

## Effects of Dapagliflozin on Body Weight, Total Fat Mass, and Regional Adipose Tissue Distribution in Patients with Type 2 Diabetes Mellitus with Inadequate Glycemic Control on Metformin

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**Context:** Dapagliflozin, a selective sodium-glucose cotransporter 2 (SGLT2) inhibitor, reduces hyperglycemia in patients with type 2 diabetes mellitus (T2DM) by increasing urinary glucose excretion, and weight loss is a consistent associated finding.

**Objectives:** Our objectives were to confirm weight loss with dapagliflozin and establish through body composition measurements whether weight loss is accounted for by changes in fat or fluid components.

**Design and Setting:** This was a 24-wk, international, multicenter, randomized, parallel-group, double-blind, placebo-controlled study with ongoing 78-wk site- and patient-blinded extension period at 40 sites in five countries.

**Patients:** Included were 182 patients with T2DM (mean values: women 63.3 and men 58.6 yr of age; hemoglobin A1c 7.17%, body mass index 31.9 kg/m<sup>2</sup>, and body weight 91.5 kg) inadequately controlled on metformin.

**Intervention:** Dapagliflozin 10 mg/d or placebo was added to open-label metformin for 24 wk.

**Main Outcome Measures:** Primary endpoint was total body weight (TBW) change from baseline at wk 24. Key secondary endpoints were waist circumference and dual-energy x-ray absorptiometry total-body fat mass (FM) changes from baseline at wk 24, and patient proportion achieving body weight reduction of at least 5% at wk 24. In a subset of patients, magnetic resonance assessment of visceral adipose tissue (VAT) and sc adipose tissue (SAT) volume and hepatic lipid content were also evaluated.

**Results:** At wk 24, placebo-corrected changes with dapagliflozin were as follows: TBW,  $-2.08$  kg [95% confidence interval (CI) =  $-2.84$  to  $-1.31$ ;  $P < 0.0001$ ]; waist circumference,  $-1.52$  cm (95% CI =  $-2.74$  to  $-0.31$ ;  $P = 0.0143$ ); FM,  $-1.48$  kg (95% CI =  $-2.22$  to  $-0.74$ ;  $P = 0.0001$ ); proportion of patients achieving weight reduction of at least 5%,  $+26.2\%$  (95% CI =  $15.5$  to  $36.7$ ;  $P < 0.0001$ ); VAT,  $-258.4$  cm<sup>3</sup> (95% CI =  $-448.1$  to  $-68.6$ ; nominal  $P = 0.0084$ ); SAT,  $-184.9$  cm<sup>3</sup> (95% CI =  $-359.7$  to  $-10.1$ ; nominal  $P = 0.0385$ ). In the dapagliflozin vs. placebo groups, respectively, serious adverse events were reported in 6.6 vs. 1.1%; events suggestive of vulvovaginitis, balanitis, and related genital infection in 3.3 vs. 0%; and lower urinary tract infections in 6.6 vs. 2.2%.

**Conclusions:** Dapagliflozin reduces TBW, predominantly by reducing FM, VAT and SAT in T2DM inadequately controlled with metformin. (*J Clin Endocrinol Metab* 97: 1020–1031, 2012)

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Abbreviations: AE, Adverse event; BMD, bone mineral density; BMI, body mass index; CI, confidence interval; DXA, dual-energy x-ray absorptiometry; FM, fat mass; FPG, fasting plasma glucose; GLP, glucagon-like peptide; HbA1c, hemoglobin A1c; HL, hepatic lipid; LM, lean mass; LOCF, last observation carried forward; MedDRA, Medical Dictionary for Regulatory Activities; MR, magnetic resonance; SAE, serious AE; SAT, sc adipose tissue; SGLT2, sodium-glucose cotransporter 2; TBW, total body weight; T2DM, type 2 diabetes mellitus; UTI, urinary tract infection; VAT, visceral adipose tissue.

**T**reatment of patients with type 2 diabetes mellitus (T2DM) continues to present challenges, with significant proportions of patients failing to achieve and maintain glycemic targets (1–5). Despite availability of treatments that address many of the multiple pathophysiological mechanisms of T2DM, therapeutic efficacy is offset by side effects such as weight gain, hypoglycemia, fluid retention, and gastrointestinal symptoms. Therefore, the search for novel therapeutic agents with an improved benefit-risk profile continues.

Interest has focused on the kidney as a potential therapeutic target, especially because renal glucose reabsorption is increased in T2DM (6). Under normal physiological conditions, the kidney filters and reabsorbs approximately 180 g glucose per day (7). Nearly all filtered glucose is reabsorbed in the proximal convoluted tubule of the nephron, principally via sodium-glucose cotransporter 2 (SGLT2) but also via SGLT1 (8). SGLT2 inhibitors are a new class of oral antidiabetic drugs, which reduce hyperglycemia by increasing urinary glucose excretion independently of insulin secretion or action (9).

Dapagliflozin, a highly selective inhibitor of SGLT2 (10), improves glycemic control in patients with T2DM when used as monotherapy (11) or when added to metformin (12), glimepiride (13), or insulin (14). Moderate weight loss has been a consistent finding in these studies.

