SUPPLEMENTARY DATA

Supplementary Table 1. Analyses of HbA1c and fasting plasma glucose (FPG) at week 24 using mixed model repeated measures (MMRM) analysis in the full analysis set using observed cases.

	Empagliflozin 25 mg/ linagliptin 5 mg	Empagliflozin 10 mg/ linagliptin 5 mg	Empagliflozin 25 mg	Empagliflozin 10 mg	Linagliptin 5 mg
HbA1c, n	121	124	120	120	112
Adjusted mean (SE) change from baseline in HbA_{1c} at week 24, % [mmol/mol]	-1.07 (0.07) [-11.7 (0.8)]	-1.26 (0.07) [-13.8 (0.8)]	-0.95 (0.07) [-10.4 (0.8)]	-0.84 (0.07) [-9.2 (0.8)]	-0.69 (0.07) [-7.5 (0.8)]
Adjusted mean (95% CI) difference vs. empagliflozin 25 mg, % [mmol/mol]	-0.12 (-0.32, 0.08) [-1.3 (-3.5, 0.9)] p=0.249	–	–	–	–
Adjusted mean (95% CI) difference vs. empagliflozin 10 mg, % [mmol/mol]	–	-0.41 (-0.62, -0.21) [-4.5 (-6.8, -2.3)] p<0.001	–	–	–
Adjusted mean (95% CI) difference vs. linagliptin 5 mg, % [mmol/mol]	-0.38 (-0.58, -0.18) [-4.2 (-6.4, -1.9)] p<0.001	-0.57 (-0.77, -0.36) [-6.2 (-8.4, -4.0)] p<0.001	–	–	–
FPG, n	122	122	119	120	111
Adjusted mean (SE) change from baseline in FPG at week 24, mg/dL	-29.9 (2.4)	-27.6 (2.4)	-24.6 (2.4)	-24.6 (2.4)	-7.9 (2.5)
Adjusted mean (95% CI) difference vs. empagliflozin 25 mg, mg/dL	-5.3 (-12.0, 1.4) p=0.118	–	–	–	–
Adjusted mean (95% CI) difference vs. empagliflozin 10 mg, mg/dL	–	-3.0 (-9.7, 3.6) p=0.374	–	–	–
Adjusted mean (95% CI) difference vs. linagliptin 5 mg, mg/dL	-22.3 (-28.8, -15.3) p<0.001	-19.8 (-26.5, -13.1) p<0.001	–	–	–

SUPPLEMENTARY DATA

Supplementary Table 2. Analyses of fasting plasma glucose (FPG) at week 52 (analysis of covariance [ANCOVA] in full analysis set using last observation carried forward [LOCF] imputation).

	Empagliflozin 25 mg/ linagliptin 5 mg (n=134)	Empagliflozin 10 mg/ linagliptin 5 mg (n=135)	Empagliflozin 25 mg (n=133)	Empagliflozin 10 mg (n=132)	Linagliptin 5 mg (n=133)
Adjusted mean (SE) change from baseline in FPG at week 52, mg/dL	-25.3 (3.0)	-23.8 (3.0)	-19.9 (3.0)	-16.8 (3.0)	2.8 (3.0)
Adjusted mean (95% CI) difference vs. empagliflozin 25 mg, mg/dL	-5.5 (-13.7, 2.8) p=0.197	–	–	–	–
Adjusted mean (95% CI) difference vs. empagliflozin 10 mg, mg/dL	–	-7.0 (-15.3, 1.3) p=0.096	–	–	–
Adjusted mean (95% CI) difference vs. linagliptin 5 mg, mg/dL	-28.1 (-36.3, -19.8) p<0.001	-26.6 (-34.8, -18.3) p<0.001	–	–	–

Supplementary Table 3. Laboratory results at week 52.

