

## SUPPLEMENTARY DATA

**Supplementary Table 1.** Sensitivity analyses of changes in HbA<sub>1c</sub>.

	<b>Empagliflozin 12.5 mg bid + metformin 1000 mg bid</b>	<b>Empagliflozin 12.5 mg bid + metformin 500 mg bid</b>	<b>Empagliflozin 5 mg bid + metformin 1000 mg bid</b>	<b>Empagliflozin 5 mg bid + metformin 500 mg bid</b>	<b>Empagliflozin 25 mg qd</b>	<b>Empagliflozin 10 mg qd</b>	<b>Metformin 1000 mg bid</b>	<b>Metformin 500 mg bid</b>
<b>MMRM, PPS (OC), n</b>	145	138	141	145	135	150	133	136
Change from baseline in HbA <sub>1c</sub> at week 24 (%)	-2.13 ± 0.08	-1.97 ± 0.09	-2.15 ± 0.08	-1.97 ± 0.08	-1.39 ± 0.09	-1.36 ± 0.08	-1.84 ± 0.09	-1.21 ± 0.09
Difference versus metformin 1000 mg bid (95% CI)	-0.29 (-0.53, -0.05)		-0.31 (-0.55, -0.07)					
p-value	0.018		0.011					
Difference versus empagliflozin 25 mg qd (95% CI)	-0.73 (-0.97, -0.50)	-0.58 (-0.82, -0.34)						
p-value	<0.001	<0.001						
Difference versus metformin 500 mg bid (95% CI)		-0.77 (-1.01, -0.53)		-0.76 (-1.00, -0.53)				
p-value		<0.001		<0.001				
Difference versus empagliflozin 10 mg qd (95% CI)			-0.79 (-1.03, -0.56)	-0.61 (-0.84, -0.38)				
p-value			<0.001	<0.001				
<b>MMRM, FAS-completers (OC), n</b>	159	149	151	151	140	156	146	142
Change from baseline in HbA <sub>1c</sub> at week 24 (%)	-2.11 ± 0.08	-1.93 ± 0.08	-2.12 ± 0.08	-1.97 ± 0.08	-1.40 ± 0.09	-1.35 ± 0.08	-1.81 ± 0.08	-1.23 ± 0.08
Difference versus metformin 1000 mg bid (95% CI)	-0.30 (-0.53, -0.07)		-0.31 (-0.54, -0.08)					
p-value	0.010		0.009					
Difference versus empagliflozin 25 mg qd (95% CI)	-0.71 (-0.94, -0.48)	-0.53 (-0.77, -0.29)						
p-value	<0.001	<0.001						
Difference versus metformin 500 mg bid		-0.71 (-0.94, -0.47)		-0.75 (-0.98, -0.51)				

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(95% CI)								
p-value		<0.001		<0.001				
Difference versus empagliflozin 10 mg qd (95% CI)			-0.76 (-0.99, -0.53)	-0.62 (-0.85, -0.39)				
p-value			<0.001	<0.001				
<b>ANCOVA, FAS (LOCF), n</b>	169	165	167	161	164	169	164	168
Change from baseline in HbA <sub>1c</sub> at week 24 (%)	-2.07 ± 0.08	-1.88 ± 0.08	-2.06 ± 0.08	-1.98 ± 0.08	-1.30 ± 0.08	-1.36 ± 0.08	-1.72 ± 0.08	-1.16 ± 0.08
Difference versus metformin 1000 mg bid (95% CI)	-0.35 (-0.58, -0.13)		-0.35 (-0.57, -0.12)					
p-value	0.002		0.002					
Difference versus empagliflozin 25 mg qd (95% CI)	-0.78 (-1.00, -0.55)	-0.58 (-0.81, -0.36)						
p-value	<0.001	<0.001						
Difference versus metformin 500 mg bid (95% CI)		-0.72 (-0.94, -0.50)		-0.82 (-1.04, -0.59)				
p-value		<0.001		<0.001				
Difference versus empagliflozin 10 mg qd (95% CI)			-0.70 (-0.93, -0.48)	-0.61 (-0.84, -0.39)				
p-value			<0.001	<0.001				

Data are adjusted mean ± SE unless otherwise indicated. ANCOVA, analysis of covariance; FAS, full analysis set; LOCF, last observation carried forward; MMRM, mixed model repeated measures; PPS (per protocol set): patients in the FAS without important protocol violations; FAS-completers: patients in the FAS who completed 23 ± 1 weeks' treatment.

