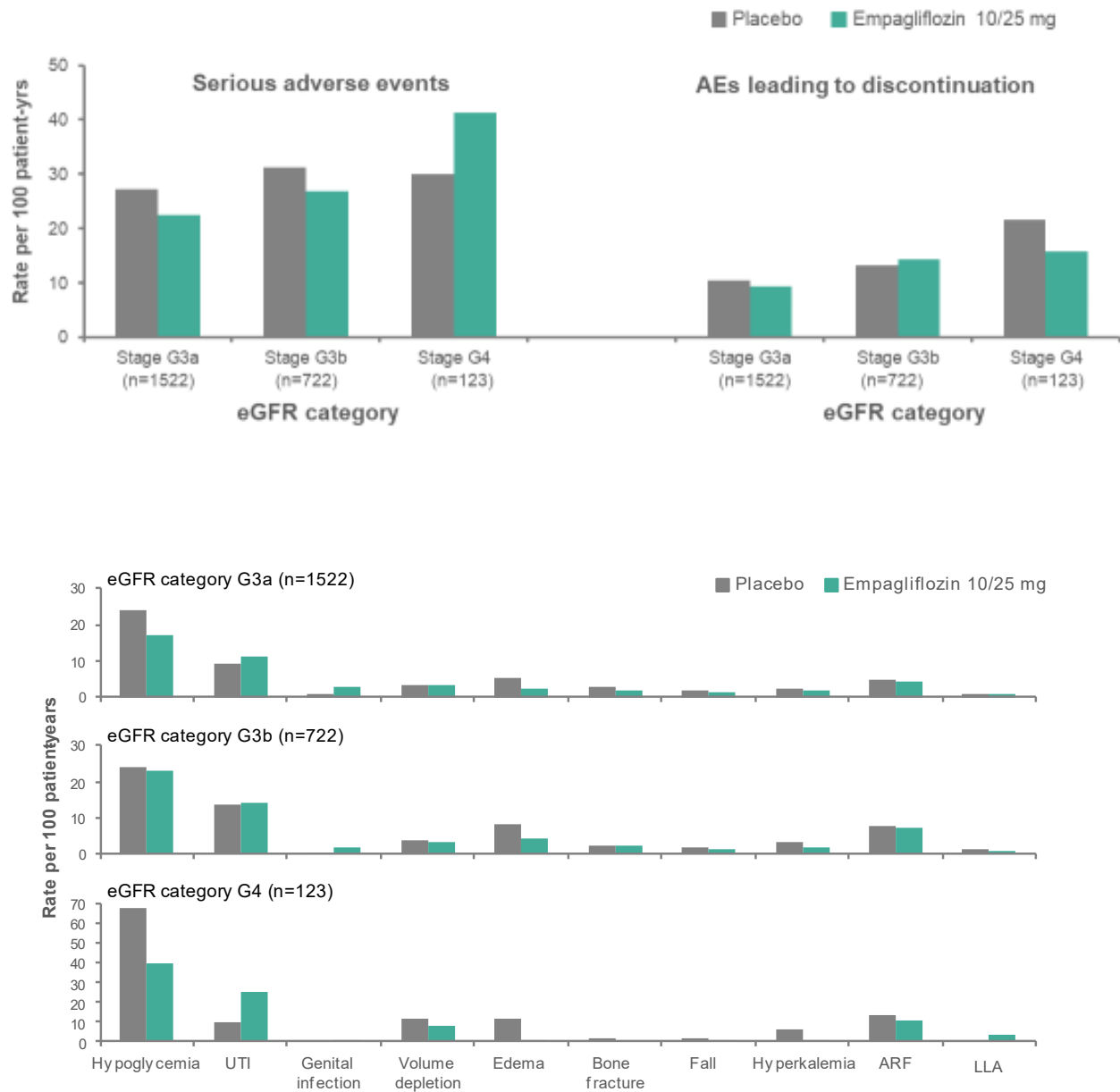


Supplemental Material

Supplementary Figure 1—Rate of adverse events.