	Empagliflozin 25 mg/ linagliptin 5 mg		Empagliflozin 10 mg/ linagliptin 5 mg		Empagliflozin 25 mg		Empagliflozin 10 mg		Linagliptin 5 mg	
	Baseline	Change from baseline*	Baseline	Change from baseline*	Baseline	Change from baseline*	Baseline	Change from baseline*	Baseline	Change from baseline*
Hematocrit, %	42.8 ± 4.9	4.8 ± 4.3	43.9 ± 4.8	4.2 ± 3.4	43.2 ± 5.3	4.8 ± 3.9	44.2 ± 5.1	4.3 ± 3.6	43.2 ± 4.8	1.3 ± 3.8
Uric acid, µmol/l	292.0 ± 116.0	-56.5 ± 83.9	320.6 ± 117.8	-70.2 ± 87.4	313.5 ± 125.5	-71.4 ± 94.6	309.9 ± 118.4	-60.1 ± 83.9	300.4 ± 123.1	3.0 ± 73.8
Serum creatinine, µmol/l	77.8 ± 12.4	-0.9 ± 8.0	78.7 ± 11.5	0.0 ± 8.8	78.7 ± 10.6	0.0 ± 7.1	78.7 ± 12.4	-0.9 ± 7.1	78.7 ± 10.6	0.0 ± 6.2
eGFR, ml/min/1.73m^2	90.3 ± 19.6		87.8 ± 17.6		88.8 ± 18.5		88.4 ± 19.0		89.7 ± 20.2	
At week 52		0.8 ± 11.6		1.5 ± 11.4		0.2 ± 11.9		1.0 ± 12.5		-0.5 ± 10.9
At follow-up		3.9 ± 12.7		4.0 ± 11.7		3.3 ± 11.1		3.7 ± 12.4		1.5 ± 11.5
Urinary albumin to creatinine ratio (mg/g)	33.5 ± 119.7	-3.9 ± 54.0	30.5 ± 86.1	8.8 ± 87.5	21.9 ± 41.4	2.5 ± 54.8	56.7 ± 340.3	-5.2 ± 44.1	31.9 ± 133.7	35.1 ± 285.6
Electrolytes, mmol/l										
Sodium	141 ± 2	1 ± 2	141 ± 2	1 ± 2	141 ± 2	1 ± 2	141 ± 2	1 ± 2	141 ± 2	0 ± 2
Potassium	4.1 ± 0.3	0.1 ± 0.3	4.1 ± 0.3	-0.0 ± 0.3	4.1 ± 0.3	0.0 ± 0.3	4.1 ± 0.3	0.1 ± 0.3	4.1 ± 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	2.4 ± 0.1	-0.0 ± 0.1	2.4 ± 0.1	-0.0 ± 0.1
Magnesium	1.0 ± 0.1	0.1 ± 0.1	1.0 ± 0.1	0.1 ± 0.1	0.1 ± 0.1	0.1 ± 0.1	1.0 ± 0.1	0.1 ± 0.1	1.0 ± 0.1	-0.0 ± 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	1.2 ± 0.1	0.0 ± 0.1
Total cholesterol (mmol/l)	5.0 ± 0.1	0.1 ± 0.1	5.1 ± 0.1	0.0 ± 0.1	4.9 ± 0.1	0.2 ± 0.1	5.1 ± 0.1	0.2 ± 0.1	5.0 ± 0.1	-0.1 ± 0.1
Difference vs. empagliflozin 25 mg		-0.1 ± 0.1 p = 0.443								
Difference vs. empagliflozin 10 mg				-0.1 ± 0.1 p = 0.164						
Difference vs. linagliptin 5 mg		0.2 ± 0.1 p = 0.036		0.1 ± 0.1 p = 0.135						
HDL-cholesterol (mmol/l)	1.2 ± 0.0	0.1 ± 0.0	1.1 ± 0.0	0.1 ± 0.0	1.2 ± 0.0	0.1 ± 0.0	1.2 ± 0.0	0.1 ± 0.0	1.2 ± 0.0	0.0 ± 0.0
Difference vs. empagliflozin 25 mg		0.0 ± 0.0 p = 0.126								
Difference vs. empagliflozin 10 mg				0.0 ± 0.0 p = 0.507						

