

SUPPLEMENTARY DATA

Supplementary Table 1. Pre-treatment demographics and characteristics (open-label FAS)

	Linagliptin 5 mg and metformin (n = 564)
Male, <i>n</i> (%)	348 (61.7)
Age (years)	55.2 (9.9)
Race, <i>n</i> (%)	
White	331 (58.7)
Asian	131 (23.2)
Other	102 (18.1)
Time since diagnosis of type 2 diabetes, <i>n</i> (%)	
≤1 year	46 (8.2)
>1 to 5 years	174 (30.9)
>5 to 10 years	196 (34.8)
>10 years	148 (26.2)
HbA _{1c} (%)	8.95 (0.81)
HbA _{1c} (mmol/mol)	74 (8.9)
HbA _{1c} , <i>n</i> (%)	
<8.5%	174 (30.9)
≥8.5%	390 (69.1)
FPG (mmol/L)*	193.1 (45.3)
Weight (kg)	85.3 (20.5)
BMI (kg/m ²)	30.4 (5.8)
SBP (mmHg)*	133.7 (15.9)
DBP (mmHg)*	81.5 (9.2)
eGFR (mL/min/1.73 m ² [MDRD])	93.2 (19.1)
eGFR (MDRD), <i>n</i> (%)	
≥90 mL/min/1.73m ²	293 (52.0)
60 to <90 mL/min/1.73m ²	263 (46.6)
<60 mL/min/1.73m ²	8 (1.4)

Data are mean (SD), unless otherwise stated, in the open-label FAS (patients treated with one or more doses of study drug during the open-label period and who had a pre-treatment and one or more on-treatment HbA_{1c} measurements during the open-label period). *FPG, *n* = 540; SBP and DBP, *n* =563

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Supplementary Table 2. Analyses of HbA_{1c}, FPG, and weight at week 24 using ANCOVA analyses in the FAS (LOCF).

	Linagliptin 5 mg and metformin		
	Placebo	Empagliflozin 10 mg	Empagliflozin 25 mg
HbA_{1c}, <i>n</i>	108	109	110
Adjusted mean (SE) change from baseline in HbA _{1c} at week 24, % (mmol/mol)	0.14 (0.08) (1.5 [0.9])	-0.66 (0.08) (-7.2 [0.9])	-0.56 (0.08) (-6.1 [0.9])
Adjusted mean (95% CI) difference vs. placebo, % (mmol/mol)	–	-0.79 (-1.01, -0.57) (-8.7 [-11.1, -6.3]) <i>P</i> < 0.001	-0.69 (-0.91, -0.47) (-7.6 [-10.0, -5.2]) <i>P</i> < 0.001
FPG, <i>n</i>	108	109	110
Adjusted mean (SE) change from baseline in FPG at week 24, mmol/L	0.4 (0.2)	-1.4 (0.2)	-1.7 (0.2)
Adjusted mean (95% CI) difference vs. placebo	–	-1.9 (-2.4, -1.4) <i>P</i> < 0.001	-2.1 (-2.6, -1.6) <i>P</i> < 0.001
Weight, <i>n</i>	108	109	110
Adjusted mean (SE) change from baseline in weight at week 24, kg	-0.3 (0.2)	-3.0 (0.2)	-2.5 (0.2)
Adjusted mean (95% CI) difference vs. placebo	–	-2.7 (-3.4, -2.0) <i>P</i> < 0.001	-2.2 (-2.8, -1.5) <i>P</i> < 0.001

n, patients analyzed

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Supplementary Table 3. AEs during the open-label period

	Linagliptin 5 mg and metformin (n = 606)
One or more AEs	296 (48.8)
One or more drug-related* AEs	31 (5.1)
One or more AEs leading to discontinuation	10 (1.7)
One or more severe AEs	13 (2.1)
One or more serious AEs	18 (3.0)
Deaths	0
Special interest categories	
Confirmed hypoglycemia [†]	4 (0.7)
Events requiring assistance	0
Events consistent with UTI [‡]	30 (5.0)
Male	4 (1.1)
Female	26 (11.2)
Events consistent with genital infection [#]	2 (0.3)
Male	1 (0.3)
Female	1 (0.4)
Hypersensitivity reactions [¶]	19 (3.1)
Pancreatitis [§]	0

Data are n (%) in the open-label treated set (patients who received at least one dose of study drug during the open-label period including the placebo-add-on period).

