SUPPLEMENTAL MATERIAL

Supplemental Table 1. Baseline characteristics of patients taking and not taking SGLT2 inhibitors at recruitment

	No Baseline SGLT2 inhibitors (N(%) or Mean ±(SD))		Baseline SGLT2 inhibitors (N(%) or Mean ±(SD))		P value
	Efpeglenatide 4/6mg	**Placebo**	**Efpeglenatide 4/6mg**	**Placebo**	
Randomized	2305	1153	412	206	
Age (years)	64.64± 8.21	64.59± 8.39	64.37± 8.10	63.38± 7.91	0.103
Females	808 (35.05)	362 (31.40)	117 (28.40)	57 (27.67)	0.005
Region: Canada/US	571 (24.77)	260 (22.55)	157 (38.11)	91 (44.17)	<0.001
Mexico/South America	573 (24.86)	306 (26.54)	32 (7.77)	13 (6.31)	
Europe	684 (29.67)	340 (29.49)	178 (43.20)	83 (40.29)	
Other	477 (20.69)	247 (21.42)	45 (10.92)	19 (9.22)	
White Ancestry	2018 (87.55)	992 (86.04)	354 (85.92)	170 (82.52)	0.128
Diabetes Duration	15.50± 8.89	14.81± 8.72	16.01± 8.37	16.55± 8.73	0.004
Current tobacco Use	366 (15.88)	175 (15.18)	61 (14.81)	31 (15.05)	0.631
Prior cardiovascular diseasea	2060 (89.37)	1041 (90.29)	360 (87.38)	189 (91.75)	0.529
eGFR <60 ml/min/1.73m^2	741 (32.15)	360 (31.28)	122 (29.61)	64 (31.07)	0.385
Prior CVD & eGFR <60 ml/min/1.73m^2	510 (22.13)	254 (22.07)	75 (18.20)	49 (23.79)	0.257
Prior heart failure	432 (18.74)	220 (19.08)	55 (13.35)	30 (14.56)	0.002
Prior hypertension	2112 (91.63)	1056 (91.59)	372 (90.29)	182 (88.35)	0.109
Prior diabetic retinopathy*	781 (33.88)	357 (30.96)	131 (31.80)	73 (35.44)	0.960
Albuminuria (%)†	1154 (50.11)	564 (48.92)	165 (40.05)	94 (45.63)	<0.001
Body Mass Index (kg/m^2)	32.87± 6.26	32.31± 5.88	32.73± 5.94	32.91± 6.68	0.762
Heart Rate (beats/min)	72.74±10.51	72.87±10.59	72.87±11.13	72.72±11.15	0.931
Systolic BP	135.6±15.57	135.0±15.47	132.2±14.75	131.0±15.66	<0.001

	No Baseline SGLT2 inhibitors (N(%) or Mean ±(SD))		Baseline SGLT2 inhibitors (N(%) or Mean ±(SD))		P value
	Efpeglenatide 4/6mg	**Placebo**	**Efpeglenatide 4/6mg**	**Placebo**	
Diastolic BP	76.94± 9.70	76.89± 9.68	75.77± 9.55	75.14±10.62	0.001
HbA1c (%)	8.96± 1.49	8.98± 1.56	8.51± 1.22	8.67± 1.26	<0.001
eGFR (ml/min/1.73m^2)	71.93±22.31	72.72±23.23	73.47±19.75	74.00±23.41	0.173
Median albumin/creatinine (mg/mmol)	3.39 (1.13-15.48)	3.164 (1.24-12.09)	2.147 (0.90-	2.8815 (1.13- 9.94)	<0.001
Cholesterol (mmol/L)	4.24± 1.24	4.21± 1.20	4.06± 1.22	4.19± 1.34	<0.001
LDL cholesterol (mmol/L)	2.12± 0.99	2.10± 0.95	1.79± 0.92	1.98± 1.06	<0.001
HDL cholesterol (mmol/L)	1.12± 0.31	1.10± 0.30	1.11± 0.30	1.10± 0.34	0.298
Median triglycerides (mmol/L)	1.87 (1.35- 2.68)	1.91 (1.38- 2.70)	2.13 (1.42-	2.055 (1.46- 3.43)	<0.001
Any Insulin	1472 (63.86)	709 (61.49)	248 (60.19)	131 (63.59)	0.408
Metformin	1644 (71.32)	822 (71.29)	349 (84.71)	170 (82.52)	<0.001
Any Sulfonylurea	586 (25.42)	296 (25.67)	109 (26.46)	45 (21.84)	0.757
No glucose-lowering drug	57 (2.47)	28 (2.43)	0 (0.00)	0 (0.00)	---
ACE-I or ARB or ARNi	1838 (79.74)	914 (79.27)	339 (82.28)	171 (83.01)	0.092
Beta Blocker	1517 (65.81)	743 (64.44)	278 (67.48)	132 (64.08)	0.634
Statin	1846 (80.09)	920 (79.79)	356 (86.41)	172 (83.50)	0.001
Fibrate	196 (8.50)	95 (8.24)	37 (8.98)	22 (10.68)	0.355
Acetylsalicylic acid	1574 (68.29)	771 (66.87)	281 (68.20)	142 (68.93)	0.756
Other antiplatelet drugs	598 (25.94)	298 (25.85)	107 (25.97)	46 (22.33)	0.545