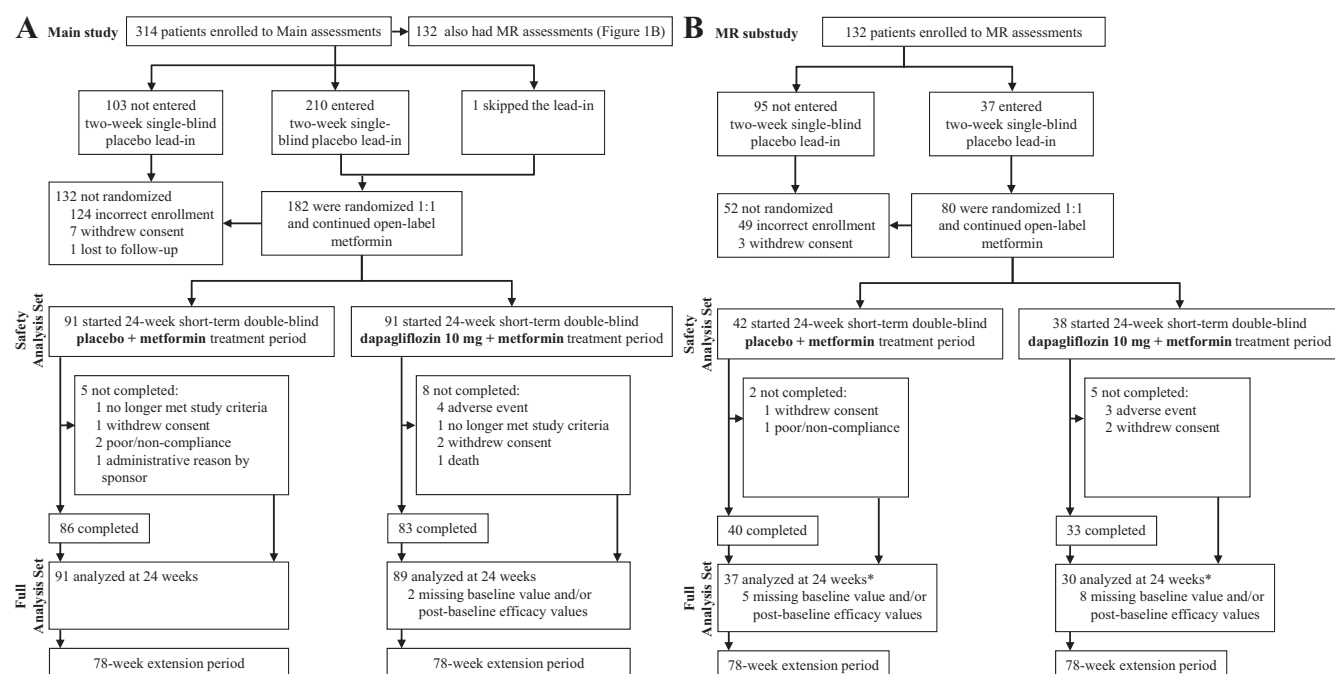
Because dapagliflozin increases urinary glucose excretion, this weight decrease could result from reduced body fat secondary to caloric loss or from fluid loss secondary to osmotic diuresis or from a combination of both factors.

We aimed to investigate the underlying components of this weight loss through body composition measurements during dapagliflozin treatment of patients with T2DM with inadequate glycemic control on metformin alone. Specifically, we aimed to confirm weight loss with dapagliflozin treatment and then to determine the relative contribution of changes in fat mass (FM) *vs.* lean mass (LM) (incorporating the fluid component) to overall weight loss using dual-energy x-ray absorptiometry (DXA). In addition, dapagliflozin effects on regional adipose tissue distribution and hepatic lipid content were investigated in a subset of patients using magnetic resonance (MR) methods.

## Patients and Methods

### Study design

This was a 24-wk, international, multicenter, randomized, parallel-group, double-blind, placebo-controlled Phase III study with a 78-wk site- and patient-blinded extension period conducted from February 13, 2009, and ongoing at 40 sites in Bulgaria, Czech Republic, Hungary, Poland, and Sweden. Results of the first 24-wk double-blind treatment period are presented here. Figure 1 shows the disposition of the patients recruited to the main study and MR substudy. The study complied with the Declaration of Helsinki and the International Conference on Harmonization/Good Clinical Practice Guidelines, was approved by institutional review boards and independent ethics committees for participating centers, and is registered with [www.ClinicalTrials.gov](http://www.ClinicalTrials.gov) (NCT00855166). All participants provided informed consent before entering the study.



## Patients

Inclusion criteria were as follows: patients with T2DM; women aged 55–75 yr who were postmenopausal for a period of at least 5 yr or men aged 30–75 yr; hemoglobin A1c (HbA1c) 6.5–8.5%; fasting plasma glucose (FPG) less than or equal to 240 mg/dl ( $\leq 13.2$  mmol/liter); body mass index (BMI) of 25 kg/m<sup>2</sup> or higher; body weight no higher than 120 kg (due to limitations imposed by DXA equipment); and treatment exclusively with metformin at a stable dose of at least 1500 mg/d for at least 12 wk before enrollment.

Safety objectives for the long-term extension period included change in bone mineral density (BMD). Including patients with rapid changes in BMD might have introduced confounding, so men under 30 yr and perimenopausal women were excluded. Patients with poor glycemic control (HbA1c > 8.5%) were excluded to maximize long-term patient retention without need for rescue therapy for BMD evaluation. For detailed exclusion criteria, see Supplemental Data 1 (published on The Endocrine Society's Journals Online web site at <http://jcem.endojournals.org>).

## Treatments and interventions

Eligible patients entered a 2-wk single-blind placebo lead-in period. Patients were randomized in a 1:1 ratio to double-blind treatment with either dapagliflozin 10 mg or placebo (taken once daily in the morning just before or together with a meal) as add-on therapy to continuing open-label metformin.

Patients could receive rescue therapy exclusively with sitagliptin 100 mg and remain in the trial if their FPG was higher than 240 mg/dl ( $> 13.2$  mmol/liter) during wk 4–7 or higher than 200 mg/dl ( $> 11.1$  mmol/liter) during wk 8–24. Patients could be discontinued due to inadequate glycemic control at the discretion of the study investigator. Because metformin therapy is contraindicated with renal impairment, patients were also discontinued at any point if calculated creatinine clearance was lower than 60 ml/min using the Cockcroft-Gault equation (15).

All patients received diet and lifestyle counseling, including advice on exercise, according to usual clinical routine commencing during the lead-in period and continuing throughout the study.

## Allocation concealment and blinding

Randomization was performed in two strata, men and women, and was done within balanced block sizes of four to ensure approximately equal numbers of patients across the treatment groups and within each stratum. Patients were allocated to study treatments according to a predefined computer-generated randomization scheme provided by AstraZeneca. No patients, investigators, or personnel at AstraZeneca or Bristol-Myers Squibb had access to the randomization codes during the 24-wk double-blind treatment period.

Patients and investigators were blinded to study treatment. All investigational products (dapagliflozin 10 mg and matching placebo) were identical in appearance, smell, and taste and packaged into identical bottles.

