

## SUPPLEMENTARY MATERIALS

**Supplemental Table 1:** Characteristics of the patients at baseline according to glycemic status and randomized treatment assignment.

	Normal glucose (n=738)		Pre-diabetes (n=660)		Diabetes (n=2,906)	
	Dapagliflozin N=368	Placebo N=370	Dapagliflozin N=329	Placebo N=331	Dapagliflozin N=1,455	Placebo N=1,451
Age, years	51.8 (14.7)	51.3 (15.0)	62.6 (12.0)	61.3 (12.1)	64.1 (9.8)	64.7 (9.5)
Female, n (%)	115 (31.2)	122 (33.0)	100 (30.4)	123 (37.2)	494 (33.9)	471 (32.4)
Race <sup>†</sup> , n (%)						
White	190 (51.6)	197 (53.2)	183 (55.6)	179 (54.1)	751 (51.6)	790 (54.4)
Black or African American	15 (4.1)	8 (2.2)	13 (4.0)	18 (5.4)	76 (5.2)	61 (4.2)
Asian	150 (40.8)	149 (40.3)	118 (35.9)	118 (35.7)	481 (33.1)	451 (31.1)
Other	13 (3.5)	16 (4.3)	15 (4.6)	16 (4.8)	147 (10.1)	149 (10.3)
HbA <sub>1c</sub> , %	5.3 (0.3)	5.3 (0.3)	5.9 (0.2)	5.9 (0.3)	7.8 (1.7)	7.8 (1.6)
HbA <sub>1c</sub> , mmol/mol	34 (3.3)	34 (3.3)	41 (2.2)	41 (0.3)	62 (18.6)	62 (17.5)
Diabetes duration, years	-	-	-	-	13.7 (7.1, 20.8)	13.8 (7.5, 20.6)
Weight, kg	75.8 (17.2)	76.7 (20.3)	80.1 (18.2)	80.1 (19.2)	83.2 (20.9)	83.8 (21.2)
Body mass index, kg/m <sup>2</sup>	26.8 (4.8)	27.3 (5.9)	28.7 (5.5)	29.0 (5.8)	30.2 (6.2)	30.4 (6.3)
Current smoker, n (%)	51 (13.9)	44 (11.9)	37 (11.3)	57 (17.2)	195 (13.4)	200 (13.8)
Blood pressure, mm Hg						

Systolic	131.3 (16.7)	131.9 (16.6)	133.5 (16.0)	134.0 (17.2)	138.8 (17.6)	139.6 (17.1)
Diastolic	79.8 (10.9)	80.4 (11.1)	79.3 (11.0)	78.6 (10.4)	76.5 (10.4)	76.5 (9.9)
Estimated GFR, mL/min/1.73 m <sup>2</sup>	41.9 (11.4)	42.0 (12.2)	41.4 (11.7)	41.5 (11.6)	44.0 (12.6)	43.6 (12.6)
Hemoglobin, g/L	133.1 (18.9)	132.9 (18.0)	133.8 (16.8)	132.5 (16.4)	126.3 (17.7)	125.6 (17.9)
Median urinary albumin-to-creatinine ratio (Q1–Q3)	812 (448–1466)	790 (462–1534)	940 (507–1585)	891 (456–1568)	1025 (473–2114)	1005 (493–2018)
Urinary albumin-to-creatinine ratio >1000 mg/g, n (%)	154 (41.9)	151 (40.8)	153 (46.5)	148 (44.7)	741 (50.9)	732 (50.5)
Cardiovascular disease, n (%)	57 (15.5)	63 (17.0)	116 (35.3)	93 (28.1)	640 (44.0)	641 (44.2)
Heart failure diagnosis, n (%)	15 (4.1)	20 (5.4)	43 (13.1)	29 (8.8)	177 (12.2)	184 (12.7)
Baseline medication, n (%)						
ACE inhibitor/ARB	354 (96.2)	360 (97.3)	321 (97.6)	322 (97.3)	1,419 (97.5)	1,398 (96.3)
Diuretic	95 (25.8)	78 (21.1)	115 (34.9)	129 (39.0)	718 (49.3)	747 (51.5)
Statin	134 (36.4)	150 (40.5)	222 (67.5)	206 (62.2)	1,039 (71.4)	1,043 (71.9)
Anti-hyperglycemic medication						
Insulin	-	-	-	-	814 (56.0)	784 (54.0)
GLP-1 receptor agonist	-	-	-	-	63 (4.3)	59 (4.1)
Biguanide	-	-	3 (0.9)	3 (0.9)	631 (43.4)	613 (42.2)
Sulphonylurea	-	-	-	-	390 (26.8)	386 (26.6)
DPP-4 inhibitor	-	-	-	-	364 (25.0)	378 (26.1)
Alpha-glucosidase inhibitor	-	-	-	-	42 (2.9)	57 (3.9)

