

SUPPLEMENTAL MATERIAL

Supplemental Table I

Baseline characteristics of patients with prediabetes vs those with normoglycemia

	Prediabetes (n=1268)		Normoglycemia (n=606)	
	Empagliflozin (n=632)	Placebo (n=636)	Empagliflozin (n=304)	Placebo (n=302)
Age — yr	68.1±11.2	67.1±11.7	66.5±12.5	64.7±12.6
Female sex — no. (%)	147 (23.3)	163 (25.6)	80 (26.3)	75 (24.8)
Race — no. (%)				
White	447 (70.7)	443 (69.7)	232 (76.3)	222 (73.5)
Black	46 (7.3)	46 (7.2)	20 (6.6)	25 (8.3)
Asian	112 (17.7)	125 (19.7)	42 (13.8)	35 (11.6)
Other or Missing	27 (4.3)	22 (3.5)	10 (3.3)	20 (6.6)
Region — no. (%)				
North America	81 (12.8)	70 (11.0)	24 (7.9)	28 (9.3)
Latin America	207 (32.8)	213 (33.5)	123 (40.5)	118 (39.1)
Europe	231 (36.6)	231 (36.3)	113 (37.2)	118 (39.1)
Asia	90 (14.2)	93 (14.6)	35 (11.5)	31 (10.3)
Other	23 (3.6)	29 (4.6)	9 (3.0)	7 (2.3)
NYHA functional classification — no. (%)				
II	498 (78.8)	498 (78.3)	244 (80.3)	235 (77.8)
III	132 (20.9)	136 (21.4)	58 (19.1)	66 (21.9)
IV	2 (0.3)	2 (0.3)	2 (0.7)	1 (0.3)
Body mass index	27.3±5.3	26.9±5.2	26.9±5.3	27.2±5.1
Heart rate — beats/min	70.1±11.7	71.1±12.3	68.9±11.5	70.5±11.8
Systolic blood pressure — mm Hg	121.3±15.3	118.9±14.4	123.5±17.1	122.0±15.9
HbA1c, %	5.9±0.3	6.0±0.2	5.3±0.3	5.3±0.3
Left ventricular ejection fraction — %	27.9±5.8	27.1±6.2	27.9±6.2	27.4±5.6
Median NT-proBNP (IQR) — pg/mL	1921 (1083, 3276)	1866 (1158, 3654)	1729 (1034, 3238)	1926 (1164, 3349)
Principal cause of heart failure — no. (%)				
Ischemic	303 (47.9)	317 (49.8)	126 (41.4)	116 (38.4)
Nonischemic	329 (52.1)	319 (50.2)	178 (58.6)	181 (59.9)
Medical history — no. (%)				
Hospitalization for heart failure in last 12 months	174 (27.5)	178 (28.0)	87 (28.6)	82 (27.2)
Atrial fibrillation*	251 (39.7)	261 (41.0)	103 (33.9)	121 (40.1)
Hypertension	420 (66.5)	430 (67.6)	199 (65.5)	190 (62.9)
Estimated GFR				
Mean— ml/min/1.73 m ²	61.6±20.7	62.0±20.6	64.8±21.8	65.1±21.7
Rate of <60 ml/min/1.73 m ² — no./total no. (%)	300 (47.5)	294 (46.2)	459 (49.5)	480 (51.7)
Device therapy — no. (%)				
Implantable cardioverter-defibrillator [†]	232 (36.7)	198 (31.1)	88 (28.9)	96 (31.8)
Cardiac resynchronization therapy [‡]	93 (14.7)	69 (10.8)	24 (7.9)	36 (11.9)
Heart failure medication — no. (%)				
ACE inhibitor	311 (49.2)	278 (43.7)	140 (46.1)	147 (48.7)

ARB [§]	148 (23.4)	151 (23.7)	65 (21.4)	76 (25.2)
ARNi	112 (17.7)	139 (21.9)	66 (21.7)	54 (17.9)
Diuretic	535 (84.7)	564 (88.7)	244 (80.3)	245 (81.1)
Mineralocorticoid Receptor Antagonist	447 (70.7)	468 (73.6)	220 (72.4)	226 (74.8)
Beta blocker	602 (95.3)	600 (94.3)	288 (94.7)	285 (94.4)
Glucose lowering therapy – no. (%)				
Any glucose lowering therapy	6 (0.9)	5 (0.8)	2 (0.7)	2 (0.3)
Biguanide	6 (0.9)	4 (0.6)	1 (0.3)	0
Insulin	0	0	0	0
Sulfonylurea	0	0	0	0
DPP4-inhibitors	0	0	0	0
GLP1 receptor analogues	0	0	0	0

Data given as mean±standard deviation unless otherwise stated

*Atrial fibrillation reported in any ECG before treatment intake or history of atrial fibrillation reported as medical history

†Implantable cardioverter defibrillator with or without cardiac resynchronization therapy.

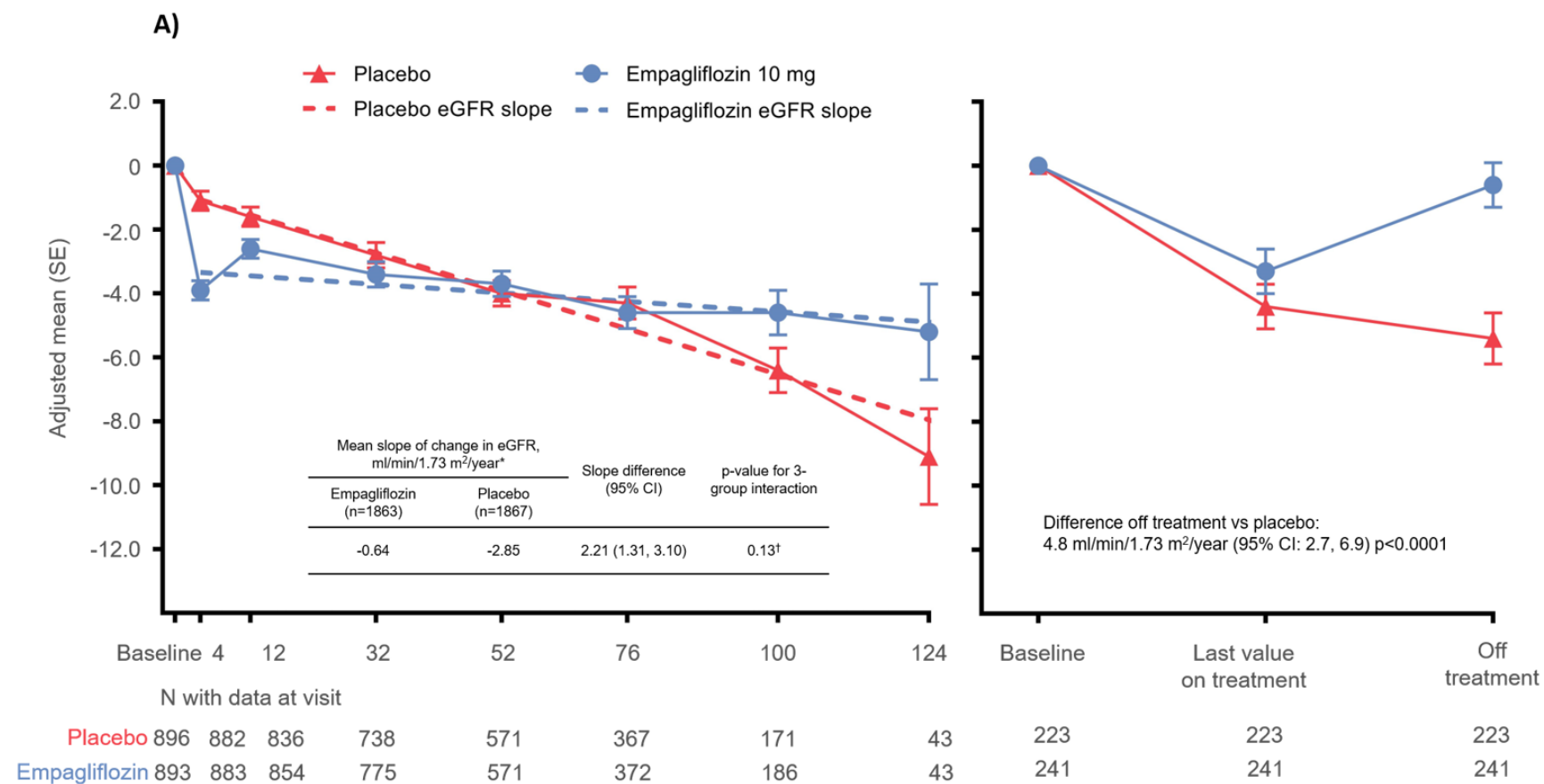
‡Cardiac resynchronization therapy with or without a defibrillator