Difference vs. linagliptin 5 mg		0.1 ± 0.0 p = 0.004		0.1 ± 0.0 p < 0.001						
LDL-cholesterol (mmol/l)	2.9 ± 0.1	0.0 ± 0.1	3.0 ± 0.1	-0.1 ± 0.1	2.9 ± 0.1	0.1 ± 0.1	3.0 ± 0.1	0.0 ± 0.1	2.9 ± 0.1	-0.1 ± 0.1
Difference vs. empagliflozin 25 mg		-0.0 ± 0.1 p = 0.759								
Difference vs. empagliflozin 10 mg				-0.1 ± 0.1 p = 0.355						
Difference vs. linagliptin 5 mg		0.1 ± 0.1 p = 0.155		0.0 ± 0.1 p = 0.639						
Triglycerides (mmol/l)	2.0 ± 0.1	-0.1 ± 0.1	2.1 ± 0.1	-0.0 ± 0.1	2.0 ± 0.1	-0.1 ± 0.1	2.3 ± 0.1	0.2 ± 0.1	2.1 ± 0.3	-0.2 ± 0.1
Difference vs. empagliflozin 25 mg		0.0 ± 0.1 p = 0.905								
Difference vs. empagliflozin 10 mg				-0.2 ± 0.1 p = 0.227						
Difference vs. linagliptin 5 mg		0.1 ± 0.1 p = 0.534		0.1 ± 0.1 p = 0.292						

Data are mean (SD) in the treated set except for lipid parameters, which are adjusted mean ± standard error based on ANCOVA with treatment, region and eGFR at baseline as fixed effects and baseline HbA1c and the baseline value for the endpoint in question as linear covariates.

Data are normalized to a standard reference range, except for eGFR and lipids.

*Changes from baseline at last value on treatment, except for eGFR and lipids which are changes from baseline at week 52 or follow-up.

SUPPLEMENTARY DATA

Supplementary Table 4. Subjects with shifts in urine albumin to creatinine ratio (mg/g)

	Baseline		
	No albuminuria	**Microalbuminuria**	**Macroalbuminuria**
Empagliflozin 25 mg/linagliptin 5 mg			
At end of treatment, n (%)			
No albuminuria	113 (98.3)	1 (10.0)	0
Microalbuminuria	2 (1.7)	9 (90.0)	2 (50.0)
Macroalbuminuria	0	0	2 (50.0)
Empagliflozin 10 mg/linagliptin 5 mg			
At end of treatment, n (%)			
No albuminuria	104 (93.7)	3 (15.8)	1 (33.3)
Microalbuminuria	6 (5.5)	16 (84.2)	0
Macroalbuminuria	1 (0.9)	0	2 (66.7)
Empagliflozin 25 mg			
At end of treatment, n (%)			
No albuminuria	103 (94.5)	8 (40.0)	0
Microalbuminuria	6 (5.4)	11 (55.0)	0
Macroalbuminuria	0	1 (5.0)	0
Empagliflozin 10 mg			

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At end of treatment, n (%)			
No albuminuria	96 (90.6)	10 (47.6)	0
Microalbuminuria	10 (9.4)	11 (52.4)	1 (33.3)
Macroalbuminuria	0	0	2 (66.7)
Linagliptin 5 mg			
At end of treatment, n (%)			
No albuminuria	100 (90.1)	9 (56.3)	0
Microalbuminuria	10 (9.0)	6 (37.5)	0
Macroalbuminuria	1 (0.9)	1 (6.3)	2 (100.0)

Data are n (%) in the treated set. No albuminuria was defined as urine albumin to creatinine ratio <30 mg/g, microalbuminuria as urine albumin to creatinine ratio ≥30 to <300 mg/g and macroalbuminuria as urine albumin to creatinine ratio ≥300 mg/g.