*Diabetic Retinopathy definition includes Reported Diabetic Retinopathy, Vitrectomy, Diabetic laser therapy, or Anti-vascular Endothelial Growth Factor Injections
†Urine albumin/creatinine ratio > = 3.39 g/mol
P values refer to the difference between patients treated or not treated with a SGLT2 inhibitor at baseline, combining patients in the two randomized treatment groups.
eGFR, estimated glomerular filtration rate; CVD, cardiovascular disease; UACR, urinary albumin:creatinine ratio; LDL, low density lipoprotein cholesterol; HDL, high density lipoprotein cholesterol; ACE-I, angiotensin converting enzyme inhibitor; ARB, angiotensin receptor blocker; ARNi, angiotensin receptor neprilysin inhibitor.
For continuous variables used two-sample test for normally distributed (age, heart rate, systolic and diastolic blood pressure, eGFR), Wilcoxen for non-normally distributed (diabetes duration, cholesterol, LDL, HDL,triglycerides) and used chi-square test of homogeneity for categorical variables.

Supplemental Table 2. Effects of Efpeglenatide (4/6 mg) on clinical events in patients taking and not taking SGLT2 inhibitors at baseline

	No Baseline SGLT2 inhibitors			Baseline SGLT2 inhibitors			
	Efpeglenatide	**Placebo**	**HR (95%CI)**	**Efpeglenatide**	**Placebo**	**HR (95%CI)**	**Interaction P-value**
	n/N (%); N/100py	**n/N (%); N/100py**		**n/N (%); N/100py**	**n/N (%); N/100py**		
Primary Outcome (MACE)	164/2305(7.1); 4.0	108/1153(9.4); 5.4	0.74 (0.58-0.94)	25/412(6.1); 3.4	17/206(8.3); 4.7	0.70 (0.37-1.30)	0.6841
Expanded MACE*	217/2305(9.4); 5.4	136/1153(11.8); 6.9	0.77 (0.62-0.96)	40/412(9.7); 5.6	22/206(10.7); 6.1	0.87 (0.51-1.48)	0.2319
Renal Composite†	316/2305(13.7); 8.2	216/1153(18.7); 11.9	0.70 (0.59-0.83)	37/412(9.0); 5.1	34/206(16.5); 10.0	0.52 (0.33-0.83)	0.3787
MACE or non-CV Death	190/2305(8.2); 4.6	124/1153(10.8); 6.2	0.74 (0.59-0.93)	26/412(6.3); 3.5	19/206(9.2); 5.2	0.65 (0.36-1.19)	0.7497
Heart Failure hospitalization	37/2305(1.6); 0.9	25/1153(2.2); 1.2	0.70 (0.42- .17)	3/412(0.7); 0.4	6/206(2.9); 1.6	0.23 (0.05-0.97)	0.3529

*Expanded MACE comprised major adverse cardiovascular event (MACE, defined as a non-fatal myocardial infarction, a non-fatal stroke, or death from CV or undetermined causes) or coronary revascularization or hospitalization for unstable angina, and a composite kidney outcome

†Renal composite outcome comprised incident macroalbuminuria (i.e., a UACR > 300 mg/g or 33.9 mg/mmol) plus ≥ 30% rise of UACR from baseline, a sustained ≥ 30 days) decrease in eGFR by ≥ 40%, renal replacement therapy, and a sustained (≥ 30 days) eGFR < 15 ml/min/1.73 m^1

Supplemental Table 3. Effects of Efpeglenatide (4/6 mg) on clinical events in patients taking and not taking SGLT2 inhibitors at baseline, including secondary analyses of heart rate as a time-varying covariate