§Excluding valsartan when taken with sacubitril because sacubitril/valsartan is shown as ARNI

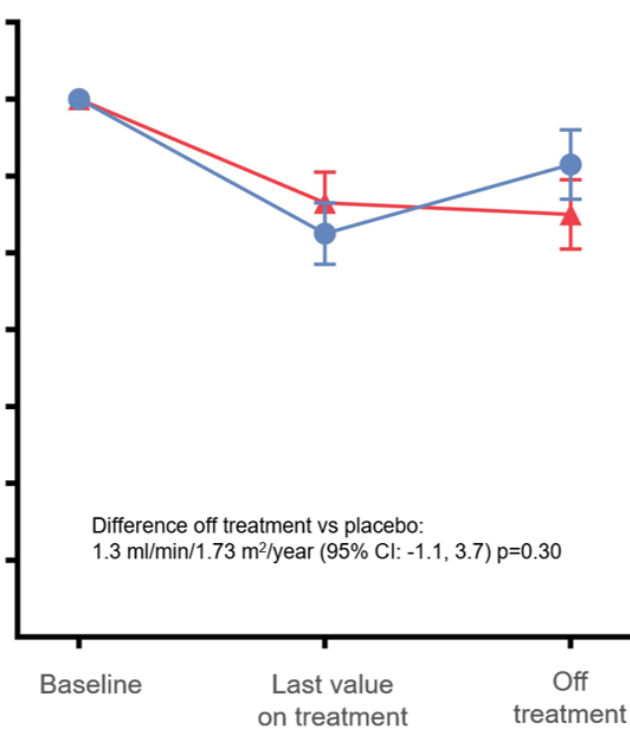
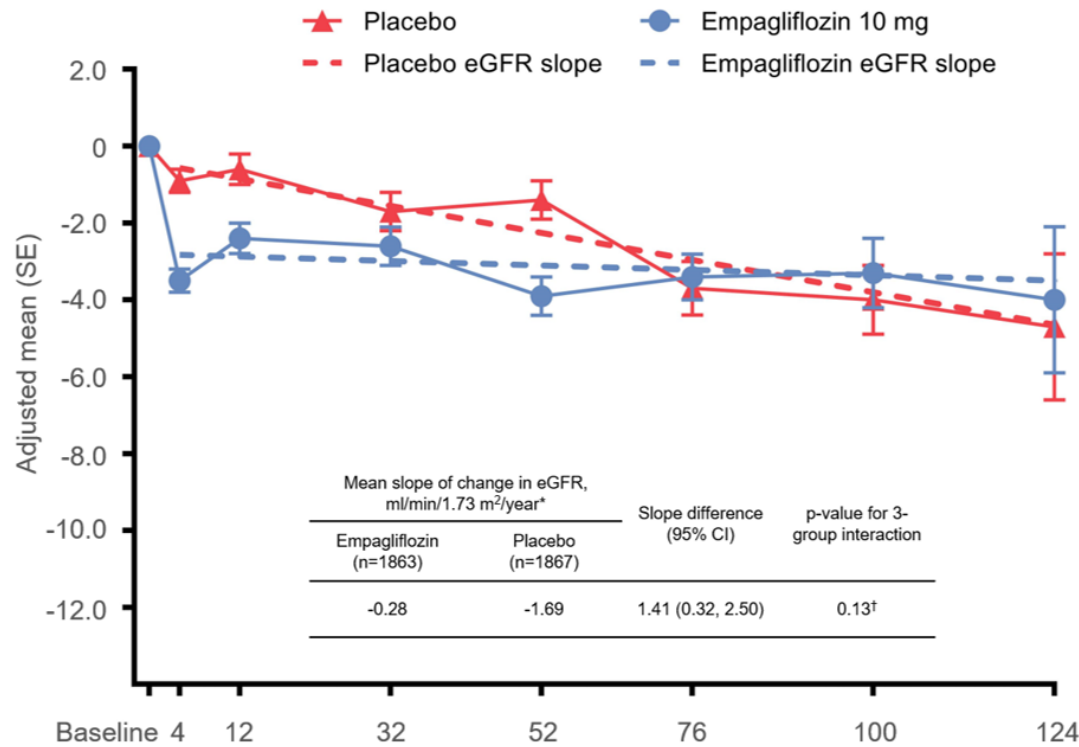
||Diuretics other than mineralocorticoid receptor antagonists

NYHA=New York Heart Association; ARB=Angiotensin Receptor Blocker; ACE=Angiotensin Converting enzyme; ARNI=Angiotensin receptor neprilysin inhibition; GFR= Glomerular filtration rate; NT-pro BNP=N-Terminal prohormone B-type natriuretic peptide

Supplementary Figure I – Adjusted mean changes in eGFR (CKD-EPI) from baseline over time, mean slope of change in eGFR, and change in eGFR from baseline to follow-up in patients with diabetes (A), prediabetes (B), and normoglycemia (C).