All data are mean (SD) unless otherwise stated

**Supplemental Table 2:** Safety outcomes according to glycemic status

	Dapagliflozin (N=2149)	Placebo (N=2149)	Odds ratio (95% CI)	P-value interaction
<b>Normal glucose (N=736)</b>	367	369		
<b>Pre-diabetes (N=659)</b>	329	330		
<b>Diabetes (N=2,903)</b>	1,453	1,450		
<b>Discontinuation due to adverse event, n (%)</b>				
Normal glucose	21 (5.7)	12 (3.3)	1.83 (0.88, 3.81)	0.18
Pre-diabetes	15 (4.6)	17 (5.2)	0.88 (0.43, 1.79)	
Diabetes	82 (5.6)	94 (6.5)	0.87 (0.64, 1.19)	
<b>Any serious adverse event*, n (%)</b>				
Normal glucose	67 (18.3)	89 (24.1)	0.70 (0.49, 1.00)	0.18
Pre-diabetes	83 (25.2)	78 (23.6)	1.09 (0.76, 1.56)	
Diabetes	483 (33.2)	562 (38.8)	0.79 (0.68, 0.92)	
<b>Adverse events of interest, n (%)</b>				
<b>Amputation†</b>				
Normal glucose	0	0	-	-
Pre-diabetes	0	1 (0.3)	-	
Diabetes	35 (2.4)	38 (2.6)	0.91 (0.57, 1.45)	
<b>Any definite or probable diabetic ketoacidosis</b>				
Normal glucose	0	0	-	-
Pre-diabetes	0	0	-	
Diabetes	0	2 (0.1)	-	