SUPPLEMENTARY DATA

Supplementary Figure 1. Subject disposition.
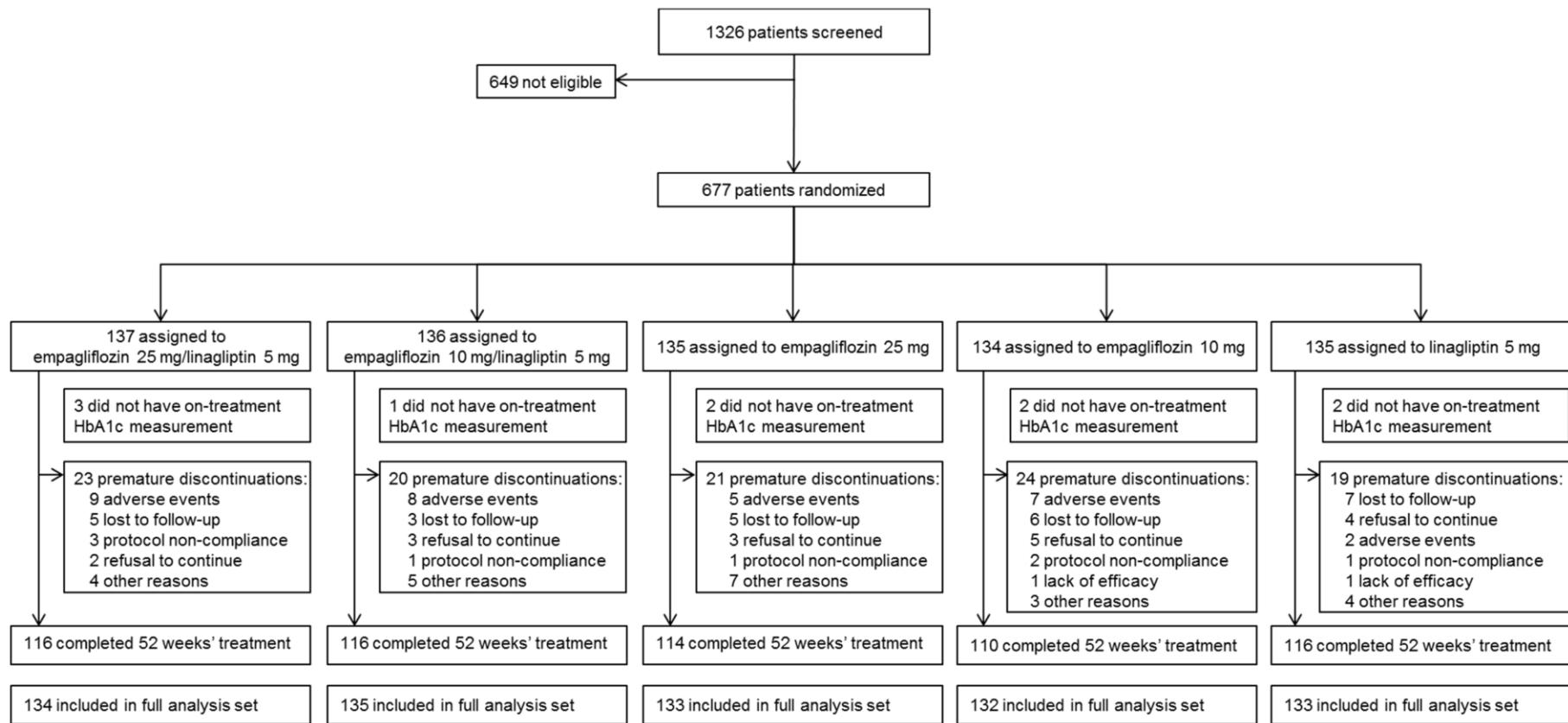
Supplementary Figure 2. Change from baseline in HbA1c at week 24 in subjects with baseline HbA1c <8.5% (<69 mmol/mol) (analysis of covariance [ANCOVA] in the full analysis set using last observation carried forward [LOCF] imputation). Data are adjusted mean ± standard error.

