SUPPLEMENTARY DATA

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 HbA1c 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 HbA1c. For FPG and blood pressure, the MMRM analysis included the baseline value for the endpoint in question as an additional linear covariate.

The models of the logistic regression of categorical change in HbA1c and the proportion of patients with >5% weight loss included baseline HbA1c, 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. Analyses of HbA1c were performed using the parameter in %. For presentation in this manuscript, estimates from the statistical analyses were converted to mmol/mol using the conversion tool at http://www.ngsp.org/.

SUPPLEMENTARY DATA

Supplementary Table 1. Summary of changes in HbA_{1c} and blood glucose at week 24.

	Placebo	**Empagliflozin 10 mg**	**Empagliflozin 25 mg**	**Open-label empagliflozin 25 mg (HbA_{1c} >10% [>86 mmol/mol])**
Primary endpoint				
HbA_{1c} at week 24 (%) [mmol/mol]	7.77 (0.07) [61 (0.8)]	7.22 (0.05) [55 (0.5)]	7.11 (0.06) [54 (0.7)]	7.86 (0.14) [62 (1.5)]
Change from baseline in HbA_{1c} (%) [mmol/mol]	−0.13 (0.05) [–1.4 (0.5)]	−0.70 (0.05) [–7.7 (0.5)]	−0.77 (0.05) [–8.4 (0.5)]	−3.23 (0.22) [–35.3 (2.4)]
Difference vs. placebo [mmol/mol]		−0.57 (0.07) [–6.2 (0.8)]	−0.64 (0.07) [–7.0 (0.8)]	
95% CI [mmol/mol]		–0.70, –0.43 [–7.7, –4.7]	–0.77, –0.50 [–8.4, –5.5]	
p-value		<0.001	<0.001	
Key secondary endpoint				
MDG at week 24 (mmol/l)	9.28 (0.15)	8.79 (0.15)	8.53 (0.14)	8.83 (0.34)
Change from baseline in MDG (mmol/l)	–0.11 (0.11)	–0.54 (0.10)	–0.80 (0.10)	–4.23 (0.53)
Difference vs. placebo		–0.42 (0.15)	–0.69 (0.15)	
95% CI		–0.72, –0.13	–0.99, –0.39	
p-value		0.006	<0.001	
Exploratory endpoints				
Patients with HbA_{1c} ≥7.0% (≥53 mmol/mol) at baseline* who reached HbA_{1c} <7.0% (<53 mmol/mol) at week 24	23 (12.5)	75 (37.7)	74 (38.7)	6 (8.7)
Odds ratio vs. placebo		4.72	4.67	
95% CI		2.74, 8.11	2.71, 8.05	
p-value		<0.001	<0.001	
FPG at week 24 (mmol/l)	8.91 (0.15)	7.43 (0.09)	7.19 (0.08)	8.19 (0.44)
Change from baseline in FPG (mmol/l)	0.35 (0.10)	–1.11 (0.10)	–1.24 (0.10)	–3.02 (0.57)
Difference vs. placebo		–1.47 (0.14)	–1.59 (0.14)	
95% CI		–1.74, -1.20	–1.86, –1.32	
p-value		<0.001	<0.001	

2-hour PPG at week 24 (mmol/l)†	14.80 (0.47)	11.66 (0.35)	11.65 (0.41)	NM
Change from baseline (mmol/l)	0.33 (0.34)	–2.55 (0.35)	–2.47 (0.33)	NM
Difference vs. placebo		–2.88 (0.49)	–2.80 (0.48)	
95% CI		–3.84, –1.92	–3.74, –1.86	
p-value		<0.001	<0.001	

Data are n (%) or mean (SE) except for changes from baseline values in randomised 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). HbA1c <7.0% (<53 mmol/mol) at week 24 analyzed in the FAS using non-completers considered failures approach. CI=confidence interval; NM=not measured. *n=184 for placebo, n=199 for empagliflozin 10 mg, n=191 for empagliflozin 25 mg, n=69 for open-label group. †2-hour PPG was evaluated in a subset of 167 randomized patients who had a valid MTT (n=57 for placebo, n=52 for empagliflozin 10 mg, n=58 for empagliflozin 25 mg) using LOCF.