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**Supplementary Table 2.** Changes in blood pressure.

	<b>Empagliflozin 12.5 mg bid + metformin 1000 mg bid</b>	<b>Empagliflozin 12.5 mg bid + metformin 500 mg bid</b>	<b>Empagliflozin 5 mg bid + metformin 1000 mg bid</b>	<b>Empagliflozin 5 mg bid + metformin 500 mg bid</b>	<b>Empagliflozin 25 mg qd</b>	<b>Empagliflozin 10 mg qd</b>	<b>Metformin 1000 mg bid</b>	<b>Metformin 500 mg bid</b>
Number of analyzed patients, n	160	149	150	155	143	156	148	140
<b>SBP</b>								
Baseline (mmHg)	126.9 ± 1.1	127.2 ± 1.1	127.2 ± 1.1	126.3 ± 1.0	128.3 ± 1.2	128.4 ± 1.1	128.4 ± 1.2	128.0 ± 1.1
Week 24 (mmHg)	124.0 ± 1.0	123.7 ± 1.1	123.9 ± 1.2	124.2 ± 1.1	125.6 ± 1.3	125.9 ± 1.0	127.9 ± 1.3	128.6 ± 1.2
Change from baseline at week 24 (mmHg)	-3.2 ± 0.9	-3.2 ± 0.9	-2.9 ± 0.9	-2.2 ± 0.9	-2.4 ± 0.9	-2.2 ± 0.9	-0.2 ± 0.9	0.8 ± 0.9
Difference versus metformin 1000 mg bid (95% CI)	-3.1 (-5.5, -0.6)		-2.8 (-5.3, -0.3)					
p-value	0.015		0.031					
Difference versus empagliflozin 25 mg qd (95% CI)	-0.9 (-3.4, 1.6)	-0.9 (-3.4, 1.7)						
p-value	0.480	0.499						
Difference versus metformin 500 mg bid (95% CI)		-4.0 (-6.5, -1.5)		-3.0 (-5.5, -0.5)				
p-value		0.002		0.021				
Difference versus empagliflozin 10 mg qd (95% CI)			-0.8 (-3.3, 1.7)	-0.0 (-2.5, 2.4)				
p-value			0.528	0.976				
<b>DBP</b>								
Baseline (mmHg)	78.7 ± 0.6	79.2 ± 0.7	78.2 ± 0.7	78.4 ± 0.7	79.4 ± 0.7	79.0 ± 0.7	79.1 ± 0.7	78.6 ± 0.7
Week 24 (mmHg)	76.8 ± 0.7	77.5 ± 0.7	76.4 ± 0.7	76.7 ± 0.7	78.1 ± 0.8	77.0 ± 0.6	78.8 ± 0.7	79.6 ± 0.7
Change from baseline at week 24 (mmHg)	-1.9 ± 0.6	-1.6 ± 0.6	-1.9 ± 0.6	-1.6 ± 0.6	-1.0 ± 0.6	-1.7 ± 0.6	0 ± 0.6	0.6 ± 0.6
Difference versus metformin 1000 mg bid (95% CI)	-1.9 (-3.5, -0.3)		-1.9 (-3.6, -0.3)					
p-value	0.019		0.019					

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Difference versus empagliflozin 25 mg qd (95% CI)	-0.9 (-2.5, 0.7)	-0.7 (-2.3, 0.9)						
p-value	0.254	0.402						
Difference versus metformin 500 mg bid (95% CI)		-2.3 (-3.9, -0.6)		-2.3 (-3.9, -0.6)				
p-value		0.007		0.006				
Difference versus empagliflozin 10 mg qd (95% CI)			-0.2 (-1.8, 1.4)	0.1 (-1.5, 1.6)				
p-value			0.784	0.950				

Baseline and week 24 values are mean  $\pm$  SE. Changes from baseline are adjusted mean (SE) from mixed model repeated measures based on observed cases in the full analysis set. DBP, diastolic blood pressure; SBP, systolic blood pressure.

