Supplementary Tables

Table S1: Inclusion and exclusion criteria

Inclusion criteria
1 Signed written informed consent: (a) Participants (or designee) had to be willing and able to give signed and dated written informed consent. Minor's parents or legally acceptable representatives had to give fully informed written consent. Assent had to be obtained according to local regulations and if child was capable **2 Target population** (a) Previously diagnosed with T2D by WHO/ADA diagnostic criteria (b) HbA1c ≥6·5% and ≤11% (≥48 and ≤97 mmol/mol) obtained at screening visit (c) Currently on diet and exercise and a stable dose of metformin (at least 1000 mg daily) for a minimum of 8 weeks, or stable dose of insulin for a minimum of 8 weeks, or a stable combination of metformin (at least 1000 mg daily) and insulin for a minimum of 8 weeks prior to screening (d) FPG ≤14·2 mmol/L (≤255 mg/dL) obtained at screening visit (e) Participant re-enrolment: This study permitted the re-enrolment of a participant who had discontinued the study as a pre-treatment failure (ie, participant had not been randomized/had not been treated) Note: If re-enrolled, the participant had to be re-consented. All screening procedures were repeated. Participants could only be re-enrolled once. **3 Age and reproductive status**: (a) Males and females, 10 years of age, up to but not including 25 years of age at the time of randomization (i) Recruitment (randomization) of participants ≥18 and <25 years old was limited to <40% of participants (ii) Recruitment (randomization) of participants ≥10 and ≤15 years old included at least 20% of participants (b) WOCBP* had to have a negative serum or urine pregnancy test (minimum sensitivity 25 IU/L or equivalent units of beta-human chorionic gonadotrophin) within 24 hours prior to the start of study drug (c) Women could not be breastfeeding (d) WOCBP had to agree to follow instructions for method of contraception for the duration of treatment with study drug, plus 5 half-lives of study drug or 30 days (whichever is longer), plus 30 days (duration of ovulatory cycle), for a total of 60

days post-treatment completion

(e) WOCBP who were continuously not heterosexually active were exempt from contraceptive requirements. However, they still had to undergo pregnancy testing as described in this section.

Exclusion criteria

1 Target disease exceptions

(a) Previous diagnosis of type 1 diabetes

(b) Previous diagnosis: of monogenic etiology of T2D such as MODY, genetic disorders with strong associations with insulin resistance/diabetes and/or obesity such as Turner's Syndrome and Prader-Willi, or secondary diabetes (steroid use, Cushing's disease, acromegaly)

(c) DKA within 6 months of screening

(d) Current use of the following medications for the treatment of diabetes, or use within the specified timeframe prior to screening for the main study:

(i) Eight weeks: sulfonylureas, alpha glucosidase inhibitors, metiglinide, oral or injectable incretins or incretin mimetics or other diabetic medications not otherwise specified

(ii) Sixteen weeks: thiazolidinediones

(iii) Any previous history or current use of an SGLT2 inhibitor, including dapagliflozin

(e) Initiation or discontinuation of prescription or non-prescription weight loss drugs within 8 weeks of screening. Use of prescription or non-prescription weight loss drugs had to be stable during the study.

2 Medical history and concurrent diseases

(a) Pregnant, positive serum pregnancy test, planning to become pregnant during the clinical trials, or breastfeeding

(b) History of unstable or rapidly progressive renal disease

(c) History of unresolved vesico-ureteral reflux

(d) History of hemoglobinopathy, with the exception of sickle cell trait or thalassemia minor; or chronic or recurrent hemolysis

(e) Malignancy within 5 years of the screening visit (with the exception of treated basal cell or treated squamous cell carcinoma)

(f) Significant co-morbidity that, in the opinion of the investigators, would increase the risk to the participant such as coronary artery disease, any heart disease that increases risk associated with exercise, or immune-suppression

(g) Replacement or chronic systemic corticosteroid therapy, defined as any dose of systemic corticosteroid taken for >4 weeks within 3 months prior to the Day 1 visit

NOTE: Topical, nasal, or inhaled corticosteroids were allowed

3 Physical and laboratory test findings

(a) Abnormal renal function, which was defined in participants <18 years of age as an eGFR calculated by the Schwartz formula <80 mL/min/1·73 m^2 (1·33 mL/s), and in participants ≥18 years as an eGFR calculated by the MDRD formula <60 mL/min/1·73 m^2 (1·33 mL/s)

(b) Presence of either: antibodies to GAD or protein tyrosine phosphatase-like protein antibodies

(c) An abnormal TSH value at screening was further evaluated for free thyroxine. Participants with abnormal free thyroxine values were excluded.