SUPPLEMENTARY DATA

Supplementary Table 2. Summary of changes in body weight and waist circumference at week 24.

	Placebo	Empagliflozin 10 mg	Empagliflozin 25 mg	Open-label empagliflozin 25 mg (HbA_{1c} >10% [>86 mmol/mol])
Key secondary endpoint				
Body weight at week 24 (kg)	79.33 (1.28)	79.51 (1.22)	79.71 (1.27)	81.26 (2.72)
Change from baseline in body weight (kg)	−0.45 (0.17)	−2.08 (0.17)	−2.46 (0.17)	−1.91 (0.59)
Difference vs. placebo		−1.63 (0.24)	−2.01 (0.24)	
95% CI		–2.11, –1.15	–2.49, –1.53	
p-value		<0.001	<0.001	
Exploratory endpoints				
Patients with >5% reduction from baseline in body weight at week 24	10 (4.8%)	46 (21.2%)	49 (23.0%)	11 (15.9%)
Odds ratio vs. placebo		5.35	5.86	
95% CI		2.61, 10.94	2.87, 11.95	
p-value		<0.001	<0.001	
Waist circumference at week 24 (cm)	98.76 (0.90)	97.61 (0.92)	98.40 (0.98)	96.62 (1.82)
Change from baseline in waist circumference (cm)	−0.54 (0.25)	−1.55 (0.25)	−1.57 (0.25)	-2.52 (1.26)
Difference vs. placebo		−1.01 (0.35)	−1.04 (0.36)	
95% CI		–1.71, –0.31	–1.74, –0.34	
p-value		0.005	0.004	

Data are n (%) or mean (SE) except for changes from baseline values in randomised groups, which are adjusted mean (SE). Values are from the (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 approach. CI=confidence interval.

SUPPLEMENTARY DATA

Supplementary Table 3. Summary of changes in blood pressure at week 24 (exploratory endpoints).

	Placebo	**Empagliflozin 10 mg**	**Empagliflozin 25 mg**	**Open-label empagliflozin 25 mg (HbA_{1c} >10% [>86 mmol/mol])**
SBP at week 24 (mmHg)	128.5 (1.0)	125.0 (0.9)	124.6 (1.0)	124.2 (1.8)
Change from baseline in SBP (mmHg)	−0.4 (0.7)	−4.5 (0.7)	−5.2 (0.7)	−2.4 (1.6)
Difference vs. placebo		−4.1 (1.0)	−4.8 (1.0)	
95% CI		–6.2, –2.1	–6.9, –2.7	
p-value		<0.001	<0.001	
DBP at week 24 (mmHg)	78.4 (0.6)	77.3 (0.5)	76.9 (0.6)	75.5 (1.1)
Change from baseline in DBP (mmHg)	0.0 (0.5)	−2.0 (0.5)	−1.6 (0.5)	−3.6 (1.3)
Difference vs. placebo		−1.9 (0.7)	−1.6 (0.7)	
95% CI		−3.3, −0.6	−2.9, −0.2	
p-value		0.006	0.026	
Patients with uncontrolled BP at baseline* who had controlled BP (SBP <130 mmHg and DBP <80 mmHg) at week 24	18 (13.2%)	51 (35.9%)	42 (30.4%)	17 (36.2%)
Odds ratio vs. placebo		3.76	2.95	
95%CI		2.04, 6.92	1.59, 5.50	
p-value		<0.001	<0.001	

Data are n (%) or mean (SE) except for changes 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 controlled BP at week 24 analyzed in the FAS using non-completers considered failures approach. *n=136 for placebo, n=142 for empagliflozin 10 mg, n=138 for empagliflozin 25 mg; n=47 for open-label group.

SUPPLEMENTARY DATA

Supplementary Table 4. Laboratory measurements.