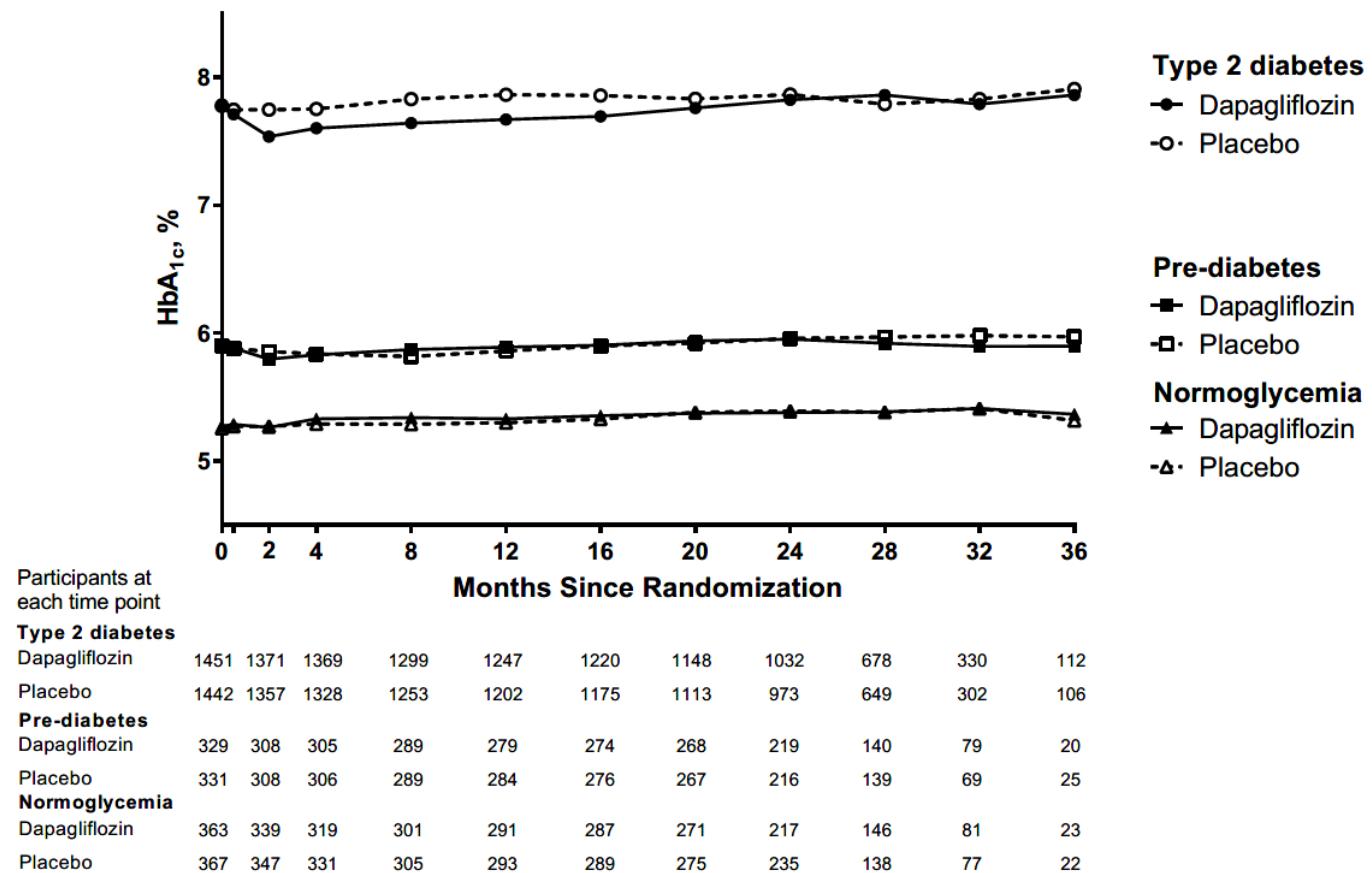
Fracture <sup>‡</sup>				
Normal glucose	8 (2.2)	8 (2.2)	1.02 (0.38, 2.75)	0.89
Pre-diabetes	12 (3.7)	10 (3.0)	1.21 (0.51, 2.85)	
Diabetes	65 (4.5)	51 (3.5)	1.29 (0.89, 1.88)	
Renal related adverse event <sup>‡</sup>				
Normal glucose	15 (4.1)	25 (6.8)	0.59 (0.30, 1.13)	0.27
Pre-diabetes	19 (5.8)	15 (4.6)	1.29 (0.64, 2.58)	
Diabetes	121 (8.3)	148 (10.2)	0.81 (0.63, 1.04)	
Major hypoglycemia <sup>§</sup>				
Normal glucose	0	0	-	-
Pre-diabetes	0	0	-	
Diabetes	14 (1.0)	28 (1.9)	0.50 (0.26, 0.95)	
Volume depletion <sup>‡</sup>				
Normal glucose	19 (5.2)	13 (3.5)	1.50 (0.73, 3.08)	0.35
Pre-diabetes	16 (4.9)	6 (1.8)	2.76 (1.06, 7.17)	
Diabetes	92 (6.3)	71 (4.9)	1.32 (0.96, 1.81)	

<sup>\*</sup>Includes death; <sup>†</sup>Surgical or spontaneous/non-surgical amputation, excluding amputation due to trauma; <sup>‡</sup>Based on pre-defined list of preferred terms;

<sup>§</sup>Adverse event with the following criteria confirmed by the investigator: i) Symptoms of severe impairment in consciousness or behavior, ii) need of external assistance, iii) intervention to treat hypoglycemia, iv) prompt recovery of acute symptoms following the intervention.