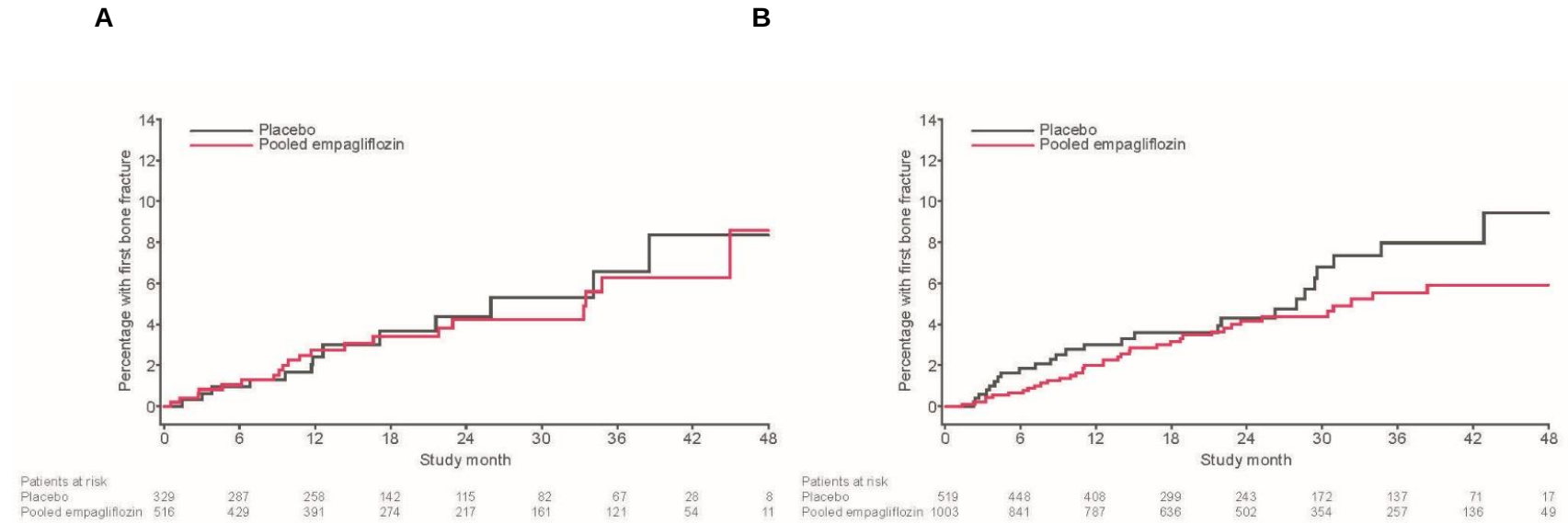


Exposure-adjusted incidence rates were calculated per 100 patient-years as $100 \times n/T$, where n was the number of subjects with the event and T was the total patient-years at risk of the event. Patient-years at risk were defined as the time from the first dose of study treatment to the onset of the first event (for patients with an event) or to the last dose +7 days (for those without an event). eGFR (mL/min/1.73m²) calculated using the Chronic Kidney Disease Epidemiology

Collaboration (CKD-EPI) equation. eGFR categories (mL/min/1.73 m²): G3A, 45 to <60; G3B, 30 to <45; G4, 15 to <30.

AE, adverse event; ARF, acute renal failure; LLA, lower limb amputation; UTI, urinary tract infection.

Supplementary Figure 2—Kaplan-Meier estimates of time to first event of bone fracture in patients with (A) eGFR <45 and (B) 45 to <60 mL/min/1.73 m².



eGFR (mL/min/1.73 m²) calculated using the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equation. eGFR, estimated glomerular filtration rate.