	Placebo		Empagliflozin 10 mg		Empagliflozin 25 mg		Open-label empagliflozin 25 mg (HbA_{1c} >10% [>86 mmol/mol])	
	Baseline	Change from baseline*	Baseline	Change from baseline*	Baseline	Change from baseline*	Baseline	Change from baseline*
Haematocrit (%)†	42.1 (4.3)	−0.8 (3.0)	42.4 (4.4)	2.4 (3.4)	41.9 (4.7)	2.7 (3.4)	43.1 (4.9)	0.8 (3.9)
Uric acid (µmol/l)†	313 (133)	3 (80)	300 (122)	−45 (91)	317 (117)	−56 (86)	234 (115)	7 (76)
eGFR (ml/min/1.73m^2 [MDRD])	89.6 (21.4)	1.0 (11.2)	89.5 (19.6)	0.1 (13.5)	87.8 (19.3)	−1.7 (10.5)	95.5 (20.7)	−0.03 (13.2)
Electrolytes (mmol/l)†								
Sodium	141 (2)	0 (1)	141 (2)	0 (1)	141 (2)	0 (1)	139 (2)	1 (2)
Potassium	4.1 (0.3)	0.0 (0.3)	4.1 (0.3)	0.0 (0.3)	4.1 (0.3)	0.0 (0.3)	4.2 (0.3)	-0.1 (0.4)
Calcium	2.4 (0.1)	0.0 (0.1)	2.4 (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)	0.0 (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)	0.0 (0.1)
Total cholesterol (mmol/l)‡	4.55 (0.07)	0.09 (0.05)	4.50 (0.06)	0.23 (0.05)	4.59 (0.07)	0.21 (0.05)	4.94 (0.11)	0.16 (0.11)
Difference vs. placebo				0.14 (0.07)		0.13 (0.07)		
p-value				0.043		0.071		
HDL cholesterol (mmol/l)‡	1.22 (0.02)	0.00 (0.01)	1.28 (0.02)	0.08 (0.01)	1.28 (0.02)	0.06 (0.01)	1.15 (0.03)	0.03 (0.03)
Difference vs. placebo				0.08 (0.02)		0.06 (0.02)		
p-value				<0.001		0.001		
LDL cholesterol (mmol/l)‡	2.46 (0.06)	0.03 (0.04)	2.40 (0.06)	0.15 (0.04)	2.48 (0.06)	0.15 (0.04)	2.81 (0.10)	0.09 (0.10)
Difference vs. placebo				0.12 (0.06)		0.12 (0.06)		
p-value				0.043		0.032		
Triglycerides (mmol/l)‡	1.96 (0.09)	0.11 (0.08)	1.95 (0.09)	0.00 (0.08)	1.84 (0.08)	−0.04 (0.08)	2.41 (0.22)	0.19 (0.22)
Difference vs. placebo				−0.11 (0.11)		−0.14 (0.11)		
p-value				0.327		0.204		