## Endpoints, assessments, and safety evaluation

### Endpoints

All endpoints were prespecified. The primary endpoint was change from baseline at wk 24 in total body weight (TBW). The assessment of weight was standardized across study centers: all

centers used calibrated VETEK AV-200-EC-P scales (<http://www.vetek.com/Dynamics/Documents/16d4fef4-d607-4277-94d5-c115b5422b53/DATASHEET-AV-200-EC.pdf>) in accordance with the manufacturer's instructions, the same scale was used for all measurements for any given patient, and all patients were measured in the fasting state with light clothing and no shoes.

Key secondary endpoints were change from baseline at wk 24 in waist circumference, total FM as measured by DXA and the proportion of patients achieving a body weight reduction of at least 5% at wk 24.

Exploratory endpoints included change from baseline at wk 24 for total LM as measured by DXA, the glycemic variables HbA1c and FPG, the adipose tissue markers adiponectin and leptin, and seated systolic and diastolic blood pressure.

The above endpoints were assessed in all 182 patients (main study), and in addition, MR assessments were conducted in 80 of these patients (MR substudy) to evaluate change from baseline at wk 24 for visceral adipose tissue (VAT) volume, sc adipose tissue (SAT) volume, and hepatic lipid (HL) content.

## DXA and MR assessment procedures

Whole-body DXA is widely used for the estimation of body composition (17, 18). The relative attenuation of two different x-ray energies by body tissues produces a three-component model comprising total FM, total LM (including fluid and muscle), and total bone mass. Whole-body DXA was performed at 15 separate DXA sites in the participating countries using Hologic (three sites), Lunar Prodigy (11 sites), and Lunar DPX-L (one site). DXA measurements and quality control of equipment were performed according to manufacturer protocol and supervised via a central DXA core laboratory (Uppsala Osteoporosis Research Unit, Uppsala University Hospital, Uppsala, Sweden). Before the study, personnel from the core laboratory visited all 15 DXA sites to ensure that local technicians positioned patients and employed manufacturer quality control procedures in accordance with the routines conducted at the core laboratory. In addition, a DXA spine phantom was circulated to all 15 DXA sites to calibrate all DXA equipment before study start. Scans were sent to the core laboratory for central reading and analyses continuously during the study period.

The determination of VAT and SAT volumes was undertaken using a fully automated algorithm for segmentation of VAT and SAT from axial abdominal MR imaging data, which excluded intermuscular adipose tissue and bone marrow components. HL content was determined using single-volume localized MR spectroscopy of a  $3 \times 3 \times 3$  cm<sup>3</sup> volume of interest positioned in the right liver lobe, avoiding major vessels and bile ducts. The technique has established reproducibility (19). For further details on MR methods, see Supplemental Data 2.

## Safety evaluation

Safety and tolerability were assessed by collating data on adverse events (AE) using the Medical Dictionary for Regulatory Activities (MedDRA version 13.0), hypoglycemic events, laboratory tests, electrocardiographic and physical examinations, and vital signs. In addition, patients were actively questioned at each study visit to assess signs, symptoms, and reports suggestive of genital infection and of urinary tract infection (UTI). These responses, and those obtained spontaneously, were categorized in the database using a predefined list of MedDRA terms suggestive of vulvovaginitis, balanitis, and related genital infection

and UTI. AE of renal impairment, renal failure, kidney stones, and hypotension/dehydration/hypovolemia were also categorized according to predefined lists of MedDRA terms. Change from baseline in total BMD (grams per square centimeter) at 24 wk was evaluated *post hoc*. Prespecified analyses of regional changes in BMD are planned at 50 and 102 wk.

## Statistical analysis

A closed testing procedure was used to control the type I error rate at less than or equal to 0.05 (two-sided) across the primary and three key secondary endpoints. If the primary endpoint was significant at a level  $P < 0.05$ , then the results of the key secondary endpoints were interpreted using Hochberg's method (20).

Continuous endpoints were evaluated using analysis of covariance, with treatment and sex as fixed effects and baseline value as covariate. Proportions were analyzed using logistic regression with adjustment for baseline values and sex as described by Zhang *et al.* (21).  $P$  values are reported for the primary and key secondary endpoints and confidence intervals with nominal  $P$  values for exploratory endpoints.

Two analysis sets were defined: the safety analysis set, consisting of all patients who received at least one dose of investigational product, and the full analysis set, consisting of all randomized patients who received at least one dose of investigational product and who had both a baseline and at least one post-baseline efficacy value for at least one efficacy variable. Because the MR assessments were conducted at a different center, originally a  $\pm 7$ -d window was set for conducting the 24-wk MR assessments in relation to other study assessments. However, this narrow window proved impractical for a proportion of patients, and therefore, the window was expanded to  $\pm 21$  d. The MR substudy full analysis set reported here includes patients from this expanded window.

Primary, key secondary, and exploratory endpoints were analyzed using the full analysis set. For glycemic variables, observations after initiation of rescue therapy were excluded from the analysis, with these and other missing values for glycemic and nonglycemic variables at wk 24 replaced using the last observation carried forward (LOCF) method.

To probe the validity of the missing completely at random (MCAR) assumption underlying LOCF, and to explore the potential impact of informative missing data, missing not at random (MNAR), a sensitivity analysis was conducted using pattern mixture modeling assuming control-based pattern imputation (<http://www.quintiles.com/elements/media/inthenews/implementation-pattern-mixture-models-using-standard-sasstat-procedures.pdf>) (23).

Safety analyses, including the *post hoc* analysis of BMD, were performed using descriptive statistics for the safety analysis set. For sample size calculations, see Supplemental Data 3.

## Results

### Patients

Figure 1 shows the disposition of the patients, with 92.9% of randomized patients completing the 24-wk double-blind treatment period. The most common reasons for discontinuation were withdrawal of consent and AE. Demographic and baseline characteristics were balanced

across treatment groups for the study population (Table 1), and characteristics of patients discontinuing *vs.* those completing are shown in Supplemental Data 4. Of the patients with available 24-wk MR assessment data, 82.1% were assessed within the prespecified narrow  $\pm 7$ -d time window.

Concomitant diuretic use at randomization was balanced across treatment groups (Table 1). Three patients commenced diuretics or commenced additional diuretics, one in the placebo group and two in the dapagliflozin group, but otherwise, diuretic use remained stable during the course of the double-blind treatment period.

