
p-value		0.4110
Baseline BMI [kg/m²] (2 cat.): >=30		
Number of patients in analysis set	567	600
Number of analysed patients, N (%)	512 (100.0)	559 (100.0)
Number of patients with endpoint, N (%)	445 (86.9)	491 (87.8)
95% confidence interval*	(83.7, 89.6)	(84.9, 90.3)
Comparison vs Placebo**		
Odds ratio (SE)		1.084 (0.202)
95% confidence interval***		(0.752, 1.561)
p-value		0.6666

* Wilson confidence intervals.
** Logistic regression includes terms for baseline KCCQ - clinical summary score (p<0.0001), age (p=0.1338), baseline eGFR (CKD-EPI) (p=0.0045), Treatment (p=0.4079), region (5 cat.) (p=0.0935), baseline diabetes status (3 cat.) (p=0.9163), sex (p=0.7739), baseline LVEF (3 cat.) (p=0.9291), baseline BMI (2 cat.) (p=0.0466) and Treatment by baseline BMI (2 cat.) interaction (p=0.8998).
***Wald confidence intervals.

Data taken from study 1245.121 only.
LOCF: For a missing value at week 52 the last available post-baseline value before week 52 is imputed.

Table R.1.2.5.8: 4 Responder analysis (displaying risk ratio) in KCCQ-CSS change from baseline at week 52 of > -15 points (stability) by baseline BMI [kg/m2] - RS (LOCF-AD) - 1245.121

Subgroup Description	Placebo	Empa 10mg
Baseline BMI [kg/m²] (2 cat.): <30		
Number of patients in analysis set	1300	1263
Number of analysed patients, N (%)	1197 (100.0)	1181 (100.0)
Number of patients with endpoint, N (%)	1060 (88.6)	1057 (89.5)
95% confidence interval*	(86.6, 90.2)	(87.6, 91.1)
Comparison vs Placebo**		
Risk ratio (SE)		1.011 (0.014)
95% confidence interval***		(0.983, 1.040)
p-value		0.4404
Baseline BMI [kg/m²] (2 cat.): >=30		
Number of patients in analysis set	567	600
Number of analysed patients, N (%)	512 (100.0)	559 (100.0)
Number of patients with endpoint, N (%)	445 (86.9)	491 (87.8)
95% confidence interval*	(83.7, 89.6)	(84.9, 90.3)
Comparison vs Placebo**		
Risk ratio (SE)		1.011 (0.023)
95% confidence interval***		(0.966, 1.057)
p-value		0.6413

* Wilson confidence intervals.
** Log-linked Poisson model with robust estimate of variance includes terms for baseline KCCQ - clinical summary score (p<0.0001), age (p=0.2009), baseline eGFR (CKD-EPI) (p=0.0053), Treatment (p=0.4216), region (5 cat.) (p=0.0082), baseline diabetes status (3 cat.) (p=0.9147), sex (p=0.7907), baseline LVEF (3 cat.) (p=0.9373), baseline BMI (2 cat.) (p=0.0663) and Treatment by baseline BMI (2 cat.) interaction (p=0.9896).
***Wald confidence intervals.

Data taken from study 1245.121 only.
LOCF: For a missing value at week 52 the last available post-baseline value before week 52 is imputed.

Table R.1.2.5.8: 5 Responder analysis (displaying odds ratio) in KCCQ-CSS change from baseline at week 52 of >= 15 points (improvement) by baseline BMI [kg/m2] - RS (LOCF-AD) - 1245.121

Subgroup Description	Placebo	Empa 10mg
Baseline BMI [kg/m²] (2 cat.): <30		
Number of patients in analysis set	1300	1263
Number of analysed patients, N (%)	1197 (100.0)	1181 (100.0)
Number of patients with endpoint, N (%)	240 (20.1)	272 (23.0)
95% confidence interval*	(17.9, 22.4)	(20.7, 25.5)
Comparison vs Placebo**		
Odds ratio (SE)		1.293 (0.149)
95% confidence interval***		(1.032, 1.620)
p-value		0.0255
Baseline BMI [kg/m²] (2 cat.): >=30		
Number of patients in analysis set	567	600
Number of analysed patients, N (%)	512 (100.0)	559 (100.0)
Number of patients with endpoint, N (%)	117 (22.9)	152 (27.2)
95% confidence interval*	(19.4, 26.7)	(23.7, 31.0)
Comparison vs Placebo**		
Odds ratio (SE)		1.248 (0.203)
95% confidence interval***		(0.907, 1.718)
p-value		0.1729

* Wilson confidence intervals.
** Logistic regression includes terms for baseline KCCQ - clinical summary score (p<0.0001), age (p=0.0623), baseline eGFR (CKD-EPI) (p=0.2056), Treatment (p=0.0163), region (5 cat.) (p<0.0001), baseline diabetes status (3 cat.) (p=0.9660), sex (p=0.4485), baseline LVEF (3 cat.) (p=0.4045), baseline BMI (2 cat.) (p=0.5540) and Treatment by baseline BMI (2 cat.) interaction (p=0.8605).
***Wald confidence intervals.

Data taken from study 1245.121 only.
LOCF: For a missing value at week 52 the last available post-baseline value before week 52 is imputed.

Table R.1.2.5.8: 6 Responder analysis (displaying risk ratio) in KCCQ-CSS change from baseline at week 52 of >= 15 points (improvement) by baseline BMI [kg/m2] - RS (LOCF-AD) - 1245.121

Subgroup Description	Placebo	Empa 10mg
Baseline BMI [kg/m²] (2 cat.): <30		
Number of patients in analysis set	1300	1263
Number of analysed patients, N (%)	1197 (100.0)	1181 (100.0)
Number of patients with endpoint, N (%)	240 (20.1)	272 (23.0)
95% confidence interval*	(17.9, 22.4)	(20.7, 25.5)
Comparison vs Placebo**		
Risk ratio (SE)		1.149 (0.082)
95% confidence interval***		(1.000, 1.320)
p-value		0.0507
Baseline BMI [kg/m²] (2 cat.): >=30		
Number of patients in analysis set	567	600
Number of analysed patients, N (%)	512 (100.0)	559 (100.0)
Number of patients with endpoint, N (%)	117 (22.9)	152 (27.2)
95% confidence interval*	(19.4, 26.7)	(23.7, 31.0)
Comparison vs Placebo**		
Risk ratio (SE)		1.139 (0.117)
95% confidence interval***		(0.931, 1.393)
p-value		0.2057

* Wilson confidence intervals.
** Log-linked Poisson model with robust estimate of variance includes terms for baseline KCCQ - clinical summary score (p<0.0001), age (p=0.1181), baseline eGFR (CKD-EPI) (p=0.2557), Treatment (p=0.0319), region (5 cat.) (p<0.0001), baseline diabetes status (3 cat.) (p=0.9273), sex (p=0.3021), baseline LVEF (3 cat.) (p=0.2918), baseline BMI (2 cat.) (p=0.6129) and Treatment by baseline BMI (2 cat.) interaction (p=0.9448).
***Wald confidence intervals.

Data taken from study 1245.121 only.
LOCF: For a missing value at week 52 the last available post-baseline value before week 52 is imputed.

R.1.2.5.9 Subgroup analysis by eGFR at baseline (<60, >=60)

Table R.1.2.5.9: 1 Responder analysis (displaying odds ratio) in KCCQ-CSS change from baseline at week 52 of <= -15 points (deterioration) by baseline eGFR (2 cat.) - RS (LOCF-AD) - 1245.121

Subgroup Description	Placebo	Empa 10mg
Baseline eGFR (CKD-EPI) [mL/min/1.73m²] (2 cat.): >=60		
Number of patients in analysis set	960	969
Number of analysed patients, N (%)	875 (100.0)	903 (100.0)
Number of patients with endpoint, N (%)	96 (11.0)	84 (9.3)
95% confidence interval*	(9.1, 13.2)	(7.6, 11.4)
Comparison vs Placebo**		
Odds ratio (SE)		0.813 (0.129)
95% confidence interval***		(0.595, 1.110)
p-value		0.1932
Baseline eGFR (CKD-EPI) [mL/min/1.73m²] (2 cat.): <60		
Number of patients in analysis set	906	893
Number of analysed patients, N (%)	834 (100.0)	837 (100.0)
Number of patients with endpoint, N (%)	108 (12.9)	108 (12.9)
95% confidence interval*	(10.8, 15.4)	(10.8, 15.3)
Comparison vs Placebo**		
Odds ratio (SE)		1.002 (0.147)
95% confidence interval***		(0.751, 1.337)
p-value		0.9884

* Wilson confidence intervals.
** Logistic regression includes terms for baseline KCCQ - clinical summary score (p<0.0001), age (p=0.0270), Treatment (p=0.3442), region (5 cat.) (p=0.0374), baseline diabetes status (3 cat.) (p=0.8633), sex (p=0.6841), baseline LVEF (3 cat.) (p=0.9478), baseline eGFR (CKD-EPI) (2 cat.) (p=0.1414) and Treatment by baseline eGFR (CKD-EPI) (2 cat.) interaction (p=0.3345).
***Wald confidence intervals.
2 patients were excluded as the subgroup variable was missing.

Data taken from study 1245.121 only.
LOCF: For a missing value at week 52 the last available post-baseline value before week 52 is imputed.

Table R.1.2.5.9: 2 Responder analysis (displaying risk ratio) in KCCQ-CSS change from baseline at week 52 of <= -15 points (deterioration) by baseline eGFR (2 cat.) - RS (LOCF-AD) - 1245.121

Subgroup Description	Placebo	Empa 10mg
Baseline eGFR (CKD-EPI) [mL/min/1.73m²] (2 cat.): >=60		
Number of patients in analysis set	960	969
Number of analysed patients, N (%)	875 (100.0)	903 (100.0)
Number of patients with endpoint, N (%)	96 (11.0)	84 (9.3)
95% confidence interval*	(9.1, 13.2)	(7.6, 11.4)
Comparison vs Placebo**		
Risk ratio (SE)		0.832 (0.117)
95% confidence interval***		(0.631, 1.097)
p-value		0.1924
Baseline eGFR (CKD-EPI) [mL/min/1.73m²] (2 cat.): <60		
Number of patients in analysis set	906	893
Number of analysed patients, N (%)	834 (100.0)	837 (100.0)
Number of patients with endpoint, N (%)	108 (12.9)	108 (12.9)
95% confidence interval*	(10.8, 15.4)	(10.8, 15.3)
Comparison vs Placebo**		
Risk ratio (SE)		1.002 (0.126)
95% confidence interval***		(0.783, 1.282)
p-value		0.9883

* Wilson confidence intervals.
** Log-linked Poisson model with robust estimate of variance includes terms for baseline KCCQ - clinical summary score (p<0.0001), age (p=0.0369), Treatment (p=0.3346), region (5 cat.) (p=0.0481), baseline diabetes status (3 cat.) (p=0.8659), sex (p=0.6802), baseline LVEF (3 cat.) (p=0.9480), baseline eGFR (CKD-EPI) (2 cat.) (p=0.1422) and Treatment by baseline eGFR (CKD-EPI) (2 cat.) interaction (p=0.3267).
***Wald confidence intervals.
2 patients were excluded as the subgroup variable was missing.

Data taken from study 1245.121 only.
LOCF: For a missing value at week 52 the last available post-baseline value before week 52 is imputed.

Table R.1.2.5.9: 3 Responder analysis (displaying odds ratio) in KCCQ-CSS change from baseline at week 52 of > -15 points (stability) by baseline eGFR (2 cat.) - RS (LOCF-AD) - 1245.121

Subgroup Description	Placebo	Empa 10mg
Baseline eGFR (CKD-EPI) [mL/min/1.73m²] (2 cat.): >=60		
Number of patients in analysis set	960	969
Number of analysed patients, N (%)	875 (100.0)	903 (100.0)
Number of patients with endpoint, N (%)	779 (89.0)	819 (90.7)
95% confidence interval*	(86.8, 90.9)	(88.6, 92.4)
Comparison vs Placebo**		
Odds ratio (SE)		1.230 (0.195)
95% confidence interval***		(0.901, 1.679)
p-value		0.1932
Baseline eGFR (CKD-EPI) [mL/min/1.73m²] (2 cat.): <60		
Number of patients in analysis set	906	893
Number of analysed patients, N (%)	834 (100.0)	837 (100.0)
Number of patients with endpoint, N (%)	726 (87.1)	729 (87.1)
95% confidence interval*	(84.6, 89.2)	(84.7, 89.2)
Comparison vs Placebo**		
Odds ratio (SE)		0.998 (0.147)
95% confidence interval***		(0.748, 1.331)
p-value		0.9884

* Wilson confidence intervals.
** Logistic regression includes terms for baseline KCCQ - clinical summary score (p<0.0001), age (p=0.0270), Treatment (p=0.3442), region (5 cat.) (p=0.0374), baseline diabetes status (3 cat.) (p=0.8633), sex (p=0.6841), baseline LVEF (3 cat.) (p=0.9478), baseline eGFR (CKD-EPI) (2 cat.) (p=0.1414) and Treatment by baseline eGFR (CKD-EPI) (2 cat.) interaction (p=0.3345).
***Wald confidence intervals.
2 patients were excluded as the subgroup variable was missing.

Data taken from study 1245.121 only.
LOCF: For a missing value at week 52 the last available post-baseline value before week 52 is imputed.

Table R.1.2.5.9: 4 Responder analysis (displaying risk ratio) in KCCQ-CSS change from baseline at week 52 of > -15 points (stability) by baseline eGFR (2 cat.) - RS (LOCF-AD) - 1245.121

Subgroup Description	Placebo	Empa 10mg
Baseline eGFR (CKD-EPI) [mL/min/1.73m²] (2 cat.): >=60		
Number of patients in analysis set	960	969
Number of analysed patients, N (%)	875 (100.0)	903 (100.0)
Number of patients with endpoint, N (%)	779 (89.0)	819 (90.7)
95% confidence interval*	(86.8, 90.9)	(88.6, 92.4)
Comparison vs Placebo**		
Risk ratio (SE)		1.020 (0.016)
95% confidence interval***		(0.989, 1.052)
p-value		0.2137
Baseline eGFR (CKD-EPI) [mL/min/1.73m²] (2 cat.): <60		
Number of patients in analysis set	906	893
Number of analysed patients, N (%)	834 (100.0)	837 (100.0)
Number of patients with endpoint, N (%)	726 (87.1)	729 (87.1)
95% confidence interval*	(84.6, 89.2)	(84.7, 89.2)
Comparison vs Placebo**		
Risk ratio (SE)		1.000 (0.019)
95% confidence interval***		(0.964, 1.037)
p-value		0.9981

* Wilson confidence intervals.
** Log-linked Poisson model with robust estimate of variance includes terms for baseline KCCQ - clinical summary score (p<0.0001), age (p=0.0391), Treatment (p=0.4195), region (5 cat.) (p=0.0013), baseline diabetes status (3 cat.) (p=0.8658), sex (p=0.7154), baseline LVEF (3 cat.) (p=0.9499), baseline eGFR (CKD-EPI) (2 cat.) (p=0.1448) and Treatment by baseline eGFR (CKD-EPI) (2 cat.) interaction (p=0.4223).
***Wald confidence intervals.
2 patients were excluded as the subgroup variable was missing.

Data taken from study 1245.121 only.
LOCF: For a missing value at week 52 the last available post-baseline value before week 52 is imputed.

Table R.1.2.5.9: 5 Responder analysis (displaying odds ratio) in KCCQ-CSS change from baseline at week 52 of >= 15 points (improvement) by baseline eGFR (2 cat.) - RS (LOCF-AD) - 1245.121

Subgroup Description	Placebo	Empa 10mg
Baseline eGFR (CKD-EPI) [mL/min/1.73m²] (2 cat.): >=60		
Number of patients in analysis set	960	969
Number of analysed patients, N (%)	875 (100.0)	903 (100.0)
Number of patients with endpoint, N (%)	185 (21.1)	233 (25.8)
95% confidence interval*	(18.6, 24.0)	(23.1, 28.8)
Comparison vs Placebo**		
Odds ratio (SE)		1.372 (0.178)
95% confidence interval***		(1.064, 1.769)
p-value		0.0147
Baseline eGFR (CKD-EPI) [mL/min/1.73m²] (2 cat.): <60		
Number of patients in analysis set	906	893
Number of analysed patients, N (%)	834 (100.0)	837 (100.0)
Number of patients with endpoint, N (%)	172 (20.6)	191 (22.8)
95% confidence interval*	(18.0, 23.5)	(20.1, 25.8)
Comparison vs Placebo**		
Odds ratio (SE)		1.175 (0.160)
95% confidence interval***		(0.900, 1.533)
p-value		0.2366

* Wilson confidence intervals.
** Logistic regression includes terms for baseline KCCQ - clinical summary score (p<0.0001), age (p=0.0116), Treatment (p=0.0111), region (5 cat.) (p<0.0001), baseline diabetes status (3 cat.) (p=0.9436), sex (p=0.5027), baseline LVEF (3 cat.) (p=0.3907), baseline eGFR (CKD-EPI) (2 cat.) (p=0.8359) and Treatment by baseline eGFR (CKD-EPI) (2 cat.) interaction (p=0.4077).
***Wald confidence intervals.
2 patients were excluded as the subgroup variable was missing.

Data taken from study 1245.121 only.
LOCF: For a missing value at week 52 the last available post-baseline value before week 52 is imputed.

Table R.1.2.5.9: 6 Responder analysis (displaying risk ratio) in KCCQ-CSS change from baseline at week 52 of >= 15 points (improvement) by baseline eGFR (2 cat.) - RS (LOCF-AD) - 1245.121

Subgroup Description	Placebo	Empa 10mg
Baseline eGFR (CKD-EPI) [mL/min/1.73m²] (2 cat.): >=60		
Number of patients in analysis set	960	969
Number of analysed patients, N (%)	875 (100.0)	903 (100.0)
Number of patients with endpoint, N (%)	185 (21.1)	233 (25.8)
95% confidence interval*	(18.6, 24.0)	(23.1, 28.8)
Comparison vs Placebo**		
Risk ratio (SE)		1.185 (0.097)
95% confidence interval***		(1.010, 1.391)
p-value		0.0375
Baseline eGFR (CKD-EPI) [mL/min/1.73m²] (2 cat.): <60		
Number of patients in analysis set	906	893
Number of analysed patients, N (%)	834 (100.0)	837 (100.0)
Number of patients with endpoint, N (%)	172 (20.6)	191 (22.8)
95% confidence interval*	(18.0, 23.5)	(20.1, 25.8)
Comparison vs Placebo**		
Risk ratio (SE)		1.100 (0.092)
95% confidence interval***		(0.934, 1.295)
p-value		0.2544

* Wilson confidence intervals.
** Log-linked Poisson model with robust estimate of variance includes terms for baseline KCCQ - clinical summary score (p<0.0001), age (p=0.0314), Treatment (p=0.0234), region (5 cat.) (p<0.0001), baseline diabetes status (3 cat.) (p=0.8812), sex (p=0.3327), baseline LVEF (3 cat.) (p=0.2931), baseline eGFR (CKD-EPI) (2 cat.) (p=0.7590) and Treatment by baseline eGFR (CKD-EPI) (2 cat.) interaction (p=0.5205).
***Wald confidence intervals.
2 patients were excluded as the subgroup variable was missing.

Data taken from study 1245.121 only.
LOCF: For a missing value at week 52 the last available post-baseline value before week 52 is imputed.

R.1.2.5.10

Table R.1.2.5.10: 1 Responder analysis (displaying odds ratio) in KCCQ-CSS change from baseline at week 52 of <= -15 points (deterioration) by history of HHF - RS (LOCF-AD) - 1245.121

Subgroup Description	Placebo	Empa 10mg
History of HHF (in the last 12 months): No		
Number of patients in analysis set	1293	1286
Number of analysed patients, N (%)	1194 (100.0)	1212 (100.0)
Number of patients with endpoint, N (%)	142 (11.9)	137 (11.3)
95% confidence interval*	(10.2, 13.9)	(9.6, 13.2)
Comparison vs Placebo**		
Odds ratio (SE)		0.959 (0.123)
95% confidence interval***		(0.745, 1.234)
p-value		0.7459
History of HHF (in the last 12 months): Yes		
Number of patients in analysis set	574	577
Number of analysed patients, N (%)	515 (100.0)	528 (100.0)
Number of patients with endpoint, N (%)	62 (12.0)	55 (10.4)
95% confidence interval*	(9.5, 15.1)	(8.1, 13.3)
Comparison vs Placebo**		
Odds ratio (SE)		0.804 (0.160)
95% confidence interval***		(0.545, 1.187)
p-value		0.2730

* Wilson confidence intervals.
** Logistic regression includes terms for baseline KCCQ - clinical summary score (p<0.0001), age (p=0.2199), baseline eGFR (CKD-EPI) (p=0.0038), Treatment (p=0.2728), region (5 cat.) (p=0.0447), baseline diabetes status (3 cat.) (p=0.8728), sex (p=0.7283), baseline LVEF (3 cat.) (p=0.9146), history of HHF (in the last 12 months) (p=0.9704) and Treatment by history of HHF (in the last 12 months) interaction (p=0.4571).
***Wald confidence intervals.

Data taken from study 1245.121 only.
LOCF: For a missing value at week 52 the last available post-baseline value before week 52 is imputed.

Table R.1.2.5.10: 2 Responder analysis (displaying risk ratio) in KCCQ-CSS change from baseline at week 52 of <= -15 points (deterioration) by history of HHF - RS (LOCF-AD) - 1245.121

Subgroup Description	Placebo	Empa 10mg
History of HHF (in the last 12 months): No		
Number of patients in analysis set	1293	1286
Number of analysed patients, N (%)	1194 (100.0)	1212 (100.0)
Number of patients with endpoint, N (%)	142 (11.9)	137 (11.3)
95% confidence interval*	(10.2, 13.9)	(9.6, 13.2)
Comparison vs Placebo**		
Risk ratio (SE)		0.965 (0.108)
95% confidence interval***		(0.775, 1.201)
p-value		0.7466
History of HHF (in the last 12 months): Yes		
Number of patients in analysis set	574	577
Number of analysed patients, N (%)	515 (100.0)	528 (100.0)
Number of patients with endpoint, N (%)	62 (12.0)	55 (10.4)
95% confidence interval*	(9.5, 15.1)	(8.1, 13.3)
Comparison vs Placebo**		
Risk ratio (SE)		0.826 (0.143)
95% confidence interval***		(0.588, 1.159)
p-value		0.2687

* Wilson confidence intervals.
** Log-linked Poisson model with robust estimate of variance includes terms for baseline KCCQ - clinical summary score (p<0.0001), age (p=0.2445), baseline eGFR (CKD-EPI) (p=0.0041), Treatment (p=0.2681), region (5 cat.) (p=0.0567), baseline diabetes status (3 cat.) (p=0.8760), sex (p=0.7241), baseline LVEF (3 cat.) (p=0.9156), history of HHF (in the last 12 months) (p=0.9707) and Treatment by history of HHF (in the last 12 months) interaction (p=0.4524).
***Wald confidence intervals.

Data taken from study 1245.121 only.
LOCF: For a missing value at week 52 the last available post-baseline value before week 52 is imputed.

Table R.1.2.5.10: 3 Responder analysis (displaying odds ratio) in KCCQ-CSS change from baseline at week 52 of > -15 points (stability) by history of HHF - RS (LOCF-AD) - 1245.121

Subgroup Description	Placebo	Empa 10mg
History of HHF (in the last 12 months): No		
Number of patients in analysis set	1293	1286
Number of analysed patients, N (%)	1194 (100.0)	1212 (100.0)
Number of patients with endpoint, N (%)	1052 (88.1)	1075 (88.7)
95% confidence interval*	(86.1, 89.8)	(86.8, 90.4)
Comparison vs Placebo**		
Odds ratio (SE)		1.043 (0.134)
95% confidence interval***		(0.810, 1.341)
p-value		0.7459
History of HHF (in the last 12 months): Yes		
Number of patients in analysis set	574	577
Number of analysed patients, N (%)	515 (100.0)	528 (100.0)
Number of patients with endpoint, N (%)	453 (88.0)	473 (89.6)
95% confidence interval*	(84.9, 90.5)	(86.7, 91.9)
Comparison vs Placebo**		
Odds ratio (SE)		1.243 (0.247)
95% confidence interval***		(0.842, 1.835)
p-value		0.2730

* Wilson confidence intervals.
** Logistic regression includes terms for baseline KCCQ - clinical summary score (p<0.0001), age (p=0.2199), baseline eGFR (CKD-EPI) (p=0.0038), Treatment (p=0.2728), region (5 cat.) (p=0.0447), baseline diabetes status (3 cat.) (p=0.8728), sex (p=0.7283), baseline LVEF (3 cat.) (p=0.9146), history of HHF (in the last 12 months) (p=0.9704) and Treatment by history of HHF (in the last 12 months) interaction (p=0.4571).
***Wald confidence intervals.

Data taken from study 1245.121 only.
LOCF: For a missing value at week 52 the last available post-baseline value before week 52 is imputed.

Table R.1.2.5.10: 4 Responder analysis (displaying risk ratio) in KCCQ-CSS change from baseline at week 52 of > -15 points (stability) by history of HHF - RS (LOCF-AD) - 1245.121

Subgroup Description	Placebo	Empa 10mg
History of HHF (in the last 12 months): No		
Number of patients in analysis set	1293	1286
Number of analysed patients, N (%)	1194 (100.0)	1212 (100.0)
Number of patients with endpoint, N (%)	1052 (88.1)	1075 (88.7)
95% confidence interval*	(86.1, 89.8)	(86.8, 90.4)
Comparison vs Placebo**		
Risk ratio (SE)		1.005 (0.015)
95% confidence interval***		(0.976, 1.034)
p-value		0.7553
History of HHF (in the last 12 months): Yes		
Number of patients in analysis set	574	577
Number of analysed patients, N (%)	515 (100.0)	528 (100.0)
Number of patients with endpoint, N (%)	453 (88.0)	473 (89.6)
95% confidence interval*	(84.9, 90.5)	(86.7, 91.9)
Comparison vs Placebo**		
Risk ratio (SE)		1.024 (0.022)
95% confidence interval***		(0.981, 1.068)
p-value		0.2866

* Wilson confidence intervals.
** Log-linked Poisson model with robust estimate of variance includes terms for baseline KCCQ - clinical summary score (p<0.0001), age (p=0.3024), baseline eGFR (CKD-EPI) (p=0.0045), Treatment (p=0.2887), region (5 cat.) (p=0.0018), baseline diabetes status (3 cat.) (p=0.8637), sex (p=0.7408), baseline LVEF (3 cat.) (p=0.9338), history of HHF (in the last 12 months) (p=0.9936) and Treatment by history of HHF (in the last 12 months) interaction (p=0.4778).
***Wald confidence intervals.

Data taken from study 1245.121 only.
LOCF: For a missing value at week 52 the last available post-baseline value before week 52 is imputed.

Table R.1.2.5.10: 5 Responder analysis (displaying odds ratio) in KCCQ-CSS change from baseline at week 52 of >= 15 points (improvement) by history of HHF - RS (LOCF-AD) - 1245.121

Subgroup Description	Placebo	Empa 10mg
History of HHF (in the last 12 months): No		
Number of patients in analysis set	1293	1286
Number of analysed patients, N (%)	1194 (100.0)	1212 (100.0)
Number of patients with endpoint, N (%)	251 (21.0)	304 (25.1)
95% confidence interval*	(18.8, 23.4)	(22.7, 27.6)
Comparison vs Placebo**		
Odds ratio (SE)		1.311 (0.147)
95% confidence interval***		(1.053, 1.633)
p-value		0.0154
History of HHF (in the last 12 months): Yes		
Number of patients in analysis set	574	577
Number of analysed patients, N (%)	515 (100.0)	528 (100.0)
Number of patients with endpoint, N (%)	106 (20.6)	120 (22.7)
95% confidence interval*	(17.3, 24.3)	(19.4, 26.5)
Comparison vs Placebo**		
Odds ratio (SE)		1.191 (0.205)
95% confidence interval***		(0.849, 1.670)
p-value		0.3113

* Wilson confidence intervals.
** Logistic regression includes terms for baseline KCCQ - clinical summary score (p<0.0001), age (p=0.0716), baseline eGFR (CKD-EPI) (p=0.2030), Treatment (p=0.0301), region (5 cat.) (p<0.0001), baseline diabetes status (3 cat.) (p=0.9579), sex (p=0.4642), baseline LVEF (3 cat.) (p=0.4271), history of HHF (in the last 12 months) (p=0.7338) and Treatment by history of HHF (in the last 12 months) interaction (p=0.6393).
***Wald confidence intervals.

Data taken from study 1245.121 only.
LOCF: For a missing value at week 52 the last available post-baseline value before week 52 is imputed.

Table R.1.2.5.10: 6 Responder analysis (displaying risk ratio) in KCCQ-CSS change from baseline at week 52 of >= 15 points (improvement) by history of HHF - RS (LOCF-AD) - 1245.121

Subgroup Description	Placebo	Empa 10mg
History of HHF (in the last 12 months): No		
Number of patients in analysis set	1293	1286
Number of analysed patients, N (%)	1194 (100.0)	1212 (100.0)
Number of patients with endpoint, N (%)	251 (21.0)	304 (25.1)
95% confidence interval*	(18.8, 23.4)	(22.7, 27.6)
Comparison vs Placebo**		
Risk ratio (SE)		1.162 (0.080)
95% confidence interval***		(1.015, 1.330)
p-value		0.0292
History of HHF (in the last 12 months): Yes		
Number of patients in analysis set	574	577
Number of analysed patients, N (%)	515 (100.0)	528 (100.0)
Number of patients with endpoint, N (%)	106 (20.6)	120 (22.7)
95% confidence interval*	(17.3, 24.3)	(19.4, 26.5)
Comparison vs Placebo**		
Risk ratio (SE)		1.100 (0.122)
95% confidence interval***		(0.884, 1.368)
p-value		0.3918

* Wilson confidence intervals.
** Log-linked Poisson model with robust estimate of variance includes terms for baseline KCCQ - clinical summary score (p<0.0001), age (p=0.1341), baseline eGFR (CKD-EPI) (p=0.2493), Treatment (p=0.0609), region (5 cat.) (p<0.0001), baseline diabetes status (3 cat.) (p=0.9060), sex (p=0.3154), baseline LVEF (3 cat.) (p=0.3019), history of HHF (in the last 12 months) (p=0.8313) and Treatment by history of HHF (in the last 12 months) interaction (p=0.6742).
***Wald confidence intervals.

Data taken from study 1245.121 only.
LOCF: For a missing value at week 52 the last available post-baseline value before week 52 is imputed.

R.1.2.5.11

Table R.1.2.5.11: 1 Responder analysis (displaying odds ratio) in KCCQ-CSS change from baseline at week 52 of <= -15 points (deterioration) by cause of heart failure - RS (LOCF-AD) - 1245.121

Subgroup Description	Placebo	Empa 10mg
Cause of heart failure: Ischemic		
Number of patients in analysis set	946	983
Number of analysed patients, N (%)	876 (100.0)	923 (100.0)
Number of patients with endpoint, N (%)	108 (12.3)	108 (11.7)
95% confidence interval*	(10.3, 14.7)	(9.8, 13.9)
Comparison vs Placebo**		
Odds ratio (SE)		0.955 (0.140)
95% confidence interval***		(0.717, 1.273)
p-value		0.7551
Cause of heart failure: Non-ischemic		
Number of patients in analysis set	921	880
Number of analysed patients, N (%)	833 (100.0)	817 (100.0)
Number of patients with endpoint, N (%)	96 (11.5)	84 (10.3)
95% confidence interval*	(9.5, 13.9)	(8.4, 12.6)
Comparison vs Placebo**		
Odds ratio (SE)		0.860 (0.137)
95% confidence interval***		(0.628, 1.176)
p-value		0.3437

* Wilson confidence intervals.
** Logistic regression includes terms for baseline KCCQ - clinical summary score (p<0.0001), age (p=0.2421), baseline eGFR (CKD-EPI) (p=0.0039), Treatment (p=0.3632), region (5 cat.) (p=0.0479), baseline diabetes status (3 cat.) (p=0.8841), sex (p=0.7195), baseline LVEF (3 cat.) (p=0.9182), cause of heart failure (p=0.7646) and Treatment by cause of heart failure interaction (p=0.6264).
***Wald confidence intervals.

Data taken from study 1245.121 only.
LOCF: For a missing value at week 52 the last available post-baseline value before week 52 is imputed.

Table R.1.2.5.11: 2 Responder analysis (displaying risk ratio) in KCCQ-CSS change from baseline at week 52 of <= -15 points (deterioration) by cause of heart failure - RS (LOCF-AD) - 1245.121

Subgroup Description	Placebo	Empa 10mg
Cause of heart failure: Ischemic		
Number of patients in analysis set	946	983
Number of analysed patients, N (%)	876 (100.0)	923 (100.0)
Number of patients with endpoint, N (%)	108 (12.3)	108 (11.7)
95% confidence interval*	(10.3, 14.7)	(9.8, 13.9)
Comparison vs Placebo**		
Risk ratio (SE)		0.961 (0.122)
95% confidence interval***		(0.750, 1.232)
p-value		0.7549
Cause of heart failure: Non-ischemic		
Number of patients in analysis set	921	880
Number of analysed patients, N (%)	833 (100.0)	817 (100.0)
Number of patients with endpoint, N (%)	96 (11.5)	84 (10.3)
95% confidence interval*	(9.5, 13.9)	(8.4, 12.6)
Comparison vs Placebo**		
Risk ratio (SE)		0.875 (0.123)
95% confidence interval***		(0.665, 1.152)
p-value		0.3415

* Wilson confidence intervals.
** Log-linked Poisson model with robust estimate of variance includes terms for baseline KCCQ - clinical summary score (p<0.0001), age (p=0.2688), baseline eGFR (CKD-EPI) (p=0.0043), Treatment (p=0.3590), region (5 cat.) (p=0.0575), baseline diabetes status (3 cat.) (p=0.8870), sex (p=0.7179), baseline LVEF (3 cat.) (p=0.9169), cause of heart failure (p=0.7608) and Treatment by cause of heart failure interaction (p=0.6204).
***Wald confidence intervals.

Data taken from study 1245.121 only.
LOCF: For a missing value at week 52 the last available post-baseline value before week 52 is imputed.

Table R.1.2.5.11: 3 Responder analysis (displaying odds ratio) in KCCQ-CSS change from baseline at week 52 of > -15 points (stability) by cause of heart failure - RS (LOCF-AD) - 1245.121

Subgroup Description	Placebo	Empa 10mg
Cause of heart failure: Ischemic		
Number of patients in analysis set	946	983
Number of analysed patients, N (%)	876 (100.0)	923 (100.0)
Number of patients with endpoint, N (%)	768 (87.7)	815 (88.3)
95% confidence interval*	(85.3, 89.7)	(86.1, 90.2)
Comparison vs Placebo**		
Odds ratio (SE)		1.047 (0.153)
95% confidence interval***		(0.785, 1.395)
p-value		0.7551
Cause of heart failure: Non-ischemic		
Number of patients in analysis set	921	880
Number of analysed patients, N (%)	833 (100.0)	817 (100.0)
Number of patients with endpoint, N (%)	737 (88.5)	733 (89.7)
95% confidence interval*	(86.1, 90.5)	(87.4, 91.6)
Comparison vs Placebo**		
Odds ratio (SE)		1.163 (0.186)
95% confidence interval***		(0.851, 1.591)
p-value		0.3437

* Wilson confidence intervals.
** Logistic regression includes terms for baseline KCCQ - clinical summary score (p<0.0001), age (p=0.2421), baseline eGFR (CKD-EPI) (p=0.0039), Treatment (p=0.3632), region (5 cat.) (p=0.0479), baseline diabetes status (3 cat.) (p=0.8841), sex (p=0.7195), baseline LVEF (3 cat.) (p=0.9182), cause of heart failure (p=0.7646) and Treatment by cause of heart failure interaction (p=0.6264).
***Wald confidence intervals.

Data taken from study 1245.121 only.
LOCF: For a missing value at week 52 the last available post-baseline value before week 52 is imputed.

Table R.1.2.5.11: 4 Responder analysis (displaying risk ratio) in KCCQ-CSS change from baseline at week 52 of > -15 points (stability) by cause of heart failure - RS (LOCF-AD) - 1245.121

Subgroup Description	Placebo	Empa 10mg
Cause of heart failure: Ischemic		
Number of patients in analysis set	946	983
Number of analysed patients, N (%)	876 (100.0)	923 (100.0)
Number of patients with endpoint, N (%)	768 (87.7)	815 (88.3)
95% confidence interval*	(85.3, 89.7)	(86.1, 90.2)
Comparison vs Placebo**		
Risk ratio (SE)		1.006 (0.017)
95% confidence interval***		(0.972, 1.041)
p-value		0.7350
Cause of heart failure: Non-ischemic		
Number of patients in analysis set	921	880
Number of analysed patients, N (%)	833 (100.0)	817 (100.0)
Number of patients with endpoint, N (%)	737 (88.5)	733 (89.7)
95% confidence interval*	(86.1, 90.5)	(87.4, 91.6)
Comparison vs Placebo**		
Risk ratio (SE)		1.015 (0.017)
95% confidence interval***		(0.982, 1.050)
p-value		0.3776

* Wilson confidence intervals.
** Log-linked Poisson model with robust estimate of variance includes terms for baseline KCCQ - clinical summary score (p<0.0001), age (p=0.3295), baseline eGFR (CKD-EPI) (p=0.0047), Treatment (p=0.3882), region (5 cat.) (p=0.0019), baseline diabetes status (3 cat.) (p=0.8778), sex (p=0.7252), baseline LVEF (3 cat.) (p=0.9317), cause of heart failure (p=0.7526) and Treatment by cause of heart failure interaction (p=0.7046).
***Wald confidence intervals.

Data taken from study 1245.121 only.
LOCF: For a missing value at week 52 the last available post-baseline value before week 52 is imputed.

Table R.1.2.5.11: 5 Responder analysis (displaying odds ratio) in KCCQ-CSS change from baseline at week 52 of >= 15 points (improvement) by cause of heart failure - RS (LOCF-AD) - 1245.121

Subgroup Description	Placebo	Empa 10mg
Cause of heart failure: Ischemic		
Number of patients in analysis set	946	983
Number of analysed patients, N (%)	876 (100.0)	923 (100.0)
Number of patients with endpoint, N (%)	168 (19.2)	225 (24.4)
95% confidence interval*	(16.7, 21.9)	(21.7, 27.2)
Comparison vs Placebo**		
Odds ratio (SE)		1.415 (0.187)
95% confidence interval***		(1.093, 1.832)
p-value		0.0085
Cause of heart failure: Non-ischemic		
Number of patients in analysis set	921	880
Number of analysed patients, N (%)	833 (100.0)	817 (100.0)
Number of patients with endpoint, N (%)	189 (22.7)	199 (24.4)
95% confidence interval*	(20.0, 25.7)	(21.5, 27.4)
Comparison vs Placebo**		
Odds ratio (SE)		1.143 (0.153)
95% confidence interval***		(0.879, 1.486)
p-value		0.3185

* Wilson confidence intervals.
** Logistic regression includes terms for baseline KCCQ - clinical summary score (p<0.0001), age (p=0.0735), baseline eGFR (CKD-EPI) (p=0.1878), Treatment (p=0.0105), region (5 cat.) (p<0.0001), baseline diabetes status (3 cat.) (p=0.9331), sex (p=0.4697), baseline LVEF (3 cat.) (p=0.3919), cause of heart failure (p=0.8541) and Treatment by cause of heart failure interaction (p=0.2567).
***Wald confidence intervals.

Data taken from study 1245.121 only.
LOCF: For a missing value at week 52 the last available post-baseline value before week 52 is imputed.

Table R.1.2.5.11: 6 Responder analysis (displaying risk ratio) in KCCQ-CSS change from baseline at week 52 of >= 15 points (improvement) by cause of heart failure - RS (LOCF-AD) - 1245.121

Subgroup Description	Placebo	Empa 10mg
Cause of heart failure: Ischemic		
Number of patients in analysis set	946	983
Number of analysed patients, N (%)	876 (100.0)	923 (100.0)
Number of patients with endpoint, N (%)	168 (19.2)	225 (24.4)
95% confidence interval*	(16.7, 21.9)	(21.7, 27.2)
Comparison vs Placebo**		
Risk ratio (SE)		1.224 (0.103)
95% confidence interval***		(1.037, 1.445)
p-value		0.0166
Cause of heart failure: Non-ischemic		
Number of patients in analysis set	921	880
Number of analysed patients, N (%)	833 (100.0)	817 (100.0)
Number of patients with endpoint, N (%)	189 (22.7)	199 (24.4)
95% confidence interval*	(20.0, 25.7)	(21.5, 27.4)
Comparison vs Placebo**		
Risk ratio (SE)		1.069 (0.087)
95% confidence interval***		(0.911, 1.255)
p-value		0.4152

* Wilson confidence intervals.
** Log-linked Poisson model with robust estimate of variance includes terms for baseline KCCQ - clinical summary score (p<0.0001), age (p=0.1419), baseline eGFR (CKD-EPI) (p=0.2281), Treatment (p=0.0219), region (5 cat.) (p<0.0001), baseline diabetes status (3 cat.) (p=0.8649), sex (p=0.3329), baseline LVEF (3 cat.) (p=0.2752), cause of heart failure (p=0.9292) and Treatment by cause of heart failure interaction (p=0.2496).
***Wald confidence intervals.

Data taken from study 1245.121 only.
LOCF: For a missing value at week 52 the last available post-baseline value before week 52 is imputed.

R.1.2.5.12 Subgroup analysis by heart failure physiology (LVEF <= 30% and NTproBNP<median; LVEF <= 30% and NTproBNP>=median; LVEF > 30%)

Table R.1.2.5.12: 1 Responder analysis (displaying odds ratio) in KCCQ-CSS change from baseline at week 52 of <= -15 points (deterioration) by heart failure physiology - RS (LOCF-AD) - 1245.121

Subgroup Description	Placebo	Empa 10mg
Heart failure physiology: LVEF <= 30% and NTproBNP < median		
Number of patients in analysis set	723	698
Number of analysed patients, N (%)	679 (100.0)	655 (100.0)
Number of patients with endpoint, N (%)	66 (9.7)	60 (9.2)
95% confidence interval*	(7.7, 12.2)	(7.2, 11.6)
Comparison vs Placebo**		
Odds ratio (SE)		0.920 (0.174)
95% confidence interval***		(0.635, 1.332)
p-value		0.6597
Heart failure physiology: LVEF <= 30% and NTproBNP >= median		
Number of patients in analysis set	661	631
Number of analysed patients, N (%)	588 (100.0)	586 (100.0)
Number of patients with endpoint, N (%)	88 (15.0)	71 (12.1)
95% confidence interval*	(12.3, 18.1)	(9.7, 15.0)
Comparison vs Placebo**		
Odds ratio (SE)		0.786 (0.136)
95% confidence interval***		(0.560, 1.105)
p-value		0.1656

* Wilson confidence intervals.
** Logistic regression includes terms for baseline KCCQ - clinical summary score (p<0.0001), age (p=0.2325), baseline eGFR (CKD-EPI) (p=0.0192), Treatment (p=0.4433), region (5 cat.) (p=0.0245), baseline diabetes status (3 cat.) (p=0.9003), sex (p=0.7430), heart failure physiology (p=0.0056) and Treatment by heart failure physiology interaction (p=0.5066).
***Wald confidence intervals.
16 patients were excluded as the subgroup variable was missing.

Data taken from study 1245.121 only.
LOCF: For a missing value at week 52 the last available post-baseline value before week 52 is imputed.
NTproBNP median [pg/mL]: with a. fibrillation/flutter at baseline: 2265; without a. fibrillation/flutter at baseline: 1671.

Table R.1.2.5.12: 1 Responder analysis (displaying odds ratio) in KCCQ-CSS change from baseline at week 52 of <= -15 points (deterioration) by heart failure physiology - RS (LOCF-AD) - 1245.121

Subgroup Description	Placebo	Empa 10mg
Heart failure physiology: LVEF > 30%		
Number of patients in analysis set	475	526
Number of analysed patients, N (%)	437 (100.0)	495 (100.0)
Number of patients with endpoint, N (%)	50 (11.4)	60 (12.1)
95% confidence interval*	(8.8, 14.8)	(9.5, 15.3)
Comparison vs Placebo**		
Odds ratio (SE)		1.074 (0.221)
95% confidence interval***		(0.718, 1.608)
p-value		0.7270

* Wilson confidence intervals.
** Logistic regression includes terms for baseline KCCQ - clinical summary score (p<0.0001), age (p=0.2325), baseline eGFR (CKD-EPI) (p=0.0192), Treatment (p=0.4433), region (5 cat.) (p=0.0245), baseline diabetes status (3 cat.) (p=0.9003), sex (p=0.7430), heart failure physiology (p=0.0056) and Treatment by heart failure physiology interaction (p=0.5066).
***Wald confidence intervals.
16 patients were excluded as the subgroup variable was missing.

Data taken from study 1245.121 only.
LOCF: For a missing value at week 52 the last available post-baseline value before week 52 is imputed.
NTproBNP median [pg/mL]: with a. fibrillation/flutter at baseline: 2265; without a. fibrillation/flutter at baseline: 1671.

Table R.1.2.5.12: 2 Responder analysis (displaying risk ratio) in KCCQ-CSS change from baseline at week 52 of <= -15 points (deterioration) by heart failure physiology - RS (LOCF-AD) - 1245.121

Subgroup Description	Placebo	Empa 10mg
Heart failure physiology: LVEF <= 30% and NTproBNP < median		
Number of patients in analysis set	723	698
Number of analysed patients, N (%)	679 (100.0)	655 (100.0)
Number of patients with endpoint, N (%)	66 (9.7)	60 (9.2)
95% confidence interval*	(7.7, 12.2)	(7.2, 11.6)
Comparison vs Placebo**		
Risk ratio (SE)		0.929 (0.157)
95% confidence interval***		(0.667, 1.292)
p-value		0.6604
Heart failure physiology: LVEF <= 30% and NTproBNP >= median		
Number of patients in analysis set	661	631
Number of analysed patients, N (%)	588 (100.0)	586 (100.0)
Number of patients with endpoint, N (%)	88 (15.0)	71 (12.1)
95% confidence interval*	(12.3, 18.1)	(9.7, 15.0)
Comparison vs Placebo**		
Risk ratio (SE)		0.815 (0.120)
95% confidence interval***		(0.611, 1.088)
p-value		0.1649

* Wilson confidence intervals.
** Log-linked Poisson model with robust estimate of variance includes terms for baseline KCCQ - clinical summary score (p<0.0001), age (p=0.2576), baseline eGFR (CKD-EPI) (p=0.0194), Treatment (p=0.4491), region (5 cat.) (p=0.0321), baseline diabetes status (3 cat.) (p=0.9039), sex (p=0.7399), heart failure physiology (p=0.0058) and Treatment by heart failure physiology interaction (p=0.5140).
***Wald confidence intervals.
16 patients were excluded as the subgroup variable was missing.

Data taken from study 1245.121 only.
LOCF: For a missing value at week 52 the last available post-baseline value before week 52 is imputed.
NTproBNP median [pg/mL]: with a. fibrillation/flutter at baseline: 2265; without a. fibrillation/flutter at baseline: 1671.

Table R.1.2.5.12: 2 Responder analysis (displaying risk ratio) in KCCQ-CSS change from baseline at week 52 of <= -15 points (deterioration) by heart failure physiology - RS (LOCF-AD) - 1245.121

Subgroup Description	Placebo	Empa 10mg
Heart failure physiology: LVEF > 30%		
Number of patients in analysis set	475	526
Number of analysed patients, N (%)	437 (100.0)	495 (100.0)
Number of patients with endpoint, N (%)	50 (11.4)	60 (12.1)
95% confidence interval*	(8.8, 14.8)	(9.5, 15.3)
Comparison vs Placebo**		
Risk ratio (SE)		1.064 (0.190)
95% confidence interval***		(0.750, 1.509)
p-value		0.7285

* Wilson confidence intervals.
** Log-linked Poisson model with robust estimate of variance includes terms for baseline KCCQ - clinical summary score (p<0.0001), age (p=0.2576), baseline eGFR (CKD-EPI) (p=0.0194), Treatment (p=0.4491), region (5 cat.) (p=0.0321), baseline diabetes status (3 cat.) (p=0.9039), sex (p=0.7399), heart failure physiology (p=0.0058) and Treatment by heart failure physiology interaction (p=0.5140).
***Wald confidence intervals.
16 patients were excluded as the subgroup variable was missing.

Data taken from study 1245.121 only.
LOCF: For a missing value at week 52 the last available post-baseline value before week 52 is imputed.
NTproBNP median [pg/mL]: with a. fibrillation/flutter at baseline: 2265; without a. fibrillation/flutter at baseline: 1671.

Table R.1.2.5.12: 3 Responder analysis (displaying odds ratio) in KCCQ-CSS change from baseline at week 52 of > -15 points (stability) by heart failure physiology - RS (LOCF-AD) - 1245.121

Subgroup Description	Placebo	Empa 10mg
Heart failure physiology: LVEF <= 30% and NTproBNP < median		
Number of patients in analysis set	723	698
Number of analysed patients, N (%)	679 (100.0)	655 (100.0)
Number of patients with endpoint, N (%)	613 (90.3)	595 (90.8)
95% confidence interval*	(87.8, 92.3)	(88.4, 92.8)
Comparison vs Placebo**		
Odds ratio (SE)		1.087 (0.205)
95% confidence interval***		(0.751, 1.574)
p-value		0.6597
Heart failure physiology: LVEF <= 30% and NTproBNP >= median		
Number of patients in analysis set	661	631
Number of analysed patients, N (%)	588 (100.0)	586 (100.0)
Number of patients with endpoint, N (%)	500 (85.0)	515 (87.9)
95% confidence interval*	(81.9, 87.7)	(85.0, 90.3)
Comparison vs Placebo**		
Odds ratio (SE)		1.272 (0.221)
95% confidence interval***		(0.905, 1.787)
p-value		0.1656

* Wilson confidence intervals.
** Logistic regression includes terms for baseline KCCQ - clinical summary score (p<0.0001), age (p=0.2325), baseline eGFR (CKD-EPI) (p=0.0192), Treatment (p=0.4433), region (5 cat.) (p=0.0245), baseline diabetes status (3 cat.) (p=0.9003), sex (p=0.7430), heart failure physiology (p=0.0056) and Treatment by heart failure physiology interaction (p=0.5066).
***Wald confidence intervals.
16 patients were excluded as the subgroup variable was missing.

Data taken from study 1245.121 only.
LOCF: For a missing value at week 52 the last available post-baseline value before week 52 is imputed.
NTproBNP median [pg/mL]: with a. fibrillation/flutter at baseline: 2265; without a. fibrillation/flutter at baseline: 1671.

Table R.1.2.5.12: 3 Responder analysis (displaying odds ratio) in KCCQ-CSS change from baseline at week 52 of > -15 points (stability) by heart failure physiology - RS (LOCF-AD) - 1245.121

Subgroup Description	Placebo	Empa 10mg
Heart failure physiology: LVEF > 30%		
Number of patients in analysis set	475	526
Number of analysed patients, N (%)	437 (100.0)	495 (100.0)
Number of patients with endpoint, N (%)	387 (88.6)	435 (87.9)
95% confidence interval*	(85.2, 91.2)	(84.7, 90.5)
Comparison vs Placebo**		
Odds ratio (SE)		0.931 (0.191)
95% confidence interval***		(0.622, 1.393)
p-value		0.7270

* Wilson confidence intervals.
** Logistic regression includes terms for baseline KCCQ - clinical summary score (p<0.0001), age (p=0.2325), baseline eGFR (CKD-EPI) (p=0.0192), Treatment (p=0.4433), region (5 cat.) (p=0.0245), baseline diabetes status (3 cat.) (p=0.9003), sex (p=0.7430), heart failure physiology (p=0.0056) and Treatment by heart failure physiology interaction (p=0.5066).
***Wald confidence intervals.
16 patients were excluded as the subgroup variable was missing.

Data taken from study 1245.121 only.
LOCF: For a missing value at week 52 the last available post-baseline value before week 52 is imputed.
NTproBNP median [pg/mL]: with a. fibrillation/flutter at baseline: 2265; without a. fibrillation/flutter at baseline: 1671.

Table R.1.2.5.12: 4 Responder analysis (displaying risk ratio) in KCCQ-CSS change from baseline at week 52 of > -15 points (stability) by heart failure physiology - RS (LOCF-AD) - 1245.121

Subgroup Description	Placebo	Empa 10mg
Heart failure physiology: LVEF <= 30% and NTproBNP < median		
Number of patients in analysis set	723	698
Number of analysed patients, N (%)	679 (100.0)	655 (100.0)
Number of patients with endpoint, N (%)	613 (90.3)	595 (90.8)
95% confidence interval*	(87.8, 92.3)	(88.4, 92.8)
Comparison vs Placebo**		
Risk ratio (SE)		1.008 (0.018)
95% confidence interval***		(0.974, 1.044)
p-value		0.6411
Heart failure physiology: LVEF <= 30% and NTproBNP >= median		
Number of patients in analysis set	661	631
Number of analysed patients, N (%)	588 (100.0)	586 (100.0)
Number of patients with endpoint, N (%)	500 (85.0)	515 (87.9)
95% confidence interval*	(81.9, 87.7)	(85.0, 90.3)
Comparison vs Placebo**		
Risk ratio (SE)		1.032 (0.024)
95% confidence interval***		(0.987, 1.080)
p-value		0.1672

* Wilson confidence intervals.
** Log-linked Poisson model with robust estimate of variance includes terms for baseline KCCQ - clinical summary score (p<0.0001), age (p=0.3001), baseline eGFR (CKD-EPI) (p=0.0207), Treatment (p=0.4169), region (5 cat.) (p=0.0007), baseline diabetes status (3 cat.) (p=0.8858), sex (p=0.7288), heart failure physiology (p=0.0046) and Treatment by heart failure physiology interaction (p=0.4560).
***Wald confidence intervals.
16 patients were excluded as the subgroup variable was missing.

Data taken from study 1245.121 only.
LOCF: For a missing value at week 52 the last available post-baseline value before week 52 is imputed.
NTproBNP median [pg/mL]: with a. fibrillation/flutter at baseline: 2265; without a. fibrillation/flutter at baseline: 1671.

Table R.1.2.5.12: 4 Responder analysis (displaying risk ratio) in KCCQ-CSS change from baseline at week 52 of > -15 points (stability) by heart failure physiology - RS (LOCF-AD) - 1245.121

Subgroup Description	Placebo	Empa 10mg
Heart failure physiology: LVEF > 30%		
Number of patients in analysis set	475	526
Number of analysed patients, N (%)	437 (100.0)	495 (100.0)
Number of patients with endpoint, N (%)	387 (88.6)	435 (87.9)
95% confidence interval*	(85.2, 91.2)	(84.7, 90.5)
Comparison vs Placebo**		
Risk ratio (SE)		0.991 (0.024)
95% confidence interval***		(0.945, 1.038)
p-value		0.6906

* Wilson confidence intervals.
** Log-linked Poisson model with robust estimate of variance includes terms for baseline KCCQ - clinical summary score (p<0.0001), age (p=0.3001), baseline eGFR (CKD-EPI) (p=0.0207), Treatment (p=0.4169), region (5 cat.) (p=0.0007), baseline diabetes status (3 cat.) (p=0.8858), sex (p=0.7288), heart failure physiology (p=0.0046) and Treatment by heart failure physiology interaction (p=0.4560).
***Wald confidence intervals.
16 patients were excluded as the subgroup variable was missing.

Data taken from study 1245.121 only.
LOCF: For a missing value at week 52 the last available post-baseline value before week 52 is imputed.
NTproBNP median [pg/mL]: with a. fibrillation/flutter at baseline: 2265; without a. fibrillation/flutter at baseline: 1671.

Table R.1.2.5.12: 5 Responder analysis (displaying odds ratio) in KCCQ-CSS change from baseline at week 52 of >= 15 points (improvement) by heart failure physiology - RS (LOCF-AD) - 1245.121

Subgroup Description	Placebo	Empa 10mg
Heart failure physiology: LVEF <= 30% and NTproBNP < median		
Number of patients in analysis set	723	698
Number of analysed patients, N (%)	679 (100.0)	655 (100.0)
Number of patients with endpoint, N (%)	141 (20.8)	154 (23.5)
95% confidence interval*	(17.9, 24.0)	(20.4, 26.9)
Comparison vs Placebo**		
Odds ratio (SE)		1.272 (0.192)
95% confidence interval***		(0.946, 1.711)
p-value		0.1106
Heart failure physiology: LVEF <= 30% and NTproBNP >= median		
Number of patients in analysis set	661	631
Number of analysed patients, N (%)	588 (100.0)	586 (100.0)
Number of patients with endpoint, N (%)	128 (21.8)	159 (27.1)
95% confidence interval*	(18.6, 25.3)	(23.7, 30.9)
Comparison vs Placebo**		
Odds ratio (SE)		1.371 (0.216)
95% confidence interval***		(1.006, 1.868)
p-value		0.0456

* Wilson confidence intervals.
** Logistic regression includes terms for baseline KCCQ - clinical summary score (p<0.0001), age (p=0.0645), baseline eGFR (CKD-EPI) (p=0.2647), Treatment (p=0.0122), region (5 cat.) (p<0.0001), baseline diabetes status (3 cat.) (p=0.9378), sex (p=0.4394), heart failure physiology (p=0.4475) and Treatment by heart failure physiology interaction (p=0.8208).
***Wald confidence intervals.
16 patients were excluded as the subgroup variable was missing.

Data taken from study 1245.121 only.
LOCF: For a missing value at week 52 the last available post-baseline value before week 52 is imputed.
NTproBNP median [pg/mL]: with a. fibrillation/flutter at baseline: 2265; without a. fibrillation/flutter at baseline: 1671.

Table R.1.2.5.12: 5 Responder analysis (displaying odds ratio) in KCCQ-CSS change from baseline at week 52 of >= 15 points (improvement) by heart failure physiology - RS (LOCF-AD) - 1245.121

Subgroup Description	Placebo	Empa 10mg
Heart failure physiology: LVEF > 30%		
Number of patients in analysis set	475	526
Number of analysed patients, N (%)	437 (100.0)	495 (100.0)
Number of patients with endpoint, N (%)	85 (19.5)	109 (22.0)
95% confidence interval*	(16.0, 23.4)	(18.6, 25.9)
Comparison vs Placebo**		
Odds ratio (SE)		1.177 (0.219)
95% confidence interval***		(0.817, 1.695)
p-value		0.3811

* Wilson confidence intervals.
** Logistic regression includes terms for baseline KCCQ - clinical summary score (p<0.0001), age (p=0.0645), baseline eGFR (CKD-EPI) (p=0.2647), Treatment (p=0.0122), region (5 cat.) (p<0.0001), baseline diabetes status (3 cat.) (p=0.9378), sex (p=0.4394), heart failure physiology (p=0.4475) and Treatment by heart failure physiology interaction (p=0.8208).
***Wald confidence intervals.
16 patients were excluded as the subgroup variable was missing.

Data taken from study 1245.121 only.
LOCF: For a missing value at week 52 the last available post-baseline value before week 52 is imputed.
NTproBNP median [pg/mL]: with a. fibrillation/flutter at baseline: 2265; without a. fibrillation/flutter at baseline: 1671.

Table R.1.2.5.12: 6 Responder analysis (displaying risk ratio) in KCCQ-CSS change from baseline at week 52 of >= 15 points (improvement) by heart failure physiology - RS (LOCF-AD) - 1245.121

Subgroup Description	Placebo	Empa 10mg
Heart failure physiology: LVEF <= 30% and NTproBNP < median		
Number of patients in analysis set	723	698
Number of analysed patients, N (%)	679 (100.0)	655 (100.0)
Number of patients with endpoint, N (%)	141 (20.8)	154 (23.5)
95% confidence interval*	(17.9, 24.0)	(20.4, 26.9)
Comparison vs Placebo**		
Risk ratio (SE)		1.144 (0.111)
95% confidence interval***		(0.946, 1.382)
p-value		0.1651
Heart failure physiology: LVEF <= 30% and NTproBNP >= median		
Number of patients in analysis set	661	631
Number of analysed patients, N (%)	588 (100.0)	586 (100.0)
Number of patients with endpoint, N (%)	128 (21.8)	159 (27.1)
95% confidence interval*	(18.6, 25.3)	(23.7, 30.9)
Comparison vs Placebo**		
Risk ratio (SE)		1.218 (0.116)
95% confidence interval***		(1.011, 1.468)
p-value		0.0382

* Wilson confidence intervals.
** Log-linked Poisson model with robust estimate of variance includes terms for baseline KCCQ - clinical summary score (p<0.0001), age (p=0.1176), baseline eGFR (CKD-EPI) (p=0.3466), Treatment (p=0.0332), region (5 cat.) (p<0.0001), baseline diabetes status (3 cat.) (p=0.9012), sex (p=0.3420), heart failure physiology (p=0.3565) and Treatment by heart failure physiology interaction (p=0.6230).
***Wald confidence intervals.
16 patients were excluded as the subgroup variable was missing.

Data taken from study 1245.121 only.
LOCF: For a missing value at week 52 the last available post-baseline value before week 52 is imputed.
NTproBNP median [pg/mL]: with a. fibrillation/flutter at baseline: 2265; without a. fibrillation/flutter at baseline: 1671.

Table R.1.2.5.12: 6 Responder analysis (displaying risk ratio) in KCCQ-CSS change from baseline at week 52 of >= 15 points (improvement) by heart failure physiology - RS (LOCF-AD) - 1245.121

Subgroup Description	Placebo	Empa 10mg
Heart failure physiology: LVEF > 30%		
Number of patients in analysis set	475	526
Number of analysed patients, N (%)	437 (100.0)	495 (100.0)
Number of patients with endpoint, N (%)	85 (19.5)	109 (22.0)
95% confidence interval*	(16.0, 23.4)	(18.6, 25.9)
Comparison vs Placebo**		
Risk ratio (SE)		1.052 (0.123)
95% confidence interval***		(0.836, 1.323)
p-value		0.6653

* Wilson confidence intervals.
** Log-linked Poisson model with robust estimate of variance includes terms for baseline KCCQ - clinical summary score (p<0.0001), age (p=0.1176), baseline eGFR (CKD-EPI) (p=0.3466), Treatment (p=0.0332), region (5 cat.) (p<0.0001), baseline diabetes status (3 cat.) (p=0.9012), sex (p=0.3420), heart failure physiology (p=0.3565) and Treatment by heart failure physiology interaction (p=0.6230).
***Wald confidence intervals.
16 patients were excluded as the subgroup variable was missing.

Data taken from study 1245.121 only.
LOCF: For a missing value at week 52 the last available post-baseline value before week 52 is imputed.
NTproBNP median [pg/mL]: with a. fibrillation/flutter at baseline: 2265; without a. fibrillation/flutter at baseline: 1671.

R.1.2.5.13

R.1.2.5.13 Subgroup analysis by baseline use of MRA

Table R.1.2.5.13: 1 Responder analysis (displaying odds ratio) in KCCQ-CSS change from baseline at week 52 of <= -15 points (deterioration) by baseline use of MRA (Y/N) - RS (LOCF-AD) - 1245.121

Subgroup Description	Placebo	Empa 10mg
Baseline use of MRA: No		
Number of patients in analysis set	512	557
Number of analysed patients, N (%)	475 (100.0)	522 (100.0)
Number of patients with endpoint, N (%)	56 (11.8)	55 (10.5)
95% confidence interval*	(9.2, 15.0)	(8.2, 13.5)
Comparison vs Placebo**		
Odds ratio (SE)		0.884 (0.180)
95% confidence interval***		(0.594, 1.316)
p-value		0.5441
Baseline use of MRA: Yes		
Number of patients in analysis set	1355	1306
Number of analysed patients, N (%)	1234 (100.0)	1218 (100.0)
Number of patients with endpoint, N (%)	148 (12.0)	137 (11.2)
95% confidence interval*	(10.3, 13.9)	(9.6, 13.1)
Comparison vs Placebo**		
Odds ratio (SE)		0.923 (0.118)
95% confidence interval***		(0.719, 1.185)
p-value		0.5320

* Wilson confidence intervals.
** Logistic regression includes terms for baseline KCCQ - clinical summary score (p<0.0001), age (p=0.2015), baseline eGFR (CKD-EPI) (p=0.0032), Treatment (p=0.3974), region (5 cat.) (p=0.0581), baseline diabetes status (3 cat.) (p=0.8623), sex (p=0.7622), baseline LVEF (3 cat.) (p=0.9369), baseline use of MRA (p=0.3085) and Treatment by baseline use of MRA interaction (p=0.8559).
***Wald confidence intervals.

Data taken from study 1245.121 only.
LOCF: For a missing value at week 52 the last available post-baseline value before week 52 is imputed.

Table R.1.2.5.13: 2 Responder analysis (displaying risk ratio) in KCCQ-CSS change from baseline at week 52 of <= -15 points (deterioration) by baseline use of MRA (Y/N) - RS (LOCF-AD) - 1245.121

Subgroup Description	Placebo	Empa 10mg
Baseline use of MRA: No		
Number of patients in analysis set	512	557
Number of analysed patients, N (%)	475 (100.0)	522 (100.0)
Number of patients with endpoint, N (%)	56 (11.8)	55 (10.5)
95% confidence interval*	(9.2, 15.0)	(8.2, 13.5)
Comparison vs Placebo**		
Risk ratio (SE)		0.898 (0.159)
95% confidence interval***		(0.634, 1.270)
p-value		0.5423
Baseline use of MRA: Yes		
Number of patients in analysis set	1355	1306
Number of analysed patients, N (%)	1234 (100.0)	1218 (100.0)
Number of patients with endpoint, N (%)	148 (12.0)	137 (11.2)
95% confidence interval*	(10.3, 13.9)	(9.6, 13.1)
Comparison vs Placebo**		
Risk ratio (SE)		0.933 (0.103)
95% confidence interval***		(0.751, 1.158)
p-value		0.5292

* Wilson confidence intervals.
** Log-linked Poisson model with robust estimate of variance includes terms for baseline KCCQ - clinical summary score (p<0.0001), age (p=0.2242), baseline eGFR (CKD-EPI) (p=0.0038), Treatment (p=0.3947), region (5 cat.) (p=0.0730), baseline diabetes status (3 cat.) (p=0.8650), sex (p=0.7595), baseline LVEF (3 cat.) (p=0.9364), baseline use of MRA (p=0.3077) and Treatment by baseline use of MRA interaction (p=0.8542).
***Wald confidence intervals.

Data taken from study 1245.121 only.
LOCF: For a missing value at week 52 the last available post-baseline value before week 52 is imputed.

Table R.1.2.5.13: 3 Responder analysis (displaying odds ratio) in KCCQ-CSS change from baseline at week 52 of > -15 points (stability) by baseline use of MRA (Y/N) - RS (LOCF-AD) - 1245.121

Subgroup Description	Placebo	Empa 10mg
Baseline use of MRA: No		
Number of patients in analysis set	512	557
Number of analysed patients, N (%)	475 (100.0)	522 (100.0)
Number of patients with endpoint, N (%)	419 (88.2)	467 (89.5)
95% confidence interval*	(85.0, 90.8)	(86.5, 91.8)
Comparison vs Placebo**		
Odds ratio (SE)		1.131 (0.230)
95% confidence interval***		(0.760, 1.684)
p-value		0.5441
Baseline use of MRA: Yes		
Number of patients in analysis set	1355	1306
Number of analysed patients, N (%)	1234 (100.0)	1218 (100.0)
Number of patients with endpoint, N (%)	1086 (88.0)	1081 (88.8)
95% confidence interval*	(86.1, 89.7)	(86.9, 90.4)
Comparison vs Placebo**		
Odds ratio (SE)		1.083 (0.138)
95% confidence interval***		(0.844, 1.390)
p-value		0.5320

* Wilson confidence intervals.
** Logistic regression includes terms for baseline KCCQ - clinical summary score (p<0.0001), age (p=0.2015), baseline eGFR (CKD-EPI) (p=0.0032), Treatment (p=0.3974), region (5 cat.) (p=0.0581), baseline diabetes status (3 cat.) (p=0.8623), sex (p=0.7622), baseline LVEF (3 cat.) (p=0.9369), baseline use of MRA (p=0.3085) and Treatment by baseline use of MRA interaction (p=0.8559).
***Wald confidence intervals.

Data taken from study 1245.121 only.
LOCF: For a missing value at week 52 the last available post-baseline value before week 52 is imputed.

Table R.1.2.5.13: 4 Responder analysis (displaying risk ratio) in KCCQ-CSS change from baseline at week 52 of > -15 points (stability) by baseline use of MRA (Y/N) - RS (LOCF-AD) - 1245.121

Subgroup Description	Placebo	Empa 10mg
Baseline use of MRA: No		
Number of patients in analysis set	512	557
Number of analysed patients, N (%)	475 (100.0)	522 (100.0)
Number of patients with endpoint, N (%)	419 (88.2)	467 (89.5)
95% confidence interval*	(85.0, 90.8)	(86.5, 91.8)
Comparison vs Placebo**		
Risk ratio (SE)		1.013 (0.023)
95% confidence interval***		(0.970, 1.058)
p-value		0.5577
Baseline use of MRA: Yes		
Number of patients in analysis set	1355	1306
Number of analysed patients, N (%)	1234 (100.0)	1218 (100.0)
Number of patients with endpoint, N (%)	1086 (88.0)	1081 (88.8)
95% confidence interval*	(86.1, 89.7)	(86.9, 90.4)
Comparison vs Placebo**		
Risk ratio (SE)		1.009 (0.015)
95% confidence interval***		(0.980, 1.038)
p-value		0.5464

* Wilson confidence intervals.
** Log-linked Poisson model with robust estimate of variance includes terms for baseline KCCQ - clinical summary score (p<0.0001), age (p=0.2725), baseline eGFR (CKD-EPI) (p=0.0039), Treatment (p=0.4116), region (5 cat.) (p=0.0028), baseline diabetes status (3 cat.) (p=0.8574), sex (p=0.7591), baseline LVEF (3 cat.) (p=0.9492), baseline use of MRA (p=0.3010) and Treatment by baseline use of MRA interaction (p=0.8716).
***Wald confidence intervals.

Data taken from study 1245.121 only.
LOCF: For a missing value at week 52 the last available post-baseline value before week 52 is imputed.

Table R.1.2.5.13: 5 Responder analysis (displaying odds ratio) in KCCQ-CSS change from baseline at week 52 of >= 15 points (improvement) by baseline use of MRA (Y/N) - RS (LOCF-AD) - 1245.121

Subgroup Description	Placebo	Empa 10mg
Baseline use of MRA: No		
Number of patients in analysis set	512	557
Number of analysed patients, N (%)	475 (100.0)	522 (100.0)
Number of patients with endpoint, N (%)	78 (16.4)	118 (22.6)
95% confidence interval*	(13.4, 20.0)	(19.2, 26.4)
Comparison vs Placebo**		
Odds ratio (SE)		1.583 (0.291)
95% confidence interval***		(1.104, 2.271)
p-value		0.0125
Baseline use of MRA: Yes		
Number of patients in analysis set	1355	1306
Number of analysed patients, N (%)	1234 (100.0)	1218 (100.0)
Number of patients with endpoint, N (%)	279 (22.6)	306 (25.1)
95% confidence interval*	(20.4, 25.0)	(22.8, 27.6)
Comparison vs Placebo**		
Odds ratio (SE)		1.181 (0.129)
95% confidence interval***		(0.953, 1.463)
p-value		0.1279

* Wilson confidence intervals.
** Logistic regression includes terms for baseline KCCQ - clinical summary score (p<0.0001), age (p=0.0768), baseline eGFR (CKD-EPI) (p=0.2010), Treatment (p=0.0034), region (5 cat.) (p<0.0001), baseline diabetes status (3 cat.) (p=0.9560), sex (p=0.4683), baseline LVEF (3 cat.) (p=0.4233), baseline use of MRA (p=0.6100) and Treatment by baseline use of MRA interaction (p=0.1706).
***Wald confidence intervals.

Data taken from study 1245.121 only.
LOCF: For a missing value at week 52 the last available post-baseline value before week 52 is imputed.

Table R.1.2.5.13: 6 Responder analysis (displaying risk ratio) in KCCQ-CSS change from baseline at week 52 of >= 15 points (improvement) by baseline use of MRA (Y/N) - RS (LOCF-AD) - 1245.121

Subgroup Description	Placebo	Empa 10mg
Baseline use of MRA: No		
Number of patients in analysis set	512	557
Number of analysed patients, N (%)	475 (100.0)	522 (100.0)
Number of patients with endpoint, N (%)	78 (16.4)	118 (22.6)
95% confidence interval*	(13.4, 20.0)	(19.2, 26.4)
Comparison vs Placebo**		
Risk ratio (SE)		1.298 (0.160)
95% confidence interval***		(1.019, 1.654)
p-value		0.0346
Baseline use of MRA: Yes		
Number of patients in analysis set	1355	1306
Number of analysed patients, N (%)	1234 (100.0)	1218 (100.0)
Number of patients with endpoint, N (%)	279 (22.6)	306 (25.1)
95% confidence interval*	(20.4, 25.0)	(22.8, 27.6)
Comparison vs Placebo**		
Risk ratio (SE)		1.099 (0.073)
95% confidence interval***		(0.965, 1.253)
p-value		0.1556

* Wilson confidence intervals.
** Log-linked Poisson model with robust estimate of variance includes terms for baseline KCCQ - clinical summary score (p<0.0001), age (p=0.1459), baseline eGFR (CKD-EPI) (p=0.2643), Treatment (p=0.0114), region (5 cat.) (p<0.0001), baseline diabetes status (3 cat.) (p=0.9028), sex (p=0.3159), baseline LVEF (3 cat.) (p=0.3188), baseline use of MRA (p=0.4425) and Treatment by baseline use of MRA interaction (p=0.2348).
***Wald confidence intervals.

Data taken from study 1245.121 only.
LOCF: For a missing value at week 52 the last available post-baseline value before week 52 is imputed.

R.1.2.5.14

Table R.1.2.5.14: 1 Responder analysis (displaying odds ratio) in KCCQ-CSS change from baseline at week 52 of <= -15 points (deterioration) by baseline use of ARNi (Y/N) - RS (LOCF-AD) - 1245.121

Subgroup Description	Placebo	Empa 10mg
Baseline use of ARNi: No		
Number of patients in analysis set	1480	1523
Number of analysed patients, N (%)	1350 (100.0)	1418 (100.0)
Number of patients with endpoint, N (%)	169 (12.5)	162 (11.4)
95% confidence interval*	(10.9, 14.4)	(9.9, 13.2)
Comparison vs Placebo**		
Odds ratio (SE)		0.891 (0.105)
95% confidence interval***		(0.706, 1.123)
p-value		0.3287
Baseline use of ARNi: Yes		
Number of patients in analysis set	387	340
Number of analysed patients, N (%)	359 (100.0)	322 (100.0)
Number of patients with endpoint, N (%)	35 (9.7)	30 (9.3)
95% confidence interval*	(7.1, 13.3)	(6.6, 13.0)
Comparison vs Placebo**		
Odds ratio (SE)		0.969 (0.256)
95% confidence interval***		(0.578, 1.626)
p-value		0.9051

* Wilson confidence intervals.
** Logistic regression includes terms for baseline KCCQ - clinical summary score (p<0.0001), age (p=0.2578), baseline eGFR (CKD-EPI) (p=0.0034), Treatment (p=0.6111), region (5 cat.) (p=0.0458), baseline diabetes status (3 cat.) (p=0.8847), sex (p=0.7110), baseline LVEF (3 cat.) (p=0.8824), baseline use of ARNi (p=0.0551) and Treatment by baseline use of ARNi interaction (p=0.7712).
***Wald confidence intervals.

Data taken from study 1245.121 only.
LOCF: For a missing value at week 52 the last available post-baseline value before week 52 is imputed.

Table R.1.2.5.14: 2 Responder analysis (displaying risk ratio) in KCCQ-CSS change from baseline at week 52 of <= -15 points (deterioration) by baseline use of ARNi (Y/N) - RS (LOCF-AD) - 1245.121

Subgroup Description	Placebo	Empa 10mg
Baseline use of ARNi: No		
Number of patients in analysis set	1480	1523
Number of analysed patients, N (%)	1350 (100.0)	1418 (100.0)
Number of patients with endpoint, N (%)	169 (12.5)	162 (11.4)
95% confidence interval*	(10.9, 14.4)	(9.9, 13.2)
Comparison vs Placebo**		
Risk ratio (SE)		0.904 (0.092)
95% confidence interval***		(0.740, 1.105)
p-value		0.3252
Baseline use of ARNi: Yes		
Number of patients in analysis set	387	340
Number of analysed patients, N (%)	359 (100.0)	322 (100.0)
Number of patients with endpoint, N (%)	35 (9.7)	30 (9.3)
95% confidence interval*	(7.1, 13.3)	(6.6, 13.0)
Comparison vs Placebo**		
Risk ratio (SE)		0.972 (0.227)
95% confidence interval***		(0.615, 1.537)
p-value		0.9031

* Wilson confidence intervals.
** Log-linked Poisson model with robust estimate of variance includes terms for baseline KCCQ - clinical summary score (p<0.0001), age (p=0.2839), baseline eGFR (CKD-EPI) (p=0.0037), Treatment (p=0.6129), region (5 cat.) (p=0.0573), baseline diabetes status (3 cat.) (p=0.8891), sex (p=0.7097), baseline LVEF (3 cat.) (p=0.8816), baseline use of ARNi (p=0.0565) and Treatment by baseline use of ARNi interaction (p=0.7776).
***Wald confidence intervals.

Data taken from study 1245.121 only.
LOCF: For a missing value at week 52 the last available post-baseline value before week 52 is imputed.

Table R.1.2.5.14: 3 Responder analysis (displaying odds ratio) in KCCQ-CSS change from baseline at week 52 of > -15 points (stability) by baseline use of ARNi (Y/N) - RS (LOCF-AD) - 1245.121

Subgroup Description	Placebo	Empa 10mg
Baseline use of ARNi: No		
Number of patients in analysis set	1480	1523
Number of analysed patients, N (%)	1350 (100.0)	1418 (100.0)
Number of patients with endpoint, N (%)	1181 (87.5)	1256 (88.6)
95% confidence interval*	(85.6, 89.1)	(86.8, 90.1)
Comparison vs Placebo**		
Odds ratio (SE)		1.123 (0.133)
95% confidence interval***		(0.890, 1.416)
p-value		0.3287
Baseline use of ARNi: Yes		
Number of patients in analysis set	387	340
Number of analysed patients, N (%)	359 (100.0)	322 (100.0)
Number of patients with endpoint, N (%)	324 (90.3)	292 (90.7)
95% confidence interval*	(86.7, 92.9)	(87.0, 93.4)
Comparison vs Placebo**		
Odds ratio (SE)		1.032 (0.272)
95% confidence interval***		(0.615, 1.732)
p-value		0.9051

* Wilson confidence intervals.
** Logistic regression includes terms for baseline KCCQ - clinical summary score (p<0.0001), age (p=0.2578), baseline eGFR (CKD-EPI) (p=0.0034), Treatment (p=0.6111), region (5 cat.) (p=0.0458), baseline diabetes status (3 cat.) (p=0.8847), sex (p=0.7110), baseline LVEF (3 cat.) (p=0.8824), baseline use of ARNi (p=0.0551) and Treatment by baseline use of ARNi interaction (p=0.7712).
***Wald confidence intervals.

Data taken from study 1245.121 only.
LOCF: For a missing value at week 52 the last available post-baseline value before week 52 is imputed.

Table R.1.2.5.14: 4 Responder analysis (displaying risk ratio) in KCCQ-CSS change from baseline at week 52 of > -15 points (stability) by baseline use of ARNi (Y/N) - RS (LOCF-AD) - 1245.121

Subgroup Description	Placebo	Empa 10mg
Baseline use of ARNi: No		
Number of patients in analysis set	1480	1523
Number of analysed patients, N (%)	1350 (100.0)	1418 (100.0)
Number of patients with endpoint, N (%)	1181 (87.5)	1256 (88.6)
95% confidence interval*	(85.6, 89.1)	(86.8, 90.1)
Comparison vs Placebo**		
Risk ratio (SE)		1.013 (0.014)
95% confidence interval***		(0.986, 1.041)
p-value		0.3544
Baseline use of ARNi: Yes		
Number of patients in analysis set	387	340
Number of analysed patients, N (%)	359 (100.0)	322 (100.0)
Number of patients with endpoint, N (%)	324 (90.3)	292 (90.7)
95% confidence interval*	(86.7, 92.9)	(87.0, 93.4)
Comparison vs Placebo**		
Risk ratio (SE)		1.003 (0.025)
95% confidence interval***		(0.956, 1.053)
p-value		0.9026

* Wilson confidence intervals.
** Log-linked Poisson model with robust estimate of variance includes terms for baseline KCCQ - clinical summary score (p<0.0001), age (p=0.3530), baseline eGFR (CKD-EPI) (p=0.0041), Treatment (p=0.5738), region (5 cat.) (p=0.0031), baseline diabetes status (3 cat.) (p=0.8722), sex (p=0.7171), baseline LVEF (3 cat.) (p=0.9035), baseline use of ARNi (p=0.0511) and Treatment by baseline use of ARNi interaction (p=0.7273).
***Wald confidence intervals.

Data taken from study 1245.121 only.
LOCF: For a missing value at week 52 the last available post-baseline value before week 52 is imputed.

Table R.1.2.5.14: 5 Responder analysis (displaying odds ratio) in KCCQ-CSS change from baseline at week 52 of >= 15 points (improvement) by baseline use of ARNi (Y/N) - RS (LOCF-AD) - 1245.121

Subgroup Description	Placebo	Empa 10mg
Baseline use of ARNi: No		
Number of patients in analysis set	1480	1523
Number of analysed patients, N (%)	1350 (100.0)	1418 (100.0)
Number of patients with endpoint, N (%)	284 (21.0)	355 (25.0)
95% confidence interval*	(18.9, 23.3)	(22.8, 27.4)
Comparison vs Placebo**		
Odds ratio (SE)		1.303 (0.136)
95% confidence interval***		(1.063, 1.598)
p-value		0.0109
Baseline use of ARNi: Yes		
Number of patients in analysis set	387	340
Number of analysed patients, N (%)	359 (100.0)	322 (100.0)
Number of patients with endpoint, N (%)	73 (20.3)	69 (21.4)
95% confidence interval*	(16.5, 24.8)	(17.3, 26.2)
Comparison vs Placebo**		
Odds ratio (SE)		1.151 (0.252)
95% confidence interval***		(0.749, 1.769)
p-value		0.5211

* Wilson confidence intervals.
** Logistic regression includes terms for baseline KCCQ - clinical summary score (p<0.0001), age (p=0.0716), baseline eGFR (CKD-EPI) (p=0.1924), Treatment (p=0.0945), region (5 cat.) (p<0.0001), baseline diabetes status (3 cat.) (p=0.9539), sex (p=0.4498), baseline LVEF (3 cat.) (p=0.3899), baseline use of ARNi (p=0.7105) and Treatment by baseline use of ARNi interaction (p=0.6095).
***Wald confidence intervals.

Data taken from study 1245.121 only.
LOCF: For a missing value at week 52 the last available post-baseline value before week 52 is imputed.

Table R.1.2.5.14: 6 Responder analysis (displaying risk ratio) in KCCQ-CSS change from baseline at week 52 of >= 15 points (improvement) by baseline use of ARNi (Y/N) - RS (LOCF-AD) - 1245.121

Subgroup Description	Placebo	Empa 10mg
Baseline use of ARNi: No		
Number of patients in analysis set	1480	1523
Number of analysed patients, N (%)	1350 (100.0)	1418 (100.0)
Number of patients with endpoint, N (%)	284 (21.0)	355 (25.0)
95% confidence interval*	(18.9, 23.3)	(22.8, 27.4)
Comparison vs Placebo**		
Risk ratio (SE)		1.154 (0.075)
95% confidence interval***		(1.016, 1.311)
p-value		0.0277
Baseline use of ARNi: Yes		
Number of patients in analysis set	387	340
Number of analysed patients, N (%)	359 (100.0)	322 (100.0)
Number of patients with endpoint, N (%)	73 (20.3)	69 (21.4)
95% confidence interval*	(16.5, 24.8)	(17.3, 26.2)
Comparison vs Placebo**		
Risk ratio (SE)		1.093 (0.149)
95% confidence interval***		(0.838, 1.427)
p-value		0.5119

* Wilson confidence intervals.
** Log-linked Poisson model with robust estimate of variance includes terms for baseline KCCQ - clinical summary score (p<0.0001), age (p=0.1298), baseline eGFR (CKD-EPI) (p=0.2414), Treatment (p=0.1234), region (5 cat.) (p<0.0001), baseline diabetes status (3 cat.) (p=0.8978), sex (p=0.3061), baseline LVEF (3 cat.) (p=0.2724), baseline use of ARNi (p=0.5615) and Treatment by baseline use of ARNi interaction (p=0.7199).
***Wald confidence intervals.

Data taken from study 1245.121 only.
LOCF: For a missing value at week 52 the last available post-baseline value before week 52 is imputed.

R.1.2.5.15

R.1.2.5.15 Subgroup analysis by bl. LVEF (<= 30%, >30% -<= 35% , > 35%)

Table R.1.2.5.15: 1 Responder analysis (displaying odds ratio) in KCCQ-CSS change from baseline at week 52 of <= -15 points (deterioration) by baseline LVEF (3 cat.) - RS (LOCF-AD) - 1245.121

Subgroup Description	Placebo	Empa 10mg
Baseline LVEF (3 cat.): <=30		
Number of patients in analysis set	1392	1337
Number of analysed patients, N (%)	1272 (100.0)	1245 (100.0)
Number of patients with endpoint, N (%)	154 (12.1)	132 (10.6)
95% confidence interval*	(10.4, 14.0)	(9.0, 12.4)
Comparison vs Placebo**		
Odds ratio (SE)		0.853 (0.108)
95% confidence interval***		(0.665, 1.094)
p-value		0.2100
Baseline LVEF (3 cat.): >30 to <=35		
Number of patients in analysis set	361	398
Number of analysed patients, N (%)	333 (100.0)	375 (100.0)
Number of patients with endpoint, N (%)	38 (11.4)	48 (12.8)
95% confidence interval*	(8.4, 15.3)	(9.8, 16.6)
Comparison vs Placebo**		
Odds ratio (SE)		1.155 (0.270)
95% confidence interval***		(0.731, 1.827)
p-value		0.5370

* Wilson confidence intervals.
** Logistic regression includes terms for baseline KCCQ - clinical summary score (p<0.0001), age (p=0.2249), baseline eGFR (CKD-EPI) (p=0.0036), Treatment (p=0.7388), region (5 cat.) (p=0.0480), baseline diabetes status (3 cat.) (p=0.8672), sex (p=0.7243), baseline LVEF (3 cat.) (p=0.9201) and Treatment by baseline LVEF (3 cat.) interaction (p=0.5162).
***Wald confidence intervals.

Data taken from study 1245.121 only.
LOCF: For a missing value at week 52 the last available post-baseline value before week 52 is imputed.

Table R.1.2.5.15: 1 Responder analysis (displaying odds ratio) in KCCQ-CSS change from baseline at week 52 of <= -15 points (deterioration) by baseline LVEF (3 cat.) - RS (LOCF-AD) - 1245.121

Subgroup Description	Placebo	Empa 10mg
Baseline LVEF (3 cat.): >35		
Number of patients in analysis set	114	128
Number of analysed patients, N (%)	104 (100.0)	120 (100.0)
Number of patients with endpoint, N (%)	12 (11.5)	12 (10.0)
95% confidence interval*	(6.7, 19.1)	(5.8, 16.7)
Comparison vs Placebo**		
Odds ratio (SE)		0.856 (0.374)
95% confidence interval***		(0.364, 2.014)
p-value		0.7219

* Wilson confidence intervals.
** Logistic regression includes terms for baseline KCCQ - clinical summary score (p<0.0001), age (p=0.2249), baseline eGFR (CKD-EPI) (p=0.0036), Treatment (p=0.7388), region (5 cat.) (p=0.0480), baseline diabetes status (3 cat.) (p=0.8672), sex (p=0.7243), baseline LVEF (3 cat.) (p=0.9201) and Treatment by baseline LVEF (3 cat.) interaction (p=0.5162).
***Wald confidence intervals.

Data taken from study 1245.121 only.
LOCF: For a missing value at week 52 the last available post-baseline value before week 52 is imputed.

Table R.1.2.5.15: 2 Responder analysis (displaying risk ratio) in KCCQ-CSS change from baseline at week 52 of <= -15 points (deterioration) by baseline LVEF (3 cat.) - RS (LOCF-AD) - 1245.121

Subgroup Description	Placebo	Empa 10mg
Baseline LVEF (3 cat.): <=30		
Number of patients in analysis set	1392	1337
Number of analysed patients, N (%)	1272 (100.0)	1245 (100.0)
Number of patients with endpoint, N (%)	154 (12.1)	132 (10.6)
95% confidence interval*	(10.4, 14.0)	(9.0, 12.4)
Comparison vs Placebo**		
Risk ratio (SE)		0.870 (0.096)
95% confidence interval***		(0.700, 1.081)
p-value		0.2085
Baseline LVEF (3 cat.): >30 to <=35		
Number of patients in analysis set	361	398
Number of analysed patients, N (%)	333 (100.0)	375 (100.0)
Number of patients with endpoint, N (%)	38 (11.4)	48 (12.8)
95% confidence interval*	(8.4, 15.3)	(9.8, 16.6)
Comparison vs Placebo**		
Risk ratio (SE)		1.133 (0.228)
95% confidence interval***		(0.763, 1.681)
p-value		0.5368

* Wilson confidence intervals.
** Log-linked Poisson model with robust estimate of variance includes terms for baseline KCCQ - clinical summary score (p<0.0001), age (p=0.2494), baseline eGFR (CKD-EPI) (p=0.0040), Treatment (p=0.7349), region (5 cat.) (p=0.0599), baseline diabetes status (3 cat.) (p=0.8696), sex (p=0.7217), baseline LVEF (3 cat.) (p=0.9190) and Treatment by baseline LVEF (3 cat.) interaction (p=0.5122).
***Wald confidence intervals.

Data taken from study 1245.121 only.
LOCF: For a missing value at week 52 the last available post-baseline value before week 52 is imputed.

Table R.1.2.5.15: 2 Responder analysis (displaying risk ratio) in KCCQ-CSS change from baseline at week 52 of <= -15 points (deterioration) by baseline LVEF (3 cat.) - RS (LOCF-AD) - 1245.121

Subgroup Description	Placebo	Empa 10mg
Baseline LVEF (3 cat.): >35		
Number of patients in analysis set	114	128
Number of analysed patients, N (%)	104 (100.0)	120 (100.0)
Number of patients with endpoint, N (%)	12 (11.5)	12 (10.0)
95% confidence interval*	(6.7, 19.1)	(5.8, 16.7)
Comparison vs Placebo**		
Risk ratio (SE)		0.872 (0.334)
95% confidence interval***		(0.412, 1.847)
p-value		0.7210

* Wilson confidence intervals.
** Log-linked Poisson model with robust estimate of variance includes terms for baseline KCCQ - clinical summary score (p<0.0001), age (p=0.2494), baseline eGFR (CKD-EPI) (p=0.0040), Treatment (p=0.7349), region (5 cat.) (p=0.0599), baseline diabetes status (3 cat.) (p=0.8696), sex (p=0.7217), baseline LVEF (3 cat.) (p=0.9190) and Treatment by baseline LVEF (3 cat.) interaction (p=0.5122).
***Wald confidence intervals.

Data taken from study 1245.121 only.
LOCF: For a missing value at week 52 the last available post-baseline value before week 52 is imputed.

Table R.1.2.5.15: 3 Responder analysis (displaying odds ratio) in KCCQ-CSS change from baseline at week 52 of > -15 points (stability) by baseline LVEF (3 cat.) - RS (LOCF-AD) - 1245.121

Subgroup Description	Placebo	Empa 10mg
Baseline LVEF (3 cat.): <=30		
Number of patients in analysis set	1392	1337
Number of analysed patients, N (%)	1272 (100.0)	1245 (100.0)
Number of patients with endpoint, N (%)	1118 (87.9)	1113 (89.4)
95% confidence interval*	(86.0, 89.6)	(87.6, 91.0)
Comparison vs Placebo**		
Odds ratio (SE)		1.173 (0.149)
95% confidence interval***		(0.914, 1.504)
p-value		0.2100
Baseline LVEF (3 cat.): >30 to <=35		
Number of patients in analysis set	361	398
Number of analysed patients, N (%)	333 (100.0)	375 (100.0)
Number of patients with endpoint, N (%)	295 (88.6)	327 (87.2)
95% confidence interval*	(84.7, 91.6)	(83.4, 90.2)
Comparison vs Placebo**		
Odds ratio (SE)		0.866 (0.202)
95% confidence interval***		(0.547, 1.369)
p-value		0.5370

* Wilson confidence intervals.
** Logistic regression includes terms for baseline KCCQ - clinical summary score (p<0.0001), age (p=0.2249), baseline eGFR (CKD-EPI) (p=0.0036), Treatment (p=0.7388), region (5 cat.) (p=0.0480), baseline diabetes status (3 cat.) (p=0.8672), sex (p=0.7243), baseline LVEF (3 cat.) (p=0.9201) and Treatment by baseline LVEF (3 cat.) interaction (p=0.5162).
***Wald confidence intervals.

Data taken from study 1245.121 only.
LOCF: For a missing value at week 52 the last available post-baseline value before week 52 is imputed.

Table R.1.2.5.15: 3 Responder analysis (displaying odds ratio) in KCCQ-CSS change from baseline at week 52 of > -15 points (stability) by baseline LVEF (3 cat.) - RS (LOCF-AD) - 1245.121

Subgroup Description	Placebo	Empa 10mg
Baseline LVEF (3 cat.): >35		
Number of patients in analysis set	114	128
Number of analysed patients, N (%)	104 (100.0)	120 (100.0)
Number of patients with endpoint, N (%)	92 (88.5)	108 (90.0)
95% confidence interval*	(80.9, 93.3)	(83.3, 94.2)
Comparison vs Placebo**		
Odds ratio (SE)		1.168 (0.510)
95% confidence interval***		(0.497, 2.748)
p-value		0.7219

* Wilson confidence intervals.
** Logistic regression includes terms for baseline KCCQ - clinical summary score (p<0.0001), age (p=0.2249), baseline eGFR (CKD-EPI) (p=0.0036), Treatment (p=0.7388), region (5 cat.) (p=0.0480), baseline diabetes status (3 cat.) (p=0.8672), sex (p=0.7243), baseline LVEF (3 cat.) (p=0.9201) and Treatment by baseline LVEF (3 cat.) interaction (p=0.5162).
***Wald confidence intervals.

Data taken from study 1245.121 only.
LOCF: For a missing value at week 52 the last available post-baseline value before week 52 is imputed.

Table R.1.2.5.15: 4 Responder analysis (displaying risk ratio) in KCCQ-CSS change from baseline at week 52 of > -15 points (stability) by baseline LVEF (3 cat.) - RS (LOCF-AD) - 1245.121

Subgroup Description	Placebo	Empa 10mg
Baseline LVEF (3 cat.): <=30		
Number of patients in analysis set	1392	1337
Number of analysed patients, N (%)	1272 (100.0)	1245 (100.0)
Number of patients with endpoint, N (%)	1118 (87.9)	1113 (89.4)
95% confidence interval*	(86.0, 89.6)	(87.6, 91.0)
Comparison vs Placebo**		
Risk ratio (SE)		1.018 (0.014)
95% confidence interval***		(0.990, 1.046)
p-value		0.2109
Baseline LVEF (3 cat.): >30 to <=35		
Number of patients in analysis set	361	398
Number of analysed patients, N (%)	333 (100.0)	375 (100.0)
Number of patients with endpoint, N (%)	295 (88.6)	327 (87.2)
95% confidence interval*	(84.7, 91.6)	(83.4, 90.2)
Comparison vs Placebo**		
Risk ratio (SE)		0.982 (0.027)
95% confidence interval***		(0.930, 1.037)
p-value		0.5183

* Wilson confidence intervals.
** Log-linked Poisson model with robust estimate of variance includes terms for baseline KCCQ - clinical summary score (p<0.0001), age (p=0.3070), baseline eGFR (CKD-EPI) (p=0.0043), Treatment (p=0.7978), region (5 cat.) (p=0.0020), baseline diabetes status (3 cat.) (p=0.8616), sex (p=0.7261), baseline LVEF (3 cat.) (p=0.9352) and Treatment by baseline LVEF (3 cat.) interaction (p=0.5170).
***Wald confidence intervals.

Data taken from study 1245.121 only.
LOCF: For a missing value at week 52 the last available post-baseline value before week 52 is imputed.

Table R.1.2.5.15: 4 Responder analysis (displaying risk ratio) in KCCQ-CSS change from baseline at week 52 of > -15 points (stability) by baseline LVEF (3 cat.) - RS (LOCF-AD) - 1245.121

Subgroup Description	Placebo	Empa 10mg
Baseline LVEF (3 cat.): >35		
Number of patients in analysis set	114	128
Number of analysed patients, N (%)	104 (100.0)	120 (100.0)
Number of patients with endpoint, N (%)	92 (88.5)	108 (90.0)
95% confidence interval*	(80.9, 93.3)	(83.3, 94.2)
Comparison vs Placebo**		
Risk ratio (SE)		1.015 (0.047)
95% confidence interval***		(0.927, 1.111)
p-value		0.7542

* Wilson confidence intervals.
** Log-linked Poisson model with robust estimate of variance includes terms for baseline KCCQ - clinical summary score (p<0.0001), age (p=0.3070), baseline eGFR (CKD-EPI) (p=0.0043), Treatment (p=0.7978), region (5 cat.) (p=0.0020), baseline diabetes status (3 cat.) (p=0.8616), sex (p=0.7261), baseline LVEF (3 cat.) (p=0.9352) and Treatment by baseline LVEF (3 cat.) interaction (p=0.5170).
***Wald confidence intervals.

Data taken from study 1245.121 only.
LOCF: For a missing value at week 52 the last available post-baseline value before week 52 is imputed.

Table R.1.2.5.15: 5 Responder analysis (displaying odds ratio) in KCCQ-CSS change from baseline at week 52 of >= 15 points (improvement) by baseline LVEF (3 cat.) - RS (LOCF-AD) - 1245.121

Subgroup Description	Placebo	Empa 10mg
Baseline LVEF (3 cat.): <=30		
Number of patients in analysis set	1392	1337
Number of analysed patients, N (%)	1272 (100.0)	1245 (100.0)
Number of patients with endpoint, N (%)	272 (21.4)	315 (25.3)
95% confidence interval*	(19.2, 23.7)	(23.0, 27.8)
Comparison vs Placebo**		
Odds ratio (SE)		1.310 (0.142)
95% confidence interval***		(1.059, 1.621)
p-value		0.0128
Baseline LVEF (3 cat.): >30 to <=35		
Number of patients in analysis set	361	398
Number of analysed patients, N (%)	333 (100.0)	375 (100.0)
Number of patients with endpoint, N (%)	69 (20.7)	81 (21.6)
95% confidence interval*	(16.7, 25.4)	(17.7, 26.0)
Comparison vs Placebo**		
Odds ratio (SE)		1.028 (0.216)
95% confidence interval***		(0.680, 1.553)
p-value		0.8961

* Wilson confidence intervals.
** Logistic regression includes terms for baseline KCCQ - clinical summary score (p<0.0001), age (p=0.0693), baseline eGFR (CKD-EPI) (p=0.1965), Treatment (p=0.0435), region (5 cat.) (p<0.0001), baseline diabetes status (3 cat.) (p=0.9526), sex (p=0.4900), baseline LVEF (3 cat.) (p=0.3590) and Treatment by baseline LVEF (3 cat.) interaction (p=0.3503).
***Wald confidence intervals.

Data taken from study 1245.121 only.
LOCF: For a missing value at week 52 the last available post-baseline value before week 52 is imputed.

Table R.1.2.5.15: 5 Responder analysis (displaying odds ratio) in KCCQ-CSS change from baseline at week 52 of >= 15 points (improvement) by baseline LVEF (3 cat.) - RS (LOCF-AD) - 1245.121

Subgroup Description	Placebo	Empa 10mg
Baseline LVEF (3 cat.): >35		
Number of patients in analysis set	114	128
Number of analysed patients, N (%)	104 (100.0)	120 (100.0)
Number of patients with endpoint, N (%)	16 (15.4)	28 (23.3)
95% confidence interval*	(9.7, 23.5)	(16.7, 31.7)
Comparison vs Placebo**		
Odds ratio (SE)		1.899 (0.761)
95% confidence interval***		(0.866, 4.164)
p-value		0.1093

* Wilson confidence intervals.
** Logistic regression includes terms for baseline KCCQ - clinical summary score (p<0.0001), age (p=0.0693), baseline eGFR (CKD-EPI) (p=0.1965), Treatment (p=0.0435), region (5 cat.) (p<0.0001), baseline diabetes status (3 cat.) (p=0.9526), sex (p=0.4900), baseline LVEF (3 cat.) (p=0.3590) and Treatment by baseline LVEF (3 cat.) interaction (p=0.3503).
***Wald confidence intervals.

Data taken from study 1245.121 only.
LOCF: For a missing value at week 52 the last available post-baseline value before week 52 is imputed.

Table R.1.2.5.15: 6 Responder analysis (displaying risk ratio) in KCCQ-CSS change from baseline at week 52 of >= 15 points (improvement) by baseline LVEF (3 cat.) - RS (LOCF-AD) - 1245.121

Subgroup Description	Placebo	Empa 10mg
Baseline LVEF (3 cat.): <=30		
Number of patients in analysis set	1392	1337
Number of analysed patients, N (%)	1272 (100.0)	1245 (100.0)
Number of patients with endpoint, N (%)	272 (21.4)	315 (25.3)
95% confidence interval*	(19.2, 23.7)	(23.0, 27.8)
Comparison vs Placebo**		
Risk ratio (SE)		1.175 (0.079)
95% confidence interval***		(1.029, 1.341)
p-value		0.0173
Baseline LVEF (3 cat.): >30 to <=35		
Number of patients in analysis set	361	398
Number of analysed patients, N (%)	333 (100.0)	375 (100.0)
Number of patients with endpoint, N (%)	69 (20.7)	81 (21.6)
95% confidence interval*	(16.7, 25.4)	(17.7, 26.0)
Comparison vs Placebo**		
Risk ratio (SE)		0.977 (0.128)
95% confidence interval***		(0.756, 1.263)
p-value		0.8595

* Wilson confidence intervals.
** Log-linked Poisson model with robust estimate of variance includes terms for baseline KCCQ - clinical summary score (p<0.0001), age (p=0.1252), baseline eGFR (CKD-EPI) (p=0.2507), Treatment (p=0.1292), region (5 cat.) (p<0.0001), baseline diabetes status (3 cat.) (p=0.9018), sex (p=0.3469), baseline LVEF (3 cat.) (p=0.2762) and Treatment by baseline LVEF (3 cat.) interaction (p=0.3482).
***Wald confidence intervals.

Data taken from study 1245.121 only.
LOCF: For a missing value at week 52 the last available post-baseline value before week 52 is imputed.

Table R.1.2.5.15: 6 Responder analysis (displaying risk ratio) in KCCQ-CSS change from baseline at week 52 of >= 15 points (improvement) by baseline LVEF (3 cat.) - RS (LOCF-AD) - 1245.121

Subgroup Description	Placebo	Empa 10mg
Baseline LVEF (3 cat.): >35		
Number of patients in analysis set	114	128
Number of analysed patients, N (%)	104 (100.0)	120 (100.0)
Number of patients with endpoint, N (%)	16 (15.4)	28 (23.3)
95% confidence interval*	(9.7, 23.5)	(16.7, 31.7)
Comparison vs Placebo**		
Risk ratio (SE)		1.377 (0.362)
95% confidence interval***		(0.823, 2.304)
p-value		0.2232

* Wilson confidence intervals.
** Log-linked Poisson model with robust estimate of variance includes terms for baseline KCCQ - clinical summary score (p<0.0001), age (p=0.1252), baseline eGFR (CKD-EPI) (p=0.2507), Treatment (p=0.1292), region (5 cat.) (p<0.0001), baseline diabetes status (3 cat.) (p=0.9018), sex (p=0.3469), baseline LVEF (3 cat.) (p=0.2762) and Treatment by baseline LVEF (3 cat.) interaction (p=0.3482).
***Wald confidence intervals.

Data taken from study 1245.121 only.
LOCF: For a missing value at week 52 the last available post-baseline value before week 52 is imputed.

R.1.2.5.16 Subgroup analysis by bl. NTproBNP </>= median (median based on total patients)

Table R.1.2.5.16: 1 Responder analysis (displaying odds ratio) in KCCQ-CSS change from baseline at week 52 of <= -15 points (deterioration) by bl. NTproBNP (<median, >= median) (median based on total patients) - RS (LOCF-AD) - 1245.121

Subgroup Description	Placebo	Empa 10mg
Baseline NTproBNP (<median, >= median): < median		
Number of patients in analysis set	920	942
Number of analysed patients, N (%)	866 (100.0)	886 (100.0)
Number of patients with endpoint, N (%)	88 (10.2)	76 (8.6)
95% confidence interval*	(8.3, 12.4)	(6.9, 10.6)
Comparison vs Placebo**		
Odds ratio (SE)		0.823 (0.136)
95% confidence interval***		(0.595, 1.139)
p-value		0.2411
Baseline NTproBNP (<median, >= median): >= median		
Number of patients in analysis set	946	920
Number of analysed patients, N (%)	843 (100.0)	854 (100.0)
Number of patients with endpoint, N (%)	116 (13.8)	116 (13.6)
95% confidence interval*	(11.6, 16.3)	(11.4, 16.0)
Comparison vs Placebo**		
Odds ratio (SE)		0.985 (0.141)
95% confidence interval***		(0.745, 1.304)
p-value		0.9178

* Wilson confidence intervals.
** Logistic regression includes terms for baseline KCCQ - clinical summary score (p<0.0001), age (p=0.2751), baseline eGFR (CKD-EPI) (p=0.0386), Treatment (p=0.3395), region (5 cat.) (p=0.0260), baseline diabetes status (3 cat.) (p=0.8666), sex (p=0.6692), baseline LVEF (3 cat.) (p=0.7428), baseline NTproBNP (<median, >= median) (p<0.0001) and Treatment by baseline NTproBNP (<median, >= median) interaction (p=0.4121).
***Wald confidence intervals.
2 patients were excluded as the subgroup variable was missing.

Data taken from study 1245.121 only.
LOCF: For a missing value at week 52 the last available post-baseline value before week 52 is imputed.
Median: 1910 [pg/mL]

Table R.1.2.5.16: 2 Responder analysis (displaying risk ratio) in KCCQ-CSS change from baseline at week 52 of <= -15 points (deterioration) by bl. NTproBNP (<median, >= median) (median based on total patients) - RS (LOCF-AD) - 1245.121

Subgroup Description	Placebo	Empa 10mg
Baseline NTproBNP (<median, >= median): < median		
Number of patients in analysis set	920	942
Number of analysed patients, N (%)	866 (100.0)	886 (100.0)
Number of patients with endpoint, N (%)	88 (10.2)	76 (8.6)
95% confidence interval*	(8.3, 12.4)	(6.9, 10.6)
Comparison vs Placebo**		
Risk ratio (SE)		0.841 (0.124)
95% confidence interval***		(0.629, 1.123)
p-value		0.2407
Baseline NTproBNP (<median, >= median): >= median		
Number of patients in analysis set	946	920
Number of analysed patients, N (%)	843 (100.0)	854 (100.0)
Number of patients with endpoint, N (%)	116 (13.8)	116 (13.6)
95% confidence interval*	(11.6, 16.3)	(11.4, 16.0)
Comparison vs Placebo**		
Risk ratio (SE)		0.987 (0.119)
95% confidence interval***		(0.779, 1.250)
p-value		0.9109

* Wilson confidence intervals.
** Log-linked Poisson model with robust estimate of variance includes terms for baseline KCCQ - clinical summary score (p<0.0001), age (p=0.3033), baseline eGFR (CKD-EPI) (p=0.0390), Treatment (p=0.3271), region (5 cat.) (p=0.0336), baseline diabetes status (3 cat.) (p=0.8726), sex (p=0.6684), baseline LVEF (3 cat.) (p=0.7410), baseline NTproBNP (<median, >= median) (p<0.0001) and Treatment by baseline NTproBNP (<median, >= median) interaction (p=0.4023).
***Wald confidence intervals.
2 patients were excluded as the subgroup variable was missing.

Data taken from study 1245.121 only.
LOCF: For a missing value at week 52 the last available post-baseline value before week 52 is imputed.
Median: 1910 [pg/mL]

Table R.1.2.5.16: 3 Responder analysis (displaying odds ratio) in KCCQ-CSS change from baseline at week 52 of > -15 points (stability) by bl. NTproBNP (<median, >= median) (median based on total patients) - RS (LOCF-AD) - 1245.121

Subgroup Description	Placebo	Empa 10mg
Baseline NTproBNP (<median, >= median): < median		
Number of patients in analysis set	920	942
Number of analysed patients, N (%)	866 (100.0)	886 (100.0)
Number of patients with endpoint, N (%)	778 (89.8)	810 (91.4)
95% confidence interval*	(87.6, 91.7)	(89.4, 93.1)
Comparison vs Placebo**		
Odds ratio (SE)		1.214 (0.201)
95% confidence interval***		(0.878, 1.680)
p-value		0.2411
Baseline NTproBNP (<median, >= median): >= median		
Number of patients in analysis set	946	920
Number of analysed patients, N (%)	843 (100.0)	854 (100.0)
Number of patients with endpoint, N (%)	727 (86.2)	738 (86.4)
95% confidence interval*	(83.7, 88.4)	(84.0, 88.6)
Comparison vs Placebo**		
Odds ratio (SE)		1.015 (0.145)
95% confidence interval***		(0.767, 1.343)
p-value		0.9178

* Wilson confidence intervals.
** Logistic regression includes terms for baseline KCCQ - clinical summary score (p<0.0001), age (p=0.2751), baseline eGFR (CKD-EPI) (p=0.0386), Treatment (p=0.3395), region (5 cat.) (p=0.0260), baseline diabetes status (3 cat.) (p=0.8666), sex (p=0.6692), baseline LVEF (3 cat.) (p=0.7428), baseline NTproBNP (<median, >= median) (p<0.0001) and Treatment by baseline NTproBNP (<median, >= median) interaction (p=0.4121).
***Wald confidence intervals.
2 patients were excluded as the subgroup variable was missing.

Data taken from study 1245.121 only.
LOCF: For a missing value at week 52 the last available post-baseline value before week 52 is imputed.
Median: 1910 [pg/mL]

Table R.1.2.5.16: 4 Responder analysis (displaying risk ratio) in KCCQ-CSS change from baseline at week 52 of > -15 points (stability) by bl. NTproBNP (<median, >= median) (median based on total patients) - RS (LOCF-AD) - 1245.121

Subgroup Description	Placebo	Empa 10mg
Baseline NTproBNP (<median, >= median): < median		
Number of patients in analysis set	920	942
Number of analysed patients, N (%)	866 (100.0)	886 (100.0)
Number of patients with endpoint, N (%)	778 (89.8)	810 (91.4)
95% confidence interval*	(87.6, 91.7)	(89.4, 93.1)
Comparison vs Placebo**		
Risk ratio (SE)		1.018 (0.016)
95% confidence interval***		(0.988, 1.049)
p-value		0.2394
Baseline NTproBNP (<median, >= median): >= median		
Number of patients in analysis set	946	920
Number of analysed patients, N (%)	843 (100.0)	854 (100.0)
Number of patients with endpoint, N (%)	727 (86.2)	738 (86.4)
95% confidence interval*	(83.7, 88.4)	(84.0, 88.6)
Comparison vs Placebo**		
Risk ratio (SE)		1.001 (0.019)
95% confidence interval***		(0.964, 1.039)
p-value		0.9543

* Wilson confidence intervals.
** Log-linked Poisson model with robust estimate of variance includes terms for baseline KCCQ - clinical summary score (p<0.0001), age (p=0.3646), baseline eGFR (CKD-EPI) (p=0.0403), Treatment (p=0.4361), region (5 cat.) (p=0.0011), baseline diabetes status (3 cat.) (p=0.8532), sex (p=0.6535), baseline LVEF (3 cat.) (p=0.7417), baseline NTproBNP (<median, >= median) (p<0.0001) and Treatment by baseline NTproBNP (<median, >= median) interaction (p=0.4906).
***Wald confidence intervals.
2 patients were excluded as the subgroup variable was missing.

Data taken from study 1245.121 only.
LOCF: For a missing value at week 52 the last available post-baseline value before week 52 is imputed.
Median: 1910 [pg/mL]

Table R.1.2.5.16: 5 Responder analysis (displaying odds ratio) in KCCQ-CSS change from baseline at week 52 of >= 15 points (improvement) by bl. NTproBNP (<median, >= median) (median based on total patients) - RS (LOCF-AD) - 1245.121

Subgroup Description	Placebo	Empa 10mg
Baseline NTproBNP (<median, >= median): < median		
Number of patients in analysis set	920	942
Number of analysed patients, N (%)	866 (100.0)	886 (100.0)
Number of patients with endpoint, N (%)	170 (19.6)	198 (22.3)
95% confidence interval*	(17.1, 22.4)	(19.7, 25.2)
Comparison vs Placebo**		
Odds ratio (SE)		1.248 (0.167)
95% confidence interval***		(0.961, 1.622)
p-value		0.0971
Baseline NTproBNP (<median, >= median): >= median		
Number of patients in analysis set	946	920
Number of analysed patients, N (%)	843 (100.0)	854 (100.0)
Number of patients with endpoint, N (%)	187 (22.2)	226 (26.5)
95% confidence interval*	(19.5, 25.1)	(23.6, 29.5)
Comparison vs Placebo**		
Odds ratio (SE)		1.301 (0.171)
95% confidence interval***		(1.005, 1.684)
p-value		0.0457

* Wilson confidence intervals.
** Logistic regression includes terms for baseline KCCQ - clinical summary score (p<0.0001), age (p=0.0741), baseline eGFR (CKD-EPI) (p=0.2239), Treatment (p=0.0098), region (5 cat.) (p<0.0001), baseline diabetes status (3 cat.) (p=0.9511), sex (p=0.4683), baseline LVEF (3 cat.) (p=0.4230), baseline NTproBNP (<median, >= median) (p=0.7687) and Treatment by baseline NTproBNP (<median, >= median) interaction (p=0.8256).
***Wald confidence intervals.
2 patients were excluded as the subgroup variable was missing.

Data taken from study 1245.121 only.
LOCF: For a missing value at week 52 the last available post-baseline value before week 52 is imputed.
Median: 1910 [pg/mL]

Table R.1.2.5.16: 6 Responder analysis (displaying risk ratio) in KCCQ-CSS change from baseline at week 52 of >= 15 points (improvement) by bl. NTproBNP (<median, >= median) (median based on total patients) - RS (LOCF-AD) - 1245.121

Subgroup Description	Placebo	Empa 10mg
Baseline NTproBNP (<median, >= median): < median		
Number of patients in analysis set	920	942
Number of analysed patients, N (%)	866 (100.0)	886 (100.0)
Number of patients with endpoint, N (%)	170 (19.6)	198 (22.3)
95% confidence interval*	(17.1, 22.4)	(19.7, 25.2)
Comparison vs Placebo**		
Risk ratio (SE)		1.125 (0.098)
95% confidence interval***		(0.949, 1.334)
p-value		0.1754
Baseline NTproBNP (<median, >= median): >= median		
Number of patients in analysis set	946	920
Number of analysed patients, N (%)	843 (100.0)	854 (100.0)
Number of patients with endpoint, N (%)	187 (22.2)	226 (26.5)
95% confidence interval*	(19.5, 25.1)	(23.6, 29.5)
Comparison vs Placebo**		
Risk ratio (SE)		1.160 (0.092)
95% confidence interval***		(0.994, 1.355)
p-value		0.0602

* Wilson confidence intervals.
** Log-linked Poisson model with robust estimate of variance includes terms for baseline KCCQ - clinical summary score (p<0.0001), age (p=0.1378), baseline eGFR (CKD-EPI) (p=0.2890), Treatment (p=0.0237), region (5 cat.) (p<0.0001), baseline diabetes status (3 cat.) (p=0.8960), sex (p=0.3325), baseline LVEF (3 cat.) (p=0.3240), baseline NTproBNP (<median, >= median) (p=0.5850) and Treatment by baseline NTproBNP (<median, >= median) interaction (p=0.7918).
***Wald confidence intervals.
2 patients were excluded as the subgroup variable was missing.

Data taken from study 1245.121 only.
LOCF: For a missing value at week 52 the last available post-baseline value before week 52 is imputed.
Median: 1910 [pg/mL]

R.1.2.6

R.1.2.6 KCCQ Total Symptom Score responder analysis (5 points)

R.1.2.6.1

Table R.1.2.6.1: 1 Responder analysis (displaying odds ratio) in KCCQ-TSS change from baseline at week 52 of <= -5 points (deterioration) - RS (LOCF-AD) - 1245.121

	Placebo	Empa 10mg
Number of patients in analysis set	1867	1863
Number of analysed patients, N (%)	1709 (100.0)	1740 (100.0)
Number of patients with endpoint, N (%)	428 (25.0)	390 (22.4)
95% confidence interval*	(23.0, 27.2)	(20.5, 24.4)
Comparison vs Placebo**		
Odds ratio (SE)		0.862 (0.070)
95% confidence interval***		(0.735, 1.012)
p-value		0.0694

* Wilson confidence intervals.
** Logistic regression includes terms for baseline KCCQ - total symptom score (p<0.0001), age (p=0.6000), baseline eGFR (CKD-EPI) (p=0.0004), Treatment (p=0.0694), region (5 cat.) (p=0.0004), baseline diabetes status (3 cat.) (p=0.4731), sex (p=0.4288) and baseline LVEF (3 cat.) (p=0.5759).
***Wald confidence intervals.

Data taken from study 1245.121 only.
LOCF: For a missing value at week 52 the last available post-baseline value before week 52 is imputed.

Table R.1.2.6.1: 2 Responder analysis (displaying risk ratio) in KCCQ-TSS change from baseline at week 52 of <= -5 points (deterioration) - RS (LOCF-AD) - 1245.121

	Placebo	Empa 10mg
Number of patients in analysis set	1867	1863
Number of analysed patients, N (%)	1709 (100.0)	1740 (100.0)
Number of patients with endpoint, N (%)	428 (25.0)	390 (22.4)
95% confidence interval*	(23.0, 27.2)	(20.5, 24.4)
Comparison vs Placebo**		
Risk ratio (SE)		0.896 (0.054)
95% confidence interval***		(0.796, 1.008)
p-value		0.0671

* Wilson confidence intervals.
** Log-linked Poisson model with robust estimate of variance includes terms for baseline KCCQ - total symptom score (p<0.0001), age (p=0.5836), baseline eGFR (CKD-EPI) (p=0.0004), Treatment (p=0.0671), region (5 cat.) (p=0.0006), baseline diabetes status (3 cat.) (p=0.4681), sex (p=0.4219) and baseline LVEF (3 cat.) (p=0.5709).
***Wald confidence intervals.

Data taken from study 1245.121 only.
LOCF: For a missing value at week 52 the last available post-baseline value before week 52 is imputed.

Table R.1.2.6.1: 3 Responder analysis (displaying odds ratio) in KCCQ-TSS change from baseline at week 52 of > -5 points (stability) - RS (LOCF-AD) - 1245.121

	Placebo	Empa 10mg
Number of patients in analysis set	1867	1863
Number of analysed patients, N (%)	1709 (100.0)	1740 (100.0)
Number of patients with endpoint, N (%)	1281 (75.0)	1350 (77.6)
95% confidence interval*	(72.8, 77.0)	(75.6, 79.5)
Comparison vs Placebo**		
Odds ratio (SE)		1.160 (0.095)
95% confidence interval***		(0.988, 1.361)
p-value		0.0694

* Wilson confidence intervals.
** Logistic regression includes terms for baseline KCCQ - total symptom score (p<0.0001), age (p=0.6000), baseline eGFR (CKD-EPI) (p=0.0004), Treatment (p=0.0694), region (5 cat.) (p=0.0004), baseline diabetes status (3 cat.) (p=0.4731), sex (p=0.4288) and baseline LVEF (3 cat.) (p=0.5759).
***Wald confidence intervals.

Data taken from study 1245.121 only.
LOCF: For a missing value at week 52 the last available post-baseline value before week 52 is imputed.

Table R.1.2.6.1: 4 Responder analysis (displaying risk ratio) in KCCQ-TSS change from baseline at week 52 of > -5 points (stability) - RS (LOCF-AD) - 1245.121

	Placebo	Empa 10mg
Number of patients in analysis set	1867	1863
Number of analysed patients, N (%)	1709 (100.0)	1740 (100.0)
Number of patients with endpoint, N (%)	1281 (75.0)	1350 (77.6)
95% confidence interval*	(72.8, 77.0)	(75.6, 79.5)
Comparison vs Placebo**		
Risk ratio (SE)		1.033 (0.019)
95% confidence interval***		(0.996, 1.072)
p-value		0.0816

* Wilson confidence intervals.
** Log-linked Poisson model with robust estimate of variance includes terms for baseline KCCQ - total symptom score (p<0.0001), age (p=0.7120), baseline eGFR (CKD-EPI) (p=0.0004), Treatment (p=0.0816), region (5 cat.) (p<0.0001), baseline diabetes status (3 cat.) (p=0.5171), sex (p=0.4445) and baseline LVEF (3 cat.) (p=0.5957).
***Wald confidence intervals.

Data taken from study 1245.121 only.
LOCF: For a missing value at week 52 the last available post-baseline value before week 52 is imputed.

Table R.1.2.6.1: 5 Responder analysis (displaying odds ratio) in KCCQ-TSS change from baseline at week 52 of >= 5 points (improvement) - RS (LOCF-AD) - 1245.121

	Placebo	Empa 10mg
Number of patients in analysis set	1867	1863
Number of analysed patients, N (%)	1709 (100.0)	1740 (100.0)
Number of patients with endpoint, N (%)	751 (43.9)	812 (46.7)
95% confidence interval*	(41.6, 46.3)	(44.3, 49.0)
Comparison vs Placebo**		
Odds ratio (SE)		1.146 (0.090)
95% confidence interval***		(0.982, 1.337)
p-value		0.0835

* Wilson confidence intervals.
** Logistic regression includes terms for baseline KCCQ - total symptom score (p<0.0001), age (p=0.5127), baseline eGFR (CKD-EPI) (p=0.2142), Treatment (p=0.0835), region (5 cat.) (p<0.0001), baseline diabetes status (3 cat.) (p=0.9569), sex (p=0.5100) and baseline LVEF (3 cat.) (p=0.5027).
***Wald confidence intervals.

Data taken from study 1245.121 only.
LOCF: For a missing value at week 52 the last available post-baseline value before week 52 is imputed.

Table R.1.2.6.1: 6 Responder analysis (displaying risk ratio) in KCCQ-TSS change from baseline at week 52 of >= 5 points (improvement) - RS (LOCF-AD) - 1245.121

	Placebo	Empa 10mg
Number of patients in analysis set	1867	1863
Number of analysed patients, N (%)	1709 (100.0)	1740 (100.0)
Number of patients with endpoint, N (%)	751 (43.9)	812 (46.7)
95% confidence interval*	(41.6, 46.3)	(44.3, 49.0)
Comparison vs Placebo**		
Risk ratio (SE)		1.043 (0.036)
95% confidence interval***		(0.975, 1.116)
p-value		0.2169

* Wilson confidence intervals.
** Log-linked Poisson model with robust estimate of variance includes terms for baseline KCCQ - total symptom score (p<0.0001), age (p=0.7709), baseline eGFR (CKD-EPI) (p=0.1433), Treatment (p=0.2169), region (5 cat.) (p<0.0001), baseline diabetes status (3 cat.) (p=0.8735), sex (p=0.3684) and baseline LVEF (3 cat.) (p=0.5067).
***Wald confidence intervals.

Data taken from study 1245.121 only.
LOCF: For a missing value at week 52 the last available post-baseline value before week 52 is imputed.

R.1.2.6.2

R.1.2.6.2 Subgroup analysis by sex

Table R.1.2.6.2: 1 Responder analysis (displaying odds ratio) in KCCQ-TSS change from baseline at week 52 of <= -5 points (deterioration) by sex - RS (LOCF-AD) - 1245.121

Subgroup Description	Placebo	Empa 10mg
Sex: Male		
Number of patients in analysis set	1411	1426
Number of analysed patients, N (%)	1297 (100.0)	1332 (100.0)
Number of patients with endpoint, N (%)	334 (25.8)	293 (22.0)
95% confidence interval*	(23.4, 28.2)	(19.9, 24.3)
Comparison vs Placebo**		
Odds ratio (SE)		0.810 (0.076)
95% confidence interval***		(0.675, 0.973)
p-value		0.0244
Sex: Female		
Number of patients in analysis set	456	437
Number of analysed patients, N (%)	412 (100.0)	408 (100.0)
Number of patients with endpoint, N (%)	94 (22.8)	97 (23.8)
95% confidence interval*	(19.0, 27.1)	(19.9, 28.1)
Comparison vs Placebo**		
Odds ratio (SE)		1.055 (0.178)
95% confidence interval***		(0.758, 1.468)
p-value		0.7503

* Wilson confidence intervals.
** Logistic regression includes terms for baseline KCCQ - total symptom score (p<0.0001), age (p=0.5763), baseline eGFR (CKD-EPI) (p=0.0004), Treatment (p=0.4166), region (5 cat.) (p=0.0005), baseline diabetes status (3 cat.) (p=0.4771), baseline LVEF (3 cat.) (p=0.5786), sex (p=0.4162) and Treatment by sex interaction (p=0.1712).
***Wald confidence intervals.

Data taken from study 1245.121 only.
LOCF: For a missing value at week 52 the last available post-baseline value before week 52 is imputed.

Table R.1.2.6.2: 2 Responder analysis (displaying risk ratio) in KCCQ-TSS change from baseline at week 52 of <= -5 points (deterioration) by sex - RS (LOCF-AD) - 1245.121

Subgroup Description	Placebo	Empa 10mg
Sex: Male		
Number of patients in analysis set	1411	1426
Number of analysed patients, N (%)	1297 (100.0)	1332 (100.0)
Number of patients with endpoint, N (%)	334 (25.8)	293 (22.0)
95% confidence interval*	(23.4, 28.2)	(19.9, 24.3)
Comparison vs Placebo**		
Risk ratio (SE)		0.857 (0.059)
95% confidence interval***		(0.748, 0.981)
p-value		0.0250
Sex: Female		
Number of patients in analysis set	456	437
Number of analysed patients, N (%)	412 (100.0)	408 (100.0)
Number of patients with endpoint, N (%)	94 (22.8)	97 (23.8)
95% confidence interval*	(19.0, 27.1)	(19.9, 28.1)
Comparison vs Placebo**		
Risk ratio (SE)		1.036 (0.128)
95% confidence interval***		(0.814, 1.320)
p-value		0.7715

* Wilson confidence intervals.
** Log-linked Poisson model with robust estimate of variance includes terms for baseline KCCQ - total symptom score (p<0.0001), age (p=0.5594), baseline eGFR (CKD-EPI) (p=0.0003), Treatment (p=0.4003), region (5 cat.) (p=0.0006), baseline diabetes status (3 cat.) (p=0.4731), baseline LVEF (3 cat.) (p=0.5734), sex (p=0.4047) and Treatment by sex interaction (p=0.1786).
***Wald confidence intervals.

Data taken from study 1245.121 only.
LOCF: For a missing value at week 52 the last available post-baseline value before week 52 is imputed.

Table R.1.2.6.2: 3 Responder analysis (displaying odds ratio) in KCCQ-TSS change from baseline at week 52 of > -5 points (stability) by sex - RS (LOCF-AD) - 1245.121

Subgroup Description	Placebo	Empa 10mg
Sex: Male		
Number of patients in analysis set	1411	1426
Number of analysed patients, N (%)	1297 (100.0)	1332 (100.0)
Number of patients with endpoint, N (%)	963 (74.2)	1039 (78.0)
95% confidence interval*	(71.8, 76.6)	(75.7, 80.1)
Comparison vs Placebo**		
Odds ratio (SE)		1.234 (0.115)
95% confidence interval***		(1.027, 1.482)
p-value		0.0244
Sex: Female		
Number of patients in analysis set	456	437
Number of analysed patients, N (%)	412 (100.0)	408 (100.0)
Number of patients with endpoint, N (%)	318 (77.2)	311 (76.2)
95% confidence interval*	(72.9, 81.0)	(71.9, 80.1)
Comparison vs Placebo**		
Odds ratio (SE)		0.948 (0.160)
95% confidence interval***		(0.681, 1.319)
p-value		0.7503

* Wilson confidence intervals.
** Logistic regression includes terms for baseline KCCQ - total symptom score (p<0.0001), age (p=0.5763), baseline eGFR (CKD-EPI) (p=0.0004), Treatment (p=0.4166), region (5 cat.) (p=0.0005), baseline diabetes status (3 cat.) (p=0.4771), baseline LVEF (3 cat.) (p=0.5786), sex (p=0.4162) and Treatment by sex interaction (p=0.1712).
***Wald confidence intervals.

Data taken from study 1245.121 only.
LOCF: For a missing value at week 52 the last available post-baseline value before week 52 is imputed.

Table R.1.2.6.2: 4 Responder analysis (displaying risk ratio) in KCCQ-TSS change from baseline at week 52 of > -5 points (stability) by sex - RS (LOCF-AD) - 1245.121

Subgroup Description	Placebo	Empa 10mg
Sex: Male		
Number of patients in analysis set	1411	1426
Number of analysed patients, N (%)	1297 (100.0)	1332 (100.0)
Number of patients with endpoint, N (%)	963 (74.2)	1039 (78.0)
95% confidence interval*	(71.8, 76.6)	(75.7, 80.1)
Comparison vs Placebo**		
Risk ratio (SE)		1.049 (0.023)
95% confidence interval***		(1.005, 1.094)
p-value		0.0281
Sex: Female		
Number of patients in analysis set	456	437
Number of analysed patients, N (%)	412 (100.0)	408 (100.0)
Number of patients with endpoint, N (%)	318 (77.2)	311 (76.2)
95% confidence interval*	(72.9, 81.0)	(71.9, 80.1)
Comparison vs Placebo**		
Risk ratio (SE)		0.986 (0.037)
95% confidence interval***		(0.915, 1.061)
p-value		0.6989

* Wilson confidence intervals.
** Log-linked Poisson model with robust estimate of variance includes terms for baseline KCCQ - total symptom score (p<0.0001), age (p=0.6929), baseline eGFR (CKD-EPI) (p=0.0003), Treatment (p=0.4479), region (5 cat.) (p<0.0001), baseline diabetes status (3 cat.) (p=0.5217), baseline LVEF (3 cat.) (p=0.6046), sex (p=0.4555) and Treatment by sex interaction (p=0.1532).
***Wald confidence intervals.

Data taken from study 1245.121 only.
LOCF: For a missing value at week 52 the last available post-baseline value before week 52 is imputed.

Table R.1.2.6.2: 5 Responder analysis (displaying odds ratio) in KCCQ-TSS change from baseline at week 52 of >= 5 points (improvement) by sex - RS (LOCF-AD) - 1245.121

Subgroup Description	Placebo	Empa 10mg
Sex: Male		
Number of patients in analysis set	1411	1426
Number of analysed patients, N (%)	1297 (100.0)	1332 (100.0)
Number of patients with endpoint, N (%)	539 (41.6)	598 (44.9)
95% confidence interval*	(38.9, 44.3)	(42.2, 47.6)
Comparison vs Placebo**		
Odds ratio (SE)		1.170 (0.105)
95% confidence interval***		(0.981, 1.396)
p-value		0.0815
Sex: Female		
Number of patients in analysis set	456	437
Number of analysed patients, N (%)	412 (100.0)	408 (100.0)
Number of patients with endpoint, N (%)	212 (51.5)	214 (52.5)
95% confidence interval*	(46.6, 56.2)	(47.6, 57.3)
Comparison vs Placebo**		
Odds ratio (SE)		1.072 (0.174)
95% confidence interval***		(0.780, 1.474)
p-value		0.6690

* Wilson confidence intervals.
** Logistic regression includes terms for baseline KCCQ - total symptom score (p<0.0001), age (p=0.5077), baseline eGFR (CKD-EPI) (p=0.2101), Treatment (p=0.2227), region (5 cat.) (p<0.0001), baseline diabetes status (3 cat.) (p=0.9587), baseline LVEF (3 cat.) (p=0.5037), sex (p=0.5116) and Treatment by sex interaction (p=0.6374).
***Wald confidence intervals.

Data taken from study 1245.121 only.
LOCF: For a missing value at week 52 the last available post-baseline value before week 52 is imputed.

Table R.1.2.6.2: 6 Responder analysis (displaying risk ratio) in KCCQ-TSS change from baseline at week 52 of >= 5 points (improvement) by sex - RS (LOCF-AD) - 1245.121

Subgroup Description	Placebo	Empa 10mg
Sex: Male		
Number of patients in analysis set	1411	1426
Number of analysed patients, N (%)	1297 (100.0)	1332 (100.0)
Number of patients with endpoint, N (%)	539 (41.6)	598 (44.9)
95% confidence interval*	(38.9, 44.3)	(42.2, 47.6)
Comparison vs Placebo**		
Risk ratio (SE)		1.049 (0.043)
95% confidence interval***		(0.968, 1.137)
p-value		0.2449
Sex: Female		
Number of patients in analysis set	456	437
Number of analysed patients, N (%)	412 (100.0)	408 (100.0)
Number of patients with endpoint, N (%)	212 (51.5)	214 (52.5)
95% confidence interval*	(46.6, 56.2)	(47.6, 57.3)
Comparison vs Placebo**		
Risk ratio (SE)		1.029 (0.064)
95% confidence interval***		(0.910, 1.163)
p-value		0.6499

* Wilson confidence intervals.
** Log-linked Poisson model with robust estimate of variance includes terms for baseline KCCQ - total symptom score (p<0.0001), age (p=0.7672), baseline eGFR (CKD-EPI) (p=0.1415), Treatment (p=0.3088), region (5 cat.) (p<0.0001), baseline diabetes status (3 cat.) (p=0.8720), baseline LVEF (3 cat.) (p=0.5103), sex (p=0.3657) and Treatment by sex interaction (p=0.7959).
***Wald confidence intervals.

Data taken from study 1245.121 only.
LOCF: For a missing value at week 52 the last available post-baseline value before week 52 is imputed.

R.1.2.6.3

R.1.2.6.3 Subgroup analysis by age

Table R.1.2.6.3: 1 Responder analysis (displaying odds ratio) in KCCQ-TSS change from baseline at week 52 of <= -5 points (deterioration) by age (2 cat.) - RS (LOCF-AD) - 1245.121

Subgroup Description	Placebo	Empa 10mg
Age [years] (2 cat.): < 65		
Number of patients in analysis set	740	675
Number of analysed patients, N (%)	675 (100.0)	635 (100.0)
Number of patients with endpoint, N (%)	154 (22.8)	119 (18.7)
95% confidence interval*	(19.8, 26.1)	(15.9, 22.0)
Comparison vs Placebo**		
Odds ratio (SE)		0.787 (0.110)
95% confidence interval***		(0.599, 1.034)
p-value		0.0859
Age [years] (2 cat.): >= 65		
Number of patients in analysis set	1127	1188
Number of analysed patients, N (%)	1034 (100.0)	1105 (100.0)
Number of patients with endpoint, N (%)	274 (26.5)	271 (24.5)
95% confidence interval*	(23.9, 29.3)	(22.1, 27.1)
Comparison vs Placebo**		
Odds ratio (SE)		0.905 (0.091)
95% confidence interval***		(0.743, 1.103)
p-value		0.3246

* Wilson confidence intervals.
** Logistic regression includes terms for baseline KCCQ - total symptom score (p<0.0001), baseline eGFR (CKD-EPI) (p<0.0001), Treatment (p=0.0488), region (5 cat.) (p=0.0004), baseline diabetes status (3 cat.) (p=0.4936), sex (p=0.4006), baseline LVEF (3 cat.) (p=0.5969), age (2 cat.) (p=0.7617) and Treatment by age (2 cat.) interaction (p=0.4157).
***Wald confidence intervals.

Data taken from study 1245.121 only.
LOCF: For a missing value at week 52 the last available post-baseline value before week 52 is imputed.

Table R.1.2.6.3: 2 Responder analysis (displaying risk ratio) in KCCQ-TSS change from baseline at week 52 of <= -5 points (deterioration) by age (2 cat.) - RS (LOCF-AD) - 1245.121

Subgroup Description	Placebo	Empa 10mg
Age [years] (2 cat.): < 65		
Number of patients in analysis set	740	675
Number of analysed patients, N (%)	675 (100.0)	635 (100.0)
Number of patients with endpoint, N (%)	154 (22.8)	119 (18.7)
95% confidence interval*	(19.8, 26.1)	(15.9, 22.0)
Comparison vs Placebo**		
Risk ratio (SE)		0.831 (0.090)
95% confidence interval***		(0.673, 1.028)
p-value		0.0879
Age [years] (2 cat.): >= 65		
Number of patients in analysis set	1127	1188
Number of analysed patients, N (%)	1034 (100.0)	1105 (100.0)
Number of patients with endpoint, N (%)	274 (26.5)	271 (24.5)
95% confidence interval*	(23.9, 29.3)	(22.1, 27.1)
Comparison vs Placebo**		
Risk ratio (SE)		0.930 (0.067)
95% confidence interval***		(0.807, 1.072)
p-value		0.3179

* Wilson confidence intervals.
** Log-linked Poisson model with robust estimate of variance includes terms for baseline KCCQ - total symptom score (p<0.0001), baseline eGFR (CKD-EPI) (p<0.0001), Treatment (p=0.0480), region (5 cat.) (p=0.0005), baseline diabetes status (3 cat.) (p=0.4902), sex (p=0.3931), baseline LVEF (3 cat.) (p=0.5935), age (2 cat.) (p=0.7219) and Treatment by age (2 cat.) interaction (p=0.3902).
***Wald confidence intervals.

Data taken from study 1245.121 only.
LOCF: For a missing value at week 52 the last available post-baseline value before week 52 is imputed.

Table R.1.2.6.3: 3 Responder analysis (displaying odds ratio) in KCCQ-TSS change from baseline at week 52 of > -5 points (stability) by age (2 cat.) - RS (LOCF-AD) - 1245.121

Subgroup Description	Placebo	Empa 10mg
Age [years] (2 cat.): < 65		
Number of patients in analysis set	740	675
Number of analysed patients, N (%)	675 (100.0)	635 (100.0)
Number of patients with endpoint, N (%)	521 (77.2)	516 (81.3)
95% confidence interval*	(73.9, 80.2)	(78.0, 84.1)
Comparison vs Placebo**		
Odds ratio (SE)		1.271 (0.177)
95% confidence interval***		(0.967, 1.671)
p-value		0.0859
Age [years] (2 cat.): >= 65		
Number of patients in analysis set	1127	1188
Number of analysed patients, N (%)	1034 (100.0)	1105 (100.0)
Number of patients with endpoint, N (%)	760 (73.5)	834 (75.5)
95% confidence interval*	(70.7, 76.1)	(72.9, 77.9)
Comparison vs Placebo**		
Odds ratio (SE)		1.105 (0.111)
95% confidence interval***		(0.906, 1.346)
p-value		0.3246

* Wilson confidence intervals.
** Logistic regression includes terms for baseline KCCQ - total symptom score (p<0.0001), baseline eGFR (CKD-EPI) (p<0.0001), Treatment (p=0.0488), region (5 cat.) (p=0.0004), baseline diabetes status (3 cat.) (p=0.4936), sex (p=0.4006), baseline LVEF (3 cat.) (p=0.5969), age (2 cat.) (p=0.7617) and Treatment by age (2 cat.) interaction (p=0.4157).
***Wald confidence intervals.

Data taken from study 1245.121 only.
LOCF: For a missing value at week 52 the last available post-baseline value before week 52 is imputed.

Table R.1.2.6.3: 4 Responder analysis (displaying risk ratio) in KCCQ-TSS change from baseline at week 52 of > -5 points (stability) by age (2 cat.) - RS (LOCF-AD) - 1245.121

Subgroup Description	Placebo	Empa 10mg
Age [years] (2 cat.): < 65		
Number of patients in analysis set	740	675
Number of analysed patients, N (%)	675 (100.0)	635 (100.0)
Number of patients with endpoint, N (%)	521 (77.2)	516 (81.3)
95% confidence interval*	(73.9, 80.2)	(78.0, 84.1)
Comparison vs Placebo**		
Risk ratio (SE)		1.047 (0.030)
95% confidence interval***		(0.991, 1.106)
p-value		0.1049
Age [years] (2 cat.): >= 65		
Number of patients in analysis set	1127	1188
Number of analysed patients, N (%)	1034 (100.0)	1105 (100.0)
Number of patients with endpoint, N (%)	760 (73.5)	834 (75.5)
95% confidence interval*	(70.7, 76.1)	(72.9, 77.9)
Comparison vs Placebo**		
Risk ratio (SE)		1.024 (0.026)
95% confidence interval***		(0.975, 1.076)
p-value		0.3379

* Wilson confidence intervals.
** Log-linked Poisson model with robust estimate of variance includes terms for baseline KCCQ - total symptom score (p<0.0001), baseline eGFR (CKD-EPI) (p<0.0001), Treatment (p=0.0639), region (5 cat.) (p<0.0001), baseline diabetes status (3 cat.) (p=0.5327), sex (p=0.4228), baseline LVEF (3 cat.) (p=0.6140), age (2 cat.) (p=0.8659) and Treatment by age (2 cat.) interaction (p=0.5639).
***Wald confidence intervals.

Data taken from study 1245.121 only.
LOCF: For a missing value at week 52 the last available post-baseline value before week 52 is imputed.

Table R.1.2.6.3: 5 Responder analysis (displaying odds ratio) in KCCQ-TSS change from baseline at week 52 of >= 5 points (improvement) by age (2 cat.) - RS (LOCF-AD) - 1245.121

Subgroup Description	Placebo	Empa 10mg
Age [years] (2 cat.): < 65		
Number of patients in analysis set	740	675
Number of analysed patients, N (%)	675 (100.0)	635 (100.0)
Number of patients with endpoint, N (%)	310 (45.9)	323 (50.9)
95% confidence interval*	(42.2, 49.7)	(47.0, 54.7)
Comparison vs Placebo**		
Odds ratio (SE)		1.230 (0.159)
95% confidence interval***		(0.955, 1.584)
p-value		0.1081
Age [years] (2 cat.): >= 65		
Number of patients in analysis set	1127	1188
Number of analysed patients, N (%)	1034 (100.0)	1105 (100.0)
Number of patients with endpoint, N (%)	441 (42.6)	489 (44.3)
95% confidence interval*	(39.7, 45.7)	(41.3, 47.2)
Comparison vs Placebo**		
Odds ratio (SE)		1.094 (0.109)
95% confidence interval***		(0.900, 1.330)
p-value		0.3674

* Wilson confidence intervals.
** Logistic regression includes terms for baseline KCCQ - total symptom score (p<0.0001), baseline eGFR (CKD-EPI) (p=0.0613), Treatment (p=0.0683), region (5 cat.) (p<0.0001), baseline diabetes status (3 cat.) (p=0.9763), sex (p=0.5488), baseline LVEF (3 cat.) (p=0.5684), age (2 cat.) (p=0.5581) and Treatment by age (2 cat.) interaction (p=0.4720).
***Wald confidence intervals.

Data taken from study 1245.121 only.
LOCF: For a missing value at week 52 the last available post-baseline value before week 52 is imputed.

Table R.1.2.6.3: 6 Responder analysis (displaying risk ratio) in KCCQ-TSS change from baseline at week 52 of >= 5 points (improvement) by age (2 cat.) - RS (LOCF-AD) - 1245.121

Subgroup Description	Placebo	Empa 10mg
Age [years] (2 cat.): < 65		
Number of patients in analysis set	740	675
Number of analysed patients, N (%)	675 (100.0)	635 (100.0)
Number of patients with endpoint, N (%)	310 (45.9)	323 (50.9)
95% confidence interval*	(42.2, 49.7)	(47.0, 54.7)
Comparison vs Placebo**		
Risk ratio (SE)		1.066 (0.057)
95% confidence interval***		(0.960, 1.184)
p-value		0.2298
Age [years] (2 cat.): >= 65		
Number of patients in analysis set	1127	1188
Number of analysed patients, N (%)	1034 (100.0)	1105 (100.0)
Number of patients with endpoint, N (%)	441 (42.6)	489 (44.3)
95% confidence interval*	(39.7, 45.7)	(41.3, 47.2)
Comparison vs Placebo**		
Risk ratio (SE)		1.026 (0.046)
95% confidence interval***		(0.940, 1.120)
p-value		0.5667

* Wilson confidence intervals.
** Log-linked Poisson model with robust estimate of variance includes terms for baseline KCCQ - total symptom score (p<0.0001), baseline eGFR (CKD-EPI) (p=0.0413), Treatment (p=0.1976), region (5 cat.) (p<0.0001), baseline diabetes status (3 cat.) (p=0.8865), sex (p=0.3889), baseline LVEF (3 cat.) (p=0.5678), age (2 cat.) (p=0.3881) and Treatment by age (2 cat.) interaction (p=0.5823).
***Wald confidence intervals.

Data taken from study 1245.121 only.
LOCF: For a missing value at week 52 the last available post-baseline value before week 52 is imputed.

R.1.2.6.4 Subgroup analysis by region (North America, Latin America, Europe, Asia, Other)

Table R.1.2.6.4: 1 Responder analysis (displaying odds ratio) in KCCQ-TSS change from baseline at week 52 of <= -5 points (deterioration) by region - RS (LOCF-AD) - 1245.121

Subgroup Description	Placebo	Empa 10mg
Region (5 cat.): North America		
Number of patients in analysis set	213	212
Number of analysed patients, N (%)	192 (100.0)	204 (100.0)
Number of patients with endpoint, N (%)	47 (24.5)	48 (23.5)
95% confidence interval*	(18.9, 31.0)	(18.2, 29.8)
Comparison vs Placebo**		
Odds ratio (SE)		0.930 (0.223)
95% confidence interval***		(0.581, 1.487)
p-value		0.7609
Region (5 cat.): Latin America		
Number of patients in analysis set	645	641
Number of analysed patients, N (%)	577 (100.0)	586 (100.0)
Number of patients with endpoint, N (%)	136 (23.6)	112 (19.1)
95% confidence interval*	(20.3, 27.2)	(16.1, 22.5)
Comparison vs Placebo**		
Odds ratio (SE)		0.784 (0.115)
95% confidence interval***		(0.589, 1.045)
p-value		0.0967

* Wilson confidence intervals.
** Logistic regression includes terms for baseline KCCQ - total symptom score (p<0.0001), age (p=0.5793), baseline eGFR (CKD-EPI) (p=0.0004), Treatment (p=0.0469), baseline diabetes status (3 cat.) (p=0.4533), sex (p=0.4489), baseline LVEF (3 cat.) (p=0.5657), region (5 cat.) (p=0.0004) and Treatment by region (5 cat.) interaction (p=0.6188).
***Wald confidence intervals.

Data taken from study 1245.121 only.
LOCF: For a missing value at week 52 the last available post-baseline value before week 52 is imputed.

Table R.1.2.6.4: 1 Responder analysis (displaying odds ratio) in KCCQ-TSS change from baseline at week 52 of <= -5 points (deterioration) by region - RS (LOCF-AD) - 1245.121

Subgroup Description	Placebo	Empa 10mg
Region (5 cat.): Europe		
Number of patients in analysis set	677	676
Number of analysed patients, N (%)	631 (100.0)	638 (100.0)
Number of patients with endpoint, N (%)	175 (27.7)	176 (27.6)
95% confidence interval*	(24.4, 31.4)	(24.3, 31.2)
Comparison vs Placebo**		
Odds ratio (SE)		0.972 (0.124)
95% confidence interval***		(0.757, 1.248)
p-value		0.8237
Region (5 cat.): Asia		
Number of patients in analysis set	245	248
Number of analysed patients, N (%)	232 (100.0)	236 (100.0)
Number of patients with endpoint, N (%)	57 (24.6)	47 (19.9)
95% confidence interval*	(19.5, 30.5)	(15.3, 25.5)
Comparison vs Placebo**		
Odds ratio (SE)		0.772 (0.174)
95% confidence interval***		(0.496, 1.201)
p-value		0.2505

* Wilson confidence intervals.
** Logistic regression includes terms for baseline KCCQ - total symptom score (p<0.0001), age (p=0.5793), baseline eGFR (CKD-EPI) (p=0.0004), Treatment (p=0.0469), baseline diabetes status (3 cat.) (p=0.4533), sex (p=0.4489), baseline LVEF (3 cat.) (p=0.5657), region (5 cat.) (p=0.0004) and Treatment by region (5 cat.) interaction (p=0.6188).
***Wald confidence intervals.

Data taken from study 1245.121 only.
LOCF: For a missing value at week 52 the last available post-baseline value before week 52 is imputed.

Table R.1.2.6.4: 1 Responder analysis (displaying odds ratio) in KCCQ-TSS change from baseline at week 52 of <= -5 points (deterioration) by region - RS (LOCF-AD) - 1245.121

Subgroup Description	Placebo	Empa 10mg
Region (5 cat.): Other		
Number of patients in analysis set	87	86
Number of analysed patients, N (%)	77 (100.0)	76 (100.0)
Number of patients with endpoint, N (%)	13 (16.9)	7 (9.2)
95% confidence interval*	(10.1, 26.8)	(4.5, 17.8)
Comparison vs Placebo**		
Odds ratio (SE)		0.521 (0.262)
95% confidence interval***		(0.194, 1.396)
p-value		0.1947

* Wilson confidence intervals.
** Logistic regression includes terms for baseline KCCQ - total symptom score (p<0.0001), age (p=0.5793), baseline eGFR (CKD-EPI) (p=0.0004), Treatment (p=0.0469), baseline diabetes status (3 cat.) (p=0.4533), sex (p=0.4489), baseline LVEF (3 cat.) (p=0.5657), region (5 cat.) (p=0.0004) and Treatment by region (5 cat.) interaction (p=0.6188).
***Wald confidence intervals.

Data taken from study 1245.121 only.
LOCF: For a missing value at week 52 the last available post-baseline value before week 52 is imputed.

Table R.1.2.6.4: 2 Responder analysis (displaying risk ratio) in KCCQ-TSS change from baseline at week 52 of <= -5 points (deterioration) by region - RS (LOCF-AD) - 1245.121

Subgroup Description	Placebo	Empa 10mg
Region (5 cat.): North America		
Number of patients in analysis set	213	212
Number of analysed patients, N (%)	192 (100.0)	204 (100.0)
Number of patients with endpoint, N (%)	47 (24.5)	48 (23.5)
95% confidence interval*	(18.9, 31.0)	(18.2, 29.8)
Comparison vs Placebo**		
Risk ratio (SE)		0.949 (0.168)
95% confidence interval***		(0.670, 1.343)
p-value		0.7659
Region (5 cat.): Latin America		
Number of patients in analysis set	645	641
Number of analysed patients, N (%)	577 (100.0)	586 (100.0)
Number of patients with endpoint, N (%)	136 (23.6)	112 (19.1)
95% confidence interval*	(20.3, 27.2)	(16.1, 22.5)
Comparison vs Placebo**		
Risk ratio (SE)		0.830 (0.093)
95% confidence interval***		(0.667, 1.033)
p-value		0.0944

* Wilson confidence intervals.
** Log-linked Poisson model with robust estimate of variance includes terms for baseline KCCQ - total symptom score (p<0.0001), age (p=0.5639), baseline eGFR (CKD-EPI) (p=0.0004), Treatment (p=0.0481), baseline diabetes status (3 cat.) (p=0.4451), sex (p=0.4454), baseline LVEF (3 cat.) (p=0.5598), region (5 cat.) (p=0.0004) and Treatment by region (5 cat.) interaction (p=0.5662).
***Wald confidence intervals.

Data taken from study 1245.121 only.
LOCF: For a missing value at week 52 the last available post-baseline value before week 52 is imputed.

Table R.1.2.6.4: 2 Responder analysis (displaying risk ratio) in KCCQ-TSS change from baseline at week 52 of <= -5 points (deterioration) by region - RS (LOCF-AD) - 1245.121

Subgroup Description	Placebo	Empa 10mg
Region (5 cat.): Europe		
Number of patients in analysis set	677	676
Number of analysed patients, N (%)	631 (100.0)	638 (100.0)
Number of patients with endpoint, N (%)	175 (27.7)	176 (27.6)
95% confidence interval*	(24.4, 31.4)	(24.3, 31.2)
Comparison vs Placebo**		
Risk ratio (SE)		0.980 (0.087)
95% confidence interval***		(0.823, 1.167)
p-value		0.8183
Region (5 cat.): Asia		
Number of patients in analysis set	245	248
Number of analysed patients, N (%)	232 (100.0)	236 (100.0)
Number of patients with endpoint, N (%)	57 (24.6)	47 (19.9)
95% confidence interval*	(19.5, 30.5)	(15.3, 25.5)
Comparison vs Placebo**		
Risk ratio (SE)		0.820 (0.142)
95% confidence interval***		(0.584, 1.152)
p-value		0.2530

* Wilson confidence intervals.
** Log-linked Poisson model with robust estimate of variance includes terms for baseline KCCQ - total symptom score (p<0.0001), age (p=0.5639), baseline eGFR (CKD-EPI) (p=0.0004), Treatment (p=0.0481), baseline diabetes status (3 cat.) (p=0.4451), sex (p=0.4454), baseline LVEF (3 cat.) (p=0.5598), region (5 cat.) (p=0.0004) and Treatment by region (5 cat.) interaction (p=0.5662).
***Wald confidence intervals.

Data taken from study 1245.121 only.
LOCF: For a missing value at week 52 the last available post-baseline value before week 52 is imputed.

Table R.1.2.6.4: 2 Responder analysis (displaying risk ratio) in KCCQ-TSS change from baseline at week 52 of <= -5 points (deterioration) by region - RS (LOCF-AD) - 1245.121

Subgroup Description	Placebo	Empa 10mg
Region (5 cat.): Other		
Number of patients in analysis set	87	86
Number of analysed patients, N (%)	77 (100.0)	76 (100.0)
Number of patients with endpoint, N (%)	13 (16.9)	7 (9.2)
95% confidence interval*	(10.1, 26.8)	(4.5, 17.8)
Comparison vs Placebo**		
Risk ratio (SE)		0.567 (0.245)
95% confidence interval***		(0.243, 1.322)
p-value		0.1888

* Wilson confidence intervals.
** Log-linked Poisson model with robust estimate of variance includes terms for baseline KCCQ - total symptom score (p<0.0001), age (p=0.5639), baseline eGFR (CKD-EPI) (p=0.0004), Treatment (p=0.0481), baseline diabetes status (3 cat.) (p=0.4451), sex (p=0.4454), baseline LVEF (3 cat.) (p=0.5598), region (5 cat.) (p=0.0004) and Treatment by region (5 cat.) interaction (p=0.5662).
***Wald confidence intervals.

Data taken from study 1245.121 only.
LOCF: For a missing value at week 52 the last available post-baseline value before week 52 is imputed.

Table R.1.2.6.4: 3 Responder analysis (displaying odds ratio) in KCCQ-TSS change from baseline at week 52 of > -5 points (stability) by region - RS (LOCF-AD) - 1245.121

Subgroup Description	Placebo	Empa 10mg
Region (5 cat.): North America		
Number of patients in analysis set	213	212
Number of analysed patients, N (%)	192 (100.0)	204 (100.0)
Number of patients with endpoint, N (%)	145 (75.5)	156 (76.5)
95% confidence interval*	(69.0, 81.1)	(70.2, 81.8)
Comparison vs Placebo**		
Odds ratio (SE)		1.076 (0.258)
95% confidence interval***		(0.673, 1.720)
p-value		0.7609
Region (5 cat.): Latin America		
Number of patients in analysis set	645	641
Number of analysed patients, N (%)	577 (100.0)	586 (100.0)
Number of patients with endpoint, N (%)	441 (76.4)	474 (80.9)
95% confidence interval*	(72.8, 79.7)	(77.5, 83.9)
Comparison vs Placebo**		
Odds ratio (SE)		1.275 (0.186)
95% confidence interval***		(0.957, 1.697)
p-value		0.0967

* Wilson confidence intervals.
** Logistic regression includes terms for baseline KCCQ - total symptom score (p<0.0001), age (p=0.5793), baseline eGFR (CKD-EPI) (p=0.0004), Treatment (p=0.0469), baseline diabetes status (3 cat.) (p=0.4533), sex (p=0.4489), baseline LVEF (3 cat.) (p=0.5657), region (5 cat.) (p=0.0004) and Treatment by region (5 cat.) interaction (p=0.6188).
***Wald confidence intervals.

Data taken from study 1245.121 only.
LOCF: For a missing value at week 52 the last available post-baseline value before week 52 is imputed.

Table R.1.2.6.4: 3 Responder analysis (displaying odds ratio) in KCCQ-TSS change from baseline at week 52 of > -5 points (stability) by region - RS (LOCF-AD) - 1245.121

Subgroup Description	Placebo	Empa 10mg
Region (5 cat.): Europe		
Number of patients in analysis set	677	676
Number of analysed patients, N (%)	631 (100.0)	638 (100.0)
Number of patients with endpoint, N (%)	456 (72.3)	462 (72.4)
95% confidence interval*	(68.6, 75.6)	(68.8, 75.7)
Comparison vs Placebo**		
Odds ratio (SE)		1.029 (0.131)
95% confidence interval***		(0.802, 1.320)
p-value		0.8237
Region (5 cat.): Asia		
Number of patients in analysis set	245	248
Number of analysed patients, N (%)	232 (100.0)	236 (100.0)
Number of patients with endpoint, N (%)	175 (75.4)	189 (80.1)
95% confidence interval*	(69.5, 80.5)	(74.5, 84.7)
Comparison vs Placebo**		
Odds ratio (SE)		1.296 (0.292)
95% confidence interval***		(0.833, 2.016)
p-value		0.2505

* Wilson confidence intervals.
** Logistic regression includes terms for baseline KCCQ - total symptom score (p<0.0001), age (p=0.5793), baseline eGFR (CKD-EPI) (p=0.0004), Treatment (p=0.0469), baseline diabetes status (3 cat.) (p=0.4533), sex (p=0.4489), baseline LVEF (3 cat.) (p=0.5657), region (5 cat.) (p=0.0004) and Treatment by region (5 cat.) interaction (p=0.6188).
***Wald confidence intervals.

Data taken from study 1245.121 only.
LOCF: For a missing value at week 52 the last available post-baseline value before week 52 is imputed.

Table R.1.2.6.4: 3 Responder analysis (displaying odds ratio) in KCCQ-TSS change from baseline at week 52 of > -5 points (stability) by region - RS (LOCF-AD) - 1245.121

Subgroup Description	Placebo	Empa 10mg
Region (5 cat.): Other		
Number of patients in analysis set	87	86
Number of analysed patients, N (%)	77 (100.0)	76 (100.0)
Number of patients with endpoint, N (%)	64 (83.1)	69 (90.8)
95% confidence interval*	(73.2, 89.9)	(82.2, 95.5)
Comparison vs Placebo**		
Odds ratio (SE)		1.921 (0.967)
95% confidence interval***		(0.716, 5.152)
p-value		0.1947

* Wilson confidence intervals.
** Logistic regression includes terms for baseline KCCQ - total symptom score (p<0.0001), age (p=0.5793), baseline eGFR (CKD-EPI) (p=0.0004), Treatment (p=0.0469), baseline diabetes status (3 cat.) (p=0.4533), sex (p=0.4489), baseline LVEF (3 cat.) (p=0.5657), region (5 cat.) (p=0.0004) and Treatment by region (5 cat.) interaction (p=0.6188).
***Wald confidence intervals.

Data taken from study 1245.121 only.
LOCF: For a missing value at week 52 the last available post-baseline value before week 52 is imputed.

Table R.1.2.6.4: 4 Responder analysis (displaying risk ratio) in KCCQ-TSS change from baseline at week 52 of > -5 points (stability) by region - RS (LOCF-AD) - 1245.121

Subgroup Description	Placebo	Empa 10mg
Region (5 cat.): North America		
Number of patients in analysis set	213	212
Number of analysed patients, N (%)	192 (100.0)	204 (100.0)
Number of patients with endpoint, N (%)	145 (75.5)	156 (76.5)
95% confidence interval*	(69.0, 81.1)	(70.2, 81.8)
Comparison vs Placebo**		
Risk ratio (SE)		1.017 (0.057)
95% confidence interval***		(0.911, 1.136)
p-value		0.7583
Region (5 cat.): Latin America		
Number of patients in analysis set	645	641
Number of analysed patients, N (%)	577 (100.0)	586 (100.0)
Number of patients with endpoint, N (%)	441 (76.4)	474 (80.9)
95% confidence interval*	(72.8, 79.7)	(77.5, 83.9)
Comparison vs Placebo**		
Risk ratio (SE)		1.049 (0.032)
95% confidence interval***		(0.989, 1.113)
p-value		0.1141

* Wilson confidence intervals.
** Log-linked Poisson model with robust estimate of variance includes terms for baseline KCCQ - total symptom score (p<0.0001), age (p=0.6901), baseline eGFR (CKD-EPI) (p=0.0004), Treatment (p=0.0548), baseline diabetes status (3 cat.) (p=0.5051), sex (p=0.4506), baseline LVEF (3 cat.) (p=0.5850), region (5 cat.) (p<0.0001) and Treatment by region (5 cat.) interaction (p=0.8033).
***Wald confidence intervals.

Data taken from study 1245.121 only.
LOCF: For a missing value at week 52 the last available post-baseline value before week 52 is imputed.

Table R.1.2.6.4: 4 Responder analysis (displaying risk ratio) in KCCQ-TSS change from baseline at week 52 of > -5 points (stability) by region - RS (LOCF-AD) - 1245.121

Subgroup Description	Placebo	Empa 10mg
Region (5 cat.): Europe		
Number of patients in analysis set	677	676
Number of analysed patients, N (%)	631 (100.0)	638 (100.0)
Number of patients with endpoint, N (%)	456 (72.3)	462 (72.4)
95% confidence interval*	(68.6, 75.6)	(68.8, 75.7)
Comparison vs Placebo**		
Risk ratio (SE)		1.007 (0.034)
95% confidence interval***		(0.942, 1.077)
p-value		0.8409
Region (5 cat.): Asia		
Number of patients in analysis set	245	248
Number of analysed patients, N (%)	232 (100.0)	236 (100.0)
Number of patients with endpoint, N (%)	175 (75.4)	189 (80.1)
95% confidence interval*	(69.5, 80.5)	(74.5, 84.7)
Comparison vs Placebo**		
Risk ratio (SE)		1.057 (0.052)
95% confidence interval***		(0.959, 1.165)
p-value		0.2619

* Wilson confidence intervals.
** Log-linked Poisson model with robust estimate of variance includes terms for baseline KCCQ - total symptom score (p<0.0001), age (p=0.6901), baseline eGFR (CKD-EPI) (p=0.0004), Treatment (p=0.0548), baseline diabetes status (3 cat.) (p=0.5051), sex (p=0.4506), baseline LVEF (3 cat.) (p=0.5850), region (5 cat.) (p<0.0001) and Treatment by region (5 cat.) interaction (p=0.8033).
***Wald confidence intervals.

Data taken from study 1245.121 only.
LOCF: For a missing value at week 52 the last available post-baseline value before week 52 is imputed.

Table R.1.2.6.4: 4 Responder analysis (displaying risk ratio) in KCCQ-TSS change from baseline at week 52 of > -5 points (stability) by region - RS (LOCF-AD) - 1245.121

Subgroup Description	Placebo	Empa 10mg
Region (5 cat.): Other		
Number of patients in analysis set	87	86
Number of analysed patients, N (%)	77 (100.0)	76 (100.0)
Number of patients with endpoint, N (%)	64 (83.1)	69 (90.8)
95% confidence interval*	(73.2, 89.9)	(82.2, 95.5)
Comparison vs Placebo**		
Risk ratio (SE)		1.082 (0.067)
95% confidence interval***		(0.959, 1.222)
p-value		0.2001

* Wilson confidence intervals.
** Log-linked Poisson model with robust estimate of variance includes terms for baseline KCCQ - total symptom score (p<0.0001), age (p=0.6901), baseline eGFR (CKD-EPI) (p=0.0004), Treatment (p=0.0548), baseline diabetes status (3 cat.) (p=0.5051), sex (p=0.4506), baseline LVEF (3 cat.) (p=0.5850), region (5 cat.) (p<0.0001) and Treatment by region (5 cat.) interaction (p=0.8033).
***Wald confidence intervals.

Data taken from study 1245.121 only.
LOCF: For a missing value at week 52 the last available post-baseline value before week 52 is imputed.

Table R.1.2.6.4: 5 Responder analysis (displaying odds ratio) in KCCQ-TSS change from baseline at week 52 of >= 5 points (improvement) by region - RS (LOCF-AD) - 1245.121

Subgroup Description	Placebo	Empa 10mg
Region (5 cat.): North America		
Number of patients in analysis set	213	212
Number of analysed patients, N (%)	192 (100.0)	204 (100.0)
Number of patients with endpoint, N (%)	78 (40.6)	90 (44.1)
95% confidence interval*	(33.9, 47.7)	(37.5, 51.0)
Comparison vs Placebo**		
Odds ratio (SE)		1.259 (0.300)
95% confidence interval***		(0.789, 2.010)
p-value		0.3343
Region (5 cat.): Latin America		
Number of patients in analysis set	645	641
Number of analysed patients, N (%)	577 (100.0)	586 (100.0)
Number of patients with endpoint, N (%)	285 (49.4)	322 (54.9)
95% confidence interval*	(45.3, 53.5)	(50.9, 58.9)
Comparison vs Placebo**		
Odds ratio (SE)		1.266 (0.173)
95% confidence interval***		(0.969, 1.654)
p-value		0.0843

* Wilson confidence intervals.
** Logistic regression includes terms for baseline KCCQ - total symptom score (p<0.0001), age (p=0.4758), baseline eGFR (CKD-EPI) (p=0.2309), Treatment (p=0.0449), baseline diabetes status (3 cat.) (p=0.9549), sex (p=0.4967), baseline LVEF (3 cat.) (p=0.4936), region (5 cat.) (p<0.0001) and Treatment by region (5 cat.) interaction (p=0.5129).
***Wald confidence intervals.

Data taken from study 1245.121 only.
LOCF: For a missing value at week 52 the last available post-baseline value before week 52 is imputed.

Table R.1.2.6.4: 5 Responder analysis (displaying odds ratio) in KCCQ-TSS change from baseline at week 52 of >= 5 points (improvement) by region - RS (LOCF-AD) - 1245.121

Subgroup Description	Placebo	Empa 10mg
Region (5 cat.): Europe		
Number of patients in analysis set	677	676
Number of analysed patients, N (%)	631 (100.0)	638 (100.0)
Number of patients with endpoint, N (%)	272 (43.1)	261 (40.9)
95% confidence interval*	(39.3, 47.0)	(37.2, 44.8)
Comparison vs Placebo**		
Odds ratio (SE)		0.958 (0.124)
95% confidence interval***		(0.743, 1.234)
p-value		0.7387
Region (5 cat.): Asia		
Number of patients in analysis set	245	248
Number of analysed patients, N (%)	232 (100.0)	236 (100.0)
Number of patients with endpoint, N (%)	76 (32.8)	91 (38.6)
95% confidence interval*	(27.0, 39.0)	(32.6, 44.9)
Comparison vs Placebo**		
Odds ratio (SE)		1.237 (0.262)
95% confidence interval***		(0.816, 1.875)
p-value		0.3155

* Wilson confidence intervals.
** Logistic regression includes terms for baseline KCCQ - total symptom score (p<0.0001), age (p=0.4758), baseline eGFR (CKD-EPI) (p=0.2309), Treatment (p=0.0449), baseline diabetes status (3 cat.) (p=0.9549), sex (p=0.4967), baseline LVEF (3 cat.) (p=0.4936), region (5 cat.) (p<0.0001) and Treatment by region (5 cat.) interaction (p=0.5129).
***Wald confidence intervals.

Data taken from study 1245.121 only.
LOCF: For a missing value at week 52 the last available post-baseline value before week 52 is imputed.

Table R.1.2.6.4: 5 Responder analysis (displaying odds ratio) in KCCQ-TSS change from baseline at week 52 of >= 5 points (improvement) by region - RS (LOCF-AD) - 1245.121

Subgroup Description	Placebo	Empa 10mg
Region (5 cat.): Other		
Number of patients in analysis set	87	86
Number of analysed patients, N (%)	77 (100.0)	76 (100.0)
Number of patients with endpoint, N (%)	40 (51.9)	48 (63.2)
95% confidence interval*	(41.0, 62.7)	(51.9, 73.1)
Comparison vs Placebo**		
Odds ratio (SE)		1.490 (0.535)
95% confidence interval***		(0.738, 3.010)
p-value		0.2662

* Wilson confidence intervals.
** Logistic regression includes terms for baseline KCCQ - total symptom score (p<0.0001), age (p=0.4758), baseline eGFR (CKD-EPI) (p=0.2309), Treatment (p=0.0449), baseline diabetes status (3 cat.) (p=0.9549), sex (p=0.4967), baseline LVEF (3 cat.) (p=0.4936), region (5 cat.) (p<0.0001) and Treatment by region (5 cat.) interaction (p=0.5129).
***Wald confidence intervals.

Data taken from study 1245.121 only.
LOCF: For a missing value at week 52 the last available post-baseline value before week 52 is imputed.

Table R.1.2.6.4: 6 Responder analysis (displaying risk ratio) in KCCQ-TSS change from baseline at week 52 of >= 5 points (improvement) by region - RS (LOCF-AD) - 1245.121

Subgroup Description	Placebo	Empa 10mg
Region (5 cat.): North America		
Number of patients in analysis set	213	212
Number of analysed patients, N (%)	192 (100.0)	204 (100.0)
Number of patients with endpoint, N (%)	78 (40.6)	90 (44.1)
95% confidence interval*	(33.9, 47.7)	(37.5, 51.0)
Comparison vs Placebo**		
Risk ratio (SE)		1.098 (0.122)
95% confidence interval***		(0.883, 1.365)
p-value		0.3998
Region (5 cat.): Latin America		
Number of patients in analysis set	645	641
Number of analysed patients, N (%)	577 (100.0)	586 (100.0)
Number of patients with endpoint, N (%)	285 (49.4)	322 (54.9)
95% confidence interval*	(45.3, 53.5)	(50.9, 58.9)
Comparison vs Placebo**		
Risk ratio (SE)		1.052 (0.055)
95% confidence interval***		(0.949, 1.166)
p-value		0.3344

* Wilson confidence intervals.
** Log-linked Poisson model with robust estimate of variance includes terms for baseline KCCQ - total symptom score (p<0.0001), age (p=0.7185), baseline eGFR (CKD-EPI) (p=0.1644), Treatment (p=0.0554), baseline diabetes status (3 cat.) (p=0.8695), sex (p=0.3821), baseline LVEF (3 cat.) (p=0.4899), region (5 cat.) (p<0.0001) and Treatment by region (5 cat.) interaction (p=0.4791).
***Wald confidence intervals.

Data taken from study 1245.121 only.
LOCF: For a missing value at week 52 the last available post-baseline value before week 52 is imputed.

Table R.1.2.6.4: 6 Responder analysis (displaying risk ratio) in KCCQ-TSS change from baseline at week 52 of >= 5 points (improvement) by region - RS (LOCF-AD) - 1245.121

Subgroup Description	Placebo	Empa 10mg
Region (5 cat.): Europe		
Number of patients in analysis set	677	676
Number of analysed patients, N (%)	631 (100.0)	638 (100.0)
Number of patients with endpoint, N (%)	272 (43.1)	261 (40.9)
95% confidence interval*	(39.3, 47.0)	(37.2, 44.8)
Comparison vs Placebo**		
Risk ratio (SE)		0.969 (0.058)
95% confidence interval***		(0.862, 1.090)
p-value		0.6050
Region (5 cat.): Asia		
Number of patients in analysis set	245	248
Number of analysed patients, N (%)	232 (100.0)	236 (100.0)
Number of patients with endpoint, N (%)	76 (32.8)	91 (38.6)
95% confidence interval*	(27.0, 39.0)	(32.6, 44.9)
Comparison vs Placebo**		
Risk ratio (SE)		1.125 (0.130)
95% confidence interval***		(0.897, 1.410)
p-value		0.3081

* Wilson confidence intervals.
** Log-linked Poisson model with robust estimate of variance includes terms for baseline KCCQ - total symptom score (p<0.0001), age (p=0.7185), baseline eGFR (CKD-EPI) (p=0.1644), Treatment (p=0.0554), baseline diabetes status (3 cat.) (p=0.8695), sex (p=0.3821), baseline LVEF (3 cat.) (p=0.4899), region (5 cat.) (p<0.0001) and Treatment by region (5 cat.) interaction (p=0.4791).
***Wald confidence intervals.

Data taken from study 1245.121 only.
LOCF: For a missing value at week 52 the last available post-baseline value before week 52 is imputed.

Table R.1.2.6.4: 6 Responder analysis (displaying risk ratio) in KCCQ-TSS change from baseline at week 52 of >= 5 points (improvement) by region - RS (LOCF-AD) - 1245.121

Subgroup Description	Placebo	Empa 10mg
Region (5 cat.): Other		
Number of patients in analysis set	87	86
Number of analysed patients, N (%)	77 (100.0)	76 (100.0)
Number of patients with endpoint, N (%)	40 (51.9)	48 (63.2)
95% confidence interval*	(41.0, 62.7)	(51.9, 73.1)
Comparison vs Placebo**		
Risk ratio (SE)		1.213 (0.158)
95% confidence interval***		(0.939, 1.566)
p-value		0.1387

* Wilson confidence intervals.
** Log-linked Poisson model with robust estimate of variance includes terms for baseline KCCQ - total symptom score (p<0.0001), age (p=0.7185), baseline eGFR (CKD-EPI) (p=0.1644), Treatment (p=0.0554), baseline diabetes status (3 cat.) (p=0.8695), sex (p=0.3821), baseline LVEF (3 cat.) (p=0.4899), region (5 cat.) (p<0.0001) and Treatment by region (5 cat.) interaction (p=0.4791).
***Wald confidence intervals.

Data taken from study 1245.121 only.
LOCF: For a missing value at week 52 the last available post-baseline value before week 52 is imputed.

R.1.2.6.5

R.1.2.6.5 Subgroup analysis by OECD (N/Y)

Table R.1.2.6.5: 1 Responder analysis (displaying odds ratio) in KCCQ-TSS change from baseline at week 52 of <= -5 points (deterioration) by OECD member (N/Y) - RS (LOCF-AD) - 1245.121

Subgroup Description	Placebo	Empa 10mg
OECD member: No		
Number of patients in analysis set	741	713
Number of analysed patients, N (%)	663 (100.0)	647 (100.0)
Number of patients with endpoint, N (%)	152 (22.9)	119 (18.4)
95% confidence interval*	(19.9, 26.3)	(15.6, 21.6)
Comparison vs Placebo**		
Odds ratio (SE)		0.770 (0.107)
95% confidence interval***		(0.586, 1.013)
p-value		0.0615
OECD member: Yes		
Number of patients in analysis set	1126	1150
Number of analysed patients, N (%)	1046 (100.0)	1093 (100.0)
Number of patients with endpoint, N (%)	276 (26.4)	271 (24.8)
95% confidence interval*	(23.8, 29.1)	(22.3, 27.4)
Comparison vs Placebo**		
Odds ratio (SE)		0.914 (0.092)
95% confidence interval***		(0.751, 1.113)
p-value		0.3727

* Wilson confidence intervals.
** Logistic regression includes terms for baseline KCCQ - total symptom score (p<0.0001), age (p=0.3993), baseline eGFR (CKD-EPI) (p=0.0002), Treatment (p=0.0413), sex (p=0.4595), baseline diabetes status (3 cat.) (p=0.2903), baseline LVEF (3 cat.) (p=0.4485), OECD member (p=0.0497) and Treatment by OECD member interaction (p=0.3198).
***Wald confidence intervals.

Data taken from study 1245.121 only.
LOCF: For a missing value at week 52 the last available post-baseline value before week 52 is imputed.
OECD member (yes/no) countries included:
Yes: United States, Canada, Mexico, Poland, Netherlands, Hungary, Germany, Czech Republic, Italy, France, Spain, United Kingdom, Belgium, Japan, Australia, 'Korea; Republic Of South Korea';
No: Brazil, Argentina, China, India.

Table R.1.2.6.5: 2 Responder analysis (displaying risk ratio) in KCCQ-TSS change from baseline at week 52 of <= -5 points (deterioration) by OECD member (N/Y) - RS (LOCF-AD) - 1245.121

Subgroup Description	Placebo	Empa 10mg
OECD member: No		
Number of patients in analysis set	741	713
Number of analysed patients, N (%)	663 (100.0)	647 (100.0)
Number of patients with endpoint, N (%)	152 (22.9)	119 (18.4)
95% confidence interval*	(19.9, 26.3)	(15.6, 21.6)
Comparison vs Placebo**		
Risk ratio (SE)		0.816 (0.088)
95% confidence interval***		(0.661, 1.009)
p-value		0.0601
OECD member: Yes		
Number of patients in analysis set	1126	1150
Number of analysed patients, N (%)	1046 (100.0)	1093 (100.0)
Number of patients with endpoint, N (%)	276 (26.4)	271 (24.8)
95% confidence interval*	(23.8, 29.1)	(22.3, 27.4)
Comparison vs Placebo**		
Risk ratio (SE)		0.937 (0.068)
95% confidence interval***		(0.812, 1.081)
p-value		0.3745

* Wilson confidence intervals.
** Log-linked Poisson model with robust estimate of variance includes terms for baseline KCCQ - total symptom score (p<0.0001), age (p=0.3932), baseline eGFR (CKD-EPI) (p=0.0002), Treatment (p=0.0397), sex (p=0.4575), baseline diabetes status (3 cat.) (p=0.2777), baseline LVEF (3 cat.) (p=0.4443), OECD member (p=0.0443) and Treatment by OECD member interaction (p=0.2894).
***Wald confidence intervals.

Data taken from study 1245.121 only.
LOCF: For a missing value at week 52 the last available post-baseline value before week 52 is imputed.
OECD member (yes/no) countries included:
Yes: United States, Canada, Mexico, Poland, Netherlands, Hungary, Germany, Czech Republic, Italy, France, Spain, United Kingdom, Belgium, Japan, Australia, 'Korea; Republic Of South Korea';
No: Brazil, Argentina, China, India.

Table R.1.2.6.5: 3 Responder analysis (displaying odds ratio) in KCCQ-TSS change from baseline at week 52 of > -5 points (stability) by OECD member (N/Y) - RS (LOCF-AD) - 1245.121

Subgroup Description	Placebo	Empa 10mg
OECD member: No		
Number of patients in analysis set	741	713
Number of analysed patients, N (%)	663 (100.0)	647 (100.0)
Number of patients with endpoint, N (%)	511 (77.1)	528 (81.6)
95% confidence interval*	(73.7, 80.1)	(78.4, 84.4)
Comparison vs Placebo**		
Odds ratio (SE)		1.298 (0.181)
95% confidence interval***		(0.988, 1.706)
p-value		0.0615
OECD member: Yes		
Number of patients in analysis set	1126	1150
Number of analysed patients, N (%)	1046 (100.0)	1093 (100.0)
Number of patients with endpoint, N (%)	770 (73.6)	822 (75.2)
95% confidence interval*	(70.9, 76.2)	(72.6, 77.7)
Comparison vs Placebo**		
Odds ratio (SE)		1.094 (0.110)
95% confidence interval***		(0.898, 1.332)
p-value		0.3727

* Wilson confidence intervals.
** Logistic regression includes terms for baseline KCCQ - total symptom score (p<0.0001), age (p=0.3993), baseline eGFR (CKD-EPI) (p=0.0002), Treatment (p=0.0413), sex (p=0.4595), baseline diabetes status (3 cat.) (p=0.2903), baseline LVEF (3 cat.) (p=0.4485), OECD member (p=0.0497) and Treatment by OECD member interaction (p=0.3198).
***Wald confidence intervals.

Data taken from study 1245.121 only.
LOCF: For a missing value at week 52 the last available post-baseline value before week 52 is imputed.
OECD member (yes/no) countries included:
Yes: United States, Canada, Mexico, Poland, Netherlands, Hungary, Germany, Czech Republic, Italy, France, Spain, United Kingdom, Belgium, Japan, Australia, 'Korea; Republic Of South Korea';
No: Brazil, Argentina, China, India.

Table R.1.2.6.5: 4 Responder analysis (displaying risk ratio) in KCCQ-TSS change from baseline at week 52 of > -5 points (stability) by OECD member (N/Y) - RS (LOCF-AD) - 1245.121

Subgroup Description	Placebo	Empa 10mg
OECD member: No		
Number of patients in analysis set	741	713
Number of analysed patients, N (%)	663 (100.0)	647 (100.0)
Number of patients with endpoint, N (%)	511 (77.1)	528 (81.6)
95% confidence interval*	(73.7, 80.1)	(78.4, 84.4)
Comparison vs Placebo**		
Risk ratio (SE)		1.051 (0.029)
95% confidence interval***		(0.995, 1.110)
p-value		0.0750
OECD member: Yes		
Number of patients in analysis set	1126	1150
Number of analysed patients, N (%)	1046 (100.0)	1093 (100.0)
Number of patients with endpoint, N (%)	770 (73.6)	822 (75.2)
95% confidence interval*	(70.9, 76.2)	(72.6, 77.7)
Comparison vs Placebo**		
Risk ratio (SE)		1.023 (0.026)
95% confidence interval***		(0.974, 1.075)
p-value		0.3635

* Wilson confidence intervals.
** Log-linked Poisson model with robust estimate of variance includes terms for baseline KCCQ - total symptom score (p<0.0001), age (p=0.4661), baseline eGFR (CKD-EPI) (p=0.0002), Treatment (p=0.0533), sex (p=0.4596), baseline diabetes status (3 cat.) (p=0.3388), baseline LVEF (3 cat.) (p=0.4766), OECD member (p=0.0656) and Treatment by OECD member interaction (p=0.4735).
***Wald confidence intervals.

Data taken from study 1245.121 only.
LOCF: For a missing value at week 52 the last available post-baseline value before week 52 is imputed.
OECD member (yes/no) countries included:
Yes: United States, Canada, Mexico, Poland, Netherlands, Hungary, Germany, Czech Republic, Italy, France, Spain, United Kingdom, Belgium, Japan, Australia, 'Korea; Republic Of South Korea';
No: Brazil, Argentina, China, India.

Table R.1.2.6.5: 5 Responder analysis (displaying odds ratio) in KCCQ-TSS change from baseline at week 52 of >= 5 points (improvement) by OECD member (N/Y) - RS (LOCF-AD) - 1245.121

Subgroup Description	Placebo	Empa 10mg
OECD member: No		
Number of patients in analysis set	741	713
Number of analysed patients, N (%)	663 (100.0)	647 (100.0)
Number of patients with endpoint, N (%)	321 (48.4)	359 (55.5)
95% confidence interval*	(44.6, 52.2)	(51.6, 59.3)
Comparison vs Placebo**		
Odds ratio (SE)		1.366 (0.174)
95% confidence interval***		(1.064, 1.755)
p-value		0.0144
OECD member: Yes		
Number of patients in analysis set	1126	1150
Number of analysed patients, N (%)	1046 (100.0)	1093 (100.0)
Number of patients with endpoint, N (%)	430 (41.1)	453 (41.4)
95% confidence interval*	(38.2, 44.1)	(38.6, 44.4)
Comparison vs Placebo**		
Odds ratio (SE)		1.036 (0.103)
95% confidence interval***		(0.852, 1.259)
p-value		0.7259

* Wilson confidence intervals.
** Logistic regression includes terms for baseline KCCQ - total symptom score (p<0.0001), age (p=0.3340), baseline eGFR (CKD-EPI) (p=0.1848), Treatment (p=0.0319), sex (p=0.5165), baseline diabetes status (3 cat.) (p=0.9013), baseline LVEF (3 cat.) (p=0.4600), OECD member (p<0.0001) and Treatment by OECD member interaction (p=0.0873).
***Wald confidence intervals.

Data taken from study 1245.121 only.
LOCF: For a missing value at week 52 the last available post-baseline value before week 52 is imputed.
OECD member (yes/no) countries included:
Yes: United States, Canada, Mexico, Poland, Netherlands, Hungary, Germany, Czech Republic, Italy, France, Spain, United Kingdom, Belgium, Japan, Australia, 'Korea; Republic Of South Korea';
No: Brazil, Argentina, China, India.

Table R.1.2.6.5: 6 Responder analysis (displaying risk ratio) in KCCQ-TSS change from baseline at week 52 of >= 5 points (improvement) by OECD member (N/Y) - RS (LOCF-AD) - 1245.121

Subgroup Description	Placebo	Empa 10mg
OECD member: No		
Number of patients in analysis set	741	713
Number of analysed patients, N (%)	663 (100.0)	647 (100.0)
Number of patients with endpoint, N (%)	321 (48.4)	359 (55.5)
95% confidence interval*	(44.6, 52.2)	(51.6, 59.3)
Comparison vs Placebo**		
Risk ratio (SE)		1.089 (0.054)
95% confidence interval***		(0.988, 1.201)
p-value		0.0862
OECD member: Yes		
Number of patients in analysis set	1126	1150
Number of analysed patients, N (%)	1046 (100.0)	1093 (100.0)
Number of patients with endpoint, N (%)	430 (41.1)	453 (41.4)
95% confidence interval*	(38.2, 44.1)	(38.6, 44.4)
Comparison vs Placebo**		
Risk ratio (SE)		1.013 (0.048)
95% confidence interval***		(0.923, 1.111)
p-value		0.7914

* Wilson confidence intervals.
** Log-linked Poisson model with robust estimate of variance includes terms for baseline KCCQ - total symptom score (p<0.0001), age (p=0.5582), baseline eGFR (CKD-EPI) (p=0.1438), Treatment (p=0.1540), sex (p=0.4337), baseline diabetes status (3 cat.) (p=0.9415), baseline LVEF (3 cat.) (p=0.5492), OECD member (p=0.0011) and Treatment by OECD member interaction (p=0.2902).
***Wald confidence intervals.

Data taken from study 1245.121 only.
LOCF: For a missing value at week 52 the last available post-baseline value before week 52 is imputed.
OECD member (yes/no) countries included:
Yes: United States, Canada, Mexico, Poland, Netherlands, Hungary, Germany, Czech Republic, Italy, France, Spain, United Kingdom, Belgium, Japan, Australia, 'Korea; Republic Of South Korea';
No: Brazil, Argentina, China, India.

R.1.2.6.6 Subgroup analysis by NYHA at baseline (II, III/IV - 2 cat.)

Table R.1.2.6.6: 1 Responder analysis (displaying odds ratio) in KCCQ-TSS change from baseline at week 52 of <= -5 points (deterioration) by NYHA (2 cat.) - RS (LOCF-AD) - 1245.121

Subgroup Description	Placebo	Empa 10mg
Baseline NYHA (2 cat.): II		
Number of patients in analysis set	1401	1399
Number of analysed patients, N (%)	1306 (100.0)	1307 (100.0)
Number of patients with endpoint, N (%)	326 (25.0)	283 (21.7)
95% confidence interval*	(22.7, 27.4)	(19.5, 24.0)
Comparison vs Placebo**		
Odds ratio (SE)		0.812 (0.077)
95% confidence interval***		(0.675, 0.977)
p-value		0.0273
Baseline NYHA (2 cat.): III/IV		
Number of patients in analysis set	466	464
Number of analysed patients, N (%)	403 (100.0)	433 (100.0)
Number of patients with endpoint, N (%)	102 (25.3)	107 (24.7)
95% confidence interval*	(21.3, 29.8)	(20.9, 29.0)
Comparison vs Placebo**		
Odds ratio (SE)		1.024 (0.168)
95% confidence interval***		(0.742, 1.413)
p-value		0.8855

* Wilson confidence intervals.
** Logistic regression includes terms for baseline KCCQ - total symptom score (p<0.0001), age (p=0.6373), baseline eGFR (CKD-EPI) (p=0.0007), Treatment (p=0.3293), region (5 cat.) (p=0.0006), baseline diabetes status (3 cat.) (p=0.4382), sex (p=0.4430), baseline LVEF (3 cat.) (p=0.6541), baseline NYHA (2 cat.) (p=0.0001) and Treatment by baseline NYHA (2 cat.) interaction (p=0.2207).
***Wald confidence intervals.

Data taken from study 1245.121 only.
LOCF: For a missing value at week 52 the last available post-baseline value before week 52 is imputed.

Table R.1.2.6.6: 2 Responder analysis (displaying risk ratio) in KCCQ-TSS change from baseline at week 52 of <= -5 points (deterioration) by NYHA (2 cat.) - RS (LOCF-AD) - 1245.121

Subgroup Description	Placebo	Empa 10mg
Baseline NYHA (2 cat.): II		
Number of patients in analysis set	1401	1399
Number of analysed patients, N (%)	1306 (100.0)	1307 (100.0)
Number of patients with endpoint, N (%)	326 (25.0)	283 (21.7)
95% confidence interval*	(22.7, 27.4)	(19.5, 24.0)
Comparison vs Placebo**		
Risk ratio (SE)		0.857 (0.060)
95% confidence interval***		(0.747, 0.983)
p-value		0.0274
Baseline NYHA (2 cat.): III/IV		
Number of patients in analysis set	466	464
Number of analysed patients, N (%)	403 (100.0)	433 (100.0)
Number of patients with endpoint, N (%)	102 (25.3)	107 (24.7)
95% confidence interval*	(21.3, 29.8)	(20.9, 29.0)
Comparison vs Placebo**		
Risk ratio (SE)		1.015 (0.118)
95% confidence interval***		(0.809, 1.274)
p-value		0.8966

* Wilson confidence intervals.
** Log-linked Poisson model with robust estimate of variance includes terms for baseline KCCQ - total symptom score (p<0.0001), age (p=0.6244), baseline eGFR (CKD-EPI) (p=0.0007), Treatment (p=0.3037), region (5 cat.) (p=0.0009), baseline diabetes status (3 cat.) (p=0.4288), sex (p=0.4297), baseline LVEF (3 cat.) (p=0.6503), baseline NYHA (2 cat.) (p<0.0001) and Treatment by baseline NYHA (2 cat.) interaction (p=0.2110).
***Wald confidence intervals.

Data taken from study 1245.121 only.
LOCF: For a missing value at week 52 the last available post-baseline value before week 52 is imputed.

Table R.1.2.6.6: 3 Responder analysis (displaying odds ratio) in KCCQ-TSS change from baseline at week 52 of > -5 points (stability) by NYHA (2 cat.) - RS (LOCF-AD) - 1245.121

Subgroup Description	Placebo	Empa 10mg
Baseline NYHA (2 cat.): II		
Number of patients in analysis set	1401	1399
Number of analysed patients, N (%)	1306 (100.0)	1307 (100.0)
Number of patients with endpoint, N (%)	980 (75.0)	1024 (78.3)
95% confidence interval*	(72.6, 77.3)	(76.0, 80.5)
Comparison vs Placebo**		
Odds ratio (SE)		1.232 (0.116)
95% confidence interval***		(1.024, 1.482)
p-value		0.0273
Baseline NYHA (2 cat.): III/IV		
Number of patients in analysis set	466	464
Number of analysed patients, N (%)	403 (100.0)	433 (100.0)
Number of patients with endpoint, N (%)	301 (74.7)	326 (75.3)
95% confidence interval*	(70.2, 78.7)	(71.0, 79.1)
Comparison vs Placebo**		
Odds ratio (SE)		0.977 (0.160)
95% confidence interval***		(0.708, 1.348)
p-value		0.8855

* Wilson confidence intervals.
** Logistic regression includes terms for baseline KCCQ - total symptom score (p<0.0001), age (p=0.6373), baseline eGFR (CKD-EPI) (p=0.0007), Treatment (p=0.3293), region (5 cat.) (p=0.0006), baseline diabetes status (3 cat.) (p=0.4382), sex (p=0.4430), baseline LVEF (3 cat.) (p=0.6541), baseline NYHA (2 cat.) (p=0.0001) and Treatment by baseline NYHA (2 cat.) interaction (p=0.2207).
***Wald confidence intervals.

Data taken from study 1245.121 only.
LOCF: For a missing value at week 52 the last available post-baseline value before week 52 is imputed.

Table R.1.2.6.6: 4 Responder analysis (displaying risk ratio) in KCCQ-TSS change from baseline at week 52 of > -5 points (stability) by NYHA (2 cat.) - RS (LOCF-AD) - 1245.121

Subgroup Description	Placebo	Empa 10mg
Baseline NYHA (2 cat.): II		
Number of patients in analysis set	1401	1399
Number of analysed patients, N (%)	1306 (100.0)	1307 (100.0)
Number of patients with endpoint, N (%)	980 (75.0)	1024 (78.3)
95% confidence interval*	(72.6, 77.3)	(76.0, 80.5)
Comparison vs Placebo**		
Risk ratio (SE)		1.047 (0.022)
95% confidence interval***		(1.005, 1.092)
p-value		0.0297
Baseline NYHA (2 cat.): III/IV		
Number of patients in analysis set	466	464
Number of analysed patients, N (%)	403 (100.0)	433 (100.0)
Number of patients with endpoint, N (%)	301 (74.7)	326 (75.3)
95% confidence interval*	(70.2, 78.7)	(71.0, 79.1)
Comparison vs Placebo**		
Risk ratio (SE)		0.994 (0.039)
95% confidence interval***		(0.921, 1.072)
p-value		0.8681

* Wilson confidence intervals.
** Log-linked Poisson model with robust estimate of variance includes terms for baseline KCCQ - total symptom score (p<0.0001), age (p=0.7669), baseline eGFR (CKD-EPI) (p=0.0006), Treatment (p=0.3692), region (5 cat.) (p<0.0001), baseline diabetes status (3 cat.) (p=0.4879), sex (p=0.4635), baseline LVEF (3 cat.) (p=0.6541), baseline NYHA (2 cat.) (p=0.0003) and Treatment by baseline NYHA (2 cat.) interaction (p=0.2341).
***Wald confidence intervals.

Data taken from study 1245.121 only.
LOCF: For a missing value at week 52 the last available post-baseline value before week 52 is imputed.

Table R.1.2.6.6: 5 Responder analysis (displaying odds ratio) in KCCQ-TSS change from baseline at week 52 of >= 5 points (improvement) by NYHA (2 cat.) - RS (LOCF-AD) - 1245.121

Subgroup Description	Placebo	Empa 10mg
Baseline NYHA (2 cat.): II		
Number of patients in analysis set	1401	1399
Number of analysed patients, N (%)	1306 (100.0)	1307 (100.0)
Number of patients with endpoint, N (%)	540 (41.3)	572 (43.8)
95% confidence interval*	(38.7, 44.0)	(41.1, 46.5)
Comparison vs Placebo**		
Odds ratio (SE)		1.208 (0.109)
95% confidence interval***		(1.012, 1.441)
p-value		0.0365
Baseline NYHA (2 cat.): III/IV		
Number of patients in analysis set	466	464
Number of analysed patients, N (%)	403 (100.0)	433 (100.0)
Number of patients with endpoint, N (%)	211 (52.4)	240 (55.4)
95% confidence interval*	(47.5, 57.2)	(50.7, 60.0)
Comparison vs Placebo**		
Odds ratio (SE)		0.980 (0.161)
95% confidence interval***		(0.710, 1.352)
p-value		0.9026

* Wilson confidence intervals.
** Logistic regression includes terms for baseline KCCQ - total symptom score (p<0.0001), age (p=0.5274), baseline eGFR (CKD-EPI) (p=0.2897), Treatment (p=0.3681), region (5 cat.) (p<0.0001), baseline diabetes status (3 cat.) (p=0.9864), sex (p=0.4607), baseline LVEF (3 cat.) (p=0.5691), baseline NYHA (2 cat.) (p<0.0001) and Treatment by baseline NYHA (2 cat.) interaction (p=0.2655).
***Wald confidence intervals.

Data taken from study 1245.121 only.
LOCF: For a missing value at week 52 the last available post-baseline value before week 52 is imputed.

Table R.1.2.6.6: 6 Responder analysis (displaying risk ratio) in KCCQ-TSS change from baseline at week 52 of >= 5 points (improvement) by NYHA (2 cat.) - RS (LOCF-AD) - 1245.121

Subgroup Description	Placebo	Empa 10mg
Baseline NYHA (2 cat.): II		
Number of patients in analysis set	1401	1399
Number of analysed patients, N (%)	1306 (100.0)	1307 (100.0)
Number of patients with endpoint, N (%)	540 (41.3)	572 (43.8)
95% confidence interval*	(38.7, 44.0)	(41.1, 46.5)
Comparison vs Placebo**		
Risk ratio (SE)		1.079 (0.044)
95% confidence interval***		(0.996, 1.169)
p-value		0.0628
Baseline NYHA (2 cat.): III/IV		
Number of patients in analysis set	466	464
Number of analysed patients, N (%)	403 (100.0)	433 (100.0)
Number of patients with endpoint, N (%)	211 (52.4)	240 (55.4)
95% confidence interval*	(47.5, 57.2)	(50.7, 60.0)
Comparison vs Placebo**		
Risk ratio (SE)		0.974 (0.061)
95% confidence interval***		(0.861, 1.102)
p-value		0.6794

* Wilson confidence intervals.
** Log-linked Poisson model with robust estimate of variance includes terms for baseline KCCQ - total symptom score (p<0.0001), age (p=0.8596), baseline eGFR (CKD-EPI) (p=0.1717), Treatment (p=0.5066), region (5 cat.) (p<0.0001), baseline diabetes status (3 cat.) (p=0.9527), sex (p=0.3636), baseline LVEF (3 cat.) (p=0.5538), baseline NYHA (2 cat.) (p=0.0002) and Treatment by baseline NYHA (2 cat.) interaction (p=0.1744).
***Wald confidence intervals.

Data taken from study 1245.121 only.
LOCF: For a missing value at week 52 the last available post-baseline value before week 52 is imputed.

R.1.2.6.7

R.1.2.6.7 Subgroup analysis by diabetes at baseline

Table R.1.2.6.7: 1 Responder analysis (displaying odds ratio) in KCCQ-TSS change from baseline at week 52 of <= -5 points (deterioration) by diabetes at baseline - RS (LOCF-AD) - 1245.121

Subgroup Description	Placebo	Empa 10mg
Diabetes at baseline (2 cat.): Diabetic		
Number of patients in analysis set	929	927
Number of analysed patients, N (%)	850 (100.0)	861 (100.0)
Number of patients with endpoint, N (%)	202 (23.8)	192 (22.3)
95% confidence interval*	(21.0, 26.7)	(19.6, 25.2)
Comparison vs Placebo**		
Odds ratio (SE)		0.911 (0.107)
95% confidence interval***		(0.725, 1.146)
p-value		0.4278
Diabetes at baseline (2 cat.): Non-Diabetic		
Number of patients in analysis set	938	936
Number of analysed patients, N (%)	859 (100.0)	879 (100.0)
Number of patients with endpoint, N (%)	226 (26.3)	198 (22.5)
95% confidence interval*	(23.5, 29.4)	(19.9, 25.4)
Comparison vs Placebo**		
Odds ratio (SE)		0.818 (0.093)
95% confidence interval***		(0.654, 1.022)
p-value		0.0770

* Wilson confidence intervals.
** Logistic regression includes terms for baseline KCCQ - total symptom score (p<0.0001), age (p=0.6169), baseline eGFR (CKD-EPI) (p=0.0004), Treatment (p=0.0717), region (5 cat.) (p=0.0004), sex (p=0.4315), baseline LVEF (3 cat.) (p=0.5733), diabetes at baseline (2 cat.) (p=0.7183) and Treatment by diabetes at baseline (2 cat.) interaction (p=0.5062).
***Wald confidence intervals.

Data taken from study 1245.121 only.
LOCF: For a missing value at week 52 the last available post-baseline value before week 52 is imputed.

Table R.1.2.6.7: 2 Responder analysis (displaying risk ratio) in KCCQ-TSS change from baseline at week 52 of <= -5 points (deterioration) by diabetes at baseline - RS (LOCF-AD) - 1245.121

Subgroup Description	Placebo	Empa 10mg
Diabetes at baseline (2 cat.): Diabetic		
Number of patients in analysis set	929	927
Number of analysed patients, N (%)	850 (100.0)	861 (100.0)
Number of patients with endpoint, N (%)	202 (23.8)	192 (22.3)
95% confidence interval*	(21.0, 26.7)	(19.6, 25.2)
Comparison vs Placebo**		
Risk ratio (SE)		0.932 (0.081)
95% confidence interval***		(0.787, 1.104)
p-value		0.4141
Diabetes at baseline (2 cat.): Non-Diabetic		
Number of patients in analysis set	938	936
Number of analysed patients, N (%)	859 (100.0)	879 (100.0)
Number of patients with endpoint, N (%)	226 (26.3)	198 (22.5)
95% confidence interval*	(23.5, 29.4)	(19.9, 25.4)
Comparison vs Placebo**		
Risk ratio (SE)		0.863 (0.072)
95% confidence interval***		(0.732, 1.017)
p-value		0.0780

* Wilson confidence intervals.
** Log-linked Poisson model with robust estimate of variance includes terms for baseline KCCQ - total symptom score (p<0.0001), age (p=0.5989), baseline eGFR (CKD-EPI) (p=0.0004), Treatment (p=0.0698), region (5 cat.) (p=0.0005), sex (p=0.4237), baseline LVEF (3 cat.) (p=0.5683), diabetes at baseline (2 cat.) (p=0.7215) and Treatment by diabetes at baseline (2 cat.) interaction (p=0.5230).
***Wald confidence intervals.

Data taken from study 1245.121 only.
LOCF: For a missing value at week 52 the last available post-baseline value before week 52 is imputed.

Table R.1.2.6.7: 3 Responder analysis (displaying odds ratio) in KCCQ-TSS change from baseline at week 52 of > -5 points (stability) by diabetes at baseline - RS (LOCF-AD) - 1245.121

Subgroup Description	Placebo	Empa 10mg
Diabetes at baseline (2 cat.): Diabetic		
Number of patients in analysis set	929	927
Number of analysed patients, N (%)	850 (100.0)	861 (100.0)
Number of patients with endpoint, N (%)	648 (76.2)	669 (77.7)
95% confidence interval*	(73.3, 79.0)	(74.8, 80.4)
Comparison vs Placebo**		
Odds ratio (SE)		1.097 (0.128)
95% confidence interval***		(0.872, 1.380)
p-value		0.4278
Diabetes at baseline (2 cat.): Non-Diabetic		
Number of patients in analysis set	938	936
Number of analysed patients, N (%)	859 (100.0)	879 (100.0)
Number of patients with endpoint, N (%)	633 (73.7)	681 (77.5)
95% confidence interval*	(70.6, 76.5)	(74.6, 80.1)
Comparison vs Placebo**		
Odds ratio (SE)		1.223 (0.139)
95% confidence interval***		(0.978, 1.529)
p-value		0.0770

* Wilson confidence intervals.
** Logistic regression includes terms for baseline KCCQ - total symptom score (p<0.0001), age (p=0.6169), baseline eGFR (CKD-EPI) (p=0.0004), Treatment (p=0.0717), region (5 cat.) (p=0.0004), sex (p=0.4315), baseline LVEF (3 cat.) (p=0.5733), diabetes at baseline (2 cat.) (p=0.7183) and Treatment by diabetes at baseline (2 cat.) interaction (p=0.5062).
***Wald confidence intervals.

Data taken from study 1245.121 only.
LOCF: For a missing value at week 52 the last available post-baseline value before week 52 is imputed.

Table R.1.2.6.7: 4 Responder analysis (displaying risk ratio) in KCCQ-TSS change from baseline at week 52 of > -5 points (stability) by diabetes at baseline - RS (LOCF-AD) - 1245.121

Subgroup Description	Placebo	Empa 10mg
Diabetes at baseline (2 cat.): Diabetic		
Number of patients in analysis set	929	927
Number of analysed patients, N (%)	850 (100.0)	861 (100.0)
Number of patients with endpoint, N (%)	648 (76.2)	669 (77.7)
95% confidence interval*	(73.3, 79.0)	(74.8, 80.4)
Comparison vs Placebo**		
Risk ratio (SE)		1.018 (0.026)
95% confidence interval***		(0.968, 1.072)
p-value		0.4810
Diabetes at baseline (2 cat.): Non-Diabetic		
Number of patients in analysis set	938	936
Number of analysed patients, N (%)	859 (100.0)	879 (100.0)
Number of patients with endpoint, N (%)	633 (73.7)	681 (77.5)
95% confidence interval*	(70.6, 76.5)	(74.6, 80.1)
Comparison vs Placebo**		
Risk ratio (SE)		1.048 (0.028)
95% confidence interval***		(0.994, 1.105)
p-value		0.0810

* Wilson confidence intervals.
** Log-linked Poisson model with robust estimate of variance includes terms for baseline KCCQ - total symptom score (p<0.0001), age (p=0.7341), baseline eGFR (CKD-EPI) (p=0.0004), Treatment (p=0.0810), region (5 cat.) (p<0.0001), sex (p=0.4422), baseline LVEF (3 cat.) (p=0.5947), diabetes at baseline (2 cat.) (p=0.7250) and Treatment by diabetes at baseline (2 cat.) interaction (p=0.4409).
***Wald confidence intervals.

Data taken from study 1245.121 only.
LOCF: For a missing value at week 52 the last available post-baseline value before week 52 is imputed.

Table R.1.2.6.7: 5 Responder analysis (displaying odds ratio) in KCCQ-TSS change from baseline at week 52 of >= 5 points (improvement) by diabetes at baseline - RS (LOCF-AD) - 1245.121

Subgroup Description	Placebo	Empa 10mg
Diabetes at baseline (2 cat.): Diabetic		
Number of patients in analysis set	929	927
Number of analysed patients, N (%)	850 (100.0)	861 (100.0)
Number of patients with endpoint, N (%)	385 (45.3)	415 (48.2)
95% confidence interval*	(42.0, 48.7)	(44.9, 51.5)
Comparison vs Placebo**		
Odds ratio (SE)		1.185 (0.133)
95% confidence interval***		(0.951, 1.478)
p-value		0.1306
Diabetes at baseline (2 cat.): Non-Diabetic		
Number of patients in analysis set	938	936
Number of analysed patients, N (%)	859 (100.0)	879 (100.0)
Number of patients with endpoint, N (%)	366 (42.6)	397 (45.2)
95% confidence interval*	(39.3, 45.9)	(41.9, 48.5)
Comparison vs Placebo**		
Odds ratio (SE)		1.109 (0.122)
95% confidence interval***		(0.894, 1.377)
p-value		0.3462

* Wilson confidence intervals.
** Logistic regression includes terms for baseline KCCQ - total symptom score (p<0.0001), age (p=0.5245), baseline eGFR (CKD-EPI) (p=0.2146), Treatment (p=0.0822), region (5 cat.) (p<0.0001), sex (p=0.5143), baseline LVEF (3 cat.) (p=0.5016), diabetes at baseline (2 cat.) (p=0.8220) and Treatment by diabetes at baseline (2 cat.) interaction (p=0.6741).
***Wald confidence intervals.

Data taken from study 1245.121 only.
LOCF: For a missing value at week 52 the last available post-baseline value before week 52 is imputed.

Table R.1.2.6.7: 6 Responder analysis (displaying risk ratio) in KCCQ-TSS change from baseline at week 52 of >= 5 points (improvement) by diabetes at baseline - RS (LOCF-AD) - 1245.121

Subgroup Description	Placebo	Empa 10mg
Diabetes at baseline (2 cat.): Diabetic		
Number of patients in analysis set	929	927
Number of analysed patients, N (%)	850 (100.0)	861 (100.0)
Number of patients with endpoint, N (%)	385 (45.3)	415 (48.2)
95% confidence interval*	(42.0, 48.7)	(44.9, 51.5)
Comparison vs Placebo**		
Risk ratio (SE)		1.055 (0.051)
95% confidence interval***		(0.960, 1.159)
p-value		0.2637
Diabetes at baseline (2 cat.): Non-Diabetic		
Number of patients in analysis set	938	936
Number of analysed patients, N (%)	859 (100.0)	879 (100.0)
Number of patients with endpoint, N (%)	366 (42.6)	397 (45.2)
95% confidence interval*	(39.3, 45.9)	(41.9, 48.5)
Comparison vs Placebo**		
Risk ratio (SE)		1.031 (0.051)
95% confidence interval***		(0.937, 1.135)
p-value		0.5333

* Wilson confidence intervals.
** Log-linked Poisson model with robust estimate of variance includes terms for baseline KCCQ - total symptom score (p<0.0001), age (p=0.7765), baseline eGFR (CKD-EPI) (p=0.1445), Treatment (p=0.2200), region (5 cat.) (p<0.0001), sex (p=0.3656), baseline LVEF (3 cat.) (p=0.5063), diabetes at baseline (2 cat.) (p=0.5980) and Treatment by diabetes at baseline (2 cat.) interaction (p=0.7363).
***Wald confidence intervals.

Data taken from study 1245.121 only.
LOCF: For a missing value at week 52 the last available post-baseline value before week 52 is imputed.

R.1.2.6.8 Subgroup analysis by BMI at baseline (<30, >=30)

Table R.1.2.6.8: 1 Responder analysis (displaying odds ratio) in KCCQ-TSS change from baseline at week 52 of <= -5 points (deterioration) by baseline BMI [kg/m2] - RS (LOCF-AD) - 1245.121

Subgroup Description	Placebo	Empa 10mg
Baseline BMI [kg/m²] (2 cat.): <30		
Number of patients in analysis set	1300	1263
Number of analysed patients, N (%)	1197 (100.0)	1181 (100.0)
Number of patients with endpoint, N (%)	289 (24.1)	257 (21.8)
95% confidence interval*	(21.8, 26.6)	(19.5, 24.2)
Comparison vs Placebo**		
Odds ratio (SE)		0.864 (0.086)
95% confidence interval***		(0.711, 1.049)
p-value		0.1404
Baseline BMI [kg/m²] (2 cat.): >=30		
Number of patients in analysis set	567	600
Number of analysed patients, N (%)	512 (100.0)	559 (100.0)
Number of patients with endpoint, N (%)	139 (27.1)	133 (23.8)
95% confidence interval*	(23.5, 31.2)	(20.4, 27.5)
Comparison vs Placebo**		
Odds ratio (SE)		0.846 (0.121)
95% confidence interval***		(0.639, 1.121)
p-value		0.2442

* Wilson confidence intervals.
** Logistic regression includes terms for baseline KCCQ - total symptom score (p<0.0001), age (p=0.3839), baseline eGFR (CKD-EPI) (p=0.0005), Treatment (p=0.0724), region (5 cat.) (p=0.0030), baseline diabetes status (3 cat.) (p=0.3908), sex (p=0.4630), baseline LVEF (3 cat.) (p=0.5805), baseline BMI (2 cat.) (p=0.0238) and Treatment by baseline BMI (2 cat.) interaction (p=0.9060).
***Wald confidence intervals.

Data taken from study 1245.121 only.
LOCF: For a missing value at week 52 the last available post-baseline value before week 52 is imputed.

Table R.1.2.6.8: 2 Responder analysis (displaying risk ratio) in KCCQ-TSS change from baseline at week 52 of <= -5 points (deterioration) by baseline BMI [kg/m2] - RS (LOCF-AD) - 1245.121

Subgroup Description	Placebo	Empa 10mg
Baseline BMI [kg/m²] (2 cat.): <30		
Number of patients in analysis set	1300	1263
Number of analysed patients, N (%)	1197 (100.0)	1181 (100.0)
Number of patients with endpoint, N (%)	289 (24.1)	257 (21.8)
95% confidence interval*	(21.8, 26.6)	(19.5, 24.2)
Comparison vs Placebo**		
Risk ratio (SE)		0.896 (0.066)
95% confidence interval***		(0.775, 1.036)
p-value		0.1371
Baseline BMI [kg/m²] (2 cat.): >=30		
Number of patients in analysis set	567	600
Number of analysed patients, N (%)	512 (100.0)	559 (100.0)
Number of patients with endpoint, N (%)	139 (27.1)	133 (23.8)
95% confidence interval*	(23.5, 31.2)	(20.4, 27.5)
Comparison vs Placebo**		
Risk ratio (SE)		0.887 (0.091)
95% confidence interval***		(0.726, 1.085)
p-value		0.2434

* Wilson confidence intervals.
** Log-linked Poisson model with robust estimate of variance includes terms for baseline KCCQ - total symptom score (p<0.0001), age (p=0.3784), baseline eGFR (CKD-EPI) (p=0.0005), Treatment (p=0.0696), region (5 cat.) (p=0.0037), baseline diabetes status (3 cat.) (p=0.3801), sex (p=0.4549), baseline LVEF (3 cat.) (p=0.5750), baseline BMI (2 cat.) (p=0.0231) and Treatment by baseline BMI (2 cat.) interaction (p=0.9394).
***Wald confidence intervals.

Data taken from study 1245.121 only.
LOCF: For a missing value at week 52 the last available post-baseline value before week 52 is imputed.

Table R.1.2.6.8: 3 Responder analysis (displaying odds ratio) in KCCQ-TSS change from baseline at week 52 of > -5 points (stability) by baseline BMI [kg/m2] - RS (LOCF-AD) - 1245.121

Subgroup Description	Placebo	Empa 10mg
Baseline BMI [kg/m²] (2 cat.): <30		
Number of patients in analysis set	1300	1263
Number of analysed patients, N (%)	1197 (100.0)	1181 (100.0)
Number of patients with endpoint, N (%)	908 (75.9)	924 (78.2)
95% confidence interval*	(73.4, 78.2)	(75.8, 80.5)
Comparison vs Placebo**		
Odds ratio (SE)		1.158 (0.115)
95% confidence interval***		(0.953, 1.407)
p-value		0.1404
Baseline BMI [kg/m²] (2 cat.): >=30		
Number of patients in analysis set	567	600
Number of analysed patients, N (%)	512 (100.0)	559 (100.0)
Number of patients with endpoint, N (%)	373 (72.9)	426 (76.2)
95% confidence interval*	(68.8, 76.5)	(72.5, 79.6)
Comparison vs Placebo**		
Odds ratio (SE)		1.182 (0.170)
95% confidence interval***		(0.892, 1.566)
p-value		0.2442

* Wilson confidence intervals.
** Logistic regression includes terms for baseline KCCQ - total symptom score (p<0.0001), age (p=0.3839), baseline eGFR (CKD-EPI) (p=0.0005), Treatment (p=0.0724), region (5 cat.) (p=0.0030), baseline diabetes status (3 cat.) (p=0.3908), sex (p=0.4630), baseline LVEF (3 cat.) (p=0.5805), baseline BMI (2 cat.) (p=0.0238) and Treatment by baseline BMI (2 cat.) interaction (p=0.9060).
***Wald confidence intervals.

Data taken from study 1245.121 only.
LOCF: For a missing value at week 52 the last available post-baseline value before week 52 is imputed.

Table R.1.2.6.8: 4 Responder analysis (displaying risk ratio) in KCCQ-TSS change from baseline at week 52 of > -5 points (stability) by baseline BMI [kg/m2] - RS (LOCF-AD) - 1245.121

Subgroup Description	Placebo	Empa 10mg
Baseline BMI [kg/m²] (2 cat.): <30		
Number of patients in analysis set	1300	1263
Number of analysed patients, N (%)	1197 (100.0)	1181 (100.0)
Number of patients with endpoint, N (%)	908 (75.9)	924 (78.2)
95% confidence interval*	(73.4, 78.2)	(75.8, 80.5)
Comparison vs Placebo**		
Risk ratio (SE)		1.031 (0.023)
95% confidence interval***		(0.987, 1.077)
p-value		0.1676
Baseline BMI [kg/m²] (2 cat.): >=30		
Number of patients in analysis set	567	600
Number of analysed patients, N (%)	512 (100.0)	559 (100.0)
Number of patients with endpoint, N (%)	373 (72.9)	426 (76.2)
95% confidence interval*	(68.8, 76.5)	(72.5, 79.6)
Comparison vs Placebo**		
Risk ratio (SE)		1.043 (0.037)
95% confidence interval***		(0.973, 1.117)
p-value		0.2371

* Wilson confidence intervals.
** Log-linked Poisson model with robust estimate of variance includes terms for baseline KCCQ - total symptom score (p<0.0001), age (p=0.4884), baseline eGFR (CKD-EPI) (p=0.0005), Treatment (p=0.0831), region (5 cat.) (p=0.0006), baseline diabetes status (3 cat.) (p=0.4495), sex (p=0.4850), baseline LVEF (3 cat.) (p=0.5914), baseline BMI (2 cat.) (p=0.0329) and Treatment by baseline BMI (2 cat.) interaction (p=0.7869).
***Wald confidence intervals.

Data taken from study 1245.121 only.
LOCF: For a missing value at week 52 the last available post-baseline value before week 52 is imputed.

Table R.1.2.6.8: 5 Responder analysis (displaying odds ratio) in KCCQ-TSS change from baseline at week 52 of >= 5 points (improvement) by baseline BMI [kg/m2] - RS (LOCF-AD) - 1245.121

Subgroup Description	Placebo	Empa 10mg
Baseline BMI [kg/m²] (2 cat.): <30		
Number of patients in analysis set	1300	1263
Number of analysed patients, N (%)	1197 (100.0)	1181 (100.0)
Number of patients with endpoint, N (%)	510 (42.6)	532 (45.0)
95% confidence interval*	(39.8, 45.4)	(42.2, 47.9)
Comparison vs Placebo**		
Odds ratio (SE)		1.169 (0.111)
95% confidence interval***		(0.971, 1.407)
p-value		0.0984
Baseline BMI [kg/m²] (2 cat.): >=30		
Number of patients in analysis set	567	600
Number of analysed patients, N (%)	512 (100.0)	559 (100.0)
Number of patients with endpoint, N (%)	241 (47.1)	280 (50.1)
95% confidence interval*	(42.8, 51.4)	(46.0, 54.2)
Comparison vs Placebo**		
Odds ratio (SE)		1.102 (0.157)
95% confidence interval***		(0.833, 1.458)
p-value		0.4954

* Wilson confidence intervals.
** Logistic regression includes terms for baseline KCCQ - total symptom score (p<0.0001), age (p=0.4502), baseline eGFR (CKD-EPI) (p=0.2217), Treatment (p=0.1388), region (5 cat.) (p<0.0001), baseline diabetes status (3 cat.) (p=0.9744), sex (p=0.4952), baseline LVEF (3 cat.) (p=0.4973), baseline BMI (2 cat.) (p=0.4556) and Treatment by baseline BMI (2 cat.) interaction (p=0.7310).
***Wald confidence intervals.

Data taken from study 1245.121 only.
LOCF: For a missing value at week 52 the last available post-baseline value before week 52 is imputed.

Table R.1.2.6.8: 6 Responder analysis (displaying risk ratio) in KCCQ-TSS change from baseline at week 52 of >= 5 points (improvement) by baseline BMI [kg/m2] - RS (LOCF-AD) - 1245.121

Subgroup Description	Placebo	Empa 10mg
Baseline BMI [kg/m²] (2 cat.): <30		
Number of patients in analysis set	1300	1263
Number of analysed patients, N (%)	1197 (100.0)	1181 (100.0)
Number of patients with endpoint, N (%)	510 (42.6)	532 (45.0)
95% confidence interval*	(39.8, 45.4)	(42.2, 47.9)
Comparison vs Placebo**		
Risk ratio (SE)		1.048 (0.044)
95% confidence interval***		(0.965, 1.137)
p-value		0.2633
Baseline BMI [kg/m²] (2 cat.): >=30		
Number of patients in analysis set	567	600
Number of analysed patients, N (%)	512 (100.0)	559 (100.0)
Number of patients with endpoint, N (%)	241 (47.1)	280 (50.1)
95% confidence interval*	(42.8, 51.4)	(46.0, 54.2)
Comparison vs Placebo**		
Risk ratio (SE)		1.037 (0.063)
95% confidence interval***		(0.921, 1.167)
p-value		0.5493

* Wilson confidence intervals.
** Log-linked Poisson model with robust estimate of variance includes terms for baseline KCCQ - total symptom score (p<0.0001), age (p=0.6992), baseline eGFR (CKD-EPI) (p=0.1515), Treatment (p=0.2591), region (5 cat.) (p<0.0001), baseline diabetes status (3 cat.) (p=0.9119), sex (p=0.3466), baseline LVEF (3 cat.) (p=0.5001), baseline BMI (2 cat.) (p=0.5067) and Treatment by baseline BMI (2 cat.) interaction (p=0.8864).
***Wald confidence intervals.

Data taken from study 1245.121 only.
LOCF: For a missing value at week 52 the last available post-baseline value before week 52 is imputed.

R.1.2.6.9 Subgroup analysis by eGFR at baseline (<60, >=60)

Table R.1.2.6.9: 1 Responder analysis (displaying odds ratio) in KCCQ-TSS change from baseline at week 52 of <= -5 points (deterioration) by baseline eGFR (2 cat.) - RS (LOCF-AD) - 1245.121

Subgroup Description	Placebo	Empa 10mg
Baseline eGFR (CKD-EPI) [mL/min/1.73m²] (2 cat.): >=60		
Number of patients in analysis set	960	969
Number of analysed patients, N (%)	875 (100.0)	903 (100.0)
Number of patients with endpoint, N (%)	213 (24.3)	179 (19.8)
95% confidence interval*	(21.6, 27.3)	(17.4, 22.5)
Comparison vs Placebo**		
Odds ratio (SE)		0.751 (0.088)
95% confidence interval***		(0.597, 0.944)
p-value		0.0143
Baseline eGFR (CKD-EPI) [mL/min/1.73m²] (2 cat.): <60		
Number of patients in analysis set	906	893
Number of analysed patients, N (%)	834 (100.0)	837 (100.0)
Number of patients with endpoint, N (%)	215 (25.8)	211 (25.2)
95% confidence interval*	(22.9, 28.9)	(22.4, 28.3)
Comparison vs Placebo**		
Odds ratio (SE)		0.981 (0.112)
95% confidence interval***		(0.784, 1.226)
p-value		0.8643

* Wilson confidence intervals.
** Logistic regression includes terms for baseline KCCQ - total symptom score (p<0.0001), age (p=0.0446), Treatment (p=0.0610), region (5 cat.) (p=0.0002), baseline diabetes status (3 cat.) (p=0.5535), sex (p=0.3568), baseline LVEF (3 cat.) (p=0.6741), baseline eGFR (CKD-EPI) (2 cat.) (p=0.2490) and Treatment by baseline eGFR (CKD-EPI) (2 cat.) interaction (p=0.1023).
***Wald confidence intervals.
2 patients were excluded as the subgroup variable was missing.

Data taken from study 1245.121 only.
LOCF: For a missing value at week 52 the last available post-baseline value before week 52 is imputed.

Table R.1.2.6.9: 2 Responder analysis (displaying risk ratio) in KCCQ-TSS change from baseline at week 52 of <= -5 points (deterioration) by baseline eGFR (2 cat.) - RS (LOCF-AD) - 1245.121

Subgroup Description	Placebo	Empa 10mg
Baseline eGFR (CKD-EPI) [mL/min/1.73m²] (2 cat.): >=60		
Number of patients in analysis set	960	969
Number of analysed patients, N (%)	875 (100.0)	903 (100.0)
Number of patients with endpoint, N (%)	213 (24.3)	179 (19.8)
95% confidence interval*	(21.6, 27.3)	(17.4, 22.5)
Comparison vs Placebo**		
Risk ratio (SE)		0.804 (0.072)
95% confidence interval***		(0.675, 0.958)
p-value		0.0147
Baseline eGFR (CKD-EPI) [mL/min/1.73m²] (2 cat.): <60		
Number of patients in analysis set	906	893
Number of analysed patients, N (%)	834 (100.0)	837 (100.0)
Number of patients with endpoint, N (%)	215 (25.8)	211 (25.2)
95% confidence interval*	(22.9, 28.9)	(22.4, 28.3)
Comparison vs Placebo**		
Risk ratio (SE)		0.986 (0.081)
95% confidence interval***		(0.840, 1.157)
p-value		0.8616

* Wilson confidence intervals.
** Log-linked Poisson model with robust estimate of variance includes terms for baseline KCCQ - total symptom score (p<0.0001), age (p=0.0475), Treatment (p=0.0545), region (5 cat.) (p=0.0003), baseline diabetes status (3 cat.) (p=0.5545), sex (p=0.3455), baseline LVEF (3 cat.) (p=0.6773), baseline eGFR (CKD-EPI) (2 cat.) (p=0.2339) and Treatment by baseline eGFR (CKD-EPI) (2 cat.) interaction (p=0.0926).
***Wald confidence intervals.
2 patients were excluded as the subgroup variable was missing.

Data taken from study 1245.121 only.
LOCF: For a missing value at week 52 the last available post-baseline value before week 52 is imputed.

Table R.1.2.6.9: 3 Responder analysis (displaying odds ratio) in KCCQ-TSS change from baseline at week 52 of > -5 points (stability) by baseline eGFR (2 cat.) - RS (LOCF-AD) - 1245.121

Subgroup Description	Placebo	Empa 10mg
Baseline eGFR (CKD-EPI) [mL/min/1.73m²] (2 cat.): >=60		
Number of patients in analysis set	960	969
Number of analysed patients, N (%)	875 (100.0)	903 (100.0)
Number of patients with endpoint, N (%)	662 (75.7)	724 (80.2)
95% confidence interval*	(72.7, 78.4)	(77.5, 82.6)
Comparison vs Placebo**		
Odds ratio (SE)		1.331 (0.156)
95% confidence interval***		(1.059, 1.674)
p-value		0.0143
Baseline eGFR (CKD-EPI) [mL/min/1.73m²] (2 cat.): <60		
Number of patients in analysis set	906	893
Number of analysed patients, N (%)	834 (100.0)	837 (100.0)
Number of patients with endpoint, N (%)	619 (74.2)	626 (74.8)
95% confidence interval*	(71.1, 77.1)	(71.7, 77.6)
Comparison vs Placebo**		
Odds ratio (SE)		1.020 (0.116)
95% confidence interval***		(0.815, 1.275)
p-value		0.8643

* Wilson confidence intervals.
** Logistic regression includes terms for baseline KCCQ - total symptom score (p<0.0001), age (p=0.0446), Treatment (p=0.0610), region (5 cat.) (p=0.0002), baseline diabetes status (3 cat.) (p=0.5535), sex (p=0.3568), baseline LVEF (3 cat.) (p=0.6741), baseline eGFR (CKD-EPI) (2 cat.) (p=0.2490) and Treatment by baseline eGFR (CKD-EPI) (2 cat.) interaction (p=0.1023).
***Wald confidence intervals.
2 patients were excluded as the subgroup variable was missing.

Data taken from study 1245.121 only.
LOCF: For a missing value at week 52 the last available post-baseline value before week 52 is imputed.

Table R.1.2.6.9: 4 Responder analysis (displaying risk ratio) in KCCQ-TSS change from baseline at week 52 of > -5 points (stability) by baseline eGFR (2 cat.) - RS (LOCF-AD) - 1245.121

Subgroup Description	Placebo	Empa 10mg
Baseline eGFR (CKD-EPI) [mL/min/1.73m²] (2 cat.): >=60		
Number of patients in analysis set	960	969
Number of analysed patients, N (%)	875 (100.0)	903 (100.0)
Number of patients with endpoint, N (%)	662 (75.7)	724 (80.2)
95% confidence interval*	(72.7, 78.4)	(77.5, 82.6)
Comparison vs Placebo**		
Risk ratio (SE)		1.060 (0.027)
95% confidence interval***		(1.009, 1.114)
p-value		0.0212
Baseline eGFR (CKD-EPI) [mL/min/1.73m²] (2 cat.): <60		
Number of patients in analysis set	906	893
Number of analysed patients, N (%)	834 (100.0)	837 (100.0)
Number of patients with endpoint, N (%)	619 (74.2)	626 (74.8)
95% confidence interval*	(71.1, 77.1)	(71.7, 77.6)
Comparison vs Placebo**		
Risk ratio (SE)		1.005 (0.028)
95% confidence interval***		(0.951, 1.062)
p-value		0.8537

* Wilson confidence intervals.
** Log-linked Poisson model with robust estimate of variance includes terms for baseline KCCQ - total symptom score (p<0.0001), age (p=0.0574), Treatment (p=0.0928), region (5 cat.) (p<0.0001), baseline diabetes status (3 cat.) (p=0.5891), sex (p=0.3957), baseline LVEF (3 cat.) (p=0.6700), baseline eGFR (CKD-EPI) (2 cat.) (p=0.2688) and Treatment by baseline eGFR (CKD-EPI) (2 cat.) interaction (p=0.1603).
***Wald confidence intervals.
2 patients were excluded as the subgroup variable was missing.

Data taken from study 1245.121 only.
LOCF: For a missing value at week 52 the last available post-baseline value before week 52 is imputed.

Table R.1.2.6.9: 5 Responder analysis (displaying odds ratio) in KCCQ-TSS change from baseline at week 52 of >= 5 points (improvement) by baseline eGFR (2 cat.) - RS (LOCF-AD) - 1245.121

Subgroup Description	Placebo	Empa 10mg
Baseline eGFR (CKD-EPI) [mL/min/1.73m²] (2 cat.): >=60		
Number of patients in analysis set	960	969
Number of analysed patients, N (%)	875 (100.0)	903 (100.0)
Number of patients with endpoint, N (%)	390 (44.6)	432 (47.8)
95% confidence interval*	(41.3, 47.9)	(44.6, 51.1)
Comparison vs Placebo**		
Odds ratio (SE)		1.206 (0.132)
95% confidence interval***		(0.973, 1.495)
p-value		0.0875
Baseline eGFR (CKD-EPI) [mL/min/1.73m²] (2 cat.): <60		
Number of patients in analysis set	906	893
Number of analysed patients, N (%)	834 (100.0)	837 (100.0)
Number of patients with endpoint, N (%)	361 (43.3)	380 (45.4)
95% confidence interval*	(40.0, 46.7)	(42.1, 48.8)
Comparison vs Placebo**		
Odds ratio (SE)		1.086 (0.123)
95% confidence interval***		(0.869, 1.356)
p-value		0.4682

* Wilson confidence intervals.
** Logistic regression includes terms for baseline KCCQ - total symptom score (p<0.0001), age (p=0.2594), Treatment (p=0.0872), region (5 cat.) (p<0.0001), baseline diabetes status (3 cat.) (p=0.9517), sex (p=0.5337), baseline LVEF (3 cat.) (p=0.5252), baseline eGFR (CKD-EPI) (2 cat.) (p=0.5066) and Treatment by baseline eGFR (CKD-EPI) (2 cat.) interaction (p=0.5046).
***Wald confidence intervals.
2 patients were excluded as the subgroup variable was missing.

Data taken from study 1245.121 only.
LOCF: For a missing value at week 52 the last available post-baseline value before week 52 is imputed.

Table R.1.2.6.9: 6 Responder analysis (displaying risk ratio) in KCCQ-TSS change from baseline at week 52 of >= 5 points (improvement) by baseline eGFR (2 cat.) - RS (LOCF-AD) - 1245.121

Subgroup Description	Placebo	Empa 10mg
Baseline eGFR (CKD-EPI) [mL/min/1.73m²] (2 cat.): >=60		
Number of patients in analysis set	960	969
Number of analysed patients, N (%)	875 (100.0)	903 (100.0)
Number of patients with endpoint, N (%)	390 (44.6)	432 (47.8)
95% confidence interval*	(41.3, 47.9)	(44.6, 51.1)
Comparison vs Placebo**		
Risk ratio (SE)		1.049 (0.050)
95% confidence interval***		(0.955, 1.151)
p-value		0.3180
Baseline eGFR (CKD-EPI) [mL/min/1.73m²] (2 cat.): <60		
Number of patients in analysis set	906	893
Number of analysed patients, N (%)	834 (100.0)	837 (100.0)
Number of patients with endpoint, N (%)	361 (43.3)	380 (45.4)
95% confidence interval*	(40.0, 46.7)	(42.1, 48.8)
Comparison vs Placebo**		
Risk ratio (SE)		1.037 (0.052)
95% confidence interval***		(0.941, 1.143)
p-value		0.4615

* Wilson confidence intervals.
** Log-linked Poisson model with robust estimate of variance includes terms for baseline KCCQ - total symptom score (p<0.0001), age (p=0.4336), Treatment (p=0.2220), region (5 cat.) (p<0.0001), baseline diabetes status (3 cat.) (p=0.8627), sex (p=0.3693), baseline LVEF (3 cat.) (p=0.5225), baseline eGFR (CKD-EPI) (2 cat.) (p=0.4060) and Treatment by baseline eGFR (CKD-EPI) (2 cat.) interaction (p=0.8746).
***Wald confidence intervals.
2 patients were excluded as the subgroup variable was missing.

Data taken from study 1245.121 only.
LOCF: For a missing value at week 52 the last available post-baseline value before week 52 is imputed.

R.1.2.6.10

Table R.1.2.6.10: 1 Responder analysis (displaying odds ratio) in KCCQ-TSS change from baseline at week 52 of <= -5 points (deterioration) by history of HHF - RS (LOCF-AD) - 1245.121

Subgroup Description	Placebo	Empa 10mg
History of HHF (in the last 12 months): No		
Number of patients in analysis set	1293	1286
Number of analysed patients, N (%)	1194 (100.0)	1212 (100.0)
Number of patients with endpoint, N (%)	288 (24.1)	270 (22.3)
95% confidence interval*	(21.8, 26.6)	(20.0, 24.7)
Comparison vs Placebo**		
Odds ratio (SE)		0.912 (0.090)
95% confidence interval***		(0.752, 1.106)
p-value		0.3488
History of HHF (in the last 12 months): Yes		
Number of patients in analysis set	574	577
Number of analysed patients, N (%)	515 (100.0)	528 (100.0)
Number of patients with endpoint, N (%)	140 (27.2)	120 (22.7)
95% confidence interval*	(23.5, 31.2)	(19.4, 26.5)
Comparison vs Placebo**		
Odds ratio (SE)		0.759 (0.111)
95% confidence interval***		(0.570, 1.012)
p-value		0.0603

* Wilson confidence intervals.
** Logistic regression includes terms for baseline KCCQ - total symptom score (p<0.0001), age (p=0.4964), baseline eGFR (CKD-EPI) (p=0.0004), Treatment (p=0.0374), region (5 cat.) (p=0.0004), baseline diabetes status (3 cat.) (p=0.4436), sex (p=0.4156), baseline LVEF (3 cat.) (p=0.5137), history of HHF (in the last 12 months) (p=0.1237) and Treatment by history of HHF (in the last 12 months) interaction (p=0.3001).
***Wald confidence intervals.

Data taken from study 1245.121 only.
LOCF: For a missing value at week 52 the last available post-baseline value before week 52 is imputed.

Table R.1.2.6.10: 2 Responder analysis (displaying risk ratio) in KCCQ-TSS change from baseline at week 52 of <= -5 points (deterioration) by history of HHF - RS (LOCF-AD) - 1245.121

Subgroup Description	Placebo	Empa 10mg
History of HHF (in the last 12 months): No		
Number of patients in analysis set	1293	1286
Number of analysed patients, N (%)	1194 (100.0)	1212 (100.0)
Number of patients with endpoint, N (%)	288 (24.1)	270 (22.3)
95% confidence interval*	(21.8, 26.6)	(20.0, 24.7)
Comparison vs Placebo**		
Risk ratio (SE)		0.934 (0.068)
95% confidence interval***		(0.809, 1.077)
p-value		0.3460
History of HHF (in the last 12 months): Yes		
Number of patients in analysis set	574	577
Number of analysed patients, N (%)	515 (100.0)	528 (100.0)
Number of patients with endpoint, N (%)	140 (27.2)	120 (22.7)
95% confidence interval*	(23.5, 31.2)	(19.4, 26.5)
Comparison vs Placebo**		
Risk ratio (SE)		0.817 (0.086)
95% confidence interval***		(0.664, 1.006)
p-value		0.0566

* Wilson confidence intervals.
** Log-linked Poisson model with robust estimate of variance includes terms for baseline KCCQ - total symptom score (p<0.0001), age (p=0.4833), baseline eGFR (CKD-EPI) (p=0.0004), Treatment (p=0.0353), region (5 cat.) (p=0.0005), baseline diabetes status (3 cat.) (p=0.4346), sex (p=0.4063), baseline LVEF (3 cat.) (p=0.5094), history of HHF (in the last 12 months) (p=0.1248) and Treatment by history of HHF (in the last 12 months) interaction (p=0.3010).
***Wald confidence intervals.

Data taken from study 1245.121 only.
LOCF: For a missing value at week 52 the last available post-baseline value before week 52 is imputed.

Table R.1.2.6.10: 3 Responder analysis (displaying odds ratio) in KCCQ-TSS change from baseline at week 52 of > -5 points (stability) by history of HHF - RS (LOCF-AD) - 1245.121

Subgroup Description	Placebo	Empa 10mg
History of HHF (in the last 12 months): No		
Number of patients in analysis set	1293	1286
Number of analysed patients, N (%)	1194 (100.0)	1212 (100.0)
Number of patients with endpoint, N (%)	906 (75.9)	942 (77.7)
95% confidence interval*	(73.4, 78.2)	(75.3, 80.0)
Comparison vs Placebo**		
Odds ratio (SE)		1.097 (0.108)
95% confidence interval***		(0.904, 1.330)
p-value		0.3488
History of HHF (in the last 12 months): Yes		
Number of patients in analysis set	574	577
Number of analysed patients, N (%)	515 (100.0)	528 (100.0)
Number of patients with endpoint, N (%)	375 (72.8)	408 (77.3)
95% confidence interval*	(68.8, 76.5)	(73.5, 80.6)
Comparison vs Placebo**		
Odds ratio (SE)		1.317 (0.193)
95% confidence interval***		(0.988, 1.754)
p-value		0.0603

* Wilson confidence intervals.
** Logistic regression includes terms for baseline KCCQ - total symptom score (p<0.0001), age (p=0.4964), baseline eGFR (CKD-EPI) (p=0.0004), Treatment (p=0.0374), region (5 cat.) (p=0.0004), baseline diabetes status (3 cat.) (p=0.4436), sex (p=0.4156), baseline LVEF (3 cat.) (p=0.5137), history of HHF (in the last 12 months) (p=0.1237) and Treatment by history of HHF (in the last 12 months) interaction (p=0.3001).
***Wald confidence intervals.

Data taken from study 1245.121 only.
LOCF: For a missing value at week 52 the last available post-baseline value before week 52 is imputed.

Table R.1.2.6.10: 4 Responder analysis (displaying risk ratio) in KCCQ-TSS change from baseline at week 52 of > -5 points (stability) by history of HHF - RS (LOCF-AD) - 1245.121

Subgroup Description	Placebo	Empa 10mg
History of HHF (in the last 12 months): No		
Number of patients in analysis set	1293	1286
Number of analysed patients, N (%)	1194 (100.0)	1212 (100.0)
Number of patients with endpoint, N (%)	906 (75.9)	942 (77.7)
95% confidence interval*	(73.4, 78.2)	(75.3, 80.0)
Comparison vs Placebo**		
Risk ratio (SE)		1.020 (0.023)
95% confidence interval***		(0.976, 1.065)
p-value		0.3778
History of HHF (in the last 12 months): Yes		
Number of patients in analysis set	574	577
Number of analysed patients, N (%)	515 (100.0)	528 (100.0)
Number of patients with endpoint, N (%)	375 (72.8)	408 (77.3)
95% confidence interval*	(68.8, 76.5)	(73.5, 80.6)
Comparison vs Placebo**		
Risk ratio (SE)		1.066 (0.038)
95% confidence interval***		(0.995, 1.142)
p-value		0.0711

* Wilson confidence intervals.
** Log-linked Poisson model with robust estimate of variance includes terms for baseline KCCQ - total symptom score (p<0.0001), age (p=0.6101), baseline eGFR (CKD-EPI) (p=0.0004), Treatment (p=0.0456), region (5 cat.) (p<0.0001), baseline diabetes status (3 cat.) (p=0.4965), sex (p=0.4337), baseline LVEF (3 cat.) (p=0.5388), history of HHF (in the last 12 months) (p=0.1401) and Treatment by history of HHF (in the last 12 months) interaction (p=0.2876).
***Wald confidence intervals.

Data taken from study 1245.121 only.
LOCF: For a missing value at week 52 the last available post-baseline value before week 52 is imputed.

Table R.1.2.6.10: 5 Responder analysis (displaying odds ratio) in KCCQ-TSS change from baseline at week 52 of >= 5 points (improvement) by history of HHF - RS (LOCF-AD) - 1245.121

Subgroup Description	Placebo	Empa 10mg
History of HHF (in the last 12 months): No		
Number of patients in analysis set	1293	1286
Number of analysed patients, N (%)	1194 (100.0)	1212 (100.0)
Number of patients with endpoint, N (%)	532 (44.6)	568 (46.9)
95% confidence interval*	(41.8, 47.4)	(44.1, 49.7)
Comparison vs Placebo**		
Odds ratio (SE)		1.120 (0.106)
95% confidence interval***		(0.931, 1.347)
p-value		0.2288
History of HHF (in the last 12 months): Yes		
Number of patients in analysis set	574	577
Number of analysed patients, N (%)	515 (100.0)	528 (100.0)
Number of patients with endpoint, N (%)	219 (42.5)	244 (46.2)
95% confidence interval*	(38.3, 46.8)	(42.0, 50.5)
Comparison vs Placebo**		
Odds ratio (SE)		1.208 (0.174)
95% confidence interval***		(0.911, 1.602)
p-value		0.1885

* Wilson confidence intervals.
** Logistic regression includes terms for baseline KCCQ - total symptom score (p<0.0001), age (p=0.4697), baseline eGFR (CKD-EPI) (p=0.2140), Treatment (p=0.0785), region (5 cat.) (p<0.0001), baseline diabetes status (3 cat.) (p=0.9657), sex (p=0.5132), baseline LVEF (3 cat.) (p=0.4789), history of HHF (in the last 12 months) (p=0.4383) and Treatment by history of HHF (in the last 12 months) interaction (p=0.6594).
***Wald confidence intervals.

Data taken from study 1245.121 only.
LOCF: For a missing value at week 52 the last available post-baseline value before week 52 is imputed.

Table R.1.2.6.10: 6 Responder analysis (displaying risk ratio) in KCCQ-TSS change from baseline at week 52 of >= 5 points (improvement) by history of HHF - RS (LOCF-AD) - 1245.121

Subgroup Description	Placebo	Empa 10mg
History of HHF (in the last 12 months): No		
Number of patients in analysis set	1293	1286
Number of analysed patients, N (%)	1194 (100.0)	1212 (100.0)
Number of patients with endpoint, N (%)	532 (44.6)	568 (46.9)
95% confidence interval*	(41.8, 47.4)	(44.1, 49.7)
Comparison vs Placebo**		
Risk ratio (SE)		1.039 (0.042)
95% confidence interval***		(0.959, 1.125)
p-value		0.3475
History of HHF (in the last 12 months): Yes		
Number of patients in analysis set	574	577
Number of analysed patients, N (%)	515 (100.0)	528 (100.0)
Number of patients with endpoint, N (%)	219 (42.5)	244 (46.2)
95% confidence interval*	(38.3, 46.8)	(42.0, 50.5)
Comparison vs Placebo**		
Risk ratio (SE)		1.055 (0.068)
95% confidence interval***		(0.930, 1.196)
p-value		0.4079

* Wilson confidence intervals.
** Log-linked Poisson model with robust estimate of variance includes terms for baseline KCCQ - total symptom score (p<0.0001), age (p=0.7327), baseline eGFR (CKD-EPI) (p=0.1567), Treatment (p=0.2296), region (5 cat.) (p<0.0001), baseline diabetes status (3 cat.) (p=0.8945), sex (p=0.3745), baseline LVEF (3 cat.) (p=0.5060), history of HHF (in the last 12 months) (p=0.4509) and Treatment by history of HHF (in the last 12 months) interaction (p=0.8432).
***Wald confidence intervals.

Data taken from study 1245.121 only.
LOCF: For a missing value at week 52 the last available post-baseline value before week 52 is imputed.

R.1.2.6.11

Table R.1.2.6.11: 1 Responder analysis (displaying odds ratio) in KCCQ-TSS change from baseline at week 52 of <= -5 points (deterioration) by cause of heart failure - RS (LOCF-AD) - 1245.121

Subgroup Description	Placebo	Empa 10mg
Cause of heart failure: Ischemic		
Number of patients in analysis set	946	983
Number of analysed patients, N (%)	876 (100.0)	923 (100.0)
Number of patients with endpoint, N (%)	223 (25.5)	216 (23.4)
95% confidence interval*	(22.7, 28.4)	(20.8, 26.2)
Comparison vs Placebo**		
Odds ratio (SE)		0.910 (0.102)
95% confidence interval***		(0.731, 1.133)
p-value		0.3989
Cause of heart failure: Non-ischemic		
Number of patients in analysis set	921	880
Number of analysed patients, N (%)	833 (100.0)	817 (100.0)
Number of patients with endpoint, N (%)	205 (24.6)	174 (21.3)
95% confidence interval*	(21.8, 27.6)	(18.6, 24.2)
Comparison vs Placebo**		
Odds ratio (SE)		0.811 (0.097)
95% confidence interval***		(0.642, 1.025)
p-value		0.0799

* Wilson confidence intervals.
** Logistic regression includes terms for baseline KCCQ - total symptom score (p<0.0001), age (p=0.5913), baseline eGFR (CKD-EPI) (p=0.0004), Treatment (p=0.0634), region (5 cat.) (p=0.0004), baseline diabetes status (3 cat.) (p=0.4886), sex (p=0.4508), baseline LVEF (3 cat.) (p=0.5687), cause of heart failure (p=0.9208) and Treatment by cause of heart failure interaction (p=0.4823).
***Wald confidence intervals.

Data taken from study 1245.121 only.
LOCF: For a missing value at week 52 the last available post-baseline value before week 52 is imputed.

Table R.1.2.6.11: 2 Responder analysis (displaying risk ratio) in KCCQ-TSS change from baseline at week 52 of <= -5 points (deterioration) by cause of heart failure - RS (LOCF-AD) - 1245.121

Subgroup Description	Placebo	Empa 10mg
Cause of heart failure: Ischemic		
Number of patients in analysis set	946	983
Number of analysed patients, N (%)	876 (100.0)	923 (100.0)
Number of patients with endpoint, N (%)	223 (25.5)	216 (23.4)
95% confidence interval*	(22.7, 28.4)	(20.8, 26.2)
Comparison vs Placebo**		
Risk ratio (SE)		0.933 (0.076)
95% confidence interval***		(0.796, 1.094)
p-value		0.3944
Cause of heart failure: Non-ischemic		
Number of patients in analysis set	921	880
Number of analysed patients, N (%)	833 (100.0)	817 (100.0)
Number of patients with endpoint, N (%)	205 (24.6)	174 (21.3)
95% confidence interval*	(21.8, 27.6)	(18.6, 24.2)
Comparison vs Placebo**		
Risk ratio (SE)		0.854 (0.076)
95% confidence interval***		(0.717, 1.018)
p-value		0.0783

* Wilson confidence intervals.
** Log-linked Poisson model with robust estimate of variance includes terms for baseline KCCQ - total symptom score (p<0.0001), age (p=0.5766), baseline eGFR (CKD-EPI) (p=0.0004), Treatment (p=0.0606), region (5 cat.) (p=0.0005), baseline diabetes status (3 cat.) (p=0.4831), sex (p=0.4452), baseline LVEF (3 cat.) (p=0.5630), cause of heart failure (p=0.9318) and Treatment by cause of heart failure interaction (p=0.4652).
***Wald confidence intervals.

Data taken from study 1245.121 only.
LOCF: For a missing value at week 52 the last available post-baseline value before week 52 is imputed.

Table R.1.2.6.11: 3 Responder analysis (displaying odds ratio) in KCCQ-TSS change from baseline at week 52 of > -5 points (stability) by cause of heart failure - RS (LOCF-AD) - 1245.121

Subgroup Description	Placebo	Empa 10mg
Cause of heart failure: Ischemic		
Number of patients in analysis set	946	983
Number of analysed patients, N (%)	876 (100.0)	923 (100.0)
Number of patients with endpoint, N (%)	653 (74.5)	707 (76.6)
95% confidence interval*	(71.6, 77.3)	(73.8, 79.2)
Comparison vs Placebo**		
Odds ratio (SE)		1.099 (0.123)
95% confidence interval***		(0.883, 1.368)
p-value		0.3989
Cause of heart failure: Non-ischemic		
Number of patients in analysis set	921	880
Number of analysed patients, N (%)	833 (100.0)	817 (100.0)
Number of patients with endpoint, N (%)	628 (75.4)	643 (78.7)
95% confidence interval*	(72.4, 78.2)	(75.8, 81.4)
Comparison vs Placebo**		
Odds ratio (SE)		1.233 (0.147)
95% confidence interval***		(0.975, 1.559)
p-value		0.0799

* Wilson confidence intervals.
** Logistic regression includes terms for baseline KCCQ - total symptom score (p<0.0001), age (p=0.5913), baseline eGFR (CKD-EPI) (p=0.0004), Treatment (p=0.0634), region (5 cat.) (p=0.0004), baseline diabetes status (3 cat.) (p=0.4886), sex (p=0.4508), baseline LVEF (3 cat.) (p=0.5687), cause of heart failure (p=0.9208) and Treatment by cause of heart failure interaction (p=0.4823).
***Wald confidence intervals.

Data taken from study 1245.121 only.
LOCF: For a missing value at week 52 the last available post-baseline value before week 52 is imputed.

Table R.1.2.6.11: 4 Responder analysis (displaying risk ratio) in KCCQ-TSS change from baseline at week 52 of > -5 points (stability) by cause of heart failure - RS (LOCF-AD) - 1245.121

Subgroup Description	Placebo	Empa 10mg
Cause of heart failure: Ischemic		
Number of patients in analysis set	946	983
Number of analysed patients, N (%)	876 (100.0)	923 (100.0)
Number of patients with endpoint, N (%)	653 (74.5)	707 (76.6)
95% confidence interval*	(71.6, 77.3)	(73.8, 79.2)
Comparison vs Placebo**		
Risk ratio (SE)		1.022 (0.027)
95% confidence interval***		(0.970, 1.076)
p-value		0.4098
Cause of heart failure: Non-ischemic		
Number of patients in analysis set	921	880
Number of analysed patients, N (%)	833 (100.0)	817 (100.0)
Number of patients with endpoint, N (%)	628 (75.4)	643 (78.7)
95% confidence interval*	(72.4, 78.2)	(75.8, 81.4)
Comparison vs Placebo**		
Risk ratio (SE)		1.045 (0.028)
95% confidence interval***		(0.992, 1.101)
p-value		0.0966

* Wilson confidence intervals.
** Log-linked Poisson model with robust estimate of variance includes terms for baseline KCCQ - total symptom score (p<0.0001), age (p=0.7068), baseline eGFR (CKD-EPI) (p=0.0004), Treatment (p=0.0783), region (5 cat.) (p<0.0001), baseline diabetes status (3 cat.) (p=0.5264), sex (p=0.4630), baseline LVEF (3 cat.) (p=0.5869), cause of heart failure (p=0.9400) and Treatment by cause of heart failure interaction (p=0.5480).
***Wald confidence intervals.

Data taken from study 1245.121 only.
LOCF: For a missing value at week 52 the last available post-baseline value before week 52 is imputed.

Table R.1.2.6.11: 5 Responder analysis (displaying odds ratio) in KCCQ-TSS change from baseline at week 52 of >= 5 points (improvement) by cause of heart failure - RS (LOCF-AD) - 1245.121

Subgroup Description	Placebo	Empa 10mg
Cause of heart failure: Ischemic		
Number of patients in analysis set	946	983
Number of analysed patients, N (%)	876 (100.0)	923 (100.0)
Number of patients with endpoint, N (%)	376 (42.9)	430 (46.6)
95% confidence interval*	(39.7, 46.2)	(43.4, 49.8)
Comparison vs Placebo**		
Odds ratio (SE)		1.164 (0.127)
95% confidence interval***		(0.940, 1.441)
p-value		0.1631
Cause of heart failure: Non-ischemic		
Number of patients in analysis set	921	880
Number of analysed patients, N (%)	833 (100.0)	817 (100.0)
Number of patients with endpoint, N (%)	375 (45.0)	382 (46.8)
95% confidence interval*	(41.7, 48.4)	(43.4, 50.2)
Comparison vs Placebo**		
Odds ratio (SE)		1.124 (0.128)
95% confidence interval***		(0.899, 1.406)
p-value		0.3051

* Wilson confidence intervals.
** Logistic regression includes terms for baseline KCCQ - total symptom score (p<0.0001), age (p=0.4570), baseline eGFR (CKD-EPI) (p=0.2006), Treatment (p=0.0882), region (5 cat.) (p<0.0001), baseline diabetes status (3 cat.) (p=0.9342), sex (p=0.4386), baseline LVEF (3 cat.) (p=0.4921), cause of heart failure (p=0.2967) and Treatment by cause of heart failure interaction (p=0.8250).
***Wald confidence intervals.

Data taken from study 1245.121 only.
LOCF: For a missing value at week 52 the last available post-baseline value before week 52 is imputed.

Table R.1.2.6.11: 6 Responder analysis (displaying risk ratio) in KCCQ-TSS change from baseline at week 52 of >= 5 points (improvement) by cause of heart failure - RS (LOCF-AD) - 1245.121

Subgroup Description	Placebo	Empa 10mg
Cause of heart failure: Ischemic		
Number of patients in analysis set	946	983
Number of analysed patients, N (%)	876 (100.0)	923 (100.0)
Number of patients with endpoint, N (%)	376 (42.9)	430 (46.6)
95% confidence interval*	(39.7, 46.2)	(43.4, 49.8)
Comparison vs Placebo**		
Risk ratio (SE)		1.048 (0.051)
95% confidence interval***		(0.953, 1.154)
p-value		0.3326
Cause of heart failure: Non-ischemic		
Number of patients in analysis set	921	880
Number of analysed patients, N (%)	833 (100.0)	817 (100.0)
Number of patients with endpoint, N (%)	375 (45.0)	382 (46.8)
95% confidence interval*	(41.7, 48.4)	(43.4, 50.2)
Comparison vs Placebo**		
Risk ratio (SE)		1.037 (0.050)
95% confidence interval***		(0.943, 1.140)
p-value		0.4587

* Wilson confidence intervals.
** Log-linked Poisson model with robust estimate of variance includes terms for baseline KCCQ - total symptom score (p<0.0001), age (p=0.7231), baseline eGFR (CKD-EPI) (p=0.1387), Treatment (p=0.2257), region (5 cat.) (p<0.0001), baseline diabetes status (3 cat.) (p=0.8314), sex (p=0.3240), baseline LVEF (3 cat.) (p=0.5077), cause of heart failure (p=0.4908) and Treatment by cause of heart failure interaction (p=0.8677).
***Wald confidence intervals.

Data taken from study 1245.121 only.
LOCF: For a missing value at week 52 the last available post-baseline value before week 52 is imputed.

R.1.2.6.12 Subgroup analysis by heart failure physiology (LVEF <= 30% and NTproBNP<median; LVEF <= 30% and NTproBNP>=median; LVEF > 30%)

Table R.1.2.6.12: 1 Responder analysis (displaying odds ratio) in KCCQ-TSS change from baseline at week 52 of <= -5 points (deterioration) by heart failure physiology - RS (LOCF-AD) - 1245.121

Subgroup Description	Placebo	Empa 10mg
Heart failure physiology: LVEF <= 30% and NTproBNP < median		
Number of patients in analysis set	723	698
Number of analysed patients, N (%)	679 (100.0)	655 (100.0)
Number of patients with endpoint, N (%)	152 (22.4)	138 (21.1)
95% confidence interval*	(19.4, 25.7)	(18.1, 24.4)
Comparison vs Placebo**		
Odds ratio (SE)		0.902 (0.122)
95% confidence interval***		(0.692, 1.175)
p-value		0.4449
Heart failure physiology: LVEF <= 30% and NTproBNP >= median		
Number of patients in analysis set	661	631
Number of analysed patients, N (%)	588 (100.0)	586 (100.0)
Number of patients with endpoint, N (%)	172 (29.3)	139 (23.7)
95% confidence interval*	(25.7, 33.1)	(20.5, 27.3)
Comparison vs Placebo**		
Odds ratio (SE)		0.767 (0.104)
95% confidence interval***		(0.588, 1.001)
p-value		0.0508

* Wilson confidence intervals.
** Logistic regression includes terms for baseline KCCQ - total symptom score (p<0.0001), age (p=0.5836), baseline eGFR (CKD-EPI) (p=0.0024), Treatment (p=0.0700), region (5 cat.) (p=0.0002), baseline diabetes status (3 cat.) (p=0.5149), sex (p=0.4193), heart failure physiology (p=0.0061) and Treatment by heart failure physiology interaction (p=0.6008).
***Wald confidence intervals.
16 patients were excluded as the subgroup variable was missing.

Data taken from study 1245.121 only.
LOCF: For a missing value at week 52 the last available post-baseline value before week 52 is imputed.
NTproBNP median [pg/mL]: with a. fibrillation/flutter at baseline: 2265; without a. fibrillation/flutter at baseline: 1671.

Table R.1.2.6.12: 1 Responder analysis (displaying odds ratio) in KCCQ-TSS change from baseline at week 52 of <= -5 points (deterioration) by heart failure physiology - RS (LOCF-AD) - 1245.121

Subgroup Description	Placebo	Empa 10mg
Heart failure physiology: LVEF > 30%		
Number of patients in analysis set	475	526
Number of analysed patients, N (%)	437 (100.0)	495 (100.0)
Number of patients with endpoint, N (%)	104 (23.8)	111 (22.4)
95% confidence interval*	(20.0, 28.0)	(19.0, 26.3)
Comparison vs Placebo**		
Odds ratio (SE)		0.922 (0.146)
95% confidence interval***		(0.676, 1.257)
p-value		0.6062

* Wilson confidence intervals.
** Logistic regression includes terms for baseline KCCQ - total symptom score (p<0.0001), age (p=0.5836), baseline eGFR (CKD-EPI) (p=0.0024), Treatment (p=0.0700), region (5 cat.) (p=0.0002), baseline diabetes status (3 cat.) (p=0.5149), sex (p=0.4193), heart failure physiology (p=0.0061) and Treatment by heart failure physiology interaction (p=0.6008).
***Wald confidence intervals.
16 patients were excluded as the subgroup variable was missing.

Data taken from study 1245.121 only.
LOCF: For a missing value at week 52 the last available post-baseline value before week 52 is imputed.
NTproBNP median [pg/mL]: with a. fibrillation/flutter at baseline: 2265; without a. fibrillation/flutter at baseline: 1671.

Table R.1.2.6.12: 2 Responder analysis (displaying risk ratio) in KCCQ-TSS change from baseline at week 52 of <= -5 points (deterioration) by heart failure physiology - RS (LOCF-AD) - 1245.121

Subgroup Description	Placebo	Empa 10mg
Heart failure physiology: LVEF <= 30% and NTproBNP < median		
Number of patients in analysis set	723	698
Number of analysed patients, N (%)	679 (100.0)	655 (100.0)
Number of patients with endpoint, N (%)	152 (22.4)	138 (21.1)
95% confidence interval*	(19.4, 25.7)	(18.1, 24.4)
Comparison vs Placebo**		
Risk ratio (SE)		0.925 (0.095)
95% confidence interval***		(0.756, 1.132)
p-value		0.4491
Heart failure physiology: LVEF <= 30% and NTproBNP >= median		
Number of patients in analysis set	661	631
Number of analysed patients, N (%)	588 (100.0)	586 (100.0)
Number of patients with endpoint, N (%)	172 (29.3)	139 (23.7)
95% confidence interval*	(25.7, 33.1)	(20.5, 27.3)
Comparison vs Placebo**		
Risk ratio (SE)		0.828 (0.079)
95% confidence interval***		(0.687, 0.998)
p-value		0.0479

* Wilson confidence intervals.
** Log-linked Poisson model with robust estimate of variance includes terms for baseline KCCQ - total symptom score (p<0.0001), age (p=0.5719), baseline eGFR (CKD-EPI) (p=0.0025), Treatment (p=0.0731), region (5 cat.) (p=0.0003), baseline diabetes status (3 cat.) (p=0.5130), sex (p=0.4158), heart failure physiology (p=0.0065) and Treatment by heart failure physiology interaction (p=0.6282).
***Wald confidence intervals.
16 patients were excluded as the subgroup variable was missing.

Data taken from study 1245.121 only.
LOCF: For a missing value at week 52 the last available post-baseline value before week 52 is imputed.
NTproBNP median [pg/mL]: with a. fibrillation/flutter at baseline: 2265; without a. fibrillation/flutter at baseline: 1671.

Table R.1.2.6.12: 2 Responder analysis (displaying risk ratio) in KCCQ-TSS change from baseline at week 52 of <= -5 points (deterioration) by heart failure physiology - RS (LOCF-AD) - 1245.121

Subgroup Description	Placebo	Empa 10mg
Heart failure physiology: LVEF > 30%		
Number of patients in analysis set	475	526
Number of analysed patients, N (%)	437 (100.0)	495 (100.0)
Number of patients with endpoint, N (%)	104 (23.8)	111 (22.4)
95% confidence interval*	(20.0, 28.0)	(19.0, 26.3)
Comparison vs Placebo**		
Risk ratio (SE)		0.940 (0.111)
95% confidence interval***		(0.746, 1.185)
p-value		0.6016

* Wilson confidence intervals.
** Log-linked Poisson model with robust estimate of variance includes terms for baseline KCCQ - total symptom score (p<0.0001), age (p=0.5719), baseline eGFR (CKD-EPI) (p=0.0025), Treatment (p=0.0731), region (5 cat.) (p=0.0003), baseline diabetes status (3 cat.) (p=0.5130), sex (p=0.4158), heart failure physiology (p=0.0065) and Treatment by heart failure physiology interaction (p=0.6282).
***Wald confidence intervals.
16 patients were excluded as the subgroup variable was missing.

Data taken from study 1245.121 only.
LOCF: For a missing value at week 52 the last available post-baseline value before week 52 is imputed.
NTproBNP median [pg/mL]: with a. fibrillation/flutter at baseline: 2265; without a. fibrillation/flutter at baseline: 1671.

Table R.1.2.6.12: 3 Responder analysis (displaying odds ratio) in KCCQ-TSS change from baseline at week 52 of > -5 points (stability) by heart failure physiology - RS (LOCF-AD) - 1245.121

Subgroup Description	Placebo	Empa 10mg
Heart failure physiology: LVEF <= 30% and NTproBNP < median		
Number of patients in analysis set	723	698
Number of analysed patients, N (%)	679 (100.0)	655 (100.0)
Number of patients with endpoint, N (%)	527 (77.6)	517 (78.9)
95% confidence interval*	(74.3, 80.6)	(75.6, 81.9)
Comparison vs Placebo**		
Odds ratio (SE)		1.109 (0.150)
95% confidence interval***		(0.851, 1.445)
p-value		0.4449
Heart failure physiology: LVEF <= 30% and NTproBNP >= median		
Number of patients in analysis set	661	631
Number of analysed patients, N (%)	588 (100.0)	586 (100.0)
Number of patients with endpoint, N (%)	416 (70.7)	447 (76.3)
95% confidence interval*	(66.9, 74.3)	(72.7, 79.5)
Comparison vs Placebo**		
Odds ratio (SE)		1.304 (0.177)
95% confidence interval***		(0.999, 1.702)
p-value		0.0508

* Wilson confidence intervals.
** Logistic regression includes terms for baseline KCCQ - total symptom score (p<0.0001), age (p=0.5836), baseline eGFR (CKD-EPI) (p=0.0024), Treatment (p=0.0700), region (5 cat.) (p=0.0002), baseline diabetes status (3 cat.) (p=0.5149), sex (p=0.4193), heart failure physiology (p=0.0061) and Treatment by heart failure physiology interaction (p=0.6008).
***Wald confidence intervals.
16 patients were excluded as the subgroup variable was missing.

Data taken from study 1245.121 only.
LOCF: For a missing value at week 52 the last available post-baseline value before week 52 is imputed.
NTproBNP median [pg/mL]: with a. fibrillation/flutter at baseline: 2265; without a. fibrillation/flutter at baseline: 1671.

Table R.1.2.6.12: 3 Responder analysis (displaying odds ratio) in KCCQ-TSS change from baseline at week 52 of > -5 points (stability) by heart failure physiology - RS (LOCF-AD) - 1245.121

Subgroup Description	Placebo	Empa 10mg
Heart failure physiology: LVEF > 30%		
Number of patients in analysis set	475	526
Number of analysed patients, N (%)	437 (100.0)	495 (100.0)
Number of patients with endpoint, N (%)	333 (76.2)	384 (77.6)
95% confidence interval*	(72.0, 80.0)	(73.7, 81.0)
Comparison vs Placebo**		
Odds ratio (SE)		1.085 (0.172)
95% confidence interval***		(0.795, 1.480)
p-value		0.6062

* Wilson confidence intervals.
** Logistic regression includes terms for baseline KCCQ - total symptom score (p<0.0001), age (p=0.5836), baseline eGFR (CKD-EPI) (p=0.0024), Treatment (p=0.0700), region (5 cat.) (p=0.0002), baseline diabetes status (3 cat.) (p=0.5149), sex (p=0.4193), heart failure physiology (p=0.0061) and Treatment by heart failure physiology interaction (p=0.6008).
***Wald confidence intervals.
16 patients were excluded as the subgroup variable was missing.

Data taken from study 1245.121 only.
LOCF: For a missing value at week 52 the last available post-baseline value before week 52 is imputed.
NTproBNP median [pg/mL]: with a. fibrillation/flutter at baseline: 2265; without a. fibrillation/flutter at baseline: 1671.

Table R.1.2.6.12: 4 Responder analysis (displaying risk ratio) in KCCQ-TSS change from baseline at week 52 of > -5 points (stability) by heart failure physiology - RS (LOCF-AD) - 1245.121

Subgroup Description	Placebo	Empa 10mg
Heart failure physiology: LVEF <= 30% and NTproBNP < median		
Number of patients in analysis set	723	698
Number of analysed patients, N (%)	679 (100.0)	655 (100.0)
Number of patients with endpoint, N (%)	527 (77.6)	517 (78.9)
95% confidence interval*	(74.3, 80.6)	(75.6, 81.9)
Comparison vs Placebo**		
Risk ratio (SE)		1.023 (0.029)
95% confidence interval***		(0.967, 1.082)
p-value		0.4357
Heart failure physiology: LVEF <= 30% and NTproBNP >= median		
Number of patients in analysis set	661	631
Number of analysed patients, N (%)	588 (100.0)	586 (100.0)
Number of patients with endpoint, N (%)	416 (70.7)	447 (76.3)
95% confidence interval*	(66.9, 74.3)	(72.7, 79.5)
Comparison vs Placebo**		
Risk ratio (SE)		1.068 (0.037)
95% confidence interval***		(0.998, 1.143)
p-value		0.0557

* Wilson confidence intervals.
** Log-linked Poisson model with robust estimate of variance includes terms for baseline KCCQ - total symptom score (p<0.0001), age (p=0.6741), baseline eGFR (CKD-EPI) (p=0.0025), Treatment (p=0.0677), region (5 cat.) (p<0.0001), baseline diabetes status (3 cat.) (p=0.5480), sex (p=0.4156), heart failure physiology (p=0.0052) and Treatment by heart failure physiology interaction (p=0.5306).
***Wald confidence intervals.
16 patients were excluded as the subgroup variable was missing.

Data taken from study 1245.121 only.
LOCF: For a missing value at week 52 the last available post-baseline value before week 52 is imputed.
NTproBNP median [pg/mL]: with a. fibrillation/flutter at baseline: 2265; without a. fibrillation/flutter at baseline: 1671.

Table R.1.2.6.12: 4 Responder analysis (displaying risk ratio) in KCCQ-TSS change from baseline at week 52 of > -5 points (stability) by heart failure physiology - RS (LOCF-AD) - 1245.121

Subgroup Description	Placebo	Empa 10mg
Heart failure physiology: LVEF > 30%		
Number of patients in analysis set	475	526
Number of analysed patients, N (%)	437 (100.0)	495 (100.0)
Number of patients with endpoint, N (%)	333 (76.2)	384 (77.6)
95% confidence interval*	(72.0, 80.0)	(73.7, 81.0)
Comparison vs Placebo**		
Risk ratio (SE)		1.016 (0.036)
95% confidence interval***		(0.948, 1.090)
p-value		0.6467

* Wilson confidence intervals.
** Log-linked Poisson model with robust estimate of variance includes terms for baseline KCCQ - total symptom score (p<0.0001), age (p=0.6741), baseline eGFR (CKD-EPI) (p=0.0025), Treatment (p=0.0677), region (5 cat.) (p<0.0001), baseline diabetes status (3 cat.) (p=0.5480), sex (p=0.4156), heart failure physiology (p=0.0052) and Treatment by heart failure physiology interaction (p=0.5306).
***Wald confidence intervals.
16 patients were excluded as the subgroup variable was missing.

Data taken from study 1245.121 only.
LOCF: For a missing value at week 52 the last available post-baseline value before week 52 is imputed.
NTproBNP median [pg/mL]: with a. fibrillation/flutter at baseline: 2265; without a. fibrillation/flutter at baseline: 1671.

Table R.1.2.6.12: 5 Responder analysis (displaying odds ratio) in KCCQ-TSS change from baseline at week 52 of >= 5 points (improvement) by heart failure physiology - RS (LOCF-AD) - 1245.121

Subgroup Description	Placebo	Empa 10mg
Heart failure physiology: LVEF <= 30% and NTproBNP < median		
Number of patients in analysis set	723	698
Number of analysed patients, N (%)	679 (100.0)	655 (100.0)
Number of patients with endpoint, N (%)	295 (43.4)	304 (46.4)
95% confidence interval*	(39.8, 47.2)	(42.6, 50.2)
Comparison vs Placebo**		
Odds ratio (SE)		1.256 (0.158)
95% confidence interval***		(0.981, 1.608)
p-value		0.0706
Heart failure physiology: LVEF <= 30% and NTproBNP >= median		
Number of patients in analysis set	661	631
Number of analysed patients, N (%)	588 (100.0)	586 (100.0)
Number of patients with endpoint, N (%)	250 (42.5)	283 (48.3)
95% confidence interval*	(38.6, 46.5)	(44.3, 52.3)
Comparison vs Placebo**		
Odds ratio (SE)		1.192 (0.163)
95% confidence interval***		(0.912, 1.559)
p-value		0.1982

* Wilson confidence intervals.
** Logistic regression includes terms for baseline KCCQ - total symptom score (p<0.0001), age (p=0.5039), baseline eGFR (CKD-EPI) (p=0.3809), Treatment (p=0.1163), region (5 cat.) (p<0.0001), baseline diabetes status (3 cat.) (p=0.9343), sex (p=0.5019), heart failure physiology (p=0.0295) and Treatment by heart failure physiology interaction (p=0.4111).
***Wald confidence intervals.
16 patients were excluded as the subgroup variable was missing.

Data taken from study 1245.121 only.
LOCF: For a missing value at week 52 the last available post-baseline value before week 52 is imputed.
NTproBNP median [pg/mL]: with a. fibrillation/flutter at baseline: 2265; without a. fibrillation/flutter at baseline: 1671.

Table R.1.2.6.12: 5 Responder analysis (displaying odds ratio) in KCCQ-TSS change from baseline at week 52 of >= 5 points (improvement) by heart failure physiology - RS (LOCF-AD) - 1245.121

Subgroup Description	Placebo	Empa 10mg
Heart failure physiology: LVEF > 30%		
Number of patients in analysis set	475	526
Number of analysed patients, N (%)	437 (100.0)	495 (100.0)
Number of patients with endpoint, N (%)	202 (46.2)	223 (45.1)
95% confidence interval*	(41.6, 50.9)	(40.7, 49.5)
Comparison vs Placebo**		
Odds ratio (SE)		0.973 (0.147)
95% confidence interval***		(0.723, 1.309)
p-value		0.8568

* Wilson confidence intervals.
** Logistic regression includes terms for baseline KCCQ - total symptom score (p<0.0001), age (p=0.5039), baseline eGFR (CKD-EPI) (p=0.3809), Treatment (p=0.1163), region (5 cat.) (p<0.0001), baseline diabetes status (3 cat.) (p=0.9343), sex (p=0.5019), heart failure physiology (p=0.0295) and Treatment by heart failure physiology interaction (p=0.4111).
***Wald confidence intervals.
16 patients were excluded as the subgroup variable was missing.

Data taken from study 1245.121 only.
LOCF: For a missing value at week 52 the last available post-baseline value before week 52 is imputed.
NTproBNP median [pg/mL]: with a. fibrillation/flutter at baseline: 2265; without a. fibrillation/flutter at baseline: 1671.

Table R.1.2.6.12: 6 Responder analysis (displaying risk ratio) in KCCQ-TSS change from baseline at week 52 of >= 5 points (improvement) by heart failure physiology - RS (LOCF-AD) - 1245.121

Subgroup Description	Placebo	Empa 10mg
Heart failure physiology: LVEF <= 30% and NTproBNP < median		
Number of patients in analysis set	723	698
Number of analysed patients, N (%)	679 (100.0)	655 (100.0)
Number of patients with endpoint, N (%)	295 (43.4)	304 (46.4)
95% confidence interval*	(39.8, 47.2)	(42.6, 50.2)
Comparison vs Placebo**		
Risk ratio (SE)		1.090 (0.061)
95% confidence interval***		(0.976, 1.217)
p-value		0.1254
Heart failure physiology: LVEF <= 30% and NTproBNP >= median		
Number of patients in analysis set	661	631
Number of analysed patients, N (%)	588 (100.0)	586 (100.0)
Number of patients with endpoint, N (%)	250 (42.5)	283 (48.3)
95% confidence interval*	(38.6, 46.5)	(44.3, 52.3)
Comparison vs Placebo**		
Risk ratio (SE)		1.066 (0.062)
95% confidence interval***		(0.951, 1.195)
p-value		0.2743

* Wilson confidence intervals.
** Log-linked Poisson model with robust estimate of variance includes terms for baseline KCCQ - total symptom score (p<0.0001), age (p=0.7445), baseline eGFR (CKD-EPI) (p=0.2826), Treatment (p=0.2668), region (5 cat.) (p<0.0001), baseline diabetes status (3 cat.) (p=0.8394), sex (p=0.4367), heart failure physiology (p=0.0244) and Treatment by heart failure physiology interaction (p=0.3368).
***Wald confidence intervals.
16 patients were excluded as the subgroup variable was missing.

Data taken from study 1245.121 only.
LOCF: For a missing value at week 52 the last available post-baseline value before week 52 is imputed.
NTproBNP median [pg/mL]: with a. fibrillation/flutter at baseline: 2265; without a. fibrillation/flutter at baseline: 1671.

Table R.1.2.6.12: 6 Responder analysis (displaying risk ratio) in KCCQ-TSS change from baseline at week 52 of >= 5 points (improvement) by heart failure physiology - RS (LOCF-AD) - 1245.121

Subgroup Description	Placebo	Empa 10mg
Heart failure physiology: LVEF > 30%		
Number of patients in analysis set	475	526
Number of analysed patients, N (%)	437 (100.0)	495 (100.0)
Number of patients with endpoint, N (%)	202 (46.2)	223 (45.1)
95% confidence interval*	(41.6, 50.9)	(40.7, 49.5)
Comparison vs Placebo**		
Risk ratio (SE)		0.966 (0.062)
95% confidence interval***		(0.851, 1.096)
p-value		0.5875

* Wilson confidence intervals.
** Log-linked Poisson model with robust estimate of variance includes terms for baseline KCCQ - total symptom score (p<0.0001), age (p=0.7445), baseline eGFR (CKD-EPI) (p=0.2826), Treatment (p=0.2668), region (5 cat.) (p<0.0001), baseline diabetes status (3 cat.) (p=0.8394), sex (p=0.4367), heart failure physiology (p=0.0244) and Treatment by heart failure physiology interaction (p=0.3368).
***Wald confidence intervals.
16 patients were excluded as the subgroup variable was missing.

Data taken from study 1245.121 only.
LOCF: For a missing value at week 52 the last available post-baseline value before week 52 is imputed.
NTproBNP median [pg/mL]: with a. fibrillation/flutter at baseline: 2265; without a. fibrillation/flutter at baseline: 1671.

R.1.2.6.13

Table R.1.2.6.13: 1 Responder analysis (displaying odds ratio) in KCCQ-TSS change from baseline at week 52 of <= -5 points (deterioration) by baseline use of MRA (Y/N) - RS (LOCF-AD) - 1245.121

Subgroup Description	Placebo	Empa 10mg
Baseline use of MRA: No		
Number of patients in analysis set	512	557
Number of analysed patients, N (%)	475 (100.0)	522 (100.0)
Number of patients with endpoint, N (%)	125 (26.3)	106 (20.3)
95% confidence interval*	(22.6, 30.5)	(17.1, 24.0)
Comparison vs Placebo**		
Odds ratio (SE)		0.719 (0.110)
95% confidence interval***		(0.533, 0.971)
p-value		0.0312
Baseline use of MRA: Yes		
Number of patients in analysis set	1355	1306
Number of analysed patients, N (%)	1234 (100.0)	1218 (100.0)
Number of patients with endpoint, N (%)	303 (24.6)	284 (23.3)
95% confidence interval*	(22.2, 27.0)	(21.0, 25.8)
Comparison vs Placebo**		
Odds ratio (SE)		0.929 (0.090)
95% confidence interval***		(0.769, 1.123)
p-value		0.4464

* Wilson confidence intervals.
** Logistic regression includes terms for baseline KCCQ - total symptom score (p<0.0001), age (p=0.5371), baseline eGFR (CKD-EPI) (p=0.0003), Treatment (p=0.0258), region (5 cat.) (p=0.0005), baseline diabetes status (3 cat.) (p=0.4661), sex (p=0.4511), baseline LVEF (3 cat.) (p=0.6230), baseline use of MRA (p=0.1936) and Treatment by baseline use of MRA interaction (p=0.1569).
***Wald confidence intervals.

Data taken from study 1245.121 only.
LOCF: For a missing value at week 52 the last available post-baseline value before week 52 is imputed.

Table R.1.2.6.13: 2 Responder analysis (displaying risk ratio) in KCCQ-TSS change from baseline at week 52 of <= -5 points (deterioration) by baseline use of MRA (Y/N) - RS (LOCF-AD) - 1245.121

Subgroup Description	Placebo	Empa 10mg
Baseline use of MRA: No		
Number of patients in analysis set	512	557
Number of analysed patients, N (%)	475 (100.0)	522 (100.0)
Number of patients with endpoint, N (%)	125 (26.3)	106 (20.3)
95% confidence interval*	(22.6, 30.5)	(17.1, 24.0)
Comparison vs Placebo**		
Risk ratio (SE)		0.782 (0.088)
95% confidence interval***		(0.627, 0.975)
p-value		0.0291
Baseline use of MRA: Yes		
Number of patients in analysis set	1355	1306
Number of analysed patients, N (%)	1234 (100.0)	1218 (100.0)
Number of patients with endpoint, N (%)	303 (24.6)	284 (23.3)
95% confidence interval*	(22.2, 27.0)	(21.0, 25.8)
Comparison vs Placebo**		
Risk ratio (SE)		0.947 (0.067)
95% confidence interval***		(0.824, 1.088)
p-value		0.4397

* Wilson confidence intervals.
** Log-linked Poisson model with robust estimate of variance includes terms for baseline KCCQ - total symptom score (p<0.0001), age (p=0.5210), baseline eGFR (CKD-EPI) (p=0.0003), Treatment (p=0.0239), region (5 cat.) (p=0.0007), baseline diabetes status (3 cat.) (p=0.4588), sex (p=0.4470), baseline LVEF (3 cat.) (p=0.6185), baseline use of MRA (p=0.1790) and Treatment by baseline use of MRA interaction (p=0.1516).
***Wald confidence intervals.

Data taken from study 1245.121 only.
LOCF: For a missing value at week 52 the last available post-baseline value before week 52 is imputed.

Table R.1.2.6.13: 3 Responder analysis (displaying odds ratio) in KCCQ-TSS change from baseline at week 52 of > -5 points (stability) by baseline use of MRA (Y/N) - RS (LOCF-AD) - 1245.121

Subgroup Description	Placebo	Empa 10mg
Baseline use of MRA: No		
Number of patients in analysis set	512	557
Number of analysed patients, N (%)	475 (100.0)	522 (100.0)
Number of patients with endpoint, N (%)	350 (73.7)	416 (79.7)
95% confidence interval*	(69.5, 77.4)	(76.0, 82.9)
Comparison vs Placebo**		
Odds ratio (SE)		1.391 (0.213)
95% confidence interval***		(1.030, 1.878)
p-value		0.0312
Baseline use of MRA: Yes		
Number of patients in analysis set	1355	1306
Number of analysed patients, N (%)	1234 (100.0)	1218 (100.0)
Number of patients with endpoint, N (%)	931 (75.4)	934 (76.7)
95% confidence interval*	(73.0, 77.8)	(74.2, 79.0)
Comparison vs Placebo**		
Odds ratio (SE)		1.076 (0.104)
95% confidence interval***		(0.891, 1.301)
p-value		0.4464

* Wilson confidence intervals.
** Logistic regression includes terms for baseline KCCQ - total symptom score (p<0.0001), age (p=0.5371), baseline eGFR (CKD-EPI) (p=0.0003), Treatment (p=0.0258), region (5 cat.) (p=0.0005), baseline diabetes status (3 cat.) (p=0.4661), sex (p=0.4511), baseline LVEF (3 cat.) (p=0.6230), baseline use of MRA (p=0.1936) and Treatment by baseline use of MRA interaction (p=0.1569).
***Wald confidence intervals.

Data taken from study 1245.121 only.
LOCF: For a missing value at week 52 the last available post-baseline value before week 52 is imputed.

Table R.1.2.6.13: 4 Responder analysis (displaying risk ratio) in KCCQ-TSS change from baseline at week 52 of > -5 points (stability) by baseline use of MRA (Y/N) - RS (LOCF-AD) - 1245.121

Subgroup Description	Placebo	Empa 10mg
Baseline use of MRA: No		
Number of patients in analysis set	512	557
Number of analysed patients, N (%)	475 (100.0)	522 (100.0)
Number of patients with endpoint, N (%)	350 (73.7)	416 (79.7)
95% confidence interval*	(69.5, 77.4)	(76.0, 82.9)
Comparison vs Placebo**		
Risk ratio (SE)		1.075 (0.037)
95% confidence interval***		(1.005, 1.150)
p-value		0.0357
Baseline use of MRA: Yes		
Number of patients in analysis set	1355	1306
Number of analysed patients, N (%)	1234 (100.0)	1218 (100.0)
Number of patients with endpoint, N (%)	931 (75.4)	934 (76.7)
95% confidence interval*	(73.0, 77.8)	(74.2, 79.0)
Comparison vs Placebo**		
Risk ratio (SE)		1.016 (0.023)
95% confidence interval***		(0.972, 1.061)
p-value		0.4821

* Wilson confidence intervals.
** Log-linked Poisson model with robust estimate of variance includes terms for baseline KCCQ - total symptom score (p<0.0001), age (p=0.6453), baseline eGFR (CKD-EPI) (p=0.0003), Treatment (p=0.0320), region (5 cat.) (p<0.0001), baseline diabetes status (3 cat.) (p=0.5162), sex (p=0.4558), baseline LVEF (3 cat.) (p=0.6358), baseline use of MRA (p=0.2200) and Treatment by baseline use of MRA interaction (p=0.1684).
***Wald confidence intervals.

Data taken from study 1245.121 only.
LOCF: For a missing value at week 52 the last available post-baseline value before week 52 is imputed.

Table R.1.2.6.13: 5 Responder analysis (displaying odds ratio) in KCCQ-TSS change from baseline at week 52 of >= 5 points (improvement) by baseline use of MRA (Y/N) - RS (LOCF-AD) - 1245.121

Subgroup Description	Placebo	Empa 10mg
Baseline use of MRA: No		
Number of patients in analysis set	512	557
Number of analysed patients, N (%)	475 (100.0)	522 (100.0)
Number of patients with endpoint, N (%)	199 (41.9)	249 (47.7)
95% confidence interval*	(37.5, 46.4)	(43.4, 52.0)
Comparison vs Placebo**		
Odds ratio (SE)		1.313 (0.192)
95% confidence interval***		(0.986, 1.748)
p-value		0.0624
Baseline use of MRA: Yes		
Number of patients in analysis set	1355	1306
Number of analysed patients, N (%)	1234 (100.0)	1218 (100.0)
Number of patients with endpoint, N (%)	552 (44.7)	563 (46.2)
95% confidence interval*	(42.0, 47.5)	(43.4, 49.0)
Comparison vs Placebo**		
Odds ratio (SE)		1.081 (0.101)
95% confidence interval***		(0.900, 1.299)
p-value		0.4048

* Wilson confidence intervals.
** Logistic regression includes terms for baseline KCCQ - total symptom score (p<0.0001), age (p=0.4383), baseline eGFR (CKD-EPI) (p=0.1738), Treatment (p=0.0436), region (5 cat.) (p<0.0001), baseline diabetes status (3 cat.) (p=0.9504), sex (p=0.4929), baseline LVEF (3 cat.) (p=0.5640), baseline use of MRA (p=0.1356) and Treatment by baseline use of MRA interaction (p=0.2634).
***Wald confidence intervals.

Data taken from study 1245.121 only.
LOCF: For a missing value at week 52 the last available post-baseline value before week 52 is imputed.

Table R.1.2.6.13: 6 Responder analysis (displaying risk ratio) in KCCQ-TSS change from baseline at week 52 of >= 5 points (improvement) by baseline use of MRA (Y/N) - RS (LOCF-AD) - 1245.121

Subgroup Description	Placebo	Empa 10mg
Baseline use of MRA: No		
Number of patients in analysis set	512	557
Number of analysed patients, N (%)	475 (100.0)	522 (100.0)
Number of patients with endpoint, N (%)	199 (41.9)	249 (47.7)
95% confidence interval*	(37.5, 46.4)	(43.4, 52.0)
Comparison vs Placebo**		
Risk ratio (SE)		1.101 (0.072)
95% confidence interval***		(0.969, 1.251)
p-value		0.1380
Baseline use of MRA: Yes		
Number of patients in analysis set	1355	1306
Number of analysed patients, N (%)	1234 (100.0)	1218 (100.0)
Number of patients with endpoint, N (%)	552 (44.7)	563 (46.2)
95% confidence interval*	(42.0, 47.5)	(43.4, 49.0)
Comparison vs Placebo**		
Risk ratio (SE)		1.019 (0.041)
95% confidence interval***		(0.942, 1.104)
p-value		0.6360

* Wilson confidence intervals.
** Log-linked Poisson model with robust estimate of variance includes terms for baseline KCCQ - total symptom score (p<0.0001), age (p=0.7059), baseline eGFR (CKD-EPI) (p=0.1206), Treatment (p=0.1312), region (5 cat.) (p<0.0001), baseline diabetes status (3 cat.) (p=0.8634), sex (p=0.3550), baseline LVEF (3 cat.) (p=0.5256), baseline use of MRA (p=0.1975) and Treatment by baseline use of MRA interaction (p=0.3127).
***Wald confidence intervals.

Data taken from study 1245.121 only.
LOCF: For a missing value at week 52 the last available post-baseline value before week 52 is imputed.

R.1.2.6.14

Table R.1.2.6.14: 1 Responder analysis (displaying odds ratio) in KCCQ-TSS change from baseline at week 52 of <= -5 points (deterioration) by baseline use of ARNi (Y/N) - RS (LOCF-AD) - 1245.121

Subgroup Description	Placebo	Empa 10mg
Baseline use of ARNi: No		
Number of patients in analysis set	1480	1523
Number of analysed patients, N (%)	1350 (100.0)	1418 (100.0)
Number of patients with endpoint, N (%)	335 (24.8)	323 (22.8)
95% confidence interval*	(22.6, 27.2)	(20.7, 25.0)
Comparison vs Placebo**		
Odds ratio (SE)		0.891 (0.081)
95% confidence interval***		(0.746, 1.065)
p-value		0.2056
Baseline use of ARNi: Yes		
Number of patients in analysis set	387	340
Number of analysed patients, N (%)	359 (100.0)	322 (100.0)
Number of patients with endpoint, N (%)	93 (25.9)	67 (20.8)
95% confidence interval*	(21.6, 30.7)	(16.7, 25.6)
Comparison vs Placebo**		
Odds ratio (SE)		0.744 (0.139)
95% confidence interval***		(0.516, 1.071)
p-value		0.1117

* Wilson confidence intervals.
** Logistic regression includes terms for baseline KCCQ - total symptom score (p<0.0001), age (p=0.6087), baseline eGFR (CKD-EPI) (p=0.0004), Treatment (p=0.0471), region (5 cat.) (p=0.0004), baseline diabetes status (3 cat.) (p=0.4590), sex (p=0.4112), baseline LVEF (3 cat.) (p=0.5428), baseline use of ARNi (p=0.3770) and Treatment by baseline use of ARNi interaction (p=0.3824).
***Wald confidence intervals.

Data taken from study 1245.121 only.
LOCF: For a missing value at week 52 the last available post-baseline value before week 52 is imputed.

Table R.1.2.6.14: 2 Responder analysis (displaying risk ratio) in KCCQ-TSS change from baseline at week 52 of <= -5 points (deterioration) by baseline use of ARNi (Y/N) - RS (LOCF-AD) - 1245.121

Subgroup Description	Placebo	Empa 10mg
Baseline use of ARNi: No		
Number of patients in analysis set	1480	1523
Number of analysed patients, N (%)	1350 (100.0)	1418 (100.0)
Number of patients with endpoint, N (%)	335 (24.8)	323 (22.8)
95% confidence interval*	(22.6, 27.2)	(20.7, 25.0)
Comparison vs Placebo**		
Risk ratio (SE)		0.918 (0.061)
95% confidence interval***		(0.805, 1.046)
p-value		0.1980
Baseline use of ARNi: Yes		
Number of patients in analysis set	387	340
Number of analysed patients, N (%)	359 (100.0)	322 (100.0)
Number of patients with endpoint, N (%)	93 (25.9)	67 (20.8)
95% confidence interval*	(21.6, 30.7)	(16.7, 25.6)
Comparison vs Placebo**		
Risk ratio (SE)		0.803 (0.112)
95% confidence interval***		(0.612, 1.055)
p-value		0.1153

* Wilson confidence intervals.
** Log-linked Poisson model with robust estimate of variance includes terms for baseline KCCQ - total symptom score (p<0.0001), age (p=0.5925), baseline eGFR (CKD-EPI) (p=0.0004), Treatment (p=0.0480), region (5 cat.) (p=0.0005), baseline diabetes status (3 cat.) (p=0.4560), sex (p=0.4047), baseline LVEF (3 cat.) (p=0.5375), baseline use of ARNi (p=0.3575) and Treatment by baseline use of ARNi interaction (p=0.3884).
***Wald confidence intervals.

Data taken from study 1245.121 only.
LOCF: For a missing value at week 52 the last available post-baseline value before week 52 is imputed.

Table R.1.2.6.14: 3 Responder analysis (displaying odds ratio) in KCCQ-TSS change from baseline at week 52 of > -5 points (stability) by baseline use of ARNi (Y/N) - RS (LOCF-AD) - 1245.121

Subgroup Description	Placebo	Empa 10mg
Baseline use of ARNi: No		
Number of patients in analysis set	1480	1523
Number of analysed patients, N (%)	1350 (100.0)	1418 (100.0)
Number of patients with endpoint, N (%)	1015 (75.2)	1095 (77.2)
95% confidence interval*	(72.8, 77.4)	(75.0, 79.3)
Comparison vs Placebo**		
Odds ratio (SE)		1.122 (0.102)
95% confidence interval***		(0.939, 1.341)
p-value		0.2056
Baseline use of ARNi: Yes		
Number of patients in analysis set	387	340
Number of analysed patients, N (%)	359 (100.0)	322 (100.0)
Number of patients with endpoint, N (%)	266 (74.1)	255 (79.2)
95% confidence interval*	(69.3, 78.4)	(74.4, 83.3)
Comparison vs Placebo**		
Odds ratio (SE)		1.345 (0.251)
95% confidence interval***		(0.934, 1.938)
p-value		0.1117

* Wilson confidence intervals.
** Logistic regression includes terms for baseline KCCQ - total symptom score (p<0.0001), age (p=0.6087), baseline eGFR (CKD-EPI) (p=0.0004), Treatment (p=0.0471), region (5 cat.) (p=0.0004), baseline diabetes status (3 cat.) (p=0.4590), sex (p=0.4112), baseline LVEF (3 cat.) (p=0.5428), baseline use of ARNi (p=0.3770) and Treatment by baseline use of ARNi interaction (p=0.3824).
***Wald confidence intervals.

Data taken from study 1245.121 only.
LOCF: For a missing value at week 52 the last available post-baseline value before week 52 is imputed.

Table R.1.2.6.14: 4 Responder analysis (displaying risk ratio) in KCCQ-TSS change from baseline at week 52 of > -5 points (stability) by baseline use of ARNi (Y/N) - RS (LOCF-AD) - 1245.121

Subgroup Description	Placebo	Empa 10mg
Baseline use of ARNi: No		
Number of patients in analysis set	1480	1523
Number of analysed patients, N (%)	1350 (100.0)	1418 (100.0)
Number of patients with endpoint, N (%)	1015 (75.2)	1095 (77.2)
95% confidence interval*	(72.8, 77.4)	(75.0, 79.3)
Comparison vs Placebo**		
Risk ratio (SE)		1.025 (0.021)
95% confidence interval***		(0.984, 1.068)
p-value		0.2381
Baseline use of ARNi: Yes		
Number of patients in analysis set	387	340
Number of analysed patients, N (%)	359 (100.0)	322 (100.0)
Number of patients with endpoint, N (%)	266 (74.1)	255 (79.2)
95% confidence interval*	(69.3, 78.4)	(74.4, 83.3)
Comparison vs Placebo**		
Risk ratio (SE)		1.069 (0.045)
95% confidence interval***		(0.984, 1.161)
p-value		0.1139

* Wilson confidence intervals.
** Log-linked Poisson model with robust estimate of variance includes terms for baseline KCCQ - total symptom score (p<0.0001), age (p=0.7187), baseline eGFR (CKD-EPI) (p=0.0004), Treatment (p=0.0523), region (5 cat.) (p<0.0001), baseline diabetes status (3 cat.) (p=0.4991), sex (p=0.4246), baseline LVEF (3 cat.) (p=0.5687), baseline use of ARNi (p=0.4773) and Treatment by baseline use of ARNi interaction (p=0.3715).
***Wald confidence intervals.

Data taken from study 1245.121 only.
LOCF: For a missing value at week 52 the last available post-baseline value before week 52 is imputed.

Table R.1.2.6.14: 5 Responder analysis (displaying odds ratio) in KCCQ-TSS change from baseline at week 52 of >= 5 points (improvement) by baseline use of ARNi (Y/N) - RS (LOCF-AD) - 1245.121

Subgroup Description	Placebo	Empa 10mg
Baseline use of ARNi: No		
Number of patients in analysis set	1480	1523
Number of analysed patients, N (%)	1350 (100.0)	1418 (100.0)
Number of patients with endpoint, N (%)	609 (45.1)	680 (48.0)
95% confidence interval*	(42.5, 47.8)	(45.4, 50.6)
Comparison vs Placebo**		
Odds ratio (SE)		1.139 (0.100)
95% confidence interval***		(0.959, 1.352)
p-value		0.1384
Baseline use of ARNi: Yes		
Number of patients in analysis set	387	340
Number of analysed patients, N (%)	359 (100.0)	322 (100.0)
Number of patients with endpoint, N (%)	142 (39.6)	132 (41.0)
95% confidence interval*	(34.6, 44.7)	(35.8, 46.4)
Comparison vs Placebo**		
Odds ratio (SE)		1.162 (0.211)
95% confidence interval***		(0.814, 1.658)
p-value		0.4085

* Wilson confidence intervals.
** Logistic regression includes terms for baseline KCCQ - total symptom score (p<0.0001), age (p=0.4707), baseline eGFR (CKD-EPI) (p=0.2213), Treatment (p=0.1650), region (5 cat.) (p<0.0001), baseline diabetes status (3 cat.) (p=0.9546), sex (p=0.4819), baseline LVEF (3 cat.) (p=0.5653), baseline use of ARNi (p=0.0826) and Treatment by baseline use of ARNi interaction (p=0.9198).
***Wald confidence intervals.

Data taken from study 1245.121 only.
LOCF: For a missing value at week 52 the last available post-baseline value before week 52 is imputed.

Table R.1.2.6.14: 6 Responder analysis (displaying risk ratio) in KCCQ-TSS change from baseline at week 52 of >= 5 points (improvement) by baseline use of ARNi (Y/N) - RS (LOCF-AD) - 1245.121

Subgroup Description	Placebo	Empa 10mg
Baseline use of ARNi: No		
Number of patients in analysis set	1480	1523
Number of analysed patients, N (%)	1350 (100.0)	1418 (100.0)
Number of patients with endpoint, N (%)	609 (45.1)	680 (48.0)
95% confidence interval*	(42.5, 47.8)	(45.4, 50.6)
Comparison vs Placebo**		
Risk ratio (SE)		1.032 (0.038)
95% confidence interval***		(0.960, 1.110)
p-value		0.3917
Baseline use of ARNi: Yes		
Number of patients in analysis set	387	340
Number of analysed patients, N (%)	359 (100.0)	322 (100.0)
Number of patients with endpoint, N (%)	142 (39.6)	132 (41.0)
95% confidence interval*	(34.6, 44.7)	(35.8, 46.4)
Comparison vs Placebo**		
Risk ratio (SE)		1.077 (0.095)
95% confidence interval***		(0.907, 1.280)
p-value		0.3971

* Wilson confidence intervals.
** Log-linked Poisson model with robust estimate of variance includes terms for baseline KCCQ - total symptom score (p<0.0001), age (p=0.6886), baseline eGFR (CKD-EPI) (p=0.1631), Treatment (p=0.2651), region (5 cat.) (p<0.0001), baseline diabetes status (3 cat.) (p=0.8501), sex (p=0.3377), baseline LVEF (3 cat.) (p=0.5864), baseline use of ARNi (p=0.0318) and Treatment by baseline use of ARNi interaction (p=0.6557).
***Wald confidence intervals.

Data taken from study 1245.121 only.
LOCF: For a missing value at week 52 the last available post-baseline value before week 52 is imputed.

R.1.2.6.15

R.1.2.6.15 Subgroup analysis by bl. LVEF (<= 30%, >30% -<= 35% , > 35%)

Table R.1.2.6.15: 1 Responder analysis (displaying odds ratio) in KCCQ-TSS change from baseline at week 52 of <= -5 points (deterioration) by baseline LVEF (3 cat.) - RS (LOCF-AD) - 1245.121

Subgroup Description	Placebo	Empa 10mg
Baseline LVEF (3 cat.): <=30		
Number of patients in analysis set	1392	1337
Number of analysed patients, N (%)	1272 (100.0)	1245 (100.0)
Number of patients with endpoint, N (%)	324 (25.5)	279 (22.4)
95% confidence interval*	(23.2, 27.9)	(20.2, 24.8)
Comparison vs Placebo**		
Odds ratio (SE)		0.841 (0.080)
95% confidence interval***		(0.697, 1.013)
p-value		0.0685
Baseline LVEF (3 cat.): >30 to <=35		
Number of patients in analysis set	361	398
Number of analysed patients, N (%)	333 (100.0)	375 (100.0)
Number of patients with endpoint, N (%)	78 (23.4)	87 (23.2)
95% confidence interval*	(19.2, 28.3)	(19.2, 27.7)
Comparison vs Placebo**		
Odds ratio (SE)		0.987 (0.179)
95% confidence interval***		(0.692, 1.408)
p-value		0.9439

* Wilson confidence intervals.
** Logistic regression includes terms for baseline KCCQ - total symptom score (p<0.0001), age (p=0.5880), baseline eGFR (CKD-EPI) (p=0.0004), Treatment (p=0.2159), region (5 cat.) (p=0.0005), baseline diabetes status (3 cat.) (p=0.4631), sex (p=0.4197), baseline LVEF (3 cat.) (p=0.5652) and Treatment by baseline LVEF (3 cat.) interaction (p=0.6633).
***Wald confidence intervals.

Data taken from study 1245.121 only.
LOCF: For a missing value at week 52 the last available post-baseline value before week 52 is imputed.

Table R.1.2.6.15: 1 Responder analysis (displaying odds ratio) in KCCQ-TSS change from baseline at week 52 of <= -5 points (deterioration) by baseline LVEF (3 cat.) - RS (LOCF-AD) - 1245.121

Subgroup Description	Placebo	Empa 10mg
Baseline LVEF (3 cat.): >35		
Number of patients in analysis set	114	128
Number of analysed patients, N (%)	104 (100.0)	120 (100.0)
Number of patients with endpoint, N (%)	26 (25.0)	24 (20.0)
95% confidence interval*	(17.7, 34.1)	(13.8, 28.0)
Comparison vs Placebo**		
Odds ratio (SE)		0.747 (0.245)
95% confidence interval***		(0.393, 1.420)
p-value		0.3736

* Wilson confidence intervals.
** Logistic regression includes terms for baseline KCCQ - total symptom score (p<0.0001), age (p=0.5880), baseline eGFR (CKD-EPI) (p=0.0004), Treatment (p=0.2159), region (5 cat.) (p=0.0005), baseline diabetes status (3 cat.) (p=0.4631), sex (p=0.4197), baseline LVEF (3 cat.) (p=0.5652) and Treatment by baseline LVEF (3 cat.) interaction (p=0.6633).
***Wald confidence intervals.

Data taken from study 1245.121 only.
LOCF: For a missing value at week 52 the last available post-baseline value before week 52 is imputed.

Table R.1.2.6.15: 2 Responder analysis (displaying risk ratio) in KCCQ-TSS change from baseline at week 52 of <= -5 points (deterioration) by baseline LVEF (3 cat.) - RS (LOCF-AD) - 1245.121

Subgroup Description	Placebo	Empa 10mg
Baseline LVEF (3 cat.): <=30		
Number of patients in analysis set	1392	1337
Number of analysed patients, N (%)	1272 (100.0)	1245 (100.0)
Number of patients with endpoint, N (%)	324 (25.5)	279 (22.4)
95% confidence interval*	(23.2, 27.9)	(20.2, 24.8)
Comparison vs Placebo**		
Risk ratio (SE)		0.880 (0.062)
95% confidence interval***		(0.767, 1.009)
p-value		0.0665
Baseline LVEF (3 cat.): >30 to <=35		
Number of patients in analysis set	361	398
Number of analysed patients, N (%)	333 (100.0)	375 (100.0)
Number of patients with endpoint, N (%)	78 (23.4)	87 (23.2)
95% confidence interval*	(19.2, 28.3)	(19.2, 27.7)
Comparison vs Placebo**		
Risk ratio (SE)		0.990 (0.133)
95% confidence interval***		(0.761, 1.287)
p-value		0.9384

* Wilson confidence intervals.
** Log-linked Poisson model with robust estimate of variance includes terms for baseline KCCQ - total symptom score (p<0.0001), age (p=0.5713), baseline eGFR (CKD-EPI) (p=0.0004), Treatment (p=0.2194), region (5 cat.) (p=0.0006), baseline diabetes status (3 cat.) (p=0.4574), sex (p=0.4131), baseline LVEF (3 cat.) (p=0.5626) and Treatment by baseline LVEF (3 cat.) interaction (p=0.6664).
***Wald confidence intervals.

Data taken from study 1245.121 only.
LOCF: For a missing value at week 52 the last available post-baseline value before week 52 is imputed.

Table R.1.2.6.15: 2 Responder analysis (displaying risk ratio) in KCCQ-TSS change from baseline at week 52 of <= -5 points (deterioration) by baseline LVEF (3 cat.) - RS (LOCF-AD) - 1245.121

Subgroup Description	Placebo	Empa 10mg
Baseline LVEF (3 cat.): >35		
Number of patients in analysis set	114	128
Number of analysed patients, N (%)	104 (100.0)	120 (100.0)
Number of patients with endpoint, N (%)	26 (25.0)	24 (20.0)
95% confidence interval*	(17.7, 34.1)	(13.8, 28.0)
Comparison vs Placebo**		
Risk ratio (SE)		0.804 (0.199)
95% confidence interval***		(0.495, 1.307)
p-value		0.3791

* Wilson confidence intervals.
** Log-linked Poisson model with robust estimate of variance includes terms for baseline KCCQ - total symptom score (p<0.0001), age (p=0.5713), baseline eGFR (CKD-EPI) (p=0.0004), Treatment (p=0.2194), region (5 cat.) (p=0.0006), baseline diabetes status (3 cat.) (p=0.4574), sex (p=0.4131), baseline LVEF (3 cat.) (p=0.5626) and Treatment by baseline LVEF (3 cat.) interaction (p=0.6664).
***Wald confidence intervals.

Data taken from study 1245.121 only.
LOCF: For a missing value at week 52 the last available post-baseline value before week 52 is imputed.

Table R.1.2.6.15: 3 Responder analysis (displaying odds ratio) in KCCQ-TSS change from baseline at week 52 of > -5 points (stability) by baseline LVEF (3 cat.) - RS (LOCF-AD) - 1245.121

Subgroup Description	Placebo	Empa 10mg
Baseline LVEF (3 cat.): <=30		
Number of patients in analysis set	1392	1337
Number of analysed patients, N (%)	1272 (100.0)	1245 (100.0)
Number of patients with endpoint, N (%)	948 (74.5)	966 (77.6)
95% confidence interval*	(72.1, 76.8)	(75.2, 79.8)
Comparison vs Placebo**		
Odds ratio (SE)		1.190 (0.113)
95% confidence interval***		(0.987, 1.434)
p-value		0.0685
Baseline LVEF (3 cat.): >30 to <=35		
Number of patients in analysis set	361	398
Number of analysed patients, N (%)	333 (100.0)	375 (100.0)
Number of patients with endpoint, N (%)	255 (76.6)	288 (76.8)
95% confidence interval*	(71.7, 80.8)	(72.3, 80.8)
Comparison vs Placebo**		
Odds ratio (SE)		1.013 (0.183)
95% confidence interval***		(0.710, 1.445)
p-value		0.9439

* Wilson confidence intervals.
** Logistic regression includes terms for baseline KCCQ - total symptom score (p<0.0001), age (p=0.5880), baseline eGFR (CKD-EPI) (p=0.0004), Treatment (p=0.2159), region (5 cat.) (p=0.0005), baseline diabetes status (3 cat.) (p=0.4631), sex (p=0.4197), baseline LVEF (3 cat.) (p=0.5652) and Treatment by baseline LVEF (3 cat.) interaction (p=0.6633).
***Wald confidence intervals.

Data taken from study 1245.121 only.
LOCF: For a missing value at week 52 the last available post-baseline value before week 52 is imputed.

Table R.1.2.6.15: 3 Responder analysis (displaying odds ratio) in KCCQ-TSS change from baseline at week 52 of > -5 points (stability) by baseline LVEF (3 cat.) - RS (LOCF-AD) - 1245.121

Subgroup Description	Placebo	Empa 10mg
Baseline LVEF (3 cat.): >35		
Number of patients in analysis set	114	128
Number of analysed patients, N (%)	104 (100.0)	120 (100.0)
Number of patients with endpoint, N (%)	78 (75.0)	96 (80.0)
95% confidence interval*	(65.9, 82.3)	(72.0, 86.2)
Comparison vs Placebo**		
Odds ratio (SE)		1.338 (0.438)
95% confidence interval***		(0.704, 2.544)
p-value		0.3736

* Wilson confidence intervals.
** Logistic regression includes terms for baseline KCCQ - total symptom score (p<0.0001), age (p=0.5880), baseline eGFR (CKD-EPI) (p=0.0004), Treatment (p=0.2159), region (5 cat.) (p=0.0005), baseline diabetes status (3 cat.) (p=0.4631), sex (p=0.4197), baseline LVEF (3 cat.) (p=0.5652) and Treatment by baseline LVEF (3 cat.) interaction (p=0.6633).
***Wald confidence intervals.

Data taken from study 1245.121 only.
LOCF: For a missing value at week 52 the last available post-baseline value before week 52 is imputed.

Table R.1.2.6.15: 4 Responder analysis (displaying risk ratio) in KCCQ-TSS change from baseline at week 52 of > -5 points (stability) by baseline LVEF (3 cat.) - RS (LOCF-AD) - 1245.121

Subgroup Description	Placebo	Empa 10mg
Baseline LVEF (3 cat.): <=30		
Number of patients in analysis set	1392	1337
Number of analysed patients, N (%)	1272 (100.0)	1245 (100.0)
Number of patients with endpoint, N (%)	948 (74.5)	966 (77.6)
95% confidence interval*	(72.1, 76.8)	(75.2, 79.8)
Comparison vs Placebo**		
Risk ratio (SE)		1.040 (0.023)
95% confidence interval***		(0.996, 1.086)
p-value		0.0769
Baseline LVEF (3 cat.): >30 to <=35		
Number of patients in analysis set	361	398
Number of analysed patients, N (%)	333 (100.0)	375 (100.0)
Number of patients with endpoint, N (%)	255 (76.6)	288 (76.8)
95% confidence interval*	(71.7, 80.8)	(72.3, 80.8)
Comparison vs Placebo**		
Risk ratio (SE)		1.001 (0.041)
95% confidence interval***		(0.924, 1.085)
p-value		0.9731

* Wilson confidence intervals.
** Log-linked Poisson model with robust estimate of variance includes terms for baseline KCCQ - total symptom score (p<0.0001), age (p=0.7018), baseline eGFR (CKD-EPI) (p=0.0004), Treatment (p=0.2409), region (5 cat.) (p<0.0001), baseline diabetes status (3 cat.) (p=0.5127), sex (p=0.4315), baseline LVEF (3 cat.) (p=0.5757) and Treatment by baseline LVEF (3 cat.) interaction (p=0.6656).
***Wald confidence intervals.

Data taken from study 1245.121 only.
LOCF: For a missing value at week 52 the last available post-baseline value before week 52 is imputed.

Table R.1.2.6.15: 4 Responder analysis (displaying risk ratio) in KCCQ-TSS change from baseline at week 52 of > -5 points (stability) by baseline LVEF (3 cat.) - RS (LOCF-AD) - 1245.121

Subgroup Description	Placebo	Empa 10mg
Baseline LVEF (3 cat.): >35		
Number of patients in analysis set	114	128
Number of analysed patients, N (%)	104 (100.0)	120 (100.0)
Number of patients with endpoint, N (%)	78 (75.0)	96 (80.0)
95% confidence interval*	(65.9, 82.3)	(72.0, 86.2)
Comparison vs Placebo**		
Risk ratio (SE)		1.062 (0.077)
95% confidence interval***		(0.922, 1.223)
p-value		0.4030

* Wilson confidence intervals.
** Log-linked Poisson model with robust estimate of variance includes terms for baseline KCCQ - total symptom score (p<0.0001), age (p=0.7018), baseline eGFR (CKD-EPI) (p=0.0004), Treatment (p=0.2409), region (5 cat.) (p<0.0001), baseline diabetes status (3 cat.) (p=0.5127), sex (p=0.4315), baseline LVEF (3 cat.) (p=0.5757) and Treatment by baseline LVEF (3 cat.) interaction (p=0.6656).
***Wald confidence intervals.

Data taken from study 1245.121 only.
LOCF: For a missing value at week 52 the last available post-baseline value before week 52 is imputed.

Table R.1.2.6.15: 5 Responder analysis (displaying odds ratio) in KCCQ-TSS change from baseline at week 52 of >= 5 points (improvement) by baseline LVEF (3 cat.) - RS (LOCF-AD) - 1245.121

Subgroup Description	Placebo	Empa 10mg
Baseline LVEF (3 cat.): <=30		
Number of patients in analysis set	1392	1337
Number of analysed patients, N (%)	1272 (100.0)	1245 (100.0)
Number of patients with endpoint, N (%)	549 (43.2)	589 (47.3)
95% confidence interval*	(40.5, 45.9)	(44.5, 50.1)
Comparison vs Placebo**		
Odds ratio (SE)		1.219 (0.113)
95% confidence interval***		(1.017, 1.461)
p-value		0.0318
Baseline LVEF (3 cat.): >30 to <=35		
Number of patients in analysis set	361	398
Number of analysed patients, N (%)	333 (100.0)	375 (100.0)
Number of patients with endpoint, N (%)	156 (46.8)	165 (44.0)
95% confidence interval*	(41.6, 52.2)	(39.1, 49.1)
Comparison vs Placebo**		
Odds ratio (SE)		0.882 (0.152)
95% confidence interval***		(0.628, 1.237)
p-value		0.4662

* Wilson confidence intervals.
** Logistic regression includes terms for baseline KCCQ - total symptom score (p<0.0001), age (p=0.5038), baseline eGFR (CKD-EPI) (p=0.2039), Treatment (p=0.3336), region (5 cat.) (p<0.0001), baseline diabetes status (3 cat.) (p=0.9519), sex (p=0.5290), baseline LVEF (3 cat.) (p=0.4750) and Treatment by baseline LVEF (3 cat.) interaction (p=0.2261).
***Wald confidence intervals.

Data taken from study 1245.121 only.
LOCF: For a missing value at week 52 the last available post-baseline value before week 52 is imputed.

Table R.1.2.6.15: 5 Responder analysis (displaying odds ratio) in KCCQ-TSS change from baseline at week 52 of >= 5 points (improvement) by baseline LVEF (3 cat.) - RS (LOCF-AD) - 1245.121

Subgroup Description	Placebo	Empa 10mg
Baseline LVEF (3 cat.): >35		
Number of patients in analysis set	114	128
Number of analysed patients, N (%)	104 (100.0)	120 (100.0)
Number of patients with endpoint, N (%)	46 (44.2)	58 (48.3)
95% confidence interval*	(35.1, 53.8)	(39.6, 57.2)
Comparison vs Placebo**		
Odds ratio (SE)		1.328 (0.414)
95% confidence interval***		(0.721, 2.447)
p-value		0.3629

* Wilson confidence intervals.
** Logistic regression includes terms for baseline KCCQ - total symptom score (p<0.0001), age (p=0.5038), baseline eGFR (CKD-EPI) (p=0.2039), Treatment (p=0.3336), region (5 cat.) (p<0.0001), baseline diabetes status (3 cat.) (p=0.9519), sex (p=0.5290), baseline LVEF (3 cat.) (p=0.4750) and Treatment by baseline LVEF (3 cat.) interaction (p=0.2261).
***Wald confidence intervals.

Data taken from study 1245.121 only.
LOCF: For a missing value at week 52 the last available post-baseline value before week 52 is imputed.

Table R.1.2.6.15: 6 Responder analysis (displaying risk ratio) in KCCQ-TSS change from baseline at week 52 of >= 5 points (improvement) by baseline LVEF (3 cat.) - RS (LOCF-AD) - 1245.121

Subgroup Description	Placebo	Empa 10mg
Baseline LVEF (3 cat.): <=30		
Number of patients in analysis set	1392	1337
Number of analysed patients, N (%)	1272 (100.0)	1245 (100.0)
Number of patients with endpoint, N (%)	549 (43.2)	589 (47.3)
95% confidence interval*	(40.5, 45.9)	(44.5, 50.1)
Comparison vs Placebo**		
Risk ratio (SE)		1.074 (0.043)
95% confidence interval***		(0.992, 1.163)
p-value		0.0779
Baseline LVEF (3 cat.): >30 to <=35		
Number of patients in analysis set	361	398
Number of analysed patients, N (%)	333 (100.0)	375 (100.0)
Number of patients with endpoint, N (%)	156 (46.8)	165 (44.0)
95% confidence interval*	(41.6, 52.2)	(39.1, 49.1)
Comparison vs Placebo**		
Risk ratio (SE)		0.924 (0.069)
95% confidence interval***		(0.799, 1.069)
p-value		0.2895

* Wilson confidence intervals.
** Log-linked Poisson model with robust estimate of variance includes terms for baseline KCCQ - total symptom score (p<0.0001), age (p=0.7470), baseline eGFR (CKD-EPI) (p=0.1400), Treatment (p=0.5599), region (5 cat.) (p<0.0001), baseline diabetes status (3 cat.) (p=0.8705), sex (p=0.3962), baseline LVEF (3 cat.) (p=0.4450) and Treatment by baseline LVEF (3 cat.) interaction (p=0.1874).
***Wald confidence intervals.

Data taken from study 1245.121 only.
LOCF: For a missing value at week 52 the last available post-baseline value before week 52 is imputed.

Table R.1.2.6.15: 6 Responder analysis (displaying risk ratio) in KCCQ-TSS change from baseline at week 52 of >= 5 points (improvement) by baseline LVEF (3 cat.) - RS (LOCF-AD) - 1245.121

Subgroup Description	Placebo	Empa 10mg
Baseline LVEF (3 cat.): >35		
Number of patients in analysis set	114	128
Number of analysed patients, N (%)	104 (100.0)	120 (100.0)
Number of patients with endpoint, N (%)	46 (44.2)	58 (48.3)
95% confidence interval*	(35.1, 53.8)	(39.6, 57.2)
Comparison vs Placebo**		
Risk ratio (SE)		1.103 (0.144)
95% confidence interval***		(0.853, 1.426)
p-value		0.4541

* Wilson confidence intervals.
** Log-linked Poisson model with robust estimate of variance includes terms for baseline KCCQ - total symptom score (p<0.0001), age (p=0.7470), baseline eGFR (CKD-EPI) (p=0.1400), Treatment (p=0.5599), region (5 cat.) (p<0.0001), baseline diabetes status (3 cat.) (p=0.8705), sex (p=0.3962), baseline LVEF (3 cat.) (p=0.4450) and Treatment by baseline LVEF (3 cat.) interaction (p=0.1874).
***Wald confidence intervals.

Data taken from study 1245.121 only.
LOCF: For a missing value at week 52 the last available post-baseline value before week 52 is imputed.

R.1.2.6.16

R.1.2.6.16 Subgroup analysis by bl. NTproBNP </>= median (median based on total patients)

Table R.1.2.6.16: 1 Responder analysis (displaying odds ratio) in KCCQ-TSS change from baseline at week 52 of <= -5 points (deterioration) by bl. NTproBNP (<median, >= median) (median based on total patients) - RS (LOCF-AD) - 1245.121

Subgroup Description	Placebo	Empa 10mg
Baseline NTproBNP (<median, >= median): < median		
Number of patients in analysis set	920	942
Number of analysed patients, N (%)	866 (100.0)	886 (100.0)
Number of patients with endpoint, N (%)	199 (23.0)	182 (20.5)
95% confidence interval*	(20.3, 25.9)	(18.0, 23.3)
Comparison vs Placebo**		
Odds ratio (SE)		0.857 (0.101)
95% confidence interval***		(0.680, 1.080)
p-value		0.1906
Baseline NTproBNP (<median, >= median): >= median		
Number of patients in analysis set	946	920
Number of analysed patients, N (%)	843 (100.0)	854 (100.0)
Number of patients with endpoint, N (%)	229 (27.2)	208 (24.4)
95% confidence interval*	(24.3, 30.3)	(21.6, 27.3)
Comparison vs Placebo**		
Odds ratio (SE)		0.870 (0.099)
95% confidence interval***		(0.697, 1.087)
p-value		0.2212

* Wilson confidence intervals.
** Logistic regression includes terms for baseline KCCQ - total symptom score (p<0.0001), age (p=0.6670), baseline eGFR (CKD-EPI) (p=0.0037), Treatment (p=0.0733), region (5 cat.) (p=0.0002), baseline diabetes status (3 cat.) (p=0.5027), sex (p=0.4050), baseline LVEF (3 cat.) (p=0.4497), baseline NTproBNP (<median, >= median) (p=0.0024) and Treatment by baseline NTproBNP (<median, >= median) interaction (p=0.9254).
***Wald confidence intervals.
2 patients were excluded as the subgroup variable was missing.