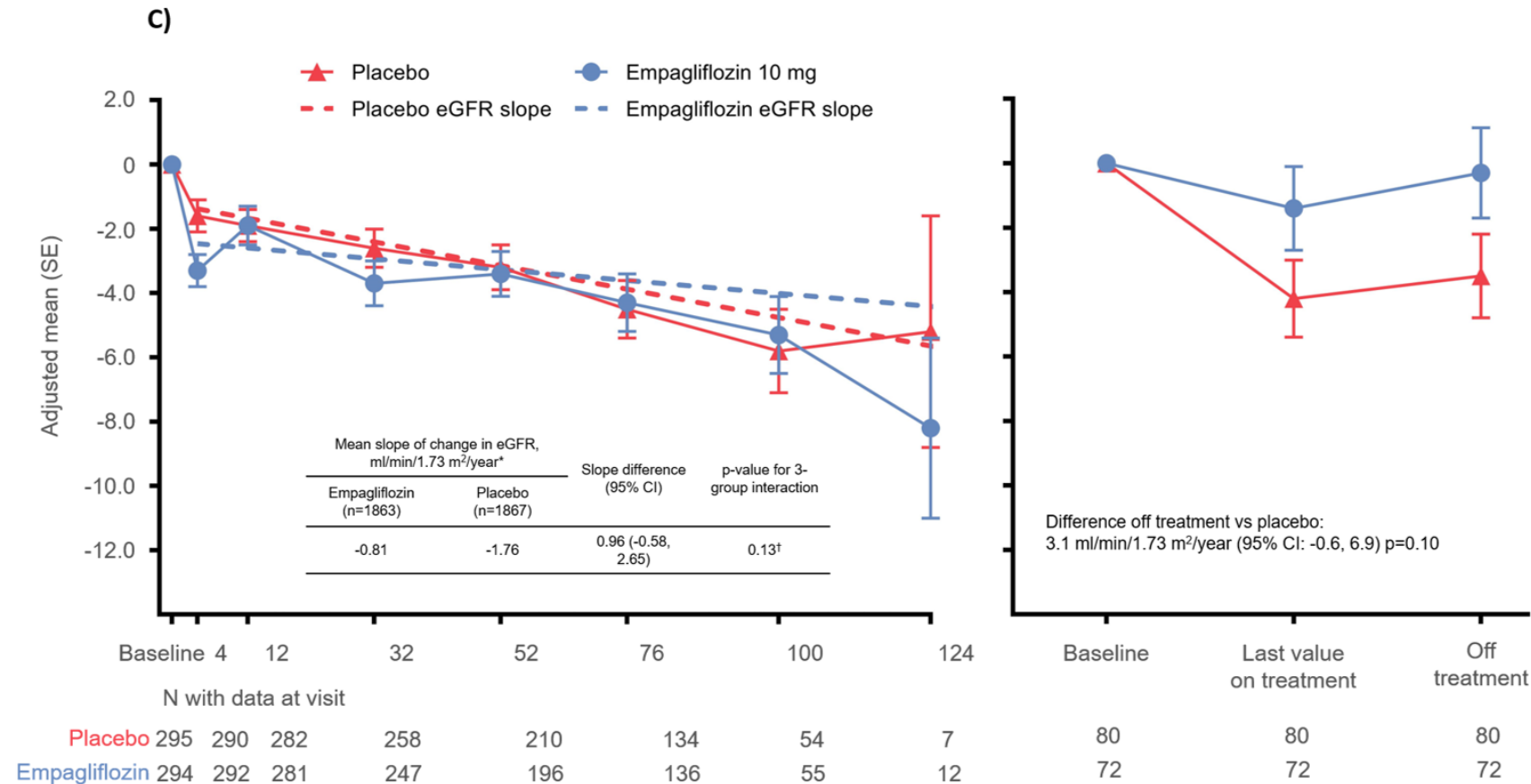


B)



	Baseline	4	12	32	52	76	100	124
N with data at visit								

Placebo	601	593	565	504	365	244	118	26	176	176	176
Empagliflozin	612	607	585	532	399	245	115	25	174	174	174



The adjusted mean change in eGFR and the mean slope of change is based on on-treatment data.

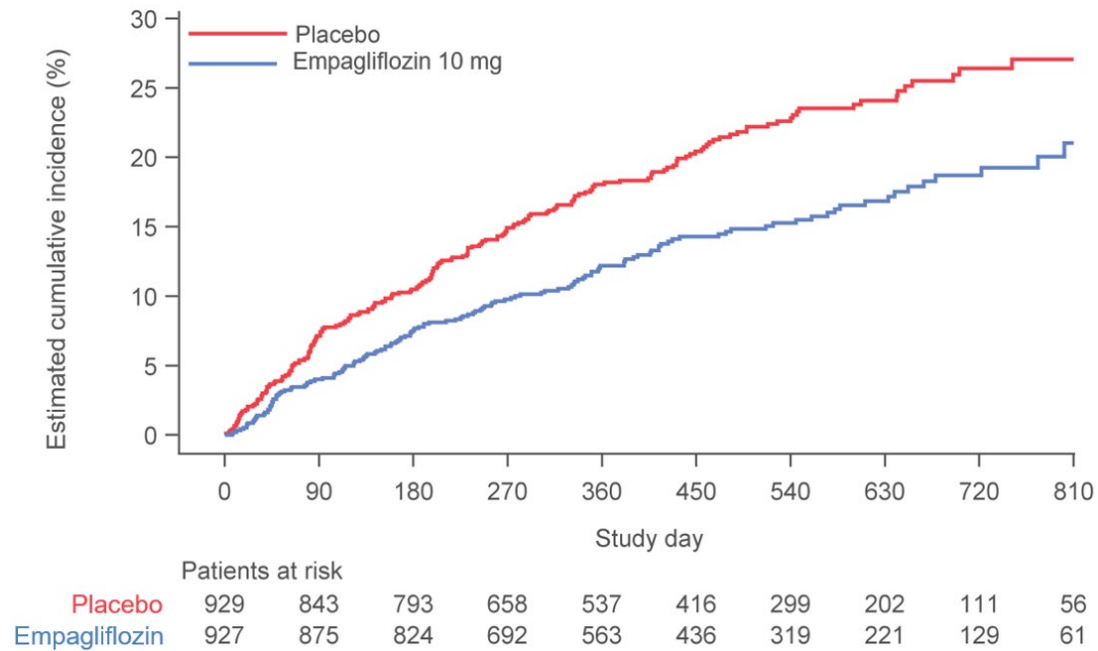
* The slope of eGFR was analyzed on the basis of on-treatment data with a random coefficient model that included age and baseline eGFR as linear covariates and sex, region, baseline left ventricular ejection fraction, baseline eGFR according to time, diabetes according to treatment and treatment* diabetes according to time interaction as fixed effects; the model allows for randomly varying slope and intercept between patients.

[†]interaction p-value assuming ordered categories (i.e. a trend analysis that reflects an assumed ordering of the subgroups from normoglycemia to prediabetes to diabetes testing a linear trend across subgroups.)