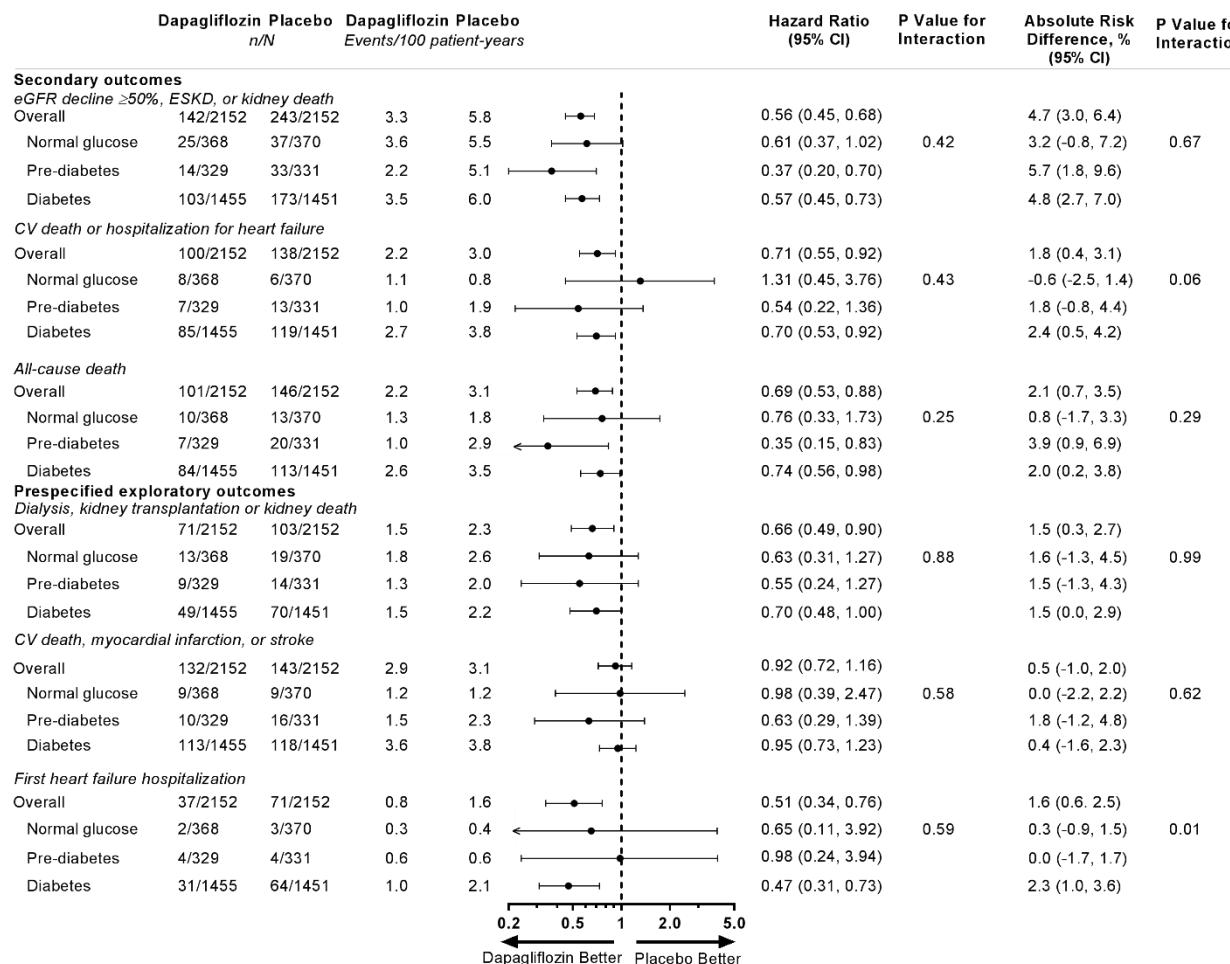
Safety data are summarized for all participants who were randomized and received at least one dose of study medication

**Supplemental Figure 1.** HbA<sub>1c</sub> trajectory during the study in participants with type 2 diabetes, pre-diabetes and normoglycemia according to randomized treatment assignment



The between-group difference in HbA<sub>1c</sub> during follow-up was 0.0% (95%CI -0.2, 0.2; p=0.8597; 0.2 mmol/mol [95%CI -1.8, 2.2]) in participants with normoglycemia, -0.0% (95%CI -0.2, 0.2; p=0.8764; -0.2 mmol/mol [95%CI -2.3, 1.9]) in participants with pre-diabetes, and -0.1% (-0.2, 0.0; p=0.0378; -1.1 mmol/mol [95%CI -2.1, 0.0]) in participants with type 2 diabetes.

**Supplemental Figure 2:** Forest plot of the secondary and pre-specified exploratory endpoints according to glycemic status at baseline



CV, cardiovascular; eGFR, estimated glomerular filtration rate; ESKD, end-stage kidney disease

**Supplemental Figure 3.** Treatment effect of dapagliflozin compared to placebo as a function of baseline HbA<sub>1c</sub> (continuous) for the (A) composite of cardiovascular death or heart failure hospitalization and (B) all-cause mortality. The solid black line represents the hazard ratio of the treatment effect. The grey shaded area represents the 95% confidence interval around the treatment effects. The dotted horizontal line represents a hazard ratio of 1 (i. e. no difference between randomized groups)