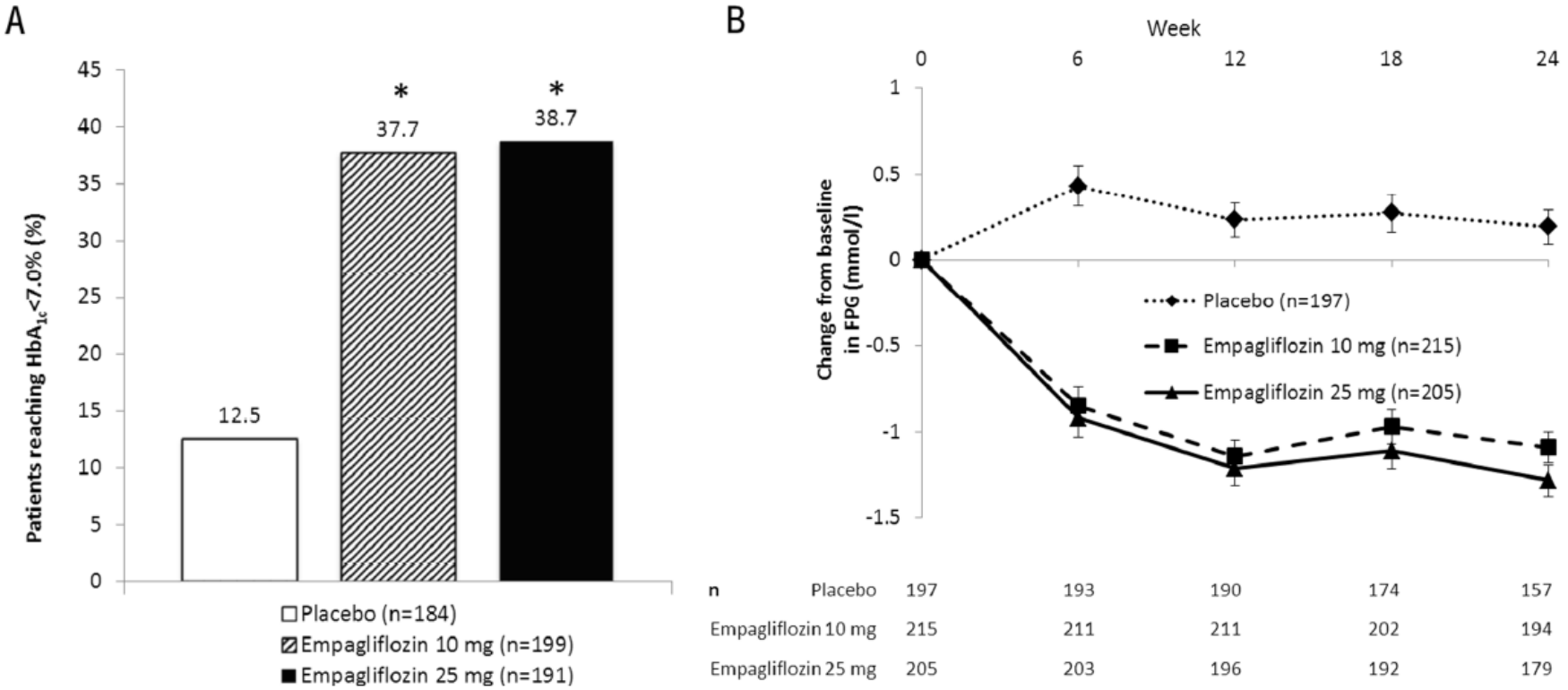
Data are mean (SD) unless otherwise indicated. Treated set (all patients treated with ≥1 dose of study drug, randomised or open-label).

SUPPLEMENTARY DATA

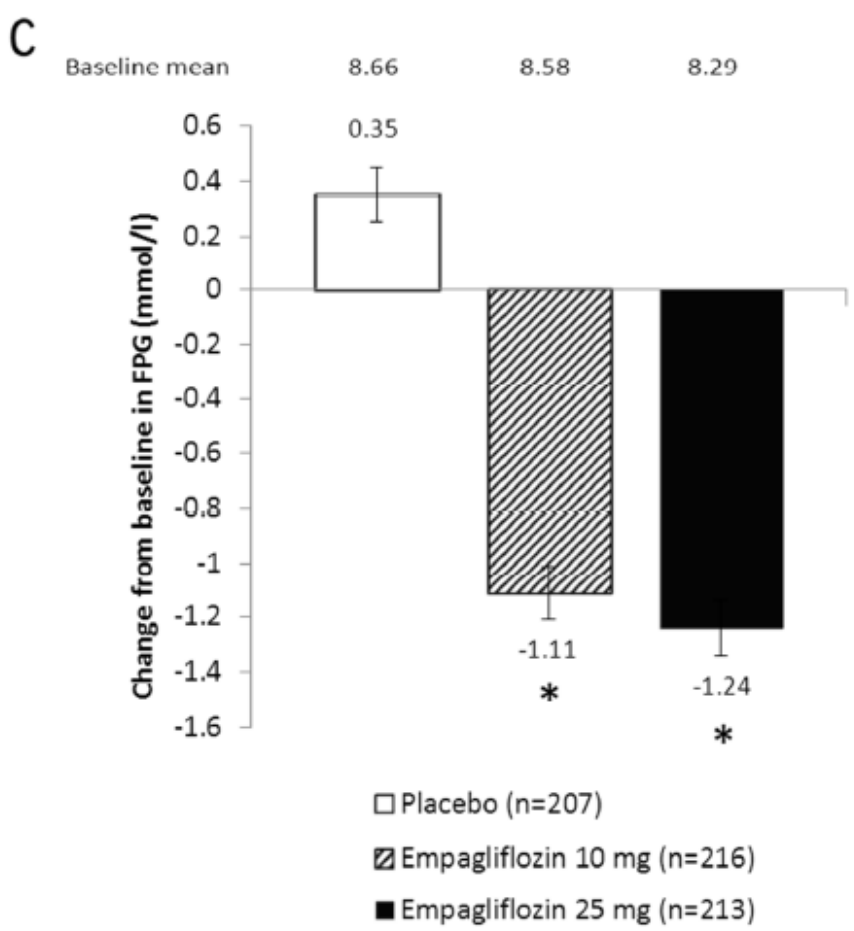
*****Change from baseline at last value on treatment for hematocrit, uric acid and electrolytes; change from baseline at week 24 for eGFR and cholesterol. [†]Normalized to a standard reference range. [‡]Baseline data are mean (SE), change from baseline data are adjusted mean (SE) for randomized groups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

