



# Dapagliflozin Is Effective as Add-on Therapy to Sitagliptin With or Without Metformin: A 24-Week, Multicenter, Randomized, Double-Blind, Placebo-Controlled Study

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## OBJECTIVE

To assess the efficacy and safety of dapagliflozin as add-on therapy in patients with type 2 diabetes who were inadequately controlled with a dipeptidyl peptidase-4 inhibitor with or without metformin.

## RESEARCH DESIGN AND METHODS

In this 24-week, multicenter, randomized, double-blind, placebo-controlled, parallel-group, phase 3 study with a 24-week blinded extension period, 432 patients were randomized to receive dapagliflozin 10 mg/day or placebo added to sitagliptin (100 mg/day) ± metformin (≥1,500 mg/day).

## RESULTS

Baseline HbA<sub>1c</sub> and FPG levels were 7.9% (63.0 mmol/mol) and 162.2 mg/dL (9.0 mmol/L) for the dapagliflozin group and 8.0% (64.0 mmol/mol) and 163 mg/dL (9.0 mmol/L) for placebo. At week 24, dapagliflozin significantly reduced mean HbA<sub>1c</sub> levels (−0.5% [−4.9 mmol/mol]) versus placebo (0.0% [+0.4 mmol/mol]). Dapagliflozin reduced body weight versus placebo (−2.1 and −0.3 kg) and reduced HbA<sub>1c</sub> levels in patients with baseline values ≥8.0% (−0.8% [8.7 mmol/mol] and 0.0% [0.3 mmol/mol]) and fasting plasma glucose levels (−24.1 mg/dL [−1.3 mmol/L] and 3.8 mg/dL [0.2 mmol/L]). Similar results were observed when data were stratified by background therapy. Glycemic and weight benefits observed at week 24 were maintained through week 48. Changes from baseline in systolic blood pressure at week 8 were not significantly different between treatment groups. Over 48 weeks, fewer patients receiving dapagliflozin were discontinued or rescued for failing to achieve glycemic targets compared with placebo. Adverse events were balanced between groups, and discontinuation rates were low. At week 48, signs and symptoms suggestive of genital infection were more frequent with dapagliflozin (9.8%) than with placebo (0.4%). Signs and symptoms suggestive of urinary tract infection were balanced between dapagliflozin (6.7%) and placebo (6.2%).

## CONCLUSIONS

These results suggest that in patients with type 2 diabetes, inadequately controlled on sitagliptin with or without metformin, add-on treatment with dapagliflozin provides additional clinical benefit and is well tolerated.

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\*A complete list of the Study 10 investigators can be found in the Supplementary Data online.

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For patients with type 2 diabetes, multiple agents with complementary mechanisms of action are often required to adequately manage hyperglycemia (1). Most currently available oral antidiabetic agents (OADs) act by increasing insulin secretion or sensitizing tissues to insulin action and therefore depend upon pancreatic  $\beta$ -cell function for efficacy. Due to a progressive loss of  $\beta$ -cell function (2), many patients eventually require multiple agents to achieve target hemoglobin A<sub>1c</sub> (HbA<sub>1c</sub>) levels (1). Many currently available agents are associated with hypoglycemia and/or weight gain, effects that act as barriers to the achievement of glycemic and weight control. An unmet need therefore exists for new agents that are weight neutral or lead to weight loss without causing hypoglycemia.

Sodium glucose cotransporter 2 (SGLT2) is involved in the reabsorption of the majority of glucose filtered from the glomerular filtrate back into the bloodstream (3,4).

PCR data show SGLT2 expression to be highly specific to the kidney and that the signal for renal expression was 100-fold higher in the kidney than in the next highest tissue observed (the ileum) (5). SGLT2 is expressed predominantly in the luminal brush border of the renal cortex (6).