Supplementary Table 1—Randomized, placebo-controlled trials included in the pooled analysis

Study	Reference	Population	Intervention	Comparator	Clinical phase	Duration	Primary endpoint	Number of patients (% of overall pool)		
								Placebo	Empagliflozin 10/25 mg	Total patients
1245.4	Heise et al. 2013 (31)	Patients with type 2 diabetes	EMPA 10, 25, or 100 mg qd	PBO	1	4 weeks	Safety	16 (0.3)	32 (0.3)	48 (0.3)
1245.9	Ferrannini et al. 2013 (32)	Patients with type 2 diabetes	EMPA 5, 10, or 25 mg qd Met	PBO	2b	12 weeks	Change in HbA _{1c}	82 (1.7)	163 (1.6)	245 (1.6)
1245.10	Rosenstock et al. 2013 (33)	Patients with type 2 diabetes not controlled on Met	Met plus EMPA 1, 5, 10, 25, or 50 mg qd	Met plus PBO Met plus sitagliptin 100 mg qd	2b	78 weeks	Change in HbA _{1c}	71 (1.4)	141 (1.4)	212 (1.4)
1245.15	Kanada et al. 2013 (34)	Japanese patients with type 2 diabetes	EMPA 1, 5, 10, or 25 mg qd	PBO	2	4 weeks	Change in UGE, FPG, and 8-point glucose profile	21 (0.4)	39 (0.4)	60 (0.4)
EMPA-REG PIO, EMPA-REG EXTEND PIO 1245.19 (plus extn)	Kovacs et al. 2014, 2015 (35,36)	Patients with type 2 diabetes	Pioglitazone with or without Met plus EMPA 10 or 25 mg qd PBO	Pioglitazone with or without Met plus PBO	3	76 weeks (24-week study and 52-week extn)	Change in HbA _{1c}	165 (3.4)	333 (3.3)	498 (3.3)
EMPA-REG MONO, EMPA-REG EXTEND MONO 1245.20 (plus extn)	Roden et al. 2013, 2015 (37,38)	Drug-naïve patients with type 2 diabetes	EMPA 10 or 25 mg qd	Sitagliptin 100 mg qd PBO	3	76 weeks (24-week study and 52-week extn)	Change in HbA _{1c}	229 (4.7)	447 (4.4)	676 (4.2)

EMPA-REG MET, EMPA-REG EXTEND MET 1245.23 (Met only) (plus extn)	Häring et al. 2014, Merker et al. 2015 (39,40)	Patients with type 2 diabetes not controlled on Met	Met plus EMPA 10 or 25 mg qd	Met plus PBO	3	76 weeks (24-week study and 52-week extn)	Change in HbA _{1c}	206 (4.2)	431 (4.2)	637 (4.2)
EMPA-REG METSU, EMPA-REG EXTEND METSU 1245.23 (Met+SU) (plus extn)	Häring et al. 2013 (41,42)	Patients with type 2 diabetes not controlled on Met plus SU	Met plus SU plus EMPA 10 or 25 mg qd	Met plus SU plus PBO	3	76 weeks (24-week study and 52-week extn)	Change in HbA _{1c}	225 (4.6)	441 (4.3)	666 (4.4)
EMPA-REG OUTCOME 1245.25	Zinman et al. 2015 (11)	Patients with type 2 diabetes at high cardiovascular risk	EMPA 10 or 25 mg qd	PBO	3	Event-driven	3P-MACE	2,333 (47.6)	4,687 (46.1)	7,020 (46.5)
1245.29	Ferdinand et al. 2019 (43)							77 (1.6)	80 (0.8)	157 (1.0)
EMPA-REG BASAL 1245.33	Rosenstock et al. 2015 (44)	Patients with type 2 diabetes not controlled on basal insulin	Basal insulin plus EMPA 10 or 25 mg qd	Basal insulin plus PBO	2b	78 weeks	Change in HbA _{1c}	170 (3.5)	324 (3.2)	494 (3.3)
1245.35	Nishimura et al. 2015 (45)	Japanese patients with type 2 diabetes (either drug-naïve or treated with 1 oral antidiabetic agent)	EMPA 10 or 25 mg qd	PBO	3	28 days	Change in AUC _{1-4h} for PPG	21 (0.4)	39 (0.4)	60 (0.4)
EMPA-REG RENAL 1245.36	Barnett et al. 2014 (8)	Patients with type 2 diabetes and CKD category 2-4 not controlled on	Background antidiabetic agent plus	Background antidiabetic agent plus PBO	3	52 weeks	Change in HbA _{1c}	319 (6.5)	419 (4.1)	738 (4.9)