*As reported by the investigator. [†]Plasma glucose ≤ 3.9 mmol/L and/or requiring assistance. [‡]Based on 79 MedDRA preferred terms. [#]Based on 88 MedDRA preferred terms. [¶]Based on 236 MedDRA preferred terms. [§]Based on 18 MedDRA preferred terms.

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Supplementary Table 4. Laboratory results (double-blind period)

	Linagliptin 5 mg and metformin					
	Placebo		Empagliflozin 10 mg		Empagliflozin 25 mg	
	Baseline	Change from baseline*	Baseline	Change from baseline*	Baseline	Change from baseline*
Hematocrit, %	42.7 (5.1)	0.2 (3.9)	42.3 (5.4)	3.3 (3.6)	42.1 (4.4)	4.2 (3.6)
Uric acid, μmol/L	310 (118)	8 (88)	301 (124)	-47 (88)	297 (116)	-41 (81)
Serum creatinine, μmol/L	76 (10)	2 (8)	78 (11)	1 (6)	77 (10)	1 (7)
eGFR, mL/min/1.73m ²	93.0 (16.4)	-2.4 (9.3)	90.4 (19.0)	-1.4 (10.8)	93.4 (18.6)	-2.5 (11.6)
Urinary albumin to creatinine ratio (mg/g)	62.3 (154.9)	21.9 (141.7)	87.8 (435.2)	-20.3 (196.5)	91.2 (406.3)	-36.0 (279.2)
Electrolytes, mmol/L						
Sodium	141 (2)	0 (2)	141 (1)	0 (2)	141 (2)	0.0 (2)
Potassium	4.2 (0.3)	0.0 (0.3)	4.2 (0.3)	0.0 (0.3)	4.3 (0.3)	0.0 (0.3)
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)
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)
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)
Total cholesterol (mmol/L)	4.7 (0.1)	-0.1 (0.1)	4.8 (0.1)	0.1 (0.1)	4.7 (0.1)	0.2 (0.1)
Difference vs. placebo			0.2 (0.1) <i>P</i> = 0.095		0.2 (0.1) <i>P</i> = 0.051	
HDL-cholesterol (mmol/L)	1.2 (0.0)	0.0 (0.0)	1.2 (0.0)	0.1 (0.0)	1.2 (0.0)	0.1 (0.0)
Difference vs. placebo			0.1 (0.0) <i>P</i> < 0.001		0.1 (0.0) <i>P</i> = 0.015	
LDL-cholesterol (mmol/L)	2.5 (0.1)	0.0 (0.1)	2.6 (0.1)	0.1 (0.1)	2.5 (0.1)	0.1 (0.1)
Difference vs. placebo			0.1 (0.1)		0.1 (0.1)	

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			<i>P</i> = 0.415		<i>P</i> = 0.129	
Triglycerides (mmol/L)	2.1 (0.1)	0.0 (0.1)	2.1 (0.1)	-0.1 (0.1)	2.0 (0.1)	-0.1 (0.1)
Difference vs. placebo			0.0 (0.2)		0.0 (0.2)	
			<i>P</i> = 0.851		<i>P</i> = 0.806	

Data are mean (SD) in the treated set, except for lipid parameters, which are adjusted mean (SE) in the treated set using observed cases including values after rescue therapy, based on mixed model repeated measures (MMRM) with baseline eGFR, treatment, region, visit, and treatment by visit as fixed effects and baseline HbA_{1c} and the baseline value for lipid parameter in question as linear covariates. Data are normalized to a standard reference range, except for eGFR and lipid parameters. *Change from baseline at last value on treatment, except for eGFR and lipid parameters, which are changes from baseline at week 24.

