SUPPLEMENTARY DATA

Supplementary Section 1. *Methods: Statistical analysis*

In the primary analysis, each empagliflozin dose was to be compared to placebo at the significance level of 0.025. A sample of 205 patients per randomized treatment group was required to ensure a power of 95% for the pairwise comparison and an overall power of ≥90% to detect a 0.5% treatment difference in HbA_{1c} for each empagliflozin dose compared to placebo, assuming a standard deviation of 1.2% and a 15% drop-out rate.

MMRM analyses were performed in the FAS using OC and included the fixed effects of randomized treatment, region, baseline eGFR, visit and treatment-by-visit interaction, as well as continuous baseline HbA_{1c}. For FPG and blood pressure, the MMRM analysis included the baseline value for the endpoint in question as an additional linear covariate.

Subgroup analysis of HbA_{1c} change from baseline by renal impairment categories was performed by including a treatment-by-baseline eGFR interaction term in the model described for the primary endpoint.

The models of the logistic regression of categorical change in HbA_{1c} and the proportion of patients with >5% weight loss included baseline HbA_{1c}, treatment, region and baseline eGFR (and baseline weight for the responder analysis of weight).

Analyses of MDG, FPG, and PPG were performed using the parameter in mg/dL. For presentation in this manuscript, estimates from the statistical analyses were converted to mmol/L using a factor of 0.0555.

Supplementary Section 2 . *Results: FPG and 2-hour PPG*

Changes in FPG over time are shown in Supplementary Figure 1B. After 24 weeks' treatment, adjusted mean (SE) changes from baseline were 0.31 (0.11) mmol/L with placebo compared with -1.29 (0.11) mmol/L with empagliflozin 10 mg and 25 mg (differences of adjusted means versus placebo were -1.60 mmol/L [95% CI -1.90, -1.30] for empagliflozin 10 mg and -1.60 mmol/L [95% CI -1.90, -1.29] for empagliflozin 25 mg; $p<0.001$ for both doses; Supplementary Figure 1C, Supplementary Table 1). Compared with placebo, at week 24 there was a significant reduction in 2-hour PPG with both doses: adjusted mean (SE) changes from baseline were -0.13 (0.46) mmol/L with placebo compared with -1.98 (0.41) mmol/L with empagliflozin 10 mg and -2.03 (0.40) mmol/L with empagliflozin 25 mg (differences of adjusted means versus placebo were -1.86 mmol/L [95% CI -3.07, -0.65] for empagliflozin 10 mg and -1.90 mmol/L [95% CI -3.12, -0.68] for empagliflozin 25 mg; $p=0.003$ for both doses; Supplementary Figure 1D, Supplementary Table 1).

SUPPLEMENTARY DATA

Supplementary Table 1. Changes in HbA_{1c} and plasma glucose.

	Placebo	Empagliflozin 10 mg	Empagliflozin 25 mg	Open-label empagliflozin 25 mg (baseline HbA_{1c} >10%)
Primary endpoint				
HbA_{1c} at week 24 (%)	7.97 (0.07)	7.26 (0.05)	7.33 (0.06)	8.20 (0.14)
Change from baseline in HbA_{1c} (%)	−0.17 (0.05)	−0.82 (0.05)	−0.77 (0.05)	−2.89 (0.16)
Difference vs. placebo		−0.64 (0.07)	−0.59 (0.07)	
95% CI		−0.77, −0.51	−0.73, −0.46	
p-value		<0.001	<0.001	
Key secondary endpoint				
MDG at week 24 (mmol/L)	9.49 (0.14)	8.91 (0.15)	8.81 (0.17)	9.51 (0.38)
Change from baseline in MDG (mmol/L)	0.00 (0.10)	−0.56 (0.10)	−0.72 (0.11)	−3.39 (0.58)
Difference vs. placebo		−0.56 (0.14)	−0.72 (0.15)	
95% CI		−0.83, −0.28	−1.02, −0.43	
p-value		<0.001	<0.001	
Exploratory endpoints				
Patients with HbA_{1c} ≥7.0% at baseline* who reached HbA1c <7.0% at week 24	20 (9.3)	55 (26.3)	65 (32.2)	9 (8.9)
Odds ratio vs. placebo		3.85	5.22	
95% CI		2.17, 6.85	2.95, 9.24	
p-value		<0.001	<0.001	
FPG at week 24 (mmol/L)	8.78 (0.16)	7.13 (0.11)	7.29 (0.12)	7.83 (0.30)
Change from baseline in FPG (mmol/L)	0.31 (0.11)	−1.29 (0.11)	−1.29 (0.11)	−3.02 (0.37)
Difference vs. placebo		−1.60 (0.15)	−1.60 (0.16)	
95% CI		−1.90, −1.30	−1.90, −1.29	
p-value		<0.001	<0.001	
2-hour PPG at week 24 (mmol/L)†	16.16 (0.57)	14.41 (0.64)	13.82 (0.50)	NM
Change from baseline (mmol/L)	-0.13 (0.46)	-1.98 (0.41)	-2.03 (0.40)	NM
Difference vs. placebo		-1.86 (0.61)	-1.90 (0.62)	
95% CI		−3.07, −0.65	−3.12 −0.68	
p-value		0.003	0.003	