	No Baseline SGLT2 inhibitors			Baseline SGLT2 inhibitors			
	Efpeglenatide	**Placebo**	**HR(95%CI)**	**Efpeglenatide**	**Placebo**	**HR(95%CI)**	**Interaction P-value**
	n/N (%); N/100py	**n/N (%); N/100py**		**n/N (%); N/100py**	**n/N (%); N/100py**		
Primary Outcome (MACE)	164/2305(7.1); 4.0	108/1153(9.4); 5.4	0.74 (0.58- 0.94)	25/412(6.1); 3.4	17/206(8.3); 4.7	0.70 (0.37- 1.30)	0.6841
Updated HR Time-varying*			0.73 (0.57- 0.93)			0.69 (0.37- 1.29)	0.6912
Updated HR Time-varying†			0.72 (0.57- 0.92)			0.68 (0.36- 1.28)	0.6892
Expanded MACE‡	217/2305(9.4); 5.4	136/1153(11.8); 6.9	0.77 (0.62- 0.96)	40/412(9.7); 5.6	22/206(10.7); 6.1	0.87 (0.51- 1.48)	0.2319
Updated HR Time-varying*			0.78 (0.63- 0.97)			0.88 (0.52- 1.50)	0.2266
Updated HR Time-varying†			0.77 (0.62- 0.95)			0.86 (0.51- 1.47)	0.2342
Renal Composite§	316/2305(13.7); 8.2	216/1153(18.7); 11.9	0.70 (0.59- 0.83)	37/412(9.0); 5.1	34/206(16.5); 10.0	0.52 (0.33- 0.83)	0.3787
Updated HR Time-varying*			0.67 (0.56- 0.80)			0.50 (0.31- 0.80)	0.3691
Updated HR Time-varying†			0.66 (0.56- 0.79)			0.49 (0.31- 0.78)	0.3746
MACE or non-CV Death	190/2305(8.2); 4.6	124/1153(10.8); 6.2	0.74 (0.59- 0.93)	26/412(6.3); 3.5	19/206(9.2); 5.2	0.65 (0.36- 1.19)	0.7497
Updated HR Time-varying*			0.74 (0.59- 0.93)			0.65 (0.35- 1.18)	0.7550
Updated HR Time-varying†			0.73 (0.58- 0.91)			0.64 (0.35- 1.16)	0.7523
Heart Failure hospitalization	37/2305(1.6); 0.9	25/1153(2.2); 1.2	0.70 (0.42- 1.17)	3/412(0.7); 0.4	6/206(2.9); 1.6	0.23 (0.05- 0.97)	0.3529
Updated HR Time-varying*			0.68 (0.41- 1.15)			0.22 (0.05- 0.94)	0.3515
Updated HR Time-varying†			0.68 (0.40- 1.13)			0.22 (0.05- 0.93)	0.3466

*analysis with time-varying updated mean HR (heart rate), calculated the on-treatment mean HR for each person

†analysis with HR (heart rate) reported at each visit as time-varying covariate

‡Expanded MACE comprised major adverse cardiovascular event (MACE, defined as a non-fatal myocardial infarction, a non-fatal stroke, or death from CV or undetermined causes) or coronary revascularization or hospitalization for unstable angina, and a composite kidney outcome

§Renal composite outcome comprised incident macroalbuminuria (i.e., a UACR > 300 mg/g or 33.9 mg/mmol) plus ≥ 30% rise of UACR from baseline, a sustained ≥ 30 days) decrease in eGFR by ≥ 40%, renal replacement therapy, and a sustained (≥ 30 days) eGFR < 15 ml/min/1.73 m^1

Supplemental Table 4. Effects of Efpeglenatide (4/6 mg) on clinical events according to exposure to SGLT2 at baseline or during follow-up