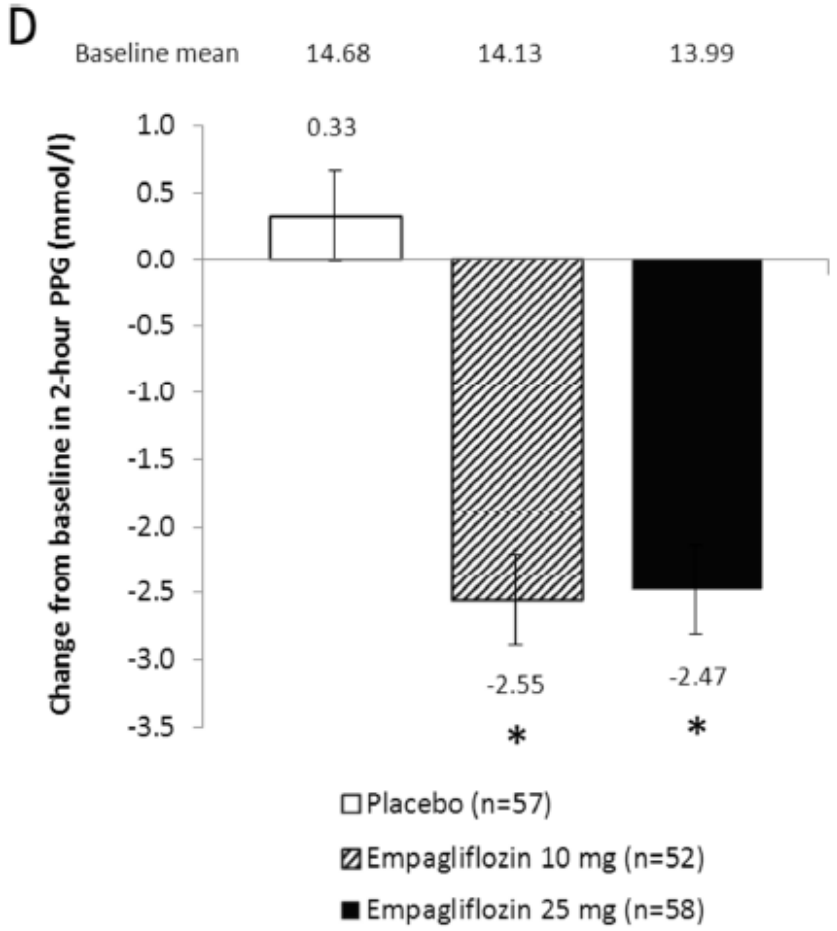
SUPPLEMENTARY DATA

Supplementary Figure 1. (A) Percentage of patients in randomized groups with HbA_{1c} ≥7.0% (≥53 mmol/mol) at baseline who reached HbA_{1c} <7.0% (<53 mmol/mol) 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.