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Supplementary Table 5. Laboratory results (open-label period)

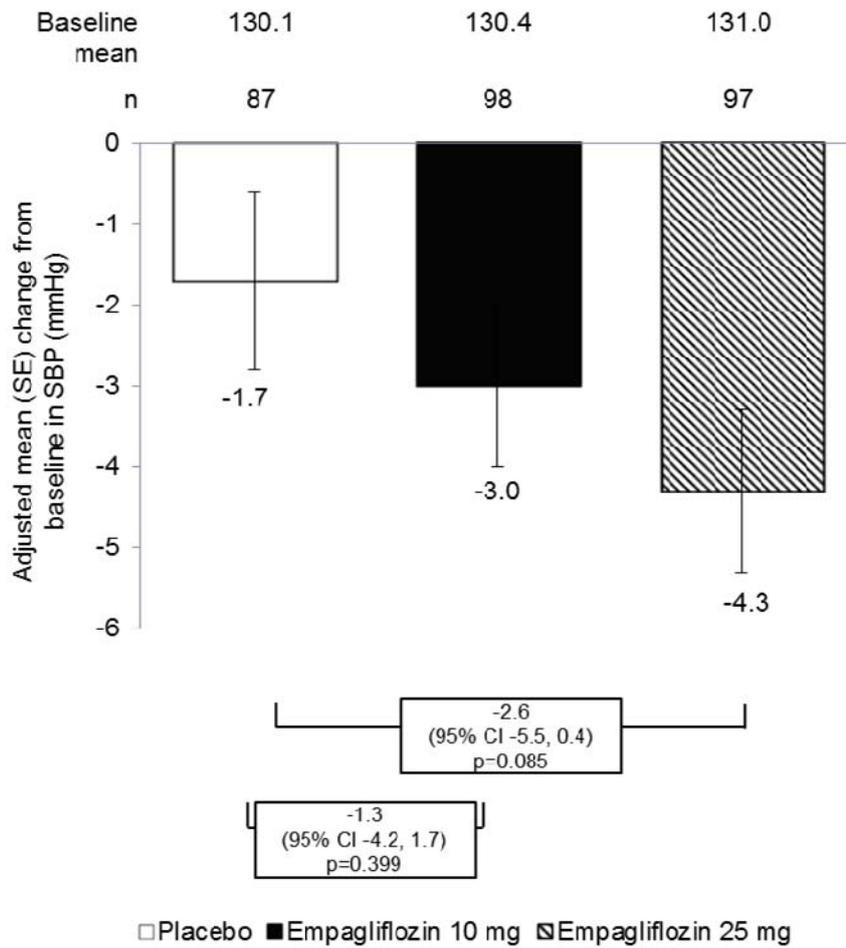
	Linagliptin 5 mg and metformin	
	Pre-treatment	Change from pre-treatment*
Hematocrit, %	43.2 (4.9)	-0.5 (3.4)
Uric acid, $\mu\text{mol/L}$	279 (118)	27 (82)
Serum creatinine, $\mu\text{mol/L}$	77 (11)	1 (7)
eGFR, $\text{mL/min}/1.73\text{m}^2$	93.3 (19.0)	-1.2 (11.4)
Urinary albumin to creatinine ratio (mg/g)	72.7 (238.8)	18.0 (311.3)
Electrolytes, mmol/L		
Sodium	141 (2)	0 (2)
Potassium	4.2 (0.3)	0.0 (0.3)
Calcium	2.4 (0.1)	0.0 (0.1)
Magnesium	0.9 (0.1)	0.0 (0.1)
Phosphate	1.2 (0.1)	0.0 (0.1)
Total cholesterol (mmol/L)	4.8 (1.1)	-0.1 (0.8)
HDL-cholesterol (mmol/L)	1.2 (0.3)	0.0 (0.2)
LDL-cholesterol (mmol/L)	2.6 (0.9)	-0.1 (0.7)
Triglycerides (mmol/L)	2.2 (1.4)	-0.1 (1.0)

Data are mean (SD) in the open-label treated set. Data are normalized to a standard reference range, except for eGFR and lipid parameters.*Change from pre-treatment at last value on treatment, except for eGFR and lipid parameters, which are changes from pre-treatment at week 16.