Data taken from study 1245.121 only.
LOCF: For a missing value at week 52 the last available post-baseline value before week 52 is imputed.
Median: 1910 [pg/mL]

Table R.1.2.6.16: 2 Responder analysis (displaying risk ratio) in KCCQ-TSS change from baseline at week 52 of <= -5 points (deterioration) by bl. NTproBNP (<median, >= median) (median based on total patients) - RS (LOCF-AD) - 1245.121

Subgroup Description	Placebo	Empa 10mg
Baseline NTproBNP (<median, >= median): < median		
Number of patients in analysis set	920	942
Number of analysed patients, N (%)	866 (100.0)	886 (100.0)
Number of patients with endpoint, N (%)	199 (23.0)	182 (20.5)
95% confidence interval*	(20.3, 25.9)	(18.0, 23.3)
Comparison vs Placebo**		
Risk ratio (SE)		0.890 (0.080)
95% confidence interval***		(0.746, 1.061)
p-value		0.1923
Baseline NTproBNP (<median, >= median): >= median		
Number of patients in analysis set	946	920
Number of analysed patients, N (%)	843 (100.0)	854 (100.0)
Number of patients with endpoint, N (%)	229 (27.2)	208 (24.4)
95% confidence interval*	(24.3, 30.3)	(21.6, 27.3)
Comparison vs Placebo**		
Risk ratio (SE)		0.904 (0.073)
95% confidence interval***		(0.772, 1.059)
p-value		0.2106

* Wilson confidence intervals.
** Log-linked Poisson model with robust estimate of variance includes terms for baseline KCCQ - total symptom score (p<0.0001), age (p=0.6512), baseline eGFR (CKD-EPI) (p=0.0036), Treatment (p=0.0709), region (5 cat.) (p=0.0002), baseline diabetes status (3 cat.) (p=0.5012), sex (p=0.4018), baseline LVEF (3 cat.) (p=0.4443), baseline NTproBNP (<median, >= median) (p=0.0026) and Treatment by baseline NTproBNP (<median, >= median) interaction (p=0.8933).
***Wald confidence intervals.
2 patients were excluded as the subgroup variable was missing.

Data taken from study 1245.121 only.
LOCF: For a missing value at week 52 the last available post-baseline value before week 52 is imputed.
Median: 1910 [pg/mL]

Table R.1.2.6.16: 3 Responder analysis (displaying odds ratio) in KCCQ-TSS change from baseline at week 52 of > -5 points (stability) by bl. NTproBNP (<median, >= median) (median based on total patients) - RS (LOCF-AD) - 1245.121

Subgroup Description	Placebo	Empa 10mg
Baseline NTproBNP (<median, >= median): < median		
Number of patients in analysis set	920	942
Number of analysed patients, N (%)	866 (100.0)	886 (100.0)
Number of patients with endpoint, N (%)	667 (77.0)	704 (79.5)
95% confidence interval*	(74.1, 79.7)	(76.7, 82.0)
Comparison vs Placebo**		
Odds ratio (SE)		1.167 (0.137)
95% confidence interval***		(0.926, 1.470)
p-value		0.1906
Baseline NTproBNP (<median, >= median): >= median		
Number of patients in analysis set	946	920
Number of analysed patients, N (%)	843 (100.0)	854 (100.0)
Number of patients with endpoint, N (%)	614 (72.8)	646 (75.6)
95% confidence interval*	(69.7, 75.7)	(72.7, 78.4)
Comparison vs Placebo**		
Odds ratio (SE)		1.149 (0.130)
95% confidence interval***		(0.920, 1.435)
p-value		0.2212

* Wilson confidence intervals.
** Logistic regression includes terms for baseline KCCQ - total symptom score (p<0.0001), age (p=0.6670), baseline eGFR (CKD-EPI) (p=0.0037), Treatment (p=0.0733), region (5 cat.) (p=0.0002), baseline diabetes status (3 cat.) (p=0.5027), sex (p=0.4050), baseline LVEF (3 cat.) (p=0.4497), baseline NTproBNP (<median, >= median) (p=0.0024) and Treatment by baseline NTproBNP (<median, >= median) interaction (p=0.9254).
***Wald confidence intervals.
2 patients were excluded as the subgroup variable was missing.

Data taken from study 1245.121 only.
LOCF: For a missing value at week 52 the last available post-baseline value before week 52 is imputed.
Median: 1910 [pg/mL]

Table R.1.2.6.16: 4 Responder analysis (displaying risk ratio) in KCCQ-TSS change from baseline at week 52 of > -5 points (stability) by bl. NTproBNP (<median, >= median) (median based on total patients) - RS (LOCF-AD) - 1245.121

Subgroup Description	Placebo	Empa 10mg
Baseline NTproBNP (<median, >= median): < median		
Number of patients in analysis set	920	942
Number of analysed patients, N (%)	866 (100.0)	886 (100.0)
Number of patients with endpoint, N (%)	667 (77.0)	704 (79.5)
95% confidence interval*	(74.1, 79.7)	(76.7, 82.0)
Comparison vs Placebo**		
Risk ratio (SE)		1.033 (0.026)
95% confidence interval***		(0.983, 1.085)
p-value		0.1966
Baseline NTproBNP (<median, >= median): >= median		
Number of patients in analysis set	946	920
Number of analysed patients, N (%)	843 (100.0)	854 (100.0)
Number of patients with endpoint, N (%)	614 (72.8)	646 (75.6)
95% confidence interval*	(69.7, 75.7)	(72.7, 78.4)
Comparison vs Placebo**		
Risk ratio (SE)		1.033 (0.029)
95% confidence interval***		(0.977, 1.091)
p-value		0.2519

* Wilson confidence intervals.
** Log-linked Poisson model with robust estimate of variance includes terms for baseline KCCQ - total symptom score (p<0.0001), age (p=0.7849), baseline eGFR (CKD-EPI) (p=0.0036), Treatment (p=0.0866), region (5 cat.) (p<0.0001), baseline diabetes status (3 cat.) (p=0.5346), sex (p=0.4000), baseline LVEF (3 cat.) (p=0.4647), baseline NTproBNP (<median, >= median) (p=0.0018) and Treatment by baseline NTproBNP (<median, >= median) interaction (p=0.9962).
***Wald confidence intervals.
2 patients were excluded as the subgroup variable was missing.

Data taken from study 1245.121 only.
LOCF: For a missing value at week 52 the last available post-baseline value before week 52 is imputed.
Median: 1910 [pg/mL]

Table R.1.2.6.16: 5 Responder analysis (displaying odds ratio) in KCCQ-TSS change from baseline at week 52 of >= 5 points (improvement) by bl. NTproBNP (<median, >= median) (median based on total patients) - RS (LOCF-AD) - 1245.121

Subgroup Description	Placebo	Empa 10mg
Baseline NTproBNP (<median, >= median): < median		
Number of patients in analysis set	920	942
Number of analysed patients, N (%)	866 (100.0)	886 (100.0)
Number of patients with endpoint, N (%)	374 (43.2)	405 (45.7)
95% confidence interval*	(39.9, 46.5)	(42.5, 49.0)
Comparison vs Placebo**		
Odds ratio (SE)		1.178 (0.129)
95% confidence interval***		(0.950, 1.461)
p-value		0.1346
Baseline NTproBNP (<median, >= median): >= median		
Number of patients in analysis set	946	920
Number of analysed patients, N (%)	843 (100.0)	854 (100.0)
Number of patients with endpoint, N (%)	377 (44.7)	407 (47.7)
95% confidence interval*	(41.4, 48.1)	(44.3, 51.0)
Comparison vs Placebo**		
Odds ratio (SE)		1.108 (0.126)
95% confidence interval***		(0.887, 1.383)
p-value		0.3670

* Wilson confidence intervals.
** Logistic regression includes terms for baseline KCCQ - total symptom score (p<0.0001), age (p=0.5440), baseline eGFR (CKD-EPI) (p=0.4111), Treatment (p=0.0913), region (5 cat.) (p<0.0001), baseline diabetes status (3 cat.) (p=0.9438), sex (p=0.5280), baseline LVEF (3 cat.) (p=0.4373), baseline NTproBNP (<median, >= median) (p=0.0433) and Treatment by baseline NTproBNP (<median, >= median) interaction (p=0.6949).
***Wald confidence intervals.
2 patients were excluded as the subgroup variable was missing.

Data taken from study 1245.121 only.
LOCF: For a missing value at week 52 the last available post-baseline value before week 52 is imputed.
Median: 1910 [pg/mL]

Table R.1.2.6.16: 6 Responder analysis (displaying risk ratio) in KCCQ-TSS change from baseline at week 52 of >= 5 points (improvement) by bl. NTproBNP (<median, >= median) (median based on total patients) - RS (LOCF-AD) - 1245.121

Subgroup Description	Placebo	Empa 10mg
Baseline NTproBNP (<median, >= median): < median		
Number of patients in analysis set	920	942
Number of analysed patients, N (%)	866 (100.0)	886 (100.0)
Number of patients with endpoint, N (%)	374 (43.2)	405 (45.7)
95% confidence interval*	(39.9, 46.5)	(42.5, 49.0)
Comparison vs Placebo**		
Risk ratio (SE)		1.062 (0.052)
95% confidence interval***		(0.965, 1.170)
p-value		0.2193
Baseline NTproBNP (<median, >= median): >= median		
Number of patients in analysis set	946	920
Number of analysed patients, N (%)	843 (100.0)	854 (100.0)
Number of patients with endpoint, N (%)	377 (44.7)	407 (47.7)
95% confidence interval*	(41.4, 48.1)	(44.3, 51.0)
Comparison vs Placebo**		
Risk ratio (SE)		1.024 (0.049)
95% confidence interval***		(0.933, 1.125)
p-value		0.6183

* Wilson confidence intervals.
** Log-linked Poisson model with robust estimate of variance includes terms for baseline KCCQ - total symptom score (p<0.0001), age (p=0.8401), baseline eGFR (CKD-EPI) (p=0.2961), Treatment (p=0.2192), region (5 cat.) (p<0.0001), baseline diabetes status (3 cat.) (p=0.8628), sex (p=0.4494), baseline LVEF (3 cat.) (p=0.4523), baseline NTproBNP (<median, >= median) (p=0.0262) and Treatment by baseline NTproBNP (<median, >= median) interaction (p=0.5920).
***Wald confidence intervals.
2 patients were excluded as the subgroup variable was missing.

Data taken from study 1245.121 only.
LOCF: For a missing value at week 52 the last available post-baseline value before week 52 is imputed.
Median: 1910 [pg/mL]

R.1.2.7

R.1.2.7 KCCQ Total Symptom Score responder analysis (15 points)

R.1.2.7.1

Table R.1.2.7.1: 1 Responder analysis (displaying odds ratio) in KCCQ-TSS change from baseline at week 52 of <= -15 points (deterioration) - RS (LOCF-AD) - 1245.121

	Placebo	Empa 10mg
Number of patients in analysis set	1867	1863
Number of analysed patients, N (%)	1709 (100.0)	1740 (100.0)
Number of patients with endpoint, N (%)	215 (12.6)	182 (10.5)
95% confidence interval*	(11.1, 14.2)	(9.1, 12.0)
Comparison vs Placebo**		
Odds ratio (SE)		0.810 (0.088)
95% confidence interval***		(0.654, 1.002)
p-value		0.0522

* Wilson confidence intervals.
** Logistic regression includes terms for baseline KCCQ - total symptom score (p<0.0001), age (p=0.3275), baseline eGFR (CKD-EPI) (p<0.0001), Treatment (p=0.0522), region (5 cat.) (p=0.0126), baseline diabetes status (3 cat.) (p=0.8334), sex (p=0.1387) and baseline LVEF (3 cat.) (p=0.0502).
***Wald confidence intervals.

Data taken from study 1245.121 only.
LOCF: For a missing value at week 52 the last available post-baseline value before week 52 is imputed.

Table R.1.2.7.1: 2 Responder analysis (displaying risk ratio) in KCCQ-TSS change from baseline at week 52 of <= -15 points (deterioration) - RS (LOCF-AD) - 1245.121

	Placebo	Empa 10mg
Number of patients in analysis set	1867	1863
Number of analysed patients, N (%)	1709 (100.0)	1740 (100.0)
Number of patients with endpoint, N (%)	215 (12.6)	182 (10.5)
95% confidence interval*	(11.1, 14.2)	(9.1, 12.0)
Comparison vs Placebo**		
Risk ratio (SE)		0.834 (0.078)
95% confidence interval***		(0.694, 1.001)
p-value		0.0508

* Wilson confidence intervals.
** Log-linked Poisson model with robust estimate of variance includes terms for baseline KCCQ - total symptom score (p<0.0001), age (p=0.3435), baseline eGFR (CKD-EPI) (p<0.0001), Treatment (p=0.0508), region (5 cat.) (p=0.0167), baseline diabetes status (3 cat.) (p=0.8352), sex (p=0.1347) and baseline LVEF (3 cat.) (p=0.0495).
***Wald confidence intervals.

Data taken from study 1245.121 only.
LOCF: For a missing value at week 52 the last available post-baseline value before week 52 is imputed.

Table R.1.2.7.1: 3 Responder analysis (displaying odds ratio) in KCCQ-TSS change from baseline at week 52 of > -15 points (stability) - RS (LOCF-AD) - 1245.121

	Placebo	Empa 10mg
Number of patients in analysis set	1867	1863
Number of analysed patients, N (%)	1709 (100.0)	1740 (100.0)
Number of patients with endpoint, N (%)	1494 (87.4)	1558 (89.5)
95% confidence interval*	(85.8, 88.9)	(88.0, 90.9)
Comparison vs Placebo**		
Odds ratio (SE)		1.235 (0.134)
95% confidence interval***		(0.998, 1.528)
p-value		0.0522

* Wilson confidence intervals.
** Logistic regression includes terms for baseline KCCQ - total symptom score (p<0.0001), age (p=0.3275), baseline eGFR (CKD-EPI) (p<0.0001), Treatment (p=0.0522), region (5 cat.) (p=0.0126), baseline diabetes status (3 cat.) (p=0.8334), sex (p=0.1387) and baseline LVEF (3 cat.) (p=0.0502).
***Wald confidence intervals.

Data taken from study 1245.121 only.
LOCF: For a missing value at week 52 the last available post-baseline value before week 52 is imputed.

Table R.1.2.7.1: 4 Responder analysis (displaying risk ratio) in KCCQ-TSS change from baseline at week 52 of > -15 points (stability) - RS (LOCF-AD) - 1245.121

	Placebo	Empa 10mg
Number of patients in analysis set	1867	1863
Number of analysed patients, N (%)	1709 (100.0)	1740 (100.0)
Number of patients with endpoint, N (%)	1494 (87.4)	1558 (89.5)
95% confidence interval*	(85.8, 88.9)	(88.0, 90.9)
Comparison vs Placebo**		
Risk ratio (SE)		1.023 (0.012)
95% confidence interval***		(0.999, 1.048)
p-value		0.0598

* Wilson confidence intervals.
** Log-linked Poisson model with robust estimate of variance includes terms for baseline KCCQ - total symptom score (p<0.0001), age (p=0.4510), baseline eGFR (CKD-EPI) (p<0.0001), Treatment (p=0.0598), region (5 cat.) (p<0.0001), baseline diabetes status (3 cat.) (p=0.8572), sex (p=0.1515) and baseline LVEF (3 cat.) (p=0.0329).
***Wald confidence intervals.

Data taken from study 1245.121 only.
LOCF: For a missing value at week 52 the last available post-baseline value before week 52 is imputed.

Table R.1.2.7.1: 5 Responder analysis (displaying odds ratio) in KCCQ-TSS change from baseline at week 52 of >= 15 points (improvement) - RS (LOCF-AD) - 1245.121

	Placebo	Empa 10mg
Number of patients in analysis set	1867	1863
Number of analysed patients, N (%)	1709 (100.0)	1740 (100.0)
Number of patients with endpoint, N (%)	396 (23.2)	466 (26.8)
95% confidence interval*	(21.2, 25.2)	(24.8, 28.9)
Comparison vs Placebo**		
Odds ratio (SE)		1.254 (0.118)
95% confidence interval***		(1.043, 1.508)
p-value		0.0162

* Wilson confidence intervals.
** Logistic regression includes terms for baseline KCCQ - total symptom score (p<0.0001), age (p=0.8896), baseline eGFR (CKD-EPI) (p=0.8394), Treatment (p=0.0162), region (5 cat.) (p<0.0001), baseline diabetes status (3 cat.) (p=0.6119), sex (p=0.2654) and baseline LVEF (3 cat.) (p=0.7943).
***Wald confidence intervals.

Data taken from study 1245.121 only.
LOCF: For a missing value at week 52 the last available post-baseline value before week 52 is imputed.

Table R.1.2.7.1: 6 Responder analysis (displaying risk ratio) in KCCQ-TSS change from baseline at week 52 of >= 15 points (improvement) - RS (LOCF-AD) - 1245.121

	Placebo	Empa 10mg
Number of patients in analysis set	1867	1863
Number of analysed patients, N (%)	1709 (100.0)	1740 (100.0)
Number of patients with endpoint, N (%)	396 (23.2)	466 (26.8)
95% confidence interval*	(21.2, 25.2)	(24.8, 28.9)
Comparison vs Placebo**		
Risk ratio (SE)		1.105 (0.060)
95% confidence interval***		(0.993, 1.230)
p-value		0.0668

* Wilson confidence intervals.
** Log-linked Poisson model with robust estimate of variance includes terms for baseline KCCQ - total symptom score (p<0.0001), age (p=0.9719), baseline eGFR (CKD-EPI) (p=0.9330), Treatment (p=0.0668), region (5 cat.) (p<0.0001), baseline diabetes status (3 cat.) (p=0.4942), sex (p=0.5724) and baseline LVEF (3 cat.) (p=0.8704).
***Wald confidence intervals.

Data taken from study 1245.121 only.
LOCF: For a missing value at week 52 the last available post-baseline value before week 52 is imputed.

R.1.2.7.2

R.1.2.7.2 Subgroup analysis by sex

Table R.1.2.7.2: 1 Responder analysis (displaying odds ratio) in KCCQ-TSS change from baseline at week 52 of <= -15 points (deterioration) by sex - RS (LOCF-AD) - 1245.121

Subgroup Description	Placebo	Empa 10mg
Sex: Male		
Number of patients in analysis set	1411	1426
Number of analysed patients, N (%)	1297 (100.0)	1332 (100.0)
Number of patients with endpoint, N (%)	164 (12.6)	133 (10.0)
95% confidence interval*	(10.9, 14.6)	(8.5, 11.7)
Comparison vs Placebo**		
Odds ratio (SE)		0.764 (0.096)
95% confidence interval***		(0.597, 0.977)
p-value		0.0320
Sex: Female		
Number of patients in analysis set	456	437
Number of analysed patients, N (%)	412 (100.0)	408 (100.0)
Number of patients with endpoint, N (%)	51 (12.4)	49 (12.0)
95% confidence interval*	(9.5, 15.9)	(9.2, 15.5)
Comparison vs Placebo**		
Odds ratio (SE)		0.965 (0.210)
95% confidence interval***		(0.630, 1.478)
p-value		0.8701

* Wilson confidence intervals.
** Logistic regression includes terms for baseline KCCQ - total symptom score (p<0.0001), age (p=0.3137), baseline eGFR (CKD-EPI) (p<0.0001), Treatment (p=0.2241), region (5 cat.) (p=0.0131), baseline diabetes status (3 cat.) (p=0.8349), baseline LVEF (3 cat.) (p=0.0512), sex (p=0.1271) and Treatment by sex interaction (p=0.3515).
***Wald confidence intervals.

Data taken from study 1245.121 only.
LOCF: For a missing value at week 52 the last available post-baseline value before week 52 is imputed.

Table R.1.2.7.2: 2 Responder analysis (displaying risk ratio) in KCCQ-TSS change from baseline at week 52 of <= -15 points (deterioration) by sex - RS (LOCF-AD) - 1245.121

Subgroup Description	Placebo	Empa 10mg
Sex: Male		
Number of patients in analysis set	1411	1426
Number of analysed patients, N (%)	1297 (100.0)	1332 (100.0)
Number of patients with endpoint, N (%)	164 (12.6)	133 (10.0)
95% confidence interval*	(10.9, 14.6)	(8.5, 11.7)
Comparison vs Placebo**		
Risk ratio (SE)		0.793 (0.086)
95% confidence interval***		(0.641, 0.980)
p-value		0.0321
Sex: Female		
Number of patients in analysis set	456	437
Number of analysed patients, N (%)	412 (100.0)	408 (100.0)
Number of patients with endpoint, N (%)	51 (12.4)	49 (12.0)
95% confidence interval*	(9.5, 15.9)	(9.2, 15.5)
Comparison vs Placebo**		
Risk ratio (SE)		0.967 (0.178)
95% confidence interval***		(0.675, 1.386)
p-value		0.8545

* Wilson confidence intervals.
** Log-linked Poisson model with robust estimate of variance includes terms for baseline KCCQ - total symptom score (p<0.0001), age (p=0.3295), baseline eGFR (CKD-EPI) (p<0.0001), Treatment (p=0.2117), region (5 cat.) (p=0.0173), baseline diabetes status (3 cat.) (p=0.8372), baseline LVEF (3 cat.) (p=0.0506), sex (p=0.1213) and Treatment by sex interaction (p=0.3520).
***Wald confidence intervals.

Data taken from study 1245.121 only.
LOCF: For a missing value at week 52 the last available post-baseline value before week 52 is imputed.

Table R.1.2.7.2: 3 Responder analysis (displaying odds ratio) in KCCQ-TSS change from baseline at week 52 of > -15 points (stability) by sex - RS (LOCF-AD) - 1245.121

Subgroup Description	Placebo	Empa 10mg
Sex: Male		
Number of patients in analysis set	1411	1426
Number of analysed patients, N (%)	1297 (100.0)	1332 (100.0)
Number of patients with endpoint, N (%)	1133 (87.4)	1199 (90.0)
95% confidence interval*	(85.4, 89.1)	(88.3, 91.5)
Comparison vs Placebo**		
Odds ratio (SE)		1.309 (0.165)
95% confidence interval***		(1.023, 1.675)
p-value		0.0320
Sex: Female		
Number of patients in analysis set	456	437
Number of analysed patients, N (%)	412 (100.0)	408 (100.0)
Number of patients with endpoint, N (%)	361 (87.6)	359 (88.0)
95% confidence interval*	(84.1, 90.5)	(84.5, 90.8)
Comparison vs Placebo**		
Odds ratio (SE)		1.036 (0.225)
95% confidence interval***		(0.677, 1.586)
p-value		0.8701

* Wilson confidence intervals.
** Logistic regression includes terms for baseline KCCQ - total symptom score (p<0.0001), age (p=0.3137), baseline eGFR (CKD-EPI) (p<0.0001), Treatment (p=0.2241), region (5 cat.) (p=0.0131), baseline diabetes status (3 cat.) (p=0.8349), baseline LVEF (3 cat.) (p=0.0512), sex (p=0.1271) and Treatment by sex interaction (p=0.3515).
***Wald confidence intervals.

Data taken from study 1245.121 only.
LOCF: For a missing value at week 52 the last available post-baseline value before week 52 is imputed.

Table R.1.2.7.2: 4 Responder analysis (displaying risk ratio) in KCCQ-TSS change from baseline at week 52 of > -15 points (stability) by sex - RS (LOCF-AD) - 1245.121

Subgroup Description	Placebo	Empa 10mg
Sex: Male		
Number of patients in analysis set	1411	1426
Number of analysed patients, N (%)	1297 (100.0)	1332 (100.0)
Number of patients with endpoint, N (%)	1133 (87.4)	1199 (90.0)
95% confidence interval*	(85.4, 89.1)	(88.3, 91.5)
Comparison vs Placebo**		
Risk ratio (SE)		1.030 (0.014)
95% confidence interval***		(1.002, 1.058)
p-value		0.0348
Sex: Female		
Number of patients in analysis set	456	437
Number of analysed patients, N (%)	412 (100.0)	408 (100.0)
Number of patients with endpoint, N (%)	361 (87.6)	359 (88.0)
95% confidence interval*	(84.1, 90.5)	(84.5, 90.8)
Comparison vs Placebo**		
Risk ratio (SE)		1.003 (0.026)
95% confidence interval***		(0.954, 1.054)
p-value		0.9153

* Wilson confidence intervals.
** Log-linked Poisson model with robust estimate of variance includes terms for baseline KCCQ - total symptom score (p<0.0001), age (p=0.4408), baseline eGFR (CKD-EPI) (p<0.0001), Treatment (p=0.2743), region (5 cat.) (p<0.0001), baseline diabetes status (3 cat.) (p=0.8583), baseline LVEF (3 cat.) (p=0.0342), sex (p=0.1548) and Treatment by sex interaction (p=0.3652).
***Wald confidence intervals.

Data taken from study 1245.121 only.
LOCF: For a missing value at week 52 the last available post-baseline value before week 52 is imputed.

Table R.1.2.7.2: 5 Responder analysis (displaying odds ratio) in KCCQ-TSS change from baseline at week 52 of >= 15 points (improvement) by sex - RS (LOCF-AD) - 1245.121

Subgroup Description	Placebo	Empa 10mg
Sex: Male		
Number of patients in analysis set	1411	1426
Number of analysed patients, N (%)	1297 (100.0)	1332 (100.0)
Number of patients with endpoint, N (%)	286 (22.1)	335 (25.2)
95% confidence interval*	(19.9, 24.4)	(22.9, 27.5)
Comparison vs Placebo**		
Odds ratio (SE)		1.193 (0.130)
95% confidence interval***		(0.963, 1.477)
p-value		0.1065
Sex: Female		
Number of patients in analysis set	456	437
Number of analysed patients, N (%)	412 (100.0)	408 (100.0)
Number of patients with endpoint, N (%)	110 (26.7)	131 (32.1)
95% confidence interval*	(22.7, 31.2)	(27.8, 36.8)
Comparison vs Placebo**		
Odds ratio (SE)		1.451 (0.270)
95% confidence interval***		(1.007, 2.090)
p-value		0.0458

* Wilson confidence intervals.
** Logistic regression includes terms for baseline KCCQ - total symptom score (p<0.0001), age (p=0.8943), baseline eGFR (CKD-EPI) (p=0.8210), Treatment (p=0.0111), region (5 cat.) (p<0.0001), baseline diabetes status (3 cat.) (p=0.6124), baseline LVEF (3 cat.) (p=0.7964), sex (p=0.2560) and Treatment by sex interaction (p=0.3641).
***Wald confidence intervals.

Data taken from study 1245.121 only.
LOCF: For a missing value at week 52 the last available post-baseline value before week 52 is imputed.

Table R.1.2.7.2: 6 Responder analysis (displaying risk ratio) in KCCQ-TSS change from baseline at week 52 of >= 15 points (improvement) by sex - RS (LOCF-AD) - 1245.121

Subgroup Description	Placebo	Empa 10mg
Sex: Male		
Number of patients in analysis set	1411	1426
Number of analysed patients, N (%)	1297 (100.0)	1332 (100.0)
Number of patients with endpoint, N (%)	286 (22.1)	335 (25.2)
95% confidence interval*	(19.9, 24.4)	(22.9, 27.5)
Comparison vs Placebo**		
Risk ratio (SE)		1.060 (0.069)
95% confidence interval***		(0.934, 1.204)
p-value		0.3669
Sex: Female		
Number of patients in analysis set	456	437
Number of analysed patients, N (%)	412 (100.0)	408 (100.0)
Number of patients with endpoint, N (%)	110 (26.7)	131 (32.1)
95% confidence interval*	(22.7, 31.2)	(27.8, 36.8)
Comparison vs Placebo**		
Risk ratio (SE)		1.228 (0.123)
95% confidence interval***		(1.009, 1.495)
p-value		0.0401

* Wilson confidence intervals.
** Log-linked Poisson model with robust estimate of variance includes terms for baseline KCCQ - total symptom score (p<0.0001), age (p=0.9430), baseline eGFR (CKD-EPI) (p=0.9516), Treatment (p=0.0269), region (5 cat.) (p<0.0001), baseline diabetes status (3 cat.) (p=0.5234), baseline LVEF (3 cat.) (p=0.8620), sex (p=0.5160) and Treatment by sex interaction (p=0.2174).
***Wald confidence intervals.

Data taken from study 1245.121 only.
LOCF: For a missing value at week 52 the last available post-baseline value before week 52 is imputed.

R.1.2.7.3

R.1.2.7.3 Subgroup analysis by age

Table R.1.2.7.3: 1 Responder analysis (displaying odds ratio) in KCCQ-TSS change from baseline at week 52 of <= -15 points (deterioration) by age (2 cat.) - RS (LOCF-AD) - 1245.121

Subgroup Description	Placebo	Empa 10mg
Age [years] (2 cat.): < 65		
Number of patients in analysis set	740	675
Number of analysed patients, N (%)	675 (100.0)	635 (100.0)
Number of patients with endpoint, N (%)	74 (11.0)	50 (7.9)
95% confidence interval*	(8.8, 13.5)	(6.0, 10.2)
Comparison vs Placebo**		
Odds ratio (SE)		0.702 (0.137)
95% confidence interval***		(0.479, 1.030)
p-value		0.0702
Age [years] (2 cat.): >= 65		
Number of patients in analysis set	1127	1188
Number of analysed patients, N (%)	1034 (100.0)	1105 (100.0)
Number of patients with endpoint, N (%)	141 (13.6)	132 (11.9)
95% confidence interval*	(11.7, 15.9)	(10.2, 14.0)
Comparison vs Placebo**		
Odds ratio (SE)		0.867 (0.114)
95% confidence interval***		(0.670, 1.122)
p-value		0.2779

* Wilson confidence intervals.
** Logistic regression includes terms for baseline KCCQ - total symptom score (p<0.0001), baseline eGFR (CKD-EPI) (p<0.0001), Treatment (p=0.0348), region (5 cat.) (p=0.0101), baseline diabetes status (3 cat.) (p=0.8484), sex (p=0.1220), baseline LVEF (3 cat.) (p=0.0606), age (2 cat.) (p=0.7719) and Treatment by age (2 cat.) interaction (p=0.3713).
***Wald confidence intervals.

Data taken from study 1245.121 only.
LOCF: For a missing value at week 52 the last available post-baseline value before week 52 is imputed.

Table R.1.2.7.3: 2 Responder analysis (displaying risk ratio) in KCCQ-TSS change from baseline at week 52 of <= -15 points (deterioration) by age (2 cat.) - RS (LOCF-AD) - 1245.121

Subgroup Description	Placebo	Empa 10mg
Age [years] (2 cat.): < 65		
Number of patients in analysis set	740	675
Number of analysed patients, N (%)	675 (100.0)	635 (100.0)
Number of patients with endpoint, N (%)	74 (11.0)	50 (7.9)
95% confidence interval*	(8.8, 13.5)	(6.0, 10.2)
Comparison vs Placebo**		
Risk ratio (SE)		0.732 (0.126)
95% confidence interval***		(0.523, 1.026)
p-value		0.0698
Age [years] (2 cat.): >= 65		
Number of patients in analysis set	1127	1188
Number of analysed patients, N (%)	1034 (100.0)	1105 (100.0)
Number of patients with endpoint, N (%)	141 (13.6)	132 (11.9)
95% confidence interval*	(11.7, 15.9)	(10.2, 14.0)
Comparison vs Placebo**		
Risk ratio (SE)		0.885 (0.099)
95% confidence interval***		(0.710, 1.102)
p-value		0.2751

* Wilson confidence intervals.
** Log-linked Poisson model with robust estimate of variance includes terms for baseline KCCQ - total symptom score (p<0.0001), baseline eGFR (CKD-EPI) (p<0.0001), Treatment (p=0.0340), region (5 cat.) (p=0.0146), baseline diabetes status (3 cat.) (p=0.8509), sex (p=0.1171), baseline LVEF (3 cat.) (p=0.0600), age (2 cat.) (p=0.7485) and Treatment by age (2 cat.) interaction (p=0.3576).
***Wald confidence intervals.

Data taken from study 1245.121 only.
LOCF: For a missing value at week 52 the last available post-baseline value before week 52 is imputed.

Table R.1.2.7.3: 3 Responder analysis (displaying odds ratio) in KCCQ-TSS change from baseline at week 52 of > -15 points (stability) by age (2 cat.) - RS (LOCF-AD) - 1245.121

Subgroup Description	Placebo	Empa 10mg
Age [years] (2 cat.): < 65		
Number of patients in analysis set	740	675
Number of analysed patients, N (%)	675 (100.0)	635 (100.0)
Number of patients with endpoint, N (%)	601 (89.0)	585 (92.1)
95% confidence interval*	(86.5, 91.2)	(89.8, 94.0)
Comparison vs Placebo**		
Odds ratio (SE)		1.424 (0.278)
95% confidence interval***		(0.971, 2.087)
p-value		0.0702
Age [years] (2 cat.): >= 65		
Number of patients in analysis set	1127	1188
Number of analysed patients, N (%)	1034 (100.0)	1105 (100.0)
Number of patients with endpoint, N (%)	893 (86.4)	973 (88.1)
95% confidence interval*	(84.1, 88.3)	(86.0, 89.8)
Comparison vs Placebo**		
Odds ratio (SE)		1.153 (0.152)
95% confidence interval***		(0.891, 1.493)
p-value		0.2779

* Wilson confidence intervals.
** Logistic regression includes terms for baseline KCCQ - total symptom score (p<0.0001), baseline eGFR (CKD-EPI) (p<0.0001), Treatment (p=0.0348), region (5 cat.) (p=0.0101), baseline diabetes status (3 cat.) (p=0.8484), sex (p=0.1220), baseline LVEF (3 cat.) (p=0.0606), age (2 cat.) (p=0.7719) and Treatment by age (2 cat.) interaction (p=0.3713).
***Wald confidence intervals.

Data taken from study 1245.121 only.
LOCF: For a missing value at week 52 the last available post-baseline value before week 52 is imputed.

Table R.1.2.7.3: 4 Responder analysis (displaying risk ratio) in KCCQ-TSS change from baseline at week 52 of > -15 points (stability) by age (2 cat.) - RS (LOCF-AD) - 1245.121

Subgroup Description	Placebo	Empa 10mg
Age [years] (2 cat.): < 65		
Number of patients in analysis set	740	675
Number of analysed patients, N (%)	675 (100.0)	635 (100.0)
Number of patients with endpoint, N (%)	601 (89.0)	585 (92.1)
95% confidence interval*	(86.5, 91.2)	(89.8, 94.0)
Comparison vs Placebo**		
Risk ratio (SE)		1.031 (0.018)
95% confidence interval***		(0.996, 1.067)
p-value		0.0822
Age [years] (2 cat.): >= 65		
Number of patients in analysis set	1127	1188
Number of analysed patients, N (%)	1034 (100.0)	1105 (100.0)
Number of patients with endpoint, N (%)	893 (86.4)	973 (88.1)
95% confidence interval*	(84.1, 88.3)	(86.0, 89.8)
Comparison vs Placebo**		
Risk ratio (SE)		1.018 (0.017)
95% confidence interval***		(0.985, 1.051)
p-value		0.2870

* Wilson confidence intervals.
** Log-linked Poisson model with robust estimate of variance includes terms for baseline KCCQ - total symptom score (p<0.0001), baseline eGFR (CKD-EPI) (p<0.0001), Treatment (p=0.0454), region (5 cat.) (p<0.0001), baseline diabetes status (3 cat.) (p=0.8693), sex (p=0.1394), baseline LVEF (3 cat.) (p=0.0397), age (2 cat.) (p=0.9376) and Treatment by age (2 cat.) interaction (p=0.5908).
***Wald confidence intervals.

Data taken from study 1245.121 only.
LOCF: For a missing value at week 52 the last available post-baseline value before week 52 is imputed.

Table R.1.2.7.3: 5 Responder analysis (displaying odds ratio) in KCCQ-TSS change from baseline at week 52 of >= 15 points (improvement) by age (2 cat.) - RS (LOCF-AD) - 1245.121

Subgroup Description	Placebo	Empa 10mg
Age [years] (2 cat.): < 65		
Number of patients in analysis set	740	675
Number of analysed patients, N (%)	675 (100.0)	635 (100.0)
Number of patients with endpoint, N (%)	177 (26.2)	182 (28.7)
95% confidence interval*	(23.0, 29.7)	(25.3, 32.3)
Comparison vs Placebo**		
Odds ratio (SE)		1.078 (0.162)
95% confidence interval***		(0.803, 1.449)
p-value		0.6173
Age [years] (2 cat.): >= 65		
Number of patients in analysis set	1127	1188
Number of analysed patients, N (%)	1034 (100.0)	1105 (100.0)
Number of patients with endpoint, N (%)	219 (21.2)	284 (25.7)
95% confidence interval*	(18.8, 23.8)	(23.2, 28.4)
Comparison vs Placebo**		
Odds ratio (SE)		1.376 (0.167)
95% confidence interval***		(1.085, 1.746)
p-value		0.0084

* Wilson confidence intervals.
** Logistic regression includes terms for baseline KCCQ - total symptom score (p<0.0001), baseline eGFR (CKD-EPI) (p=0.7874), Treatment (p=0.0409), region (5 cat.) (p<0.0001), baseline diabetes status (3 cat.) (p=0.6452), sex (p=0.2927), baseline LVEF (3 cat.) (p=0.8325), age (2 cat.) (p=0.3112) and Treatment by age (2 cat.) interaction (p=0.2073).
***Wald confidence intervals.

Data taken from study 1245.121 only.
LOCF: For a missing value at week 52 the last available post-baseline value before week 52 is imputed.

Table R.1.2.7.3: 6 Responder analysis (displaying risk ratio) in KCCQ-TSS change from baseline at week 52 of >= 15 points (improvement) by age (2 cat.) - RS (LOCF-AD) - 1245.121

Subgroup Description	Placebo	Empa 10mg
Age [years] (2 cat.): < 65		
Number of patients in analysis set	740	675
Number of analysed patients, N (%)	675 (100.0)	635 (100.0)
Number of patients with endpoint, N (%)	177 (26.2)	182 (28.7)
95% confidence interval*	(23.0, 29.7)	(25.3, 32.3)
Comparison vs Placebo**		
Risk ratio (SE)		1.030 (0.087)
95% confidence interval***		(0.873, 1.215)
p-value		0.7249
Age [years] (2 cat.): >= 65		
Number of patients in analysis set	1127	1188
Number of analysed patients, N (%)	1034 (100.0)	1105 (100.0)
Number of patients with endpoint, N (%)	219 (21.2)	284 (25.7)
95% confidence interval*	(18.8, 23.8)	(23.2, 28.4)
Comparison vs Placebo**		
Risk ratio (SE)		1.160 (0.083)
95% confidence interval***		(1.007, 1.336)
p-value		0.0393

* Wilson confidence intervals.
** Log-linked Poisson model with robust estimate of variance includes terms for baseline KCCQ - total symptom score (p<0.0001), baseline eGFR (CKD-EPI) (p=0.6227), Treatment (p=0.1080), region (5 cat.) (p<0.0001), baseline diabetes status (3 cat.) (p=0.5326), sex (p=0.6376), baseline LVEF (3 cat.) (p=0.8826), age (2 cat.) (p=0.3775) and Treatment by age (2 cat.) interaction (p=0.2840).
***Wald confidence intervals.

Data taken from study 1245.121 only.
LOCF: For a missing value at week 52 the last available post-baseline value before week 52 is imputed.

R.1.2.7.4 Subgroup analysis by region (North America, Latin America, Europe, Asia, Other)

Table R.1.2.7.4: 1 Responder analysis (displaying odds ratio) in KCCQ-TSS change from baseline at week 52 of <= -15 points (deterioration) by region - RS (LOCF-AD) - 1245.121

Subgroup Description	Placebo	Empa 10mg
Region (5 cat.): North America		
Number of patients in analysis set	213	212
Number of analysed patients, N (%)	192 (100.0)	204 (100.0)
Number of patients with endpoint, N (%)	22 (11.5)	22 (10.8)
95% confidence interval*	(7.7, 16.7)	(7.2, 15.8)
Comparison vs Placebo**		
Odds ratio (SE)		0.918 (0.298)
95% confidence interval***		(0.486, 1.733)
p-value		0.7912
Region (5 cat.): Latin America		
Number of patients in analysis set	645	641
Number of analysed patients, N (%)	577 (100.0)	586 (100.0)
Number of patients with endpoint, N (%)	74 (12.8)	51 (8.7)
95% confidence interval*	(10.3, 15.8)	(6.7, 11.3)
Comparison vs Placebo**		
Odds ratio (SE)		0.665 (0.130)
95% confidence interval***		(0.454, 0.974)
p-value		0.0363

* Wilson confidence intervals.
** Logistic regression includes terms for baseline KCCQ - total symptom score (p<0.0001), age (p=0.3153), baseline eGFR (CKD-EPI) (p<0.0001), Treatment (p=0.1534), baseline diabetes status (3 cat.) (p=0.8142), sex (p=0.1493), baseline LVEF (3 cat.) (p=0.0473), region (5 cat.) (p=0.0186) and Treatment by region (5 cat.) interaction (p=0.6875).
***Wald confidence intervals.

Data taken from study 1245.121 only.
LOCF: For a missing value at week 52 the last available post-baseline value before week 52 is imputed.

Table R.1.2.7.4: 1 Responder analysis (displaying odds ratio) in KCCQ-TSS change from baseline at week 52 of <= -15 points (deterioration) by region - RS (LOCF-AD) - 1245.121

Subgroup Description	Placebo	Empa 10mg
Region (5 cat.): Europe		
Number of patients in analysis set	677	676
Number of analysed patients, N (%)	631 (100.0)	638 (100.0)
Number of patients with endpoint, N (%)	88 (13.9)	84 (13.2)
95% confidence interval*	(11.5, 16.9)	(10.8, 16.0)
Comparison vs Placebo**		
Odds ratio (SE)		0.918 (0.153)
95% confidence interval***		(0.663, 1.272)
p-value		0.6089
Region (5 cat.): Asia		
Number of patients in analysis set	245	248
Number of analysed patients, N (%)	232 (100.0)	236 (100.0)
Number of patients with endpoint, N (%)	28 (12.1)	24 (10.2)
95% confidence interval*	(8.5, 16.9)	(6.9, 14.7)
Comparison vs Placebo**		
Odds ratio (SE)		0.826 (0.246)
95% confidence interval***		(0.460, 1.481)
p-value		0.5203

* Wilson confidence intervals.
** Logistic regression includes terms for baseline KCCQ - total symptom score (p<0.0001), age (p=0.3153), baseline eGFR (CKD-EPI) (p<0.0001), Treatment (p=0.1534), baseline diabetes status (3 cat.) (p=0.8142), sex (p=0.1493), baseline LVEF (3 cat.) (p=0.0473), region (5 cat.) (p=0.0186) and Treatment by region (5 cat.) interaction (p=0.6875).
***Wald confidence intervals.

Data taken from study 1245.121 only.
LOCF: For a missing value at week 52 the last available post-baseline value before week 52 is imputed.

Table R.1.2.7.4: 1 Responder analysis (displaying odds ratio) in KCCQ-TSS change from baseline at week 52 of <= -15 points (deterioration) by region - RS (LOCF-AD) - 1245.121

Subgroup Description	Placebo	Empa 10mg
Region (5 cat.): Other		
Number of patients in analysis set	87	86
Number of analysed patients, N (%)	77 (100.0)	76 (100.0)
Number of patients with endpoint, N (%)	3 (3.9)	1 (1.3)
95% confidence interval*	(1.3, 10.8)	(0.2, 7.1)
Comparison vs Placebo**		
Odds ratio (SE)		0.350 (0.409)
95% confidence interval***		(0.035, 3.460)
p-value		0.3691

* Wilson confidence intervals.
** Logistic regression includes terms for baseline KCCQ - total symptom score (p<0.0001), age (p=0.3153), baseline eGFR (CKD-EPI) (p<0.0001), Treatment (p=0.1534), baseline diabetes status (3 cat.) (p=0.8142), sex (p=0.1493), baseline LVEF (3 cat.) (p=0.0473), region (5 cat.) (p=0.0186) and Treatment by region (5 cat.) interaction (p=0.6875).
***Wald confidence intervals.

Data taken from study 1245.121 only.
LOCF: For a missing value at week 52 the last available post-baseline value before week 52 is imputed.

Table R.1.2.7.4: 2 Responder analysis (displaying risk ratio) in KCCQ-TSS change from baseline at week 52 of <= -15 points (deterioration) by region - RS (LOCF-AD) - 1245.121

Subgroup Description	Placebo	Empa 10mg
Region (5 cat.): North America		
Number of patients in analysis set	213	212
Number of analysed patients, N (%)	192 (100.0)	204 (100.0)
Number of patients with endpoint, N (%)	22 (11.5)	22 (10.8)
95% confidence interval*	(7.7, 16.7)	(7.2, 15.8)
Comparison vs Placebo**		
Risk ratio (SE)		0.929 (0.262)
95% confidence interval***		(0.534, 1.615)
p-value		0.7941
Region (5 cat.): Latin America		
Number of patients in analysis set	645	641
Number of analysed patients, N (%)	577 (100.0)	586 (100.0)
Number of patients with endpoint, N (%)	74 (12.8)	51 (8.7)
95% confidence interval*	(10.3, 15.8)	(6.7, 11.3)
Comparison vs Placebo**		
Risk ratio (SE)		0.700 (0.120)
95% confidence interval***		(0.501, 0.979)
p-value		0.0373

* Wilson confidence intervals.
** Log-linked Poisson model with robust estimate of variance includes terms for baseline KCCQ - total symptom score (p<0.0001), age (p=0.3326), baseline eGFR (CKD-EPI) (p<0.0001), Treatment (p=0.1631), baseline diabetes status (3 cat.) (p=0.8138), sex (p=0.1458), baseline LVEF (3 cat.) (p=0.0465), region (5 cat.) (p=0.0249) and Treatment by region (5 cat.) interaction (p=0.6682).
***Wald confidence intervals.

Data taken from study 1245.121 only.
LOCF: For a missing value at week 52 the last available post-baseline value before week 52 is imputed.

Table R.1.2.7.4: 2 Responder analysis (displaying risk ratio) in KCCQ-TSS change from baseline at week 52 of <= -15 points (deterioration) by region - RS (LOCF-AD) - 1245.121

Subgroup Description	Placebo	Empa 10mg
Region (5 cat.): Europe		
Number of patients in analysis set	677	676
Number of analysed patients, N (%)	631 (100.0)	638 (100.0)
Number of patients with endpoint, N (%)	88 (13.9)	84 (13.2)
95% confidence interval*	(11.5, 16.9)	(10.8, 16.0)
Comparison vs Placebo**		
Risk ratio (SE)		0.930 (0.129)
95% confidence interval***		(0.708, 1.222)
p-value		0.6031
Region (5 cat.): Asia		
Number of patients in analysis set	245	248
Number of analysed patients, N (%)	232 (100.0)	236 (100.0)
Number of patients with endpoint, N (%)	28 (12.1)	24 (10.2)
95% confidence interval*	(8.5, 16.9)	(6.9, 14.7)
Comparison vs Placebo**		
Risk ratio (SE)		0.845 (0.221)
95% confidence interval***		(0.506, 1.411)
p-value		0.5206

* Wilson confidence intervals.
** Log-linked Poisson model with robust estimate of variance includes terms for baseline KCCQ - total symptom score (p<0.0001), age (p=0.3326), baseline eGFR (CKD-EPI) (p<0.0001), Treatment (p=0.1631), baseline diabetes status (3 cat.) (p=0.8138), sex (p=0.1458), baseline LVEF (3 cat.) (p=0.0465), region (5 cat.) (p=0.0249) and Treatment by region (5 cat.) interaction (p=0.6682).
***Wald confidence intervals.

Data taken from study 1245.121 only.
LOCF: For a missing value at week 52 the last available post-baseline value before week 52 is imputed.

Table R.1.2.7.4: 2 Responder analysis (displaying risk ratio) in KCCQ-TSS change from baseline at week 52 of <= -15 points (deterioration) by region - RS (LOCF-AD) - 1245.121

Subgroup Description	Placebo	Empa 10mg
Region (5 cat.): Other		
Number of patients in analysis set	87	86
Number of analysed patients, N (%)	77 (100.0)	76 (100.0)
Number of patients with endpoint, N (%)	3 (3.9)	1 (1.3)
95% confidence interval*	(1.3, 10.8)	(0.2, 7.1)
Comparison vs Placebo**		
Risk ratio (SE)		0.358 (0.406)
95% confidence interval***		(0.039, 3.302)
p-value		0.3651

* Wilson confidence intervals.
** Log-linked Poisson model with robust estimate of variance includes terms for baseline KCCQ - total symptom score (p<0.0001), age (p=0.3326), baseline eGFR (CKD-EPI) (p<0.0001), Treatment (p=0.1631), baseline diabetes status (3 cat.) (p=0.8138), sex (p=0.1458), baseline LVEF (3 cat.) (p=0.0465), region (5 cat.) (p=0.0249) and Treatment by region (5 cat.) interaction (p=0.6682).
***Wald confidence intervals.

Data taken from study 1245.121 only.
LOCF: For a missing value at week 52 the last available post-baseline value before week 52 is imputed.

Table R.1.2.7.4: 3 Responder analysis (displaying odds ratio) in KCCQ-TSS change from baseline at week 52 of > -15 points (stability) by region - RS (LOCF-AD) - 1245.121

Subgroup Description	Placebo	Empa 10mg
Region (5 cat.): North America		
Number of patients in analysis set	213	212
Number of analysed patients, N (%)	192 (100.0)	204 (100.0)
Number of patients with endpoint, N (%)	170 (88.5)	182 (89.2)
95% confidence interval*	(83.3, 92.3)	(84.2, 92.8)
Comparison vs Placebo**		
Odds ratio (SE)		1.090 (0.353)
95% confidence interval***		(0.577, 2.058)
p-value		0.7912
Region (5 cat.): Latin America		
Number of patients in analysis set	645	641
Number of analysed patients, N (%)	577 (100.0)	586 (100.0)
Number of patients with endpoint, N (%)	503 (87.2)	535 (91.3)
95% confidence interval*	(84.2, 89.7)	(88.7, 93.3)
Comparison vs Placebo**		
Odds ratio (SE)		1.504 (0.293)
95% confidence interval***		(1.026, 2.205)
p-value		0.0363

* Wilson confidence intervals.
** Logistic regression includes terms for baseline KCCQ - total symptom score (p<0.0001), age (p=0.3153), baseline eGFR (CKD-EPI) (p<0.0001), Treatment (p=0.1534), baseline diabetes status (3 cat.) (p=0.8142), sex (p=0.1493), baseline LVEF (3 cat.) (p=0.0473), region (5 cat.) (p=0.0186) and Treatment by region (5 cat.) interaction (p=0.6875).
***Wald confidence intervals.

Data taken from study 1245.121 only.
LOCF: For a missing value at week 52 the last available post-baseline value before week 52 is imputed.

Table R.1.2.7.4: 3 Responder analysis (displaying odds ratio) in KCCQ-TSS change from baseline at week 52 of > -15 points (stability) by region - RS (LOCF-AD) - 1245.121

Subgroup Description	Placebo	Empa 10mg
Region (5 cat.): Europe		
Number of patients in analysis set	677	676
Number of analysed patients, N (%)	631 (100.0)	638 (100.0)
Number of patients with endpoint, N (%)	543 (86.1)	554 (86.8)
95% confidence interval*	(83.1, 88.5)	(84.0, 89.2)
Comparison vs Placebo**		
Odds ratio (SE)		1.089 (0.181)
95% confidence interval***		(0.786, 1.508)
p-value		0.6089
Region (5 cat.): Asia		
Number of patients in analysis set	245	248
Number of analysed patients, N (%)	232 (100.0)	236 (100.0)
Number of patients with endpoint, N (%)	204 (87.9)	212 (89.8)
95% confidence interval*	(83.1, 91.5)	(85.3, 93.1)
Comparison vs Placebo**		
Odds ratio (SE)		1.211 (0.361)
95% confidence interval***		(0.675, 2.173)
p-value		0.5203

* Wilson confidence intervals.
** Logistic regression includes terms for baseline KCCQ - total symptom score (p<0.0001), age (p=0.3153), baseline eGFR (CKD-EPI) (p<0.0001), Treatment (p=0.1534), baseline diabetes status (3 cat.) (p=0.8142), sex (p=0.1493), baseline LVEF (3 cat.) (p=0.0473), region (5 cat.) (p=0.0186) and Treatment by region (5 cat.) interaction (p=0.6875).
***Wald confidence intervals.

Data taken from study 1245.121 only.
LOCF: For a missing value at week 52 the last available post-baseline value before week 52 is imputed.

Table R.1.2.7.4: 3 Responder analysis (displaying odds ratio) in KCCQ-TSS change from baseline at week 52 of > -15 points (stability) by region - RS (LOCF-AD) - 1245.121

Subgroup Description	Placebo	Empa 10mg
Region (5 cat.): Other		
Number of patients in analysis set	87	86
Number of analysed patients, N (%)	77 (100.0)	76 (100.0)
Number of patients with endpoint, N (%)	74 (96.1)	75 (98.7)
95% confidence interval*	(89.2, 98.7)	(92.9, 99.8)
Comparison vs Placebo**		
Odds ratio (SE)		2.858 (3.342)
95% confidence interval***		(0.289,28.265)
p-value		0.3691

* Wilson confidence intervals.
** Logistic regression includes terms for baseline KCCQ - total symptom score (p<0.0001), age (p=0.3153), baseline eGFR (CKD-EPI) (p<0.0001), Treatment (p=0.1534), baseline diabetes status (3 cat.) (p=0.8142), sex (p=0.1493), baseline LVEF (3 cat.) (p=0.0473), region (5 cat.) (p=0.0186) and Treatment by region (5 cat.) interaction (p=0.6875).
***Wald confidence intervals.

Data taken from study 1245.121 only.
LOCF: For a missing value at week 52 the last available post-baseline value before week 52 is imputed.

Table R.1.2.7.4: 4 Responder analysis (displaying risk ratio) in KCCQ-TSS change from baseline at week 52 of > -15 points (stability) by region - RS (LOCF-AD) - 1245.121

Subgroup Description	Placebo	Empa 10mg
Region (5 cat.): North America		
Number of patients in analysis set	213	212
Number of analysed patients, N (%)	192 (100.0)	204 (100.0)
Number of patients with endpoint, N (%)	170 (88.5)	182 (89.2)
95% confidence interval*	(83.3, 92.3)	(84.2, 92.8)
Comparison vs Placebo**		
Risk ratio (SE)		1.011 (0.036)
95% confidence interval***		(0.943, 1.083)
p-value		0.7667
Region (5 cat.): Latin America		
Number of patients in analysis set	645	641
Number of analysed patients, N (%)	577 (100.0)	586 (100.0)
Number of patients with endpoint, N (%)	503 (87.2)	535 (91.3)
95% confidence interval*	(84.2, 89.7)	(88.7, 93.3)
Comparison vs Placebo**		
Risk ratio (SE)		1.042 (0.021)
95% confidence interval***		(1.001, 1.084)
p-value		0.0427

* Wilson confidence intervals.
** Log-linked Poisson model with robust estimate of variance includes terms for baseline KCCQ - total symptom score (p<0.0001), age (p=0.4398), baseline eGFR (CKD-EPI) (p<0.0001), Treatment (p=0.0999), baseline diabetes status (3 cat.) (p=0.8526), sex (p=0.1551), baseline LVEF (3 cat.) (p=0.0310), region (5 cat.) (p<0.0001) and Treatment by region (5 cat.) interaction (p=0.8690).
***Wald confidence intervals.

Data taken from study 1245.121 only.
LOCF: For a missing value at week 52 the last available post-baseline value before week 52 is imputed.

Table R.1.2.7.4: 4 Responder analysis (displaying risk ratio) in KCCQ-TSS change from baseline at week 52 of > -15 points (stability) by region - RS (LOCF-AD) - 1245.121

Subgroup Description	Placebo	Empa 10mg
Region (5 cat.): Europe		
Number of patients in analysis set	677	676
Number of analysed patients, N (%)	631 (100.0)	638 (100.0)
Number of patients with endpoint, N (%)	543 (86.1)	554 (86.8)
95% confidence interval*	(83.1, 88.5)	(84.0, 89.2)
Comparison vs Placebo**		
Risk ratio (SE)		1.011 (0.022)
95% confidence interval***		(0.968, 1.055)
p-value		0.6195
Region (5 cat.): Asia		
Number of patients in analysis set	245	248
Number of analysed patients, N (%)	232 (100.0)	236 (100.0)
Number of patients with endpoint, N (%)	204 (87.9)	212 (89.8)
95% confidence interval*	(83.1, 91.5)	(85.3, 93.1)
Comparison vs Placebo**		
Risk ratio (SE)		1.021 (0.033)
95% confidence interval***		(0.957, 1.088)
p-value		0.5311

* Wilson confidence intervals.
** Log-linked Poisson model with robust estimate of variance includes terms for baseline KCCQ - total symptom score (p<0.0001), age (p=0.4398), baseline eGFR (CKD-EPI) (p<0.0001), Treatment (p=0.0999), baseline diabetes status (3 cat.) (p=0.8526), sex (p=0.1551), baseline LVEF (3 cat.) (p=0.0310), region (5 cat.) (p<0.0001) and Treatment by region (5 cat.) interaction (p=0.8690).
***Wald confidence intervals.

Data taken from study 1245.121 only.
LOCF: For a missing value at week 52 the last available post-baseline value before week 52 is imputed.

Table R.1.2.7.4: 4 Responder analysis (displaying risk ratio) in KCCQ-TSS change from baseline at week 52 of > -15 points (stability) by region - RS (LOCF-AD) - 1245.121

Subgroup Description	Placebo	Empa 10mg
Region (5 cat.): Other		
Number of patients in analysis set	87	86
Number of analysed patients, N (%)	77 (100.0)	76 (100.0)
Number of patients with endpoint, N (%)	74 (96.1)	75 (98.7)
95% confidence interval*	(89.2, 98.7)	(92.9, 99.8)
Comparison vs Placebo**		
Risk ratio (SE)		1.020 (0.027)
95% confidence interval***		(0.969, 1.074)
p-value		0.4528

* Wilson confidence intervals.
** Log-linked Poisson model with robust estimate of variance includes terms for baseline KCCQ - total symptom score (p<0.0001), age (p=0.4398), baseline eGFR (CKD-EPI) (p<0.0001), Treatment (p=0.0999), baseline diabetes status (3 cat.) (p=0.8526), sex (p=0.1551), baseline LVEF (3 cat.) (p=0.0310), region (5 cat.) (p<0.0001) and Treatment by region (5 cat.) interaction (p=0.8690).
***Wald confidence intervals.

Data taken from study 1245.121 only.
LOCF: For a missing value at week 52 the last available post-baseline value before week 52 is imputed.

Table R.1.2.7.4: 5 Responder analysis (displaying odds ratio) in KCCQ-TSS change from baseline at week 52 of >= 15 points (improvement) by region - RS (LOCF-AD) - 1245.121

Subgroup Description	Placebo	Empa 10mg
Region (5 cat.): North America		
Number of patients in analysis set	213	212
Number of analysed patients, N (%)	192 (100.0)	204 (100.0)
Number of patients with endpoint, N (%)	33 (17.2)	50 (24.5)
95% confidence interval*	(12.5, 23.2)	(19.1, 30.8)
Comparison vs Placebo**		
Odds ratio (SE)		2.046 (0.616)
95% confidence interval***		(1.135, 3.690)
p-value		0.0173
Region (5 cat.): Latin America		
Number of patients in analysis set	645	641
Number of analysed patients, N (%)	577 (100.0)	586 (100.0)
Number of patients with endpoint, N (%)	174 (30.2)	211 (36.0)
95% confidence interval*	(26.6, 34.0)	(32.2, 40.0)
Comparison vs Placebo**		
Odds ratio (SE)		1.296 (0.197)
95% confidence interval***		(0.963, 1.745)
p-value		0.0874

* Wilson confidence intervals.
** Logistic regression includes terms for baseline KCCQ - total symptom score (p<0.0001), age (p=0.8681), baseline eGFR (CKD-EPI) (p=0.8323), Treatment (p=0.0218), baseline diabetes status (3 cat.) (p=0.5975), sex (p=0.2507), baseline LVEF (3 cat.) (p=0.8200), region (5 cat.) (p<0.0001) and Treatment by region (5 cat.) interaction (p=0.4548).
***Wald confidence intervals.

Data taken from study 1245.121 only.
LOCF: For a missing value at week 52 the last available post-baseline value before week 52 is imputed.

Table R.1.2.7.4: 5 Responder analysis (displaying odds ratio) in KCCQ-TSS change from baseline at week 52 of >= 15 points (improvement) by region - RS (LOCF-AD) - 1245.121

Subgroup Description	Placebo	Empa 10mg
Region (5 cat.): Europe		
Number of patients in analysis set	677	676
Number of analysed patients, N (%)	631 (100.0)	638 (100.0)
Number of patients with endpoint, N (%)	133 (21.1)	137 (21.5)
95% confidence interval*	(18.1, 24.4)	(18.5, 24.8)
Comparison vs Placebo**		
Odds ratio (SE)		1.092 (0.174)
95% confidence interval***		(0.799, 1.491)
p-value		0.5814
Region (5 cat.): Asia		
Number of patients in analysis set	245	248
Number of analysed patients, N (%)	232 (100.0)	236 (100.0)
Number of patients with endpoint, N (%)	32 (13.8)	39 (16.5)
95% confidence interval*	(9.9, 18.8)	(12.3, 21.8)
Comparison vs Placebo**		
Odds ratio (SE)		1.102 (0.320)
95% confidence interval***		(0.624, 1.949)
p-value		0.7375

* Wilson confidence intervals.
** Logistic regression includes terms for baseline KCCQ - total symptom score (p<0.0001), age (p=0.8681), baseline eGFR (CKD-EPI) (p=0.8323), Treatment (p=0.0218), baseline diabetes status (3 cat.) (p=0.5975), sex (p=0.2507), baseline LVEF (3 cat.) (p=0.8200), region (5 cat.) (p<0.0001) and Treatment by region (5 cat.) interaction (p=0.4548).
***Wald confidence intervals.

Data taken from study 1245.121 only.
LOCF: For a missing value at week 52 the last available post-baseline value before week 52 is imputed.

Table R.1.2.7.4: 5 Responder analysis (displaying odds ratio) in KCCQ-TSS change from baseline at week 52 of >= 15 points (improvement) by region - RS (LOCF-AD) - 1245.121

Subgroup Description	Placebo	Empa 10mg
Region (5 cat.): Other		
Number of patients in analysis set	87	86
Number of analysed patients, N (%)	77 (100.0)	76 (100.0)
Number of patients with endpoint, N (%)	24 (31.2)	29 (38.2)
95% confidence interval*	(21.9, 42.2)	(28.1, 49.4)
Comparison vs Placebo**		
Odds ratio (SE)		1.271 (0.492)
95% confidence interval***		(0.595, 2.715)
p-value		0.5357

* Wilson confidence intervals.
** Logistic regression includes terms for baseline KCCQ - total symptom score (p<0.0001), age (p=0.8681), baseline eGFR (CKD-EPI) (p=0.8323), Treatment (p=0.0218), baseline diabetes status (3 cat.) (p=0.5975), sex (p=0.2507), baseline LVEF (3 cat.) (p=0.8200), region (5 cat.) (p<0.0001) and Treatment by region (5 cat.) interaction (p=0.4548).
***Wald confidence intervals.

Data taken from study 1245.121 only.
LOCF: For a missing value at week 52 the last available post-baseline value before week 52 is imputed.

Table R.1.2.7.4: 6 Responder analysis (displaying risk ratio) in KCCQ-TSS change from baseline at week 52 of >= 15 points (improvement) by region - RS (LOCF-AD) - 1245.121

Subgroup Description	Placebo	Empa 10mg
Region (5 cat.): North America		
Number of patients in analysis set	213	212
Number of analysed patients, N (%)	192 (100.0)	204 (100.0)
Number of patients with endpoint, N (%)	33 (17.2)	50 (24.5)
95% confidence interval*	(12.5, 23.2)	(19.1, 30.8)
Comparison vs Placebo**		
Risk ratio (SE)		1.449 (0.267)
95% confidence interval***		(1.010, 2.080)
p-value		0.0443
Region (5 cat.): Latin America		
Number of patients in analysis set	645	641
Number of analysed patients, N (%)	577 (100.0)	586 (100.0)
Number of patients with endpoint, N (%)	174 (30.2)	211 (36.0)
95% confidence interval*	(26.6, 34.0)	(32.2, 40.0)
Comparison vs Placebo**		
Risk ratio (SE)		1.067 (0.085)
95% confidence interval***		(0.912, 1.248)
p-value		0.4176

* Wilson confidence intervals.
** Log-linked Poisson model with robust estimate of variance includes terms for baseline KCCQ - total symptom score (p<0.0001), age (p=0.9989), baseline eGFR (CKD-EPI) (p=0.9553), Treatment (p=0.0244), baseline diabetes status (3 cat.) (p=0.4810), sex (p=0.5484), baseline LVEF (3 cat.) (p=0.8804), region (5 cat.) (p<0.0001) and Treatment by region (5 cat.) interaction (p=0.5029).
***Wald confidence intervals.

Data taken from study 1245.121 only.
LOCF: For a missing value at week 52 the last available post-baseline value before week 52 is imputed.

Table R.1.2.7.4: 6 Responder analysis (displaying risk ratio) in KCCQ-TSS change from baseline at week 52 of >= 15 points (improvement) by region - RS (LOCF-AD) - 1245.121

Subgroup Description	Placebo	Empa 10mg
Region (5 cat.): Europe		
Number of patients in analysis set	677	676
Number of analysed patients, N (%)	631 (100.0)	638 (100.0)
Number of patients with endpoint, N (%)	133 (21.1)	137 (21.5)
95% confidence interval*	(18.1, 24.4)	(18.5, 24.8)
Comparison vs Placebo**		
Risk ratio (SE)		1.040 (0.102)
95% confidence interval***		(0.857, 1.262)
p-value		0.6896
Region (5 cat.): Asia		
Number of patients in analysis set	245	248
Number of analysed patients, N (%)	232 (100.0)	236 (100.0)
Number of patients with endpoint, N (%)	32 (13.8)	39 (16.5)
95% confidence interval*	(9.9, 18.8)	(12.3, 21.8)
Comparison vs Placebo**		
Risk ratio (SE)		1.095 (0.221)
95% confidence interval***		(0.737, 1.626)
p-value		0.6538

* Wilson confidence intervals.
** Log-linked Poisson model with robust estimate of variance includes terms for baseline KCCQ - total symptom score (p<0.0001), age (p=0.9989), baseline eGFR (CKD-EPI) (p=0.9553), Treatment (p=0.0244), baseline diabetes status (3 cat.) (p=0.4810), sex (p=0.5484), baseline LVEF (3 cat.) (p=0.8804), region (5 cat.) (p<0.0001) and Treatment by region (5 cat.) interaction (p=0.5029).
***Wald confidence intervals.

Data taken from study 1245.121 only.
LOCF: For a missing value at week 52 the last available post-baseline value before week 52 is imputed.

Table R.1.2.7.4: 6 Responder analysis (displaying risk ratio) in KCCQ-TSS change from baseline at week 52 of >= 15 points (improvement) by region - RS (LOCF-AD) - 1245.121

Subgroup Description	Placebo	Empa 10mg
Region (5 cat.): Other		
Number of patients in analysis set	87	86
Number of analysed patients, N (%)	77 (100.0)	76 (100.0)
Number of patients with endpoint, N (%)	24 (31.2)	29 (38.2)
95% confidence interval*	(21.9, 42.2)	(28.1, 49.4)
Comparison vs Placebo**		
Risk ratio (SE)		1.295 (0.269)
95% confidence interval***		(0.862, 1.945)
p-value		0.2125

* Wilson confidence intervals.
** Log-linked Poisson model with robust estimate of variance includes terms for baseline KCCQ - total symptom score (p<0.0001), age (p=0.9989), baseline eGFR (CKD-EPI) (p=0.9553), Treatment (p=0.0244), baseline diabetes status (3 cat.) (p=0.4810), sex (p=0.5484), baseline LVEF (3 cat.) (p=0.8804), region (5 cat.) (p<0.0001) and Treatment by region (5 cat.) interaction (p=0.5029).
***Wald confidence intervals.

Data taken from study 1245.121 only.
LOCF: For a missing value at week 52 the last available post-baseline value before week 52 is imputed.

R.1.2.7.5

R.1.2.7.5 Subgroup analysis by OECD (N/Y)

Table R.1.2.7.5: 1 Responder analysis (displaying odds ratio) in KCCQ-TSS change from baseline at week 52 of <= -15 points (deterioration) by OECD member (N/Y) - RS (LOCF-AD) - 1245.121

Subgroup Description	Placebo	Empa 10mg
OECD member: No		
Number of patients in analysis set	741	713
Number of analysed patients, N (%)	663 (100.0)	647 (100.0)
Number of patients with endpoint, N (%)	80 (12.1)	51 (7.9)
95% confidence interval*	(9.8, 14.8)	(6.0, 10.2)
Comparison vs Placebo**		
Odds ratio (SE)		0.632 (0.121)
95% confidence interval***		(0.434, 0.919)
p-value		0.0164
OECD member: Yes		
Number of patients in analysis set	1126	1150
Number of analysed patients, N (%)	1046 (100.0)	1093 (100.0)
Number of patients with endpoint, N (%)	135 (12.9)	131 (12.0)
95% confidence interval*	(11.0, 15.1)	(10.2, 14.0)
Comparison vs Placebo**		
Odds ratio (SE)		0.917 (0.122)
95% confidence interval***		(0.707, 1.190)
p-value		0.5142

* Wilson confidence intervals.
** Logistic regression includes terms for baseline KCCQ - total symptom score (p<0.0001), age (p=0.2029), baseline eGFR (CKD-EPI) (p<0.0001), Treatment (p=0.0190), sex (p=0.1445), baseline diabetes status (3 cat.) (p=0.6029), baseline LVEF (3 cat.) (p=0.0447), OECD member (p=0.3130) and Treatment by OECD member interaction (p=0.1100).
***Wald confidence intervals.

Data taken from study 1245.121 only.
LOCF: For a missing value at week 52 the last available post-baseline value before week 52 is imputed.
OECD member (yes/no) countries included:
Yes: United States, Canada, Mexico, Poland, Netherlands, Hungary, Germany, Czech Republic, Italy, France, Spain, United Kingdom, Belgium, Japan, Australia, 'Korea; Republic Of South Korea';
No: Brazil, Argentina, China, India.

Table R.1.2.7.5: 2 Responder analysis (displaying risk ratio) in KCCQ-TSS change from baseline at week 52 of <= -15 points (deterioration) by OECD member (N/Y) - RS (LOCF-AD) - 1245.121

Subgroup Description	Placebo	Empa 10mg
OECD member: No		
Number of patients in analysis set	741	713
Number of analysed patients, N (%)	663 (100.0)	647 (100.0)
Number of patients with endpoint, N (%)	80 (12.1)	51 (7.9)
95% confidence interval*	(9.8, 14.8)	(6.0, 10.2)
Comparison vs Placebo**		
Risk ratio (SE)		0.667 (0.113)
95% confidence interval***		(0.479, 0.929)
p-value		0.0165
OECD member: Yes		
Number of patients in analysis set	1126	1150
Number of analysed patients, N (%)	1046 (100.0)	1093 (100.0)
Number of patients with endpoint, N (%)	135 (12.9)	131 (12.0)
95% confidence interval*	(11.0, 15.1)	(10.2, 14.0)
Comparison vs Placebo**		
Risk ratio (SE)		0.928 (0.105)
95% confidence interval***		(0.743, 1.159)
p-value		0.5112

* Wilson confidence intervals.
** Log-linked Poisson model with robust estimate of variance includes terms for baseline KCCQ - total symptom score (p<0.0001), age (p=0.2184), baseline eGFR (CKD-EPI) (p<0.0001), Treatment (p=0.0183), sex (p=0.1407), baseline diabetes status (3 cat.) (p=0.5979), baseline LVEF (3 cat.) (p=0.0448), OECD member (p=0.2940) and Treatment by OECD member interaction (p=0.1043).
***Wald confidence intervals.

Data taken from study 1245.121 only.
LOCF: For a missing value at week 52 the last available post-baseline value before week 52 is imputed.
OECD member (yes/no) countries included:
Yes: United States, Canada, Mexico, Poland, Netherlands, Hungary, Germany, Czech Republic, Italy, France, Spain, United Kingdom, Belgium, Japan, Australia, 'Korea; Republic Of South Korea';
No: Brazil, Argentina, China, India.

Table R.1.2.7.5: 3 Responder analysis (displaying odds ratio) in KCCQ-TSS change from baseline at week 52 of > -15 points (stability) by OECD member (N/Y) - RS (LOCF-AD) - 1245.121

Subgroup Description	Placebo	Empa 10mg
OECD member: No		
Number of patients in analysis set	741	713
Number of analysed patients, N (%)	663 (100.0)	647 (100.0)
Number of patients with endpoint, N (%)	583 (87.9)	596 (92.1)
95% confidence interval*	(85.2, 90.2)	(89.8, 94.0)
Comparison vs Placebo**		
Odds ratio (SE)		1.582 (0.303)
95% confidence interval***		(1.088, 2.302)
p-value		0.0164
OECD member: Yes		
Number of patients in analysis set	1126	1150
Number of analysed patients, N (%)	1046 (100.0)	1093 (100.0)
Number of patients with endpoint, N (%)	911 (87.1)	962 (88.0)
95% confidence interval*	(84.9, 89.0)	(86.0, 89.8)
Comparison vs Placebo**		
Odds ratio (SE)		1.090 (0.145)
95% confidence interval***		(0.841, 1.415)
p-value		0.5142

* Wilson confidence intervals.
** Logistic regression includes terms for baseline KCCQ - total symptom score (p<0.0001), age (p=0.2029), baseline eGFR (CKD-EPI) (p<0.0001), Treatment (p=0.0190), sex (p=0.1445), baseline diabetes status (3 cat.) (p=0.6029), baseline LVEF (3 cat.) (p=0.0447), OECD member (p=0.3130) and Treatment by OECD member interaction (p=0.1100).
***Wald confidence intervals.

Data taken from study 1245.121 only.
LOCF: For a missing value at week 52 the last available post-baseline value before week 52 is imputed.
OECD member (yes/no) countries included:
Yes: United States, Canada, Mexico, Poland, Netherlands, Hungary, Germany, Czech Republic, Italy, France, Spain, United Kingdom, Belgium, Japan, Australia, 'Korea; Republic Of South Korea';
No: Brazil, Argentina, China, India.

Table R.1.2.7.5: 4 Responder analysis (displaying risk ratio) in KCCQ-TSS change from baseline at week 52 of > -15 points (stability) by OECD member (N/Y) - RS (LOCF-AD) - 1245.121

Subgroup Description	Placebo	Empa 10mg
OECD member: No		
Number of patients in analysis set	741	713
Number of analysed patients, N (%)	663 (100.0)	647 (100.0)
Number of patients with endpoint, N (%)	583 (87.9)	596 (92.1)
95% confidence interval*	(85.2, 90.2)	(89.8, 94.0)
Comparison vs Placebo**		
Risk ratio (SE)		1.043 (0.019)
95% confidence interval***		(1.007, 1.081)
p-value		0.0199
OECD member: Yes		
Number of patients in analysis set	1126	1150
Number of analysed patients, N (%)	1046 (100.0)	1093 (100.0)
Number of patients with endpoint, N (%)	911 (87.1)	962 (88.0)
95% confidence interval*	(84.9, 89.0)	(86.0, 89.8)
Comparison vs Placebo**		
Risk ratio (SE)		1.011 (0.016)
95% confidence interval***		(0.979, 1.043)
p-value		0.4994

* Wilson confidence intervals.
** Log-linked Poisson model with robust estimate of variance includes terms for baseline KCCQ - total symptom score (p<0.0001), age (p=0.2796), baseline eGFR (CKD-EPI) (p<0.0001), Treatment (p=0.0283), sex (p=0.1493), baseline diabetes status (3 cat.) (p=0.6743), baseline LVEF (3 cat.) (p=0.0286), OECD member (p=0.4804) and Treatment by OECD member interaction (p=0.1944).
***Wald confidence intervals.

Data taken from study 1245.121 only.
LOCF: For a missing value at week 52 the last available post-baseline value before week 52 is imputed.
OECD member (yes/no) countries included:
Yes: United States, Canada, Mexico, Poland, Netherlands, Hungary, Germany, Czech Republic, Italy, France, Spain, United Kingdom, Belgium, Japan, Australia, 'Korea; Republic Of South Korea';
No: Brazil, Argentina, China, India.

Table R.1.2.7.5: 5 Responder analysis (displaying odds ratio) in KCCQ-TSS change from baseline at week 52 of >= 15 points (improvement) by OECD member (N/Y) - RS (LOCF-AD) - 1245.121

Subgroup Description	Placebo	Empa 10mg
OECD member: No		
Number of patients in analysis set	741	713
Number of analysed patients, N (%)	663 (100.0)	647 (100.0)
Number of patients with endpoint, N (%)	193 (29.1)	234 (36.2)
95% confidence interval*	(25.8, 32.7)	(32.6, 39.9)
Comparison vs Placebo**		
Odds ratio (SE)		1.400 (0.199)
95% confidence interval***		(1.059, 1.850)
p-value		0.0180
OECD member: Yes		
Number of patients in analysis set	1126	1150
Number of analysed patients, N (%)	1046 (100.0)	1093 (100.0)
Number of patients with endpoint, N (%)	203 (19.4)	232 (21.2)
95% confidence interval*	(17.1, 21.9)	(18.9, 23.7)
Comparison vs Placebo**		
Odds ratio (SE)		1.179 (0.147)
95% confidence interval***		(0.923, 1.507)
p-value		0.1869

* Wilson confidence intervals.
** Logistic regression includes terms for baseline KCCQ - total symptom score (p<0.0001), age (p=0.7586), baseline eGFR (CKD-EPI) (p=0.8576), Treatment (p=0.0081), sex (p=0.2359), baseline diabetes status (3 cat.) (p=0.8304), baseline LVEF (3 cat.) (p=0.8342), OECD member (p<0.0001) and Treatment by OECD member interaction (p=0.3649).
***Wald confidence intervals.

Data taken from study 1245.121 only.
LOCF: For a missing value at week 52 the last available post-baseline value before week 52 is imputed.
OECD member (yes/no) countries included:
Yes: United States, Canada, Mexico, Poland, Netherlands, Hungary, Germany, Czech Republic, Italy, France, Spain, United Kingdom, Belgium, Japan, Australia, 'Korea; Republic Of South Korea';
No: Brazil, Argentina, China, India.

Table R.1.2.7.5: 6 Responder analysis (displaying risk ratio) in KCCQ-TSS change from baseline at week 52 of >= 15 points (improvement) by OECD member (N/Y) - RS (LOCF-AD) - 1245.121

Subgroup Description	Placebo	Empa 10mg
OECD member: No		
Number of patients in analysis set	741	713
Number of analysed patients, N (%)	663 (100.0)	647 (100.0)
Number of patients with endpoint, N (%)	193 (29.1)	234 (36.2)
95% confidence interval*	(25.8, 32.7)	(32.6, 39.9)
Comparison vs Placebo**		
Risk ratio (SE)		1.122 (0.086)
95% confidence interval***		(0.966, 1.303)
p-value		0.1323
OECD member: Yes		
Number of patients in analysis set	1126	1150
Number of analysed patients, N (%)	1046 (100.0)	1093 (100.0)
Number of patients with endpoint, N (%)	203 (19.4)	232 (21.2)
95% confidence interval*	(17.1, 21.9)	(18.9, 23.7)
Comparison vs Placebo**		
Risk ratio (SE)		1.095 (0.086)
95% confidence interval***		(0.939, 1.276)
p-value		0.2461

* Wilson confidence intervals.
** Log-linked Poisson model with robust estimate of variance includes terms for baseline KCCQ - total symptom score (p<0.0001), age (p=0.8704), baseline eGFR (CKD-EPI) (p=0.9974), Treatment (p=0.0598), sex (p=0.4957), baseline diabetes status (3 cat.) (p=0.7112), baseline LVEF (3 cat.) (p=0.9641), OECD member (p<0.0001) and Treatment by OECD member interaction (p=0.8249).
***Wald confidence intervals.

Data taken from study 1245.121 only.
LOCF: For a missing value at week 52 the last available post-baseline value before week 52 is imputed.
OECD member (yes/no) countries included:
Yes: United States, Canada, Mexico, Poland, Netherlands, Hungary, Germany, Czech Republic, Italy, France, Spain, United Kingdom, Belgium, Japan, Australia, 'Korea; Republic Of South Korea';
No: Brazil, Argentina, China, India.

R.1.2.7.6 Subgroup analysis by NYHA at baseline (II, III/IV - 2 cat.)

Table R.1.2.7.6: 1 Responder analysis (displaying odds ratio) in KCCQ-TSS change from baseline at week 52 of <= -15 points (deterioration) by NYHA (2 cat.) - RS (LOCF-AD) - 1245.121

Subgroup Description	Placebo	Empa 10mg
Baseline NYHA (2 cat.): II		
Number of patients in analysis set	1401	1399
Number of analysed patients, N (%)	1306 (100.0)	1307 (100.0)
Number of patients with endpoint, N (%)	163 (12.5)	132 (10.1)
95% confidence interval*	(10.8, 14.4)	(8.6, 11.9)
Comparison vs Placebo**		
Odds ratio (SE)		0.770 (0.097)
95% confidence interval***		(0.601, 0.986)
p-value		0.0385
Baseline NYHA (2 cat.): III/IV		
Number of patients in analysis set	466	464
Number of analysed patients, N (%)	403 (100.0)	433 (100.0)
Number of patients with endpoint, N (%)	52 (12.9)	50 (11.5)
95% confidence interval*	(10.0, 16.5)	(8.9, 14.9)
Comparison vs Placebo**		
Odds ratio (SE)		0.934 (0.202)
95% confidence interval***		(0.611, 1.427)
p-value		0.7520

* Wilson confidence intervals.
** Logistic regression includes terms for baseline KCCQ - total symptom score (p<0.0001), age (p=0.3458), baseline eGFR (CKD-EPI) (p<0.0001), Treatment (p=0.1882), region (5 cat.) (p=0.0132), baseline diabetes status (3 cat.) (p=0.7859), sex (p=0.1413), baseline LVEF (3 cat.) (p=0.0627), baseline NYHA (2 cat.) (p=0.0049) and Treatment by baseline NYHA (2 cat.) interaction (p=0.4417).
***Wald confidence intervals.

Data taken from study 1245.121 only.
LOCF: For a missing value at week 52 the last available post-baseline value before week 52 is imputed.

Table R.1.2.7.6: 2 Responder analysis (displaying risk ratio) in KCCQ-TSS change from baseline at week 52 of <= -15 points (deterioration) by NYHA (2 cat.) - RS (LOCF-AD) - 1245.121

Subgroup Description	Placebo	Empa 10mg
Baseline NYHA (2 cat.): II		
Number of patients in analysis set	1401	1399
Number of analysed patients, N (%)	1306 (100.0)	1307 (100.0)
Number of patients with endpoint, N (%)	163 (12.5)	132 (10.1)
95% confidence interval*	(10.8, 14.4)	(8.6, 11.9)
Comparison vs Placebo**		
Risk ratio (SE)		0.798 (0.087)
95% confidence interval***		(0.644, 0.989)
p-value		0.0389
Baseline NYHA (2 cat.): III/IV		
Number of patients in analysis set	466	464
Number of analysed patients, N (%)	403 (100.0)	433 (100.0)
Number of patients with endpoint, N (%)	52 (12.9)	50 (11.5)
95% confidence interval*	(10.0, 16.5)	(8.9, 14.9)
Comparison vs Placebo**		
Risk ratio (SE)		0.943 (0.170)
95% confidence interval***		(0.663, 1.342)
p-value		0.7455

* Wilson confidence intervals.
** Log-linked Poisson model with robust estimate of variance includes terms for baseline KCCQ - total symptom score (p<0.0001), age (p=0.3635), baseline eGFR (CKD-EPI) (p<0.0001), Treatment (p=0.1764), region (5 cat.) (p=0.0184), baseline diabetes status (3 cat.) (p=0.7859), sex (p=0.1350), baseline LVEF (3 cat.) (p=0.0616), baseline NYHA (2 cat.) (p=0.0053) and Treatment by baseline NYHA (2 cat.) interaction (p=0.4279).
***Wald confidence intervals.

Data taken from study 1245.121 only.
LOCF: For a missing value at week 52 the last available post-baseline value before week 52 is imputed.

Table R.1.2.7.6: 3 Responder analysis (displaying odds ratio) in KCCQ-TSS change from baseline at week 52 of > -15 points (stability) by NYHA (2 cat.) - RS (LOCF-AD) - 1245.121

Subgroup Description	Placebo	Empa 10mg
Baseline NYHA (2 cat.): II		
Number of patients in analysis set	1401	1399
Number of analysed patients, N (%)	1306 (100.0)	1307 (100.0)
Number of patients with endpoint, N (%)	1143 (87.5)	1175 (89.9)
95% confidence interval*	(85.6, 89.2)	(88.1, 91.4)
Comparison vs Placebo**		
Odds ratio (SE)		1.298 (0.164)
95% confidence interval***		(1.014, 1.663)
p-value		0.0385
Baseline NYHA (2 cat.): III/IV		
Number of patients in analysis set	466	464
Number of analysed patients, N (%)	403 (100.0)	433 (100.0)
Number of patients with endpoint, N (%)	351 (87.1)	383 (88.5)
95% confidence interval*	(83.5, 90.0)	(85.1, 91.1)
Comparison vs Placebo**		
Odds ratio (SE)		1.071 (0.232)
95% confidence interval***		(0.701, 1.636)
p-value		0.7520

* Wilson confidence intervals.
** Logistic regression includes terms for baseline KCCQ - total symptom score (p<0.0001), age (p=0.3458), baseline eGFR (CKD-EPI) (p<0.0001), Treatment (p=0.1882), region (5 cat.) (p=0.0132), baseline diabetes status (3 cat.) (p=0.7859), sex (p=0.1413), baseline LVEF (3 cat.) (p=0.0627), baseline NYHA (2 cat.) (p=0.0049) and Treatment by baseline NYHA (2 cat.) interaction (p=0.4417).
***Wald confidence intervals.

Data taken from study 1245.121 only.
LOCF: For a missing value at week 52 the last available post-baseline value before week 52 is imputed.

Table R.1.2.7.6: 4 Responder analysis (displaying risk ratio) in KCCQ-TSS change from baseline at week 52 of > -15 points (stability) by NYHA (2 cat.) - RS (LOCF-AD) - 1245.121

Subgroup Description	Placebo	Empa 10mg
Baseline NYHA (2 cat.): II		
Number of patients in analysis set	1401	1399
Number of analysed patients, N (%)	1306 (100.0)	1307 (100.0)
Number of patients with endpoint, N (%)	1143 (87.5)	1175 (89.9)
95% confidence interval*	(85.6, 89.2)	(88.1, 91.4)
Comparison vs Placebo**		
Risk ratio (SE)		1.029 (0.014)
95% confidence interval***		(1.001, 1.057)
p-value		0.0410
Baseline NYHA (2 cat.): III/IV		
Number of patients in analysis set	466	464
Number of analysed patients, N (%)	403 (100.0)	433 (100.0)
Number of patients with endpoint, N (%)	351 (87.1)	383 (88.5)
95% confidence interval*	(83.5, 90.0)	(85.1, 91.1)
Comparison vs Placebo**		
Risk ratio (SE)		1.008 (0.025)
95% confidence interval***		(0.959, 1.059)
p-value		0.7654

* Wilson confidence intervals.
** Log-linked Poisson model with robust estimate of variance includes terms for baseline KCCQ - total symptom score (p<0.0001), age (p=0.4828), baseline eGFR (CKD-EPI) (p<0.0001), Treatment (p=0.2114), region (5 cat.) (p<0.0001), baseline diabetes status (3 cat.) (p=0.8192), sex (p=0.1578), baseline LVEF (3 cat.) (p=0.0405), baseline NYHA (2 cat.) (p=0.0106) and Treatment by baseline NYHA (2 cat.) interaction (p=0.4698).
***Wald confidence intervals.

Data taken from study 1245.121 only.
LOCF: For a missing value at week 52 the last available post-baseline value before week 52 is imputed.

Table R.1.2.7.6: 5 Responder analysis (displaying odds ratio) in KCCQ-TSS change from baseline at week 52 of >= 15 points (improvement) by NYHA (2 cat.) - RS (LOCF-AD) - 1245.121

Subgroup Description	Placebo	Empa 10mg
Baseline NYHA (2 cat.): II		
Number of patients in analysis set	1401	1399
Number of analysed patients, N (%)	1306 (100.0)	1307 (100.0)
Number of patients with endpoint, N (%)	268 (20.5)	296 (22.6)
95% confidence interval*	(18.4, 22.8)	(20.5, 25.0)
Comparison vs Placebo**		
Odds ratio (SE)		1.264 (0.141)
95% confidence interval***		(1.015, 1.573)
p-value		0.0362
Baseline NYHA (2 cat.): III/IV		
Number of patients in analysis set	466	464
Number of analysed patients, N (%)	403 (100.0)	433 (100.0)
Number of patients with endpoint, N (%)	128 (31.8)	170 (39.3)
95% confidence interval*	(27.4, 36.5)	(34.8, 43.9)
Comparison vs Placebo**		
Odds ratio (SE)		1.250 (0.220)
95% confidence interval***		(0.886, 1.765)
p-value		0.2041

* Wilson confidence intervals.
** Logistic regression includes terms for baseline KCCQ - total symptom score (p<0.0001), age (p=0.9153), baseline eGFR (CKD-EPI) (p=0.7779), Treatment (p=0.0281), region (5 cat.) (p<0.0001), baseline diabetes status (3 cat.) (p=0.6615), sex (p=0.2867), baseline LVEF (3 cat.) (p=0.8144), baseline NYHA (2 cat.) (p=0.0381) and Treatment by baseline NYHA (2 cat.) interaction (p=0.9594).
***Wald confidence intervals.

Data taken from study 1245.121 only.
LOCF: For a missing value at week 52 the last available post-baseline value before week 52 is imputed.

Table R.1.2.7.6: 6 Responder analysis (displaying risk ratio) in KCCQ-TSS change from baseline at week 52 of >= 15 points (improvement) by NYHA (2 cat.) - RS (LOCF-AD) - 1245.121

Subgroup Description	Placebo	Empa 10mg
Baseline NYHA (2 cat.): II		
Number of patients in analysis set	1401	1399
Number of analysed patients, N (%)	1306 (100.0)	1307 (100.0)
Number of patients with endpoint, N (%)	268 (20.5)	296 (22.6)
95% confidence interval*	(18.4, 22.8)	(20.5, 25.0)
Comparison vs Placebo**		
Risk ratio (SE)		1.134 (0.075)
95% confidence interval***		(0.997, 1.291)
p-value		0.0557
Baseline NYHA (2 cat.): III/IV		
Number of patients in analysis set	466	464
Number of analysed patients, N (%)	403 (100.0)	433 (100.0)
Number of patients with endpoint, N (%)	128 (31.8)	170 (39.3)
95% confidence interval*	(27.4, 36.5)	(34.8, 43.9)
Comparison vs Placebo**		
Risk ratio (SE)		1.067 (0.103)
95% confidence interval***		(0.883, 1.290)
p-value		0.5011

* Wilson confidence intervals.
** Log-linked Poisson model with robust estimate of variance includes terms for baseline KCCQ - total symptom score (p<0.0001), age (p=0.9109), baseline eGFR (CKD-EPI) (p=0.9582), Treatment (p=0.1023), region (5 cat.) (p<0.0001), baseline diabetes status (3 cat.) (p=0.5399), sex (p=0.5729), baseline LVEF (3 cat.) (p=0.8849), baseline NYHA (2 cat.) (p=0.0509) and Treatment by baseline NYHA (2 cat.) interaction (p=0.6032).
***Wald confidence intervals.

Data taken from study 1245.121 only.
LOCF: For a missing value at week 52 the last available post-baseline value before week 52 is imputed.

R.1.2.7.7 Subgroup analysis by diabetes at baseline

Table R.1.2.7.7: 1 Responder analysis (displaying odds ratio) in KCCQ-TSS change from baseline at week 52 of <= -15 points (deterioration) by diabetes at baseline - RS (LOCF-AD) - 1245.121

Subgroup Description	Placebo	Empa 10mg
Diabetes at baseline (2 cat.): Diabetic		
Number of patients in analysis set	929	927
Number of analysed patients, N (%)	850 (100.0)	861 (100.0)
Number of patients with endpoint, N (%)	106 (12.5)	84 (9.8)
95% confidence interval*	(10.4, 14.9)	(7.9, 11.9)
Comparison vs Placebo**		
Odds ratio (SE)		0.749 (0.118)
95% confidence interval***		(0.550, 1.019)
p-value		0.0660
Diabetes at baseline (2 cat.): Non-Diabetic		
Number of patients in analysis set	938	936
Number of analysed patients, N (%)	859 (100.0)	879 (100.0)
Number of patients with endpoint, N (%)	109 (12.7)	98 (11.1)
95% confidence interval*	(10.6, 15.1)	(9.2, 13.4)
Comparison vs Placebo**		
Odds ratio (SE)		0.870 (0.131)
95% confidence interval***		(0.647, 1.168)
p-value		0.3542

* Wilson confidence intervals.
** Logistic regression includes terms for baseline KCCQ - total symptom score (p<0.0001), age (p=0.3467), baseline eGFR (CKD-EPI) (p<0.0001), Treatment (p=0.0490), region (5 cat.) (p=0.0116), sex (p=0.1348), baseline LVEF (3 cat.) (p=0.0499), diabetes at baseline (2 cat.) (p=0.7064) and Treatment by diabetes at baseline (2 cat.) interaction (p=0.4918).
***Wald confidence intervals.

Data taken from study 1245.121 only.
LOCF: For a missing value at week 52 the last available post-baseline value before week 52 is imputed.

Table R.1.2.7.7: 2 Responder analysis (displaying risk ratio) in KCCQ-TSS change from baseline at week 52 of <= -15 points (deterioration) by diabetes at baseline - RS (LOCF-AD) - 1245.121

Subgroup Description	Placebo	Empa 10mg
Diabetes at baseline (2 cat.): Diabetic		
Number of patients in analysis set	929	927
Number of analysed patients, N (%)	850 (100.0)	861 (100.0)
Number of patients with endpoint, N (%)	106 (12.5)	84 (9.8)
95% confidence interval*	(10.4, 14.9)	(7.9, 11.9)
Comparison vs Placebo**		
Risk ratio (SE)		0.778 (0.106)
95% confidence interval***		(0.596, 1.016)
p-value		0.0653
Diabetes at baseline (2 cat.): Non-Diabetic		
Number of patients in analysis set	938	936
Number of analysed patients, N (%)	859 (100.0)	879 (100.0)
Number of patients with endpoint, N (%)	109 (12.7)	98 (11.1)
95% confidence interval*	(10.6, 15.1)	(9.2, 13.4)
Comparison vs Placebo**		
Risk ratio (SE)		0.887 (0.114)
95% confidence interval***		(0.690, 1.141)
p-value		0.3512

* Wilson confidence intervals.
** Log-linked Poisson model with robust estimate of variance includes terms for baseline KCCQ - total symptom score (p<0.0001), age (p=0.3628), baseline eGFR (CKD-EPI) (p<0.0001), Treatment (p=0.0474), region (5 cat.) (p=0.0150), sex (p=0.1302), baseline LVEF (3 cat.) (p=0.0491), diabetes at baseline (2 cat.) (p=0.6988) and Treatment by diabetes at baseline (2 cat.) interaction (p=0.4844).
***Wald confidence intervals.

Data taken from study 1245.121 only.
LOCF: For a missing value at week 52 the last available post-baseline value before week 52 is imputed.

Table R.1.2.7.7: 3 Responder analysis (displaying odds ratio) in KCCQ-TSS change from baseline at week 52 of > -15 points (stability) by diabetes at baseline - RS (LOCF-AD) - 1245.121

Subgroup Description	Placebo	Empa 10mg
Diabetes at baseline (2 cat.): Diabetic		
Number of patients in analysis set	929	927
Number of analysed patients, N (%)	850 (100.0)	861 (100.0)
Number of patients with endpoint, N (%)	744 (87.5)	777 (90.2)
95% confidence interval*	(85.1, 89.6)	(88.1, 92.1)
Comparison vs Placebo**		
Odds ratio (SE)		1.335 (0.210)
95% confidence interval***		(0.981, 1.818)
p-value		0.0660
Diabetes at baseline (2 cat.): Non-Diabetic		
Number of patients in analysis set	938	936
Number of analysed patients, N (%)	859 (100.0)	879 (100.0)
Number of patients with endpoint, N (%)	750 (87.3)	781 (88.9)
95% confidence interval*	(84.9, 89.4)	(86.6, 90.8)
Comparison vs Placebo**		
Odds ratio (SE)		1.150 (0.173)
95% confidence interval***		(0.856, 1.544)
p-value		0.3542

* Wilson confidence intervals.
** Logistic regression includes terms for baseline KCCQ - total symptom score (p<0.0001), age (p=0.3467), baseline eGFR (CKD-EPI) (p<0.0001), Treatment (p=0.0490), region (5 cat.) (p=0.0116), sex (p=0.1348), baseline LVEF (3 cat.) (p=0.0499), diabetes at baseline (2 cat.) (p=0.7064) and Treatment by diabetes at baseline (2 cat.) interaction (p=0.4918).
***Wald confidence intervals.

Data taken from study 1245.121 only.
LOCF: For a missing value at week 52 the last available post-baseline value before week 52 is imputed.

Table R.1.2.7.7: 4 Responder analysis (displaying risk ratio) in KCCQ-TSS change from baseline at week 52 of > -15 points (stability) by diabetes at baseline - RS (LOCF-AD) - 1245.121

Subgroup Description	Placebo	Empa 10mg
Diabetes at baseline (2 cat.): Diabetic		
Number of patients in analysis set	929	927
Number of analysed patients, N (%)	850 (100.0)	861 (100.0)
Number of patients with endpoint, N (%)	744 (87.5)	777 (90.2)
95% confidence interval*	(85.1, 89.6)	(88.1, 92.1)
Comparison vs Placebo**		
Risk ratio (SE)		1.030 (0.017)
95% confidence interval***		(0.997, 1.065)
p-value		0.0783
Diabetes at baseline (2 cat.): Non-Diabetic		
Number of patients in analysis set	938	936
Number of analysed patients, N (%)	859 (100.0)	879 (100.0)
Number of patients with endpoint, N (%)	750 (87.3)	781 (88.9)
95% confidence interval*	(84.9, 89.4)	(86.6, 90.8)
Comparison vs Placebo**		
Risk ratio (SE)		1.016 (0.018)
95% confidence interval***		(0.982, 1.051)
p-value		0.3590

* Wilson confidence intervals.
** Log-linked Poisson model with robust estimate of variance includes terms for baseline KCCQ - total symptom score (p<0.0001), age (p=0.4677), baseline eGFR (CKD-EPI) (p<0.0001), Treatment (p=0.0594), region (5 cat.) (p<0.0001), sex (p=0.1487), baseline LVEF (3 cat.) (p=0.0320), diabetes at baseline (2 cat.) (p=0.7827) and Treatment by diabetes at baseline (2 cat.) interaction (p=0.5677).
***Wald confidence intervals.

Data taken from study 1245.121 only.
LOCF: For a missing value at week 52 the last available post-baseline value before week 52 is imputed.

Table R.1.2.7.7: 5 Responder analysis (displaying odds ratio) in KCCQ-TSS change from baseline at week 52 of >= 15 points (improvement) by diabetes at baseline - RS (LOCF-AD) - 1245.121

Subgroup Description	Placebo	Empa 10mg
Diabetes at baseline (2 cat.): Diabetic		
Number of patients in analysis set	929	927
Number of analysed patients, N (%)	850 (100.0)	861 (100.0)
Number of patients with endpoint, N (%)	203 (23.9)	245 (28.5)
95% confidence interval*	(21.1, 26.9)	(25.5, 31.6)
Comparison vs Placebo**		
Odds ratio (SE)		1.375 (0.183)
95% confidence interval***		(1.059, 1.786)
p-value		0.0170
Diabetes at baseline (2 cat.): Non-Diabetic		
Number of patients in analysis set	938	936
Number of analysed patients, N (%)	859 (100.0)	879 (100.0)
Number of patients with endpoint, N (%)	193 (22.5)	221 (25.1)
95% confidence interval*	(19.8, 25.4)	(22.4, 28.1)
Comparison vs Placebo**		
Odds ratio (SE)		1.145 (0.152)
95% confidence interval***		(0.883, 1.486)
p-value		0.3078

* Wilson confidence intervals.
** Logistic regression includes terms for baseline KCCQ - total symptom score (p<0.0001), age (p=0.8926), baseline eGFR (CKD-EPI) (p=0.8541), Treatment (p=0.0160), region (5 cat.) (p<0.0001), sex (p=0.2650), baseline LVEF (3 cat.) (p=0.7910), diabetes at baseline (2 cat.) (p=0.3552) and Treatment by diabetes at baseline (2 cat.) interaction (p=0.3316).
***Wald confidence intervals.

Data taken from study 1245.121 only.
LOCF: For a missing value at week 52 the last available post-baseline value before week 52 is imputed.

Table R.1.2.7.7: 6 Responder analysis (displaying risk ratio) in KCCQ-TSS change from baseline at week 52 of >= 15 points (improvement) by diabetes at baseline - RS (LOCF-AD) - 1245.121

Subgroup Description	Placebo	Empa 10mg
Diabetes at baseline (2 cat.): Diabetic		
Number of patients in analysis set	929	927
Number of analysed patients, N (%)	850 (100.0)	861 (100.0)
Number of patients with endpoint, N (%)	203 (23.9)	245 (28.5)
95% confidence interval*	(21.1, 26.9)	(25.5, 31.6)
Comparison vs Placebo**		
Risk ratio (SE)		1.157 (0.089)
95% confidence interval***		(0.995, 1.346)
p-value		0.0578
Diabetes at baseline (2 cat.): Non-Diabetic		
Number of patients in analysis set	938	936
Number of analysed patients, N (%)	859 (100.0)	879 (100.0)
Number of patients with endpoint, N (%)	193 (22.5)	221 (25.1)
95% confidence interval*	(19.8, 25.4)	(22.4, 28.1)
Comparison vs Placebo**		
Risk ratio (SE)		1.051 (0.081)
95% confidence interval***		(0.904, 1.223)
p-value		0.5159

* Wilson confidence intervals.
** Log-linked Poisson model with robust estimate of variance includes terms for baseline KCCQ - total symptom score (p<0.0001), age (p=0.9727), baseline eGFR (CKD-EPI) (p=0.9277), Treatment (p=0.0719), region (5 cat.) (p<0.0001), sex (p=0.6008), baseline LVEF (3 cat.) (p=0.8642), diabetes at baseline (2 cat.) (p=0.2619) and Treatment by diabetes at baseline (2 cat.) interaction (p=0.3774).
***Wald confidence intervals.

Data taken from study 1245.121 only.
LOCF: For a missing value at week 52 the last available post-baseline value before week 52 is imputed.

R.1.2.7.8 Subgroup analysis by BMI at baseline (<30, >=30)

Table R.1.2.7.8: 1 Responder analysis (displaying odds ratio) in KCCQ-TSS change from baseline at week 52 of <= -15 points (deterioration) by baseline BMI [kg/m2] - RS (LOCF-AD) - 1245.121

Subgroup Description	Placebo	Empa 10mg
Baseline BMI [kg/m²] (2 cat.): <30		
Number of patients in analysis set	1300	1263
Number of analysed patients, N (%)	1197 (100.0)	1181 (100.0)
Number of patients with endpoint, N (%)	139 (11.6)	122 (10.3)
95% confidence interval*	(9.9, 13.6)	(8.7, 12.2)
Comparison vs Placebo**		
Odds ratio (SE)		0.866 (0.116)
95% confidence interval***		(0.667, 1.125)
p-value		0.2816
Baseline BMI [kg/m²] (2 cat.): >=30		
Number of patients in analysis set	567	600
Number of analysed patients, N (%)	512 (100.0)	559 (100.0)
Number of patients with endpoint, N (%)	76 (14.8)	60 (10.7)
95% confidence interval*	(12.0, 18.2)	(8.4, 13.6)
Comparison vs Placebo**		
Odds ratio (SE)		0.697 (0.131)
95% confidence interval***		(0.482, 1.008)
p-value		0.0549

* Wilson confidence intervals.
** Logistic regression includes terms for baseline KCCQ - total symptom score (p<0.0001), age (p=0.1845), baseline eGFR (CKD-EPI) (p<0.0001), Treatment (p=0.0286), region (5 cat.) (p=0.0293), baseline diabetes status (3 cat.) (p=0.7154), sex (p=0.1495), baseline LVEF (3 cat.) (p=0.0519), baseline BMI (2 cat.) (p=0.0320) and Treatment by baseline BMI (2 cat.) interaction (p=0.3462).
***Wald confidence intervals.

Data taken from study 1245.121 only.
LOCF: For a missing value at week 52 the last available post-baseline value before week 52 is imputed.

Table R.1.2.7.8: 2 Responder analysis (displaying risk ratio) in KCCQ-TSS change from baseline at week 52 of <= -15 points (deterioration) by baseline BMI [kg/m2] - RS (LOCF-AD) - 1245.121

Subgroup Description	Placebo	Empa 10mg
Baseline BMI [kg/m²] (2 cat.): <30		
Number of patients in analysis set	1300	1263
Number of analysed patients, N (%)	1197 (100.0)	1181 (100.0)
Number of patients with endpoint, N (%)	139 (11.6)	122 (10.3)
95% confidence interval*	(9.9, 13.6)	(8.7, 12.2)
Comparison vs Placebo**		
Risk ratio (SE)		0.882 (0.102)
95% confidence interval***		(0.704, 1.106)
p-value		0.2780
Baseline BMI [kg/m²] (2 cat.): >=30		
Number of patients in analysis set	567	600
Number of analysed patients, N (%)	512 (100.0)	559 (100.0)
Number of patients with endpoint, N (%)	76 (14.8)	60 (10.7)
95% confidence interval*	(12.0, 18.2)	(8.4, 13.6)
Comparison vs Placebo**		
Risk ratio (SE)		0.738 (0.116)
95% confidence interval***		(0.542, 1.005)
p-value		0.0535

* Wilson confidence intervals.
** Log-linked Poisson model with robust estimate of variance includes terms for baseline KCCQ - total symptom score (p<0.0001), age (p=0.2024), baseline eGFR (CKD-EPI) (p<0.0001), Treatment (p=0.0279), region (5 cat.) (p=0.0363), baseline diabetes status (3 cat.) (p=0.7135), sex (p=0.1452), baseline LVEF (3 cat.) (p=0.0509), baseline BMI (2 cat.) (p=0.0333) and Treatment by baseline BMI (2 cat.) interaction (p=0.3592).
***Wald confidence intervals.

Data taken from study 1245.121 only.
LOCF: For a missing value at week 52 the last available post-baseline value before week 52 is imputed.

Table R.1.2.7.8: 3 Responder analysis (displaying odds ratio) in KCCQ-TSS change from baseline at week 52 of > -15 points (stability) by baseline BMI [kg/m2] - RS (LOCF-AD) - 1245.121

Subgroup Description	Placebo	Empa 10mg
Baseline BMI [kg/m²] (2 cat.): <30		
Number of patients in analysis set	1300	1263
Number of analysed patients, N (%)	1197 (100.0)	1181 (100.0)
Number of patients with endpoint, N (%)	1058 (88.4)	1059 (89.7)
95% confidence interval*	(86.4, 90.1)	(87.8, 91.3)
Comparison vs Placebo**		
Odds ratio (SE)		1.155 (0.154)
95% confidence interval***		(0.889, 1.500)
p-value		0.2816
Baseline BMI [kg/m²] (2 cat.): >=30		
Number of patients in analysis set	567	600
Number of analysed patients, N (%)	512 (100.0)	559 (100.0)
Number of patients with endpoint, N (%)	436 (85.2)	499 (89.3)
95% confidence interval*	(81.8, 88.0)	(86.4, 91.6)
Comparison vs Placebo**		
Odds ratio (SE)		1.435 (0.270)
95% confidence interval***		(0.993, 2.074)
p-value		0.0549

* Wilson confidence intervals.
** Logistic regression includes terms for baseline KCCQ - total symptom score (p<0.0001), age (p=0.1845), baseline eGFR (CKD-EPI) (p<0.0001), Treatment (p=0.0286), region (5 cat.) (p=0.0293), baseline diabetes status (3 cat.) (p=0.7154), sex (p=0.1495), baseline LVEF (3 cat.) (p=0.0519), baseline BMI (2 cat.) (p=0.0320) and Treatment by baseline BMI (2 cat.) interaction (p=0.3462).
***Wald confidence intervals.

Data taken from study 1245.121 only.
LOCF: For a missing value at week 52 the last available post-baseline value before week 52 is imputed.

Table R.1.2.7.8: 4 Responder analysis (displaying risk ratio) in KCCQ-TSS change from baseline at week 52 of > -15 points (stability) by baseline BMI [kg/m2] - RS (LOCF-AD) - 1245.121

Subgroup Description	Placebo	Empa 10mg
Baseline BMI [kg/m²] (2 cat.): <30		
Number of patients in analysis set	1300	1263
Number of analysed patients, N (%)	1197 (100.0)	1181 (100.0)
Number of patients with endpoint, N (%)	1058 (88.4)	1059 (89.7)
95% confidence interval*	(86.4, 90.1)	(87.8, 91.3)
Comparison vs Placebo**		
Risk ratio (SE)		1.014 (0.014)
95% confidence interval***		(0.986, 1.043)
p-value		0.3341
Baseline BMI [kg/m²] (2 cat.): >=30		
Number of patients in analysis set	567	600
Number of analysed patients, N (%)	512 (100.0)	559 (100.0)
Number of patients with endpoint, N (%)	436 (85.2)	499 (89.3)
95% confidence interval*	(81.8, 88.0)	(86.4, 91.6)
Comparison vs Placebo**		
Risk ratio (SE)		1.047 (0.024)
95% confidence interval***		(1.001, 1.096)
p-value		0.0464

* Wilson confidence intervals.
** Log-linked Poisson model with robust estimate of variance includes terms for baseline KCCQ - total symptom score (p<0.0001), age (p=0.2794), baseline eGFR (CKD-EPI) (p<0.0001), Treatment (p=0.0277), region (5 cat.) (p<0.0001), baseline diabetes status (3 cat.) (p=0.7633), sex (p=0.1619), baseline LVEF (3 cat.) (p=0.0339), baseline BMI (2 cat.) (p=0.0370) and Treatment by baseline BMI (2 cat.) interaction (p=0.2352).
***Wald confidence intervals.

Data taken from study 1245.121 only.
LOCF: For a missing value at week 52 the last available post-baseline value before week 52 is imputed.

Table R.1.2.7.8: 5 Responder analysis (displaying odds ratio) in KCCQ-TSS change from baseline at week 52 of >= 15 points (improvement) by baseline BMI [kg/m2] - RS (LOCF-AD) - 1245.121

Subgroup Description	Placebo	Empa 10mg
Baseline BMI [kg/m²] (2 cat.): <30		
Number of patients in analysis set	1300	1263
Number of analysed patients, N (%)	1197 (100.0)	1181 (100.0)
Number of patients with endpoint, N (%)	265 (22.1)	289 (24.5)
95% confidence interval*	(19.9, 24.6)	(22.1, 27.0)
Comparison vs Placebo**		
Odds ratio (SE)		1.195 (0.137)
95% confidence interval***		(0.954, 1.497)
p-value		0.1216
Baseline BMI [kg/m²] (2 cat.): >=30		
Number of patients in analysis set	567	600
Number of analysed patients, N (%)	512 (100.0)	559 (100.0)
Number of patients with endpoint, N (%)	131 (25.6)	177 (31.7)
95% confidence interval*	(22.0, 29.5)	(27.9, 35.6)
Comparison vs Placebo**		
Odds ratio (SE)		1.384 (0.228)
95% confidence interval***		(1.002, 1.912)
p-value		0.0483

* Wilson confidence intervals.
** Logistic regression includes terms for baseline KCCQ - total symptom score (p<0.0001), age (p=0.8870), baseline eGFR (CKD-EPI) (p=0.8457), Treatment (p=0.0123), region (5 cat.) (p<0.0001), baseline diabetes status (3 cat.) (p=0.6079), sex (p=0.2604), baseline LVEF (3 cat.) (p=0.7974), baseline BMI (2 cat.) (p=0.9986) and Treatment by baseline BMI (2 cat.) interaction (p=0.4628).
***Wald confidence intervals.

Data taken from study 1245.121 only.
LOCF: For a missing value at week 52 the last available post-baseline value before week 52 is imputed.

Table R.1.2.7.8: 6 Responder analysis (displaying risk ratio) in KCCQ-TSS change from baseline at week 52 of >= 15 points (improvement) by baseline BMI [kg/m2] - RS (LOCF-AD) - 1245.121

Subgroup Description	Placebo	Empa 10mg
Baseline BMI [kg/m²] (2 cat.): <30		
Number of patients in analysis set	1300	1263
Number of analysed patients, N (%)	1197 (100.0)	1181 (100.0)
Number of patients with endpoint, N (%)	265 (22.1)	289 (24.5)
95% confidence interval*	(19.9, 24.6)	(22.1, 27.0)
Comparison vs Placebo**		
Risk ratio (SE)		1.066 (0.071)
95% confidence interval***		(0.935, 1.215)
p-value		0.3429
Baseline BMI [kg/m²] (2 cat.): >=30		
Number of patients in analysis set	567	600
Number of analysed patients, N (%)	512 (100.0)	559 (100.0)
Number of patients with endpoint, N (%)	131 (25.6)	177 (31.7)
95% confidence interval*	(22.0, 29.5)	(27.9, 35.6)
Comparison vs Placebo**		
Risk ratio (SE)		1.181 (0.112)
95% confidence interval***		(0.981, 1.421)
p-value		0.0791

* Wilson confidence intervals.
** Log-linked Poisson model with robust estimate of variance includes terms for baseline KCCQ - total symptom score (p<0.0001), age (p=0.9751), baseline eGFR (CKD-EPI) (p=0.9116), Treatment (p=0.0476), region (5 cat.) (p<0.0001), baseline diabetes status (3 cat.) (p=0.4847), sex (p=0.5431), baseline LVEF (3 cat.) (p=0.8694), baseline BMI (2 cat.) (p=0.9510) and Treatment by baseline BMI (2 cat.) interaction (p=0.3763).
***Wald confidence intervals.

Data taken from study 1245.121 only.
LOCF: For a missing value at week 52 the last available post-baseline value before week 52 is imputed.

R.1.2.7.9 Subgroup analysis by eGFR at baseline (<60, >=60)

Table R.1.2.7.9: 1 Responder analysis (displaying odds ratio) in KCCQ-TSS change from baseline at week 52 of <= -15 points (deterioration) by baseline eGFR (2 cat.) - RS (LOCF-AD) - 1245.121

Subgroup Description	Placebo	Empa 10mg
Baseline eGFR (CKD-EPI) [mL/min/1.73m²] (2 cat.): >=60		
Number of patients in analysis set	960	969
Number of analysed patients, N (%)	875 (100.0)	903 (100.0)
Number of patients with endpoint, N (%)	95 (10.9)	74 (8.2)
95% confidence interval*	(9.0, 13.1)	(6.6, 10.2)
Comparison vs Placebo**		
Odds ratio (SE)		0.715 (0.118)
95% confidence interval***		(0.517, 0.987)
p-value		0.0416
Baseline eGFR (CKD-EPI) [mL/min/1.73m²] (2 cat.): <60		
Number of patients in analysis set	906	893
Number of analysed patients, N (%)	834 (100.0)	837 (100.0)
Number of patients with endpoint, N (%)	120 (14.4)	108 (12.9)
95% confidence interval*	(12.2, 16.9)	(10.8, 15.3)
Comparison vs Placebo**		
Odds ratio (SE)		0.893 (0.129)
95% confidence interval***		(0.673, 1.185)
p-value		0.4341

* Wilson confidence intervals.
** Logistic regression includes terms for baseline KCCQ - total symptom score (p<0.0001), age (p=0.0234), Treatment (p=0.0405), region (5 cat.) (p=0.0092), baseline diabetes status (3 cat.) (p=0.9108), sex (p=0.1117), baseline LVEF (3 cat.) (p=0.0632), baseline eGFR (CKD-EPI) (2 cat.) (p=0.0092) and Treatment by baseline eGFR (CKD-EPI) (2 cat.) interaction (p=0.3094).
***Wald confidence intervals.
2 patients were excluded as the subgroup variable was missing.

Data taken from study 1245.121 only.
LOCF: For a missing value at week 52 the last available post-baseline value before week 52 is imputed.

Table R.1.2.7.9: 2 Responder analysis (displaying risk ratio) in KCCQ-TSS change from baseline at week 52 of <= -15 points (deterioration) by baseline eGFR (2 cat.) - RS (LOCF-AD) - 1245.121

Subgroup Description	Placebo	Empa 10mg
Baseline eGFR (CKD-EPI) [mL/min/1.73m²] (2 cat.): >=60		
Number of patients in analysis set	960	969
Number of analysed patients, N (%)	875 (100.0)	903 (100.0)
Number of patients with endpoint, N (%)	95 (10.9)	74 (8.2)
95% confidence interval*	(9.0, 13.1)	(6.6, 10.2)
Comparison vs Placebo**		
Risk ratio (SE)		0.742 (0.109)
95% confidence interval***		(0.556, 0.990)
p-value		0.0424
Baseline eGFR (CKD-EPI) [mL/min/1.73m²] (2 cat.): <60		
Number of patients in analysis set	906	893
Number of analysed patients, N (%)	834 (100.0)	837 (100.0)
Number of patients with endpoint, N (%)	120 (14.4)	108 (12.9)
95% confidence interval*	(12.2, 16.9)	(10.8, 15.3)
Comparison vs Placebo**		
Risk ratio (SE)		0.909 (0.111)
95% confidence interval***		(0.716, 1.153)
p-value		0.4313

* Wilson confidence intervals.
** Log-linked Poisson model with robust estimate of variance includes terms for baseline KCCQ - total symptom score (p<0.0001), age (p=0.0303), Treatment (p=0.0384), region (5 cat.) (p=0.0127), baseline diabetes status (3 cat.) (p=0.9136), sex (p=0.1075), baseline LVEF (3 cat.) (p=0.0624), baseline eGFR (CKD-EPI) (2 cat.) (p=0.0100) and Treatment by baseline eGFR (CKD-EPI) (2 cat.) interaction (p=0.2896).
***Wald confidence intervals.
2 patients were excluded as the subgroup variable was missing.

Data taken from study 1245.121 only.
LOCF: For a missing value at week 52 the last available post-baseline value before week 52 is imputed.

Table R.1.2.7.9: 3 Responder analysis (displaying odds ratio) in KCCQ-TSS change from baseline at week 52 of > -15 points (stability) by baseline eGFR (2 cat.) - RS (LOCF-AD) - 1245.121

Subgroup Description	Placebo	Empa 10mg
Baseline eGFR (CKD-EPI) [mL/min/1.73m²] (2 cat.): >=60		
Number of patients in analysis set	960	969
Number of analysed patients, N (%)	875 (100.0)	903 (100.0)
Number of patients with endpoint, N (%)	780 (89.1)	829 (91.8)
95% confidence interval*	(86.9, 91.0)	(89.8, 93.4)
Comparison vs Placebo**		
Odds ratio (SE)		1.399 (0.231)
95% confidence interval***		(1.013, 1.933)
p-value		0.0416
Baseline eGFR (CKD-EPI) [mL/min/1.73m²] (2 cat.): <60		
Number of patients in analysis set	906	893
Number of analysed patients, N (%)	834 (100.0)	837 (100.0)
Number of patients with endpoint, N (%)	714 (85.6)	729 (87.1)
95% confidence interval*	(83.1, 87.8)	(84.7, 89.2)
Comparison vs Placebo**		
Odds ratio (SE)		1.120 (0.162)
95% confidence interval***		(0.844, 1.486)
p-value		0.4341

* Wilson confidence intervals.
** Logistic regression includes terms for baseline KCCQ - total symptom score (p<0.0001), age (p=0.0234), Treatment (p=0.0405), region (5 cat.) (p=0.0092), baseline diabetes status (3 cat.) (p=0.9108), sex (p=0.1117), baseline LVEF (3 cat.) (p=0.0632), baseline eGFR (CKD-EPI) (2 cat.) (p=0.0092) and Treatment by baseline eGFR (CKD-EPI) (2 cat.) interaction (p=0.3094).
***Wald confidence intervals.
2 patients were excluded as the subgroup variable was missing.

Data taken from study 1245.121 only.
LOCF: For a missing value at week 52 the last available post-baseline value before week 52 is imputed.

Table R.1.2.7.9: 4 Responder analysis (displaying risk ratio) in KCCQ-TSS change from baseline at week 52 of > -15 points (stability) by baseline eGFR (2 cat.) - RS (LOCF-AD) - 1245.121

Subgroup Description	Placebo	Empa 10mg
Baseline eGFR (CKD-EPI) [mL/min/1.73m²] (2 cat.): >=60		
Number of patients in analysis set	960	969
Number of analysed patients, N (%)	875 (100.0)	903 (100.0)
Number of patients with endpoint, N (%)	780 (89.1)	829 (91.8)
95% confidence interval*	(86.9, 91.0)	(89.8, 93.4)
Comparison vs Placebo**		
Risk ratio (SE)		1.030 (0.016)
95% confidence interval***		(1.000, 1.062)
p-value		0.0527
Baseline eGFR (CKD-EPI) [mL/min/1.73m²] (2 cat.): <60		
Number of patients in analysis set	906	893
Number of analysed patients, N (%)	834 (100.0)	837 (100.0)
Number of patients with endpoint, N (%)	714 (85.6)	729 (87.1)
95% confidence interval*	(83.1, 87.8)	(84.7, 89.2)
Comparison vs Placebo**		
Risk ratio (SE)		1.015 (0.020)
95% confidence interval***		(0.978, 1.054)
p-value		0.4274

* Wilson confidence intervals.
** Log-linked Poisson model with robust estimate of variance includes terms for baseline KCCQ - total symptom score (p<0.0001), age (p=0.0325), Treatment (p=0.0668), region (5 cat.) (p<0.0001), baseline diabetes status (3 cat.) (p=0.9172), sex (p=0.1445), baseline LVEF (3 cat.) (p=0.0408), baseline eGFR (CKD-EPI) (2 cat.) (p=0.0112) and Treatment by baseline eGFR (CKD-EPI) (2 cat.) interaction (p=0.5554).
***Wald confidence intervals.
2 patients were excluded as the subgroup variable was missing.

Data taken from study 1245.121 only.
LOCF: For a missing value at week 52 the last available post-baseline value before week 52 is imputed.

Table R.1.2.7.9: 5 Responder analysis (displaying odds ratio) in KCCQ-TSS change from baseline at week 52 of >= 15 points (improvement) by baseline eGFR (2 cat.) - RS (LOCF-AD) - 1245.121

Subgroup Description	Placebo	Empa 10mg
Baseline eGFR (CKD-EPI) [mL/min/1.73m²] (2 cat.): >=60		
Number of patients in analysis set	960	969
Number of analysed patients, N (%)	875 (100.0)	903 (100.0)
Number of patients with endpoint, N (%)	205 (23.4)	236 (26.1)
95% confidence interval*	(20.7, 26.3)	(23.4, 29.1)
Comparison vs Placebo**		
Odds ratio (SE)		1.170 (0.154)
95% confidence interval***		(0.905, 1.514)
p-value		0.2315
Baseline eGFR (CKD-EPI) [mL/min/1.73m²] (2 cat.): <60		
Number of patients in analysis set	906	893
Number of analysed patients, N (%)	834 (100.0)	837 (100.0)
Number of patients with endpoint, N (%)	191 (22.9)	230 (27.5)
95% confidence interval*	(20.2, 25.9)	(24.6, 30.6)
Comparison vs Placebo**		
Odds ratio (SE)		1.350 (0.182)
95% confidence interval***		(1.036, 1.759)
p-value		0.0265

* Wilson confidence intervals.
** Logistic regression includes terms for baseline KCCQ - total symptom score (p<0.0001), age (p=0.7261), Treatment (p=0.0153), region (5 cat.) (p<0.0001), baseline diabetes status (3 cat.) (p=0.5965), sex (p=0.2696), baseline LVEF (3 cat.) (p=0.7955), baseline eGFR (CKD-EPI) (2 cat.) (p=0.3868) and Treatment by baseline eGFR (CKD-EPI) (2 cat.) interaction (p=0.4497).
***Wald confidence intervals.
2 patients were excluded as the subgroup variable was missing.

Data taken from study 1245.121 only.
LOCF: For a missing value at week 52 the last available post-baseline value before week 52 is imputed.

Table R.1.2.7.9: 6 Responder analysis (displaying risk ratio) in KCCQ-TSS change from baseline at week 52 of >= 15 points (improvement) by baseline eGFR (2 cat.) - RS (LOCF-AD) - 1245.121

Subgroup Description	Placebo	Empa 10mg
Baseline eGFR (CKD-EPI) [mL/min/1.73m²] (2 cat.): >=60		
Number of patients in analysis set	960	969
Number of analysed patients, N (%)	875 (100.0)	903 (100.0)
Number of patients with endpoint, N (%)	205 (23.4)	236 (26.1)
95% confidence interval*	(20.7, 26.3)	(23.4, 29.1)
Comparison vs Placebo**		
Risk ratio (SE)		1.048 (0.081)
95% confidence interval***		(0.901, 1.218)
p-value		0.5442
Baseline eGFR (CKD-EPI) [mL/min/1.73m²] (2 cat.): <60		
Number of patients in analysis set	906	893
Number of analysed patients, N (%)	834 (100.0)	837 (100.0)
Number of patients with endpoint, N (%)	191 (22.9)	230 (27.5)
95% confidence interval*	(20.2, 25.9)	(24.6, 30.6)
Comparison vs Placebo**		
Risk ratio (SE)		1.171 (0.090)
95% confidence interval***		(1.007, 1.363)
p-value		0.0403

* Wilson confidence intervals.
** Log-linked Poisson model with robust estimate of variance includes terms for baseline KCCQ - total symptom score (p<0.0001), age (p=0.8370), Treatment (p=0.0605), region (5 cat.) (p<0.0001), baseline diabetes status (3 cat.) (p=0.4974), sex (p=0.5929), baseline LVEF (3 cat.) (p=0.8648), baseline eGFR (CKD-EPI) (2 cat.) (p=0.6576) and Treatment by baseline eGFR (CKD-EPI) (2 cat.) interaction (p=0.3054).
***Wald confidence intervals.
2 patients were excluded as the subgroup variable was missing.

Data taken from study 1245.121 only.
LOCF: For a missing value at week 52 the last available post-baseline value before week 52 is imputed.

R.1.2.7.10

Table R.1.2.7.10: 1 Responder analysis (displaying odds ratio) in KCCQ-TSS change from baseline at week 52 of <= -15 points (deterioration) by history of HHF - RS (LOCF-AD) - 1245.121

Subgroup Description	Placebo	Empa 10mg
History of HHF (in the last 12 months): No		
Number of patients in analysis set	1293	1286
Number of analysed patients, N (%)	1194 (100.0)	1212 (100.0)
Number of patients with endpoint, N (%)	147 (12.3)	130 (10.7)
95% confidence interval*	(10.6, 14.3)	(9.1, 12.6)
Comparison vs Placebo**		
Odds ratio (SE)		0.875 (0.114)
95% confidence interval***		(0.678, 1.129)
p-value		0.3040
History of HHF (in the last 12 months): Yes		
Number of patients in analysis set	574	577
Number of analysed patients, N (%)	515 (100.0)	528 (100.0)
Number of patients with endpoint, N (%)	68 (13.2)	52 (9.8)
95% confidence interval*	(10.6, 16.4)	(7.6, 12.7)
Comparison vs Placebo**		
Odds ratio (SE)		0.675 (0.134)
95% confidence interval***		(0.457, 0.997)
p-value		0.0483

* Wilson confidence intervals.
** Logistic regression includes terms for baseline KCCQ - total symptom score (p<0.0001), age (p=0.2936), baseline eGFR (CKD-EPI) (p<0.0001), Treatment (p=0.0267), region (5 cat.) (p=0.0118), baseline diabetes status (3 cat.) (p=0.8193), sex (p=0.1334), baseline LVEF (3 cat.) (p=0.0472), history of HHF (in the last 12 months) (p=0.7560) and Treatment by history of HHF (in the last 12 months) interaction (p=0.2752).
***Wald confidence intervals.

Data taken from study 1245.121 only.
LOCF: For a missing value at week 52 the last available post-baseline value before week 52 is imputed.

Table R.1.2.7.10: 2 Responder analysis (displaying risk ratio) in KCCQ-TSS change from baseline at week 52 of <= -15 points (deterioration) by history of HHF - RS (LOCF-AD) - 1245.121

Subgroup Description	Placebo	Empa 10mg
History of HHF (in the last 12 months): No		
Number of patients in analysis set	1293	1286
Number of analysed patients, N (%)	1194 (100.0)	1212 (100.0)
Number of patients with endpoint, N (%)	147 (12.3)	130 (10.7)
95% confidence interval*	(10.6, 14.3)	(9.1, 12.6)
Comparison vs Placebo**		
Risk ratio (SE)		0.892 (0.100)
95% confidence interval***		(0.716, 1.110)
p-value		0.3042
History of HHF (in the last 12 months): Yes		
Number of patients in analysis set	574	577
Number of analysed patients, N (%)	515 (100.0)	528 (100.0)
Number of patients with endpoint, N (%)	68 (13.2)	52 (9.8)
95% confidence interval*	(10.6, 16.4)	(7.6, 12.7)
Comparison vs Placebo**		
Risk ratio (SE)		0.712 (0.121)
95% confidence interval***		(0.509, 0.994)
p-value		0.0461

* Wilson confidence intervals.
** Log-linked Poisson model with robust estimate of variance includes terms for baseline KCCQ - total symptom score (p<0.0001), age (p=0.3106), baseline eGFR (CKD-EPI) (p<0.0001), Treatment (p=0.0254), region (5 cat.) (p=0.0163), baseline diabetes status (3 cat.) (p=0.8201), sex (p=0.1282), baseline LVEF (3 cat.) (p=0.0458), history of HHF (in the last 12 months) (p=0.7694) and Treatment by history of HHF (in the last 12 months) interaction (p=0.2698).
***Wald confidence intervals.

Data taken from study 1245.121 only.
LOCF: For a missing value at week 52 the last available post-baseline value before week 52 is imputed.

Table R.1.2.7.10: 3 Responder analysis (displaying odds ratio) in KCCQ-TSS change from baseline at week 52 of > -15 points (stability) by history of HHF - RS (LOCF-AD) - 1245.121

Subgroup Description	Placebo	Empa 10mg
History of HHF (in the last 12 months): No		
Number of patients in analysis set	1293	1286
Number of analysed patients, N (%)	1194 (100.0)	1212 (100.0)
Number of patients with endpoint, N (%)	1047 (87.7)	1082 (89.3)
95% confidence interval*	(85.7, 89.4)	(87.4, 90.9)
Comparison vs Placebo**		
Odds ratio (SE)		1.143 (0.149)
95% confidence interval***		(0.886, 1.475)
p-value		0.3040
History of HHF (in the last 12 months): Yes		
Number of patients in analysis set	574	577
Number of analysed patients, N (%)	515 (100.0)	528 (100.0)
Number of patients with endpoint, N (%)	447 (86.8)	476 (90.2)
95% confidence interval*	(83.6, 89.4)	(87.3, 92.4)
Comparison vs Placebo**		
Odds ratio (SE)		1.481 (0.295)
95% confidence interval***		(1.003, 2.188)
p-value		0.0483

* Wilson confidence intervals.
** Logistic regression includes terms for baseline KCCQ - total symptom score (p<0.0001), age (p=0.2936), baseline eGFR (CKD-EPI) (p<0.0001), Treatment (p=0.0267), region (5 cat.) (p=0.0118), baseline diabetes status (3 cat.) (p=0.8193), sex (p=0.1334), baseline LVEF (3 cat.) (p=0.0472), history of HHF (in the last 12 months) (p=0.7560) and Treatment by history of HHF (in the last 12 months) interaction (p=0.2752).
***Wald confidence intervals.

Data taken from study 1245.121 only.
LOCF: For a missing value at week 52 the last available post-baseline value before week 52 is imputed.

Table R.1.2.7.10: 4 Responder analysis (displaying risk ratio) in KCCQ-TSS change from baseline at week 52 of > -15 points (stability) by history of HHF - RS (LOCF-AD) - 1245.121

Subgroup Description	Placebo	Empa 10mg
History of HHF (in the last 12 months): No		
Number of patients in analysis set	1293	1286
Number of analysed patients, N (%)	1194 (100.0)	1212 (100.0)
Number of patients with endpoint, N (%)	1047 (87.7)	1082 (89.3)
95% confidence interval*	(85.7, 89.4)	(87.4, 90.9)
Comparison vs Placebo**		
Risk ratio (SE)		1.015 (0.015)
95% confidence interval***		(0.986, 1.044)
p-value		0.3190
History of HHF (in the last 12 months): Yes		
Number of patients in analysis set	574	577
Number of analysed patients, N (%)	515 (100.0)	528 (100.0)
Number of patients with endpoint, N (%)	447 (86.8)	476 (90.2)
95% confidence interval*	(83.6, 89.4)	(87.3, 92.4)
Comparison vs Placebo**		
Risk ratio (SE)		1.043 (0.023)
95% confidence interval***		(0.999, 1.089)
p-value		0.0572

* Wilson confidence intervals.
** Log-linked Poisson model with robust estimate of variance includes terms for baseline KCCQ - total symptom score (p<0.0001), age (p=0.4191), baseline eGFR (CKD-EPI) (p<0.0001), Treatment (p=0.0323), region (5 cat.) (p<0.0001), baseline diabetes status (3 cat.) (p=0.8492), sex (p=0.1492), baseline LVEF (3 cat.) (p=0.0315), history of HHF (in the last 12 months) (p=0.7732) and Treatment by history of HHF (in the last 12 months) interaction (p=0.2979).
***Wald confidence intervals.

Data taken from study 1245.121 only.
LOCF: For a missing value at week 52 the last available post-baseline value before week 52 is imputed.

Table R.1.2.7.10: 5 Responder analysis (displaying odds ratio) in KCCQ-TSS change from baseline at week 52 of >= 15 points (improvement) by history of HHF - RS (LOCF-AD) - 1245.121

Subgroup Description	Placebo	Empa 10mg
History of HHF (in the last 12 months): No		
Number of patients in analysis set	1293	1286
Number of analysed patients, N (%)	1194 (100.0)	1212 (100.0)
Number of patients with endpoint, N (%)	283 (23.7)	330 (27.2)
95% confidence interval*	(21.4, 26.2)	(24.8, 29.8)
Comparison vs Placebo**		
Odds ratio (SE)		1.261 (0.141)
95% confidence interval***		(1.013, 1.571)
p-value		0.0382
History of HHF (in the last 12 months): Yes		
Number of patients in analysis set	574	577
Number of analysed patients, N (%)	515 (100.0)	528 (100.0)
Number of patients with endpoint, N (%)	113 (21.9)	136 (25.8)
95% confidence interval*	(18.6, 25.7)	(22.2, 29.7)
Comparison vs Placebo**		
Odds ratio (SE)		1.235 (0.216)
95% confidence interval***		(0.877, 1.739)
p-value		0.2274

* Wilson confidence intervals.
** Logistic regression includes terms for baseline KCCQ - total symptom score (p<0.0001), age (p=0.8585), baseline eGFR (CKD-EPI) (p=0.8200), Treatment (p=0.0327), region (5 cat.) (p<0.0001), baseline diabetes status (3 cat.) (p=0.6411), sex (p=0.2644), baseline LVEF (3 cat.) (p=0.7441), history of HHF (in the last 12 months) (p=0.3867) and Treatment by history of HHF (in the last 12 months) interaction (p=0.9187).
***Wald confidence intervals.

Data taken from study 1245.121 only.
LOCF: For a missing value at week 52 the last available post-baseline value before week 52 is imputed.

Table R.1.2.7.10: 6 Responder analysis (displaying risk ratio) in KCCQ-TSS change from baseline at week 52 of >= 15 points (improvement) by history of HHF - RS (LOCF-AD) - 1245.121

Subgroup Description	Placebo	Empa 10mg
History of HHF (in the last 12 months): No		
Number of patients in analysis set	1293	1286
Number of analysed patients, N (%)	1194 (100.0)	1212 (100.0)
Number of patients with endpoint, N (%)	283 (23.7)	330 (27.2)
95% confidence interval*	(21.4, 26.2)	(24.8, 29.8)
Comparison vs Placebo**		
Risk ratio (SE)		1.113 (0.071)
95% confidence interval***		(0.983, 1.262)
p-value		0.0918
History of HHF (in the last 12 months): Yes		
Number of patients in analysis set	574	577
Number of analysed patients, N (%)	515 (100.0)	528 (100.0)
Number of patients with endpoint, N (%)	113 (21.9)	136 (25.8)
95% confidence interval*	(18.6, 25.7)	(22.2, 29.7)
Comparison vs Placebo**		
Risk ratio (SE)		1.088 (0.114)
95% confidence interval***		(0.886, 1.336)
p-value		0.4209

* Wilson confidence intervals.
** Log-linked Poisson model with robust estimate of variance includes terms for baseline KCCQ - total symptom score (p<0.0001), age (p=0.9944), baseline eGFR (CKD-EPI) (p=0.9940), Treatment (p=0.1182), region (5 cat.) (p<0.0001), baseline diabetes status (3 cat.) (p=0.5085), sex (p=0.5584), baseline LVEF (3 cat.) (p=0.8389), history of HHF (in the last 12 months) (p=0.3032) and Treatment by history of HHF (in the last 12 months) interaction (p=0.8499).
***Wald confidence intervals.

Data taken from study 1245.121 only.
LOCF: For a missing value at week 52 the last available post-baseline value before week 52 is imputed.

R.1.2.7.11

Table R.1.2.7.11: 1 Responder analysis (displaying odds ratio) in KCCQ-TSS change from baseline at week 52 of <= -15 points (deterioration) by cause of heart failure - RS (LOCF-AD) - 1245.121

Subgroup Description	Placebo	Empa 10mg
Cause of heart failure: Ischemic		
Number of patients in analysis set	946	983
Number of analysed patients, N (%)	876 (100.0)	923 (100.0)
Number of patients with endpoint, N (%)	111 (12.7)	106 (11.5)
95% confidence interval*	(10.6, 15.0)	(9.6, 13.7)
Comparison vs Placebo**		
Odds ratio (SE)		0.912 (0.134)
95% confidence interval***		(0.684, 1.217)
p-value		0.5327
Cause of heart failure: Non-ischemic		
Number of patients in analysis set	921	880
Number of analysed patients, N (%)	833 (100.0)	817 (100.0)
Number of patients with endpoint, N (%)	104 (12.5)	76 (9.3)
95% confidence interval*	(10.4, 14.9)	(7.5, 11.5)
Comparison vs Placebo**		
Odds ratio (SE)		0.701 (0.114)
95% confidence interval***		(0.510, 0.963)
p-value		0.0286

* Wilson confidence intervals.
** Logistic regression includes terms for baseline KCCQ - total symptom score (p<0.0001), age (p=0.3388), baseline eGFR (CKD-EPI) (p<0.0001), Treatment (p=0.0412), region (5 cat.) (p=0.0125), baseline diabetes status (3 cat.) (p=0.8236), sex (p=0.1390), baseline LVEF (3 cat.) (p=0.0498), cause of heart failure (p=0.6968) and Treatment by cause of heart failure interaction (p=0.2294).
***Wald confidence intervals.

Data taken from study 1245.121 only.
LOCF: For a missing value at week 52 the last available post-baseline value before week 52 is imputed.

Table R.1.2.7.11: 2 Responder analysis (displaying risk ratio) in KCCQ-TSS change from baseline at week 52 of <= -15 points (deterioration) by cause of heart failure - RS (LOCF-AD) - 1245.121

Subgroup Description	Placebo	Empa 10mg
Cause of heart failure: Ischemic		
Number of patients in analysis set	946	983
Number of analysed patients, N (%)	876 (100.0)	923 (100.0)
Number of patients with endpoint, N (%)	111 (12.7)	106 (11.5)
95% confidence interval*	(10.6, 15.0)	(9.6, 13.7)
Comparison vs Placebo**		
Risk ratio (SE)		0.924 (0.116)
95% confidence interval***		(0.723, 1.181)
p-value		0.5284
Cause of heart failure: Non-ischemic		
Number of patients in analysis set	921	880
Number of analysed patients, N (%)	833 (100.0)	817 (100.0)
Number of patients with endpoint, N (%)	104 (12.5)	76 (9.3)
95% confidence interval*	(10.4, 14.9)	(7.5, 11.5)
Comparison vs Placebo**		
Risk ratio (SE)		0.735 (0.104)
95% confidence interval***		(0.557, 0.969)
p-value		0.0289

* Wilson confidence intervals.
** Log-linked Poisson model with robust estimate of variance includes terms for baseline KCCQ - total symptom score (p<0.0001), age (p=0.3559), baseline eGFR (CKD-EPI) (p<0.0001), Treatment (p=0.0396), region (5 cat.) (p=0.0154), baseline diabetes status (3 cat.) (p=0.8250), sex (p=0.1381), baseline LVEF (3 cat.) (p=0.0493), cause of heart failure (p=0.6796) and Treatment by cause of heart failure interaction (p=0.2260).
***Wald confidence intervals.

Data taken from study 1245.121 only.
LOCF: For a missing value at week 52 the last available post-baseline value before week 52 is imputed.

Table R.1.2.7.11: 3 Responder analysis (displaying odds ratio) in KCCQ-TSS change from baseline at week 52 of > -15 points (stability) by cause of heart failure - RS (LOCF-AD) - 1245.121

Subgroup Description	Placebo	Empa 10mg
Cause of heart failure: Ischemic		
Number of patients in analysis set	946	983
Number of analysed patients, N (%)	876 (100.0)	923 (100.0)
Number of patients with endpoint, N (%)	765 (87.3)	817 (88.5)
95% confidence interval*	(85.0, 89.4)	(86.3, 90.4)
Comparison vs Placebo**		
Odds ratio (SE)		1.096 (0.161)
95% confidence interval***		(0.822, 1.463)
p-value		0.5327
Cause of heart failure: Non-ischemic		
Number of patients in analysis set	921	880
Number of analysed patients, N (%)	833 (100.0)	817 (100.0)
Number of patients with endpoint, N (%)	729 (87.5)	741 (90.7)
95% confidence interval*	(85.1, 89.6)	(88.5, 92.5)
Comparison vs Placebo**		
Odds ratio (SE)		1.426 (0.231)
95% confidence interval***		(1.038, 1.960)
p-value		0.0286

* Wilson confidence intervals.
** Logistic regression includes terms for baseline KCCQ - total symptom score (p<0.0001), age (p=0.3388), baseline eGFR (CKD-EPI) (p<0.0001), Treatment (p=0.0412), region (5 cat.) (p=0.0125), baseline diabetes status (3 cat.) (p=0.8236), sex (p=0.1390), baseline LVEF (3 cat.) (p=0.0498), cause of heart failure (p=0.6968) and Treatment by cause of heart failure interaction (p=0.2294).
***Wald confidence intervals.

Data taken from study 1245.121 only.
LOCF: For a missing value at week 52 the last available post-baseline value before week 52 is imputed.

Table R.1.2.7.11: 4 Responder analysis (displaying risk ratio) in KCCQ-TSS change from baseline at week 52 of > -15 points (stability) by cause of heart failure - RS (LOCF-AD) - 1245.121

Subgroup Description	Placebo	Empa 10mg
Cause of heart failure: Ischemic		
Number of patients in analysis set	946	983
Number of analysed patients, N (%)	876 (100.0)	923 (100.0)
Number of patients with endpoint, N (%)	765 (87.3)	817 (88.5)
95% confidence interval*	(85.0, 89.4)	(86.3, 90.4)
Comparison vs Placebo**		
Risk ratio (SE)		1.011 (0.017)
95% confidence interval***		(0.977, 1.046)
p-value		0.5384
Cause of heart failure: Non-ischemic		
Number of patients in analysis set	921	880
Number of analysed patients, N (%)	833 (100.0)	817 (100.0)
Number of patients with endpoint, N (%)	729 (87.5)	741 (90.7)
95% confidence interval*	(85.1, 89.6)	(88.5, 92.5)
Comparison vs Placebo**		
Risk ratio (SE)		1.037 (0.018)
95% confidence interval***		(1.003, 1.072)
p-value		0.0346

* Wilson confidence intervals.
** Log-linked Poisson model with robust estimate of variance includes terms for baseline KCCQ - total symptom score (p<0.0001), age (p=0.4692), baseline eGFR (CKD-EPI) (p<0.0001), Treatment (p=0.0538), region (5 cat.) (p<0.0001), baseline diabetes status (3 cat.) (p=0.8419), sex (p=0.1524), baseline LVEF (3 cat.) (p=0.0318), cause of heart failure (p=0.7334) and Treatment by cause of heart failure interaction (p=0.2965).
***Wald confidence intervals.

Data taken from study 1245.121 only.
LOCF: For a missing value at week 52 the last available post-baseline value before week 52 is imputed.

Table R.1.2.7.11: 5 Responder analysis (displaying odds ratio) in KCCQ-TSS change from baseline at week 52 of >= 15 points (improvement) by cause of heart failure - RS (LOCF-AD) - 1245.121

Subgroup Description	Placebo	Empa 10mg
Cause of heart failure: Ischemic		
Number of patients in analysis set	946	983
Number of analysed patients, N (%)	876 (100.0)	923 (100.0)
Number of patients with endpoint, N (%)	188 (21.5)	232 (25.1)
95% confidence interval*	(18.9, 24.3)	(22.4, 28.0)
Comparison vs Placebo**		
Odds ratio (SE)		1.205 (0.161)
95% confidence interval***		(0.928, 1.565)
p-value		0.1619
Cause of heart failure: Non-ischemic		
Number of patients in analysis set	921	880
Number of analysed patients, N (%)	833 (100.0)	817 (100.0)
Number of patients with endpoint, N (%)	208 (25.0)	234 (28.6)
95% confidence interval*	(22.2, 28.0)	(25.6, 31.8)
Comparison vs Placebo**		
Odds ratio (SE)		1.311 (0.175)
95% confidence interval***		(1.009, 1.702)
p-value		0.0425

* Wilson confidence intervals.
** Logistic regression includes terms for baseline KCCQ - total symptom score (p<0.0001), age (p=0.9644), baseline eGFR (CKD-EPI) (p=0.8065), Treatment (p=0.0153), region (5 cat.) (p<0.0001), baseline diabetes status (3 cat.) (p=0.7065), sex (p=0.2177), baseline LVEF (3 cat.) (p=0.8025), cause of heart failure (p=0.2779) and Treatment by cause of heart failure interaction (p=0.6562).
***Wald confidence intervals.

Data taken from study 1245.121 only.
LOCF: For a missing value at week 52 the last available post-baseline value before week 52 is imputed.

Table R.1.2.7.11: 6 Responder analysis (displaying risk ratio) in KCCQ-TSS change from baseline at week 52 of >= 15 points (improvement) by cause of heart failure - RS (LOCF-AD) - 1245.121

Subgroup Description	Placebo	Empa 10mg
Cause of heart failure: Ischemic		
Number of patients in analysis set	946	983
Number of analysed patients, N (%)	876 (100.0)	923 (100.0)
Number of patients with endpoint, N (%)	188 (21.5)	232 (25.1)
95% confidence interval*	(18.9, 24.3)	(22.4, 28.0)
Comparison vs Placebo**		
Risk ratio (SE)		1.085 (0.085)
95% confidence interval***		(0.930, 1.266)
p-value		0.2999
Cause of heart failure: Non-ischemic		
Number of patients in analysis set	921	880
Number of analysed patients, N (%)	833 (100.0)	817 (100.0)
Number of patients with endpoint, N (%)	208 (25.0)	234 (28.6)
95% confidence interval*	(22.2, 28.0)	(25.6, 31.8)
Comparison vs Placebo**		
Risk ratio (SE)		1.130 (0.086)
95% confidence interval***		(0.974, 1.311)
p-value		0.1066

* Wilson confidence intervals.
** Log-linked Poisson model with robust estimate of variance includes terms for baseline KCCQ - total symptom score (p<0.0001), age (p=0.8748), baseline eGFR (CKD-EPI) (p=0.9521), Treatment (p=0.0623), region (5 cat.) (p<0.0001), baseline diabetes status (3 cat.) (p=0.6239), sex (p=0.4480), baseline LVEF (3 cat.) (p=0.8568), cause of heart failure (p=0.1818) and Treatment by cause of heart failure interaction (p=0.7094).
***Wald confidence intervals.

Data taken from study 1245.121 only.
LOCF: For a missing value at week 52 the last available post-baseline value before week 52 is imputed.

R.1.2.7.12

R.1.2.7.12 Subgroup analysis by heart failure physiology (LVEF <= 30% and NTproBNP<median; LVEF <= 30% and NTproBNP>=median; LVEF > 30%)

Table R.1.2.7.12: 1 Responder analysis (displaying odds ratio) in KCCQ-TSS change from baseline at week 52 of <= -15 points (deterioration) by heart failure physiology - RS (LOCF-AD) - 1245.121

Subgroup Description	Placebo	Empa 10mg
Heart failure physiology: LVEF <= 30% and NTproBNP < median		
Number of patients in analysis set	723	698
Number of analysed patients, N (%)	679 (100.0)	655 (100.0)
Number of patients with endpoint, N (%)	73 (10.8)	66 (10.1)
95% confidence interval*	(8.6, 13.3)	(8.0, 12.6)
Comparison vs Placebo**		
Odds ratio (SE)		0.910 (0.165)
95% confidence interval***		(0.637, 1.299)
p-value		0.6022
Heart failure physiology: LVEF <= 30% and NTproBNP >= median		
Number of patients in analysis set	661	631
Number of analysed patients, N (%)	588 (100.0)	586 (100.0)
Number of patients with endpoint, N (%)	96 (16.3)	67 (11.4)
95% confidence interval*	(13.6, 19.5)	(9.1, 14.3)
Comparison vs Placebo**		
Odds ratio (SE)		0.660 (0.115)
95% confidence interval***		(0.469, 0.929)
p-value		0.0174

* Wilson confidence intervals.
** Logistic regression includes terms for baseline KCCQ - total symptom score (p<0.0001), age (p=0.3728), baseline eGFR (CKD-EPI) (p<0.0001), Treatment (p=0.0903), region (5 cat.) (p=0.0104), baseline diabetes status (3 cat.) (p=0.8251), sex (p=0.1385), heart failure physiology (p=0.0053) and Treatment by heart failure physiology interaction (p=0.3206).
***Wald confidence intervals.
16 patients were excluded as the subgroup variable was missing.

Data taken from study 1245.121 only.
LOCF: For a missing value at week 52 the last available post-baseline value before week 52 is imputed.
NTproBNP median [pg/mL]: with a. fibrillation/flutter at baseline: 2265; without a. fibrillation/flutter at baseline: 1671.

Table R.1.2.7.12: 1 Responder analysis (displaying odds ratio) in KCCQ-TSS change from baseline at week 52 of <= -15 points (deterioration) by heart failure physiology - RS (LOCF-AD) - 1245.121

Subgroup Description	Placebo	Empa 10mg
Heart failure physiology: LVEF > 30%		
Number of patients in analysis set	475	526
Number of analysed patients, N (%)	437 (100.0)	495 (100.0)
Number of patients with endpoint, N (%)	46 (10.5)	49 (9.9)
95% confidence interval*	(8.0, 13.8)	(7.6, 12.8)
Comparison vs Placebo**		
Odds ratio (SE)		0.946 (0.208)
95% confidence interval***		(0.615, 1.454)
p-value		0.7994

* Wilson confidence intervals.
** Logistic regression includes terms for baseline KCCQ - total symptom score (p<0.0001), age (p=0.3728), baseline eGFR (CKD-EPI) (p<0.0001), Treatment (p=0.0903), region (5 cat.) (p=0.0104), baseline diabetes status (3 cat.) (p=0.8251), sex (p=0.1385), heart failure physiology (p=0.0053) and Treatment by heart failure physiology interaction (p=0.3206).
***Wald confidence intervals.
16 patients were excluded as the subgroup variable was missing.

Data taken from study 1245.121 only.
LOCF: For a missing value at week 52 the last available post-baseline value before week 52 is imputed.
NTproBNP median [pg/mL]: with a. fibrillation/flutter at baseline: 2265; without a. fibrillation/flutter at baseline: 1671.

Table R.1.2.7.12: 2 Responder analysis (displaying risk ratio) in KCCQ-TSS change from baseline at week 52 of <= -15 points (deterioration) by heart failure physiology - RS (LOCF-AD) - 1245.121

Subgroup Description	Placebo	Empa 10mg
Heart failure physiology: LVEF <= 30% and NTproBNP < median		
Number of patients in analysis set	723	698
Number of analysed patients, N (%)	679 (100.0)	655 (100.0)
Number of patients with endpoint, N (%)	73 (10.8)	66 (10.1)
95% confidence interval*	(8.6, 13.3)	(8.0, 12.6)
Comparison vs Placebo**		
Risk ratio (SE)		0.921 (0.146)
95% confidence interval***		(0.675, 1.255)
p-value		0.6007
Heart failure physiology: LVEF <= 30% and NTproBNP >= median		
Number of patients in analysis set	661	631
Number of analysed patients, N (%)	588 (100.0)	586 (100.0)
Number of patients with endpoint, N (%)	96 (16.3)	67 (11.4)
95% confidence interval*	(13.6, 19.5)	(9.1, 14.3)
Comparison vs Placebo**		
Risk ratio (SE)		0.707 (0.103)
95% confidence interval***		(0.531, 0.941)
p-value		0.0173

* Wilson confidence intervals.
** Log-linked Poisson model with robust estimate of variance includes terms for baseline KCCQ - total symptom score (p<0.0001), age (p=0.3898), baseline eGFR (CKD-EPI) (p=0.0001), Treatment (p=0.0964), region (5 cat.) (p=0.0138), baseline diabetes status (3 cat.) (p=0.8254), sex (p=0.1362), heart failure physiology (p=0.0053) and Treatment by heart failure physiology interaction (p=0.3418).
***Wald confidence intervals.
16 patients were excluded as the subgroup variable was missing.

Data taken from study 1245.121 only.
LOCF: For a missing value at week 52 the last available post-baseline value before week 52 is imputed.
NTproBNP median [pg/mL]: with a. fibrillation/flutter at baseline: 2265; without a. fibrillation/flutter at baseline: 1671.

Table R.1.2.7.12: 2 Responder analysis (displaying risk ratio) in KCCQ-TSS change from baseline at week 52 of <= -15 points (deterioration) by heart failure physiology - RS (LOCF-AD) - 1245.121

Subgroup Description	Placebo	Empa 10mg
Heart failure physiology: LVEF > 30%		
Number of patients in analysis set	475	526
Number of analysed patients, N (%)	437 (100.0)	495 (100.0)
Number of patients with endpoint, N (%)	46 (10.5)	49 (9.9)
95% confidence interval*	(8.0, 13.8)	(7.6, 12.8)
Comparison vs Placebo**		
Risk ratio (SE)		0.952 (0.183)
95% confidence interval***		(0.654, 1.386)
p-value		0.7971

* Wilson confidence intervals.
** Log-linked Poisson model with robust estimate of variance includes terms for baseline KCCQ - total symptom score (p<0.0001), age (p=0.3898), baseline eGFR (CKD-EPI) (p=0.0001), Treatment (p=0.0964), region (5 cat.) (p=0.0138), baseline diabetes status (3 cat.) (p=0.8254), sex (p=0.1362), heart failure physiology (p=0.0053) and Treatment by heart failure physiology interaction (p=0.3418).
***Wald confidence intervals.
16 patients were excluded as the subgroup variable was missing.

Data taken from study 1245.121 only.
LOCF: For a missing value at week 52 the last available post-baseline value before week 52 is imputed.
NTproBNP median [pg/mL]: with a. fibrillation/flutter at baseline: 2265; without a. fibrillation/flutter at baseline: 1671.

Table R.1.2.7.12: 3 Responder analysis (displaying odds ratio) in KCCQ-TSS change from baseline at week 52 of > -15 points (stability) by heart failure physiology - RS (LOCF-AD) - 1245.121

Subgroup Description	Placebo	Empa 10mg
Heart failure physiology: LVEF <= 30% and NTproBNP < median		
Number of patients in analysis set	723	698
Number of analysed patients, N (%)	679 (100.0)	655 (100.0)
Number of patients with endpoint, N (%)	606 (89.2)	589 (89.9)
95% confidence interval*	(86.7, 91.4)	(87.4, 92.0)
Comparison vs Placebo**		
Odds ratio (SE)		1.099 (0.200)
95% confidence interval***		(0.770, 1.570)
p-value		0.6022
Heart failure physiology: LVEF <= 30% and NTproBNP >= median		
Number of patients in analysis set	661	631
Number of analysed patients, N (%)	588 (100.0)	586 (100.0)
Number of patients with endpoint, N (%)	492 (83.7)	519 (88.6)
95% confidence interval*	(80.5, 86.4)	(85.7, 90.9)
Comparison vs Placebo**		
Odds ratio (SE)		1.515 (0.264)
95% confidence interval***		(1.076, 2.133)
p-value		0.0174

* Wilson confidence intervals.
** Logistic regression includes terms for baseline KCCQ - total symptom score (p<0.0001), age (p=0.3728), baseline eGFR (CKD-EPI) (p<0.0001), Treatment (p=0.0903), region (5 cat.) (p=0.0104), baseline diabetes status (3 cat.) (p=0.8251), sex (p=0.1385), heart failure physiology (p=0.0053) and Treatment by heart failure physiology interaction (p=0.3206).
***Wald confidence intervals.
16 patients were excluded as the subgroup variable was missing.

Data taken from study 1245.121 only.
LOCF: For a missing value at week 52 the last available post-baseline value before week 52 is imputed.
NTproBNP median [pg/mL]: with a. fibrillation/flutter at baseline: 2265; without a. fibrillation/flutter at baseline: 1671.

Table R.1.2.7.12: 3 Responder analysis (displaying odds ratio) in KCCQ-TSS change from baseline at week 52 of > -15 points (stability) by heart failure physiology - RS (LOCF-AD) - 1245.121

Subgroup Description	Placebo	Empa 10mg
Heart failure physiology: LVEF > 30%		
Number of patients in analysis set	475	526
Number of analysed patients, N (%)	437 (100.0)	495 (100.0)
Number of patients with endpoint, N (%)	391 (89.5)	446 (90.1)
95% confidence interval*	(86.2, 92.0)	(87.2, 92.4)
Comparison vs Placebo**		
Odds ratio (SE)		1.057 (0.232)
95% confidence interval***		(0.688, 1.626)
p-value		0.7994

* Wilson confidence intervals.
** Logistic regression includes terms for baseline KCCQ - total symptom score (p<0.0001), age (p=0.3728), baseline eGFR (CKD-EPI) (p<0.0001), Treatment (p=0.0903), region (5 cat.) (p=0.0104), baseline diabetes status (3 cat.) (p=0.8251), sex (p=0.1385), heart failure physiology (p=0.0053) and Treatment by heart failure physiology interaction (p=0.3206).
***Wald confidence intervals.
16 patients were excluded as the subgroup variable was missing.

Data taken from study 1245.121 only.
LOCF: For a missing value at week 52 the last available post-baseline value before week 52 is imputed.
NTproBNP median [pg/mL]: with a. fibrillation/flutter at baseline: 2265; without a. fibrillation/flutter at baseline: 1671.

Table R.1.2.7.12: 4 Responder analysis (displaying risk ratio) in KCCQ-TSS change from baseline at week 52 of > -15 points (stability) by heart failure physiology - RS (LOCF-AD) - 1245.121

Subgroup Description	Placebo	Empa 10mg
Heart failure physiology: LVEF <= 30% and NTproBNP < median		
Number of patients in analysis set	723	698
Number of analysed patients, N (%)	679 (100.0)	655 (100.0)
Number of patients with endpoint, N (%)	606 (89.2)	589 (89.9)
95% confidence interval*	(86.7, 91.4)	(87.4, 92.0)
Comparison vs Placebo**		
Risk ratio (SE)		1.011 (0.019)
95% confidence interval***		(0.975, 1.048)
p-value		0.5622
Heart failure physiology: LVEF <= 30% and NTproBNP >= median		
Number of patients in analysis set	661	631
Number of analysed patients, N (%)	588 (100.0)	586 (100.0)
Number of patients with endpoint, N (%)	492 (83.7)	519 (88.6)
95% confidence interval*	(80.5, 86.4)	(85.7, 90.9)
Comparison vs Placebo**		
Risk ratio (SE)		1.055 (0.024)
95% confidence interval***		(1.008, 1.104)
p-value		0.0219

* Wilson confidence intervals.
** Log-linked Poisson model with robust estimate of variance includes terms for baseline KCCQ - total symptom score (p<0.0001), age (p=0.4780), baseline eGFR (CKD-EPI) (p=0.0001), Treatment (p=0.0636), region (5 cat.) (p<0.0001), baseline diabetes status (3 cat.) (p=0.8483), sex (p=0.1396), heart failure physiology (p=0.0035) and Treatment by heart failure physiology interaction (p=0.2467).
***Wald confidence intervals.
16 patients were excluded as the subgroup variable was missing.

Data taken from study 1245.121 only.
LOCF: For a missing value at week 52 the last available post-baseline value before week 52 is imputed.
NTproBNP median [pg/mL]: with a. fibrillation/flutter at baseline: 2265; without a. fibrillation/flutter at baseline: 1671.

Table R.1.2.7.12: 4 Responder analysis (displaying risk ratio) in KCCQ-TSS change from baseline at week 52 of > -15 points (stability) by heart failure physiology - RS (LOCF-AD) - 1245.121

Subgroup Description	Placebo	Empa 10mg
Heart failure physiology: LVEF > 30%		
Number of patients in analysis set	475	526
Number of analysed patients, N (%)	437 (100.0)	495 (100.0)
Number of patients with endpoint, N (%)	391 (89.5)	446 (90.1)
95% confidence interval*	(86.2, 92.0)	(87.2, 92.4)
Comparison vs Placebo**		
Risk ratio (SE)		1.005 (0.022)
95% confidence interval***		(0.962, 1.049)
p-value		0.8372

* Wilson confidence intervals.
** Log-linked Poisson model with robust estimate of variance includes terms for baseline KCCQ - total symptom score (p<0.0001), age (p=0.4780), baseline eGFR (CKD-EPI) (p=0.0001), Treatment (p=0.0636), region (5 cat.) (p<0.0001), baseline diabetes status (3 cat.) (p=0.8483), sex (p=0.1396), heart failure physiology (p=0.0035) and Treatment by heart failure physiology interaction (p=0.2467).
***Wald confidence intervals.
16 patients were excluded as the subgroup variable was missing.

Data taken from study 1245.121 only.
LOCF: For a missing value at week 52 the last available post-baseline value before week 52 is imputed.
NTproBNP median [pg/mL]: with a. fibrillation/flutter at baseline: 2265; without a. fibrillation/flutter at baseline: 1671.

Table R.1.2.7.12: 5 Responder analysis (displaying odds ratio) in KCCQ-TSS change from baseline at week 52 of >= 15 points (improvement) by heart failure physiology - RS (LOCF-AD) - 1245.121

Subgroup Description	Placebo	Empa 10mg
Heart failure physiology: LVEF <= 30% and NTproBNP < median		
Number of patients in analysis set	723	698
Number of analysed patients, N (%)	679 (100.0)	655 (100.0)
Number of patients with endpoint, N (%)	160 (23.6)	157 (24.0)
95% confidence interval*	(20.5, 26.9)	(20.9, 27.4)
Comparison vs Placebo**		
Odds ratio (SE)		1.124 (0.171)
95% confidence interval***		(0.834, 1.514)
p-value		0.4428
Heart failure physiology: LVEF <= 30% and NTproBNP >= median		
Number of patients in analysis set	661	631
Number of analysed patients, N (%)	588 (100.0)	586 (100.0)
Number of patients with endpoint, N (%)	132 (22.4)	178 (30.4)
95% confidence interval*	(19.3, 26.0)	(26.8, 34.2)
Comparison vs Placebo**		
Odds ratio (SE)		1.456 (0.235)
95% confidence interval***		(1.061, 1.997)
p-value		0.0198

* Wilson confidence intervals.
** Logistic regression includes terms for baseline KCCQ - total symptom score (p<0.0001), age (p=0.8464), baseline eGFR (CKD-EPI) (p=0.6471), Treatment (p=0.0132), region (5 cat.) (p<0.0001), baseline diabetes status (3 cat.) (p=0.6216), sex (p=0.2833), heart failure physiology (p=0.2373) and Treatment by heart failure physiology interaction (p=0.5039).
***Wald confidence intervals.
16 patients were excluded as the subgroup variable was missing.

Data taken from study 1245.121 only.
LOCF: For a missing value at week 52 the last available post-baseline value before week 52 is imputed.
NTproBNP median [pg/mL]: with a. fibrillation/flutter at baseline: 2265; without a. fibrillation/flutter at baseline: 1671.

Table R.1.2.7.12: 5 Responder analysis (displaying odds ratio) in KCCQ-TSS change from baseline at week 52 of >= 15 points (improvement) by heart failure physiology - RS (LOCF-AD) - 1245.121

Subgroup Description	Placebo	Empa 10mg
Heart failure physiology: LVEF > 30%		
Number of patients in analysis set	475	526
Number of analysed patients, N (%)	437 (100.0)	495 (100.0)
Number of patients with endpoint, N (%)	101 (23.1)	129 (26.1)
95% confidence interval*	(19.4, 27.3)	(22.4, 30.1)
Comparison vs Placebo**		
Odds ratio (SE)		1.245 (0.227)
95% confidence interval***		(0.871, 1.781)
p-value		0.2297

* Wilson confidence intervals.
** Logistic regression includes terms for baseline KCCQ - total symptom score (p<0.0001), age (p=0.8464), baseline eGFR (CKD-EPI) (p=0.6471), Treatment (p=0.0132), region (5 cat.) (p<0.0001), baseline diabetes status (3 cat.) (p=0.6216), sex (p=0.2833), heart failure physiology (p=0.2373) and Treatment by heart failure physiology interaction (p=0.5039).
***Wald confidence intervals.
16 patients were excluded as the subgroup variable was missing.

Data taken from study 1245.121 only.
LOCF: For a missing value at week 52 the last available post-baseline value before week 52 is imputed.
NTproBNP median [pg/mL]: with a. fibrillation/flutter at baseline: 2265; without a. fibrillation/flutter at baseline: 1671.

Table R.1.2.7.12: 6 Responder analysis (displaying risk ratio) in KCCQ-TSS change from baseline at week 52 of >= 15 points (improvement) by heart failure physiology - RS (LOCF-AD) - 1245.121

Subgroup Description	Placebo	Empa 10mg
Heart failure physiology: LVEF <= 30% and NTproBNP < median		
Number of patients in analysis set	723	698
Number of analysed patients, N (%)	679 (100.0)	655 (100.0)
Number of patients with endpoint, N (%)	160 (23.6)	157 (24.0)
95% confidence interval*	(20.5, 26.9)	(20.9, 27.4)
Comparison vs Placebo**		
Risk ratio (SE)		1.039 (0.093)
95% confidence interval***		(0.872, 1.238)
p-value		0.6706
Heart failure physiology: LVEF <= 30% and NTproBNP >= median		
Number of patients in analysis set	661	631
Number of analysed patients, N (%)	588 (100.0)	586 (100.0)
Number of patients with endpoint, N (%)	132 (22.4)	178 (30.4)
95% confidence interval*	(19.3, 26.0)	(26.8, 34.2)
Comparison vs Placebo**		
Risk ratio (SE)		1.211 (0.112)
95% confidence interval***		(1.010, 1.453)
p-value		0.0389

* Wilson confidence intervals.
** Log-linked Poisson model with robust estimate of variance includes terms for baseline KCCQ - total symptom score (p<0.0001), age (p=0.9246), baseline eGFR (CKD-EPI) (p=0.8017), Treatment (p=0.0604), region (5 cat.) (p<0.0001), baseline diabetes status (3 cat.) (p=0.4925), sex (p=0.5371), heart failure physiology (p=0.1178) and Treatment by heart failure physiology interaction (p=0.4783).
***Wald confidence intervals.
16 patients were excluded as the subgroup variable was missing.

Data taken from study 1245.121 only.
LOCF: For a missing value at week 52 the last available post-baseline value before week 52 is imputed.
NTproBNP median [pg/mL]: with a. fibrillation/flutter at baseline: 2265; without a. fibrillation/flutter at baseline: 1671.

Table R.1.2.7.12: 6 Responder analysis (displaying risk ratio) in KCCQ-TSS change from baseline at week 52 of >= 15 points (improvement) by heart failure physiology - RS (LOCF-AD) - 1245.121

Subgroup Description	Placebo	Empa 10mg
Heart failure physiology: LVEF > 30%		
Number of patients in analysis set	475	526
Number of analysed patients, N (%)	437 (100.0)	495 (100.0)
Number of patients with endpoint, N (%)	101 (23.1)	129 (26.1)
95% confidence interval*	(19.4, 27.3)	(22.4, 30.1)
Comparison vs Placebo**		
Risk ratio (SE)		1.085 (0.113)
95% confidence interval***		(0.884, 1.331)
p-value		0.4355

* Wilson confidence intervals.
** Log-linked Poisson model with robust estimate of variance includes terms for baseline KCCQ - total symptom score (p<0.0001), age (p=0.9246), baseline eGFR (CKD-EPI) (p=0.8017), Treatment (p=0.0604), region (5 cat.) (p<0.0001), baseline diabetes status (3 cat.) (p=0.4925), sex (p=0.5371), heart failure physiology (p=0.1178) and Treatment by heart failure physiology interaction (p=0.4783).
***Wald confidence intervals.
16 patients were excluded as the subgroup variable was missing.

Data taken from study 1245.121 only.
LOCF: For a missing value at week 52 the last available post-baseline value before week 52 is imputed.
NTproBNP median [pg/mL]: with a. fibrillation/flutter at baseline: 2265; without a. fibrillation/flutter at baseline: 1671.

R.1.2.7.13

Table R.1.2.7.13: 1 Responder analysis (displaying odds ratio) in KCCQ-TSS change from baseline at week 52 of <= -15 points (deterioration) by baseline use of MRA (Y/N) - RS (LOCF-AD) - 1245.121

Subgroup Description	Placebo	Empa 10mg
Baseline use of MRA: No		
Number of patients in analysis set	512	557
Number of analysed patients, N (%)	475 (100.0)	522 (100.0)
Number of patients with endpoint, N (%)	55 (11.6)	47 (9.0)
95% confidence interval*	(9.0, 14.8)	(6.8, 11.8)
Comparison vs Placebo**		
Odds ratio (SE)		0.764 (0.162)
95% confidence interval***		(0.504, 1.159)
p-value		0.2055
Baseline use of MRA: Yes		
Number of patients in analysis set	1355	1306
Number of analysed patients, N (%)	1234 (100.0)	1218 (100.0)
Number of patients with endpoint, N (%)	160 (13.0)	135 (11.1)
95% confidence interval*	(11.2, 15.0)	(9.4, 13.0)
Comparison vs Placebo**		
Odds ratio (SE)		0.830 (0.105)
95% confidence interval***		(0.647, 1.064)
p-value		0.1419

* Wilson confidence intervals.
** Logistic regression includes terms for baseline KCCQ - total symptom score (p<0.0001), age (p=0.2463), baseline eGFR (CKD-EPI) (p<0.0001), Treatment (p=0.0657), region (5 cat.) (p=0.0179), baseline diabetes status (3 cat.) (p=0.8361), sex (p=0.1624), baseline LVEF (3 cat.) (p=0.0680), baseline use of MRA (p=0.0294) and Treatment by baseline use of MRA interaction (p=0.7383).
***Wald confidence intervals.

Data taken from study 1245.121 only.
LOCF: For a missing value at week 52 the last available post-baseline value before week 52 is imputed.

Table R.1.2.7.13: 2 Responder analysis (displaying risk ratio) in KCCQ-TSS change from baseline at week 52 of <= -15 points (deterioration) by baseline use of MRA (Y/N) - RS (LOCF-AD) - 1245.121

Subgroup Description	Placebo	Empa 10mg
Baseline use of MRA: No		
Number of patients in analysis set	512	557
Number of analysed patients, N (%)	475 (100.0)	522 (100.0)
Number of patients with endpoint, N (%)	55 (11.6)	47 (9.0)
95% confidence interval*	(9.0, 14.8)	(6.8, 11.8)
Comparison vs Placebo**		
Risk ratio (SE)		0.790 (0.146)
95% confidence interval***		(0.550, 1.136)
p-value		0.2035
Baseline use of MRA: Yes		
Number of patients in analysis set	1355	1306
Number of analysed patients, N (%)	1234 (100.0)	1218 (100.0)
Number of patients with endpoint, N (%)	160 (13.0)	135 (11.1)
95% confidence interval*	(11.2, 15.0)	(9.4, 13.0)
Comparison vs Placebo**		
Risk ratio (SE)		0.852 (0.092)
95% confidence interval***		(0.690, 1.053)
p-value		0.1381

* Wilson confidence intervals.
** Log-linked Poisson model with robust estimate of variance includes terms for baseline KCCQ - total symptom score (p<0.0001), age (p=0.2614), baseline eGFR (CKD-EPI) (p<0.0001), Treatment (p=0.0649), region (5 cat.) (p=0.0233), baseline diabetes status (3 cat.) (p=0.8382), sex (p=0.1588), baseline LVEF (3 cat.) (p=0.0677), baseline use of MRA (p=0.0280) and Treatment by baseline use of MRA interaction (p=0.7241).
***Wald confidence intervals.

Data taken from study 1245.121 only.
LOCF: For a missing value at week 52 the last available post-baseline value before week 52 is imputed.

Table R.1.2.7.13: 3 Responder analysis (displaying odds ratio) in KCCQ-TSS change from baseline at week 52 of > -15 points (stability) by baseline use of MRA (Y/N) - RS (LOCF-AD) - 1245.121

Subgroup Description	Placebo	Empa 10mg
Baseline use of MRA: No		
Number of patients in analysis set	512	557
Number of analysed patients, N (%)	475 (100.0)	522 (100.0)
Number of patients with endpoint, N (%)	420 (88.4)	475 (91.0)
95% confidence interval*	(85.2, 91.0)	(88.2, 93.2)
Comparison vs Placebo**		
Odds ratio (SE)		1.308 (0.278)
95% confidence interval***		(0.863, 1.984)
p-value		0.2055
Baseline use of MRA: Yes		
Number of patients in analysis set	1355	1306
Number of analysed patients, N (%)	1234 (100.0)	1218 (100.0)
Number of patients with endpoint, N (%)	1074 (87.0)	1083 (88.9)
95% confidence interval*	(85.0, 88.8)	(87.0, 90.6)
Comparison vs Placebo**		
Odds ratio (SE)		1.205 (0.153)
95% confidence interval***		(0.940, 1.544)
p-value		0.1419

* Wilson confidence intervals.
** Logistic regression includes terms for baseline KCCQ - total symptom score (p<0.0001), age (p=0.2463), baseline eGFR (CKD-EPI) (p<0.0001), Treatment (p=0.0657), region (5 cat.) (p=0.0179), baseline diabetes status (3 cat.) (p=0.8361), sex (p=0.1624), baseline LVEF (3 cat.) (p=0.0680), baseline use of MRA (p=0.0294) and Treatment by baseline use of MRA interaction (p=0.7383).
***Wald confidence intervals.

Data taken from study 1245.121 only.
LOCF: For a missing value at week 52 the last available post-baseline value before week 52 is imputed.

Table R.1.2.7.13: 4 Responder analysis (displaying risk ratio) in KCCQ-TSS change from baseline at week 52 of > -15 points (stability) by baseline use of MRA (Y/N) - RS (LOCF-AD) - 1245.121

Subgroup Description	Placebo	Empa 10mg
Baseline use of MRA: No		
Number of patients in analysis set	512	557
Number of analysed patients, N (%)	475 (100.0)	522 (100.0)
Number of patients with endpoint, N (%)	420 (88.4)	475 (91.0)
95% confidence interval*	(85.2, 91.0)	(88.2, 93.2)
Comparison vs Placebo**		
Risk ratio (SE)		1.027 (0.022)
95% confidence interval***		(0.985, 1.070)
p-value		0.2154
Baseline use of MRA: Yes		
Number of patients in analysis set	1355	1306
Number of analysed patients, N (%)	1234 (100.0)	1218 (100.0)
Number of patients with endpoint, N (%)	1074 (87.0)	1083 (88.9)
95% confidence interval*	(85.0, 88.8)	(87.0, 90.6)
Comparison vs Placebo**		
Risk ratio (SE)		1.021 (0.015)
95% confidence interval***		(0.992, 1.051)
p-value		0.1602

* Wilson confidence intervals.
** Log-linked Poisson model with robust estimate of variance includes terms for baseline KCCQ - total symptom score (p<0.0001), age (p=0.3470), baseline eGFR (CKD-EPI) (p<0.0001), Treatment (p=0.0691), region (5 cat.) (p<0.0001), baseline diabetes status (3 cat.) (p=0.8607), sex (p=0.1622), baseline LVEF (3 cat.) (p=0.0444), baseline use of MRA (p=0.0216) and Treatment by baseline use of MRA interaction (p=0.8273).
***Wald confidence intervals.

Data taken from study 1245.121 only.
LOCF: For a missing value at week 52 the last available post-baseline value before week 52 is imputed.

Table R.1.2.7.13: 5 Responder analysis (displaying odds ratio) in KCCQ-TSS change from baseline at week 52 of >= 15 points (improvement) by baseline use of MRA (Y/N) - RS (LOCF-AD) - 1245.121

Subgroup Description	Placebo	Empa 10mg
Baseline use of MRA: No		
Number of patients in analysis set	512	557
Number of analysed patients, N (%)	475 (100.0)	522 (100.0)
Number of patients with endpoint, N (%)	93 (19.6)	141 (27.0)
95% confidence interval*	(16.3, 23.4)	(23.4, 31.0)
Comparison vs Placebo**		
Odds ratio (SE)		1.624 (0.292)
95% confidence interval***		(1.141, 2.311)
p-value		0.0070
Baseline use of MRA: Yes		
Number of patients in analysis set	1355	1306
Number of analysed patients, N (%)	1234 (100.0)	1218 (100.0)
Number of patients with endpoint, N (%)	303 (24.6)	325 (26.7)
95% confidence interval*	(22.2, 27.0)	(24.3, 29.2)
Comparison vs Placebo**		
Odds ratio (SE)		1.134 (0.126)
95% confidence interval***		(0.913, 1.410)
p-value		0.2551

* Wilson confidence intervals.
** Logistic regression includes terms for baseline KCCQ - total symptom score (p<0.0001), age (p=0.8629), baseline eGFR (CKD-EPI) (p=0.9009), Treatment (p=0.0038), region (5 cat.) (p<0.0001), baseline diabetes status (3 cat.) (p=0.6079), sex (p=0.2623), baseline LVEF (3 cat.) (p=0.8097), baseline use of MRA (p=0.7011) and Treatment by baseline use of MRA interaction (p=0.0896).
***Wald confidence intervals.

Data taken from study 1245.121 only.
LOCF: For a missing value at week 52 the last available post-baseline value before week 52 is imputed.

Table R.1.2.7.13: 6 Responder analysis (displaying risk ratio) in KCCQ-TSS change from baseline at week 52 of >= 15 points (improvement) by baseline use of MRA (Y/N) - RS (LOCF-AD) - 1245.121

Subgroup Description	Placebo	Empa 10mg
Baseline use of MRA: No		
Number of patients in analysis set	512	557
Number of analysed patients, N (%)	475 (100.0)	522 (100.0)
Number of patients with endpoint, N (%)	93 (19.6)	141 (27.0)
95% confidence interval*	(16.3, 23.4)	(23.4, 31.0)
Comparison vs Placebo**		
Risk ratio (SE)		1.276 (0.139)
95% confidence interval***		(1.030, 1.579)
p-value		0.0255
Baseline use of MRA: Yes		
Number of patients in analysis set	1355	1306
Number of analysed patients, N (%)	1234 (100.0)	1218 (100.0)
Number of patients with endpoint, N (%)	303 (24.6)	325 (26.7)
95% confidence interval*	(22.2, 27.0)	(24.3, 29.2)
Comparison vs Placebo**		
Risk ratio (SE)		1.048 (0.066)
95% confidence interval***		(0.926, 1.187)
p-value		0.4559

* Wilson confidence intervals.
** Log-linked Poisson model with robust estimate of variance includes terms for baseline KCCQ - total symptom score (p<0.0001), age (p=0.9725), baseline eGFR (CKD-EPI) (p=0.9258), Treatment (p=0.0213), region (5 cat.) (p<0.0001), baseline diabetes status (3 cat.) (p=0.4843), sex (p=0.5829), baseline LVEF (3 cat.) (p=0.8642), baseline use of MRA (p=0.8973) and Treatment by baseline use of MRA interaction (p=0.1191).
***Wald confidence intervals.

Data taken from study 1245.121 only.
LOCF: For a missing value at week 52 the last available post-baseline value before week 52 is imputed.

R.1.2.7.14

Table R.1.2.7.14: 1 Responder analysis (displaying odds ratio) in KCCQ-TSS change from baseline at week 52 of <= -15 points (deterioration) by baseline use of ARNi (Y/N) - RS (LOCF-AD) - 1245.121

Subgroup Description	Placebo	Empa 10mg
Baseline use of ARNi: No		
Number of patients in analysis set	1480	1523
Number of analysed patients, N (%)	1350 (100.0)	1418 (100.0)
Number of patients with endpoint, N (%)	171 (12.7)	156 (11.0)
95% confidence interval*	(11.0, 14.5)	(9.5, 12.7)
Comparison vs Placebo**		
Odds ratio (SE)		0.849 (0.102)
95% confidence interval***		(0.671, 1.073)
p-value		0.1711
Baseline use of ARNi: Yes		
Number of patients in analysis set	387	340
Number of analysed patients, N (%)	359 (100.0)	322 (100.0)
Number of patients with endpoint, N (%)	44 (12.3)	26 (8.1)
95% confidence interval*	(9.3, 16.1)	(5.6, 11.6)
Comparison vs Placebo**		
Odds ratio (SE)		0.626 (0.165)
95% confidence interval***		(0.373, 1.051)
p-value		0.0764

* Wilson confidence intervals.
** Logistic regression includes terms for baseline KCCQ - total symptom score (p<0.0001), age (p=0.3408), baseline eGFR (CKD-EPI) (p<0.0001), Treatment (p=0.0293), region (5 cat.) (p=0.0123), baseline diabetes status (3 cat.) (p=0.8238), sex (p=0.1257), baseline LVEF (3 cat.) (p=0.0419), baseline use of ARNi (p=0.0972) and Treatment by baseline use of ARNi interaction (p=0.2947).
***Wald confidence intervals.

Data taken from study 1245.121 only.
LOCF: For a missing value at week 52 the last available post-baseline value before week 52 is imputed.

Table R.1.2.7.14: 2 Responder analysis (displaying risk ratio) in KCCQ-TSS change from baseline at week 52 of <= -15 points (deterioration) by baseline use of ARNi (Y/N) - RS (LOCF-AD) - 1245.121

Subgroup Description	Placebo	Empa 10mg
Baseline use of ARNi: No		
Number of patients in analysis set	1480	1523
Number of analysed patients, N (%)	1350 (100.0)	1418 (100.0)
Number of patients with endpoint, N (%)	171 (12.7)	156 (11.0)
95% confidence interval*	(11.0, 14.5)	(9.5, 12.7)
Comparison vs Placebo**		
Risk ratio (SE)		0.869 (0.089)
95% confidence interval***		(0.711, 1.061)
p-value		0.1679
Baseline use of ARNi: Yes		
Number of patients in analysis set	387	340
Number of analysed patients, N (%)	359 (100.0)	322 (100.0)
Number of patients with endpoint, N (%)	44 (12.3)	26 (8.1)
95% confidence interval*	(9.3, 16.1)	(5.6, 11.6)
Comparison vs Placebo**		
Risk ratio (SE)		0.663 (0.154)
95% confidence interval***		(0.421, 1.045)
p-value		0.0766

* Wilson confidence intervals.
** Log-linked Poisson model with robust estimate of variance includes terms for baseline KCCQ - total symptom score (p<0.0001), age (p=0.3564), baseline eGFR (CKD-EPI) (p<0.0001), Treatment (p=0.0295), region (5 cat.) (p=0.0164), baseline diabetes status (3 cat.) (p=0.8279), sex (p=0.1213), baseline LVEF (3 cat.) (p=0.0412), baseline use of ARNi (p=0.0928) and Treatment by baseline use of ARNi interaction (p=0.2876).
***Wald confidence intervals.

Data taken from study 1245.121 only.
LOCF: For a missing value at week 52 the last available post-baseline value before week 52 is imputed.

Table R.1.2.7.14: 3 Responder analysis (displaying odds ratio) in KCCQ-TSS change from baseline at week 52 of > -15 points (stability) by baseline use of ARNi (Y/N) - RS (LOCF-AD) - 1245.121

Subgroup Description	Placebo	Empa 10mg
Baseline use of ARNi: No		
Number of patients in analysis set	1480	1523
Number of analysed patients, N (%)	1350 (100.0)	1418 (100.0)
Number of patients with endpoint, N (%)	1179 (87.3)	1262 (89.0)
95% confidence interval*	(85.5, 89.0)	(87.3, 90.5)
Comparison vs Placebo**		
Odds ratio (SE)		1.178 (0.141)
95% confidence interval***		(0.932, 1.490)
p-value		0.1711
Baseline use of ARNi: Yes		
Number of patients in analysis set	387	340
Number of analysed patients, N (%)	359 (100.0)	322 (100.0)
Number of patients with endpoint, N (%)	315 (87.7)	296 (91.9)
95% confidence interval*	(83.9, 90.7)	(88.4, 94.4)
Comparison vs Placebo**		
Odds ratio (SE)		1.597 (0.422)
95% confidence interval***		(0.951, 2.680)
p-value		0.0764

* Wilson confidence intervals.
** Logistic regression includes terms for baseline KCCQ - total symptom score (p<0.0001), age (p=0.3408), baseline eGFR (CKD-EPI) (p<0.0001), Treatment (p=0.0293), region (5 cat.) (p=0.0123), baseline diabetes status (3 cat.) (p=0.8238), sex (p=0.1257), baseline LVEF (3 cat.) (p=0.0419), baseline use of ARNi (p=0.0972) and Treatment by baseline use of ARNi interaction (p=0.2947).
***Wald confidence intervals.

Data taken from study 1245.121 only.
LOCF: For a missing value at week 52 the last available post-baseline value before week 52 is imputed.

Table R.1.2.7.14: 4 Responder analysis (displaying risk ratio) in KCCQ-TSS change from baseline at week 52 of > -15 points (stability) by baseline use of ARNi (Y/N) - RS (LOCF-AD) - 1245.121

Subgroup Description	Placebo	Empa 10mg
Baseline use of ARNi: No		
Number of patients in analysis set	1480	1523
Number of analysed patients, N (%)	1350 (100.0)	1418 (100.0)
Number of patients with endpoint, N (%)	1179 (87.3)	1262 (89.0)
95% confidence interval*	(85.5, 89.0)	(87.3, 90.5)
Comparison vs Placebo**		
Risk ratio (SE)		1.018 (0.014)
95% confidence interval***		(0.991, 1.046)
p-value		0.1906
Baseline use of ARNi: Yes		
Number of patients in analysis set	387	340
Number of analysed patients, N (%)	359 (100.0)	322 (100.0)
Number of patients with endpoint, N (%)	315 (87.7)	296 (91.9)
95% confidence interval*	(83.9, 90.7)	(88.4, 94.4)
Comparison vs Placebo**		
Risk ratio (SE)		1.046 (0.027)
95% confidence interval***		(0.995, 1.099)
p-value		0.0801

* Wilson confidence intervals.
** Log-linked Poisson model with robust estimate of variance includes terms for baseline KCCQ - total symptom score (p<0.0001), age (p=0.4754), baseline eGFR (CKD-EPI) (p<0.0001), Treatment (p=0.0305), region (5 cat.) (p<0.0001), baseline diabetes status (3 cat.) (p=0.8380), sex (p=0.1385), baseline LVEF (3 cat.) (p=0.0274), baseline use of ARNi (p=0.1222) and Treatment by baseline use of ARNi interaction (p=0.3579).
***Wald confidence intervals.

Data taken from study 1245.121 only.
LOCF: For a missing value at week 52 the last available post-baseline value before week 52 is imputed.

Table R.1.2.7.14: 5 Responder analysis (displaying odds ratio) in KCCQ-TSS change from baseline at week 52 of >= 15 points (improvement) by baseline use of ARNi (Y/N) - RS (LOCF-AD) - 1245.121

Subgroup Description	Placebo	Empa 10mg
Baseline use of ARNi: No		
Number of patients in analysis set	1480	1523
Number of analysed patients, N (%)	1350 (100.0)	1418 (100.0)
Number of patients with endpoint, N (%)	320 (23.7)	399 (28.1)
95% confidence interval*	(21.5, 26.0)	(25.9, 30.5)
Comparison vs Placebo**		
Odds ratio (SE)		1.280 (0.133)
95% confidence interval***		(1.045, 1.569)
p-value		0.0171
Baseline use of ARNi: Yes		
Number of patients in analysis set	387	340
Number of analysed patients, N (%)	359 (100.0)	322 (100.0)
Number of patients with endpoint, N (%)	76 (21.2)	67 (20.8)
95% confidence interval*	(17.3, 25.7)	(16.7, 25.6)
Comparison vs Placebo**		
Odds ratio (SE)		1.113 (0.253)
95% confidence interval***		(0.713, 1.737)
p-value		0.6379

* Wilson confidence intervals.
** Logistic regression includes terms for baseline KCCQ - total symptom score (p<0.0001), age (p=0.8445), baseline eGFR (CKD-EPI) (p=0.8496), Treatment (p=0.1559), region (5 cat.) (p<0.0001), baseline diabetes status (3 cat.) (p=0.5793), sex (p=0.2880), baseline LVEF (3 cat.) (p=0.8503), baseline use of ARNi (p=0.1249) and Treatment by baseline use of ARNi interaction (p=0.5746).
***Wald confidence intervals.

Data taken from study 1245.121 only.
LOCF: For a missing value at week 52 the last available post-baseline value before week 52 is imputed.

Table R.1.2.7.14: 6 Responder analysis (displaying risk ratio) in KCCQ-TSS change from baseline at week 52 of >= 15 points (improvement) by baseline use of ARNi (Y/N) - RS (LOCF-AD) - 1245.121

Subgroup Description	Placebo	Empa 10mg
Baseline use of ARNi: No		
Number of patients in analysis set	1480	1523
Number of analysed patients, N (%)	1350 (100.0)	1418 (100.0)
Number of patients with endpoint, N (%)	320 (23.7)	399 (28.1)
95% confidence interval*	(21.5, 26.0)	(25.9, 30.5)
Comparison vs Placebo**		
Risk ratio (SE)		1.106 (0.066)
95% confidence interval***		(0.984, 1.243)
p-value		0.0899
Baseline use of ARNi: Yes		
Number of patients in analysis set	387	340
Number of analysed patients, N (%)	359 (100.0)	322 (100.0)
Number of patients with endpoint, N (%)	76 (21.2)	67 (20.8)
95% confidence interval*	(17.3, 25.7)	(16.7, 25.6)
Comparison vs Placebo**		
Risk ratio (SE)		1.066 (0.147)
95% confidence interval***		(0.813, 1.397)
p-value		0.6439

* Wilson confidence intervals.
** Log-linked Poisson model with robust estimate of variance includes terms for baseline KCCQ - total symptom score (p<0.0001), age (p=0.9735), baseline eGFR (CKD-EPI) (p=0.9544), Treatment (p=0.2723), region (5 cat.) (p<0.0001), baseline diabetes status (3 cat.) (p=0.4568), sex (p=0.6154), baseline LVEF (3 cat.) (p=0.9320), baseline use of ARNi (p=0.0746) and Treatment by baseline use of ARNi interaction (p=0.8051).
***Wald confidence intervals.

Data taken from study 1245.121 only.
LOCF: For a missing value at week 52 the last available post-baseline value before week 52 is imputed.

R.1.2.7.15

R.1.2.7.15 Subgroup analysis by bl. LVEF (<= 30%, >30% -<= 35% , > 35%)

Table R.1.2.7.15: 1 Responder analysis (displaying odds ratio) in KCCQ-TSS change from baseline at week 52 of <= -15 points (deterioration) by baseline LVEF (3 cat.) - RS (LOCF-AD) - 1245.121

Subgroup Description	Placebo	Empa 10mg
Baseline LVEF (3 cat.): <=30		
Number of patients in analysis set	1392	1337
Number of analysed patients, N (%)	1272 (100.0)	1245 (100.0)
Number of patients with endpoint, N (%)	169 (13.3)	133 (10.7)
95% confidence interval*	(11.5, 15.3)	(9.1, 12.5)
Comparison vs Placebo**		
Odds ratio (SE)		0.769 (0.097)
95% confidence interval***		(0.602, 0.984)
p-value		0.0367
Baseline LVEF (3 cat.): >30 to <=35		
Number of patients in analysis set	361	398
Number of analysed patients, N (%)	333 (100.0)	375 (100.0)
Number of patients with endpoint, N (%)	33 (9.9)	36 (9.6)
95% confidence interval*	(7.1, 13.6)	(7.0, 13.0)
Comparison vs Placebo**		
Odds ratio (SE)		0.982 (0.252)
95% confidence interval***		(0.593, 1.625)
p-value		0.9435

* Wilson confidence intervals.
** Logistic regression includes terms for baseline KCCQ - total symptom score (p<0.0001), age (p=0.3235), baseline eGFR (CKD-EPI) (p<0.0001), Treatment (p=0.3961), region (5 cat.) (p=0.0130), baseline diabetes status (3 cat.) (p=0.8266), sex (p=0.1363), baseline LVEF (3 cat.) (p=0.0513) and Treatment by baseline LVEF (3 cat.) interaction (p=0.6884).
***Wald confidence intervals.

Data taken from study 1245.121 only.
LOCF: For a missing value at week 52 the last available post-baseline value before week 52 is imputed.

Table R.1.2.7.15: 1 Responder analysis (displaying odds ratio) in KCCQ-TSS change from baseline at week 52 of <= -15 points (deterioration) by baseline LVEF (3 cat.) - RS (LOCF-AD) - 1245.121

Subgroup Description	Placebo	Empa 10mg
Baseline LVEF (3 cat.): >35		
Number of patients in analysis set	114	128
Number of analysed patients, N (%)	104 (100.0)	120 (100.0)
Number of patients with endpoint, N (%)	13 (12.5)	13 (10.8)
95% confidence interval*	(7.5, 20.2)	(6.4, 17.7)
Comparison vs Placebo**		
Odds ratio (SE)		0.857 (0.364)
95% confidence interval***		(0.373, 1.970)
p-value		0.7169

* Wilson confidence intervals.
** Logistic regression includes terms for baseline KCCQ - total symptom score (p<0.0001), age (p=0.3235), baseline eGFR (CKD-EPI) (p<0.0001), Treatment (p=0.3961), region (5 cat.) (p=0.0130), baseline diabetes status (3 cat.) (p=0.8266), sex (p=0.1363), baseline LVEF (3 cat.) (p=0.0513) and Treatment by baseline LVEF (3 cat.) interaction (p=0.6884).
***Wald confidence intervals.

Data taken from study 1245.121 only.
LOCF: For a missing value at week 52 the last available post-baseline value before week 52 is imputed.

Table R.1.2.7.15: 2 Responder analysis (displaying risk ratio) in KCCQ-TSS change from baseline at week 52 of <= -15 points (deterioration) by baseline LVEF (3 cat.) - RS (LOCF-AD) - 1245.121

Subgroup Description	Placebo	Empa 10mg
Baseline LVEF (3 cat.): <=30		
Number of patients in analysis set	1392	1337
Number of analysed patients, N (%)	1272 (100.0)	1245 (100.0)
Number of patients with endpoint, N (%)	169 (13.3)	133 (10.7)
95% confidence interval*	(11.5, 15.3)	(9.1, 12.5)
Comparison vs Placebo**		
Risk ratio (SE)		0.799 (0.085)
95% confidence interval***		(0.648, 0.985)
p-value		0.0357
Baseline LVEF (3 cat.): >30 to <=35		
Number of patients in analysis set	361	398
Number of analysed patients, N (%)	333 (100.0)	375 (100.0)
Number of patients with endpoint, N (%)	33 (9.9)	36 (9.6)
95% confidence interval*	(7.1, 13.6)	(7.0, 13.0)
Comparison vs Placebo**		
Risk ratio (SE)		0.983 (0.221)
95% confidence interval***		(0.633, 1.528)
p-value		0.9399

* Wilson confidence intervals.
** Log-linked Poisson model with robust estimate of variance includes terms for baseline KCCQ - total symptom score (p<0.0001), age (p=0.3401), baseline eGFR (CKD-EPI) (p<0.0001), Treatment (p=0.4020), region (5 cat.) (p=0.0172), baseline diabetes status (3 cat.) (p=0.8283), sex (p=0.1321), baseline LVEF (3 cat.) (p=0.0517) and Treatment by baseline LVEF (3 cat.) interaction (p=0.6986).
***Wald confidence intervals.

Data taken from study 1245.121 only.
LOCF: For a missing value at week 52 the last available post-baseline value before week 52 is imputed.

Table R.1.2.7.15: 2 Responder analysis (displaying risk ratio) in KCCQ-TSS change from baseline at week 52 of <= -15 points (deterioration) by baseline LVEF (3 cat.) - RS (LOCF-AD) - 1245.121

Subgroup Description	Placebo	Empa 10mg
Baseline LVEF (3 cat.): >35		
Number of patients in analysis set	114	128
Number of analysed patients, N (%)	104 (100.0)	120 (100.0)
Number of patients with endpoint, N (%)	13 (12.5)	13 (10.8)
95% confidence interval*	(7.5, 20.2)	(6.4, 17.7)
Comparison vs Placebo**		
Risk ratio (SE)		0.878 (0.322)
95% confidence interval***		(0.427, 1.803)
p-value		0.7226

* Wilson confidence intervals.
** Log-linked Poisson model with robust estimate of variance includes terms for baseline KCCQ - total symptom score (p<0.0001), age (p=0.3401), baseline eGFR (CKD-EPI) (p<0.0001), Treatment (p=0.4020), region (5 cat.) (p=0.0172), baseline diabetes status (3 cat.) (p=0.8283), sex (p=0.1321), baseline LVEF (3 cat.) (p=0.0517) and Treatment by baseline LVEF (3 cat.) interaction (p=0.6986).
***Wald confidence intervals.

Data taken from study 1245.121 only.
LOCF: For a missing value at week 52 the last available post-baseline value before week 52 is imputed.

Table R.1.2.7.15: 3 Responder analysis (displaying odds ratio) in KCCQ-TSS change from baseline at week 52 of > -15 points (stability) by baseline LVEF (3 cat.) - RS (LOCF-AD) - 1245.121

Subgroup Description	Placebo	Empa 10mg
Baseline LVEF (3 cat.): <=30		
Number of patients in analysis set	1392	1337
Number of analysed patients, N (%)	1272 (100.0)	1245 (100.0)
Number of patients with endpoint, N (%)	1103 (86.7)	1112 (89.3)
95% confidence interval*	(84.7, 88.5)	(87.5, 90.9)
Comparison vs Placebo**		
Odds ratio (SE)		1.300 (0.163)
95% confidence interval***		(1.016, 1.662)
p-value		0.0367
Baseline LVEF (3 cat.): >30 to <=35		
Number of patients in analysis set	361	398
Number of analysed patients, N (%)	333 (100.0)	375 (100.0)
Number of patients with endpoint, N (%)	300 (90.1)	339 (90.4)
95% confidence interval*	(86.4, 92.9)	(87.0, 93.0)
Comparison vs Placebo**		
Odds ratio (SE)		1.018 (0.262)
95% confidence interval***		(0.615, 1.685)
p-value		0.9435

* Wilson confidence intervals.
** Logistic regression includes terms for baseline KCCQ - total symptom score (p<0.0001), age (p=0.3235), baseline eGFR (CKD-EPI) (p<0.0001), Treatment (p=0.3961), region (5 cat.) (p=0.0130), baseline diabetes status (3 cat.) (p=0.8266), sex (p=0.1363), baseline LVEF (3 cat.) (p=0.0513) and Treatment by baseline LVEF (3 cat.) interaction (p=0.6884).
***Wald confidence intervals.

Data taken from study 1245.121 only.
LOCF: For a missing value at week 52 the last available post-baseline value before week 52 is imputed.

Table R.1.2.7.15: 3 Responder analysis (displaying odds ratio) in KCCQ-TSS change from baseline at week 52 of > -15 points (stability) by baseline LVEF (3 cat.) - RS (LOCF-AD) - 1245.121

Subgroup Description	Placebo	Empa 10mg
Baseline LVEF (3 cat.): >35		
Number of patients in analysis set	114	128
Number of analysed patients, N (%)	104 (100.0)	120 (100.0)
Number of patients with endpoint, N (%)	91 (87.5)	107 (89.2)
95% confidence interval*	(79.8, 92.5)	(82.3, 93.6)
Comparison vs Placebo**		
Odds ratio (SE)		1.166 (0.495)
95% confidence interval***		(0.508, 2.680)
p-value		0.7169

* Wilson confidence intervals.
** Logistic regression includes terms for baseline KCCQ - total symptom score (p<0.0001), age (p=0.3235), baseline eGFR (CKD-EPI) (p<0.0001), Treatment (p=0.3961), region (5 cat.) (p=0.0130), baseline diabetes status (3 cat.) (p=0.8266), sex (p=0.1363), baseline LVEF (3 cat.) (p=0.0513) and Treatment by baseline LVEF (3 cat.) interaction (p=0.6884).
***Wald confidence intervals.

Data taken from study 1245.121 only.
LOCF: For a missing value at week 52 the last available post-baseline value before week 52 is imputed.

Table R.1.2.7.15: 4 Responder analysis (displaying risk ratio) in KCCQ-TSS change from baseline at week 52 of > -15 points (stability) by baseline LVEF (3 cat.) - RS (LOCF-AD) - 1245.121

Subgroup Description	Placebo	Empa 10mg
Baseline LVEF (3 cat.): <=30		
Number of patients in analysis set	1392	1337
Number of analysed patients, N (%)	1272 (100.0)	1245 (100.0)
Number of patients with endpoint, N (%)	1103 (86.7)	1112 (89.3)
95% confidence interval*	(84.7, 88.5)	(87.5, 90.9)
Comparison vs Placebo**		
Risk ratio (SE)		1.030 (0.015)
95% confidence interval***		(1.001, 1.060)
p-value		0.0401
Baseline LVEF (3 cat.): >30 to <=35		
Number of patients in analysis set	361	398
Number of analysed patients, N (%)	333 (100.0)	375 (100.0)
Number of patients with endpoint, N (%)	300 (90.1)	339 (90.4)
95% confidence interval*	(86.4, 92.9)	(87.0, 93.0)
Comparison vs Placebo**		
Risk ratio (SE)		1.001 (0.024)
95% confidence interval***		(0.954, 1.050)
p-value		0.9825

* Wilson confidence intervals.
** Log-linked Poisson model with robust estimate of variance includes terms for baseline KCCQ - total symptom score (p<0.0001), age (p=0.4463), baseline eGFR (CKD-EPI) (p<0.0001), Treatment (p=0.4023), region (5 cat.) (p<0.0001), baseline diabetes status (3 cat.) (p=0.8551), sex (p=0.1469), baseline LVEF (3 cat.) (p=0.0287) and Treatment by baseline LVEF (3 cat.) interaction (p=0.5848).
***Wald confidence intervals.

Data taken from study 1245.121 only.
LOCF: For a missing value at week 52 the last available post-baseline value before week 52 is imputed.

Table R.1.2.7.15: 4 Responder analysis (displaying risk ratio) in KCCQ-TSS change from baseline at week 52 of > -15 points (stability) by baseline LVEF (3 cat.) - RS (LOCF-AD) - 1245.121

Subgroup Description	Placebo	Empa 10mg
Baseline LVEF (3 cat.): >35		
Number of patients in analysis set	114	128
Number of analysed patients, N (%)	104 (100.0)	120 (100.0)
Number of patients with endpoint, N (%)	91 (87.5)	107 (89.2)
95% confidence interval*	(79.8, 92.5)	(82.3, 93.6)
Comparison vs Placebo**		
Risk ratio (SE)		1.017 (0.049)
95% confidence interval***		(0.925, 1.118)
p-value		0.7295

* Wilson confidence intervals.
** Log-linked Poisson model with robust estimate of variance includes terms for baseline KCCQ - total symptom score (p<0.0001), age (p=0.4463), baseline eGFR (CKD-EPI) (p<0.0001), Treatment (p=0.4023), region (5 cat.) (p<0.0001), baseline diabetes status (3 cat.) (p=0.8551), sex (p=0.1469), baseline LVEF (3 cat.) (p=0.0287) and Treatment by baseline LVEF (3 cat.) interaction (p=0.5848).
***Wald confidence intervals.

Data taken from study 1245.121 only.
LOCF: For a missing value at week 52 the last available post-baseline value before week 52 is imputed.

Table R.1.2.7.15: 5 Responder analysis (displaying odds ratio) in KCCQ-TSS change from baseline at week 52 of >= 15 points (improvement) by baseline LVEF (3 cat.) - RS (LOCF-AD) - 1245.121

Subgroup Description	Placebo	Empa 10mg
Baseline LVEF (3 cat.): <=30		
Number of patients in analysis set	1392	1337
Number of analysed patients, N (%)	1272 (100.0)	1245 (100.0)
Number of patients with endpoint, N (%)	295 (23.2)	337 (27.1)
95% confidence interval*	(21.0, 25.6)	(24.7, 29.6)
Comparison vs Placebo**		
Odds ratio (SE)		1.258 (0.138)
95% confidence interval***		(1.014, 1.561)
p-value		0.0368
Baseline LVEF (3 cat.): >30 to <=35		
Number of patients in analysis set	361	398
Number of analysed patients, N (%)	333 (100.0)	375 (100.0)
Number of patients with endpoint, N (%)	77 (23.1)	93 (24.8)
95% confidence interval*	(18.9, 27.9)	(20.7, 29.4)
Comparison vs Placebo**		
Odds ratio (SE)		1.106 (0.231)
95% confidence interval***		(0.734, 1.667)
p-value		0.6287

* Wilson confidence intervals.
** Logistic regression includes terms for baseline KCCQ - total symptom score (p<0.0001), age (p=0.8804), baseline eGFR (CKD-EPI) (p=0.8386), Treatment (p=0.0382), region (5 cat.) (p<0.0001), baseline diabetes status (3 cat.) (p=0.6116), sex (p=0.2555), baseline LVEF (3 cat.) (p=0.8288) and Treatment by baseline LVEF (3 cat.) interaction (p=0.5268).
***Wald confidence intervals.

Data taken from study 1245.121 only.
LOCF: For a missing value at week 52 the last available post-baseline value before week 52 is imputed.

Table R.1.2.7.15: 5 Responder analysis (displaying odds ratio) in KCCQ-TSS change from baseline at week 52 of >= 15 points (improvement) by baseline LVEF (3 cat.) - RS (LOCF-AD) - 1245.121

Subgroup Description	Placebo	Empa 10mg
Baseline LVEF (3 cat.): >35		
Number of patients in analysis set	114	128
Number of analysed patients, N (%)	104 (100.0)	120 (100.0)
Number of patients with endpoint, N (%)	24 (23.1)	36 (30.0)
95% confidence interval*	(16.0, 32.0)	(22.5, 38.7)
Comparison vs Placebo**		
Odds ratio (SE)		1.795 (0.670)
95% confidence interval***		(0.864, 3.729)
p-value		0.1171

* Wilson confidence intervals.
** Logistic regression includes terms for baseline KCCQ - total symptom score (p<0.0001), age (p=0.8804), baseline eGFR (CKD-EPI) (p=0.8386), Treatment (p=0.0382), region (5 cat.) (p<0.0001), baseline diabetes status (3 cat.) (p=0.6116), sex (p=0.2555), baseline LVEF (3 cat.) (p=0.8288) and Treatment by baseline LVEF (3 cat.) interaction (p=0.5268).
***Wald confidence intervals.

Data taken from study 1245.121 only.
LOCF: For a missing value at week 52 the last available post-baseline value before week 52 is imputed.

Table R.1.2.7.15: 6 Responder analysis (displaying risk ratio) in KCCQ-TSS change from baseline at week 52 of >= 15 points (improvement) by baseline LVEF (3 cat.) - RS (LOCF-AD) - 1245.121

Subgroup Description	Placebo	Empa 10mg
Baseline LVEF (3 cat.): <=30		
Number of patients in analysis set	1392	1337
Number of analysed patients, N (%)	1272 (100.0)	1245 (100.0)
Number of patients with endpoint, N (%)	295 (23.2)	337 (27.1)
95% confidence interval*	(21.0, 25.6)	(24.7, 29.6)
Comparison vs Placebo**		
Risk ratio (SE)		1.113 (0.071)
95% confidence interval***		(0.981, 1.261)
p-value		0.0954
Baseline LVEF (3 cat.): >30 to <=35		
Number of patients in analysis set	361	398
Number of analysed patients, N (%)	333 (100.0)	375 (100.0)
Number of patients with endpoint, N (%)	77 (23.1)	93 (24.8)
95% confidence interval*	(18.9, 27.9)	(20.7, 29.4)
Comparison vs Placebo**		
Risk ratio (SE)		1.016 (0.122)
95% confidence interval***		(0.804, 1.285)
p-value		0.8924

* Wilson confidence intervals.
** Log-linked Poisson model with robust estimate of variance includes terms for baseline KCCQ - total symptom score (p<0.0001), age (p=0.9908), baseline eGFR (CKD-EPI) (p=0.9523), Treatment (p=0.1199), region (5 cat.) (p<0.0001), baseline diabetes status (3 cat.) (p=0.4855), sex (p=0.5535), baseline LVEF (3 cat.) (p=0.8640) and Treatment by baseline LVEF (3 cat.) interaction (p=0.5654).
***Wald confidence intervals.

Data taken from study 1245.121 only.
LOCF: For a missing value at week 52 the last available post-baseline value before week 52 is imputed.

Table R.1.2.7.15: 6 Responder analysis (displaying risk ratio) in KCCQ-TSS change from baseline at week 52 of >= 15 points (improvement) by baseline LVEF (3 cat.) - RS (LOCF-AD) - 1245.121

Subgroup Description	Placebo	Empa 10mg
Baseline LVEF (3 cat.): >35		
Number of patients in analysis set	114	128
Number of analysed patients, N (%)	104 (100.0)	120 (100.0)
Number of patients with endpoint, N (%)	24 (23.1)	36 (30.0)
95% confidence interval*	(16.0, 32.0)	(22.5, 38.7)
Comparison vs Placebo**		
Risk ratio (SE)		1.308 (0.277)
95% confidence interval***		(0.864, 1.982)
p-value		0.2044

* Wilson confidence intervals.
** Log-linked Poisson model with robust estimate of variance includes terms for baseline KCCQ - total symptom score (p<0.0001), age (p=0.9908), baseline eGFR (CKD-EPI) (p=0.9523), Treatment (p=0.1199), region (5 cat.) (p<0.0001), baseline diabetes status (3 cat.) (p=0.4855), sex (p=0.5535), baseline LVEF (3 cat.) (p=0.8640) and Treatment by baseline LVEF (3 cat.) interaction (p=0.5654).
***Wald confidence intervals.

Data taken from study 1245.121 only.
LOCF: For a missing value at week 52 the last available post-baseline value before week 52 is imputed.

R.1.2.7.16

R.1.2.7.16 Subgroup analysis by bl. NTproBNP </>= median (median based on total patients)

Table R.1.2.7.16: 1 Responder analysis (displaying odds ratio) in KCCQ-TSS change from baseline at week 52 of <= -15 points (deterioration) by bl. NTproBNP (<median, >= median) (median based on total patients) - RS (LOCF-AD) - 1245.121

Subgroup Description	Placebo	Empa 10mg
Baseline NTproBNP (<median, >= median): < median		
Number of patients in analysis set	920	942
Number of analysed patients, N (%)	866 (100.0)	886 (100.0)
Number of patients with endpoint, N (%)	93 (10.7)	84 (9.5)
95% confidence interval*	(8.8, 13.0)	(7.7, 11.6)
Comparison vs Placebo**		
Odds ratio (SE)		0.872 (0.140)
95% confidence interval***		(0.636, 1.195)
p-value		0.3939
Baseline NTproBNP (<median, >= median): >= median		
Number of patients in analysis set	946	920
Number of analysed patients, N (%)	843 (100.0)	854 (100.0)
Number of patients with endpoint, N (%)	122 (14.5)	98 (11.5)
95% confidence interval*	(12.3, 17.0)	(9.5, 13.8)
Comparison vs Placebo**		
Odds ratio (SE)		0.763 (0.113)
95% confidence interval***		(0.571, 1.019)
p-value		0.0669

* Wilson confidence intervals.
** Logistic regression includes terms for baseline KCCQ - total symptom score (p<0.0001), age (p=0.3735), baseline eGFR (CKD-EPI) (p=0.0001), Treatment (p=0.0617), region (5 cat.) (p=0.0093), baseline diabetes status (3 cat.) (p=0.8527), sex (p=0.1339), baseline LVEF (3 cat.) (p=0.0390), baseline NTproBNP (<median, >= median) (p=0.0248) and Treatment by baseline NTproBNP (<median, >= median) interaction (p=0.5400).
***Wald confidence intervals.
2 patients were excluded as the subgroup variable was missing.

Data taken from study 1245.121 only.
LOCF: For a missing value at week 52 the last available post-baseline value before week 52 is imputed.
Median: 1910 [pg/mL]

Table R.1.2.7.16: 2 Responder analysis (displaying risk ratio) in KCCQ-TSS change from baseline at week 52 of <= -15 points (deterioration) by bl. NTproBNP (<median, >= median) (median based on total patients) - RS (LOCF-AD) - 1245.121

Subgroup Description	Placebo	Empa 10mg
Baseline NTproBNP (<median, >= median): < median		
Number of patients in analysis set	920	942
Number of analysed patients, N (%)	866 (100.0)	886 (100.0)
Number of patients with endpoint, N (%)	93 (10.7)	84 (9.5)
95% confidence interval*	(8.8, 13.0)	(7.7, 11.6)
Comparison vs Placebo**		
Risk ratio (SE)		0.887 (0.125)
95% confidence interval***		(0.673, 1.168)
p-value		0.3921
Baseline NTproBNP (<median, >= median): >= median		
Number of patients in analysis set	946	920
Number of analysed patients, N (%)	843 (100.0)	854 (100.0)
Number of patients with endpoint, N (%)	122 (14.5)	98 (11.5)
95% confidence interval*	(12.3, 17.0)	(9.5, 13.8)
Comparison vs Placebo**		
Risk ratio (SE)		0.795 (0.099)
95% confidence interval***		(0.623, 1.014)
p-value		0.0646

* Wilson confidence intervals.
** Log-linked Poisson model with robust estimate of variance includes terms for baseline KCCQ - total symptom score (p<0.0001), age (p=0.3916), baseline eGFR (CKD-EPI) (p=0.0002), Treatment (p=0.0622), region (5 cat.) (p=0.0125), baseline diabetes status (3 cat.) (p=0.8528), sex (p=0.1306), baseline LVEF (3 cat.) (p=0.0388), baseline NTproBNP (<median, >= median) (p=0.0282) and Treatment by baseline NTproBNP (<median, >= median) interaction (p=0.5586).
***Wald confidence intervals.
2 patients were excluded as the subgroup variable was missing.

Data taken from study 1245.121 only.
LOCF: For a missing value at week 52 the last available post-baseline value before week 52 is imputed.
Median: 1910 [pg/mL]

Table R.1.2.7.16: 3 Responder analysis (displaying odds ratio) in KCCQ-TSS change from baseline at week 52 of > -15 points (stability) by bl. NTproBNP (<median, >= median) (median based on total patients) - RS (LOCF-AD) - 1245.121

Subgroup Description	Placebo	Empa 10mg
Baseline NTproBNP (<median, >= median): < median		
Number of patients in analysis set	920	942
Number of analysed patients, N (%)	866 (100.0)	886 (100.0)
Number of patients with endpoint, N (%)	773 (89.3)	802 (90.5)
95% confidence interval*	(87.0, 91.2)	(88.4, 92.3)
Comparison vs Placebo**		
Odds ratio (SE)		1.147 (0.185)
95% confidence interval***		(0.837, 1.572)
p-value		0.3939
Baseline NTproBNP (<median, >= median): >= median		
Number of patients in analysis set	946	920
Number of analysed patients, N (%)	843 (100.0)	854 (100.0)
Number of patients with endpoint, N (%)	721 (85.5)	756 (88.5)
95% confidence interval*	(83.0, 87.7)	(86.2, 90.5)
Comparison vs Placebo**		
Odds ratio (SE)		1.311 (0.194)
95% confidence interval***		(0.981, 1.752)
p-value		0.0669

* Wilson confidence intervals.
** Logistic regression includes terms for baseline KCCQ - total symptom score (p<0.0001), age (p=0.3735), baseline eGFR (CKD-EPI) (p=0.0001), Treatment (p=0.0617), region (5 cat.) (p=0.0093), baseline diabetes status (3 cat.) (p=0.8527), sex (p=0.1339), baseline LVEF (3 cat.) (p=0.0390), baseline NTproBNP (<median, >= median) (p=0.0248) and Treatment by baseline NTproBNP (<median, >= median) interaction (p=0.5400).
***Wald confidence intervals.
2 patients were excluded as the subgroup variable was missing.

Data taken from study 1245.121 only.
LOCF: For a missing value at week 52 the last available post-baseline value before week 52 is imputed.
Median: 1910 [pg/mL]

Table R.1.2.7.16: 4 Responder analysis (displaying risk ratio) in KCCQ-TSS change from baseline at week 52 of > -15 points (stability) by bl. NTproBNP (<median, >= median) (median based on total patients) - RS (LOCF-AD) - 1245.121

Subgroup Description	Placebo	Empa 10mg
Baseline NTproBNP (<median, >= median): < median		
Number of patients in analysis set	920	942
Number of analysed patients, N (%)	866 (100.0)	886 (100.0)
Number of patients with endpoint, N (%)	773 (89.3)	802 (90.5)
95% confidence interval*	(87.0, 91.2)	(88.4, 92.3)
Comparison vs Placebo**		
Risk ratio (SE)		1.014 (0.016)
95% confidence interval***		(0.983, 1.046)
p-value		0.3819
Baseline NTproBNP (<median, >= median): >= median		
Number of patients in analysis set	946	920
Number of analysed patients, N (%)	843 (100.0)	854 (100.0)
Number of patients with endpoint, N (%)	721 (85.5)	756 (88.5)
95% confidence interval*	(83.0, 87.7)	(86.2, 90.5)
Comparison vs Placebo**		
Risk ratio (SE)		1.032 (0.019)
95% confidence interval***		(0.996, 1.071)
p-value		0.0843

* Wilson confidence intervals.
** Log-linked Poisson model with robust estimate of variance includes terms for baseline KCCQ - total symptom score (p<0.0001), age (p=0.4980), baseline eGFR (CKD-EPI) (p=0.0003), Treatment (p=0.0600), region (5 cat.) (p<0.0001), baseline diabetes status (3 cat.) (p=0.8750), sex (p=0.1409), baseline LVEF (3 cat.) (p=0.0264), baseline NTproBNP (<median, >= median) (p=0.0171) and Treatment by baseline NTproBNP (<median, >= median) interaction (p=0.4571).
***Wald confidence intervals.
2 patients were excluded as the subgroup variable was missing.

Data taken from study 1245.121 only.
LOCF: For a missing value at week 52 the last available post-baseline value before week 52 is imputed.
Median: 1910 [pg/mL]

Table R.1.2.7.16: 5 Responder analysis (displaying odds ratio) in KCCQ-TSS change from baseline at week 52 of >= 15 points (improvement) by bl. NTproBNP (<median, >= median) (median based on total patients) - RS (LOCF-AD) - 1245.121

Subgroup Description	Placebo	Empa 10mg
Baseline NTproBNP (<median, >= median): < median		
Number of patients in analysis set	920	942
Number of analysed patients, N (%)	866 (100.0)	886 (100.0)
Number of patients with endpoint, N (%)	185 (21.4)	211 (23.8)
95% confidence interval*	(18.8, 24.2)	(21.1, 26.7)
Comparison vs Placebo**		
Odds ratio (SE)		1.250 (0.168)
95% confidence interval***		(0.960, 1.626)
p-value		0.0970
Baseline NTproBNP (<median, >= median): >= median		
Number of patients in analysis set	946	920
Number of analysed patients, N (%)	843 (100.0)	854 (100.0)
Number of patients with endpoint, N (%)	211 (25.0)	255 (29.9)
95% confidence interval*	(22.2, 28.1)	(26.9, 33.0)
Comparison vs Placebo**		
Odds ratio (SE)		1.258 (0.166)
95% confidence interval***		(0.971, 1.630)
p-value		0.0822

* Wilson confidence intervals.
** Logistic regression includes terms for baseline KCCQ - total symptom score (p<0.0001), age (p=0.8971), baseline eGFR (CKD-EPI) (p=0.8103), Treatment (p=0.0163), region (5 cat.) (p<0.0001), baseline diabetes status (3 cat.) (p=0.6090), sex (p=0.2630), baseline LVEF (3 cat.) (p=0.7840), baseline NTproBNP (<median, >= median) (p=0.8194) and Treatment by baseline NTproBNP (<median, >= median) interaction (p=0.9721).
***Wald confidence intervals.
2 patients were excluded as the subgroup variable was missing.

Data taken from study 1245.121 only.
LOCF: For a missing value at week 52 the last available post-baseline value before week 52 is imputed.
Median: 1910 [pg/mL]

Table R.1.2.7.16: 6 Responder analysis (displaying risk ratio) in KCCQ-TSS change from baseline at week 52 of >= 15 points (improvement) by bl. NTproBNP (<median, >= median) (median based on total patients) - RS (LOCF-AD) - 1245.121

Subgroup Description	Placebo	Empa 10mg
Baseline NTproBNP (<median, >= median): < median		
Number of patients in analysis set	920	942
Number of analysed patients, N (%)	866 (100.0)	886 (100.0)
Number of patients with endpoint, N (%)	185 (21.4)	211 (23.8)
95% confidence interval*	(18.8, 24.2)	(21.1, 26.7)
Comparison vs Placebo**		
Risk ratio (SE)		1.108 (0.089)
95% confidence interval***		(0.946, 1.298)
p-value		0.2043
Baseline NTproBNP (<median, >= median): >= median		
Number of patients in analysis set	946	920
Number of analysed patients, N (%)	843 (100.0)	854 (100.0)
Number of patients with endpoint, N (%)	211 (25.0)	255 (29.9)
95% confidence interval*	(22.2, 28.1)	(26.9, 33.0)
Comparison vs Placebo**		
Risk ratio (SE)		1.103 (0.082)
95% confidence interval***		(0.954, 1.275)
p-value		0.1867

* Wilson confidence intervals.
** Log-linked Poisson model with robust estimate of variance includes terms for baseline KCCQ - total symptom score (p<0.0001), age (p=0.9470), baseline eGFR (CKD-EPI) (p=0.9683), Treatment (p=0.0675), region (5 cat.) (p<0.0001), baseline diabetes status (3 cat.) (p=0.4915), sex (p=0.5339), baseline LVEF (3 cat.) (p=0.8373), baseline NTproBNP (<median, >= median) (p=0.4550) and Treatment by baseline NTproBNP (<median, >= median) interaction (p=0.9656).
***Wald confidence intervals.
2 patients were excluded as the subgroup variable was missing.

Data taken from study 1245.121 only.
LOCF: For a missing value at week 52 the last available post-baseline value before week 52 is imputed.
Median: 1910 [pg/mL]

R.1.2.8 KCCQ Overall Summary Score responder analysis (5 points)

R.1.2.8.1

Table R.1.2.8.1: 1 Responder analysis (displaying odds ratio) in KCCQ-OSS change from baseline at week 52 of <= -5 points (deterioration) - RS (LOCF-AD) - 1245.121

	Placebo	Empa 10mg
Number of patients in analysis set	1867	1863
Number of analysed patients, N (%)	1709 (100.0)	1740 (100.0)
Number of patients with endpoint, N (%)	424 (24.8)	371 (21.3)
95% confidence interval*	(22.8, 26.9)	(19.5, 23.3)
Comparison vs Placebo**		
Odds ratio (SE)		0.808 (0.067)
95% confidence interval***		(0.687, 0.950)
p-value		0.0098

* Wilson confidence intervals.
** Logistic regression includes terms for baseline KCCQ - overall summary score (p<0.0001), age (p=0.0934), baseline eGFR (CKD-EPI) (p=0.0205), Treatment (p=0.0098), region (5 cat.) (p<0.0001), baseline diabetes status (3 cat.) (p=0.4549), sex (p=0.1090) and baseline LVEF (3 cat.) (p=0.9843).
***Wald confidence intervals.

Data taken from study 1245.121 only.
LOCF: For a missing value at week 52 the last available post-baseline value before week 52 is imputed.

Table R.1.2.8.1: 2 Responder analysis (displaying risk ratio) in KCCQ-OSS change from baseline at week 52 of <= -5 points (deterioration) - RS (LOCF-AD) - 1245.121

	Placebo	Empa 10mg
Number of patients in analysis set	1867	1863
Number of analysed patients, N (%)	1709 (100.0)	1740 (100.0)
Number of patients with endpoint, N (%)	424 (24.8)	371 (21.3)
95% confidence interval*	(22.8, 26.9)	(19.5, 23.3)
Comparison vs Placebo**		
Risk ratio (SE)		0.853 (0.052)
95% confidence interval***		(0.757, 0.962)
p-value		0.0096

* Wilson confidence intervals.
** Log-linked Poisson model with robust estimate of variance includes terms for baseline KCCQ - overall summary score (p<0.0001), age (p=0.0931), baseline eGFR (CKD-EPI) (p=0.0211), Treatment (p=0.0096), region (5 cat.) (p<0.0001), baseline diabetes status (3 cat.) (p=0.4610), sex (p=0.1156) and baseline LVEF (3 cat.) (p=0.9844).
***Wald confidence intervals.

Data taken from study 1245.121 only.
LOCF: For a missing value at week 52 the last available post-baseline value before week 52 is imputed.

Table R.1.2.8.1: 3 Responder analysis (displaying odds ratio) in KCCQ-OSS change from baseline at week 52 of > -5 points (stability) - RS (LOCF-AD) - 1245.121

	Placebo	Empa 10mg
Number of patients in analysis set	1867	1863
Number of analysed patients, N (%)	1709 (100.0)	1740 (100.0)
Number of patients with endpoint, N (%)	1285 (75.2)	1369 (78.7)
95% confidence interval*	(73.1, 77.2)	(76.7, 80.5)
Comparison vs Placebo**		
Odds ratio (SE)		1.237 (0.102)
95% confidence interval***		(1.053, 1.455)
p-value		0.0098

* Wilson confidence intervals.
** Logistic regression includes terms for baseline KCCQ - overall summary score (p<0.0001), age (p=0.0934), baseline eGFR (CKD-EPI) (p=0.0205), Treatment (p=0.0098), region (5 cat.) (p<0.0001), baseline diabetes status (3 cat.) (p=0.4549), sex (p=0.1090) and baseline LVEF (3 cat.) (p=0.9843).
***Wald confidence intervals.

Data taken from study 1245.121 only.
LOCF: For a missing value at week 52 the last available post-baseline value before week 52 is imputed.

Table R.1.2.8.1: 4 Responder analysis (displaying risk ratio) in KCCQ-OSS change from baseline at week 52 of > -5 points (stability) - RS (LOCF-AD) - 1245.121

	Placebo	Empa 10mg
Number of patients in analysis set	1867	1863
Number of analysed patients, N (%)	1709 (100.0)	1740 (100.0)
Number of patients with endpoint, N (%)	1285 (75.2)	1369 (78.7)
95% confidence interval*	(73.1, 77.2)	(76.7, 80.5)
Comparison vs Placebo**		
Risk ratio (SE)		1.048 (0.019)
95% confidence interval***		(1.011, 1.086)
p-value		0.0113

* Wilson confidence intervals.
** Log-linked Poisson model with robust estimate of variance includes terms for baseline KCCQ - overall summary score (p<0.0001), age (p=0.1228), baseline eGFR (CKD-EPI) (p=0.0262), Treatment (p=0.0113), region (5 cat.) (p<0.0001), baseline diabetes status (3 cat.) (p=0.4580), sex (p=0.0944) and baseline LVEF (3 cat.) (p=0.9753).
***Wald confidence intervals.

Data taken from study 1245.121 only.
LOCF: For a missing value at week 52 the last available post-baseline value before week 52 is imputed.

Table R.1.2.8.1: 5 Responder analysis (displaying odds ratio) in KCCQ-OSS change from baseline at week 52 of >= 5 points (improvement) - RS (LOCF-AD) - 1245.121

	Placebo	Empa 10mg
Number of patients in analysis set	1867	1863
Number of analysed patients, N (%)	1709 (100.0)	1740 (100.0)
Number of patients with endpoint, N (%)	800 (46.8)	876 (50.3)
95% confidence interval*	(44.5, 49.2)	(48.0, 52.7)
Comparison vs Placebo**		
Odds ratio (SE)		1.194 (0.089)
95% confidence interval***		(1.032, 1.381)
p-value		0.0168

* Wilson confidence intervals.
** Logistic regression includes terms for baseline KCCQ - overall summary score (p<0.0001), age (p=0.0421), baseline eGFR (CKD-EPI) (p=0.0553), Treatment (p=0.0168), region (5 cat.) (p<0.0001), baseline diabetes status (3 cat.) (p=0.5471), sex (p=0.1661) and baseline LVEF (3 cat.) (p=0.8983).
***Wald confidence intervals.

Data taken from study 1245.121 only.
LOCF: For a missing value at week 52 the last available post-baseline value before week 52 is imputed.

Table R.1.2.8.1: 6 Responder analysis (displaying risk ratio) in KCCQ-OSS change from baseline at week 52 of >= 5 points (improvement) - RS (LOCF-AD) - 1245.121

	Placebo	Empa 10mg
Number of patients in analysis set	1867	1863
Number of analysed patients, N (%)	1709 (100.0)	1740 (100.0)
Number of patients with endpoint, N (%)	800 (46.8)	876 (50.3)
95% confidence interval*	(44.5, 49.2)	(48.0, 52.7)
Comparison vs Placebo**		
Risk ratio (SE)		1.072 (0.035)
95% confidence interval***		(1.005, 1.144)
p-value		0.0349

* Wilson confidence intervals.
** Log-linked Poisson model with robust estimate of variance includes terms for baseline KCCQ - overall summary score (p<0.0001), age (p=0.0670), baseline eGFR (CKD-EPI) (p=0.0589), Treatment (p=0.0349), region (5 cat.) (p<0.0001), baseline diabetes status (3 cat.) (p=0.5375), sex (p=0.1317) and baseline LVEF (3 cat.) (p=0.8271).
***Wald confidence intervals.

Data taken from study 1245.121 only.
LOCF: For a missing value at week 52 the last available post-baseline value before week 52 is imputed.

R.1.2.8.2

R.1.2.8.2 Subgroup analysis by sex

Table R.1.2.8.2: 1 Responder analysis (displaying odds ratio) in KCCQ-OSS change from baseline at week 52 of <= -5 points (deterioration) by sex - RS (LOCF-AD) - 1245.121

Subgroup Description	Placebo	Empa 10mg
Sex: Male		
Number of patients in analysis set	1411	1426
Number of analysed patients, N (%)	1297 (100.0)	1332 (100.0)
Number of patients with endpoint, N (%)	345 (26.6)	290 (21.8)
95% confidence interval*	(24.3, 29.1)	(19.6, 24.1)
Comparison vs Placebo**		
Odds ratio (SE)		0.759 (0.071)
95% confidence interval***		(0.632, 0.911)
p-value		0.0031
Sex: Female		
Number of patients in analysis set	456	437
Number of analysed patients, N (%)	412 (100.0)	408 (100.0)
Number of patients with endpoint, N (%)	79 (19.2)	81 (19.9)
95% confidence interval*	(15.7, 23.3)	(16.3, 24.0)
Comparison vs Placebo**		
Odds ratio (SE)		1.019 (0.182)
95% confidence interval***		(0.718, 1.448)
p-value		0.9144

* Wilson confidence intervals.
** Logistic regression includes terms for baseline KCCQ - overall summary score (p<0.0001), age (p=0.0859), baseline eGFR (CKD-EPI) (p=0.0197), Treatment (p=0.2035), region (5 cat.) (p<0.0001), baseline diabetes status (3 cat.) (p=0.4608), baseline LVEF (3 cat.) (p=0.9878), sex (p=0.1169) and Treatment by sex interaction (p=0.1438).
***Wald confidence intervals.

Data taken from study 1245.121 only.
LOCF: For a missing value at week 52 the last available post-baseline value before week 52 is imputed.

Table R.1.2.8.2: 2 Responder analysis (displaying risk ratio) in KCCQ-OSS change from baseline at week 52 of <= -5 points (deterioration) by sex - RS (LOCF-AD) - 1245.121

Subgroup Description	Placebo	Empa 10mg
Sex: Male		
Number of patients in analysis set	1411	1426
Number of analysed patients, N (%)	1297 (100.0)	1332 (100.0)
Number of patients with endpoint, N (%)	345 (26.6)	290 (21.8)
95% confidence interval*	(24.3, 29.1)	(19.6, 24.1)
Comparison vs Placebo**		
Risk ratio (SE)		0.817 (0.056)
95% confidence interval***		(0.715, 0.934)
p-value		0.0032
Sex: Female		
Number of patients in analysis set	456	437
Number of analysed patients, N (%)	412 (100.0)	408 (100.0)
Number of patients with endpoint, N (%)	79 (19.2)	81 (19.9)
95% confidence interval*	(15.7, 23.3)	(16.3, 24.0)
Comparison vs Placebo**		
Risk ratio (SE)		1.012 (0.141)
95% confidence interval***		(0.771, 1.330)
p-value		0.9296

* Wilson confidence intervals.
** Log-linked Poisson model with robust estimate of variance includes terms for baseline KCCQ - overall summary score (p<0.0001), age (p=0.0856), baseline eGFR (CKD-EPI) (p=0.0206), Treatment (p=0.2210), region (5 cat.) (p<0.0001), baseline diabetes status (3 cat.) (p=0.4672), baseline LVEF (3 cat.) (p=0.9877), sex (p=0.1252) and Treatment by sex interaction (p=0.1680).
***Wald confidence intervals.

Data taken from study 1245.121 only.
LOCF: For a missing value at week 52 the last available post-baseline value before week 52 is imputed.

Table R.1.2.8.2: 3 Responder analysis (displaying odds ratio) in KCCQ-OSS change from baseline at week 52 of > -5 points (stability) by sex - RS (LOCF-AD) - 1245.121

Subgroup Description	Placebo	Empa 10mg
Sex: Male		
Number of patients in analysis set	1411	1426
Number of analysed patients, N (%)	1297 (100.0)	1332 (100.0)
Number of patients with endpoint, N (%)	952 (73.4)	1042 (78.2)
95% confidence interval*	(70.9, 75.7)	(75.9, 80.4)
Comparison vs Placebo**		
Odds ratio (SE)		1.318 (0.123)
95% confidence interval***		(1.098, 1.581)
p-value		0.0031
Sex: Female		
Number of patients in analysis set	456	437
Number of analysed patients, N (%)	412 (100.0)	408 (100.0)
Number of patients with endpoint, N (%)	333 (80.8)	327 (80.1)
95% confidence interval*	(76.7, 84.3)	(76.0, 83.7)
Comparison vs Placebo**		
Odds ratio (SE)		0.981 (0.176)
95% confidence interval***		(0.691, 1.393)
p-value		0.9144

* Wilson confidence intervals.
** Logistic regression includes terms for baseline KCCQ - overall summary score (p<0.0001), age (p=0.0859), baseline eGFR (CKD-EPI) (p=0.0197), Treatment (p=0.2035), region (5 cat.) (p<0.0001), baseline diabetes status (3 cat.) (p=0.4608), baseline LVEF (3 cat.) (p=0.9878), sex (p=0.1169) and Treatment by sex interaction (p=0.1438).
***Wald confidence intervals.

Data taken from study 1245.121 only.
LOCF: For a missing value at week 52 the last available post-baseline value before week 52 is imputed.

Table R.1.2.8.2: 4 Responder analysis (displaying risk ratio) in KCCQ-OSS change from baseline at week 52 of > -5 points (stability) by sex - RS (LOCF-AD) - 1245.121

Subgroup Description	Placebo	Empa 10mg
Sex: Male		
Number of patients in analysis set	1411	1426
Number of analysed patients, N (%)	1297 (100.0)	1332 (100.0)
Number of patients with endpoint, N (%)	952 (73.4)	1042 (78.2)
95% confidence interval*	(70.9, 75.7)	(75.9, 80.4)
Comparison vs Placebo**		
Risk ratio (SE)		1.066 (0.023)
95% confidence interval***		(1.022, 1.113)
p-value		0.0032
Sex: Female		
Number of patients in analysis set	456	437
Number of analysed patients, N (%)	412 (100.0)	408 (100.0)
Number of patients with endpoint, N (%)	333 (80.8)	327 (80.1)
95% confidence interval*	(76.7, 84.3)	(76.0, 83.7)
Comparison vs Placebo**		
Risk ratio (SE)		0.993 (0.034)
95% confidence interval***		(0.930, 1.061)
p-value		0.8390

* Wilson confidence intervals.
** Log-linked Poisson model with robust estimate of variance includes terms for baseline KCCQ - overall summary score (p<0.0001), age (p=0.1151), baseline eGFR (CKD-EPI) (p=0.0243), Treatment (p=0.1527), region (5 cat.) (p<0.0001), baseline diabetes status (3 cat.) (p=0.4642), baseline LVEF (3 cat.) (p=0.9816), sex (p=0.0888) and Treatment by sex interaction (p=0.0771).
***Wald confidence intervals.

Data taken from study 1245.121 only.
LOCF: For a missing value at week 52 the last available post-baseline value before week 52 is imputed.

Table R.1.2.8.2: 5 Responder analysis (displaying odds ratio) in KCCQ-OSS change from baseline at week 52 of >= 5 points (improvement) by sex - RS (LOCF-AD) - 1245.121

Subgroup Description	Placebo	Empa 10mg
Sex: Male		
Number of patients in analysis set	1411	1426
Number of analysed patients, N (%)	1297 (100.0)	1332 (100.0)
Number of patients with endpoint, N (%)	570 (43.9)	648 (48.6)
95% confidence interval*	(41.3, 46.7)	(46.0, 51.3)
Comparison vs Placebo**		
Odds ratio (SE)		1.241 (0.105)
95% confidence interval***		(1.051, 1.466)
p-value		0.0108
Sex: Female		
Number of patients in analysis set	456	437
Number of analysed patients, N (%)	412 (100.0)	408 (100.0)
Number of patients with endpoint, N (%)	230 (55.8)	228 (55.9)
95% confidence interval*	(51.0, 60.5)	(51.0, 60.6)
Comparison vs Placebo**		
Odds ratio (SE)		1.052 (0.161)
95% confidence interval***		(0.780, 1.419)
p-value		0.7393

* Wilson confidence intervals.
** Logistic regression includes terms for baseline KCCQ - overall summary score (p<0.0001), age (p=0.0404), baseline eGFR (CKD-EPI) (p=0.0528), Treatment (p=0.1263), region (5 cat.) (p<0.0001), baseline diabetes status (3 cat.) (p=0.5539), baseline LVEF (3 cat.) (p=0.9033), sex (p=0.1686) and Treatment by sex interaction (p=0.3439).
***Wald confidence intervals.

Data taken from study 1245.121 only.
LOCF: For a missing value at week 52 the last available post-baseline value before week 52 is imputed.

Table R.1.2.8.2: 6 Responder analysis (displaying risk ratio) in KCCQ-OSS change from baseline at week 52 of >= 5 points (improvement) by sex - RS (LOCF-AD) - 1245.121

Subgroup Description	Placebo	Empa 10mg
Sex: Male		
Number of patients in analysis set	1411	1426
Number of analysed patients, N (%)	1297 (100.0)	1332 (100.0)
Number of patients with endpoint, N (%)	570 (43.9)	648 (48.6)
95% confidence interval*	(41.3, 46.7)	(46.0, 51.3)
Comparison vs Placebo**		
Risk ratio (SE)		1.100 (0.044)
95% confidence interval***		(1.018, 1.189)
p-value		0.0156
Sex: Female		
Number of patients in analysis set	456	437
Number of analysed patients, N (%)	412 (100.0)	408 (100.0)
Number of patients with endpoint, N (%)	230 (55.8)	228 (55.9)
95% confidence interval*	(51.0, 60.5)	(51.0, 60.6)
Comparison vs Placebo**		
Risk ratio (SE)		1.001 (0.060)
95% confidence interval***		(0.890, 1.124)
p-value		0.9918

* Wilson confidence intervals.
** Log-linked Poisson model with robust estimate of variance includes terms for baseline KCCQ - overall summary score (p<0.0001), age (p=0.0635), baseline eGFR (CKD-EPI) (p=0.0552), Treatment (p=0.1776), region (5 cat.) (p<0.0001), baseline diabetes status (3 cat.) (p=0.5402), baseline LVEF (3 cat.) (p=0.8342), sex (p=0.1235) and Treatment by sex interaction (p=0.1832).
***Wald confidence intervals.

Data taken from study 1245.121 only.
LOCF: For a missing value at week 52 the last available post-baseline value before week 52 is imputed.

R.1.2.8.3

R.1.2.8.3 Subgroup analysis by age

Table R.1.2.8.3: 1 Responder analysis (displaying odds ratio) in KCCQ-OSS change from baseline at week 52 of <= -5 points (deterioration) by age (2 cat.) - RS (LOCF-AD) - 1245.121

Subgroup Description	Placebo	Empa 10mg
Age [years] (2 cat.): < 65		
Number of patients in analysis set	740	675
Number of analysed patients, N (%)	675 (100.0)	635 (100.0)
Number of patients with endpoint, N (%)	154 (22.8)	109 (17.2)
95% confidence interval*	(19.8, 26.1)	(14.4, 20.3)
Comparison vs Placebo**		
Odds ratio (SE)		0.696 (0.099)
95% confidence interval***		(0.526, 0.919)
p-value		0.0107
Age [years] (2 cat.): >= 65		
Number of patients in analysis set	1127	1188
Number of analysed patients, N (%)	1034 (100.0)	1105 (100.0)
Number of patients with endpoint, N (%)	270 (26.1)	262 (23.7)
95% confidence interval*	(23.5, 28.9)	(21.3, 26.3)
Comparison vs Placebo**		
Odds ratio (SE)		0.877 (0.089)
95% confidence interval***		(0.718, 1.070)
p-value		0.1958

* Wilson confidence intervals.
** Logistic regression includes terms for baseline KCCQ - overall summary score (p<0.0001), baseline eGFR (CKD-EPI) (p=0.0018), Treatment (p=0.0046), region (5 cat.) (p<0.0001), baseline diabetes status (3 cat.) (p=0.4770), sex (p=0.1325), baseline LVEF (3 cat.) (p=0.9878), age (2 cat.) (p=0.6365) and Treatment by age (2 cat.) interaction (p=0.1858).
***Wald confidence intervals.

Data taken from study 1245.121 only.
LOCF: For a missing value at week 52 the last available post-baseline value before week 52 is imputed.

Table R.1.2.8.3: 2 Responder analysis (displaying risk ratio) in KCCQ-OSS change from baseline at week 52 of <= -5 points (deterioration) by age (2 cat.) - RS (LOCF-AD) - 1245.121

Subgroup Description	Placebo	Empa 10mg
Age [years] (2 cat.): < 65		
Number of patients in analysis set	740	675
Number of analysed patients, N (%)	675 (100.0)	635 (100.0)
Number of patients with endpoint, N (%)	154 (22.8)	109 (17.2)
95% confidence interval*	(19.8, 26.1)	(14.4, 20.3)
Comparison vs Placebo**		
Risk ratio (SE)		0.753 (0.083)
95% confidence interval***		(0.606, 0.936)
p-value		0.0106
Age [years] (2 cat.): >= 65		
Number of patients in analysis set	1127	1188
Number of analysed patients, N (%)	1034 (100.0)	1105 (100.0)
Number of patients with endpoint, N (%)	270 (26.1)	262 (23.7)
95% confidence interval*	(23.5, 28.9)	(21.3, 26.3)
Comparison vs Placebo**		
Risk ratio (SE)		0.909 (0.067)
95% confidence interval***		(0.786, 1.051)
p-value		0.1978

* Wilson confidence intervals.
** Log-linked Poisson model with robust estimate of variance includes terms for baseline KCCQ - overall summary score (p<0.0001), baseline eGFR (CKD-EPI) (p=0.0017), Treatment (p=0.0045), region (5 cat.) (p<0.0001), baseline diabetes status (3 cat.) (p=0.4826), sex (p=0.1379), baseline LVEF (3 cat.) (p=0.9897), age (2 cat.) (p=0.5957) and Treatment by age (2 cat.) interaction (p=0.1600).
***Wald confidence intervals.

Data taken from study 1245.121 only.
LOCF: For a missing value at week 52 the last available post-baseline value before week 52 is imputed.

Table R.1.2.8.3: 3 Responder analysis (displaying odds ratio) in KCCQ-OSS change from baseline at week 52 of > -5 points (stability) by age (2 cat.) - RS (LOCF-AD) - 1245.121

Subgroup Description	Placebo	Empa 10mg
Age [years] (2 cat.): < 65		
Number of patients in analysis set	740	675
Number of analysed patients, N (%)	675 (100.0)	635 (100.0)
Number of patients with endpoint, N (%)	521 (77.2)	526 (82.8)
95% confidence interval*	(73.9, 80.2)	(79.7, 85.6)
Comparison vs Placebo**		
Odds ratio (SE)		1.438 (0.204)
95% confidence interval***		(1.088, 1.900)
p-value		0.0107
Age [years] (2 cat.): >= 65		
Number of patients in analysis set	1127	1188
Number of analysed patients, N (%)	1034 (100.0)	1105 (100.0)
Number of patients with endpoint, N (%)	764 (73.9)	843 (76.3)
95% confidence interval*	(71.1, 76.5)	(73.7, 78.7)
Comparison vs Placebo**		
Odds ratio (SE)		1.141 (0.116)
95% confidence interval***		(0.934, 1.392)
p-value		0.1958

* Wilson confidence intervals.
** Logistic regression includes terms for baseline KCCQ - overall summary score (p<0.0001), baseline eGFR (CKD-EPI) (p=0.0018), Treatment (p=0.0046), region (5 cat.) (p<0.0001), baseline diabetes status (3 cat.) (p=0.4770), sex (p=0.1325), baseline LVEF (3 cat.) (p=0.9878), age (2 cat.) (p=0.6365) and Treatment by age (2 cat.) interaction (p=0.1858).
***Wald confidence intervals.

Data taken from study 1245.121 only.
LOCF: For a missing value at week 52 the last available post-baseline value before week 52 is imputed.

Table R.1.2.8.3: 4 Responder analysis (displaying risk ratio) in KCCQ-OSS change from baseline at week 52 of > -5 points (stability) by age (2 cat.) - RS (LOCF-AD) - 1245.121

Subgroup Description	Placebo	Empa 10mg
Age [years] (2 cat.): < 65		
Number of patients in analysis set	740	675
Number of analysed patients, N (%)	675 (100.0)	635 (100.0)
Number of patients with endpoint, N (%)	521 (77.2)	526 (82.8)
95% confidence interval*	(73.9, 80.2)	(79.7, 85.6)
Comparison vs Placebo**		
Risk ratio (SE)		1.070 (0.029)
95% confidence interval***		(1.014, 1.129)
p-value		0.0131
Age [years] (2 cat.): >= 65		
Number of patients in analysis set	1127	1188
Number of analysed patients, N (%)	1034 (100.0)	1105 (100.0)
Number of patients with endpoint, N (%)	764 (73.9)	843 (76.3)
95% confidence interval*	(71.1, 76.5)	(73.7, 78.7)
Comparison vs Placebo**		
Risk ratio (SE)		1.032 (0.025)
95% confidence interval***		(0.983, 1.083)
p-value		0.1991

* Wilson confidence intervals.
** Log-linked Poisson model with robust estimate of variance includes terms for baseline KCCQ - overall summary score (p<0.0001), baseline eGFR (CKD-EPI) (p=0.0023), Treatment (p=0.0068), region (5 cat.) (p<0.0001), baseline diabetes status (3 cat.) (p=0.4685), sex (p=0.1141), baseline LVEF (3 cat.) (p=0.9719), age (2 cat.) (p=0.7392) and Treatment by age (2 cat.) interaction (p=0.3270).
***Wald confidence intervals.

Data taken from study 1245.121 only.
LOCF: For a missing value at week 52 the last available post-baseline value before week 52 is imputed.

Table R.1.2.8.3: 5 Responder analysis (displaying odds ratio) in KCCQ-OSS change from baseline at week 52 of >= 5 points (improvement) by age (2 cat.) - RS (LOCF-AD) - 1245.121

Subgroup Description	Placebo	Empa 10mg
Age [years] (2 cat.): < 65		
Number of patients in analysis set	740	675
Number of analysed patients, N (%)	675 (100.0)	635 (100.0)
Number of patients with endpoint, N (%)	350 (51.9)	353 (55.6)
95% confidence interval*	(48.1, 55.6)	(51.7, 59.4)
Comparison vs Placebo**		
Odds ratio (SE)		1.178 (0.142)
95% confidence interval***		(0.929, 1.492)
p-value		0.1762
Age [years] (2 cat.): >= 65		
Number of patients in analysis set	1127	1188
Number of analysed patients, N (%)	1034 (100.0)	1105 (100.0)
Number of patients with endpoint, N (%)	450 (43.5)	523 (47.3)
95% confidence interval*	(40.5, 46.6)	(44.4, 50.3)
Comparison vs Placebo**		
Odds ratio (SE)		1.201 (0.113)
95% confidence interval***		(0.999, 1.444)
p-value		0.0514

* Wilson confidence intervals.
** Logistic regression includes terms for baseline KCCQ - overall summary score (p<0.0001), baseline eGFR (CKD-EPI) (p=0.0066), Treatment (p=0.0235), region (5 cat.) (p<0.0001), baseline diabetes status (3 cat.) (p=0.5830), sex (p=0.1784), baseline LVEF (3 cat.) (p=0.8799), age (2 cat.) (p=0.3457) and Treatment by age (2 cat.) interaction (p=0.8978).
***Wald confidence intervals.

Data taken from study 1245.121 only.
LOCF: For a missing value at week 52 the last available post-baseline value before week 52 is imputed.

Table R.1.2.8.3: 6 Responder analysis (displaying risk ratio) in KCCQ-OSS change from baseline at week 52 of >= 5 points (improvement) by age (2 cat.) - RS (LOCF-AD) - 1245.121

Subgroup Description	Placebo	Empa 10mg
Age [years] (2 cat.): < 65		
Number of patients in analysis set	740	675
Number of analysed patients, N (%)	675 (100.0)	635 (100.0)
Number of patients with endpoint, N (%)	350 (51.9)	353 (55.6)
95% confidence interval*	(48.1, 55.6)	(51.7, 59.4)
Comparison vs Placebo**		
Risk ratio (SE)		1.054 (0.053)
95% confidence interval***		(0.956, 1.162)
p-value		0.2921
Age [years] (2 cat.): >= 65		
Number of patients in analysis set	1127	1188
Number of analysed patients, N (%)	1034 (100.0)	1105 (100.0)
Number of patients with endpoint, N (%)	450 (43.5)	523 (47.3)
95% confidence interval*	(40.5, 46.6)	(44.4, 50.3)
Comparison vs Placebo**		
Risk ratio (SE)		1.083 (0.048)
95% confidence interval***		(0.994, 1.181)
p-value		0.0693

* Wilson confidence intervals.
** Log-linked Poisson model with robust estimate of variance includes terms for baseline KCCQ - overall summary score (p<0.0001), baseline eGFR (CKD-EPI) (p=0.0078), Treatment (p=0.0461), region (5 cat.) (p<0.0001), baseline diabetes status (3 cat.) (p=0.5517), sex (p=0.1409), baseline LVEF (3 cat.) (p=0.7919), age (2 cat.) (p=0.4114) and Treatment by age (2 cat.) interaction (p=0.6786).
***Wald confidence intervals.

Data taken from study 1245.121 only.
LOCF: For a missing value at week 52 the last available post-baseline value before week 52 is imputed.

R.1.2.8.4 Subgroup analysis by region (North America, Latin America, Europe, Asia, Other)

Table R.1.2.8.4: 1 Responder analysis (displaying odds ratio) in KCCQ-OSS change from baseline at week 52 of <= -5 points (deterioration) by region - RS (LOCF-AD) - 1245.121

Subgroup Description	Placebo	Empa 10mg
Region (5 cat.): North America		
Number of patients in analysis set	213	212
Number of analysed patients, N (%)	192 (100.0)	204 (100.0)
Number of patients with endpoint, N (%)	51 (26.6)	53 (26.0)
95% confidence interval*	(20.8, 33.2)	(20.4, 32.4)
Comparison vs Placebo**		
Odds ratio (SE)		0.924 (0.214)
95% confidence interval***		(0.586, 1.456)
p-value		0.7321
Region (5 cat.): Latin America		
Number of patients in analysis set	645	641
Number of analysed patients, N (%)	577 (100.0)	586 (100.0)
Number of patients with endpoint, N (%)	120 (20.8)	107 (18.3)
95% confidence interval*	(17.7, 24.3)	(15.3, 21.6)
Comparison vs Placebo**		
Odds ratio (SE)		0.848 (0.127)
95% confidence interval***		(0.632, 1.138)
p-value		0.2713

* Wilson confidence intervals.
** Logistic regression includes terms for baseline KCCQ - overall summary score (p<0.0001), age (p=0.0946), baseline eGFR (CKD-EPI) (p=0.0210), Treatment (p=0.0028), baseline diabetes status (3 cat.) (p=0.4551), sex (p=0.1035), baseline LVEF (3 cat.) (p=0.9782), region (5 cat.) (p<0.0001) and Treatment by region (5 cat.) interaction (p=0.2784).
***Wald confidence intervals.

Data taken from study 1245.121 only.
LOCF: For a missing value at week 52 the last available post-baseline value before week 52 is imputed.

Table R.1.2.8.4: 1 Responder analysis (displaying odds ratio) in KCCQ-OSS change from baseline at week 52 of <= -5 points (deterioration) by region - RS (LOCF-AD) - 1245.121

Subgroup Description	Placebo	Empa 10mg
Region (5 cat.): Europe		
Number of patients in analysis set	677	676
Number of analysed patients, N (%)	631 (100.0)	638 (100.0)
Number of patients with endpoint, N (%)	184 (29.2)	165 (25.9)
95% confidence interval*	(25.7, 32.8)	(22.6, 29.4)
Comparison vs Placebo**		
Odds ratio (SE)		0.833 (0.106)
95% confidence interval***		(0.649, 1.069)
p-value		0.1507
Region (5 cat.): Asia		
Number of patients in analysis set	245	248
Number of analysed patients, N (%)	232 (100.0)	236 (100.0)
Number of patients with endpoint, N (%)	58 (25.0)	44 (18.6)
95% confidence interval*	(19.9, 30.9)	(14.2, 24.1)
Comparison vs Placebo**		
Odds ratio (SE)		0.707 (0.161)
95% confidence interval***		(0.453, 1.105)
p-value		0.1278

* Wilson confidence intervals.
** Logistic regression includes terms for baseline KCCQ - overall summary score (p<0.0001), age (p=0.0946), baseline eGFR (CKD-EPI) (p=0.0210), Treatment (p=0.0028), baseline diabetes status (3 cat.) (p=0.4551), sex (p=0.1035), baseline LVEF (3 cat.) (p=0.9782), region (5 cat.) (p<0.0001) and Treatment by region (5 cat.) interaction (p=0.2784).
***Wald confidence intervals.

Data taken from study 1245.121 only.
LOCF: For a missing value at week 52 the last available post-baseline value before week 52 is imputed.

Table R.1.2.8.4: 1 Responder analysis (displaying odds ratio) in KCCQ-OSS change from baseline at week 52 of <= -5 points (deterioration) by region - RS (LOCF-AD) - 1245.121

Subgroup Description	Placebo	Empa 10mg
Region (5 cat.): Other		
Number of patients in analysis set	87	86
Number of analysed patients, N (%)	77 (100.0)	76 (100.0)
Number of patients with endpoint, N (%)	11 (14.3)	2 (2.6)
95% confidence interval*	(8.2, 23.8)	(0.7, 9.1)
Comparison vs Placebo**		
Odds ratio (SE)		0.158 (0.125)
95% confidence interval***		(0.034, 0.744)
p-value		0.0195

* Wilson confidence intervals.
** Logistic regression includes terms for baseline KCCQ - overall summary score (p<0.0001), age (p=0.0946), baseline eGFR (CKD-EPI) (p=0.0210), Treatment (p=0.0028), baseline diabetes status (3 cat.) (p=0.4551), sex (p=0.1035), baseline LVEF (3 cat.) (p=0.9782), region (5 cat.) (p<0.0001) and Treatment by region (5 cat.) interaction (p=0.2784).
***Wald confidence intervals.

Data taken from study 1245.121 only.
LOCF: For a missing value at week 52 the last available post-baseline value before week 52 is imputed.

Table R.1.2.8.4: 2 Responder analysis (displaying risk ratio) in KCCQ-OSS change from baseline at week 52 of <= -5 points (deterioration) by region - RS (LOCF-AD) - 1245.121

Subgroup Description	Placebo	Empa 10mg
Region (5 cat.): North America		
Number of patients in analysis set	213	212
Number of analysed patients, N (%)	192 (100.0)	204 (100.0)
Number of patients with endpoint, N (%)	51 (26.6)	53 (26.0)
95% confidence interval*	(20.8, 33.2)	(20.4, 32.4)
Comparison vs Placebo**		
Risk ratio (SE)		0.944 (0.159)
95% confidence interval***		(0.678, 1.314)
p-value		0.7325
Region (5 cat.): Latin America		
Number of patients in analysis set	645	641
Number of analysed patients, N (%)	577 (100.0)	586 (100.0)
Number of patients with endpoint, N (%)	120 (20.8)	107 (18.3)
95% confidence interval*	(17.7, 24.3)	(15.3, 21.6)
Comparison vs Placebo**		
Risk ratio (SE)		0.878 (0.103)
95% confidence interval***		(0.697, 1.106)
p-value		0.2687

* Wilson confidence intervals.
** Log-linked Poisson model with robust estimate of variance includes terms for baseline KCCQ - overall summary score (p<0.0001), age (p=0.0941), baseline eGFR (CKD-EPI) (p=0.0216), Treatment (p=0.0042), baseline diabetes status (3 cat.) (p=0.4620), sex (p=0.1093), baseline LVEF (3 cat.) (p=0.9769), region (5 cat.) (p<0.0001) and Treatment by region (5 cat.) interaction (p=0.2724).
***Wald confidence intervals.

Data taken from study 1245.121 only.
LOCF: For a missing value at week 52 the last available post-baseline value before week 52 is imputed.

Table R.1.2.8.4: 2 Responder analysis (displaying risk ratio) in KCCQ-OSS change from baseline at week 52 of <= -5 points (deterioration) by region - RS (LOCF-AD) - 1245.121

Subgroup Description	Placebo	Empa 10mg
Region (5 cat.): Europe		
Number of patients in analysis set	677	676
Number of analysed patients, N (%)	631 (100.0)	638 (100.0)
Number of patients with endpoint, N (%)	184 (29.2)	165 (25.9)
95% confidence interval*	(25.7, 32.8)	(22.6, 29.4)
Comparison vs Placebo**		
Risk ratio (SE)		0.878 (0.079)
95% confidence interval***		(0.736, 1.049)
p-value		0.1516
Region (5 cat.): Asia		
Number of patients in analysis set	245	248
Number of analysed patients, N (%)	232 (100.0)	236 (100.0)
Number of patients with endpoint, N (%)	58 (25.0)	44 (18.6)
95% confidence interval*	(19.9, 30.9)	(14.2, 24.1)
Comparison vs Placebo**		
Risk ratio (SE)		0.764 (0.134)
95% confidence interval***		(0.541, 1.079)
p-value		0.1267

* Wilson confidence intervals.
** Log-linked Poisson model with robust estimate of variance includes terms for baseline KCCQ - overall summary score (p<0.0001), age (p=0.0941), baseline eGFR (CKD-EPI) (p=0.0216), Treatment (p=0.0042), baseline diabetes status (3 cat.) (p=0.4620), sex (p=0.1093), baseline LVEF (3 cat.) (p=0.9769), region (5 cat.) (p<0.0001) and Treatment by region (5 cat.) interaction (p=0.2724).
***Wald confidence intervals.

Data taken from study 1245.121 only.
LOCF: For a missing value at week 52 the last available post-baseline value before week 52 is imputed.

Table R.1.2.8.4: 2 Responder analysis (displaying risk ratio) in KCCQ-OSS change from baseline at week 52 of <= -5 points (deterioration) by region - RS (LOCF-AD) - 1245.121

Subgroup Description	Placebo	Empa 10mg
Region (5 cat.): Other		
Number of patients in analysis set	87	86
Number of analysed patients, N (%)	77 (100.0)	76 (100.0)
Number of patients with endpoint, N (%)	11 (14.3)	2 (2.6)
95% confidence interval*	(8.2, 23.8)	(0.7, 9.1)
Comparison vs Placebo**		
Risk ratio (SE)		0.182 (0.136)
95% confidence interval***		(0.042, 0.788)
p-value		0.0227

* Wilson confidence intervals.
** Log-linked Poisson model with robust estimate of variance includes terms for baseline KCCQ - overall summary score (p<0.0001), age (p=0.0941), baseline eGFR (CKD-EPI) (p=0.0216), Treatment (p=0.0042), baseline diabetes status (3 cat.) (p=0.4620), sex (p=0.1093), baseline LVEF (3 cat.) (p=0.9769), region (5 cat.) (p<0.0001) and Treatment by region (5 cat.) interaction (p=0.2724).
***Wald confidence intervals.

Data taken from study 1245.121 only.
LOCF: For a missing value at week 52 the last available post-baseline value before week 52 is imputed.

Table R.1.2.8.4: 3 Responder analysis (displaying odds ratio) in KCCQ-OSS change from baseline at week 52 of > -5 points (stability) by region - RS (LOCF-AD) - 1245.121

Subgroup Description	Placebo	Empa 10mg
Region (5 cat.): North America		
Number of patients in analysis set	213	212
Number of analysed patients, N (%)	192 (100.0)	204 (100.0)
Number of patients with endpoint, N (%)	141 (73.4)	151 (74.0)
95% confidence interval*	(66.8, 79.2)	(67.6, 79.6)
Comparison vs Placebo**		
Odds ratio (SE)		1.083 (0.251)
95% confidence interval***		(0.687, 1.706)
p-value		0.7321
Region (5 cat.): Latin America		
Number of patients in analysis set	645	641
Number of analysed patients, N (%)	577 (100.0)	586 (100.0)
Number of patients with endpoint, N (%)	457 (79.2)	479 (81.7)
95% confidence interval*	(75.7, 82.3)	(78.4, 84.7)
Comparison vs Placebo**		
Odds ratio (SE)		1.180 (0.177)
95% confidence interval***		(0.879, 1.583)
p-value		0.2713

* Wilson confidence intervals.
** Logistic regression includes terms for baseline KCCQ - overall summary score (p<0.0001), age (p=0.0946), baseline eGFR (CKD-EPI) (p=0.0210), Treatment (p=0.0028), baseline diabetes status (3 cat.) (p=0.4551), sex (p=0.1035), baseline LVEF (3 cat.) (p=0.9782), region (5 cat.) (p<0.0001) and Treatment by region (5 cat.) interaction (p=0.2784).
***Wald confidence intervals.

Data taken from study 1245.121 only.
LOCF: For a missing value at week 52 the last available post-baseline value before week 52 is imputed.

Table R.1.2.8.4: 3 Responder analysis (displaying odds ratio) in KCCQ-OSS change from baseline at week 52 of > -5 points (stability) by region - RS (LOCF-AD) - 1245.121

Subgroup Description	Placebo	Empa 10mg
Region (5 cat.): Europe		
Number of patients in analysis set	677	676
Number of analysed patients, N (%)	631 (100.0)	638 (100.0)
Number of patients with endpoint, N (%)	447 (70.8)	473 (74.1)
95% confidence interval*	(67.2, 74.3)	(70.6, 77.4)
Comparison vs Placebo**		
Odds ratio (SE)		1.201 (0.153)
95% confidence interval***		(0.936, 1.541)
p-value		0.1507
Region (5 cat.): Asia		
Number of patients in analysis set	245	248
Number of analysed patients, N (%)	232 (100.0)	236 (100.0)
Number of patients with endpoint, N (%)	174 (75.0)	192 (81.4)
95% confidence interval*	(69.1, 80.1)	(75.9, 85.8)
Comparison vs Placebo**		
Odds ratio (SE)		1.414 (0.322)
95% confidence interval***		(0.905, 2.209)
p-value		0.1278

* Wilson confidence intervals.
** Logistic regression includes terms for baseline KCCQ - overall summary score (p<0.0001), age (p=0.0946), baseline eGFR (CKD-EPI) (p=0.0210), Treatment (p=0.0028), baseline diabetes status (3 cat.) (p=0.4551), sex (p=0.1035), baseline LVEF (3 cat.) (p=0.9782), region (5 cat.) (p<0.0001) and Treatment by region (5 cat.) interaction (p=0.2784).
***Wald confidence intervals.

Data taken from study 1245.121 only.
LOCF: For a missing value at week 52 the last available post-baseline value before week 52 is imputed.

Table R.1.2.8.4: 3 Responder analysis (displaying odds ratio) in KCCQ-OSS change from baseline at week 52 of > -5 points (stability) by region - RS (LOCF-AD) - 1245.121

Subgroup Description	Placebo	Empa 10mg
Region (5 cat.): Other		
Number of patients in analysis set	87	86
Number of analysed patients, N (%)	77 (100.0)	76 (100.0)
Number of patients with endpoint, N (%)	66 (85.7)	74 (97.4)
95% confidence interval*	(76.2, 91.8)	(90.9, 99.3)
Comparison vs Placebo**		
Odds ratio (SE)		6.310 (4.977)
95% confidence interval***		(1.345,29.612)
p-value		0.0195

* Wilson confidence intervals.
** Logistic regression includes terms for baseline KCCQ - overall summary score (p<0.0001), age (p=0.0946), baseline eGFR (CKD-EPI) (p=0.0210), Treatment (p=0.0028), baseline diabetes status (3 cat.) (p=0.4551), sex (p=0.1035), baseline LVEF (3 cat.) (p=0.9782), region (5 cat.) (p<0.0001) and Treatment by region (5 cat.) interaction (p=0.2784).
***Wald confidence intervals.

Data taken from study 1245.121 only.
LOCF: For a missing value at week 52 the last available post-baseline value before week 52 is imputed.

Table R.1.2.8.4: 4 Responder analysis (displaying risk ratio) in KCCQ-OSS change from baseline at week 52 of > -5 points (stability) by region - RS (LOCF-AD) - 1245.121

Subgroup Description	Placebo	Empa 10mg
Region (5 cat.): North America		
Number of patients in analysis set	213	212
Number of analysed patients, N (%)	192 (100.0)	204 (100.0)
Number of patients with endpoint, N (%)	141 (73.4)	151 (74.0)
95% confidence interval*	(66.8, 79.2)	(67.6, 79.6)
Comparison vs Placebo**		
Risk ratio (SE)		1.019 (0.061)
95% confidence interval***		(0.906, 1.146)
p-value		0.7533
Region (5 cat.): Latin America		
Number of patients in analysis set	645	641
Number of analysed patients, N (%)	577 (100.0)	586 (100.0)
Number of patients with endpoint, N (%)	457 (79.2)	479 (81.7)
95% confidence interval*	(75.7, 82.3)	(78.4, 84.7)
Comparison vs Placebo**		
Risk ratio (SE)		1.031 (0.029)
95% confidence interval***		(0.975, 1.090)
p-value		0.2846

* Wilson confidence intervals.
** Log-linked Poisson model with robust estimate of variance includes terms for baseline KCCQ - overall summary score (p<0.0001), age (p=0.1243), baseline eGFR (CKD-EPI) (p=0.0265), Treatment (p=0.0031), baseline diabetes status (3 cat.) (p=0.4547), sex (p=0.0915), baseline LVEF (3 cat.) (p=0.9725), region (5 cat.) (p<0.0001) and Treatment by region (5 cat.) interaction (p=0.4510).
***Wald confidence intervals.

Data taken from study 1245.121 only.
LOCF: For a missing value at week 52 the last available post-baseline value before week 52 is imputed.

Table R.1.2.8.4: 4 Responder analysis (displaying risk ratio) in KCCQ-OSS change from baseline at week 52 of > -5 points (stability) by region - RS (LOCF-AD) - 1245.121

Subgroup Description	Placebo	Empa 10mg
Region (5 cat.): Europe		
Number of patients in analysis set	677	676
Number of analysed patients, N (%)	631 (100.0)	638 (100.0)
Number of patients with endpoint, N (%)	447 (70.8)	473 (74.1)
95% confidence interval*	(67.2, 74.3)	(70.6, 77.4)
Comparison vs Placebo**		
Risk ratio (SE)		1.050 (0.036)
95% confidence interval***		(0.982, 1.123)
p-value		0.1566
Region (5 cat.): Asia		
Number of patients in analysis set	245	248
Number of analysed patients, N (%)	232 (100.0)	236 (100.0)
Number of patients with endpoint, N (%)	174 (75.0)	192 (81.4)
95% confidence interval*	(69.1, 80.1)	(75.9, 85.8)
Comparison vs Placebo**		
Risk ratio (SE)		1.075 (0.052)
95% confidence interval***		(0.977, 1.182)
p-value		0.1395

* Wilson confidence intervals.
** Log-linked Poisson model with robust estimate of variance includes terms for baseline KCCQ - overall summary score (p<0.0001), age (p=0.1243), baseline eGFR (CKD-EPI) (p=0.0265), Treatment (p=0.0031), baseline diabetes status (3 cat.) (p=0.4547), sex (p=0.0915), baseline LVEF (3 cat.) (p=0.9725), region (5 cat.) (p<0.0001) and Treatment by region (5 cat.) interaction (p=0.4510).
***Wald confidence intervals.

Data taken from study 1245.121 only.
LOCF: For a missing value at week 52 the last available post-baseline value before week 52 is imputed.

Table R.1.2.8.4: 4 Responder analysis (displaying risk ratio) in KCCQ-OSS change from baseline at week 52 of > -5 points (stability) by region - RS (LOCF-AD) - 1245.121

Subgroup Description	Placebo	Empa 10mg
Region (5 cat.): Other		
Number of patients in analysis set	87	86
Number of analysed patients, N (%)	77 (100.0)	76 (100.0)
Number of patients with endpoint, N (%)	66 (85.7)	74 (97.4)
95% confidence interval*	(76.2, 91.8)	(90.9, 99.3)
Comparison vs Placebo**		
Risk ratio (SE)		1.141 (0.056)
95% confidence interval***		(1.036, 1.257)
p-value		0.0075

* Wilson confidence intervals.
** Log-linked Poisson model with robust estimate of variance includes terms for baseline KCCQ - overall summary score (p<0.0001), age (p=0.1243), baseline eGFR (CKD-EPI) (p=0.0265), Treatment (p=0.0031), baseline diabetes status (3 cat.) (p=0.4547), sex (p=0.0915), baseline LVEF (3 cat.) (p=0.9725), region (5 cat.) (p<0.0001) and Treatment by region (5 cat.) interaction (p=0.4510).
***Wald confidence intervals.

Data taken from study 1245.121 only.
LOCF: For a missing value at week 52 the last available post-baseline value before week 52 is imputed.

Table R.1.2.8.4: 5 Responder analysis (displaying odds ratio) in KCCQ-OSS change from baseline at week 52 of >= 5 points (improvement) by region - RS (LOCF-AD) - 1245.121

Subgroup Description	Placebo	Empa 10mg
Region (5 cat.): North America		
Number of patients in analysis set	213	212
Number of analysed patients, N (%)	192 (100.0)	204 (100.0)
Number of patients with endpoint, N (%)	79 (41.1)	88 (43.1)
95% confidence interval*	(34.4, 48.2)	(36.5, 50.0)
Comparison vs Placebo**		
Odds ratio (SE)		1.207 (0.269)
95% confidence interval***		(0.780, 1.867)
p-value		0.3978
Region (5 cat.): Latin America		
Number of patients in analysis set	645	641
Number of analysed patients, N (%)	577 (100.0)	586 (100.0)
Number of patients with endpoint, N (%)	317 (54.9)	349 (59.6)
95% confidence interval*	(50.9, 59.0)	(55.5, 63.5)
Comparison vs Placebo**		
Odds ratio (SE)		1.250 (0.161)
95% confidence interval***		(0.971, 1.609)
p-value		0.0837

* Wilson confidence intervals.
** Logistic regression includes terms for baseline KCCQ - overall summary score (p<0.0001), age (p=0.0383), baseline eGFR (CKD-EPI) (p=0.0608), Treatment (p=0.0098), baseline diabetes status (3 cat.) (p=0.5339), sex (p=0.1605), baseline LVEF (3 cat.) (p=0.8852), region (5 cat.) (p<0.0001) and Treatment by region (5 cat.) interaction (p=0.6570).
***Wald confidence intervals.

Data taken from study 1245.121 only.
LOCF: For a missing value at week 52 the last available post-baseline value before week 52 is imputed.

Table R.1.2.8.4: 5 Responder analysis (displaying odds ratio) in KCCQ-OSS change from baseline at week 52 of >= 5 points (improvement) by region - RS (LOCF-AD) - 1245.121

Subgroup Description	Placebo	Empa 10mg
Region (5 cat.): Europe		
Number of patients in analysis set	677	676
Number of analysed patients, N (%)	631 (100.0)	638 (100.0)
Number of patients with endpoint, N (%)	270 (42.8)	276 (43.3)
95% confidence interval*	(39.0, 46.7)	(39.5, 47.1)
Comparison vs Placebo**		
Odds ratio (SE)		1.056 (0.128)
95% confidence interval***		(0.832, 1.340)
p-value		0.6556
Region (5 cat.): Asia		
Number of patients in analysis set	245	248
Number of analysed patients, N (%)	232 (100.0)	236 (100.0)
Number of patients with endpoint, N (%)	91 (39.2)	112 (47.5)
95% confidence interval*	(33.2, 45.6)	(41.2, 53.8)
Comparison vs Placebo**		
Odds ratio (SE)		1.310 (0.258)
95% confidence interval***		(0.890, 1.929)
p-value		0.1705

* Wilson confidence intervals.
** Logistic regression includes terms for baseline KCCQ - overall summary score (p<0.0001), age (p=0.0383), baseline eGFR (CKD-EPI) (p=0.0608), Treatment (p=0.0098), baseline diabetes status (3 cat.) (p=0.5339), sex (p=0.1605), baseline LVEF (3 cat.) (p=0.8852), region (5 cat.) (p<0.0001) and Treatment by region (5 cat.) interaction (p=0.6570).
***Wald confidence intervals.

Data taken from study 1245.121 only.
LOCF: For a missing value at week 52 the last available post-baseline value before week 52 is imputed.

Table R.1.2.8.4: 5 Responder analysis (displaying odds ratio) in KCCQ-OSS change from baseline at week 52 of >= 5 points (improvement) by region - RS (LOCF-AD) - 1245.121

Subgroup Description	Placebo	Empa 10mg
Region (5 cat.): Other		
Number of patients in analysis set	87	86
Number of analysed patients, N (%)	77 (100.0)	76 (100.0)
Number of patients with endpoint, N (%)	43 (55.8)	51 (67.1)
95% confidence interval*	(44.7, 66.4)	(55.9, 76.6)
Comparison vs Placebo**		
Odds ratio (SE)		1.712 (0.599)
95% confidence interval***		(0.862, 3.400)
p-value		0.1248

* Wilson confidence intervals.
** Logistic regression includes terms for baseline KCCQ - overall summary score (p<0.0001), age (p=0.0383), baseline eGFR (CKD-EPI) (p=0.0608), Treatment (p=0.0098), baseline diabetes status (3 cat.) (p=0.5339), sex (p=0.1605), baseline LVEF (3 cat.) (p=0.8852), region (5 cat.) (p<0.0001) and Treatment by region (5 cat.) interaction (p=0.6570).
***Wald confidence intervals.

Data taken from study 1245.121 only.
LOCF: For a missing value at week 52 the last available post-baseline value before week 52 is imputed.

Table R.1.2.8.4: 6 Responder analysis (displaying risk ratio) in KCCQ-OSS change from baseline at week 52 of >= 5 points (improvement) by region - RS (LOCF-AD) - 1245.121

Subgroup Description	Placebo	Empa 10mg
Region (5 cat.): North America		
Number of patients in analysis set	213	212
Number of analysed patients, N (%)	192 (100.0)	204 (100.0)
Number of patients with endpoint, N (%)	79 (41.1)	88 (43.1)
95% confidence interval*	(34.4, 48.2)	(36.5, 50.0)
Comparison vs Placebo**		
Risk ratio (SE)		1.082 (0.123)
95% confidence interval***		(0.867, 1.352)
p-value		0.4852
Region (5 cat.): Latin America		
Number of patients in analysis set	645	641
Number of analysed patients, N (%)	577 (100.0)	586 (100.0)
Number of patients with endpoint, N (%)	317 (54.9)	349 (59.6)
95% confidence interval*	(50.9, 59.0)	(55.5, 63.5)
Comparison vs Placebo**		
Risk ratio (SE)		1.072 (0.052)
95% confidence interval***		(0.974, 1.180)
p-value		0.1547

* Wilson confidence intervals.
** Log-linked Poisson model with robust estimate of variance includes terms for baseline KCCQ - overall summary score (p<0.0001), age (p=0.0599), baseline eGFR (CKD-EPI) (p=0.0649), Treatment (p=0.0141), baseline diabetes status (3 cat.) (p=0.5270), sex (p=0.1329), baseline LVEF (3 cat.) (p=0.8123), region (5 cat.) (p<0.0001) and Treatment by region (5 cat.) interaction (p=0.6551).
***Wald confidence intervals.

Data taken from study 1245.121 only.
LOCF: For a missing value at week 52 the last available post-baseline value before week 52 is imputed.

Table R.1.2.8.4: 6 Responder analysis (displaying risk ratio) in KCCQ-OSS change from baseline at week 52 of >= 5 points (improvement) by region - RS (LOCF-AD) - 1245.121

Subgroup Description	Placebo	Empa 10mg
Region (5 cat.): Europe		
Number of patients in analysis set	677	676
Number of analysed patients, N (%)	631 (100.0)	638 (100.0)
Number of patients with endpoint, N (%)	270 (42.8)	276 (43.3)
95% confidence interval*	(39.0, 46.7)	(39.5, 47.1)
Comparison vs Placebo**		
Risk ratio (SE)		1.019 (0.062)
95% confidence interval***		(0.904, 1.149)
p-value		0.7553
Region (5 cat.): Asia		
Number of patients in analysis set	245	248
Number of analysed patients, N (%)	232 (100.0)	236 (100.0)
Number of patients with endpoint, N (%)	91 (39.2)	112 (47.5)
95% confidence interval*	(33.2, 45.6)	(41.2, 53.8)
Comparison vs Placebo**		
Risk ratio (SE)		1.145 (0.114)
95% confidence interval***		(0.942, 1.391)
p-value		0.1739

* Wilson confidence intervals.
** Log-linked Poisson model with robust estimate of variance includes terms for baseline KCCQ - overall summary score (p<0.0001), age (p=0.0599), baseline eGFR (CKD-EPI) (p=0.0649), Treatment (p=0.0141), baseline diabetes status (3 cat.) (p=0.5270), sex (p=0.1329), baseline LVEF (3 cat.) (p=0.8123), region (5 cat.) (p<0.0001) and Treatment by region (5 cat.) interaction (p=0.6551).
***Wald confidence intervals.

Data taken from study 1245.121 only.
LOCF: For a missing value at week 52 the last available post-baseline value before week 52 is imputed.

Table R.1.2.8.4: 6 Responder analysis (displaying risk ratio) in KCCQ-OSS change from baseline at week 52 of >= 5 points (improvement) by region - RS (LOCF-AD) - 1245.121

Subgroup Description	Placebo	Empa 10mg
Region (5 cat.): Other		
Number of patients in analysis set	87	86
Number of analysed patients, N (%)	77 (100.0)	76 (100.0)
Number of patients with endpoint, N (%)	43 (55.8)	51 (67.1)
95% confidence interval*	(44.7, 66.4)	(55.9, 76.6)
Comparison vs Placebo**		
Risk ratio (SE)		1.231 (0.148)
95% confidence interval***		(0.973, 1.558)
p-value		0.0835

* Wilson confidence intervals.
** Log-linked Poisson model with robust estimate of variance includes terms for baseline KCCQ - overall summary score (p<0.0001), age (p=0.0599), baseline eGFR (CKD-EPI) (p=0.0649), Treatment (p=0.0141), baseline diabetes status (3 cat.) (p=0.5270), sex (p=0.1329), baseline LVEF (3 cat.) (p=0.8123), region (5 cat.) (p<0.0001) and Treatment by region (5 cat.) interaction (p=0.6551).
***Wald confidence intervals.

Data taken from study 1245.121 only.
LOCF: For a missing value at week 52 the last available post-baseline value before week 52 is imputed.

R.1.2.8.5

R.1.2.8.5 Subgroup analysis by OECD (N/Y)

Table R.1.2.8.5: 1 Responder analysis (displaying odds ratio) in KCCQ-OSS change from baseline at week 52 of <= -5 points (deterioration) by OECD member (N/Y) - RS (LOCF-AD) - 1245.121

Subgroup Description	Placebo	Empa 10mg
OECD member: No		
Number of patients in analysis set	741	713
Number of analysed patients, N (%)	663 (100.0)	647 (100.0)
Number of patients with endpoint, N (%)	129 (19.5)	109 (16.8)
95% confidence interval*	(16.6, 22.6)	(14.2, 19.9)
Comparison vs Placebo**		
Odds ratio (SE)		0.829 (0.121)
95% confidence interval***		(0.624, 1.103)
p-value		0.1986
OECD member: Yes		
Number of patients in analysis set	1126	1150
Number of analysed patients, N (%)	1046 (100.0)	1093 (100.0)
Number of patients with endpoint, N (%)	295 (28.2)	262 (24.0)
95% confidence interval*	(25.6, 31.0)	(21.5, 26.6)
Comparison vs Placebo**		
Odds ratio (SE)		0.797 (0.080)
95% confidence interval***		(0.656, 0.970)
p-value		0.0233

* Wilson confidence intervals.
** Logistic regression includes terms for baseline KCCQ - overall summary score (p<0.0001), age (p=0.0550), baseline eGFR (CKD-EPI) (p=0.0125), Treatment (p=0.0190), sex (p=0.1292), baseline diabetes status (3 cat.) (p=0.6334), baseline LVEF (3 cat.) (p=0.9857), OECD member (p=0.0005) and Treatment by OECD member interaction (p=0.8232).
***Wald confidence intervals.

Data taken from study 1245.121 only.
LOCF: For a missing value at week 52 the last available post-baseline value before week 52 is imputed.
OECD member (yes/no) countries included:
Yes: United States, Canada, Mexico, Poland, Netherlands, Hungary, Germany, Czech Republic, Italy, France, Spain, United Kingdom, Belgium, Japan, Australia, 'Korea; Republic Of South Korea';
No: Brazil, Argentina, China, India.

Table R.1.2.8.5: 2 Responder analysis (displaying risk ratio) in KCCQ-OSS change from baseline at week 52 of <= -5 points (deterioration) by OECD member (N/Y) - RS (LOCF-AD) - 1245.121

Subgroup Description	Placebo	Empa 10mg
OECD member: No		
Number of patients in analysis set	741	713
Number of analysed patients, N (%)	663 (100.0)	647 (100.0)
Number of patients with endpoint, N (%)	129 (19.5)	109 (16.8)
95% confidence interval*	(16.6, 22.6)	(14.2, 19.9)
Comparison vs Placebo**		
Risk ratio (SE)		0.861 (0.100)
95% confidence interval***		(0.685, 1.081)
p-value		0.1975
OECD member: Yes		
Number of patients in analysis set	1126	1150
Number of analysed patients, N (%)	1046 (100.0)	1093 (100.0)
Number of patients with endpoint, N (%)	295 (28.2)	262 (24.0)
95% confidence interval*	(25.6, 31.0)	(21.5, 26.6)
Comparison vs Placebo**		
Risk ratio (SE)		0.849 (0.061)
95% confidence interval***		(0.736, 0.978)
p-value		0.0237

* Wilson confidence intervals.
** Log-linked Poisson model with robust estimate of variance includes terms for baseline KCCQ - overall summary score (p<0.0001), age (p=0.0548), baseline eGFR (CKD-EPI) (p=0.0130), Treatment (p=0.0219), sex (p=0.1360), baseline diabetes status (3 cat.) (p=0.6412), baseline LVEF (3 cat.) (p=0.9835), OECD member (p=0.0006) and Treatment by OECD member interaction (p=0.9209).
***Wald confidence intervals.

Data taken from study 1245.121 only.
LOCF: For a missing value at week 52 the last available post-baseline value before week 52 is imputed.
OECD member (yes/no) countries included:
Yes: United States, Canada, Mexico, Poland, Netherlands, Hungary, Germany, Czech Republic, Italy, France, Spain, United Kingdom, Belgium, Japan, Australia, 'Korea; Republic Of South Korea';
No: Brazil, Argentina, China, India.

Table R.1.2.8.5: 3 Responder analysis (displaying odds ratio) in KCCQ-OSS change from baseline at week 52 of > -5 points (stability) by OECD member (N/Y) - RS (LOCF-AD) - 1245.121

Subgroup Description	Placebo	Empa 10mg
OECD member: No		
Number of patients in analysis set	741	713
Number of analysed patients, N (%)	663 (100.0)	647 (100.0)
Number of patients with endpoint, N (%)	534 (80.5)	538 (83.2)
95% confidence interval*	(77.4, 83.4)	(80.1, 85.8)
Comparison vs Placebo**		
Odds ratio (SE)		1.206 (0.175)
95% confidence interval***		(0.907, 1.603)
p-value		0.1986
OECD member: Yes		
Number of patients in analysis set	1126	1150
Number of analysed patients, N (%)	1046 (100.0)	1093 (100.0)
Number of patients with endpoint, N (%)	751 (71.8)	831 (76.0)
95% confidence interval*	(69.0, 74.4)	(73.4, 78.5)
Comparison vs Placebo**		
Odds ratio (SE)		1.254 (0.125)
95% confidence interval***		(1.031, 1.525)
p-value		0.0233

* Wilson confidence intervals.
** Logistic regression includes terms for baseline KCCQ - overall summary score (p<0.0001), age (p=0.0550), baseline eGFR (CKD-EPI) (p=0.0125), Treatment (p=0.0190), sex (p=0.1292), baseline diabetes status (3 cat.) (p=0.6334), baseline LVEF (3 cat.) (p=0.9857), OECD member (p=0.0005) and Treatment by OECD member interaction (p=0.8232).
***Wald confidence intervals.

Data taken from study 1245.121 only.
LOCF: For a missing value at week 52 the last available post-baseline value before week 52 is imputed.
OECD member (yes/no) countries included:
Yes: United States, Canada, Mexico, Poland, Netherlands, Hungary, Germany, Czech Republic, Italy, France, Spain, United Kingdom, Belgium, Japan, Australia, 'Korea; Republic Of South Korea';
No: Brazil, Argentina, China, India.

Table R.1.2.8.5: 4 Responder analysis (displaying risk ratio) in KCCQ-OSS change from baseline at week 52 of > -5 points (stability) by OECD member (N/Y) - RS (LOCF-AD) - 1245.121

Subgroup Description	Placebo	Empa 10mg
OECD member: No		
Number of patients in analysis set	741	713
Number of analysed patients, N (%)	663 (100.0)	647 (100.0)
Number of patients with endpoint, N (%)	534 (80.5)	538 (83.2)
95% confidence interval*	(77.4, 83.4)	(80.1, 85.8)
Comparison vs Placebo**		
Risk ratio (SE)		1.033 (0.027)
95% confidence interval***		(0.982, 1.086)
p-value		0.2098
OECD member: Yes		
Number of patients in analysis set	1126	1150
Number of analysed patients, N (%)	1046 (100.0)	1093 (100.0)
Number of patients with endpoint, N (%)	751 (71.8)	831 (76.0)
95% confidence interval*	(69.0, 74.4)	(73.4, 78.5)
Comparison vs Placebo**		
Risk ratio (SE)		1.060 (0.027)
95% confidence interval***		(1.008, 1.114)
p-value		0.0234

* Wilson confidence intervals.
** Log-linked Poisson model with robust estimate of variance includes terms for baseline KCCQ - overall summary score (p<0.0001), age (p=0.0705), baseline eGFR (CKD-EPI) (p=0.0147), Treatment (p=0.0128), sex (p=0.1199), baseline diabetes status (3 cat.) (p=0.6324), baseline LVEF (3 cat.) (p=0.9922), OECD member (p=0.0003) and Treatment by OECD member interaction (p=0.4806).
***Wald confidence intervals.

Data taken from study 1245.121 only.
LOCF: For a missing value at week 52 the last available post-baseline value before week 52 is imputed.
OECD member (yes/no) countries included:
Yes: United States, Canada, Mexico, Poland, Netherlands, Hungary, Germany, Czech Republic, Italy, France, Spain, United Kingdom, Belgium, Japan, Australia, 'Korea; Republic Of South Korea';
No: Brazil, Argentina, China, India.

Table R.1.2.8.5: 5 Responder analysis (displaying odds ratio) in KCCQ-OSS change from baseline at week 52 of >= 5 points (improvement) by OECD member (N/Y) - RS (LOCF-AD) - 1245.121

Subgroup Description	Placebo	Empa 10mg
OECD member: No		
Number of patients in analysis set	741	713
Number of analysed patients, N (%)	663 (100.0)	647 (100.0)
Number of patients with endpoint, N (%)	367 (55.4)	387 (59.8)
95% confidence interval*	(51.6, 59.1)	(56.0, 63.5)
Comparison vs Placebo**		
Odds ratio (SE)		1.257 (0.152)
95% confidence interval***		(0.992, 1.592)
p-value		0.0583
OECD member: Yes		
Number of patients in analysis set	1126	1150
Number of analysed patients, N (%)	1046 (100.0)	1093 (100.0)
Number of patients with endpoint, N (%)	433 (41.4)	489 (44.7)
95% confidence interval*	(38.4, 44.4)	(41.8, 47.7)
Comparison vs Placebo**		
Odds ratio (SE)		1.166 (0.109)
95% confidence interval***		(0.971, 1.402)
p-value		0.1006

* Wilson confidence intervals.
** Logistic regression includes terms for baseline KCCQ - overall summary score (p<0.0001), age (p=0.0249), baseline eGFR (CKD-EPI) (p=0.0429), Treatment (p=0.0123), sex (p=0.1819), baseline diabetes status (3 cat.) (p=0.4132), baseline LVEF (3 cat.) (p=0.9260), OECD member (p<0.0001) and Treatment by OECD member interaction (p=0.6259).
***Wald confidence intervals.

Data taken from study 1245.121 only.
LOCF: For a missing value at week 52 the last available post-baseline value before week 52 is imputed.
OECD member (yes/no) countries included:
Yes: United States, Canada, Mexico, Poland, Netherlands, Hungary, Germany, Czech Republic, Italy, France, Spain, United Kingdom, Belgium, Japan, Australia, 'Korea; Republic Of South Korea';
No: Brazil, Argentina, China, India.

Table R.1.2.8.5: 6 Responder analysis (displaying risk ratio) in KCCQ-OSS change from baseline at week 52 of >= 5 points (improvement) by OECD member (N/Y) - RS (LOCF-AD) - 1245.121

Subgroup Description	Placebo	Empa 10mg
OECD member: No		
Number of patients in analysis set	741	713
Number of analysed patients, N (%)	663 (100.0)	647 (100.0)
Number of patients with endpoint, N (%)	367 (55.4)	387 (59.8)
95% confidence interval*	(51.6, 59.1)	(56.0, 63.5)
Comparison vs Placebo**		
Risk ratio (SE)		1.076 (0.049)
95% confidence interval***		(0.983, 1.176)
p-value		0.1114
OECD member: Yes		
Number of patients in analysis set	1126	1150
Number of analysed patients, N (%)	1046 (100.0)	1093 (100.0)
Number of patients with endpoint, N (%)	433 (41.4)	489 (44.7)
95% confidence interval*	(38.4, 44.4)	(41.8, 47.7)
Comparison vs Placebo**		
Risk ratio (SE)		1.076 (0.051)
95% confidence interval***		(0.981, 1.180)
p-value		0.1185

* Wilson confidence intervals.
** Log-linked Poisson model with robust estimate of variance includes terms for baseline KCCQ - overall summary score (p<0.0001), age (p=0.0430), baseline eGFR (CKD-EPI) (p=0.0440), Treatment (p=0.0258), sex (p=0.1624), baseline diabetes status (3 cat.) (p=0.4278), baseline LVEF (3 cat.) (p=0.8658), OECD member (p<0.0001) and Treatment by OECD member interaction (p=0.9923).
***Wald confidence intervals.

Data taken from study 1245.121 only.
LOCF: For a missing value at week 52 the last available post-baseline value before week 52 is imputed.
OECD member (yes/no) countries included:
Yes: United States, Canada, Mexico, Poland, Netherlands, Hungary, Germany, Czech Republic, Italy, France, Spain, United Kingdom, Belgium, Japan, Australia, 'Korea; Republic Of South Korea';
No: Brazil, Argentina, China, India.

R.1.2.8.6 Subgroup analysis by NYHA at baseline (II, III/IV - 2 cat.)

Table R.1.2.8.6: 1 Responder analysis (displaying odds ratio) in KCCQ-OSS change from baseline at week 52 of <= -5 points (deterioration) by NYHA (2 cat.) - RS (LOCF-AD) - 1245.121

Subgroup Description	Placebo	Empa 10mg
Baseline NYHA (2 cat.): II		
Number of patients in analysis set	1401	1399
Number of analysed patients, N (%)	1306 (100.0)	1307 (100.0)
Number of patients with endpoint, N (%)	322 (24.7)	277 (21.2)
95% confidence interval*	(22.4, 27.1)	(19.1, 23.5)
Comparison vs Placebo**		
Odds ratio (SE)		0.796 (0.076)
95% confidence interval***		(0.661, 0.959)
p-value		0.0164
Baseline NYHA (2 cat.): III/IV		
Number of patients in analysis set	466	464
Number of analysed patients, N (%)	403 (100.0)	433 (100.0)
Number of patients with endpoint, N (%)	102 (25.3)	94 (21.7)
95% confidence interval*	(21.3, 29.8)	(18.1, 25.8)
Comparison vs Placebo**		
Odds ratio (SE)		0.838 (0.140)
95% confidence interval***		(0.603, 1.163)
p-value		0.2894

* Wilson confidence intervals.
** Logistic regression includes terms for baseline KCCQ - overall summary score (p<0.0001), age (p=0.1069), baseline eGFR (CKD-EPI) (p=0.0253), Treatment (p=0.0351), region (5 cat.) (p<0.0001), baseline diabetes status (3 cat.) (p=0.5555), sex (p=0.1129), baseline LVEF (3 cat.) (p=0.9860), baseline NYHA (2 cat.) (p=0.0061) and Treatment by baseline NYHA (2 cat.) interaction (p=0.7915).
***Wald confidence intervals.

Data taken from study 1245.121 only.
LOCF: For a missing value at week 52 the last available post-baseline value before week 52 is imputed.

Table R.1.2.8.6: 2 Responder analysis (displaying risk ratio) in KCCQ-OSS change from baseline at week 52 of <= -5 points (deterioration) by NYHA (2 cat.) - RS (LOCF-AD) - 1245.121

Subgroup Description	Placebo	Empa 10mg
Baseline NYHA (2 cat.): II		
Number of patients in analysis set	1401	1399
Number of analysed patients, N (%)	1306 (100.0)	1307 (100.0)
Number of patients with endpoint, N (%)	322 (24.7)	277 (21.2)
95% confidence interval*	(22.4, 27.1)	(19.1, 23.5)
Comparison vs Placebo**		
Risk ratio (SE)		0.844 (0.060)
95% confidence interval***		(0.735, 0.970)
p-value		0.0168
Baseline NYHA (2 cat.): III/IV		
Number of patients in analysis set	466	464
Number of analysed patients, N (%)	403 (100.0)	433 (100.0)
Number of patients with endpoint, N (%)	102 (25.3)	94 (21.7)
95% confidence interval*	(21.3, 29.8)	(18.1, 25.8)
Comparison vs Placebo**		
Risk ratio (SE)		0.877 (0.107)
95% confidence interval***		(0.690, 1.113)
p-value		0.2803

* Wilson confidence intervals.
** Log-linked Poisson model with robust estimate of variance includes terms for baseline KCCQ - overall summary score (p<0.0001), age (p=0.1086), baseline eGFR (CKD-EPI) (p=0.0261), Treatment (p=0.0325), region (5 cat.) (p<0.0001), baseline diabetes status (3 cat.) (p=0.5661), sex (p=0.1203), baseline LVEF (3 cat.) (p=0.9867), baseline NYHA (2 cat.) (p=0.0058) and Treatment by baseline NYHA (2 cat.) interaction (p=0.7879).
***Wald confidence intervals.

Data taken from study 1245.121 only.
LOCF: For a missing value at week 52 the last available post-baseline value before week 52 is imputed.

Table R.1.2.8.6: 3 Responder analysis (displaying odds ratio) in KCCQ-OSS change from baseline at week 52 of > -5 points (stability) by NYHA (2 cat.) - RS (LOCF-AD) - 1245.121

Subgroup Description	Placebo	Empa 10mg
Baseline NYHA (2 cat.): II		
Number of patients in analysis set	1401	1399
Number of analysed patients, N (%)	1306 (100.0)	1307 (100.0)
Number of patients with endpoint, N (%)	984 (75.3)	1030 (78.8)
95% confidence interval*	(72.9, 77.6)	(76.5, 80.9)
Comparison vs Placebo**		
Odds ratio (SE)		1.256 (0.119)
95% confidence interval***		(1.043, 1.514)
p-value		0.0164
Baseline NYHA (2 cat.): III/IV		
Number of patients in analysis set	466	464
Number of analysed patients, N (%)	403 (100.0)	433 (100.0)
Number of patients with endpoint, N (%)	301 (74.7)	339 (78.3)
95% confidence interval*	(70.2, 78.7)	(74.2, 81.9)
Comparison vs Placebo**		
Odds ratio (SE)		1.194 (0.200)
95% confidence interval***		(0.860, 1.657)
p-value		0.2894

* Wilson confidence intervals.
** Logistic regression includes terms for baseline KCCQ - overall summary score (p<0.0001), age (p=0.1069), baseline eGFR (CKD-EPI) (p=0.0253), Treatment (p=0.0351), region (5 cat.) (p<0.0001), baseline diabetes status (3 cat.) (p=0.5555), sex (p=0.1129), baseline LVEF (3 cat.) (p=0.9860), baseline NYHA (2 cat.) (p=0.0061) and Treatment by baseline NYHA (2 cat.) interaction (p=0.7915).
***Wald confidence intervals.

Data taken from study 1245.121 only.
LOCF: For a missing value at week 52 the last available post-baseline value before week 52 is imputed.

Table R.1.2.8.6: 4 Responder analysis (displaying risk ratio) in KCCQ-OSS change from baseline at week 52 of > -5 points (stability) by NYHA (2 cat.) - RS (LOCF-AD) - 1245.121

Subgroup Description	Placebo	Empa 10mg
Baseline NYHA (2 cat.): II		
Number of patients in analysis set	1401	1399
Number of analysed patients, N (%)	1306 (100.0)	1307 (100.0)
Number of patients with endpoint, N (%)	984 (75.3)	1030 (78.8)
95% confidence interval*	(72.9, 77.6)	(76.5, 80.9)
Comparison vs Placebo**		
Risk ratio (SE)		1.052 (0.022)
95% confidence interval***		(1.009, 1.096)
p-value		0.0167
Baseline NYHA (2 cat.): III/IV		
Number of patients in analysis set	466	464
Number of analysed patients, N (%)	403 (100.0)	433 (100.0)
Number of patients with endpoint, N (%)	301 (74.7)	339 (78.3)
95% confidence interval*	(70.2, 78.7)	(74.2, 81.9)
Comparison vs Placebo**		
Risk ratio (SE)		1.039 (0.039)
95% confidence interval***		(0.965, 1.118)
p-value		0.3110

* Wilson confidence intervals.
** Log-linked Poisson model with robust estimate of variance includes terms for baseline KCCQ - overall summary score (p<0.0001), age (p=0.1395), baseline eGFR (CKD-EPI) (p=0.0317), Treatment (p=0.0399), region (5 cat.) (p<0.0001), baseline diabetes status (3 cat.) (p=0.5616), sex (p=0.0941), baseline LVEF (3 cat.) (p=0.9768), baseline NYHA (2 cat.) (p=0.0088) and Treatment by baseline NYHA (2 cat.) interaction (p=0.7757).
***Wald confidence intervals.

Data taken from study 1245.121 only.
LOCF: For a missing value at week 52 the last available post-baseline value before week 52 is imputed.

Table R.1.2.8.6: 5 Responder analysis (displaying odds ratio) in KCCQ-OSS change from baseline at week 52 of >= 5 points (improvement) by NYHA (2 cat.) - RS (LOCF-AD) - 1245.121

Subgroup Description	Placebo	Empa 10mg
Baseline NYHA (2 cat.): II		
Number of patients in analysis set	1401	1399
Number of analysed patients, N (%)	1306 (100.0)	1307 (100.0)
Number of patients with endpoint, N (%)	571 (43.7)	626 (47.9)
95% confidence interval*	(41.1, 46.4)	(45.2, 50.6)
Comparison vs Placebo**		
Odds ratio (SE)		1.289 (0.110)
95% confidence interval***		(1.091, 1.523)
p-value		0.0028
Baseline NYHA (2 cat.): III/IV		
Number of patients in analysis set	466	464
Number of analysed patients, N (%)	403 (100.0)	433 (100.0)
Number of patients with endpoint, N (%)	229 (56.8)	250 (57.7)
95% confidence interval*	(51.9, 61.6)	(53.0, 62.3)
Comparison vs Placebo**		
Odds ratio (SE)		0.937 (0.143)
95% confidence interval***		(0.694, 1.265)
p-value		0.6719

* Wilson confidence intervals.
** Logistic regression includes terms for baseline KCCQ - overall summary score (p<0.0001), age (p=0.0421), baseline eGFR (CKD-EPI) (p=0.0652), Treatment (p=0.2791), region (5 cat.) (p<0.0001), baseline diabetes status (3 cat.) (p=0.5531), sex (p=0.1751), baseline LVEF (3 cat.) (p=0.8873), baseline NYHA (2 cat.) (p=0.1464) and Treatment by baseline NYHA (2 cat.) interaction (p=0.0687).
***Wald confidence intervals.

Data taken from study 1245.121 only.
LOCF: For a missing value at week 52 the last available post-baseline value before week 52 is imputed.

Table R.1.2.8.6: 6 Responder analysis (displaying risk ratio) in KCCQ-OSS change from baseline at week 52 of >= 5 points (improvement) by NYHA (2 cat.) - RS (LOCF-AD) - 1245.121

Subgroup Description	Placebo	Empa 10mg
Baseline NYHA (2 cat.): II		
Number of patients in analysis set	1401	1399
Number of analysed patients, N (%)	1306 (100.0)	1307 (100.0)
Number of patients with endpoint, N (%)	571 (43.7)	626 (47.9)
95% confidence interval*	(41.1, 46.4)	(45.2, 50.6)
Comparison vs Placebo**		
Risk ratio (SE)		1.118 (0.044)
95% confidence interval***		(1.034, 1.209)
p-value		0.0049
Baseline NYHA (2 cat.): III/IV		
Number of patients in analysis set	466	464
Number of analysed patients, N (%)	403 (100.0)	433 (100.0)
Number of patients with endpoint, N (%)	229 (56.8)	250 (57.7)
95% confidence interval*	(51.9, 61.6)	(53.0, 62.3)
Comparison vs Placebo**		
Risk ratio (SE)		0.969 (0.057)
95% confidence interval***		(0.864, 1.088)
p-value		0.5940

* Wilson confidence intervals.
** Log-linked Poisson model with robust estimate of variance includes terms for baseline KCCQ - overall summary score (p<0.0001), age (p=0.0723), baseline eGFR (CKD-EPI) (p=0.0654), Treatment (p=0.2577), region (5 cat.) (p<0.0001), baseline diabetes status (3 cat.) (p=0.5368), sex (p=0.1365), baseline LVEF (3 cat.) (p=0.8267), baseline NYHA (2 cat.) (p=0.1387) and Treatment by baseline NYHA (2 cat.) interaction (p=0.0438).
***Wald confidence intervals.

Data taken from study 1245.121 only.
LOCF: For a missing value at week 52 the last available post-baseline value before week 52 is imputed.

R.1.2.8.7

R.1.2.8.7 Subgroup analysis by diabetes at baseline

Table R.1.2.8.7: 1 Responder analysis (displaying odds ratio) in KCCQ-OSS change from baseline at week 52 of <= -5 points (deterioration) by diabetes at baseline - RS (LOCF-AD) - 1245.121

Subgroup Description	Placebo	Empa 10mg
Diabetes at baseline (2 cat.): Diabetic		
Number of patients in analysis set	929	927
Number of analysed patients, N (%)	850 (100.0)	861 (100.0)
Number of patients with endpoint, N (%)	220 (25.9)	184 (21.4)
95% confidence interval*	(23.1, 28.9)	(18.8, 24.2)
Comparison vs Placebo**		
Odds ratio (SE)		0.765 (0.089)
95% confidence interval***		(0.609, 0.961)
p-value		0.0211
Diabetes at baseline (2 cat.): Non-Diabetic		
Number of patients in analysis set	938	936
Number of analysed patients, N (%)	859 (100.0)	879 (100.0)
Number of patients with endpoint, N (%)	204 (23.7)	187 (21.3)
95% confidence interval*	(21.0, 26.7)	(18.7, 24.1)
Comparison vs Placebo**		
Odds ratio (SE)		0.855 (0.100)
95% confidence interval***		(0.680, 1.075)
p-value		0.1803

* Wilson confidence intervals.
** Logistic regression includes terms for baseline KCCQ - overall summary score (p<0.0001), age (p=0.0960), baseline eGFR (CKD-EPI) (p=0.0199), Treatment (p=0.0100), region (5 cat.) (p<0.0001), sex (p=0.1108), baseline LVEF (3 cat.) (p=0.9847), diabetes at baseline (2 cat.) (p=0.2249) and Treatment by diabetes at baseline (2 cat.) interaction (p=0.4984).
***Wald confidence intervals.

Data taken from study 1245.121 only.
LOCF: For a missing value at week 52 the last available post-baseline value before week 52 is imputed.

Table R.1.2.8.7: 2 Responder analysis (displaying risk ratio) in KCCQ-OSS change from baseline at week 52 of <= -5 points (deterioration) by diabetes at baseline - RS (LOCF-AD) - 1245.121

Subgroup Description	Placebo	Empa 10mg
Diabetes at baseline (2 cat.): Diabetic		
Number of patients in analysis set	929	927
Number of analysed patients, N (%)	850 (100.0)	861 (100.0)
Number of patients with endpoint, N (%)	220 (25.9)	184 (21.4)
95% confidence interval*	(23.1, 28.9)	(18.8, 24.2)
Comparison vs Placebo**		
Risk ratio (SE)		0.820 (0.070)
95% confidence interval***		(0.693, 0.970)
p-value		0.0204
Diabetes at baseline (2 cat.): Non-Diabetic		
Number of patients in analysis set	938	936
Number of analysed patients, N (%)	859 (100.0)	879 (100.0)
Number of patients with endpoint, N (%)	204 (23.7)	187 (21.3)
95% confidence interval*	(21.0, 26.7)	(18.7, 24.1)
Comparison vs Placebo**		
Risk ratio (SE)		0.889 (0.078)
95% confidence interval***		(0.749, 1.057)
p-value		0.1826

* Wilson confidence intervals.
** Log-linked Poisson model with robust estimate of variance includes terms for baseline KCCQ - overall summary score (p<0.0001), age (p=0.0955), baseline eGFR (CKD-EPI) (p=0.0205), Treatment (p=0.0100), region (5 cat.) (p<0.0001), sex (p=0.1176), baseline LVEF (3 cat.) (p=0.9847), diabetes at baseline (2 cat.) (p=0.2361) and Treatment by diabetes at baseline (2 cat.) interaction (p=0.5071).
***Wald confidence intervals.

Data taken from study 1245.121 only.
LOCF: For a missing value at week 52 the last available post-baseline value before week 52 is imputed.

Table R.1.2.8.7: 3 Responder analysis (displaying odds ratio) in KCCQ-OSS change from baseline at week 52 of > -5 points (stability) by diabetes at baseline - RS (LOCF-AD) - 1245.121

Subgroup Description	Placebo	Empa 10mg
Diabetes at baseline (2 cat.): Diabetic		
Number of patients in analysis set	929	927
Number of analysed patients, N (%)	850 (100.0)	861 (100.0)
Number of patients with endpoint, N (%)	630 (74.1)	677 (78.6)
95% confidence interval*	(71.1, 76.9)	(75.8, 81.2)
Comparison vs Placebo**		
Odds ratio (SE)		1.308 (0.152)
95% confidence interval***		(1.041, 1.643)
p-value		0.0211
Diabetes at baseline (2 cat.): Non-Diabetic		
Number of patients in analysis set	938	936
Number of analysed patients, N (%)	859 (100.0)	879 (100.0)
Number of patients with endpoint, N (%)	655 (76.3)	692 (78.7)
95% confidence interval*	(73.3, 79.0)	(75.9, 81.3)
Comparison vs Placebo**		
Odds ratio (SE)		1.170 (0.137)
95% confidence interval***		(0.930, 1.471)
p-value		0.1803

* Wilson confidence intervals.
** Logistic regression includes terms for baseline KCCQ - overall summary score (p<0.0001), age (p=0.0960), baseline eGFR (CKD-EPI) (p=0.0199), Treatment (p=0.0100), region (5 cat.) (p<0.0001), sex (p=0.1108), baseline LVEF (3 cat.) (p=0.9847), diabetes at baseline (2 cat.) (p=0.2249) and Treatment by diabetes at baseline (2 cat.) interaction (p=0.4984).
***Wald confidence intervals.

Data taken from study 1245.121 only.
LOCF: For a missing value at week 52 the last available post-baseline value before week 52 is imputed.

Table R.1.2.8.7: 4 Responder analysis (displaying risk ratio) in KCCQ-OSS change from baseline at week 52 of > -5 points (stability) by diabetes at baseline - RS (LOCF-AD) - 1245.121

Subgroup Description	Placebo	Empa 10mg
Diabetes at baseline (2 cat.): Diabetic		
Number of patients in analysis set	929	927
Number of analysed patients, N (%)	850 (100.0)	861 (100.0)
Number of patients with endpoint, N (%)	630 (74.1)	677 (78.6)
95% confidence interval*	(71.1, 76.9)	(75.8, 81.2)
Comparison vs Placebo**		
Risk ratio (SE)		1.061 (0.028)
95% confidence interval***		(1.007, 1.117)
p-value		0.0254
Diabetes at baseline (2 cat.): Non-Diabetic		
Number of patients in analysis set	938	936
Number of analysed patients, N (%)	859 (100.0)	879 (100.0)
Number of patients with endpoint, N (%)	655 (76.3)	692 (78.7)
95% confidence interval*	(73.3, 79.0)	(75.9, 81.3)
Comparison vs Placebo**		
Risk ratio (SE)		1.035 (0.026)
95% confidence interval***		(0.984, 1.088)
p-value		0.1782

* Wilson confidence intervals.
** Log-linked Poisson model with robust estimate of variance includes terms for baseline KCCQ - overall summary score (p<0.0001), age (p=0.1231), baseline eGFR (CKD-EPI) (p=0.0257), Treatment (p=0.0110), region (5 cat.) (p<0.0001), sex (p=0.0951), baseline LVEF (3 cat.) (p=0.9761), diabetes at baseline (2 cat.) (p=0.2103) and Treatment by diabetes at baseline (2 cat.) interaction (p=0.5014).
***Wald confidence intervals.

Data taken from study 1245.121 only.
LOCF: For a missing value at week 52 the last available post-baseline value before week 52 is imputed.

Table R.1.2.8.7: 5 Responder analysis (displaying odds ratio) in KCCQ-OSS change from baseline at week 52 of >= 5 points (improvement) by diabetes at baseline - RS (LOCF-AD) - 1245.121

Subgroup Description	Placebo	Empa 10mg
Diabetes at baseline (2 cat.): Diabetic		
Number of patients in analysis set	929	927
Number of analysed patients, N (%)	850 (100.0)	861 (100.0)
Number of patients with endpoint, N (%)	411 (48.4)	432 (50.2)
95% confidence interval*	(45.0, 51.7)	(46.8, 53.5)
Comparison vs Placebo**		
Odds ratio (SE)		1.100 (0.116)
95% confidence interval***		(0.895, 1.353)
p-value		0.3647
Diabetes at baseline (2 cat.): Non-Diabetic		
Number of patients in analysis set	938	936
Number of analysed patients, N (%)	859 (100.0)	879 (100.0)
Number of patients with endpoint, N (%)	389 (45.3)	444 (50.5)
95% confidence interval*	(42.0, 48.6)	(47.2, 53.8)
Comparison vs Placebo**		
Odds ratio (SE)		1.293 (0.135)
95% confidence interval***		(1.054, 1.585)
p-value		0.0137

* Wilson confidence intervals.
** Logistic regression includes terms for baseline KCCQ - overall summary score (p<0.0001), age (p=0.0442), baseline eGFR (CKD-EPI) (p=0.0599), Treatment (p=0.0175), region (5 cat.) (p<0.0001), sex (p=0.1610), baseline LVEF (3 cat.) (p=0.8923), diabetes at baseline (2 cat.) (p=0.8164) and Treatment by diabetes at baseline (2 cat.) interaction (p=0.2770).
***Wald confidence intervals.

Data taken from study 1245.121 only.
LOCF: For a missing value at week 52 the last available post-baseline value before week 52 is imputed.

Table R.1.2.8.7: 6 Responder analysis (displaying risk ratio) in KCCQ-OSS change from baseline at week 52 of >= 5 points (improvement) by diabetes at baseline - RS (LOCF-AD) - 1245.121

Subgroup Description	Placebo	Empa 10mg
Diabetes at baseline (2 cat.): Diabetic		
Number of patients in analysis set	929	927
Number of analysed patients, N (%)	850 (100.0)	861 (100.0)
Number of patients with endpoint, N (%)	411 (48.4)	432 (50.2)
95% confidence interval*	(45.0, 51.7)	(46.8, 53.5)
Comparison vs Placebo**		
Risk ratio (SE)		1.030 (0.048)
95% confidence interval***		(0.940, 1.128)
p-value		0.5261
Diabetes at baseline (2 cat.): Non-Diabetic		
Number of patients in analysis set	938	936
Number of analysed patients, N (%)	859 (100.0)	879 (100.0)
Number of patients with endpoint, N (%)	389 (45.3)	444 (50.5)
95% confidence interval*	(42.0, 48.6)	(47.2, 53.8)
Comparison vs Placebo**		
Risk ratio (SE)		1.117 (0.052)
95% confidence interval***		(1.019, 1.224)
p-value		0.0184

* Wilson confidence intervals.
** Log-linked Poisson model with robust estimate of variance includes terms for baseline KCCQ - overall summary score (p<0.0001), age (p=0.0697), baseline eGFR (CKD-EPI) (p=0.0638), Treatment (p=0.0340), region (5 cat.) (p<0.0001), sex (p=0.1371), baseline LVEF (3 cat.) (p=0.8116), diabetes at baseline (2 cat.) (p=0.7465) and Treatment by diabetes at baseline (2 cat.) interaction (p=0.2188).
***Wald confidence intervals.

Data taken from study 1245.121 only.
LOCF: For a missing value at week 52 the last available post-baseline value before week 52 is imputed.

R.1.2.8.8 Subgroup analysis by BMI at baseline (<30, >=30)

Table R.1.2.8.8: 1 Responder analysis (displaying odds ratio) in KCCQ-OSS change from baseline at week 52 of <= -5 points (deterioration) by baseline BMI [kg/m2] - RS (LOCF-AD) - 1245.121

Subgroup Description	Placebo	Empa 10mg
Baseline BMI [kg/m²] (2 cat.): <30		
Number of patients in analysis set	1300	1263
Number of analysed patients, N (%)	1197 (100.0)	1181 (100.0)
Number of patients with endpoint, N (%)	283 (23.6)	246 (20.8)
95% confidence interval*	(21.3, 26.1)	(18.6, 23.2)
Comparison vs Placebo**		
Odds ratio (SE)		0.829 (0.083)
95% confidence interval***		(0.681, 1.010)
p-value		0.0631
Baseline BMI [kg/m²] (2 cat.): >=30		
Number of patients in analysis set	567	600
Number of analysed patients, N (%)	512 (100.0)	559 (100.0)
Number of patients with endpoint, N (%)	141 (27.5)	125 (22.4)
95% confidence interval*	(23.8, 31.6)	(19.1, 26.0)
Comparison vs Placebo**		
Odds ratio (SE)		0.757 (0.109)
95% confidence interval***		(0.570, 1.004)
p-value		0.0536

* Wilson confidence intervals.
** Logistic regression includes terms for baseline KCCQ - overall summary score (p<0.0001), age (p=0.0501), baseline eGFR (CKD-EPI) (p=0.0229), Treatment (p=0.0082), region (5 cat.) (p<0.0001), baseline diabetes status (3 cat.) (p=0.6143), sex (p=0.1006), baseline LVEF (3 cat.) (p=0.9816), baseline BMI (2 cat.) (p=0.0680) and Treatment by baseline BMI (2 cat.) interaction (p=0.6026).
***Wald confidence intervals.

Data taken from study 1245.121 only.
LOCF: For a missing value at week 52 the last available post-baseline value before week 52 is imputed.

Table R.1.2.8.8: 2 Responder analysis (displaying risk ratio) in KCCQ-OSS change from baseline at week 52 of <= -5 points (deterioration) by baseline BMI [kg/m2] - RS (LOCF-AD) - 1245.121

Subgroup Description	Placebo	Empa 10mg
Baseline BMI [kg/m²] (2 cat.): <30		
Number of patients in analysis set	1300	1263
Number of analysed patients, N (%)	1197 (100.0)	1181 (100.0)
Number of patients with endpoint, N (%)	283 (23.6)	246 (20.8)
95% confidence interval*	(21.3, 26.1)	(18.6, 23.2)
Comparison vs Placebo**		
Risk ratio (SE)		0.869 (0.066)
95% confidence interval***		(0.749, 1.007)
p-value		0.0623
Baseline BMI [kg/m²] (2 cat.): >=30		
Number of patients in analysis set	567	600
Number of analysed patients, N (%)	512 (100.0)	559 (100.0)
Number of patients with endpoint, N (%)	141 (27.5)	125 (22.4)
95% confidence interval*	(23.8, 31.6)	(19.1, 26.0)
Comparison vs Placebo**		
Risk ratio (SE)		0.817 (0.086)
95% confidence interval***		(0.665, 1.003)
p-value		0.0538

* Wilson confidence intervals.
** Log-linked Poisson model with robust estimate of variance includes terms for baseline KCCQ - overall summary score (p<0.0001), age (p=0.0503), baseline eGFR (CKD-EPI) (p=0.0237), Treatment (p=0.0080), region (5 cat.) (p<0.0001), baseline diabetes status (3 cat.) (p=0.6248), sex (p=0.1074), baseline LVEF (3 cat.) (p=0.9810), baseline BMI (2 cat.) (p=0.0653) and Treatment by baseline BMI (2 cat.) interaction (p=0.6328).
***Wald confidence intervals.

Data taken from study 1245.121 only.
LOCF: For a missing value at week 52 the last available post-baseline value before week 52 is imputed.