Note: In participants who had a prior diagnosis of a thyroid disorder and who were currently receiving thyroid replacement therapy, a 1-time re-test of TSH could be allowed, as determined by the Investigator, after a minimum of 6 weeks following the adjustment of thyroid hormone replacement therapy. Such cases were to be discussed with the Sponsor prior to re-testing. The participants had to have all enrolment procedures and laboratory assessments performed as part of this re-test, and all of these had to meet enrolment eligibility criteria. The participant's number however remained the same as initially assigned

(d) Hematuria (confirmed by microscopy at screening) with no explanation as judged by the Investigator up to randomization

(e) Aspartate aminotransferase or ALT >2 × ULN, or clinically significant hepatic disease

(f) Serum total bilirubin ≥2 × ULN, unless exclusively caused by Gilbert's syndrome

(g) History of positive serologic evidence of current infectious liver disease including HAV (IgM), HBsAg, or anti-HCV. Participants who might have isolated positive hepatitis B surface antibodies could be included

(h) Anemia of any etiology defined as hemoglobin ≤10·7 g/dL (107 g/L) for females and ≤11·3 g/dL (113 g/L) for males. Participants who were considered to have anemia according to local guidelines had to be excluded

(i) Volume-depleted participants. Participants at risk for volume depletion due to co-existing conditions or concomitant medications, such as loop diuretics, were to carefully monitor their volume status

(j) Clinically significant abnormalities in any pre-randomization laboratory analyses or ECG that, in the Investigator's opinion, would preclude randomization

4 Allergies and adverse drug reaction

(a) Known allergy, sensitivity or contraindication to any study drug or its

excipient/vehicle.

5 Other exclusion criteria

(a) Person was currently abusing alcohol or other drugs or has done so within the last 6 months prior to the screening visit.

(b) Prisoners or people who were involuntarily incarcerated

(c) People who were compulsorily detained for treatment of either a psychiatric or physical (eg, infectious disease) illness

(d) Psychiatric or cognitive disorder that would, in the opinion of investigators, limit the person's ability to comply with the study drugs and monitoring.

(e) People who had contraindications to therapy as outlined in the dapagliflozin Investigator's Brochure or local package inserts

(f) Participation and receiving investigational product in another clinical study during the prior 3 months

*A WOCBP was defined as any female who had experienced menarche and who had not undergone surgical sterilization (hysterectomy or bilateral oophorectomy) and was not postmenopausal. Investigators counselled WOCBP on the importance of pregnancy prevention and the implications of an unexpected pregnancy. Investigators advised WOCBP on the use of highly effective methods of contraception; ADA=American Diabetes Association; ALT=alanine aminotransferase; DKA=diabetes ketoacidosis; eGFR=estimated glomerular filtration rate; ECG=electrocardiogram; FPG=fasting plasma glucose; HAV=hepatitis A virus; HCV=hepatitis C virus; IgM=immunoglobulin M; MDRD=Modification of Diet in Renal Disease; MODY; maturity onset diabetes of the young; SGLT2=sodium−glucose co-transporter-2; T2D=type 2 diabetes; TSH=thyroid-stimulating hormone; ULN=upper limit of normal; WHO=World Health Organization; WOCBP=woman of child-bearing potential

Table S2: Criteria for glycemic rescue

Study week	Glycemic rescue criteria

Double-blind short-term period (from Day 1 visit up to and including Week 24 visit)	• FPG >13·3 mmol/L (>240 mg/dL) based on:
	  • SMBG for 3 consecutive days followed by a confirmatory central laboratory FPG, **or**
	  • Single central laboratory FPG followed by a confirmatory central laboratory FPG

Open-label long-term period (after Week 24 visit up to and not including Week 52 visit)	• FPG >10 mmol/L (>180 mg/dL) based on:
	  • SMBG for 3 consecutive days followed by a confirmatory central laboratory FPG, **or**
	  • Single central laboratory FPG followed by a central laboratory FPG, **or**
	• HbA1c >8·0% (>64 mmol/mol)