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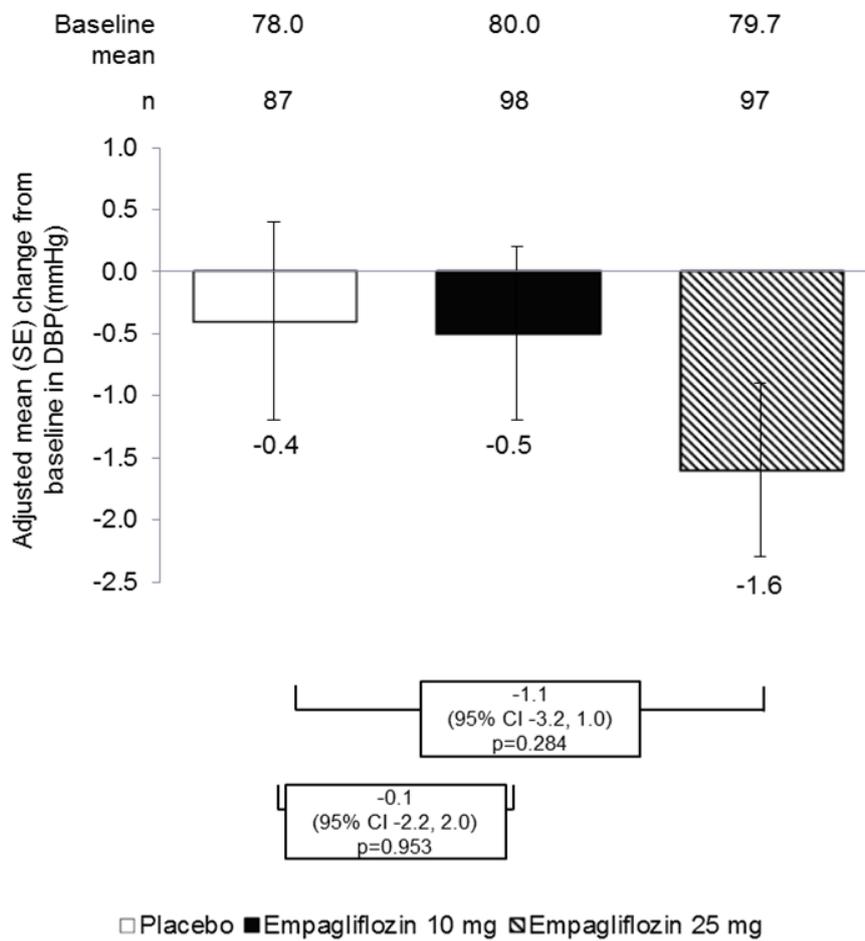
Supplementary Figure 1. Effect on BP. *A:* Change from baseline in SBP at week 24 (MMRM in FAS using OC). *B:* Change from baseline in DBP at week 24 (MMRM in FAS using OC). *C:* SBP over time (MMRM in FAS using OC). *D:* DBP over time (MMRM in FAS using OC). Data are adjusted mean \pm SE, except linagliptin open-label data, which are unadjusted mean. n, number of patients with data at week 24; treatment differences are presented as empagliflozin compared with placebo.