Table R.1.2.8.8: 3 Responder analysis (displaying odds ratio) in KCCQ-OSS change from baseline at week 52 of > -5 points (stability) by baseline BMI [kg/m2] - RS (LOCF-AD) - 1245.121

Subgroup Description	Placebo	Empa 10mg
Baseline BMI [kg/m²] (2 cat.): <30		
Number of patients in analysis set	1300	1263
Number of analysed patients, N (%)	1197 (100.0)	1181 (100.0)
Number of patients with endpoint, N (%)	914 (76.4)	935 (79.2)
95% confidence interval*	(73.9, 78.7)	(76.8, 81.4)
Comparison vs Placebo**		
Odds ratio (SE)		1.206 (0.121)
95% confidence interval***		(0.990, 1.469)
p-value		0.0631
Baseline BMI [kg/m²] (2 cat.): >=30		
Number of patients in analysis set	567	600
Number of analysed patients, N (%)	512 (100.0)	559 (100.0)
Number of patients with endpoint, N (%)	371 (72.5)	434 (77.6)
95% confidence interval*	(68.4, 76.2)	(74.0, 80.9)
Comparison vs Placebo**		
Odds ratio (SE)		1.321 (0.191)
95% confidence interval***		(0.996, 1.754)
p-value		0.0536

* Wilson confidence intervals.
** Logistic regression includes terms for baseline KCCQ - overall summary score (p<0.0001), age (p=0.0501), baseline eGFR (CKD-EPI) (p=0.0229), Treatment (p=0.0082), region (5 cat.) (p<0.0001), baseline diabetes status (3 cat.) (p=0.6143), sex (p=0.1006), baseline LVEF (3 cat.) (p=0.9816), baseline BMI (2 cat.) (p=0.0680) and Treatment by baseline BMI (2 cat.) interaction (p=0.6026).
***Wald confidence intervals.

Data taken from study 1245.121 only.
LOCF: For a missing value at week 52 the last available post-baseline value before week 52 is imputed.

Table R.1.2.8.8: 4 Responder analysis (displaying risk ratio) in KCCQ-OSS change from baseline at week 52 of > -5 points (stability) by baseline BMI [kg/m2] - RS (LOCF-AD) - 1245.121

Subgroup Description	Placebo	Empa 10mg
Baseline BMI [kg/m²] (2 cat.): <30		
Number of patients in analysis set	1300	1263
Number of analysed patients, N (%)	1197 (100.0)	1181 (100.0)
Number of patients with endpoint, N (%)	914 (76.4)	935 (79.2)
95% confidence interval*	(73.9, 78.7)	(76.8, 81.4)
Comparison vs Placebo**		
Risk ratio (SE)		1.040 (0.022)
95% confidence interval***		(0.997, 1.085)
p-value		0.0676
Baseline BMI [kg/m²] (2 cat.): >=30		
Number of patients in analysis set	567	600
Number of analysed patients, N (%)	512 (100.0)	559 (100.0)
Number of patients with endpoint, N (%)	371 (72.5)	434 (77.6)
95% confidence interval*	(68.4, 76.2)	(74.0, 80.9)
Comparison vs Placebo**		
Risk ratio (SE)		1.069 (0.037)
95% confidence interval***		(0.998, 1.145)
p-value		0.0577

* Wilson confidence intervals.
** Log-linked Poisson model with robust estimate of variance includes terms for baseline KCCQ - overall summary score (p<0.0001), age (p=0.0706), baseline eGFR (CKD-EPI) (p=0.0297), Treatment (p=0.0100), region (5 cat.) (p<0.0001), baseline diabetes status (3 cat.) (p=0.5992), sex (p=0.0858), baseline LVEF (3 cat.) (p=0.9737), baseline BMI (2 cat.) (p=0.0839) and Treatment by baseline BMI (2 cat.) interaction (p=0.5108).
***Wald confidence intervals.

Data taken from study 1245.121 only.
LOCF: For a missing value at week 52 the last available post-baseline value before week 52 is imputed.

Table R.1.2.8.8: 5 Responder analysis (displaying odds ratio) in KCCQ-OSS change from baseline at week 52 of >= 5 points (improvement) by baseline BMI [kg/m2] - RS (LOCF-AD) - 1245.121

Subgroup Description	Placebo	Empa 10mg
Baseline BMI [kg/m²] (2 cat.): <30		
Number of patients in analysis set	1300	1263
Number of analysed patients, N (%)	1197 (100.0)	1181 (100.0)
Number of patients with endpoint, N (%)	555 (46.4)	584 (49.4)
95% confidence interval*	(43.6, 49.2)	(46.6, 52.3)
Comparison vs Placebo**		
Odds ratio (SE)		1.197 (0.107)
95% confidence interval***		(1.005, 1.426)
p-value		0.0442
Baseline BMI [kg/m²] (2 cat.): >=30		
Number of patients in analysis set	567	600
Number of analysed patients, N (%)	512 (100.0)	559 (100.0)
Number of patients with endpoint, N (%)	245 (47.9)	292 (52.2)
95% confidence interval*	(43.6, 52.2)	(48.1, 56.3)
Comparison vs Placebo**		
Odds ratio (SE)		1.193 (0.159)
95% confidence interval***		(0.919, 1.549)
p-value		0.1852

* Wilson confidence intervals.
** Logistic regression includes terms for baseline KCCQ - overall summary score (p<0.0001), age (p=0.0351), baseline eGFR (CKD-EPI) (p=0.0575), Treatment (p=0.0264), region (5 cat.) (p<0.0001), baseline diabetes status (3 cat.) (p=0.5533), sex (p=0.1610), baseline LVEF (3 cat.) (p=0.8956), baseline BMI (2 cat.) (p=0.5200) and Treatment by baseline BMI (2 cat.) interaction (p=0.9847).
***Wald confidence intervals.

Data taken from study 1245.121 only.
LOCF: For a missing value at week 52 the last available post-baseline value before week 52 is imputed.

Table R.1.2.8.8: 6 Responder analysis (displaying risk ratio) in KCCQ-OSS change from baseline at week 52 of >= 5 points (improvement) by baseline BMI [kg/m2] - RS (LOCF-AD) - 1245.121

Subgroup Description	Placebo	Empa 10mg
Baseline BMI [kg/m²] (2 cat.): <30		
Number of patients in analysis set	1300	1263
Number of analysed patients, N (%)	1197 (100.0)	1181 (100.0)
Number of patients with endpoint, N (%)	555 (46.4)	584 (49.4)
95% confidence interval*	(43.6, 49.2)	(46.6, 52.3)
Comparison vs Placebo**		
Risk ratio (SE)		1.074 (0.043)
95% confidence interval***		(0.994, 1.161)
p-value		0.0719
Baseline BMI [kg/m²] (2 cat.): >=30		
Number of patients in analysis set	567	600
Number of analysed patients, N (%)	512 (100.0)	559 (100.0)
Number of patients with endpoint, N (%)	245 (47.9)	292 (52.2)
95% confidence interval*	(43.6, 52.2)	(48.1, 56.3)
Comparison vs Placebo**		
Risk ratio (SE)		1.069 (0.063)
95% confidence interval***		(0.952, 1.201)
p-value		0.2586

* Wilson confidence intervals.
** Log-linked Poisson model with robust estimate of variance includes terms for baseline KCCQ - overall summary score (p<0.0001), age (p=0.0620), baseline eGFR (CKD-EPI) (p=0.0612), Treatment (p=0.0523), region (5 cat.) (p<0.0001), baseline diabetes status (3 cat.) (p=0.5471), sex (p=0.1271), baseline LVEF (3 cat.) (p=0.8262), baseline BMI (2 cat.) (p=0.7024) and Treatment by baseline BMI (2 cat.) interaction (p=0.9501).
***Wald confidence intervals.

Data taken from study 1245.121 only.
LOCF: For a missing value at week 52 the last available post-baseline value before week 52 is imputed.

R.1.2.8.9 Subgroup analysis by eGFR at baseline (<60, >=60)

Table R.1.2.8.9: 1 Responder analysis (displaying odds ratio) in KCCQ-OSS change from baseline at week 52 of <= -5 points (deterioration) by baseline eGFR (2 cat.) - RS (LOCF-AD) - 1245.121

Subgroup Description	Placebo	Empa 10mg
Baseline eGFR (CKD-EPI) [mL/min/1.73m²] (2 cat.): >=60		
Number of patients in analysis set	960	969
Number of analysed patients, N (%)	875 (100.0)	903 (100.0)
Number of patients with endpoint, N (%)	204 (23.3)	174 (19.3)
95% confidence interval*	(20.6, 26.2)	(16.8, 22.0)
Comparison vs Placebo**		
Odds ratio (SE)		0.760 (0.090)
95% confidence interval***		(0.602, 0.958)
p-value		0.0202
Baseline eGFR (CKD-EPI) [mL/min/1.73m²] (2 cat.): <60		
Number of patients in analysis set	906	893
Number of analysed patients, N (%)	834 (100.0)	837 (100.0)
Number of patients with endpoint, N (%)	220 (26.4)	197 (23.5)
95% confidence interval*	(23.5, 29.5)	(20.8, 26.5)
Comparison vs Placebo**		
Odds ratio (SE)		0.856 (0.098)
95% confidence interval***		(0.683, 1.072)
p-value		0.1764

* Wilson confidence intervals.
** Logistic regression includes terms for baseline KCCQ - overall summary score (p<0.0001), age (p=0.0075), Treatment (p=0.0091), region (5 cat.) (p<0.0001), baseline diabetes status (3 cat.) (p=0.3991), sex (p=0.1252), baseline LVEF (3 cat.) (p=0.9734), baseline eGFR (CKD-EPI) (2 cat.) (p=0.4050) and Treatment by baseline eGFR (CKD-EPI) (2 cat.) interaction (p=0.4692).
***Wald confidence intervals.
2 patients were excluded as the subgroup variable was missing.

Data taken from study 1245.121 only.
LOCF: For a missing value at week 52 the last available post-baseline value before week 52 is imputed.

Table R.1.2.8.9: 2 Responder analysis (displaying risk ratio) in KCCQ-OSS change from baseline at week 52 of <= -5 points (deterioration) by baseline eGFR (2 cat.) - RS (LOCF-AD) - 1245.121

Subgroup Description	Placebo	Empa 10mg
Baseline eGFR (CKD-EPI) [mL/min/1.73m²] (2 cat.): >=60		
Number of patients in analysis set	960	969
Number of analysed patients, N (%)	875 (100.0)	903 (100.0)
Number of patients with endpoint, N (%)	204 (23.3)	174 (19.3)
95% confidence interval*	(20.6, 26.2)	(16.8, 22.0)
Comparison vs Placebo**		
Risk ratio (SE)		0.809 (0.073)
95% confidence interval***		(0.678, 0.966)
p-value		0.0190
Baseline eGFR (CKD-EPI) [mL/min/1.73m²] (2 cat.): <60		
Number of patients in analysis set	906	893
Number of analysed patients, N (%)	834 (100.0)	837 (100.0)
Number of patients with endpoint, N (%)	220 (26.4)	197 (23.5)
95% confidence interval*	(23.5, 29.5)	(20.8, 26.5)
Comparison vs Placebo**		
Risk ratio (SE)		0.894 (0.075)
95% confidence interval***		(0.758, 1.053)
p-value		0.1808

* Wilson confidence intervals.
** Log-linked Poisson model with robust estimate of variance includes terms for baseline KCCQ - overall summary score (p<0.0001), age (p=0.0074), Treatment (p=0.0085), region (5 cat.) (p<0.0001), baseline diabetes status (3 cat.) (p=0.4024), sex (p=0.1342), baseline LVEF (3 cat.) (p=0.9721), baseline eGFR (CKD-EPI) (2 cat.) (p=0.4008) and Treatment by baseline eGFR (CKD-EPI) (2 cat.) interaction (p=0.4198).
***Wald confidence intervals.
2 patients were excluded as the subgroup variable was missing.

Data taken from study 1245.121 only.
LOCF: For a missing value at week 52 the last available post-baseline value before week 52 is imputed.

Table R.1.2.8.9: 3 Responder analysis (displaying odds ratio) in KCCQ-OSS change from baseline at week 52 of > -5 points (stability) by baseline eGFR (2 cat.) - RS (LOCF-AD) - 1245.121

Subgroup Description	Placebo	Empa 10mg
Baseline eGFR (CKD-EPI) [mL/min/1.73m²] (2 cat.): >=60		
Number of patients in analysis set	960	969
Number of analysed patients, N (%)	875 (100.0)	903 (100.0)
Number of patients with endpoint, N (%)	671 (76.7)	729 (80.7)
95% confidence interval*	(73.8, 79.4)	(78.0, 83.2)
Comparison vs Placebo**		
Odds ratio (SE)		1.317 (0.156)
95% confidence interval***		(1.044, 1.661)
p-value		0.0202
Baseline eGFR (CKD-EPI) [mL/min/1.73m²] (2 cat.): <60		
Number of patients in analysis set	906	893
Number of analysed patients, N (%)	834 (100.0)	837 (100.0)
Number of patients with endpoint, N (%)	614 (73.6)	640 (76.5)
95% confidence interval*	(70.5, 76.5)	(73.5, 79.2)
Comparison vs Placebo**		
Odds ratio (SE)		1.168 (0.134)
95% confidence interval***		(0.932, 1.464)
p-value		0.1764

* Wilson confidence intervals.
** Logistic regression includes terms for baseline KCCQ - overall summary score (p<0.0001), age (p=0.0075), Treatment (p=0.0091), region (5 cat.) (p<0.0001), baseline diabetes status (3 cat.) (p=0.3991), sex (p=0.1252), baseline LVEF (3 cat.) (p=0.9734), baseline eGFR (CKD-EPI) (2 cat.) (p=0.4050) and Treatment by baseline eGFR (CKD-EPI) (2 cat.) interaction (p=0.4692).
***Wald confidence intervals.
2 patients were excluded as the subgroup variable was missing.

Data taken from study 1245.121 only.
LOCF: For a missing value at week 52 the last available post-baseline value before week 52 is imputed.

Table R.1.2.8.9: 4 Responder analysis (displaying risk ratio) in KCCQ-OSS change from baseline at week 52 of > -5 points (stability) by baseline eGFR (2 cat.) - RS (LOCF-AD) - 1245.121

Subgroup Description	Placebo	Empa 10mg
Baseline eGFR (CKD-EPI) [mL/min/1.73m²] (2 cat.): >=60		
Number of patients in analysis set	960	969
Number of analysed patients, N (%)	875 (100.0)	903 (100.0)
Number of patients with endpoint, N (%)	671 (76.7)	729 (80.7)
95% confidence interval*	(73.8, 79.4)	(78.0, 83.2)
Comparison vs Placebo**		
Risk ratio (SE)		1.056 (0.026)
95% confidence interval***		(1.006, 1.107)
p-value		0.0263
Baseline eGFR (CKD-EPI) [mL/min/1.73m²] (2 cat.): <60		
Number of patients in analysis set	906	893
Number of analysed patients, N (%)	834 (100.0)	837 (100.0)
Number of patients with endpoint, N (%)	614 (73.6)	640 (76.5)
95% confidence interval*	(70.5, 76.5)	(73.5, 79.2)
Comparison vs Placebo**		
Risk ratio (SE)		1.039 (0.029)
95% confidence interval***		(0.984, 1.098)
p-value		0.1659

* Wilson confidence intervals.
** Log-linked Poisson model with robust estimate of variance includes terms for baseline KCCQ - overall summary score (p<0.0001), age (p=0.0090), Treatment (p=0.0121), region (5 cat.) (p<0.0001), baseline diabetes status (3 cat.) (p=0.4086), sex (p=0.1019), baseline LVEF (3 cat.) (p=0.9666), baseline eGFR (CKD-EPI) (2 cat.) (p=0.4235) and Treatment by baseline eGFR (CKD-EPI) (2 cat.) interaction (p=0.6729).
***Wald confidence intervals.
2 patients were excluded as the subgroup variable was missing.

Data taken from study 1245.121 only.
LOCF: For a missing value at week 52 the last available post-baseline value before week 52 is imputed.

Table R.1.2.8.9: 5 Responder analysis (displaying odds ratio) in KCCQ-OSS change from baseline at week 52 of >= 5 points (improvement) by baseline eGFR (2 cat.) - RS (LOCF-AD) - 1245.121

Subgroup Description	Placebo	Empa 10mg
Baseline eGFR (CKD-EPI) [mL/min/1.73m²] (2 cat.): >=60		
Number of patients in analysis set	960	969
Number of analysed patients, N (%)	875 (100.0)	903 (100.0)
Number of patients with endpoint, N (%)	428 (48.9)	481 (53.3)
95% confidence interval*	(45.6, 52.2)	(50.0, 56.5)
Comparison vs Placebo**		
Odds ratio (SE)		1.267 (0.131)
95% confidence interval***		(1.035, 1.551)
p-value		0.0219
Baseline eGFR (CKD-EPI) [mL/min/1.73m²] (2 cat.): <60		
Number of patients in analysis set	906	893
Number of analysed patients, N (%)	834 (100.0)	837 (100.0)
Number of patients with endpoint, N (%)	372 (44.6)	395 (47.2)
95% confidence interval*	(41.3, 48.0)	(43.8, 50.6)
Comparison vs Placebo**		
Odds ratio (SE)		1.119 (0.119)
95% confidence interval***		(0.908, 1.379)
p-value		0.2902

* Wilson confidence intervals.
** Logistic regression includes terms for baseline KCCQ - overall summary score (p<0.0001), age (p=0.0088), Treatment (p=0.0185), region (5 cat.) (p<0.0001), baseline diabetes status (3 cat.) (p=0.5698), sex (p=0.1758), baseline LVEF (3 cat.) (p=0.8855), baseline eGFR (CKD-EPI) (2 cat.) (p=0.1043) and Treatment by baseline eGFR (CKD-EPI) (2 cat.) interaction (p=0.4037).
***Wald confidence intervals.
2 patients were excluded as the subgroup variable was missing.

Data taken from study 1245.121 only.
LOCF: For a missing value at week 52 the last available post-baseline value before week 52 is imputed.

Table R.1.2.8.9: 6 Responder analysis (displaying risk ratio) in KCCQ-OSS change from baseline at week 52 of >= 5 points (improvement) by baseline eGFR (2 cat.) - RS (LOCF-AD) - 1245.121

Subgroup Description	Placebo	Empa 10mg
Baseline eGFR (CKD-EPI) [mL/min/1.73m²] (2 cat.): >=60		
Number of patients in analysis set	960	969
Number of analysed patients, N (%)	875 (100.0)	903 (100.0)
Number of patients with endpoint, N (%)	428 (48.9)	481 (53.3)
95% confidence interval*	(45.6, 52.2)	(50.0, 56.5)
Comparison vs Placebo**		
Risk ratio (SE)		1.088 (0.049)
95% confidence interval***		(0.996, 1.187)
p-value		0.0600
Baseline eGFR (CKD-EPI) [mL/min/1.73m²] (2 cat.): <60		
Number of patients in analysis set	906	893
Number of analysed patients, N (%)	834 (100.0)	837 (100.0)
Number of patients with endpoint, N (%)	372 (44.6)	395 (47.2)
95% confidence interval*	(41.3, 48.0)	(43.8, 50.6)
Comparison vs Placebo**		
Risk ratio (SE)		1.053 (0.051)
95% confidence interval***		(0.957, 1.159)
p-value		0.2902

* Wilson confidence intervals.
** Log-linked Poisson model with robust estimate of variance includes terms for baseline KCCQ - overall summary score (p<0.0001), age (p=0.0172), Treatment (p=0.0405), region (5 cat.) (p<0.0001), baseline diabetes status (3 cat.) (p=0.5695), sex (p=0.1307), baseline LVEF (3 cat.) (p=0.8178), baseline eGFR (CKD-EPI) (2 cat.) (p=0.0993) and Treatment by baseline eGFR (CKD-EPI) (2 cat.) interaction (p=0.6244).
***Wald confidence intervals.
2 patients were excluded as the subgroup variable was missing.

Data taken from study 1245.121 only.
LOCF: For a missing value at week 52 the last available post-baseline value before week 52 is imputed.

R.1.2.8.10

Table R.1.2.8.10: 1 Responder analysis (displaying odds ratio) in KCCQ-OSS change from baseline at week 52 of <= -5 points (deterioration) by history of HHF - RS (LOCF-AD) - 1245.121

Subgroup Description	Placebo	Empa 10mg
History of HHF (in the last 12 months): No		
Number of patients in analysis set	1293	1286
Number of analysed patients, N (%)	1194 (100.0)	1212 (100.0)
Number of patients with endpoint, N (%)	294 (24.6)	258 (21.3)
95% confidence interval*	(22.3, 27.1)	(19.1, 23.7)
Comparison vs Placebo**		
Odds ratio (SE)		0.833 (0.082)
95% confidence interval***		(0.686, 1.011)
p-value		0.0648
History of HHF (in the last 12 months): Yes		
Number of patients in analysis set	574	577
Number of analysed patients, N (%)	515 (100.0)	528 (100.0)
Number of patients with endpoint, N (%)	130 (25.2)	113 (21.4)
95% confidence interval*	(21.7, 29.2)	(18.1, 25.1)
Comparison vs Placebo**		
Odds ratio (SE)		0.752 (0.113)
95% confidence interval***		(0.561, 1.009)
p-value		0.0573

* Wilson confidence intervals.
** Logistic regression includes terms for baseline KCCQ - overall summary score (p<0.0001), age (p=0.0812), baseline eGFR (CKD-EPI) (p=0.0206), Treatment (p=0.0092), region (5 cat.) (p<0.0001), baseline diabetes status (3 cat.) (p=0.4782), sex (p=0.1128), baseline LVEF (3 cat.) (p=0.9922), history of HHF (in the last 12 months) (p=0.5261) and Treatment by history of HHF (in the last 12 months) interaction (p=0.5711).
***Wald confidence intervals.

Data taken from study 1245.121 only.
LOCF: For a missing value at week 52 the last available post-baseline value before week 52 is imputed.

Table R.1.2.8.10: 2 Responder analysis (displaying risk ratio) in KCCQ-OSS change from baseline at week 52 of <= -5 points (deterioration) by history of HHF - RS (LOCF-AD) - 1245.121

Subgroup Description	Placebo	Empa 10mg
History of HHF (in the last 12 months): No		
Number of patients in analysis set	1293	1286
Number of analysed patients, N (%)	1194 (100.0)	1212 (100.0)
Number of patients with endpoint, N (%)	294 (24.6)	258 (21.3)
95% confidence interval*	(22.3, 27.1)	(19.1, 23.7)
Comparison vs Placebo**		
Risk ratio (SE)		0.873 (0.064)
95% confidence interval***		(0.756, 1.009)
p-value		0.0652
History of HHF (in the last 12 months): Yes		
Number of patients in analysis set	574	577
Number of analysed patients, N (%)	515 (100.0)	528 (100.0)
Number of patients with endpoint, N (%)	130 (25.2)	113 (21.4)
95% confidence interval*	(21.7, 29.2)	(18.1, 25.1)
Comparison vs Placebo**		
Risk ratio (SE)		0.808 (0.090)
95% confidence interval***		(0.650, 1.004)
p-value		0.0547

* Wilson confidence intervals.
** Log-linked Poisson model with robust estimate of variance includes terms for baseline KCCQ - overall summary score (p<0.0001), age (p=0.0798), baseline eGFR (CKD-EPI) (p=0.0212), Treatment (p=0.0087), region (5 cat.) (p<0.0001), baseline diabetes status (3 cat.) (p=0.4854), sex (p=0.1198), baseline LVEF (3 cat.) (p=0.9919), history of HHF (in the last 12 months) (p=0.5179) and Treatment by history of HHF (in the last 12 months) interaction (p=0.5619).
***Wald confidence intervals.

Data taken from study 1245.121 only.
LOCF: For a missing value at week 52 the last available post-baseline value before week 52 is imputed.

Table R.1.2.8.10: 3 Responder analysis (displaying odds ratio) in KCCQ-OSS change from baseline at week 52 of > -5 points (stability) by history of HHF - RS (LOCF-AD) - 1245.121

Subgroup Description	Placebo	Empa 10mg
History of HHF (in the last 12 months): No		
Number of patients in analysis set	1293	1286
Number of analysed patients, N (%)	1194 (100.0)	1212 (100.0)
Number of patients with endpoint, N (%)	900 (75.4)	954 (78.7)
95% confidence interval*	(72.9, 77.7)	(76.3, 80.9)
Comparison vs Placebo**		
Odds ratio (SE)		1.201 (0.119)
95% confidence interval***		(0.989, 1.458)
p-value		0.0648
History of HHF (in the last 12 months): Yes		
Number of patients in analysis set	574	577
Number of analysed patients, N (%)	515 (100.0)	528 (100.0)
Number of patients with endpoint, N (%)	385 (74.8)	415 (78.6)
95% confidence interval*	(70.8, 78.3)	(74.9, 81.9)
Comparison vs Placebo**		
Odds ratio (SE)		1.329 (0.199)
95% confidence interval***		(0.991, 1.782)
p-value		0.0573

* Wilson confidence intervals.
** Logistic regression includes terms for baseline KCCQ - overall summary score (p<0.0001), age (p=0.0812), baseline eGFR (CKD-EPI) (p=0.0206), Treatment (p=0.0092), region (5 cat.) (p<0.0001), baseline diabetes status (3 cat.) (p=0.4782), sex (p=0.1128), baseline LVEF (3 cat.) (p=0.9922), history of HHF (in the last 12 months) (p=0.5261) and Treatment by history of HHF (in the last 12 months) interaction (p=0.5711).
***Wald confidence intervals.

Data taken from study 1245.121 only.
LOCF: For a missing value at week 52 the last available post-baseline value before week 52 is imputed.

Table R.1.2.8.10: 4 Responder analysis (displaying risk ratio) in KCCQ-OSS change from baseline at week 52 of > -5 points (stability) by history of HHF - RS (LOCF-AD) - 1245.121

Subgroup Description	Placebo	Empa 10mg
History of HHF (in the last 12 months): No		
Number of patients in analysis set	1293	1286
Number of analysed patients, N (%)	1194 (100.0)	1212 (100.0)
Number of patients with endpoint, N (%)	900 (75.4)	954 (78.7)
95% confidence interval*	(72.9, 77.7)	(76.3, 80.9)
Comparison vs Placebo**		
Risk ratio (SE)		1.041 (0.023)
95% confidence interval***		(0.997, 1.086)
p-value		0.0685
History of HHF (in the last 12 months): Yes		
Number of patients in analysis set	574	577
Number of analysed patients, N (%)	515 (100.0)	528 (100.0)
Number of patients with endpoint, N (%)	385 (74.8)	415 (78.6)
95% confidence interval*	(70.8, 78.3)	(74.9, 81.9)
Comparison vs Placebo**		
Risk ratio (SE)		1.064 (0.036)
95% confidence interval***		(0.996, 1.137)
p-value		0.0666

* Wilson confidence intervals.
** Log-linked Poisson model with robust estimate of variance includes terms for baseline KCCQ - overall summary score (p<0.0001), age (p=0.1101), baseline eGFR (CKD-EPI) (p=0.0268), Treatment (p=0.0113), region (5 cat.) (p<0.0001), baseline diabetes status (3 cat.) (p=0.4796), sex (p=0.0968), baseline LVEF (3 cat.) (p=0.9878), history of HHF (in the last 12 months) (p=0.5822) and Treatment by history of HHF (in the last 12 months) interaction (p=0.5859).
***Wald confidence intervals.

Data taken from study 1245.121 only.
LOCF: For a missing value at week 52 the last available post-baseline value before week 52 is imputed.

Table R.1.2.8.10: 5 Responder analysis (displaying odds ratio) in KCCQ-OSS change from baseline at week 52 of >= 5 points (improvement) by history of HHF - RS (LOCF-AD) - 1245.121

Subgroup Description	Placebo	Empa 10mg
History of HHF (in the last 12 months): No		
Number of patients in analysis set	1293	1286
Number of analysed patients, N (%)	1194 (100.0)	1212 (100.0)
Number of patients with endpoint, N (%)	546 (45.7)	611 (50.4)
95% confidence interval*	(42.9, 48.6)	(47.6, 53.2)
Comparison vs Placebo**		
Odds ratio (SE)		1.234 (0.110)
95% confidence interval***		(1.037, 1.469)
p-value		0.0180
History of HHF (in the last 12 months): Yes		
Number of patients in analysis set	574	577
Number of analysed patients, N (%)	515 (100.0)	528 (100.0)
Number of patients with endpoint, N (%)	254 (49.3)	265 (50.2)
95% confidence interval*	(45.0, 53.6)	(45.9, 54.4)
Comparison vs Placebo**		
Odds ratio (SE)		1.107 (0.149)
95% confidence interval***		(0.851, 1.441)
p-value		0.4480

* Wilson confidence intervals.
** Logistic regression includes terms for baseline KCCQ - overall summary score (p<0.0001), age (p=0.0476), baseline eGFR (CKD-EPI) (p=0.0551), Treatment (p=0.0526), region (5 cat.) (p<0.0001), baseline diabetes status (3 cat.) (p=0.5487), sex (p=0.1632), baseline LVEF (3 cat.) (p=0.8816), history of HHF (in the last 12 months) (p=0.7648) and Treatment by history of HHF (in the last 12 months) interaction (p=0.5010).
***Wald confidence intervals.

Data taken from study 1245.121 only.
LOCF: For a missing value at week 52 the last available post-baseline value before week 52 is imputed.

Table R.1.2.8.10: 6 Responder analysis (displaying risk ratio) in KCCQ-OSS change from baseline at week 52 of >= 5 points (improvement) by history of HHF - RS (LOCF-AD) - 1245.121

Subgroup Description	Placebo	Empa 10mg
History of HHF (in the last 12 months): No		
Number of patients in analysis set	1293	1286
Number of analysed patients, N (%)	1194 (100.0)	1212 (100.0)
Number of patients with endpoint, N (%)	546 (45.7)	611 (50.4)
95% confidence interval*	(42.9, 48.6)	(47.6, 53.2)
Comparison vs Placebo**		
Risk ratio (SE)		1.091 (0.043)
95% confidence interval***		(1.010, 1.180)
p-value		0.0279
History of HHF (in the last 12 months): Yes		
Number of patients in analysis set	574	577
Number of analysed patients, N (%)	515 (100.0)	528 (100.0)
Number of patients with endpoint, N (%)	254 (49.3)	265 (50.2)
95% confidence interval*	(45.0, 53.6)	(45.9, 54.4)
Comparison vs Placebo**		
Risk ratio (SE)		1.031 (0.061)
95% confidence interval***		(0.918, 1.157)
p-value		0.6110

* Wilson confidence intervals.
** Log-linked Poisson model with robust estimate of variance includes terms for baseline KCCQ - overall summary score (p<0.0001), age (p=0.0759), baseline eGFR (CKD-EPI) (p=0.0566), Treatment (p=0.0992), region (5 cat.) (p<0.0001), baseline diabetes status (3 cat.) (p=0.5350), sex (p=0.1289), baseline LVEF (3 cat.) (p=0.7913), history of HHF (in the last 12 months) (p=0.5906) and Treatment by history of HHF (in the last 12 months) interaction (p=0.4212).
***Wald confidence intervals.

Data taken from study 1245.121 only.
LOCF: For a missing value at week 52 the last available post-baseline value before week 52 is imputed.

R.1.2.8.11

Table R.1.2.8.11: 1 Responder analysis (displaying odds ratio) in KCCQ-OSS change from baseline at week 52 of <= -5 points (deterioration) by cause of heart failure - RS (LOCF-AD) - 1245.121

Subgroup Description	Placebo	Empa 10mg
Cause of heart failure: Ischemic		
Number of patients in analysis set	946	983
Number of analysed patients, N (%)	876 (100.0)	923 (100.0)
Number of patients with endpoint, N (%)	234 (26.7)	205 (22.2)
95% confidence interval*	(23.9, 29.7)	(19.6, 25.0)
Comparison vs Placebo**		
Odds ratio (SE)		0.793 (0.089)
95% confidence interval***		(0.636, 0.987)
p-value		0.0380
Cause of heart failure: Non-ischemic		
Number of patients in analysis set	921	880
Number of analysed patients, N (%)	833 (100.0)	817 (100.0)
Number of patients with endpoint, N (%)	190 (22.8)	166 (20.3)
95% confidence interval*	(20.1, 25.8)	(17.7, 23.2)
Comparison vs Placebo**		
Odds ratio (SE)		0.827 (0.101)
95% confidence interval***		(0.651, 1.050)
p-value		0.1192

* Wilson confidence intervals.
** Logistic regression includes terms for baseline KCCQ - overall summary score (p<0.0001), age (p=0.0989), baseline eGFR (CKD-EPI) (p=0.0210), Treatment (p=0.0107), region (5 cat.) (p<0.0001), baseline diabetes status (3 cat.) (p=0.4748), sex (p=0.1200), baseline LVEF (3 cat.) (p=0.9823), cause of heart failure (p=0.8116) and Treatment by cause of heart failure interaction (p=0.7993).
***Wald confidence intervals.

Data taken from study 1245.121 only.
LOCF: For a missing value at week 52 the last available post-baseline value before week 52 is imputed.

Table R.1.2.8.11: 2 Responder analysis (displaying risk ratio) in KCCQ-OSS change from baseline at week 52 of <= -5 points (deterioration) by cause of heart failure - RS (LOCF-AD) - 1245.121

Subgroup Description	Placebo	Empa 10mg
Cause of heart failure: Ischemic		
Number of patients in analysis set	946	983
Number of analysed patients, N (%)	876 (100.0)	923 (100.0)
Number of patients with endpoint, N (%)	234 (26.7)	205 (22.2)
95% confidence interval*	(23.9, 29.7)	(19.6, 25.0)
Comparison vs Placebo**		
Risk ratio (SE)		0.844 (0.069)
95% confidence interval***		(0.718, 0.992)
p-value		0.0393
Cause of heart failure: Non-ischemic		
Number of patients in analysis set	921	880
Number of analysed patients, N (%)	833 (100.0)	817 (100.0)
Number of patients with endpoint, N (%)	190 (22.8)	166 (20.3)
95% confidence interval*	(20.1, 25.8)	(17.7, 23.2)
Comparison vs Placebo**		
Risk ratio (SE)		0.865 (0.080)
95% confidence interval***		(0.722, 1.036)
p-value		0.1153

* Wilson confidence intervals.
** Log-linked Poisson model with robust estimate of variance includes terms for baseline KCCQ - overall summary score (p<0.0001), age (p=0.0984), baseline eGFR (CKD-EPI) (p=0.0216), Treatment (p=0.0107), region (5 cat.) (p<0.0001), baseline diabetes status (3 cat.) (p=0.4820), sex (p=0.1283), baseline LVEF (3 cat.) (p=0.9825), cause of heart failure (p=0.8091) and Treatment by cause of heart failure interaction (p=0.8445).
***Wald confidence intervals.

Data taken from study 1245.121 only.
LOCF: For a missing value at week 52 the last available post-baseline value before week 52 is imputed.

Table R.1.2.8.11: 3 Responder analysis (displaying odds ratio) in KCCQ-OSS change from baseline at week 52 of > -5 points (stability) by cause of heart failure - RS (LOCF-AD) - 1245.121

Subgroup Description	Placebo	Empa 10mg
Cause of heart failure: Ischemic		
Number of patients in analysis set	946	983
Number of analysed patients, N (%)	876 (100.0)	923 (100.0)
Number of patients with endpoint, N (%)	642 (73.3)	718 (77.8)
95% confidence interval*	(70.3, 76.1)	(75.0, 80.4)
Comparison vs Placebo**		
Odds ratio (SE)		1.262 (0.141)
95% confidence interval***		(1.013, 1.571)
p-value		0.0380
Cause of heart failure: Non-ischemic		
Number of patients in analysis set	921	880
Number of analysed patients, N (%)	833 (100.0)	817 (100.0)
Number of patients with endpoint, N (%)	643 (77.2)	651 (79.7)
95% confidence interval*	(74.2, 79.9)	(76.8, 82.3)
Comparison vs Placebo**		
Odds ratio (SE)		1.210 (0.148)
95% confidence interval***		(0.952, 1.537)
p-value		0.1192

* Wilson confidence intervals.
** Logistic regression includes terms for baseline KCCQ - overall summary score (p<0.0001), age (p=0.0989), baseline eGFR (CKD-EPI) (p=0.0210), Treatment (p=0.0107), region (5 cat.) (p<0.0001), baseline diabetes status (3 cat.) (p=0.4748), sex (p=0.1200), baseline LVEF (3 cat.) (p=0.9823), cause of heart failure (p=0.8116) and Treatment by cause of heart failure interaction (p=0.7993).
***Wald confidence intervals.

Data taken from study 1245.121 only.
LOCF: For a missing value at week 52 the last available post-baseline value before week 52 is imputed.

Table R.1.2.8.11: 4 Responder analysis (displaying risk ratio) in KCCQ-OSS change from baseline at week 52 of > -5 points (stability) by cause of heart failure - RS (LOCF-AD) - 1245.121

Subgroup Description	Placebo	Empa 10mg
Cause of heart failure: Ischemic		
Number of patients in analysis set	946	983
Number of analysed patients, N (%)	876 (100.0)	923 (100.0)
Number of patients with endpoint, N (%)	642 (73.3)	718 (77.8)
95% confidence interval*	(70.3, 76.1)	(75.0, 80.4)
Comparison vs Placebo**		
Risk ratio (SE)		1.057 (0.028)
95% confidence interval***		(1.003, 1.114)
p-value		0.0367
Cause of heart failure: Non-ischemic		
Number of patients in analysis set	921	880
Number of analysed patients, N (%)	833 (100.0)	817 (100.0)
Number of patients with endpoint, N (%)	643 (77.2)	651 (79.7)
95% confidence interval*	(74.2, 79.9)	(76.8, 82.3)
Comparison vs Placebo**		
Risk ratio (SE)		1.038 (0.026)
95% confidence interval***		(0.988, 1.091)
p-value		0.1424

* Wilson confidence intervals.
** Log-linked Poisson model with robust estimate of variance includes terms for baseline KCCQ - overall summary score (p<0.0001), age (p=0.1334), baseline eGFR (CKD-EPI) (p=0.0264), Treatment (p=0.0114), region (5 cat.) (p<0.0001), baseline diabetes status (3 cat.) (p=0.4791), sex (p=0.1096), baseline LVEF (3 cat.) (p=0.9714), cause of heart failure (p=0.7636) and Treatment by cause of heart failure interaction (p=0.6164).
***Wald confidence intervals.

Data taken from study 1245.121 only.
LOCF: For a missing value at week 52 the last available post-baseline value before week 52 is imputed.

Table R.1.2.8.11: 5 Responder analysis (displaying odds ratio) in KCCQ-OSS change from baseline at week 52 of >= 5 points (improvement) by cause of heart failure - RS (LOCF-AD) - 1245.121

Subgroup Description	Placebo	Empa 10mg
Cause of heart failure: Ischemic		
Number of patients in analysis set	946	983
Number of analysed patients, N (%)	876 (100.0)	923 (100.0)
Number of patients with endpoint, N (%)	392 (44.7)	447 (48.4)
95% confidence interval*	(41.5, 48.1)	(45.2, 51.7)
Comparison vs Placebo**		
Odds ratio (SE)		1.155 (0.119)
95% confidence interval***		(0.944, 1.412)
p-value		0.1607
Cause of heart failure: Non-ischemic		
Number of patients in analysis set	921	880
Number of analysed patients, N (%)	833 (100.0)	817 (100.0)
Number of patients with endpoint, N (%)	408 (49.0)	429 (52.5)
95% confidence interval*	(45.6, 52.4)	(49.1, 55.9)
Comparison vs Placebo**		
Odds ratio (SE)		1.240 (0.133)
95% confidence interval***		(1.004, 1.530)
p-value		0.0453

* Wilson confidence intervals.
** Logistic regression includes terms for baseline KCCQ - overall summary score (p<0.0001), age (p=0.0469), baseline eGFR (CKD-EPI) (p=0.0581), Treatment (p=0.0157), region (5 cat.) (p<0.0001), baseline diabetes status (3 cat.) (p=0.5461), sex (p=0.1849), baseline LVEF (3 cat.) (p=0.8953), cause of heart failure (p=0.6401) and Treatment by cause of heart failure interaction (p=0.6336).
***Wald confidence intervals.

Data taken from study 1245.121 only.
LOCF: For a missing value at week 52 the last available post-baseline value before week 52 is imputed.

Table R.1.2.8.11: 6 Responder analysis (displaying risk ratio) in KCCQ-OSS change from baseline at week 52 of >= 5 points (improvement) by cause of heart failure - RS (LOCF-AD) - 1245.121

Subgroup Description	Placebo	Empa 10mg
Cause of heart failure: Ischemic		
Number of patients in analysis set	946	983
Number of analysed patients, N (%)	876 (100.0)	923 (100.0)
Number of patients with endpoint, N (%)	392 (44.7)	447 (48.4)
95% confidence interval*	(41.5, 48.1)	(45.2, 51.7)
Comparison vs Placebo**		
Risk ratio (SE)		1.064 (0.051)
95% confidence interval***		(0.968, 1.169)
p-value		0.1987
Cause of heart failure: Non-ischemic		
Number of patients in analysis set	921	880
Number of analysed patients, N (%)	833 (100.0)	817 (100.0)
Number of patients with endpoint, N (%)	408 (49.0)	429 (52.5)
95% confidence interval*	(45.6, 52.4)	(49.1, 55.9)
Comparison vs Placebo**		
Risk ratio (SE)		1.081 (0.049)
95% confidence interval***		(0.990, 1.182)
p-value		0.0839

* Wilson confidence intervals.
** Log-linked Poisson model with robust estimate of variance includes terms for baseline KCCQ - overall summary score (p<0.0001), age (p=0.0780), baseline eGFR (CKD-EPI) (p=0.0613), Treatment (p=0.0338), region (5 cat.) (p<0.0001), baseline diabetes status (3 cat.) (p=0.5398), sex (p=0.1554), baseline LVEF (3 cat.) (p=0.8258), cause of heart failure (p=0.5609) and Treatment by cause of heart failure interaction (p=0.8019).
***Wald confidence intervals.

Data taken from study 1245.121 only.
LOCF: For a missing value at week 52 the last available post-baseline value before week 52 is imputed.

R.1.2.8.12

R.1.2.8.12 Subgroup analysis by heart failure physiology (LVEF <= 30% and NTproBNP<median; LVEF <= 30% and NTproBNP>=median; LVEF > 30%)

Table R.1.2.8.12: 1 Responder analysis (displaying odds ratio) in KCCQ-OSS change from baseline at week 52 of <= -5 points (deterioration) by heart failure physiology - RS (LOCF-AD) - 1245.121

Subgroup Description	Placebo	Empa 10mg
Heart failure physiology: LVEF <= 30% and NTproBNP < median		
Number of patients in analysis set	723	698
Number of analysed patients, N (%)	679 (100.0)	655 (100.0)
Number of patients with endpoint, N (%)	149 (21.9)	126 (19.2)
95% confidence interval*	(19.0, 25.2)	(16.4, 22.4)
Comparison vs Placebo**		
Odds ratio (SE)		0.820 (0.113)
95% confidence interval***		(0.626, 1.075)
p-value		0.1516
Heart failure physiology: LVEF <= 30% and NTproBNP >= median		
Number of patients in analysis set	661	631
Number of analysed patients, N (%)	588 (100.0)	586 (100.0)
Number of patients with endpoint, N (%)	170 (28.9)	129 (22.0)
95% confidence interval*	(25.4, 32.7)	(18.8, 25.5)
Comparison vs Placebo**		
Odds ratio (SE)		0.692 (0.095)
95% confidence interval***		(0.528, 0.907)
p-value		0.0077

* Wilson confidence intervals.
** Logistic regression includes terms for baseline KCCQ - overall summary score (p<0.0001), age (p=0.1027), baseline eGFR (CKD-EPI) (p=0.0672), Treatment (p=0.0158), region (5 cat.) (p<0.0001), baseline diabetes status (3 cat.) (p=0.4687), sex (p=0.0944), heart failure physiology (p=0.0061) and Treatment by heart failure physiology interaction (p=0.2903).
***Wald confidence intervals.
16 patients were excluded as the subgroup variable was missing.

Data taken from study 1245.121 only.
LOCF: For a missing value at week 52 the last available post-baseline value before week 52 is imputed.
NTproBNP median [pg/mL]: with a. fibrillation/flutter at baseline: 2265; without a. fibrillation/flutter at baseline: 1671.

Table R.1.2.8.12: 1 Responder analysis (displaying odds ratio) in KCCQ-OSS change from baseline at week 52 of <= -5 points (deterioration) by heart failure physiology - RS (LOCF-AD) - 1245.121

Subgroup Description	Placebo	Empa 10mg
Heart failure physiology: LVEF > 30%		
Number of patients in analysis set	475	526
Number of analysed patients, N (%)	437 (100.0)	495 (100.0)
Number of patients with endpoint, N (%)	104 (23.8)	115 (23.2)
95% confidence interval*	(20.0, 28.0)	(19.7, 27.2)
Comparison vs Placebo**		
Odds ratio (SE)		0.961 (0.151)
95% confidence interval***		(0.706, 1.309)
p-value		0.8004

* Wilson confidence intervals.
** Logistic regression includes terms for baseline KCCQ - overall summary score (p<0.0001), age (p=0.1027), baseline eGFR (CKD-EPI) (p=0.0672), Treatment (p=0.0158), region (5 cat.) (p<0.0001), baseline diabetes status (3 cat.) (p=0.4687), sex (p=0.0944), heart failure physiology (p=0.0061) and Treatment by heart failure physiology interaction (p=0.2903).
***Wald confidence intervals.
16 patients were excluded as the subgroup variable was missing.

Data taken from study 1245.121 only.
LOCF: For a missing value at week 52 the last available post-baseline value before week 52 is imputed.
NTproBNP median [pg/mL]: with a. fibrillation/flutter at baseline: 2265; without a. fibrillation/flutter at baseline: 1671.

Table R.1.2.8.12: 2 Responder analysis (displaying risk ratio) in KCCQ-OSS change from baseline at week 52 of <= -5 points (deterioration) by heart failure physiology - RS (LOCF-AD) - 1245.121

Subgroup Description	Placebo	Empa 10mg
Heart failure physiology: LVEF <= 30% and NTproBNP < median		
Number of patients in analysis set	723	698
Number of analysed patients, N (%)	679 (100.0)	655 (100.0)
Number of patients with endpoint, N (%)	149 (21.9)	126 (19.2)
95% confidence interval*	(19.0, 25.2)	(16.4, 22.4)
Comparison vs Placebo**		
Risk ratio (SE)		0.859 (0.091)
95% confidence interval***		(0.697, 1.058)
p-value		0.1532
Heart failure physiology: LVEF <= 30% and NTproBNP >= median		
Number of patients in analysis set	661	631
Number of analysed patients, N (%)	588 (100.0)	586 (100.0)
Number of patients with endpoint, N (%)	170 (28.9)	129 (22.0)
95% confidence interval*	(25.4, 32.7)	(18.8, 25.5)
Comparison vs Placebo**		
Risk ratio (SE)		0.769 (0.076)
95% confidence interval***		(0.633, 0.934)
p-value		0.0080

* Wilson confidence intervals.
** Log-linked Poisson model with robust estimate of variance includes terms for baseline KCCQ - overall summary score (p<0.0001), age (p=0.1024), baseline eGFR (CKD-EPI) (p=0.0679), Treatment (p=0.0168), region (5 cat.) (p<0.0001), baseline diabetes status (3 cat.) (p=0.4769), sex (p=0.0997), heart failure physiology (p=0.0071) and Treatment by heart failure physiology interaction (p=0.3122).
***Wald confidence intervals.
16 patients were excluded as the subgroup variable was missing.

Data taken from study 1245.121 only.
LOCF: For a missing value at week 52 the last available post-baseline value before week 52 is imputed.
NTproBNP median [pg/mL]: with a. fibrillation/flutter at baseline: 2265; without a. fibrillation/flutter at baseline: 1671.

Table R.1.2.8.12: 2 Responder analysis (displaying risk ratio) in KCCQ-OSS change from baseline at week 52 of <= -5 points (deterioration) by heart failure physiology - RS (LOCF-AD) - 1245.121

Subgroup Description	Placebo	Empa 10mg
Heart failure physiology: LVEF > 30%		
Number of patients in analysis set	475	526
Number of analysed patients, N (%)	437 (100.0)	495 (100.0)
Number of patients with endpoint, N (%)	104 (23.8)	115 (23.2)
95% confidence interval*	(20.0, 28.0)	(19.7, 27.2)
Comparison vs Placebo**		
Risk ratio (SE)		0.971 (0.113)
95% confidence interval***		(0.773, 1.219)
p-value		0.7970

* Wilson confidence intervals.
** Log-linked Poisson model with robust estimate of variance includes terms for baseline KCCQ - overall summary score (p<0.0001), age (p=0.1024), baseline eGFR (CKD-EPI) (p=0.0679), Treatment (p=0.0168), region (5 cat.) (p<0.0001), baseline diabetes status (3 cat.) (p=0.4769), sex (p=0.0997), heart failure physiology (p=0.0071) and Treatment by heart failure physiology interaction (p=0.3122).
***Wald confidence intervals.
16 patients were excluded as the subgroup variable was missing.

Data taken from study 1245.121 only.
LOCF: For a missing value at week 52 the last available post-baseline value before week 52 is imputed.
NTproBNP median [pg/mL]: with a. fibrillation/flutter at baseline: 2265; without a. fibrillation/flutter at baseline: 1671.

Table R.1.2.8.12: 3 Responder analysis (displaying odds ratio) in KCCQ-OSS change from baseline at week 52 of > -5 points (stability) by heart failure physiology - RS (LOCF-AD) - 1245.121

Subgroup Description	Placebo	Empa 10mg
Heart failure physiology: LVEF <= 30% and NTproBNP < median		
Number of patients in analysis set	723	698
Number of analysed patients, N (%)	679 (100.0)	655 (100.0)
Number of patients with endpoint, N (%)	530 (78.1)	529 (80.8)
95% confidence interval*	(74.8, 81.0)	(77.6, 83.6)
Comparison vs Placebo**		
Odds ratio (SE)		1.219 (0.168)
95% confidence interval***		(0.930, 1.598)
p-value		0.1516
Heart failure physiology: LVEF <= 30% and NTproBNP >= median		
Number of patients in analysis set	661	631
Number of analysed patients, N (%)	588 (100.0)	586 (100.0)
Number of patients with endpoint, N (%)	418 (71.1)	457 (78.0)
95% confidence interval*	(67.3, 74.6)	(74.5, 81.2)
Comparison vs Placebo**		
Odds ratio (SE)		1.444 (0.199)
95% confidence interval***		(1.102, 1.892)
p-value		0.0077

* Wilson confidence intervals.
** Logistic regression includes terms for baseline KCCQ - overall summary score (p<0.0001), age (p=0.1027), baseline eGFR (CKD-EPI) (p=0.0672), Treatment (p=0.0158), region (5 cat.) (p<0.0001), baseline diabetes status (3 cat.) (p=0.4687), sex (p=0.0944), heart failure physiology (p=0.0061) and Treatment by heart failure physiology interaction (p=0.2903).
***Wald confidence intervals.
16 patients were excluded as the subgroup variable was missing.

Data taken from study 1245.121 only.
LOCF: For a missing value at week 52 the last available post-baseline value before week 52 is imputed.
NTproBNP median [pg/mL]: with a. fibrillation/flutter at baseline: 2265; without a. fibrillation/flutter at baseline: 1671.

Table R.1.2.8.12: 3 Responder analysis (displaying odds ratio) in KCCQ-OSS change from baseline at week 52 of > -5 points (stability) by heart failure physiology - RS (LOCF-AD) - 1245.121

Subgroup Description	Placebo	Empa 10mg
Heart failure physiology: LVEF > 30%		
Number of patients in analysis set	475	526
Number of analysed patients, N (%)	437 (100.0)	495 (100.0)
Number of patients with endpoint, N (%)	333 (76.2)	380 (76.8)
95% confidence interval*	(72.0, 80.0)	(72.8, 80.3)
Comparison vs Placebo**		
Odds ratio (SE)		1.041 (0.164)
95% confidence interval***		(0.764, 1.417)
p-value		0.8004

* Wilson confidence intervals.
** Logistic regression includes terms for baseline KCCQ - overall summary score (p<0.0001), age (p=0.1027), baseline eGFR (CKD-EPI) (p=0.0672), Treatment (p=0.0158), region (5 cat.) (p<0.0001), baseline diabetes status (3 cat.) (p=0.4687), sex (p=0.0944), heart failure physiology (p=0.0061) and Treatment by heart failure physiology interaction (p=0.2903).
***Wald confidence intervals.
16 patients were excluded as the subgroup variable was missing.

Data taken from study 1245.121 only.
LOCF: For a missing value at week 52 the last available post-baseline value before week 52 is imputed.
NTproBNP median [pg/mL]: with a. fibrillation/flutter at baseline: 2265; without a. fibrillation/flutter at baseline: 1671.

Table R.1.2.8.12: 4 Responder analysis (displaying risk ratio) in KCCQ-OSS change from baseline at week 52 of > -5 points (stability) by heart failure physiology - RS (LOCF-AD) - 1245.121

Subgroup Description	Placebo	Empa 10mg
Heart failure physiology: LVEF <= 30% and NTproBNP < median		
Number of patients in analysis set	723	698
Number of analysed patients, N (%)	679 (100.0)	655 (100.0)
Number of patients with endpoint, N (%)	530 (78.1)	529 (80.8)
95% confidence interval*	(74.8, 81.0)	(77.6, 83.6)
Comparison vs Placebo**		
Risk ratio (SE)		1.040 (0.029)
95% confidence interval***		(0.985, 1.097)
p-value		0.1599
Heart failure physiology: LVEF <= 30% and NTproBNP >= median		
Number of patients in analysis set	661	631
Number of analysed patients, N (%)	588 (100.0)	586 (100.0)
Number of patients with endpoint, N (%)	418 (71.1)	457 (78.0)
95% confidence interval*	(67.3, 74.6)	(74.5, 81.2)
Comparison vs Placebo**		
Risk ratio (SE)		1.095 (0.037)
95% confidence interval***		(1.025, 1.169)
p-value		0.0071

* Wilson confidence intervals.
** Log-linked Poisson model with robust estimate of variance includes terms for baseline KCCQ - overall summary score (p<0.0001), age (p=0.1296), baseline eGFR (CKD-EPI) (p=0.0823), Treatment (p=0.0156), region (5 cat.) (p<0.0001), baseline diabetes status (3 cat.) (p=0.4689), sex (p=0.0905), heart failure physiology (p=0.0042) and Treatment by heart failure physiology interaction (p=0.2219).
***Wald confidence intervals.
16 patients were excluded as the subgroup variable was missing.

Data taken from study 1245.121 only.
LOCF: For a missing value at week 52 the last available post-baseline value before week 52 is imputed.
NTproBNP median [pg/mL]: with a. fibrillation/flutter at baseline: 2265; without a. fibrillation/flutter at baseline: 1671.

Table R.1.2.8.12: 4 Responder analysis (displaying risk ratio) in KCCQ-OSS change from baseline at week 52 of > -5 points (stability) by heart failure physiology - RS (LOCF-AD) - 1245.121

Subgroup Description	Placebo	Empa 10mg
Heart failure physiology: LVEF > 30%		
Number of patients in analysis set	475	526
Number of analysed patients, N (%)	437 (100.0)	495 (100.0)
Number of patients with endpoint, N (%)	333 (76.2)	380 (76.8)
95% confidence interval*	(72.0, 80.0)	(72.8, 80.3)
Comparison vs Placebo**		
Risk ratio (SE)		1.007 (0.036)
95% confidence interval***		(0.939, 1.080)
p-value		0.8474

* Wilson confidence intervals.
** Log-linked Poisson model with robust estimate of variance includes terms for baseline KCCQ - overall summary score (p<0.0001), age (p=0.1296), baseline eGFR (CKD-EPI) (p=0.0823), Treatment (p=0.0156), region (5 cat.) (p<0.0001), baseline diabetes status (3 cat.) (p=0.4689), sex (p=0.0905), heart failure physiology (p=0.0042) and Treatment by heart failure physiology interaction (p=0.2219).
***Wald confidence intervals.
16 patients were excluded as the subgroup variable was missing.

Data taken from study 1245.121 only.
LOCF: For a missing value at week 52 the last available post-baseline value before week 52 is imputed.
NTproBNP median [pg/mL]: with a. fibrillation/flutter at baseline: 2265; without a. fibrillation/flutter at baseline: 1671.

Table R.1.2.8.12: 5 Responder analysis (displaying odds ratio) in KCCQ-OSS change from baseline at week 52 of >= 5 points (improvement) by heart failure physiology - RS (LOCF-AD) - 1245.121

Subgroup Description	Placebo	Empa 10mg
Heart failure physiology: LVEF <= 30% and NTproBNP < median		
Number of patients in analysis set	723	698
Number of analysed patients, N (%)	679 (100.0)	655 (100.0)
Number of patients with endpoint, N (%)	308 (45.4)	340 (51.9)
95% confidence interval*	(41.7, 49.1)	(48.1, 55.7)
Comparison vs Placebo**		
Odds ratio (SE)		1.429 (0.170)
95% confidence interval***		(1.132, 1.805)
p-value		0.0027
Heart failure physiology: LVEF <= 30% and NTproBNP >= median		
Number of patients in analysis set	661	631
Number of analysed patients, N (%)	588 (100.0)	586 (100.0)
Number of patients with endpoint, N (%)	279 (47.4)	304 (51.9)
95% confidence interval*	(43.4, 51.5)	(47.8, 55.9)
Comparison vs Placebo**		
Odds ratio (SE)		1.186 (0.151)
95% confidence interval***		(0.924, 1.522)
p-value		0.1813

* Wilson confidence intervals.
** Logistic regression includes terms for baseline KCCQ - overall summary score (p<0.0001), age (p=0.0402), baseline eGFR (CKD-EPI) (p=0.0829), Treatment (p=0.0382), region (5 cat.) (p<0.0001), baseline diabetes status (3 cat.) (p=0.5138), sex (p=0.1647), heart failure physiology (p=0.5389) and Treatment by heart failure physiology interaction (p=0.0802).
***Wald confidence intervals.
16 patients were excluded as the subgroup variable was missing.

Data taken from study 1245.121 only.
LOCF: For a missing value at week 52 the last available post-baseline value before week 52 is imputed.
NTproBNP median [pg/mL]: with a. fibrillation/flutter at baseline: 2265; without a. fibrillation/flutter at baseline: 1671.

Table R.1.2.8.12: 5 Responder analysis (displaying odds ratio) in KCCQ-OSS change from baseline at week 52 of >= 5 points (improvement) by heart failure physiology - RS (LOCF-AD) - 1245.121

Subgroup Description	Placebo	Empa 10mg
Heart failure physiology: LVEF > 30%		
Number of patients in analysis set	475	526
Number of analysed patients, N (%)	437 (100.0)	495 (100.0)
Number of patients with endpoint, N (%)	209 (47.8)	230 (46.5)
95% confidence interval*	(43.2, 52.5)	(42.1, 50.9)
Comparison vs Placebo**		
Odds ratio (SE)		0.942 (0.135)
95% confidence interval***		(0.711, 1.246)
p-value		0.6733

* Wilson confidence intervals.
** Logistic regression includes terms for baseline KCCQ - overall summary score (p<0.0001), age (p=0.0402), baseline eGFR (CKD-EPI) (p=0.0829), Treatment (p=0.0382), region (5 cat.) (p<0.0001), baseline diabetes status (3 cat.) (p=0.5138), sex (p=0.1647), heart failure physiology (p=0.5389) and Treatment by heart failure physiology interaction (p=0.0802).
***Wald confidence intervals.
16 patients were excluded as the subgroup variable was missing.

Data taken from study 1245.121 only.
LOCF: For a missing value at week 52 the last available post-baseline value before week 52 is imputed.
NTproBNP median [pg/mL]: with a. fibrillation/flutter at baseline: 2265; without a. fibrillation/flutter at baseline: 1671.

Table R.1.2.8.12: 6 Responder analysis (displaying risk ratio) in KCCQ-OSS change from baseline at week 52 of >= 5 points (improvement) by heart failure physiology - RS (LOCF-AD) - 1245.121

Subgroup Description	Placebo	Empa 10mg
Heart failure physiology: LVEF <= 30% and NTproBNP < median		
Number of patients in analysis set	723	698
Number of analysed patients, N (%)	679 (100.0)	655 (100.0)
Number of patients with endpoint, N (%)	308 (45.4)	340 (51.9)
95% confidence interval*	(41.7, 49.1)	(48.1, 55.7)
Comparison vs Placebo**		
Risk ratio (SE)		1.162 (0.062)
95% confidence interval***		(1.047, 1.290)
p-value		0.0048
Heart failure physiology: LVEF <= 30% and NTproBNP >= median		
Number of patients in analysis set	661	631
Number of analysed patients, N (%)	588 (100.0)	586 (100.0)
Number of patients with endpoint, N (%)	279 (47.4)	304 (51.9)
95% confidence interval*	(43.4, 51.5)	(47.8, 55.9)
Comparison vs Placebo**		
Risk ratio (SE)		1.076 (0.059)
95% confidence interval***		(0.966, 1.199)
p-value		0.1841

* Wilson confidence intervals.
** Log-linked Poisson model with robust estimate of variance includes terms for baseline KCCQ - overall summary score (p<0.0001), age (p=0.0673), baseline eGFR (CKD-EPI) (p=0.0831), Treatment (p=0.0792), region (5 cat.) (p<0.0001), baseline diabetes status (3 cat.) (p=0.4959), sex (p=0.1568), heart failure physiology (p=0.4998) and Treatment by heart failure physiology interaction (p=0.0620).
***Wald confidence intervals.
16 patients were excluded as the subgroup variable was missing.

Data taken from study 1245.121 only.
LOCF: For a missing value at week 52 the last available post-baseline value before week 52 is imputed.
NTproBNP median [pg/mL]: with a. fibrillation/flutter at baseline: 2265; without a. fibrillation/flutter at baseline: 1671.

Table R.1.2.8.12: 6 Responder analysis (displaying risk ratio) in KCCQ-OSS change from baseline at week 52 of >= 5 points (improvement) by heart failure physiology - RS (LOCF-AD) - 1245.121

Subgroup Description	Placebo	Empa 10mg
Heart failure physiology: LVEF > 30%		
Number of patients in analysis set	475	526
Number of analysed patients, N (%)	437 (100.0)	495 (100.0)
Number of patients with endpoint, N (%)	209 (47.8)	230 (46.5)
95% confidence interval*	(43.2, 52.5)	(42.1, 50.9)
Comparison vs Placebo**		
Risk ratio (SE)		0.954 (0.062)
95% confidence interval***		(0.840, 1.083)
p-value		0.4637

* Wilson confidence intervals.
** Log-linked Poisson model with robust estimate of variance includes terms for baseline KCCQ - overall summary score (p<0.0001), age (p=0.0673), baseline eGFR (CKD-EPI) (p=0.0831), Treatment (p=0.0792), region (5 cat.) (p<0.0001), baseline diabetes status (3 cat.) (p=0.4959), sex (p=0.1568), heart failure physiology (p=0.4998) and Treatment by heart failure physiology interaction (p=0.0620).
***Wald confidence intervals.
16 patients were excluded as the subgroup variable was missing.

Data taken from study 1245.121 only.
LOCF: For a missing value at week 52 the last available post-baseline value before week 52 is imputed.
NTproBNP median [pg/mL]: with a. fibrillation/flutter at baseline: 2265; without a. fibrillation/flutter at baseline: 1671.

R.1.2.8.13

Table R.1.2.8.13: 1 Responder analysis (displaying odds ratio) in KCCQ-OSS change from baseline at week 52 of <= -5 points (deterioration) by baseline use of MRA (Y/N) - RS (LOCF-AD) - 1245.121

Subgroup Description	Placebo	Empa 10mg
Baseline use of MRA: No		
Number of patients in analysis set	512	557
Number of analysed patients, N (%)	475 (100.0)	522 (100.0)
Number of patients with endpoint, N (%)	124 (26.1)	104 (19.9)
95% confidence interval*	(22.4, 30.2)	(16.7, 23.6)
Comparison vs Placebo**		
Odds ratio (SE)		0.705 (0.109)
95% confidence interval***		(0.522, 0.953)
p-value		0.0232
Baseline use of MRA: Yes		
Number of patients in analysis set	1355	1306
Number of analysed patients, N (%)	1234 (100.0)	1218 (100.0)
Number of patients with endpoint, N (%)	300 (24.3)	267 (21.9)
95% confidence interval*	(22.0, 26.8)	(19.7, 24.3)
Comparison vs Placebo**		
Odds ratio (SE)		0.856 (0.084)
95% confidence interval***		(0.707, 1.037)
p-value		0.1121

* Wilson confidence intervals.
** Logistic regression includes terms for baseline KCCQ - overall summary score (p<0.0001), age (p=0.0735), baseline eGFR (CKD-EPI) (p=0.0164), Treatment (p=0.0056), region (5 cat.) (p<0.0001), baseline diabetes status (3 cat.) (p=0.4404), sex (p=0.0998), baseline LVEF (3 cat.) (p=0.9776), baseline use of MRA (p=0.1416) and Treatment by baseline use of MRA interaction (p=0.2879).
***Wald confidence intervals.

Data taken from study 1245.121 only.
LOCF: For a missing value at week 52 the last available post-baseline value before week 52 is imputed.

Table R.1.2.8.13: 2 Responder analysis (displaying risk ratio) in KCCQ-OSS change from baseline at week 52 of <= -5 points (deterioration) by baseline use of MRA (Y/N) - RS (LOCF-AD) - 1245.121

Subgroup Description	Placebo	Empa 10mg
Baseline use of MRA: No		
Number of patients in analysis set	512	557
Number of analysed patients, N (%)	475 (100.0)	522 (100.0)
Number of patients with endpoint, N (%)	124 (26.1)	104 (19.9)
95% confidence interval*	(22.4, 30.2)	(16.7, 23.6)
Comparison vs Placebo**		
Risk ratio (SE)		0.770 (0.088)
95% confidence interval***		(0.615, 0.964)
p-value		0.0225
Baseline use of MRA: Yes		
Number of patients in analysis set	1355	1306
Number of analysed patients, N (%)	1234 (100.0)	1218 (100.0)
Number of patients with endpoint, N (%)	300 (24.3)	267 (21.9)
95% confidence interval*	(22.0, 26.8)	(19.7, 24.3)
Comparison vs Placebo**		
Risk ratio (SE)		0.891 (0.065)
95% confidence interval***		(0.773, 1.027)
p-value		0.1113

* Wilson confidence intervals.
** Log-linked Poisson model with robust estimate of variance includes terms for baseline KCCQ - overall summary score (p<0.0001), age (p=0.0727), baseline eGFR (CKD-EPI) (p=0.0180), Treatment (p=0.0054), region (5 cat.) (p<0.0001), baseline diabetes status (3 cat.) (p=0.4458), sex (p=0.1055), baseline LVEF (3 cat.) (p=0.9788), baseline use of MRA (p=0.1353) and Treatment by baseline use of MRA interaction (p=0.2834).
***Wald confidence intervals.

Data taken from study 1245.121 only.
LOCF: For a missing value at week 52 the last available post-baseline value before week 52 is imputed.

Table R.1.2.8.13: 3 Responder analysis (displaying odds ratio) in KCCQ-OSS change from baseline at week 52 of > -5 points (stability) by baseline use of MRA (Y/N) - RS (LOCF-AD) - 1245.121

Subgroup Description	Placebo	Empa 10mg
Baseline use of MRA: No		
Number of patients in analysis set	512	557
Number of analysed patients, N (%)	475 (100.0)	522 (100.0)
Number of patients with endpoint, N (%)	351 (73.9)	418 (80.1)
95% confidence interval*	(69.8, 77.6)	(76.4, 83.3)
Comparison vs Placebo**		
Odds ratio (SE)		1.418 (0.218)
95% confidence interval***		(1.049, 1.917)
p-value		0.0232
Baseline use of MRA: Yes		
Number of patients in analysis set	1355	1306
Number of analysed patients, N (%)	1234 (100.0)	1218 (100.0)
Number of patients with endpoint, N (%)	934 (75.7)	951 (78.1)
95% confidence interval*	(73.2, 78.0)	(75.7, 80.3)
Comparison vs Placebo**		
Odds ratio (SE)		1.168 (0.114)
95% confidence interval***		(0.964, 1.415)
p-value		0.1121

* Wilson confidence intervals.
** Logistic regression includes terms for baseline KCCQ - overall summary score (p<0.0001), age (p=0.0735), baseline eGFR (CKD-EPI) (p=0.0164), Treatment (p=0.0056), region (5 cat.) (p<0.0001), baseline diabetes status (3 cat.) (p=0.4404), sex (p=0.0998), baseline LVEF (3 cat.) (p=0.9776), baseline use of MRA (p=0.1416) and Treatment by baseline use of MRA interaction (p=0.2879).
***Wald confidence intervals.

Data taken from study 1245.121 only.
LOCF: For a missing value at week 52 the last available post-baseline value before week 52 is imputed.

Table R.1.2.8.13: 4 Responder analysis (displaying risk ratio) in KCCQ-OSS change from baseline at week 52 of > -5 points (stability) by baseline use of MRA (Y/N) - RS (LOCF-AD) - 1245.121

Subgroup Description	Placebo	Empa 10mg
Baseline use of MRA: No		
Number of patients in analysis set	512	557
Number of analysed patients, N (%)	475 (100.0)	522 (100.0)
Number of patients with endpoint, N (%)	351 (73.9)	418 (80.1)
95% confidence interval*	(69.8, 77.6)	(76.4, 83.3)
Comparison vs Placebo**		
Risk ratio (SE)		1.079 (0.037)
95% confidence interval***		(1.009, 1.155)
p-value		0.0268
Baseline use of MRA: Yes		
Number of patients in analysis set	1355	1306
Number of analysed patients, N (%)	1234 (100.0)	1218 (100.0)
Number of patients with endpoint, N (%)	934 (75.7)	951 (78.1)
95% confidence interval*	(73.2, 78.0)	(75.7, 80.3)
Comparison vs Placebo**		
Risk ratio (SE)		1.034 (0.023)
95% confidence interval***		(0.991, 1.079)
p-value		0.1216

* Wilson confidence intervals.
** Log-linked Poisson model with robust estimate of variance includes terms for baseline KCCQ - overall summary score (p<0.0001), age (p=0.0982), baseline eGFR (CKD-EPI) (p=0.0205), Treatment (p=0.0069), region (5 cat.) (p<0.0001), baseline diabetes status (3 cat.) (p=0.4440), sex (p=0.0896), baseline LVEF (3 cat.) (p=0.9618), baseline use of MRA (p=0.1669) and Treatment by baseline use of MRA interaction (p=0.2977).
***Wald confidence intervals.

Data taken from study 1245.121 only.
LOCF: For a missing value at week 52 the last available post-baseline value before week 52 is imputed.

Table R.1.2.8.13: 5 Responder analysis (displaying odds ratio) in KCCQ-OSS change from baseline at week 52 of >= 5 points (improvement) by baseline use of MRA (Y/N) - RS (LOCF-AD) - 1245.121

Subgroup Description	Placebo	Empa 10mg
Baseline use of MRA: No		
Number of patients in analysis set	512	557
Number of analysed patients, N (%)	475 (100.0)	522 (100.0)
Number of patients with endpoint, N (%)	212 (44.6)	276 (52.9)
95% confidence interval*	(40.2, 49.1)	(48.6, 57.1)
Comparison vs Placebo**		
Odds ratio (SE)		1.438 (0.198)
95% confidence interval***		(1.098, 1.882)
p-value		0.0082
Baseline use of MRA: Yes		
Number of patients in analysis set	1355	1306
Number of analysed patients, N (%)	1234 (100.0)	1218 (100.0)
Number of patients with endpoint, N (%)	588 (47.6)	600 (49.3)
95% confidence interval*	(44.9, 50.4)	(46.5, 52.1)
Comparison vs Placebo**		
Odds ratio (SE)		1.100 (0.097)
95% confidence interval***		(0.926, 1.308)
p-value		0.2784

* Wilson confidence intervals.
** Logistic regression includes terms for baseline KCCQ - overall summary score (p<0.0001), age (p=0.0249), baseline eGFR (CKD-EPI) (p=0.0323), Treatment (p=0.0050), region (5 cat.) (p<0.0001), baseline diabetes status (3 cat.) (p=0.5208), sex (p=0.1473), baseline LVEF (3 cat.) (p=0.8310), baseline use of MRA (p=0.0049) and Treatment by baseline use of MRA interaction (p=0.1017).
***Wald confidence intervals.

Data taken from study 1245.121 only.
LOCF: For a missing value at week 52 the last available post-baseline value before week 52 is imputed.

Table R.1.2.8.13: 6 Responder analysis (displaying risk ratio) in KCCQ-OSS change from baseline at week 52 of >= 5 points (improvement) by baseline use of MRA (Y/N) - RS (LOCF-AD) - 1245.121

Subgroup Description	Placebo	Empa 10mg
Baseline use of MRA: No		
Number of patients in analysis set	512	557
Number of analysed patients, N (%)	475 (100.0)	522 (100.0)
Number of patients with endpoint, N (%)	212 (44.6)	276 (52.9)
95% confidence interval*	(40.2, 49.1)	(48.6, 57.1)
Comparison vs Placebo**		
Risk ratio (SE)		1.156 (0.072)
95% confidence interval***		(1.023, 1.306)
p-value		0.0201
Baseline use of MRA: Yes		
Number of patients in analysis set	1355	1306
Number of analysed patients, N (%)	1234 (100.0)	1218 (100.0)
Number of patients with endpoint, N (%)	588 (47.6)	600 (49.3)
95% confidence interval*	(44.9, 50.4)	(46.5, 52.1)
Comparison vs Placebo**		
Risk ratio (SE)		1.036 (0.040)
95% confidence interval***		(0.960, 1.119)
p-value		0.3589

* Wilson confidence intervals.
** Log-linked Poisson model with robust estimate of variance includes terms for baseline KCCQ - overall summary score (p<0.0001), age (p=0.0427), baseline eGFR (CKD-EPI) (p=0.0364), Treatment (p=0.0140), region (5 cat.) (p<0.0001), baseline diabetes status (3 cat.) (p=0.5281), sex (p=0.1235), baseline LVEF (3 cat.) (p=0.7373), baseline use of MRA (p=0.0091) and Treatment by baseline use of MRA interaction (p=0.1380).
***Wald confidence intervals.

Data taken from study 1245.121 only.
LOCF: For a missing value at week 52 the last available post-baseline value before week 52 is imputed.

R.1.2.8.14

Table R.1.2.8.14: 1 Responder analysis (displaying odds ratio) in KCCQ-OSS change from baseline at week 52 of <= -5 points (deterioration) by baseline use of ARNi (Y/N) - RS (LOCF-AD) - 1245.121

Subgroup Description	Placebo	Empa 10mg
Baseline use of ARNi: No		
Number of patients in analysis set	1480	1523
Number of analysed patients, N (%)	1350 (100.0)	1418 (100.0)
Number of patients with endpoint, N (%)	329 (24.4)	304 (21.4)
95% confidence interval*	(22.2, 26.7)	(19.4, 23.7)
Comparison vs Placebo**		
Odds ratio (SE)		0.829 (0.076)
95% confidence interval***		(0.692, 0.993)
p-value		0.0418
Baseline use of ARNi: Yes		
Number of patients in analysis set	387	340
Number of analysed patients, N (%)	359 (100.0)	322 (100.0)
Number of patients with endpoint, N (%)	95 (26.5)	67 (20.8)
95% confidence interval*	(22.2, 31.3)	(16.7, 25.6)
Comparison vs Placebo**		
Odds ratio (SE)		0.728 (0.135)
95% confidence interval***		(0.506, 1.048)
p-value		0.0881

* Wilson confidence intervals.
** Logistic regression includes terms for baseline KCCQ - overall summary score (p<0.0001), age (p=0.0923), baseline eGFR (CKD-EPI) (p=0.0216), Treatment (p=0.0150), region (5 cat.) (p<0.0001), baseline diabetes status (3 cat.) (p=0.4593), sex (p=0.1120), baseline LVEF (3 cat.) (p=0.9836), baseline use of ARNi (p=0.8528) and Treatment by baseline use of ARNi interaction (p=0.5322).
***Wald confidence intervals.

Data taken from study 1245.121 only.
LOCF: For a missing value at week 52 the last available post-baseline value before week 52 is imputed.

Table R.1.2.8.14: 2 Responder analysis (displaying risk ratio) in KCCQ-OSS change from baseline at week 52 of <= -5 points (deterioration) by baseline use of ARNi (Y/N) - RS (LOCF-AD) - 1245.121

Subgroup Description	Placebo	Empa 10mg
Baseline use of ARNi: No		
Number of patients in analysis set	1480	1523
Number of analysed patients, N (%)	1350 (100.0)	1418 (100.0)
Number of patients with endpoint, N (%)	329 (24.4)	304 (21.4)
95% confidence interval*	(22.2, 26.7)	(19.4, 23.7)
Comparison vs Placebo**		
Risk ratio (SE)		0.869 (0.060)
95% confidence interval***		(0.759, 0.994)
p-value		0.0409
Baseline use of ARNi: Yes		
Number of patients in analysis set	387	340
Number of analysed patients, N (%)	359 (100.0)	322 (100.0)
Number of patients with endpoint, N (%)	95 (26.5)	67 (20.8)
95% confidence interval*	(22.2, 31.3)	(16.7, 25.6)
Comparison vs Placebo**		
Risk ratio (SE)		0.792 (0.109)
95% confidence interval***		(0.605, 1.037)
p-value		0.0899

* Wilson confidence intervals.
** Log-linked Poisson model with robust estimate of variance includes terms for baseline KCCQ - overall summary score (p<0.0001), age (p=0.0925), baseline eGFR (CKD-EPI) (p=0.0220), Treatment (p=0.0149), region (5 cat.) (p<0.0001), baseline diabetes status (3 cat.) (p=0.4653), sex (p=0.1190), baseline LVEF (3 cat.) (p=0.9835), baseline use of ARNi (p=0.8063) and Treatment by baseline use of ARNi interaction (p=0.5482).
***Wald confidence intervals.

Data taken from study 1245.121 only.
LOCF: For a missing value at week 52 the last available post-baseline value before week 52 is imputed.

Table R.1.2.8.14: 3 Responder analysis (displaying odds ratio) in KCCQ-OSS change from baseline at week 52 of > -5 points (stability) by baseline use of ARNi (Y/N) - RS (LOCF-AD) - 1245.121

Subgroup Description	Placebo	Empa 10mg
Baseline use of ARNi: No		
Number of patients in analysis set	1480	1523
Number of analysed patients, N (%)	1350 (100.0)	1418 (100.0)
Number of patients with endpoint, N (%)	1021 (75.6)	1114 (78.6)
95% confidence interval*	(73.3, 77.8)	(76.3, 80.6)
Comparison vs Placebo**		
Odds ratio (SE)		1.206 (0.111)
95% confidence interval***		(1.007, 1.446)
p-value		0.0418
Baseline use of ARNi: Yes		
Number of patients in analysis set	387	340
Number of analysed patients, N (%)	359 (100.0)	322 (100.0)
Number of patients with endpoint, N (%)	264 (73.5)	255 (79.2)
95% confidence interval*	(68.7, 77.8)	(74.4, 83.3)
Comparison vs Placebo**		
Odds ratio (SE)		1.374 (0.256)
95% confidence interval***		(0.954, 1.978)
p-value		0.0881

* Wilson confidence intervals.
** Logistic regression includes terms for baseline KCCQ - overall summary score (p<0.0001), age (p=0.0923), baseline eGFR (CKD-EPI) (p=0.0216), Treatment (p=0.0150), region (5 cat.) (p<0.0001), baseline diabetes status (3 cat.) (p=0.4593), sex (p=0.1120), baseline LVEF (3 cat.) (p=0.9836), baseline use of ARNi (p=0.8528) and Treatment by baseline use of ARNi interaction (p=0.5322).
***Wald confidence intervals.

Data taken from study 1245.121 only.
LOCF: For a missing value at week 52 the last available post-baseline value before week 52 is imputed.

Table R.1.2.8.14: 4 Responder analysis (displaying risk ratio) in KCCQ-OSS change from baseline at week 52 of > -5 points (stability) by baseline use of ARNi (Y/N) - RS (LOCF-AD) - 1245.121

Subgroup Description	Placebo	Empa 10mg
Baseline use of ARNi: No		
Number of patients in analysis set	1480	1523
Number of analysed patients, N (%)	1350 (100.0)	1418 (100.0)
Number of patients with endpoint, N (%)	1021 (75.6)	1114 (78.6)
95% confidence interval*	(73.3, 77.8)	(76.3, 80.6)
Comparison vs Placebo**		
Risk ratio (SE)		1.041 (0.021)
95% confidence interval***		(1.000, 1.084)
p-value		0.0485
Baseline use of ARNi: Yes		
Number of patients in analysis set	387	340
Number of analysed patients, N (%)	359 (100.0)	322 (100.0)
Number of patients with endpoint, N (%)	264 (73.5)	255 (79.2)
95% confidence interval*	(68.7, 77.8)	(74.4, 83.3)
Comparison vs Placebo**		
Risk ratio (SE)		1.075 (0.045)
95% confidence interval***		(0.990, 1.167)
p-value		0.0868

* Wilson confidence intervals.
** Log-linked Poisson model with robust estimate of variance includes terms for baseline KCCQ - overall summary score (p<0.0001), age (p=0.1192), baseline eGFR (CKD-EPI) (p=0.0288), Treatment (p=0.0161), region (5 cat.) (p<0.0001), baseline diabetes status (3 cat.) (p=0.4617), sex (p=0.0976), baseline LVEF (3 cat.) (p=0.9759), baseline use of ARNi (p=0.9907) and Treatment by baseline use of ARNi interaction (p=0.4998).
***Wald confidence intervals.

Data taken from study 1245.121 only.
LOCF: For a missing value at week 52 the last available post-baseline value before week 52 is imputed.

Table R.1.2.8.14: 5 Responder analysis (displaying odds ratio) in KCCQ-OSS change from baseline at week 52 of >= 5 points (improvement) by baseline use of ARNi (Y/N) - RS (LOCF-AD) - 1245.121

Subgroup Description	Placebo	Empa 10mg
Baseline use of ARNi: No		
Number of patients in analysis set	1480	1523
Number of analysed patients, N (%)	1350 (100.0)	1418 (100.0)
Number of patients with endpoint, N (%)	640 (47.4)	740 (52.2)
95% confidence interval*	(44.8, 50.1)	(49.6, 54.8)
Comparison vs Placebo**		
Odds ratio (SE)		1.260 (0.104)
95% confidence interval***		(1.072, 1.482)
p-value		0.0051
Baseline use of ARNi: Yes		
Number of patients in analysis set	387	340
Number of analysed patients, N (%)	359 (100.0)	322 (100.0)
Number of patients with endpoint, N (%)	160 (44.6)	136 (42.2)
95% confidence interval*	(39.5, 49.7)	(37.0, 47.7)
Comparison vs Placebo**		
Odds ratio (SE)		0.932 (0.158)
95% confidence interval***		(0.668, 1.300)
p-value		0.6785

* Wilson confidence intervals.
** Logistic regression includes terms for baseline KCCQ - overall summary score (p<0.0001), age (p=0.0389), baseline eGFR (CKD-EPI) (p=0.0490), Treatment (p=0.3940), region (5 cat.) (p<0.0001), baseline diabetes status (3 cat.) (p=0.5763), sex (p=0.1436), baseline LVEF (3 cat.) (p=0.8594), baseline use of ARNi (p=0.0472) and Treatment by baseline use of ARNi interaction (p=0.1102).
***Wald confidence intervals.

Data taken from study 1245.121 only.
LOCF: For a missing value at week 52 the last available post-baseline value before week 52 is imputed.

Table R.1.2.8.14: 6 Responder analysis (displaying risk ratio) in KCCQ-OSS change from baseline at week 52 of >= 5 points (improvement) by baseline use of ARNi (Y/N) - RS (LOCF-AD) - 1245.121

Subgroup Description	Placebo	Empa 10mg
Baseline use of ARNi: No		
Number of patients in analysis set	1480	1523
Number of analysed patients, N (%)	1350 (100.0)	1418 (100.0)
Number of patients with endpoint, N (%)	640 (47.4)	740 (52.2)
95% confidence interval*	(44.8, 50.1)	(49.6, 54.8)
Comparison vs Placebo**		
Risk ratio (SE)		1.093 (0.039)
95% confidence interval***		(1.018, 1.173)
p-value		0.0139
Baseline use of ARNi: Yes		
Number of patients in analysis set	387	340
Number of analysed patients, N (%)	359 (100.0)	322 (100.0)
Number of patients with endpoint, N (%)	160 (44.6)	136 (42.2)
95% confidence interval*	(39.5, 49.7)	(37.0, 47.7)
Comparison vs Placebo**		
Risk ratio (SE)		0.968 (0.080)
95% confidence interval***		(0.823, 1.137)
p-value		0.6878

* Wilson confidence intervals.
** Log-linked Poisson model with robust estimate of variance includes terms for baseline KCCQ - overall summary score (p<0.0001), age (p=0.0581), baseline eGFR (CKD-EPI) (p=0.0537), Treatment (p=0.5337), region (5 cat.) (p<0.0001), baseline diabetes status (3 cat.) (p=0.5692), sex (p=0.1102), baseline LVEF (3 cat.) (p=0.7572), baseline use of ARNi (p=0.0272) and Treatment by baseline use of ARNi interaction (p=0.1756).
***Wald confidence intervals.

Data taken from study 1245.121 only.
LOCF: For a missing value at week 52 the last available post-baseline value before week 52 is imputed.

R.1.2.8.15 Subgroup analysis by bl. LVEF (<= 30%, >30% -<= 35% , > 35%)

Table R.1.2.8.15: 1 Responder analysis (displaying odds ratio) in KCCQ-OSS change from baseline at week 52 of <= -5 points (deterioration) by baseline LVEF (3 cat.) - RS (LOCF-AD) - 1245.121

Subgroup Description	Placebo	Empa 10mg
Baseline LVEF (3 cat.): <=30		
Number of patients in analysis set	1392	1337
Number of analysed patients, N (%)	1272 (100.0)	1245 (100.0)
Number of patients with endpoint, N (%)	320 (25.2)	256 (20.6)
95% confidence interval*	(22.8, 27.6)	(18.4, 22.9)
Comparison vs Placebo**		
Odds ratio (SE)		0.756 (0.073)
95% confidence interval***		(0.625, 0.914)
p-value		0.0039
Baseline LVEF (3 cat.): >30 to <=35		
Number of patients in analysis set	361	398
Number of analysed patients, N (%)	333 (100.0)	375 (100.0)
Number of patients with endpoint, N (%)	76 (22.8)	91 (24.3)
95% confidence interval*	(18.6, 27.6)	(20.2, 28.9)
Comparison vs Placebo**		
Odds ratio (SE)		1.072 (0.194)
95% confidence interval***		(0.752, 1.528)
p-value		0.6995

* Wilson confidence intervals.
** Logistic regression includes terms for baseline KCCQ - overall summary score (p<0.0001), age (p=0.0871), baseline eGFR (CKD-EPI) (p=0.0196), Treatment (p=0.1261), region (5 cat.) (p<0.0001), baseline diabetes status (3 cat.) (p=0.4535), sex (p=0.1147), baseline LVEF (3 cat.) (p=0.9771) and Treatment by baseline LVEF (3 cat.) interaction (p=0.2044).
***Wald confidence intervals.

Data taken from study 1245.121 only.
LOCF: For a missing value at week 52 the last available post-baseline value before week 52 is imputed.

Table R.1.2.8.15: 1 Responder analysis (displaying odds ratio) in KCCQ-OSS change from baseline at week 52 of <= -5 points (deterioration) by baseline LVEF (3 cat.) - RS (LOCF-AD) - 1245.121

Subgroup Description	Placebo	Empa 10mg
Baseline LVEF (3 cat.): >35		
Number of patients in analysis set	114	128
Number of analysed patients, N (%)	104 (100.0)	120 (100.0)
Number of patients with endpoint, N (%)	28 (26.9)	24 (20.0)
95% confidence interval*	(19.3, 36.2)	(13.8, 28.0)
Comparison vs Placebo**		
Odds ratio (SE)		0.687 (0.222)
95% confidence interval***		(0.364, 1.295)
p-value		0.2456

* Wilson confidence intervals.
** Logistic regression includes terms for baseline KCCQ - overall summary score (p<0.0001), age (p=0.0871), baseline eGFR (CKD-EPI) (p=0.0196), Treatment (p=0.1261), region (5 cat.) (p<0.0001), baseline diabetes status (3 cat.) (p=0.4535), sex (p=0.1147), baseline LVEF (3 cat.) (p=0.9771) and Treatment by baseline LVEF (3 cat.) interaction (p=0.2044).
***Wald confidence intervals.

Data taken from study 1245.121 only.
LOCF: For a missing value at week 52 the last available post-baseline value before week 52 is imputed.

Table R.1.2.8.15: 2 Responder analysis (displaying risk ratio) in KCCQ-OSS change from baseline at week 52 of <= -5 points (deterioration) by baseline LVEF (3 cat.) - RS (LOCF-AD) - 1245.121

Subgroup Description	Placebo	Empa 10mg
Baseline LVEF (3 cat.): <=30		
Number of patients in analysis set	1392	1337
Number of analysed patients, N (%)	1272 (100.0)	1245 (100.0)
Number of patients with endpoint, N (%)	320 (25.2)	256 (20.6)
95% confidence interval*	(22.8, 27.6)	(18.4, 22.9)
Comparison vs Placebo**		
Risk ratio (SE)		0.811 (0.059)
95% confidence interval***		(0.704, 0.935)
p-value		0.0039
Baseline LVEF (3 cat.): >30 to <=35		
Number of patients in analysis set	361	398
Number of analysed patients, N (%)	333 (100.0)	375 (100.0)
Number of patients with endpoint, N (%)	76 (22.8)	91 (24.3)
95% confidence interval*	(18.6, 27.6)	(20.2, 28.9)
Comparison vs Placebo**		
Risk ratio (SE)		1.053 (0.141)
95% confidence interval***		(0.810, 1.369)
p-value		0.6993

* Wilson confidence intervals.
** Log-linked Poisson model with robust estimate of variance includes terms for baseline KCCQ - overall summary score (p<0.0001), age (p=0.0863), baseline eGFR (CKD-EPI) (p=0.0204), Treatment (p=0.1221), region (5 cat.) (p<0.0001), baseline diabetes status (3 cat.) (p=0.4595), sex (p=0.1209), baseline LVEF (3 cat.) (p=0.9818) and Treatment by baseline LVEF (3 cat.) interaction (p=0.2004).
***Wald confidence intervals.

Data taken from study 1245.121 only.
LOCF: For a missing value at week 52 the last available post-baseline value before week 52 is imputed.

Table R.1.2.8.15: 2 Responder analysis (displaying risk ratio) in KCCQ-OSS change from baseline at week 52 of <= -5 points (deterioration) by baseline LVEF (3 cat.) - RS (LOCF-AD) - 1245.121

Subgroup Description	Placebo	Empa 10mg
Baseline LVEF (3 cat.): >35		
Number of patients in analysis set	114	128
Number of analysed patients, N (%)	104 (100.0)	120 (100.0)
Number of patients with endpoint, N (%)	28 (26.9)	24 (20.0)
95% confidence interval*	(19.3, 36.2)	(13.8, 28.0)
Comparison vs Placebo**		
Risk ratio (SE)		0.756 (0.180)
95% confidence interval***		(0.473, 1.206)
p-value		0.2402

* Wilson confidence intervals.
** Log-linked Poisson model with robust estimate of variance includes terms for baseline KCCQ - overall summary score (p<0.0001), age (p=0.0863), baseline eGFR (CKD-EPI) (p=0.0204), Treatment (p=0.1221), region (5 cat.) (p<0.0001), baseline diabetes status (3 cat.) (p=0.4595), sex (p=0.1209), baseline LVEF (3 cat.) (p=0.9818) and Treatment by baseline LVEF (3 cat.) interaction (p=0.2004).
***Wald confidence intervals.

Data taken from study 1245.121 only.
LOCF: For a missing value at week 52 the last available post-baseline value before week 52 is imputed.

Table R.1.2.8.15: 3 Responder analysis (displaying odds ratio) in KCCQ-OSS change from baseline at week 52 of > -5 points (stability) by baseline LVEF (3 cat.) - RS (LOCF-AD) - 1245.121

Subgroup Description	Placebo	Empa 10mg
Baseline LVEF (3 cat.): <=30		
Number of patients in analysis set	1392	1337
Number of analysed patients, N (%)	1272 (100.0)	1245 (100.0)
Number of patients with endpoint, N (%)	952 (74.8)	989 (79.4)
95% confidence interval*	(72.4, 77.2)	(77.1, 81.6)
Comparison vs Placebo**		
Odds ratio (SE)		1.323 (0.129)
95% confidence interval***		(1.094, 1.601)
p-value		0.0039
Baseline LVEF (3 cat.): >30 to <=35		
Number of patients in analysis set	361	398
Number of analysed patients, N (%)	333 (100.0)	375 (100.0)
Number of patients with endpoint, N (%)	257 (77.2)	284 (75.7)
95% confidence interval*	(72.4, 81.4)	(71.1, 79.8)
Comparison vs Placebo**		
Odds ratio (SE)		0.933 (0.169)
95% confidence interval***		(0.654, 1.329)
p-value		0.6995

* Wilson confidence intervals.
** Logistic regression includes terms for baseline KCCQ - overall summary score (p<0.0001), age (p=0.0871), baseline eGFR (CKD-EPI) (p=0.0196), Treatment (p=0.1261), region (5 cat.) (p<0.0001), baseline diabetes status (3 cat.) (p=0.4535), sex (p=0.1147), baseline LVEF (3 cat.) (p=0.9771) and Treatment by baseline LVEF (3 cat.) interaction (p=0.2044).
***Wald confidence intervals.

Data taken from study 1245.121 only.
LOCF: For a missing value at week 52 the last available post-baseline value before week 52 is imputed.

Table R.1.2.8.15: 3 Responder analysis (displaying odds ratio) in KCCQ-OSS change from baseline at week 52 of > -5 points (stability) by baseline LVEF (3 cat.) - RS (LOCF-AD) - 1245.121

Subgroup Description	Placebo	Empa 10mg
Baseline LVEF (3 cat.): >35		
Number of patients in analysis set	114	128
Number of analysed patients, N (%)	104 (100.0)	120 (100.0)
Number of patients with endpoint, N (%)	76 (73.1)	96 (80.0)
95% confidence interval*	(63.8, 80.7)	(72.0, 86.2)
Comparison vs Placebo**		
Odds ratio (SE)		1.456 (0.472)
95% confidence interval***		(0.772, 2.747)
p-value		0.2456

* Wilson confidence intervals.
** Logistic regression includes terms for baseline KCCQ - overall summary score (p<0.0001), age (p=0.0871), baseline eGFR (CKD-EPI) (p=0.0196), Treatment (p=0.1261), region (5 cat.) (p<0.0001), baseline diabetes status (3 cat.) (p=0.4535), sex (p=0.1147), baseline LVEF (3 cat.) (p=0.9771) and Treatment by baseline LVEF (3 cat.) interaction (p=0.2044).
***Wald confidence intervals.

Data taken from study 1245.121 only.
LOCF: For a missing value at week 52 the last available post-baseline value before week 52 is imputed.

Table R.1.2.8.15: 4 Responder analysis (displaying risk ratio) in KCCQ-OSS change from baseline at week 52 of > -5 points (stability) by baseline LVEF (3 cat.) - RS (LOCF-AD) - 1245.121

Subgroup Description	Placebo	Empa 10mg
Baseline LVEF (3 cat.): <=30		
Number of patients in analysis set	1392	1337
Number of analysed patients, N (%)	1272 (100.0)	1245 (100.0)
Number of patients with endpoint, N (%)	952 (74.8)	989 (79.4)
95% confidence interval*	(72.4, 77.2)	(77.1, 81.6)
Comparison vs Placebo**		
Risk ratio (SE)		1.063 (0.023)
95% confidence interval***		(1.020, 1.109)
p-value		0.0042
Baseline LVEF (3 cat.): >30 to <=35		
Number of patients in analysis set	361	398
Number of analysed patients, N (%)	333 (100.0)	375 (100.0)
Number of patients with endpoint, N (%)	257 (77.2)	284 (75.7)
95% confidence interval*	(72.4, 81.4)	(71.1, 79.8)
Comparison vs Placebo**		
Risk ratio (SE)		0.983 (0.040)
95% confidence interval***		(0.907, 1.066)
p-value		0.6793

* Wilson confidence intervals.
** Log-linked Poisson model with robust estimate of variance includes terms for baseline KCCQ - overall summary score (p<0.0001), age (p=0.1177), baseline eGFR (CKD-EPI) (p=0.0249), Treatment (p=0.1513), region (5 cat.) (p<0.0001), baseline diabetes status (3 cat.) (p=0.4554), sex (p=0.1047), baseline LVEF (3 cat.) (p=0.9511) and Treatment by baseline LVEF (3 cat.) interaction (p=0.2156).
***Wald confidence intervals.

Data taken from study 1245.121 only.
LOCF: For a missing value at week 52 the last available post-baseline value before week 52 is imputed.

Table R.1.2.8.15: 4 Responder analysis (displaying risk ratio) in KCCQ-OSS change from baseline at week 52 of > -5 points (stability) by baseline LVEF (3 cat.) - RS (LOCF-AD) - 1245.121

Subgroup Description	Placebo	Empa 10mg
Baseline LVEF (3 cat.): >35		
Number of patients in analysis set	114	128
Number of analysed patients, N (%)	104 (100.0)	120 (100.0)
Number of patients with endpoint, N (%)	76 (73.1)	96 (80.0)
95% confidence interval*	(63.8, 80.7)	(72.0, 86.2)
Comparison vs Placebo**		
Risk ratio (SE)		1.083 (0.079)
95% confidence interval***		(0.939, 1.250)
p-value		0.2736

* Wilson confidence intervals.
** Log-linked Poisson model with robust estimate of variance includes terms for baseline KCCQ - overall summary score (p<0.0001), age (p=0.1177), baseline eGFR (CKD-EPI) (p=0.0249), Treatment (p=0.1513), region (5 cat.) (p<0.0001), baseline diabetes status (3 cat.) (p=0.4554), sex (p=0.1047), baseline LVEF (3 cat.) (p=0.9511) and Treatment by baseline LVEF (3 cat.) interaction (p=0.2156).
***Wald confidence intervals.

Data taken from study 1245.121 only.
LOCF: For a missing value at week 52 the last available post-baseline value before week 52 is imputed.

Table R.1.2.8.15: 5 Responder analysis (displaying odds ratio) in KCCQ-OSS change from baseline at week 52 of >= 5 points (improvement) by baseline LVEF (3 cat.) - RS (LOCF-AD) - 1245.121

Subgroup Description	Placebo	Empa 10mg
Baseline LVEF (3 cat.): <=30		
Number of patients in analysis set	1392	1337
Number of analysed patients, N (%)	1272 (100.0)	1245 (100.0)
Number of patients with endpoint, N (%)	591 (46.5)	646 (51.9)
95% confidence interval*	(43.7, 49.2)	(49.1, 54.7)
Comparison vs Placebo**		
Odds ratio (SE)		1.304 (0.113)
95% confidence interval***		(1.100, 1.545)
p-value		0.0023
Baseline LVEF (3 cat.): >30 to <=35		
Number of patients in analysis set	361	398
Number of analysed patients, N (%)	333 (100.0)	375 (100.0)
Number of patients with endpoint, N (%)	159 (47.7)	174 (46.4)
95% confidence interval*	(42.4, 53.1)	(41.4, 51.5)
Comparison vs Placebo**		
Odds ratio (SE)		0.943 (0.154)
95% confidence interval***		(0.684, 1.299)
p-value		0.7186

* Wilson confidence intervals.
** Logistic regression includes terms for baseline KCCQ - overall summary score (p<0.0001), age (p=0.0414), baseline eGFR (CKD-EPI) (p=0.0496), Treatment (p=0.6910), region (5 cat.) (p<0.0001), baseline diabetes status (3 cat.) (p=0.5392), sex (p=0.1720), baseline LVEF (3 cat.) (p=0.9115) and Treatment by baseline LVEF (3 cat.) interaction (p=0.1488).
***Wald confidence intervals.

Data taken from study 1245.121 only.
LOCF: For a missing value at week 52 the last available post-baseline value before week 52 is imputed.

Table R.1.2.8.15: 5 Responder analysis (displaying odds ratio) in KCCQ-OSS change from baseline at week 52 of >= 5 points (improvement) by baseline LVEF (3 cat.) - RS (LOCF-AD) - 1245.121

Subgroup Description	Placebo	Empa 10mg
Baseline LVEF (3 cat.): >35		
Number of patients in analysis set	114	128
Number of analysed patients, N (%)	104 (100.0)	120 (100.0)
Number of patients with endpoint, N (%)	50 (48.1)	56 (46.7)
95% confidence interval*	(38.7, 57.6)	(38.0, 55.6)
Comparison vs Placebo**		
Odds ratio (SE)		0.934 (0.274)
95% confidence interval***		(0.526, 1.659)
p-value		0.8156

* Wilson confidence intervals.
** Logistic regression includes terms for baseline KCCQ - overall summary score (p<0.0001), age (p=0.0414), baseline eGFR (CKD-EPI) (p=0.0496), Treatment (p=0.6910), region (5 cat.) (p<0.0001), baseline diabetes status (3 cat.) (p=0.5392), sex (p=0.1720), baseline LVEF (3 cat.) (p=0.9115) and Treatment by baseline LVEF (3 cat.) interaction (p=0.1488).
***Wald confidence intervals.

Data taken from study 1245.121 only.
LOCF: For a missing value at week 52 the last available post-baseline value before week 52 is imputed.

Table R.1.2.8.15: 6 Responder analysis (displaying risk ratio) in KCCQ-OSS change from baseline at week 52 of >= 5 points (improvement) by baseline LVEF (3 cat.) - RS (LOCF-AD) - 1245.121

Subgroup Description	Placebo	Empa 10mg
Baseline LVEF (3 cat.): <=30		
Number of patients in analysis set	1392	1337
Number of analysed patients, N (%)	1272 (100.0)	1245 (100.0)
Number of patients with endpoint, N (%)	591 (46.5)	646 (51.9)
95% confidence interval*	(43.7, 49.2)	(49.1, 54.7)
Comparison vs Placebo**		
Risk ratio (SE)		1.117 (0.043)
95% confidence interval***		(1.036, 1.204)
p-value		0.0038
Baseline LVEF (3 cat.): >30 to <=35		
Number of patients in analysis set	361	398
Number of analysed patients, N (%)	333 (100.0)	375 (100.0)
Number of patients with endpoint, N (%)	159 (47.7)	174 (46.4)
95% confidence interval*	(42.4, 53.1)	(41.4, 51.5)
Comparison vs Placebo**		
Risk ratio (SE)		0.957 (0.071)
95% confidence interval***		(0.828, 1.107)
p-value		0.5550

* Wilson confidence intervals.
** Log-linked Poisson model with robust estimate of variance includes terms for baseline KCCQ - overall summary score (p<0.0001), age (p=0.0670), baseline eGFR (CKD-EPI) (p=0.0508), Treatment (p=0.9560), region (5 cat.) (p<0.0001), baseline diabetes status (3 cat.) (p=0.5331), sex (p=0.1448), baseline LVEF (3 cat.) (p=0.8680) and Treatment by baseline LVEF (3 cat.) interaction (p=0.1086).
***Wald confidence intervals.

Data taken from study 1245.121 only.
LOCF: For a missing value at week 52 the last available post-baseline value before week 52 is imputed.

Table R.1.2.8.15: 6 Responder analysis (displaying risk ratio) in KCCQ-OSS change from baseline at week 52 of >= 5 points (improvement) by baseline LVEF (3 cat.) - RS (LOCF-AD) - 1245.121

Subgroup Description	Placebo	Empa 10mg
Baseline LVEF (3 cat.): >35		
Number of patients in analysis set	114	128
Number of analysed patients, N (%)	104 (100.0)	120 (100.0)
Number of patients with endpoint, N (%)	50 (48.1)	56 (46.7)
95% confidence interval*	(38.7, 57.6)	(38.0, 55.6)
Comparison vs Placebo**		
Risk ratio (SE)		0.943 (0.124)
95% confidence interval***		(0.728, 1.221)
p-value		0.6575

* Wilson confidence intervals.
** Log-linked Poisson model with robust estimate of variance includes terms for baseline KCCQ - overall summary score (p<0.0001), age (p=0.0670), baseline eGFR (CKD-EPI) (p=0.0508), Treatment (p=0.9560), region (5 cat.) (p<0.0001), baseline diabetes status (3 cat.) (p=0.5331), sex (p=0.1448), baseline LVEF (3 cat.) (p=0.8680) and Treatment by baseline LVEF (3 cat.) interaction (p=0.1086).
***Wald confidence intervals.

Data taken from study 1245.121 only.
LOCF: For a missing value at week 52 the last available post-baseline value before week 52 is imputed.

R.1.2.8.16 Subgroup analysis by bl. NTproBNP </>= median (median based on total patients)

Table R.1.2.8.16: 1 Responder analysis (displaying odds ratio) in KCCQ-OSS change from baseline at week 52 of <= -5 points (deterioration) by bl. NTproBNP (<median, >= median) (median based on total patients) - RS (LOCF-AD) - 1245.121

Subgroup Description	Placebo	Empa 10mg
Baseline NTproBNP (<median, >= median): < median		
Number of patients in analysis set	920	942
Number of analysed patients, N (%)	866 (100.0)	886 (100.0)
Number of patients with endpoint, N (%)	192 (22.2)	172 (19.4)
95% confidence interval*	(19.5, 25.1)	(16.9, 22.1)
Comparison vs Placebo**		
Odds ratio (SE)		0.828 (0.099)
95% confidence interval***		(0.655, 1.048)
p-value		0.1162
Baseline NTproBNP (<median, >= median): >= median		
Number of patients in analysis set	946	920
Number of analysed patients, N (%)	843 (100.0)	854 (100.0)
Number of patients with endpoint, N (%)	232 (27.5)	199 (23.3)
95% confidence interval*	(24.6, 30.6)	(20.6, 26.3)
Comparison vs Placebo**		
Odds ratio (SE)		0.792 (0.090)
95% confidence interval***		(0.633, 0.991)
p-value		0.0412

* Wilson confidence intervals.
** Logistic regression includes terms for baseline KCCQ - overall summary score (p<0.0001), age (p=0.1196), baseline eGFR (CKD-EPI) (p=0.1082), Treatment (p=0.0109), region (5 cat.) (p<0.0001), baseline diabetes status (3 cat.) (p=0.4286), sex (p=0.1221), baseline LVEF (3 cat.) (p=0.9619), baseline NTproBNP (<median, >= median) (p=0.0003) and Treatment by baseline NTproBNP (<median, >= median) interaction (p=0.7884).
***Wald confidence intervals.
2 patients were excluded as the subgroup variable was missing.

Data taken from study 1245.121 only.
LOCF: For a missing value at week 52 the last available post-baseline value before week 52 is imputed.
Median: 1910 [pg/mL]

Table R.1.2.8.16: 2 Responder analysis (displaying risk ratio) in KCCQ-OSS change from baseline at week 52 of <= -5 points (deterioration) by bl. NTproBNP (<median, >= median) (median based on total patients) - RS (LOCF-AD) - 1245.121

Subgroup Description	Placebo	Empa 10mg
Baseline NTproBNP (<median, >= median): < median		
Number of patients in analysis set	920	942
Number of analysed patients, N (%)	866 (100.0)	886 (100.0)
Number of patients with endpoint, N (%)	192 (22.2)	172 (19.4)
95% confidence interval*	(19.5, 25.1)	(16.9, 22.1)
Comparison vs Placebo**		
Risk ratio (SE)		0.866 (0.080)
95% confidence interval***		(0.723, 1.037)
p-value		0.1166
Baseline NTproBNP (<median, >= median): >= median		
Number of patients in analysis set	946	920
Number of analysed patients, N (%)	843 (100.0)	854 (100.0)
Number of patients with endpoint, N (%)	232 (27.5)	199 (23.3)
95% confidence interval*	(24.6, 30.6)	(20.6, 26.3)
Comparison vs Placebo**		
Risk ratio (SE)		0.846 (0.069)
95% confidence interval***		(0.720, 0.993)
p-value		0.0410

* Wilson confidence intervals.
** Log-linked Poisson model with robust estimate of variance includes terms for baseline KCCQ - overall summary score (p<0.0001), age (p=0.1195), baseline eGFR (CKD-EPI) (p=0.1056), Treatment (p=0.0113), region (5 cat.) (p<0.0001), baseline diabetes status (3 cat.) (p=0.4370), sex (p=0.1279), baseline LVEF (3 cat.) (p=0.9611), baseline NTproBNP (<median, >= median) (p=0.0003) and Treatment by baseline NTproBNP (<median, >= median) interaction (p=0.8512).
***Wald confidence intervals.
2 patients were excluded as the subgroup variable was missing.

Data taken from study 1245.121 only.
LOCF: For a missing value at week 52 the last available post-baseline value before week 52 is imputed.
Median: 1910 [pg/mL]

Table R.1.2.8.16: 3 Responder analysis (displaying odds ratio) in KCCQ-OSS change from baseline at week 52 of > -5 points (stability) by bl. NTproBNP (<median, >= median) (median based on total patients) - RS (LOCF-AD) - 1245.121

Subgroup Description	Placebo	Empa 10mg
Baseline NTproBNP (<median, >= median): < median		
Number of patients in analysis set	920	942
Number of analysed patients, N (%)	866 (100.0)	886 (100.0)
Number of patients with endpoint, N (%)	674 (77.8)	714 (80.6)
95% confidence interval*	(74.9, 80.5)	(77.9, 83.1)
Comparison vs Placebo**		
Odds ratio (SE)		1.207 (0.145)
95% confidence interval***		(0.954, 1.528)
p-value		0.1162
Baseline NTproBNP (<median, >= median): >= median		
Number of patients in analysis set	946	920
Number of analysed patients, N (%)	843 (100.0)	854 (100.0)
Number of patients with endpoint, N (%)	611 (72.5)	655 (76.7)
95% confidence interval*	(69.4, 75.4)	(73.7, 79.4)
Comparison vs Placebo**		
Odds ratio (SE)		1.262 (0.144)
95% confidence interval***		(1.009, 1.579)
p-value		0.0412

* Wilson confidence intervals.
** Logistic regression includes terms for baseline KCCQ - overall summary score (p<0.0001), age (p=0.1196), baseline eGFR (CKD-EPI) (p=0.1082), Treatment (p=0.0109), region (5 cat.) (p<0.0001), baseline diabetes status (3 cat.) (p=0.4286), sex (p=0.1221), baseline LVEF (3 cat.) (p=0.9619), baseline NTproBNP (<median, >= median) (p=0.0003) and Treatment by baseline NTproBNP (<median, >= median) interaction (p=0.7884).
***Wald confidence intervals.
2 patients were excluded as the subgroup variable was missing.

Data taken from study 1245.121 only.
LOCF: For a missing value at week 52 the last available post-baseline value before week 52 is imputed.
Median: 1910 [pg/mL]

Table R.1.2.8.16: 4 Responder analysis (displaying risk ratio) in KCCQ-OSS change from baseline at week 52 of > -5 points (stability) by bl. NTproBNP (<median, >= median) (median based on total patients) - RS (LOCF-AD) - 1245.121

Subgroup Description	Placebo	Empa 10mg
Baseline NTproBNP (<median, >= median): < median		
Number of patients in analysis set	920	942
Number of analysed patients, N (%)	866 (100.0)	886 (100.0)
Number of patients with endpoint, N (%)	674 (77.8)	714 (80.6)
95% confidence interval*	(74.9, 80.5)	(77.9, 83.1)
Comparison vs Placebo**		
Risk ratio (SE)		1.037 (0.025)
95% confidence interval***		(0.989, 1.088)
p-value		0.1305
Baseline NTproBNP (<median, >= median): >= median		
Number of patients in analysis set	946	920
Number of analysed patients, N (%)	843 (100.0)	854 (100.0)
Number of patients with endpoint, N (%)	611 (72.5)	655 (76.7)
95% confidence interval*	(69.4, 75.4)	(73.7, 79.4)
Comparison vs Placebo**		
Risk ratio (SE)		1.058 (0.030)
95% confidence interval***		(1.002, 1.118)
p-value		0.0431

* Wilson confidence intervals.
** Log-linked Poisson model with robust estimate of variance includes terms for baseline KCCQ - overall summary score (p<0.0001), age (p=0.1541), baseline eGFR (CKD-EPI) (p=0.1304), Treatment (p=0.0117), region (5 cat.) (p<0.0001), baseline diabetes status (3 cat.) (p=0.4332), sex (p=0.1157), baseline LVEF (3 cat.) (p=0.9701), baseline NTproBNP (<median, >= median) (p=0.0002) and Treatment by baseline NTproBNP (<median, >= median) interaction (p=0.5900).
***Wald confidence intervals.
2 patients were excluded as the subgroup variable was missing.

Data taken from study 1245.121 only.
LOCF: For a missing value at week 52 the last available post-baseline value before week 52 is imputed.
Median: 1910 [pg/mL]

Table R.1.2.8.16: 5 Responder analysis (displaying odds ratio) in KCCQ-OSS change from baseline at week 52 of >= 5 points (improvement) by bl. NTproBNP (<median, >= median) (median based on total patients) - RS (LOCF-AD) - 1245.121

Subgroup Description	Placebo	Empa 10mg
Baseline NTproBNP (<median, >= median): < median		
Number of patients in analysis set	920	942
Number of analysed patients, N (%)	866 (100.0)	886 (100.0)
Number of patients with endpoint, N (%)	395 (45.6)	443 (50.0)
95% confidence interval*	(42.3, 48.9)	(46.7, 53.3)
Comparison vs Placebo**		
Odds ratio (SE)		1.272 (0.132)
95% confidence interval***		(1.038, 1.559)
p-value		0.0203
Baseline NTproBNP (<median, >= median): >= median		
Number of patients in analysis set	946	920
Number of analysed patients, N (%)	843 (100.0)	854 (100.0)
Number of patients with endpoint, N (%)	405 (48.0)	433 (50.7)
95% confidence interval*	(44.7, 51.4)	(47.4, 54.0)
Comparison vs Placebo**		
Odds ratio (SE)		1.116 (0.118)
95% confidence interval***		(0.906, 1.373)
p-value		0.3025

* Wilson confidence intervals.
** Logistic regression includes terms for baseline KCCQ - overall summary score (p<0.0001), age (p=0.0445), baseline eGFR (CKD-EPI) (p=0.0998), Treatment (p=0.0183), region (5 cat.) (p<0.0001), baseline diabetes status (3 cat.) (p=0.5371), sex (p=0.1781), baseline LVEF (3 cat.) (p=0.9375), baseline NTproBNP (<median, >= median) (p=0.2576) and Treatment by baseline NTproBNP (<median, >= median) interaction (p=0.3761).
***Wald confidence intervals.
2 patients were excluded as the subgroup variable was missing.

Data taken from study 1245.121 only.
LOCF: For a missing value at week 52 the last available post-baseline value before week 52 is imputed.
Median: 1910 [pg/mL]

Table R.1.2.8.16: 6 Responder analysis (displaying risk ratio) in KCCQ-OSS change from baseline at week 52 of >= 5 points (improvement) by bl. NTproBNP (<median, >= median) (median based on total patients) - RS (LOCF-AD) - 1245.121

Subgroup Description	Placebo	Empa 10mg
Baseline NTproBNP (<median, >= median): < median		
Number of patients in analysis set	920	942
Number of analysed patients, N (%)	866 (100.0)	886 (100.0)
Number of patients with endpoint, N (%)	395 (45.6)	443 (50.0)
95% confidence interval*	(42.3, 48.9)	(46.7, 53.3)
Comparison vs Placebo**		
Risk ratio (SE)		1.101 (0.052)
95% confidence interval***		(1.004, 1.208)
p-value		0.0413
Baseline NTproBNP (<median, >= median): >= median		
Number of patients in analysis set	946	920
Number of analysed patients, N (%)	843 (100.0)	854 (100.0)
Number of patients with endpoint, N (%)	405 (48.0)	433 (50.7)
95% confidence interval*	(44.7, 51.4)	(47.4, 54.0)
Comparison vs Placebo**		
Risk ratio (SE)		1.043 (0.048)
95% confidence interval***		(0.953, 1.142)
p-value		0.3585

* Wilson confidence intervals.
** Log-linked Poisson model with robust estimate of variance includes terms for baseline KCCQ - overall summary score (p<0.0001), age (p=0.0750), baseline eGFR (CKD-EPI) (p=0.1022), Treatment (p=0.0357), region (5 cat.) (p<0.0001), baseline diabetes status (3 cat.) (p=0.5250), sex (p=0.1552), baseline LVEF (3 cat.) (p=0.8846), baseline NTproBNP (<median, >= median) (p=0.2394) and Treatment by baseline NTproBNP (<median, >= median) interaction (p=0.4135).
***Wald confidence intervals.
2 patients were excluded as the subgroup variable was missing.

Data taken from study 1245.121 only.
LOCF: For a missing value at week 52 the last available post-baseline value before week 52 is imputed.
Median: 1910 [pg/mL]

R.1.2.9

R.1.2.9 KCCQ Overall Summary Score responder analysis (15 points)

R.1.2.9.1

Table R.1.2.9.1: 1 Responder analysis (displaying odds ratio) in KCCQ-OSS change from baseline at week 52 of <= -15 points (deterioration) - RS (LOCF-AD) - 1245.121

	Placebo	Empa 10mg
Number of patients in analysis set	1867	1863
Number of analysed patients, N (%)	1709 (100.0)	1740 (100.0)
Number of patients with endpoint, N (%)	208 (12.2)	174 (10.0)
95% confidence interval*	(10.7, 13.8)	(8.7, 11.5)
Comparison vs Placebo**		
Odds ratio (SE)		0.795 (0.088)
95% confidence interval***		(0.640, 0.987)
p-value		0.0374

* Wilson confidence intervals.
** Logistic regression includes terms for baseline KCCQ - overall summary score (p<0.0001), age (p=0.3304), baseline eGFR (CKD-EPI) (p=0.0014), Treatment (p=0.0374), region (5 cat.) (p=0.0109), baseline diabetes status (3 cat.) (p=0.2845), sex (p=0.7722) and baseline LVEF (3 cat.) (p=0.6966).
***Wald confidence intervals.

Data taken from study 1245.121 only.
LOCF: For a missing value at week 52 the last available post-baseline value before week 52 is imputed.

Table R.1.2.9.1: 2 Responder analysis (displaying risk ratio) in KCCQ-OSS change from baseline at week 52 of <= -15 points (deterioration) - RS (LOCF-AD) - 1245.121

	Placebo	Empa 10mg
Number of patients in analysis set	1867	1863
Number of analysed patients, N (%)	1709 (100.0)	1740 (100.0)
Number of patients with endpoint, N (%)	208 (12.2)	174 (10.0)
95% confidence interval*	(10.7, 13.8)	(8.7, 11.5)
Comparison vs Placebo**		
Risk ratio (SE)		0.819 (0.078)
95% confidence interval***		(0.679, 0.988)
p-value		0.0373

* Wilson confidence intervals.
** Log-linked Poisson model with robust estimate of variance includes terms for baseline KCCQ - overall summary score (p<0.0001), age (p=0.3562), baseline eGFR (CKD-EPI) (p=0.0019), Treatment (p=0.0373), region (5 cat.) (p=0.0142), baseline diabetes status (3 cat.) (p=0.2952), sex (p=0.7771) and baseline LVEF (3 cat.) (p=0.6917).
***Wald confidence intervals.

Data taken from study 1245.121 only.
LOCF: For a missing value at week 52 the last available post-baseline value before week 52 is imputed.

Table R.1.2.9.1: 3 Responder analysis (displaying odds ratio) in KCCQ-OSS change from baseline at week 52 of > -15 points (stability) - RS (LOCF-AD) - 1245.121

	Placebo	Empa 10mg
Number of patients in analysis set	1867	1863
Number of analysed patients, N (%)	1709 (100.0)	1740 (100.0)
Number of patients with endpoint, N (%)	1501 (87.8)	1566 (90.0)
95% confidence interval*	(86.2, 89.3)	(88.5, 91.3)
Comparison vs Placebo**		
Odds ratio (SE)		1.258 (0.139)
95% confidence interval***		(1.013, 1.562)
p-value		0.0374

* Wilson confidence intervals.
** Logistic regression includes terms for baseline KCCQ - overall summary score (p<0.0001), age (p=0.3304), baseline eGFR (CKD-EPI) (p=0.0014), Treatment (p=0.0374), region (5 cat.) (p=0.0109), baseline diabetes status (3 cat.) (p=0.2845), sex (p=0.7722) and baseline LVEF (3 cat.) (p=0.6966).
***Wald confidence intervals.

Data taken from study 1245.121 only.
LOCF: For a missing value at week 52 the last available post-baseline value before week 52 is imputed.

Table R.1.2.9.1: 4 Responder analysis (displaying risk ratio) in KCCQ-OSS change from baseline at week 52 of > -15 points (stability) - RS (LOCF-AD) - 1245.121

	Placebo	Empa 10mg
Number of patients in analysis set	1867	1863
Number of analysed patients, N (%)	1709 (100.0)	1740 (100.0)
Number of patients with endpoint, N (%)	1501 (87.8)	1566 (90.0)
95% confidence interval*	(86.2, 89.3)	(88.5, 91.3)
Comparison vs Placebo**		
Risk ratio (SE)		1.025 (0.012)
95% confidence interval***		(1.001, 1.049)
p-value		0.0405

* Wilson confidence intervals.
** Log-linked Poisson model with robust estimate of variance includes terms for baseline KCCQ - overall summary score (p<0.0001), age (p=0.4403), baseline eGFR (CKD-EPI) (p=0.0022), Treatment (p=0.0405), region (5 cat.) (p<0.0001), baseline diabetes status (3 cat.) (p=0.2596), sex (p=0.7626) and baseline LVEF (3 cat.) (p=0.7191).
***Wald confidence intervals.

Data taken from study 1245.121 only.
LOCF: For a missing value at week 52 the last available post-baseline value before week 52 is imputed.

Table R.1.2.9.1: 5 Responder analysis (displaying odds ratio) in KCCQ-OSS change from baseline at week 52 of >= 15 points (improvement) - RS (LOCF-AD) - 1245.121

	Placebo	Empa 10mg
Number of patients in analysis set	1867	1863
Number of analysed patients, N (%)	1709 (100.0)	1740 (100.0)
Number of patients with endpoint, N (%)	402 (23.5)	445 (25.6)
95% confidence interval*	(21.6, 25.6)	(23.6, 27.7)
Comparison vs Placebo**		
Odds ratio (SE)		1.140 (0.102)
95% confidence interval***		(0.956, 1.359)
p-value		0.1452

* Wilson confidence intervals.
** Logistic regression includes terms for baseline KCCQ - overall summary score (p<0.0001), age (p=0.9795), baseline eGFR (CKD-EPI) (p=0.0025), Treatment (p=0.1452), region (5 cat.) (p<0.0001), baseline diabetes status (3 cat.) (p=0.4591), sex (p=0.3382) and baseline LVEF (3 cat.) (p=0.6528).
***Wald confidence intervals.

Data taken from study 1245.121 only.
LOCF: For a missing value at week 52 the last available post-baseline value before week 52 is imputed.

Table R.1.2.9.1: 6 Responder analysis (displaying risk ratio) in KCCQ-OSS change from baseline at week 52 of >= 15 points (improvement) - RS (LOCF-AD) - 1245.121

	Placebo	Empa 10mg
Number of patients in analysis set	1867	1863
Number of analysed patients, N (%)	1709 (100.0)	1740 (100.0)
Number of patients with endpoint, N (%)	402 (23.5)	445 (25.6)
95% confidence interval*	(21.6, 25.6)	(23.6, 27.7)
Comparison vs Placebo**		
Risk ratio (SE)		1.064 (0.059)
95% confidence interval***		(0.954, 1.187)
p-value		0.2644

* Wilson confidence intervals.
** Log-linked Poisson model with robust estimate of variance includes terms for baseline KCCQ - overall summary score (p<0.0001), age (p=0.8851), baseline eGFR (CKD-EPI) (p=0.0026), Treatment (p=0.2644), region (5 cat.) (p<0.0001), baseline diabetes status (3 cat.) (p=0.4606), sex (p=0.3080) and baseline LVEF (3 cat.) (p=0.5271).
***Wald confidence intervals.

Data taken from study 1245.121 only.
LOCF: For a missing value at week 52 the last available post-baseline value before week 52 is imputed.

R.1.2.9.2

R.1.2.9.2 Subgroup analysis by sex

Table R.1.2.9.2: 1 Responder analysis (displaying odds ratio) in KCCQ-OSS change from baseline at week 52 of <= -15 points (deterioration) by sex - RS (LOCF-AD) - 1245.121

Subgroup Description	Placebo	Empa 10mg
Sex: Male		
Number of patients in analysis set	1411	1426
Number of analysed patients, N (%)	1297 (100.0)	1332 (100.0)
Number of patients with endpoint, N (%)	171 (13.2)	130 (9.8)
95% confidence interval*	(11.5, 15.1)	(8.3, 11.5)
Comparison vs Placebo**		
Odds ratio (SE)		0.709 (0.089)
95% confidence interval***		(0.555, 0.906)
p-value		0.0060
Sex: Female		
Number of patients in analysis set	456	437
Number of analysed patients, N (%)	412 (100.0)	408 (100.0)
Number of patients with endpoint, N (%)	37 (9.0)	44 (10.8)
95% confidence interval*	(6.6, 12.1)	(8.1, 14.2)
Comparison vs Placebo**		
Odds ratio (SE)		1.201 (0.286)
95% confidence interval***		(0.753, 1.914)
p-value		0.4420

* Wilson confidence intervals.
** Logistic regression includes terms for baseline KCCQ - overall summary score (p<0.0001), age (p=0.3013), baseline eGFR (CKD-EPI) (p=0.0014), Treatment (p=0.5488), region (5 cat.) (p=0.0123), baseline diabetes status (3 cat.) (p=0.2951), baseline LVEF (3 cat.) (p=0.7031), sex (p=0.7965) and Treatment by sex interaction (p=0.0501).
***Wald confidence intervals.

Data taken from study 1245.121 only.
LOCF: For a missing value at week 52 the last available post-baseline value before week 52 is imputed.

Table R.1.2.9.2: 2 Responder analysis (displaying risk ratio) in KCCQ-OSS change from baseline at week 52 of <= -15 points (deterioration) by sex - RS (LOCF-AD) - 1245.121

Subgroup Description	Placebo	Empa 10mg
Sex: Male		
Number of patients in analysis set	1411	1426
Number of analysed patients, N (%)	1297 (100.0)	1332 (100.0)
Number of patients with endpoint, N (%)	171 (13.2)	130 (9.8)
95% confidence interval*	(11.5, 15.1)	(8.3, 11.5)
Comparison vs Placebo**		
Risk ratio (SE)		0.743 (0.081)
95% confidence interval***		(0.601, 0.920)
p-value		0.0064
Sex: Female		
Number of patients in analysis set	456	437
Number of analysed patients, N (%)	412 (100.0)	408 (100.0)
Number of patients with endpoint, N (%)	37 (9.0)	44 (10.8)
95% confidence interval*	(6.6, 12.1)	(8.1, 14.2)
Comparison vs Placebo**		
Risk ratio (SE)		1.171 (0.245)
95% confidence interval***		(0.777, 1.765)
p-value		0.4494

* Wilson confidence intervals.
** Log-linked Poisson model with robust estimate of variance includes terms for baseline KCCQ - overall summary score (p<0.0001), age (p=0.3275), baseline eGFR (CKD-EPI) (p=0.0018), Treatment (p=0.5560), region (5 cat.) (p=0.0159), baseline diabetes status (3 cat.) (p=0.3062), baseline LVEF (3 cat.) (p=0.6988), sex (p=0.8001) and Treatment by sex interaction (p=0.0544).
***Wald confidence intervals.

Data taken from study 1245.121 only.
LOCF: For a missing value at week 52 the last available post-baseline value before week 52 is imputed.

Table R.1.2.9.2: 3 Responder analysis (displaying odds ratio) in KCCQ-OSS change from baseline at week 52 of > -15 points (stability) by sex - RS (LOCF-AD) - 1245.121

Subgroup Description	Placebo	Empa 10mg
Sex: Male		
Number of patients in analysis set	1411	1426
Number of analysed patients, N (%)	1297 (100.0)	1332 (100.0)
Number of patients with endpoint, N (%)	1126 (86.8)	1202 (90.2)
95% confidence interval*	(84.9, 88.5)	(88.5, 91.7)
Comparison vs Placebo**		
Odds ratio (SE)		1.411 (0.177)
95% confidence interval***		(1.104, 1.803)
p-value		0.0060
Sex: Female		
Number of patients in analysis set	456	437
Number of analysed patients, N (%)	412 (100.0)	408 (100.0)
Number of patients with endpoint, N (%)	375 (91.0)	364 (89.2)
95% confidence interval*	(87.9, 93.4)	(85.8, 91.9)
Comparison vs Placebo**		
Odds ratio (SE)		0.833 (0.198)
95% confidence interval***		(0.523, 1.328)
p-value		0.4420

* Wilson confidence intervals.
** Logistic regression includes terms for baseline KCCQ - overall summary score (p<0.0001), age (p=0.3013), baseline eGFR (CKD-EPI) (p=0.0014), Treatment (p=0.5488), region (5 cat.) (p=0.0123), baseline diabetes status (3 cat.) (p=0.2951), baseline LVEF (3 cat.) (p=0.7031), sex (p=0.7965) and Treatment by sex interaction (p=0.0501).
***Wald confidence intervals.

Data taken from study 1245.121 only.
LOCF: For a missing value at week 52 the last available post-baseline value before week 52 is imputed.

Table R.1.2.9.2: 4 Responder analysis (displaying risk ratio) in KCCQ-OSS change from baseline at week 52 of > -15 points (stability) by sex - RS (LOCF-AD) - 1245.121

Subgroup Description	Placebo	Empa 10mg
Sex: Male		
Number of patients in analysis set	1411	1426
Number of analysed patients, N (%)	1297 (100.0)	1332 (100.0)
Number of patients with endpoint, N (%)	1126 (86.8)	1202 (90.2)
95% confidence interval*	(84.9, 88.5)	(88.5, 91.7)
Comparison vs Placebo**		
Risk ratio (SE)		1.039 (0.015)
95% confidence interval***		(1.011, 1.068)
p-value		0.0058
Sex: Female		
Number of patients in analysis set	456	437
Number of analysed patients, N (%)	412 (100.0)	408 (100.0)
Number of patients with endpoint, N (%)	375 (91.0)	364 (89.2)
95% confidence interval*	(87.9, 93.4)	(85.8, 91.9)
Comparison vs Placebo**		
Risk ratio (SE)		0.980 (0.022)
95% confidence interval***		(0.937, 1.025)
p-value		0.3836

* Wilson confidence intervals.
** Log-linked Poisson model with robust estimate of variance includes terms for baseline KCCQ - overall summary score (p<0.0001), age (p=0.4174), baseline eGFR (CKD-EPI) (p=0.0020), Treatment (p=0.4865), region (5 cat.) (p<0.0001), baseline diabetes status (3 cat.) (p=0.2698), baseline LVEF (3 cat.) (p=0.7334), sex (p=0.7483) and Treatment by sex interaction (p=0.0296).
***Wald confidence intervals.

Data taken from study 1245.121 only.
LOCF: For a missing value at week 52 the last available post-baseline value before week 52 is imputed.

Table R.1.2.9.2: 5 Responder analysis (displaying odds ratio) in KCCQ-OSS change from baseline at week 52 of >= 15 points (improvement) by sex - RS (LOCF-AD) - 1245.121

Subgroup Description	Placebo	Empa 10mg
Sex: Male		
Number of patients in analysis set	1411	1426
Number of analysed patients, N (%)	1297 (100.0)	1332 (100.0)
Number of patients with endpoint, N (%)	281 (21.7)	309 (23.2)
95% confidence interval*	(19.5, 24.0)	(21.0, 25.5)
Comparison vs Placebo**		
Odds ratio (SE)		1.093 (0.115)
95% confidence interval***		(0.890, 1.344)
p-value		0.3963
Sex: Female		
Number of patients in analysis set	456	437
Number of analysed patients, N (%)	412 (100.0)	408 (100.0)
Number of patients with endpoint, N (%)	121 (29.4)	136 (33.3)
95% confidence interval*	(25.2, 33.9)	(28.9, 38.0)
Comparison vs Placebo**		
Odds ratio (SE)		1.273 (0.219)
95% confidence interval***		(0.908, 1.784)
p-value		0.1608

* Wilson confidence intervals.
** Logistic regression includes terms for baseline KCCQ - overall summary score (p<0.0001), age (p=0.9842), baseline eGFR (CKD-EPI) (p=0.0027), Treatment (p=0.1011), region (5 cat.) (p<0.0001), baseline diabetes status (3 cat.) (p=0.4557), baseline LVEF (3 cat.) (p=0.6475), sex (p=0.3404) and Treatment by sex interaction (p=0.4512).
***Wald confidence intervals.

Data taken from study 1245.121 only.
LOCF: For a missing value at week 52 the last available post-baseline value before week 52 is imputed.

Table R.1.2.9.2: 6 Responder analysis (displaying risk ratio) in KCCQ-OSS change from baseline at week 52 of >= 15 points (improvement) by sex - RS (LOCF-AD) - 1245.121

Subgroup Description	Placebo	Empa 10mg
Sex: Male		
Number of patients in analysis set	1411	1426
Number of analysed patients, N (%)	1297 (100.0)	1332 (100.0)
Number of patients with endpoint, N (%)	281 (21.7)	309 (23.2)
95% confidence interval*	(19.5, 24.0)	(21.0, 25.5)
Comparison vs Placebo**		
Risk ratio (SE)		1.044 (0.070)
95% confidence interval***		(0.915, 1.192)
p-value		0.5186
Sex: Female		
Number of patients in analysis set	456	437
Number of analysed patients, N (%)	412 (100.0)	408 (100.0)
Number of patients with endpoint, N (%)	121 (29.4)	136 (33.3)
95% confidence interval*	(25.2, 33.9)	(28.9, 38.0)
Comparison vs Placebo**		
Risk ratio (SE)		1.111 (0.109)
95% confidence interval***		(0.916, 1.347)
p-value		0.2861

* Wilson confidence intervals.
** Log-linked Poisson model with robust estimate of variance includes terms for baseline KCCQ - overall summary score (p<0.0001), age (p=0.8755), baseline eGFR (CKD-EPI) (p=0.0027), Treatment (p=0.2142), region (5 cat.) (p<0.0001), baseline diabetes status (3 cat.) (p=0.4602), baseline LVEF (3 cat.) (p=0.5227), sex (p=0.3208) and Treatment by sex interaction (p=0.6051).
***Wald confidence intervals.

Data taken from study 1245.121 only.
LOCF: For a missing value at week 52 the last available post-baseline value before week 52 is imputed.

R.1.2.9.3

Table R.1.2.9.3: 1 Responder analysis (displaying odds ratio) in KCCQ-OSS change from baseline at week 52 of <= -15 points (deterioration) by age (2 cat.) - RS (LOCF-AD) - 1245.121

Subgroup Description	Placebo	Empa 10mg
Age [years] (2 cat.): < 65		
Number of patients in analysis set	740	675
Number of analysed patients, N (%)	675 (100.0)	635 (100.0)
Number of patients with endpoint, N (%)	70 (10.4)	45 (7.1)
95% confidence interval*	(8.3, 12.9)	(5.3, 9.4)
Comparison vs Placebo**		
Odds ratio (SE)		0.660 (0.133)
95% confidence interval***		(0.444, 0.981)
p-value		0.0400
Age [years] (2 cat.): >= 65		
Number of patients in analysis set	1127	1188
Number of analysed patients, N (%)	1034 (100.0)	1105 (100.0)
Number of patients with endpoint, N (%)	138 (13.3)	129 (11.7)
95% confidence interval*	(11.4, 15.6)	(9.9, 13.7)
Comparison vs Placebo**		
Odds ratio (SE)		0.861 (0.114)
95% confidence interval***		(0.664, 1.116)
p-value		0.2567

* Wilson confidence intervals.
** Logistic regression includes terms for baseline KCCQ - overall summary score (p<0.0001), baseline eGFR (CKD-EPI) (p=0.0006), Treatment (p=0.0192), region (5 cat.) (p=0.0107), baseline diabetes status (3 cat.) (p=0.2975), sex (p=0.8234), baseline LVEF (3 cat.) (p=0.7156), age (2 cat.) (p=0.2451) and Treatment by age (2 cat.) interaction (p=0.2734).
***Wald confidence intervals.

Data taken from study 1245.121 only.
LOCF: For a missing value at week 52 the last available post-baseline value before week 52 is imputed.

Table R.1.2.9.3: 2 Responder analysis (displaying risk ratio) in KCCQ-OSS change from baseline at week 52 of <= -15 points (deterioration) by age (2 cat.) - RS (LOCF-AD) - 1245.121

Subgroup Description	Placebo	Empa 10mg
Age [years] (2 cat.): < 65		
Number of patients in analysis set	740	675
Number of analysed patients, N (%)	675 (100.0)	635 (100.0)
Number of patients with endpoint, N (%)	70 (10.4)	45 (7.1)
95% confidence interval*	(8.3, 12.9)	(5.3, 9.4)
Comparison vs Placebo**		
Risk ratio (SE)		0.689 (0.125)
95% confidence interval***		(0.483, 0.982)
p-value		0.0395
Age [years] (2 cat.): >= 65		
Number of patients in analysis set	1127	1188
Number of analysed patients, N (%)	1034 (100.0)	1105 (100.0)
Number of patients with endpoint, N (%)	138 (13.3)	129 (11.7)
95% confidence interval*	(11.4, 15.6)	(9.9, 13.7)
Comparison vs Placebo**		
Risk ratio (SE)		0.880 (0.100)
95% confidence interval***		(0.704, 1.100)
p-value		0.2611

* Wilson confidence intervals.
** Log-linked Poisson model with robust estimate of variance includes terms for baseline KCCQ - overall summary score (p<0.0001), baseline eGFR (CKD-EPI) (p=0.0007), Treatment (p=0.0189), region (5 cat.) (p=0.0142), baseline diabetes status (3 cat.) (p=0.3081), sex (p=0.8283), baseline LVEF (3 cat.) (p=0.7111), age (2 cat.) (p=0.2357) and Treatment by age (2 cat.) interaction (p=0.2545).
***Wald confidence intervals.

Data taken from study 1245.121 only.
LOCF: For a missing value at week 52 the last available post-baseline value before week 52 is imputed.

Table R.1.2.9.3: 3 Responder analysis (displaying odds ratio) in KCCQ-OSS change from baseline at week 52 of > -15 points (stability) by age (2 cat.) - RS (LOCF-AD) - 1245.121

Subgroup Description	Placebo	Empa 10mg
Age [years] (2 cat.): < 65		
Number of patients in analysis set	740	675
Number of analysed patients, N (%)	675 (100.0)	635 (100.0)
Number of patients with endpoint, N (%)	605 (89.6)	590 (92.9)
95% confidence interval*	(87.1, 91.7)	(90.6, 94.7)
Comparison vs Placebo**		
Odds ratio (SE)		1.515 (0.306)
95% confidence interval***		(1.019, 2.251)
p-value		0.0400
Age [years] (2 cat.): >= 65		
Number of patients in analysis set	1127	1188
Number of analysed patients, N (%)	1034 (100.0)	1105 (100.0)
Number of patients with endpoint, N (%)	896 (86.7)	976 (88.3)
95% confidence interval*	(84.4, 88.6)	(86.3, 90.1)
Comparison vs Placebo**		
Odds ratio (SE)		1.162 (0.154)
95% confidence interval***		(0.896, 1.507)
p-value		0.2567

* Wilson confidence intervals.
** Logistic regression includes terms for baseline KCCQ - overall summary score (p<0.0001), baseline eGFR (CKD-EPI) (p=0.0006), Treatment (p=0.0192), region (5 cat.) (p=0.0107), baseline diabetes status (3 cat.) (p=0.2975), sex (p=0.8234), baseline LVEF (3 cat.) (p=0.7156), age (2 cat.) (p=0.2451) and Treatment by age (2 cat.) interaction (p=0.2734).
***Wald confidence intervals.

Data taken from study 1245.121 only.
LOCF: For a missing value at week 52 the last available post-baseline value before week 52 is imputed.

Table R.1.2.9.3: 4 Responder analysis (displaying risk ratio) in KCCQ-OSS change from baseline at week 52 of > -15 points (stability) by age (2 cat.) - RS (LOCF-AD) - 1245.121

Subgroup Description	Placebo	Empa 10mg
Age [years] (2 cat.): < 65		
Number of patients in analysis set	740	675
Number of analysed patients, N (%)	675 (100.0)	635 (100.0)
Number of patients with endpoint, N (%)	605 (89.6)	590 (92.9)
95% confidence interval*	(87.1, 91.7)	(90.6, 94.7)
Comparison vs Placebo**		
Risk ratio (SE)		1.034 (0.017)
95% confidence interval***		(1.000, 1.069)
p-value		0.0474
Age [years] (2 cat.): >= 65		
Number of patients in analysis set	1127	1188
Number of analysed patients, N (%)	1034 (100.0)	1105 (100.0)
Number of patients with endpoint, N (%)	896 (86.7)	976 (88.3)
95% confidence interval*	(84.4, 88.6)	(86.3, 90.1)
Comparison vs Placebo**		
Risk ratio (SE)		1.019 (0.017)
95% confidence interval***		(0.987, 1.052)
p-value		0.2533

* Wilson confidence intervals.
** Log-linked Poisson model with robust estimate of variance includes terms for baseline KCCQ - overall summary score (p<0.0001), baseline eGFR (CKD-EPI) (p=0.0009), Treatment (p=0.0258), region (5 cat.) (p<0.0001), baseline diabetes status (3 cat.) (p=0.2650), sex (p=0.8036), baseline LVEF (3 cat.) (p=0.7286), age (2 cat.) (p=0.3235) and Treatment by age (2 cat.) interaction (p=0.5280).
***Wald confidence intervals.

Data taken from study 1245.121 only.
LOCF: For a missing value at week 52 the last available post-baseline value before week 52 is imputed.

Table R.1.2.9.3: 5 Responder analysis (displaying odds ratio) in KCCQ-OSS change from baseline at week 52 of >= 15 points (improvement) by age (2 cat.) - RS (LOCF-AD) - 1245.121

Subgroup Description	Placebo	Empa 10mg
Age [years] (2 cat.): < 65		
Number of patients in analysis set	740	675
Number of analysed patients, N (%)	675 (100.0)	635 (100.0)
Number of patients with endpoint, N (%)	179 (26.5)	188 (29.6)
95% confidence interval*	(23.3, 30.0)	(26.2, 33.3)
Comparison vs Placebo**		
Odds ratio (SE)		1.157 (0.164)
95% confidence interval***		(0.877, 1.527)
p-value		0.3014
Age [years] (2 cat.): >= 65		
Number of patients in analysis set	1127	1188
Number of analysed patients, N (%)	1034 (100.0)	1105 (100.0)
Number of patients with endpoint, N (%)	223 (21.6)	257 (23.3)
95% confidence interval*	(19.2, 24.2)	(20.9, 25.8)
Comparison vs Placebo**		
Odds ratio (SE)		1.124 (0.131)
95% confidence interval***		(0.894, 1.412)
p-value		0.3171

* Wilson confidence intervals.
** Logistic regression includes terms for baseline KCCQ - overall summary score (p<0.0001), baseline eGFR (CKD-EPI) (p=0.0004), Treatment (p=0.1511), region (5 cat.) (p<0.0001), baseline diabetes status (3 cat.) (p=0.4763), sex (p=0.3435), baseline LVEF (3 cat.) (p=0.6425), age (2 cat.) (p=0.3578) and Treatment by age (2 cat.) interaction (p=0.8719).
***Wald confidence intervals.

Data taken from study 1245.121 only.
LOCF: For a missing value at week 52 the last available post-baseline value before week 52 is imputed.

Table R.1.2.9.3: 6 Responder analysis (displaying risk ratio) in KCCQ-OSS change from baseline at week 52 of >= 15 points (improvement) by age (2 cat.) - RS (LOCF-AD) - 1245.121

Subgroup Description	Placebo	Empa 10mg
Age [years] (2 cat.): < 65		
Number of patients in analysis set	740	675
Number of analysed patients, N (%)	675 (100.0)	635 (100.0)
Number of patients with endpoint, N (%)	179 (26.5)	188 (29.6)
95% confidence interval*	(23.3, 30.0)	(26.2, 33.3)
Comparison vs Placebo**		
Risk ratio (SE)		1.069 (0.091)
95% confidence interval***		(0.905, 1.262)
p-value		0.4342
Age [years] (2 cat.): >= 65		
Number of patients in analysis set	1127	1188
Number of analysed patients, N (%)	1034 (100.0)	1105 (100.0)
Number of patients with endpoint, N (%)	223 (21.6)	257 (23.3)
95% confidence interval*	(19.2, 24.2)	(20.9, 25.8)
Comparison vs Placebo**		
Risk ratio (SE)		1.059 (0.078)
95% confidence interval***		(0.917, 1.223)
p-value		0.4373

* Wilson confidence intervals.
** Log-linked Poisson model with robust estimate of variance includes terms for baseline KCCQ - overall summary score (p<0.0001), baseline eGFR (CKD-EPI) (p=0.0005), Treatment (p=0.2717), region (5 cat.) (p<0.0001), baseline diabetes status (3 cat.) (p=0.4721), sex (p=0.3041), baseline LVEF (3 cat.) (p=0.5211), age (2 cat.) (p=0.3480) and Treatment by age (2 cat.) interaction (p=0.9344).
***Wald confidence intervals.

Data taken from study 1245.121 only.
LOCF: For a missing value at week 52 the last available post-baseline value before week 52 is imputed.

R.1.2.9.4 Subgroup analysis by region (North America, Latin America, Europe, Asia, Other)

Table R.1.2.9.4: 1 Responder analysis (displaying odds ratio) in KCCQ-OSS change from baseline at week 52 of <= -15 points (deterioration) by region - RS (LOCF-AD) - 1245.121

Subgroup Description	Placebo	Empa 10mg
Region (5 cat.): North America		
Number of patients in analysis set	213	212
Number of analysed patients, N (%)	192 (100.0)	204 (100.0)
Number of patients with endpoint, N (%)	19 (9.9)	24 (11.8)
95% confidence interval*	(6.4, 14.9)	(8.0, 16.9)
Comparison vs Placebo**		
Odds ratio (SE)		1.162 (0.378)
95% confidence interval***		(0.614, 2.198)
p-value		0.6442
Region (5 cat.): Latin America		
Number of patients in analysis set	645	641
Number of analysed patients, N (%)	577 (100.0)	586 (100.0)
Number of patients with endpoint, N (%)	67 (11.6)	46 (7.8)
95% confidence interval*	(9.2, 14.5)	(5.9, 10.3)
Comparison vs Placebo**		
Odds ratio (SE)		0.653 (0.132)
95% confidence interval***		(0.439, 0.969)
p-value		0.0346

* Wilson confidence intervals.
** Logistic regression includes terms for baseline KCCQ - overall summary score (p<0.0001), age (p=0.3400), baseline eGFR (CKD-EPI) (p=0.0015), Treatment (p=0.0579), baseline diabetes status (3 cat.) (p=0.2754), sex (p=0.7408), baseline LVEF (3 cat.) (p=0.7098), region (5 cat.) (p=0.0392) and Treatment by region (5 cat.) interaction (p=0.2970).
***Wald confidence intervals.
The model used Firth's penalised maximum likelihood estimation.
NC. = Not calculated.

Data taken from study 1245.121 only.
LOCF: For a missing value at week 52 the last available post-baseline value before week 52 is imputed.

Table R.1.2.9.4: 1 Responder analysis (displaying odds ratio) in KCCQ-OSS change from baseline at week 52 of <= -15 points (deterioration) by region - RS (LOCF-AD) - 1245.121

Subgroup Description	Placebo	Empa 10mg
Region (5 cat.): Europe		
Number of patients in analysis set	677	676
Number of analysed patients, N (%)	631 (100.0)	638 (100.0)
Number of patients with endpoint, N (%)	90 (14.3)	79 (12.4)
95% confidence interval*	(11.8, 17.2)	(10.0, 15.2)
Comparison vs Placebo**		
Odds ratio (SE)		0.838 (0.139)
95% confidence interval***		(0.605, 1.161)
p-value		0.2878
Region (5 cat.): Asia		
Number of patients in analysis set	245	248
Number of analysed patients, N (%)	232 (100.0)	236 (100.0)
Number of patients with endpoint, N (%)	27 (11.6)	25 (10.6)
95% confidence interval*	(8.1, 16.4)	(7.3, 15.2)
Comparison vs Placebo**		
Odds ratio (SE)		0.928 (0.273)
95% confidence interval***		(0.522, 1.650)
p-value		0.7987

* Wilson confidence intervals.
** Logistic regression includes terms for baseline KCCQ - overall summary score (p<0.0001), age (p=0.3400), baseline eGFR (CKD-EPI) (p=0.0015), Treatment (p=0.0579), baseline diabetes status (3 cat.) (p=0.2754), sex (p=0.7408), baseline LVEF (3 cat.) (p=0.7098), region (5 cat.) (p=0.0392) and Treatment by region (5 cat.) interaction (p=0.2970).
***Wald confidence intervals.
The model used Firth's penalised maximum likelihood estimation.
NC. = Not calculated.

Data taken from study 1245.121 only.
LOCF: For a missing value at week 52 the last available post-baseline value before week 52 is imputed.

Table R.1.2.9.4: 1 Responder analysis (displaying odds ratio) in KCCQ-OSS change from baseline at week 52 of <= -15 points (deterioration) by region - RS (LOCF-AD) - 1245.121

Subgroup Description	Placebo	Empa 10mg
Region (5 cat.): Other		
Number of patients in analysis set	87	86
Number of analysed patients, N (%)	77 (100.0)	76 (100.0)
Number of patients with endpoint, N (%)	5 (6.5)	0
95% confidence interval*	(2.8, 14.3)	NC.
Comparison vs Placebo**		
Odds ratio (SE)		0.086 (0.127)
95% confidence interval***		(0.005, 1.587)
p-value		0.0989

* Wilson confidence intervals.
** Logistic regression includes terms for baseline KCCQ - overall summary score (p<0.0001), age (p=0.3400), baseline eGFR (CKD-EPI) (p=0.0015), Treatment (p=0.0579), baseline diabetes status (3 cat.) (p=0.2754), sex (p=0.7408), baseline LVEF (3 cat.) (p=0.7098), region (5 cat.) (p=0.0392) and Treatment by region (5 cat.) interaction (p=0.2970).
***Wald confidence intervals.
The model used Firth's penalised maximum likelihood estimation.
NC. = Not calculated.

Data taken from study 1245.121 only.
LOCF: For a missing value at week 52 the last available post-baseline value before week 52 is imputed.

Table R.1.2.9.4: 2 Responder analysis (displaying risk ratio) in KCCQ-OSS change from baseline at week 52 of <= -15 points (deterioration) by region - RS (LOCF-AD) - 1245.121

Subgroup Description	Placebo	Empa 10mg
Region (5 cat.): North America		
Number of patients in analysis set	213	212
Number of analysed patients, N (%)	192 (100.0)	204 (100.0)
Number of patients with endpoint, N (%)	19 (9.9)	24 (11.8)
95% confidence interval*	(6.4, 14.9)	(8.0, 16.9)
Comparison vs Placebo**		
Risk ratio (SE)		1.146 (0.334)
95% confidence interval***		(0.647, 2.029)
p-value		0.6407
Region (5 cat.): Latin America		
Number of patients in analysis set	645	641
Number of analysed patients, N (%)	577 (100.0)	586 (100.0)
Number of patients with endpoint, N (%)	67 (11.6)	46 (7.8)
95% confidence interval*	(9.2, 14.5)	(5.9, 10.3)
Comparison vs Placebo**		
Risk ratio (SE)		0.682 (0.124)
95% confidence interval***		(0.478, 0.973)
p-value		0.0346

* Wilson confidence intervals.
** Log-linked Poisson model with robust estimate of variance includes terms for baseline KCCQ - overall summary score (p<0.0001), age (p=0.3576), baseline eGFR (CKD-EPI) (p=0.0039), Treatment (p=0.3036), baseline diabetes status (3 cat.) (p=0.2117), sex (p=0.8226), baseline LVEF (3 cat.) (p=0.7627), region (5 cat.) (p=0.1665) and Treatment by region (5 cat.) interaction (p=0.4488).
***Wald confidence intervals.

Data taken from study 1245.121 only.
LOCF: For a missing value at week 52 the last available post-baseline value before week 52 is imputed.
Region Other is excluded due to rare events and non-convergence of the model.

Table R.1.2.9.4: 2 Responder analysis (displaying risk ratio) in KCCQ-OSS change from baseline at week 52 of <= -15 points (deterioration) by region - RS (LOCF-AD) - 1245.121

Subgroup Description	Placebo	Empa 10mg
Region (5 cat.): Europe		
Number of patients in analysis set	677	676
Number of analysed patients, N (%)	631 (100.0)	638 (100.0)
Number of patients with endpoint, N (%)	90 (14.3)	79 (12.4)
95% confidence interval*	(11.8, 17.2)	(10.0, 15.2)
Comparison vs Placebo**		
Risk ratio (SE)		0.860 (0.122)
95% confidence interval***		(0.651, 1.134)
p-value		0.2843
Region (5 cat.): Asia		
Number of patients in analysis set	245	248
Number of analysed patients, N (%)	232 (100.0)	236 (100.0)
Number of patients with endpoint, N (%)	27 (11.6)	25 (10.6)
95% confidence interval*	(8.1, 16.4)	(7.3, 15.2)
Comparison vs Placebo**		
Risk ratio (SE)		0.934 (0.244)
95% confidence interval***		(0.560, 1.557)
p-value		0.7927

* Wilson confidence intervals.
** Log-linked Poisson model with robust estimate of variance includes terms for baseline KCCQ - overall summary score (p<0.0001), age (p=0.3576), baseline eGFR (CKD-EPI) (p=0.0039), Treatment (p=0.3036), baseline diabetes status (3 cat.) (p=0.2117), sex (p=0.8226), baseline LVEF (3 cat.) (p=0.7627), region (5 cat.) (p=0.1665) and Treatment by region (5 cat.) interaction (p=0.4488).
***Wald confidence intervals.

Data taken from study 1245.121 only.
LOCF: For a missing value at week 52 the last available post-baseline value before week 52 is imputed.
Region Other is excluded due to rare events and non-convergence of the model.

Table R.1.2.9.4: 3 Responder analysis (displaying odds ratio) in KCCQ-OSS change from baseline at week 52 of > -15 points (stability) by region - RS (LOCF-AD) - 1245.121

Subgroup Description	Placebo	Empa 10mg
Region (5 cat.): North America		
Number of patients in analysis set	213	212
Number of analysed patients, N (%)	192 (100.0)	204 (100.0)
Number of patients with endpoint, N (%)	173 (90.1)	180 (88.2)
95% confidence interval*	(85.1, 93.6)	(83.1, 92.0)
Comparison vs Placebo**		
Odds ratio (SE)		0.861 (0.280)
95% confidence interval***		(0.455, 1.628)
p-value		0.6442
Region (5 cat.): Latin America		
Number of patients in analysis set	645	641
Number of analysed patients, N (%)	577 (100.0)	586 (100.0)
Number of patients with endpoint, N (%)	510 (88.4)	540 (92.2)
95% confidence interval*	(85.5, 90.8)	(89.7, 94.1)
Comparison vs Placebo**		
Odds ratio (SE)		1.532 (0.309)
95% confidence interval***		(1.031, 2.276)
p-value		0.0346

* Wilson confidence intervals.
** Logistic regression includes terms for baseline KCCQ - overall summary score (p<0.0001), age (p=0.3400), baseline eGFR (CKD-EPI) (p=0.0015), Treatment (p=0.0579), baseline diabetes status (3 cat.) (p=0.2754), sex (p=0.7408), baseline LVEF (3 cat.) (p=0.7098), region (5 cat.) (p=0.0392) and Treatment by region (5 cat.) interaction (p=0.2970).
***Wald confidence intervals.
The model used Firth's penalised maximum likelihood estimation.

Data taken from study 1245.121 only.
LOCF: For a missing value at week 52 the last available post-baseline value before week 52 is imputed.

Table R.1.2.9.4: 3 Responder analysis (displaying odds ratio) in KCCQ-OSS change from baseline at week 52 of > -15 points (stability) by region - RS (LOCF-AD) - 1245.121

Subgroup Description	Placebo	Empa 10mg
Region (5 cat.): Europe		
Number of patients in analysis set	677	676
Number of analysed patients, N (%)	631 (100.0)	638 (100.0)
Number of patients with endpoint, N (%)	541 (85.7)	559 (87.6)
95% confidence interval*	(82.8, 88.2)	(84.8, 90.0)
Comparison vs Placebo**		
Odds ratio (SE)		1.194 (0.199)
95% confidence interval***		(0.861, 1.654)
p-value		0.2878
Region (5 cat.): Asia		
Number of patients in analysis set	245	248
Number of analysed patients, N (%)	232 (100.0)	236 (100.0)
Number of patients with endpoint, N (%)	205 (88.4)	211 (89.4)
95% confidence interval*	(83.6, 91.9)	(84.8, 92.7)
Comparison vs Placebo**		
Odds ratio (SE)		1.078 (0.317)
95% confidence interval***		(0.606, 1.917)
p-value		0.7987

* Wilson confidence intervals.
** Logistic regression includes terms for baseline KCCQ - overall summary score (p<0.0001), age (p=0.3400), baseline eGFR (CKD-EPI) (p=0.0015), Treatment (p=0.0579), baseline diabetes status (3 cat.) (p=0.2754), sex (p=0.7408), baseline LVEF (3 cat.) (p=0.7098), region (5 cat.) (p=0.0392) and Treatment by region (5 cat.) interaction (p=0.2970).
***Wald confidence intervals.
The model used Firth's penalised maximum likelihood estimation.

Data taken from study 1245.121 only.
LOCF: For a missing value at week 52 the last available post-baseline value before week 52 is imputed.

Table R.1.2.9.4: 3 Responder analysis (displaying odds ratio) in KCCQ-OSS change from baseline at week 52 of > -15 points (stability) by region - RS (LOCF-AD) - 1245.121

Subgroup Description	Placebo	Empa 10mg
Region (5 cat.): Other		
Number of patients in analysis set	87	86
Number of analysed patients, N (%)	77 (100.0)	76 (100.0)
Number of patients with endpoint, N (%)	72 (93.5)	76 (100.0)
95% confidence interval*	(85.7, 97.2)	(95.2, 100.0)
Comparison vs Placebo**		
Odds ratio (SE)		11.693 (17.425)
95% confidence interval***		(0.630,216.962)
p-value		0.0989

* Wilson confidence intervals.
** Logistic regression includes terms for baseline KCCQ - overall summary score (p<0.0001), age (p=0.3400), baseline eGFR (CKD-EPI) (p=0.0015), Treatment (p=0.0579), baseline diabetes status (3 cat.) (p=0.2754), sex (p=0.7408), baseline LVEF (3 cat.) (p=0.7098), region (5 cat.) (p=0.0392) and Treatment by region (5 cat.) interaction (p=0.2970).
***Wald confidence intervals.
The model used Firth's penalised maximum likelihood estimation.

Data taken from study 1245.121 only.
LOCF: For a missing value at week 52 the last available post-baseline value before week 52 is imputed.

Table R.1.2.9.4: 4 Responder analysis (displaying risk ratio) in KCCQ-OSS change from baseline at week 52 of > -15 points (stability) by region - RS (LOCF-AD) - 1245.121

Subgroup Description	Placebo	Empa 10mg
Region (5 cat.): North America		
Number of patients in analysis set	213	212
Number of analysed patients, N (%)	192 (100.0)	204 (100.0)
Number of patients with endpoint, N (%)	173 (90.1)	180 (88.2)
95% confidence interval*	(85.1, 93.6)	(83.1, 92.0)
Comparison vs Placebo**		
Risk ratio (SE)		0.984 (0.034)
95% confidence interval***		(0.919, 1.054)
p-value		0.6398
Region (5 cat.): Latin America		
Number of patients in analysis set	645	641
Number of analysed patients, N (%)	577 (100.0)	586 (100.0)
Number of patients with endpoint, N (%)	510 (88.4)	540 (92.2)
95% confidence interval*	(85.5, 90.8)	(89.7, 94.1)
Comparison vs Placebo**		
Risk ratio (SE)		1.041 (0.020)
95% confidence interval***		(1.002, 1.080)
p-value		0.0367

* Wilson confidence intervals.
** Log-linked Poisson model with robust estimate of variance includes terms for baseline KCCQ - overall summary score (p<0.0001), age (p=0.4421), baseline eGFR (CKD-EPI) (p=0.0025), Treatment (p=0.0541), baseline diabetes status (3 cat.) (p=0.2445), sex (p=0.7313), baseline LVEF (3 cat.) (p=0.7106), region (5 cat.) (p<0.0001) and Treatment by region (5 cat.) interaction (p=0.3701).
***Wald confidence intervals.

Data taken from study 1245.121 only.
LOCF: For a missing value at week 52 the last available post-baseline value before week 52 is imputed.

Table R.1.2.9.4: 4 Responder analysis (displaying risk ratio) in KCCQ-OSS change from baseline at week 52 of > -15 points (stability) by region - RS (LOCF-AD) - 1245.121

Subgroup Description	Placebo	Empa 10mg
Region (5 cat.): Europe		
Number of patients in analysis set	677	676
Number of analysed patients, N (%)	631 (100.0)	638 (100.0)
Number of patients with endpoint, N (%)	541 (85.7)	559 (87.6)
95% confidence interval*	(82.8, 88.2)	(84.8, 90.0)
Comparison vs Placebo**		
Risk ratio (SE)		1.023 (0.022)
95% confidence interval***		(0.981, 1.068)
p-value		0.2856
Region (5 cat.): Asia		
Number of patients in analysis set	245	248
Number of analysed patients, N (%)	232 (100.0)	236 (100.0)
Number of patients with endpoint, N (%)	205 (88.4)	211 (89.4)
95% confidence interval*	(83.6, 91.9)	(84.8, 92.7)
Comparison vs Placebo**		
Risk ratio (SE)		1.007 (0.033)
95% confidence interval***		(0.945, 1.074)
p-value		0.8244

* Wilson confidence intervals.
** Log-linked Poisson model with robust estimate of variance includes terms for baseline KCCQ - overall summary score (p<0.0001), age (p=0.4421), baseline eGFR (CKD-EPI) (p=0.0025), Treatment (p=0.0541), baseline diabetes status (3 cat.) (p=0.2445), sex (p=0.7313), baseline LVEF (3 cat.) (p=0.7106), region (5 cat.) (p<0.0001) and Treatment by region (5 cat.) interaction (p=0.3701).
***Wald confidence intervals.

Data taken from study 1245.121 only.
LOCF: For a missing value at week 52 the last available post-baseline value before week 52 is imputed.

Table R.1.2.9.4: 4 Responder analysis (displaying risk ratio) in KCCQ-OSS change from baseline at week 52 of > -15 points (stability) by region - RS (LOCF-AD) - 1245.121

Subgroup Description	Placebo	Empa 10mg
Region (5 cat.): Other		
Number of patients in analysis set	87	86
Number of analysed patients, N (%)	77 (100.0)	76 (100.0)
Number of patients with endpoint, N (%)	72 (93.5)	76 (100.0)
95% confidence interval*	(85.7, 97.2)	(95.2, 100.0)
Comparison vs Placebo**		
Risk ratio (SE)		1.071 (0.032)
95% confidence interval***		(1.010, 1.135)
p-value		0.0220

* Wilson confidence intervals.
** Log-linked Poisson model with robust estimate of variance includes terms for baseline KCCQ - overall summary score (p<0.0001), age (p=0.4421), baseline eGFR (CKD-EPI) (p=0.0025), Treatment (p=0.0541), baseline diabetes status (3 cat.) (p=0.2445), sex (p=0.7313), baseline LVEF (3 cat.) (p=0.7106), region (5 cat.) (p<0.0001) and Treatment by region (5 cat.) interaction (p=0.3701).
***Wald confidence intervals.

Data taken from study 1245.121 only.
LOCF: For a missing value at week 52 the last available post-baseline value before week 52 is imputed.

Table R.1.2.9.4: 5 Responder analysis (displaying odds ratio) in KCCQ-OSS change from baseline at week 52 of >= 15 points (improvement) by region - RS (LOCF-AD) - 1245.121

Subgroup Description	Placebo	Empa 10mg
Region (5 cat.): North America		
Number of patients in analysis set	213	212
Number of analysed patients, N (%)	192 (100.0)	204 (100.0)
Number of patients with endpoint, N (%)	35 (18.2)	44 (21.6)
95% confidence interval*	(13.4, 24.3)	(16.5, 27.7)
Comparison vs Placebo**		
Odds ratio (SE)		1.470 (0.418)
95% confidence interval***		(0.842, 2.566)
p-value		0.1756
Region (5 cat.): Latin America		
Number of patients in analysis set	645	641
Number of analysed patients, N (%)	577 (100.0)	586 (100.0)
Number of patients with endpoint, N (%)	195 (33.8)	209 (35.7)
95% confidence interval*	(30.1, 37.8)	(31.9, 39.6)
Comparison vs Placebo**		
Odds ratio (SE)		1.081 (0.152)
95% confidence interval***		(0.820, 1.425)
p-value		0.5807

* Wilson confidence intervals.
** Logistic regression includes terms for baseline KCCQ - overall summary score (p<0.0001), age (p=0.9925), baseline eGFR (CKD-EPI) (p=0.0022), Treatment (p=0.3513), baseline diabetes status (3 cat.) (p=0.4871), sex (p=0.3444), baseline LVEF (3 cat.) (p=0.6628), region (5 cat.) (p<0.0001) and Treatment by region (5 cat.) interaction (p=0.7881).
***Wald confidence intervals.

Data taken from study 1245.121 only.
LOCF: For a missing value at week 52 the last available post-baseline value before week 52 is imputed.

Table R.1.2.9.4: 5 Responder analysis (displaying odds ratio) in KCCQ-OSS change from baseline at week 52 of >= 15 points (improvement) by region - RS (LOCF-AD) - 1245.121

Subgroup Description	Placebo	Empa 10mg
Region (5 cat.): Europe		
Number of patients in analysis set	677	676
Number of analysed patients, N (%)	631 (100.0)	638 (100.0)
Number of patients with endpoint, N (%)	117 (18.5)	131 (20.5)
95% confidence interval*	(15.7, 21.8)	(17.6, 23.8)
Comparison vs Placebo**		
Odds ratio (SE)		1.197 (0.186)
95% confidence interval***		(0.883, 1.623)
p-value		0.2460
Region (5 cat.): Asia		
Number of patients in analysis set	245	248
Number of analysed patients, N (%)	232 (100.0)	236 (100.0)
Number of patients with endpoint, N (%)	31 (13.4)	40 (16.9)
95% confidence interval*	(9.6, 18.3)	(12.7, 22.3)
Comparison vs Placebo**		
Odds ratio (SE)		1.101 (0.307)
95% confidence interval***		(0.638, 1.901)
p-value		0.7287

* Wilson confidence intervals.
** Logistic regression includes terms for baseline KCCQ - overall summary score (p<0.0001), age (p=0.9925), baseline eGFR (CKD-EPI) (p=0.0022), Treatment (p=0.3513), baseline diabetes status (3 cat.) (p=0.4871), sex (p=0.3444), baseline LVEF (3 cat.) (p=0.6628), region (5 cat.) (p<0.0001) and Treatment by region (5 cat.) interaction (p=0.7881).
***Wald confidence intervals.

Data taken from study 1245.121 only.
LOCF: For a missing value at week 52 the last available post-baseline value before week 52 is imputed.

Table R.1.2.9.4: 5 Responder analysis (displaying odds ratio) in KCCQ-OSS change from baseline at week 52 of >= 15 points (improvement) by region - RS (LOCF-AD) - 1245.121

Subgroup Description	Placebo	Empa 10mg
Region (5 cat.): Other		
Number of patients in analysis set	87	86
Number of analysed patients, N (%)	77 (100.0)	76 (100.0)
Number of patients with endpoint, N (%)	24 (31.2)	21 (27.6)
95% confidence interval*	(21.9, 42.2)	(18.8, 38.6)
Comparison vs Placebo**		
Odds ratio (SE)		0.831 (0.323)
95% confidence interval***		(0.388, 1.780)
p-value		0.6332

* Wilson confidence intervals.
** Logistic regression includes terms for baseline KCCQ - overall summary score (p<0.0001), age (p=0.9925), baseline eGFR (CKD-EPI) (p=0.0022), Treatment (p=0.3513), baseline diabetes status (3 cat.) (p=0.4871), sex (p=0.3444), baseline LVEF (3 cat.) (p=0.6628), region (5 cat.) (p<0.0001) and Treatment by region (5 cat.) interaction (p=0.7881).
***Wald confidence intervals.

Data taken from study 1245.121 only.
LOCF: For a missing value at week 52 the last available post-baseline value before week 52 is imputed.

Table R.1.2.9.4: 6 Responder analysis (displaying risk ratio) in KCCQ-OSS change from baseline at week 52 of >= 15 points (improvement) by region - RS (LOCF-AD) - 1245.121

Subgroup Description	Placebo	Empa 10mg
Region (5 cat.): North America		
Number of patients in analysis set	213	212
Number of analysed patients, N (%)	192 (100.0)	204 (100.0)
Number of patients with endpoint, N (%)	35 (18.2)	44 (21.6)
95% confidence interval*	(13.4, 24.3)	(16.5, 27.7)
Comparison vs Placebo**		
Risk ratio (SE)		1.235 (0.234)
95% confidence interval***		(0.852, 1.791)
p-value		0.2647
Region (5 cat.): Latin America		
Number of patients in analysis set	645	641
Number of analysed patients, N (%)	577 (100.0)	586 (100.0)
Number of patients with endpoint, N (%)	195 (33.8)	209 (35.7)
95% confidence interval*	(30.1, 37.8)	(31.9, 39.6)
Comparison vs Placebo**		
Risk ratio (SE)		1.013 (0.079)
95% confidence interval***		(0.870, 1.179)
p-value		0.8667

* Wilson confidence intervals.
** Log-linked Poisson model with robust estimate of variance includes terms for baseline KCCQ - overall summary score (p<0.0001), age (p=0.8609), baseline eGFR (CKD-EPI) (p=0.0023), Treatment (p=0.3448), baseline diabetes status (3 cat.) (p=0.4882), sex (p=0.3100), baseline LVEF (3 cat.) (p=0.5504), region (5 cat.) (p<0.0001) and Treatment by region (5 cat.) interaction (p=0.8272).
***Wald confidence intervals.

Data taken from study 1245.121 only.
LOCF: For a missing value at week 52 the last available post-baseline value before week 52 is imputed.

Table R.1.2.9.4: 6 Responder analysis (displaying risk ratio) in KCCQ-OSS change from baseline at week 52 of >= 15 points (improvement) by region - RS (LOCF-AD) - 1245.121

Subgroup Description	Placebo	Empa 10mg
Region (5 cat.): Europe		
Number of patients in analysis set	677	676
Number of analysed patients, N (%)	631 (100.0)	638 (100.0)
Number of patients with endpoint, N (%)	117 (18.5)	131 (20.5)
95% confidence interval*	(15.7, 21.8)	(17.6, 23.8)
Comparison vs Placebo**		
Risk ratio (SE)		1.113 (0.119)
95% confidence interval***		(0.902, 1.372)
p-value		0.3173
Region (5 cat.): Asia		
Number of patients in analysis set	245	248
Number of analysed patients, N (%)	232 (100.0)	236 (100.0)
Number of patients with endpoint, N (%)	31 (13.4)	40 (16.9)
95% confidence interval*	(9.6, 18.3)	(12.7, 22.3)
Comparison vs Placebo**		
Risk ratio (SE)		1.104 (0.218)
95% confidence interval***		(0.750, 1.624)
p-value		0.6173

* Wilson confidence intervals.
** Log-linked Poisson model with robust estimate of variance includes terms for baseline KCCQ - overall summary score (p<0.0001), age (p=0.8609), baseline eGFR (CKD-EPI) (p=0.0023), Treatment (p=0.3448), baseline diabetes status (3 cat.) (p=0.4882), sex (p=0.3100), baseline LVEF (3 cat.) (p=0.5504), region (5 cat.) (p<0.0001) and Treatment by region (5 cat.) interaction (p=0.8272).
***Wald confidence intervals.

Data taken from study 1245.121 only.
LOCF: For a missing value at week 52 the last available post-baseline value before week 52 is imputed.

Table R.1.2.9.4: 6 Responder analysis (displaying risk ratio) in KCCQ-OSS change from baseline at week 52 of >= 15 points (improvement) by region - RS (LOCF-AD) - 1245.121

Subgroup Description	Placebo	Empa 10mg
Region (5 cat.): Other		
Number of patients in analysis set	87	86
Number of analysed patients, N (%)	77 (100.0)	76 (100.0)
Number of patients with endpoint, N (%)	24 (31.2)	21 (27.6)
95% confidence interval*	(21.9, 42.2)	(18.8, 38.6)
Comparison vs Placebo**		
Risk ratio (SE)		0.939 (0.226)
95% confidence interval***		(0.586, 1.505)
p-value		0.7933

* Wilson confidence intervals.
** Log-linked Poisson model with robust estimate of variance includes terms for baseline KCCQ - overall summary score (p<0.0001), age (p=0.8609), baseline eGFR (CKD-EPI) (p=0.0023), Treatment (p=0.3448), baseline diabetes status (3 cat.) (p=0.4882), sex (p=0.3100), baseline LVEF (3 cat.) (p=0.5504), region (5 cat.) (p<0.0001) and Treatment by region (5 cat.) interaction (p=0.8272).
***Wald confidence intervals.

Data taken from study 1245.121 only.
LOCF: For a missing value at week 52 the last available post-baseline value before week 52 is imputed.

R.1.2.9.5

R.1.2.9.5 Subgroup analysis by OECD (N/Y)

Table R.1.2.9.5: 1 Responder analysis (displaying odds ratio) in KCCQ-OSS change from baseline at week 52 of <= -15 points (deterioration) by OECD member (N/Y) - RS (LOCF-AD) - 1245.121

Subgroup Description	Placebo	Empa 10mg
OECD member: No		
Number of patients in analysis set	741	713
Number of analysed patients, N (%)	663 (100.0)	647 (100.0)
Number of patients with endpoint, N (%)	69 (10.4)	45 (7.0)
95% confidence interval*	(8.3, 13.0)	(5.2, 9.2)
Comparison vs Placebo**		
Odds ratio (SE)		0.636 (0.129)
95% confidence interval***		(0.428, 0.945)
p-value		0.0253
OECD member: Yes		
Number of patients in analysis set	1126	1150
Number of analysed patients, N (%)	1046 (100.0)	1093 (100.0)
Number of patients with endpoint, N (%)	139 (13.3)	129 (11.8)
95% confidence interval*	(11.4, 15.5)	(10.0, 13.9)
Comparison vs Placebo**		
Odds ratio (SE)		0.874 (0.115)
95% confidence interval***		(0.674, 1.132)
p-value		0.3070

* Wilson confidence intervals.
** Logistic regression includes terms for baseline KCCQ - overall summary score (p<0.0001), age (p=0.2553), baseline eGFR (CKD-EPI) (p=0.0012), Treatment (p=0.0149), sex (p=0.7941), baseline diabetes status (3 cat.) (p=0.2554), baseline LVEF (3 cat.) (p=0.6654), OECD member (p=0.0328) and Treatment by OECD member interaction (p=0.1890).
***Wald confidence intervals.

Data taken from study 1245.121 only.
LOCF: For a missing value at week 52 the last available post-baseline value before week 52 is imputed.
OECD member (yes/no) countries included:
Yes: United States, Canada, Mexico, Poland, Netherlands, Hungary, Germany, Czech Republic, Italy, France, Spain, United Kingdom, Belgium, Japan, Australia, 'Korea; Republic Of South Korea';
No: Brazil, Argentina, China, India.

Table R.1.2.9.5: 2 Responder analysis (displaying risk ratio) in KCCQ-OSS change from baseline at week 52 of <= -15 points (deterioration) by OECD member (N/Y) - RS (LOCF-AD) - 1245.121

Subgroup Description	Placebo	Empa 10mg
OECD member: No		
Number of patients in analysis set	741	713
Number of analysed patients, N (%)	663 (100.0)	647 (100.0)
Number of patients with endpoint, N (%)	69 (10.4)	45 (7.0)
95% confidence interval*	(8.3, 13.0)	(5.2, 9.2)
Comparison vs Placebo**		
Risk ratio (SE)		0.665 (0.121)
95% confidence interval***		(0.465, 0.951)
p-value		0.0255
OECD member: Yes		
Number of patients in analysis set	1126	1150
Number of analysed patients, N (%)	1046 (100.0)	1093 (100.0)
Number of patients with endpoint, N (%)	139 (13.3)	129 (11.8)
95% confidence interval*	(11.4, 15.5)	(10.0, 13.9)
Comparison vs Placebo**		
Risk ratio (SE)		0.891 (0.101)
95% confidence interval***		(0.713, 1.113)
p-value		0.3082

* Wilson confidence intervals.
** Log-linked Poisson model with robust estimate of variance includes terms for baseline KCCQ - overall summary score (p<0.0001), age (p=0.2783), baseline eGFR (CKD-EPI) (p=0.0016), Treatment (p=0.0148), sex (p=0.7940), baseline diabetes status (3 cat.) (p=0.2621), baseline LVEF (3 cat.) (p=0.6613), OECD member (p=0.0315) and Treatment by OECD member interaction (p=0.1745).
***Wald confidence intervals.

Data taken from study 1245.121 only.
LOCF: For a missing value at week 52 the last available post-baseline value before week 52 is imputed.
OECD member (yes/no) countries included:
Yes: United States, Canada, Mexico, Poland, Netherlands, Hungary, Germany, Czech Republic, Italy, France, Spain, United Kingdom, Belgium, Japan, Australia, 'Korea; Republic Of South Korea';
No: Brazil, Argentina, China, India.

Table R.1.2.9.5: 3 Responder analysis (displaying odds ratio) in KCCQ-OSS change from baseline at week 52 of > -15 points (stability) by OECD member (N/Y) - RS (LOCF-AD) - 1245.121

Subgroup Description	Placebo	Empa 10mg
OECD member: No		
Number of patients in analysis set	741	713
Number of analysed patients, N (%)	663 (100.0)	647 (100.0)
Number of patients with endpoint, N (%)	594 (89.6)	602 (93.0)
95% confidence interval*	(87.0, 91.7)	(90.8, 94.8)
Comparison vs Placebo**		
Odds ratio (SE)		1.572 (0.318)
95% confidence interval***		(1.058, 2.337)
p-value		0.0253
OECD member: Yes		
Number of patients in analysis set	1126	1150
Number of analysed patients, N (%)	1046 (100.0)	1093 (100.0)
Number of patients with endpoint, N (%)	907 (86.7)	964 (88.2)
95% confidence interval*	(84.5, 88.6)	(86.1, 90.0)
Comparison vs Placebo**		
Odds ratio (SE)		1.144 (0.151)
95% confidence interval***		(0.883, 1.483)
p-value		0.3070

* Wilson confidence intervals.
** Logistic regression includes terms for baseline KCCQ - overall summary score (p<0.0001), age (p=0.2553), baseline eGFR (CKD-EPI) (p=0.0012), Treatment (p=0.0149), sex (p=0.7941), baseline diabetes status (3 cat.) (p=0.2554), baseline LVEF (3 cat.) (p=0.6654), OECD member (p=0.0328) and Treatment by OECD member interaction (p=0.1890).
***Wald confidence intervals.

Data taken from study 1245.121 only.
LOCF: For a missing value at week 52 the last available post-baseline value before week 52 is imputed.
OECD member (yes/no) countries included:
Yes: United States, Canada, Mexico, Poland, Netherlands, Hungary, Germany, Czech Republic, Italy, France, Spain, United Kingdom, Belgium, Japan, Australia, 'Korea; Republic Of South Korea';
No: Brazil, Argentina, China, India.

Table R.1.2.9.5: 4 Responder analysis (displaying risk ratio) in KCCQ-OSS change from baseline at week 52 of > -15 points (stability) by OECD member (N/Y) - RS (LOCF-AD) - 1245.121

Subgroup Description	Placebo	Empa 10mg
OECD member: No		
Number of patients in analysis set	741	713
Number of analysed patients, N (%)	663 (100.0)	647 (100.0)
Number of patients with endpoint, N (%)	594 (89.6)	602 (93.0)
95% confidence interval*	(87.0, 91.7)	(90.8, 94.8)
Comparison vs Placebo**		
Risk ratio (SE)		1.038 (0.018)
95% confidence interval***		(1.004, 1.073)
p-value		0.0272
OECD member: Yes		
Number of patients in analysis set	1126	1150
Number of analysed patients, N (%)	1046 (100.0)	1093 (100.0)
Number of patients with endpoint, N (%)	907 (86.7)	964 (88.2)
95% confidence interval*	(84.5, 88.6)	(86.1, 90.0)
Comparison vs Placebo**		
Risk ratio (SE)		1.017 (0.017)
95% confidence interval***		(0.985, 1.050)
p-value		0.3000

* Wilson confidence intervals.
** Log-linked Poisson model with robust estimate of variance includes terms for baseline KCCQ - overall summary score (p<0.0001), age (p=0.3476), baseline eGFR (CKD-EPI) (p=0.0018), Treatment (p=0.0211), sex (p=0.8080), baseline diabetes status (3 cat.) (p=0.2340), baseline LVEF (3 cat.) (p=0.7005), OECD member (p=0.0425) and Treatment by OECD member interaction (p=0.3825).
***Wald confidence intervals.

Data taken from study 1245.121 only.
LOCF: For a missing value at week 52 the last available post-baseline value before week 52 is imputed.
OECD member (yes/no) countries included:
Yes: United States, Canada, Mexico, Poland, Netherlands, Hungary, Germany, Czech Republic, Italy, France, Spain, United Kingdom, Belgium, Japan, Australia, 'Korea; Republic Of South Korea';
No: Brazil, Argentina, China, India.

Table R.1.2.9.5: 5 Responder analysis (displaying odds ratio) in KCCQ-OSS change from baseline at week 52 of >= 15 points (improvement) by OECD member (N/Y) - RS (LOCF-AD) - 1245.121

Subgroup Description	Placebo	Empa 10mg
OECD member: No		
Number of patients in analysis set	741	713
Number of analysed patients, N (%)	663 (100.0)	647 (100.0)
Number of patients with endpoint, N (%)	213 (32.1)	221 (34.2)
95% confidence interval*	(28.7, 35.8)	(30.6, 37.9)
Comparison vs Placebo**		
Odds ratio (SE)		1.113 (0.148)
95% confidence interval***		(0.857, 1.445)
p-value		0.4240
OECD member: Yes		
Number of patients in analysis set	1126	1150
Number of analysed patients, N (%)	1046 (100.0)	1093 (100.0)
Number of patients with endpoint, N (%)	189 (18.1)	224 (20.5)
95% confidence interval*	(15.9, 20.5)	(18.2, 23.0)
Comparison vs Placebo**		
Odds ratio (SE)		1.190 (0.144)
95% confidence interval***		(0.938, 1.508)
p-value		0.1514

* Wilson confidence intervals.
** Logistic regression includes terms for baseline KCCQ - overall summary score (p<0.0001), age (p=0.8766), baseline eGFR (CKD-EPI) (p=0.0026), Treatment (p=0.1195), sex (p=0.3057), baseline diabetes status (3 cat.) (p=0.3805), baseline LVEF (3 cat.) (p=0.5678), OECD member (p<0.0001) and Treatment by OECD member interaction (p=0.7105).
***Wald confidence intervals.

Data taken from study 1245.121 only.
LOCF: For a missing value at week 52 the last available post-baseline value before week 52 is imputed.
OECD member (yes/no) countries included:
Yes: United States, Canada, Mexico, Poland, Netherlands, Hungary, Germany, Czech Republic, Italy, France, Spain, United Kingdom, Belgium, Japan, Australia, 'Korea; Republic Of South Korea';
No: Brazil, Argentina, China, India.

Table R.1.2.9.5: 6 Responder analysis (displaying risk ratio) in KCCQ-OSS change from baseline at week 52 of >= 15 points (improvement) by OECD member (N/Y) - RS (LOCF-AD) - 1245.121

Subgroup Description	Placebo	Empa 10mg
OECD member: No		
Number of patients in analysis set	741	713
Number of analysed patients, N (%)	663 (100.0)	647 (100.0)
Number of patients with endpoint, N (%)	213 (32.1)	221 (34.2)
95% confidence interval*	(28.7, 35.8)	(30.6, 37.9)
Comparison vs Placebo**		
Risk ratio (SE)		1.033 (0.077)
95% confidence interval***		(0.893, 1.196)
p-value		0.6595
OECD member: Yes		
Number of patients in analysis set	1126	1150
Number of analysed patients, N (%)	1046 (100.0)	1093 (100.0)
Number of patients with endpoint, N (%)	189 (18.1)	224 (20.5)
95% confidence interval*	(15.9, 20.5)	(18.2, 23.0)
Comparison vs Placebo**		
Risk ratio (SE)		1.112 (0.092)
95% confidence interval***		(0.946, 1.308)
p-value		0.1988

* Wilson confidence intervals.
** Log-linked Poisson model with robust estimate of variance includes terms for baseline KCCQ - overall summary score (p<0.0001), age (p=0.9963), baseline eGFR (CKD-EPI) (p=0.0027), Treatment (p=0.2124), sex (p=0.2749), baseline diabetes status (3 cat.) (p=0.4149), baseline LVEF (3 cat.) (p=0.4458), OECD member (p<0.0001) and Treatment by OECD member interaction (p=0.5102).
***Wald confidence intervals.

Data taken from study 1245.121 only.
LOCF: For a missing value at week 52 the last available post-baseline value before week 52 is imputed.
OECD member (yes/no) countries included:
Yes: United States, Canada, Mexico, Poland, Netherlands, Hungary, Germany, Czech Republic, Italy, France, Spain, United Kingdom, Belgium, Japan, Australia, 'Korea; Republic Of South Korea';
No: Brazil, Argentina, China, India.

R.1.2.9.6 Subgroup analysis by NYHA at baseline (II, III/IV - 2 cat.)

Table R.1.2.9.6: 1 Responder analysis (displaying odds ratio) in KCCQ-OSS change from baseline at week 52 of <= -15 points (deterioration) by NYHA (2 cat.) - RS (LOCF-AD) - 1245.121

Subgroup Description	Placebo	Empa 10mg
Baseline NYHA (2 cat.): II		
Number of patients in analysis set	1401	1399
Number of analysed patients, N (%)	1306 (100.0)	1307 (100.0)
Number of patients with endpoint, N (%)	162 (12.4)	125 (9.6)
95% confidence interval*	(10.7, 14.3)	(8.1, 11.3)
Comparison vs Placebo**		
Odds ratio (SE)		0.726 (0.093)
95% confidence interval***		(0.565, 0.933)
p-value		0.0123
Baseline NYHA (2 cat.): III/IV		
Number of patients in analysis set	466	464
Number of analysed patients, N (%)	403 (100.0)	433 (100.0)
Number of patients with endpoint, N (%)	46 (11.4)	49 (11.3)
95% confidence interval*	(8.7, 14.9)	(8.7, 14.6)
Comparison vs Placebo**		
Odds ratio (SE)		1.036 (0.230)
95% confidence interval***		(0.670, 1.601)
p-value		0.8732

* Wilson confidence intervals.
** Logistic regression includes terms for baseline KCCQ - overall summary score (p<0.0001), age (p=0.3560), baseline eGFR (CKD-EPI) (p=0.0020), Treatment (p=0.2668), region (5 cat.) (p=0.0118), baseline diabetes status (3 cat.) (p=0.3342), sex (p=0.8154), baseline LVEF (3 cat.) (p=0.7403), baseline NYHA (2 cat.) (p=0.0087) and Treatment by baseline NYHA (2 cat.) interaction (p=0.1659).
***Wald confidence intervals.

Data taken from study 1245.121 only.
LOCF: For a missing value at week 52 the last available post-baseline value before week 52 is imputed.

Table R.1.2.9.6: 2 Responder analysis (displaying risk ratio) in KCCQ-OSS change from baseline at week 52 of <= -15 points (deterioration) by NYHA (2 cat.) - RS (LOCF-AD) - 1245.121

Subgroup Description	Placebo	Empa 10mg
Baseline NYHA (2 cat.): II		
Number of patients in analysis set	1401	1399
Number of analysed patients, N (%)	1306 (100.0)	1307 (100.0)
Number of patients with endpoint, N (%)	162 (12.4)	125 (9.6)
95% confidence interval*	(10.7, 14.3)	(8.1, 11.3)
Comparison vs Placebo**		
Risk ratio (SE)		0.758 (0.084)
95% confidence interval***		(0.609, 0.943)
p-value		0.0128
Baseline NYHA (2 cat.): III/IV		
Number of patients in analysis set	466	464
Number of analysed patients, N (%)	403 (100.0)	433 (100.0)
Number of patients with endpoint, N (%)	46 (11.4)	49 (11.3)
95% confidence interval*	(8.7, 14.9)	(8.7, 14.6)
Comparison vs Placebo**		
Risk ratio (SE)		1.030 (0.195)
95% confidence interval***		(0.711, 1.493)
p-value		0.8754

* Wilson confidence intervals.
** Log-linked Poisson model with robust estimate of variance includes terms for baseline KCCQ - overall summary score (p<0.0001), age (p=0.3837), baseline eGFR (CKD-EPI) (p=0.0027), Treatment (p=0.2587), region (5 cat.) (p=0.0161), baseline diabetes status (3 cat.) (p=0.3473), sex (p=0.8256), baseline LVEF (3 cat.) (p=0.7371), baseline NYHA (2 cat.) (p=0.0113) and Treatment by baseline NYHA (2 cat.) interaction (p=0.1626).
***Wald confidence intervals.

Data taken from study 1245.121 only.
LOCF: For a missing value at week 52 the last available post-baseline value before week 52 is imputed.

Table R.1.2.9.6: 3 Responder analysis (displaying odds ratio) in KCCQ-OSS change from baseline at week 52 of > -15 points (stability) by NYHA (2 cat.) - RS (LOCF-AD) - 1245.121

Subgroup Description	Placebo	Empa 10mg
Baseline NYHA (2 cat.): II		
Number of patients in analysis set	1401	1399
Number of analysed patients, N (%)	1306 (100.0)	1307 (100.0)
Number of patients with endpoint, N (%)	1144 (87.6)	1182 (90.4)
95% confidence interval*	(85.7, 89.3)	(88.7, 91.9)
Comparison vs Placebo**		
Odds ratio (SE)		1.377 (0.176)
95% confidence interval***		(1.072, 1.769)
p-value		0.0123
Baseline NYHA (2 cat.): III/IV		
Number of patients in analysis set	466	464
Number of analysed patients, N (%)	403 (100.0)	433 (100.0)
Number of patients with endpoint, N (%)	357 (88.6)	384 (88.7)
95% confidence interval*	(85.1, 91.3)	(85.4, 91.3)
Comparison vs Placebo**		
Odds ratio (SE)		0.965 (0.214)
95% confidence interval***		(0.624, 1.492)
p-value		0.8732

* Wilson confidence intervals.
** Logistic regression includes terms for baseline KCCQ - overall summary score (p<0.0001), age (p=0.3560), baseline eGFR (CKD-EPI) (p=0.0020), Treatment (p=0.2668), region (5 cat.) (p=0.0118), baseline diabetes status (3 cat.) (p=0.3342), sex (p=0.8154), baseline LVEF (3 cat.) (p=0.7403), baseline NYHA (2 cat.) (p=0.0087) and Treatment by baseline NYHA (2 cat.) interaction (p=0.1659).
***Wald confidence intervals.

Data taken from study 1245.121 only.
LOCF: For a missing value at week 52 the last available post-baseline value before week 52 is imputed.

Table R.1.2.9.6: 4 Responder analysis (displaying risk ratio) in KCCQ-OSS change from baseline at week 52 of > -15 points (stability) by NYHA (2 cat.) - RS (LOCF-AD) - 1245.121

Subgroup Description	Placebo	Empa 10mg
Baseline NYHA (2 cat.): II		
Number of patients in analysis set	1401	1399
Number of analysed patients, N (%)	1306 (100.0)	1307 (100.0)
Number of patients with endpoint, N (%)	1144 (87.6)	1182 (90.4)
95% confidence interval*	(85.7, 89.3)	(88.7, 91.9)
Comparison vs Placebo**		
Risk ratio (SE)		1.035 (0.014)
95% confidence interval***		(1.008, 1.063)
p-value		0.0119
Baseline NYHA (2 cat.): III/IV		
Number of patients in analysis set	466	464
Number of analysed patients, N (%)	403 (100.0)	433 (100.0)
Number of patients with endpoint, N (%)	357 (88.6)	384 (88.7)
95% confidence interval*	(85.1, 91.3)	(85.4, 91.3)
Comparison vs Placebo**		
Risk ratio (SE)		0.995 (0.024)
95% confidence interval***		(0.949, 1.044)
p-value		0.8399

* Wilson confidence intervals.
** Log-linked Poisson model with robust estimate of variance includes terms for baseline KCCQ - overall summary score (p<0.0001), age (p=0.4674), baseline eGFR (CKD-EPI) (p=0.0029), Treatment (p=0.2909), region (5 cat.) (p<0.0001), baseline diabetes status (3 cat.) (p=0.3092), sex (p=0.7783), baseline LVEF (3 cat.) (p=0.7480), baseline NYHA (2 cat.) (p=0.0222) and Treatment by baseline NYHA (2 cat.) interaction (p=0.1601).
***Wald confidence intervals.

Data taken from study 1245.121 only.
LOCF: For a missing value at week 52 the last available post-baseline value before week 52 is imputed.

Table R.1.2.9.6: 5 Responder analysis (displaying odds ratio) in KCCQ-OSS change from baseline at week 52 of >= 15 points (improvement) by NYHA (2 cat.) - RS (LOCF-AD) - 1245.121

Subgroup Description	Placebo	Empa 10mg
Baseline NYHA (2 cat.): II		
Number of patients in analysis set	1401	1399
Number of analysed patients, N (%)	1306 (100.0)	1307 (100.0)
Number of patients with endpoint, N (%)	275 (21.1)	297 (22.7)
95% confidence interval*	(18.9, 23.4)	(20.5, 25.1)
Comparison vs Placebo**		
Odds ratio (SE)		1.214 (0.129)
95% confidence interval***		(0.985, 1.495)
p-value		0.0685
Baseline NYHA (2 cat.): III/IV		
Number of patients in analysis set	466	464
Number of analysed patients, N (%)	403 (100.0)	433 (100.0)
Number of patients with endpoint, N (%)	127 (31.5)	148 (34.2)
95% confidence interval*	(27.2, 36.2)	(29.9, 38.8)
Comparison vs Placebo**		
Odds ratio (SE)		0.996 (0.169)
95% confidence interval***		(0.714, 1.388)
p-value		0.9793

* Wilson confidence intervals.
** Logistic regression includes terms for baseline KCCQ - overall summary score (p<0.0001), age (p=0.9977), baseline eGFR (CKD-EPI) (p=0.0033), Treatment (p=0.3436), region (5 cat.) (p<0.0001), baseline diabetes status (3 cat.) (p=0.4528), sex (p=0.3366), baseline LVEF (3 cat.) (p=0.6449), baseline NYHA (2 cat.) (p=0.0160) and Treatment by baseline NYHA (2 cat.) interaction (p=0.3224).
***Wald confidence intervals.

Data taken from study 1245.121 only.
LOCF: For a missing value at week 52 the last available post-baseline value before week 52 is imputed.

Table R.1.2.9.6: 6 Responder analysis (displaying risk ratio) in KCCQ-OSS change from baseline at week 52 of >= 15 points (improvement) by NYHA (2 cat.) - RS (LOCF-AD) - 1245.121

Subgroup Description	Placebo	Empa 10mg
Baseline NYHA (2 cat.): II		
Number of patients in analysis set	1401	1399
Number of analysed patients, N (%)	1306 (100.0)	1307 (100.0)
Number of patients with endpoint, N (%)	275 (21.1)	297 (22.7)
95% confidence interval*	(18.9, 23.4)	(20.5, 25.1)
Comparison vs Placebo**		
Risk ratio (SE)		1.112 (0.075)
95% confidence interval***		(0.975, 1.268)
p-value		0.1129
Baseline NYHA (2 cat.): III/IV		
Number of patients in analysis set	466	464
Number of analysed patients, N (%)	403 (100.0)	433 (100.0)
Number of patients with endpoint, N (%)	127 (31.5)	148 (34.2)
95% confidence interval*	(27.2, 36.2)	(29.9, 38.8)
Comparison vs Placebo**		
Risk ratio (SE)		0.986 (0.097)
95% confidence interval***		(0.813, 1.195)
p-value		0.8835

* Wilson confidence intervals.
** Log-linked Poisson model with robust estimate of variance includes terms for baseline KCCQ - overall summary score (p<0.0001), age (p=0.8036), baseline eGFR (CKD-EPI) (p=0.0032), Treatment (p=0.4412), region (5 cat.) (p<0.0001), baseline diabetes status (3 cat.) (p=0.4879), sex (p=0.3055), baseline LVEF (3 cat.) (p=0.5503), baseline NYHA (2 cat.) (p=0.0115) and Treatment by baseline NYHA (2 cat.) interaction (p=0.3102).
***Wald confidence intervals.

Data taken from study 1245.121 only.
LOCF: For a missing value at week 52 the last available post-baseline value before week 52 is imputed.

R.1.2.9.7

R.1.2.9.7 Subgroup analysis by diabetes at baseline

Table R.1.2.9.7: 1 Responder analysis (displaying odds ratio) in KCCQ-OSS change from baseline at week 52 of <= -15 points (deterioration) by diabetes at baseline - RS (LOCF-AD) - 1245.121

Subgroup Description	Placebo	Empa 10mg
Diabetes at baseline (2 cat.): Diabetic		
Number of patients in analysis set	929	927
Number of analysed patients, N (%)	850 (100.0)	861 (100.0)
Number of patients with endpoint, N (%)	105 (12.4)	91 (10.6)
95% confidence interval*	(10.3, 14.7)	(8.7, 12.8)
Comparison vs Placebo**		
Odds ratio (SE)		0.829 (0.128)
95% confidence interval***		(0.613, 1.122)
p-value		0.2243
Diabetes at baseline (2 cat.): Non-Diabetic		
Number of patients in analysis set	938	936
Number of analysed patients, N (%)	859 (100.0)	879 (100.0)
Number of patients with endpoint, N (%)	103 (12.0)	83 (9.4)
95% confidence interval*	(10.0, 14.3)	(7.7, 11.6)
Comparison vs Placebo**		
Odds ratio (SE)		0.759 (0.120)
95% confidence interval***		(0.557, 1.035)
p-value		0.0812

* Wilson confidence intervals.
** Logistic regression includes terms for baseline KCCQ - overall summary score (p<0.0001), age (p=0.3447), baseline eGFR (CKD-EPI) (p=0.0016), Treatment (p=0.0360), region (5 cat.) (p=0.0097), sex (p=0.7691), baseline LVEF (3 cat.) (p=0.6908), diabetes at baseline (2 cat.) (p=0.2913) and Treatment by diabetes at baseline (2 cat.) interaction (p=0.6908).
***Wald confidence intervals.

Data taken from study 1245.121 only.
LOCF: For a missing value at week 52 the last available post-baseline value before week 52 is imputed.

Table R.1.2.9.7: 2 Responder analysis (displaying risk ratio) in KCCQ-OSS change from baseline at week 52 of <= -15 points (deterioration) by diabetes at baseline - RS (LOCF-AD) - 1245.121

Subgroup Description	Placebo	Empa 10mg
Diabetes at baseline (2 cat.): Diabetic		
Number of patients in analysis set	929	927
Number of analysed patients, N (%)	850 (100.0)	861 (100.0)
Number of patients with endpoint, N (%)	105 (12.4)	91 (10.6)
95% confidence interval*	(10.3, 14.7)	(8.7, 12.8)
Comparison vs Placebo**		
Risk ratio (SE)		0.850 (0.113)
95% confidence interval***		(0.656, 1.103)
p-value		0.2215
Diabetes at baseline (2 cat.): Non-Diabetic		
Number of patients in analysis set	938	936
Number of analysed patients, N (%)	859 (100.0)	879 (100.0)
Number of patients with endpoint, N (%)	103 (12.0)	83 (9.4)
95% confidence interval*	(10.0, 14.3)	(7.7, 11.6)
Comparison vs Placebo**		
Risk ratio (SE)		0.786 (0.109)
95% confidence interval***		(0.599, 1.032)
p-value		0.0832

* Wilson confidence intervals.
** Log-linked Poisson model with robust estimate of variance includes terms for baseline KCCQ - overall summary score (p<0.0001), age (p=0.3706), baseline eGFR (CKD-EPI) (p=0.0020), Treatment (p=0.0357), region (5 cat.) (p=0.0128), sex (p=0.7739), baseline LVEF (3 cat.) (p=0.6859), diabetes at baseline (2 cat.) (p=0.2968) and Treatment by diabetes at baseline (2 cat.) interaction (p=0.6838).
***Wald confidence intervals.

Data taken from study 1245.121 only.
LOCF: For a missing value at week 52 the last available post-baseline value before week 52 is imputed.

Table R.1.2.9.7: 3 Responder analysis (displaying odds ratio) in KCCQ-OSS change from baseline at week 52 of > -15 points (stability) by diabetes at baseline - RS (LOCF-AD) - 1245.121

Subgroup Description	Placebo	Empa 10mg
Diabetes at baseline (2 cat.): Diabetic		
Number of patients in analysis set	929	927
Number of analysed patients, N (%)	850 (100.0)	861 (100.0)
Number of patients with endpoint, N (%)	745 (87.6)	770 (89.4)
95% confidence interval*	(85.3, 89.7)	(87.2, 91.3)
Comparison vs Placebo**		
Odds ratio (SE)		1.206 (0.186)
95% confidence interval***		(0.891, 1.632)
p-value		0.2243
Diabetes at baseline (2 cat.): Non-Diabetic		
Number of patients in analysis set	938	936
Number of analysed patients, N (%)	859 (100.0)	879 (100.0)
Number of patients with endpoint, N (%)	756 (88.0)	796 (90.6)
95% confidence interval*	(85.7, 90.0)	(88.4, 92.3)
Comparison vs Placebo**		
Odds ratio (SE)		1.317 (0.208)
95% confidence interval***		(0.966, 1.794)
p-value		0.0812

* Wilson confidence intervals.
** Logistic regression includes terms for baseline KCCQ - overall summary score (p<0.0001), age (p=0.3447), baseline eGFR (CKD-EPI) (p=0.0016), Treatment (p=0.0360), region (5 cat.) (p=0.0097), sex (p=0.7691), baseline LVEF (3 cat.) (p=0.6908), diabetes at baseline (2 cat.) (p=0.2913) and Treatment by diabetes at baseline (2 cat.) interaction (p=0.6908).
***Wald confidence intervals.

Data taken from study 1245.121 only.
LOCF: For a missing value at week 52 the last available post-baseline value before week 52 is imputed.

Table R.1.2.9.7: 4 Responder analysis (displaying risk ratio) in KCCQ-OSS change from baseline at week 52 of > -15 points (stability) by diabetes at baseline - RS (LOCF-AD) - 1245.121

Subgroup Description	Placebo	Empa 10mg
Diabetes at baseline (2 cat.): Diabetic		
Number of patients in analysis set	929	927
Number of analysed patients, N (%)	850 (100.0)	861 (100.0)
Number of patients with endpoint, N (%)	745 (87.6)	770 (89.4)
95% confidence interval*	(85.3, 89.7)	(87.2, 91.3)
Comparison vs Placebo**		
Risk ratio (SE)		1.020 (0.017)
95% confidence interval***		(0.986, 1.055)
p-value		0.2485
Diabetes at baseline (2 cat.): Non-Diabetic		
Number of patients in analysis set	938	936
Number of analysed patients, N (%)	859 (100.0)	879 (100.0)
Number of patients with endpoint, N (%)	756 (88.0)	796 (90.6)
95% confidence interval*	(85.7, 90.0)	(88.4, 92.3)
Comparison vs Placebo**		
Risk ratio (SE)		1.029 (0.017)
95% confidence interval***		(0.997, 1.063)
p-value		0.0800

* Wilson confidence intervals.
** Log-linked Poisson model with robust estimate of variance includes terms for baseline KCCQ - overall summary score (p<0.0001), age (p=0.4620), baseline eGFR (CKD-EPI) (p=0.0025), Treatment (p=0.0407), region (5 cat.) (p<0.0001), sex (p=0.7661), baseline LVEF (3 cat.) (p=0.7148), diabetes at baseline (2 cat.) (p=0.3024) and Treatment by diabetes at baseline (2 cat.) interaction (p=0.6999).
***Wald confidence intervals.

Data taken from study 1245.121 only.
LOCF: For a missing value at week 52 the last available post-baseline value before week 52 is imputed.

Table R.1.2.9.7: 5 Responder analysis (displaying odds ratio) in KCCQ-OSS change from baseline at week 52 of >= 15 points (improvement) by diabetes at baseline - RS (LOCF-AD) - 1245.121

Subgroup Description	Placebo	Empa 10mg
Diabetes at baseline (2 cat.): Diabetic		
Number of patients in analysis set	929	927
Number of analysed patients, N (%)	850 (100.0)	861 (100.0)
Number of patients with endpoint, N (%)	203 (23.9)	233 (27.1)
95% confidence interval*	(21.1, 26.9)	(24.2, 30.1)
Comparison vs Placebo**		
Odds ratio (SE)		1.208 (0.153)
95% confidence interval***		(0.942, 1.549)
p-value		0.1355
Diabetes at baseline (2 cat.): Non-Diabetic		
Number of patients in analysis set	938	936
Number of analysed patients, N (%)	859 (100.0)	879 (100.0)
Number of patients with endpoint, N (%)	199 (23.2)	212 (24.1)
95% confidence interval*	(20.5, 26.1)	(21.4, 27.1)
Comparison vs Placebo**		
Odds ratio (SE)		1.074 (0.136)
95% confidence interval***		(0.837, 1.377)
p-value		0.5769

* Wilson confidence intervals.
** Logistic regression includes terms for baseline KCCQ - overall summary score (p<0.0001), age (p=0.9734), baseline eGFR (CKD-EPI) (p=0.0030), Treatment (p=0.1475), region (5 cat.) (p<0.0001), sex (p=0.3437), baseline LVEF (3 cat.) (p=0.6341), diabetes at baseline (2 cat.) (p=0.9801) and Treatment by diabetes at baseline (2 cat.) interaction (p=0.5098).
***Wald confidence intervals.

Data taken from study 1245.121 only.
LOCF: For a missing value at week 52 the last available post-baseline value before week 52 is imputed.

Table R.1.2.9.7: 6 Responder analysis (displaying risk ratio) in KCCQ-OSS change from baseline at week 52 of >= 15 points (improvement) by diabetes at baseline - RS (LOCF-AD) - 1245.121

Subgroup Description	Placebo	Empa 10mg
Diabetes at baseline (2 cat.): Diabetic		
Number of patients in analysis set	929	927
Number of analysed patients, N (%)	850 (100.0)	861 (100.0)
Number of patients with endpoint, N (%)	203 (23.9)	233 (27.1)
95% confidence interval*	(21.1, 26.9)	(24.2, 30.1)
Comparison vs Placebo**		
Risk ratio (SE)		1.097 (0.086)
95% confidence interval***		(0.941, 1.279)
p-value		0.2355
Diabetes at baseline (2 cat.): Non-Diabetic		
Number of patients in analysis set	938	936
Number of analysed patients, N (%)	859 (100.0)	879 (100.0)
Number of patients with endpoint, N (%)	199 (23.2)	212 (24.1)
95% confidence interval*	(20.5, 26.1)	(21.4, 27.1)
Comparison vs Placebo**		
Risk ratio (SE)		1.031 (0.081)
95% confidence interval***		(0.883, 1.203)
p-value		0.6993

* Wilson confidence intervals.
** Log-linked Poisson model with robust estimate of variance includes terms for baseline KCCQ - overall summary score (p<0.0001), age (p=0.8653), baseline eGFR (CKD-EPI) (p=0.0035), Treatment (p=0.2677), region (5 cat.) (p<0.0001), sex (p=0.3150), baseline LVEF (3 cat.) (p=0.4993), diabetes at baseline (2 cat.) (p=0.8489) and Treatment by diabetes at baseline (2 cat.) interaction (p=0.5734).
***Wald confidence intervals.

Data taken from study 1245.121 only.
LOCF: For a missing value at week 52 the last available post-baseline value before week 52 is imputed.

R.1.2.9.8

R.1.2.9.8 Subgroup analysis by BMI at baseline (<30, >=30)

Table R.1.2.9.8: 1 Responder analysis (displaying odds ratio) in KCCQ-OSS change from baseline at week 52 of <= -15 points (deterioration) by baseline BMI [kg/m2] - RS (LOCF-AD) - 1245.121

Subgroup Description	Placebo	Empa 10mg
Baseline BMI [kg/m²] (2 cat.): <30		
Number of patients in analysis set	1300	1263
Number of analysed patients, N (%)	1197 (100.0)	1181 (100.0)
Number of patients with endpoint, N (%)	140 (11.7)	118 (10.0)
95% confidence interval*	(10.0, 13.6)	(8.4, 11.8)
Comparison vs Placebo**		
Odds ratio (SE)		0.824 (0.110)
95% confidence interval***		(0.634, 1.072)
p-value		0.1486
Baseline BMI [kg/m²] (2 cat.): >=30		
Number of patients in analysis set	567	600
Number of analysed patients, N (%)	512 (100.0)	559 (100.0)
Number of patients with endpoint, N (%)	68 (13.3)	56 (10.0)
95% confidence interval*	(10.6, 16.5)	(7.8, 12.8)
Comparison vs Placebo**		
Odds ratio (SE)		0.731 (0.142)
95% confidence interval***		(0.499, 1.070)
p-value		0.1071

* Wilson confidence intervals.
** Logistic regression includes terms for baseline KCCQ - overall summary score (p<0.0001), age (p=0.2589), baseline eGFR (CKD-EPI) (p=0.0016), Treatment (p=0.0319), region (5 cat.) (p=0.0178), baseline diabetes status (3 cat.) (p=0.3256), sex (p=0.7611), baseline LVEF (3 cat.) (p=0.7028), baseline BMI (2 cat.) (p=0.3298) and Treatment by baseline BMI (2 cat.) interaction (p=0.6120).
***Wald confidence intervals.

Data taken from study 1245.121 only.
LOCF: For a missing value at week 52 the last available post-baseline value before week 52 is imputed.

Table R.1.2.9.8: 2 Responder analysis (displaying risk ratio) in KCCQ-OSS change from baseline at week 52 of <= -15 points (deterioration) by baseline BMI [kg/m2] - RS (LOCF-AD) - 1245.121

Subgroup Description	Placebo	Empa 10mg
Baseline BMI [kg/m²] (2 cat.): <30		
Number of patients in analysis set	1300	1263
Number of analysed patients, N (%)	1197 (100.0)	1181 (100.0)
Number of patients with endpoint, N (%)	140 (11.7)	118 (10.0)
95% confidence interval*	(10.0, 13.6)	(8.4, 11.8)
Comparison vs Placebo**		
Risk ratio (SE)		0.845 (0.099)
95% confidence interval***		(0.672, 1.063)
p-value		0.1510
Baseline BMI [kg/m²] (2 cat.): >=30		
Number of patients in analysis set	567	600
Number of analysed patients, N (%)	512 (100.0)	559 (100.0)
Number of patients with endpoint, N (%)	68 (13.3)	56 (10.0)
95% confidence interval*	(10.6, 16.5)	(7.8, 12.8)
Comparison vs Placebo**		
Risk ratio (SE)		0.763 (0.127)
95% confidence interval***		(0.551, 1.057)
p-value		0.1041

* Wilson confidence intervals.
** Log-linked Poisson model with robust estimate of variance includes terms for baseline KCCQ - overall summary score (p<0.0001), age (p=0.2861), baseline eGFR (CKD-EPI) (p=0.0021), Treatment (p=0.0309), region (5 cat.) (p=0.0218), baseline diabetes status (3 cat.) (p=0.3417), sex (p=0.7667), baseline LVEF (3 cat.) (p=0.6972), baseline BMI (2 cat.) (p=0.3348) and Treatment by baseline BMI (2 cat.) interaction (p=0.6178).
***Wald confidence intervals.

Data taken from study 1245.121 only.
LOCF: For a missing value at week 52 the last available post-baseline value before week 52 is imputed.

Table R.1.2.9.8: 3 Responder analysis (displaying odds ratio) in KCCQ-OSS change from baseline at week 52 of > -15 points (stability) by baseline BMI [kg/m2] - RS (LOCF-AD) - 1245.121

Subgroup Description	Placebo	Empa 10mg
Baseline BMI [kg/m²] (2 cat.): <30		
Number of patients in analysis set	1300	1263
Number of analysed patients, N (%)	1197 (100.0)	1181 (100.0)
Number of patients with endpoint, N (%)	1057 (88.3)	1063 (90.0)
95% confidence interval*	(86.4, 90.0)	(88.2, 91.6)
Comparison vs Placebo**		
Odds ratio (SE)		1.214 (0.163)
95% confidence interval***		(0.933, 1.578)
p-value		0.1486
Baseline BMI [kg/m²] (2 cat.): >=30		
Number of patients in analysis set	567	600
Number of analysed patients, N (%)	512 (100.0)	559 (100.0)
Number of patients with endpoint, N (%)	444 (86.7)	503 (90.0)
95% confidence interval*	(83.5, 89.4)	(87.2, 92.2)
Comparison vs Placebo**		
Odds ratio (SE)		1.368 (0.266)
95% confidence interval***		(0.934, 2.003)
p-value		0.1071

* Wilson confidence intervals.
** Logistic regression includes terms for baseline KCCQ - overall summary score (p<0.0001), age (p=0.2589), baseline eGFR (CKD-EPI) (p=0.0016), Treatment (p=0.0319), region (5 cat.) (p=0.0178), baseline diabetes status (3 cat.) (p=0.3256), sex (p=0.7611), baseline LVEF (3 cat.) (p=0.7028), baseline BMI (2 cat.) (p=0.3298) and Treatment by baseline BMI (2 cat.) interaction (p=0.6120).
***Wald confidence intervals.

Data taken from study 1245.121 only.
LOCF: For a missing value at week 52 the last available post-baseline value before week 52 is imputed.

Table R.1.2.9.8: 4 Responder analysis (displaying risk ratio) in KCCQ-OSS change from baseline at week 52 of > -15 points (stability) by baseline BMI [kg/m2] - RS (LOCF-AD) - 1245.121

Subgroup Description	Placebo	Empa 10mg
Baseline BMI [kg/m²] (2 cat.): <30		
Number of patients in analysis set	1300	1263
Number of analysed patients, N (%)	1197 (100.0)	1181 (100.0)
Number of patients with endpoint, N (%)	1057 (88.3)	1063 (90.0)
95% confidence interval*	(86.4, 90.0)	(88.2, 91.6)
Comparison vs Placebo**		
Risk ratio (SE)		1.020 (0.014)
95% confidence interval***		(0.992, 1.049)
p-value		0.1600
Baseline BMI [kg/m²] (2 cat.): >=30		
Number of patients in analysis set	567	600
Number of analysed patients, N (%)	512 (100.0)	559 (100.0)
Number of patients with endpoint, N (%)	444 (86.7)	503 (90.0)
95% confidence interval*	(83.5, 89.4)	(87.2, 92.2)
Comparison vs Placebo**		
Risk ratio (SE)		1.036 (0.023)
95% confidence interval***		(0.992, 1.082)
p-value		0.1063

* Wilson confidence intervals.
** Log-linked Poisson model with robust estimate of variance includes terms for baseline KCCQ - overall summary score (p<0.0001), age (p=0.3615), baseline eGFR (CKD-EPI) (p=0.0024), Treatment (p=0.0341), region (5 cat.) (p<0.0001), baseline diabetes status (3 cat.) (p=0.2997), sex (p=0.7497), baseline LVEF (3 cat.) (p=0.7227), baseline BMI (2 cat.) (p=0.3544) and Treatment by baseline BMI (2 cat.) interaction (p=0.5537).
***Wald confidence intervals.

Data taken from study 1245.121 only.
LOCF: For a missing value at week 52 the last available post-baseline value before week 52 is imputed.

Table R.1.2.9.8: 5 Responder analysis (displaying odds ratio) in KCCQ-OSS change from baseline at week 52 of >= 15 points (improvement) by baseline BMI [kg/m2] - RS (LOCF-AD) - 1245.121

Subgroup Description	Placebo	Empa 10mg
Baseline BMI [kg/m²] (2 cat.): <30		
Number of patients in analysis set	1300	1263
Number of analysed patients, N (%)	1197 (100.0)	1181 (100.0)
Number of patients with endpoint, N (%)	280 (23.4)	286 (24.2)
95% confidence interval*	(21.1, 25.9)	(21.9, 26.7)
Comparison vs Placebo**		
Odds ratio (SE)		1.094 (0.120)
95% confidence interval***		(0.883, 1.356)
p-value		0.4110
Baseline BMI [kg/m²] (2 cat.): >=30		
Number of patients in analysis set	567	600
Number of analysed patients, N (%)	512 (100.0)	559 (100.0)
Number of patients with endpoint, N (%)	122 (23.8)	159 (28.4)
95% confidence interval*	(20.3, 27.7)	(24.9, 32.3)
Comparison vs Placebo**		
Odds ratio (SE)		1.252 (0.198)
95% confidence interval***		(0.919, 1.707)
p-value		0.1547

* Wilson confidence intervals.
** Logistic regression includes terms for baseline KCCQ - overall summary score (p<0.0001), age (p=0.8796), baseline eGFR (CKD-EPI) (p=0.0027), Treatment (p=0.1014), region (5 cat.) (p<0.0001), baseline diabetes status (3 cat.) (p=0.4637), sex (p=0.3296), baseline LVEF (3 cat.) (p=0.6562), baseline BMI (2 cat.) (p=0.4060) and Treatment by baseline BMI (2 cat.) interaction (p=0.4825).
***Wald confidence intervals.

Data taken from study 1245.121 only.
LOCF: For a missing value at week 52 the last available post-baseline value before week 52 is imputed.

Table R.1.2.9.8: 6 Responder analysis (displaying risk ratio) in KCCQ-OSS change from baseline at week 52 of >= 15 points (improvement) by baseline BMI [kg/m2] - RS (LOCF-AD) - 1245.121

Subgroup Description	Placebo	Empa 10mg
Baseline BMI [kg/m²] (2 cat.): <30		
Number of patients in analysis set	1300	1263
Number of analysed patients, N (%)	1197 (100.0)	1181 (100.0)
Number of patients with endpoint, N (%)	280 (23.4)	286 (24.2)
95% confidence interval*	(21.1, 25.9)	(21.9, 26.7)
Comparison vs Placebo**		
Risk ratio (SE)		1.040 (0.069)
95% confidence interval***		(0.913, 1.185)
p-value		0.5579
Baseline BMI [kg/m²] (2 cat.): >=30		
Number of patients in analysis set	567	600
Number of analysed patients, N (%)	512 (100.0)	559 (100.0)
Number of patients with endpoint, N (%)	122 (23.8)	159 (28.4)
95% confidence interval*	(20.3, 27.7)	(24.9, 32.3)
Comparison vs Placebo**		
Risk ratio (SE)		1.122 (0.113)
95% confidence interval***		(0.921, 1.367)
p-value		0.2532

* Wilson confidence intervals.
** Log-linked Poisson model with robust estimate of variance includes terms for baseline KCCQ - overall summary score (p<0.0001), age (p=0.9816), baseline eGFR (CKD-EPI) (p=0.0030), Treatment (p=0.2025), region (5 cat.) (p<0.0001), baseline diabetes status (3 cat.) (p=0.4705), sex (p=0.2983), baseline LVEF (3 cat.) (p=0.5336), baseline BMI (2 cat.) (p=0.4835) and Treatment by baseline BMI (2 cat.) interaction (p=0.5282).
***Wald confidence intervals.

Data taken from study 1245.121 only.
LOCF: For a missing value at week 52 the last available post-baseline value before week 52 is imputed.

R.1.2.9.9 Subgroup analysis by eGFR at baseline (<60, >=60)

Table R.1.2.9.9: 1 Responder analysis (displaying odds ratio) in KCCQ-OSS change from baseline at week 52 of <= -15 points (deterioration) by baseline eGFR (2 cat.) - RS (LOCF-AD) - 1245.121

Subgroup Description	Placebo	Empa 10mg
Baseline eGFR (CKD-EPI) [mL/min/1.73m²] (2 cat.): >=60		
Number of patients in analysis set	960	969
Number of analysed patients, N (%)	875 (100.0)	903 (100.0)
Number of patients with endpoint, N (%)	97 (11.1)	77 (8.5)
95% confidence interval*	(9.2, 13.3)	(6.9, 10.5)
Comparison vs Placebo**		
Odds ratio (SE)		0.722 (0.117)
95% confidence interval***		(0.525, 0.993)
p-value		0.0454
Baseline eGFR (CKD-EPI) [mL/min/1.73m²] (2 cat.): <60		
Number of patients in analysis set	906	893
Number of analysed patients, N (%)	834 (100.0)	837 (100.0)
Number of patients with endpoint, N (%)	111 (13.3)	97 (11.6)
95% confidence interval*	(11.2, 15.8)	(9.6, 13.9)
Comparison vs Placebo**		
Odds ratio (SE)		0.861 (0.129)
95% confidence interval***		(0.642, 1.156)
p-value		0.3198

* Wilson confidence intervals.
** Logistic regression includes terms for baseline KCCQ - overall summary score (p<0.0001), age (p=0.0295), Treatment (p=0.0319), region (5 cat.) (p=0.0082), baseline diabetes status (3 cat.) (p=0.2711), sex (p=0.8403), baseline LVEF (3 cat.) (p=0.7706), baseline eGFR (CKD-EPI) (2 cat.) (p=0.1931) and Treatment by baseline eGFR (CKD-EPI) (2 cat.) interaction (p=0.4263).
***Wald confidence intervals.
2 patients were excluded as the subgroup variable was missing.

Data taken from study 1245.121 only.
LOCF: For a missing value at week 52 the last available post-baseline value before week 52 is imputed.

Table R.1.2.9.9: 2 Responder analysis (displaying risk ratio) in KCCQ-OSS change from baseline at week 52 of <= -15 points (deterioration) by baseline eGFR (2 cat.) - RS (LOCF-AD) - 1245.121

Subgroup Description	Placebo	Empa 10mg
Baseline eGFR (CKD-EPI) [mL/min/1.73m²] (2 cat.): >=60		
Number of patients in analysis set	960	969
Number of analysed patients, N (%)	875 (100.0)	903 (100.0)
Number of patients with endpoint, N (%)	97 (11.1)	77 (8.5)
95% confidence interval*	(9.2, 13.3)	(6.9, 10.5)
Comparison vs Placebo**		
Risk ratio (SE)		0.749 (0.108)
95% confidence interval***		(0.565, 0.994)
p-value		0.0450
Baseline eGFR (CKD-EPI) [mL/min/1.73m²] (2 cat.): <60		
Number of patients in analysis set	906	893
Number of analysed patients, N (%)	834 (100.0)	837 (100.0)
Number of patients with endpoint, N (%)	111 (13.3)	97 (11.6)
95% confidence interval*	(11.2, 15.8)	(9.6, 13.9)
Comparison vs Placebo**		
Risk ratio (SE)		0.880 (0.114)
95% confidence interval***		(0.683, 1.134)
p-value		0.3229

* Wilson confidence intervals.
** Log-linked Poisson model with robust estimate of variance includes terms for baseline KCCQ - overall summary score (p<0.0001), age (p=0.0392), Treatment (p=0.0310), region (5 cat.) (p=0.0108), baseline diabetes status (3 cat.) (p=0.2812), sex (p=0.8467), baseline LVEF (3 cat.) (p=0.7687), baseline eGFR (CKD-EPI) (2 cat.) (p=0.2004) and Treatment by baseline eGFR (CKD-EPI) (2 cat.) interaction (p=0.4063).
***Wald confidence intervals.
2 patients were excluded as the subgroup variable was missing.

Data taken from study 1245.121 only.
LOCF: For a missing value at week 52 the last available post-baseline value before week 52 is imputed.

Table R.1.2.9.9: 3 Responder analysis (displaying odds ratio) in KCCQ-OSS change from baseline at week 52 of > -15 points (stability) by baseline eGFR (2 cat.) - RS (LOCF-AD) - 1245.121

Subgroup Description	Placebo	Empa 10mg
Baseline eGFR (CKD-EPI) [mL/min/1.73m²] (2 cat.): >=60		
Number of patients in analysis set	960	969
Number of analysed patients, N (%)	875 (100.0)	903 (100.0)
Number of patients with endpoint, N (%)	778 (88.9)	826 (91.5)
95% confidence interval*	(86.7, 90.8)	(89.5, 93.1)
Comparison vs Placebo**		
Odds ratio (SE)		1.385 (0.225)
95% confidence interval***		(1.007, 1.904)
p-value		0.0454
Baseline eGFR (CKD-EPI) [mL/min/1.73m²] (2 cat.): <60		
Number of patients in analysis set	906	893
Number of analysed patients, N (%)	834 (100.0)	837 (100.0)
Number of patients with endpoint, N (%)	723 (86.7)	740 (88.4)
95% confidence interval*	(84.2, 88.8)	(86.1, 90.4)
Comparison vs Placebo**		
Odds ratio (SE)		1.161 (0.174)
95% confidence interval***		(0.865, 1.558)
p-value		0.3198

* Wilson confidence intervals.
** Logistic regression includes terms for baseline KCCQ - overall summary score (p<0.0001), age (p=0.0295), Treatment (p=0.0319), region (5 cat.) (p=0.0082), baseline diabetes status (3 cat.) (p=0.2711), sex (p=0.8403), baseline LVEF (3 cat.) (p=0.7706), baseline eGFR (CKD-EPI) (2 cat.) (p=0.1931) and Treatment by baseline eGFR (CKD-EPI) (2 cat.) interaction (p=0.4263).
***Wald confidence intervals.
2 patients were excluded as the subgroup variable was missing.

Data taken from study 1245.121 only.
LOCF: For a missing value at week 52 the last available post-baseline value before week 52 is imputed.

Table R.1.2.9.9: 4 Responder analysis (displaying risk ratio) in KCCQ-OSS change from baseline at week 52 of > -15 points (stability) by baseline eGFR (2 cat.) - RS (LOCF-AD) - 1245.121

Subgroup Description	Placebo	Empa 10mg
Baseline eGFR (CKD-EPI) [mL/min/1.73m²] (2 cat.): >=60		
Number of patients in analysis set	960	969
Number of analysed patients, N (%)	875 (100.0)	903 (100.0)
Number of patients with endpoint, N (%)	778 (88.9)	826 (91.5)
95% confidence interval*	(86.7, 90.8)	(89.5, 93.1)
Comparison vs Placebo**		
Risk ratio (SE)		1.030 (0.016)
95% confidence interval***		(0.999, 1.062)
p-value		0.0548
Baseline eGFR (CKD-EPI) [mL/min/1.73m²] (2 cat.): <60		
Number of patients in analysis set	906	893
Number of analysed patients, N (%)	834 (100.0)	837 (100.0)
Number of patients with endpoint, N (%)	723 (86.7)	740 (88.4)
95% confidence interval*	(84.2, 88.8)	(86.1, 90.4)
Comparison vs Placebo**		
Risk ratio (SE)		1.019 (0.019)
95% confidence interval***		(0.983, 1.056)
p-value		0.3054

* Wilson confidence intervals.
** Log-linked Poisson model with robust estimate of variance includes terms for baseline KCCQ - overall summary score (p<0.0001), age (p=0.0428), Treatment (p=0.0427), region (5 cat.) (p<0.0001), baseline diabetes status (3 cat.) (p=0.2605), sex (p=0.7942), baseline LVEF (3 cat.) (p=0.7694), baseline eGFR (CKD-EPI) (2 cat.) (p=0.2166) and Treatment by baseline eGFR (CKD-EPI) (2 cat.) interaction (p=0.6453).
***Wald confidence intervals.
2 patients were excluded as the subgroup variable was missing.

Data taken from study 1245.121 only.
LOCF: For a missing value at week 52 the last available post-baseline value before week 52 is imputed.

Table R.1.2.9.9: 5 Responder analysis (displaying odds ratio) in KCCQ-OSS change from baseline at week 52 of >= 15 points (improvement) by baseline eGFR (2 cat.) - RS (LOCF-AD) - 1245.121

Subgroup Description	Placebo	Empa 10mg
Baseline eGFR (CKD-EPI) [mL/min/1.73m²] (2 cat.): >=60		
Number of patients in analysis set	960	969
Number of analysed patients, N (%)	875 (100.0)	903 (100.0)
Number of patients with endpoint, N (%)	220 (25.1)	254 (28.1)
95% confidence interval*	(22.4, 28.1)	(25.3, 31.1)
Comparison vs Placebo**		
Odds ratio (SE)		1.208 (0.147)
95% confidence interval***		(0.951, 1.534)
p-value		0.1217
Baseline eGFR (CKD-EPI) [mL/min/1.73m²] (2 cat.): <60		
Number of patients in analysis set	906	893
Number of analysed patients, N (%)	834 (100.0)	837 (100.0)
Number of patients with endpoint, N (%)	182 (21.8)	191 (22.8)
95% confidence interval*	(19.2, 24.8)	(20.1, 25.8)
Comparison vs Placebo**		
Odds ratio (SE)		1.059 (0.140)
95% confidence interval***		(0.816, 1.373)
p-value		0.6674

* Wilson confidence intervals.
** Logistic regression includes terms for baseline KCCQ - overall summary score (p<0.0001), age (p=0.4244), Treatment (p=0.1724), region (5 cat.) (p<0.0001), baseline diabetes status (3 cat.) (p=0.5098), sex (p=0.3437), baseline LVEF (3 cat.) (p=0.6311), baseline eGFR (CKD-EPI) (2 cat.) (p=0.0198) and Treatment by baseline eGFR (CKD-EPI) (2 cat.) interaction (p=0.4643).
***Wald confidence intervals.
2 patients were excluded as the subgroup variable was missing.

Data taken from study 1245.121 only.
LOCF: For a missing value at week 52 the last available post-baseline value before week 52 is imputed.

Table R.1.2.9.9: 6 Responder analysis (displaying risk ratio) in KCCQ-OSS change from baseline at week 52 of >= 15 points (improvement) by baseline eGFR (2 cat.) - RS (LOCF-AD) - 1245.121

Subgroup Description	Placebo	Empa 10mg
Baseline eGFR (CKD-EPI) [mL/min/1.73m²] (2 cat.): >=60		
Number of patients in analysis set	960	969
Number of analysed patients, N (%)	875 (100.0)	903 (100.0)
Number of patients with endpoint, N (%)	220 (25.1)	254 (28.1)
95% confidence interval*	(22.4, 28.1)	(25.3, 31.1)
Comparison vs Placebo**		
Risk ratio (SE)		1.094 (0.082)
95% confidence interval***		(0.944, 1.267)
p-value		0.2336
Baseline eGFR (CKD-EPI) [mL/min/1.73m²] (2 cat.): <60		
Number of patients in analysis set	906	893
Number of analysed patients, N (%)	834 (100.0)	837 (100.0)
Number of patients with endpoint, N (%)	182 (21.8)	191 (22.8)
95% confidence interval*	(19.2, 24.8)	(20.1, 25.8)
Comparison vs Placebo**		
Risk ratio (SE)		1.026 (0.085)
95% confidence interval***		(0.873, 1.207)
p-value		0.7522

* Wilson confidence intervals.
** Log-linked Poisson model with robust estimate of variance includes terms for baseline KCCQ - overall summary score (p<0.0001), age (p=0.5729), Treatment (p=0.3009), region (5 cat.) (p<0.0001), baseline diabetes status (3 cat.) (p=0.5312), sex (p=0.2955), baseline LVEF (3 cat.) (p=0.5289), baseline eGFR (CKD-EPI) (2 cat.) (p=0.0197) and Treatment by baseline eGFR (CKD-EPI) (2 cat.) interaction (p=0.5697).
***Wald confidence intervals.
2 patients were excluded as the subgroup variable was missing.

Data taken from study 1245.121 only.
LOCF: For a missing value at week 52 the last available post-baseline value before week 52 is imputed.

R.1.2.9.10

Table R.1.2.9.10: 1 Responder analysis (displaying odds ratio) in KCCQ-OSS change from baseline at week 52 of <= -15 points (deterioration) by history of HHF - RS (LOCF-AD) - 1245.121

Subgroup Description	Placebo	Empa 10mg
History of HHF (in the last 12 months): No		
Number of patients in analysis set	1293	1286
Number of analysed patients, N (%)	1194 (100.0)	1212 (100.0)
Number of patients with endpoint, N (%)	142 (11.9)	126 (10.4)
95% confidence interval*	(10.2, 13.9)	(8.8, 12.2)
Comparison vs Placebo**		
Odds ratio (SE)		0.877 (0.115)
95% confidence interval***		(0.678, 1.135)
p-value		0.3174
History of HHF (in the last 12 months): Yes		
Number of patients in analysis set	574	577
Number of analysed patients, N (%)	515 (100.0)	528 (100.0)
Number of patients with endpoint, N (%)	66 (12.8)	48 (9.1)
95% confidence interval*	(10.2, 16.0)	(6.9, 11.8)
Comparison vs Placebo**		
Odds ratio (SE)		0.629 (0.128)
95% confidence interval***		(0.422, 0.938)
p-value		0.0229

* Wilson confidence intervals.
** Logistic regression includes terms for baseline KCCQ - overall summary score (p<0.0001), age (p=0.2952), baseline eGFR (CKD-EPI) (p=0.0014), Treatment (p=0.0141), region (5 cat.) (p=0.0101), baseline diabetes status (3 cat.) (p=0.2835), sex (p=0.7923), baseline LVEF (3 cat.) (p=0.6714), history of HHF (in the last 12 months) (p=0.8816) and Treatment by history of HHF (in the last 12 months) interaction (p=0.1713).
***Wald confidence intervals.

Data taken from study 1245.121 only.
LOCF: For a missing value at week 52 the last available post-baseline value before week 52 is imputed.

Table R.1.2.9.10: 2 Responder analysis (displaying risk ratio) in KCCQ-OSS change from baseline at week 52 of <= -15 points (deterioration) by history of HHF - RS (LOCF-AD) - 1245.121

Subgroup Description	Placebo	Empa 10mg
History of HHF (in the last 12 months): No		
Number of patients in analysis set	1293	1286
Number of analysed patients, N (%)	1194 (100.0)	1212 (100.0)
Number of patients with endpoint, N (%)	142 (11.9)	126 (10.4)
95% confidence interval*	(10.2, 13.9)	(8.8, 12.2)
Comparison vs Placebo**		
Risk ratio (SE)		0.893 (0.102)
95% confidence interval***		(0.714, 1.117)
p-value		0.3211
History of HHF (in the last 12 months): Yes		
Number of patients in analysis set	574	577
Number of analysed patients, N (%)	515 (100.0)	528 (100.0)
Number of patients with endpoint, N (%)	66 (12.8)	48 (9.1)
95% confidence interval*	(10.2, 16.0)	(6.9, 11.8)
Comparison vs Placebo**		
Risk ratio (SE)		0.667 (0.118)
95% confidence interval***		(0.471, 0.944)
p-value		0.0224

* Wilson confidence intervals.
** Log-linked Poisson model with robust estimate of variance includes terms for baseline KCCQ - overall summary score (p<0.0001), age (p=0.3201), baseline eGFR (CKD-EPI) (p=0.0018), Treatment (p=0.0139), region (5 cat.) (p=0.0132), baseline diabetes status (3 cat.) (p=0.2939), sex (p=0.7997), baseline LVEF (3 cat.) (p=0.6632), history of HHF (in the last 12 months) (p=0.8932) and Treatment by history of HHF (in the last 12 months) interaction (p=0.1671).
***Wald confidence intervals.

Data taken from study 1245.121 only.
LOCF: For a missing value at week 52 the last available post-baseline value before week 52 is imputed.

Table R.1.2.9.10: 3 Responder analysis (displaying odds ratio) in KCCQ-OSS change from baseline at week 52 of > -15 points (stability) by history of HHF - RS (LOCF-AD) - 1245.121

Subgroup Description	Placebo	Empa 10mg
History of HHF (in the last 12 months): No		
Number of patients in analysis set	1293	1286
Number of analysed patients, N (%)	1194 (100.0)	1212 (100.0)
Number of patients with endpoint, N (%)	1052 (88.1)	1086 (89.6)
95% confidence interval*	(86.1, 89.8)	(87.8, 91.2)
Comparison vs Placebo**		
Odds ratio (SE)		1.141 (0.150)
95% confidence interval***		(0.881, 1.476)
p-value		0.3174
History of HHF (in the last 12 months): Yes		
Number of patients in analysis set	574	577
Number of analysed patients, N (%)	515 (100.0)	528 (100.0)
Number of patients with endpoint, N (%)	449 (87.2)	480 (90.9)
95% confidence interval*	(84.0, 89.8)	(88.2, 93.1)
Comparison vs Placebo**		
Odds ratio (SE)		1.589 (0.324)
95% confidence interval***		(1.066, 2.369)
p-value		0.0229

* Wilson confidence intervals.
** Logistic regression includes terms for baseline KCCQ - overall summary score (p<0.0001), age (p=0.2952), baseline eGFR (CKD-EPI) (p=0.0014), Treatment (p=0.0141), region (5 cat.) (p=0.0101), baseline diabetes status (3 cat.) (p=0.2835), sex (p=0.7923), baseline LVEF (3 cat.) (p=0.6714), history of HHF (in the last 12 months) (p=0.8816) and Treatment by history of HHF (in the last 12 months) interaction (p=0.1713).
***Wald confidence intervals.

Data taken from study 1245.121 only.
LOCF: For a missing value at week 52 the last available post-baseline value before week 52 is imputed.

Table R.1.2.9.10: 4 Responder analysis (displaying risk ratio) in KCCQ-OSS change from baseline at week 52 of > -15 points (stability) by history of HHF - RS (LOCF-AD) - 1245.121

Subgroup Description	Placebo	Empa 10mg
History of HHF (in the last 12 months): No		
Number of patients in analysis set	1293	1286
Number of analysed patients, N (%)	1194 (100.0)	1212 (100.0)
Number of patients with endpoint, N (%)	1052 (88.1)	1086 (89.6)
95% confidence interval*	(86.1, 89.8)	(87.8, 91.2)
Comparison vs Placebo**		
Risk ratio (SE)		1.014 (0.014)
95% confidence interval***		(0.986, 1.043)
p-value		0.3187
History of HHF (in the last 12 months): Yes		
Number of patients in analysis set	574	577
Number of analysed patients, N (%)	515 (100.0)	528 (100.0)
Number of patients with endpoint, N (%)	449 (87.2)	480 (90.9)
95% confidence interval*	(84.0, 89.8)	(88.2, 93.1)
Comparison vs Placebo**		
Risk ratio (SE)		1.049 (0.023)
95% confidence interval***		(1.005, 1.094)
p-value		0.0270

* Wilson confidence intervals.
** Log-linked Poisson model with robust estimate of variance includes terms for baseline KCCQ - overall summary score (p<0.0001), age (p=0.4089), baseline eGFR (CKD-EPI) (p=0.0023), Treatment (p=0.0166), region (5 cat.) (p<0.0001), baseline diabetes status (3 cat.) (p=0.2566), sex (p=0.7726), baseline LVEF (3 cat.) (p=0.7038), history of HHF (in the last 12 months) (p=0.8643) and Treatment by history of HHF (in the last 12 months) interaction (p=0.1955).
***Wald confidence intervals.

Data taken from study 1245.121 only.
LOCF: For a missing value at week 52 the last available post-baseline value before week 52 is imputed.

Table R.1.2.9.10: 5 Responder analysis (displaying odds ratio) in KCCQ-OSS change from baseline at week 52 of >= 15 points (improvement) by history of HHF - RS (LOCF-AD) - 1245.121

Subgroup Description	Placebo	Empa 10mg
History of HHF (in the last 12 months): No		
Number of patients in analysis set	1293	1286
Number of analysed patients, N (%)	1194 (100.0)	1212 (100.0)
Number of patients with endpoint, N (%)	273 (22.9)	309 (25.5)
95% confidence interval*	(20.6, 25.3)	(23.1, 28.0)
Comparison vs Placebo**		
Odds ratio (SE)		1.179 (0.128)
95% confidence interval***		(0.953, 1.458)
p-value		0.1287
History of HHF (in the last 12 months): Yes		
Number of patients in analysis set	574	577
Number of analysed patients, N (%)	515 (100.0)	528 (100.0)
Number of patients with endpoint, N (%)	129 (25.0)	136 (25.8)
95% confidence interval*	(21.5, 29.0)	(22.2, 29.7)
Comparison vs Placebo**		
Odds ratio (SE)		1.060 (0.171)
95% confidence interval***		(0.773, 1.454)
p-value		0.7171

* Wilson confidence intervals.
** Logistic regression includes terms for baseline KCCQ - overall summary score (p<0.0001), age (p=0.9753), baseline eGFR (CKD-EPI) (p=0.0024), Treatment (p=0.2508), region (5 cat.) (p<0.0001), baseline diabetes status (3 cat.) (p=0.4587), sex (p=0.3326), baseline LVEF (3 cat.) (p=0.5914), history of HHF (in the last 12 months) (p=0.3962) and Treatment by history of HHF (in the last 12 months) interaction (p=0.5846).
***Wald confidence intervals.

Data taken from study 1245.121 only.
LOCF: For a missing value at week 52 the last available post-baseline value before week 52 is imputed.

Table R.1.2.9.10: 6 Responder analysis (displaying risk ratio) in KCCQ-OSS change from baseline at week 52 of >= 15 points (improvement) by history of HHF - RS (LOCF-AD) - 1245.121

Subgroup Description	Placebo	Empa 10mg
History of HHF (in the last 12 months): No		
Number of patients in analysis set	1293	1286
Number of analysed patients, N (%)	1194 (100.0)	1212 (100.0)
Number of patients with endpoint, N (%)	273 (22.9)	309 (25.5)
95% confidence interval*	(20.6, 25.3)	(23.1, 28.0)
Comparison vs Placebo**		
Risk ratio (SE)		1.088 (0.073)
95% confidence interval***		(0.953, 1.241)
p-value		0.2106
History of HHF (in the last 12 months): Yes		
Number of patients in analysis set	574	577
Number of analysed patients, N (%)	515 (100.0)	528 (100.0)
Number of patients with endpoint, N (%)	129 (25.0)	136 (25.8)
95% confidence interval*	(21.5, 29.0)	(22.2, 29.7)
Comparison vs Placebo**		
Risk ratio (SE)		1.014 (0.100)
95% confidence interval***		(0.835, 1.232)
p-value		0.8864

* Wilson confidence intervals.
** Log-linked Poisson model with robust estimate of variance includes terms for baseline KCCQ - overall summary score (p<0.0001), age (p=0.8399), baseline eGFR (CKD-EPI) (p=0.0022), Treatment (p=0.4111), region (5 cat.) (p<0.0001), baseline diabetes status (3 cat.) (p=0.4495), sex (p=0.3025), baseline LVEF (3 cat.) (p=0.4548), history of HHF (in the last 12 months) (p=0.3220) and Treatment by history of HHF (in the last 12 months) interaction (p=0.5581).
***Wald confidence intervals.

Data taken from study 1245.121 only.
LOCF: For a missing value at week 52 the last available post-baseline value before week 52 is imputed.

R.1.2.9.11

Table R.1.2.9.11: 1 Responder analysis (displaying odds ratio) in KCCQ-OSS change from baseline at week 52 of <= -15 points (deterioration) by cause of heart failure - RS (LOCF-AD) - 1245.121

Subgroup Description	Placebo	Empa 10mg
Cause of heart failure: Ischemic		
Number of patients in analysis set	946	983
Number of analysed patients, N (%)	876 (100.0)	923 (100.0)
Number of patients with endpoint, N (%)	117 (13.4)	105 (11.4)
95% confidence interval*	(11.3, 15.8)	(9.5, 13.6)
Comparison vs Placebo**		
Odds ratio (SE)		0.848 (0.123)
95% confidence interval***		(0.637, 1.128)
p-value		0.2569
Cause of heart failure: Non-ischemic		
Number of patients in analysis set	921	880
Number of analysed patients, N (%)	833 (100.0)	817 (100.0)
Number of patients with endpoint, N (%)	91 (10.9)	69 (8.4)
95% confidence interval*	(9.0, 13.2)	(6.7, 10.6)
Comparison vs Placebo**		
Odds ratio (SE)		0.726 (0.123)
95% confidence interval***		(0.521, 1.013)
p-value		0.0597

* Wilson confidence intervals.
** Logistic regression includes terms for baseline KCCQ - overall summary score (p<0.0001), age (p=0.3918), baseline eGFR (CKD-EPI) (p=0.0017), Treatment (p=0.0301), region (5 cat.) (p=0.0162), baseline diabetes status (3 cat.) (p=0.3046), sex (p=0.9075), baseline LVEF (3 cat.) (p=0.6993), cause of heart failure (p=0.1217) and Treatment by cause of heart failure interaction (p=0.4890).
***Wald confidence intervals.

Data taken from study 1245.121 only.
LOCF: For a missing value at week 52 the last available post-baseline value before week 52 is imputed.

Table R.1.2.9.11: 2 Responder analysis (displaying risk ratio) in KCCQ-OSS change from baseline at week 52 of <= -15 points (deterioration) by cause of heart failure - RS (LOCF-AD) - 1245.121

Subgroup Description	Placebo	Empa 10mg
Cause of heart failure: Ischemic		
Number of patients in analysis set	946	983
Number of analysed patients, N (%)	876 (100.0)	923 (100.0)
Number of patients with endpoint, N (%)	117 (13.4)	105 (11.4)
95% confidence interval*	(11.3, 15.8)	(9.5, 13.6)
Comparison vs Placebo**		
Risk ratio (SE)		0.869 (0.108)
95% confidence interval***		(0.681, 1.110)
p-value		0.2600
Cause of heart failure: Non-ischemic		
Number of patients in analysis set	921	880
Number of analysed patients, N (%)	833 (100.0)	817 (100.0)
Number of patients with endpoint, N (%)	91 (10.9)	69 (8.4)
95% confidence interval*	(9.0, 13.2)	(6.7, 10.6)
Comparison vs Placebo**		
Risk ratio (SE)		0.754 (0.113)
95% confidence interval***		(0.561, 1.012)
p-value		0.0600

* Wilson confidence intervals.
** Log-linked Poisson model with robust estimate of variance includes terms for baseline KCCQ - overall summary score (p<0.0001), age (p=0.4173), baseline eGFR (CKD-EPI) (p=0.0022), Treatment (p=0.0298), region (5 cat.) (p=0.0211), baseline diabetes status (3 cat.) (p=0.3133), sex (p=0.9128), baseline LVEF (3 cat.) (p=0.6945), cause of heart failure (p=0.1205) and Treatment by cause of heart failure interaction (p=0.4669).
***Wald confidence intervals.

Data taken from study 1245.121 only.
LOCF: For a missing value at week 52 the last available post-baseline value before week 52 is imputed.

Table R.1.2.9.11: 3 Responder analysis (displaying odds ratio) in KCCQ-OSS change from baseline at week 52 of > -15 points (stability) by cause of heart failure - RS (LOCF-AD) - 1245.121

Subgroup Description	Placebo	Empa 10mg
Cause of heart failure: Ischemic		
Number of patients in analysis set	946	983
Number of analysed patients, N (%)	876 (100.0)	923 (100.0)
Number of patients with endpoint, N (%)	759 (86.6)	818 (88.6)
95% confidence interval*	(84.2, 88.7)	(86.4, 90.5)
Comparison vs Placebo**		
Odds ratio (SE)		1.179 (0.172)
95% confidence interval***		(0.887, 1.569)
p-value		0.2569
Cause of heart failure: Non-ischemic		
Number of patients in analysis set	921	880
Number of analysed patients, N (%)	833 (100.0)	817 (100.0)
Number of patients with endpoint, N (%)	742 (89.1)	748 (91.6)
95% confidence interval*	(86.8, 91.0)	(89.4, 93.3)
Comparison vs Placebo**		
Odds ratio (SE)		1.377 (0.234)
95% confidence interval***		(0.987, 1.921)
p-value		0.0597

* Wilson confidence intervals.
** Logistic regression includes terms for baseline KCCQ - overall summary score (p<0.0001), age (p=0.3918), baseline eGFR (CKD-EPI) (p=0.0017), Treatment (p=0.0301), region (5 cat.) (p=0.0162), baseline diabetes status (3 cat.) (p=0.3046), sex (p=0.9075), baseline LVEF (3 cat.) (p=0.6993), cause of heart failure (p=0.1217) and Treatment by cause of heart failure interaction (p=0.4890).
***Wald confidence intervals.

Data taken from study 1245.121 only.
LOCF: For a missing value at week 52 the last available post-baseline value before week 52 is imputed.

Table R.1.2.9.11: 4 Responder analysis (displaying risk ratio) in KCCQ-OSS change from baseline at week 52 of > -15 points (stability) by cause of heart failure - RS (LOCF-AD) - 1245.121

Subgroup Description	Placebo	Empa 10mg
Cause of heart failure: Ischemic		
Number of patients in analysis set	946	983
Number of analysed patients, N (%)	876 (100.0)	923 (100.0)
Number of patients with endpoint, N (%)	759 (86.6)	818 (88.6)
95% confidence interval*	(84.2, 88.7)	(86.4, 90.5)
Comparison vs Placebo**		
Risk ratio (SE)		1.021 (0.018)
95% confidence interval***		(0.986, 1.057)
p-value		0.2419
Cause of heart failure: Non-ischemic		
Number of patients in analysis set	921	880
Number of analysed patients, N (%)	833 (100.0)	817 (100.0)
Number of patients with endpoint, N (%)	742 (89.1)	748 (91.6)
95% confidence interval*	(86.8, 91.0)	(89.4, 93.3)
Comparison vs Placebo**		
Risk ratio (SE)		1.029 (0.017)
95% confidence interval***		(0.998, 1.062)
p-value		0.0704

* Wilson confidence intervals.
** Log-linked Poisson model with robust estimate of variance includes terms for baseline KCCQ - overall summary score (p<0.0001), age (p=0.5305), baseline eGFR (CKD-EPI) (p=0.0026), Treatment (p=0.0366), region (5 cat.) (p<0.0001), baseline diabetes status (3 cat.) (p=0.2834), sex (p=0.9128), baseline LVEF (3 cat.) (p=0.7215), cause of heart failure (p=0.1284) and Treatment by cause of heart failure interaction (p=0.7242).
***Wald confidence intervals.

Data taken from study 1245.121 only.
LOCF: For a missing value at week 52 the last available post-baseline value before week 52 is imputed.

Table R.1.2.9.11: 5 Responder analysis (displaying odds ratio) in KCCQ-OSS change from baseline at week 52 of >= 15 points (improvement) by cause of heart failure - RS (LOCF-AD) - 1245.121

Subgroup Description	Placebo	Empa 10mg
Cause of heart failure: Ischemic		
Number of patients in analysis set	946	983
Number of analysed patients, N (%)	876 (100.0)	923 (100.0)
Number of patients with endpoint, N (%)	186 (21.2)	230 (24.9)
95% confidence interval*	(18.7, 24.1)	(22.2, 27.8)
Comparison vs Placebo**		
Odds ratio (SE)		1.223 (0.155)
95% confidence interval***		(0.954, 1.568)
p-value		0.1121
Cause of heart failure: Non-ischemic		
Number of patients in analysis set	921	880
Number of analysed patients, N (%)	833 (100.0)	817 (100.0)
Number of patients with endpoint, N (%)	216 (25.9)	215 (26.3)
95% confidence interval*	(23.1, 29.0)	(23.4, 29.4)
Comparison vs Placebo**		
Odds ratio (SE)		1.061 (0.136)
95% confidence interval***		(0.826, 1.363)
p-value		0.6410

* Wilson confidence intervals.
** Logistic regression includes terms for baseline KCCQ - overall summary score (p<0.0001), age (p=0.9996), baseline eGFR (CKD-EPI) (p=0.0025), Treatment (p=0.1468), region (5 cat.) (p<0.0001), baseline diabetes status (3 cat.) (p=0.4461), sex (p=0.3634), baseline LVEF (3 cat.) (p=0.6412), cause of heart failure (p=0.8980) and Treatment by cause of heart failure interaction (p=0.4312).
***Wald confidence intervals.

Data taken from study 1245.121 only.
LOCF: For a missing value at week 52 the last available post-baseline value before week 52 is imputed.

Table R.1.2.9.11: 6 Responder analysis (displaying risk ratio) in KCCQ-OSS change from baseline at week 52 of >= 15 points (improvement) by cause of heart failure - RS (LOCF-AD) - 1245.121

Subgroup Description	Placebo	Empa 10mg
Cause of heart failure: Ischemic		
Number of patients in analysis set	946	983
Number of analysed patients, N (%)	876 (100.0)	923 (100.0)
Number of patients with endpoint, N (%)	186 (21.2)	230 (24.9)
95% confidence interval*	(18.7, 24.1)	(22.2, 27.8)
Comparison vs Placebo**		
Risk ratio (SE)		1.118 (0.091)
95% confidence interval***		(0.953, 1.310)
p-value		0.1707
Cause of heart failure: Non-ischemic		
Number of patients in analysis set	921	880
Number of analysed patients, N (%)	833 (100.0)	817 (100.0)
Number of patients with endpoint, N (%)	216 (25.9)	215 (26.3)
95% confidence interval*	(23.1, 29.0)	(23.4, 29.4)
Comparison vs Placebo**		
Risk ratio (SE)		1.016 (0.078)
95% confidence interval***		(0.875, 1.181)
p-value		0.8323

* Wilson confidence intervals.
** Log-linked Poisson model with robust estimate of variance includes terms for baseline KCCQ - overall summary score (p<0.0001), age (p=0.8472), baseline eGFR (CKD-EPI) (p=0.0024), Treatment (p=0.2538), region (5 cat.) (p<0.0001), baseline diabetes status (3 cat.) (p=0.4397), sex (p=0.3429), baseline LVEF (3 cat.) (p=0.5161), cause of heart failure (p=0.7224) and Treatment by cause of heart failure interaction (p=0.3941).
***Wald confidence intervals.

Data taken from study 1245.121 only.
LOCF: For a missing value at week 52 the last available post-baseline value before week 52 is imputed.

R.1.2.9.12 Subgroup analysis by heart failure physiology (LVEF <= 30% and NTproBNP<median; LVEF <= 30% and NTproBNP>=median; LVEF > 30%)

Table R.1.2.9.12: 1 Responder analysis (displaying odds ratio) in KCCQ-OSS change from baseline at week 52 of <= -15 points (deterioration) by heart failure physiology - RS (LOCF-AD) - 1245.121

Subgroup Description	Placebo	Empa 10mg
Heart failure physiology: LVEF <= 30% and NTproBNP < median		
Number of patients in analysis set	723	698
Number of analysed patients, N (%)	679 (100.0)	655 (100.0)
Number of patients with endpoint, N (%)	62 (9.1)	57 (8.7)
95% confidence interval*	(7.2, 11.5)	(6.8, 11.1)
Comparison vs Placebo**		
Odds ratio (SE)		0.923 (0.179)
95% confidence interval***		(0.631, 1.351)
p-value		0.6813
Heart failure physiology: LVEF <= 30% and NTproBNP >= median		
Number of patients in analysis set	661	631
Number of analysed patients, N (%)	588 (100.0)	586 (100.0)
Number of patients with endpoint, N (%)	97 (16.5)	64 (10.9)
95% confidence interval*	(13.7, 19.7)	(8.6, 13.7)
Comparison vs Placebo**		
Odds ratio (SE)		0.619 (0.109)
95% confidence interval***		(0.438, 0.873)
p-value		0.0063

* Wilson confidence intervals.
** Logistic regression includes terms for baseline KCCQ - overall summary score (p<0.0001), age (p=0.3537), baseline eGFR (CKD-EPI) (p=0.0100), Treatment (p=0.0637), region (5 cat.) (p=0.0058), baseline diabetes status (3 cat.) (p=0.3252), sex (p=0.7315), heart failure physiology (p=0.0007) and Treatment by heart failure physiology interaction (p=0.2015).
***Wald confidence intervals.
16 patients were excluded as the subgroup variable was missing.

Data taken from study 1245.121 only.
LOCF: For a missing value at week 52 the last available post-baseline value before week 52 is imputed.
NTproBNP median [pg/mL]: with a. fibrillation/flutter at baseline: 2265; without a. fibrillation/flutter at baseline: 1671.

Table R.1.2.9.12: 1 Responder analysis (displaying odds ratio) in KCCQ-OSS change from baseline at week 52 of <= -15 points (deterioration) by heart failure physiology - RS (LOCF-AD) - 1245.121

Subgroup Description	Placebo	Empa 10mg
Heart failure physiology: LVEF > 30%		
Number of patients in analysis set	475	526
Number of analysed patients, N (%)	437 (100.0)	495 (100.0)
Number of patients with endpoint, N (%)	49 (11.2)	52 (10.5)
95% confidence interval*	(8.6, 14.5)	(8.1, 13.5)
Comparison vs Placebo**		
Odds ratio (SE)		0.936 (0.200)
95% confidence interval***		(0.616, 1.422)
p-value		0.7564

* Wilson confidence intervals.
** Logistic regression includes terms for baseline KCCQ - overall summary score (p<0.0001), age (p=0.3537), baseline eGFR (CKD-EPI) (p=0.0100), Treatment (p=0.0637), region (5 cat.) (p=0.0058), baseline diabetes status (3 cat.) (p=0.3252), sex (p=0.7315), heart failure physiology (p=0.0007) and Treatment by heart failure physiology interaction (p=0.2015).
***Wald confidence intervals.
16 patients were excluded as the subgroup variable was missing.

Data taken from study 1245.121 only.
LOCF: For a missing value at week 52 the last available post-baseline value before week 52 is imputed.
NTproBNP median [pg/mL]: with a. fibrillation/flutter at baseline: 2265; without a. fibrillation/flutter at baseline: 1671.

Table R.1.2.9.12: 2 Responder analysis (displaying risk ratio) in KCCQ-OSS change from baseline at week 52 of <= -15 points (deterioration) by heart failure physiology - RS (LOCF-AD) - 1245.121

Subgroup Description	Placebo	Empa 10mg
Heart failure physiology: LVEF <= 30% and NTproBNP < median		
Number of patients in analysis set	723	698
Number of analysed patients, N (%)	679 (100.0)	655 (100.0)
Number of patients with endpoint, N (%)	62 (9.1)	57 (8.7)
95% confidence interval*	(7.2, 11.5)	(6.8, 11.1)
Comparison vs Placebo**		
Risk ratio (SE)		0.932 (0.161)
95% confidence interval***		(0.664, 1.309)
p-value		0.6841
Heart failure physiology: LVEF <= 30% and NTproBNP >= median		
Number of patients in analysis set	661	631
Number of analysed patients, N (%)	588 (100.0)	586 (100.0)
Number of patients with endpoint, N (%)	97 (16.5)	64 (10.9)
95% confidence interval*	(13.7, 19.7)	(8.6, 13.7)
Comparison vs Placebo**		
Risk ratio (SE)		0.669 (0.099)
95% confidence interval***		(0.500, 0.895)
p-value		0.0068

* Wilson confidence intervals.
** Log-linked Poisson model with robust estimate of variance includes terms for baseline KCCQ - overall summary score (p<0.0001), age (p=0.3795), baseline eGFR (CKD-EPI) (p=0.0117), Treatment (p=0.0711), region (5 cat.) (p=0.0078), baseline diabetes status (3 cat.) (p=0.3374), sex (p=0.7342), heart failure physiology (p=0.0008) and Treatment by heart failure physiology interaction (p=0.2248).
***Wald confidence intervals.
16 patients were excluded as the subgroup variable was missing.

Data taken from study 1245.121 only.
LOCF: For a missing value at week 52 the last available post-baseline value before week 52 is imputed.
NTproBNP median [pg/mL]: with a. fibrillation/flutter at baseline: 2265; without a. fibrillation/flutter at baseline: 1671.

Table R.1.2.9.12: 2 Responder analysis (displaying risk ratio) in KCCQ-OSS change from baseline at week 52 of <= -15 points (deterioration) by heart failure physiology - RS (LOCF-AD) - 1245.121

Subgroup Description	Placebo	Empa 10mg
Heart failure physiology: LVEF > 30%		
Number of patients in analysis set	475	526
Number of analysed patients, N (%)	437 (100.0)	495 (100.0)
Number of patients with endpoint, N (%)	49 (11.2)	52 (10.5)
95% confidence interval*	(8.6, 14.5)	(8.1, 13.5)
Comparison vs Placebo**		
Risk ratio (SE)		0.944 (0.175)
95% confidence interval***		(0.656, 1.358)
p-value		0.7556

* Wilson confidence intervals.
** Log-linked Poisson model with robust estimate of variance includes terms for baseline KCCQ - overall summary score (p<0.0001), age (p=0.3795), baseline eGFR (CKD-EPI) (p=0.0117), Treatment (p=0.0711), region (5 cat.) (p=0.0078), baseline diabetes status (3 cat.) (p=0.3374), sex (p=0.7342), heart failure physiology (p=0.0008) and Treatment by heart failure physiology interaction (p=0.2248).
***Wald confidence intervals.
16 patients were excluded as the subgroup variable was missing.

Data taken from study 1245.121 only.
LOCF: For a missing value at week 52 the last available post-baseline value before week 52 is imputed.
NTproBNP median [pg/mL]: with a. fibrillation/flutter at baseline: 2265; without a. fibrillation/flutter at baseline: 1671.

Table R.1.2.9.12: 3 Responder analysis (displaying odds ratio) in KCCQ-OSS change from baseline at week 52 of > -15 points (stability) by heart failure physiology - RS (LOCF-AD) - 1245.121

Subgroup Description	Placebo	Empa 10mg
Heart failure physiology: LVEF <= 30% and NTproBNP < median		
Number of patients in analysis set	723	698
Number of analysed patients, N (%)	679 (100.0)	655 (100.0)
Number of patients with endpoint, N (%)	617 (90.9)	598 (91.3)
95% confidence interval*	(88.5, 92.8)	(88.9, 93.2)
Comparison vs Placebo**		
Odds ratio (SE)		1.083 (0.210)
95% confidence interval***		(0.740, 1.585)
p-value		0.6813
Heart failure physiology: LVEF <= 30% and NTproBNP >= median		
Number of patients in analysis set	661	631
Number of analysed patients, N (%)	588 (100.0)	586 (100.0)
Number of patients with endpoint, N (%)	491 (83.5)	522 (89.1)
95% confidence interval*	(80.3, 86.3)	(86.3, 91.4)
Comparison vs Placebo**		
Odds ratio (SE)		1.617 (0.284)
95% confidence interval***		(1.145, 2.282)
p-value		0.0063

* Wilson confidence intervals.
** Logistic regression includes terms for baseline KCCQ - overall summary score (p<0.0001), age (p=0.3537), baseline eGFR (CKD-EPI) (p=0.0100), Treatment (p=0.0637), region (5 cat.) (p=0.0058), baseline diabetes status (3 cat.) (p=0.3252), sex (p=0.7315), heart failure physiology (p=0.0007) and Treatment by heart failure physiology interaction (p=0.2015).
***Wald confidence intervals.
16 patients were excluded as the subgroup variable was missing.

Data taken from study 1245.121 only.
LOCF: For a missing value at week 52 the last available post-baseline value before week 52 is imputed.
NTproBNP median [pg/mL]: with a. fibrillation/flutter at baseline: 2265; without a. fibrillation/flutter at baseline: 1671.

Table R.1.2.9.12: 3 Responder analysis (displaying odds ratio) in KCCQ-OSS change from baseline at week 52 of > -15 points (stability) by heart failure physiology - RS (LOCF-AD) - 1245.121

Subgroup Description	Placebo	Empa 10mg
Heart failure physiology: LVEF > 30%		
Number of patients in analysis set	475	526
Number of analysed patients, N (%)	437 (100.0)	495 (100.0)
Number of patients with endpoint, N (%)	388 (88.8)	443 (89.5)
95% confidence interval*	(85.5, 91.4)	(86.5, 91.9)
Comparison vs Placebo**		
Odds ratio (SE)		1.068 (0.228)
95% confidence interval***		(0.703, 1.624)
p-value		0.7564

* Wilson confidence intervals.
** Logistic regression includes terms for baseline KCCQ - overall summary score (p<0.0001), age (p=0.3537), baseline eGFR (CKD-EPI) (p=0.0100), Treatment (p=0.0637), region (5 cat.) (p=0.0058), baseline diabetes status (3 cat.) (p=0.3252), sex (p=0.7315), heart failure physiology (p=0.0007) and Treatment by heart failure physiology interaction (p=0.2015).
***Wald confidence intervals.
16 patients were excluded as the subgroup variable was missing.

Data taken from study 1245.121 only.
LOCF: For a missing value at week 52 the last available post-baseline value before week 52 is imputed.
NTproBNP median [pg/mL]: with a. fibrillation/flutter at baseline: 2265; without a. fibrillation/flutter at baseline: 1671.

Table R.1.2.9.12: 4 Responder analysis (displaying risk ratio) in KCCQ-OSS change from baseline at week 52 of > -15 points (stability) by heart failure physiology - RS (LOCF-AD) - 1245.121

Subgroup Description	Placebo	Empa 10mg
Heart failure physiology: LVEF <= 30% and NTproBNP < median		
Number of patients in analysis set	723	698
Number of analysed patients, N (%)	679 (100.0)	655 (100.0)
Number of patients with endpoint, N (%)	617 (90.9)	598 (91.3)
95% confidence interval*	(88.5, 92.8)	(88.9, 93.2)
Comparison vs Placebo**		
Risk ratio (SE)		1.008 (0.017)
95% confidence interval***		(0.975, 1.042)
p-value		0.6459
Heart failure physiology: LVEF <= 30% and NTproBNP >= median		
Number of patients in analysis set	661	631
Number of analysed patients, N (%)	588 (100.0)	586 (100.0)
Number of patients with endpoint, N (%)	491 (83.5)	522 (89.1)
95% confidence interval*	(80.3, 86.3)	(86.3, 91.4)
Comparison vs Placebo**		
Risk ratio (SE)		1.065 (0.025)
95% confidence interval***		(1.018, 1.114)
p-value		0.0065

* Wilson confidence intervals.
** Log-linked Poisson model with robust estimate of variance includes terms for baseline KCCQ - overall summary score (p<0.0001), age (p=0.4465), baseline eGFR (CKD-EPI) (p=0.0138), Treatment (p=0.0368), region (5 cat.) (p<0.0001), baseline diabetes status (3 cat.) (p=0.2818), sex (p=0.7620), heart failure physiology (p=0.0004) and Treatment by heart failure physiology interaction (p=0.1138).
***Wald confidence intervals.
16 patients were excluded as the subgroup variable was missing.

Data taken from study 1245.121 only.
LOCF: For a missing value at week 52 the last available post-baseline value before week 52 is imputed.
NTproBNP median [pg/mL]: with a. fibrillation/flutter at baseline: 2265; without a. fibrillation/flutter at baseline: 1671.

Table R.1.2.9.12: 4 Responder analysis (displaying risk ratio) in KCCQ-OSS change from baseline at week 52 of > -15 points (stability) by heart failure physiology - RS (LOCF-AD) - 1245.121

Subgroup Description	Placebo	Empa 10mg
Heart failure physiology: LVEF > 30%		
Number of patients in analysis set	475	526
Number of analysed patients, N (%)	437 (100.0)	495 (100.0)
Number of patients with endpoint, N (%)	388 (88.8)	443 (89.5)
95% confidence interval*	(85.5, 91.4)	(86.5, 91.9)
Comparison vs Placebo**		
Risk ratio (SE)		1.006 (0.023)
95% confidence interval***		(0.962, 1.051)
p-value		0.8027

* Wilson confidence intervals.
** Log-linked Poisson model with robust estimate of variance includes terms for baseline KCCQ - overall summary score (p<0.0001), age (p=0.4465), baseline eGFR (CKD-EPI) (p=0.0138), Treatment (p=0.0368), region (5 cat.) (p<0.0001), baseline diabetes status (3 cat.) (p=0.2818), sex (p=0.7620), heart failure physiology (p=0.0004) and Treatment by heart failure physiology interaction (p=0.1138).
***Wald confidence intervals.
16 patients were excluded as the subgroup variable was missing.

Data taken from study 1245.121 only.
LOCF: For a missing value at week 52 the last available post-baseline value before week 52 is imputed.
NTproBNP median [pg/mL]: with a. fibrillation/flutter at baseline: 2265; without a. fibrillation/flutter at baseline: 1671.

Table R.1.2.9.12: 5 Responder analysis (displaying odds ratio) in KCCQ-OSS change from baseline at week 52 of >= 15 points (improvement) by heart failure physiology - RS (LOCF-AD) - 1245.121

Subgroup Description	Placebo	Empa 10mg
Heart failure physiology: LVEF <= 30% and NTproBNP < median		
Number of patients in analysis set	723	698
Number of analysed patients, N (%)	679 (100.0)	655 (100.0)
Number of patients with endpoint, N (%)	167 (24.6)	163 (24.9)
95% confidence interval*	(21.5, 28.0)	(21.7, 28.3)
Comparison vs Placebo**		
Odds ratio (SE)		1.089 (0.156)
95% confidence interval***		(0.822, 1.441)
p-value		0.5534
Heart failure physiology: LVEF <= 30% and NTproBNP >= median		
Number of patients in analysis set	661	631
Number of analysed patients, N (%)	588 (100.0)	586 (100.0)
Number of patients with endpoint, N (%)	139 (23.6)	158 (27.0)
95% confidence interval*	(20.4, 27.2)	(23.5, 30.7)
Comparison vs Placebo**		
Odds ratio (SE)		1.166 (0.179)
95% confidence interval***		(0.864, 1.575)
p-value		0.3156

* Wilson confidence intervals.
** Logistic regression includes terms for baseline KCCQ - overall summary score (p<0.0001), age (p=0.9427), baseline eGFR (CKD-EPI) (p=0.0068), Treatment (p=0.1201), region (5 cat.) (p<0.0001), baseline diabetes status (3 cat.) (p=0.4241), sex (p=0.3319), heart failure physiology (p=0.2024) and Treatment by heart failure physiology interaction (p=0.8919).
***Wald confidence intervals.
16 patients were excluded as the subgroup variable was missing.

Data taken from study 1245.121 only.
LOCF: For a missing value at week 52 the last available post-baseline value before week 52 is imputed.
NTproBNP median [pg/mL]: with a. fibrillation/flutter at baseline: 2265; without a. fibrillation/flutter at baseline: 1671.

Table R.1.2.9.12: 5 Responder analysis (displaying odds ratio) in KCCQ-OSS change from baseline at week 52 of >= 15 points (improvement) by heart failure physiology - RS (LOCF-AD) - 1245.121

Subgroup Description	Placebo	Empa 10mg
Heart failure physiology: LVEF > 30%		
Number of patients in analysis set	475	526
Number of analysed patients, N (%)	437 (100.0)	495 (100.0)
Number of patients with endpoint, N (%)	93 (21.3)	122 (24.6)
95% confidence interval*	(17.7, 25.4)	(21.1, 28.6)
Comparison vs Placebo**		
Odds ratio (SE)		1.207 (0.215)
95% confidence interval***		(0.852, 1.710)
p-value		0.2887

* Wilson confidence intervals.
** Logistic regression includes terms for baseline KCCQ - overall summary score (p<0.0001), age (p=0.9427), baseline eGFR (CKD-EPI) (p=0.0068), Treatment (p=0.1201), region (5 cat.) (p<0.0001), baseline diabetes status (3 cat.) (p=0.4241), sex (p=0.3319), heart failure physiology (p=0.2024) and Treatment by heart failure physiology interaction (p=0.8919).
***Wald confidence intervals.
16 patients were excluded as the subgroup variable was missing.

Data taken from study 1245.121 only.
LOCF: For a missing value at week 52 the last available post-baseline value before week 52 is imputed.
NTproBNP median [pg/mL]: with a. fibrillation/flutter at baseline: 2265; without a. fibrillation/flutter at baseline: 1671.

Table R.1.2.9.12: 6 Responder analysis (displaying risk ratio) in KCCQ-OSS change from baseline at week 52 of >= 15 points (improvement) by heart failure physiology - RS (LOCF-AD) - 1245.121

Subgroup Description	Placebo	Empa 10mg
Heart failure physiology: LVEF <= 30% and NTproBNP < median		
Number of patients in analysis set	723	698
Number of analysed patients, N (%)	679 (100.0)	655 (100.0)
Number of patients with endpoint, N (%)	167 (24.6)	163 (24.9)
95% confidence interval*	(21.5, 28.0)	(21.7, 28.3)
Comparison vs Placebo**		
Risk ratio (SE)		1.035 (0.093)
95% confidence interval***		(0.868, 1.234)
p-value		0.6988
Heart failure physiology: LVEF <= 30% and NTproBNP >= median		
Number of patients in analysis set	661	631
Number of analysed patients, N (%)	588 (100.0)	586 (100.0)
Number of patients with endpoint, N (%)	139 (23.6)	158 (27.0)
95% confidence interval*	(20.4, 27.2)	(23.5, 30.7)
Comparison vs Placebo**		
Risk ratio (SE)		1.100 (0.103)
95% confidence interval***		(0.915, 1.322)
p-value		0.3112

* Wilson confidence intervals.
** Log-linked Poisson model with robust estimate of variance includes terms for baseline KCCQ - overall summary score (p<0.0001), age (p=0.9439), baseline eGFR (CKD-EPI) (p=0.0081), Treatment (p=0.2388), region (5 cat.) (p<0.0001), baseline diabetes status (3 cat.) (p=0.4241), sex (p=0.3463), heart failure physiology (p=0.1538) and Treatment by heart failure physiology interaction (p=0.8963).
***Wald confidence intervals.
16 patients were excluded as the subgroup variable was missing.

Data taken from study 1245.121 only.
LOCF: For a missing value at week 52 the last available post-baseline value before week 52 is imputed.
NTproBNP median [pg/mL]: with a. fibrillation/flutter at baseline: 2265; without a. fibrillation/flutter at baseline: 1671.

Table R.1.2.9.12: 6 Responder analysis (displaying risk ratio) in KCCQ-OSS change from baseline at week 52 of >= 15 points (improvement) by heart failure physiology - RS (LOCF-AD) - 1245.121

Subgroup Description	Placebo	Empa 10mg
Heart failure physiology: LVEF > 30%		
Number of patients in analysis set	475	526
Number of analysed patients, N (%)	437 (100.0)	495 (100.0)
Number of patients with endpoint, N (%)	93 (21.3)	122 (24.6)
95% confidence interval*	(17.7, 25.4)	(21.1, 28.6)
Comparison vs Placebo**		
Risk ratio (SE)		1.073 (0.117)
95% confidence interval***		(0.866, 1.330)
p-value		0.5186

* Wilson confidence intervals.
** Log-linked Poisson model with robust estimate of variance includes terms for baseline KCCQ - overall summary score (p<0.0001), age (p=0.9439), baseline eGFR (CKD-EPI) (p=0.0081), Treatment (p=0.2388), region (5 cat.) (p<0.0001), baseline diabetes status (3 cat.) (p=0.4241), sex (p=0.3463), heart failure physiology (p=0.1538) and Treatment by heart failure physiology interaction (p=0.8963).
***Wald confidence intervals.
16 patients were excluded as the subgroup variable was missing.

Data taken from study 1245.121 only.
LOCF: For a missing value at week 52 the last available post-baseline value before week 52 is imputed.
NTproBNP median [pg/mL]: with a. fibrillation/flutter at baseline: 2265; without a. fibrillation/flutter at baseline: 1671.

R.1.2.9.13

Table R.1.2.9.13: 1 Responder analysis (displaying odds ratio) in KCCQ-OSS change from baseline at week 52 of <= -15 points (deterioration) by baseline use of MRA (Y/N) - RS (LOCF-AD) - 1245.121

Subgroup Description	Placebo	Empa 10mg
Baseline use of MRA: No		
Number of patients in analysis set	512	557
Number of analysed patients, N (%)	475 (100.0)	522 (100.0)
Number of patients with endpoint, N (%)	60 (12.6)	48 (9.2)
95% confidence interval*	(9.9, 15.9)	(7.0, 12.0)
Comparison vs Placebo**		
Odds ratio (SE)		0.707 (0.147)
95% confidence interval***		(0.471, 1.061)
p-value		0.0942
Baseline use of MRA: Yes		
Number of patients in analysis set	1355	1306
Number of analysed patients, N (%)	1234 (100.0)	1218 (100.0)
Number of patients with endpoint, N (%)	148 (12.0)	126 (10.3)
95% confidence interval*	(10.3, 13.9)	(8.8, 12.2)
Comparison vs Placebo**		
Odds ratio (SE)		0.835 (0.109)
95% confidence interval***		(0.646, 1.078)
p-value		0.1655

* Wilson confidence intervals.
** Logistic regression includes terms for baseline KCCQ - overall summary score (p<0.0001), age (p=0.2919), baseline eGFR (CKD-EPI) (p=0.0012), Treatment (p=0.0311), region (5 cat.) (p=0.0132), baseline diabetes status (3 cat.) (p=0.2734), sex (p=0.7421), baseline LVEF (3 cat.) (p=0.7405), baseline use of MRA (p=0.2729) and Treatment by baseline use of MRA interaction (p=0.4980).
***Wald confidence intervals.

Data taken from study 1245.121 only.
LOCF: For a missing value at week 52 the last available post-baseline value before week 52 is imputed.

Table R.1.2.9.13: 2 Responder analysis (displaying risk ratio) in KCCQ-OSS change from baseline at week 52 of <= -15 points (deterioration) by baseline use of MRA (Y/N) - RS (LOCF-AD) - 1245.121

Subgroup Description	Placebo	Empa 10mg
Baseline use of MRA: No		
Number of patients in analysis set	512	557
Number of analysed patients, N (%)	475 (100.0)	522 (100.0)
Number of patients with endpoint, N (%)	60 (12.6)	48 (9.2)
95% confidence interval*	(9.9, 15.9)	(7.0, 12.0)
Comparison vs Placebo**		
Risk ratio (SE)		0.739 (0.134)
95% confidence interval***		(0.518, 1.054)
p-value		0.0949
Baseline use of MRA: Yes		
Number of patients in analysis set	1355	1306
Number of analysed patients, N (%)	1234 (100.0)	1218 (100.0)
Number of patients with endpoint, N (%)	148 (12.0)	126 (10.3)
95% confidence interval*	(10.3, 13.9)	(8.8, 12.2)
Comparison vs Placebo**		
Risk ratio (SE)		0.855 (0.097)
95% confidence interval***		(0.685, 1.067)
p-value		0.1656

* Wilson confidence intervals.
** Log-linked Poisson model with robust estimate of variance includes terms for baseline KCCQ - overall summary score (p<0.0001), age (p=0.3167), baseline eGFR (CKD-EPI) (p=0.0017), Treatment (p=0.0312), region (5 cat.) (p=0.0167), baseline diabetes status (3 cat.) (p=0.2829), sex (p=0.7461), baseline LVEF (3 cat.) (p=0.7364), baseline use of MRA (p=0.2703) and Treatment by baseline use of MRA interaction (p=0.4952).
***Wald confidence intervals.

Data taken from study 1245.121 only.
LOCF: For a missing value at week 52 the last available post-baseline value before week 52 is imputed.

Table R.1.2.9.13: 3 Responder analysis (displaying odds ratio) in KCCQ-OSS change from baseline at week 52 of > -15 points (stability) by baseline use of MRA (Y/N) - RS (LOCF-AD) - 1245.121

Subgroup Description	Placebo	Empa 10mg
Baseline use of MRA: No		
Number of patients in analysis set	512	557
Number of analysed patients, N (%)	475 (100.0)	522 (100.0)
Number of patients with endpoint, N (%)	415 (87.4)	474 (90.8)
95% confidence interval*	(84.1, 90.1)	(88.0, 93.0)
Comparison vs Placebo**		
Odds ratio (SE)		1.415 (0.293)
95% confidence interval***		(0.942, 2.123)
p-value		0.0942
Baseline use of MRA: Yes		
Number of patients in analysis set	1355	1306
Number of analysed patients, N (%)	1234 (100.0)	1218 (100.0)
Number of patients with endpoint, N (%)	1086 (88.0)	1092 (89.7)
95% confidence interval*	(86.1, 89.7)	(87.8, 91.2)
Comparison vs Placebo**		
Odds ratio (SE)		1.198 (0.156)
95% confidence interval***		(0.928, 1.547)
p-value		0.1655

* Wilson confidence intervals.
** Logistic regression includes terms for baseline KCCQ - overall summary score (p<0.0001), age (p=0.2919), baseline eGFR (CKD-EPI) (p=0.0012), Treatment (p=0.0311), region (5 cat.) (p=0.0132), baseline diabetes status (3 cat.) (p=0.2734), sex (p=0.7421), baseline LVEF (3 cat.) (p=0.7405), baseline use of MRA (p=0.2729) and Treatment by baseline use of MRA interaction (p=0.4980).
***Wald confidence intervals.

Data taken from study 1245.121 only.
LOCF: For a missing value at week 52 the last available post-baseline value before week 52 is imputed.

Table R.1.2.9.13: 4 Responder analysis (displaying risk ratio) in KCCQ-OSS change from baseline at week 52 of > -15 points (stability) by baseline use of MRA (Y/N) - RS (LOCF-AD) - 1245.121

Subgroup Description	Placebo	Empa 10mg
Baseline use of MRA: No		
Number of patients in analysis set	512	557
Number of analysed patients, N (%)	475 (100.0)	522 (100.0)
Number of patients with endpoint, N (%)	415 (87.4)	474 (90.8)
95% confidence interval*	(84.1, 90.1)	(88.0, 93.0)
Comparison vs Placebo**		
Risk ratio (SE)		1.037 (0.023)
95% confidence interval***		(0.993, 1.083)
p-value		0.1017
Baseline use of MRA: Yes		
Number of patients in analysis set	1355	1306
Number of analysed patients, N (%)	1234 (100.0)	1218 (100.0)
Number of patients with endpoint, N (%)	1086 (88.0)	1092 (89.7)
95% confidence interval*	(86.1, 89.7)	(87.8, 91.2)
Comparison vs Placebo**		
Risk ratio (SE)		1.019 (0.014)
95% confidence interval***		(0.991, 1.048)
p-value		0.1751

* Wilson confidence intervals.
** Log-linked Poisson model with robust estimate of variance includes terms for baseline KCCQ - overall summary score (p<0.0001), age (p=0.3922), baseline eGFR (CKD-EPI) (p=0.0019), Treatment (p=0.0347), region (5 cat.) (p<0.0001), baseline diabetes status (3 cat.) (p=0.2505), sex (p=0.7477), baseline LVEF (3 cat.) (p=0.7532), baseline use of MRA (p=0.2885) and Treatment by baseline use of MRA interaction (p=0.5178).
***Wald confidence intervals.

Data taken from study 1245.121 only.
LOCF: For a missing value at week 52 the last available post-baseline value before week 52 is imputed.

Table R.1.2.9.13: 5 Responder analysis (displaying odds ratio) in KCCQ-OSS change from baseline at week 52 of >= 15 points (improvement) by baseline use of MRA (Y/N) - RS (LOCF-AD) - 1245.121

Subgroup Description	Placebo	Empa 10mg
Baseline use of MRA: No		
Number of patients in analysis set	512	557
Number of analysed patients, N (%)	475 (100.0)	522 (100.0)
Number of patients with endpoint, N (%)	87 (18.3)	127 (24.3)
95% confidence interval*	(15.1, 22.0)	(20.8, 28.2)
Comparison vs Placebo**		
Odds ratio (SE)		1.464 (0.257)
95% confidence interval***		(1.038, 2.064)
p-value		0.0296
Baseline use of MRA: Yes		
Number of patients in analysis set	1355	1306
Number of analysed patients, N (%)	1234 (100.0)	1218 (100.0)
Number of patients with endpoint, N (%)	315 (25.5)	318 (26.1)
95% confidence interval*	(23.2, 28.0)	(23.7, 28.6)
Comparison vs Placebo**		
Odds ratio (SE)		1.041 (0.109)
95% confidence interval***		(0.848, 1.279)
p-value		0.7002

* Wilson confidence intervals.
** Logistic regression includes terms for baseline KCCQ - overall summary score (p<0.0001), age (p=0.9826), baseline eGFR (CKD-EPI) (p=0.0024), Treatment (p=0.0390), region (5 cat.) (p<0.0001), baseline diabetes status (3 cat.) (p=0.4615), sex (p=0.3395), baseline LVEF (3 cat.) (p=0.6464), baseline use of MRA (p=0.8883) and Treatment by baseline use of MRA interaction (p=0.0954).
***Wald confidence intervals.

Data taken from study 1245.121 only.
LOCF: For a missing value at week 52 the last available post-baseline value before week 52 is imputed.

Table R.1.2.9.13: 6 Responder analysis (displaying risk ratio) in KCCQ-OSS change from baseline at week 52 of >= 15 points (improvement) by baseline use of MRA (Y/N) - RS (LOCF-AD) - 1245.121

Subgroup Description	Placebo	Empa 10mg
Baseline use of MRA: No		
Number of patients in analysis set	512	557
Number of analysed patients, N (%)	475 (100.0)	522 (100.0)
Number of patients with endpoint, N (%)	87 (18.3)	127 (24.3)
95% confidence interval*	(15.1, 22.0)	(20.8, 28.2)
Comparison vs Placebo**		
Risk ratio (SE)		1.231 (0.141)
95% confidence interval***		(0.983, 1.540)
p-value		0.0699
Baseline use of MRA: Yes		
Number of patients in analysis set	1355	1306
Number of analysed patients, N (%)	1234 (100.0)	1218 (100.0)
Number of patients with endpoint, N (%)	315 (25.5)	318 (26.1)
95% confidence interval*	(23.2, 28.0)	(23.7, 28.6)
Comparison vs Placebo**		
Risk ratio (SE)		1.015 (0.065)
95% confidence interval***		(0.896, 1.150)
p-value		0.8150

* Wilson confidence intervals.
** Log-linked Poisson model with robust estimate of variance includes terms for baseline KCCQ - overall summary score (p<0.0001), age (p=0.8742), baseline eGFR (CKD-EPI) (p=0.0030), Treatment (p=0.0902), region (5 cat.) (p<0.0001), baseline diabetes status (3 cat.) (p=0.4750), sex (p=0.3043), baseline LVEF (3 cat.) (p=0.5414), baseline use of MRA (p=0.6550) and Treatment by baseline use of MRA interaction (p=0.1413).
***Wald confidence intervals.

Data taken from study 1245.121 only.
LOCF: For a missing value at week 52 the last available post-baseline value before week 52 is imputed.

R.1.2.9.14

Table R.1.2.9.14: 1 Responder analysis (displaying odds ratio) in KCCQ-OSS change from baseline at week 52 of <= -15 points (deterioration) by baseline use of ARNi (Y/N) - RS (LOCF-AD) - 1245.121

Subgroup Description	Placebo	Empa 10mg
Baseline use of ARNi: No		
Number of patients in analysis set	1480	1523
Number of analysed patients, N (%)	1350 (100.0)	1418 (100.0)
Number of patients with endpoint, N (%)	168 (12.4)	147 (10.4)
95% confidence interval*	(10.8, 14.3)	(8.9, 12.1)
Comparison vs Placebo**		
Odds ratio (SE)		0.803 (0.098)
95% confidence interval***		(0.633, 1.019)
p-value		0.0710
Baseline use of ARNi: Yes		
Number of patients in analysis set	387	340
Number of analysed patients, N (%)	359 (100.0)	322 (100.0)
Number of patients with endpoint, N (%)	40 (11.1)	27 (8.4)
95% confidence interval*	(8.3, 14.8)	(5.8, 11.9)
Comparison vs Placebo**		
Odds ratio (SE)		0.731 (0.194)
95% confidence interval***		(0.435, 1.230)
p-value		0.2384

* Wilson confidence intervals.
** Logistic regression includes terms for baseline KCCQ - overall summary score (p<0.0001), age (p=0.3539), baseline eGFR (CKD-EPI) (p=0.0014), Treatment (p=0.0681), region (5 cat.) (p=0.0101), baseline diabetes status (3 cat.) (p=0.2913), sex (p=0.7967), baseline LVEF (3 cat.) (p=0.6539), baseline use of ARNi (p=0.1260) and Treatment by baseline use of ARNi interaction (p=0.7492).
***Wald confidence intervals.

Data taken from study 1245.121 only.
LOCF: For a missing value at week 52 the last available post-baseline value before week 52 is imputed.

Table R.1.2.9.14: 2 Responder analysis (displaying risk ratio) in KCCQ-OSS change from baseline at week 52 of <= -15 points (deterioration) by baseline use of ARNi (Y/N) - RS (LOCF-AD) - 1245.121

Subgroup Description	Placebo	Empa 10mg
Baseline use of ARNi: No		
Number of patients in analysis set	1480	1523
Number of analysed patients, N (%)	1350 (100.0)	1418 (100.0)
Number of patients with endpoint, N (%)	168 (12.4)	147 (10.4)
95% confidence interval*	(10.8, 14.3)	(8.9, 12.1)
Comparison vs Placebo**		
Risk ratio (SE)		0.827 (0.087)
95% confidence interval***		(0.673, 1.016)
p-value		0.0705
Baseline use of ARNi: Yes		
Number of patients in analysis set	387	340
Number of analysed patients, N (%)	359 (100.0)	322 (100.0)
Number of patients with endpoint, N (%)	40 (11.1)	27 (8.4)
95% confidence interval*	(8.3, 14.8)	(5.8, 11.9)
Comparison vs Placebo**		
Risk ratio (SE)		0.759 (0.178)
95% confidence interval***		(0.480, 1.202)
p-value		0.2401

* Wilson confidence intervals.
** Log-linked Poisson model with robust estimate of variance includes terms for baseline KCCQ - overall summary score (p<0.0001), age (p=0.3783), baseline eGFR (CKD-EPI) (p=0.0018), Treatment (p=0.0700), region (5 cat.) (p=0.0133), baseline diabetes status (3 cat.) (p=0.3032), sex (p=0.8007), baseline LVEF (3 cat.) (p=0.6482), baseline use of ARNi (p=0.1266) and Treatment by baseline use of ARNi interaction (p=0.7390).
***Wald confidence intervals.

Data taken from study 1245.121 only.
LOCF: For a missing value at week 52 the last available post-baseline value before week 52 is imputed.

Table R.1.2.9.14: 3 Responder analysis (displaying odds ratio) in KCCQ-OSS change from baseline at week 52 of > -15 points (stability) by baseline use of ARNi (Y/N) - RS (LOCF-AD) - 1245.121

Subgroup Description	Placebo	Empa 10mg
Baseline use of ARNi: No		
Number of patients in analysis set	1480	1523
Number of analysed patients, N (%)	1350 (100.0)	1418 (100.0)
Number of patients with endpoint, N (%)	1182 (87.6)	1271 (89.6)
95% confidence interval*	(85.7, 89.2)	(87.9, 91.1)
Comparison vs Placebo**		
Odds ratio (SE)		1.245 (0.151)
95% confidence interval***		(0.981, 1.581)
p-value		0.0710
Baseline use of ARNi: Yes		
Number of patients in analysis set	387	340
Number of analysed patients, N (%)	359 (100.0)	322 (100.0)
Number of patients with endpoint, N (%)	319 (88.9)	295 (91.6)
95% confidence interval*	(85.2, 91.7)	(88.1, 94.2)
Comparison vs Placebo**		
Odds ratio (SE)		1.367 (0.363)
95% confidence interval***		(0.813, 2.300)
p-value		0.2384

* Wilson confidence intervals.
** Logistic regression includes terms for baseline KCCQ - overall summary score (p<0.0001), age (p=0.3539), baseline eGFR (CKD-EPI) (p=0.0014), Treatment (p=0.0681), region (5 cat.) (p=0.0101), baseline diabetes status (3 cat.) (p=0.2913), sex (p=0.7967), baseline LVEF (3 cat.) (p=0.6539), baseline use of ARNi (p=0.1260) and Treatment by baseline use of ARNi interaction (p=0.7492).
***Wald confidence intervals.

Data taken from study 1245.121 only.
LOCF: For a missing value at week 52 the last available post-baseline value before week 52 is imputed.

Table R.1.2.9.14: 4 Responder analysis (displaying risk ratio) in KCCQ-OSS change from baseline at week 52 of > -15 points (stability) by baseline use of ARNi (Y/N) - RS (LOCF-AD) - 1245.121

Subgroup Description	Placebo	Empa 10mg
Baseline use of ARNi: No		
Number of patients in analysis set	1480	1523
Number of analysed patients, N (%)	1350 (100.0)	1418 (100.0)
Number of patients with endpoint, N (%)	1182 (87.6)	1271 (89.6)
95% confidence interval*	(85.7, 89.2)	(87.9, 91.1)
Comparison vs Placebo**		
Risk ratio (SE)		1.024 (0.014)
95% confidence interval***		(0.997, 1.051)
p-value		0.0790
Baseline use of ARNi: Yes		
Number of patients in analysis set	387	340
Number of analysed patients, N (%)	359 (100.0)	322 (100.0)
Number of patients with endpoint, N (%)	319 (88.9)	295 (91.6)
95% confidence interval*	(85.2, 91.7)	(88.1, 94.2)
Comparison vs Placebo**		
Risk ratio (SE)		1.030 (0.026)
95% confidence interval***		(0.981, 1.082)
p-value		0.2395

* Wilson confidence intervals.
** Log-linked Poisson model with robust estimate of variance includes terms for baseline KCCQ - overall summary score (p<0.0001), age (p=0.4694), baseline eGFR (CKD-EPI) (p=0.0022), Treatment (p=0.0614), region (5 cat.) (p<0.0001), baseline diabetes status (3 cat.) (p=0.2598), sex (p=0.7914), baseline LVEF (3 cat.) (p=0.6727), baseline use of ARNi (p=0.1455) and Treatment by baseline use of ARNi interaction (p=0.8407).
***Wald confidence intervals.

Data taken from study 1245.121 only.
LOCF: For a missing value at week 52 the last available post-baseline value before week 52 is imputed.

Table R.1.2.9.14: 5 Responder analysis (displaying odds ratio) in KCCQ-OSS change from baseline at week 52 of >= 15 points (improvement) by baseline use of ARNi (Y/N) - RS (LOCF-AD) - 1245.121

Subgroup Description	Placebo	Empa 10mg
Baseline use of ARNi: No		
Number of patients in analysis set	1480	1523
Number of analysed patients, N (%)	1350 (100.0)	1418 (100.0)
Number of patients with endpoint, N (%)	325 (24.1)	372 (26.2)
95% confidence interval*	(21.9, 26.4)	(24.0, 28.6)
Comparison vs Placebo**		
Odds ratio (SE)		1.132 (0.113)
95% confidence interval***		(0.932, 1.376)
p-value		0.2117
Baseline use of ARNi: Yes		
Number of patients in analysis set	387	340
Number of analysed patients, N (%)	359 (100.0)	322 (100.0)
Number of patients with endpoint, N (%)	77 (21.4)	73 (22.7)
95% confidence interval*	(17.5, 26.0)	(18.4, 27.6)
Comparison vs Placebo**		
Odds ratio (SE)		1.164 (0.246)
95% confidence interval***		(0.770, 1.760)
p-value		0.4719

* Wilson confidence intervals.
** Logistic regression includes terms for baseline KCCQ - overall summary score (p<0.0001), age (p=0.9558), baseline eGFR (CKD-EPI) (p=0.0027), Treatment (p=0.2363), region (5 cat.) (p<0.0001), baseline diabetes status (3 cat.) (p=0.4641), sex (p=0.3288), baseline LVEF (3 cat.) (p=0.6401), baseline use of ARNi (p=0.5188) and Treatment by baseline use of ARNi interaction (p=0.9059).
***Wald confidence intervals.

Data taken from study 1245.121 only.
LOCF: For a missing value at week 52 the last available post-baseline value before week 52 is imputed.

Table R.1.2.9.14: 6 Responder analysis (displaying risk ratio) in KCCQ-OSS change from baseline at week 52 of >= 15 points (improvement) by baseline use of ARNi (Y/N) - RS (LOCF-AD) - 1245.121

Subgroup Description	Placebo	Empa 10mg
Baseline use of ARNi: No		
Number of patients in analysis set	1480	1523
Number of analysed patients, N (%)	1350 (100.0)	1418 (100.0)
Number of patients with endpoint, N (%)	325 (24.1)	372 (26.2)
95% confidence interval*	(21.9, 26.4)	(24.0, 28.6)
Comparison vs Placebo**		
Risk ratio (SE)		1.056 (0.065)
95% confidence interval***		(0.937, 1.190)
p-value		0.3710
Baseline use of ARNi: Yes		
Number of patients in analysis set	387	340
Number of analysed patients, N (%)	359 (100.0)	322 (100.0)
Number of patients with endpoint, N (%)	77 (21.4)	73 (22.7)
95% confidence interval*	(17.5, 26.0)	(18.4, 27.6)
Comparison vs Placebo**		
Risk ratio (SE)		1.091 (0.147)
95% confidence interval***		(0.838, 1.421)
p-value		0.5174

* Wilson confidence intervals.
** Log-linked Poisson model with robust estimate of variance includes terms for baseline KCCQ - overall summary score (p<0.0001), age (p=0.9188), baseline eGFR (CKD-EPI) (p=0.0030), Treatment (p=0.3378), region (5 cat.) (p<0.0001), baseline diabetes status (3 cat.) (p=0.4622), sex (p=0.2964), baseline LVEF (3 cat.) (p=0.5052), baseline use of ARNi (p=0.4154) and Treatment by baseline use of ARNi interaction (p=0.8253).
***Wald confidence intervals.

Data taken from study 1245.121 only.
LOCF: For a missing value at week 52 the last available post-baseline value before week 52 is imputed.

R.1.2.9.15 Subgroup analysis by bl. LVEF (<= 30%, >30% -<= 35% , > 35%)

Table R.1.2.9.15: 1 Responder analysis (displaying odds ratio) in KCCQ-OSS change from baseline at week 52 of <= -15 points (deterioration) by baseline LVEF (3 cat.) - RS (LOCF-AD) - 1245.121

Subgroup Description	Placebo	Empa 10mg
Baseline LVEF (3 cat.): <=30		
Number of patients in analysis set	1392	1337
Number of analysed patients, N (%)	1272 (100.0)	1245 (100.0)
Number of patients with endpoint, N (%)	159 (12.5)	122 (9.8)
95% confidence interval*	(10.8, 14.4)	(8.3, 11.6)
Comparison vs Placebo**		
Odds ratio (SE)		0.747 (0.097)
95% confidence interval***		(0.580, 0.963)
p-value		0.0241
Baseline LVEF (3 cat.): >30 to <=35		
Number of patients in analysis set	361	398
Number of analysed patients, N (%)	333 (100.0)	375 (100.0)
Number of patients with endpoint, N (%)	36 (10.8)	41 (10.9)
95% confidence interval*	(7.9, 14.6)	(8.2, 14.5)
Comparison vs Placebo**		
Odds ratio (SE)		1.032 (0.253)
95% confidence interval***		(0.639, 1.668)
p-value		0.8972

* Wilson confidence intervals.
** Logistic regression includes terms for baseline KCCQ - overall summary score (p<0.0001), age (p=0.3181), baseline eGFR (CKD-EPI) (p=0.0014), Treatment (p=0.2348), region (5 cat.) (p=0.0113), baseline diabetes status (3 cat.) (p=0.2765), sex (p=0.7857), baseline LVEF (3 cat.) (p=0.6980) and Treatment by baseline LVEF (3 cat.) interaction (p=0.4845).
***Wald confidence intervals.

Data taken from study 1245.121 only.
LOCF: For a missing value at week 52 the last available post-baseline value before week 52 is imputed.

Table R.1.2.9.15: 1 Responder analysis (displaying odds ratio) in KCCQ-OSS change from baseline at week 52 of <= -15 points (deterioration) by baseline LVEF (3 cat.) - RS (LOCF-AD) - 1245.121

Subgroup Description	Placebo	Empa 10mg
Baseline LVEF (3 cat.): >35		
Number of patients in analysis set	114	128
Number of analysed patients, N (%)	104 (100.0)	120 (100.0)
Number of patients with endpoint, N (%)	13 (12.5)	11 (9.2)
95% confidence interval*	(7.5, 20.2)	(5.2, 15.7)
Comparison vs Placebo**		
Odds ratio (SE)		0.700 (0.308)
95% confidence interval***		(0.296, 1.656)
p-value		0.4163

* Wilson confidence intervals.
** Logistic regression includes terms for baseline KCCQ - overall summary score (p<0.0001), age (p=0.3181), baseline eGFR (CKD-EPI) (p=0.0014), Treatment (p=0.2348), region (5 cat.) (p=0.0113), baseline diabetes status (3 cat.) (p=0.2765), sex (p=0.7857), baseline LVEF (3 cat.) (p=0.6980) and Treatment by baseline LVEF (3 cat.) interaction (p=0.4845).
***Wald confidence intervals.

Data taken from study 1245.121 only.
LOCF: For a missing value at week 52 the last available post-baseline value before week 52 is imputed.

Table R.1.2.9.15: 2 Responder analysis (displaying risk ratio) in KCCQ-OSS change from baseline at week 52 of <= -15 points (deterioration) by baseline LVEF (3 cat.) - RS (LOCF-AD) - 1245.121

Subgroup Description	Placebo	Empa 10mg
Baseline LVEF (3 cat.): <=30		
Number of patients in analysis set	1392	1337
Number of analysed patients, N (%)	1272 (100.0)	1245 (100.0)
Number of patients with endpoint, N (%)	159 (12.5)	122 (9.8)
95% confidence interval*	(10.8, 14.4)	(8.3, 11.6)
Comparison vs Placebo**		
Risk ratio (SE)		0.777 (0.087)
95% confidence interval***		(0.624, 0.968)
p-value		0.0244
Baseline LVEF (3 cat.): >30 to <=35		
Number of patients in analysis set	361	398
Number of analysed patients, N (%)	333 (100.0)	375 (100.0)
Number of patients with endpoint, N (%)	36 (10.8)	41 (10.9)
95% confidence interval*	(7.9, 14.6)	(8.2, 14.5)
Comparison vs Placebo**		
Risk ratio (SE)		1.028 (0.219)
95% confidence interval***		(0.677, 1.561)
p-value		0.8961

* Wilson confidence intervals.
** Log-linked Poisson model with robust estimate of variance includes terms for baseline KCCQ - overall summary score (p<0.0001), age (p=0.3430), baseline eGFR (CKD-EPI) (p=0.0018), Treatment (p=0.2354), region (5 cat.) (p=0.0147), baseline diabetes status (3 cat.) (p=0.2859), sex (p=0.7908), baseline LVEF (3 cat.) (p=0.6996) and Treatment by baseline LVEF (3 cat.) interaction (p=0.4850).
***Wald confidence intervals.

Data taken from study 1245.121 only.
LOCF: For a missing value at week 52 the last available post-baseline value before week 52 is imputed.

Table R.1.2.9.15: 2 Responder analysis (displaying risk ratio) in KCCQ-OSS change from baseline at week 52 of <= -15 points (deterioration) by baseline LVEF (3 cat.) - RS (LOCF-AD) - 1245.121

Subgroup Description	Placebo	Empa 10mg
Baseline LVEF (3 cat.): >35		
Number of patients in analysis set	114	128
Number of analysed patients, N (%)	104 (100.0)	120 (100.0)
Number of patients with endpoint, N (%)	13 (12.5)	11 (9.2)
95% confidence interval*	(7.5, 20.2)	(5.2, 15.7)
Comparison vs Placebo**		
Risk ratio (SE)		0.732 (0.281)
95% confidence interval***		(0.345, 1.552)
p-value		0.4154

* Wilson confidence intervals.
** Log-linked Poisson model with robust estimate of variance includes terms for baseline KCCQ - overall summary score (p<0.0001), age (p=0.3430), baseline eGFR (CKD-EPI) (p=0.0018), Treatment (p=0.2354), region (5 cat.) (p=0.0147), baseline diabetes status (3 cat.) (p=0.2859), sex (p=0.7908), baseline LVEF (3 cat.) (p=0.6996) and Treatment by baseline LVEF (3 cat.) interaction (p=0.4850).
***Wald confidence intervals.

Data taken from study 1245.121 only.
LOCF: For a missing value at week 52 the last available post-baseline value before week 52 is imputed.

Table R.1.2.9.15: 3 Responder analysis (displaying odds ratio) in KCCQ-OSS change from baseline at week 52 of > -15 points (stability) by baseline LVEF (3 cat.) - RS (LOCF-AD) - 1245.121

Subgroup Description	Placebo	Empa 10mg
Baseline LVEF (3 cat.): <=30		
Number of patients in analysis set	1392	1337
Number of analysed patients, N (%)	1272 (100.0)	1245 (100.0)
Number of patients with endpoint, N (%)	1113 (87.5)	1123 (90.2)
95% confidence interval*	(85.6, 89.2)	(88.4, 91.7)
Comparison vs Placebo**		
Odds ratio (SE)		1.338 (0.173)
95% confidence interval***		(1.039, 1.724)
p-value		0.0241
Baseline LVEF (3 cat.): >30 to <=35		
Number of patients in analysis set	361	398
Number of analysed patients, N (%)	333 (100.0)	375 (100.0)
Number of patients with endpoint, N (%)	297 (89.2)	334 (89.1)
95% confidence interval*	(85.4, 92.1)	(85.5, 91.8)
Comparison vs Placebo**		
Odds ratio (SE)		0.969 (0.237)
95% confidence interval***		(0.599, 1.566)
p-value		0.8972

* Wilson confidence intervals.
** Logistic regression includes terms for baseline KCCQ - overall summary score (p<0.0001), age (p=0.3181), baseline eGFR (CKD-EPI) (p=0.0014), Treatment (p=0.2348), region (5 cat.) (p=0.0113), baseline diabetes status (3 cat.) (p=0.2765), sex (p=0.7857), baseline LVEF (3 cat.) (p=0.6980) and Treatment by baseline LVEF (3 cat.) interaction (p=0.4845).
***Wald confidence intervals.

Data taken from study 1245.121 only.
LOCF: For a missing value at week 52 the last available post-baseline value before week 52 is imputed.

Table R.1.2.9.15: 3 Responder analysis (displaying odds ratio) in KCCQ-OSS change from baseline at week 52 of > -15 points (stability) by baseline LVEF (3 cat.) - RS (LOCF-AD) - 1245.121

Subgroup Description	Placebo	Empa 10mg
Baseline LVEF (3 cat.): >35		
Number of patients in analysis set	114	128
Number of analysed patients, N (%)	104 (100.0)	120 (100.0)
Number of patients with endpoint, N (%)	91 (87.5)	109 (90.8)
95% confidence interval*	(79.8, 92.5)	(84.3, 94.8)
Comparison vs Placebo**		
Odds ratio (SE)		1.430 (0.629)
95% confidence interval***		(0.604, 3.384)
p-value		0.4163

* Wilson confidence intervals.
** Logistic regression includes terms for baseline KCCQ - overall summary score (p<0.0001), age (p=0.3181), baseline eGFR (CKD-EPI) (p=0.0014), Treatment (p=0.2348), region (5 cat.) (p=0.0113), baseline diabetes status (3 cat.) (p=0.2765), sex (p=0.7857), baseline LVEF (3 cat.) (p=0.6980) and Treatment by baseline LVEF (3 cat.) interaction (p=0.4845).
***Wald confidence intervals.

Data taken from study 1245.121 only.
LOCF: For a missing value at week 52 the last available post-baseline value before week 52 is imputed.

Table R.1.2.9.15: 4 Responder analysis (displaying risk ratio) in KCCQ-OSS change from baseline at week 52 of > -15 points (stability) by baseline LVEF (3 cat.) - RS (LOCF-AD) - 1245.121

Subgroup Description	Placebo	Empa 10mg
Baseline LVEF (3 cat.): <=30		
Number of patients in analysis set	1392	1337
Number of analysed patients, N (%)	1272 (100.0)	1245 (100.0)
Number of patients with endpoint, N (%)	1113 (87.5)	1123 (90.2)
95% confidence interval*	(85.6, 89.2)	(88.4, 91.7)
Comparison vs Placebo**		
Risk ratio (SE)		1.032 (0.014)
95% confidence interval***		(1.004, 1.061)
p-value		0.0241
Baseline LVEF (3 cat.): >30 to <=35		
Number of patients in analysis set	361	398
Number of analysed patients, N (%)	333 (100.0)	375 (100.0)
Number of patients with endpoint, N (%)	297 (89.2)	334 (89.1)
95% confidence interval*	(85.4, 92.1)	(85.5, 91.8)
Comparison vs Placebo**		
Risk ratio (SE)		0.996 (0.026)
95% confidence interval***		(0.946, 1.048)
p-value		0.8796

* Wilson confidence intervals.
** Log-linked Poisson model with robust estimate of variance includes terms for baseline KCCQ - overall summary score (p<0.0001), age (p=0.4324), baseline eGFR (CKD-EPI) (p=0.0022), Treatment (p=0.2644), region (5 cat.) (p<0.0001), baseline diabetes status (3 cat.) (p=0.2534), sex (p=0.7855), baseline LVEF (3 cat.) (p=0.6815) and Treatment by baseline LVEF (3 cat.) interaction (p=0.4762).
***Wald confidence intervals.

Data taken from study 1245.121 only.
LOCF: For a missing value at week 52 the last available post-baseline value before week 52 is imputed.

Table R.1.2.9.15: 4 Responder analysis (displaying risk ratio) in KCCQ-OSS change from baseline at week 52 of > -15 points (stability) by baseline LVEF (3 cat.) - RS (LOCF-AD) - 1245.121

Subgroup Description	Placebo	Empa 10mg
Baseline LVEF (3 cat.): >35		
Number of patients in analysis set	114	128
Number of analysed patients, N (%)	104 (100.0)	120 (100.0)
Number of patients with endpoint, N (%)	91 (87.5)	109 (90.8)
95% confidence interval*	(79.8, 92.5)	(84.3, 94.8)
Comparison vs Placebo**		
Risk ratio (SE)		1.035 (0.048)
95% confidence interval***		(0.944, 1.133)
p-value		0.4654

* Wilson confidence intervals.
** Log-linked Poisson model with robust estimate of variance includes terms for baseline KCCQ - overall summary score (p<0.0001), age (p=0.4324), baseline eGFR (CKD-EPI) (p=0.0022), Treatment (p=0.2644), region (5 cat.) (p<0.0001), baseline diabetes status (3 cat.) (p=0.2534), sex (p=0.7855), baseline LVEF (3 cat.) (p=0.6815) and Treatment by baseline LVEF (3 cat.) interaction (p=0.4762).
***Wald confidence intervals.

Data taken from study 1245.121 only.
LOCF: For a missing value at week 52 the last available post-baseline value before week 52 is imputed.

Table R.1.2.9.15: 5 Responder analysis (displaying odds ratio) in KCCQ-OSS change from baseline at week 52 of >= 15 points (improvement) by baseline LVEF (3 cat.) - RS (LOCF-AD) - 1245.121

Subgroup Description	Placebo	Empa 10mg
Baseline LVEF (3 cat.): <=30		
Number of patients in analysis set	1392	1337
Number of analysed patients, N (%)	1272 (100.0)	1245 (100.0)
Number of patients with endpoint, N (%)	309 (24.3)	323 (25.9)
95% confidence interval*	(22.0, 26.7)	(23.6, 28.4)
Comparison vs Placebo**		
Odds ratio (SE)		1.118 (0.116)
95% confidence interval***		(0.911, 1.371)
p-value		0.2858
Baseline LVEF (3 cat.): >30 to <=35		
Number of patients in analysis set	361	398
Number of analysed patients, N (%)	333 (100.0)	375 (100.0)
Number of patients with endpoint, N (%)	73 (21.9)	92 (24.5)
95% confidence interval*	(17.8, 26.7)	(20.5, 29.1)
Comparison vs Placebo**		
Odds ratio (SE)		1.148 (0.232)
95% confidence interval***		(0.772, 1.706)
p-value		0.4951

* Wilson confidence intervals.
** Logistic regression includes terms for baseline KCCQ - overall summary score (p<0.0001), age (p=0.9784), baseline eGFR (CKD-EPI) (p=0.0026), Treatment (p=0.1650), region (5 cat.) (p<0.0001), baseline diabetes status (3 cat.) (p=0.4600), sex (p=0.3399), baseline LVEF (3 cat.) (p=0.6231) and Treatment by baseline LVEF (3 cat.) interaction (p=0.8173).
***Wald confidence intervals.

Data taken from study 1245.121 only.
LOCF: For a missing value at week 52 the last available post-baseline value before week 52 is imputed.

Table R.1.2.9.15: 5 Responder analysis (displaying odds ratio) in KCCQ-OSS change from baseline at week 52 of >= 15 points (improvement) by baseline LVEF (3 cat.) - RS (LOCF-AD) - 1245.121

Subgroup Description	Placebo	Empa 10mg
Baseline LVEF (3 cat.): >35		
Number of patients in analysis set	114	128
Number of analysed patients, N (%)	104 (100.0)	120 (100.0)
Number of patients with endpoint, N (%)	20 (19.2)	30 (25.0)
95% confidence interval*	(12.8, 27.8)	(18.1, 33.4)
Comparison vs Placebo**		
Odds ratio (SE)		1.427 (0.531)
95% confidence interval***		(0.689, 2.958)
p-value		0.3385

* Wilson confidence intervals.
** Logistic regression includes terms for baseline KCCQ - overall summary score (p<0.0001), age (p=0.9784), baseline eGFR (CKD-EPI) (p=0.0026), Treatment (p=0.1650), region (5 cat.) (p<0.0001), baseline diabetes status (3 cat.) (p=0.4600), sex (p=0.3399), baseline LVEF (3 cat.) (p=0.6231) and Treatment by baseline LVEF (3 cat.) interaction (p=0.8173).
***Wald confidence intervals.

Data taken from study 1245.121 only.
LOCF: For a missing value at week 52 the last available post-baseline value before week 52 is imputed.

Table R.1.2.9.15: 6 Responder analysis (displaying risk ratio) in KCCQ-OSS change from baseline at week 52 of >= 15 points (improvement) by baseline LVEF (3 cat.) - RS (LOCF-AD) - 1245.121

Subgroup Description	Placebo	Empa 10mg
Baseline LVEF (3 cat.): <=30		
Number of patients in analysis set	1392	1337
Number of analysed patients, N (%)	1272 (100.0)	1245 (100.0)
Number of patients with endpoint, N (%)	309 (24.3)	323 (25.9)
95% confidence interval*	(22.0, 26.7)	(23.6, 28.4)
Comparison vs Placebo**		
Risk ratio (SE)		1.061 (0.068)
95% confidence interval***		(0.935, 1.204)
p-value		0.3612
Baseline LVEF (3 cat.): >30 to <=35		
Number of patients in analysis set	361	398
Number of analysed patients, N (%)	333 (100.0)	375 (100.0)
Number of patients with endpoint, N (%)	73 (21.9)	92 (24.5)
95% confidence interval*	(17.8, 26.7)	(20.5, 29.1)
Comparison vs Placebo**		
Risk ratio (SE)		1.044 (0.129)
95% confidence interval***		(0.819, 1.330)
p-value		0.7283

* Wilson confidence intervals.
** Log-linked Poisson model with robust estimate of variance includes terms for baseline KCCQ - overall summary score (p<0.0001), age (p=0.8903), baseline eGFR (CKD-EPI) (p=0.0029), Treatment (p=0.3194), region (5 cat.) (p<0.0001), baseline diabetes status (3 cat.) (p=0.4618), sex (p=0.3126), baseline LVEF (3 cat.) (p=0.5053) and Treatment by baseline LVEF (3 cat.) interaction (p=0.8885).
***Wald confidence intervals.

Data taken from study 1245.121 only.
LOCF: For a missing value at week 52 the last available post-baseline value before week 52 is imputed.

Table R.1.2.9.15: 6 Responder analysis (displaying risk ratio) in KCCQ-OSS change from baseline at week 52 of >= 15 points (improvement) by baseline LVEF (3 cat.) - RS (LOCF-AD) - 1245.121

Subgroup Description	Placebo	Empa 10mg
Baseline LVEF (3 cat.): >35		
Number of patients in analysis set	114	128
Number of analysed patients, N (%)	104 (100.0)	120 (100.0)
Number of patients with endpoint, N (%)	20 (19.2)	30 (25.0)
95% confidence interval*	(12.8, 27.8)	(18.1, 33.4)
Comparison vs Placebo**		
Risk ratio (SE)		1.183 (0.274)
95% confidence interval***		(0.751, 1.864)
p-value		0.4682

* Wilson confidence intervals.
** Log-linked Poisson model with robust estimate of variance includes terms for baseline KCCQ - overall summary score (p<0.0001), age (p=0.8903), baseline eGFR (CKD-EPI) (p=0.0029), Treatment (p=0.3194), region (5 cat.) (p<0.0001), baseline diabetes status (3 cat.) (p=0.4618), sex (p=0.3126), baseline LVEF (3 cat.) (p=0.5053) and Treatment by baseline LVEF (3 cat.) interaction (p=0.8885).
***Wald confidence intervals.

Data taken from study 1245.121 only.
LOCF: For a missing value at week 52 the last available post-baseline value before week 52 is imputed.

R.1.2.9.16 Subgroup analysis by bl. NTproBNP </>= median (median based on total patients)

Table R.1.2.9.16: 1 Responder analysis (displaying odds ratio) in KCCQ-OSS change from baseline at week 52 of <= -15 points (deterioration) by bl. NTproBNP (<median, >= median) (median based on total patients) - RS (LOCF-AD) - 1245.121

Subgroup Description	Placebo	Empa 10mg
Baseline NTproBNP (<median, >= median): < median		
Number of patients in analysis set	920	942
Number of analysed patients, N (%)	866 (100.0)	886 (100.0)
Number of patients with endpoint, N (%)	86 (9.9)	78 (8.8)
95% confidence interval*	(8.1, 12.1)	(7.1, 10.9)
Comparison vs Placebo**		
Odds ratio (SE)		0.866 (0.144)
95% confidence interval***		(0.625, 1.199)
p-value		0.3858
Baseline NTproBNP (<median, >= median): >= median		
Number of patients in analysis set	946	920
Number of analysed patients, N (%)	843 (100.0)	854 (100.0)
Number of patients with endpoint, N (%)	122 (14.5)	96 (11.2)
95% confidence interval*	(12.3, 17.0)	(9.3, 13.5)
Comparison vs Placebo**		
Odds ratio (SE)		0.745 (0.110)
95% confidence interval***		(0.557, 0.996)
p-value		0.0472

* Wilson confidence intervals.
** Logistic regression includes terms for baseline KCCQ - overall summary score (p<0.0001), age (p=0.3935), baseline eGFR (CKD-EPI) (p=0.0115), Treatment (p=0.0490), region (5 cat.) (p=0.0066), baseline diabetes status (3 cat.) (p=0.3009), sex (p=0.8058), baseline LVEF (3 cat.) (p=0.5616), baseline NTproBNP (<median, >= median) (p=0.0011) and Treatment by baseline NTproBNP (<median, >= median) interaction (p=0.4998).
***Wald confidence intervals.
2 patients were excluded as the subgroup variable was missing.

Data taken from study 1245.121 only.
LOCF: For a missing value at week 52 the last available post-baseline value before week 52 is imputed.
Median: 1910 [pg/mL]

Table R.1.2.9.16: 2 Responder analysis (displaying risk ratio) in KCCQ-OSS change from baseline at week 52 of <= -15 points (deterioration) by bl. NTproBNP (<median, >= median) (median based on total patients) - RS (LOCF-AD) - 1245.121

Subgroup Description	Placebo	Empa 10mg
Baseline NTproBNP (<median, >= median): < median		
Number of patients in analysis set	920	942
Number of analysed patients, N (%)	866 (100.0)	886 (100.0)
Number of patients with endpoint, N (%)	86 (9.9)	78 (8.8)
95% confidence interval*	(8.1, 12.1)	(7.1, 10.9)
Comparison vs Placebo**		
Risk ratio (SE)		0.880 (0.130)
95% confidence interval***		(0.660, 1.175)
p-value		0.3867
Baseline NTproBNP (<median, >= median): >= median		
Number of patients in analysis set	946	920
Number of analysed patients, N (%)	843 (100.0)	854 (100.0)
Number of patients with endpoint, N (%)	122 (14.5)	96 (11.2)
95% confidence interval*	(12.3, 17.0)	(9.3, 13.5)
Comparison vs Placebo**		
Risk ratio (SE)		0.779 (0.099)
95% confidence interval***		(0.608, 0.998)
p-value		0.0483

* Wilson confidence intervals.
** Log-linked Poisson model with robust estimate of variance includes terms for baseline KCCQ - overall summary score (p<0.0001), age (p=0.4205), baseline eGFR (CKD-EPI) (p=0.0130), Treatment (p=0.0514), region (5 cat.) (p=0.0087), baseline diabetes status (3 cat.) (p=0.3152), sex (p=0.8086), baseline LVEF (3 cat.) (p=0.5588), baseline NTproBNP (<median, >= median) (p=0.0011) and Treatment by baseline NTproBNP (<median, >= median) interaction (p=0.5287).
***Wald confidence intervals.
2 patients were excluded as the subgroup variable was missing.