FPG=fasting plasma glucose; SMBG self-monitored blood glucose

Table S3: Predefined list of relevant protocol deviations

1. Randomized participants without Type 2 diabetes, or with a central laboratory HbA1c obtained at enrolment not within ±0·2% (2·.2 mmol/mol) of the protocol-specific HbA1c range
2. Randomized participants not satisfying the target population baseline antihyperglycemic therapy requirement
3. Randomized participants that used antihyperglycemic medication (other than protocol allowed medication, and/or open-label rescue medication) for 14 or more consecutive days during short-term double-blind treatment period (including situations where participants randomized to placebo mistakenly received active blinded treatment during the treatment period)
4. Randomized participants that were treated with any systemic corticosteroid therapy for ≥5 consecutive days during short-term double-blind treatment period
5. Randomized participants with treatment compliance <80% during the 24-week double-blind short-term period
6. Abnormal free T4 values at enrolment
7. History of hemoglobinopathy, with the exception of sickle cell trait (SA) or thalassemia minor; or chronic or recurrent hemolysis

Table S4: Failure to meet randomization criteria

Exclusion violations	Number of participants
Abnormal renal function	3
Abnormal thyroid stimulating hormone	1
Anemia	7
Aspartate transaminase or alanine aminotransferase >2x upper limit of normal	7
Use of diabetes medications	1
Hematuria	2
Malignancy within 5 years	1
Glutamic acid decarboxylase antibodies or islet tyrosine phosphatase 2 antibodies	13
Stable metformin/insulin dose	5
Inclusion violations	
Fasting plasma glucose >14·2 mmol/L (>255 mg/dL) at screening	7
HbA1c <6·5 or >11% (<48 or >97 mmol/mol) at screening	35
No type 2 diabetes diagnosis	1
Consent	1
Re-enrollment	1

Table S5: Clinical laboratory hepatic parameters

	Double-blind short-term period only (24 weeks)		Open-label long-term period only (28 weeks)	Double-blind period plus open-label period (52 weeks)
	Dapagliflozin 10 mg (N=39)	Placebo (N=33)	Placebo switched to dapagliflozin 10 mg (N=27)	Dapagliflozin 10 mg (N=39)
AST elevation (any)	0	0	0	0
ALT elevation (>3x ULN)	3/37 (8)	1/30 (3)	0	4/37 (11)
Bilirubin elevation (>1·5x ULN)	0	2/30 (7)	1/27 (4)	0
ALP elevation (>1·5x ULN)	1/37 (3)	0	0	1/37 (3)
Creatine kinase elevation	0	0	0	0

Data are n/N# (%) where N# is the number of participants with non-missing post-baseline values; All analyses include data after glycemic rescue; ALP=alkaline phosphatase; ALT=alanine aminotransferase; AST=Aspartate aminotransaminase; ULN=upper limit of normal

Table S6: Vital signs, hematology and growth and maturation markers

	Dapagliflozin 10 mg (N=39)	Placebo (N=33)	Placebo switched to dapagliflozin 10 mg (N=27)
BMI z-score			
Baseline	1·69 (0·91)	1·84 (1·08)	-
Change at 24 weeks	−0·08 (0·26)	−0·11 (0·23)	-
Change at 52 weeks	−0·24 (0·49)	-	−0·19 (0·17)
Systolic blood pressure, mmHg			
Baseline	119·4 (12·9)	118·2 (15·2)	-
Change at 24 weeks	−0·3 (10·3)	1·6 (15·2)	-
Change at 52 weeks	1·4 (11·6)	-	−1·8 (10·7)
Diastolic blood pressure, mmHg			
Baseline	73·4 (8·8)	75·8 (7·6)	-
Change at 24 weeks	0·2 (7·0)	−0·7 (11·4)	-
Change at 52 weeks	3·3 (10·9)	-	−1·5 (8·9)
Hematocrit, ratio			
Baseline	0·426 (0·051)	0·432 (0·038)	-
Change at 24 weeks	0·018 (0·036)	0·004 (0·022)	-
Change at 52 weeks	0·029 (0·043)	-	0·030 (0·028)
Hemoglobin, g/L			
Baseline	137·1 (18·4)	139·8 (13·2)	-
Change at 24 weeks	6·3 (12·0)	0·6 (8·2)	-
Change at 52 weeks	10·5 (15·0)	-	7·5 (8·7)
Leukocytes, x 10^9/L			
Baseline	7·86 (2·25)	7·91 (2·02)	-
Change at 24 weeks	−0·18 (1·75)	−0·06 (−1·49)	-
Change at 52 weeks	−0·98 (1·63)	-	0·13 (1·91)
Platelets, x 10^9/L			
Baseline	282·8 (64·4)	284·1 (65·9)	-
Change at 24 weeks	7·5 (41·1)	−4·3 (43·9)	-
Change at 52 weeks	3·1 (41·9)	-	2·7 (41·3)
Calcitonin, pg/mL			
Baseline	2·04 (0·16)	2·29 (1·08)	-
Change at 24 weeks	0·13 (0·48)	−0·06 (0·65)	-
Change at 52 weeks	0·16 (0·56)	-	0·06 (0·20)
Estradiol, pmol/L – males			
Baseline	105·71 (53·25), n=15	89·37 (44·44), n=14	-
Change at 24 weeks	11·16 (49·96)	15·95 (24·27)	-
Change at 52 weeks	10·46 (46·86)	-	47·13 (52·50)
Estradiol, pmol/L – females			
Baseline	173·76 (105·21), n=24	288·46 (292·33), n=19	-
Change at 24 weeks	23·51 (250·32)	−22·27 (283·30)	-
Change at 52 weeks	63·19 (259·44)	-	−43·78 (436·94)
Follicle stimulating hormone, IU/L – males			
Baseline	4·11 (2·05), n=12	3·49 (1·49), n=10	-
Change at 24 weeks	0·50 (1·27)	0·28 (0·86)	-
Change at 52 weeks	1·01 (2·07)	-	0·75 (1·20)
Follicle stimulating hormone, IU/L – females			
Baseline	8·45 (9·43), n=22	5·96 (4·65), n=16	-
Change at 24 weeks	−0·43 (3·03)	4·99 (13·86)	-
Change at 52 weeks	2·93 (12·27)	-	4·72 (14·33)
Insulin-like growth factor-1, µg/L			
Baseline	306·41 (115·48)	293·67 (103·76)	-
Change at 24 weeks	2·57 (70·46)	−26·42 (96·36)	-
Change at 52 weeks	−27·64 (84·01)	-	−22·62 (104·49)