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**Supplementary Table 3.** Laboratory measurements.

	<b>Empagliflozin 12.5 mg bid + metformin 1000 mg bid</b>	<b>Empagliflozin 12.5 mg bid + metformin 500 mg bid</b>	<b>Empagliflozin 5 mg bid + metformin 1000 mg bid</b>	<b>Empagliflozin 5 mg bid + metformin 500 mg bid</b>	<b>Empagliflozin 25 mg qd</b>	<b>Empagliflozin 10 mg qd</b>	<b>Metformin 1000 mg bid</b>	<b>Metformin 500 mg bid</b>
<sup>†</sup> Hematocrit (%)								
Baseline	44.8 ± 4.6	45.3 ± 5.1	45.7 ± 4.3	45.0 ± 5.2	45.6 ± 5.4	45.4 ± 5.0	45.0 ± 5.3	45.6 ± 4.8
Change from baseline*	1.8 ± 3.3	2.4 ± 3.9	2.2 ± 3.5	2.8 ± 3.8	3.0 ± 3.9	3.1 ± 3.8	-1.5 ± 3.3	-0.4 ± 3.1
<sup>†</sup> Uric acid (μmol/L)								
Baseline	277.2 ± 123.1	283.1 ± 118.4	275.4 ± 127.9	270.1 ± 119.0	278.4 ± 107.7	279.6 ± 114.8	275.4 ± 130.9	283.1 ± 110.6
Change from baseline*	-41.6 ± 91.0	-30.3 ± 96.4	-32.1 ± 79.7	-19.6 ± 91.6	-37.5 ± 85.7	-41.0 ± 85.7	56.5 ± 92.8	32.7 ± 78.5
<sup>2</sup> eGFR (mL/min/1.73m <sup>2</sup> [MDRD])								
Baseline	92.2 ± 19.2	95.0 ± 20.9	93.3 ± 22.0	93.6 ± 22.3	91.8 ± 19.8	94.1 ± 21.4	93.4 ± 20.1	90.8 ± 19.3
Change from baseline*	3.4 ± 16.6	0.3 ± 13.4	2.2 ± 11.5	-0.5 ± 13.8	-0.8 ± 11.5	-1.5 ± 12.3	2.1 ± 12.9	-1.7 ± 12.7
<sup>†</sup> Electrolytes (mmol/L)								
<i>Sodium</i>								
Baseline	141 ± 2	141 ± 2	141 ± 2	141 ± 2	141 ± 2	141 ± 2	141 ± 2	141 ± 2
Change from baseline*	0 ± 2	0 ± 2	0 ± 2	0 ± 2	0 ± 2	0 ± 2	0 ± 2	0 ± 2
<i>Potassium</i>								
Baseline	4.2 ± 0.3	4.2 ± 0.3	4.2 ± 0.3	4.1 ± 0.3	4.2 ± 0.3	4.1 ± 0.3	4.2 ± 0.3	4.2 ± 0.3
Change from baseline*	0 ± 0.3	0 ± 0.3	0 ± 0.3	0 ± 0.3	-0.1 ± 0.3	0 ± 0.3	0 ± 0.3	0 ± 0.3
<i>Calcium</i>								
Baseline	2.5 ± 0.1	2.5 ± 0.1	2.4 ± 0.1	2.4 ± 0.1	2.4 ± 0.1	2.4 ± 0.1	2.4 ± 0.1	2.5 ± 0.1
Change from baseline*	0 ± 0.1	0 ± 0.1	0 ± 0.1	0 ± 0.1	0 ± 0.1	0 ± 0.1	0 ± 0.1	0 ± 0.1
<i>Magnesium</i>								
Baseline	1.0 ± 0.1	1.0 ± 0.1	1.0 ± 0.1	1.0 ± 0.1	1.0 ± 0.1	1.0 ± 0.1	1.0 ± 0.1	1.0 ± 0.1
Change from baseline*	0 ± 0.1	0.1 ± 0.1	0 ± 0.1	0.1 ± 0.1	0.1 ± 0.1	0.1 ± 0.1	-0.1 ± 0.1	0 ± 0.1
Total cholesterol (mmol/L)								