Dapagliflozin is a selective inhibitor of SGLT2 and acts to reduce hyperglycemia independently of insulin secretion or action. Dapagliflozin reduces systemic glycemic load by inhibiting this transporter, allowing some filtered glucose to pass into the urine for elimination (3). Reduction in HbA<sub>1c</sub> with dapagliflozin was relatively consistent across randomized, controlled, clinical trials in a variety of settings from treatment-naïve patients (7,8) to first add-on to metformin, sulfonylurea, or pioglitazone (9–12), and to patients requiring insulin, with or without concomitant OADs (13). The blood glucose-lowering effect of dapagliflozin after 6 months of treatment was similar to that of metformin-XR monotherapy (12) and, after 1 year of treatment, was similar to glipizide in patients poorly controlled on metformin monotherapy (10).

An additional secondary benefit of SGLT2 inhibition is the elimination of calories in the form of glucose. Consistent long-term weight loss with 10 mg dapagliflozin of  $\sim$ 1.0–2.6 kg (placebo subtracted) has been observed (7,9,11,13).

The current study assesses the efficacy and safety of dapagliflozin in patients whose HbA<sub>1c</sub> levels were not adequately controlled with a dipeptidyl peptidase-4 (DPP-4) inhibitor, sitagliptin. Dapagliflozin was evaluated as a dual combination therapy with sitagliptin and as a triple combination therapy with sitagliptin plus metformin.

Although the treatment algorithm from the American Diabetes Association/European Association for the Study of Diabetes notes that adding insulin may be more effective than adding a third oral agent to two oral agents, the algorithm includes triple oral therapy as a treatment option when dual therapy fails to control HbA<sub>1c</sub> levels (14). The American Association of Clinical Endocrinologists also suggests the use of triple therapy as a first approach for the treatment of asymptomatic patients with HbA<sub>1c</sub> levels  $>9\%$  (75 mmol/mol) (15). In patients with HbA<sub>1c</sub> levels  $\leq 9\%$  (75 mmol/mol), triple therapy is recommended if the patient has an inadequate response to monotherapy or dual therapy. In addition, the algorithm recommends avoiding weight gain and emphasizes the benefits of weight loss in this patient population.

Because previous studies have suggested a reduction in blood pressure (BP) with dapagliflozin treatment, this study also included change from baseline in systolic BP (SBP) as a secondary outcome measure in addition to measures of glycemic efficacy and body weight. Background BP medications were controlled in this study to avoid confounding effects on BP measurements.

## RESEARCH DESIGN AND METHODS

### Study Design

This 24-week, multicenter, randomized, double-blind, placebo-controlled, parallel-group, international phase 3 study (NCT00984867) was conducted in Argentina, Germany, Mexico, Poland, the U.K., and the U.S. It was designed

and monitored in accordance with the ethical principles of Good Clinical Practice as defined by the International Conference on Harmonization and Declaration of Helsinki. An institutional review board approved the protocol, and all subjects gave written, informed consent.

During a 10-week dose-stabilization period, all patients received sitagliptin 100 mg/day (patients initially taking vildagliptin switched to sitagliptin). A 2-week placebo lead-in period followed, after which patients with a lead-in HbA<sub>1c</sub> value  $\geq 7.0\%$  (53 mmol/mol) and  $\leq 10.0\%$  (86 mmol/mol) were randomized equally to dapagliflozin 10 mg or placebo for a 24-week double-blind period. Randomized patients were stratified by concomitant metformin use at baseline: in stratum 1, study treatment was added to sitagliptin monotherapy; in stratum 2, study treatment was added to sitagliptin plus metformin IR ( $\geq 1,500$  mg/day, administered BID with meals). Sitagliptin monotherapy was allowed only in countries where it was approved. No other OADs were permitted. After completion of the double-blind period, patients could participate in a 24-week, site- and patient-blind extension period.

Adult patients ( $\geq 18$  years) with type 2 diabetes were eligible for inclusion. An upper age limit was imposed for those receiving metformin where local label restrictions applied. HbA<sub>1c</sub> values between 7.7% (61 mmol/mol) and 10.5% (91 mmol/mol) were required for individuals not receiving a DPP-4 inhibitor at enrollment and between 7.2% (55 mmol/mol) and 10.0% (86 mmol/mol) for those receiving a DPP-4 inhibitor. Prior to randomization, HbA<sub>1c</sub> values were required to be between 7.0% (53 mmol/mol) and 10.0% (86 mmol/mol) for all patients. Treatment with OADs other than metformin or DPP-4 inhibitors within the 10 weeks prior to enrollment was not permitted.