		existing antidiabetic medication	EMPA 10 or 25 mg qd							
1245.38	Kadowaki et al. 2015 (46)	Japanese patients with type 2 diabetes	EMPA 5, 10, 25, or 50 mg qd	PBO	2	52 weeks	Change in HbA _{1c}	109 (2.2)	218 (2.1)	327 (2.2)
EMPA-REG BP 1245.48	Tikkanen et al. 2015 (47)	Patients with type 2 diabetes and hypertension	EMPA 10 or 25 mg qd	PBO	3	12 weeks	Change in HbA _{1c} , change in SBP	272 (5.5)	552 (5.4)	824 (5.5)
EMPA-REG MDI 1245.49	Rosenstock et al. 2014 (48)	Obese patients with type 2 diabetes not controlled on MDI of insulin plus Met	MDI of insulin plus Met plus EMPA 10 or 25 mg qd	MDI of insulin plus Met plus PBO	3	52 weeks	Change in HbA _{1c}	188 (3.8)	375 (3.7)	563 (3.7)
1245.107	NCT02589639	Japanese patients with type 2 diabetes with insufficient glycemic control	EMPA 10 or 25 mg qd	PBO	4	52 weeks	Change in HbA _{1c}	90 (1.8)	176 (1.7)	266 (1.8)
1275.9	Søfteland et al. 2017 (49)	Patients with type 2 diabetes and insufficient glycemic control with linagliptin 5 mg qd on Met background therapy	EMPA 10 or 25 mg qd and linagliptin high dose or linagliptin low dose	Linagliptin 5 mg qd	3	24 weeks	Change in HbA _{1c}	110 (2.2)	222 (2.2)	332 (2.2)
1275.19	Kawamori et al. 2018 (50)	Japanese patients with type 2 diabetes	Linagliptin 5 mg + EMPA 10 mg or 25 mg bid	Linagliptin 5 mg qd	3	52 weeks	Change in HbA _{1c}	93 (1.9)	182 (1.8)	275 (1.8)

1276.10	NCT01649297	Patients with type 2 diabetes and insufficient glycemic control	Met + EMPA qd or bid	Met + PBO	3	24 weeks	Change in HbA _{1c}	107 (2.2)	876 (8.6)	983 (6.5)
Total								4,904 (100.0)	15,081 (100.0)	15,081 (100.0)

3P-MACE, 3-point major cardiovascular adverse events; AUC_{1-4h} for PPG, area under the glucose concentration-time curve 3 h after breakfast; bid, twice daily; CKD, chronic kidney disease; EMPA, empagliflozin; extn, extension; FPG, fasting plasma glucose; HbA_{1c}, glycated hemoglobin; MDI, multiple daily injections Met, metformin; PBO, placebo; PPG, post-prandial glucose; qd, once daily; SBP, systolic blood pressure; SU, sulfonylurea; UGE, urinary glucose excretion.