### Primary endpoint

Dapagliflozin produced a statistically significant weight reduction compared with placebo at 24 wk; a greater adjusted mean TBW change of  $-2.96$  kg [95% confidence interval (CI) =  $-3.51$  to  $-2.41$ ] was observed in the dapagliflozin group compared with a change of  $-0.88$  kg (95% CI =  $-1.43$  to  $-0.34$ ) in the placebo group, with a significant difference between groups of  $-2.08$  kg (95% CI =  $-2.84$  to  $-1.31$ ;  $P < 0.0001$ ). In the dapagliflozin group, mean change in TBW from baseline showed a faster decline over the first few weeks, followed by a more gradual decline that had not plateaued by 24 wk (Fig. 2A). This pattern of weight change with dapagliflozin occurred in the context of an initial rapid increase in daily spot urinary glucose, which thereafter remained stable at 2000–2500 mg/dl (111–139 mmol/liter) (Fig. 2B). However, changes in blood urea nitrogen, reflective of fluid loss, showed a different pattern: an initial rise, followed by a fall to a stable level (Fig. 2C).

A significant sex-by-treatment interaction was noted ( $P = 0.0481$ ), with men showing a greater placebo-corrected mean decrease in TBW ( $-2.76$  kg, 95% CI =  $-3.78$  to  $-1.74$ ) at 24 wk with dapagliflozin treatment than women ( $-1.22$  kg, 95% CI =  $-2.36$  to  $-0.08$ ).

A sensitivity analysis using a pattern mixture model (under the assumption that dapagliflozin patients who discontinued the study exhibited the same future evolution of disease as placebo patients) provided results similar to those from the LOCF analysis of TBW (Supplemental Data 4).

### Secondary endpoints

Dapagliflozin treatment met all three key secondary endpoints at 24 wk (Table 2), showing statistically significant placebo-corrected reductions in waist circumference ( $-1.52$  cm; 95% CI =  $-2.74$  to  $-0.31$ ;  $P = 0.0143$ ) and FM ( $-1.48$  kg; 95% CI =  $-2.22$  to  $-0.74$ ;  $P = 0.0001$ ) and a significant placebo-corrected increase in the proportion of patients achieving weight reduction of at least

**TABLE 1.** Demographic and baseline characteristics of the full analysis set

	Placebo + metformin	Dapagliflozin 10 mg + metformin
Number of patients	91	89
Sex [n (%)]		
Men	51 (56.0)	49 (55.1)
Women	40 (44.0)	40 (44.9)
Age (yr), mean ± sd	60.8 ± 6.9	60.6 ± 8.2
Men	59.2 ± 7.9	58.0 ± 8.9
Women	62.9 ± 4.5	63.7 ± 5.8
Race [n (%)]		
White	91 (100.0)	89 (100.0)
Physical measurements		
Weight (kg), mean ± sd	90.9 ± 13.7	92.1 ± 14.1
Men	95.9 ± 12.2	98.1 ± 12.8
Women	84.6 ± 13.0	84.7 ± 12.1
BMI (kg/m <sup>2</sup> ) mean ± sd	31.7 ± 3.9	32.1 ± 3.9
BMI ≥27 kg/m <sup>2</sup> [n (%)]	79 (86.8)	78 (87.6)
BMI ≥30 kg/m <sup>2</sup> [n (%)]	60 (65.9)	60 (67.4)
Waist circumference (cm), mean ± sd	104.5 ± 12.3	105.6 ± 10.1
Duration of T2DM (yr), mean ± sd	5.5 ± 5.3	6.0 ± 4.5
HbA1c (%), mean ± sd	7.16 ± 0.53	7.19 ± 0.44
FPG [mg/dl (mmol/liter)], mean ± sd	149.6 ± 25.1 (8.3 ± 1.4)	148.0 ± 24.7 (8.2 ± 1.4)
Metformin use at randomization <sup>a</sup>		
<1500 mg/d (n)	0	0
≥1500 to <2000 mg/d [n (%)]	41 (45.1)	36 (39.6)
≥2000 mg/d [n (%)]	50 (54.7)	55 (60.4)
Dose (mg), mean ± sd	1901 ± 430	1989 ± 477
Diuretic use at randomization <sup>a</sup> [n (%)]	37 (40.7)	36 (39.6)
Diabetes-related diseases [n (%)]		
Neuropathy	4 (4.4)	7 (7.9)
Retinopathy	4 (4.4)	1 (1.1)
Nephropathy	1 (1.1)	0
Microalbuminuria	3 (3.3)	4 (4.5)
Previous history of CVD <sup>b</sup> [n (%)]	26 (28.6)	21 (23.6)
Hypertension [n (%)]	75 (82.4)	77 (86.5)
Dyslipidemia [n (%)]	53 (58.2)	51 (57.3)
Estimated GFR <sup>c</sup> [n (%)]		
<30 ml/min · 1.73 m <sup>2</sup>	0	0
≥30 and <60 ml/min · 1.73 m <sup>2</sup>	5 (5.5)	1 (1.1)
≥60 and <90 ml/min · 1.73 m <sup>2</sup>	56 (61.5)	54 (60.7)
≥90 ml/min · 1.73 m <sup>2</sup>	30 (33.0)	34 (38.2)

CVD, Cardiovascular disease; GFR, glomerular filtration rate.