Insulin-like growth factor binding prot3, mg/L			
Baseline	5·86 (1·41)	6·20 (1·74)	-
Change at 24 weeks	−0·02 (1·04)	−0·34 (1·65)	-
Change at 52 weeks	0·25 (0·84)	-	−0·03 (1·67)
Luteinizing hormone, IU/L – males			
Baseline	4·55 (4·30), n=15	7·98 (14·13), n=14	-
Change at 24 weeks	−0·49 (3·49)	0·74 (2·21)	-
Change at 52 weeks	0·49 (4·91)	-	0·73 (1·32)
Luteinizing hormone, IU/L – females			
Baseline	8·97 (10·57), n=24	9·97 (16·36), n=19	-
Change at 24 weeks	−2·50 (9·61)	0·05 (20·28)	-
Change at 52 weeks	−1·43 (14·84)	-	2·51 (21·26)
Parathyroid hormone intact, pmol/L			
Baseline	2·29 (1·39)	2·65 (1·47)	-
Change at 24 weeks	0·18 (1·53)	0·10 (0·87)	-
Change at 52 weeks	0·76 (1·77)	-	0·25 (1·77)
Testosterone, nmol/L – males			
Baseline	12·36 (6·27), n=15	10·54 (6·03), n=14	-
Change at 24 weeks	0·81 (4·06)	−0·20 (1·82)	-
Change at 52 weeks	1·91 (6·38)	-	3·52 (2·63)
Testosterone, nmol/L – females			
Baseline	1·56 (3·44), n=24	0·93 (0·52), n=17	-
Change at 24 weeks	−0·94 (3·49)	−0·10 (0·36)	-
Change at 52 weeks	−0·96 (3·24)	-	−0·30 (0·38)
Thyrotropin, mU/L			
Baseline	1·94 (0·84)	2·19 (1·50)	-
Change at 24 weeks	−0·06 (0·90)	−0·06 (1·82)	-
Change at 52 weeks	−0·11 (0·82)	-	−0·15 (1·49)
25-hydroxyvitamin D, nmol/L			
Baseline	48·2 (22·5)	47·9 (21·2)	-
Change at 24 weeks	−0·15 (23·54)	2·25 (18·46)	-
Change at 52 weeks	2·28 (15·26)	-	−0·025 (14·99)

Data are mean (SD) or mean change (SD)