Data are n (%) or mean (SE) except for change from baseline values in randomized groups, which are adjusted mean (SE). Values are from the full analysis set (FAS) using last observation carried forward (LOCF) and from the open-label set using observed cases (OC). HbA_{1c} <7.0% at week 24 analyzed in the FAS using non-completers considered failures

approach. CI=confidence interval; NM=not measured. *n=216 for placebo, n=209 for empagliflozin 10 mg, n=202 for empagliflozin 25 mg, n=101 for open-label group. †2-hour PPG was evaluated in a subset of 125 randomized patients who had a valid MTT (n=35 for placebo, n=43 for empagliflozin 10 mg, n=46 for empagliflozin 25 mg) using LOCF.

Supplementary Table 2. Changes from baseline in HbA_{1c} in renal function subgroups.

	Placebo	Empagliflozin 10 mg	Empagliflozin 25 mg
Patients with eGFR ≥90 ml/min/1.73m^2, n	94	92	94
Change from baseline in HbA_{1c} (%)	−0.17 (0.07)	−0.90 (0.07)	−0.92 (0.07)
Difference vs. placebo		−0.73 (0.10)	−0.75 (0.10)
95% CI		−0.94,−0.53	−0.96,−0.55
p-value		<0.001	<0.001
Patients with eGFR ≥60 to <90 ml/min/1.73m^2, n	109	114	105
Change from baseline in HbA_{1c} (%)	−0.23 (0.07)	−0.81 (0.07)	−0.68 (0.07)
Difference vs. placebo		−0.58 (0.10)	−0.45 (0.10)
95% CI		−0.76,−0.39	−0.64,−0.26
p-value		<0.001	<0.001
Patients with eGFR ≥30 to <60 ml/min/1.73m^2, n	22	19	17
Change from baseline in HbA_{1c} (%)	0.15 (0.15)	−0.44 (0.16)	−0.48 (0.17)
Difference vs. placebo		−0.58 (0.22)	−0.63 (0.23)
95% CI		−1.02,−0.14	−1.08,−0.18
p-value		0.009	0.006

Change from baseline values are adjusted mean (SE). Values are from the full analysis set (FAS) using last observation carried forward (LOCF). CI=confidence interval.

Supplementary Table 3. Changes in body weight and waist circumference.

	Placebo	Empagliflozin 10 mg	Empagliflozin 25 mg	Open-label empagliflozin 25 mg (baseline HbA_{1c} >10%)
Key secondary endpoint				
Body weight at week 24 (kg)	75.86 (1.12)	74.91 (1.22)	75.10 (1.26)	75.99 (2.23)
Change from baseline in body weight (kg)	−0.39 (0.15)	−2.16 (0.15)	−2.39 (0.16)	−1.76 (0.40)
Difference vs. placebo		−1.76 (0.22)	−1.99 (0.22)	
95% CI		−2.19, −1.34	−2.42, −1.56	
p-value		<0.001	<0.001	
Exploratory endpoints				
Patients with >5% reduction from baseline in body weight at week 24	13 (5.8%)	62 (27.6%)	51 (23.6%)	19 (18.8%)
Odds ratio vs. placebo		6.36	5.19	
95% CI		3.36, 12.02	2.72, 9.91	
p-value		<0.001	<0.001	
Waist circumference at week 24 (cm)	95.40 (0.87)	95.21 (0.89)	95.34 (0.93)	97.60 (1.75)
Change from baseline in waist circumference (cm)	−0.31 (0.28)	−1.46 (0.27)	−1.48 (0.28)	−1.36 (0.54)
Difference vs. placebo		−1.15 (0.39)	−1.17 (0.39)	
95% CI		−1.92, −0.39	−1.94, −0.40	
p-value		0.003	0.003	