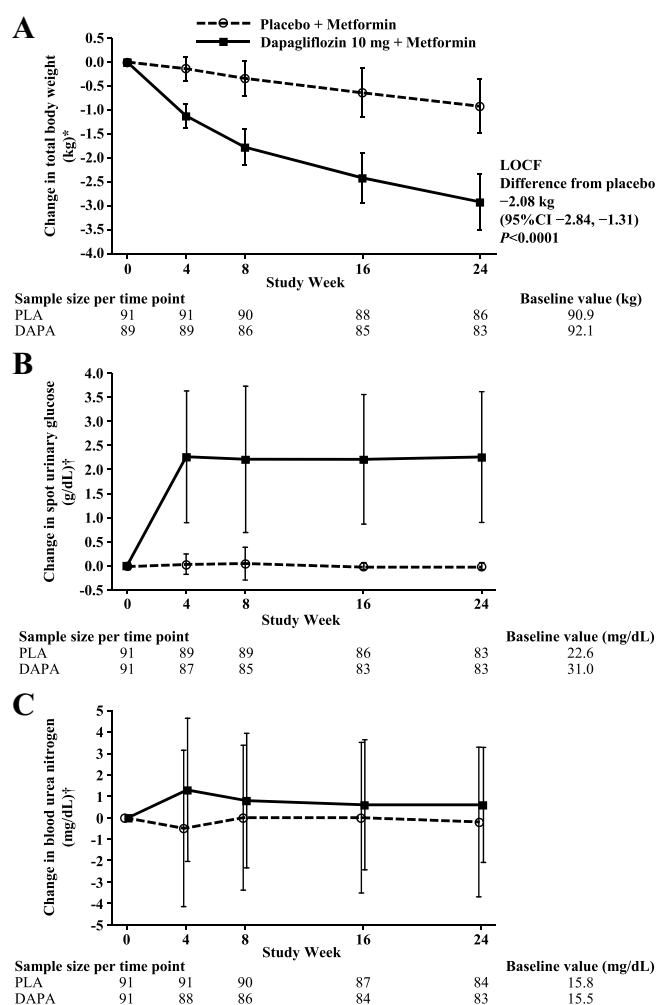
<sup>a</sup> Patient numbers based on safety analysis set.<sup>b</sup> Does not include patients with a cardiovascular history of hypertension only.<sup>c</sup> Calculation of GFR based upon the Modification of Diet in Renal Disease formula; eGFR (milliliters per minute per 1.73 m<sup>2</sup>) = 186 × [serum creatinine (milligrams per deciliter)]<sup>-1.154</sup> × (age)<sup>-0.203</sup> × (0.742 if female) × (1.21 if black).

5% (26.2%; 95% CI = 15.5 to 36.7;  $P < 0.0001$ ). Reduction in FM accounted for two thirds of the total weight loss observed with dapagliflozin as measured by DXA (Fig. 3A).

### Exploratory endpoints

Dapagliflozin produced greater mean reductions from baseline in LM at 24 wk compared with placebo (Fig. 3A), resulting in a placebo-corrected difference of  $-0.6$  kg (95% CI =  $-1.1$  to  $-0.1$ ; nominal  $P = 0.0211$ ). Although dapagliflozin appeared to produce a proportionally greater reduction in FM than LM, this was not statistically tested. Dapagliflozin reduced HbA1c (placebo-corrected

difference  $-0.28\%$ ; 95% CI =  $-0.42$  to  $-0.15$ ; nominal  $P < 0.0001$ ) and FPG (placebo-corrected difference 17.1 mg/dl; 95% CI =  $-23.9$  to  $-10.2$ ; nominal  $P < 0.0001$ ) at 24 wk (Table 2), with no discontinuations due to poor glycemic control in either treatment group. One man and one woman, both receiving placebo and both included in the MR substudy, required rescue therapy during the 24-wk double-blind treatment period. No differences between dapagliflozin and placebo groups were noted in mean changes from baseline at 24 wk for adiponectin, leptin, or systolic or diastolic blood pressure (Table 2). *Post hoc* regression analyses showed that increased spot urinary glucose excretion was significantly associated



**FIG. 2.** Change in TBW (A) (kilograms), spot urinary glucose (B) (grams per deciliter), and blood urea nitrogen (C) (milligrams per deciliter). \*, Data are adjusted mean change from baseline and 95% CI derived from analysis of covariance using the full analysis set and include data after rescue therapy. †, Data are mean change from baseline and SD using the safety analysis set and including data after rescue therapy.

with decreases in both TBW and FM (Supplemental Data 5).

### MR substudy

Dapagliflozin produced greater mean reductions from baseline in VAT and SAT compared with placebo at 24 wk (Fig. 3B), resulting in placebo-corrected differences of  $-258.4 \text{ cm}^3$  (95% CI =  $-448.1$  to  $-68.6$ ; nominal  $P = 0.0084$ ) and  $-184.9 \text{ cm}^3$  (95% CI =  $-359.7$  to  $-10.1$ ; nominal  $P = 0.0385$ ), respectively. These absolute reductions in VAT and SAT with dapagliflozin appeared to be similar, with a decrease from baseline in VAT/SAT ratio at 24 wk of  $-0.03$  (95% CI =  $-0.07$  to  $0.00$ ) compared with an increase of  $0.01$  (95% CI =  $-0.02$  to  $0.04$ ) with placebo (placebo-corrected difference  $-0.04$ ; 95% CI =  $-0.09$  to  $0.00$ ; nominal  $P = 0.0645$ ). Of note, there was a difference in baseline VAT between the dapagliflozin and placebo groups of  $443.8 \text{ cm}^3$ , a chance consequence

of four patients with the highest baseline VAT being in the dapagliflozin group. Change from baseline at 24 wk in mean percent HL content with dapagliflozin was  $-2.35\%$  and  $-1.53\%$  with placebo, resulting in a placebo-corrected difference of  $-0.82\%$  (95% CI =  $-2.97$  to  $1.33$ ; nominal  $P = 0.4499$ ).

### Safety and tolerability

#### Overall AE

Proportions of patients with at least one AE were similar in the dapagliflozin (42.9%) and placebo group (39.6%). A higher proportion of patients in the dapagliflozin group experienced at least one serious AE (SAE) compared with placebo (6.6 vs. 1.1%), or were discontinued from study medication due to an AE (4.4 vs. 0.0%). SAE reported in the dapagliflozin group were pneumonia (two events), esophageal variceal hemorrhage, vertigo, spinal osteoarthritis, transient ischemic attack, and hypertension; and in the placebo group, ulcerative keratitis. The patient experiencing a transient ischemic attack showed no meaningful change in hematocrit (baseline value, 42%; value before event, 40%; value after event 44%). One patient in the dapagliflozin group died during hospitalization for pneumonia due to esophageal variceal hemorrhage. Another three patients receiving dapagliflozin discontinued the study consequent to spinal osteoarthritis, dysuria, and vulvovaginal pruritus.

#### Prespecified safety analyses of special interest

Two patients in the dapagliflozin group and three patients in the placebo group experienced at least one hypoglycemic event. No hypoglycemic event was classified as major (see Table 3 for definition), and no patient was discontinued from the study or study medication due to a hypoglycemic event.