Individuals with type 1 diabetes or fasting plasma glucose (FPG)  $>270$  mg/dL (15.0 mmol/L) were excluded, as were pregnant or breast-feeding women and patients receiving metformin with a calculated creatinine clearance  $<60$  mL/min or serum

creatinine values  $\geq 1.5$  mg/dL for men or  $\geq 1.4$  mg/dL for women. Patients not treated with metformin and with a baseline calculated creatinine clearance  $< 50$  mL/min were excluded. At enrollment, individuals with SBP  $\geq 170$  mmHg and/or diastolic BP  $\geq 110$  mmHg were excluded, and at randomization, patients were required to have an SBP  $< 160$  mmHg and/or a diastolic BP  $< 100$  mmHg.

### Study Treatments

Dapagliflozin 10 mg or placebo was administered orally once daily during the 24-week double-blind and 24-week extension periods. All patients received open-label oral sitagliptin 100 mg once daily for the 10-week dose-stabilization period, the 2-week placebo lead-in period, the 24-week double-blind treatment period, and the 24-week extension period. Patients in stratum 2 received open-label oral metformin immediate release 500-mg tablets ( $\geq 1,500$  mg/day). A rescue therapy, open-label oral glimepiride  $\leq 6$  mg/day was given to patients with FPG  $> 270$  mg/dL (15.0 mmol/L), weeks 0–4; FPG  $> 240$  mg/dL (13.3 mmol/L), weeks 4–12; or FPG  $> 200$  mg/dL (11.1 mmol/L) or HbA<sub>1c</sub>  $> 8.0\%$  (64 mmol/mol), weeks 12–24.

### Efficacy End Points

The primary end point was change in HbA<sub>1c</sub> from baseline at week 24. Key secondary end points were change in total body weight from baseline to week 24, change in HbA<sub>1c</sub> in patients with baseline HbA<sub>1c</sub>  $\geq 8\%$  (64 mmol/mol) from baseline to week 24, change in FPG from baseline to week 24, change in seated SBP in patients with baseline seated SBP  $\geq 130$  mmHg from baseline to week 8, and glycemic response rate (HbA<sub>1c</sub> reduction  $\geq 0.7\%$  [7.7 mmol/mol] from baseline) at week 24. The change in 2-h postliquid meal glucose (PPG) from baseline (day 0) to week 24 was also evaluated. Patients fasted for  $\geq 12$  h prior to the visit. The liquid meal was administered immediately after a time 0 blood sample was drawn, and blood samples were drawn 2 h after the start of the liquid meal for PPG, C-peptide, and insulin determination.

Exploratory end points included proportion of subjects achieving a

therapeutic glycemic response (HbA<sub>1c</sub>  $< 7.0\%$  [53 mmol/mol]) at week 24, change in seated SBP from baseline to week 24, percent change in fasting lipids (total cholesterol, LDL cholesterol, HDL cholesterol, and triglycerides) from baseline to week 24, and change in  $\beta$ -cell function (as measured by the updated model of the homeostasis model assessment [HOMA-2]) and insulin resistance (as measured by the HOMA for insulin resistance) (16).

### Safety End Points

Safety was evaluated based on reported adverse events (AEs), laboratory values, electrocardiogram, pulse, BP, hypoglycemic events, calculated creatinine clearance, estimated glomerular filtration rate, and physical examination findings.

### Statistical Analysis

The data were analyzed for the overall study population and for each stratum separately. Efficacy data were analyzed with a full analysis set (FAS) that included all randomized individuals who took at least one dose of double-blind study medication and had a nonmissing baseline value and one or more postbaseline efficacy values for one or more efficacy variables. The safety set comprised patients who took one or more doses of double-blind study medication.