Data are n (%) or mean (SE) except for change from baseline values in randomized groups, which are adjusted mean (SE). Values are from the full analysis set (FAS) using last observation carried forward (LOCF) and from the open-label set using observed cases (OC). Patients with >5% reduction from baseline in body weight at week 24 analyzed in the FAS using non-completers considered failures (NCF) approach. CI=confidence interval.

Supplementary Table 4. Changes in BP.

	Placebo	Empagliflozin 10 mg	Empagliflozin 25 mg	Open-label empagliflozin 25 mg (baseline HbA_{1c} >10%)
SBP at week 24 (mmHg)	127.4 (0.9)	124.7 (1.0)	125.7 (0.8)	122.0 (1.7)
Change from baseline in SBP (mmHg)	−1.4 (0.7)	−4.1 (0.7)	−3.5 (0.7)	−4.3 (1.2)
Difference vs. placebo		−2.7 (1.0)	−2.1 (1.0)	
95% CI		−4.6, −0.8	−4.0, −0.2	
p-value		0.005	0.032	
DBP at week 24 (mmHg)	76.6 (0.6)	76.3 (0.6)	76.7 (0.5)	75.4 (1.2)
Change from baseline in DBP (mmHg)	−1.8 (0.4)	−2.1 (0.4)	−2.2 (0.4)	−3.4 (1.0)
Difference vs. placebo		−0.4 (0.6)	−0.4 (0.6)	
95% CI		−1.6, 0.9	−1.6, 0.8	
p-value		0.557	0.534	

Data are n (%) or mean (SE) except for change from baseline values in randomized groups, which are adjusted mean (SE). Values are from the full analysis set (FAS) using last observation carried forward (LOCF) and from the open-label set using observed cases (OC).

SUPPLEMENTARY DATA

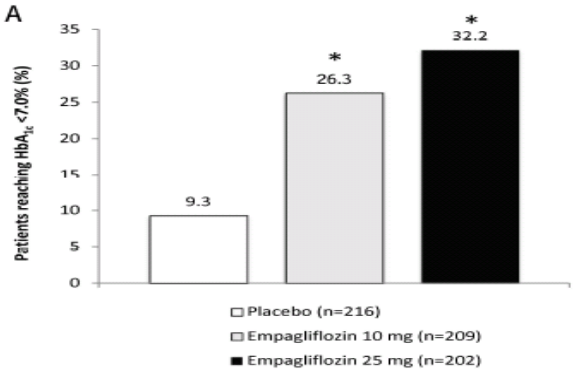
Supplementary Table 5. Laboratory measurements.