Supplementary Table 2—MedDRA preferred terms

ARF	Acute renal failure (narrow SMQ) -> see table below for preferred term listing
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ARF	Acute kidney injury	10069339
	Acute phosphate nephropathy	10069688
	Anuria	10002847
	Azotemia	10003885
	Continuous hemodiafiltration	10066338
	Dialysis	10061105
	Fetal renal impairment	10078987
	Hemodialysis	10018875
	Hemofiltration	10053090
	Hyponatriuria	10077515
	Neonatal anuria	10049778
	Nephropathy toxic	10029155
	Oliguria	10030302
	Peritoneal dialysis	10034660
	Prerenal failure	10072370
	Renal failure	10038435
	Renal failure neonatal	10038447
	Renal impairment	10062237
	Renal impairment neonatal	10049776

Bone fracture	Acetabulum fracture	10000397
	Ankle fracture	10002544
	Atypical femur fracture	10070884
	Atypical fracture	10072395
	Avulsion fracture	10066184
	Bone fissure	10064210
	Bone fragmentation	10064211
	Cervical vertebral fracture	10049946
	Chance fracture	10073162
	Clavicle fracture	10009245
	Closed fracture manipulation	10009506
	Comminuted fracture	10052614
	Complicated fracture	10010149
	Compression fracture	10010214
	Craniofacial fracture	10077603
	Elevation skull fracture	10014487
	Epiphyseal fracture	10053962
	External fixation of fracture	10015741
	Facial bones fracture	10016042
	Femoral neck fracture	10016450
	Femur fracture	10016454
	Fibula fracture	10016667
	Flail chest	10016747
	Foot fracture	10016970
	Forearm fracture	10016997
	Fracture	10017076
	Fracture debridement	10057147
	Fracture displacement	10053206
	Fracture infection	10079813
	Fracture of clavicle due to birth trauma	10017107
	Fracture pain	10072132
	Fracture reduction	10057609
	Fracture treatment	10061959
	Fractured coccyx	10049164
	Fractured ischium	10017290
	Fractured maxilla elevation	10017296
	Fractured sacrum	10017308
	Fractured skull depressed	10017310
	Fractured zygomatic arch elevation	10059362
	Greenstick fracture	10018720
	Hand fracture	10019114
	Hip fracture	10020100
	Humerus fracture	10020462
	Ilium fracture	10021343

Impacted fracture	10066386
Internal fixation of fracture	10022576
Intramedullary rod insertion	10069066
Jaw fracture	10023149
Limb fracture	10074551
Lisfranc fracture	10078749
Lower limb fracture	10061599
Lumbar vertebral fracture	10049947
Metaphyseal corner fracture	10079667
Multiple fractures	10028200
Open fracture	10030527
Open reduction of fracture	10030682
Osteochondral fracture	10073853
Osteophyte fracture	10080550
Osteoporotic fracture	10031290
Patella fracture	10034122
Pathological fracture	10034156
Pelvic fracture	10061161
Periprosthetic fracture	10069135
Pubis fracture	10070286
Radius fracture	10037802
Rib fracture	10039117
Sacroiliac fracture	10074362
Scapula fracture	10039579
Skull fracture	10061365
Skull fractured base	10040960
Spinal compression fracture	10041541
Spinal fracture	10041569
Spinal fusion fracture	10074807
Sternal fracture	10042015
Stress fracture	10042212
Subchondral insufficiency fracture	10079864
Surgical fixation of rib fracture	10077270
Thoracic vertebral fracture	10049948
Tibia fracture	10043827
Torus fracture	10066094
Traumatic fracture	10049514
Ulna fracture	10045375
Upper limb fracture	10061394
Wrist fracture	10048049
Skeletal traction	10040782

Edema	Edema defined by preferred terms Fluid overload, Fluid retention, Generalized edema, Edema, Edema peripheral, and Peripheral swelling
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Hyperkalemia	Hyperkalemia defined by preferred terms Hyperkalemia and Blood potassium increased
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Volume decreased	Blood pressure ambulatory decreased	10005731
	Blood pressure decreased	10005734
	Blood pressure diastolic decreased	10005737
	Blood pressure orthostatic decreased	10053356
	Blood pressure systolic decreased	10005758
	Circulatory collapse	10009192
	Dehydration	10012174
	Diastolic hypotension	10066077
	Hypotension	10021097
	Hypovolemia	10021137
	Hypovolemic shock	10021138
	Mean arterial pressure decreased	10026983
	Orthostatic hypotension	10031127
	Presyncope	10036653
	Syncope	10042772

ARF, acute renal failure; MedDRA, Medical Dictionary for Regulatory Activities.