The primary efficacy end point (change from baseline HbA<sub>1c</sub> at week 24) was assessed by an ANCOVA model with fixed terms for treatment group and strata (for the overall population) and baseline value as a covariate, using last observation carried forward (LOCF) to calculate a least squares estimate of the treatment difference. The longitudinal repeated measures model included fixed categorical effects of treatment, week, treatment-by-week interaction, and stratum as well as the continuous fixed covariates of baseline value and baseline value-by-week interaction.

Hierarchical closed testing controlled for type I errors for the primary and key secondary end points. Within-stratum treatment comparisons were individually tested at a two-sided significance level of 0.05 for variables found to be significant in the combined strata analysis. For exploratory

variables, nominal *P* values were reported for both overall and within-strata comparisons, although the significance of the result cannot be concluded.

The proportion of subjects achieving therapeutic glycemic response (reduction in HbA<sub>1c</sub>  $\geq 0.7\%$  [7.7 mmol/mol] at week 24) was analyzed using previously published methodology (17,18) when there were at least five responders on average by treatment group.

## RESULTS

### Patients

The disposition of patients is shown in Supplementary Fig. 1. In summary, 451 patients were randomized to receive dapagliflozin (*n* = 225) or placebo (*n* = 226). Of the patients randomized to dapagliflozin, 208 (92%) completed the 24-week double-blind period, with 202 (90%) going on to complete the additional 24-week extension period. This compared with 203 (90%) of those receiving placebo at 24 weeks and 185 (82%) at 48 weeks. Patient demographic and baseline characteristics are shown in Table 1 and were balanced between treatments. Mean age was  $\sim 55$  years, 55% were male, mean weight was  $\sim 90$  kg, mean duration of diabetes was 5.7 years, and mean baseline HbA<sub>1c</sub> was  $\sim 7.9\%$  (63 mmol/mol).

European sites contributed fewer patients to stratum 1 because of the European label restrictions regarding the use of sitagliptin as monotherapy, resulting in racial/ethnic differences between the two strata. Patients in stratum 1 (treatment added to sitagliptin monotherapy) had a higher mean baseline HbA<sub>1c</sub> and were younger, with a shorter duration of diabetes and a lower rate of hypertension at baseline, than those in stratum 2 (treatment added to metformin plus sitagliptin).

### Efficacy

Efficacy of dapagliflozin compared with placebo is presented in Table 2 (24 weeks, LOCF analyses) and Table 3 (24 and 48 weeks, longitudinal analyses [LA]).

### Primary End Point

A statistically significant reduction from baseline in HbA<sub>1c</sub> was observed in the

dapagliflozin group compared with placebo at week 24 excluding data after rescue (placebo subtracted,  $-0.5\%$  [ $-5.2$  mmol/mol];  $P < 0.0001$ , LOCF) (Table 2). Dapagliflozin also decreased HbA<sub>1c</sub> significantly versus placebo when added to sitagliptin alone (stratum 1: placebo subtracted,  $-0.6\%$  [ $-6.1$  mmol/mol];  $P < 0.0001$ , LOCF) or to sitagliptin plus metformin (stratum 2: placebo subtracted,  $-0.4\%$  [ $-4.4$  mmol/mol];  $P < 0.0001$ , LOCF).

Improvements in HbA<sub>1c</sub> were maintained through 48 weeks (Table 3 and Fig. 1) in the overall study population (placebo subtracted,  $-0.7\%$  [ $-7.4$  mmol/mol] LA), stratum 1 (placebo subtracted,  $-0.9\%$  [ $-9.3$  mmol/mol] LA), and stratum 2 (placebo subtracted,  $-0.6\%$  [ $-6.4$  mmol/mol] LA).

Over 48 weeks, 31.8% of patients receiving dapagliflozin were discontinued for lack of efficacy or were rescued for failing to maintain glycemic parameters below prespecified rescue criteria versus 57.6% of patients receiving placebo. When data after rescue were included, improvements in HbA<sub>1c</sub> were similar (Table 3).

**Key Secondary End Points**

Statistically significant improvements were observed in the dapagliflozin group compared with placebo for change in total body weight in the overall study population and each stratum (Table 2) and were maintained out to 48 weeks. When data after rescue were included, reductions in body weight were similar (Table 3).