A



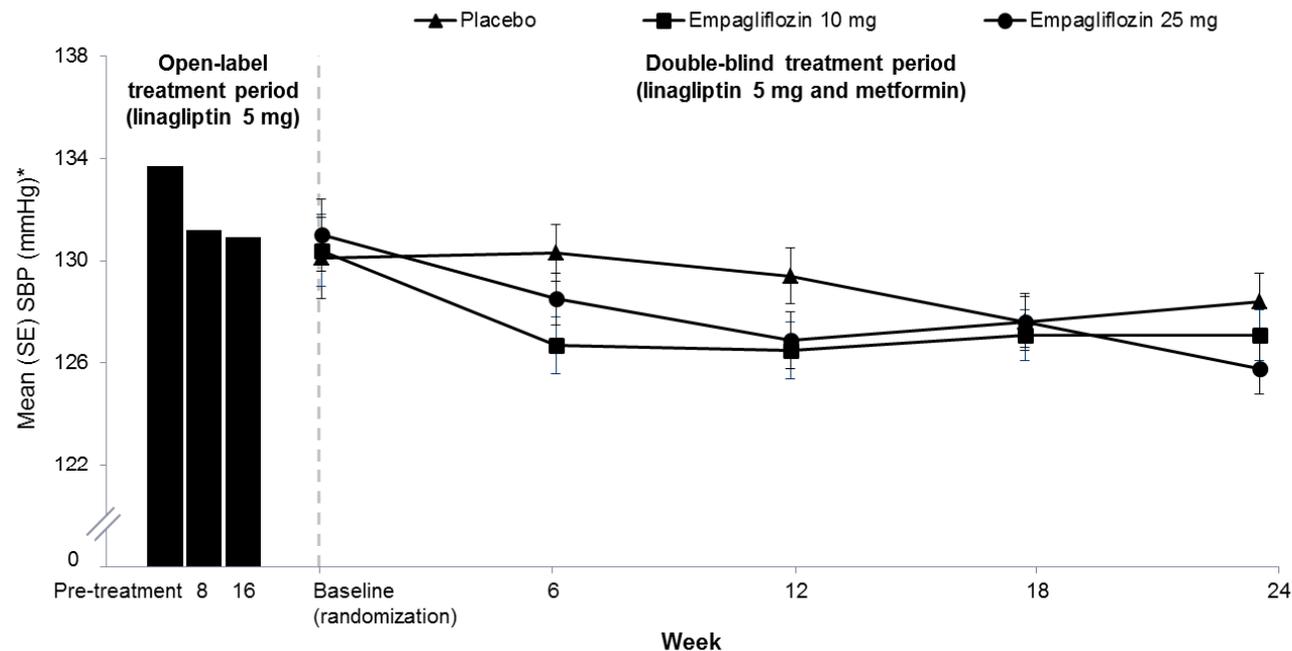
SUPPLEMENTARY DATA

B



SUPPLEMENTARY DATA

C



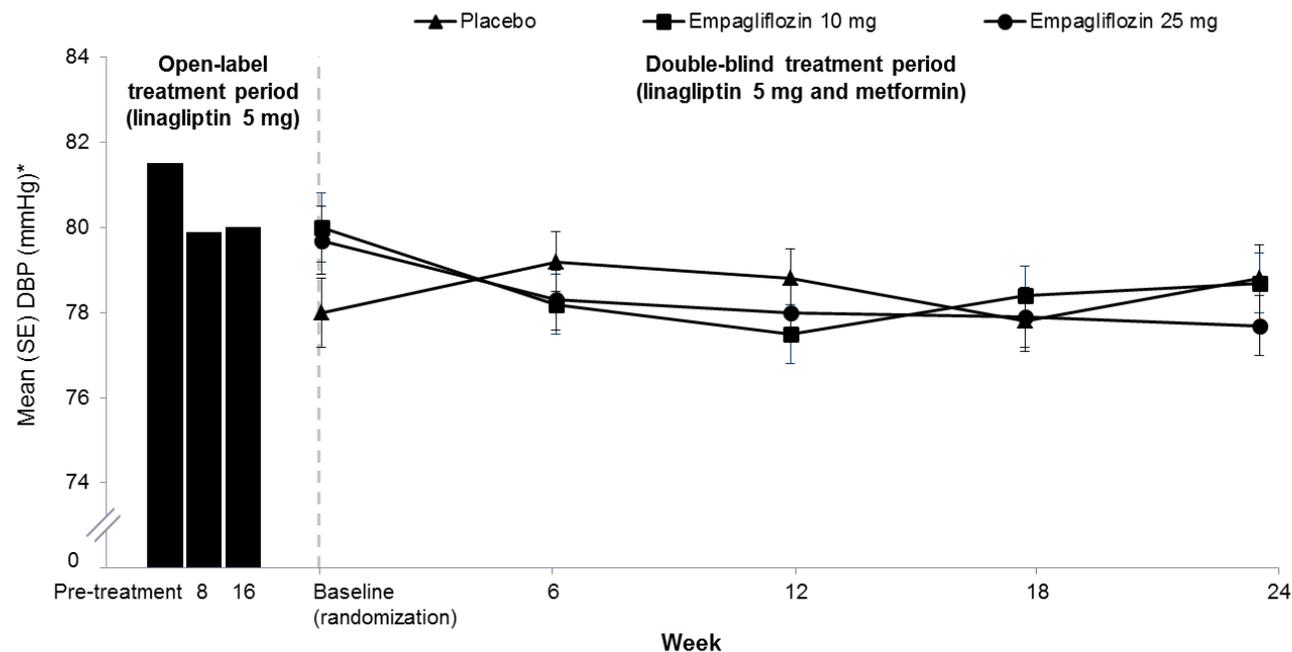
Number of patients

	Pre-treatment	8	16	Baseline (randomization)	6	12	18	24
Linagliptin 5 mg open-label	563	558	545	-	-	-	-	-
Placebo	-	-	-	106	105	102	96	87
Empagliflozin 10 mg	-	-	-	109	108	106	105	98
Empagliflozin 25 mg	-	-	-	110	110	106	103	97