Data taken from study 1245.121 only.
LOCF: For a missing value at week 52 the last available post-baseline value before week 52 is imputed.
Median: 1910 [pg/mL]

Table R.1.2.9.16: 3 Responder analysis (displaying odds ratio) in KCCQ-OSS change from baseline at week 52 of > -15 points (stability) by bl. NTproBNP (<median, >= median) (median based on total patients) - RS (LOCF-AD) - 1245.121

Subgroup Description	Placebo	Empa 10mg
Baseline NTproBNP (<median, >= median): < median		
Number of patients in analysis set	920	942
Number of analysed patients, N (%)	866 (100.0)	886 (100.0)
Number of patients with endpoint, N (%)	780 (90.1)	808 (91.2)
95% confidence interval*	(87.9, 91.9)	(89.1, 92.9)
Comparison vs Placebo**		
Odds ratio (SE)		1.155 (0.192)
95% confidence interval***		(0.834, 1.599)
p-value		0.3858
Baseline NTproBNP (<median, >= median): >= median		
Number of patients in analysis set	946	920
Number of analysed patients, N (%)	843 (100.0)	854 (100.0)
Number of patients with endpoint, N (%)	721 (85.5)	758 (88.8)
95% confidence interval*	(83.0, 87.7)	(86.5, 90.7)
Comparison vs Placebo**		
Odds ratio (SE)		1.342 (0.199)
95% confidence interval***		(1.004, 1.795)
p-value		0.0472

* Wilson confidence intervals.
** Logistic regression includes terms for baseline KCCQ - overall summary score (p<0.0001), age (p=0.3935), baseline eGFR (CKD-EPI) (p=0.0115), Treatment (p=0.0490), region (5 cat.) (p=0.0066), baseline diabetes status (3 cat.) (p=0.3009), sex (p=0.8058), baseline LVEF (3 cat.) (p=0.5616), baseline NTproBNP (<median, >= median) (p=0.0011) and Treatment by baseline NTproBNP (<median, >= median) interaction (p=0.4998).
***Wald confidence intervals.
2 patients were excluded as the subgroup variable was missing.

Data taken from study 1245.121 only.
LOCF: For a missing value at week 52 the last available post-baseline value before week 52 is imputed.
Median: 1910 [pg/mL]

Table R.1.2.9.16: 4 Responder analysis (displaying risk ratio) in KCCQ-OSS change from baseline at week 52 of > -15 points (stability) by bl. NTproBNP (<median, >= median) (median based on total patients) - RS (LOCF-AD) - 1245.121

Subgroup Description	Placebo	Empa 10mg
Baseline NTproBNP (<median, >= median): < median		
Number of patients in analysis set	920	942
Number of analysed patients, N (%)	866 (100.0)	886 (100.0)
Number of patients with endpoint, N (%)	780 (90.1)	808 (91.2)
95% confidence interval*	(87.9, 91.9)	(89.1, 92.9)
Comparison vs Placebo**		
Risk ratio (SE)		1.013 (0.015)
95% confidence interval***		(0.984, 1.044)
p-value		0.3857
Baseline NTproBNP (<median, >= median): >= median		
Number of patients in analysis set	946	920
Number of analysed patients, N (%)	843 (100.0)	854 (100.0)
Number of patients with endpoint, N (%)	721 (85.5)	758 (88.8)
95% confidence interval*	(83.0, 87.7)	(86.5, 90.7)
Comparison vs Placebo**		
Risk ratio (SE)		1.036 (0.019)
95% confidence interval***		(1.000, 1.075)
p-value		0.0529

* Wilson confidence intervals.
** Log-linked Poisson model with robust estimate of variance includes terms for baseline KCCQ - overall summary score (p<0.0001), age (p=0.5087), baseline eGFR (CKD-EPI) (p=0.0158), Treatment (p=0.0406), region (5 cat.) (p<0.0001), baseline diabetes status (3 cat.) (p=0.2636), sex (p=0.8196), baseline LVEF (3 cat.) (p=0.5834), baseline NTproBNP (<median, >= median) (p=0.0006) and Treatment by baseline NTproBNP (<median, >= median) interaction (p=0.3455).
***Wald confidence intervals.
2 patients were excluded as the subgroup variable was missing.

Data taken from study 1245.121 only.
LOCF: For a missing value at week 52 the last available post-baseline value before week 52 is imputed.
Median: 1910 [pg/mL]

Table R.1.2.9.16: 5 Responder analysis (displaying odds ratio) in KCCQ-OSS change from baseline at week 52 of >= 15 points (improvement) by bl. NTproBNP (<median, >= median) (median based on total patients) - RS (LOCF-AD) - 1245.121

Subgroup Description	Placebo	Empa 10mg
Baseline NTproBNP (<median, >= median): < median		
Number of patients in analysis set	920	942
Number of analysed patients, N (%)	866 (100.0)	886 (100.0)
Number of patients with endpoint, N (%)	196 (22.6)	215 (24.3)
95% confidence interval*	(20.0, 25.5)	(21.6, 27.2)
Comparison vs Placebo**		
Odds ratio (SE)		1.159 (0.147)
95% confidence interval***		(0.904, 1.487)
p-value		0.2439
Baseline NTproBNP (<median, >= median): >= median		
Number of patients in analysis set	946	920
Number of analysed patients, N (%)	843 (100.0)	854 (100.0)
Number of patients with endpoint, N (%)	206 (24.4)	230 (26.9)
95% confidence interval*	(21.7, 27.4)	(24.1, 30.0)
Comparison vs Placebo**		
Odds ratio (SE)		1.120 (0.142)
95% confidence interval***		(0.873, 1.437)
p-value		0.3727

* Wilson confidence intervals.
** Logistic regression includes terms for baseline KCCQ - overall summary score (p<0.0001), age (p=0.9892), baseline eGFR (CKD-EPI) (p=0.0054), Treatment (p=0.1458), region (5 cat.) (p<0.0001), baseline diabetes status (3 cat.) (p=0.4521), sex (p=0.3634), baseline LVEF (3 cat.) (p=0.7103), baseline NTproBNP (<median, >= median) (p=0.3014) and Treatment by baseline NTproBNP (<median, >= median) interaction (p=0.8475).
***Wald confidence intervals.
2 patients were excluded as the subgroup variable was missing.

Data taken from study 1245.121 only.
LOCF: For a missing value at week 52 the last available post-baseline value before week 52 is imputed.
Median: 1910 [pg/mL]

Table R.1.2.9.16: 6 Responder analysis (displaying risk ratio) in KCCQ-OSS change from baseline at week 52 of >= 15 points (improvement) by bl. NTproBNP (<median, >= median) (median based on total patients) - RS (LOCF-AD) - 1245.121

Subgroup Description	Placebo	Empa 10mg
Baseline NTproBNP (<median, >= median): < median		
Number of patients in analysis set	920	942
Number of analysed patients, N (%)	866 (100.0)	886 (100.0)
Number of patients with endpoint, N (%)	196 (22.6)	215 (24.3)
95% confidence interval*	(20.0, 25.5)	(21.6, 27.2)
Comparison vs Placebo**		
Risk ratio (SE)		1.062 (0.086)
95% confidence interval***		(0.907, 1.244)
p-value		0.4543
Baseline NTproBNP (<median, >= median): >= median		
Number of patients in analysis set	946	920
Number of analysed patients, N (%)	843 (100.0)	854 (100.0)
Number of patients with endpoint, N (%)	206 (24.4)	230 (26.9)
95% confidence interval*	(21.7, 27.4)	(24.1, 30.0)
Comparison vs Placebo**		
Risk ratio (SE)		1.064 (0.082)
95% confidence interval***		(0.916, 1.237)
p-value		0.4159

* Wilson confidence intervals.
** Log-linked Poisson model with robust estimate of variance includes terms for baseline KCCQ - overall summary score (p<0.0001), age (p=0.8492), baseline eGFR (CKD-EPI) (p=0.0058), Treatment (p=0.2707), region (5 cat.) (p<0.0001), baseline diabetes status (3 cat.) (p=0.4551), sex (p=0.3503), baseline LVEF (3 cat.) (p=0.6038), baseline NTproBNP (<median, >= median) (p=0.2510) and Treatment by baseline NTproBNP (<median, >= median) interaction (p=0.9844).
***Wald confidence intervals.
2 patients were excluded as the subgroup variable was missing.

Data taken from study 1245.121 only.
LOCF: For a missing value at week 52 the last available post-baseline value before week 52 is imputed.
Median: 1910 [pg/mL]

R.1.3

R.1.3.1

R.1.3.1.1

Table R.1.3.1.1: 1 EQ-VAS change from baseline MMRM results over time - RS (OC-AD - no imputation for deaths) - 1245.121

Visit Description Statistic	Placebo	Empa 10mg
Number of patients in analysis set	1867	1863
Number of analysed patients	1754	1771
Baseline mean (SE)	68.10 (0.43)	67.89 (0.44)
Week 12		
Values at visit		
Number of analysed patients	1729	1749
Mean (SE)	70.80 (0.43)	72.01 (0.43)
Adjusted* mean (SE)	70.71 (0.36)	71.94 (0.36)
95% confidence interval	(70.00,71.42)	(71.23,72.65)
Change from baseline		
Mean (SE)	2.64 (0.43)	4.01 (0.41)
Adjusted* mean (SE)	2.58 (0.36)	3.81 (0.36)
95% confidence interval	(1.87, 3.29)	(3.11, 4.52)
Comparison vs Placebo		
Adjusted* mean (SE)		1.23 (0.51)
95% confidence interval		(0.23, 2.23)
p-value		0.0159
Hedges g		
Estimate		0.08
95% confidence interval		(0.02, 0.15)

* Model includes Age (p=0.1865), baseline eGFR (CKD-EPI) (p=0.0160) as linear covariate(s) and region (p<0.0001), baseline diabetes status (p=0.6743), sex (p=0.0846), baseline LVEF (p=0.2179), week reachable (p=0.1370), Treatment by Visit interaction (p<0.0001), baseline EQ-VAS score by Visit interaction (p<0.0001) as fixed effect(s).
The following covariance structure has been used to fit the mixed model: Unstructured

For patients who died, only observed values are considered (no imputation after date of death).
Data taken from study 1245.121 only.

Table R.1.3.1.1: 1 EQ-VAS change from baseline MMRM results over time - RS (OC-AD - no imputation for deaths) - 1245.121

Visit Description Statistic	Placebo	Empa 10mg
Week 32		
Values at visit		
Number of analysed patients	1567	1611
Mean (SE)	71.11 (0.45)	72.61 (0.44)
Adjusted* mean (SE)	71.06 (0.39)	72.42 (0.38)
95% confidence interval	(70.30,71.82)	(71.67,73.18)
Change from baseline		
Mean (SE)	3.07 (0.47)	4.50 (0.47)
Adjusted* mean (SE)	2.94 (0.39)	4.30 (0.38)
95% confidence interval	(2.18, 3.70)	(3.55, 5.05)
Comparison vs Placebo		
Adjusted* mean (SE)		1.36 (0.54)
95% confidence interval		(0.29, 2.43)
p-value		0.0125
Hedges g		
Estimate		0.09
95% confidence interval		(0.02, 0.16)

* Model includes Age (p=0.1865), baseline eGFR (CKD-EPI) (p=0.0160) as linear covariate(s) and region (p<0.0001), baseline diabetes status (p=0.6743), sex (p=0.0846), baseline LVEF (p=0.2179), week reachable (p=0.1370), Treatment by Visit interaction (p<0.0001), baseline EQ-VAS score by Visit interaction (p<0.0001) as fixed effect(s).
The following covariance structure has been used to fit the mixed model: Unstructured

For patients who died, only observed values are considered (no imputation after date of death).
Data taken from study 1245.121 only.

Table R.1.3.1.1: 1 EQ-VAS change from baseline MMRM results over time - RS (OC-AD - no imputation for deaths) - 1245.121

Visit Description Statistic	Placebo	Empa 10mg
Week 52		
Values at visit		
Number of analysed patients	1221	1232
Mean (SE)	71.61 (0.52)	73.39 (0.51)
Adjusted* mean (SE)	71.60 (0.43)	73.21 (0.43)
95% confidence interval	(70.76,72.45)	(72.37,74.05)
Change from baseline		
Mean (SE)	3.37 (0.54)	5.12 (0.54)
Adjusted* mean (SE)	3.48 (0.43)	5.09 (0.43)
95% confidence interval	(2.63, 4.32)	(4.25, 5.93)
Comparison vs Placebo		
Adjusted* mean (SE)		1.61 (0.61)
95% confidence interval		(0.42, 2.81)
p-value		0.0081
Hedges g		
Estimate		0.10
95% confidence interval		(0.03, 0.18)

* Model includes Age (p=0.1865), baseline eGFR (CKD-EPI) (p=0.0160) as linear covariate(s) and region (p<0.0001), baseline diabetes status (p=0.6743), sex (p=0.0846), baseline LVEF (p=0.2179), week reachable (p=0.1370), Treatment by Visit interaction (p<0.0001), baseline EQ-VAS score by Visit interaction (p<0.0001) as fixed effect(s).
The following covariance structure has been used to fit the mixed model: Unstructured

For patients who died, only observed values are considered (no imputation after date of death).
Data taken from study 1245.121 only.

Figure R.1.3.1.1: 1

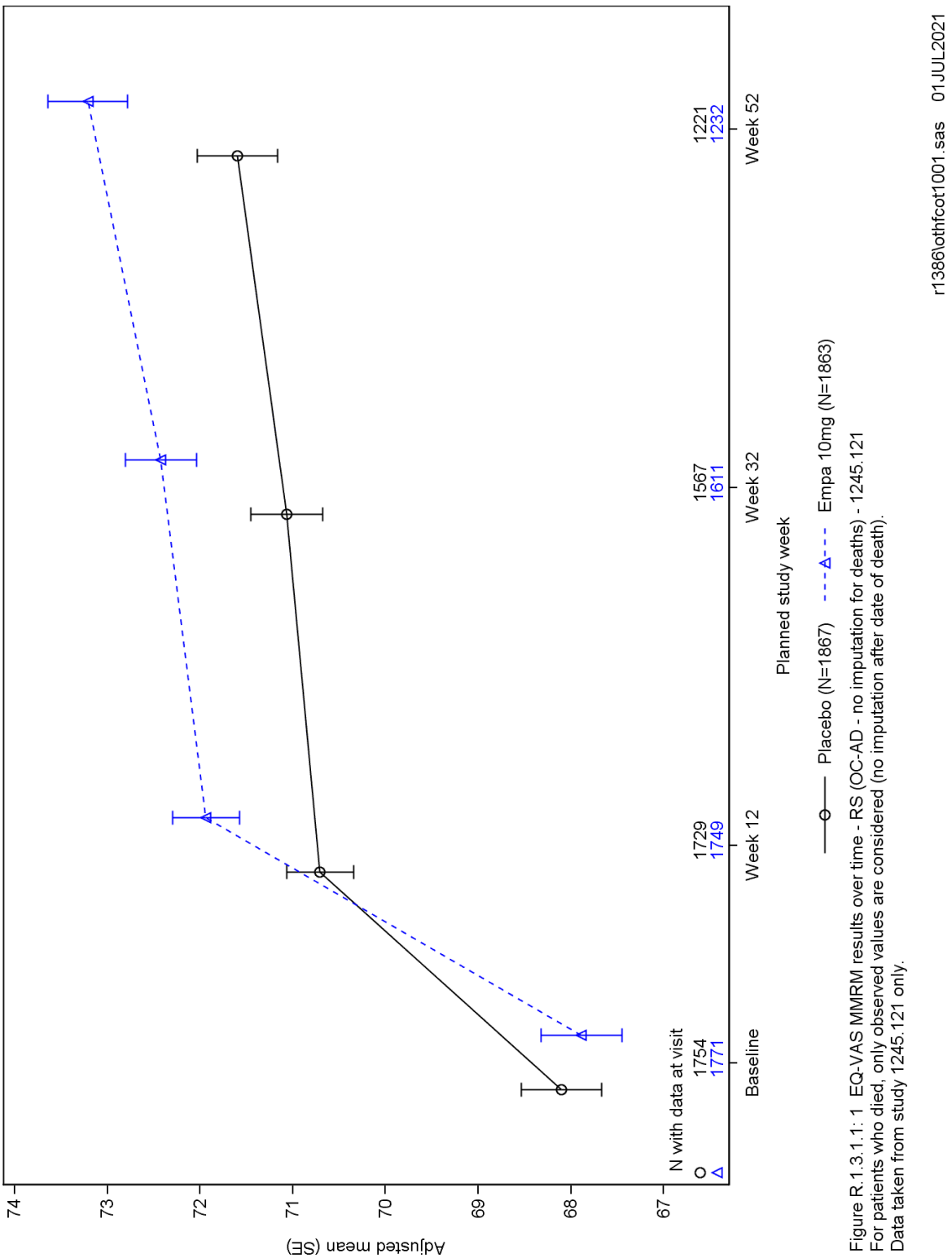

Figure R.1.3.1.1: 1 EQ-VAS MMRM results over time - RS (OC-AD - no imputation for deaths) - 1245.121
For patients who died, only observed values are considered (no imputation after date of death).
Data taken from study 1245.121 only.

R.1.3.1.2

R.1.3.1.2 Subgroup analysis by sex

Table R.1.3.1.2: 1 EQ-VAS change from baseline at week 52 (MMRM) by sex - RS (OC-AD - no imputation for deaths) - 1245.121

Subgroup / Visit / Description / Statistic	Placebo	Empa 10mg
Sex: Male		
Number of patients in analysis set	1411	1426
Number of analysed patients	1333	1359
Baseline mean (SE)	68.36 (0.49)	68.22 (0.49)
Week 52		
Values at visit		
Number of analysed patients	942	951
Mean (SE)	71.68 (0.59)	73.54 (0.57)
Adjusted* mean (SE)	71.69 (0.49)	73.48 (0.49)
95% confidence interval	(70.72,72.65)	(72.52,74.44)
Change from baseline		
Mean (SE)	3.27 (0.60)	4.88 (0.58)
Adjusted* mean (SE)	3.40 (0.49)	5.19 (0.49)
95% confidence interval	(2.44, 4.37)	(4.23, 6.15)
Comparison vs Placebo		
Adjusted* mean (SE)		1.79 (0.69)
95% confidence interval		(0.43, 3.15)
p-value		0.0100

* Model includes Age, baseline eGFR (CKD-EPI) as linear covariate(s) and region, baseline diabetes status, baseline LVEF, week reachable, Visit by Treatment by sex interaction, baseline EQ-VAS score by Visit interaction as fixed effect(s).
The Visit by Treatment by sex p-value at Week 52 is 0.5935.
The following covariance structure has been used to fit the mixed model: Unstructured
Note: All covariate effects are set equal to their mean values within subgroup for the calculation of adjusted means.

For patients who died, only observed values are considered (no imputation after date of death).
Data taken from study 1245.121 only.
The MMRM includes all outcome values (change from baseline) at the planned Visits week 12, week 32 and week 52

Table R.1.3.1.2: 1 EQ-VAS change from baseline at week 52 (MMRM) by sex - RS (OC-AD - no imputation for deaths) - 1245.121

Subgroup / Visit / Description / Statistic	Placebo	Empa 10mg
Sex: Female		
Number of patients in analysis set	456	437
Number of analysed patients	421	412
Baseline mean (SE)	67.30 (0.93)	66.79 (0.97)
Week 52		
Values at visit		
Number of analysed patients	279	281
Mean (SE)	71.38 (1.11)	72.88 (1.12)
Adjusted* mean (SE)	71.04 (0.90)	72.05 (0.90)
95% confidence interval	(69.27,72.80)	(70.29,73.81)
Change from baseline		
Mean (SE)	3.70 (1.20)	5.94 (1.34)
Adjusted* mean (SE)	3.99 (0.90)	5.00 (0.90)
95% confidence interval	(2.22, 5.75)	(3.24, 6.76)
Comparison vs Placebo		
Adjusted* mean (SE)		1.02 (1.27)
95% confidence interval		(-1.47, 3.50)
p-value		0.4238

* Model includes Age, baseline eGFR (CKD-EPI) as linear covariate(s) and region, baseline diabetes status, baseline LVEF, week reachable, Visit by Treatment by sex interaction, baseline EQ-VAS score by Visit interaction as fixed effect(s).
The Visit by Treatment by sex p-value at Week 52 is 0.5935.
The following covariance structure has been used to fit the mixed model: Unstructured
Note: All covariate effects are set equal to their mean values within subgroup for the calculation of adjusted means.

For patients who died, only observed values are considered (no imputation after date of death).
Data taken from study 1245.121 only.
The MMRM includes all outcome values (change from baseline) at the planned Visits week 12, week 32 and week 52

R.1.3.1.3

R.1.3.1.3 Subgroup analysis by age

Table R.1.3.1.3: 1 EQ-VAS change from baseline at week 52 (MMRM) by age (2 cat.) - RS (OC-AD - no imputation for deaths) - 1245.121

Subgroup / Visit / Description / Statistic	Placebo	Empa 10mg
Age [years] (2 cat.): < 65		
Number of patients in analysis set	740	675
Number of analysed patients	697	644
Baseline mean (SE)	67.87 (0.69)	66.33 (0.74)
Week 52		
Values at visit		
Number of analysed patients	496	451
Mean (SE)	72.68 (0.82)	73.61 (0.85)
Adjusted* mean (SE)	71.98 (0.68)	73.59 (0.71)
95% confidence interval	(70.64,73.32)	(72.20,74.99)
Change from baseline		
Mean (SE)	4.84 (0.80)	7.21 (0.89)
Adjusted* mean (SE)	4.85 (0.68)	6.46 (0.71)
95% confidence interval	(3.51, 6.19)	(5.07, 7.86)
Comparison vs Placebo		
Adjusted* mean (SE)		1.61 (0.98)
95% confidence interval		(-0.31, 3.54)
p-value		0.1006

* Model includes baseline eGFR (CKD-EPI) as linear covariate(s) and region, baseline diabetes status, sex, baseline LVEF, week reachable, Visit by Treatment by age [years] (2 cat.) interaction, baseline EQ-VAS score by Visit interaction as fixed effect(s).
The Visit by Treatment by age [years] (2 cat.) p-value at Week 52 is 0.9928.
The following covariance structure has been used to fit the mixed model: Unstructured
Note: All covariate effects are set equal to their mean values within subgroup for the calculation of adjusted means.

For patients who died, only observed values are considered (no imputation after date of death).
Data taken from study 1245.121 only.
The MMRM includes all outcome values (change from baseline) at the planned Visits week 12, week 32 and week 52

Table R.1.3.1.3: 1 EQ-VAS change from baseline at week 52 (MMRM) by age (2 cat.) - RS (OC-AD - no imputation for deaths) - 1245.121

Subgroup / Visit / Description / Statistic	Placebo	Empa 10mg
Age [years] (2 cat.): >= 65		
Number of patients in analysis set	1127	1188
Number of analysed patients	1057	1127
Baseline mean (SE)	68.25 (0.56)	68.78 (0.55)
Week 52		
Values at visit		
Number of analysed patients	725	781
Mean (SE)	70.88 (0.67)	73.26 (0.64)
Adjusted* mean (SE)	71.24 (0.56)	72.87 (0.54)
95% confidence interval	(70.14,72.34)	(71.81,73.93)
Change from baseline		
Mean (SE)	2.36 (0.72)	3.91 (0.68)
Adjusted* mean (SE)	2.71 (0.56)	4.34 (0.54)
95% confidence interval	(1.61, 3.81)	(3.28, 5.40)
Comparison vs Placebo		
Adjusted* mean (SE)		1.63 (0.78)
95% confidence interval		(0.10, 3.15)
p-value		0.0365

* Model includes baseline eGFR (CKD-EPI) as linear covariate(s) and region, baseline diabetes status, sex, baseline LVEF, week reachable, Visit by Treatment by age [years] (2 cat.) interaction, baseline EQ-VAS score by Visit interaction as fixed effect(s).
The Visit by Treatment by age [years] (2 cat.) p-value at Week 52 is 0.9928.
The following covariance structure has been used to fit the mixed model: Unstructured
Note: All covariate effects are set equal to their mean values within subgroup for the calculation of adjusted means.

For patients who died, only observed values are considered (no imputation after date of death).
Data taken from study 1245.121 only.
The MMRM includes all outcome values (change from baseline) at the planned Visits week 12, week 32 and week 52

R.1.3.1.4 Subgroup analysis by region (North America, Latin America, Europe, Asia, Other)

Table R.1.3.1.4: 1 EQ-VAS change from baseline at week 52 (MMRM) by region - RS (OC-AD - no imputation for deaths) - 1245.121

Subgroup / Visit / Description / Statistic	Placebo	Empa 10mg
Region (5 cat.): North America		
Number of patients in analysis set	213	212
Number of analysed patients	195	206
Baseline mean (SE)	72.55 (1.34)	71.36 (1.34)
Week 52		
Values at visit		
Number of analysed patients	129	152
Mean (SE)	75.53 (1.50)	77.72 (1.22)
Adjusted* mean (SE)	74.94 (1.32)	76.94 (1.23)
95% confidence interval	(72.35,77.53)	(74.52,79.35)
Change from baseline		
Mean (SE)	3.38 (1.38)	4.22 (1.52)
Adjusted* mean (SE)	3.00 (1.32)	5.00 (1.23)
95% confidence interval	(0.41, 5.59)	(2.58, 7.41)
Comparison vs Placebo		
Adjusted* mean (SE)		2.00 (1.81)
95% confidence interval		(-1.54, 5.54)
p-value		0.2685

* Model includes Age, baseline eGFR (CKD-EPI) as linear covariate(s) and baseline diabetes status, sex, baseline LVEF, week reachable, Visit by Treatment by region (5 cat.) interaction, baseline EQ-VAS score by Visit interaction as fixed effect(s).
The Visit by Treatment by region (5 cat.) p-value at Week 52 is 0.9926.
The following covariance structure has been used to fit the mixed model: Unstructured
Note: All covariate effects are set equal to their mean values within subgroup for the calculation of adjusted means.

For patients who died, only observed values are considered (no imputation after date of death).
Data taken from study 1245.121 only.
The MMRM includes all outcome values (change from baseline) at the planned Visits week 12, week 32 and week 52

Table R.1.3.1.4: 1 EQ-VAS change from baseline at week 52 (MMRM) by region - RS (OC-AD - no imputation for deaths) - 1245.121

Subgroup / Visit / Description / Statistic	Placebo	Empa 10mg
Region (5 cat.): Latin America		
Number of patients in analysis set	645	641
Number of analysed patients	599	601
Baseline mean (SE)	67.58 (0.78)	67.76 (0.77)
Week 52		
Values at visit		
Number of analysed patients	389	370
Mean (SE)	74.06 (0.94)	76.19 (0.90)
Adjusted* mean (SE)	74.62 (0.76)	76.16 (0.77)
95% confidence interval	(73.13,76.11)	(74.64,77.68)
Change from baseline		
Mean (SE)	7.21 (1.05)	8.87 (1.03)
Adjusted* mean (SE)	6.94 (0.76)	8.49 (0.77)
95% confidence interval	(5.45, 8.43)	(6.97,10.01)
Comparison vs Placebo		
Adjusted* mean (SE)		1.55 (1.08)
95% confidence interval		(-0.58, 3.67)
p-value		0.1538

* Model includes Age, baseline eGFR (CKD-EPI) as linear covariate(s) and baseline diabetes status, sex, baseline LVEF, week reachable, Visit by Treatment by region (5 cat.) interaction, baseline EQ-VAS score by Visit interaction as fixed effect(s).
The Visit by Treatment by region (5 cat.) p-value at Week 52 is 0.9926.
The following covariance structure has been used to fit the mixed model: Unstructured
Note: All covariate effects are set equal to their mean values within subgroup for the calculation of adjusted means.

For patients who died, only observed values are considered (no imputation after date of death).
Data taken from study 1245.121 only.
The MMRM includes all outcome values (change from baseline) at the planned Visits week 12, week 32 and week 52

Table R.1.3.1.4: 1 EQ-VAS change from baseline at week 52 (MMRM) by region - RS (OC-AD - no imputation for deaths) - 1245.121

Subgroup / Visit / Description / Statistic	Placebo	Empa 10mg
Region (5 cat.): Europe		
Number of patients in analysis set	677	676
Number of analysed patients	644	645
Baseline mean (SE)	65.04 (0.69)	66.05 (0.72)
Week 52		
Values at visit		
Number of analysed patients	470	465
Mean (SE)	66.62 (0.83)	68.47 (0.86)
Adjusted* mean (SE)	66.25 (0.70)	67.79 (0.70)
95% confidence interval	(64.88,67.62)	(66.41,69.16)
Change from baseline		
Mean (SE)	0.73 (0.83)	2.07 (0.83)
Adjusted* mean (SE)	0.71 (0.70)	2.24 (0.70)
95% confidence interval	(-0.66, 2.08)	(0.87, 3.62)
Comparison vs Placebo		
Adjusted* mean (SE)		1.53 (0.99)
95% confidence interval		(-0.40, 3.47)
p-value		0.1209

* Model includes Age, baseline eGFR (CKD-EPI) as linear covariate(s) and baseline diabetes status, sex, baseline LVEF, week reachable, Visit by Treatment by region (5 cat.) interaction, baseline EQ-VAS score by Visit interaction as fixed effect(s).
The Visit by Treatment by region (5 cat.) p-value at Week 52 is 0.9926.
The following covariance structure has been used to fit the mixed model: Unstructured
Note: All covariate effects are set equal to their mean values within subgroup for the calculation of adjusted means.

For patients who died, only observed values are considered (no imputation after date of death).
Data taken from study 1245.121 only.
The MMRM includes all outcome values (change from baseline) at the planned Visits week 12, week 32 and week 52

Table R.1.3.1.4: 1 EQ-VAS change from baseline at week 52 (MMRM) by region - RS (OC-AD - no imputation for deaths) - 1245.121

Subgroup / Visit / Description / Statistic	Placebo	Empa 10mg
Region (5 cat.): Asia		
Number of patients in analysis set	245	248
Number of analysed patients	238	243
Baseline mean (SE)	74.65 (1.00)	72.37 (1.09)
Week 52		
Values at visit		
Number of analysed patients	182	189
Mean (SE)	75.84 (1.26)	76.33 (1.34)
Adjusted* mean (SE)	75.46 (1.13)	76.61 (1.11)
95% confidence interval	(73.24,77.67)	(74.44,78.79)
Change from baseline		
Mean (SE)	0.88 (1.32)	3.38 (1.46)
Adjusted* mean (SE)	1.96 (1.13)	3.11 (1.11)
95% confidence interval	(-0.26, 4.17)	(0.94, 5.29)
Comparison vs Placebo		
Adjusted* mean (SE)		1.16 (1.58)
95% confidence interval		(-1.94, 4.26)
p-value		0.4645

* Model includes Age, baseline eGFR (CKD-EPI) as linear covariate(s) and baseline diabetes status, sex, baseline LVEF, week reachable, Visit by Treatment by region (5 cat.) interaction, baseline EQ-VAS score by Visit interaction as fixed effect(s).
The Visit by Treatment by region (5 cat.) p-value at Week 52 is 0.9926.
The following covariance structure has been used to fit the mixed model: Unstructured
Note: All covariate effects are set equal to their mean values within subgroup for the calculation of adjusted means.

For patients who died, only observed values are considered (no imputation after date of death).
Data taken from study 1245.121 only.
The MMRM includes all outcome values (change from baseline) at the planned Visits week 12, week 32 and week 52

Table R.1.3.1.4: 1 EQ-VAS change from baseline at week 52 (MMRM) by region - RS (OC-AD - no imputation for deaths) - 1245.121

Subgroup / Visit / Description / Statistic	Placebo	Empa 10mg
Region (5 cat.): Other		
Number of patients in analysis set	87	86
Number of analysed patients	78	76
Baseline mean (SE)	66.28 (1.84)	60.74 (1.91)
Week 52		
Values at visit		
Number of analysed patients	51	56
Mean (SE)	73.90 (1.97)	74.05 (1.45)
Adjusted* mean (SE)	72.61 (2.10)	75.22 (2.03)
95% confidence interval	(68.48,76.73)	(71.25,79.19)
Change from baseline		
Mean (SE)	7.29 (2.42)	13.96 (1.77)
Adjusted* mean (SE)	9.06 (2.10)	11.68 (2.03)
95% confidence interval	(4.94,13.19)	(7.70,15.65)
Comparison vs Placebo		
Adjusted* mean (SE)		2.61 (2.92)
95% confidence interval		(-3.11, 8.34)
p-value		0.3708

* Model includes Age, baseline eGFR (CKD-EPI) as linear covariate(s) and baseline diabetes status, sex, baseline LVEF, week reachable, Visit by Treatment by region (5 cat.) interaction, baseline EQ-VAS score by Visit interaction as fixed effect(s).
The Visit by Treatment by region (5 cat.) p-value at Week 52 is 0.9926.
The following covariance structure has been used to fit the mixed model: Unstructured
Note: All covariate effects are set equal to their mean values within subgroup for the calculation of adjusted means.

For patients who died, only observed values are considered (no imputation after date of death).
Data taken from study 1245.121 only.
The MMRM includes all outcome values (change from baseline) at the planned Visits week 12, week 32 and week 52

R.1.3.1.5

R.1.3.1.5 Subgroup analysis by OECD (N/Y)

Table R.1.3.1.5: 1 EQ-VAS change from baseline at week 52 (MMRM) by OECD member (N/Y) - RS (OC-AD - no imputation for deaths) - 1245.121

Subgroup / Visit / Description / Statistic	Placebo	Empa 10mg
OECD member: No		
Number of patients in analysis set	741	713
Number of analysed patients	687	663
Baseline mean (SE)	67.40 (0.71)	66.80 (0.72)
Week 52		
Values at visit		
Number of analysed patients	444	419
Mean (SE)	74.00 (0.86)	75.62 (0.80)
Adjusted* mean (SE)	74.36 (0.72)	76.08 (0.73)
95% confidence interval	(72.96,75.77)	(74.64,77.52)
Change from baseline		
Mean (SE)	7.18 (0.96)	9.57 (0.93)
Adjusted* mean (SE)	7.26 (0.72)	8.97 (0.73)
95% confidence interval	(5.85, 8.66)	(7.53,10.41)
Comparison vs Placebo		
Adjusted* mean (SE)		1.72 (1.03)
95% confidence interval		(-0.29, 3.73)
p-value		0.0943

* Model includes Age, baseline eGFR (CKD-EPI) as linear covariate(s) and baseline diabetes status, sex, baseline LVEF, week reachable, Visit by Treatment by OECD Member (N) interaction, baseline EQ-VAS score by Visit interaction as fixed effect(s).
The Visit by Treatment by OECD Member (N) p-value at Week 52 is 0.9973.
The following covariance structure has been used to fit the mixed model: Unstructured
Note: All covariate effects are set equal to their mean values within subgroup for the calculation of adjusted means.

For patients who died, only observed values are considered (no imputation after date of death).
Data taken from study 1245.121 only.
OECD member (yes/no) countries included:
Yes: United States, Canada, Mexico, Poland, Netherlands, Hungary, Germany, Czech Republic, Italy, France, Spain, United Kingdom, Belgium, Japan, Australia, 'Korea; Republic Of South Korea';
No: Brazil, Argentina, China, India.
The MMRM includes all outcome values (change from baseline) at the planned Visits week 12, week 32 and week 52

Table R.1.3.1.5: 1 EQ-VAS change from baseline at week 52 (MMRM) by OECD member (N/Y) - RS (OC-AD - no imputation for deaths) - 1245.121

Subgroup / Visit / Description / Statistic	Placebo	Empa 10mg
OECD member: Yes		
Number of patients in analysis set	1126	1150
Number of analysed patients	1067	1108
Baseline mean (SE)	68.56 (0.55)	68.54 (0.56)
Week 52		
Values at visit		
Number of analysed patients	777	813
Mean (SE)	70.24 (0.65)	72.24 (0.65)
Adjusted* mean (SE)	69.80 (0.55)	71.52 (0.54)
95% confidence interval	(68.73,70.88)	(70.47,72.58)
Change from baseline		
Mean (SE)	1.19 (0.63)	2.82 (0.66)
Adjusted* mean (SE)	1.26 (0.55)	2.98 (0.54)
95% confidence interval	(0.18, 2.33)	(1.93, 4.03)
Comparison vs Placebo		
Adjusted* mean (SE)		1.72 (0.77)
95% confidence interval		(0.22, 3.22)
p-value		0.0247

* Model includes Age, baseline eGFR (CKD-EPI) as linear covariate(s) and baseline diabetes status, sex, baseline LVEF, week reachable, Visit by Treatment by OECD Member (N) interaction, baseline EQ-VAS score by Visit interaction as fixed effect(s).
The Visit by Treatment by OECD Member (N) p-value at Week 52 is 0.9973.
The following covariance structure has been used to fit the mixed model: Unstructured
Note: All covariate effects are set equal to their mean values within subgroup for the calculation of adjusted means.

For patients who died, only observed values are considered (no imputation after date of death).
Data taken from study 1245.121 only.
OECD member (yes/no) countries included:
Yes: United States, Canada, Mexico, Poland, Netherlands, Hungary, Germany, Czech Republic, Italy, France, Spain, United Kingdom, Belgium, Japan, Australia, 'Korea; Republic Of South Korea';
No: Brazil, Argentina, China, India.
The MMRM includes all outcome values (change from baseline) at the planned Visits week 12, week 32 and week 52

R.1.3.1.6 Subgroup analysis by NYHA at baseline (II, III/IV - 2 cat.)

Table R.1.3.1.6: 1 EQ-VAS change from baseline at week 52 (MMRM) by NYHA (2 cat.) - RS (OC-AD - no imputation for deaths) - 1245.121

Subgroup / Visit / Description / Statistic	Placebo	Empa 10mg
Baseline NYHA (2 cat.): II		
Number of patients in analysis set	1401	1399
Number of analysed patients	1341	1330
Baseline mean (SE)	70.51 (0.47)	70.71 (0.47)
Week 52		
Values at visit		
Number of analysed patients	946	945
Mean (SE)	73.61 (0.56)	75.42 (0.56)
Adjusted* mean (SE)	73.57 (0.49)	75.12 (0.49)
95% confidence interval	(72.61,74.53)	(74.16,76.08)
Change from baseline		
Mean (SE)	2.95 (0.59)	4.66 (0.60)
Adjusted* mean (SE)	2.96 (0.49)	4.51 (0.49)
95% confidence interval	(2.00, 3.92)	(3.55, 5.47)
Comparison vs Placebo		
Adjusted* mean (SE)		1.55 (0.69)
95% confidence interval		(0.19, 2.90)
p-value		0.0252

* Model includes Age, baseline eGFR (CKD-EPI) as linear covariate(s) and region, baseline diabetes status, sex, baseline LVEF, week reachable, Visit by Treatment by baseline NYHA (2 cat.) interaction, baseline EQ-VAS score by Visit interaction as fixed effect(s).
The Visit by Treatment by baseline NYHA (2 cat.) p-value at Week 52 is 0.7561.
The following covariance structure has been used to fit the mixed model: Unstructured
Note: All covariate effects are set equal to their mean values within subgroup for the calculation of adjusted means.

For patients who died, only observed values are considered (no imputation after date of death).
Data taken from study 1245.121 only.
The MMRM includes all outcome values (change from baseline) at the planned Visits week 12, week 32 and week 52

Table R.1.3.1.6: 1 EQ-VAS change from baseline at week 52 (MMRM) by NYHA (2 cat.) - RS (OC-AD - no imputation for deaths) - 1245.121

Subgroup / Visit / Description / Statistic	Placebo	Empa 10mg
Baseline NYHA (2 cat.): III/IV		
Number of patients in analysis set	466	464
Number of analysed patients	413	441
Baseline mean (SE)	60.29 (0.93)	59.36 (0.93)
Week 52		
Values at visit		
Number of analysed patients	275	287
Mean (SE)	64.74 (1.20)	66.72 (1.08)
Adjusted* mean (SE)	64.95 (0.90)	66.94 (0.88)
95% confidence interval	(63.18,66.72)	(65.21,68.67)
Change from baseline		
Mean (SE)	4.80 (1.25)	6.61 (1.25)
Adjusted* mean (SE)	5.14 (0.90)	7.13 (0.88)
95% confidence interval	(3.37, 6.91)	(5.40, 8.86)
Comparison vs Placebo		
Adjusted* mean (SE)		2.00 (1.26)
95% confidence interval		(-0.48, 4.47)
p-value		0.1136

* Model includes Age, baseline eGFR (CKD-EPI) as linear covariate(s) and region, baseline diabetes status, sex, baseline LVEF, week reachable, Visit by Treatment by baseline NYHA (2 cat.) interaction, baseline EQ-VAS score by Visit interaction as fixed effect(s).
The Visit by Treatment by baseline NYHA (2 cat.) p-value at Week 52 is 0.7561.
The following covariance structure has been used to fit the mixed model: Unstructured
Note: All covariate effects are set equal to their mean values within subgroup for the calculation of adjusted means.

For patients who died, only observed values are considered (no imputation after date of death).
Data taken from study 1245.121 only.
The MMRM includes all outcome values (change from baseline) at the planned Visits week 12, week 32 and week 52

R.1.3.1.7

R.1.3.1.7 Subgroup analysis by diabetes at baseline

Table R.1.3.1.7: 1 EQ-VAS change from baseline at week 52 (MMRM) by diabetes at baseline - RS (OC-AD - no imputation for deaths) - 1245.121

Subgroup / Visit / Description / Statistic	Placebo	Empa 10mg
Diabetes at baseline (2 cat.):		
Diabetic		
Number of patients in analysis set	929	927
Number of analysed patients	868	879
Baseline mean (SE)	67.71 (0.63)	67.29 (0.63)
Week 52		
Values at visit		
Number of analysed patients	606	607
Mean (SE)	71.69 (0.73)	72.75 (0.76)
Adjusted* mean (SE)	71.34 (0.61)	72.67 (0.61)
95% confidence interval	(70.13,72.54)	(71.47,73.87)
Change from baseline		
Mean (SE)	3.25 (0.79)	5.12 (0.78)
Adjusted* mean (SE)	3.84 (0.61)	5.17 (0.61)
95% confidence interval	(2.64, 5.04)	(3.98, 6.37)
Comparison vs Placebo		
Adjusted* mean (SE)		1.33 (0.87)
95% confidence interval		(-0.36, 3.03)
p-value		0.1235

* Model includes Age, baseline eGFR (CKD-EPI) as linear covariate(s) and region, sex, baseline LVEF, week reachable, Visit by Treatment by diabetes at baseline (2 cat.) interaction, baseline EQ-VAS score by Visit interaction as fixed effect(s).
The Visit by Treatment by diabetes at baseline (2 cat.) p-value at Week 52 is 0.6441.
The following covariance structure has been used to fit the mixed model: Unstructured
Note: All covariate effects are set equal to their mean values within subgroup for the calculation of adjusted means.

For patients who died, only observed values are considered (no imputation after date of death).
Data taken from study 1245.121 only.
The MMRM includes all outcome values (change from baseline) at the planned Visits week 12, week 32 and week 52

Table R.1.3.1.7: 1 EQ-VAS change from baseline at week 52 (MMRM) by diabetes at baseline - RS (OC-AD - no imputation for deaths) - 1245.121

Subgroup / Visit / Description / Statistic	Placebo	Empa 10mg
Diabetes at baseline (2 cat.):		
Non-Diabetic		
Number of patients in analysis set	938	936
Number of analysed patients	886	892
Baseline mean (SE)	68.49 (0.59)	68.48 (0.61)
Week 52		
Values at visit		
Number of analysed patients	615	625
Mean (SE)	71.53 (0.75)	74.01 (0.69)
Adjusted* mean (SE)	71.72 (0.61)	73.61 (0.60)
95% confidence interval	(70.53,72.91)	(72.43,74.80)
Change from baseline		
Mean (SE)	3.49 (0.73)	5.12 (0.76)
Adjusted* mean (SE)	3.23 (0.61)	5.13 (0.60)
95% confidence interval	(2.04, 4.42)	(3.95, 6.31)
Comparison vs Placebo		
Adjusted* mean (SE)		1.90 (0.86)
95% confidence interval		(0.22, 3.57)
p-value		0.0269

* Model includes Age, baseline eGFR (CKD-EPI) as linear covariate(s) and region, sex, baseline LVEF, week reachable, Visit by Treatment by diabetes at baseline (2 cat.) interaction, baseline EQ-VAS score by Visit interaction as fixed effect(s).
The Visit by Treatment by diabetes at baseline (2 cat.) p-value at Week 52 is 0.6441.
The following covariance structure has been used to fit the mixed model: Unstructured
Note: All covariate effects are set equal to their mean values within subgroup for the calculation of adjusted means.

For patients who died, only observed values are considered (no imputation after date of death).
Data taken from study 1245.121 only.
The MMRM includes all outcome values (change from baseline) at the planned Visits week 12, week 32 and week 52

R.1.3.1.8 Subgroup analysis by BMI at baseline (<30, >=30)

Table R.1.3.1.8: 1 EQ-VAS change from baseline at week 52 (MMRM) by baseline BMI [kg/m2] - RS (OC-AD - no imputation for deaths) - 1245.121

Subgroup / Visit / Description / Statistic	Placebo	Empa 10mg
Baseline BMI [kg/m²] (2 cat.): <30		
Number of patients in analysis set	1300	1263
Number of analysed patients	1229	1199
Baseline mean (SE)	69.00 (0.52)	69.37 (0.52)
Week 52		
Values at visit		
Number of analysed patients	868	825
Mean (SE)	72.20 (0.61)	74.90 (0.61)
Adjusted* mean (SE)	72.22 (0.51)	74.27 (0.53)
95% confidence interval	(71.21,73.22)	(73.23,75.30)
Change from baseline		
Mean (SE)	3.17 (0.64)	4.70 (0.64)
Adjusted* mean (SE)	3.03 (0.51)	5.08 (0.53)
95% confidence interval	(2.03, 4.04)	(4.05, 6.11)
Comparison vs Placebo		
Adjusted* mean (SE)		2.05 (0.73)
95% confidence interval		(0.61, 3.48)
p-value		0.0052

* Model includes Age, baseline eGFR (CKD-EPI) as linear covariate(s) and region, baseline diabetes status, sex, baseline LVEF, week reachable, Visit by Treatment by baseline BMI [kg/m²] (2 cat.) interaction, baseline EQ-VAS score by Visit interaction as fixed effect(s).
The Visit by Treatment by baseline BMI [kg/m²] (2 cat.) p-value at Week 52 is 0.3404.
The following covariance structure has been used to fit the mixed model: Unstructured
Note: All covariate effects are set equal to their mean values within subgroup for the calculation of adjusted means.

For patients who died, only observed values are considered (no imputation after date of death).
Data taken from study 1245.121 only.
The MMRM includes all outcome values (change from baseline) at the planned Visits week 12, week 32 and week 52

Table R.1.3.1.8: 1 EQ-VAS change from baseline at week 52 (MMRM) by baseline BMI [kg/m2] - RS (OC-AD - no imputation for deaths) - 1245.121

Subgroup / Visit / Description / Statistic	Placebo	Empa 10mg
Baseline BMI [kg/m²] (2 cat.): >=30		
Number of patients in analysis set	567	600
Number of analysed patients	525	572
Baseline mean (SE)	65.99 (0.79)	64.78 (0.79)
Week 52		
Values at visit		
Number of analysed patients	353	407
Mean (SE)	70.16 (0.99)	70.33 (0.90)
Adjusted* mean (SE)	69.98 (0.80)	70.77 (0.75)
95% confidence interval	(68.40,71.56)	(69.29,72.25)
Change from baseline		
Mean (SE)	3.87 (0.98)	5.97 (1.00)
Adjusted* mean (SE)	4.62 (0.80)	5.41 (0.75)
95% confidence interval	(3.04, 6.20)	(3.93, 6.89)
Comparison vs Placebo		
Adjusted* mean (SE)		0.79 (1.10)
95% confidence interval		(-1.36, 2.94)
p-value		0.4704

* Model includes Age, baseline eGFR (CKD-EPI) as linear covariate(s) and region, baseline diabetes status, sex, baseline LVEF, week reachable, Visit by Treatment by baseline BMI [kg/m²] (2 cat.) interaction, baseline EQ-VAS score by Visit interaction as fixed effect(s).
The Visit by Treatment by baseline BMI [kg/m²] (2 cat.) p-value at Week 52 is 0.3404.
The following covariance structure has been used to fit the mixed model: Unstructured
Note: All covariate effects are set equal to their mean values within subgroup for the calculation of adjusted means.

For patients who died, only observed values are considered (no imputation after date of death).
Data taken from study 1245.121 only.
The MMRM includes all outcome values (change from baseline) at the planned Visits week 12, week 32 and week 52

R.1.3.1.9 Subgroup analysis by eGFR at baseline (<60, >=60)

Table R.1.3.1.9: 1 EQ-VAS change from baseline at week 52 (MMRM) by baseline eGFR (2 cat.) - RS (OC-AD - no imputation for deaths) - 1245.121

Subgroup / Visit / Description / Statistic	Placebo	Empa 10mg
Baseline eGFR (CKD-EPI) [mL/min/1.73m²] (2 cat.): >=60		
Number of patients in analysis set	960	969
Number of analysed patients	901	919
Baseline mean (SE)	68.34 (0.60)	68.24 (0.62)
Week 52		
Values at visit		
Number of analysed patients	648	649
Mean (SE)	72.28 (0.72)	74.83 (0.70)
Adjusted* mean (SE)	72.34 (0.60)	74.45 (0.59)
95% confidence interval	(71.17,73.50)	(73.29,75.61)
Change from baseline		
Mean (SE)	4.11 (0.71)	6.43 (0.74)
Adjusted* mean (SE)	4.05 (0.60)	6.16 (0.59)
95% confidence interval	(2.88, 5.21)	(5.00, 7.32)
Comparison vs Placebo		
Adjusted* mean (SE)		2.11 (0.84)
95% confidence interval		(0.47, 3.76)
p-value		0.0119

* Model includes Age as linear covariate(s) and region, baseline diabetes status, sex, baseline LVEF, week reachable, Visit by Treatment by baseline eGFR (CKD-EPI) [mL/min/1.73m²] (2 cat.) interaction, baseline EQ-VAS score by Visit interaction as fixed effect(s).
The Visit by Treatment by baseline eGFR (CKD-EPI) [mL/min/1.73m²] (2 cat.) p-value at Week 52 is 0.3754.
The following covariance structure has been used to fit the mixed model: Unstructured
2 patients were excluded as the subgroup variable was missing.
Note: All covariate effects are set equal to their mean values within subgroup for the calculation of adjusted means.

For patients who died, only observed values are considered (no imputation after date of death).
Data taken from study 1245.121 only.
The MMRM includes all outcome values (change from baseline) at the planned Visits week 12, week 32 and week 52

Table R.1.3.1.9: 1 EQ-VAS change from baseline at week 52 (MMRM) by baseline eGFR (2 cat.) - RS (OC-AD - no imputation for deaths) - 1245.121

Subgroup / Visit / Description / Statistic	Placebo	Empa 10mg
Baseline eGFR (CKD-EPI) [mL/min/1.73m²] (2 cat.): <60		
Number of patients in analysis set	906	893
Number of analysed patients	853	852
Baseline mean (SE)	67.85 (0.63)	67.51 (0.62)
Week 52		
Values at visit		
Number of analysed patients	573	583
Mean (SE)	70.85 (0.75)	71.78 (0.74)
Adjusted* mean (SE)	70.68 (0.63)	71.71 (0.62)
95% confidence interval	(69.45,71.91)	(70.49,72.94)
Change from baseline		
Mean (SE)	2.53 (0.81)	3.66 (0.79)
Adjusted* mean (SE)	3.00 (0.63)	4.03 (0.62)
95% confidence interval	(1.77, 4.24)	(2.81, 5.26)
Comparison vs Placebo		
Adjusted* mean (SE)		1.03 (0.88)
95% confidence interval		(-0.70, 2.77)
p-value		0.2437

* Model includes Age as linear covariate(s) and region, baseline diabetes status, sex, baseline LVEF, week reachable, Visit by Treatment by baseline eGFR (CKD-EPI) [mL/min/1.73m²] (2 cat.) interaction, baseline EQ-VAS score by Visit interaction as fixed effect(s).
The Visit by Treatment by baseline eGFR (CKD-EPI) [mL/min/1.73m²] (2 cat.) p-value at Week 52 is 0.3754.
The following covariance structure has been used to fit the mixed model: Unstructured
2 patients were excluded as the subgroup variable was missing.
Note: All covariate effects are set equal to their mean values within subgroup for the calculation of adjusted means.

For patients who died, only observed values are considered (no imputation after date of death).
Data taken from study 1245.121 only.
The MMRM includes all outcome values (change from baseline) at the planned Visits week 12, week 32 and week 52

R.1.3.1.10

Table R.1.3.1.10: 1

Table R.1.3.1.10: 1 EQ-VAS change from baseline at week 52 (MMRM) by history of HHF - RS (OC-AD - no imputation for deaths) - 1245.121

Subgroup / Visit / Description / Statistic	Placebo	Empa 10mg
History of HHF (in the last 12 months): No		
Number of patients in analysis set	1293	1286
Number of analysed patients	1219	1230
Baseline mean (SE)	67.93 (0.52)	67.92 (0.52)
Week 52		
Values at visit		
Number of analysed patients	871	869
Mean (SE)	70.79 (0.63)	73.58 (0.59)
Adjusted* mean (SE)	71.26 (0.51)	73.32 (0.51)
95% confidence interval	(70.25,72.27)	(72.31,74.32)
Change from baseline		
Mean (SE)	3.36 (0.65)	5.57 (0.64)
Adjusted* mean (SE)	3.34 (0.51)	5.39 (0.51)
95% confidence interval	(2.33, 4.34)	(4.39, 6.40)
Comparison vs Placebo		
Adjusted* mean (SE)		2.06 (0.72)
95% confidence interval		(0.64, 3.48)
p-value		0.0045

* Model includes Age, baseline eGFR (CKD-EPI) as linear covariate(s) and region, baseline diabetes status, sex, baseline LVEF, week reachable, Visit by Treatment by history of HHF (in the last 12 months) interaction, baseline EQ-VAS score by Visit interaction as fixed effect(s).
The Visit by Treatment by history of HHF (in the last 12 months) p-value at Week 52 is 0.2446.
The following covariance structure has been used to fit the mixed model: Unstructured
Note: All covariate effects are set equal to their mean values within subgroup for the calculation of adjusted means.

For patients who died, only observed values are considered (no imputation after date of death).
Data taken from study 1245.121 only.
The MMRM includes all outcome values (change from baseline) at the planned Visits week 12, week 32 and week 52

Table R.1.3.1.10: 1 EQ-VAS change from baseline at week 52 (MMRM) by history of HHF - RS (OC-AD - no imputation for deaths) - 1245.121

Subgroup / Visit / Description / Statistic	Placebo	Empa 10mg
History of HHF (in the last 12 months): Yes		
Number of patients in analysis set	574	577
Number of analysed patients	535	541
Baseline mean (SE)	68.50 (0.78)	67.82 (0.81)
Week 52		
Values at visit		
Number of analysed patients	350	363
Mean (SE)	73.64 (0.91)	72.93 (1.00)
Adjusted* mean (SE)	72.21 (0.80)	72.71 (0.79)
95% confidence interval	(70.64,73.79)	(71.16,74.26)
Change from baseline		
Mean (SE)	3.38 (0.95)	4.04 (1.02)
Adjusted* mean (SE)	4.05 (0.80)	4.56 (0.79)
95% confidence interval	(2.48, 5.63)	(3.00, 6.11)
Comparison vs Placebo		
Adjusted* mean (SE)		0.50 (1.12)
95% confidence interval		(-1.70, 2.70)
p-value		0.6561

* Model includes Age, baseline eGFR (CKD-EPI) as linear covariate(s) and region, baseline diabetes status, sex, baseline LVEF, week reachable, Visit by Treatment by history of HHF (in the last 12 months) interaction, baseline EQ-VAS score by Visit interaction as fixed effect(s).
The Visit by Treatment by history of HHF (in the last 12 months) p-value at Week 52 is 0.2446.
The following covariance structure has been used to fit the mixed model: Unstructured
Note: All covariate effects are set equal to their mean values within subgroup for the calculation of adjusted means.

For patients who died, only observed values are considered (no imputation after date of death).
Data taken from study 1245.121 only.
The MMRM includes all outcome values (change from baseline) at the planned Visits week 12, week 32 and week 52

R.1.3.1.11

R.1.3.1.11 Subgroup analysis by cause of heart failure

Table R.1.3.1.11: 1 EQ-VAS change from baseline at week 52 (MMRM) by cause of heart failure - RS (OC-AD - no imputation for deaths) - 1245.121

Subgroup / Visit / Description / Statistic	Placebo	Empa 10mg
Cause of heart failure: Ischemic		
Number of patients in analysis set	946	983
Number of analysed patients	894	932
Baseline mean (SE)	67.31 (0.61)	67.31 (0.61)
Week 52		
Values at visit		
Number of analysed patients	635	664
Mean (SE)	70.37 (0.72)	72.34 (0.70)
Adjusted* mean (SE)	70.78 (0.60)	72.27 (0.59)
95% confidence interval	(69.60,71.97)	(71.12,73.43)
Change from baseline		
Mean (SE)	2.78 (0.71)	4.46 (0.75)
Adjusted* mean (SE)	3.47 (0.60)	4.96 (0.59)
95% confidence interval	(2.29, 4.66)	(3.81, 6.12)
Comparison vs Placebo		
Adjusted* mean (SE)		1.49 (0.84)
95% confidence interval		(-0.16, 3.13)
p-value		0.0760

* Model includes Age, baseline eGFR (CKD-EPI) as linear covariate(s) and region, baseline diabetes status, sex, baseline LVEF, week reachable, Visit by Treatment by cause of heart failure interaction, baseline EQ-VAS score by Visit interaction as fixed effect(s).
The Visit by Treatment by cause of heart failure p-value at Week 52 is 0.8274.
The following covariance structure has been used to fit the mixed model: Unstructured
Note: All covariate effects are set equal to their mean values within subgroup for the calculation of adjusted means.

For patients who died, only observed values are considered (no imputation after date of death).
Data taken from study 1245.121 only.
The MMRM includes all outcome values (change from baseline) at the planned Visits week 12, week 32 and week 52

Table R.1.3.1.11: 1 EQ-VAS change from baseline at week 52 (MMRM) by cause of heart failure - RS (OC-AD - no imputation for deaths) - 1245.121

Subgroup / Visit / Description / Statistic	Placebo	Empa 10mg
Cause of heart failure: Non-ischemic		
Number of patients in analysis set	921	880
Number of analysed patients	860	839
Baseline mean (SE)	68.92 (0.62)	68.53 (0.63)
Week 52		
Values at visit		
Number of analysed patients	586	568
Mean (SE)	72.96 (0.75)	74.62 (0.74)
Adjusted* mean (SE)	72.35 (0.63)	74.10 (0.63)
95% confidence interval	(71.12,73.57)	(72.86,75.34)
Change from baseline		
Mean (SE)	4.01 (0.81)	5.89 (0.79)
Adjusted* mean (SE)	3.62 (0.63)	5.37 (0.63)
95% confidence interval	(2.39, 4.84)	(4.13, 6.61)
Comparison vs Placebo		
Adjusted* mean (SE)		1.75 (0.89)
95% confidence interval		(0.02, 3.49)
p-value		0.0476

* Model includes Age, baseline eGFR (CKD-EPI) as linear covariate(s) and region, baseline diabetes status, sex, baseline LVEF, week reachable, Visit by Treatment by cause of heart failure interaction, baseline EQ-VAS score by Visit interaction as fixed effect(s).
The Visit by Treatment by cause of heart failure p-value at Week 52 is 0.8274.
The following covariance structure has been used to fit the mixed model: Unstructured
Note: All covariate effects are set equal to their mean values within subgroup for the calculation of adjusted means.

For patients who died, only observed values are considered (no imputation after date of death).
Data taken from study 1245.121 only.
The MMRM includes all outcome values (change from baseline) at the planned Visits week 12, week 32 and week 52

R.1.3.1.12

R.1.3.1.12 Subgroup analysis by heart failure physiology (LVEF <= 30% and NTproBNP<median; LVEF <= 30% and NTproBNP>=median; LVEF > 30%)

Table R.1.3.1.12: 1 EQ-VAS change from baseline at week 52 (MMRM) by heart failure physiology - RS (OC-AD - no imputation for deaths) - 1245.121

Subgroup / Visit / Description / Statistic	Placebo	Empa 10mg
Heart failure physiology: LVEF <= 30% and NTproBNP < median		
Number of patients in analysis set	723	698
Number of analysed patients	694	672
Baseline mean (SE)	68.97 (0.68)	68.95 (0.67)
Week 52		
Values at visit		
Number of analysed patients	510	493
Mean (SE)	72.75 (0.78)	73.85 (0.76)
Adjusted* mean (SE)	72.88 (0.67)	73.84 (0.68)
95% confidence interval	(71.57,74.19)	(72.50,75.17)
Change from baseline		
Mean (SE)	4.21 (0.80)	4.78 (0.80)
Adjusted* mean (SE)	3.92 (0.67)	4.88 (0.68)
95% confidence interval	(2.60, 5.23)	(3.54, 6.21)
Comparison vs Placebo		
Adjusted* mean (SE)		0.96 (0.95)
95% confidence interval		(-0.91, 2.83)
p-value		0.3159

* Model includes Age, baseline eGFR (CKD-EPI) as linear covariate(s) and region, baseline diabetes status, sex, week reachable, Visit by Treatment by heart failure physiology interaction, baseline EQ-VAS score by Visit interaction as fixed effect(s).
The Visit by Treatment by heart failure physiology p-value at Week 52 is 0.5205.
The following covariance structure has been used to fit the mixed model: Unstructured
16 patients were excluded as the subgroup variable was missing.
Note: All covariate effects are set equal to their mean values within subgroup for the calculation of adjusted means.
The p-value for the visit by treatment by subgroup interaction trend test at Week 52 is 0.6474

For patients who died, only observed values are considered (no imputation after date of death).
Data taken from study 1245.121 only.
NTproBNP median [pg/mL]: with a. fibrillation/flutter at baseline: 2265; without a. fibrillation/flutter at baseline: 1671.
The MMRM includes all outcome values (change from baseline) at the planned Visits week 12, week 32 and week 52

Table R.1.3.1.12: 1 EQ-VAS change from baseline at week 52 (MMRM) by heart failure physiology - RS (OC-AD - no imputation for deaths) - 1245.121

Subgroup / Visit / Description / Statistic	Placebo	Empa 10mg
Heart failure physiology: LVEF <= 30% and NTproBNP >= median		
Number of patients in analysis set	661	631
Number of analysed patients	604	589
Baseline mean (SE)	66.16 (0.74)	66.94 (0.80)
Week 52		
Values at visit		
Number of analysed patients	411	402
Mean (SE)	69.62 (0.92)	73.07 (0.96)
Adjusted* mean (SE)	69.58 (0.74)	72.13 (0.75)
95% confidence interval	(68.12,71.03)	(70.66,73.60)
Change from baseline		
Mean (SE)	2.92 (0.95)	5.24 (1.02)
Adjusted* mean (SE)	3.03 (0.74)	5.59 (0.75)
95% confidence interval	(1.58, 4.49)	(4.12, 7.06)
Comparison vs Placebo		
Adjusted* mean (SE)		2.55 (1.05)
95% confidence interval		(0.49, 4.62)
p-value		0.0155

* Model includes Age, baseline eGFR (CKD-EPI) as linear covariate(s) and region, baseline diabetes status, sex, week reachable, Visit by Treatment by heart failure physiology interaction, baseline EQ-VAS score by Visit interaction as fixed effect(s).
The Visit by Treatment by heart failure physiology p-value at Week 52 is 0.5205.
The following covariance structure has been used to fit the mixed model: Unstructured
16 patients were excluded as the subgroup variable was missing.
Note: All covariate effects are set equal to their mean values within subgroup for the calculation of adjusted means.
The p-value for the visit by treatment by subgroup interaction trend test at Week 52 is 0.6474

For patients who died, only observed values are considered (no imputation after date of death).
Data taken from study 1245.121 only.
NTproBNP median [pg/mL]: with a. fibrillation/flutter at baseline: 2265; without a. fibrillation/flutter at baseline: 1671.
The MMRM includes all outcome values (change from baseline) at the planned Visits week 12, week 32 and week 52

Table R.1.3.1.12: 1 EQ-VAS change from baseline at week 52 (MMRM) by heart failure physiology - RS (OC-AD - no imputation for deaths) - 1245.121

Subgroup / Visit / Description / Statistic	Placebo	Empa 10mg
Heart failure physiology: LVEF > 30%		
Number of patients in analysis set	475	526
Number of analysed patients	451	505
Baseline mean (SE)	69.46 (0.86)	67.60 (0.84)
Week 52		
Values at visit		
Number of analysed patients	296	336
Mean (SE)	72.58 (1.04)	73.10 (0.98)
Adjusted* mean (SE)	72.05 (0.87)	73.42 (0.82)
95% confidence interval	(70.34,73.76)	(71.82,75.03)
Change from baseline		
Mean (SE)	2.66 (1.11)	5.42 (1.04)
Adjusted* mean (SE)	3.57 (0.87)	4.94 (0.82)
95% confidence interval	(1.86, 5.28)	(3.34, 6.54)
Comparison vs Placebo		
Adjusted* mean (SE)		1.37 (1.19)
95% confidence interval		(-0.97, 3.71)
p-value		0.2500

* Model includes Age, baseline eGFR (CKD-EPI) as linear covariate(s) and region, baseline diabetes status, sex, week reachable, Visit by Treatment by heart failure physiology interaction, baseline EQ-VAS score by Visit interaction as fixed effect(s).
The Visit by Treatment by heart failure physiology p-value at Week 52 is 0.5205.
The following covariance structure has been used to fit the mixed model: Unstructured
16 patients were excluded as the subgroup variable was missing.
Note: All covariate effects are set equal to their mean values within subgroup for the calculation of adjusted means.
The p-value for the visit by treatment by subgroup interaction trend test at Week 52 is 0.6474

For patients who died, only observed values are considered (no imputation after date of death).
Data taken from study 1245.121 only.
NTproBNP median [pg/mL]: with a. fibrillation/flutter at baseline: 2265; without a. fibrillation/flutter at baseline: 1671.
The MMRM includes all outcome values (change from baseline) at the planned Visits week 12, week 32 and week 52

R.1.3.1.13

R.1.3.1.13 Subgroup analysis by baseline use of MRA

Table R.1.3.1.13: 1 EQ-VAS change from baseline at week 52 (MMRM) by baseline use of MRA (Y/N) - RS (OC-AD - no imputation for deaths) - 1245.121

Subgroup / Visit / Description / Statistic	Placebo	Empa 10mg
Baseline use of MRA: No		
Number of patients in analysis set	512	557
Number of analysed patients	485	531
Baseline mean (SE)	68.82 (0.81)	68.29 (0.81)
Week 52		
Values at visit		
Number of analysed patients	344	380
Mean (SE)	70.78 (1.01)	74.32 (0.87)
Adjusted* mean (SE)	70.79 (0.82)	73.38 (0.78)
95% confidence interval	(69.19,72.39)	(71.85,74.91)
Change from baseline		
Mean (SE)	1.71 (0.99)	4.85 (1.01)
Adjusted* mean (SE)	2.25 (0.82)	4.84 (0.78)
95% confidence interval	(0.65, 3.85)	(3.31, 6.37)
Comparison vs Placebo		
Adjusted* mean (SE)		2.59 (1.12)
95% confidence interval		(0.39, 4.80)
p-value		0.0212

* Model includes Age, baseline eGFR (CKD-EPI) as linear covariate(s) and region, baseline diabetes status, sex, baseline LVEF, week reachable, Visit by Treatment by baseline use of MRA interaction, baseline EQ-VAS score by Visit interaction as fixed effect(s).
The Visit by Treatment by baseline use of MRA p-value at Week 52 is 0.3051.
The following covariance structure has been used to fit the mixed model: Unstructured
Note: All covariate effects are set equal to their mean values within subgroup for the calculation of adjusted means.

For patients who died, only observed values are considered (no imputation after date of death).
Data taken from study 1245.121 only.
The MMRM includes all outcome values (change from baseline) at the planned Visits week 12, week 32 and week 52

Table R.1.3.1.13: 1 EQ-VAS change from baseline at week 52 (MMRM) by baseline use of MRA (Y/N) - RS (OC-AD - no imputation for deaths) - 1245.121

Subgroup / Visit / Description / Statistic	Placebo	Empa 10mg
Baseline use of MRA: Yes		
Number of patients in analysis set	1355	1306
Number of analysed patients	1269	1240
Baseline mean (SE)	67.83 (0.51)	67.72 (0.52)
Week 52		
Values at visit		
Number of analysed patients	877	852
Mean (SE)	71.94 (0.61)	72.97 (0.63)
Adjusted* mean (SE)	71.82 (0.51)	73.04 (0.52)
95% confidence interval	(70.82,72.82)	(72.03,74.05)
Change from baseline		
Mean (SE)	4.02 (0.64)	5.24 (0.64)
Adjusted* mean (SE)	4.05 (0.51)	5.27 (0.52)
95% confidence interval	(3.05, 5.05)	(4.25, 6.28)
Comparison vs Placebo		
Adjusted* mean (SE)		1.22 (0.72)
95% confidence interval		(-0.20, 2.64)
p-value		0.0923

* Model includes Age, baseline eGFR (CKD-EPI) as linear covariate(s) and region, baseline diabetes status, sex, baseline LVEF, week reachable, Visit by Treatment by baseline use of MRA interaction, baseline EQ-VAS score by Visit interaction as fixed effect(s).
The Visit by Treatment by baseline use of MRA p-value at Week 52 is 0.3051.
The following covariance structure has been used to fit the mixed model: Unstructured
Note: All covariate effects are set equal to their mean values within subgroup for the calculation of adjusted means.

For patients who died, only observed values are considered (no imputation after date of death).
Data taken from study 1245.121 only.
The MMRM includes all outcome values (change from baseline) at the planned Visits week 12, week 32 and week 52

R.1.3.1.14

Table R.1.3.1.14: 1 EQ-VAS change from baseline at week 52 (MMRM) by baseline use of ARNi (Y/N) - RS (OC-AD - no imputation for deaths) - 1245.121

Subgroup / Visit / Description / Statistic	Placebo	Empa 10mg
Baseline use of ARNi: No		
Number of patients in analysis set	1480	1523
Number of analysed patients	1392	1443
Baseline mean (SE)	67.92 (0.48)	67.69 (0.49)
Week 52		
Values at visit		
Number of analysed patients	964	1019
Mean (SE)	71.33 (0.59)	73.17 (0.56)
Adjusted* mean (SE)	71.19 (0.49)	72.75 (0.47)
95% confidence interval	(70.24,72.15)	(71.82,73.68)
Change from baseline		
Mean (SE)	3.25 (0.61)	4.86 (0.58)
Adjusted* mean (SE)	3.39 (0.49)	4.95 (0.47)
95% confidence interval	(2.44, 4.34)	(4.02, 5.87)
Comparison vs Placebo		
Adjusted* mean (SE)		1.56 (0.68)
95% confidence interval		(0.23, 2.89)
p-value		0.0215

* Model includes Age, baseline eGFR (CKD-EPI) as linear covariate(s) and region, baseline diabetes status, sex, baseline LVEF, week reachable, Visit by Treatment by baseline use of ARNi interaction, baseline EQ-VAS score by Visit interaction as fixed effect(s).
The Visit by Treatment by baseline use of ARNi p-value at Week 52 is 0.7418.
The following covariance structure has been used to fit the mixed model: Unstructured
Note: All covariate effects are set equal to their mean values within subgroup for the calculation of adjusted means.

For patients who died, only observed values are considered (no imputation after date of death).
Data taken from study 1245.121 only.
The MMRM includes all outcome values (change from baseline) at the planned Visits week 12, week 32 and week 52

Table R.1.3.1.14: 1 EQ-VAS change from baseline at week 52 (MMRM) by baseline use of ARNi (Y/N) - RS (OC-AD - no imputation for deaths) - 1245.121

Subgroup / Visit / Description / Statistic	Placebo	Empa 10mg
Baseline use of ARNi: Yes		
Number of patients in analysis set	387	340
Number of analysed patients	362	328
Baseline mean (SE)	68.80 (0.98)	68.74 (1.04)
Week 52		
Values at visit		
Number of analysed patients	257	213
Mean (SE)	72.65 (1.13)	74.46 (1.18)
Adjusted* mean (SE)	72.84 (0.95)	74.91 (1.03)
95% confidence interval	(70.98,74.70)	(72.89,76.93)
Change from baseline		
Mean (SE)	3.82 (1.17)	6.36 (1.43)
Adjusted* mean (SE)	4.07 (0.95)	6.14 (1.03)
95% confidence interval	(2.21, 5.92)	(4.12, 8.16)
Comparison vs Placebo		
Adjusted* mean (SE)		2.07 (1.39)
95% confidence interval		(-0.66, 4.80)
p-value		0.1378

* Model includes Age, baseline eGFR (CKD-EPI) as linear covariate(s) and region, baseline diabetes status, sex, baseline LVEF, week reachable, Visit by Treatment by baseline use of ARNi interaction, baseline EQ-VAS score by Visit interaction as fixed effect(s).
The Visit by Treatment by baseline use of ARNi p-value at Week 52 is 0.7418.
The following covariance structure has been used to fit the mixed model: Unstructured
Note: All covariate effects are set equal to their mean values within subgroup for the calculation of adjusted means.

For patients who died, only observed values are considered (no imputation after date of death).
Data taken from study 1245.121 only.
The MMRM includes all outcome values (change from baseline) at the planned Visits week 12, week 32 and week 52

R.1.3.1.15

R.1.3.1.15 Subgroup analysis by bl. LVEF (<= 30%, >30% -<= 35% , > 35%)

Table R.1.3.1.15: 1 EQ-VAS change from baseline at week 52 (MMRM) by baseline LVEF (3 cat.) - RS (OC-AD - no imputation for deaths) - 1245.121

Subgroup / Visit / Description / Statistic	Placebo	Empa 10mg
Baseline LVEF (3 cat.): <=30		
Number of patients in analysis set	1392	1337
Number of analysed patients	1303	1266
Baseline mean (SE)	67.63 (0.50)	68.00 (0.52)
Week 52		
Values at visit		
Number of analysed patients	925	896
Mean (SE)	71.30 (0.60)	73.50 (0.60)
Adjusted* mean (SE)	71.33 (0.50)	73.04 (0.50)
95% confidence interval	(70.36,72.31)	(72.05,74.03)
Change from baseline		
Mean (SE)	3.60 (0.61)	5.01 (0.64)
Adjusted* mean (SE)	3.52 (0.50)	5.23 (0.50)
95% confidence interval	(2.55, 4.50)	(4.24, 6.22)
Comparison vs Placebo		
Adjusted* mean (SE)		1.71 (0.71)
95% confidence interval		(0.32, 3.09)
p-value		0.0159

* Model includes Age, baseline eGFR (CKD-EPI) as linear covariate(s) and region, baseline diabetes status, sex, week reachable, Visit by Treatment by baseline LVEF (3 cat.) interaction, baseline EQ-VAS score by Visit interaction as fixed effect(s).
The Visit by Treatment by baseline LVEF (3 cat.) p-value at Week 52 is 0.7036.
The following covariance structure has been used to fit the mixed model: Unstructured
Note: All covariate effects are set equal to their mean values within subgroup for the calculation of adjusted means.
The p-value for the visit by treatment by subgroup interaction trend test at Week 52 is 0.9396

For patients who died, only observed values are considered (no imputation after date of death).
Data taken from study 1245.121 only.
The MMRM includes all outcome values (change from baseline) at the planned Visits week 12, week 32 and week 52

Table R.1.3.1.15: 1 EQ-VAS change from baseline at week 52 (MMRM) by baseline LVEF (3 cat.) - RS (OC-AD - no imputation for deaths) - 1245.121

Subgroup / Visit / Description / Statistic	Placebo	Empa 10mg
Baseline LVEF (3 cat.): >30 to <=35		
Number of patients in analysis set	361	398
Number of analysed patients	343	384
Baseline mean (SE)	69.63 (0.98)	68.20 (0.95)
Week 52		
Values at visit		
Number of analysed patients	233	254
Mean (SE)	72.77 (1.19)	72.52 (1.12)
Adjusted* mean (SE)	72.31 (0.99)	73.13 (0.94)
95% confidence interval	(70.38,74.24)	(71.29,74.97)
Change from baseline		
Mean (SE)	2.70 (1.25)	4.41 (1.15)
Adjusted* mean (SE)	3.44 (0.99)	4.26 (0.94)
95% confidence interval	(1.51, 5.37)	(2.42, 6.10)
Comparison vs Placebo		
Adjusted* mean (SE)		0.82 (1.36)
95% confidence interval		(-1.85, 3.49)
p-value		0.5483

* Model includes Age, baseline eGFR (CKD-EPI) as linear covariate(s) and region, baseline diabetes status, sex, week reachable, Visit by Treatment by baseline LVEF (3 cat.) interaction, baseline EQ-VAS score by Visit interaction as fixed effect(s).
The Visit by Treatment by baseline LVEF (3 cat.) p-value at Week 52 is 0.7036.
The following covariance structure has been used to fit the mixed model: Unstructured
Note: All covariate effects are set equal to their mean values within subgroup for the calculation of adjusted means.
The p-value for the visit by treatment by subgroup interaction trend test at Week 52 is 0.9396

For patients who died, only observed values are considered (no imputation after date of death).
Data taken from study 1245.121 only.
The MMRM includes all outcome values (change from baseline) at the planned Visits week 12, week 32 and week 52

Table R.1.3.1.15: 1 EQ-VAS change from baseline at week 52 (MMRM) by baseline LVEF (3 cat.) - RS (OC-AD - no imputation for deaths) - 1245.121

Subgroup / Visit / Description / Statistic	Placebo	Empa 10mg
Baseline LVEF (3 cat.): >35		
Number of patients in analysis set	114	128
Number of analysed patients	108	121
Baseline mean (SE)	68.94 (1.76)	65.73 (1.79)
Week 52		
Values at visit		
Number of analysed patients	63	82
Mean (SE)	71.89 (2.16)	74.91 (2.00)
Adjusted* mean (SE)	71.23 (1.87)	74.31 (1.66)
95% confidence interval	(67.56,74.91)	(71.06,77.57)
Change from baseline		
Mean (SE)	2.51 (2.42)	8.54 (2.31)
Adjusted* mean (SE)	3.99 (1.87)	7.07 (1.66)
95% confidence interval	(0.31, 7.66)	(3.81,10.32)
Comparison vs Placebo		
Adjusted* mean (SE)		3.08 (2.50)
95% confidence interval		(-1.83, 7.99)
p-value		0.2183

* Model includes Age, baseline eGFR (CKD-EPI) as linear covariate(s) and region, baseline diabetes status, sex, week reachable, Visit by Treatment by baseline LVEF (3 cat.) interaction, baseline EQ-VAS score by Visit interaction as fixed effect(s).
The Visit by Treatment by baseline LVEF (3 cat.) p-value at Week 52 is 0.7036.
The following covariance structure has been used to fit the mixed model: Unstructured
Note: All covariate effects are set equal to their mean values within subgroup for the calculation of adjusted means.
The p-value for the visit by treatment by subgroup interaction trend test at Week 52 is 0.9396

For patients who died, only observed values are considered (no imputation after date of death).
Data taken from study 1245.121 only.
The MMRM includes all outcome values (change from baseline) at the planned Visits week 12, week 32 and week 52

R.1.3.1.16 Subgroup analysis by bl. NTproBNP </>= median (median based on total patients)

Table R.1.3.1.16: 1 EQ-VAS change from baseline at week 52 (MMRM) by bl. NTproBNP (<median, >= median) (median based on total patients) - RS (OC-AD - no imputation for deaths) - 1245.121

Subgroup / Visit / Description / Statistic	Placebo	Empa 10mg
Baseline NTproBNP: < median		
Number of patients in analysis set	920	942
Number of analysed patients	884	907
Baseline mean (SE)	69.80 (0.60)	69.13 (0.58)
Week 52		
Values at visit		
Number of analysed patients	650	664
Mean (SE)	72.92 (0.69)	74.24 (0.66)
Adjusted* mean (SE)	73.09 (0.59)	74.53 (0.59)
95% confidence interval	(71.93,74.26)	(73.38,75.68)
Change from baseline		
Mean (SE)	3.45 (0.70)	5.14 (0.71)
Adjusted* mean (SE)	3.64 (0.59)	5.07 (0.59)
95% confidence interval	(2.47, 4.80)	(3.92, 6.22)
Comparison vs Placebo		
Adjusted* mean (SE)		1.43 (0.84)
95% confidence interval		(-0.20, 3.07)
p-value		0.0858

* Model includes Age, baseline eGFR (CKD-EPI) as linear covariate(s) and region, baseline diabetes status, sex, baseline LVEF, week reachable, Visit by Treatment by baseline NTproBNP (<median, >= median) interaction, baseline EQ-VAS score by Visit interaction as fixed effect(s). The Visit by Treatment by baseline NTproBNP (<median, >= median) p-value at Week 52 is 0.7967.
The following covariance structure has been used to fit the mixed model: Unstructured
2 patients were excluded as the subgroup variable was missing.
Note: All covariate effects are set equal to their mean values within subgroup for the calculation of adjusted means.

For patients who died, only observed values are considered (no imputation after date of death).
Data taken from study 1245.121 only.
Median: 1910 [pg/mL]
The MMRM includes all outcome values (change from baseline) at the planned Visits week 12, week 32 and week 52

Table R.1.3.1.16: 1 EQ-VAS change from baseline at week 52 (MMRM) by bl. NTproBNP (<median, >= median) (median based on total patients) - RS (OC-AD - no imputation for deaths) - 1245.121

Subgroup / Visit / Description / Statistic	Placebo	Empa 10mg
Baseline NTproBNP: >= median		
Number of patients in analysis set	946	920
Number of analysed patients	870	864
Baseline mean (SE)	66.38 (0.63)	66.59 (0.66)
Week 52		
Values at visit		
Number of analysed patients	571	568
Mean (SE)	70.12 (0.78)	72.39 (0.80)
Adjusted* mean (SE)	69.89 (0.63)	71.64 (0.63)
95% confidence interval	(68.66,71.12)	(70.40,72.87)
Change from baseline		
Mean (SE)	3.27 (0.83)	5.10 (0.84)
Adjusted* mean (SE)	3.40 (0.63)	5.15 (0.63)
95% confidence interval	(2.17, 4.63)	(3.92, 6.39)
Comparison vs Placebo		
Adjusted* mean (SE)		1.75 (0.89)
95% confidence interval		(0.01, 3.49)
p-value		0.0490

* Model includes Age, baseline eGFR (CKD-EPI) as linear covariate(s) and region, baseline diabetes status, sex, baseline LVEF, week reachable, Visit by Treatment by baseline NTproBNP (<median, >= median) interaction, baseline EQ-VAS score by Visit interaction as fixed effect(s). The Visit by Treatment by baseline NTproBNP (<median, >= median) p-value at Week 52 is 0.7967.
The following covariance structure has been used to fit the mixed model: Unstructured
2 patients were excluded as the subgroup variable was missing.
Note: All covariate effects are set equal to their mean values within subgroup for the calculation of adjusted means.

For patients who died, only observed values are considered (no imputation after date of death).
Data taken from study 1245.121 only.
Median: 1910 [pg/mL]
The MMRM includes all outcome values (change from baseline) at the planned Visits week 12, week 32 and week 52

R.1.3.2

R.1.3.2 KCCQ Clinical Summary Score MMRM analysis

R.1.3.2.1

Table R.1.3.2.1: 1 KCCQ-CSS change from baseline MMRM results over time - RS (OC-AD - no imputation for deaths) - 1245.121

Visit Description Statistic	Placebo	Empa 10mg
Number of patients in analysis set	1867	1863
Number of analysed patients	1753	1776
Baseline mean (SE)	71.24 (0.51)	71.07 (0.52)
Week 12		
Values at visit		
Number of analysed patients	1732	1755
Mean (SE)	74.79 (0.49)	76.57 (0.49)
Adjusted* mean (SE)	74.83 (0.36)	76.77 (0.36)
95% confidence interval	(74.13,75.53)	(76.08,77.47)
Change from baseline		
Mean (SE)	3.43 (0.39)	5.42 (0.41)
Adjusted* mean (SE)	3.25 (0.36)	5.19 (0.36)
95% confidence interval	(2.55, 3.95)	(4.50, 5.89)
Comparison vs Placebo		
Adjusted* mean (SE)		1.94 (0.50)
95% confidence interval		(0.96, 2.93)
p-value		0.0001
Hedges g		
Estimate		0.13
95% confidence interval		(0.06, 0.20)

* Model includes Age (p=0.0846), baseline eGFR (CKD-EPI) (p=0.0030) as linear covariate(s) and region (p<0.0001), baseline diabetes status (p=0.4591), sex (p=0.0019), baseline LVEF (p=0.4617), week reachable (p=0.1119), Treatment by Visit interaction (p<0.0001), baseline KCCQ - clinical summary score by Visit interaction (p<0.0001) as fixed effect(s).
The following covariance structure has been used to fit the mixed model: Unstructured

For patients who died, only observed values are considered (no imputation after date of death).
Data taken from study 1245.121 only.

Table R.1.3.2.1: 1 KCCQ-CSS change from baseline MMRM results over time - RS (OC-AD - no imputation for deaths) - 1245.121

Visit Description Statistic	Placebo	Empa 10mg
Week 32		
Values at visit		
Number of analysed patients	1568	1618
Mean (SE)	75.64 (0.52)	76.96 (0.52)
Adjusted* mean (SE)	75.33 (0.39)	76.69 (0.38)
95% confidence interval	(74.57,76.10)	(75.93,77.44)
Change from baseline		
Mean (SE)	4.11 (0.45)	5.42 (0.43)
Adjusted* mean (SE)	3.76 (0.39)	5.11 (0.38)
95% confidence interval	(2.99, 4.52)	(4.36, 5.86)
Comparison vs Placebo		
Adjusted* mean (SE)		1.35 (0.55)
95% confidence interval		(0.28, 2.42)
p-value		0.0132
Hedges g		
Estimate		0.09
95% confidence interval		(0.02, 0.16)

* Model includes Age (p=0.0846), baseline eGFR (CKD-EPI) (p=0.0030) as linear covariate(s) and region (p<0.0001), baseline diabetes status (p=0.4591), sex (p=0.0019), baseline LVEF (p=0.4617), week reachable (p=0.1119), Treatment by Visit interaction (p<0.0001), baseline KCCQ - clinical summary score by Visit interaction (p<0.0001) as fixed effect(s).
The following covariance structure has been used to fit the mixed model: Unstructured

For patients who died, only observed values are considered (no imputation after date of death).
Data taken from study 1245.121 only.

Table R.1.3.2.1: 1 KCCQ-CSS change from baseline MMRM results over time - RS (OC-AD - no imputation for deaths) - 1245.121

Visit Description Statistic	Placebo	Empa 10mg
Week 52		
Values at visit		
Number of analysed patients	1218	1239
Mean (SE)	76.04 (0.60)	77.62 (0.58)
Adjusted* mean (SE)	75.47 (0.44)	77.08 (0.44)
95% confidence interval	(74.60,76.34)	(76.22,77.95)
Change from baseline		
Mean (SE)	4.17 (0.54)	5.31 (0.51)
Adjusted* mean (SE)	3.89 (0.44)	5.51 (0.44)
95% confidence interval	(3.02, 4.76)	(4.64, 6.37)
Comparison vs Placebo		
Adjusted* mean (SE)		1.61 (0.63)
95% confidence interval		(0.39, 2.84)
p-value		0.0099
Hedges g		
Estimate		0.10
95% confidence interval		(0.02, 0.17)

* Model includes Age (p=0.0846), baseline eGFR (CKD-EPI) (p=0.0030) as linear covariate(s) and region (p<0.0001), baseline diabetes status (p=0.4591), sex (p=0.0019), baseline LVEF (p=0.4617), week reachable (p=0.1119), Treatment by Visit interaction (p<0.0001), baseline KCCQ - clinical summary score by Visit interaction (p<0.0001) as fixed effect(s).
The following covariance structure has been used to fit the mixed model: Unstructured

For patients who died, only observed values are considered (no imputation after date of death).
Data taken from study 1245.121 only.

Figure R.1.3.2.1: 1

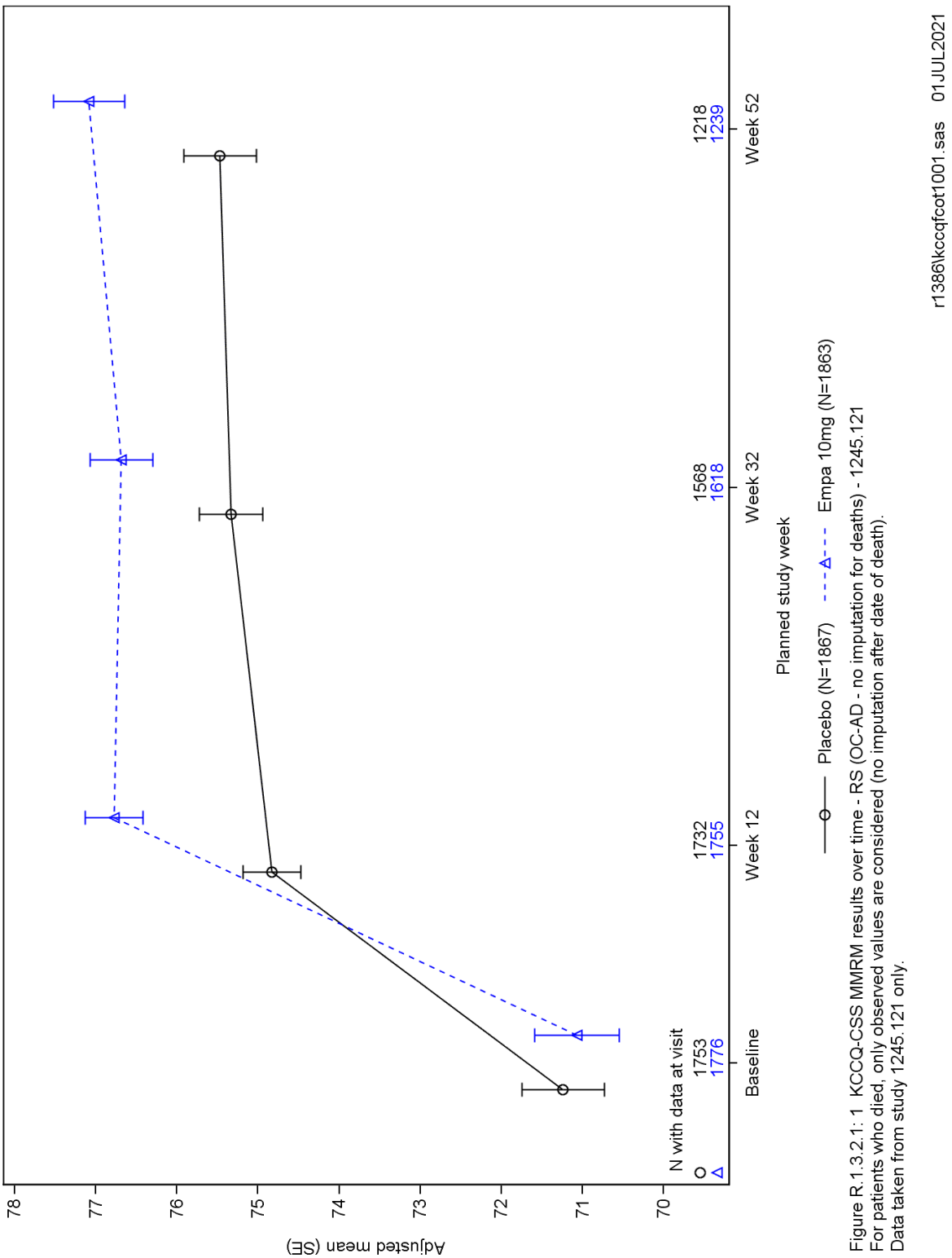

Figure R.1.3.2.1: 1 KCCQ-CSS MMRM results over time - RS (OC-AD - no imputation for deaths) - 1245.121
For patients who died, only observed values are considered (no imputation after date of death).
Data taken from study 1245.121 only.

R.1.3.2.2

R.1.3.2.2 Subgroup analysis by sex

Table R.1.3.2.2: 1 KCCQ-CSS change from baseline at week 52 (MMRM) by sex - RS (OC-AD - no imputation for deaths) - 1245.121

Subgroup / Visit / Description / Statistic	Placebo	Empa 10mg
Sex: Male		
Number of patients in analysis set	1411	1426
Number of analysed patients	1333	1361
Baseline mean (SE)	73.37 (0.57)	72.81 (0.58)
Week 52		
Values at visit		
Number of analysed patients	939	954
Mean (SE)	77.08 (0.67)	79.14 (0.65)
Adjusted* mean (SE)	76.16 (0.51)	78.49 (0.50)
95% confidence interval	(75.17,77.16)	(77.51,79.48)
Change from baseline		
Mean (SE)	2.92 (0.61)	5.11 (0.57)
Adjusted* mean (SE)	3.08 (0.51)	5.41 (0.50)
95% confidence interval	(2.09, 4.07)	(4.42, 6.39)
Comparison vs Placebo		
Adjusted* mean (SE)		2.33 (0.71)
95% confidence interval		(0.93, 3.72)
p-value		0.0011

* Model includes Age, baseline eGFR (CKD-EPI) as linear covariate(s) and region, baseline diabetes status, baseline LVEF, week reachable, Visit by Treatment by sex interaction, baseline KCCQ - clinical summary score by Visit interaction as fixed effect(s).
The Visit by Treatment by sex p-value at Week 52 is 0.0381.
The following covariance structure has been used to fit the mixed model: Unstructured
Note: All covariate effects are set equal to their mean values within subgroup for the calculation of adjusted means.

For patients who died, only observed values are considered (no imputation after date of death).
Data taken from study 1245.121 only.
The MMRM includes all outcome values (change from baseline) at the planned Visits week 12, week 32 and week 52

Table R.1.3.2.2: 1 KCCQ-CSS change from baseline at week 52 (MMRM) by sex - RS (OC-AD - no imputation for deaths) - 1245.121

Subgroup / Visit / Description / Statistic	Placebo	Empa 10mg
Sex: Female		
Number of patients in analysis set	456	437
Number of analysed patients	420	415
Baseline mean (SE)	64.49 (1.07)	65.36 (1.11)
Week 52		
Values at visit		
Number of analysed patients	279	285
Mean (SE)	72.53 (1.27)	72.51 (1.27)
Adjusted* mean (SE)	72.12 (0.92)	71.38 (0.92)
95% confidence interval	(70.31,73.94)	(69.58,73.17)
Change from baseline		
Mean (SE)	8.39 (1.13)	5.98 (1.14)
Adjusted* mean (SE)	7.20 (0.92)	6.45 (0.92)
95% confidence interval	(5.39, 9.01)	(4.66, 8.25)
Comparison vs Placebo		
Adjusted* mean (SE)		-0.75 (1.30)
95% confidence interval		(-3.30, 1.80)
p-value		0.5648

* Model includes Age, baseline eGFR (CKD-EPI) as linear covariate(s) and region, baseline diabetes status, baseline LVEF, week reachable, Visit by Treatment by sex interaction, baseline KCCQ - clinical summary score by Visit interaction as fixed effect(s).
The Visit by Treatment by sex p-value at Week 52 is 0.0381.
The following covariance structure has been used to fit the mixed model: Unstructured
Note: All covariate effects are set equal to their mean values within subgroup for the calculation of adjusted means.

For patients who died, only observed values are considered (no imputation after date of death).
Data taken from study 1245.121 only.
The MMRM includes all outcome values (change from baseline) at the planned Visits week 12, week 32 and week 52

R.1.3.2.3

R.1.3.2.3 Subgroup analysis by age

Table R.1.3.2.3: 1 KCCQ-CSS change from baseline at week 52 (MMRM) by age (2 cat.) - RS (OC-AD - no imputation for deaths) - 1245.121

Subgroup / Visit / Description / Statistic	Placebo	Empa 10mg
Age [years] (2 cat.): < 65		
Number of patients in analysis set	740	675
Number of analysed patients	697	645
Baseline mean (SE)	70.73 (0.85)	70.10 (0.89)
Week 52		
Values at visit		
Number of analysed patients	494	454
Mean (SE)	76.37 (0.96)	78.14 (1.01)
Adjusted* mean (SE)	75.35 (0.70)	77.33 (0.73)
95% confidence interval	(73.97,76.73)	(75.90,78.77)
Change from baseline		
Mean (SE)	5.54 (0.89)	7.26 (0.81)
Adjusted* mean (SE)	4.92 (0.70)	6.91 (0.73)
95% confidence interval	(3.54, 6.30)	(5.47, 8.34)
Comparison vs Placebo		
Adjusted* mean (SE)		1.99 (1.01)
95% confidence interval		(0.01, 3.97)
p-value		0.0494

* Model includes baseline eGFR (CKD-EPI) as linear covariate(s) and region, baseline diabetes status, sex, baseline LVEF, week reachable, Visit by Treatment by age [years] (2 cat.) interaction, baseline KCCQ - clinical summary score by Visit interaction as fixed effect(s).
The Visit by Treatment by age [years] (2 cat.) p-value at Week 52 is 0.6380.
The following covariance structure has been used to fit the mixed model: Unstructured
Note: All covariate effects are set equal to their mean values within subgroup for the calculation of adjusted means.

For patients who died, only observed values are considered (no imputation after date of death).
Data taken from study 1245.121 only.
The MMRM includes all outcome values (change from baseline) at the planned Visits week 12, week 32 and week 52

Table R.1.3.2.3: 1 KCCQ-CSS change from baseline at week 52 (MMRM) by age (2 cat.) - RS (OC-AD - no imputation for deaths) - 1245.121

Subgroup / Visit / Description / Statistic	Placebo	Empa 10mg
Age [years] (2 cat.): >= 65		
Number of patients in analysis set	1127	1188
Number of analysed patients	1056	1131
Baseline mean (SE)	71.58 (0.63)	71.62 (0.64)
Week 52		
Values at visit		
Number of analysed patients	724	785
Mean (SE)	75.81 (0.76)	77.32 (0.71)
Adjusted* mean (SE)	75.12 (0.58)	76.50 (0.56)
95% confidence interval	(73.98,76.25)	(75.41,77.59)
Change from baseline		
Mean (SE)	3.23 (0.68)	4.19 (0.65)
Adjusted* mean (SE)	3.52 (0.58)	4.90 (0.56)
95% confidence interval	(2.38, 4.65)	(3.81, 5.99)
Comparison vs Placebo		
Adjusted* mean (SE)		1.38 (0.80)
95% confidence interval		(-0.19, 2.95)
p-value		0.0842

* Model includes baseline eGFR (CKD-EPI) as linear covariate(s) and region, baseline diabetes status, sex, baseline LVEF, week reachable, Visit by Treatment by age [years] (2 cat.) interaction, baseline KCCQ - clinical summary score by Visit interaction as fixed effect(s).
The Visit by Treatment by age [years] (2 cat.) p-value at Week 52 is 0.6380.
The following covariance structure has been used to fit the mixed model: Unstructured
Note: All covariate effects are set equal to their mean values within subgroup for the calculation of adjusted means.

For patients who died, only observed values are considered (no imputation after date of death).
Data taken from study 1245.121 only.
The MMRM includes all outcome values (change from baseline) at the planned Visits week 12, week 32 and week 52

R.1.3.2.4 Subgroup analysis by region (North America, Latin America, Europe, Asia, Other)

Table R.1.3.2.4: 1 KCCQ-CSS change from baseline at week 52 (MMRM) by region - RS (OC-AD - no imputation for deaths) - 1245.121

Subgroup / Visit / Description / Statistic	Placebo	Empa 10mg
Region (5 cat.): North America		
Number of patients in analysis set	213	212
Number of analysed patients	195	206
Baseline mean (SE)	70.57 (1.60)	70.55 (1.53)
Week 52		
Values at visit		
Number of analysed patients	129	151
Mean (SE)	74.46 (1.88)	76.26 (1.65)
Adjusted* mean (SE)	73.39 (1.36)	74.87 (1.27)
95% confidence interval	(70.73,76.05)	(72.38,77.36)
Change from baseline		
Mean (SE)	4.06 (1.39)	3.79 (1.38)
Adjusted* mean (SE)	2.83 (1.36)	4.31 (1.27)
95% confidence interval	(0.17, 5.49)	(1.82, 6.80)
Comparison vs Placebo		
Adjusted* mean (SE)		1.49 (1.86)
95% confidence interval		(-2.16, 5.13)
p-value		0.4241

* Model includes Age, baseline eGFR (CKD-EPI) as linear covariate(s) and baseline diabetes status, sex, baseline LVEF, week reachable, Visit by Treatment by region (5 cat.) interaction, baseline KCCQ - clinical summary score by Visit interaction as fixed effect(s).
The Visit by Treatment by region (5 cat.) p-value at Week 52 is 0.9781.
The following covariance structure has been used to fit the mixed model: Unstructured
Note: All covariate effects are set equal to their mean values within subgroup for the calculation of adjusted means.

For patients who died, only observed values are considered (no imputation after date of death).
Data taken from study 1245.121 only.
The MMRM includes all outcome values (change from baseline) at the planned Visits week 12, week 32 and week 52

Table R.1.3.2.4: 1 KCCQ-CSS change from baseline at week 52 (MMRM) by region - RS (OC-AD - no imputation for deaths) - 1245.121

Subgroup / Visit / Description / Statistic	Placebo	Empa 10mg
Region (5 cat.): Latin America		
Number of patients in analysis set	645	641
Number of analysed patients	599	602
Baseline mean (SE)	67.50 (0.92)	67.03 (0.97)
Week 52		
Values at visit		
Number of analysed patients	391	374
Mean (SE)	75.70 (1.10)	76.88 (1.12)
Adjusted* mean (SE)	75.40 (0.78)	76.76 (0.79)
95% confidence interval	(73.88,76.93)	(75.21,78.31)
Change from baseline		
Mean (SE)	8.64 (1.13)	9.86 (1.09)
Adjusted* mean (SE)	8.14 (0.78)	9.50 (0.79)
95% confidence interval	(6.61, 9.67)	(7.94,11.05)
Comparison vs Placebo		
Adjusted* mean (SE)		1.36 (1.11)
95% confidence interval		(-0.82, 3.53)
p-value		0.2214

* Model includes Age, baseline eGFR (CKD-EPI) as linear covariate(s) and baseline diabetes status, sex, baseline LVEF, week reachable, Visit by Treatment by region (5 cat.) interaction, baseline KCCQ - clinical summary score by Visit interaction as fixed effect(s).
The Visit by Treatment by region (5 cat.) p-value at Week 52 is 0.9781.
The following covariance structure has been used to fit the mixed model: Unstructured
Note: All covariate effects are set equal to their mean values within subgroup for the calculation of adjusted means.

For patients who died, only observed values are considered (no imputation after date of death).
Data taken from study 1245.121 only.
The MMRM includes all outcome values (change from baseline) at the planned Visits week 12, week 32 and week 52

Table R.1.3.2.4: 1 KCCQ-CSS change from baseline at week 52 (MMRM) by region - RS (OC-AD - no imputation for deaths) - 1245.121

Subgroup / Visit / Description / Statistic	Placebo	Empa 10mg
Region (5 cat.): Europe		
Number of patients in analysis set	677	676
Number of analysed patients	644	649
Baseline mean (SE)	69.56 (0.80)	70.31 (0.82)
Week 52		
Values at visit		
Number of analysed patients	468	469
Mean (SE)	72.32 (0.96)	73.91 (0.94)
Adjusted* mean (SE)	71.56 (0.72)	72.92 (0.72)
95% confidence interval	(70.15,72.97)	(71.51,74.33)
Change from baseline		
Mean (SE)	1.66 (0.79)	2.55 (0.73)
Adjusted* mean (SE)	1.62 (0.72)	2.98 (0.72)
95% confidence interval	(0.21, 3.03)	(1.58, 4.39)
Comparison vs Placebo		
Adjusted* mean (SE)		1.36 (1.02)
95% confidence interval		(-0.63, 3.35)
p-value		0.1798

* Model includes Age, baseline eGFR (CKD-EPI) as linear covariate(s) and baseline diabetes status, sex, baseline LVEF, week reachable, Visit by Treatment by region (5 cat.) interaction, baseline KCCQ - clinical summary score by Visit interaction as fixed effect(s).
The Visit by Treatment by region (5 cat.) p-value at Week 52 is 0.9781.
The following covariance structure has been used to fit the mixed model: Unstructured
Note: All covariate effects are set equal to their mean values within subgroup for the calculation of adjusted means.

For patients who died, only observed values are considered (no imputation after date of death).
Data taken from study 1245.121 only.
The MMRM includes all outcome values (change from baseline) at the planned Visits week 12, week 32 and week 52

Table R.1.3.2.4: 1 KCCQ-CSS change from baseline at week 52 (MMRM) by region - RS (OC-AD - no imputation for deaths) - 1245.121

Subgroup / Visit / Description / Statistic	Placebo	Empa 10mg
Region (5 cat.): Asia		
Number of patients in analysis set	245	248
Number of analysed patients	237	243
Baseline mean (SE)	84.34 (0.98)	82.09 (1.13)
Week 52		
Values at visit		
Number of analysed patients	180	189
Mean (SE)	84.33 (1.19)	85.94 (1.26)
Adjusted* mean (SE)	83.18 (1.17)	85.61 (1.14)
95% confidence interval	(80.89,85.48)	(83.37,87.85)
Change from baseline		
Mean (SE)	-0.50 (1.07)	2.26 (1.15)
Adjusted* mean (SE)	-0.02 (1.17)	2.41 (1.14)
95% confidence interval	(-2.31, 2.27)	(0.17, 4.65)
Comparison vs Placebo		
Adjusted* mean (SE)		2.43 (1.63)
95% confidence interval		(-0.77, 5.63)
p-value		0.1368

* Model includes Age, baseline eGFR (CKD-EPI) as linear covariate(s) and baseline diabetes status, sex, baseline LVEF, week reachable, Visit by Treatment by region (5 cat.) interaction, baseline KCCQ - clinical summary score by Visit interaction as fixed effect(s).
The Visit by Treatment by region (5 cat.) p-value at Week 52 is 0.9781.
The following covariance structure has been used to fit the mixed model: Unstructured
Note: All covariate effects are set equal to their mean values within subgroup for the calculation of adjusted means.

For patients who died, only observed values are considered (no imputation after date of death).
Data taken from study 1245.121 only.
The MMRM includes all outcome values (change from baseline) at the planned Visits week 12, week 32 and week 52

Table R.1.3.2.4: 1 KCCQ-CSS change from baseline at week 52 (MMRM) by region - RS (OC-AD - no imputation for deaths) - 1245.121

Subgroup / Visit / Description / Statistic	Placebo	Empa 10mg
Region (5 cat.): Other		
Number of patients in analysis set	87	86
Number of analysed patients	78	76
Baseline mean (SE)	75.68 (2.19)	75.73 (1.95)
Week 52		
Values at visit		
Number of analysed patients	50	56
Mean (SE)	87.65 (2.05)	89.13 (1.43)
Adjusted* mean (SE)	85.61 (2.18)	88.10 (2.08)
95% confidence interval	(81.34,89.88)	(84.02,92.18)
Change from baseline		
Mean (SE)	9.83 (2.70)	12.46 (1.84)
Adjusted* mean (SE)	9.91 (2.18)	12.39 (2.08)
95% confidence interval	(5.63,14.18)	(8.31,16.48)
Comparison vs Placebo		
Adjusted* mean (SE)		2.49 (3.01)
95% confidence interval		(-3.42, 8.40)
p-value		0.4086

* Model includes Age, baseline eGFR (CKD-EPI) as linear covariate(s) and baseline diabetes status, sex, baseline LVEF, week reachable, Visit by Treatment by region (5 cat.) interaction, baseline KCCQ - clinical summary score by Visit interaction as fixed effect(s).
The Visit by Treatment by region (5 cat.) p-value at Week 52 is 0.9781.
The following covariance structure has been used to fit the mixed model: Unstructured
Note: All covariate effects are set equal to their mean values within subgroup for the calculation of adjusted means.

For patients who died, only observed values are considered (no imputation after date of death).
Data taken from study 1245.121 only.
The MMRM includes all outcome values (change from baseline) at the planned Visits week 12, week 32 and week 52

R.1.3.2.5

R.1.3.2.5 Subgroup analysis by OECD (N/Y)

Table R.1.3.2.5: 1 KCCQ-CSS change from baseline at week 52 (MMRM) by OECD member (N/Y) - RS (OC-AD - no imputation for deaths) - 1245.121

Subgroup / Visit / Description / Statistic	Placebo	Empa 10mg
OECD member: No		
Number of patients in analysis set	741	713
Number of analysed patients	686	664
Baseline mean (SE)	69.22 (0.85)	68.55 (0.90)
Week 52		
Values at visit		
Number of analysed patients	443	421
Mean (SE)	77.29 (1.00)	79.21 (0.99)
Adjusted* mean (SE)	76.77 (0.73)	79.02 (0.75)
95% confidence interval	(75.33,78.21)	(77.55,80.49)
Change from baseline		
Mean (SE)	8.25 (1.03)	10.57 (0.98)
Adjusted* mean (SE)	7.88 (0.73)	10.13 (0.75)
95% confidence interval	(6.44, 9.32)	(8.66,11.60)
Comparison vs Placebo		
Adjusted* mean (SE)		2.25 (1.05)
95% confidence interval		(0.19, 4.30)
p-value		0.0320

* Model includes Age, baseline eGFR (CKD-EPI) as linear covariate(s) and baseline diabetes status, sex, baseline LVEF, week reachable, Visit by Treatment by OECD Member (N) interaction, baseline KCCQ - clinical summary score by Visit interaction as fixed effect(s).
The Visit by Treatment by OECD Member (N) p-value at Week 52 is 0.5055.
The following covariance structure has been used to fit the mixed model: Unstructured
Note: All covariate effects are set equal to their mean values within subgroup for the calculation of adjusted means.

For patients who died, only observed values are considered (no imputation after date of death).
Data taken from study 1245.121 only.
OECD member (yes/no) countries included:
Yes: United States, Canada, Mexico, Poland, Netherlands, Hungary, Germany, Czech Republic, Italy, France, Spain, United Kingdom, Belgium, Japan, Australia, 'Korea; Republic Of South Korea';
No: Brazil, Argentina, China, India.
The MMRM includes all outcome values (change from baseline) at the planned Visits week 12, week 32 and week 52

Table R.1.3.2.5: 1 KCCQ-CSS change from baseline at week 52 (MMRM) by OECD member (N/Y) - RS (OC-AD - no imputation for deaths) - 1245.121

Subgroup / Visit / Description / Statistic	Placebo	Empa 10mg
OECD member: Yes		
Number of patients in analysis set	1126	1150
Number of analysed patients	1067	1112
Baseline mean (SE)	72.54 (0.63)	72.57 (0.63)
Week 52		
Values at visit		
Number of analysed patients	775	818
Mean (SE)	75.32 (0.74)	76.80 (0.72)
Adjusted* mean (SE)	74.26 (0.56)	75.64 (0.55)
95% confidence interval	(73.16,75.36)	(74.56,76.71)
Change from baseline		
Mean (SE)	1.84 (0.60)	2.61 (0.56)
Adjusted* mean (SE)	1.70 (0.56)	3.08 (0.55)
95% confidence interval	(0.60, 2.81)	(2.01, 4.15)
Comparison vs Placebo		
Adjusted* mean (SE)		1.38 (0.78)
95% confidence interval		(-0.16, 2.91)
p-value		0.0790

* Model includes Age, baseline eGFR (CKD-EPI) as linear covariate(s) and baseline diabetes status, sex, baseline LVEF, week reachable, Visit by Treatment by OECD Member (N) interaction, baseline KCCQ - clinical summary score by Visit interaction as fixed effect(s).
The Visit by Treatment by OECD Member (N) p-value at Week 52 is 0.5055.
The following covariance structure has been used to fit the mixed model: Unstructured
Note: All covariate effects are set equal to their mean values within subgroup for the calculation of adjusted means.

For patients who died, only observed values are considered (no imputation after date of death).
Data taken from study 1245.121 only.
OECD member (yes/no) countries included:
Yes: United States, Canada, Mexico, Poland, Netherlands, Hungary, Germany, Czech Republic, Italy, France, Spain, United Kingdom, Belgium, Japan, Australia, 'Korea; Republic Of South Korea';
No: Brazil, Argentina, China, India.
The MMRM includes all outcome values (change from baseline) at the planned Visits week 12, week 32 and week 52

R.1.3.2.6 Subgroup analysis by NYHA at baseline (II, III/IV - 2 cat.)

Table R.1.3.2.6: 1 KCCQ-CSS change from baseline at week 52 (MMRM) by NYHA (2 cat.) - RS (OC-AD - no imputation for deaths) - 1245.121

Subgroup / Visit / Description / Statistic	Placebo	Empa 10mg
Baseline NYHA (2 cat.): II		
Number of patients in analysis set	1401	1399
Number of analysed patients	1340	1332
Baseline mean (SE)	75.16 (0.53)	76.26 (0.53)
Week 52		
Values at visit		
Number of analysed patients	946	951
Mean (SE)	78.54 (0.63)	80.97 (0.62)
Adjusted* mean (SE)	78.33 (0.50)	80.21 (0.50)
95% confidence interval	(77.34,79.32)	(79.22,81.19)
Change from baseline		
Mean (SE)	3.09 (0.59)	4.16 (0.55)
Adjusted* mean (SE)	2.62 (0.50)	4.49 (0.50)
95% confidence interval	(1.63, 3.61)	(3.51, 5.48)
Comparison vs Placebo		
Adjusted* mean (SE)		1.88 (0.71)
95% confidence interval		(0.48, 3.27)
p-value		0.0085

* Model includes Age, baseline eGFR (CKD-EPI) as linear covariate(s) and region, baseline diabetes status, sex, baseline LVEF, week reachable, Visit by Treatment by baseline NYHA (2 cat.) interaction, baseline KCCQ - clinical summary score by Visit interaction as fixed effect(s).
The Visit by Treatment by baseline NYHA (2 cat.) p-value at Week 52 is 0.4966.
The following covariance structure has been used to fit the mixed model: Unstructured
Note: All covariate effects are set equal to their mean values within subgroup for the calculation of adjusted means.

For patients who died, only observed values are considered (no imputation after date of death).
Data taken from study 1245.121 only.
The MMRM includes all outcome values (change from baseline) at the planned Visits week 12, week 32 and week 52

Table R.1.3.2.6: 1 KCCQ-CSS change from baseline at week 52 (MMRM) by NYHA (2 cat.) - RS (OC-AD - no imputation for deaths) - 1245.121

Subgroup / Visit / Description / Statistic	Placebo	Empa 10mg
Baseline NYHA (2 cat.): III/IV		
Number of patients in analysis set	466	464
Number of analysed patients	413	444
Baseline mean (SE)	58.52 (1.12)	55.49 (1.05)
Week 52		
Values at visit		
Number of analysed patients	272	288
Mean (SE)	67.35 (1.37)	66.55 (1.26)
Adjusted* mean (SE)	65.39 (0.94)	66.26 (0.91)
95% confidence interval	(63.56,67.23)	(64.48,68.04)
Change from baseline		
Mean (SE)	7.93 (1.28)	9.12 (1.20)
Adjusted* mean (SE)	8.44 (0.94)	9.31 (0.91)
95% confidence interval	(6.61,10.28)	(7.53,11.09)
Comparison vs Placebo		
Adjusted* mean (SE)		0.87 (1.30)
95% confidence interval		(-1.68, 3.42)
p-value		0.5049

* Model includes Age, baseline eGFR (CKD-EPI) as linear covariate(s) and region, baseline diabetes status, sex, baseline LVEF, week reachable, Visit by Treatment by baseline NYHA (2 cat.) interaction, baseline KCCQ - clinical summary score by Visit interaction as fixed effect(s).
The Visit by Treatment by baseline NYHA (2 cat.) p-value at Week 52 is 0.4966.
The following covariance structure has been used to fit the mixed model: Unstructured
Note: All covariate effects are set equal to their mean values within subgroup for the calculation of adjusted means.

For patients who died, only observed values are considered (no imputation after date of death).
Data taken from study 1245.121 only.
The MMRM includes all outcome values (change from baseline) at the planned Visits week 12, week 32 and week 52

R.1.3.2.7

R.1.3.2.7 Subgroup analysis by diabetes at baseline

Table R.1.3.2.7: 1 KCCQ-CSS change from baseline at week 52 (MMRM) by diabetes at baseline - RS (OC-AD - no imputation for deaths) - 1245.121

Subgroup / Visit / Description / Statistic	Placebo	Empa 10mg
Diabetes at baseline (2 cat.):		
Diabetic		
Number of patients in analysis set	929	927
Number of analysed patients	868	882
Baseline mean (SE)	70.04 (0.75)	69.81 (0.77)
Week 52		
Values at visit		
Number of analysed patients	606	614
Mean (SE)	75.60 (0.86)	77.17 (0.85)
Adjusted* mean (SE)	74.09 (0.63)	76.19 (0.63)
95% confidence interval	(72.85,75.33)	(74.96,77.41)
Change from baseline		
Mean (SE)	4.07 (0.77)	5.58 (0.74)
Adjusted* mean (SE)	4.17 (0.63)	6.27 (0.63)
95% confidence interval	(2.93, 5.40)	(5.04, 7.49)
Comparison vs Placebo		
Adjusted* mean (SE)		2.10 (0.89)
95% confidence interval		(0.36, 3.84)
p-value		0.0180

* Model includes Age, baseline eGFR (CKD-EPI) as linear covariate(s) and region, sex, baseline LVEF, week reachable,
Visit by Treatment by diabetes at baseline (2 cat.) interaction,
baseline KCCQ - clinical summary score by Visit interaction as fixed effect(s).
The Visit by Treatment by diabetes at baseline (2 cat.) p-value at Week 52 is 0.4454.
The following covariance structure has been used to fit the mixed model: Unstructured
Note: All covariate effects are set equal to their mean values within subgroup for the calculation of adjusted means.

For patients who died, only observed values are considered (no imputation after date of death).
Data taken from study 1245.121 only.
The MMRM includes all outcome values (change from baseline) at the planned Visits week 12, week 32 and week 52

Table R.1.3.2.7: 1

Table R.1.3.2.7: 1 KCCQ-CSS change from baseline at week 52 (MMRM) by diabetes at baseline - RS (OC-AD - no imputation for deaths) - 1245.121

Subgroup / Visit / Description / Statistic	Placebo	Empa 10mg
Diabetes at baseline (2 cat.):		
Non-Diabetic		
Number of patients in analysis set	938	936
Number of analysed patients	885	894
Baseline mean (SE)	72.42 (0.69)	72.31 (0.71)
Week 52		
Values at visit		
Number of analysed patients	612	625
Mean (SE)	76.48 (0.82)	78.06 (0.80)
Adjusted* mean (SE)	76.30 (0.63)	77.44 (0.62)
95% confidence interval	(75.07,77.52)	(76.23,78.66)
Change from baseline		
Mean (SE)	4.27 (0.77)	5.05 (0.70)
Adjusted* mean (SE)	3.93 (0.63)	5.08 (0.62)
95% confidence interval	(2.70, 5.16)	(3.86, 6.29)
Comparison vs Placebo		
Adjusted* mean (SE)		1.15 (0.88)
95% confidence interval		(-0.58, 2.87)
p-value		0.1935

* Model includes Age, baseline eGFR (CKD-EPI) as linear covariate(s) and region, sex, baseline LVEF, week reachable,
Visit by Treatment by diabetes at baseline (2 cat.) interaction,
baseline KCCQ - clinical summary score by Visit interaction as fixed effect(s).
The Visit by Treatment by diabetes at baseline (2 cat.) p-value at Week 52 is 0.4454.
The following covariance structure has been used to fit the mixed model: Unstructured
Note: All covariate effects are set equal to their mean values within subgroup for the calculation of adjusted means.

For patients who died, only observed values are considered (no imputation after date of death).
Data taken from study 1245.121 only.
The MMRM includes all outcome values (change from baseline) at the planned Visits week 12, week 32 and week 52

R.1.3.2.8

R.1.3.2.8 Subgroup analysis by BMI at baseline (<30, >=30)

Table R.1.3.2.8: 1

Table R.1.3.2.8: 1 KCCQ-CSS change from baseline at week 52 (MMRM) by baseline BMI [kg/m2] - RS (OC-AD - no imputation for deaths) - 1245.121

Subgroup / Visit / Description / Statistic	Placebo	Empa 10mg
Baseline BMI [kg/m²] (2 cat.): <30		
Number of patients in analysis set	1300	1263
Number of analysed patients	1229	1201
Baseline mean (SE)	72.90 (0.59)	73.30 (0.62)
Week 52		
Values at visit		
Number of analysed patients	865	826
Mean (SE)	77.38 (0.67)	80.04 (0.68)
Adjusted* mean (SE)	76.69 (0.53)	78.60 (0.54)
95% confidence interval	(75.66,77.73)	(77.54,79.66)
Change from baseline		
Mean (SE)	3.86 (0.62)	5.07 (0.60)
Adjusted* mean (SE)	3.60 (0.53)	5.50 (0.54)
95% confidence interval	(2.56, 4.64)	(4.44, 6.56)
Comparison vs Placebo		
Adjusted* mean (SE)		1.90 (0.75)
95% confidence interval		(0.42, 3.38)
p-value		0.0117

* Model includes Age, baseline eGFR (CKD-EPI) as linear covariate(s) and region, baseline diabetes status, sex, baseline LVEF, week reachable, Visit by Treatment by baseline BMI [kg/m²] (2 cat.) interaction, baseline KCCQ - clinical summary score by Visit interaction as fixed effect(s).
The Visit by Treatment by baseline BMI [kg/m²] (2 cat.) p-value at Week 52 is 0.6045.
The following covariance structure has been used to fit the mixed model: Unstructured
Note: All covariate effects are set equal to their mean values within subgroup for the calculation of adjusted means.

For patients who died, only observed values are considered (no imputation after date of death).
Data taken from study 1245.121 only.
The MMRM includes all outcome values (change from baseline) at the planned Visits week 12, week 32 and week 52

Table R.1.3.2.8: 1 KCCQ-CSS change from baseline at week 52 (MMRM) by baseline BMI [kg/m2] - RS (OC-AD - no imputation for deaths) - 1245.121

Subgroup / Visit / Description / Statistic	Placebo	Empa 10mg
Baseline BMI [kg/m²] (2 cat.): >=30		
Number of patients in analysis set	567	600
Number of analysed patients	524	575
Baseline mean (SE)	67.36 (0.96)	66.41 (0.93)
Week 52		
Values at visit		
Number of analysed patients	353	413
Mean (SE)	72.76 (1.21)	72.77 (1.07)
Adjusted* mean (SE)	71.83 (0.83)	73.03 (0.77)
95% confidence interval	(70.21,73.46)	(71.52,74.55)
Change from baseline		
Mean (SE)	4.93 (1.08)	5.81 (0.95)
Adjusted* mean (SE)	4.97 (0.83)	6.17 (0.77)
95% confidence interval	(3.35, 6.59)	(4.66, 7.68)
Comparison vs Placebo		
Adjusted* mean (SE)		1.20 (1.12)
95% confidence interval		(-1.00, 3.40)
p-value		0.2847

* Model includes Age, baseline eGFR (CKD-EPI) as linear covariate(s) and region, baseline diabetes status, sex, baseline LVEF, week reachable, Visit by Treatment by baseline BMI [kg/m²] (2 cat.) interaction, baseline KCCQ - clinical summary score by Visit interaction as fixed effect(s).
The Visit by Treatment by baseline BMI [kg/m²] (2 cat.) p-value at Week 52 is 0.6045.
The following covariance structure has been used to fit the mixed model: Unstructured
Note: All covariate effects are set equal to their mean values within subgroup for the calculation of adjusted means.

For patients who died, only observed values are considered (no imputation after date of death).
Data taken from study 1245.121 only.
The MMRM includes all outcome values (change from baseline) at the planned Visits week 12, week 32 and week 52

R.1.3.2.9 Subgroup analysis by eGFR at baseline (<60, >=60)

Table R.1.3.2.9: 1 KCCQ-CSS change from baseline at week 52 (MMRM) by baseline eGFR (2 cat.) - RS (OC-AD - no imputation for deaths) - 1245.121

Subgroup / Visit / Description / Statistic	Placebo	Empa 10mg
Baseline eGFR (CKD-EPI) [mL/min/1.73m²] (2 cat.): >=60		
Number of patients in analysis set	960	969
Number of analysed patients	901	921
Baseline mean (SE)	72.03 (0.71)	71.80 (0.73)
Week 52		
Values at visit		
Number of analysed patients	647	650
Mean (SE)	76.46 (0.81)	79.49 (0.82)
Adjusted* mean (SE)	75.62 (0.61)	78.56 (0.61)
95% confidence interval	(74.41,76.82)	(77.36,79.75)
Change from baseline		
Mean (SE)	3.83 (0.72)	6.48 (0.69)
Adjusted* mean (SE)	3.70 (0.61)	6.64 (0.61)
95% confidence interval	(2.50, 4.90)	(5.45, 7.83)
Comparison vs Placebo		
Adjusted* mean (SE)		2.94 (0.86)
95% confidence interval		(1.25, 4.63)
p-value		0.0007

* Model includes Age as linear covariate(s) and region, baseline diabetes status, sex, baseline LVEF, week reachable, Visit by Treatment by baseline eGFR (CKD-EPI) [mL/min/1.73m²] (2 cat.) interaction, baseline KCCQ - clinical summary score by Visit interaction as fixed effect(s).
The Visit by Treatment by baseline eGFR (CKD-EPI) [mL/min/1.73m²] (2 cat.) p-value at Week 52 is 0.0242.
The following covariance structure has been used to fit the mixed model: Unstructured
2 patients were excluded as the subgroup variable was missing.
Note: All covariate effects are set equal to their mean values within subgroup for the calculation of adjusted means.

For patients who died, only observed values are considered (no imputation after date of death).
Data taken from study 1245.121 only.
The MMRM includes all outcome values (change from baseline) at the planned Visits week 12, week 32 and week 52

Table R.1.3.2.9: 1 KCCQ-CSS change from baseline at week 52 (MMRM) by baseline eGFR (2 cat.) - RS (OC-AD - no imputation for deaths) - 1245.121

Subgroup / Visit / Description / Statistic	Placebo	Empa 10mg
Baseline eGFR (CKD-EPI) [mL/min/1.73m²] (2 cat.): <60		
Number of patients in analysis set	906	893
Number of analysed patients	852	855
Baseline mean (SE)	70.40 (0.73)	70.28 (0.74)
Week 52		
Values at visit		
Number of analysed patients	571	589
Mean (SE)	75.56 (0.88)	75.55 (0.82)
Adjusted* mean (SE)	74.82 (0.65)	74.94 (0.64)
95% confidence interval	(73.55,76.09)	(73.68,76.19)
Change from baseline		
Mean (SE)	4.55 (0.82)	4.03 (0.76)
Adjusted* mean (SE)	4.48 (0.65)	4.60 (0.64)
95% confidence interval	(3.21, 5.75)	(3.34, 5.85)
Comparison vs Placebo		
Adjusted* mean (SE)		0.12 (0.91)
95% confidence interval		(-1.66, 1.90)
p-value		0.8967

* Model includes Age as linear covariate(s) and region, baseline diabetes status, sex, baseline LVEF, week reachable, Visit by Treatment by baseline eGFR (CKD-EPI) [mL/min/1.73m²] (2 cat.) interaction, baseline KCCQ - clinical summary score by Visit interaction as fixed effect(s).
The Visit by Treatment by baseline eGFR (CKD-EPI) [mL/min/1.73m²] (2 cat.) p-value at Week 52 is 0.0242.
The following covariance structure has been used to fit the mixed model: Unstructured
2 patients were excluded as the subgroup variable was missing.
Note: All covariate effects are set equal to their mean values within subgroup for the calculation of adjusted means.

For patients who died, only observed values are considered (no imputation after date of death).
Data taken from study 1245.121 only.
The MMRM includes all outcome values (change from baseline) at the planned Visits week 12, week 32 and week 52

R.1.3.2.10

Table R.1.3.2.10: 1 KCCQ-CSS change from baseline at week 52 (MMRM) by history of HHF - RS (OC-AD - no imputation for deaths) - 1245.121

Subgroup / Visit / Description / Statistic	Placebo	Empa 10mg
History of HHF (in the last 12 months): No		
Number of patients in analysis set	1293	1286
Number of analysed patients	1220	1231
Baseline mean (SE)	71.28 (0.61)	71.03 (0.62)
Week 52		
Values at visit		
Number of analysed patients	869	873
Mean (SE)	75.14 (0.72)	77.59 (0.69)
Adjusted* mean (SE)	74.87 (0.53)	76.98 (0.53)
95% confidence interval	(73.83,75.90)	(75.94,78.01)
Change from baseline		
Mean (SE)	3.80 (0.65)	5.62 (0.62)
Adjusted* mean (SE)	3.71 (0.53)	5.82 (0.53)
95% confidence interval	(2.68, 4.75)	(4.79, 6.85)
Comparison vs Placebo		
Adjusted* mean (SE)		2.11 (0.74)
95% confidence interval		(0.65, 3.57)
p-value		0.0046

* Model includes Age, baseline eGFR (CKD-EPI) as linear covariate(s) and region, baseline diabetes status, sex, baseline LVEF, week reachable, Visit by Treatment by history of HHF (in the last 12 months) interaction, baseline KCCQ - clinical summary score by Visit interaction as fixed effect(s).
The Visit by Treatment by history of HHF (in the last 12 months) p-value at Week 52 is 0.2047.
The following covariance structure has been used to fit the mixed model: Unstructured
Note: All covariate effects are set equal to their mean values within subgroup for the calculation of adjusted means.

For patients who died, only observed values are considered (no imputation after date of death).
Data taken from study 1245.121 only.
The MMRM includes all outcome values (change from baseline) at the planned Visits week 12, week 32 and week 52

Table R.1.3.2.10: 1 KCCQ-CSS change from baseline at week 52 (MMRM) by history of HHF - RS (OC-AD - no imputation for deaths) - 1245.121

Subgroup / Visit / Description / Statistic	Placebo	Empa 10mg
History of HHF (in the last 12 months): Yes		
Number of patients in analysis set	574	577
Number of analysed patients	533	545
Baseline mean (SE)	71.16 (0.91)	71.16 (0.96)
Week 52		
Values at visit		
Number of analysed patients	349	366
Mean (SE)	78.28 (1.04)	77.69 (1.10)
Adjusted* mean (SE)	76.07 (0.83)	76.44 (0.81)
95% confidence interval	(74.45,77.69)	(74.85,78.03)
Change from baseline		
Mean (SE)	5.10 (0.99)	4.57 (0.91)
Adjusted* mean (SE)	4.91 (0.83)	5.28 (0.81)
95% confidence interval	(3.29, 6.53)	(3.69, 6.87)
Comparison vs Placebo		
Adjusted* mean (SE)		0.37 (1.15)
95% confidence interval		(-1.89, 2.63)
p-value		0.7490

* Model includes Age, baseline eGFR (CKD-EPI) as linear covariate(s) and region, baseline diabetes status, sex, baseline LVEF, week reachable, Visit by Treatment by history of HHF (in the last 12 months) interaction, baseline KCCQ - clinical summary score by Visit interaction as fixed effect(s).
The Visit by Treatment by history of HHF (in the last 12 months) p-value at Week 52 is 0.2047.
The following covariance structure has been used to fit the mixed model: Unstructured
Note: All covariate effects are set equal to their mean values within subgroup for the calculation of adjusted means.

For patients who died, only observed values are considered (no imputation after date of death).
Data taken from study 1245.121 only.
The MMRM includes all outcome values (change from baseline) at the planned Visits week 12, week 32 and week 52

R.1.3.2.11

R.1.3.2.11 Subgroup analysis by cause of heart failure

Table R.1.3.2.11: 1 KCCQ-CSS change from baseline at week 52 (MMRM) by cause of heart failure - RS (OC-AD - no imputation for deaths) - 1245.121

Subgroup / Visit / Description / Statistic	Placebo	Empa 10mg
Cause of heart failure: Ischemic		
Number of patients in analysis set	946	983
Number of analysed patients	896	936
Baseline mean (SE)	71.30 (0.70)	70.79 (0.72)
Week 52		
Values at visit		
Number of analysed patients	634	667
Mean (SE)	75.97 (0.83)	77.07 (0.80)
Adjusted* mean (SE)	75.13 (0.62)	76.21 (0.60)
95% confidence interval	(73.92,76.35)	(75.02,77.39)
Change from baseline		
Mean (SE)	3.74 (0.72)	4.67 (0.69)
Adjusted* mean (SE)	4.09 (0.62)	5.17 (0.60)
95% confidence interval	(2.88, 5.31)	(3.98, 6.35)
Comparison vs Placebo		
Adjusted* mean (SE)		1.07 (0.86)
95% confidence interval		(-0.62, 2.76)
p-value		0.2128

* Model includes Age, baseline eGFR (CKD-EPI) as linear covariate(s) and region, baseline diabetes status, sex, baseline LVEF, week reachable, Visit by Treatment by cause of heart failure interaction, baseline KCCQ - clinical summary score by Visit interaction as fixed effect(s).
The Visit by Treatment by cause of heart failure p-value at Week 52 is 0.3606.
The following covariance structure has been used to fit the mixed model: Unstructured
Note: All covariate effects are set equal to their mean values within subgroup for the calculation of adjusted means.

For patients who died, only observed values are considered (no imputation after date of death).
Data taken from study 1245.121 only.
The MMRM includes all outcome values (change from baseline) at the planned Visits week 12, week 32 and week 52

Table R.1.3.2.11: 1 KCCQ-CSS change from baseline at week 52 (MMRM) by cause of heart failure - RS (OC-AD - no imputation for deaths) - 1245.121

Subgroup / Visit / Description / Statistic	Placebo	Empa 10mg
Cause of heart failure: Non-ischemic		
Number of patients in analysis set	921	880
Number of analysed patients	857	840
Baseline mean (SE)	71.18 (0.74)	71.38 (0.76)
Week 52		
Values at visit		
Number of analysed patients	584	572
Mean (SE)	76.11 (0.85)	78.26 (0.85)
Adjusted* mean (SE)	75.28 (0.64)	77.50 (0.65)
95% confidence interval	(74.02,76.55)	(76.23,78.77)
Change from baseline		
Mean (SE)	4.64 (0.82)	6.06 (0.75)
Adjusted* mean (SE)	4.00 (0.64)	6.22 (0.65)
95% confidence interval	(2.74, 5.27)	(4.95, 7.50)
Comparison vs Placebo		
Adjusted* mean (SE)		2.22 (0.91)
95% confidence interval		(0.44, 4.00)
p-value		0.0147

* Model includes Age, baseline eGFR (CKD-EPI) as linear covariate(s) and region, baseline diabetes status, sex, baseline LVEF, week reachable, Visit by Treatment by cause of heart failure interaction, baseline KCCQ - clinical summary score by Visit interaction as fixed effect(s).
The Visit by Treatment by cause of heart failure p-value at Week 52 is 0.3606.
The following covariance structure has been used to fit the mixed model: Unstructured
Note: All covariate effects are set equal to their mean values within subgroup for the calculation of adjusted means.

For patients who died, only observed values are considered (no imputation after date of death).
Data taken from study 1245.121 only.
The MMRM includes all outcome values (change from baseline) at the planned Visits week 12, week 32 and week 52

R.1.3.2.12 Subgroup analysis by heart failure physiology (LVEF <= 30% and NTproBNP<median; LVEF <= 30% and NTproBNP>=median; LVEF > 30%)

Table R.1.3.2.12: 1 KCCQ-CSS change from baseline at week 52 (MMRM) by heart failure physiology - RS (OC-AD - no imputation for deaths) - 1245.121

Subgroup / Visit / Description / Statistic	Placebo	Empa 10mg
Heart failure physiology: LVEF <= 30% and NTproBNP < median		
Number of patients in analysis set	723	698
Number of analysed patients	694	672
Baseline mean (SE)	72.61 (0.79)	73.16 (0.81)
Week 52		
Values at visit		
Number of analysed patients	511	494
Mean (SE)	77.55 (0.89)	79.05 (0.89)
Adjusted* mean (SE)	77.16 (0.69)	78.81 (0.70)
95% confidence interval	(75.81,78.51)	(77.44,80.18)
Change from baseline		
Mean (SE)	4.96 (0.75)	5.69 (0.71)
Adjusted* mean (SE)	4.28 (0.69)	5.92 (0.70)
95% confidence interval	(2.93, 5.63)	(4.55, 7.30)
Comparison vs Placebo		
Adjusted* mean (SE)		1.64 (0.98)
95% confidence interval		(-0.28, 3.57)
p-value		0.0943

* Model includes Age, baseline eGFR (CKD-EPI) as linear covariate(s) and region, baseline diabetes status, sex, week reachable, Visit by Treatment by heart failure physiology interaction, baseline KCCQ - clinical summary score by Visit interaction as fixed effect(s).
The Visit by Treatment by heart failure physiology p-value at Week 52 is 0.4683.
The following covariance structure has been used to fit the mixed model: Unstructured
16 patients were excluded as the subgroup variable was missing.
Note: All covariate effects are set equal to their mean values within subgroup for the calculation of adjusted means.
The p-value for the visit by treatment by subgroup interaction trend test at Week 52 is 0.5871

For patients who died, only observed values are considered (no imputation after date of death).
Data taken from study 1245.121 only.
NTproBNP median [pg/mL]: with a. fibrillation/flutter at baseline: 2265; without a. fibrillation/flutter at baseline: 1671.
The MMRM includes all outcome values (change from baseline) at the planned Visits week 12, week 32 and week 52

Table R.1.3.2.12: 1 KCCQ-CSS change from baseline at week 52 (MMRM) by heart failure physiology - RS (OC-AD - no imputation for deaths) - 1245.121

Subgroup / Visit / Description / Statistic	Placebo	Empa 10mg
Heart failure physiology: LVEF <= 30% and NTproBNP >= median		
Number of patients in analysis set	661	631
Number of analysed patients	604	593
Baseline mean (SE)	68.96 (0.89)	67.93 (0.92)
Week 52		
Values at visit		
Number of analysed patients	409	405
Mean (SE)	73.31 (1.07)	75.69 (1.07)
Adjusted* mean (SE)	72.08 (0.76)	74.59 (0.77)
95% confidence interval	(70.58,73.58)	(73.08,76.10)
Change from baseline		
Mean (SE)	3.20 (1.07)	5.87 (0.98)
Adjusted* mean (SE)	3.62 (0.76)	6.14 (0.77)
95% confidence interval	(2.13, 5.12)	(4.63, 7.65)
Comparison vs Placebo		
Adjusted* mean (SE)		2.51 (1.08)
95% confidence interval		(0.39, 4.64)
p-value		0.0204

* Model includes Age, baseline eGFR (CKD-EPI) as linear covariate(s) and region, baseline diabetes status, sex, week reachable, Visit by Treatment by heart failure physiology interaction, baseline KCCQ - clinical summary score by Visit interaction as fixed effect(s).
The Visit by Treatment by heart failure physiology p-value at Week 52 is 0.4683.
The following covariance structure has been used to fit the mixed model: Unstructured
16 patients were excluded as the subgroup variable was missing.
Note: All covariate effects are set equal to their mean values within subgroup for the calculation of adjusted means.
The p-value for the visit by treatment by subgroup interaction trend test at Week 52 is 0.5871

For patients who died, only observed values are considered (no imputation after date of death).
Data taken from study 1245.121 only.
NTproBNP median [pg/mL]: with a. fibrillation/flutter at baseline: 2265; without a. fibrillation/flutter at baseline: 1671.
The MMRM includes all outcome values (change from baseline) at the planned Visits week 12, week 32 and week 52

Table R.1.3.2.12: 1 KCCQ-CSS change from baseline at week 52 (MMRM) by heart failure physiology - RS (OC-AD - no imputation for deaths) - 1245.121

Subgroup / Visit / Description / Statistic	Placebo	Empa 10mg
Heart failure physiology: LVEF > 30%		
Number of patients in analysis set	475	526
Number of analysed patients	450	506
Baseline mean (SE)	72.38 (0.99)	72.00 (1.00)
Week 52		
Values at visit		
Number of analysed patients	294	339
Mean (SE)	77.34 (1.15)	77.80 (1.10)
Adjusted* mean (SE)	76.34 (0.90)	76.83 (0.84)
95% confidence interval	(74.58,78.10)	(75.20,78.47)
Change from baseline		
Mean (SE)	4.03 (1.05)	4.13 (1.02)
Adjusted* mean (SE)	4.16 (0.90)	4.65 (0.84)
95% confidence interval	(2.40, 5.92)	(3.01, 6.29)
Comparison vs Placebo		
Adjusted* mean (SE)		0.50 (1.23)
95% confidence interval		(-1.90, 2.90)
p-value		0.6845

* Model includes Age, baseline eGFR (CKD-EPI) as linear covariate(s) and region, baseline diabetes status, sex, week reachable, Visit by Treatment by heart failure physiology interaction, baseline KCCQ - clinical summary score by Visit interaction as fixed effect(s).
The Visit by Treatment by heart failure physiology p-value at Week 52 is 0.4683.
The following covariance structure has been used to fit the mixed model: Unstructured
16 patients were excluded as the subgroup variable was missing.
Note: All covariate effects are set equal to their mean values within subgroup for the calculation of adjusted means.
The p-value for the visit by treatment by subgroup interaction trend test at Week 52 is 0.5871

For patients who died, only observed values are considered (no imputation after date of death).
Data taken from study 1245.121 only.
NTproBNP median [pg/mL]: with a. fibrillation/flutter at baseline: 2265; without a. fibrillation/flutter at baseline: 1671.
The MMRM includes all outcome values (change from baseline) at the planned Visits week 12, week 32 and week 52

R.1.3.2.13

R.1.3.2.13 Subgroup analysis by baseline use of MRA

Table R.1.3.2.13: 1 KCCQ-CSS change from baseline at week 52 (MMRM) by baseline use of MRA (Y/N) - RS (OC-AD - no imputation for deaths) - 1245.121

Subgroup / Visit / Description / Statistic	Placebo	Empa 10mg
Baseline use of MRA: No		
Number of patients in analysis set	512	557
Number of analysed patients	486	531
Baseline mean (SE)	72.57 (0.92)	72.01 (0.95)
Week 52		
Values at visit		
Number of analysed patients	340	383
Mean (SE)	74.43 (1.14)	79.17 (1.02)
Adjusted* mean (SE)	74.71 (0.84)	78.02 (0.80)
95% confidence interval	(73.06,76.36)	(76.45,79.59)
Change from baseline		
Mean (SE)	2.47 (1.00)	5.28 (0.93)
Adjusted* mean (SE)	2.43 (0.84)	5.74 (0.80)
95% confidence interval	(0.78, 4.09)	(4.17, 7.31)
Comparison vs Placebo		
Adjusted* mean (SE)		3.31 (1.16)
95% confidence interval		(1.04, 5.58)
p-value		0.0043

* Model includes Age, baseline eGFR (CKD-EPI) as linear covariate(s) and region, baseline diabetes status, sex, baseline LVEF, week reachable, Visit by Treatment by baseline use of MRA interaction, baseline KCCQ - clinical summary score by Visit interaction as fixed effect(s).
The Visit by Treatment by baseline use of MRA p-value at Week 52 is 0.0821.
The following covariance structure has been used to fit the mixed model: Unstructured
Note: All covariate effects are set equal to their mean values within subgroup for the calculation of adjusted means.

For patients who died, only observed values are considered (no imputation after date of death).
Data taken from study 1245.121 only.
The MMRM includes all outcome values (change from baseline) at the planned Visits week 12, week 32 and week 52

Table R.1.3.2.13: 1 KCCQ-CSS change from baseline at week 52 (MMRM) by baseline use of MRA (Y/N) - RS (OC-AD - no imputation for deaths) - 1245.121

Subgroup / Visit / Description / Statistic	Placebo	Empa 10mg
Baseline use of MRA: Yes		
Number of patients in analysis set	1355	1306
Number of analysed patients	1267	1245
Baseline mean (SE)	70.73 (0.61)	70.67 (0.63)
Week 52		
Values at visit		
Number of analysed patients	878	856
Mean (SE)	76.66 (0.70)	76.92 (0.71)
Adjusted* mean (SE)	75.39 (0.52)	76.30 (0.53)
95% confidence interval	(74.36,76.42)	(75.27,77.34)
Change from baseline		
Mean (SE)	4.83 (0.64)	5.33 (0.61)
Adjusted* mean (SE)	4.69 (0.52)	5.60 (0.53)
95% confidence interval	(3.66, 5.72)	(4.57, 6.64)
Comparison vs Placebo		
Adjusted* mean (SE)		0.92 (0.74)
95% confidence interval		(-0.54, 2.37)
p-value		0.2186

* Model includes Age, baseline eGFR (CKD-EPI) as linear covariate(s) and region, baseline diabetes status, sex, baseline LVEF, week reachable, Visit by Treatment by baseline use of MRA interaction, baseline KCCQ - clinical summary score by Visit interaction as fixed effect(s).
The Visit by Treatment by baseline use of MRA p-value at Week 52 is 0.0821.
The following covariance structure has been used to fit the mixed model: Unstructured
Note: All covariate effects are set equal to their mean values within subgroup for the calculation of adjusted means.

For patients who died, only observed values are considered (no imputation after date of death).
Data taken from study 1245.121 only.
The MMRM includes all outcome values (change from baseline) at the planned Visits week 12, week 32 and week 52

R.1.3.2.14

Table R.1.3.2.14: 1 KCCQ-CSS change from baseline at week 52 (MMRM) by baseline use of ARNi (Y/N) - RS (OC-AD - no imputation for deaths) - 1245.121

Subgroup / Visit / Description / Statistic	Placebo	Empa 10mg
Baseline use of ARNi: No		
Number of patients in analysis set	1480	1523
Number of analysed patients	1390	1447
Baseline mean (SE)	71.09 (0.57)	70.64 (0.58)
Week 52		
Values at visit		
Number of analysed patients	960	1026
Mean (SE)	75.83 (0.66)	77.24 (0.64)
Adjusted* mean (SE)	74.81 (0.50)	76.46 (0.49)
95% confidence interval	(73.83,75.80)	(75.51,77.41)
Change from baseline		
Mean (SE)	4.17 (0.62)	5.34 (0.56)
Adjusted* mean (SE)	3.95 (0.50)	5.60 (0.49)
95% confidence interval	(2.97, 4.93)	(4.64, 6.55)
Comparison vs Placebo		
Adjusted* mean (SE)		1.64 (0.70)
95% confidence interval		(0.28, 3.01)
p-value		0.0183

* Model includes Age, baseline eGFR (CKD-EPI) as linear covariate(s) and region, baseline diabetes status, sex, baseline LVEF, week reachable, Visit by Treatment by baseline use of ARNi interaction, baseline KCCQ - clinical summary score by Visit interaction as fixed effect(s).
The Visit by Treatment by baseline use of ARNi p-value at Week 52 is 0.9824.
The following covariance structure has been used to fit the mixed model: Unstructured
Note: All covariate effects are set equal to their mean values within subgroup for the calculation of adjusted means.

For patients who died, only observed values are considered (no imputation after date of death).
Data taken from study 1245.121 only.
The MMRM includes all outcome values (change from baseline) at the planned Visits week 12, week 32 and week 52

Table R.1.3.2.14: 1 KCCQ-CSS change from baseline at week 52 (MMRM) by baseline use of ARNi (Y/N) - RS (OC-AD - no imputation for deaths) - 1245.121

Subgroup / Visit / Description / Statistic	Placebo	Empa 10mg
Baseline use of ARNi: Yes		
Number of patients in analysis set	387	340
Number of analysed patients	363	329
Baseline mean (SE)	71.81 (1.17)	72.95 (1.19)
Week 52		
Values at visit		
Number of analysed patients	258	213
Mean (SE)	76.83 (1.34)	79.44 (1.35)
Adjusted* mean (SE)	76.73 (0.97)	78.41 (1.06)
95% confidence interval	(74.82,78.64)	(76.33,80.48)
Change from baseline		
Mean (SE)	4.16 (1.14)	5.17 (1.22)
Adjusted* mean (SE)	4.38 (0.97)	6.06 (1.06)
95% confidence interval	(2.47, 6.29)	(3.98, 8.13)
Comparison vs Placebo		
Adjusted* mean (SE)		1.68 (1.43)
95% confidence interval		(-1.13, 4.49)
p-value		0.2410

* Model includes Age, baseline eGFR (CKD-EPI) as linear covariate(s) and region, baseline diabetes status, sex, baseline LVEF, week reachable, Visit by Treatment by baseline use of ARNi interaction, baseline KCCQ - clinical summary score by Visit interaction as fixed effect(s).
The Visit by Treatment by baseline use of ARNi p-value at Week 52 is 0.9824.
The following covariance structure has been used to fit the mixed model: Unstructured
Note: All covariate effects are set equal to their mean values within subgroup for the calculation of adjusted means.

For patients who died, only observed values are considered (no imputation after date of death).
Data taken from study 1245.121 only.
The MMRM includes all outcome values (change from baseline) at the planned Visits week 12, week 32 and week 52

R.1.3.2.15 Subgroup analysis by bl. LVEF (<= 30%, >30% -<= 35% , > 35%)

Table R.1.3.2.15: 1 KCCQ-CSS change from baseline at week 52 (MMRM) by baseline LVEF (3 cat.) - RS (OC-AD - no imputation for deaths) - 1245.121

Subgroup / Visit / Description / Statistic	Placebo	Empa 10mg
Baseline LVEF (3 cat.): <=30		
Number of patients in analysis set	1392	1337
Number of analysed patients	1303	1270
Baseline mean (SE)	70.85 (0.59)	70.70 (0.61)
Week 52		
Values at visit		
Number of analysed patients	924	900
Mean (SE)	75.63 (0.69)	77.55 (0.69)
Adjusted* mean (SE)	74.82 (0.51)	76.82 (0.52)
95% confidence interval	(73.82,75.82)	(75.80,77.83)
Change from baseline		
Mean (SE)	4.22 (0.63)	5.76 (0.59)
Adjusted* mean (SE)	4.05 (0.51)	6.04 (0.52)
95% confidence interval	(3.04, 5.05)	(5.03, 7.06)
Comparison vs Placebo		
Adjusted* mean (SE)		2.00 (0.73)
95% confidence interval		(0.57, 3.42)
p-value		0.0060

* Model includes Age, baseline eGFR (CKD-EPI) as linear covariate(s) and region, baseline diabetes status, sex, week reachable, Visit by Treatment by baseline LVEF (3 cat.) interaction, baseline KCCQ - clinical summary score by Visit interaction as fixed effect(s).
The Visit by Treatment by baseline LVEF (3 cat.) p-value at Week 52 is 0.0371.
The following covariance structure has been used to fit the mixed model: Unstructured
Note: All covariate effects are set equal to their mean values within subgroup for the calculation of adjusted means.
The p-value for the visit by treatment by subgroup interaction trend test at Week 52 is 0.8931

For patients who died, only observed values are considered (no imputation after date of death).
Data taken from study 1245.121 only.
The MMRM includes all outcome values (change from baseline) at the planned Visits week 12, week 32 and week 52

Table R.1.3.2.15: 1 KCCQ-CSS change from baseline at week 52 (MMRM) by baseline LVEF (3 cat.) - RS (OC-AD - no imputation for deaths) - 1245.121

Subgroup / Visit / Description / Statistic	Placebo	Empa 10mg
Baseline LVEF (3 cat.): >30 to <=35		
Number of patients in analysis set	361	398
Number of analysed patients	342	385
Baseline mean (SE)	72.70 (1.10)	72.09 (1.14)
Week 52		
Values at visit		
Number of analysed patients	233	256
Mean (SE)	78.75 (1.20)	77.06 (1.29)
Adjusted* mean (SE)	77.50 (1.01)	76.45 (0.96)
95% confidence interval	(75.51,79.49)	(74.57,78.34)
Change from baseline		
Mean (SE)	4.65 (1.16)	3.31 (1.17)
Adjusted* mean (SE)	5.12 (1.01)	4.07 (0.96)
95% confidence interval	(3.13, 7.11)	(2.19, 5.96)
Comparison vs Placebo		
Adjusted* mean (SE)		-1.05 (1.40)
95% confidence interval		(-3.78, 1.69)
p-value		0.4540

* Model includes Age, baseline eGFR (CKD-EPI) as linear covariate(s) and region, baseline diabetes status, sex, week reachable, Visit by Treatment by baseline LVEF (3 cat.) interaction, baseline KCCQ - clinical summary score by Visit interaction as fixed effect(s).
The Visit by Treatment by baseline LVEF (3 cat.) p-value at Week 52 is 0.0371.
The following covariance structure has been used to fit the mixed model: Unstructured
Note: All covariate effects are set equal to their mean values within subgroup for the calculation of adjusted means.
The p-value for the visit by treatment by subgroup interaction trend test at Week 52 is 0.8931

For patients who died, only observed values are considered (no imputation after date of death).
Data taken from study 1245.121 only.
The MMRM includes all outcome values (change from baseline) at the planned Visits week 12, week 32 and week 52

Table R.1.3.2.15: 1 KCCQ-CSS change from baseline at week 52 (MMRM) by baseline LVEF (3 cat.) - RS (OC-AD - no imputation for deaths) - 1245.121

Subgroup / Visit / Description / Statistic	Placebo	Empa 10mg
Baseline LVEF (3 cat.): >35		
Number of patients in analysis set	114	128
Number of analysed patients	108	121
Baseline mean (SE)	71.37 (2.16)	71.71 (2.13)
Week 52		
Values at visit		
Number of analysed patients	61	83
Mean (SE)	71.95 (3.06)	80.11 (2.10)
Adjusted* mean (SE)	72.12 (1.95)	77.97 (1.70)
95% confidence interval	(68.31,75.94)	(74.64,81.30)
Change from baseline		
Mean (SE)	1.66 (2.47)	6.64 (2.05)
Adjusted* mean (SE)	0.57 (1.95)	6.42 (1.70)
95% confidence interval	(-3.24, 4.39)	(3.09, 9.75)
Comparison vs Placebo		
Adjusted* mean (SE)		5.85 (2.58)
95% confidence interval		(0.79,10.91)
p-value		0.0235

* Model includes Age, baseline eGFR (CKD-EPI) as linear covariate(s) and region, baseline diabetes status, sex, week reachable, Visit by Treatment by baseline LVEF (3 cat.) interaction, baseline KCCQ - clinical summary score by Visit interaction as fixed effect(s).
The Visit by Treatment by baseline LVEF (3 cat.) p-value at Week 52 is 0.0371.
The following covariance structure has been used to fit the mixed model: Unstructured
Note: All covariate effects are set equal to their mean values within subgroup for the calculation of adjusted means.
The p-value for the visit by treatment by subgroup interaction trend test at Week 52 is 0.8931

For patients who died, only observed values are considered (no imputation after date of death).
Data taken from study 1245.121 only.
The MMRM includes all outcome values (change from baseline) at the planned Visits week 12, week 32 and week 52

R.1.3.2.16 Subgroup analysis by bl. NTproBNP </>= median (median based on total patients)

Table R.1.3.2.16: 1 KCCQ-CSS change from baseline at week 52 (MMRM) by bl. NTproBNP (<median, >= median) (median based on total patients) - RS (OC-AD - no imputation for deaths) - 1245.121

Subgroup / Visit / Description / Statistic	Placebo	Empa 10mg
Baseline NTproBNP (<median, >= median): < median		
Number of patients in analysis set	920	942
Number of analysed patients	884	908
Baseline mean (SE)	73.64 (0.68)	73.69 (0.69)
Week 52		
Values at visit		
Number of analysed patients	651	666
Mean (SE)	77.60 (0.79)	79.18 (0.76)
Adjusted* mean (SE)	77.30 (0.61)	79.07 (0.60)
95% confidence interval	(76.10,78.49)	(77.89,80.26)
Change from baseline		
Mean (SE)	4.19 (0.65)	5.21 (0.62)
Adjusted* mean (SE)	3.63 (0.61)	5.41 (0.60)
95% confidence interval	(2.43, 4.83)	(4.23, 6.59)
Comparison vs Placebo		
Adjusted* mean (SE)		1.78 (0.86)
95% confidence interval		(0.09, 3.46)
p-value		0.0384

* Model includes Age, baseline eGFR (CKD-EPI) as linear covariate(s) and region, baseline diabetes status, sex, baseline LVEF, week reachable, Visit by Treatment by baseline NTproBNP (<median, >= median) interaction, baseline KCCQ - clinical summary score by Visit interaction as fixed effect(s). The Visit by Treatment by baseline NTproBNP (<median, >= median) p-value at Week 52 is 0.7465.
The following covariance structure has been used to fit the mixed model: Unstructured
2 patients were excluded as the subgroup variable was missing.
Note: All covariate effects are set equal to their mean values within subgroup for the calculation of adjusted means.

For patients who died, only observed values are considered (no imputation after date of death).
Data taken from study 1245.121 only.
Median: 1910 [pg/mL]
The MMRM includes all outcome values (change from baseline) at the planned Visits week 12, week 32 and week 52

Table R.1.3.2.16: 1 KCCQ-CSS change from baseline at week 52 (MMRM) by bl. NTproBNP (<median, >= median) (median based on total patients) - RS (OC-AD - no imputation for deaths) - 1245.121

Subgroup / Visit / Description / Statistic	Placebo	Empa 10mg
Baseline NTproBNP (<median, >= median): >= median		
Number of patients in analysis set	946	920
Number of analysed patients	869	868
Baseline mean (SE)	68.80 (0.75)	68.33 (0.78)
Week 52		
Values at visit		
Number of analysed patients	567	573
Mean (SE)	74.25 (0.90)	75.80 (0.90)
Adjusted* mean (SE)	73.05 (0.65)	74.43 (0.65)
95% confidence interval	(71.78,74.32)	(73.16,75.69)
Change from baseline		
Mean (SE)	4.15 (0.90)	5.43 (0.84)
Adjusted* mean (SE)	4.49 (0.65)	5.86 (0.65)
95% confidence interval	(3.22, 5.75)	(4.59, 7.12)
Comparison vs Placebo		
Adjusted* mean (SE)		1.37 (0.91)
95% confidence interval		(-0.42, 3.16)
p-value		0.1326

* Model includes Age, baseline eGFR (CKD-EPI) as linear covariate(s) and region, baseline diabetes status, sex, baseline LVEF, week reachable, Visit by Treatment by baseline NTproBNP (<median, >= median) interaction, baseline KCCQ - clinical summary score by Visit interaction as fixed effect(s). The Visit by Treatment by baseline NTproBNP (<median, >= median) p-value at Week 52 is 0.7465.
The following covariance structure has been used to fit the mixed model: Unstructured
2 patients were excluded as the subgroup variable was missing.
Note: All covariate effects are set equal to their mean values within subgroup for the calculation of adjusted means.

For patients who died, only observed values are considered (no imputation after date of death).
Data taken from study 1245.121 only.
Median: 1910 [pg/mL]
The MMRM includes all outcome values (change from baseline) at the planned Visits week 12, week 32 and week 52

R.1.3.3

R.1.3.3 KCCQ Total Symptom Score MMRM analysis

R.1.3.3.1

R.1.3.3.1 Overall analysis

Table R.1.3.3.1: 1

Table R.1.3.3.1: 1 KCCQ-TSS change from baseline MMRM results over time - RS (OC-AD - no imputation for deaths) - 1245.121

Visit Description Statistic	Placebo	Empa 10mg
Number of patients in analysis set	1867	1863
Number of analysed patients	1753	1776
Baseline mean (SE)	75.03 (0.52)	74.70 (0.54)
Week 12		
Values at visit		
Number of analysed patients	1732	1755
Mean (SE)	78.64 (0.51)	80.93 (0.49)
Adjusted* mean (SE)	78.56 (0.39)	81.09 (0.38)
95% confidence interval	(77.81,79.32)	(80.33,81.84)
Change from baseline		
Mean (SE)	3.52 (0.44)	6.20 (0.45)
Adjusted* mean (SE)	3.35 (0.39)	5.88 (0.38)
95% confidence interval	(2.59, 4.11)	(5.12, 6.63)
Comparison vs Placebo		
Adjusted* mean (SE)		2.52 (0.54)
95% confidence interval		(1.46, 3.59)
p-value		<0.0001
Hedges g		
Estimate		0.16
95% confidence interval		(0.09, 0.22)

* Model includes Age (p=0.7682), baseline eGFR (CKD-EPI) (p=0.0138) as linear covariate(s) and region (p<0.0001), baseline diabetes status (p=0.6410), sex (p=0.0015), baseline LVEF (p=0.2257), week reachable (p=0.0392), Treatment by Visit interaction (p<0.0001), baseline KCCQ - total symptom score by Visit interaction (p<0.0001) as fixed effect(s).
The following covariance structure has been used to fit the mixed model: Unstructured

For patients who died, only observed values are considered (no imputation after date of death).
Data taken from study 1245.121 only.

Table R.1.3.3.1: 1

Table R.1.3.3.1: 1 KCCQ-TSS change from baseline MMRM results over time - RS (OC-AD - no imputation for deaths) - 1245.121

Visit Description Statistic	Placebo	Empa 10mg
Week 32		
Values at visit		
Number of analysed patients	1568	1617
Mean (SE)	79.84 (0.52)	81.39 (0.51)
Adjusted* mean (SE)	79.51 (0.42)	81.14 (0.41)
95% confidence interval	(78.69,80.33)	(80.33,81.95)
Change from baseline		
Mean (SE)	4.52 (0.50)	6.19 (0.49)
Adjusted* mean (SE)	4.30 (0.42)	5.93 (0.41)
95% confidence interval	(3.47, 5.12)	(5.12, 6.74)
Comparison vs Placebo		
Adjusted* mean (SE)		1.64 (0.59)
95% confidence interval		(0.48, 2.79)
p-value		0.0054
Hedges g		
Estimate		0.10
95% confidence interval		(0.03, 0.17)

* Model includes Age (p=0.7682), baseline eGFR (CKD-EPI) (p=0.0138) as linear covariate(s) and region (p<0.0001), baseline diabetes status (p=0.6410), sex (p=0.0015), baseline LVEF (p=0.2257), week reachable (p=0.0392), Treatment by Visit interaction (p<0.0001), baseline KCCQ - total symptom score by Visit interaction (p<0.0001) as fixed effect(s).
The following covariance structure has been used to fit the mixed model: Unstructured

For patients who died, only observed values are considered (no imputation after date of death).
Data taken from study 1245.121 only.

Table R.1.3.3.1: 1 KCCQ-TSS change from baseline MMRM results over time - RS (OC-AD - no imputation for deaths) - 1245.121

Visit Description Statistic	Placebo	Empa 10mg
Week 52		
Values at visit		
Number of analysed patients	1218	1239
Mean (SE)	80.49 (0.60)	82.26 (0.56)
Adjusted* mean (SE)	80.21 (0.47)	81.90 (0.46)
95% confidence interval	(79.29,81.12)	(80.99,82.81)
Change from baseline		
Mean (SE)	5.08 (0.59)	6.54 (0.56)
Adjusted* mean (SE)	4.99 (0.47)	6.69 (0.46)
95% confidence interval	(4.08, 5.91)	(5.78, 7.60)
Comparison vs Placebo		
Adjusted* mean (SE)		1.69 (0.66)
95% confidence interval		(0.40, 2.98)
p-value		0.0104
Hedges g		
Estimate		0.10
95% confidence interval		(0.02, 0.18)

* Model includes Age (p=0.7682), baseline eGFR (CKD-EPI) (p=0.0138) as linear covariate(s) and region (p<0.0001), baseline diabetes status (p=0.6410), sex (p=0.0015), baseline LVEF (p=0.2257), week reachable (p=0.0392), Treatment by Visit interaction (p<0.0001), baseline KCCQ - total symptom score by Visit interaction (p<0.0001) as fixed effect(s).
The following covariance structure has been used to fit the mixed model: Unstructured

For patients who died, only observed values are considered (no imputation after date of death).
Data taken from study 1245.121 only.

Figure R.1.3.3.1: 1

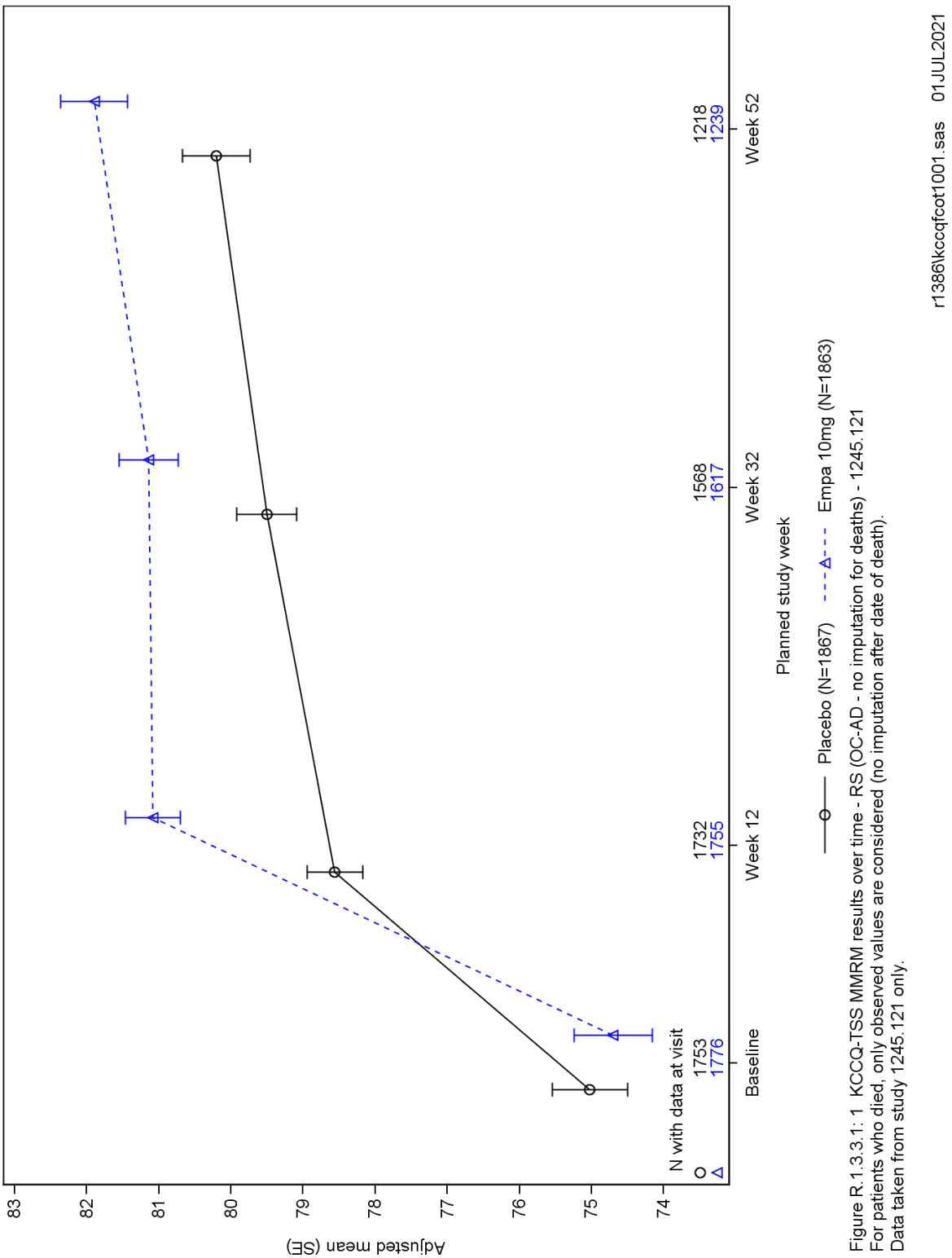

Figure R.1.3.3.1: 1 KCCQ-TSS MMRM results over time - RS (OC-AD - no imputation for deaths) - 1245.121
For patients who died, only observed values are considered (no imputation after date of death).
Data taken from study 1245.121 only.

R.1.3.3.2

R.1.3.3.2 Subgroup analysis by sex

Table R.1.3.3.2: 1 KCCQ-TSS change from baseline at week 52 (MMRM) by sex - RS (OC-AD - no imputation for deaths) - 1245.121

Subgroup / Visit / Description / Statistic	Placebo	Empa 10mg
Sex: Male		
Number of patients in analysis set	1411	1426
Number of analysed patients	1333	1361
Baseline mean (SE)	76.71 (0.57)	76.20 (0.60)
Week 52		
Values at visit		
Number of analysed patients	939	954
Mean (SE)	81.25 (0.67)	83.57 (0.62)
Adjusted* mean (SE)	80.82 (0.53)	83.07 (0.53)
95% confidence interval	(79.77,81.86)	(82.03,84.11)
Change from baseline		
Mean (SE)	4.05 (0.66)	6.23 (0.62)
Adjusted* mean (SE)	4.36 (0.53)	6.62 (0.53)
95% confidence interval	(3.31, 5.41)	(5.58, 7.65)
Comparison vs Placebo		
Adjusted* mean (SE)		2.26 (0.75)
95% confidence interval		(0.78, 3.73)
p-value		0.0027

* Model includes Age, baseline eGFR (CKD-EPI) as linear covariate(s) and region, baseline diabetes status, baseline LVEF, week reachable, Visit by Treatment by sex interaction, baseline KCCQ - total symptom score by Visit interaction as fixed effect(s).
The Visit by Treatment by sex p-value at Week 52 is 0.1232.
The following covariance structure has been used to fit the mixed model: Unstructured
Note: All covariate effects are set equal to their mean values within subgroup for the calculation of adjusted means.

For patients who died, only observed values are considered (no imputation after date of death).
Data taken from study 1245.121 only.
The MMRM includes all outcome values (change from baseline) at the planned Visits week 12, week 32 and week 52

Table R.1.3.3.2: 1 KCCQ-TSS change from baseline at week 52 (MMRM) by sex - RS (OC-AD - no imputation for deaths) - 1245.121

Subgroup / Visit / Description / Statistic	Placebo	Empa 10mg
Sex: Female		
Number of patients in analysis set	456	437
Number of analysed patients	420	415
Baseline mean (SE)	69.68 (1.16)	69.78 (1.16)
Week 52		
Values at visit		
Number of analysed patients	279	285
Mean (SE)	77.93 (1.30)	77.87 (1.27)
Adjusted* mean (SE)	77.45 (0.98)	77.29 (0.97)
95% confidence interval	(75.54,79.37)	(75.40,79.19)
Change from baseline		
Mean (SE)	8.52 (1.28)	7.59 (1.26)
Adjusted* mean (SE)	7.72 (0.98)	7.56 (0.97)
95% confidence interval	(5.81, 9.64)	(5.67, 9.46)
Comparison vs Placebo		
Adjusted* mean (SE)		-0.16 (1.37)
95% confidence interval		(-2.85, 2.53)
p-value		0.9082

* Model includes Age, baseline eGFR (CKD-EPI) as linear covariate(s) and region, baseline diabetes status, baseline LVEF, week reachable, Visit by Treatment by sex interaction, baseline KCCQ - total symptom score by Visit interaction as fixed effect(s).
The Visit by Treatment by sex p-value at Week 52 is 0.1232.
The following covariance structure has been used to fit the mixed model: Unstructured
Note: All covariate effects are set equal to their mean values within subgroup for the calculation of adjusted means.

For patients who died, only observed values are considered (no imputation after date of death).
Data taken from study 1245.121 only.
The MMRM includes all outcome values (change from baseline) at the planned Visits week 12, week 32 and week 52

R.1.3.3.3

R.1.3.3.3 Subgroup analysis by age

Table R.1.3.3.3: 1 KCCQ-TSS change from baseline at week 52 (MMRM) by age (2 cat.) - RS (OC-AD - no imputation for deaths) - 1245.121

Subgroup / Visit / Description / Statistic	Placebo	Empa 10mg
Age [years] (2 cat.): < 65		
Number of patients in analysis set	740	675
Number of analysed patients	697	645
Baseline mean (SE)	73.57 (0.88)	72.62 (0.94)
Week 52		
Values at visit		
Number of analysed patients	494	454
Mean (SE)	80.28 (0.97)	81.87 (1.02)
Adjusted* mean (SE)	79.49 (0.74)	81.39 (0.77)
95% confidence interval	(78.04,80.95)	(79.89,82.90)
Change from baseline		
Mean (SE)	6.66 (0.98)	8.67 (0.92)
Adjusted* mean (SE)	6.38 (0.74)	8.28 (0.77)
95% confidence interval	(4.93, 7.84)	(6.78, 9.79)
Comparison vs Placebo		
Adjusted* mean (SE)		1.90 (1.06)
95% confidence interval		(-0.19, 3.99)
p-value		0.0743

* Model includes baseline eGFR (CKD-EPI) as linear covariate(s) and region, baseline diabetes status, sex, baseline LVEF, week reachable, Visit by Treatment by age [years] (2 cat.) interaction, baseline KCCQ - total symptom score by Visit interaction as fixed effect(s).
The Visit by Treatment by age [years] (2 cat.) p-value at Week 52 is 0.8146.
The following covariance structure has been used to fit the mixed model: Unstructured
Note: All covariate effects are set equal to their mean values within subgroup for the calculation of adjusted means.

For patients who died, only observed values are considered (no imputation after date of death).
Data taken from study 1245.121 only.
The MMRM includes all outcome values (change from baseline) at the planned Visits week 12, week 32 and week 52

Table R.1.3.3.3: 1 KCCQ-TSS change from baseline at week 52 (MMRM) by age (2 cat.) - RS (OC-AD - no imputation for deaths) - 1245.121

Subgroup / Visit / Description / Statistic	Placebo	Empa 10mg
Age [years] (2 cat.): >= 65		
Number of patients in analysis set	1127	1188
Number of analysed patients	1056	1131
Baseline mean (SE)	75.99 (0.65)	75.89 (0.65)
Week 52		
Values at visit		
Number of analysed patients	724	785
Mean (SE)	80.64 (0.75)	82.48 (0.66)
Adjusted* mean (SE)	80.32 (0.61)	81.91 (0.59)
95% confidence interval	(79.13,81.52)	(80.76,83.05)
Change from baseline		
Mean (SE)	4.00 (0.74)	5.31 (0.71)
Adjusted* mean (SE)	4.38 (0.61)	5.97 (0.59)
95% confidence interval	(3.19, 5.58)	(4.82, 7.11)
Comparison vs Placebo		
Adjusted* mean (SE)		1.58 (0.84)
95% confidence interval		(-0.07, 3.23)
p-value		0.0604

* Model includes baseline eGFR (CKD-EPI) as linear covariate(s) and region, baseline diabetes status, sex, baseline LVEF, week reachable, Visit by Treatment by age [years] (2 cat.) interaction, baseline KCCQ - total symptom score by Visit interaction as fixed effect(s).
The Visit by Treatment by age [years] (2 cat.) p-value at Week 52 is 0.8146.
The following covariance structure has been used to fit the mixed model: Unstructured
Note: All covariate effects are set equal to their mean values within subgroup for the calculation of adjusted means.

For patients who died, only observed values are considered (no imputation after date of death).
Data taken from study 1245.121 only.
The MMRM includes all outcome values (change from baseline) at the planned Visits week 12, week 32 and week 52

R.1.3.3.4 Subgroup analysis by region (North America, Latin America, Europe, Asia, Other)

Table R.1.3.3.4: 1 KCCQ-TSS change from baseline at week 52 (MMRM) by region - RS (OC-AD - no imputation for deaths) - 1245.121

Subgroup / Visit / Description / Statistic	Placebo	Empa 10mg
Region (5 cat.): North America		
Number of patients in analysis set	213	212
Number of analysed patients	195	206
Baseline mean (SE)	72.61 (1.70)	72.48 (1.67)
Week 52		
Values at visit		
Number of analysed patients	129	151
Mean (SE)	77.54 (1.97)	80.28 (1.65)
Adjusted* mean (SE)	76.89 (1.43)	78.91 (1.34)
95% confidence interval	(74.09,79.70)	(76.29,81.53)
Change from baseline		
Mean (SE)	5.31 (1.50)	5.69 (1.63)
Adjusted* mean (SE)	4.35 (1.43)	6.37 (1.34)
95% confidence interval	(1.54, 7.16)	(3.75, 8.99)
Comparison vs Placebo		
Adjusted* mean (SE)		2.02 (1.96)
95% confidence interval		(-1.82, 5.86)
p-value		0.3027

* Model includes Age, baseline eGFR (CKD-EPI) as linear covariate(s) and baseline diabetes status, sex, baseline LVEF, week reachable, Visit by Treatment by region (5 cat.) interaction, baseline KCCQ - total symptom score by Visit interaction as fixed effect(s).
The Visit by Treatment by region (5 cat.) p-value at Week 52 is 0.8796.
The following covariance structure has been used to fit the mixed model: Unstructured
Note: All covariate effects are set equal to their mean values within subgroup for the calculation of adjusted means.

For patients who died, only observed values are considered (no imputation after date of death).
Data taken from study 1245.121 only.
The MMRM includes all outcome values (change from baseline) at the planned Visits week 12, week 32 and week 52

Table R.1.3.3.4: 1

Table R.1.3.3.4: 1 KCCQ-TSS change from baseline at week 52 (MMRM) by region - RS (OC-AD - no imputation for deaths) - 1245.121

Subgroup / Visit / Description / Statistic	Placebo	Empa 10mg
Region (5 cat.): Latin America		
Number of patients in analysis set	645	641
Number of analysed patients	599	602
Baseline mean (SE)	72.34 (0.95)	70.93 (1.02)
Week 52		
Values at visit		
Number of analysed patients	391	374
Mean (SE)	80.67 (1.10)	82.50 (1.08)
Adjusted* mean (SE)	80.25 (0.82)	82.74 (0.84)
95% confidence interval	(78.64,81.87)	(81.10,84.38)
Change from baseline		
Mean (SE)	8.66 (1.25)	11.80 (1.15)
Adjusted* mean (SE)	8.62 (0.82)	11.11 (0.84)
95% confidence interval	(7.01,10.23)	(9.47,12.75)
Comparison vs Placebo		
Adjusted* mean (SE)		2.49 (1.17)
95% confidence interval		(0.19, 4.78)
p-value		0.0339

* Model includes Age, baseline eGFR (CKD-EPI) as linear covariate(s) and baseline diabetes status, sex, baseline LVEF, week reachable, Visit by Treatment by region (5 cat.) interaction, baseline KCCQ - total symptom score by Visit interaction as fixed effect(s).
The Visit by Treatment by region (5 cat.) p-value at Week 52 is 0.8796.
The following covariance structure has been used to fit the mixed model: Unstructured
Note: All covariate effects are set equal to their mean values within subgroup for the calculation of adjusted means.

For patients who died, only observed values are considered (no imputation after date of death).
Data taken from study 1245.121 only.
The MMRM includes all outcome values (change from baseline) at the planned Visits week 12, week 32 and week 52

Table R.1.3.3.4: 1 KCCQ-TSS change from baseline at week 52 (MMRM) by region - RS (OC-AD - no imputation for deaths) - 1245.121

Subgroup / Visit / Description / Statistic	Placebo	Empa 10mg
Region (5 cat.): Europe		
Number of patients in analysis set	677	676
Number of analysed patients	644	649
Baseline mean (SE)	74.03 (0.82)	75.28 (0.84)
Week 52		
Values at visit		
Number of analysed patients	468	469
Mean (SE)	77.70 (0.95)	79.34 (0.90)
Adjusted* mean (SE)	77.58 (0.76)	78.49 (0.76)
95% confidence interval	(76.10,79.07)	(77.01,79.97)
Change from baseline		
Mean (SE)	3.00 (0.89)	3.43 (0.84)
Adjusted* mean (SE)	2.93 (0.76)	3.83 (0.76)
95% confidence interval	(1.44, 4.41)	(2.35, 5.32)
Comparison vs Placebo		
Adjusted* mean (SE)		0.91 (1.07)
95% confidence interval		(-1.19, 3.00)
p-value		0.3968

* Model includes Age, baseline eGFR (CKD-EPI) as linear covariate(s) and baseline diabetes status, sex, baseline LVEF, week reachable, Visit by Treatment by region (5 cat.) interaction, baseline KCCQ - total symptom score by Visit interaction as fixed effect(s).
The Visit by Treatment by region (5 cat.) p-value at Week 52 is 0.8796.
The following covariance structure has been used to fit the mixed model: Unstructured
Note: All covariate effects are set equal to their mean values within subgroup for the calculation of adjusted means.

For patients who died, only observed values are considered (no imputation after date of death).
Data taken from study 1245.121 only.
The MMRM includes all outcome values (change from baseline) at the planned Visits week 12, week 32 and week 52

Table R.1.3.3.4: 1 KCCQ-TSS change from baseline at week 52 (MMRM) by region - RS (OC-AD - no imputation for deaths) - 1245.121

Subgroup / Visit / Description / Statistic	Placebo	Empa 10mg
Region (5 cat.): Asia		
Number of patients in analysis set	245	248
Number of analysed patients	237	243
Baseline mean (SE)	84.64 (1.06)	83.10 (1.17)
Week 52		
Values at visit		
Number of analysed patients	180	189
Mean (SE)	86.22 (1.24)	87.12 (1.29)
Adjusted* mean (SE)	85.40 (1.23)	86.67 (1.20)
95% confidence interval	(82.99,87.81)	(84.32,89.02)
Change from baseline		
Mean (SE)	1.11 (1.13)	2.24 (1.20)
Adjusted* mean (SE)	1.54 (1.23)	2.81 (1.20)
95% confidence interval	(-0.87, 3.95)	(0.46, 5.16)
Comparison vs Placebo		
Adjusted* mean (SE)		1.27 (1.72)
95% confidence interval		(-2.09, 4.64)
p-value		0.4580

* Model includes Age, baseline eGFR (CKD-EPI) as linear covariate(s) and baseline diabetes status, sex, baseline LVEF, week reachable, Visit by Treatment by region (5 cat.) interaction, baseline KCCQ - total symptom score by Visit interaction as fixed effect(s).
The Visit by Treatment by region (5 cat.) p-value at Week 52 is 0.8796.
The following covariance structure has been used to fit the mixed model: Unstructured
Note: All covariate effects are set equal to their mean values within subgroup for the calculation of adjusted means.

For patients who died, only observed values are considered (no imputation after date of death).
Data taken from study 1245.121 only.
The MMRM includes all outcome values (change from baseline) at the planned Visits week 12, week 32 and week 52

Table R.1.3.3.4: 1 KCCQ-TSS change from baseline at week 52 (MMRM) by region - RS (OC-AD - no imputation for deaths) - 1245.121

Subgroup / Visit / Description / Statistic	Placebo	Empa 10mg
Region (5 cat.): Other		
Number of patients in analysis set	87	86
Number of analysed patients	78	76
Baseline mean (SE)	80.74 (2.30)	78.87 (2.03)
Week 52		
Values at visit		
Number of analysed patients	50	56
Mean (SE)	92.25 (2.17)	94.03 (1.19)
Adjusted* mean (SE)	91.15 (2.30)	93.88 (2.19)
95% confidence interval	(86.64,95.66)	(89.58,98.18)
Change from baseline		
Mean (SE)	10.17 (2.82)	14.40 (2.15)
Adjusted* mean (SE)	11.33 (2.30)	14.06 (2.19)
95% confidence interval	(6.83,15.84)	(9.76,18.36)
Comparison vs Placebo		
Adjusted* mean (SE)		2.73 (3.18)
95% confidence interval		(-3.50, 8.95)
p-value		0.3906

* Model includes Age, baseline eGFR (CKD-EPI) as linear covariate(s) and baseline diabetes status, sex, baseline LVEF, week reachable, Visit by Treatment by region (5 cat.) interaction, baseline KCCQ - total symptom score by Visit interaction as fixed effect(s).
The Visit by Treatment by region (5 cat.) p-value at Week 52 is 0.8796.
The following covariance structure has been used to fit the mixed model: Unstructured
Note: All covariate effects are set equal to their mean values within subgroup for the calculation of adjusted means.

For patients who died, only observed values are considered (no imputation after date of death).
Data taken from study 1245.121 only.
The MMRM includes all outcome values (change from baseline) at the planned Visits week 12, week 32 and week 52

R.1.3.3.5 Subgroup analysis by OECD (N/Y)

Table R.1.3.3.5: 1 KCCQ-TSS change from baseline at week 52 (MMRM) by OECD member (N/Y) - RS (OC-AD - no imputation for deaths) - 1245.121

Subgroup / Visit / Description / Statistic	Placebo	Empa 10mg
OECD member: No		
Number of patients in analysis set	741	713
Number of analysed patients	686	664
Baseline mean (SE)	73.47 (0.88)	72.10 (0.95)
Week 52		
Values at visit		
Number of analysed patients	443	421
Mean (SE)	81.74 (1.01)	84.16 (0.94)
Adjusted* mean (SE)	81.32 (0.78)	84.33 (0.79)
95% confidence interval	(79.80,82.84)	(82.77,85.88)
Change from baseline		
Mean (SE)	8.41 (1.14)	12.18 (1.05)
Adjusted* mean (SE)	8.53 (0.78)	11.53 (0.79)
95% confidence interval	(7.01,10.05)	(9.98,13.08)
Comparison vs Placebo		
Adjusted* mean (SE)		3.00 (1.11)
95% confidence interval		(0.83, 5.18)
p-value		0.0067

* Model includes Age, baseline eGFR (CKD-EPI) as linear covariate(s) and baseline diabetes status, sex, baseline LVEF, week reachable, Visit by Treatment by OECD Member (N) interaction, baseline KCCQ - total symptom score by Visit interaction as fixed effect(s).
The Visit by Treatment by OECD Member (N) p-value at Week 52 is 0.1647.
The following covariance structure has been used to fit the mixed model: Unstructured
Note: All covariate effects are set equal to their mean values within subgroup for the calculation of adjusted means.

For patients who died, only observed values are considered (no imputation after date of death).
Data taken from study 1245.121 only.
OECD member (yes/no) countries included:
Yes: United States, Canada, Mexico, Poland, Netherlands, Hungary, Germany, Czech Republic, Italy, France, Spain, United Kingdom, Belgium, Japan, Australia, 'Korea; Republic Of South Korea';
No: Brazil, Argentina, China, India.
The MMRM includes all outcome values (change from baseline) at the planned Visits week 12, week 32 and week 52

Table R.1.3.3.5: 1 KCCQ-TSS change from baseline at week 52 (MMRM) by OECD member (N/Y) - RS (OC-AD - no imputation for deaths) - 1245.121

Subgroup / Visit / Description / Statistic	Placebo	Empa 10mg
OECD member: Yes		
Number of patients in analysis set	1126	1150
Number of analysed patients	1067	1112
Baseline mean (SE)	76.03 (0.65)	76.25 (0.65)
Week 52		
Values at visit		
Number of analysed patients	775	818
Mean (SE)	79.78 (0.74)	81.28 (0.69)
Adjusted* mean (SE)	79.23 (0.59)	80.32 (0.58)
95% confidence interval	(78.07,80.39)	(79.19,81.45)
Change from baseline		
Mean (SE)	3.17 (0.65)	3.64 (0.63)
Adjusted* mean (SE)	3.09 (0.59)	4.17 (0.58)
95% confidence interval	(1.93, 4.25)	(3.04, 5.30)
Comparison vs Placebo		
Adjusted* mean (SE)		1.08 (0.83)
95% confidence interval		(-0.53, 2.70)
p-value		0.1891

* Model includes Age, baseline eGFR (CKD-EPI) as linear covariate(s) and baseline diabetes status, sex, baseline LVEF, week reachable, Visit by Treatment by OECD Member (N) interaction, baseline KCCQ - total symptom score by Visit interaction as fixed effect(s).
The Visit by Treatment by OECD Member (N) p-value at Week 52 is 0.1647.
The following covariance structure has been used to fit the mixed model: Unstructured
Note: All covariate effects are set equal to their mean values within subgroup for the calculation of adjusted means.

For patients who died, only observed values are considered (no imputation after date of death).
Data taken from study 1245.121 only.
OECD member (yes/no) countries included:
Yes: United States, Canada, Mexico, Poland, Netherlands, Hungary, Germany, Czech Republic, Italy, France, Spain, United Kingdom, Belgium, Japan, Australia, 'Korea; Republic Of South Korea';
No: Brazil, Argentina, China, India.
The MMRM includes all outcome values (change from baseline) at the planned Visits week 12, week 32 and week 52

R.1.3.3.6 Subgroup analysis by NYHA at baseline (II, III/IV - 2 cat.)

Table R.1.3.3.6: 1

Table R.1.3.3.6: 1 KCCQ-TSS change from baseline at week 52 (MMRM) by NYHA (2 cat.) - RS (OC-AD - no imputation for deaths) - 1245.121

Subgroup / Visit / Description / Statistic	Placebo	Empa 10mg
Baseline NYHA (2 cat.): II		
Number of patients in analysis set	1401	1399
Number of analysed patients	1340	1332
Baseline mean (SE)	78.71 (0.54)	79.63 (0.55)
Week 52		
Values at visit		
Number of analysed patients	946	951
Mean (SE)	82.75 (0.63)	85.36 (0.58)
Adjusted* mean (SE)	82.76 (0.53)	84.88 (0.53)
95% confidence interval	(81.72,83.80)	(83.84,85.92)
Change from baseline		
Mean (SE)	4.05 (0.65)	5.48 (0.60)
Adjusted* mean (SE)	3.59 (0.53)	5.71 (0.53)
95% confidence interval	(2.55, 4.63)	(4.67, 6.75)
Comparison vs Placebo		
Adjusted* mean (SE)		2.11 (0.75)
95% confidence interval		(0.64, 3.58)
p-value		0.0048

* Model includes Age, baseline eGFR (CKD-EPI) as linear covariate(s) and region, baseline diabetes status, sex, baseline LVEF, week reachable, Visit by Treatment by baseline NYHA (2 cat.) interaction, baseline KCCQ - total symptom score by Visit interaction as fixed effect(s).
The Visit by Treatment by baseline NYHA (2 cat.) p-value at Week 52 is 0.2804.
The following covariance structure has been used to fit the mixed model: Unstructured
Note: All covariate effects are set equal to their mean values within subgroup for the calculation of adjusted means.

For patients who died, only observed values are considered (no imputation after date of death).
Data taken from study 1245.121 only.
The MMRM includes all outcome values (change from baseline) at the planned Visits week 12, week 32 and week 52

Table R.1.3.3.6: 1 KCCQ-TSS change from baseline at week 52 (MMRM) by NYHA (2 cat.) - RS (OC-AD - no imputation for deaths) - 1245.121

Subgroup / Visit / Description / Statistic	Placebo	Empa 10mg
Baseline NYHA (2 cat.): III/IV		
Number of patients in analysis set	466	464
Number of analysed patients	413	444
Baseline mean (SE)	63.08 (1.17)	59.91 (1.15)
Week 52		
Values at visit		
Number of analysed patients	272	288
Mean (SE)	72.65 (1.42)	72.00 (1.30)
Adjusted* mean (SE)	71.36 (0.99)	71.79 (0.96)
95% confidence interval	(69.43,73.30)	(69.91,73.66)
Change from baseline		
Mean (SE)	8.66 (1.37)	10.05 (1.38)
Adjusted* mean (SE)	9.92 (0.99)	10.35 (0.96)
95% confidence interval	(7.99,11.86)	(8.48,12.22)
Comparison vs Placebo		
Adjusted* mean (SE)		0.43 (1.37)
95% confidence interval		(-2.26, 3.11)
p-value		0.7563

* Model includes Age, baseline eGFR (CKD-EPI) as linear covariate(s) and region, baseline diabetes status, sex, baseline LVEF, week reachable, Visit by Treatment by baseline NYHA (2 cat.) interaction, baseline KCCQ - total symptom score by Visit interaction as fixed effect(s).
The Visit by Treatment by baseline NYHA (2 cat.) p-value at Week 52 is 0.2804.
The following covariance structure has been used to fit the mixed model: Unstructured
Note: All covariate effects are set equal to their mean values within subgroup for the calculation of adjusted means.

For patients who died, only observed values are considered (no imputation after date of death).
Data taken from study 1245.121 only.
The MMRM includes all outcome values (change from baseline) at the planned Visits week 12, week 32 and week 52

R.1.3.3.7

R.1.3.3.7 Subgroup analysis by diabetes at baseline

Table R.1.3.3.7: 1 KCCQ-TSS change from baseline at week 52 (MMRM) by diabetes at baseline - RS (OC-AD - no imputation for deaths) - 1245.121

Subgroup / Visit / Description / Statistic	Placebo	Empa 10mg
Diabetes at baseline (2 cat.):		
Diabetic		
Number of patients in analysis set	929	927
Number of analysed patients	868	882
Baseline mean (SE)	73.42 (0.78)	73.38 (0.80)
Week 52		
Values at visit		
Number of analysed patients	606	614
Mean (SE)	80.18 (0.86)	82.04 (0.81)
Adjusted* mean (SE)	79.18 (0.67)	81.07 (0.66)
95% confidence interval	(77.88,80.49)	(79.77,82.36)
Change from baseline		
Mean (SE)	5.41 (0.83)	7.00 (0.81)
Adjusted* mean (SE)	5.78 (0.67)	7.66 (0.66)
95% confidence interval	(4.48, 7.09)	(6.37, 8.96)
Comparison vs Placebo		
Adjusted* mean (SE)		1.88 (0.94)
95% confidence interval		(0.05, 3.72)
p-value		0.0443

* Model includes Age, baseline eGFR (CKD-EPI) as linear covariate(s) and region, sex, baseline LVEF, week reachable,
Visit by Treatment by diabetes at baseline (2 cat.) interaction,
baseline KCCQ - total symptom score by Visit interaction as fixed effect(s).
The Visit by Treatment by diabetes at baseline (2 cat.) p-value at Week 52 is 0.7784.
The following covariance structure has been used to fit the mixed model: Unstructured
Note: All covariate effects are set equal to their mean values within subgroup for the calculation of adjusted means.

For patients who died, only observed values are considered (no imputation after date of death).
Data taken from study 1245.121 only.
The MMRM includes all outcome values (change from baseline) at the planned Visits week 12, week 32 and week 52

Table R.1.3.3.7: 1 KCCQ-TSS change from baseline at week 52 (MMRM) by diabetes at baseline - RS (OC-AD - no imputation for deaths) - 1245.121

Subgroup / Visit / Description / Statistic	Placebo	Empa 10mg
Diabetes at baseline (2 cat.):		
Non-Diabetic		
Number of patients in analysis set	938	936
Number of analysed patients	885	894
Baseline mean (SE)	76.60 (0.70)	76.00 (0.73)
Week 52		
Values at visit		
Number of analysed patients	612	625
Mean (SE)	80.81 (0.83)	82.48 (0.78)
Adjusted* mean (SE)	80.84 (0.66)	82.35 (0.65)
95% confidence interval	(79.54,82.13)	(81.07,83.63)
Change from baseline		
Mean (SE)	4.75 (0.84)	6.09 (0.78)
Adjusted* mean (SE)	4.54 (0.66)	6.05 (0.65)
95% confidence interval	(3.24, 5.83)	(4.77, 7.33)
Comparison vs Placebo		
Adjusted* mean (SE)		1.51 (0.93)
95% confidence interval		(-0.31, 3.33)
p-value		0.1038

* Model includes Age, baseline eGFR (CKD-EPI) as linear covariate(s) and region, sex, baseline LVEF, week reachable,
Visit by Treatment by diabetes at baseline (2 cat.) interaction,
baseline KCCQ - total symptom score by Visit interaction as fixed effect(s).
The Visit by Treatment by diabetes at baseline (2 cat.) p-value at Week 52 is 0.7784.
The following covariance structure has been used to fit the mixed model: Unstructured
Note: All covariate effects are set equal to their mean values within subgroup for the calculation of adjusted means.

For patients who died, only observed values are considered (no imputation after date of death).
Data taken from study 1245.121 only.
The MMRM includes all outcome values (change from baseline) at the planned Visits week 12, week 32 and week 52

R.1.3.3.8 Subgroup analysis by BMI at baseline (<30, >=30)

Table R.1.3.3.8: 1 KCCQ-TSS change from baseline at week 52 (MMRM) by baseline BMI [kg/m2] - RS (OC-AD - no imputation for deaths) - 1245.121

Subgroup / Visit / Description / Statistic	Placebo	Empa 10mg
Baseline BMI [kg/m²] (2 cat.): <30		
Number of patients in analysis set	1300	1263
Number of analysed patients	1229	1201
Baseline mean (SE)	76.88 (0.60)	77.05 (0.63)
Week 52		
Values at visit		
Number of analysed patients	865	826
Mean (SE)	81.98 (0.66)	84.13 (0.65)
Adjusted* mean (SE)	81.69 (0.56)	83.18 (0.57)
95% confidence interval	(80.59,82.78)	(82.06,84.30)
Change from baseline		
Mean (SE)	4.77 (0.65)	5.84 (0.66)
Adjusted* mean (SE)	4.72 (0.56)	6.21 (0.57)
95% confidence interval	(3.63, 5.82)	(5.10, 7.33)
Comparison vs Placebo		
Adjusted* mean (SE)		1.49 (0.79)
95% confidence interval		(-0.07, 3.05)
p-value		0.0605

* Model includes Age, baseline eGFR (CKD-EPI) as linear covariate(s) and region, baseline diabetes status, sex, baseline LVEF, week reachable, Visit by Treatment by baseline BMI [kg/m²] (2 cat.) interaction, baseline KCCQ - total symptom score by Visit interaction as fixed effect(s).
The Visit by Treatment by baseline BMI [kg/m²] (2 cat.) p-value at Week 52 is 0.5403.
The following covariance structure has been used to fit the mixed model: Unstructured
Note: All covariate effects are set equal to their mean values within subgroup for the calculation of adjusted means.

For patients who died, only observed values are considered (no imputation after date of death).
Data taken from study 1245.121 only.
The MMRM includes all outcome values (change from baseline) at the planned Visits week 12, week 32 and week 52

Table R.1.3.3.8: 1 KCCQ-TSS change from baseline at week 52 (MMRM) by baseline BMI [kg/m2] - RS (OC-AD - no imputation for deaths) - 1245.121

Subgroup / Visit / Description / Statistic	Placebo	Empa 10mg
Baseline BMI [kg/m²] (2 cat.): >=30		
Number of patients in analysis set	567	600
Number of analysed patients	524	575
Baseline mean (SE)	70.67 (1.03)	69.80 (0.99)
Week 52		
Values at visit		
Number of analysed patients	353	413
Mean (SE)	76.84 (1.24)	78.51 (1.06)
Adjusted* mean (SE)	76.21 (0.87)	78.57 (0.81)
95% confidence interval	(74.49,77.92)	(76.98,80.16)
Change from baseline		
Mean (SE)	5.84 (1.26)	7.95 (1.04)
Adjusted* mean (SE)	5.99 (0.87)	8.35 (0.81)
95% confidence interval	(4.28, 7.70)	(6.76, 9.95)
Comparison vs Placebo		
Adjusted* mean (SE)		2.37 (1.18)
95% confidence interval		(0.04, 4.69)
p-value		0.0458

* Model includes Age, baseline eGFR (CKD-EPI) as linear covariate(s) and region, baseline diabetes status, sex, baseline LVEF, week reachable, Visit by Treatment by baseline BMI [kg/m²] (2 cat.) interaction, baseline KCCQ - total symptom score by Visit interaction as fixed effect(s).
The Visit by Treatment by baseline BMI [kg/m²] (2 cat.) p-value at Week 52 is 0.5403.
The following covariance structure has been used to fit the mixed model: Unstructured
Note: All covariate effects are set equal to their mean values within subgroup for the calculation of adjusted means.

For patients who died, only observed values are considered (no imputation after date of death).
Data taken from study 1245.121 only.
The MMRM includes all outcome values (change from baseline) at the planned Visits week 12, week 32 and week 52

R.1.3.3.9 Subgroup analysis by eGFR at baseline (<60, >=60)

Table R.1.3.3.9: 1 KCCQ-TSS change from baseline at week 52 (MMRM) by baseline eGFR (2 cat.) - RS (OC-AD - no imputation for deaths) - 1245.121

Subgroup Visit Description Statistic	Placebo	Empa 10mg
Baseline eGFR (CKD-EPI) [mL/min/1.73m²] (2 cat.): >=60		
Number of patients in analysis set	960	969
Number of analysed patients	901	921
Baseline mean (SE)	75.38 (0.72)	75.15 (0.76)
Week 52		
Values at visit		
Number of analysed patients	647	650
Mean (SE)	80.55 (0.81)	83.60 (0.78)
Adjusted* mean (SE)	80.01 (0.65)	82.99 (0.64)
95% confidence interval	(78.75,81.28)	(81.73,84.25)
Change from baseline		
Mean (SE)	4.80 (0.77)	7.48 (0.76)
Adjusted* mean (SE)	4.75 (0.65)	7.73 (0.64)
95% confidence interval	(3.48, 6.02)	(6.47, 8.99)
Comparison vs Placebo		
Adjusted* mean (SE)		2.98 (0.91)
95% confidence interval		(1.20, 4.76)
p-value		0.0011

* Model includes Age as linear covariate(s) and region, baseline diabetes status, sex, baseline LVEF, week reachable, Visit by Treatment by baseline eGFR (CKD-EPI) [mL/min/1.73m²] (2 cat.) interaction, baseline KCCQ - total symptom score by Visit interaction as fixed effect(s).
The Visit by Treatment by baseline eGFR (CKD-EPI) [mL/min/1.73m²] (2 cat.) p-value at Week 52 is 0.0388.
The following covariance structure has been used to fit the mixed model: Unstructured
2 patients were excluded as the subgroup variable was missing.
Note: All covariate effects are set equal to their mean values within subgroup for the calculation of adjusted means.

For patients who died, only observed values are considered (no imputation after date of death).
Data taken from study 1245.121 only.
The MMRM includes all outcome values (change from baseline) at the planned Visits week 12, week 32 and week 52

Table R.1.3.3.9: 1 KCCQ-TSS change from baseline at week 52 (MMRM) by baseline eGFR (2 cat.) - RS (OC-AD - no imputation for deaths) - 1245.121

Subgroup Visit Description Statistic	Placebo	Empa 10mg
Baseline eGFR (CKD-EPI) [mL/min/1.73m²] (2 cat.): <60		
Number of patients in analysis set	906	893
Number of analysed patients	852	855
Baseline mean (SE)	74.66 (0.76)	74.22 (0.76)
Week 52		
Values at visit		
Number of analysed patients	571	589
Mean (SE)	80.42 (0.88)	80.78 (0.80)
Adjusted* mean (SE)	80.08 (0.68)	80.33 (0.67)
95% confidence interval	(78.74,81.42)	(79.01,81.65)
Change from baseline		
Mean (SE)	5.39 (0.91)	5.51 (0.82)
Adjusted* mean (SE)	5.64 (0.68)	5.89 (0.67)
95% confidence interval	(4.30, 6.98)	(4.57, 7.21)
Comparison vs Placebo		
Adjusted* mean (SE)		0.25 (0.96)
95% confidence interval		(-1.63, 2.13)
p-value		0.7950

* Model includes Age as linear covariate(s) and region, baseline diabetes status, sex, baseline LVEF, week reachable, Visit by Treatment by baseline eGFR (CKD-EPI) [mL/min/1.73m²] (2 cat.) interaction, baseline KCCQ - total symptom score by Visit interaction as fixed effect(s).
The Visit by Treatment by baseline eGFR (CKD-EPI) [mL/min/1.73m²] (2 cat.) p-value at Week 52 is 0.0388.
The following covariance structure has been used to fit the mixed model: Unstructured
2 patients were excluded as the subgroup variable was missing.
Note: All covariate effects are set equal to their mean values within subgroup for the calculation of adjusted means.

For patients who died, only observed values are considered (no imputation after date of death).
Data taken from study 1245.121 only.
The MMRM includes all outcome values (change from baseline) at the planned Visits week 12, week 32 and week 52

R.1.3.3.10

Table R.1.3.3.10: 1 KCCQ-TSS change from baseline at week 52 (MMRM) by history of HHF - RS (OC-AD - no imputation for deaths) - 1245.121

Subgroup / Visit / Description / Statistic	Placebo	Empa 10mg
History of HHF (in the last 12 months): No		
Number of patients in analysis set	1293	1286
Number of analysed patients	1220	1231
Baseline mean (SE)	74.93 (0.63)	74.86 (0.64)
Week 52		
Values at visit		
Number of analysed patients	869	873
Mean (SE)	79.79 (0.72)	82.29 (0.66)
Adjusted* mean (SE)	79.79 (0.56)	81.97 (0.55)
95% confidence interval	(78.70,80.89)	(80.89,83.06)
Change from baseline		
Mean (SE)	4.90 (0.72)	6.96 (0.66)
Adjusted* mean (SE)	4.90 (0.56)	7.08 (0.55)
95% confidence interval	(3.81, 5.99)	(5.99, 8.16)
Comparison vs Placebo		
Adjusted* mean (SE)		2.18 (0.78)
95% confidence interval		(0.64, 3.72)
p-value		0.0055

* Model includes Age, baseline eGFR (CKD-EPI) as linear covariate(s) and region, baseline diabetes status, sex, baseline LVEF, week reachable, Visit by Treatment by history of HHF (in the last 12 months) interaction, baseline KCCQ - total symptom score by Visit interaction as fixed effect(s).
The Visit by Treatment by history of HHF (in the last 12 months) p-value at Week 52 is 0.2389.
The following covariance structure has been used to fit the mixed model: Unstructured
Note: All covariate effects are set equal to their mean values within subgroup for the calculation of adjusted means.

For patients who died, only observed values are considered (no imputation after date of death).
Data taken from study 1245.121 only.
The MMRM includes all outcome values (change from baseline) at the planned Visits week 12, week 32 and week 52

Table R.1.3.3.10: 1 KCCQ-TSS change from baseline at week 52 (MMRM) by history of HHF - RS (OC-AD - no imputation for deaths) - 1245.121

Subgroup / Visit / Description / Statistic	Placebo	Empa 10mg
History of HHF (in the last 12 months): Yes		
Number of patients in analysis set	574	577
Number of analysed patients	533	545
Baseline mean (SE)	75.24 (0.93)	74.34 (1.01)
Week 52		
Values at visit		
Number of analysed patients	349	366
Mean (SE)	82.25 (1.04)	82.19 (1.05)
Adjusted* mean (SE)	80.61 (0.87)	81.08 (0.86)
95% confidence interval	(78.89,82.32)	(79.40,82.76)
Change from baseline		
Mean (SE)	5.52 (1.04)	5.54 (1.07)
Adjusted* mean (SE)	5.82 (0.87)	6.29 (0.86)
95% confidence interval	(4.11, 7.53)	(4.62, 7.97)
Comparison vs Placebo		
Adjusted* mean (SE)		0.47 (1.22)
95% confidence interval		(-1.91, 2.86)
p-value		0.6978

* Model includes Age, baseline eGFR (CKD-EPI) as linear covariate(s) and region, baseline diabetes status, sex, baseline LVEF, week reachable, Visit by Treatment by history of HHF (in the last 12 months) interaction, baseline KCCQ - total symptom score by Visit interaction as fixed effect(s).
The Visit by Treatment by history of HHF (in the last 12 months) p-value at Week 52 is 0.2389.
The following covariance structure has been used to fit the mixed model: Unstructured
Note: All covariate effects are set equal to their mean values within subgroup for the calculation of adjusted means.

For patients who died, only observed values are considered (no imputation after date of death).
Data taken from study 1245.121 only.
The MMRM includes all outcome values (change from baseline) at the planned Visits week 12, week 32 and week 52

R.1.3.3.11

R.1.3.3.11 Subgroup analysis by cause of heart failure

Table R.1.3.3.11: 1 KCCQ-TSS change from baseline at week 52 (MMRM) by cause of heart failure - RS (OC-AD - no imputation for deaths) - 1245.121

Subgroup / Visit / Description / Statistic	Placebo	Empa 10mg
Cause of heart failure: Ischemic		
Number of patients in analysis set	946	983
Number of analysed patients	896	936
Baseline mean (SE)	75.50 (0.71)	74.88 (0.74)
Week 52		
Values at visit		
Number of analysed patients	634	667
Mean (SE)	80.42 (0.83)	82.03 (0.76)
Adjusted* mean (SE)	80.14 (0.65)	81.45 (0.64)
95% confidence interval	(78.85,81.42)	(80.20,82.70)
Change from baseline		
Mean (SE)	4.42 (0.79)	5.79 (0.77)
Adjusted* mean (SE)	4.95 (0.65)	6.27 (0.64)
95% confidence interval	(3.67, 6.24)	(5.02, 7.52)
Comparison vs Placebo		
Adjusted* mean (SE)		1.31 (0.91)
95% confidence interval		(-0.47, 3.09)
p-value		0.1484

* Model includes Age, baseline eGFR (CKD-EPI) as linear covariate(s) and region, baseline diabetes status, sex, baseline LVEF, week reachable, Visit by Treatment by cause of heart failure interaction, baseline KCCQ - total symptom score by Visit interaction as fixed effect(s).
The Visit by Treatment by cause of heart failure p-value at Week 52 is 0.5448.
The following covariance structure has been used to fit the mixed model: Unstructured
Note: All covariate effects are set equal to their mean values within subgroup for the calculation of adjusted means.

For patients who died, only observed values are considered (no imputation after date of death).
Data taken from study 1245.121 only.
The MMRM includes all outcome values (change from baseline) at the planned Visits week 12, week 32 and week 52

Table R.1.3.3.11: 1 KCCQ-TSS change from baseline at week 52 (MMRM) by cause of heart failure - RS (OC-AD - no imputation for deaths) - 1245.121

Subgroup / Visit / Description / Statistic	Placebo	Empa 10mg
Cause of heart failure: Non-ischemic		
Number of patients in analysis set	921	880
Number of analysed patients	857	840
Baseline mean (SE)	74.53 (0.77)	74.51 (0.79)
Week 52		
Values at visit		
Number of analysed patients	584	572
Mean (SE)	80.57 (0.86)	82.53 (0.83)
Adjusted* mean (SE)	79.90 (0.68)	82.01 (0.68)
95% confidence interval	(78.57,81.23)	(80.67,83.36)
Change from baseline		
Mean (SE)	5.79 (0.89)	7.42 (0.82)
Adjusted* mean (SE)	5.38 (0.68)	7.50 (0.68)
95% confidence interval	(4.05, 6.72)	(6.15, 8.84)
Comparison vs Placebo		
Adjusted* mean (SE)		2.11 (0.96)
95% confidence interval		(0.23, 4.00)
p-value		0.0277

* Model includes Age, baseline eGFR (CKD-EPI) as linear covariate(s) and region, baseline diabetes status, sex, baseline LVEF, week reachable, Visit by Treatment by cause of heart failure interaction, baseline KCCQ - total symptom score by Visit interaction as fixed effect(s).
The Visit by Treatment by cause of heart failure p-value at Week 52 is 0.5448.
The following covariance structure has been used to fit the mixed model: Unstructured
Note: All covariate effects are set equal to their mean values within subgroup for the calculation of adjusted means.

For patients who died, only observed values are considered (no imputation after date of death).
Data taken from study 1245.121 only.
The MMRM includes all outcome values (change from baseline) at the planned Visits week 12, week 32 and week 52

R.1.3.3.12 Subgroup analysis by heart failure physiology (LVEF <= 30% and NTproBNP<median; LVEF <= 30% and NTproBNP>=median; LVEF > 30%)

Table R.1.3.3.12: 1 KCCQ-TSS change from baseline at week 52 (MMRM) by heart failure physiology - RS (OC-AD - no imputation for deaths) - 1245.121

Subgroup / Visit / Description / Statistic	Placebo	Empa 10mg
Heart failure physiology: LVEF <= 30% and NTproBNP < median		
Number of patients in analysis set	723	698
Number of analysed patients	694	672
Baseline mean (SE)	76.02 (0.82)	77.16 (0.81)
Week 52		
Values at visit		
Number of analysed patients	511	494
Mean (SE)	81.75 (0.94)	83.12 (0.87)
Adjusted* mean (SE)	81.57 (0.73)	82.96 (0.74)
95% confidence interval	(80.14,82.99)	(81.51,84.41)
Change from baseline		
Mean (SE)	5.65 (0.87)	6.09 (0.80)
Adjusted* mean (SE)	4.99 (0.73)	6.38 (0.74)
95% confidence interval	(3.56, 6.41)	(4.93, 7.83)
Comparison vs Placebo		
Adjusted* mean (SE)		1.39 (1.03)
95% confidence interval		(-0.64, 3.42)
p-value		0.1791

* Model includes Age, baseline eGFR (CKD-EPI) as linear covariate(s) and region, baseline diabetes status, sex, week reachable, Visit by Treatment by heart failure physiology interaction, baseline KCCQ - total symptom score by Visit interaction as fixed effect(s).
The Visit by Treatment by heart failure physiology p-value at Week 52 is 0.5942.
The following covariance structure has been used to fit the mixed model: Unstructured
16 patients were excluded as the subgroup variable was missing.
Note: All covariate effects are set equal to their mean values within subgroup for the calculation of adjusted means.
The p-value for the visit by treatment by subgroup interaction trend test at Week 52 is 0.9316

For patients who died, only observed values are considered (no imputation after date of death).
Data taken from study 1245.121 only.
NTproBNP median [pg/mL]: with a. fibrillation/flutter at baseline: 2265; without a. fibrillation/flutter at baseline: 1671.
The MMRM includes all outcome values (change from baseline) at the planned Visits week 12, week 32 and week 52

Table R.1.3.3.12: 1 KCCQ-TSS change from baseline at week 52 (MMRM) by heart failure physiology - RS (OC-AD - no imputation for deaths) - 1245.121

Subgroup / Visit / Description / Statistic	Placebo	Empa 10mg
Heart failure physiology: LVEF <= 30% and NTproBNP >= median		
Number of patients in analysis set	661	631
Number of analysed patients	604	593
Baseline mean (SE)	73.36 (0.92)	70.96 (0.99)
Week 52		
Values at visit		
Number of analysed patients	409	405
Mean (SE)	77.98 (1.07)	80.74 (1.02)
Adjusted* mean (SE)	77.35 (0.81)	79.98 (0.81)
95% confidence interval	(75.77,78.93)	(78.38,81.57)
Change from baseline		
Mean (SE)	4.13 (1.12)	7.86 (1.12)
Adjusted* mean (SE)	5.18 (0.81)	7.80 (0.81)
95% confidence interval	(3.59, 6.76)	(6.21, 9.39)
Comparison vs Placebo		
Adjusted* mean (SE)		2.62 (1.14)
95% confidence interval		(0.38, 4.87)
p-value		0.0219

* Model includes Age, baseline eGFR (CKD-EPI) as linear covariate(s) and region, baseline diabetes status, sex, week reachable, Visit by Treatment by heart failure physiology interaction, baseline KCCQ - total symptom score by Visit interaction as fixed effect(s).
The Visit by Treatment by heart failure physiology p-value at Week 52 is 0.5942.
The following covariance structure has been used to fit the mixed model: Unstructured
16 patients were excluded as the subgroup variable was missing.
Note: All covariate effects are set equal to their mean values within subgroup for the calculation of adjusted means.
The p-value for the visit by treatment by subgroup interaction trend test at Week 52 is 0.9316

For patients who died, only observed values are considered (no imputation after date of death).
Data taken from study 1245.121 only.
NTproBNP median [pg/mL]: with a. fibrillation/flutter at baseline: 2265; without a. fibrillation/flutter at baseline: 1671.
The MMRM includes all outcome values (change from baseline) at the planned Visits week 12, week 32 and week 52

Table R.1.3.3.12: 1 KCCQ-TSS change from baseline at week 52 (MMRM) by heart failure physiology - RS (OC-AD - no imputation for deaths) - 1245.121

Subgroup / Visit / Description / Statistic	Placebo	Empa 10mg
Heart failure physiology: LVEF > 30%		
Number of patients in analysis set	475	526
Number of analysed patients	450	506
Baseline mean (SE)	75.97 (1.00)	75.93 (1.01)
Week 52		
Values at visit		
Number of analysed patients	294	339
Mean (SE)	82.00 (1.06)	82.81 (1.05)
Adjusted* mean (SE)	81.20 (0.95)	82.19 (0.88)
95% confidence interval	(79.34,83.06)	(80.46,83.92)
Change from baseline		
Mean (SE)	5.23 (1.12)	5.66 (1.03)
Adjusted* mean (SE)	5.25 (0.95)	6.24 (0.88)
95% confidence interval	(3.39, 7.11)	(4.51, 7.97)
Comparison vs Placebo		
Adjusted* mean (SE)		0.99 (1.30)
95% confidence interval		(-1.55, 3.53)
p-value		0.4445

* Model includes Age, baseline eGFR (CKD-EPI) as linear covariate(s) and region, baseline diabetes status, sex, week reachable, Visit by Treatment by heart failure physiology interaction, baseline KCCQ - total symptom score by Visit interaction as fixed effect(s).
The Visit by Treatment by heart failure physiology p-value at Week 52 is 0.5942.
The following covariance structure has been used to fit the mixed model: Unstructured
16 patients were excluded as the subgroup variable was missing.
Note: All covariate effects are set equal to their mean values within subgroup for the calculation of adjusted means.
The p-value for the visit by treatment by subgroup interaction trend test at Week 52 is 0.9316

For patients who died, only observed values are considered (no imputation after date of death).
Data taken from study 1245.121 only.
NTproBNP median [pg/mL]: with a. fibrillation/flutter at baseline: 2265; without a. fibrillation/flutter at baseline: 1671.
The MMRM includes all outcome values (change from baseline) at the planned Visits week 12, week 32 and week 52

R.1.3.3.13

R.1.3.3.13 Subgroup analysis by baseline use of MRA

Table R.1.3.3.13: 1 KCCQ-TSS change from baseline at week 52 (MMRM) by baseline use of MRA (Y/N) - RS (OC-AD - no imputation for deaths) - 1245.121

Subgroup / Visit / Description / Statistic	Placebo	Empa 10mg
Baseline use of MRA: No		
Number of patients in analysis set	512	557
Number of analysed patients	486	531
Baseline mean (SE)	76.64 (0.96)	75.28 (0.98)
Week 52		
Values at visit		
Number of analysed patients	340	383
Mean (SE)	78.97 (1.14)	84.20 (0.95)
Adjusted* mean (SE)	79.37 (0.89)	83.74 (0.84)
95% confidence interval	(77.63,81.11)	(82.09,85.39)
Change from baseline		
Mean (SE)	2.98 (1.07)	7.49 (1.03)
Adjusted* mean (SE)	3.44 (0.89)	7.81 (0.84)
95% confidence interval	(1.70, 5.18)	(6.16, 9.46)
Comparison vs Placebo		
Adjusted* mean (SE)		4.38 (1.22)
95% confidence interval		(1.99, 6.76)
p-value		0.0003

* Model includes Age, baseline eGFR (CKD-EPI) as linear covariate(s) and region, baseline diabetes status, sex, baseline LVEF, week reachable, Visit by Treatment by baseline use of MRA interaction, baseline KCCQ - total symptom score by Visit interaction as fixed effect(s).
The Visit by Treatment by baseline use of MRA p-value at Week 52 is 0.0086.
The following covariance structure has been used to fit the mixed model: Unstructured
Note: All covariate effects are set equal to their mean values within subgroup for the calculation of adjusted means.

For patients who died, only observed values are considered (no imputation after date of death).
Data taken from study 1245.121 only.
The MMRM includes all outcome values (change from baseline) at the planned Visits week 12, week 32 and week 52

Table R.1.3.3.13: 1 KCCQ-TSS change from baseline at week 52 (MMRM) by baseline use of MRA (Y/N) - RS (OC-AD - no imputation for deaths) - 1245.121

Subgroup / Visit / Description / Statistic	Placebo	Empa 10mg
Baseline use of MRA: Yes		
Number of patients in analysis set	1355	1306
Number of analysed patients	1267	1245
Baseline mean (SE)	74.41 (0.62)	74.46 (0.65)
Week 52		
Values at visit		
Number of analysed patients	878	856
Mean (SE)	81.08 (0.70)	81.39 (0.69)
Adjusted* mean (SE)	80.27 (0.55)	80.83 (0.56)
95% confidence interval	(79.19,81.35)	(79.74,81.93)
Change from baseline		
Mean (SE)	5.89 (0.71)	6.12 (0.67)
Adjusted* mean (SE)	5.84 (0.55)	6.40 (0.56)
95% confidence interval	(4.75, 6.92)	(5.31, 7.49)
Comparison vs Placebo		
Adjusted* mean (SE)		0.57 (0.78)
95% confidence interval		(-0.97, 2.10)
p-value		0.4702

* Model includes Age, baseline eGFR (CKD-EPI) as linear covariate(s) and region, baseline diabetes status, sex, baseline LVEF, week reachable, Visit by Treatment by baseline use of MRA interaction, baseline KCCQ - total symptom score by Visit interaction as fixed effect(s).
The Visit by Treatment by baseline use of MRA p-value at Week 52 is 0.0086.
The following covariance structure has been used to fit the mixed model: Unstructured
Note: All covariate effects are set equal to their mean values within subgroup for the calculation of adjusted means.

For patients who died, only observed values are considered (no imputation after date of death).
Data taken from study 1245.121 only.
The MMRM includes all outcome values (change from baseline) at the planned Visits week 12, week 32 and week 52

R.1.3.3.14

Table R.1.3.3.14: 1 KCCQ-TSS change from baseline at week 52 (MMRM) by baseline use of ARNi (Y/N) - RS (OC-AD - no imputation for deaths) - 1245.121

Subgroup / Visit / Description / Statistic	Placebo	Empa 10mg
Baseline use of ARNi: No		
Number of patients in analysis set	1480	1523
Number of analysed patients	1390	1447
Baseline mean (SE)	74.93 (0.58)	74.12 (0.60)
Week 52		
Values at visit		
Number of analysed patients	960	1026
Mean (SE)	80.56 (0.66)	81.96 (0.62)
Adjusted* mean (SE)	79.87 (0.53)	81.47 (0.51)
95% confidence interval	(78.84,80.91)	(80.47,82.47)
Change from baseline		
Mean (SE)	5.23 (0.68)	6.84 (0.63)
Adjusted* mean (SE)	5.36 (0.53)	6.95 (0.51)
95% confidence interval	(4.32, 6.39)	(5.95, 7.96)
Comparison vs Placebo		
Adjusted* mean (SE)		1.60 (0.73)
95% confidence interval		(0.16, 3.04)
p-value		0.0299

* Model includes Age, baseline eGFR (CKD-EPI) as linear covariate(s) and region, baseline diabetes status, sex, baseline LVEF, week reachable, Visit by Treatment by baseline use of ARNi interaction, baseline KCCQ - total symptom score by Visit interaction as fixed effect(s).
The Visit by Treatment by baseline use of ARNi p-value at Week 52 is 0.7595.
The following covariance structure has been used to fit the mixed model: Unstructured
Note: All covariate effects are set equal to their mean values within subgroup for the calculation of adjusted means.

For patients who died, only observed values are considered (no imputation after date of death).
Data taken from study 1245.121 only.
The MMRM includes all outcome values (change from baseline) at the planned Visits week 12, week 32 and week 52

Table R.1.3.3.14: 1 KCCQ-TSS change from baseline at week 52 (MMRM) by baseline use of ARNi (Y/N) - RS (OC-AD - no imputation for deaths) - 1245.121

Subgroup / Visit / Description / Statistic	Placebo	Empa 10mg
Baseline use of ARNi: Yes		
Number of patients in analysis set	387	340
Number of analysed patients	363	329
Baseline mean (SE)	75.39 (1.22)	77.27 (1.20)
Week 52		
Values at visit		
Number of analysed patients	258	213
Mean (SE)	80.22 (1.35)	83.67 (1.33)
Adjusted* mean (SE)	80.62 (1.02)	82.73 (1.12)
95% confidence interval	(78.61,82.63)	(80.54,84.93)
Change from baseline		
Mean (SE)	4.51 (1.22)	5.11 (1.25)
Adjusted* mean (SE)	4.34 (1.02)	6.45 (1.12)
95% confidence interval	(2.33, 6.35)	(4.25, 8.64)
Comparison vs Placebo		
Adjusted* mean (SE)		2.11 (1.51)
95% confidence interval		(-0.85, 5.07)
p-value		0.1627

* Model includes Age, baseline eGFR (CKD-EPI) as linear covariate(s) and region, baseline diabetes status, sex, baseline LVEF, week reachable, Visit by Treatment by baseline use of ARNi interaction, baseline KCCQ - total symptom score by Visit interaction as fixed effect(s).
The Visit by Treatment by baseline use of ARNi p-value at Week 52 is 0.7595.
The following covariance structure has been used to fit the mixed model: Unstructured
Note: All covariate effects are set equal to their mean values within subgroup for the calculation of adjusted means.

For patients who died, only observed values are considered (no imputation after date of death).
Data taken from study 1245.121 only.
The MMRM includes all outcome values (change from baseline) at the planned Visits week 12, week 32 and week 52

R.1.3.3.15 Subgroup analysis by bl. LVEF (<= 30%, >30% -<= 35% , > 35%)

Table R.1.3.3.15: 1 KCCQ-TSS change from baseline at week 52 (MMRM) by baseline LVEF (3 cat.) - RS (OC-AD - no imputation for deaths) - 1245.121

Subgroup / Visit / Description / Statistic	Placebo	Empa 10mg
Baseline LVEF (3 cat.): <=30		
Number of patients in analysis set	1392	1337
Number of analysed patients	1303	1270
Baseline mean (SE)	74.70 (0.61)	74.21 (0.64)
Week 52		
Values at visit		
Number of analysed patients	924	900
Mean (SE)	80.01 (0.71)	82.05 (0.66)
Adjusted* mean (SE)	79.60 (0.54)	81.54 (0.55)
95% confidence interval	(78.54,80.65)	(80.47,82.61)
Change from baseline		
Mean (SE)	5.03 (0.69)	6.88 (0.67)
Adjusted* mean (SE)	5.14 (0.54)	7.08 (0.55)
95% confidence interval	(4.08, 6.19)	(6.01, 8.15)
Comparison vs Placebo		
Adjusted* mean (SE)		1.95 (0.77)
95% confidence interval		(0.44, 3.45)
p-value		0.0111

* Model includes Age, baseline eGFR (CKD-EPI) as linear covariate(s) and region, baseline diabetes status, sex, week reachable, Visit by Treatment by baseline LVEF (3 cat.) interaction, baseline KCCQ - total symptom score by Visit interaction as fixed effect(s).
The Visit by Treatment by baseline LVEF (3 cat.) p-value at Week 52 is 0.2334.
The following covariance structure has been used to fit the mixed model: Unstructured
Note: All covariate effects are set equal to their mean values within subgroup for the calculation of adjusted means.
The p-value for the visit by treatment by subgroup interaction trend test at Week 52 is 0.9875

For patients who died, only observed values are considered (no imputation after date of death).
Data taken from study 1245.121 only.
The MMRM includes all outcome values (change from baseline) at the planned Visits week 12, week 32 and week 52

Table R.1.3.3.15: 1 KCCQ-TSS change from baseline at week 52 (MMRM) by baseline LVEF (3 cat.) - RS (OC-AD - no imputation for deaths) - 1245.121

Subgroup / Visit / Description / Statistic	Placebo	Empa 10mg
Baseline LVEF (3 cat.): >30 to <=35		
Number of patients in analysis set	361	398
Number of analysed patients	342	385
Baseline mean (SE)	76.57 (1.11)	76.07 (1.14)
Week 52		
Values at visit		
Number of analysed patients	233	256
Mean (SE)	83.04 (1.11)	82.14 (1.21)
Adjusted* mean (SE)	82.00 (1.07)	81.87 (1.02)
95% confidence interval	(79.90,84.09)	(79.88,83.87)
Change from baseline		
Mean (SE)	5.38 (1.24)	4.59 (1.10)
Adjusted* mean (SE)	5.69 (1.07)	5.57 (1.02)
95% confidence interval	(3.59, 7.79)	(3.58, 7.56)
Comparison vs Placebo		
Adjusted* mean (SE)		-0.12 (1.47)
95% confidence interval		(-3.01, 2.77)
p-value		0.9336

* Model includes Age, baseline eGFR (CKD-EPI) as linear covariate(s) and region, baseline diabetes status, sex, week reachable, Visit by Treatment by baseline LVEF (3 cat.) interaction, baseline KCCQ - total symptom score by Visit interaction as fixed effect(s).
The Visit by Treatment by baseline LVEF (3 cat.) p-value at Week 52 is 0.2334.
The following covariance structure has been used to fit the mixed model: Unstructured
Note: All covariate effects are set equal to their mean values within subgroup for the calculation of adjusted means.
The p-value for the visit by treatment by subgroup interaction trend test at Week 52 is 0.9875

For patients who died, only observed values are considered (no imputation after date of death).
Data taken from study 1245.121 only.
The MMRM includes all outcome values (change from baseline) at the planned Visits week 12, week 32 and week 52

Table R.1.3.3.15: 1 KCCQ-TSS change from baseline at week 52 (MMRM) by baseline LVEF (3 cat.) - RS (OC-AD - no imputation for deaths) - 1245.121

Subgroup / Visit / Description / Statistic	Placebo	Empa 10mg
Baseline LVEF (3 cat.): >35		
Number of patients in analysis set	114	128
Number of analysed patients	108	121
Baseline mean (SE)	74.07 (2.24)	75.46 (2.16)
Week 52		
Values at visit		
Number of analysed patients	61	83
Mean (SE)	78.06 (2.84)	84.89 (2.09)
Adjusted* mean (SE)	78.33 (2.06)	83.11 (1.79)
95% confidence interval	(74.28,82.37)	(79.60,86.63)
Change from baseline		
Mean (SE)	4.66 (2.62)	8.95 (2.44)
Adjusted* mean (SE)	3.52 (2.06)	8.31 (1.79)
95% confidence interval	(-0.52, 7.56)	(4.79,11.82)
Comparison vs Placebo		
Adjusted* mean (SE)		4.79 (2.73)
95% confidence interval		(-0.57,10.14)
p-value		0.0796

* Model includes Age, baseline eGFR (CKD-EPI) as linear covariate(s) and region, baseline diabetes status, sex, week reachable, Visit by Treatment by baseline LVEF (3 cat.) interaction, baseline KCCQ - total symptom score by Visit interaction as fixed effect(s).
The Visit by Treatment by baseline LVEF (3 cat.) p-value at Week 52 is 0.2334.
The following covariance structure has been used to fit the mixed model: Unstructured
Note: All covariate effects are set equal to their mean values within subgroup for the calculation of adjusted means.
The p-value for the visit by treatment by subgroup interaction trend test at Week 52 is 0.9875

For patients who died, only observed values are considered (no imputation after date of death).
Data taken from study 1245.121 only.
The MMRM includes all outcome values (change from baseline) at the planned Visits week 12, week 32 and week 52

R.1.3.3.16 Subgroup analysis by bl. NTproBNP </>= median (median based on total patients)

Table R.1.3.3.16: 1 KCCQ-TSS change from baseline at week 52 (MMRM) by bl. NTproBNP (<median, >= median) (median based on total patients) - RS (OC-AD - no imputation for deaths) - 1245.121

Subgroup / Visit / Description / Statistic	Placebo	Empa 10mg
Baseline NTproBNP (<median, >= median): < median		
Number of patients in analysis set	920	942
Number of analysed patients	884	908
Baseline mean (SE)	77.08 (0.70)	77.42 (0.70)
Week 52		
Values at visit		
Number of analysed patients	651	666
Mean (SE)	81.86 (0.80)	83.30 (0.74)
Adjusted* mean (SE)	81.70 (0.64)	83.32 (0.64)
95% confidence interval	(80.44,82.97)	(82.07,84.56)
Change from baseline		
Mean (SE)	5.08 (0.74)	5.98 (0.68)
Adjusted* mean (SE)	4.45 (0.64)	6.07 (0.64)
95% confidence interval	(3.19, 5.71)	(4.82, 7.31)
Comparison vs Placebo		
Adjusted* mean (SE)		1.62 (0.90)
95% confidence interval		(-0.16, 3.39)
p-value		0.0740

* Model includes Age, baseline eGFR (CKD-EPI) as linear covariate(s) and region, baseline diabetes status, sex, baseline LVEF, week reachable, Visit by Treatment by baseline NTproBNP (<median, >= median) interaction, baseline KCCQ - total symptom score by Visit interaction as fixed effect(s). The Visit by Treatment by baseline NTproBNP (<median, >= median) p-value at Week 52 is 0.9342.
The following covariance structure has been used to fit the mixed model: Unstructured
2 patients were excluded as the subgroup variable was missing.
Note: All covariate effects are set equal to their mean values within subgroup for the calculation of adjusted means.

For patients who died, only observed values are considered (no imputation after date of death).
Data taken from study 1245.121 only.
Median: 1910 [pg/mL]
The MMRM includes all outcome values (change from baseline) at the planned Visits week 12, week 32 and week 52

Table R.1.3.3.16: 1 KCCQ-TSS change from baseline at week 52 (MMRM) by bl. NTproBNP (<median, >= median) (median based on total patients) - RS (OC-AD - no imputation for deaths) - 1245.121

Subgroup / Visit / Description / Statistic	Placebo	Empa 10mg
Baseline NTproBNP (<median, >= median): >= median		
Number of patients in analysis set	946	920
Number of analysed patients	869	868
Baseline mean (SE)	72.94 (0.77)	71.86 (0.82)
Week 52		
Values at visit		
Number of analysed patients	567	573
Mean (SE)	78.92 (0.89)	81.05 (0.86)
Adjusted* mean (SE)	78.29 (0.68)	80.01 (0.68)
95% confidence interval	(76.95,79.63)	(78.68,81.35)
Change from baseline		
Mean (SE)	5.08 (0.94)	7.20 (0.92)
Adjusted* mean (SE)	5.89 (0.68)	7.61 (0.68)
95% confidence interval	(4.55, 7.23)	(6.28, 8.95)
Comparison vs Placebo		
Adjusted* mean (SE)		1.73 (0.96)
95% confidence interval		(-0.16, 3.62)
p-value		0.0736

* Model includes Age, baseline eGFR (CKD-EPI) as linear covariate(s) and region, baseline diabetes status, sex, baseline LVEF, week reachable, Visit by Treatment by baseline NTproBNP (<median, >= median) interaction, baseline KCCQ - total symptom score by Visit interaction as fixed effect(s). The Visit by Treatment by baseline NTproBNP (<median, >= median) p-value at Week 52 is 0.9342.
The following covariance structure has been used to fit the mixed model: Unstructured
2 patients were excluded as the subgroup variable was missing.
Note: All covariate effects are set equal to their mean values within subgroup for the calculation of adjusted means.

For patients who died, only observed values are considered (no imputation after date of death).
Data taken from study 1245.121 only.
Median: 1910 [pg/mL]
The MMRM includes all outcome values (change from baseline) at the planned Visits week 12, week 32 and week 52

R.1.3.4

R.1.3.4 KCCQ Overall Summary Score MMRM analysis

R.1.3.4.1

Table R.1.3.4.1: 1

Table R.1.3.4.1: 1 KCCQ-OSS change from baseline MMRM results over time - RS (OC-AD - no imputation for deaths) - 1245.121

Visit Description Statistic	Placebo	Empa 10mg
Number of patients in analysis set	1867	1863
Number of analysed patients	1753	1776
Baseline mean (SE)	67.59 (0.51)	67.58 (0.53)
Week 12		
Values at visit		
Number of analysed patients	1732	1755
Mean (SE)	71.83 (0.49)	73.58 (0.50)
Adjusted* mean (SE)	71.95 (0.35)	73.72 (0.35)
95% confidence interval	(71.26,72.64)	(73.04,74.40)
Change from baseline		
Mean (SE)	4.16 (0.39)	5.92 (0.39)
Adjusted* mean (SE)	3.95 (0.35)	5.72 (0.35)
95% confidence interval	(3.26, 4.63)	(5.04, 6.40)
Comparison vs Placebo		
Adjusted* mean (SE)		1.77 (0.49)
95% confidence interval		(0.81, 2.73)
p-value		0.0003
Hedges g		
Estimate		0.12
95% confidence interval		(0.06, 0.19)

* Model includes Age (p=0.2587), baseline eGFR (CKD-EPI) (p=0.0013) as linear covariate(s) and region (p<0.0001), baseline diabetes status (p=0.3989), sex (p=0.3259), baseline LVEF (p=0.4731), week reachable (p=0.1346), Treatment by Visit interaction (p<0.0001), baseline KCCQ - overall summary score by Visit interaction (p<0.0001) as fixed effect(s).
The following covariance structure has been used to fit the mixed model: Unstructured

For patients who died, only observed values are considered (no imputation after date of death).
Data taken from study 1245.121 only.

Table R.1.3.4.1: 1 KCCQ-OSS change from baseline MMRM results over time - RS (OC-AD - no imputation for deaths) - 1245.121

Visit Description Statistic	Placebo	Empa 10mg
Week 32		
Values at visit		
Number of analysed patients	1568	1618
Mean (SE)	73.03 (0.52)	74.38 (0.52)
Adjusted* mean (SE)	72.76 (0.39)	74.06 (0.39)
95% confidence interval	(71.99,73.53)	(73.30,74.82)
Change from baseline		
Mean (SE)	5.10 (0.45)	6.31 (0.44)
Adjusted* mean (SE)	4.76 (0.39)	6.06 (0.39)
95% confidence interval	(3.98, 5.53)	(5.29, 6.82)
Comparison vs Placebo		
Adjusted* mean (SE)		1.30 (0.55)
95% confidence interval		(0.22, 2.38)
p-value		0.0186
Hedges g		
Estimate		0.08
95% confidence interval		(0.01, 0.15)

* Model includes Age (p=0.2587), baseline eGFR (CKD-EPI) (p=0.0013) as linear covariate(s) and region (p<0.0001), baseline diabetes status (p=0.3989), sex (p=0.3259), baseline LVEF (p=0.4731), week reachable (p=0.1346), Treatment by Visit interaction (p<0.0001), baseline KCCQ - overall summary score by Visit interaction (p<0.0001) as fixed effect(s).
The following covariance structure has been used to fit the mixed model: Unstructured

For patients who died, only observed values are considered (no imputation after date of death).
Data taken from study 1245.121 only.

Table R.1.3.4.1: 1 KCCQ-OSS change from baseline MMRM results over time - RS (OC-AD - no imputation for deaths) - 1245.121

Visit Description Statistic	Placebo	Empa 10mg
Week 52		
Values at visit		
Number of analysed patients	1218	1239
Mean (SE)	73.54 (0.60)	75.12 (0.59)
Adjusted* mean (SE)	73.01 (0.44)	74.53 (0.44)
95% confidence interval	(72.14,73.88)	(73.67,75.39)
Change from baseline		
Mean (SE)	5.23 (0.55)	6.49 (0.51)
Adjusted* mean (SE)	5.01 (0.44)	6.53 (0.44)
95% confidence interval	(4.14, 5.88)	(5.67, 7.39)
Comparison vs Placebo		
Adjusted* mean (SE)		1.52 (0.62)
95% confidence interval		(0.29, 2.74)
p-value		0.0151
Hedges g		
Estimate		0.09
95% confidence interval		(0.02, 0.17)

* Model includes Age (p=0.2587), baseline eGFR (CKD-EPI) (p=0.0013) as linear covariate(s) and region (p<0.0001), baseline diabetes status (p=0.3989), sex (p=0.3259), baseline LVEF (p=0.4731), week reachable (p=0.1346), Treatment by Visit interaction (p<0.0001), baseline KCCQ - overall summary score by Visit interaction (p<0.0001) as fixed effect(s).
The following covariance structure has been used to fit the mixed model: Unstructured

For patients who died, only observed values are considered (no imputation after date of death).
Data taken from study 1245.121 only.

Figure R.1.3.4.1: 1

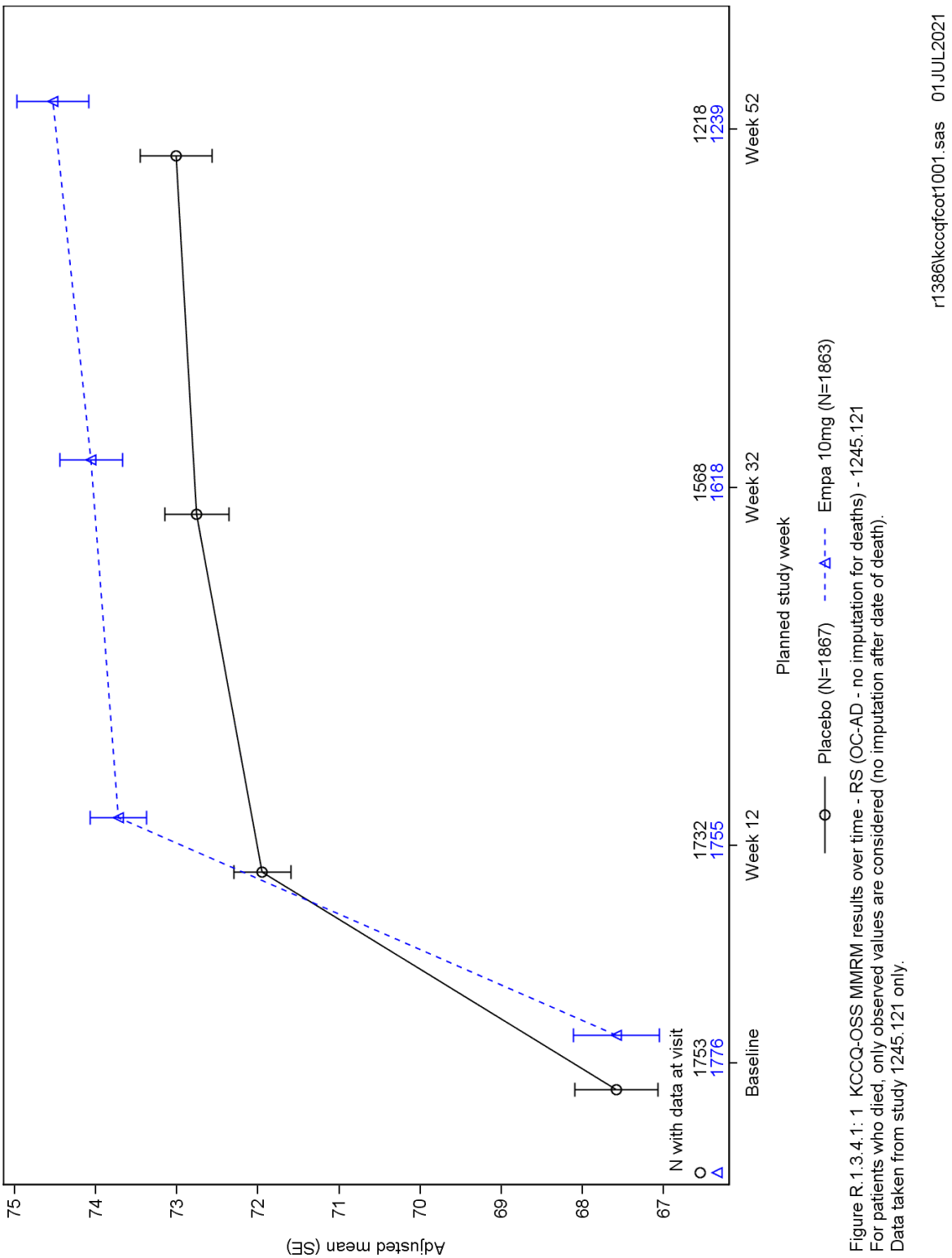

Figure R.1.3.4.1: 1 KCCQ-OSS MMRM results over time - RS (OC-AD - no imputation for deaths) - 1245.121
For patients who died, only observed values are considered (no imputation after date of death).
Data taken from study 1245.121 only.

R.1.3.4.2

R.1.3.4.2 Subgroup analysis by sex

Table R.1.3.4.2: 1 KCCQ-OSS change from baseline at week 52 (MMRM) by sex - RS (OC-AD - no imputation for deaths) - 1245.121

Subgroup / Visit / Description / Statistic	Placebo	Empa 10mg
Sex: Male		
Number of patients in analysis set	1411	1426
Number of analysed patients	1333	1361
Baseline mean (SE)	69.57 (0.57)	69.33 (0.59)
Week 52		
Values at visit		
Number of analysed patients	939	954
Mean (SE)	74.33 (0.68)	76.48 (0.65)
Adjusted* mean (SE)	73.55 (0.51)	75.71 (0.50)
95% confidence interval	(72.55,74.54)	(74.73,76.69)
Change from baseline		
Mean (SE)	3.88 (0.62)	6.05 (0.57)
Adjusted* mean (SE)	4.10 (0.51)	6.26 (0.50)
95% confidence interval	(3.11, 5.09)	(5.28, 7.24)
Comparison vs Placebo		
Adjusted* mean (SE)		2.16 (0.71)
95% confidence interval		(0.77, 3.56)
p-value		0.0024

* Model includes Age, baseline eGFR (CKD-EPI) as linear covariate(s) and region, baseline diabetes status, baseline LVEF, week reachable, Visit by Treatment by sex interaction, baseline KCCQ - overall summary score by Visit interaction as fixed effect(s).
The Visit by Treatment by sex p-value at Week 52 is 0.0627.
The following covariance structure has been used to fit the mixed model: Unstructured
Note: All covariate effects are set equal to their mean values within subgroup for the calculation of adjusted means.

For patients who died, only observed values are considered (no imputation after date of death).
Data taken from study 1245.121 only.
The MMRM includes all outcome values (change from baseline) at the planned Visits week 12, week 32 and week 52

Table R.1.3.4.2: 1 KCCQ-OSS change from baseline at week 52 (MMRM) by sex - RS (OC-AD - no imputation for deaths) - 1245.121

Subgroup / Visit / Description / Statistic	Placebo	Empa 10mg
Sex: Female		
Number of patients in analysis set	456	437
Number of analysed patients	420	415
Baseline mean (SE)	61.29 (1.06)	61.86 (1.13)
Week 52		
Values at visit		
Number of analysed patients	279	285
Mean (SE)	70.88 (1.23)	70.56 (1.28)
Adjusted* mean (SE)	70.17 (0.92)	69.58 (0.91)
95% confidence interval	(68.36,71.98)	(67.78,71.37)
Change from baseline		
Mean (SE)	9.76 (1.14)	7.93 (1.10)
Adjusted* mean (SE)	8.60 (0.92)	8.01 (0.91)
95% confidence interval	(6.79,10.41)	(6.21, 9.80)
Comparison vs Placebo		
Adjusted* mean (SE)		-0.59 (1.30)
95% confidence interval		(-3.14, 1.95)
p-value		0.6472

* Model includes Age, baseline eGFR (CKD-EPI) as linear covariate(s) and region, baseline diabetes status, baseline LVEF, week reachable, Visit by Treatment by sex interaction, baseline KCCQ - overall summary score by Visit interaction as fixed effect(s).
The Visit by Treatment by sex p-value at Week 52 is 0.0627.
The following covariance structure has been used to fit the mixed model: Unstructured
Note: All covariate effects are set equal to their mean values within subgroup for the calculation of adjusted means.

For patients who died, only observed values are considered (no imputation after date of death).
Data taken from study 1245.121 only.
The MMRM includes all outcome values (change from baseline) at the planned Visits week 12, week 32 and week 52

R.1.3.4.3

R.1.3.4.3 Subgroup analysis by age

Table R.1.3.4.3: 1

Table R.1.3.4.3: 1 KCCQ-OSS change from baseline at week 52 (MMRM) by age (2 cat.) - RS (OC-AD - no imputation for deaths) - 1245.121

Subgroup / Visit / Description / Statistic	Placebo	Empa 10mg
Age [years] (2 cat.): < 65		
Number of patients in analysis set	740	675
Number of analysed patients	697	645
Baseline mean (SE)	66.03 (0.84)	65.72 (0.91)
Week 52		
Values at visit		
Number of analysed patients	494	454
Mean (SE)	73.29 (0.97)	75.16 (1.03)
Adjusted* mean (SE)	72.28 (0.70)	74.38 (0.73)
95% confidence interval	(70.90,73.66)	(72.95,75.81)
Change from baseline		
Mean (SE)	6.89 (0.89)	9.05 (0.82)
Adjusted* mean (SE)	6.40 (0.70)	8.50 (0.73)
95% confidence interval	(5.02, 7.77)	(7.07, 9.92)
Comparison vs Placebo		
Adjusted* mean (SE)		2.10 (1.01)
95% confidence interval		(0.12, 4.07)
p-value		0.0373

* Model includes baseline eGFR (CKD-EPI) as linear covariate(s) and region, baseline diabetes status, sex, baseline LVEF, week reachable, Visit by Treatment by age [years] (2 cat.) interaction, baseline KCCQ - overall summary score by Visit interaction as fixed effect(s).
The Visit by Treatment by age [years] (2 cat.) p-value at Week 52 is 0.4729.
The following covariance structure has been used to fit the mixed model: Unstructured
Note: All covariate effects are set equal to their mean values within subgroup for the calculation of adjusted means.

For patients who died, only observed values are considered (no imputation after date of death).
Data taken from study 1245.121 only.
The MMRM includes all outcome values (change from baseline) at the planned Visits week 12, week 32 and week 52

Table R.1.3.4.3: 1 KCCQ-OSS change from baseline at week 52 (MMRM) by age (2 cat.) - RS (OC-AD - no imputation for deaths) - 1245.121

Subgroup / Visit / Description / Statistic	Placebo	Empa 10mg
Age [years] (2 cat.): >= 65		
Number of patients in analysis set	1127	1188
Number of analysed patients	1056	1131
Baseline mean (SE)	68.61 (0.64)	68.65 (0.64)
Week 52		
Values at visit		
Number of analysed patients	724	785
Mean (SE)	73.71 (0.76)	75.09 (0.71)
Adjusted* mean (SE)	73.02 (0.58)	74.20 (0.55)
95% confidence interval	(71.89,74.15)	(73.12,75.29)
Change from baseline		
Mean (SE)	4.10 (0.70)	5.00 (0.64)
Adjusted* mean (SE)	4.39 (0.58)	5.57 (0.55)
95% confidence interval	(3.26, 5.52)	(4.48, 6.66)
Comparison vs Placebo		
Adjusted* mean (SE)		1.18 (0.80)
95% confidence interval		(-0.38, 2.74)
p-value		0.1396

* Model includes baseline eGFR (CKD-EPI) as linear covariate(s) and region, baseline diabetes status, sex, baseline LVEF, week reachable, Visit by Treatment by age [years] (2 cat.) interaction, baseline KCCQ - overall summary score by Visit interaction as fixed effect(s).
The Visit by Treatment by age [years] (2 cat.) p-value at Week 52 is 0.4729.
The following covariance structure has been used to fit the mixed model: Unstructured
Note: All covariate effects are set equal to their mean values within subgroup for the calculation of adjusted means.

For patients who died, only observed values are considered (no imputation after date of death).
Data taken from study 1245.121 only.
The MMRM includes all outcome values (change from baseline) at the planned Visits week 12, week 32 and week 52

R.1.3.4.4 Subgroup analysis by region (North America, Latin America, Europe, Asia, Other)

Table R.1.3.4.4: 1 KCCQ-OSS change from baseline at week 52 (MMRM) by region - RS (OC-AD - no imputation for deaths) - 1245.121

Subgroup / Visit / Description / Statistic	Placebo	Empa 10mg
Region (5 cat.): North America		
Number of patients in analysis set	213	212
Number of analysed patients	195	206
Baseline mean (SE)	67.39 (1.64)	68.70 (1.62)
Week 52		
Values at visit		
Number of analysed patients	129	151
Mean (SE)	72.67 (1.97)	74.83 (1.69)
Adjusted* mean (SE)	72.03 (1.35)	73.14 (1.27)
95% confidence interval	(69.37,74.68)	(70.66,75.62)
Change from baseline		
Mean (SE)	5.26 (1.42)	4.75 (1.38)
Adjusted* mean (SE)	3.96 (1.35)	5.08 (1.27)
95% confidence interval	(1.31, 6.61)	(2.59, 7.56)
Comparison vs Placebo		
Adjusted* mean (SE)		1.12 (1.85)
95% confidence interval		(-2.52, 4.75)
p-value		0.5469

* Model includes Age, baseline eGFR (CKD-EPI) as linear covariate(s) and baseline diabetes status, sex, baseline LVEF, week reachable, Visit by Treatment by region (5 cat.) interaction, baseline KCCQ - overall summary score by Visit interaction as fixed effect(s).
The Visit by Treatment by region (5 cat.) p-value at Week 52 is 0.9747.
The following covariance structure has been used to fit the mixed model: Unstructured
Note: All covariate effects are set equal to their mean values within subgroup for the calculation of adjusted means.

For patients who died, only observed values are considered (no imputation after date of death).
Data taken from study 1245.121 only.
The MMRM includes all outcome values (change from baseline) at the planned Visits week 12, week 32 and week 52

Table R.1.3.4.4: 1 KCCQ-OSS change from baseline at week 52 (MMRM) by region - RS (OC-AD - no imputation for deaths) - 1245.121

Subgroup / Visit / Description / Statistic	Placebo	Empa 10mg
Region (5 cat.): Latin America		
Number of patients in analysis set	645	641
Number of analysed patients	599	602
Baseline mean (SE)	63.62 (0.93)	63.44 (0.96)
Week 52		
Values at visit		
Number of analysed patients	391	374
Mean (SE)	73.48 (1.10)	75.05 (1.11)
Adjusted* mean (SE)	73.20 (0.78)	74.75 (0.79)
95% confidence interval	(71.68,74.73)	(73.20,76.29)
Change from baseline		
Mean (SE)	10.37 (1.14)	11.58 (1.04)
Adjusted* mean (SE)	9.68 (0.78)	11.22 (0.79)
95% confidence interval	(8.15,11.20)	(9.67,12.76)
Comparison vs Placebo		
Adjusted* mean (SE)		1.54 (1.10)
95% confidence interval		(-0.62, 3.71)
p-value		0.1625

* Model includes Age, baseline eGFR (CKD-EPI) as linear covariate(s) and baseline diabetes status, sex, baseline LVEF, week reachable, Visit by Treatment by region (5 cat.) interaction, baseline KCCQ - overall summary score by Visit interaction as fixed effect(s).
The Visit by Treatment by region (5 cat.) p-value at Week 52 is 0.9747.
The following covariance structure has been used to fit the mixed model: Unstructured
Note: All covariate effects are set equal to their mean values within subgroup for the calculation of adjusted means.

For patients who died, only observed values are considered (no imputation after date of death).
Data taken from study 1245.121 only.
The MMRM includes all outcome values (change from baseline) at the planned Visits week 12, week 32 and week 52

Table R.1.3.4.4: 1 KCCQ-OSS change from baseline at week 52 (MMRM) by region - RS (OC-AD - no imputation for deaths) - 1245.121

Subgroup / Visit / Description / Statistic	Placebo	Empa 10mg
Region (5 cat.): Europe		
Number of patients in analysis set	677	676
Number of analysed patients	644	649
Baseline mean (SE)	66.82 (0.81)	67.59 (0.83)
Week 52		
Values at visit		
Number of analysed patients	468	469
Mean (SE)	70.23 (0.96)	71.65 (0.96)
Adjusted* mean (SE)	69.42 (0.72)	70.62 (0.72)
95% confidence interval	(68.01,70.82)	(69.22,72.03)
Change from baseline		
Mean (SE)	2.14 (0.79)	3.19 (0.76)
Adjusted* mean (SE)	2.21 (0.72)	3.42 (0.72)
95% confidence interval	(0.81, 3.62)	(2.01, 4.82)
Comparison vs Placebo		
Adjusted* mean (SE)		1.20 (1.01)
95% confidence interval		(-0.78, 3.19)
p-value		0.2346

* Model includes Age, baseline eGFR (CKD-EPI) as linear covariate(s) and baseline diabetes status, sex, baseline LVEF, week reachable, Visit by Treatment by region (5 cat.) interaction, baseline KCCQ - overall summary score by Visit interaction as fixed effect(s).
The Visit by Treatment by region (5 cat.) p-value at Week 52 is 0.9747.
The following covariance structure has been used to fit the mixed model: Unstructured
Note: All covariate effects are set equal to their mean values within subgroup for the calculation of adjusted means.

For patients who died, only observed values are considered (no imputation after date of death).
Data taken from study 1245.121 only.
The MMRM includes all outcome values (change from baseline) at the planned Visits week 12, week 32 and week 52

Table R.1.3.4.4: 1 KCCQ-OSS change from baseline at week 52 (MMRM) by region - RS (OC-AD - no imputation for deaths) - 1245.121

Subgroup / Visit / Description / Statistic	Placebo	Empa 10mg
Region (5 cat.): Asia		
Number of patients in analysis set	245	248
Number of analysed patients	237	243
Baseline mean (SE)	78.09 (1.01)	75.11 (1.21)
Week 52		
Values at visit		
Number of analysed patients	180	189
Mean (SE)	79.29 (1.27)	80.60 (1.36)
Adjusted* mean (SE)	78.00 (1.17)	80.48 (1.14)
95% confidence interval	(75.72,80.29)	(78.25,82.71)
Change from baseline		
Mean (SE)	0.42 (1.17)	4.17 (1.12)
Adjusted* mean (SE)	1.42 (1.17)	3.90 (1.14)
95% confidence interval	(-0.87, 3.71)	(1.66, 6.13)
Comparison vs Placebo		
Adjusted* mean (SE)		2.47 (1.63)
95% confidence interval		(-0.72, 5.67)
p-value		0.1288

* Model includes Age, baseline eGFR (CKD-EPI) as linear covariate(s) and baseline diabetes status, sex, baseline LVEF, week reachable, Visit by Treatment by region (5 cat.) interaction, baseline KCCQ - overall summary score by Visit interaction as fixed effect(s).
The Visit by Treatment by region (5 cat.) p-value at Week 52 is 0.9747.
The following covariance structure has been used to fit the mixed model: Unstructured
Note: All covariate effects are set equal to their mean values within subgroup for the calculation of adjusted means.

For patients who died, only observed values are considered (no imputation after date of death).
Data taken from study 1245.121 only.
The MMRM includes all outcome values (change from baseline) at the planned Visits week 12, week 32 and week 52

Table R.1.3.4.4: 1 KCCQ-OSS change from baseline at week 52 (MMRM) by region - RS (OC-AD - no imputation for deaths) - 1245.121

Subgroup / Visit / Description / Statistic	Placebo	Empa 10mg
Region (5 cat.): Other		
Number of patients in analysis set	87	86
Number of analysed patients	78	76
Baseline mean (SE)	72.98 (2.18)	73.26 (2.04)
Week 52		
Values at visit		
Number of analysed patients	50	56
Mean (SE)	86.52 (1.94)	86.94 (1.40)
Adjusted* mean (SE)	84.39 (2.17)	85.93 (2.08)
95% confidence interval	(80.13,88.65)	(81.85,90.00)
Change from baseline		
Mean (SE)	11.17 (2.47)	12.53 (1.85)
Adjusted* mean (SE)	11.27 (2.17)	12.81 (2.08)
95% confidence interval	(7.02,15.53)	(8.73,16.88)
Comparison vs Placebo		
Adjusted* mean (SE)		1.54 (3.00)
95% confidence interval		(-4.35, 7.42)
p-value		0.6092

* Model includes Age, baseline eGFR (CKD-EPI) as linear covariate(s) and baseline diabetes status, sex, baseline LVEF, week reachable, Visit by Treatment by region (5 cat.) interaction, baseline KCCQ - overall summary score by Visit interaction as fixed effect(s).
The Visit by Treatment by region (5 cat.) p-value at Week 52 is 0.9747.
The following covariance structure has been used to fit the mixed model: Unstructured
Note: All covariate effects are set equal to their mean values within subgroup for the calculation of adjusted means.

For patients who died, only observed values are considered (no imputation after date of death).
Data taken from study 1245.121 only.
The MMRM includes all outcome values (change from baseline) at the planned Visits week 12, week 32 and week 52

R.1.3.4.5

R.1.3.4.5 Subgroup analysis by OECD (N/Y)

Table R.1.3.4.5: 1

Table R.1.3.4.5: 1 KCCQ-OSS change from baseline at week 52 (MMRM) by OECD member (N/Y) - RS (OC-AD - no imputation for deaths) - 1245.121

Subgroup / Visit / Description / Statistic	Placebo	Empa 10mg
OECD member: No		
Number of patients in analysis set	741	713
Number of analysed patients	686	664
Baseline mean (SE)	64.77 (0.85)	64.86 (0.90)
Week 52		
Values at visit		
Number of analysed patients	443	421
Mean (SE)	74.79 (0.99)	76.70 (0.98)
Adjusted* mean (SE)	74.40 (0.73)	76.15 (0.75)
95% confidence interval	(72.97,75.84)	(74.68,77.61)
Change from baseline		
Mean (SE)	10.14 (1.02)	11.60 (0.93)
Adjusted* mean (SE)	9.58 (0.73)	11.33 (0.75)
95% confidence interval	(8.15,11.02)	(9.87,12.80)
Comparison vs Placebo		
Adjusted* mean (SE)		1.75 (1.04)
95% confidence interval		(-0.30, 3.80)
p-value		0.0943

* Model includes Age, baseline eGFR (CKD-EPI) as linear covariate(s) and baseline diabetes status, sex, baseline LVEF, week reachable, Visit by Treatment by OECD Member (N) interaction, baseline KCCQ - overall summary score by Visit interaction as fixed effect(s).
The Visit by Treatment by OECD Member (N) p-value at Week 52 is 0.8695.
The following covariance structure has been used to fit the mixed model: Unstructured
Note: All covariate effects are set equal to their mean values within subgroup for the calculation of adjusted means.

For patients who died, only observed values are considered (no imputation after date of death).
Data taken from study 1245.121 only.
OECD member (yes/no) countries included:
Yes: United States, Canada, Mexico, Poland, Netherlands, Hungary, Germany, Czech Republic, Italy, France, Spain, United Kingdom, Belgium, Japan, Australia, 'Korea; Republic Of South Korea';
No: Brazil, Argentina, China, India.
The MMRM includes all outcome values (change from baseline) at the planned Visits week 12, week 32 and week 52

Table R.1.3.4.5: 1 KCCQ-OSS change from baseline at week 52 (MMRM) by OECD member (N/Y) - RS (OC-AD - no imputation for deaths) - 1245.121

Subgroup / Visit / Description / Statistic	Placebo	Empa 10mg
OECD member: Yes		
Number of patients in analysis set	1126	1150
Number of analysed patients	1067	1112
Baseline mean (SE)	69.40 (0.63)	69.21 (0.64)
Week 52		
Values at visit		
Number of analysed patients	775	818
Mean (SE)	72.83 (0.75)	74.31 (0.73)
Adjusted* mean (SE)	71.76 (0.56)	73.29 (0.55)
95% confidence interval	(70.66,72.86)	(72.22,74.36)
Change from baseline		
Mean (SE)	2.42 (0.61)	3.85 (0.58)
Adjusted* mean (SE)	2.46 (0.56)	3.99 (0.55)
95% confidence interval	(1.36, 3.56)	(2.92, 5.06)
Comparison vs Placebo		
Adjusted* mean (SE)		1.53 (0.78)
95% confidence interval		(0.00, 3.07)
p-value		0.0499

* Model includes Age, baseline eGFR (CKD-EPI) as linear covariate(s) and baseline diabetes status, sex, baseline LVEF, week reachable, Visit by Treatment by OECD Member (N) interaction, baseline KCCQ - overall summary score by Visit interaction as fixed effect(s).
The Visit by Treatment by OECD Member (N) p-value at Week 52 is 0.8695.
The following covariance structure has been used to fit the mixed model: Unstructured
Note: All covariate effects are set equal to their mean values within subgroup for the calculation of adjusted means.

For patients who died, only observed values are considered (no imputation after date of death).
Data taken from study 1245.121 only.
OECD member (yes/no) countries included:
Yes: United States, Canada, Mexico, Poland, Netherlands, Hungary, Germany, Czech Republic, Italy, France, Spain, United Kingdom, Belgium, Japan, Australia, 'Korea; Republic Of South Korea';
No: Brazil, Argentina, China, India.
The MMRM includes all outcome values (change from baseline) at the planned Visits week 12, week 32 and week 52

R.1.3.4.6 Subgroup analysis by NYHA at baseline (II, III/IV - 2 cat.)

Table R.1.3.4.6: 1 KCCQ-OSS change from baseline at week 52 (MMRM) by NYHA (2 cat.) - RS (OC-AD - no imputation for deaths) - 1245.121

Subgroup / Visit / Description / Statistic	Placebo	Empa 10mg
Baseline NYHA (2 cat.): II		
Number of patients in analysis set	1401	1399
Number of analysed patients	1340	1332
Baseline mean (SE)	71.43 (0.53)	72.67 (0.55)
Week 52		
Values at visit		
Number of analysed patients	946	951
Mean (SE)	75.64 (0.65)	78.61 (0.62)
Adjusted* mean (SE)	75.55 (0.50)	77.81 (0.50)
95% confidence interval	(74.57,76.54)	(76.82,78.79)
Change from baseline		
Mean (SE)	3.88 (0.59)	5.57 (0.56)
Adjusted* mean (SE)	3.51 (0.50)	5.76 (0.50)
95% confidence interval	(2.52, 4.49)	(4.77, 6.74)
Comparison vs Placebo		
Adjusted* mean (SE)		2.25 (0.71)
95% confidence interval		(0.86, 3.65)
p-value		0.0015

* Model includes Age, baseline eGFR (CKD-EPI) as linear covariate(s) and region, baseline diabetes status, sex, baseline LVEF, week reachable, Visit by Treatment by baseline NYHA (2 cat.) interaction, baseline KCCQ - overall summary score by Visit interaction as fixed effect(s).
The Visit by Treatment by baseline NYHA (2 cat.) p-value at Week 52 is 0.0344.
The following covariance structure has been used to fit the mixed model: Unstructured
Note: All covariate effects are set equal to their mean values within subgroup for the calculation of adjusted means.

For patients who died, only observed values are considered (no imputation after date of death).
Data taken from study 1245.121 only.
The MMRM includes all outcome values (change from baseline) at the planned Visits week 12, week 32 and week 52

Table R.1.3.4.6: 1 KCCQ-OSS change from baseline at week 52 (MMRM) by NYHA (2 cat.) - RS (OC-AD - no imputation for deaths) - 1245.121

Subgroup / Visit / Description / Statistic	Placebo	Empa 10mg
Baseline NYHA (2 cat.): III/IV		
Number of patients in analysis set	466	464
Number of analysed patients	413	444
Baseline mean (SE)	55.11 (1.11)	52.33 (1.04)
Week 52		
Values at visit		
Number of analysed patients	272	288
Mean (SE)	66.23 (1.35)	63.60 (1.25)
Adjusted* mean (SE)	64.04 (0.93)	63.17 (0.90)
95% confidence interval	(62.21,65.87)	(61.39,64.94)
Change from baseline		
Mean (SE)	9.91 (1.29)	9.50 (1.15)
Adjusted* mean (SE)	10.37 (0.93)	9.50 (0.90)
95% confidence interval	(8.54,12.20)	(7.72,11.27)
Comparison vs Placebo		
Adjusted* mean (SE)		-0.88 (1.30)
95% confidence interval		(-3.42, 1.67)
p-value		0.4983

* Model includes Age, baseline eGFR (CKD-EPI) as linear covariate(s) and region, baseline diabetes status, sex, baseline LVEF, week reachable, Visit by Treatment by baseline NYHA (2 cat.) interaction, baseline KCCQ - overall summary score by Visit interaction as fixed effect(s).
The Visit by Treatment by baseline NYHA (2 cat.) p-value at Week 52 is 0.0344.
The following covariance structure has been used to fit the mixed model: Unstructured
Note: All covariate effects are set equal to their mean values within subgroup for the calculation of adjusted means.

For patients who died, only observed values are considered (no imputation after date of death).
Data taken from study 1245.121 only.
The MMRM includes all outcome values (change from baseline) at the planned Visits week 12, week 32 and week 52

R.1.3.4.7

R.1.3.4.7 Subgroup analysis by diabetes at baseline

Table R.1.3.4.7: 1 KCCQ-OSS change from baseline at week 52 (MMRM) by diabetes at baseline - RS (OC-AD - no imputation for deaths) - 1245.121

Subgroup / Visit / Description / Statistic	Placebo	Empa 10mg
Diabetes at baseline (2 cat.):		
Diabetic		
Number of patients in analysis set	929	927
Number of analysed patients	868	882
Baseline mean (SE)	66.69 (0.75)	66.58 (0.77)
Week 52		
Values at visit		
Number of analysed patients	606	614
Mean (SE)	73.41 (0.85)	74.43 (0.86)
Adjusted* mean (SE)	72.05 (0.63)	73.40 (0.62)
95% confidence interval	(70.82,73.29)	(72.18,74.63)
Change from baseline		
Mean (SE)	5.34 (0.77)	6.29 (0.73)
Adjusted* mean (SE)	5.41 (0.63)	6.76 (0.62)
95% confidence interval	(4.18, 6.65)	(5.54, 7.99)
Comparison vs Placebo		
Adjusted* mean (SE)		1.35 (0.89)
95% confidence interval		(-0.39, 3.09)
p-value		0.1278

* Model includes Age, baseline eGFR (CKD-EPI) as linear covariate(s) and region, sex, baseline LVEF, week reachable,
Visit by Treatment by diabetes at baseline (2 cat.) interaction,
baseline KCCQ - overall summary score by Visit interaction as fixed effect(s).
The Visit by Treatment by diabetes at baseline (2 cat.) p-value at Week 52 is 0.7831.
The following covariance structure has been used to fit the mixed model: Unstructured
Note: All covariate effects are set equal to their mean values within subgroup for the calculation of adjusted means.

For patients who died, only observed values are considered (no imputation after date of death).
Data taken from study 1245.121 only.
The MMRM includes all outcome values (change from baseline) at the planned Visits week 12, week 32 and week 52

Table R.1.3.4.7: 1

Table R.1.3.4.7: 1 KCCQ-OSS change from baseline at week 52 (MMRM) by diabetes at baseline - RS (OC-AD - no imputation for deaths) - 1245.121

Subgroup / Visit / Description / Statistic	Placebo	Empa 10mg
Diabetes at baseline (2 cat.):		
Non-Diabetic		
Number of patients in analysis set	938	936
Number of analysed patients	885	894
Baseline mean (SE)	68.46 (0.70)	68.57 (0.72)
Week 52		
Values at visit		
Number of analysed patients	612	625
Mean (SE)	73.67 (0.84)	75.80 (0.80)
Adjusted* mean (SE)	73.42 (0.62)	75.11 (0.62)
95% confidence interval	(72.19,74.64)	(73.90,76.33)
Change from baseline		
Mean (SE)	5.12 (0.78)	6.67 (0.70)
Adjusted* mean (SE)	4.90 (0.62)	6.60 (0.62)
95% confidence interval	(3.68, 6.13)	(5.38, 7.81)
Comparison vs Placebo		
Adjusted* mean (SE)		1.69 (0.88)
95% confidence interval		(-0.03, 3.42)
p-value		0.0543

* Model includes Age, baseline eGFR (CKD-EPI) as linear covariate(s) and region, sex, baseline LVEF, week reachable,
Visit by Treatment by diabetes at baseline (2 cat.) interaction,
baseline KCCQ - overall summary score by Visit interaction as fixed effect(s).
The Visit by Treatment by diabetes at baseline (2 cat.) p-value at Week 52 is 0.7831.
The following covariance structure has been used to fit the mixed model: Unstructured
Note: All covariate effects are set equal to their mean values within subgroup for the calculation of adjusted means.

For patients who died, only observed values are considered (no imputation after date of death).
Data taken from study 1245.121 only.
The MMRM includes all outcome values (change from baseline) at the planned Visits week 12, week 32 and week 52

R.1.3.4.8 Subgroup analysis by BMI at baseline (<30, >=30)

Table R.1.3.4.8: 1 KCCQ-OSS change from baseline at week 52 (MMRM) by baseline BMI [kg/m2] - RS (OC-AD - no imputation for deaths) - 1245.121

Subgroup / Visit / Description / Statistic	Placebo	Empa 10mg
Baseline BMI [kg/m²] (2 cat.): <30		
Number of patients in analysis set	1300	1263
Number of analysed patients	1229	1201
Baseline mean (SE)	68.95 (0.60)	69.43 (0.63)
Week 52		
Values at visit		
Number of analysed patients	865	826
Mean (SE)	74.65 (0.69)	77.13 (0.69)
Adjusted* mean (SE)	74.01 (0.53)	75.73 (0.54)
95% confidence interval	(72.98,75.05)	(74.68,76.79)
Change from baseline		
Mean (SE)	4.90 (0.63)	6.26 (0.61)
Adjusted* mean (SE)	4.82 (0.53)	6.54 (0.54)
95% confidence interval	(3.79, 5.86)	(5.49, 7.60)
Comparison vs Placebo		
Adjusted* mean (SE)		1.72 (0.75)
95% confidence interval		(0.25, 3.20)
p-value		0.0221

* Model includes Age, baseline eGFR (CKD-EPI) as linear covariate(s) and region, baseline diabetes status, sex, baseline LVEF, week reachable, Visit by Treatment by baseline BMI [kg/m²] (2 cat.) interaction, baseline KCCQ - overall summary score by Visit interaction as fixed effect(s).
The Visit by Treatment by baseline BMI [kg/m²] (2 cat.) p-value at Week 52 is 0.7197.
The following covariance structure has been used to fit the mixed model: Unstructured
Note: All covariate effects are set equal to their mean values within subgroup for the calculation of adjusted means.

For patients who died, only observed values are considered (no imputation after date of death).
Data taken from study 1245.121 only.
The MMRM includes all outcome values (change from baseline) at the planned Visits week 12, week 32 and week 52

Table R.1.3.4.8: 1 KCCQ-OSS change from baseline at week 52 (MMRM) by baseline BMI [kg/m2] - RS (OC-AD - no imputation for deaths) - 1245.121

Subgroup / Visit / Description / Statistic	Placebo	Empa 10mg
Baseline BMI [kg/m²] (2 cat.): >=30		
Number of patients in analysis set	567	600
Number of analysed patients	524	575
Baseline mean (SE)	64.38 (0.96)	63.72 (0.94)
Week 52		
Values at visit		
Number of analysed patients	353	413
Mean (SE)	70.82 (1.18)	71.09 (1.06)
Adjusted* mean (SE)	69.88 (0.83)	71.12 (0.77)
95% confidence interval	(68.27,71.50)	(69.61,72.63)
Change from baseline		
Mean (SE)	6.05 (1.08)	6.94 (0.91)
Adjusted* mean (SE)	5.85 (0.83)	7.09 (0.77)
95% confidence interval	(4.23, 7.47)	(5.58, 8.60)
Comparison vs Placebo		
Adjusted* mean (SE)		1.24 (1.12)
95% confidence interval		(-0.96, 3.44)
p-value		0.2693

* Model includes Age, baseline eGFR (CKD-EPI) as linear covariate(s) and region, baseline diabetes status, sex, baseline LVEF, week reachable, Visit by Treatment by baseline BMI [kg/m²] (2 cat.) interaction, baseline KCCQ - overall summary score by Visit interaction as fixed effect(s).
The Visit by Treatment by baseline BMI [kg/m²] (2 cat.) p-value at Week 52 is 0.7197.
The following covariance structure has been used to fit the mixed model: Unstructured
Note: All covariate effects are set equal to their mean values within subgroup for the calculation of adjusted means.

For patients who died, only observed values are considered (no imputation after date of death).
Data taken from study 1245.121 only.
The MMRM includes all outcome values (change from baseline) at the planned Visits week 12, week 32 and week 52

R.1.3.4.9 Subgroup analysis by eGFR at baseline (<60, >=60)

Table R.1.3.4.9: 1 KCCQ-OSS change from baseline at week 52 (MMRM) by baseline eGFR (2 cat.) - RS (OC-AD - no imputation for deaths) - 1245.121

Subgroup / Visit / Description / Statistic	Placebo	Empa 10mg
Baseline eGFR (CKD-EPI) [mL/min/1.73m²] (2 cat.): >=60		
Number of patients in analysis set	960	969
Number of analysed patients	901	921
Baseline mean (SE)	67.83 (0.71)	68.15 (0.74)
Week 52		
Values at visit		
Number of analysed patients	647	650
Mean (SE)	73.65 (0.81)	76.81 (0.82)
Adjusted* mean (SE)	73.02 (0.61)	75.85 (0.61)
95% confidence interval	(71.83,74.22)	(74.66,77.04)
Change from baseline		
Mean (SE)	5.31 (0.72)	7.77 (0.70)
Adjusted* mean (SE)	5.03 (0.61)	7.86 (0.61)
95% confidence interval	(3.83, 6.23)	(6.67, 9.05)
Comparison vs Placebo		
Adjusted* mean (SE)		2.83 (0.86)
95% confidence interval		(1.14, 4.51)
p-value		0.0010

* Model includes Age as linear covariate(s) and region, baseline diabetes status, sex, baseline LVEF, week reachable, Visit by Treatment by baseline eGFR (CKD-EPI) [mL/min/1.73m²] (2 cat.) interaction, baseline KCCQ - overall summary score by Visit interaction as fixed effect(s).
The Visit by Treatment by baseline eGFR (CKD-EPI) [mL/min/1.73m²] (2 cat.) p-value at Week 52 is 0.0261.
The following covariance structure has been used to fit the mixed model: Unstructured
2 patients were excluded as the subgroup variable was missing.
Note: All covariate effects are set equal to their mean values within subgroup for the calculation of adjusted means.

For patients who died, only observed values are considered (no imputation after date of death).
Data taken from study 1245.121 only.
The MMRM includes all outcome values (change from baseline) at the planned Visits week 12, week 32 and week 52

Table R.1.3.4.9: 1

Table R.1.3.4.9: 1 KCCQ-OSS change from baseline at week 52 (MMRM) by baseline eGFR (2 cat.) - RS (OC-AD - no imputation for deaths) - 1245.121

Subgroup / Visit / Description / Statistic	Placebo	Empa 10mg
Baseline eGFR (CKD-EPI) [mL/min/1.73m²] (2 cat.): <60		
Number of patients in analysis set	906	893
Number of analysed patients	852	855
Baseline mean (SE)	67.33 (0.74)	66.98 (0.75)
Week 52		
Values at visit		
Number of analysed patients	571	589
Mean (SE)	73.42 (0.88)	73.26 (0.83)
Adjusted* mean (SE)	72.50 (0.65)	72.54 (0.64)
95% confidence interval	(71.23,73.76)	(71.29,73.79)
Change from baseline		
Mean (SE)	5.14 (0.84)	5.07 (0.73)
Adjusted* mean (SE)	5.35 (0.65)	5.39 (0.64)
95% confidence interval	(4.08, 6.61)	(4.14, 6.64)
Comparison vs Placebo		
Adjusted* mean (SE)		0.04 (0.91)
95% confidence interval		(-1.73, 1.82)
p-value		0.9605

* Model includes Age as linear covariate(s) and region, baseline diabetes status, sex, baseline LVEF, week reachable, Visit by Treatment by baseline eGFR (CKD-EPI) [mL/min/1.73m²] (2 cat.) interaction, baseline KCCQ - overall summary score by Visit interaction as fixed effect(s).
The Visit by Treatment by baseline eGFR (CKD-EPI) [mL/min/1.73m²] (2 cat.) p-value at Week 52 is 0.0261.
The following covariance structure has been used to fit the mixed model: Unstructured
2 patients were excluded as the subgroup variable was missing.
Note: All covariate effects are set equal to their mean values within subgroup for the calculation of adjusted means.

For patients who died, only observed values are considered (no imputation after date of death).
Data taken from study 1245.121 only.
The MMRM includes all outcome values (change from baseline) at the planned Visits week 12, week 32 and week 52

R.1.3.4.10

Table R.1.3.4.10: 1 KCCQ-OSS change from baseline at week 52 (MMRM) by history of HHF - RS (OC-AD - no imputation for deaths) - 1245.121

Subgroup / Visit / Description / Statistic	Placebo	Empa 10mg
History of HHF (in the last 12 months): No		
Number of patients in analysis set	1293	1286
Number of analysed patients	1220	1231
Baseline mean (SE)	68.20 (0.62)	68.03 (0.63)
Week 52		
Values at visit		
Number of analysed patients	869	873
Mean (SE)	72.99 (0.72)	75.38 (0.69)
Adjusted* mean (SE)	72.68 (0.53)	74.76 (0.53)
95% confidence interval	(71.64,73.71)	(73.73,75.79)
Change from baseline		
Mean (SE)	4.73 (0.65)	6.64 (0.60)
Adjusted* mean (SE)	4.56 (0.53)	6.64 (0.53)
95% confidence interval	(3.53, 5.59)	(5.61, 7.67)
Comparison vs Placebo		
Adjusted* mean (SE)		2.08 (0.74)
95% confidence interval		(0.63, 3.54)
p-value		0.0051

* Model includes Age, baseline eGFR (CKD-EPI) as linear covariate(s) and region, baseline diabetes status, sex, baseline LVEF, week reachable, Visit by Treatment by history of HHF (in the last 12 months) interaction, baseline KCCQ - overall summary score by Visit interaction as fixed effect(s).
The Visit by Treatment by history of HHF (in the last 12 months) p-value at Week 52 is 0.1476.
The following covariance structure has been used to fit the mixed model: Unstructured
Note: All covariate effects are set equal to their mean values within subgroup for the calculation of adjusted means.

For patients who died, only observed values are considered (no imputation after date of death).
Data taken from study 1245.121 only.
The MMRM includes all outcome values (change from baseline) at the planned Visits week 12, week 32 and week 52

Table R.1.3.4.10: 1 KCCQ-OSS change from baseline at week 52 (MMRM) by history of HHF - RS (OC-AD - no imputation for deaths) - 1245.121

Subgroup / Visit / Description / Statistic	Placebo	Empa 10mg
History of HHF (in the last 12 months): Yes		
Number of patients in analysis set	574	577
Number of analysed patients	533	545
Baseline mean (SE)	66.18 (0.92)	66.58 (0.98)
Week 52		
Values at visit		
Number of analysed patients	349	366
Mean (SE)	74.90 (1.07)	74.51 (1.11)
Adjusted* mean (SE)	73.00 (0.82)	73.10 (0.81)
95% confidence interval	(71.38,74.62)	(71.52,74.68)
Change from baseline		
Mean (SE)	6.48 (1.03)	6.12 (0.93)
Adjusted* mean (SE)	6.62 (0.82)	6.72 (0.81)
95% confidence interval	(5.00, 8.24)	(5.14, 8.30)
Comparison vs Placebo		
Adjusted* mean (SE)		0.10 (1.15)
95% confidence interval		(-2.15, 2.35)
p-value		0.9310

* Model includes Age, baseline eGFR (CKD-EPI) as linear covariate(s) and region, baseline diabetes status, sex, baseline LVEF, week reachable, Visit by Treatment by history of HHF (in the last 12 months) interaction, baseline KCCQ - overall summary score by Visit interaction as fixed effect(s).
The Visit by Treatment by history of HHF (in the last 12 months) p-value at Week 52 is 0.1476.
The following covariance structure has been used to fit the mixed model: Unstructured
Note: All covariate effects are set equal to their mean values within subgroup for the calculation of adjusted means.

For patients who died, only observed values are considered (no imputation after date of death).
Data taken from study 1245.121 only.
The MMRM includes all outcome values (change from baseline) at the planned Visits week 12, week 32 and week 52

R.1.3.4.11

R.1.3.4.11 Subgroup analysis by cause of heart failure

Table R.1.3.4.11: 1 KCCQ-OSS change from baseline at week 52 (MMRM) by cause of heart failure - RS (OC-AD - no imputation for deaths) - 1245.121

Subgroup / Visit / Description / Statistic	Placebo	Empa 10mg
Cause of heart failure: Ischemic		
Number of patients in analysis set	946	983
Number of analysed patients	896	936
Baseline mean (SE)	68.07 (0.71)	67.52 (0.73)
Week 52		
Values at visit		
Number of analysed patients	634	667
Mean (SE)	73.49 (0.83)	74.45 (0.81)
Adjusted* mean (SE)	72.66 (0.62)	73.67 (0.60)
95% confidence interval	(71.45,73.88)	(72.49,74.85)
Change from baseline		
Mean (SE)	4.28 (0.71)	5.50 (0.68)
Adjusted* mean (SE)	4.88 (0.62)	5.89 (0.60)
95% confidence interval	(3.66, 6.09)	(4.70, 7.07)
Comparison vs Placebo		
Adjusted* mean (SE)		1.01 (0.86)
95% confidence interval		(-0.68, 2.70)
p-value		0.2408

* Model includes Age, baseline eGFR (CKD-EPI) as linear covariate(s) and region, baseline diabetes status, sex, baseline LVEF, week reachable, Visit by Treatment by cause of heart failure interaction, baseline KCCQ - overall summary score by Visit interaction as fixed effect(s).
The Visit by Treatment by cause of heart failure p-value at Week 52 is 0.3860.
The following covariance structure has been used to fit the mixed model: Unstructured
Note: All covariate effects are set equal to their mean values within subgroup for the calculation of adjusted means.

For patients who died, only observed values are considered (no imputation after date of death).
Data taken from study 1245.121 only.
The MMRM includes all outcome values (change from baseline) at the planned Visits week 12, week 32 and week 52

Table R.1.3.4.11: 1 KCCQ-OSS change from baseline at week 52 (MMRM) by cause of heart failure - RS (OC-AD - no imputation for deaths) - 1245.121

Subgroup / Visit / Description / Statistic	Placebo	Empa 10mg
Cause of heart failure: Non-ischemic		
Number of patients in analysis set	921	880
Number of analysed patients	857	840
Baseline mean (SE)	67.09 (0.74)	67.66 (0.77)
Week 52		
Values at visit		
Number of analysed patients	584	572
Mean (SE)	73.59 (0.86)	75.90 (0.86)
Adjusted* mean (SE)	72.84 (0.64)	74.93 (0.65)
95% confidence interval	(71.58,74.10)	(73.66,76.20)
Change from baseline		
Mean (SE)	6.26 (0.84)	7.64 (0.76)
Adjusted* mean (SE)	5.47 (0.64)	7.56 (0.65)
95% confidence interval	(4.21, 6.73)	(6.29, 8.83)
Comparison vs Placebo		
Adjusted* mean (SE)		2.09 (0.91)
95% confidence interval		(0.31, 3.87)
p-value		0.0211

* Model includes Age, baseline eGFR (CKD-EPI) as linear covariate(s) and region, baseline diabetes status, sex, baseline LVEF, week reachable, Visit by Treatment by cause of heart failure interaction, baseline KCCQ - overall summary score by Visit interaction as fixed effect(s).
The Visit by Treatment by cause of heart failure p-value at Week 52 is 0.3860.
The following covariance structure has been used to fit the mixed model: Unstructured
Note: All covariate effects are set equal to their mean values within subgroup for the calculation of adjusted means.

For patients who died, only observed values are considered (no imputation after date of death).
Data taken from study 1245.121 only.
The MMRM includes all outcome values (change from baseline) at the planned Visits week 12, week 32 and week 52

R.1.3.4.12 Subgroup analysis by heart failure physiology (LVEF <= 30% and NTproBNP<median; LVEF <= 30% and NTproBNP>=median; LVEF > 30%)

Table R.1.3.4.12: 1 KCCQ-OSS change from baseline at week 52 (MMRM) by heart failure physiology - RS (OC-AD - no imputation for deaths) - 1245.121

Subgroup / Visit / Description / Statistic	Placebo	Empa 10mg
Heart failure physiology: LVEF <= 30% and NTproBNP < median		
Number of patients in analysis set	723	698
Number of analysed patients	694	672
Baseline mean (SE)	68.70 (0.81)	69.66 (0.81)
Week 52		
Values at visit		
Number of analysed patients	511	494
Mean (SE)	74.86 (0.90)	76.49 (0.90)
Adjusted* mean (SE)	74.60 (0.69)	76.12 (0.70)
95% confidence interval	(73.25,75.95)	(74.75,77.49)
Change from baseline		
Mean (SE)	6.27 (0.74)	6.90 (0.74)
Adjusted* mean (SE)	5.43 (0.69)	6.95 (0.70)
95% confidence interval	(4.08, 6.78)	(5.58, 8.32)
Comparison vs Placebo		
Adjusted* mean (SE)		1.52 (0.98)
95% confidence interval		(-0.40, 3.44)
p-value		0.1216

* Model includes Age, baseline eGFR (CKD-EPI) as linear covariate(s) and region, baseline diabetes status, sex, week reachable, Visit by Treatment by heart failure physiology interaction, baseline KCCQ - overall summary score by Visit interaction as fixed effect(s).
The Visit by Treatment by heart failure physiology p-value at Week 52 is 0.5260.
The following covariance structure has been used to fit the mixed model: Unstructured
16 patients were excluded as the subgroup variable was missing.
Note: All covariate effects are set equal to their mean values within subgroup for the calculation of adjusted means.
The p-value for the visit by treatment by subgroup interaction trend test at Week 52 is 0.6411

For patients who died, only observed values are considered (no imputation after date of death).
Data taken from study 1245.121 only.
NTproBNP median [pg/mL]: with a. fibrillation/flutter at baseline: 2265; without a. fibrillation/flutter at baseline: 1671.
The MMRM includes all outcome values (change from baseline) at the planned Visits week 12, week 32 and week 52

Table R.1.3.4.12: 1 KCCQ-OSS change from baseline at week 52 (MMRM) by heart failure physiology - RS (OC-AD - no imputation for deaths) - 1245.121

Subgroup / Visit / Description / Statistic	Placebo	Empa 10mg
Heart failure physiology: LVEF <= 30% and NTproBNP >= median		
Number of patients in analysis set	661	631
Number of analysed patients	604	593
Baseline mean (SE)	65.32 (0.89)	64.35 (0.94)
Week 52		
Values at visit		
Number of analysed patients	409	405
Mean (SE)	70.92 (1.08)	73.25 (1.09)
Adjusted* mean (SE)	69.72 (0.76)	72.10 (0.77)
95% confidence interval	(68.23,71.22)	(70.60,73.61)
Change from baseline		
Mean (SE)	4.17 (1.08)	7.30 (0.97)
Adjusted* mean (SE)	4.88 (0.76)	7.26 (0.77)
95% confidence interval	(3.39, 6.37)	(5.76, 8.77)
Comparison vs Placebo		
Adjusted* mean (SE)		2.38 (1.08)
95% confidence interval		(0.26, 4.50)
p-value		0.0276

* Model includes Age, baseline eGFR (CKD-EPI) as linear covariate(s) and region, baseline diabetes status, sex, week reachable, Visit by Treatment by heart failure physiology interaction, baseline KCCQ - overall summary score by Visit interaction as fixed effect(s).
The Visit by Treatment by heart failure physiology p-value at Week 52 is 0.5260.
The following covariance structure has been used to fit the mixed model: Unstructured
16 patients were excluded as the subgroup variable was missing.
Note: All covariate effects are set equal to their mean values within subgroup for the calculation of adjusted means.
The p-value for the visit by treatment by subgroup interaction trend test at Week 52 is 0.6411

For patients who died, only observed values are considered (no imputation after date of death).
Data taken from study 1245.121 only.
NTproBNP median [pg/mL]: with a. fibrillation/flutter at baseline: 2265; without a. fibrillation/flutter at baseline: 1671.
The MMRM includes all outcome values (change from baseline) at the planned Visits week 12, week 32 and week 52

Table R.1.3.4.12: 1 KCCQ-OSS change from baseline at week 52 (MMRM) by heart failure physiology - RS (OC-AD - no imputation for deaths) - 1245.121

Subgroup / Visit / Description / Statistic	Placebo	Empa 10mg
Heart failure physiology: LVEF > 30%		
Number of patients in analysis set	475	526
Number of analysed patients	450	506
Baseline mean (SE)	69.15 (0.98)	68.67 (1.01)
Week 52		
Values at visit		
Number of analysed patients	294	339
Mean (SE)	75.06 (1.16)	75.34 (1.10)
Adjusted* mean (SE)	73.88 (0.90)	74.41 (0.83)
95% confidence interval	(72.12,75.63)	(72.78,76.05)
Change from baseline		
Mean (SE)	4.74 (1.11)	4.93 (0.95)
Adjusted* mean (SE)	4.98 (0.90)	5.52 (0.83)
95% confidence interval	(3.23, 6.74)	(3.88, 7.15)
Comparison vs Placebo		
Adjusted* mean (SE)		0.53 (1.22)
95% confidence interval		(-1.86, 2.93)
p-value		0.6617

* Model includes Age, baseline eGFR (CKD-EPI) as linear covariate(s) and region, baseline diabetes status, sex, week reachable, Visit by Treatment by heart failure physiology interaction, baseline KCCQ - overall summary score by Visit interaction as fixed effect(s).
The Visit by Treatment by heart failure physiology p-value at Week 52 is 0.5260.
The following covariance structure has been used to fit the mixed model: Unstructured
16 patients were excluded as the subgroup variable was missing.
Note: All covariate effects are set equal to their mean values within subgroup for the calculation of adjusted means.
The p-value for the visit by treatment by subgroup interaction trend test at Week 52 is 0.6411

For patients who died, only observed values are considered (no imputation after date of death).
Data taken from study 1245.121 only.
NTproBNP median [pg/mL]: with a. fibrillation/flutter at baseline: 2265; without a. fibrillation/flutter at baseline: 1671.
The MMRM includes all outcome values (change from baseline) at the planned Visits week 12, week 32 and week 52

R.1.3.4.13

Table R.1.3.4.13: 1 KCCQ-OSS change from baseline at week 52 (MMRM) by baseline use of MRA (Y/N) - RS (OC-AD - no imputation for deaths) - 1245.121

Subgroup / Visit / Description / Statistic	Placebo	Empa 10mg
Baseline use of MRA: No		
Number of patients in analysis set	512	557
Number of analysed patients	486	531
Baseline mean (SE)	69.73 (0.93)	68.67 (0.95)
Week 52		
Values at visit		
Number of analysed patients	340	383
Mean (SE)	72.36 (1.13)	76.67 (1.03)
Adjusted* mean (SE)	72.69 (0.84)	75.81 (0.80)
95% confidence interval	(71.04,74.34)	(74.25,77.38)
Change from baseline		
Mean (SE)	2.96 (1.02)	6.37 (0.90)
Adjusted* mean (SE)	3.51 (0.84)	6.64 (0.80)
95% confidence interval	(1.86, 5.16)	(5.07, 8.20)
Comparison vs Placebo		
Adjusted* mean (SE)		3.13 (1.15)
95% confidence interval		(0.86, 5.39)
p-value		0.0068

* Model includes Age, baseline eGFR (CKD-EPI) as linear covariate(s) and region, baseline diabetes status, sex, baseline LVEF, week reachable, Visit by Treatment by baseline use of MRA interaction, baseline KCCQ - overall summary score by Visit interaction as fixed effect(s).
The Visit by Treatment by baseline use of MRA p-value at Week 52 is 0.0965.
The following covariance structure has been used to fit the mixed model: Unstructured
Note: All covariate effects are set equal to their mean values within subgroup for the calculation of adjusted means.

For patients who died, only observed values are considered (no imputation after date of death).
Data taken from study 1245.121 only.
The MMRM includes all outcome values (change from baseline) at the planned Visits week 12, week 32 and week 52

Table R.1.3.4.13: 1 KCCQ-OSS change from baseline at week 52 (MMRM) by baseline use of MRA (Y/N) - RS (OC-AD - no imputation for deaths) - 1245.121

Subgroup / Visit / Description / Statistic	Placebo	Empa 10mg
Baseline use of MRA: Yes		
Number of patients in analysis set	1355	1306
Number of analysed patients	1267	1245
Baseline mean (SE)	66.77 (0.61)	67.12 (0.63)
Week 52		
Values at visit		
Number of analysed patients	878	856
Mean (SE)	74.00 (0.70)	74.43 (0.71)
Adjusted* mean (SE)	72.76 (0.52)	73.60 (0.53)
95% confidence interval	(71.73,73.78)	(72.57,74.64)
Change from baseline		
Mean (SE)	6.11 (0.65)	6.54 (0.61)
Adjusted* mean (SE)	5.82 (0.52)	6.66 (0.53)
95% confidence interval	(4.79, 6.84)	(5.63, 7.70)
Comparison vs Placebo		
Adjusted* mean (SE)		0.85 (0.74)
95% confidence interval		(-0.61, 2.30)
p-value		0.2547

* Model includes Age, baseline eGFR (CKD-EPI) as linear covariate(s) and region, baseline diabetes status, sex, baseline LVEF, week reachable, Visit by Treatment by baseline use of MRA interaction, baseline KCCQ - overall summary score by Visit interaction as fixed effect(s).
The Visit by Treatment by baseline use of MRA p-value at Week 52 is 0.0965.
The following covariance structure has been used to fit the mixed model: Unstructured
Note: All covariate effects are set equal to their mean values within subgroup for the calculation of adjusted means.

For patients who died, only observed values are considered (no imputation after date of death).
Data taken from study 1245.121 only.
The MMRM includes all outcome values (change from baseline) at the planned Visits week 12, week 32 and week 52

R.1.3.4.14

Table R.1.3.4.14: 1 KCCQ-OSS change from baseline at week 52 (MMRM) by baseline use of ARNi (Y/N) - RS (OC-AD - no imputation for deaths) - 1245.121

Subgroup / Visit / Description / Statistic	Placebo	Empa 10mg
Baseline use of ARNi: No		
Number of patients in analysis set	1480	1523
Number of analysed patients	1390	1447
Baseline mean (SE)	67.44 (0.57)	67.05 (0.58)
Week 52		
Values at visit		
Number of analysed patients	960	1026
Mean (SE)	73.50 (0.67)	74.76 (0.65)
Adjusted* mean (SE)	72.52 (0.50)	73.94 (0.48)
95% confidence interval	(71.54,73.50)	(72.99,74.89)
Change from baseline		
Mean (SE)	5.45 (0.63)	6.66 (0.56)
Adjusted* mean (SE)	5.28 (0.50)	6.70 (0.48)
95% confidence interval	(4.30, 6.26)	(5.75, 7.65)
Comparison vs Placebo		
Adjusted* mean (SE)		1.42 (0.69)
95% confidence interval		(0.05, 2.78)
p-value		0.0415

* Model includes Age, baseline eGFR (CKD-EPI) as linear covariate(s) and region, baseline diabetes status, sex, baseline LVEF, week reachable, Visit by Treatment by baseline use of ARNi interaction, baseline KCCQ - overall summary score by Visit interaction as fixed effect(s).
The Visit by Treatment by baseline use of ARNi p-value at Week 52 is 0.6987.
The following covariance structure has been used to fit the mixed model: Unstructured
Note: All covariate effects are set equal to their mean values within subgroup for the calculation of adjusted means.

For patients who died, only observed values are considered (no imputation after date of death).
Data taken from study 1245.121 only.
The MMRM includes all outcome values (change from baseline) at the planned Visits week 12, week 32 and week 52

Table R.1.3.4.14: 1 KCCQ-OSS change from baseline at week 52 (MMRM) by baseline use of ARNi (Y/N) - RS (OC-AD - no imputation for deaths) - 1245.121

Subgroup / Visit / Description / Statistic	Placebo	Empa 10mg
Baseline use of ARNi: Yes		
Number of patients in analysis set	387	340
Number of analysed patients	363	329
Baseline mean (SE)	68.13 (1.18)	69.94 (1.21)
Week 52		
Values at visit		
Number of analysed patients	258	213
Mean (SE)	73.69 (1.35)	76.86 (1.35)
Adjusted* mean (SE)	73.66 (0.97)	75.69 (1.06)
95% confidence interval	(71.75,75.56)	(73.62,77.76)
Change from baseline		
Mean (SE)	4.42 (1.13)	5.66 (1.20)
Adjusted* mean (SE)	4.67 (0.97)	6.70 (1.06)
95% confidence interval	(2.76, 6.57)	(4.63, 8.77)
Comparison vs Placebo		
Adjusted* mean (SE)		2.03 (1.43)
95% confidence interval		(-0.77, 4.83)
p-value		0.1549

* Model includes Age, baseline eGFR (CKD-EPI) as linear covariate(s) and region, baseline diabetes status, sex, baseline LVEF, week reachable, Visit by Treatment by baseline use of ARNi interaction, baseline KCCQ - overall summary score by Visit interaction as fixed effect(s).
The Visit by Treatment by baseline use of ARNi p-value at Week 52 is 0.6987.
The following covariance structure has been used to fit the mixed model: Unstructured
Note: All covariate effects are set equal to their mean values within subgroup for the calculation of adjusted means.

For patients who died, only observed values are considered (no imputation after date of death).
Data taken from study 1245.121 only.
The MMRM includes all outcome values (change from baseline) at the planned Visits week 12, week 32 and week 52

R.1.3.4.15

R.1.3.4.15 Subgroup analysis by bl. LVEF (<= 30%, >30% -<= 35% , > 35%)

Table R.1.3.4.15: 1 KCCQ-OSS change from baseline at week 52 (MMRM) by baseline LVEF (3 cat.) - RS (OC-AD - no imputation for deaths) - 1245.121

Subgroup / Visit / Description / Statistic	Placebo	Empa 10mg
Baseline LVEF (3 cat.): <=30		
Number of patients in analysis set	1392	1337
Number of analysed patients	1303	1270
Baseline mean (SE)	67.05 (0.60)	67.15 (0.62)
Week 52		
Values at visit		
Number of analysed patients	924	900
Mean (SE)	73.05 (0.70)	75.04 (0.70)
Adjusted* mean (SE)	72.34 (0.51)	74.22 (0.52)
95% confidence interval	(71.34,73.34)	(73.20,75.23)
Change from baseline		
Mean (SE)	5.39 (0.63)	7.07 (0.60)
Adjusted* mean (SE)	5.24 (0.51)	7.12 (0.52)
95% confidence interval	(4.24, 6.24)	(6.10, 8.13)
Comparison vs Placebo		
Adjusted* mean (SE)		1.88 (0.73)
95% confidence interval		(0.46, 3.30)
p-value		0.0096

* Model includes Age, baseline eGFR (CKD-EPI) as linear covariate(s) and region, baseline diabetes status, sex, week reachable, Visit by Treatment by baseline LVEF (3 cat.) interaction, baseline KCCQ - overall summary score by Visit interaction as fixed effect(s).
The Visit by Treatment by baseline LVEF (3 cat.) p-value at Week 52 is 0.1771.
The following covariance structure has been used to fit the mixed model: Unstructured
Note: All covariate effects are set equal to their mean values within subgroup for the calculation of adjusted means.
The p-value for the visit by treatment by subgroup interaction trend test at Week 52 is 0.7695

For patients who died, only observed values are considered (no imputation after date of death).
Data taken from study 1245.121 only.
The MMRM includes all outcome values (change from baseline) at the planned Visits week 12, week 32 and week 52

Table R.1.3.4.15: 1 KCCQ-OSS change from baseline at week 52 (MMRM) by baseline LVEF (3 cat.) - RS (OC-AD - no imputation for deaths) - 1245.121

Subgroup / Visit / Description / Statistic	Placebo	Empa 10mg
Baseline LVEF (3 cat.): >30 to <=35		
Number of patients in analysis set	361	398
Number of analysed patients	342	385
Baseline mean (SE)	69.82 (1.11)	68.82 (1.15)
Week 52		
Values at visit		
Number of analysed patients	233	256
Mean (SE)	76.48 (1.24)	74.85 (1.29)
Adjusted* mean (SE)	74.85 (1.01)	74.34 (0.96)
95% confidence interval	(72.87,76.83)	(72.46,76.22)
Change from baseline		
Mean (SE)	5.23 (1.24)	4.14 (1.07)
Adjusted* mean (SE)	5.56 (1.01)	5.05 (0.96)
95% confidence interval	(3.58, 7.54)	(3.17, 6.93)
Comparison vs Placebo		
Adjusted* mean (SE)		-0.51 (1.39)
95% confidence interval		(-3.24, 2.22)
p-value		0.7148

* Model includes Age, baseline eGFR (CKD-EPI) as linear covariate(s) and region, baseline diabetes status, sex, week reachable, Visit by Treatment by baseline LVEF (3 cat.) interaction, baseline KCCQ - overall summary score by Visit interaction as fixed effect(s).
The Visit by Treatment by baseline LVEF (3 cat.) p-value at Week 52 is 0.1771.
The following covariance structure has been used to fit the mixed model: Unstructured
Note: All covariate effects are set equal to their mean values within subgroup for the calculation of adjusted means.
The p-value for the visit by treatment by subgroup interaction trend test at Week 52 is 0.7695

For patients who died, only observed values are considered (no imputation after date of death).
Data taken from study 1245.121 only.
The MMRM includes all outcome values (change from baseline) at the planned Visits week 12, week 32 and week 52

Table R.1.3.4.15: 1 KCCQ-OSS change from baseline at week 52 (MMRM) by baseline LVEF (3 cat.) - RS (OC-AD - no imputation for deaths) - 1245.121

Subgroup / Visit / Description / Statistic	Placebo	Empa 10mg
Baseline LVEF (3 cat.): >35		
Number of patients in analysis set	114	128
Number of analysed patients	108	121
Baseline mean (SE)	67.01 (2.09)	68.19 (2.16)
Week 52		
Values at visit		
Number of analysed patients	61	83
Mean (SE)	69.66 (2.85)	76.84 (2.10)
Adjusted* mean (SE)	70.38 (1.94)	74.59 (1.69)
95% confidence interval	(66.57,74.18)	(71.27,77.91)
Change from baseline		
Mean (SE)	2.86 (2.50)	7.35 (2.03)
Adjusted* mean (SE)	2.74 (1.94)	6.96 (1.69)
95% confidence interval	(-1.06, 6.54)	(3.63,10.28)
Comparison vs Placebo		
Adjusted* mean (SE)		4.21 (2.57)
95% confidence interval		(-0.83, 9.26)
p-value		0.1015

* Model includes Age, baseline eGFR (CKD-EPI) as linear covariate(s) and region, baseline diabetes status, sex, week reachable, Visit by Treatment by baseline LVEF (3 cat.) interaction, baseline KCCQ - overall summary score by Visit interaction as fixed effect(s).
The Visit by Treatment by baseline LVEF (3 cat.) p-value at Week 52 is 0.1771.
The following covariance structure has been used to fit the mixed model: Unstructured
Note: All covariate effects are set equal to their mean values within subgroup for the calculation of adjusted means.
The p-value for the visit by treatment by subgroup interaction trend test at Week 52 is 0.7695

For patients who died, only observed values are considered (no imputation after date of death).
Data taken from study 1245.121 only.
The MMRM includes all outcome values (change from baseline) at the planned Visits week 12, week 32 and week 52

R.1.3.4.16 Subgroup analysis by bl. NTproBNP </>= median (median based on total patients)

Table R.1.3.4.16: 1 KCCQ-OSS change from baseline at week 52 (MMRM) by bl. NTproBNP (<median, >= median) (median based on total patients) - RS (OC-AD - no imputation for deaths) - 1245.121

Subgroup / Visit / Description / Statistic	Placebo	Empa 10mg
Baseline NTproBNP (<median, >= median): < median		
Number of patients in analysis set	920	942
Number of analysed patients	884	908
Baseline mean (SE)	69.97 (0.70)	70.37 (0.70)
Week 52		
Values at visit		
Number of analysed patients	651	666
Mean (SE)	75.02 (0.80)	76.70 (0.76)
Adjusted* mean (SE)	74.87 (0.61)	76.46 (0.60)
95% confidence interval	(73.67,76.06)	(75.28,77.64)
Change from baseline		
Mean (SE)	5.30 (0.65)	6.19 (0.64)
Adjusted* mean (SE)	4.69 (0.61)	6.29 (0.60)
95% confidence interval	(3.49, 5.89)	(5.11, 7.47)
Comparison vs Placebo		
Adjusted* mean (SE)		1.60 (0.86)
95% confidence interval		(-0.08, 3.28)
p-value		0.0627

* Model includes Age, baseline eGFR (CKD-EPI) as linear covariate(s) and region, baseline diabetes status, sex, baseline LVEF, week reachable, Visit by Treatment by baseline NTproBNP (<median, >= median) interaction, baseline KCCQ - overall summary score by Visit interaction as fixed effect(s). The Visit by Treatment by baseline NTproBNP (<median, >= median) p-value at Week 52 is 0.8545.
The following covariance structure has been used to fit the mixed model: Unstructured
2 patients were excluded as the subgroup variable was missing.
Note: All covariate effects are set equal to their mean values within subgroup for the calculation of adjusted means.

For patients who died, only observed values are considered (no imputation after date of death).
Data taken from study 1245.121 only.
Median: 1910 [pg/mL]
The MMRM includes all outcome values (change from baseline) at the planned Visits week 12, week 32 and week 52

Table R.1.3.4.16: 1 KCCQ-OSS change from baseline at week 52 (MMRM) by bl. NTproBNP (<median, >= median) (median based on total patients) - RS (OC-AD - no imputation for deaths) - 1245.121

Subgroup / Visit / Description / Statistic	Placebo	Empa 10mg
Baseline NTproBNP (<median, >= median): >= median		
Number of patients in analysis set	946	920
Number of analysed patients	869	868
Baseline mean (SE)	65.16 (0.74)	64.67 (0.78)
Week 52		
Values at visit		
Number of analysed patients	567	573
Mean (SE)	71.83 (0.90)	73.28 (0.91)
Adjusted* mean (SE)	70.58 (0.65)	71.94 (0.64)
95% confidence interval	(69.31,71.84)	(70.68,73.21)
Change from baseline		
Mean (SE)	5.14 (0.92)	6.83 (0.81)
Adjusted* mean (SE)	5.66 (0.65)	7.03 (0.64)
95% confidence interval	(4.40, 6.93)	(5.77, 8.29)
Comparison vs Placebo		
Adjusted* mean (SE)		1.37 (0.91)
95% confidence interval		(-0.42, 3.15)
p-value		0.1334

* Model includes Age, baseline eGFR (CKD-EPI) as linear covariate(s) and region, baseline diabetes status, sex, baseline LVEF, week reachable, Visit by Treatment by baseline NTproBNP (<median, >= median) interaction, baseline KCCQ - overall summary score by Visit interaction as fixed effect(s). The Visit by Treatment by baseline NTproBNP (<median, >= median) p-value at Week 52 is 0.8545.
The following covariance structure has been used to fit the mixed model: Unstructured
2 patients were excluded as the subgroup variable was missing.
Note: All covariate effects are set equal to their mean values within subgroup for the calculation of adjusted means.

For patients who died, only observed values are considered (no imputation after date of death).
Data taken from study 1245.121 only.
Median: 1910 [pg/mL]
The MMRM includes all outcome values (change from baseline) at the planned Visits week 12, week 32 and week 52

R.1.3.5

R.1.3.5 KCCQ physical limitation score MMRM analysis

R.1.3.5.1

R.1.3.5.1 Overall analysis

Table R.1.3.5.1: 1

Table R.1.3.5.1: 1 KCCQ physical limitation score change from baseline MMRM results over time - RS (OC-AD - no imputation for deaths) - 1245.121

Visit Description Statistic	Placebo	Empa 10mg
Number of patients in analysis set	1867	1863
Number of analysed patients	1741	1753
Baseline mean (SE)	67.44 (0.59)	67.36 (0.59)
Week 12		
Values at visit		
Number of analysed patients	1705	1718
Mean (SE)	70.79 (0.58)	72.18 (0.58)
Adjusted* mean (SE)	71.02 (0.43)	72.40 (0.43)
95% confidence interval	(70.18,71.87)	(71.56,73.25)
Change from baseline		
Mean (SE)	3.25 (0.48)	4.57 (0.48)
Adjusted* mean (SE)	3.02 (0.43)	4.40 (0.43)
95% confidence interval	(2.17, 3.86)	(3.56, 5.24)
Comparison vs Placebo		
Adjusted* mean (SE)		1.38 (0.61)
95% confidence interval		(0.19, 2.57)
p-value		0.0228
Hedges g		
Estimate		0.08
95% confidence interval		(0.01, 0.14)

* Model includes Age (p=0.0260), baseline eGFR (CKD-EPI) (p=0.0040) as linear covariate(s) and region (p<0.0001), baseline diabetes status (p=0.5645), sex (p=0.0004), baseline LVEF (p=0.2655), week reachable (p=0.2047), Treatment by Visit interaction (p=0.0672), baseline KCCQ physical limitation score by Visit interaction (p<0.0001) as fixed effect(s).
The following covariance structure has been used to fit the mixed model: Unstructured

For patients who died, only observed values are considered (no imputation after date of death).
Data taken from study 1245.121 only.

Table R.1.3.5.1: 1 KCCQ physical limitation score change from baseline MMRM results over time - RS (OC-AD - no imputation for deaths) - 1245.121

Visit Description Statistic	Placebo	Empa 10mg
Week 32		
Values at visit		
Number of analysed patients	1546	1577
Mean (SE)	71.52 (0.62)	72.51 (0.61)
Adjusted* mean (SE)	71.14 (0.46)	72.25 (0.46)
95% confidence interval	(70.23,72.05)	(71.35,73.15)
Change from baseline		
Mean (SE)	3.66 (0.54)	4.57 (0.51)
Adjusted* mean (SE)	3.14 (0.46)	4.25 (0.46)
95% confidence interval	(2.23, 4.05)	(3.34, 5.15)
Comparison vs Placebo		
Adjusted* mean (SE)		1.11 (0.65)
95% confidence interval		(-0.17, 2.39)
p-value		0.0904
Week 52		
Values at visit		
Number of analysed patients	1205	1210
Mean (SE)	71.58 (0.71)	72.91 (0.70)
Adjusted* mean (SE)	70.78 (0.54)	72.19 (0.54)
95% confidence interval	(69.73,71.84)	(71.14,73.25)
Change from baseline		
Mean (SE)	3.16 (0.65)	3.84 (0.61)
Adjusted* mean (SE)	2.78 (0.54)	4.19 (0.54)
95% confidence interval	(1.72, 3.84)	(3.14, 5.24)
Comparison vs Placebo		
Adjusted* mean (SE)		1.41 (0.76)
95% confidence interval		(-0.08, 2.90)
p-value		0.0640

* Model includes Age (p=0.0260), baseline eGFR (CKD-EPI) (p=0.0040) as linear covariate(s) and region (p<0.0001), baseline diabetes status (p=0.5645), sex (p=0.0004), baseline LVEF (p=0.2655), week reachable (p=0.2047), Treatment by Visit interaction (p=0.0672), baseline KCCQ physical limitation score by Visit interaction (p<0.0001) as fixed effect(s).
The following covariance structure has been used to fit the mixed model: Unstructured

For patients who died, only observed values are considered (no imputation after date of death).
Data taken from study 1245.121 only.

Figure R.1.3.5.1: 1

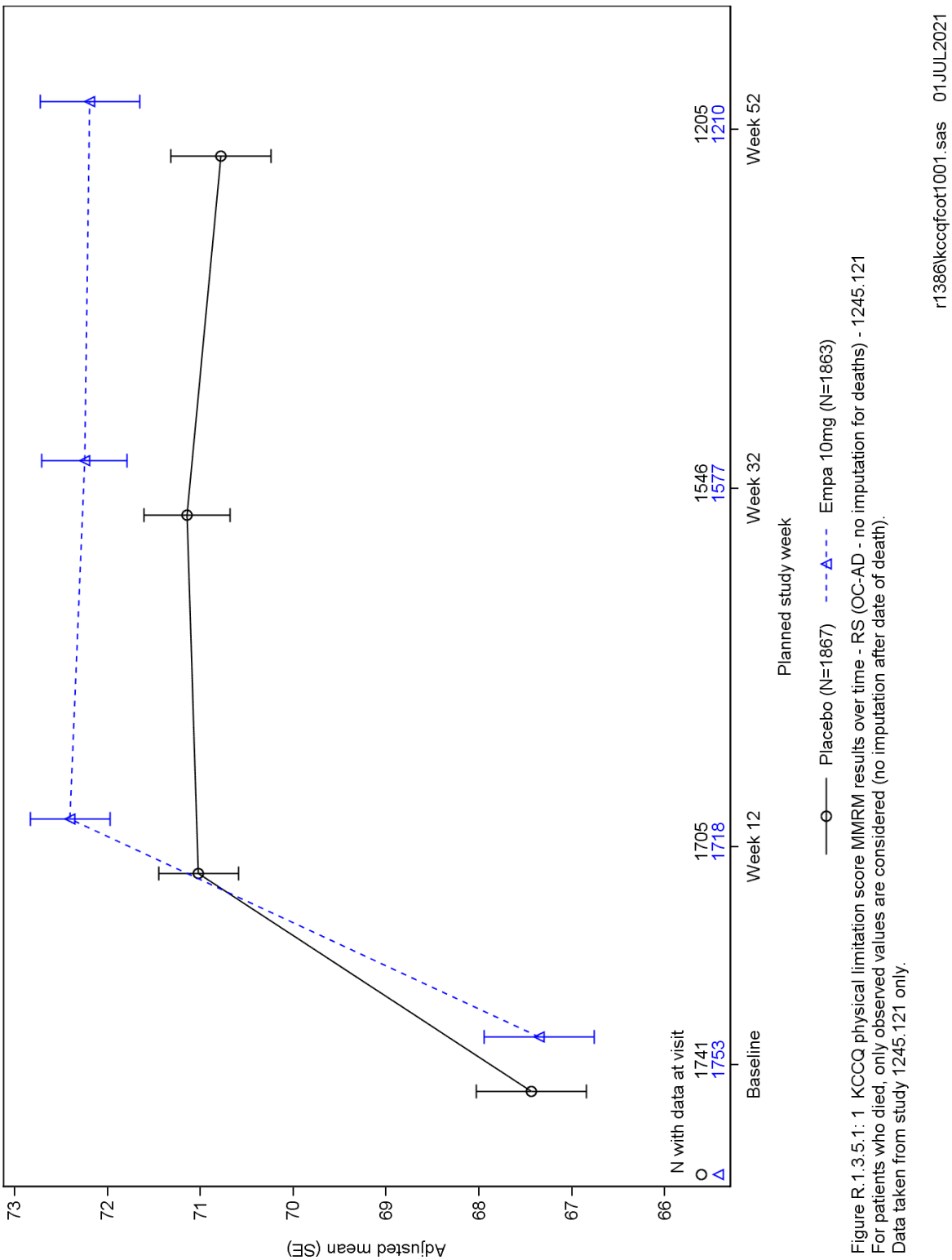

Figure R.1.3.5.1: 1 KCCQ physical limitation score MMRM results over time - RS (OC-AD - no imputation for deaths) - 1245.121
For patients who died, only observed values are considered (no imputation after date of death).
Data taken from study 1245.121 only.

R.1.3.5.2

R.1.3.5.2 Subgroup analysis by sex

Table R.1.3.5.2: 1 KCCQ physical limitation score change from baseline at week 52 (MMRM) by sex - RS (OC-AD - no imputation for deaths) - 1245.121

Subgroup / Visit / Description / Statistic	Placebo	Empa 10mg
Sex: Male		
Number of patients in analysis set	1411	1426
Number of analysed patients	1327	1347
Baseline mean (SE)	70.01 (0.66)	69.32 (0.67)
Week 52		
Values at visit		
Number of analysed patients	932	935
Mean (SE)	73.00 (0.80)	74.55 (0.79)
Adjusted* mean (SE)	71.67 (0.61)	73.85 (0.61)
95% confidence interval	(70.47,72.87)	(72.65,75.05)
Change from baseline		
Mean (SE)	1.85 (0.73)	3.73 (0.69)
Adjusted* mean (SE)	2.01 (0.61)	4.18 (0.61)
95% confidence interval	(0.80, 3.21)	(2.98, 5.38)
Comparison vs Placebo		
Adjusted* mean (SE)		2.18 (0.87)
95% confidence interval		(0.48, 3.88)
p-value		0.0120

* Model includes Age, baseline eGFR (CKD-EPI) as linear covariate(s) and region, baseline diabetes status, baseline LVEF, week reachable, Visit by Treatment by sex interaction, baseline KCCQ physical limitation score by Visit interaction as fixed effect(s).
The Visit by Treatment by sex p-value at Week 52 is 0.0637.
The following covariance structure has been used to fit the mixed model: Unstructured
Note: All covariate effects are set equal to their mean values within subgroup for the calculation of adjusted means.

For patients who died, only observed values are considered (no imputation after date of death).
Data taken from study 1245.121 only.
The MMRM includes all outcome values (change from baseline) at the planned Visits week 12, week 32 and week 52

Table R.1.3.5.2: 1 KCCQ physical limitation score change from baseline at week 52 (MMRM) by sex - RS (OC-AD - no imputation for deaths) - 1245.121

Subgroup / Visit / Description / Statistic	Placebo	Empa 10mg
Sex: Female		
Number of patients in analysis set	456	437
Number of analysed patients	414	406
Baseline mean (SE)	59.18 (1.22)	60.84 (1.22)
Week 52		
Values at visit		
Number of analysed patients	273	275
Mean (SE)	66.72 (1.50)	67.33 (1.48)
Adjusted* mean (SE)	66.24 (1.13)	65.05 (1.13)
95% confidence interval	(64.03,68.45)	(62.85,67.26)
Change from baseline		
Mean (SE)	7.63 (1.34)	4.19 (1.28)
Adjusted* mean (SE)	6.24 (1.13)	5.05 (1.13)
95% confidence interval	(4.03, 8.45)	(2.85, 7.26)
Comparison vs Placebo		
Adjusted* mean (SE)		-1.18 (1.59)
95% confidence interval		(-4.31, 1.94)
p-value		0.4569

* Model includes Age, baseline eGFR (CKD-EPI) as linear covariate(s) and region, baseline diabetes status, baseline LVEF, week reachable, Visit by Treatment by sex interaction, baseline KCCQ physical limitation score by Visit interaction as fixed effect(s).
The Visit by Treatment by sex p-value at Week 52 is 0.0637.
The following covariance structure has been used to fit the mixed model: Unstructured
Note: All covariate effects are set equal to their mean values within subgroup for the calculation of adjusted means.