Change in HbA<sub>1c</sub> in patients with baseline HbA<sub>1c</sub>  $\geq 8\%$  and change in FPG from baseline to week 24 in the entire cohort (Table 2) were also significantly reduced with dapagliflozin compared with placebo and were also observed within each stratum.

In patients with baseline seated SBP  $\geq 130$  mmHg, there were no significant changes in seated SBP with dapagliflozin compared with placebo at week 8 (Table 2), with a mean decrease observed in each treatment group in the overall study population and in each stratum.

In the entire patient cohort and in each stratum, significance was not assessed for change in PPG and the proportion of

**Table 1—Demographics and baseline characteristics (FAS)**

	Entire cohort		Sitagliptin monotherapy		Sitagliptin plus metformin	
	Placebo (N = 224)	Dapagliflozin 10 mg (N = 223)	Placebo (N = 111)	Dapagliflozin 10 mg (N = 110)	Placebo (N = 113)	Dapagliflozin 10 mg (N = 113)
Mean age, years (SD)	55.0 (10.2)	54.8 (10.4)	53.3 (11.3)	52.6 (10.1)	56.6 (8.8)	56.8 (10.3)
Sex (%)						
Male	118 (52.7)	127 (57.0)	51 (45.9)	60 (54.5)	67 (59.3)	67 (59.3)
Race (%)						
White	171 (76.3)	161 (72.2)	66 (59.5)	65 (59.1)	105 (92.9)	96 (85.0)
Black	6 (2.7)	11 (4.9)	5 (4.5)	4 (3.6)	1 (0.9)	7 (6.2)
Asian	2 (0.9)	2 (0.9)	0	1 (0.9)	2 (1.8)	1 (0.9)
Other	45 (20.1)	49 (22.0)	40 (36.0)	40 (36.4)	5 (4.4)	9 (8.0)
Mean weight, kg (SD)	89.2 (20.9)	91.0 (21.6)	84.2 (19.7)	88.0 (23.1)	94.2 (20.9)	94.0 (19.8)
Mean seated baseline SBP in patients with SBP $\geq 130$ mmHg, mmHg (SD)	N = 111 139.3 (8.5)	N = 101 140.5 (8.0)	N = 45 137.9 (6.7)	N = 43 138.5 (7.6)	N = 66 140.3 (9.5)	N = 58 141.9 (8.1)
Mean duration of diabetes, years (SD)	5.64 (5.40)	5.70 (4.87)	4.80 (5.76)	4.68 (4.14)	6.47 (4.91)	6.69 (5.32)
Mean HbA <sub>1c</sub> (SD), % [mmol/mol]	8.0 (0.8) [64.0 (8.5)]	7.9 (0.8) [63.0 (8.9)]	8.1 (0.8) [65.0 (8.7)]	8.0 (0.8) [64.0 (8.7)]	7.9 (0.8) [63.0 (8.2)]	7.8 (0.8) [62.0 (8.9)]
Mean FPG (SD), mg/dL [mmol/L]	163.0 (34.5) [9.0 (1.9)]	162.2 (36.8) [9.0 (2.0)]	161.4 (34.3) [9.0 (1.9)]	157.3 (32.1) [8.7 (1.8)]	164.6 (34.7) [9.1 (1.9)]	167.0 (40.5) [9.3 (2.3)]
Absolute 2-h postliquid meal glucose (SD), mg/dL [mmol/L]	226.3 (54.0) [12.6 (3.0)]	227.8 (58.9) [12.6 (3.3)]	231.2 (55.0) [12.8 (3.1)]	225.3 (59.0) [12.5 (3.3)]	221.0 (52.7) [12.3 (2.9)]	230.2 (59.0) [12.8 (3.3)]
Mean HbA <sub>1c</sub> (SD) in subgroup with baseline HbA <sub>1c</sub> $\geq 8.0\%$ , % [mmol/mol]	8.7 (0.5) [71.0 (6.0)]	8.7 (0.5) [71.0 (6.0)]	8.7 (0.6) [72.0 (6.2)]	8.6 (0.5) [71.0 (5.8)]	8.7 (0.5) [71.0 (5.8)]	8.7 (0.6) [71.0 (6.2)]

N is the number of subjects in the FAS. Percentages reported are based on the total number of subjects in each treatment group. The race subgroup of "other" includes subjects with reported race of American Indian/Alaska Native or other.