*Data are adjusted mean (SE; MMRM in FAS, observed cases), except for linagliptin 5 mg open-label data which are unadjusted mean (descriptive statistics, open-label FAS using observed cases).

SUPPLEMENTARY DATA

D



Number of patients

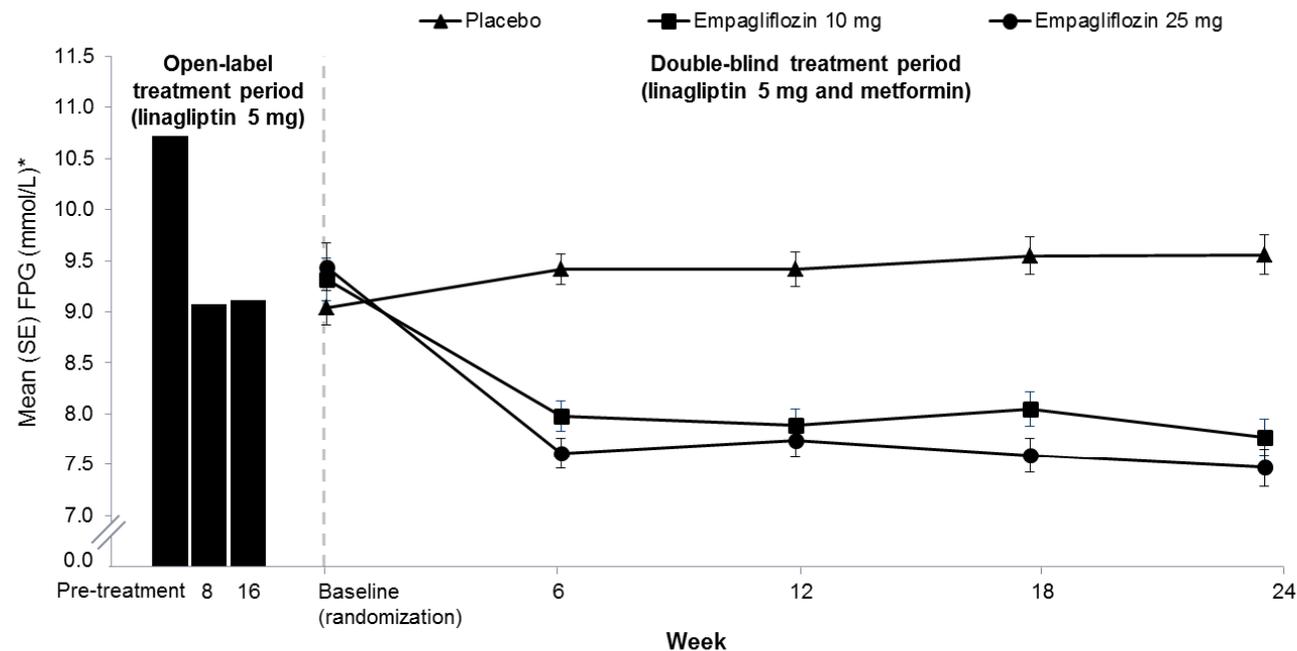
	Pre-treatment	8	16	Baseline (randomization)	6	12	18	24
Linagliptin 5 mg open-label	563	558	545	-	-	-	-	-
Placebo	-	-	-	106	105	103	96	87
Empagliflozin 10 mg	-	-	-	109	108	106	105	98
Empagliflozin 25 mg	-	-	-	110	110	106	103	97

*Data are adjusted mean (SE; MMRM in FAS, observed cases), except for linagliptin 5 mg open-label data which are unadjusted mean (descriptive statistics, open-label FAS using observed cases).