Events suggestive of vulvovaginitis, balanitis, and related genital infection and lower UTI were observed more frequently with dapagliflozin compared with placebo (Table 3). In dapagliflozin-treated patients, women reported more genital infections [two of 42 (4.8%)] than men [one of 49 (2.0%)], and similarly, women reported more lower UTI [five of 42 (11.9%)] than men [one of 49 (2.0%)]. No kidney infections or AE suggestive of renal impairment, renal failure, or renal stones were reported. One patient receiving dapagliflozin experienced hypotension, which resolved after concomitant amlodipine treatment was stopped.

#### Laboratory values and vital signs

At wk 24, dapagliflozin treatment was associated with a slight increase in hematocrit and blood urea nitrogen, a decrease in calculated creatinine renal clearance but with-

**TABLE 2.** Key secondary, glycemic, and exploratory endpoints at 24 wk

	Placebo + metformin (N = 91)	Dapagliflozin 10 mg + metformin (N = 89)
Waist circumference (cm)		
n	91	89
Baseline mean	104.5	105.6
Adjusted mean change from baseline <sup>a</sup>	−0.99	−2.51
Difference from placebo + metformin		−1.52
95% two-sided CI of difference		−2.74 to −0.31
P value of difference		0.0143 <sup>b</sup>
FM (kg)		
n	79	82
Baseline mean	33.1	33.6
Adjusted mean change from baseline <sup>a</sup>	−0.74	−2.22
Difference from placebo + metformin		−1.48
95% two-sided CI of difference		−2.22 to −0.74
P value of difference		0.0001 <sup>b</sup>
Proportion with body weight decrease ≥5%		
x/n	4/91	27/89
Adjusted proportion <sup>c</sup>	4.3%	30.5%
Difference from placebo + metformin		26.2%
95% two-sided CI of difference		15.5% to 36.7%
P value of difference		<0.0001 <sup>b</sup>
HbA1c (%)		
n	91	88
Baseline mean	7.16	7.19
Adjusted mean change from baseline <sup>d</sup>	−0.10	−0.39
Difference from placebo + metformin		−0.28
95% two-sided CI of difference		−0.42 to −0.15
Nominal P value of difference		<0.0001
FPG [mg/dl (mmol/liter)]		
n	91	88
Baseline mean	149.6 (8.30)	147.9 (8.21)
Adjusted mean change from baseline <sup>d</sup>	2.4 (0.13)	−14.7 (−0.82)
Difference from placebo + metformin		−17.1 (−0.95)
95% two-sided CI of difference		−23.9 to −10.2
Nominal P value of difference		(−1.33 to −0.57) <0.0001
Serum adiponectin (ng/ml)		
n	83	82
Baseline mean	6587.2	6717.9
Adjusted mean change from baseline <sup>a</sup>	1363.2	−373.1
Difference from placebo + metformin		−1736.3
95% two-sided CI of difference		−4462.5 to 989.8
Nominal P value of difference		0.2103
Serum leptin (ng/ml)		
n	81	83
Baseline mean	23.2	23.81
Adjusted mean change from baseline <sup>a</sup>	0.09	−2.64
Difference from placebo + metformin		−2.72
95% two-sided CI of difference		−5.92 to 0.47
Nominal P value of difference		0.0944
Seated systolic/diastolic blood pressure (mm Hg)		
n	91	88
Baseline mean	133.3/80.4	135.9/80.6
Adjusted mean change from baseline <sup>a</sup>	0.1/0.3	−2.7/−0.7
Difference from placebo + metformin		−2.8/−1.0
95% two-sided CI of difference		−5.9 to 0.2/−2.9 to 1.0
Nominal P value of difference		0.0637/0.3458

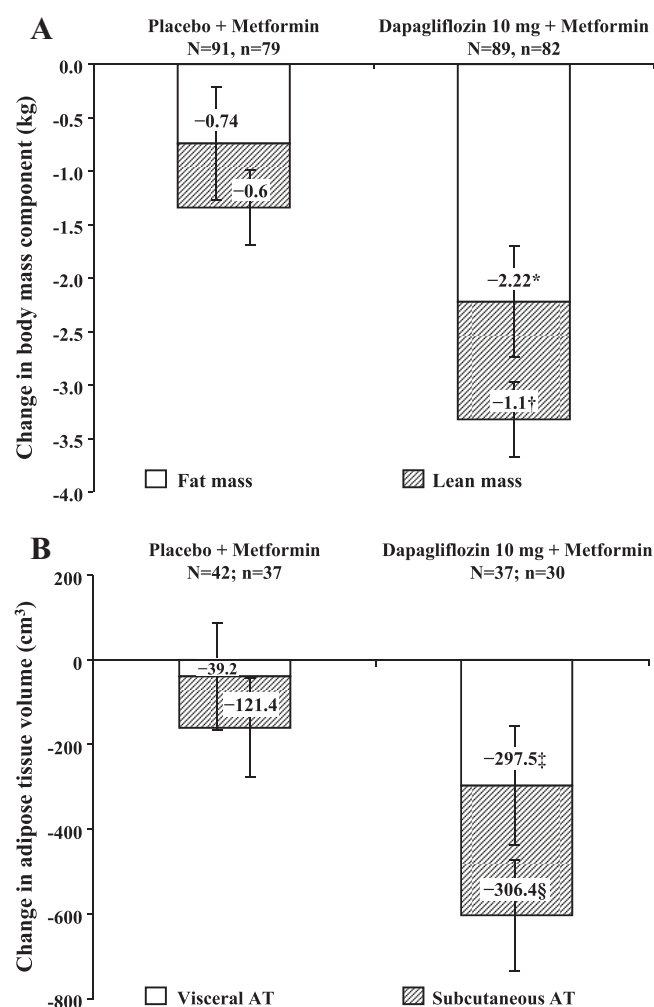
N represents the number of patients in the full analysis set; n represents the number of patients in the full analysis set with nonmissing baseline and wk 24 (LOCF) values.

<sup>a</sup> Data are adjusted mean changes from baseline to wk 24 derived from analysis of covariance using the full analysis set and LOCF and include data after rescue therapy.

<sup>b</sup> Significant P value using Hochberg's procedure.

<sup>c</sup> Data are adjusted percentage derived from logistic regression with the methodology of Zhang *et al.* (21) using the full analysis set and LOCF and include data after rescue therapy.