**Table 2—Adjusted mean change from baseline (LOCF) at week 24 (week 8 and 24 for seated SBP) for efficacy end points (excluding data after rescue; including data after rescue for SBP)**

	Entire primary analysis cohort		Sitagliptin monotherapy		Sitagliptin plus metformin	
	Placebo (N = 224)	Dapagliflozin 10 mg (N = 223)	Placebo (N = 111)	Dapagliflozin 10 mg (N = 110)	Placebo (N = 113)	Dapagliflozin 10 mg (N = 113)
HbA <sub>1c</sub> % [mmol/mol] (95% CI)	0.0 (−0.1 to 0.1) [0.4 (−0.7 to 1.5)]	−0.5 (−0.6 to −0.4) [−4.9 (−6.0 to −3.8)] −0.5 (−0.6 to −0.3) [−5.2 (−6.8 to −3.7)] P < 0.0001†	0.1 (−0.1 to 0.3) [1.1 (−0.7 to 2.7)]	−0.5 (−0.6 to −0.3) [−5.1 (−6.9 to −3.4)] −0.6 (−0.8 to −0.3) [−6.1 (−8.6 to −3.7)] P < 0.0001*	0.0 (−0.2 to 0.1) [−0.2 (−1.6 to 1.1)]	−0.4 (−0.6 to −0.3) [−4.7 (−6.0 to −3.3)] −0.4 (−0.6 to −0.2) [−4.4 (−6.3 to −2.5)] P < 0.0001*
Body weight, kg (95% CI)	−0.3 (−0.6 to 0.1)	−2.1 (−2.5 to −1.8) [−1.9 (−2.4 to −1.4)] P < 0.0001†	−0.1 (−0.5 to 0.4)	−1.9 (−2.4 to −1.5) [−1.9 (−2.5 to −1.2)] P < 0.0001*	−0.5 (−1.0 to 0.1)	−2.4 (−2.9 to −1.8) [−1.9 (−2.6 to −1.1)] P < 0.0001*
HbA <sub>1c</sub> in patients with baseline HbA <sub>1c</sub> ≥8%, % [mmol/mol] (95% CI)	n = 99 0.0 (−0.1 to 0.2) [0.3 (−1.3 to 2.0)]	n = 94 −0.8 (−1.0 to −0.7) [−8.7 (−10.5 to −7.1)] −0.8 (−1.1 to −0.6) [−9.1 (11.5 to −6.8)] P < 0.0001†	n = 56 0.1 (−0.2 to 0.3) [0.7 (−1.7 to 3.1)]	n = 55 −0.8 (−1.0 to −0.6) [−8.9 (−11.3 to −6.4)] −0.9 (−1.2 to −0.6) [−9.5 (−12.9 to −6.0)] P < 0.0001*	n = 43 0.0 (−0.2 to 0.2) [0.0 (−2.3 to 2.3)]	n = 39 −0.8 (−1.0 to −0.6) [−8.6 (−11.0 to −6.2)] −0.8 (−1.1 to −0.5) [−8.7 (−12.0 to −5.4)] P < 0.0001*