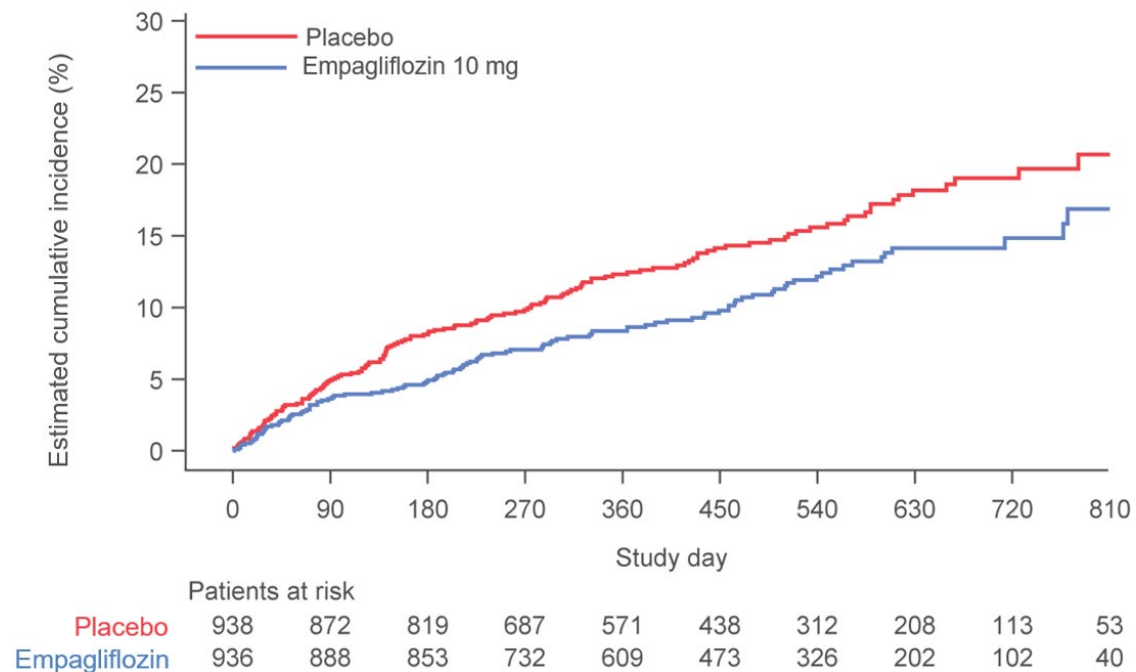
Supplementary Figure II: Components of the primary outcome by diabetes status.

The figures show the cumulative incidence curves of first hospitalization for heart failure in the empagliflozin and placebo group in those with (A) and without (B) diabetes, and cardiovascular mortality in the empagliflozin and placebo group in those with (C) and without (D) diabetes

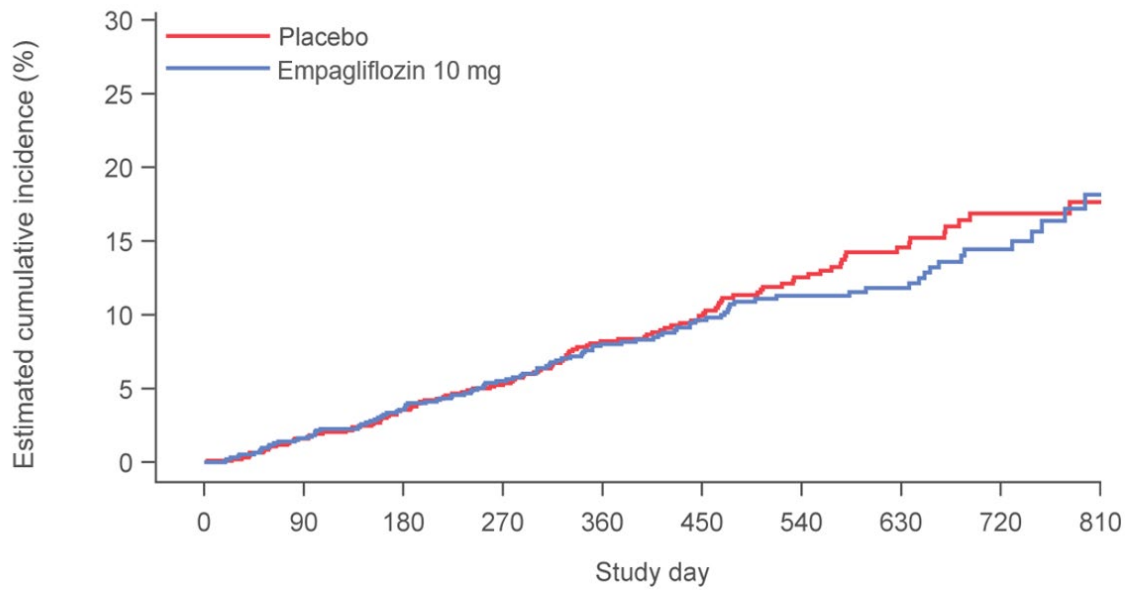
A)



B)

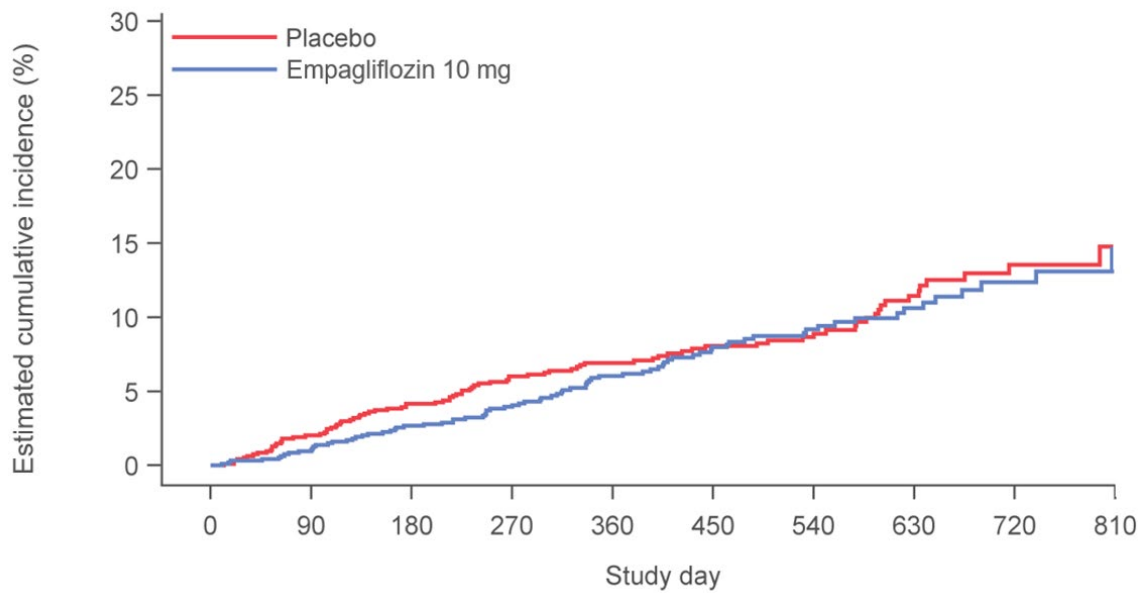


C)