Table S7: Bone biomarkers

	Dapagliflozin 10 mg (N=39)					Placebo (N=33) or Placebo switched to dapagliflozin 10 mg (N=27)				
	Pre-puberty	Early puberty	Mid puberty	Late puberty and young adult	Total	Pre-puberty	Early puberty	Mid puberty	Late puberty and young adult	Total
Bone specific alkaline phosphatase (µg/L)										
Baseline	-	113·5 (27·7) n=2	41·4 (30·0) n=4	22·1 (11·8) n=32	28·4 (25·4) n=39	27·4 n=1	46·4 (44·3) n=2	55·4 (50·6) n=5	29·3 (31·1) n=24	34·0 (34·4 n=33
Change at 24 wks	-	−19·0 (5·7) n=2	−8·3 (11·1) n=4	−1·1 (6·4) n=30	−2·8 (8·1) n=37	-	3·0 (1·3) n=2	−14·2 (15·2) n=5	−1·2 (3·7) n=20	−3·3 (8·6 n=27
Change at 52 wks	-	−23·2 n=1	−4·7 (6·1) n=3	−3·6 (8·4) n=23	−4·2 (8·7) n=28	-	−6·6 (20·2) n=2	−21·2 (27·2) n=4	−2·0 (4·4) n=15	−6·1 (14·2 n=21
Osteocalcin (µg/L)										
Baseline	-	110·1 (1·3) n=2	61·0 (58·7) n=4	27·5 (15·1) n=32	34·8 (29·8) n=39	33·6 n=1	66·5 (68·9) n=2	48·9 (30·4) n=5	27·7 (19·8) n=24	33·5 (26·0 n=33
Change at 24 wks		15·7 (36·6) n=2	−12·5 (17·0) n=4	−1·8 (5·3) n=30	−1·8 (11·1) n=37	-	15·4 (19·4) n=2	−1·5 (20·1) n=5	−0·5 (10·0) n=20	0·5 (13·0 n=27
Change at 52 wks		−17·6 n=1	−15·5 (15·3) n=4	−7·4 (11·1) n=23	−8·4 (12·0) n=29	-	−4·4 (9·4) n=2	−6·1 (13·8) n=4	0·7 (8·0) n=15	−1·1 (9·3 n=21

Data are mean (SD) or mean change (SD)