FPG, mg/dL [mmol/L] (95% CI)	3.8 (−0.8 to 8.4) [0.2 (−0.0 to 0.5)]	−24.1 (−28.7 to −19.5) [−1.3 (−1.6 to −1.1)] −27.9 (−34.5 to −21.4) [−1.6 (−1.9 to −1.2)] P < 0.0001†	4.6 (−2.3 to 11.5) [0.3 (−0.1 to 0.6)]	−22.0 (−28.8 to −15.1) [−1.2 (−1.6 to −0.8)] −26.6 (−36.3 to −16.9) [−1.5 (−2.0 to −0.9)] P < 0.0001*	3.0 (−3.2 to 9.3) [0.2 (−0.2 to 0.5)]	−26.2 (−32.4 to −19.9) [−1.5 (−1.8 to −1.1)] −29.2 (−38.0 to −20.4) [−1.6 (−2.1 to −1.1)] P < 0.0001*
Seated SBP in patients with baseline seated SBP ≥130 at week 8, mmHg (95% CI)	−5.1 (−7.1 to −3.1)	−6.0 (−8.1 to −3.9) [−0.9 (−3.8 to 2.0)] P = 0.5583	−4.2 (−7.1 to −1.4)	−6.6 (−9.5 to −3.7) [−2.4 (−6.4 to 1.7)] P = 0.2443	−5.5 (−8.3 to −2.7)	−5.3 (−8.3 to −2.3) 0.2 (−3.9 to 4.3) P = 0.9100
2-h postliquid meal glucose, mg/dL [mmol/L] (95% CI)	(n = 197) −4.8 (−11.3 to 1.8) [−0.3 (−0.6 to 0.1)]	(n = 207) −47.7 (−54.1 to −41.3) [−2.7 (−3.0 to −2.3)] −42.9 (−52.1 to −33.8) [−2.4 (−2.9 to −1.9)]	(n = 102) −2.6 (−11.2 to 5.9) [−0.1 (−0.6 to 0.3)]	(n = 99) −46.3 (−55.0 to −37.6) [−2.6 (−3.1 to −2.1)] −43.7 (−55.9 to −31.5) [−2.4 (−3.1 to −1.8)]	(n = 95) −7.2 (−17.3 to 2.8) [−0.4 (−1.0 to 0.2)]	(n = 108) −48.9 (−58.3 to −39.5) [−2.7 (−3.2 to −2.2)] −41.6 (−55.4 to −27.8) [−2.3 (−3.1 to −1.5)]
Percent of patients with decrease in HbA <sub>1c</sub> ≥0.7% (95% CI)	16.6 (11.7 to 21.4)	35.3 (29.3 to 41.2)	17.2 (10.1 to 24.2)	42.8 (33.9 to 51.6)	16.0 (9.2 to 22.7)	28.0 (20.1 to 35.9) 12.1 (1.7 to 22.5)