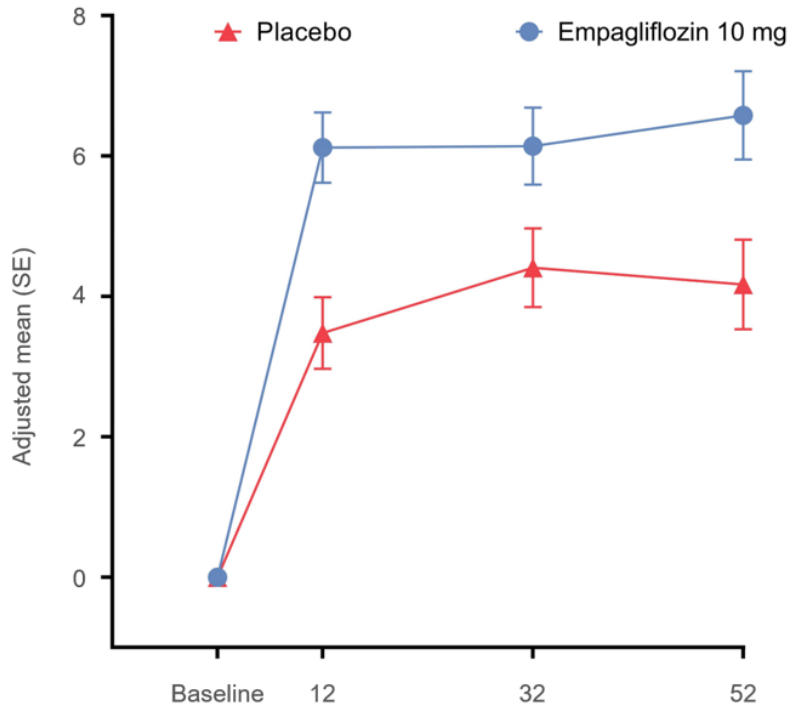
	Patients at risk									
Placebo	929	910	885	777	645	515	373	259	144	76
Empagliflozin	927	906	878	756	629	499	374	264	156	70

D)



	Patients at risk									
Placebo	938	915	885	757	649	512	370	248	138	62
Empagliflozin	936	923	894	781	660	516	368	242	125	52

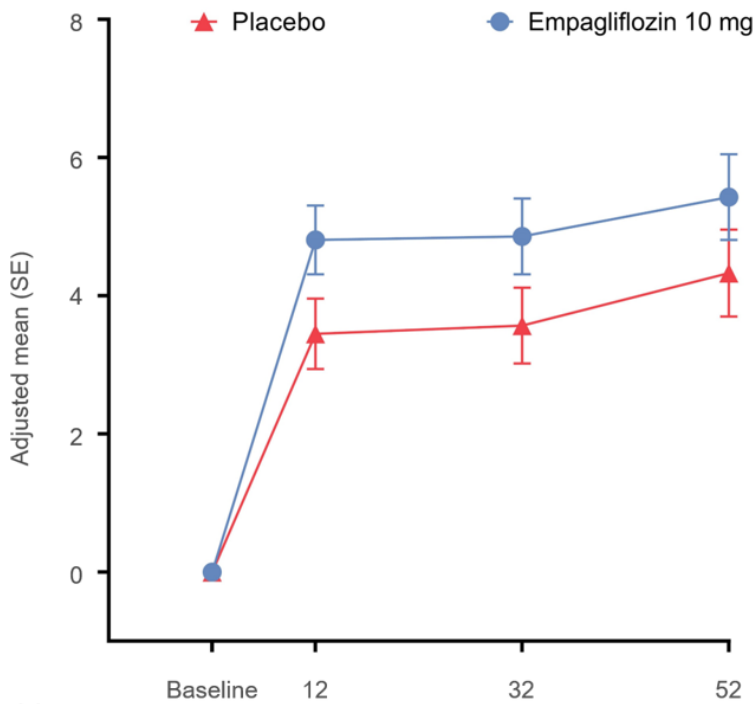
Supplementary Figure III – Adjusted mean changes in KCCQ clinical summary score from baseline in patients with (A) and without (B) diabetes based on on-treatment data
A)



N with data at visit

	Baseline	12	32	52
Placebo	845	837	736	570
Empagliflozin	862	856	781	577

B)



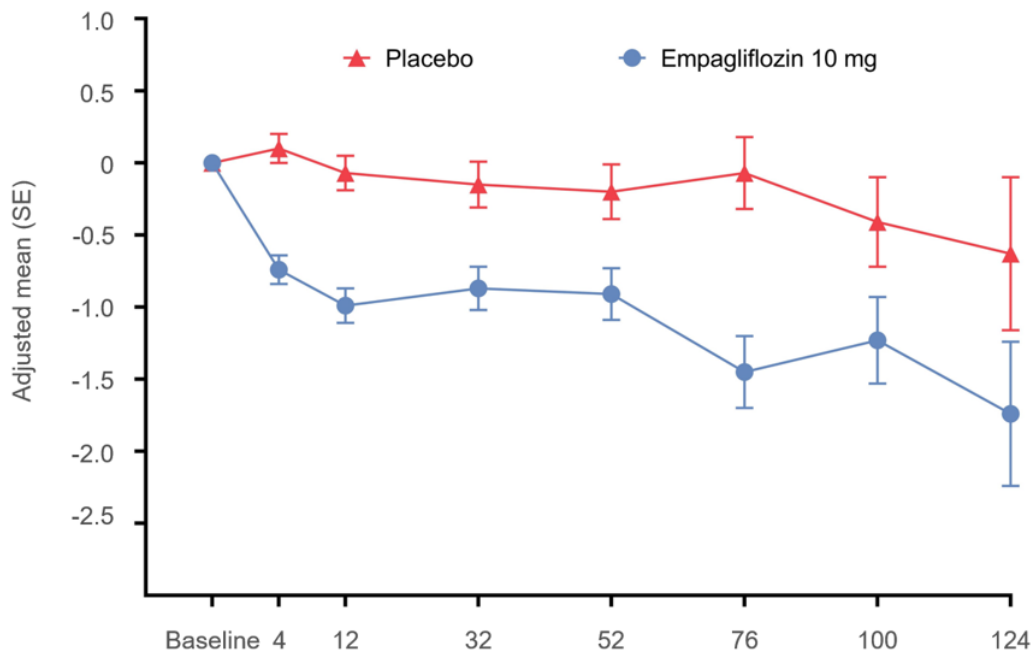
N with data at visit

	Baseline	12	32	52
Placebo	856	851	769	581
Empagliflozin	872	864	780	599

Legend: KCCQ, Kansas City Cardiomyopathy Questionnaire

Supplementary Figure IV – Adjusted mean changes in body weight from baseline in patients with (A) and without (B) diabetes