Supplementary Table 3—Multivariable Cox regression for time to first key safety endpoint events by baseline eGFR group

	eGFR <45 mL/min/1.73 m ² <i>n</i> = 349, PBO; <i>n</i> = 554, EMPA 10/25 mg	eGFR 45 to <60 mL/min/1.73 m ² <i>n</i> = 618, PBO; <i>n</i> = 1207, EMPA 10/25 mg
Hyperkalemia	0.48 (0.26–0.91)	0.59 (0.37–0.96)
Volume depletion	0.83 (0.50–1.39)	0.91 (0.61–1.35)
ARF	0.75 (0.35–1.64)	0.61 (0.31–1.20)
Edema	0.44 (0.28–0.69)	0.47 (0.33–0.68)

All values are hazard ratio (95% CI). Cox regression models include age, baseline BMI, baseline HbA_{1c}, sex, baseline eGFR, and treatment-by-baseline eGFR interaction term.

AKI, acute kidney injury; BMI, body mass index; eGFR, estimated glomerular filtration rate; EMPA, empagliflozin; HbA_{1c}, glycated hemoglobin; PBO, placebo.

Supplementary Table 4—Patients in the pooled by contributing study
and eGFR (CKD–EPI):

A) eGFR 45 to <60 ml/min/1.73m² (Cat 3A)

Study	Group	Placebo N (%)	EMPA 10mg N (%)	EMPA 25mg N (%)	EMPA 10/25 mg N (%)	Total N (%)
1245.4		0	0	0	0	0
1245.9		2 (0.3)	0	3 (0.5)	3 (0.2)	5 (0.3)
1245.10		4 (0.6)	1 (0.2)	5 (0.8)	6 (0.5)	10 (0.5)
1245.15		0	0	0	0	0
1245.19		17 (2.8)	18 (3.2)	14 (2.2)	32 (2.7)	49 (2.7)
1245.20		12 (1.9)	12 (2.1)	10 (1.6)	22 (1.8)	34 (1.9)
1245.23	(Met only)	10 (1.6)	8 (1.4)	11 (1.7)	19 (1.6)	29 (1.6)
1245.23	(Met+SU)	20 (3.2)	13 (2.3)	15 (2.4)	28 (2.3)	48 (2.6)
1245.25		418 (67.6)	420 (74.2)	411 (64.5)	831 (68.8)	1249 (68.4)
1245.29		1 (0.2)	0	0	1 (0.1)	2 (0.1)
1245.33		16 (2.6)	19 (3.4)	24 (3.8)	43 (3.6)	59 (3.2)
1245.35		0	1 (0.2)	0	1 (0.1)	1 (0.1)
1245.36		78 (12.6)	8 (1.4)	87 (13.7)	95 (7.9)	173 (9.5)
1245.38		2 (0.3)	4 (0.7)	1 (0.2)	5 (0.4)	7 (0.4)
1245.48		11 (1.8)	13 (2.3)	20 (3.1)	33 (2.7)	44 (2.4)
1245.49		8 (1.3)	13 (2.3)	7 (1.1)	20 (1.7)	28 (1.5)
1245.107		10 (1.6)	5 (0.9)	9 (1.4)	14 (1.2)	24 (1.3)
1275.9		2 (0.3)	2 (0.4)	1 (0.2)	3 (0.2)	5 (0.3)
1275.19		4 (0.6)	0	0	3 (0.2)	7 (0.4)
1276.10		3 (0.5)	29 (5.1)	19 (3.0)	48 (4.0)	51 (2.8)
Total		618 (100.0)	566 (100.0)	637 (100.0)	1207 (100.0)	1825 (100.0)