For patients who died, only observed values are considered (no imputation after date of death).
Data taken from study 1245.121 only.
The MMRM includes all outcome values (change from baseline) at the planned Visits week 12, week 32 and week 52

R.1.3.5.3

Table R.1.3.5.3: 1 KCCQ physical limitation score change from baseline at week 52 (MMRM) by age (2 cat.) - RS (OC-AD - no imputation for deaths) - 1245.121

Subgroup / Visit / Description / Statistic	Placebo	Empa 10mg
Age [years] (2 cat.): < 65		
Number of patients in analysis set	740	675
Number of analysed patients	695	637
Baseline mean (SE)	68.00 (0.96)	67.61 (0.98)
Week 52		
Values at visit		
Number of analysed patients	491	445
Mean (SE)	72.50 (1.11)	74.47 (1.15)
Adjusted* mean (SE)	71.24 (0.85)	73.17 (0.89)
95% confidence interval	(69.57,72.91)	(71.43,74.92)
Change from baseline		
Mean (SE)	4.37 (1.06)	5.58 (0.96)
Adjusted* mean (SE)	3.43 (0.85)	5.36 (0.89)
95% confidence interval	(1.75, 5.10)	(3.61, 7.10)
Comparison vs Placebo		
Adjusted* mean (SE)		1.93 (1.23)
95% confidence interval		(-0.47, 4.34)
p-value		0.1153

* Model includes baseline eGFR (CKD-EPI) as linear covariate(s) and region, baseline diabetes status, sex, baseline LVEF, week reachable, Visit by Treatment by age [years] (2 cat.) interaction, baseline KCCQ physical limitation score by Visit interaction as fixed effect(s).
The Visit by Treatment by age [years] (2 cat.) p-value at Week 52 is 0.5703.
The following covariance structure has been used to fit the mixed model: Unstructured
Note: All covariate effects are set equal to their mean values within subgroup for the calculation of adjusted means.

For patients who died, only observed values are considered (no imputation after date of death).
Data taken from study 1245.121 only.
The MMRM includes all outcome values (change from baseline) at the planned Visits week 12, week 32 and week 52

Table R.1.3.5.3: 1 KCCQ physical limitation score change from baseline at week 52 (MMRM) by age (2 cat.) - RS (OC-AD - no imputation for deaths) - 1245.121

Subgroup / Visit / Description / Statistic	Placebo	Empa 10mg
Age [years] (2 cat.): >= 65		
Number of patients in analysis set	1127	1188
Number of analysed patients	1046	1116
Baseline mean (SE)	67.06 (0.74)	67.21 (0.74)
Week 52		
Values at visit		
Number of analysed patients	714	765
Mean (SE)	70.94 (0.92)	72.00 (0.89)
Adjusted* mean (SE)	69.90 (0.70)	70.94 (0.68)
95% confidence interval	(68.52,71.28)	(69.61,72.27)
Change from baseline		
Mean (SE)	2.33 (0.81)	2.82 (0.78)
Adjusted* mean (SE)	2.76 (0.70)	3.80 (0.68)
95% confidence interval	(1.38, 4.14)	(2.47, 5.13)
Comparison vs Placebo		
Adjusted* mean (SE)		1.04 (0.97)
95% confidence interval		(-0.87, 2.95)
p-value		0.2838

* Model includes baseline eGFR (CKD-EPI) as linear covariate(s) and region, baseline diabetes status, sex, baseline LVEF, week reachable, Visit by Treatment by age [years] (2 cat.) interaction, baseline KCCQ physical limitation score by Visit interaction as fixed effect(s).
The Visit by Treatment by age [years] (2 cat.) p-value at Week 52 is 0.5703.
The following covariance structure has been used to fit the mixed model: Unstructured
Note: All covariate effects are set equal to their mean values within subgroup for the calculation of adjusted means.

For patients who died, only observed values are considered (no imputation after date of death).
Data taken from study 1245.121 only.
The MMRM includes all outcome values (change from baseline) at the planned Visits week 12, week 32 and week 52

R.1.3.5.4 Subgroup analysis by region (North America, Latin America, Europe, Asia, Other)

Table R.1.3.5.4: 1 KCCQ physical limitation score change from baseline at week 52 (MMRM) by region - RS (OC-AD - no imputation for deaths) - 1245.121

Subgroup / Visit / Description / Statistic	Placebo	Empa 10mg
Region (5 cat.): North America		
Number of patients in analysis set	213	212
Number of analysed patients	194	203
Baseline mean (SE)	68.49 (1.73)	69.14 (1.65)
Week 52		
Values at visit		
Number of analysed patients	127	146
Mean (SE)	71.28 (2.15)	72.50 (1.94)
Adjusted* mean (SE)	70.06 (1.65)	70.61 (1.56)
95% confidence interval	(66.82,73.29)	(67.55,73.66)
Change from baseline		
Mean (SE)	2.67 (1.83)	1.14 (1.68)
Adjusted* mean (SE)	1.23 (1.65)	1.78 (1.56)
95% confidence interval	(-2.00, 4.47)	(-1.27, 4.83)
Comparison vs Placebo		
Adjusted* mean (SE)		0.55 (2.27)
95% confidence interval		(-3.90, 5.00)
p-value		0.8091

* Model includes Age, baseline eGFR (CKD-EPI) as linear covariate(s) and baseline diabetes status, sex, baseline LVEF, week reachable, Visit by Treatment by region (5 cat.) interaction, baseline KCCQ physical limitation score by Visit interaction as fixed effect(s).
The Visit by Treatment by region (5 cat.) p-value at Week 52 is 0.6586.
The following covariance structure has been used to fit the mixed model: Unstructured
Note: All covariate effects are set equal to their mean values within subgroup for the calculation of adjusted means.

For patients who died, only observed values are considered (no imputation after date of death).
Data taken from study 1245.121 only.
The MMRM includes all outcome values (change from baseline) at the planned Visits week 12, week 32 and week 52

Table R.1.3.5.4: 1 KCCQ physical limitation score change from baseline at week 52 (MMRM) by region - RS (OC-AD - no imputation for deaths) - 1245.121

Subgroup / Visit / Description / Statistic	Placebo	Empa 10mg
Region (5 cat.): Latin America		
Number of patients in analysis set	645	641
Number of analysed patients	592	591
Baseline mean (SE)	62.55 (1.05)	62.80 (1.08)
Week 52		
Values at visit		
Number of analysed patients	384	360
Mean (SE)	70.59 (1.30)	70.69 (1.37)
Adjusted* mean (SE)	70.46 (0.95)	70.36 (0.97)
95% confidence interval	(68.60,72.32)	(68.45,72.27)
Change from baseline		
Mean (SE)	8.36 (1.31)	7.63 (1.32)
Adjusted* mean (SE)	7.78 (0.95)	7.68 (0.97)
95% confidence interval	(5.92, 9.65)	(5.78, 9.59)
Comparison vs Placebo		
Adjusted* mean (SE)		-0.10 (1.36)
95% confidence interval		(-2.76, 2.56)
p-value		0.9402

* Model includes Age, baseline eGFR (CKD-EPI) as linear covariate(s) and baseline diabetes status, sex, baseline LVEF, week reachable, Visit by Treatment by region (5 cat.) interaction, baseline KCCQ physical limitation score by Visit interaction as fixed effect(s).
The Visit by Treatment by region (5 cat.) p-value at Week 52 is 0.6586.
The following covariance structure has been used to fit the mixed model: Unstructured
Note: All covariate effects are set equal to their mean values within subgroup for the calculation of adjusted means.

For patients who died, only observed values are considered (no imputation after date of death).
Data taken from study 1245.121 only.
The MMRM includes all outcome values (change from baseline) at the planned Visits week 12, week 32 and week 52

Table R.1.3.5.4: 1 KCCQ physical limitation score change from baseline at week 52 (MMRM) by region - RS (OC-AD - no imputation for deaths) - 1245.121

Subgroup / Visit / Description / Statistic	Placebo	Empa 10mg
Region (5 cat.): Europe		
Number of patients in analysis set	677	676
Number of analysed patients	642	643
Baseline mean (SE)	65.17 (0.92)	65.15 (0.93)
Week 52		
Values at visit		
Number of analysed patients	466	463
Mean (SE)	67.06 (1.15)	68.57 (1.14)
Adjusted* mean (SE)	65.47 (0.87)	67.55 (0.87)
95% confidence interval	(63.77,67.18)	(65.83,69.26)
Change from baseline		
Mean (SE)	0.33 (0.93)	1.59 (0.87)
Adjusted* mean (SE)	0.31 (0.87)	2.38 (0.87)
95% confidence interval	(-1.40, 2.02)	(0.67, 4.10)
Comparison vs Placebo		
Adjusted* mean (SE)		2.07 (1.23)
95% confidence interval		(-0.34, 4.49)
p-value		0.0928

* Model includes Age, baseline eGFR (CKD-EPI) as linear covariate(s) and baseline diabetes status, sex, baseline LVEF, week reachable, Visit by Treatment by region (5 cat.) interaction, baseline KCCQ physical limitation score by Visit interaction as fixed effect(s).
The Visit by Treatment by region (5 cat.) p-value at Week 52 is 0.6586.
The following covariance structure has been used to fit the mixed model: Unstructured
Note: All covariate effects are set equal to their mean values within subgroup for the calculation of adjusted means.

For patients who died, only observed values are considered (no imputation after date of death).
Data taken from study 1245.121 only.
The MMRM includes all outcome values (change from baseline) at the planned Visits week 12, week 32 and week 52

Table R.1.3.5.4: 1 KCCQ physical limitation score change from baseline at week 52 (MMRM) by region - RS (OC-AD - no imputation for deaths) - 1245.121

Subgroup / Visit / Description / Statistic	Placebo	Empa 10mg
Region (5 cat.): Asia		
Number of patients in analysis set	245	248
Number of analysed patients	236	240
Baseline mean (SE)	84.07 (1.16)	81.32 (1.34)
Week 52		
Values at visit		
Number of analysed patients	179	185
Mean (SE)	82.61 (1.40)	84.97 (1.42)
Adjusted* mean (SE)	81.24 (1.42)	84.33 (1.39)
95% confidence interval	(78.46,84.01)	(81.60,87.06)
Change from baseline		
Mean (SE)	-1.99 (1.43)	2.19 (1.38)
Adjusted* mean (SE)	-1.45 (1.42)	1.64 (1.39)
95% confidence interval	(-4.22, 1.33)	(-1.08, 4.37)
Comparison vs Placebo		
Adjusted* mean (SE)		3.09 (1.98)
95% confidence interval		(-0.79, 6.98)
p-value		0.1189

* Model includes Age, baseline eGFR (CKD-EPI) as linear covariate(s) and baseline diabetes status, sex, baseline LVEF, week reachable, Visit by Treatment by region (5 cat.) interaction, baseline KCCQ physical limitation score by Visit interaction as fixed effect(s).
The Visit by Treatment by region (5 cat.) p-value at Week 52 is 0.6586.
The following covariance structure has been used to fit the mixed model: Unstructured
Note: All covariate effects are set equal to their mean values within subgroup for the calculation of adjusted means.

For patients who died, only observed values are considered (no imputation after date of death).
Data taken from study 1245.121 only.
The MMRM includes all outcome values (change from baseline) at the planned Visits week 12, week 32 and week 52

Table R.1.3.5.4: 1 KCCQ physical limitation score change from baseline at week 52 (MMRM) by region - RS (OC-AD - no imputation for deaths) - 1245.121

Subgroup / Visit / Description / Statistic	Placebo	Empa 10mg
Region (5 cat.): Other		
Number of patients in analysis set	87	86
Number of analysed patients	77	76
Baseline mean (SE)	70.23 (2.80)	72.60 (2.31)
Week 52		
Values at visit		
Number of analysed patients	49	56
Mean (SE)	82.71 (2.46)	84.23 (2.07)
Adjusted* mean (SE)	80.12 (2.66)	82.20 (2.52)
95% confidence interval	(74.91,85.33)	(77.26,87.13)
Change from baseline		
Mean (SE)	9.57 (3.29)	10.51 (2.10)
Adjusted* mean (SE)	8.71 (2.66)	10.78 (2.52)
95% confidence interval	(3.50,13.92)	(5.85,15.72)
Comparison vs Placebo		
Adjusted* mean (SE)		2.07 (3.66)
95% confidence interval		(-5.10, 9.25)
p-value		0.5705

* Model includes Age, baseline eGFR (CKD-EPI) as linear covariate(s) and baseline diabetes status, sex, baseline LVEF, week reachable, Visit by Treatment by region (5 cat.) interaction, baseline KCCQ physical limitation score by Visit interaction as fixed effect(s).
The Visit by Treatment by region (5 cat.) p-value at Week 52 is 0.6586.
The following covariance structure has been used to fit the mixed model: Unstructured
Note: All covariate effects are set equal to their mean values within subgroup for the calculation of adjusted means.

For patients who died, only observed values are considered (no imputation after date of death).
Data taken from study 1245.121 only.
The MMRM includes all outcome values (change from baseline) at the planned Visits week 12, week 32 and week 52

R.1.3.5.5 Subgroup analysis by OECD (N/Y)

Table R.1.3.5.5: 1 KCCQ physical limitation score change from baseline at week 52 (MMRM) by OECD member (N/Y) - RS (OC-AD - no imputation for deaths) - 1245.121

Subgroup / Visit / Description / Statistic	Placebo	Empa 10mg
OECD member: No		
Number of patients in analysis set	741	713
Number of analysed patients	678	653
Baseline mean (SE)	64.85 (0.99)	64.73 (1.01)
Week 52		
Values at visit		
Number of analysed patients	436	408
Mean (SE)	72.58 (1.19)	73.90 (1.22)
Adjusted* mean (SE)	72.00 (0.89)	73.39 (0.92)
95% confidence interval	(70.25,73.75)	(71.59,75.20)
Change from baseline		
Mean (SE)	7.70 (1.21)	8.71 (1.15)
Adjusted* mean (SE)	7.21 (0.89)	8.60 (0.92)
95% confidence interval	(5.45, 8.96)	(6.80,10.41)
Comparison vs Placebo		
Adjusted* mean (SE)		1.40 (1.28)
95% confidence interval		(-1.11, 3.91)
p-value		0.2757

* Model includes Age, baseline eGFR (CKD-EPI) as linear covariate(s) and baseline diabetes status, sex, baseline LVEF, week reachable, Visit by Treatment by OECD Member (N) interaction, baseline KCCQ physical limitation score by Visit interaction as fixed effect(s). The Visit by Treatment by OECD Member (N) p-value at Week 52 is 0.9349.
The following covariance structure has been used to fit the mixed model: Unstructured
Note: All covariate effects are set equal to their mean values within subgroup for the calculation of adjusted means.

For patients who died, only observed values are considered (no imputation after date of death).
Data taken from study 1245.121 only.
OECD member (yes/no) countries included:
Yes: United States, Canada, Mexico, Poland, Netherlands, Hungary, Germany, Czech Republic, Italy, France, Spain, United Kingdom, Belgium, Japan, Australia, 'Korea; Republic Of South Korea';
No: Brazil, Argentina, China, India.
The MMRM includes all outcome values (change from baseline) at the planned Visits week 12, week 32 and week 52

Table R.1.3.5.5: 1 KCCQ physical limitation score change from baseline at week 52 (MMRM) by OECD member (N/Y) - RS (OC-AD - no imputation for deaths) - 1245.121

Subgroup / Visit / Description / Statistic	Placebo	Empa 10mg
OECD member: Yes		
Number of patients in analysis set	1126	1150
Number of analysed patients	1063	1100
Baseline mean (SE)	69.09 (0.73)	68.92 (0.72)
Week 52		
Values at visit		
Number of analysed patients	769	802
Mean (SE)	71.01 (0.88)	72.40 (0.86)
Adjusted* mean (SE)	69.43 (0.68)	70.95 (0.67)
95% confidence interval	(68.09,70.76)	(69.64,72.26)
Change from baseline		
Mean (SE)	0.59 (0.73)	1.36 (0.69)
Adjusted* mean (SE)	0.42 (0.68)	1.95 (0.67)
95% confidence interval	(-0.91, 1.76)	(0.64, 3.26)
Comparison vs Placebo		
Adjusted* mean (SE)		1.53 (0.95)
95% confidence interval		(-0.34, 3.39)
p-value		0.1089

* Model includes Age, baseline eGFR (CKD-EPI) as linear covariate(s) and baseline diabetes status, sex, baseline LVEF, week reachable, Visit by Treatment by OECD Member (N) interaction, baseline KCCQ physical limitation score by Visit interaction as fixed effect(s). The Visit by Treatment by OECD Member (N) p-value at Week 52 is 0.9349.
The following covariance structure has been used to fit the mixed model: Unstructured
Note: All covariate effects are set equal to their mean values within subgroup for the calculation of adjusted means.

For patients who died, only observed values are considered (no imputation after date of death).
Data taken from study 1245.121 only.
OECD member (yes/no) countries included:
Yes: United States, Canada, Mexico, Poland, Netherlands, Hungary, Germany, Czech Republic, Italy, France, Spain, United Kingdom, Belgium, Japan, Australia, 'Korea; Republic Of South Korea';
No: Brazil, Argentina, China, India.
The MMRM includes all outcome values (change from baseline) at the planned Visits week 12, week 32 and week 52

R.1.3.5.6 Subgroup analysis by NYHA at baseline (II, III/IV - 2 cat.)

Table R.1.3.5.6: 1 KCCQ physical limitation score change from baseline at week 52 (MMRM) by NYHA (2 cat.) - RS (OC-AD - no imputation for deaths) - 1245.121

Subgroup / Visit / Description / Statistic	Placebo	Empa 10mg
Baseline NYHA (2 cat.): II		
Number of patients in analysis set	1401	1399
Number of analysed patients	1332	1315
Baseline mean (SE)	71.62 (0.62)	72.86 (0.62)
Week 52		
Values at visit		
Number of analysed patients	935	930
Mean (SE)	74.28 (0.77)	76.65 (0.76)
Adjusted* mean (SE)	73.80 (0.61)	75.62 (0.61)
95% confidence interval	(72.60,75.00)	(74.42,76.83)
Change from baseline		
Mean (SE)	1.98 (0.71)	2.76 (0.67)
Adjusted* mean (SE)	1.56 (0.61)	3.39 (0.61)
95% confidence interval	(0.36, 2.76)	(2.18, 4.59)
Comparison vs Placebo		
Adjusted* mean (SE)		1.83 (0.87)
95% confidence interval		(0.13, 3.53)
p-value		0.0350

* Model includes Age, baseline eGFR (CKD-EPI) as linear covariate(s) and region, baseline diabetes status, sex, baseline LVEF, week reachable, Visit by Treatment by baseline NYHA (2 cat.) interaction, baseline KCCQ physical limitation score by Visit interaction as fixed effect(s).
The Visit by Treatment by baseline NYHA (2 cat.) p-value at Week 52 is 0.3728.
The following covariance structure has been used to fit the mixed model: Unstructured
Note: All covariate effects are set equal to their mean values within subgroup for the calculation of adjusted means.

For patients who died, only observed values are considered (no imputation after date of death).
Data taken from study 1245.121 only.
The MMRM includes all outcome values (change from baseline) at the planned Visits week 12, week 32 and week 52

Table R.1.3.5.6: 1 KCCQ physical limitation score change from baseline at week 52 (MMRM) by NYHA (2 cat.) - RS (OC-AD - no imputation for deaths) - 1245.121

Subgroup / Visit / Description / Statistic	Placebo	Empa 10mg
Baseline NYHA (2 cat.): III/IV		
Number of patients in analysis set	466	464
Number of analysed patients	409	438
Baseline mean (SE)	53.81 (1.27)	50.84 (1.15)
Week 52		
Values at visit		
Number of analysed patients	270	280
Mean (SE)	62.21 (1.59)	60.46 (1.45)
Adjusted* mean (SE)	59.67 (1.14)	59.88 (1.11)
95% confidence interval	(57.44,61.89)	(57.71,62.06)
Change from baseline		
Mean (SE)	7.26 (1.49)	7.43 (1.38)
Adjusted* mean (SE)	7.39 (1.14)	7.61 (1.11)
95% confidence interval	(5.17, 9.62)	(5.43, 9.79)
Comparison vs Placebo		
Adjusted* mean (SE)		0.22 (1.59)
95% confidence interval		(-2.89, 3.33)
p-value		0.8914

* Model includes Age, baseline eGFR (CKD-EPI) as linear covariate(s) and region, baseline diabetes status, sex, baseline LVEF, week reachable, Visit by Treatment by baseline NYHA (2 cat.) interaction, baseline KCCQ physical limitation score by Visit interaction as fixed effect(s).
The Visit by Treatment by baseline NYHA (2 cat.) p-value at Week 52 is 0.3728.
The following covariance structure has been used to fit the mixed model: Unstructured
Note: All covariate effects are set equal to their mean values within subgroup for the calculation of adjusted means.

For patients who died, only observed values are considered (no imputation after date of death).
Data taken from study 1245.121 only.
The MMRM includes all outcome values (change from baseline) at the planned Visits week 12, week 32 and week 52

R.1.3.5.7

R.1.3.5.7 Subgroup analysis by diabetes at baseline

Table R.1.3.5.7: 1 KCCQ physical limitation score change from baseline at week 52 (MMRM) by diabetes at baseline - RS (OC-AD - no imputation for deaths) - 1245.121

Subgroup / Visit / Description / Statistic	Placebo	Empa 10mg
Diabetes at baseline (2 cat.):		
Diabetic		
Number of patients in analysis set	929	927
Number of analysed patients	861	865
Baseline mean (SE)	66.66 (0.85)	66.10 (0.87)
Week 52		
Values at visit		
Number of analysed patients	600	596
Mean (SE)	70.99 (1.01)	72.26 (1.02)
Adjusted* mean (SE)	68.98 (0.77)	71.11 (0.77)
95% confidence interval	(67.48,70.48)	(69.61,72.61)
Change from baseline		
Mean (SE)	2.61 (0.91)	3.94 (0.88)
Adjusted* mean (SE)	2.60 (0.77)	4.73 (0.77)
95% confidence interval	(1.10, 4.10)	(3.23, 6.23)
Comparison vs Placebo		
Adjusted* mean (SE)		2.13 (1.08)
95% confidence interval		(0.01, 4.25)
p-value		0.0493

* Model includes Age, baseline eGFR (CKD-EPI) as linear covariate(s) and region, sex, baseline LVEF, week reachable, Visit by Treatment by diabetes at baseline (2 cat.) interaction, baseline KCCQ physical limitation score by Visit interaction as fixed effect(s).
The Visit by Treatment by diabetes at baseline (2 cat.) p-value at Week 52 is 0.3520.
The following covariance structure has been used to fit the mixed model: Unstructured
Note: All covariate effects are set equal to their mean values within subgroup for the calculation of adjusted means.

For patients who died, only observed values are considered (no imputation after date of death).
Data taken from study 1245.121 only.
The MMRM includes all outcome values (change from baseline) at the planned Visits week 12, week 32 and week 52

Table R.1.3.5.7: 1 KCCQ physical limitation score change from baseline at week 52 (MMRM) by diabetes at baseline - RS (OC-AD - no imputation for deaths) - 1245.121

Subgroup / Visit / Description / Statistic	Placebo	Empa 10mg
Diabetes at baseline (2 cat.):		
Non-Diabetic		
Number of patients in analysis set	938	936
Number of analysed patients	880	888
Baseline mean (SE)	68.20 (0.82)	68.58 (0.80)
Week 52		
Values at visit		
Number of analysed patients	605	614
Mean (SE)	72.16 (0.99)	73.53 (0.97)
Adjusted* mean (SE)	71.77 (0.76)	72.48 (0.75)
95% confidence interval	(70.28,73.26)	(71.00,73.96)
Change from baseline		
Mean (SE)	3.71 (0.92)	3.74 (0.84)
Adjusted* mean (SE)	3.38 (0.76)	4.09 (0.75)
95% confidence interval	(1.89, 4.87)	(2.61, 5.57)
Comparison vs Placebo		
Adjusted* mean (SE)		0.71 (1.07)
95% confidence interval		(-1.39, 2.81)
p-value		0.5066

* Model includes Age, baseline eGFR (CKD-EPI) as linear covariate(s) and region, sex, baseline LVEF, week reachable, Visit by Treatment by diabetes at baseline (2 cat.) interaction, baseline KCCQ physical limitation score by Visit interaction as fixed effect(s).
The Visit by Treatment by diabetes at baseline (2 cat.) p-value at Week 52 is 0.3520.
The following covariance structure has been used to fit the mixed model: Unstructured
Note: All covariate effects are set equal to their mean values within subgroup for the calculation of adjusted means.

For patients who died, only observed values are considered (no imputation after date of death).
Data taken from study 1245.121 only.
The MMRM includes all outcome values (change from baseline) at the planned Visits week 12, week 32 and week 52

R.1.3.5.8 Subgroup analysis by BMI at baseline (<30, >=30)

Table R.1.3.5.8: 1 KCCQ physical limitation score change from baseline at week 52 (MMRM) by baseline BMI [kg/m2] - RS (OC-AD - no imputation for deaths) - 1245.121

Subgroup / Visit / Description / Statistic	Placebo	Empa 10mg
Baseline BMI [kg/m²] (2 cat.): <30		
Number of patients in analysis set	1300	1263
Number of analysed patients	1220	1188
Baseline mean (SE)	68.90 (0.70)	69.50 (0.72)
Week 52		
Values at visit		
Number of analysed patients	857	812
Mean (SE)	72.72 (0.82)	75.82 (0.82)
Adjusted* mean (SE)	71.57 (0.64)	73.81 (0.66)
95% confidence interval	(70.31,72.83)	(72.52,75.10)
Change from baseline		
Mean (SE)	2.82 (0.77)	4.08 (0.72)
Adjusted* mean (SE)	2.38 (0.64)	4.62 (0.66)
95% confidence interval	(1.12, 3.63)	(3.33, 5.91)
Comparison vs Placebo		
Adjusted* mean (SE)		2.24 (0.92)
95% confidence interval		(0.45, 4.04)
p-value		0.0144

* Model includes Age, baseline eGFR (CKD-EPI) as linear covariate(s) and region, baseline diabetes status, sex, baseline LVEF, week reachable, Visit by Treatment by baseline BMI [kg/m²] (2 cat.) interaction, baseline KCCQ physical limitation score by Visit interaction as fixed effect(s).
The Visit by Treatment by baseline BMI [kg/m²] (2 cat.) p-value at Week 52 is 0.1338.
The following covariance structure has been used to fit the mixed model: Unstructured
Note: All covariate effects are set equal to their mean values within subgroup for the calculation of adjusted means.

For patients who died, only observed values are considered (no imputation after date of death).
Data taken from study 1245.121 only.
The MMRM includes all outcome values (change from baseline) at the planned Visits week 12, week 32 and week 52

Table R.1.3.5.8: 1 KCCQ physical limitation score change from baseline at week 52 (MMRM) by baseline BMI [kg/m2] - RS (OC-AD - no imputation for deaths) - 1245.121

Subgroup / Visit / Description / Statistic	Placebo	Empa 10mg
Baseline BMI [kg/m²] (2 cat.): >=30		
Number of patients in analysis set	567	600
Number of analysed patients	521	565
Baseline mean (SE)	64.02 (1.07)	62.86 (1.02)
Week 52		
Values at visit		
Number of analysed patients	348	398
Mean (SE)	68.77 (1.39)	66.96 (1.29)
Adjusted* mean (SE)	67.76 (1.00)	67.53 (0.94)
95% confidence interval	(65.79,69.73)	(65.68,69.38)
Change from baseline		
Mean (SE)	4.01 (1.20)	3.33 (1.13)
Adjusted* mean (SE)	4.34 (1.00)	4.11 (0.94)
95% confidence interval	(2.37, 6.31)	(2.26, 5.97)
Comparison vs Placebo		
Adjusted* mean (SE)		-0.23 (1.37)
95% confidence interval		(-2.92, 2.46)
p-value		0.8669

* Model includes Age, baseline eGFR (CKD-EPI) as linear covariate(s) and region, baseline diabetes status, sex, baseline LVEF, week reachable, Visit by Treatment by baseline BMI [kg/m²] (2 cat.) interaction, baseline KCCQ physical limitation score by Visit interaction as fixed effect(s).
The Visit by Treatment by baseline BMI [kg/m²] (2 cat.) p-value at Week 52 is 0.1338.
The following covariance structure has been used to fit the mixed model: Unstructured
Note: All covariate effects are set equal to their mean values within subgroup for the calculation of adjusted means.

For patients who died, only observed values are considered (no imputation after date of death).
Data taken from study 1245.121 only.
The MMRM includes all outcome values (change from baseline) at the planned Visits week 12, week 32 and week 52

R.1.3.5.9 Subgroup analysis by eGFR at baseline (<60, >=60)

Table R.1.3.5.9: 1 KCCQ physical limitation score change from baseline at week 52 (MMRM) by baseline eGFR (2 cat.) - RS (OC-AD - no imputation for deaths) - 1245.121

Subgroup / Visit / Description / Statistic	Placebo	Empa 10mg
Baseline eGFR (CKD-EPI) [mL/min/1.73m²] (2 cat.): >=60		
Number of patients in analysis set	960	969
Number of analysed patients	896	909
Baseline mean (SE)	68.69 (0.82)	68.37 (0.83)
Week 52		
Values at visit		
Number of analysed patients	641	640
Mean (SE)	72.24 (0.96)	75.39 (0.99)
Adjusted* mean (SE)	71.12 (0.74)	74.03 (0.74)
95% confidence interval	(69.66,72.57)	(72.58,75.48)
Change from baseline		
Mean (SE)	2.76 (0.89)	5.36 (0.81)
Adjusted* mean (SE)	2.59 (0.74)	5.50 (0.74)
95% confidence interval	(1.13, 4.04)	(4.05, 6.95)
Comparison vs Placebo		
Adjusted* mean (SE)		2.91 (1.05)
95% confidence interval		(0.86, 4.97)
p-value		0.0054

* Model includes Age as linear covariate(s) and region, baseline diabetes status, sex, baseline LVEF, week reachable, Visit by Treatment by baseline eGFR (CKD-EPI) [mL/min/1.73m²] (2 cat.) interaction, baseline KCCQ physical limitation score by Visit interaction as fixed effect(s).
The Visit by Treatment by baseline eGFR (CKD-EPI) [mL/min/1.73m²] (2 cat.) p-value at Week 52 is 0.0346.
The following covariance structure has been used to fit the mixed model: Unstructured
2 patients were excluded as the subgroup variable was missing.
Note: All covariate effects are set equal to their mean values within subgroup for the calculation of adjusted means.

For patients who died, only observed values are considered (no imputation after date of death).
Data taken from study 1245.121 only.
The MMRM includes all outcome values (change from baseline) at the planned Visits week 12, week 32 and week 52

Table R.1.3.5.9: 1 KCCQ physical limitation score change from baseline at week 52 (MMRM) by baseline eGFR (2 cat.) - RS (OC-AD - no imputation for deaths) - 1245.121

Subgroup / Visit / Description / Statistic	Placebo	Empa 10mg
Baseline eGFR (CKD-EPI) [mL/min/1.73m²] (2 cat.): <60		
Number of patients in analysis set	906	893
Number of analysed patients	845	844
Baseline mean (SE)	66.11 (0.85)	66.26 (0.84)
Week 52		
Values at visit		
Number of analysed patients	564	570
Mean (SE)	70.83 (1.04)	70.12 (0.99)
Adjusted* mean (SE)	69.68 (0.79)	69.37 (0.78)
95% confidence interval	(68.14,71.22)	(67.84,70.91)
Change from baseline		
Mean (SE)	3.62 (0.95)	2.13 (0.91)
Adjusted* mean (SE)	3.49 (0.79)	3.19 (0.78)
95% confidence interval	(1.95, 5.04)	(1.65, 4.72)
Comparison vs Placebo		
Adjusted* mean (SE)		-0.31 (1.11)
95% confidence interval		(-2.48, 1.86)
p-value		0.7803

* Model includes Age as linear covariate(s) and region, baseline diabetes status, sex, baseline LVEF, week reachable, Visit by Treatment by baseline eGFR (CKD-EPI) [mL/min/1.73m²] (2 cat.) interaction, baseline KCCQ physical limitation score by Visit interaction as fixed effect(s).
The Visit by Treatment by baseline eGFR (CKD-EPI) [mL/min/1.73m²] (2 cat.) p-value at Week 52 is 0.0346.
The following covariance structure has been used to fit the mixed model: Unstructured
2 patients were excluded as the subgroup variable was missing.
Note: All covariate effects are set equal to their mean values within subgroup for the calculation of adjusted means.

For patients who died, only observed values are considered (no imputation after date of death).
Data taken from study 1245.121 only.
The MMRM includes all outcome values (change from baseline) at the planned Visits week 12, week 32 and week 52

R.1.3.5.10

Table R.1.3.5.10: 1 KCCQ physical limitation score change from baseline at week 52 (MMRM) by history of HHF - RS (OC-AD - no imputation for deaths) - 1245.121

Subgroup / Visit / Description / Statistic	Placebo	Empa 10mg
History of HHF (in the last 12 months): No		
Number of patients in analysis set	1293	1286
Number of analysed patients	1210	1219
Baseline mean (SE)	67.63 (0.70)	67.14 (0.71)
Week 52		
Values at visit		
Number of analysed patients	858	851
Mean (SE)	70.51 (0.85)	72.63 (0.84)
Adjusted* mean (SE)	69.88 (0.64)	71.70 (0.64)
95% confidence interval	(68.63,71.14)	(70.44,72.96)
Change from baseline		
Mean (SE)	2.58 (0.76)	3.71 (0.75)
Adjusted* mean (SE)	2.50 (0.64)	4.31 (0.64)
95% confidence interval	(1.24, 3.76)	(3.05, 5.57)
Comparison vs Placebo		
Adjusted* mean (SE)		1.81 (0.91)
95% confidence interval		(0.04, 3.59)
p-value		0.0455

* Model includes Age, baseline eGFR (CKD-EPI) as linear covariate(s) and region, baseline diabetes status, sex, baseline LVEF, week reachable, Visit by Treatment by history of HHF (in the last 12 months) interaction, baseline KCCQ physical limitation score by Visit interaction as fixed effect(s).
The Visit by Treatment by history of HHF (in the last 12 months) p-value at Week 52 is 0.3903.
The following covariance structure has been used to fit the mixed model: Unstructured
Note: All covariate effects are set equal to their mean values within subgroup for the calculation of adjusted means.

For patients who died, only observed values are considered (no imputation after date of death).
Data taken from study 1245.121 only.
The MMRM includes all outcome values (change from baseline) at the planned Visits week 12, week 32 and week 52

Table R.1.3.5.10: 1 KCCQ physical limitation score change from baseline at week 52 (MMRM) by history of HHF - RS (OC-AD - no imputation for deaths) - 1245.121

Subgroup / Visit / Description / Statistic	Placebo	Empa 10mg
History of HHF (in the last 12 months): Yes		
Number of patients in analysis set	574	577
Number of analysed patients	531	534
Baseline mean (SE)	67.00 (1.09)	67.84 (1.07)
Week 52		
Values at visit		
Number of analysed patients	347	359
Mean (SE)	74.22 (1.24)	73.56 (1.29)
Adjusted* mean (SE)	71.67 (1.00)	72.05 (0.99)
95% confidence interval	(69.71,73.63)	(70.11,73.99)
Change from baseline		
Mean (SE)	4.60 (1.22)	4.14 (1.01)
Adjusted* mean (SE)	4.25 (1.00)	4.63 (0.99)
95% confidence interval	(2.28, 6.21)	(2.69, 6.56)
Comparison vs Placebo		
Adjusted* mean (SE)		0.38 (1.40)
95% confidence interval		(-2.37, 3.13)
p-value		0.7865

* Model includes Age, baseline eGFR (CKD-EPI) as linear covariate(s) and region, baseline diabetes status, sex, baseline LVEF, week reachable, Visit by Treatment by history of HHF (in the last 12 months) interaction, baseline KCCQ physical limitation score by Visit interaction as fixed effect(s).
The Visit by Treatment by history of HHF (in the last 12 months) p-value at Week 52 is 0.3903.
The following covariance structure has been used to fit the mixed model: Unstructured
Note: All covariate effects are set equal to their mean values within subgroup for the calculation of adjusted means.

For patients who died, only observed values are considered (no imputation after date of death).
Data taken from study 1245.121 only.
The MMRM includes all outcome values (change from baseline) at the planned Visits week 12, week 32 and week 52

R.1.3.5.11

Table R.1.3.5.11: 1 KCCQ physical limitation score change from baseline at week 52 (MMRM) by cause of heart failure - RS (OC-AD - no imputation for deaths) - 1245.121

Subgroup / Visit / Description / Statistic	Placebo	Empa 10mg
Cause of heart failure: Ischemic		
Number of patients in analysis set	946	983
Number of analysed patients	889	920
Baseline mean (SE)	67.04 (0.83)	66.49 (0.81)
Week 52		
Values at visit		
Number of analysed patients	627	642
Mean (SE)	71.40 (1.00)	71.98 (0.98)
Adjusted* mean (SE)	70.05 (0.75)	70.75 (0.74)
95% confidence interval	(68.57,71.53)	(69.30,72.21)
Change from baseline		
Mean (SE)	2.93 (0.86)	3.22 (0.83)
Adjusted* mean (SE)	3.29 (0.75)	3.99 (0.74)
95% confidence interval	(1.81, 4.77)	(2.54, 5.45)
Comparison vs Placebo		
Adjusted* mean (SE)		0.70 (1.05)
95% confidence interval		(-1.36, 2.77)
p-value		0.5033

* Model includes Age, baseline eGFR (CKD-EPI) as linear covariate(s) and region, baseline diabetes status, sex, baseline LVEF, week reachable, Visit by Treatment by cause of heart failure interaction, baseline KCCQ physical limitation score by Visit interaction as fixed effect(s).
The Visit by Treatment by cause of heart failure p-value at Week 52 is 0.3289.
The following covariance structure has been used to fit the mixed model: Unstructured
Note: All covariate effects are set equal to their mean values within subgroup for the calculation of adjusted means.

For patients who died, only observed values are considered (no imputation after date of death).
Data taken from study 1245.121 only.
The MMRM includes all outcome values (change from baseline) at the planned Visits week 12, week 32 and week 52

Table R.1.3.5.11: 1 KCCQ physical limitation score change from baseline at week 52 (MMRM) by cause of heart failure - RS (OC-AD - no imputation for deaths) - 1245.121

Subgroup / Visit / Description / Statistic	Placebo	Empa 10mg
Cause of heart failure: Non-ischemic		
Number of patients in analysis set	921	880
Number of analysed patients	852	833
Baseline mean (SE)	67.86 (0.84)	68.31 (0.86)
Week 52		
Values at visit		
Number of analysed patients	578	568
Mean (SE)	71.77 (1.01)	73.95 (1.01)
Adjusted* mean (SE)	70.76 (0.78)	72.95 (0.79)
95% confidence interval	(69.22,72.29)	(71.41,74.49)
Change from baseline		
Mean (SE)	3.41 (0.97)	4.54 (0.90)
Adjusted* mean (SE)	2.67 (0.78)	4.87 (0.79)
95% confidence interval	(1.14, 4.21)	(3.33, 6.41)
Comparison vs Placebo		
Adjusted* mean (SE)		2.19 (1.10)
95% confidence interval		(0.03, 4.36)
p-value		0.0469

* Model includes Age, baseline eGFR (CKD-EPI) as linear covariate(s) and region, baseline diabetes status, sex, baseline LVEF, week reachable, Visit by Treatment by cause of heart failure interaction, baseline KCCQ physical limitation score by Visit interaction as fixed effect(s).
The Visit by Treatment by cause of heart failure p-value at Week 52 is 0.3289.
The following covariance structure has been used to fit the mixed model: Unstructured
Note: All covariate effects are set equal to their mean values within subgroup for the calculation of adjusted means.

For patients who died, only observed values are considered (no imputation after date of death).
Data taken from study 1245.121 only.
The MMRM includes all outcome values (change from baseline) at the planned Visits week 12, week 32 and week 52

R.1.3.5.12

R.1.3.5.12 Subgroup analysis by heart failure physiology (LVEF <= 30% and NTproBNP<median; LVEF <= 30% and NTproBNP>=median; LVEF > 30%)

Table R.1.3.5.12: 1 KCCQ physical limitation score change from baseline at week 52 (MMRM) by heart failure physiology - RS (OC-AD - no imputation for deaths) - 1245.121

Subgroup / Visit / Description / Statistic	Placebo	Empa 10mg
Heart failure physiology: LVEF <= 30% and NTproBNP < median		
Number of patients in analysis set	723	698
Number of analysed patients	690	666
Baseline mean (SE)	69.19 (0.91)	68.98 (0.95)
Week 52		
Values at visit		
Number of analysed patients	506	482
Mean (SE)	73.30 (1.04)	74.91 (1.08)
Adjusted* mean (SE)	72.68 (0.83)	74.65 (0.85)
95% confidence interval	(71.04,74.32)	(72.98,76.32)
Change from baseline		
Mean (SE)	4.24 (0.89)	5.00 (0.88)
Adjusted* mean (SE)	3.59 (0.83)	5.56 (0.85)
95% confidence interval	(1.96, 5.23)	(3.89, 7.24)
Comparison vs Placebo		
Adjusted* mean (SE)		1.97 (1.19)
95% confidence interval		(-0.37, 4.31)
p-value		0.0989

* Model includes Age, baseline eGFR (CKD-EPI) as linear covariate(s) and region, baseline diabetes status, sex, week reachable, Visit by Treatment by heart failure physiology interaction, baseline KCCQ physical limitation score by Visit interaction as fixed effect(s).
The Visit by Treatment by heart failure physiology p-value at Week 52 is 0.4566.
The following covariance structure has been used to fit the mixed model: Unstructured
16 patients were excluded as the subgroup variable was missing.
Note: All covariate effects are set equal to their mean values within subgroup for the calculation of adjusted means.
The p-value for the visit by treatment by subgroup interaction trend test at Week 52 is 0.3391

For patients who died, only observed values are considered (no imputation after date of death).
Data taken from study 1245.121 only.
NTproBNP median [pg/mL]: with a. fibrillation/flutter at baseline: 2265; without a. fibrillation/flutter at baseline: 1671.
The MMRM includes all outcome values (change from baseline) at the planned Visits week 12, week 32 and week 52

Table R.1.3.5.12: 1 KCCQ physical limitation score change from baseline at week 52 (MMRM) by heart failure physiology - RS (OC-AD - no imputation for deaths) - 1245.121

Subgroup Visit Description Statistic	Placebo	Empa 10mg
Heart failure physiology: LVEF <= 30% and NTproBNP >= median		
Number of patients in analysis set	661	631
Number of analysed patients	600	587
Baseline mean (SE)	64.52 (1.03)	64.87 (1.00)
Week 52		
Values at visit		
Number of analysed patients	404	396
Mean (SE)	68.58 (1.29)	70.67 (1.27)
Adjusted* mean (SE)	66.89 (0.93)	68.94 (0.94)
95% confidence interval	(65.07,68.71)	(67.10,70.77)
Change from baseline		
Mean (SE)	2.21 (1.25)	3.71 (1.12)
Adjusted* mean (SE)	2.19 (0.93)	4.24 (0.94)
95% confidence interval	(0.37, 4.01)	(2.40, 6.08)
Comparison vs Placebo		
Adjusted* mean (SE)		2.05 (1.32)
95% confidence interval		(-0.54, 4.63)
p-value		0.1205

* Model includes Age, baseline eGFR (CKD-EPI) as linear covariate(s) and region, baseline diabetes status, sex, week reachable, Visit by Treatment by heart failure physiology interaction, baseline KCCQ physical limitation score by Visit interaction as fixed effect(s).
The Visit by Treatment by heart failure physiology p-value at Week 52 is 0.4566.
The following covariance structure has been used to fit the mixed model: Unstructured
16 patients were excluded as the subgroup variable was missing.
Note: All covariate effects are set equal to their mean values within subgroup for the calculation of adjusted means.
The p-value for the visit by treatment by subgroup interaction trend test at Week 52 is 0.3391

For patients who died, only observed values are considered (no imputation after date of death).
Data taken from study 1245.121 only.
NTproBNP median [pg/mL]: with a. fibrillation/flutter at baseline: 2265; without a. fibrillation/flutter at baseline: 1671.
The MMRM includes all outcome values (change from baseline) at the planned Visits week 12, week 32 and week 52

Table R.1.3.5.12: 1 KCCQ physical limitation score change from baseline at week 52 (MMRM) by heart failure physiology - RS (OC-AD - no imputation for deaths) - 1245.121

Subgroup / Visit / Description / Statistic	Placebo	Empa 10mg
Heart failure physiology: LVEF > 30%		
Number of patients in analysis set	475	526
Number of analysed patients	446	495
Baseline mean (SE)	68.80 (1.17)	68.09 (1.15)
Week 52		
Values at visit		
Number of analysed patients	291	331
Mean (SE)	72.78 (1.43)	72.63 (1.35)
Adjusted* mean (SE)	71.50 (1.09)	71.34 (1.02)
95% confidence interval	(69.37,73.64)	(69.33,73.34)
Change from baseline		
Mean (SE)	2.56 (1.32)	2.34 (1.22)
Adjusted* mean (SE)	3.08 (1.09)	2.91 (1.02)
95% confidence interval	(0.94, 5.21)	(0.91, 4.92)
Comparison vs Placebo		
Adjusted* mean (SE)		-0.17 (1.49)
95% confidence interval		(-3.09, 2.76)
p-value		0.9113

* Model includes Age, baseline eGFR (CKD-EPI) as linear covariate(s) and region, baseline diabetes status, sex, week reachable, Visit by Treatment by heart failure physiology interaction, baseline KCCQ physical limitation score by Visit interaction as fixed effect(s).
The Visit by Treatment by heart failure physiology p-value at Week 52 is 0.4566.
The following covariance structure has been used to fit the mixed model: Unstructured
16 patients were excluded as the subgroup variable was missing.
Note: All covariate effects are set equal to their mean values within subgroup for the calculation of adjusted means.
The p-value for the visit by treatment by subgroup interaction trend test at Week 52 is 0.3391

For patients who died, only observed values are considered (no imputation after date of death).
Data taken from study 1245.121 only.
NTproBNP median [pg/mL]: with a. fibrillation/flutter at baseline: 2265; without a. fibrillation/flutter at baseline: 1671.
The MMRM includes all outcome values (change from baseline) at the planned Visits week 12, week 32 and week 52

R.1.3.5.13

Table R.1.3.5.13: 1 KCCQ physical limitation score change from baseline at week 52 (MMRM) by baseline use of MRA (Y/N) – RS (OC-AD - no imputation for deaths) - 1245.121

Subgroup / Visit / Description / Statistic	Placebo	Empa 10mg
Baseline use of MRA: No		
Number of patients in analysis set	512	557
Number of analysed patients	481	522
Baseline mean (SE)	68.34 (1.09)	69.00 (1.08)
Week 52		
Values at visit		
Number of analysed patients	338	372
Mean (SE)	69.94 (1.35)	73.82 (1.28)
Adjusted* mean (SE)	70.19 (1.02)	71.72 (0.98)
95% confidence interval	(68.19,72.20)	(69.80,73.64)
Change from baseline		
Mean (SE)	2.01 (1.21)	2.28 (1.13)
Adjusted* mean (SE)	1.51 (1.02)	3.03 (0.98)
95% confidence interval	(-0.50, 3.51)	(1.11, 4.95)
Comparison vs Placebo		
Adjusted* mean (SE)		1.52 (1.41)
95% confidence interval		(-1.24, 4.29)
p-value		0.2798

* Model includes Age, baseline eGFR (CKD-EPI) as linear covariate(s) and region, baseline diabetes status, sex, baseline LVEF, week reachable, Visit by Treatment by baseline use of MRA interaction, baseline KCCQ physical limitation score by Visit interaction as fixed effect(s).
The Visit by Treatment by baseline use of MRA p-value at Week 52 is 0.9342.
The following covariance structure has been used to fit the mixed model: Unstructured
Note: All covariate effects are set equal to their mean values within subgroup for the calculation of adjusted means.

For patients who died, only observed values are considered (no imputation after date of death).
Data taken from study 1245.121 only.
The MMRM includes all outcome values (change from baseline) at the planned Visits week 12, week 32 and week 52

Table R.1.3.5.13: 1 KCCQ physical limitation score change from baseline at week 52 (MMRM) by baseline use of MRA (Y/N) - RS (OC-AD - no imputation for deaths) - 1245.121

Subgroup / Visit / Description / Statistic	Placebo	Empa 10mg
Baseline use of MRA: Yes		
Number of patients in analysis set	1355	1306
Number of analysed patients	1260	1231
Baseline mean (SE)	67.09 (0.70)	66.66 (0.71)
Week 52		
Values at visit		
Number of analysed patients	867	838
Mean (SE)	72.21 (0.83)	72.50 (0.84)
Adjusted* mean (SE)	70.46 (0.64)	71.85 (0.65)
95% confidence interval	(69.22,71.71)	(70.58,73.12)
Change from baseline		
Mean (SE)	3.61 (0.76)	4.53 (0.72)
Adjusted* mean (SE)	3.59 (0.64)	4.97 (0.65)
95% confidence interval	(2.34, 4.84)	(3.71, 6.24)
Comparison vs Placebo		
Adjusted* mean (SE)		1.39 (0.91)
95% confidence interval		(-0.39, 3.16)
p-value		0.1261

* Model includes Age, baseline eGFR (CKD-EPI) as linear covariate(s) and region, baseline diabetes status, sex, baseline LVEF, week reachable, Visit by Treatment by baseline use of MRA interaction, baseline KCCQ physical limitation score by Visit interaction as fixed effect(s).
The Visit by Treatment by baseline use of MRA p-value at Week 52 is 0.9342.
The following covariance structure has been used to fit the mixed model: Unstructured
Note: All covariate effects are set equal to their mean values within subgroup for the calculation of adjusted means.

For patients who died, only observed values are considered (no imputation after date of death).
Data taken from study 1245.121 only.
The MMRM includes all outcome values (change from baseline) at the planned Visits week 12, week 32 and week 52

R.1.3.5.14

Table R.1.3.5.14: 1 KCCQ physical limitation score change from baseline at week 52 (MMRM) by baseline use of ARNi (Y/N) - RS (OC-AD - no imputation for deaths) - 1245.121

Subgroup / Visit / Description / Statistic	Placebo	Empa 10mg
Baseline use of ARNi: No		
Number of patients in analysis set	1480	1523
Number of analysed patients	1382	1432
Baseline mean (SE)	67.24 (0.66)	67.08 (0.66)
Week 52		
Values at visit		
Number of analysed patients	951	1005
Mean (SE)	71.07 (0.80)	72.44 (0.78)
Adjusted* mean (SE)	69.75 (0.61)	71.27 (0.59)
95% confidence interval	(68.56,70.94)	(70.11,72.43)
Change from baseline		
Mean (SE)	2.98 (0.73)	3.72 (0.66)
Adjusted* mean (SE)	2.59 (0.61)	4.12 (0.59)
95% confidence interval	(1.40, 3.78)	(2.96, 5.28)
Comparison vs Placebo		
Adjusted* mean (SE)		1.52 (0.85)
95% confidence interval		(-0.14, 3.18)
p-value		0.0721

* Model includes Age, baseline eGFR (CKD-EPI) as linear covariate(s) and region, baseline diabetes status, sex, baseline LVEF, week reachable, Visit by Treatment by baseline use of ARNi interaction, baseline KCCQ physical limitation score by Visit interaction as fixed effect(s).
The Visit by Treatment by baseline use of ARNi p-value at Week 52 is 0.9198.
The following covariance structure has been used to fit the mixed model: Unstructured
Note: All covariate effects are set equal to their mean values within subgroup for the calculation of adjusted means.

For patients who died, only observed values are considered (no imputation after date of death).
Data taken from study 1245.121 only.
The MMRM includes all outcome values (change from baseline) at the planned Visits week 12, week 32 and week 52

Table R.1.3.5.14: 1 KCCQ physical limitation score change from baseline at week 52 (MMRM) by baseline use of ARNi (Y/N) - RS (OC-AD - no imputation for deaths) - 1245.121

Subgroup / Visit / Description / Statistic	Placebo	Empa 10mg
Baseline use of ARNi: Yes		
Number of patients in analysis set	387	340
Number of analysed patients	359	321
Baseline mean (SE)	68.21 (1.33)	68.60 (1.38)
Week 52		
Values at visit		
Number of analysed patients	254	205
Mean (SE)	73.47 (1.52)	75.20 (1.63)
Adjusted* mean (SE)	72.90 (1.18)	74.23 (1.30)
95% confidence interval	(70.58,75.22)	(71.68,76.78)
Change from baseline		
Mean (SE)	3.86 (1.38)	4.39 (1.50)
Adjusted* mean (SE)	4.51 (1.18)	5.83 (1.30)
95% confidence interval	(2.19, 6.83)	(3.28, 8.38)
Comparison vs Placebo		
Adjusted* mean (SE)		1.33 (1.75)
95% confidence interval		(-2.11, 4.76)
p-value		0.4486

* Model includes Age, baseline eGFR (CKD-EPI) as linear covariate(s) and region, baseline diabetes status, sex, baseline LVEF, week reachable, Visit by Treatment by baseline use of ARNi interaction, baseline KCCQ physical limitation score by Visit interaction as fixed effect(s).
The Visit by Treatment by baseline use of ARNi p-value at Week 52 is 0.9198.
The following covariance structure has been used to fit the mixed model: Unstructured
Note: All covariate effects are set equal to their mean values within subgroup for the calculation of adjusted means.

For patients who died, only observed values are considered (no imputation after date of death).
Data taken from study 1245.121 only.
The MMRM includes all outcome values (change from baseline) at the planned Visits week 12, week 32 and week 52

R.1.3.5.15 Subgroup analysis by bl. LVEF (<= 30%, >30% -<= 35% , > 35%)

Table R.1.3.5.15: 1 KCCQ physical limitation score change from baseline at week 52 (MMRM) by baseline LVEF (3 cat.) - RS (OC-AD - no imputation for deaths) - 1245.121

Subgroup / Visit / Description / Statistic	Placebo	Empa 10mg
Baseline LVEF (3 cat.): <=30		
Number of patients in analysis set	1392	1337
Number of analysed patients	1295	1258
Baseline mean (SE)	66.97 (0.68)	67.07 (0.69)
Week 52		
Values at visit		
Number of analysed patients	914	879
Mean (SE)	71.19 (0.81)	73.01 (0.83)
Adjusted* mean (SE)	70.04 (0.62)	71.97 (0.63)
95% confidence interval	(68.82,71.26)	(70.73,73.21)
Change from baseline		
Mean (SE)	3.36 (0.74)	4.40 (0.70)
Adjusted* mean (SE)	3.02 (0.62)	4.95 (0.63)
95% confidence interval	(1.80, 4.24)	(3.71, 6.19)
Comparison vs Placebo		
Adjusted* mean (SE)		1.93 (0.88)
95% confidence interval		(0.19, 3.66)
p-value		0.0293

* Model includes Age, baseline eGFR (CKD-EPI) as linear covariate(s) and region, baseline diabetes status, sex, week reachable, Visit by Treatment by baseline LVEF (3 cat.) interaction, baseline KCCQ physical limitation score by Visit interaction as fixed effect(s).
The Visit by Treatment by baseline LVEF (3 cat.) p-value at Week 52 is 0.0471.
The following covariance structure has been used to fit the mixed model: Unstructured
Note: All covariate effects are set equal to their mean values within subgroup for the calculation of adjusted means.
The p-value for the visit by treatment by subgroup interaction trend test at Week 52 is 0.7253

For patients who died, only observed values are considered (no imputation after date of death).
Data taken from study 1245.121 only.
The MMRM includes all outcome values (change from baseline) at the planned Visits week 12, week 32 and week 52

Table R.1.3.5.15: 1 KCCQ physical limitation score change from baseline at week 52 (MMRM) by baseline LVEF (3 cat.) - RS (OC-AD - no imputation for deaths) - 1245.121

Subgroup / Visit / Description / Statistic	Placebo	Empa 10mg
Baseline LVEF (3 cat.): >30 to <=35		
Number of patients in analysis set	361	398
Number of analysed patients	340	375
Baseline mean (SE)	68.75 (1.33)	68.00 (1.31)
Week 52		
Values at visit		
Number of analysed patients	231	248
Mean (SE)	74.29 (1.52)	71.73 (1.59)
Adjusted* mean (SE)	72.75 (1.23)	70.85 (1.18)
95% confidence interval	(70.34,75.16)	(68.54,73.17)
Change from baseline		
Mean (SE)	3.44 (1.44)	1.67 (1.41)
Adjusted* mean (SE)	4.39 (1.23)	2.49 (1.18)
95% confidence interval	(1.98, 6.80)	(0.18, 4.81)
Comparison vs Placebo		
Adjusted* mean (SE)		-1.90 (1.70)
95% confidence interval		(-5.24, 1.44)
p-value		0.2644

* Model includes Age, baseline eGFR (CKD-EPI) as linear covariate(s) and region, baseline diabetes status, sex, week reachable, Visit by Treatment by baseline LVEF (3 cat.) interaction, baseline KCCQ physical limitation score by Visit interaction as fixed effect(s).
The Visit by Treatment by baseline LVEF (3 cat.) p-value at Week 52 is 0.0471.
The following covariance structure has been used to fit the mixed model: Unstructured
Note: All covariate effects are set equal to their mean values within subgroup for the calculation of adjusted means.
The p-value for the visit by treatment by subgroup interaction trend test at Week 52 is 0.7253

For patients who died, only observed values are considered (no imputation after date of death).
Data taken from study 1245.121 only.
The MMRM includes all outcome values (change from baseline) at the planned Visits week 12, week 32 and week 52

Table R.1.3.5.15: 1 KCCQ physical limitation score change from baseline at week 52 (MMRM) by baseline LVEF (3 cat.) - RS (OC-AD - no imputation for deaths) - 1245.121

Subgroup / Visit / Description / Statistic	Placebo	Empa 10mg
Baseline LVEF (3 cat.): >35		
Number of patients in analysis set	114	128
Number of analysed patients	106	120
Baseline mean (SE)	68.94 (2.49)	68.35 (2.40)
Week 52		
Values at visit		
Number of analysed patients	60	83
Mean (SE)	66.94 (3.61)	75.33 (2.56)
Adjusted* mean (SE)	66.90 (2.37)	72.74 (2.06)
95% confidence interval	(62.24,71.55)	(68.71,76.77)
Change from baseline		
Mean (SE)	-0.83 (3.21)	4.34 (2.41)
Adjusted* mean (SE)	-1.73 (2.37)	4.11 (2.06)
95% confidence interval	(-6.38, 2.92)	(0.08, 8.14)
Comparison vs Placebo		
Adjusted* mean (SE)		5.84 (3.14)
95% confidence interval		(-0.31,11.99)
p-value		0.0628

* Model includes Age, baseline eGFR (CKD-EPI) as linear covariate(s) and region, baseline diabetes status, sex, week reachable, Visit by Treatment by baseline LVEF (3 cat.) interaction, baseline KCCQ physical limitation score by Visit interaction as fixed effect(s).
The Visit by Treatment by baseline LVEF (3 cat.) p-value at Week 52 is 0.0471.
The following covariance structure has been used to fit the mixed model: Unstructured
Note: All covariate effects are set equal to their mean values within subgroup for the calculation of adjusted means.
The p-value for the visit by treatment by subgroup interaction trend test at Week 52 is 0.7253

For patients who died, only observed values are considered (no imputation after date of death).
Data taken from study 1245.121 only.
The MMRM includes all outcome values (change from baseline) at the planned Visits week 12, week 32 and week 52

R.1.3.5.16

R.1.3.5.16 Subgroup analysis by bl. NTproBNP </>= median (median based on total patients)

Table R.1.3.5.16: 1 KCCQ physical limitation score change from baseline at week 52 (MMRM) by bl. NTproBNP (<median, >= median) (median based on total patients) - RS (OC-AD - no imputation for deaths) - 1245.121

Subgroup / Visit / Description / Statistic	Placebo	Empa 10mg
Baseline NTproBNP (<median, >= median): < median		
Number of patients in analysis set	920	942
Number of analysed patients	880	903
Baseline mean (SE)	70.21 (0.79)	69.87 (0.80)
Week 52		
Values at visit		
Number of analysed patients	644	654
Mean (SE)	73.37 (0.93)	74.98 (0.92)
Adjusted* mean (SE)	72.98 (0.74)	74.76 (0.73)
95% confidence interval	(71.53,74.44)	(73.32,76.20)
Change from baseline		
Mean (SE)	3.32 (0.78)	4.19 (0.76)
Adjusted* mean (SE)	2.95 (0.74)	4.73 (0.73)
95% confidence interval	(1.49, 4.40)	(3.29, 6.16)
Comparison vs Placebo		
Adjusted* mean (SE)		1.78 (1.04)
95% confidence interval		(-0.26, 3.82)
p-value		0.0879

* Model includes Age, baseline eGFR (CKD-EPI) as linear covariate(s) and region, baseline diabetes status, sex, baseline LVEF, week reachable, Visit by Treatment by baseline NTproBNP (<median, >= median) interaction, baseline KCCQ physical limitation score by Visit interaction as fixed effect(s). The Visit by Treatment by baseline NTproBNP (<median, >= median) p-value at Week 52 is 0.5638.
The following covariance structure has been used to fit the mixed model: Unstructured
2 patients were excluded as the subgroup variable was missing.
Note: All covariate effects are set equal to their mean values within subgroup for the calculation of adjusted means.

For patients who died, only observed values are considered (no imputation after date of death).
Data taken from study 1245.121 only.
Median: 1910 [pg/mL]
The MMRM includes all outcome values (change from baseline) at the planned Visits week 12, week 32 and week 52

Table R.1.3.5.16: 1 KCCQ physical limitation score change from baseline at week 52 (MMRM) by bl. NTproBNP (<median, >= median) (median based on total patients) - RS (OC-AD - no imputation for deaths) - 1245.121

Subgroup / Visit / Description / Statistic	Placebo	Empa 10mg
Baseline NTproBNP (<median, >= median): >= median		
Number of patients in analysis set	946	920
Number of analysed patients	861	850
Baseline mean (SE)	64.61 (0.86)	64.69 (0.87)
Week 52		
Values at visit		
Number of analysed patients	561	556
Mean (SE)	69.51 (1.08)	70.47 (1.08)
Adjusted* mean (SE)	67.70 (0.79)	68.60 (0.79)
95% confidence interval	(66.16,69.24)	(67.05,70.15)
Change from baseline		
Mean (SE)	2.98 (1.06)	3.42 (0.97)
Adjusted* mean (SE)	3.05 (0.79)	3.95 (0.79)
95% confidence interval	(1.51, 4.59)	(2.40, 5.51)
Comparison vs Placebo		
Adjusted* mean (SE)		0.90 (1.11)
95% confidence interval		(-1.28, 3.08)
p-value		0.4190

* Model includes Age, baseline eGFR (CKD-EPI) as linear covariate(s) and region, baseline diabetes status, sex, baseline LVEF, week reachable, Visit by Treatment by baseline NTproBNP (<median, >= median) interaction, baseline KCCQ physical limitation score by Visit interaction as fixed effect(s). The Visit by Treatment by baseline NTproBNP (<median, >= median) p-value at Week 52 is 0.5638.
The following covariance structure has been used to fit the mixed model: Unstructured
2 patients were excluded as the subgroup variable was missing.
Note: All covariate effects are set equal to their mean values within subgroup for the calculation of adjusted means.

For patients who died, only observed values are considered (no imputation after date of death).
Data taken from study 1245.121 only.
Median: 1910 [pg/mL]
The MMRM includes all outcome values (change from baseline) at the planned Visits week 12, week 32 and week 52

R.1.3.6 KCCQ symptom stability score MMRM analysis

R.1.3.6.1

Table R.1.3.6.1: 1 KCCQ symptom stability score change from baseline MMRM results over time - RS (OC-AD - no imputation for deaths) - 1245.121

Visit Description Statistic	Placebo	Empa 10mg
Number of patients in analysis set	1867	1863
Number of analysed patients	1752	1776
Baseline mean (SE)	55.79 (0.45)	55.43 (0.45)
Week 12		
Values at visit		
Number of analysed patients	1730	1755
Mean (SE)	58.93 (0.51)	60.37 (0.52)
Adjusted* mean (SE)	58.86 (0.50)	60.42 (0.50)
95% confidence interval	(57.88,59.84)	(59.45,61.40)
Change from baseline		
Mean (SE)	3.09 (0.62)	4.87 (0.62)
Adjusted* mean (SE)	3.22 (0.50)	4.78 (0.50)
95% confidence interval	(2.24, 4.20)	(3.81, 5.76)
Comparison vs Placebo		
Adjusted* mean (SE)		1.56 (0.70)
95% confidence interval		(0.18, 2.94)
p-value		0.0264
Hedges g		
Estimate		0.08
95% confidence interval		(0.01, 0.14)

* Model includes Age (p=0.0045), baseline eGFR (CKD-EPI) (p=0.0422) as linear covariate(s) and region (p<0.0001), baseline diabetes status (p=0.0049), sex (p=0.1759), baseline LVEF (p=0.5881), week reachable (p=0.2964), Treatment by Visit interaction (p=0.1260), baseline KCCQ symptom stability score by Visit interaction (p<0.0001) as fixed effect(s).
The following covariance structure has been used to fit the mixed model: Unstructured

For patients who died, only observed values are considered (no imputation after date of death).
Data taken from study 1245.121 only.

Table R.1.3.6.1: 1 KCCQ symptom stability score change from baseline MMRM results over time - RS (OC-AD - no imputation for deaths) - 1245.121

Visit Description Statistic	Placebo	Empa 10mg
Week 32		
Values at visit		
Number of analysed patients	1567	1616
Mean (SE)	57.13 (0.54)	57.29 (0.51)
Adjusted* mean (SE)	57.11 (0.51)	57.29 (0.50)
95% confidence interval	(56.12,58.11)	(56.31,58.27)
Change from baseline		
Mean (SE)	1.40 (0.64)	1.92 (0.64)
Adjusted* mean (SE)	1.47 (0.51)	1.65 (0.50)
95% confidence interval	(0.48, 2.47)	(0.67, 2.63)
Comparison vs Placebo		
Adjusted* mean (SE)		0.18 (0.71)
95% confidence interval		(-1.22, 1.58)
p-value		0.8027
Week 52		
Values at visit		
Number of analysed patients	1217	1239
Mean (SE)	56.49 (0.58)	55.89 (0.57)
Adjusted* mean (SE)	56.36 (0.56)	55.88 (0.55)
95% confidence interval	(55.27,57.45)	(54.80,56.97)
Change from baseline		
Mean (SE)	0.49 (0.71)	0.42 (0.70)
Adjusted* mean (SE)	0.72 (0.56)	0.24 (0.55)
95% confidence interval	(-0.38, 1.81)	(-0.84, 1.32)
Comparison vs Placebo		
Adjusted* mean (SE)		-0.48 (0.78)
95% confidence interval		(-2.01, 1.06)
p-value		0.5430

* Model includes Age (p=0.0045), baseline eGFR (CKD-EPI) (p=0.0422) as linear covariate(s) and region (p<0.0001), baseline diabetes status (p=0.0049), sex (p=0.1759), baseline LVEF (p=0.5881), week reachable (p=0.2964), Treatment by Visit interaction (p=0.1260), baseline KCCQ symptom stability score by Visit interaction (p<0.0001) as fixed effect(s).
The following covariance structure has been used to fit the mixed model: Unstructured

For patients who died, only observed values are considered (no imputation after date of death).
Data taken from study 1245.121 only.

Figure R.1.3.6.1: 1

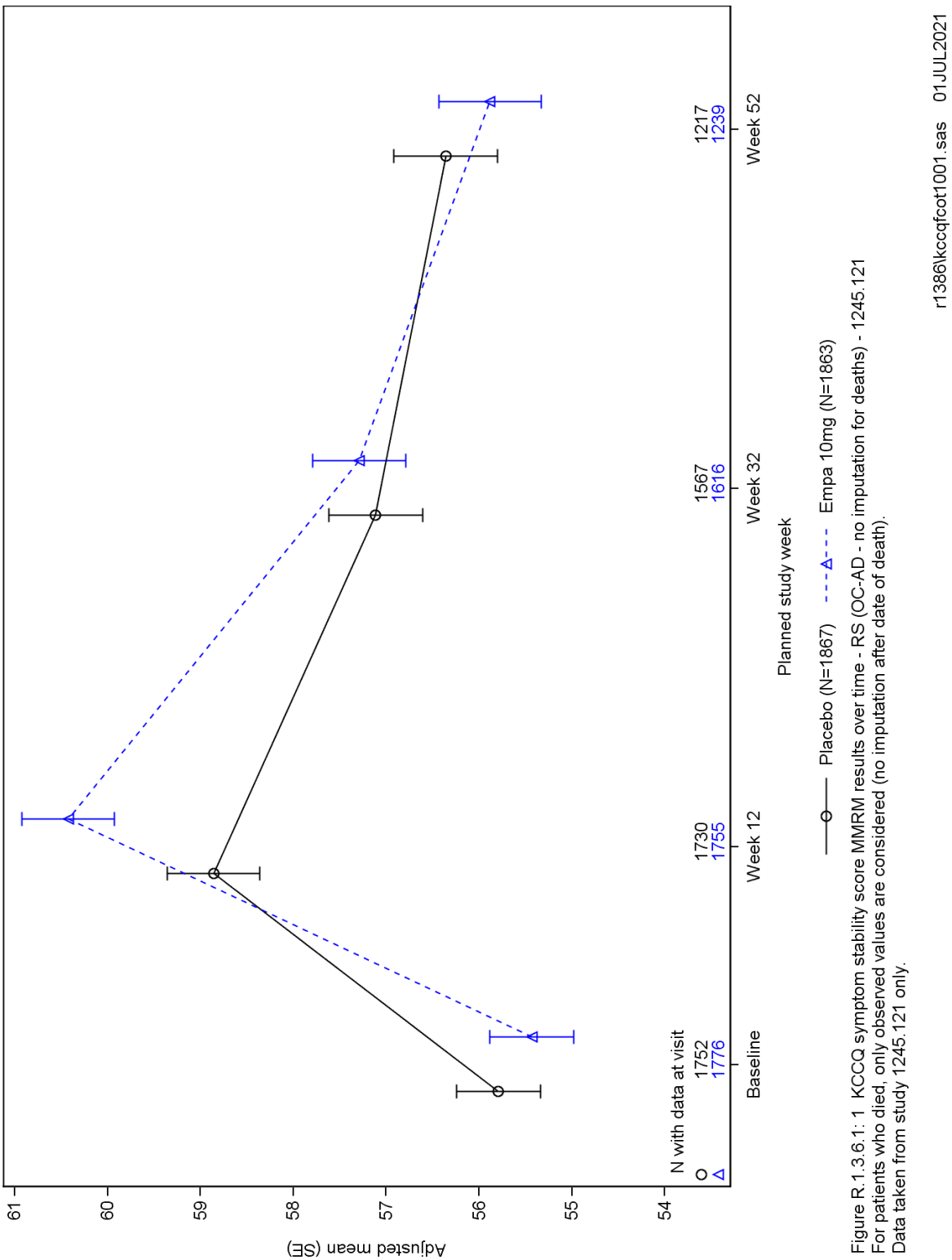

Figure R.1.3.6.1: 1 KCCQ symptom stability score MMRM results over time - RS (OC-AD - no imputation for deaths) - 1245.121
For patients who died, only observed values are considered (no imputation after date of death).
Data taken from study 1245.121 only.

R.1.3.6.2

R.1.3.6.2 Subgroup analysis by sex

Table R.1.3.6.2: 1 KCCQ symptom stability score change from baseline at week 52 (MMRM) by sex - RS (OC-AD - no imputation for deaths) - 1245.121

Subgroup / Visit / Description / Statistic	Placebo	Empa 10mg
Sex: Male		
Number of patients in analysis set	1411	1426
Number of analysed patients	1332	1361
Baseline mean (SE)	55.82 (0.51)	55.62 (0.50)
Week 52		
Values at visit		
Number of analysed patients	938	954
Mean (SE)	56.69 (0.67)	55.84 (0.65)
Adjusted* mean (SE)	56.71 (0.64)	55.96 (0.63)
95% confidence interval	(55.46,57.96)	(54.72,57.19)
Change from baseline		
Mean (SE)	0.45 (0.79)	0.13 (0.81)
Adjusted* mean (SE)	0.99 (0.64)	0.24 (0.63)
95% confidence interval	(-0.26, 2.24)	(-0.99, 1.47)
Comparison vs Placebo		
Adjusted* mean (SE)		-0.75 (0.89)
95% confidence interval		(-2.50, 1.00)
p-value		0.3999

* Model includes Age, baseline eGFR (CKD-EPI) as linear covariate(s) and region, baseline diabetes status, baseline LVEF, week reachable, Visit by Treatment by sex interaction, baseline KCCQ symptom stability score by Visit interaction as fixed effect(s).
The Visit by Treatment by sex p-value at Week 52 is 0.5083.
The following covariance structure has been used to fit the mixed model: Unstructured
Note: All covariate effects are set equal to their mean values within subgroup for the calculation of adjusted means.

For patients who died, only observed values are considered (no imputation after date of death).
Data taken from study 1245.121 only.
The MMRM includes all outcome values (change from baseline) at the planned Visits week 12, week 32 and week 52

Table R.1.3.6.2: 1 KCCQ symptom stability score change from baseline at week 52 (MMRM) by sex - RS (OC-AD - no imputation for deaths) - 1245.121

Subgroup / Visit / Description / Statistic	Placebo	Empa 10mg
Sex: Female		
Number of patients in analysis set	456	437
Number of analysed patients	420	415
Baseline mean (SE)	55.71 (0.97)	54.82 (1.00)
Week 52		
Values at visit		
Number of analysed patients	279	285
Mean (SE)	55.82 (1.20)	56.05 (1.19)
Adjusted* mean (SE)	55.06 (1.16)	55.54 (1.15)
95% confidence interval	(52.78,57.34)	(53.29,57.80)
Change from baseline		
Mean (SE)	0.63 (1.57)	1.40 (1.41)
Adjusted* mean (SE)	-0.21 (1.16)	0.27 (1.15)
95% confidence interval	(-2.49, 2.07)	(-1.98, 2.53)
Comparison vs Placebo		
Adjusted* mean (SE)		0.48 (1.63)
95% confidence interval		(-2.72, 3.68)
p-value		0.7689

* Model includes Age, baseline eGFR (CKD-EPI) as linear covariate(s) and region, baseline diabetes status, baseline LVEF, week reachable, Visit by Treatment by sex interaction, baseline KCCQ symptom stability score by Visit interaction as fixed effect(s).
The Visit by Treatment by sex p-value at Week 52 is 0.5083.
The following covariance structure has been used to fit the mixed model: Unstructured
Note: All covariate effects are set equal to their mean values within subgroup for the calculation of adjusted means.

For patients who died, only observed values are considered (no imputation after date of death).
Data taken from study 1245.121 only.
The MMRM includes all outcome values (change from baseline) at the planned Visits week 12, week 32 and week 52

R.1.3.6.3

Table R.1.3.6.3: 1 KCCQ symptom stability score change from baseline at week 52 (MMRM) by age (2 cat.) - RS (OC-AD - no imputation for deaths) - 1245.121

Subgroup / Visit / Description / Statistic	Placebo	Empa 10mg
Age [years] (2 cat.): < 65		
Number of patients in analysis set	740	675
Number of analysed patients	696	645
Baseline mean (SE)	58.26 (0.77)	57.02 (0.79)
Week 52		
Values at visit		
Number of analysed patients	494	454
Mean (SE)	58.30 (0.98)	58.15 (1.03)
Adjusted* mean (SE)	57.22 (0.88)	57.46 (0.91)
95% confidence interval	(55.50,58.94)	(55.67,59.25)
Change from baseline		
Mean (SE)	-0.05 (1.20)	1.43 (1.26)
Adjusted* mean (SE)	-0.44 (0.88)	-0.20 (0.91)
95% confidence interval	(-2.16, 1.28)	(-1.99, 1.59)
Comparison vs Placebo		
Adjusted* mean (SE)		0.24 (1.26)
95% confidence interval		(-2.24, 2.71)
p-value		0.8505

* Model includes baseline eGFR (CKD-EPI) as linear covariate(s) and region, baseline diabetes status, sex, baseline LVEF, week reachable, Visit by Treatment by age [years] (2 cat.) interaction, baseline KCCQ symptom stability score by Visit interaction as fixed effect(s).
The Visit by Treatment by age [years] (2 cat.) p-value at Week 52 is 0.4526.
The following covariance structure has been used to fit the mixed model: Unstructured
Note: All covariate effects are set equal to their mean values within subgroup for the calculation of adjusted means.

For patients who died, only observed values are considered (no imputation after date of death).
Data taken from study 1245.121 only.
The MMRM includes all outcome values (change from baseline) at the planned Visits week 12, week 32 and week 52

Table R.1.3.6.3: 1 KCCQ symptom stability score change from baseline at week 52 (MMRM) by age (2 cat.) - RS (OC-AD - no imputation for deaths) - 1245.121

Subgroup / Visit / Description / Statistic	Placebo	Empa 10mg
Age [years] (2 cat.): >= 65		
Number of patients in analysis set	1127	1188
Number of analysed patients	1056	1131
Baseline mean (SE)	54.17 (0.55)	54.53 (0.55)
Week 52		
Values at visit		
Number of analysed patients	723	785
Mean (SE)	55.26 (0.71)	54.59 (0.68)
Adjusted* mean (SE)	55.85 (0.72)	54.88 (0.70)
95% confidence interval	(54.43,57.27)	(53.52,56.24)
Change from baseline		
Mean (SE)	0.86 (0.87)	-0.16 (0.84)
Adjusted* mean (SE)	1.50 (0.72)	0.52 (0.70)
95% confidence interval	(0.07, 2.92)	(-0.84, 1.89)
Comparison vs Placebo		
Adjusted* mean (SE)		-0.97 (1.00)
95% confidence interval		(-2.93, 0.99)
p-value		0.3309

* Model includes baseline eGFR (CKD-EPI) as linear covariate(s) and region, baseline diabetes status, sex, baseline LVEF, week reachable, Visit by Treatment by age [years] (2 cat.) interaction, baseline KCCQ symptom stability score by Visit interaction as fixed effect(s).
The Visit by Treatment by age [years] (2 cat.) p-value at Week 52 is 0.4526.
The following covariance structure has been used to fit the mixed model: Unstructured
Note: All covariate effects are set equal to their mean values within subgroup for the calculation of adjusted means.

For patients who died, only observed values are considered (no imputation after date of death).
Data taken from study 1245.121 only.
The MMRM includes all outcome values (change from baseline) at the planned Visits week 12, week 32 and week 52

R.1.3.6.4 Subgroup analysis by region (North America, Latin America, Europe, Asia, Other)

Table R.1.3.6.4: 1 KCCQ symptom stability score change from baseline at week 52 (MMRM) by region - RS (OC-AD - no imputation for deaths) - 1245.121

Subgroup / Visit / Description / Statistic	Placebo	Empa 10mg
Region (5 cat.): North America		
Number of patients in analysis set	213	212
Number of analysed patients	195	206
Baseline mean (SE)	55.77 (1.28)	52.67 (1.33)
Week 52		
Values at visit		
Number of analysed patients	129	151
Mean (SE)	55.43 (1.74)	50.83 (1.36)
Adjusted* mean (SE)	54.60 (1.71)	50.96 (1.58)
95% confidence interval	(51.25,57.94)	(47.86,54.06)
Change from baseline		
Mean (SE)	-0.58 (1.97)	-2.32 (1.88)
Adjusted* mean (SE)	0.42 (1.71)	-3.22 (1.58)
95% confidence interval	(-2.93, 3.76)	(-6.32,-0.12)
Comparison vs Placebo		
Adjusted* mean (SE)		-3.64 (2.33)
95% confidence interval		(-8.20, 0.92)
p-value		0.1181

* Model includes Age, baseline eGFR (CKD-EPI) as linear covariate(s) and baseline diabetes status, sex, baseline LVEF, week reachable, Visit by Treatment by region (5 cat.) interaction, baseline KCCQ symptom stability score by Visit interaction as fixed effect(s).
The Visit by Treatment by region (5 cat.) p-value at Week 52 is 0.5177.
The following covariance structure has been used to fit the mixed model: Unstructured
Note: All covariate effects are set equal to their mean values within subgroup for the calculation of adjusted means.

For patients who died, only observed values are considered (no imputation after date of death).
Data taken from study 1245.121 only.
The MMRM includes all outcome values (change from baseline) at the planned Visits week 12, week 32 and week 52

Table R.1.3.6.4: 1 KCCQ symptom stability score change from baseline at week 52 (MMRM) by region - RS (OC-AD - no imputation for deaths) - 1245.121

Subgroup / Visit / Description / Statistic	Placebo	Empa 10mg
Region (5 cat.): Latin America		
Number of patients in analysis set	645	641
Number of analysed patients	598	602
Baseline mean (SE)	57.48 (0.86)	57.81 (0.86)
Week 52		
Values at visit		
Number of analysed patients	391	374
Mean (SE)	59.34 (1.13)	59.89 (1.15)
Adjusted* mean (SE)	59.10 (0.98)	59.65 (1.00)
95% confidence interval	(57.17,61.02)	(57.68,61.61)
Change from baseline		
Mean (SE)	1.02 (1.48)	2.01 (1.44)
Adjusted* mean (SE)	1.45 (0.98)	2.00 (1.00)
95% confidence interval	(-0.47, 3.37)	(0.04, 3.96)
Comparison vs Placebo		
Adjusted* mean (SE)		0.55 (1.40)
95% confidence interval		(-2.19, 3.29)
p-value		0.6944

* Model includes Age, baseline eGFR (CKD-EPI) as linear covariate(s) and baseline diabetes status, sex, baseline LVEF, week reachable, Visit by Treatment by region (5 cat.) interaction, baseline KCCQ symptom stability score by Visit interaction as fixed effect(s).
The Visit by Treatment by region (5 cat.) p-value at Week 52 is 0.5177.
The following covariance structure has been used to fit the mixed model: Unstructured
Note: All covariate effects are set equal to their mean values within subgroup for the calculation of adjusted means.

For patients who died, only observed values are considered (no imputation after date of death).
Data taken from study 1245.121 only.
The MMRM includes all outcome values (change from baseline) at the planned Visits week 12, week 32 and week 52

Table R.1.3.6.4: 1 KCCQ symptom stability score change from baseline at week 52 (MMRM) by region - RS (OC-AD - no imputation for deaths) - 1245.121

Subgroup / Visit / Description / Statistic	Placebo	Empa 10mg
Region (5 cat.): Europe		
Number of patients in analysis set	677	676
Number of analysed patients	644	649
Baseline mean (SE)	52.76 (0.63)	54.16 (0.68)
Week 52		
Values at visit		
Number of analysed patients	467	469
Mean (SE)	53.10 (0.84)	53.14 (0.84)
Adjusted* mean (SE)	53.15 (0.90)	52.75 (0.90)
95% confidence interval	(51.38,54.91)	(50.99,54.51)
Change from baseline		
Mean (SE)	0.37 (0.99)	-0.91 (1.07)
Adjusted* mean (SE)	-0.32 (0.90)	-0.71 (0.90)
95% confidence interval	(-2.08, 1.45)	(-2.47, 1.05)
Comparison vs Placebo		
Adjusted* mean (SE)		-0.39 (1.27)
95% confidence interval		(-2.88, 2.10)
p-value		0.7581

* Model includes Age, baseline eGFR (CKD-EPI) as linear covariate(s) and baseline diabetes status, sex, baseline LVEF, week reachable, Visit by Treatment by region (5 cat.) interaction, baseline KCCQ symptom stability score by Visit interaction as fixed effect(s).
The Visit by Treatment by region (5 cat.) p-value at Week 52 is 0.5177.
The following covariance structure has been used to fit the mixed model: Unstructured
Note: All covariate effects are set equal to their mean values within subgroup for the calculation of adjusted means.

For patients who died, only observed values are considered (no imputation after date of death).
Data taken from study 1245.121 only.
The MMRM includes all outcome values (change from baseline) at the planned Visits week 12, week 32 and week 52

Table R.1.3.6.4: 1 KCCQ symptom stability score change from baseline at week 52 (MMRM) by region - RS (OC-AD - no imputation for deaths) - 1245.121

Subgroup / Visit / Description / Statistic	Placebo	Empa 10mg
Region (5 cat.): Asia		
Number of patients in analysis set	245	248
Number of analysed patients	237	243
Baseline mean (SE)	56.86 (1.11)	53.40 (1.01)
Week 52		
Values at visit		
Number of analysed patients	180	189
Mean (SE)	55.69 (1.30)	53.84 (1.28)
Adjusted* mean (SE)	55.23 (1.45)	53.82 (1.41)
95% confidence interval	(52.39,58.07)	(51.05,56.59)
Change from baseline		
Mean (SE)	-1.39 (1.61)	0.00 (1.54)
Adjusted* mean (SE)	0.13 (1.45)	-1.29 (1.41)
95% confidence interval	(-2.72, 2.97)	(-4.06, 1.49)
Comparison vs Placebo		
Adjusted* mean (SE)		-1.41 (2.02)
95% confidence interval		(-5.38, 2.56)
p-value		0.4855

* Model includes Age, baseline eGFR (CKD-EPI) as linear covariate(s) and baseline diabetes status, sex, baseline LVEF, week reachable, Visit by Treatment by region (5 cat.) interaction, baseline KCCQ symptom stability score by Visit interaction as fixed effect(s).
The Visit by Treatment by region (5 cat.) p-value at Week 52 is 0.5177.
The following covariance structure has been used to fit the mixed model: Unstructured
Note: All covariate effects are set equal to their mean values within subgroup for the calculation of adjusted means.

For patients who died, only observed values are considered (no imputation after date of death).
Data taken from study 1245.121 only.
The MMRM includes all outcome values (change from baseline) at the planned Visits week 12, week 32 and week 52

Table R.1.3.6.4: 1 KCCQ symptom stability score change from baseline at week 52 (MMRM) by region - RS (OC-AD - no imputation for deaths) - 1245.121

Subgroup / Visit / Description / Statistic	Placebo	Empa 10mg
Region (5 cat.): Other		
Number of patients in analysis set	87	86
Number of analysed patients	78	76
Baseline mean (SE)	64.74 (2.90)	61.51 (2.36)
Week 52		
Values at visit		
Number of analysed patients	50	56
Mean (SE)	71.50 (3.64)	72.77 (3.39)
Adjusted* mean (SE)	70.28 (2.74)	72.84 (2.59)
95% confidence interval	(64.91,75.66)	(67.75,77.92)
Change from baseline		
Mean (SE)	7.00 (4.29)	9.82 (3.81)
Adjusted* mean (SE)	7.13 (2.74)	9.69 (2.59)
95% confidence interval	(1.76,12.51)	(4.60,14.77)
Comparison vs Placebo		
Adjusted* mean (SE)		2.55 (3.77)
95% confidence interval		(-4.84, 9.95)
p-value		0.4983

* Model includes Age, baseline eGFR (CKD-EPI) as linear covariate(s) and baseline diabetes status, sex, baseline LVEF, week reachable, Visit by Treatment by region (5 cat.) interaction, baseline KCCQ symptom stability score by Visit interaction as fixed effect(s).
The Visit by Treatment by region (5 cat.) p-value at Week 52 is 0.5177.
The following covariance structure has been used to fit the mixed model: Unstructured
Note: All covariate effects are set equal to their mean values within subgroup for the calculation of adjusted means.

For patients who died, only observed values are considered (no imputation after date of death).
Data taken from study 1245.121 only.
The MMRM includes all outcome values (change from baseline) at the planned Visits week 12, week 32 and week 52

R.1.3.6.5

R.1.3.6.5 Subgroup analysis by OECD (N/Y)

Table R.1.3.6.5: 1 KCCQ symptom stability score change from baseline at week 52 (MMRM) by OECD member (N/Y) - RS (OC-AD - no imputation for deaths) - 1245.121

Subgroup / Visit / Description / Statistic	Placebo	Empa 10mg
OECD member: No		
Number of patients in analysis set	741	713
Number of analysed patients	685	664
Baseline mean (SE)	58.87 (0.83)	58.77 (0.82)
Week 52		
Values at visit		
Number of analysed patients	443	421
Mean (SE)	60.84 (1.09)	61.88 (1.13)
Adjusted* mean (SE)	60.62 (0.93)	61.68 (0.95)
95% confidence interval	(58.80,62.43)	(59.82,63.54)
Change from baseline		
Mean (SE)	1.69 (1.38)	2.79 (1.37)
Adjusted* mean (SE)	1.80 (0.93)	2.86 (0.95)
95% confidence interval	(-0.02, 3.61)	(1.00, 4.72)
Comparison vs Placebo		
Adjusted* mean (SE)		1.06 (1.32)
95% confidence interval		(-1.53, 3.66)
p-value		0.4211

* Model includes Age, baseline eGFR (CKD-EPI) as linear covariate(s) and baseline diabetes status, sex, baseline LVEF, week reachable, Visit by Treatment by OECD Member (N) interaction, baseline KCCQ symptom stability score by Visit interaction as fixed effect(s).
The Visit by Treatment by OECD Member (N) p-value at Week 52 is 0.1781.
The following covariance structure has been used to fit the mixed model: Unstructured
Note: All covariate effects are set equal to their mean values within subgroup for the calculation of adjusted means.

For patients who died, only observed values are considered (no imputation after date of death).
Data taken from study 1245.121 only.
OECD member (yes/no) countries included:
Yes: United States, Canada, Mexico, Poland, Netherlands, Hungary, Germany, Czech Republic, Italy, France, Spain, United Kingdom, Belgium, Japan, Australia, 'Korea; Republic Of South Korea';
No: Brazil, Argentina, China, India.
The MMRM includes all outcome values (change from baseline) at the planned Visits week 12, week 32 and week 52

Table R.1.3.6.5: 1 KCCQ symptom stability score change from baseline at week 52 (MMRM) by OECD member (N/Y) - RS (OC-AD - no imputation for deaths) - 1245.121

Subgroup / Visit / Description / Statistic	Placebo	Empa 10mg
OECD member: Yes		
Number of patients in analysis set	1126	1150
Number of analysed patients	1067	1112
Baseline mean (SE)	53.82 (0.51)	53.44 (0.52)
Week 52		
Values at visit		
Number of analysed patients	774	818
Mean (SE)	54.01 (0.66)	52.81 (0.62)
Adjusted* mean (SE)	53.69 (0.70)	52.53 (0.68)
95% confidence interval	(52.31,55.07)	(51.20,53.87)
Change from baseline		
Mean (SE)	-0.19 (0.79)	-0.79 (0.80)
Adjusted* mean (SE)	0.06 (0.70)	-1.09 (0.68)
95% confidence interval	(-1.32, 1.44)	(-2.43, 0.25)
Comparison vs Placebo		
Adjusted* mean (SE)		-1.15 (0.98)
95% confidence interval		(-3.07, 0.76)
p-value		0.2385

* Model includes Age, baseline eGFR (CKD-EPI) as linear covariate(s) and baseline diabetes status, sex, baseline LVEF, week reachable, Visit by Treatment by OECD Member (N) interaction, baseline KCCQ symptom stability score by Visit interaction as fixed effect(s).
The Visit by Treatment by OECD Member (N) p-value at Week 52 is 0.1781.
The following covariance structure has been used to fit the mixed model: Unstructured
Note: All covariate effects are set equal to their mean values within subgroup for the calculation of adjusted means.

For patients who died, only observed values are considered (no imputation after date of death).
Data taken from study 1245.121 only.
OECD member (yes/no) countries included:
Yes: United States, Canada, Mexico, Poland, Netherlands, Hungary, Germany, Czech Republic, Italy, France, Spain, United Kingdom, Belgium, Japan, Australia, 'Korea; Republic Of South Korea';
No: Brazil, Argentina, China, India.
The MMRM includes all outcome values (change from baseline) at the planned Visits week 12, week 32 and week 52

R.1.3.6.6 Subgroup analysis by NYHA at baseline (II, III/IV - 2 cat.)

Table R.1.3.6.6: 1 KCCQ symptom stability score change from baseline at week 52 (MMRM) by NYHA (2 cat.) - RS (OC-AD - no imputation for deaths) - 1245.121

Subgroup / Visit / Description / Statistic	Placebo	Empa 10mg
Baseline NYHA (2 cat.): II		
Number of patients in analysis set	1401	1399
Number of analysed patients	1339	1332
Baseline mean (SE)	56.68 (0.51)	55.95 (0.50)
Week 52		
Values at visit		
Number of analysed patients	945	951
Mean (SE)	56.01 (0.65)	55.78 (0.64)
Adjusted* mean (SE)	55.72 (0.63)	55.81 (0.63)
95% confidence interval	(54.48,56.96)	(54.57,57.04)
Change from baseline		
Mean (SE)	-1.06 (0.80)	0.16 (0.79)
Adjusted* mean (SE)	-0.60 (0.63)	-0.51 (0.63)
95% confidence interval	(-1.83, 0.64)	(-1.74, 0.73)
Comparison vs Placebo		
Adjusted* mean (SE)		0.09 (0.89)
95% confidence interval		(-1.66, 1.83)
p-value		0.9222

* Model includes Age, baseline eGFR (CKD-EPI) as linear covariate(s) and region, baseline diabetes status, sex, baseline LVEF, week reachable, Visit by Treatment by baseline NYHA (2 cat.) interaction, baseline KCCQ symptom stability score by Visit interaction as fixed effect(s).
The Visit by Treatment by baseline NYHA (2 cat.) p-value at Week 52 is 0.1704.
The following covariance structure has been used to fit the mixed model: Unstructured
Note: All covariate effects are set equal to their mean values within subgroup for the calculation of adjusted means.

For patients who died, only observed values are considered (no imputation after date of death).
Data taken from study 1245.121 only.
The MMRM includes all outcome values (change from baseline) at the planned Visits week 12, week 32 and week 52

Table R.1.3.6.6: 1 KCCQ symptom stability score change from baseline at week 52 (MMRM) by NYHA (2 cat.) - RS (OC-AD - no imputation for deaths) - 1245.121

Subgroup / Visit / Description / Statistic	Placebo	Empa 10mg
Baseline NYHA (2 cat.): III/IV		
Number of patients in analysis set	466	464
Number of analysed patients	413	444
Baseline mean (SE)	52.91 (0.98)	53.89 (0.99)
Week 52		
Values at visit		
Number of analysed patients	272	288
Mean (SE)	58.18 (1.33)	56.25 (1.28)
Adjusted* mean (SE)	58.50 (1.18)	56.03 (1.14)
95% confidence interval	(56.20,60.81)	(53.79,58.27)
Change from baseline		
Mean (SE)	5.88 (1.48)	1.30 (1.53)
Adjusted* mean (SE)	5.09 (1.18)	2.62 (1.14)
95% confidence interval	(2.78, 7.39)	(0.38, 4.86)
Comparison vs Placebo		
Adjusted* mean (SE)		-2.47 (1.64)
95% confidence interval		(-5.68, 0.74)
p-value		0.1315

* Model includes Age, baseline eGFR (CKD-EPI) as linear covariate(s) and region, baseline diabetes status, sex, baseline LVEF, week reachable, Visit by Treatment by baseline NYHA (2 cat.) interaction, baseline KCCQ symptom stability score by Visit interaction as fixed effect(s).
The Visit by Treatment by baseline NYHA (2 cat.) p-value at Week 52 is 0.1704.
The following covariance structure has been used to fit the mixed model: Unstructured
Note: All covariate effects are set equal to their mean values within subgroup for the calculation of adjusted means.

For patients who died, only observed values are considered (no imputation after date of death).
Data taken from study 1245.121 only.
The MMRM includes all outcome values (change from baseline) at the planned Visits week 12, week 32 and week 52

R.1.3.6.7 Subgroup analysis by diabetes at baseline

Table R.1.3.6.7: 1 KCCQ symptom stability score change from baseline at week 52 (MMRM) by diabetes at baseline - RS (OC-AD - no imputation for deaths) - 1245.121

Subgroup / Visit / Description / Statistic	Placebo	Empa 10mg
Diabetes at baseline (2 cat.):		
Diabetic		
Number of patients in analysis set	929	927
Number of analysed patients	868	882
Baseline mean (SE)	55.99 (0.66)	55.75 (0.68)
Week 52		
Values at visit		
Number of analysed patients	605	614
Mean (SE)	57.27 (0.83)	56.72 (0.81)
Adjusted* mean (SE)	56.79 (0.79)	56.39 (0.78)
95% confidence interval	(55.24,58.34)	(54.85,57.93)
Change from baseline		
Mean (SE)	0.70 (1.02)	0.49 (1.02)
Adjusted* mean (SE)	0.92 (0.79)	0.52 (0.78)
95% confidence interval	(-0.63, 2.47)	(-1.02, 2.05)
Comparison vs Placebo		
Adjusted* mean (SE)		-0.40 (1.11)
95% confidence interval		(-2.58, 1.78)
p-value		0.7177

* Model includes Age, baseline eGFR (CKD-EPI) as linear covariate(s) and region, sex, baseline LVEF, week reachable, Visit by Treatment by diabetes at baseline (2 cat.) interaction, baseline KCCQ symptom stability score by Visit interaction as fixed effect(s).
The Visit by Treatment by diabetes at baseline (2 cat.) p-value at Week 52 is 0.9320.
The following covariance structure has been used to fit the mixed model: Unstructured
Note: All covariate effects are set equal to their mean values within subgroup for the calculation of adjusted means.

For patients who died, only observed values are considered (no imputation after date of death).
Data taken from study 1245.121 only.
The MMRM includes all outcome values (change from baseline) at the planned Visits week 12, week 32 and week 52

Table R.1.3.6.7: 1 KCCQ symptom stability score change from baseline at week 52 (MMRM) by diabetes at baseline - RS (OC-AD - no imputation for deaths) - 1245.121

Subgroup / Visit / Description / Statistic	Placebo	Empa 10mg
Diabetes at baseline (2 cat.):		
Non-Diabetic		
Number of patients in analysis set	938	936
Number of analysed patients	884	894
Baseline mean (SE)	55.60 (0.62)	55.12 (0.59)
Week 52		
Values at visit		
Number of analysed patients	612	625
Mean (SE)	55.72 (0.82)	55.08 (0.81)
Adjusted* mean (SE)	55.88 (0.79)	55.34 (0.78)
95% confidence interval	(54.34,57.42)	(53.82,56.87)
Change from baseline		
Mean (SE)	0.29 (0.99)	0.36 (0.97)
Adjusted* mean (SE)	0.52 (0.79)	-0.01 (0.78)
95% confidence interval	(-1.02, 2.06)	(-1.53, 1.51)
Comparison vs Placebo		
Adjusted* mean (SE)		-0.53 (1.10)
95% confidence interval		(-2.70, 1.63)
p-value		0.6276

* Model includes Age, baseline eGFR (CKD-EPI) as linear covariate(s) and region, sex, baseline LVEF, week reachable, Visit by Treatment by diabetes at baseline (2 cat.) interaction, baseline KCCQ symptom stability score by Visit interaction as fixed effect(s).
The Visit by Treatment by diabetes at baseline (2 cat.) p-value at Week 52 is 0.9320.
The following covariance structure has been used to fit the mixed model: Unstructured
Note: All covariate effects are set equal to their mean values within subgroup for the calculation of adjusted means.

For patients who died, only observed values are considered (no imputation after date of death).
Data taken from study 1245.121 only.
The MMRM includes all outcome values (change from baseline) at the planned Visits week 12, week 32 and week 52

R.1.3.6.8 Subgroup analysis by BMI at baseline (<30, >=30)

Table R.1.3.6.8: 1 KCCQ symptom stability score change from baseline at week 52 (MMRM) by baseline BMI [kg/m2] - RS (OC-AD - no imputation for deaths) - 1245.121

Subgroup / Visit / Description / Statistic	Placebo	Empa 10mg
Baseline BMI [kg/m²] (2 cat.): <30		
Number of patients in analysis set	1300	1263
Number of analysed patients	1229	1201
Baseline mean (SE)	56.00 (0.54)	55.70 (0.53)
Week 52		
Values at visit		
Number of analysed patients	864	826
Mean (SE)	56.83 (0.69)	56.84 (0.71)
Adjusted* mean (SE)	56.56 (0.66)	56.74 (0.68)
95% confidence interval	(55.26,57.86)	(55.41,58.07)
Change from baseline		
Mean (SE)	0.75 (0.85)	0.82 (0.87)
Adjusted* mean (SE)	0.71 (0.66)	0.89 (0.68)
95% confidence interval	(-0.59, 2.01)	(-0.44, 2.21)
Comparison vs Placebo		
Adjusted* mean (SE)		0.18 (0.94)
95% confidence interval		(-1.67, 2.02)
p-value		0.8517

* Model includes Age, baseline eGFR (CKD-EPI) as linear covariate(s) and region, baseline diabetes status, sex, baseline LVEF, week reachable, Visit by Treatment by baseline BMI [kg/m²] (2 cat.) interaction, baseline KCCQ symptom stability score by Visit interaction as fixed effect(s).
The Visit by Treatment by baseline BMI [kg/m²] (2 cat.) p-value at Week 52 is 0.2774.
The following covariance structure has been used to fit the mixed model: Unstructured
Note: All covariate effects are set equal to their mean values within subgroup for the calculation of adjusted means.

For patients who died, only observed values are considered (no imputation after date of death).
Data taken from study 1245.121 only.
The MMRM includes all outcome values (change from baseline) at the planned Visits week 12, week 32 and week 52

Table R.1.3.6.8: 1 KCCQ symptom stability score change from baseline at week 52 (MMRM) by baseline BMI [kg/m2] - RS (OC-AD - no imputation for deaths) - 1245.121

Subgroup / Visit / Description / Statistic	Placebo	Empa 10mg
Baseline BMI [kg/m²] (2 cat.): >=30		
Number of patients in analysis set	567	600
Number of analysed patients	523	575
Baseline mean (SE)	55.31 (0.82)	54.87 (0.83)
Week 52		
Values at visit		
Number of analysed patients	353	413
Mean (SE)	55.67 (1.09)	54.00 (0.97)
Adjusted* mean (SE)	55.77 (1.04)	54.10 (0.96)
95% confidence interval	(53.73,57.80)	(52.22,55.99)
Change from baseline		
Mean (SE)	-0.14 (1.29)	-0.36 (1.20)
Adjusted* mean (SE)	0.69 (1.04)	-0.97 (0.96)
95% confidence interval	(-1.34, 2.72)	(-2.86, 0.91)
Comparison vs Placebo		
Adjusted* mean (SE)		-1.66 (1.41)
95% confidence interval		(-4.42, 1.09)
p-value		0.2371

* Model includes Age, baseline eGFR (CKD-EPI) as linear covariate(s) and region, baseline diabetes status, sex, baseline LVEF, week reachable, Visit by Treatment by baseline BMI [kg/m²] (2 cat.) interaction, baseline KCCQ symptom stability score by Visit interaction as fixed effect(s).
The Visit by Treatment by baseline BMI [kg/m²] (2 cat.) p-value at Week 52 is 0.2774.
The following covariance structure has been used to fit the mixed model: Unstructured
Note: All covariate effects are set equal to their mean values within subgroup for the calculation of adjusted means.

For patients who died, only observed values are considered (no imputation after date of death).
Data taken from study 1245.121 only.
The MMRM includes all outcome values (change from baseline) at the planned Visits week 12, week 32 and week 52

R.1.3.6.9 Subgroup analysis by eGFR at baseline (<60, >=60)

Table R.1.3.6.9: 1 KCCQ symptom stability score change from baseline at week 52 (MMRM) by baseline eGFR (2 cat.) - RS (OC-AD - no imputation for deaths) - 1245.121

Subgroup Visit Description Statistic	Placebo	Empa 10mg
Baseline eGFR (CKD-EPI) [mL/min/1.73m²] (2 cat.): >=60		
Number of patients in analysis set	960	969
Number of analysed patients	900	921
Baseline mean (SE)	56.61 (0.65)	56.16 (0.63)
Week 52		
Values at visit		
Number of analysed patients	647	650
Mean (SE)	56.57 (0.83)	57.62 (0.81)
Adjusted* mean (SE)	56.21 (0.77)	57.52 (0.76)
95% confidence interval	(54.71,57.71)	(56.03,59.01)
Change from baseline		
Mean (SE)	-0.43 (1.02)	1.81 (0.99)
Adjusted* mean (SE)	-0.18 (0.77)	1.13 (0.76)
95% confidence interval	(-1.68, 1.32)	(-0.36, 2.63)
Comparison vs Placebo		
Adjusted* mean (SE)		1.31 (1.08)
95% confidence interval		(-0.80, 3.42)
p-value		0.2230

* Model includes Age as linear covariate(s) and region, baseline diabetes status, sex, baseline LVEF, week reachable, Visit by Treatment by baseline eGFR (CKD-EPI) [mL/min/1.73m²] (2 cat.) interaction, baseline KCCQ symptom stability score by Visit interaction as fixed effect(s).
The Visit by Treatment by baseline eGFR (CKD-EPI) [mL/min/1.73m²] (2 cat.) p-value at Week 52 is 0.0155.
The following covariance structure has been used to fit the mixed model: Unstructured
2 patients were excluded as the subgroup variable was missing.
Note: All covariate effects are set equal to their mean values within subgroup for the calculation of adjusted means.

For patients who died, only observed values are considered (no imputation after date of death).
Data taken from study 1245.121 only.
The MMRM includes all outcome values (change from baseline) at the planned Visits week 12, week 32 and week 52

Table R.1.3.6.9: 1 KCCQ symptom stability score change from baseline at week 52 (MMRM) by baseline eGFR (2 cat.) - RS (OC-AD - no imputation for deaths) - 1245.121

Subgroup / Visit / Description / Statistic	Placebo	Empa 10mg
Baseline eGFR (CKD-EPI) [mL/min/1.73m²] (2 cat.): <60		
Number of patients in analysis set	906	893
Number of analysed patients	852	855
Baseline mean (SE)	54.93 (0.62)	54.65 (0.65)
Week 52		
Values at visit		
Number of analysed patients	570	589
Mean (SE)	56.40 (0.82)	53.99 (0.80)
Adjusted* mean (SE)	56.54 (0.81)	54.06 (0.80)
95% confidence interval	(54.95,58.14)	(52.49,55.63)
Change from baseline		
Mean (SE)	1.54 (0.97)	-1.10 (1.00)
Adjusted* mean (SE)	1.75 (0.81)	-0.73 (0.80)
95% confidence interval	(0.16, 3.35)	(-2.30, 0.84)
Comparison vs Placebo		
Adjusted* mean (SE)		-2.48 (1.14)
95% confidence interval		(-4.71,-0.25)
p-value		0.0291

* Model includes Age as linear covariate(s) and region, baseline diabetes status, sex, baseline LVEF, week reachable, Visit by Treatment by baseline eGFR (CKD-EPI) [mL/min/1.73m²] (2 cat.) interaction, baseline KCCQ symptom stability score by Visit interaction as fixed effect(s).
The Visit by Treatment by baseline eGFR (CKD-EPI) [mL/min/1.73m²] (2 cat.) p-value at Week 52 is 0.0155.
The following covariance structure has been used to fit the mixed model: Unstructured
2 patients were excluded as the subgroup variable was missing.
Note: All covariate effects are set equal to their mean values within subgroup for the calculation of adjusted means.

For patients who died, only observed values are considered (no imputation after date of death).
Data taken from study 1245.121 only.
The MMRM includes all outcome values (change from baseline) at the planned Visits week 12, week 32 and week 52

R.1.3.6.10

R.1.3.6.10 Subgroup analysis by history of HHF

Table R.1.3.6.10: 1 KCCQ symptom stability score change from baseline at week 52 (MMRM) by history of HHF - RS (OC-AD - no imputation for deaths) - 1245.121

Subgroup / Visit / Description / Statistic	Placebo	Empa 10mg
History of HHF (in the last 12 months): No		
Number of patients in analysis set	1293	1286
Number of analysed patients	1219	1231
Baseline mean (SE)	54.25 (0.51)	54.81 (0.51)
Week 52		
Values at visit		
Number of analysed patients	869	873
Mean (SE)	55.81 (0.70)	55.58 (0.68)
Adjusted* mean (SE)	55.70 (0.66)	55.28 (0.66)
95% confidence interval	(54.41,57.00)	(53.99,56.57)
Change from baseline		
Mean (SE)	1.21 (0.83)	0.95 (0.81)
Adjusted* mean (SE)	1.17 (0.66)	0.75 (0.66)
95% confidence interval	(-0.12, 2.47)	(-0.54, 2.04)
Comparison vs Placebo		
Adjusted* mean (SE)		-0.42 (0.93)
95% confidence interval		(-2.25, 1.40)
p-value		0.6487

* Model includes Age, baseline eGFR (CKD-EPI) as linear covariate(s) and region, baseline diabetes status, sex, baseline LVEF, week reachable, Visit by Treatment by history of HHF (in the last 12 months) interaction, baseline KCCQ symptom stability score by Visit interaction as fixed effect(s).
The Visit by Treatment by history of HHF (in the last 12 months) p-value at Week 52 is 0.8961.
The following covariance structure has been used to fit the mixed model: Unstructured
Note: All covariate effects are set equal to their mean values within subgroup for the calculation of adjusted means.

For patients who died, only observed values are considered (no imputation after date of death).
Data taken from study 1245.121 only.
The MMRM includes all outcome values (change from baseline) at the planned Visits week 12, week 32 and week 52

Table R.1.3.6.10: 1 KCCQ symptom stability score change from baseline at week 52 (MMRM) by history of HHF - RS (OC-AD - no imputation for deaths) - 1245.121

Subgroup / Visit / Description / Statistic	Placebo	Empa 10mg
History of HHF (in the last 12 months): Yes		
Number of patients in analysis set	574	577
Number of analysed patients	533	545
Baseline mean (SE)	59.33 (0.90)	56.83 (0.92)
Week 52		
Values at visit		
Number of analysed patients	348	366
Mean (SE)	58.19 (1.05)	56.63 (1.06)
Adjusted* mean (SE)	57.82 (1.04)	57.17 (1.02)
95% confidence interval	(55.78,59.86)	(55.18,59.16)
Change from baseline		
Mean (SE)	-1.29 (1.34)	-0.82 (1.40)
Adjusted* mean (SE)	-0.25 (1.04)	-0.90 (1.02)
95% confidence interval	(-2.29, 1.79)	(-2.89, 1.09)
Comparison vs Placebo		
Adjusted* mean (SE)		-0.65 (1.45)
95% confidence interval		(-3.49, 2.20)
p-value		0.6550

* Model includes Age, baseline eGFR (CKD-EPI) as linear covariate(s) and region, baseline diabetes status, sex, baseline LVEF, week reachable, Visit by Treatment by history of HHF (in the last 12 months) interaction, baseline KCCQ symptom stability score by Visit interaction as fixed effect(s).
The Visit by Treatment by history of HHF (in the last 12 months) p-value at Week 52 is 0.8961.
The following covariance structure has been used to fit the mixed model: Unstructured
Note: All covariate effects are set equal to their mean values within subgroup for the calculation of adjusted means.

For patients who died, only observed values are considered (no imputation after date of death).
Data taken from study 1245.121 only.
The MMRM includes all outcome values (change from baseline) at the planned Visits week 12, week 32 and week 52

R.1.3.6.11

Table R.1.3.6.11: 1 KCCQ symptom stability score change from baseline at week 52 (MMRM) by cause of heart failure - RS (OC-AD - no imputation for deaths) - 1245.121

Subgroup / Visit / Description / Statistic	Placebo	Empa 10mg
Cause of heart failure: Ischemic		
Number of patients in analysis set	946	983
Number of analysed patients	896	936
Baseline mean (SE)	54.38 (0.61)	54.99 (0.61)
Week 52		
Values at visit		
Number of analysed patients	633	667
Mean (SE)	55.53 (0.75)	54.76 (0.75)
Adjusted* mean (SE)	55.87 (0.78)	54.77 (0.75)
95% confidence interval	(54.35,57.39)	(53.29,56.25)
Change from baseline		
Mean (SE)	0.79 (0.93)	-0.15 (0.93)
Adjusted* mean (SE)	1.18 (0.78)	0.07 (0.75)
95% confidence interval	(-0.35, 2.70)	(-1.41, 1.55)
Comparison vs Placebo		
Adjusted* mean (SE)		-1.11 (1.08)
95% confidence interval		(-3.22, 1.00)
p-value		0.3044

* Model includes Age, baseline eGFR (CKD-EPI) as linear covariate(s) and region, baseline diabetes status, sex, baseline LVEF, week reachable, Visit by Treatment by cause of heart failure interaction, baseline KCCQ symptom stability score by Visit interaction as fixed effect(s).
The Visit by Treatment by cause of heart failure p-value at Week 52 is 0.3834.
The following covariance structure has been used to fit the mixed model: Unstructured
Note: All covariate effects are set equal to their mean values within subgroup for the calculation of adjusted means.

For patients who died, only observed values are considered (no imputation after date of death).
Data taken from study 1245.121 only.
The MMRM includes all outcome values (change from baseline) at the planned Visits week 12, week 32 and week 52

Table R.1.3.6.11: 1 KCCQ symptom stability score change from baseline at week 52 (MMRM) by cause of heart failure - RS (OC-AD - no imputation for deaths) - 1245.121

Subgroup / Visit / Description / Statistic	Placebo	Empa 10mg
Cause of heart failure: Non-ischemic		
Number of patients in analysis set	921	880
Number of analysed patients	856	840
Baseline mean (SE)	57.27 (0.67)	55.92 (0.67)
Week 52		
Values at visit		
Number of analysed patients	584	572
Mean (SE)	57.53 (0.90)	57.21 (0.88)
Adjusted* mean (SE)	56.82 (0.81)	57.09 (0.81)
95% confidence interval	(55.24,58.41)	(55.49,58.68)
Change from baseline		
Mean (SE)	0.17 (1.08)	1.09 (1.08)
Adjusted* mean (SE)	0.22 (0.81)	0.48 (0.81)
95% confidence interval	(-1.36, 1.80)	(-1.11, 2.08)
Comparison vs Placebo		
Adjusted* mean (SE)		0.26 (1.14)
95% confidence interval		(-1.97, 2.50)
p-value		0.8186

* Model includes Age, baseline eGFR (CKD-EPI) as linear covariate(s) and region, baseline diabetes status, sex, baseline LVEF, week reachable, Visit by Treatment by cause of heart failure interaction, baseline KCCQ symptom stability score by Visit interaction as fixed effect(s).
The Visit by Treatment by cause of heart failure p-value at Week 52 is 0.3834.
The following covariance structure has been used to fit the mixed model: Unstructured
Note: All covariate effects are set equal to their mean values within subgroup for the calculation of adjusted means.

For patients who died, only observed values are considered (no imputation after date of death).
Data taken from study 1245.121 only.
The MMRM includes all outcome values (change from baseline) at the planned Visits week 12, week 32 and week 52

R.1.3.6.12 Subgroup analysis by heart failure physiology (LVEF <= 30% and NTproBNP<median; LVEF <= 30% and NTproBNP>=median; LVEF > 30%)

Table R.1.3.6.12: 1 KCCQ symptom stability score change from baseline at week 52 (MMRM) by heart failure physiology - RS (OC-AD - no imputation for deaths) - 1245.121

Subgroup / Visit / Description / Statistic	Placebo	Empa 10mg
Heart failure physiology: LVEF <= 30% and NTproBNP < median		
Number of patients in analysis set	723	698
Number of analysed patients	693	672
Baseline mean (SE)	55.77 (0.68)	56.14 (0.68)
Week 52		
Values at visit		
Number of analysed patients	511	494
Mean (SE)	55.92 (0.88)	56.73 (0.89)
Adjusted* mean (SE)	55.68 (0.86)	56.61 (0.87)
95% confidence interval	(54.00,57.37)	(54.90,58.33)
Change from baseline		
Mean (SE)	0.10 (1.07)	0.91 (1.03)
Adjusted* mean (SE)	-0.27 (0.86)	0.66 (0.87)
95% confidence interval	(-1.95, 1.42)	(-1.06, 2.37)
Comparison vs Placebo		
Adjusted* mean (SE)		0.93 (1.22)
95% confidence interval		(-1.47, 3.33)
p-value		0.4491

* Model includes Age, baseline eGFR (CKD-EPI) as linear covariate(s) and region, baseline diabetes status, sex, week reachable, Visit by Treatment by heart failure physiology interaction, baseline KCCQ symptom stability score by Visit interaction as fixed effect(s).
The Visit by Treatment by heart failure physiology p-value at Week 52 is 0.2345.
The following covariance structure has been used to fit the mixed model: Unstructured
16 patients were excluded as the subgroup variable was missing.
Note: All covariate effects are set equal to their mean values within subgroup for the calculation of adjusted means.
The p-value for the visit by treatment by subgroup interaction trend test at Week 52 is 0.0866

For patients who died, only observed values are considered (no imputation after date of death).
Data taken from study 1245.121 only.
NTproBNP median [pg/mL]: with a. fibrillation/flutter at baseline: 2265; without a. fibrillation/flutter at baseline: 1671.
The MMRM includes all outcome values (change from baseline) at the planned Visits week 12, week 32 and week 52

Table R.1.3.6.12: 1 KCCQ symptom stability score change from baseline at week 52 (MMRM) by heart failure physiology - RS (OC-AD - no imputation for deaths) - 1245.121

Subgroup / Visit / Description / Statistic	Placebo	Empa 10mg
Heart failure physiology: LVEF <= 30% and NTproBNP >= median		
Number of patients in analysis set	661	631
Number of analysed patients	604	593
Baseline mean (SE)	55.38 (0.82)	55.35 (0.85)
Week 52		
Values at visit		
Number of analysed patients	408	405
Mean (SE)	56.99 (1.08)	55.93 (1.06)
Adjusted* mean (SE)	56.56 (0.96)	55.86 (0.96)
95% confidence interval	(54.67,58.44)	(53.97,57.75)
Change from baseline		
Mean (SE)	0.74 (1.32)	0.19 (1.36)
Adjusted* mean (SE)	1.19 (0.96)	0.49 (0.96)
95% confidence interval	(-0.70, 3.07)	(-1.40, 2.38)
Comparison vs Placebo		
Adjusted* mean (SE)		-0.69 (1.36)
95% confidence interval		(-3.36, 1.97)
p-value		0.6101

* Model includes Age, baseline eGFR (CKD-EPI) as linear covariate(s) and region, baseline diabetes status, sex, week reachable, Visit by Treatment by heart failure physiology interaction, baseline KCCQ symptom stability score by Visit interaction as fixed effect(s).
The Visit by Treatment by heart failure physiology p-value at Week 52 is 0.2345.
The following covariance structure has been used to fit the mixed model: Unstructured
16 patients were excluded as the subgroup variable was missing.
Note: All covariate effects are set equal to their mean values within subgroup for the calculation of adjusted means.
The p-value for the visit by treatment by subgroup interaction trend test at Week 52 is 0.0866

For patients who died, only observed values are considered (no imputation after date of death).
Data taken from study 1245.121 only.
NTproBNP median [pg/mL]: with a. fibrillation/flutter at baseline: 2265; without a. fibrillation/flutter at baseline: 1671.
The MMRM includes all outcome values (change from baseline) at the planned Visits week 12, week 32 and week 52

Table R.1.3.6.12: 1 KCCQ symptom stability score change from baseline at week 52 (MMRM) by heart failure physiology - RS (OC-AD - no imputation for deaths) - 1245.121

Subgroup / Visit / Description / Statistic	Placebo	Empa 10mg
Heart failure physiology: LVEF > 30%		
Number of patients in analysis set	475	526
Number of analysed patients	450	506
Baseline mean (SE)	56.28 (0.87)	54.64 (0.83)
Week 52		
Values at visit		
Number of analysed patients	294	339
Mean (SE)	56.89 (1.12)	54.65 (1.05)
Adjusted* mean (SE)	57.20 (1.13)	54.80 (1.05)
95% confidence interval	(54.98,59.42)	(52.73,56.86)
Change from baseline		
Mean (SE)	0.94 (1.35)	0.00 (1.32)
Adjusted* mean (SE)	1.79 (1.13)	-0.62 (1.05)
95% confidence interval	(-0.43, 4.01)	(-2.68, 1.45)
Comparison vs Placebo		
Adjusted* mean (SE)		-2.41 (1.54)
95% confidence interval		(-5.43, 0.62)
p-value		0.1191

* Model includes Age, baseline eGFR (CKD-EPI) as linear covariate(s) and region, baseline diabetes status, sex, week reachable, Visit by Treatment by heart failure physiology interaction, baseline KCCQ symptom stability score by Visit interaction as fixed effect(s).
The Visit by Treatment by heart failure physiology p-value at Week 52 is 0.2345.
The following covariance structure has been used to fit the mixed model: Unstructured
16 patients were excluded as the subgroup variable was missing.
Note: All covariate effects are set equal to their mean values within subgroup for the calculation of adjusted means.
The p-value for the visit by treatment by subgroup interaction trend test at Week 52 is 0.0866

For patients who died, only observed values are considered (no imputation after date of death).
Data taken from study 1245.121 only.
NTproBNP median [pg/mL]: with a. fibrillation/flutter at baseline: 2265; without a. fibrillation/flutter at baseline: 1671.
The MMRM includes all outcome values (change from baseline) at the planned Visits week 12, week 32 and week 52

R.1.3.6.13

R.1.3.6.13 Subgroup analysis by baseline use of MRA

Table R.1.3.6.13: 1 KCCQ symptom stability score change from baseline at week 52 (MMRM) by baseline use of MRA (Y/N) - RS (OC-AD - no imputation for deaths) - 1245.121

Subgroup / Visit / Description / Statistic	Placebo	Empa 10mg
Baseline use of MRA: No		
Number of patients in analysis set	512	557
Number of analysed patients	486	531
Baseline mean (SE)	54.06 (0.82)	54.76 (0.74)
Week 52		
Values at visit		
Number of analysed patients	340	383
Mean (SE)	54.85 (1.10)	54.83 (0.98)
Adjusted* mean (SE)	55.16 (1.05)	54.86 (1.00)
95% confidence interval	(53.09,57.23)	(52.90,56.81)
Change from baseline		
Mean (SE)	0.81 (1.33)	-0.46 (1.22)
Adjusted* mean (SE)	0.73 (1.05)	0.43 (1.00)
95% confidence interval	(-1.33, 2.80)	(-1.52, 2.39)
Comparison vs Placebo		
Adjusted* mean (SE)		-0.30 (1.45)
95% confidence interval		(-3.14, 2.53)
p-value		0.8344

* Model includes Age, baseline eGFR (CKD-EPI) as linear covariate(s) and region, baseline diabetes status, sex, baseline LVEF, week reachable, Visit by Treatment by baseline use of MRA interaction, baseline KCCQ symptom stability score by Visit interaction as fixed effect(s).
The Visit by Treatment by baseline use of MRA p-value at Week 52 is 0.8954.
The following covariance structure has been used to fit the mixed model: Unstructured
Note: All covariate effects are set equal to their mean values within subgroup for the calculation of adjusted means.

For patients who died, only observed values are considered (no imputation after date of death).
Data taken from study 1245.121 only.
The MMRM includes all outcome values (change from baseline) at the planned Visits week 12, week 32 and week 52

Table R.1.3.6.13: 1 KCCQ symptom stability score change from baseline at week 52 (MMRM) by baseline use of MRA (Y/N) - RS (OC-AD - no imputation for deaths) - 1245.121

Subgroup / Visit / Description / Statistic	Placebo	Empa 10mg
Baseline use of MRA: Yes		
Number of patients in analysis set	1355	1306
Number of analysed patients	1266	1245
Baseline mean (SE)	56.46 (0.54)	55.72 (0.56)
Week 52		
Values at visit		
Number of analysed patients	877	856
Mean (SE)	57.13 (0.69)	56.37 (0.70)
Adjusted* mean (SE)	56.80 (0.66)	56.27 (0.66)
95% confidence interval	(55.51,58.09)	(54.97,57.57)
Change from baseline		
Mean (SE)	0.37 (0.84)	0.82 (0.86)
Adjusted* mean (SE)	0.71 (0.66)	0.18 (0.66)
95% confidence interval	(-0.58, 2.00)	(-1.12, 1.48)
Comparison vs Placebo		
Adjusted* mean (SE)		-0.53 (0.93)
95% confidence interval		(-2.36, 1.30)
p-value		0.5706

* Model includes Age, baseline eGFR (CKD-EPI) as linear covariate(s) and region, baseline diabetes status, sex, baseline LVEF, week reachable, Visit by Treatment by baseline use of MRA interaction, baseline KCCQ symptom stability score by Visit interaction as fixed effect(s).
The Visit by Treatment by baseline use of MRA p-value at Week 52 is 0.8954.
The following covariance structure has been used to fit the mixed model: Unstructured
Note: All covariate effects are set equal to their mean values within subgroup for the calculation of adjusted means.

For patients who died, only observed values are considered (no imputation after date of death).
Data taken from study 1245.121 only.
The MMRM includes all outcome values (change from baseline) at the planned Visits week 12, week 32 and week 52

R.1.3.6.14

Table R.1.3.6.14: 1 KCCQ symptom stability score change from baseline at week 52 (MMRM) by baseline use of ARNi (Y/N) - RS (OC-AD - no imputation for deaths) - 1245.121

Subgroup / Visit / Description / Statistic	Placebo	Empa 10mg
Baseline use of ARNi: No		
Number of patients in analysis set	1480	1523
Number of analysed patients	1389	1447
Baseline mean (SE)	55.92 (0.51)	55.37 (0.50)
Week 52		
Values at visit		
Number of analysed patients	959	1026
Mean (SE)	56.67 (0.66)	55.73 (0.62)
Adjusted* mean (SE)	56.37 (0.63)	55.63 (0.61)
95% confidence interval	(55.14,57.60)	(54.44,56.82)
Change from baseline		
Mean (SE)	0.68 (0.80)	0.39 (0.77)
Adjusted* mean (SE)	0.73 (0.63)	-0.01 (0.61)
95% confidence interval	(-0.50, 1.96)	(-1.20, 1.18)
Comparison vs Placebo		
Adjusted* mean (SE)		-0.74 (0.87)
95% confidence interval		(-2.45, 0.97)
p-value		0.3956

* Model includes Age, baseline eGFR (CKD-EPI) as linear covariate(s) and region, baseline diabetes status, sex, baseline LVEF, week reachable, Visit by Treatment by baseline use of ARNi interaction, baseline KCCQ symptom stability score by Visit interaction as fixed effect(s).
The Visit by Treatment by baseline use of ARNi p-value at Week 52 is 0.4529.
The following covariance structure has been used to fit the mixed model: Unstructured
Note: All covariate effects are set equal to their mean values within subgroup for the calculation of adjusted means.

For patients who died, only observed values are considered (no imputation after date of death).
Data taken from study 1245.121 only.
The MMRM includes all outcome values (change from baseline) at the planned Visits week 12, week 32 and week 52

Table R.1.3.6.14: 1 KCCQ symptom stability score change from baseline at week 52 (MMRM) by baseline use of ARNi (Y/N) - RS (OC-AD - no imputation for deaths) - 1245.121

Subgroup / Visit / Description / Statistic	Placebo	Empa 10mg
Baseline use of ARNi: Yes		
Number of patients in analysis set	387	340
Number of analysed patients	363	329
Baseline mean (SE)	55.30 (0.99)	55.70 (1.02)
Week 52		
Values at visit		
Number of analysed patients	258	213
Mean (SE)	55.81 (1.27)	56.69 (1.46)
Adjusted* mean (SE)	56.19 (1.21)	56.95 (1.33)
95% confidence interval	(53.82,58.57)	(54.34,59.56)
Change from baseline		
Mean (SE)	-0.19 (1.50)	0.59 (1.68)
Adjusted* mean (SE)	0.70 (1.21)	1.46 (1.33)
95% confidence interval	(-1.67, 3.08)	(-1.15, 4.07)
Comparison vs Placebo		
Adjusted* mean (SE)		0.76 (1.79)
95% confidence interval		(-2.76, 4.28)
p-value		0.6728

* Model includes Age, baseline eGFR (CKD-EPI) as linear covariate(s) and region, baseline diabetes status, sex, baseline LVEF, week reachable, Visit by Treatment by baseline use of ARNi interaction, baseline KCCQ symptom stability score by Visit interaction as fixed effect(s).
The Visit by Treatment by baseline use of ARNi p-value at Week 52 is 0.4529.
The following covariance structure has been used to fit the mixed model: Unstructured
Note: All covariate effects are set equal to their mean values within subgroup for the calculation of adjusted means.

For patients who died, only observed values are considered (no imputation after date of death).
Data taken from study 1245.121 only.
The MMRM includes all outcome values (change from baseline) at the planned Visits week 12, week 32 and week 52

R.1.3.6.15 Subgroup analysis by bl. LVEF (<= 30%, >30% -<= 35% , > 35%)

Table R.1.3.6.15: 1 KCCQ symptom stability score change from baseline at week 52 (MMRM) by baseline LVEF (3 cat.) - RS (OC-AD - no imputation for deaths) - 1245.121

Subgroup / Visit / Description / Statistic	Placebo	Empa 10mg
Baseline LVEF (3 cat.): <=30		
Number of patients in analysis set	1392	1337
Number of analysed patients	1302	1270
Baseline mean (SE)	55.63 (0.53)	55.75 (0.54)
Week 52		
Values at visit		
Number of analysed patients	923	900
Mean (SE)	56.37 (0.68)	56.36 (0.68)
Adjusted* mean (SE)	56.06 (0.64)	56.26 (0.65)
95% confidence interval	(54.80,57.31)	(54.99,57.53)
Change from baseline		
Mean (SE)	0.35 (0.83)	0.58 (0.83)
Adjusted* mean (SE)	0.37 (0.64)	0.58 (0.65)
95% confidence interval	(-0.88, 1.62)	(-0.69, 1.84)
Comparison vs Placebo		
Adjusted* mean (SE)		0.21 (0.91)
95% confidence interval		(-1.57, 1.99)
p-value		0.8202

* Model includes Age, baseline eGFR (CKD-EPI) as linear covariate(s) and region, baseline diabetes status, sex, week reachable, Visit by Treatment by baseline LVEF (3 cat.) interaction, baseline KCCQ symptom stability score by Visit interaction as fixed effect(s).
The Visit by Treatment by baseline LVEF (3 cat.) p-value at Week 52 is 0.0362.
The following covariance structure has been used to fit the mixed model: Unstructured
Note: All covariate effects are set equal to their mean values within subgroup for the calculation of adjusted means.
The p-value for the visit by treatment by subgroup interaction trend test at Week 52 is 0.5713

For patients who died, only observed values are considered (no imputation after date of death).
Data taken from study 1245.121 only.
The MMRM includes all outcome values (change from baseline) at the planned Visits week 12, week 32 and week 52

Table R.1.3.6.15: 1 KCCQ symptom stability score change from baseline at week 52 (MMRM) by baseline LVEF (3 cat.) - RS (OC-AD - no imputation for deaths) - 1245.121

Subgroup / Visit / Description / Statistic	Placebo	Empa 10mg
Baseline LVEF (3 cat.): >30 to <=35		
Number of patients in analysis set	361	398
Number of analysed patients	342	385
Baseline mean (SE)	56.07 (0.98)	53.83 (0.96)
Week 52		
Values at visit		
Number of analysed patients	233	256
Mean (SE)	57.40 (1.27)	52.73 (1.15)
Adjusted* mean (SE)	57.48 (1.27)	53.25 (1.21)
95% confidence interval	(54.99,59.97)	(50.88,55.62)
Change from baseline		
Mean (SE)	1.82 (1.56)	-1.27 (1.50)
Adjusted* mean (SE)	2.60 (1.27)	-1.63 (1.21)
95% confidence interval	(0.11, 5.09)	(-4.00, 0.74)
Comparison vs Placebo		
Adjusted* mean (SE)		-4.23 (1.75)
95% confidence interval		(-7.66,-0.79)
p-value		0.0159

* Model includes Age, baseline eGFR (CKD-EPI) as linear covariate(s) and region, baseline diabetes status, sex, week reachable, Visit by Treatment by baseline LVEF (3 cat.) interaction, baseline KCCQ symptom stability score by Visit interaction as fixed effect(s).
The Visit by Treatment by baseline LVEF (3 cat.) p-value at Week 52 is 0.0362.
The following covariance structure has been used to fit the mixed model: Unstructured
Note: All covariate effects are set equal to their mean values within subgroup for the calculation of adjusted means.
The p-value for the visit by treatment by subgroup interaction trend test at Week 52 is 0.5713

For patients who died, only observed values are considered (no imputation after date of death).
Data taken from study 1245.121 only.
The MMRM includes all outcome values (change from baseline) at the planned Visits week 12, week 32 and week 52

Table R.1.3.6.15: 1 KCCQ symptom stability score change from baseline at week 52 (MMRM) by baseline LVEF (3 cat.) - RS (OC-AD - no imputation for deaths) - 1245.121

Subgroup / Visit / Description / Statistic	Placebo	Empa 10mg
Baseline LVEF (3 cat.): >35		
Number of patients in analysis set	114	128
Number of analysed patients	108	121
Baseline mean (SE)	56.94 (1.91)	57.23 (1.67)
Week 52		
Values at visit		
Number of analysed patients	61	83
Mean (SE)	54.92 (2.32)	60.54 (2.27)
Adjusted* mean (SE)	56.04 (2.47)	59.56 (2.13)
95% confidence interval	(51.19,60.89)	(55.39,63.72)
Change from baseline		
Mean (SE)	-2.46 (2.66)	3.92 (2.73)
Adjusted* mean (SE)	-1.05 (2.47)	2.46 (2.13)
95% confidence interval	(-5.90, 3.80)	(-1.71, 6.63)
Comparison vs Placebo		
Adjusted* mean (SE)		3.51 (3.26)
95% confidence interval		(-2.88, 9.90)
p-value		0.2813

* Model includes Age, baseline eGFR (CKD-EPI) as linear covariate(s) and region, baseline diabetes status, sex, week reachable, Visit by Treatment by baseline LVEF (3 cat.) interaction, baseline KCCQ symptom stability score by Visit interaction as fixed effect(s).
The Visit by Treatment by baseline LVEF (3 cat.) p-value at Week 52 is 0.0362.
The following covariance structure has been used to fit the mixed model: Unstructured
Note: All covariate effects are set equal to their mean values within subgroup for the calculation of adjusted means.
The p-value for the visit by treatment by subgroup interaction trend test at Week 52 is 0.5713

For patients who died, only observed values are considered (no imputation after date of death).
Data taken from study 1245.121 only.
The MMRM includes all outcome values (change from baseline) at the planned Visits week 12, week 32 and week 52

R.1.3.6.16 Subgroup analysis by bl. NTproBNP </>= median (median based on total patients)

Table R.1.3.6.16: 1 KCCQ symptom stability score change from baseline at week 52 (MMRM) by bl. NTproBNP (<median, >= median) (median based on total patients) - RS (OC-AD - no imputation for deaths) - 1245.121

Subgroup / Visit / Description / Statistic	Placebo	Empa 10mg
Baseline NTproBNP (<median, >= median): < median		
Number of patients in analysis set	920	942
Number of analysed patients	883	908
Baseline mean (SE)	56.03 (0.60)	56.22 (0.59)
Week 52		
Values at visit		
Number of analysed patients	651	666
Mean (SE)	55.80 (0.76)	56.16 (0.78)
Adjusted* mean (SE)	55.83 (0.76)	56.13 (0.75)
95% confidence interval	(54.34,57.33)	(54.65,57.60)
Change from baseline		
Mean (SE)	-0.27 (0.95)	0.38 (0.91)
Adjusted* mean (SE)	-0.30 (0.76)	0.00 (0.75)
95% confidence interval	(-1.79, 1.20)	(-1.48, 1.48)
Comparison vs Placebo		
Adjusted* mean (SE)		0.30 (1.07)
95% confidence interval		(-1.80, 2.39)
p-value		0.7823

* Model includes Age, baseline eGFR (CKD-EPI) as linear covariate(s) and region, baseline diabetes status, sex, baseline LVEF, week reachable, Visit by Treatment by baseline NTproBNP (<median, >= median) interaction, baseline KCCQ symptom stability score by Visit interaction as fixed effect(s). The Visit by Treatment by baseline NTproBNP (<median, >= median) p-value at Week 52 is 0.2897.
The following covariance structure has been used to fit the mixed model: Unstructured
2 patients were excluded as the subgroup variable was missing.
Note: All covariate effects are set equal to their mean values within subgroup for the calculation of adjusted means.

For patients who died, only observed values are considered (no imputation after date of death).
Data taken from study 1245.121 only.
Median: 1910 [pg/mL]
The MMRM includes all outcome values (change from baseline) at the planned Visits week 12, week 32 and week 52

Table R.1.3.6.16: 1 KCCQ symptom stability score change from baseline at week 52 (MMRM) by bl. NTproBNP (<median, >= median) (median based on total patients) - RS (OC-AD - no imputation for deaths) - 1245.121

Subgroup / Visit / Description / Statistic	Placebo	Empa 10mg
Baseline NTproBNP (<median, >= median): >= median		
Number of patients in analysis set	946	920
Number of analysed patients	869	868
Baseline mean (SE)	55.55 (0.67)	54.61 (0.69)
Week 52		
Values at visit		
Number of analysed patients	566	573
Mean (SE)	57.29 (0.89)	55.58 (0.84)
Adjusted* mean (SE)	56.94 (0.82)	55.58 (0.81)
95% confidence interval	(55.35,58.54)	(53.99,57.17)
Change from baseline		
Mean (SE)	1.37 (1.06)	0.48 (1.10)
Adjusted* mean (SE)	1.86 (0.82)	0.50 (0.81)
95% confidence interval	(0.26, 3.46)	(-1.09, 2.09)
Comparison vs Placebo		
Adjusted* mean (SE)		-1.37 (1.15)
95% confidence interval		(-3.62, 0.88)
p-value		0.2343

* Model includes Age, baseline eGFR (CKD-EPI) as linear covariate(s) and region, baseline diabetes status, sex, baseline LVEF, week reachable, Visit by Treatment by baseline NTproBNP (<median, >= median) interaction, baseline KCCQ symptom stability score by Visit interaction as fixed effect(s). The Visit by Treatment by baseline NTproBNP (<median, >= median) p-value at Week 52 is 0.2897.
The following covariance structure has been used to fit the mixed model: Unstructured
2 patients were excluded as the subgroup variable was missing.
Note: All covariate effects are set equal to their mean values within subgroup for the calculation of adjusted means.

For patients who died, only observed values are considered (no imputation after date of death).
Data taken from study 1245.121 only.
Median: 1910 [pg/mL]
The MMRM includes all outcome values (change from baseline) at the planned Visits week 12, week 32 and week 52

R.1.3.7

R.1.3.7 KCCQ symptom frequency score MMRM analysis

R.1.3.7.1

Table R.1.3.7.1: 1 KCCQ symptom frequency score change from baseline MMRM results over time - RS (OC-AD - no imputation for deaths) - 1245.121

Visit Description Statistic	Placebo	Empa 10mg
Number of patients in analysis set	1867	1863
Number of analysed patients	1753	1776
Baseline mean (SE)	73.96 (0.56)	73.41 (0.58)
Week 12		
Values at visit		
Number of analysed patients	1731	1755
Mean (SE)	77.63 (0.54)	80.02 (0.52)
Adjusted* mean (SE)	77.50 (0.42)	80.26 (0.42)
95% confidence interval	(76.67,78.32)	(79.44,81.08)
Change from baseline		
Mean (SE)	3.56 (0.48)	6.58 (0.49)
Adjusted* mean (SE)	3.42 (0.42)	6.18 (0.42)
95% confidence interval	(2.59, 4.25)	(5.36, 7.00)
Comparison vs Placebo		
Adjusted* mean (SE)		2.76 (0.59)
95% confidence interval		(1.60, 3.92)
p-value		<0.0001
Hedges g		
Estimate		0.16
95% confidence interval		(0.09, 0.22)

* Model includes Age (p=0.6352), baseline eGFR (CKD-EPI) (p=0.0095) as linear covariate(s) and region (p<0.0001), baseline diabetes status (p=0.7130), sex (p=0.0014), baseline LVEF (p=0.1756), week reachable (p=0.0257), Treatment by Visit interaction (p<0.0001), baseline KCCQ symptom frequency score by Visit interaction (p<0.0001) as fixed effect(s).
The following covariance structure has been used to fit the mixed model: Unstructured

For patients who died, only observed values are considered (no imputation after date of death).
Data taken from study 1245.121 only.

Table R.1.3.7.1: 1 KCCQ symptom frequency score change from baseline MMRM results over time - RS (OC-AD - no imputation for deaths) - 1245.121

Visit Description Statistic	Placebo	Empa 10mg
Week 32		
Values at visit		
Number of analysed patients	1567	1617
Mean (SE)	79.27 (0.55)	80.66 (0.54)
Adjusted* mean (SE)	78.85 (0.45)	80.43 (0.44)
95% confidence interval	(77.97,79.73)	(79.55,81.30)
Change from baseline		
Mean (SE)	4.96 (0.55)	6.70 (0.54)
Adjusted* mean (SE)	4.77 (0.45)	6.35 (0.44)
95% confidence interval	(3.89, 5.66)	(5.48, 7.22)
Comparison vs Placebo		
Adjusted* mean (SE)		1.58 (0.63)
95% confidence interval		(0.34, 2.82)
p-value		0.0128
Hedges g		
Estimate		0.09
95% confidence interval		(0.02, 0.16)

* Model includes Age (p=0.6352), baseline eGFR (CKD-EPI) (p=0.0095) as linear covariate(s) and region (p<0.0001), baseline diabetes status (p=0.7130), sex (p=0.0014), baseline LVEF (p=0.1756), week reachable (p=0.0257), Treatment by Visit interaction (p<0.0001), baseline KCCQ symptom frequency score by Visit interaction (p<0.0001) as fixed effect(s).
The following covariance structure has been used to fit the mixed model: Unstructured

For patients who died, only observed values are considered (no imputation after date of death).
Data taken from study 1245.121 only.

Table R.1.3.7.1: 1 KCCQ symptom frequency score change from baseline MMRM results over time - RS (OC-AD - no imputation for deaths) - 1245.121

Visit Description Statistic	Placebo	Empa 10mg
Week 52		
Values at visit		
Number of analysed patients	1218	1239
Mean (SE)	79.61 (0.63)	81.65 (0.60)
Adjusted* mean (SE)	79.37 (0.51)	81.21 (0.51)
95% confidence interval	(78.36,80.37)	(80.22,82.21)
Change from baseline		
Mean (SE)	5.31 (0.65)	7.02 (0.61)
Adjusted* mean (SE)	5.29 (0.51)	7.14 (0.51)
95% confidence interval	(4.29, 6.30)	(6.14, 8.13)
Comparison vs Placebo		
Adjusted* mean (SE)		1.84 (0.72)
95% confidence interval		(0.43, 3.26)
p-value		0.0106
Hedges g		
Estimate		0.10
95% confidence interval		(0.02, 0.18)

* Model includes Age (p=0.6352), baseline eGFR (CKD-EPI) (p=0.0095) as linear covariate(s) and region (p<0.0001), baseline diabetes status (p=0.7130), sex (p=0.0014), baseline LVEF (p=0.1756), week reachable (p=0.0257), Treatment by Visit interaction (p<0.0001), baseline KCCQ symptom frequency score by Visit interaction (p<0.0001) as fixed effect(s).
The following covariance structure has been used to fit the mixed model: Unstructured

For patients who died, only observed values are considered (no imputation after date of death).
Data taken from study 1245.121 only.

Figure R.1.3.7.1: 1

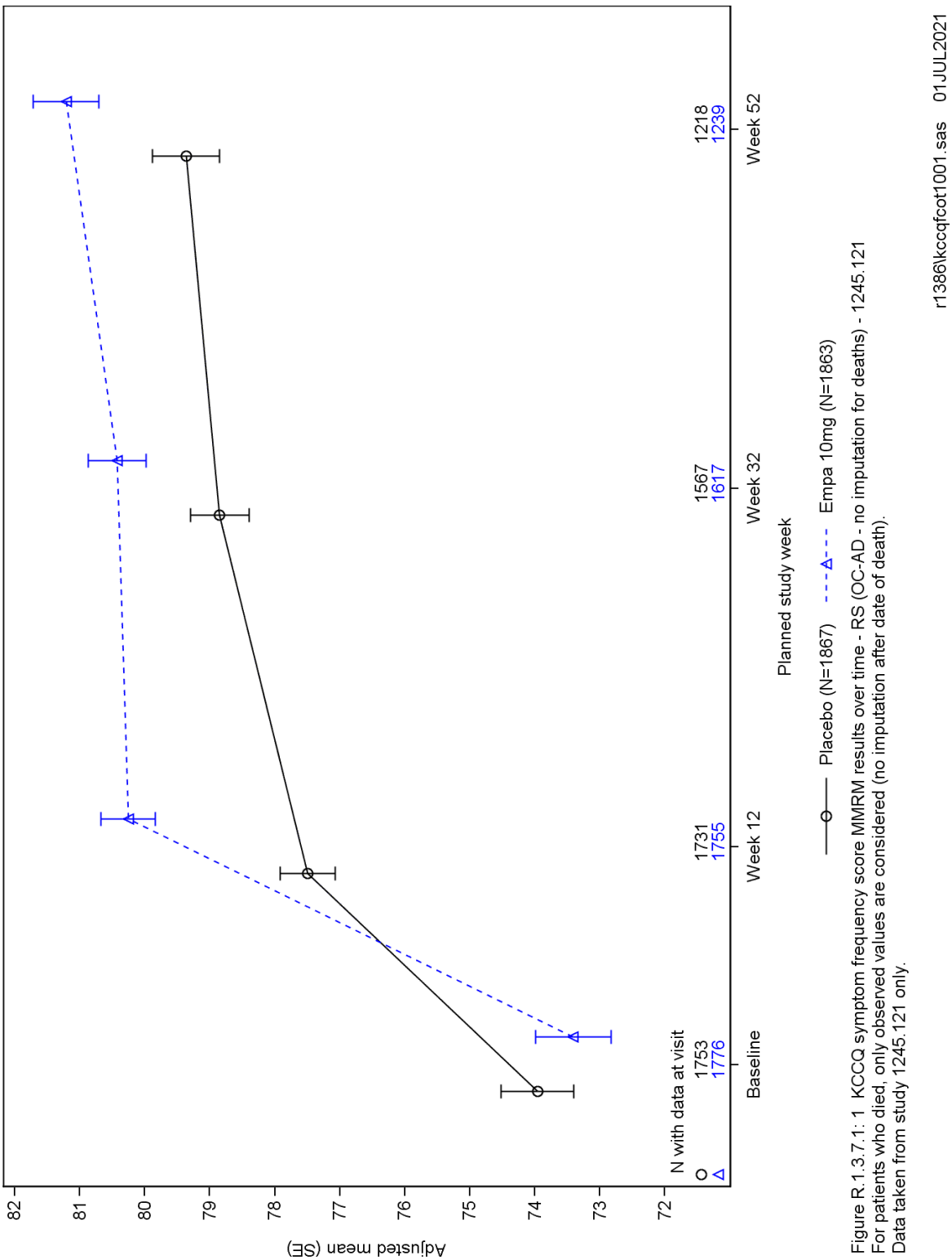

Figure R.1.3.7.1: 1 KCCQ symptom frequency score MMRM results over time - RS (OC-AD - no imputation for deaths) - 1245.121
For patients who died, only observed values are considered (no imputation after date of death).
Data taken from study 1245.121 only.

R.1.3.7.2

R.1.3.7.2 Subgroup analysis by sex

Table R.1.3.7.2: 1 KCCQ symptom frequency score change from baseline at week 52 (MMRM) by sex - RS (OC-AD - no imputation for deaths) - 1245.121

Subgroup / Visit / Description / Statistic	Placebo	Empa 10mg
Sex: Male		
Number of patients in analysis set	1411	1426
Number of analysed patients	1333	1361
Baseline mean (SE)	75.77 (0.61)	74.88 (0.65)
Week 52		
Values at visit		
Number of analysed patients	939	954
Mean (SE)	80.38 (0.72)	83.08 (0.66)
Adjusted* mean (SE)	79.91 (0.58)	82.52 (0.58)
95% confidence interval	(78.77,81.06)	(81.38,83.66)
Change from baseline		
Mean (SE)	4.13 (0.73)	6.84 (0.69)
Adjusted* mean (SE)	4.59 (0.58)	7.20 (0.58)
95% confidence interval	(3.45, 5.74)	(6.06, 8.33)
Comparison vs Placebo		
Adjusted* mean (SE)		2.61 (0.82)
95% confidence interval		(0.99, 4.22)
p-value		0.0015

* Model includes Age, baseline eGFR (CKD-EPI) as linear covariate(s) and region, baseline diabetes status, baseline LVEF, week reachable, Visit by Treatment by sex interaction, baseline KCCQ symptom frequency score by Visit interaction as fixed effect(s).
The Visit by Treatment by sex p-value at Week 52 is 0.0567.
The following covariance structure has been used to fit the mixed model: Unstructured
Note: All covariate effects are set equal to their mean values within subgroup for the calculation of adjusted means.

For patients who died, only observed values are considered (no imputation after date of death).
Data taken from study 1245.121 only.
The MMRM includes all outcome values (change from baseline) at the planned Visits week 12, week 32 and week 52

Table R.1.3.7.2: 1 KCCQ symptom frequency score change from baseline at week 52 (MMRM) by sex - RS (OC-AD - no imputation for deaths) - 1245.121

Subgroup / Visit / Description / Statistic	Placebo	Empa 10mg
Sex: Female		
Number of patients in analysis set	456	437
Number of analysed patients	420	415
Baseline mean (SE)	68.22 (1.26)	68.58 (1.25)
Week 52		
Values at visit		
Number of analysed patients	279	285
Mean (SE)	77.05 (1.35)	76.86 (1.37)
Adjusted* mean (SE)	76.76 (1.07)	76.10 (1.06)
95% confidence interval	(74.66,78.85)	(74.03,78.18)
Change from baseline		
Mean (SE)	9.31 (1.43)	7.60 (1.36)
Adjusted* mean (SE)	8.36 (1.07)	7.70 (1.06)
95% confidence interval	(6.27,10.46)	(5.63, 9.78)
Comparison vs Placebo		
Adjusted* mean (SE)		-0.66 (1.50)
95% confidence interval		(-3.60, 2.29)
p-value		0.6615

* Model includes Age, baseline eGFR (CKD-EPI) as linear covariate(s) and region, baseline diabetes status, baseline LVEF, week reachable, Visit by Treatment by sex interaction, baseline KCCQ symptom frequency score by Visit interaction as fixed effect(s).
The Visit by Treatment by sex p-value at Week 52 is 0.0567.
The following covariance structure has been used to fit the mixed model: Unstructured
Note: All covariate effects are set equal to their mean values within subgroup for the calculation of adjusted means.

For patients who died, only observed values are considered (no imputation after date of death).
Data taken from study 1245.121 only.
The MMRM includes all outcome values (change from baseline) at the planned Visits week 12, week 32 and week 52

R.1.3.7.3

R.1.3.7.3 Subgroup analysis by age

Table R.1.3.7.3: 1 KCCQ symptom frequency score change from baseline at week 52 (MMRM) by age (2 cat.) - RS (OC-AD - no imputation for deaths) - 1245.121

Subgroup / Visit / Description / Statistic	Placebo	Empa 10mg
Age [years] (2 cat.): < 65		
Number of patients in analysis set	740	675
Number of analysed patients	697	645
Baseline mean (SE)	72.53 (0.93)	71.13 (1.01)
Week 52		
Values at visit		
Number of analysed patients	494	454
Mean (SE)	79.55 (1.04)	81.38 (1.08)
Adjusted* mean (SE)	78.86 (0.81)	80.95 (0.84)
95% confidence interval	(77.27,80.45)	(79.30,82.59)
Change from baseline		
Mean (SE)	7.01 (1.06)	9.55 (1.00)
Adjusted* mean (SE)	7.00 (0.81)	9.09 (0.84)
95% confidence interval	(5.41, 8.59)	(7.44,10.74)
Comparison vs Placebo		
Adjusted* mean (SE)		2.09 (1.16)
95% confidence interval		(-0.19, 4.37)
p-value		0.0728

* Model includes baseline eGFR (CKD-EPI) as linear covariate(s) and region, baseline diabetes status, sex, baseline LVEF, week reachable, Visit by Treatment by age [years] (2 cat.) interaction, baseline KCCQ symptom frequency score by Visit interaction as fixed effect(s).
The Visit by Treatment by age [years] (2 cat.) p-value at Week 52 is 0.8062.
The following covariance structure has been used to fit the mixed model: Unstructured
Note: All covariate effects are set equal to their mean values within subgroup for the calculation of adjusted means.

For patients who died, only observed values are considered (no imputation after date of death).
Data taken from study 1245.121 only.
The MMRM includes all outcome values (change from baseline) at the planned Visits week 12, week 32 and week 52

Table R.1.3.7.3: 1 KCCQ symptom frequency score change from baseline at week 52 (MMRM) by age (2 cat.) - RS (OC-AD - no imputation for deaths) - 1245.121

Subgroup / Visit / Description / Statistic	Placebo	Empa 10mg
Age [years] (2 cat.): >= 65		
Number of patients in analysis set	1127	1188
Number of analysed patients	1056	1131
Baseline mean (SE)	74.90 (0.69)	74.71 (0.70)
Week 52		
Values at visit		
Number of analysed patients	724	785
Mean (SE)	79.65 (0.80)	81.80 (0.72)
Adjusted* mean (SE)	79.33 (0.67)	81.06 (0.64)
95% confidence interval	(78.03,80.64)	(79.80,82.31)
Change from baseline		
Mean (SE)	4.16 (0.82)	5.55 (0.77)
Adjusted* mean (SE)	4.53 (0.67)	6.25 (0.64)
95% confidence interval	(3.22, 5.83)	(5.00, 7.51)
Comparison vs Placebo		
Adjusted* mean (SE)		1.72 (0.92)
95% confidence interval		(-0.08, 3.53)
p-value		0.0612

* Model includes baseline eGFR (CKD-EPI) as linear covariate(s) and region, baseline diabetes status, sex, baseline LVEF, week reachable, Visit by Treatment by age [years] (2 cat.) interaction, baseline KCCQ symptom frequency score by Visit interaction as fixed effect(s).
The Visit by Treatment by age [years] (2 cat.) p-value at Week 52 is 0.8062.
The following covariance structure has been used to fit the mixed model: Unstructured
Note: All covariate effects are set equal to their mean values within subgroup for the calculation of adjusted means.

For patients who died, only observed values are considered (no imputation after date of death).
Data taken from study 1245.121 only.
The MMRM includes all outcome values (change from baseline) at the planned Visits week 12, week 32 and week 52

R.1.3.7.4 Subgroup analysis by region (North America, Latin America, Europe, Asia, Other)

Table R.1.3.7.4: 1 KCCQ symptom frequency score change from baseline at week 52 (MMRM) by region - RS (OC-AD - no imputation for deaths) - 1245.121

Subgroup / Visit / Description / Statistic	Placebo	Empa 10mg
Region (5 cat.): North America		
Number of patients in analysis set	213	212
Number of analysed patients	195	206
Baseline mean (SE)	70.91 (1.82)	70.03 (1.84)
Week 52		
Values at visit		
Number of analysed patients	129	151
Mean (SE)	76.20 (2.06)	78.61 (1.78)
Adjusted* mean (SE)	75.75 (1.57)	77.29 (1.46)
95% confidence interval	(72.68,78.83)	(74.43,80.16)
Change from baseline		
Mean (SE)	5.98 (1.73)	6.35 (1.80)
Adjusted* mean (SE)	5.30 (1.57)	6.84 (1.46)
95% confidence interval	(2.23, 8.37)	(3.97, 9.70)
Comparison vs Placebo		
Adjusted* mean (SE)		1.54 (2.14)
95% confidence interval		(-2.66, 5.74)
p-value		0.4727

* Model includes Age, baseline eGFR (CKD-EPI) as linear covariate(s) and baseline diabetes status, sex, baseline LVEF, week reachable, Visit by Treatment by region (5 cat.) interaction, baseline KCCQ symptom frequency score by Visit interaction as fixed effect(s).
The Visit by Treatment by region (5 cat.) p-value at Week 52 is 0.7774.
The following covariance structure has been used to fit the mixed model: Unstructured
Note: All covariate effects are set equal to their mean values within subgroup for the calculation of adjusted means.

For patients who died, only observed values are considered (no imputation after date of death).
Data taken from study 1245.121 only.
The MMRM includes all outcome values (change from baseline) at the planned Visits week 12, week 32 and week 52

Table R.1.3.7.4: 1 KCCQ symptom frequency score change from baseline at week 52 (MMRM) by region - RS (OC-AD - no imputation for deaths) - 1245.121

Subgroup / Visit / Description / Statistic	Placebo	Empa 10mg
Region (5 cat.): Latin America		
Number of patients in analysis set	645	641
Number of analysed patients	599	602
Baseline mean (SE)	71.55 (0.99)	69.49 (1.07)
Week 52		
Values at visit		
Number of analysed patients	391	374
Mean (SE)	79.84 (1.14)	81.85 (1.13)
Adjusted* mean (SE)	79.24 (0.90)	82.07 (0.91)
95% confidence interval	(77.47,81.00)	(80.28,83.86)
Change from baseline		
Mean (SE)	8.74 (1.34)	12.36 (1.24)
Adjusted* mean (SE)	8.72 (0.90)	11.55 (0.91)
95% confidence interval	(6.95,10.48)	(9.76,13.35)
Comparison vs Placebo		
Adjusted* mean (SE)		2.83 (1.28)
95% confidence interval		(0.32, 5.35)
p-value		0.0272

* Model includes Age, baseline eGFR (CKD-EPI) as linear covariate(s) and baseline diabetes status, sex, baseline LVEF, week reachable, Visit by Treatment by region (5 cat.) interaction, baseline KCCQ symptom frequency score by Visit interaction as fixed effect(s).
The Visit by Treatment by region (5 cat.) p-value at Week 52 is 0.7774.
The following covariance structure has been used to fit the mixed model: Unstructured
Note: All covariate effects are set equal to their mean values within subgroup for the calculation of adjusted means.

For patients who died, only observed values are considered (no imputation after date of death).
Data taken from study 1245.121 only.
The MMRM includes all outcome values (change from baseline) at the planned Visits week 12, week 32 and week 52

Table R.1.3.7.4: 1 KCCQ symptom frequency score change from baseline at week 52 (MMRM) by region - RS (OC-AD - no imputation for deaths) - 1245.121

Subgroup / Visit / Description / Statistic	Placebo	Empa 10mg
Region (5 cat.): Europe		
Number of patients in analysis set	677	676
Number of analysed patients	644	649
Baseline mean (SE)	73.21 (0.89)	74.86 (0.89)
Week 52		
Values at visit		
Number of analysed patients	468	469
Mean (SE)	77.16 (1.03)	78.98 (0.99)
Adjusted* mean (SE)	77.23 (0.83)	77.92 (0.83)
95% confidence interval	(75.60,78.85)	(76.29,79.54)
Change from baseline		
Mean (SE)	3.22 (0.98)	3.35 (0.89)
Adjusted* mean (SE)	3.19 (0.83)	3.88 (0.83)
95% confidence interval	(1.56, 4.81)	(2.25, 5.50)
Comparison vs Placebo		
Adjusted* mean (SE)		0.69 (1.17)
95% confidence interval		(-1.61, 2.98)
p-value		0.5559

* Model includes Age, baseline eGFR (CKD-EPI) as linear covariate(s) and baseline diabetes status, sex, baseline LVEF, week reachable, Visit by Treatment by region (5 cat.) interaction, baseline KCCQ symptom frequency score by Visit interaction as fixed effect(s).
The Visit by Treatment by region (5 cat.) p-value at Week 52 is 0.7774.
The following covariance structure has been used to fit the mixed model: Unstructured
Note: All covariate effects are set equal to their mean values within subgroup for the calculation of adjusted means.

For patients who died, only observed values are considered (no imputation after date of death).
Data taken from study 1245.121 only.
The MMRM includes all outcome values (change from baseline) at the planned Visits week 12, week 32 and week 52

Table R.1.3.7.4: 1 KCCQ symptom frequency score change from baseline at week 52 (MMRM) by region - RS (OC-AD - no imputation for deaths) - 1245.121

Subgroup / Visit / Description / Statistic	Placebo	Empa 10mg
Region (5 cat.): Asia		
Number of patients in analysis set	245	248
Number of analysed patients	237	243
Baseline mean (SE)	83.20 (1.26)	81.52 (1.33)
Week 52		
Values at visit		
Number of analysed patients	180	189
Mean (SE)	84.84 (1.45)	86.89 (1.43)
Adjusted* mean (SE)	84.09 (1.34)	86.33 (1.31)
95% confidence interval	(81.46,86.73)	(83.76,88.90)
Change from baseline		
Mean (SE)	1.20 (1.38)	3.28 (1.42)
Adjusted* mean (SE)	1.74 (1.34)	3.98 (1.31)
95% confidence interval	(-0.90, 4.37)	(1.41, 6.55)
Comparison vs Placebo		
Adjusted* mean (SE)		2.24 (1.88)
95% confidence interval		(-1.44, 5.92)
p-value		0.2323

* Model includes Age, baseline eGFR (CKD-EPI) as linear covariate(s) and baseline diabetes status, sex, baseline LVEF, week reachable, Visit by Treatment by region (5 cat.) interaction, baseline KCCQ symptom frequency score by Visit interaction as fixed effect(s).
The Visit by Treatment by region (5 cat.) p-value at Week 52 is 0.7774.
The following covariance structure has been used to fit the mixed model: Unstructured
Note: All covariate effects are set equal to their mean values within subgroup for the calculation of adjusted means.

For patients who died, only observed values are considered (no imputation after date of death).
Data taken from study 1245.121 only.
The MMRM includes all outcome values (change from baseline) at the planned Visits week 12, week 32 and week 52

Table R.1.3.7.4: 1 KCCQ symptom frequency score change from baseline at week 52 (MMRM) by region - RS (OC-AD - no imputation for deaths) - 1245.121

Subgroup / Visit / Description / Statistic	Placebo	Empa 10mg
Region (5 cat.): Other		
Number of patients in analysis set	87	86
Number of analysed patients	78	76
Baseline mean (SE)	78.15 (2.59)	75.27 (2.43)
Week 52		
Values at visit		
Number of analysed patients	50	56
Mean (SE)	90.83 (2.49)	93.12 (1.37)
Adjusted* mean (SE)	89.56 (2.52)	92.73 (2.40)
95% confidence interval	(84.63,94.49)	(88.02,97.43)
Change from baseline		
Mean (SE)	11.17 (3.19)	16.44 (2.55)
Adjusted* mean (SE)	12.83 (2.52)	15.99 (2.40)
95% confidence interval	(7.90,17.76)	(11.29,20.69)
Comparison vs Placebo		
Adjusted* mean (SE)		3.16 (3.47)
95% confidence interval		(-3.65, 9.97)
p-value		0.3626

* Model includes Age, baseline eGFR (CKD-EPI) as linear covariate(s) and baseline diabetes status, sex, baseline LVEF, week reachable, Visit by Treatment by region (5 cat.) interaction, baseline KCCQ symptom frequency score by Visit interaction as fixed effect(s).
The Visit by Treatment by region (5 cat.) p-value at Week 52 is 0.7774.
The following covariance structure has been used to fit the mixed model: Unstructured
Note: All covariate effects are set equal to their mean values within subgroup for the calculation of adjusted means.

For patients who died, only observed values are considered (no imputation after date of death).
Data taken from study 1245.121 only.
The MMRM includes all outcome values (change from baseline) at the planned Visits week 12, week 32 and week 52

R.1.3.7.5 Subgroup analysis by OECD (N/Y)

Table R.1.3.7.5: 1 KCCQ symptom frequency score change from baseline at week 52 (MMRM) by OECD member (N/Y) - RS (OC-AD - no imputation for deaths) - 1245.121

Subgroup / Visit / Description / Statistic	Placebo	Empa 10mg
OECD member: No		
Number of patients in analysis set	741	713
Number of analysed patients	686	664
Baseline mean (SE)	72.56 (0.93)	70.64 (1.00)
Week 52		
Values at visit		
Number of analysed patients	443	421
Mean (SE)	81.00 (1.05)	83.78 (0.99)
Adjusted* mean (SE)	80.39 (0.85)	83.95 (0.87)
95% confidence interval	(78.73,82.05)	(82.25,85.64)
Change from baseline		
Mean (SE)	8.61 (1.23)	13.18 (1.15)
Adjusted* mean (SE)	8.77 (0.85)	12.33 (0.87)
95% confidence interval	(7.11,10.44)	(10.63,14.03)
Comparison vs Placebo		
Adjusted* mean (SE)		3.56 (1.21)
95% confidence interval		(1.18, 5.93)
p-value		0.0033

* Model includes Age, baseline eGFR (CKD-EPI) as linear covariate(s) and baseline diabetes status, sex, baseline LVEF, week reachable, Visit by Treatment by OECD Member (N) interaction, baseline KCCQ symptom frequency score by Visit interaction as fixed effect(s).
The Visit by Treatment by OECD Member (N) p-value at Week 52 is 0.0902.
The following covariance structure has been used to fit the mixed model: Unstructured
Note: All covariate effects are set equal to their mean values within subgroup for the calculation of adjusted means.

For patients who died, only observed values are considered (no imputation after date of death).
Data taken from study 1245.121 only.
OECD member (yes/no) countries included:
Yes: United States, Canada, Mexico, Poland, Netherlands, Hungary, Germany, Czech Republic, Italy, France, Spain, United Kingdom, Belgium, Japan, Australia, 'Korea; Republic Of South Korea';
No: Brazil, Argentina, China, India.
The MMRM includes all outcome values (change from baseline) at the planned Visits week 12, week 32 and week 52

Table R.1.3.7.5: 1 KCCQ symptom frequency score change from baseline at week 52 (MMRM) by OECD member (N/Y) - RS (OC-AD - no imputation for deaths) - 1245.121

Subgroup / Visit / Description / Statistic	Placebo	Empa 10mg
OECD member: Yes		
Number of patients in analysis set	1126	1150
Number of analysed patients	1067	1112
Baseline mean (SE)	74.86 (0.70)	75.06 (0.70)
Week 52		
Values at visit		
Number of analysed patients	775	818
Mean (SE)	78.82 (0.80)	80.55 (0.76)
Adjusted* mean (SE)	78.44 (0.65)	79.43 (0.63)
95% confidence interval	(77.17,79.71)	(78.20,80.67)
Change from baseline		
Mean (SE)	3.43 (0.74)	3.85 (0.69)
Adjusted* mean (SE)	3.48 (0.65)	4.47 (0.63)
95% confidence interval	(2.21, 4.74)	(3.24, 5.71)
Comparison vs Placebo		
Adjusted* mean (SE)		1.00 (0.90)
95% confidence interval		(-0.77, 2.76)
p-value		0.2694

* Model includes Age, baseline eGFR (CKD-EPI) as linear covariate(s) and baseline diabetes status, sex, baseline LVEF, week reachable, Visit by Treatment by OECD Member (N) interaction, baseline KCCQ symptom frequency score by Visit interaction as fixed effect(s).
The Visit by Treatment by OECD Member (N) p-value at Week 52 is 0.0902.
The following covariance structure has been used to fit the mixed model: Unstructured
Note: All covariate effects are set equal to their mean values within subgroup for the calculation of adjusted means.

For patients who died, only observed values are considered (no imputation after date of death).
Data taken from study 1245.121 only.
OECD member (yes/no) countries included:
Yes: United States, Canada, Mexico, Poland, Netherlands, Hungary, Germany, Czech Republic, Italy, France, Spain, United Kingdom, Belgium, Japan, Australia, 'Korea; Republic Of South Korea';
No: Brazil, Argentina, China, India.
The MMRM includes all outcome values (change from baseline) at the planned Visits week 12, week 32 and week 52

R.1.3.7.6 Subgroup analysis by NYHA at baseline (II, III/IV - 2 cat.)

Table R.1.3.7.6: 1 KCCQ symptom frequency score change from baseline at week 52 (MMRM) by NYHA (2 cat.) - RS (OC-AD - no imputation for deaths) - 1245.121

Subgroup / Visit / Description / Statistic	Placebo	Empa 10mg
Baseline NYHA (2 cat.): II		
Number of patients in analysis set	1401	1399
Number of analysed patients	1340	1332
Baseline mean (SE)	77.66 (0.58)	78.56 (0.59)
Week 52		
Values at visit		
Number of analysed patients	946	951
Mean (SE)	81.96 (0.67)	85.09 (0.61)
Adjusted* mean (SE)	82.02 (0.58)	84.48 (0.58)
95% confidence interval	(80.88,83.15)	(83.34,85.61)
Change from baseline		
Mean (SE)	4.40 (0.73)	6.05 (0.65)
Adjusted* mean (SE)	3.91 (0.58)	6.37 (0.58)
95% confidence interval	(2.77, 5.04)	(5.23, 7.50)
Comparison vs Placebo		
Adjusted* mean (SE)		2.46 (0.82)
95% confidence interval		(0.86, 4.06)
p-value		0.0027

* Model includes Age, baseline eGFR (CKD-EPI) as linear covariate(s) and region, baseline diabetes status, sex, baseline LVEF, week reachable, Visit by Treatment by baseline NYHA (2 cat.) interaction, baseline KCCQ symptom frequency score by Visit interaction as fixed effect(s).
The Visit by Treatment by baseline NYHA (2 cat.) p-value at Week 52 is 0.1445.
The following covariance structure has been used to fit the mixed model: Unstructured
Note: All covariate effects are set equal to their mean values within subgroup for the calculation of adjusted means.

For patients who died, only observed values are considered (no imputation after date of death).
Data taken from study 1245.121 only.
The MMRM includes all outcome values (change from baseline) at the planned Visits week 12, week 32 and week 52

Table R.1.3.7.6: 1 KCCQ symptom frequency score change from baseline at week 52 (MMRM) by NYHA (2 cat.) - RS (OC-AD - no imputation for deaths) - 1245.121

Subgroup / Visit / Description / Statistic	Placebo	Empa 10mg
Baseline NYHA (2 cat.): III/IV		
Number of patients in analysis set	466	464
Number of analysed patients	413	444
Baseline mean (SE)	61.96 (1.26)	57.96 (1.24)
Week 52		
Values at visit		
Number of analysed patients	272	288
Mean (SE)	71.44 (1.51)	70.28 (1.44)
Adjusted* mean (SE)	70.16 (1.08)	70.13 (1.04)
95% confidence interval	(68.05,72.27)	(68.08,72.18)
Change from baseline		
Mean (SE)	8.48 (1.46)	10.23 (1.54)
Adjusted* mean (SE)	10.27 (1.08)	10.24 (1.04)
95% confidence interval	(8.16,12.39)	(8.19,12.29)
Comparison vs Placebo		
Adjusted* mean (SE)		-0.03 (1.50)
95% confidence interval		(-2.97, 2.91)
p-value		0.9826

* Model includes Age, baseline eGFR (CKD-EPI) as linear covariate(s) and region, baseline diabetes status, sex, baseline LVEF, week reachable, Visit by Treatment by baseline NYHA (2 cat.) interaction, baseline KCCQ symptom frequency score by Visit interaction as fixed effect(s).
The Visit by Treatment by baseline NYHA (2 cat.) p-value at Week 52 is 0.1445.
The following covariance structure has been used to fit the mixed model: Unstructured
Note: All covariate effects are set equal to their mean values within subgroup for the calculation of adjusted means.

For patients who died, only observed values are considered (no imputation after date of death).
Data taken from study 1245.121 only.
The MMRM includes all outcome values (change from baseline) at the planned Visits week 12, week 32 and week 52

R.1.3.7.7

R.1.3.7.7 Subgroup analysis by diabetes at baseline

Table R.1.3.7.7: 1 KCCQ symptom frequency score change from baseline at week 52 (MMRM) by diabetes at baseline - RS (OC-AD - no imputation for deaths) - 1245.121

Subgroup / Visit / Description / Statistic	Placebo	Empa 10mg
Diabetes at baseline (2 cat.):		
Diabetic		
Number of patients in analysis set	929	927
Number of analysed patients	868	882
Baseline mean (SE)	72.01 (0.83)	71.83 (0.85)
Week 52		
Values at visit		
Number of analysed patients	606	614
Mean (SE)	79.19 (0.92)	81.24 (0.87)
Adjusted* mean (SE)	78.28 (0.73)	80.27 (0.72)
95% confidence interval	(76.85,79.70)	(78.85,81.68)
Change from baseline		
Mean (SE)	5.89 (0.92)	7.75 (0.90)
Adjusted* mean (SE)	6.36 (0.73)	8.35 (0.72)
95% confidence interval	(4.94, 7.79)	(6.94, 9.77)
Comparison vs Placebo		
Adjusted* mean (SE)		1.99 (1.02)
95% confidence interval		(-0.02, 4.00)
p-value		0.0519

* Model includes Age, baseline eGFR (CKD-EPI) as linear covariate(s) and region, sex, baseline LVEF, week reachable, Visit by Treatment by diabetes at baseline (2 cat.) interaction, baseline KCCQ symptom frequency score by Visit interaction as fixed effect(s).
The Visit by Treatment by diabetes at baseline (2 cat.) p-value at Week 52 is 0.8456.
The following covariance structure has been used to fit the mixed model: Unstructured
Note: All covariate effects are set equal to their mean values within subgroup for the calculation of adjusted means.

For patients who died, only observed values are considered (no imputation after date of death).
Data taken from study 1245.121 only.
The MMRM includes all outcome values (change from baseline) at the planned Visits week 12, week 32 and week 52

Table R.1.3.7.7: 1 KCCQ symptom frequency score change from baseline at week 52 (MMRM) by diabetes at baseline - RS (OC-AD - no imputation for deaths) - 1245.121

Subgroup / Visit / Description / Statistic	Placebo	Empa 10mg
Diabetes at baseline (2 cat.):		
Non-Diabetic		
Number of patients in analysis set	938	936
Number of analysed patients	885	894
Baseline mean (SE)	75.87 (0.75)	74.97 (0.78)
Week 52		
Values at visit		
Number of analysed patients	612	625
Mean (SE)	80.03 (0.88)	82.04 (0.84)
Adjusted* mean (SE)	80.04 (0.72)	81.75 (0.72)
95% confidence interval	(78.62,81.45)	(80.34,83.15)
Change from baseline		
Mean (SE)	4.74 (0.93)	6.30 (0.84)
Adjusted* mean (SE)	4.62 (0.72)	6.33 (0.72)
95% confidence interval	(3.20, 6.03)	(4.92, 7.73)
Comparison vs Placebo		
Adjusted* mean (SE)		1.71 (1.02)
95% confidence interval		(-0.28, 3.70)
p-value		0.0927

* Model includes Age, baseline eGFR (CKD-EPI) as linear covariate(s) and region, sex, baseline LVEF, week reachable, Visit by Treatment by diabetes at baseline (2 cat.) interaction, baseline KCCQ symptom frequency score by Visit interaction as fixed effect(s).
The Visit by Treatment by diabetes at baseline (2 cat.) p-value at Week 52 is 0.8456.
The following covariance structure has been used to fit the mixed model: Unstructured
Note: All covariate effects are set equal to their mean values within subgroup for the calculation of adjusted means.

For patients who died, only observed values are considered (no imputation after date of death).
Data taken from study 1245.121 only.
The MMRM includes all outcome values (change from baseline) at the planned Visits week 12, week 32 and week 52

R.1.3.7.8 Subgroup analysis by BMI at baseline (<30, >=30)

Table R.1.3.7.8: 1 KCCQ symptom frequency score change from baseline at week 52 (MMRM) by baseline BMI [kg/m2] - RS (OC-AD - no imputation for deaths) - 1245.121

Subgroup / Visit / Description / Statistic	Placebo	Empa 10mg
Baseline BMI [kg/m²] (2 cat.): <30		
Number of patients in analysis set	1300	1263
Number of analysed patients	1229	1201
Baseline mean (SE)	76.08 (0.64)	75.80 (0.67)
Week 52		
Values at visit		
Number of analysed patients	865	826
Mean (SE)	81.29 (0.71)	83.69 (0.69)
Adjusted* mean (SE)	80.96 (0.61)	82.70 (0.62)
95% confidence interval	(79.76,82.15)	(81.48,83.92)
Change from baseline		
Mean (SE)	4.88 (0.72)	6.39 (0.72)
Adjusted* mean (SE)	5.01 (0.61)	6.76 (0.62)
95% confidence interval	(3.82, 6.21)	(5.54, 7.98)
Comparison vs Placebo		
Adjusted* mean (SE)		1.75 (0.87)
95% confidence interval		(0.04, 3.45)
p-value		0.0446

* Model includes Age, baseline eGFR (CKD-EPI) as linear covariate(s) and region, baseline diabetes status, sex, baseline LVEF, week reachable, Visit by Treatment by baseline BMI [kg/m²] (2 cat.) interaction, baseline KCCQ symptom frequency score by Visit interaction as fixed effect(s).
The Visit by Treatment by baseline BMI [kg/m²] (2 cat.) p-value at Week 52 is 0.6917.
The following covariance structure has been used to fit the mixed model: Unstructured
Note: All covariate effects are set equal to their mean values within subgroup for the calculation of adjusted means.

For patients who died, only observed values are considered (no imputation after date of death).
Data taken from study 1245.121 only.
The MMRM includes all outcome values (change from baseline) at the planned Visits week 12, week 32 and week 52

Table R.1.3.7.8: 1 KCCQ symptom frequency score change from baseline at week 52 (MMRM) by baseline BMI [kg/m2] - RS (OC-AD - no imputation for deaths) - 1245.121

Subgroup / Visit / Description / Statistic	Placebo	Empa 10mg
Baseline BMI [kg/m²] (2 cat.): >=30		
Number of patients in analysis set	567	600
Number of analysed patients	524	575
Baseline mean (SE)	68.98 (1.10)	68.42 (1.08)
Week 52		
Values at visit		
Number of analysed patients	353	413
Mean (SE)	75.52 (1.32)	77.57 (1.14)
Adjusted* mean (SE)	75.06 (0.95)	77.43 (0.89)
95% confidence interval	(73.19,76.93)	(75.69,79.17)
Change from baseline		
Mean (SE)	6.38 (1.39)	8.27 (1.15)
Adjusted* mean (SE)	6.38 (0.95)	8.74 (0.89)
95% confidence interval	(4.51, 8.25)	(7.00,10.48)
Comparison vs Placebo		
Adjusted* mean (SE)		2.36 (1.29)
95% confidence interval		(-0.17, 4.90)
p-value		0.0680

* Model includes Age, baseline eGFR (CKD-EPI) as linear covariate(s) and region, baseline diabetes status, sex, baseline LVEF, week reachable, Visit by Treatment by baseline BMI [kg/m²] (2 cat.) interaction, baseline KCCQ symptom frequency score by Visit interaction as fixed effect(s).
The Visit by Treatment by baseline BMI [kg/m²] (2 cat.) p-value at Week 52 is 0.6917.
The following covariance structure has been used to fit the mixed model: Unstructured
Note: All covariate effects are set equal to their mean values within subgroup for the calculation of adjusted means.

For patients who died, only observed values are considered (no imputation after date of death).
Data taken from study 1245.121 only.
The MMRM includes all outcome values (change from baseline) at the planned Visits week 12, week 32 and week 52

R.1.3.7.9 Subgroup analysis by eGFR at baseline (<60, >=60)

Table R.1.3.7.9: 1 KCCQ symptom frequency score change from baseline at week 52 (MMRM) by baseline eGFR (2 cat.) - RS (OC-AD - no imputation for deaths) - 1245.121

Subgroup / Visit / Description / Statistic	Placebo	Empa 10mg
Baseline eGFR (CKD-EPI) [mL/min/1.73m²] (2 cat.): >=60		
Number of patients in analysis set	960	969
Number of analysed patients	901	921
Baseline mean (SE)	74.28 (0.76)	73.64 (0.82)
Week 52		
Values at visit		
Number of analysed patients	647	650
Mean (SE)	79.48 (0.87)	83.28 (0.83)
Adjusted* mean (SE)	78.85 (0.71)	82.73 (0.70)
95% confidence interval	(77.47,80.24)	(81.36,84.11)
Change from baseline		
Mean (SE)	4.76 (0.85)	8.53 (0.84)
Adjusted* mean (SE)	4.89 (0.71)	8.77 (0.70)
95% confidence interval	(3.51, 6.28)	(7.40,10.15)
Comparison vs Placebo		
Adjusted* mean (SE)		3.88 (0.99)
95% confidence interval		(1.93, 5.82)
p-value		<0.0001

* Model includes Age as linear covariate(s) and region, baseline diabetes status, sex, baseline LVEF, week reachable, Visit by Treatment by baseline eGFR (CKD-EPI) [mL/min/1.73m²] (2 cat.) interaction, baseline KCCQ symptom frequency score by Visit interaction as fixed effect(s).
The Visit by Treatment by baseline eGFR (CKD-EPI) [mL/min/1.73m²] (2 cat.) p-value at Week 52 is 0.0029.
The following covariance structure has been used to fit the mixed model: Unstructured
2 patients were excluded as the subgroup variable was missing.
Note: All covariate effects are set equal to their mean values within subgroup for the calculation of adjusted means.

For patients who died, only observed values are considered (no imputation after date of death).
Data taken from study 1245.121 only.
The MMRM includes all outcome values (change from baseline) at the planned Visits week 12, week 32 and week 52

Table R.1.3.7.9: 1 KCCQ symptom frequency score change from baseline at week 52 (MMRM) by baseline eGFR (2 cat.) - RS (OC-AD - no imputation for deaths) - 1245.121

Subgroup / Visit / Description / Statistic	Placebo	Empa 10mg
Baseline eGFR (CKD-EPI) [mL/min/1.73m²] (2 cat.): <60		
Number of patients in analysis set	906	893
Number of analysed patients	852	855
Baseline mean (SE)	73.62 (0.82)	73.16 (0.82)
Week 52		
Values at visit		
Number of analysed patients	571	589
Mean (SE)	79.76 (0.92)	79.84 (0.87)
Adjusted* mean (SE)	79.57 (0.75)	79.14 (0.74)
95% confidence interval	(78.10,81.03)	(77.70,80.59)
Change from baseline		
Mean (SE)	5.94 (1.01)	5.35 (0.90)
Adjusted* mean (SE)	6.18 (0.75)	5.76 (0.74)
95% confidence interval	(4.72, 7.65)	(4.31, 7.20)
Comparison vs Placebo		
Adjusted* mean (SE)		-0.43 (1.05)
95% confidence interval		(-2.48, 1.63)
p-value		0.6842

* Model includes Age as linear covariate(s) and region, baseline diabetes status, sex, baseline LVEF, week reachable, Visit by Treatment by baseline eGFR (CKD-EPI) [mL/min/1.73m²] (2 cat.) interaction, baseline KCCQ symptom frequency score by Visit interaction as fixed effect(s).
The Visit by Treatment by baseline eGFR (CKD-EPI) [mL/min/1.73m²] (2 cat.) p-value at Week 52 is 0.0029.
The following covariance structure has been used to fit the mixed model: Unstructured
2 patients were excluded as the subgroup variable was missing.
Note: All covariate effects are set equal to their mean values within subgroup for the calculation of adjusted means.

For patients who died, only observed values are considered (no imputation after date of death).
Data taken from study 1245.121 only.
The MMRM includes all outcome values (change from baseline) at the planned Visits week 12, week 32 and week 52

R.1.3.7.10

R.1.3.7.10 Subgroup analysis by history of HHF

Table R.1.3.7.10: 1 KCCQ symptom frequency score change from baseline at week 52 (MMRM) by history of HHF - RS (OC-AD - no imputation for deaths) - 1245.121

Subgroup / Visit / Description / Statistic	Placebo	Empa 10mg
History of HHF (in the last 12 months): No		
Number of patients in analysis set	1293	1286
Number of analysed patients	1220	1231
Baseline mean (SE)	74.10 (0.67)	73.90 (0.68)
Week 52		
Values at visit		
Number of analysed patients	869	873
Mean (SE)	79.02 (0.77)	81.85 (0.70)
Adjusted* mean (SE)	79.09 (0.61)	81.54 (0.61)
95% confidence interval	(77.89,80.28)	(80.35,82.73)
Change from baseline		
Mean (SE)	5.01 (0.79)	7.44 (0.72)
Adjusted* mean (SE)	5.09 (0.61)	7.54 (0.61)
95% confidence interval	(3.90, 6.28)	(6.35, 8.73)
Comparison vs Placebo		
Adjusted* mean (SE)		2.45 (0.86)
95% confidence interval		(0.77, 4.13)
p-value		0.0044

* Model includes Age, baseline eGFR (CKD-EPI) as linear covariate(s) and region, baseline diabetes status, sex, baseline LVEF, week reachable, Visit by Treatment by history of HHF (in the last 12 months) interaction, baseline KCCQ symptom frequency score by Visit interaction as fixed effect(s).
The Visit by Treatment by history of HHF (in the last 12 months) p-value at Week 52 is 0.1871.
The following covariance structure has been used to fit the mixed model: Unstructured
Note: All covariate effects are set equal to their mean values within subgroup for the calculation of adjusted means.

For patients who died, only observed values are considered (no imputation after date of death).
Data taken from study 1245.121 only.
The MMRM includes all outcome values (change from baseline) at the planned Visits week 12, week 32 and week 52

Table R.1.3.7.10: 1 KCCQ symptom frequency score change from baseline at week 52 (MMRM) by history of HHF - RS (OC-AD - no imputation for deaths) - 1245.121

Subgroup / Visit / Description / Statistic	Placebo	Empa 10mg
History of HHF (in the last 12 months): Yes		
Number of patients in analysis set	574	577
Number of analysed patients	533	545
Baseline mean (SE)	73.64 (1.03)	72.31 (1.11)
Week 52		
Values at visit		
Number of analysed patients	349	366
Mean (SE)	81.09 (1.11)	81.16 (1.16)
Adjusted* mean (SE)	79.41 (0.96)	79.77 (0.94)
95% confidence interval	(77.54,81.28)	(77.93,81.60)
Change from baseline		
Mean (SE)	6.08 (1.17)	6.01 (1.16)
Adjusted* mean (SE)	6.45 (0.96)	6.80 (0.94)
95% confidence interval	(4.57, 8.32)	(4.97, 8.64)
Comparison vs Placebo		
Adjusted* mean (SE)		0.36 (1.33)
95% confidence interval		(-2.26, 2.97)
p-value		0.7888

* Model includes Age, baseline eGFR (CKD-EPI) as linear covariate(s) and region, baseline diabetes status, sex, baseline LVEF, week reachable, Visit by Treatment by history of HHF (in the last 12 months) interaction, baseline KCCQ symptom frequency score by Visit interaction as fixed effect(s).
The Visit by Treatment by history of HHF (in the last 12 months) p-value at Week 52 is 0.1871.
The following covariance structure has been used to fit the mixed model: Unstructured
Note: All covariate effects are set equal to their mean values within subgroup for the calculation of adjusted means.

For patients who died, only observed values are considered (no imputation after date of death).
Data taken from study 1245.121 only.
The MMRM includes all outcome values (change from baseline) at the planned Visits week 12, week 32 and week 52

R.1.3.7.11

Table R.1.3.7.11: 1 KCCQ symptom frequency score change from baseline at week 52 (MMRM) by cause of heart failure - RS (OC-AD - no imputation for deaths) - 1245.121

Subgroup / Visit / Description / Statistic	Placebo	Empa 10mg
Cause of heart failure: Ischemic		
Number of patients in analysis set	946	983
Number of analysed patients	896	936
Baseline mean (SE)	74.61 (0.76)	73.69 (0.79)
Week 52		
Values at visit		
Number of analysed patients	634	667
Mean (SE)	79.64 (0.89)	81.40 (0.82)
Adjusted* mean (SE)	79.32 (0.72)	80.79 (0.70)
95% confidence interval	(77.92,80.73)	(79.42,82.15)
Change from baseline		
Mean (SE)	4.57 (0.87)	6.18 (0.84)
Adjusted* mean (SE)	5.18 (0.72)	6.65 (0.70)
95% confidence interval	(3.78, 6.59)	(5.28, 8.01)
Comparison vs Placebo		
Adjusted* mean (SE)		1.46 (0.99)
95% confidence interval		(-0.49, 3.41)
p-value		0.1410

* Model includes Age, baseline eGFR (CKD-EPI) as linear covariate(s) and region, baseline diabetes status, sex, baseline LVEF, week reachable, Visit by Treatment by cause of heart failure interaction, baseline KCCQ symptom frequency score by Visit interaction as fixed effect(s).
The Visit by Treatment by cause of heart failure p-value at Week 52 is 0.5750.
The following covariance structure has been used to fit the mixed model: Unstructured
Note: All covariate effects are set equal to their mean values within subgroup for the calculation of adjusted means.

For patients who died, only observed values are considered (no imputation after date of death).
Data taken from study 1245.121 only.
The MMRM includes all outcome values (change from baseline) at the planned Visits week 12, week 32 and week 52

Table R.1.3.7.11: 1 KCCQ symptom frequency score change from baseline at week 52 (MMRM) by cause of heart failure - RS (OC-AD - no imputation for deaths) - 1245.121

Subgroup / Visit / Description / Statistic	Placebo	Empa 10mg
Cause of heart failure: Non-ischemic		
Number of patients in analysis set	921	880
Number of analysed patients	857	840
Baseline mean (SE)	73.28 (0.82)	73.10 (0.85)
Week 52		
Values at visit		
Number of analysed patients	584	572
Mean (SE)	79.59 (0.91)	81.94 (0.89)
Adjusted* mean (SE)	79.01 (0.74)	81.28 (0.75)
95% confidence interval	(77.55,80.47)	(79.81,82.75)
Change from baseline		
Mean (SE)	6.12 (0.98)	7.99 (0.91)
Adjusted* mean (SE)	5.82 (0.74)	8.09 (0.75)
95% confidence interval	(4.36, 7.28)	(6.63, 9.56)
Comparison vs Placebo		
Adjusted* mean (SE)		2.27 (1.05)
95% confidence interval		(0.22, 4.33)
p-value		0.0304

* Model includes Age, baseline eGFR (CKD-EPI) as linear covariate(s) and region, baseline diabetes status, sex, baseline LVEF, week reachable, Visit by Treatment by cause of heart failure interaction, baseline KCCQ symptom frequency score by Visit interaction as fixed effect(s).
The Visit by Treatment by cause of heart failure p-value at Week 52 is 0.5750.
The following covariance structure has been used to fit the mixed model: Unstructured
Note: All covariate effects are set equal to their mean values within subgroup for the calculation of adjusted means.

For patients who died, only observed values are considered (no imputation after date of death).
Data taken from study 1245.121 only.
The MMRM includes all outcome values (change from baseline) at the planned Visits week 12, week 32 and week 52

R.1.3.7.12 Subgroup analysis by heart failure physiology (LVEF <= 30% and NTproBNP<median; LVEF <= 30% and NTproBNP>=median; LVEF > 30%)

Table R.1.3.7.12: 1 KCCQ symptom frequency score change from baseline at week 52 (MMRM) by heart failure physiology - RS (OC-AD - no imputation for deaths) - 1245.121

Subgroup / Visit / Description / Statistic	Placebo	Empa 10mg
Heart failure physiology: LVEF <= 30% and NTproBNP < median		
Number of patients in analysis set	723	698
Number of analysed patients	694	672
Baseline mean (SE)	75.31 (0.86)	76.26 (0.87)
Week 52		
Values at visit		
Number of analysed patients	511	494
Mean (SE)	80.69 (1.01)	82.78 (0.93)
Adjusted* mean (SE)	80.59 (0.79)	82.60 (0.81)
95% confidence interval	(79.04,82.15)	(81.02,84.19)
Change from baseline		
Mean (SE)	5.36 (0.99)	6.74 (0.88)
Adjusted* mean (SE)	4.82 (0.79)	6.83 (0.81)
95% confidence interval	(3.26, 6.38)	(5.25, 8.41)
Comparison vs Placebo		
Adjusted* mean (SE)		2.01 (1.13)
95% confidence interval		(-0.21, 4.23)
p-value		0.0760

* Model includes Age, baseline eGFR (CKD-EPI) as linear covariate(s) and region, baseline diabetes status, sex, week reachable, Visit by Treatment by heart failure physiology interaction, baseline KCCQ symptom frequency score by Visit interaction as fixed effect(s).
The Visit by Treatment by heart failure physiology p-value at Week 52 is 0.6181.
The following covariance structure has been used to fit the mixed model: Unstructured
16 patients were excluded as the subgroup variable was missing.
Note: All covariate effects are set equal to their mean values within subgroup for the calculation of adjusted means.
The p-value for the visit by treatment by subgroup interaction trend test at Week 52 is 0.5537

For patients who died, only observed values are considered (no imputation after date of death).
Data taken from study 1245.121 only.
NTproBNP median [pg/mL]: with a. fibrillation/flutter at baseline: 2265; without a. fibrillation/flutter at baseline: 1671.
The MMRM includes all outcome values (change from baseline) at the planned Visits week 12, week 32 and week 52

Table R.1.3.7.12: 1 KCCQ symptom frequency score change from baseline at week 52 (MMRM) by heart failure physiology - RS (OC-AD - no imputation for deaths) - 1245.121

Subgroup / Visit / Description / Statistic	Placebo	Empa 10mg
Heart failure physiology: LVEF <= 30% and NTproBNP >= median		
Number of patients in analysis set	661	631
Number of analysed patients	604	593
Baseline mean (SE)	72.19 (0.99)	68.90 (1.07)
Week 52		
Values at visit		
Number of analysed patients	409	405
Mean (SE)	77.22 (1.13)	79.77 (1.10)
Adjusted* mean (SE)	76.43 (0.88)	78.98 (0.89)
95% confidence interval	(74.70,78.16)	(77.24,80.72)
Change from baseline		
Mean (SE)	4.51 (1.21)	8.50 (1.25)
Adjusted* mean (SE)	5.87 (0.88)	8.42 (0.89)
95% confidence interval	(4.14, 7.60)	(6.68,10.16)
Comparison vs Placebo		
Adjusted* mean (SE)		2.55 (1.25)
95% confidence interval		(0.09, 5.00)
p-value		0.0420

* Model includes Age, baseline eGFR (CKD-EPI) as linear covariate(s) and region, baseline diabetes status, sex, week reachable, Visit by Treatment by heart failure physiology interaction, baseline KCCQ symptom frequency score by Visit interaction as fixed effect(s).
The Visit by Treatment by heart failure physiology p-value at Week 52 is 0.6181.
The following covariance structure has been used to fit the mixed model: Unstructured
16 patients were excluded as the subgroup variable was missing.
Note: All covariate effects are set equal to their mean values within subgroup for the calculation of adjusted means.
The p-value for the visit by treatment by subgroup interaction trend test at Week 52 is 0.5537

For patients who died, only observed values are considered (no imputation after date of death).
Data taken from study 1245.121 only.
NTproBNP median [pg/mL]: with a. fibrillation/flutter at baseline: 2265; without a. fibrillation/flutter at baseline: 1671.
The MMRM includes all outcome values (change from baseline) at the planned Visits week 12, week 32 and week 52

Table R.1.3.7.12: 1 KCCQ symptom frequency score change from baseline at week 52 (MMRM) by heart failure physiology - RS (OC-AD - no imputation for deaths) - 1245.121

Subgroup / Visit / Description / Statistic	Placebo	Empa 10mg
Heart failure physiology: LVEF > 30%		
Number of patients in analysis set	475	526
Number of analysed patients	450	506
Baseline mean (SE)	74.49 (1.08)	75.01 (1.07)
Week 52		
Values at visit		
Number of analysed patients	294	339
Mean (SE)	81.21 (1.15)	82.24 (1.13)
Adjusted* mean (SE)	80.62 (1.04)	81.35 (0.97)
95% confidence interval	(78.59,82.66)	(79.45,83.24)
Change from baseline		
Mean (SE)	6.16 (1.25)	5.68 (1.09)
Adjusted* mean (SE)	5.86 (1.04)	6.58 (0.97)
95% confidence interval	(3.82, 7.90)	(4.69, 8.48)
Comparison vs Placebo		
Adjusted* mean (SE)		0.72 (1.42)
95% confidence interval		(-2.06, 3.50)
p-value		0.6104

* Model includes Age, baseline eGFR (CKD-EPI) as linear covariate(s) and region, baseline diabetes status, sex, week reachable, Visit by Treatment by heart failure physiology interaction, baseline KCCQ symptom frequency score by Visit interaction as fixed effect(s).
The Visit by Treatment by heart failure physiology p-value at Week 52 is 0.6181.
The following covariance structure has been used to fit the mixed model: Unstructured
16 patients were excluded as the subgroup variable was missing.
Note: All covariate effects are set equal to their mean values within subgroup for the calculation of adjusted means.
The p-value for the visit by treatment by subgroup interaction trend test at Week 52 is 0.5537

For patients who died, only observed values are considered (no imputation after date of death).
Data taken from study 1245.121 only.
NTproBNP median [pg/mL]: with a. fibrillation/flutter at baseline: 2265; without a. fibrillation/flutter at baseline: 1671.
The MMRM includes all outcome values (change from baseline) at the planned Visits week 12, week 32 and week 52

R.1.3.7.13

R.1.3.7.13 Subgroup analysis by baseline use of MRA

Table R.1.3.7.13: 1 KCCQ symptom frequency score change from baseline at week 52 (MMRM) by baseline use of MRA (Y/N) - RS (OC-AD - no imputation for deaths) - 1245.121

Subgroup / Visit / Description / Statistic	Placebo	Empa 10mg
Baseline use of MRA: No		
Number of patients in analysis set	512	557
Number of analysed patients	486	531
Baseline mean (SE)	75.23 (1.03)	73.91 (1.08)
Week 52		
Values at visit		
Number of analysed patients	340	383
Mean (SE)	77.73 (1.23)	83.17 (1.03)
Adjusted* mean (SE)	78.21 (0.97)	82.59 (0.92)
95% confidence interval	(76.30,80.11)	(80.78,84.39)
Change from baseline		
Mean (SE)	3.24 (1.23)	7.37 (1.12)
Adjusted* mean (SE)	3.67 (0.97)	8.05 (0.92)
95% confidence interval	(1.76, 5.57)	(6.24, 9.85)
Comparison vs Placebo		
Adjusted* mean (SE)		4.38 (1.33)
95% confidence interval		(1.77, 6.99)
p-value		0.0010

* Model includes Age, baseline eGFR (CKD-EPI) as linear covariate(s) and region, baseline diabetes status, sex, baseline LVEF, week reachable, Visit by Treatment by baseline use of MRA interaction, baseline KCCQ symptom frequency score by Visit interaction as fixed effect(s).
The Visit by Treatment by baseline use of MRA p-value at Week 52 is 0.0236.
The following covariance structure has been used to fit the mixed model: Unstructured
Note: All covariate effects are set equal to their mean values within subgroup for the calculation of adjusted means.

For patients who died, only observed values are considered (no imputation after date of death).
Data taken from study 1245.121 only.
The MMRM includes all outcome values (change from baseline) at the planned Visits week 12, week 32 and week 52

Table R.1.3.7.13: 1 KCCQ symptom frequency score change from baseline at week 52 (MMRM) by baseline use of MRA (Y/N) - RS (OC-AD - no imputation for deaths) - 1245.121

Subgroup / Visit / Description / Statistic	Placebo	Empa 10mg
Baseline use of MRA: Yes		
Number of patients in analysis set	1355	1306
Number of analysed patients	1267	1245
Baseline mean (SE)	73.47 (0.66)	73.20 (0.69)
Week 52		
Values at visit		
Number of analysed patients	878	856
Mean (SE)	80.34 (0.74)	80.97 (0.74)
Adjusted* mean (SE)	79.54 (0.60)	80.33 (0.61)
95% confidence interval	(78.35,80.72)	(79.13,81.52)
Change from baseline		
Mean (SE)	6.12 (0.77)	6.86 (0.74)
Adjusted* mean (SE)	6.20 (0.60)	6.99 (0.61)
95% confidence interval	(5.02, 7.39)	(5.79, 8.19)
Comparison vs Placebo		
Adjusted* mean (SE)		0.79 (0.86)
95% confidence interval		(-0.89, 2.47)
p-value		0.3576

* Model includes Age, baseline eGFR (CKD-EPI) as linear covariate(s) and region, baseline diabetes status, sex, baseline LVEF, week reachable, Visit by Treatment by baseline use of MRA interaction, baseline KCCQ symptom frequency score by Visit interaction as fixed effect(s).
The Visit by Treatment by baseline use of MRA p-value at Week 52 is 0.0236.
The following covariance structure has been used to fit the mixed model: Unstructured
Note: All covariate effects are set equal to their mean values within subgroup for the calculation of adjusted means.

For patients who died, only observed values are considered (no imputation after date of death).
Data taken from study 1245.121 only.
The MMRM includes all outcome values (change from baseline) at the planned Visits week 12, week 32 and week 52

R.1.3.7.14

Table R.1.3.7.14: 1 KCCQ symptom frequency score change from baseline at week 52 (MMRM) by baseline use of ARNi (Y/N) - RS (OC-AD - no imputation for deaths) - 1245.121

Subgroup / Visit / Description / Statistic	Placebo	Empa 10mg
Baseline use of ARNi: No		
Number of patients in analysis set	1480	1523
Number of analysed patients	1390	1447
Baseline mean (SE)	73.83 (0.62)	72.84 (0.65)
Week 52		
Values at visit		
Number of analysed patients	960	1026
Mean (SE)	79.56 (0.71)	81.38 (0.67)
Adjusted* mean (SE)	78.92 (0.58)	80.78 (0.56)
95% confidence interval	(77.78,80.05)	(79.68,81.88)
Change from baseline		
Mean (SE)	5.46 (0.74)	7.34 (0.69)
Adjusted* mean (SE)	5.59 (0.58)	7.45 (0.56)
95% confidence interval	(4.46, 6.73)	(6.36, 8.55)
Comparison vs Placebo		
Adjusted* mean (SE)		1.86 (0.80)
95% confidence interval		(0.28, 3.44)
p-value		0.0207

* Model includes Age, baseline eGFR (CKD-EPI) as linear covariate(s) and region, baseline diabetes status, sex, baseline LVEF, week reachable, Visit by Treatment by baseline use of ARNi interaction, baseline KCCQ symptom frequency score by Visit interaction as fixed effect(s).
The Visit by Treatment by baseline use of ARNi p-value at Week 52 is 0.9916.
The following covariance structure has been used to fit the mixed model: Unstructured
Note: All covariate effects are set equal to their mean values within subgroup for the calculation of adjusted means.

For patients who died, only observed values are considered (no imputation after date of death).
Data taken from study 1245.121 only.
The MMRM includes all outcome values (change from baseline) at the planned Visits week 12, week 32 and week 52

Table R.1.3.7.14: 1 KCCQ symptom frequency score change from baseline at week 52 (MMRM) by baseline use of ARNi (Y/N) - RS (OC-AD - no imputation for deaths) - 1245.121

Subgroup / Visit / Description / Statistic	Placebo	Empa 10mg
Baseline use of ARNi: Yes		
Number of patients in analysis set	387	340
Number of analysed patients	363	329
Baseline mean (SE)	74.47 (1.31)	75.92 (1.29)
Week 52		
Values at visit		
Number of analysed patients	258	213
Mean (SE)	79.83 (1.42)	82.91 (1.43)
Adjusted* mean (SE)	80.16 (1.12)	82.00 (1.22)
95% confidence interval	(77.96,82.35)	(79.60,84.40)
Change from baseline		
Mean (SE)	4.77 (1.37)	5.48 (1.30)
Adjusted* mean (SE)	5.00 (1.12)	6.84 (1.22)
95% confidence interval	(2.80, 7.20)	(4.44, 9.24)
Comparison vs Placebo		
Adjusted* mean (SE)		1.84 (1.65)
95% confidence interval		(-1.40, 5.08)
p-value		0.2656

* Model includes Age, baseline eGFR (CKD-EPI) as linear covariate(s) and region, baseline diabetes status, sex, baseline LVEF, week reachable, Visit by Treatment by baseline use of ARNi interaction, baseline KCCQ symptom frequency score by Visit interaction as fixed effect(s).
The Visit by Treatment by baseline use of ARNi p-value at Week 52 is 0.9916.
The following covariance structure has been used to fit the mixed model: Unstructured
Note: All covariate effects are set equal to their mean values within subgroup for the calculation of adjusted means.

For patients who died, only observed values are considered (no imputation after date of death).
Data taken from study 1245.121 only.
The MMRM includes all outcome values (change from baseline) at the planned Visits week 12, week 32 and week 52

R.1.3.7.15 Subgroup analysis by bl. LVEF (<= 30%, >30% -<= 35% , > 35%)

Table R.1.3.7.15: 1 KCCQ symptom frequency score change from baseline at week 52 (MMRM) by baseline LVEF (3 cat.) - RS (OC-AD - no imputation for deaths) - 1245.121

Subgroup / Visit / Description / Statistic	Placebo	Empa 10mg
Baseline LVEF (3 cat.): <=30		
Number of patients in analysis set	1392	1337
Number of analysed patients	1303	1270
Baseline mean (SE)	73.78 (0.65)	72.77 (0.69)
Week 52		
Values at visit		
Number of analysed patients	924	900
Mean (SE)	79.10 (0.75)	81.42 (0.71)
Adjusted* mean (SE)	78.66 (0.59)	80.90 (0.60)
95% confidence interval	(77.50,79.81)	(79.73,82.07)
Change from baseline		
Mean (SE)	5.04 (0.76)	7.52 (0.74)
Adjusted* mean (SE)	5.37 (0.59)	7.62 (0.60)
95% confidence interval	(4.22, 6.53)	(6.45, 8.79)
Comparison vs Placebo		
Adjusted* mean (SE)		2.24 (0.84)
95% confidence interval		(0.60, 3.89)
p-value		0.0075

* Model includes Age, baseline eGFR (CKD-EPI) as linear covariate(s) and region, baseline diabetes status, sex, week reachable, Visit by Treatment by baseline LVEF (3 cat.) interaction, baseline KCCQ symptom frequency score by Visit interaction as fixed effect(s).
The Visit by Treatment by baseline LVEF (3 cat.) p-value at Week 52 is 0.4714.
The following covariance structure has been used to fit the mixed model: Unstructured
Note: All covariate effects are set equal to their mean values within subgroup for the calculation of adjusted means.
The p-value for the visit by treatment by subgroup interaction trend test at Week 52 is 0.5672

For patients who died, only observed values are considered (no imputation after date of death).
Data taken from study 1245.121 only.
The MMRM includes all outcome values (change from baseline) at the planned Visits week 12, week 32 and week 52

Table R.1.3.7.15: 1 KCCQ symptom frequency score change from baseline at week 52 (MMRM) by baseline LVEF (3 cat.) - RS (OC-AD - no imputation for deaths) - 1245.121

Subgroup / Visit / Description / Statistic	Placebo	Empa 10mg
Baseline LVEF (3 cat.): >30 to <=35		
Number of patients in analysis set	361	398
Number of analysed patients	342	385
Baseline mean (SE)	75.40 (1.20)	75.13 (1.19)
Week 52		
Values at visit		
Number of analysed patients	233	256
Mean (SE)	82.21 (1.23)	81.69 (1.29)
Adjusted* mean (SE)	81.23 (1.17)	81.33 (1.11)
95% confidence interval	(78.94,83.53)	(79.15,83.51)
Change from baseline		
Mean (SE)	5.97 (1.39)	4.85 (1.16)
Adjusted* mean (SE)	5.98 (1.17)	6.08 (1.11)
95% confidence interval	(3.69, 8.27)	(3.90, 8.26)
Comparison vs Placebo		
Adjusted* mean (SE)		0.10 (1.61)
95% confidence interval		(-3.06, 3.26)
p-value		0.9515

* Model includes Age, baseline eGFR (CKD-EPI) as linear covariate(s) and region, baseline diabetes status, sex, week reachable, Visit by Treatment by baseline LVEF (3 cat.) interaction, baseline KCCQ symptom frequency score by Visit interaction as fixed effect(s).
The Visit by Treatment by baseline LVEF (3 cat.) p-value at Week 52 is 0.4714.
The following covariance structure has been used to fit the mixed model: Unstructured
Note: All covariate effects are set equal to their mean values within subgroup for the calculation of adjusted means.
The p-value for the visit by treatment by subgroup interaction trend test at Week 52 is 0.5672

For patients who died, only observed values are considered (no imputation after date of death).
Data taken from study 1245.121 only.
The MMRM includes all outcome values (change from baseline) at the planned Visits week 12, week 32 and week 52

Table R.1.3.7.15: 1 KCCQ symptom frequency score change from baseline at week 52 (MMRM) by baseline LVEF (3 cat.) - RS (OC-AD - no imputation for deaths) - 1245.121

Subgroup / Visit / Description / Statistic	Placebo	Empa 10mg
Baseline LVEF (3 cat.): >35		
Number of patients in analysis set	114	128
Number of analysed patients	108	121
Baseline mean (SE)	71.60 (2.42)	74.62 (2.38)
Week 52		
Values at visit		
Number of analysed patients	61	83
Mean (SE)	77.42 (2.98)	83.94 (2.30)
Adjusted* mean (SE)	78.49 (2.26)	81.31 (1.96)
95% confidence interval	(74.07,82.92)	(77.47,85.16)
Change from baseline		
Mean (SE)	6.86 (2.83)	8.26 (2.63)
Adjusted* mean (SE)	5.30 (2.26)	8.11 (1.96)
95% confidence interval	(0.87, 9.72)	(4.27,11.96)
Comparison vs Placebo		
Adjusted* mean (SE)		2.82 (2.99)
95% confidence interval		(-3.04, 8.68)
p-value		0.3461

* Model includes Age, baseline eGFR (CKD-EPI) as linear covariate(s) and region, baseline diabetes status, sex, week reachable, Visit by Treatment by baseline LVEF (3 cat.) interaction, baseline KCCQ symptom frequency score by Visit interaction as fixed effect(s).
The Visit by Treatment by baseline LVEF (3 cat.) p-value at Week 52 is 0.4714.
The following covariance structure has been used to fit the mixed model: Unstructured
Note: All covariate effects are set equal to their mean values within subgroup for the calculation of adjusted means.
The p-value for the visit by treatment by subgroup interaction trend test at Week 52 is 0.5672

For patients who died, only observed values are considered (no imputation after date of death).
Data taken from study 1245.121 only.
The MMRM includes all outcome values (change from baseline) at the planned Visits week 12, week 32 and week 52

R.1.3.7.16

R.1.3.7.16 Subgroup analysis by bl. NTproBNP </>= median (median based on total patients)

Table R.1.3.7.16: 1 KCCQ symptom frequency score change from baseline at week 52 (MMRM) by bl. NTproBNP (<median, >= median) (median based on total patients) - RS (OC-AD - no imputation for deaths) - 1245.121

Subgroup / Visit / Description / Statistic	Placebo	Empa 10mg
Baseline NTproBNP (<median, >= median): < median		
Number of patients in analysis set	920	942
Number of analysed patients	884	908
Baseline mean (SE)	76.25 (0.74)	76.63 (0.74)
Week 52		
Values at visit		
Number of analysed patients	651	666
Mean (SE)	80.93 (0.86)	82.86 (0.80)
Adjusted* mean (SE)	80.87 (0.70)	82.83 (0.70)
95% confidence interval	(79.48,82.25)	(81.46,84.19)
Change from baseline		
Mean (SE)	4.98 (0.84)	6.34 (0.74)
Adjusted* mean (SE)	4.43 (0.70)	6.39 (0.70)
95% confidence interval	(3.04, 5.81)	(5.02, 7.75)
Comparison vs Placebo		
Adjusted* mean (SE)		1.96 (0.99)
95% confidence interval		(0.02, 3.90)
p-value		0.0475

* Model includes Age, baseline eGFR (CKD-EPI) as linear covariate(s) and region, baseline diabetes status, sex, baseline LVEF, week reachable, Visit by Treatment by baseline NTproBNP (<median, >= median) interaction, baseline KCCQ symptom frequency score by Visit interaction as fixed effect(s). The Visit by Treatment by baseline NTproBNP (<median, >= median) p-value at Week 52 is 0.8326.
The following covariance structure has been used to fit the mixed model: Unstructured
2 patients were excluded as the subgroup variable was missing.
Note: All covariate effects are set equal to their mean values within subgroup for the calculation of adjusted means.

For patients who died, only observed values are considered (no imputation after date of death).
Data taken from study 1245.121 only.
Median: 1910 [pg/mL]
The MMRM includes all outcome values (change from baseline) at the planned Visits week 12, week 32 and week 52

Table R.1.3.7.16: 1 KCCQ symptom frequency score change from baseline at week 52 (MMRM) by bl. NTproBNP (<median, >= median) (median based on total patients) - RS (OC-AD - no imputation for deaths) - 1245.121

Subgroup / Visit / Description / Statistic	Placebo	Empa 10mg
Baseline NTproBNP (<median, >= median): >= median		
Number of patients in analysis set	946	920
Number of analysed patients	869	868
Baseline mean (SE)	71.63 (0.83)	70.05 (0.88)
Week 52		
Values at visit		
Number of analysed patients	567	573
Mean (SE)	78.10 (0.94)	80.24 (0.92)
Adjusted* mean (SE)	77.43 (0.75)	79.09 (0.75)
95% confidence interval	(75.97,78.90)	(77.63,80.55)
Change from baseline		
Mean (SE)	5.69 (1.03)	7.80 (1.01)
Adjusted* mean (SE)	6.59 (0.75)	8.25 (0.75)
95% confidence interval	(5.13, 8.06)	(6.79, 9.71)
Comparison vs Placebo		
Adjusted* mean (SE)		1.66 (1.05)
95% confidence interval		(-0.41, 3.72)
p-value		0.1165

* Model includes Age, baseline eGFR (CKD-EPI) as linear covariate(s) and region, baseline diabetes status, sex, baseline LVEF, week reachable, Visit by Treatment by baseline NTproBNP (<median, >= median) interaction, baseline KCCQ symptom frequency score by Visit interaction as fixed effect(s). The Visit by Treatment by baseline NTproBNP (<median, >= median) p-value at Week 52 is 0.8326.
The following covariance structure has been used to fit the mixed model: Unstructured
2 patients were excluded as the subgroup variable was missing.
Note: All covariate effects are set equal to their mean values within subgroup for the calculation of adjusted means.

For patients who died, only observed values are considered (no imputation after date of death).
Data taken from study 1245.121 only.
Median: 1910 [pg/mL]
The MMRM includes all outcome values (change from baseline) at the planned Visits week 12, week 32 and week 52

R.1.3.8

R.1.3.8 KCCQ symptom burden score MMRM analysis

R.1.3.8.1

Table R.1.3.8.1: 1

Table R.1.3.8.1: 1 KCCQ symptom burden score change from baseline MMRM results over time - RS (OC-AD - no imputation for deaths) - 1245.121

Visit Description Statistic	Placebo	Empa 10mg
Number of patients in analysis set	1867	1863
Number of analysed patients	1753	1776
Baseline mean (SE)	76.10 (0.53)	75.99 (0.54)
Week 12		
Values at visit		
Number of analysed patients	1732	1755
Mean (SE)	79.66 (0.51)	81.83 (0.50)
Adjusted* mean (SE)	79.63 (0.40)	81.89 (0.40)
95% confidence interval	(78.84,80.42)	(81.11,82.68)
Change from baseline		
Mean (SE)	3.46 (0.46)	5.81 (0.47)
Adjusted* mean (SE)	3.28 (0.40)	5.54 (0.40)
95% confidence interval	(2.49, 4.07)	(4.75, 6.32)
Comparison vs Placebo		
Adjusted* mean (SE)		2.26 (0.57)
95% confidence interval		(1.15, 3.37)
p-value		<0.0001
Hedges g		
Estimate		0.13
95% confidence interval		(0.07, 0.20)

* Model includes Age (p=0.7716), baseline eGFR (CKD-EPI) (p=0.0242) as linear covariate(s) and region (p<0.0001), baseline diabetes status (p=0.5156), sex (p=0.0007), baseline LVEF (p=0.3173), week reachable (p=0.0696), Treatment by Visit interaction (p<0.0001), baseline KCCQ symptom burden score by Visit interaction (p<0.0001) as fixed effect(s).
The following covariance structure has been used to fit the mixed model: Unstructured

For patients who died, only observed values are considered (no imputation after date of death).
Data taken from study 1245.121 only.

Table R.1.3.8.1: 1 KCCQ symptom burden score change from baseline MMRM results over time - RS (OC-AD - no imputation for deaths) - 1245.121

Visit Description Statistic	Placebo	Empa 10mg
Week 32		
Values at visit		
Number of analysed patients	1568	1616
Mean (SE)	80.42 (0.53)	82.13 (0.52)
Adjusted* mean (SE)	80.20 (0.43)	81.87 (0.43)
95% confidence interval	(79.35,81.06)	(81.03,82.71)
Change from baseline		
Mean (SE)	4.12 (0.52)	5.70 (0.51)
Adjusted* mean (SE)	3.85 (0.43)	5.52 (0.43)
95% confidence interval	(2.99, 4.70)	(4.67, 6.36)
Comparison vs Placebo		
Adjusted* mean (SE)		1.67 (0.61)
95% confidence interval		(0.47, 2.87)
p-value		0.0063
Hedges g		
Estimate		0.10
95% confidence interval		(0.03, 0.17)

* Model includes Age (p=0.7716), baseline eGFR (CKD-EPI) (p=0.0242) as linear covariate(s) and region (p<0.0001), baseline diabetes status (p=0.5156), sex (p=0.0007), baseline LVEF (p=0.3173), week reachable (p=0.0696), Treatment by Visit interaction (p<0.0001), baseline KCCQ symptom burden score by Visit interaction (p<0.0001) as fixed effect(s).
The following covariance structure has been used to fit the mixed model: Unstructured

For patients who died, only observed values are considered (no imputation after date of death).
Data taken from study 1245.121 only.

Table R.1.3.8.1: 1 KCCQ symptom burden score change from baseline MMRM results over time - RS (OC-AD - no imputation for deaths) - 1245.121

Visit Description Statistic	Placebo	Empa 10mg
Week 52		
Values at visit		
Number of analysed patients	1217	1239
Mean (SE)	81.41 (0.60)	82.87 (0.55)
Adjusted* mean (SE)	81.11 (0.48)	82.60 (0.47)
95% confidence interval	(80.17,82.04)	(81.67,83.52)
Change from baseline		
Mean (SE)	4.84 (0.61)	6.07 (0.58)
Adjusted* mean (SE)	4.75 (0.48)	6.24 (0.47)
95% confidence interval	(3.81, 5.69)	(5.31, 7.17)
Comparison vs Placebo		
Adjusted* mean (SE)		1.49 (0.67)
95% confidence interval		(0.17, 2.81)
p-value		0.0265
Hedges g		
Estimate		0.09
95% confidence interval		(0.01, 0.16)

* Model includes Age (p=0.7716), baseline eGFR (CKD-EPI) (p=0.0242) as linear covariate(s) and region (p<0.0001), baseline diabetes status (p=0.5156), sex (p=0.0007), baseline LVEF (p=0.3173), week reachable (p=0.0696), Treatment by Visit interaction (p<0.0001), baseline KCCQ symptom burden score by Visit interaction (p<0.0001) as fixed effect(s).
The following covariance structure has been used to fit the mixed model: Unstructured

For patients who died, only observed values are considered (no imputation after date of death).
Data taken from study 1245.121 only.

Figure R.1.3.8.1: 1

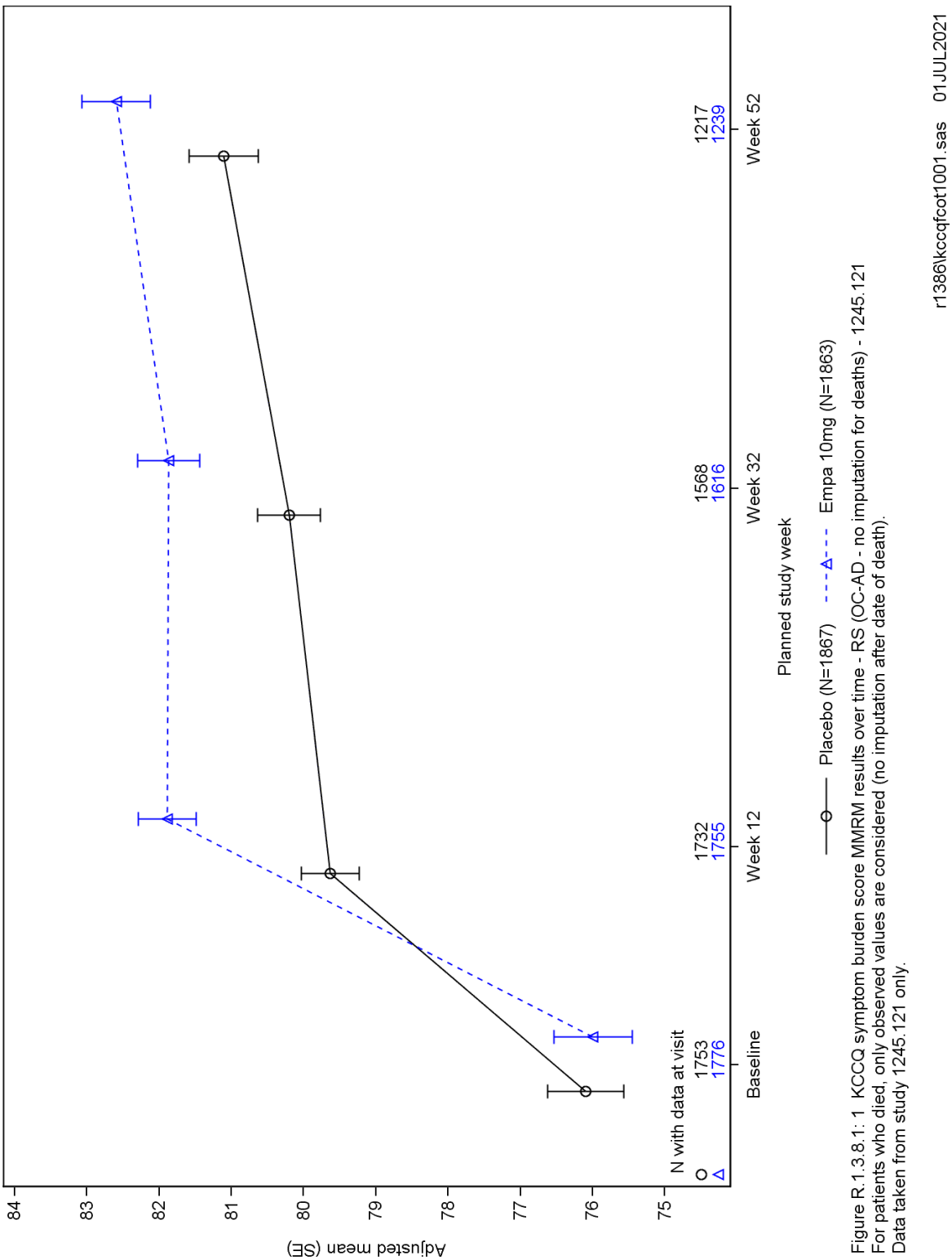

Figure R.1.3.8.1: 1 KCCQ symptom burden score MMRM results over time - RS (OC-AD - no imputation for deaths) - 1245.121
For patients who died, only observed values are considered (no imputation after date of death).
Data taken from study 1245.121 only.

R.1.3.8.2

R.1.3.8.2 Subgroup analysis by sex

Table R.1.3.8.2: 1 KCCQ symptom burden score change from baseline at week 52 (MMRM) by sex - RS (OC-AD - no imputation for deaths) - 1245.121

Subgroup / Visit / Description / Statistic	Placebo	Empa 10mg
Sex: Male		
Number of patients in analysis set	1411	1426
Number of analysed patients	1333	1361
Baseline mean (SE)	77.66 (0.58)	77.52 (0.61)
Week 52		
Values at visit		
Number of analysed patients	938	954
Mean (SE)	82.18 (0.66)	84.06 (0.61)
Adjusted* mean (SE)	81.80 (0.54)	83.65 (0.54)
95% confidence interval	(80.73,82.87)	(82.59,84.71)
Change from baseline		
Mean (SE)	3.98 (0.68)	5.62 (0.64)
Adjusted* mean (SE)	4.21 (0.54)	6.06 (0.54)
95% confidence interval	(3.14, 5.28)	(5.01, 7.12)
Comparison vs Placebo		
Adjusted* mean (SE)		1.85 (0.77)
95% confidence interval		(0.35, 3.35)
p-value		0.0157

* Model includes Age, baseline eGFR (CKD-EPI) as linear covariate(s) and region, baseline diabetes status, baseline LVEF, week reachable, Visit by Treatment by sex interaction, baseline KCCQ symptom burden score by Visit interaction as fixed effect(s).
The Visit by Treatment by sex p-value at Week 52 is 0.3358.
The following covariance structure has been used to fit the mixed model: Unstructured
Note: All covariate effects are set equal to their mean values within subgroup for the calculation of adjusted means.

For patients who died, only observed values are considered (no imputation after date of death).
Data taken from study 1245.121 only.
The MMRM includes all outcome values (change from baseline) at the planned Visits week 12, week 32 and week 52

Table R.1.3.8.2: 1 KCCQ symptom burden score change from baseline at week 52 (MMRM) by sex - RS (OC-AD - no imputation for deaths) - 1245.121

Subgroup / Visit / Description / Statistic	Placebo	Empa 10mg
Sex: Female		
Number of patients in analysis set	456	437
Number of analysed patients	420	415
Baseline mean (SE)	71.14 (1.16)	70.98 (1.15)
Week 52		
Values at visit		
Number of analysed patients	279	285
Mean (SE)	78.82 (1.36)	78.89 (1.26)
Adjusted* mean (SE)	78.20 (1.00)	78.52 (0.99)
95% confidence interval	(76.25,80.15)	(76.59,80.45)
Change from baseline		
Mean (SE)	7.72 (1.33)	7.57 (1.30)
Adjusted* mean (SE)	7.14 (1.00)	7.45 (0.99)
95% confidence interval	(5.19, 9.09)	(5.52, 9.39)
Comparison vs Placebo		
Adjusted* mean (SE)		0.32 (1.40)
95% confidence interval		(-2.42, 3.06)
p-value		0.8203

* Model includes Age, baseline eGFR (CKD-EPI) as linear covariate(s) and region, baseline diabetes status, baseline LVEF, week reachable, Visit by Treatment by sex interaction, baseline KCCQ symptom burden score by Visit interaction as fixed effect(s).
The Visit by Treatment by sex p-value at Week 52 is 0.3358.
The following covariance structure has been used to fit the mixed model: Unstructured
Note: All covariate effects are set equal to their mean values within subgroup for the calculation of adjusted means.

For patients who died, only observed values are considered (no imputation after date of death).
Data taken from study 1245.121 only.
The MMRM includes all outcome values (change from baseline) at the planned Visits week 12, week 32 and week 52

R.1.3.8.3

R.1.3.8.3 Subgroup analysis by age

Table R.1.3.8.3: 1 KCCQ symptom burden score change from baseline at week 52 (MMRM) by age (2 cat.) - RS (OC-AD - no imputation for deaths) - 1245.121

Subgroup / Visit / Description / Statistic	Placebo	Empa 10mg
Age [years] (2 cat.): < 65		
Number of patients in analysis set	740	675
Number of analysed patients	697	645
Baseline mean (SE)	74.61 (0.89)	74.11 (0.95)
Week 52		
Values at visit		
Number of analysed patients	494	454
Mean (SE)	81.01 (0.98)	82.36 (1.00)
Adjusted* mean (SE)	80.16 (0.75)	81.84 (0.78)
95% confidence interval	(78.68,81.64)	(80.31,83.38)
Change from baseline		
Mean (SE)	6.31 (1.00)	7.78 (0.94)
Adjusted* mean (SE)	5.80 (0.75)	7.48 (0.78)
95% confidence interval	(4.32, 7.28)	(5.94, 9.01)
Comparison vs Placebo		
Adjusted* mean (SE)		1.68 (1.08)
95% confidence interval		(-0.45, 3.80)
p-value		0.1212

* Model includes baseline eGFR (CKD-EPI) as linear covariate(s) and region, baseline diabetes status, sex, baseline LVEF, week reachable, Visit by Treatment by age [years] (2 cat.) interaction, baseline KCCQ symptom burden score by Visit interaction as fixed effect(s).
The Visit by Treatment by age [years] (2 cat.) p-value at Week 52 is 0.8291.
The following covariance structure has been used to fit the mixed model: Unstructured
Note: All covariate effects are set equal to their mean values within subgroup for the calculation of adjusted means.

For patients who died, only observed values are considered (no imputation after date of death).
Data taken from study 1245.121 only.
The MMRM includes all outcome values (change from baseline) at the planned Visits week 12, week 32 and week 52

Table R.1.3.8.3: 1 KCCQ symptom burden score change from baseline at week 52 (MMRM) by age (2 cat.) - RS (OC-AD - no imputation for deaths) - 1245.121

Subgroup / Visit / Description / Statistic	Placebo	Empa 10mg
Age [years] (2 cat.): >= 65		
Number of patients in analysis set	1127	1188
Number of analysed patients	1056	1131
Baseline mean (SE)	77.08 (0.65)	77.07 (0.66)
Week 52		
Values at visit		
Number of analysed patients	723	785
Mean (SE)	81.69 (0.76)	83.16 (0.66)
Adjusted* mean (SE)	81.42 (0.62)	82.80 (0.60)
95% confidence interval	(80.20,82.64)	(81.63,83.97)
Change from baseline		
Mean (SE)	3.83 (0.75)	5.07 (0.73)
Adjusted* mean (SE)	4.35 (0.62)	5.73 (0.60)
95% confidence interval	(3.13, 5.56)	(4.56, 6.90)
Comparison vs Placebo		
Adjusted* mean (SE)		1.38 (0.86)
95% confidence interval		(-0.30, 3.06)
p-value		0.1073

* Model includes baseline eGFR (CKD-EPI) as linear covariate(s) and region, baseline diabetes status, sex, baseline LVEF, week reachable, Visit by Treatment by age [years] (2 cat.) interaction, baseline KCCQ symptom burden score by Visit interaction as fixed effect(s).
The Visit by Treatment by age [years] (2 cat.) p-value at Week 52 is 0.8291.
The following covariance structure has been used to fit the mixed model: Unstructured
Note: All covariate effects are set equal to their mean values within subgroup for the calculation of adjusted means.

For patients who died, only observed values are considered (no imputation after date of death).
Data taken from study 1245.121 only.
The MMRM includes all outcome values (change from baseline) at the planned Visits week 12, week 32 and week 52

R.1.3.8.4 Subgroup analysis by region (North America, Latin America, Europe, Asia, Other)

Table R.1.3.8.4: 1 KCCQ symptom burden score change from baseline at week 52 (MMRM) by region - RS (OC-AD - no imputation for deaths) - 1245.121

Subgroup / Visit / Description / Statistic	Placebo	Empa 10mg
Region (5 cat.): North America		
Number of patients in analysis set	213	212
Number of analysed patients	195	206
Baseline mean (SE)	74.32 (1.69)	74.92 (1.61)
Week 52		
Values at visit		
Number of analysed patients	129	151
Mean (SE)	78.88 (1.98)	81.95 (1.65)
Adjusted* mean (SE)	78.14 (1.46)	80.61 (1.36)
95% confidence interval	(75.28,81.01)	(77.94,83.27)
Change from baseline		
Mean (SE)	4.65 (1.55)	5.02 (1.62)
Adjusted* mean (SE)	3.52 (1.46)	5.98 (1.36)
95% confidence interval	(0.66, 6.38)	(3.31, 8.65)
Comparison vs Placebo		
Adjusted* mean (SE)		2.46 (2.00)
95% confidence interval		(-1.45, 6.38)
p-value		0.2179

* Model includes Age, baseline eGFR (CKD-EPI) as linear covariate(s) and baseline diabetes status, sex, baseline LVEF, week reachable, Visit by Treatment by region (5 cat.) interaction, baseline KCCQ symptom burden score by Visit interaction as fixed effect(s).
The Visit by Treatment by region (5 cat.) p-value at Week 52 is 0.8969.
The following covariance structure has been used to fit the mixed model: Unstructured
Note: All covariate effects are set equal to their mean values within subgroup for the calculation of adjusted means.

For patients who died, only observed values are considered (no imputation after date of death).
Data taken from study 1245.121 only.
The MMRM includes all outcome values (change from baseline) at the planned Visits week 12, week 32 and week 52

Table R.1.3.8.4: 1 KCCQ symptom burden score change from baseline at week 52 (MMRM) by region - RS (OC-AD - no imputation for deaths) - 1245.121

Subgroup / Visit / Description / Statistic	Placebo	Empa 10mg
Region (5 cat.): Latin America		
Number of patients in analysis set	645	641
Number of analysed patients	599	602
Baseline mean (SE)	73.12 (1.00)	72.37 (1.04)
Week 52		
Values at visit		
Number of analysed patients	391	374
Mean (SE)	81.50 (1.14)	83.16 (1.09)
Adjusted* mean (SE)	81.37 (0.84)	83.40 (0.85)
95% confidence interval	(79.73,83.01)	(81.73,85.07)
Change from baseline		
Mean (SE)	8.57 (1.29)	11.23 (1.18)
Adjusted* mean (SE)	8.63 (0.84)	10.66 (0.85)
95% confidence interval	(6.98,10.27)	(8.99,12.33)
Comparison vs Placebo		
Adjusted* mean (SE)		2.03 (1.19)
95% confidence interval		(-0.31, 4.38)
p-value		0.0889

* Model includes Age, baseline eGFR (CKD-EPI) as linear covariate(s) and baseline diabetes status, sex, baseline LVEF, week reachable, Visit by Treatment by region (5 cat.) interaction, baseline KCCQ symptom burden score by Visit interaction as fixed effect(s).
The Visit by Treatment by region (5 cat.) p-value at Week 52 is 0.8969.
The following covariance structure has been used to fit the mixed model: Unstructured
Note: All covariate effects are set equal to their mean values within subgroup for the calculation of adjusted means.

For patients who died, only observed values are considered (no imputation after date of death).
Data taken from study 1245.121 only.
The MMRM includes all outcome values (change from baseline) at the planned Visits week 12, week 32 and week 52

Table R.1.3.8.4: 1 KCCQ symptom burden score change from baseline at week 52 (MMRM) by region - RS (OC-AD - no imputation for deaths) - 1245.121

Subgroup / Visit / Description / Statistic	Placebo	Empa 10mg
Region (5 cat.): Europe		
Number of patients in analysis set	677	676
Number of analysed patients	644	649
Baseline mean (SE)	74.85 (0.82)	75.69 (0.86)
Week 52		
Values at visit		
Number of analysed patients	467	469
Mean (SE)	78.34 (0.95)	79.69 (0.88)
Adjusted* mean (SE)	77.97 (0.77)	79.12 (0.77)
95% confidence interval	(76.46,79.49)	(77.61,80.63)
Change from baseline		
Mean (SE)	2.77 (0.92)	3.50 (0.90)
Adjusted* mean (SE)	2.70 (0.77)	3.85 (0.77)
95% confidence interval	(1.18, 4.22)	(2.33, 5.36)
Comparison vs Placebo		
Adjusted* mean (SE)		1.15 (1.09)
95% confidence interval		(-0.99, 3.28)
p-value		0.2931

* Model includes Age, baseline eGFR (CKD-EPI) as linear covariate(s) and baseline diabetes status, sex, baseline LVEF, week reachable, Visit by Treatment by region (5 cat.) interaction, baseline KCCQ symptom burden score by Visit interaction as fixed effect(s).
The Visit by Treatment by region (5 cat.) p-value at Week 52 is 0.8969.
The following covariance structure has been used to fit the mixed model: Unstructured
Note: All covariate effects are set equal to their mean values within subgroup for the calculation of adjusted means.

For patients who died, only observed values are considered (no imputation after date of death).
Data taken from study 1245.121 only.
The MMRM includes all outcome values (change from baseline) at the planned Visits week 12, week 32 and week 52

Table R.1.3.8.4: 1 KCCQ symptom burden score change from baseline at week 52 (MMRM) by region - RS (OC-AD - no imputation for deaths) - 1245.121

Subgroup / Visit / Description / Statistic	Placebo	Empa 10mg
Region (5 cat.): Asia		
Number of patients in analysis set	245	248
Number of analysed patients	237	243
Baseline mean (SE)	86.08 (0.95)	84.67 (1.14)
Week 52		
Values at visit		
Number of analysed patients	180	189
Mean (SE)	87.59 (1.17)	87.35 (1.22)
Adjusted* mean (SE)	86.76 (1.25)	87.01 (1.22)
95% confidence interval	(84.30,89.21)	(84.62,89.41)
Change from baseline		
Mean (SE)	1.02 (1.06)	1.19 (1.19)
Adjusted* mean (SE)	1.39 (1.25)	1.65 (1.22)
95% confidence interval	(-1.06, 3.85)	(-0.75, 4.04)
Comparison vs Placebo		
Adjusted* mean (SE)		0.26 (1.75)
95% confidence interval		(-3.17, 3.68)
p-value		0.8835

* Model includes Age, baseline eGFR (CKD-EPI) as linear covariate(s) and baseline diabetes status, sex, baseline LVEF, week reachable, Visit by Treatment by region (5 cat.) interaction, baseline KCCQ symptom burden score by Visit interaction as fixed effect(s).
The Visit by Treatment by region (5 cat.) p-value at Week 52 is 0.8969.
The following covariance structure has been used to fit the mixed model: Unstructured
Note: All covariate effects are set equal to their mean values within subgroup for the calculation of adjusted means.

For patients who died, only observed values are considered (no imputation after date of death).
Data taken from study 1245.121 only.
The MMRM includes all outcome values (change from baseline) at the planned Visits week 12, week 32 and week 52

Table R.1.3.8.4: 1 KCCQ symptom burden score change from baseline at week 52 (MMRM) by region - RS (OC-AD - no imputation for deaths) - 1245.121

Subgroup / Visit / Description / Statistic	Placebo	Empa 10mg
Region (5 cat.): Other		
Number of patients in analysis set	87	86
Number of analysed patients	78	76
Baseline mean (SE)	83.33 (2.18)	82.46 (1.80)
Week 52		
Values at visit		
Number of analysed patients	50	56
Mean (SE)	93.67 (1.93)	94.94 (1.14)
Adjusted* mean (SE)	92.84 (2.34)	95.00 (2.23)
95% confidence interval	(88.24,97.44)	(90.62,99.38)
Change from baseline		
Mean (SE)	9.17 (2.60)	12.35 (1.96)
Adjusted* mean (SE)	9.94 (2.34)	12.10 (2.23)
95% confidence interval	(5.34,14.54)	(7.72,16.48)
Comparison vs Placebo		
Adjusted* mean (SE)		2.16 (3.24)
95% confidence interval		(-4.19, 8.50)
p-value		0.5051

* Model includes Age, baseline eGFR (CKD-EPI) as linear covariate(s) and baseline diabetes status, sex, baseline LVEF, week reachable, Visit by Treatment by region (5 cat.) interaction, baseline KCCQ symptom burden score by Visit interaction as fixed effect(s).
The Visit by Treatment by region (5 cat.) p-value at Week 52 is 0.8969.
The following covariance structure has been used to fit the mixed model: Unstructured
Note: All covariate effects are set equal to their mean values within subgroup for the calculation of adjusted means.

For patients who died, only observed values are considered (no imputation after date of death).
Data taken from study 1245.121 only.
The MMRM includes all outcome values (change from baseline) at the planned Visits week 12, week 32 and week 52

R.1.3.8.5

R.1.3.8.5 Subgroup analysis by OECD (N/Y)

Table R.1.3.8.5: 1 KCCQ symptom burden score change from baseline at week 52 (MMRM) by OECD member (N/Y) - RS (OC-AD - no imputation for deaths) - 1245.121

Subgroup / Visit / Description / Statistic	Placebo	Empa 10mg
OECD member: No		
Number of patients in analysis set	741	713
Number of analysed patients	686	664
Baseline mean (SE)	74.37 (0.90)	73.57 (0.97)
Week 52		
Values at visit		
Number of analysed patients	443	421
Mean (SE)	82.49 (1.04)	84.54 (0.96)
Adjusted* mean (SE)	82.35 (0.79)	84.70 (0.81)
95% confidence interval	(80.80,83.90)	(83.11,86.28)
Change from baseline		
Mean (SE)	8.20 (1.17)	11.18 (1.07)
Adjusted* mean (SE)	8.37 (0.79)	10.72 (0.81)
95% confidence interval	(6.82, 9.92)	(9.14,12.31)
Comparison vs Placebo		
Adjusted* mean (SE)		2.35 (1.13)
95% confidence interval		(0.13, 4.56)
p-value		0.0379

* Model includes Age, baseline eGFR (CKD-EPI) as linear covariate(s) and baseline diabetes status, sex, baseline LVEF, week reachable, Visit by Treatment by OECD Member (N) interaction, baseline KCCQ symptom burden score by Visit interaction as fixed effect(s).
The Visit by Treatment by OECD Member (N) p-value at Week 52 is 0.4001.
The following covariance structure has been used to fit the mixed model: Unstructured
Note: All covariate effects are set equal to their mean values within subgroup for the calculation of adjusted means.

For patients who died, only observed values are considered (no imputation after date of death).
Data taken from study 1245.121 only.
OECD member (yes/no) countries included:
Yes: United States, Canada, Mexico, Poland, Netherlands, Hungary, Germany, Czech Republic, Italy, France, Spain, United Kingdom, Belgium, Japan, Australia, 'Korea; Republic Of South Korea';
No: Brazil, Argentina, China, India.
The MMRM includes all outcome values (change from baseline) at the planned Visits week 12, week 32 and week 52

Table R.1.3.8.5: 1 KCCQ symptom burden score change from baseline at week 52 (MMRM) by OECD member (N/Y) - RS (OC-AD - no imputation for deaths) - 1245.121

Subgroup / Visit / Description / Statistic	Placebo	Empa 10mg
OECD member: Yes		
Number of patients in analysis set	1126	1150
Number of analysed patients	1067	1112
Baseline mean (SE)	77.21 (0.64)	77.44 (0.64)
Week 52		
Values at visit		
Number of analysed patients	774	818
Mean (SE)	80.79 (0.73)	82.01 (0.68)
Adjusted* mean (SE)	80.09 (0.60)	81.25 (0.59)
95% confidence interval	(78.90,81.27)	(80.10,82.40)
Change from baseline		
Mean (SE)	2.91 (0.67)	3.43 (0.66)
Adjusted* mean (SE)	2.76 (0.60)	3.92 (0.59)
95% confidence interval	(1.58, 3.95)	(2.77, 5.08)
Comparison vs Placebo		
Adjusted* mean (SE)		1.16 (0.84)
95% confidence interval		(-0.49, 2.81)
p-value		0.1676

* Model includes Age, baseline eGFR (CKD-EPI) as linear covariate(s) and baseline diabetes status, sex, baseline LVEF, week reachable, Visit by Treatment by OECD Member (N) interaction, baseline KCCQ symptom burden score by Visit interaction as fixed effect(s).
The Visit by Treatment by OECD Member (N) p-value at Week 52 is 0.4001.
The following covariance structure has been used to fit the mixed model: Unstructured
Note: All covariate effects are set equal to their mean values within subgroup for the calculation of adjusted means.

For patients who died, only observed values are considered (no imputation after date of death).
Data taken from study 1245.121 only.
OECD member (yes/no) countries included:
Yes: United States, Canada, Mexico, Poland, Netherlands, Hungary, Germany, Czech Republic, Italy, France, Spain, United Kingdom, Belgium, Japan, Australia, 'Korea; Republic Of South Korea';
No: Brazil, Argentina, China, India.
The MMRM includes all outcome values (change from baseline) at the planned Visits week 12, week 32 and week 52

R.1.3.8.6 Subgroup analysis by NYHA at baseline (II, III/IV - 2 cat.)

Table R.1.3.8.6: 1 KCCQ symptom burden score change from baseline at week 52 (MMRM) by NYHA (2 cat.) - RS (OC-AD - no imputation for deaths) - 1245.121

Subgroup / Visit / Description / Statistic	Placebo	Empa 10mg
Baseline NYHA (2 cat.): II		
Number of patients in analysis set	1401	1399
Number of analysed patients	1340	1332
Baseline mean (SE)	79.76 (0.55)	80.71 (0.55)
Week 52		
Values at visit		
Number of analysed patients	945	951
Mean (SE)	83.58 (0.64)	85.64 (0.59)
Adjusted* mean (SE)	83.54 (0.54)	85.31 (0.54)
95% confidence interval	(82.48,84.60)	(84.25,86.37)
Change from baseline		
Mean (SE)	3.69 (0.66)	4.92 (0.62)
Adjusted* mean (SE)	3.31 (0.54)	5.08 (0.54)
95% confidence interval	(2.25, 4.37)	(4.02, 6.13)
Comparison vs Placebo		
Adjusted* mean (SE)		1.77 (0.76)
95% confidence interval		(0.27, 3.27)
p-value		0.0207

* Model includes Age, baseline eGFR (CKD-EPI) as linear covariate(s) and region, baseline diabetes status, sex, baseline LVEF, week reachable, Visit by Treatment by baseline NYHA (2 cat.) interaction, baseline KCCQ symptom burden score by Visit interaction as fixed effect(s).
The Visit by Treatment by baseline NYHA (2 cat.) p-value at Week 52 is 0.5125.
The following covariance structure has been used to fit the mixed model: Unstructured
Note: All covariate effects are set equal to their mean values within subgroup for the calculation of adjusted means.

For patients who died, only observed values are considered (no imputation after date of death).
Data taken from study 1245.121 only.
The MMRM includes all outcome values (change from baseline) at the planned Visits week 12, week 32 and week 52

Table R.1.3.8.6: 1 KCCQ symptom burden score change from baseline at week 52 (MMRM) by NYHA (2 cat.) - RS (OC-AD - no imputation for deaths) - 1245.121

Subgroup / Visit / Description / Statistic	Placebo	Empa 10mg
Baseline NYHA (2 cat.): III/IV		
Number of patients in analysis set	466	464
Number of analysed patients	413	444
Baseline mean (SE)	64.19 (1.17)	61.86 (1.17)
Week 52		
Values at visit		
Number of analysed patients	272	288
Mean (SE)	73.87 (1.43)	73.73 (1.25)
Adjusted* mean (SE)	72.75 (1.01)	73.48 (0.98)
95% confidence interval	(70.78,74.73)	(71.57,75.39)
Change from baseline		
Mean (SE)	8.84 (1.44)	9.87 (1.38)
Adjusted* mean (SE)	9.77 (1.01)	10.49 (0.98)
95% confidence interval	(7.80,11.74)	(8.58,12.41)
Comparison vs Placebo		
Adjusted* mean (SE)		0.73 (1.40)
95% confidence interval		(-2.02, 3.47)
p-value		0.6041

* Model includes Age, baseline eGFR (CKD-EPI) as linear covariate(s) and region, baseline diabetes status, sex, baseline LVEF, week reachable, Visit by Treatment by baseline NYHA (2 cat.) interaction, baseline KCCQ symptom burden score by Visit interaction as fixed effect(s).
The Visit by Treatment by baseline NYHA (2 cat.) p-value at Week 52 is 0.5125.
The following covariance structure has been used to fit the mixed model: Unstructured
Note: All covariate effects are set equal to their mean values within subgroup for the calculation of adjusted means.

For patients who died, only observed values are considered (no imputation after date of death).
Data taken from study 1245.121 only.
The MMRM includes all outcome values (change from baseline) at the planned Visits week 12, week 32 and week 52

R.1.3.8.7

R.1.3.8.7 Subgroup analysis by diabetes at baseline

Table R.1.3.8.7: 1 KCCQ symptom burden score change from baseline at week 52 (MMRM) by diabetes at baseline – RS (OC-AD - no imputation for deaths) - 1245.121

Subgroup / Visit / Description / Statistic	Placebo	Empa 10mg
Diabetes at baseline (2 cat.):		
Diabetic		
Number of patients in analysis set	929	927
Number of analysed patients	868	882
Baseline mean (SE)	74.83 (0.79)	74.94 (0.80)
Week 52		
Values at visit		
Number of analysed patients	605	614
Mean (SE)	81.24 (0.85)	82.83 (0.80)
Adjusted* mean (SE)	80.19 (0.68)	81.91 (0.67)
95% confidence interval	(78.86,81.52)	(80.59,83.23)
Change from baseline		
Mean (SE)	4.92 (0.86)	6.26 (0.81)
Adjusted* mean (SE)	5.30 (0.68)	7.02 (0.67)
95% confidence interval	(3.97, 6.63)	(5.70, 8.34)
Comparison vs Placebo		
Adjusted* mean (SE)		1.72 (0.95)
95% confidence interval		(-0.15, 3.59)
p-value		0.0714

* Model includes Age, baseline eGFR (CKD-EPI) as linear covariate(s) and region, sex, baseline LVEF, week reachable, Visit by Treatment by diabetes at baseline (2 cat.) interaction, baseline KCCQ symptom burden score by Visit interaction as fixed effect(s).
The Visit by Treatment by diabetes at baseline (2 cat.) p-value at Week 52 is 0.7421.
The following covariance structure has been used to fit the mixed model: Unstructured
Note: All covariate effects are set equal to their mean values within subgroup for the calculation of adjusted means.

For patients who died, only observed values are considered (no imputation after date of death).
Data taken from study 1245.121 only.
The MMRM includes all outcome values (change from baseline) at the planned Visits week 12, week 32 and week 52

Table R.1.3.8.7: 1 KCCQ symptom burden score change from baseline at week 52 (MMRM) by diabetes at baseline – RS (OC-AD - no imputation for deaths) - 1245.121

Subgroup / Visit / Description / Statistic	Placebo	Empa 10mg
Diabetes at baseline (2 cat.):		
Non-Diabetic		
Number of patients in analysis set	938	936
Number of analysed patients	885	894
Baseline mean (SE)	77.34 (0.70)	77.03 (0.74)
Week 52		
Values at visit		
Number of analysed patients	612	625
Mean (SE)	81.58 (0.85)	82.91 (0.77)
Adjusted* mean (SE)	81.69 (0.67)	82.97 (0.67)
95% confidence interval	(80.37,83.01)	(81.66,84.27)
Change from baseline		
Mean (SE)	4.75 (0.86)	5.88 (0.82)
Adjusted* mean (SE)	4.51 (0.67)	5.78 (0.67)
95% confidence interval	(3.19, 5.83)	(4.48, 7.09)
Comparison vs Placebo		
Adjusted* mean (SE)		1.28 (0.95)
95% confidence interval		(-0.58, 3.13)
p-value		0.1771

* Model includes Age, baseline eGFR (CKD-EPI) as linear covariate(s) and region, sex, baseline LVEF, week reachable, Visit by Treatment by diabetes at baseline (2 cat.) interaction, baseline KCCQ symptom burden score by Visit interaction as fixed effect(s).
The Visit by Treatment by diabetes at baseline (2 cat.) p-value at Week 52 is 0.7421.
The following covariance structure has been used to fit the mixed model: Unstructured
Note: All covariate effects are set equal to their mean values within subgroup for the calculation of adjusted means.

For patients who died, only observed values are considered (no imputation after date of death).
Data taken from study 1245.121 only.
The MMRM includes all outcome values (change from baseline) at the planned Visits week 12, week 32 and week 52

R.1.3.8.8 Subgroup analysis by BMI at baseline (<30, >=30)

Table R.1.3.8.8: 1 KCCQ symptom burden score change from baseline at week 52 (MMRM) by baseline BMI [kg/m2] - RS (OC-AD - no imputation for deaths) - 1245.121

Subgroup / Visit / Description / Statistic	Placebo	Empa 10mg
Baseline BMI [kg/m²] (2 cat.): <30		
Number of patients in analysis set	1300	1263
Number of analysed patients	1229	1201
Baseline mean (SE)	77.69 (0.61)	78.30 (0.64)
Week 52		
Values at visit		
Number of analysed patients	864	826
Mean (SE)	82.74 (0.67)	84.57 (0.64)
Adjusted* mean (SE)	82.45 (0.57)	83.67 (0.58)
95% confidence interval	(81.33,83.56)	(82.53,84.80)
Change from baseline		
Mean (SE)	4.65 (0.68)	5.29 (0.69)
Adjusted* mean (SE)	4.46 (0.57)	5.68 (0.58)
95% confidence interval	(3.35, 5.58)	(4.54, 6.82)
Comparison vs Placebo		
Adjusted* mean (SE)		1.22 (0.81)
95% confidence interval		(-0.37, 2.81)
p-value		0.1328

* Model includes Age, baseline eGFR (CKD-EPI) as linear covariate(s) and region, baseline diabetes status, sex, baseline LVEF, week reachable, Visit by Treatment by baseline BMI [kg/m²] (2 cat.) interaction, baseline KCCQ symptom burden score by Visit interaction as fixed effect(s).
The Visit by Treatment by baseline BMI [kg/m²] (2 cat.) p-value at Week 52 is 0.4588.
The following covariance structure has been used to fit the mixed model: Unstructured
Note: All covariate effects are set equal to their mean values within subgroup for the calculation of adjusted means.

For patients who died, only observed values are considered (no imputation after date of death).
Data taken from study 1245.121 only.
The MMRM includes all outcome values (change from baseline) at the planned Visits week 12, week 32 and week 52

Table R.1.3.8.8: 1 KCCQ symptom burden score change from baseline at week 52 (MMRM) by baseline BMI [kg/m2] - RS (OC-AD - no imputation for deaths) - 1245.121

Subgroup / Visit / Description / Statistic	Placebo	Empa 10mg
Baseline BMI [kg/m²] (2 cat.): >=30		
Number of patients in analysis set	567	600
Number of analysed patients	524	575
Baseline mean (SE)	72.37 (1.03)	71.19 (0.99)
Week 52		
Values at visit		
Number of analysed patients	353	413
Mean (SE)	78.16 (1.24)	79.46 (1.04)
Adjusted* mean (SE)	77.52 (0.89)	79.81 (0.83)
95% confidence interval	(75.77,79.26)	(78.19,81.43)
Change from baseline		
Mean (SE)	5.30 (1.26)	7.63 (1.05)
Adjusted* mean (SE)	5.77 (0.89)	8.06 (0.83)
95% confidence interval	(4.02, 7.51)	(6.44, 9.68)
Comparison vs Placebo		
Adjusted* mean (SE)		2.29 (1.21)
95% confidence interval		(-0.07, 4.66)
p-value		0.0574

* Model includes Age, baseline eGFR (CKD-EPI) as linear covariate(s) and region, baseline diabetes status, sex, baseline LVEF, week reachable, Visit by Treatment by baseline BMI [kg/m²] (2 cat.) interaction, baseline KCCQ symptom burden score by Visit interaction as fixed effect(s).
The Visit by Treatment by baseline BMI [kg/m²] (2 cat.) p-value at Week 52 is 0.4588.
The following covariance structure has been used to fit the mixed model: Unstructured
Note: All covariate effects are set equal to their mean values within subgroup for the calculation of adjusted means.

For patients who died, only observed values are considered (no imputation after date of death).
Data taken from study 1245.121 only.
The MMRM includes all outcome values (change from baseline) at the planned Visits week 12, week 32 and week 52

R.1.3.8.9 Subgroup analysis by eGFR at baseline (<60, >=60)

Table R.1.3.8.9: 1 KCCQ symptom burden score change from baseline at week 52 (MMRM) by baseline eGFR (2 cat.) - RS (OC-AD - no imputation for deaths) - 1245.121

Subgroup / Visit / Description / Statistic	Placebo	Empa 10mg
Baseline eGFR (CKD-EPI) [mL/min/1.73m²] (2 cat.): >=60		
Number of patients in analysis set	960	969
Number of analysed patients	901	921
Baseline mean (SE)	76.47 (0.73)	76.66 (0.76)
Week 52		
Values at visit		
Number of analysed patients	647	650
Mean (SE)	81.62 (0.81)	83.91 (0.78)
Adjusted* mean (SE)	81.19 (0.66)	83.26 (0.65)
95% confidence interval	(79.90,82.48)	(81.98,84.54)
Change from baseline		
Mean (SE)	4.84 (0.81)	6.42 (0.77)
Adjusted* mean (SE)	4.62 (0.66)	6.69 (0.65)
95% confidence interval	(3.33, 5.91)	(5.41, 7.98)
Comparison vs Placebo		
Adjusted* mean (SE)		2.07 (0.93)
95% confidence interval		(0.25, 3.89)
p-value		0.0255

* Model includes Age as linear covariate(s) and region, baseline diabetes status, sex, baseline LVEF, week reachable, Visit by Treatment by baseline eGFR (CKD-EPI) [mL/min/1.73m²] (2 cat.) interaction, baseline KCCQ symptom burden score by Visit interaction as fixed effect(s).
The Visit by Treatment by baseline eGFR (CKD-EPI) [mL/min/1.73m²] (2 cat.) p-value at Week 52 is 0.3595.
The following covariance structure has been used to fit the mixed model: Unstructured
2 patients were excluded as the subgroup variable was missing.
Note: All covariate effects are set equal to their mean values within subgroup for the calculation of adjusted means.

For patients who died, only observed values are considered (no imputation after date of death).
Data taken from study 1245.121 only.
The MMRM includes all outcome values (change from baseline) at the planned Visits week 12, week 32 and week 52

Table R.1.3.8.9: 1 KCCQ symptom burden score change from baseline at week 52 (MMRM) by baseline eGFR (2 cat.) - RS (OC-AD - no imputation for deaths) - 1245.121

Subgroup / Visit / Description / Statistic	Placebo	Empa 10mg
Baseline eGFR (CKD-EPI) [mL/min/1.73m²] (2 cat.): <60		
Number of patients in analysis set	906	893
Number of analysed patients	852	855
Baseline mean (SE)	75.70 (0.76)	75.28 (0.78)
Week 52		
Values at visit		
Number of analysed patients	570	589
Mean (SE)	81.17 (0.89)	81.72 (0.79)
Adjusted* mean (SE)	80.73 (0.70)	81.56 (0.69)
95% confidence interval	(79.36,82.10)	(80.22,82.91)
Change from baseline		
Mean (SE)	4.83 (0.91)	5.67 (0.87)
Adjusted* mean (SE)	5.24 (0.70)	6.07 (0.69)
95% confidence interval	(3.87, 6.60)	(4.73, 7.42)
Comparison vs Placebo		
Adjusted* mean (SE)		0.84 (0.98)
95% confidence interval		(-1.08, 2.75)
p-value		0.3917

* Model includes Age as linear covariate(s) and region, baseline diabetes status, sex, baseline LVEF, week reachable, Visit by Treatment by baseline eGFR (CKD-EPI) [mL/min/1.73m²] (2 cat.) interaction, baseline KCCQ symptom burden score by Visit interaction as fixed effect(s).
The Visit by Treatment by baseline eGFR (CKD-EPI) [mL/min/1.73m²] (2 cat.) p-value at Week 52 is 0.3595.
The following covariance structure has been used to fit the mixed model: Unstructured
2 patients were excluded as the subgroup variable was missing.
Note: All covariate effects are set equal to their mean values within subgroup for the calculation of adjusted means.

For patients who died, only observed values are considered (no imputation after date of death).
Data taken from study 1245.121 only.
The MMRM includes all outcome values (change from baseline) at the planned Visits week 12, week 32 and week 52

R.1.3.8.10

Table R.1.3.8.10: 1 KCCQ symptom burden score change from baseline at week 52 (MMRM) by history of HHF - RS (OC-AD - no imputation for deaths) - 1245.121

Subgroup / Visit / Description / Statistic	Placebo	Empa 10mg
History of HHF (in the last 12 months): No		
Number of patients in analysis set	1293	1286
Number of analysed patients	1220	1231
Baseline mean (SE)	75.77 (0.65)	75.83 (0.65)
Week 52		
Values at visit		
Number of analysed patients	869	873
Mean (SE)	80.55 (0.73)	82.72 (0.67)
Adjusted* mean (SE)	80.55 (0.57)	82.45 (0.57)
95% confidence interval	(79.44,81.66)	(81.34,83.56)
Change from baseline		
Mean (SE)	4.79 (0.74)	6.48 (0.68)
Adjusted* mean (SE)	4.75 (0.57)	6.65 (0.57)
95% confidence interval	(3.64, 5.87)	(5.54, 7.76)
Comparison vs Placebo		
Adjusted* mean (SE)		1.90 (0.80)
95% confidence interval		(0.33, 3.47)
p-value		0.0175

* Model includes Age, baseline eGFR (CKD-EPI) as linear covariate(s) and region, baseline diabetes status, sex, baseline LVEF, week reachable, Visit by Treatment by history of HHF (in the last 12 months) interaction, baseline KCCQ symptom burden score by Visit interaction as fixed effect(s).
The Visit by Treatment by history of HHF (in the last 12 months) p-value at Week 52 is 0.3288.
The following covariance structure has been used to fit the mixed model: Unstructured
Note: All covariate effects are set equal to their mean values within subgroup for the calculation of adjusted means.

For patients who died, only observed values are considered (no imputation after date of death).
Data taken from study 1245.121 only.
The MMRM includes all outcome values (change from baseline) at the planned Visits week 12, week 32 and week 52

Table R.1.3.8.10: 1 KCCQ symptom burden score change from baseline at week 52 (MMRM) by history of HHF - RS (OC-AD - no imputation for deaths) - 1245.121

Subgroup / Visit / Description / Statistic	Placebo	Empa 10mg
History of HHF (in the last 12 months): Yes		
Number of patients in analysis set	574	577
Number of analysed patients	533	545
Baseline mean (SE)	76.84 (0.91)	76.38 (1.00)
Week 52		
Values at visit		
Number of analysed patients	348	366
Mean (SE)	83.55 (1.04)	83.22 (1.00)
Adjusted* mean (SE)	81.95 (0.89)	82.41 (0.87)
95% confidence interval	(80.20,83.70)	(80.70,84.12)
Change from baseline		
Mean (SE)	4.96 (1.05)	5.08 (1.10)
Adjusted* mean (SE)	5.34 (0.89)	5.80 (0.87)
95% confidence interval	(3.60, 7.09)	(4.09, 7.51)
Comparison vs Placebo		
Adjusted* mean (SE)		0.46 (1.24)
95% confidence interval		(-1.98, 2.89)
p-value		0.7126

* Model includes Age, baseline eGFR (CKD-EPI) as linear covariate(s) and region, baseline diabetes status, sex, baseline LVEF, week reachable, Visit by Treatment by history of HHF (in the last 12 months) interaction, baseline KCCQ symptom burden score by Visit interaction as fixed effect(s).
The Visit by Treatment by history of HHF (in the last 12 months) p-value at Week 52 is 0.3288.
The following covariance structure has been used to fit the mixed model: Unstructured
Note: All covariate effects are set equal to their mean values within subgroup for the calculation of adjusted means.

For patients who died, only observed values are considered (no imputation after date of death).
Data taken from study 1245.121 only.
The MMRM includes all outcome values (change from baseline) at the planned Visits week 12, week 32 and week 52

R.1.3.8.11

R.1.3.8.11 Subgroup analysis by cause of heart failure

Table R.1.3.8.11: 1 KCCQ symptom burden score change from baseline at week 52 (MMRM) by cause of heart failure - RS (OC-AD - no imputation for deaths) - 1245.121

Subgroup / Visit / Description / Statistic	Placebo	Empa 10mg
Cause of heart failure: Ischemic		
Number of patients in analysis set	946	983
Number of analysed patients	896	936
Baseline mean (SE)	76.40 (0.72)	76.07 (0.75)
Week 52		
Values at visit		
Number of analysed patients	633	667
Mean (SE)	81.28 (0.83)	82.66 (0.76)
Adjusted* mean (SE)	81.05 (0.67)	82.16 (0.65)
95% confidence interval	(79.74,82.36)	(80.88,83.43)
Change from baseline		
Mean (SE)	4.27 (0.80)	5.40 (0.79)
Adjusted* mean (SE)	4.82 (0.67)	5.93 (0.65)
95% confidence interval	(3.51, 6.13)	(4.66, 7.20)
Comparison vs Placebo		
Adjusted* mean (SE)		1.11 (0.93)
95% confidence interval		(-0.71, 2.92)
p-value		0.2322

* Model includes Age, baseline eGFR (CKD-EPI) as linear covariate(s) and region, baseline diabetes status, sex, baseline LVEF, week reachable, Visit by Treatment by cause of heart failure interaction, baseline KCCQ symptom burden score by Visit interaction as fixed effect(s).
The Visit by Treatment by cause of heart failure p-value at Week 52 is 0.5451.
The following covariance structure has been used to fit the mixed model: Unstructured
Note: All covariate effects are set equal to their mean values within subgroup for the calculation of adjusted means.

For patients who died, only observed values are considered (no imputation after date of death).
Data taken from study 1245.121 only.
The MMRM includes all outcome values (change from baseline) at the planned Visits week 12, week 32 and week 52

Table R.1.3.8.11: 1 KCCQ symptom burden score change from baseline at week 52 (MMRM) by cause of heart failure - RS (OC-AD - no imputation for deaths) - 1245.121

Subgroup / Visit / Description / Statistic	Placebo	Empa 10mg
Cause of heart failure: Non-ischemic		
Number of patients in analysis set	921	880
Number of analysed patients	857	840
Baseline mean (SE)	75.78 (0.78)	75.91 (0.79)
Week 52		
Values at visit		
Number of analysed patients	584	572
Mean (SE)	81.55 (0.87)	83.11 (0.82)
Adjusted* mean (SE)	80.85 (0.69)	82.77 (0.70)
95% confidence interval	(79.49,82.21)	(81.40,84.13)
Change from baseline		
Mean (SE)	5.46 (0.91)	6.85 (0.85)
Adjusted* mean (SE)	5.00 (0.69)	6.92 (0.70)
95% confidence interval	(3.64, 6.36)	(5.55, 8.29)
Comparison vs Placebo		
Adjusted* mean (SE)		1.92 (0.98)
95% confidence interval		(0.00, 3.84)
p-value		0.0496

* Model includes Age, baseline eGFR (CKD-EPI) as linear covariate(s) and region, baseline diabetes status, sex, baseline LVEF, week reachable, Visit by Treatment by cause of heart failure interaction, baseline KCCQ symptom burden score by Visit interaction as fixed effect(s).
The Visit by Treatment by cause of heart failure p-value at Week 52 is 0.5451.
The following covariance structure has been used to fit the mixed model: Unstructured
Note: All covariate effects are set equal to their mean values within subgroup for the calculation of adjusted means.

For patients who died, only observed values are considered (no imputation after date of death).
Data taken from study 1245.121 only.
The MMRM includes all outcome values (change from baseline) at the planned Visits week 12, week 32 and week 52

R.1.3.8.12 Subgroup analysis by heart failure physiology (LVEF <= 30% and NTproBNP<median; LVEF <= 30% and NTproBNP>=median; LVEF > 30%)

Table R.1.3.8.12: 1 KCCQ symptom burden score change from baseline at week 52 (MMRM) by heart failure physiology - RS (OC-AD - no imputation for deaths) - 1245.121

Subgroup / Visit / Description / Statistic	Placebo	Empa 10mg
Heart failure physiology: LVEF <= 30% and NTproBNP < median		
Number of patients in analysis set	723	698
Number of analysed patients	694	672
Baseline mean (SE)	76.73 (0.83)	78.06 (0.82)
Week 52		
Values at visit		
Number of analysed patients	511	494
Mean (SE)	82.81 (0.92)	83.47 (0.86)
Adjusted* mean (SE)	82.58 (0.74)	83.36 (0.75)
95% confidence interval	(81.13,84.03)	(81.89,84.83)
Change from baseline		
Mean (SE)	5.94 (0.86)	5.45 (0.82)
Adjusted* mean (SE)	5.19 (0.74)	5.98 (0.75)
95% confidence interval	(3.74, 6.64)	(4.50, 7.45)
Comparison vs Placebo		
Adjusted* mean (SE)		0.78 (1.05)
95% confidence interval		(-1.28, 2.85)
p-value		0.4572

* Model includes Age, baseline eGFR (CKD-EPI) as linear covariate(s) and region, baseline diabetes status, sex, week reachable, Visit by Treatment by heart failure physiology interaction, baseline KCCQ symptom burden score by Visit interaction as fixed effect(s).
The Visit by Treatment by heart failure physiology p-value at Week 52 is 0.5057.
The following covariance structure has been used to fit the mixed model: Unstructured
16 patients were excluded as the subgroup variable was missing.
Note: All covariate effects are set equal to their mean values within subgroup for the calculation of adjusted means.
The p-value for the visit by treatment by subgroup interaction trend test at Week 52 is 0.6652

For patients who died, only observed values are considered (no imputation after date of death).
Data taken from study 1245.121 only.
NTproBNP median [pg/mL]: with a. fibrillation/flutter at baseline: 2265; without a. fibrillation/flutter at baseline: 1671.
The MMRM includes all outcome values (change from baseline) at the planned Visits week 12, week 32 and week 52

Table R.1.3.8.12: 1 KCCQ symptom burden score change from baseline at week 52 (MMRM) by heart failure physiology - RS (OC-AD - no imputation for deaths) - 1245.121

Subgroup / Visit / Description / Statistic	Placebo	Empa 10mg
Heart failure physiology: LVEF <= 30% and NTproBNP >= median		
Number of patients in analysis set	661	631
Number of analysed patients	604	593
Baseline mean (SE)	74.54 (0.93)	73.03 (1.00)
Week 52		
Values at visit		
Number of analysed patients	408	405
Mean (SE)	78.84 (1.09)	81.71 (1.01)
Adjusted* mean (SE)	78.41 (0.82)	80.99 (0.83)
95% confidence interval	(76.80,80.02)	(79.37,82.61)
Change from baseline		
Mean (SE)	3.75 (1.18)	7.22 (1.13)
Adjusted* mean (SE)	4.62 (0.82)	7.20 (0.83)
95% confidence interval	(3.01, 6.23)	(5.58, 8.81)
Comparison vs Placebo		
Adjusted* mean (SE)		2.58 (1.16)
95% confidence interval		(0.29, 4.86)
p-value		0.0271

* Model includes Age, baseline eGFR (CKD-EPI) as linear covariate(s) and region, baseline diabetes status, sex, week reachable, Visit by Treatment by heart failure physiology interaction, baseline KCCQ symptom burden score by Visit interaction as fixed effect(s).
The Visit by Treatment by heart failure physiology p-value at Week 52 is 0.5057.
The following covariance structure has been used to fit the mixed model: Unstructured
16 patients were excluded as the subgroup variable was missing.
Note: All covariate effects are set equal to their mean values within subgroup for the calculation of adjusted means.
The p-value for the visit by treatment by subgroup interaction trend test at Week 52 is 0.6652

For patients who died, only observed values are considered (no imputation after date of death).
Data taken from study 1245.121 only.
NTproBNP median [pg/mL]: with a. fibrillation/flutter at baseline: 2265; without a. fibrillation/flutter at baseline: 1671.
The MMRM includes all outcome values (change from baseline) at the planned Visits week 12, week 32 and week 52

Table R.1.3.8.12: 1 KCCQ symptom burden score change from baseline at week 52 (MMRM) by heart failure physiology - RS (OC-AD - no imputation for deaths) - 1245.121

Subgroup / Visit / Description / Statistic	Placebo	Empa 10mg
Heart failure physiology: LVEF > 30%		
Number of patients in analysis set	475	526
Number of analysed patients	450	506
Baseline mean (SE)	77.46 (1.00)	76.84 (1.03)
Week 52		
Values at visit		
Number of analysed patients	294	339
Mean (SE)	82.79 (1.10)	83.38 (1.04)
Adjusted* mean (SE)	81.84 (0.97)	83.05 (0.90)
95% confidence interval	(79.95,83.73)	(81.29,84.81)
Change from baseline		
Mean (SE)	4.31 (1.17)	5.63 (1.09)
Adjusted* mean (SE)	4.70 (0.97)	5.92 (0.90)
95% confidence interval	(2.81, 6.60)	(4.15, 7.68)
Comparison vs Placebo		
Adjusted* mean (SE)		1.21 (1.32)
95% confidence interval		(-1.37, 3.80)
p-value		0.3583

* Model includes Age, baseline eGFR (CKD-EPI) as linear covariate(s) and region, baseline diabetes status, sex, week reachable, Visit by Treatment by heart failure physiology interaction, baseline KCCQ symptom burden score by Visit interaction as fixed effect(s).
The Visit by Treatment by heart failure physiology p-value at Week 52 is 0.5057.
The following covariance structure has been used to fit the mixed model: Unstructured
16 patients were excluded as the subgroup variable was missing.
Note: All covariate effects are set equal to their mean values within subgroup for the calculation of adjusted means.
The p-value for the visit by treatment by subgroup interaction trend test at Week 52 is 0.6652

For patients who died, only observed values are considered (no imputation after date of death).
Data taken from study 1245.121 only.
NTproBNP median [pg/mL]: with a. fibrillation/flutter at baseline: 2265; without a. fibrillation/flutter at baseline: 1671.
The MMRM includes all outcome values (change from baseline) at the planned Visits week 12, week 32 and week 52

R.1.3.8.13

Table R.1.3.8.13: 1 KCCQ symptom burden score change from baseline at week 52 (MMRM) by baseline use of MRA (Y/N) - RS (OC-AD - no imputation for deaths) - 1245.121

Subgroup / Visit / Description / Statistic	Placebo	Empa 10mg
Baseline use of MRA: No		
Number of patients in analysis set	512	557
Number of analysed patients	486	531
Baseline mean (SE)	78.05 (0.97)	76.65 (0.97)
Week 52		
Values at visit		
Number of analysed patients	340	383
Mean (SE)	80.22 (1.14)	85.23 (0.93)
Adjusted* mean (SE)	80.55 (0.90)	84.91 (0.86)
95% confidence interval	(78.78,82.32)	(83.23,86.59)
Change from baseline		
Mean (SE)	2.72 (1.06)	7.62 (1.07)
Adjusted* mean (SE)	3.23 (0.90)	7.59 (0.86)
95% confidence interval	(1.46, 5.01)	(5.91, 9.27)
Comparison vs Placebo		
Adjusted* mean (SE)		4.35 (1.24)
95% confidence interval		(1.92, 6.79)
p-value		0.0005

* Model includes Age, baseline eGFR (CKD-EPI) as linear covariate(s) and region, baseline diabetes status, sex, baseline LVEF, week reachable, Visit by Treatment by baseline use of MRA interaction, baseline KCCQ symptom burden score by Visit interaction as fixed effect(s).
The Visit by Treatment by baseline use of MRA p-value at Week 52 is 0.0058.
The following covariance structure has been used to fit the mixed model: Unstructured
Note: All covariate effects are set equal to their mean values within subgroup for the calculation of adjusted means.

For patients who died, only observed values are considered (no imputation after date of death).
Data taken from study 1245.121 only.
The MMRM includes all outcome values (change from baseline) at the planned Visits week 12, week 32 and week 52

Table R.1.3.8.13: 1 KCCQ symptom burden score change from baseline at week 52 (MMRM) by baseline use of MRA (Y/N) - RS (OC-AD - no imputation for deaths) - 1245.121

Subgroup / Visit / Description / Statistic	Placebo	Empa 10mg
Baseline use of MRA: Yes		
Number of patients in analysis set	1355	1306
Number of analysed patients	1267	1245
Baseline mean (SE)	75.35 (0.63)	75.72 (0.66)
Week 52		
Values at visit		
Number of analysed patients	877	856
Mean (SE)	81.87 (0.71)	81.81 (0.68)
Adjusted* mean (SE)	81.10 (0.56)	81.38 (0.57)
95% confidence interval	(79.99,82.20)	(80.27,82.49)
Change from baseline		
Mean (SE)	5.66 (0.73)	5.37 (0.69)
Adjusted* mean (SE)	5.57 (0.56)	5.85 (0.57)
95% confidence interval	(4.46, 6.67)	(4.74, 6.96)
Comparison vs Placebo		
Adjusted* mean (SE)		0.28 (0.80)
95% confidence interval		(-1.28, 1.85)
p-value		0.7220

* Model includes Age, baseline eGFR (CKD-EPI) as linear covariate(s) and region, baseline diabetes status, sex, baseline LVEF, week reachable, Visit by Treatment by baseline use of MRA interaction, baseline KCCQ symptom burden score by Visit interaction as fixed effect(s).
The Visit by Treatment by baseline use of MRA p-value at Week 52 is 0.0058.
The following covariance structure has been used to fit the mixed model: Unstructured
Note: All covariate effects are set equal to their mean values within subgroup for the calculation of adjusted means.

For patients who died, only observed values are considered (no imputation after date of death).
Data taken from study 1245.121 only.
The MMRM includes all outcome values (change from baseline) at the planned Visits week 12, week 32 and week 52

R.1.3.8.14

Table R.1.3.8.14: 1 KCCQ symptom burden score change from baseline at week 52 (MMRM) by baseline use of ARNi (Y/N) - RS (OC-AD - no imputation for deaths) - 1245.121

Subgroup / Visit / Description / Statistic	Placebo	Empa 10mg
Baseline use of ARNi: No		
Number of patients in analysis set	1480	1523
Number of analysed patients	1390	1447
Baseline mean (SE)	76.04 (0.59)	75.40 (0.61)
Week 52		
Values at visit		
Number of analysed patients	959	1026
Mean (SE)	81.62 (0.67)	82.55 (0.61)
Adjusted* mean (SE)	80.92 (0.54)	82.18 (0.52)
95% confidence interval	(79.86,81.97)	(81.16,83.20)
Change from baseline		
Mean (SE)	5.00 (0.69)	6.34 (0.64)
Adjusted* mean (SE)	5.21 (0.54)	6.47 (0.52)
95% confidence interval	(4.15, 6.26)	(5.45, 7.49)
Comparison vs Placebo		
Adjusted* mean (SE)		1.26 (0.75)
95% confidence interval		(-0.20, 2.73)
p-value		0.0914

* Model includes Age, baseline eGFR (CKD-EPI) as linear covariate(s) and region, baseline diabetes status, sex, baseline LVEF, week reachable, Visit by Treatment by baseline use of ARNi interaction, baseline KCCQ symptom burden score by Visit interaction as fixed effect(s).
The Visit by Treatment by baseline use of ARNi p-value at Week 52 is 0.4902.
The following covariance structure has been used to fit the mixed model: Unstructured
Note: All covariate effects are set equal to their mean values within subgroup for the calculation of adjusted means.

For patients who died, only observed values are considered (no imputation after date of death).
Data taken from study 1245.121 only.
The MMRM includes all outcome values (change from baseline) at the planned Visits week 12, week 32 and week 52

Table R.1.3.8.14: 1 KCCQ symptom burden score change from baseline at week 52 (MMRM) by baseline use of ARNi (Y/N) - RS (OC-AD - no imputation for deaths) - 1245.121

Subgroup / Visit / Description / Statistic	Placebo	Empa 10mg
Baseline use of ARNi: Yes		
Number of patients in analysis set	387	340
Number of analysed patients	363	329
Baseline mean (SE)	76.32 (1.22)	78.62 (1.21)
Week 52		
Values at visit		
Number of analysed patients	258	213
Mean (SE)	80.62 (1.35)	84.43 (1.33)
Adjusted* mean (SE)	81.12 (1.04)	83.56 (1.14)
95% confidence interval	(79.07,83.17)	(81.33,85.80)
Change from baseline		
Mean (SE)	4.25 (1.24)	4.73 (1.35)
Adjusted* mean (SE)	3.70 (1.04)	6.15 (1.14)
95% confidence interval	(1.66, 5.75)	(3.91, 8.39)
Comparison vs Placebo		
Adjusted* mean (SE)		2.45 (1.54)
95% confidence interval		(-0.57, 5.47)
p-value		0.1124

* Model includes Age, baseline eGFR (CKD-EPI) as linear covariate(s) and region, baseline diabetes status, sex, baseline LVEF, week reachable, Visit by Treatment by baseline use of ARNi interaction, baseline KCCQ symptom burden score by Visit interaction as fixed effect(s).
The Visit by Treatment by baseline use of ARNi p-value at Week 52 is 0.4902.
The following covariance structure has been used to fit the mixed model: Unstructured
Note: All covariate effects are set equal to their mean values within subgroup for the calculation of adjusted means.

For patients who died, only observed values are considered (no imputation after date of death).
Data taken from study 1245.121 only.
The MMRM includes all outcome values (change from baseline) at the planned Visits week 12, week 32 and week 52

R.1.3.8.15

R.1.3.8.15 Subgroup analysis by bl. LVEF (<= 30%, >30% -<= 35% , > 35%)

Table R.1.3.8.15: 1 KCCQ symptom burden score change from baseline at week 52 (MMRM) by baseline LVEF (3 cat.) - RS (OC-AD - no imputation for deaths) - 1245.121

Subgroup / Visit / Description / Statistic	Placebo	Empa 10mg
Baseline LVEF (3 cat.): <=30		
Number of patients in analysis set	1392	1337
Number of analysed patients	1303	1270
Baseline mean (SE)	75.62 (0.62)	75.66 (0.64)
Week 52		
Values at visit		
Number of analysed patients	923	900
Mean (SE)	80.97 (0.71)	82.68 (0.66)
Adjusted* mean (SE)	80.62 (0.55)	82.22 (0.56)
95% confidence interval	(79.54,81.70)	(81.13,83.31)
Change from baseline		
Mean (SE)	5.01 (0.71)	6.23 (0.68)
Adjusted* mean (SE)	4.98 (0.55)	6.58 (0.56)
95% confidence interval	(3.90, 6.06)	(5.49, 7.67)
Comparison vs Placebo		
Adjusted* mean (SE)		1.60 (0.78)
95% confidence interval		(0.07, 3.13)
p-value		0.0400

* Model includes Age, baseline eGFR (CKD-EPI) as linear covariate(s) and region, baseline diabetes status, sex, week reachable, Visit by Treatment by baseline LVEF (3 cat.) interaction, baseline KCCQ symptom burden score by Visit interaction as fixed effect(s).
The Visit by Treatment by baseline LVEF (3 cat.) p-value at Week 52 is 0.0695.
The following covariance structure has been used to fit the mixed model: Unstructured
Note: All covariate effects are set equal to their mean values within subgroup for the calculation of adjusted means.
The p-value for the visit by treatment by subgroup interaction trend test at Week 52 is 0.5489

For patients who died, only observed values are considered (no imputation after date of death).
Data taken from study 1245.121 only.
The MMRM includes all outcome values (change from baseline) at the planned Visits week 12, week 32 and week 52

Table R.1.3.8.15: 1 KCCQ symptom burden score change from baseline at week 52 (MMRM) by baseline LVEF (3 cat.) - RS (OC-AD - no imputation for deaths) - 1245.121

Subgroup / Visit / Description / Statistic	Placebo	Empa 10mg
Baseline LVEF (3 cat.): >30 to <=35		
Number of patients in analysis set	361	398
Number of analysed patients	342	385
Baseline mean (SE)	77.75 (1.13)	77.01 (1.18)
Week 52		
Values at visit		
Number of analysed patients	233	256
Mean (SE)	83.87 (1.15)	82.58 (1.21)
Adjusted* mean (SE)	82.85 (1.09)	82.42 (1.03)
95% confidence interval	(80.71,84.98)	(80.39,84.45)
Change from baseline		
Mean (SE)	4.79 (1.30)	4.33 (1.19)
Adjusted* mean (SE)	5.49 (1.09)	5.06 (1.03)
95% confidence interval	(3.35, 7.62)	(3.03, 7.09)
Comparison vs Placebo		
Adjusted* mean (SE)		-0.43 (1.50)
95% confidence interval		(-3.37, 2.52)
p-value		0.7766

* Model includes Age, baseline eGFR (CKD-EPI) as linear covariate(s) and region, baseline diabetes status, sex, week reachable, Visit by Treatment by baseline LVEF (3 cat.) interaction, baseline KCCQ symptom burden score by Visit interaction as fixed effect(s).
The Visit by Treatment by baseline LVEF (3 cat.) p-value at Week 52 is 0.0695.
The following covariance structure has been used to fit the mixed model: Unstructured
Note: All covariate effects are set equal to their mean values within subgroup for the calculation of adjusted means.
The p-value for the visit by treatment by subgroup interaction trend test at Week 52 is 0.5489

For patients who died, only observed values are considered (no imputation after date of death).
Data taken from study 1245.121 only.
The MMRM includes all outcome values (change from baseline) at the planned Visits week 12, week 32 and week 52

Table R.1.3.8.15: 1 KCCQ symptom burden score change from baseline at week 52 (MMRM) by baseline LVEF (3 cat.) - RS (OC-AD - no imputation for deaths) - 1245.121

Subgroup / Visit / Description / Statistic	Placebo	Empa 10mg
Baseline LVEF (3 cat.): >35		
Number of patients in analysis set	114	128
Number of analysed patients	108	121
Baseline mean (SE)	76.54 (2.17)	76.31 (2.10)
Week 52		
Values at visit		
Number of analysed patients	61	83
Mean (SE)	78.69 (2.92)	85.84 (2.03)
Adjusted* mean (SE)	78.12 (2.10)	84.96 (1.82)
95% confidence interval	(74.00,82.25)	(81.38,88.54)
Change from baseline		
Mean (SE)	2.46 (2.68)	9.64 (2.50)
Adjusted* mean (SE)	1.71 (2.10)	8.54 (1.82)
95% confidence interval	(-2.42, 5.83)	(4.96,12.12)
Comparison vs Placebo		
Adjusted* mean (SE)		6.83 (2.78)
95% confidence interval		(1.38,12.29)
p-value		0.0141

* Model includes Age, baseline eGFR (CKD-EPI) as linear covariate(s) and region, baseline diabetes status, sex, week reachable, Visit by Treatment by baseline LVEF (3 cat.) interaction, baseline KCCQ symptom burden score by Visit interaction as fixed effect(s).
The Visit by Treatment by baseline LVEF (3 cat.) p-value at Week 52 is 0.0695.
The following covariance structure has been used to fit the mixed model: Unstructured
Note: All covariate effects are set equal to their mean values within subgroup for the calculation of adjusted means.
The p-value for the visit by treatment by subgroup interaction trend test at Week 52 is 0.5489

For patients who died, only observed values are considered (no imputation after date of death).
Data taken from study 1245.121 only.
The MMRM includes all outcome values (change from baseline) at the planned Visits week 12, week 32 and week 52

R.1.3.8.16

R.1.3.8.16 Subgroup analysis by bl. NTproBNP </>= median (median based on total patients)

Table R.1.3.8.16: 1 KCCQ symptom burden score change from baseline at week 52 (MMRM) by bl. NTproBNP (<median, >= median) (median based on total patients) - RS (OC-AD - no imputation for deaths) - 1245.121

Subgroup / Visit / Description / Statistic	Placebo	Empa 10mg
Baseline NTproBNP (<median, >= median): < median		
Number of patients in analysis set	920	942
Number of analysed patients	884	908
Baseline mean (SE)	77.91 (0.71)	78.21 (0.70)
Week 52		
Values at visit		
Number of analysed patients	651	666
Mean (SE)	82.80 (0.79)	83.73 (0.73)
Adjusted* mean (SE)	82.59 (0.66)	83.83 (0.65)
95% confidence interval	(81.30,83.87)	(82.56,85.10)
Change from baseline		
Mean (SE)	5.17 (0.75)	5.62 (0.71)
Adjusted* mean (SE)	4.52 (0.66)	5.77 (0.65)
95% confidence interval	(3.24, 5.81)	(4.50, 7.04)
Comparison vs Placebo		
Adjusted* mean (SE)		1.24 (0.92)
95% confidence interval		(-0.56, 3.05)
p-value		0.1768

* Model includes Age, baseline eGFR (CKD-EPI) as linear covariate(s) and region, baseline diabetes status, sex, baseline LVEF, week reachable, Visit by Treatment by baseline NTproBNP (<median, >= median) interaction, baseline KCCQ symptom burden score by Visit interaction as fixed effect(s). The Visit by Treatment by baseline NTproBNP (<median, >= median) p-value at Week 52 is 0.7205.
The following covariance structure has been used to fit the mixed model: Unstructured
2 patients were excluded as the subgroup variable was missing.
Note: All covariate effects are set equal to their mean values within subgroup for the calculation of adjusted means.

For patients who died, only observed values are considered (no imputation after date of death).
Data taken from study 1245.121 only.
Median: 1910 [pg/mL]
The MMRM includes all outcome values (change from baseline) at the planned Visits week 12, week 32 and week 52

Table R.1.3.8.16: 1 KCCQ symptom burden score change from baseline at week 52 (MMRM) by bl. NTproBNP (<median, >= median) (median based on total patients) - RS (OC-AD - no imputation for deaths) - 1245.121

Subgroup / Visit / Description / Statistic	Placebo	Empa 10mg
Baseline NTproBNP (<median, >= median): >= median		
Number of patients in analysis set	946	920
Number of analysed patients	869	868
Baseline mean (SE)	74.25 (0.78)	73.68 (0.83)
Week 52		
Values at visit		
Number of analysed patients	566	573
Mean (SE)	79.81 (0.91)	81.86 (0.85)
Adjusted* mean (SE)	79.24 (0.70)	80.97 (0.69)
95% confidence interval	(77.88,80.61)	(79.61,82.33)
Change from baseline		
Mean (SE)	4.45 (0.98)	6.59 (0.94)
Adjusted* mean (SE)	5.28 (0.70)	7.01 (0.69)
95% confidence interval	(3.92, 6.65)	(5.65, 8.37)
Comparison vs Placebo		
Adjusted* mean (SE)		1.73 (0.98)
95% confidence interval		(-0.20, 3.65)
p-value		0.0791

* Model includes Age, baseline eGFR (CKD-EPI) as linear covariate(s) and region, baseline diabetes status, sex, baseline LVEF, week reachable, Visit by Treatment by baseline NTproBNP (<median, >= median) interaction, baseline KCCQ symptom burden score by Visit interaction as fixed effect(s). The Visit by Treatment by baseline NTproBNP (<median, >= median) p-value at Week 52 is 0.7205.
The following covariance structure has been used to fit the mixed model: Unstructured
2 patients were excluded as the subgroup variable was missing.
Note: All covariate effects are set equal to their mean values within subgroup for the calculation of adjusted means.

For patients who died, only observed values are considered (no imputation after date of death).
Data taken from study 1245.121 only.
Median: 1910 [pg/mL]
The MMRM includes all outcome values (change from baseline) at the planned Visits week 12, week 32 and week 52

R.1.3.9

R.1.3.9 KCCQ self efficacy score MMRM analysis

R.1.3.9.1

Table R.1.3.9.1: 1 KCCQ self efficacy score change from baseline MMRM results over time - RS (OC-AD - no imputation for deaths) - 1245.121

Visit Description Statistic	Placebo	Empa 10mg
Number of patients in analysis set	1867	1863
Number of analysed patients	1751	1776
Baseline mean (SE)	74.68 (0.56)	73.91 (0.56)
Week 12		
Values at visit		
Number of analysed patients	1728	1755
Mean (SE)	78.15 (0.52)	78.82 (0.54)
Adjusted* mean (SE)	77.86 (0.46)	78.95 (0.45)
95% confidence interval	(76.97,78.76)	(78.06,79.84)
Change from baseline		
Mean (SE)	3.50 (0.52)	4.91 (0.56)
Adjusted* mean (SE)	3.60 (0.46)	4.68 (0.45)
95% confidence interval	(2.70, 4.49)	(3.80, 5.57)
Comparison vs Placebo		
Adjusted* mean (SE)		1.09 (0.64)
95% confidence interval		(-0.17, 2.34)
p-value		0.0901

* Model includes Age (p<0.0001), baseline eGFR (CKD-EPI) (p=0.9635) as linear covariate(s) and region (p<0.0001), baseline diabetes status (p=0.1273), sex (p=0.4358), baseline LVEF (p=0.6644), week reachable (p=0.0394), Treatment by Visit interaction (p<0.0001), baseline KCCQ self efficacy score by Visit interaction (p<0.0001) as fixed effect(s).
The following covariance structure has been used to fit the mixed model: Unstructured

For patients who died, only observed values are considered (no imputation after date of death).
Data taken from study 1245.121 only.

Table R.1.3.9.1: 1 KCCQ self efficacy score change from baseline MMRM results over time - RS (OC-AD - no imputation for deaths) - 1245.121

Visit Description Statistic	Placebo	Empa 10mg
Week 32		
Values at visit		
Number of analysed patients	1567	1616
Mean (SE)	79.51 (0.54)	79.72 (0.55)
Adjusted* mean (SE)	79.20 (0.48)	79.80 (0.48)
95% confidence interval	(78.25,80.14)	(78.86,80.73)
Change from baseline		
Mean (SE)	4.80 (0.61)	5.85 (0.58)
Adjusted* mean (SE)	4.93 (0.48)	5.53 (0.48)
95% confidence interval	(3.99, 5.88)	(4.60, 6.46)
Comparison vs Placebo		
Adjusted* mean (SE)		0.60 (0.68)
95% confidence interval		(-0.73, 1.93)
p-value		0.3766
Week 52		
Values at visit		
Number of analysed patients	1214	1239
Mean (SE)	80.57 (0.58)	80.52 (0.60)
Adjusted* mean (SE)	80.52 (0.51)	80.69 (0.51)
95% confidence interval	(79.51,81.52)	(79.69,81.68)
Change from baseline		
Mean (SE)	5.75 (0.66)	6.87 (0.70)
Adjusted* mean (SE)	6.25 (0.51)	6.42 (0.51)
95% confidence interval	(5.24, 7.26)	(5.42, 7.42)
Comparison vs Placebo		
Adjusted* mean (SE)		0.17 (0.72)
95% confidence interval		(-1.25, 1.59)
p-value		0.8154

* Model includes Age (p<0.0001), baseline eGFR (CKD-EPI) (p=0.9635) as linear covariate(s) and region (p<0.0001),
baseline diabetes status (p=0.1273), sex (p=0.4358), baseline LVEF (p=0.6644), week reachable (p=0.0394),
Treatment by Visit interaction (p<0.0001), baseline KCCQ self efficacy score by Visit interaction (p<0.0001) as fixed effect(s).
The following covariance structure has been used to fit the mixed model: Unstructured

For patients who died, only observed values are considered (no imputation after date of death).
Data taken from study 1245.121 only.

Figure R.1.3.9.1: 1

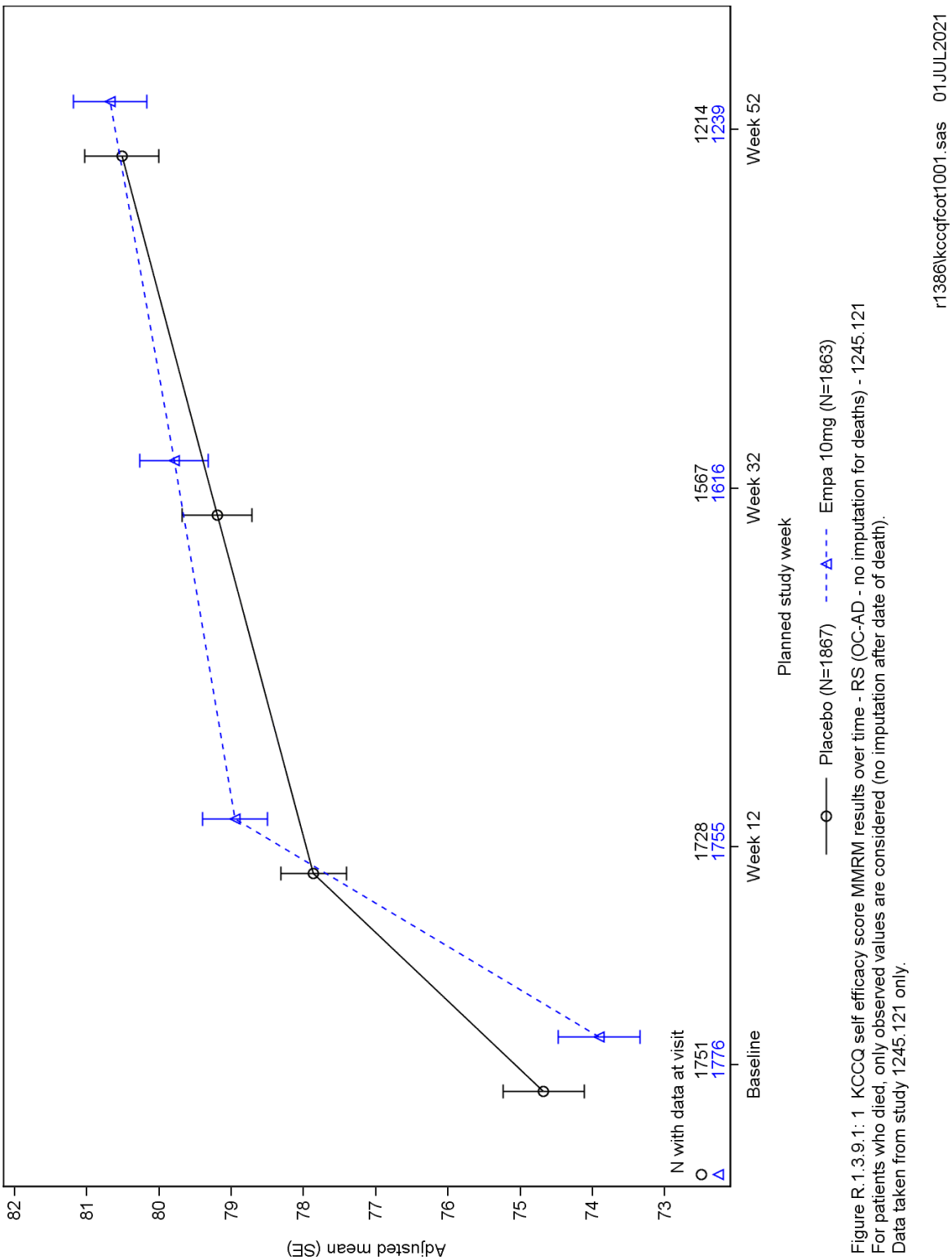

Figure R.1.3.9.1: 1 KCCQ self efficacy score MMRM results over time - RS (OC-AD - no imputation for deaths) - 1245.121
For patients who died, only observed values are considered (no imputation after date of death).
Data taken from study 1245.121 only.

R.1.3.9.2

R.1.3.9.2 Subgroup analysis by sex

Table R.1.3.9.2: 1 KCCQ self efficacy score change from baseline at week 52 (MMRM) by sex - RS (OC-AD - no imputation for deaths) - 1245.121

Subgroup / Visit / Description / Statistic	Placebo	Empa 10mg
Sex: Male		
Number of patients in analysis set	1411	1426
Number of analysed patients	1332	1361
Baseline mean (SE)	75.27 (0.63)	74.20 (0.64)
Week 52		
Values at visit		
Number of analysed patients	936	954
Mean (SE)	80.62 (0.66)	80.42 (0.68)
Adjusted* mean (SE)	80.53 (0.59)	80.50 (0.58)
95% confidence interval	(79.38,81.68)	(79.36,81.63)
Change from baseline		
Mean (SE)	5.30 (0.74)	6.00 (0.79)
Adjusted* mean (SE)	5.80 (0.59)	5.77 (0.58)
95% confidence interval	(4.65, 6.95)	(4.63, 6.90)
Comparison vs Placebo		
Adjusted* mean (SE)		-0.03 (0.82)
95% confidence interval		(-1.65, 1.58)
p-value		0.9670

* Model includes Age, baseline eGFR (CKD-EPI) as linear covariate(s) and region, baseline diabetes status, baseline LVEF, week reachable, Visit by Treatment by sex interaction, baseline KCCQ self efficacy score by Visit interaction as fixed effect(s).
The Visit by Treatment by sex p-value at Week 52 is 0.6107.
The following covariance structure has been used to fit the mixed model: Unstructured
Note: All covariate effects are set equal to their mean values within subgroup for the calculation of adjusted means.

For patients who died, only observed values are considered (no imputation after date of death).
Data taken from study 1245.121 only.
The MMRM includes all outcome values (change from baseline) at the planned Visits week 12, week 32 and week 52

Table R.1.3.9.2: 1 KCCQ self efficacy score change from baseline at week 52 (MMRM) by sex - RS (OC-AD - no imputation for deaths) - 1245.121

Subgroup / Visit / Description / Statistic	Placebo	Empa 10mg
Sex: Female		
Number of patients in analysis set	456	437
Number of analysed patients	419	415
Baseline mean (SE)	72.79 (1.18)	72.95 (1.19)
Week 52		
Values at visit		
Number of analysed patients	278	285
Mean (SE)	80.40 (1.24)	80.83 (1.26)
Adjusted* mean (SE)	80.46 (1.07)	81.30 (1.06)
95% confidence interval	(78.35,82.56)	(79.22,83.38)
Change from baseline		
Mean (SE)	7.24 (1.40)	9.78 (1.52)
Adjusted* mean (SE)	7.59 (1.07)	8.43 (1.06)
95% confidence interval	(5.48, 9.69)	(6.35,10.50)
Comparison vs Placebo		
Adjusted* mean (SE)		0.84 (1.51)
95% confidence interval		(-2.11, 3.79)
p-value		0.5770

* Model includes Age, baseline eGFR (CKD-EPI) as linear covariate(s) and region, baseline diabetes status, baseline LVEF, week reachable, Visit by Treatment by sex interaction, baseline KCCQ self efficacy score by Visit interaction as fixed effect(s).
The Visit by Treatment by sex p-value at Week 52 is 0.6107.
The following covariance structure has been used to fit the mixed model: Unstructured
Note: All covariate effects are set equal to their mean values within subgroup for the calculation of adjusted means.

For patients who died, only observed values are considered (no imputation after date of death).
Data taken from study 1245.121 only.
The MMRM includes all outcome values (change from baseline) at the planned Visits week 12, week 32 and week 52

R.1.3.9.3

R.1.3.9.3 Subgroup analysis by age

Table R.1.3.9.3: 1 KCCQ self efficacy score change from baseline at week 52 (MMRM) by age (2 cat.) - RS (OC-AD - no imputation for deaths) - 1245.121

Subgroup / Visit / Description / Statistic	Placebo	Empa 10mg
Age [years] (2 cat.): < 65		
Number of patients in analysis set	740	675
Number of analysed patients	697	645
Baseline mean (SE)	74.32 (0.92)	72.38 (0.99)
Week 52		
Values at visit		
Number of analysed patients	494	454
Mean (SE)	81.38 (0.93)	82.43 (0.94)
Adjusted* mean (SE)	80.92 (0.81)	82.86 (0.84)
95% confidence interval	(79.33,82.52)	(81.21,84.52)
Change from baseline		
Mean (SE)	6.71 (1.05)	10.74 (1.17)
Adjusted* mean (SE)	7.53 (0.81)	9.48 (0.84)
95% confidence interval	(5.94, 9.13)	(7.82,11.13)
Comparison vs Placebo		
Adjusted* mean (SE)		1.94 (1.17)
95% confidence interval		(-0.35, 4.23)
p-value		0.0964

* Model includes baseline eGFR (CKD-EPI) as linear covariate(s) and region, baseline diabetes status, sex, baseline LVEF, week reachable, Visit by Treatment by age [years] (2 cat.) interaction, baseline KCCQ self efficacy score by Visit interaction as fixed effect(s).
The Visit by Treatment by age [years] (2 cat.) p-value at Week 52 is 0.0528.
The following covariance structure has been used to fit the mixed model: Unstructured
Note: All covariate effects are set equal to their mean values within subgroup for the calculation of adjusted means.

For patients who died, only observed values are considered (no imputation after date of death).
Data taken from study 1245.121 only.
The MMRM includes all outcome values (change from baseline) at the planned Visits week 12, week 32 and week 52

Table R.1.3.9.3: 1 KCCQ self efficacy score change from baseline at week 52 (MMRM) by age (2 cat.) - RS (OC-AD - no imputation for deaths) - 1245.121

Subgroup / Visit / Description / Statistic	Placebo	Empa 10mg
Age [years] (2 cat.): >= 65		
Number of patients in analysis set	1127	1188
Number of analysed patients	1054	1131
Baseline mean (SE)	74.92 (0.70)	74.78 (0.68)
Week 52		
Values at visit		
Number of analysed patients	720	785
Mean (SE)	80.02 (0.75)	79.41 (0.77)
Adjusted* mean (SE)	80.32 (0.67)	79.37 (0.64)
95% confidence interval	(79.01,81.63)	(78.12,80.63)
Change from baseline		
Mean (SE)	5.09 (0.84)	4.63 (0.87)
Adjusted* mean (SE)	5.47 (0.67)	4.53 (0.64)
95% confidence interval	(4.16, 6.78)	(3.27, 5.79)
Comparison vs Placebo		
Adjusted* mean (SE)		-0.94 (0.92)
95% confidence interval		(-2.76, 0.87)
p-value		0.3070

* Model includes baseline eGFR (CKD-EPI) as linear covariate(s) and region, baseline diabetes status, sex, baseline LVEF, week reachable, Visit by Treatment by age [years] (2 cat.) interaction, baseline KCCQ self efficacy score by Visit interaction as fixed effect(s).
The Visit by Treatment by age [years] (2 cat.) p-value at Week 52 is 0.0528.
The following covariance structure has been used to fit the mixed model: Unstructured
Note: All covariate effects are set equal to their mean values within subgroup for the calculation of adjusted means.

For patients who died, only observed values are considered (no imputation after date of death).
Data taken from study 1245.121 only.
The MMRM includes all outcome values (change from baseline) at the planned Visits week 12, week 32 and week 52

R.1.3.9.4 Subgroup analysis by region (North America, Latin America, Europe, Asia, Other)

Table R.1.3.9.4: 1 KCCQ self efficacy score change from baseline at week 52 (MMRM) by region - RS (OC-AD - no imputation for deaths) - 1245.121

Subgroup / Visit / Description / Statistic	Placebo	Empa 10mg
Region (5 cat.): North America		
Number of patients in analysis set	213	212
Number of analysed patients	195	206
Baseline mean (SE)	84.74 (1.34)	85.07 (1.37)
Week 52		
Values at visit		
Number of analysed patients	129	151
Mean (SE)	88.18 (1.50)	88.66 (1.46)
Adjusted* mean (SE)	88.94 (1.57)	88.57 (1.46)
95% confidence interval	(85.86,92.02)	(85.70,91.44)
Change from baseline		
Mean (SE)	5.14 (1.82)	3.73 (1.87)
Adjusted* mean (SE)	4.03 (1.57)	3.66 (1.46)
95% confidence interval	(0.95, 7.11)	(0.78, 6.53)
Comparison vs Placebo		
Adjusted* mean (SE)		-0.37 (2.15)
95% confidence interval		(-4.59, 3.84)
p-value		0.8624

* Model includes Age, baseline eGFR (CKD-EPI) as linear covariate(s) and baseline diabetes status, sex, baseline LVEF, week reachable, Visit by Treatment by region (5 cat.) interaction, baseline KCCQ self efficacy score by Visit interaction as fixed effect(s).
The Visit by Treatment by region (5 cat.) p-value at Week 52 is 0.5813.
The following covariance structure has been used to fit the mixed model: Unstructured
Note: All covariate effects are set equal to their mean values within subgroup for the calculation of adjusted means.

For patients who died, only observed values are considered (no imputation after date of death).
Data taken from study 1245.121 only.
The MMRM includes all outcome values (change from baseline) at the planned Visits week 12, week 32 and week 52

Table R.1.3.9.4: 1 KCCQ self efficacy score change from baseline at week 52 (MMRM) by region - RS (OC-AD - no imputation for deaths) - 1245.121

Subgroup / Visit / Description / Statistic	Placebo	Empa 10mg
Region (5 cat.): Latin America		
Number of patients in analysis set	645	641
Number of analysed patients	599	602
Baseline mean (SE)	70.43 (1.01)	69.37 (1.03)
Week 52		
Values at visit		
Number of analysed patients	391	374
Mean (SE)	78.58 (1.09)	79.01 (1.16)
Adjusted* mean (SE)	77.57 (0.90)	79.42 (0.92)
95% confidence interval	(75.80,79.34)	(77.62,81.22)
Change from baseline		
Mean (SE)	6.39 (1.24)	10.66 (1.42)
Adjusted* mean (SE)	7.67 (0.90)	9.52 (0.92)
95% confidence interval	(5.90, 9.44)	(7.72,11.32)
Comparison vs Placebo		
Adjusted* mean (SE)		1.85 (1.29)
95% confidence interval		(-0.67, 4.38)
p-value		0.1503

* Model includes Age, baseline eGFR (CKD-EPI) as linear covariate(s) and baseline diabetes status, sex, baseline LVEF, week reachable, Visit by Treatment by region (5 cat.) interaction, baseline KCCQ self efficacy score by Visit interaction as fixed effect(s).
The Visit by Treatment by region (5 cat.) p-value at Week 52 is 0.5813.
The following covariance structure has been used to fit the mixed model: Unstructured
Note: All covariate effects are set equal to their mean values within subgroup for the calculation of adjusted means.

For patients who died, only observed values are considered (no imputation after date of death).
Data taken from study 1245.121 only.
The MMRM includes all outcome values (change from baseline) at the planned Visits week 12, week 32 and week 52

Table R.1.3.9.4: 1 KCCQ self efficacy score change from baseline at week 52 (MMRM) by region - RS (OC-AD - no imputation for deaths) - 1245.121

Subgroup / Visit / Description / Statistic	Placebo	Empa 10mg
Region (5 cat.): Europe		
Number of patients in analysis set	677	676
Number of analysed patients	642	649
Baseline mean (SE)	75.43 (0.90)	75.31 (0.88)
Week 52		
Values at visit		
Number of analysed patients	464	469
Mean (SE)	80.04 (0.91)	80.06 (0.92)
Adjusted* mean (SE)	80.73 (0.83)	80.23 (0.83)
95% confidence interval	(79.09,82.36)	(78.60,81.86)
Change from baseline		
Mean (SE)	5.60 (1.01)	5.04 (1.02)
Adjusted* mean (SE)	5.36 (0.83)	4.86 (0.83)
95% confidence interval	(3.72, 7.00)	(3.23, 6.49)
Comparison vs Placebo		
Adjusted* mean (SE)		-0.50 (1.18)
95% confidence interval		(-2.80, 1.80)
p-value		0.6706

* Model includes Age, baseline eGFR (CKD-EPI) as linear covariate(s) and baseline diabetes status, sex, baseline LVEF, week reachable, Visit by Treatment by region (5 cat.) interaction, baseline KCCQ self efficacy score by Visit interaction as fixed effect(s).
The Visit by Treatment by region (5 cat.) p-value at Week 52 is 0.5813.
The following covariance structure has been used to fit the mixed model: Unstructured
Note: All covariate effects are set equal to their mean values within subgroup for the calculation of adjusted means.

For patients who died, only observed values are considered (no imputation after date of death).
Data taken from study 1245.121 only.
The MMRM includes all outcome values (change from baseline) at the planned Visits week 12, week 32 and week 52

Table R.1.3.9.4: 1 KCCQ self efficacy score change from baseline at week 52 (MMRM) by region - RS (OC-AD - no imputation for deaths) - 1245.121

Subgroup / Visit / Description / Statistic	Placebo	Empa 10mg
Region (5 cat.): Asia		
Number of patients in analysis set	245	248
Number of analysed patients	237	243
Baseline mean (SE)	72.57 (1.42)	69.80 (1.48)
Week 52		
Values at visit		
Number of analysed patients	180	189
Mean (SE)	77.64 (1.54)	75.53 (1.54)
Adjusted* mean (SE)	77.43 (1.35)	75.96 (1.31)
95% confidence interval	(74.78,80.07)	(73.38,78.54)
Change from baseline		
Mean (SE)	5.00 (1.76)	5.36 (1.91)
Adjusted* mean (SE)	6.26 (1.35)	4.79 (1.31)
95% confidence interval	(3.61, 8.90)	(2.21, 7.36)
Comparison vs Placebo		
Adjusted* mean (SE)		-1.47 (1.88)
95% confidence interval		(-5.15, 2.22)
p-value		0.4349

* Model includes Age, baseline eGFR (CKD-EPI) as linear covariate(s) and baseline diabetes status, sex, baseline LVEF, week reachable, Visit by Treatment by region (5 cat.) interaction, baseline KCCQ self efficacy score by Visit interaction as fixed effect(s).
The Visit by Treatment by region (5 cat.) p-value at Week 52 is 0.5813.
The following covariance structure has been used to fit the mixed model: Unstructured
Note: All covariate effects are set equal to their mean values within subgroup for the calculation of adjusted means.

For patients who died, only observed values are considered (no imputation after date of death).
Data taken from study 1245.121 only.
The MMRM includes all outcome values (change from baseline) at the planned Visits week 12, week 32 and week 52

Table R.1.3.9.4: 1 KCCQ self efficacy score change from baseline at week 52 (MMRM) by region - RS (OC-AD - no imputation for deaths) - 1245.121

Subgroup / Visit / Description / Statistic	Placebo	Empa 10mg
Region (5 cat.): Other		
Number of patients in analysis set	87	86
Number of analysed patients	78	76
Baseline mean (SE)	82.37 (2.50)	80.76 (2.60)
Week 52		
Values at visit		
Number of analysed patients	50	56
Mean (SE)	92.00 (2.28)	89.29 (2.41)
Adjusted* mean (SE)	89.57 (2.52)	89.98 (2.40)
95% confidence interval	(84.62,94.52)	(85.27,94.69)
Change from baseline		
Mean (SE)	6.25 (3.26)	10.49 (3.15)
Adjusted* mean (SE)	7.99 (2.52)	8.41 (2.40)
95% confidence interval	(3.04,12.94)	(3.69,13.12)
Comparison vs Placebo		
Adjusted* mean (SE)		0.41 (3.48)
95% confidence interval		(-6.42, 7.24)
p-value		0.9057

* Model includes Age, baseline eGFR (CKD-EPI) as linear covariate(s) and baseline diabetes status, sex, baseline LVEF, week reachable, Visit by Treatment by region (5 cat.) interaction, baseline KCCQ self efficacy score by Visit interaction as fixed effect(s).
The Visit by Treatment by region (5 cat.) p-value at Week 52 is 0.5813.
The following covariance structure has been used to fit the mixed model: Unstructured
Note: All covariate effects are set equal to their mean values within subgroup for the calculation of adjusted means.

For patients who died, only observed values are considered (no imputation after date of death).
Data taken from study 1245.121 only.
The MMRM includes all outcome values (change from baseline) at the planned Visits week 12, week 32 and week 52

R.1.3.9.5

R.1.3.9.5 Subgroup analysis by OECD (N/Y)

Table R.1.3.9.5: 1 KCCQ self efficacy score change from baseline at week 52 (MMRM) by OECD member (N/Y) - RS (OC-AD - no imputation for deaths) - 1245.121

Subgroup / Visit / Description / Statistic	Placebo	Empa 10mg
OECD member: No		
Number of patients in analysis set	741	713
Number of analysed patients	686	664
Baseline mean (SE)	71.68 (0.95)	69.82 (0.98)
Week 52		
Values at visit		
Number of analysed patients	443	421
Mean (SE)	79.60 (1.02)	80.20 (1.06)
Adjusted* mean (SE)	78.42 (0.85)	80.84 (0.87)
95% confidence interval	(76.75,80.09)	(79.13,82.55)
Change from baseline		
Mean (SE)	6.57 (1.18)	11.61 (1.32)
Adjusted* mean (SE)	7.65 (0.85)	10.07 (0.87)
95% confidence interval	(5.98, 9.32)	(8.36,11.78)
Comparison vs Placebo		
Adjusted* mean (SE)		2.42 (1.22)
95% confidence interval		(0.03, 4.81)
p-value		0.0472

* Model includes Age, baseline eGFR (CKD-EPI) as linear covariate(s) and baseline diabetes status, sex, baseline LVEF, week reachable, Visit by Treatment by OECD Member (N) interaction, baseline KCCQ self efficacy score by Visit interaction as fixed effect(s).
The Visit by Treatment by OECD Member (N) p-value at Week 52 is 0.0260.
The following covariance structure has been used to fit the mixed model: Unstructured
Note: All covariate effects are set equal to their mean values within subgroup for the calculation of adjusted means.

For patients who died, only observed values are considered (no imputation after date of death).
Data taken from study 1245.121 only.
OECD member (yes/no) countries included:
Yes: United States, Canada, Mexico, Poland, Netherlands, Hungary, Germany, Czech Republic, Italy, France, Spain, United Kingdom, Belgium, Japan, Australia, 'Korea; Republic Of South Korea';
No: Brazil, Argentina, China, India.
The MMRM includes all outcome values (change from baseline) at the planned Visits week 12, week 32 and week 52

Table R.1.3.9.5: 1 KCCQ self efficacy score change from baseline at week 52 (MMRM) by OECD member (N/Y) - RS (OC-AD - no imputation for deaths) - 1245.121

Subgroup / Visit / Description / Statistic	Placebo	Empa 10mg
OECD member: Yes		
Number of patients in analysis set	1126	1150
Number of analysed patients	1065	1112
Baseline mean (SE)	76.61 (0.68)	76.35 (0.68)
Week 52		
Values at visit		
Number of analysed patients	771	818
Mean (SE)	81.13 (0.71)	80.68 (0.72)
Adjusted* mean (SE)	81.72 (0.65)	80.75 (0.63)
95% confidence interval	(80.44,83.00)	(79.51,81.99)
Change from baseline		
Mean (SE)	5.27 (0.78)	4.43 (0.80)
Adjusted* mean (SE)	5.24 (0.65)	4.28 (0.63)
95% confidence interval	(3.97, 6.52)	(3.04, 5.52)
Comparison vs Placebo		
Adjusted* mean (SE)		-0.96 (0.91)
95% confidence interval		(-2.74, 0.81)
p-value		0.2876

* Model includes Age, baseline eGFR (CKD-EPI) as linear covariate(s) and baseline diabetes status, sex, baseline LVEF, week reachable, Visit by Treatment by OECD Member (N) interaction, baseline KCCQ self efficacy score by Visit interaction as fixed effect(s).
The Visit by Treatment by OECD Member (N) p-value at Week 52 is 0.0260.
The following covariance structure has been used to fit the mixed model: Unstructured
Note: All covariate effects are set equal to their mean values within subgroup for the calculation of adjusted means.

For patients who died, only observed values are considered (no imputation after date of death).
Data taken from study 1245.121 only.
OECD member (yes/no) countries included:
Yes: United States, Canada, Mexico, Poland, Netherlands, Hungary, Germany, Czech Republic, Italy, France, Spain, United Kingdom, Belgium, Japan, Australia, 'Korea; Republic Of South Korea';
No: Brazil, Argentina, China, India.
The MMRM includes all outcome values (change from baseline) at the planned Visits week 12, week 32 and week 52

R.1.3.9.6 Subgroup analysis by NYHA at baseline (II, III/IV - 2 cat.)

Table R.1.3.9.6: 1 KCCQ self efficacy score change from baseline at week 52 (MMRM) by NYHA (2 cat.) - RS (OC-AD - no imputation for deaths) - 1245.121

Subgroup / Visit / Description / Statistic	Placebo	Empa 10mg
Baseline NYHA (2 cat.): II		
Number of patients in analysis set	1401	1399
Number of analysed patients	1339	1332
Baseline mean (SE)	75.59 (0.62)	75.42 (0.64)
Week 52		
Values at visit		
Number of analysed patients	944	951
Mean (SE)	81.00 (0.65)	81.62 (0.67)
Adjusted* mean (SE)	81.22 (0.58)	81.91 (0.58)
95% confidence interval	(80.08,82.37)	(80.77,83.05)
Change from baseline		
Mean (SE)	5.35 (0.75)	6.83 (0.80)
Adjusted* mean (SE)	5.72 (0.58)	6.41 (0.58)
95% confidence interval	(4.58, 6.86)	(5.27, 7.55)
Comparison vs Placebo		
Adjusted* mean (SE)		0.69 (0.82)
95% confidence interval		(-0.92, 2.30)
p-value		0.4026

* Model includes Age, baseline eGFR (CKD-EPI) as linear covariate(s) and region, baseline diabetes status, sex, baseline LVEF, week reachable, Visit by Treatment by baseline NYHA (2 cat.) interaction, baseline KCCQ self efficacy score by Visit interaction as fixed effect(s).
The Visit by Treatment by baseline NYHA (2 cat.) p-value at Week 52 is 0.2017.
The following covariance structure has been used to fit the mixed model: Unstructured
Note: All covariate effects are set equal to their mean values within subgroup for the calculation of adjusted means.