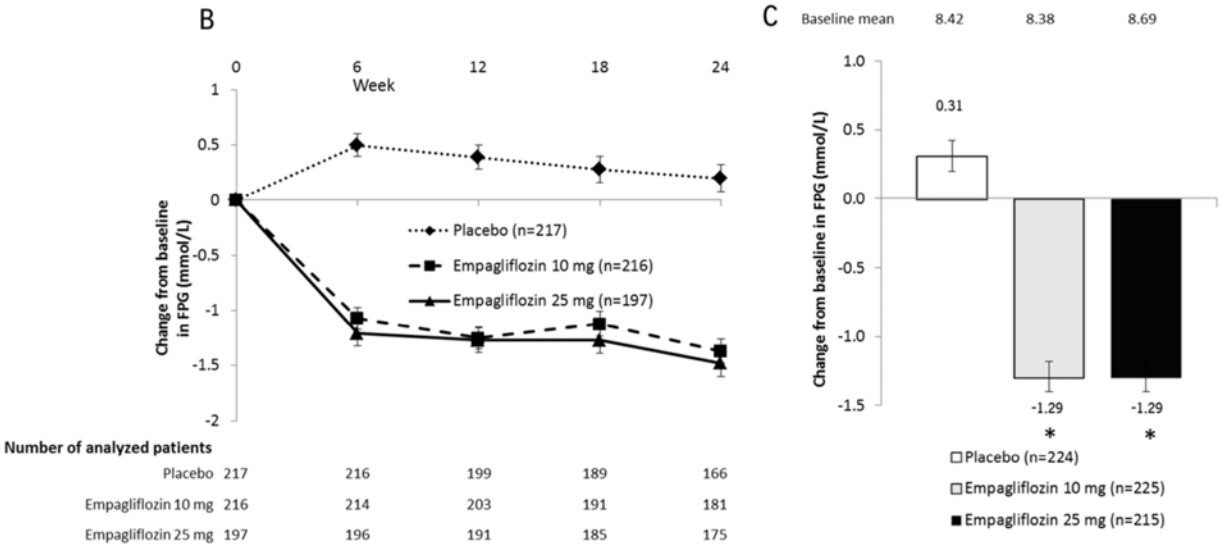
	Placebo		Empagliflozin 10 mg		Empagliflozin 25 mg		Open-label empagliflozin 25 mg (baseline HbA_{1c} >10%)	
	Baseline	Change from baseline*	Baseline	Change from baseline*	Baseline	Change from baseline*	Baseline	Change from baseline*
Hematocrit (%)†	41.7 (4.3)	−0.8 (3.1)	41.8 (5.0)	2.5 (3.4)	42.2 (4.1)	2.7 (3.4)	43.4 (4.9)	1.2 (3.4)
Uric acid (μmol/L)†	307 (110)	11 (81)	314 (127)	−28 (87)	298 (115)	−26 (81)	269 (113)	14 (74)
eGFR (mL/min/1.73m^2 [MDRD])	86.9 (20.1)	−1.9 (10.1)	86.4 (21.7)	−1.3 (10.6)	88.4 (22.7)	−2.5 (13.4)	93.1 (23.7)	−4.1 (13.3)
Electrolytes (mmol/L)†								
Sodium	141 (2)	0 (2)	141 (2)	0 (1)	141 (2)	0 (2)	140 (1)	1 (1)
Potassium	4.2 (0.3)	0.0 (0.3)	4.2 (0.3)	-0.1 (0.3)	4.1 (0.3)	0.0 (0.3)	4.2 (0.3)	-0.1 (0.3)
Calcium	2.4 (0.1)	0.0 (0.1)	2.5 (0.1)	0.0 (0.1)	2.4 (0.1)	0.0 (0.1)	2.4 (0.1)	0.0 (0.1)
Magnesium	0.9 (0.1)	0.0 (0.1)	0.9 (0.1)	0.1 (0.1)	0.9 (0.1)	0.1 (0.1)	0.9 (0.1)	0.1 (0.1)
Phosphate	1.2 (0.1)	0.0 (0.1)	1.2 (0.1)	0.0 (0.1)	1.2 (0.1)	0.0 (0.1)	1.2 (0.1)	0.1 (0.1)
Total cholesterol (mmol/L)‡	4.40 (0.07)	0.03 (0.04)	4.42 (0.06)	0.08 (0.04)	4.50 (0.07)	0.20 (0.05)	4.63 (0.12)	0.03 (0.10)
Difference vs. placebo				0.06 (0.06)		0.17 (0.06)		
p-value				0.377		0.007		
HDL-cholesterol (mmol/L)‡	1.25 (0.02)	−0.02 (0.01)	1.26 (0.02)	0.05 (0.01)	1.27 (0.02)	0.05 (0.01)	1.26 (0.03)	−0.02 (0.02)
Difference vs. placebo				0.06 (0.02)		0.07 (0.02)		
p-value				p<0.001		p<0.001		
LDL-cholesterol (mmol/L)‡	2.39 (0.06)	0.02 (0.04)	2.35 (0.06)	0.04 (0.04)	2.41 (0.06)	0.10 (0.04)	2.60 (0.11)	−0.06 (0.08)
Difference vs. placebo				0.01 (0.05)		0.08 (0.05)		
p-value				0.807		0.131		
Triglycerides (mmol/L)‡	1.70 (0.09)	0.08 (0.09)	1.87 (0.09)	0.03 (0.09)	1.82 (0.07)	0.17 (0.09)	1.83 (0.12)	0.37 (0.31)
Difference vs. placebo				−0.05 (0.12)		0.09 (0.12)		
p-value				0.672		0.459		