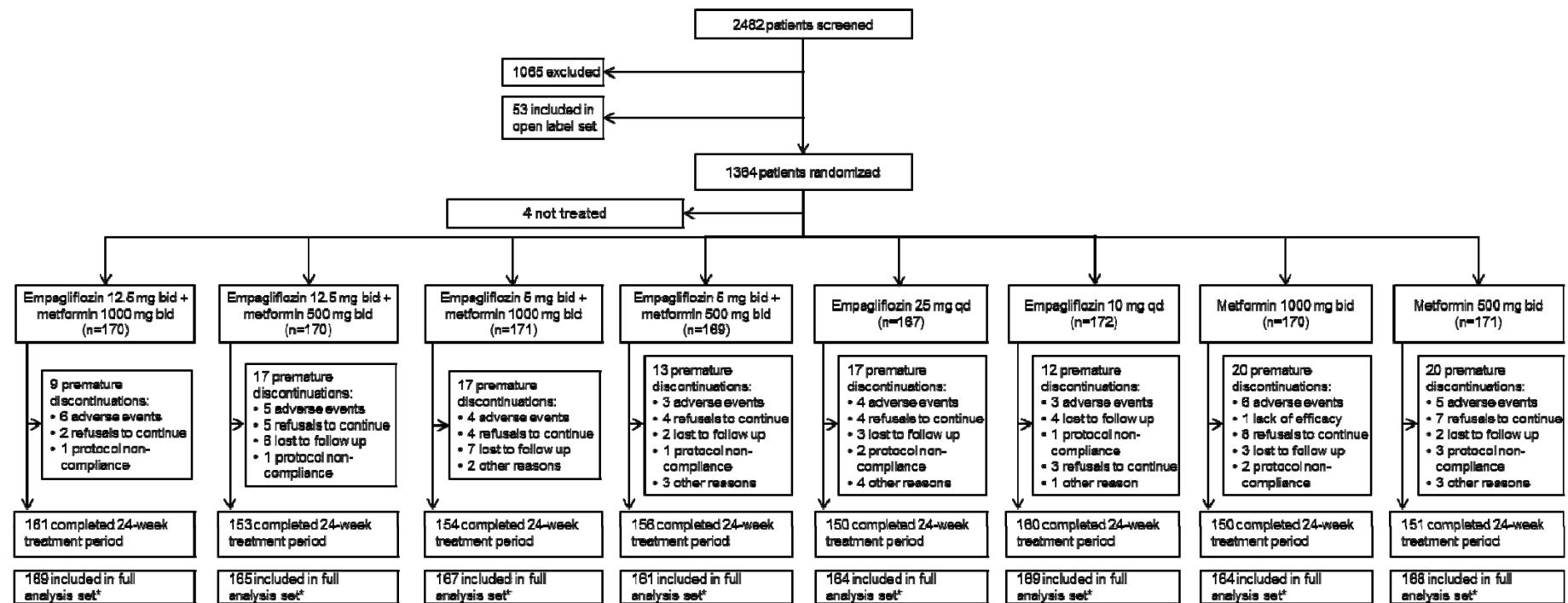
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Baseline	$5.11 \pm 1.60$	$4.71 \pm 1.38$	$4.91 \pm 1.64$	$4.90 \pm 1.87$	$4.74 \pm 1.48$	$4.99 \pm 1.58$	$5.10 \pm 2.20$	$5.01 \pm 1.47$
Change from baseline*	$-0.12 \pm 1.31$	$0.21 \pm 1.28$	$0.05 \pm 1.21$	$0.26 \pm 1.42$	$0.50 \pm 1.28$	$0.09 \pm 1.35$	$-0.22 \pm 1.89$	$0.08 \pm 1.32$
HDL-cholesterol (mmol/L)								
Baseline	$1.10 \pm 0.16$	$1.10 \pm 0.16$	$1.09 \pm 0.14$	$1.11 \pm 0.17$	$1.11 \pm 0.14$	$1.10 \pm 0.16$	$1.12 \pm 0.17$	$1.10 \pm 0.14$
Change from baseline*	$0.06 \pm 0.11$	$0.07 \pm 0.09$	$0.05 \pm 0.10$	$0.06 \pm 0.11$	$0.05 \pm 0.11$	$0.06 \pm 0.13$	$0.02 \pm 0.10$	$0.03 \pm 0.10$
LDL-cholesterol (mmol/L)								
Baseline	$2.36 \pm 0.75$	$2.16 \pm 0.64$	$2.26 \pm 0.68$	$2.23 \pm 0.85$	$2.16 \pm 0.66$	$2.25 \pm 0.72$	$2.32 \pm 0.98$	$2.30 \pm 0.68$
Change from baseline*	$-0.14 \pm 0.57$	$0.06 \pm 0.60$	$-0.06 \pm 0.57$	$0 \pm 0.66$	$0.19 \pm 0.58$	$0.04 \pm 0.55$	$-0.24 \pm 0.83$	$-0.06 \pm 0.59$
Triglycerides (mmol/L)								
Baseline	$1.26 \pm 0.74$	$1.27 \pm 0.84$	$1.32 \pm 1.30$	$1.34 \pm 1.07$	$1.19 \pm 0.80$	$1.39 \pm 1.44$	$1.26 \pm 0.95$	$1.26 \pm 0.71$
Change from baseline*	$-0.01 \pm 1.24$	$-0.13 \pm 0.61$	$-0.03 \pm 0.97$	$0.09 \pm 0.76$	$0.05 \pm 0.70$	$-0.12 \pm 0.92$	$0.19 \pm 1.19$	$0.10 \pm 0.64$