<sup>d</sup> Data are adjusted mean changes from baseline to wk 24 derived from analysis of covariance using the full analysis set and LOCF and exclude data after rescue therapy.



**FIG. 3.** A, Change in DXA FM and LM with treatment at 24 wk; B, MR substudy, mean change from baseline in VAT and SAT volume with treatment at 24 wk. N represents the number of patients in the full analysis set (A) or full analysis set MR substudy (B); n represents the number of patients in the full analysis set (A) or full analysis set MR substudy (B) with nonmissing baseline and wk 24 (LOCF) values. Data are adjusted mean change from baseline and 95% CI derived from analysis of covariance using the full analysis set and LOCF values and include data after rescue therapy. Baseline values are as follows: FM, 33.1 kg on placebo and 33.6 kg on dapagliflozin; LM, 55.6 kg on placebo and 56.2 kg on dapagliflozin; VAT, 2798.2 cm³ on placebo and 3242.0 cm³ on dapagliflozin; SAT, 4679.3 cm³ on placebo and 4582.2 cm³ on dapagliflozin. Mean dapagliflozin vs. placebo differences are as follows: \*, FM,  $-1.48$  kg (95% CI =  $-2.22$  to  $-0.74$ ;  $P = 0.0001$ ); †, LM,  $-0.60$  kg (95% CI =  $-1.10$  to  $-0.10$ ; nominal  $P = 0.0211$ ); ‡, VAT,  $-258.4$  cm³ (95% CI =  $-448.1$  to  $-68.6$ ; nominal  $P = 0.0084$ ); §, SAT,  $-184.9$  cm³ (95% CI =  $-359.7$  to  $-10.1$ ; nominal  $P = 0.0385$ ).

out clinically meaningful changes in serum creatinine or estimated glomerular filtration rate, and a decrease in serum uric acid (Supplemental Data 6). Reticulocyte count increased at 4 and 8 wk, but no difference compared with placebo was observed at 24 wk (Supplemental Data 6). One patient had a hematocrit value of 55.2% at 24 wk but did not experience any thromboembolic event. No change in seated heart rate was observed (Supplemental Data 6).

## Bone mineral density

Total BMD (mean  $\pm$  SD) at baseline was  $1.193 \pm 0.127$  g/cm² in the dapagliflozin group ( $n = 88$ ) and  $1.200 \pm 0.115$  g/cm² in the placebo group ( $n = 88$ ), with mean changes from baseline at 24 wk of  $-0.194$  and  $-0.200$  g/cm², respectively, corresponding to a mean dapagliflozin vs. placebo difference at 24 wk of  $0.006$  g/cm² (95% CI =  $-0.030$  to  $0.041$ ).

## Discussion

Dapagliflozin 10 mg produced a placebo-corrected reduction in TBW of 2.1 kg at 24 wk and improved glycemic control in overweight patients with inadequately controlled T2DM on metformin. In common with many clinical diabetes trials, these patients also received general diet and exercise advice. The magnitude of this change in TBW is similar to the 1.7-kg weight loss estimate reported in a meta-analysis of 22 randomized controlled trials examining specific diet and/or exercise interventions of 1–5 yr duration in patients with T2DM (24) and comparable to the placebo-corrected reductions of 1.0–2.6 kg observed with the 10-mg dose in other dapagliflozin treatment studies (11–14). Longer-term data will be required to establish whether the weight loss observed with dapagliflozin treatment is sustained.

Obesity, and especially visceral/abdominal adiposity, is associated with diabetes (25), insulin resistance (26), metabolic syndrome (27), and increased cardiovascular risk (28, 29). However, many treatments for diabetes increase weight (sulfonylureas, insulin, and thiazolidinediones), whereas some are weight neutral (metformin, dipeptidyl peptidase-4 inhibitors, acarbose), and only a few reduce weight [glucagon-like peptide (GLP)-1 analogs] (30). The change in TBW with dapagliflozin treatment in this study was similar to the 2- to 3-kg reduction achieved with the GLP-1 analogs exenatide and liraglutide (31). However, GLP-1 analogs must be injected and are associated with gastrointestinal side effects, which may potentially limit the tolerability and acceptability of these agents. Thus, new antidiabetic agents that improve glycemic control, reduce weight, and are well tolerated would represent a significant advance in T2DM treatment.

Studies of body composition assessing changes in FM and LM have been conducted for a number of antidiabetic treatments in patients with T2DM. The increase in TBW seen with thiazolidinediones is largely attributable to an increase in total FM and total body water (32–34), the latter contributing to the increased risk of peripheral edema and heart failure with these agents. Although GLP-1 analogs reduce TBW, recent studies with exenatide

**TABLE 3.** Overall summary of number of patients with an AE, number of patients with an AE with frequency at least 2% in either group, and number of patients with AE of special interest during the 24-wk double-blind treatment period

	Placebo + metformin (N = 91)	Dapagliflozin 10 mg + metformin (N = 91)
Overall summary of number (%) of patients with an AE		
≥1 AE	36 (39.6)	39 (42.9)
≥1 AE related to study treatment	5 (5.5)	9 (9.9)
Deaths	0	1 (1.1)
≥1 SAE	1 (1.1)	6 (6.6)
≥1 SAE related to study treatment	0	0
SAE leading to discontinuation	0	1 (1.1)
AE leading to discontinuation	0	4 (4.4)
Number (%) of patients with an AE with frequency ≥2% in either group <sup>a</sup>		
Nasopharyngitis	5 (5.5)	6 (6.6)
Hypertension	4 (4.4)	4 (4.4)
Pneumonia	0	3 (3.3)
Angina pectoris	0	2 (2.2)
Cystitis	1 (1.1)	2 (2.2)
UTI <sup>b</sup>	0	2 (2.2)
Arthralgia	5 (5.5)	1 (1.1)
Headache	2 (2.2)	1 (1.1)
Diarrhea	2 (2.2)	0
Number (%) of patients with AE of special interest		
Hypoglycemic events <sup>c</sup>		
Total	3 (3.3)	2 (2.2)
Major episode	0	0
Minor episode	2 (2.2)	2 (2.2)
Other episode	1 (1.1)	0
Leading to discontinuation	0	0
Signs and symptoms suggestive of genital infection <sup>d</sup>		
Total	0	3 (3.3)
Balanitis	0	1 (1.1)
Genital infection	0	1 (1.1)
Vulvovaginal pruritus	0	1 (1.1) <sup>e</sup>
Signs and symptoms suggestive of UTI <sup>d</sup>		
Total	2 (2.2)	6 (6.6)
Cystitis	1 (1.1)	2 (2.2)
Lower UTI	0	2 (2.2)
Candiduria	0	1 (1.1)
Dysuria	0	1 (1.1) <sup>e</sup>
White blood cell urine positive	1 (1.1)	0
Pyelonephritis	0	0
Renal impairment/renal failure/urinary stones/fracture/edema <sup>f</sup>	0	0
Hypotension	0	1 (1.1)

N represents the number of patients in the safety analysis set and including data after rescue therapy.