B) eGFR 30 to <45 ml/min/1.73m² (Cat 3B)

Study	Group	Placebo N (%)	EMPA 10mg N (%)	EMPA 25mg N (%)	EMPA 10/25 mg N (%)	Total N (%)
1245.4		0	0	0	0	0
1245.9		0	0	0	0	0
1245.10		0	0	1 (0.3)	1 (0.2)	1 (0.1)
1245.15		0	0	0	0	0
1245.19		1 (0.3)	2 (1.0)	2 (0.7)	4 (0.8)	5 (0.6)
1245.20		1 (0.3)	1 (0.5)	0	1 (0.2)	2 (0.3)
1245.23	(Met only)	2 (0.7)	1 (0.5)	3 (1.0)	4 (0.8)	6 (0.8)
1245.23	(Met+SU)	2 (0.7)	6 (3.1)	2 (0.7)	8 (1.6)	10 (1.3)
1245.25		183 (61.8)	178 (91.8)	182 (62.3)	360 (73.9)	543 (69.3)

1245.29	2 (0.7)	0	0	1 (0.2)	3 (0.4)
1245.33	8 (2.7)	4 (2.1)	6 (2.1)	10 (2.1)	18 (2.3)
1245.35	0	0	0	0	0
1245.36	96 (32.4)	0	90 (30.8)	90 (18.5)	186 (23.8)
1245.38	0	0	0	0	0
1245.48	0	0	1 (0.3)	1 (0.2)	1 (0.1)
1245.49	0	0	0	0	0
1245.107	1 (0.3)	0	1 (0.3)	1 (0.2)	2 (0.3)
1275.9	0	0	0	0	0
1275.19	0	0	0	0	0
1276.10	0	2 (1.0)	4 (1.4)	6 (1.2)	6 (0.8)
Total	296 (100.0)	194 (100.0)	292 (100.0)	487 (100.0)	783 (100.0)

C) eGFR <30 ml/min/1.73m² (Cat 4)

Study	Group	Placebo N (%)	EMPA 10mg N (%)	EMPA 25mg N (%)	EMPA 10/25 mg N (%)	Total N (%)
1245.4		0	0	0	0	0
1245.9		0	0	0	0	0
1245.10		0	0	0	0	0
1245.15		0	0	0	0	0
1245.19		0	0	0	0	0
1245.20		0	0	0	0	0
1245.23	(Met only)	0	0	0	0	0
1245.23	(Met+SU)	0	0	0	0	0
1245.25		6 (11.3)	7 (77.8)	14 (24.1)	21 (31.3)	27 (22.5)
1245.29		0	0	0	0	0
1245.33		1 (1.9)	2 (22.2)	1 (1.7)	3 (4.5)	4 (3.3)
1245.35		0	0	0	0	0
1245.36		46 (86.8)	0	42 (72.4)	42 (62.7)	88 (73.3)
1245.38		0	0	0	0	0
1245.48		0	0	1 (1.7)	1 (1.5)	1 (0.8)
1245.49		0	0	0	0	0
1245.107		0	0	0	0	0
1275.9		0	0	0	0	0
1275.19		0	0	0	0	0
1276.10		0	0	0	0	0
Total		53 (100.0)	9 (100.0)	58 (100.0)	67 (100.0)	120 (100.0)

eGFR, estimated glomerular filtration rate; EMPA, empagliflozin; Met, metformin; SU, sulfonylurea.