For patients who died, only observed values are considered (no imputation after date of death).
Data taken from study 1245.121 only.
The MMRM includes all outcome values (change from baseline) at the planned Visits week 12, week 32 and week 52

Table R.1.3.9.6: 1 KCCQ self efficacy score change from baseline at week 52 (MMRM) by NYHA (2 cat.) - RS (OC-AD - no imputation for deaths) - 1245.121

Subgroup / Visit / Description / Statistic	Placebo	Empa 10mg
Baseline NYHA (2 cat.): III/IV		
Number of patients in analysis set	466	464
Number of analysed patients	412	444
Baseline mean (SE)	71.72 (1.22)	69.37 (1.17)
Week 52		
Values at visit		
Number of analysed patients	270	288
Mean (SE)	79.07 (1.30)	76.87 (1.30)
Adjusted* mean (SE)	78.24 (1.09)	76.73 (1.05)
95% confidence interval	(76.11,80.37)	(74.67,78.79)
Change from baseline		
Mean (SE)	7.13 (1.37)	6.99 (1.49)
Adjusted* mean (SE)	7.74 (1.09)	6.23 (1.05)
95% confidence interval	(5.61, 9.86)	(4.17, 8.29)
Comparison vs Placebo		
Adjusted* mean (SE)		-1.50 (1.51)
95% confidence interval		(-4.46, 1.45)
p-value		0.3185

* Model includes Age, baseline eGFR (CKD-EPI) as linear covariate(s) and region, baseline diabetes status, sex, baseline LVEF, week reachable, Visit by Treatment by baseline NYHA (2 cat.) interaction, baseline KCCQ self efficacy score by Visit interaction as fixed effect(s).
The Visit by Treatment by baseline NYHA (2 cat.) p-value at Week 52 is 0.2017.
The following covariance structure has been used to fit the mixed model: Unstructured
Note: All covariate effects are set equal to their mean values within subgroup for the calculation of adjusted means.

For patients who died, only observed values are considered (no imputation after date of death).
Data taken from study 1245.121 only.
The MMRM includes all outcome values (change from baseline) at the planned Visits week 12, week 32 and week 52

R.1.3.9.7

R.1.3.9.7 Subgroup analysis by diabetes at baseline

Table R.1.3.9.7: 1 KCCQ self efficacy score change from baseline at week 52 (MMRM) by diabetes at baseline - RS (OC-AD - no imputation for deaths) - 1245.121

Subgroup / Visit / Description / Statistic	Placebo	Empa 10mg
Diabetes at baseline (2 cat.):		
Diabetic		
Number of patients in analysis set	929	927
Number of analysed patients	866	882
Baseline mean (SE)	74.15 (0.82)	73.48 (0.81)
Week 52		
Values at visit		
Number of analysed patients	603	614
Mean (SE)	80.33 (0.84)	80.11 (0.86)
Adjusted* mean (SE)	80.03 (0.73)	80.15 (0.72)
95% confidence interval	(78.60,81.46)	(78.74,81.57)
Change from baseline		
Mean (SE)	5.83 (0.94)	6.27 (1.01)
Adjusted* mean (SE)	6.22 (0.73)	6.34 (0.72)
95% confidence interval	(4.79, 7.65)	(4.92, 7.76)
Comparison vs Placebo		
Adjusted* mean (SE)		0.12 (1.03)
95% confidence interval		(-1.89, 2.14)
p-value		0.9044

* Model includes Age, baseline eGFR (CKD-EPI) as linear covariate(s) and region, sex, baseline LVEF, week reachable, Visit by Treatment by diabetes at baseline (2 cat.) interaction, baseline KCCQ self efficacy score by Visit interaction as fixed effect(s).
The Visit by Treatment by diabetes at baseline (2 cat.) p-value at Week 52 is 0.9461.
The following covariance structure has been used to fit the mixed model: Unstructured
Note: All covariate effects are set equal to their mean values within subgroup for the calculation of adjusted means.

For patients who died, only observed values are considered (no imputation after date of death).
Data taken from study 1245.121 only.
The MMRM includes all outcome values (change from baseline) at the planned Visits week 12, week 32 and week 52

Table R.1.3.9.7: 1 KCCQ self efficacy score change from baseline at week 52 (MMRM) by diabetes at baseline - RS (OC-AD - no imputation for deaths) - 1245.121

Subgroup / Visit / Description / Statistic	Placebo	Empa 10mg
Diabetes at baseline (2 cat.):		
Non-Diabetic		
Number of patients in analysis set	938	936
Number of analysed patients	885	894
Baseline mean (SE)	75.20 (0.76)	74.33 (0.79)
Week 52		
Values at visit		
Number of analysed patients	611	625
Mean (SE)	80.81 (0.81)	80.92 (0.83)
Adjusted* mean (SE)	80.97 (0.72)	81.19 (0.72)
95% confidence interval	(79.55,82.39)	(79.79,82.60)
Change from baseline		
Mean (SE)	5.67 (0.92)	7.46 (0.98)
Adjusted* mean (SE)	6.21 (0.72)	6.43 (0.72)
95% confidence interval	(4.79, 7.63)	(5.03, 7.84)
Comparison vs Placebo		
Adjusted* mean (SE)		0.22 (1.02)
95% confidence interval		(-1.78, 2.22)
p-value		0.8283

* Model includes Age, baseline eGFR (CKD-EPI) as linear covariate(s) and region, sex, baseline LVEF, week reachable, Visit by Treatment by diabetes at baseline (2 cat.) interaction, baseline KCCQ self efficacy score by Visit interaction as fixed effect(s).
The Visit by Treatment by diabetes at baseline (2 cat.) p-value at Week 52 is 0.9461.
The following covariance structure has been used to fit the mixed model: Unstructured
Note: All covariate effects are set equal to their mean values within subgroup for the calculation of adjusted means.

For patients who died, only observed values are considered (no imputation after date of death).
Data taken from study 1245.121 only.
The MMRM includes all outcome values (change from baseline) at the planned Visits week 12, week 32 and week 52

R.1.3.9.8 Subgroup analysis by BMI at baseline (<30, >=30)

Table R.1.3.9.8: 1 KCCQ self efficacy score change from baseline at week 52 (MMRM) by baseline BMI [kg/m2] - RS (OC-AD - no imputation for deaths) - 1245.121

Subgroup / Visit / Description / Statistic	Placebo	Empa 10mg
Baseline BMI [kg/m²] (2 cat.): <30		
Number of patients in analysis set	1300	1263
Number of analysed patients	1229	1201
Baseline mean (SE)	75.01 (0.66)	74.73 (0.68)
Week 52		
Values at visit		
Number of analysed patients	862	826
Mean (SE)	80.26 (0.71)	80.61 (0.73)
Adjusted* mean (SE)	80.56 (0.61)	80.70 (0.62)
95% confidence interval	(79.36,81.76)	(79.48,81.93)
Change from baseline		
Mean (SE)	4.93 (0.78)	6.01 (0.84)
Adjusted* mean (SE)	5.69 (0.61)	5.83 (0.62)
95% confidence interval	(4.49, 6.89)	(4.61, 7.06)
Comparison vs Placebo		
Adjusted* mean (SE)		0.14 (0.87)
95% confidence interval		(-1.57, 1.85)
p-value		0.8695

* Model includes Age, baseline eGFR (CKD-EPI) as linear covariate(s) and region, baseline diabetes status, sex, baseline LVEF, week reachable, Visit by Treatment by baseline BMI [kg/m²] (2 cat.) interaction, baseline KCCQ self efficacy score by Visit interaction as fixed effect(s).
The Visit by Treatment by baseline BMI [kg/m²] (2 cat.) p-value at Week 52 is 0.9714.
The following covariance structure has been used to fit the mixed model: Unstructured
Note: All covariate effects are set equal to their mean values within subgroup for the calculation of adjusted means.

For patients who died, only observed values are considered (no imputation after date of death).
Data taken from study 1245.121 only.
The MMRM includes all outcome values (change from baseline) at the planned Visits week 12, week 32 and week 52

Table R.1.3.9.8: 1 KCCQ self efficacy score change from baseline at week 52 (MMRM) by baseline BMI [kg/m2] - RS (OC-AD - no imputation for deaths) - 1245.121

Subgroup / Visit / Description / Statistic	Placebo	Empa 10mg
Baseline BMI [kg/m²] (2 cat.): >=30		
Number of patients in analysis set	567	600
Number of analysed patients	522	575
Baseline mean (SE)	73.90 (1.02)	72.20 (1.01)
Week 52		
Values at visit		
Number of analysed patients	352	413
Mean (SE)	81.32 (1.02)	80.33 (1.03)
Adjusted* mean (SE)	80.42 (0.96)	80.62 (0.89)
95% confidence interval	(78.54,82.30)	(78.87,82.36)
Change from baseline		
Mean (SE)	7.74 (1.21)	8.60 (1.26)
Adjusted* mean (SE)	7.41 (0.96)	7.61 (0.89)
95% confidence interval	(5.53, 9.29)	(5.87, 9.36)
Comparison vs Placebo		
Adjusted* mean (SE)		0.20 (1.30)
95% confidence interval		(-2.35, 2.75)
p-value		0.8782

* Model includes Age, baseline eGFR (CKD-EPI) as linear covariate(s) and region, baseline diabetes status, sex, baseline LVEF, week reachable, Visit by Treatment by baseline BMI [kg/m²] (2 cat.) interaction, baseline KCCQ self efficacy score by Visit interaction as fixed effect(s).
The Visit by Treatment by baseline BMI [kg/m²] (2 cat.) p-value at Week 52 is 0.9714.
The following covariance structure has been used to fit the mixed model: Unstructured
Note: All covariate effects are set equal to their mean values within subgroup for the calculation of adjusted means.

For patients who died, only observed values are considered (no imputation after date of death).
Data taken from study 1245.121 only.
The MMRM includes all outcome values (change from baseline) at the planned Visits week 12, week 32 and week 52

R.1.3.9.9 Subgroup analysis by eGFR at baseline (<60, >=60)

Table R.1.3.9.9: 1 KCCQ self efficacy score change from baseline at week 52 (MMRM) by baseline eGFR (2 cat.) - RS (OC-AD - no imputation for deaths) - 1245.121

Subgroup / Visit / Description / Statistic	Placebo	Empa 10mg
Baseline eGFR (CKD-EPI) [mL/min/1.73m²] (2 cat.): >=60		
Number of patients in analysis set	960	969
Number of analysed patients	901	921
Baseline mean (SE)	73.56 (0.80)	72.87 (0.82)
Week 52		
Values at visit		
Number of analysed patients	646	650
Mean (SE)	80.22 (0.79)	80.92 (0.82)
Adjusted* mean (SE)	80.28 (0.71)	81.28 (0.70)
95% confidence interval	(78.89,81.67)	(79.90,82.66)
Change from baseline		
Mean (SE)	6.13 (0.91)	8.31 (0.96)
Adjusted* mean (SE)	7.07 (0.71)	8.07 (0.70)
95% confidence interval	(5.68, 8.46)	(6.69, 9.45)
Comparison vs Placebo		
Adjusted* mean (SE)		1.00 (1.00)
95% confidence interval		(-0.95, 2.96)
p-value		0.3150

* Model includes Age as linear covariate(s) and region, baseline diabetes status, sex, baseline LVEF, week reachable, Visit by Treatment by baseline eGFR (CKD-EPI) [mL/min/1.73m²] (2 cat.) interaction, baseline KCCQ self efficacy score by Visit interaction as fixed effect(s).
The Visit by Treatment by baseline eGFR (CKD-EPI) [mL/min/1.73m²] (2 cat.) p-value at Week 52 is 0.2322.
The following covariance structure has been used to fit the mixed model: Unstructured
2 patients were excluded as the subgroup variable was missing.
Note: All covariate effects are set equal to their mean values within subgroup for the calculation of adjusted means.

For patients who died, only observed values are considered (no imputation after date of death).
Data taken from study 1245.121 only.
The MMRM includes all outcome values (change from baseline) at the planned Visits week 12, week 32 and week 52

Table R.1.3.9.9: 1 KCCQ self efficacy score change from baseline at week 52 (MMRM) by baseline eGFR (2 cat.) - RS (OC-AD - no imputation for deaths) - 1245.121

Subgroup / Visit / Description / Statistic	Placebo	Empa 10mg
Baseline eGFR (CKD-EPI) [mL/min/1.73m²] (2 cat.): <60		
Number of patients in analysis set	906	893
Number of analysed patients	850	855
Baseline mean (SE)	75.87 (0.77)	75.03 (0.77)
Week 52		
Values at visit		
Number of analysed patients	568	589
Mean (SE)	80.96 (0.86)	80.07 (0.87)
Adjusted* mean (SE)	80.75 (0.75)	80.02 (0.74)
95% confidence interval	(79.28,82.22)	(78.57,81.47)
Change from baseline		
Mean (SE)	5.30 (0.95)	5.28 (1.02)
Adjusted* mean (SE)	5.30 (0.75)	4.57 (0.74)
95% confidence interval	(3.83, 6.77)	(3.12, 6.02)
Comparison vs Placebo		
Adjusted* mean (SE)		-0.73 (1.05)
95% confidence interval		(-2.79, 1.33)
p-value		0.4879

* Model includes Age as linear covariate(s) and region, baseline diabetes status, sex, baseline LVEF, week reachable, Visit by Treatment by baseline eGFR (CKD-EPI) [mL/min/1.73m²] (2 cat.) interaction, baseline KCCQ self efficacy score by Visit interaction as fixed effect(s).
The Visit by Treatment by baseline eGFR (CKD-EPI) [mL/min/1.73m²] (2 cat.) p-value at Week 52 is 0.2322.
The following covariance structure has been used to fit the mixed model: Unstructured
2 patients were excluded as the subgroup variable was missing.
Note: All covariate effects are set equal to their mean values within subgroup for the calculation of adjusted means.

For patients who died, only observed values are considered (no imputation after date of death).
Data taken from study 1245.121 only.
The MMRM includes all outcome values (change from baseline) at the planned Visits week 12, week 32 and week 52

R.1.3.9.10

Table R.1.3.9.10: 1 KCCQ self efficacy score change from baseline at week 52 (MMRM) by history of HHF - RS (OC-AD - no imputation for deaths) - 1245.121

Subgroup / Visit / Description / Statistic	Placebo	Empa 10mg
History of HHF (in the last 12 months): No		
Number of patients in analysis set	1293	1286
Number of analysed patients	1218	1231
Baseline mean (SE)	74.47 (0.66)	74.38 (0.67)
Week 52		
Values at visit		
Number of analysed patients	867	873
Mean (SE)	80.31 (0.69)	81.00 (0.70)
Adjusted* mean (SE)	80.55 (0.61)	80.90 (0.61)
95% confidence interval	(79.36,81.75)	(79.71,82.09)
Change from baseline		
Mean (SE)	6.14 (0.77)	6.82 (0.83)
Adjusted* mean (SE)	6.13 (0.61)	6.47 (0.61)
95% confidence interval	(4.93, 7.33)	(5.28, 7.67)
Comparison vs Placebo		
Adjusted* mean (SE)		0.34 (0.86)
95% confidence interval		(-1.34, 2.03)
p-value		0.6896

* Model includes Age, baseline eGFR (CKD-EPI) as linear covariate(s) and region, baseline diabetes status, sex, baseline LVEF, week reachable, Visit by Treatment by history of HHF (in the last 12 months) interaction, baseline KCCQ self efficacy score by Visit interaction as fixed effect(s).
The Visit by Treatment by history of HHF (in the last 12 months) p-value at Week 52 is 0.6826.
The following covariance structure has been used to fit the mixed model: Unstructured
Note: All covariate effects are set equal to their mean values within subgroup for the calculation of adjusted means.

For patients who died, only observed values are considered (no imputation after date of death).
Data taken from study 1245.121 only.
The MMRM includes all outcome values (change from baseline) at the planned Visits week 12, week 32 and week 52

Table R.1.3.9.10: 1 KCCQ self efficacy score change from baseline at week 52 (MMRM) by history of HHF - RS (OC-AD - no imputation for deaths) - 1245.121

Subgroup / Visit / Description / Statistic	Placebo	Empa 10mg
History of HHF (in the last 12 months): Yes		
Number of patients in analysis set	574	577
Number of analysed patients	533	545
Baseline mean (SE)	75.16 (1.02)	72.84 (1.04)
Week 52		
Values at visit		
Number of analysed patients	347	366
Mean (SE)	81.23 (1.10)	79.37 (1.12)
Adjusted* mean (SE)	80.43 (0.96)	80.12 (0.94)
95% confidence interval	(78.54,82.31)	(78.28,81.96)
Change from baseline		
Mean (SE)	4.76 (1.25)	7.00 (1.31)
Adjusted* mean (SE)	6.43 (0.96)	6.13 (0.94)
95% confidence interval	(4.55, 8.32)	(4.29, 7.97)
Comparison vs Placebo		
Adjusted* mean (SE)		-0.31 (1.34)
95% confidence interval		(-2.93, 2.32)
p-value		0.8184

* Model includes Age, baseline eGFR (CKD-EPI) as linear covariate(s) and region, baseline diabetes status, sex, baseline LVEF, week reachable, Visit by Treatment by history of HHF (in the last 12 months) interaction, baseline KCCQ self efficacy score by Visit interaction as fixed effect(s).
The Visit by Treatment by history of HHF (in the last 12 months) p-value at Week 52 is 0.6826.
The following covariance structure has been used to fit the mixed model: Unstructured
Note: All covariate effects are set equal to their mean values within subgroup for the calculation of adjusted means.

For patients who died, only observed values are considered (no imputation after date of death).
Data taken from study 1245.121 only.
The MMRM includes all outcome values (change from baseline) at the planned Visits week 12, week 32 and week 52

R.1.3.9.11

R.1.3.9.11 Subgroup analysis by cause of heart failure

Table R.1.3.9.11: 1 KCCQ self efficacy score change from baseline at week 52 (MMRM) by cause of heart failure - RS (OC-AD - no imputation for deaths) - 1245.121

Subgroup / Visit / Description / Statistic	Placebo	Empa 10mg
Cause of heart failure: Ischemic		
Number of patients in analysis set	946	983
Number of analysed patients	895	936
Baseline mean (SE)	75.29 (0.77)	74.23 (0.77)
Week 52		
Values at visit		
Number of analysed patients	632	667
Mean (SE)	81.17 (0.81)	79.87 (0.83)
Adjusted* mean (SE)	80.75 (0.72)	79.96 (0.70)
95% confidence interval	(79.34,82.16)	(78.59,81.33)
Change from baseline		
Mean (SE)	5.30 (0.85)	5.79 (0.95)
Adjusted* mean (SE)	6.01 (0.72)	5.21 (0.70)
95% confidence interval	(4.60, 7.41)	(3.84, 6.58)
Comparison vs Placebo		
Adjusted* mean (SE)		-0.80 (1.00)
95% confidence interval		(-2.75, 1.16)
p-value		0.4245

* Model includes Age, baseline eGFR (CKD-EPI) as linear covariate(s) and region, baseline diabetes status, sex, baseline LVEF, week reachable, Visit by Treatment by cause of heart failure interaction, baseline KCCQ self efficacy score by Visit interaction as fixed effect(s).
The Visit by Treatment by cause of heart failure p-value at Week 52 is 0.1576.
The following covariance structure has been used to fit the mixed model: Unstructured
Note: All covariate effects are set equal to their mean values within subgroup for the calculation of adjusted means.

For patients who died, only observed values are considered (no imputation after date of death).
Data taken from study 1245.121 only.
The MMRM includes all outcome values (change from baseline) at the planned Visits week 12, week 32 and week 52

Table R.1.3.9.11: 1 KCCQ self efficacy score change from baseline at week 52 (MMRM) by cause of heart failure - RS (OC-AD - no imputation for deaths) - 1245.121

Subgroup / Visit / Description / Statistic	Placebo	Empa 10mg
Cause of heart failure: Non-ischemic		
Number of patients in analysis set	921	880
Number of analysed patients	856	840
Baseline mean (SE)	74.04 (0.81)	73.56 (0.83)
Week 52		
Values at visit		
Number of analysed patients	582	572
Mean (SE)	79.92 (0.84)	81.27 (0.86)
Adjusted* mean (SE)	80.25 (0.75)	81.50 (0.75)
95% confidence interval	(78.79,81.71)	(80.03,82.97)
Change from baseline		
Mean (SE)	6.23 (1.01)	8.13 (1.05)
Adjusted* mean (SE)	6.45 (0.75)	7.70 (0.75)
95% confidence interval	(4.99, 7.91)	(6.23, 9.17)
Comparison vs Placebo		
Adjusted* mean (SE)		1.25 (1.05)
95% confidence interval		(-0.81, 3.31)
p-value		0.2340

* Model includes Age, baseline eGFR (CKD-EPI) as linear covariate(s) and region, baseline diabetes status, sex, baseline LVEF, week reachable, Visit by Treatment by cause of heart failure interaction, baseline KCCQ self efficacy score by Visit interaction as fixed effect(s).
The Visit by Treatment by cause of heart failure p-value at Week 52 is 0.1576.
The following covariance structure has been used to fit the mixed model: Unstructured
Note: All covariate effects are set equal to their mean values within subgroup for the calculation of adjusted means.

For patients who died, only observed values are considered (no imputation after date of death).
Data taken from study 1245.121 only.
The MMRM includes all outcome values (change from baseline) at the planned Visits week 12, week 32 and week 52

R.1.3.9.12 Subgroup analysis by heart failure physiology (LVEF <= 30% and NTproBNP<median; LVEF <= 30% and NTproBNP>=median; LVEF > 30%)

Table R.1.3.9.12: 1 KCCQ self efficacy score change from baseline at week 52 (MMRM) by heart failure physiology - RS (OC-AD - no imputation for deaths) - 1245.121

Subgroup / Visit / Description / Statistic	Placebo	Empa 10mg
Heart failure physiology: LVEF <= 30% and NTproBNP < median		
Number of patients in analysis set	723	698
Number of analysed patients	694	672
Baseline mean (SE)	75.07 (0.89)	74.89 (0.90)
Week 52		
Values at visit		
Number of analysed patients	511	494
Mean (SE)	80.33 (0.92)	81.65 (0.90)
Adjusted* mean (SE)	80.73 (0.80)	82.06 (0.81)
95% confidence interval	(79.17,82.29)	(80.47,83.64)
Change from baseline		
Mean (SE)	5.77 (1.05)	7.49 (1.03)
Adjusted* mean (SE)	5.75 (0.80)	7.08 (0.81)
95% confidence interval	(4.19, 7.31)	(5.49, 8.66)
Comparison vs Placebo		
Adjusted* mean (SE)		1.33 (1.13)
95% confidence interval		(-0.89, 3.55)
p-value		0.2407

* Model includes Age, baseline eGFR (CKD-EPI) as linear covariate(s) and region, baseline diabetes status, sex, week reachable, Visit by Treatment by heart failure physiology interaction, baseline KCCQ self efficacy score by Visit interaction as fixed effect(s).
The Visit by Treatment by heart failure physiology p-value at Week 52 is 0.1088.
The following covariance structure has been used to fit the mixed model: Unstructured
16 patients were excluded as the subgroup variable was missing.
Note: All covariate effects are set equal to their mean values within subgroup for the calculation of adjusted means.
The p-value for the visit by treatment by subgroup interaction trend test at Week 52 is 0.0530

For patients who died, only observed values are considered (no imputation after date of death).
Data taken from study 1245.121 only.
NTproBNP median [pg/mL]: with a. fibrillation/flutter at baseline: 2265; without a. fibrillation/flutter at baseline: 1671.
The MMRM includes all outcome values (change from baseline) at the planned Visits week 12, week 32 and week 52

Table R.1.3.9.12: 1 KCCQ self efficacy score change from baseline at week 52 (MMRM) by heart failure physiology - RS (OC-AD - no imputation for deaths) - 1245.121

Subgroup / Visit / Description / Statistic	Placebo	Empa 10mg
Heart failure physiology: LVEF <= 30% and NTproBNP >= median		
Number of patients in analysis set	661	631
Number of analysed patients	602	593
Baseline mean (SE)	74.25 (0.96)	72.66 (1.01)
Week 52		
Values at visit		
Number of analysed patients	406	405
Mean (SE)	80.30 (1.04)	80.56 (1.06)
Adjusted* mean (SE)	79.69 (0.89)	80.41 (0.89)
95% confidence interval	(77.95,81.44)	(78.66,82.15)
Change from baseline		
Mean (SE)	4.93 (1.13)	7.50 (1.35)
Adjusted* mean (SE)	6.23 (0.89)	6.95 (0.89)
95% confidence interval	(4.49, 7.97)	(5.20, 8.69)
Comparison vs Placebo		
Adjusted* mean (SE)		0.71 (1.26)
95% confidence interval		(-1.75, 3.18)
p-value		0.5704

* Model includes Age, baseline eGFR (CKD-EPI) as linear covariate(s) and region, baseline diabetes status, sex, week reachable, Visit by Treatment by heart failure physiology interaction, baseline KCCQ self efficacy score by Visit interaction as fixed effect(s).
The Visit by Treatment by heart failure physiology p-value at Week 52 is 0.1088.
The following covariance structure has been used to fit the mixed model: Unstructured
16 patients were excluded as the subgroup variable was missing.
Note: All covariate effects are set equal to their mean values within subgroup for the calculation of adjusted means.
The p-value for the visit by treatment by subgroup interaction trend test at Week 52 is 0.0530

For patients who died, only observed values are considered (no imputation after date of death).
Data taken from study 1245.121 only.
NTproBNP median [pg/mL]: with a. fibrillation/flutter at baseline: 2265; without a. fibrillation/flutter at baseline: 1671.
The MMRM includes all outcome values (change from baseline) at the planned Visits week 12, week 32 and week 52

Table R.1.3.9.12: 1 KCCQ self efficacy score change from baseline at week 52 (MMRM) by heart failure physiology - RS (OC-AD - no imputation for deaths) - 1245.121

Subgroup / Visit / Description / Statistic	Placebo	Empa 10mg
Heart failure physiology: LVEF > 30%		
Number of patients in analysis set	475	526
Number of analysed patients	450	506
Baseline mean (SE)	74.56 (1.09)	74.16 (1.04)
Week 52		
Values at visit		
Number of analysed patients	293	339
Mean (SE)	81.36 (1.09)	78.87 (1.19)
Adjusted* mean (SE)	81.43 (1.04)	79.05 (0.97)
95% confidence interval	(79.39,83.47)	(77.15,80.95)
Change from baseline		
Mean (SE)	6.95 (1.25)	5.24 (1.32)
Adjusted* mean (SE)	7.08 (1.04)	4.71 (0.97)
95% confidence interval	(5.04, 9.13)	(2.81, 6.61)
Comparison vs Placebo		
Adjusted* mean (SE)		-2.38 (1.42)
95% confidence interval		(-5.16, 0.41)
p-value		0.0949

* Model includes Age, baseline eGFR (CKD-EPI) as linear covariate(s) and region, baseline diabetes status, sex, week reachable, Visit by Treatment by heart failure physiology interaction, baseline KCCQ self efficacy score by Visit interaction as fixed effect(s). The Visit by Treatment by heart failure physiology p-value at Week 52 is 0.1088.
The following covariance structure has been used to fit the mixed model: Unstructured
16 patients were excluded as the subgroup variable was missing.
Note: All covariate effects are set equal to their mean values within subgroup for the calculation of adjusted means.
The p-value for the visit by treatment by subgroup interaction trend test at Week 52 is 0.0530

For patients who died, only observed values are considered (no imputation after date of death).
Data taken from study 1245.121 only.
NTproBNP median [pg/mL]: with a. fibrillation/flutter at baseline: 2265; without a. fibrillation/flutter at baseline: 1671.
The MMRM includes all outcome values (change from baseline) at the planned Visits week 12, week 32 and week 52

R.1.3.9.13

Table R.1.3.9.13: 1 KCCQ self efficacy score change from baseline at week 52 (MMRM) by baseline use of MRA (Y/N) - RS (OC-AD - no imputation for deaths) - 1245.121

Subgroup / Visit / Description / Statistic	Placebo	Empa 10mg
Baseline use of MRA: No		
Number of patients in analysis set	512	557
Number of analysed patients	485	531
Baseline mean (SE)	75.93 (1.02)	74.03 (0.99)
Week 52		
Values at visit		
Number of analysed patients	339	383
Mean (SE)	79.28 (1.05)	80.45 (1.06)
Adjusted* mean (SE)	78.93 (0.98)	80.28 (0.92)
95% confidence interval	(77.01,80.84)	(78.47,82.09)
Change from baseline		
Mean (SE)	3.24 (1.31)	6.59 (1.16)
Adjusted* mean (SE)	3.99 (0.98)	5.34 (0.92)
95% confidence interval	(2.08, 5.90)	(3.53, 7.15)
Comparison vs Placebo		
Adjusted* mean (SE)		1.35 (1.34)
95% confidence interval		(-1.27, 3.97)
p-value		0.3125

* Model includes Age, baseline eGFR (CKD-EPI) as linear covariate(s) and region, baseline diabetes status, sex, baseline LVEF, week reachable, Visit by Treatment by baseline use of MRA interaction, baseline KCCQ self efficacy score by Visit interaction as fixed effect(s).
The Visit by Treatment by baseline use of MRA p-value at Week 52 is 0.2996.
The following covariance structure has been used to fit the mixed model: Unstructured
Note: All covariate effects are set equal to their mean values within subgroup for the calculation of adjusted means.

For patients who died, only observed values are considered (no imputation after date of death).
Data taken from study 1245.121 only.
The MMRM includes all outcome values (change from baseline) at the planned Visits week 12, week 32 and week 52

Table R.1.3.9.13: 1 KCCQ self efficacy score change from baseline at week 52 (MMRM) by baseline use of MRA (Y/N) - RS (OC-AD - no imputation for deaths) - 1245.121

Subgroup / Visit / Description / Statistic	Placebo	Empa 10mg
Baseline use of MRA: Yes		
Number of patients in analysis set	1355	1306
Number of analysed patients	1266	1245
Baseline mean (SE)	74.20 (0.67)	73.86 (0.69)
Week 52		
Values at visit		
Number of analysed patients	875	856
Mean (SE)	81.07 (0.70)	80.55 (0.72)
Adjusted* mean (SE)	81.13 (0.61)	80.83 (0.61)
95% confidence interval	(79.94,82.32)	(79.64,82.03)
Change from baseline		
Mean (SE)	6.71 (0.75)	6.99 (0.87)
Adjusted* mean (SE)	7.10 (0.61)	6.81 (0.61)
95% confidence interval	(5.91, 8.29)	(5.61, 8.00)
Comparison vs Placebo		
Adjusted* mean (SE)		-0.30 (0.86)
95% confidence interval		(-1.99, 1.39)
p-value		0.7283

* Model includes Age, baseline eGFR (CKD-EPI) as linear covariate(s) and region, baseline diabetes status, sex, baseline LVEF, week reachable, Visit by Treatment by baseline use of MRA interaction, baseline KCCQ self efficacy score by Visit interaction as fixed effect(s).
The Visit by Treatment by baseline use of MRA p-value at Week 52 is 0.2996.
The following covariance structure has been used to fit the mixed model: Unstructured
Note: All covariate effects are set equal to their mean values within subgroup for the calculation of adjusted means.

For patients who died, only observed values are considered (no imputation after date of death).
Data taken from study 1245.121 only.
The MMRM includes all outcome values (change from baseline) at the planned Visits week 12, week 32 and week 52

R.1.3.9.14

Table R.1.3.9.14: 1 KCCQ self efficacy score change from baseline at week 52 (MMRM) by baseline use of ARNi (Y/N) - RS (OC-AD - no imputation for deaths) - 1245.121

Subgroup / Visit / Description / Statistic	Placebo	Empa 10mg
Baseline use of ARNi: No		
Number of patients in analysis set	1480	1523
Number of analysed patients	1389	1447
Baseline mean (SE)	73.54 (0.63)	72.81 (0.62)
Week 52		
Values at visit		
Number of analysed patients	957	1026
Mean (SE)	80.15 (0.66)	80.13 (0.66)
Adjusted* mean (SE)	80.33 (0.58)	80.49 (0.56)
95% confidence interval	(79.19,81.46)	(79.39,81.59)
Change from baseline		
Mean (SE)	6.45 (0.75)	7.74 (0.77)
Adjusted* mean (SE)	7.16 (0.58)	7.32 (0.56)
95% confidence interval	(6.02, 8.30)	(6.22, 8.42)
Comparison vs Placebo		
Adjusted* mean (SE)		0.16 (0.80)
95% confidence interval		(-1.41, 1.74)
p-value		0.8386

* Model includes Age, baseline eGFR (CKD-EPI) as linear covariate(s) and region, baseline diabetes status, sex, baseline LVEF, week reachable, Visit by Treatment by baseline use of ARNi interaction, baseline KCCQ self efficacy score by Visit interaction as fixed effect(s).
The Visit by Treatment by baseline use of ARNi p-value at Week 52 is 0.8842.
The following covariance structure has been used to fit the mixed model: Unstructured
Note: All covariate effects are set equal to their mean values within subgroup for the calculation of adjusted means.

For patients who died, only observed values are considered (no imputation after date of death).
Data taken from study 1245.121 only.
The MMRM includes all outcome values (change from baseline) at the planned Visits week 12, week 32 and week 52

Table R.1.3.9.14: 1 KCCQ self efficacy score change from baseline at week 52 (MMRM) by baseline use of ARNi (Y/N) - RS (OC-AD - no imputation for deaths) - 1245.121

Subgroup / Visit / Description / Statistic	Placebo	Empa 10mg
Baseline use of ARNi: Yes		
Number of patients in analysis set	387	340
Number of analysed patients	362	329
Baseline mean (SE)	79.04 (1.16)	78.76 (1.30)
Week 52		
Values at visit		
Number of analysed patients	257	213
Mean (SE)	82.15 (1.22)	82.39 (1.41)
Adjusted* mean (SE)	81.33 (1.12)	81.22 (1.23)
95% confidence interval	(79.12,83.53)	(78.82,83.63)
Change from baseline		
Mean (SE)	3.11 (1.34)	2.70 (1.71)
Adjusted* mean (SE)	2.42 (1.12)	2.31 (1.23)
95% confidence interval	(0.21, 4.62)	(-0.09, 4.72)
Comparison vs Placebo		
Adjusted* mean (SE)		-0.10 (1.66)
95% confidence interval		(-3.35, 3.14)
p-value		0.9498

* Model includes Age, baseline eGFR (CKD-EPI) as linear covariate(s) and region, baseline diabetes status, sex, baseline LVEF, week reachable, Visit by Treatment by baseline use of ARNi interaction, baseline KCCQ self efficacy score by Visit interaction as fixed effect(s).
The Visit by Treatment by baseline use of ARNi p-value at Week 52 is 0.8842.
The following covariance structure has been used to fit the mixed model: Unstructured
Note: All covariate effects are set equal to their mean values within subgroup for the calculation of adjusted means.

For patients who died, only observed values are considered (no imputation after date of death).
Data taken from study 1245.121 only.
The MMRM includes all outcome values (change from baseline) at the planned Visits week 12, week 32 and week 52

R.1.3.9.15

R.1.3.9.15 Subgroup analysis by bl. LVEF (<= 30%, >30% -<= 35% , > 35%)

Table R.1.3.9.15: 1 KCCQ self efficacy score change from baseline at week 52 (MMRM) by baseline LVEF (3 cat.) - RS (OC-AD - no imputation for deaths) - 1245.121

Subgroup / Visit / Description / Statistic	Placebo	Empa 10mg
Baseline LVEF (3 cat.): <=30		
Number of patients in analysis set	1392	1337
Number of analysed patients	1301	1270
Baseline mean (SE)	74.72 (0.65)	73.81 (0.67)
Week 52		
Values at visit		
Number of analysed patients	921	900
Mean (SE)	80.32 (0.69)	81.14 (0.69)
Adjusted* mean (SE)	80.22 (0.59)	81.29 (0.60)
95% confidence interval	(79.07,81.38)	(80.12,82.46)
Change from baseline		
Mean (SE)	5.36 (0.77)	7.49 (0.83)
Adjusted* mean (SE)	5.95 (0.59)	7.02 (0.60)
95% confidence interval	(4.79, 7.11)	(5.85, 8.19)
Comparison vs Placebo		
Adjusted* mean (SE)		1.07 (0.84)
95% confidence interval		(-0.58, 2.71)
p-value		0.2040

* Model includes Age, baseline eGFR (CKD-EPI) as linear covariate(s) and region, baseline diabetes status, sex, week reachable, Visit by Treatment by baseline LVEF (3 cat.) interaction, baseline KCCQ self efficacy score by Visit interaction as fixed effect(s).
The Visit by Treatment by baseline LVEF (3 cat.) p-value at Week 52 is 0.0674.
The following covariance structure has been used to fit the mixed model: Unstructured
Note: All covariate effects are set equal to their mean values within subgroup for the calculation of adjusted means.
The p-value for the visit by treatment by subgroup interaction trend test at Week 52 is 0.1174

For patients who died, only observed values are considered (no imputation after date of death).
Data taken from study 1245.121 only.
The MMRM includes all outcome values (change from baseline) at the planned Visits week 12, week 32 and week 52

Table R.1.3.9.15: 1 KCCQ self efficacy score change from baseline at week 52 (MMRM) by baseline LVEF (3 cat.) - RS (OC-AD - no imputation for deaths) - 1245.121

Subgroup / Visit / Description / Statistic	Placebo	Empa 10mg
Baseline LVEF (3 cat.): >30 to <=35		
Number of patients in analysis set	361	398
Number of analysed patients	342	385
Baseline mean (SE)	75.55 (1.24)	75.36 (1.17)
Week 52		
Values at visit		
Number of analysed patients	232	256
Mean (SE)	81.68 (1.17)	78.66 (1.36)
Adjusted* mean (SE)	81.88 (1.17)	78.72 (1.11)
95% confidence interval	(79.58,84.18)	(76.53,80.90)
Change from baseline		
Mean (SE)	6.90 (1.44)	3.13 (1.43)
Adjusted* mean (SE)	6.43 (1.17)	3.27 (1.11)
95% confidence interval	(4.13, 8.73)	(1.09, 5.45)
Comparison vs Placebo		
Adjusted* mean (SE)		-3.16 (1.62)
95% confidence interval		(-6.33, 0.00)
p-value		0.0503

* Model includes Age, baseline eGFR (CKD-EPI) as linear covariate(s) and region, baseline diabetes status, sex, week reachable, Visit by Treatment by baseline LVEF (3 cat.) interaction, baseline KCCQ self efficacy score by Visit interaction as fixed effect(s).
The Visit by Treatment by baseline LVEF (3 cat.) p-value at Week 52 is 0.0674.
The following covariance structure has been used to fit the mixed model: Unstructured
Note: All covariate effects are set equal to their mean values within subgroup for the calculation of adjusted means.
The p-value for the visit by treatment by subgroup interaction trend test at Week 52 is 0.1174

For patients who died, only observed values are considered (no imputation after date of death).
Data taken from study 1245.121 only.
The MMRM includes all outcome values (change from baseline) at the planned Visits week 12, week 32 and week 52

Table R.1.3.9.15: 1 KCCQ self efficacy score change from baseline at week 52 (MMRM) by baseline LVEF (3 cat.) - RS (OC-AD - no imputation for deaths) - 1245.121

Subgroup / Visit / Description / Statistic	Placebo	Empa 10mg
Baseline LVEF (3 cat.): >35		
Number of patients in analysis set	114	128
Number of analysed patients	108	121
Baseline mean (SE)	71.41 (2.25)	70.35 (2.23)
Week 52		
Values at visit		
Number of analysed patients	61	83
Mean (SE)	80.12 (2.79)	79.52 (2.46)
Adjusted* mean (SE)	80.05 (2.26)	80.12 (1.96)
95% confidence interval	(75.61,84.48)	(76.27,83.97)
Change from baseline		
Mean (SE)	7.17 (2.56)	11.75 (3.01)
Adjusted* mean (SE)	9.19 (2.26)	9.27 (1.96)
95% confidence interval	(4.76,13.63)	(5.42,13.12)
Comparison vs Placebo		
Adjusted* mean (SE)		0.08 (2.99)
95% confidence interval		(-5.79, 5.95)
p-value		0.9796

* Model includes Age, baseline eGFR (CKD-EPI) as linear covariate(s) and region, baseline diabetes status, sex, week reachable, Visit by Treatment by baseline LVEF (3 cat.) interaction, baseline KCCQ self efficacy score by Visit interaction as fixed effect(s).
The Visit by Treatment by baseline LVEF (3 cat.) p-value at Week 52 is 0.0674.
The following covariance structure has been used to fit the mixed model: Unstructured
Note: All covariate effects are set equal to their mean values within subgroup for the calculation of adjusted means.
The p-value for the visit by treatment by subgroup interaction trend test at Week 52 is 0.1174

For patients who died, only observed values are considered (no imputation after date of death).
Data taken from study 1245.121 only.
The MMRM includes all outcome values (change from baseline) at the planned Visits week 12, week 32 and week 52

R.1.3.9.16 Subgroup analysis by bl. NTproBNP </>= median (median based on total patients)

Table R.1.3.9.16: 1 KCCQ self efficacy score change from baseline at week 52 (MMRM) by bl. NTproBNP (<median, >= median) (median based on total patients) - RS (OC-AD - no imputation for deaths) - 1245.121

Subgroup / Visit / Description / Statistic	Placebo	Empa 10mg
Baseline NTproBNP (<median, >= median): < median		
Number of patients in analysis set	920	942
Number of analysed patients	884	908
Baseline mean (SE)	75.58 (0.77)	75.08 (0.77)
Week 52		
Values at visit		
Number of analysed patients	650	666
Mean (SE)	80.90 (0.80)	81.31 (0.80)
Adjusted* mean (SE)	81.11 (0.71)	81.68 (0.70)
95% confidence interval	(79.73,82.50)	(80.31,83.04)
Change from baseline		
Mean (SE)	5.85 (0.90)	6.89 (0.92)
Adjusted* mean (SE)	5.79 (0.71)	6.35 (0.70)
95% confidence interval	(4.40, 7.17)	(4.98, 7.72)
Comparison vs Placebo		
Adjusted* mean (SE)		0.56 (0.99)
95% confidence interval		(-1.38, 2.51)
p-value		0.5699

* Model includes Age, baseline eGFR (CKD-EPI) as linear covariate(s) and region, baseline diabetes status, sex, baseline LVEF, week reachable, Visit by Treatment by baseline NTproBNP (<median, >= median) interaction, baseline KCCQ self efficacy score by Visit interaction as fixed effect(s). The Visit by Treatment by baseline NTproBNP (<median, >= median) p-value at Week 52 is 0.5579.
The following covariance structure has been used to fit the mixed model: Unstructured
2 patients were excluded as the subgroup variable was missing.
Note: All covariate effects are set equal to their mean values within subgroup for the calculation of adjusted means.

For patients who died, only observed values are considered (no imputation after date of death).
Data taken from study 1245.121 only.
Median: 1910 [pg/mL]
The MMRM includes all outcome values (change from baseline) at the planned Visits week 12, week 32 and week 52

Table R.1.3.9.16: 1 KCCQ self efficacy score change from baseline at week 52 (MMRM) by bl. NTproBNP (<median, >= median) (median based on total patients) - RS (OC-AD - no imputation for deaths) - 1245.121

Subgroup / Visit / Description / Statistic	Placebo	Empa 10mg
Baseline NTproBNP (<median, >= median): >= median		
Number of patients in analysis set	946	920
Number of analysed patients	867	868
Baseline mean (SE)	73.76 (0.80)	72.68 (0.82)
Week 52		
Values at visit		
Number of analysed patients	564	573
Mean (SE)	80.19 (0.86)	79.60 (0.90)
Adjusted* mean (SE)	79.89 (0.75)	79.61 (0.75)
95% confidence interval	(78.42,81.37)	(78.14,81.07)
Change from baseline		
Mean (SE)	5.63 (0.96)	6.85 (1.08)
Adjusted* mean (SE)	6.67 (0.75)	6.39 (0.75)
95% confidence interval	(5.20, 8.15)	(4.92, 7.85)
Comparison vs Placebo		
Adjusted* mean (SE)		-0.29 (1.06)
95% confidence interval		(-2.36, 1.79)
p-value		0.7868

* Model includes Age, baseline eGFR (CKD-EPI) as linear covariate(s) and region, baseline diabetes status, sex, baseline LVEF, week reachable, Visit by Treatment by baseline NTproBNP (<median, >= median) interaction, baseline KCCQ self efficacy score by Visit interaction as fixed effect(s). The Visit by Treatment by baseline NTproBNP (<median, >= median) p-value at Week 52 is 0.5579.
The following covariance structure has been used to fit the mixed model: Unstructured
2 patients were excluded as the subgroup variable was missing.
Note: All covariate effects are set equal to their mean values within subgroup for the calculation of adjusted means.

For patients who died, only observed values are considered (no imputation after date of death).
Data taken from study 1245.121 only.
Median: 1910 [pg/mL]
The MMRM includes all outcome values (change from baseline) at the planned Visits week 12, week 32 and week 52

R.1.3.10

R.1.3.10 KCCQ quality of life score MMRM analysis

R.1.3.10.1

Table R.1.3.10.1: 1 KCCQ quality of life score change from baseline MMRM results over time - RS (OC-AD - no imputation for deaths) - 1245.121

Visit Description Statistic	Placebo	Empa 10mg
Number of patients in analysis set	1867	1863
Number of analysed patients	1753	1776
Baseline mean (SE)	61.55 (0.57)	62.25 (0.59)
Week 12		
Values at visit		
Number of analysed patients	1731	1755
Mean (SE)	66.51 (0.54)	68.85 (0.55)
Adjusted* mean (SE)	66.81 (0.43)	68.70 (0.43)
95% confidence interval	(65.97,67.66)	(67.86,69.54)
Change from baseline		
Mean (SE)	4.91 (0.50)	6.53 (0.50)
Adjusted* mean (SE)	4.55 (0.43)	6.43 (0.43)
95% confidence interval	(3.70, 5.39)	(5.59, 7.27)
Comparison vs Placebo		
Adjusted* mean (SE)		1.88 (0.61)
95% confidence interval		(0.69, 3.08)
p-value		0.0020
Hedges g		
Estimate		0.10
95% confidence interval		(0.04, 0.17)

* Model includes Age (p=0.0197), baseline eGFR (CKD-EPI) (p=0.0101) as linear covariate(s) and region (p<0.0001), baseline diabetes status (p=0.5549), sex (p=0.2850), baseline LVEF (p=0.7624), week reachable (p=0.1380), Treatment by Visit interaction (p<0.0001), baseline KCCQ quality of life score by Visit interaction (p<0.0001) as fixed effect(s).
The following covariance structure has been used to fit the mixed model: Unstructured

For patients who died, only observed values are considered (no imputation after date of death).
Data taken from study 1245.121 only.

Table R.1.3.10.1: 1 KCCQ quality of life score change from baseline MMRM results over time - RS (OC-AD - no imputation for deaths) - 1245.121

Visit Description Statistic	Placebo	Empa 10mg
Week 32		
Values at visit		
Number of analysed patients	1568	1618
Mean (SE)	68.29 (0.58)	70.13 (0.57)
Adjusted* mean (SE)	68.21 (0.48)	69.64 (0.47)
95% confidence interval	(67.27,69.15)	(68.71,70.56)
Change from baseline		
Mean (SE)	6.36 (0.58)	7.40 (0.54)
Adjusted* mean (SE)	5.94 (0.48)	7.37 (0.47)
95% confidence interval	(5.00, 6.88)	(6.44, 8.29)
Comparison vs Placebo		
Adjusted* mean (SE)		1.43 (0.67)
95% confidence interval		(0.11, 2.75)
p-value		0.0342
Hedges g		
Estimate		0.07
95% confidence interval		(0.01, 0.14)
Week 52		
Values at visit		
Number of analysed patients	1218	1239
Mean (SE)	69.47 (0.65)	71.28 (0.64)
Adjusted* mean (SE)	69.38 (0.53)	70.57 (0.52)
95% confidence interval	(68.35,70.42)	(69.54,71.60)
Change from baseline		
Mean (SE)	7.32 (0.66)	8.22 (0.63)
Adjusted* mean (SE)	7.12 (0.53)	8.30 (0.52)
95% confidence interval	(6.08, 8.15)	(7.27, 9.33)
Comparison vs Placebo		
Adjusted* mean (SE)		1.19 (0.74)
95% confidence interval		(-0.27, 2.64)
p-value		0.1108

* Model includes Age (p=0.0197), baseline eGFR (CKD-EPI) (p=0.0101) as linear covariate(s) and region (p<0.0001), baseline diabetes status (p=0.5549), sex (p=0.2850), baseline LVEF (p=0.7624), week reachable (p=0.1380), Treatment by Visit interaction (p<0.0001), baseline KCCQ quality of life score by Visit interaction (p<0.0001) as fixed effect(s).
The following covariance structure has been used to fit the mixed model: Unstructured

For patients who died, only observed values are considered (no imputation after date of death).
Data taken from study 1245.121 only.

Figure R.1.3.10.1: 1

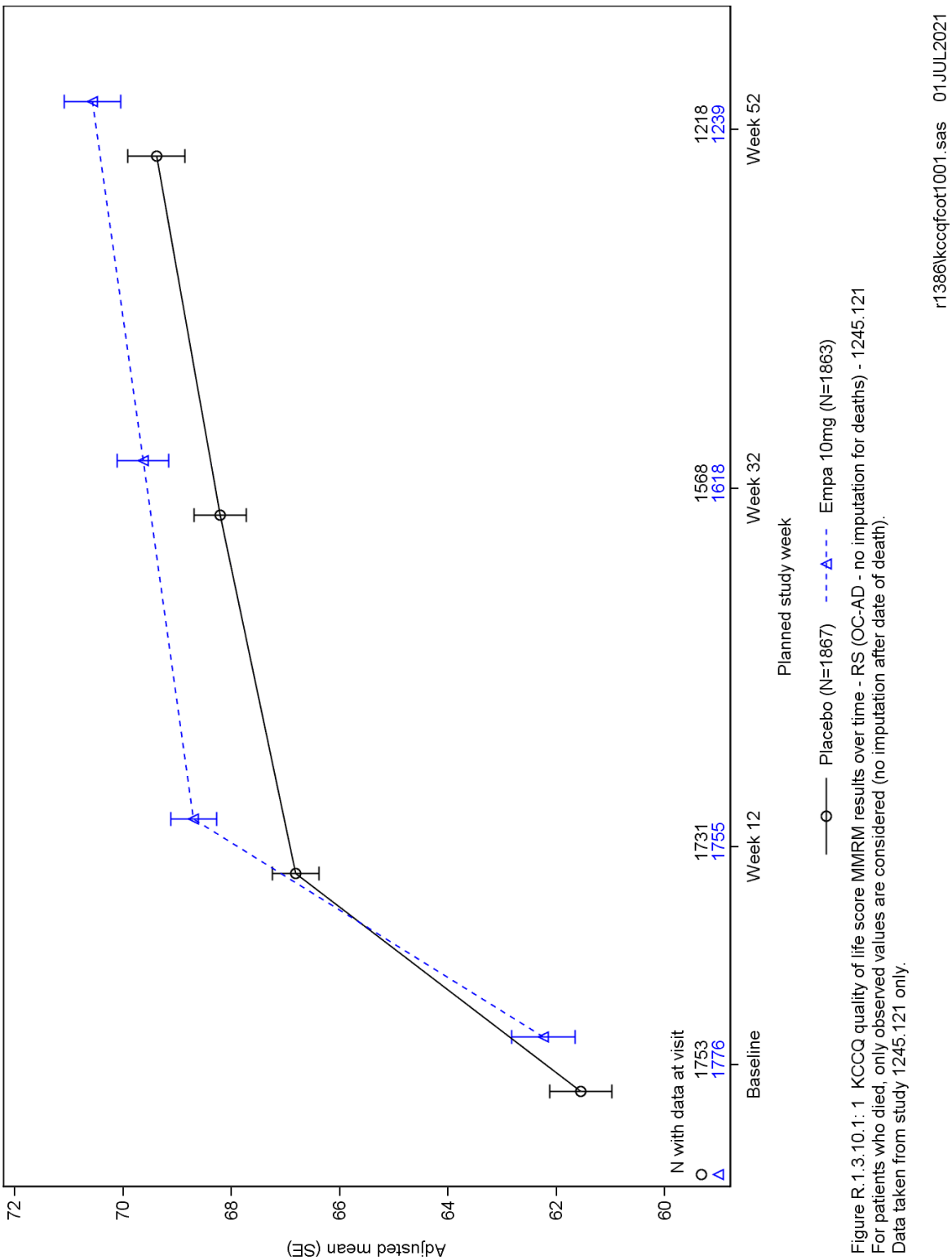

Figure R.1.3.10.1: 1 KCCQ quality of life score MMRM results over time - RS (OC-AD - no imputation for deaths) - 1245.121
For patients who died, only observed values are considered (no imputation after date of death).
Data taken from study 1245.121 only.

R.1.3.10.2

Table R.1.3.10.2: 1 KCCQ quality of life score change from baseline at week 52 (MMRM) by sex - RS (OC-AD - no imputation for deaths) - 1245.121

Subgroup / Visit / Description / Statistic	Placebo	Empa 10mg
Sex: Male		
Number of patients in analysis set	1411	1426
Number of analysed patients	1333	1361
Baseline mean (SE)	63.26 (0.65)	64.21 (0.66)
Week 52		
Values at visit		
Number of analysed patients	939	954
Mean (SE)	70.14 (0.75)	72.66 (0.70)
Adjusted* mean (SE)	70.10 (0.60)	71.59 (0.60)
95% confidence interval	(68.92,71.28)	(70.42,72.76)
Change from baseline		
Mean (SE)	6.20 (0.76)	7.33 (0.71)
Adjusted* mean (SE)	6.36 (0.60)	7.85 (0.60)
95% confidence interval	(5.18, 7.55)	(6.68, 9.02)
Comparison vs Placebo		
Adjusted* mean (SE)		1.49 (0.85)
95% confidence interval		(-0.18, 3.15)
p-value		0.0795

* Model includes Age, baseline eGFR (CKD-EPI) as linear covariate(s) and region, baseline diabetes status, baseline LVEF, week reachable, Visit by Treatment by sex interaction, baseline KCCQ quality of life score by Visit interaction as fixed effect(s).
The Visit by Treatment by sex p-value at Week 52 is 0.4715.
The following covariance structure has been used to fit the mixed model: Unstructured
Note: All covariate effects are set equal to their mean values within subgroup for the calculation of adjusted means.

For patients who died, only observed values are considered (no imputation after date of death).
Data taken from study 1245.121 only.
The MMRM includes all outcome values (change from baseline) at the planned Visits week 12, week 32 and week 52

Table R.1.3.10.2: 1 KCCQ quality of life score change from baseline at week 52 (MMRM) by sex - RS (OC-AD - no imputation for deaths) - 1245.121

Subgroup / Visit / Description / Statistic	Placebo	Empa 10mg
Sex: Female		
Number of patients in analysis set	456	437
Number of analysed patients	420	415
Baseline mean (SE)	56.15 (1.16)	55.82 (1.22)
Week 52		
Values at visit		
Number of analysed patients	279	285
Mean (SE)	67.20 (1.33)	66.67 (1.44)
Adjusted* mean (SE)	66.27 (1.10)	66.48 (1.09)
95% confidence interval	(64.11,68.43)	(64.35,68.62)
Change from baseline		
Mean (SE)	11.11 (1.35)	11.17 (1.40)
Adjusted* mean (SE)	10.28 (1.10)	10.50 (1.09)
95% confidence interval	(8.12,12.44)	(8.36,12.63)
Comparison vs Placebo		
Adjusted* mean (SE)		0.22 (1.55)
95% confidence interval		(-2.82, 3.25)
p-value		0.8886

* Model includes Age, baseline eGFR (CKD-EPI) as linear covariate(s) and region, baseline diabetes status, baseline LVEF, week reachable, Visit by Treatment by sex interaction, baseline KCCQ quality of life score by Visit interaction as fixed effect(s).
The Visit by Treatment by sex p-value at Week 52 is 0.4715.
The following covariance structure has been used to fit the mixed model: Unstructured
Note: All covariate effects are set equal to their mean values within subgroup for the calculation of adjusted means.

For patients who died, only observed values are considered (no imputation after date of death).
Data taken from study 1245.121 only.
The MMRM includes all outcome values (change from baseline) at the planned Visits week 12, week 32 and week 52

R.1.3.10.3

Table R.1.3.10.3: 1 KCCQ quality of life score change from baseline at week 52 (MMRM) by age (2 cat.) - RS (OC-AD - no imputation for deaths) - 1245.121

Subgroup / Visit / Description / Statistic	Placebo	Empa 10mg
Age [years] (2 cat.): < 65		
Number of patients in analysis set	740	675
Number of analysed patients	697	645
Baseline mean (SE)	58.02 (0.92)	58.40 (1.01)
Week 52		
Values at visit		
Number of analysed patients	494	454
Mean (SE)	67.19 (1.06)	69.75 (1.13)
Adjusted* mean (SE)	66.47 (0.83)	69.15 (0.87)
95% confidence interval	(64.84,68.11)	(67.45,70.84)
Change from baseline		
Mean (SE)	8.42 (1.06)	11.33 (1.06)
Adjusted* mean (SE)	8.27 (0.83)	10.94 (0.87)
95% confidence interval	(6.63, 9.91)	(9.24,12.64)
Comparison vs Placebo		
Adjusted* mean (SE)		2.67 (1.20)
95% confidence interval		(0.32, 5.02)
p-value		0.0258

* Model includes baseline eGFR (CKD-EPI) as linear covariate(s) and region, baseline diabetes status, sex, baseline LVEF, week reachable, Visit by Treatment by age [years] (2 cat.) interaction, baseline KCCQ quality of life score by Visit interaction as fixed effect(s).
The Visit by Treatment by age [years] (2 cat.) p-value at Week 52 is 0.1224.
The following covariance structure has been used to fit the mixed model: Unstructured
Note: All covariate effects are set equal to their mean values within subgroup for the calculation of adjusted means.

For patients who died, only observed values are considered (no imputation after date of death).
Data taken from study 1245.121 only.
The MMRM includes all outcome values (change from baseline) at the planned Visits week 12, week 32 and week 52

Table R.1.3.10.3: 1 KCCQ quality of life score change from baseline at week 52 (MMRM) by age (2 cat.) - RS (OC-AD - no imputation for deaths) - 1245.121

Subgroup / Visit / Description / Statistic	Placebo	Empa 10mg
Age [years] (2 cat.): >= 65		
Number of patients in analysis set	1127	1188
Number of analysed patients	1056	1131
Baseline mean (SE)	63.88 (0.73)	64.44 (0.71)
Week 52		
Values at visit		
Number of analysed patients	724	785
Mean (SE)	71.02 (0.82)	72.17 (0.76)
Adjusted* mean (SE)	70.86 (0.69)	71.17 (0.66)
95% confidence interval	(69.52,72.21)	(69.88,72.47)
Change from baseline		
Mean (SE)	6.58 (0.84)	6.42 (0.79)
Adjusted* mean (SE)	6.69 (0.69)	7.00 (0.66)
95% confidence interval	(5.35, 8.04)	(5.71, 8.29)
Comparison vs Placebo		
Adjusted* mean (SE)		0.31 (0.95)
95% confidence interval		(-1.55, 2.17)
p-value		0.7432

* Model includes baseline eGFR (CKD-EPI) as linear covariate(s) and region, baseline diabetes status, sex, baseline LVEF, week reachable, Visit by Treatment by age [years] (2 cat.) interaction, baseline KCCQ quality of life score by Visit interaction as fixed effect(s).
The Visit by Treatment by age [years] (2 cat.) p-value at Week 52 is 0.1224.
The following covariance structure has been used to fit the mixed model: Unstructured
Note: All covariate effects are set equal to their mean values within subgroup for the calculation of adjusted means.

For patients who died, only observed values are considered (no imputation after date of death).
Data taken from study 1245.121 only.
The MMRM includes all outcome values (change from baseline) at the planned Visits week 12, week 32 and week 52

R.1.3.10.4

R.1.3.10.4 Subgroup analysis by region (North America, Latin America, Europe, Asia, Other)

Table R.1.3.10.4: 1 KCCQ quality of life score change from baseline at week 52 (MMRM) by region - RS (OC-AD - no imputation for deaths) - 1245.121

Subgroup / Visit / Description / Statistic	Placebo	Empa 10mg
Region (5 cat.): North America		
Number of patients in analysis set	213	212
Number of analysed patients	195	206
Baseline mean (SE)	62.78 (1.87)	66.02 (1.88)
Week 52		
Values at visit		
Number of analysed patients	129	151
Mean (SE)	70.54 (2.26)	73.21 (1.90)
Adjusted* mean (SE)	70.98 (1.61)	71.11 (1.51)
95% confidence interval	(67.82,74.14)	(68.16,74.06)
Change from baseline		
Mean (SE)	7.30 (1.99)	6.04 (1.69)
Adjusted* mean (SE)	6.53 (1.61)	6.67 (1.51)
95% confidence interval	(3.37, 9.70)	(3.72, 9.62)
Comparison vs Placebo		
Adjusted* mean (SE)		0.13 (2.21)
95% confidence interval		(-4.19, 4.46)
p-value		0.9519

* Model includes Age, baseline eGFR (CKD-EPI) as linear covariate(s) and baseline diabetes status, sex, baseline LVEF, week reachable, Visit by Treatment by region (5 cat.) interaction, baseline KCCQ quality of life score by Visit interaction as fixed effect(s).
The Visit by Treatment by region (5 cat.) p-value at Week 52 is 0.8799.
The following covariance structure has been used to fit the mixed model: Unstructured
Note: All covariate effects are set equal to their mean values within subgroup for the calculation of adjusted means.

For patients who died, only observed values are considered (no imputation after date of death).
Data taken from study 1245.121 only.
The MMRM includes all outcome values (change from baseline) at the planned Visits week 12, week 32 and week 52

Table R.1.3.10.4: 1 KCCQ quality of life score change from baseline at week 52 (MMRM) by region - RS (OC-AD - no imputation for deaths) - 1245.121

Subgroup / Visit / Description / Statistic	Placebo	Empa 10mg
Region (5 cat.): Latin America		
Number of patients in analysis set	645	641
Number of analysed patients	599	602
Baseline mean (SE)	56.69 (1.01)	56.76 (1.04)
Week 52		
Values at visit		
Number of analysed patients	391	374
Mean (SE)	68.56 (1.20)	70.79 (1.20)
Adjusted* mean (SE)	68.80 (0.93)	70.19 (0.94)
95% confidence interval	(66.98,70.62)	(68.35,72.04)
Change from baseline		
Mean (SE)	12.92 (1.30)	13.55 (1.25)
Adjusted* mean (SE)	12.08 (0.93)	13.47 (0.94)
95% confidence interval	(10.26,13.89)	(11.63,15.32)
Comparison vs Placebo		
Adjusted* mean (SE)		1.40 (1.32)
95% confidence interval		(-1.19, 3.98)
p-value		0.2900

* Model includes Age, baseline eGFR (CKD-EPI) as linear covariate(s) and baseline diabetes status, sex, baseline LVEF, week reachable, Visit by Treatment by region (5 cat.) interaction, baseline KCCQ quality of life score by Visit interaction as fixed effect(s).
The Visit by Treatment by region (5 cat.) p-value at Week 52 is 0.8799.
The following covariance structure has been used to fit the mixed model: Unstructured
Note: All covariate effects are set equal to their mean values within subgroup for the calculation of adjusted means.

For patients who died, only observed values are considered (no imputation after date of death).
Data taken from study 1245.121 only.
The MMRM includes all outcome values (change from baseline) at the planned Visits week 12, week 32 and week 52

Table R.1.3.10.4: 1 KCCQ quality of life score change from baseline at week 52 (MMRM) by region - RS (OC-AD - no imputation for deaths) - 1245.121

Subgroup / Visit / Description / Statistic	Placebo	Empa 10mg
Region (5 cat.): Europe		
Number of patients in analysis set	677	676
Number of analysed patients	644	649
Baseline mean (SE)	63.67 (0.93)	65.05 (0.95)
Week 52		
Values at visit		
Number of analysed patients	468	469
Mean (SE)	68.44 (1.03)	70.33 (1.02)
Adjusted* mean (SE)	67.85 (0.85)	69.48 (0.85)
95% confidence interval	(66.17,69.52)	(67.81,71.15)
Change from baseline		
Mean (SE)	3.43 (0.97)	4.90 (1.00)
Adjusted* mean (SE)	3.48 (0.85)	5.12 (0.85)
95% confidence interval	(1.81, 5.16)	(3.45, 6.79)
Comparison vs Placebo		
Adjusted* mean (SE)		1.64 (1.21)
95% confidence interval		(-0.73, 4.00)
p-value		0.1748

* Model includes Age, baseline eGFR (CKD-EPI) as linear covariate(s) and baseline diabetes status, sex, baseline LVEF, week reachable, Visit by Treatment by region (5 cat.) interaction, baseline KCCQ quality of life score by Visit interaction as fixed effect(s).
The Visit by Treatment by region (5 cat.) p-value at Week 52 is 0.8799.
The following covariance structure has been used to fit the mixed model: Unstructured
Note: All covariate effects are set equal to their mean values within subgroup for the calculation of adjusted means.

For patients who died, only observed values are considered (no imputation after date of death).
Data taken from study 1245.121 only.
The MMRM includes all outcome values (change from baseline) at the planned Visits week 12, week 32 and week 52

Table R.1.3.10.4: 1 KCCQ quality of life score change from baseline at week 52 (MMRM) by region - RS (OC-AD - no imputation for deaths) - 1245.121

Subgroup / Visit / Description / Statistic	Placebo	Empa 10mg
Region (5 cat.): Asia		
Number of patients in analysis set	245	248
Number of analysed patients	237	243
Baseline mean (SE)	65.33 (1.37)	63.82 (1.38)
Week 52		
Values at visit		
Number of analysed patients	180	189
Mean (SE)	69.58 (1.52)	70.41 (1.59)
Adjusted* mean (SE)	68.99 (1.39)	70.27 (1.35)
95% confidence interval	(66.27,71.71)	(67.62,72.92)
Change from baseline		
Mean (SE)	3.33 (1.53)	6.26 (1.47)
Adjusted* mean (SE)	4.43 (1.39)	5.70 (1.35)
95% confidence interval	(1.71, 7.14)	(3.05, 8.35)
Comparison vs Placebo		
Adjusted* mean (SE)		1.28 (1.93)
95% confidence interval		(-2.51, 5.07)
p-value		0.5090

* Model includes Age, baseline eGFR (CKD-EPI) as linear covariate(s) and baseline diabetes status, sex, baseline LVEF, week reachable, Visit by Treatment by region (5 cat.) interaction, baseline KCCQ quality of life score by Visit interaction as fixed effect(s).
The Visit by Treatment by region (5 cat.) p-value at Week 52 is 0.8799.
The following covariance structure has been used to fit the mixed model: Unstructured
Note: All covariate effects are set equal to their mean values within subgroup for the calculation of adjusted means.

For patients who died, only observed values are considered (no imputation after date of death).
Data taken from study 1245.121 only.
The MMRM includes all outcome values (change from baseline) at the planned Visits week 12, week 32 and week 52

Table R.1.3.10.4: 1 KCCQ quality of life score change from baseline at week 52 (MMRM) by region - RS (OC-AD - no imputation for deaths) - 1245.121

Subgroup / Visit / Description / Statistic	Placebo	Empa 10mg
Region (5 cat.): Other		
Number of patients in analysis set	87	86
Number of analysed patients	78	76
Baseline mean (SE)	66.88 (2.29)	66.56 (2.34)
Week 52		
Values at visit		
Number of analysed patients	50	56
Mean (SE)	83.00 (2.25)	80.36 (1.97)
Adjusted* mean (SE)	81.89 (2.59)	79.89 (2.47)
95% confidence interval	(76.81,86.96)	(75.04,84.73)
Change from baseline		
Mean (SE)	14.50 (2.74)	12.80 (2.59)
Adjusted* mean (SE)	15.17 (2.59)	13.17 (2.47)
95% confidence interval	(10.09,20.24)	(8.32,18.01)
Comparison vs Placebo		
Adjusted* mean (SE)		-2.00 (3.58)
95% confidence interval		(-9.01, 5.01)
p-value		0.5758

* Model includes Age, baseline eGFR (CKD-EPI) as linear covariate(s) and baseline diabetes status, sex, baseline LVEF, week reachable, Visit by Treatment by region (5 cat.) interaction, baseline KCCQ quality of life score by Visit interaction as fixed effect(s).
The Visit by Treatment by region (5 cat.) p-value at Week 52 is 0.8799.
The following covariance structure has been used to fit the mixed model: Unstructured
Note: All covariate effects are set equal to their mean values within subgroup for the calculation of adjusted means.

For patients who died, only observed values are considered (no imputation after date of death).
Data taken from study 1245.121 only.
The MMRM includes all outcome values (change from baseline) at the planned Visits week 12, week 32 and week 52

R.1.3.10.5

R.1.3.10.5 Subgroup analysis by OECD (N/Y)

Table R.1.3.10.5: 1 KCCQ quality of life score change from baseline at week 52 (MMRM) by OECD member (N/Y) - RS (OC-AD - no imputation for deaths) - 1245.121

Subgroup / Visit / Description / Statistic	Placebo	Empa 10mg
OECD member: No		
Number of patients in analysis set	741	713
Number of analysed patients	686	664
Baseline mean (SE)	56.66 (0.92)	57.62 (0.97)
Week 52		
Values at visit		
Number of analysed patients	443	421
Mean (SE)	69.13 (1.11)	71.22 (1.07)
Adjusted* mean (SE)	69.44 (0.87)	70.41 (0.89)
95% confidence interval	(67.73,71.15)	(68.66,72.16)
Change from baseline		
Mean (SE)	13.17 (1.16)	13.18 (1.12)
Adjusted* mean (SE)	12.31 (0.87)	13.28 (0.89)
95% confidence interval	(10.60,14.02)	(11.53,15.03)
Comparison vs Placebo		
Adjusted* mean (SE)		0.97 (1.25)
95% confidence interval		(-1.48, 3.42)
p-value		0.4371

* Model includes Age, baseline eGFR (CKD-EPI) as linear covariate(s) and baseline diabetes status, sex, baseline LVEF, week reachable, Visit by Treatment by OECD Member (N) interaction, baseline KCCQ quality of life score by Visit interaction as fixed effect(s).
The Visit by Treatment by OECD Member (N) p-value at Week 52 is 0.7617.
The following covariance structure has been used to fit the mixed model: Unstructured
Note: All covariate effects are set equal to their mean values within subgroup for the calculation of adjusted means.

For patients who died, only observed values are considered (no imputation after date of death).
Data taken from study 1245.121 only.
OECD member (yes/no) countries included:
Yes: United States, Canada, Mexico, Poland, Netherlands, Hungary, Germany, Czech Republic, Italy, France, Spain, United Kingdom, Belgium, Japan, Australia, 'Korea; Republic Of South Korea';
No: Brazil, Argentina, China, India.
The MMRM includes all outcome values (change from baseline) at the planned Visits week 12, week 32 and week 52

Table R.1.3.10.5: 1 KCCQ quality of life score change from baseline at week 52 (MMRM) by OECD member (N/Y) - RS (OC-AD - no imputation for deaths) - 1245.121

Subgroup / Visit / Description / Statistic	Placebo	Empa 10mg
OECD member: Yes		
Number of patients in analysis set	1126	1150
Number of analysed patients	1067	1112
Baseline mean (SE)	64.70 (0.72)	65.01 (0.73)
Week 52		
Values at visit		
Number of analysed patients	775	818
Mean (SE)	69.66 (0.81)	71.32 (0.79)
Adjusted* mean (SE)	69.10 (0.67)	70.54 (0.65)
95% confidence interval	(67.79,70.40)	(69.26,71.81)
Change from baseline		
Mean (SE)	3.98 (0.78)	5.66 (0.75)
Adjusted* mean (SE)	4.24 (0.67)	5.68 (0.65)
95% confidence interval	(2.93, 5.54)	(4.40, 6.95)
Comparison vs Placebo		
Adjusted* mean (SE)		1.44 (0.93)
95% confidence interval		(-0.38, 3.26)
p-value		0.1212

* Model includes Age, baseline eGFR (CKD-EPI) as linear covariate(s) and baseline diabetes status, sex, baseline LVEF, week reachable, Visit by Treatment by OECD Member (N) interaction, baseline KCCQ quality of life score by Visit interaction as fixed effect(s).
The Visit by Treatment by OECD Member (N) p-value at Week 52 is 0.7617.
The following covariance structure has been used to fit the mixed model: Unstructured
Note: All covariate effects are set equal to their mean values within subgroup for the calculation of adjusted means.

For patients who died, only observed values are considered (no imputation after date of death).
Data taken from study 1245.121 only.
OECD member (yes/no) countries included:
Yes: United States, Canada, Mexico, Poland, Netherlands, Hungary, Germany, Czech Republic, Italy, France, Spain, United Kingdom, Belgium, Japan, Australia, 'Korea; Republic Of South Korea';
No: Brazil, Argentina, China, India.
The MMRM includes all outcome values (change from baseline) at the planned Visits week 12, week 32 and week 52

R.1.3.10.6

R.1.3.10.6 Subgroup analysis by NYHA at baseline (II, III/IV - 2 cat.)

Table R.1.3.10.6: 1 KCCQ quality of life score change from baseline at week 52 (MMRM) by NYHA (2 cat.) - RS (OC-AD - no imputation for deaths) - 1245.121

Subgroup / Visit / Description / Statistic	Placebo	Empa 10mg
Baseline NYHA (2 cat.): II		
Number of patients in analysis set	1401	1399
Number of analysed patients	1340	1332
Baseline mean (SE)	65.00 (0.62)	66.42 (0.64)
Week 52		
Values at visit		
Number of analysed patients	946	951
Mean (SE)	70.81 (0.73)	74.03 (0.69)
Adjusted* mean (SE)	71.01 (0.60)	73.37 (0.60)
95% confidence interval	(69.84,72.18)	(72.20,74.54)
Change from baseline		
Mean (SE)	5.57 (0.72)	7.47 (0.71)
Adjusted* mean (SE)	5.30 (0.60)	7.67 (0.60)
95% confidence interval	(4.13, 6.48)	(6.49, 8.84)
Comparison vs Placebo		
Adjusted* mean (SE)		2.36 (0.85)
95% confidence interval		(0.71, 4.02)
p-value		0.0052

* Model includes Age, baseline eGFR (CKD-EPI) as linear covariate(s) and region, baseline diabetes status, sex, baseline LVEF, week reachable, Visit by Treatment by baseline NYHA (2 cat.) interaction, baseline KCCQ quality of life score by Visit interaction as fixed effect(s).
The Visit by Treatment by baseline NYHA (2 cat.) p-value at Week 52 is 0.0043.
The following covariance structure has been used to fit the mixed model: Unstructured
Note: All covariate effects are set equal to their mean values within subgroup for the calculation of adjusted means.

For patients who died, only observed values are considered (no imputation after date of death).
Data taken from study 1245.121 only.
The MMRM includes all outcome values (change from baseline) at the planned Visits week 12, week 32 and week 52

Table R.1.3.10.6: 1 KCCQ quality of life score change from baseline at week 52 (MMRM) by NYHA (2 cat.) - RS (OC-AD - no imputation for deaths) - 1245.121

Subgroup / Visit / Description / Statistic	Placebo	Empa 10mg
Baseline NYHA (2 cat.): III/IV		
Number of patients in analysis set	466	464
Number of analysed patients	413	444
Baseline mean (SE)	50.36 (1.20)	49.74 (1.19)
Week 52		
Values at visit		
Number of analysed patients	272	288
Mean (SE)	64.80 (1.42)	62.23 (1.38)
Adjusted* mean (SE)	63.67 (1.11)	61.00 (1.08)
95% confidence interval	(61.49,65.85)	(58.88,63.11)
Change from baseline		
Mean (SE)	13.42 (1.53)	10.66 (1.41)
Adjusted* mean (SE)	13.63 (1.11)	10.96 (1.08)
95% confidence interval	(11.45,15.81)	(8.85,13.07)
Comparison vs Placebo		
Adjusted* mean (SE)		-2.67 (1.55)
95% confidence interval		(-5.70, 0.36)
p-value		0.0847

* Model includes Age, baseline eGFR (CKD-EPI) as linear covariate(s) and region, baseline diabetes status, sex, baseline LVEF, week reachable, Visit by Treatment by baseline NYHA (2 cat.) interaction, baseline KCCQ quality of life score by Visit interaction as fixed effect(s).
The Visit by Treatment by baseline NYHA (2 cat.) p-value at Week 52 is 0.0043.
The following covariance structure has been used to fit the mixed model: Unstructured
Note: All covariate effects are set equal to their mean values within subgroup for the calculation of adjusted means.

For patients who died, only observed values are considered (no imputation after date of death).
Data taken from study 1245.121 only.
The MMRM includes all outcome values (change from baseline) at the planned Visits week 12, week 32 and week 52

R.1.3.10.7

R.1.3.10.7 Subgroup analysis by diabetes at baseline

Table R.1.3.10.7: 1 KCCQ quality of life score change from baseline at week 52 (MMRM) by diabetes at baseline - RS (OC-AD - no imputation for deaths) - 1245.121

Subgroup / Visit / Description / Statistic	Placebo	Empa 10mg
Diabetes at baseline (2 cat.):		
Diabetic		
Number of patients in analysis set	929	927
Number of analysed patients	868	882
Baseline mean (SE)	61.06 (0.83)	61.88 (0.86)
Week 52		
Values at visit		
Number of analysed patients	606	614
Mean (SE)	69.95 (0.90)	70.96 (0.92)
Adjusted* mean (SE)	69.33 (0.75)	69.80 (0.74)
95% confidence interval	(67.87,70.80)	(68.34,71.25)
Change from baseline		
Mean (SE)	7.74 (0.93)	7.81 (0.93)
Adjusted* mean (SE)	7.86 (0.75)	8.32 (0.74)
95% confidence interval	(6.39, 9.33)	(6.87, 9.78)
Comparison vs Placebo		
Adjusted* mean (SE)		0.46 (1.05)
95% confidence interval		(-1.61, 2.53)
p-value		0.6609

* Model includes Age, baseline eGFR (CKD-EPI) as linear covariate(s) and region, sex, baseline LVEF, week reachable, Visit by Treatment by diabetes at baseline (2 cat.) interaction, baseline KCCQ quality of life score by Visit interaction as fixed effect(s).
The Visit by Treatment by diabetes at baseline (2 cat.) p-value at Week 52 is 0.3320.
The following covariance structure has been used to fit the mixed model: Unstructured
Note: All covariate effects are set equal to their mean values within subgroup for the calculation of adjusted means.

For patients who died, only observed values are considered (no imputation after date of death).
Data taken from study 1245.121 only.
The MMRM includes all outcome values (change from baseline) at the planned Visits week 12, week 32 and week 52

Table R.1.3.10.7: 1 KCCQ quality of life score change from baseline at week 52 (MMRM) by diabetes at baseline - RS (OC-AD - no imputation for deaths) - 1245.121

Subgroup / Visit / Description / Statistic	Placebo	Empa 10mg
Diabetes at baseline (2 cat.):		
Non-Diabetic		
Number of patients in analysis set	938	936
Number of analysed patients	885	894
Baseline mean (SE)	62.03 (0.80)	62.61 (0.80)
Week 52		
Values at visit		
Number of analysed patients	612	625
Mean (SE)	69.00 (0.94)	71.60 (0.88)
Adjusted* mean (SE)	69.05 (0.74)	70.96 (0.74)
95% confidence interval	(67.59,70.51)	(69.51,72.40)
Change from baseline		
Mean (SE)	6.92 (0.94)	8.61 (0.87)
Adjusted* mean (SE)	6.73 (0.74)	8.63 (0.74)
95% confidence interval	(5.27, 8.19)	(7.19,10.08)
Comparison vs Placebo		
Adjusted* mean (SE)		1.90 (1.05)
95% confidence interval		(-0.15, 3.96)
p-value		0.0691

* Model includes Age, baseline eGFR (CKD-EPI) as linear covariate(s) and region, sex, baseline LVEF, week reachable, Visit by Treatment by diabetes at baseline (2 cat.) interaction, baseline KCCQ quality of life score by Visit interaction as fixed effect(s).
The Visit by Treatment by diabetes at baseline (2 cat.) p-value at Week 52 is 0.3320.
The following covariance structure has been used to fit the mixed model: Unstructured
Note: All covariate effects are set equal to their mean values within subgroup for the calculation of adjusted means.

For patients who died, only observed values are considered (no imputation after date of death).
Data taken from study 1245.121 only.
The MMRM includes all outcome values (change from baseline) at the planned Visits week 12, week 32 and week 52

R.1.3.10.8

R.1.3.10.8 Subgroup analysis by BMI at baseline (<30, >=30)

Table R.1.3.10.8: 1 KCCQ quality of life score change from baselineat week 52 (MMRM) by baseline BMI [kg/m2] - RS (OC-AD - no imputation for deaths) - 1245.121

Subgroup / Visit / Description / Statistic	Placebo	Empa 10mg
Baseline BMI [kg/m²] (2 cat.): <30		
Number of patients in analysis set	1300	1263
Number of analysed patients	1229	1201
Baseline mean (SE)	62.23 (0.69)	63.62 (0.70)
Week 52		
Values at visit		
Number of analysed patients	865	826
Mean (SE)	70.19 (0.78)	72.43 (0.76)
Adjusted* mean (SE)	70.18 (0.63)	71.26 (0.64)
95% confidence interval	(68.95,71.41)	(70.01,72.52)
Change from baseline		
Mean (SE)	7.21 (0.78)	7.90 (0.78)
Adjusted* mean (SE)	7.27 (0.63)	8.35 (0.64)
95% confidence interval	(6.03, 8.50)	(7.09, 9.61)
Comparison vs Placebo		
Adjusted* mean (SE)		1.08 (0.90)
95% confidence interval		(-0.67, 2.84)
p-value		0.2265

* Model includes Age, baseline eGFR (CKD-EPI) as linear covariate(s) and region, baseline diabetes status, sex, baseline LVEF, week reachable, Visit by Treatment by baseline BMI [kg/m²] (2 cat.) interaction, baseline KCCQ quality of life score by Visit interaction as fixed effect(s).
The Visit by Treatment by baseline BMI [kg/m²] (2 cat.) p-value at Week 52 is 0.7670.
The following covariance structure has been used to fit the mixed model: Unstructured
Note: All covariate effects are set equal to their mean values within subgroup for the calculation of adjusted means.

For patients who died, only observed values are considered (no imputation after date of death).
Data taken from study 1245.121 only.
The MMRM includes all outcome values (change from baseline) at the planned Visits week 12, week 32 and week 52

Table R.1.3.10.8: 1 KCCQ quality of life score change from baselineat week 52 (MMRM) by baseline BMI [kg/m2] - RS (OC-AD - no imputation for deaths) - 1245.121

Subgroup / Visit / Description / Statistic	Placebo	Empa 10mg
Baseline BMI [kg/m²] (2 cat.): >=30		
Number of patients in analysis set	567	600
Number of analysed patients	524	575
Baseline mean (SE)	59.98 (1.04)	59.38 (1.06)
Week 52		
Values at visit		
Number of analysed patients	353	413
Mean (SE)	67.71 (1.20)	69.00 (1.14)
Adjusted* mean (SE)	66.95 (0.98)	68.51 (0.92)
95% confidence interval	(65.02,68.88)	(66.71,70.30)
Change from baseline		
Mean (SE)	7.60 (1.25)	8.85 (1.08)
Adjusted* mean (SE)	7.28 (0.98)	8.84 (0.92)
95% confidence interval	(5.35, 9.21)	(7.05,10.64)
Comparison vs Placebo		
Adjusted* mean (SE)		1.56 (1.34)
95% confidence interval		(-1.06, 4.18)
p-value		0.2426

* Model includes Age, baseline eGFR (CKD-EPI) as linear covariate(s) and region, baseline diabetes status, sex, baseline LVEF, week reachable, Visit by Treatment by baseline BMI [kg/m²] (2 cat.) interaction, baseline KCCQ quality of life score by Visit interaction as fixed effect(s).
The Visit by Treatment by baseline BMI [kg/m²] (2 cat.) p-value at Week 52 is 0.7670.
The following covariance structure has been used to fit the mixed model: Unstructured
Note: All covariate effects are set equal to their mean values within subgroup for the calculation of adjusted means.

For patients who died, only observed values are considered (no imputation after date of death).
Data taken from study 1245.121 only.
The MMRM includes all outcome values (change from baseline) at the planned Visits week 12, week 32 and week 52

R.1.3.10.9

R.1.3.10.9 Subgroup analysis by eGFR at baseline (<60, >=60)

Table R.1.3.10.9: 1 KCCQ quality of life score change from baseline at week 52 (MMRM) by baseline eGFR (2 cat.) - RS (OC-AD - no imputation for deaths) - 1245.121

Subgroup / Visit / Description / Statistic	Placebo	Empa 10mg
Baseline eGFR (CKD-EPI) [mL/min/1.73m²] (2 cat.): >=60		
Number of patients in analysis set	960	969
Number of analysed patients	901	921
Baseline mean (SE)	60.50 (0.79)	61.63 (0.83)
Week 52		
Values at visit		
Number of analysed patients	647	650
Mean (SE)	68.61 (0.89)	71.83 (0.90)
Adjusted* mean (SE)	68.54 (0.73)	71.03 (0.72)
95% confidence interval	(67.12,69.97)	(69.61,72.45)
Change from baseline		
Mean (SE)	7.91 (0.88)	9.74 (0.90)
Adjusted* mean (SE)	7.48 (0.73)	9.96 (0.72)
95% confidence interval	(6.05, 8.90)	(8.55,11.38)
Comparison vs Placebo		
Adjusted* mean (SE)		2.49 (1.03)
95% confidence interval		(0.48, 4.50)
p-value		0.0153

* Model includes Age as linear covariate(s) and region, baseline diabetes status, sex, baseline LVEF, week reachable, Visit by Treatment by baseline eGFR (CKD-EPI) [mL/min/1.73m²] (2 cat.) interaction, baseline KCCQ quality of life score by Visit interaction as fixed effect(s).
The Visit by Treatment by baseline eGFR (CKD-EPI) [mL/min/1.73m²] (2 cat.) p-value at Week 52 is 0.0657.
The following covariance structure has been used to fit the mixed model: Unstructured
2 patients were excluded as the subgroup variable was missing.
Note: All covariate effects are set equal to their mean values within subgroup for the calculation of adjusted means.

For patients who died, only observed values are considered (no imputation after date of death).
Data taken from study 1245.121 only.
The MMRM includes all outcome values (change from baseline) at the planned Visits week 12, week 32 and week 52

Table R.1.3.10.9: 1 KCCQ quality of life score change from baseline at week 52 (MMRM) by baseline eGFR (2 cat.) - RS (OC-AD - no imputation for deaths) - 1245.121

Subgroup / Visit / Description / Statistic	Placebo	Empa 10mg
Baseline eGFR (CKD-EPI) [mL/min/1.73m²] (2 cat.): <60		
Number of patients in analysis set	906	893
Number of analysed patients	852	855
Baseline mean (SE)	62.67 (0.83)	62.91 (0.83)
Week 52		
Values at visit		
Number of analysed patients	571	589
Mean (SE)	70.44 (0.95)	70.68 (0.89)
Adjusted* mean (SE)	69.92 (0.77)	69.66 (0.76)
95% confidence interval	(68.40,71.43)	(68.17,71.15)
Change from baseline		
Mean (SE)	6.66 (1.00)	6.53 (0.89)
Adjusted* mean (SE)	7.12 (0.77)	6.87 (0.76)
95% confidence interval	(5.61, 8.63)	(5.38, 8.36)
Comparison vs Placebo		
Adjusted* mean (SE)		-0.25 (1.08)
95% confidence interval		(-2.37, 1.86)
p-value		0.8146

* Model includes Age as linear covariate(s) and region, baseline diabetes status, sex, baseline LVEF, week reachable, Visit by Treatment by baseline eGFR (CKD-EPI) [mL/min/1.73m²] (2 cat.) interaction, baseline KCCQ quality of life score by Visit interaction as fixed effect(s).
The Visit by Treatment by baseline eGFR (CKD-EPI) [mL/min/1.73m²] (2 cat.) p-value at Week 52 is 0.0657.
The following covariance structure has been used to fit the mixed model: Unstructured
2 patients were excluded as the subgroup variable was missing.
Note: All covariate effects are set equal to their mean values within subgroup for the calculation of adjusted means.

For patients who died, only observed values are considered (no imputation after date of death).
Data taken from study 1245.121 only.
The MMRM includes all outcome values (change from baseline) at the planned Visits week 12, week 32 and week 52

R.1.3.10.10

Table R.1.3.10.10: 1 KCCQ quality of life score change from baseline at week 52 (MMRM) by history of HHF - RS (OC-AD - no imputation for deaths) - 1245.121

Subgroup / Visit / Description / Statistic	Placebo	Empa 10mg
History of HHF (in the last 12 months): No		
Number of patients in analysis set	1293	1286
Number of analysed patients	1220	1231
Baseline mean (SE)	62.75 (0.69)	63.00 (0.70)
Week 52		
Values at visit		
Number of analysed patients	869	873
Mean (SE)	69.51 (0.77)	71.87 (0.76)
Adjusted* mean (SE)	69.49 (0.63)	71.27 (0.63)
95% confidence interval	(68.26,70.72)	(70.04,72.49)
Change from baseline		
Mean (SE)	6.80 (0.77)	8.34 (0.75)
Adjusted* mean (SE)	6.62 (0.63)	8.39 (0.63)
95% confidence interval	(5.38, 7.85)	(7.16, 9.62)
Comparison vs Placebo		
Adjusted* mean (SE)		1.78 (0.88)
95% confidence interval		(0.04, 3.51)
p-value		0.0448

* Model includes Age, baseline eGFR (CKD-EPI) as linear covariate(s) and region, baseline diabetes status, sex, baseline LVEF, week reachable, Visit by Treatment by history of HHF (in the last 12 months) interaction, baseline KCCQ quality of life score by Visit interaction as fixed effect(s).
The Visit by Treatment by history of HHF (in the last 12 months) p-value at Week 52 is 0.2092.
The following covariance structure has been used to fit the mixed model: Unstructured
Note: All covariate effects are set equal to their mean values within subgroup for the calculation of adjusted means.

For patients who died, only observed values are considered (no imputation after date of death).
Data taken from study 1245.121 only.
The MMRM includes all outcome values (change from baseline) at the planned Visits week 12, week 32 and week 52

Table R.1.3.10.10: 1 KCCQ quality of life score change from baseline at week 52 (MMRM) by history of HHF - RS (OC-AD - no imputation for deaths) - 1245.121

Subgroup / Visit / Description / Statistic	Placebo	Empa 10mg
History of HHF (in the last 12 months): Yes		
Number of patients in analysis set	574	577
Number of analysed patients	533	545
Baseline mean (SE)	58.82 (1.03)	60.55 (1.07)
Week 52		
Values at visit		
Number of analysed patients	349	366
Mean (SE)	69.38 (1.21)	69.89 (1.17)
Adjusted* mean (SE)	68.59 (0.98)	68.32 (0.96)
95% confidence interval	(66.66,70.52)	(66.43,70.21)
Change from baseline		
Mean (SE)	8.63 (1.27)	7.91 (1.19)
Adjusted* mean (SE)	8.90 (0.98)	8.62 (0.96)
95% confidence interval	(6.97,10.83)	(6.73,10.51)
Comparison vs Placebo		
Adjusted* mean (SE)		-0.28 (1.37)
95% confidence interval		(-2.97, 2.42)
p-value		0.8410

* Model includes Age, baseline eGFR (CKD-EPI) as linear covariate(s) and region, baseline diabetes status, sex, baseline LVEF, week reachable, Visit by Treatment by history of HHF (in the last 12 months) interaction, baseline KCCQ quality of life score by Visit interaction as fixed effect(s).
The Visit by Treatment by history of HHF (in the last 12 months) p-value at Week 52 is 0.2092.
The following covariance structure has been used to fit the mixed model: Unstructured
Note: All covariate effects are set equal to their mean values within subgroup for the calculation of adjusted means.

For patients who died, only observed values are considered (no imputation after date of death).
Data taken from study 1245.121 only.
The MMRM includes all outcome values (change from baseline) at the planned Visits week 12, week 32 and week 52

R.1.3.10.11

Table R.1.3.10.11: 1 KCCQ quality of life score change from baseline at week 52 (MMRM) by cause of heart failure - RS (OC-AD - no imputation for deaths) - 1245.121

Subgroup / Visit / Description / Statistic	Placebo	Empa 10mg
Cause of heart failure: Ischemic		
Number of patients in analysis set	946	983
Number of analysed patients	896	936
Baseline mean (SE)	62.95 (0.78)	62.88 (0.81)
Week 52		
Values at visit		
Number of analysed patients	634	667
Mean (SE)	69.89 (0.89)	71.03 (0.86)
Adjusted* mean (SE)	69.45 (0.74)	70.30 (0.72)
95% confidence interval	(68.00,70.90)	(68.89,71.71)
Change from baseline		
Mean (SE)	5.79 (0.83)	6.97 (0.85)
Adjusted* mean (SE)	6.53 (0.74)	7.38 (0.72)
95% confidence interval	(5.09, 7.98)	(5.97, 8.79)
Comparison vs Placebo		
Adjusted* mean (SE)		0.85 (1.02)
95% confidence interval		(-1.16, 2.86)
p-value		0.4079

* Model includes Age, baseline eGFR (CKD-EPI) as linear covariate(s) and region, baseline diabetes status, sex, baseline LVEF, week reachable, Visit by Treatment by cause of heart failure interaction, baseline KCCQ quality of life score by Visit interaction as fixed effect(s).
The Visit by Treatment by cause of heart failure p-value at Week 52 is 0.6262.
The following covariance structure has been used to fit the mixed model: Unstructured
Note: All covariate effects are set equal to their mean values within subgroup for the calculation of adjusted means.

For patients who died, only observed values are considered (no imputation after date of death).
Data taken from study 1245.121 only.
The MMRM includes all outcome values (change from baseline) at the planned Visits week 12, week 32 and week 52

Table R.1.3.10.11: 1 KCCQ quality of life score change from baseline at week 52 (MMRM) by cause of heart failure - RS (OC-AD - no imputation for deaths) - 1245.121

Subgroup / Visit / Description / Statistic	Placebo	Empa 10mg
Cause of heart failure: Non-ischemic		
Number of patients in analysis set	921	880
Number of analysed patients	857	840
Baseline mean (SE)	60.09 (0.84)	61.54 (0.85)
Week 52		
Values at visit		
Number of analysed patients	584	572
Mean (SE)	69.01 (0.96)	71.58 (0.94)
Adjusted* mean (SE)	68.93 (0.77)	70.50 (0.77)
95% confidence interval	(67.43,70.43)	(68.99,72.01)
Change from baseline		
Mean (SE)	8.99 (1.04)	9.67 (0.95)
Adjusted* mean (SE)	8.12 (0.77)	9.69 (0.77)
95% confidence interval	(6.62, 9.62)	(8.18,11.21)
Comparison vs Placebo		
Adjusted* mean (SE)		1.57 (1.08)
95% confidence interval		(-0.55, 3.69)
p-value		0.1460

* Model includes Age, baseline eGFR (CKD-EPI) as linear covariate(s) and region, baseline diabetes status, sex, baseline LVEF, week reachable, Visit by Treatment by cause of heart failure interaction, baseline KCCQ quality of life score by Visit interaction as fixed effect(s).
The Visit by Treatment by cause of heart failure p-value at Week 52 is 0.6262.
The following covariance structure has been used to fit the mixed model: Unstructured
Note: All covariate effects are set equal to their mean values within subgroup for the calculation of adjusted means.

For patients who died, only observed values are considered (no imputation after date of death).
Data taken from study 1245.121 only.
The MMRM includes all outcome values (change from baseline) at the planned Visits week 12, week 32 and week 52

R.1.3.10.12 Subgroup analysis by heart failure physiology (LVEF <= 30% and NTproBNP<median; LVEF <= 30% and NTproBNP>=median; LVEF > 30%)

Table R.1.3.10.12: 1 KCCQ quality of life score change from baseline at week 52 (MMRM) by heart failure physiology - RS (OC-AD - no imputation for deaths) - 1245.121

Subgroup Visit Description Statistic	Placebo	Empa 10mg
Heart failure physiology: LVEF <= 30% and NTproBNP < median		
Number of patients in analysis set	723	698
Number of analysed patients	694	672
Baseline mean (SE)	62.22 (0.92)	64.04 (0.93)
Week 52		
Values at visit		
Number of analysed patients	511	494
Mean (SE)	70.21 (1.00)	72.03 (0.99)
Adjusted* mean (SE)	70.32 (0.82)	71.33 (0.83)
95% confidence interval	(68.71,71.92)	(69.70,72.96)
Change from baseline		
Mean (SE)	8.24 (0.92)	8.38 (0.97)
Adjusted* mean (SE)	7.20 (0.82)	8.21 (0.83)
95% confidence interval	(5.60, 8.81)	(6.58, 9.84)
Comparison vs Placebo		
Adjusted* mean (SE)		1.01 (1.17)
95% confidence interval		(-1.28, 3.30)
p-value		0.3867

* Model includes Age, baseline eGFR (CKD-EPI) as linear covariate(s) and region, baseline diabetes status, sex, week reachable, Visit by Treatment by heart failure physiology interaction, baseline KCCQ quality of life score by Visit interaction as fixed effect(s).
The Visit by Treatment by heart failure physiology p-value at Week 52 is 0.3600.
The following covariance structure has been used to fit the mixed model: Unstructured
16 patients were excluded as the subgroup variable was missing.
Note: All covariate effects are set equal to their mean values within subgroup for the calculation of adjusted means.
The p-value for the visit by treatment by subgroup interaction trend test at Week 52 is 0.6105

For patients who died, only observed values are considered (no imputation after date of death).
Data taken from study 1245.121 only.
NTproBNP median [pg/mL]: with a. fibrillation/flutter at baseline: 2265; without a. fibrillation/flutter at baseline: 1671.
The MMRM includes all outcome values (change from baseline) at the planned Visits week 12, week 32 and week 52

Table R.1.3.10.12: 1 KCCQ quality of life score change from baseline at week 52 (MMRM) by heart failure physiology - RS (OC-AD - no imputation for deaths) - 1245.121

Subgroup / Visit / Description / Statistic	Placebo	Empa 10mg
Heart failure physiology: LVEF <= 30% and NTproBNP >= median		
Number of patients in analysis set	661	631
Number of analysed patients	604	593
Baseline mean (SE)	59.62 (0.99)	58.92 (1.03)
Week 52		
Values at visit		
Number of analysed patients	409	405
Mean (SE)	67.61 (1.15)	70.95 (1.16)
Adjusted* mean (SE)	67.10 (0.91)	69.62 (0.91)
95% confidence interval	(65.31,68.88)	(67.83,71.41)
Change from baseline		
Mean (SE)	6.98 (1.27)	10.25 (1.20)
Adjusted* mean (SE)	7.82 (0.91)	10.34 (0.91)
95% confidence interval	(6.04, 9.60)	(8.55,12.14)
Comparison vs Placebo		
Adjusted* mean (SE)		2.52 (1.29)
95% confidence interval		(-0.01, 5.05)
p-value		0.0505

* Model includes Age, baseline eGFR (CKD-EPI) as linear covariate(s) and region, baseline diabetes status, sex, week reachable, Visit by Treatment by heart failure physiology interaction, baseline KCCQ quality of life score by Visit interaction as fixed effect(s).
The Visit by Treatment by heart failure physiology p-value at Week 52 is 0.3600.
The following covariance structure has been used to fit the mixed model: Unstructured
16 patients were excluded as the subgroup variable was missing.
Note: All covariate effects are set equal to their mean values within subgroup for the calculation of adjusted means.
The p-value for the visit by treatment by subgroup interaction trend test at Week 52 is 0.6105

For patients who died, only observed values are considered (no imputation after date of death).
Data taken from study 1245.121 only.
NTproBNP median [pg/mL]: with a. fibrillation/flutter at baseline: 2265; without a. fibrillation/flutter at baseline: 1671.
The MMRM includes all outcome values (change from baseline) at the planned Visits week 12, week 32 and week 52

Table R.1.3.10.12: 1 KCCQ quality of life score change from baseline at week 52 (MMRM) by heart failure physiology - RS (OC-AD - no imputation for deaths) - 1245.121

Subgroup / Visit / Description / Statistic	Placebo	Empa 10mg
Heart failure physiology: LVEF > 30%		
Number of patients in analysis set	475	526
Number of analysed patients	450	506
Baseline mean (SE)	63.33 (1.09)	63.93 (1.10)
Week 52		
Values at visit		
Number of analysed patients	294	339
Mean (SE)	71.03 (1.28)	70.59 (1.19)
Adjusted* mean (SE)	70.32 (1.07)	70.09 (1.00)
95% confidence interval	(68.23,72.42)	(68.14,72.04)
Change from baseline		
Mean (SE)	6.15 (1.34)	5.49 (1.14)
Adjusted* mean (SE)	6.67 (1.07)	6.44 (1.00)
95% confidence interval	(4.58, 8.77)	(4.49, 8.39)
Comparison vs Placebo		
Adjusted* mean (SE)		-0.23 (1.46)
95% confidence interval		(-3.10, 2.63)
p-value		0.8726

* Model includes Age, baseline eGFR (CKD-EPI) as linear covariate(s) and region, baseline diabetes status, sex, week reachable, Visit by Treatment by heart failure physiology interaction, baseline KCCQ quality of life score by Visit interaction as fixed effect(s).
The Visit by Treatment by heart failure physiology p-value at Week 52 is 0.3600.
The following covariance structure has been used to fit the mixed model: Unstructured
16 patients were excluded as the subgroup variable was missing.
Note: All covariate effects are set equal to their mean values within subgroup for the calculation of adjusted means.
The p-value for the visit by treatment by subgroup interaction trend test at Week 52 is 0.6105

For patients who died, only observed values are considered (no imputation after date of death).
Data taken from study 1245.121 only.
NTproBNP median [pg/mL]: with a. fibrillation/flutter at baseline: 2265; without a. fibrillation/flutter at baseline: 1671.
The MMRM includes all outcome values (change from baseline) at the planned Visits week 12, week 32 and week 52

R.1.3.10.13

R.1.3.10.13 Subgroup analysis by baseline use of MRA

Table R.1.3.10.13: 1 KCCQ quality of life score change from baseline at week 52 (MMRM) by baseline use of MRA (Y/N) - RS (OC-AD - no imputation for deaths) - 1245.121

Subgroup / Visit / Description / Statistic	Placebo	Empa 10mg
Baseline use of MRA: No		
Number of patients in analysis set	512	557
Number of analysed patients	486	531
Baseline mean (SE)	64.91 (1.04)	63.54 (1.06)
Week 52		
Values at visit		
Number of analysed patients	340	383
Mean (SE)	69.75 (1.19)	72.58 (1.13)
Adjusted* mean (SE)	70.26 (1.00)	72.33 (0.95)
95% confidence interval	(68.29,72.23)	(70.47,74.19)
Change from baseline		
Mean (SE)	4.95 (1.19)	8.18 (1.12)
Adjusted* mean (SE)	6.06 (1.00)	8.14 (0.95)
95% confidence interval	(4.10, 8.03)	(6.27,10.00)
Comparison vs Placebo		
Adjusted* mean (SE)		2.07 (1.38)
95% confidence interval		(-0.63, 4.77)
p-value		0.1323

* Model includes Age, baseline eGFR (CKD-EPI) as linear covariate(s) and region, baseline diabetes status, sex, baseline LVEF, week reachable, Visit by Treatment by baseline use of MRA interaction, baseline KCCQ quality of life score by Visit interaction as fixed effect(s).
The Visit by Treatment by baseline use of MRA p-value at Week 52 is 0.4365.
The following covariance structure has been used to fit the mixed model: Unstructured
Note: All covariate effects are set equal to their mean values within subgroup for the calculation of adjusted means.

For patients who died, only observed values are considered (no imputation after date of death).
Data taken from study 1245.121 only.
The MMRM includes all outcome values (change from baseline) at the planned Visits week 12, week 32 and week 52

Table R.1.3.10.13: 1 KCCQ quality of life score change from baseline at week 52 (MMRM) by baseline use of MRA (Y/N) - RS (OC-AD - no imputation for deaths) - 1245.121

Subgroup / Visit / Description / Statistic	Placebo	Empa 10mg
Baseline use of MRA: Yes		
Number of patients in analysis set	1355	1306
Number of analysed patients	1267	1245
Baseline mean (SE)	60.27 (0.68)	61.69 (0.70)
Week 52		
Values at visit		
Number of analysed patients	878	856
Mean (SE)	69.36 (0.78)	70.70 (0.77)
Adjusted* mean (SE)	68.77 (0.62)	69.57 (0.63)
95% confidence interval	(67.55,69.99)	(68.33,70.80)
Change from baseline		
Mean (SE)	8.24 (0.79)	8.23 (0.77)
Adjusted* mean (SE)	7.79 (0.62)	8.59 (0.63)
95% confidence interval	(6.57, 9.02)	(7.36, 9.83)
Comparison vs Placebo		
Adjusted* mean (SE)		0.80 (0.88)
95% confidence interval		(-0.94, 2.53)
p-value		0.3671

* Model includes Age, baseline eGFR (CKD-EPI) as linear covariate(s) and region, baseline diabetes status, sex, baseline LVEF, week reachable, Visit by Treatment by baseline use of MRA interaction, baseline KCCQ quality of life score by Visit interaction as fixed effect(s).
The Visit by Treatment by baseline use of MRA p-value at Week 52 is 0.4365.
The following covariance structure has been used to fit the mixed model: Unstructured
Note: All covariate effects are set equal to their mean values within subgroup for the calculation of adjusted means.

For patients who died, only observed values are considered (no imputation after date of death).
Data taken from study 1245.121 only.
The MMRM includes all outcome values (change from baseline) at the planned Visits week 12, week 32 and week 52

R.1.3.10.14

R.1.3.10.14 Subgroup analysis by baseline use of ARNi

Table R.1.3.10.14: 1 KCCQ quality of life score change from baseline at week 52 (MMRM) by baseline use of ARNi (Y/N) - RS (OC-AD - no imputation for deaths) - 1245.121

Subgroup / Visit / Description / Statistic	Placebo	Empa 10mg
Baseline use of ARNi: No		
Number of patients in analysis set	1480	1523
Number of analysed patients	1390	1447
Baseline mean (SE)	61.25 (0.63)	61.45 (0.64)
Week 52		
Values at visit		
Number of analysed patients	960	1026
Mean (SE)	69.51 (0.73)	70.78 (0.70)
Adjusted* mean (SE)	69.21 (0.59)	69.94 (0.58)
95% confidence interval	(68.05,70.38)	(68.81,71.08)
Change from baseline		
Mean (SE)	7.94 (0.76)	8.52 (0.70)
Adjusted* mean (SE)	7.86 (0.59)	8.59 (0.58)
95% confidence interval	(6.69, 9.02)	(7.46, 9.72)
Comparison vs Placebo		
Adjusted* mean (SE)		0.73 (0.83)
95% confidence interval		(-0.89, 2.36)
p-value		0.3760

* Model includes Age, baseline eGFR (CKD-EPI) as linear covariate(s) and region, baseline diabetes status, sex, baseline LVEF, week reachable, Visit by Treatment by baseline use of ARNi interaction, baseline KCCQ quality of life score by Visit interaction as fixed effect(s).
The Visit by Treatment by baseline use of ARNi p-value at Week 52 is 0.2175.
The following covariance structure has been used to fit the mixed model: Unstructured
Note: All covariate effects are set equal to their mean values within subgroup for the calculation of adjusted means.

For patients who died, only observed values are considered (no imputation after date of death).
Data taken from study 1245.121 only.
The MMRM includes all outcome values (change from baseline) at the planned Visits week 12, week 32 and week 52

Table R.1.3.10.14: 1 KCCQ quality of life score change from baseline at week 52 (MMRM) by baseline use of ARNi (Y/N) - RS (OC-AD - no imputation for deaths) - 1245.121

Subgroup / Visit / Description / Statistic	Placebo	Empa 10mg
Baseline use of ARNi: Yes		
Number of patients in analysis set	387	340
Number of analysed patients	363	329
Baseline mean (SE)	62.72 (1.34)	65.73 (1.42)
Week 52		
Values at visit		
Number of analysed patients	258	213
Mean (SE)	69.32 (1.47)	73.71 (1.49)
Adjusted* mean (SE)	69.24 (1.16)	72.31 (1.26)
95% confidence interval	(66.97,71.50)	(69.83,74.78)
Change from baseline		
Mean (SE)	5.04 (1.34)	6.77 (1.49)
Adjusted* mean (SE)	5.09 (1.16)	8.16 (1.26)
95% confidence interval	(2.82, 7.35)	(5.68,10.63)
Comparison vs Placebo		
Adjusted* mean (SE)		3.07 (1.70)
95% confidence interval		(-0.27, 6.41)
p-value		0.0716

* Model includes Age, baseline eGFR (CKD-EPI) as linear covariate(s) and region, baseline diabetes status, sex, baseline LVEF, week reachable, Visit by Treatment by baseline use of ARNi interaction, baseline KCCQ quality of life score by Visit interaction as fixed effect(s).
The Visit by Treatment by baseline use of ARNi p-value at Week 52 is 0.2175.
The following covariance structure has been used to fit the mixed model: Unstructured
Note: All covariate effects are set equal to their mean values within subgroup for the calculation of adjusted means.

For patients who died, only observed values are considered (no imputation after date of death).
Data taken from study 1245.121 only.
The MMRM includes all outcome values (change from baseline) at the planned Visits week 12, week 32 and week 52

R.1.3.10.15

R.1.3.10.15 Subgroup analysis by bl. LVEF (<= 30%, >30% -<= 35% , > 35%)

Table R.1.3.10.15: 1 KCCQ quality of life score change from baseline at week 52 (MMRM) by baseline LVEF (3 cat.) - RS (OC-AD - no imputation for deaths) - 1245.121

Subgroup / Visit / Description / Statistic	Placebo	Empa 10mg
Baseline LVEF (3 cat.): <=30		
Number of patients in analysis set	1392	1337
Number of analysed patients	1303	1270
Baseline mean (SE)	60.94 (0.67)	61.57 (0.69)
Week 52		
Values at visit		
Number of analysed patients	924	900
Mean (SE)	68.97 (0.76)	71.55 (0.75)
Adjusted* mean (SE)	68.77 (0.61)	70.50 (0.61)
95% confidence interval	(67.58,69.96)	(69.29,71.70)
Change from baseline		
Mean (SE)	7.70 (0.76)	9.24 (0.76)
Adjusted* mean (SE)	7.52 (0.61)	9.24 (0.61)
95% confidence interval	(6.33, 8.71)	(8.04,10.45)
Comparison vs Placebo		
Adjusted* mean (SE)		1.73 (0.86)
95% confidence interval		(0.03, 3.42)
p-value		0.0458

* Model includes Age, baseline eGFR (CKD-EPI) as linear covariate(s) and region, baseline diabetes status, sex, week reachable, Visit by Treatment by baseline LVEF (3 cat.) interaction, baseline KCCQ quality of life score by Visit interaction as fixed effect(s).
The Visit by Treatment by baseline LVEF (3 cat.) p-value at Week 52 is 0.3776.
The following covariance structure has been used to fit the mixed model: Unstructured
Note: All covariate effects are set equal to their mean values within subgroup for the calculation of adjusted means.
The p-value for the visit by treatment by subgroup interaction trend test at Week 52 is 0.4447

For patients who died, only observed values are considered (no imputation after date of death).
Data taken from study 1245.121 only.
The MMRM includes all outcome values (change from baseline) at the planned Visits week 12, week 32 and week 52

Table R.1.3.10.15: 1 KCCQ quality of life score change from baseline at week 52 (MMRM) by baseline LVEF (3 cat.) - RS (OC-AD - no imputation for deaths) - 1245.121

Subgroup / Visit / Description / Statistic	Placebo	Empa 10mg
Baseline LVEF (3 cat.): >30 to <=35		
Number of patients in analysis set	361	398
Number of analysed patients	342	385
Baseline mean (SE)	64.60 (1.25)	64.22 (1.23)
Week 52		
Values at visit		
Number of analysed patients	233	256
Mean (SE)	72.39 (1.43)	70.26 (1.40)
Adjusted* mean (SE)	71.16 (1.20)	70.32 (1.14)
95% confidence interval	(68.80,73.52)	(68.07,72.56)
Change from baseline		
Mean (SE)	6.58 (1.47)	4.67 (1.29)
Adjusted* mean (SE)	6.76 (1.20)	5.92 (1.14)
95% confidence interval	(4.40, 9.12)	(3.68, 8.16)
Comparison vs Placebo		
Adjusted* mean (SE)		-0.84 (1.66)
95% confidence interval		(-4.10, 2.41)
p-value		0.6111

* Model includes Age, baseline eGFR (CKD-EPI) as linear covariate(s) and region, baseline diabetes status, sex, week reachable, Visit by Treatment by baseline LVEF (3 cat.) interaction, baseline KCCQ quality of life score by Visit interaction as fixed effect(s).
The Visit by Treatment by baseline LVEF (3 cat.) p-value at Week 52 is 0.3776.
The following covariance structure has been used to fit the mixed model: Unstructured
Note: All covariate effects are set equal to their mean values within subgroup for the calculation of adjusted means.
The p-value for the visit by treatment by subgroup interaction trend test at Week 52 is 0.4447

For patients who died, only observed values are considered (no imputation after date of death).
Data taken from study 1245.121 only.
The MMRM includes all outcome values (change from baseline) at the planned Visits week 12, week 32 and week 52

Table R.1.3.10.15: 1 KCCQ quality of life score change from baseline at week 52 (MMRM) by baseline LVEF (3 cat.) - RS (OC-AD - no imputation for deaths) - 1245.121

Subgroup / Visit / Description / Statistic	Placebo	Empa 10mg
Baseline LVEF (3 cat.): >35		
Number of patients in analysis set	114	128
Number of analysed patients	108	121
Baseline mean (SE)	59.34 (2.20)	63.02 (2.42)
Week 52		
Values at visit		
Number of analysed patients	61	83
Mean (SE)	65.85 (2.75)	71.59 (2.26)
Adjusted* mean (SE)	67.37 (2.32)	69.35 (2.02)
95% confidence interval	(62.82,71.92)	(65.39,73.31)
Change from baseline		
Mean (SE)	4.51 (3.20)	8.03 (2.42)
Adjusted* mean (SE)	6.09 (2.32)	8.07 (2.02)
95% confidence interval	(1.54,10.64)	(4.11,12.02)
Comparison vs Placebo		
Adjusted* mean (SE)		1.98 (3.07)
95% confidence interval		(-4.05, 8.00)
p-value		0.5203

* Model includes Age, baseline eGFR (CKD-EPI) as linear covariate(s) and region, baseline diabetes status, sex, week reachable, Visit by Treatment by baseline LVEF (3 cat.) interaction, baseline KCCQ quality of life score by Visit interaction as fixed effect(s).
The Visit by Treatment by baseline LVEF (3 cat.) p-value at Week 52 is 0.3776.
The following covariance structure has been used to fit the mixed model: Unstructured
Note: All covariate effects are set equal to their mean values within subgroup for the calculation of adjusted means.
The p-value for the visit by treatment by subgroup interaction trend test at Week 52 is 0.4447

For patients who died, only observed values are considered (no imputation after date of death).
Data taken from study 1245.121 only.
The MMRM includes all outcome values (change from baseline) at the planned Visits week 12, week 32 and week 52

R.1.3.10.16 Subgroup analysis by bl. NTproBNP </>= median (median based on total patients)

Table R.1.3.10.16: 1 KCCQ quality of life score change from baseline at week 52 (MMRM) by bl. NTproBNP (<median, >= median) (median based on total patients) - RS (OC-AD - no imputation for deaths) - 1245.121

Subgroup / Visit / Description / Statistic	Placebo	Empa 10mg
Baseline NTproBNP (<median, >= median): < median		
Number of patients in analysis set	920	942
Number of analysed patients	884	908
Baseline mean (SE)	63.57 (0.80)	64.76 (0.80)
Week 52		
Values at visit		
Number of analysed patients	651	666
Mean (SE)	70.43 (0.88)	72.23 (0.84)
Adjusted* mean (SE)	70.60 (0.73)	71.68 (0.72)
95% confidence interval	(69.17,72.02)	(70.27,73.08)
Change from baseline		
Mean (SE)	7.09 (0.80)	7.45 (0.83)
Adjusted* mean (SE)	6.43 (0.73)	7.51 (0.72)
95% confidence interval	(5.00, 7.86)	(6.10, 8.91)
Comparison vs Placebo		
Adjusted* mean (SE)		1.08 (1.02)
95% confidence interval		(-0.92, 3.08)
p-value		0.2918

* Model includes Age, baseline eGFR (CKD-EPI) as linear covariate(s) and region, baseline diabetes status, sex, baseline LVEF, week reachable, Visit by Treatment by baseline NTproBNP (<median, >= median) interaction, baseline KCCQ quality of life score by Visit interaction as fixed effect(s). The Visit by Treatment by baseline NTproBNP (<median, >= median) p-value at Week 52 is 0.9013.
The following covariance structure has been used to fit the mixed model: Unstructured
2 patients were excluded as the subgroup variable was missing.
Note: All covariate effects are set equal to their mean values within subgroup for the calculation of adjusted means.

For patients who died, only observed values are considered (no imputation after date of death).
Data taken from study 1245.121 only.
Median: 1910 [pg/mL]
The MMRM includes all outcome values (change from baseline) at the planned Visits week 12, week 32 and week 52

Table R.1.3.10.16: 1 KCCQ quality of life score change from baseline at week 52 (MMRM) by bl. NTproBNP (<median, >= median) (median based on total patients) - RS (OC-AD - no imputation for deaths) - 1245.121

Subgroup / Visit / Description / Statistic	Placebo	Empa 10mg
Baseline NTproBNP (<median, >= median): >= median		
Number of patients in analysis set	946	920
Number of analysed patients	869	868
Baseline mean (SE)	59.51 (0.81)	59.62 (0.86)
Week 52		
Values at visit		
Number of analysed patients	567	573
Mean (SE)	68.36 (0.97)	70.19 (0.97)
Adjusted* mean (SE)	67.78 (0.77)	69.04 (0.77)
95% confidence interval	(66.27,69.29)	(67.54,70.55)
Change from baseline		
Mean (SE)	7.59 (1.09)	9.10 (0.98)
Adjusted* mean (SE)	8.22 (0.77)	9.48 (0.77)
95% confidence interval	(6.71, 9.73)	(7.97,10.98)
Comparison vs Placebo		
Adjusted* mean (SE)		1.26 (1.09)
95% confidence interval		(-0.87, 3.39)
p-value		0.2461

* Model includes Age, baseline eGFR (CKD-EPI) as linear covariate(s) and region, baseline diabetes status, sex, baseline LVEF, week reachable, Visit by Treatment by baseline NTproBNP (<median, >= median) interaction, baseline KCCQ quality of life score by Visit interaction as fixed effect(s). The Visit by Treatment by baseline NTproBNP (<median, >= median) p-value at Week 52 is 0.9013.
The following covariance structure has been used to fit the mixed model: Unstructured
2 patients were excluded as the subgroup variable was missing.
Note: All covariate effects are set equal to their mean values within subgroup for the calculation of adjusted means.

For patients who died, only observed values are considered (no imputation after date of death).
Data taken from study 1245.121 only.
Median: 1910 [pg/mL]
The MMRM includes all outcome values (change from baseline) at the planned Visits week 12, week 32 and week 52

R.1.3.11

R.1.3.11 KCCQ social limitation score MMRM analysis

R.1.3.11.1

Table R.1.3.11.1: 1 KCCQ social limitation score change from baseline MMRM results over time - RS (OC-AD - no imputation for deaths) - 1245.121

Visit Description Statistic	Placebo	Empa 10mg
Number of patients in analysis set	1867	1863
Number of analysed patients	1672	1682
Baseline mean (SE)	66.25 (0.70)	65.83 (0.70)
Week 12		
Values at visit		
Number of analysed patients	1602	1603
Mean (SE)	71.12 (0.68)	72.01 (0.67)
Adjusted* mean (SE)	71.10 (0.52)	72.20 (0.52)
95% confidence interval	(70.08,72.11)	(71.18,73.21)
Change from baseline		
Mean (SE)	4.98 (0.61)	6.19 (0.58)
Adjusted* mean (SE)	4.84 (0.52)	5.94 (0.52)
95% confidence interval	(3.83, 5.86)	(4.93, 6.96)
Comparison vs Placebo		
Adjusted* mean (SE)		1.10 (0.73)
95% confidence interval		(-0.33, 2.53)
p-value		0.1322

* Model includes Age (p=0.1160), baseline eGFR (CKD-EPI) (p=0.0002) as linear covariate(s) and region (p<0.0001), baseline diabetes status (p=0.0597), sex (p=0.3416), baseline LVEF (p=0.1323), week reachable (p=0.1294), Treatment by Visit interaction (p<0.0001), baseline KCCQ social limitation score by Visit interaction (p<0.0001) as fixed effect(s).
The following covariance structure has been used to fit the mixed model: Unstructured

For patients who died, only observed values are considered (no imputation after date of death).
Data taken from study 1245.121 only.

Table R.1.3.11.1: 1 KCCQ social limitation score change from baseline MMRM results over time - RS (OC-AD - no imputation for deaths) - 1245.121

Visit Description Statistic	Placebo	Empa 10mg
Week 32		
Values at visit		
Number of analysed patients	1457	1470
Mean (SE)	72.38 (0.71)	73.01 (0.72)
Adjusted* mean (SE)	71.83 (0.58)	72.77 (0.58)
95% confidence interval	(70.70,72.96)	(71.64,73.90)
Change from baseline		
Mean (SE)	5.77 (0.69)	6.80 (0.67)
Adjusted* mean (SE)	5.58 (0.58)	6.51 (0.58)
95% confidence interval	(4.44, 6.71)	(5.39, 7.64)
Comparison vs Placebo		
Adjusted* mean (SE)		0.94 (0.81)
95% confidence interval		(-0.66, 2.53)
p-value		0.2484
Week 52		
Values at visit		
Number of analysed patients	1132	1126
Mean (SE)	72.36 (0.81)	73.14 (0.82)
Adjusted* mean (SE)	71.81 (0.65)	73.14 (0.65)
95% confidence interval	(70.53,73.08)	(71.87,74.41)
Change from baseline		
Mean (SE)	5.46 (0.83)	7.14 (0.76)
Adjusted* mean (SE)	5.55 (0.65)	6.88 (0.65)
95% confidence interval	(4.28, 6.82)	(5.61, 8.16)
Comparison vs Placebo		
Adjusted* mean (SE)		1.33 (0.92)
95% confidence interval		(-0.47, 3.13)
p-value		0.1469

* Model includes Age (p=0.1160), baseline eGFR (CKD-EPI) (p=0.0002) as linear covariate(s) and region (p<0.0001), baseline diabetes status (p=0.0597), sex (p=0.3416), baseline LVEF (p=0.1323), week reachable (p=0.1294), Treatment by Visit interaction (p<0.0001), baseline KCCQ social limitation score by Visit interaction (p<0.0001) as fixed effect(s).
The following covariance structure has been used to fit the mixed model: Unstructured

For patients who died, only observed values are considered (no imputation after date of death).
Data taken from study 1245.121 only.

Figure R.1.3.11.1: 1

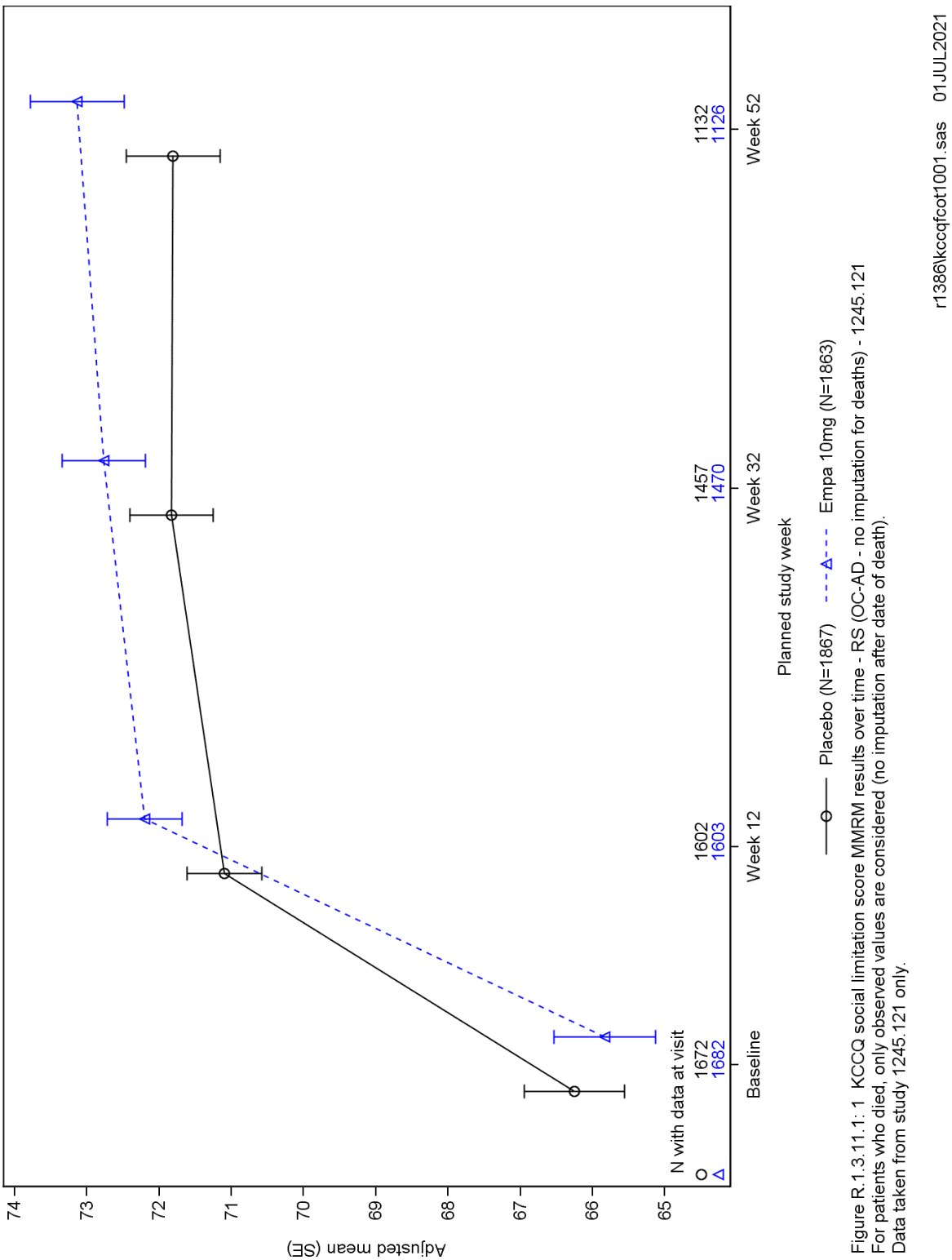

Figure R.1.3.11.1: 1 KCCQ social limitation score MMRM results over time - RS (OC-AD - no imputation for deaths) - 1245.121
For patients who died, only observed values are considered (no imputation after date of death).
Data taken from study 1245.121 only.

R.1.3.11.2

R.1.3.11.2 Subgroup analysis by sex

Table R.1.3.11.2: 1 KCCQ social limitation score change from baseline at week 52 (MMRM) by sex - RS (OC-AD - no imputation for deaths) - 1245.121

Subgroup / Visit / Description / Statistic	Placebo	Empa 10mg
Sex: Male		
Number of patients in analysis set	1411	1426
Number of analysed patients	1276	1294
Baseline mean (SE)	68.22 (0.78)	67.32 (0.79)
Week 52		
Values at visit		
Number of analysed patients	872	867
Mean (SE)	72.79 (0.93)	74.00 (0.93)
Adjusted* mean (SE)	72.08 (0.74)	74.07 (0.74)
95% confidence interval	(70.62,73.53)	(72.62,75.53)
Change from baseline		
Mean (SE)	3.90 (0.93)	6.58 (0.86)
Adjusted* mean (SE)	4.31 (0.74)	6.31 (0.74)
95% confidence interval	(2.86, 5.77)	(4.86, 7.76)
Comparison vs Placebo		
Adjusted* mean (SE)		2.00 (1.05)
95% confidence interval		(-0.06, 4.05)
p-value		0.0567

* Model includes Age, baseline eGFR (CKD-EPI) as linear covariate(s) and region, baseline diabetes status, baseline LVEF, week reachable, Visit by Treatment by sex interaction, baseline KCCQ social limitation score by Visit interaction as fixed effect(s).
The Visit by Treatment by sex p-value at Week 52 is 0.1910.
The following covariance structure has been used to fit the mixed model: Unstructured
Note: All covariate effects are set equal to their mean values within subgroup for the calculation of adjusted means.

For patients who died, only observed values are considered (no imputation after date of death).
Data taken from study 1245.121 only.
The MMRM includes all outcome values (change from baseline) at the planned Visits week 12, week 32 and week 52

Table R.1.3.11.2: 1 KCCQ social limitation score change from baseline at week 52 (MMRM) by sex - RS (OC-AD - no imputation for deaths) - 1245.121

Subgroup / Visit / Description / Statistic	Placebo	Empa 10mg
Sex: Female		
Number of patients in analysis set	456	437
Number of analysed patients	396	388
Baseline mean (SE)	59.93 (1.48)	60.89 (1.52)
Week 52		
Values at visit		
Number of analysed patients	260	259
Mean (SE)	70.94 (1.66)	70.26 (1.73)
Adjusted* mean (SE)	70.25 (1.35)	69.39 (1.36)
95% confidence interval	(67.60,72.91)	(66.74,72.05)
Change from baseline		
Mean (SE)	10.71 (1.77)	9.02 (1.62)
Adjusted* mean (SE)	9.85 (1.35)	8.99 (1.36)
95% confidence interval	(7.19,12.50)	(6.33,11.65)
Comparison vs Placebo		
Adjusted* mean (SE)		-0.86 (1.91)
95% confidence interval		(-4.61, 2.89)
p-value		0.6542

* Model includes Age, baseline eGFR (CKD-EPI) as linear covariate(s) and region, baseline diabetes status, baseline LVEF, week reachable, Visit by Treatment by sex interaction, baseline KCCQ social limitation score by Visit interaction as fixed effect(s).
The Visit by Treatment by sex p-value at Week 52 is 0.1910.
The following covariance structure has been used to fit the mixed model: Unstructured
Note: All covariate effects are set equal to their mean values within subgroup for the calculation of adjusted means.

For patients who died, only observed values are considered (no imputation after date of death).
Data taken from study 1245.121 only.
The MMRM includes all outcome values (change from baseline) at the planned Visits week 12, week 32 and week 52

R.1.3.11.3

Table R.1.3.11.3: 1 KCCQ social limitation score change from baseline at week 52 (MMRM) by age (2 cat.) - RS (OC-AD - no imputation for deaths) - 1245.121

Subgroup / Visit / Description / Statistic	Placebo	Empa 10mg
Age [years] (2 cat.): < 65		
Number of patients in analysis set	740	675
Number of analysed patients	671	628
Baseline mean (SE)	64.40 (1.12)	64.20 (1.19)
Week 52		
Values at visit		
Number of analysed patients	467	428
Mean (SE)	72.96 (1.23)	74.26 (1.33)
Adjusted* mean (SE)	72.14 (1.02)	73.70 (1.06)
95% confidence interval	(70.14,74.14)	(71.63,75.78)
Change from baseline		
Mean (SE)	8.16 (1.32)	10.34 (1.25)
Adjusted* mean (SE)	7.84 (1.02)	9.40 (1.06)
95% confidence interval	(5.84, 9.84)	(7.32,11.47)
Comparison vs Placebo		
Adjusted* mean (SE)		1.56 (1.46)
95% confidence interval		(-1.31, 4.43)
p-value		0.2861

* Model includes baseline eGFR (CKD-EPI) as linear covariate(s) and region, baseline diabetes status, sex, baseline LVEF, week reachable, Visit by Treatment by age [years] (2 cat.) interaction, baseline KCCQ social limitation score by Visit interaction as fixed effect(s).
The Visit by Treatment by age [years] (2 cat.) p-value at Week 52 is 0.8509.
The following covariance structure has been used to fit the mixed model: Unstructured
Note: All covariate effects are set equal to their mean values within subgroup for the calculation of adjusted means.

For patients who died, only observed values are considered (no imputation after date of death).
Data taken from study 1245.121 only.
The MMRM includes all outcome values (change from baseline) at the planned Visits week 12, week 32 and week 52

Table R.1.3.11.3: 1 KCCQ social limitation score change from baseline at week 52 (MMRM) by age (2 cat.) - RS (OC-AD - no imputation for deaths) - 1245.121

Subgroup / Visit / Description / Statistic	Placebo	Empa 10mg
Age [years] (2 cat.): >= 65		
Number of patients in analysis set	1127	1188
Number of analysed patients	1001	1054
Baseline mean (SE)	67.50 (0.89)	66.81 (0.87)
Week 52		
Values at visit		
Number of analysed patients	665	698
Mean (SE)	71.94 (1.07)	72.46 (1.04)
Adjusted* mean (SE)	71.33 (0.85)	72.54 (0.83)
95% confidence interval	(69.67,73.00)	(70.92,74.16)
Change from baseline		
Mean (SE)	3.57 (1.06)	5.18 (0.95)
Adjusted* mean (SE)	4.19 (0.85)	5.40 (0.83)
95% confidence interval	(2.52, 5.85)	(3.77, 7.02)
Comparison vs Placebo		
Adjusted* mean (SE)		1.21 (1.18)
95% confidence interval		(-1.11, 3.53)
p-value		0.3068

* Model includes baseline eGFR (CKD-EPI) as linear covariate(s) and region, baseline diabetes status, sex, baseline LVEF, week reachable, Visit by Treatment by age [years] (2 cat.) interaction, baseline KCCQ social limitation score by Visit interaction as fixed effect(s).
The Visit by Treatment by age [years] (2 cat.) p-value at Week 52 is 0.8509.
The following covariance structure has been used to fit the mixed model: Unstructured
Note: All covariate effects are set equal to their mean values within subgroup for the calculation of adjusted means.

For patients who died, only observed values are considered (no imputation after date of death).
Data taken from study 1245.121 only.
The MMRM includes all outcome values (change from baseline) at the planned Visits week 12, week 32 and week 52

R.1.3.11.4 Subgroup analysis by region (North America, Latin America, Europe, Asia, Other)

Table R.1.3.11.4: 1 KCCQ social limitation score change from baseline at week 52 (MMRM) by region - RS (OC-AD - no imputation for deaths) - 1245.121

Subgroup / Visit / Description / Statistic	Placebo	Empa 10mg
Region (5 cat.): North America		
Number of patients in analysis set	213	212
Number of analysed patients	188	201
Baseline mean (SE)	65.25 (2.13)	67.04 (2.14)
Week 52		
Values at visit		
Number of analysed patients	121	136
Mean (SE)	70.80 (2.58)	73.53 (2.34)
Adjusted* mean (SE)	70.46 (1.98)	72.09 (1.87)
95% confidence interval	(66.58,74.33)	(68.42,75.76)
Change from baseline		
Mean (SE)	6.10 (2.08)	5.13 (2.21)
Adjusted* mean (SE)	4.28 (1.98)	5.92 (1.87)
95% confidence interval	(0.41, 8.16)	(2.25, 9.59)
Comparison vs Placebo		
Adjusted* mean (SE)		1.63 (2.72)
95% confidence interval		(-3.71, 6.97)
p-value		0.5487

* Model includes Age, baseline eGFR (CKD-EPI) as linear covariate(s) and baseline diabetes status, sex, baseline LVEF, week reachable, Visit by Treatment by region (5 cat.) interaction, baseline KCCQ social limitation score by Visit interaction as fixed effect(s).
The Visit by Treatment by region (5 cat.) p-value at Week 52 is 0.9720.
The following covariance structure has been used to fit the mixed model: Unstructured
Note: All covariate effects are set equal to their mean values within subgroup for the calculation of adjusted means.

For patients who died, only observed values are considered (no imputation after date of death).
Data taken from study 1245.121 only.
The MMRM includes all outcome values (change from baseline) at the planned Visits week 12, week 32 and week 52

Table R.1.3.11.4: 1 KCCQ social limitation score change from baseline at week 52 (MMRM) by region - RS (OC-AD - no imputation for deaths) - 1245.121

Subgroup / Visit / Description / Statistic	Placebo	Empa 10mg
Region (5 cat.): Latin America		
Number of patients in analysis set	645	641
Number of analysed patients	562	556
Baseline mean (SE)	62.80 (1.27)	63.23 (1.29)
Week 52		
Values at visit		
Number of analysed patients	354	333
Mean (SE)	73.82 (1.49)	75.13 (1.51)
Adjusted* mean (SE)	73.80 (1.15)	75.67 (1.18)
95% confidence interval	(71.54,76.06)	(73.35,77.99)
Change from baseline		
Mean (SE)	11.75 (1.71)	13.15 (1.51)
Adjusted* mean (SE)	10.79 (1.15)	12.65 (1.18)
95% confidence interval	(8.53,13.05)	(10.33,14.97)
Comparison vs Placebo		
Adjusted* mean (SE)		1.86 (1.65)
95% confidence interval		(-1.37, 5.10)
p-value		0.2588

* Model includes Age, baseline eGFR (CKD-EPI) as linear covariate(s) and baseline diabetes status, sex, baseline LVEF, week reachable, Visit by Treatment by region (5 cat.) interaction, baseline KCCQ social limitation score by Visit interaction as fixed effect(s).
The Visit by Treatment by region (5 cat.) p-value at Week 52 is 0.9720.
The following covariance structure has been used to fit the mixed model: Unstructured
Note: All covariate effects are set equal to their mean values within subgroup for the calculation of adjusted means.

For patients who died, only observed values are considered (no imputation after date of death).
Data taken from study 1245.121 only.
The MMRM includes all outcome values (change from baseline) at the planned Visits week 12, week 32 and week 52

Table R.1.3.11.4: 1 KCCQ social limitation score change from baseline at week 52 (MMRM) by region - RS (OC-AD - no imputation for deaths) - 1245.121

Subgroup / Visit / Description / Statistic	Placebo	Empa 10mg
Region (5 cat.): Europe		
Number of patients in analysis set	677	676
Number of analysed patients	623	631
Baseline mean (SE)	64.56 (1.10)	64.55 (1.08)
Week 52		
Values at visit		
Number of analysed patients	445	446
Mean (SE)	67.79 (1.31)	67.87 (1.31)
Adjusted* mean (SE)	66.86 (1.04)	67.41 (1.04)
95% confidence interval	(64.82,68.90)	(65.38,69.45)
Change from baseline		
Mean (SE)	1.90 (1.24)	3.19 (1.17)
Adjusted* mean (SE)	2.30 (1.04)	2.86 (1.04)
95% confidence interval	(0.26, 4.34)	(0.82, 4.89)
Comparison vs Placebo		
Adjusted* mean (SE)		0.55 (1.47)
95% confidence interval		(-2.32, 3.43)
p-value		0.7056

* Model includes Age, baseline eGFR (CKD-EPI) as linear covariate(s) and baseline diabetes status, sex, baseline LVEF, week reachable, Visit by Treatment by region (5 cat.) interaction, baseline KCCQ social limitation score by Visit interaction as fixed effect(s).
The Visit by Treatment by region (5 cat.) p-value at Week 52 is 0.9720.
The following covariance structure has been used to fit the mixed model: Unstructured
Note: All covariate effects are set equal to their mean values within subgroup for the calculation of adjusted means.

For patients who died, only observed values are considered (no imputation after date of death).
Data taken from study 1245.121 only.
The MMRM includes all outcome values (change from baseline) at the planned Visits week 12, week 32 and week 52

Table R.1.3.11.4: 1 KCCQ social limitation score change from baseline at week 52 (MMRM) by region - RS (OC-AD - no imputation for deaths) - 1245.121

Subgroup / Visit / Description / Statistic	Placebo	Empa 10mg
Region (5 cat.): Asia		
Number of patients in analysis set	245	248
Number of analysed patients	222	218
Baseline mean (SE)	78.06 (1.53)	71.87 (1.92)
Week 52		
Values at visit		
Number of analysed patients	164	156
Mean (SE)	78.23 (1.77)	78.07 (2.12)
Adjusted* mean (SE)	76.98 (1.73)	78.79 (1.76)
95% confidence interval	(73.59,80.36)	(75.34,82.23)
Change from baseline		
Mean (SE)	-0.55 (1.87)	5.42 (1.70)
Adjusted* mean (SE)	1.99 (1.73)	3.80 (1.76)
95% confidence interval	(-1.40, 5.37)	(0.35, 7.24)
Comparison vs Placebo		
Adjusted* mean (SE)		1.81 (2.46)
95% confidence interval		(-3.02, 6.63)
p-value		0.4622

* Model includes Age, baseline eGFR (CKD-EPI) as linear covariate(s) and baseline diabetes status, sex, baseline LVEF, week reachable, Visit by Treatment by region (5 cat.) interaction, baseline KCCQ social limitation score by Visit interaction as fixed effect(s).
The Visit by Treatment by region (5 cat.) p-value at Week 52 is 0.9720.
The following covariance structure has been used to fit the mixed model: Unstructured
Note: All covariate effects are set equal to their mean values within subgroup for the calculation of adjusted means.

For patients who died, only observed values are considered (no imputation after date of death).
Data taken from study 1245.121 only.
The MMRM includes all outcome values (change from baseline) at the planned Visits week 12, week 32 and week 52

Table R.1.3.11.4: 1 KCCQ social limitation score change from baseline at week 52 (MMRM) by region - RS (OC-AD - no imputation for deaths) - 1245.121

Subgroup / Visit / Description / Statistic	Placebo	Empa 10mg
Region (5 cat.): Other		
Number of patients in analysis set	87	86
Number of analysed patients	77	76
Baseline mean (SE)	73.62 (3.21)	75.03 (2.87)
Week 52		
Values at visit		
Number of analysed patients	48	55
Mean (SE)	87.85 (2.72)	88.94 (2.37)
Adjusted* mean (SE)	85.23 (3.14)	87.78 (2.96)
95% confidence interval	(79.08,91.38)	(81.98,93.59)
Change from baseline		
Mean (SE)	11.07 (3.68)	12.65 (2.74)
Adjusted* mean (SE)	10.91 (3.14)	13.46 (2.96)
95% confidence interval	(4.76,17.06)	(7.66,19.27)
Comparison vs Placebo		
Adjusted* mean (SE)		2.55 (4.31)
95% confidence interval		(-5.90,11.00)
p-value		0.5534

* Model includes Age, baseline eGFR (CKD-EPI) as linear covariate(s) and baseline diabetes status, sex, baseline LVEF, week reachable, Visit by Treatment by region (5 cat.) interaction, baseline KCCQ social limitation score by Visit interaction as fixed effect(s).
The Visit by Treatment by region (5 cat.) p-value at Week 52 is 0.9720.
The following covariance structure has been used to fit the mixed model: Unstructured
Note: All covariate effects are set equal to their mean values within subgroup for the calculation of adjusted means.

For patients who died, only observed values are considered (no imputation after date of death).
Data taken from study 1245.121 only.
The MMRM includes all outcome values (change from baseline) at the planned Visits week 12, week 32 and week 52

R.1.3.11.5

Table R.1.3.11.5: 1 KCCQ social limitation score change from baseline at week 52 (MMRM) by OECD member (N/Y) - RS (OC-AD - no imputation for deaths) - 1245.121

Subgroup / Visit / Description / Statistic	Placebo	Empa 10mg
OECD member: No		
Number of patients in analysis set	741	713
Number of analysed patients	647	621
Baseline mean (SE)	64.09 (1.18)	65.16 (1.20)
Week 52		
Values at visit		
Number of analysed patients	408	381
Mean (SE)	75.36 (1.32)	76.88 (1.35)
Adjusted* mean (SE)	75.23 (1.08)	76.64 (1.11)
95% confidence interval	(73.11,77.34)	(74.46,78.82)
Change from baseline		
Mean (SE)	11.21 (1.53)	12.10 (1.34)
Adjusted* mean (SE)	10.61 (1.08)	12.03 (1.11)
95% confidence interval	(8.49,12.73)	(9.84,14.21)
Comparison vs Placebo		
Adjusted* mean (SE)		1.41 (1.55)
95% confidence interval		(-1.62, 4.45)
p-value		0.3617

* Model includes Age, baseline eGFR (CKD-EPI) as linear covariate(s) and baseline diabetes status, sex, baseline LVEF, week reachable, Visit by Treatment by OECD Member (N) interaction, baseline KCCQ social limitation score by Visit interaction as fixed effect(s).
The Visit by Treatment by OECD Member (N) p-value at Week 52 is 0.9796.
The following covariance structure has been used to fit the mixed model: Unstructured
Note: All covariate effects are set equal to their mean values within subgroup for the calculation of adjusted means.

For patients who died, only observed values are considered (no imputation after date of death).
Data taken from study 1245.121 only.
OECD member (yes/no) countries included:
Yes: United States, Canada, Mexico, Poland, Netherlands, Hungary, Germany, Czech Republic, Italy, France, Spain, United Kingdom, Belgium, Japan, Australia, 'Korea; Republic Of South Korea';
No: Brazil, Argentina, China, India.
The MMRM includes all outcome values (change from baseline) at the planned Visits week 12, week 32 and week 52

Table R.1.3.11.5: 1 KCCQ social limitation score change from baseline at week 52 (MMRM) by OECD member (N/Y) - RS (OC-AD - no imputation for deaths) - 1245.121

Subgroup / Visit / Description / Statistic	Placebo	Empa 10mg
OECD member: Yes		
Number of patients in analysis set	1126	1150
Number of analysed patients	1025	1061
Baseline mean (SE)	67.62 (0.86)	66.23 (0.86)
Week 52		
Values at visit		
Number of analysed patients	724	745
Mean (SE)	70.67 (1.02)	71.23 (1.02)
Adjusted* mean (SE)	69.55 (0.82)	71.02 (0.81)
95% confidence interval	(67.95,71.16)	(69.44,72.60)
Change from baseline		
Mean (SE)	2.22 (0.95)	4.61 (0.90)
Adjusted* mean (SE)	2.64 (0.82)	4.10 (0.81)
95% confidence interval	(1.04, 4.25)	(2.52, 5.69)
Comparison vs Placebo		
Adjusted* mean (SE)		1.46 (1.15)
95% confidence interval		(-0.79, 3.72)
p-value		0.2027

* Model includes Age, baseline eGFR (CKD-EPI) as linear covariate(s) and baseline diabetes status, sex, baseline LVEF, week reachable, Visit by Treatment by OECD Member (N) interaction, baseline KCCQ social limitation score by Visit interaction as fixed effect(s).
The Visit by Treatment by OECD Member (N) p-value at Week 52 is 0.9796.
The following covariance structure has been used to fit the mixed model: Unstructured
Note: All covariate effects are set equal to their mean values within subgroup for the calculation of adjusted means.

For patients who died, only observed values are considered (no imputation after date of death).
Data taken from study 1245.121 only.
OECD member (yes/no) countries included:
Yes: United States, Canada, Mexico, Poland, Netherlands, Hungary, Germany, Czech Republic, Italy, France, Spain, United Kingdom, Belgium, Japan, Australia, 'Korea; Republic Of South Korea';
No: Brazil, Argentina, China, India.
The MMRM includes all outcome values (change from baseline) at the planned Visits week 12, week 32 and week 52

R.1.3.11.6

R.1.3.11.6 Subgroup analysis by NYHA at baseline (II, III/IV - 2 cat.)

Table R.1.3.11.6: 1 KCCQ social limitation score change from baseline at week 52 (MMRM) by NYHA (2 cat.) - RS (OC-AD - no imputation for deaths) - 1245.121

Subgroup / Visit / Description / Statistic	Placebo	Empa 10mg
Baseline NYHA (2 cat.): II		
Number of patients in analysis set	1401	1399
Number of analysed patients	1279	1263
Baseline mean (SE)	70.34 (0.74)	71.71 (0.75)
Week 52		
Values at visit		
Number of analysed patients	874	857
Mean (SE)	74.47 (0.89)	77.62 (0.86)
Adjusted* mean (SE)	74.64 (0.74)	77.36 (0.74)
95% confidence interval	(73.20,76.09)	(75.90,78.81)
Change from baseline		
Mean (SE)	4.15 (0.91)	6.45 (0.85)
Adjusted* mean (SE)	3.62 (0.74)	6.34 (0.74)
95% confidence interval	(2.18, 5.07)	(4.88, 7.79)
Comparison vs Placebo		
Adjusted* mean (SE)		2.71 (1.05)
95% confidence interval		(0.66, 4.77)
p-value		0.0095

* Model includes Age, baseline eGFR (CKD-EPI) as linear covariate(s) and region, baseline diabetes status, sex, baseline LVEF, week reachable, Visit by Treatment by baseline NYHA (2 cat.) interaction, baseline KCCQ social limitation score by Visit interaction as fixed effect(s).
The Visit by Treatment by baseline NYHA (2 cat.) p-value at Week 52 is 0.0079.
The following covariance structure has been used to fit the mixed model: Unstructured
Note: All covariate effects are set equal to their mean values within subgroup for the calculation of adjusted means.

For patients who died, only observed values are considered (no imputation after date of death).
Data taken from study 1245.121 only.
The MMRM includes all outcome values (change from baseline) at the planned Visits week 12, week 32 and week 52

Table R.1.3.11.6: 1 KCCQ social limitation score change from baseline at week 52 (MMRM) by NYHA (2 cat.) - RS (OC-AD - no imputation for deaths) - 1245.121

Subgroup / Visit / Description / Statistic	Placebo	Empa 10mg
Baseline NYHA (2 cat.): III/IV		
Number of patients in analysis set	466	464
Number of analysed patients	393	419
Baseline mean (SE)	52.97 (1.53)	48.11 (1.39)
Week 52		
Values at visit		
Number of analysed patients	258	269
Mean (SE)	65.23 (1.81)	58.87 (1.80)
Adjusted* mean (SE)	62.33 (1.36)	59.29 (1.32)
95% confidence interval	(59.67,64.98)	(56.69,61.88)
Change from baseline		
Mean (SE)	9.92 (1.89)	9.36 (1.64)
Adjusted* mean (SE)	11.86 (1.36)	8.82 (1.32)
95% confidence interval	(9.21,14.52)	(6.23,11.42)
Comparison vs Placebo		
Adjusted* mean (SE)		-3.04 (1.89)
95% confidence interval		(-6.75, 0.67)
p-value		0.1083

* Model includes Age, baseline eGFR (CKD-EPI) as linear covariate(s) and region, baseline diabetes status, sex, baseline LVEF, week reachable, Visit by Treatment by baseline NYHA (2 cat.) interaction, baseline KCCQ social limitation score by Visit interaction as fixed effect(s).
The Visit by Treatment by baseline NYHA (2 cat.) p-value at Week 52 is 0.0079.
The following covariance structure has been used to fit the mixed model: Unstructured
Note: All covariate effects are set equal to their mean values within subgroup for the calculation of adjusted means.

For patients who died, only observed values are considered (no imputation after date of death).
Data taken from study 1245.121 only.
The MMRM includes all outcome values (change from baseline) at the planned Visits week 12, week 32 and week 52

R.1.3.11.7

Table R.1.3.11.7: 1 KCCQ social limitation score change from baseline at week 52 (MMRM) by diabetes at baseline - RS (OC-AD - no imputation for deaths) - 1245.121

Subgroup / Visit / Description / Statistic	Placebo	Empa 10mg
Diabetes at baseline (2 cat.):		
Diabetic		
Number of patients in analysis set	929	927
Number of analysed patients	827	839
Baseline mean (SE)	65.69 (1.00)	64.45 (1.02)
Week 52		
Values at visit		
Number of analysed patients	562	563
Mean (SE)	72.28 (1.14)	71.35 (1.22)
Adjusted* mean (SE)	70.90 (0.92)	70.88 (0.92)
95% confidence interval	(69.09,72.70)	(69.08,72.68)
Change from baseline		
Mean (SE)	5.62 (1.18)	6.06 (1.10)
Adjusted* mean (SE)	5.83 (0.92)	5.81 (0.92)
95% confidence interval	(4.02, 7.63)	(4.01, 7.61)
Comparison vs Placebo		
Adjusted* mean (SE)		-0.01 (1.30)
95% confidence interval		(-2.57, 2.54)
p-value		0.9909

* Model includes Age, baseline eGFR (CKD-EPI) as linear covariate(s) and region, sex, baseline LVEF, week reachable, Visit by Treatment by diabetes at baseline (2 cat.) interaction, baseline KCCQ social limitation score by Visit interaction as fixed effect(s).
The Visit by Treatment by diabetes at baseline (2 cat.) p-value at Week 52 is 0.1406.
The following covariance structure has been used to fit the mixed model: Unstructured
Note: All covariate effects are set equal to their mean values within subgroup for the calculation of adjusted means.

For patients who died, only observed values are considered (no imputation after date of death).
Data taken from study 1245.121 only.
The MMRM includes all outcome values (change from baseline) at the planned Visits week 12, week 32 and week 52

Table R.1.3.11.7: 1 KCCQ social limitation score change from baseline at week 52 (MMRM) by diabetes at baseline - RS (OC-AD - no imputation for deaths) - 1245.121

Subgroup / Visit / Description / Statistic	Placebo	Empa 10mg
Diabetes at baseline (2 cat.):		
Non-Diabetic		
Number of patients in analysis set	938	936
Number of analysed patients	845	843
Baseline mean (SE)	66.80 (0.97)	67.21 (0.97)
Week 52		
Values at visit		
Number of analysed patients	570	563
Mean (SE)	72.44 (1.15)	74.94 (1.09)
Adjusted* mean (SE)	72.39 (0.91)	75.08 (0.92)
95% confidence interval	(70.60,74.18)	(73.28,76.88)
Change from baseline		
Mean (SE)	5.31 (1.17)	8.23 (1.04)
Adjusted* mean (SE)	5.38 (0.91)	8.07 (0.92)
95% confidence interval	(3.59, 7.18)	(6.27, 9.88)
Comparison vs Placebo		
Adjusted* mean (SE)		2.69 (1.30)
95% confidence interval		(0.15, 5.23)
p-value		0.0379

* Model includes Age, baseline eGFR (CKD-EPI) as linear covariate(s) and region, sex, baseline LVEF, week reachable, Visit by Treatment by diabetes at baseline (2 cat.) interaction, baseline KCCQ social limitation score by Visit interaction as fixed effect(s).
The Visit by Treatment by diabetes at baseline (2 cat.) p-value at Week 52 is 0.1406.
The following covariance structure has been used to fit the mixed model: Unstructured
Note: All covariate effects are set equal to their mean values within subgroup for the calculation of adjusted means.

For patients who died, only observed values are considered (no imputation after date of death).
Data taken from study 1245.121 only.
The MMRM includes all outcome values (change from baseline) at the planned Visits week 12, week 32 and week 52

R.1.3.11.8

R.1.3.11.8 Subgroup analysis by BMI at baseline (<30, >=30)

Table R.1.3.11.8: 1 KCCQ social limitation score change from baseline at week 52 (MMRM) by baseline BMI [kg/m2] - RS (OC-AD - no imputation for deaths) - 1245.121

Subgroup / Visit / Description / Statistic	Placebo	Empa 10mg
Baseline BMI [kg/m²] (2 cat.): <30		
Number of patients in analysis set	1300	1263
Number of analysed patients	1167	1128
Baseline mean (SE)	67.72 (0.83)	67.52 (0.85)
Week 52		
Values at visit		
Number of analysed patients	800	747
Mean (SE)	73.34 (0.94)	75.10 (0.98)
Adjusted* mean (SE)	72.42 (0.78)	74.24 (0.80)
95% confidence interval	(70.90,73.94)	(72.67,75.81)
Change from baseline		
Mean (SE)	4.72 (0.97)	6.84 (0.89)
Adjusted* mean (SE)	4.80 (0.78)	6.62 (0.80)
95% confidence interval	(3.28, 6.32)	(5.05, 8.19)
Comparison vs Placebo		
Adjusted* mean (SE)		1.82 (1.11)
95% confidence interval		(-0.36, 4.00)
p-value		0.1014

* Model includes Age, baseline eGFR (CKD-EPI) as linear covariate(s) and region, baseline diabetes status, sex, baseline LVEF, week reachable, Visit by Treatment by baseline BMI [kg/m²] (2 cat.) interaction, baseline KCCQ social limitation score by Visit interaction as fixed effect(s).
The Visit by Treatment by baseline BMI [kg/m²] (2 cat.) p-value at Week 52 is 0.4614.
The following covariance structure has been used to fit the mixed model: Unstructured
Note: All covariate effects are set equal to their mean values within subgroup for the calculation of adjusted means.

For patients who died, only observed values are considered (no imputation after date of death).
Data taken from study 1245.121 only.
The MMRM includes all outcome values (change from baseline) at the planned Visits week 12, week 32 and week 52

Table R.1.3.11.8: 1 KCCQ social limitation score change from baseline at week 52 (MMRM) by baseline BMI [kg/m2] - RS (OC-AD - no imputation for deaths) - 1245.121

Subgroup / Visit / Description / Statistic	Placebo	Empa 10mg
Baseline BMI [kg/m²] (2 cat.): >=30		
Number of patients in analysis set	567	600
Number of analysed patients	505	554
Baseline mean (SE)	62.86 (1.28)	62.41 (1.24)
Week 52		
Values at visit		
Number of analysed patients	332	379
Mean (SE)	70.00 (1.56)	69.28 (1.45)
Adjusted* mean (SE)	69.98 (1.20)	70.34 (1.13)
95% confidence interval	(67.62,72.34)	(68.12,72.56)
Change from baseline		
Mean (SE)	7.26 (1.60)	7.75 (1.40)
Adjusted* mean (SE)	7.36 (1.20)	7.72 (1.13)
95% confidence interval	(5.00, 9.72)	(5.50, 9.93)
Comparison vs Placebo		
Adjusted* mean (SE)		0.36 (1.64)
95% confidence interval		(-2.86, 3.58)
p-value		0.8263

* Model includes Age, baseline eGFR (CKD-EPI) as linear covariate(s) and region, baseline diabetes status, sex, baseline LVEF, week reachable, Visit by Treatment by baseline BMI [kg/m²] (2 cat.) interaction, baseline KCCQ social limitation score by Visit interaction as fixed effect(s).
The Visit by Treatment by baseline BMI [kg/m²] (2 cat.) p-value at Week 52 is 0.4614.
The following covariance structure has been used to fit the mixed model: Unstructured
Note: All covariate effects are set equal to their mean values within subgroup for the calculation of adjusted means.

For patients who died, only observed values are considered (no imputation after date of death).
Data taken from study 1245.121 only.
The MMRM includes all outcome values (change from baseline) at the planned Visits week 12, week 32 and week 52

R.1.3.11.9

R.1.3.11.9 Subgroup analysis by eGFR at baseline (<60, >=60)

Table R.1.3.11.9: 1 KCCQ social limitation score change from baseline at week 52 (MMRM) by baseline eGFR (2 cat.) - RS (OC-AD - no imputation for deaths) - 1245.121

Subgroup / Visit / Description / Statistic	Placebo	Empa 10mg
Baseline eGFR (CKD-EPI) [mL/min/1.73m²] (2 cat.): >=60		
Number of patients in analysis set	960	969
Number of analysed patients	867	881
Baseline mean (SE)	66.79 (0.96)	67.24 (0.97)
Week 52		
Values at visit		
Number of analysed patients	608	603
Mean (SE)	73.02 (1.08)	76.00 (1.08)
Adjusted* mean (SE)	72.63 (0.89)	75.19 (0.89)
95% confidence interval	(70.88,74.38)	(73.45,76.94)
Change from baseline		
Mean (SE)	6.01 (1.14)	8.24 (1.05)
Adjusted* mean (SE)	5.61 (0.89)	8.17 (0.89)
95% confidence interval	(3.86, 7.36)	(6.43, 9.92)
Comparison vs Placebo		
Adjusted* mean (SE)		2.56 (1.26)
95% confidence interval		(0.10, 5.03)
p-value		0.0418

* Model includes Age as linear covariate(s) and region, baseline diabetes status, sex, baseline LVEF, week reachable, Visit by Treatment by baseline eGFR (CKD-EPI) [mL/min/1.73m²] (2 cat.) interaction, baseline KCCQ social limitation score by Visit interaction as fixed effect(s).
The Visit by Treatment by baseline eGFR (CKD-EPI) [mL/min/1.73m²] (2 cat.) p-value at Week 52 is 0.1456.
The following covariance structure has been used to fit the mixed model: Unstructured
2 patients were excluded as the subgroup variable was missing.
Note: All covariate effects are set equal to their mean values within subgroup for the calculation of adjusted means.

For patients who died, only observed values are considered (no imputation after date of death).
Data taken from study 1245.121 only.
The MMRM includes all outcome values (change from baseline) at the planned Visits week 12, week 32 and week 52

Table R.1.3.11.9: 1 KCCQ social limitation score change from baseline at week 52 (MMRM) by baseline eGFR (2 cat.) - RS (OC-AD - no imputation for deaths) - 1245.121

Subgroup / Visit / Description / Statistic	Placebo	Empa 10mg
Baseline eGFR (CKD-EPI) [mL/min/1.73m²] (2 cat.): <60		
Number of patients in analysis set	906	893
Number of analysed patients	805	801
Baseline mean (SE)	65.68 (1.02)	64.28 (1.02)
Week 52		
Values at visit		
Number of analysed patients	524	523
Mean (SE)	71.60 (1.22)	69.85 (1.23)
Adjusted* mean (SE)	70.67 (0.95)	70.55 (0.95)
95% confidence interval	(68.80,72.54)	(68.67,72.42)
Change from baseline		
Mean (SE)	4.83 (1.22)	5.88 (1.10)
Adjusted* mean (SE)	5.69 (0.95)	5.57 (0.95)
95% confidence interval	(3.82, 7.56)	(3.69, 7.44)
Comparison vs Placebo		
Adjusted* mean (SE)		-0.12 (1.35)
95% confidence interval		(-2.76, 2.52)
p-value		0.9286

* Model includes Age as linear covariate(s) and region, baseline diabetes status, sex, baseline LVEF, week reachable, Visit by Treatment by baseline eGFR (CKD-EPI) [mL/min/1.73m²] (2 cat.) interaction, baseline KCCQ social limitation score by Visit interaction as fixed effect(s).
The Visit by Treatment by baseline eGFR (CKD-EPI) [mL/min/1.73m²] (2 cat.) p-value at Week 52 is 0.1456.
The following covariance structure has been used to fit the mixed model: Unstructured
2 patients were excluded as the subgroup variable was missing.
Note: All covariate effects are set equal to their mean values within subgroup for the calculation of adjusted means.

For patients who died, only observed values are considered (no imputation after date of death).
Data taken from study 1245.121 only.
The MMRM includes all outcome values (change from baseline) at the planned Visits week 12, week 32 and week 52

R.1.3.11.10

Table R.1.3.11.10: 1 KCCQ social limitation score change from baseline at week 52 (MMRM) by history of HHF - RS (OC-AD - no imputation for deaths) - 1245.121

Subgroup / Visit / Description / Statistic	Placebo	Empa 10mg
History of HHF (in the last 12 months): No		
Number of patients in analysis set	1293	1286
Number of analysed patients	1166	1169
Baseline mean (SE)	67.59 (0.82)	67.04 (0.83)
Week 52		
Values at visit		
Number of analysed patients	810	794
Mean (SE)	72.05 (0.98)	73.75 (0.96)
Adjusted* mean (SE)	71.88 (0.77)	74.00 (0.78)
95% confidence interval	(70.37,73.39)	(72.48,75.53)
Change from baseline		
Mean (SE)	4.79 (0.97)	7.07 (0.90)
Adjusted* mean (SE)	4.56 (0.77)	6.68 (0.78)
95% confidence interval	(3.05, 6.07)	(5.16, 8.21)
Comparison vs Placebo		
Adjusted* mean (SE)		2.12 (1.09)
95% confidence interval		(-0.02, 4.26)
p-value		0.0522

* Model includes Age, baseline eGFR (CKD-EPI) as linear covariate(s) and region, baseline diabetes status, sex, baseline LVEF, week reachable, Visit by Treatment by history of HHF (in the last 12 months) interaction, baseline KCCQ social limitation score by Visit interaction as fixed effect(s).
The Visit by Treatment by history of HHF (in the last 12 months) p-value at Week 52 is 0.1719.
The following covariance structure has been used to fit the mixed model: Unstructured
Note: All covariate effects are set equal to their mean values within subgroup for the calculation of adjusted means.

For patients who died, only observed values are considered (no imputation after date of death).
Data taken from study 1245.121 only.
The MMRM includes all outcome values (change from baseline) at the planned Visits week 12, week 32 and week 52

Table R.1.3.11.10: 1 KCCQ social limitation score change from baseline at week 52 (MMRM) by history of HHF - RS (OC-AD - no imputation for deaths) - 1245.121

Subgroup / Visit / Description / Statistic	Placebo	Empa 10mg
History of HHF (in the last 12 months): Yes		
Number of patients in analysis set	574	577
Number of analysed patients	506	513
Baseline mean (SE)	63.17 (1.29)	63.08 (1.33)
Week 52		
Values at visit		
Number of analysed patients	322	332
Mean (SE)	73.15 (1.44)	71.68 (1.56)
Adjusted* mean (SE)	71.24 (1.21)	70.60 (1.20)
95% confidence interval	(68.86,73.62)	(68.25,72.95)
Change from baseline		
Mean (SE)	7.16 (1.59)	7.31 (1.41)
Adjusted* mean (SE)	8.12 (1.21)	7.48 (1.20)
95% confidence interval	(5.74,10.50)	(5.13, 9.83)
Comparison vs Placebo		
Adjusted* mean (SE)		-0.64 (1.70)
95% confidence interval		(-3.97, 2.69)
p-value		0.7066

* Model includes Age, baseline eGFR (CKD-EPI) as linear covariate(s) and region, baseline diabetes status, sex, baseline LVEF, week reachable, Visit by Treatment by history of HHF (in the last 12 months) interaction, baseline KCCQ social limitation score by Visit interaction as fixed effect(s).
The Visit by Treatment by history of HHF (in the last 12 months) p-value at Week 52 is 0.1719.
The following covariance structure has been used to fit the mixed model: Unstructured
Note: All covariate effects are set equal to their mean values within subgroup for the calculation of adjusted means.

For patients who died, only observed values are considered (no imputation after date of death).
Data taken from study 1245.121 only.
The MMRM includes all outcome values (change from baseline) at the planned Visits week 12, week 32 and week 52

R.1.3.11.11

R.1.3.11.11 Subgroup analysis by cause of heart failure

Table R.1.3.11.11: 1 KCCQ social limitation score change from baseline at week 52 (MMRM) by cause of heart failure - RS (OC-AD - no imputation for deaths) - 1245.121

Subgroup / Visit / Description / Statistic	Placebo	Empa 10mg
Cause of heart failure: Ischemic		
Number of patients in analysis set	946	983
Number of analysed patients	849	890
Baseline mean (SE)	66.67 (0.97)	65.15 (0.96)
Week 52		
Values at visit		
Number of analysed patients	588	602
Mean (SE)	71.84 (1.13)	71.58 (1.14)
Adjusted* mean (SE)	71.04 (0.91)	71.73 (0.89)
95% confidence interval	(69.26,72.82)	(69.98,73.48)
Change from baseline		
Mean (SE)	3.64 (1.11)	5.80 (1.02)
Adjusted* mean (SE)	5.15 (0.91)	5.84 (0.89)
95% confidence interval	(3.36, 6.93)	(4.09, 7.59)
Comparison vs Placebo		
Adjusted* mean (SE)		0.69 (1.27)
95% confidence interval		(-1.79, 3.18)
p-value		0.5845

* Model includes Age, baseline eGFR (CKD-EPI) as linear covariate(s) and region, baseline diabetes status, sex, baseline LVEF, week reachable, Visit by Treatment by cause of heart failure interaction, baseline KCCQ social limitation score by Visit interaction as fixed effect(s).
The Visit by Treatment by cause of heart failure p-value at Week 52 is 0.4580.
The following covariance structure has been used to fit the mixed model: Unstructured
Note: All covariate effects are set equal to their mean values within subgroup for the calculation of adjusted means.

For patients who died, only observed values are considered (no imputation after date of death).
Data taken from study 1245.121 only.
The MMRM includes all outcome values (change from baseline) at the planned Visits week 12, week 32 and week 52

Table R.1.3.11.11: 1 KCCQ social limitation score change from baseline at week 52 (MMRM) by cause of heart failure - RS (OC-AD - no imputation for deaths) - 1245.121

Subgroup / Visit / Description / Statistic	Placebo	Empa 10mg
Cause of heart failure: Non-ischemic		
Number of patients in analysis set	921	880
Number of analysed patients	823	792
Baseline mean (SE)	65.83 (1.00)	66.60 (1.03)
Week 52		
Values at visit		
Number of analysed patients	544	524
Mean (SE)	72.93 (1.16)	74.93 (1.17)
Adjusted* mean (SE)	72.32 (0.94)	74.38 (0.95)
95% confidence interval	(70.47,74.16)	(72.50,76.25)
Change from baseline		
Mean (SE)	7.43 (1.23)	8.69 (1.13)
Adjusted* mean (SE)	6.11 (0.94)	8.17 (0.95)
95% confidence interval	(4.26, 7.96)	(6.30,10.04)
Comparison vs Placebo		
Adjusted* mean (SE)		2.06 (1.33)
95% confidence interval		(-0.56, 4.68)
p-value		0.1226

* Model includes Age, baseline eGFR (CKD-EPI) as linear covariate(s) and region, baseline diabetes status, sex, baseline LVEF, week reachable, Visit by Treatment by cause of heart failure interaction, baseline KCCQ social limitation score by Visit interaction as fixed effect(s).
The Visit by Treatment by cause of heart failure p-value at Week 52 is 0.4580.
The following covariance structure has been used to fit the mixed model: Unstructured
Note: All covariate effects are set equal to their mean values within subgroup for the calculation of adjusted means.

For patients who died, only observed values are considered (no imputation after date of death).
Data taken from study 1245.121 only.
The MMRM includes all outcome values (change from baseline) at the planned Visits week 12, week 32 and week 52

R.1.3.11.12 Subgroup analysis by heart failure physiology (LVEF <= 30% and NTproBNP<median; LVEF <= 30% and NTproBNP>=median; LVEF > 30%)

Table R.1.3.11.12: 1 KCCQ social limitation score change from baseline at week 52 (MMRM) by heart failure physiology - RS (OC-AD - no imputation for deaths) - 1245.121

Subgroup Visit Description Statistic	Placebo	Empa 10mg
Heart failure physiology: LVEF <= 30% and NTproBNP < median		
Number of patients in analysis set	723	698
Number of analysed patients	669	647
Baseline mean (SE)	67.16 (1.07)	68.21 (1.07)
Week 52		
Values at visit		
Number of analysed patients	485	453
Mean (SE)	73.96 (1.18)	75.01 (1.21)
Adjusted* mean (SE)	74.05 (1.00)	75.26 (1.03)
95% confidence interval	(72.09,76.00)	(73.24,77.27)
Change from baseline		
Mean (SE)	7.32 (1.15)	7.29 (1.16)
Adjusted* mean (SE)	6.38 (1.00)	7.59 (1.03)
95% confidence interval	(4.42, 8.33)	(5.57, 9.60)
Comparison vs Placebo		
Adjusted* mean (SE)		1.21 (1.43)
95% confidence interval		(-1.60, 4.02)
p-value		0.3978

* Model includes Age, baseline eGFR (CKD-EPI) as linear covariate(s) and region, baseline diabetes status, sex, week reachable, Visit by Treatment by heart failure physiology interaction, baseline KCCQ social limitation score by Visit interaction as fixed effect(s).
The Visit by Treatment by heart failure physiology p-value at Week 52 is 0.7327.
The following covariance structure has been used to fit the mixed model: Unstructured
16 patients were excluded as the subgroup variable was missing.
Note: All covariate effects are set equal to their mean values within subgroup for the calculation of adjusted means.
The p-value for the visit by treatment by subgroup interaction trend test at Week 52 is 0.8963

For patients who died, only observed values are considered (no imputation after date of death).
Data taken from study 1245.121 only.
NTproBNP median [pg/mL]: with a. fibrillation/flutter at baseline: 2265; without a. fibrillation/flutter at baseline: 1671.
The MMRM includes all outcome values (change from baseline) at the planned Visits week 12, week 32 and week 52

Table R.1.3.11.12: 1 KCCQ social limitation score change from baseline at week 52 (MMRM) by heart failure physiology - RS (OC-AD - no imputation for deaths) - 1245.121

Subgroup / Visit / Description / Statistic	Placebo	Empa 10mg
Heart failure physiology: LVEF <= 30% and NTproBNP >= median		
Number of patients in analysis set	661	631
Number of analysed patients	578	561
Baseline mean (SE)	63.75 (1.22)	62.44 (1.26)
Week 52		
Values at visit		
Number of analysed patients	384	367
Mean (SE)	69.24 (1.48)	69.90 (1.53)
Adjusted* mean (SE)	67.69 (1.11)	70.04 (1.14)
95% confidence interval	(65.51,69.88)	(67.82,72.27)
Change from baseline		
Mean (SE)	3.04 (1.59)	7.85 (1.40)
Adjusted* mean (SE)	4.59 (1.11)	6.94 (1.14)
95% confidence interval	(2.40, 6.77)	(4.71, 9.17)
Comparison vs Placebo		
Adjusted* mean (SE)		2.35 (1.59)
95% confidence interval		(-0.77, 5.47)
p-value		0.1395

* Model includes Age, baseline eGFR (CKD-EPI) as linear covariate(s) and region, baseline diabetes status, sex, week reachable, Visit by Treatment by heart failure physiology interaction, baseline KCCQ social limitation score by Visit interaction as fixed effect(s).
The Visit by Treatment by heart failure physiology p-value at Week 52 is 0.7327.
The following covariance structure has been used to fit the mixed model: Unstructured
16 patients were excluded as the subgroup variable was missing.
Note: All covariate effects are set equal to their mean values within subgroup for the calculation of adjusted means.
The p-value for the visit by treatment by subgroup interaction trend test at Week 52 is 0.8963

For patients who died, only observed values are considered (no imputation after date of death).
Data taken from study 1245.121 only.
NTproBNP median [pg/mL]: with a. fibrillation/flutter at baseline: 2265; without a. fibrillation/flutter at baseline: 1671.
The MMRM includes all outcome values (change from baseline) at the planned Visits week 12, week 32 and week 52

Table R.1.3.11.12: 1 KCCQ social limitation score change from baseline at week 52 (MMRM) by heart failure physiology - RS (OC-AD - no imputation for deaths) - 1245.121

Subgroup / Visit / Description / Statistic	Placebo	Empa 10mg
Heart failure physiology: LVEF > 30%		
Number of patients in analysis set	475	526
Number of analysed patients	420	469
Baseline mean (SE)	68.59 (1.39)	66.64 (1.36)
Week 52		
Values at visit		
Number of analysed patients	259	305
Mean (SE)	74.14 (1.65)	74.24 (1.57)
Adjusted* mean (SE)	73.10 (1.35)	73.59 (1.24)
95% confidence interval	(70.46,75.74)	(71.15,76.03)
Change from baseline		
Mean (SE)	5.24 (1.71)	6.11 (1.43)
Adjusted* mean (SE)	5.54 (1.35)	6.03 (1.24)
95% confidence interval	(2.90, 8.18)	(3.59, 8.47)
Comparison vs Placebo		
Adjusted* mean (SE)		0.49 (1.83)
95% confidence interval		(-3.10, 4.08)
p-value		0.7888

* Model includes Age, baseline eGFR (CKD-EPI) as linear covariate(s) and region, baseline diabetes status, sex, week reachable, Visit by Treatment by heart failure physiology interaction, baseline KCCQ social limitation score by Visit interaction as fixed effect(s).
The Visit by Treatment by heart failure physiology p-value at Week 52 is 0.7327.
The following covariance structure has been used to fit the mixed model: Unstructured
16 patients were excluded as the subgroup variable was missing.
Note: All covariate effects are set equal to their mean values within subgroup for the calculation of adjusted means.
The p-value for the visit by treatment by subgroup interaction trend test at Week 52 is 0.8963

For patients who died, only observed values are considered (no imputation after date of death).
Data taken from study 1245.121 only.
NTproBNP median [pg/mL]: with a. fibrillation/flutter at baseline: 2265; without a. fibrillation/flutter at baseline: 1671.
The MMRM includes all outcome values (change from baseline) at the planned Visits week 12, week 32 and week 52

R.1.3.11.13

R.1.3.11.13 Subgroup analysis by baseline use of MRA

Table R.1.3.11.13: 1 KCCQ social limitation score change from baseline at week 52 (MMRM) by baseline use of MRA (Y/N) - RS (OC-AD - no imputation for deaths) - 1245.121

Subgroup / Visit / Description / Statistic	Placebo	Empa 10mg
Baseline use of MRA: No		
Number of patients in analysis set	512	557
Number of analysed patients	466	496
Baseline mean (SE)	68.74 (1.31)	67.04 (1.27)
Week 52		
Values at visit		
Number of analysed patients	315	339
Mean (SE)	70.26 (1.60)	74.77 (1.49)
Adjusted* mean (SE)	71.07 (1.23)	74.15 (1.19)
95% confidence interval	(68.65,73.48)	(71.81,76.49)
Change from baseline		
Mean (SE)	2.60 (1.60)	6.46 (1.33)
Adjusted* mean (SE)	3.21 (1.23)	6.29 (1.19)
95% confidence interval	(0.79, 5.62)	(3.95, 8.63)
Comparison vs Placebo		
Adjusted* mean (SE)		3.09 (1.71)
95% confidence interval		(-0.26, 6.44)
p-value		0.0710

* Model includes Age, baseline eGFR (CKD-EPI) as linear covariate(s) and region, baseline diabetes status, sex, baseline LVEF, week reachable, Visit by Treatment by baseline use of MRA interaction, baseline KCCQ social limitation score by Visit interaction as fixed effect(s).
The Visit by Treatment by baseline use of MRA p-value at Week 52 is 0.2239.
The following covariance structure has been used to fit the mixed model: Unstructured
Note: All covariate effects are set equal to their mean values within subgroup for the calculation of adjusted means.

For patients who died, only observed values are considered (no imputation after date of death).
Data taken from study 1245.121 only.
The MMRM includes all outcome values (change from baseline) at the planned Visits week 12, week 32 and week 52

Table R.1.3.11.13: 1 KCCQ social limitation score change from baseline at week 52 (MMRM) by baseline use of MRA (Y/N) - RS (OC-AD - no imputation for deaths) - 1245.121

Subgroup / Visit / Description / Statistic	Placebo	Empa 10mg
Baseline use of MRA: Yes		
Number of patients in analysis set	1355	1306
Number of analysed patients	1206	1186
Baseline mean (SE)	65.30 (0.82)	65.33 (0.84)
Week 52		
Values at visit		
Number of analysed patients	817	787
Mean (SE)	73.17 (0.94)	72.44 (0.98)
Adjusted* mean (SE)	71.87 (0.77)	72.49 (0.78)
95% confidence interval	(70.37,73.38)	(70.97,74.02)
Change from baseline		
Mean (SE)	6.57 (0.97)	7.44 (0.92)
Adjusted* mean (SE)	6.56 (0.77)	7.18 (0.78)
95% confidence interval	(5.06, 8.06)	(5.66, 8.70)
Comparison vs Placebo		
Adjusted* mean (SE)		0.62 (1.09)
95% confidence interval		(-1.52, 2.76)
p-value		0.5699

* Model includes Age, baseline eGFR (CKD-EPI) as linear covariate(s) and region, baseline diabetes status, sex, baseline LVEF, week reachable, Visit by Treatment by baseline use of MRA interaction, baseline KCCQ social limitation score by Visit interaction as fixed effect(s).
The Visit by Treatment by baseline use of MRA p-value at Week 52 is 0.2239.
The following covariance structure has been used to fit the mixed model: Unstructured
Note: All covariate effects are set equal to their mean values within subgroup for the calculation of adjusted means.

For patients who died, only observed values are considered (no imputation after date of death).
Data taken from study 1245.121 only.
The MMRM includes all outcome values (change from baseline) at the planned Visits week 12, week 32 and week 52

R.1.3.11.14

R.1.3.11.14 Subgroup analysis by baseline use of ARNi

Table R.1.3.11.14: 1 KCCQ social limitation score change from baseline at week 52 (MMRM) by baseline use of ARNi (Y/N) - RS (OC-AD - no imputation for deaths) - 1245.121

Subgroup / Visit / Description / Statistic	Placebo	Empa 10mg
Baseline use of ARNi: No		
Number of patients in analysis set	1480	1523
Number of analysed patients	1323	1370
Baseline mean (SE)	66.30 (0.78)	65.36 (0.78)
Week 52		
Values at visit		
Number of analysed patients	886	934
Mean (SE)	72.68 (0.91)	72.89 (0.91)
Adjusted* mean (SE)	71.67 (0.73)	72.84 (0.72)
95% confidence interval	(70.23,73.11)	(71.44,74.24)
Change from baseline		
Mean (SE)	5.69 (0.95)	7.48 (0.83)
Adjusted* mean (SE)	5.85 (0.73)	7.02 (0.72)
95% confidence interval	(4.41, 7.29)	(5.62, 8.43)
Comparison vs Placebo		
Adjusted* mean (SE)		1.17 (1.02)
95% confidence interval		(-0.84, 3.18)
p-value		0.2532

* Model includes Age, baseline eGFR (CKD-EPI) as linear covariate(s) and region, baseline diabetes status, sex, baseline LVEF, week reachable, Visit by Treatment by baseline use of ARNi interaction, baseline KCCQ social limitation score by Visit interaction as fixed effect(s).
The Visit by Treatment by baseline use of ARNi p-value at Week 52 is 0.7158.
The following covariance structure has been used to fit the mixed model: Unstructured
Note: All covariate effects are set equal to their mean values within subgroup for the calculation of adjusted means.

For patients who died, only observed values are considered (no imputation after date of death).
Data taken from study 1245.121 only.
The MMRM includes all outcome values (change from baseline) at the planned Visits week 12, week 32 and week 52

Table R.1.3.11.14: 1 KCCQ social limitation score change from baseline at week 52 (MMRM) by baseline use of ARNi (Y/N) - RS (OC-AD - no imputation for deaths) - 1245.121

Subgroup / Visit / Description / Statistic	Placebo	Empa 10mg
Baseline use of ARNi: Yes		
Number of patients in analysis set	387	340
Number of analysed patients	349	312
Baseline mean (SE)	66.10 (1.55)	67.93 (1.59)
Week 52		
Values at visit		
Number of analysed patients	246	192
Mean (SE)	71.20 (1.74)	74.39 (1.89)
Adjusted* mean (SE)	71.64 (1.41)	73.66 (1.57)
95% confidence interval	(68.89,74.40)	(70.59,76.74)
Change from baseline		
Mean (SE)	4.66 (1.67)	5.48 (1.89)
Adjusted* mean (SE)	4.68 (1.41)	6.70 (1.57)
95% confidence interval	(1.92, 7.44)	(3.63, 9.78)
Comparison vs Placebo		
Adjusted* mean (SE)		2.02 (2.10)
95% confidence interval		(-2.09, 6.14)
p-value		0.3356

* Model includes Age, baseline eGFR (CKD-EPI) as linear covariate(s) and region, baseline diabetes status, sex, baseline LVEF, week reachable, Visit by Treatment by baseline use of ARNi interaction, baseline KCCQ social limitation score by Visit interaction as fixed effect(s).
The Visit by Treatment by baseline use of ARNi p-value at Week 52 is 0.7158.
The following covariance structure has been used to fit the mixed model: Unstructured
Note: All covariate effects are set equal to their mean values within subgroup for the calculation of adjusted means.

For patients who died, only observed values are considered (no imputation after date of death).
Data taken from study 1245.121 only.
The MMRM includes all outcome values (change from baseline) at the planned Visits week 12, week 32 and week 52

R.1.3.11.15

R.1.3.11.15 Subgroup analysis by bl. LVEF (<= 30%, >30% -<= 35% , > 35%)

Table R.1.3.11.15: 1 KCCQ social limitation score change from baseline at week 52 (MMRM) by baseline LVEF (3 cat.) - RS (OC-AD - no imputation for deaths) - 1245.121

Subgroup / Visit / Description / Statistic	Placebo	Empa 10mg
Baseline LVEF (3 cat.): <=30		
Number of patients in analysis set	1392	1337
Number of analysed patients	1252	1213
Baseline mean (SE)	65.47 (0.80)	65.52 (0.82)
Week 52		
Values at visit		
Number of analysed patients	873	821
Mean (SE)	71.83 (0.93)	72.73 (0.96)
Adjusted* mean (SE)	71.14 (0.74)	72.80 (0.76)
95% confidence interval	(69.68,72.59)	(71.30,74.29)
Change from baseline		
Mean (SE)	5.53 (0.95)	7.52 (0.89)
Adjusted* mean (SE)	5.64 (0.74)	7.30 (0.76)
95% confidence interval	(4.19, 7.09)	(5.81, 8.80)
Comparison vs Placebo		
Adjusted* mean (SE)		1.66 (1.06)
95% confidence interval		(-0.42, 3.75)
p-value		0.1182

* Model includes Age, baseline eGFR (CKD-EPI) as linear covariate(s) and region, baseline diabetes status, sex, week reachable, Visit by Treatment by baseline LVEF (3 cat.) interaction, baseline KCCQ social limitation score by Visit interaction as fixed effect(s).
The Visit by Treatment by baseline LVEF (3 cat.) p-value at Week 52 is 0.7387.
The following covariance structure has been used to fit the mixed model: Unstructured
Note: All covariate effects are set equal to their mean values within subgroup for the calculation of adjusted means.
The p-value for the visit by treatment by subgroup interaction trend test at Week 52 is 0.7433

For patients who died, only observed values are considered (no imputation after date of death).
Data taken from study 1245.121 only.
The MMRM includes all outcome values (change from baseline) at the planned Visits week 12, week 32 and week 52

Table R.1.3.11.15: 1 KCCQ social limitation score change from baseline at week 52 (MMRM) by baseline LVEF (3 cat.) - RS (OC-AD - no imputation for deaths) - 1245.121

Subgroup / Visit / Description / Statistic	Placebo	Empa 10mg
Baseline LVEF (3 cat.): >30 to <=35		
Number of patients in analysis set	361	398
Number of analysed patients	318	359
Baseline mean (SE)	69.18 (1.60)	66.81 (1.56)
Week 52		
Values at visit		
Number of analysed patients	202	232
Mean (SE)	75.40 (1.84)	74.20 (1.82)
Adjusted* mean (SE)	73.81 (1.53)	73.75 (1.43)
95% confidence interval	(70.81,76.81)	(70.96,76.55)
Change from baseline		
Mean (SE)	5.57 (2.02)	5.37 (1.60)
Adjusted* mean (SE)	5.89 (1.53)	5.83 (1.43)
95% confidence interval	(2.89, 8.88)	(3.03, 8.62)
Comparison vs Placebo		
Adjusted* mean (SE)		-0.06 (2.09)
95% confidence interval		(-4.15, 4.04)
p-value		0.9783

* Model includes Age, baseline eGFR (CKD-EPI) as linear covariate(s) and region, baseline diabetes status, sex, week reachable, Visit by Treatment by baseline LVEF (3 cat.) interaction, baseline KCCQ social limitation score by Visit interaction as fixed effect(s).
The Visit by Treatment by baseline LVEF (3 cat.) p-value at Week 52 is 0.7387.
The following covariance structure has been used to fit the mixed model: Unstructured
Note: All covariate effects are set equal to their mean values within subgroup for the calculation of adjusted means.
The p-value for the visit by treatment by subgroup interaction trend test at Week 52 is 0.7433

For patients who died, only observed values are considered (no imputation after date of death).
Data taken from study 1245.121 only.
The MMRM includes all outcome values (change from baseline) at the planned Visits week 12, week 32 and week 52

Table R.1.3.11.15: 1 KCCQ social limitation score change from baseline at week 52 (MMRM) by baseline LVEF (3 cat.) - RS (OC-AD - no imputation for deaths) - 1245.121

Subgroup / Visit / Description / Statistic	Placebo	Empa 10mg
Baseline LVEF (3 cat.): >35		
Number of patients in analysis set	114	128
Number of analysed patients	102	110
Baseline mean (SE)	66.75 (2.84)	66.08 (2.73)
Week 52		
Values at visit		
Number of analysed patients	57	73
Mean (SE)	69.66 (3.67)	74.37 (3.12)
Adjusted* mean (SE)	70.71 (2.85)	73.05 (2.55)
95% confidence interval	(65.12,76.30)	(68.04,78.06)
Change from baseline		
Mean (SE)	4.06 (3.02)	8.48 (3.11)
Adjusted* mean (SE)	4.31 (2.85)	6.65 (2.55)
95% confidence interval	(-1.28, 9.90)	(1.64,11.66)
Comparison vs Placebo		
Adjusted* mean (SE)		2.34 (3.83)
95% confidence interval		(-5.16, 9.84)
p-value		0.5409

* Model includes Age, baseline eGFR (CKD-EPI) as linear covariate(s) and region, baseline diabetes status, sex, week reachable, Visit by Treatment by baseline LVEF (3 cat.) interaction, baseline KCCQ social limitation score by Visit interaction as fixed effect(s).
The Visit by Treatment by baseline LVEF (3 cat.) p-value at Week 52 is 0.7387.
The following covariance structure has been used to fit the mixed model: Unstructured
Note: All covariate effects are set equal to their mean values within subgroup for the calculation of adjusted means.
The p-value for the visit by treatment by subgroup interaction trend test at Week 52 is 0.7433

For patients who died, only observed values are considered (no imputation after date of death).
Data taken from study 1245.121 only.
The MMRM includes all outcome values (change from baseline) at the planned Visits week 12, week 32 and week 52

R.1.3.11.16 Subgroup analysis by bl. NTproBNP </>= median (median based on total patients)

Table R.1.3.11.16: 1 KCCQ social limitation score change from baseline at week 52 (MMRM) by bl. NTproBNP (<median, >= median) (median based on total patients) - RS (OC-AD - no imputation for deaths) - 1245.121

Subgroup / Visit / Description / Statistic	Placebo	Empa 10mg
Baseline NTproBNP (<median, >= median): < median		
Number of patients in analysis set	920	942
Number of analysed patients	846	868
Baseline mean (SE)	68.97 (0.93)	69.03 (0.95)
Week 52		
Values at visit		
Number of analysed patients	610	608
Mean (SE)	74.32 (1.05)	75.53 (1.04)
Adjusted* mean (SE)	74.60 (0.89)	75.85 (0.89)
95% confidence interval	(72.86,76.35)	(74.11,77.59)
Change from baseline		
Mean (SE)	6.24 (1.02)	6.79 (1.00)
Adjusted* mean (SE)	5.60 (0.89)	6.85 (0.89)
95% confidence interval	(3.86, 7.35)	(5.11, 8.58)
Comparison vs Placebo		
Adjusted* mean (SE)		1.25 (1.26)
95% confidence interval		(-1.22, 3.71)
p-value		0.3214

* Model includes Age, baseline eGFR (CKD-EPI) as linear covariate(s) and region, baseline diabetes status, sex, baseline LVEF, week reachable, Visit by Treatment by baseline NTproBNP (<median, >= median) interaction, baseline KCCQ social limitation score by Visit interaction as fixed effect(s). The Visit by Treatment by baseline NTproBNP (<median, >= median) p-value at Week 52 is 0.9597.
The following covariance structure has been used to fit the mixed model: Unstructured
2 patients were excluded as the subgroup variable was missing.
Note: All covariate effects are set equal to their mean values within subgroup for the calculation of adjusted means.

For patients who died, only observed values are considered (no imputation after date of death).
Data taken from study 1245.121 only.
Median: 1910 [pg/mL]
The MMRM includes all outcome values (change from baseline) at the planned Visits week 12, week 32 and week 52

Table R.1.3.11.16: 1 KCCQ social limitation score change from baseline at week 52 (MMRM) by bl. NTproBNP (<median, >= median) (median based on total patients) - RS (OC-AD - no imputation for deaths) - 1245.121

Subgroup / Visit / Description / Statistic	Placebo	Empa 10mg
Baseline NTproBNP (<median, >= median): >= median		
Number of patients in analysis set	946	920
Number of analysed patients	826	814
Baseline mean (SE)	63.47 (1.03)	62.42 (1.03)
Week 52		
Values at visit		
Number of analysed patients	522	518
Mean (SE)	70.07 (1.24)	70.34 (1.28)
Adjusted* mean (SE)	68.58 (0.95)	69.91 (0.96)
95% confidence interval	(66.71,70.44)	(68.04,71.79)
Change from baseline		
Mean (SE)	4.56 (1.35)	7.55 (1.16)
Adjusted* mean (SE)	5.62 (0.95)	6.96 (0.96)
95% confidence interval	(3.76, 7.49)	(5.09, 8.84)
Comparison vs Placebo		
Adjusted* mean (SE)		1.34 (1.35)
95% confidence interval		(-1.30, 3.98)
p-value		0.3205

* Model includes Age, baseline eGFR (CKD-EPI) as linear covariate(s) and region, baseline diabetes status, sex, baseline LVEF, week reachable, Visit by Treatment by baseline NTproBNP (<median, >= median) interaction, baseline KCCQ social limitation score by Visit interaction as fixed effect(s). The Visit by Treatment by baseline NTproBNP (<median, >= median) p-value at Week 52 is 0.9597.
The following covariance structure has been used to fit the mixed model: Unstructured
2 patients were excluded as the subgroup variable was missing.
Note: All covariate effects are set equal to their mean values within subgroup for the calculation of adjusted means.

For patients who died, only observed values are considered (no imputation after date of death).
Data taken from study 1245.121 only.
Median: 1910 [pg/mL]
The MMRM includes all outcome values (change from baseline) at the planned Visits week 12, week 32 and week 52

R.1.4

R.1.4.1

R.1.4.1 Adverse events overall

Table R.1.4.1: 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	1863	1463	78.5	1863	1420	76.2	0.0922	0.97	(0.94,1.00)	0.88	(0.75,1.02)	-0.02	(-0.05, 0.00)	
Sex														0.5159
Male	1410	1108	78.6	1426	1095	76.8	0.2515	0.98	(0.94,1.02)	0.90	(0.76,1.08)	-0.02	(-0.05, 0.01)	
Female	453	355	78.4	437	325	74.4	0.1605	0.95	(0.88,1.02)	0.80	(0.59,1.09)	-0.04	(-0.10, 0.02)	
Age [years]														0.8899
< 65	739	558	75.5	675	493	73.0	0.2881	0.97	(0.91,1.03)	0.88	(0.69,1.12)	-0.02	(-0.07, 0.02)	
>= 65	1124	905	80.5	1188	927	78.0	0.1408	0.97	(0.93,1.01)	0.86	(0.70,1.05)	-0.02	(-0.06, 0.01)	
Region														0.8503
North America	213	186	87.3	212	179	84.4	0.3923	0.97	(0.90,1.04)	0.79	(0.45,1.36)	-0.03	(-0.10, 0.04)	
Latin America	645	484	75.0	641	465	72.5	0.3088	0.97	(0.91,1.03)	0.88	(0.69,1.13)	-0.02	(-0.07, 0.02)	
Europe	674	518	76.9	676	508	75.1	0.4629	0.98	(0.92,1.04)	0.91	(0.71,1.17)	-0.02	(-0.06, 0.03)	
Asia	244	218	89.3	248	211	85.1	0.1570	0.95	(0.89,1.02)	0.68	(0.40,1.16)	-0.04	(-0.10, 0.02)	
Other	87	57	65.5	86	57	66.3	0.9158	1.01	(0.82,1.25)	1.03	(0.55,1.94)	0.01	(-0.13, 0.15)	
OECD Member														0.6048
No	741	568	76.7	713	522	73.2	0.1300	0.96	(0.90,1.01)	0.83	(0.66,1.06)	-0.03	(-0.08, 0.01)	
Yes	1122	895	79.8	1150	898	78.1	0.3260	0.98	(0.94,1.02)	0.90	(0.74,1.11)	-0.02	(-0.05, 0.02)	
Baseline NYHA														0.0429
II	1399	1080	77.2	1399	1025	73.3	0.0160	0.95	(0.91,0.99)	0.81	(0.68,0.96)	-0.04	(-0.07,-0.01)	
III/IV	464	383	82.5	464	395	85.1	0.2846	1.03	(0.97,1.09)	1.21	(0.85,1.72)	0.03	(-0.02, 0.07)	
Baseline Diabetes Status														0.6814
Diabetic	926	741	80.0	927	716	77.2	0.1439	0.97	(0.92,1.01)	0.85	(0.68,1.06)	-0.03	(-0.07, 0.01)	
Non-Diabetic	937	722	77.1	936	704	75.2	0.3501	0.98	(0.93,1.03)	0.90	(0.73,1.12)	-0.02	(-0.06, 0.02)	
Baseline BMI [kg/m²]														0.4040
<30	1299	1028	79.1	1263	961	76.1	0.0641	0.96	(0.92,1.00)	0.84	(0.70,1.01)	-0.03	(-0.06, 0.00)	
>=30	564	435	77.1	600	459	76.5	0.7998	0.99	(0.93,1.06)	0.97	(0.74,1.27)	-0.01	(-0.05, 0.04)	

Risk ratios and odds ratios with confidence intervals (CIs) are estimated by Cochran-Mantel-Haenszel method. For risk differences standard Wald asymptotic confidence limits are calculated. A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied 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: 23.0. * Chi-square test for treatment effect ** Breslow-Day test for homogeneity of odds ratios (treatment by subgroup interaction).

Table R.1.4.1: 1 Proportion of patients with any adverse event - Overall and by subgroup - TS

Subgroup Category	Placebo N	Placebo n	Placebo %	Empa 10mg N	Empa 10mg n	Empa 10mg %	Empa 10mg vs Placebo p-value *	Risk ratio	Risk (95% CI)	Odds ratio	Odds (95% CI)	Risk diff.	Risk diff. (95% CI)	p-value **
Baseline eGFR (CKD-EPI) [mL/min/1.73m²]														0.8280
>=60	958	716	74.7	969	703	72.5	0.2753	0.97	(0.92,1.02)	0.89	(0.73,1.09)	-0.02	(-0.06, 0.02)	
<60	904	746	82.5	893	717	80.3	0.2241	0.97	(0.93,1.02)	0.86	(0.68,1.09)	-0.02	(-0.06, 0.01)	
History of HHF (in the last 12 months)														0.6818
No	1290	997	77.3	1286	958	74.5	0.0976	0.96	(0.92,1.01)	0.86	(0.72,1.03)	-0.03	(-0.06, 0.01)	
Yes	573	466	81.3	577	462	80.1	0.5892	0.98	(0.93,1.04)	0.92	(0.69,1.24)	-0.01	(-0.06, 0.03)	
Cause of Heart Failure														0.6372
Ischemic	944	739	78.3	983	753	76.6	0.3774	0.98	(0.93,1.03)	0.91	(0.73,1.12)	-0.02	(-0.05, 0.02)	
Non-ischemic	919	724	78.8	880	667	75.8	0.1306	0.96	(0.91,1.01)	0.84	(0.68,1.05)	-0.03	(-0.07, 0.01)	
Heart Failure Physiology														0.3338
LVEF <= 30% and NTproBNP < median	723	533	73.7	698	504	72.2	0.5205	0.98	(0.92,1.04)	0.93	(0.73,1.17)	-0.02	(-0.06, 0.03)	
LVEF <= 30% and NTproBNP >= median	660	552	83.6	631	498	78.9	0.0298	0.94	(0.90,0.99)	0.73	(0.55,0.97)	-0.05	(-0.09, 0.00)	
LVEF > 30%	473	373	78.9	526	412	78.3	0.8381	0.99	(0.93,1.06)	0.97	(0.72,1.31)	-0.01	(-0.06, 0.05)	
Baseline use of MRA														0.6777
No	512	420	82.0	557	440	79.0	0.2111	0.96	(0.91,1.02)	0.82	(0.61,1.12)	-0.03	(-0.08, 0.02)	
Yes	1351	1043	77.2	1306	980	75.0	0.1908	0.97	(0.93,1.01)	0.89	(0.74,1.06)	-0.02	(-0.05, 0.01)	
Baseline use of ARNi														0.1243
No	1476	1142	77.4	1523	1159	76.1	0.4101	0.98	(0.95,1.02)	0.93	(0.79,1.10)	-0.01	(-0.04, 0.02)	
Yes	387	321	82.9	340	261	76.8	0.0374	0.93	(0.86,1.00)	0.68	(0.47,0.98)	-0.06	(-0.12, 0.00)	
Baseline LVEF														0.3194
<=30	1390	1090	78.4	1337	1008	75.4	0.0609	0.96	(0.92,1.00)	0.84	(0.71,1.01)	-0.03	(-0.06, 0.00)	
>30 to <=35	359	276	76.9	398	311	78.1	0.6782	1.02	(0.94,1.10)	1.08	(0.76,1.51)	0.01	(-0.05, 0.07)	
>35	114	97	85.1	128	101	78.9	0.2133	0.93	(0.82,1.04)	0.66	(0.34,1.28)	-0.06	(-0.16, 0.03)	

Risk ratios and odds ratios with confidence intervals (CIs) are estimated by Cochran-Mantel-Haenszel method. For risk differences standard Wald asymptotic confidence limits are calculated. A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied 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: 23.0. * Chi-square test for treatment effect ** Breslow-Day test for homogeneity of odds ratios (treatment by subgroup interaction).

Table R.1.4.1: 1 Proportion of patients with any adverse event - Overall and by subgroup - TS

Subgroup Category	Placebo N	Placebo n	Placebo %	Empa 10mg N	Empa 10mg n	Empa 10mg %	Empa 10mg vs Placebo p-value *	Risk ratio	Risk (95% CI)	Odds ratio	Odds (95% CI)	Risk diff.	Risk diff. (95% CI)	p-value **
Baseline NTproBNP														0.2736
< median	919	678	73.8	942	686	72.8	0.6426	0.99	(0.93,1.04)	0.95	(0.78,1.17)	-0.01	(-0.05, 0.03)	
>= median	943	784	83.1	920	734	79.8	0.0622	0.96	(0.92,1.00)	0.80	(0.63,1.01)	-0.03	(-0.07, 0.00)	

Risk ratios and odds ratios with confidence intervals (CIs) are estimated by Cochran-Mantel-Haenszel method. For risk differences standard Wald asymptotic confidence limits are calculated. A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied 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: 23.0. * Chi-square test for treatment effect ** Breslow-Day test for homogeneity of odds ratios (treatment by subgroup interaction).

Table R.1.4.1: 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	1863	1362	73.1	1863	1325	71.1	0.1765	0.97	(0.93,1.01)	0.91	(0.79,1.05)	-0.02	(-0.05, 0.01)	
Sex														0.8181
Male	1410	1027	72.8	1426	1013	71.0	0.2864	0.98	(0.93,1.02)	0.91	(0.78,1.08)	-0.02	(-0.05, 0.02)	
Female	453	335	74.0	437	312	71.4	0.3923	0.97	(0.89,1.05)	0.88	(0.65,1.18)	-0.03	(-0.08, 0.03)	
Age [years]														0.7325
< 65	739	522	70.6	675	457	67.7	0.2327	0.96	(0.89,1.03)	0.87	(0.70,1.09)	-0.03	(-0.08, 0.02)	
>= 65	1124	840	74.7	1188	868	73.1	0.3612	0.98	(0.93,1.03)	0.92	(0.76,1.10)	-0.02	(-0.05, 0.02)	
Region														0.7349
North America	213	177	83.1	212	175	82.5	0.8802	0.99	(0.91,1.08)	0.96	(0.58,1.59)	-0.01	(-0.08, 0.07)	
Latin America	645	444	68.8	641	415	64.7	0.1190	0.94	(0.87,1.02)	0.83	(0.66,1.05)	-0.04	(-0.09, 0.01)	
Europe	674	473	70.2	676	473	70.0	0.9336	1.00	(0.93,1.07)	0.99	(0.78,1.25)	0.00	(-0.05, 0.05)	
Asia	244	214	87.7	248	208	83.9	0.2235	0.96	(0.89,1.03)	0.73	(0.44,1.21)	-0.04	(-0.10, 0.02)	
Other	87	54	62.1	86	54	62.8	0.9219	1.01	(0.80,1.27)	1.03	(0.56,1.91)	0.01	(-0.14, 0.15)	
OECD Member														0.1470
No	741	525	70.9	713	470	65.9	0.0431	0.93	(0.87,1.00)	0.80	(0.64,0.99)	-0.05	(-0.10, 0.00)	
Yes	1122	837	74.6	1150	855	74.3	0.8908	1.00	(0.95,1.05)	0.99	(0.82,1.19)	0.00	(-0.04, 0.03)	
Baseline NYHA														0.0129
II	1399	1015	72.6	1399	958	68.5	0.0181	0.94	(0.90,0.99)	0.82	(0.70,0.97)	-0.04	(-0.07,-0.01)	
III/IV	464	347	74.8	464	367	79.1	0.1191	1.06	(0.99,1.13)	1.28	(0.94,1.73)	0.04	(-0.01, 0.10)	
Baseline Diabetes Status														0.9484
Diabetic	926	690	74.5	927	672	72.5	0.3240	0.97	(0.92,1.03)	0.90	(0.73,1.11)	-0.02	(-0.06, 0.02)	
Non-Diabetic	937	672	71.7	936	653	69.8	0.3529	0.97	(0.92,1.03)	0.91	(0.75,1.11)	-0.02	(-0.06, 0.02)	
Baseline BMI [kg/m²]														0.3430
<30	1299	962	74.1	1263	899	71.2	0.1024	0.96	(0.92,1.01)	0.87	(0.73,1.03)	-0.03	(-0.06, 0.01)	
>=30	564	400	70.9	600	426	71.0	0.9766	1.00	(0.93,1.08)	1.00	(0.78,1.29)	0.00	(-0.05, 0.05)	

Risk ratios and odds ratios with confidence intervals (CIs) are estimated by Cochran-Mantel-Haenszel method. For risk differences standard Wald asymptotic confidence limits are calculated. A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied 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: 23.0. * Chi-square test for treatment effect ** Breslow-Day test for homogeneity of odds ratios (treatment by subgroup interaction).

Table R.1.4.1: 2 Proportion of patients with any adverse event (excluding disease related events) - Overall and by subgroup - TS

Subgroup Category	Placebo N	Placebo n	Placebo %	Empa 10mg N	Empa 10mg n	Empa 10mg %	Empa 10mg vs Placebo p-value *	Risk ratio	Risk (95% CI)	Odds ratio	Odds (95% CI)	Risk diff.	Risk diff. (95% CI)	p-value **
Baseline eGFR (CKD-EPI) [mL/min/1.73m²]														0.7708
>=60	958	670	69.9	969	654	67.5	0.2471	0.97	(0.91,1.02)	0.89	(0.74,1.08)	-0.02	(-0.07, 0.02)	
<60	904	691	76.4	893	671	75.1	0.5207	0.98	(0.93,1.04)	0.93	(0.75,1.16)	-0.01	(-0.05, 0.03)	
History of HHF (in the last 12 months)														0.4686
No	1290	938	72.7	1286	900	70.0	0.1256	0.96	(0.92,1.01)	0.87	(0.74,1.04)	-0.03	(-0.06, 0.01)	
Yes	573	424	74.0	577	425	73.7	0.8958	1.00	(0.93,1.07)	0.98	(0.76,1.28)	0.00	(-0.05, 0.05)	
Cause of Heart Failure														0.4142
Ischemic	944	681	72.1	983	701	71.3	0.6868	0.99	(0.93,1.05)	0.96	(0.79,1.17)	-0.01	(-0.05, 0.03)	
Non-ischemic	919	681	74.1	880	624	70.9	0.1293	0.96	(0.90,1.01)	0.85	(0.69,1.05)	-0.03	(-0.07, 0.01)	
Heart Failure Physiology														0.6466
LVEF <= 30% and NTproBNP < median	723	509	70.4	698	472	67.6	0.2573	0.96	(0.90,1.03)	0.88	(0.70,1.10)	-0.03	(-0.08, 0.02)	
LVEF <= 30% and NTproBNP >= median	660	501	75.9	631	460	72.9	0.2154	0.96	(0.90,1.02)	0.85	(0.66,1.10)	-0.03	(-0.08, 0.02)	
LVEF > 30%	473	347	73.4	526	387	73.6	0.9394	1.00	(0.93,1.08)	1.01	(0.76,1.34)	0.00	(-0.05, 0.06)	
Baseline use of MRA														0.7727
No	512	392	76.6	557	412	74.0	0.3263	0.97	(0.90,1.03)	0.87	(0.66,1.15)	-0.03	(-0.08, 0.03)	
Yes	1351	970	71.8	1306	913	69.9	0.2836	0.97	(0.93,1.02)	0.91	(0.77,1.08)	-0.02	(-0.05, 0.02)	
Baseline use of ARNi														0.0823
No	1476	1056	71.5	1523	1079	70.8	0.6732	0.99	(0.95,1.04)	0.97	(0.83,1.13)	-0.01	(-0.04, 0.03)	
Yes	387	306	79.1	340	246	72.4	0.0345	0.92	(0.84,0.99)	0.69	(0.49,0.97)	-0.07	(-0.13, 0.00)	
Baseline LVEF														0.4663
<=30	1390	1015	73.0	1337	938	70.2	0.0972	0.96	(0.92,1.01)	0.87	(0.74,1.03)	-0.03	(-0.06, 0.01)	
>30 to <=35	359	258	71.9	398	292	73.4	0.6437	1.02	(0.94,1.11)	1.08	(0.78,1.48)	0.02	(-0.05, 0.08)	
>35	114	89	78.1	128	95	74.2	0.4836	0.95	(0.83,1.09)	0.81	(0.45,1.47)	-0.04	(-0.15, 0.07)	

Risk ratios and odds ratios with confidence intervals (CIs) are estimated by Cochran-Mantel-Haenszel method. For risk differences standard Wald asymptotic confidence limits are calculated. A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied 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: 23.0. * Chi-square test for treatment effect ** Breslow-Day test for homogeneity of odds ratios (treatment by subgroup interaction).

Table R.1.4.1: 2 Proportion of patients with any adverse event (excluding disease related events) - Overall and by subgroup - TS

Subgroup Category	Placebo N	Placebo n	Placebo %	Empa 10mg N	Empa 10mg n	Empa 10mg %	Empa 10mg vs Placebo p-value *	Risk ratio (95% CI)	Odds ratio (95% CI)	Risk diff. (95% CI)	p-value **
Baseline NTproBNP											0.9746
< median	919	647	70.4	942	645	68.5	0.3659	0.97 (0.92,1.03)	0.91 (0.75,1.11)	-0.02 (-0.06, 0.02)	
>= median	943	714	75.7	920	680	73.9	0.3701	0.98 (0.93,1.03)	0.91 (0.74,1.12)	-0.02 (-0.06, 0.02)	

Risk ratios and odds ratios with confidence intervals (CIs) are estimated by Cochran-Mantel-Haenszel method. For risk differences standard Wald asymptotic confidence limits are calculated. A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied 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: 23.0. * Chi-square test for treatment effect ** Breslow-Day test for homogeneity of odds ratios (treatment by subgroup interaction).

Table R.1.4.1: 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	1863	896	48.1	1863	772	41.4	<0.0001	0.86	(0.80,0.93)	0.76	(0.67,0.87)	-0.07	(-0.10,-0.03)	
Sex														0.6542
Male	1410	685	48.6	1426	603	42.3	0.0008	0.87	(0.80,0.94)	0.78	(0.67,0.90)	-0.06	(-0.10,-0.03)	
Female	453	211	46.6	437	169	38.7	0.0171	0.83	(0.71,0.97)	0.72	(0.55,0.94)	-0.08	(-0.14,-0.01)	
Age [years]														0.2486
< 65	739	340	46.0	675	249	36.9	0.0005	0.80	(0.71,0.91)	0.69	(0.55,0.85)	-0.09	(-0.14,-0.04)	
>= 65	1124	556	49.5	1188	523	44.0	0.0087	0.89	(0.82,0.97)	0.80	(0.68,0.95)	-0.05	(-0.10,-0.01)	
Region														0.2766
North America	213	115	54.0	212	108	50.9	0.5294	0.94	(0.79,1.13)	0.88	(0.60,1.30)	-0.03	(-0.13, 0.06)	
Latin America	645	287	44.5	641	255	39.8	0.0869	0.89	(0.79,1.02)	0.82	(0.66,1.03)	-0.05	(-0.10, 0.01)	
Europe	674	331	49.1	676	290	42.9	0.0221	0.87	(0.78,0.98)	0.78	(0.63,0.96)	-0.06	(-0.12,-0.01)	
Asia	244	136	55.7	248	103	41.5	0.0016	0.75	(0.62,0.90)	0.56	(0.39,0.81)	-0.14	(-0.23,-0.05)	
Other	87	27	31.0	86	16	18.6	0.0586	0.60	(0.35,1.03)	0.51	(0.25,1.03)	-0.12	(-0.25, 0.00)	
OECD Member														0.9824
No	741	329	44.4	713	269	37.7	0.0098	0.85	(0.75,0.96)	0.76	(0.62,0.94)	-0.07	(-0.12,-0.02)	
Yes	1122	567	50.5	1150	503	43.7	0.0012	0.87	(0.79,0.94)	0.76	(0.65,0.90)	-0.07	(-0.11,-0.03)	
Baseline NYHA														0.0527
II	1399	621	44.4	1399	503	36.0	<0.0001	0.81	(0.74,0.89)	0.70	(0.60,0.82)	-0.08	(-0.12,-0.05)	
III/IV	464	275	59.3	464	269	58.0	0.6892	0.98	(0.88,1.09)	0.95	(0.73,1.23)	-0.01	(-0.08, 0.05)	
Baseline Diabetes Status														0.9176
Diabetic	926	457	49.4	927	397	42.8	0.0048	0.87	(0.79,0.96)	0.77	(0.64,0.92)	-0.07	(-0.11,-0.02)	
Non-Diabetic	937	439	46.9	936	375	40.1	0.0030	0.86	(0.77,0.95)	0.76	(0.63,0.91)	-0.07	(-0.11,-0.02)	
Baseline BMI [kg/m²]														0.2370
<30	1299	630	48.5	1263	512	40.5	<0.0001	0.84	(0.77,0.91)	0.72	(0.62,0.85)	-0.08	(-0.12,-0.04)	
>=30	564	266	47.2	600	260	43.3	0.1895	0.92	(0.81,1.04)	0.86	(0.68,1.08)	-0.04	(-0.10, 0.02)	

Risk ratios and odds ratios with confidence intervals (CIs) are estimated by Cochran-Mantel-Haenszel method. For risk differences standard Wald asymptotic confidence limits are calculated. A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied 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: 23.0. * Chi-square test for treatment effect ** Breslow-Day test for homogeneity of odds ratios (treatment by subgroup interaction).

Table R.1.4.1: 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 eGFR (CKD-EPI) [mL/min/1.73m²]														0.0518
>=60	958	437	45.6	969	350	36.1	<0.0001	0.79	(0.71,0.88)	0.67	(0.56,0.81)	-0.09	(-0.14,-0.05)	
<60	904	458	50.7	893	422	47.3	0.1486	0.93	(0.85,1.03)	0.87	(0.73,1.05)	-0.03	(-0.08, 0.01)	
History of HHF (in the last 12 months)														0.1179
No	1290	607	47.1	1286	498	38.7	<0.0001	0.82	(0.75,0.90)	0.71	(0.61,0.83)	-0.08	(-0.12,-0.05)	
Yes	573	289	50.4	577	274	47.5	0.3171	0.94	(0.84,1.06)	0.89	(0.71,1.12)	-0.03	(-0.09, 0.03)	
Cause of Heart Failure														0.2274
Ischemic	944	463	49.0	983	434	44.2	0.0312	0.90	(0.82,0.99)	0.82	(0.69,0.98)	-0.05	(-0.09, 0.00)	
Non-ischemic	919	433	47.1	880	338	38.4	0.0002	0.82	(0.73,0.91)	0.70	(0.58,0.84)	-0.09	(-0.13,-0.04)	
Heart Failure Physiology														0.4149
LVEF <= 30% and NTproBNP < median	723	289	40.0	698	227	32.5	0.0035	0.81	(0.71,0.94)	0.72	(0.58,0.90)	-0.07	(-0.12,-0.02)	
LVEF <= 30% and NTproBNP >= median	660	388	58.8	631	318	50.4	0.0025	0.86	(0.78,0.95)	0.71	(0.57,0.89)	-0.08	(-0.14,-0.03)	
LVEF > 30%	473	216	45.7	526	223	42.4	0.2984	0.93	(0.81,1.07)	0.88	(0.68,1.12)	-0.03	(-0.09, 0.03)	
Baseline use of MRA														0.5051
No	512	253	49.4	557	247	44.3	0.0970	0.90	(0.79,1.02)	0.82	(0.64,1.04)	-0.05	(-0.11, 0.01)	
Yes	1351	643	47.6	1306	525	40.2	0.0001	0.84	(0.77,0.92)	0.74	(0.63,0.86)	-0.07	(-0.11,-0.04)	
Baseline use of ARNi														0.5444
No	1476	702	47.6	1523	631	41.4	0.0007	0.87	(0.80,0.94)	0.78	(0.68,0.90)	-0.06	(-0.10,-0.03)	
Yes	387	194	50.1	340	141	41.5	0.0194	0.83	(0.70,0.97)	0.70	(0.53,0.95)	-0.09	(-0.16,-0.01)	
Baseline LVEF														0.4016
<=30	1390	680	48.9	1337	549	41.1	<0.0001	0.84	(0.77,0.91)	0.73	(0.63,0.85)	-0.08	(-0.12,-0.04)	
>30 to <=35	359	158	44.0	398	166	41.7	0.5226	0.95	(0.80,1.12)	0.91	(0.68,1.21)	-0.02	(-0.09, 0.05)	
>35	114	58	50.9	128	57	44.5	0.3238	0.88	(0.67,1.14)	0.78	(0.47,1.29)	-0.06	(-0.19, 0.06)	

Risk ratios and odds ratios with confidence intervals (CIs) are estimated by Cochran-Mantel-Haenszel method. For risk differences standard Wald asymptotic confidence limits are calculated. A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied 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: 23.0. * Chi-square test for treatment effect ** Breslow-Day test for homogeneity of odds ratios (treatment by subgroup interaction).

Table R.1.4.1: 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 NTproBNP														0.7342
< median	919	363	39.5	942	319	33.9	0.0117	0.86	(0.76,0.97)	0.78	(0.65,0.95)	-0.06	(-0.10,-0.01)	
>= median	943	532	56.4	920	453	49.2	0.0019	0.87	(0.80,0.95)	0.75	(0.62,0.90)	-0.07	(-0.12,-0.03)	

Risk ratios and odds ratios with confidence intervals (CIs) are estimated by Cochran-Mantel-Haenszel method. For risk differences standard Wald asymptotic confidence limits are calculated. A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied 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: 23.0. * Chi-square test for treatment effect ** Breslow-Day test for homogeneity of odds ratios (treatment by subgroup interaction).

Table R.1.4.1: 4 Proportion of patients with serious 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	1863	605	32.5	1863	540	29.0	0.0210	0.89	(0.81,0.98)	0.85	(0.74,0.98)	-0.03	(-0.06,-0.01)	
Sex														0.7978
Male	1410	464	32.9	1426	416	29.2	0.0316	0.89	(0.79,0.99)	0.84	(0.72,0.98)	-0.04	(-0.07, 0.00)	
Female	453	141	31.1	437	124	28.4	0.3697	0.91	(0.74,1.12)	0.88	(0.66,1.17)	-0.03	(-0.09, 0.03)	
Age [years]														0.1069
< 65	739	230	31.1	675	166	24.6	0.0063	0.79	(0.67,0.94)	0.72	(0.57,0.91)	-0.07	(-0.11,-0.02)	
>= 65	1124	375	33.4	1188	374	31.5	0.3339	0.94	(0.84,1.06)	0.92	(0.77,1.09)	-0.02	(-0.06, 0.02)	
Region														0.3027
North America	213	86	40.4	212	93	43.9	0.4660	1.09	(0.87,1.36)	1.15	(0.79,1.70)	0.03	(-0.06, 0.13)	
Latin America	645	185	28.7	641	156	24.3	0.0776	0.85	(0.71,1.02)	0.80	(0.62,1.03)	-0.04	(-0.09, 0.00)	
Europe	674	224	33.2	676	205	30.3	0.2511	0.91	(0.78,1.07)	0.87	(0.70,1.10)	-0.03	(-0.08, 0.02)	
Asia	244	92	37.7	248	76	30.6	0.0987	0.81	(0.63,1.04)	0.73	(0.50,1.06)	-0.07	(-0.15, 0.01)	
Other	87	18	20.7	86	10	11.6	0.1057	0.56	(0.28,1.15)	0.50	(0.22,1.17)	-0.09	(-0.20, 0.02)	
OECD Member														0.1965
No	741	209	28.2	713	161	22.6	0.0138	0.80	(0.67,0.96)	0.74	(0.59,0.94)	-0.06	(-0.10,-0.01)	
Yes	1122	396	35.3	1150	379	33.0	0.2400	0.93	(0.83,1.05)	0.90	(0.76,1.07)	-0.02	(-0.06, 0.02)	
Baseline NYHA														0.0376
II	1399	432	30.9	1399	359	25.7	0.0022	0.83	(0.74,0.94)	0.77	(0.66,0.91)	-0.05	(-0.09,-0.02)	
III/IV	464	173	37.3	464	181	39.0	0.5888	1.05	(0.89,1.23)	1.08	(0.83,1.40)	0.02	(-0.05, 0.08)	
Baseline Diabetes Status														0.2412
Diabetic	926	300	32.4	927	284	30.6	0.4146	0.95	(0.83,1.08)	0.92	(0.76,1.12)	-0.02	(-0.06, 0.02)	
Non-Diabetic	937	305	32.6	936	256	27.4	0.0140	0.84	(0.73,0.97)	0.78	(0.64,0.95)	-0.05	(-0.09,-0.01)	
Baseline BMI [kg/m²]														0.5742
<30	1299	422	32.5	1263	359	28.4	0.0255	0.87	(0.78,0.98)	0.83	(0.70,0.98)	-0.04	(-0.08,-0.01)	
>=30	564	183	32.4	600	181	30.2	0.4017	0.93	(0.78,1.10)	0.90	(0.70,1.15)	-0.02	(-0.08, 0.03)	

Risk ratios and odds ratios with confidence intervals (CIs) are estimated by Cochran-Mantel-Haenszel method. For risk differences standard Wald asymptotic confidence limits are calculated. A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied 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: 23.0. * Chi-square test for treatment effect ** Breslow-Day test for homogeneity of odds ratios (treatment by subgroup interaction).

Table R.1.4.1: 4 Proportion of patients with serious adverse event (excluding disease related events) - Overall and by subgroup - TS

Subgroup Category	Placebo N	Placebo n	Placebo %	Empa 10mg N	Empa 10mg n	Empa 10mg %	Empa 10mg vs Placebo p-value *	Risk ratio	Risk (95% CI)	Odds ratio	Odds (95% CI)	Risk diff.	Risk diff. (95% CI)	p-value **
Baseline eGFR (CKD-EPI) [mL/min/1.73m²]														0.0044
>=60	958	303	31.6	969	235	24.3	0.0003	0.77	(0.66,0.89)	0.69	(0.57,0.85)	-0.07	(-0.11,-0.03)	
<60	904	301	33.3	893	305	34.2	0.7005	1.03	(0.90,1.17)	1.04	(0.85,1.26)	0.01	(-0.04, 0.05)	
History of HHF (in the last 12 months)														0.0762
No	1290	425	32.9	1286	356	27.7	0.0037	0.84	(0.75,0.95)	0.78	(0.66,0.92)	-0.05	(-0.09,-0.02)	
Yes	573	180	31.4	577	184	31.9	0.8624	1.02	(0.86,1.20)	1.02	(0.80,1.31)	0.00	(-0.05, 0.06)	
Cause of Heart Failure														0.3583
Ischemic	944	319	33.8	983	309	31.4	0.2696	0.93	(0.82,1.06)	0.90	(0.74,1.09)	-0.02	(-0.07, 0.02)	
Non-ischemic	919	286	31.1	880	231	26.3	0.0225	0.84	(0.73,0.98)	0.79	(0.64,0.97)	-0.05	(-0.09,-0.01)	
Heart Failure Physiology														0.1581
LVEF <= 30% and NTproBNP < median	723	215	29.7	698	160	22.9	0.0036	0.77	(0.65,0.92)	0.70	(0.55,0.89)	-0.07	(-0.11,-0.02)	
LVEF <= 30% and NTproBNP >= median	660	243	36.8	631	224	35.5	0.6220	0.96	(0.83,1.11)	0.94	(0.75,1.19)	-0.01	(-0.07, 0.04)	
LVEF > 30%	473	145	30.7	526	153	29.1	0.5886	0.95	(0.78,1.15)	0.93	(0.71,1.22)	-0.02	(-0.07, 0.04)	
Baseline use of MRA														0.2774
No	512	171	33.4	557	180	32.3	0.7066	0.97	(0.82,1.15)	0.95	(0.74,1.23)	-0.01	(-0.07, 0.05)	
Yes	1351	434	32.1	1306	360	27.6	0.0103	0.86	(0.76,0.96)	0.80	(0.68,0.95)	-0.05	(-0.08,-0.01)	
Baseline use of ARNi														0.2727
No	1476	477	32.3	1523	428	28.1	0.0119	0.87	(0.78,0.97)	0.82	(0.70,0.96)	-0.04	(-0.07,-0.01)	
Yes	387	128	33.1	340	112	32.9	0.9695	1.00	(0.81,1.23)	0.99	(0.73,1.35)	0.00	(-0.07, 0.07)	
Baseline LVEF														0.7413
<=30	1390	460	33.1	1337	387	28.9	0.0193	0.87	(0.78,0.98)	0.82	(0.70,0.97)	-0.04	(-0.08,-0.01)	
>30 to <=35	359	107	29.8	398	114	28.6	0.7255	0.96	(0.77,1.20)	0.95	(0.69,1.29)	-0.01	(-0.08, 0.05)	
>35	114	38	33.3	128	39	30.5	0.6330	0.91	(0.63,1.32)	0.88	(0.51,1.51)	-0.03	(-0.15, 0.09)	

Risk ratios and odds ratios with confidence intervals (CIs) are estimated by Cochran-Mantel-Haenszel method. For risk differences standard Wald asymptotic confidence limits are calculated. A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied 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: 23.0. * Chi-square test for treatment effect ** Breslow-Day test for homogeneity of odds ratios (treatment by subgroup interaction).

Table R.1.4.1: 4 Proportion of patients with serious adverse event (excluding disease related events) - Overall and by subgroup - TS

Subgroup Category	Placebo N	Placebo n	Placebo %	Empa 10mg N	Empa 10mg n	Empa 10mg %	Empa 10mg vs Placebo p-value *	Risk ratio	(95% CI)	Odds ratio	(95% CI)	Risk diff.	(95% CI)	p-value **
Baseline NTproBNP														0.2790
< median	919	271	29.5	942	233	24.7	0.0210	0.84	(0.72,0.97)	0.79	(0.64,0.96)	-0.05	(-0.09,-0.01)	
>= median	943	333	35.3	920	307	33.4	0.3772	0.94	(0.83,1.07)	0.92	(0.76,1.11)	-0.02	(-0.06, 0.02)	

Risk ratios and odds ratios with confidence intervals (CIs) are estimated by Cochran-Mantel-Haenszel method. For risk differences standard Wald asymptotic confidence limits are calculated. A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied 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: 23.0. * Chi-square test for treatment effect ** Breslow-Day test for homogeneity of odds ratios (treatment by subgroup interaction).

Table R.1.4.1: 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	1863	502	26.9	1863	459	24.6	0.1074	0.91	(0.82,1.02)	0.89	(0.77,1.03)	-0.02	(-0.05, 0.01)	
Sex														0.9698
Male	1410	392	27.8	1426	362	25.4	0.1454	0.91	(0.81,1.03)	0.88	(0.75,1.04)	-0.02	(-0.06, 0.01)	
Female	453	110	24.3	437	97	22.2	0.4615	0.91	(0.72,1.16)	0.89	(0.65,1.21)	-0.02	(-0.08, 0.03)	
Age [years]														0.8536
< 65	739	198	26.8	675	163	24.1	0.2546	0.90	(0.75,1.08)	0.87	(0.68,1.11)	-0.03	(-0.07, 0.02)	
>= 65	1124	304	27.0	1188	296	24.9	0.2428	0.92	(0.80,1.06)	0.90	(0.74,1.08)	-0.02	(-0.06, 0.01)	
Region														0.4834
North America	213	72	33.8	212	67	31.6	0.6290	0.93	(0.71,1.23)	0.90	(0.60,1.36)	-0.02	(-0.11, 0.07)	
Latin America	645	172	26.7	641	173	27.0	0.8962	1.01	(0.84,1.21)	1.02	(0.79,1.30)	0.00	(-0.05, 0.05)	
Europe	674	174	25.8	676	156	23.1	0.2416	0.89	(0.74,1.08)	0.86	(0.67,1.11)	-0.03	(-0.07, 0.02)	
Asia	244	66	27.0	248	52	21.0	0.1142	0.78	(0.56,1.06)	0.72	(0.47,1.08)	-0.06	(-0.14, 0.01)	
Other	87	18	20.7	86	11	12.8	0.1643	0.62	(0.31,1.23)	0.56	(0.25,1.27)	-0.08	(-0.19, 0.03)	
OECD Member														0.2474
No	741	193	26.0	713	184	25.8	0.9171	0.99	(0.83,1.18)	0.99	(0.78,1.25)	0.00	(-0.05, 0.04)	
Yes	1122	309	27.5	1150	275	23.9	0.0479	0.87	(0.75,1.00)	0.83	(0.68,1.00)	-0.04	(-0.07, 0.00)	
Baseline NYHA														0.4477
II	1399	330	23.6	1399	291	20.8	0.0760	0.88	(0.77,1.01)	0.85	(0.71,1.02)	-0.03	(-0.06, 0.00)	
III/IV	464	172	37.1	464	168	36.2	0.7852	0.98	(0.82,1.16)	0.96	(0.74,1.26)	-0.01	(-0.07, 0.05)	
Baseline Diabetes Status														0.5982
Diabetic	926	268	28.9	927	239	25.8	0.1272	0.89	(0.77,1.03)	0.85	(0.70,1.05)	-0.03	(-0.07, 0.01)	
Non-Diabetic	937	234	25.0	936	220	23.5	0.4582	0.94	(0.80,1.10)	0.92	(0.75,1.14)	-0.01	(-0.05, 0.02)	
Baseline BMI [kg/m²]														0.0509
<30	1299	351	27.0	1263	288	22.8	0.0136	0.84	(0.74,0.97)	0.80	(0.67,0.95)	-0.04	(-0.08,-0.01)	
>=30	564	151	26.8	600	171	28.5	0.5104	1.06	(0.88,1.28)	1.09	(0.84,1.41)	0.02	(-0.03, 0.07)	

Risk ratios and odds ratios with confidence intervals (CIs) are estimated by Cochran-Mantel-Haenszel method. For risk differences standard Wald asymptotic confidence limits are calculated. A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied 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: 23.0. * Chi-square test for treatment effect ** Breslow-Day test for homogeneity of odds ratios (treatment by subgroup interaction).

Table R.1.4.1: 5 Proportion of patients with severe adverse events
- Overall and by subgroup - TS

Subgroup Category	Placebo N	Placebo n	Placebo %	Empa 10mg N	Empa 10mg n	Empa 10mg %	Empa 10mg vs Placebo p-value *	Risk ratio	Risk (95% CI)	Odds ratio	Odds (95% CI)	Risk diff.	Risk diff. (95% CI)	p-value **
Baseline eGFR (CKD-EPI) [mL/min/1.73m²]														0.5808
>=60	958	239	24.9	969	214	22.1	0.1384	0.89	(0.75,1.04)	0.85	(0.69,1.05)	-0.03	(-0.07, 0.01)	
<60	904	262	29.0	893	245	27.4	0.4663	0.95	(0.82,1.10)	0.93	(0.75,1.14)	-0.02	(-0.06, 0.03)	
History of HHF (in the last 12 months)														0.4690
No	1290	336	26.0	1286	297	23.1	0.0819	0.89	(0.77,1.02)	0.85	(0.71,1.02)	-0.03	(-0.06, 0.00)	
Yes	573	166	29.0	577	162	28.1	0.7371	0.97	(0.81,1.16)	0.96	(0.74,1.24)	-0.01	(-0.06, 0.04)	
Cause of Heart Failure														0.9256
Ischemic	944	271	28.7	983	259	26.3	0.2462	0.92	(0.79,1.06)	0.89	(0.73,1.09)	-0.02	(-0.06, 0.02)	
Non-ischemic	919	231	25.1	880	200	22.7	0.2315	0.90	(0.77,1.07)	0.88	(0.71,1.09)	-0.02	(-0.06, 0.02)	
Heart Failure Physiology														0.2001
LVEF <= 30% and NTproBNP < median	723	148	20.5	698	126	18.1	0.2479	0.88	(0.71,1.09)	0.86	(0.66,1.11)	-0.02	(-0.07, 0.02)	
LVEF <= 30% and NTproBNP >= median	660	236	35.8	631	192	30.4	0.0420	0.85	(0.73,0.99)	0.79	(0.62,0.99)	-0.05	(-0.10, 0.00)	
LVEF > 30%	473	115	24.3	526	137	26.0	0.5289	1.07	(0.86,1.33)	1.10	(0.82,1.46)	0.02	(-0.04, 0.07)	
Baseline use of MRA														0.6052
No	512	143	27.9	557	136	24.4	0.1914	0.87	(0.71,1.07)	0.83	(0.63,1.10)	-0.04	(-0.09, 0.02)	
Yes	1351	359	26.6	1306	323	24.7	0.2775	0.93	(0.82,1.06)	0.91	(0.76,1.08)	-0.02	(-0.05, 0.01)	
Baseline use of ARNi														0.2917
No	1476	390	26.4	1523	379	24.9	0.3350	0.94	(0.83,1.06)	0.92	(0.78,1.09)	-0.02	(-0.05, 0.02)	
Yes	387	112	28.9	340	80	23.5	0.0987	0.81	(0.63,1.04)	0.76	(0.54,1.05)	-0.05	(-0.12, 0.01)	
Baseline LVEF														0.1895
<=30	1390	387	27.8	1337	322	24.1	0.0253	0.87	(0.76,0.98)	0.82	(0.69,0.98)	-0.04	(-0.07, 0.00)	
>30 to <=35	359	82	22.8	398	102	25.6	0.3721	1.12	(0.87,1.45)	1.16	(0.83,1.63)	0.03	(-0.03, 0.09)	
>35	114	33	28.9	128	35	27.3	0.7818	0.94	(0.63,1.41)	0.92	(0.53,1.62)	-0.02	(-0.13, 0.10)	

Risk ratios and odds ratios with confidence intervals (CIs) are estimated by Cochran-Mantel-Haenszel method. For risk differences standard Wald asymptotic confidence limits are calculated. A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied 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: 23.0. * Chi-square test for treatment effect ** Breslow-Day test for homogeneity of odds ratios (treatment by subgroup interaction).

Table R.1.4.1: 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 NTproBNP														0.7641
< median	919	193	21.0	942	177	18.8	0.2321	0.89	(0.75,1.07)	0.87	(0.69,1.09)	-0.02	(-0.06, 0.01)	
>= median	943	308	32.7	920	282	30.7	0.3512	0.94	(0.82,1.07)	0.91	(0.75,1.11)	-0.02	(-0.06, 0.02)	

Risk ratios and odds ratios with confidence intervals (CIs) are estimated by Cochran-Mantel-Haenszel method. For risk differences standard Wald asymptotic confidence limits are calculated. A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied 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: 23.0. * Chi-square test for treatment effect ** Breslow-Day test for homogeneity of odds ratios (treatment by subgroup interaction).

Table R.1.4.1: 6 Proportion of patients with severe 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	1863	251	13.5	1863	250	13.4	0.9617	1.00	(0.85,1.17)	1.00	(0.82,1.20)	0.00	(-0.02, 0.02)	
Sex														0.4039
Male	1410	196	13.9	1426	190	13.3	0.6543	0.96	(0.80,1.15)	0.95	(0.77,1.18)	-0.01	(-0.03, 0.02)	
Female	453	55	12.1	437	60	13.7	0.4800	1.13	(0.80,1.59)	1.15	(0.78,1.70)	0.02	(-0.03, 0.06)	
Age [years]														0.9971
< 65	739	99	13.4	675	90	13.3	0.9722	1.00	(0.76,1.30)	0.99	(0.73,1.35)	0.00	(-0.04, 0.03)	
>= 65	1124	152	13.5	1188	160	13.5	0.9691	1.00	(0.81,1.22)	1.00	(0.78,1.26)	0.00	(-0.03, 0.03)	
Region														0.2050
North America	213	48	22.5	212	53	25.0	0.5506	1.11	(0.79,1.56)	1.15	(0.73,1.79)	0.02	(-0.06, 0.11)	
Latin America	645	79	12.2	641	86	13.4	0.5310	1.10	(0.82,1.46)	1.11	(0.80,1.54)	0.01	(-0.02, 0.05)	
Europe	674	81	12.0	676	85	12.6	0.7557	1.05	(0.79,1.39)	1.05	(0.76,1.46)	0.01	(-0.03, 0.04)	
Asia	244	36	14.8	248	21	8.5	0.0294	0.57	(0.35,0.95)	0.53	(0.30,0.95)	-0.06	(-0.12,-0.01)	
Other	87	7	8.0	86	5	5.8	0.5634	0.72	(0.24,2.19)	0.71	(0.21,2.32)	-0.02	(-0.10, 0.05)	
OECD Member														0.6211
No	741	84	11.3	713	85	11.9	0.7277	1.05	(0.79,1.40)	1.06	(0.77,1.46)	0.01	(-0.03, 0.04)	
Yes	1122	167	14.9	1150	165	14.3	0.7175	0.96	(0.79,1.18)	0.96	(0.76,1.21)	-0.01	(-0.03, 0.02)	
Baseline NYHA														0.1131
II	1399	175	12.5	1399	159	11.4	0.3509	0.91	(0.74,1.11)	0.90	(0.71,1.13)	-0.01	(-0.04, 0.01)	
III/IV	464	76	16.4	464	91	19.6	0.1999	1.20	(0.91,1.58)	1.25	(0.89,1.74)	0.03	(-0.02, 0.08)	
Baseline Diabetes Status														0.5896
Diabetic	926	139	15.0	927	133	14.3	0.6866	0.96	(0.77,1.19)	0.95	(0.73,1.23)	-0.01	(-0.04, 0.03)	
Non-Diabetic	937	112	12.0	936	117	12.5	0.7179	1.05	(0.82,1.33)	1.05	(0.80,1.39)	0.01	(-0.02, 0.04)	
Baseline BMI [kg/m²]														0.0264
<30	1299	173	13.3	1263	145	11.5	0.1585	0.86	(0.70,1.06)	0.84	(0.67,1.07)	-0.02	(-0.04, 0.01)	
>=30	564	78	13.8	600	105	17.5	0.0856	1.27	(0.97,1.66)	1.32	(0.96,1.82)	0.04	(0.00, 0.08)	

Risk ratios and odds ratios with confidence intervals (CIs) are estimated by Cochran-Mantel-Haenszel method. For risk differences standard Wald asymptotic confidence limits are calculated. A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied 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: 23.0. * Chi-square test for treatment effect ** Breslow-Day test for homogeneity of odds ratios (treatment by subgroup interaction).

Table R.1.4.1: 6 Proportion of patients with severe adverse event (excluding disease related events) - Overall and by subgroup - TS

Subgroup Category	Placebo N	Placebo n	Placebo %	Empa 10mg N	Empa 10mg n	Empa 10mg %	Empa 10mg vs Placebo p-value *	Risk ratio	Risk (95% CI)	Odds ratio	Odds (95% CI)	Risk diff.	Risk diff. (95% CI)	p-value **
Baseline eGFR (CKD-EPI) [mL/min/1.73m²]														0.3121
>=60	958	117	12.2	969	108	11.1	0.4657	0.91	(0.71,1.17)	0.90	(0.68,1.19)	-0.01	(-0.04, 0.02)	
<60	904	133	14.7	893	142	15.9	0.4839	1.08	(0.87,1.34)	1.10	(0.85,1.42)	0.01	(-0.02, 0.05)	
History of HHF (in the last 12 months)														0.1066
No	1290	176	13.6	1286	159	12.4	0.3344	0.91	(0.74,1.11)	0.89	(0.71,1.12)	-0.01	(-0.04, 0.01)	
Yes	573	75	13.1	577	91	15.8	0.1956	1.20	(0.91,1.60)	1.24	(0.89,1.73)	0.03	(-0.01, 0.07)	
Cause of Heart Failure														0.8799
Ischemic	944	144	15.3	983	147	15.0	0.8541	0.98	(0.79,1.21)	0.98	(0.76,1.25)	0.00	(-0.03, 0.03)	
Non-ischemic	919	107	11.6	880	103	11.7	0.9676	1.01	(0.78,1.30)	1.01	(0.75,1.34)	0.00	(-0.03, 0.03)	
Heart Failure Physiology														0.4472
LVEF <= 30% and NTproBNP < median	723	89	12.3	698	74	10.6	0.3124	0.86	(0.64,1.15)	0.84	(0.61,1.17)	-0.02	(-0.05, 0.02)	
LVEF <= 30% and NTproBNP >= median	660	102	15.5	631	102	16.2	0.7265	1.05	(0.81,1.35)	1.05	(0.78,1.42)	0.01	(-0.03, 0.05)	
LVEF > 30%	473	57	12.1	526	71	13.5	0.4944	1.12	(0.81,1.55)	1.14	(0.78,1.65)	0.01	(-0.03, 0.06)	
Baseline use of MRA														0.4047
No	512	77	15.0	557	75	13.5	0.4616	0.90	(0.67,1.20)	0.88	(0.62,1.24)	-0.02	(-0.06, 0.03)	
Yes	1351	174	12.9	1306	175	13.4	0.6914	1.04	(0.86,1.27)	1.05	(0.84,1.31)	0.01	(-0.02, 0.03)	
Baseline use of ARNi														0.6893
No	1476	190	12.9	1523	193	12.7	0.8695	0.98	(0.82,1.19)	0.98	(0.79,1.22)	0.00	(-0.03, 0.02)	
Yes	387	61	15.8	340	57	16.8	0.7146	1.06	(0.76,1.48)	1.08	(0.73,1.60)	0.01	(-0.04, 0.06)	
Baseline LVEF														0.5791
<=30	1390	194	14.0	1337	179	13.4	0.6657	0.96	(0.79,1.16)	0.95	(0.77,1.19)	-0.01	(-0.03, 0.02)	
>30 to <=35	359	39	10.9	398	52	13.1	0.3523	1.20	(0.81,1.78)	1.23	(0.79,1.92)	0.02	(-0.02, 0.07)	
>35	114	18	15.8	128	19	14.8	0.8383	0.94	(0.52,1.70)	0.93	(0.46,1.87)	-0.01	(-0.10, 0.08)	

Risk ratios and odds ratios with confidence intervals (CIs) are estimated by Cochran-Mantel-Haenszel method. For risk differences standard Wald asymptotic confidence limits are calculated. A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied 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: 23.0. * Chi-square test for treatment effect ** Breslow-Day test for homogeneity of odds ratios (treatment by subgroup interaction).

Table R.1.4.1: 6 Proportion of patients with severe adverse event (excluding disease related events) - Overall and by subgroup - TS

Subgroup Category	Placebo N	Placebo n	Placebo %	Empa 10mg N	Empa 10mg n	Empa 10mg %	Empa 10mg vs Placebo p-value *	Risk ratio (95% CI)	Odds ratio (95% CI)	Risk diff. (95% CI)	p-value **
Baseline NTproBNP											0.1456
< median	919	117	12.7	942	105	11.1	0.2917	0.88 (0.68,1.12)	0.86 (0.65,1.14)	-0.02 (-0.05, 0.01)	
>= median	943	133	14.1	920	145	15.8	0.3156	1.12 (0.90,1.39)	1.14 (0.88,1.47)	0.02 (-0.02, 0.05)	

Risk ratios and odds ratios with confidence intervals (CIs) are estimated by Cochran-Mantel-Haenszel method. For risk differences standard Wald asymptotic confidence limits are calculated. A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied 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: 23.0. * Chi-square test for treatment effect ** Breslow-Day test for homogeneity of odds ratios (treatment by subgroup interaction).

R.1.4.2

R.1.4.2 Adverse events leading to treatment discontinuation

Table R.1.4.2: 1 Proportion of patients with adverse events leading to treatment discontinuation of drug - 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	1863	328	17.6	1863	322	17.3	0.7956	0.98	(0.85,1.13)	0.98	(0.83,1.16)	0.00	(-0.03,0.02)	
Sex														0.5069
Male	1410	257	18.2	1426	261	18.3	0.9582	1.00	(0.86,1.17)	1.01	(0.83,1.22)	0.00	(-0.03,0.03)	
Female	453	71	15.7	437	61	14.0	0.4719	0.89	(0.65,1.22)	0.87	(0.60,1.26)	-0.02	(-0.06,0.03)	
Age [years]														0.4190
< 65	739	113	15.3	675	92	13.6	0.3755	0.89	(0.69,1.15)	0.87	(0.65,1.18)	-0.02	(-0.05,0.02)	
>= 65	1124	215	19.1	1188	230	19.4	0.8875	1.01	(0.86,1.20)	1.02	(0.83,1.25)	0.00	(-0.03,0.03)	
Region														0.1833
North America	213	53	24.9	212	40	18.9	0.1337	0.76	(0.53,1.09)	0.70	(0.44,1.12)	-0.06	(-0.14,0.02)	
Latin America	645	107	16.6	641	109	17.0	0.8420	1.03	(0.80,1.31)	1.03	(0.77,1.38)	0.00	(-0.04,0.05)	
Europe	674	125	18.5	676	132	19.5	0.6463	1.05	(0.84,1.31)	1.07	(0.81,1.40)	0.01	(-0.03,0.05)	
Asia	244	28	11.5	248	34	13.7	0.4553	1.19	(0.75,1.91)	1.23	(0.72,2.09)	0.02	(-0.04,0.08)	
Other	87	15	17.2	86	7	8.1	0.0724	0.47	(0.20,1.10)	0.43	(0.16,1.10)	-0.09	(-0.19,0.01)	
OECD Member														0.5356
No	741	116	15.7	713	116	16.3	0.7490	1.04	(0.82,1.32)	1.05	(0.79,1.39)	0.01	(-0.03,0.04)	
Yes	1122	212	18.9	1150	206	17.9	0.5459	0.95	(0.80,1.13)	0.94	(0.76,1.16)	-0.01	(-0.04,0.02)	
Baseline NYHA														0.1943
II	1399	204	14.6	1399	214	15.3	0.5959	1.05	(0.88,1.25)	1.06	(0.86,1.30)	0.01	(-0.02,0.03)	
III/IV	464	124	26.7	464	108	23.3	0.2251	0.87	(0.70,1.09)	0.83	(0.62,1.12)	-0.03	(-0.09,0.02)	
Baseline Diabetes Status														0.8617
Diabetic	926	176	19.0	927	175	18.9	0.9438	0.99	(0.82,1.20)	0.99	(0.79,1.25)	0.00	(-0.04,0.03)	
Non-Diabetic	937	152	16.2	936	147	15.7	0.7601	0.97	(0.79,1.19)	0.96	(0.75,1.23)	-0.01	(-0.04,0.03)	
Baseline BMI [kg/m²]														0.2772
<30	1299	236	18.2	1263	214	16.9	0.4156	0.93	(0.79,1.10)	0.92	(0.75,1.13)	-0.01	(-0.04,0.02)	
>=30	564	92	16.3	600	108	18.0	0.4455	1.10	(0.86,1.42)	1.13	(0.83,1.53)	0.02	(-0.03,0.06)	

Risk ratios and odds ratios with confidence intervals (CIs) are estimated by Cochran-Mantel-Haenszel method. For risk differences standard Wald asymptotic confidence limits are calculated. A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied 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: 23.0. * Chi-square test for treatment effect ** Breslow-Day test for homogeneity of odds ratios (treatment by subgroup interaction).

Table R.1.4.2: 1 Proportion of patients with adverse events leading to treatment discontinuation of drug - Overall and by subgroup - TS

Subgroup Category	Placebo N	Placebo n	Placebo %	Empa 10mg N	Empa 10mg n	Empa 10mg %	p-value *	Empa 10mg vs Placebo: Risk ratio (95% CI)	Odds ratio (95% CI)	Risk diff. (95% CI)	p-value **
Baseline eGFR (CKD-EPI) [mL/min/1.73m²]											0.4674
>=60	958	133	13.9	969	141	14.6	0.6746	1.05 (0.84,1.31)	1.06 (0.82,1.36)	0.01 (-0.02,0.04)	
<60	904	194	21.5	893	181	20.3	0.5343	0.94 (0.79,1.13)	0.93 (0.74,1.17)	-0.01 (-0.05,0.03)	
History of HHF (in the last 12 months)											0.9422
No	1290	221	17.1	1286	217	16.9	0.8618	0.98 (0.83,1.17)	0.98 (0.80,1.21)	0.00 (-0.03,0.03)	
Yes	573	107	18.7	577	105	18.2	0.8351	0.97 (0.76,1.24)	0.97 (0.72,1.31)	0.00 (-0.05,0.04)	
Cause of Heart Failure											0.5008
Ischemic	944	182	19.3	983	193	19.6	0.8444	1.02 (0.85,1.22)	1.02 (0.82,1.28)	0.00 (-0.03,0.04)	
Non-ischemic	919	146	15.9	880	129	14.7	0.4694	0.92 (0.74,1.15)	0.91 (0.70,1.18)	-0.01 (-0.05,0.02)	
Heart Failure Physiology											0.1615
LVEF <= 30% and NTproBNP < median	723	76	10.5	698	83	11.9	0.4096	1.13 (0.84,1.52)	1.15 (0.83,1.60)	0.01 (-0.02,0.05)	
LVEF <= 30% and NTproBNP >= median	660	176	26.7	631	144	22.8	0.1097	0.86 (0.71,1.04)	0.81 (0.63,1.05)	-0.04 (-0.09,0.01)	
LVEF > 30%	473	74	15.6	526	91	17.3	0.4817	1.11 (0.84,1.46)	1.13 (0.81,1.58)	0.02 (-0.03,0.06)	
Baseline use of MRA											0.9039
No	512	95	18.6	557	100	18.0	0.7992	0.97 (0.75,1.25)	0.96 (0.70,1.31)	-0.01 (-0.05,0.04)	
Yes	1351	233	17.2	1306	222	17.0	0.8653	0.99 (0.83,1.17)	0.98 (0.80,1.20)	0.00 (-0.03,0.03)	
Baseline use of ARNi											0.1474
No	1476	251	17.0	1523	268	17.6	0.6686	1.03 (0.88,1.21)	1.04 (0.86,1.26)	0.01 (-0.02,0.03)	
Yes	387	77	19.9	340	54	15.9	0.1600	0.80 (0.58,1.09)	0.76 (0.52,1.12)	-0.04 (-0.10,0.02)	
Baseline LVEF											0.6124
<=30	1390	254	18.3	1337	231	17.3	0.4966	0.95 (0.80,1.11)	0.93 (0.77,1.14)	-0.01 (-0.04,0.02)	
>30 to <=35	359	55	15.3	398	69	17.3	0.4542	1.13 (0.82,1.57)	1.16 (0.79,1.71)	0.02 (-0.03,0.07)	
>35	114	19	16.7	128	22	17.2	0.9141	1.03 (0.59,1.80)	1.04 (0.53,2.03)	0.01 (-0.09,0.10)	

Risk ratios and odds ratios with confidence intervals (CIs) are estimated by Cochran-Mantel-Haenszel method. For risk differences standard Wald asymptotic confidence limits are calculated. A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied 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: 23.0. * Chi-square test for treatment effect ** Breslow-Day test for homogeneity of odds ratios (treatment by subgroup interaction).

Table R.1.4.2: 1 Proportion of patients with adverse events leading to treatment discontinuation of drug - Overall and by subgroup - TS

Subgroup Category	Placebo N	Placebo n	Placebo %	Empa 10mg N	Empa 10mg n	Empa 10mg %	Empa 10mg vs Placebo p-value *	Risk ratio (95% CI)	Odds ratio (95% CI)	Risk diff. (95% CI)	p-value **
Baseline NTproBNP											0.6415
< median	919	110	12.0	942	117	12.4	0.7664	1.04 (0.81,1.32)	1.04 (0.79,1.38)	0.00 (-0.03,0.03)	
>= median	943	217	23.0	920	205	22.3	0.7070	0.97 (0.82,1.15)	0.96 (0.77,1.19)	-0.01 (-0.05,0.03)	

Risk ratios and odds ratios with confidence intervals (CIs) are estimated by Cochran-Mantel-Haenszel method. For risk differences standard Wald asymptotic confidence limits are calculated. A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied 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: 23.0. * Chi-square test for treatment effect ** Breslow-Day test for homogeneity of odds ratios (treatment by subgroup interaction).

R.1.4.3 AESI and specific AE (MedDRA level/investigator defined)

Table R.1.4.3: 1 Proportion of patients with adverse events of special interest and other specific AEs
- by user-defined AE category - overall population 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	1863	84	4.5	1863	76	4.1	0.5180	0.90 (0.67,	1.23)	0.90 (0.66,	1.24)	0.00 (-0.02,	0.01)	
Sex														0.1795
Male	1410	63	4.5	1426	64	4.5	0.9795	1.00 (0.71,	1.41)	1.00 (0.70,	1.43)	0.00 (-0.02,	0.02)	
Female	453	21	4.6	437	12	2.7	0.1358	0.59 (0.30,	1.19)	0.58 (0.28,	1.20)	-0.02 (-0.04,	0.01)	
Age [years]														0.4877
< 65	739	44	6.0	675	33	4.9	0.3780	0.82 (0.53,	1.27)	0.81 (0.51,	1.29)	-0.01 (-0.03,	0.01)	
>= 65	1124	40	3.6	1188	43	3.6	0.9374	1.02 (0.67,	1.55)	1.02 (0.66,	1.58)	0.00 (-0.01,	0.02)	
Region														0.9860
North America	213	6	2.8	212	6	2.8	0.9934	1.00 (0.33,	3.07)	1.00 (0.32,	3.17)	0.00 (-0.03,	0.03)	
Latin America	645	26	4.0	641	22	3.4	0.5711	0.85 (0.49,	1.49)	0.85 (0.47,	1.51)	-0.01 (-0.03,	0.01)	
Europe	674	25	3.7	676	24	3.6	0.8760	0.96 (0.55,	1.66)	0.96 (0.54,	1.69)	0.00 (-0.02,	0.02)	
Asia	244	25	10.2	248	23	9.3	0.7165	0.91 (0.53,	1.55)	0.90 (0.49,	1.63)	-0.01 (-0.06,	0.04)	
Other	87	2	2.3	86	1	1.2	0.5671	0.51 (0.05,	5.48)	0.50 (0.04,	5.62)	-0.01 (-0.05,	0.03)	
OECD Member														0.2006
No	741	37	5.0	713	25	3.5	0.1607	0.70 (0.43,	1.15)	0.69 (0.41,	1.16)	-0.01 (-0.04,	0.01)	
Yes	1122	47	4.2	1150	51	4.4	0.7731	1.06 (0.72,	1.56)	1.06 (0.71,	1.59)	0.00 (-0.01,	0.02)	
Baseline NYHA														0.1870
II	1399	59	4.2	1399	46	3.3	0.1960	0.78 (0.53,	1.14)	0.77 (0.52,	1.14)	-0.01 (-0.02,	0.00)	
III/IV	464	25	5.4	464	30	6.5	0.4870	1.20 (0.72,	2.01)	1.21 (0.70,	2.10)	0.01 (-0.02,	0.04)	
Baseline Diabetes Status														0.9699
Diabetic	926	51	5.5	927	46	5.0	0.5982	0.90 (0.61,	1.33)	0.90 (0.59,	1.35)	-0.01 (-0.03,	0.01)	
Non-Diabetic	937	33	3.5	936	30	3.2	0.7038	0.91 (0.56,	1.48)	0.91 (0.55,	1.50)	0.00 (-0.02,	0.01)	
Baseline BMI [kg/m²]														0.6202
<30	1299	67	5.2	1263	57	4.5	0.4471	0.87 (0.62,	1.23)	0.87 (0.61,	1.25)	-0.01 (-0.02,	0.01)	
>=30	564	17	3.0	600	19	3.2	0.8806	1.05 (0.55,	2.00)	1.05 (0.54,	2.05)	0.00 (-0.02,	0.02)	

*** 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).
Subgroups will only be analysed if at least 10 events occurred in at least one category (both treatments combined).
For AEs on SOC and/or PT level, subgroup analyses are only shown if overall test for treatment is significant on 5% level (i.e. 95% CI for the risk ratio does not contain 1; if this is not calculable the p-value of Chi-square test is used).
MedDRA version: 23.0. * Chi-square test for treatment effect ** Breslow-Day test for homogeneity of odds ratios (treatment by subgroup interaction).

Table R.1.4.3: 1 Proportion of patients with adverse events of special interest and other specific AEs
- by user-defined AE category - overall population 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 eGFR (CKD-EPI) [mL/min/1.73m²]											0.0031
>=60	958	53	5.5	969	31	3.2	0.0121	0.58 (0.37, 0.89)	0.56 (0.36, 0.89)	-0.02 (-0.04,-0.01)	
<60	904	31	3.4	893	45	5.0	0.0900	1.47 (0.94, 2.30)	1.49 (0.94, 2.38)	0.02 (0.00, 0.03)	
History of HHF (in the last 12 months)											0.9186
No	1290	55	4.3	1286	49	3.8	0.5589	0.89 (0.61, 1.30)	0.89 (0.60, 1.32)	0.00 (-0.02, 0.01)	
Yes	573	29	5.1	577	27	4.7	0.7636	0.92 (0.55, 1.54)	0.92 (0.54, 1.58)	0.00 (-0.03, 0.02)	
Cause of Heart Failure											0.0354
Ischemic	944	30	3.2	983	41	4.2	0.2474	1.31 (0.83, 2.08)	1.33 (0.82, 2.14)	0.01 (-0.01, 0.03)	
Non-ischemic	919	54	5.9	880	35	4.0	0.0634	0.68 (0.45, 1.03)	0.66 (0.43, 1.03)	-0.02 (-0.04, 0.00)	
Heart Failure Physiology											0.1264
LVEF <= 30% and NTproBNP < median	723	23	3.2	698	17	2.4	0.3956	0.77 (0.41, 1.42)	0.76 (0.40, 1.43)	-0.01 (-0.02, 0.01)	
LVEF <= 30% and NTproBNP >= median	660	35	5.3	631	41	6.5	0.3620	1.23 (0.79, 1.90)	1.24 (0.78, 1.98)	0.01 (-0.01, 0.04)	
LVEF > 30%	473	26	5.5	526	17	3.2	0.0782	0.59 (0.32, 1.07)	0.57 (0.31, 1.07)	-0.02 (-0.05, 0.00)	
Baseline use of MRA											0.3212
No	512	16	3.1	557	21	3.8	0.5643	1.21 (0.64, 2.29)	1.21 (0.63, 2.35)	0.01 (-0.02, 0.03)	
Yes	1351	68	5.0	1306	55	4.2	0.3134	0.84 (0.59, 1.18)	0.83 (0.58, 1.19)	-0.01 (-0.02, 0.01)	
Baseline use of ARNi											0.6202
No	1476	69	4.7	1523	62	4.1	0.4186	0.87 (0.62, 1.22)	0.87 (0.61, 1.23)	-0.01 (-0.02, 0.01)	
Yes	387	15	3.9	340	14	4.1	0.8680	1.06 (0.52, 2.17)	1.07 (0.51, 2.24)	0.00 (-0.03, 0.03)	

*** 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).
Subgroups will only be analysed if at least 10 events occurred in at least one category (both treatments combined).
For AEs on SOC and/or PT level, subgroup analyses are only shown if overall test for treatment is significant on 5% level (i.e. 95% CI for the risk ratio does not contain 1; if this is not calculable the p-value of Chi-square test is used).
MedDRA version: 23.0. * Chi-square test for treatment effect ** Breslow-Day test for homogeneity of odds ratios (treatment by subgroup interaction).

Table R.1.4.3: 1 Proportion of patients with adverse events of special interest and other specific AEs
- by user-defined AE category - overall population 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														0.2254
<=30	1390	58	4.2	1337	59	4.4	0.7570	1.06 (0.74,	1.51)	1.06 (0.73,	1.54)	0.00 (-0.01,	0.02)	
>30 to <=35	359	14	3.9	398	8	2.0	0.1222	0.52 (0.22,	1.21)	0.51 (0.21,	1.22)	-0.02 (-0.04,	0.01)	
>35	114	12	10.5	128	9	7.0	0.3350	0.67 (0.29,	1.53)	0.64 (0.26,	1.59)	-0.03 (-0.11,	0.04)	
Baseline NTproBNP														0.4549
< median	919	28	3.0	942	22	2.3	0.3427	0.77 (0.44,	1.33)	0.76 (0.43,	1.34)	-0.01 (-0.02,	0.01)	
>= median	943	56	5.9	920	54	5.9	0.9497	0.99 (0.69,	1.42)	0.99 (0.67,	1.45)	0.00 (-0.02,	0.02)	

*** 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).
Subgroups will only be analysed if at least 10 events occurred in at least one category (both treatments combined).
For AEs on SOC and/or PT level, subgroup analyses are only shown if overall test for treatment is significant on 5% level (i.e. 95% CI for the risk ratio does not contain 1; if this is not calculable the p-value of Chi-square test is used).
MedDRA version: 23.0. * Chi-square test for treatment effect ** Breslow-Day test for homogeneity of odds ratios (treatment by subgroup interaction).

Table R.1.4.3: 1 Proportion of patients with adverse events of special interest and other specific AEs
- by user-defined AE category - overall population 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	1863	192	10.3	1863	175	9.4	0.3500	0.91 (0.75,	1.11)	0.90 (0.73,	1.12)	-0.01 (-0.03, 0.01)	
Sex													0.3802
Male	1410	146	10.4	1426	128	9.0	0.2141	0.87 (0.69,	1.09)	0.85 (0.67,	1.10)	-0.01 (-0.04, 0.01)	
Female	453	46	10.2	437	47	10.8	0.7697	1.06 (0.72,	1.56)	1.07 (0.69,	1.64)	0.01 (-0.03, 0.05)	
Age [years]													0.3306
< 65	739	78	10.6	675	57	8.4	0.1774	0.80 (0.58,	1.11)	0.78 (0.55,	1.12)	-0.02 (-0.05, 0.01)	
>= 65	1124	114	10.1	1188	118	9.9	0.8668	0.98 (0.77,	1.25)	0.98 (0.74,	1.28)	0.00 (-0.03, 0.02)	
Region													0.5340
North America	213	24	11.3	212	22	10.4	0.7677	0.92 (0.53,	1.59)	0.91 (0.49,	1.68)	-0.01 (-0.07, 0.05)	
Latin America	645	64	9.9	641	60	9.4	0.7328	0.94 (0.67,	1.32)	0.94 (0.65,	1.36)	-0.01 (-0.04, 0.03)	
Europe	674	68	10.1	676	68	10.1	0.9855	1.00 (0.72,	1.37)	1.00 (0.70,	1.42)	0.00 (-0.03, 0.03)	
Asia	244	27	11.1	248	22	8.9	0.4164	0.80 (0.47,	1.37)	0.78 (0.43,	1.42)	-0.02 (-0.07, 0.03)	
Other	87	9	10.3	86	3	3.5	0.0759	0.34 (0.09,	1.20)	0.31 (0.08,	1.20)	-0.07 (-0.14, 0.01)	
OECD Member													0.6848
No	741	77	10.4	713	71	10.0	0.7847	0.96 (0.71,	1.30)	0.95 (0.68,	1.34)	0.00 (-0.04, 0.03)	
Yes	1122	115	10.2	1150	104	9.0	0.3301	0.88 (0.69,	1.14)	0.87 (0.66,	1.15)	-0.01 (-0.04, 0.01)	
Baseline NYHA													0.4669
II	1399	137	9.8	1399	119	8.5	0.2379	0.87 (0.69,	1.10)	0.86 (0.66,	1.11)	-0.01 (-0.03, 0.01)	
III/IV	464	55	11.9	464	56	12.1	0.9194	1.02 (0.72,	1.44)	1.02 (0.69,	1.52)	0.00 (-0.04, 0.04)	
Baseline Diabetes Status													0.3256
Diabetic	926	98	10.6	927	98	10.6	0.9936	1.00 (0.77,	1.30)	1.00 (0.74,	1.34)	0.00 (-0.03, 0.03)	
Non-Diabetic	937	94	10.0	936	77	8.2	0.1750	0.82 (0.62,	1.09)	0.80 (0.59,	1.10)	-0.02 (-0.04, 0.01)	
Baseline BMI [kg/m²]													0.6307
<30	1299	128	9.9	1263	109	8.6	0.2853	0.88 (0.69,	1.12)	0.86 (0.66,	1.13)	-0.01 (-0.03, 0.01)	
>=30	564	64	11.3	600	66	11.0	0.8508	0.97 (0.70,	1.34)	0.97 (0.67,	1.39)	0.00 (-0.04, 0.03)	

*** 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).
Subgroups will only be analysed if at least 10 events occurred in at least one category (both treatments combined).
For AEs on SOC and/or PT level, subgroup analyses are only shown if overall test for treatment is significant on 5% level (i.e. 95% CI for the risk ratio does not contain 1; if this is not calculable the p-value of Chi-square test is used).
MedDRA version: 23.0. * Chi-square test for treatment effect ** Breslow-Day test for homogeneity of odds ratios (treatment by subgroup interaction).

Table R.1.4.3: 1 Proportion of patients with adverse events of special interest and other specific AEs
- by user-defined AE category - overall population 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 eGFR (CKD-EPI) [mL/min/1.73m²]													0.3364
>=60	958	75	7.8	969	61	6.3	0.1887	0.80 (0.58,	1.11)	0.79 (0.56,	1.12)	-0.02 (-0.04, 0.01)	
<60	904	117	12.9	893	114	12.8	0.9110	0.99 (0.78,	1.25)	0.98 (0.75,	1.30)	0.00 (-0.03, 0.03)	
History of HHF (in the last 12 months)													0.0770
No	1290	115	8.9	1286	119	9.3	0.7648	1.04 (0.81,	1.33)	1.04 (0.80,	1.36)	0.00 (-0.02, 0.03)	
Yes	573	77	13.4	577	56	9.7	0.0478	0.72 (0.52,	1.00)	0.69 (0.48,	1.00)	-0.04 (-0.07, 0.00)	
Cause of Heart Failure													0.5974
Ischemic	944	93	9.9	983	93	9.5	0.7715	0.96 (0.73,	1.26)	0.96 (0.71,	1.29)	0.00 (-0.03, 0.02)	
Non-ischemic	919	99	10.8	880	82	9.3	0.3053	0.86 (0.66,	1.14)	0.85 (0.63,	1.16)	-0.01 (-0.04, 0.01)	
Heart Failure Physiology													0.2754
LVEF <= 30% and NTproBNP < median	723	53	7.3	698	42	6.0	0.3217	0.82 (0.56,	1.21)	0.81 (0.53,	1.23)	-0.01 (-0.04, 0.01)	
LVEF <= 30% and NTproBNP >= median	660	87	13.2	631	67	10.6	0.1554	0.81 (0.60,	1.09)	0.78 (0.56,	1.10)	-0.03 (-0.06, 0.01)	
LVEF > 30%	473	52	11.0	526	66	12.5	0.4474	1.14 (0.81,	1.61)	1.16 (0.79,	1.71)	0.02 (-0.02, 0.06)	
Baseline use of MRA													0.3645
No	512	48	9.4	557	55	9.9	0.7822	1.05 (0.73,	1.52)	1.06 (0.70,	1.59)	0.00 (-0.03, 0.04)	
Yes	1351	144	10.7	1306	120	9.2	0.2053	0.86 (0.68,	1.08)	0.85 (0.66,	1.09)	-0.01 (-0.04, 0.01)	
Baseline use of ARNi													0.1808
No	1476	141	9.6	1523	143	9.4	0.8785	0.98 (0.79,	1.23)	0.98 (0.77,	1.25)	0.00 (-0.02, 0.02)	
Yes	387	51	13.2	340	32	9.4	0.1111	0.71 (0.47,	1.08)	0.68 (0.43,	1.09)	-0.04 (-0.08, 0.01)	

*** 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).
Subgroups will only be analysed if at least 10 events occurred in at least one category (both treatments combined).
For AEs on SOC and/or PT level, subgroup analyses are only shown if overall test for treatment is significant on 5% level (i.e. 95% CI for the risk ratio does not contain 1; if this is not calculable the p-value of Chi-square test is used).
MedDRA version: 23.0. * Chi-square test for treatment effect ** Breslow-Day test for homogeneity of odds ratios (treatment by subgroup interaction).

Table R.1.4.3: 1 Proportion of patients with adverse events of special interest and other specific AEs
- by user-defined AE category - overall population 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												0.2437
<=30	1390	140	10.1	1337	109	8.2	0.0819	0.81 (0.64, 1.03)	0.79 (0.61, 1.03)	-0.02	(-0.04, 0.00)	
>30 to <=35	359	35	9.7	398	47	11.8	0.3625	1.21 (0.80, 1.83)	1.24 (0.78, 1.97)	0.02	(-0.02, 0.06)	
>35	114	17	14.9	128	19	14.8	0.9881	1.00 (0.54, 1.82)	0.99 (0.49, 2.02)	0.00	(-0.09, 0.09)	
Baseline NTproBNP												0.7849
< median	919	74	8.1	942	67	7.1	0.4437	0.88 (0.64, 1.21)	0.87 (0.62, 1.23)	-0.01	(-0.03, 0.01)	
>= median	943	118	12.5	920	108	11.7	0.6089	0.94 (0.73, 1.20)	0.93 (0.70, 1.23)	-0.01	(-0.04, 0.02)	

*** 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).
Subgroups will only be analysed if at least 10 events occurred in at least one category (both treatments combined).
For AEs on SOC and/or PT level, subgroup analyses are only shown if overall test for treatment is significant on 5% level (i.e. 95% CI for the risk ratio does not contain 1; if this is not calculable the p-value of Chi-square test is used).
MedDRA version: 23.0. * Chi-square test for treatment effect ** Breslow-Day test for homogeneity of odds ratios (treatment by subgroup interaction).

Table R.1.4.3: 1 Proportion of patients with adverse events of special interest and other specific AEs
- by user-defined AE category - overall population 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	1863	18	1.0	1863	11	0.6	0.1919	0.61 (0.29, 1.29)	0.61 (0.29, 1.29)	0.00	(-0.01, 0.00)	
Sex												0.2405
Male	1410	16	1.1	1426	8	0.6	0.0954	0.49 (0.21, 1.15)	0.49 (0.21, 1.15)	-0.01	(-0.01, 0.00)	
Female	453	2	0.4	437	3	0.7	0.6249	1.55 (0.26, 9.26)	1.56 (0.26, 9.37)	0.00	(-0.01, 0.01)	
Age [years]												0.5235
< 65	739	11	1.5	675	5	0.7	0.1842	0.50 (0.17, 1.42)	0.49 (0.17, 1.43)	-0.01	(-0.02, 0.00)	
>= 65	1124	7	0.6	1188	6	0.5	0.7052	0.81 (0.27, 2.41)	0.81 (0.27, 2.42)	0.00	(-0.01, 0.00)	
Region												0.9743
North America	213	3	1.4	212	1	0.5	0.3173	0.33 (0.04, 3.19)	0.33 (0.03, 3.22)	-0.01	(-0.03, 0.01)	
Latin America	645	9	1.4	641	6	0.9	0.4431	0.67 (0.24, 1.87)	0.67 (0.24, 1.89)	0.00	(-0.02, 0.01)	
Europe	674	5	0.7	676	3	0.4	0.4756	0.60 (0.14, 2.49)	0.60 (0.14, 2.51)	0.00	(-0.01, 0.01)	
Asia	244	1	0.4	248	1	0.4	0.9908	0.98 (0.06, 15.64)	0.98 (0.06, 15.82)	0.00	(-0.01, 0.01)	
Other	87	0	0	86	0	0	0.9954	1.01 (0.02, 50.41)	1.01 (0.02, 51.56)	0.00	(-0.02, 0.02)	
OECD Member												0.6527
No	741	10	1.3	713	5	0.7	0.2213	0.52 (0.18, 1.51)	0.52 (0.18, 1.52)	-0.01	(-0.02, 0.00)	
Yes	1122	8	0.7	1150	6	0.5	0.5602	0.73 (0.25, 2.10)	0.73 (0.25, 2.11)	0.00	(-0.01, 0.00)	
Baseline NYHA												0.0325
II	1399	17	1.2	1399	7	0.5	0.0404	0.41 (0.17, 0.99)	0.41 (0.17, 0.99)	-0.01	(-0.01, 0.00)	
III/IV	464	1	0.2	464	4	0.9	0.1785	4.00 (0.45, 35.65)	4.03 (0.45, 36.16)	0.01	(0.00, 0.02)	
Baseline Diabetes Status												0.5613
Diabetic	926	13	1.4	927	9	1.0	0.3895	0.69 (0.30, 1.61)	0.69 (0.29, 1.62)	0.00	(-0.01, 0.01)	
Non-Diabetic	937	5	0.5	936	2	0.2	0.2565	0.40 (0.08, 2.06)	0.40 (0.08, 2.06)	0.00	(-0.01, 0.00)	
Baseline BMI [kg/m²]												0.4521
<30	1299	11	0.8	1263	8	0.6	0.5291	0.75 (0.30, 1.85)	0.75 (0.30, 1.86)	0.00	(-0.01, 0.00)	
>=30	564	7	1.2	600	3	0.5	0.1709	0.40 (0.10, 1.55)	0.40 (0.10, 1.55)	-0.01	(-0.02, 0.00)	

*** 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).
Subgroups will only be analysed if at least 10 events occurred in at least one category (both treatments combined).
For AEs on SOC and/or PT level, subgroup analyses are only shown if overall test for treatment is significant on 5% level (i.e. 95% CI for the risk ratio does not contain 1; if this is not calculable the p-value of Chi-square test is used).
MedDRA version: 23.0. * Chi-square test for treatment effect ** Breslow-Day test for homogeneity of odds ratios (treatment by subgroup interaction).

Table R.1.4.3: 1 Proportion of patients with adverse events of special interest and other specific AEs
- by user-defined AE category - overall population 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 eGFR (CKD-EPI) [mL/min/1.73m²]												0.9324
>=60	958	10	1.0	969	6	0.6	0.3044	0.59 (0.22, 1.63)	0.59 (0.21, 1.63)	0.00	(-0.01, 0.00)	
<60	904	8	0.9	893	5	0.6	0.4163	0.63 (0.21, 1.93)	0.63 (0.21, 1.94)	0.00	(-0.01, 0.00)	
History of HHF (in the last 12 months)												0.5217
No	1290	12	0.9	1286	6	0.5	0.1578	0.50 (0.19, 1.33)	0.50 (0.19, 1.33)	0.00	(-0.01, 0.00)	
Yes	573	6	1.0	577	5	0.9	0.7531	0.83 (0.25, 2.70)	0.83 (0.25, 2.72)	0.00	(-0.01, 0.01)	
Cause of Heart Failure												0.2700
Ischemic	944	9	1.0	983	8	0.8	0.7433	0.85 (0.33, 2.20)	0.85 (0.33, 2.22)	0.00	(-0.01, 0.01)	
Non-ischemic	919	9	1.0	880	3	0.3	0.0963	0.35 (0.09, 1.28)	0.35 (0.09, 1.28)	-0.01	(-0.01, 0.00)	
Heart Failure Physiology												0.2062
LVEF <= 30% and NTproBNP < median	723	3	0.4	698	5	0.7	0.4478	1.73 (0.41, 7.20)	1.73 (0.41, 7.27)	0.00	(0.00, 0.01)	
LVEF <= 30% and NTproBNP >= median	660	9	1.4	631	3	0.5	0.0964	0.35 (0.09, 1.28)	0.35 (0.09, 1.28)	-0.01	(-0.02, 0.00)	
LVEF > 30%	473	6	1.3	526	3	0.6	0.2436	0.45 (0.11, 1.79)	0.45 (0.11, 1.80)	-0.01	(-0.02, 0.00)	
Baseline use of MRA												0.7334
No	512	5	1.0	557	4	0.7	0.6441	0.74 (0.20, 2.72)	0.73 (0.20, 2.75)	0.00	(-0.01, 0.01)	
Yes	1351	13	1.0	1306	7	0.5	0.2038	0.56 (0.22, 1.39)	0.55 (0.22, 1.39)	0.00	(-0.01, 0.00)	
Baseline use of ARNi												0.4843
No	1476	16	1.1	1523	11	0.7	0.2944	0.67 (0.31, 1.43)	0.66 (0.31, 1.44)	0.00	(-0.01, 0.00)	
Yes	387	2	0.5	340	0	0	0.2949	0.23 (0.01, 4.72)	0.23 (0.01, 4.73)	0.00	(-0.01, 0.00)	

*** 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).
Subgroups will only be analysed if at least 10 events occurred in at least one category (both treatments combined).
For AEs on SOC and/or PT level, subgroup analyses are only shown if overall test for treatment is significant on 5% level (i.e. 95% CI for the risk ratio does not contain 1; if this is not calculable the p-value of Chi-square test is used).
MedDRA version: 23.0. * Chi-square test for treatment effect ** Breslow-Day test for homogeneity of odds ratios (treatment by subgroup interaction).

Table R.1.4.3: 1 Proportion of patients with adverse events of special interest and other specific AEs
- by user-defined AE category - overall population 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											0.3108
<=30	1390	12	0.9	1337	8	0.6	0.4176	0.69 (0.28, 1.69)	0.69 (0.28, 1.70)	0.00 (-0.01, 0.00)	
>30 to <=35	359	5	1.4	398	1	0.3	0.0770	0.18 (0.02, 1.54)	0.18 (0.02, 1.53)	-0.01 (-0.02, 0.00)	
>35	114	1	0.9	128	2	1.6	0.6306	1.78 (0.16, 19.38)	1.79 (0.16, 20.05)	0.01 (-0.02, 0.03)	
Baseline NTproBNP											0.1250
< median	919	6	0.7	942	7	0.7	0.8153	1.14 (0.38, 3.37)	1.14 (0.38, 3.40)	0.00 (-0.01, 0.01)	
>= median	943	12	1.3	920	4	0.4	0.0501	0.34 (0.11, 1.06)	0.34 (0.11, 1.05)	-0.01 (-0.02, 0.00)	

*** 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).
Subgroups will only be analysed if at least 10 events occurred in at least one category (both treatments combined).
For AEs on SOC and/or PT level, subgroup analyses are only shown if overall test for treatment is significant on 5% level (i.e. 95% CI for the risk ratio does not contain 1; if this is not calculable the p-value of Chi-square test is used).
MedDRA version: 23.0. * Chi-square test for treatment effect ** Breslow-Day test for homogeneity of odds ratios (treatment by subgroup interaction).

Table R.1.4.3: 1 Proportion of patients with adverse events of special interest and other specific AEs
- by user-defined AE category - overall population 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	1863	0	0	1863	0	0	1.0000	1.00 (0.02, 50.37)	1.00 (0.02, 50.42)	0.00 (0.00, 0.00)	

*** 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).
Subgroups will only be analysed if at least 10 events occurred in at least one category (both treatments combined).
For AEs on SOC and/or PT level, subgroup analyses are only shown if overall test for treatment is significant on 5% level (i.e. 95% CI for the risk ratio does not contain 1; if this is not calculable the p-value of Chi-square test is used).
MedDRA version: 23.0. * Chi-square test for treatment effect ** Breslow-Day test for homogeneity of odds ratios (treatment by subgroup interaction).

Table R.1.4.3: 1 Proportion of patients with adverse events of special interest and other specific AEs
- by user-defined AE category - overall population 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	1863	6	0.3	1863	9	0.5	0.4377	1.50 (0.53, 4.21)	1.50 (0.53, 4.23)	0.00 (0.00, 0.01)		
Sex												0.7798
Male	1410	5	0.4	1426	8	0.6	0.4159	1.58 (0.52, 4.82)	1.59 (0.52, 4.86)	0.00 (0.00, 0.01)		
Female	453	1	0.2	437	1	0.2	0.9797	1.04 (0.07, 16.52)	1.04 (0.06, 16.63)	0.00 (-0.01, 0.01)		
Baseline NYHA												0.2622
II	1399	5	0.4	1399	5	0.4	1.0000	1.00 (0.29, 3.45)	1.00 (0.29, 3.46)	0.00 (0.00, 0.00)		
III/IV	464	1	0.2	464	4	0.9	0.1785	4.00 (0.45, 35.65)	4.03 (0.45, 36.16)	0.01 (0.00, 0.02)		
Baseline Diabetes Status												0.2894
Diabetic	926	5	0.5	927	9	1.0	0.2841	1.80 (0.60, 5.34)	1.81 (0.60, 5.41)	0.00 (0.00, 0.01)		
Non-Diabetic	937	1	0.1	936	0	0	0.4797	0.33 (0.01, 8.18)	0.33 (0.01, 8.19)	0.00 (0.00, 0.00)		
History of HHF (in the last 12 months)												0.2857
No	1290	5	0.4	1286	9	0.7	0.2811	1.81 (0.61, 5.37)	1.81 (0.61, 5.42)	0.00 (0.00, 0.01)		
Yes	573	1	0.2	577	0	0	0.4761	0.33 (0.01, 8.11)	0.33 (0.01, 8.13)	0.00 (-0.01, 0.00)		
Cause of Heart Failure												0.3230
Ischemic	944	4	0.4	983	8	0.8	0.2765	1.92 (0.58, 6.36)	1.93 (0.58, 6.42)	0.00 (0.00, 0.01)		
Non-ischemic	919	2	0.2	880	1	0.1	0.5889	0.52 (0.05, 5.75)	0.52 (0.05, 5.76)	0.00 (0.00, 0.00)		
Baseline use of ARNi												0.1458
No	1476	6	0.4	1523	6	0.4	0.9566	0.97 (0.31, 3.00)	0.97 (0.31, 3.01)	0.00 (0.00, 0.00)		
Yes	387	0	0	340	3	0.9	0.1017	7.96 (0.41,153.65)	8.04 (0.41,156.15)	0.01 (0.00, 0.02)		
Baseline NTproBNP												0.6021
< median	919	2	0.2	942	2	0.2	0.9803	0.98 (0.14, 6.91)	0.98 (0.14, 6.94)	0.00 (0.00, 0.00)		
>= median	943	4	0.4	920	7	0.8	0.3429	1.79 (0.53, 6.11)	1.80 (0.53, 6.17)	0.00 (0.00, 0.01)		

*** 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).
Subgroups will only be analysed if at least 10 events occurred in at least one category (both treatments combined).
For AEs on SOC and/or PT level, subgroup analyses are only shown if overall test for treatment is significant on 5% level (i.e. 95% CI for the risk ratio does not contain 1; if this is not calculable the p-value of Chi-square test is used).
MedDRA version: 23.0. * Chi-square test for treatment effect ** Breslow-Day test for homogeneity of odds ratios (treatment by subgroup interaction).

Table R.1.4.3: 1 Proportion of patients with adverse events of special interest and other specific AEs
- by user-defined AE category - overall population 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	1863	28	1.5	1863	27	1.4	0.8919	0.96 (0.57, 1.63)	0.96 (0.57, 1.64)	0.00	(-0.01, 0.01)	
Sex												0.1832
Male	1410	26	1.8	1426	22	1.5	0.5341	0.84 (0.48, 1.47)	0.83 (0.47, 1.48)	0.00	(-0.01, 0.01)	
Female	453	2	0.4	437	5	1.1	0.2355	2.59 (0.51, 13.29)	2.61 (0.50, 13.52)	0.01	(0.00, 0.02)	
Age [years]												0.0774
< 65	739	18	2.4	675	10	1.5	0.1983	0.61 (0.28, 1.31)	0.60 (0.28, 1.31)	-0.01	(-0.02, 0.00)	
>= 65	1124	10	0.9	1188	17	1.4	0.2259	1.61 (0.74, 3.50)	1.62 (0.74, 3.55)	0.01	(0.00, 0.01)	
Region												0.4452
North America	213	2	0.9	212	5	2.4	0.2503	2.51 (0.49, 12.80)	2.55 (0.49, 13.28)	0.01	(-0.01, 0.04)	
Latin America	645	10	1.6	641	11	1.7	0.8147	1.11 (0.47, 2.59)	1.11 (0.47, 2.63)	0.00	(-0.01, 0.02)	
Europe	674	7	1.0	676	7	1.0	0.9956	1.00 (0.35, 2.83)	1.00 (0.35, 2.86)	0.00	(-0.01, 0.01)	
Asia	244	5	2.0	248	3	1.2	0.4616	0.59 (0.14, 2.44)	0.59 (0.14, 2.48)	-0.01	(-0.03, 0.01)	
Other	87	4	4.6	86	1	1.2	0.1775	0.25 (0.03, 2.22)	0.24 (0.03, 2.23)	-0.03	(-0.08, 0.02)	
OECD Member												0.3993
No	741	15	2.0	713	11	1.5	0.4885	0.76 (0.35, 1.65)	0.76 (0.35, 1.66)	0.00	(-0.02, 0.01)	
Yes	1122	13	1.2	1150	16	1.4	0.6214	1.20 (0.58, 2.48)	1.20 (0.58, 2.51)	0.00	(-0.01, 0.01)	
Baseline NYHA												0.2667
II	1399	18	1.3	1399	21	1.5	0.6286	1.17 (0.62, 2.18)	1.17 (0.62, 2.20)	0.00	(-0.01, 0.01)	
III/IV	464	10	2.2	464	6	1.3	0.3131	0.60 (0.22, 1.64)	0.59 (0.21, 1.65)	-0.01	(-0.03, 0.01)	
Baseline Diabetes Status												0.6899
Diabetic	926	22	2.4	927	20	2.2	0.7522	0.91 (0.50, 1.65)	0.91 (0.49, 1.67)	0.00	(-0.02, 0.01)	
Non-Diabetic	937	6	0.6	936	7	0.7	0.7793	1.17 (0.39, 3.46)	1.17 (0.39, 3.49)	0.00	(-0.01, 0.01)	
Baseline BMI [kg/m²]												0.6057
<30	1299	20	1.5	1263	17	1.3	0.6813	0.87 (0.46, 1.66)	0.87 (0.45, 1.67)	0.00	(-0.01, 0.01)	
>=30	564	8	1.4	600	10	1.7	0.7316	1.18 (0.47, 2.96)	1.18 (0.46, 3.01)	0.00	(-0.01, 0.02)	

*** 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).
Subgroups will only be analysed if at least 10 events occurred in at least one category (both treatments combined).
For AEs on SOC and/or PT level, subgroup analyses are only shown if overall test for treatment is significant on 5% level (i.e. 95% CI for the risk ratio does not contain 1; if this is not calculable the p-value of Chi-square test is used).
MedDRA version: 23.0. * Chi-square test for treatment effect ** Breslow-Day test for homogeneity of odds ratios (treatment by subgroup interaction).

Table R.1.4.3: 1 Proportion of patients with adverse events of special interest and other specific AEs
- by user-defined AE category - overall population 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 eGFR (CKD-EPI) [mL/min/1.73m²]														0.2042
>=60	958	16	1.7	969	11	1.1	0.3178	0.68	(0.32, 1.46)	0.68	(0.31, 1.46)	-0.01	(-0.02, 0.01)	
<60	904	12	1.3	893	16	1.8	0.4269	1.35	(0.64, 2.84)	1.36	(0.64, 2.88)	0.00	(-0.01, 0.02)	
History of HHF (in the last 12 months)														0.9266
No	1290	17	1.3	1286	16	1.2	0.8680	0.94	(0.48, 1.86)	0.94	(0.47, 1.88)	0.00	(-0.01, 0.01)	
Yes	573	11	1.9	577	11	1.9	0.9869	0.99	(0.43, 2.27)	0.99	(0.43, 2.31)	0.00	(-0.02, 0.02)	
Cause of Heart Failure														0.5779
Ischemic	944	15	1.6	983	17	1.7	0.8095	1.09	(0.55, 2.17)	1.09	(0.54, 2.20)	0.00	(-0.01, 0.01)	
Non-ischemic	919	13	1.4	880	10	1.1	0.5995	0.80	(0.35, 1.82)	0.80	(0.35, 1.84)	0.00	(-0.01, 0.01)	
Heart Failure Physiology														0.8835
LVEF <= 30% and NTproBNP < median	723	8	1.1	698	9	1.3	0.7512	1.17	(0.45, 3.00)	1.17	(0.45, 3.04)	0.00	(-0.01, 0.01)	
LVEF <= 30% and NTproBNP >= median	660	11	1.7	631	9	1.4	0.7267	0.86	(0.36, 2.05)	0.85	(0.35, 2.07)	0.00	(-0.02, 0.01)	
LVEF > 30%	473	9	1.9	526	9	1.7	0.8201	0.90	(0.36, 2.25)	0.90	(0.35, 2.28)	0.00	(-0.02, 0.01)	
Baseline use of MRA														0.6757
No	512	8	1.6	557	7	1.3	0.6711	0.80	(0.29, 2.20)	0.80	(0.29, 2.23)	0.00	(-0.02, 0.01)	
Yes	1351	20	1.5	1306	20	1.5	0.9140	1.03	(0.56, 1.91)	1.03	(0.55, 1.93)	0.00	(-0.01, 0.01)	
Baseline use of ARNi														0.9744
No	1476	22	1.5	1523	22	1.4	0.9166	0.97	(0.54, 1.74)	0.97	(0.53, 1.76)	0.00	(-0.01, 0.01)	
Yes	387	6	1.6	340	5	1.5	0.9299	0.95	(0.29, 3.08)	0.95	(0.29, 3.13)	0.00	(-0.02, 0.02)	

*** 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).
Subgroups will only be analysed if at least 10 events occurred in at least one category (both treatments combined).
For AEs on SOC and/or PT level, subgroup analyses are only shown if overall test for treatment is significant on 5% level (i.e. 95% CI for the risk ratio does not contain 1; if this is not calculable the p-value of Chi-square test is used).
MedDRA version: 23.0. * Chi-square test for treatment effect ** Breslow-Day test for homogeneity of odds ratios (treatment by subgroup interaction).

Table R.1.4.3: 1 Proportion of patients with adverse events of special interest and other specific AEs
- by user-defined AE category - overall population 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												0.8816
<=30	1390	19	1.4	1337	18	1.3	0.9629	0.98 (0.52, 1.87)	0.98 (0.51, 1.88)	0.00	(-0.01, 0.01)	
>30 to <=35	359	6	1.7	398	5	1.3	0.6337	0.75 (0.23, 2.44)	0.75 (0.23, 2.47)	0.00	(-0.02, 0.01)	
>35	114	3	2.6	128	4	3.1	0.8192	1.19 (0.27, 5.19)	1.19 (0.26, 5.45)	0.00	(-0.04, 0.05)	
Baseline NTproBNP												0.7364
< median	919	15	1.6	942	16	1.7	0.9110	1.04 (0.52, 2.09)	1.04 (0.51, 2.12)	0.00	(-0.01, 0.01)	
>= median	943	13	1.4	920	11	1.2	0.7263	0.87 (0.39, 1.93)	0.87 (0.39, 1.94)	0.00	(-0.01, 0.01)	

*** 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).
Subgroups will only be analysed if at least 10 events occurred in at least one category (both treatments combined).
For AEs on SOC and/or PT level, subgroup analyses are only shown if overall test for treatment is significant on 5% level (i.e. 95% CI for the risk ratio does not contain 1; if this is not calculable the p-value of Chi-square test is used).
MedDRA version: 23.0. * Chi-square test for treatment effect ** Breslow-Day test for homogeneity of odds ratios (treatment by subgroup interaction).

Table R.1.4.3: 1 Proportion of patients with adverse events of special interest and other specific AEs
- by user-defined AE category - overall population 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	1863	83	4.5	1863	91	4.9	0.5345	1.10 (0.82,	1.47)	1.10 (0.81,	1.49)	0.00 (-0.01, 0.02)	
Sex													0.2507
Male	1410	46	3.3	1426	44	3.1	0.7882	0.95 (0.63,	1.42)	0.94 (0.62,	1.44)	0.00 (-0.01, 0.01)	
Female	453	37	8.2	437	47	10.8	0.1869	1.32 (0.87,	1.98)	1.35 (0.86,	2.13)	0.03 (-0.01, 0.06)	
Age [years]													0.1859
< 65	739	29	3.9	675	21	3.1	0.4083	0.79 (0.46,	1.38)	0.79 (0.44,	1.39)	-0.01 (-0.03, 0.01)	
>= 65	1124	54	4.8	1188	70	5.9	0.2458	1.23 (0.87,	1.73)	1.24 (0.86,	1.79)	0.01 (-0.01, 0.03)	
Region													0.1622
North America	213	19	8.9	212	13	6.1	0.2761	0.69 (0.35,	1.36)	0.67 (0.32,	1.39)	-0.03 (-0.08, 0.02)	
Latin America	645	29	4.5	641	25	3.9	0.5942	0.87 (0.51,	1.46)	0.86 (0.50,	1.49)	-0.01 (-0.03, 0.02)	
Europe	674	30	4.5	676	40	5.9	0.2245	1.33 (0.84,	2.11)	1.35 (0.83,	2.19)	0.01 (-0.01, 0.04)	
Asia	244	3	1.2	248	10	4.0	0.0526	3.28 (0.91,	11.77)	3.38 (0.92,	12.42)	0.03 (0.00, 0.06)	
Other	87	2	2.3	86	3	3.5	0.6405	1.52 (0.26,	8.86)	1.54 (0.25,	9.43)	0.01 (-0.04, 0.06)	
OECD Member													0.3700
No	741	30	4.0	713	26	3.6	0.6905	0.90 (0.54,	1.51)	0.90 (0.53,	1.53)	0.00 (-0.02, 0.02)	
Yes	1122	53	4.7	1150	65	5.7	0.3187	1.20 (0.84,	1.70)	1.21 (0.83,	1.75)	0.01 (-0.01, 0.03)	
Baseline NYHA													0.5764
II	1399	57	4.1	1399	59	4.2	0.8496	1.04 (0.72,	1.48)	1.04 (0.71,	1.50)	0.00 (-0.01, 0.02)	
III/IV	464	26	5.6	464	32	6.9	0.4158	1.23 (0.75,	2.03)	1.25 (0.73,	2.13)	0.01 (-0.02, 0.04)	
Baseline Diabetes Status													0.7942
Diabetic	926	49	5.3	927	52	5.6	0.7631	1.06 (0.73,	1.55)	1.06 (0.71,	1.59)	0.00 (-0.02, 0.02)	
Non-Diabetic	937	34	3.6	936	39	4.2	0.5474	1.15 (0.73,	1.80)	1.15 (0.72,	1.85)	0.01 (-0.01, 0.02)	
Baseline BMI [kg/m²]													0.5371
<30	1299	52	4.0	1263	51	4.0	0.9641	1.01 (0.69,	1.47)	1.01 (0.68,	1.50)	0.00 (-0.01, 0.02)	
>=30	564	31	5.5	600	40	6.7	0.4044	1.21 (0.77,	1.91)	1.23 (0.76,	1.99)	0.01 (-0.02, 0.04)	

*** 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).
Subgroups will only be analysed if at least 10 events occurred in at least one category (both treatments combined).
For AEs on SOC and/or PT level, subgroup analyses are only shown if overall test for treatment is significant on 5% level (i.e. 95% CI for the risk ratio does not contain 1; if this is not calculable the p-value of Chi-square test is used).
MedDRA version: 23.0. * Chi-square test for treatment effect ** Breslow-Day test for homogeneity of odds ratios (treatment by subgroup interaction).

Table R.1.4.3: 1 Proportion of patients with adverse events of special interest and other specific AEs
- by user-defined AE category - overall population 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 eGFR (CKD-EPI) [mL/min/1.73m²]														0.7462
>=60	958	34	3.5	969	40	4.1	0.5085	1.16	(0.74, 1.82)	1.17	(0.73, 1.87)	0.01	(-0.01, 0.02)	
<60	904	49	5.4	893	51	5.7	0.7881	1.05	(0.72, 1.54)	1.06	(0.71, 1.58)	0.00	(-0.02, 0.02)	
History of HHF (in the last 12 months)														0.3846
No	1290	65	5.0	1286	66	5.1	0.9141	1.02	(0.73, 1.42)	1.02	(0.72, 1.45)	0.00	(-0.02, 0.02)	
Yes	573	18	3.1	577	25	4.3	0.2870	1.38	(0.76, 2.50)	1.40	(0.75, 2.59)	0.01	(-0.01, 0.03)	
Cause of Heart Failure														0.3405
Ischemic	944	38	4.0	983	50	5.1	0.2647	1.26	(0.84, 1.91)	1.28	(0.83, 1.97)	0.01	(-0.01, 0.03)	
Non-ischemic	919	45	4.9	880	41	4.7	0.8134	0.95	(0.63, 1.44)	0.95	(0.62, 1.46)	0.00	(-0.02, 0.02)	
Heart Failure Physiology														0.5505
LVEF <= 30% and NTproBNP < median	723	27	3.7	698	31	4.4	0.5008	1.19	(0.72, 1.97)	1.20	(0.71, 2.03)	0.01	(-0.01, 0.03)	
LVEF <= 30% and NTproBNP >= median	660	37	5.6	631	32	5.1	0.6694	0.90	(0.57, 1.43)	0.90	(0.55, 1.46)	-0.01	(-0.03, 0.02)	
LVEF > 30%	473	19	4.0	526	28	5.3	0.3303	1.33	(0.75, 2.34)	1.34	(0.74, 2.44)	0.01	(-0.01, 0.04)	
Baseline use of MRA														0.6051
No	512	30	5.9	557	32	5.7	0.9363	0.98	(0.60, 1.59)	0.98	(0.59, 1.64)	0.00	(-0.03, 0.03)	
Yes	1351	53	3.9	1306	59	4.5	0.4457	1.15	(0.80, 1.66)	1.16	(0.79, 1.69)	0.01	(-0.01, 0.02)	
Baseline use of ARNi														0.6608
No	1476	62	4.2	1523	73	4.8	0.4339	1.14	(0.82, 1.59)	1.15	(0.81, 1.62)	0.01	(-0.01, 0.02)	
Yes	387	21	5.4	340	18	5.3	0.9371	0.98	(0.53, 1.80)	0.97	(0.51, 1.86)	0.00	(-0.03, 0.03)	

*** 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).
Subgroups will only be analysed if at least 10 events occurred in at least one category (both treatments combined).
For AEs on SOC and/or PT level, subgroup analyses are only shown if overall test for treatment is significant on 5% level (i.e. 95% CI for the risk ratio does not contain 1; if this is not calculable the p-value of Chi-square test is used).
MedDRA version: 23.0. * Chi-square test for treatment effect ** Breslow-Day test for homogeneity of odds ratios (treatment by subgroup interaction).

Table R.1.4.3: 1 Proportion of patients with adverse events of special interest and other specific AEs
- by user-defined AE category - overall population 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													0.6970
<=30	1390	64	4.6	1337	63	4.7	0.8938	1.02 (0.73,	1.44)	1.02 (0.72,	1.46)	0.00 (-0.01, 0.02)	
>30 to <=35	359	17	4.7	398	24	6.0	0.4319	1.27 (0.70,	2.33)	1.29 (0.68,	2.44)	0.01 (-0.02, 0.05)	
>35	114	2	1.8	128	4	3.1	0.4937	1.78 (0.33,	9.54)	1.81 (0.32,	10.05)	0.01 (-0.02, 0.05)	
Baseline NTproBNP													0.7323
< median	919	37	4.0	942	44	4.7	0.4955	1.16 (0.76,	1.78)	1.17 (0.75,	1.83)	0.01 (-0.01, 0.02)	
>= median	943	46	4.9	920	47	5.1	0.8192	1.05 (0.70,	1.56)	1.05 (0.69,	1.59)	0.00 (-0.02, 0.02)	

*** 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).
Subgroups will only be analysed if at least 10 events occurred in at least one category (both treatments combined).
For AEs on SOC and/or PT level, subgroup analyses are only shown if overall test for treatment is significant on 5% level (i.e. 95% CI for the risk ratio does not contain 1; if this is not calculable the p-value of Chi-square test is used).
MedDRA version: 23.0. * Chi-square test for treatment effect ** Breslow-Day test for homogeneity of odds ratios (treatment by subgroup interaction).

Table R.1.4.3: 1 Proportion of patients with adverse events of special interest and other specific AEs
- by user-defined AE category - overall population 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	1863	15	0.8	1863	19	1.0	0.4907	1.27 (0.65,	2.49)	1.27 (0.64,	2.51)	0.00 (0.00, 0.01)	
Sex													0.3136
Male	1410	11	0.8	1426	11	0.8	0.9788	0.99 (0.43,	2.27)	0.99 (0.43,	2.29)	0.00 (-0.01, 0.01)	
Female	453	4	0.9	437	8	1.8	0.2204	2.07 (0.63,	6.84)	2.09 (0.63,	7.00)	0.01 (-0.01, 0.02)	
Age [years]													0.3081
< 65	739	5	0.7	675	3	0.4	0.5610	0.66 (0.16,	2.74)	0.66 (0.16,	2.75)	0.00 (-0.01, 0.01)	
>= 65	1124	10	0.9	1188	16	1.3	0.2975	1.51 (0.69,	3.32)	1.52 (0.69,	3.37)	0.00 (0.00, 0.01)	
Region													0.3223
North America	213	5	2.3	212	1	0.5	0.1012	0.20 (0.02,	1.71)	0.20 (0.02,	1.70)	-0.02 (-0.04, 0.00)	
Latin America	645	4	0.6	641	6	0.9	0.5191	1.51 (0.43,	5.32)	1.51 (0.43,	5.39)	0.00 (-0.01, 0.01)	
Europe	674	5	0.7	676	9	1.3	0.2850	1.79 (0.60,	5.33)	1.81 (0.60,	5.42)	0.01 (0.00, 0.02)	
Asia	244	1	0.4	248	2	0.8	0.5721	1.97 (0.18,	21.56)	1.98 (0.18,	21.93)	0.00 (-0.01, 0.02)	
Other	87	0	0	86	1	1.2	0.4719	3.03 (0.13,	73.47)	3.07 (0.12,	76.42)	0.01 (-0.02, 0.04)	
OECD Member													0.6925
No	741	4	0.5	713	6	0.8	0.4865	1.56 (0.44,	5.50)	1.56 (0.44,	5.56)	0.00 (-0.01, 0.01)	
Yes	1122	11	1.0	1150	13	1.1	0.7265	1.15 (0.52,	2.56)	1.15 (0.52,	2.59)	0.00 (-0.01, 0.01)	
Baseline NYHA													0.7532
II	1399	11	0.8	1399	13	0.9	0.6818	1.18 (0.53,	2.63)	1.18 (0.53,	2.65)	0.00 (-0.01, 0.01)	
III/IV	464	4	0.9	464	6	1.3	0.5248	1.50 (0.43,	5.28)	1.51 (0.42,	5.37)	0.00 (-0.01, 0.02)	
Baseline Diabetes Status													0.9652
Diabetic	926	8	0.9	927	10	1.1	0.6373	1.25 (0.50,	3.15)	1.25 (0.49,	3.18)	0.00 (-0.01, 0.01)	
Non-Diabetic	937	7	0.7	936	9	1.0	0.6141	1.29 (0.48,	3.44)	1.29 (0.48,	3.48)	0.00 (-0.01, 0.01)	
Baseline BMI [kg/m²]													0.6894
<30	1299	10	0.8	1263	11	0.9	0.7766	1.13 (0.48,	2.65)	1.13 (0.48,	2.68)	0.00 (-0.01, 0.01)	
>=30	564	5	0.9	600	8	1.3	0.4685	1.50 (0.49,	4.57)	1.51 (0.49,	4.65)	0.00 (-0.01, 0.02)	

*** 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).
Subgroups will only be analysed if at least 10 events occurred in at least one category (both treatments combined).
For AEs on SOC and/or PT level, subgroup analyses are only shown if overall test for treatment is significant on 5% level (i.e. 95% CI for the risk ratio does not contain 1; if this is not calculable the p-value of Chi-square test is used).
MedDRA version: 23.0. * Chi-square test for treatment effect ** Breslow-Day test for homogeneity of odds ratios (treatment by subgroup interaction).

Table R.1.4.3: 1 Proportion of patients with adverse events of special interest and other specific AEs
- by user-defined AE category - overall population 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 eGFR (CKD-EPI) [mL/min/1.73m²]											0.5841
>=60	958	6	0.6	969	6	0.6	0.9842	0.99 (0.32, 3.05)	0.99 (0.32, 3.08)	0.00 (-0.01, 0.01)	
<60	904	9	1.0	893	13	1.5	0.3751	1.46 (0.63, 3.40)	1.47 (0.62, 3.45)	0.00 (-0.01, 0.01)	
History of HHF (in the last 12 months)											0.7641
No	1290	11	0.9	1286	13	1.0	0.6761	1.19 (0.53, 2.64)	1.19 (0.53, 2.66)	0.00 (-0.01, 0.01)	
Yes	573	4	0.7	577	6	1.0	0.5325	1.49 (0.42, 5.25)	1.49 (0.42, 5.33)	0.00 (-0.01, 0.01)	
Cause of Heart Failure											0.8709
Ischemic	944	8	0.8	983	10	1.0	0.6984	1.20 (0.48, 3.03)	1.20 (0.47, 3.06)	0.00 (-0.01, 0.01)	
Non-ischemic	919	7	0.8	880	9	1.0	0.5555	1.34 (0.50, 3.59)	1.35 (0.50, 3.63)	0.00 (-0.01, 0.01)	
Heart Failure Physiology											0.1847
LVEF <= 30% and NTproBNP < median	723	6	0.8	698	3	0.4	0.3419	0.52 (0.13, 2.06)	0.52 (0.13, 2.07)	0.00 (-0.01, 0.00)	
LVEF <= 30% and NTproBNP >= median	660	4	0.6	631	10	1.6	0.0896	2.61 (0.82, 8.29)	2.64 (0.82, 8.46)	0.01 (0.00, 0.02)	
LVEF > 30%	473	5	1.1	526	6	1.1	0.8994	1.08 (0.33, 3.51)	1.08 (0.33, 3.56)	0.00 (-0.01, 0.01)	
Baseline use of MRA											0.7183
No	512	5	1.0	557	8	1.4	0.4933	1.47 (0.48, 4.47)	1.48 (0.48, 4.55)	0.00 (-0.01, 0.02)	
Yes	1351	10	0.7	1306	11	0.8	0.7664	1.14 (0.48, 2.67)	1.14 (0.48, 2.69)	0.00 (-0.01, 0.01)	
Baseline use of ARNi											0.2948
No	1476	11	0.7	1523	17	1.1	0.2910	1.50 (0.70, 3.19)	1.50 (0.70, 3.22)	0.00 (0.00, 0.01)	
Yes	387	4	1.0	340	2	0.6	0.5078	0.57 (0.10, 3.09)	0.57 (0.10, 3.11)	0.00 (-0.02, 0.01)	

*** 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).
Subgroups will only be analysed if at least 10 events occurred in at least one category (both treatments combined).
For AEs on SOC and/or PT level, subgroup analyses are only shown if overall test for treatment is significant on 5% level (i.e. 95% CI for the risk ratio does not contain 1; if this is not calculable the p-value of Chi-square test is used).
MedDRA version: 23.0. * Chi-square test for treatment effect ** Breslow-Day test for homogeneity of odds ratios (treatment by subgroup interaction).

Table R.1.4.3: 1 Proportion of patients with adverse events of special interest and other specific AEs
- by user-defined AE category - overall population and by subgroup - TS
User-defined AE category: Complicated urinary tract infection (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											0.9433
<=30	1390	10	0.7	1337	13	1.0	0.4703	1.35 (0.59, 3.07)	1.35 (0.59, 3.10)	0.00 (0.00, 0.01)	
>30 to <=35	359	4	1.1	398	5	1.3	0.8571	1.13 (0.31, 4.17)	1.13 (0.30, 4.24)	0.00 (-0.01, 0.02)	
>35	114	1	0.9	128	1	0.8	0.9344	0.89 (0.06, 14.08)	0.89 (0.06, 14.39)	0.00 (-0.02, 0.02)	
Baseline NTproBNP											0.0823
< median	919	9	1.0	942	6	0.6	0.4089	0.65 (0.23, 1.82)	0.65 (0.23, 1.83)	0.00 (-0.01, 0.00)	
>= median	943	6	0.6	920	13	1.4	0.0952	2.22 (0.85, 5.82)	2.24 (0.85, 5.91)	0.01 (0.00, 0.02)	

*** 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).
Subgroups will only be analysed if at least 10 events occurred in at least one category (both treatments combined).
For AEs on SOC and/or PT level, subgroup analyses are only shown if overall test for treatment is significant on 5% level (i.e. 95% CI for the risk ratio does not contain 1; if this is not calculable the p-value of Chi-square test is used).
MedDRA version: 23.0. * Chi-square test for treatment effect ** Breslow-Day test for homogeneity of odds ratios (treatment by subgroup interaction).

Table R.1.4.3: 1 Proportion of patients with adverse events of special interest and other specific AEs
- by user-defined AE category - overall population 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	1863	12	0.6	1863	31	1.7	0.0036	2.58 (1.33, 5.01)	2.61 (1.34, 5.10)	0.01 (0.00, 0.02)	
Sex											0.4265
Male	1410	6	0.4	1426	20	1.4	0.0063	3.30 (1.33, 8.18)	3.33 (1.33, 8.31)	0.01 (0.00, 0.02)	
Female	453	6	1.3	437	11	2.5	0.1938	1.90 (0.71, 5.09)	1.92 (0.71, 5.25)	0.01 (-0.01, 0.03)	
Age [years]											0.1748
< 65	739	7	0.9	675	10	1.5	0.3572	1.56 (0.60, 4.09)	1.57 (0.60, 4.15)	0.01 (-0.01, 0.02)	
>= 65	1124	5	0.4	1188	21	1.8	0.0026	3.97 (1.50, 10.50)	4.03 (1.51, 10.72)	0.01 (0.00, 0.02)	
Region											0.9897
North America	213	3	1.4	212	6	2.8	0.3087	2.01 (0.51, 7.93)	2.04 (0.50, 8.26)	0.01 (-0.01, 0.04)	
Latin America	645	5	0.8	641	12	1.9	0.0851	2.41 (0.86, 6.82)	2.44 (0.86, 6.97)	0.01 (0.00, 0.02)	
Europe	674	4	0.6	676	10	1.5	0.1082	2.49 (0.79, 7.91)	2.52 (0.78, 8.06)	0.01 (0.00, 0.02)	
Asia	244	0	0	248	2	0.8	0.2525	4.92 (0.24,101.95)	4.96 (0.24,103.84)	0.01 (-0.01, 0.02)	
Other	87	0	0	86	1	1.2	0.4719	3.03 (0.13, 73.47)	3.07 (0.12, 76.42)	0.01 (-0.02, 0.04)	
OECD Member											0.9123
No	741	5	0.7	713	13	1.8	0.0477	2.70 (0.97, 7.54)	2.73 (0.97, 7.71)	0.01 (0.00, 0.02)	
Yes	1122	7	0.6	1150	18	1.6	0.0315	2.51 (1.05, 5.98)	2.53 (1.05, 6.09)	0.01 (0.00, 0.02)	
Baseline NYHA											0.8877
II	1399	8	0.6	1399	20	1.4	0.0227	2.50 (1.10, 5.66)	2.52 (1.11, 5.74)	0.01 (0.00, 0.02)	
III/IV	464	4	0.9	464	11	2.4	0.0684	2.75 (0.88, 8.57)	2.79 (0.88, 8.83)	0.02 (0.00, 0.03)	
Baseline Diabetes Status											0.1444
Diabetic	926	4	0.4	927	18	1.9	0.0027	4.50 (1.53, 13.23)	4.56 (1.54, 13.54)	0.02 (0.01, 0.02)	
Non-Diabetic	937	8	0.9	936	13	1.4	0.2715	1.63 (0.68, 3.91)	1.64 (0.67, 3.96)	0.01 (0.00, 0.01)	
Baseline BMI [kg/m²]											0.9923
<30	1299	8	0.6	1263	20	1.6	0.0185	2.57 (1.14, 5.82)	2.60 (1.14, 5.92)	0.01 (0.00, 0.02)	
>=30	564	4	0.7	600	11	1.8	0.0892	2.59 (0.83, 8.07)	2.61 (0.83, 8.26)	0.01 (0.00, 0.02)	

*** 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).
Subgroups will only be analysed if at least 10 events occurred in at least one category (both treatments combined).
For AEs on SOC and/or PT level, subgroup analyses are only shown if overall test for treatment is significant on 5% level (i.e. 95% CI for the risk ratio does not contain 1; if this is not calculable the p-value of Chi-square test is used).
MedDRA version: 23.0. * Chi-square test for treatment effect ** Breslow-Day test for homogeneity of odds ratios (treatment by subgroup interaction).

Table R.1.4.3: 1 Proportion of patients with adverse events of special interest and other specific AEs
- by user-defined AE category - overall population 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 eGFR (CKD-EPI) [mL/min/1.73m²]											0.3537
>=60	958	8	0.8	969	16	1.7	0.1063	1.98 (0.85, 4.60)	1.99 (0.85, 4.68)	0.01 (0.00, 0.02)	
<60	904	4	0.4	893	15	1.7	0.0104	3.80 (1.26, 11.39)	3.84 (1.27, 11.63)	0.01 (0.00, 0.02)	
History of HHF (in the last 12 months)											0.2028
No	1290	7	0.5	1286	24	1.9	0.0021	3.44 (1.49, 7.95)	3.49 (1.50, 8.12)	0.01 (0.00, 0.02)	
Yes	573	5	0.9	577	7	1.2	0.5698	1.39 (0.44, 4.35)	1.40 (0.44, 4.42)	0.00 (-0.01, 0.02)	
Cause of Heart Failure											0.0431
Ischemic	944	3	0.3	983	19	1.9	0.0008	6.08 (1.81, 20.49)	6.18 (1.82, 20.96)	0.02 (0.01, 0.03)	
Non-ischemic	919	9	1.0	880	12	1.4	0.4481	1.39 (0.59, 3.29)	1.40 (0.59, 3.33)	0.00 (-0.01, 0.01)	
Heart Failure Physiology											0.0586
LVEF <= 30% and NTproBNP < median	723	4	0.6	698	13	1.9	0.0232	3.37 (1.10, 10.27)	3.41 (1.11, 10.51)	0.01 (0.00, 0.02)	
LVEF <= 30% and NTproBNP >= median	660	1	0.2	631	10	1.6	0.0051	10.46 (1.34, 81.47)	10.61 (1.35, 83.14)	0.01 (0.00, 0.02)	
LVEF > 30%	473	7	1.5	526	8	1.5	0.9576	1.03 (0.38, 2.81)	1.03 (0.37, 2.86)	0.00 (-0.01, 0.02)	
Baseline use of MRA											0.1410
No	512	6	1.2	557	9	1.6	0.5376	1.38 (0.49, 3.85)	1.39 (0.49, 3.92)	0.00 (-0.01, 0.02)	
Yes	1351	6	0.4	1306	22	1.7	0.0017	3.79 (1.54, 9.32)	3.84 (1.55, 9.50)	0.01 (0.00, 0.02)	
Baseline use of ARNi											0.7077
No	1476	8	0.5	1523	20	1.3	0.0281	2.42 (1.07, 5.48)	2.44 (1.07, 5.56)	0.01 (0.00, 0.01)	
Yes	387	4	1.0	340	11	3.2	0.0372	3.13 (1.01, 9.74)	3.20 (1.01, 10.15)	0.02 (0.00, 0.04)	

*** 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).
Subgroups will only be analysed if at least 10 events occurred in at least one category (both treatments combined).
For AEs on SOC and/or PT level, subgroup analyses are only shown if overall test for treatment is significant on 5% level (i.e. 95% CI for the risk ratio does not contain 1; if this is not calculable the p-value of Chi-square test is used).
MedDRA version: 23.0. * Chi-square test for treatment effect ** Breslow-Day test for homogeneity of odds ratios (treatment by subgroup interaction).

Table R.1.4.3: 1 Proportion of patients with adverse events of special interest and other specific AEs
- by user-defined AE category - overall population 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											0.0462
<=30	1390	5	0.4	1337	23	1.7	0.0004	4.78 (1.82, 12.54)	4.85 (1.84, 12.79)	0.01 (0.01, 0.02)	
>30 to <=35	359	6	1.7	398	8	2.0	0.7298	1.20 (0.42, 3.43)	1.21 (0.41, 3.51)	0.00 (-0.02, 0.02)	
>35	114	1	0.9	128	0	0	0.4279	0.30 (0.01, 7.22)	0.29 (0.01, 7.30)	-0.01 (-0.03, 0.01)	
Baseline NTproBNP											0.7819
< median	919	7	0.8	942	17	1.8	0.0462	2.37 (0.99, 5.69)	2.39 (0.99, 5.80)	0.01 (0.00, 0.02)	
>= median	943	5	0.5	920	14	1.5	0.0332	2.87 (1.04, 7.94)	2.90 (1.04, 8.08)	0.01 (0.00, 0.02)	

*** 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).
Subgroups will only be analysed if at least 10 events occurred in at least one category (both treatments combined).
For AEs on SOC and/or PT level, subgroup analyses are only shown if overall test for treatment is significant on 5% level (i.e. 95% CI for the risk ratio does not contain 1; if this is not calculable the p-value of Chi-square test is used).
MedDRA version: 23.0. * Chi-square test for treatment effect ** Breslow-Day test for homogeneity of odds ratios (treatment by subgroup interaction).

Table R.1.4.3: 1 Proportion of patients with adverse events of special interest and other specific AEs
- by user-defined AE category - overall population 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	1863	5	0.3	1863	6	0.3	0.7627	1.20 (0.37, 3.93)	1.20 (0.37, 3.94)	0.00 (0.00, 0.00)	
Sex											0.3807
Male	1410	4	0.3	1426	6	0.4	0.5381	1.48 (0.42, 5.24)	1.49 (0.42, 5.27)	0.00 (0.00, 0.01)	
Female	453	1	0.2	437	0	0	0.4949	0.35 (0.01, 8.46)	0.34 (0.01, 8.49)	0.00 (-0.01, 0.00)	
OECD Member											0.4916
No	741	0	0	713	1	0.1	0.4624	3.12 (0.13, 76.40)	3.12 (0.13, 76.77)	0.00 (0.00, 0.01)	
Yes	1122	5	0.4	1150	5	0.4	0.9688	0.98 (0.28, 3.36)	0.98 (0.28, 3.38)	0.00 (-0.01, 0.01)	

*** 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).
Subgroups will only be analysed if at least 10 events occurred in at least one category (both treatments combined).
For AEs on SOC and/or PT level, subgroup analyses are only shown if overall test for treatment is significant on 5% level (i.e. 95% CI for the risk ratio does not contain 1; if this is not calculable the p-value of Chi-square test is used).
MedDRA version: 23.0. * Chi-square test for treatment effect ** Breslow-Day test for homogeneity of odds ratios (treatment by subgroup interaction).

Table R.1.4.3: 1 Proportion of patients with adverse events of special interest and other specific AEs
- by user-defined AE category - overall population 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	1863	4	0.2	1863	1	0.1	0.1794	0.25 (0.03, 2.23)	0.25 (0.03, 2.24)	0.00 (0.00, 0.00)	

*** 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).
Subgroups will only be analysed if at least 10 events occurred in at least one category (both treatments combined).
For AEs on SOC and/or PT level, subgroup analyses are only shown if overall test for treatment is significant on 5% level (i.e. 95% CI for the risk ratio does not contain 1; if this is not calculable the p-value of Chi-square test is used).
MedDRA version: 23.0. * Chi-square test for treatment effect ** Breslow-Day test for homogeneity of odds ratios (treatment by subgroup interaction).

Table R.1.4.3: 1 Proportion of patients with adverse events of special interest and other specific AEs
- by user-defined AE category - overall population 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	1863	4	0.2	1863	5	0.3	0.7386	1.25 (0.34, 4.65)	1.25 (0.34, 4.66)	0.00 (0.00, 0.00)	

*** 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).
Subgroups will only be analysed if at least 10 events occurred in at least one category (both treatments combined).
For AEs on SOC and/or PT level, subgroup analyses are only shown if overall test for treatment is significant on 5% level
(i.e. 95% CI for the risk ratio does not contain 1; if this is not calculable the p-value of Chi-square test is used).
MedDRA version: 23.0. * Chi-square test for treatment effect ** Breslow-Day test for homogeneity of odds ratios (treatment by subgroup interaction).