<sup>a</sup> By MedDRA version 13.0 preferred term.

<sup>b</sup> Based upon definitive MedDRA term.

<sup>c</sup> Major hypoglycemia was defined as a symptomatic episode requiring external assistance due to severely impaired consciousness or behavior, with capillary or plasma glucose levels below 3.0 mmol/liter and recovery after glucose or glucagon administration. Minor hypoglycemia was defined as either symptomatic episode with capillary or plasma glucose levels below 3.5 mmol/liter, irrespective of the need for external assistance, or an asymptomatic episode with capillary or plasma glucose levels below 3.5 mmol/liter that does not qualify as a major episode. Other hypoglycemia was defined as an episode with symptoms suggestive of hypoglycemia but without confirmative measurement.

<sup>d</sup> These events represented a predefined group of MedDRA terms used to report AE via protocol-mandated active questioning that could potentially suggest a genital infection or UTI.

<sup>e</sup> This patient had both vulvovaginal pruritus and dysuria.

<sup>f</sup> These events were also identified in the database using prespecified lists of preferred terms but also included, for example, laboratory values such as serum creatinine.

(35, 36) and liraglutide (16, 37) have demonstrated statistically significant changes only in FM *vs.* glimepiride and not *vs.* placebo. In contrast to these studies, dapagli-

flozin significantly reduced both TBW and DXA FM *vs.* placebo. About two thirds of the weight loss observed with dapagliflozin was attributable to reductions in fat (FM *vs.*

LM,  $-2.2$  vs.  $-1.1$  kg), and for weight loss with placebo, about one half was attributable to reductions in fat (FM vs. LM,  $-0.74$  vs.  $-0.6$  kg). Moreover, the reductions in TBW, FM, and waist circumference with dapagliflozin treatment occurred in the context of a sustained elevation in spot urinary glucose excretion, which itself was significantly associated with decreases in TBW and FM. This supports the DXA findings that caloric loss from glucosuria, and not fluid loss, was principally responsible for these changes. However, fluid loss may have contributed to the more rapid initial decline in TBW.

Given the importance of visceral/abdominal adiposity for diabetes risk, studies have been conducted examining the effect of antidiabetic treatments on regional adipose distribution. The increase in FM with thiazolidinediones is driven by an increase in SAT but without statistically significant change in VAT (33, 34). Although liraglutide decreases VAT and SAT area, as measured by single-slice computerized tomography, these decreases vs. placebo were not statistically significant (16). In the present study, using a more sophisticated methodology of automated MR imaging assessment of abdominal adipose tissue volumes, dapagliflozin significantly reduced both VAT and SAT volumes compared with placebo. The lack of significant changes in HL content, adiponectin, and leptin may reflect insufficient sample size.

Dapagliflozin treatment increased signs, symptoms, and reports suggestive of vulvovaginitis, balanitis, and related genital infection and of lower UTI, which mainly occurred in women. These suggestive events have been noted in previous studies with dapagliflozin, where they have responded to routine management and have rarely led to study discontinuation (12, 13).

A potential relationship between changes in hematocrit and fluid loss with dapagliflozin is difficult to evaluate owing to the temporary increase in reticulocyte count. Additional studies are ongoing to establish the mechanism of this effect. Despite this hematocrit increase, there was no evidence of an increased incidence of thromboembolic events with dapagliflozin. Although blood urea nitrogen increased and calculated creatinine clearance decreased with dapagliflozin, no meaningful changes in seated heart rate or estimated glomerular filtration rate were evident; in addition, no AE of renal impairment or failure were reported. Taken together, these findings suggest that dapagliflozin was not associated with dehydration or impairment in renal function.

The study has some potential limitations. First, to assess long-term changes in BMD, pre- and perimenopausal women were excluded to avoid potential confounding by the rapid changes in BMD occurring in

women of this age range. In the main study, this resulted in men being on average 5 yr younger and 12 kg heavier, which may have explained the significant effect of sex on change in TBW. In the MR substudy, baseline VAT volume was higher in the dapagliflozin vs. placebo groups. However, these baseline differences are unlikely to have affected the results because statistical analyses controlled for sex and baseline values. Second, patients with body weight over 120 kg were excluded. Third, baseline HbA1c was low in this study, and consequently, changes in HbA1c with dapagliflozin were modest. The low baseline HbA1c was deliberately chosen to reduce study discontinuation secondary to inadequate glycemic control to enable the long-term evaluation of BMD. Fourth, the precise mechanism of dapagliflozin-induced weight loss cannot be confirmed in the absence of control for food and fluid intake, and 24-h quantification of urinary glucose excretion. In addition, the effect of dapagliflozin on food intake and satiety is not known. Full calorimetric and fluid-balance studies are required to resolve these questions. However, the weight loss observed in the current study is unlikely to have been caused by concomitant medication use. Although uncontrolled, patterns of diuretic use during the study were stable and balanced across treatment groups. In addition, pharmacokinetic interaction between dapagliflozin and metformin has not been demonstrated in a previous study (22). Fifth, nominal *P* values were provided for the exploratory and MR substudy analyses. Although these findings support the primary and secondary analyses, they were not *a priori* adjusted for multiplicity.

In conclusion, this study confirms significant weight loss and improved glycemic control with dapagliflozin 10 mg/d added to metformin in overweight T2DM patients over 24 wk, consistent with results from other clinical studies of dapagliflozin. Most weight change was accounted for by fat loss, with significant reductions vs. placebo in both abdominal VAT and SAT volumes.

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