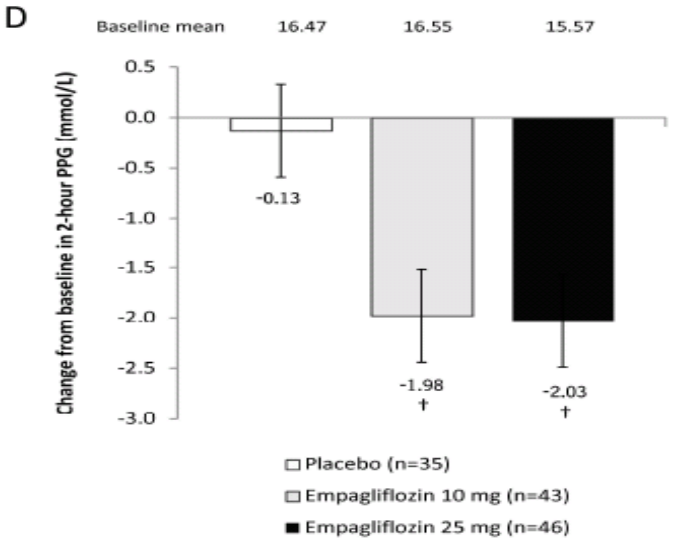
Data are mean (SD) unless otherwise indicated. MDRD, Modification of Diet in Renal Disease. Treated set (all patients treated with ≥1 dose of study drug).*Change from baseline

at last value on treatment for hematocrit, uric acid and electrolytes; change from baseline at week 24 for eGFR and cholesterol. †Normalized to a standard reference range. ‡Baseline data are mean (SE), change from baseline data are adjusted mean (SE) for randomized groups (ANCOVA, treated set, LOCF-IR) and mean (SE) for open-label group.

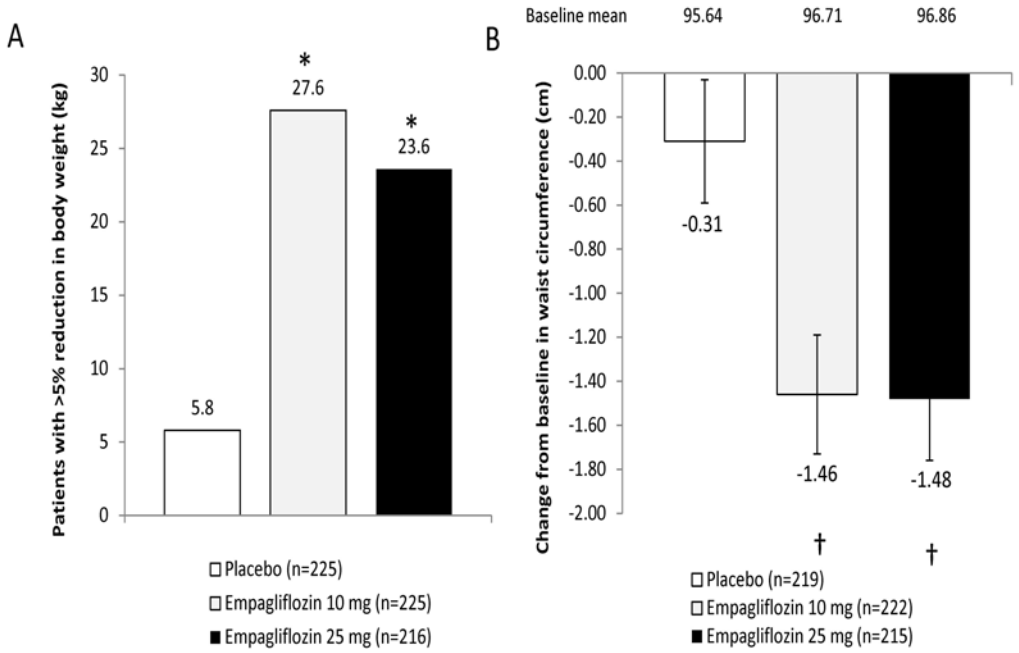
Supplementary Figure 1. (A) percentage of patients in randomized groups with HbA1c ≥7.0% at baseline who reached HbA1c <7.0% at week 24 (logistic regression, FAS, non-completers considered failures [NCF] imputation); (B) change in FPG over time in randomized groups (MMRM, FAS, OC); (C) change from baseline in FPG at week 24 in randomized groups (ANCOVA, FAS, LOCF); (D) change from baseline in 2-hour PPG at week 24 in randomized groups (ANCOVA on patients in the FAS with a baseline and ≥1 on-treatment meal tolerance test measurement, LOCF). Data are adjusted mean (SE) for randomized groups, or percentage of patients. *p<0.001 vs placebo; †p=0.003 vs placebo.