Table R.1.4.3: 1 Proportion of patients with adverse events of special interest and other specific AEs
- by user-defined AE category - overall population and by subgroup - TS
User-defined AE category: Sepsis (investigator-defined)

Subgroup Category	Placebo N	Placebo n	Placebo %	Empa 10mg N	Empa 10mg n	Empa 10mg %	Empa 10mg vs Placebo p-value *	Risk ratio (95% CI)	Odds ratio (95% CI)	Risk diff. (95% CI)	p-value **
Overall	1863	15	0.8	1863	33	1.8	0.0089	2.20 (1.20, 4.04)	2.22 (1.20, 4.10)	0.01 (0.00, 0.02)	
Sex											0.0592
Male	1410	13	0.9	1426	20	1.4	0.2328	1.52 (0.76, 3.05)	1.53 (0.76, 3.08)	0.00 (0.00, 0.01)	
Female	453	2	0.4	437	13	3.0	0.0033	6.74 (1.53, 29.69)	6.91 (1.55, 30.82)	0.03 (0.01, 0.04)	
Age [years]											0.8283
< 65	739	5	0.7	675	9	1.3	0.2128	1.97 (0.66, 5.85)	1.98 (0.66, 5.95)	0.01 (0.00, 0.02)	
>= 65	1124	10	0.9	1188	24	2.0	0.0240	2.27 (1.09, 4.73)	2.30 (1.09, 4.83)	0.01 (0.00, 0.02)	
Region											0.2362
North America	213	1	0.5	212	9	4.2	0.0102	9.04 (1.16, 70.75)	9.40 (1.18, 74.85)	0.04 (0.01, 0.07)	
Latin America	645	5	0.8	641	14	2.2	0.0363	2.82 (1.02, 7.78)	2.86 (1.02, 7.98)	0.01 (0.00, 0.03)	
Europe	674	9	1.3	676	9	1.3	0.9950	1.00 (0.40, 2.50)	1.00 (0.39, 2.53)	0.00 (-0.01, 0.01)	
Asia	244	0	0	248	1	0.4	0.4857	2.95 (0.12, 72.11)	2.96 (0.12, 73.11)	0.00 (-0.01, 0.02)	
Other	87	0	0	86	0	0	0.9954	1.01 (0.02, 50.41)	1.01 (0.02, 51.56)	0.00 (-0.02, 0.02)	
OECD Member											0.2519
No	741	4	0.5	713	14	2.0	0.0141	3.64 (1.20, 11.00)	3.69 (1.21, 11.27)	0.01 (0.00, 0.03)	
Yes	1122	11	1.0	1150	19	1.7	0.1608	1.69 (0.81, 3.53)	1.70 (0.80, 3.58)	0.01 (0.00, 0.02)	
Baseline NYHA											0.8162
II	1399	9	0.6	1399	21	1.5	0.0276	2.33 (1.07, 5.08)	2.35 (1.07, 5.16)	0.01 (0.00, 0.02)	
III/IV	464	6	1.3	464	12	2.6	0.1533	2.00 (0.76, 5.28)	2.03 (0.75, 5.45)	0.01 (0.00, 0.03)	
Baseline Diabetes Status											0.3639
Diabetic	926	7	0.8	927	20	2.2	0.0118	2.85 (1.21, 6.72)	2.89 (1.22, 6.88)	0.01 (0.00, 0.02)	
Non-Diabetic	937	8	0.9	936	13	1.4	0.2715	1.63 (0.68, 3.91)	1.64 (0.67, 3.96)	0.01 (0.00, 0.01)	
Baseline BMI [kg/m²]											0.0209
<30	1299	5	0.4	1263	22	1.7	0.0008	4.53 (1.72, 11.91)	4.59 (1.73, 12.15)	0.01 (0.01, 0.02)	
>=30	564	10	1.8	600	11	1.8	0.9384	1.03 (0.44, 2.42)	1.03 (0.44, 2.46)	0.00 (-0.01, 0.02)	

*** 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).
Subgroups will only be analysed if at least 10 events occurred in at least one category (both treatments combined).
For AEs on SOC and/or PT level, subgroup analyses are only shown if overall test for treatment is significant on 5% level (i.e. 95% CI for the risk ratio does not contain 1; if this is not calculable the p-value of Chi-square test is used).
MedDRA version: 23.0. * Chi-square test for treatment effect ** Breslow-Day test for homogeneity of odds ratios (treatment by subgroup interaction).

Table R.1.4.3: 1 Proportion of patients with adverse events of special interest and other specific AEs
- by user-defined AE category - overall population 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 eGFR (CKD-EPI) [mL/min/1.73m²]											0.6191
>=60	958	6	0.6	969	11	1.1	0.2323	1.81 (0.67, 4.88)	1.82 (0.67, 4.95)	0.01 (0.00, 0.01)	
<60	904	9	1.0	893	22	2.5	0.0169	2.47 (1.15, 5.34)	2.51 (1.15, 5.49)	0.01 (0.00, 0.03)	
History of HHF (in the last 12 months)											0.7997
No	1290	9	0.7	1286	21	1.6	0.0269	2.34 (1.08, 5.09)	2.36 (1.08, 5.18)	0.01 (0.00, 0.02)	
Yes	573	6	1.0	577	12	2.1	0.1584	1.99 (0.75, 5.26)	2.01 (0.75, 5.38)	0.01 (0.00, 0.02)	
Cause of Heart Failure											0.6528
Ischemic	944	8	0.8	983	16	1.6	0.1226	1.92 (0.83, 4.47)	1.94 (0.82, 4.54)	0.01 (0.00, 0.02)	
Non-ischemic	919	7	0.8	880	17	1.9	0.0306	2.54 (1.06, 6.09)	2.57 (1.06, 6.22)	0.01 (0.00, 0.02)	
Heart Failure Physiology											0.4180
LVEF <= 30% and NTproBNP < median	723	5	0.7	698	8	1.1	0.3683	1.66 (0.54, 5.04)	1.66 (0.54, 5.11)	0.00 (-0.01, 0.01)	
LVEF <= 30% and NTproBNP >= median	660	8	1.2	631	13	2.1	0.2285	1.70 (0.71, 4.07)	1.71 (0.71, 4.16)	0.01 (-0.01, 0.02)	
LVEF > 30%	473	2	0.4	526	11	2.1	0.0202	4.95 (1.10, 22.20)	5.03 (1.11, 22.81)	0.02 (0.00, 0.03)	
Baseline use of MRA											0.1939
No	512	2	0.4	557	11	2.0	0.0182	5.06 (1.13, 22.70)	5.14 (1.13, 23.29)	0.02 (0.00, 0.03)	
Yes	1351	13	1.0	1306	22	1.7	0.1026	1.75 (0.89, 3.46)	1.76 (0.88, 3.52)	0.01 (0.00, 0.02)	
Baseline use of ARNi											0.4754
No	1476	11	0.7	1523	22	1.4	0.0665	1.94 (0.94, 3.98)	1.95 (0.94, 4.04)	0.01 (0.00, 0.01)	
Yes	387	4	1.0	340	11	3.2	0.0372	3.13 (1.01, 9.74)	3.20 (1.01, 10.15)	0.02 (0.00, 0.04)	

*** 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).
Subgroups will only be analysed if at least 10 events occurred in at least one category (both treatments combined).
For AEs on SOC and/or PT level, subgroup analyses are only shown if overall test for treatment is significant on 5% level (i.e. 95% CI for the risk ratio does not contain 1; if this is not calculable the p-value of Chi-square test is used).
MedDRA version: 23.0. * Chi-square test for treatment effect ** Breslow-Day test for homogeneity of odds ratios (treatment by subgroup interaction).

Table R.1.4.3: 1 Proportion of patients with adverse events of special interest and other specific AEs
- by user-defined AE category - overall population 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											0.5314
<=30	1390	13	0.9	1337	22	1.6	0.0995	1.76 (0.89, 3.48)	1.77 (0.89, 3.53)	0.01 (0.00, 0.02)	
>30 to <=35	359	2	0.6	398	9	2.3	0.0504	4.06 (0.88, 18.66)	4.13 (0.89, 19.24)	0.02 (0.00, 0.03)	
>35	114	0	0	128	2	1.6	0.2875	4.46 (0.22, 91.88)	4.53 (0.22, 95.26)	0.02 (-0.01, 0.04)	
Baseline NTproBNP											0.7428
< median	919	6	0.7	942	12	1.3	0.1712	1.95 (0.74, 5.18)	1.96 (0.73, 5.25)	0.01 (0.00, 0.02)	
>= median	943	9	1.0	920	21	2.3	0.0228	2.39 (1.10, 5.19)	2.42 (1.10, 5.32)	0.01 (0.00, 0.02)	

*** 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).
Subgroups will only be analysed if at least 10 events occurred in at least one category (both treatments combined).
For AEs on SOC and/or PT level, subgroup analyses are only shown if overall test for treatment is significant on 5% level (i.e. 95% CI for the risk ratio does not contain 1; if this is not calculable the p-value of Chi-square test is used).
MedDRA version: 23.0. * Chi-square test for treatment effect ** Breslow-Day test for homogeneity of odds ratios (treatment by subgroup interaction).

Table R.1.4.3: 1 Proportion of patients with adverse events of special interest and other specific AEs
- by user-defined AE category - overall population 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	1863	1	0.1	1863	5	0.3	0.1022	5.00 (0.58, 42.76)	5.01 (0.58, 42.93)	0.00 (0.00, 0.00)	

*** 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).
Subgroups will only be analysed if at least 10 events occurred in at least one category (both treatments combined).
For AEs on SOC and/or PT level, subgroup analyses are only shown if overall test for treatment is significant on 5% level (i.e. 95% CI for the risk ratio does not contain 1; if this is not calculable the p-value of Chi-square test is used).
MedDRA version: 23.0. * Chi-square test for treatment effect ** Breslow-Day test for homogeneity of odds ratios (treatment by subgroup interaction).

Table R.1.4.3: 1 Proportion of patients with adverse events of special interest and other specific AEs
- by user-defined AE category - overall population 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	1863	14	0.8	1863	28	1.5	0.0298	2.00 (1.06, 3.79)	2.02 (1.06, 3.84)	0.01 (0.00, 0.01)	
Sex											0.2769
Male	1410	12	0.9	1426	20	1.4	0.1645	1.65 (0.81, 3.36)	1.66 (0.81, 3.40)	0.01 (0.00, 0.01)	
Female	453	2	0.4	437	8	1.8	0.0493	4.15 (0.89, 19.42)	4.21 (0.89, 19.91)	0.01 (0.00, 0.03)	
Age [years]											0.9565
< 65	739	4	0.5	675	7	1.0	0.2892	1.92 (0.56, 6.52)	1.93 (0.56, 6.61)	0.00 (0.00, 0.01)	
>= 65	1124	10	0.9	1188	21	1.8	0.0666	1.99 (0.94, 4.20)	2.00 (0.94, 4.28)	0.01 (0.00, 0.02)	
Region											0.0901
North America	213	1	0.5	212	9	4.2	0.0102	9.04 (1.16, 70.75)	9.40 (1.18, 74.85)	0.04 (0.01, 0.07)	
Latin America	645	4	0.6	641	12	1.9	0.0429	3.02 (0.98, 9.31)	3.06 (0.98, 9.53)	0.01 (0.00, 0.02)	
Europe	674	9	1.3	676	6	0.9	0.4326	0.66 (0.24, 1.86)	0.66 (0.23, 1.87)	0.00 (-0.02, 0.01)	
Asia	244	0	0	248	1	0.4	0.4857	2.95 (0.12, 72.11)	2.96 (0.12, 73.11)	0.00 (-0.01, 0.02)	
Other	87	0	0	86	0	0	0.9954	1.01 (0.02, 50.41)	1.01 (0.02, 51.56)	0.00 (-0.02, 0.02)	
OECD Member											0.1443
No	741	3	0.4	713	12	1.7	0.0159	4.16 (1.18, 14.67)	4.21 (1.18, 14.99)	0.01 (0.00, 0.02)	
Yes	1122	11	1.0	1150	16	1.4	0.3662	1.42 (0.66, 3.04)	1.43 (0.66, 3.08)	0.00 (0.00, 0.01)	
Baseline NYHA											0.6570
II	1399	8	0.6	1399	18	1.3	0.0488	2.25 (0.98, 5.16)	2.27 (0.98, 5.23)	0.01 (0.00, 0.01)	
III/IV	464	6	1.3	464	10	2.2	0.3131	1.67 (0.61, 4.55)	1.68 (0.61, 4.66)	0.01 (-0.01, 0.03)	
Baseline Diabetes Status											0.0706
Diabetic	926	6	0.6	927	20	2.2	0.0057	3.33 (1.34, 8.25)	3.38 (1.35, 8.46)	0.02 (0.00, 0.03)	
Non-Diabetic	937	8	0.9	936	8	0.9	0.9983	1.00 (0.38, 2.66)	1.00 (0.37, 2.68)	0.00 (-0.01, 0.01)	
Baseline BMI [kg/m²]											0.0580
<30	1299	5	0.4	1263	18	1.4	0.0053	3.70 (1.38, 9.94)	3.74 (1.38, 10.11)	0.01 (0.00, 0.02)	
>=30	564	9	1.6	600	10	1.7	0.9240	1.04 (0.43, 2.55)	1.05 (0.42, 2.59)	0.00 (-0.01, 0.02)	

*** 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).
Subgroups will only be analysed if at least 10 events occurred in at least one category (both treatments combined).
For AEs on SOC and/or PT level, subgroup analyses are only shown if overall test for treatment is significant on 5% level (i.e. 95% CI for the risk ratio does not contain 1; if this is not calculable the p-value of Chi-square test is used).
MedDRA version: 23.0. * Chi-square test for treatment effect ** Breslow-Day test for homogeneity of odds ratios (treatment by subgroup interaction).

Table R.1.4.3: 1 Proportion of patients with adverse events of special interest and other specific AEs
- by user-defined AE category - overall population 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 eGFR (CKD-EPI) [mL/min/1.73m²]											0.6047
>=60	958	5	0.5	969	8	0.8	0.4155	1.58 (0.52, 4.82)	1.59 (0.52, 4.87)	0.00 (0.00, 0.01)	
<60	904	9	1.0	893	20	2.2	0.0364	2.25 (1.03, 4.91)	2.28 (1.03, 5.03)	0.01 (0.00, 0.02)	
History of HHF (in the last 12 months)											0.6432
No	1290	8	0.6	1286	18	1.4	0.0478	2.26 (0.98, 5.17)	2.27 (0.99, 5.25)	0.01 (0.00, 0.02)	
Yes	573	6	1.0	577	10	1.7	0.3207	1.66 (0.61, 4.52)	1.67 (0.60, 4.62)	0.01 (-0.01, 0.02)	
Cause of Heart Failure											0.8968
Ischemic	944	7	0.7	983	14	1.4	0.1490	1.92 (0.78, 4.74)	1.93 (0.78, 4.81)	0.01 (0.00, 0.02)	
Non-ischemic	919	7	0.8	880	14	1.6	0.1017	2.09 (0.85, 5.15)	2.11 (0.85, 5.24)	0.01 (0.00, 0.02)	
Heart Failure Physiology											0.6331
LVEF <= 30% and NTproBNP < median	723	5	0.7	698	7	1.0	0.5215	1.45 (0.46, 4.55)	1.45 (0.46, 4.61)	0.00 (-0.01, 0.01)	
LVEF <= 30% and NTproBNP >= median	660	7	1.1	631	12	1.9	0.2096	1.79 (0.71, 4.53)	1.81 (0.71, 4.62)	0.01 (0.00, 0.02)	
LVEF > 30%	473	2	0.4	526	8	1.5	0.0817	3.60 (0.77, 16.85)	3.64 (0.77, 17.21)	0.01 (0.00, 0.02)	
Baseline use of MRA											0.1314
No	512	2	0.4	557	11	2.0	0.0182	5.06 (1.13, 22.70)	5.14 (1.13, 23.29)	0.02 (0.00, 0.03)	
Yes	1351	12	0.9	1306	17	1.3	0.3052	1.47 (0.70, 3.06)	1.47 (0.70, 3.09)	0.00 (0.00, 0.01)	
Baseline use of ARNi											0.3413
No	1476	11	0.7	1523	19	1.2	0.1670	1.67 (0.80, 3.51)	1.68 (0.80, 3.55)	0.01 (0.00, 0.01)	
Yes	387	3	0.8	340	9	2.6	0.0481	3.41 (0.93, 12.51)	3.48 (0.93, 12.96)	0.02 (0.00, 0.04)	

*** 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).
Subgroups will only be analysed if at least 10 events occurred in at least one category (both treatments combined).
For AEs on SOC and/or PT level, subgroup analyses are only shown if overall test for treatment is significant on 5% level (i.e. 95% CI for the risk ratio does not contain 1; if this is not calculable the p-value of Chi-square test is used).
MedDRA version: 23.0. * Chi-square test for treatment effect ** Breslow-Day test for homogeneity of odds ratios (treatment by subgroup interaction).

Table R.1.4.3: 1 Proportion of patients with adverse events of special interest and other specific AEs
- by user-defined AE category - overall population 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											0.7724
<=30	1390	12	0.9	1337	20	1.5	0.1252	1.73 (0.85, 3.53)	1.74 (0.85, 3.58)	0.01 (0.00, 0.01)	
>30 to <=35	359	2	0.6	398	7	1.8	0.1277	3.16 (0.66, 15.10)	3.20 (0.66, 15.48)	0.01 (0.00, 0.03)	
>35	114	0	0	128	1	0.8	0.5290	2.67 (0.11, 65.00)	2.69 (0.11, 66.79)	0.01 (-0.01, 0.03)	
Baseline NTproBNP											0.5950
< median	919	6	0.7	942	10	1.1	0.3397	1.63 (0.59, 4.46)	1.63 (0.59, 4.51)	0.00 (0.00, 0.01)	
>= median	943	8	0.8	920	18	2.0	0.0415	2.31 (1.01, 5.28)	2.33 (1.01, 5.39)	0.01 (0.00, 0.02)	

*** 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).
Subgroups will only be analysed if at least 10 events occurred in at least one category (both treatments combined).
For AEs on SOC and/or PT level, subgroup analyses are only shown if overall test for treatment is significant on 5% level (i.e. 95% CI for the risk ratio does not contain 1; if this is not calculable the p-value of Chi-square test is used).
MedDRA version: 23.0. * Chi-square test for treatment effect ** Breslow-Day test for homogeneity of odds ratios (treatment by subgroup interaction).

Table R.1.4.3: 1 Proportion of patients with adverse events of special interest and other specific AEs
- by user-defined AE category - overall population 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	1863	42	2.3	1863	45	2.4	0.7448	1.07 (0.71,	1.62)	1.07 (0.70,	1.64)	0.00 (-0.01, 0.01)	
Sex													0.2936
Male	1410	26	1.8	1426	33	2.3	0.3804	1.25 (0.75,	2.09)	1.26 (0.75,	2.12)	0.00 (-0.01, 0.02)	
Female	453	16	3.5	437	12	2.7	0.5019	0.78 (0.37,	1.62)	0.77 (0.36,	1.65)	-0.01 (-0.03, 0.02)	
Age [years]													0.3385
< 65	739	11	1.5	675	7	1.0	0.4494	0.70 (0.27,	1.79)	0.69 (0.27,	1.80)	0.00 (-0.02, 0.01)	
>= 65	1124	31	2.8	1188	38	3.2	0.5337	1.16 (0.73,	1.85)	1.17 (0.72,	1.89)	0.00 (-0.01, 0.02)	
Region													0.2660
North America	213	4	1.9	212	9	4.2	0.1565	2.26 (0.71,	7.23)	2.32 (0.70,	7.64)	0.02 (-0.01, 0.06)	
Latin America	645	11	1.7	641	7	1.1	0.3492	0.64 (0.25,	1.64)	0.64 (0.25,	1.65)	-0.01 (-0.02, 0.01)	
Europe	674	21	3.1	676	17	2.5	0.5045	0.81 (0.43,	1.52)	0.80 (0.42,	1.53)	-0.01 (-0.02, 0.01)	
Asia	244	6	2.5	248	12	4.8	0.1598	1.97 (0.75,	5.16)	2.02 (0.74,	5.46)	0.02 (-0.01, 0.06)	
Other	87	0	0	86	0	0	0.9954	1.01 (0.02,	50.41)	1.01 (0.02,	51.56)	0.00 (-0.02, 0.02)	
OECD Member													0.1103
No	741	13	1.8	713	7	1.0	0.2061	0.56 (0.22,	1.39)	0.56 (0.22,	1.40)	-0.01 (-0.02, 0.00)	
Yes	1122	29	2.6	1150	38	3.3	0.3107	1.28 (0.79,	2.06)	1.29 (0.79,	2.10)	0.01 (-0.01, 0.02)	
Baseline NYHA													0.5116
II	1399	28	2.0	1399	27	1.9	0.8917	0.96 (0.57,	1.63)	0.96 (0.56,	1.64)	0.00 (-0.01, 0.01)	
III/IV	464	14	3.0	464	18	3.9	0.4718	1.29 (0.65,	2.55)	1.30 (0.64,	2.64)	0.01 (-0.01, 0.03)	
Baseline Diabetes Status													0.0981
Diabetic	926	26	2.8	927	20	2.2	0.3684	0.77 (0.43,	1.37)	0.76 (0.42,	1.38)	-0.01 (-0.02, 0.01)	
Non-Diabetic	937	16	1.7	936	25	2.7	0.1543	1.56 (0.84,	2.91)	1.58 (0.84,	2.98)	0.01 (0.00, 0.02)	
Baseline BMI [kg/m²]													0.7223
<30	1299	32	2.5	1263	32	2.5	0.9094	1.03 (0.63,	1.67)	1.03 (0.63,	1.69)	0.00 (-0.01, 0.01)	
>=30	564	10	1.8	600	13	2.2	0.6296	1.22 (0.54,	2.76)	1.23 (0.53,	2.82)	0.00 (-0.01, 0.02)	

*** 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).
Subgroups will only be analysed if at least 10 events occurred in at least one category (both treatments combined).
For AEs on SOC and/or PT level, subgroup analyses are only shown if overall test for treatment is significant on 5% level (i.e. 95% CI for the risk ratio does not contain 1; if this is not calculable the p-value of Chi-square test is used).
MedDRA version: 23.0. * Chi-square test for treatment effect ** Breslow-Day test for homogeneity of odds ratios (treatment by subgroup interaction).

Table R.1.4.3: 1 Proportion of patients with adverse events of special interest and other specific AEs
- by user-defined AE category - overall population 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 eGFR (CKD-EPI) [mL/min/1.73m²]														0.8843
>=60	958	15	1.6	969	17	1.8	0.7460	1.12	(0.56,	2.23)	1.12 (0.56,	2.26)	0.00 (-0.01, 0.01)	
<60	904	27	3.0	893	28	3.1	0.8547	1.05	(0.62,	1.77)	1.05 (0.61,	1.80)	0.00 (-0.01, 0.02)	
History of HHF (in the last 12 months)														0.1737
No	1290	31	2.4	1286	27	2.1	0.6036	0.87	(0.52,	1.46)	0.87 (0.52,	1.47)	0.00 (-0.01, 0.01)	
Yes	573	11	1.9	577	18	3.1	0.1944	1.63	(0.77,	3.41)	1.65 (0.77,	3.51)	0.01 (-0.01, 0.03)	
Cause of Heart Failure														0.4520
Ischemic	944	23	2.4	983	22	2.2	0.7731	0.92	(0.52,	1.64)	0.92 (0.51,	1.66)	0.00 (-0.02, 0.01)	
Non-ischemic	919	19	2.1	880	23	2.6	0.4431	1.26	(0.69,	2.30)	1.27 (0.69,	2.35)	0.01 (-0.01, 0.02)	
Heart Failure Physiology														0.7036
LVEF <= 30% and NTproBNP < median	723	11	1.5	698	9	1.3	0.7105	0.85	(0.35,	2.03)	0.85 (0.35,	2.05)	0.00 (-0.01, 0.01)	
LVEF <= 30% and NTproBNP >= median	660	17	2.6	631	21	3.3	0.4241	1.29	(0.69,	2.43)	1.30 (0.68,	2.49)	0.01 (-0.01, 0.03)	
LVEF > 30%	473	14	3.0	526	15	2.9	0.9190	0.96	(0.47,	1.97)	0.96 (0.46,	2.02)	0.00 (-0.02, 0.02)	
Baseline use of MRA														0.3829
No	512	12	2.3	557	18	3.2	0.3799	1.38	(0.67,	2.83)	1.39 (0.66,	2.92)	0.01 (-0.01, 0.03)	
Yes	1351	30	2.2	1306	27	2.1	0.7853	0.93	(0.56,	1.56)	0.93 (0.55,	1.57)	0.00 (-0.01, 0.01)	
Baseline use of ARNi														0.2964
No	1476	33	2.2	1523	40	2.6	0.4877	1.17	(0.75,	1.85)	1.18 (0.74,	1.88)	0.00 (-0.01, 0.01)	
Yes	387	9	2.3	340	5	1.5	0.4026	0.63	(0.21,	1.87)	0.63 (0.21,	1.89)	-0.01 (-0.03, 0.01)	

*** 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).
Subgroups will only be analysed if at least 10 events occurred in at least one category (both treatments combined).
For AEs on SOC and/or PT level, subgroup analyses are only shown if overall test for treatment is significant on 5% level (i.e. 95% CI for the risk ratio does not contain 1; if this is not calculable the p-value of Chi-square test is used).
MedDRA version: 23.0. * Chi-square test for treatment effect ** Breslow-Day test for homogeneity of odds ratios (treatment by subgroup interaction).

Table R.1.4.3: 1 Proportion of patients with adverse events of special interest and other specific AEs
- by user-defined AE category - overall population 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												0.1073
<=30	1390	28	2.0	1337	30	2.2	0.6780	1.11 (0.67, 1.85)	1.12 (0.66, 1.88)	0.00	(-0.01, 0.01)	
>30 to <=35	359	13	3.6	398	9	2.3	0.2661	0.62 (0.27, 1.44)	0.62 (0.26, 1.46)	-0.01	(-0.04, 0.01)	
>35	114	1	0.9	128	6	4.7	0.0775	5.34 (0.65, 43.72)	5.56 (0.66, 46.88)	0.04	(0.00, 0.08)	
Baseline NTproBNP												0.8841
< median	919	16	1.7	942	17	1.8	0.9172	1.04 (0.53, 2.04)	1.04 (0.52, 2.07)	0.00	(-0.01, 0.01)	
>= median	943	26	2.8	920	28	3.0	0.7127	1.10 (0.65, 1.87)	1.11 (0.64, 1.90)	0.00	(-0.01, 0.02)	

*** 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).
Subgroups will only be analysed if at least 10 events occurred in at least one category (both treatments combined).
For AEs on SOC and/or PT level, subgroup analyses are only shown if overall test for treatment is significant on 5% level (i.e. 95% CI for the risk ratio does not contain 1; if this is not calculable the p-value of Chi-square test is used).
MedDRA version: 23.0. * Chi-square test for treatment effect ** Breslow-Day test for homogeneity of odds ratios (treatment by subgroup interaction).

Table R.1.4.3: 1 Proportion of patients with adverse events of special interest and other specific AEs
- by user-defined AE category - overall population 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	1863	6	0.3	1863	7	0.4	0.7811	1.17 (0.39, 3.46)	1.17 (0.39, 3.48)	0.00 (0.00, 0.00)	
Sex											0.1582
Male	1410	4	0.3	1426	7	0.5	0.3748	1.73 (0.51, 5.90)	1.73 (0.51, 5.94)	0.00 (0.00, 0.01)	
Female	453	2	0.4	437	0	0	0.2603	0.21 (<0.01, 4.31)	0.21 (<0.01, 4.31)	0.00 (-0.01, 0.00)	
OECD Member											0.9648
No	741	0	0	713	0	0	0.9846	1.04 (0.02, 52.30)	1.04 (0.02, 52.45)	0.00 (0.00, 0.00)	
Yes	1122	6	0.5	1150	7	0.6	0.8153	1.14 (0.38, 3.38)	1.14 (0.38, 3.40)	0.00 (-0.01, 0.01)	
Baseline NYHA											0.4157
II	1399	4	0.3	1399	6	0.4	0.5263	1.50 (0.42, 5.30)	1.50 (0.42, 5.33)	0.00 (0.00, 0.01)	
III/IV	464	2	0.4	464	1	0.2	0.5631	0.50 (0.05, 5.50)	0.50 (0.05, 5.52)	0.00 (-0.01, 0.01)	
Baseline Diabetes Status											0.1480
Diabetic	926	4	0.4	927	7	0.8	0.3652	1.75 (0.51, 5.95)	1.75 (0.51, 6.01)	0.00 (0.00, 0.01)	
Non-Diabetic	937	2	0.2	936	0	0	0.2482	0.20 (<0.01, 4.16)	0.20 (<0.01, 4.17)	0.00 (-0.01, 0.00)	
Baseline BMI [kg/m²]											0.8589
<30	1299	5	0.4	1263	6	0.5	0.7272	1.23 (0.38, 4.03)	1.24 (0.38, 4.06)	0.00 (0.00, 0.01)	
>=30	564	1	0.2	600	1	0.2	0.9651	0.94 (0.06, 14.99)	0.94 (0.06, 15.06)	0.00 (0.00, 0.00)	
History of HHF (in the last 12 months)											0.9001
No	1290	5	0.4	1286	6	0.5	0.7586	1.20 (0.37, 3.93)	1.20 (0.37, 3.96)	0.00 (0.00, 0.01)	
Yes	573	1	0.2	577	1	0.2	0.9961	0.99 (0.06, 15.84)	0.99 (0.06, 15.91)	0.00 (0.00, 0.00)	
Baseline use of ARNi											0.9888
No	1476	5	0.3	1523	6	0.4	0.8026	1.16 (0.36, 3.80)	1.16 (0.35, 3.82)	0.00 (0.00, 0.00)	
Yes	387	1	0.3	340	1	0.3	0.9269	1.14 (0.07, 18.13)	1.14 (0.07, 18.27)	0.00 (-0.01, 0.01)	

*** 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).
Subgroups will only be analysed if at least 10 events occurred in at least one category (both treatments combined).
For AEs on SOC and/or PT level, subgroup analyses are only shown if overall test for treatment is significant on 5% level (i.e. 95% CI for the risk ratio does not contain 1; if this is not calculable the p-value of Chi-square test is used).
MedDRA version: 23.0. * Chi-square test for treatment effect ** Breslow-Day test for homogeneity of odds ratios (treatment by subgroup interaction).

Table R.1.4.3: 1 Proportion of patients with adverse events of special interest and other specific AEs
- by user-defined AE category - overall population 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 LVEF											0.9685
<=30	1390	5	0.4	1337	6	0.4	0.7138	1.25 (0.38, 4.08)	1.25 (0.38, 4.10)	0.00 (0.00, 0.01)	
>30 to <=35	359	1	0.3	398	1	0.3	0.9418	0.90 (0.06, 14.37)	0.90 (0.06, 14.47)	0.00 (-0.01, 0.01)	
>35	114	0	0	128	0	0	0.9541	0.89 (0.02, 44.57)	0.89 (0.02, 45.27)	0.00 (-0.02, 0.02)	

*** 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).
Subgroups will only be analysed if at least 10 events occurred in at least one category (both treatments combined).
For AEs on SOC and/or PT level, subgroup analyses are only shown if overall test for treatment is significant on 5% level (i.e. 95% CI for the risk ratio does not contain 1; if this is not calculable the p-value of Chi-square test is used).
MedDRA version: 23.0. * Chi-square test for treatment effect ** Breslow-Day test for homogeneity of odds ratios (treatment by subgroup interaction).

Table R.1.4.3: 1 Proportion of patients with adverse events of special interest and other specific AEs
- by user-defined AE category - overall population 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	1863	184	9.9	1863	197	10.6	0.4821	1.07	(0.89, 1.30)	1.08	(0.87, 1.33)	0.01	(-0.01, 0.03)	
Sex														0.6753
Male	1410	137	9.7	1426	145	10.2	0.6876	1.05	(0.84, 1.31)	1.05	(0.82, 1.35)	0.00	(-0.02, 0.03)	
Female	453	47	10.4	437	52	11.9	0.4697	1.15	(0.79, 1.66)	1.17	(0.77, 1.77)	0.02	(-0.03, 0.06)	
Age [years]														0.7958
< 65	739	70	9.5	675	66	9.8	0.8457	1.03	(0.75, 1.42)	1.04	(0.73, 1.48)	0.00	(-0.03, 0.03)	
>= 65	1124	114	10.1	1188	131	11.0	0.4898	1.09	(0.86, 1.38)	1.10	(0.84, 1.43)	0.01	(-0.02, 0.03)	
Region														0.7573
North America	213	40	18.8	212	42	19.8	0.7875	1.05	(0.71, 1.56)	1.07	(0.66, 1.73)	0.01	(-0.06, 0.09)	
Latin America	645	59	9.1	641	55	8.6	0.7206	0.94	(0.66, 1.33)	0.93	(0.63, 1.37)	-0.01	(-0.04, 0.03)	
Europe	674	59	8.8	676	63	9.3	0.7169	1.06	(0.76, 1.49)	1.07	(0.74, 1.55)	0.01	(-0.02, 0.04)	
Asia	244	23	9.4	248	32	12.9	0.2211	1.37	(0.83, 2.27)	1.42	(0.81, 2.51)	0.03	(-0.02, 0.09)	
Other	87	3	3.4	86	5	5.8	0.4588	1.69	(0.42, 6.84)	1.73	(0.40, 7.47)	0.02	(-0.04, 0.09)	
OECD Member														0.9187
No	741	67	9.0	713	68	9.5	0.7449	1.05	(0.76, 1.45)	1.06	(0.74, 1.51)	0.00	(-0.02, 0.03)	
Yes	1122	117	10.4	1150	129	11.2	0.5448	1.08	(0.85, 1.36)	1.09	(0.83, 1.41)	0.01	(-0.02, 0.03)	
Baseline NYHA														0.4897
II	1399	126	9.0	1399	141	10.1	0.3344	1.12	(0.89, 1.41)	1.13	(0.88, 1.46)	0.01	(-0.01, 0.03)	
III/IV	464	58	12.5	464	56	12.1	0.8415	0.97	(0.68, 1.36)	0.96	(0.65, 1.42)	0.00	(-0.05, 0.04)	
Baseline Diabetes Status														0.1759
Diabetic	926	84	9.1	927	103	11.1	0.1450	1.22	(0.93, 1.61)	1.25	(0.92, 1.70)	0.02	(-0.01, 0.05)	
Non-Diabetic	937	100	10.7	936	94	10.0	0.6548	0.94	(0.72, 1.23)	0.93	(0.69, 1.26)	-0.01	(-0.03, 0.02)	
Baseline BMI [kg/m²]														0.3042
<30	1299	123	9.5	1263	137	10.8	0.2480	1.15	(0.91, 1.44)	1.16	(0.90, 1.50)	0.01	(-0.01, 0.04)	
>=30	564	61	10.8	600	60	10.0	0.6486	0.92	(0.66, 1.30)	0.92	(0.63, 1.34)	-0.01	(-0.04, 0.03)	

*** 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).
Subgroups will only be analysed if at least 10 events occurred in at least one category (both treatments combined).
For AEs on SOC and/or PT level, subgroup analyses are only shown if overall test for treatment is significant on 5% level (i.e. 95% CI for the risk ratio does not contain 1; if this is not calculable the p-value of Chi-square test is used).
MedDRA version: 23.0. * Chi-square test for treatment effect ** Breslow-Day test for homogeneity of odds ratios (treatment by subgroup interaction).

Table R.1.4.3: 1 Proportion of patients with adverse events of special interest and other specific AEs
- by user-defined AE category - overall population 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 eGFR (CKD-EPI) [mL/min/1.73m²]												0.9170
>=60	958	81	8.5	969	87	9.0	0.6840	1.06 (0.80, 1.42)	1.07 (0.78, 1.47)	0.01	(-0.02, 0.03)	
<60	904	103	11.4	893	110	12.3	0.5445	1.08 (0.84, 1.39)	1.09 (0.82, 1.45)	0.01	(-0.02, 0.04)	
History of HHF (in the last 12 months)												0.4640
No	1290	127	9.8	1286	129	10.0	0.8745	1.02 (0.81, 1.29)	1.02 (0.79, 1.32)	0.00	(-0.02, 0.02)	
Yes	573	57	9.9	577	68	11.8	0.3169	1.18 (0.85, 1.65)	1.21 (0.83, 1.76)	0.02	(-0.02, 0.05)	
Cause of Heart Failure												0.7236
Ischemic	944	92	9.7	983	106	10.8	0.4533	1.11 (0.85, 1.44)	1.12 (0.83, 1.50)	0.01	(-0.02, 0.04)	
Non-ischemic	919	92	10.0	880	91	10.3	0.8169	1.03 (0.78, 1.36)	1.04 (0.76, 1.41)	0.00	(-0.02, 0.03)	
Heart Failure Physiology												0.2383
LVEF <= 30% and NTproBNP < median	723	64	8.9	698	78	11.2	0.1444	1.26 (0.92, 1.73)	1.30 (0.91, 1.84)	0.02	(-0.01, 0.05)	
LVEF <= 30% and NTproBNP >= median	660	67	10.2	631	69	10.9	0.6467	1.08 (0.78, 1.48)	1.09 (0.76, 1.55)	0.01	(-0.03, 0.04)	
LVEF > 30%	473	52	11.0	526	48	9.1	0.3260	0.83 (0.57, 1.20)	0.81 (0.54, 1.23)	-0.02	(-0.06, 0.02)	
Baseline use of MRA												0.2581
No	512	57	11.1	557	56	10.1	0.5665	0.90 (0.64, 1.28)	0.89 (0.60, 1.32)	-0.01	(-0.05, 0.03)	
Yes	1351	127	9.4	1306	141	10.8	0.2323	1.15 (0.91, 1.44)	1.17 (0.91, 1.50)	0.01	(-0.01, 0.04)	
Baseline use of ARNi												0.0828
No	1476	144	9.8	1523	146	9.6	0.8750	0.98 (0.79, 1.22)	0.98 (0.77, 1.25)	0.00	(-0.02, 0.02)	
Yes	387	40	10.3	340	51	15.0	0.0579	1.45 (0.99, 2.14)	1.53 (0.98, 2.38)	0.05	(0.00, 0.10)	

*** 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).
Subgroups will only be analysed if at least 10 events occurred in at least one category (both treatments combined).
For AEs on SOC and/or PT level, subgroup analyses are only shown if overall test for treatment is significant on 5% level (i.e. 95% CI for the risk ratio does not contain 1; if this is not calculable the p-value of Chi-square test is used).
MedDRA version: 23.0. * Chi-square test for treatment effect ** Breslow-Day test for homogeneity of odds ratios (treatment by subgroup interaction).

Table R.1.4.3: 1 Proportion of patients with adverse events of special interest and other specific AEs
- by user-defined AE category - overall population 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														0.1859
<=30	1390	132	9.5	1337	149	11.1	0.1570	1.17 (0.94,	1.47)	1.20 (0.93,	1.53)	0.02 (-0.01,	0.04)	
>30 to <=35	359	41	11.4	398	34	8.5	0.1857	0.75 (0.49,	1.15)	0.72 (0.45,	1.17)	-0.03 (-0.07,	0.01)	
>35	114	11	9.6	128	14	10.9	0.7424	1.13 (0.54,	2.40)	1.15 (0.50,	2.65)	0.01 (-0.06,	0.09)	
Baseline NTproBNP														0.5717
< median	919	87	9.5	942	101	10.7	0.3691	1.13 (0.86,	1.49)	1.15 (0.85,	1.55)	0.01 (-0.01,	0.04)	
>= median	943	97	10.3	920	96	10.4	0.9163	1.01 (0.78,	1.33)	1.02 (0.75,	1.37)	0.00 (-0.03,	0.03)	

*** 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).
Subgroups will only be analysed if at least 10 events occurred in at least one category (both treatments combined).
For AEs on SOC and/or PT level, subgroup analyses are only shown if overall test for treatment is significant on 5% level (i.e. 95% CI for the risk ratio does not contain 1; if this is not calculable the p-value of Chi-square test is used).
MedDRA version: 23.0. * Chi-square test for treatment effect ** Breslow-Day test for homogeneity of odds ratios (treatment by subgroup interaction).

Table R.1.4.3: 1 Proportion of patients with adverse events of special interest and other specific AEs
- by user-defined AE category - overall population 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	1863	163	8.7	1863	176	9.4	0.4590	1.08 (0.88,	1.32)	1.09 (0.87,	1.36)	0.01 (-0.01,	0.03)	
Sex														0.7810
Male	1410	120	8.5	1426	129	9.0	0.6143	1.06 (0.84,	1.35)	1.07 (0.82,	1.39)	0.01 (-0.02,	0.03)	
Female	453	43	9.5	437	47	10.8	0.5322	1.13 (0.77,	1.68)	1.15 (0.74,	1.78)	0.01 (-0.03,	0.05)	
Age [years]														0.8218
< 65	739	63	8.5	675	64	9.5	0.5298	1.11 (0.80,	1.55)	1.12 (0.78,	1.62)	0.01 (-0.02,	0.04)	
>= 65	1124	100	8.9	1188	112	9.4	0.6585	1.06 (0.82,	1.37)	1.07 (0.80,	1.41)	0.01 (-0.02,	0.03)	
Region														0.4659
North America	213	35	16.4	212	37	17.5	0.7791	1.06 (0.70,	1.62)	1.08 (0.65,	1.79)	0.01 (-0.06,	0.08)	
Latin America	645	55	8.5	641	53	8.3	0.8671	0.97 (0.68,	1.39)	0.97 (0.65,	1.43)	0.00 (-0.03,	0.03)	
Europe	674	55	8.2	676	57	8.4	0.8564	1.03 (0.72,	1.47)	1.04 (0.70,	1.53)	0.00 (-0.03,	0.03)	
Asia	244	17	7.0	248	24	9.7	0.2768	1.39 (0.77,	2.52)	1.43 (0.75,	2.74)	0.03 (-0.02,	0.08)	
Other	87	1	1.1	86	5	5.8	0.0936	5.06 (0.60,	42.40)	5.31 (0.61,	46.42)	0.05 (-0.01,	0.10)	
OECD Member														0.8519
No	741	62	8.4	713	66	9.3	0.5495	1.11 (0.79,	1.54)	1.12 (0.78,	1.61)	0.01 (-0.02,	0.04)	
Yes	1122	101	9.0	1150	110	9.6	0.6436	1.06 (0.82,	1.37)	1.07 (0.81,	1.42)	0.01 (-0.02,	0.03)	
Baseline NYHA														0.3253
II	1399	109	7.8	1399	126	9.0	0.2466	1.16 (0.90,	1.48)	1.17 (0.90,	1.53)	0.01 (-0.01,	0.03)	
III/IV	464	54	11.6	464	50	10.8	0.6772	0.93 (0.64,	1.33)	0.92 (0.61,	1.38)	-0.01 (-0.05,	0.03)	
Baseline Diabetes Status														0.1494
Diabetic	926	72	7.8	927	91	9.8	0.1209	1.26 (0.94,	1.70)	1.29 (0.93,	1.78)	0.02 (-0.01,	0.05)	
Non-Diabetic	937	91	9.7	936	85	9.1	0.6400	0.94 (0.71,	1.24)	0.93 (0.68,	1.27)	-0.01 (-0.03,	0.02)	
Baseline BMI [kg/m²]														0.5832
<30	1299	110	8.5	1263	120	9.5	0.3604	1.12 (0.88,	1.44)	1.13 (0.87,	1.49)	0.01 (-0.01,	0.03)	
>=30	564	53	9.4	600	56	9.3	0.9702	0.99 (0.69,	1.42)	0.99 (0.67,	1.47)	0.00 (-0.03,	0.03)	

*** 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).
Subgroups will only be analysed if at least 10 events occurred in at least one category (both treatments combined).
For AEs on SOC and/or PT level, subgroup analyses are only shown if overall test for treatment is significant on 5% level (i.e. 95% CI for the risk ratio does not contain 1; if this is not calculable the p-value of Chi-square test is used).
MedDRA version: 23.0. * Chi-square test for treatment effect ** Breslow-Day test for homogeneity of odds ratios (treatment by subgroup interaction).

Table R.1.4.3: 1 Proportion of patients with adverse events of special interest and other specific AEs
- by user-defined AE category - overall population 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 eGFR (CKD-EPI) [mL/min/1.73m²]													0.7233
>=60	958	71	7.4	969	81	8.4	0.4402	1.13 (0.83,	1.53)	1.14 (0.82,	1.59)	0.01 (-0.01, 0.03)	
<60	904	92	10.2	893	95	10.6	0.7488	1.05 (0.80,	1.37)	1.05 (0.78,	1.42)	0.00 (-0.02, 0.03)	
History of HHF (in the last 12 months)													0.3515
No	1290	116	9.0	1286	117	9.1	0.9255	1.01 (0.79,	1.29)	1.01 (0.77,	1.33)	0.00 (-0.02, 0.02)	
Yes	573	47	8.2	577	59	10.2	0.2357	1.25 (0.87,	1.80)	1.27 (0.85,	1.91)	0.02 (-0.01, 0.05)	
Cause of Heart Failure													0.5832
Ischemic	944	79	8.4	983	94	9.6	0.3594	1.14 (0.86,	1.52)	1.16 (0.85,	1.58)	0.01 (-0.01, 0.04)	
Non-ischemic	919	84	9.1	880	82	9.3	0.8964	1.02 (0.76,	1.36)	1.02 (0.74,	1.41)	0.00 (-0.02, 0.03)	
Heart Failure Physiology													0.1814
LVEF <= 30% and NTproBNP < median	723	61	8.4	698	74	10.6	0.1642	1.26 (0.91,	1.73)	1.29 (0.90,	1.84)	0.02 (-0.01, 0.05)	
LVEF <= 30% and NTproBNP >= median	660	55	8.3	631	60	9.5	0.4586	1.14 (0.80,	1.62)	1.16 (0.79,	1.70)	0.01 (-0.02, 0.04)	
LVEF > 30%	473	46	9.7	526	40	7.6	0.2328	0.78 (0.52,	1.17)	0.76 (0.49,	1.19)	-0.02 (-0.06, 0.01)	
Baseline use of MRA													0.2113
No	512	51	10.0	557	49	8.8	0.5139	0.88 (0.61,	1.28)	0.87 (0.58,	1.32)	-0.01 (-0.05, 0.02)	
Yes	1351	112	8.3	1306	127	9.7	0.1964	1.17 (0.92,	1.49)	1.19 (0.91,	1.56)	0.01 (-0.01, 0.04)	
Baseline use of ARNi													0.3533
No	1476	124	8.4	1523	132	8.7	0.7944	1.03 (0.82,	1.30)	1.03 (0.80,	1.34)	0.00 (-0.02, 0.02)	
Yes	387	39	10.1	340	44	12.9	0.2257	1.28 (0.86,	1.93)	1.33 (0.84,	2.10)	0.03 (-0.02, 0.08)	

*** 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).
Subgroups will only be analysed if at least 10 events occurred in at least one category (both treatments combined).
For AEs on SOC and/or PT level, subgroup analyses are only shown if overall test for treatment is significant on 5% level (i.e. 95% CI for the risk ratio does not contain 1; if this is not calculable the p-value of Chi-square test is used).
MedDRA version: 23.0. * Chi-square test for treatment effect ** Breslow-Day test for homogeneity of odds ratios (treatment by subgroup interaction).

Table R.1.4.3: 1 Proportion of patients with adverse events of special interest and other specific AEs
- by user-defined AE category - overall population 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													0.0962
<=30	1390	117	8.4	1337	136	10.2	0.1143	1.21 (0.95,	1.53)	1.23 (0.95,	1.60)	0.02 (0.00, 0.04)	
>30 to <=35	359	38	10.6	398	29	7.3	0.1106	0.69 (0.43,	1.09)	0.66 (0.40,	1.10)	-0.03 (-0.07, 0.01)	
>35	114	8	7.0	128	11	8.6	0.6491	1.22 (0.51,	2.94)	1.25 (0.48,	3.21)	0.02 (-0.05, 0.08)	
Baseline NTproBNP													0.4825
< median	919	81	8.8	942	96	10.2	0.3113	1.16 (0.87,	1.53)	1.17 (0.86,	1.60)	0.01 (-0.01, 0.04)	
>= median	943	82	8.7	920	80	8.7	1.0000	1.00 (0.75,	1.34)	1.00 (0.72,	1.38)	0.00 (-0.03, 0.03)	

*** 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).
Subgroups will only be analysed if at least 10 events occurred in at least one category (both treatments combined).
For AEs on SOC and/or PT level, subgroup analyses are only shown if overall test for treatment is significant on 5% level (i.e. 95% CI for the risk ratio does not contain 1; if this is not calculable the p-value of Chi-square test is used).
MedDRA version: 23.0. * Chi-square test for treatment effect ** Breslow-Day test for homogeneity of odds ratios (treatment by subgroup interaction).

Table R.1.4.3: 1 Proportion of patients with adverse events of special interest and other specific AEs
- by user-defined AE category - overall population 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	1863	103	5.5	1863	106	5.7	0.8309	1.03 (0.79,	1.34)	1.03 (0.78,	1.36)	0.00 (-0.01, 0.02)	
Sex													0.3201
Male	1410	78	5.5	1426	75	5.3	0.7481	0.95 (0.70,	1.29)	0.95 (0.68,	1.31)	0.00 (-0.02, 0.01)	
Female	453	25	5.5	437	31	7.1	0.3333	1.29 (0.77,	2.14)	1.31 (0.76,	2.25)	0.02 (-0.02, 0.05)	
Age [years]													0.6122
< 65	739	39	5.3	675	40	5.9	0.5959	1.12 (0.73,	1.72)	1.13 (0.72,	1.78)	0.01 (-0.02, 0.03)	
>= 65	1124	64	5.7	1188	66	5.6	0.8852	0.98 (0.70,	1.36)	0.97 (0.68,	1.39)	0.00 (-0.02, 0.02)	
Region													0.5215
North America	213	25	11.7	212	23	10.8	0.7724	0.92 (0.54,	1.58)	0.92 (0.50,	1.67)	-0.01 (-0.07, 0.05)	
Latin America	645	34	5.3	641	36	5.6	0.7852	1.07 (0.68,	1.68)	1.07 (0.66,	1.73)	0.00 (-0.02, 0.03)	
Europe	674	39	5.8	676	35	5.2	0.6231	0.89 (0.57,	1.39)	0.89 (0.56,	1.42)	-0.01 (-0.03, 0.02)	
Asia	244	5	2.0	248	12	4.8	0.0903	2.36 (0.84,	6.60)	2.43 (0.84,	7.01)	0.03 (0.00, 0.06)	
Other	87	0	0	86	0	0	0.9954	1.01 (0.02,	50.41)	1.01 (0.02,	51.56)	0.00 (-0.02, 0.02)	
OECD Member													0.6042
No	741	34	4.6	713	37	5.2	0.5950	1.13 (0.72,	1.78)	1.14 (0.71,	1.83)	0.01 (-0.02, 0.03)	
Yes	1122	69	6.1	1150	69	6.0	0.8812	0.98 (0.71,	1.35)	0.97 (0.69,	1.37)	0.00 (-0.02, 0.02)	
Baseline NYHA													0.8855
II	1399	67	4.8	1399	68	4.9	0.9297	1.01 (0.73,	1.41)	1.02 (0.72,	1.44)	0.00 (-0.02, 0.02)	
III/IV	464	36	7.8	464	38	8.2	0.8085	1.06 (0.68,	1.63)	1.06 (0.66,	1.71)	0.00 (-0.03, 0.04)	
Baseline Diabetes Status													0.6127
Diabetic	926	46	5.0	927	51	5.5	0.6058	1.11 (0.75,	1.63)	1.11 (0.74,	1.68)	0.01 (-0.01, 0.03)	
Non-Diabetic	937	57	6.1	936	55	5.9	0.8500	0.97 (0.67,	1.38)	0.96 (0.66,	1.41)	0.00 (-0.02, 0.02)	
Baseline BMI [kg/m²]													0.5508
<30	1299	72	5.5	1263	68	5.4	0.8597	0.97 (0.70,	1.34)	0.97 (0.69,	1.36)	0.00 (-0.02, 0.02)	
>=30	564	31	5.5	600	38	6.3	0.5457	1.15 (0.73,	1.83)	1.16 (0.71,	1.90)	0.01 (-0.02, 0.04)	

*** 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).
Subgroups will only be analysed if at least 10 events occurred in at least one category (both treatments combined).
For AEs on SOC and/or PT level, subgroup analyses are only shown if overall test for treatment is significant on 5% level (i.e. 95% CI for the risk ratio does not contain 1; if this is not calculable the p-value of Chi-square test is used).
MedDRA version: 23.0. * Chi-square test for treatment effect ** Breslow-Day test for homogeneity of odds ratios (treatment by subgroup interaction).

Table R.1.4.3: 1 Proportion of patients with adverse events of special interest and other specific AEs
- by user-defined AE category - overall population 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 eGFR (CKD-EPI) [mL/min/1.73m²]											0.7682
>=60	958	44	4.6	969	48	5.0	0.7104	1.08 (0.72, 1.61)	1.08 (0.71, 1.65)	0.00 (-0.02, 0.02)	
<60	904	59	6.5	893	58	6.5	0.9784	1.00 (0.70, 1.41)	0.99 (0.68, 1.45)	0.00 (-0.02, 0.02)	
History of HHF (in the last 12 months)											0.4463
No	1290	75	5.8	1286	72	5.6	0.8139	0.96 (0.70, 1.32)	0.96 (0.69, 1.34)	0.00 (-0.02, 0.02)	
Yes	573	28	4.9	577	34	5.9	0.4501	1.21 (0.74, 1.96)	1.22 (0.73, 2.04)	0.01 (-0.02, 0.04)	
Cause of Heart Failure											0.9753
Ischemic	944	54	5.7	983	58	5.9	0.8660	1.03 (0.72, 1.48)	1.03 (0.71, 1.51)	0.00 (-0.02, 0.02)	
Non-ischemic	919	49	5.3	880	48	5.5	0.9083	1.02 (0.69, 1.51)	1.02 (0.68, 1.54)	0.00 (-0.02, 0.02)	
Heart Failure Physiology											0.2445
LVEF <= 30% and NTproBNP < median	723	35	4.8	698	43	6.2	0.2749	1.27 (0.82, 1.96)	1.29 (0.82, 2.04)	0.01 (-0.01, 0.04)	
LVEF <= 30% and NTproBNP >= median	660	39	5.9	631	40	6.3	0.7473	1.07 (0.70, 1.64)	1.08 (0.68, 1.70)	0.00 (-0.02, 0.03)	
LVEF > 30%	473	28	5.9	526	22	4.2	0.2087	0.71 (0.41, 1.22)	0.69 (0.39, 1.23)	-0.02 (-0.04, 0.01)	
Baseline use of MRA											0.2446
No	512	32	6.3	557	28	5.0	0.3854	0.80 (0.49, 1.32)	0.79 (0.47, 1.34)	-0.01 (-0.04, 0.02)	
Yes	1351	71	5.3	1306	78	6.0	0.4219	1.14 (0.83, 1.55)	1.15 (0.82, 1.59)	0.01 (-0.01, 0.02)	
Baseline use of ARNi											0.4640
No	1476	75	5.1	1523	76	5.0	0.9091	0.98 (0.72, 1.34)	0.98 (0.71, 1.36)	0.00 (-0.02, 0.01)	
Yes	387	28	7.2	340	30	8.8	0.4303	1.22 (0.74, 2.00)	1.24 (0.73, 2.12)	0.02 (-0.02, 0.06)	

*** 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).
Subgroups will only be analysed if at least 10 events occurred in at least one category (both treatments combined).
For AEs on SOC and/or PT level, subgroup analyses are only shown if overall test for treatment is significant on 5% level (i.e. 95% CI for the risk ratio does not contain 1; if this is not calculable the p-value of Chi-square test is used).
MedDRA version: 23.0. * Chi-square test for treatment effect ** Breslow-Day test for homogeneity of odds ratios (treatment by subgroup interaction).

Table R.1.4.3: 1 Proportion of patients with adverse events of special interest and other specific AEs
- by user-defined AE category - overall population 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												0.0068
<=30	1390	75	5.4	1337	84	6.3	0.3230	1.16 (0.86, 1.58)	1.18 (0.85, 1.62)	0.01	(-0.01, 0.03)	
>30 to <=35	359	27	7.5	398	15	3.8	0.0243	0.50 (0.27, 0.93)	0.48 (0.25, 0.92)	-0.04	(-0.07, 0.00)	
>35	114	1	0.9	128	7	5.5	0.0461	6.23 (0.78, 49.90)	6.54 (0.79, 53.97)	0.05	(0.00, 0.09)	
Baseline NTproBNP												0.5519
< median	919	50	5.4	942	57	6.1	0.5718	1.11 (0.77, 1.61)	1.12 (0.76, 1.66)	0.01	(-0.02, 0.03)	
>= median	943	53	5.6	920	49	5.3	0.7801	0.95 (0.65, 1.38)	0.94 (0.63, 1.41)	0.00	(-0.02, 0.02)	

*** 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).
Subgroups will only be analysed if at least 10 events occurred in at least one category (both treatments combined).
For AEs on SOC and/or PT level, subgroup analyses are only shown if overall test for treatment is significant on 5% level (i.e. 95% CI for the risk ratio does not contain 1; if this is not calculable the p-value of Chi-square test is used).
MedDRA version: 23.0. * Chi-square test for treatment effect ** Breslow-Day test for homogeneity of odds ratios (treatment by subgroup interaction).

Table R.1.4.3: 1 Proportion of patients with adverse events of special interest and other specific AEs
- by user-defined AE category - overall population and by subgroup - TS
User-defined AE category: Pruritus (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 **
Overall	1863	28	1.5	1863	30	1.6	0.7913	1.07 (0.64, 1.79)	1.07 (0.64, 1.80)	0.00 (-0.01, 0.01)	
Sex											0.6095
Male	1410	21	1.5	1426	21	1.5	0.9706	0.99 (0.54, 1.80)	0.99 (0.54, 1.82)	0.00 (-0.01, 0.01)	
Female	453	7	1.5	437	9	2.1	0.5638	1.33 (0.50, 3.55)	1.34 (0.49, 3.63)	0.01 (-0.01, 0.02)	
Age [years]											0.8367
< 65	739	11	1.5	675	10	1.5	0.9913	1.00 (0.43, 2.33)	1.00 (0.42, 2.36)	0.00 (-0.01, 0.01)	
>= 65	1124	17	1.5	1188	20	1.7	0.7432	1.11 (0.59, 2.11)	1.12 (0.58, 2.14)	0.00 (-0.01, 0.01)	
Region											0.8408
North America	213	1	0.5	212	1	0.5	0.9973	1.00 (0.06, 15.96)	1.00 (0.06, 16.17)	0.00 (-0.01, 0.01)	
Latin America	645	4	0.6	641	7	1.1	0.3582	1.76 (0.52, 5.99)	1.77 (0.52, 6.07)	0.00 (-0.01, 0.01)	
Europe	674	13	1.9	676	12	1.8	0.8342	0.92 (0.42, 2.00)	0.92 (0.42, 2.03)	0.00 (-0.02, 0.01)	
Asia	244	10	4.1	248	9	3.6	0.7871	0.89 (0.37, 2.14)	0.88 (0.35, 2.21)	0.00 (-0.04, 0.03)	
Other	87	0	0	86	1	1.2	0.4719	3.03 (0.13, 73.47)	3.07 (0.12, 76.42)	0.01 (-0.02, 0.04)	
OECD Member											0.2596
No	741	6	0.8	713	10	1.4	0.2787	1.73 (0.63, 4.74)	1.74 (0.63, 4.82)	0.01 (0.00, 0.02)	
Yes	1122	22	2.0	1150	20	1.7	0.6950	0.89 (0.49, 1.62)	0.88 (0.48, 1.63)	0.00 (-0.01, 0.01)	
Baseline NYHA											0.0475
II	1399	21	1.5	1399	15	1.1	0.3142	0.71 (0.37, 1.38)	0.71 (0.37, 1.39)	0.00 (-0.01, 0.00)	
III/IV	464	7	1.5	464	15	3.2	0.0843	2.14 (0.88, 5.21)	2.18 (0.88, 5.40)	0.02 (0.00, 0.04)	
Baseline Diabetes Status											0.6370
Diabetic	926	17	1.8	927	20	2.2	0.6207	1.18 (0.62, 2.23)	1.18 (0.61, 2.27)	0.00 (-0.01, 0.02)	
Non-Diabetic	937	11	1.2	936	10	1.1	0.8282	0.91 (0.39, 2.13)	0.91 (0.38, 2.15)	0.00 (-0.01, 0.01)	
Baseline BMI [kg/m²]											0.7660
<30	1299	21	1.6	1263	23	1.8	0.6905	1.13 (0.63, 2.02)	1.13 (0.62, 2.05)	0.00 (-0.01, 0.01)	
>=30	564	7	1.2	600	7	1.2	0.9073	0.94 (0.33, 2.66)	0.94 (0.33, 2.69)	0.00 (-0.01, 0.01)	

*** 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).
Subgroups will only be analysed if at least 10 events occurred in at least one category (both treatments combined).
For AEs on SOC and/or PT level, subgroup analyses are only shown if overall test for treatment is significant on 5% level (i.e. 95% CI for the risk ratio does not contain 1; if this is not calculable the p-value of Chi-square test is used).
MedDRA version: 23.0. * Chi-square test for treatment effect ** Breslow-Day test for homogeneity of odds ratios (treatment by subgroup interaction).

Table R.1.4.3: 1 Proportion of patients with adverse events of special interest and other specific AEs
- by user-defined AE category - overall population and by subgroup - TS
User-defined AE category: Pruritus (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 eGFR (CKD-EPI) [mL/min/1.73m²]											0.6402
>=60	958	14	1.5	969	17	1.8	0.6092	1.20 (0.60, 2.42)	1.20 (0.59, 2.46)	0.00 (-0.01, 0.01)	
<60	904	14	1.5	893	13	1.5	0.8714	0.94 (0.44, 1.99)	0.94 (0.44, 2.01)	0.00 (-0.01, 0.01)	
History of HHF (in the last 12 months)											0.7062
No	1290	20	1.6	1286	20	1.6	0.9921	1.00 (0.54, 1.86)	1.00 (0.54, 1.87)	0.00 (-0.01, 0.01)	
Yes	573	8	1.4	577	10	1.7	0.6453	1.24 (0.49, 3.12)	1.25 (0.49, 3.18)	0.00 (-0.01, 0.02)	
Cause of Heart Failure											0.4780
Ischemic	944	16	1.7	983	15	1.5	0.7682	0.90 (0.45, 1.81)	0.90 (0.44, 1.83)	0.00 (-0.01, 0.01)	
Non-ischemic	919	12	1.3	880	15	1.7	0.4868	1.31 (0.61, 2.77)	1.31 (0.61, 2.82)	0.00 (-0.01, 0.02)	
Heart Failure Physiology											0.5283
LVEF <= 30% and NTproBNP < median	723	12	1.7	698	9	1.3	0.5630	0.78 (0.33, 1.83)	0.77 (0.32, 1.85)	0.00 (-0.02, 0.01)	
LVEF <= 30% and NTproBNP >= median	660	8	1.2	631	12	1.9	0.3159	1.57 (0.65, 3.81)	1.58 (0.64, 3.89)	0.01 (-0.01, 0.02)	
LVEF > 30%	473	8	1.7	526	9	1.7	0.9808	1.01 (0.39, 2.60)	1.01 (0.39, 2.64)	0.00 (-0.02, 0.02)	
Baseline use of MRA											0.2087
No	512	4	0.8	557	9	1.6	0.2136	2.07 (0.64, 6.67)	2.09 (0.64, 6.81)	0.01 (0.00, 0.02)	
Yes	1351	24	1.8	1306	21	1.6	0.7365	0.91 (0.51, 1.62)	0.90 (0.50, 1.63)	0.00 (-0.01, 0.01)	
Baseline use of ARNi											0.9081
No	1476	21	1.4	1523	23	1.5	0.8422	1.06 (0.59, 1.91)	1.06 (0.59, 1.93)	0.00 (-0.01, 0.01)	
Yes	387	7	1.8	340	7	2.1	0.8066	1.14 (0.40, 3.21)	1.14 (0.40, 3.29)	0.00 (-0.02, 0.02)	

*** 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).
Subgroups will only be analysed if at least 10 events occurred in at least one category (both treatments combined).
For AEs on SOC and/or PT level, subgroup analyses are only shown if overall test for treatment is significant on 5% level (i.e. 95% CI for the risk ratio does not contain 1; if this is not calculable the p-value of Chi-square test is used).
MedDRA version: 23.0. * Chi-square test for treatment effect ** Breslow-Day test for homogeneity of odds ratios (treatment by subgroup interaction).

Table R.1.4.3: 1 Proportion of patients with adverse events of special interest and other specific AEs
- by user-defined AE category - overall population and by subgroup - TS
User-defined AE category: Pruritus (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												0.9259
<=30	1390	20	1.4	1337	21	1.6	0.7773	1.09 (0.59, 2.00)	1.09 (0.59, 2.03)	0.00	(-0.01, 0.01)	
>30 to <=35	359	6	1.7	398	6	1.5	0.8570	0.90 (0.29, 2.77)	0.90 (0.29, 2.82)	0.00	(-0.02, 0.02)	
>35	114	2	1.8	128	3	2.3	0.7477	1.34 (0.23, 7.85)	1.34 (0.22, 8.19)	0.01	(-0.03, 0.04)	
Baseline NTproBNP												0.9390
< median	919	13	1.4	942	14	1.5	0.8972	1.05 (0.50, 2.22)	1.05 (0.49, 2.25)	0.00	(-0.01, 0.01)	
>= median	943	15	1.6	920	16	1.7	0.8022	1.09 (0.54, 2.20)	1.09 (0.54, 2.23)	0.00	(-0.01, 0.01)	

*** 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).
Subgroups will only be analysed if at least 10 events occurred in at least one category (both treatments combined).
For AEs on SOC and/or PT level, subgroup analyses are only shown if overall test for treatment is significant on 5% level (i.e. 95% CI for the risk ratio does not contain 1; if this is not calculable the p-value of Chi-square test is used).
MedDRA version: 23.0. * Chi-square test for treatment effect ** Breslow-Day test for homogeneity of odds ratios (treatment by subgroup interaction).

Table R.1.4.3: 1 Proportion of patients with adverse events of special interest and other specific AEs
- by user-defined AE category - overall population and by subgroup - TS
User-defined AE category: Allergic skin reactions (BIcMQ)

Subgroup Category	Placebo N	Placebo n	Placebo %	Empa 10mg N	Empa 10mg n	Empa 10mg %	Empa 10mg vs Placebo p-value *	Risk ratio (95% CI)	Odds ratio (95% CI)	Risk diff. (95% CI)	p-value **
Overall	1863	39	2.1	1863	36	1.9	0.7264	0.92 (0.59, 1.45)	0.92 (0.58, 1.46)	0.00 (-0.01, 0.01)	
Sex											0.4053
Male	1410	31	2.2	1426	26	1.8	0.4764	0.83 (0.50, 1.39)	0.83 (0.49, 1.40)	0.00 (-0.01, 0.01)	
Female	453	8	1.8	437	10	2.3	0.5800	1.30 (0.52, 3.25)	1.30 (0.51, 3.33)	0.01 (-0.01, 0.02)	
Age [years]											0.0678
< 65	739	7	0.9	675	12	1.8	0.1755	1.88 (0.74, 4.74)	1.89 (0.74, 4.84)	0.01 (0.00, 0.02)	
>= 65	1124	32	2.8	1188	24	2.0	0.1962	0.71 (0.42, 1.20)	0.70 (0.41, 1.20)	-0.01 (-0.02, 0.00)	
Region											0.3787
North America	213	8	3.8	212	7	3.3	0.7998	0.88 (0.32, 2.38)	0.88 (0.31, 2.46)	0.00 (-0.04, 0.03)	
Latin America	645	3	0.5	641	7	1.1	0.2006	2.35 (0.61, 9.04)	2.36 (0.61, 9.18)	0.01 (0.00, 0.02)	
Europe	674	14	2.1	676	9	1.3	0.2897	0.64 (0.28, 1.47)	0.64 (0.27, 1.48)	-0.01 (-0.02, 0.01)	
Asia	244	13	5.3	248	10	4.0	0.4961	0.76 (0.34, 1.69)	0.75 (0.32, 1.74)	-0.01 (-0.05, 0.02)	
Other	87	1	1.1	86	3	3.5	0.3061	3.03 (0.32, 28.61)	3.11 (0.32, 30.49)	0.02 (-0.02, 0.07)	
OECD Member											0.0451
No	741	5	0.7	713	11	1.5	0.1127	2.29 (0.80, 6.55)	2.31 (0.80, 6.67)	0.01 (0.00, 0.02)	
Yes	1122	34	3.0	1150	25	2.2	0.1994	0.72 (0.43, 1.19)	0.71 (0.42, 1.20)	-0.01 (-0.02, 0.00)	
Baseline NYHA											0.2050
II	1399	31	2.2	1399	24	1.7	0.3404	0.77 (0.46, 1.31)	0.77 (0.45, 1.32)	-0.01 (-0.02, 0.01)	
III/IV	464	8	1.7	464	12	2.6	0.3659	1.50 (0.62, 3.64)	1.51 (0.61, 3.74)	0.01 (-0.01, 0.03)	
Baseline Diabetes Status											0.5816
Diabetic	926	23	2.5	927	19	2.0	0.5301	0.83 (0.45, 1.50)	0.82 (0.44, 1.52)	0.00 (-0.02, 0.01)	
Non-Diabetic	937	16	1.7	936	17	1.8	0.8582	1.06 (0.54, 2.09)	1.06 (0.53, 2.12)	0.00 (-0.01, 0.01)	
Baseline BMI [kg/m²]											0.1915
<30	1299	27	2.1	1263	29	2.3	0.7065	1.10 (0.66, 1.86)	1.11 (0.65, 1.88)	0.00 (-0.01, 0.01)	
>=30	564	12	2.1	600	7	1.2	0.1960	0.55 (0.22, 1.38)	0.54 (0.21, 1.39)	-0.01 (-0.02, 0.01)	

*** 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).
Subgroups will only be analysed if at least 10 events occurred in at least one category (both treatments combined).
For AEs on SOC and/or PT level, subgroup analyses are only shown if overall test for treatment is significant on 5% level (i.e. 95% CI for the risk ratio does not contain 1; if this is not calculable the p-value of Chi-square test is used).
MedDRA version: 23.0. * Chi-square test for treatment effect ** Breslow-Day test for homogeneity of odds ratios (treatment by subgroup interaction).

Table R.1.4.3: 1 Proportion of patients with adverse events of special interest and other specific AEs
- by user-defined AE category - overall population 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 eGFR (CKD-EPI) [mL/min/1.73m²]															0.4877
>=60	958	11	1.1	969	13	1.3	0.7020	1.17	(0.53, | 2.60)	1.17	(0.52, | 2.63)	0.00 (-0.01, 0.01)	
<60	904	28	3.1	893	23	2.6	0.5054	0.83	(0.48, | 1.43)	0.83	(0.47, | 1.45)	-0.01 (-0.02, 0.01)	
History of HHF (in the last 12 months)															0.5615
No	1290	27	2.1	1286	27	2.1	0.9908	1.00	(0.59, | 1.70)	1.00	(0.59, | 1.72)	0.00 (-0.01, 0.01)	
Yes	573	12	2.1	577	9	1.6	0.4985	0.74	(0.32, | 1.75)	0.74	(0.31, | 1.77)	-0.01 (-0.02, 0.01)	
Cause of Heart Failure															0.5646
Ischemic	944	18	1.9	983	15	1.5	0.5195	0.80	(0.41, | 1.58)	0.80	(0.40, | 1.59)	0.00 (-0.02, 0.01)	
Non-ischemic	919	21	2.3	880	21	2.4	0.8869	1.04	(0.57, | 1.90)	1.05	(0.57, | 1.93)	0.00 (-0.01, 0.01)	
Heart Failure Physiology															0.4094
LVEF <= 30% and NTproBNP < median	723	11	1.5	698	14	2.0	0.4876	1.32	(0.60, | 2.88)	1.32	(0.60, | 2.94)	0.00 (-0.01, 0.02)	
LVEF <= 30% and NTproBNP >= median	660	18	2.7	631	11	1.7	0.2330	0.64	(0.30, | 1.34)	0.63	(0.30, | 1.35)	-0.01 (-0.03, 0.01)	
LVEF > 30%	473	10	2.1	526	11	2.1	0.9799	0.99	(0.42, | 2.31)	0.99	(0.42, | 2.35)	0.00 (-0.02, 0.02)	
Baseline use of MRA															0.4508
No	512	10	2.0	557	13	2.3	0.6682	1.19	(0.53, | 2.70)	1.20	(0.52, | 2.76)	0.00 (-0.01, 0.02)	
Yes	1351	29	2.1	1306	23	1.8	0.4733	0.82	(0.48, | 1.41)	0.82	(0.47, | 1.42)	0.00 (-0.01, 0.01)	
Baseline use of ARNi															0.7061
No	1476	34	2.3	1523	31	2.0	0.6143	0.88	(0.55, | 1.43)	0.88	(0.54, | 1.44)	0.00 (-0.01, 0.01)	
Yes	387	5	1.3	340	5	1.5	0.8366	1.14	(0.33, | 3.90)	1.14	(0.33, | 3.97)	0.00 (-0.02, 0.02)	

*** 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).
Subgroups will only be analysed if at least 10 events occurred in at least one category (both treatments combined).
For AEs on SOC and/or PT level, subgroup analyses are only shown if overall test for treatment is significant on 5% level (i.e. 95% CI for the risk ratio does not contain 1; if this is not calculable the p-value of Chi-square test is used).
MedDRA version: 23.0. * Chi-square test for treatment effect ** Breslow-Day test for homogeneity of odds ratios (treatment by subgroup interaction).

Table R.1.4.3: 1 Proportion of patients with adverse events of special interest and other specific AEs
- by user-defined AE category - overall population 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													0.4550
<=30	1390	29	2.1	1337	25	1.9	0.6850	0.90 (0.53,	1.52)	0.89 (0.52,	1.53)	0.00 (-0.01, 0.01)	
>30 to <=35	359	7	1.9	398	10	2.5	0.6018	1.29 (0.50,	3.35)	1.30 (0.49,	3.44)	0.01 (-0.02, 0.03)	
>35	114	3	2.6	128	1	0.8	0.2598	0.30 (0.03,	2.81)	0.29 (0.03,	2.84)	-0.02 (-0.05, 0.01)	
Baseline NTproBNP													0.2568
< median	919	13	1.4	942	17	1.8	0.5041	1.28 (0.62,	2.61)	1.28 (0.62,	2.65)	0.00 (-0.01, 0.02)	
>= median	943	26	2.8	920	19	2.1	0.3308	0.75 (0.42,	1.34)	0.74 (0.41,	1.35)	-0.01 (-0.02, 0.01)	

*** 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).
Subgroups will only be analysed if at least 10 events occurred in at least one category (both treatments combined).
For AEs on SOC and/or PT level, subgroup analyses are only shown if overall test for treatment is significant on 5% level (i.e. 95% CI for the risk ratio does not contain 1; if this is not calculable the p-value of Chi-square test is used).
MedDRA version: 23.0. * Chi-square test for treatment effect ** Breslow-Day test for homogeneity of odds ratios (treatment by subgroup interaction).

Table R.1.4.3: 1 Proportion of patients with adverse events of special interest and other specific AEs
- by user-defined AE category - overall population and by subgroup - TS
User-defined AE category: Increased urination (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 **
Overall	1863	7	0.4	1863	13	0.7	0.1785	1.86 (0.74, 4.64)	1.86 (0.74, 4.68)	0.00 (0.00, 0.01)	
Sex											0.8810
Male	1410	5	0.4	1426	9	0.6	0.2935	1.78 (0.60, 5.30)	1.78 (0.60, 5.34)	0.00 (0.00, 0.01)	
Female	453	2	0.4	437	4	0.9	0.3878	2.07 (0.38, 11.26)	2.08 (0.38, 11.43)	0.00 (-0.01, 0.02)	
Age [years]											0.8926
< 65	739	2	0.3	675	3	0.4	0.5823	1.64 (0.28, 9.80)	1.65 (0.27, 9.88)	0.00 (0.00, 0.01)	
>= 65	1124	5	0.4	1188	10	0.8	0.2348	1.89 (0.65, 5.52)	1.90 (0.65, 5.58)	0.00 (0.00, 0.01)	
OECD Member											0.6038
No	741	1	0.1	713	3	0.4	0.2983	3.12 (0.33, 29.90)	3.13 (0.32, 30.13)	0.00 (0.00, 0.01)	
Yes	1122	6	0.5	1150	10	0.9	0.3400	1.63 (0.59, 4.46)	1.63 (0.59, 4.50)	0.00 (0.00, 0.01)	
Baseline NYHA											0.8499
II	1399	4	0.3	1399	8	0.6	0.2472	2.00 (0.60, 6.63)	2.01 (0.60, 6.68)	0.00 (0.00, 0.01)	
III/IV	464	3	0.6	464	5	1.1	0.4776	1.67 (0.40, 6.93)	1.67 (0.40, 7.05)	0.00 (-0.01, 0.02)	
Baseline Diabetes Status											0.1593
Diabetic	926	2	0.2	927	8	0.9	0.0573	4.00 (0.85, 18.77)	4.02 (0.85, 18.99)	0.01 (0.00, 0.01)	
Non-Diabetic	937	5	0.5	936	5	0.5	0.9986	1.00 (0.29, 3.45)	1.00 (0.29, 3.47)	0.00 (-0.01, 0.01)	
Baseline BMI [kg/m²]											0.3128
<30	1299	7	0.5	1263	10	0.8	0.4306	1.47 (0.56, 3.85)	1.47 (0.56, 3.88)	0.00 (0.00, 0.01)	
>=30	564	0	0	600	3	0.5	0.1495	6.58 (0.34,127.12)	6.61 (0.34,128.32)	0.00 (0.00, 0.01)	
Baseline eGFR (CKD-EPI) [mL/min/1.73m²]											0.4583
>=60	958	2	0.2	969	6	0.6	0.1612	2.97 (0.60, 14.66)	2.98 (0.60, 14.79)	0.00 (0.00, 0.01)	
<60	904	5	0.6	893	7	0.8	0.5481	1.42 (0.45, 4.45)	1.42 (0.45, 4.49)	0.00 (-0.01, 0.01)	

*** 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).
Subgroups will only be analysed if at least 10 events occurred in at least one category (both treatments combined).
For AEs on SOC and/or PT level, subgroup analyses are only shown if overall test for treatment is significant on 5% level (i.e. 95% CI for the risk ratio does not contain 1; if this is not calculable the p-value of Chi-square test is used).
MedDRA version: 23.0. * Chi-square test for treatment effect ** Breslow-Day test for homogeneity of odds ratios (treatment by subgroup interaction).

Table R.1.4.3: 1 Proportion of patients with adverse events of special interest and other specific AEs
- by user-defined AE category - overall population 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 **
History of HHF (in the last 12 months)											0.2632
No	1290	6	0.5	1286	8	0.6	0.5880	1.34 (0.47, 3.84)	1.34 (0.46, 3.87)	0.00 (0.00, 0.01)	
Yes	573	1	0.2	577	5	0.9	0.1034	4.97 (0.58, 42.37)	5.00 (0.58, 42.93)	0.01 (0.00, 0.02)	
Cause of Heart Failure											0.7038
Ischemic	944	3	0.3	983	7	0.7	0.2285	2.24 (0.58, 8.64)	2.25 (0.58, 8.73)	0.00 (0.00, 0.01)	
Non-ischemic	919	4	0.4	880	6	0.7	0.4820	1.57 (0.44, 5.53)	1.57 (0.44, 5.58)	0.00 (0.00, 0.01)	
Baseline use of MRA											0.7011
No	512	2	0.4	557	3	0.5	0.7232	1.38 (0.23, 8.22)	1.38 (0.23, 8.30)	0.00 (-0.01, 0.01)	
Yes	1351	5	0.4	1306	10	0.8	0.1736	2.07 (0.71, 6.04)	2.08 (0.71, 6.09)	0.00 (0.00, 0.01)	
Baseline use of ARNi											0.3393
No	1476	6	0.4	1523	9	0.6	0.4741	1.45 (0.52, 4.07)	1.46 (0.52, 4.10)	0.00 (0.00, 0.01)	
Yes	387	1	0.3	340	4	1.2	0.1351	4.55 (0.51, 40.54)	4.60 (0.51, 41.31)	0.01 (0.00, 0.02)	
Baseline LVEF											0.3074
<=30	1390	6	0.4	1337	10	0.7	0.2796	1.73 (0.63, 4.75)	1.74 (0.63, 4.80)	0.00 (0.00, 0.01)	
>30 to <=35	359	0	0	398	3	0.8	0.1607	6.32 (0.33,121.85)	6.36 (0.33,123.61)	0.01 (0.00, 0.02)	
>35	114	1	0.9	128	0	0	0.4279	0.30 (0.01, 7.22)	0.29 (0.01, 7.30)	-0.01 (-0.03, 0.01)	
Baseline NTproBNP											0.8062
< median	919	3	0.3	942	5	0.5	0.5005	1.63 (0.39, 6.78)	1.63 (0.39, 6.84)	0.00 (0.00, 0.01)	
>= median	943	4	0.4	920	8	0.9	0.2296	2.05 (0.62, 6.78)	2.06 (0.62, 6.86)	0.00 (0.00, 0.01)	

*** 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).
Subgroups will only be analysed if at least 10 events occurred in at least one category (both treatments combined).
For AEs on SOC and/or PT level, subgroup analyses are only shown if overall test for treatment is significant on 5% level (i.e. 95% CI for the risk ratio does not contain 1; if this is not calculable the p-value of Chi-square test is used).
MedDRA version: 23.0. * Chi-square test for treatment effect ** Breslow-Day test for homogeneity of odds ratios (treatment by subgroup interaction).

Table R.1.4.3: 1 Proportion of patients with adverse events of special interest and other specific AEs
- by user-defined AE category - overall population 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	1863	1	0.1	1863	5	0.3	0.1022	5.00 (0.58, 42.76)	5.01 (0.58, 42.93)	0.00 (0.00, 0.00)	

*** 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).
Subgroups will only be analysed if at least 10 events occurred in at least one category (both treatments combined).
For AEs on SOC and/or PT level, subgroup analyses are only shown if overall test for treatment is significant on 5% level (i.e. 95% CI for the risk ratio does not contain 1; if this is not calculable the p-value of Chi-square test is used).
MedDRA version: 23.0. * Chi-square test for treatment effect ** Breslow-Day test for homogeneity of odds ratios (treatment by subgroup interaction).

Table R.1.4.3: 1 Proportion of patients with adverse events of special interest and other specific AEs
- by user-defined AE category - overall population 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	1863	52	2.8	1863	53	2.8	0.9211	1.02 (0.70,	1.49)	1.02 (0.69,	1.50)	0.00 (-0.01, 0.01)	
Sex													0.0937
Male	1410	43	3.0	1426	37	2.6	0.4644	0.85 (0.55,	1.31)	0.85 (0.54,	1.32)	0.00 (-0.02, 0.01)	
Female	453	9	2.0	437	16	3.7	0.1307	1.84 (0.82,	4.13)	1.87 (0.82,	4.29)	0.02 (-0.01, 0.04)	
Age [years]													0.3411
< 65	739	34	4.6	675	28	4.1	0.6780	0.90 (0.55,	1.47)	0.90 (0.54,	1.50)	0.00 (-0.03, 0.02)	
>= 65	1124	18	1.6	1188	25	2.1	0.3710	1.31 (0.72,	2.40)	1.32 (0.72,	2.43)	0.01 (-0.01, 0.02)	
Region													0.7248
North America	213	2	0.9	212	4	1.9	0.4076	2.01 (0.37,	10.85)	2.03 (0.37,	11.20)	0.01 (-0.01, 0.03)	
Latin America	645	27	4.2	641	22	3.4	0.4801	0.82 (0.47,	1.42)	0.81 (0.46,	1.44)	-0.01 (-0.03, 0.01)	
Europe	674	9	1.3	676	12	1.8	0.5138	1.33 (0.56,	3.13)	1.34 (0.56,	3.19)	0.00 (-0.01, 0.02)	
Asia	244	12	4.9	248	14	5.6	0.7185	1.15 (0.54,	2.43)	1.16 (0.52,	2.55)	0.01 (-0.03, 0.05)	
Other	87	2	2.3	86	1	1.2	0.5671	0.51 (0.05,	5.48)	0.50 (0.04,	5.62)	-0.01 (-0.05, 0.03)	
OECD Member													0.5789
No	741	32	4.3	713	29	4.1	0.8113	0.94 (0.58,	1.54)	0.94 (0.56,	1.57)	0.00 (-0.02, 0.02)	
Yes	1122	20	1.8	1150	24	2.1	0.5986	1.17 (0.65,	2.11)	1.17 (0.65,	2.14)	0.00 (-0.01, 0.01)	
Baseline NYHA													0.5342
II	1399	40	2.9	1399	38	2.7	0.8183	0.95 (0.61,	1.47)	0.95 (0.60,	1.49)	0.00 (-0.01, 0.01)	
III/IV	464	12	2.6	464	15	3.2	0.5579	1.25 (0.59,	2.64)	1.26 (0.58,	2.72)	0.01 (-0.02, 0.03)	
Baseline Diabetes Status													0.7700
Diabetic	926	25	2.7	927	27	2.9	0.7815	1.08 (0.63,	1.84)	1.08 (0.62,	1.88)	0.00 (-0.01, 0.02)	
Non-Diabetic	937	27	2.9	936	26	2.8	0.8923	0.96 (0.57,	1.64)	0.96 (0.56,	1.66)	0.00 (-0.02, 0.01)	
Baseline BMI [kg/m²]													0.1633
<30	1299	36	2.8	1263	42	3.3	0.4145	1.20 (0.77,	1.86)	1.21 (0.77,	1.90)	0.01 (-0.01, 0.02)	
>=30	564	16	2.8	600	11	1.8	0.2556	0.65 (0.30,	1.38)	0.64 (0.29,	1.39)	-0.01 (-0.03, 0.01)	

*** 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).
Subgroups will only be analysed if at least 10 events occurred in at least one category (both treatments combined).
For AEs on SOC and/or PT level, subgroup analyses are only shown if overall test for treatment is significant on 5% level (i.e. 95% CI for the risk ratio does not contain 1; if this is not calculable the p-value of Chi-square test is used).
MedDRA version: 23.0. * Chi-square test for treatment effect ** Breslow-Day test for homogeneity of odds ratios (treatment by subgroup interaction).

Table R.1.4.3: 1 Proportion of patients with adverse events of special interest and other specific AEs
- by user-defined AE category - overall population 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 eGFR (CKD-EPI) [mL/min/1.73m²]														0.2325
>=60	958	38	4.0	969	44	4.5	0.5324	1.14	(0.75, 1.75)	1.15	(0.74, 1.79)	0.01	(-0.01, 0.02)	
<60	904	14	1.5	893	9	1.0	0.3078	0.65	(0.28, 1.50)	0.65	(0.28, 1.50)	-0.01	(-0.02, 0.00)	
History of HHF (in the last 12 months)														0.7599
No	1290	33	2.6	1286	32	2.5	0.9101	0.97	(0.60, 1.57)	0.97	(0.59, 1.59)	0.00	(-0.01, 0.01)	
Yes	573	19	3.3	577	21	3.6	0.7646	1.10	(0.60, 2.02)	1.10	(0.59, 2.07)	0.00	(-0.02, 0.02)	
Cause of Heart Failure														0.1733
Ischemic	944	15	1.6	983	23	2.3	0.2360	1.47	(0.77, 2.80)	1.48	(0.77, 2.86)	0.01	(0.00, 0.02)	
Non-ischemic	919	37	4.0	880	30	3.4	0.4896	0.85	(0.53, 1.36)	0.84	(0.52, 1.37)	-0.01	(-0.02, 0.01)	
Heart Failure Physiology														0.9819
LVEF <= 30% and NTproBNP < median	723	24	3.3	698	24	3.4	0.9013	1.04	(0.59, 1.81)	1.04	(0.58, 1.84)	0.00	(-0.02, 0.02)	
LVEF <= 30% and NTproBNP >= median	660	13	2.0	631	13	2.1	0.9079	1.05	(0.49, 2.24)	1.05	(0.48, 2.28)	0.00	(-0.01, 0.02)	
LVEF > 30%	473	15	3.2	526	16	3.0	0.9062	0.96	(0.48, 1.92)	0.96	(0.47, 1.96)	0.00	(-0.02, 0.02)	
Baseline use of MRA														0.5024
No	512	9	1.8	557	13	2.3	0.5075	1.33	(0.57, 3.08)	1.34	(0.57, 3.15)	0.01	(-0.01, 0.02)	
Yes	1351	43	3.2	1306	40	3.1	0.8589	0.96	(0.63, 1.47)	0.96	(0.62, 1.49)	0.00	(-0.01, 0.01)	
Baseline use of ARNi														0.9858
No	1476	42	2.8	1523	44	2.9	0.9431	1.02	(0.67, 1.54)	1.02	(0.66, 1.56)	0.00	(-0.01, 0.01)	
Yes	387	10	2.6	340	9	2.6	0.9576	1.02	(0.42, 2.49)	1.03	(0.41, 2.55)	0.00	(-0.02, 0.02)	

*** 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).
Subgroups will only be analysed if at least 10 events occurred in at least one category (both treatments combined).
For AEs on SOC and/or PT level, subgroup analyses are only shown if overall test for treatment is significant on 5% level (i.e. 95% CI for the risk ratio does not contain 1; if this is not calculable the p-value of Chi-square test is used).
MedDRA version: 23.0. * Chi-square test for treatment effect ** Breslow-Day test for homogeneity of odds ratios (treatment by subgroup interaction).

Table R.1.4.3: 1 Proportion of patients with adverse events of special interest and other specific AEs
- by user-defined AE category - overall population and by subgroup - TS
User-defined AE category: Serum lipids increased (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 LVEF											0.5498
<=30	1390	37	2.7	1337	37	2.8	0.8654	1.04 (0.66, 1.63)	1.04 (0.66, 1.65)	0.00 (-0.01, 0.01)	
>30 to <=35	359	12	3.3	398	10	2.5	0.4972	0.75 (0.33, 1.72)	0.75 (0.32, 1.75)	-0.01 (-0.03, 0.02)	
>35	114	3	2.6	128	6	4.7	0.3989	1.78 (0.46, 6.96)	1.82 (0.44, 7.45)	0.02 (-0.03, 0.07)	
Baseline NTproBNP											0.6499
< median	919	33	3.6	942	32	3.4	0.8199	0.95 (0.59, 1.53)	0.94 (0.58, 1.55)	0.00 (-0.02, 0.01)	
>= median	943	19	2.0	920	21	2.3	0.6902	1.13 (0.61, 2.09)	1.14 (0.61, 2.13)	0.00 (-0.01, 0.02)	

*** 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).
Subgroups will only be analysed if at least 10 events occurred in at least one category (both treatments combined).
For AEs on SOC and/or PT level, subgroup analyses are only shown if overall test for treatment is significant on 5% level (i.e. 95% CI for the risk ratio does not contain 1; if this is not calculable the p-value of Chi-square test is used).
MedDRA version: 23.0. * Chi-square test for treatment effect ** Breslow-Day test for homogeneity of odds ratios (treatment by subgroup interaction).

Table R.1.4.3: 1 Proportion of patients with adverse events of special interest and other specific AEs
- by user-defined AE category - overall population and by subgroup - TS
User-defined AE category: Angioedema (narrow SMQ)

Subgroup Category	Placebo N	Placebo n	Placebo %	Empa 10mg N	Empa 10mg n	Empa 10mg %	Empa 10mg vs Placebo p-value *	Risk ratio (95% CI)	Odds ratio (95% CI)	Risk diff. (95% CI)	p-value **
Overall	1863	10	0.5	1863	9	0.5	0.8181	0.90 (0.37, 2.21)	0.90 (0.36, 2.22)	0.00 (-0.01, 0.00)	
Sex											0.2604
Male	1410	8	0.6	1426	9	0.6	0.8259	1.11 (0.43, 2.87)	1.11 (0.43, 2.89)	0.00 (-0.01, 0.01)	
Female	453	2	0.4	437	0	0	0.2603	0.21 (<0.01, 4.31)	0.21 (<0.01, 4.31)	0.00 (-0.01, 0.00)	
Age [years]											0.1587
< 65	739	5	0.7	675	7	1.0	0.4605	1.53 (0.49, 4.81)	1.54 (0.49, 4.87)	0.00 (-0.01, 0.01)	
>= 65	1124	5	0.4	1188	2	0.2	0.2265	0.38 (0.07, 1.95)	0.38 (0.07, 1.95)	0.00 (-0.01, 0.00)	
OECD Member											0.4714
No	741	3	0.4	713	4	0.6	0.6672	1.39 (0.31, 6.17)	1.39 (0.31, 6.22)	0.00 (-0.01, 0.01)	
Yes	1122	7	0.6	1150	5	0.4	0.5341	0.70 (0.22, 2.19)	0.70 (0.22, 2.20)	0.00 (-0.01, 0.00)	
Baseline NYHA											0.5135
II	1399	7	0.5	1399	5	0.4	0.5629	0.71 (0.23, 2.25)	0.71 (0.23, 2.25)	0.00 (-0.01, 0.00)	
III/IV	464	3	0.6	464	4	0.9	0.7044	1.33 (0.30, 5.92)	1.34 (0.30, 6.00)	0.00 (-0.01, 0.01)	
Baseline Diabetes Status											0.8100
Diabetic	926	5	0.5	927	5	0.5	0.9986	1.00 (0.29, 3.44)	1.00 (0.29, 3.46)	0.00 (-0.01, 0.01)	
Non-Diabetic	937	5	0.5	936	4	0.4	0.7395	0.80 (0.22, 2.97)	0.80 (0.21, 2.99)	0.00 (-0.01, 0.01)	
Baseline BMI [kg/m²]											0.0424
<30	1299	6	0.5	1263	9	0.7	0.4057	1.54 (0.55, 4.32)	1.55 (0.55, 4.36)	0.00 (0.00, 0.01)	
>=30	564	4	0.7	600	0	0	0.0625	0.10 (<0.01, 1.94)	0.10 (<0.01, 1.93)	-0.01 (-0.01, 0.00)	
Baseline eGFR (CKD-EPI) [mL/min/1.73m²]											0.4179
>=60	958	6	0.6	969	7	0.7	0.7967	1.15 (0.39, 3.42)	1.15 (0.39, 3.45)	0.00 (-0.01, 0.01)	
<60	904	4	0.4	893	2	0.2	0.4221	0.51 (0.09, 2.76)	0.51 (0.09, 2.76)	0.00 (-0.01, 0.00)	

*** 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).
Subgroups will only be analysed if at least 10 events occurred in at least one category (both treatments combined).
For AEs on SOC and/or PT level, subgroup analyses are only shown if overall test for treatment is significant on 5% level (i.e. 95% CI for the risk ratio does not contain 1; if this is not calculable the p-value of Chi-square test is used).
MedDRA version: 23.0. * Chi-square test for treatment effect ** Breslow-Day test for homogeneity of odds ratios (treatment by subgroup interaction).

Table R.1.4.3: 1 Proportion of patients with adverse events of special interest and other specific AEs
- by user-defined AE category - overall population and by subgroup - TS
User-defined AE category: Angioedema (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 **
History of HHF (in the last 12 months)											0.4683
No	1290	5	0.4	1286	3	0.2	0.4816	0.60 (0.14, 2.51)	0.60 (0.14, 2.52)	0.00 (-0.01, 0.00)	
Yes	573	5	0.9	577	6	1.0	0.7708	1.19 (0.37, 3.88)	1.19 (0.36, 3.93)	0.00 (-0.01, 0.01)	
Cause of Heart Failure											0.0785
Ischemic	944	6	0.6	983	2	0.2	0.1403	0.32 (0.06, 1.58)	0.32 (0.06, 1.58)	0.00 (-0.01, 0.00)	
Non-ischemic	919	4	0.4	880	7	0.8	0.3273	1.83 (0.54, 6.22)	1.83 (0.54, 6.29)	0.00 (0.00, 0.01)	
Baseline use of MRA											1.0000
No	512	1	0.2	557	1	0.2	0.9524	0.92 (0.06, 14.66)	0.92 (0.06, 14.73)	0.00 (-0.01, 0.01)	
Yes	1351	9	0.7	1306	8	0.6	0.8624	0.92 (0.36, 2.38)	0.92 (0.35, 2.39)	0.00 (-0.01, 0.01)	
Baseline use of ARNi											0.7929
No	1476	8	0.5	1523	7	0.5	0.7492	0.85 (0.31, 2.33)	0.85 (0.31, 2.34)	0.00 (-0.01, 0.00)	
Yes	387	2	0.5	340	2	0.6	0.8966	1.14 (0.16, 8.04)	1.14 (0.16, 8.13)	0.00 (-0.01, 0.01)	
Baseline LVEF											0.3141
<=30	1390	9	0.6	1337	5	0.4	0.3178	0.58 (0.19, 1.72)	0.58 (0.19, 1.72)	0.00 (-0.01, 0.00)	
>30 to <=35	359	0	0	398	2	0.5	0.2850	4.51 (0.22, 93.65)	4.53 (0.22, 94.75)	0.00 (0.00, 0.01)	
>35	114	1	0.9	128	2	1.6	0.6306	1.78 (0.16, 19.38)	1.79 (0.16, 20.05)	0.01 (-0.02, 0.03)	
Baseline NTproBNP											0.7240
< median	919	4	0.4	942	3	0.3	0.6807	0.73 (0.16, 3.26)	0.73 (0.16, 3.27)	0.00 (-0.01, 0.00)	
>= median	943	6	0.6	920	6	0.7	0.9658	1.03 (0.33, 3.17)	1.03 (0.33, 3.19)	0.00 (-0.01, 0.01)	

*** 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).
Subgroups will only be analysed if at least 10 events occurred in at least one category (both treatments combined).
For AEs on SOC and/or PT level, subgroup analyses are only shown if overall test for treatment is significant on 5% level (i.e. 95% CI for the risk ratio does not contain 1; if this is not calculable the p-value of Chi-square test is used).
MedDRA version: 23.0. * Chi-square test for treatment effect ** Breslow-Day test for homogeneity of odds ratios (treatment by subgroup interaction).

Table R.1.4.3: 1 Proportion of patients with adverse events of special interest and other specific AEs
- by user-defined AE category - overall population 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	1863	67	3.6	1863	67	3.6	1.0000	1.00 (0.72, 1.39)		1.00 (0.71, 1.41)		0.00 (-0.01, 0.01)	
Sex													0.7467
Male	1410	50	3.5	1426	49	3.4	0.8733	0.97 (0.66, 1.43)		0.97 (0.65, 1.45)		0.00 (-0.01, 0.01)	
Female	453	17	3.8	437	18	4.1	0.7787	1.10 (0.57, 2.10)		1.10 (0.56, 2.17)		0.00 (-0.02, 0.03)	
Age [years]													0.2472
< 65	739	19	2.6	675	23	3.4	0.3548	1.33 (0.73, 2.41)		1.34 (0.72, 2.48)		0.01 (-0.01, 0.03)	
>= 65	1124	48	4.3	1188	44	3.7	0.4859	0.87 (0.58, 1.29)		0.86 (0.57, 1.31)		-0.01 (-0.02, 0.01)	
Region													0.6583
North America	213	12	5.6	212	10	4.7	0.6697	0.84 (0.37, 1.90)		0.83 (0.35, 1.96)		-0.01 (-0.05, 0.03)	
Latin America	645	9	1.4	641	15	2.3	0.2107	1.68 (0.74, 3.80)		1.69 (0.74, 3.90)		0.01 (-0.01, 0.02)	
Europe	674	20	3.0	676	16	2.4	0.4935	0.80 (0.42, 1.53)		0.79 (0.41, 1.54)		-0.01 (-0.02, 0.01)	
Asia	244	23	9.4	248	22	8.9	0.8308	0.94 (0.54, 1.64)		0.94 (0.51, 1.73)		-0.01 (-0.06, 0.05)	
Other	87	3	3.4	86	4	4.7	0.6881	1.35 (0.31, 5.85)		1.37 (0.30, 6.29)		0.01 (-0.05, 0.07)	
OECD Member													0.0881
No	741	16	2.2	713	24	3.4	0.1596	1.56 (0.84, 2.91)		1.58 (0.83, 3.00)		0.01 (0.00, 0.03)	
Yes	1122	51	4.5	1150	43	3.7	0.3346	0.82 (0.55, 1.22)		0.82 (0.54, 1.23)		-0.01 (-0.02, 0.01)	
Baseline NYHA													0.1678
II	1399	52	3.7	1399	45	3.2	0.4694	0.87 (0.58, 1.28)		0.86 (0.57, 1.29)		-0.01 (-0.02, 0.01)	
III/IV	464	15	3.2	464	22	4.7	0.2402	1.47 (0.77, 2.79)		1.49 (0.76, 2.91)		0.02 (-0.01, 0.04)	
Baseline Diabetes Status													0.8544
Diabetic	926	38	4.1	927	37	4.0	0.9024	0.97 (0.62, 1.52)		0.97 (0.61, 1.54)		0.00 (-0.02, 0.02)	
Non-Diabetic	937	29	3.1	936	30	3.2	0.8915	1.04 (0.63, 1.71)		1.04 (0.62, 1.74)		0.00 (-0.01, 0.02)	
Baseline BMI [kg/m²]													0.2225
<30	1299	46	3.5	1263	51	4.0	0.5101	1.14 (0.77, 1.69)		1.15 (0.76, 1.72)		0.00 (-0.01, 0.02)	
>=30	564	21	3.7	600	16	2.7	0.3044	0.72 (0.38, 1.36)		0.71 (0.37, 1.37)		-0.01 (-0.03, 0.01)	

*** 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).
Subgroups will only be analysed if at least 10 events occurred in at least one category (both treatments combined).
For AEs on SOC and/or PT level, subgroup analyses are only shown if overall test for treatment is significant on 5% level (i.e. 95% CI for the risk ratio does not contain 1; if this is not calculable the p-value of Chi-square test is used).
MedDRA version: 23.0. * Chi-square test for treatment effect ** Breslow-Day test for homogeneity of odds ratios (treatment by subgroup interaction).

Table R.1.4.3: 1 Proportion of patients with adverse events of special interest and other specific AEs
- by user-defined AE category - overall population 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 eGFR (CKD-EPI) [mL/min/1.73m²]													0.7769
>=60	958	30	3.1	969	32	3.3	0.8317	1.05 (0.65,	1.72)	1.06 (0.64,	1.75)	0.00 (-0.01, 0.02)	
<60	904	37	4.1	893	35	3.9	0.8512	0.96 (0.61,	1.51)	0.96 (0.60,	1.53)	0.00 (-0.02, 0.02)	
History of HHF (in the last 12 months)													0.5635
No	1290	41	3.2	1286	44	3.4	0.7297	1.08 (0.71,	1.64)	1.08 (0.70,	1.66)	0.00 (-0.01, 0.02)	
Yes	573	26	4.5	577	23	4.0	0.6434	0.88 (0.51,	1.52)	0.87 (0.49,	1.55)	-0.01 (-0.03, 0.02)	
Cause of Heart Failure													0.8053
Ischemic	944	31	3.3	983	31	3.2	0.8713	0.96 (0.59,	1.57)	0.96 (0.58,	1.59)	0.00 (-0.02, 0.01)	
Non-ischemic	919	36	3.9	880	36	4.1	0.8510	1.04 (0.66,	1.64)	1.05 (0.65,	1.68)	0.00 (-0.02, 0.02)	
Heart Failure Physiology													0.8909
LVEF <= 30% and NTproBNP < median	723	25	3.5	698	22	3.2	0.7471	0.91 (0.52,	1.60)	0.91 (0.51,	1.63)	0.00 (-0.02, 0.02)	
LVEF <= 30% and NTproBNP >= median	660	24	3.6	631	24	3.8	0.8739	1.05 (0.60,	1.82)	1.05 (0.59,	1.87)	0.00 (-0.02, 0.02)	
LVEF > 30%	473	17	3.6	526	21	4.0	0.7425	1.11 (0.59,	2.08)	1.12 (0.58,	2.14)	0.00 (-0.02, 0.03)	
Baseline use of MRA													0.1346
No	512	13	2.5	557	22	3.9	0.1954	1.56 (0.79,	3.06)	1.58 (0.79,	3.17)	0.01 (-0.01, 0.04)	
Yes	1351	54	4.0	1306	45	3.4	0.4531	0.86 (0.58,	1.27)	0.86 (0.57,	1.28)	-0.01 (-0.02, 0.01)	
Baseline use of ARNi													0.2829
No	1476	53	3.6	1523	59	3.9	0.6827	1.08 (0.75,	1.55)	1.08 (0.74,	1.58)	0.00 (-0.01, 0.02)	
Yes	387	14	3.6	340	8	2.4	0.3206	0.65 (0.28,	1.53)	0.64 (0.27,	1.55)	-0.01 (-0.04, 0.01)	

*** 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).
Subgroups will only be analysed if at least 10 events occurred in at least one category (both treatments combined).
For AEs on SOC and/or PT level, subgroup analyses are only shown if overall test for treatment is significant on 5% level (i.e. 95% CI for the risk ratio does not contain 1; if this is not calculable the p-value of Chi-square test is used).
MedDRA version: 23.0. * Chi-square test for treatment effect ** Breslow-Day test for homogeneity of odds ratios (treatment by subgroup interaction).

Table R.1.4.3: 1 Proportion of patients with adverse events of special interest and other specific AEs
- by user-defined AE category - overall population 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													0.4430
<=30	1390	50	3.6	1337	46	3.4	0.8245	0.96 (0.65,	1.42)	0.95 (0.64,	1.44)	0.00 (-0.02, 0.01)	
>30 to <=35	359	9	2.5	398	15	3.8	0.3224	1.50 (0.67,	3.39)	1.52 (0.66,	3.52)	0.01 (-0.01, 0.04)	
>35	114	8	7.0	128	6	4.7	0.4383	0.67 (0.24,	1.87)	0.65 (0.22,	1.94)	-0.02 (-0.08, 0.04)	
Baseline NTproBNP													0.8848
< median	919	30	3.3	942	30	3.2	0.9225	0.98 (0.59,	1.60)	0.97 (0.58,	1.63)	0.00 (-0.02, 0.02)	
>= median	943	37	3.9	920	37	4.0	0.9137	1.03 (0.66,	1.60)	1.03 (0.64,	1.63)	0.00 (-0.02, 0.02)	

*** 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).
Subgroups will only be analysed if at least 10 events occurred in at least one category (both treatments combined).
For AEs on SOC and/or PT level, subgroup analyses are only shown if overall test for treatment is significant on 5% level (i.e. 95% CI for the risk ratio does not contain 1; if this is not calculable the p-value of Chi-square test is used).
MedDRA version: 23.0. * Chi-square test for treatment effect ** Breslow-Day test for homogeneity of odds ratios (treatment by subgroup interaction).

Table R.1.4.3: 2 Proportion of patients with serious adverse events of special interest and other specific AEs
- by user-defined AE category - overall population 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	1863	17	0.9	1863	13	0.7	0.4634	0.76	(0.37, 1.57)	0.76	(0.37, 1.58)	0.00	(-0.01, 0.00)	
Sex														0.0580
Male	1410	12	0.9	1426	13	0.9	0.8630	1.07	(0.49, 2.34)	1.07	(0.49, 2.36)	0.00	(-0.01, 0.01)	
Female	453	5	1.1	437	0	0	0.0450	0.09	(<0.01, 1.70)	0.09	(<0.01, 1.69)	-0.01	(-0.02, 0.00)	
Age [years]														0.3885
< 65	739	7	0.9	675	3	0.4	0.2598	0.47	(0.12, 1.81)	0.47	(0.12, 1.81)	-0.01	(-0.01, 0.00)	
>= 65	1124	10	0.9	1188	10	0.8	0.9010	0.95	(0.40, 2.26)	0.95	(0.39, 2.28)	0.00	(-0.01, 0.01)	
Region														0.9722
North America	213	1	0.5	212	1	0.5	0.9973	1.00	(0.06, 15.96)	1.00	(0.06, 16.17)	0.00	(-0.01, 0.01)	
Latin America	645	4	0.6	641	3	0.5	0.7108	0.75	(0.17, 3.36)	0.75	(0.17, 3.38)	0.00	(-0.01, 0.01)	
Europe	674	6	0.9	676	4	0.6	0.5225	0.66	(0.19, 2.34)	0.66	(0.19, 2.36)	0.00	(-0.01, 0.01)	
Asia	244	5	2.0	248	5	2.0	0.9793	0.98	(0.29, 3.36)	0.98	(0.28, 3.44)	0.00	(-0.03, 0.02)	
Other	87	1	1.1	86	0	0	0.4820	0.34	(0.01, 8.16)	0.33	(0.01, 8.30)	-0.01	(-0.04, 0.02)	
OECD Member														0.8723
No	741	5	0.7	713	4	0.6	0.7822	0.83	(0.22, 3.08)	0.83	(0.22, 3.11)	0.00	(-0.01, 0.01)	
Yes	1122	12	1.1	1150	9	0.8	0.4749	0.73	(0.31, 1.73)	0.73	(0.31, 1.74)	0.00	(-0.01, 0.01)	
Baseline NYHA														0.9769
II	1399	13	0.9	1399	10	0.7	0.5299	0.77	(0.34, 1.75)	0.77	(0.34, 1.76)	0.00	(-0.01, 0.00)	
III/IV	464	4	0.9	464	3	0.6	0.7044	0.75	(0.17, 3.33)	0.75	(0.17, 3.36)	0.00	(-0.01, 0.01)	
Baseline Diabetes Status														0.9632
Diabetic	926	9	1.0	927	7	0.8	0.6140	0.78	(0.29, 2.08)	0.78	(0.29, 2.09)	0.00	(-0.01, 0.01)	
Non-Diabetic	937	8	0.9	936	6	0.6	0.5930	0.75	(0.26, 2.16)	0.75	(0.26, 2.17)	0.00	(-0.01, 0.01)	
Baseline BMI [kg/m²]														0.1973
<30	1299	16	1.2	1263	10	0.8	0.2667	0.64	(0.29, 1.41)	0.64	(0.29, 1.42)	0.00	(-0.01, 0.00)	
>=30	564	1	0.2	600	3	0.5	0.3471	2.82	(0.29, 27.03)	2.83	(0.29, 27.28)	0.00	(0.00, 0.01)	

*** 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).
Subgroups will only be analysed if at least 10 events occurred in at least one category (both treatments combined).
For AEs on SOC and/or PT level, subgroup analyses are only shown if overall test for treatment is significant on 5% level (i.e. 95% CI for the risk ratio does not contain 1; if this is not calculable the p-value of Chi-square test is used).
MedDRA version: 23.0. * Chi-square test for treatment effect ** Breslow-Day test for homogeneity of odds ratios (treatment by subgroup interaction).

Table R.1.4.3: 2 Proportion of patients with serious adverse events of special interest and other specific AEs
- by user-defined AE category - overall population 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 eGFR (CKD-EPI) [mL/min/1.73m²]														0.1179
>=60	958	10	1.0	969	4	0.4	0.1029	0.40	(0.12, 1.26)	0.39	(0.12, 1.26)	-0.01	(-0.01, 0.00)	
<60	904	7	0.8	893	9	1.0	0.5983	1.30	(0.49, 3.48)	1.30	(0.48, 3.52)	0.00	(-0.01, 0.01)	
History of HHF (in the last 12 months)														0.6102
No	1290	12	0.9	1286	8	0.6	0.3730	0.67	(0.27, 1.63)	0.67	(0.27, 1.64)	0.00	(-0.01, 0.00)	
Yes	573	5	0.9	577	5	0.9	0.9912	0.99	(0.29, 3.41)	0.99	(0.29, 3.45)	0.00	(-0.01, 0.01)	
Cause of Heart Failure														0.1210
Ischemic	944	8	0.8	983	10	1.0	0.6984	1.20	(0.48, 3.03)	1.20	(0.47, 3.06)	0.00	(-0.01, 0.01)	
Non-ischemic	919	9	1.0	880	3	0.3	0.0963	0.35	(0.09, 1.28)	0.35	(0.09, 1.28)	-0.01	(-0.01, 0.00)	
Heart Failure Physiology														0.9519
LVEF <= 30% and NTproBNP < median	723	5	0.7	698	4	0.6	0.7783	0.83	(0.22, 3.07)	0.83	(0.22, 3.09)	0.00	(-0.01, 0.01)	
LVEF <= 30% and NTproBNP >= median	660	9	1.4	631	7	1.1	0.6797	0.81	(0.30, 2.17)	0.81	(0.30, 2.19)	0.00	(-0.01, 0.01)	
LVEF > 30%	473	3	0.6	526	2	0.4	0.5700	0.60	(0.10, 3.57)	0.60	(0.10, 3.59)	0.00	(-0.01, 0.01)	
Baseline use of MRA														0.4604
No	512	4	0.8	557	5	0.9	0.8351	1.15	(0.31, 4.26)	1.15	(0.31, 4.31)	0.00	(-0.01, 0.01)	
Yes	1351	13	1.0	1306	8	0.6	0.3088	0.64	(0.26, 1.53)	0.63	(0.26, 1.54)	0.00	(-0.01, 0.00)	
Baseline use of ARNi														0.2936
No	1476	17	1.2	1523	12	0.8	0.3087	0.68	(0.33, 1.43)	0.68	(0.32, 1.43)	0.00	(-0.01, 0.00)	
Yes	387	0	0	340	1	0.3	0.4231	3.41	(0.14, 83.52)	3.42	(0.14, 84.33)	0.00	(0.00, 0.01)	

*** 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).
Subgroups will only be analysed if at least 10 events occurred in at least one category (both treatments combined).
For AEs on SOC and/or PT level, subgroup analyses are only shown if overall test for treatment is significant on 5% level (i.e. 95% CI for the risk ratio does not contain 1; if this is not calculable the p-value of Chi-square test is used).
MedDRA version: 23.0. * Chi-square test for treatment effect ** Breslow-Day test for homogeneity of odds ratios (treatment by subgroup interaction).

Table R.1.4.3: 2 Proportion of patients with serious adverse events of special interest and other specific AEs
- by user-defined AE category - overall population 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														0.8859
<=30	1390	14	1.0	1337	11	0.8	0.6134	0.82	(0.37, 1.79)	0.82	(0.37, 1.80)	0.00	(-0.01, 0.01)	
>30 to <=35	359	1	0.3	398	1	0.3	0.9418	0.90	(0.06, 14.37)	0.90	(0.06, 14.47)	0.00	(-0.01, 0.01)	
>35	114	2	1.8	128	1	0.8	0.4946	0.45	(0.04, 4.85)	0.44	(0.04, 4.93)	-0.01	(-0.04, 0.02)	
Baseline NTproBNP														0.7468
< median	919	6	0.7	942	4	0.4	0.5007	0.65	(0.18, 2.30)	0.65	(0.18, 2.31)	0.00	(-0.01, 0.00)	
>= median	943	11	1.2	920	9	1.0	0.6935	0.84	(0.35, 2.01)	0.84	(0.35, 2.03)	0.00	(-0.01, 0.01)	

*** 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).
Subgroups will only be analysed if at least 10 events occurred in at least one category (both treatments combined).
For AEs on SOC and/or PT level, subgroup analyses are only shown if overall test for treatment is significant on 5% level (i.e. 95% CI for the risk ratio does not contain 1; if this is not calculable the p-value of Chi-square test is used).
MedDRA version: 23.0. * Chi-square test for treatment effect ** Breslow-Day test for homogeneity of odds ratios (treatment by subgroup interaction).

Table R.1.4.3: 2 Proportion of patients with serious adverse events of special interest and other specific AEs
- by user-defined AE category - overall population 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	1863	95	5.1	1863	59	3.2	0.0030	0.62	(0.45, 0.85)	0.61	(0.44, 0.85)	-0.02	(-0.03,-0.01)	
Sex														0.6004
Male	1410	75	5.3	1426	45	3.2	0.0042	0.59	(0.41, 0.85)	0.58	(0.40, 0.85)	-0.02	(-0.04,-0.01)	
Female	453	20	4.4	437	14	3.2	0.3459	0.73	(0.37, 1.42)	0.72	(0.36, 1.44)	-0.01	(-0.04, 0.01)	
Age [years]														0.5458
< 65	739	40	5.4	675	20	3.0	0.0225	0.55	(0.32, 0.93)	0.53	(0.31, 0.92)	-0.02	(-0.05, 0.00)	
>= 65	1124	55	4.9	1188	39	3.3	0.0500	0.67	(0.45, 1.00)	0.66	(0.43, 1.00)	-0.02	(-0.03, 0.00)	
Region														0.6630
North America	213	20	9.4	212	17	8.0	0.6162	0.85	(0.46, 1.58)	0.84	(0.43, 1.65)	-0.01	(-0.07, 0.04)	
Latin America	645	37	5.7	641	20	3.1	0.0226	0.54	(0.32, 0.93)	0.53	(0.30, 0.92)	-0.03	(-0.05, 0.00)	
Europe	674	30	4.5	676	18	2.7	0.0760	0.60	(0.34, 1.06)	0.59	(0.32, 1.06)	-0.02	(-0.04, 0.00)	
Asia	244	5	2.0	248	4	1.6	0.7181	0.79	(0.21, 2.90)	0.78	(0.21, 2.95)	0.00	(-0.03, 0.02)	
Other	87	3	3.4	86	0	0	0.1321	0.14	(<0.01, 2.76)	0.14	(<0.01, 2.74)	-0.03	(-0.08, 0.01)	
OECD Member														0.6865
No	741	35	4.7	713	19	2.7	0.0380	0.56	(0.33, 0.98)	0.55	(0.31, 0.97)	-0.02	(-0.04, 0.00)	
Yes	1122	60	5.3	1150	40	3.5	0.0299	0.65	(0.44, 0.96)	0.64	(0.42, 0.96)	-0.02	(-0.04, 0.00)	
Baseline NYHA														0.3712
II	1399	63	4.5	1399	43	3.1	0.0477	0.68	(0.47, 1.00)	0.67	(0.45, 1.00)	-0.01	(-0.03, 0.00)	
III/IV	464	32	6.9	464	16	3.4	0.0177	0.50	(0.28, 0.90)	0.48	(0.26, 0.89)	-0.03	(-0.06,-0.01)	
Baseline Diabetes Status														0.3216
Diabetic	926	47	5.1	927	34	3.7	0.1383	0.72	(0.47, 1.11)	0.71	(0.45, 1.12)	-0.01	(-0.03, 0.00)	
Non-Diabetic	937	48	5.1	936	25	2.7	0.0061	0.52	(0.32, 0.84)	0.51	(0.31, 0.83)	-0.02	(-0.04,-0.01)	
Baseline BMI [kg/m²]														0.7892
<30	1299	59	4.5	1263	34	2.7	0.0123	0.59	(0.39, 0.90)	0.58	(0.38, 0.89)	-0.02	(-0.03, 0.00)	
>=30	564	36	6.4	600	25	4.2	0.0899	0.65	(0.40, 1.07)	0.64	(0.38, 1.08)	-0.02	(-0.05, 0.00)	

*** 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).
Subgroups will only be analysed if at least 10 events occurred in at least one category (both treatments combined).
For AEs on SOC and/or PT level, subgroup analyses are only shown if overall test for treatment is significant on 5% level (i.e. 95% CI for the risk ratio does not contain 1; if this is not calculable the p-value of Chi-square test is used).
MedDRA version: 23.0. * Chi-square test for treatment effect ** Breslow-Day test for homogeneity of odds ratios (treatment by subgroup interaction).

Table R.1.4.3: 2 Proportion of patients with serious adverse events of special interest and other specific AEs
- by user-defined AE category - overall population 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 eGFR (CKD-EPI) [mL/min/1.73m²]														0.8272
>=60	958	32	3.3	969	21	2.2	0.1154	0.65	(0.38, 1.12)	0.64	(0.37, 1.12)	-0.01	(-0.03, 0.00)	
<60	904	63	7.0	893	38	4.3	0.0125	0.61	(0.41, 0.90)	0.59	(0.39, 0.90)	-0.03	(-0.05,-0.01)	
History of HHF (in the last 12 months)														0.6635
No	1290	60	4.7	1286	35	2.7	0.0094	0.59	(0.39, 0.88)	0.57	(0.38, 0.88)	-0.02	(-0.03, 0.00)	
Yes	573	35	6.1	577	24	4.2	0.1342	0.68	(0.41, 1.13)	0.67	(0.39, 1.14)	-0.02	(-0.04, 0.01)	
Cause of Heart Failure														0.2887
Ischemic	944	43	4.6	983	33	3.4	0.1768	0.74	(0.47, 1.15)	0.73	(0.46, 1.16)	-0.01	(-0.03, 0.01)	
Non-ischemic	919	52	5.7	880	26	3.0	0.0049	0.52	(0.33, 0.83)	0.51	(0.31, 0.82)	-0.03	(-0.05,-0.01)	
Heart Failure Physiology														0.8276
LVEF <= 30% and NTproBNP < median	723	25	3.5	698	15	2.1	0.1359	0.62	(0.33, 1.17)	0.61	(0.32, 1.17)	-0.01	(-0.03, 0.00)	
LVEF <= 30% and NTproBNP >= median	660	49	7.4	631	27	4.3	0.0164	0.58	(0.36, 0.91)	0.56	(0.34, 0.90)	-0.03	(-0.06,-0.01)	
LVEF > 30%	473	21	4.4	526	17	3.2	0.3190	0.73	(0.39, 1.36)	0.72	(0.37, 1.38)	-0.01	(-0.04, 0.01)	
Baseline use of MRA														0.9822
No	512	28	5.5	557	19	3.4	0.1012	0.62	(0.35, 1.10)	0.61	(0.34, 1.11)	-0.02	(-0.05, 0.00)	
Yes	1351	67	5.0	1306	40	3.1	0.0129	0.62	(0.42, 0.91)	0.61	(0.41, 0.90)	-0.02	(-0.03, 0.00)	
Baseline use of ARNi														0.9662
No	1476	70	4.7	1523	45	3.0	0.0108	0.62	(0.43, 0.90)	0.61	(0.42, 0.90)	-0.02	(-0.03, 0.00)	
Yes	387	25	6.5	340	14	4.1	0.1619	0.64	(0.34, 1.21)	0.62	(0.32, 1.22)	-0.02	(-0.06, 0.01)	

*** 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).
Subgroups will only be analysed if at least 10 events occurred in at least one category (both treatments combined).
For AEs on SOC and/or PT level, subgroup analyses are only shown if overall test for treatment is significant on 5% level (i.e. 95% CI for the risk ratio does not contain 1; if this is not calculable the p-value of Chi-square test is used).
MedDRA version: 23.0. * Chi-square test for treatment effect ** Breslow-Day test for homogeneity of odds ratios (treatment by subgroup interaction).

Table R.1.4.3: 2 Proportion of patients with serious adverse events of special interest and other specific AEs
- by user-defined AE category - overall population 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														0.7760
<=30	1390	74	5.3	1337	42	3.1	0.0048	0.59	(0.41, 0.86)	0.58	(0.39, 0.85)	-0.02	(-0.04,-0.01)	
>30 to <=35	359	15	4.2	398	11	2.8	0.2860	0.66	(0.31, 1.42)	0.65	(0.30, 1.44)	-0.01	(-0.04, 0.01)	
>35	114	6	5.3	128	6	4.7	0.8369	0.89	(0.30, 2.68)	0.89	(0.28, 2.83)	-0.01	(-0.06, 0.05)	
Baseline NTproBNP														0.8403
< median	919	30	3.3	942	20	2.1	0.1279	0.65	(0.37, 1.14)	0.64	(0.36, 1.14)	-0.01	(-0.03, 0.00)	
>= median	943	65	6.9	920	39	4.2	0.0126	0.62	(0.42, 0.91)	0.60	(0.40, 0.90)	-0.03	(-0.05,-0.01)	

*** 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).
Subgroups will only be analysed if at least 10 events occurred in at least one category (both treatments combined).
For AEs on SOC and/or PT level, subgroup analyses are only shown if overall test for treatment is significant on 5% level (i.e. 95% CI for the risk ratio does not contain 1; if this is not calculable the p-value of Chi-square test is used).
MedDRA version: 23.0. * Chi-square test for treatment effect ** Breslow-Day test for homogeneity of odds ratios (treatment by subgroup interaction).

Table R.1.4.3: 2 Proportion of patients with serious adverse events of special interest and other specific AEs
- by user-defined AE category - overall population and by subgroup - TS
User-defined AE category: Ketoacidosis (broad BIcMQ)

Subgroup Category	Placebo N	Placebo n	Placebo %	Empa 10mg N	Empa 10mg n	Empa 10mg %	Empa 10mg vs Placebo p-value *	Risk ratio	Risk (95% CI)	Odds ratio	Odds (95% CI)	Risk diff.	Risk diff. (95% CI)	p-value **
Overall	1863	12	0.6	1863	6	0.3	0.1563	0.50	(0.19, 1.33)	0.50	(0.19, 1.33)	0.00	(-0.01, 0.00)	
Sex														0.9711
Male	1410	10	0.7	1426	5	0.4	0.1881	0.49	(0.17, 1.44)	0.49	(0.17, 1.44)	0.00	(-0.01, 0.00)	
Female	453	2	0.4	437	1	0.2	0.5842	0.52	(0.05, 5.70)	0.52	(0.05, 5.72)	0.00	(-0.01, 0.01)	
Age [years]														0.5958
< 65	739	6	0.8	675	2	0.3	0.1966	0.36	(0.07, 1.80)	0.36	(0.07, 1.80)	-0.01	(-0.01, 0.00)	
>= 65	1124	6	0.5	1188	4	0.3	0.4704	0.63	(0.18, 2.23)	0.63	(0.18, 2.24)	0.00	(-0.01, 0.00)	
OECD Member														0.1892
No	741	6	0.8	713	1	0.1	0.0652	0.17	(0.02, 1.44)	0.17	(0.02, 1.43)	-0.01	(-0.01, 0.00)	
Yes	1122	6	0.5	1150	5	0.4	0.7314	0.81	(0.25, 2.66)	0.81	(0.25, 2.67)	0.00	(-0.01, 0.00)	
Baseline NYHA														0.1974
II	1399	12	0.9	1399	5	0.4	0.0886	0.42	(0.15, 1.18)	0.41	(0.15, 1.18)	-0.01	(-0.01, 0.00)	
III/IV	464	0	0	464	1	0.2	0.4790	3.00	(0.12, 73.45)	3.01	(0.12, 73.99)	0.00	(0.00, 0.01)	
Baseline Diabetes Status														0.6914
Diabetic	926	9	1.0	927	5	0.5	0.2823	0.55	(0.19, 1.65)	0.55	(0.18, 1.66)	0.00	(-0.01, 0.00)	
Non-Diabetic	937	3	0.3	936	1	0.1	0.3173	0.33	(0.03, 3.20)	0.33	(0.03, 3.21)	0.00	(-0.01, 0.00)	
Baseline BMI [kg/m²]														0.0470
<30	1299	6	0.5	1263	6	0.5	0.9611	1.03	(0.33, 3.18)	1.03	(0.33, 3.20)	0.00	(-0.01, 0.01)	
>=30	564	6	1.1	600	0	0	0.0184	0.07	(<0.01, 1.28)	0.07	(<0.01, 1.27)	-0.01	(-0.02, 0.00)	
Baseline eGFR (CKD-EPI) [mL/min/1.73m²]														0.7186
>=60	958	7	0.7	969	3	0.3	0.1983	0.42	(0.11, 1.63)	0.42	(0.11, 1.64)	0.00	(-0.01, 0.00)	
<60	904	5	0.6	893	3	0.3	0.4893	0.61	(0.15, 2.53)	0.61	(0.14, 2.54)	0.00	(-0.01, 0.00)	

*** 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).
Subgroups will only be analysed if at least 10 events occurred in at least one category (both treatments combined).
For AEs on SOC and/or PT level, subgroup analyses are only shown if overall test for treatment is significant on 5% level (i.e. 95% CI for the risk ratio does not contain 1; if this is not calculable the p-value of Chi-square test is used).
MedDRA version: 23.0. * Chi-square test for treatment effect ** Breslow-Day test for homogeneity of odds ratios (treatment by subgroup interaction).

Table R.1.4.3: 2 Proportion of patients with serious adverse events of special interest and other specific AEs
- by user-defined AE category - overall population and by subgroup - TS
User-defined AE category: Ketoacidosis (broad 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 **
History of HHF (in the last 12 months)											0.2925
No	1290	9	0.7	1286	3	0.2	0.0835	0.33 (0.09, 1.23)	0.33 (0.09, 1.23)	0.00 (-0.01, 0.00)	
Yes	573	3	0.5	577	3	0.5	0.9932	0.99 (0.20, 4.90)	0.99 (0.20, 4.94)	0.00 (-0.01, 0.01)	
Cause of Heart Failure											0.1960
Ischemic	944	6	0.6	983	5	0.5	0.7116	0.80 (0.25, 2.61)	0.80 (0.24, 2.63)	0.00 (-0.01, 0.01)	
Non-ischemic	919	6	0.7	880	1	0.1	0.0663	0.17 (0.02, 1.44)	0.17 (0.02, 1.44)	-0.01 (-0.01, 0.00)	
Baseline use of MRA											0.7918
No	512	3	0.6	557	2	0.4	0.5871	0.61 (0.10, 3.65)	0.61 (0.10, 3.67)	0.00 (-0.01, 0.01)	
Yes	1351	9	0.7	1306	4	0.3	0.1838	0.46 (0.14, 1.49)	0.46 (0.14, 1.49)	0.00 (-0.01, 0.00)	
Baseline use of ARNi											0.5543
No	1476	10	0.7	1523	6	0.4	0.2866	0.58 (0.21, 1.60)	0.58 (0.21, 1.60)	0.00 (-0.01, 0.00)	
Yes	387	2	0.5	340	0	0	0.2949	0.23 (0.01, 4.72)	0.23 (0.01, 4.73)	0.00 (-0.01, 0.00)	
Baseline LVEF											0.8289
<=30	1390	8	0.6	1337	4	0.3	0.2757	0.52 (0.16, 1.72)	0.52 (0.16, 1.73)	0.00 (-0.01, 0.00)	
>30 to <=35	359	3	0.8	398	1	0.3	0.2681	0.30 (0.03, 2.88)	0.30 (0.03, 2.89)	-0.01 (-0.02, 0.00)	
>35	114	1	0.9	128	1	0.8	0.9344	0.89 (0.06, 14.08)	0.89 (0.06, 14.39)	0.00 (-0.02, 0.02)	
Baseline NTproBNP											0.5240
< median	919	4	0.4	942	3	0.3	0.6807	0.73 (0.16, 3.26)	0.73 (0.16, 3.27)	0.00 (-0.01, 0.00)	
>= median	943	8	0.8	920	3	0.3	0.1413	0.38 (0.10, 1.44)	0.38 (0.10, 1.45)	-0.01 (-0.01, 0.00)	

*** 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).
Subgroups will only be analysed if at least 10 events occurred in at least one category (both treatments combined).
For AEs on SOC and/or PT level, subgroup analyses are only shown if overall test for treatment is significant on 5% level (i.e. 95% CI for the risk ratio does not contain 1; if this is not calculable the p-value of Chi-square test is used).
MedDRA version: 23.0. * Chi-square test for treatment effect ** Breslow-Day test for homogeneity of odds ratios (treatment by subgroup interaction).

Table R.1.4.3: 2 Proportion of patients with serious adverse events of special interest and other specific AEs
- by user-defined AE category - overall population 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	1863	0	0	1863	0	0	1.0000	1.00	(0.02, 50.37)	1.00	(0.02, 50.42)	0.00	(0.00, 0.00)	

*** 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).
Subgroups will only be analysed if at least 10 events occurred in at least one category (both treatments combined).
For AEs on SOC and/or PT level, subgroup analyses are only shown if overall test for treatment is significant on 5% level (i.e. 95% CI for the risk ratio does not contain 1; if this is not calculable the p-value of Chi-square test is used).
MedDRA version: 23.0. * Chi-square test for treatment effect ** Breslow-Day test for homogeneity of odds ratios (treatment by subgroup interaction).

Table R.1.4.3: 2 Proportion of patients with serious adverse events of special interest and other specific AEs
- by user-defined AE category - overall population 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	1863	6	0.3	1863	9	0.5	0.4377	1.50	(0.53, 4.21)	1.50	(0.53, 4.23)	0.00	(0.00, 0.01)	
Sex														0.7798
Male	1410	5	0.4	1426	8	0.6	0.4159	1.58	(0.52, 4.82)	1.59	(0.52, 4.86)	0.00	(0.00, 0.01)	
Female	453	1	0.2	437	1	0.2	0.9797	1.04	(0.07, 16.52)	1.04	(0.06, 16.63)	0.00	(-0.01, 0.01)	
Baseline NYHA														0.2622
II	1399	5	0.4	1399	5	0.4	1.0000	1.00	(0.29, 3.45)	1.00	(0.29, 3.46)	0.00	(0.00, 0.00)	
III/IV	464	1	0.2	464	4	0.9	0.1785	4.00	(0.45, 35.65)	4.03	(0.45, 36.16)	0.01	(0.00, 0.02)	
Baseline Diabetes Status														0.2894
Diabetic	926	5	0.5	927	9	1.0	0.2841	1.80	(0.60, 5.34)	1.81	(0.60, 5.41)	0.00	(0.00, 0.01)	
Non-Diabetic	937	1	0.1	936	0	0	0.4797	0.33	(0.01, 8.18)	0.33	(0.01, 8.19)	0.00	(0.00, 0.00)	
History of HHF (in the last 12 months)														0.2857
No	1290	5	0.4	1286	9	0.7	0.2811	1.81	(0.61, 5.37)	1.81	(0.61, 5.42)	0.00	(0.00, 0.01)	
Yes	573	1	0.2	577	0	0	0.4761	0.33	(0.01, 8.11)	0.33	(0.01, 8.13)	0.00	(-0.01, 0.00)	
Cause of Heart Failure														0.3230
Ischemic	944	4	0.4	983	8	0.8	0.2765	1.92	(0.58, 6.36)	1.93	(0.58, 6.42)	0.00	(0.00, 0.01)	
Non-ischemic	919	2	0.2	880	1	0.1	0.5889	0.52	(0.05, 5.75)	0.52	(0.05, 5.76)	0.00	(0.00, 0.00)	
Baseline use of ARNi														0.1458
No	1476	6	0.4	1523	6	0.4	0.9566	0.97	(0.31, 3.00)	0.97	(0.31, 3.01)	0.00	(0.00, 0.00)	
Yes	387	0	0	340	3	0.9	0.1017	7.96	(0.41,153.65)	8.04	(0.41,156.15)	0.01	(0.00, 0.02)	
Baseline NTproBNP														0.6021
< median	919	2	0.2	942	2	0.2	0.9803	0.98	(0.14, 6.91)	0.98	(0.14, 6.94)	0.00	(0.00, 0.00)	
>= median	943	4	0.4	920	7	0.8	0.3429	1.79	(0.53, 6.11)	1.80	(0.53, 6.17)	0.00	(0.00, 0.01)	

*** 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).
Subgroups will only be analysed if at least 10 events occurred in at least one category (both treatments combined).
For AEs on SOC and/or PT level, subgroup analyses are only shown if overall test for treatment is significant on 5% level (i.e. 95% CI for the risk ratio does not contain 1; if this is not calculable the p-value of Chi-square test is used).
MedDRA version: 23.0. * Chi-square test for treatment effect ** Breslow-Day test for homogeneity of odds ratios (treatment by subgroup interaction).

Table R.1.4.3: 2 Proportion of patients with serious adverse events of special interest and other specific AEs
- by user-defined AE category - overall population 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	1863	4	0.2	1863	6	0.3	0.5265	1.50	(0.42, 5.31)	1.50	(0.42, 5.33)	0.00	(0.00, 0.00)	
Baseline Diabetes Status														0.8463
Diabetic	926	4	0.4	927	6	0.6	0.5271	1.50	(0.42, 5.29)	1.50	(0.42, 5.34)	0.00	(0.00, 0.01)	
Non-Diabetic	937	0	0	936	0	0	0.9996	1.00	(0.02, 50.40)	1.00	(0.02, 50.50)	0.00	(0.00, 0.00)	

*** 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).
Subgroups will only be analysed if at least 10 events occurred in at least one category (both treatments combined).
For AEs on SOC and/or PT level, subgroup analyses are only shown if overall test for treatment is significant on 5% level (i.e. 95% CI for the risk ratio does not contain 1; if this is not calculable the p-value of Chi-square test is used).
MedDRA version: 23.0. * Chi-square test for treatment effect ** Breslow-Day test for homogeneity of odds ratios (treatment by subgroup interaction).

Table R.1.4.3: 2 Proportion of patients with serious adverse events of special interest and other specific AEs
- by user-defined AE category - overall population 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	1863	14	0.8	1863	19	1.0	0.3820	1.36	(0.68, 2.70)	1.36	(0.68, 2.72)	0.00	(0.00, 0.01)	
Sex														0.3843
Male	1410	10	0.7	1426	11	0.8	0.8469	1.09	(0.46, 2.55)	1.09	(0.46, 2.57)	0.00	(-0.01, 0.01)	
Female	453	4	0.9	437	8	1.8	0.2204	2.07	(0.63, 6.84)	2.09	(0.63, 7.00)	0.01	(-0.01, 0.02)	
Age [years]														0.2533
< 65	739	5	0.7	675	3	0.4	0.5610	0.66	(0.16, 2.74)	0.66	(0.16, 2.75)	0.00	(-0.01, 0.01)	
>= 65	1124	9	0.8	1188	16	1.3	0.2045	1.68	(0.75, 3.79)	1.69	(0.74, 3.84)	0.01	(0.00, 0.01)	
Region														0.2647
North America	213	5	2.3	212	1	0.5	0.1012	0.20	(0.02, 1.71)	0.20	(0.02, 1.70)	-0.02	(-0.04, 0.00)	
Latin America	645	4	0.6	641	6	0.9	0.5191	1.51	(0.43, 5.32)	1.51	(0.43, 5.39)	0.00	(-0.01, 0.01)	
Europe	674	4	0.6	676	9	1.3	0.1651	2.24	(0.69, 7.25)	2.26	(0.69, 7.37)	0.01	(0.00, 0.02)	
Asia	244	1	0.4	248	2	0.8	0.5721	1.97	(0.18, 21.56)	1.98	(0.18, 21.93)	0.00	(-0.01, 0.02)	
Other	87	0	0	86	1	1.2	0.4719	3.03	(0.13, 73.47)	3.07	(0.12, 76.42)	0.01	(-0.02, 0.04)	
OECD Member														0.7889
No	741	4	0.5	713	6	0.8	0.4865	1.56	(0.44, 5.50)	1.56	(0.44, 5.56)	0.00	(-0.01, 0.01)	
Yes	1122	10	0.9	1150	13	1.1	0.5691	1.27	(0.56, 2.88)	1.27	(0.56, 2.91)	0.00	(-0.01, 0.01)	
Baseline NYHA														0.8511
II	1399	10	0.7	1399	13	0.9	0.5299	1.30	(0.57, 2.95)	1.30	(0.57, 2.98)	0.00	(0.00, 0.01)	
III/IV	464	4	0.9	464	6	1.3	0.5248	1.50	(0.43, 5.28)	1.51	(0.42, 5.37)	0.00	(-0.01, 0.02)	
Baseline Diabetes Status														0.7944
Diabetic	926	8	0.9	927	10	1.1	0.6373	1.25	(0.50, 3.15)	1.25	(0.49, 3.18)	0.00	(-0.01, 0.01)	
Non-Diabetic	937	6	0.6	936	9	1.0	0.4355	1.50	(0.54, 4.20)	1.51	(0.53, 4.25)	0.00	(0.00, 0.01)	
Baseline BMI [kg/m²]														0.8028
<30	1299	9	0.7	1263	11	0.9	0.6086	1.26	(0.52, 3.02)	1.26	(0.52, 3.05)	0.00	(-0.01, 0.01)	
>=30	564	5	0.9	600	8	1.3	0.4685	1.50	(0.49, 4.57)	1.51	(0.49, 4.65)	0.00	(-0.01, 0.02)	

*** 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).
Subgroups will only be analysed if at least 10 events occurred in at least one category (both treatments combined).
For AEs on SOC and/or PT level, subgroup analyses are only shown if overall test for treatment is significant on 5% level (i.e. 95% CI for the risk ratio does not contain 1; if this is not calculable the p-value of Chi-square test is used).
MedDRA version: 23.0. * Chi-square test for treatment effect ** Breslow-Day test for homogeneity of odds ratios (treatment by subgroup interaction).

Table R.1.4.3: 2 Proportion of patients with serious adverse events of special interest and other specific AEs
- by user-defined AE category - overall population 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 eGFR (CKD-EPI) [mL/min/1.73m²]																0.7759
>=60	958	5	0.5	969	6	0.6	0.7769	1.19	(0.36,	3.87)	1.19	(0.36,	3.90)	0.00	(-0.01, 0.01)	
<60	904	9	1.0	893	13	1.5	0.3751	1.46	(0.63,	3.40)	1.47	(0.62,	3.45)	0.00	(-0.01, 0.01)	
History of HHF (in the last 12 months)																0.8624
No	1290	10	0.8	1286	13	1.0	0.5249	1.30	(0.57,	2.96)	1.31	(0.57,	2.99)	0.00	(0.00, 0.01)	
Yes	573	4	0.7	577	6	1.0	0.5325	1.49	(0.42,	5.25)	1.49	(0.42,	5.33)	0.00	(-0.01, 0.01)	
Cause of Heart Failure																0.9756
Ischemic	944	7	0.7	983	10	1.0	0.5175	1.37	(0.52,	3.59)	1.38	(0.52,	3.63)	0.00	(-0.01, 0.01)	
Non-ischemic	919	7	0.8	880	9	1.0	0.5555	1.34	(0.50,	3.59)	1.35	(0.50,	3.63)	0.00	(-0.01, 0.01)	
Heart Failure Physiology																0.2666
LVEF <= 30% and NTproBNP < median	723	5	0.7	698	3	0.4	0.5097	0.62	(0.15,	2.59)	0.62	(0.15,	2.60)	0.00	(-0.01, 0.01)	
LVEF <= 30% and NTproBNP >= median	660	4	0.6	631	10	1.6	0.0896	2.61	(0.82,	8.29)	2.64	(0.82,	8.46)	0.01	(0.00, 0.02)	
LVEF > 30%	473	5	1.1	526	6	1.1	0.8994	1.08	(0.33,	3.51)	1.08	(0.33,	3.56)	0.00	(-0.01, 0.01)	
Baseline use of MRA																0.5194
No	512	4	0.8	557	8	1.4	0.3099	1.84	(0.56,	6.07)	1.85	(0.55,	6.18)	0.01	(-0.01, 0.02)	
Yes	1351	10	0.7	1306	11	0.8	0.7664	1.14	(0.48,	2.67)	1.14	(0.48,	2.69)	0.00	(-0.01, 0.01)	
Baseline use of ARNi																0.2504
No	1476	10	0.7	1523	17	1.1	0.2035	1.65	(0.76,	3.59)	1.65	(0.76,	3.63)	0.00	(0.00, 0.01)	
Yes	387	4	1.0	340	2	0.6	0.5078	0.57	(0.10,	3.09)	0.57	(0.10,	3.11)	0.00	(-0.02, 0.01)	

*** 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).
Subgroups will only be analysed if at least 10 events occurred in at least one category (both treatments combined).
For AEs on SOC and/or PT level, subgroup analyses are only shown if overall test for treatment is significant on 5% level (i.e. 95% CI for the risk ratio does not contain 1; if this is not calculable the p-value of Chi-square test is used).
MedDRA version: 23.0. * Chi-square test for treatment effect ** Breslow-Day test for homogeneity of odds ratios (treatment by subgroup interaction).

Table R.1.4.3: 2 Proportion of patients with serious adverse events of special interest and other specific AEs
- by user-defined AE category - overall population 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														0.8953
<=30	1390	9	0.6	1337	13	1.0	0.3431	1.50	(0.64, 3.50)	1.51	(0.64, 3.54)	0.00	(0.00, 0.01)	
>30 to <=35	359	4	1.1	398	5	1.3	0.8571	1.13	(0.31, 4.17)	1.13	(0.30, 4.24)	0.00	(-0.01, 0.02)	
>35	114	1	0.9	128	1	0.8	0.9344	0.89	(0.06, 14.08)	0.89	(0.06, 14.39)	0.00	(-0.02, 0.02)	
Baseline NTproBNP														0.1220
< median	919	8	0.9	942	6	0.6	0.5599	0.73	(0.25, 2.10)	0.73	(0.25, 2.11)	0.00	(-0.01, 0.01)	
>= median	943	6	0.6	920	13	1.4	0.0952	2.22	(0.85, 5.82)	2.24	(0.85, 5.91)	0.01	(0.00, 0.02)	

*** 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).
Subgroups will only be analysed if at least 10 events occurred in at least one category (both treatments combined).
For AEs on SOC and/or PT level, subgroup analyses are only shown if overall test for treatment is significant on 5% level (i.e. 95% CI for the risk ratio does not contain 1; if this is not calculable the p-value of Chi-square test is used).
MedDRA version: 23.0. * Chi-square test for treatment effect ** Breslow-Day test for homogeneity of odds ratios (treatment by subgroup interaction).

Table R.1.4.3: 2 Proportion of patients with serious adverse events of special interest and other specific AEs
- by user-defined AE category - overall population 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	1863	14	0.8	1863	19	1.0	0.3820	1.36	(0.68, 2.70)	1.36	(0.68, 2.72)	0.00	(0.00, 0.01)	
Sex														0.3843
Male	1410	10	0.7	1426	11	0.8	0.8469	1.09	(0.46, 2.55)	1.09	(0.46, 2.57)	0.00	(-0.01, 0.01)	
Female	453	4	0.9	437	8	1.8	0.2204	2.07	(0.63, 6.84)	2.09	(0.63, 7.00)	0.01	(-0.01, 0.02)	
Age [years]														0.2533
< 65	739	5	0.7	675	3	0.4	0.5610	0.66	(0.16, 2.74)	0.66	(0.16, 2.75)	0.00	(-0.01, 0.01)	
>= 65	1124	9	0.8	1188	16	1.3	0.2045	1.68	(0.75, 3.79)	1.69	(0.74, 3.84)	0.01	(0.00, 0.01)	
Region														0.2647
North America	213	5	2.3	212	1	0.5	0.1012	0.20	(0.02, 1.71)	0.20	(0.02, 1.70)	-0.02	(-0.04, 0.00)	
Latin America	645	4	0.6	641	6	0.9	0.5191	1.51	(0.43, 5.32)	1.51	(0.43, 5.39)	0.00	(-0.01, 0.01)	
Europe	674	4	0.6	676	9	1.3	0.1651	2.24	(0.69, 7.25)	2.26	(0.69, 7.37)	0.01	(0.00, 0.02)	
Asia	244	1	0.4	248	2	0.8	0.5721	1.97	(0.18, 21.56)	1.98	(0.18, 21.93)	0.00	(-0.01, 0.02)	
Other	87	0	0	86	1	1.2	0.4719	3.03	(0.13, 73.47)	3.07	(0.12, 76.42)	0.01	(-0.02, 0.04)	
OECD Member														0.7889
No	741	4	0.5	713	6	0.8	0.4865	1.56	(0.44, 5.50)	1.56	(0.44, 5.56)	0.00	(-0.01, 0.01)	
Yes	1122	10	0.9	1150	13	1.1	0.5691	1.27	(0.56, 2.88)	1.27	(0.56, 2.91)	0.00	(-0.01, 0.01)	
Baseline NYHA														0.8511
II	1399	10	0.7	1399	13	0.9	0.5299	1.30	(0.57, 2.95)	1.30	(0.57, 2.98)	0.00	(0.00, 0.01)	
III/IV	464	4	0.9	464	6	1.3	0.5248	1.50	(0.43, 5.28)	1.51	(0.42, 5.37)	0.00	(-0.01, 0.02)	
Baseline Diabetes Status														0.7944
Diabetic	926	8	0.9	927	10	1.1	0.6373	1.25	(0.50, 3.15)	1.25	(0.49, 3.18)	0.00	(-0.01, 0.01)	
Non-Diabetic	937	6	0.6	936	9	1.0	0.4355	1.50	(0.54, 4.20)	1.51	(0.53, 4.25)	0.00	(0.00, 0.01)	
Baseline BMI [kg/m²]														0.8028
<30	1299	9	0.7	1263	11	0.9	0.6086	1.26	(0.52, 3.02)	1.26	(0.52, 3.05)	0.00	(-0.01, 0.01)	
>=30	564	5	0.9	600	8	1.3	0.4685	1.50	(0.49, 4.57)	1.51	(0.49, 4.65)	0.00	(-0.01, 0.02)	

*** 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).
Subgroups will only be analysed if at least 10 events occurred in at least one category (both treatments combined).
For AEs on SOC and/or PT level, subgroup analyses are only shown if overall test for treatment is significant on 5% level (i.e. 95% CI for the risk ratio does not contain 1; if this is not calculable the p-value of Chi-square test is used).
MedDRA version: 23.0. * Chi-square test for treatment effect ** Breslow-Day test for homogeneity of odds ratios (treatment by subgroup interaction).

Table R.1.4.3: 2 Proportion of patients with serious adverse events of special interest and other specific AEs
- by user-defined AE category - overall population 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 eGFR (CKD-EPI) [mL/min/1.73m²]														0.7759
>=60	958	5	0.5	969	6	0.6	0.7769	1.19	(0.36, 3.87)	1.19	(0.36, 3.90)	0.00	(-0.01, 0.01)	
<60	904	9	1.0	893	13	1.5	0.3751	1.46	(0.63, 3.40)	1.47	(0.62, 3.45)	0.00	(-0.01, 0.01)	
History of HHF (in the last 12 months)														0.8624
No	1290	10	0.8	1286	13	1.0	0.5249	1.30	(0.57, 2.96)	1.31	(0.57, 2.99)	0.00	(0.00, 0.01)	
Yes	573	4	0.7	577	6	1.0	0.5325	1.49	(0.42, 5.25)	1.49	(0.42, 5.33)	0.00	(-0.01, 0.01)	
Cause of Heart Failure														0.9756
Ischemic	944	7	0.7	983	10	1.0	0.5175	1.37	(0.52, 3.59)	1.38	(0.52, 3.63)	0.00	(-0.01, 0.01)	
Non-ischemic	919	7	0.8	880	9	1.0	0.5555	1.34	(0.50, 3.59)	1.35	(0.50, 3.63)	0.00	(-0.01, 0.01)	
Heart Failure Physiology														0.2666
LVEF <= 30% and NTproBNP < median	723	5	0.7	698	3	0.4	0.5097	0.62	(0.15, 2.59)	0.62	(0.15, 2.60)	0.00	(-0.01, 0.01)	
LVEF <= 30% and NTproBNP >= median	660	4	0.6	631	10	1.6	0.0896	2.61	(0.82, 8.29)	2.64	(0.82, 8.46)	0.01	(0.00, 0.02)	
LVEF > 30%	473	5	1.1	526	6	1.1	0.8994	1.08	(0.33, 3.51)	1.08	(0.33, 3.56)	0.00	(-0.01, 0.01)	
Baseline use of MRA														0.5194
No	512	4	0.8	557	8	1.4	0.3099	1.84	(0.56, 6.07)	1.85	(0.55, 6.18)	0.01	(-0.01, 0.02)	
Yes	1351	10	0.7	1306	11	0.8	0.7664	1.14	(0.48, 2.67)	1.14	(0.48, 2.69)	0.00	(-0.01, 0.01)	
Baseline use of ARNi														0.2504
No	1476	10	0.7	1523	17	1.1	0.2035	1.65	(0.76, 3.59)	1.65	(0.76, 3.63)	0.00	(0.00, 0.01)	
Yes	387	4	1.0	340	2	0.6	0.5078	0.57	(0.10, 3.09)	0.57	(0.10, 3.11)	0.00	(-0.02, 0.01)	

*** 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).
Subgroups will only be analysed if at least 10 events occurred in at least one category (both treatments combined).
For AEs on SOC and/or PT level, subgroup analyses are only shown if overall test for treatment is significant on 5% level (i.e. 95% CI for the risk ratio does not contain 1; if this is not calculable the p-value of Chi-square test is used).
MedDRA version: 23.0. * Chi-square test for treatment effect ** Breslow-Day test for homogeneity of odds ratios (treatment by subgroup interaction).

Table R.1.4.3: 2 Proportion of patients with serious adverse events of special interest and other specific AEs
- by user-defined AE category - overall population 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														0.8953
<=30	1390	9	0.6	1337	13	1.0	0.3431	1.50	(0.64, 3.50)	1.51	(0.64, 3.54)	0.00	(0.00, 0.01)	
>30 to <=35	359	4	1.1	398	5	1.3	0.8571	1.13	(0.31, 4.17)	1.13	(0.30, 4.24)	0.00	(-0.01, 0.02)	
>35	114	1	0.9	128	1	0.8	0.9344	0.89	(0.06, 14.08)	0.89	(0.06, 14.39)	0.00	(-0.02, 0.02)	
Baseline NTproBNP														0.1220
< median	919	8	0.9	942	6	0.6	0.5599	0.73	(0.25, 2.10)	0.73	(0.25, 2.11)	0.00	(-0.01, 0.01)	
>= median	943	6	0.6	920	13	1.4	0.0952	2.22	(0.85, 5.82)	2.24	(0.85, 5.91)	0.01	(0.00, 0.02)	

*** 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).
Subgroups will only be analysed if at least 10 events occurred in at least one category (both treatments combined).
For AEs on SOC and/or PT level, subgroup analyses are only shown if overall test for treatment is significant on 5% level (i.e. 95% CI for the risk ratio does not contain 1; if this is not calculable the p-value of Chi-square test is used).
MedDRA version: 23.0. * Chi-square test for treatment effect ** Breslow-Day test for homogeneity of odds ratios (treatment by subgroup interaction).

Table R.1.4.3: 2 Proportion of patients with serious adverse events of special interest and other specific AEs
- by user-defined AE category - overall population 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	1863	2	0.1	1863	1	0.1	0.5635	0.50	(0.05, 5.51)	0.50	(0.05, 5.52)	0.00	(0.00, 0.00)	

*** 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).
Subgroups will only be analysed if at least 10 events occurred in at least one category (both treatments combined).
For AEs on SOC and/or PT level, subgroup analyses are only shown if overall test for treatment is significant on 5% level (i.e. 95% CI for the risk ratio does not contain 1; if this is not calculable the p-value of Chi-square test is used).
MedDRA version: 23.0. * Chi-square test for treatment effect ** Breslow-Day test for homogeneity of odds ratios (treatment by subgroup interaction).

Table R.1.4.3: 2 Proportion of patients with serious adverse events of special interest and other specific AEs
- by user-defined AE category - overall population 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	1863	2	0.1	1863	1	0.1	0.5635	0.50	(0.05, 5.51)	0.50	(0.05, 5.52)	0.00	(0.00, 0.00)	

*** 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).
Subgroups will only be analysed if at least 10 events occurred in at least one category (both treatments combined).
For AEs on SOC and/or PT level, subgroup analyses are only shown if overall test for treatment is significant on 5% level (i.e. 95% CI for the risk ratio does not contain 1; if this is not calculable the p-value of Chi-square test is used).
MedDRA version: 23.0. * Chi-square test for treatment effect ** Breslow-Day test for homogeneity of odds ratios (treatment by subgroup interaction).

Table R.1.4.3: 2 Proportion of patients with serious adverse events of special interest and other specific AEs
- by user-defined AE category - overall population 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	1863	3	0.2	1863	1	0.1	0.3171	0.33	(0.03, 3.20)	0.33	(0.03, 3.20)	0.00	(0.00, 0.00)	

*** 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).
Subgroups will only be analysed if at least 10 events occurred in at least one category (both treatments combined).
For AEs on SOC and/or PT level, subgroup analyses are only shown if overall test for treatment is significant on 5% level (i.e. 95% CI for the risk ratio does not contain 1; if this is not calculable the p-value of Chi-square test is used).
MedDRA version: 23.0. * Chi-square test for treatment effect ** Breslow-Day test for homogeneity of odds ratios (treatment by subgroup interaction).

Table R.1.4.3: 2 Proportion of patients with serious adverse events of special interest and other specific AEs
- by user-defined AE category - overall population 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	1863	3	0.2	1863	5	0.3	0.4790	1.67	(0.40, 6.96)	1.67	(0.40, 6.99)	0.00	(0.00, 0.00)	

*** 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).
Subgroups will only be analysed if at least 10 events occurred in at least one category (both treatments combined).
For AEs on SOC and/or PT level, subgroup analyses are only shown if overall test for treatment is significant on 5% level
(i.e. 95% CI for the risk ratio does not contain 1; if this is not calculable the p-value of Chi-square test is used).
MedDRA version: 23.0. * Chi-square test for treatment effect ** Breslow-Day test for homogeneity of odds ratios (treatment by subgroup interaction).

Table R.1.4.3: 2 Proportion of patients with serious adverse events of special interest and other specific AEs
- by user-defined AE category - overall population 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	1863	15	0.8	1863	33	1.8	0.0089	2.20	(1.20, 4.04)	2.22	(1.20, 4.10)	0.01	(0.00, 0.02)	
Sex														0.0592
Male	1410	13	0.9	1426	20	1.4	0.2328	1.52	(0.76, 3.05)	1.53	(0.76, 3.08)	0.00	(0.00, 0.01)	
Female	453	2	0.4	437	13	3.0	0.0033	6.74	(1.53, 29.69)	6.91	(1.55, 30.82)	0.03	(0.01, 0.04)	
Age [years]														0.8283
< 65	739	5	0.7	675	9	1.3	0.2128	1.97	(0.66, 5.85)	1.98	(0.66, 5.95)	0.01	(0.00, 0.02)	
>= 65	1124	10	0.9	1188	24	2.0	0.0240	2.27	(1.09, 4.73)	2.30	(1.09, 4.83)	0.01	(0.00, 0.02)	
Region														0.2362
North America	213	1	0.5	212	9	4.2	0.0102	9.04	(1.16, 70.75)	9.40	(1.18, 74.85)	0.04	(0.01, 0.07)	
Latin America	645	5	0.8	641	14	2.2	0.0363	2.82	(1.02, 7.78)	2.86	(1.02, 7.98)	0.01	(0.00, 0.03)	
Europe	674	9	1.3	676	9	1.3	0.9950	1.00	(0.40, 2.50)	1.00	(0.39, 2.53)	0.00	(-0.01, 0.01)	
Asia	244	0	0	248	1	0.4	0.4857	2.95	(0.12, 72.11)	2.96	(0.12, 73.11)	0.00	(-0.01, 0.02)	
Other	87	0	0	86	0	0	0.9954	1.01	(0.02, 50.41)	1.01	(0.02, 51.56)	0.00	(-0.02, 0.02)	
OECD Member														0.2519
No	741	4	0.5	713	14	2.0	0.0141	3.64	(1.20, 11.00)	3.69	(1.21, 11.27)	0.01	(0.00, 0.03)	
Yes	1122	11	1.0	1150	19	1.7	0.1608	1.69	(0.81, 3.53)	1.70	(0.80, 3.58)	0.01	(0.00, 0.02)	
Baseline NYHA														0.8162
II	1399	9	0.6	1399	21	1.5	0.0276	2.33	(1.07, 5.08)	2.35	(1.07, 5.16)	0.01	(0.00, 0.02)	
III/IV	464	6	1.3	464	12	2.6	0.1533	2.00	(0.76, 5.28)	2.03	(0.75, 5.45)	0.01	(0.00, 0.03)	
Baseline Diabetes Status														0.3639
Diabetic	926	7	0.8	927	20	2.2	0.0118	2.85	(1.21, 6.72)	2.89	(1.22, 6.88)	0.01	(0.00, 0.02)	
Non-Diabetic	937	8	0.9	936	13	1.4	0.2715	1.63	(0.68, 3.91)	1.64	(0.67, 3.96)	0.01	(0.00, 0.01)	
Baseline BMI [kg/m²]														0.0209
<30	1299	5	0.4	1263	22	1.7	0.0008	4.53	(1.72, 11.91)	4.59	(1.73, 12.15)	0.01	(0.01, 0.02)	
>=30	564	10	1.8	600	11	1.8	0.9384	1.03	(0.44, 2.42)	1.03	(0.44, 2.46)	0.00	(-0.01, 0.02)	

*** 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).
Subgroups will only be analysed if at least 10 events occurred in at least one category (both treatments combined).
For AEs on SOC and/or PT level, subgroup analyses are only shown if overall test for treatment is significant on 5% level (i.e. 95% CI for the risk ratio does not contain 1; if this is not calculable the p-value of Chi-square test is used).
MedDRA version: 23.0. * Chi-square test for treatment effect ** Breslow-Day test for homogeneity of odds ratios (treatment by subgroup interaction).

Table R.1.4.3: 2 Proportion of patients with serious adverse events of special interest and other specific AEs
- by user-defined AE category - overall population 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 eGFR (CKD-EPI) [mL/min/1.73m²]														0.6191
>=60	958	6	0.6	969	11	1.1	0.2323	1.81	(0.67, 4.88)	1.82	(0.67, 4.95)	0.01	(0.00, 0.01)	
<60	904	9	1.0	893	22	2.5	0.0169	2.47	(1.15, 5.34)	2.51	(1.15, 5.49)	0.01	(0.00, 0.03)	
History of HHF (in the last 12 months)														0.7997
No	1290	9	0.7	1286	21	1.6	0.0269	2.34	(1.08, 5.09)	2.36	(1.08, 5.18)	0.01	(0.00, 0.02)	
Yes	573	6	1.0	577	12	2.1	0.1584	1.99	(0.75, 5.26)	2.01	(0.75, 5.38)	0.01	(0.00, 0.02)	
Cause of Heart Failure														0.6528
Ischemic	944	8	0.8	983	16	1.6	0.1226	1.92	(0.83, 4.47)	1.94	(0.82, 4.54)	0.01	(0.00, 0.02)	
Non-ischemic	919	7	0.8	880	17	1.9	0.0306	2.54	(1.06, 6.09)	2.57	(1.06, 6.22)	0.01	(0.00, 0.02)	
Heart Failure Physiology														0.4180
LVEF <= 30% and NTproBNP < median	723	5	0.7	698	8	1.1	0.3683	1.66	(0.54, 5.04)	1.66	(0.54, 5.11)	0.00	(-0.01, 0.01)	
LVEF <= 30% and NTproBNP >= median	660	8	1.2	631	13	2.1	0.2285	1.70	(0.71, 4.07)	1.71	(0.71, 4.16)	0.01	(-0.01, 0.02)	
LVEF > 30%	473	2	0.4	526	11	2.1	0.0202	4.95	(1.10, 22.20)	5.03	(1.11, 22.81)	0.02	(0.00, 0.03)	
Baseline use of MRA														0.1939
No	512	2	0.4	557	11	2.0	0.0182	5.06	(1.13, 22.70)	5.14	(1.13, 23.29)	0.02	(0.00, 0.03)	
Yes	1351	13	1.0	1306	22	1.7	0.1026	1.75	(0.89, 3.46)	1.76	(0.88, 3.52)	0.01	(0.00, 0.02)	
Baseline use of ARNi														0.4754
No	1476	11	0.7	1523	22	1.4	0.0665	1.94	(0.94, 3.98)	1.95	(0.94, 4.04)	0.01	(0.00, 0.01)	
Yes	387	4	1.0	340	11	3.2	0.0372	3.13	(1.01, 9.74)	3.20	(1.01, 10.15)	0.02	(0.00, 0.04)	

*** 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).
Subgroups will only be analysed if at least 10 events occurred in at least one category (both treatments combined).
For AEs on SOC and/or PT level, subgroup analyses are only shown if overall test for treatment is significant on 5% level (i.e. 95% CI for the risk ratio does not contain 1; if this is not calculable the p-value of Chi-square test is used).
MedDRA version: 23.0. * Chi-square test for treatment effect ** Breslow-Day test for homogeneity of odds ratios (treatment by subgroup interaction).

Table R.1.4.3: 2 Proportion of patients with serious adverse events of special interest and other specific AEs
- by user-defined AE category - overall population 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														0.5314
<=30	1390	13	0.9	1337	22	1.6	0.0995	1.76	(0.89, 3.48)	1.77	(0.89, 3.53)	0.01	(0.00, 0.02)	
>30 to <=35	359	2	0.6	398	9	2.3	0.0504	4.06	(0.88, 18.66)	4.13	(0.89, 19.24)	0.02	(0.00, 0.03)	
>35	114	0	0	128	2	1.6	0.2875	4.46	(0.22, 91.88)	4.53	(0.22, 95.26)	0.02	(-0.01, 0.04)	
Baseline NTproBNP														0.7428
< median	919	6	0.7	942	12	1.3	0.1712	1.95	(0.74, 5.18)	1.96	(0.73, 5.25)	0.01	(0.00, 0.02)	
>= median	943	9	1.0	920	21	2.3	0.0228	2.39	(1.10, 5.19)	2.42	(1.10, 5.32)	0.01	(0.00, 0.02)	

*** 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).
Subgroups will only be analysed if at least 10 events occurred in at least one category (both treatments combined).
For AEs on SOC and/or PT level, subgroup analyses are only shown if overall test for treatment is significant on 5% level (i.e. 95% CI for the risk ratio does not contain 1; if this is not calculable the p-value of Chi-square test is used).
MedDRA version: 23.0. * Chi-square test for treatment effect ** Breslow-Day test for homogeneity of odds ratios (treatment by subgroup interaction).

Table R.1.4.3: 2 Proportion of patients with serious adverse events of special interest and other specific AEs
- by user-defined AE category - overall population 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	1863	1	0.1	1863	5	0.3	0.1022	5.00	(0.58, 42.76)	5.01	(0.58, 42.93)	0.00	(0.00, 0.00)	

*** 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).
Subgroups will only be analysed if at least 10 events occurred in at least one category (both treatments combined).
For AEs on SOC and/or PT level, subgroup analyses are only shown if overall test for treatment is significant on 5% level (i.e. 95% CI for the risk ratio does not contain 1; if this is not calculable the p-value of Chi-square test is used).
MedDRA version: 23.0. * Chi-square test for treatment effect ** Breslow-Day test for homogeneity of odds ratios (treatment by subgroup interaction).

Table R.1.4.3: 2 Proportion of patients with serious adverse events of special interest and other specific AEs
- by user-defined AE category - overall population 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	1863	14	0.8	1863	28	1.5	0.0298	2.00	(1.06, 3.79)	2.02	(1.06, 3.84)	0.01	(0.00, 0.01)	
Sex														0.2769
Male	1410	12	0.9	1426	20	1.4	0.1645	1.65	(0.81, 3.36)	1.66	(0.81, 3.40)	0.01	(0.00, 0.01)	
Female	453	2	0.4	437	8	1.8	0.0493	4.15	(0.89, 19.42)	4.21	(0.89, 19.91)	0.01	(0.00, 0.03)	
Age [years]														0.9565
< 65	739	4	0.5	675	7	1.0	0.2892	1.92	(0.56, 6.52)	1.93	(0.56, 6.61)	0.00	(0.00, 0.01)	
>= 65	1124	10	0.9	1188	21	1.8	0.0666	1.99	(0.94, 4.20)	2.00	(0.94, 4.28)	0.01	(0.00, 0.02)	
Region														0.0901
North America	213	1	0.5	212	9	4.2	0.0102	9.04	(1.16, 70.75)	9.40	(1.18, 74.85)	0.04	(0.01, 0.07)	
Latin America	645	4	0.6	641	12	1.9	0.0429	3.02	(0.98, 9.31)	3.06	(0.98, 9.53)	0.01	(0.00, 0.02)	
Europe	674	9	1.3	676	6	0.9	0.4326	0.66	(0.24, 1.86)	0.66	(0.23, 1.87)	0.00	(-0.02, 0.01)	
Asia	244	0	0	248	1	0.4	0.4857	2.95	(0.12, 72.11)	2.96	(0.12, 73.11)	0.00	(-0.01, 0.02)	
Other	87	0	0	86	0	0	0.9954	1.01	(0.02, 50.41)	1.01	(0.02, 51.56)	0.00	(-0.02, 0.02)	
OECD Member														0.1443
No	741	3	0.4	713	12	1.7	0.0159	4.16	(1.18, 14.67)	4.21	(1.18, 14.99)	0.01	(0.00, 0.02)	
Yes	1122	11	1.0	1150	16	1.4	0.3662	1.42	(0.66, 3.04)	1.43	(0.66, 3.08)	0.00	(0.00, 0.01)	
Baseline NYHA														0.6570
II	1399	8	0.6	1399	18	1.3	0.0488	2.25	(0.98, 5.16)	2.27	(0.98, 5.23)	0.01	(0.00, 0.01)	
III/IV	464	6	1.3	464	10	2.2	0.3131	1.67	(0.61, 4.55)	1.68	(0.61, 4.66)	0.01	(-0.01, 0.03)	
Baseline Diabetes Status														0.0706
Diabetic	926	6	0.6	927	20	2.2	0.0057	3.33	(1.34, 8.25)	3.38	(1.35, 8.46)	0.02	(0.00, 0.03)	
Non-Diabetic	937	8	0.9	936	8	0.9	0.9983	1.00	(0.38, 2.66)	1.00	(0.37, 2.68)	0.00	(-0.01, 0.01)	
Baseline BMI [kg/m²]														0.0580
<30	1299	5	0.4	1263	18	1.4	0.0053	3.70	(1.38, 9.94)	3.74	(1.38, 10.11)	0.01	(0.00, 0.02)	
>=30	564	9	1.6	600	10	1.7	0.9240	1.04	(0.43, 2.55)	1.05	(0.42, 2.59)	0.00	(-0.01, 0.02)	

*** 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).
Subgroups will only be analysed if at least 10 events occurred in at least one category (both treatments combined).
For AEs on SOC and/or PT level, subgroup analyses are only shown if overall test for treatment is significant on 5% level (i.e. 95% CI for the risk ratio does not contain 1; if this is not calculable the p-value of Chi-square test is used).
MedDRA version: 23.0. * Chi-square test for treatment effect ** Breslow-Day test for homogeneity of odds ratios (treatment by subgroup interaction).

Table R.1.4.3: 2 Proportion of patients with serious adverse events of special interest and other specific AEs
- by user-defined AE category - overall population 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 eGFR (CKD-EPI) [mL/min/1.73m²]														0.6047
>=60	958	5	0.5	969	8	0.8	0.4155	1.58	(0.52, 4.82)	1.59	(0.52, 4.87)	0.00	(0.00, 0.01)	
<60	904	9	1.0	893	20	2.2	0.0364	2.25	(1.03, 4.91)	2.28	(1.03, 5.03)	0.01	(0.00, 0.02)	
History of HHF (in the last 12 months)														0.6432
No	1290	8	0.6	1286	18	1.4	0.0478	2.26	(0.98, 5.17)	2.27	(0.99, 5.25)	0.01	(0.00, 0.02)	
Yes	573	6	1.0	577	10	1.7	0.3207	1.66	(0.61, 4.52)	1.67	(0.60, 4.62)	0.01	(-0.01, 0.02)	
Cause of Heart Failure														0.8968
Ischemic	944	7	0.7	983	14	1.4	0.1490	1.92	(0.78, 4.74)	1.93	(0.78, 4.81)	0.01	(0.00, 0.02)	
Non-ischemic	919	7	0.8	880	14	1.6	0.1017	2.09	(0.85, 5.15)	2.11	(0.85, 5.24)	0.01	(0.00, 0.02)	
Heart Failure Physiology														0.6331
LVEF <= 30% and NTproBNP < median	723	5	0.7	698	7	1.0	0.5215	1.45	(0.46, 4.55)	1.45	(0.46, 4.61)	0.00	(-0.01, 0.01)	
LVEF <= 30% and NTproBNP >= median	660	7	1.1	631	12	1.9	0.2096	1.79	(0.71, 4.53)	1.81	(0.71, 4.62)	0.01	(0.00, 0.02)	
LVEF > 30%	473	2	0.4	526	8	1.5	0.0817	3.60	(0.77, 16.85)	3.64	(0.77, 17.21)	0.01	(0.00, 0.02)	
Baseline use of MRA														0.1314
No	512	2	0.4	557	11	2.0	0.0182	5.06	(1.13, 22.70)	5.14	(1.13, 23.29)	0.02	(0.00, 0.03)	
Yes	1351	12	0.9	1306	17	1.3	0.3052	1.47	(0.70, 3.06)	1.47	(0.70, 3.09)	0.00	(0.00, 0.01)	
Baseline use of ARNi														0.3413
No	1476	11	0.7	1523	19	1.2	0.1670	1.67	(0.80, 3.51)	1.68	(0.80, 3.55)	0.01	(0.00, 0.01)	
Yes	387	3	0.8	340	9	2.6	0.0481	3.41	(0.93, 12.51)	3.48	(0.93, 12.96)	0.02	(0.00, 0.04)	

*** 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).
Subgroups will only be analysed if at least 10 events occurred in at least one category (both treatments combined).
For AEs on SOC and/or PT level, subgroup analyses are only shown if overall test for treatment is significant on 5% level (i.e. 95% CI for the risk ratio does not contain 1; if this is not calculable the p-value of Chi-square test is used).
MedDRA version: 23.0. * Chi-square test for treatment effect ** Breslow-Day test for homogeneity of odds ratios (treatment by subgroup interaction).

Table R.1.4.3: 2 Proportion of patients with serious adverse events of special interest and other specific AEs
- by user-defined AE category - overall population 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														0.7724
<=30	1390	12	0.9	1337	20	1.5	0.1252	1.73	(0.85, 3.53)	1.74	(0.85, 3.58)	0.01	(0.00, 0.01)	
>30 to <=35	359	2	0.6	398	7	1.8	0.1277	3.16	(0.66, 15.10)	3.20	(0.66, 15.48)	0.01	(0.00, 0.03)	
>35	114	0	0	128	1	0.8	0.5290	2.67	(0.11, 65.00)	2.69	(0.11, 66.79)	0.01	(-0.01, 0.03)	
Baseline NTproBNP														0.5950
< median	919	6	0.7	942	10	1.1	0.3397	1.63	(0.59, 4.46)	1.63	(0.59, 4.51)	0.00	(0.00, 0.01)	
>= median	943	8	0.8	920	18	2.0	0.0415	2.31	(1.01, 5.28)	2.33	(1.01, 5.39)	0.01	(0.00, 0.02)	

*** 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).
Subgroups will only be analysed if at least 10 events occurred in at least one category (both treatments combined).
For AEs on SOC and/or PT level, subgroup analyses are only shown if overall test for treatment is significant on 5% level (i.e. 95% CI for the risk ratio does not contain 1; if this is not calculable the p-value of Chi-square test is used).
MedDRA version: 23.0. * Chi-square test for treatment effect ** Breslow-Day test for homogeneity of odds ratios (treatment by subgroup interaction).

Table R.1.4.3: 2 Proportion of patients with serious adverse events of special interest and other specific AEs
- by user-defined AE category - overall population 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	1863	21	1.1	1863	25	1.3	0.5529	1.19	(0.67, 2.12)	1.19	(0.67, 2.14)	0.00	(0.00, 0.01)	
Sex														0.3338
Male	1410	13	0.9	1426	19	1.3	0.3008	1.45	(0.72, 2.91)	1.45	(0.71, 2.95)	0.00	(0.00, 0.01)	
Female	453	8	1.8	437	6	1.4	0.6376	0.78	(0.27, 2.22)	0.77	(0.27, 2.25)	0.00	(-0.02, 0.01)	
Age [years]														0.4069
< 65	739	6	0.8	675	4	0.6	0.6230	0.73	(0.21, 2.58)	0.73	(0.20, 2.59)	0.00	(-0.01, 0.01)	
>= 65	1124	15	1.3	1188	21	1.8	0.4005	1.32	(0.69, 2.56)	1.33	(0.68, 2.59)	0.00	(-0.01, 0.01)	
Region														0.4375
North America	213	3	1.4	212	4	1.9	0.6985	1.34	(0.30, 5.91)	1.35	(0.30, 6.09)	0.00	(-0.02, 0.03)	
Latin America	645	6	0.9	641	4	0.6	0.5319	0.67	(0.19, 2.37)	0.67	(0.19, 2.38)	0.00	(-0.01, 0.01)	
Europe	674	11	1.6	676	11	1.6	0.9944	1.00	(0.44, 2.28)	1.00	(0.43, 2.32)	0.00	(-0.01, 0.01)	
Asia	244	1	0.4	248	6	2.4	0.0599	5.90	(0.72, 48.67)	6.02	(0.72, 50.42)	0.02	(0.00, 0.04)	
Other	87	0	0	86	0	0	0.9954	1.01	(0.02, 50.41)	1.01	(0.02, 51.56)	0.00	(-0.02, 0.02)	
OECD Member														0.5541
No	741	6	0.8	713	5	0.7	0.8114	0.87	(0.27, 2.83)	0.87	(0.26, 2.85)	0.00	(-0.01, 0.01)	
Yes	1122	15	1.3	1150	20	1.7	0.4364	1.30	(0.67, 2.53)	1.31	(0.67, 2.56)	0.00	(-0.01, 0.01)	
Baseline NYHA														0.8459
II	1399	12	0.9	1399	15	1.1	0.5618	1.25	(0.59, 2.66)	1.25	(0.58, 2.69)	0.00	(-0.01, 0.01)	
III/IV	464	9	1.9	464	10	2.2	0.8167	1.11	(0.46, 2.71)	1.11	(0.45, 2.77)	0.00	(-0.02, 0.02)	
Baseline Diabetes Status														0.3697
Diabetic	926	12	1.3	927	11	1.2	0.8318	0.92	(0.41, 2.06)	0.91	(0.40, 2.08)	0.00	(-0.01, 0.01)	
Non-Diabetic	937	9	1.0	936	14	1.5	0.2930	1.56	(0.68, 3.58)	1.57	(0.67, 3.64)	0.01	(0.00, 0.02)	
Baseline BMI [kg/m²]														0.2527
<30	1299	17	1.3	1263	16	1.3	0.9251	0.97	(0.49, 1.91)	0.97	(0.49, 1.92)	0.00	(-0.01, 0.01)	
>=30	564	4	0.7	600	9	1.5	0.1995	2.12	(0.66, 6.83)	2.13	(0.65, 6.96)	0.01	(0.00, 0.02)	

*** 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).
Subgroups will only be analysed if at least 10 events occurred in at least one category (both treatments combined).
For AEs on SOC and/or PT level, subgroup analyses are only shown if overall test for treatment is significant on 5% level (i.e. 95% CI for the risk ratio does not contain 1; if this is not calculable the p-value of Chi-square test is used).
MedDRA version: 23.0. * Chi-square test for treatment effect ** Breslow-Day test for homogeneity of odds ratios (treatment by subgroup interaction).

Table R.1.4.3: 2 Proportion of patients with serious adverse events of special interest and other specific AEs
- by user-defined AE category - overall population 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 eGFR (CKD-EPI) [mL/min/1.73m²]														0.8811
>=60	958	7	0.7	969	9	0.9	0.6318	1.27	(0.48, 3.40)	1.27	(0.47, 3.43)	0.00	(-0.01, 0.01)	
<60	904	14	1.5	893	16	1.8	0.6876	1.16	(0.57, 2.36)	1.16	(0.56, 2.39)	0.00	(-0.01, 0.01)	
History of HHF (in the last 12 months)														0.0728
No	1290	17	1.3	1286	14	1.1	0.5938	0.83	(0.41, 1.67)	0.82	(0.40, 1.68)	0.00	(-0.01, 0.01)	
Yes	573	4	0.7	577	11	1.9	0.0710	2.73	(0.87, 8.53)	2.76	(0.88, 8.73)	0.01	(0.00, 0.03)	
Cause of Heart Failure														0.1556
Ischemic	944	14	1.5	983	12	1.2	0.6178	0.82	(0.38, 1.77)	0.82	(0.38, 1.78)	0.00	(-0.01, 0.01)	
Non-ischemic	919	7	0.8	880	13	1.5	0.1479	1.94	(0.78, 4.84)	1.95	(0.78, 4.92)	0.01	(0.00, 0.02)	
Heart Failure Physiology														0.4028
LVEF <= 30% and NTproBNP < median	723	7	1.0	698	4	0.6	0.3955	0.59	(0.17, 2.01)	0.59	(0.17, 2.02)	0.00	(-0.01, 0.01)	
LVEF <= 30% and NTproBNP >= median	660	10	1.5	631	15	2.4	0.2612	1.57	(0.71, 3.47)	1.58	(0.71, 3.55)	0.01	(-0.01, 0.02)	
LVEF > 30%	473	4	0.8	526	6	1.1	0.6400	1.35	(0.38, 4.75)	1.35	(0.38, 4.82)	0.00	(-0.01, 0.02)	
Baseline use of MRA														0.2096
No	512	5	1.0	557	11	2.0	0.1793	2.02	(0.71, 5.78)	2.04	(0.70, 5.92)	0.01	(0.00, 0.02)	
Yes	1351	16	1.2	1306	14	1.1	0.7841	0.91	(0.44, 1.85)	0.90	(0.44, 1.86)	0.00	(-0.01, 0.01)	
Baseline use of ARNi														0.9477
No	1476	17	1.2	1523	21	1.4	0.5783	1.20	(0.63, 2.26)	1.20	(0.63, 2.28)	0.00	(-0.01, 0.01)	
Yes	387	4	1.0	340	4	1.2	0.8538	1.14	(0.29, 4.52)	1.14	(0.28, 4.59)	0.00	(-0.01, 0.02)	

*** 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).
Subgroups will only be analysed if at least 10 events occurred in at least one category (both treatments combined).
For AEs on SOC and/or PT level, subgroup analyses are only shown if overall test for treatment is significant on 5% level (i.e. 95% CI for the risk ratio does not contain 1; if this is not calculable the p-value of Chi-square test is used).
MedDRA version: 23.0. * Chi-square test for treatment effect ** Breslow-Day test for homogeneity of odds ratios (treatment by subgroup interaction).

Table R.1.4.3: 2 Proportion of patients with serious adverse events of special interest and other specific AEs
- by user-defined AE category - overall population 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														0.6033
<=30	1390	17	1.2	1337	19	1.4	0.6505	1.16	(0.61, 2.23)	1.16	(0.60, 2.25)	0.00	(-0.01, 0.01)	
>30 to <=35	359	4	1.1	398	4	1.0	0.8834	0.90	(0.23, 3.58)	0.90	(0.22, 3.63)	0.00	(-0.02, 0.01)	
>35	114	0	0	128	2	1.6	0.2875	4.46	(0.22, 91.88)	4.53	(0.22, 95.26)	0.02	(-0.01, 0.04)	
Baseline NTproBNP														0.9031
< median	919	6	0.7	942	7	0.7	0.8153	1.14	(0.38, 3.37)	1.14	(0.38, 3.40)	0.00	(-0.01, 0.01)	
>= median	943	15	1.6	920	18	2.0	0.5495	1.23	(0.62, 2.43)	1.23	(0.62, 2.46)	0.00	(-0.01, 0.02)	

*** 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).
Subgroups will only be analysed if at least 10 events occurred in at least one category (both treatments combined).
For AEs on SOC and/or PT level, subgroup analyses are only shown if overall test for treatment is significant on 5% level (i.e. 95% CI for the risk ratio does not contain 1; if this is not calculable the p-value of Chi-square test is used).
MedDRA version: 23.0. * Chi-square test for treatment effect ** Breslow-Day test for homogeneity of odds ratios (treatment by subgroup interaction).

Table R.1.4.3: 2 Proportion of patients with serious adverse events of special interest and other specific AEs
- by user-defined AE category - overall population 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	1863	6	0.3	1863	7	0.4	0.7811	1.17	(0.39, 3.46)	1.17	(0.39, 3.48)	0.00	(0.00, 0.00)	
Sex														0.1582
Male	1410	4	0.3	1426	7	0.5	0.3748	1.73	(0.51, 5.90)	1.73	(0.51, 5.94)	0.00	(0.00, 0.01)	
Female	453	2	0.4	437	0	0	0.2603	0.21	(<0.01, 4.31)	0.21	(<0.01, 4.31)	0.00	(-0.01, 0.00)	
OECD Member														0.9648
No	741	0	0	713	0	0	0.9846	1.04	(0.02, 52.30)	1.04	(0.02, 52.45)	0.00	(0.00, 0.00)	
Yes	1122	6	0.5	1150	7	0.6	0.8153	1.14	(0.38, 3.38)	1.14	(0.38, 3.40)	0.00	(-0.01, 0.01)	
Baseline NYHA														0.4157
II	1399	4	0.3	1399	6	0.4	0.5263	1.50	(0.42, 5.30)	1.50	(0.42, 5.33)	0.00	(0.00, 0.01)	
III/IV	464	2	0.4	464	1	0.2	0.5631	0.50	(0.05, 5.50)	0.50	(0.05, 5.52)	0.00	(-0.01, 0.01)	
Baseline Diabetes Status														0.1480
Diabetic	926	4	0.4	927	7	0.8	0.3652	1.75	(0.51, 5.95)	1.75	(0.51, 6.01)	0.00	(0.00, 0.01)	
Non-Diabetic	937	2	0.2	936	0	0	0.2482	0.20	(<0.01, 4.16)	0.20	(<0.01, 4.17)	0.00	(-0.01, 0.00)	
Baseline BMI [kg/m²]														0.8589
<30	1299	5	0.4	1263	6	0.5	0.7272	1.23	(0.38, 4.03)	1.24	(0.38, 4.06)	0.00	(0.00, 0.01)	
>=30	564	1	0.2	600	1	0.2	0.9651	0.94	(0.06, 14.99)	0.94	(0.06, 15.06)	0.00	(0.00, 0.00)	
History of HHF (in the last 12 months)														0.9001
No	1290	5	0.4	1286	6	0.5	0.7586	1.20	(0.37, 3.93)	1.20	(0.37, 3.96)	0.00	(0.00, 0.01)	
Yes	573	1	0.2	577	1	0.2	0.9961	0.99	(0.06, 15.84)	0.99	(0.06, 15.91)	0.00	(0.00, 0.00)	
Baseline use of ARNi														0.9888
No	1476	5	0.3	1523	6	0.4	0.8026	1.16	(0.36, 3.80)	1.16	(0.35, 3.82)	0.00	(0.00, 0.00)	
Yes	387	1	0.3	340	1	0.3	0.9269	1.14	(0.07, 18.13)	1.14	(0.07, 18.27)	0.00	(-0.01, 0.01)	

*** 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).
Subgroups will only be analysed if at least 10 events occurred in at least one category (both treatments combined).
For AEs on SOC and/or PT level, subgroup analyses are only shown if overall test for treatment is significant on 5% level (i.e. 95% CI for the risk ratio does not contain 1; if this is not calculable the p-value of Chi-square test is used).
MedDRA version: 23.0. * Chi-square test for treatment effect ** Breslow-Day test for homogeneity of odds ratios (treatment by subgroup interaction).

Table R.1.4.3: 2 Proportion of patients with serious adverse events of special interest and other specific AEs
- by user-defined AE category - overall population 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														0.9685
<=30	1390	5	0.4	1337	6	0.4	0.7138	1.25	(0.38, 4.08)	1.25	(0.38, 4.10)	0.00	(0.00, 0.01)	
>30 to <=35	359	1	0.3	398	1	0.3	0.9418	0.90	(0.06, 14.37)	0.90	(0.06, 14.47)	0.00	(-0.01, 0.01)	
>35	114	0	0	128	0	0	0.9541	0.89	(0.02, 44.57)	0.89	(0.02, 45.27)	0.00	(-0.02, 0.02)	

*** 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).
Subgroups will only be analysed if at least 10 events occurred in at least one category (both treatments combined).
For AEs on SOC and/or PT level, subgroup analyses are only shown if overall test for treatment is significant on 5% level (i.e. 95% CI for the risk ratio does not contain 1; if this is not calculable the p-value of Chi-square test is used).
MedDRA version: 23.0. * Chi-square test for treatment effect ** Breslow-Day test for homogeneity of odds ratios (treatment by subgroup interaction).

Table R.1.4.3: 2 Proportion of patients with serious adverse events of special interest and other specific AEs
- by user-defined AE category - overall population 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	1863	33	1.8	1863	43	2.3	0.2465	1.30	(0.83,	2.04)	1.31	(0.83,	2.07)	0.01	(0.00, 0.01)	
Sex																0.4448
Male	1410	26	1.8	1426	31	2.2	0.5313	1.18	(0.70,	1.98)	1.18	(0.70,	2.00)	0.00	(-0.01, 0.01)	
Female	453	7	1.5	437	12	2.7	0.2154	1.78	(0.71,	4.47)	1.80	(0.70,	4.61)	0.01	(-0.01, 0.03)	
Age [years]																0.8224
< 65	739	11	1.5	675	12	1.8	0.6675	1.19	(0.53,	2.69)	1.20	(0.53,	2.73)	0.00	(-0.01, 0.02)	
>= 65	1124	22	2.0	1188	31	2.6	0.2950	1.33	(0.78,	2.29)	1.34	(0.77,	2.33)	0.01	(-0.01, 0.02)	
Region																0.6412
North America	213	10	4.7	212	11	5.2	0.8143	1.11	(0.48,	2.55)	1.11	(0.46,	2.67)	0.00	(-0.04, 0.05)	
Latin America	645	8	1.2	641	13	2.0	0.2651	1.64	(0.68,	3.92)	1.65	(0.68,	4.00)	0.01	(-0.01, 0.02)	
Europe	674	9	1.3	676	14	2.1	0.2963	1.55	(0.68,	3.56)	1.56	(0.67,	3.64)	0.01	(-0.01, 0.02)	
Asia	244	4	1.6	248	5	2.0	0.7552	1.23	(0.33,	4.53)	1.23	(0.33,	4.65)	0.00	(-0.02, 0.03)	
Other	87	2	2.3	86	0	0	0.2482	0.20	(<0.01,	4.15)	0.20	(<0.01,	4.18)	-0.02	(-0.06, 0.02)	
OECD Member																0.6225
No	741	13	1.8	713	14	2.0	0.7677	1.12	(0.53,	2.36)	1.12	(0.52,	2.40)	0.00	(-0.01, 0.02)	
Yes	1122	20	1.8	1150	29	2.5	0.2252	1.41	(0.81,	2.49)	1.43	(0.80,	2.53)	0.01	(0.00, 0.02)	
Baseline NYHA																0.3748
II	1399	19	1.4	1399	29	2.1	0.1454	1.53	(0.86,	2.71)	1.54	(0.86,	2.76)	0.01	(0.00, 0.02)	
III/IV	464	14	3.0	464	14	3.0	1.0000	1.00	(0.48,	2.07)	1.00	(0.47,	2.12)	0.00	(-0.02, 0.02)	
Baseline Diabetes Status																0.5239
Diabetic	926	16	1.7	927	24	2.6	0.2022	1.50	(0.80,	2.80)	1.51	(0.80,	2.86)	0.01	(0.00, 0.02)	
Non-Diabetic	937	17	1.8	936	19	2.0	0.7340	1.12	(0.59,	2.14)	1.12	(0.58,	2.17)	0.00	(-0.01, 0.01)	
Baseline BMI [kg/m²]																0.2793
<30	1299	19	1.5	1263	29	2.3	0.1198	1.57	(0.88,	2.78)	1.58	(0.88,	2.84)	0.01	(0.00, 0.02)	
>=30	564	14	2.5	600	14	2.3	0.8684	0.94	(0.45,	1.95)	0.94	(0.44,	1.99)	0.00	(-0.02, 0.02)	

*** 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).
Subgroups will only be analysed if at least 10 events occurred in at least one category (both treatments combined).
For AEs on SOC and/or PT level, subgroup analyses are only shown if overall test for treatment is significant on 5% level (i.e. 95% CI for the risk ratio does not contain 1; if this is not calculable the p-value of Chi-square test is used).
MedDRA version: 23.0. * Chi-square test for treatment effect ** Breslow-Day test for homogeneity of odds ratios (treatment by subgroup interaction).

Table R.1.4.3: 2 Proportion of patients with serious adverse events of special interest and other specific AEs
- by user-defined AE category - overall population 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 eGFR (CKD-EPI) [mL/min/1.73m²]														0.3172
>=60	958	15	1.6	969	15	1.5	0.9749	0.99	(0.49, 2.01)	0.99	(0.48, 2.03)	0.00	(-0.01, 0.01)	
<60	904	18	2.0	893	28	3.1	0.1246	1.57	(0.88, 2.83)	1.59	(0.87, 2.90)	0.01	(0.00, 0.03)	
History of HHF (in the last 12 months)														0.8306
No	1290	20	1.6	1286	27	2.1	0.2978	1.35	(0.76, 2.40)	1.36	(0.76, 2.44)	0.01	(0.00, 0.02)	
Yes	573	13	2.3	577	16	2.8	0.5856	1.22	(0.59, 2.52)	1.23	(0.59, 2.58)	0.01	(-0.01, 0.02)	
Cause of Heart Failure														0.6926
Ischemic	944	20	2.1	983	25	2.5	0.5373	1.20	(0.67, 2.15)	1.21	(0.67, 2.19)	0.00	(-0.01, 0.02)	
Non-ischemic	919	13	1.4	880	18	2.0	0.3040	1.45	(0.71, 2.93)	1.46	(0.71, 2.99)	0.01	(-0.01, 0.02)	
Heart Failure Physiology														0.7135
LVEF <= 30% and NTproBNP < median	723	12	1.7	698	16	2.3	0.3911	1.38	(0.66, 2.90)	1.39	(0.65, 2.96)	0.01	(-0.01, 0.02)	
LVEF <= 30% and NTproBNP >= median	660	13	2.0	631	18	2.9	0.3003	1.45	(0.72, 2.93)	1.46	(0.71, 3.01)	0.01	(-0.01, 0.03)	
LVEF > 30%	473	8	1.7	526	8	1.5	0.8304	0.90	(0.34, 2.38)	0.90	(0.33, 2.41)	0.00	(-0.02, 0.01)	
Baseline use of MRA														0.7220
No	512	8	1.6	557	13	2.3	0.3639	1.49	(0.62, 3.57)	1.51	(0.62, 3.66)	0.01	(-0.01, 0.02)	
Yes	1351	25	1.9	1306	30	2.3	0.4189	1.24	(0.73, 2.10)	1.25	(0.73, 2.13)	0.00	(-0.01, 0.02)	
Baseline use of ARNi														0.4423
No	1476	23	1.6	1523	28	1.8	0.5529	1.18	(0.68, 2.04)	1.18	(0.68, 2.06)	0.00	(-0.01, 0.01)	
Yes	387	10	2.6	340	15	4.4	0.1772	1.71	(0.78, 3.75)	1.74	(0.77, 3.93)	0.02	(-0.01, 0.05)	

*** 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).
Subgroups will only be analysed if at least 10 events occurred in at least one category (both treatments combined).
For AEs on SOC and/or PT level, subgroup analyses are only shown if overall test for treatment is significant on 5% level (i.e. 95% CI for the risk ratio does not contain 1; if this is not calculable the p-value of Chi-square test is used).
MedDRA version: 23.0. * Chi-square test for treatment effect ** Breslow-Day test for homogeneity of odds ratios (treatment by subgroup interaction).

Table R.1.4.3: 2 Proportion of patients with serious adverse events of special interest and other specific AEs
- by user-defined AE category - overall population 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														0.6862
<=30	1390	25	1.8	1337	35	2.6	0.1449	1.46	(0.88, 2.42)	1.47	(0.87, 2.47)	0.01	(0.00, 0.02)	
>30 to <=35	359	6	1.7	398	6	1.5	0.8570	0.90	(0.29, 2.77)	0.90	(0.29, 2.82)	0.00	(-0.02, 0.02)	
>35	114	2	1.8	128	2	1.6	0.9070	0.89	(0.13, 6.22)	0.89	(0.12, 6.42)	0.00	(-0.03, 0.03)	
Baseline NTproBNP														0.2232
< median	919	18	2.0	942	18	1.9	0.9403	0.98	(0.51, 1.86)	0.98	(0.50, 1.89)	0.00	(-0.01, 0.01)	
>= median	943	15	1.6	920	25	2.7	0.0935	1.71	(0.91, 3.22)	1.73	(0.91, 3.30)	0.01	(0.00, 0.02)	

*** 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).
Subgroups will only be analysed if at least 10 events occurred in at least one category (both treatments combined).
For AEs on SOC and/or PT level, subgroup analyses are only shown if overall test for treatment is significant on 5% level (i.e. 95% CI for the risk ratio does not contain 1; if this is not calculable the p-value of Chi-square test is used).
MedDRA version: 23.0. * Chi-square test for treatment effect ** Breslow-Day test for homogeneity of odds ratios (treatment by subgroup interaction).

Table R.1.4.3: 2 Proportion of patients with serious adverse events of special interest and other specific AEs
- by user-defined AE category - overall population 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	1863	28	1.5	1863	36	1.9	0.3131	1.29	(0.79, 2.10)	1.29	(0.78, 2.13)	0.00	(0.00, 0.01)	
Sex														0.6768
Male	1410	22	1.6	1426	27	1.9	0.4961	1.21	(0.69, 2.12)	1.22	(0.69, 2.15)	0.00	(-0.01, 0.01)	
Female	453	6	1.3	437	9	2.1	0.3945	1.55	(0.56, 4.33)	1.57	(0.55, 4.44)	0.01	(-0.01, 0.02)	
Age [years]														0.8951
< 65	739	9	1.2	675	11	1.6	0.5125	1.34	(0.56, 3.21)	1.34	(0.55, 3.26)	0.00	(-0.01, 0.02)	
>= 65	1124	19	1.7	1188	25	2.1	0.4665	1.24	(0.69, 2.25)	1.25	(0.68, 2.28)	0.00	(-0.01, 0.02)	
Region														0.9477
North America	213	9	4.2	212	9	4.2	0.9919	1.00	(0.41, 2.48)	1.00	(0.39, 2.58)	0.00	(-0.04, 0.04)	
Latin America	645	7	1.1	641	11	1.7	0.3357	1.58	(0.62, 4.05)	1.59	(0.61, 4.13)	0.01	(-0.01, 0.02)	
Europe	674	8	1.2	676	12	1.8	0.3711	1.50	(0.62, 3.64)	1.50	(0.61, 3.70)	0.01	(-0.01, 0.02)	
Asia	244	4	1.6	248	4	1.6	0.9815	0.98	(0.25, 3.89)	0.98	(0.24, 3.98)	0.00	(-0.02, 0.02)	
Other	87	0	0	86	0	0	0.9954	1.01	(0.02, 50.41)	1.01	(0.02, 51.56)	0.00	(-0.02, 0.02)	
OECD Member														0.9347
No	741	10	1.3	713	12	1.7	0.6025	1.25	(0.54, 2.87)	1.25	(0.54, 2.91)	0.00	(-0.01, 0.02)	
Yes	1122	18	1.6	1150	24	2.1	0.3931	1.30	(0.71, 2.38)	1.31	(0.71, 2.42)	0.00	(-0.01, 0.02)	
Baseline NYHA														0.2845
II	1399	15	1.1	1399	24	1.7	0.1467	1.60	(0.84, 3.04)	1.61	(0.84, 3.08)	0.01	(0.00, 0.02)	
III/IV	464	13	2.8	464	12	2.6	0.8393	0.92	(0.43, 2.00)	0.92	(0.42, 2.04)	0.00	(-0.02, 0.02)	
Baseline Diabetes Status														0.8268
Diabetic	926	14	1.5	927	19	2.0	0.3815	1.36	(0.68, 2.69)	1.36	(0.68, 2.74)	0.01	(-0.01, 0.02)	
Non-Diabetic	937	14	1.5	936	17	1.8	0.5848	1.22	(0.60, 2.45)	1.22	(0.60, 2.49)	0.00	(-0.01, 0.01)	
Baseline BMI [kg/m²]														0.2302
<30	1299	16	1.2	1263	25	2.0	0.1316	1.61	(0.86, 3.00)	1.62	(0.86, 3.05)	0.01	(0.00, 0.02)	
>=30	564	12	2.1	600	11	1.8	0.7184	0.86	(0.38, 1.94)	0.86	(0.38, 1.96)	0.00	(-0.02, 0.01)	

*** 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).
Subgroups will only be analysed if at least 10 events occurred in at least one category (both treatments combined).
For AEs on SOC and/or PT level, subgroup analyses are only shown if overall test for treatment is significant on 5% level (i.e. 95% CI for the risk ratio does not contain 1; if this is not calculable the p-value of Chi-square test is used).
MedDRA version: 23.0. * Chi-square test for treatment effect ** Breslow-Day test for homogeneity of odds ratios (treatment by subgroup interaction).

Table R.1.4.3: 2 Proportion of patients with serious adverse events of special interest and other specific AEs
- by user-defined AE category - overall population 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 eGFR (CKD-EPI) [mL/min/1.73m²]																0.5085
>=60	958	13	1.4	969	14	1.4	0.8698	1.06	(0.50,	2.25)	1.07	(0.50,	2.28)	0.00	(-0.01, 0.01)	
<60	904	15	1.7	893	22	2.5	0.2300	1.48	(0.78,	2.84)	1.50	(0.77,	2.90)	0.01	(-0.01, 0.02)	
History of HHF (in the last 12 months)																0.9874
No	1290	18	1.4	1286	23	1.8	0.4253	1.28	(0.70,	2.36)	1.29	(0.69,	2.40)	0.00	(-0.01, 0.01)	
Yes	573	10	1.7	577	13	2.3	0.5385	1.29	(0.57,	2.92)	1.30	(0.56,	2.98)	0.01	(-0.01, 0.02)	
Cause of Heart Failure																0.9464
Ischemic	944	16	1.7	983	21	2.1	0.4803	1.26	(0.66,	2.40)	1.27	(0.66,	2.44)	0.00	(-0.01, 0.02)	
Non-ischemic	919	12	1.3	880	15	1.7	0.4868	1.31	(0.61,	2.77)	1.31	(0.61,	2.82)	0.00	(-0.01, 0.02)	
Heart Failure Physiology																0.3840
LVEF <= 30% and NTproBNP < median	723	10	1.4	698	16	2.3	0.2011	1.66	(0.76,	3.63)	1.67	(0.75,	3.71)	0.01	(0.00, 0.02)	
LVEF <= 30% and NTproBNP >= median	660	10	1.5	631	13	2.1	0.4593	1.36	(0.60,	3.08)	1.37	(0.60,	3.14)	0.01	(-0.01, 0.02)	
LVEF > 30%	473	8	1.7	526	6	1.1	0.4597	0.67	(0.24,	1.93)	0.67	(0.23,	1.95)	-0.01	(-0.02, 0.01)	
Baseline use of MRA																0.8458
No	512	8	1.6	557	12	2.2	0.4755	1.38	(0.57,	3.35)	1.39	(0.56,	3.42)	0.01	(-0.01, 0.02)	
Yes	1351	20	1.5	1306	24	1.8	0.4706	1.24	(0.69,	2.24)	1.25	(0.68,	2.27)	0.00	(-0.01, 0.01)	
Baseline use of ARNi																0.8658
No	1476	19	1.3	1523	25	1.6	0.4199	1.28	(0.71,	2.31)	1.28	(0.70,	2.33)	0.00	(-0.01, 0.01)	
Yes	387	9	2.3	340	11	3.2	0.4543	1.39	(0.58,	3.32)	1.40	(0.57,	3.43)	0.01	(-0.01, 0.03)	

*** 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).
Subgroups will only be analysed if at least 10 events occurred in at least one category (both treatments combined).
For AEs on SOC and/or PT level, subgroup analyses are only shown if overall test for treatment is significant on 5% level (i.e. 95% CI for the risk ratio does not contain 1; if this is not calculable the p-value of Chi-square test is used).
MedDRA version: 23.0. * Chi-square test for treatment effect ** Breslow-Day test for homogeneity of odds ratios (treatment by subgroup interaction).

Table R.1.4.3: 2 Proportion of patients with serious adverse events of special interest and other specific AEs
- by user-defined AE category - overall population 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														0.3543
<=30	1390	20	1.4	1337	30	2.2	0.1173	1.56	(0.89, 2.73)	1.57	(0.89, 2.78)	0.01	(0.00, 0.02)	
>30 to <=35	359	6	1.7	398	4	1.0	0.4227	0.60	(0.17, 2.11)	0.60	(0.17, 2.13)	-0.01	(-0.02, 0.01)	
>35	114	2	1.8	128	2	1.6	0.9070	0.89	(0.13, 6.22)	0.89	(0.12, 6.42)	0.00	(-0.03, 0.03)	
Baseline NTproBNP														0.7007
< median	919	15	1.6	942	18	1.9	0.6489	1.17	(0.59, 2.31)	1.17	(0.59, 2.34)	0.00	(-0.01, 0.01)	
>= median	943	13	1.4	920	18	2.0	0.3296	1.42	(0.70, 2.88)	1.43	(0.70, 2.93)	0.01	(-0.01, 0.02)	

*** 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).
Subgroups will only be analysed if at least 10 events occurred in at least one category (both treatments combined).
For AEs on SOC and/or PT level, subgroup analyses are only shown if overall test for treatment is significant on 5% level (i.e. 95% CI for the risk ratio does not contain 1; if this is not calculable the p-value of Chi-square test is used).
MedDRA version: 23.0. * Chi-square test for treatment effect ** Breslow-Day test for homogeneity of odds ratios (treatment by subgroup interaction).

Table R.1.4.3: 2 Proportion of patients with serious adverse events of special interest and other specific AEs
- by user-defined AE category - overall population and by subgroup - TS
User-defined AE category: Symptomatic hypotension (investigator-defined)

Subgroup Category	Placebo N	Placebo n	Placebo %	Empa 10mg N	Empa 10mg n	Empa 10mg %	Empa 10mg vs Placebo p-value *	Risk ratio	Risk ratio (95% CI)	Odds ratio	Odds ratio (95% CI)	Risk diff.	Risk diff. (95% CI)	p-value **
Overall	1863	16	0.9	1863	19	1.0	0.6104	1.19	(0.61, 2.30)	1.19	(0.61, 2.32)	0.00	(0.00, 0.01)	
Sex														0.0874
Male	1410	14	1.0	1426	12	0.8	0.6723	0.85	(0.39, 1.83)	0.85	(0.39, 1.84)	0.00	(-0.01, 0.01)	
Female	453	2	0.4	437	7	1.6	0.0837	3.63	(0.76, 17.37)	3.67	(0.76, 17.77)	0.01	(0.00, 0.02)	
Age [years]														0.3401
< 65	739	4	0.5	675	7	1.0	0.2892	1.92	(0.56, 6.52)	1.93	(0.56, 6.61)	0.00	(0.00, 0.01)	
>= 65	1124	12	1.1	1188	12	1.0	0.8915	0.95	(0.43, 2.10)	0.95	(0.42, 2.11)	0.00	(-0.01, 0.01)	
Region														0.8486
North America	213	8	3.8	212	6	2.8	0.5929	0.75	(0.27, 2.13)	0.75	(0.25, 2.19)	-0.01	(-0.04, 0.02)	
Latin America	645	3	0.5	641	5	0.8	0.4727	1.68	(0.40, 6.99)	1.68	(0.40, 7.07)	0.00	(-0.01, 0.01)	
Europe	674	5	0.7	676	7	1.0	0.5654	1.40	(0.45, 4.38)	1.40	(0.44, 4.43)	0.00	(-0.01, 0.01)	
Asia	244	0	0	248	1	0.4	0.4857	2.95	(0.12, 72.11)	2.96	(0.12, 73.11)	0.00	(-0.01, 0.02)	
Other	87	0	0	86	0	0	0.9954	1.01	(0.02, 50.41)	1.01	(0.02, 51.56)	0.00	(-0.02, 0.02)	
OECD Member														0.5423
No	741	3	0.4	713	5	0.7	0.4450	1.73	(0.42, 7.22)	1.74	(0.41, 7.30)	0.00	(0.00, 0.01)	
Yes	1122	13	1.2	1150	14	1.2	0.8972	1.05	(0.50, 2.23)	1.05	(0.49, 2.25)	0.00	(-0.01, 0.01)	
Baseline NYHA														0.3284
II	1399	11	0.8	1399	10	0.7	0.8266	0.91	(0.39, 2.13)	0.91	(0.38, 2.15)	0.00	(-0.01, 0.01)	
III/IV	464	5	1.1	464	9	1.9	0.2814	1.80	(0.61, 5.33)	1.82	(0.60, 5.46)	0.01	(-0.01, 0.02)	
Baseline Diabetes Status														0.8785
Diabetic	926	8	0.9	927	10	1.1	0.6373	1.25	(0.50, 3.15)	1.25	(0.49, 3.18)	0.00	(-0.01, 0.01)	
Non-Diabetic	937	8	0.9	936	9	1.0	0.8058	1.13	(0.44, 2.91)	1.13	(0.43, 2.93)	0.00	(-0.01, 0.01)	
Baseline BMI [kg/m²]														0.5267
<30	1299	12	0.9	1263	12	1.0	0.9449	1.03	(0.46, 2.28)	1.03	(0.46, 2.30)	0.00	(-0.01, 0.01)	
>=30	564	4	0.7	600	7	1.2	0.4202	1.65	(0.48, 5.59)	1.65	(0.48, 5.68)	0.00	(-0.01, 0.02)	

*** 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).
Subgroups will only be analysed if at least 10 events occurred in at least one category (both treatments combined).
For AEs on SOC and/or PT level, subgroup analyses are only shown if overall test for treatment is significant on 5% level (i.e. 95% CI for the risk ratio does not contain 1; if this is not calculable the p-value of Chi-square test is used).
MedDRA version: 23.0. * Chi-square test for treatment effect ** Breslow-Day test for homogeneity of odds ratios (treatment by subgroup interaction).

Table R.1.4.3: 2 Proportion of patients with serious adverse events of special interest and other specific AEs
- by user-defined AE category - overall population 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 eGFR (CKD-EPI) [mL/min/1.73m²]																0.2506
>=60	958	8	0.8	969	6	0.6	0.5769	0.74	(0.26,	2.13)	0.74	(0.26,	2.14)	0.00	(-0.01, 0.01)	
<60	904	8	0.9	893	13	1.5	0.2603	1.65	(0.69,	3.95)	1.65	(0.68,	4.01)	0.01	(0.00, 0.02)	
History of HHF (in the last 12 months)																0.7015
No	1290	10	0.8	1286	13	1.0	0.5249	1.30	(0.57,	2.96)	1.31	(0.57,	2.99)	0.00	(0.00, 0.01)	
Yes	573	6	1.0	577	6	1.0	0.9903	0.99	(0.32,	3.06)	0.99	(0.32,	3.10)	0.00	(-0.01, 0.01)	
Cause of Heart Failure																0.8008
Ischemic	944	10	1.1	983	13	1.3	0.5949	1.25	(0.55,	2.83)	1.25	(0.55,	2.87)	0.00	(-0.01, 0.01)	
Non-ischemic	919	6	0.7	880	6	0.7	0.9399	1.04	(0.34,	3.23)	1.04	(0.34,	3.25)	0.00	(-0.01, 0.01)	
Heart Failure Physiology																0.9187
LVEF <= 30% and NTproBNP < median	723	6	0.8	698	6	0.9	0.9512	1.04	(0.34,	3.20)	1.04	(0.33,	3.23)	0.00	(-0.01, 0.01)	
LVEF <= 30% and NTproBNP >= median	660	8	1.2	631	10	1.6	0.5681	1.31	(0.52,	3.29)	1.31	(0.51,	3.35)	0.00	(-0.01, 0.02)	
LVEF > 30%	473	2	0.4	526	2	0.4	0.9152	0.90	(0.13,	6.36)	0.90	(0.13,	6.41)	0.00	(-0.01, 0.01)	
Baseline use of MRA																0.1066
No	512	7	1.4	557	4	0.7	0.2935	0.53	(0.15,	1.78)	0.52	(0.15,	1.79)	-0.01	(-0.02, 0.01)	
Yes	1351	9	0.7	1306	15	1.1	0.1889	1.72	(0.76,	3.93)	1.73	(0.76,	3.97)	0.00	(0.00, 0.01)	
Baseline use of ARNi																0.5631
No	1476	11	0.7	1523	12	0.8	0.8935	1.06	(0.47,	2.39)	1.06	(0.47,	2.40)	0.00	(-0.01, 0.01)	
Yes	387	5	1.3	340	7	2.1	0.4181	1.59	(0.51,	4.97)	1.61	(0.50,	5.11)	0.01	(-0.01, 0.03)	

*** 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).
Subgroups will only be analysed if at least 10 events occurred in at least one category (both treatments combined).
For AEs on SOC and/or PT level, subgroup analyses are only shown if overall test for treatment is significant on 5% level (i.e. 95% CI for the risk ratio does not contain 1; if this is not calculable the p-value of Chi-square test is used).
MedDRA version: 23.0. * Chi-square test for treatment effect ** Breslow-Day test for homogeneity of odds ratios (treatment by subgroup interaction).

Table R.1.4.3: 2 Proportion of patients with serious adverse events of special interest and other specific AEs
- by user-defined AE category - overall population 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														0.9391
<=30	1390	14	1.0	1337	17	1.3	0.5151	1.26	(0.62, 2.55)	1.27	(0.62, 2.58)	0.00	(-0.01, 0.01)	
>30 to <=35	359	2	0.6	398	2	0.5	0.9176	0.90	(0.13, 6.37)	0.90	(0.13, 6.43)	0.00	(-0.01, 0.01)	
>35	114	0	0	128	0	0	0.9541	0.89	(0.02, 44.57)	0.89	(0.02, 45.27)	0.00	(-0.02, 0.02)	
Baseline NTproBNP														0.8638
< median	919	7	0.8	942	8	0.8	0.8327	1.11	(0.41, 3.06)	1.12	(0.40, 3.09)	0.00	(-0.01, 0.01)	
>= median	943	9	1.0	920	11	1.2	0.6134	1.25	(0.52, 3.01)	1.26	(0.52, 3.04)	0.00	(-0.01, 0.01)	

*** 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).
Subgroups will only be analysed if at least 10 events occurred in at least one category (both treatments combined).
For AEs on SOC and/or PT level, subgroup analyses are only shown if overall test for treatment is significant on 5% level (i.e. 95% CI for the risk ratio does not contain 1; if this is not calculable the p-value of Chi-square test is used).
MedDRA version: 23.0. * Chi-square test for treatment effect ** Breslow-Day test for homogeneity of odds ratios (treatment by subgroup interaction).

Table R.1.4.3: 2 Proportion of patients with serious adverse events of special interest and other specific AEs
- by user-defined AE category - overall population and by subgroup - TS
User-defined AE category: Pruritus (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	1863	0	0	1863	0	0	1.0000	1.00	(0.02, 50.37)	1.00	(0.02, 50.42)	0.00 (0.00, 0.00)	

*** 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).
Subgroups will only be analysed if at least 10 events occurred in at least one category (both treatments combined).
For AEs on SOC and/or PT level, subgroup analyses are only shown if overall test for treatment is significant on 5% level (i.e. 95% CI for the risk ratio does not contain 1; if this is not calculable the p-value of Chi-square test is used).
MedDRA version: 23.0. * Chi-square test for treatment effect ** Breslow-Day test for homogeneity of odds ratios (treatment by subgroup interaction).

Table R.1.4.3: 2 Proportion of patients with serious adverse events of special interest and other specific AEs
- by user-defined AE category - overall population and by subgroup - TS
User-defined AE category: Allergic skin reactions (BIcMQ)

Subgroup Category	Placebo N	Placebo n	Placebo %	Empa 10mg N	Empa 10mg n	Empa 10mg %	Empa 10mg vs Placebo p-value *	Risk ratio (95% CI)	Odds ratio (95% CI)	Risk diff. (95% CI)	p-value **
Overall	1863	0	0	1863	0	0	1.0000	1.00 (0.02, 50.37)	1.00 (0.02, 50.42)	0.00 (0.00, 0.00)	

*** 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).
Subgroups will only be analysed if at least 10 events occurred in at least one category (both treatments combined).
For AEs on SOC and/or PT level, subgroup analyses are only shown if overall test for treatment is significant on 5% level (i.e. 95% CI for the risk ratio does not contain 1; if this is not calculable the p-value of Chi-square test is used).
MedDRA version: 23.0. * Chi-square test for treatment effect ** Breslow-Day test for homogeneity of odds ratios (treatment by subgroup interaction).

Table R.1.4.3: 2 Proportion of patients with serious adverse events of special interest and other specific AEs
- by user-defined AE category - overall population 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	1863	0	0	1863	0	0	1.0000	1.00	(0.02, 50.37)	1.00	(0.02, 50.42)	0.00	(0.00, 0.00)	

*** 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).
Subgroups will only be analysed if at least 10 events occurred in at least one category (both treatments combined).
For AEs on SOC and/or PT level, subgroup analyses are only shown if overall test for treatment is significant on 5% level (i.e. 95% CI for the risk ratio does not contain 1; if this is not calculable the p-value of Chi-square test is used).
MedDRA version: 23.0. * Chi-square test for treatment effect ** Breslow-Day test for homogeneity of odds ratios (treatment by subgroup interaction).

Table R.1.4.3: 2 Proportion of patients with serious adverse events of special interest and other specific AEs
- by user-defined AE category - overall population 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 **
Overall	1863	0	0	1863	0	0	1.0000	1.00 (0.02, 50.37)	1.00 (0.02, 50.42)	0.00 (0.00, 0.00)	

*** 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).
Subgroups will only be analysed if at least 10 events occurred in at least one category (both treatments combined).
For AEs on SOC and/or PT level, subgroup analyses are only shown if overall test for treatment is significant on 5% level (i.e. 95% CI for the risk ratio does not contain 1; if this is not calculable the p-value of Chi-square test is used).
MedDRA version: 23.0. * Chi-square test for treatment effect ** Breslow-Day test for homogeneity of odds ratios (treatment by subgroup interaction).

Table R.1.4.3: 2 Proportion of patients with serious adverse events of special interest and other specific AEs
- by user-defined AE category - overall population 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	1863	0	0	1863	0	0	1.0000	1.00	(0.02, 50.37)	1.00	(0.02, 50.42)	0.00	(0.00, 0.00)	

*** 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).
Subgroups will only be analysed if at least 10 events occurred in at least one category (both treatments combined).
For AEs on SOC and/or PT level, subgroup analyses are only shown if overall test for treatment is significant on 5% level
(i.e. 95% CI for the risk ratio does not contain 1; if this is not calculable the p-value of Chi-square test is used).
MedDRA version: 23.0. * Chi-square test for treatment effect ** Breslow-Day test for homogeneity of odds ratios (treatment by subgroup interaction).

Table R.1.4.3: 2 Proportion of patients with serious adverse events of special interest and other specific AEs
- by user-defined AE category - overall population and by subgroup - TS
User-defined AE category: Angioedema (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	1863	3	0.2	1863	0	0	0.1334	0.14	(<0.01, 2.76)	0.14	(<0.01, 2.76)	0.00	(0.00, 0.00)	

*** 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).
Subgroups will only be analysed if at least 10 events occurred in at least one category (both treatments combined).
For AEs on SOC and/or PT level, subgroup analyses are only shown if overall test for treatment is significant on 5% level (i.e. 95% CI for the risk ratio does not contain 1; if this is not calculable the p-value of Chi-square test is used).
MedDRA version: 23.0. * Chi-square test for treatment effect ** Breslow-Day test for homogeneity of odds ratios (treatment by subgroup interaction).

Table R.1.4.3: 2 Proportion of patients with serious adverse events of special interest and other specific AEs
- by user-defined AE category - overall population 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	1863	8	0.4	1863	4	0.2	0.2475	0.50	(0.15, 1.66)	0.50	(0.15, 1.66)	0.00	(-0.01, 0.00)	
Baseline use of MRA														0.2224
No	512	0	0	557	1	0.2	0.5164	2.76	(0.11, 67.55)	2.76	(0.11, 67.97)	0.00	(0.00, 0.01)	
Yes	1351	8	0.6	1306	3	0.2	0.1458	0.39	(0.10, 1.46)	0.39	(0.10, 1.46)	0.00	(-0.01, 0.00)	
Baseline LVEF														0.8934
<=30	1390	7	0.5	1337	4	0.3	0.3998	0.59	(0.17, 2.02)	0.59	(0.17, 2.03)	0.00	(-0.01, 0.00)	
>30 to <=35	359	0	0	398	0	0	0.9589	0.90	(0.02, 45.35)	0.90	(0.02, 45.58)	0.00	(-0.01, 0.01)	
>35	114	1	0.9	128	0	0	0.4279	0.30	(0.01, 7.22)	0.29	(0.01, 7.30)	-0.01	(-0.03, 0.01)	

*** 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).
Subgroups will only be analysed if at least 10 events occurred in at least one category (both treatments combined).
For AEs on SOC and/or PT level, subgroup analyses are only shown if overall test for treatment is significant on 5% level (i.e. 95% CI for the risk ratio does not contain 1; if this is not calculable the p-value of Chi-square test is used).
MedDRA version: 23.0. * Chi-square test for treatment effect ** Breslow-Day test for homogeneity of odds ratios (treatment by subgroup interaction).

Table R.1.4.3: 3 Proportion of patients with severe adverse events of special interest and other specific AEs
- by user-defined AE category - overall population 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	1863	9	0.5	1863	5	0.3	0.2841	0.56	(0.19, 1.65)	0.55	(0.19, 1.66)	0.00	(-0.01,0.00)	
Sex														0.2549
Male	1410	6	0.4	1426	5	0.4	0.7483	0.82	(0.25, 2.69)	0.82	(0.25, 2.70)	0.00	(-0.01,0.00)	
Female	453	3	0.7	437	0	0	0.1422	0.15	(<0.01, 2.86)	0.15	(<0.01, 2.86)	-0.01	(-0.02,0.00)	
Age [years]														0.4806
< 65	739	2	0.3	675	0	0	0.2807	0.22	(0.01, 4.55)	0.22	(0.01, 4.56)	0.00	(-0.01,0.00)	
>= 65	1124	7	0.6	1188	5	0.4	0.4995	0.68	(0.22, 2.12)	0.67	(0.21, 2.13)	0.00	(-0.01,0.00)	
Baseline NYHA														0.4799
II	1399	7	0.5	1399	3	0.2	0.2051	0.43	(0.11, 1.65)	0.43	(0.11, 1.66)	0.00	(-0.01,0.00)	
III/IV	464	2	0.4	464	2	0.4	1.0000	1.00	(0.14, 7.07)	1.00	(0.14, 7.13)	0.00	(-0.01,0.01)	
Baseline BMI [kg/m²]														0.2339
<30	1299	8	0.6	1263	3	0.2	0.1431	0.39	(0.10, 1.45)	0.38	(0.10, 1.45)	0.00	(-0.01,0.00)	
>=30	564	1	0.2	600	2	0.3	0.5998	1.88	(0.17, 20.68)	1.88	(0.17, 20.82)	0.00	(0.00,0.01)	
Baseline eGFR (CKD-EPI) [mL/min/1.73m²]														0.1246
>=60	958	4	0.4	969	0	0	0.0712	0.11	(<0.01, 2.04)	0.11	(<0.01, 2.03)	0.00	(-0.01,0.00)	
<60	904	5	0.6	893	5	0.6	0.9845	1.01	(0.29, 3.48)	1.01	(0.29, 3.51)	0.00	(-0.01,0.01)	
History of HHF (in the last 12 months)														0.4850
No	1290	7	0.5	1286	3	0.2	0.2068	0.43	(0.11, 1.66)	0.43	(0.11, 1.66)	0.00	(-0.01,0.00)	
Yes	573	2	0.3	577	2	0.3	0.9944	0.99	(0.14, 7.03)	0.99	(0.14, 7.07)	0.00	(-0.01,0.01)	
Baseline use of MRA														0.3759
No	512	2	0.4	557	0	0	0.2186	0.18	(<0.01, 3.82)	0.18	(<0.01, 3.82)	0.00	(-0.01,0.00)	
Yes	1351	7	0.5	1306	5	0.4	0.6031	0.74	(0.24, 2.32)	0.74	(0.23, 2.33)	0.00	(-0.01,0.00)	

***Confirmed hypoglycaemic adverse events are defined as hypoglycaemic adverse events that had a glucose concentration <=70 mg/dL (3.9 mmol/L) or
Risk ratios and odds ratios with confidence intervals (CIs) are estimated by Cochran-Mantel-Haenszel method. For risk differences standard
Wald asymptotic confidence limits are calculated. A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied 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).
For AEs on SOC and/or PT level, subgroup analyses are only shown if overall test for treatment is significant on 5% level
(i.e. 95% CI for the risk ratio does not contain 1; if this is not calculable the p-value of Chi-square test is used).
MedDRA version: 23.0. * Chi-square test for treatment effect ** Breslow-Day test for homogeneity of odds ratios (treatment by subgroup interaction).

Table R.1.4.3: 3 Proportion of patients with severe adverse events of special interest and other specific AEs
- by user-defined AE category - overall population 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 use of ARNi												0.1824
No	1476	9	0.6	1523	4	0.3	0.1480	0.43 (0.13, 1.40)	0.43 (0.13, 1.40)	0.00	(-0.01,0.00)	
Yes	387	0	0	340	1	0.3	0.4231	3.41 (0.14, 83.52)	3.42 (0.14, 84.33)	0.00	(0.00,0.01)	
Baseline LVEF												0.5260
<=30	1390	7	0.5	1337	3	0.2	0.2279	0.45 (0.12, 1.72)	0.44 (0.11, 1.72)	0.00	(-0.01,0.00)	
>30 to <=35	359	0	0	398	1	0.3	0.5247	2.71 (0.11, 66.23)	2.71 (0.11, 66.81)	0.00	(0.00,0.01)	
>35	114	2	1.8	128	1	0.8	0.4946	0.45 (0.04, 4.85)	0.44 (0.04, 4.93)	-0.01	(-0.04,0.02)	
Baseline NTproBNP												0.6922
< median	919	1	0.1	942	0	0	0.4684	0.33 (0.01, 7.97)	0.32 (0.01, 7.98)	0.00	(0.00,0.00)	
>= median	943	8	0.8	920	5	0.5	0.4293	0.64 (0.21, 1.95)	0.64 (0.21, 1.96)	0.00	(-0.01,0.00)	

***Confirmed hypoglycaemic adverse events are defined as hypoglycaemic adverse events that had a glucose concentration <=70 mg/dL (3.9 mmol/L) or
Risk ratios and odds ratios with confidence intervals (CIs) are estimated by Cochran-Mantel-Haenszel method. For risk differences standard
Wald asymptotic confidence limits are calculated. A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied 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).
For AEs on SOC and/or PT level, subgroup analyses are only shown if overall test for treatment is significant on 5% level
(i.e. 95% CI for the risk ratio does not contain 1; if this is not calculable the p-value of Chi-square test is used).
MedDRA version: 23.0. * Chi-square test for treatment effect ** Breslow-Day test for homogeneity of odds ratios (treatment by subgroup interaction).

Table R.1.4.3: 3 Proportion of patients with severe adverse events of special interest and other specific AEs
- by user-defined AE category - overall population 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	1863	44	2.4	1863	29	1.6	0.0762	0.66 (0.41, 1.05)	0.65 (0.41, 1.05)	-0.01	(-0.02,0.00)	
Sex												0.7263
Male	1410	38	2.7	1426	26	1.8	0.1181	0.68 (0.41, 1.11)	0.67 (0.40, 1.11)	-0.01	(-0.02,0.00)	
Female	453	6	1.3	437	3	0.7	0.3416	0.52 (0.13, 2.06)	0.51 (0.13, 2.07)	-0.01	(-0.02,0.01)	
Age [years]												0.2528
< 65	739	14	1.9	675	12	1.8	0.8704	0.94 (0.44, 2.01)	0.94 (0.43, 2.04)	0.00	(-0.02,0.01)	
>= 65	1124	30	2.7	1188	17	1.4	0.0350	0.54 (0.30, 0.97)	0.53 (0.29, 0.97)	-0.01	(-0.02,0.00)	
Region												0.2072
North America	213	10	4.7	212	9	4.2	0.8226	0.90 (0.37, 2.18)	0.90 (0.36, 2.26)	0.00	(-0.04,0.03)	
Latin America	645	15	2.3	641	10	1.6	0.3201	0.67 (0.30, 1.48)	0.67 (0.30, 1.49)	-0.01	(-0.02,0.01)	
Europe	674	18	2.7	676	7	1.0	0.0259	0.39 (0.16, 0.92)	0.38 (0.16, 0.92)	-0.02	(-0.03,0.00)	
Asia	244	0	0	248	3	1.2	0.1363	6.89 (0.36,132.64)	6.97 (0.36,135.68)	0.01	(0.00,0.03)	
Other	87	1	1.1	86	0	0	0.4820	0.34 (0.01, 8.16)	0.33 (0.01, 8.30)	-0.01	(-0.04,0.02)	
OECD Member												0.4280
No	741	12	1.6	713	10	1.4	0.7348	0.87 (0.38, 1.99)	0.86 (0.37, 2.01)	0.00	(-0.01,0.01)	
Yes	1122	32	2.9	1150	19	1.7	0.0536	0.58 (0.33, 1.02)	0.57 (0.32, 1.02)	-0.01	(-0.02,0.00)	
Baseline NYHA												0.3208
II	1399	27	1.9	1399	21	1.5	0.3824	0.78 (0.44, 1.37)	0.77 (0.44, 1.38)	0.00	(-0.01,0.01)	
III/IV	464	17	3.7	464	8	1.7	0.0680	0.47 (0.21, 1.08)	0.46 (0.20, 1.08)	-0.02	(-0.04,0.00)	
Baseline Diabetes Status												0.0559
Diabetic	926	22	2.4	927	21	2.3	0.8746	0.95 (0.53, 1.72)	0.95 (0.52, 1.74)	0.00	(-0.01,0.01)	
Non-Diabetic	937	22	2.3	936	8	0.9	0.0101	0.36 (0.16, 0.81)	0.36 (0.16, 0.81)	-0.01	(-0.03,0.00)	
Baseline BMI [kg/m²]												0.9590
<30	1299	28	2.2	1263	18	1.4	0.1640	0.66 (0.37, 1.19)	0.66 (0.36, 1.19)	-0.01	(-0.02,0.00)	
>=30	564	16	2.8	600	11	1.8	0.2556	0.65 (0.30, 1.38)	0.64 (0.29, 1.39)	-0.01	(-0.03,0.01)	

***Confirmed hypoglycaemic adverse events are defined as hypoglycaemic adverse events that had a glucose concentration <=70 mg/dL (3.9 mmol/L) or
Risk ratios and odds ratios with confidence intervals (CIs) are estimated by Cochran-Mantel-Haenszel method. For risk differences standard
Wald asymptotic confidence limits are calculated. A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied 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).
For AEs on SOC and/or PT level, subgroup analyses are only shown if overall test for treatment is significant on 5% level
(i.e. 95% CI for the risk ratio does not contain 1; if this is not calculable the p-value of Chi-square test is used).
MedDRA version: 23.0. * Chi-square test for treatment effect ** Breslow-Day test for homogeneity of odds ratios (treatment by subgroup interaction).

Table R.1.4.3: 3 Proportion of patients with severe adverse events of special interest and other specific AEs
- by user-defined AE category - overall population 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 eGFR (CKD-EPI) [mL/min/1.73m²]												0.4731
>=60	958	13	1.4	969	11	1.1	0.6607	0.84 (0.38, 1.86)	0.83 (0.37, 1.87)	0.00	(-0.01,0.01)	
<60	904	31	3.4	893	18	2.0	0.0658	0.59 (0.33, 1.04)	0.58 (0.32, 1.04)	-0.01	(-0.03,0.00)	
History of HHF (in the last 12 months)												0.7607
No	1290	26	2.0	1286	16	1.2	0.1222	0.62 (0.33, 1.15)	0.61 (0.33, 1.15)	-0.01	(-0.02,0.00)	
Yes	573	18	3.1	577	13	2.3	0.3524	0.72 (0.35, 1.45)	0.71 (0.34, 1.46)	-0.01	(-0.03,0.01)	
Cause of Heart Failure												0.5827
Ischemic	944	19	2.0	983	15	1.5	0.4172	0.76 (0.39, 1.48)	0.75 (0.38, 1.49)	0.00	(-0.02,0.01)	
Non-ischemic	919	25	2.7	880	14	1.6	0.1001	0.58 (0.31, 1.12)	0.58 (0.30, 1.12)	-0.01	(-0.02,0.00)	
Heart Failure Physiology												0.9347
LVEF <= 30% and NTproBNP < median	723	10	1.4	698	7	1.0	0.5098	0.73 (0.28, 1.89)	0.72 (0.27, 1.91)	0.00	(-0.02,0.01)	
LVEF <= 30% and NTproBNP >= median	660	23	3.5	631	15	2.4	0.2392	0.68 (0.36, 1.30)	0.67 (0.35, 1.30)	-0.01	(-0.03,0.01)	
LVEF > 30%	473	11	2.3	526	7	1.3	0.2379	0.57 (0.22, 1.46)	0.57 (0.22, 1.47)	-0.01	(-0.03,0.01)	
Baseline use of MRA												0.7635
No	512	14	2.7	557	11	2.0	0.4117	0.72 (0.33, 1.58)	0.72 (0.32, 1.59)	-0.01	(-0.03,0.01)	
Yes	1351	30	2.2	1306	18	1.4	0.1032	0.62 (0.35, 1.11)	0.62 (0.34, 1.11)	-0.01	(-0.02,0.00)	
Baseline use of ARNi												0.0886
No	1476	31	2.1	1523	26	1.7	0.4306	0.81 (0.49, 1.36)	0.81 (0.48, 1.37)	0.00	(-0.01,0.01)	
Yes	387	13	3.4	340	3	0.9	0.0231	0.26 (0.08, 0.91)	0.26 (0.07, 0.91)	-0.02	(-0.05,0.00)	

***Confirmed hypoglycaemic adverse events are defined as hypoglycaemic adverse events that had a glucose concentration <=70 mg/dL (3.9 mmol/L) or
Risk ratios and odds ratios with confidence intervals (CIs) are estimated by Cochran-Mantel-Haenszel method. For risk differences standard
Wald asymptotic confidence limits are calculated. A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied 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).
For AEs on SOC and/or PT level, subgroup analyses are only shown if overall test for treatment is significant on 5% level
(i.e. 95% CI for the risk ratio does not contain 1; if this is not calculable the p-value of Chi-square test is used).
MedDRA version: 23.0. * Chi-square test for treatment effect ** Breslow-Day test for homogeneity of odds ratios (treatment by subgroup interaction).

Table R.1.4.3: 3 Proportion of patients with severe adverse events of special interest and other specific AEs
- by user-defined AE category - overall population 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												0.9103
<=30	1390	33	2.4	1337	22	1.6	0.1760	0.69 (0.41, 1.18)	0.69 (0.40, 1.19)	-0.01	(-0.02,0.00)	
>30 to <=35	359	7	1.9	398	4	1.0	0.2780	0.52 (0.15, 1.75)	0.51 (0.15, 1.76)	-0.01	(-0.03,0.01)	
>35	114	4	3.5	128	3	2.3	0.5893	0.67 (0.15, 2.92)	0.66 (0.14, 3.01)	-0.01	(-0.05,0.03)	
Baseline NTproBNP												0.7923
< median	919	13	1.4	942	8	0.8	0.2484	0.60 (0.25, 1.44)	0.60 (0.25, 1.45)	-0.01	(-0.02,0.00)	
>= median	943	31	3.3	920	21	2.3	0.1881	0.69 (0.40, 1.20)	0.69 (0.39, 1.20)	-0.01	(-0.02,0.00)	

***Confirmed hypoglycaemic adverse events are defined as hypoglycaemic adverse events that had a glucose concentration <=70 mg/dL (3.9 mmol/L) or
Risk ratios and odds ratios with confidence intervals (CIs) are estimated by Cochran-Mantel-Haenszel method. For risk differences standard
Wald asymptotic confidence limits are calculated. A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied 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).
For AEs on SOC and/or PT level, subgroup analyses are only shown if overall test for treatment is significant on 5% level
(i.e. 95% CI for the risk ratio does not contain 1; if this is not calculable the p-value of Chi-square test is used).
MedDRA version: 23.0. * Chi-square test for treatment effect ** Breslow-Day test for homogeneity of odds ratios (treatment by subgroup interaction).

Table R.1.4.3: 3 Proportion of patients with severe adverse events of special interest and other specific AEs
- by user-defined AE category - overall population 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	1863	3	0.2	1863	4	0.2	0.7052	1.33 (0.30, 5.95)	1.33 (0.30, 5.97)	0.00 (0.00,0.00)	

***Confirmed hypoglycaemic adverse events are defined as hypoglycaemic adverse events that had a glucose concentration <=70 mg/dL (3.9 mmol/L) or
Risk ratios and odds ratios with confidence intervals (CIs) are estimated by Cochran-Mantel-Haenszel method. For risk differences standard
Wald asymptotic confidence limits are calculated. A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied 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).
For AEs on SOC and/or PT level, subgroup analyses are only shown if overall test for treatment is significant on 5% level
(i.e. 95% CI for the risk ratio does not contain 1; if this is not calculable the p-value of Chi-square test is used).
MedDRA version: 23.0. * Chi-square test for treatment effect ** Breslow-Day test for homogeneity of odds ratios (treatment by subgroup interaction).

Table R.1.4.3: 3 Proportion of patients with severe adverse events of special interest and other specific AEs
- by user-defined AE category - overall population 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 **
Overall	1863	0	0	1863	0	0	1.0000	1.00 (0.02, 50.37)	1.00 (0.02, 50.42)	0.00 (0.00,0.00)	

***Confirmed hypoglycaemic adverse events are defined as hypoglycaemic adverse events that had a glucose concentration <=70 mg/dL (3.9 mmol/L) or
Risk ratios and odds ratios with confidence intervals (CIs) are estimated by Cochran-Mantel-Haenszel method. For risk differences standard
Wald asymptotic confidence limits are calculated. A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied 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).
For AEs on SOC and/or PT level, subgroup analyses are only shown if overall test for treatment is significant on 5% level
(i.e. 95% CI for the risk ratio does not contain 1; if this is not calculable the p-value of Chi-square test is used).
MedDRA version: 23.0. * Chi-square test for treatment effect ** Breslow-Day test for homogeneity of odds ratios (treatment by subgroup interaction).

Table R.1.4.3: 3 Proportion of patients with severe adverse events of special interest and other specific AEs
- by user-defined AE category - overall population and by subgroup - TS
User-defined AE category: AE leading to Lower limb amputation (investigator-defined)

Subgroup Category	Placebo N	Placebo n	Placebo %	Empa 10mg N	Empa 10mg n	Empa 10mg %	Empa 10mg vs Placebo p-value *	Risk ratio (95% CI)	Odds ratio (95% CI)	Risk diff. (95% CI)	p-value **
Overall	1863	3	0.2	1863	6	0.3	0.3167	2.00 (0.50, 7.98)	2.00 (0.50, 8.02)	0.00 (0.00,0.00)	

***Confirmed hypoglycaemic adverse events are defined as hypoglycaemic adverse events that had a glucose concentration <=70 mg/dL (3.9 mmol/L) or
Risk ratios and odds ratios with confidence intervals (CIs) are estimated by Cochran-Mantel-Haenszel method. For risk differences standard
Wald asymptotic confidence limits are calculated. A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied 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).
For AEs on SOC and/or PT level, subgroup analyses are only shown if overall test for treatment is significant on 5% level
(i.e. 95% CI for the risk ratio does not contain 1; if this is not calculable the p-value of Chi-square test is used).
MedDRA version: 23.0. * Chi-square test for treatment effect ** Breslow-Day test for homogeneity of odds ratios (treatment by subgroup interaction).

Table R.1.4.3: 3 Proportion of patients with severe adverse events of special interest and other specific AEs
- by user-defined AE category - overall population 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	1863	4	0.2	1863	6	0.3	0.5265	1.50 (0.42, 5.31)	1.50 (0.42, 5.33)	0.00 (0.00,0.00)	

***Confirmed hypoglycaemic adverse events are defined as hypoglycaemic adverse events that had a glucose concentration <=70 mg/dL (3.9 mmol/L) or
Risk ratios and odds ratios with confidence intervals (CIs) are estimated by Cochran-Mantel-Haenszel method. For risk differences standard
Wald asymptotic confidence limits are calculated. A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied 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).
For AEs on SOC and/or PT level, subgroup analyses are only shown if overall test for treatment is significant on 5% level
(i.e. 95% CI for the risk ratio does not contain 1; if this is not calculable the p-value of Chi-square test is used).
MedDRA version: 23.0. * Chi-square test for treatment effect ** Breslow-Day test for homogeneity of odds ratios (treatment by subgroup interaction).

Table R.1.4.3: 3 Proportion of patients with severe adverse events of special interest and other specific AEs - by user-defined AE category - overall population 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 **
Overall	1863	3	0.2	1863	7	0.4	0.2053	2.33 (0.60, 9.01)	2.34 (0.60, 9.06)	0.00 (0.00,0.01)	

***Confirmed hypoglycaemic adverse events are defined as hypoglycaemic adverse events that had a glucose concentration <=70 mg/dL (3.9 mmol/L) or
Risk ratios and odds ratios with confidence intervals (CIs) are estimated by Cochran-Mantel-Haenszel method. For risk differences standard
Wald asymptotic confidence limits are calculated. A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied 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).
For AEs on SOC and/or PT level, subgroup analyses are only shown if overall test for treatment is significant on 5% level
(i.e. 95% CI for the risk ratio does not contain 1; if this is not calculable the p-value of Chi-square test is used).
MedDRA version: 23.0. * Chi-square test for treatment effect ** Breslow-Day test for homogeneity of odds ratios (treatment by subgroup interaction).

Table R.1.4.3: 3 Proportion of patients with severe adverse events of special interest and other specific AEs - by user-defined AE category - overall population and by subgroup - TS
User-defined AE category: Complicated urinary tract infection (BIcMQ)

Subgroup Category	Placebo N	Placebo n	Placebo %	Empa 10mg N	Empa 10mg n	Empa 10mg %	Empa 10mg vs Placebo p-value *	Risk ratio (95% CI)	Odds ratio (95% CI)	Risk diff. (95% CI)	p-value **
Overall	1863	3	0.2	1863	6	0.3	0.3167	2.00 (0.50, 7.98)	2.00 (0.50, 8.02)	0.00 (0.00,0.00)	

***Confirmed hypoglycaemic adverse events are defined as hypoglycaemic adverse events that had a glucose concentration <=70 mg/dL (3.9 mmol/L) or
Risk ratios and odds ratios with confidence intervals (CIs) are estimated by Cochran-Mantel-Haenszel method. For risk differences standard
Wald asymptotic confidence limits are calculated. A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied 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).
For AEs on SOC and/or PT level, subgroup analyses are only shown if overall test for treatment is significant on 5% level
(i.e. 95% CI for the risk ratio does not contain 1; if this is not calculable the p-value of Chi-square test is used).
MedDRA version: 23.0. * Chi-square test for treatment effect ** Breslow-Day test for homogeneity of odds ratios (treatment by subgroup interaction).

Table R.1.4.3: 3 Proportion of patients with severe adverse events of special interest and other specific AEs
- by user-defined AE category - overall population 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 **
Overall	1863	0	0	1863	0	0	1.0000	1.00 (0.02, 50.37)	1.00 (0.02, 50.42)	0.00 (0.00,0.00)	

***Confirmed hypoglycaemic adverse events are defined as hypoglycaemic adverse events that had a glucose concentration <=70 mg/dL (3.9 mmol/L) or
Risk ratios and odds ratios with confidence intervals (CIs) are estimated by Cochran-Mantel-Haenszel method. For risk differences standard
Wald asymptotic confidence limits are calculated. A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied 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).
For AEs on SOC and/or PT level, subgroup analyses are only shown if overall test for treatment is significant on 5% level
(i.e. 95% CI for the risk ratio does not contain 1; if this is not calculable the p-value of Chi-square test is used).
MedDRA version: 23.0. * Chi-square test for treatment effect ** Breslow-Day test for homogeneity of odds ratios (treatment by subgroup interaction).

Table R.1.4.3: 3 Proportion of patients with severe adverse events of special interest and other specific AEs
- by user-defined AE category - overall population 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	1863	0	0	1863	0	0	1.0000	1.00 (0.02, 50.37)	1.00 (0.02, 50.42)	0.00 (0.00,0.00)	

***Confirmed hypoglycaemic adverse events are defined as hypoglycaemic adverse events that had a glucose concentration <=70 mg/dL (3.9 mmol/L) or
Risk ratios and odds ratios with confidence intervals (CIs) are estimated by Cochran-Mantel-Haenszel method. For risk differences standard
Wald asymptotic confidence limits are calculated. A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied 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).
For AEs on SOC and/or PT level, subgroup analyses are only shown if overall test for treatment is significant on 5% level
(i.e. 95% CI for the risk ratio does not contain 1; if this is not calculable the p-value of Chi-square test is used).
MedDRA version: 23.0. * Chi-square test for treatment effect ** Breslow-Day test for homogeneity of odds ratios (treatment by subgroup interaction).

Table R.1.4.3: 3 Proportion of patients with severe adverse events of special interest and other specific AEs
- by user-defined AE category - overall population and by subgroup - TS
User-defined AE category: Acute pyelonephritis (investigator-defined)

Subgroup Category	Placebo N	Placebo n	Placebo %	Empa 10mg N	Empa 10mg n	Empa 10mg %	Empa 10mg vs Placebo p-value *	Risk ratio (95% CI)	Odds ratio (95% CI)	Risk diff. (95% CI)	p-value **
Overall	1863	0	0	1863	1	0.1	0.4794	3.00 (0.12, 73.59)	3.00 (0.12, 73.73)	0.00 (0.00,0.00)	

***Confirmed hypoglycaemic adverse events are defined as hypoglycaemic adverse events that had a glucose concentration <=70 mg/dL (3.9 mmol/L) or
Risk ratios and odds ratios with confidence intervals (CIs) are estimated by Cochran-Mantel-Haenszel method. For risk differences standard
Wald asymptotic confidence limits are calculated. A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied 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).
For AEs on SOC and/or PT level, subgroup analyses are only shown if overall test for treatment is significant on 5% level
(i.e. 95% CI for the risk ratio does not contain 1; if this is not calculable the p-value of Chi-square test is used).
MedDRA version: 23.0. * Chi-square test for treatment effect ** Breslow-Day test for homogeneity of odds ratios (treatment by subgroup interaction).

Table R.1.4.3: 3 Proportion of patients with severe adverse events of special interest and other specific AEs
- by user-defined AE category - overall population and by subgroup - TS
User-defined AE category: Urosepsis (PT) or pyelonephritis (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 **
Overall	1863	0	0	1863	3	0.2	0.1334	7.00 (0.36,135.42)	7.01 (0.36,135.83)	0.00 (0.00,0.00)	

***Confirmed hypoglycaemic adverse events are defined as hypoglycaemic adverse events that had a glucose concentration <=70 mg/dL (3.9 mmol/L) or
Risk ratios and odds ratios with confidence intervals (CIs) are estimated by Cochran-Mantel-Haenszel method. For risk differences standard
Wald asymptotic confidence limits are calculated. A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied 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).
For AEs on SOC and/or PT level, subgroup analyses are only shown if overall test for treatment is significant on 5% level
(i.e. 95% CI for the risk ratio does not contain 1; if this is not calculable the p-value of Chi-square test is used).
MedDRA version: 23.0. * Chi-square test for treatment effect ** Breslow-Day test for homogeneity of odds ratios (treatment by subgroup interaction).

Table R.1.4.3: 3 Proportion of patients with severe adverse events of special interest and other specific AEs
- by user-defined AE category - overall population and by subgroup - TS
User-defined AE category: Sepsis (investigator-defined)

Subgroup Category	Placebo N	Placebo n	Placebo %	Empa 10mg N	Empa 10mg n	Empa 10mg %	Empa 10mg vs Placebo p-value *	Risk ratio (95% CI)	Odds ratio (95% CI)	Risk diff. (95% CI)	p-value **
Overall	1863	13	0.7	1863	26	1.4	0.0364	2.00 (1.03, 3.88)	2.01 (1.03, 3.93)	0.01 (0.00,0.01)	
Sex											0.2712
Male	1410	11	0.8	1426	18	1.3	0.2019	1.62 (0.77, 3.41)	1.63 (0.77, 3.45)	0.00 (0.00,0.01)	
Female	453	2	0.4	437	8	1.8	0.0493	4.15 (0.89, 19.42)	4.21 (0.89, 19.91)	0.01 (0.00,0.03)	
Age [years]											0.5914
< 65	739	5	0.7	675	7	1.0	0.4605	1.53 (0.49, 4.81)	1.54 (0.49, 4.87)	0.00 (-0.01,0.01)	
>= 65	1124	8	0.7	1188	19	1.6	0.0471	2.25 (0.99, 5.11)	2.27 (0.99, 5.20)	0.01 (0.00,0.02)	
Region											0.1391
North America	213	0	0	212	8	3.8	0.0069	17.08 (0.99,294.05)	17.75 (1.02,309.48)	0.04 (0.01,0.06)	
Latin America	645	5	0.8	641	11	1.7	0.1280	2.21 (0.77, 6.34)	2.23 (0.77, 6.47)	0.01 (0.00,0.02)	
Europe	674	8	1.2	676	6	0.9	0.5872	0.75 (0.26, 2.14)	0.75 (0.26, 2.16)	0.00 (-0.01,0.01)	
Asia	244	0	0	248	1	0.4	0.4857	2.95 (0.12, 72.11)	2.96 (0.12, 73.11)	0.00 (-0.01,0.02)	
Other	87	0	0	86	0	0	0.9954	1.01 (0.02, 50.41)	1.01 (0.02, 51.56)	0.00 (-0.02,0.02)	
OECD Member											0.4292
No	741	4	0.5	713	11	1.5	0.0585	2.86 (0.91, 8.93)	2.89 (0.92, 9.11)	0.01 (0.00,0.02)	
Yes	1122	9	0.8	1150	15	1.3	0.2417	1.63 (0.71, 3.70)	1.63 (0.71, 3.75)	0.01 (0.00,0.01)	
Baseline NYHA											0.4871
II	1399	7	0.5	1399	17	1.2	0.0404	2.43 (1.01, 5.84)	2.45 (1.01, 5.92)	0.01 (0.00,0.01)	
III/IV	464	6	1.3	464	9	1.9	0.4348	1.50 (0.54, 4.18)	1.51 (0.53, 4.28)	0.01 (-0.01,0.02)	
Baseline Diabetes Status											0.0643
Diabetic	926	5	0.5	927	18	1.9	0.0064	3.60 (1.34, 9.65)	3.65 (1.35, 9.87)	0.01 (0.00,0.02)	
Non-Diabetic	937	8	0.9	936	8	0.9	0.9983	1.00 (0.38, 2.66)	1.00 (0.37, 2.68)	0.00 (-0.01,0.01)	
Baseline BMI [kg/m²]											0.1344
<30	1299	5	0.4	1263	16	1.3	0.0133	3.29 (1.21, 8.96)	3.32 (1.21, 9.09)	0.01 (0.00,0.02)	
>=30	564	8	1.4	600	10	1.7	0.7316	1.18 (0.47, 2.96)	1.18 (0.46, 3.01)	0.00 (-0.01,0.02)	

***Confirmed hypoglycaemic adverse events are defined as hypoglycaemic adverse events that had a glucose concentration <=70 mg/dL (3.9 mmol/L) or
Risk ratios and odds ratios with confidence intervals (CIs) are estimated by Cochran-Mantel-Haenszel method. For risk differences standard
Wald asymptotic confidence limits are calculated. A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied 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).
For AEs on SOC and/or PT level, subgroup analyses are only shown if overall test for treatment is significant on 5% level
(i.e. 95% CI for the risk ratio does not contain 1; if this is not calculable the p-value of Chi-square test is used).
MedDRA version: 23.0. * Chi-square test for treatment effect ** Breslow-Day test for homogeneity of odds ratios (treatment by subgroup interaction).

Table R.1.4.3: 3 Proportion of patients with severe adverse events of special interest and other specific AEs
- by user-defined AE category - overall population 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 eGFR (CKD-EPI) [mL/min/1.73m²]											0.4350
>=60	958	5	0.5	969	7	0.7	0.5759	1.38 (0.44, 4.35)	1.39 (0.44, 4.39)	0.00 (-0.01,0.01)	
<60	904	8	0.9	893	19	2.1	0.0304	2.40 (1.06, 5.46)	2.43 (1.06, 5.59)	0.01 (0.00,0.02)	
History of HHF (in the last 12 months)											0.9913
No	1290	8	0.6	1286	16	1.2	0.0993	2.01 (0.86, 4.67)	2.02 (0.86, 4.73)	0.01 (0.00,0.01)	
Yes	573	5	0.9	577	10	1.7	0.1985	1.99 (0.68, 5.77)	2.00 (0.68, 5.90)	0.01 (0.00,0.02)	
Cause of Heart Failure											0.4198
Ischemic	944	8	0.8	983	13	1.3	0.3154	1.56 (0.65, 3.75)	1.57 (0.65, 3.80)	0.00 (0.00,0.01)	
Non-ischemic	919	5	0.5	880	13	1.5	0.0468	2.72 (0.97, 7.58)	2.74 (0.97, 7.72)	0.01 (0.00,0.02)	
Heart Failure Physiology											0.4299
LVEF <= 30% and NTproBNP < median	723	5	0.7	698	5	0.7	0.9555	1.04 (0.30, 3.56)	1.04 (0.30, 3.59)	0.00 (-0.01,0.01)	
LVEF <= 30% and NTproBNP >= median	660	6	0.9	631	12	1.9	0.1284	2.09 (0.79, 5.54)	2.11 (0.79, 5.66)	0.01 (0.00,0.02)	
LVEF > 30%	473	2	0.4	526	8	1.5	0.0817	3.60 (0.77, 16.85)	3.64 (0.77, 17.21)	0.01 (0.00,0.02)	
Baseline use of MRA											0.2632
No	512	2	0.4	557	9	1.6	0.0474	4.14 (0.90, 19.05)	4.19 (0.90, 19.47)	0.01 (0.00,0.02)	
Yes	1351	11	0.8	1306	17	1.3	0.2186	1.60 (0.75, 3.40)	1.61 (0.75, 3.44)	0.00 (0.00,0.01)	
Baseline use of ARNi											0.7614
No	1476	9	0.6	1523	20	1.3	0.0491	2.15 (0.98, 4.71)	2.17 (0.98, 4.78)	0.01 (0.00,0.01)	
Yes	387	4	1.0	340	6	1.8	0.3984	1.71 (0.49, 6.00)	1.72 (0.48, 6.15)	0.01 (-0.01,0.02)	

***Confirmed hypoglycaemic adverse events are defined as hypoglycaemic adverse events that had a glucose concentration <=70 mg/dL (3.9 mmol/L) or
Risk ratios and odds ratios with confidence intervals (CIs) are estimated by Cochran-Mantel-Haenszel method. For risk differences standard
Wald asymptotic confidence limits are calculated. A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied 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).
For AEs on SOC and/or PT level, subgroup analyses are only shown if overall test for treatment is significant on 5% level
(i.e. 95% CI for the risk ratio does not contain 1; if this is not calculable the p-value of Chi-square test is used).
MedDRA version: 23.0. * Chi-square test for treatment effect ** Breslow-Day test for homogeneity of odds ratios (treatment by subgroup interaction).

Table R.1.4.3: 3 Proportion of patients with severe adverse events of special interest and other specific AEs
- by user-defined AE category - overall population 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											0.7411
<=30	1390	11	0.8	1337	18	1.3	0.1579	1.70 (0.81, 3.59)	1.71 (0.80, 3.64)	0.01 (0.00,0.01)	
>30 to <=35	359	2	0.6	398	6	1.5	0.2016	2.71 (0.55, 13.32)	2.73 (0.55, 13.62)	0.01 (0.00,0.02)	
>35	114	0	0	128	2	1.6	0.2875	4.46 (0.22, 91.88)	4.53 (0.22, 95.26)	0.02 (-0.01,0.04)	
Baseline NTproBNP											0.5759
< median	919	5	0.5	942	8	0.8	0.4293	1.56 (0.51, 4.75)	1.57 (0.51, 4.80)	0.00 (0.00,0.01)	
>= median	943	8	0.8	920	18	2.0	0.0415	2.31 (1.01, 5.28)	2.33 (1.01, 5.39)	0.01 (0.00,0.02)	

***Confirmed hypoglycaemic adverse events are defined as hypoglycaemic adverse events that had a glucose concentration <=70 mg/dL (3.9 mmol/L) or
Risk ratios and odds ratios with confidence intervals (CIs) are estimated by Cochran-Mantel-Haenszel method. For risk differences standard
Wald asymptotic confidence limits are calculated. A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied 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).
For AEs on SOC and/or PT level, subgroup analyses are only shown if overall test for treatment is significant on 5% level
(i.e. 95% CI for the risk ratio does not contain 1; if this is not calculable the p-value of Chi-square test is used).
MedDRA version: 23.0. * Chi-square test for treatment effect ** Breslow-Day test for homogeneity of odds ratios (treatment by subgroup interaction).

Table R.1.4.3: 3 Proportion of patients with severe adverse events of special interest and other specific AEs
- by user-defined AE category - overall population 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 **
Overall	1863	1	0.1	1863	2	0.1	0.5635	2.00 (0.18, 22.04)	2.00 (0.18, 22.09)	0.00 (0.00,0.00)	

***Confirmed hypoglycaemic adverse events are defined as hypoglycaemic adverse events that had a glucose concentration <=70 mg/dL (3.9 mmol/L) or
Risk ratios and odds ratios with confidence intervals (CIs) are estimated by Cochran-Mantel-Haenszel method. For risk differences standard
Wald asymptotic confidence limits are calculated. A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied 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).
For AEs on SOC and/or PT level, subgroup analyses are only shown if overall test for treatment is significant on 5% level
(i.e. 95% CI for the risk ratio does not contain 1; if this is not calculable the p-value of Chi-square test is used).
MedDRA version: 23.0. * Chi-square test for treatment effect ** Breslow-Day test for homogeneity of odds ratios (treatment by subgroup interaction).

Table R.1.4.3: 3 Proportion of patients with severe adverse events of special interest and other specific AEs
- by user-defined AE category - overall population 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	1863	12	0.6	1863	24	1.3	0.0445	2.00 (1.00, 3.99)	2.01 (1.00, 4.04)	0.01 (0.00,0.01)	
Sex											0.5339
Male	1410	10	0.7	1426	18	1.3	0.1364	1.78 (0.82, 3.84)	1.79 (0.82, 3.89)	0.01 (0.00,0.01)	
Female	453	2	0.4	437	6	1.4	0.1410	3.11 (0.63, 15.32)	3.14 (0.63, 15.64)	0.01 (0.00,0.02)	
Age [years]											0.7331
< 65	739	4	0.5	675	6	0.9	0.4359	1.64 (0.47, 5.79)	1.65 (0.46, 5.87)	0.00 (-0.01,0.01)	
>= 65	1124	8	0.7	1188	18	1.5	0.0671	2.13 (0.93, 4.88)	2.15 (0.93, 4.96)	0.01 (0.00,0.02)	
Region											0.0874
North America	213	0	0	212	8	3.8	0.0069	17.08 (0.99,294.05)	17.75 (1.02,309.48)	0.04 (0.01,0.06)	
Latin America	645	4	0.6	641	10	1.6	0.1044	2.52 (0.79, 7.98)	2.54 (0.79, 8.14)	0.01 (0.00,0.02)	
Europe	674	8	1.2	676	5	0.7	0.4001	0.62 (0.20, 1.90)	0.62 (0.20, 1.91)	0.00 (-0.01,0.01)	
Asia	244	0	0	248	1	0.4	0.4857	2.95 (0.12, 72.11)	2.96 (0.12, 73.11)	0.00 (-0.01,0.02)	
Other	87	0	0	86	0	0	0.9954	1.01 (0.02, 50.41)	1.01 (0.02, 51.56)	0.00 (-0.02,0.02)	
OECD Member											0.2856
No	741	3	0.4	713	10	1.4	0.0434	3.46 (0.96, 12.54)	3.50 (0.96, 12.77)	0.01 (0.00,0.02)	
Yes	1122	9	0.8	1150	14	1.2	0.3229	1.52 (0.66, 3.49)	1.52 (0.66, 3.54)	0.00 (0.00,0.01)	
Baseline NYHA											0.3343
II	1399	6	0.4	1399	16	1.1	0.0323	2.67 (1.05, 6.79)	2.69 (1.05, 6.88)	0.01 (0.00,0.01)	
III/IV	464	6	1.3	464	8	1.7	0.5902	1.33 (0.47, 3.81)	1.34 (0.46, 3.89)	0.00 (-0.01,0.02)	
Baseline Diabetes Status											0.0152
Diabetic	926	4	0.4	927	18	1.9	0.0027	4.50 (1.53, 13.23)	4.56 (1.54, 13.54)	0.02 (0.01,0.02)	
Non-Diabetic	937	8	0.9	936	6	0.6	0.5930	0.75 (0.26, 2.16)	0.75 (0.26, 2.17)	0.00 (-0.01,0.01)	
Baseline BMI [kg/m²]											0.2843
<30	1299	5	0.4	1263	14	1.1	0.0328	2.88 (1.04, 7.97)	2.90 (1.04, 8.08)	0.01 (0.00,0.01)	
>=30	564	7	1.2	600	10	1.7	0.5453	1.34 (0.51, 3.50)	1.35 (0.51, 3.57)	0.00 (-0.01,0.02)	

***Confirmed hypoglycaemic adverse events are defined as hypoglycaemic adverse events that had a glucose concentration <=70 mg/dL (3.9 mmol/L) or
Risk ratios and odds ratios with confidence intervals (CIs) are estimated by Cochran-Mantel-Haenszel method. For risk differences standard
Wald asymptotic confidence limits are calculated. A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied 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).
For AEs on SOC and/or PT level, subgroup analyses are only shown if overall test for treatment is significant on 5% level
(i.e. 95% CI for the risk ratio does not contain 1; if this is not calculable the p-value of Chi-square test is used).
MedDRA version: 23.0. * Chi-square test for treatment effect ** Breslow-Day test for homogeneity of odds ratios (treatment by subgroup interaction).

Table R.1.4.3: 3 Proportion of patients with severe adverse events of special interest and other specific AEs
- by user-defined AE category - overall population 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 eGFR (CKD-EPI) [mL/min/1.73m²]											0.5705
>=60	958	4	0.4	969	6	0.6	0.5379	1.48 (0.42, 5.24)	1.49 (0.42, 5.28)	0.00 (0.00,0.01)	
<60	904	8	0.9	893	18	2.0	0.0448	2.28 (1.00, 5.21)	2.30 (1.00, 5.33)	0.01 (0.00,0.02)	
History of HHF (in the last 12 months)											0.7998
No	1290	7	0.5	1286	15	1.2	0.0854	2.15 (0.88, 5.25)	2.16 (0.88, 5.32)	0.01 (0.00,0.01)	
Yes	573	5	0.9	577	9	1.6	0.2880	1.79 (0.60, 5.30)	1.80 (0.60, 5.40)	0.01 (-0.01,0.02)	
Cause of Heart Failure											0.7226
Ischemic	944	7	0.7	983	13	1.3	0.2084	1.78 (0.71, 4.45)	1.79 (0.71, 4.52)	0.01 (0.00,0.01)	
Non-ischemic	919	5	0.5	880	11	1.3	0.1109	2.30 (0.80, 6.59)	2.31 (0.80, 6.69)	0.01 (0.00,0.02)	
Heart Failure Physiology											0.4716
LVEF <= 30% and NTproBNP < median	723	5	0.7	698	5	0.7	0.9555	1.04 (0.30, 3.56)	1.04 (0.30, 3.59)	0.00 (-0.01,0.01)	
LVEF <= 30% and NTproBNP >= median	660	5	0.8	631	11	1.7	0.1096	2.30 (0.80, 6.59)	2.32 (0.80, 6.73)	0.01 (0.00,0.02)	
LVEF > 30%	473	2	0.4	526	7	1.3	0.1294	3.15 (0.66, 15.08)	3.18 (0.66, 15.37)	0.01 (0.00,0.02)	
Baseline use of MRA											0.2533
No	512	2	0.4	557	9	1.6	0.0474	4.14 (0.90, 19.05)	4.19 (0.90, 19.47)	0.01 (0.00,0.02)	
Yes	1351	10	0.7	1306	15	1.1	0.2757	1.55 (0.70, 3.44)	1.56 (0.70, 3.48)	0.00 (0.00,0.01)	
Baseline use of ARNi											0.9288
No	1476	9	0.6	1523	19	1.2	0.0694	2.05 (0.93, 4.51)	2.06 (0.93, 4.57)	0.01 (0.00,0.01)	
Yes	387	3	0.8	340	5	1.5	0.3698	1.90 (0.46, 7.88)	1.91 (0.45, 8.05)	0.01 (-0.01,0.02)	

***Confirmed hypoglycaemic adverse events are defined as hypoglycaemic adverse events that had a glucose concentration <=70 mg/dL (3.9 mmol/L) or
Risk ratios and odds ratios with confidence intervals (CIs) are estimated by Cochran-Mantel-Haenszel method. For risk differences standard
Wald asymptotic confidence limits are calculated. A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied 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).
For AEs on SOC and/or PT level, subgroup analyses are only shown if overall test for treatment is significant on 5% level
(i.e. 95% CI for the risk ratio does not contain 1; if this is not calculable the p-value of Chi-square test is used).
MedDRA version: 23.0. * Chi-square test for treatment effect ** Breslow-Day test for homogeneity of odds ratios (treatment by subgroup interaction).

Table R.1.4.3: 3 Proportion of patients with severe adverse events of special interest and other specific AEs
- by user-defined AE category - overall population 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											0.8764
<=30	1390	10	0.7	1337	17	1.3	0.1455	1.77 (0.81, 3.85)	1.78 (0.81, 3.90)	0.01 (0.00,0.01)	
>30 to <=35	359	2	0.6	398	6	1.5	0.2016	2.71 (0.55, 13.32)	2.73 (0.55, 13.62)	0.01 (0.00,0.02)	
>35	114	0	0	128	1	0.8	0.5290	2.67 (0.11, 65.00)	2.69 (0.11, 66.79)	0.01 (-0.01,0.03)	
Baseline NTproBNP											0.5712
< median	919	5	0.5	942	8	0.8	0.4293	1.56 (0.51, 4.75)	1.57 (0.51, 4.80)	0.00 (0.00,0.01)	
>= median	943	7	0.7	920	16	1.7	0.0514	2.34 (0.97, 5.67)	2.37 (0.97, 5.78)	0.01 (0.00,0.02)	

***Confirmed hypoglycaemic adverse events are defined as hypoglycaemic adverse events that had a glucose concentration <=70 mg/dL (3.9 mmol/L) or
Risk ratios and odds ratios with confidence intervals (CIs) are estimated by Cochran-Mantel-Haenszel method. For risk differences standard
Wald asymptotic confidence limits are calculated. A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied 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).
For AEs on SOC and/or PT level, subgroup analyses are only shown if overall test for treatment is significant on 5% level
(i.e. 95% CI for the risk ratio does not contain 1; if this is not calculable the p-value of Chi-square test is used).
MedDRA version: 23.0. * Chi-square test for treatment effect ** Breslow-Day test for homogeneity of odds ratios (treatment by subgroup interaction).

Table R.1.4.3: 3 Proportion of patients with severe adverse events of special interest and other specific AEs
- by user-defined AE category - overall population 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	1863	9	0.5	1863	12	0.6	0.5115	1.33 (0.56, 3.16)	1.34 (0.56, 3.18)	0.00 (0.00,0.01)		
Sex												0.9422
Male	1410	5	0.4	1426	7	0.5	0.5762	1.38 (0.44, 4.35)	1.39 (0.44, 4.38)	0.00 (0.00,0.01)		
Female	453	4	0.9	437	5	1.1	0.6971	1.30 (0.35, 4.79)	1.30 (0.35, 4.87)	0.00 (-0.01,0.02)		
Age [years]												0.2135
< 65	739	4	0.5	675	2	0.3	0.4790	0.55 (0.10, 2.98)	0.55 (0.10, 2.99)	0.00 (-0.01,0.00)		
>= 65	1124	5	0.4	1188	10	0.8	0.2348	1.89 (0.65, 5.52)	1.90 (0.65, 5.58)	0.00 (0.00,0.01)		
Region												0.6405
North America	213	2	0.9	212	0	0	0.2482	0.20 (<0.01, 4.16)	0.20 (<0.01, 4.17)	-0.01 (-0.03,0.01)		
Latin America	645	2	0.3	641	3	0.5	0.6491	1.51 (0.25, 9.00)	1.51 (0.25, 9.08)	0.00 (-0.01,0.01)		
Europe	674	4	0.6	676	8	1.2	0.2482	1.99 (0.60, 6.59)	2.01 (0.60, 6.69)	0.01 (0.00,0.02)		
Asia	244	1	0.4	248	1	0.4	0.9908	0.98 (0.06, 15.64)	0.98 (0.06, 15.82)	0.00 (-0.01,0.01)		
Other	87	0	0	86	0	0	0.9954	1.01 (0.02, 50.41)	1.01 (0.02, 51.56)	0.00 (-0.02,0.02)		
OECD Member												0.8352
No	741	2	0.3	713	3	0.4	0.6233	1.56 (0.26, 9.30)	1.56 (0.26, 9.37)	0.00 (0.00,0.01)		
Yes	1122	7	0.6	1150	9	0.8	0.6510	1.25 (0.47, 3.36)	1.26 (0.47, 3.39)	0.00 (-0.01,0.01)		
Baseline NYHA												0.8022
II	1399	4	0.3	1399	6	0.4	0.5263	1.50 (0.42, 5.30)	1.50 (0.42, 5.33)	0.00 (0.00,0.01)		
III/IV	464	5	1.1	464	6	1.3	0.7617	1.20 (0.37, 3.90)	1.20 (0.36, 3.97)	0.00 (-0.01,0.02)		
Baseline Diabetes Status												0.5254
Diabetic	926	5	0.5	927	5	0.5	0.9986	1.00 (0.29, 3.44)	1.00 (0.29, 3.46)	0.00 (-0.01,0.01)		
Non-Diabetic	937	4	0.4	936	7	0.7	0.3634	1.75 (0.51, 5.96)	1.76 (0.51, 6.02)	0.00 (0.00,0.01)		
Baseline BMI [kg/m²]												0.6395
<30	1299	7	0.5	1263	8	0.6	0.7538	1.18 (0.43, 3.23)	1.18 (0.43, 3.25)	0.00 (0.00,0.01)		
>=30	564	2	0.4	600	4	0.7	0.4575	1.88 (0.35, 10.22)	1.89 (0.34, 10.34)	0.00 (-0.01,0.01)		

***Confirmed hypoglycaemic adverse events are defined as hypoglycaemic adverse events that had a glucose concentration <=70 mg/dL (3.9 mmol/L) or
Risk ratios and odds ratios with confidence intervals (CIs) are estimated by Cochran-Mantel-Haenszel method. For risk differences standard
Wald asymptotic confidence limits are calculated. A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied 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).
For AEs on SOC and/or PT level, subgroup analyses are only shown if overall test for treatment is significant on 5% level
(i.e. 95% CI for the risk ratio does not contain 1; if this is not calculable the p-value of Chi-square test is used).
MedDRA version: 23.0. * Chi-square test for treatment effect ** Breslow-Day test for homogeneity of odds ratios (treatment by subgroup interaction).

Table R.1.4.3: 3 Proportion of patients with severe adverse events of special interest and other specific AEs
- by user-defined AE category - overall population 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 eGFR (CKD-EPI) [mL/min/1.73m²]											0.0920
>=60	958	7	0.7	969	5	0.5	0.5492	0.71 (0.22, 2.22)	0.70 (0.22, 2.23)	0.00 (-0.01,0.00)	
<60	904	2	0.2	893	7	0.8	0.0912	3.54 (0.74, 17.01)	3.56 (0.74, 17.20)	0.01 (0.00,0.01)	
History of HHF (in the last 12 months)											0.7040
No	1290	6	0.5	1286	7	0.5	0.7767	1.17 (0.39, 3.47)	1.17 (0.39, 3.49)	0.00 (0.00,0.01)	
Yes	573	3	0.5	577	5	0.9	0.4841	1.66 (0.40, 6.89)	1.66 (0.40, 6.98)	0.00 (-0.01,0.01)	
Cause of Heart Failure											0.2175
Ischemic	944	6	0.6	983	5	0.5	0.7116	0.80 (0.25, 2.61)	0.80 (0.24, 2.63)	0.00 (-0.01,0.01)	
Non-ischemic	919	3	0.3	880	7	0.8	0.1811	2.44 (0.63, 9.39)	2.45 (0.63, 9.50)	0.00 (0.00,0.01)	
Heart Failure Physiology											0.5762
LVEF <= 30% and NTproBNP < median	723	2	0.3	698	2	0.3	0.9719	1.04 (0.15, 7.33)	1.04 (0.15, 7.37)	0.00 (-0.01,0.01)	
LVEF <= 30% and NTproBNP >= median	660	6	0.9	631	6	1.0	0.9377	1.05 (0.34, 3.23)	1.05 (0.34, 3.26)	0.00 (-0.01,0.01)	
LVEF > 30%	473	1	0.2	526	4	0.8	0.2195	3.60 (0.40, 32.07)	3.62 (0.40, 32.47)	0.01 (0.00,0.01)	
Baseline use of MRA											0.2400
No	512	2	0.4	557	6	1.1	0.1932	2.76 (0.56, 13.60)	2.78 (0.56, 13.82)	0.01 (0.00,0.02)	
Yes	1351	7	0.5	1306	6	0.5	0.8283	0.89 (0.30, 2.63)	0.89 (0.30, 2.64)	0.00 (-0.01,0.00)	
Baseline use of ARNi											0.8600
No	1476	7	0.5	1523	10	0.7	0.5061	1.38 (0.53, 3.63)	1.39 (0.53, 3.65)	0.00 (0.00,0.01)	
Yes	387	2	0.5	340	2	0.6	0.8966	1.14 (0.16, 8.04)	1.14 (0.16, 8.13)	0.00 (-0.01,0.01)	

***Confirmed hypoglycaemic adverse events are defined as hypoglycaemic adverse events that had a glucose concentration <=70 mg/dL (3.9 mmol/L) or
Risk ratios and odds ratios with confidence intervals (CIs) are estimated by Cochran-Mantel-Haenszel method. For risk differences standard
Wald asymptotic confidence limits are calculated. A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied 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).
For AEs on SOC and/or PT level, subgroup analyses are only shown if overall test for treatment is significant on 5% level
(i.e. 95% CI for the risk ratio does not contain 1; if this is not calculable the p-value of Chi-square test is used).
MedDRA version: 23.0. * Chi-square test for treatment effect ** Breslow-Day test for homogeneity of odds ratios (treatment by subgroup interaction).

Table R.1.4.3: 3 Proportion of patients with severe adverse events of special interest and other specific AEs
- by user-defined AE category - overall population 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											0.6597
<=30	1390	8	0.6	1337	8	0.6	0.9378	1.04 (0.39, 2.76)	1.04 (0.39, 2.78)	0.00 (-0.01,0.01)	
>30 to <=35	359	1	0.3	398	3	0.8	0.3678	2.71 (0.28, 25.90)	2.72 (0.28, 26.26)	0.00 (-0.01,0.01)	
>35	114	0	0	128	1	0.8	0.5290	2.67 (0.11, 65.00)	2.69 (0.11, 66.79)	0.01 (-0.01,0.03)	
Baseline NTproBNP											0.3762
< median	919	2	0.2	942	5	0.5	0.2699	2.44 (0.47, 12.54)	2.45 (0.47, 12.64)	0.00 (0.00,0.01)	
>= median	943	7	0.7	920	7	0.8	0.9630	1.03 (0.36, 2.91)	1.03 (0.36, 2.93)	0.00 (-0.01,0.01)	

***Confirmed hypoglycaemic adverse events are defined as hypoglycaemic adverse events that had a glucose concentration <=70 mg/dL (3.9 mmol/L) or
Risk ratios and odds ratios with confidence intervals (CIs) are estimated by Cochran-Mantel-Haenszel method. For risk differences standard
Wald asymptotic confidence limits are calculated. A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied 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).
For AEs on SOC and/or PT level, subgroup analyses are only shown if overall test for treatment is significant on 5% level
(i.e. 95% CI for the risk ratio does not contain 1; if this is not calculable the p-value of Chi-square test is used).
MedDRA version: 23.0. * Chi-square test for treatment effect ** Breslow-Day test for homogeneity of odds ratios (treatment by subgroup interaction).

Table R.1.4.3: 3 Proportion of patients with severe adverse events of special interest and other specific AEs - by user-defined AE category - overall population 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 **
Overall	1863	3	0.2	1863	4	0.2	0.7052	1.33 (0.30, 5.95)	1.33 (0.30, 5.97)	0.00 (0.00,0.00)	

***Confirmed hypoglycaemic adverse events are defined as hypoglycaemic adverse events that had a glucose concentration <=70 mg/dL (3.9 mmol/L) or
Risk ratios and odds ratios with confidence intervals (CIs) are estimated by Cochran-Mantel-Haenszel method. For risk differences standard
Wald asymptotic confidence limits are calculated. A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied 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).
For AEs on SOC and/or PT level, subgroup analyses are only shown if overall test for treatment is significant on 5% level
(i.e. 95% CI for the risk ratio does not contain 1; if this is not calculable the p-value of Chi-square test is used).
MedDRA version: 23.0. * Chi-square test for treatment effect ** Breslow-Day test for homogeneity of odds ratios (treatment by subgroup interaction).

Table R.1.4.3: 3 Proportion of patients with severe adverse events of special interest and other specific AEs
- by user-defined AE category - overall population 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	1863	16	0.9	1863	16	0.9	1.0000	1.00 (0.50, 1.99)	1.00 (0.50, 2.01)	0.00	(-0.01,0.01)	
Sex												0.6278
Male	1410	13	0.9	1426	12	0.8	0.8187	0.91 (0.42, 1.99)	0.91 (0.41, 2.01)	0.00	(-0.01,0.01)	
Female	453	3	0.7	437	4	0.9	0.6692	1.38 (0.31, 6.14)	1.39 (0.31, 6.23)	0.00	(-0.01,0.01)	
Age [years]												0.5733
< 65	739	7	0.9	675	8	1.2	0.6626	1.25 (0.46, 3.43)	1.25 (0.45, 3.48)	0.00	(-0.01,0.01)	
>= 65	1124	9	0.8	1188	8	0.7	0.7202	0.84 (0.33, 2.17)	0.84 (0.32, 2.18)	0.00	(-0.01,0.01)	
Region												0.3981
North America	213	6	2.8	212	4	1.9	0.5271	0.67 (0.19, 2.34)	0.66 (0.18, 2.39)	-0.01	(-0.04,0.02)	
Latin America	645	4	0.6	641	7	1.1	0.3582	1.76 (0.52, 5.99)	1.77 (0.52, 6.07)	0.00	(-0.01,0.01)	
Europe	674	3	0.4	676	5	0.7	0.4808	1.66 (0.40, 6.93)	1.67 (0.40, 7.00)	0.00	(-0.01,0.01)	
Asia	244	3	1.2	248	0	0	0.1279	0.14 (<0.01, 2.71)	0.14 (<0.01, 2.70)	-0.01	(-0.03,0.00)	
Other	87	0	0	86	0	0	0.9954	1.01 (0.02, 50.41)	1.01 (0.02, 51.56)	0.00	(-0.02,0.02)	
OECD Member												0.6529
No	741	6	0.8	713	7	1.0	0.7275	1.21 (0.41, 3.59)	1.21 (0.41, 3.63)	0.00	(-0.01,0.01)	
Yes	1122	10	0.9	1150	9	0.8	0.7761	0.88 (0.36, 2.15)	0.88 (0.36, 2.17)	0.00	(-0.01,0.01)	
Baseline NYHA												0.2617
II	1399	9	0.6	1399	12	0.9	0.5111	1.33 (0.56, 3.15)	1.34 (0.56, 3.18)	0.00	(0.00,0.01)	
III/IV	464	7	1.5	464	4	0.9	0.3629	0.57 (0.17, 1.94)	0.57 (0.17, 1.95)	-0.01	(-0.02,0.01)	
Baseline Diabetes Status												0.2845
Diabetic	926	10	1.1	927	7	0.8	0.4634	0.70 (0.27, 1.83)	0.70 (0.26, 1.84)	0.00	(-0.01,0.01)	
Non-Diabetic	937	6	0.6	936	9	1.0	0.4355	1.50 (0.54, 4.20)	1.51 (0.53, 4.25)	0.00	(0.00,0.01)	
Baseline BMI [kg/m²]												0.1635
<30	1299	11	0.8	1263	14	1.1	0.5006	1.31 (0.60, 2.87)	1.31 (0.59, 2.90)	0.00	(-0.01,0.01)	
>=30	564	5	0.9	600	2	0.3	0.2225	0.38 (0.07, 1.93)	0.37 (0.07, 1.94)	-0.01	(-0.01,0.00)	

***Confirmed hypoglycaemic adverse events are defined as hypoglycaemic adverse events that had a glucose concentration <=70 mg/dL (3.9 mmol/L) or
Risk ratios and odds ratios with confidence intervals (CIs) are estimated by Cochran-Mantel-Haenszel method. For risk differences standard
Wald asymptotic confidence limits are calculated. A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied 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).
For AEs on SOC and/or PT level, subgroup analyses are only shown if overall test for treatment is significant on 5% level
(i.e. 95% CI for the risk ratio does not contain 1; if this is not calculable the p-value of Chi-square test is used).
MedDRA version: 23.0. * Chi-square test for treatment effect ** Breslow-Day test for homogeneity of odds ratios (treatment by subgroup interaction).

Table R.1.4.3: 3 Proportion of patients with severe adverse events of special interest and other specific AEs
- by user-defined AE category - overall population 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 eGFR (CKD-EPI) [mL/min/1.73m²]											0.9732
>=60	958	8	0.8	969	8	0.8	0.9817	0.99 (0.37, 2.62)	0.99 (0.37, 2.64)	0.00 (-0.01,0.01)	
<60	904	8	0.9	893	8	0.9	0.9804	1.01 (0.38, 2.69)	1.01 (0.38, 2.71)	0.00 (-0.01,0.01)	
History of HHF (in the last 12 months)											0.2563
No	1290	9	0.7	1286	12	0.9	0.5064	1.34 (0.57, 3.16)	1.34 (0.56, 3.19)	0.00 (0.00,0.01)	
Yes	573	7	1.2	577	4	0.7	0.3573	0.57 (0.17, 1.93)	0.56 (0.16, 1.94)	-0.01 (-0.02,0.01)	
Cause of Heart Failure											0.8127
Ischemic	944	8	0.8	983	9	0.9	0.8730	1.08 (0.42, 2.79)	1.08 (0.42, 2.81)	0.00 (-0.01,0.01)	
Non-ischemic	919	8	0.9	880	7	0.8	0.8611	0.91 (0.33, 2.51)	0.91 (0.33, 2.53)	0.00 (-0.01,0.01)	
Heart Failure Physiology											0.1061
LVEF <= 30% and NTproBNP < median	723	4	0.6	698	7	1.0	0.3337	1.81 (0.53, 6.16)	1.82 (0.53, 6.25)	0.00 (0.00,0.01)	
LVEF <= 30% and NTproBNP >= median	660	8	1.2	631	2	0.3	0.0667	0.26 (0.06, 1.23)	0.26 (0.05, 1.23)	-0.01 (-0.02,0.00)	
LVEF > 30%	473	4	0.8	526	6	1.1	0.6400	1.35 (0.38, 4.75)	1.35 (0.38, 4.82)	0.00 (-0.01,0.02)	
Baseline use of MRA											0.8845
No	512	4	0.8	557	4	0.7	0.9048	0.92 (0.23, 3.66)	0.92 (0.23, 3.69)	0.00 (-0.01,0.01)	
Yes	1351	12	0.9	1306	12	0.9	0.9336	1.03 (0.47, 2.29)	1.03 (0.46, 2.31)	0.00 (-0.01,0.01)	
Baseline use of ARNi											0.0976
No	1476	8	0.5	1523	13	0.9	0.3063	1.57 (0.65, 3.79)	1.58 (0.65, 3.82)	0.00 (0.00,0.01)	
Yes	387	8	2.1	340	3	0.9	0.1916	0.43 (0.11, 1.60)	0.42 (0.11, 1.60)	-0.01 (-0.03,0.01)	

***Confirmed hypoglycaemic adverse events are defined as hypoglycaemic adverse events that had a glucose concentration <=70 mg/dL (3.9 mmol/L) or
Risk ratios and odds ratios with confidence intervals (CIs) are estimated by Cochran-Mantel-Haenszel method. For risk differences standard
Wald asymptotic confidence limits are calculated. A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied 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).
For AEs on SOC and/or PT level, subgroup analyses are only shown if overall test for treatment is significant on 5% level
(i.e. 95% CI for the risk ratio does not contain 1; if this is not calculable the p-value of Chi-square test is used).
MedDRA version: 23.0. * Chi-square test for treatment effect ** Breslow-Day test for homogeneity of odds ratios (treatment by subgroup interaction).

Table R.1.4.3: 3 Proportion of patients with severe adverse events of special interest and other specific AEs
- by user-defined AE category - overall population 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												0.4805
<=30	1390	12	0.9	1337	10	0.7	0.7364	0.87 (0.38, 2.00)	0.87 (0.37, 2.01)	0.00	(-0.01,0.01)	
>30 to <=35	359	3	0.8	398	6	1.5	0.3944	1.80 (0.45, 7.16)	1.82 (0.45, 7.32)	0.01	(-0.01,0.02)	
>35	114	1	0.9	128	0	0	0.4279	0.30 (0.01, 7.22)	0.29 (0.01, 7.30)	-0.01	(-0.03,0.01)	
Baseline NTproBNP												0.5182
< median	919	6	0.7	942	8	0.8	0.6240	1.30 (0.45, 3.73)	1.30 (0.45, 3.77)	0.00	(-0.01,0.01)	
>= median	943	10	1.1	920	8	0.9	0.6737	0.82 (0.33, 2.07)	0.82 (0.32, 2.08)	0.00	(-0.01,0.01)	

***Confirmed hypoglycaemic adverse events are defined as hypoglycaemic adverse events that had a glucose concentration <=70 mg/dL (3.9 mmol/L) or
Risk ratios and odds ratios with confidence intervals (CIs) are estimated by Cochran-Mantel-Haenszel method. For risk differences standard
Wald asymptotic confidence limits are calculated. A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied 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).
For AEs on SOC and/or PT level, subgroup analyses are only shown if overall test for treatment is significant on 5% level
(i.e. 95% CI for the risk ratio does not contain 1; if this is not calculable the p-value of Chi-square test is used).
MedDRA version: 23.0. * Chi-square test for treatment effect ** Breslow-Day test for homogeneity of odds ratios (treatment by subgroup interaction).

Table R.1.4.3: 3 Proportion of patients with severe adverse events of special interest and other specific AEs
- by user-defined AE category - overall population 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	1863	15	0.8	1863	14	0.8	0.8521	0.93 (0.45, 1.93)	0.93 (0.45, 1.94)	0.00	(-0.01,0.01)	
Sex												0.5511
Male	1410	12	0.9	1426	10	0.7	0.6494	0.82 (0.36, 1.90)	0.82 (0.35, 1.91)	0.00	(-0.01,0.00)	
Female	453	3	0.7	437	4	0.9	0.6692	1.38 (0.31, 6.14)	1.39 (0.31, 6.23)	0.00	(-0.01,0.01)	
Age [years]												0.7060
< 65	739	7	0.9	675	7	1.0	0.8647	1.09 (0.39, 3.11)	1.10 (0.38, 3.14)	0.00	(-0.01,0.01)	
>= 65	1124	8	0.7	1188	7	0.6	0.7138	0.83 (0.30, 2.28)	0.83 (0.30, 2.29)	0.00	(-0.01,0.01)	
Region												0.5657
North America	213	5	2.3	212	4	1.9	0.7416	0.80 (0.22, 2.95)	0.80 (0.21, 3.02)	0.00	(-0.03,0.02)	
Latin America	645	4	0.6	641	6	0.9	0.5191	1.51 (0.43, 5.32)	1.51 (0.43, 5.39)	0.00	(-0.01,0.01)	
Europe	674	3	0.4	676	4	0.6	0.7076	1.33 (0.30, 5.92)	1.33 (0.30, 5.97)	0.00	(-0.01,0.01)	
Asia	244	3	1.2	248	0	0	0.1279	0.14 (<0.01, 2.71)	0.14 (<0.01, 2.70)	-0.01	(-0.03,0.00)	
Other	87	0	0	86	0	0	0.9954	1.01 (0.02, 50.41)	1.01 (0.02, 51.56)	0.00	(-0.02,0.02)	
OECD Member												0.8097
No	741	6	0.8	713	6	0.8	0.9466	1.04 (0.34, 3.21)	1.04 (0.33, 3.24)	0.00	(-0.01,0.01)	
Yes	1122	9	0.8	1150	8	0.7	0.7684	0.87 (0.34, 2.24)	0.87 (0.33, 2.25)	0.00	(-0.01,0.01)	
Baseline NYHA												0.3130
II	1399	8	0.6	1399	10	0.7	0.6363	1.25 (0.49, 3.16)	1.25 (0.49, 3.18)	0.00	(0.00,0.01)	
III/IV	464	7	1.5	464	4	0.9	0.3629	0.57 (0.17, 1.94)	0.57 (0.17, 1.95)	-0.01	(-0.02,0.01)	
Baseline Diabetes Status												0.3525
Diabetic	926	9	1.0	927	6	0.6	0.4355	0.67 (0.24, 1.86)	0.66 (0.24, 1.87)	0.00	(-0.01,0.00)	
Non-Diabetic	937	6	0.6	936	8	0.9	0.5902	1.33 (0.46, 3.83)	1.34 (0.46, 3.87)	0.00	(-0.01,0.01)	
Baseline BMI [kg/m²]												0.3561
<30	1299	11	0.8	1263	12	1.0	0.7816	1.12 (0.50, 2.53)	1.12 (0.49, 2.55)	0.00	(-0.01,0.01)	
>=30	564	4	0.7	600	2	0.3	0.3708	0.47 (0.09, 2.56)	0.47 (0.09, 2.57)	0.00	(-0.01,0.00)	

***Confirmed hypoglycaemic adverse events are defined as hypoglycaemic adverse events that had a glucose concentration <=70 mg/dL (3.9 mmol/L) or
Risk ratios and odds ratios with confidence intervals (CIs) are estimated by Cochran-Mantel-Haenszel method. For risk differences standard
Wald asymptotic confidence limits are calculated. A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied 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).
For AEs on SOC and/or PT level, subgroup analyses are only shown if overall test for treatment is significant on 5% level
(i.e. 95% CI for the risk ratio does not contain 1; if this is not calculable the p-value of Chi-square test is used).
MedDRA version: 23.0. * Chi-square test for treatment effect ** Breslow-Day test for homogeneity of odds ratios (treatment by subgroup interaction).

Table R.1.4.3: 3 Proportion of patients with severe adverse events of special interest and other specific AEs
- by user-defined AE category - overall population 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 eGFR (CKD-EPI) [mL/min/1.73m²]												0.8320
>=60	958	8	0.8	969	7	0.7	0.7784	0.87 (0.31, 2.38)	0.86 (0.31, 2.39)	0.00	(-0.01,0.01)	
<60	904	7	0.8	893	7	0.8	0.9817	1.01 (0.36, 2.87)	1.01 (0.35, 2.90)	0.00	(-0.01,0.01)	
History of HHF (in the last 12 months)												0.2726
No	1290	9	0.7	1286	11	0.9	0.6484	1.23 (0.51, 2.95)	1.23 (0.51, 2.97)	0.00	(-0.01,0.01)	
Yes	573	6	1.0	577	3	0.5	0.3104	0.50 (0.12, 1.98)	0.49 (0.12, 1.98)	-0.01	(-0.02,0.00)	
Cause of Heart Failure												0.9249
Ischemic	944	8	0.8	983	8	0.8	0.9352	0.96 (0.36, 2.55)	0.96 (0.36, 2.57)	0.00	(-0.01,0.01)	
Non-ischemic	919	7	0.8	880	6	0.7	0.8415	0.90 (0.30, 2.65)	0.89 (0.30, 2.67)	0.00	(-0.01,0.01)	
Heart Failure Physiology												0.0776
LVEF <= 30% and NTproBNP < median	723	4	0.6	698	7	1.0	0.3337	1.81 (0.53, 6.16)	1.82 (0.53, 6.25)	0.00	(0.00,0.01)	
LVEF <= 30% and NTproBNP >= median	660	7	1.1	631	1	0.2	0.0390	0.15 (0.02, 1.21)	0.15 (0.02, 1.21)	-0.01	(-0.02,0.00)	
LVEF > 30%	473	4	0.8	526	5	1.0	0.8609	1.12 (0.30, 4.16)	1.13 (0.30, 4.22)	0.00	(-0.01,0.01)	
Baseline use of MRA												0.9781
No	512	4	0.8	557	4	0.7	0.9048	0.92 (0.23, 3.66)	0.92 (0.23, 3.69)	0.00	(-0.01,0.01)	
Yes	1351	11	0.8	1306	10	0.8	0.8877	0.94 (0.40, 2.21)	0.94 (0.40, 2.22)	0.00	(-0.01,0.01)	
Baseline use of ARNi												0.0897
No	1476	8	0.5	1523	12	0.8	0.4081	1.45 (0.60, 3.55)	1.46 (0.59, 3.58)	0.00	(0.00,0.01)	
Yes	387	7	1.8	340	2	0.6	0.1375	0.33 (0.07, 1.55)	0.32 (0.07, 1.56)	-0.01	(-0.03,0.00)	

***Confirmed hypoglycaemic adverse events are defined as hypoglycaemic adverse events that had a glucose concentration <=70 mg/dL (3.9 mmol/L) or
Risk ratios and odds ratios with confidence intervals (CIs) are estimated by Cochran-Mantel-Haenszel method. For risk differences standard
Wald asymptotic confidence limits are calculated. A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied 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).
For AEs on SOC and/or PT level, subgroup analyses are only shown if overall test for treatment is significant on 5% level
(i.e. 95% CI for the risk ratio does not contain 1; if this is not calculable the p-value of Chi-square test is used).
MedDRA version: 23.0. * Chi-square test for treatment effect ** Breslow-Day test for homogeneity of odds ratios (treatment by subgroup interaction).

Table R.1.4.3: 3 Proportion of patients with severe adverse events of special interest and other specific AEs
- by user-defined AE category - overall population 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												0.5967
<=30	1390	11	0.8	1337	9	0.7	0.7176	0.85 (0.35, 2.05)	0.85 (0.35, 2.06)	0.00	(-0.01,0.01)	
>30 to <=35	359	3	0.8	398	5	1.3	0.5720	1.50 (0.36, 6.25)	1.51 (0.36, 6.36)	0.00	(-0.01,0.02)	
>35	114	1	0.9	128	0	0	0.4279	0.30 (0.01, 7.22)	0.29 (0.01, 7.30)	-0.01	(-0.03,0.01)	
Baseline NTproBNP												0.3897
< median	919	6	0.7	942	8	0.8	0.6240	1.30 (0.45, 3.73)	1.30 (0.45, 3.77)	0.00	(-0.01,0.01)	
>= median	943	9	1.0	920	6	0.7	0.4655	0.68 (0.24, 1.91)	0.68 (0.24, 1.92)	0.00	(-0.01,0.01)	

***Confirmed hypoglycaemic adverse events are defined as hypoglycaemic adverse events that had a glucose concentration <=70 mg/dL (3.9 mmol/L) or
Risk ratios and odds ratios with confidence intervals (CIs) are estimated by Cochran-Mantel-Haenszel method. For risk differences standard
Wald asymptotic confidence limits are calculated. A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied 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).
For AEs on SOC and/or PT level, subgroup analyses are only shown if overall test for treatment is significant on 5% level
(i.e. 95% CI for the risk ratio does not contain 1; if this is not calculable the p-value of Chi-square test is used).
MedDRA version: 23.0. * Chi-square test for treatment effect ** Breslow-Day test for homogeneity of odds ratios (treatment by subgroup interaction).

Table R.1.4.3: 3 Proportion of patients with severe adverse events of special interest and other specific AEs
- by user-defined AE category - overall population 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	1863	9	0.5	1863	8	0.4	0.8079	0.89 (0.34, 2.30)	0.89 (0.34, 2.31)	0.00 (0.00,0.00)	
Sex											0.0605
Male	1410	9	0.6	1426	5	0.4	0.2744	0.55 (0.18, 1.64)	0.55 (0.18, 1.64)	0.00 (-0.01,0.00)	
Female	453	0	0	437	3	0.7	0.1237	7.26 (0.38,140.06)	7.31 (0.38,141.86)	0.01 (0.00,0.02)	
OECD Member											0.4523
No	741	2	0.3	713	3	0.4	0.6233	1.56 (0.26, 9.30)	1.56 (0.26, 9.37)	0.00 (0.00,0.01)	
Yes	1122	7	0.6	1150	5	0.4	0.5341	0.70 (0.22, 2.19)	0.70 (0.22, 2.20)	0.00 (-0.01,0.00)	
Baseline NYHA											0.7705
II	1399	5	0.4	1399	5	0.4	1.0000	1.00 (0.29, 3.45)	1.00 (0.29, 3.46)	0.00 (0.00,0.00)	
III/IV	464	4	0.9	464	3	0.6	0.7044	0.75 (0.17, 3.33)	0.75 (0.17, 3.36)	0.00 (-0.01,0.01)	
Baseline BMI [kg/m²]											0.9551
<30	1299	7	0.5	1263	6	0.5	0.8202	0.88 (0.30, 2.62)	0.88 (0.30, 2.63)	0.00 (-0.01,0.00)	
>=30	564	2	0.4	600	2	0.3	0.9506	0.94 (0.13, 6.65)	0.94 (0.13, 6.69)	0.00 (-0.01,0.01)	
History of HHF (in the last 12 months)											0.3957
No	1290	5	0.4	1286	6	0.5	0.7586	1.20 (0.37, 3.93)	1.20 (0.37, 3.96)	0.00 (0.00,0.01)	
Yes	573	4	0.7	577	2	0.3	0.4081	0.50 (0.09, 2.70)	0.49 (0.09, 2.71)	0.00 (-0.01,0.00)	
Cause of Heart Failure											0.4490
Ischemic	944	5	0.5	983	6	0.6	0.8141	1.15 (0.35, 3.76)	1.15 (0.35, 3.79)	0.00 (-0.01,0.01)	
Non-ischemic	919	4	0.4	880	2	0.2	0.4444	0.52 (0.10, 2.84)	0.52 (0.10, 2.85)	0.00 (-0.01,0.00)	
Baseline use of MRA											0.9747
No	512	2	0.4	557	2	0.4	0.9327	0.92 (0.13, 6.50)	0.92 (0.13, 6.55)	0.00 (-0.01,0.01)	
Yes	1351	7	0.5	1306	6	0.5	0.8283	0.89 (0.30, 2.63)	0.89 (0.30, 2.64)	0.00 (-0.01,0.00)	

***Confirmed hypoglycaemic adverse events are defined as hypoglycaemic adverse events that had a glucose concentration <=70 mg/dL (3.9 mmol/L) or
Risk ratios and odds ratios with confidence intervals (CIs) are estimated by Cochran-Mantel-Haenszel method. For risk differences standard
Wald asymptotic confidence limits are calculated. A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied 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).
For AEs on SOC and/or PT level, subgroup analyses are only shown if overall test for treatment is significant on 5% level
(i.e. 95% CI for the risk ratio does not contain 1; if this is not calculable the p-value of Chi-square test is used).
MedDRA version: 23.0. * Chi-square test for treatment effect ** Breslow-Day test for homogeneity of odds ratios (treatment by subgroup interaction).

Table R.1.4.3: 3 Proportion of patients with severe adverse events of special interest and other specific AEs
- by user-defined AE category - overall population 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 use of ARNi												0.8199
No	1476	6	0.4	1523	6	0.4	0.9566	0.97 (0.31, 3.00)	0.97 (0.31, 3.01)	0.00	(0.00,0.00)	
Yes	387	3	0.8	340	2	0.6	0.7609	0.76 (0.13, 4.51)	0.76 (0.13, 4.56)	0.00	(-0.01,0.01)	
Baseline LVEF												0.8154
<=30	1390	8	0.6	1337	6	0.4	0.6433	0.78 (0.27, 2.24)	0.78 (0.27, 2.25)	0.00	(-0.01,0.00)	
>30 to <=35	359	1	0.3	398	2	0.5	0.6243	1.80 (0.16, 19.81)	1.81 (0.16, 20.02)	0.00	(-0.01,0.01)	
>35	114	0	0	128	0	0	0.9541	0.89 (0.02, 44.57)	0.89 (0.02, 45.27)	0.00	(-0.02,0.02)	
Baseline NTproBNP												0.5167
< median	919	3	0.3	942	4	0.4	0.7294	1.30 (0.29, 5.80)	1.30 (0.29, 5.83)	0.00	(0.00,0.01)	
>= median	943	6	0.6	920	4	0.4	0.5518	0.68 (0.19, 2.41)	0.68 (0.19, 2.42)	0.00	(-0.01,0.00)	

***Confirmed hypoglycaemic adverse events are defined as hypoglycaemic adverse events that had a glucose concentration <=70 mg/dL (3.9 mmol/L) or
Risk ratios and odds ratios with confidence intervals (CIs) are estimated by Cochran-Mantel-Haenszel method. For risk differences standard
Wald asymptotic confidence limits are calculated. A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied 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).
For AEs on SOC and/or PT level, subgroup analyses are only shown if overall test for treatment is significant on 5% level
(i.e. 95% CI for the risk ratio does not contain 1; if this is not calculable the p-value of Chi-square test is used).
MedDRA version: 23.0. * Chi-square test for treatment effect ** Breslow-Day test for homogeneity of odds ratios (treatment by subgroup interaction).

Table R.1.4.3: 3 Proportion of patients with severe adverse events of special interest and other specific AEs
- by user-defined AE category - overall population and by subgroup - TS
User-defined AE category: Pruritus (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	1863	0	0	1863	1	0.1	0.4794	3.00 (0.12, 73.59)	3.00 (0.12, 73.73)	0.00 (0.00,0.00)	

***Confirmed hypoglycaemic adverse events are defined as hypoglycaemic adverse events that had a glucose concentration <=70 mg/dL (3.9 mmol/L) or
Risk ratios and odds ratios with confidence intervals (CIs) are estimated by Cochran-Mantel-Haenszel method. For risk differences standard
Wald asymptotic confidence limits are calculated. A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied 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).
For AEs on SOC and/or PT level, subgroup analyses are only shown if overall test for treatment is significant on 5% level
(i.e. 95% CI for the risk ratio does not contain 1; if this is not calculable the p-value of Chi-square test is used).
MedDRA version: 23.0. * Chi-square test for treatment effect ** Breslow-Day test for homogeneity of odds ratios (treatment by subgroup interaction).

Table R.1.4.3: 3 Proportion of patients with severe adverse events of special interest and other specific AEs
- by user-defined AE category - overall population 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	1863	0	0	1863	1	0.1	0.4794	3.00 (0.12, 73.59)	3.00 (0.12, 73.73)	0.00 (0.00,0.00)	

***Confirmed hypoglycaemic adverse events are defined as hypoglycaemic adverse events that had a glucose concentration <=70 mg/dL (3.9 mmol/L) or
Risk ratios and odds ratios with confidence intervals (CIs) are estimated by Cochran-Mantel-Haenszel method. For risk differences standard
Wald asymptotic confidence limits are calculated. A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied 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).
For AEs on SOC and/or PT level, subgroup analyses are only shown if overall test for treatment is significant on 5% level
(i.e. 95% CI for the risk ratio does not contain 1; if this is not calculable the p-value of Chi-square test is used).
MedDRA version: 23.0. * Chi-square test for treatment effect ** Breslow-Day test for homogeneity of odds ratios (treatment by subgroup interaction).

Table R.1.4.3: 3 Proportion of patients with severe adverse events of special interest and other specific AEs
- by user-defined AE category - overall population and by subgroup - TS
User-defined AE category: Increased urination (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 **
Overall	1863	0	0	1863	0	0	1.0000	1.00 (0.02, 50.37)	1.00 (0.02, 50.42)	0.00 (0.00,0.00)	

***Confirmed hypoglycaemic adverse events are defined as hypoglycaemic adverse events that had a glucose concentration <=70 mg/dL (3.9 mmol/L) or
Risk ratios and odds ratios with confidence intervals (CIs) are estimated by Cochran-Mantel-Haenszel method. For risk differences standard
Wald asymptotic confidence limits are calculated. A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied 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).
For AEs on SOC and/or PT level, subgroup analyses are only shown if overall test for treatment is significant on 5% level
(i.e. 95% CI for the risk ratio does not contain 1; if this is not calculable the p-value of Chi-square test is used).
MedDRA version: 23.0. * Chi-square test for treatment effect ** Breslow-Day test for homogeneity of odds ratios (treatment by subgroup interaction).

Table R.1.4.3: 3 Proportion of patients with severe adverse events of special interest and other specific AEs
- by user-defined AE category - overall population 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	1863	0	0	1863	0	0	1.0000	1.00 (0.02, 50.37)	1.00 (0.02, 50.42)	0.00 (0.00,0.00)	

***Confirmed hypoglycaemic adverse events are defined as hypoglycaemic adverse events that had a glucose concentration <=70 mg/dL (3.9 mmol/L) or
Risk ratios and odds ratios with confidence intervals (CIs) are estimated by Cochran-Mantel-Haenszel method. For risk differences standard
Wald asymptotic confidence limits are calculated. A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied 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).
For AEs on SOC and/or PT level, subgroup analyses are only shown if overall test for treatment is significant on 5% level
(i.e. 95% CI for the risk ratio does not contain 1; if this is not calculable the p-value of Chi-square test is used).
MedDRA version: 23.0. * Chi-square test for treatment effect ** Breslow-Day test for homogeneity of odds ratios (treatment by subgroup interaction).

Table R.1.4.3: 3 Proportion of patients with severe adverse events of special interest and other specific AEs
- by user-defined AE category - overall population and by subgroup - TS
User-defined AE category: Serum lipids increased (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 **
Overall	1863	3	0.2	1863	0	0	0.1334	0.14 (<0.01, 2.76)	0.14 (<0.01, 2.76)	0.00 (0.00,0.00)	

***Confirmed hypoglycaemic adverse events are defined as hypoglycaemic adverse events that had a glucose concentration <=70 mg/dL (3.9 mmol/L) or
Risk ratios and odds ratios with confidence intervals (CIs) are estimated by Cochran-Mantel-Haenszel method. For risk differences standard
Wald asymptotic confidence limits are calculated. A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied 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).
For AEs on SOC and/or PT level, subgroup analyses are only shown if overall test for treatment is significant on 5% level
(i.e. 95% CI for the risk ratio does not contain 1; if this is not calculable the p-value of Chi-square test is used).
MedDRA version: 23.0. * Chi-square test for treatment effect ** Breslow-Day test for homogeneity of odds ratios (treatment by subgroup interaction).

Table R.1.4.3: 3 Proportion of patients with severe adverse events of special interest and other specific AEs
- by user-defined AE category - overall population and by subgroup - TS
User-defined AE category: Angioedema (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	1863	1	0.1	1863	0	0	0.4794	0.33 (0.01, 8.18)	0.33 (0.01, 8.18)	0.00 (0.00,0.00)	

***Confirmed hypoglycaemic adverse events are defined as hypoglycaemic adverse events that had a glucose concentration <=70 mg/dL (3.9 mmol/L) or
Risk ratios and odds ratios with confidence intervals (CIs) are estimated by Cochran-Mantel-Haenszel method. For risk differences standard
Wald asymptotic confidence limits are calculated. A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied 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).
For AEs on SOC and/or PT level, subgroup analyses are only shown if overall test for treatment is significant on 5% level
(i.e. 95% CI for the risk ratio does not contain 1; if this is not calculable the p-value of Chi-square test is used).
MedDRA version: 23.0. * Chi-square test for treatment effect ** Breslow-Day test for homogeneity of odds ratios (treatment by subgroup interaction).

Table R.1.4.3: 3 Proportion of patients with severe adverse events of special interest and other specific AEs
- by user-defined AE category - overall population and by subgroup - TS
User-defined AE category: Hypersensitivity reactions (narrow SMQ)

Subgroup Category	Placebo N	Placebo n	Placebo %	Empa 10mg N	Empa 10mg n	Empa 10mg %	Empa 10mg vs Placebo p-value *	Risk ratio (95% CI)	Odds ratio (95% CI)	Risk diff. (95% CI)	p-value **
Overall	1863	3	0.2	1863	2	0.1	0.6545	0.67 (0.11, 3.99)	0.67 (0.11, 3.99)	0.00 (0.00,0.00)	

***Confirmed hypoglycaemic adverse events are defined as hypoglycaemic adverse events that had a glucose concentration <=70 mg/dL (3.9 mmol/L) or
Risk ratios and odds ratios with confidence intervals (CIs) are estimated by Cochran-Mantel-Haenszel method. For risk differences standard
Wald asymptotic confidence limits are calculated. A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied 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).
For AEs on SOC and/or PT level, subgroup analyses are only shown if overall test for treatment is significant on 5% level
(i.e. 95% CI for the risk ratio does not contain 1; if this is not calculable the p-value of Chi-square test is used).
MedDRA version: 23.0. * Chi-square test for treatment effect ** Breslow-Day test for homogeneity of odds ratios (treatment by subgroup interaction).

R.1.4.4

Table R.1.4.4: 1 Proportion of patients with any adverse events occurring 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 **
Overall	1863	697	37.4	1863	571	30.6	<0.0001	0.82 (0.75, 0.90)	0.74 (0.65, 0.85)	-0.07 (-0.10,-0.04)	
Sex											0.8548
Male	1410	533	37.8	1426	444	31.1	0.0002	0.82 (0.74, 0.91)	0.74 (0.64, 0.87)	-0.07 (-0.10,-0.03)	
Female	453	164	36.2	437	127	29.1	0.0232	0.80 (0.66, 0.97)	0.72 (0.54, 0.96)	-0.07 (-0.13,-0.01)	
Age [years]											0.2900
< 65	739	281	38.0	675	197	29.2	0.0004	0.77 (0.66, 0.89)	0.67 (0.54, 0.84)	-0.09 (-0.14,-0.04)	
>= 65	1124	416	37.0	1188	374	31.5	0.0051	0.85 (0.76, 0.95)	0.78 (0.66, 0.93)	-0.06 (-0.09,-0.02)	
Region											0.2600
North America	213	90	42.3	212	82	38.7	0.4529	0.92 (0.73, 1.15)	0.86 (0.59, 1.27)	-0.04 (-0.13, 0.06)	
Latin America	645	219	34.0	641	181	28.2	0.0268	0.83 (0.71, 0.98)	0.77 (0.60, 0.97)	-0.06 (-0.11,-0.01)	
Europe	674	258	38.3	676	222	32.8	0.0369	0.86 (0.74, 0.99)	0.79 (0.63, 0.99)	-0.05 (-0.11, 0.00)	
Asia	244	112	45.9	248	76	30.6	0.0005	0.67 (0.53, 0.84)	0.52 (0.36, 0.75)	-0.15 (-0.24,-0.07)	
Other	87	18	20.7	86	10	11.6	0.1057	0.56 (0.28, 1.15)	0.50 (0.22, 1.17)	-0.09 (-0.20, 0.02)	
OECD Member											0.3953
No	741	260	35.1	713	192	26.9	0.0008	0.77 (0.66, 0.90)	0.68 (0.54, 0.85)	-0.08 (-0.13,-0.03)	
Yes	1122	437	38.9	1150	379	33.0	0.0029	0.85 (0.76, 0.94)	0.77 (0.65, 0.91)	-0.06 (-0.10,-0.02)	
Baseline NYHA											0.0074
II	1399	486	34.7	1399	361	25.8	<0.0001	0.74 (0.66, 0.83)	0.65 (0.56, 0.77)	-0.09 (-0.12,-0.06)	
III/IV	464	211	45.5	464	210	45.3	0.9474	1.00 (0.86, 1.15)	0.99 (0.77, 1.28)	0.00 (-0.07, 0.06)	
Baseline Diabetes Status											0.2534
Diabetic	926	368	39.7	927	288	31.1	<0.0001	0.78 (0.69, 0.89)	0.68 (0.56, 0.83)	-0.09 (-0.13,-0.04)	
Non-Diabetic	937	329	35.1	936	283	30.2	0.0244	0.86 (0.76, 0.98)	0.80 (0.66, 0.97)	-0.05 (-0.09,-0.01)	
Baseline BMI [kg/m²]											0.1646
<30	1299	486	37.4	1263	369	29.2	<0.0001	0.78 (0.70, 0.87)	0.69 (0.59, 0.81)	-0.08 (-0.12,-0.05)	
>=30	564	211	37.4	600	202	33.7	0.1820	0.90 (0.77, 1.05)	0.85 (0.67, 1.08)	-0.04 (-0.09, 0.02)	

Risk ratios and odds ratios with confidence intervals (CIs) are estimated by Cochran-Mantel-Haenszel method. For risk differences standard Wald asymptotic confidence limits are calculated. A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied 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).
For AEs on SOC and/or PT level, subgroup analyses are only shown if overall test for treatment is significant on 5% level (i.e. 95% CI for the risk ratio does not contain 1; if this is not calculable the p-value of Chi-square test is used).
MedDRA version: 23.0. * Chi-square test for treatment effect ** Breslow-Day test for homogeneity of odds ratios (treatment by subgroup interaction).

Table R.1.4.4: 1 Proportion of patients with any adverse events occurring 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 eGFR (CKD-EPI) [mL/min/1.73m²]											0.0469
>=60	958	345	36.0	969	258	26.6	<0.0001	0.74 (0.65, 0.85)	0.64 (0.53, 0.78)	-0.09 (-0.14,-0.05)	
<60	904	351	38.8	893	313	35.1	0.0972	0.90 (0.80, 1.02)	0.85 (0.70, 1.03)	-0.04 (-0.08, 0.01)	
History of HHF (in the last 12 months)											0.0152
No	1290	472	36.6	1286	353	27.4	<0.0001	0.75 (0.67, 0.84)	0.66 (0.55, 0.77)	-0.09 (-0.13,-0.06)	
Yes	573	225	39.3	577	218	37.8	0.6048	0.96 (0.83, 1.11)	0.94 (0.74, 1.19)	-0.01 (-0.07, 0.04)	
Cause of Heart Failure											0.1167
Ischemic	944	359	38.0	983	328	33.4	0.0327	0.88 (0.78, 0.99)	0.82 (0.68, 0.98)	-0.05 (-0.09, 0.00)	
Non-ischemic	919	338	36.8	880	243	27.6	<0.0001	0.75 (0.66, 0.86)	0.66 (0.54, 0.80)	-0.09 (-0.13,-0.05)	
Heart Failure Physiology											0.3096
LVEF <= 30% and NTproBNP < median	723	218	30.2	698	168	24.1	0.0100	0.80 (0.67, 0.95)	0.73 (0.58, 0.93)	-0.06 (-0.11,-0.01)	
LVEF <= 30% and NTproBNP >= median	660	312	47.3	631	234	37.1	0.0002	0.78 (0.69, 0.89)	0.66 (0.53, 0.82)	-0.10 (-0.16,-0.05)	
LVEF > 30%	473	165	34.9	526	166	31.6	0.2650	0.90 (0.76, 1.08)	0.86 (0.66, 1.12)	-0.03 (-0.09, 0.03)	
Baseline use of MRA											0.5449
No	512	201	39.3	557	172	30.9	0.0041	0.79 (0.67, 0.93)	0.69 (0.54, 0.89)	-0.08 (-0.14,-0.03)	
Yes	1351	496	36.7	1306	399	30.6	0.0008	0.83 (0.75, 0.93)	0.76 (0.65, 0.89)	-0.06 (-0.10,-0.03)	
Baseline use of ARNi											0.3114
No	1476	547	37.1	1523	473	31.1	0.0005	0.84 (0.76, 0.93)	0.77 (0.66, 0.89)	-0.06 (-0.09,-0.03)	
Yes	387	150	38.8	340	98	28.8	0.0048	0.74 (0.60, 0.92)	0.64 (0.47, 0.87)	-0.10 (-0.17,-0.03)	

Risk ratios and odds ratios with confidence intervals (CIs) are estimated by Cochran-Mantel-Haenszel method. For risk differences standard Wald asymptotic confidence limits are calculated. A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied 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).
For AEs on SOC and/or PT level, subgroup analyses are only shown if overall test for treatment is significant on 5% level (i.e. 95% CI for the risk ratio does not contain 1; if this is not calculable the p-value of Chi-square test is used).
MedDRA version: 23.0. * Chi-square test for treatment effect ** Breslow-Day test for homogeneity of odds ratios (treatment by subgroup interaction).

Table R.1.4.4: 1 Proportion of patients with any adverse events occurring 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													0.3871
<=30	1390	532	38.3	1337	405	30.3	<0.0001	0.79 (0.71,	0.88)	0.70 (0.60,	0.82)	-0.08 (-0.12,-0.04)	
>30 to <=35	359	120	33.4	398	123	30.9	0.4581	0.92 (0.75,	1.14)	0.89 (0.66,	1.21)	-0.03 (-0.09, 0.04)	
>35	114	45	39.5	128	43	33.6	0.3425	0.85 (0.61,	1.19)	0.78 (0.46,	1.31)	-0.06 (-0.18, 0.06)	
Baseline NTproBNP													0.8231
< median	919	282	30.7	942	236	25.1	0.0067	0.82 (0.70,	0.95)	0.76 (0.62,	0.93)	-0.06 (-0.10,-0.02)	
>= median	943	414	43.9	920	335	36.4	0.0010	0.83 (0.74,	0.93)	0.73 (0.61,	0.88)	-0.07 (-0.12,-0.03)	

Risk ratios and odds ratios with confidence intervals (CIs) are estimated by Cochran-Mantel-Haenszel method. For risk differences standard Wald asymptotic confidence limits are calculated. A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied 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).
For AEs on SOC and/or PT level, subgroup analyses are only shown if overall test for treatment is significant on 5% level (i.e. 95% CI for the risk ratio does not contain 1; if this is not calculable the p-value of Chi-square test is used).
MedDRA version: 23.0. * Chi-square test for treatment effect ** Breslow-Day test for homogeneity of odds ratios (treatment by subgroup interaction).

Table R.1.4.4: 1 Proportion of patients with any adverse events occurring 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 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	1863	542	29.1	1863	510	27.4	0.2442	0.94 (0.85, 1.04)	0.92 (0.80, 1.06)	-0.02 (-0.05, 0.01)	

Risk ratios and odds ratios with confidence intervals (CIs) are estimated by Cochran-Mantel-Haenszel method. For risk differences standard Wald asymptotic confidence limits are calculated. A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied 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).
For AEs on SOC and/or PT level, subgroup analyses are only shown if overall test for treatment is significant on 5% level (i.e. 95% CI for the risk ratio does not contain 1; if this is not calculable the p-value of Chi-square test is used).
MedDRA version: 23.0. * Chi-square test for treatment effect ** Breslow-Day test for homogeneity of odds ratios (treatment by subgroup interaction).