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Supplementary Figure 2. Effect on *A*: FPG over time (MMRM in FAS using OC) and *B*: weight over time (MMRM in FAS using OC). Data are adjusted mean \pm SE, except for open-label linagliptin data, which are unadjusted mean.

A



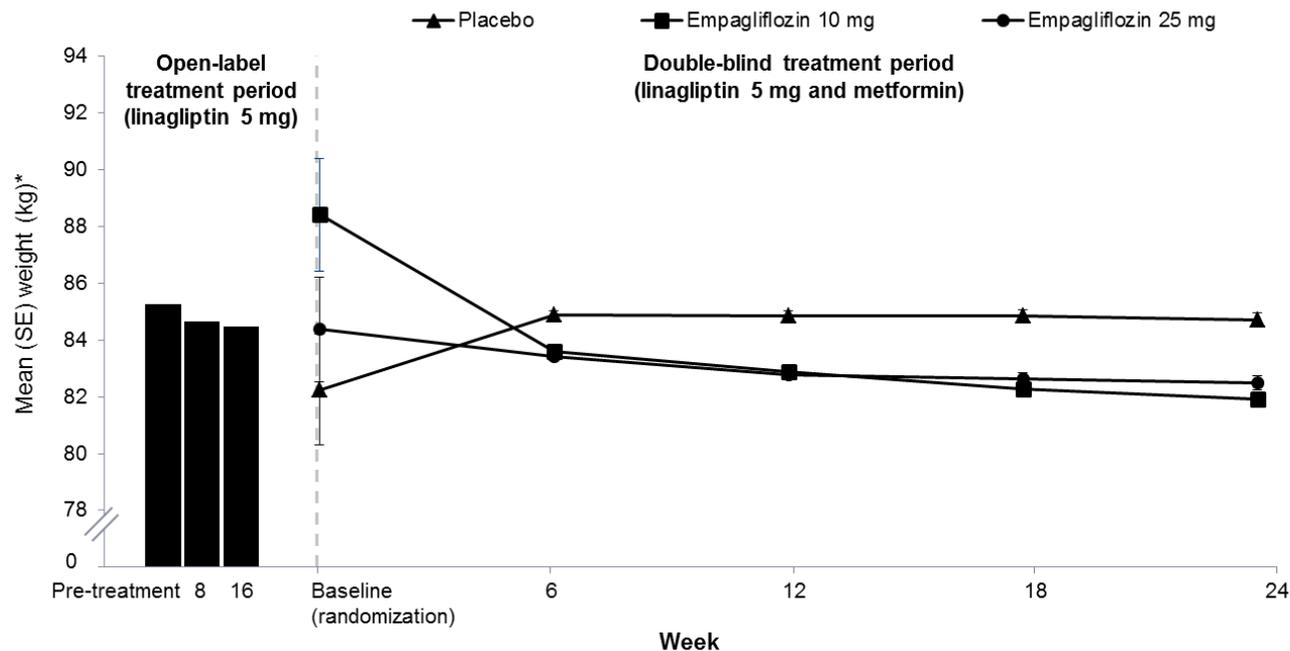
Number of patients

	Pre-treatment	8	16	Baseline (randomization)	6	12	18	24
Linagliptin 5 mg open-label	540	547	515	-	-	-	-	-
Placebo	-	-	-	106	105	103	96	84
Empagliflozin 10 mg	-	-	-	109	105	106	105	97
Empagliflozin 25 mg	-	-	-	109	108	105	104	96

*Data are adjusted mean (SE; MMRM in FAS, observed cases), except for linagliptin 5 mg open-label data which are unadjusted mean (descriptive statistics, open-label FAS using observed cases).

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B



Number of patients

	Pre-treatment	8	16	Baseline (randomization)	6	12	18	24
Linagliptin 5 mg open-label	564	558	544	-	-	-	-	-
Placebo	-	-	-	106	105	103	96	88
Empagliflozin 10 mg	-	-	-	109	107	106	105	98
Empagliflozin 25 mg	-	-	-	110	109	106	103	97

*Data are adjusted mean (SE; MMRM in FAS, observed cases), except for linagliptin 5 mg open-label data which are unadjusted mean (descriptive statistics, open-label FAS using observed cases).

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