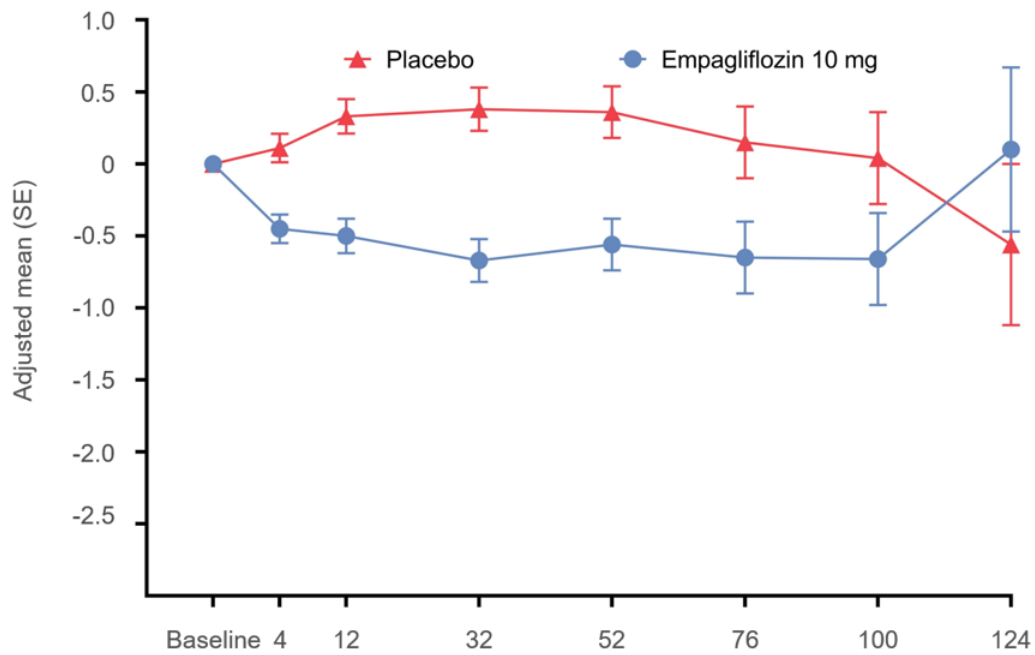
A)



N with data at visit

Placebo	907	898	861	773	612	399	193	48
Empagliflozin	906	897	879	814	617	411	210	53

B)

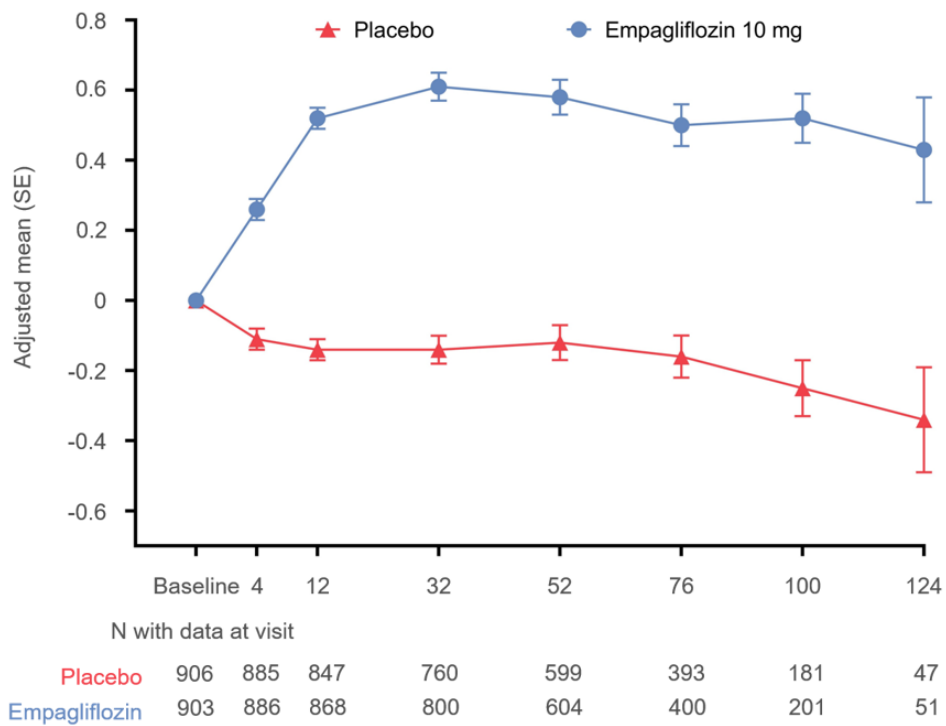


N with data at visit

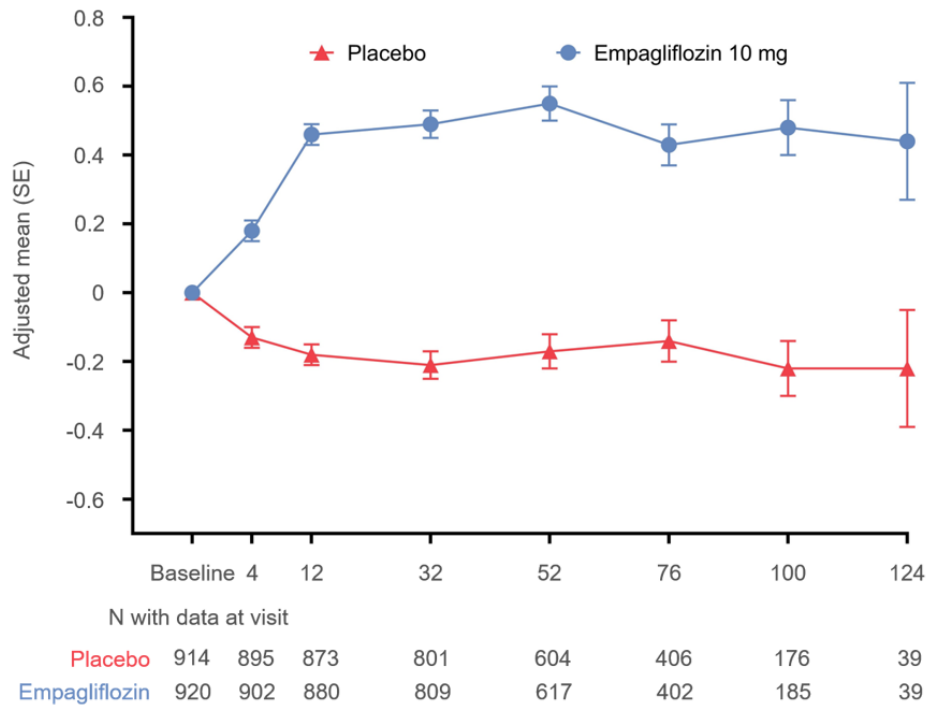
Placebo	916	905	884	813	617	414	180	41
Empagliflozin	922	911	889	815	623	407	185	40