Table R.1.4.4: 1 Proportion of patients with any adverse events occurring 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 **
Overall	1863	476	25.6	1863	411	22.1	0.0124	0.86 (0.77, 0.97)	0.82 (0.71, 0.96)	-0.03 (-0.06,-0.01)	
Sex											0.6448
Male	1410	365	25.9	1426	314	22.0	0.0158	0.85 (0.75, 0.97)	0.81 (0.68, 0.96)	-0.04 (-0.07,-0.01)	
Female	453	111	24.5	437	97	22.2	0.4163	0.91 (0.71, 1.15)	0.88 (0.64, 1.20)	-0.02 (-0.08, 0.03)	
Age [years]											0.8361
< 65	739	202	27.3	675	158	23.4	0.0904	0.86 (0.72, 1.03)	0.81 (0.64, 1.03)	-0.04 (-0.08, 0.01)	
>= 65	1124	274	24.4	1188	253	21.3	0.0776	0.87 (0.75, 1.02)	0.84 (0.69, 1.02)	-0.03 (-0.07, 0.00)	
Region											0.4987
North America	213	51	23.9	212	52	24.5	0.8882	1.02 (0.73, 1.43)	1.03 (0.66, 1.61)	0.01 (-0.08, 0.09)	
Latin America	645	164	25.4	641	135	21.1	0.0639	0.83 (0.68, 1.01)	0.78 (0.60, 1.01)	-0.04 (-0.09, 0.00)	
Europe	674	145	21.5	676	132	19.5	0.3661	0.91 (0.74, 1.12)	0.89 (0.68, 1.15)	-0.02 (-0.06, 0.02)	
Asia	244	89	36.5	248	76	30.6	0.1708	0.84 (0.65, 1.08)	0.77 (0.53, 1.12)	-0.06 (-0.14, 0.03)	
Other	87	27	31.0	86	16	18.6	0.0586	0.60 (0.35, 1.03)	0.51 (0.25, 1.03)	-0.12 (-0.25, 0.00)	
OECD Member											0.1030
No	741	211	28.5	713	157	22.0	0.0047	0.77 (0.65, 0.93)	0.71 (0.56, 0.90)	-0.06 (-0.11,-0.02)	
Yes	1122	265	23.6	1150	254	22.1	0.3846	0.94 (0.80, 1.09)	0.92 (0.75, 1.12)	-0.02 (-0.05, 0.02)	
Baseline NYHA											0.0097
II	1399	353	25.2	1399	276	19.7	0.0005	0.78 (0.68, 0.90)	0.73 (0.61, 0.87)	-0.06 (-0.09,-0.02)	
III/IV	464	123	26.5	464	135	29.1	0.3793	1.10 (0.89, 1.35)	1.14 (0.85, 1.52)	0.03 (-0.03, 0.08)	
Baseline Diabetes Status											0.1386
Diabetic	926	298	32.2	927	242	26.1	0.0040	0.81 (0.70, 0.94)	0.74 (0.61, 0.91)	-0.06 (-0.10,-0.02)	
Non-Diabetic	937	178	19.0	936	169	18.1	0.6001	0.95 (0.79, 1.15)	0.94 (0.74, 1.19)	-0.01 (-0.04, 0.03)	
Baseline BMI [kg/m²]											0.4302
<30	1299	330	25.4	1263	286	22.6	0.1022	0.89 (0.78, 1.02)	0.86 (0.72, 1.03)	-0.03 (-0.06, 0.01)	
>=30	564	146	25.9	600	125	20.8	0.0415	0.80 (0.65, 0.99)	0.75 (0.57, 0.99)	-0.05 (-0.10, 0.00)	

Risk ratios and odds ratios with confidence intervals (CIs) are estimated by Cochran-Mantel-Haenszel method. For risk differences standard Wald asymptotic confidence limits are calculated. A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied 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).
For AEs on SOC and/or PT level, subgroup analyses are only shown if overall test for treatment is significant on 5% level (i.e. 95% CI for the risk ratio does not contain 1; if this is not calculable the p-value of Chi-square test is used).
MedDRA version: 23.0. * Chi-square test for treatment effect ** Breslow-Day test for homogeneity of odds ratios (treatment by subgroup interaction).

Table R.1.4.4: 1 Proportion of patients with any adverse events occurring 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 eGFR (CKD-EPI) [mL/min/1.73m²]														0.8751
>=60	958	235	24.5	969	203	20.9	0.0607	0.85	(0.72, 1.01)	0.82	(0.66, 1.01)	-0.04	(-0.07, 0.00)	
<60	904	241	26.7	893	208	23.3	0.0993	0.87	(0.74, 1.03)	0.84	(0.67, 1.03)	-0.03	(-0.07, 0.01)	
History of HHF (in the last 12 months)														0.0067
No	1290	294	22.8	1286	283	22.0	0.6330	0.97	(0.84, 1.11)	0.96	(0.79, 1.15)	-0.01	(-0.04, 0.02)	
Yes	573	182	31.8	577	128	22.2	0.0003	0.70	(0.58, 0.85)	0.61	(0.47, 0.80)	-0.10	(-0.15,-0.04)	
Cause of Heart Failure														0.1182
Ischemic	944	220	23.3	983	217	22.1	0.5193	0.95	(0.80, 1.12)	0.93	(0.75, 1.15)	-0.01	(-0.05, 0.03)	
Non-ischemic	919	256	27.9	880	194	22.0	0.0044	0.79	(0.67, 0.93)	0.73	(0.59, 0.91)	-0.06	(-0.10,-0.02)	
Heart Failure Physiology														0.8893
LVEF <= 30% and NTproBNP < median	723	152	21.0	698	130	18.6	0.2570	0.89	(0.72, 1.09)	0.86	(0.66, 1.12)	-0.02	(-0.07, 0.02)	
LVEF <= 30% and NTproBNP >= median	660	192	29.1	631	154	24.4	0.0574	0.84	(0.70, 1.01)	0.79	(0.61, 1.01)	-0.05	(-0.10, 0.00)	
LVEF > 30%	473	131	27.7	526	125	23.8	0.1553	0.86	(0.69, 1.06)	0.81	(0.61, 1.08)	-0.04	(-0.09, 0.01)	
Baseline use of MRA														0.9544
No	512	125	24.4	557	118	21.2	0.2082	0.87	(0.70, 1.08)	0.83	(0.63, 1.11)	-0.03	(-0.08, 0.02)	
Yes	1351	351	26.0	1306	293	22.4	0.0330	0.86	(0.75, 0.99)	0.82	(0.69, 0.98)	-0.04	(-0.07, 0.00)	
Baseline use of ARNi														0.2933
No	1476	370	25.1	1523	340	22.3	0.0772	0.89	(0.78, 1.01)	0.86	(0.73, 1.02)	-0.03	(-0.06, 0.00)	
Yes	387	106	27.4	340	71	20.9	0.0414	0.76	(0.59, 0.99)	0.70	(0.50, 0.99)	-0.07	(-0.13, 0.00)	

Risk ratios and odds ratios with confidence intervals (CIs) are estimated by Cochran-Mantel-Haenszel method. For risk differences standard Wald asymptotic confidence limits are calculated. A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied 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).
For AEs on SOC and/or PT level, subgroup analyses are only shown if overall test for treatment is significant on 5% level (i.e. 95% CI for the risk ratio does not contain 1; if this is not calculable the p-value of Chi-square test is used).
MedDRA version: 23.0. * Chi-square test for treatment effect ** Breslow-Day test for homogeneity of odds ratios (treatment by subgroup interaction).

Table R.1.4.4: 1 Proportion of patients with any adverse events occurring 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														0.9471
<=30	1390	345	24.8	1337	286	21.4	0.0338	0.86	(0.75, 0.99)	0.82	(0.69, 0.99)	-0.03	(-0.07, 0.00)	
>30 to <=35	359	93	25.9	398	90	22.6	0.2908	0.87	(0.68, 1.12)	0.84	(0.60, 1.17)	-0.03	(-0.09, 0.03)	
>35	114	38	33.3	128	35	27.3	0.3109	0.82	(0.56, 1.20)	0.75	(0.43, 1.30)	-0.06	(-0.18, 0.06)	
Baseline NTproBNP														0.6270
< median	919	214	23.3	942	183	19.4	0.0422	0.83	(0.70, 0.99)	0.79	(0.64, 0.99)	-0.04	(-0.08, 0.00)	
>= median	943	262	27.8	920	228	24.8	0.1413	0.89	(0.77, 1.04)	0.86	(0.70, 1.05)	-0.03	(-0.07, 0.01)	

Risk ratios and odds ratios with confidence intervals (CIs) are estimated by Cochran-Mantel-Haenszel method. For risk differences standard Wald asymptotic confidence limits are calculated. A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied 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).
For AEs on SOC and/or PT level, subgroup analyses are only shown if overall test for treatment is significant on 5% level (i.e. 95% CI for the risk ratio does not contain 1; if this is not calculable the p-value of Chi-square test is used).
MedDRA version: 23.0. * Chi-square test for treatment effect ** Breslow-Day test for homogeneity of odds ratios (treatment by subgroup interaction).

Table R.1.4.4: 1 Proportion of patients with any adverse events occurring 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 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	1863	265	14.2	1863	284	15.2	0.3798	1.07 (0.92, 1.25)	1.08 (0.90, 1.30)	0.01 (-0.01, 0.03)	

Risk ratios and odds ratios with confidence intervals (CIs) are estimated by Cochran-Mantel-Haenszel method. For risk differences standard Wald asymptotic confidence limits are calculated. A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied 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).
For AEs on SOC and/or PT level, subgroup analyses are only shown if overall test for treatment is significant on 5% level (i.e. 95% CI for the risk ratio does not contain 1; if this is not calculable the p-value of Chi-square test is used).
MedDRA version: 23.0. * Chi-square test for treatment effect ** Breslow-Day test for homogeneity of odds ratios (treatment by subgroup interaction).

Table R.1.4.4: 1 Proportion of patients with any adverse events occurring 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 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	1863	275	14.8	1863	280	15.0	0.8180	1.02 (0.87, 1.19)	1.02 (0.85, 1.22)	0.00 (-0.02, 0.03)	

Risk ratios and odds ratios with confidence intervals (CIs) are estimated by Cochran-Mantel-Haenszel method. For risk differences standard Wald asymptotic confidence limits are calculated. A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied 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).
For AEs on SOC and/or PT level, subgroup analyses are only shown if overall test for treatment is significant on 5% level (i.e. 95% CI for the risk ratio does not contain 1; if this is not calculable the p-value of Chi-square test is used).
MedDRA version: 23.0. * Chi-square test for treatment effect ** Breslow-Day test for homogeneity of odds ratios (treatment by subgroup interaction).

Table R.1.4.4: 1 Proportion of patients with any adverse events occurring 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	1863	239	12.8	1863	241	12.9	0.9221	1.01 (0.85, 1.19)	1.01 (0.83, 1.22)	0.00 (-0.02, 0.02)	

Risk ratios and odds ratios with confidence intervals (CIs) are estimated by Cochran-Mantel-Haenszel method. For risk differences standard Wald asymptotic confidence limits are calculated. A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied 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).
For AEs on SOC and/or PT level, subgroup analyses are only shown if overall test for treatment is significant on 5% level (i.e. 95% CI for the risk ratio does not contain 1; if this is not calculable the p-value of Chi-square test is used).
MedDRA version: 23.0. * Chi-square test for treatment effect ** Breslow-Day test for homogeneity of odds ratios (treatment by subgroup interaction).

Table R.1.4.4: 1 Proportion of patients with any adverse events occurring 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	1863	211	11.3	1863	239	12.8	0.1592	1.13 (0.95, 1.35)	1.15 (0.95, 1.40)	0.02 (-0.01, 0.04)	

Risk ratios and odds ratios with confidence intervals (CIs) are estimated by Cochran-Mantel-Haenszel method. For risk differences standard Wald asymptotic confidence limits are calculated. A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied 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).
For AEs on SOC and/or PT level, subgroup analyses are only shown if overall test for treatment is significant on 5% level (i.e. 95% CI for the risk ratio does not contain 1; if this is not calculable the p-value of Chi-square test is used).
MedDRA version: 23.0. * Chi-square test for treatment effect ** Breslow-Day test for homogeneity of odds ratios (treatment by subgroup interaction).

Table R.1.4.4: 1 Proportion of patients with any adverse events occurring 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 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	1863	222	11.9	1863	190	10.2	0.0946	0.86 (0.71, 1.03)	0.84 (0.68, 1.03)	-0.02 (-0.04, 0.00)	

Risk ratios and odds ratios with confidence intervals (CIs) are estimated by Cochran-Mantel-Haenszel method. For risk differences standard Wald asymptotic confidence limits are calculated. A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied 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).
For AEs on SOC and/or PT level, subgroup analyses are only shown if overall test for treatment is significant on 5% level (i.e. 95% CI for the risk ratio does not contain 1; if this is not calculable the p-value of Chi-square test is used).
MedDRA version: 23.0. * Chi-square test for treatment effect ** Breslow-Day test for homogeneity of odds ratios (treatment by subgroup interaction).

Table R.1.4.4: 1 Proportion of patients with any adverse events occurring 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 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	1863	214	11.5	1863	189	10.1	0.1873	0.88 (0.73, 1.06)	0.87 (0.71, 1.07)	-0.01 (-0.03, 0.01)	

Risk ratios and odds ratios with confidence intervals (CIs) are estimated by Cochran-Mantel-Haenszel method. For risk differences standard Wald asymptotic confidence limits are calculated. A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied 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).
For AEs on SOC and/or PT level, subgroup analyses are only shown if overall test for treatment is significant on 5% level (i.e. 95% CI for the risk ratio does not contain 1; if this is not calculable the p-value of Chi-square test is used).
MedDRA version: 23.0. * Chi-square test for treatment effect ** Breslow-Day test for homogeneity of odds ratios (treatment by subgroup interaction).

Table R.1.4.4: 1 Proportion of patients with any adverse events occurring 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 **
Overall	1863	208	11.2	1863	177	9.5	0.0952	0.85 (0.70, 1.03)	0.84 (0.68, 1.03)	-0.02 (-0.04, 0.00)	

Risk ratios and odds ratios with confidence intervals (CIs) are estimated by Cochran-Mantel-Haenszel method. For risk differences standard Wald asymptotic confidence limits are calculated. A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied 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).
For AEs on SOC and/or PT level, subgroup analyses are only shown if overall test for treatment is significant on 5% level (i.e. 95% CI for the risk ratio does not contain 1; if this is not calculable the p-value of Chi-square test is used).
MedDRA version: 23.0. * Chi-square test for treatment effect ** Breslow-Day test for homogeneity of odds ratios (treatment by subgroup interaction).

Table R.1.4.4: 1 Proportion of patients with any adverse events occurring 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	1863	188	10.1	1863	154	8.3	0.0537	0.82 (0.67, 1.00)	0.80 (0.64, 1.00)	-0.02 (-0.04, 0.00)	

Risk ratios and odds ratios with confidence intervals (CIs) are estimated by Cochran-Mantel-Haenszel method. For risk differences standard Wald asymptotic confidence limits are calculated. A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied 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).
For AEs on SOC and/or PT level, subgroup analyses are only shown if overall test for treatment is significant on 5% level (i.e. 95% CI for the risk ratio does not contain 1; if this is not calculable the p-value of Chi-square test is used).
MedDRA version: 23.0. * Chi-square test for treatment effect ** Breslow-Day test for homogeneity of odds ratios (treatment by subgroup interaction).

Table R.1.4.4: 1 Proportion of patients with any adverse events occurring 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	1863	147	7.9	1863	176	9.4	0.0913	1.20 (0.97, 1.48)	1.22 (0.97, 1.53)	0.02 (0.00, 0.03)	

Risk ratios and odds ratios with confidence intervals (CIs) are estimated by Cochran-Mantel-Haenszel method. For risk differences standard Wald asymptotic confidence limits are calculated. A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied 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).
For AEs on SOC and/or PT level, subgroup analyses are only shown if overall test for treatment is significant on 5% level (i.e. 95% CI for the risk ratio does not contain 1; if this is not calculable the p-value of Chi-square test is used).
MedDRA version: 23.0. * Chi-square test for treatment effect ** Breslow-Day test for homogeneity of odds ratios (treatment by subgroup interaction).

Table R.1.4.4: 1 Proportion of patients with any adverse events occurring 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 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	1863	128	6.9	1863	129	6.9	0.9485	1.01 (0.80, 1.28)	1.01 (0.78, 1.30)	0.00 (-0.02, 0.02)	

Risk ratios and odds ratios with confidence intervals (CIs) are estimated by Cochran-Mantel-Haenszel method. For risk differences standard Wald asymptotic confidence limits are calculated. A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied 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).
For AEs on SOC and/or PT level, subgroup analyses are only shown if overall test for treatment is significant on 5% level (i.e. 95% CI for the risk ratio does not contain 1; if this is not calculable the p-value of Chi-square test is used).
MedDRA version: 23.0. * Chi-square test for treatment effect ** Breslow-Day test for homogeneity of odds ratios (treatment by subgroup interaction).

Table R.1.4.4: 1 Proportion of patients with any adverse events occurring 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 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	1863	108	5.8	1863	79	4.2	0.0296	0.73 (0.55, 0.97)	0.72 (0.53, 0.97)	-0.02 (-0.03, 0.00)	
Sex											0.1323
Male	1410	78	5.5	1426	65	4.6	0.2361	0.82 (0.60, 1.14)	0.82 (0.58, 1.14)	-0.01 (-0.03, 0.01)	
Female	453	30	6.6	437	14	3.2	0.0187	0.48 (0.26, 0.90)	0.47 (0.24, 0.89)	-0.03 (-0.06,-0.01)	
Age [years]											0.7091
< 65	739	42	5.7	675	26	3.9	0.1079	0.68 (0.42, 1.09)	0.66 (0.40, 1.10)	-0.02 (-0.04, 0.00)	
>= 65	1124	66	5.9	1188	53	4.5	0.1250	0.76 (0.53, 1.08)	0.75 (0.52, 1.08)	-0.01 (-0.03, 0.00)	
Region											0.1838
North America	213	17	8.0	212	9	4.2	0.1081	0.53 (0.24, 1.17)	0.51 (0.22, 1.17)	-0.04 (-0.08, 0.01)	
Latin America	645	31	4.8	641	19	3.0	0.0875	0.62 (0.35, 1.08)	0.61 (0.34, 1.08)	-0.02 (-0.04, 0.00)	
Europe	674	38	5.6	676	34	5.0	0.6189	0.89 (0.57, 1.40)	0.89 (0.55, 1.43)	-0.01 (-0.03, 0.02)	
Asia	244	20	8.2	248	11	4.4	0.0860	0.54 (0.26, 1.11)	0.52 (0.24, 1.11)	-0.04 (-0.08, 0.01)	
Other	87	2	2.3	86	6	7.0	0.1430	3.03 (0.63, 14.62)	3.19 (0.63, 16.26)	0.05 (-0.02, 0.11)	
OECD Member											0.8686
No	741	37	5.0	713	25	3.5	0.1607	0.70 (0.43, 1.15)	0.69 (0.41, 1.16)	-0.01 (-0.04, 0.01)	
Yes	1122	71	6.3	1150	54	4.7	0.0880	0.74 (0.53, 1.05)	0.73 (0.51, 1.05)	-0.02 (-0.04, 0.00)	
Baseline NYHA											0.0066
II	1399	86	6.1	1399	49	3.5	0.0011	0.57 (0.40, 0.80)	0.55 (0.39, 0.79)	-0.03 (-0.04,-0.01)	
III/IV	464	22	4.7	464	30	6.5	0.2535	1.36 (0.80, 2.33)	1.39 (0.79, 2.45)	0.02 (-0.01, 0.05)	
Baseline Diabetes Status											0.4574
Diabetic	926	63	6.8	927	42	4.5	0.0344	0.67 (0.46, 0.97)	0.65 (0.44, 0.97)	-0.02 (-0.04, 0.00)	
Non-Diabetic	937	45	4.8	936	37	4.0	0.3689	0.82 (0.54, 1.26)	0.82 (0.52, 1.27)	-0.01 (-0.03, 0.01)	
Baseline BMI [kg/m²]											0.0897
<30	1299	87	6.7	1263	54	4.3	0.0072	0.64 (0.46, 0.89)	0.62 (0.44, 0.88)	-0.02 (-0.04,-0.01)	
>=30	564	21	3.7	600	25	4.2	0.6981	1.12 (0.63, 1.98)	1.12 (0.62, 2.03)	0.00 (-0.02, 0.03)	

Risk ratios and odds ratios with confidence intervals (CIs) are estimated by Cochran-Mantel-Haenszel method. For risk differences standard Wald asymptotic confidence limits are calculated. A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied 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).
For AEs on SOC and/or PT level, subgroup analyses are only shown if overall test for treatment is significant on 5% level (i.e. 95% CI for the risk ratio does not contain 1; if this is not calculable the p-value of Chi-square test is used).
MedDRA version: 23.0. * Chi-square test for treatment effect ** Breslow-Day test for homogeneity of odds ratios (treatment by subgroup interaction).

Table R.1.4.4: 1 Proportion of patients with any adverse events occurring 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 Category	Placebo N	Placebo n	Placebo %	Empa 10mg N	Empa 10mg n	Empa 10mg %	Empa 10mg vs Placebo p-value *	Risk ratio (95% CI)	Odds ratio (95% CI)	Risk diff. (95% CI)	p-value **
Baseline eGFR (CKD-EPI) [mL/min/1.73m²]											0.8578
>=60	958	50	5.2	969	38	3.9	0.1725	0.75 (0.50, 1.13)	0.74 (0.48, 1.14)	-0.01 (-0.03, 0.01)	
<60	904	58	6.4	893	41	4.6	0.0901	0.72 (0.48, 1.06)	0.70 (0.47, 1.06)	-0.02 (-0.04, 0.00)	
History of HHF (in the last 12 months)											0.3857
No	1290	75	5.8	1286	50	3.9	0.0229	0.67 (0.47, 0.95)	0.66 (0.45, 0.95)	-0.02 (-0.04, 0.00)	
Yes	573	33	5.8	577	29	5.0	0.5820	0.87 (0.54, 1.42)	0.87 (0.52, 1.45)	-0.01 (-0.03, 0.02)	
Cause of Heart Failure											0.3447
Ischemic	944	56	5.9	983	48	4.9	0.3082	0.82 (0.57, 1.20)	0.81 (0.55, 1.21)	-0.01 (-0.03, 0.01)	
Non-ischemic	919	52	5.7	880	31	3.5	0.0309	0.62 (0.40, 0.96)	0.61 (0.39, 0.96)	-0.02 (-0.04, 0.00)	
Heart Failure Physiology											0.3311
LVEF <= 30% and NTproBNP < median	723	36	5.0	698	19	2.7	0.0274	0.55 (0.32, 0.94)	0.53 (0.30, 0.94)	-0.02 (-0.04, 0.00)	
LVEF <= 30% and NTproBNP >= median	660	42	6.4	631	37	5.9	0.7079	0.92 (0.60, 1.41)	0.92 (0.58, 1.45)	0.00 (-0.03, 0.02)	
LVEF > 30%	473	30	6.3	526	23	4.4	0.1655	0.69 (0.41, 1.17)	0.68 (0.39, 1.18)	-0.02 (-0.05, 0.01)	
Baseline use of MRA											0.9367
No	512	32	6.3	557	25	4.5	0.2003	0.72 (0.43, 1.19)	0.70 (0.41, 1.21)	-0.02 (-0.04, 0.01)	
Yes	1351	76	5.6	1306	54	4.1	0.0749	0.74 (0.52, 1.03)	0.72 (0.51, 1.03)	-0.01 (-0.03, 0.00)	
Baseline use of ARNi											0.4863
No	1476	88	6.0	1523	69	4.5	0.0785	0.76 (0.56, 1.03)	0.75 (0.54, 1.03)	-0.01 (-0.03, 0.00)	
Yes	387	20	5.2	340	10	2.9	0.1320	0.57 (0.27, 1.20)	0.56 (0.26, 1.21)	-0.02 (-0.05, 0.01)	

Risk ratios and odds ratios with confidence intervals (CIs) are estimated by Cochran-Mantel-Haenszel method. For risk differences standard Wald asymptotic confidence limits are calculated. A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied 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).
For AEs on SOC and/or PT level, subgroup analyses are only shown if overall test for treatment is significant on 5% level (i.e. 95% CI for the risk ratio does not contain 1; if this is not calculable the p-value of Chi-square test is used).
MedDRA version: 23.0. * Chi-square test for treatment effect ** Breslow-Day test for homogeneity of odds ratios (treatment by subgroup interaction).

Table R.1.4.4: 1 Proportion of patients with any adverse events occurring 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														0.6383
<=30	1390	78	5.6	1337	56	4.2	0.0857	0.75	(0.53, 1.04)	0.74	(0.52, 1.05)	-0.01	(-0.03, 0.00)	
>30 to <=35	359	23	6.4	398	15	3.8	0.0970	0.59	(0.31, 1.11)	0.57	(0.29, 1.11)	-0.03	(-0.06, 0.01)	
>35	114	7	6.1	128	8	6.3	0.9718	1.02	(0.38, 2.72)	1.02	(0.36, 2.90)	0.00	(-0.06, 0.06)	
Baseline NTproBNP														0.0221
< median	919	52	5.7	942	26	2.8	0.0018	0.49	(0.31, 0.77)	0.47	(0.29, 0.76)	-0.03	(-0.05,-0.01)	
>= median	943	56	5.9	920	53	5.8	0.8703	0.97	(0.67, 1.40)	0.97	(0.66, 1.43)	0.00	(-0.02, 0.02)	

Risk ratios and odds ratios with confidence intervals (CIs) are estimated by Cochran-Mantel-Haenszel method. For risk differences standard Wald asymptotic confidence limits are calculated. A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied 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).
For AEs on SOC and/or PT level, subgroup analyses are only shown if overall test for treatment is significant on 5% level (i.e. 95% CI for the risk ratio does not contain 1; if this is not calculable the p-value of Chi-square test is used).
MedDRA version: 23.0. * Chi-square test for treatment effect ** Breslow-Day test for homogeneity of odds ratios (treatment by subgroup interaction).

Table R.1.4.4: 1 Proportion of patients with any adverse events occurring 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 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	1863	91	4.9	1863	82	4.4	0.4835	0.90 (0.67, 1.21)	0.90 (0.66, 1.22)	0.00 (-0.02, 0.01)	

Risk ratios and odds ratios with confidence intervals (CIs) are estimated by Cochran-Mantel-Haenszel method. For risk differences standard Wald asymptotic confidence limits are calculated. A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied 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).
For AEs on SOC and/or PT level, subgroup analyses are only shown if overall test for treatment is significant on 5% level (i.e. 95% CI for the risk ratio does not contain 1; if this is not calculable the p-value of Chi-square test is used).
MedDRA version: 23.0. * Chi-square test for treatment effect ** Breslow-Day test for homogeneity of odds ratios (treatment by subgroup interaction).

Table R.1.4.4: 1 Proportion of patients with any adverse events occurring 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	1863	69	3.7	1863	59	3.2	0.3684	0.86 (0.61, 1.20)	0.85 (0.60, 1.21)	-0.01 (-0.02, 0.01)	

Risk ratios and odds ratios with confidence intervals (CIs) are estimated by Cochran-Mantel-Haenszel method. For risk differences standard Wald asymptotic confidence limits are calculated. A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied 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).
For AEs on SOC and/or PT level, subgroup analyses are only shown if overall test for treatment is significant on 5% level (i.e. 95% CI for the risk ratio does not contain 1; if this is not calculable the p-value of Chi-square test is used).
MedDRA version: 23.0. * Chi-square test for treatment effect ** Breslow-Day test for homogeneity of odds ratios (treatment by subgroup interaction).

Table R.1.4.4: 1 Proportion of patients with any adverse events occurring 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 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	1863	45	2.4	1863	57	3.1	0.2283	1.27 (0.86, 1.86)	1.28 (0.86, 1.90)	0.01 (0.00, 0.02)	

Risk ratios and odds ratios with confidence intervals (CIs) are estimated by Cochran-Mantel-Haenszel method. For risk differences standard Wald asymptotic confidence limits are calculated. A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied 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).
For AEs on SOC and/or PT level, subgroup analyses are only shown if overall test for treatment is significant on 5% level (i.e. 95% CI for the risk ratio does not contain 1; if this is not calculable the p-value of Chi-square test is used).
MedDRA version: 23.0. * Chi-square test for treatment effect ** Breslow-Day test for homogeneity of odds ratios (treatment by subgroup interaction).

Table R.1.4.4: 1 Proportion of patients with any adverse events occurring 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 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	1863	49	2.6	1863	57	3.1	0.4305	1.16 (0.80, 1.69)	1.17 (0.79, 1.72)	0.00 (-0.01, 0.01)	

Risk ratios and odds ratios with confidence intervals (CIs) are estimated by Cochran-Mantel-Haenszel method. For risk differences standard Wald asymptotic confidence limits are calculated. A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied 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).
For AEs on SOC and/or PT level, subgroup analyses are only shown if overall test for treatment is significant on 5% level (i.e. 95% CI for the risk ratio does not contain 1; if this is not calculable the p-value of Chi-square test is used).
MedDRA version: 23.0. * Chi-square test for treatment effect ** Breslow-Day test for homogeneity of odds ratios (treatment by subgroup interaction).

Table R.1.4.4: 1 Proportion of patients with any adverse events occurring 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	1863	54	2.9	1863	52	2.8	0.8438	0.96 (0.66, 1.40)	0.96 (0.65, 1.42)	0.00 (-0.01, 0.01)	

Risk ratios and odds ratios with confidence intervals (CIs) are estimated by Cochran-Mantel-Haenszel method. For risk differences standard Wald asymptotic confidence limits are calculated. A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied 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).
For AEs on SOC and/or PT level, subgroup analyses are only shown if overall test for treatment is significant on 5% level (i.e. 95% CI for the risk ratio does not contain 1; if this is not calculable the p-value of Chi-square test is used).
MedDRA version: 23.0. * Chi-square test for treatment effect ** Breslow-Day test for homogeneity of odds ratios (treatment by subgroup interaction).

Table R.1.4.4: 1 Proportion of patients with any adverse events occurring 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 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	1863	44	2.4	1863	28	1.5	0.0569	0.64 (0.40, 1.02)	0.63 (0.39, 1.02)	-0.01 (-0.02, 0.00)	

Risk ratios and odds ratios with confidence intervals (CIs) are estimated by Cochran-Mantel-Haenszel method. For risk differences standard Wald asymptotic confidence limits are calculated. A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied 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).
For AEs on SOC and/or PT level, subgroup analyses are only shown if overall test for treatment is significant on 5% level (i.e. 95% CI for the risk ratio does not contain 1; if this is not calculable the p-value of Chi-square test is used).
MedDRA version: 23.0. * Chi-square test for treatment effect ** Breslow-Day test for homogeneity of odds ratios (treatment by subgroup interaction).

Table R.1.4.4: 1 Proportion of patients with any adverse events occurring 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 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	1863	28	1.5	1863	26	1.4	0.7840	0.93 (0.55, 1.58)	0.93 (0.54, 1.59)	0.00 (-0.01, 0.01)	

Risk ratios and odds ratios with confidence intervals (CIs) are estimated by Cochran-Mantel-Haenszel method. For risk differences standard Wald asymptotic confidence limits are calculated. A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied 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).
For AEs on SOC and/or PT level, subgroup analyses are only shown if overall test for treatment is significant on 5% level (i.e. 95% CI for the risk ratio does not contain 1; if this is not calculable the p-value of Chi-square test is used).
MedDRA version: 23.0. * Chi-square test for treatment effect ** Breslow-Day test for homogeneity of odds ratios (treatment by subgroup interaction).

Table R.1.4.4: 2 Proportion of patients with serious adverse events occurring in at least 1% of the patients in either treatment arm in the overall population on SOC level - by SOC - overall and by subgroup - TS
System organ class: Cardiac disorders

Subgroup Category	Placebo N	Placebo n	Placebo %	Empa 10mg N	Empa 10mg n	Empa 10mg %	Empa 10mg vs Placebo p-value *	Risk ratio	Risk (95% CI)	Odds ratio	Odds (95% CI)	Risk diff.	Risk diff. (95% CI)	p-value **
Overall	1863	634	34.0	1863	500	26.8	<0.0001	0.79	(0.71, 0.87)	0.71	(0.62, 0.82)	-0.07	(-0.10,-0.04)	
Sex														0.8237
Male	1410	482	34.2	1426	387	27.1	<0.0001	0.79	(0.71, 0.89)	0.72	(0.61, 0.84)	-0.07	(-0.10,-0.04)	
Female	453	152	33.6	437	113	25.9	0.0121	0.77	(0.63, 0.95)	0.69	(0.52, 0.92)	-0.08	(-0.14,-0.02)	
Age [years]														0.1686
< 65	739	261	35.3	675	172	25.5	<0.0001	0.72	(0.61, 0.85)	0.63	(0.50, 0.79)	-0.10	(-0.15,-0.05)	
>= 65	1124	373	33.2	1188	328	27.6	0.0036	0.83	(0.74, 0.94)	0.77	(0.64, 0.92)	-0.06	(-0.09,-0.02)	
Region														0.0689
North America	213	79	37.1	212	75	35.4	0.7136	0.95	(0.74, 1.23)	0.93	(0.63, 1.38)	-0.02	(-0.11, 0.07)	
Latin America	645	201	31.2	641	159	24.8	0.0111	0.80	(0.67, 0.95)	0.73	(0.57, 0.93)	-0.06	(-0.11,-0.01)	
Europe	674	231	34.3	676	193	28.6	0.0235	0.83	(0.71, 0.98)	0.77	(0.61, 0.97)	-0.06	(-0.11,-0.01)	
Asia	244	106	43.4	248	66	26.6	<0.0001	0.61	(0.48, 0.79)	0.47	(0.32, 0.69)	-0.17	(-0.25,-0.09)	
Other	87	17	19.5	86	7	8.1	0.0301	0.42	(0.18, 0.95)	0.36	(0.14, 0.93)	-0.11	(-0.22,-0.01)	
OECD Member														0.3714
No	741	238	32.1	713	168	23.6	0.0003	0.73	(0.62, 0.87)	0.65	(0.52, 0.82)	-0.09	(-0.13,-0.04)	
Yes	1122	396	35.3	1150	332	28.9	0.0010	0.82	(0.73, 0.92)	0.74	(0.62, 0.89)	-0.06	(-0.10,-0.03)	
Baseline NYHA														0.0010
II	1399	440	31.5	1399	304	21.7	<0.0001	0.69	(0.61, 0.78)	0.61	(0.51, 0.72)	-0.10	(-0.13,-0.06)	
III/IV	464	194	41.8	464	196	42.2	0.8942	1.01	(0.87, 1.18)	1.02	(0.78, 1.32)	0.00	(-0.06, 0.07)	
Baseline Diabetes Status														0.2310
Diabetic	926	339	36.6	927	254	27.4	<0.0001	0.75	(0.65, 0.86)	0.65	(0.54, 0.80)	-0.09	(-0.13,-0.05)	
Non-Diabetic	937	295	31.5	936	246	26.3	0.0130	0.83	(0.72, 0.96)	0.78	(0.63, 0.95)	-0.05	(-0.09,-0.01)	
Baseline BMI [kg/m²]														0.0930
<30	1299	442	34.0	1263	318	25.2	<0.0001	0.74	(0.66, 0.84)	0.65	(0.55, 0.77)	-0.09	(-0.12,-0.05)	
>=30	564	192	34.0	600	182	30.3	0.1756	0.89	(0.75, 1.05)	0.84	(0.66, 1.08)	-0.04	(-0.09, 0.02)	

Risk ratios and odds ratios with confidence intervals (CIs) are estimated by Cochran-Mantel-Haenszel method. For risk differences standard Wald asymptotic confidence limits are calculated. A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied 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).
For AEs on SOC and/or PT level, subgroup analyses are only shown if overall test for treatment is significant on 5% level (i.e. 95% CI for the risk ratio does not contain 1; if this is not calculable the p-value of Chi-square test is used).
MedDRA version: 23.0. * Chi-square test for treatment effect ** Breslow-Day test for homogeneity of odds ratios (treatment by subgroup interaction).

Table R.1.4.4: 2 Proportion of patients with serious adverse events occurring in at least 1% of the patients in either treatment arm in the overall population on SOC level - by SOC - overall and by subgroup - TS
System organ class: Cardiac disorders

Subgroup	Placebo			Empa 10mg			Empa 10mg vs Placebo							
Category	N	n	%	N	n	%	p-value *	Risk ratio	(95% CI)	Odds ratio	(95% CI)	Risk diff.	(95% CI)	p-value **
Baseline eGFR (CKD-EPI) [mL/min/1.73m²]														0.0051
>=60	958	317	33.1	969	216	22.3	<0.0001	0.67	(0.58, 0.78)	0.58	(0.47, 0.71)	-0.11	(-0.15,-0.07)	
<60	904	316	35.0	893	284	31.8	0.1565	0.91	(0.80, 1.04)	0.87	(0.71, 1.06)	-0.03	(-0.08, 0.01)	
History of HHF (in the last 12 months)														0.0447
No	1290	424	32.9	1286	307	23.9	<0.0001	0.73	(0.64, 0.82)	0.64	(0.54, 0.76)	-0.09	(-0.12,-0.06)	
Yes	573	210	36.6	577	193	33.4	0.2554	0.91	(0.78, 1.07)	0.87	(0.68, 1.11)	-0.03	(-0.09, 0.02)	
Cause of Heart Failure														0.0694
Ischemic	944	323	34.2	983	289	29.4	0.0232	0.86	(0.75, 0.98)	0.80	(0.66, 0.97)	-0.05	(-0.09,-0.01)	
Non-ischemic	919	311	33.8	880	211	24.0	<0.0001	0.71	(0.61, 0.82)	0.62	(0.50, 0.76)	-0.10	(-0.14,-0.06)	
Heart Failure Physiology														0.3085
LVEF <= 30% and NTproBNP < median	723	192	26.6	698	132	18.9	0.0006	0.71	(0.59, 0.87)	0.64	(0.50, 0.83)	-0.08	(-0.12,-0.03)	
LVEF <= 30% and NTproBNP >= median	660	292	44.2	631	219	34.7	0.0005	0.78	(0.68, 0.90)	0.67	(0.54, 0.84)	-0.10	(-0.15,-0.04)	
LVEF > 30%	473	148	31.3	526	146	27.8	0.2212	0.89	(0.73, 1.07)	0.84	(0.64, 1.11)	-0.04	(-0.09, 0.02)	
Baseline use of MRA														0.5814
No	512	181	35.4	557	149	26.8	0.0024	0.76	(0.63, 0.91)	0.67	(0.51, 0.87)	-0.09	(-0.14,-0.03)	
Yes	1351	453	33.5	1306	351	26.9	0.0002	0.80	(0.71, 0.90)	0.73	(0.62, 0.86)	-0.07	(-0.10,-0.03)	
Baseline use of ARNi														0.2556
No	1476	496	33.6	1523	415	27.2	0.0002	0.81	(0.73, 0.90)	0.74	(0.63, 0.87)	-0.06	(-0.10,-0.03)	
Yes	387	138	35.7	340	85	25.0	0.0019	0.70	(0.56, 0.88)	0.60	(0.44, 0.83)	-0.11	(-0.17,-0.04)	

Risk ratios and odds ratios with confidence intervals (CIs) are estimated by Cochran-Mantel-Haenszel method. For risk differences standard Wald asymptotic confidence limits are calculated. A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied 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).
For AEs on SOC and/or PT level, subgroup analyses are only shown if overall test for treatment is significant on 5% level (i.e. 95% CI for the risk ratio does not contain 1; if this is not calculable the p-value of Chi-square test is used).
MedDRA version: 23.0. * Chi-square test for treatment effect ** Breslow-Day test for homogeneity of odds ratios (treatment by subgroup interaction).

Table R.1.4.4: 2 Proportion of patients with serious adverse events occurring in at least 1% of the patients in either treatment arm in the overall population on SOC level - by SOC - 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																0.3473
<=30	1390	486	35.0	1337	354	26.5	<0.0001	0.76	(0.68,	0.85)	0.67	(0.57,	0.79)	-0.08	(-0.12,-0.05)	
>30 to <=35	359	108	30.1	398	108	27.1	0.3698	0.90	(0.72,	1.13)	0.87	(0.63,	1.19)	-0.03	(-0.09, 0.04)	
>35	114	40	35.1	128	38	29.7	0.3696	0.85	(0.59,	1.22)	0.78	(0.46,	1.34)	-0.05	(-0.17, 0.06)	
Baseline NTproBNP																0.5562
< median	919	248	27.0	942	189	20.1	0.0004	0.74	(0.63,	0.88)	0.68	(0.55,	0.84)	-0.07	(-0.11,-0.03)	
>= median	943	385	40.8	920	311	33.8	0.0017	0.83	(0.74,	0.93)	0.74	(0.61,	0.89)	-0.07	(-0.11,-0.03)	

Risk ratios and odds ratios with confidence intervals (CIs) are estimated by Cochran-Mantel-Haenszel method. For risk differences standard Wald asymptotic confidence limits are calculated. A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied 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).
For AEs on SOC and/or PT level, subgroup analyses are only shown if overall test for treatment is significant on 5% level (i.e. 95% CI for the risk ratio does not contain 1; if this is not calculable the p-value of Chi-square test is used).
MedDRA version: 23.0. * Chi-square test for treatment effect ** Breslow-Day test for homogeneity of odds ratios (treatment by subgroup interaction).

Table R.1.4.4: 2 Proportion of patients with serious adverse events occurring in at least 1% of the patients in either treatment arm in the overall population on SOC level - by SOC - overall and by subgroup - TS
System organ class: Infections and infestations

Subgroup Category	Placebo N	Placebo n	Placebo %	Empa 10mg N	Empa 10mg n	Empa 10mg %	Empa 10mg vs Placebo p-value *	Risk ratio (95% CI)	Odds ratio (95% CI)	Risk diff. (95% CI)	p-value **
Overall	1863	136	7.3	1863	139	7.5	0.8509	1.02 (0.81, 1.28)	1.02 (0.80, 1.31)	0.00 (-0.02, 0.02)	

Risk ratios and odds ratios with confidence intervals (CIs) are estimated by Cochran-Mantel-Haenszel method. For risk differences standard Wald asymptotic confidence limits are calculated. A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied 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).
For AEs on SOC and/or PT level, subgroup analyses are only shown if overall test for treatment is significant on 5% level (i.e. 95% CI for the risk ratio does not contain 1; if this is not calculable the p-value of Chi-square test is used).
MedDRA version: 23.0. * Chi-square test for treatment effect ** Breslow-Day test for homogeneity of odds ratios (treatment by subgroup interaction).

Table R.1.4.4: 2 Proportion of patients with serious adverse events occurring in at least 1% of the patients in either treatment arm in the overall population on SOC level - by SOC - 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	1863	107	5.7	1863	71	3.8	0.0057	0.66	(0.49,	0.89)	0.65	(0.48,	0.88)	-0.02	(-0.03,-0.01)	
Sex																0.8174
Male	1410	85	6.0	1426	56	3.9	0.0101	0.65	(0.47,	0.91)	0.64	(0.45,	0.90)	-0.02	(-0.04,-0.01)	
Female	453	22	4.9	437	15	3.4	0.2873	0.71	(0.37,	1.34)	0.70	(0.36,	1.36)	-0.01	(-0.04, 0.01)	
Age [years]																0.1738
< 65	739	49	6.6	675	23	3.4	0.0059	0.51	(0.32,	0.83)	0.50	(0.30,	0.82)	-0.03	(-0.05,-0.01)	
>= 65	1124	58	5.2	1188	48	4.0	0.1982	0.78	(0.54,	1.14)	0.77	(0.52,	1.14)	-0.01	(-0.03, 0.01)	
Region																0.4871
North America	213	23	10.8	212	18	8.5	0.4204	0.79	(0.44,	1.41)	0.77	(0.40,	1.47)	-0.02	(-0.08, 0.03)	
Latin America	645	42	6.5	641	22	3.4	0.0111	0.53	(0.32,	0.87)	0.51	(0.30,	0.87)	-0.03	(-0.05,-0.01)	
Europe	674	34	5.0	676	25	3.7	0.2264	0.73	(0.44,	1.22)	0.72	(0.43,	1.23)	-0.01	(-0.04, 0.01)	
Asia	244	5	2.0	248	6	2.4	0.7813	1.18	(0.37,	3.82)	1.19	(0.36,	3.94)	0.00	(-0.02, 0.03)	
Other	87	3	3.4	86	0	0	0.1321	0.14	(<0.01,	2.76)	0.14	(<0.01,	2.74)	-0.03	(-0.08, 0.01)	
OECD Member																0.3748
No	741	40	5.4	713	21	2.9	0.0197	0.55	(0.33,	0.92)	0.53	(0.31,	0.91)	-0.02	(-0.04, 0.00)	
Yes	1122	67	6.0	1150	50	4.3	0.0800	0.73	(0.51,	1.04)	0.72	(0.49,	1.04)	-0.02	(-0.03, 0.00)	
Baseline NYHA																0.1738
II	1399	70	5.0	1399	53	3.8	0.1170	0.76	(0.53,	1.07)	0.75	(0.52,	1.08)	-0.01	(-0.03, 0.00)	
III/IV	464	37	8.0	464	18	3.9	0.0083	0.49	(0.28,	0.84)	0.47	(0.26,	0.83)	-0.04	(-0.07,-0.01)	
Baseline Diabetes Status																0.9869
Diabetic	926	57	6.2	927	38	4.1	0.0448	0.67	(0.45,	0.99)	0.65	(0.43,	0.99)	-0.02	(-0.04, 0.00)	
Non-Diabetic	937	50	5.3	936	33	3.5	0.0569	0.66	(0.43,	1.02)	0.65	(0.41,	1.02)	-0.02	(-0.04, 0.00)	
Baseline BMI [kg/m²]																0.5841
<30	1299	66	5.1	1263	45	3.6	0.0592	0.70	(0.48,	1.02)	0.69	(0.47,	1.02)	-0.02	(-0.03, 0.00)	
>=30	564	41	7.3	600	26	4.3	0.0316	0.60	(0.37,	0.96)	0.58	(0.35,	0.96)	-0.03	(-0.06, 0.00)	

Risk ratios and odds ratios with confidence intervals (CIs) are estimated by Cochran-Mantel-Haenszel method. For risk differences standard Wald asymptotic confidence limits are calculated. A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied 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).
For AEs on SOC and/or PT level, subgroup analyses are only shown if overall test for treatment is significant on 5% level (i.e. 95% CI for the risk ratio does not contain 1; if this is not calculable the p-value of Chi-square test is used).
MedDRA version: 23.0. * Chi-square test for treatment effect ** Breslow-Day test for homogeneity of odds ratios (treatment by subgroup interaction).

Table R.1.4.4: 2 Proportion of patients with serious adverse events occurring in at least 1% of the patients in either treatment arm in the overall population on SOC level - by SOC - overall and by subgroup - TS
System organ class: Renal and urinary disorders

Subgroup	Placebo			Empa 10mg			Empa 10mg vs Placebo							
Category	N	n	%	N	n	%	p-value *	Risk ratio	(95% CI)	Odds ratio	(95% CI)	Risk diff.	(95% CI)	p-value **
Baseline eGFR (CKD-EPI) [mL/min/1.73m²]														0.8983
>=60	958	35	3.7	969	24	2.5	0.1339	0.68	(0.41, 1.13)	0.67	(0.40, 1.13)	-0.01	(-0.03, 0.00)	
<60	904	72	8.0	893	47	5.3	0.0213	0.66	(0.46, 0.94)	0.64	(0.44, 0.94)	-0.03	(-0.05, 0.00)	
History of HHF (in the last 12 months)														0.6225
No	1290	69	5.3	1286	43	3.3	0.0126	0.63	(0.43, 0.91)	0.61	(0.41, 0.90)	-0.02	(-0.04, 0.00)	
Yes	573	38	6.6	577	28	4.9	0.1946	0.73	(0.46, 1.18)	0.72	(0.43, 1.19)	-0.02	(-0.04, 0.01)	
Cause of Heart Failure														0.4117
Ischemic	944	50	5.3	983	39	4.0	0.1646	0.75	(0.50, 1.13)	0.74	(0.48, 1.13)	-0.01	(-0.03, 0.01)	
Non-ischemic	919	57	6.2	880	32	3.6	0.0121	0.59	(0.38, 0.89)	0.57	(0.37, 0.89)	-0.03	(-0.05,-0.01)	
Heart Failure Physiology														0.5224
LVEF <= 30% and NTproBNP < median	723	31	4.3	698	16	2.3	0.0355	0.53	(0.30, 0.97)	0.52	(0.28, 0.97)	-0.02	(-0.04, 0.00)	
LVEF <= 30% and NTproBNP >= median	660	53	8.0	631	33	5.2	0.0437	0.65	(0.43, 0.99)	0.63	(0.40, 0.99)	-0.03	(-0.06, 0.00)	
LVEF > 30%	473	23	4.9	526	22	4.2	0.6048	0.86	(0.49, 1.52)	0.85	(0.47, 1.55)	-0.01	(-0.03, 0.02)	
Baseline use of MRA														0.8548
No	512	32	6.3	557	24	4.3	0.1547	0.69	(0.41, 1.15)	0.68	(0.39, 1.16)	-0.02	(-0.05, 0.01)	
Yes	1351	75	5.6	1306	47	3.6	0.0162	0.65	(0.45, 0.93)	0.64	(0.44, 0.92)	-0.02	(-0.04, 0.00)	
Baseline use of ARNi														0.6398
No	1476	80	5.4	1523	53	3.5	0.0099	0.64	(0.46, 0.90)	0.63	(0.44, 0.90)	-0.02	(-0.03, 0.00)	
Yes	387	27	7.0	340	18	5.3	0.3475	0.76	(0.43, 1.35)	0.75	(0.40, 1.38)	-0.02	(-0.05, 0.02)	

Risk ratios and odds ratios with confidence intervals (CIs) are estimated by Cochran-Mantel-Haenszel method. For risk differences standard Wald asymptotic confidence limits are calculated. A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied 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).
For AEs on SOC and/or PT level, subgroup analyses are only shown if overall test for treatment is significant on 5% level (i.e. 95% CI for the risk ratio does not contain 1; if this is not calculable the p-value of Chi-square test is used).
MedDRA version: 23.0. * Chi-square test for treatment effect ** Breslow-Day test for homogeneity of odds ratios (treatment by subgroup interaction).

Table R.1.4.4: 2 Proportion of patients with serious adverse events occurring in at least 1% of the patients in either treatment arm in the overall population on SOC level - by SOC - overall and by subgroup - TS
System organ class: Renal and urinary disorders

Subgroup	Placebo			Empa 10mg			Empa 10mg vs Placebo								
Category	N	n	%	N	n	%	p-value *	Risk ratio	(95% CI)		Odds ratio	(95% CI)		Risk diff.	(95% CI)	p-value **
Baseline LVEF																0.5869
<=30	1390	84	6.0	1337	49	3.7	0.0039	0.61	(0.43,	0.86)	0.59	(0.41,	0.85)	-0.02	(-0.04,-0.01)	
>30 to <=35	359	16	4.5	398	15	3.8	0.6334	0.85	(0.42,	1.69)	0.84	(0.41,	1.72)	-0.01	(-0.04, 0.02)	
>35	114	7	6.1	128	7	5.5	0.8232	0.89	(0.32,	2.46)	0.88	(0.30,	2.60)	-0.01	(-0.07, 0.05)	
Baseline NTproBNP																0.7202
< median	919	38	4.1	942	24	2.5	0.0565	0.62	(0.37,	1.02)	0.61	(0.36,	1.02)	-0.02	(-0.03, 0.00)	
>= median	943	69	7.3	920	47	5.1	0.0486	0.70	(0.49,	1.00)	0.68	(0.47,	1.00)	-0.02	(-0.04, 0.00)	

Risk ratios and odds ratios with confidence intervals (CIs) are estimated by Cochran-Mantel-Haenszel method. For risk differences standard Wald asymptotic confidence limits are calculated. A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied 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).
For AEs on SOC and/or PT level, subgroup analyses are only shown if overall test for treatment is significant on 5% level (i.e. 95% CI for the risk ratio does not contain 1; if this is not calculable the p-value of Chi-square test is used).
MedDRA version: 23.0. * Chi-square test for treatment effect ** Breslow-Day test for homogeneity of odds ratios (treatment by subgroup interaction).

Table R.1.4.4: 2 Proportion of patients with serious adverse events occurring in at least 1% of the patients in either treatment arm in the overall population on SOC level - by SOC - overall and by subgroup - TS
System organ class: Nervous system disorders

Subgroup Category	Placebo N	Placebo n	Placebo %	Empa 10mg N	Empa 10mg n	Empa 10mg %	Empa 10mg vs Placebo p-value *	Risk ratio (95% CI)	Odds ratio (95% CI)	Risk diff. (95% CI)	p-value **
Overall	1863	74	4.0	1863	94	5.0	0.1143	1.27 (0.94, 1.71)	1.28 (0.94, 1.75)	0.01 (0.00, 0.02)	

Risk ratios and odds ratios with confidence intervals (CIs) are estimated by Cochran-Mantel-Haenszel method. For risk differences standard Wald asymptotic confidence limits are calculated. A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied 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).
For AEs on SOC and/or PT level, subgroup analyses are only shown if overall test for treatment is significant on 5% level (i.e. 95% CI for the risk ratio does not contain 1; if this is not calculable the p-value of Chi-square test is used).
MedDRA version: 23.0. * Chi-square test for treatment effect ** Breslow-Day test for homogeneity of odds ratios (treatment by subgroup interaction).

Table R.1.4.4: 2 Proportion of patients with serious adverse events occurring in at least 1% of the patients in either treatment arm in the overall population on SOC level - by SOC - 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	1863	70	3.8	1863	54	2.9	0.1439	0.77	(0.54, 1.09)	0.76	(0.53, 1.10)	-0.01 (-0.02, 0.00)	

Risk ratios and odds ratios with confidence intervals (CIs) are estimated by Cochran-Mantel-Haenszel method. For risk differences standard Wald asymptotic confidence limits are calculated. A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied 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).
For AEs on SOC and/or PT level, subgroup analyses are only shown if overall test for treatment is significant on 5% level (i.e. 95% CI for the risk ratio does not contain 1; if this is not calculable the p-value of Chi-square test is used).
MedDRA version: 23.0. * Chi-square test for treatment effect ** Breslow-Day test for homogeneity of odds ratios (treatment by subgroup interaction).

Table R.1.4.4: 2 Proportion of patients with serious adverse events occurring in at least 1% of the patients in either treatment arm in the overall population on SOC level - by SOC - overall and by subgroup - TS
System organ class: Respiratory, thoracic and mediastinal disorders

Subgroup Category	Placebo N	Placebo n	Placebo %	Empa 10mg N	Empa 10mg n	Empa 10mg %	Empa 10mg vs Placebo p-value *	Risk ratio (95% CI)	Odds ratio (95% CI)	Risk diff. (95% CI)	p-value **
Overall	1863	63	3.4	1863	44	2.4	0.0624	0.70 (0.48, 1.02)	0.69 (0.47, 1.02)	-0.01 (-0.02, 0.00)	

Risk ratios and odds ratios with confidence intervals (CIs) are estimated by Cochran-Mantel-Haenszel method. For risk differences standard Wald asymptotic confidence limits are calculated. A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied 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).
For AEs on SOC and/or PT level, subgroup analyses are only shown if overall test for treatment is significant on 5% level (i.e. 95% CI for the risk ratio does not contain 1; if this is not calculable the p-value of Chi-square test is used).
MedDRA version: 23.0. * Chi-square test for treatment effect ** Breslow-Day test for homogeneity of odds ratios (treatment by subgroup interaction).

Table R.1.4.4: 2 Proportion of patients with serious adverse events occurring in at least 1% of the patients in either treatment arm in the overall population on SOC level - by SOC - overall and by subgroup - TS
System organ class: Gastrointestinal disorders

Subgroup Category	Placebo N	Placebo n	Placebo %	Empa 10mg N	Empa 10mg n	Empa 10mg %	Empa 10mg vs Placebo p-value *	Risk ratio (95% CI)	Odds ratio (95% CI)	Risk diff. (95% CI)	p-value **
Overall	1863	43	2.3	1863	60	3.2	0.0894	1.40 (0.95, 2.05)	1.41 (0.95, 2.09)	0.01 (0.00, 0.02)	

Risk ratios and odds ratios with confidence intervals (CIs) are estimated by Cochran-Mantel-Haenszel method. For risk differences standard Wald asymptotic confidence limits are calculated. A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied 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).
For AEs on SOC and/or PT level, subgroup analyses are only shown if overall test for treatment is significant on 5% level (i.e. 95% CI for the risk ratio does not contain 1; if this is not calculable the p-value of Chi-square test is used).
MedDRA version: 23.0. * Chi-square test for treatment effect ** Breslow-Day test for homogeneity of odds ratios (treatment by subgroup interaction).

Table R.1.4.4: 2 Proportion of patients with serious adverse events occurring in at least 1% of the patients in either treatment arm in the overall population on SOC level - by SOC - 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	1863	41	2.2	1863	53	2.8	0.2100	1.29 (0.86, 1.93)	1.30 (0.86, 1.97)	0.01 (0.00, 0.02)	

Risk ratios and odds ratios with confidence intervals (CIs) are estimated by Cochran-Mantel-Haenszel method. For risk differences standard Wald asymptotic confidence limits are calculated. A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied 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).
For AEs on SOC and/or PT level, subgroup analyses are only shown if overall test for treatment is significant on 5% level (i.e. 95% CI for the risk ratio does not contain 1; if this is not calculable the p-value of Chi-square test is used).
MedDRA version: 23.0. * Chi-square test for treatment effect ** Breslow-Day test for homogeneity of odds ratios (treatment by subgroup interaction).

Table R.1.4.4: 2 Proportion of patients with serious adverse events occurring in at least 1% of the patients in either treatment arm in the overall population on SOC level - by SOC - 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	1863	51	2.7	1863	52	2.8	0.9204	1.02	(0.70, 1.49)	1.02	(0.69, 1.51)	0.00 (-0.01, 0.01)	

Risk ratios and odds ratios with confidence intervals (CIs) are estimated by Cochran-Mantel-Haenszel method. For risk differences standard Wald asymptotic confidence limits are calculated. A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied 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).
For AEs on SOC and/or PT level, subgroup analyses are only shown if overall test for treatment is significant on 5% level (i.e. 95% CI for the risk ratio does not contain 1; if this is not calculable the p-value of Chi-square test is used).
MedDRA version: 23.0. * Chi-square test for treatment effect ** Breslow-Day test for homogeneity of odds ratios (treatment by subgroup interaction).

Table R.1.4.4: 2 Proportion of patients with serious adverse events occurring in at least 1% of the patients in either treatment arm in the overall population on SOC level - by SOC - overall and by subgroup - TS
System organ class: Metabolism and nutrition disorders

Subgroup Category	Placebo N	Placebo n	Placebo %	Empa 10mg N	Empa 10mg n	Empa 10mg %	Empa 10mg vs Placebo p-value *	Risk ratio (95% CI)	Odds ratio (95% CI)	Risk diff. (95% CI)	p-value **
Overall	1863	46	2.5	1863	34	1.8	0.1750	0.74 (0.48, 1.15)	0.73 (0.47, 1.15)	-0.01 (-0.02, 0.00)	

Risk ratios and odds ratios with confidence intervals (CIs) are estimated by Cochran-Mantel-Haenszel method. For risk differences standard Wald asymptotic confidence limits are calculated. A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied 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).
For AEs on SOC and/or PT level, subgroup analyses are only shown if overall test for treatment is significant on 5% level (i.e. 95% CI for the risk ratio does not contain 1; if this is not calculable the p-value of Chi-square test is used).
MedDRA version: 23.0. * Chi-square test for treatment effect ** Breslow-Day test for homogeneity of odds ratios (treatment by subgroup interaction).

Table R.1.4.4: 2 Proportion of patients with serious adverse events occurring in at least 1% of the patients in either treatment arm in the overall population on SOC level - by SOC - 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	1863	44	2.4	1863	40	2.1	0.6589	0.91	(0.60, 1.39)	0.91	(0.59, 1.40)	0.00 (-0.01, 0.01)	

Risk ratios and odds ratios with confidence intervals (CIs) are estimated by Cochran-Mantel-Haenszel method. For risk differences standard Wald asymptotic confidence limits are calculated. A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied 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).
For AEs on SOC and/or PT level, subgroup analyses are only shown if overall test for treatment is significant on 5% level (i.e. 95% CI for the risk ratio does not contain 1; if this is not calculable the p-value of Chi-square test is used).
MedDRA version: 23.0. * Chi-square test for treatment effect ** Breslow-Day test for homogeneity of odds ratios (treatment by subgroup interaction).

Table R.1.4.4: 2 Proportion of patients with serious adverse events occurring in at least 1% of the patients in either treatment arm in the overall population on SOC level - by SOC - overall and by subgroup - TS
System organ class: Hepatobiliary disorders

Subgroup Category	Placebo N	Placebo n	Placebo %	Empa 10mg N	Empa 10mg n	Empa 10mg %	Empa 10mg vs Placebo p-value *	Risk ratio	Risk (95% CI)	Odds ratio	Odds (95% CI)	Risk diff.	Risk diff. (95% CI)	p-value **
Overall	1863	30	1.6	1863	16	0.9	0.0378	0.53	(0.29, 0.98)	0.53	(0.29, 0.97)	-0.01	(-0.01, 0.00)	
Sex														0.2032
Male	1410	21	1.5	1426	14	1.0	0.2209	0.66	(0.34, 1.29)	0.66	(0.33, 1.29)	-0.01	(-0.01, 0.00)	
Female	453	9	2.0	437	2	0.5	0.0390	0.23	(0.05, 1.06)	0.23	(0.05, 1.06)	-0.02	(-0.03, 0.00)	
Age [years]														0.3981
< 65	739	10	1.4	675	3	0.4	0.0737	0.33	(0.09, 1.19)	0.33	(0.09, 1.19)	-0.01	(-0.02, 0.00)	
>= 65	1124	20	1.8	1188	13	1.1	0.1651	0.61	(0.31, 1.23)	0.61	(0.30, 1.23)	-0.01	(-0.02, 0.00)	
Region														0.6914
North America	213	2	0.9	212	2	0.9	0.9962	1.00	(0.14, 7.07)	1.00	(0.14, 7.20)	0.00	(-0.02, 0.02)	
Latin America	645	7	1.1	641	6	0.9	0.7891	0.86	(0.29, 2.55)	0.86	(0.29, 2.58)	0.00	(-0.01, 0.01)	
Europe	674	13	1.9	676	4	0.6	0.0276	0.31	(0.10, 0.94)	0.30	(0.10, 0.93)	-0.01	(-0.03, 0.00)	
Asia	244	7	2.9	248	4	1.6	0.3461	0.56	(0.17, 1.90)	0.56	(0.16, 1.92)	-0.01	(-0.04, 0.01)	
Other	87	1	1.1	86	0	0	0.4820	0.34	(0.01, 8.16)	0.33	(0.01, 8.30)	-0.01	(-0.04, 0.02)	
OECD Member														0.3865
No	741	8	1.1	713	6	0.8	0.6421	0.78	(0.27, 2.24)	0.78	(0.27, 2.25)	0.00	(-0.01, 0.01)	
Yes	1122	22	2.0	1150	10	0.9	0.0273	0.44	(0.21, 0.93)	0.44	(0.21, 0.93)	-0.01	(-0.02, 0.00)	
Baseline NYHA														0.2655
II	1399	22	1.6	1399	14	1.0	0.1796	0.64	(0.33, 1.24)	0.63	(0.32, 1.24)	-0.01	(-0.01, 0.00)	
III/IV	464	8	1.7	464	2	0.4	0.0564	0.25	(0.05, 1.17)	0.25	(0.05, 1.17)	-0.01	(-0.03, 0.00)	
Baseline Diabetes Status														0.2144
Diabetic	926	13	1.4	927	10	1.1	0.5273	0.77	(0.34, 1.74)	0.77	(0.33, 1.76)	0.00	(-0.01, 0.01)	
Non-Diabetic	937	17	1.8	936	6	0.6	0.0211	0.35	(0.14, 0.89)	0.35	(0.14, 0.89)	-0.01	(-0.02, 0.00)	
Baseline BMI [kg/m²]														0.2134
<30	1299	27	2.1	1263	12	1.0	0.0197	0.46	(0.23, 0.90)	0.45	(0.23, 0.90)	-0.01	(-0.02, 0.00)	
>=30	564	3	0.5	600	4	0.7	0.7663	1.25	(0.28, 5.58)	1.26	(0.28, 5.63)	0.00	(-0.01, 0.01)	

Risk ratios and odds ratios with confidence intervals (CIs) are estimated by Cochran-Mantel-Haenszel method. For risk differences standard Wald asymptotic confidence limits are calculated. A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied 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).
For AEs on SOC and/or PT level, subgroup analyses are only shown if overall test for treatment is significant on 5% level (i.e. 95% CI for the risk ratio does not contain 1; if this is not calculable the p-value of Chi-square test is used).
MedDRA version: 23.0. * Chi-square test for treatment effect ** Breslow-Day test for homogeneity of odds ratios (treatment by subgroup interaction).

Table R.1.4.4: 2 Proportion of patients with serious adverse events occurring in at least 1% of the patients in either treatment arm in the overall population on SOC level - by SOC - 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 **
Baseline eGFR (CKD-EPI) [mL/min/1.73m²]																0.0358
>=60	958	17	1.8	969	4	0.4	0.0040	0.23	(0.08,	0.69)	0.23	(0.08,	0.68)	-0.01	(-0.02, 0.00)	
<60	904	13	1.4	893	12	1.3	0.8645	0.93	(0.43,	2.04)	0.93	(0.42,	2.06)	0.00	(-0.01, 0.01)	
History of HHF (in the last 12 months)																0.3576
No	1290	21	1.6	1286	9	0.7	0.0281	0.43	(0.20,	0.94)	0.43	(0.19,	0.93)	-0.01	(-0.02, 0.00)	
Yes	573	9	1.6	577	7	1.2	0.6048	0.77	(0.29,	2.06)	0.77	(0.28,	2.08)	0.00	(-0.02, 0.01)	
Cause of Heart Failure																0.1217
Ischemic	944	17	1.8	983	13	1.3	0.3965	0.73	(0.36,	1.50)	0.73	(0.35,	1.51)	0.00	(-0.02, 0.01)	
Non-ischemic	919	13	1.4	880	3	0.3	0.0153	0.24	(0.07,	0.84)	0.24	(0.07,	0.84)	-0.01	(-0.02, 0.00)	
Heart Failure Physiology																0.6852
LVEF <= 30% and NTproBNP < median	723	8	1.1	698	4	0.6	0.2720	0.52	(0.16,	1.71)	0.52	(0.15,	1.72)	-0.01	(-0.01, 0.00)	
LVEF <= 30% and NTproBNP >= median	660	16	2.4	631	10	1.6	0.2831	0.65	(0.30,	1.43)	0.65	(0.29,	1.44)	-0.01	(-0.02, 0.01)	
LVEF > 30%	473	6	1.3	526	2	0.4	0.1158	0.30	(0.06,	1.48)	0.30	(0.06,	1.48)	-0.01	(-0.02, 0.00)	
Baseline use of MRA																0.1619
No	512	8	1.6	557	8	1.4	0.8652	0.92	(0.35,	2.43)	0.92	(0.34,	2.46)	0.00	(-0.02, 0.01)	
Yes	1351	22	1.6	1306	8	0.6	0.0132	0.38	(0.17,	0.84)	0.37	(0.17,	0.84)	-0.01	(-0.02, 0.00)	
Baseline use of ARNi																0.4020
No	1476	28	1.9	1523	14	0.9	0.0227	0.48	(0.26,	0.92)	0.48	(0.25,	0.92)	-0.01	(-0.02, 0.00)	
Yes	387	2	0.5	340	2	0.6	0.8966	1.14	(0.16,	8.04)	1.14	(0.16,	8.13)	0.00	(-0.01, 0.01)	

Risk ratios and odds ratios with confidence intervals (CIs) are estimated by Cochran-Mantel-Haenszel method. For risk differences standard Wald asymptotic confidence limits are calculated. A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied 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).
For AEs on SOC and/or PT level, subgroup analyses are only shown if overall test for treatment is significant on 5% level (i.e. 95% CI for the risk ratio does not contain 1; if this is not calculable the p-value of Chi-square test is used).
MedDRA version: 23.0. * Chi-square test for treatment effect ** Breslow-Day test for homogeneity of odds ratios (treatment by subgroup interaction).

Table R.1.4.4: 2 Proportion of patients with serious adverse events occurring in at least 1% of the patients in either treatment arm in the overall population on SOC level - by SOC - 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 **
Baseline LVEF															0.6730
<=30	1390	24	1.7	1337	14	1.0	0.1302	0.61	(0.32,	1.17)	0.60	(0.31, 1.17)	-0.01	(-0.02, 0.00)	
>30 to <=35	359	4	1.1	398	1	0.3	0.1433	0.23	(0.03,	2.01)	0.22	(0.02, 2.01)	-0.01	(-0.02, 0.00)	
>35	114	2	1.8	128	1	0.8	0.4946	0.45	(0.04,	4.85)	0.44	(0.04, 4.93)	-0.01	(-0.04, 0.02)	
Baseline NTproBNP															0.9877
< median	919	11	1.2	942	6	0.6	0.2042	0.53	(0.20,	1.43)	0.53	(0.19, 1.44)	-0.01	(-0.01, 0.00)	
>= median	943	19	2.0	920	10	1.1	0.1058	0.54	(0.25,	1.15)	0.53	(0.25, 1.16)	-0.01	(-0.02, 0.00)	

Risk ratios and odds ratios with confidence intervals (CIs) are estimated by Cochran-Mantel-Haenszel method. For risk differences standard Wald asymptotic confidence limits are calculated. A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied 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).
For AEs on SOC and/or PT level, subgroup analyses are only shown if overall test for treatment is significant on 5% level (i.e. 95% CI for the risk ratio does not contain 1; if this is not calculable the p-value of Chi-square test is used).
MedDRA version: 23.0. * Chi-square test for treatment effect ** Breslow-Day test for homogeneity of odds ratios (treatment by subgroup interaction).

Table R.1.4.4: 2 Proportion of patients with serious adverse events occurring in at least 1% of the patients in either treatment arm in the overall population on SOC level - by SOC - 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	1863	24	1.3	1863	15	0.8	0.1474	0.63	(0.33, 1.19)	0.62	(0.33, 1.19)	0.00 (-0.01, 0.00)	

Risk ratios and odds ratios with confidence intervals (CIs) are estimated by Cochran-Mantel-Haenszel method. For risk differences standard Wald asymptotic confidence limits are calculated. A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied 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).
For AEs on SOC and/or PT level, subgroup analyses are only shown if overall test for treatment is significant on 5% level (i.e. 95% CI for the risk ratio does not contain 1; if this is not calculable the p-value of Chi-square test is used).
MedDRA version: 23.0. * Chi-square test for treatment effect ** Breslow-Day test for homogeneity of odds ratios (treatment by subgroup interaction).

Table R.1.4.4: 3 Proportion of patients with severe adverse events occurring in at least 1% of the patients in either treatment arm in the overall population on SOC level - by SOC - 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	1863	294	15.8	1863	250	13.4	0.0412	0.85	(0.73,	0.99)	0.83	(0.69,	0.99)	-0.02	(-0.05, 0.00)	
Sex																0.2649
Male	1410	223	15.8	1426	201	14.1	0.1990	0.89	(0.75,	1.06)	0.87	(0.71,	1.07)	-0.02	(-0.04, 0.01)	
Female	453	71	15.7	437	49	11.2	0.0514	0.72	(0.51,	1.00)	0.68	(0.46,	1.00)	-0.04	(-0.09, 0.00)	
Age [years]																0.4870
< 65	739	131	17.7	675	96	14.2	0.0730	0.80	(0.63,	1.02)	0.77	(0.58,	1.03)	-0.04	(-0.07, 0.00)	
>= 65	1124	163	14.5	1188	154	13.0	0.2823	0.89	(0.73,	1.10)	0.88	(0.69,	1.11)	-0.02	(-0.04, 0.01)	
Region																0.2426
North America	213	43	20.2	212	41	19.3	0.8262	0.96	(0.65,	1.41)	0.95	(0.59,	1.53)	-0.01	(-0.08, 0.07)	
Latin America	645	101	15.7	641	89	13.9	0.3699	0.89	(0.68,	1.15)	0.87	(0.64,	1.18)	-0.02	(-0.06, 0.02)	
Europe	674	97	14.4	676	82	12.1	0.2205	0.84	(0.64,	1.11)	0.82	(0.60,	1.13)	-0.02	(-0.06, 0.01)	
Asia	244	40	16.4	248	35	14.1	0.4817	0.86	(0.57,	1.31)	0.84	(0.51,	1.37)	-0.02	(-0.09, 0.04)	
Other	87	13	14.9	86	3	3.5	0.0093	0.23	(0.07,	0.79)	0.21	(0.06,	0.75)	-0.11	(-0.20,-0.03)	
OECD Member																0.9173
No	741	115	15.5	713	93	13.0	0.1776	0.84	(0.65,	1.08)	0.82	(0.61,	1.10)	-0.02	(-0.06, 0.01)	
Yes	1122	179	16.0	1150	157	13.7	0.1223	0.86	(0.70,	1.04)	0.83	(0.66,	1.05)	-0.02	(-0.05, 0.01)	
Baseline NYHA																0.5244
II	1399	186	13.3	1399	151	10.8	0.0421	0.81	(0.66,	0.99)	0.79	(0.63,	0.99)	-0.03	(-0.05, 0.00)	
III/IV	464	108	23.3	464	99	21.3	0.4779	0.92	(0.72,	1.17)	0.89	(0.66,	1.22)	-0.02	(-0.07, 0.03)	
Baseline Diabetes Status																0.3305
Diabetic	926	166	17.9	927	132	14.2	0.0308	0.79	(0.64,	0.98)	0.76	(0.59,	0.98)	-0.04	(-0.07, 0.00)	
Non-Diabetic	937	128	13.7	936	118	12.6	0.4996	0.92	(0.73,	1.17)	0.91	(0.70,	1.19)	-0.01	(-0.04, 0.02)	
Baseline BMI [kg/m²]																0.0278
<30	1299	207	15.9	1263	150	11.9	0.0030	0.75	(0.61,	0.91)	0.71	(0.57,	0.89)	-0.04	(-0.07,-0.01)	
>=30	564	87	15.4	600	100	16.7	0.5644	1.08	(0.83,	1.41)	1.10	(0.80,	1.50)	0.01	(-0.03, 0.05)	

Risk ratios and odds ratios with confidence intervals (CIs) are estimated by Cochran-Mantel-Haenszel method. For risk differences standard Wald asymptotic confidence limits are calculated. A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied 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).
For AEs on SOC and/or PT level, subgroup analyses are only shown if overall test for treatment is significant on 5% level (i.e. 95% CI for the risk ratio does not contain 1; if this is not calculable the p-value of Chi-square test is used).
MedDRA version: 23.0. * Chi-square test for treatment effect ** Breslow-Day test for homogeneity of odds ratios (treatment by subgroup interaction).

Table R.1.4.4: 3 Proportion of patients with severe adverse events occurring in at least 1% of the patients in either treatment arm in the overall population on SOC level - by SOC - overall and by subgroup - TS
System organ class: Cardiac disorders

Subgroup	Placebo			Empa 10mg			Empa 10mg vs Placebo								
Category	N	n	%	N	n	%	p-value *	Risk ratio	(95% CI)		Odds ratio	(95% CI)		Risk diff.	(95% CI)	p-value **
Baseline eGFR (CKD-EPI) [mL/min/1.73m²]																0.2307
>=60	958	145	15.1	969	113	11.7	0.0251	0.77	(0.61,	0.97)	0.74	(0.57,	0.96)	-0.03	(-0.07, 0.00)	
<60	904	148	16.4	893	137	15.3	0.5500	0.94	(0.76,	1.16)	0.93	(0.72,	1.19)	-0.01	(-0.04, 0.02)	
History of HHF (in the last 12 months)																0.2775
No	1290	191	14.8	1286	151	11.7	0.0219	0.79	(0.65,	0.97)	0.77	(0.61,	0.96)	-0.03	(-0.06, 0.00)	
Yes	573	103	18.0	577	99	17.2	0.7155	0.95	(0.74,	1.23)	0.95	(0.70,	1.28)	-0.01	(-0.05, 0.04)	
Cause of Heart Failure																0.5955
Ischemic	944	151	16.0	983	139	14.1	0.2548	0.88	(0.71,	1.09)	0.86	(0.67,	1.11)	-0.02	(-0.05, 0.01)	
Non-ischemic	919	143	15.6	880	111	12.6	0.0728	0.81	(0.64,	1.02)	0.78	(0.60,	1.02)	-0.03	(-0.06, 0.00)	
Heart Failure Physiology																0.1238
LVEF <= 30% and NTproBNP < median	723	83	11.5	698	57	8.2	0.0361	0.71	(0.52,	0.98)	0.69	(0.48,	0.98)	-0.03	(-0.06, 0.00)	
LVEF <= 30% and NTproBNP >= median	660	155	23.5	631	122	19.3	0.0694	0.82	(0.67,	1.02)	0.78	(0.60,	1.02)	-0.04	(-0.09, 0.00)	
LVEF > 30%	473	54	11.4	526	68	12.9	0.4664	1.13	(0.81,	1.58)	1.15	(0.79,	1.69)	0.02	(-0.03, 0.06)	
Baseline use of MRA																0.5284
No	512	82	16.0	557	70	12.6	0.1068	0.78	(0.58,	1.05)	0.75	(0.53,	1.06)	-0.03	(-0.08, 0.01)	
Yes	1351	212	15.7	1306	180	13.8	0.1653	0.88	(0.73,	1.06)	0.86	(0.69,	1.06)	-0.02	(-0.05, 0.01)	
Baseline use of ARNi																0.0982
No	1476	224	15.2	1523	210	13.8	0.2802	0.91	(0.76,	1.08)	0.89	(0.73,	1.10)	-0.01	(-0.04, 0.01)	
Yes	387	70	18.1	340	40	11.8	0.0176	0.65	(0.45,	0.93)	0.60	(0.40,	0.92)	-0.06	(-0.11,-0.01)	

Risk ratios and odds ratios with confidence intervals (CIs) are estimated by Cochran-Mantel-Haenszel method. For risk differences standard Wald asymptotic confidence limits are calculated. A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied 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).
For AEs on SOC and/or PT level, subgroup analyses are only shown if overall test for treatment is significant on 5% level (i.e. 95% CI for the risk ratio does not contain 1; if this is not calculable the p-value of Chi-square test is used).
MedDRA version: 23.0. * Chi-square test for treatment effect ** Breslow-Day test for homogeneity of odds ratios (treatment by subgroup interaction).

Table R.1.4.4: 3 Proportion of patients with severe adverse events occurring in at least 1% of the patients in either treatment arm in the overall population on SOC level - by SOC - 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																0.1110
<=30	1390	240	17.3	1337	182	13.6	0.0084	0.79	(0.66,	0.94)	0.76	(0.61,	0.93)	-0.04	(-0.06,-0.01)	
>30 to <=35	359	37	10.3	398	51	12.8	0.2824	1.24	(0.83,	1.85)	1.28	(0.82,	2.01)	0.03	(-0.02, 0.07)	
>35	114	17	14.9	128	17	13.3	0.7155	0.89	(0.48,	1.66)	0.87	(0.42,	1.80)	-0.02	(-0.10, 0.07)	
Baseline NTproBNP																0.2065
< median	919	108	11.8	942	82	8.7	0.0300	0.74	(0.56,	0.97)	0.72	(0.53,	0.97)	-0.03	(-0.06, 0.00)	
>= median	943	185	19.6	920	168	18.3	0.4548	0.93	(0.77,	1.12)	0.92	(0.73,	1.15)	-0.01	(-0.05, 0.02)	

Risk ratios and odds ratios with confidence intervals (CIs) are estimated by Cochran-Mantel-Haenszel method. For risk differences standard Wald asymptotic confidence limits are calculated. A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied 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).
For AEs on SOC and/or PT level, subgroup analyses are only shown if overall test for treatment is significant on 5% level (i.e. 95% CI for the risk ratio does not contain 1; if this is not calculable the p-value of Chi-square test is used).
MedDRA version: 23.0. * Chi-square test for treatment effect ** Breslow-Day test for homogeneity of odds ratios (treatment by subgroup interaction).

Table R.1.4.4: 3 Proportion of patients with severe adverse events occurring in at least 1% of the patients in either treatment arm in the overall population on SOC level - by SOC - 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	1863	66	3.5	1863	80	4.3	0.2372	1.21	(0.88, 1.67)	1.22	(0.88, 1.70)	0.01	(0.00, 0.02)	

Risk ratios and odds ratios with confidence intervals (CIs) are estimated by Cochran-Mantel-Haenszel method. For risk differences standard Wald asymptotic confidence limits are calculated. A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied 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).
For AEs on SOC and/or PT level, subgroup analyses are only shown if overall test for treatment is significant on 5% level (i.e. 95% CI for the risk ratio does not contain 1; if this is not calculable the p-value of Chi-square test is used).
MedDRA version: 23.0. * Chi-square test for treatment effect ** Breslow-Day test for homogeneity of odds ratios (treatment by subgroup interaction).

Table R.1.4.4: 3 Proportion of patients with severe adverse events occurring in at least 1% of the patients in either treatment arm in the overall population on SOC level - by SOC - 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	1863	57	3.1	1863	47	2.5	0.3200	0.82	(0.56, 1.21)	0.82	(0.55, 1.21)	-0.01 (-0.02, 0.01)	

Risk ratios and odds ratios with confidence intervals (CIs) are estimated by Cochran-Mantel-Haenszel method. For risk differences standard Wald asymptotic confidence limits are calculated. A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied 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).
For AEs on SOC and/or PT level, subgroup analyses are only shown if overall test for treatment is significant on 5% level (i.e. 95% CI for the risk ratio does not contain 1; if this is not calculable the p-value of Chi-square test is used).
MedDRA version: 23.0. * Chi-square test for treatment effect ** Breslow-Day test for homogeneity of odds ratios (treatment by subgroup interaction).

Table R.1.4.4: 3 Proportion of patients with severe adverse events occurring in at least 1% of the patients in either treatment arm in the overall population on SOC level - by SOC - overall and by subgroup - TS
System organ class: Renal and urinary disorders

Subgroup Category	Placebo N	Placebo n	Placebo %	Empa 10mg N	Empa 10mg n	Empa 10mg %	Empa 10mg vs Placebo p-value *	Risk ratio (95% CI)	Odds ratio (95% CI)	Risk diff. (95% CI)	p-value **
Overall	1863	50	2.7	1863	37	2.0	0.1584	0.74 (0.49, 1.13)	0.73 (0.48, 1.13)	-0.01 (-0.02, 0.00)	

Risk ratios and odds ratios with confidence intervals (CIs) are estimated by Cochran-Mantel-Haenszel method. For risk differences standard Wald asymptotic confidence limits are calculated. A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied 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).
For AEs on SOC and/or PT level, subgroup analyses are only shown if overall test for treatment is significant on 5% level (i.e. 95% CI for the risk ratio does not contain 1; if this is not calculable the p-value of Chi-square test is used).
MedDRA version: 23.0. * Chi-square test for treatment effect ** Breslow-Day test for homogeneity of odds ratios (treatment by subgroup interaction).

Table R.1.4.4: 3 Proportion of patients with severe adverse events occurring in at least 1% of the patients in either treatment arm in the overall population on SOC level - by SOC - 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	1863	44	2.4	1863	47	2.5	0.7502	1.07	(0.71, 1.60)	1.07	(0.71, 1.62)	0.00	(-0.01, 0.01)	

Risk ratios and odds ratios with confidence intervals (CIs) are estimated by Cochran-Mantel-Haenszel method. For risk differences standard Wald asymptotic confidence limits are calculated. A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied 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).
For AEs on SOC and/or PT level, subgroup analyses are only shown if overall test for treatment is significant on 5% level (i.e. 95% CI for the risk ratio does not contain 1; if this is not calculable the p-value of Chi-square test is used).
MedDRA version: 23.0. * Chi-square test for treatment effect ** Breslow-Day test for homogeneity of odds ratios (treatment by subgroup interaction).

Table R.1.4.4: 3 Proportion of patients with severe adverse events occurring in at least 1% of the patients in either treatment arm in the overall population on SOC level - by SOC - overall and by subgroup - TS
System organ class: Respiratory, thoracic and mediastinal disorders

Subgroup Category	Placebo N	Placebo n	Placebo %	Empa 10mg N	Empa 10mg n	Empa 10mg %	Empa 10mg vs Placebo p-value *	Risk ratio (95% CI)	Odds ratio (95% CI)	Risk diff. (95% CI)	p-value **
Overall	1863	32	1.7	1863	23	1.2	0.2215	0.72 (0.42, 1.22)	0.72 (0.42, 1.23)	0.00 (-0.01, 0.00)	

Risk ratios and odds ratios with confidence intervals (CIs) are estimated by Cochran-Mantel-Haenszel method. For risk differences standard Wald asymptotic confidence limits are calculated. A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied 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).
For AEs on SOC and/or PT level, subgroup analyses are only shown if overall test for treatment is significant on 5% level (i.e. 95% CI for the risk ratio does not contain 1; if this is not calculable the p-value of Chi-square test is used).
MedDRA version: 23.0. * Chi-square test for treatment effect ** Breslow-Day test for homogeneity of odds ratios (treatment by subgroup interaction).

Table R.1.4.4: 3 Proportion of patients with severe adverse events occurring in at least 1% of the patients in either treatment arm in the overall population on SOC level - by SOC - overall and by subgroup - TS
System organ class: Metabolism and nutrition disorders

Subgroup Category	Placebo N	Placebo n	Placebo %	Empa 10mg N	Empa 10mg n	Empa 10mg %	Empa 10mg vs Placebo p-value *	Risk ratio (95% CI)	Odds ratio (95% CI)	Risk diff. (95% CI)	p-value **
Overall	1863	29	1.6	1863	30	1.6	0.8956	1.03 (0.62, 1.72)	1.04 (0.62, 1.73)	0.00 (-0.01, 0.01)	

Risk ratios and odds ratios with confidence intervals (CIs) are estimated by Cochran-Mantel-Haenszel method. For risk differences standard Wald asymptotic confidence limits are calculated. A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied 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).
For AEs on SOC and/or PT level, subgroup analyses are only shown if overall test for treatment is significant on 5% level (i.e. 95% CI for the risk ratio does not contain 1; if this is not calculable the p-value of Chi-square test is used).
MedDRA version: 23.0. * Chi-square test for treatment effect ** Breslow-Day test for homogeneity of odds ratios (treatment by subgroup interaction).

Table R.1.4.4: 3 Proportion of patients with severe adverse events occurring in at least 1% of the patients in either treatment arm in the overall population on SOC level - by SOC - 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	1863	22	1.2	1863	28	1.5	0.3930	1.27 (0.73, 2.22)	1.28 (0.73, 2.24)	0.00 (0.00, 0.01)	

Risk ratios and odds ratios with confidence intervals (CIs) are estimated by Cochran-Mantel-Haenszel method. For risk differences standard Wald asymptotic confidence limits are calculated. A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied 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).
For AEs on SOC and/or PT level, subgroup analyses are only shown if overall test for treatment is significant on 5% level (i.e. 95% CI for the risk ratio does not contain 1; if this is not calculable the p-value of Chi-square test is used).
MedDRA version: 23.0. * Chi-square test for treatment effect ** Breslow-Day test for homogeneity of odds ratios (treatment by subgroup interaction).

Table R.1.4.4: 3 Proportion of patients with severe adverse events occurring in at least 1% of the patients in either treatment arm in the overall population on SOC level - by SOC - overall and by subgroup - TS
System organ class: Gastrointestinal disorders

Subgroup Category	Placebo N	Placebo n	Placebo %	Empa 10mg N	Empa 10mg n	Empa 10mg %	Empa 10mg vs Placebo p-value *	Risk ratio (95% CI)	Odds ratio (95% CI)	Risk diff. (95% CI)	p-value **
Overall	1863	21	1.1	1863	26	1.4	0.4630	1.24 (0.70, 2.19)	1.24 (0.70, 2.21)	0.00 (0.00, 0.01)	

Risk ratios and odds ratios with confidence intervals (CIs) are estimated by Cochran-Mantel-Haenszel method. For risk differences standard Wald asymptotic confidence limits are calculated. A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied 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).
For AEs on SOC and/or PT level, subgroup analyses are only shown if overall test for treatment is significant on 5% level (i.e. 95% CI for the risk ratio does not contain 1; if this is not calculable the p-value of Chi-square test is used).
MedDRA version: 23.0. * Chi-square test for treatment effect ** Breslow-Day test for homogeneity of odds ratios (treatment by subgroup interaction).

Table R.1.4.4: 3 Proportion of patients with severe adverse events occurring in at least 1% of the patients in either treatment arm in the overall population on SOC level - by SOC - overall and by subgroup - TS
System organ class: Vascular disorders

Subgroup Category	Placebo N	Placebo n	Placebo %	Empa 10mg N	Empa 10mg n	Empa 10mg %	Empa 10mg vs Placebo p-value *	Risk ratio (95% CI)	Odds ratio (95% CI)	Risk diff. (95% CI)	p-value **
Overall	1863	23	1.2	1863	26	1.4	0.6662	1.13 (0.65, 1.97)	1.13 (0.64, 1.99)	0.00 (-0.01, 0.01)	

Risk ratios and odds ratios with confidence intervals (CIs) are estimated by Cochran-Mantel-Haenszel method. For risk differences standard Wald asymptotic confidence limits are calculated. A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied 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).
For AEs on SOC and/or PT level, subgroup analyses are only shown if overall test for treatment is significant on 5% level (i.e. 95% CI for the risk ratio does not contain 1; if this is not calculable the p-value of Chi-square test is used).
MedDRA version: 23.0. * Chi-square test for treatment effect ** Breslow-Day test for homogeneity of odds ratios (treatment by subgroup interaction).

Table R.1.4.4: 3 Proportion of patients with severe adverse events occurring in at least 1% of the patients in either treatment arm in the overall population on SOC level - by SOC - 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	1863	25	1.3	1863	14	0.8	0.0766	0.56	(0.29, 1.07)	0.56	(0.29, 1.07)	-0.01 (-0.01, 0.00)	

Risk ratios and odds ratios with confidence intervals (CIs) are estimated by Cochran-Mantel-Haenszel method. For risk differences standard Wald asymptotic confidence limits are calculated. A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied 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).
For AEs on SOC and/or PT level, subgroup analyses are only shown if overall test for treatment is significant on 5% level (i.e. 95% CI for the risk ratio does not contain 1; if this is not calculable the p-value of Chi-square test is used).
MedDRA version: 23.0. * Chi-square test for treatment effect ** Breslow-Day test for homogeneity of odds ratios (treatment by subgroup interaction).

R.1.4.5

Table R.1.4.5: 1 Proportion of patients with any adverse events occurring in at least 1% of the patients in either treatment arm in the overall population on PT level - by SOC and PT - overall and by subgroup - TS
System organ class: Cardiac disorders
Preferred term: Cardiac failure

Subgroup Category	Placebo N	Placebo n	Placebo %	Empa 10mg N	Empa 10mg n	Empa 10mg %	Empa 10mg vs Placebo p-value *	Risk ratio (95% CI)	Odds ratio (95% CI)	Risk diff. (95% CI)	p-value **
Overall	1863	444	23.8	1863	332	17.8	<0.0001	0.75 (0.66, 0.85)	0.69 (0.59, 0.81)	-0.06 (-0.09,-0.03)	
Sex											0.8097
Male	1410	340	24.1	1426	255	17.9	<0.0001	0.74 (0.64, 0.86)	0.69 (0.57, 0.82)	-0.06 (-0.09,-0.03)	
Female	453	104	23.0	437	77	17.6	0.0479	0.77 (0.59, 1.00)	0.72 (0.52, 1.00)	-0.05 (-0.11, 0.00)	
Age [years]											0.2682
< 65	739	187	25.3	675	117	17.3	0.0003	0.68 (0.56, 0.84)	0.62 (0.48, 0.80)	-0.08 (-0.12,-0.04)	
>= 65	1124	257	22.9	1188	215	18.1	0.0045	0.79 (0.67, 0.93)	0.75 (0.61, 0.91)	-0.05 (-0.08,-0.01)	
Region											0.2545
North America	213	35	16.4	212	28	13.2	0.3496	0.80 (0.51, 1.27)	0.77 (0.45, 1.33)	-0.03 (-0.10, 0.04)	
Latin America	645	159	24.7	641	115	17.9	0.0033	0.73 (0.59, 0.90)	0.67 (0.51, 0.88)	-0.07 (-0.11,-0.02)	
Europe	674	162	24.0	676	138	20.4	0.1095	0.85 (0.70, 1.04)	0.81 (0.63, 1.05)	-0.04 (-0.08, 0.01)	
Asia	244	78	32.0	248	44	17.7	0.0003	0.56 (0.40, 0.77)	0.46 (0.30, 0.70)	-0.14 (-0.22,-0.07)	
Other	87	10	11.5	86	7	8.1	0.4586	0.71 (0.28, 1.77)	0.68 (0.25, 1.88)	-0.03 (-0.12, 0.05)	
OECD Member											0.3977
No	741	188	25.4	713	127	17.8	0.0005	0.70 (0.57, 0.86)	0.64 (0.49, 0.82)	-0.08 (-0.12,-0.03)	
Yes	1122	256	22.8	1150	205	17.8	0.0031	0.78 (0.66, 0.92)	0.73 (0.60, 0.90)	-0.05 (-0.08,-0.02)	
Baseline NYHA											0.0002
II	1399	302	21.6	1399	184	13.2	<0.0001	0.61 (0.52, 0.72)	0.55 (0.45, 0.67)	-0.08 (-0.11,-0.06)	
III/IV	464	142	30.6	464	148	31.9	0.6709	1.04 (0.86, 1.26)	1.06 (0.80, 1.40)	0.01 (-0.05, 0.07)	
Baseline Diabetes Status											0.3686
Diabetic	926	239	25.8	927	170	18.3	0.0001	0.71 (0.60, 0.85)	0.65 (0.52, 0.81)	-0.07 (-0.11,-0.04)	
Non-Diabetic	937	205	21.9	936	162	17.3	0.0127	0.79 (0.66, 0.95)	0.75 (0.59, 0.94)	-0.05 (-0.08,-0.01)	
Baseline BMI [kg/m²]											0.1856
<30	1299	313	24.1	1263	214	16.9	<0.0001	0.70 (0.60, 0.82)	0.64 (0.53, 0.78)	-0.07 (-0.10,-0.04)	
>=30	564	131	23.2	600	118	19.7	0.1388	0.85 (0.68, 1.06)	0.81 (0.61, 1.07)	-0.04 (-0.08, 0.01)	

Risk ratios and odds ratios with confidence intervals (CIs) are estimated by Cochran-Mantel-Haenszel method. For risk differences standard Wald asymptotic confidence limits are calculated. A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied 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).
For AEs on SOC and/or PT level, subgroup analyses are only shown if overall test for treatment is significant on 5% level (i.e. 95% CI for the risk ratio does not contain 1; if this is not calculable the p-value of Chi-square test is used).
MedDRA version: 23.0. * Chi-square test for treatment effect ** Breslow-Day test for homogeneity of odds ratios (treatment by subgroup interaction).

Table R.1.4.5: 1 Proportion of patients with any adverse events occurring in at least 1% of the patients in either treatment arm in the overall population on PT level - by SOC and PT - overall and by subgroup - TS
System organ class: Cardiac disorders
Preferred term: Cardiac failure

Subgroup	Placebo			Empa 10mg			Empa 10mg vs Placebo					
Category	N	n	%	N	n	%	p-value *	Risk ratio (95% CI)		Odds ratio (95% CI)		Risk diff. (95% CI)	p-value **
Baseline eGFR (CKD-EPI) [mL/min/1.73m²]													0.0806
>=60	958	218	22.8	969	145	15.0	<0.0001	0.66 (0.54,	0.80)	0.60 (0.47,	0.75)	-0.08 (-0.11,-0.04)	
<60	904	226	25.0	893	187	20.9	0.0409	0.84 (0.71,	0.99)	0.79 (0.64,	0.99)	-0.04 (-0.08, 0.00)	
History of HHF (in the last 12 months)													0.0107
No	1290	294	22.8	1286	191	14.9	<0.0001	0.65 (0.55,	0.77)	0.59 (0.48,	0.72)	-0.08 (-0.11,-0.05)	
Yes	573	150	26.2	577	141	24.4	0.4971	0.93 (0.77,	1.14)	0.91 (0.70,	1.19)	-0.02 (-0.07, 0.03)	
Cause of Heart Failure													0.8568
Ischemic	944	226	23.9	983	174	17.7	0.0007	0.74 (0.62,	0.88)	0.68 (0.55,	0.85)	-0.06 (-0.10,-0.03)	
Non-ischemic	919	218	23.7	880	158	18.0	0.0026	0.76 (0.63,	0.91)	0.70 (0.56,	0.89)	-0.06 (-0.10,-0.02)	
Heart Failure Physiology													0.1264
LVEF <= 30% and NTproBNP < median	723	127	17.6	698	74	10.6	0.0002	0.60 (0.46,	0.79)	0.56 (0.41,	0.76)	-0.07 (-0.11,-0.03)	
LVEF <= 30% and NTproBNP >= median	660	218	33.0	631	159	25.2	0.0020	0.76 (0.64,	0.91)	0.68 (0.54,	0.87)	-0.08 (-0.13,-0.03)	
LVEF > 30%	473	98	20.7	526	98	18.6	0.4068	0.90 (0.70,	1.16)	0.88 (0.64,	1.20)	-0.02 (-0.07, 0.03)	
Baseline use of MRA													0.3638
No	512	122	23.8	557	90	16.2	0.0017	0.68 (0.53,	0.87)	0.62 (0.45,	0.83)	-0.08 (-0.12,-0.03)	
Yes	1351	322	23.8	1306	242	18.5	0.0008	0.78 (0.67,	0.90)	0.73 (0.60,	0.88)	-0.05 (-0.08,-0.02)	
Baseline use of ARNi													0.1157
No	1476	347	23.5	1523	281	18.5	0.0007	0.78 (0.68,	0.90)	0.74 (0.62,	0.88)	-0.05 (-0.08,-0.02)	
Yes	387	97	25.1	340	51	15.0	0.0008	0.60 (0.44,	0.81)	0.53 (0.36,	0.77)	-0.10 (-0.16,-0.04)	

Risk ratios and odds ratios with confidence intervals (CIs) are estimated by Cochran-Mantel-Haenszel method. For risk differences standard Wald asymptotic confidence limits are calculated. A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied 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).
For AEs on SOC and/or PT level, subgroup analyses are only shown if overall test for treatment is significant on 5% level (i.e. 95% CI for the risk ratio does not contain 1; if this is not calculable the p-value of Chi-square test is used).
MedDRA version: 23.0. * Chi-square test for treatment effect ** Breslow-Day test for homogeneity of odds ratios (treatment by subgroup interaction).

Table R.1.4.5: 1 Proportion of patients with any adverse events occurring in at least 1% of the patients in either treatment arm in the overall population on PT level - by SOC and PT - 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													0.2394
<=30	1390	346	24.9	1337	234	17.5	<0.0001	0.70 (0.61,	0.82)	0.64 (0.53,	0.77)	-0.07 (-0.10,-0.04)	
>30 to <=35	359	71	19.8	398	70	17.6	0.4398	0.89 (0.66,	1.20)	0.87 (0.60,	1.25)	-0.02 (-0.08, 0.03)	
>35	114	27	23.7	128	28	21.9	0.7374	0.92 (0.58,	1.47)	0.90 (0.49,	1.65)	-0.02 (-0.12, 0.09)	
Baseline NTproBNP													0.1425
< median	919	163	17.7	942	107	11.4	<0.0001	0.64 (0.51,	0.80)	0.59 (0.46,	0.77)	-0.06 (-0.10,-0.03)	
>= median	943	281	29.8	920	225	24.5	0.0095	0.82 (0.71,	0.95)	0.76 (0.62,	0.94)	-0.05 (-0.09,-0.01)	

Risk ratios and odds ratios with confidence intervals (CIs) are estimated by Cochran-Mantel-Haenszel method. For risk differences standard Wald asymptotic confidence limits are calculated. A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied 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).
For AEs on SOC and/or PT level, subgroup analyses are only shown if overall test for treatment is significant on 5% level (i.e. 95% CI for the risk ratio does not contain 1; if this is not calculable the p-value of Chi-square test is used).
MedDRA version: 23.0. * Chi-square test for treatment effect ** Breslow-Day test for homogeneity of odds ratios (treatment by subgroup interaction).

Table R.1.4.5: 1 Proportion of patients with any adverse events occurring in at least 1% of the patients in either treatment arm in the overall population on PT level - by SOC and PT - 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	1863	90	4.8	1863	68	3.7	0.0737	0.76 (0.56, 1.03)	0.75 (0.54, 1.03)	-0.01 (-0.02, 0.00)	

Risk ratios and odds ratios with confidence intervals (CIs) are estimated by Cochran-Mantel-Haenszel method. For risk differences standard Wald asymptotic confidence limits are calculated. A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied 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).
For AEs on SOC and/or PT level, subgroup analyses are only shown if overall test for treatment is significant on 5% level (i.e. 95% CI for the risk ratio does not contain 1; if this is not calculable the p-value of Chi-square test is used).
MedDRA version: 23.0. * Chi-square test for treatment effect ** Breslow-Day test for homogeneity of odds ratios (treatment by subgroup interaction).

Table R.1.4.5: 1 Proportion of patients with any adverse events occurring in at least 1% of the patients in either treatment arm in the overall population on PT level - by SOC and PT - overall and by subgroup - TS
System organ class: Cardiac disorders
Preferred term: Ventricular tachycardia

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	1863	37	2.0	1863	56	3.0	0.0460	1.51 (1.00, 2.28)	1.53 (1.00, 2.33)	0.01 (0.00, 0.02)	
Sex											0.1608
Male	1410	34	2.4	1426	46	3.2	0.1903	1.34 (0.86, 2.07)	1.35 (0.86, 2.11)	0.01 (0.00, 0.02)	
Female	453	3	0.7	437	10	2.3	0.0432	3.46 (0.96, 12.47)	3.51 (0.96, 12.85)	0.02 (0.00, 0.03)	
Age [years]											0.5116
< 65	739	10	1.4	675	17	2.5	0.1098	1.86 (0.86, 4.04)	1.88 (0.86, 4.14)	0.01 (0.00, 0.03)	
>= 65	1124	27	2.4	1188	39	3.3	0.2037	1.37 (0.84, 2.22)	1.38 (0.84, 2.27)	0.01 (0.00, 0.02)	
Region											0.8946
North America	213	10	4.7	212	13	6.1	0.5126	1.31 (0.59, 2.91)	1.33 (0.57, 3.09)	0.01 (-0.03, 0.06)	
Latin America	645	3	0.5	641	6	0.9	0.3111	2.01 (0.51, 8.01)	2.02 (0.50, 8.12)	0.00 (0.00, 0.01)	
Europe	674	21	3.1	676	29	4.3	0.2534	1.38 (0.79, 2.39)	1.39 (0.79, 2.47)	0.01 (-0.01, 0.03)	
Asia	244	3	1.2	248	8	3.2	0.1343	2.62 (0.70, 9.77)	2.68 (0.70, 10.22)	0.02 (-0.01, 0.05)	
Other	87	0	0	86	0	0	0.9954	1.01 (0.02, 50.41)	1.01 (0.02, 51.56)	0.00 (-0.02, 0.02)	
OECD Member											0.6259
No	741	3	0.4	713	6	0.8	0.2886	2.08 (0.52, 8.28)	2.09 (0.52, 8.38)	0.00 (0.00, 0.01)	
Yes	1122	34	3.0	1150	50	4.3	0.0961	1.43 (0.94, 2.20)	1.45 (0.93, 2.27)	0.01 (0.00, 0.03)	
Baseline NYHA											0.2852
II	1399	30	2.1	1399	40	2.9	0.2261	1.33 (0.84, 2.13)	1.34 (0.83, 2.17)	0.01 (0.00, 0.02)	
III/IV	464	7	1.5	464	16	3.4	0.0574	2.29 (0.95, 5.50)	2.33 (0.95, 5.72)	0.02 (0.00, 0.04)	
Baseline Diabetes Status											0.2983
Diabetic	926	10	1.1	927	21	2.3	0.0467	2.10 (0.99, 4.43)	2.12 (0.99, 4.53)	0.01 (0.00, 0.02)	
Non-Diabetic	937	27	2.9	936	35	3.7	0.2995	1.30 (0.79, 2.13)	1.31 (0.79, 2.18)	0.01 (-0.01, 0.02)	
Baseline BMI [kg/m²]											0.5572
<30	1299	21	1.6	1263	34	2.7	0.0604	1.67 (0.97, 2.85)	1.68 (0.97, 2.92)	0.01 (0.00, 0.02)	
>=30	564	16	2.8	600	22	3.7	0.4259	1.29 (0.69, 2.44)	1.30 (0.68, 2.51)	0.01 (-0.01, 0.03)	

Risk ratios and odds ratios with confidence intervals (CIs) are estimated by Cochran-Mantel-Haenszel method. For risk differences standard Wald asymptotic confidence limits are calculated. A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied 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).
For AEs on SOC and/or PT level, subgroup analyses are only shown if overall test for treatment is significant on 5% level (i.e. 95% CI for the risk ratio does not contain 1; if this is not calculable the p-value of Chi-square test is used).
MedDRA version: 23.0. * Chi-square test for treatment effect ** Breslow-Day test for homogeneity of odds ratios (treatment by subgroup interaction).

Table R.1.4.5: 1 Proportion of patients with any adverse events occurring in at least 1% of the patients in either treatment arm in the overall population on PT level - by SOC and PT - overall and by subgroup - TS
System organ class: Cardiac disorders
Preferred term: Ventricular tachycardia

Subgroup	Placebo			Empa 10mg			Empa 10mg vs Placebo					
Category	N	n	%	N	n	%	p-value *	Risk ratio (95% CI)	Odds ratio (95% CI)	Risk diff. (95% CI)		p-value **
Baseline eGFR (CKD-EPI) [mL/min/1.73m²]												0.9882
>=60	958	15	1.6	969	23	2.4	0.2022	1.52 (0.80, 2.89)	1.53 (0.79, 2.95)	0.01 (0.00, 0.02)		
<60	904	22	2.4	893	33	3.7	0.1205	1.52 (0.89, 2.58)	1.54 (0.89, 2.66)	0.01 (0.00, 0.03)		
History of HHF (in the last 12 months)												0.2035
No	1290	29	2.2	1286	37	2.9	0.3123	1.28 (0.79, 2.07)	1.29 (0.79, 2.11)	0.01 (-0.01, 0.02)		
Yes	573	8	1.4	577	19	3.3	0.0337	2.36 (1.04, 5.34)	2.40 (1.04, 5.54)	0.02 (0.00, 0.04)		
Cause of Heart Failure												0.6367
Ischemic	944	22	2.3	983	37	3.8	0.0679	1.62 (0.96, 2.72)	1.64 (0.96, 2.80)	0.01 (0.00, 0.03)		
Non-ischemic	919	15	1.6	880	19	2.2	0.4120	1.32 (0.68, 2.59)	1.33 (0.67, 2.63)	0.01 (-0.01, 0.02)		
Heart Failure Physiology												0.5079
LVEF <= 30% and NTproBNP < median	723	15	2.1	698	24	3.4	0.1157	1.66 (0.88, 3.13)	1.68 (0.87, 3.23)	0.01 (0.00, 0.03)		
LVEF <= 30% and NTproBNP >= median	660	12	1.8	631	21	3.3	0.0857	1.83 (0.91, 3.69)	1.86 (0.91, 3.81)	0.02 (0.00, 0.03)		
LVEF > 30%	473	10	2.1	526	11	2.1	0.9799	0.99 (0.42, 2.31)	0.99 (0.42, 2.35)	0.00 (-0.02, 0.02)		
Baseline use of MRA												0.9839
No	512	9	1.8	557	15	2.7	0.3025	1.53 (0.68, 3.47)	1.55 (0.67, 3.57)	0.01 (-0.01, 0.03)		
Yes	1351	28	2.1	1306	41	3.1	0.0839	1.51 (0.94, 2.43)	1.53 (0.94, 2.49)	0.01 (0.00, 0.02)		
Baseline use of ARNi												0.8559
No	1476	23	1.6	1523	38	2.5	0.0692	1.60 (0.96, 2.67)	1.62 (0.96, 2.73)	0.01 (0.00, 0.02)		
Yes	387	14	3.6	340	18	5.3	0.2715	1.46 (0.74, 2.90)	1.49 (0.73, 3.04)	0.02 (-0.01, 0.05)		

Risk ratios and odds ratios with confidence intervals (CIs) are estimated by Cochran-Mantel-Haenszel method. For risk differences standard Wald asymptotic confidence limits are calculated. A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied 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).
For AEs on SOC and/or PT level, subgroup analyses are only shown if overall test for treatment is significant on 5% level (i.e. 95% CI for the risk ratio does not contain 1; if this is not calculable the p-value of Chi-square test is used).
MedDRA version: 23.0. * Chi-square test for treatment effect ** Breslow-Day test for homogeneity of odds ratios (treatment by subgroup interaction).

Table R.1.4.5: 1 Proportion of patients with any adverse events occurring in at least 1% of the patients in either treatment arm in the overall population on PT level - by SOC and PT - overall and by subgroup - TS
System organ class: Cardiac disorders
Preferred term: Ventricular tachycardia

Subgroup	Placebo			Empa 10mg			Empa 10mg vs Placebo					
Category	N	n	%	N	n	%	p-value *	Risk ratio (95% CI)		Odds ratio (95% CI)		Risk diff. (95% CI)	p-value **
Baseline LVEF													0.4940
<=30	1390	27	1.9	1337	45	3.4	0.0205	1.73 (1.08,	2.78)	1.76 (1.08,	2.85)	0.01 (0.00, 0.03)	
>30 to <=35	359	7	1.9	398	7	1.8	0.8455	0.90 (0.32,	2.55)	0.90 (0.31,	2.59)	0.00 (-0.02, 0.02)	
>35	114	3	2.6	128	4	3.1	0.8192	1.19 (0.27,	5.19)	1.19 (0.26,	5.45)	0.00 (-0.04, 0.05)	
Baseline NTproBNP													0.3907
< median	919	24	2.6	942	32	3.4	0.3214	1.30 (0.77,	2.19)	1.31 (0.77,	2.24)	0.01 (-0.01, 0.02)	
>= median	943	13	1.4	920	24	2.6	0.0571	1.89 (0.97,	3.69)	1.92 (0.97,	3.79)	0.01 (0.00, 0.03)	

Risk ratios and odds ratios with confidence intervals (CIs) are estimated by Cochran-Mantel-Haenszel method. For risk differences standard Wald asymptotic confidence limits are calculated. A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied 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).
For AEs on SOC and/or PT level, subgroup analyses are only shown if overall test for treatment is significant on 5% level (i.e. 95% CI for the risk ratio does not contain 1; if this is not calculable the p-value of Chi-square test is used).
MedDRA version: 23.0. * Chi-square test for treatment effect ** Breslow-Day test for homogeneity of odds ratios (treatment by subgroup interaction).

Table R.1.4.5: 1 Proportion of patients with any adverse events occurring in at least 1% of the patients in either treatment arm in the overall population on PT level - by SOC and PT - 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	1863	41	2.2	1863	26	1.4	0.0644	0.63 (0.39, 1.03)	0.63 (0.38, 1.03)	-0.01 (-0.02, 0.00)	

Risk ratios and odds ratios with confidence intervals (CIs) are estimated by Cochran-Mantel-Haenszel method. For risk differences standard Wald asymptotic confidence limits are calculated. A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied 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).
For AEs on SOC and/or PT level, subgroup analyses are only shown if overall test for treatment is significant on 5% level (i.e. 95% CI for the risk ratio does not contain 1; if this is not calculable the p-value of Chi-square test is used).
MedDRA version: 23.0. * Chi-square test for treatment effect ** Breslow-Day test for homogeneity of odds ratios (treatment by subgroup interaction).

Table R.1.4.5: 1 Proportion of patients with any adverse events occurring in at least 1% of the patients in either treatment arm in the overall population on PT level - by SOC and PT - overall and by subgroup - TS
System organ class: Cardiac disorders
Preferred term: Angina pectoris

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	1863	34	1.8	1863	17	0.9	0.0165	0.50 (0.28, 0.89)	0.50 (0.28, 0.89)	-0.01 (-0.02, 0.00)	
Sex											0.5977
Male	1410	26	1.8	1426	12	0.8	0.0203	0.46 (0.23, 0.90)	0.45 (0.23, 0.90)	-0.01 (-0.02, 0.00)	
Female	453	8	1.8	437	5	1.1	0.4395	0.65 (0.21, 1.97)	0.64 (0.21, 1.98)	-0.01 (-0.02, 0.01)	
Age [years]											0.8492
< 65	739	12	1.6	675	5	0.7	0.1280	0.46 (0.16, 1.29)	0.45 (0.16, 1.29)	-0.01 (-0.02, 0.00)	
>= 65	1124	22	2.0	1188	12	1.0	0.0586	0.52 (0.26, 1.04)	0.51 (0.25, 1.04)	-0.01 (-0.02, 0.00)	
Region											0.8242
North America	213	10	4.7	212	5	2.4	0.1919	0.50 (0.17, 1.44)	0.49 (0.16, 1.46)	-0.02 (-0.06, 0.01)	
Latin America	645	13	2.0	641	4	0.6	0.0289	0.31 (0.10, 0.94)	0.31 (0.10, 0.94)	-0.01 (-0.03, 0.00)	
Europe	674	8	1.2	676	6	0.9	0.5872	0.75 (0.26, 2.14)	0.75 (0.26, 2.16)	0.00 (-0.01, 0.01)	
Asia	244	3	1.2	248	2	0.8	0.6399	0.66 (0.11, 3.89)	0.65 (0.11, 3.94)	0.00 (-0.02, 0.01)	
Other	87	0	0	86	0	0	0.9954	1.01 (0.02, 50.41)	1.01 (0.02, 51.56)	0.00 (-0.02, 0.02)	
OECD Member											0.6012
No	741	13	1.8	713	5	0.7	0.0694	0.40 (0.14, 1.12)	0.40 (0.14, 1.12)	-0.01 (-0.02, 0.00)	
Yes	1122	21	1.9	1150	12	1.0	0.0990	0.56 (0.28, 1.13)	0.55 (0.27, 1.13)	-0.01 (-0.02, 0.00)	
Baseline NYHA											0.9851
II	1399	18	1.3	1399	9	0.6	0.0818	0.50 (0.23, 1.11)	0.50 (0.22, 1.11)	-0.01 (-0.01, 0.00)	
III/IV	464	16	3.4	464	8	1.7	0.0980	0.50 (0.22, 1.16)	0.49 (0.21, 1.16)	-0.02 (-0.04, 0.00)	
Baseline Diabetes Status											0.3201
Diabetic	926	17	1.8	927	11	1.2	0.2520	0.65 (0.30, 1.37)	0.64 (0.30, 1.38)	-0.01 (-0.02, 0.00)	
Non-Diabetic	937	17	1.8	936	6	0.6	0.0211	0.35 (0.14, 0.89)	0.35 (0.14, 0.89)	-0.01 (-0.02, 0.00)	
Baseline BMI [kg/m²]											0.6352
<30	1299	23	1.8	1263	10	0.8	0.0280	0.45 (0.21, 0.94)	0.44 (0.21, 0.93)	-0.01 (-0.02, 0.00)	
>=30	564	11	2.0	600	7	1.2	0.2788	0.60 (0.23, 1.53)	0.59 (0.23, 1.54)	-0.01 (-0.02, 0.01)	

Risk ratios and odds ratios with confidence intervals (CIs) are estimated by Cochran-Mantel-Haenszel method. For risk differences standard Wald asymptotic confidence limits are calculated. A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied 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).
For AEs on SOC and/or PT level, subgroup analyses are only shown if overall test for treatment is significant on 5% level (i.e. 95% CI for the risk ratio does not contain 1; if this is not calculable the p-value of Chi-square test is used).
MedDRA version: 23.0. * Chi-square test for treatment effect ** Breslow-Day test for homogeneity of odds ratios (treatment by subgroup interaction).

Table R.1.4.5: 1 Proportion of patients with any adverse events occurring in at least 1% of the patients in either treatment arm in the overall population on PT level - by SOC and PT - 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 **
Baseline eGFR (CKD-EPI) [mL/min/1.73m²]													0.3000
>=60	958	17	1.8	969	6	0.6	0.0195	0.35 (0.14,	0.88)	0.34 (0.14,	0.88)	-0.01 (-0.02, 0.00)	
<60	904	17	1.9	893	11	1.2	0.2669	0.66 (0.31,	1.39)	0.65 (0.30,	1.40)	-0.01 (-0.02, 0.00)	
History of HHF (in the last 12 months)													0.1949
No	1290	26	2.0	1286	10	0.8	0.0074	0.39 (0.19,	0.80)	0.38 (0.18,	0.79)	-0.01 (-0.02, 0.00)	
Yes	573	8	1.4	577	7	1.2	0.7845	0.87 (0.32,	2.38)	0.87 (0.31,	2.41)	0.00 (-0.01, 0.01)	
Cause of Heart Failure													0.4330
Ischemic	944	24	2.5	983	14	1.4	0.0776	0.56 (0.29,	1.08)	0.55 (0.28,	1.08)	-0.01 (-0.02, 0.00)	
Non-ischemic	919	10	1.1	880	3	0.3	0.0614	0.31 (0.09,	1.13)	0.31 (0.09,	1.13)	-0.01 (-0.02, 0.00)	
Heart Failure Physiology													0.4951
LVEF <= 30% and NTproBNP < median	723	16	2.2	698	9	1.3	0.1855	0.58 (0.26,	1.31)	0.58 (0.25,	1.31)	-0.01 (-0.02, 0.00)	
LVEF <= 30% and NTproBNP >= median	660	10	1.5	631	6	1.0	0.3596	0.63 (0.23,	1.72)	0.62 (0.23,	1.73)	-0.01 (-0.02, 0.01)	
LVEF > 30%	473	8	1.7	526	2	0.4	0.0377	0.22 (0.05,	1.05)	0.22 (0.05,	1.05)	-0.01 (-0.03, 0.00)	
Baseline use of MRA													0.8358
No	512	14	2.7	557	7	1.3	0.0820	0.46 (0.19,	1.13)	0.45 (0.18,	1.13)	-0.01 (-0.03, 0.00)	
Yes	1351	20	1.5	1306	10	0.8	0.0813	0.52 (0.24,	1.10)	0.51 (0.24,	1.10)	-0.01 (-0.02, 0.00)	
Baseline use of ARNi													0.4205
No	1476	26	1.8	1523	15	1.0	0.0671	0.56 (0.30,	1.05)	0.55 (0.29,	1.05)	-0.01 (-0.02, 0.00)	
Yes	387	8	2.1	340	2	0.6	0.0876	0.28 (0.06,	1.33)	0.28 (0.06,	1.33)	-0.01 (-0.03, 0.00)	

Risk ratios and odds ratios with confidence intervals (CIs) are estimated by Cochran-Mantel-Haenszel method. For risk differences standard Wald asymptotic confidence limits are calculated. A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied 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).
For AEs on SOC and/or PT level, subgroup analyses are only shown if overall test for treatment is significant on 5% level (i.e. 95% CI for the risk ratio does not contain 1; if this is not calculable the p-value of Chi-square test is used).
MedDRA version: 23.0. * Chi-square test for treatment effect ** Breslow-Day test for homogeneity of odds ratios (treatment by subgroup interaction).

Table R.1.4.5: 1 Proportion of patients with any adverse events occurring in at least 1% of the patients in either treatment arm in the overall population on PT level - by SOC and PT - 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 **
Baseline LVEF													0.4159
<=30	1390	26	1.9	1337	15	1.1	0.1083	0.60 (0.32,	1.13)	0.60 (0.31,	1.13)	-0.01 (-0.02, 0.00)	
>30 to <=35	359	4	1.1	398	0	0	0.0558	0.10 (<0.01,	1.86)	0.10 (<0.01,	1.85)	-0.01 (-0.02, 0.00)	
>35	114	4	3.5	128	2	1.6	0.3311	0.45 (0.08,	2.39)	0.44 (0.08,	2.43)	-0.02 (-0.06, 0.02)	
Baseline NTproBNP													0.4864
< median	919	21	2.3	942	9	1.0	0.0228	0.42 (0.19,	0.91)	0.41 (0.19,	0.91)	-0.01 (-0.02, 0.00)	
>= median	943	13	1.4	920	8	0.9	0.2981	0.63 (0.26,	1.51)	0.63 (0.26,	1.52)	-0.01 (-0.01, 0.00)	

Risk ratios and odds ratios with confidence intervals (CIs) are estimated by Cochran-Mantel-Haenszel method. For risk differences standard Wald asymptotic confidence limits are calculated. A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied 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).
For AEs on SOC and/or PT level, subgroup analyses are only shown if overall test for treatment is significant on 5% level (i.e. 95% CI for the risk ratio does not contain 1; if this is not calculable the p-value of Chi-square test is used).
MedDRA version: 23.0. * Chi-square test for treatment effect ** Breslow-Day test for homogeneity of odds ratios (treatment by subgroup interaction).

Table R.1.4.5: 1 Proportion of patients with any adverse events occurring in at least 1% of the patients in either treatment arm in the overall population on PT level - by SOC and PT - overall and by subgroup - TS
System organ class: Cardiac disorders
Preferred term: Cardiac failure chronic

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	1863	32	1.7	1863	18	1.0	0.0462	0.56 (0.32, 1.00)	0.56 (0.31, 1.00)	-0.01 (-0.01, 0.00)	
Sex											0.2613
Male	1410	24	1.7	1426	16	1.1	0.1902	0.66 (0.35, 1.24)	0.66 (0.35, 1.24)	-0.01 (-0.01, 0.00)	
Female	453	8	1.8	437	2	0.5	0.0641	0.26 (0.06, 1.21)	0.26 (0.05, 1.21)	-0.01 (-0.03, 0.00)	
Age [years]											0.4958
< 65	739	11	1.5	675	4	0.6	0.1005	0.40 (0.13, 1.24)	0.39 (0.13, 1.24)	-0.01 (-0.02, 0.00)	
>= 65	1124	21	1.9	1188	14	1.2	0.1745	0.63 (0.32, 1.23)	0.63 (0.32, 1.24)	-0.01 (-0.02, 0.00)	
Region											0.7881
North America	213	1	0.5	212	1	0.5	0.9973	1.00 (0.06, 15.96)	1.00 (0.06, 16.17)	0.00 (-0.01, 0.01)	
Latin America	645	0	0	641	0	0	0.9975	1.01 (0.02, 50.63)	1.01 (0.02, 50.79)	0.00 (0.00, 0.00)	
Europe	674	11	1.6	676	9	1.3	0.6475	0.82 (0.34, 1.96)	0.81 (0.33, 1.98)	0.00 (-0.02, 0.01)	
Asia	244	19	7.8	248	8	3.2	0.0263	0.41 (0.18, 0.93)	0.39 (0.17, 0.92)	-0.05 (-0.09,-0.01)	
Other	87	1	1.1	86	0	0	0.4820	0.34 (0.01, 8.16)	0.33 (0.01, 8.30)	-0.01 (-0.04, 0.02)	
OECD Member											0.0635
No	741	7	0.9	713	0	0	0.0152	0.07 (<0.01, 1.21)	0.07 (<0.01, 1.20)	-0.01 (-0.02, 0.00)	
Yes	1122	25	2.2	1150	18	1.6	0.2463	0.70 (0.39, 1.28)	0.70 (0.38, 1.29)	-0.01 (-0.02, 0.00)	
Baseline NYHA											0.8823
II	1399	22	1.6	1399	12	0.9	0.0844	0.55 (0.27, 1.10)	0.54 (0.27, 1.10)	-0.01 (-0.02, 0.00)	
III/IV	464	10	2.2	464	6	1.3	0.3131	0.60 (0.22, 1.64)	0.59 (0.21, 1.65)	-0.01 (-0.03, 0.01)	
Baseline Diabetes Status											0.0518
Diabetic	926	14	1.5	927	13	1.4	0.8441	0.93 (0.44, 1.96)	0.93 (0.43, 1.98)	0.00 (-0.01, 0.01)	
Non-Diabetic	937	18	1.9	936	5	0.5	0.0064	0.28 (0.10, 0.75)	0.27 (0.10, 0.74)	-0.01 (-0.02, 0.00)	
Baseline BMI [kg/m²]											0.1536
<30	1299	26	2.0	1263	11	0.9	0.0165	0.44 (0.22, 0.88)	0.43 (0.21, 0.87)	-0.01 (-0.02, 0.00)	
>=30	564	6	1.1	600	7	1.2	0.8675	1.10 (0.37, 3.24)	1.10 (0.37, 3.29)	0.00 (-0.01, 0.01)	

Risk ratios and odds ratios with confidence intervals (CIs) are estimated by Cochran-Mantel-Haenszel method. For risk differences standard Wald asymptotic confidence limits are calculated. A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied 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).
For AEs on SOC and/or PT level, subgroup analyses are only shown if overall test for treatment is significant on 5% level (i.e. 95% CI for the risk ratio does not contain 1; if this is not calculable the p-value of Chi-square test is used).
MedDRA version: 23.0. * Chi-square test for treatment effect ** Breslow-Day test for homogeneity of odds ratios (treatment by subgroup interaction).

Table R.1.4.5: 1 Proportion of patients with any adverse events occurring in at least 1% of the patients in either treatment arm in the overall population on PT level - by SOC and PT - 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 **
Baseline eGFR (CKD-EPI) [mL/min/1.73m²]													0.0053
>=60	958	20	2.1	969	4	0.4	0.0009	0.20 (0.07,	0.58)	0.19 (0.07,	0.57)	-0.02 (-0.03,-0.01)	
<60	904	12	1.3	893	14	1.6	0.6697	1.18 (0.55,	2.54)	1.18 (0.54,	2.57)	0.00 (-0.01, 0.01)	
History of HHF (in the last 12 months)													0.4019
No	1290	14	1.1	1286	10	0.8	0.4164	0.72 (0.32,	1.61)	0.71 (0.32,	1.61)	0.00 (-0.01, 0.00)	
Yes	573	18	3.1	577	8	1.4	0.0453	0.44 (0.19,	1.01)	0.43 (0.19,	1.01)	-0.02 (-0.03, 0.00)	
Cause of Heart Failure													0.1625
Ischemic	944	16	1.7	983	13	1.3	0.5020	0.78 (0.38,	1.61)	0.78 (0.37,	1.62)	0.00 (-0.01, 0.01)	
Non-ischemic	919	16	1.7	880	5	0.6	0.0206	0.33 (0.12,	0.89)	0.32 (0.12,	0.88)	-0.01 (-0.02, 0.00)	
Heart Failure Physiology													0.5685
LVEF <= 30% and NTproBNP < median	723	7	1.0	698	4	0.6	0.3955	0.59 (0.17,	2.01)	0.59 (0.17,	2.02)	0.00 (-0.01, 0.01)	
LVEF <= 30% and NTproBNP >= median	660	16	2.4	631	6	1.0	0.0409	0.39 (0.15,	1.00)	0.39 (0.15,	0.99)	-0.01 (-0.03, 0.00)	
LVEF > 30%	473	9	1.9	526	8	1.5	0.6413	0.80 (0.31,	2.05)	0.80 (0.30,	2.08)	0.00 (-0.02, 0.01)	
Baseline use of MRA													0.7875
No	512	11	2.1	557	6	1.1	0.1619	0.50 (0.19,	1.35)	0.50 (0.18,	1.35)	-0.01 (-0.03, 0.00)	
Yes	1351	21	1.6	1306	12	0.9	0.1392	0.59 (0.29,	1.20)	0.59 (0.29,	1.20)	-0.01 (-0.01, 0.00)	
Baseline use of ARNi													0.5249
No	1476	28	1.9	1523	17	1.1	0.0787	0.59 (0.32,	1.07)	0.58 (0.32,	1.07)	-0.01 (-0.02, 0.00)	
Yes	387	4	1.0	340	1	0.3	0.2287	0.28 (0.03,	2.53)	0.28 (0.03,	2.54)	-0.01 (-0.02, 0.00)	

Risk ratios and odds ratios with confidence intervals (CIs) are estimated by Cochran-Mantel-Haenszel method. For risk differences standard Wald asymptotic confidence limits are calculated. A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied 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).
For AEs on SOC and/or PT level, subgroup analyses are only shown if overall test for treatment is significant on 5% level (i.e. 95% CI for the risk ratio does not contain 1; if this is not calculable the p-value of Chi-square test is used).
MedDRA version: 23.0. * Chi-square test for treatment effect ** Breslow-Day test for homogeneity of odds ratios (treatment by subgroup interaction).

Table R.1.4.5: 1 Proportion of patients with any adverse events occurring in at least 1% of the patients in either treatment arm in the overall population on PT level - by SOC and PT - 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 **
Baseline LVEF														0.4395
<=30	1390	23	1.7	1337	10	0.7	0.0304	0.45 (0.22,	0.95)		0.45 (0.21,	0.94)	-0.01 (-0.02, 0.00)	
>30 to <=35	359	5	1.4	398	6	1.5	0.8952	1.08 (0.33,	3.52)		1.08 (0.33,	3.58)	0.00 (-0.02, 0.02)	
>35	114	4	3.5	128	2	1.6	0.3311	0.45 (0.08,	2.39)		0.44 (0.08,	2.43)	-0.02 (-0.06, 0.02)	
Baseline NTproBNP														0.5715
< median	919	8	0.9	942	6	0.6	0.5599	0.73 (0.25,	2.10)		0.73 (0.25,	2.11)	0.00 (-0.01, 0.01)	
>= median	943	24	2.5	920	12	1.3	0.0518	0.51 (0.26,	1.02)		0.51 (0.25,	1.02)	-0.01 (-0.02, 0.00)	

Risk ratios and odds ratios with confidence intervals (CIs) are estimated by Cochran-Mantel-Haenszel method. For risk differences standard Wald asymptotic confidence limits are calculated. A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied 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).
For AEs on SOC and/or PT level, subgroup analyses are only shown if overall test for treatment is significant on 5% level (i.e. 95% CI for the risk ratio does not contain 1; if this is not calculable the p-value of Chi-square test is used).
MedDRA version: 23.0. * Chi-square test for treatment effect ** Breslow-Day test for homogeneity of odds ratios (treatment by subgroup interaction).

Table R.1.4.5: 1 Proportion of patients with any adverse events occurring in at least 1% of the patients in either treatment arm in the overall population on PT level - by SOC and PT - overall and by subgroup - TS
System organ class: Cardiac disorders
Preferred term: Cardiac failure acute

Subgroup	Placebo			Empa 10mg			Empa 10mg vs Placebo				
Category	N	n	%	N	n	%	p-value *	Risk ratio (95% CI)	Odds ratio (95% CI)	Risk diff. (95% CI)	p-value **
Overall	1863	29	1.6	1863	19	1.0	0.1463	0.66 (0.37, 1.16)	0.65 (0.36, 1.17)	-0.01 (-0.01, 0.00)	

Risk ratios and odds ratios with confidence intervals (CIs) are estimated by Cochran-Mantel-Haenszel method. For risk differences standard Wald asymptotic confidence limits are calculated. A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied 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).
For AEs on SOC and/or PT level, subgroup analyses are only shown if overall test for treatment is significant on 5% level (i.e. 95% CI for the risk ratio does not contain 1; if this is not calculable the p-value of Chi-square test is used).
MedDRA version: 23.0. * Chi-square test for treatment effect ** Breslow-Day test for homogeneity of odds ratios (treatment by subgroup interaction).

Table R.1.4.5: 1 Proportion of patients with any adverse events occurring in at least 1% of the patients in either treatment arm in the overall population on PT level - by SOC and PT - 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	1863	18	1.0	1863	24	1.3	0.3518	1.33 (0.73, 2.45)	1.34 (0.72, 2.47)	0.00 (0.00, 0.01)	

Risk ratios and odds ratios with confidence intervals (CIs) are estimated by Cochran-Mantel-Haenszel method. For risk differences standard Wald asymptotic confidence limits are calculated. A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied 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).
For AEs on SOC and/or PT level, subgroup analyses are only shown if overall test for treatment is significant on 5% level (i.e. 95% CI for the risk ratio does not contain 1; if this is not calculable the p-value of Chi-square test is used).
MedDRA version: 23.0. * Chi-square test for treatment effect ** Breslow-Day test for homogeneity of odds ratios (treatment by subgroup interaction).

Table R.1.4.5: 1 Proportion of patients with any adverse events occurring in at least 1% of the patients in either treatment arm in the overall population on PT level - by SOC and PT - 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	1863	19	1.0	1863	12	0.6	0.2068	0.63 (0.31, 1.30)	0.63 (0.30, 1.30)	0.00 (-0.01, 0.00)	

Risk ratios and odds ratios with confidence intervals (CIs) are estimated by Cochran-Mantel-Haenszel method. For risk differences standard Wald asymptotic confidence limits are calculated. A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied 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).
For AEs on SOC and/or PT level, subgroup analyses are only shown if overall test for treatment is significant on 5% level (i.e. 95% CI for the risk ratio does not contain 1; if this is not calculable the p-value of Chi-square test is used).
MedDRA version: 23.0. * Chi-square test for treatment effect ** Breslow-Day test for homogeneity of odds ratios (treatment by subgroup interaction).

Table R.1.4.5: 1 Proportion of patients with any adverse events occurring in at least 1% of the patients in either treatment arm in the overall population on PT level - by SOC and PT - 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	1863	100	5.4	1863	97	5.2	0.8262	0.97 (0.74, 1.27)	0.97 (0.73, 1.29)	0.00 (-0.02, 0.01)	

Risk ratios and odds ratios with confidence intervals (CIs) are estimated by Cochran-Mantel-Haenszel method. For risk differences standard Wald asymptotic confidence limits are calculated. A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied 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).
For AEs on SOC and/or PT level, subgroup analyses are only shown if overall test for treatment is significant on 5% level (i.e. 95% CI for the risk ratio does not contain 1; if this is not calculable the p-value of Chi-square test is used).
MedDRA version: 23.0. * Chi-square test for treatment effect ** Breslow-Day test for homogeneity of odds ratios (treatment by subgroup interaction).

Table R.1.4.5: 1 Proportion of patients with any adverse events occurring in at least 1% of the patients in either treatment arm in the overall population on PT level - by SOC and PT - 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	1863	94	5.0	1863	89	4.8	0.7047	0.95 (0.71, 1.26)	0.94 (0.70, 1.27)	0.00 (-0.02, 0.01)	

Risk ratios and odds ratios with confidence intervals (CIs) are estimated by Cochran-Mantel-Haenszel method. For risk differences standard Wald asymptotic confidence limits are calculated. A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied 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).
For AEs on SOC and/or PT level, subgroup analyses are only shown if overall test for treatment is significant on 5% level (i.e. 95% CI for the risk ratio does not contain 1; if this is not calculable the p-value of Chi-square test is used).
MedDRA version: 23.0. * Chi-square test for treatment effect ** Breslow-Day test for homogeneity of odds ratios (treatment by subgroup interaction).

Table R.1.4.5: 1 Proportion of patients with any adverse events occurring in at least 1% of the patients in either treatment arm in the overall population on PT level - by SOC and PT - 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	1863	72	3.9	1863	69	3.7	0.7967	0.96 (0.69, 1.32)	0.96 (0.68, 1.34)	0.00 (-0.01, 0.01)	

Risk ratios and odds ratios with confidence intervals (CIs) are estimated by Cochran-Mantel-Haenszel method. For risk differences standard Wald asymptotic confidence limits are calculated. A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied 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).
For AEs on SOC and/or PT level, subgroup analyses are only shown if overall test for treatment is significant on 5% level (i.e. 95% CI for the risk ratio does not contain 1; if this is not calculable the p-value of Chi-square test is used).
MedDRA version: 23.0. * Chi-square test for treatment effect ** Breslow-Day test for homogeneity of odds ratios (treatment by subgroup interaction).

Table R.1.4.5: 1 Proportion of patients with any adverse events occurring in at least 1% of the patients in either treatment arm in the overall population on PT level - by SOC and PT - 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	1863	70	3.8	1863	56	3.0	0.2045	0.80 (0.57, 1.13)	0.79 (0.56, 1.13)	-0.01 (-0.02, 0.00)	

Risk ratios and odds ratios with confidence intervals (CIs) are estimated by Cochran-Mantel-Haenszel method. For risk differences standard Wald asymptotic confidence limits are calculated. A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied 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).
For AEs on SOC and/or PT level, subgroup analyses are only shown if overall test for treatment is significant on 5% level (i.e. 95% CI for the risk ratio does not contain 1; if this is not calculable the p-value of Chi-square test is used).
MedDRA version: 23.0. * Chi-square test for treatment effect ** Breslow-Day test for homogeneity of odds ratios (treatment by subgroup interaction).

Table R.1.4.5: 1 Proportion of patients with any adverse events occurring in at least 1% of the patients in either treatment arm in the overall population on PT level - by SOC and PT - 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	1863	64	3.4	1863	56	3.0	0.4579	0.88 (0.61, 1.25)	0.87 (0.61, 1.25)	0.00 (-0.02, 0.01)	

Risk ratios and odds ratios with confidence intervals (CIs) are estimated by Cochran-Mantel-Haenszel method. For risk differences standard Wald asymptotic confidence limits are calculated. A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied 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).
For AEs on SOC and/or PT level, subgroup analyses are only shown if overall test for treatment is significant on 5% level (i.e. 95% CI for the risk ratio does not contain 1; if this is not calculable the p-value of Chi-square test is used).
MedDRA version: 23.0. * Chi-square test for treatment effect ** Breslow-Day test for homogeneity of odds ratios (treatment by subgroup interaction).

Table R.1.4.5: 1 Proportion of patients with any adverse events occurring in at least 1% of the patients in either treatment arm in the overall population on PT level - by SOC and PT - 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	1863	39	2.1	1863	29	1.6	0.2210	0.74 (0.46, 1.20)	0.74 (0.46, 1.20)	-0.01 (-0.01, 0.00)	

Risk ratios and odds ratios with confidence intervals (CIs) are estimated by Cochran-Mantel-Haenszel method. For risk differences standard Wald asymptotic confidence limits are calculated. A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied 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).
For AEs on SOC and/or PT level, subgroup analyses are only shown if overall test for treatment is significant on 5% level (i.e. 95% CI for the risk ratio does not contain 1; if this is not calculable the p-value of Chi-square test is used).
MedDRA version: 23.0. * Chi-square test for treatment effect ** Breslow-Day test for homogeneity of odds ratios (treatment by subgroup interaction).

Table R.1.4.5: 1 Proportion of patients with any adverse events occurring in at least 1% of the patients in either treatment arm in the overall population on PT level - by SOC and PT - 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	1863	24	1.3	1863	16	0.9	0.2035	0.67 (0.36, 1.25)	0.66 (0.35, 1.25)	0.00 (-0.01, 0.00)	

Risk ratios and odds ratios with confidence intervals (CIs) are estimated by Cochran-Mantel-Haenszel method. For risk differences standard Wald asymptotic confidence limits are calculated. A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied 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).
For AEs on SOC and/or PT level, subgroup analyses are only shown if overall test for treatment is significant on 5% level (i.e. 95% CI for the risk ratio does not contain 1; if this is not calculable the p-value of Chi-square test is used).
MedDRA version: 23.0. * Chi-square test for treatment effect ** Breslow-Day test for homogeneity of odds ratios (treatment by subgroup interaction).

Table R.1.4.5: 1 Proportion of patients with any adverse events occurring in at least 1% of the patients in either treatment arm in the overall population on PT level - by SOC and PT - 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	1863	12	0.6	1863	19	1.0	0.2068	1.58 (0.77, 3.25)	1.59 (0.77, 3.28)	0.00 (0.00, 0.01)	

Risk ratios and odds ratios with confidence intervals (CIs) are estimated by Cochran-Mantel-Haenszel method. For risk differences standard Wald asymptotic confidence limits are calculated. A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied 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).
For AEs on SOC and/or PT level, subgroup analyses are only shown if overall test for treatment is significant on 5% level (i.e. 95% CI for the risk ratio does not contain 1; if this is not calculable the p-value of Chi-square test is used).
MedDRA version: 23.0. * Chi-square test for treatment effect ** Breslow-Day test for homogeneity of odds ratios (treatment by subgroup interaction).

Table R.1.4.5: 1 Proportion of patients with any adverse events occurring in at least 1% of the patients in either treatment arm in the overall population on PT level - by SOC and PT - 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	1863	115	6.2	1863	101	5.4	0.3264	0.88 (0.68, 1.14)	0.87 (0.66, 1.15)	-0.01 (-0.02, 0.01)	

Risk ratios and odds ratios with confidence intervals (CIs) are estimated by Cochran-Mantel-Haenszel method. For risk differences standard Wald asymptotic confidence limits are calculated. A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied 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).
For AEs on SOC and/or PT level, subgroup analyses are only shown if overall test for treatment is significant on 5% level (i.e. 95% CI for the risk ratio does not contain 1; if this is not calculable the p-value of Chi-square test is used).
MedDRA version: 23.0. * Chi-square test for treatment effect ** Breslow-Day test for homogeneity of odds ratios (treatment by subgroup interaction).

Table R.1.4.5: 1 Proportion of patients with any adverse events occurring in at least 1% of the patients in either treatment arm in the overall population on PT level - by SOC and PT - 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	1863	115	6.2	1863	63	3.4	<0.0001	0.55	(0.41, 0.74)	0.53	(0.39, 0.73)	-0.03	(-0.04,-0.01)	
Sex														0.6576
Male	1410	87	6.2	1426	50	3.5	0.0009	0.57	(0.40, 0.80)	0.55	(0.39, 0.79)	-0.03	(-0.04,-0.01)	
Female	453	28	6.2	437	13	3.0	0.0225	0.48	(0.25, 0.92)	0.47	(0.24, 0.91)	-0.03	(-0.06, 0.00)	
Age [years]														0.5277
< 65	739	64	8.7	675	30	4.4	0.0015	0.51	(0.34, 0.78)	0.49	(0.31, 0.77)	-0.04	(-0.07,-0.02)	
>= 65	1124	51	4.5	1188	33	2.8	0.0238	0.61	(0.40, 0.94)	0.60	(0.38, 0.94)	-0.02	(-0.03, 0.00)	
Region														0.5236
North America	213	1	0.5	212	0	0	0.4805	0.33	(0.01, 8.17)	0.33	(0.01, 8.23)	0.00	(-0.02, 0.01)	
Latin America	645	60	9.3	641	26	4.1	0.0002	0.44	(0.28, 0.68)	0.41	(0.26, 0.66)	-0.05	(-0.08,-0.03)	
Europe	674	24	3.6	676	16	2.4	0.1958	0.66	(0.36, 1.24)	0.66	(0.35, 1.25)	-0.01	(-0.03, 0.01)	
Asia	244	28	11.5	248	18	7.3	0.1082	0.63	(0.36, 1.11)	0.60	(0.32, 1.12)	-0.04	(-0.09, 0.01)	
Other	87	2	2.3	86	3	3.5	0.6405	1.52	(0.26, 8.86)	1.54	(0.25, 9.43)	0.01	(-0.04, 0.06)	
OECD Member														0.7289
No	741	75	10.1	713	39	5.5	0.0010	0.54	(0.37, 0.78)	0.51	(0.34, 0.77)	-0.05	(-0.07,-0.02)	
Yes	1122	40	3.6	1150	24	2.1	0.0333	0.59	(0.36, 0.96)	0.58	(0.35, 0.96)	-0.01	(-0.03, 0.00)	
Baseline NYHA														0.0256
II	1399	78	5.6	1399	32	2.3	<0.0001	0.41	(0.27, 0.61)	0.40	(0.26, 0.60)	-0.03	(-0.05,-0.02)	
III/IV	464	37	8.0	464	31	6.7	0.4498	0.84	(0.53, 1.33)	0.83	(0.50, 1.36)	-0.01	(-0.05, 0.02)	
Baseline Diabetes Status														0.7830
Diabetic	926	66	7.1	927	35	3.8	0.0015	0.53	(0.36, 0.79)	0.51	(0.34, 0.78)	-0.03	(-0.05,-0.01)	
Non-Diabetic	937	49	5.2	936	28	3.0	0.0147	0.57	(0.36, 0.90)	0.56	(0.35, 0.90)	-0.02	(-0.04, 0.00)	
Baseline BMI [kg/m²]														0.9213
<30	1299	73	5.6	1263	39	3.1	0.0017	0.55	(0.38, 0.80)	0.54	(0.36, 0.80)	-0.03	(-0.04,-0.01)	
>=30	564	42	7.4	600	24	4.0	0.0110	0.54	(0.33, 0.88)	0.52	(0.31, 0.87)	-0.03	(-0.06,-0.01)	

Risk ratios and odds ratios with confidence intervals (CIs) are estimated by Cochran-Mantel-Haenszel method. For risk differences standard Wald asymptotic confidence limits are calculated. A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied 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).
For AEs on SOC and/or PT level, subgroup analyses are only shown if overall test for treatment is significant on 5% level (i.e. 95% CI for the risk ratio does not contain 1; if this is not calculable the p-value of Chi-square test is used).
MedDRA version: 23.0. * Chi-square test for treatment effect ** Breslow-Day test for homogeneity of odds ratios (treatment by subgroup interaction).

Table R.1.4.5: 1 Proportion of patients with any adverse events occurring in at least 1% of the patients in either treatment arm in the overall population on PT level - by SOC and PT - overall and by subgroup - TS
System organ class: Metabolism and nutrition disorders
Preferred term: Hyperuricaemia

Subgroup	Placebo			Empa 10mg			Empa 10mg vs Placebo					
Category	N	n	%	N	n	%	p-value *	Risk ratio (95% CI)		Odds ratio (95% CI)		Risk diff. (95% CI)	p-value **
Baseline eGFR (CKD-EPI) [mL/min/1.73m²]													0.2004
>=60	958	61	6.4	969	40	4.1	0.0274	0.65 (0.44,	0.96)	0.63 (0.42,	0.95)	-0.02 (-0.04, 0.00)	
<60	904	54	6.0	893	23	2.6	0.0004	0.43 (0.27,	0.70)	0.42 (0.25,	0.68)	-0.03 (-0.05,-0.02)	
History of HHF (in the last 12 months)													0.2899
No	1290	70	5.4	1286	43	3.3	0.0099	0.62 (0.42,	0.89)	0.60 (0.41,	0.89)	-0.02 (-0.04,-0.01)	
Yes	573	45	7.9	577	20	3.5	0.0013	0.44 (0.26,	0.74)	0.42 (0.25,	0.72)	-0.04 (-0.07,-0.02)	
Cause of Heart Failure													0.0435
Ischemic	944	39	4.1	983	32	3.3	0.3075	0.79 (0.50,	1.25)	0.78 (0.48,	1.26)	-0.01 (-0.03, 0.01)	
Non-ischemic	919	76	8.3	880	31	3.5	<0.0001	0.43 (0.28,	0.64)	0.41 (0.26,	0.62)	-0.05 (-0.07,-0.03)	
Heart Failure Physiology													0.7045
LVEF <= 30% and NTproBNP < median	723	34	4.7	698	21	3.0	0.0979	0.64 (0.38,	1.09)	0.63 (0.36,	1.09)	-0.02 (-0.04, 0.00)	
LVEF <= 30% and NTproBNP >= median	660	45	6.8	631	22	3.5	0.0070	0.51 (0.31,	0.84)	0.49 (0.29,	0.83)	-0.03 (-0.06,-0.01)	
LVEF > 30%	473	36	7.6	526	19	3.6	0.0057	0.47 (0.28,	0.82)	0.45 (0.26,	0.80)	-0.04 (-0.07,-0.01)	
Baseline use of MRA													0.1096
No	512	15	2.9	557	15	2.7	0.8149	0.92 (0.45,	1.86)	0.92 (0.44,	1.90)	0.00 (-0.02, 0.02)	
Yes	1351	100	7.4	1306	48	3.7	<0.0001	0.50 (0.35,	0.69)	0.48 (0.34,	0.68)	-0.04 (-0.05,-0.02)	
Baseline use of ARNi													0.5755
No	1476	90	6.1	1523	53	3.5	0.0008	0.57 (0.41,	0.80)	0.56 (0.39,	0.79)	-0.03 (-0.04,-0.01)	
Yes	387	25	6.5	340	10	2.9	0.0270	0.46 (0.22,	0.93)	0.44 (0.21,	0.93)	-0.04 (-0.07, 0.00)	

Risk ratios and odds ratios with confidence intervals (CIs) are estimated by Cochran-Mantel-Haenszel method. For risk differences standard Wald asymptotic confidence limits are calculated. A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied 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).
For AEs on SOC and/or PT level, subgroup analyses are only shown if overall test for treatment is significant on 5% level (i.e. 95% CI for the risk ratio does not contain 1; if this is not calculable the p-value of Chi-square test is used).
MedDRA version: 23.0. * Chi-square test for treatment effect ** Breslow-Day test for homogeneity of odds ratios (treatment by subgroup interaction).

Table R.1.4.5: 1 Proportion of patients with any adverse events occurring in at least 1% of the patients in either treatment arm in the overall population on PT level - by SOC and PT - 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														0.6028
<=30	1390	79	5.7	1337	44	3.3	0.0026	0.58 (0.40,	0.83)		0.56 (0.39,	0.82)	-0.02 (-0.04,-0.01)	
>30 to <=35	359	25	7.0	398	15	3.8	0.0498	0.54 (0.29,	1.01)		0.52 (0.27,	1.01)	-0.03 (-0.06, 0.00)	
>35	114	11	9.6	128	4	3.1	0.0356	0.32 (0.11,	0.99)		0.30 (0.09,	0.98)	-0.07 (-0.13, 0.00)	
Baseline NTproBNP														0.8927
< median	919	47	5.1	942	27	2.9	0.0131	0.56 (0.35,	0.89)		0.55 (0.34,	0.89)	-0.02 (-0.04, 0.00)	
>= median	943	68	7.2	920	36	3.9	0.0019	0.54 (0.37,	0.80)		0.52 (0.35,	0.79)	-0.03 (-0.05,-0.01)	

Risk ratios and odds ratios with confidence intervals (CIs) are estimated by Cochran-Mantel-Haenszel method. For risk differences standard Wald asymptotic confidence limits are calculated. A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied 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).
For AEs on SOC and/or PT level, subgroup analyses are only shown if overall test for treatment is significant on 5% level (i.e. 95% CI for the risk ratio does not contain 1; if this is not calculable the p-value of Chi-square test is used).
MedDRA version: 23.0. * Chi-square test for treatment effect ** Breslow-Day test for homogeneity of odds ratios (treatment by subgroup interaction).

Table R.1.4.5: 1 Proportion of patients with any adverse events occurring in at least 1% of the patients in either treatment arm in the overall population on PT level - by SOC and PT - 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	1863	48	2.6	1863	46	2.5	0.8345	0.96 (0.64, 1.43)	0.96 (0.64, 1.44)	0.00 (-0.01, 0.01)	

Risk ratios and odds ratios with confidence intervals (CIs) are estimated by Cochran-Mantel-Haenszel method. For risk differences standard Wald asymptotic confidence limits are calculated. A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied 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).
For AEs on SOC and/or PT level, subgroup analyses are only shown if overall test for treatment is significant on 5% level (i.e. 95% CI for the risk ratio does not contain 1; if this is not calculable the p-value of Chi-square test is used).
MedDRA version: 23.0. * Chi-square test for treatment effect ** Breslow-Day test for homogeneity of odds ratios (treatment by subgroup interaction).

Table R.1.4.5: 1 Proportion of patients with any adverse events occurring in at least 1% of the patients in either treatment arm in the overall population on PT level - by SOC and PT - 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	1863	46	2.5	1863	33	1.8	0.1393	0.72 (0.46, 1.12)	0.71 (0.45, 1.12)	-0.01 (-0.02, 0.00)	

Risk ratios and odds ratios with confidence intervals (CIs) are estimated by Cochran-Mantel-Haenszel method. For risk differences standard Wald asymptotic confidence limits are calculated. A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied 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).
For AEs on SOC and/or PT level, subgroup analyses are only shown if overall test for treatment is significant on 5% level (i.e. 95% CI for the risk ratio does not contain 1; if this is not calculable the p-value of Chi-square test is used).
MedDRA version: 23.0. * Chi-square test for treatment effect ** Breslow-Day test for homogeneity of odds ratios (treatment by subgroup interaction).

Table R.1.4.5: 1 Proportion of patients with any adverse events occurring in at least 1% of the patients in either treatment arm in the overall population on PT level - by SOC and PT - 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	1863	42	2.3	1863	27	1.4	0.0683	0.64 (0.40, 1.04)	0.64 (0.39, 1.04)	-0.01 (-0.02, 0.00)	

Risk ratios and odds ratios with confidence intervals (CIs) are estimated by Cochran-Mantel-Haenszel method. For risk differences standard Wald asymptotic confidence limits are calculated. A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied 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).
For AEs on SOC and/or PT level, subgroup analyses are only shown if overall test for treatment is significant on 5% level (i.e. 95% CI for the risk ratio does not contain 1; if this is not calculable the p-value of Chi-square test is used).
MedDRA version: 23.0. * Chi-square test for treatment effect ** Breslow-Day test for homogeneity of odds ratios (treatment by subgroup interaction).

Table R.1.4.5: 1 Proportion of patients with any adverse events occurring in at least 1% of the patients in either treatment arm in the overall population on PT level - by SOC and PT - 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	1863	35	1.9	1863	38	2.0	0.7229	1.09 (0.69, 1.71)	1.09 (0.68, 1.73)	0.00 (-0.01, 0.01)	

Risk ratios and odds ratios with confidence intervals (CIs) are estimated by Cochran-Mantel-Haenszel method. For risk differences standard Wald asymptotic confidence limits are calculated. A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied 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).
For AEs on SOC and/or PT level, subgroup analyses are only shown if overall test for treatment is significant on 5% level (i.e. 95% CI for the risk ratio does not contain 1; if this is not calculable the p-value of Chi-square test is used).
MedDRA version: 23.0. * Chi-square test for treatment effect ** Breslow-Day test for homogeneity of odds ratios (treatment by subgroup interaction).

Table R.1.4.5: 1 Proportion of patients with any adverse events occurring in at least 1% of the patients in either treatment arm in the overall population on PT level - by SOC and PT - 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	1863	28	1.5	1863	33	1.8	0.5186	1.18 (0.72, 1.94)	1.18 (0.71, 1.96)	0.00 (-0.01, 0.01)	

Risk ratios and odds ratios with confidence intervals (CIs) are estimated by Cochran-Mantel-Haenszel method. For risk differences standard Wald asymptotic confidence limits are calculated. A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied 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).
For AEs on SOC and/or PT level, subgroup analyses are only shown if overall test for treatment is significant on 5% level (i.e. 95% CI for the risk ratio does not contain 1; if this is not calculable the p-value of Chi-square test is used).
MedDRA version: 23.0. * Chi-square test for treatment effect ** Breslow-Day test for homogeneity of odds ratios (treatment by subgroup interaction).

Table R.1.4.5: 1 Proportion of patients with any adverse events occurring in at least 1% of the patients in either treatment arm in the overall population on PT level - by SOC and PT - 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	1863	21	1.1	1863	25	1.3	0.5529	1.19 (0.67, 2.12)	1.19 (0.67, 2.14)	0.00 (0.00, 0.01)	

Risk ratios and odds ratios with confidence intervals (CIs) are estimated by Cochran-Mantel-Haenszel method. For risk differences standard Wald asymptotic confidence limits are calculated. A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied 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).
For AEs on SOC and/or PT level, subgroup analyses are only shown if overall test for treatment is significant on 5% level (i.e. 95% CI for the risk ratio does not contain 1; if this is not calculable the p-value of Chi-square test is used).
MedDRA version: 23.0. * Chi-square test for treatment effect ** Breslow-Day test for homogeneity of odds ratios (treatment by subgroup interaction).

Table R.1.4.5: 1 Proportion of patients with any adverse events occurring in at least 1% of the patients in either treatment arm in the overall population on PT level - by SOC and PT - 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	1863	19	1.0	1863	24	1.3	0.4431	1.26 (0.69, 2.30)	1.27 (0.69, 2.32)	0.00 (0.00, 0.01)	

Risk ratios and odds ratios with confidence intervals (CIs) are estimated by Cochran-Mantel-Haenszel method. For risk differences standard Wald asymptotic confidence limits are calculated. A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied 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).
For AEs on SOC and/or PT level, subgroup analyses are only shown if overall test for treatment is significant on 5% level (i.e. 95% CI for the risk ratio does not contain 1; if this is not calculable the p-value of Chi-square test is used).
MedDRA version: 23.0. * Chi-square test for treatment effect ** Breslow-Day test for homogeneity of odds ratios (treatment by subgroup interaction).

Table R.1.4.5: 1 Proportion of patients with any adverse events occurring in at least 1% of the patients in either treatment arm in the overall population on PT level - by SOC and PT - 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	1863	23	1.2	1863	14	0.8	0.1370	0.61 (0.31, 1.18)	0.61 (0.31, 1.18)	0.00 (-0.01, 0.00)	

Risk ratios and odds ratios with confidence intervals (CIs) are estimated by Cochran-Mantel-Haenszel method. For risk differences standard Wald asymptotic confidence limits are calculated. A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied 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).
For AEs on SOC and/or PT level, subgroup analyses are only shown if overall test for treatment is significant on 5% level (i.e. 95% CI for the risk ratio does not contain 1; if this is not calculable the p-value of Chi-square test is used).
MedDRA version: 23.0. * Chi-square test for treatment effect ** Breslow-Day test for homogeneity of odds ratios (treatment by subgroup interaction).

Table R.1.4.5: 1 Proportion of patients with any adverse events occurring in at least 1% of the patients in either treatment arm in the overall population on PT level - by SOC and PT - 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	1863	27	1.4	1863	57	3.1	0.0009	2.11 (1.34,	3.32)	2.15 (1.35,	3.41)	0.02 (0.01, 0.03)	
Sex													0.1537
Male	1410	23	1.6	1426	41	2.9	0.0257	1.76 (1.06,	2.92)	1.79 (1.07,	2.99)	0.01 (0.00, 0.02)	
Female	453	4	0.9	437	16	3.7	0.0052	4.15 (1.40,	12.30)	4.27 (1.41,	12.86)	0.03 (0.01, 0.05)	
Age [years]													0.6777
< 65	739	8	1.1	675	13	1.9	0.1903	1.78 (0.74,	4.27)	1.79 (0.74,	4.36)	0.01 (0.00, 0.02)	
>= 65	1124	19	1.7	1188	44	3.7	0.0030	2.19 (1.29,	3.73)	2.24 (1.30,	3.86)	0.02 (0.01, 0.03)	
Region													0.7893
North America	213	2	0.9	212	7	3.3	0.0907	3.52 (0.74,	16.73)	3.60 (0.74,	17.55)	0.02 (0.00, 0.05)	
Latin America	645	4	0.6	641	7	1.1	0.3582	1.76 (0.52,	5.99)	1.77 (0.52,	6.07)	0.00 (-0.01, 0.01)	
Europe	674	6	0.9	676	11	1.6	0.2247	1.83 (0.68,	4.91)	1.84 (0.68,	5.01)	0.01 (0.00, 0.02)	
Asia	244	12	4.9	248	29	11.7	0.0066	2.38 (1.24,	4.55)	2.56 (1.27,	5.14)	0.07 (0.02, 0.12)	
Other	87	3	3.4	86	3	3.5	0.9885	1.01 (0.21,	4.87)	1.01 (0.20,	5.16)	0.00 (-0.05, 0.05)	
OECD Member													0.2637
No	741	9	1.2	713	12	1.7	0.4542	1.39 (0.59,	3.27)	1.39 (0.58,	3.32)	0.00 (-0.01, 0.02)	
Yes	1122	18	1.6	1150	45	3.9	0.0008	2.44 (1.42,	4.19)	2.50 (1.44,	4.34)	0.02 (0.01, 0.04)	
Baseline NYHA													0.8863
II	1399	19	1.4	1399	41	2.9	0.0041	2.16 (1.26,	3.70)	2.19 (1.27,	3.80)	0.02 (0.01, 0.03)	
III/IV	464	8	1.7	464	16	3.4	0.0980	2.00 (0.86,	4.63)	2.04 (0.86,	4.80)	0.02 (0.00, 0.04)	
Baseline Diabetes Status													0.5959
Diabetic	926	14	1.5	927	33	3.6	0.0051	2.35 (1.27,	4.37)	2.40 (1.28,	4.52)	0.02 (0.01, 0.03)	
Non-Diabetic	937	13	1.4	936	24	2.6	0.0673	1.85 (0.95,	3.61)	1.87 (0.95,	3.70)	0.01 (0.00, 0.02)	
Baseline BMI [kg/m²]													0.9173
<30	1299	22	1.7	1263	45	3.6	0.0030	2.10 (1.27,	3.48)	2.14 (1.28,	3.59)	0.02 (0.01, 0.03)	
>=30	564	5	0.9	600	12	2.0	0.1135	2.26 (0.80,	6.36)	2.28 (0.80,	6.52)	0.01 (0.00, 0.02)	

Risk ratios and odds ratios with confidence intervals (CIs) are estimated by Cochran-Mantel-Haenszel method. For risk differences standard Wald asymptotic confidence limits are calculated. A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied 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).
For AEs on SOC and/or PT level, subgroup analyses are only shown if overall test for treatment is significant on 5% level (i.e. 95% CI for the risk ratio does not contain 1; if this is not calculable the p-value of Chi-square test is used).
MedDRA version: 23.0. * Chi-square test for treatment effect ** Breslow-Day test for homogeneity of odds ratios (treatment by subgroup interaction).

Table R.1.4.5: 1 Proportion of patients with any adverse events occurring in at least 1% of the patients in either treatment arm in the overall population on PT level - by SOC and PT - overall and by subgroup - TS
System organ class: Gastrointestinal disorders
Preferred term: Constipation

Subgroup	Placebo			Empa 10mg			Empa 10mg vs Placebo				
Category	N	n	%	N	n	%	p-value *	Risk ratio (95% CI)	Odds ratio (95% CI)	Risk diff. (95% CI)	p-value **
Baseline eGFR (CKD-EPI) [mL/min/1.73m²]											0.9770
>=60	958	13	1.4	969	28	2.9	0.0198	2.13 (1.11, 4.09)	2.16 (1.11, 4.20)	0.02 (0.00, 0.03)	
<60	904	14	1.5	893	29	3.2	0.0185	2.10 (1.12, 3.94)	2.13 (1.12, 4.07)	0.02 (0.00, 0.03)	
History of HHF (in the last 12 months)											0.9867
No	1290	18	1.4	1286	38	3.0	0.0066	2.12 (1.22, 3.69)	2.15 (1.22, 3.79)	0.02 (0.00, 0.03)	
Yes	573	9	1.6	577	19	3.3	0.0581	2.10 (0.96, 4.59)	2.13 (0.96, 4.76)	0.02 (0.00, 0.03)	
Cause of Heart Failure											0.6474
Ischemic	944	17	1.8	983	34	3.5	0.0234	1.92 (1.08, 3.41)	1.95 (1.08, 3.52)	0.02 (0.00, 0.03)	
Non-ischemic	919	10	1.1	880	23	2.6	0.0159	2.40 (1.15, 5.02)	2.44 (1.15, 5.16)	0.02 (0.00, 0.03)	
Heart Failure Physiology											0.5946
LVEF <= 30% and NTproBNP < median	723	12	1.7	698	19	2.7	0.1706	1.64 (0.80, 3.35)	1.66 (0.80, 3.44)	0.01 (0.00, 0.03)	
LVEF <= 30% and NTproBNP >= median	660	10	1.5	631	21	3.3	0.0334	2.20 (1.04, 4.63)	2.24 (1.05, 4.79)	0.02 (0.00, 0.03)	
LVEF > 30%	473	5	1.1	526	17	3.2	0.0193	3.06 (1.14, 8.22)	3.13 (1.14, 8.54)	0.02 (0.00, 0.04)	
Baseline use of MRA											0.9415
No	512	9	1.8	557	20	3.6	0.0654	2.04 (0.94, 4.44)	2.08 (0.94, 4.61)	0.02 (0.00, 0.04)	
Yes	1351	18	1.3	1306	37	2.8	0.0066	2.13 (1.22, 3.72)	2.16 (1.22, 3.81)	0.02 (0.00, 0.03)	
Baseline use of ARNi											0.3175
No	1476	24	1.6	1523	47	3.1	0.0086	1.90 (1.17, 3.09)	1.93 (1.17, 3.17)	0.01 (0.00, 0.03)	
Yes	387	3	0.8	340	10	2.9	0.0279	3.79 (1.05, 13.67)	3.88 (1.06, 14.21)	0.02 (0.00, 0.04)	

Risk ratios and odds ratios with confidence intervals (CIs) are estimated by Cochran-Mantel-Haenszel method. For risk differences standard Wald asymptotic confidence limits are calculated. A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied 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).
For AEs on SOC and/or PT level, subgroup analyses are only shown if overall test for treatment is significant on 5% level (i.e. 95% CI for the risk ratio does not contain 1; if this is not calculable the p-value of Chi-square test is used).
MedDRA version: 23.0. * Chi-square test for treatment effect ** Breslow-Day test for homogeneity of odds ratios (treatment by subgroup interaction).

Table R.1.4.5: 1 Proportion of patients with any adverse events occurring in at least 1% of the patients in either treatment arm in the overall population on PT level - by SOC and PT - overall and by subgroup - TS
System organ class: Gastrointestinal disorders
Preferred term: Constipation

Subgroup	Placebo			Empa 10mg			Empa 10mg vs Placebo				
Category	N	n	%	N	n	%	p-value *	Risk ratio (95% CI)	Odds ratio (95% CI)	Risk diff. (95% CI)	p-value **
Baseline LVEF											0.6490
<=30	1390	22	1.6	1337	40	3.0	0.0136	1.89 (1.13, 3.16)	1.92 (1.13, 3.24)	0.01 (0.00, 0.03)	
>30 to <=35	359	5	1.4	398	14	3.5	0.0620	2.53 (0.92, 6.94)	2.58 (0.92, 7.24)	0.02 (0.00, 0.04)	
>35	114	0	0	128	3	2.3	0.1618	6.24 (0.33,119.53)	6.39 (0.33,124.98)	0.02 (-0.01, 0.05)	
Baseline NTproBNP											0.6335
< median	919	12	1.3	942	23	2.4	0.0713	1.87 (0.94, 3.74)	1.89 (0.94, 3.82)	0.01 (0.00, 0.02)	
>= median	943	15	1.6	920	34	3.7	0.0045	2.32 (1.27, 4.24)	2.37 (1.28, 4.39)	0.02 (0.01, 0.04)	

Risk ratios and odds ratios with confidence intervals (CIs) are estimated by Cochran-Mantel-Haenszel method. For risk differences standard Wald asymptotic confidence limits are calculated. A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied 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).
For AEs on SOC and/or PT level, subgroup analyses are only shown if overall test for treatment is significant on 5% level (i.e. 95% CI for the risk ratio does not contain 1; if this is not calculable the p-value of Chi-square test is used).
MedDRA version: 23.0. * Chi-square test for treatment effect ** Breslow-Day test for homogeneity of odds ratios (treatment by subgroup interaction).

Table R.1.4.5: 1 Proportion of patients with any adverse events occurring in at least 1% of the patients in either treatment arm in the overall population on PT level - by SOC and PT - 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	1863	50	2.7	1863	49	2.6	0.9189	0.98 (0.66, 1.45)	0.98 (0.66, 1.46)	0.00 (-0.01, 0.01)	

Risk ratios and odds ratios with confidence intervals (CIs) are estimated by Cochran-Mantel-Haenszel method. For risk differences standard Wald asymptotic confidence limits are calculated. A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied 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).
For AEs on SOC and/or PT level, subgroup analyses are only shown if overall test for treatment is significant on 5% level (i.e. 95% CI for the risk ratio does not contain 1; if this is not calculable the p-value of Chi-square test is used).
MedDRA version: 23.0. * Chi-square test for treatment effect ** Breslow-Day test for homogeneity of odds ratios (treatment by subgroup interaction).

Table R.1.4.5: 1 Proportion of patients with any adverse events occurring in at least 1% of the patients in either treatment arm in the overall population on PT level - by SOC and PT - 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	1863	28	1.5	1863	28	1.5	1.0000	1.00 (0.59, 1.68)	1.00 (0.59, 1.70)	0.00 (-0.01, 0.01)	

Risk ratios and odds ratios with confidence intervals (CIs) are estimated by Cochran-Mantel-Haenszel method. For risk differences standard Wald asymptotic confidence limits are calculated. A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied 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).
For AEs on SOC and/or PT level, subgroup analyses are only shown if overall test for treatment is significant on 5% level (i.e. 95% CI for the risk ratio does not contain 1; if this is not calculable the p-value of Chi-square test is used).
MedDRA version: 23.0. * Chi-square test for treatment effect ** Breslow-Day test for homogeneity of odds ratios (treatment by subgroup interaction).

Table R.1.4.5: 1 Proportion of patients with any adverse events occurring in at least 1% of the patients in either treatment arm in the overall population on PT level - by SOC and PT - 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	1863	14	0.8	1863	26	1.4	0.0564	1.86 (0.97, 3.55)	1.87 (0.97, 3.59)	0.01 (0.00, 0.01)	

Risk ratios and odds ratios with confidence intervals (CIs) are estimated by Cochran-Mantel-Haenszel method. For risk differences standard Wald asymptotic confidence limits are calculated. A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied 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).
For AEs on SOC and/or PT level, subgroup analyses are only shown if overall test for treatment is significant on 5% level (i.e. 95% CI for the risk ratio does not contain 1; if this is not calculable the p-value of Chi-square test is used).
MedDRA version: 23.0. * Chi-square test for treatment effect ** Breslow-Day test for homogeneity of odds ratios (treatment by subgroup interaction).

Table R.1.4.5: 1 Proportion of patients with any adverse events occurring in at least 1% of the patients in either treatment arm in the overall population on PT level - by SOC and PT - 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	1863	20	1.1	1863	16	0.9	0.5029	0.80 (0.42, 1.54)	0.80 (0.41, 1.55)	0.00 (-0.01, 0.00)	

Risk ratios and odds ratios with confidence intervals (CIs) are estimated by Cochran-Mantel-Haenszel method. For risk differences standard Wald asymptotic confidence limits are calculated. A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied 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).
For AEs on SOC and/or PT level, subgroup analyses are only shown if overall test for treatment is significant on 5% level (i.e. 95% CI for the risk ratio does not contain 1; if this is not calculable the p-value of Chi-square test is used).
MedDRA version: 23.0. * Chi-square test for treatment effect ** Breslow-Day test for homogeneity of odds ratios (treatment by subgroup interaction).

Table R.1.4.5: 1 Proportion of patients with any adverse events occurring in at least 1% of the patients in either treatment arm in the overall population on PT level - by SOC and PT - 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	1863	20	1.1	1863	13	0.7	0.2210	0.65 (0.32, 1.30)	0.65 (0.32, 1.31)	0.00 (-0.01, 0.00)	

Risk ratios and odds ratios with confidence intervals (CIs) are estimated by Cochran-Mantel-Haenszel method. For risk differences standard Wald asymptotic confidence limits are calculated. A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied 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).
For AEs on SOC and/or PT level, subgroup analyses are only shown if overall test for treatment is significant on 5% level (i.e. 95% CI for the risk ratio does not contain 1; if this is not calculable the p-value of Chi-square test is used).
MedDRA version: 23.0. * Chi-square test for treatment effect ** Breslow-Day test for homogeneity of odds ratios (treatment by subgroup interaction).

Table R.1.4.5: 1 Proportion of patients with any adverse events occurring in at least 1% of the patients in either treatment arm in the overall population on PT level - by SOC and PT - 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	1863	93	5.0	1863	105	5.6	0.3808	1.13 (0.86, 1.48)	1.14 (0.85, 1.51)	0.01 (-0.01, 0.02)	

Risk ratios and odds ratios with confidence intervals (CIs) are estimated by Cochran-Mantel-Haenszel method. For risk differences standard Wald asymptotic confidence limits are calculated. A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied 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).
For AEs on SOC and/or PT level, subgroup analyses are only shown if overall test for treatment is significant on 5% level (i.e. 95% CI for the risk ratio does not contain 1; if this is not calculable the p-value of Chi-square test is used).
MedDRA version: 23.0. * Chi-square test for treatment effect ** Breslow-Day test for homogeneity of odds ratios (treatment by subgroup interaction).

Table R.1.4.5: 1 Proportion of patients with any adverse events occurring in at least 1% of the patients in either treatment arm in the overall population on PT level - by SOC and PT - overall and by subgroup - TS
System organ class: Renal and urinary disorders
Preferred term: Acute kidney injury

Subgroup Category	Placebo N	Placebo n	Placebo %	Empa 10mg N	Empa 10mg n	Empa 10mg %	Empa 10mg vs Placebo p-value *	Risk ratio (95% CI)	Odds ratio (95% CI)	Risk diff. (95% CI)	p-value **
Overall	1863	55	3.0	1863	35	1.9	0.0328	0.64 (0.42, 0.97)	0.63 (0.41, 0.97)	-0.01 (-0.02, 0.00)	
Sex											0.4602
Male	1410	44	3.1	1426	26	1.8	0.0260	0.58 (0.36, 0.94)	0.58 (0.35, 0.94)	-0.01 (-0.02, 0.00)	
Female	453	11	2.4	437	9	2.1	0.7106	0.85 (0.35, 2.03)	0.84 (0.35, 2.06)	0.00 (-0.02, 0.02)	
Age [years]											0.4347
< 65	739	21	2.8	675	15	2.2	0.4601	0.78 (0.41, 1.50)	0.78 (0.40, 1.52)	-0.01 (-0.02, 0.01)	
>= 65	1124	34	3.0	1188	20	1.7	0.0328	0.56 (0.32, 0.96)	0.55 (0.31, 0.96)	-0.01 (-0.03, 0.00)	
Region											0.9534
North America	213	18	8.5	212	14	6.6	0.4706	0.78 (0.40, 1.53)	0.77 (0.37, 1.58)	-0.02 (-0.07, 0.03)	
Latin America	645	19	2.9	641	11	1.7	0.1441	0.58 (0.28, 1.21)	0.58 (0.27, 1.22)	-0.01 (-0.03, 0.00)	
Europe	674	16	2.4	676	9	1.3	0.1554	0.56 (0.25, 1.26)	0.55 (0.24, 1.26)	-0.01 (-0.02, 0.00)	
Asia	244	1	0.4	248	1	0.4	0.9908	0.98 (0.06, 15.64)	0.98 (0.06, 15.82)	0.00 (-0.01, 0.01)	
Other	87	1	1.1	86	0	0	0.4820	0.34 (0.01, 8.16)	0.33 (0.01, 8.30)	-0.01 (-0.04, 0.02)	
OECD Member											0.9246
No	741	17	2.3	713	10	1.4	0.2080	0.61 (0.28, 1.33)	0.61 (0.28, 1.33)	-0.01 (-0.02, 0.00)	
Yes	1122	38	3.4	1150	25	2.2	0.0783	0.64 (0.39, 1.06)	0.63 (0.38, 1.06)	-0.01 (-0.03, 0.00)	
Baseline NYHA											0.2110
II	1399	34	2.4	1399	26	1.9	0.2965	0.76 (0.46, 1.27)	0.76 (0.45, 1.27)	-0.01 (-0.02, 0.01)	
III/IV	464	21	4.5	464	9	1.9	0.0259	0.43 (0.20, 0.93)	0.42 (0.19, 0.92)	-0.03 (-0.05, 0.00)	
Baseline Diabetes Status											0.8310
Diabetic	926	27	2.9	927	18	1.9	0.1732	0.67 (0.37, 1.20)	0.66 (0.36, 1.21)	-0.01 (-0.02, 0.00)	
Non-Diabetic	937	28	3.0	936	17	1.8	0.0977	0.61 (0.33, 1.10)	0.60 (0.33, 1.10)	-0.01 (-0.03, 0.00)	
Baseline BMI [kg/m²]											0.9677
<30	1299	34	2.6	1263	21	1.7	0.0955	0.64 (0.37, 1.09)	0.63 (0.36, 1.09)	-0.01 (-0.02, 0.00)	
>=30	564	21	3.7	600	14	2.3	0.1652	0.63 (0.32, 1.22)	0.62 (0.31, 1.23)	-0.01 (-0.03, 0.01)	

Risk ratios and odds ratios with confidence intervals (CIs) are estimated by Cochran-Mantel-Haenszel method. For risk differences standard Wald asymptotic confidence limits are calculated. A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied 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).
For AEs on SOC and/or PT level, subgroup analyses are only shown if overall test for treatment is significant on 5% level (i.e. 95% CI for the risk ratio does not contain 1; if this is not calculable the p-value of Chi-square test is used).
MedDRA version: 23.0. * Chi-square test for treatment effect ** Breslow-Day test for homogeneity of odds ratios (treatment by subgroup interaction).

Table R.1.4.5: 1 Proportion of patients with any adverse events occurring in at least 1% of the patients in either treatment arm in the overall population on PT level - by SOC and PT - overall and by subgroup - TS
System organ class: Renal and urinary disorders
Preferred term: Acute kidney injury

Subgroup	Placebo			Empa 10mg			Empa 10mg vs Placebo					
Category	N	n	%	N	n	%	p-value *	Risk ratio (95% CI)		Odds ratio (95% CI)		Risk diff. (95% CI)	p-value **
Baseline eGFR (CKD-EPI) [mL/min/1.73m²]													0.7527
>=60	958	22	2.3	969	13	1.3	0.1166	0.58 (0.30,	1.15)	0.58 (0.29,	1.16)	-0.01 (-0.02, 0.00)	
<60	904	33	3.7	893	22	2.5	0.1442	0.67 (0.40,	1.15)	0.67 (0.39,	1.15)	-0.01 (-0.03, 0.00)	
History of HHF (in the last 12 months)													0.6830
No	1290	37	2.9	1286	22	1.7	0.0496	0.60 (0.35,	1.01)	0.59 (0.35,	1.00)	-0.01 (-0.02, 0.00)	
Yes	573	18	3.1	577	13	2.3	0.3524	0.72 (0.35,	1.45)	0.71 (0.34,	1.46)	-0.01 (-0.03, 0.01)	
Cause of Heart Failure													0.6984
Ischemic	944	28	3.0	983	20	2.0	0.1896	0.69 (0.39,	1.21)	0.68 (0.38,	1.21)	-0.01 (-0.02, 0.00)	
Non-ischemic	919	27	2.9	880	15	1.7	0.0833	0.58 (0.31,	1.08)	0.57 (0.30,	1.08)	-0.01 (-0.03, 0.00)	
Heart Failure Physiology													0.7884
LVEF <= 30% and NTproBNP < median	723	13	1.8	698	10	1.4	0.5853	0.80 (0.35,	1.81)	0.79 (0.35,	1.82)	0.00 (-0.02, 0.01)	
LVEF <= 30% and NTproBNP >= median	660	28	4.2	631	15	2.4	0.0619	0.56 (0.30,	1.04)	0.55 (0.29,	1.04)	-0.02 (-0.04, 0.00)	
LVEF > 30%	473	14	3.0	526	10	1.9	0.2752	0.64 (0.29,	1.43)	0.64 (0.28,	1.44)	-0.01 (-0.03, 0.01)	
Baseline use of MRA													0.7261
No	512	17	3.3	557	13	2.3	0.3293	0.70 (0.34,	1.43)	0.70 (0.33,	1.45)	-0.01 (-0.03, 0.01)	
Yes	1351	38	2.8	1306	22	1.7	0.0504	0.60 (0.36,	1.01)	0.59 (0.35,	1.01)	-0.01 (-0.02, 0.00)	
Baseline use of ARNi													0.9283
No	1476	38	2.6	1523	25	1.6	0.0749	0.64 (0.39,	1.05)	0.63 (0.38,	1.05)	-0.01 (-0.02, 0.00)	
Yes	387	17	4.4	340	10	2.9	0.3017	0.67 (0.31,	1.44)	0.66 (0.30,	1.46)	-0.01 (-0.04, 0.01)	

Risk ratios and odds ratios with confidence intervals (CIs) are estimated by Cochran-Mantel-Haenszel method. For risk differences standard Wald asymptotic confidence limits are calculated. A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied 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).
For AEs on SOC and/or PT level, subgroup analyses are only shown if overall test for treatment is significant on 5% level (i.e. 95% CI for the risk ratio does not contain 1; if this is not calculable the p-value of Chi-square test is used).
MedDRA version: 23.0. * Chi-square test for treatment effect ** Breslow-Day test for homogeneity of odds ratios (treatment by subgroup interaction).

Table R.1.4.5: 1 Proportion of patients with any adverse events occurring in at least 1% of the patients in either treatment arm in the overall population on PT level - by SOC and PT - overall and by subgroup - TS
System organ class: Renal and urinary disorders
Preferred term: Acute kidney injury

Subgroup	Placebo			Empa 10mg			Empa 10mg vs Placebo					
Category	N	n	%	N	n	%	p-value *	Risk ratio (95% CI)	Odds ratio (95% CI)	Risk diff. (95% CI)		p-value **
Baseline LVEF												0.8951
<=30	1390	41	2.9	1337	25	1.9	0.0666	0.63 (0.39, 1.04)	0.63 (0.38, 1.04)	-0.01	(-0.02, 0.00)	
>30 to <=35	359	11	3.1	398	7	1.8	0.2392	0.57 (0.22, 1.46)	0.57 (0.22, 1.48)	-0.01	(-0.04, 0.01)	
>35	114	3	2.6	128	3	2.3	0.8857	0.89 (0.18, 4.33)	0.89 (0.18, 4.49)	0.00	(-0.04, 0.04)	
Baseline NTproBNP												0.6003
< median	919	17	1.8	942	13	1.4	0.4211	0.75 (0.36, 1.53)	0.74 (0.36, 1.54)	0.00	(-0.02, 0.01)	
>= median	943	38	4.0	920	22	2.4	0.0452	0.59 (0.35, 1.00)	0.58 (0.34, 0.99)	-0.02	(-0.03, 0.00)	

Risk ratios and odds ratios with confidence intervals (CIs) are estimated by Cochran-Mantel-Haenszel method. For risk differences standard Wald asymptotic confidence limits are calculated. A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied 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).
For AEs on SOC and/or PT level, subgroup analyses are only shown if overall test for treatment is significant on 5% level
(i.e. 95% CI for the risk ratio does not contain 1; if this is not calculable the p-value of Chi-square test is used).
MedDRA version: 23.0. * Chi-square test for treatment effect ** Breslow-Day test for homogeneity of odds ratios (treatment by subgroup interaction).

Table R.1.4.5: 1 Proportion of patients with any adverse events occurring in at least 1% of the patients in either treatment arm in the overall population on PT level - by SOC and PT - 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	1863	48	2.6	1863	44	2.4	0.6728	0.92 (0.61, 1.37)	0.91 (0.60, 1.38)	0.00 (-0.01, 0.01)	

Risk ratios and odds ratios with confidence intervals (CIs) are estimated by Cochran-Mantel-Haenszel method. For risk differences standard Wald asymptotic confidence limits are calculated. A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied 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).
For AEs on SOC and/or PT level, subgroup analyses are only shown if overall test for treatment is significant on 5% level (i.e. 95% CI for the risk ratio does not contain 1; if this is not calculable the p-value of Chi-square test is used).
MedDRA version: 23.0. * Chi-square test for treatment effect ** Breslow-Day test for homogeneity of odds ratios (treatment by subgroup interaction).

Table R.1.4.5: 1 Proportion of patients with any adverse events occurring in at least 1% of the patients in either treatment arm in the overall population on PT level - by SOC and PT - 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	1863	19	1.0	1863	22	1.2	0.6376	1.16 (0.63, 2.13)	1.16 (0.63, 2.15)	0.00 (-0.01, 0.01)	

Risk ratios and odds ratios with confidence intervals (CIs) are estimated by Cochran-Mantel-Haenszel method. For risk differences standard Wald asymptotic confidence limits are calculated. A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied 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).
For AEs on SOC and/or PT level, subgroup analyses are only shown if overall test for treatment is significant on 5% level (i.e. 95% CI for the risk ratio does not contain 1; if this is not calculable the p-value of Chi-square test is used).
MedDRA version: 23.0. * Chi-square test for treatment effect ** Breslow-Day test for homogeneity of odds ratios (treatment by subgroup interaction).

Table R.1.4.5: 1 Proportion of patients with any adverse events occurring in at least 1% of the patients in either treatment arm in the overall population on PT level - by SOC and PT - 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	1863	13	0.7	1863	19	1.0	0.2868	1.46 (0.72, 2.95)	1.47 (0.72, 2.98)	0.00 (0.00, 0.01)	

Risk ratios and odds ratios with confidence intervals (CIs) are estimated by Cochran-Mantel-Haenszel method. For risk differences standard Wald asymptotic confidence limits are calculated. A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied 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).
For AEs on SOC and/or PT level, subgroup analyses are only shown if overall test for treatment is significant on 5% level (i.e. 95% CI for the risk ratio does not contain 1; if this is not calculable the p-value of Chi-square test is used).
MedDRA version: 23.0. * Chi-square test for treatment effect ** Breslow-Day test for homogeneity of odds ratios (treatment by subgroup interaction).

Table R.1.4.5: 1 Proportion of patients with any adverse events occurring in at least 1% of the patients in either treatment arm in the overall population on PT level - by SOC and PT - 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	1863	119	6.4	1863	130	7.0	0.4705	1.09 (0.86, 1.39)	1.10 (0.85, 1.42)	0.01 (-0.01, 0.02)	

Risk ratios and odds ratios with confidence intervals (CIs) are estimated by Cochran-Mantel-Haenszel method. For risk differences standard Wald asymptotic confidence limits are calculated. A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied 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).
For AEs on SOC and/or PT level, subgroup analyses are only shown if overall test for treatment is significant on 5% level (i.e. 95% CI for the risk ratio does not contain 1; if this is not calculable the p-value of Chi-square test is used).
MedDRA version: 23.0. * Chi-square test for treatment effect ** Breslow-Day test for homogeneity of odds ratios (treatment by subgroup interaction).

Table R.1.4.5: 1 Proportion of patients with any adverse events occurring in at least 1% of the patients in either treatment arm in the overall population on PT level - by SOC and PT - 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	1863	34	1.8	1863	39	2.1	0.5545	1.15 (0.73, 1.81)	1.15 (0.72, 1.83)	0.00 (-0.01, 0.01)	

Risk ratios and odds ratios with confidence intervals (CIs) are estimated by Cochran-Mantel-Haenszel method. For risk differences standard Wald asymptotic confidence limits are calculated. A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied 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).
For AEs on SOC and/or PT level, subgroup analyses are only shown if overall test for treatment is significant on 5% level (i.e. 95% CI for the risk ratio does not contain 1; if this is not calculable the p-value of Chi-square test is used).
MedDRA version: 23.0. * Chi-square test for treatment effect ** Breslow-Day test for homogeneity of odds ratios (treatment by subgroup interaction).

Table R.1.4.5: 1 Proportion of patients with any adverse events occurring in at least 1% of the patients in either treatment arm in the overall population on PT level - by SOC and PT - 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	1863	49	2.6	1863	55	3.0	0.5507	1.12 (0.77, 1.64)	1.13 (0.76, 1.66)	0.00 (-0.01, 0.01)	

Risk ratios and odds ratios with confidence intervals (CIs) are estimated by Cochran-Mantel-Haenszel method. For risk differences standard Wald asymptotic confidence limits are calculated. A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied 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).
For AEs on SOC and/or PT level, subgroup analyses are only shown if overall test for treatment is significant on 5% level (i.e. 95% CI for the risk ratio does not contain 1; if this is not calculable the p-value of Chi-square test is used).
MedDRA version: 23.0. * Chi-square test for treatment effect ** Breslow-Day test for homogeneity of odds ratios (treatment by subgroup interaction).

Table R.1.4.5: 1 Proportion of patients with any adverse events occurring in at least 1% of the patients in either treatment arm in the overall population on PT level - by SOC and PT - 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	1863	16	0.9	1863	35	1.9	0.0074	2.19 (1.22,	3.94)	2.21 (1.22,	4.01)	0.01 (0.00, 0.02)	
Sex													0.0165
Male	1410	14	1.0	1426	19	1.3	0.3993	1.34 (0.68,	2.67)	1.35 (0.67,	2.70)	0.00 (0.00, 0.01)	
Female	453	2	0.4	437	16	3.7	0.0006	8.29 (1.92,	35.86)	8.57 (1.96,	37.50)	0.03 (0.01, 0.05)	
Age [years]													0.1000
< 65	739	4	0.5	675	16	2.4	0.0036	4.38 (1.47,	13.03)	4.46 (1.48,	13.41)	0.02 (0.01, 0.03)	
>= 65	1124	12	1.1	1188	19	1.6	0.2666	1.50 (0.73,	3.07)	1.51 (0.73,	3.12)	0.01 (0.00, 0.01)	
Region													0.5033
North America	213	3	1.4	212	8	3.8	0.1247	2.68 (0.72,	9.96)	2.75 (0.72,	10.49)	0.02 (-0.01, 0.05)	
Latin America	645	5	0.8	641	11	1.7	0.1280	2.21 (0.77,	6.34)	2.23 (0.77,	6.47)	0.01 (0.00, 0.02)	
Europe	674	5	0.7	676	7	1.0	0.5654	1.40 (0.45,	4.38)	1.40 (0.44,	4.43)	0.00 (-0.01, 0.01)	
Asia	244	2	0.8	248	9	3.6	0.0351	4.43 (0.97,	20.28)	4.56 (0.97,	21.31)	0.03 (0.00, 0.05)	
Other	87	1	1.1	86	0	0	0.4820	0.34 (0.01,	8.16)	0.33 (0.01,	8.30)	-0.01 (-0.04, 0.02)	
OECD Member													0.5851
No	741	6	0.8	713	10	1.4	0.2787	1.73 (0.63,	4.74)	1.74 (0.63,	4.82)	0.01 (0.00, 0.02)	
Yes	1122	10	0.9	1150	25	2.2	0.0131	2.44 (1.18,	5.05)	2.47 (1.18,	5.17)	0.01 (0.00, 0.02)	
Baseline NYHA													0.0475
II	1399	14	1.0	1399	21	1.5	0.2338	1.50 (0.77,	2.94)	1.51 (0.76,	2.98)	0.01 (0.00, 0.01)	
III/IV	464	2	0.4	464	14	3.0	0.0025	7.00 (1.60,	30.63)	7.19 (1.62,	31.80)	0.03 (0.01, 0.04)	
Baseline Diabetes Status													0.6275
Diabetic	926	8	0.9	927	15	1.6	0.1426	1.87 (0.80,	4.40)	1.89 (0.80,	4.47)	0.01 (0.00, 0.02)	
Non-Diabetic	937	8	0.9	936	20	2.1	0.0222	2.50 (1.11,	5.65)	2.54 (1.11,	5.79)	0.01 (0.00, 0.02)	
Baseline BMI [kg/m²]													0.5945
<30	1299	12	0.9	1263	23	1.8	0.0505	1.97 (0.99,	3.94)	1.99 (0.99,	4.02)	0.01 (0.00, 0.02)	
>=30	564	4	0.7	600	12	2.0	0.0587	2.82 (0.91,	8.69)	2.86 (0.92,	8.91)	0.01 (0.00, 0.03)	

Risk ratios and odds ratios with confidence intervals (CIs) are estimated by Cochran-Mantel-Haenszel method. For risk differences standard Wald asymptotic confidence limits are calculated. A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied 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).
For AEs on SOC and/or PT level, subgroup analyses are only shown if overall test for treatment is significant on 5% level (i.e. 95% CI for the risk ratio does not contain 1; if this is not calculable the p-value of Chi-square test is used).
MedDRA version: 23.0. * Chi-square test for treatment effect ** Breslow-Day test for homogeneity of odds ratios (treatment by subgroup interaction).

Table R.1.4.5: 1 Proportion of patients with any adverse events occurring in at least 1% of the patients in either treatment arm in the overall population on PT level - by SOC and PT - 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 **
Baseline eGFR (CKD-EPI) [mL/min/1.73m²]												0.1464
>=60	958	7	0.7	969	23	2.4	0.0036	3.25 (1.40, 7.53)	3.30 (1.41, 7.73)	0.02 (0.01, 0.03)		
<60	904	9	1.0	893	12	1.3	0.4922	1.35 (0.57, 3.19)	1.35 (0.57, 3.23)	0.00 (-0.01, 0.01)		
History of HHF (in the last 12 months)												0.1363
No	1290	13	1.0	1286	21	1.6	0.1645	1.62 (0.81, 3.22)	1.63 (0.81, 3.27)	0.01 (0.00, 0.02)		
Yes	573	3	0.5	577	14	2.4	0.0075	4.63 (1.34, 16.04)	4.72 (1.35, 16.53)	0.02 (0.01, 0.03)		
Cause of Heart Failure												0.4922
Ischemic	944	10	1.1	983	19	1.9	0.1154	1.82 (0.85, 3.90)	1.84 (0.85, 3.98)	0.01 (0.00, 0.02)		
Non-ischemic	919	6	0.7	880	16	1.8	0.0246	2.78 (1.09, 7.08)	2.82 (1.10, 7.23)	0.01 (0.00, 0.02)		
Heart Failure Physiology												0.1669
LVEF <= 30% and NTproBNP < median	723	5	0.7	698	18	2.6	0.0048	3.73 (1.39, 9.99)	3.80 (1.40, 10.29)	0.02 (0.01, 0.03)		
LVEF <= 30% and NTproBNP >= median	660	8	1.2	631	8	1.3	0.9279	1.05 (0.39, 2.77)	1.05 (0.39, 2.81)	0.00 (-0.01, 0.01)		
LVEF > 30%	473	3	0.6	526	9	1.7	0.1188	2.70 (0.73, 9.91)	2.73 (0.73, 10.13)	0.01 (0.00, 0.02)		
Baseline use of MRA												0.0559
No	512	8	1.6	557	9	1.6	0.9445	1.03 (0.40, 2.66)	1.03 (0.40, 2.70)	0.00 (-0.01, 0.02)		
Yes	1351	8	0.6	1306	26	2.0	0.0013	3.36 (1.53, 7.40)	3.41 (1.54, 7.56)	0.01 (0.01, 0.02)		
Baseline use of ARNi												0.6631
No	1476	12	0.8	1523	29	1.9	0.0101	2.34 (1.20, 4.57)	2.37 (1.20, 4.66)	0.01 (0.00, 0.02)		
Yes	387	4	1.0	340	6	1.8	0.3984	1.71 (0.49, 6.00)	1.72 (0.48, 6.15)	0.01 (-0.01, 0.02)		

Risk ratios and odds ratios with confidence intervals (CIs) are estimated by Cochran-Mantel-Haenszel method. For risk differences standard Wald asymptotic confidence limits are calculated. A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied 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).
For AEs on SOC and/or PT level, subgroup analyses are only shown if overall test for treatment is significant on 5% level (i.e. 95% CI for the risk ratio does not contain 1; if this is not calculable the p-value of Chi-square test is used).
MedDRA version: 23.0. * Chi-square test for treatment effect ** Breslow-Day test for homogeneity of odds ratios (treatment by subgroup interaction).

Table R.1.4.5: 1 Proportion of patients with any adverse events occurring in at least 1% of the patients in either treatment arm in the overall population on PT level - by SOC and PT - 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 **
Baseline LVEF											0.0367
<=30	1390	13	0.9	1337	26	1.9	0.0265	2.08 (1.07, 4.03)	2.10 (1.07, 4.11)	0.01 (0.00, 0.02)	
>30 to <=35	359	0	0	398	8	2.0	0.0114	15.34 (0.89,264.80)	15.65 (0.90,272.13)	0.02 (0.01, 0.03)	
>35	114	3	2.6	128	1	0.8	0.2598	0.30 (0.03, 2.81)	0.29 (0.03, 2.84)	-0.02 (-0.05, 0.01)	
Baseline NTproBNP											0.1054
< median	919	6	0.7	942	22	2.3	0.0029	3.58 (1.46, 8.78)	3.64 (1.47, 9.02)	0.02 (0.01, 0.03)	
>= median	943	10	1.1	920	13	1.4	0.4908	1.33 (0.59, 3.02)	1.34 (0.58, 3.07)	0.00 (-0.01, 0.01)	

Risk ratios and odds ratios with confidence intervals (CIs) are estimated by Cochran-Mantel-Haenszel method. For risk differences standard Wald asymptotic confidence limits are calculated. A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied 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).
For AEs on SOC and/or PT level, subgroup analyses are only shown if overall test for treatment is significant on 5% level (i.e. 95% CI for the risk ratio does not contain 1; if this is not calculable the p-value of Chi-square test is used).
MedDRA version: 23.0. * Chi-square test for treatment effect ** Breslow-Day test for homogeneity of odds ratios (treatment by subgroup interaction).

Table R.1.4.5: 1 Proportion of patients with any adverse events occurring in at least 1% of the patients in either treatment arm in the overall population on PT level - by SOC and PT - 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	1863	26	1.4	1863	33	1.8	0.3583	1.27 (0.76, 2.11)	1.27 (0.76, 2.14)	0.00 (0.00, 0.01)	

Risk ratios and odds ratios with confidence intervals (CIs) are estimated by Cochran-Mantel-Haenszel method. For risk differences standard Wald asymptotic confidence limits are calculated. A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied 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).
For AEs on SOC and/or PT level, subgroup analyses are only shown if overall test for treatment is significant on 5% level (i.e. 95% CI for the risk ratio does not contain 1; if this is not calculable the p-value of Chi-square test is used).
MedDRA version: 23.0. * Chi-square test for treatment effect ** Breslow-Day test for homogeneity of odds ratios (treatment by subgroup interaction).

Table R.1.4.5: 1 Proportion of patients with any adverse events occurring in at least 1% of the patients in either treatment arm in the overall population on PT level - by SOC and PT - 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	1863	20	1.1	1863	19	1.0	0.8721	0.95 (0.51, 1.77)	0.95 (0.51, 1.78)	0.00 (-0.01, 0.01)	

Risk ratios and odds ratios with confidence intervals (CIs) are estimated by Cochran-Mantel-Haenszel method. For risk differences standard Wald asymptotic confidence limits are calculated. A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied 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).
For AEs on SOC and/or PT level, subgroup analyses are only shown if overall test for treatment is significant on 5% level (i.e. 95% CI for the risk ratio does not contain 1; if this is not calculable the p-value of Chi-square test is used).
MedDRA version: 23.0. * Chi-square test for treatment effect ** Breslow-Day test for homogeneity of odds ratios (treatment by subgroup interaction).

Table R.1.4.5: 1 Proportion of patients with any adverse events occurring in at least 1% of the patients in either treatment arm in the overall population on PT level - by SOC and PT - 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	1863	52	2.8	1863	53	2.8	0.9211	1.02 (0.70, 1.49)	1.02 (0.69, 1.50)	0.00 (-0.01, 0.01)	

Risk ratios and odds ratios with confidence intervals (CIs) are estimated by Cochran-Mantel-Haenszel method. For risk differences standard Wald asymptotic confidence limits are calculated. A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied 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).
For AEs on SOC and/or PT level, subgroup analyses are only shown if overall test for treatment is significant on 5% level (i.e. 95% CI for the risk ratio does not contain 1; if this is not calculable the p-value of Chi-square test is used).
MedDRA version: 23.0. * Chi-square test for treatment effect ** Breslow-Day test for homogeneity of odds ratios (treatment by subgroup interaction).

Table R.1.4.5: 1 Proportion of patients with any adverse events occurring in at least 1% of the patients in either treatment arm in the overall population on PT level - by SOC and PT - 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	1863	53	2.8	1863	28	1.5	0.0050	0.53	(0.34, 0.83)	0.52	(0.33, 0.83)	-0.01	(-0.02, 0.00)	
Sex														0.0062
Male	1410	43	3.0	1426	15	1.1	0.0002	0.34	(0.19, 0.62)	0.34	(0.19, 0.61)	-0.02	(-0.03,-0.01)	
Female	453	10	2.2	437	13	3.0	0.4708	1.35	(0.60, 3.04)	1.36	(0.59, 3.13)	0.01	(-0.01, 0.03)	
Age [years]														0.3649
< 65	739	21	2.8	675	13	1.9	0.2615	0.68	(0.34, 1.34)	0.67	(0.33, 1.35)	-0.01	(-0.03, 0.01)	
>= 65	1124	32	2.8	1188	15	1.3	0.0070	0.44	(0.24, 0.81)	0.44	(0.24, 0.81)	-0.02	(-0.03, 0.00)	
Region														0.9922
North America	213	14	6.6	212	8	3.8	0.1928	0.57	(0.25, 1.34)	0.56	(0.23, 1.36)	-0.03	(-0.07, 0.01)	
Latin America	645	14	2.2	641	8	1.2	0.2021	0.57	(0.24, 1.36)	0.57	(0.24, 1.37)	-0.01	(-0.02, 0.00)	
Europe	674	21	3.1	676	10	1.5	0.0447	0.47	(0.23, 1.00)	0.47	(0.22, 1.00)	-0.02	(-0.03, 0.00)	
Asia	244	4	1.6	248	2	0.8	0.4000	0.49	(0.09, 2.66)	0.49	(0.09, 2.69)	-0.01	(-0.03, 0.01)	
Other	87	0	0	86	0	0	0.9954	1.01	(0.02, 50.41)	1.01	(0.02, 51.56)	0.00	(-0.02, 0.02)	
OECD Member														0.7300
No	741	14	1.9	713	8	1.1	0.2308	0.59	(0.25, 1.41)	0.59	(0.25, 1.41)	-0.01	(-0.02, 0.00)	
Yes	1122	39	3.5	1150	20	1.7	0.0093	0.50	(0.29, 0.85)	0.49	(0.28, 0.85)	-0.02	(-0.03, 0.00)	
Baseline NYHA														0.8848
II	1399	35	2.5	1399	18	1.3	0.0184	0.51	(0.29, 0.90)	0.51	(0.29, 0.90)	-0.01	(-0.02, 0.00)	
III/IV	464	18	3.9	464	10	2.2	0.1247	0.56	(0.26, 1.19)	0.55	(0.25, 1.20)	-0.02	(-0.04, 0.00)	
Baseline Diabetes Status														0.9025
Diabetic	926	22	2.4	927	12	1.3	0.0829	0.54	(0.27, 1.09)	0.54	(0.27, 1.10)	-0.01	(-0.02, 0.00)	
Non-Diabetic	937	31	3.3	936	16	1.7	0.0269	0.52	(0.28, 0.94)	0.51	(0.28, 0.94)	-0.02	(-0.03, 0.00)	
Baseline BMI [kg/m²]														0.2988
<30	1299	34	2.6	1263	14	1.1	0.0049	0.42	(0.23, 0.79)	0.42	(0.22, 0.78)	-0.02	(-0.03, 0.00)	
>=30	564	19	3.4	600	14	2.3	0.2874	0.69	(0.35, 1.37)	0.69	(0.34, 1.38)	-0.01	(-0.03, 0.01)	

Risk ratios and odds ratios with confidence intervals (CIs) are estimated by Cochran-Mantel-Haenszel method. For risk differences standard Wald asymptotic confidence limits are calculated. A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied 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).
For AEs on SOC and/or PT level, subgroup analyses are only shown if overall test for treatment is significant on 5% level (i.e. 95% CI for the risk ratio does not contain 1; if this is not calculable the p-value of Chi-square test is used).
MedDRA version: 23.0. * Chi-square test for treatment effect ** Breslow-Day test for homogeneity of odds ratios (treatment by subgroup interaction).

Table R.1.4.5: 1 Proportion of patients with any adverse events occurring in at least 1% of the patients in either treatment arm in the overall population on PT level - by SOC and PT - overall and by subgroup - TS
System organ class: Respiratory, thoracic and mediastinal disorders
Preferred term: Dyspnoea

Subgroup	Placebo			Empa 10mg			Empa 10mg vs Placebo					
Category	N	n	%	N	n	%	p-value *	Risk ratio (95% CI)	Odds ratio (95% CI)	Risk diff. (95% CI)		p-value **
Baseline eGFR (CKD-EPI) [mL/min/1.73m²]												0.8431
>=60	958	25	2.6	969	14	1.4	0.0694	0.55 (0.29, 1.06)	0.55 (0.28, 1.06)	-0.01	(-0.02, 0.00)	
<60	904	28	3.1	893	14	1.6	0.0319	0.51 (0.27, 0.95)	0.50 (0.26, 0.95)	-0.02	(-0.03, 0.00)	
History of HHF (in the last 12 months)												0.2907
No	1290	38	2.9	1286	23	1.8	0.0534	0.61 (0.36, 1.01)	0.60 (0.36, 1.01)	-0.01	(-0.02, 0.00)	
Yes	573	15	2.6	577	5	0.9	0.0231	0.33 (0.12, 0.90)	0.33 (0.12, 0.90)	-0.02	(-0.03, 0.00)	
Cause of Heart Failure												0.2544
Ischemic	944	26	2.8	983	18	1.8	0.1751	0.66 (0.37, 1.20)	0.66 (0.36, 1.21)	-0.01	(-0.02, 0.00)	
Non-ischemic	919	27	2.9	880	10	1.1	0.0071	0.39 (0.19, 0.79)	0.38 (0.18, 0.79)	-0.02	(-0.03,-0.01)	
Heart Failure Physiology												0.3431
LVEF <= 30% and NTproBNP < median	723	21	2.9	698	14	2.0	0.2745	0.69 (0.35, 1.35)	0.68 (0.35, 1.36)	-0.01	(-0.03, 0.01)	
LVEF <= 30% and NTproBNP >= median	660	24	3.6	631	8	1.3	0.0062	0.35 (0.16, 0.77)	0.34 (0.15, 0.76)	-0.02	(-0.04,-0.01)	
LVEF > 30%	473	7	1.5	526	6	1.1	0.6367	0.77 (0.26, 2.28)	0.77 (0.26, 2.30)	0.00	(-0.02, 0.01)	
Baseline use of MRA												0.8239
No	512	18	3.5	557	11	2.0	0.1214	0.56 (0.27, 1.18)	0.55 (0.26, 1.18)	-0.02	(-0.04, 0.00)	
Yes	1351	35	2.6	1306	17	1.3	0.0165	0.50 (0.28, 0.89)	0.50 (0.28, 0.89)	-0.01	(-0.02, 0.00)	
Baseline use of ARNi												0.4837
No	1476	40	2.7	1523	20	1.3	0.0063	0.48 (0.28, 0.82)	0.48 (0.28, 0.82)	-0.01	(-0.02, 0.00)	
Yes	387	13	3.4	340	8	2.4	0.4189	0.70 (0.29, 1.67)	0.69 (0.28, 1.69)	-0.01	(-0.03, 0.01)	

Risk ratios and odds ratios with confidence intervals (CIs) are estimated by Cochran-Mantel-Haenszel method. For risk differences standard Wald asymptotic confidence limits are calculated. A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied 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).
For AEs on SOC and/or PT level, subgroup analyses are only shown if overall test for treatment is significant on 5% level (i.e. 95% CI for the risk ratio does not contain 1; if this is not calculable the p-value of Chi-square test is used).
MedDRA version: 23.0. * Chi-square test for treatment effect ** Breslow-Day test for homogeneity of odds ratios (treatment by subgroup interaction).

Table R.1.4.5: 1 Proportion of patients with any adverse events occurring in at least 1% of the patients in either treatment arm in the overall population on PT level - by SOC and PT - overall and by subgroup - TS
System organ class: Respiratory, thoracic and mediastinal disorders
Preferred term: Dyspnoea

Subgroup	Placebo			Empa 10mg			Empa 10mg vs Placebo				
Category	N	n	%	N	n	%	p-value *	Risk ratio (95% CI)	Odds ratio (95% CI)	Risk diff. (95% CI)	p-value **
Baseline LVEF											0.1046
<=30	1390	46	3.3	1337	22	1.6	0.0053	0.50 (0.30, 0.82)	0.49 (0.29, 0.82)	-0.02 (-0.03,-0.01)	
>30 to <=35	359	6	1.7	398	2	0.5	0.1163	0.30 (0.06, 1.48)	0.30 (0.06, 1.48)	-0.01 (-0.03, 0.00)	
>35	114	1	0.9	128	4	3.1	0.2198	3.56 (0.40, 31.41)	3.65 (0.40, 33.10)	0.02 (-0.01, 0.06)	
Baseline NTproBNP											0.3681
< median	919	26	2.8	942	17	1.8	0.1414	0.64 (0.35, 1.17)	0.63 (0.34, 1.17)	-0.01 (-0.02, 0.00)	
>= median	943	27	2.9	920	11	1.2	0.0109	0.42 (0.21, 0.84)	0.41 (0.20, 0.83)	-0.02 (-0.03, 0.00)	

Risk ratios and odds ratios with confidence intervals (CIs) are estimated by Cochran-Mantel-Haenszel method. For risk differences standard Wald asymptotic confidence limits are calculated. A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied 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).
For AEs on SOC and/or PT level, subgroup analyses are only shown if overall test for treatment is significant on 5% level (i.e. 95% CI for the risk ratio does not contain 1; if this is not calculable the p-value of Chi-square test is used).
MedDRA version: 23.0. * Chi-square test for treatment effect ** Breslow-Day test for homogeneity of odds ratios (treatment by subgroup interaction).

Table R.1.4.5: 1 Proportion of patients with any adverse events occurring in at least 1% of the patients in either treatment arm in the overall population on PT level - by SOC and PT - 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	1863	22	1.2	1863	29	1.6	0.3237	1.32 (0.76, 2.29)	1.32 (0.76, 2.31)	0.00 (0.00, 0.01)	

Risk ratios and odds ratios with confidence intervals (CIs) are estimated by Cochran-Mantel-Haenszel method. For risk differences standard Wald asymptotic confidence limits are calculated. A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied 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).
For AEs on SOC and/or PT level, subgroup analyses are only shown if overall test for treatment is significant on 5% level (i.e. 95% CI for the risk ratio does not contain 1; if this is not calculable the p-value of Chi-square test is used).
MedDRA version: 23.0. * Chi-square test for treatment effect ** Breslow-Day test for homogeneity of odds ratios (treatment by subgroup interaction).

Table R.1.4.5: 1 Proportion of patients with any adverse events occurring in at least 1% of the patients in either treatment arm in the overall population on PT level - by SOC and PT - 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	1863	28	1.5	1863	35	1.9	0.3738	1.25 (0.76, 2.05)	1.25 (0.76, 2.07)	0.00 (0.00, 0.01)	

Risk ratios and odds ratios with confidence intervals (CIs) are estimated by Cochran-Mantel-Haenszel method. For risk differences standard Wald asymptotic confidence limits are calculated. A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied 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).
For AEs on SOC and/or PT level, subgroup analyses are only shown if overall test for treatment is significant on 5% level (i.e. 95% CI for the risk ratio does not contain 1; if this is not calculable the p-value of Chi-square test is used).
MedDRA version: 23.0. * Chi-square test for treatment effect ** Breslow-Day test for homogeneity of odds ratios (treatment by subgroup interaction).

Table R.1.4.5: 1 Proportion of patients with any adverse events occurring in at least 1% of the patients in either treatment arm in the overall population on PT level - by SOC and PT - 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	1863	35	1.9	1863	22	1.2	0.0827	0.63 (0.37, 1.07)	0.62 (0.36, 1.07)	-0.01 (-0.01, 0.00)	

Risk ratios and odds ratios with confidence intervals (CIs) are estimated by Cochran-Mantel-Haenszel method. For risk differences standard Wald asymptotic confidence limits are calculated. A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied 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).
For AEs on SOC and/or PT level, subgroup analyses are only shown if overall test for treatment is significant on 5% level (i.e. 95% CI for the risk ratio does not contain 1; if this is not calculable the p-value of Chi-square test is used).
MedDRA version: 23.0. * Chi-square test for treatment effect ** Breslow-Day test for homogeneity of odds ratios (treatment by subgroup interaction).

Table R.1.4.5: 1 Proportion of patients with any adverse events occurring in at least 1% of the patients in either treatment arm in the overall population on PT level - by SOC and PT - 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	1863	30	1.6	1863	25	1.3	0.4970	0.83 (0.49, 1.41)	0.83 (0.49, 1.42)	0.00 (-0.01, 0.01)	

Risk ratios and odds ratios with confidence intervals (CIs) are estimated by Cochran-Mantel-Haenszel method. For risk differences standard Wald asymptotic confidence limits are calculated. A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied 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).
For AEs on SOC and/or PT level, subgroup analyses are only shown if overall test for treatment is significant on 5% level (i.e. 95% CI for the risk ratio does not contain 1; if this is not calculable the p-value of Chi-square test is used).
MedDRA version: 23.0. * Chi-square test for treatment effect ** Breslow-Day test for homogeneity of odds ratios (treatment by subgroup interaction).

Table R.1.4.5: 1 Proportion of patients with any adverse events occurring in at least 1% of the patients in either treatment arm in the overall population on PT level - by SOC and PT - 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	1863	27	1.4	1863	20	1.1	0.3042	0.74 (0.42, 1.32)	0.74 (0.41, 1.32)	0.00 (-0.01, 0.00)	

Risk ratios and odds ratios with confidence intervals (CIs) are estimated by Cochran-Mantel-Haenszel method. For risk differences standard Wald asymptotic confidence limits are calculated. A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied 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).
For AEs on SOC and/or PT level, subgroup analyses are only shown if overall test for treatment is significant on 5% level (i.e. 95% CI for the risk ratio does not contain 1; if this is not calculable the p-value of Chi-square test is used).
MedDRA version: 23.0. * Chi-square test for treatment effect ** Breslow-Day test for homogeneity of odds ratios (treatment by subgroup interaction).

Table R.1.4.5: 1 Proportion of patients with any adverse events occurring in at least 1% of the patients in either treatment arm in the overall population on PT level - by SOC and PT - 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	1863	43	2.3	1863	35	1.9	0.3600	0.81 (0.52, 1.27)	0.81 (0.52, 1.27)	0.00 (-0.01, 0.00)	

Risk ratios and odds ratios with confidence intervals (CIs) are estimated by Cochran-Mantel-Haenszel method. For risk differences standard Wald asymptotic confidence limits are calculated. A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied 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).
For AEs on SOC and/or PT level, subgroup analyses are only shown if overall test for treatment is significant on 5% level (i.e. 95% CI for the risk ratio does not contain 1; if this is not calculable the p-value of Chi-square test is used).
MedDRA version: 23.0. * Chi-square test for treatment effect ** Breslow-Day test for homogeneity of odds ratios (treatment by subgroup interaction).

Table R.1.4.5: 1 Proportion of patients with any adverse events occurring in at least 1% of the patients in either treatment arm in the overall population on PT level - by SOC and PT - 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	1863	21	1.1	1863	29	1.6	0.2547	1.38 (0.79, 2.41)	1.39 (0.79, 2.44)	0.00 (0.00, 0.01)	

Risk ratios and odds ratios with confidence intervals (CIs) are estimated by Cochran-Mantel-Haenszel method. For risk differences standard Wald asymptotic confidence limits are calculated. A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied 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).
For AEs on SOC and/or PT level, subgroup analyses are only shown if overall test for treatment is significant on 5% level (i.e. 95% CI for the risk ratio does not contain 1; if this is not calculable the p-value of Chi-square test is used).
MedDRA version: 23.0. * Chi-square test for treatment effect ** Breslow-Day test for homogeneity of odds ratios (treatment by subgroup interaction).

Table R.1.4.5: 1 Proportion of patients with any adverse events occurring in at least 1% of the patients in either treatment arm in the overall population on PT level - by SOC and PT - 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	1863	25	1.3	1863	26	1.4	0.8879	1.04 (0.60, 1.79)	1.04 (0.60, 1.81)	0.00 (-0.01, 0.01)	

Risk ratios and odds ratios with confidence intervals (CIs) are estimated by Cochran-Mantel-Haenszel method. For risk differences standard Wald asymptotic confidence limits are calculated. A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied 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).
For AEs on SOC and/or PT level, subgroup analyses are only shown if overall test for treatment is significant on 5% level (i.e. 95% CI for the risk ratio does not contain 1; if this is not calculable the p-value of Chi-square test is used).
MedDRA version: 23.0. * Chi-square test for treatment effect ** Breslow-Day test for homogeneity of odds ratios (treatment by subgroup interaction).

Table R.1.4.5: 1 Proportion of patients with any adverse events occurring in at least 1% of the patients in either treatment arm in the overall population on PT level - by SOC and PT - 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	1863	19	1.0	1863	19	1.0	1.0000	1.00 (0.53, 1.88)	1.00 (0.53, 1.89)	0.00 (-0.01, 0.01)	

Risk ratios and odds ratios with confidence intervals (CIs) are estimated by Cochran-Mantel-Haenszel method. For risk differences standard Wald asymptotic confidence limits are calculated. A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied 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).
For AEs on SOC and/or PT level, subgroup analyses are only shown if overall test for treatment is significant on 5% level (i.e. 95% CI for the risk ratio does not contain 1; if this is not calculable the p-value of Chi-square test is used).
MedDRA version: 23.0. * Chi-square test for treatment effect ** Breslow-Day test for homogeneity of odds ratios (treatment by subgroup interaction).

Table R.1.4.5: 1 Proportion of patients with any adverse events occurring in at least 1% of the patients in either treatment arm in the overall population on PT level - by SOC and PT - overall and by subgroup - TS
System organ class: Investigations
Preferred term: Glomerular filtration rate decreased

Subgroup	Placebo			Empa 10mg			Empa 10mg vs Placebo				
Category	N	n	%	N	n	%	p-value *	Risk ratio (95% CI)	Odds ratio (95% CI)	Risk diff. (95% CI)	p-value **
Overall	1863	19	1.0	1863	12	0.6	0.2068	0.63 (0.31, 1.30)	0.63 (0.30, 1.30)	0.00 (-0.01, 0.00)	

Risk ratios and odds ratios with confidence intervals (CIs) are estimated by Cochran-Mantel-Haenszel method. For risk differences standard Wald asymptotic confidence limits are calculated. A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied 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).
For AEs on SOC and/or PT level, subgroup analyses are only shown if overall test for treatment is significant on 5% level (i.e. 95% CI for the risk ratio does not contain 1; if this is not calculable the p-value of Chi-square test is used).
MedDRA version: 23.0. * Chi-square test for treatment effect ** Breslow-Day test for homogeneity of odds ratios (treatment by subgroup interaction).

Table R.1.4.5: 1 Proportion of patients with any adverse events occurring in at least 1% of the patients in either treatment arm in the overall population on PT level - by SOC and PT - 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	1863	27	1.4	1863	43	2.3	0.0535	1.59 (0.99, 2.57)	1.61 (0.99, 2.61)	0.01 (0.00, 0.02)	

Risk ratios and odds ratios with confidence intervals (CIs) are estimated by Cochran-Mantel-Haenszel method. For risk differences standard Wald asymptotic confidence limits are calculated. A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied 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).
For AEs on SOC and/or PT level, subgroup analyses are only shown if overall test for treatment is significant on 5% level (i.e. 95% CI for the risk ratio does not contain 1; if this is not calculable the p-value of Chi-square test is used).
MedDRA version: 23.0. * Chi-square test for treatment effect ** Breslow-Day test for homogeneity of odds ratios (treatment by subgroup interaction).

Table R.1.4.5: 1 Proportion of patients with any adverse events occurring in at least 1% of the patients in either treatment arm in the overall population on PT level - by SOC and PT - 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	1863	15	0.8	1863	22	1.2	0.2475	1.47 (0.76, 2.82)	1.47 (0.76, 2.85)	0.00 (0.00, 0.01)	

Risk ratios and odds ratios with confidence intervals (CIs) are estimated by Cochran-Mantel-Haenszel method. For risk differences standard Wald asymptotic confidence limits are calculated. A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied 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).
For AEs on SOC and/or PT level, subgroup analyses are only shown if overall test for treatment is significant on 5% level (i.e. 95% CI for the risk ratio does not contain 1; if this is not calculable the p-value of Chi-square test is used).
MedDRA version: 23.0. * Chi-square test for treatment effect ** Breslow-Day test for homogeneity of odds ratios (treatment by subgroup interaction).

Table R.1.4.5: 1 Proportion of patients with any adverse events occurring in at least 1% of the patients in either treatment arm in the overall population on PT level - by SOC and PT - 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	1863	28	1.5	1863	30	1.6	0.7913	1.07 (0.64, 1.79)	1.07 (0.64, 1.80)	0.00 (-0.01, 0.01)	

Risk ratios and odds ratios with confidence intervals (CIs) are estimated by Cochran-Mantel-Haenszel method. For risk differences standard Wald asymptotic confidence limits are calculated. A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied 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).
For AEs on SOC and/or PT level, subgroup analyses are only shown if overall test for treatment is significant on 5% level (i.e. 95% CI for the risk ratio does not contain 1; if this is not calculable the p-value of Chi-square test is used).
MedDRA version: 23.0. * Chi-square test for treatment effect ** Breslow-Day test for homogeneity of odds ratios (treatment by subgroup interaction).

Table R.1.4.5: 1 Proportion of patients with any adverse events occurring in at least 1% of the patients in either treatment arm in the overall population on PT level - by SOC and PT - 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	1863	62	3.3	1863	43	2.3	0.0600	0.69 (0.47, 1.02)	0.69 (0.46, 1.02)	-0.01 (-0.02, 0.00)	

Risk ratios and odds ratios with confidence intervals (CIs) are estimated by Cochran-Mantel-Haenszel method. For risk differences standard Wald asymptotic confidence limits are calculated. A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied 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).
For AEs on SOC and/or PT level, subgroup analyses are only shown if overall test for treatment is significant on 5% level (i.e. 95% CI for the risk ratio does not contain 1; if this is not calculable the p-value of Chi-square test is used).
MedDRA version: 23.0. * Chi-square test for treatment effect ** Breslow-Day test for homogeneity of odds ratios (treatment by subgroup interaction).

Table R.1.4.5: 1 Proportion of patients with any adverse events occurring in at least 1% of the patients in either treatment arm in the overall population on PT level - by SOC and PT - 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	1863	37	2.0	1863	28	1.5	0.2601	0.76 (0.47, 1.23)	0.75 (0.46, 1.24)	0.00 (-0.01, 0.00)	

Risk ratios and odds ratios with confidence intervals (CIs) are estimated by Cochran-Mantel-Haenszel method. For risk differences standard Wald asymptotic confidence limits are calculated. A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied 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).
For AEs on SOC and/or PT level, subgroup analyses are only shown if overall test for treatment is significant on 5% level (i.e. 95% CI for the risk ratio does not contain 1; if this is not calculable the p-value of Chi-square test is used).
MedDRA version: 23.0. * Chi-square test for treatment effect ** Breslow-Day test for homogeneity of odds ratios (treatment by subgroup interaction).

Table R.1.4.5: 1 Proportion of patients with any adverse events occurring in at least 1% of the patients in either treatment arm in the overall population on PT level - by SOC and PT - 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	1863	24	1.3	1863	19	1.0	0.4431	0.79 (0.44, 1.44)	0.79 (0.43, 1.45)	0.00 (-0.01, 0.00)	

Risk ratios and odds ratios with confidence intervals (CIs) are estimated by Cochran-Mantel-Haenszel method. For risk differences standard Wald asymptotic confidence limits are calculated. A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied 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).
For AEs on SOC and/or PT level, subgroup analyses are only shown if overall test for treatment is significant on 5% level (i.e. 95% CI for the risk ratio does not contain 1; if this is not calculable the p-value of Chi-square test is used).
MedDRA version: 23.0. * Chi-square test for treatment effect ** Breslow-Day test for homogeneity of odds ratios (treatment by subgroup interaction).

Table R.1.4.5: 1 Proportion of patients with any adverse events occurring in at least 1% of the patients in either treatment arm in the overall population on PT level - by SOC and PT - 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	1863	28	1.5	1863	17	0.9	0.0990	0.61 (0.33, 1.11)	0.60 (0.33, 1.11)	-0.01 (-0.01, 0.00)	

Risk ratios and odds ratios with confidence intervals (CIs) are estimated by Cochran-Mantel-Haenszel method. For risk differences standard Wald asymptotic confidence limits are calculated. A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied 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).
For AEs on SOC and/or PT level, subgroup analyses are only shown if overall test for treatment is significant on 5% level (i.e. 95% CI for the risk ratio does not contain 1; if this is not calculable the p-value of Chi-square test is used).
MedDRA version: 23.0. * Chi-square test for treatment effect ** Breslow-Day test for homogeneity of odds ratios (treatment by subgroup interaction).

Table R.1.4.5: 2 Proportion of patients with serious adverse events occurring in at least 1% of the patients in either treatment arm in the overall population on PT level - by SOC and PT - overall and by subgroup - TS
System organ class: Cardiac disorders
Preferred term: Cardiac failure

Subgroup Category	Placebo N	Placebo n	Placebo %	Empa 10mg N	Empa 10mg n	Empa 10mg %	Empa 10mg vs Placebo p-value *	Risk ratio (95% CI)	Odds ratio (95% CI)	Risk diff. (95% CI)	p-value **
Overall	1863	444	23.8	1863	332	17.8	<0.0001	0.75 (0.66, 0.85)	0.69 (0.59, 0.81)	-0.06 (-0.09,-0.03)	
Sex											0.8097
Male	1410	340	24.1	1426	255	17.9	<0.0001	0.74 (0.64, 0.86)	0.69 (0.57, 0.82)	-0.06 (-0.09,-0.03)	
Female	453	104	23.0	437	77	17.6	0.0479	0.77 (0.59, 1.00)	0.72 (0.52, 1.00)	-0.05 (-0.11, 0.00)	
Age [years]											0.2682
< 65	739	187	25.3	675	117	17.3	0.0003	0.68 (0.56, 0.84)	0.62 (0.48, 0.80)	-0.08 (-0.12,-0.04)	
>= 65	1124	257	22.9	1188	215	18.1	0.0045	0.79 (0.67, 0.93)	0.75 (0.61, 0.91)	-0.05 (-0.08,-0.01)	
Region											0.2545
North America	213	35	16.4	212	28	13.2	0.3496	0.80 (0.51, 1.27)	0.77 (0.45, 1.33)	-0.03 (-0.10, 0.04)	
Latin America	645	159	24.7	641	115	17.9	0.0033	0.73 (0.59, 0.90)	0.67 (0.51, 0.88)	-0.07 (-0.11,-0.02)	
Europe	674	162	24.0	676	138	20.4	0.1095	0.85 (0.70, 1.04)	0.81 (0.63, 1.05)	-0.04 (-0.08, 0.01)	
Asia	244	78	32.0	248	44	17.7	0.0003	0.56 (0.40, 0.77)	0.46 (0.30, 0.70)	-0.14 (-0.22,-0.07)	
Other	87	10	11.5	86	7	8.1	0.4586	0.71 (0.28, 1.77)	0.68 (0.25, 1.88)	-0.03 (-0.12, 0.05)	
OECD Member											0.3977
No	741	188	25.4	713	127	17.8	0.0005	0.70 (0.57, 0.86)	0.64 (0.49, 0.82)	-0.08 (-0.12,-0.03)	
Yes	1122	256	22.8	1150	205	17.8	0.0031	0.78 (0.66, 0.92)	0.73 (0.60, 0.90)	-0.05 (-0.08,-0.02)	
Baseline NYHA											0.0002
II	1399	302	21.6	1399	184	13.2	<0.0001	0.61 (0.52, 0.72)	0.55 (0.45, 0.67)	-0.08 (-0.11,-0.06)	
III/IV	464	142	30.6	464	148	31.9	0.6709	1.04 (0.86, 1.26)	1.06 (0.80, 1.40)	0.01 (-0.05, 0.07)	
Baseline Diabetes Status											0.3686
Diabetic	926	239	25.8	927	170	18.3	0.0001	0.71 (0.60, 0.85)	0.65 (0.52, 0.81)	-0.07 (-0.11,-0.04)	
Non-Diabetic	937	205	21.9	936	162	17.3	0.0127	0.79 (0.66, 0.95)	0.75 (0.59, 0.94)	-0.05 (-0.08,-0.01)	
Baseline BMI [kg/m²]											0.1856
<30	1299	313	24.1	1263	214	16.9	<0.0001	0.70 (0.60, 0.82)	0.64 (0.53, 0.78)	-0.07 (-0.10,-0.04)	
>=30	564	131	23.2	600	118	19.7	0.1388	0.85 (0.68, 1.06)	0.81 (0.61, 1.07)	-0.04 (-0.08, 0.01)	

Risk ratios and odds ratios with confidence intervals (CIs) are estimated by Cochran-Mantel-Haenszel method. For risk differences standard Wald asymptotic confidence limits are calculated. A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied 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).
For AEs on SOC and/or PT level, subgroup analyses are only shown if overall test for treatment is significant on 5% level (i.e. 95% CI for the risk ratio does not contain 1; if this is not calculable the p-value of Chi-square test is used).
MedDRA version: 23.0. * Chi-square test for treatment effect ** Breslow-Day test for homogeneity of odds ratios (treatment by subgroup interaction).

Table R.1.4.5: 2 Proportion of patients with serious adverse events occurring in at least 1% of the patients in either treatment arm in the overall population on PT level - by SOC and PT - overall and by subgroup - TS
System organ class: Cardiac disorders
Preferred term: Cardiac failure

Subgroup	Placebo			Empa 10mg			Empa 10mg vs Placebo				
Category	N	n	%	N	n	%	p-value *	Risk ratio (95% CI)	Odds ratio (95% CI)	Risk diff. (95% CI)	p-value **
Baseline eGFR (CKD-EPI) [mL/min/1.73m²]											0.0806
>=60	958	218	22.8	969	145	15.0	<0.0001	0.66 (0.54, 0.80)	0.60 (0.47, 0.75)	-0.08 (-0.11,-0.04)	
<60	904	226	25.0	893	187	20.9	0.0409	0.84 (0.71, 0.99)	0.79 (0.64, 0.99)	-0.04 (-0.08, 0.00)	
History of HHF (in the last 12 months)											0.0107
No	1290	294	22.8	1286	191	14.9	<0.0001	0.65 (0.55, 0.77)	0.59 (0.48, 0.72)	-0.08 (-0.11,-0.05)	
Yes	573	150	26.2	577	141	24.4	0.4971	0.93 (0.77, 1.14)	0.91 (0.70, 1.19)	-0.02 (-0.07, 0.03)	
Cause of Heart Failure											0.8568
Ischemic	944	226	23.9	983	174	17.7	0.0007	0.74 (0.62, 0.88)	0.68 (0.55, 0.85)	-0.06 (-0.10,-0.03)	
Non-ischemic	919	218	23.7	880	158	18.0	0.0026	0.76 (0.63, 0.91)	0.70 (0.56, 0.89)	-0.06 (-0.10,-0.02)	
Heart Failure Physiology											0.1264
LVEF <= 30% and NTproBNP < median	723	127	17.6	698	74	10.6	0.0002	0.60 (0.46, 0.79)	0.56 (0.41, 0.76)	-0.07 (-0.11,-0.03)	
LVEF <= 30% and NTproBNP >= median	660	218	33.0	631	159	25.2	0.0020	0.76 (0.64, 0.91)	0.68 (0.54, 0.87)	-0.08 (-0.13,-0.03)	
LVEF > 30%	473	98	20.7	526	98	18.6	0.4068	0.90 (0.70, 1.16)	0.88 (0.64, 1.20)	-0.02 (-0.07, 0.03)	
Baseline use of MRA											0.3638
No	512	122	23.8	557	90	16.2	0.0017	0.68 (0.53, 0.87)	0.62 (0.45, 0.83)	-0.08 (-0.12,-0.03)	
Yes	1351	322	23.8	1306	242	18.5	0.0008	0.78 (0.67, 0.90)	0.73 (0.60, 0.88)	-0.05 (-0.08,-0.02)	
Baseline use of ARNi											0.1157
No	1476	347	23.5	1523	281	18.5	0.0007	0.78 (0.68, 0.90)	0.74 (0.62, 0.88)	-0.05 (-0.08,-0.02)	
Yes	387	97	25.1	340	51	15.0	0.0008	0.60 (0.44, 0.81)	0.53 (0.36, 0.77)	-0.10 (-0.16,-0.04)	

Risk ratios and odds ratios with confidence intervals (CIs) are estimated by Cochran-Mantel-Haenszel method. For risk differences standard Wald asymptotic confidence limits are calculated. A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied 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).
For AEs on SOC and/or PT level, subgroup analyses are only shown if overall test for treatment is significant on 5% level (i.e. 95% CI for the risk ratio does not contain 1; if this is not calculable the p-value of Chi-square test is used).
MedDRA version: 23.0. * Chi-square test for treatment effect ** Breslow-Day test for homogeneity of odds ratios (treatment by subgroup interaction).

Table R.1.4.5: 2 Proportion of patients with serious adverse events occurring in at least 1% of the patients in either treatment arm in the overall population on PT level - by SOC and PT - 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													0.2394
<=30	1390	346	24.9	1337	234	17.5	<0.0001	0.70 (0.61,	0.82)	0.64 (0.53,	0.77)	-0.07 (-0.10,-0.04)	
>30 to <=35	359	71	19.8	398	70	17.6	0.4398	0.89 (0.66,	1.20)	0.87 (0.60,	1.25)	-0.02 (-0.08, 0.03)	
>35	114	27	23.7	128	28	21.9	0.7374	0.92 (0.58,	1.47)	0.90 (0.49,	1.65)	-0.02 (-0.12, 0.09)	
Baseline NTproBNP													0.1425
< median	919	163	17.7	942	107	11.4	<0.0001	0.64 (0.51,	0.80)	0.59 (0.46,	0.77)	-0.06 (-0.10,-0.03)	
>= median	943	281	29.8	920	225	24.5	0.0095	0.82 (0.71,	0.95)	0.76 (0.62,	0.94)	-0.05 (-0.09,-0.01)	

Risk ratios and odds ratios with confidence intervals (CIs) are estimated by Cochran-Mantel-Haenszel method. For risk differences standard Wald asymptotic confidence limits are calculated. A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied 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).
For AEs on SOC and/or PT level, subgroup analyses are only shown if overall test for treatment is significant on 5% level (i.e. 95% CI for the risk ratio does not contain 1; if this is not calculable the p-value of Chi-square test is used).
MedDRA version: 23.0. * Chi-square test for treatment effect ** Breslow-Day test for homogeneity of odds ratios (treatment by subgroup interaction).

Table R.1.4.5: 2 Proportion of patients with serious adverse events occurring in at least 1% of the patients in either treatment arm in the overall population on PT level - by SOC and PT - overall and by subgroup - TS
System organ class: Cardiac disorders
Preferred term: Ventricular tachycardia

Subgroup	Placebo			Empa 10mg			Empa 10mg vs Placebo				
Category	N	n	%	N	n	%	p-value *	Risk ratio (95% CI)	Odds ratio (95% CI)	Risk diff. (95% CI)	p-value **
Overall	1863	37	2.0	1863	55	3.0	0.0574	1.49 (0.98, 2.24)	1.50 (0.98, 2.29)	0.01 (0.00, 0.02)	

Risk ratios and odds ratios with confidence intervals (CIs) are estimated by Cochran-Mantel-Haenszel method. For risk differences standard Wald asymptotic confidence limits are calculated. A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied 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).
For AEs on SOC and/or PT level, subgroup analyses are only shown if overall test for treatment is significant on 5% level (i.e. 95% CI for the risk ratio does not contain 1; if this is not calculable the p-value of Chi-square test is used).
MedDRA version: 23.0. * Chi-square test for treatment effect ** Breslow-Day test for homogeneity of odds ratios (treatment by subgroup interaction).

Table R.1.4.5: 2 Proportion of patients with serious adverse events occurring in at least 1% of the patients in either treatment arm in the overall population on PT level - by SOC and PT - 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	1863	44	2.4	1863	24	1.3	0.0144	0.55	(0.33, 0.89)	0.54	(0.33, 0.89)	-0.01	(-0.02, 0.00)	
Sex														0.4704
Male	1410	33	2.3	1426	20	1.4	0.0652	0.60	(0.35, 1.04)	0.59	(0.34, 1.04)	-0.01	(-0.02, 0.00)	
Female	453	11	2.4	437	4	0.9	0.0796	0.38	(0.12, 1.17)	0.37	(0.12, 1.17)	-0.02	(-0.03, 0.00)	
Age [years]														0.1923
< 65	739	13	1.8	675	10	1.5	0.6801	0.84	(0.37, 1.91)	0.84	(0.37, 1.93)	0.00	(-0.02, 0.01)	
>= 65	1124	31	2.8	1188	14	1.2	0.0060	0.43	(0.23, 0.80)	0.42	(0.22, 0.79)	-0.02	(-0.03, 0.00)	
Region														0.9899
North America	213	13	6.1	212	7	3.3	0.1727	0.54	(0.22, 1.33)	0.53	(0.21, 1.34)	-0.03	(-0.07, 0.01)	
Latin America	645	7	1.1	641	3	0.5	0.2077	0.43	(0.11, 1.66)	0.43	(0.11, 1.66)	-0.01	(-0.02, 0.00)	
Europe	674	18	2.7	676	10	1.5	0.1246	0.55	(0.26, 1.19)	0.55	(0.25, 1.19)	-0.01	(-0.03, 0.00)	
Asia	244	6	2.5	248	4	1.6	0.5061	0.66	(0.19, 2.30)	0.65	(0.18, 2.33)	-0.01	(-0.03, 0.02)	
Other	87	0	0	86	0	0	0.9954	1.01	(0.02, 50.41)	1.01	(0.02, 51.56)	0.00	(-0.02, 0.02)	
OECD Member														0.7800
No	741	7	0.9	713	3	0.4	0.2269	0.45	(0.12, 1.72)	0.44	(0.11, 1.72)	-0.01	(-0.01, 0.00)	
Yes	1122	37	3.3	1150	21	1.8	0.0262	0.55	(0.33, 0.94)	0.55	(0.32, 0.94)	-0.01	(-0.03, 0.00)	
Baseline NYHA														0.0262
II	1399	39	2.8	1399	16	1.1	0.0017	0.41	(0.23, 0.73)	0.40	(0.22, 0.73)	-0.02	(-0.03,-0.01)	
III/IV	464	5	1.1	464	8	1.7	0.4021	1.60	(0.53, 4.85)	1.61	(0.52, 4.96)	0.01	(-0.01, 0.02)	
Baseline Diabetes Status														0.9764
Diabetic	926	20	2.2	927	11	1.2	0.1024	0.55	(0.26, 1.14)	0.54	(0.26, 1.14)	-0.01	(-0.02, 0.00)	
Non-Diabetic	937	24	2.6	936	13	1.4	0.0683	0.54	(0.28, 1.06)	0.54	(0.27, 1.06)	-0.01	(-0.02, 0.00)	
Baseline BMI [kg/m²]														0.4766
<30	1299	21	1.6	1263	13	1.0	0.1940	0.64	(0.32, 1.27)	0.63	(0.32, 1.27)	-0.01	(-0.01, 0.00)	
>=30	564	23	4.1	600	11	1.8	0.0230	0.45	(0.22, 0.91)	0.44	(0.21, 0.91)	-0.02	(-0.04, 0.00)	

Risk ratios and odds ratios with confidence intervals (CIs) are estimated by Cochran-Mantel-Haenszel method. For risk differences standard Wald asymptotic confidence limits are calculated. A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied 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).
For AEs on SOC and/or PT level, subgroup analyses are only shown if overall test for treatment is significant on 5% level (i.e. 95% CI for the risk ratio does not contain 1; if this is not calculable the p-value of Chi-square test is used).
MedDRA version: 23.0. * Chi-square test for treatment effect ** Breslow-Day test for homogeneity of odds ratios (treatment by subgroup interaction).

Table R.1.4.5: 2 Proportion of patients with serious adverse events occurring in at least 1% of the patients in either treatment arm in the overall population on PT level - by SOC and PT - overall and by subgroup - TS
System organ class: Cardiac disorders
Preferred term: Atrial fibrillation

Subgroup	Placebo			Empa 10mg			Empa 10mg vs Placebo					
Category	N	n	%	N	n	%	p-value *	Risk ratio (95% CI)		Odds ratio (95% CI)		Risk diff. (95% CI)	p-value **
Baseline eGFR (CKD-EPI) [mL/min/1.73m²]													0.6818
>=60	958	24	2.5	969	12	1.2	0.0400	0.49 (0.25,	0.98)	0.49 (0.24,	0.98)	-0.01 (-0.02, 0.00)	
<60	904	20	2.2	893	12	1.3	0.1639	0.61 (0.30,	1.24)	0.60 (0.29,	1.24)	-0.01 (-0.02, 0.00)	
History of HHF (in the last 12 months)													0.1243
No	1290	32	2.5	1286	13	1.0	0.0044	0.41 (0.21,	0.77)	0.40 (0.21,	0.77)	-0.01 (-0.02, 0.00)	
Yes	573	12	2.1	577	11	1.9	0.8200	0.91 (0.40,	2.05)	0.91 (0.40,	2.08)	0.00 (-0.02, 0.01)	
Cause of Heart Failure													0.8686
Ischemic	944	22	2.3	983	12	1.2	0.0643	0.52 (0.26,	1.05)	0.52 (0.25,	1.05)	-0.01 (-0.02, 0.00)	
Non-ischemic	919	22	2.4	880	12	1.4	0.1087	0.57 (0.28,	1.14)	0.56 (0.28,	1.15)	-0.01 (-0.02, 0.00)	
Heart Failure Physiology													0.5876
LVEF <= 30% and NTproBNP < median	723	19	2.6	698	7	1.0	0.0223	0.38 (0.16,	0.90)	0.38 (0.16,	0.90)	-0.02 (-0.03, 0.00)	
LVEF <= 30% and NTproBNP >= median	660	12	1.8	631	8	1.3	0.4235	0.70 (0.29,	1.69)	0.69 (0.28,	1.71)	-0.01 (-0.02, 0.01)	
LVEF > 30%	473	13	2.7	526	9	1.7	0.2646	0.62 (0.27,	1.44)	0.62 (0.26,	1.45)	-0.01 (-0.03, 0.01)	
Baseline use of MRA													0.8870
No	512	16	3.1	557	9	1.6	0.1029	0.52 (0.23,	1.16)	0.51 (0.22,	1.16)	-0.02 (-0.03, 0.00)	
Yes	1351	28	2.1	1306	15	1.1	0.0592	0.55 (0.30,	1.03)	0.55 (0.29,	1.03)	-0.01 (-0.02, 0.00)	
Baseline use of ARNi													0.7004
No	1476	36	2.4	1523	21	1.4	0.0335	0.57 (0.33,	0.96)	0.56 (0.32,	0.96)	-0.01 (-0.02, 0.00)	
Yes	387	8	2.1	340	3	0.9	0.1916	0.43 (0.11,	1.60)	0.42 (0.11,	1.60)	-0.01 (-0.03, 0.01)	

Risk ratios and odds ratios with confidence intervals (CIs) are estimated by Cochran-Mantel-Haenszel method. For risk differences standard Wald asymptotic confidence limits are calculated. A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied 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).
For AEs on SOC and/or PT level, subgroup analyses are only shown if overall test for treatment is significant on 5% level (i.e. 95% CI for the risk ratio does not contain 1; if this is not calculable the p-value of Chi-square test is used).
MedDRA version: 23.0. * Chi-square test for treatment effect ** Breslow-Day test for homogeneity of odds ratios (treatment by subgroup interaction).

Table R.1.4.5: 2 Proportion of patients with serious adverse events occurring in at least 1% of the patients in either treatment arm in the overall population on PT level - by SOC and PT - overall and by subgroup - TS
System organ class: Cardiac disorders
Preferred term: Atrial fibrillation

Subgroup	Placebo			Empa 10mg			Empa 10mg vs Placebo				
Category	N	n	%	N	n	%	p-value *	Risk ratio (95% CI)	Odds ratio (95% CI)	Risk diff. (95% CI)	p-value **
Baseline LVEF											0.2465
<=30	1390	31	2.2	1337	15	1.1	0.0247	0.50 (0.27, 0.93)	0.50 (0.27, 0.93)	-0.01 (-0.02, 0.00)	
>30 to <=35	359	13	3.6	398	7	1.8	0.1106	0.49 (0.20, 1.20)	0.48 (0.19, 1.21)	-0.02 (-0.04, 0.00)	
>35	114	0	0	128	2	1.6	0.2875	4.46 (0.22, 91.88)	4.53 (0.22, 95.26)	0.02 (-0.01, 0.04)	
Baseline NTproBNP											0.4281
< median	919	24	2.6	942	11	1.2	0.0219	0.45 (0.22, 0.91)	0.44 (0.21, 0.90)	-0.01 (-0.03, 0.00)	
>= median	943	20	2.1	920	13	1.4	0.2469	0.67 (0.33, 1.33)	0.66 (0.33, 1.34)	-0.01 (-0.02, 0.00)	

Risk ratios and odds ratios with confidence intervals (CIs) are estimated by Cochran-Mantel-Haenszel method. For risk differences standard Wald asymptotic confidence limits are calculated. A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied 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).
For AEs on SOC and/or PT level, subgroup analyses are only shown if overall test for treatment is significant on 5% level (i.e. 95% CI for the risk ratio does not contain 1; if this is not calculable the p-value of Chi-square test is used).
MedDRA version: 23.0. * Chi-square test for treatment effect ** Breslow-Day test for homogeneity of odds ratios (treatment by subgroup interaction).

Table R.1.4.5: 2 Proportion of patients with serious adverse events occurring in at least 1% of the patients in either treatment arm in the overall population on PT level - by SOC and PT - 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	1863	41	2.2	1863	26	1.4	0.0644	0.63 (0.39, 1.03)	0.63 (0.38, 1.03)	-0.01 (-0.02, 0.00)	

Risk ratios and odds ratios with confidence intervals (CIs) are estimated by Cochran-Mantel-Haenszel method. For risk differences standard Wald asymptotic confidence limits are calculated. A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied 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).
For AEs on SOC and/or PT level, subgroup analyses are only shown if overall test for treatment is significant on 5% level (i.e. 95% CI for the risk ratio does not contain 1; if this is not calculable the p-value of Chi-square test is used).
MedDRA version: 23.0. * Chi-square test for treatment effect ** Breslow-Day test for homogeneity of odds ratios (treatment by subgroup interaction).

Table R.1.4.5: 2 Proportion of patients with serious adverse events occurring in at least 1% of the patients in either treatment arm in the overall population on PT level - by SOC and PT - 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	1863	32	1.7	1863	18	1.0	0.0462	0.56	(0.32, 1.00)	0.56	(0.31, 1.00)	-0.01 (-0.01, 0.00)	
Sex													0.2613
Male	1410	24	1.7	1426	16	1.1	0.1902	0.66	(0.35, 1.24)	0.66	(0.35, 1.24)	-0.01 (-0.01, 0.00)	
Female	453	8	1.8	437	2	0.5	0.0641	0.26	(0.06, 1.21)	0.26	(0.05, 1.21)	-0.01 (-0.03, 0.00)	
Age [years]													0.4958
< 65	739	11	1.5	675	4	0.6	0.1005	0.40	(0.13, 1.24)	0.39	(0.13, 1.24)	-0.01 (-0.02, 0.00)	
>= 65	1124	21	1.9	1188	14	1.2	0.1745	0.63	(0.32, 1.23)	0.63	(0.32, 1.24)	-0.01 (-0.02, 0.00)	
Region													0.7881
North America	213	1	0.5	212	1	0.5	0.9973	1.00	(0.06, 15.96)	1.00	(0.06, 16.17)	0.00 (-0.01, 0.01)	
Latin America	645	0	0	641	0	0	0.9975	1.01	(0.02, 50.63)	1.01	(0.02, 50.79)	0.00 (0.00, 0.00)	
Europe	674	11	1.6	676	9	1.3	0.6475	0.82	(0.34, 1.96)	0.81	(0.33, 1.98)	0.00 (-0.02, 0.01)	
Asia	244	19	7.8	248	8	3.2	0.0263	0.41	(0.18, 0.93)	0.39	(0.17, 0.92)	-0.05 (-0.09,-0.01)	
Other	87	1	1.1	86	0	0	0.4820	0.34	(0.01, 8.16)	0.33	(0.01, 8.30)	-0.01 (-0.04, 0.02)	
OECD Member													0.0635
No	741	7	0.9	713	0	0	0.0152	0.07	(<0.01, 1.21)	0.07	(<0.01, 1.20)	-0.01 (-0.02, 0.00)	
Yes	1122	25	2.2	1150	18	1.6	0.2463	0.70	(0.39, 1.28)	0.70	(0.38, 1.29)	-0.01 (-0.02, 0.00)	
Baseline NYHA													0.8823
II	1399	22	1.6	1399	12	0.9	0.0844	0.55	(0.27, 1.10)	0.54	(0.27, 1.10)	-0.01 (-0.02, 0.00)	
III/IV	464	10	2.2	464	6	1.3	0.3131	0.60	(0.22, 1.64)	0.59	(0.21, 1.65)	-0.01 (-0.03, 0.01)	
Baseline Diabetes Status													0.0518
Diabetic	926	14	1.5	927	13	1.4	0.8441	0.93	(0.44, 1.96)	0.93	(0.43, 1.98)	0.00 (-0.01, 0.01)	
Non-Diabetic	937	18	1.9	936	5	0.5	0.0064	0.28	(0.10, 0.75)	0.27	(0.10, 0.74)	-0.01 (-0.02, 0.00)	
Baseline BMI [kg/m²]													0.1536
<30	1299	26	2.0	1263	11	0.9	0.0165	0.44	(0.22, 0.88)	0.43	(0.21, 0.87)	-0.01 (-0.02, 0.00)	
>=30	564	6	1.1	600	7	1.2	0.8675	1.10	(0.37, 3.24)	1.10	(0.37, 3.29)	0.00 (-0.01, 0.01)	

Risk ratios and odds ratios with confidence intervals (CIs) are estimated by Cochran-Mantel-Haenszel method. For risk differences standard Wald asymptotic confidence limits are calculated. A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied 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).
For AEs on SOC and/or PT level, subgroup analyses are only shown if overall test for treatment is significant on 5% level (i.e. 95% CI for the risk ratio does not contain 1; if this is not calculable the p-value of Chi-square test is used).
MedDRA version: 23.0. * Chi-square test for treatment effect ** Breslow-Day test for homogeneity of odds ratios (treatment by subgroup interaction).

Table R.1.4.5: 2 Proportion of patients with serious adverse events occurring in at least 1% of the patients in either treatment arm in the overall population on PT level - by SOC and PT - 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 **
Baseline eGFR (CKD-EPI) [mL/min/1.73m²]													0.0053
>=60	958	20	2.1	969	4	0.4	0.0009	0.20 (0.07,	0.58)	0.19 (0.07,	0.57)	-0.02 (-0.03,-0.01)	
<60	904	12	1.3	893	14	1.6	0.6697	1.18 (0.55,	2.54)	1.18 (0.54,	2.57)	0.00 (-0.01, 0.01)	
History of HHF (in the last 12 months)													0.4019
No	1290	14	1.1	1286	10	0.8	0.4164	0.72 (0.32,	1.61)	0.71 (0.32,	1.61)	0.00 (-0.01, 0.00)	
Yes	573	18	3.1	577	8	1.4	0.0453	0.44 (0.19,	1.01)	0.43 (0.19,	1.01)	-0.02 (-0.03, 0.00)	
Cause of Heart Failure													0.1625
Ischemic	944	16	1.7	983	13	1.3	0.5020	0.78 (0.38,	1.61)	0.78 (0.37,	1.62)	0.00 (-0.01, 0.01)	
Non-ischemic	919	16	1.7	880	5	0.6	0.0206	0.33 (0.12,	0.89)	0.32 (0.12,	0.88)	-0.01 (-0.02, 0.00)	
Heart Failure Physiology													0.5685
LVEF <= 30% and NTproBNP < median	723	7	1.0	698	4	0.6	0.3955	0.59 (0.17,	2.01)	0.59 (0.17,	2.02)	0.00 (-0.01, 0.01)	
LVEF <= 30% and NTproBNP >= median	660	16	2.4	631	6	1.0	0.0409	0.39 (0.15,	1.00)	0.39 (0.15,	0.99)	-0.01 (-0.03, 0.00)	
LVEF > 30%	473	9	1.9	526	8	1.5	0.6413	0.80 (0.31,	2.05)	0.80 (0.30,	2.08)	0.00 (-0.02, 0.01)	
Baseline use of MRA													0.7875
No	512	11	2.1	557	6	1.1	0.1619	0.50 (0.19,	1.35)	0.50 (0.18,	1.35)	-0.01 (-0.03, 0.00)	
Yes	1351	21	1.6	1306	12	0.9	0.1392	0.59 (0.29,	1.20)	0.59 (0.29,	1.20)	-0.01 (-0.01, 0.00)	
Baseline use of ARNi													0.5249
No	1476	28	1.9	1523	17	1.1	0.0787	0.59 (0.32,	1.07)	0.58 (0.32,	1.07)	-0.01 (-0.02, 0.00)	
Yes	387	4	1.0	340	1	0.3	0.2287	0.28 (0.03,	2.53)	0.28 (0.03,	2.54)	-0.01 (-0.02, 0.00)	

Risk ratios and odds ratios with confidence intervals (CIs) are estimated by Cochran-Mantel-Haenszel method. For risk differences standard Wald asymptotic confidence limits are calculated. A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied 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).
For AEs on SOC and/or PT level, subgroup analyses are only shown if overall test for treatment is significant on 5% level (i.e. 95% CI for the risk ratio does not contain 1; if this is not calculable the p-value of Chi-square test is used).
MedDRA version: 23.0. * Chi-square test for treatment effect ** Breslow-Day test for homogeneity of odds ratios (treatment by subgroup interaction).

Table R.1.4.5: 2 Proportion of patients with serious adverse events occurring in at least 1% of the patients in either treatment arm in the overall population on PT level - by SOC and PT - 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 **
Baseline LVEF													0.4395
<=30	1390	23	1.7	1337	10	0.7	0.0304	0.45 (0.22,	0.95)	0.45 (0.21,	0.94)	-0.01 (-0.02, 0.00)	
>30 to <=35	359	5	1.4	398	6	1.5	0.8952	1.08 (0.33,	3.52)	1.08 (0.33,	3.58)	0.00 (-0.02, 0.02)	
>35	114	4	3.5	128	2	1.6	0.3311	0.45 (0.08,	2.39)	0.44 (0.08,	2.43)	-0.02 (-0.06, 0.02)	
Baseline NTproBNP													0.5715
< median	919	8	0.9	942	6	0.6	0.5599	0.73 (0.25,	2.10)	0.73 (0.25,	2.11)	0.00 (-0.01, 0.01)	
>= median	943	24	2.5	920	12	1.3	0.0518	0.51 (0.26,	1.02)	0.51 (0.25,	1.02)	-0.01 (-0.02, 0.00)	

Risk ratios and odds ratios with confidence intervals (CIs) are estimated by Cochran-Mantel-Haenszel method. For risk differences standard Wald asymptotic confidence limits are calculated. A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied 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).
For AEs on SOC and/or PT level, subgroup analyses are only shown if overall test for treatment is significant on 5% level
(i.e. 95% CI for the risk ratio does not contain 1; if this is not calculable the p-value of Chi-square test is used).
MedDRA version: 23.0. * Chi-square test for treatment effect ** Breslow-Day test for homogeneity of odds ratios (treatment by subgroup interaction).

Table R.1.4.5: 2 Proportion of patients with serious adverse events occurring in at least 1% of the patients in either treatment arm in the overall population on PT level - by SOC and PT - overall and by subgroup - TS
System organ class: Cardiac disorders
Preferred term: Cardiac failure acute

Subgroup	Placebo			Empa 10mg			Empa 10mg vs Placebo				
Category	N	n	%	N	n	%	p-value *	Risk ratio (95% CI)	Odds ratio (95% CI)	Risk diff. (95% CI)	p-value **
Overall	1863	29	1.6	1863	19	1.0	0.1463	0.66 (0.37, 1.16)	0.65 (0.36, 1.17)	-0.01 (-0.01, 0.00)	

Risk ratios and odds ratios with confidence intervals (CIs) are estimated by Cochran-Mantel-Haenszel method. For risk differences standard Wald asymptotic confidence limits are calculated. A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied 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).
For AEs on SOC and/or PT level, subgroup analyses are only shown if overall test for treatment is significant on 5% level (i.e. 95% CI for the risk ratio does not contain 1; if this is not calculable the p-value of Chi-square test is used).
MedDRA version: 23.0. * Chi-square test for treatment effect ** Breslow-Day test for homogeneity of odds ratios (treatment by subgroup interaction).

Table R.1.4.5: 2 Proportion of patients with serious adverse events occurring in at least 1% of the patients in either treatment arm in the overall population on PT level - by SOC and PT - 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	1863	18	1.0	1863	24	1.3	0.3518	1.33 (0.73, 2.45)	1.34 (0.72, 2.47)	0.00 (0.00, 0.01)	

Risk ratios and odds ratios with confidence intervals (CIs) are estimated by Cochran-Mantel-Haenszel method. For risk differences standard Wald asymptotic confidence limits are calculated. A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied 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).
For AEs on SOC and/or PT level, subgroup analyses are only shown if overall test for treatment is significant on 5% level (i.e. 95% CI for the risk ratio does not contain 1; if this is not calculable the p-value of Chi-square test is used).
MedDRA version: 23.0. * Chi-square test for treatment effect ** Breslow-Day test for homogeneity of odds ratios (treatment by subgroup interaction).

Table R.1.4.5: 2 Proportion of patients with serious adverse events occurring in at least 1% of the patients in either treatment arm in the overall population on PT level - by SOC and PT - 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	1863	62	3.3	1863	53	2.8	0.3939	0.85 (0.60, 1.23)	0.85 (0.59, 1.23)	0.00 (-0.02, 0.01)	

Risk ratios and odds ratios with confidence intervals (CIs) are estimated by Cochran-Mantel-Haenszel method. For risk differences standard Wald asymptotic confidence limits are calculated. A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied 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).
For AEs on SOC and/or PT level, subgroup analyses are only shown if overall test for treatment is significant on 5% level (i.e. 95% CI for the risk ratio does not contain 1; if this is not calculable the p-value of Chi-square test is used).
MedDRA version: 23.0. * Chi-square test for treatment effect ** Breslow-Day test for homogeneity of odds ratios (treatment by subgroup interaction).

Table R.1.4.5: 2 Proportion of patients with serious adverse events occurring in at least 1% of the patients in either treatment arm in the overall population on PT level - by SOC and PT - overall and by subgroup - TS
System organ class: Renal and urinary disorders
Preferred term: Acute kidney injury

Subgroup Category	Placebo N	Placebo n	Placebo %	Empa 10mg N	Empa 10mg n	Empa 10mg %	Empa 10mg vs Placebo p-value *	Risk ratio (95% CI)	Odds ratio (95% CI)	Risk diff. (95% CI)	p-value **
Overall	1863	55	3.0	1863	35	1.9	0.0328	0.64 (0.42, 0.97)	0.63 (0.41, 0.97)	-0.01 (-0.02, 0.00)	
Sex											0.4602
Male	1410	44	3.1	1426	26	1.8	0.0260	0.58 (0.36, 0.94)	0.58 (0.35, 0.94)	-0.01 (-0.02, 0.00)	
Female	453	11	2.4	437	9	2.1	0.7106	0.85 (0.35, 2.03)	0.84 (0.35, 2.06)	0.00 (-0.02, 0.02)	
Age [years]											0.4347
< 65	739	21	2.8	675	15	2.2	0.4601	0.78 (0.41, 1.50)	0.78 (0.40, 1.52)	-0.01 (-0.02, 0.01)	
>= 65	1124	34	3.0	1188	20	1.7	0.0328	0.56 (0.32, 0.96)	0.55 (0.31, 0.96)	-0.01 (-0.03, 0.00)	
Region											0.9534
North America	213	18	8.5	212	14	6.6	0.4706	0.78 (0.40, 1.53)	0.77 (0.37, 1.58)	-0.02 (-0.07, 0.03)	
Latin America	645	19	2.9	641	11	1.7	0.1441	0.58 (0.28, 1.21)	0.58 (0.27, 1.22)	-0.01 (-0.03, 0.00)	
Europe	674	16	2.4	676	9	1.3	0.1554	0.56 (0.25, 1.26)	0.55 (0.24, 1.26)	-0.01 (-0.02, 0.00)	
Asia	244	1	0.4	248	1	0.4	0.9908	0.98 (0.06, 15.64)	0.98 (0.06, 15.82)	0.00 (-0.01, 0.01)	
Other	87	1	1.1	86	0	0	0.4820	0.34 (0.01, 8.16)	0.33 (0.01, 8.30)	-0.01 (-0.04, 0.02)	
OECD Member											0.9246
No	741	17	2.3	713	10	1.4	0.2080	0.61 (0.28, 1.33)	0.61 (0.28, 1.33)	-0.01 (-0.02, 0.00)	
Yes	1122	38	3.4	1150	25	2.2	0.0783	0.64 (0.39, 1.06)	0.63 (0.38, 1.06)	-0.01 (-0.03, 0.00)	
Baseline NYHA											0.2110
II	1399	34	2.4	1399	26	1.9	0.2965	0.76 (0.46, 1.27)	0.76 (0.45, 1.27)	-0.01 (-0.02, 0.01)	
III/IV	464	21	4.5	464	9	1.9	0.0259	0.43 (0.20, 0.93)	0.42 (0.19, 0.92)	-0.03 (-0.05, 0.00)	
Baseline Diabetes Status											0.8310
Diabetic	926	27	2.9	927	18	1.9	0.1732	0.67 (0.37, 1.20)	0.66 (0.36, 1.21)	-0.01 (-0.02, 0.00)	
Non-Diabetic	937	28	3.0	936	17	1.8	0.0977	0.61 (0.33, 1.10)	0.60 (0.33, 1.10)	-0.01 (-0.03, 0.00)	
Baseline BMI [kg/m²]											0.9677
<30	1299	34	2.6	1263	21	1.7	0.0955	0.64 (0.37, 1.09)	0.63 (0.36, 1.09)	-0.01 (-0.02, 0.00)	
>=30	564	21	3.7	600	14	2.3	0.1652	0.63 (0.32, 1.22)	0.62 (0.31, 1.23)	-0.01 (-0.03, 0.01)	

Risk ratios and odds ratios with confidence intervals (CIs) are estimated by Cochran-Mantel-Haenszel method. For risk differences standard Wald asymptotic confidence limits are calculated. A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied 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).
For AEs on SOC and/or PT level, subgroup analyses are only shown if overall test for treatment is significant on 5% level (i.e. 95% CI for the risk ratio does not contain 1; if this is not calculable the p-value of Chi-square test is used).
MedDRA version: 23.0. * Chi-square test for treatment effect ** Breslow-Day test for homogeneity of odds ratios (treatment by subgroup interaction).

Table R.1.4.5: 2 Proportion of patients with serious adverse events occurring in at least 1% of the patients in either treatment arm in the overall population on PT level - by SOC and PT - overall and by subgroup - TS
System organ class: Renal and urinary disorders
Preferred term: Acute kidney injury

Subgroup	Placebo			Empa 10mg			Empa 10mg vs Placebo					
Category	N	n	%	N	n	%	p-value *	Risk ratio (95% CI)		Odds ratio (95% CI)		Risk diff. (95% CI)	p-value **
Baseline eGFR (CKD-EPI) [mL/min/1.73m²]													0.7527
>=60	958	22	2.3	969	13	1.3	0.1166	0.58 (0.30,	1.15)	0.58 (0.29,	1.16)	-0.01 (-0.02, 0.00)	
<60	904	33	3.7	893	22	2.5	0.1442	0.67 (0.40,	1.15)	0.67 (0.39,	1.15)	-0.01 (-0.03, 0.00)	
History of HHF (in the last 12 months)													0.6830
No	1290	37	2.9	1286	22	1.7	0.0496	0.60 (0.35,	1.01)	0.59 (0.35,	1.00)	-0.01 (-0.02, 0.00)	
Yes	573	18	3.1	577	13	2.3	0.3524	0.72 (0.35,	1.45)	0.71 (0.34,	1.46)	-0.01 (-0.03, 0.01)	
Cause of Heart Failure													0.6984
Ischemic	944	28	3.0	983	20	2.0	0.1896	0.69 (0.39,	1.21)	0.68 (0.38,	1.21)	-0.01 (-0.02, 0.00)	
Non-ischemic	919	27	2.9	880	15	1.7	0.0833	0.58 (0.31,	1.08)	0.57 (0.30,	1.08)	-0.01 (-0.03, 0.00)	
Heart Failure Physiology													0.7884
LVEF <= 30% and NTproBNP < median	723	13	1.8	698	10	1.4	0.5853	0.80 (0.35,	1.81)	0.79 (0.35,	1.82)	0.00 (-0.02, 0.01)	
LVEF <= 30% and NTproBNP >= median	660	28	4.2	631	15	2.4	0.0619	0.56 (0.30,	1.04)	0.55 (0.29,	1.04)	-0.02 (-0.04, 0.00)	
LVEF > 30%	473	14	3.0	526	10	1.9	0.2752	0.64 (0.29,	1.43)	0.64 (0.28,	1.44)	-0.01 (-0.03, 0.01)	
Baseline use of MRA													0.7261
No	512	17	3.3	557	13	2.3	0.3293	0.70 (0.34,	1.43)	0.70 (0.33,	1.45)	-0.01 (-0.03, 0.01)	
Yes	1351	38	2.8	1306	22	1.7	0.0504	0.60 (0.36,	1.01)	0.59 (0.35,	1.01)	-0.01 (-0.02, 0.00)	
Baseline use of ARNi													0.9283
No	1476	38	2.6	1523	25	1.6	0.0749	0.64 (0.39,	1.05)	0.63 (0.38,	1.05)	-0.01 (-0.02, 0.00)	
Yes	387	17	4.4	340	10	2.9	0.3017	0.67 (0.31,	1.44)	0.66 (0.30,	1.46)	-0.01 (-0.04, 0.01)	

Risk ratios and odds ratios with confidence intervals (CIs) are estimated by Cochran-Mantel-Haenszel method. For risk differences standard Wald asymptotic confidence limits are calculated. A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied 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).
For AEs on SOC and/or PT level, subgroup analyses are only shown if overall test for treatment is significant on 5% level (i.e. 95% CI for the risk ratio does not contain 1; if this is not calculable the p-value of Chi-square test is used).
MedDRA version: 23.0. * Chi-square test for treatment effect ** Breslow-Day test for homogeneity of odds ratios (treatment by subgroup interaction).

Table R.1.4.5: 2 Proportion of patients with serious adverse events occurring in at least 1% of the patients in either treatment arm in the overall population on PT level - by SOC and PT - overall and by subgroup - TS
System organ class: Renal and urinary disorders
Preferred term: Acute kidney injury

Subgroup	Placebo			Empa 10mg			Empa 10mg vs Placebo					
Category	N	n	%	N	n	%	p-value *	Risk ratio (95% CI)	Odds ratio (95% CI)	Risk diff. (95% CI)		p-value **
Baseline LVEF												0.8951
<=30	1390	41	2.9	1337	25	1.9	0.0666	0.63 (0.39, 1.04)	0.63 (0.38, 1.04)	-0.01	(-0.02, 0.00)	
>30 to <=35	359	11	3.1	398	7	1.8	0.2392	0.57 (0.22, 1.46)	0.57 (0.22, 1.48)	-0.01	(-0.04, 0.01)	
>35	114	3	2.6	128	3	2.3	0.8857	0.89 (0.18, 4.33)	0.89 (0.18, 4.49)	0.00	(-0.04, 0.04)	
Baseline NTproBNP												0.6003
< median	919	17	1.8	942	13	1.4	0.4211	0.75 (0.36, 1.53)	0.74 (0.36, 1.54)	0.00	(-0.02, 0.01)	
>= median	943	38	4.0	920	22	2.4	0.0452	0.59 (0.35, 1.00)	0.58 (0.34, 0.99)	-0.02	(-0.03, 0.00)	

Risk ratios and odds ratios with confidence intervals (CIs) are estimated by Cochran-Mantel-Haenszel method. For risk differences standard Wald asymptotic confidence limits are calculated. A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied 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).
For AEs on SOC and/or PT level, subgroup analyses are only shown if overall test for treatment is significant on 5% level
(i.e. 95% CI for the risk ratio does not contain 1; if this is not calculable the p-value of Chi-square test is used).
MedDRA version: 23.0. * Chi-square test for treatment effect ** Breslow-Day test for homogeneity of odds ratios (treatment by subgroup interaction).

Table R.1.4.5: 2 Proportion of patients with serious adverse events occurring in at least 1% of the patients in either treatment arm in the overall population on PT level - by SOC and PT - 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	1863	27	1.4	1863	17	0.9	0.1294	0.63 (0.34, 1.15)	0.63 (0.34, 1.15)	-0.01 (-0.01, 0.00)	

Risk ratios and odds ratios with confidence intervals (CIs) are estimated by Cochran-Mantel-Haenszel method. For risk differences standard Wald asymptotic confidence limits are calculated. A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied 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).
For AEs on SOC and/or PT level, subgroup analyses are only shown if overall test for treatment is significant on 5% level (i.e. 95% CI for the risk ratio does not contain 1; if this is not calculable the p-value of Chi-square test is used).
MedDRA version: 23.0. * Chi-square test for treatment effect ** Breslow-Day test for homogeneity of odds ratios (treatment by subgroup interaction).

Table R.1.4.5: 2 Proportion of patients with serious adverse events occurring in at least 1% of the patients in either treatment arm in the overall population on PT level - by SOC and PT - 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	1863	20	1.1	1863	19	1.0	0.8721	0.95 (0.51, 1.77)	0.95 (0.51, 1.78)	0.00 (-0.01, 0.01)	

Risk ratios and odds ratios with confidence intervals (CIs) are estimated by Cochran-Mantel-Haenszel method. For risk differences standard Wald asymptotic confidence limits are calculated. A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied 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).
For AEs on SOC and/or PT level, subgroup analyses are only shown if overall test for treatment is significant on 5% level (i.e. 95% CI for the risk ratio does not contain 1; if this is not calculable the p-value of Chi-square test is used).
MedDRA version: 23.0. * Chi-square test for treatment effect ** Breslow-Day test for homogeneity of odds ratios (treatment by subgroup interaction).

Table R.1.4.5: 2 Proportion of patients with serious adverse events occurring in at least 1% of the patients in either treatment arm in the overall population on PT level - by SOC and PT - 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	1863	27	1.4	1863	20	1.1	0.3042	0.74 (0.42, 1.32)	0.74 (0.41, 1.32)	0.00 (-0.01, 0.00)	

Risk ratios and odds ratios with confidence intervals (CIs) are estimated by Cochran-Mantel-Haenszel method. For risk differences standard Wald asymptotic confidence limits are calculated. A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied 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).
For AEs on SOC and/or PT level, subgroup analyses are only shown if overall test for treatment is significant on 5% level (i.e. 95% CI for the risk ratio does not contain 1; if this is not calculable the p-value of Chi-square test is used).
MedDRA version: 23.0. * Chi-square test for treatment effect ** Breslow-Day test for homogeneity of odds ratios (treatment by subgroup interaction).

Table R.1.4.5: 3 Proportion of patients with severe adverse events occurring in at least 1% of the patients in either treatment arm in the overall population on PT level - by SOC and PT - 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	1863	165	8.9	1863	140	7.5	0.1352	0.85	(0.68, 1.05)	0.84	(0.66, 1.06)	-0.01	(-0.03, 0.00)	

Risk ratios and odds ratios with confidence intervals (CIs) are estimated by Cochran-Mantel-Haenszel method. For risk differences standard Wald asymptotic confidence limits are calculated. A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied 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).
For AEs on SOC and/or PT level, subgroup analyses are only shown if overall test for treatment is significant on 5% level (i.e. 95% CI for the risk ratio does not contain 1; if this is not calculable the p-value of Chi-square test is used).
MedDRA version: 23.0. * Chi-square test for treatment effect ** Breslow-Day test for homogeneity of odds ratios (treatment by subgroup interaction).

Table R.1.4.5: 3 Proportion of patients with severe adverse events occurring in at least 1% of the patients in either treatment arm in the overall population on PT level - by SOC and PT - overall and by subgroup - TS
System organ class: Cardiac disorders
Preferred term: Ventricular tachycardia

Subgroup	Placebo			Empa 10mg			Empa 10mg vs Placebo						
Category	N	n	%	N	n	%	p-value *	Risk ratio	(95% CI)	Odds ratio	(95% CI)	Risk diff.	(95% CI)	p-value **
Overall	1863	16	0.9	1863	21	1.1	0.4087	1.31	(0.69, 2.51)	1.32	(0.68, 2.53)	0.00	(0.00, 0.01)	

Risk ratios and odds ratios with confidence intervals (CIs) are estimated by Cochran-Mantel-Haenszel method. For risk differences standard Wald asymptotic confidence limits are calculated. A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied 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).
For AEs on SOC and/or PT level, subgroup analyses are only shown if overall test for treatment is significant on 5% level (i.e. 95% CI for the risk ratio does not contain 1; if this is not calculable the p-value of Chi-square test is used).
MedDRA version: 23.0. * Chi-square test for treatment effect ** Breslow-Day test for homogeneity of odds ratios (treatment by subgroup interaction).

Table R.1.4.5: 3 Proportion of patients with severe adverse events occurring in at least 1% of the patients in either treatment arm in the overall population on PT level - by SOC and PT - 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	1863	19	1.0	1863	15	0.8	0.4907	0.79	(0.40, 1.55)	0.79	(0.40, 1.55)	0.00	(-0.01, 0.00)	

Risk ratios and odds ratios with confidence intervals (CIs) are estimated by Cochran-Mantel-Haenszel method. For risk differences standard Wald asymptotic confidence limits are calculated. A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied 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).
For AEs on SOC and/or PT level, subgroup analyses are only shown if overall test for treatment is significant on 5% level (i.e. 95% CI for the risk ratio does not contain 1; if this is not calculable the p-value of Chi-square test is used).
MedDRA version: 23.0. * Chi-square test for treatment effect ** Breslow-Day test for homogeneity of odds ratios (treatment by subgroup interaction).

Table R.1.4.5: 3 Proportion of patients with severe adverse events occurring in at least 1% of the patients in either treatment arm in the overall population on PT level - by SOC and PT - 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	1863	33	1.8	1863	25	1.3	0.2897	0.76	(0.45, 1.27)	0.75	(0.45, 1.27)	0.00	(-0.01, 0.00)	

Risk ratios and odds ratios with confidence intervals (CIs) are estimated by Cochran-Mantel-Haenszel method. For risk differences standard Wald asymptotic confidence limits are calculated. A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied 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).
For AEs on SOC and/or PT level, subgroup analyses are only shown if overall test for treatment is significant on 5% level (i.e. 95% CI for the risk ratio does not contain 1; if this is not calculable the p-value of Chi-square test is used).
MedDRA version: 23.0. * Chi-square test for treatment effect ** Breslow-Day test for homogeneity of odds ratios (treatment by subgroup interaction).

Table R.1.4.5: 3 Proportion of patients with severe adverse events occurring in at least 1% of the patients in either treatment arm in the overall population on PT level - by SOC and PT - 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	1863	27	1.4	1863	20	1.1	0.3042	0.74	(0.42, 1.32)	0.74	(0.41, 1.32)	0.00	(-0.01, 0.00)	

Risk ratios and odds ratios with confidence intervals (CIs) are estimated by Cochran-Mantel-Haenszel method. For risk differences standard Wald asymptotic confidence limits are calculated. A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied 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).
For AEs on SOC and/or PT level, subgroup analyses are only shown if overall test for treatment is significant on 5% level (i.e. 95% CI for the risk ratio does not contain 1; if this is not calculable the p-value of Chi-square test is used).
MedDRA version: 23.0. * Chi-square test for treatment effect ** Breslow-Day test for homogeneity of odds ratios (treatment by subgroup interaction).

Table R.1.4.5: 3 Proportion of patients with severe adverse events occurring in at least 1% of the patients in either treatment arm in the overall population on PT level - by SOC and PT - 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	1863	25	1.3	1863	15	0.8	0.1119	0.60	(0.32, 1.13)	0.60	(0.31, 1.14)	-0.01	(-0.01, 0.00)	

Risk ratios and odds ratios with confidence intervals (CIs) are estimated by Cochran-Mantel-Haenszel method. For risk differences standard Wald asymptotic confidence limits are calculated. A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied 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).
For AEs on SOC and/or PT level, subgroup analyses are only shown if overall test for treatment is significant on 5% level (i.e. 95% CI for the risk ratio does not contain 1; if this is not calculable the p-value of Chi-square test is used).
MedDRA version: 23.0. * Chi-square test for treatment effect ** Breslow-Day test for homogeneity of odds ratios (treatment by subgroup interaction).

R.1.4.6

R.1.4.6 Medical concepts for Adverse events of special interest and other specific AEs

Listing R.1.4.6: 1 Listing of preferred terms that define adverse events of special interest and 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
				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
				10059499	Haemorrhagic urticaria
				10063438	Pruritus allergic
				10071588	Vulvovaginal rash
				10075807	Nodular rash
				10078325	Symmetrical drug-related intertriginous and flexural exanthema

* AE must be serious to qualify.

MedDRA version: 23.0

Listing R.1.4.6: 1 Listing of preferred terms that define adverse events of special interest and 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		10082290	Urticarial dermatitis
				10082571	Penile rash
				10082985	Erythrodermic atopic dermatitis
				10083156	Immune-mediated dermatitis
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
				10083834	Apolipoprotein E increased
Broad BIcMQ 'Ketoacidosis (BIcMQ)'	DKA (broad)	40000009		10000410	Acetonaemia
				10000486	Acidosis
				10002523	Anion gap abnormal

* AE must be serious to qualify.

MedDRA version: 23.0

Listing R.1.4.6: 1 Listing of preferred terms that define adverse events of special interest and specific AE categories

Source	Group	Group code	Scope	Preferred term code	Preferred term
Broad BIcMQ 'Ketoacidosis (BIcMQ)'	DKA (broad)	40000009		10002528	Anion gap increased
				10005705	Blood pH abnormal
				10005706	Blood pH decreased
				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
				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
				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
				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

* AE must be serious to qualify.

MedDRA version: 23.0

Listing R.1.4.6: 1 Listing of preferred terms that define adverse events of special interest and 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		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
				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

* AE must be serious to qualify.

MedDRA version: 23.0

Listing R.1.4.6: 1 Listing of preferred terms that define adverse events of special interest and 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		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
				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

* AE must be serious to qualify.

MedDRA version: 23.0

Listing R.1.4.6: 1 Listing of preferred terms that define adverse events of special interest and specific AE categories

Source	Group	Group code	Scope	Preferred term code	Preferred term
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
				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

* AE must be serious to qualify.

MedDRA version: 23.0

Listing R.1.4.6: 1 Listing of preferred terms that define adverse events of special interest and specific AE categories

Source	Group	Group code	Scope	Preferred term code	Preferred term
Narrow BIcMQ 'Bone fractures (BIcMQ)'	Bone fracture	40000012		10042015	Sternal fracture
				10042212	Stress fracture
				10043827	Tibia fracture
				10045375	Ulna fracture
				10048049	Wrist fracture
				10048617	Pseudarthrosis
				10049164	Fractured coccyx
				10049514	Traumatic fracture
				10049946	Cervical vertebral fracture
				10049947	Lumbar vertebral fracture
				10049948	Thoracic vertebral fracture
				10052614	Comminuted fracture
				10053206	Fracture displacement
				10053962	Epiphyseal fracture
				10057147	Fracture debridement
				10057609	Fracture reduction
				10059362	Fractured zygomatic arch elevation
				10061161	Pelvic fracture
				10061365	Skull fracture
				10061394	Upper limb fracture
				10061599	Lower limb fracture
				10061959	Fracture treatment
				10064210	Bone fissure
				10064211	Bone fragmentation
				10066094	Torus fracture
				10066184	Avulsion fracture
				10066386	Impacted fracture
				10069066	Intramedullary rod insertion
				10069135	Periprosthetic fracture
				10069723	Loss of anatomical alignment after fracture reduction
				10070884	Atypical femur fracture
				10072132	Fracture pain
				10072395	Atypical fracture
				10073162	Chance fracture
				10073853	Osteochondral fracture
				10074362	Sacroiliac fracture
				10074551	Limb fracture
				10074807	Spinal fusion fracture
				10077270	Surgical fixation of rib fracture
				10077603	Craniofacial fracture
				10078749	Lisfranc fracture

* AE must be serious to qualify.

MedDRA version: 23.0

Listing R.1.4.6: 1 Listing of preferred terms that define adverse events of special interest and specific AE categories

Source	Group	Group code	Scope	Preferred term code	Preferred term
Narrow BIcMQ 'Bone fractures (BIcMQ)'	Bone fracture	40000012		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 to 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
				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

* AE must be serious to qualify.

MedDRA version: 23.0

Listing R.1.4.6: 1 Listing of preferred terms that define adverse events of special interest and specific AE categories

Source	Group	Group code	Scope	Preferred term code	Preferred term
Narrow BIcMQ 'Genital tract infections predisposed to by glucosuria (BIcMQ)'	Genital infections	40000004		10047752	Vulval cellulitis
				10047780	Vulvitis
				10047784	Vulvovaginal candidiasis
				10047794	Vulvovaginitis
				10048461	Genital infection
				10049205	Clitoris abscess
				10049571	Scrotal abscess
				10049573	Vaginal abscess
				10049677	Salpingo-oophoritis
				10050428	Fallopian tube abscess
				10050662	Prostate infection
				10050739	Erosive balanitis
				10051458	Myometritis
				10051483	Prostatovesiculitis
				10052301	Vaginal cellulitis
				10052457	Perineal abscess
				10053043	Epididymitis ureaplasmal
				10054259	Escherichia vaginitis
				10054824	Tubo-ovarian abscess
				10056254	Intrauterine infection
				10056345	Rectovaginal septum abscess
				10056628	Ovarian bacterial infection
				10057001	Seminal vesicular infection
				10058674	Pelvic infection
				10059070	Pelvic sepsis
				10061179	Genital infection bacterial
				10061180	Genital infection fungal
				10061182	Genitourinary tract infection
				10061912	Penile infection
				10061977	Genital infection female
				10062156	Scrotal infection
				10062233	Uterine infection
				10062316	Genital abscess
				10062521	Genital infection male
				10062707	Parametric abscess
				10063012	Uterine abscess
				10064501	Spermatic cord funiculitis
				10064724	Testicular abscess
				10064899	Vulvovaginal mycotic infection
				10064929	Cellulitis of male external genital organ

* AE must be serious to qualify.

MedDRA version: 23.0

Listing R.1.4.6: 1 Listing of preferred terms that define adverse events of special interest and specific AE categories

Source	Group	Group code	Scope	Preferred term code	Preferred term
Narrow BIcMQ 'Genital tract infections predisposed to by glucosuria (BIcMQ)'	Genital infections	40000004		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
Narrow BIcMQ 'Genital tract infections predisposed to by glucosuria (BIcMQ)', Narrow BIcMQ 'Complicated genital tract infections predisposed to 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

* AE must be serious to qualify.

MedDRA version: 23.0

Listing R.1.4.6: 1 Listing of preferred terms that define adverse events of special interest and specific AE categories

Source	Group	Group code	Scope	Preferred term code	Preferred term
Narrow BIcMQ 'Genital tract infections predisposed to by glucosuria (BIcMQ)', Narrow BIcMQ 'Complicated genital tract infections predisposed to by glucosuria (BIcMQ)'	Complicated genital infections	40000005		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

* AE must be serious to qualify.

MedDRA version: 23.0

Listing R.1.4.6: 1 Listing of preferred terms that define adverse events of special interest and specific AE categories

Source	Group	Group code	Scope	Preferred term code	Preferred term
Narrow BIcMQ 'Genital tract infections predisposed to by glucosuria (BIcMQ)', Narrow BIcMQ 'Complicated genital tract infections predisposed to by glucosuria (BIcMQ)'	Complicated genital infections	40000005		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*

* AE must be serious to qualify.

MedDRA version: 23.0

Listing R.1.4.6: 1 Listing of preferred terms that define adverse events of special interest and specific AE categories

Source	Group	Group code	Scope	Preferred term code	Preferred term
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
				10072058	Perinephritis
				10074409	Escherichia pyelonephritis
				10082040	Nephritis bacterial
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

* AE must be serious to qualify.

MedDRA version: 23.0

Listing R.1.4.6: 1 Listing of preferred terms that define adverse events of special interest and specific AE categories

Source	Group	Group code	Scope	Preferred term code	Preferred term
Narrow BIcMQ 'UTI predisposed by glucosuria (BIcMQ)'	Urinary tract infections	40000002		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
				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

* AE must be serious to qualify.

MedDRA version: 23.0

Listing R.1.4.6: 1 Listing of preferred terms that define adverse events of special interest and specific AE categories

Source	Group	Group code	Scope	Preferred term code	Preferred term
Narrow BIcMQ 'UTI predisposed by glucosuria (BIcMQ)'	Urinary tract infections	40000002		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
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*
				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*

* AE must be serious to qualify.

MedDRA version: 23.0

Listing R.1.4.6: 1 Listing of preferred terms that define adverse events of special interest and 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		10046490	Urethritis ureaplasmal*
				10046571	Urinary tract infection*
				10046572	Urinary tract infection enterococcal*
				10046573	Urinary tract infection neonatal*
				10046704	Urogenital trichomoniasis*
				10048709	Urosepsis
				10049059	Urinary tract infection fungal*
				10049100	Pyelocystitis
				10051250	Ureteritis*
				10051959	Urinary bladder abscess*
				10052238	Escherichia urinary tract infection*
				10052299	Urethral carbuncle*
				10054088	Urinary tract infection bacterial*
				10056351	Emphysematous cystitis*
				10056396	Asymptomatic bacteriuria*
				10058523	Bladder candidiasis*
				10058596	Renal cyst infection
				10059517	Bacterial pyelonephritis
				10061181	Genitourinary tract gonococcal infection*
				10061395	Ureter abscess*
				10062279	Urinary tract infection pseudomonal*
				10062280	Urinary tract infection staphylococcal*
				10064850	Cystitis erosive*
				10065198	Cystitis bacterial*
				10065214	Pyelonephritis fungal
				10065582	Urogenital infection fungal*
				10065583	Urogenital infection bacterial*
				10066757	Urinary tract abscess*
				10068822	Emphysematous pyelonephritis
				10070300	Streptococcal urinary tract infection*
				10072058	Perinephritis
				10074409	Escherichia pyelonephritis
				10074457	Bladder diverticulitis*
				10075063	Urethritis mycoplasmal*
				10077375	Funguria*
				10078665	Bacterial urethritis*
				10078666	Bacterial ureteritis*
				10081163	Fungal urethritis*

* AE must be serious to qualify.

MedDRA version: 23.0

Listing R.1.4.6: 1 Listing of preferred terms that define adverse events of special interest and 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		10081185	Gonococcal infection*
				10081262	Candida urethritis*
				10082040	Nephritis bacterial
				10082818	Providencia urinary tract infection*
				10083162	Urinary tract candidiasis*
				10083524	Campylobacter urinary tract 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
				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
				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

* AE must be serious to qualify.

MedDRA version: 23.0

Listing R.1.4.6: 1 Listing of preferred terms that define adverse events of special interest and specific AE categories

Source	Group	Group code	Scope	Preferred term code	Preferred term
Narrow BIcMQ 'Volume depletion and hypotension due to dehydration (BIcMQ)' excluding PTs 'Dehydration' and 'Hypovolaemia'	Hypotension	40000001		10042772	Syncope
				10053356	Blood pressure orthostatic decreased
				10066077	Diastolic hypotension
				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
				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

* AE must be serious to qualify.

MedDRA version: 23.0

Listing R.1.4.6: 1 Listing of preferred terms that define adverse events of special interest and 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		10019668	Hepatic fibrosis
				10019670	Hepatic function abnormal
				10019692	Hepatic necrosis
				10019705	Hepatic pain
				10019708	Hepatic steatosis
				10019717	Hepatitis
				10019727	Hepatitis acute
				10019754	Hepatitis cholestatic
				10019755	Hepatitis chronic active
				10019759	Hepatitis chronic persistent
				10019772	Hepatitis fulminant
				10019795	Hepatitis toxic
				10019837	Hepatocellular injury
				10019842	Hepatomegaly
				10019845	Hepatorenal failure
				10019846	Hepatorenal syndrome
				10019847	Hepatosplenomegaly
				10019851	Hepatotoxicity
				10020575	Hyperammonaemia
				10020578	Hyperbilirubinaemia
				10021209	Icterus index increased
				10023025	Ischaemic hepatitis
				10023126	Jaundice
				10023129	Jaundice cholestatic
				10023136	Jaundice hepatocellular
				10023321	Kayser-Fleischer ring
				10024670	Liver disorder
				10024690	Liver function test abnormal
				10024712	Liver tenderness
				10024714	Liver transplant
				10025129	Lupoid hepatic cirrhosis
				10030210	Oesophageal varices haemorrhage
				10036200	Portal hypertension
				10039012	Reye's syndrome
				10045428	Ultrasound liver abnormal
				10048611	Cholaemia
				10049631	Oedema due to hepatic disease

* AE must be serious to qualify.

MedDRA version: 23.0

Listing R.1.4.6: 1 Listing of preferred terms that define adverse events of special interest and 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		10050792	Urine bilirubin increased
				10050897	Portal hypertensive gastropathy
				10051010	Duodenal varices
				10051012	Gastric varices
				10051015	Radiation hepatitis
				10051081	Nodular regenerative hyperplasia
				10051333	Guanase increased
				10051343	Bile output decreased
				10051344	Bile output abnormal
				10051924	Hypercholia
				10052274	Hepatopulmonary syndrome
				10052279	Renal and liver transplant
				10052550	Liver induration
				10052554	Foetor hepaticus
				10053219	Non-alcoholic steatohepatitis
				10053244	Hepatocellular foamy cell syndrome
				10054125	Perihepatic discomfort
				10054889	Transaminases increased
				10056091	Varices oesophageal
				10056536	X-ray hepatobiliary abnormal
				10056956	Subacute hepatic failure
				10057110	Hepatic mass
				10057572	Gastric varices haemorrhage
				10057573	Chronic hepatic failure
				10058117	Ocular icterus
				10058477	Blood bilirubin abnormal
				10059710	Galactose elimination capacity test abnormal
				10059712	Galactose elimination capacity test decreased
				10060794	Hepatic enzyme decreased
				10060795	Hepatic enzyme increased
				10061009	Bilirubin excretion disorder
				10061947	Liver scan abnormal
				10061997	Hepatectomy
				10061998	Hepatic lesion
				10062000	Hepatobiliary disease

* AE must be serious to qualify.

MedDRA version: 23.0

Listing R.1.4.6: 1 Listing of preferred terms that define adverse events of special interest and 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		10062040	Liver operation
				10062685	Hepatic enzyme abnormal
				10062688	Transaminases abnormal
				10063075	Cryptogenic cirrhosis
				10064190	Cholestatic pruritus
				10064558	Total bile acids increased
				10064668	Hepatic infiltration eosinophilic
				10064676	Graft versus host disease in liver
				10064712	Mitochondrial aspartate aminotransferase increased
				10065274	Hepatic calcification
				10066195	Hepatobiliary scan abnormal
				10066244	Hepatic sequestration
				10066263	Acute graft versus host disease in liver
				10066597	Gastrooesophageal variceal haemorrhage prophylaxis
				10066599	Hepatic encephalopathy prophylaxis
				10066758	Mixed liver injury
				10066869	Molar ratio of total branched-chain amino acid to tyrosine
				10067125	Liver injury
				10067281	Portopulmonary hypertension
				10067338	Retrograde portal vein flow
				10067365	Hepatic hydrothorax
				10067718	Bilirubin conjugated abnormal
				10067737	Lupus hepatitis
				10067823	Splenic varices
				10067969	Cholestatic liver injury
				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

* AE must be serious to qualify.

MedDRA version: 23.0

Listing R.1.4.6: 1 Listing of preferred terms that define adverse events of special interest and 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		10071198	Allergic hepatitis
				10071265	Diabetic hepatopathy
				10071502	Intestinal varices
				10072160	Chronic graft versus host disease in liver
				10072268	Drug-induced liver injury
				10072284	Varicose veins of abdominal wall
				10072319	Gallbladder varices
				10073209	Portal vein dilatation
				10073215	Peripancreatic varices
				10073979	Portal vein cavernous transformation
				10074150	Biliary ascites
				10074151	Parenteral nutrition associated liver disease
				10074726	Portal fibrosis
				10075895	Liver palpable
				10076204	Minimal hepatic encephalopathy
				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

* AE must be serious to qualify.

MedDRA version: 23.0

Listing R.1.4.6: 1 Listing of preferred terms that define adverse events of special interest and 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		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
				10083406	Immune-mediated cholangitis
				10083521	Immune-mediated hepatic disorder
				10084058	Congestive hepatopathy
PT 'Pruritus'	Pruritus	40000016		10037087	Pruritus
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

* AE must be serious to qualify.

MedDRA version: 23.0

Listing R.1.4.6: 1 Listing of preferred terms that define adverse events of special interest and specific AE categories

Source	Group	Group code	Scope	Preferred term code	Preferred term
SMQ 'Acute renal failure'	Renal impairment	20000003	Narrow	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 'Angioedema'	Angioedema	20000024	Narrow	10002424	Angioedema
				10010726	Conjunctival oedema
				10011033	Corneal oedema
				10015029	Epiglottic oedema
				10015967	Eye swelling
				10015993	Eyelid oedema
				10016029	Face oedema
				10018291	Gingival swelling
				10019860	Hereditary angioedema
				10021247	Idiopathic urticaria
				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
				10046735	Urticaria
				10046740	Urticaria cholinergic
				10046750	Urticaria papular
				10049305	Gingival oedema
				10052139	Eye oedema
				10052250	Circumoral oedema
				10052568	Urticaria chronic
				10056647	Periorbital swelling
				10056998	Palatal oedema
				10057431	Scleral oedema

* AE must be serious to qualify.

MedDRA version: 23.0

Listing R.1.4.6: 1 Listing of preferred terms that define adverse events of special interest and specific AE categories

Source	Group	Group code	Scope	Preferred term code	Preferred term
SMQ 'Angioedema'	Angioedema	20000024	Narrow	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
SMQ 'Hypersensitivity'	Hypersensitivity	20000214	Narrow	10002198	Anaphylactic reaction
				10002199	Anaphylactic shock
				10002216	Anaphylactoid reaction
				10002222	Anaphylaxis treatment
				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

* AE must be serious to qualify.

MedDRA version: 23.0

Listing R.1.4.6: 1 Listing of preferred terms that define adverse events of special interest and specific AE categories

Source	Group	Group code	Scope	Preferred term code	Preferred term
SMQ 'Hypersensitivity'	Hypersensitivity	20000214	Narrow	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
				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

* AE must be serious to qualify.

MedDRA version: 23.0

Listing R.1.4.6: 1 Listing of preferred terms that define adverse events of special interest and specific AE categories

Source	Group	Group code	Scope	Preferred term code	Preferred term
SMQ 'Hypersensitivity'	Hypersensitivity	20000214	Narrow	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
				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

* AE must be serious to qualify.

MedDRA version: 23.0

Listing R.1.4.6: 1 Listing of preferred terms that define adverse events of special interest and specific AE categories

Source	Group	Group code	Scope	Preferred term code	Preferred term
SMQ 'Hypersensitivity'	Hypersensitivity	20000214	Narrow	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
				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

* AE must be serious to qualify.

MedDRA version: 23.0

Listing R.1.4.6: 1 Listing of preferred terms that define adverse events of special interest and specific AE categories

Source	Group	Group code	Scope	Preferred term code	Preferred term
SMQ 'Hypersensitivity'	Hypersensitivity	20000214	Narrow	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
				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

* AE must be serious to qualify.

MedDRA version: 23.0

Listing R.1.4.6: 1 Listing of preferred terms that define adverse events of special interest and specific AE categories

Source	Group	Group code	Scope	Preferred term code	Preferred term
SMQ 'Hypersensitivity'	Hypersensitivity	20000214	Narrow	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
				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

* AE must be serious to qualify.

MedDRA version: 23.0

Listing R.1.4.6: 1 Listing of preferred terms that define adverse events of special interest and specific AE categories

Source	Group	Group code	Scope	Preferred term code	Preferred term
SMQ 'Hypersensitivity'	Hypersensitivity	20000214	Narrow	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
				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

* AE must be serious to qualify.

MedDRA version: 23.0

Listing R.1.4.6: 1 Listing of preferred terms that define adverse events of special interest and specific AE categories

Source	Group	Group code	Scope	Preferred term code	Preferred term
SMQ 'Hypersensitivity'	Hypersensitivity	20000214	Narrow	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
				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

* AE must be serious to qualify.

MedDRA version: 23.0

II. SUGAR-DM-HF

Nicht signifikante Ergebnisse zu verfügbaren unerwünschten Ereignissen

1. UE von besonderem Interesse (AESI) – SUGAR-DM-HF

SUGAR-DM-HF	Placebo	Empagliflozin
Anzahl Patienten, N	53	52
Leberschaden		
Patienten mit Ereignis, n (%)	0 (0)	0 (0)
Relatives Risiko [95%-KI]	-[a]	
Odds Ratio [95%-KI]	-[a]	
Risikodifferenz [95%-KI][b]	0,00 [0,00; 0,00]	
p-Wert[b,c]	1,0000	
Nierenfunktionsstörung / Hyperkaliämie / metabolische Azidose		
Patienten mit Ereignis, n (%)	9 (17,0)	6 (11,5)
Relatives Risiko [95%-KI][b]	0,68 [0,26; 1,77]	
Odds Ratio [95%-KI][b]	0,64 [0,21; 1,94]	
Risikodifferenz [95%-KI][b]	-0,05 [-0,19; 0,08]	
p-Wert[b,c]	0,5786	
Ketoazidose		
Patienten mit Ereignis, n (%)	0 (0)	0 (0)
Relatives Risiko [95%-KI]	-[a]	
Odds Ratio [95%-KI]	-[a]	
Risikodifferenz [95%-KI][b]	0,00 [0,00; 0,00]	
p-Wert[b,c]	1,0000	
Jegliche Symptome von Hypotonie, Volumenmangel einschließlich Präsynkope/Synkope und Stürze (und gemessener Blutdruck)		
Patienten mit Ereignis, n (%)	31 (58,5)	29 (55,8)
Relatives Risiko [95%-KI][b]	0,95 [0,68; 1,33]	
Odds Ratio [95%-KI][b]	0,89 [0,41; 1,94]	
Risikodifferenz [95%-KI][b]	-0,03 [-0,22; 0,16]	
p-Wert[b,c]	0,8448	
Harnwegsinfektionen		
Patienten mit Ereignis, n (%)	5 (9,4)	7 (13,5)
Relatives Risiko [95%-KI][b]	1,43 [0,48; 4,21]	
Odds Ratio [95%-KI][b]	1,49 [0,44; 5,05]	

SUGAR-DM-HF	Placebo	Empagliflozin
Risikodifferenz [95%-KI][b]	0,04 [-0,08; 0,16]	
p-Wert[b,c]	0,5553	
Genitalinfektionen		
Patienten mit Ereignis, n (%)	4 (7,5)	7 (13,5)
Relatives Risiko [95%-KI][b]	1,78 [0,56; 5,73]	
Odds Ratio [95%-KI][b]	1,91 [0,52; 6,95]	
Risikodifferenz [95%-KI][b]	0,06 [-0,06; 0,18]	
p-Wert[b,c]	0,3585	
Kreatininwert >221 µmol/l		
Patienten mit Ereignis, n (%)	1 (1,9)	1 (1,9)
Relatives Risiko [95%-KI][b]	1,02 [0,07; 15,87]	
Odds Ratio [95%-KI][b]	1,02 [0,06; 16,74]	
Risikodifferenz [95%-KI][b]	0,00 [-0,05; 0,05]	
p-Wert[b,c]	1,0000	

a: kein Effektschätzer berechnet, da Division durch 0
b: eigene Berechnung
c: exakter Test nach Fisher
KI: Konfidenzintervall; N: Anzahl ausgewerteter Patienten

Quelle: Lee, M. M. Y., Brooksbank, K. J. M., Wetherall, K., et al. 2021a. Effect of Empagliflozin on Left Ventricular Volumes in Patients With Type 2 Diabetes, or Prediabetes, and Heart Failure With Reduced Ejection Fraction (SUGAR-DM-HF). Supplemental material. *Circulation*, 143(6)**,** 516-525.

2. SUE nach SOC bzw. PT – SUGAR-DM-HF

SUGAR-DM-HF	Placebo	Empagliflozin
Anzahl Patienten, N	53	52
SOC Herzerkrankungen (SUE)		
Patienten mit Ereignis, n (%)	6 (11,3)	10 (19,2)
Relatives Risiko [95%-KI][a]	1,70 [0,67; 4,34]	
Odds Ratio [95%-KI][a]	1,87 [0,62; 5,57]	
Risikodifferenz [95%-KI][a]	0,08 [-0,06; 0,22]	
p-Wert[a,b]	0,2897	
PT Akuter Myokardinfarkt (SUE)		
Patienten mit Ereignis, n (%)	1 (1,9)	3 (5,8)
Relatives Risiko [95%-KI][a]	3,06 [0,33; 28,45]	
Odds Ratio [95%-KI][a]	3,18 [0,32; 31,65]	

SUGAR-DM-HF	**Placebo**	**Empagliflozin**
Risikodifferenz [95%-KI][a]	0,04 [-0,03; 0,11]	
p-Wert[a,b]	0,3629	
PT Herzinsuffizienz (SUE)		
Patienten mit Ereignis, n (%)	0 (0)	3 (5,8)
Relatives Risiko [95%-KI]	-[c]	
Odds Ratio [95%-KI]	-[c]	
Risikodifferenz [95%-KI][a]	0,06 [-0,01; 0,12]	
p-Wert[a,b]	0,1179	
PT Vorhofflimmern (SUE)		
Patienten mit Ereignis, n (%)	1 (1,9)	1 (1,9)
Relatives Risiko [95%-KI][a]	1,02 [0,07; 15,87]	
Odds Ratio [95%-KI][a]	1,02 [0,06; 16,74]	
Risikodifferenz [95%-KI][a]	0,00 [-0,05; 0,05]	
p-Wert[a,b]	1,0000	
PT Akutes Koronarsyndrom (SUE)		
Patienten mit Ereignis, n (%)	1 (1,9)	0 (0)
Relatives Risiko [95%-KI]	-[c]	
Odds Ratio [95%-KI]	-[c]	
Risikodifferenz [95%-KI][a]	-0,02 [-0,06; 0,02]	
p-Wert[a,b]	1,0000	
PT Angina pectoris (SUE)		
Patienten mit Ereignis, n (%)	1 (1,9)	0 (0)
Relatives Risiko [95%-KI]	-[c]	
Odds Ratio [95%-KI]	-[c]	
Risikodifferenz [95%-KI][a]	-0,02 [-0,06; 0,02]	
p-Wert[a,b]	1,0000	
PT Angina pectoris instabil (SUE)		
Patienten mit Ereignis, n (%)	1 (1,9)	0 (0)
Relatives Risiko [95%-KI]	-[c]	
Odds Ratio [95%-KI]	-[c]	
Risikodifferenz [95%-KI][a]	-0,02 [-0,06; 0,02]	
p-Wert[a,b]	1,0000	
PT Herzstillstand (SUE)		
Patienten mit Ereignis, n (%)	1 (1,9)	0 (0)
Relatives Risiko [95%-KI]	-[c]	

SUGAR-DM-HF	Placebo	Empagliflozin
Odds Ratio [95%-KI]	-[c]	
Risikodifferenz [95%-KI][a]	-0,02 [-0,06; 0,02]	
p-Wert[a,b]	1,0000	
PT Herzinsuffizienz akut (SUE)		
Patienten mit Ereignis, n (%)	0 (0)	1 (1,9)
Relatives Risiko [95%-KI]	-[c]	
Odds Ratio [95%-KI]	-[c]	
Risikodifferenz [95%-KI][a]	0,02 [-0,02; 0,06]	
p-Wert[a,b]	0,4952	
PT Kardiogener Schock (SUE)		
Patienten mit Ereignis, n (%)	0 (0)	1 (1,9)
Relatives Risiko [95%-KI]	-[c]	
Odds Ratio [95%-KI]	-[c]	
Risikodifferenz [95%-KI][a]	0,02 [-0,02; 0,06]	
p-Wert[a,b]	0,4952	
PT Myokardinfarkt (SUE)		
Patienten mit Ereignis, n (%)	1 (1,9)[d]	0 (0)
Relatives Risiko [95%-KI]	-[c]	
Odds Ratio [95%-KI]	-[c]	
Risikodifferenz [95%-KI][a]	-0,02 [-0,06; 0,02]	
p-Wert[a,b]	1,0000	
PT Palpitationen (SUE)		
Patienten mit Ereignis, n (%)	0 (0)	1 (1,9)
Relatives Risiko [95%-KI]	-[c]	
Odds Ratio [95%-KI]	-[c]	
Risikodifferenz [95%-KI][a]	0,02 [-0,02; 0,06]	
p-Wert[a,b]	0,4952	
PT Dysfunktion des Sinusknotens (SUE)		
Patienten mit Ereignis, n (%)	0 (0)	1 (1,9)
Relatives Risiko [95%-KI]	-[c]	
Odds Ratio [95%-KI]	-[c]	
Risikodifferenz [95%-KI][a]	0,02 [-0,02; 0,06]	
p-Wert[a,b]	0,4952	
SOC Metabolism and nutrition disorders (SUE)		
Patienten mit Ereignis, n (%)	5 (9,4)	4 (7,7)

SUGAR-DM-HF	Placebo	Empagliflozin
Relatives Risiko [95%-KI][a]	0,82 [0,23; 2,87]	
Odds Ratio [95%-KI][a]	0,80 [0,20; 3,16]	
Risikodifferenz [95%-KI][a]	-0,02 [-0,12; 0,09]	
p-Wert[a,b]	1,0000	
PT Hyperkaliämie (SUE)		
Patienten mit Ereignis, n (%)	5 (9,4)	4 (7,7)
Relatives Risiko [95%-KI][a]	0,82 [0,23; 2,87]	
Odds Ratio [95%-KI][a]	0,80 [0,20; 3,16]	
Risikodifferenz [95%-KI][a]	-0,02 [-0,12; 0,09]	
p-Wert[a,b]	1,0000	
SOC Infektionen und parasitäre Erkrankungen (SUE)		
Patienten mit Ereignis, n (%)	2 (3,8)	2 (3,8)
Relatives Risiko [95%-KI][a]	1,02 [0,15; 6,97]	
Odds Ratio [95%-KI][a]	1,02 [0,14; 7,52]	
Risikodifferenz [95%-KI][a]	0,00 [-0,07; 0,07]	
p-Wert[a,b]	1,0000	
PT Abszess an Gliedmaßen (SUE)		
Patienten mit Ereignis, n (%)	0 (0)	1 (1,9)
Relatives Risiko [95%-KI]	-[c]	
Odds Ratio [95%-KI]	-[c]	
Risikodifferenz [95%-KI][a]	0,02 [-0,02; 0,06]	
p-Wert[a,b]	0,4952	
PT Biliärsepsis (SUE)		
Patienten mit Ereignis, n (%)	1 (1,9)	0 (0)
Relatives Risiko [95%-KI]	-[c]	
Odds Ratio [95%-KI]	-[c]	
Risikodifferenz [95%-KI][a]	-0,02 [-0,06; 0,02]	
p-Wert[a,b]	1,0000	
PT Grippe (SUE)		
Patienten mit Ereignis, n (%)	1 (1,9)	0 (0)
Relatives Risiko [95%-KI]	-[c]	
Odds Ratio [95%-KI]	-[c]	
Risikodifferenz [95%-KI][a]	-0,02 [-0,06; 0,02]	
p-Wert[a,b]	1,0000	

SUGAR-DM-HF	Placebo	Empagliflozin
PT Infektion der unteren Atemwege (SUE)		
Patienten mit Ereignis, n (%)	0 (0)	1 (1,9)
Relatives Risiko [95%-KI]	-[c]	
Odds Ratio [95%-KI]	-[c]	
Risikodifferenz [95%-KI][a]	0,02 [-0,02; 0,06]	
p-Wert[a,b]	0,4952	
PT Pneumonie (SUE)		
Patienten mit Ereignis, n (%)	0 (0)	1 (1,9)
Relatives Risiko [95%-KI]	-[c]	
Odds Ratio [95%-KI]	-[c]	
Risikodifferenz [95%-KI][a]	0,02 [-0,02; 0,06]	
p-Wert[a,b]	0,4952	
SOC Verletzung, Vergiftung und durch Eingriffe bedingte Komplikationen (SUE)		
Patienten mit Ereignis, n (%)	2 (3,8)	1 (1,9)
Relatives Risiko [95%-KI][a]	0,51 [0,05; 5,45]	
Odds Ratio [95%-KI][a]	0,50 [0,04; 5,69]	
Risikodifferenz [95%-KI][a]	-0,02 [-0,08; 0,04]	
p-Wert[a,b]	1,0000	
PT Alkoholvergiftung (SUE)		
Patienten mit Ereignis, n (%)	1 (1,9)	0 (0)
Relatives Risiko [95%-KI]	-[c]	
Odds Ratio [95%-KI]	-[c]	
Risikodifferenz [95%-KI][a]	-0,02 [-0,06; 0,02]	
p-Wert[a,b]	1,0000	
PT Oberschenkelhalsfraktur (SUE)		
Patienten mit Ereignis, n (%)	0 (0)	1 (1,9)
Relatives Risiko [95%-KI]	-[c]	
Odds Ratio [95%-KI]	-[c]	
Risikodifferenz [95%-KI][a]	0,02 [-0,02; 0,06]	
p-Wert[a,b]	0,4952	
PT Head injury (SUE)		
Patienten mit Ereignis, n (%)	1 (1,9)	0 (0)
Relatives Risiko [95%-KI]	-[c]	
Odds Ratio [95%-KI]	-[c]	
Risikodifferenz [95%-KI][a]	-0,02 [-0,06; 0,02]	

SUGAR-DM-HF	Placebo	Empagliflozin
p-Wert[a,b]	1,0000	
SOC Erkrankungen des Gastrointestinaltrakts (SUE)		
Patienten mit Ereignis, n (%)	2 (3,8)	0 (0)
Relatives Risiko [95%-KI]	-[c]	
Odds Ratio [95%-KI]	-[c]	
Risikodifferenz [95%-KI][a]	-0,04 [-0,09; 0,01]	
p-Wert[a,b]	0,4952	
PT Gastroösophageale Refluxerkrankung (SUE)		
Patienten mit Ereignis, n (%)	1 (1,9)	0 (0)
Relatives Risiko [95%-KI]	-[c]	
Odds Ratio [95%-KI]	-[c]	
Risikodifferenz [95%-KI][a]	-0,02 [-0,06; 0,02]	
p-Wert[a,b]	1,0000	
PT Rektalblutung (SUE)		
Patienten mit Ereignis, n (%)	1 (1,9)	0 (0)
Relatives Risiko [95%-KI]	-[c]	
Odds Ratio [95%-KI]	-[c]	
Risikodifferenz [95%-KI][a]	-0,02 [-0,06; 0,02]	
p-Wert[a,b]	1,0000	
SOC Leber- und Gallenerkrankungen (SUE)		
Patienten mit Ereignis, n (%)	1 (1,9)	1 (1,9)
Relatives Risiko [95%-KI][a]	1,02 [0,07; 15,87]	
Odds Ratio [95%-KI][a]	1,02 [0,06; 16,74]	
Risikodifferenz [95%-KI][a]	0,00 [-0,05; 0,05]	
p-Wert[a,b]	1,0000	
PT Cholecystitis acute (SUE)		
Patienten mit Ereignis, n (%)	1 (1,9)	0 (0)
Relatives Risiko [95%-KI]	-[c]	
Odds Ratio [95%-KI]	-[c]	
Risikodifferenz [95%-KI][a]	-0,02 [-0,06; 0,02]	
p-Wert[a,b]	1,0000	
PT Leberverletzung (SUE)		
Patienten mit Ereignis, n (%)	0 (0)	1 (1,9)
Relatives Risiko [95%-KI]	-[c]	
Odds Ratio [95%-KI]	-[c]	

SUGAR-DM-HF	Placebo	Empagliflozin
Risikodifferenz [95%-KI][a]	0,02 [-0,02; 0,06]	
p-Wert[a,b]	0,4952	
SOC Augenerkrankungen (SUE)		
Patienten mit Ereignis, n (%)	1 (1,9)	0 (0)
Relatives Risiko [95%-KI]	-[c]	
Odds Ratio [95%-KI]	-[c]	
Risikodifferenz [95%-KI][a]	-0,02 [-0,06; 0,02]	
p-Wert[a,b]	1,0000	
PT Verschluss einer Netzhautarterie (SUE)		
Patienten mit Ereignis, n (%)	1 (1,9)	0 (0)
Relatives Risiko [95%-KI]	-[c]	
Odds Ratio [95%-KI]	-[c]	
Risikodifferenz [95%-KI][a]	-0,02 [-0,06; 0,02]	
p-Wert[a,b]	1,0000	
SOC Allgemeine Erkrankungen und Beschwerden am Verabreichungsort (SUE)		
Patienten mit Ereignis, n (%)	0 (0)	1 (1,9)
Relatives Risiko [95%-KI]	-[c]	
Odds Ratio [95%-KI]	-[c]	
Risikodifferenz [95%-KI][a]	0,02 [-0,02; 0,06]	
p-Wert[a,b]	0,4952	
PT Brustkorbschmerz (SUE)		
Patienten mit Ereignis, n (%)	0 (0)	1 (1,9)
Relatives Risiko [95%-KI]	-[c]	
Odds Ratio [95%-KI]	-[c]	
Risikodifferenz [95%-KI][a]	0,02 [-0,02; 0,06]	
p-Wert[a,b]	0,4952	
SOC Gutartige, bösartige und nicht spezifizierte Neubildungen (einschl. Zysten und Polypen) (SUE)		
Patienten mit Ereignis, n (%)	0 (0)	1 (1,9)
Relatives Risiko [95%-KI]	-[c]	
Odds Ratio [95%-KI]	-[c]	
Risikodifferenz [95%-KI][a]	0,02 [-0,02; 0,06]	
p-Wert[a,b]	0,4952	
PT Pankreaskarzinom mit Metastasen (SUE)		
Patienten mit Ereignis, n (%)	0 (0)	1 (1,9)
Relatives Risiko [95%-KI]	-[c]	

SUGAR-DM-HF	**Placebo**	**Empagliflozin**
Odds Ratio [95%-KI]	-[c]	
Risikodifferenz [95%-KI][a]	0,02 [-0,02; 0,06]	
p-Wert[a,b]	0,4952	
SOC Erkrankungen der Nieren und Harnwege (SUE)		
Patienten mit Ereignis, n (%)	0 (0)	1 (1,9)
Relatives Risiko [95%-KI]	-[c]	
Odds Ratio [95%-KI]	-[c]	
Risikodifferenz [95%-KI][a]	0,02 [-0,02; 0,06]	
p-Wert[a,b]	0,4952	
PT Akute Nierenschädigung (SUE)		
Patienten mit Ereignis, n (%)	0 (0)	1 (1,9)
Relatives Risiko [95%-KI]	-[c]	
Odds Ratio [95%-KI]	-[c]	
Risikodifferenz [95%-KI][a]	0,02 [-0,02; 0,06]	
p-Wert[a,b]	0,4952	
SOC Gefäßerkrankungen (SUE)		
Patienten mit Ereignis, n (%)	1 (1,9)	0 (0)
Relatives Risiko [95%-KI]	-[c]	
Odds Ratio [95%-KI]	-[c]	
Risikodifferenz [95%-KI][a]	-0,02 [-0,06; 0,02]	
p-Wert[a,b]	1,0000	
PT Aneurysma einer peripheren Arterie (SUE)		
Patienten mit Ereignis, n (%)	1 (1,9)	0 (0)
Relatives Risiko [95%-KI]	-[c]	
Odds Ratio [95%-KI]	-[c]	
Risikodifferenz [95%-KI][a]	-0,02 [-0,06; 0,02]	
p-Wert[a,b]	1,0000	

a: eigene Berechnung
b: exakter Test nach Fisher
c: kein Effektschätzer berechnet, da Division durch 0
d: Ein Ereignis in der Placebo-Gruppe wurde als „im Zusammenhang mit der Studienmedikation stehend“ eingestuft und ist in dieser Tabelle nicht enthalten.

KI: Konfidenzintervall; N: Anzahl ausgewerteter Patienten

Quelle: Lee, M. M. Y., Brooksbank, K. J. M., Wetherall, K., et al. 2021a. Effect of Empagliflozin on Left Ventricular Volumes in Patients With Type 2 Diabetes, or Prediabetes, and Heart Failure With Reduced Ejection Fraction (SUGAR-DM-HF). Supplemental material. *Circulation,* 143(6)**,** 516-525.

III. EMPA-TROPISM

Nicht signifikante Ergebnisse zu verfügbaren unerwünschten Ereignissen

Nicht signifikante Ergebnisse zu verfügbaren unerwünschten Ereignissen – EMPA-TROPISM

EMPA-TROPISM	Placebo	Empagliflozin
Anzahl Patienten, N[a]	40	40
SUE		
Maligne ventrikuläre Tachykardie[b]		
Patienten mit Ereignis, n (%)	0 (0)	1 (2,5)
Relatives Risiko [95%-KI]	-[c]	
Odds Ratio [95%-KI]	-[c]	
Risikodifferenz [95%-KI][d]	0,03 [-0,02; 0,07]	
p-Wert[d,e]	1,0000	
Kammerflimmern[b]		
Patienten mit Ereignis, n (%)	2 (5,0)	0 (0)
Relatives Risiko [95%-KI]	-[c]	
Odds Ratio [95%-KI]	-[c]	
Risikodifferenz [95%-KI][d]	-0,05 [-0,12; 0,02]	
p-Wert[d,e]	0,4937	
Veschlechterung Herzinsuffizienz[b]		
Patienten mit Ereignis, n (%)	1 (2,5)	0 (0)
Relatives Risiko [95%-KI]	-[c]	
Odds Ratio [95%-KI]	-[c]	
Risikodifferenz [95%-KI][d]	-0,03 [-0,07; 0,02]	
p-Wert[d,e]	1,0000	
Neuer Defibrillator[b]		
Patienten mit Ereignis, n (%)	2 (5,0)	1 (2,5)
Relatives Risiko [95%-KI][d]	0,50 [0,05; 5,30]	
Odds Ratio [95%-KI][d]	0,49 [0,04; 5,60]	
Risikodifferenz [95%-KI][d]	-0,03 [-0,11; 0,06]	
p-Wert[d,e]	1,0000	

EMPA-TROPISM	Placebo	Empagliflozin
Neues Cardiomems-Implantat[b]		
Patienten mit Ereignis, n (%)	0 (0)	1 (2,5)
Relatives Risiko [95%-KI]	-[c]	
Odds Ratio [95%-KI]	-[c]	
Risikodifferenz [95%-KI][d]	0,03 [-0,02; 0,07]	
p-Wert[d,e]	1,0000	
Pleuraerguss[b]		
Patienten mit Ereignis, n (%)	2 (5,0)	0 (0)
Relatives Risiko [95%-KI]	-[c]	
Odds Ratio [95%-KI]	-[c]	
Risikodifferenz [95%-KI][d]	-0,05 [-0,12; 0,02]	
p-Wert[d,e]	0,4937	
Nicht-schwerwiegende UE		
Leberschaden[b,f]		
Patienten mit Ereignis, n (%)	1 (2,5)	0 (0)
Relatives Risiko [95%-KI]	-[c]	
Odds Ratio [95%-KI]	-[c]	
Risikodifferenz [95%-KI][d]	-0,03 [-0,07; 0,02]	
p-Wert[d,e]	1,0000	
Migräne[b]		
Patienten mit Ereignis, n (%)	0 (0)	1 (2,5)
Relatives Risiko [95%-KI]	-[c]	
Odds Ratio [95%-KI]	-[c]	
Risikodifferenz [95%-KI][d]	0,03 [-0,02; 0,07]	
p-Wert[d,e]	1,0000	
Verkehrsunfall[b]		
Patienten mit Ereignis, n (%)	0 (0)	1 (2,5)
Relatives Risiko [95%-KI]	-[c]	
Odds Ratio [95%-KI]	-[c]	
Risikodifferenz [95%-KI][d]	0,03 [-0,02; 0,07]	
p-Wert[d,e]	1,0000	

a: Von den in der Publikation (Supplemental tables 1 und 2) angegebenen unerwünschten Ereignissen wird angenommen, dass es sich um die Anzahl der Ereignisse handelt. Daher wurden in dieser Tabelle die berichteten Ereignisraten aus dem Studienregister clinicaltrials.gov angegeben. Darüber hinaus wurden in der Studie EMPA-TROPISM (Supplemental tables 1 und 2 der Publikation) weitere Ereignisse betrachtetet, zu denen jeweils in beiden Studienarmen keine Ereignisse auftraten (ausgenommen 1 Todesfall unter Placebo, siehe Modul 4A) und die daher in der vorliegenden Tabelle nicht aufgeführt werden.
b: Systematische Erfassung dieser Ereignisse

EMPA-TROPISM	**Placebo**	**Empagliflozin**
c: kein Effektschätzer berechnet, da Division durch 0 d: eigene Berechnung e: exakter Test nach Fisher f: Alanin-Aminotransferase und/oder Aspartat-Aminotransferase ≥5-fach erhöht über Obergrenze Normalwert. KI: Konfidenzintervall; N: Anzahl ausgewerteter Patienten Quellen: Santos-Gallego, C. G., Vargas-Delgado, A. P., Requena-Ibanez, J. A., et al. 2021b. Randomized Trial of Empagliflozin in Nondiabetic Patients With Heart Failure and Reduced Ejection Fraction. Supplemental Tables 1 and 2. J Am Coll Cardiol, 77(3), 243-255. Clinicaltrials.gov. 2021b. Are the "Cardiac Benefits" of Empagliflozin Independent of Its Hypoglycemic Activity? (ATRU-4). (EMPA-TROPISM). Study results. Verfügbar: https://clinicaltrials.gov/ct2/show/results/NCT03485222 [Aufgerufen am 17.05.2021].		