Supplementary Table 5a—Cox regression for time to first outcome by eGFR category: EMPA-REG OUTCOME (study 1245.25) vs. Other and eGFR*treatment interaction term

	eGFR Cat 3A HR (95%CI), p-value	eGFR Cat3B + Cat4 HR (95%CI), p-value
Hyperkalemia	0.59 (0.37, 0.95), p=0.0306	0.48 (0.25, 0.90), p=0.0217
Based on a Cox regression model with terms for age (p=0.1771), baseline BMI (p=0.1164), baseline HbA1c (p=0.4184), sex (p=0.6583), 1245.25 vs other SAF-43 trial (p=0.1404) and treatment by baseline eGFR interaction (p=0.4341), treatment (p=0.0007), baseline eGFR (p<0.0001).		
Volume depletion	0.90 (0.61, 1.34), p=0.6166	0.79 (0.48, 1.32), p=0.3742
Based on a Cox regression model with terms for age (p<0.0001), baseline BMI (p=0.0213), baseline HbA1c (p=0.1080), sex (p=0.7494), 1245.25 vs other SAF-43 trial (p<0.0001), treatment (p=0.7048), baseline eGFR (p<0.0001) and treatment by baseline eGFR interaction (p=0.2183).		
AKI	0.61 (0.31, 1.19), p=0.1482	0.74, (0.34, 1.61), p=0.4435
Based on a Cox regression model with terms for age (p=0.0731), baseline BMI (p=0.0203), baseline HbA1c (p=0.3657), sex (p=0.5883), 1245.25 vs other SAF-43 trial (p=0.2354), treatment (p=0.0320), baseline eGFR (p<0.0001) and treatment by baseline eGFR interaction (p=0.9086).		
Edema	0.47 (0.33, 0.68), p<0.0001	0.43 (0.27, 0.66), p<0.0001
Based on a Cox regression model with terms for age (p<0.0001), baseline BMI (p<0.0001), baseline HbA1c (p=0.0841), sex (p=0.1373), 1245.25 vs other SAF-43 trial (p=0.0052), treatment (p<0.0001), baseline eGFR (p<0.0001) and treatment by baseline eGFR interaction (p=0.9387).		

Note: 4 patients were excluded from all outcomes as the subgroup variable was missing.

Supplementary Table 5b—Frailty model for time to first outcome by eGFR category including study as random effect and eGFR*treatment interaction term

	eGFR Cat 3A HR (95%CI), P-value	eGFR Cat3B + Cat4 HR (95%CI), P-value
Hyperkalemia	0.59 (0.37, 0.96), P=0.0318	0.48 (0.26, 0.91), P=0.0244
Comparison with placebo based on a Cox regression model with terms for age (p=0.1369), baseline BMI (p=0.1222), baseline HbA1c (p=0.4051), sex (p=0.7238), treatment (p=0.0008), baseline eGFR (p<0.0001), treatment by baseline eGFR interaction (p=0.4585) and trial number (random effect) (p=0.2205).		
Volume depletion	0.91 (0.61, 1.35), p=0.6268	0.82 (0.49, 1.36), p=0.4362
Based on a Cox regression model with terms for age (p<0.0001), baseline BMI (p=0.0301), baseline HbA1c (p=0.0812), sex (p=0.7463), treatment (p=0.7815), baseline eGFR (p<0.0001), treatment by baseline eGFR interaction (p=0.2391) and trial number (random effect) (p<0.0001).		
AKI	0.61 (0.31, 1.20), p=0.1496	0.75 (0.35, 1.64), p=0.4747
Based on a Cox regression model with terms for age (p=0.0557), baseline BMI (p=0.0191), baseline HbA1c (p=0.3751), sex (p=0.6495), treatment (p=0.0346), baseline eGFR (p<0.0001), treatment by baseline eGFR interaction (p=0.8889) and trial number (random effect) (p=0.2325).		
Edema	0.47 (0.33, 0.68), p<0.0001	0.43, (0.28, 0.67), p=0.0002
Based on a Cox regression model with terms for age (p<0.0001), baseline BMI (p<0.0001), baseline HbA1c (p=0.0734), sex (p=0.1459), treatment (p<0.0001), baseline eGFR (p<0.0001), treatment by baseline eGFR interaction (p=0.9540) and trial number (random effect) (p=0.0127).		

Note: 4 patients were excluded from all outcomes as the subgroup variable was missing.