	No SGLT2 inhibitors			SGLT2 inhibitors			
	Efpeglenatide	**Placebo**	**HR (95%CI)**	**Efpeglenatide**	**Placebo**	**HR (95%CI)**	**Interaction P-value**
	n/N (%); N/100py	**n/N (%); N/100py**		**n/N (%); N/100py**	**n/N (%); N/100py**		
Including all patients ever exposed to SGLT2 inhibitors from baseline to final visit in the SGLT2 inhibitor group‡							
Primary Outcome (MACE)	160/2204(7.3); 4.1	98/1036(9.5); 5.5	0.74 (0.57- 0.95)	29/513(5.7); 3.2	27/323(8.4); 4.7	0.66 (0.39- 1.14)	0.6250
Expanded MACE*	208/2204(9.4); 5.4	123/1036(11.9); 7.0	0.76 (0.61- 0.95)	49/513(9.6); 5.5	35/323(10.8); 6.2	0.90 (0.58- 1.41)	0.3337
Renal Composite†	298/2204(13.5); 8.1	205/1036(19.8); 12.7	0.65 (0.54- 0.78)	55/513(10.7); 6.2	45/323(13.9); 8.3	0.74 (0.50- 1.11)	0.8263
MACE or non-CV Death	186/2204(8.4); 4.7	114/1036(11.0); 6.4	0.74 (0.58- 0.93)	30/513(5.8); 3.3	29/323(9.0); 5.0	0.64 (0.38- 1.08)	0.6824
Heart Failure hospitalization	35/2204(1.6); 0.9	21/1036(2.0); 1.1	0.74 (0.43- 1.27)	5/513(1.0); 0.5	10/323(3.1); 1.7	0.27 (0.08- 0.94)	0.3386
HRs all adjusted for region, randomization stratum for SGLT2 inhibitor use							
Drop-in visit right censoring§							
Primary Outcome (MACE)	162/2305(7.0); 4.0	102/1153(8.8); 5.4	0.73 (0.57- 0.94)	25/412(6.1); 3.4	17/206(8.3); 4.7	0.70 (0.37- 1.31)	0.6614
Expanded MACE*	214/2305(9.3); 5.4	127/1153(11.0); 6.9	0.78 (0.63- 0.97)	40/412(9.7); 5.6	22/206(10.7); 6.1	0.87 (0.51- 1.48)	0.2357
Renal Composite†	306/2305(13.3); 8.1	211/1153(18.3); 12.4	0.66 (0.56- 0.79)	37/412(9.0); 5.1	34/206(16.5); 10.0	0.52 (0.33- 0.83)	0.4946
MACE or non-CV Death	188/2305(8.2); 4.7	118/1153(10.2); 6.3	0.74 (0.59- 0.93)	26/412(6.3); 3.5	19/206(9.2); 5.2	0.66 (0.36- 1.19)	0.7405
Heart Failure hospitalization	37/2305(1.6); 0.9	24/1153(2.1); 1.3	0.69 (0.41- 1.16)	3/412(0.7); 0.4	6/206(2.9); 1.6	0.23 (0.05- 0.97)	0.3603
HRs all adjusted for region, randomization stratum for SGLT2 inhibitor use							
Inverse-probability for treatment weighting‖							
Primary Outcome (MACE)	164/2305(7.1); 4.0	108/1153(9.4); 5.4	0.70 (0.56- 0.89)	25/412(6.1); 3.4	17/206(8.3); 4.7	0.69 (0.36- 1.32)	0.6293

	No SGLT2 inhibitors			SGLT2 inhibitors			
	Efpeglenatide	**Placebo**	**HR (95%CI)**	**Efpeglenatide**	**Placebo**	**HR (95%CI)**	**Interaction P-value**
	n/N (%); N/100py	**n/N (%); N/100py**		**n/N (%); N/100py**	**n/N (%); N/100py**		
Expanded MACE*	217/2305(9.4); 5.4	136/1153(11.8); 6.9	0.74 (0.60- 0.91)	40/412(9.7); 5.6	22/206(10.7); 6.1	0.87 (0.50- 1.49)	0.1521
Renal Composite†	316/2305(13.7); 8.2	216/1153(18.7); 11.9	0.91 (0.77- 1.07)	37/412(9.0); 5.1	34/206(16.5); 10.0	0.52 (0.32- 0.84)	0.0209
MACE or non-CV Death	190/2305(8.2); 4.6	124/1153(10.8); 6.2	0.72 (0.58- 0.89)	26/412(6.3); 3.5	19/206(9.2); 5.2	0.65 (0.35- 1.21)	0.7102
Heart Failure hospitalization	37/2305(1.6); 0.9	25/1153(2.2); 1.2	0.69 (0.42- 1.13)	3/412(0.7); 0.4	6/206(2.9); 1.6	0.23 (0.05- 1.00)	0.3741

*Expanded MACE comprised major adverse cardiovascular event (MACE, defined as a non-fatal myocardial infarction, a non-fatal stroke, or death from CV or undetermined causes) or coronary revascularization or hospitalization for unstable angina, and a composite kidney outcome

†Renal composite outcome comprised incident macroalbuminuria (i.e., a UACR > 300 mg/g or 33.9 mg/mmol) plus ≥ 30% rise of UACR from baseline, a sustained ≥ 30 days) decrease in eGFR by ≥ 40%, renal replacement therapy, and a sustained (≥ 30 days) eGFR < 15 ml/min/1.73 m^1

‡Anyone ever exposed to SGLT2 inhibitors from the baseline to the final visit versus never exposed

§Right censored anyone who started an SGLT2 inhibitor after randomization at the time that it was started

||The hazard ratios displayed here estimate the hazard of efpeglenatide for the outcomes had both groups been similar with respect to their likelihood of getting an SGLT2 inhibitor after randomization