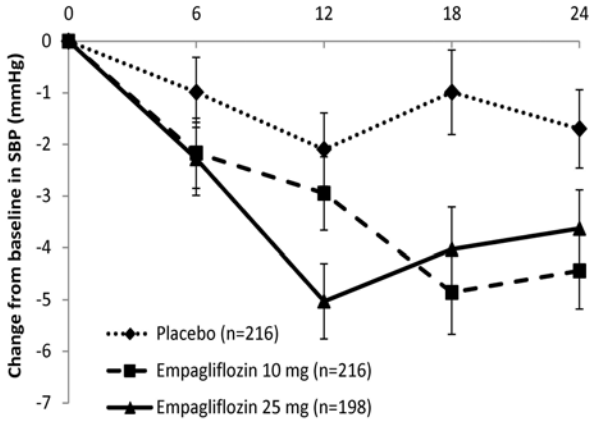


Supplementary Figure 2. (A) percentage of patients with >5% reduction in body weight at week 24 (logistic regression, FAS, non-completers considered failures imputation); (B) Change from baseline in waist circumference at week 24 (ANCOVA, FAS, LOCF). Data are adjusted mean (SE) or % of patients. *p<0.001 vs placebo; †p=0.003 vs placebo.



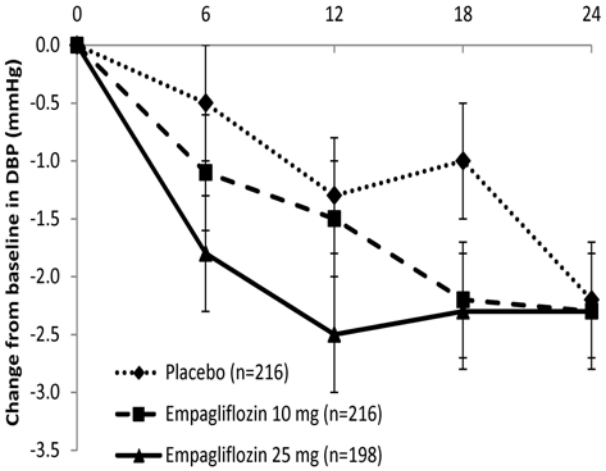
Supplementary Figure 3. Change in blood pressure over time. (A) SBP (mixed model repeated measures [MMRM], full analysis set [FAS], observed cases [OC]); (B) DBP (MMRM, FAS, OC). Data are adjusted mean (SE).

A



Number of analyzed patients					
Placebo	216	216	200	189	171
Empagliflozin 10 mg	216	216	203	191	186
Empagliflozin 25 mg	198	198	193	188	184

B



Number of analyzed patients					
Placebo	216	216	200	189	171
Empagliflozin 10 mg	216	216	203	191	186
Empagliflozin 25 mg	198	198	193	188	184