Supplementary Figure V – Adjusted mean changes in hemoglobin from baseline in patients with (A) and without (B) diabetes

A)

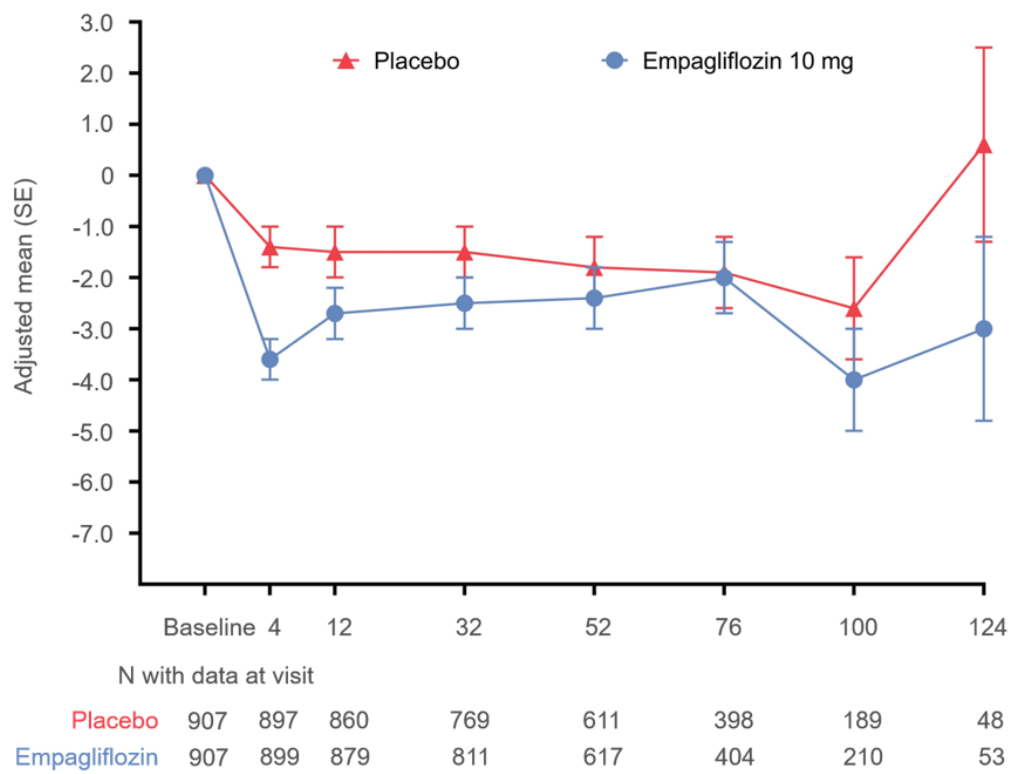


B)

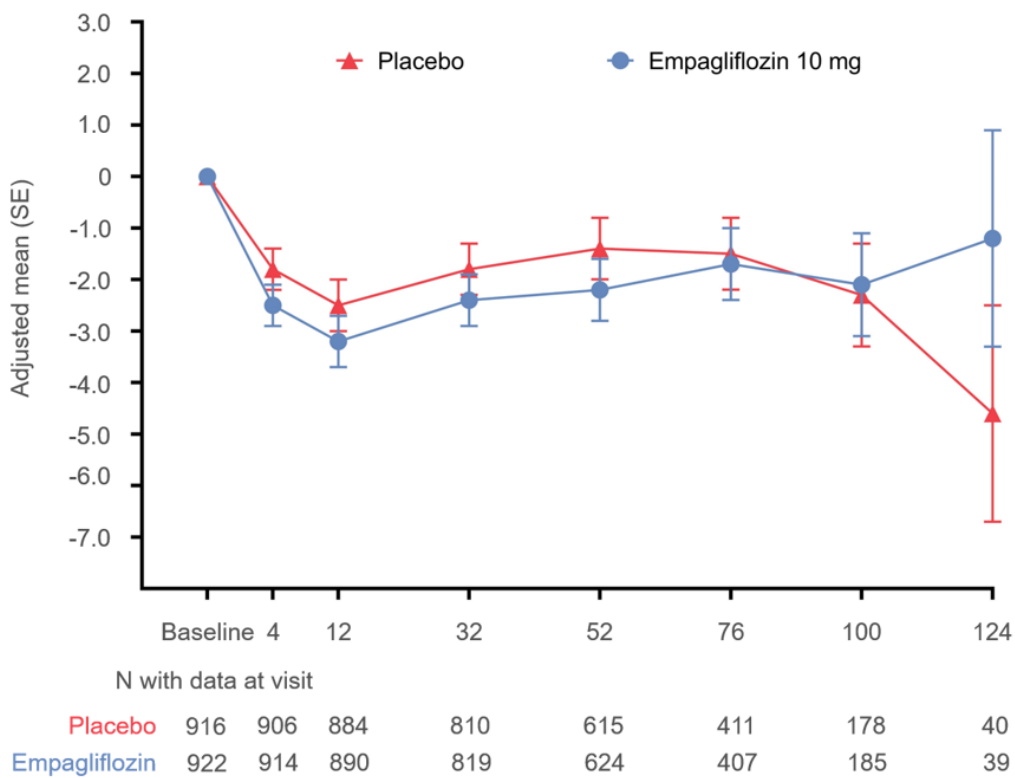


Supplementary Figure VI – Adjusted mean changes in systolic blood pressure from baseline in patients with (A) and without (B) diabetes

A)