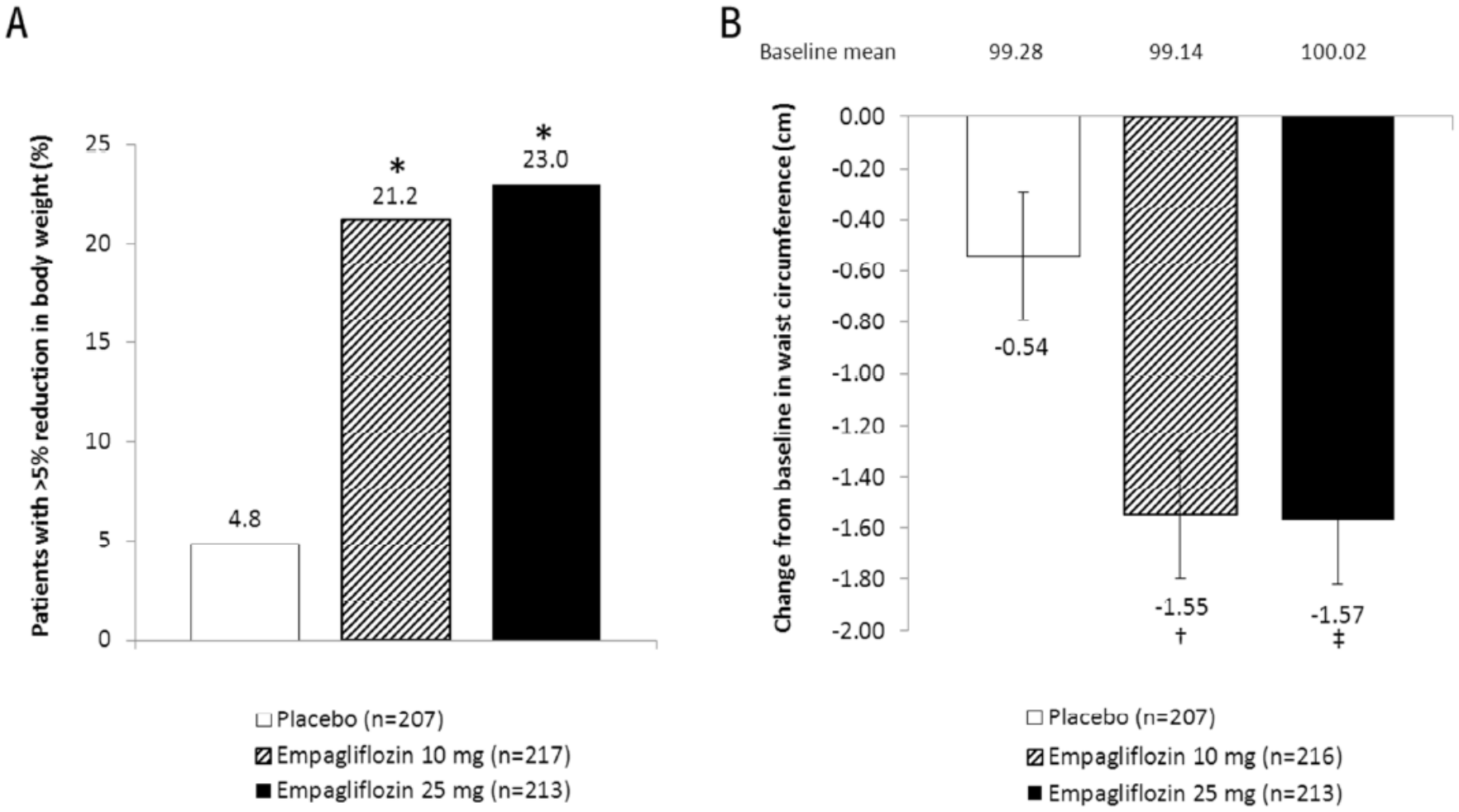
SUPPLEMENTARY DATA





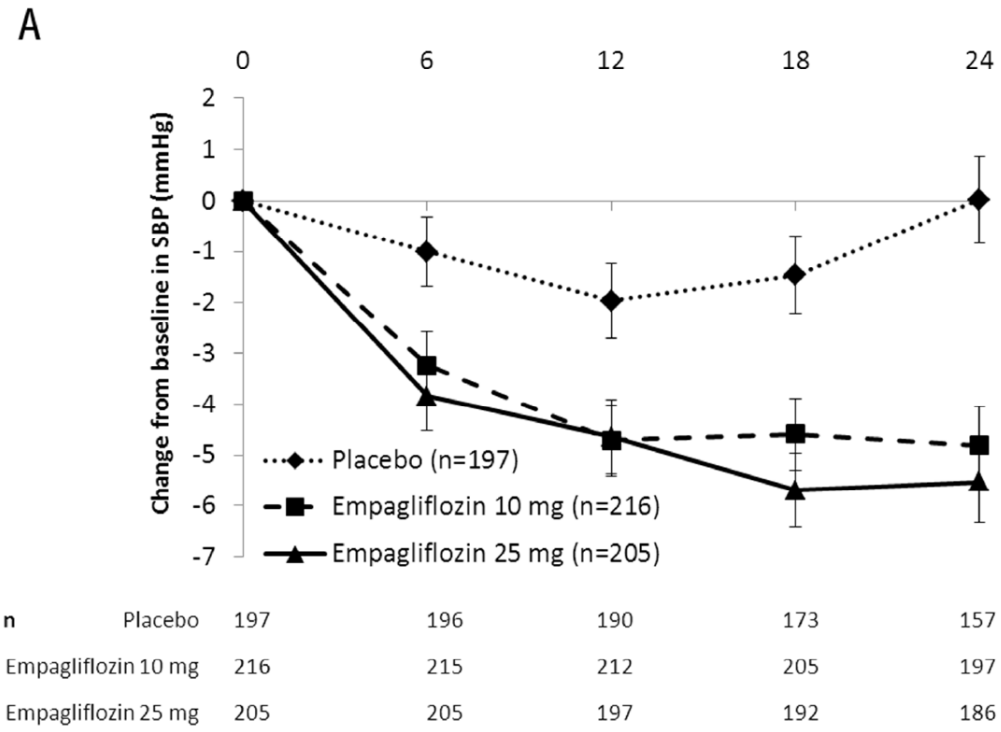
SUPPLEMENTARY DATA

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=0.005 vs. placebo; ‡p=0.004 vs. placebo.

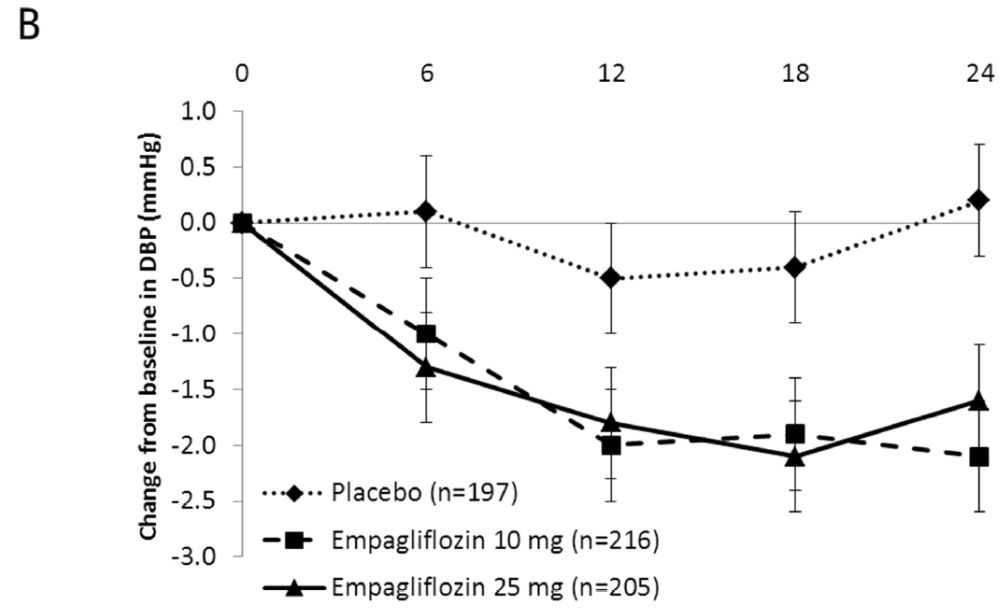


SUPPLEMENTARY DATA

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).



n						
	Placebo	197	196	190	173	157
	Empagliflozin 10 mg	216	215	212	205	197
	Empagliflozin 25 mg	205	205	197	192	186



n						
	Placebo	197	196	190	173	157
	Empagliflozin 10 mg	216	215	212	205	197
	Empagliflozin 25 mg	205	205	197	192	186