Data are mean  $\pm$  SD. Treated set (patients treated with  $\geq 1$  dose of study drug). \*Change from baseline at last value on treatment for hematocrit, uric acid, electrolytes and cholesterol; change from baseline at week 24 for eGFR. †Normalized to a standard reference range. eGFR, estimated glomerular filtration rate; HDL, high-density lipoprotein; LDL, low-density lipoprotein; MDRD, Modification of Diet in Renal Disease equation.

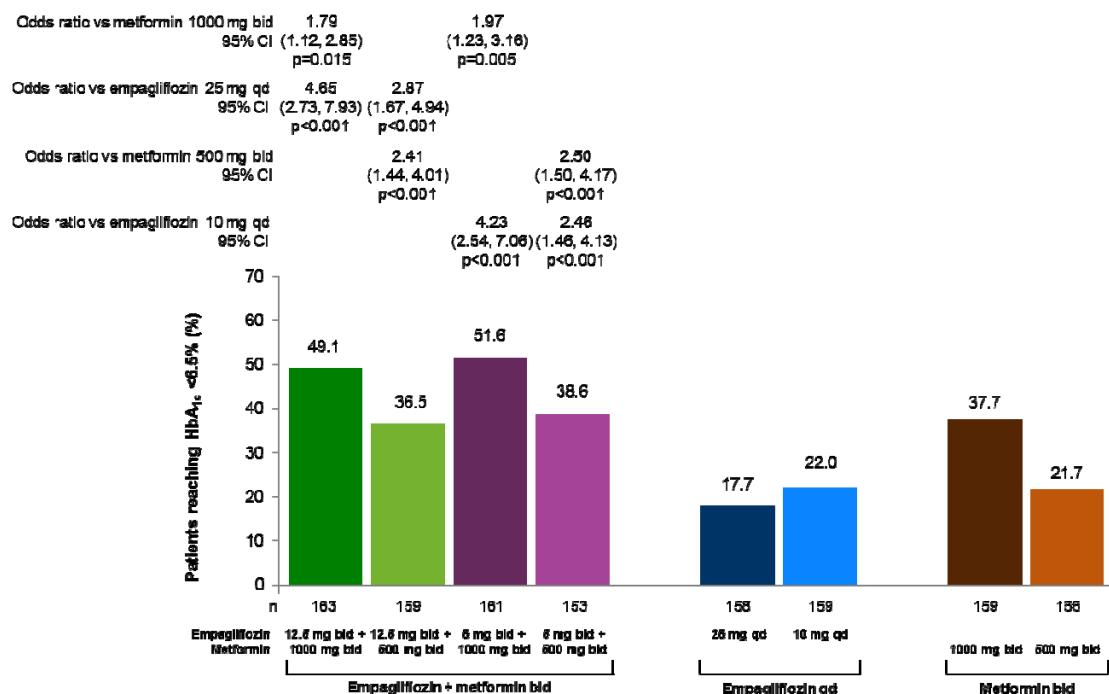
## SUPPLEMENTARY DATA

**Supplementary Figure 1.** Study flow.



## SUPPLEMENTARY DATA

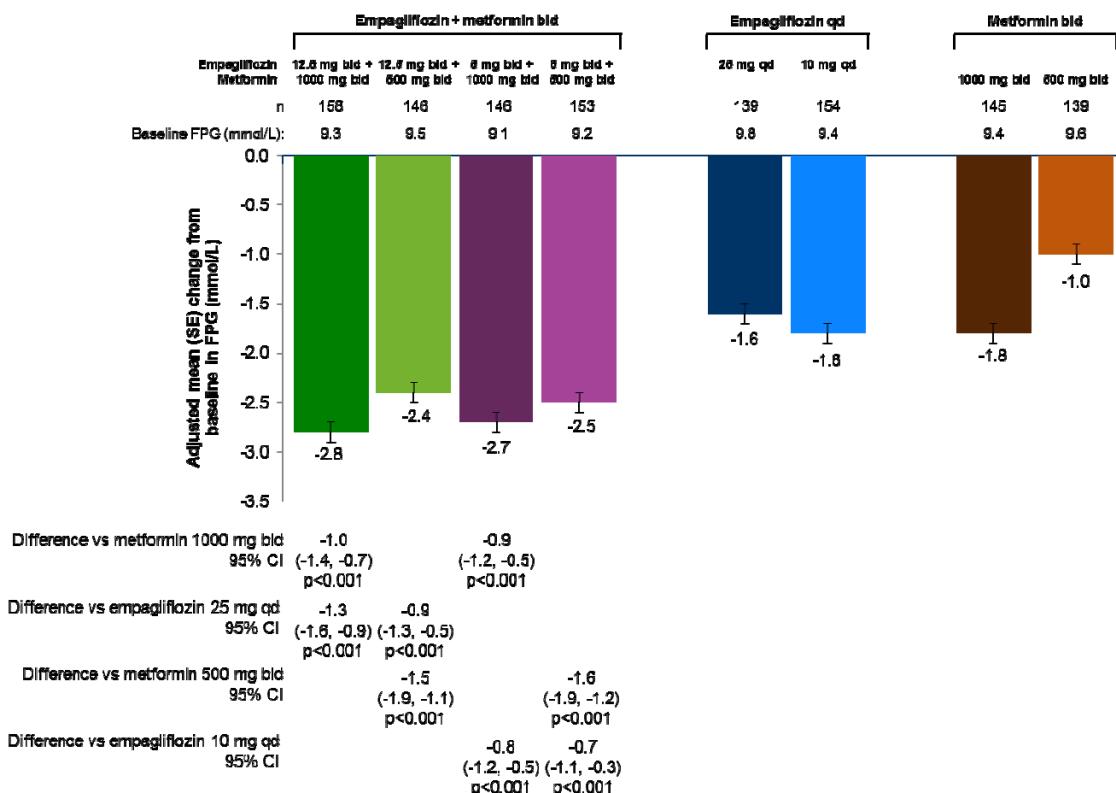
**Supplementary Figure 2.** Percentage of patients with HbA<sub>1c</sub> ≥7% at baseline who had HbA<sub>1c</sub> <6.5% at week 24 (full analysis set, logistic regression with non-completers considered failure).



## SUPPLEMENTARY DATA

**Supplementary Figure 3.** Changes in fasting plasma glucose (FPG). **(A)** Change from baseline in FPG at week 24 (mixed model repeated measures [MMRM] in the full analysis set [FAS], observed cases [OC]); **(B)** FPG over 24 weeks (MMRM, FAS, OC).

**A**



**B**