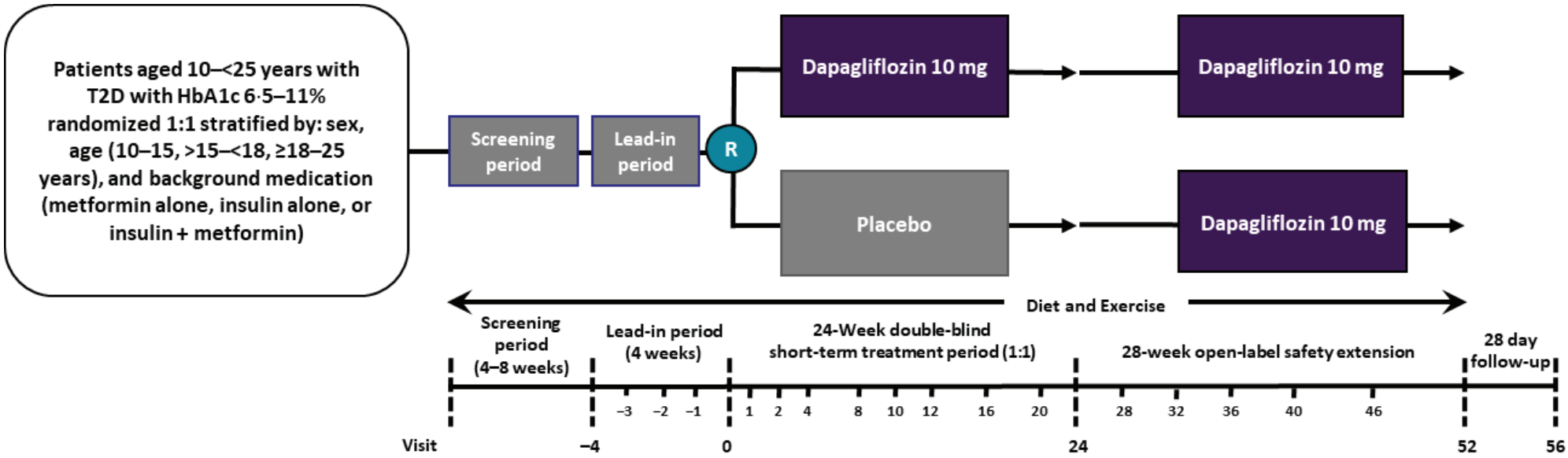
Table S8: Shift in Tanner stages

	Tanner stage at baseline	Tanner stage at Week 52			
		Stage II	**Stage III**	**Stage IV**	**Stage V**
Dapagliflozin 10 mg (N=28)	**Stage II**: 1 (4)	1 (4)	0	0	0
	Stage III: 3 (11)	0	1 (4)	2 (7)	0
	Stage IV: 3 (11)	0	0	2 (7)	1 (4)
	Stage V: 21 (75)	0	0	1 (4)	20 (71)
	Not reported: 1 (4)	0	0	0	1 (4)
Placebo (N=22)	**Stage II**: 2 (9)	1 (5)	1 (5)	0	0
	Stage III: 2 (9)	0	1 (5)	0	1 (5)
	Stage IV: 4 (18)	0	0	2 (9)	2 (9)
	Stage V: 14 (64)	0	0	0	14 (64)

Data are n (%); Green shading indicates moving to a higher Tanner stage at Week 52 versus baseline. Yellow shading indicates remaining in the same Tanner stage at Week 52 versus baseline. Red shading indicates moving to a lower Tanner stage at Week 52 versus baseline; No participants were in Tanner stage I at baseline or at Week 52.

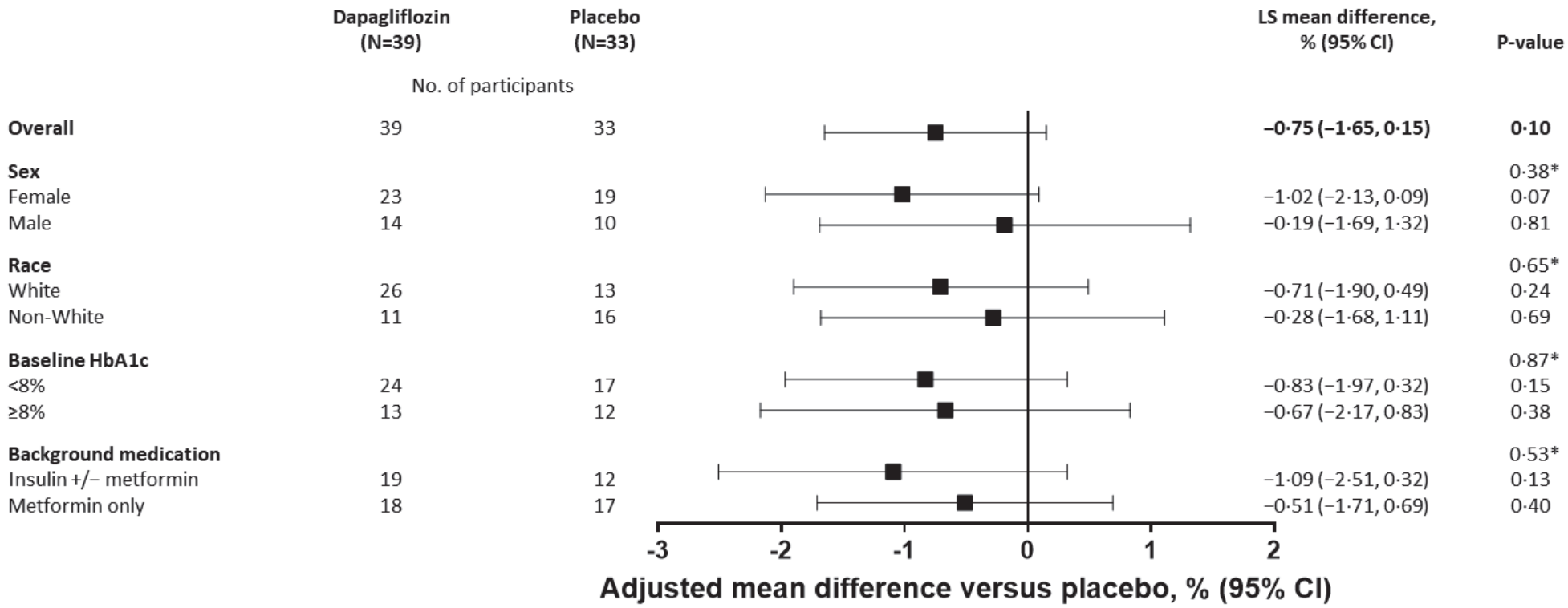
Supplementary Figures

Figure S1: Study design



Participants were to maintain their baseline types of anti-hyperglycemic therapy throughout the study; T2D=type 2 diabetes

Figure S2: Subgroup analyses of the primary outcome of change from baseline in HbA1c at Week 24



*Treatment-by-subgroup interaction at Week 24