Mean baseline 7.41% 7.53% 7.50% 7.51% 7.63%
(57 mmol/mol) (59 mmol/mol) (58 mmol/mol) (59 mmol/mol) (60 mmol/mol)

- ■ Empagliflozin 25 mg/linagliptin 5 mg (n=88)
- □ Empagliflozin 10 mg/linagliptin 5 mg (n=95)
- ▤ Empagliflozin 25 mg (n=97)
- ⅲ Empagliflozin 10 mg (n=94)
- ◨ Linagliptin 5 mg (n=99)
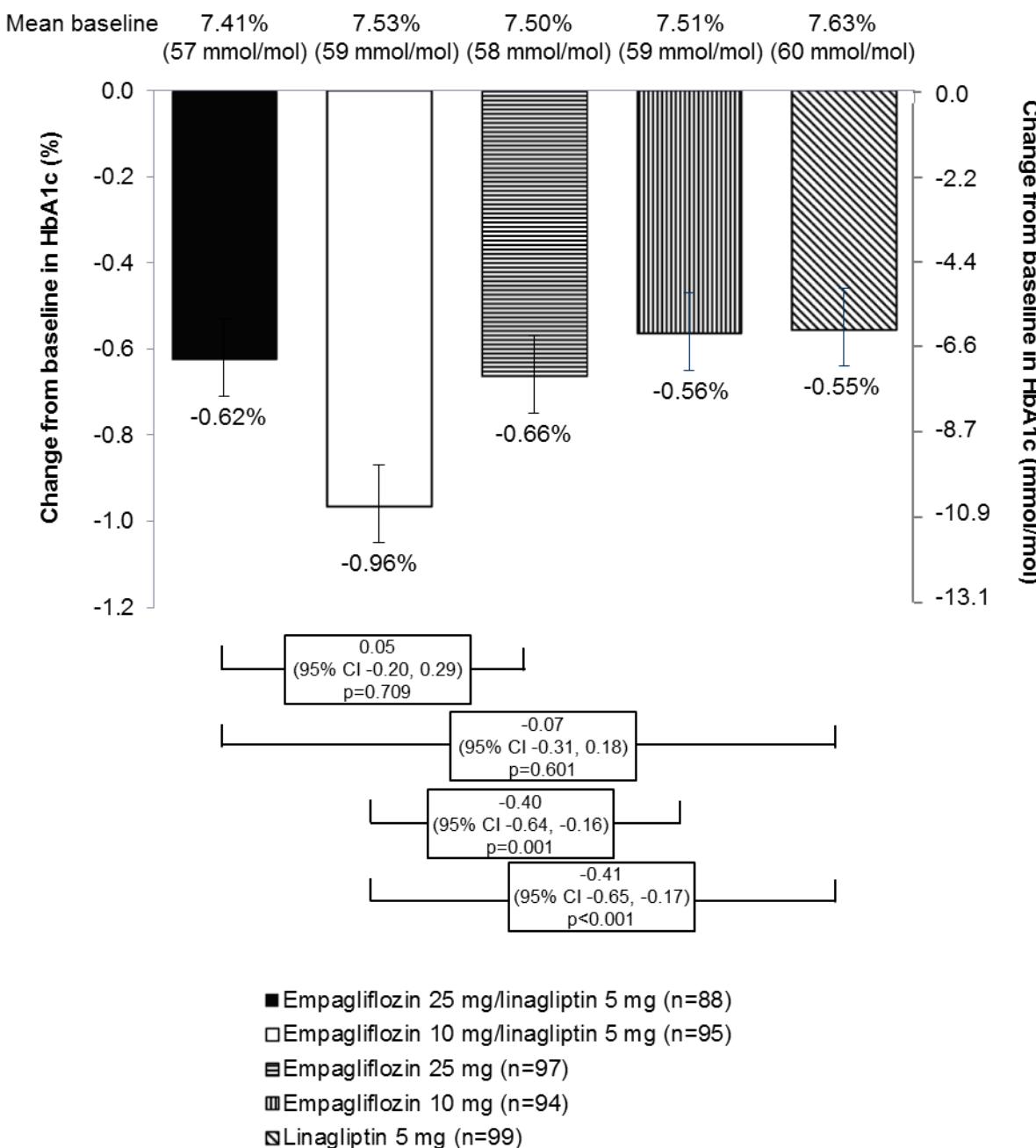
SUPPLEMENTARY DATA

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