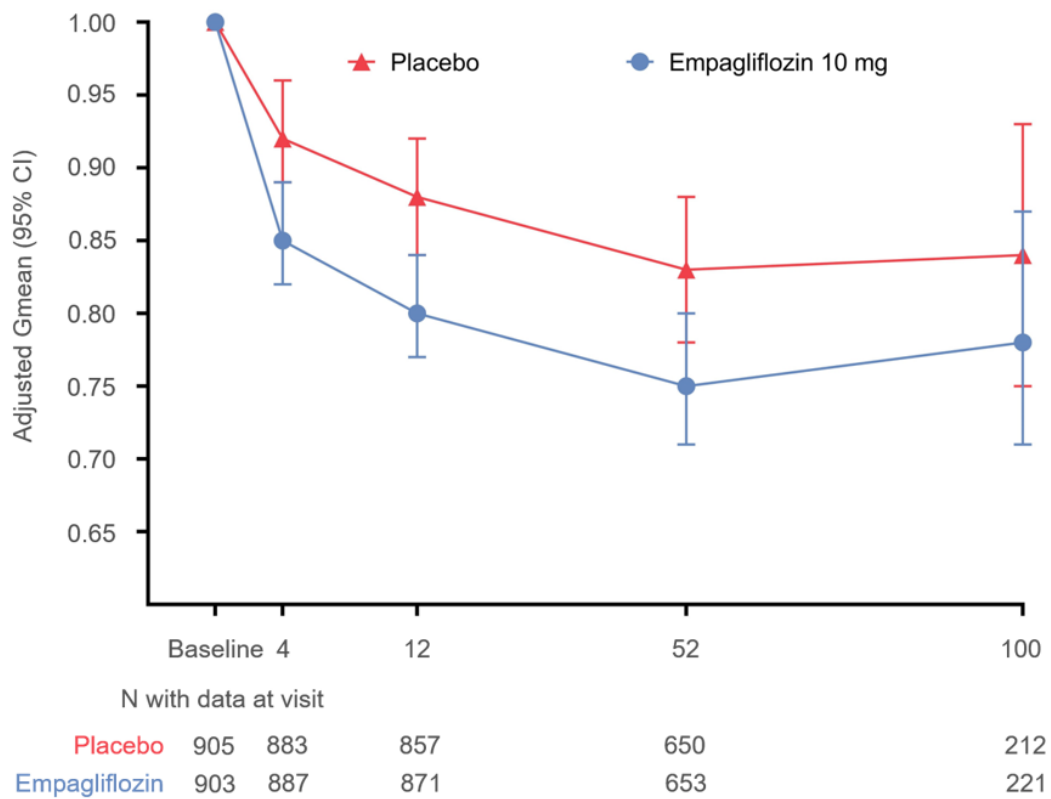


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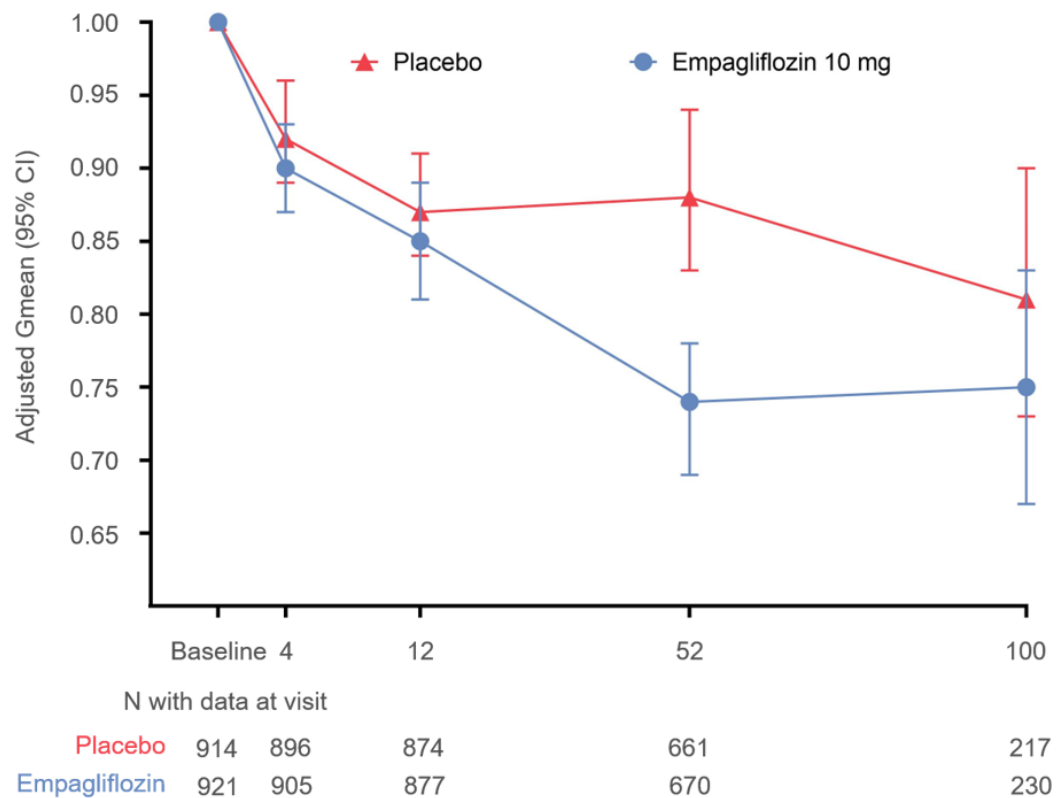


Suppl Fig VII – Adjusted mean changes in NT-proBNP from baseline in patients with (A) and without (B) diabetes

A)



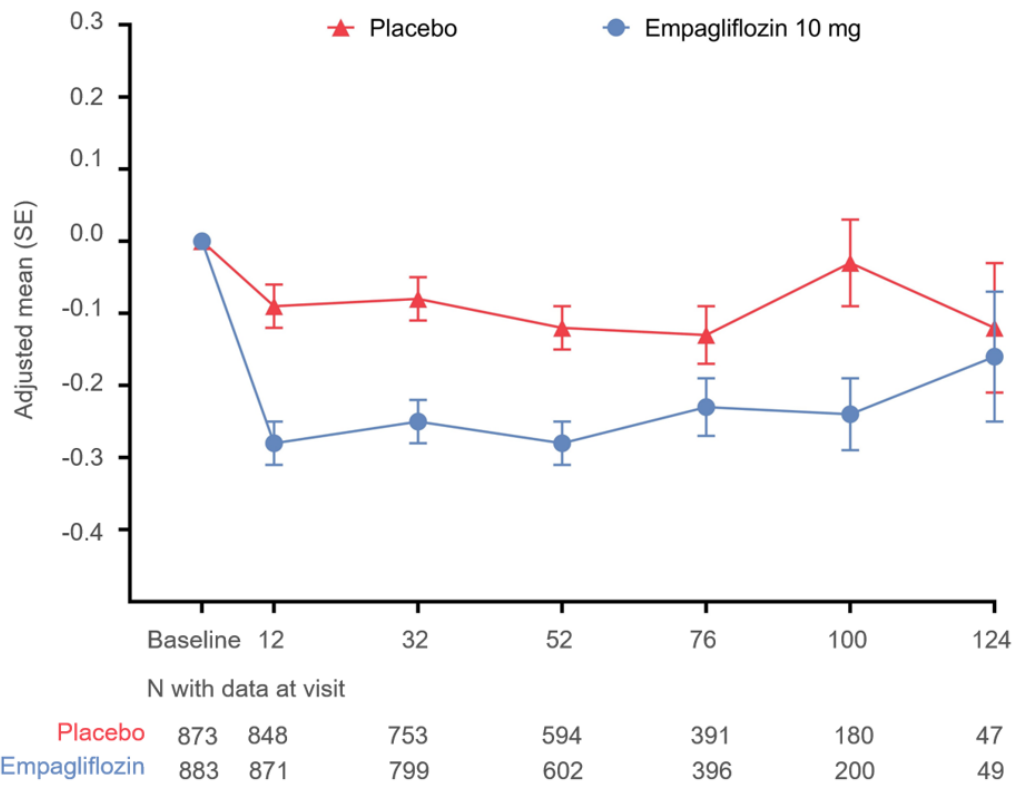
B)



Legend: NT-proBNP, N-terminal pro-hormone B-type natriuretic peptide

Supplementary Figure VIII: Changes of HbA1c from baseline in those with (A) and without (B) diabetes

A)



B)