N is the number of subjects in the FAS. n is the number of subjects in the FAS with nonmissing baseline and week 24 (LOCF) values. †Significant P value; primary end point tested at  $\alpha = 0.050$ ; key secondary end points tested sequentially at  $\alpha = 0.050$ . \*For variables found to be significant with the combined strata analysis, corresponding within-stratum treatment comparisons were individually tested at a two-sided significance level of 0.05.



**Table 3—Change from baseline at weeks 24 and 48 for efficacy end points (FAS) (excluding data after rescue unless otherwise specified, longitudinal repeated measures)**

Weeks	Entire primary analysis cohort			Sitagliptin monotherapy		Sitagliptin plus metformin
	Placebo (N = 224)	Dapagliflozin 10 mg (N = 223)	Placebo (N = 111)	Dapagliflozin 10 mg (N = 110)	Placebo (N = 113)	Dapagliflozin 10 mg (N = 113)
HbA <sub>1c</sub> % [mmol/mol] (95% CI)						
24	Adjusted mean change [1.0 (-0.4 to 2.3)]	-0.4 (-0.5 to -0.3) [-4.2 (-5.4 to -2.8)]	0.2 (0.0 to 0.4) [2.1 (-0.3 to 4.4)]	-0.4 (-0.6 to -0.2) [-4.0 (-5.1 to -1.9)]	0.0 (-0.1 to 0.2) [0.1 (-1.5 to 1.6)]	-0.4 (-0.5 to -0.3) [-4.2 (-5.6 to -2.7)]
	Placebo-corrected change	-0.5 (-0.6 to -0.3) [-5.0 (-6.9 to -3.2)]		-0.6 (-0.8 to -0.3) [-6.0 (-9.2 to -2.8)]		-0.4 (-0.6 to -0.2) [-4.3 (-6.3 to -2.1)]
48	Adjusted mean change [4.2 (2.4 to 5.9)]	-0.3 (-0.4 to -0.2) [-3.3 (-4.7 to -1.9)]	0.9 (0.5 to 1.2) [9.3 (5.9 to 12.8)]	0.0 (-0.3 to 0.3) [0.0 (-2.7 to 2.8)]	0.2 (0.0 to 0.3) [1.6 (-0.3 to 3.6)]	-0.4 (-0.6 to -0.3) [-4.8 (-6.3 to -3.3)]
	Placebo-corrected change	-0.7 (-0.9 to -0.5) [-7.4 (-9.6 to -5.2)]		-0.9 (-1.3 to -0.5) [-9.3 (-13.7 to -4.9)]		-0.6 (-0.8 to -0.4) [-6.4 (-8.9 to -3.9)]
HbA <sub>1c</sub> % [mmol/mol] (95% CI), including data after rescue						
24	Placebo-corrected change	-0.4 (-0.5 to -0.2) [-4.2 (-5.8 to -2.5)]		-0.5 (-0.8 to -0.2) [-5.4 (-8.2 to -2.6)]		-0.3 (-0.4 to -0.1) [-3.1 (-4.8 to -1.2)]
48	Placebo-corrected change	-0.6 (-0.7 to -0.4) [-6.1 (-8.0 to -4.3)]		-0.5 (-0.8 to -0.2) [-5.8 (-8.9 to -2.6)]		-0.6 (-0.8 to -0.4) [-6.3 (-8.4 to -4.3)]
Body weight, kg (95% CI)						
24	Adjusted mean change	-0.2 (-0.6 to 0.2)	0.0 (-0.6 to 0.6)	-1.9 (-2.4 to -1.4)	-0.4 (-1.1 to 0.2)	-2.5 (-3.0 to -1.9)
	Placebo-corrected change	-2.0 (-2.6 to -1.5)		-1.9 (-2.6 to -1.1)		-2.0 (-2.9 to -1.2)
48	Adjusted mean change	0.2 (-0.4 to 0.8)	0.8 (0.0 to 1.7)	-1.4 (-2.1 to -0.7)	-0.5 (-1.3 to 0.4)	-2.5 (-3.2 to -1.8)
	Placebo-corrected change	-2.2 (-3.0 to -1.5)		-2.2 (-3.3 to -1.2)		-2.1 (-3.2 to -1.0)
Body weight, kg (95% CI), including data after rescue						
24	Placebo-corrected change	-2.1 (-2.7 to -1.6)		-2.1 (-2.9 to -1.4)		-2.1 (-2.9 to -1.3)
48	Placebo-corrected change	-2.5 (-3.1 to -1.8)		-2.2 (-3.1 to -1.4)		-2.6 (-3.5 to -1.6)
HbA <sub>1c</sub> in patients with HbA <sub>1c</sub> ≥8% adj. mean, % [mmol/mol] (95% CI)						
24	Adjusted mean change	0.2 (-0.1 to 0.4) [1.9 (-0.9 to 4.6)]	0.2 (-0.1 to 0.6) [2.3 (-1.5 to 6.2)]	-0.8 (-1.1 to -0.5) [-8.4 (-11.6 to -5.1)]	-0.4 (ND) [-4.6 (ND)]	-0.9 (ND) [-9.9 (ND)]
	Placebo-corrected change	-0.9 (-1.3 to -0.6) [-10.2 (-13.8 to -6.6)]		-1.0 (-1.4 to -0.5) [-10.7 (-15.7 to -5.7)]		ND
48	Adjusted mean change	0.3 (-0.2 to 0.7) [2.8 (-2.3 to 7.9)]	-0.4 (ND) [-3.8 (ND)]	-1.2 (ND) [-13.0 (ND)]	-0.5 (ND) [-5.9 (ND)]	-1.1 (ND) [-11.5 (ND)]
	Placebo-corrected change	-1.0 (-1.5 to -0.5) [-10.7 (-16.4 to -5.0)]				ND
FPG, mg/dL [mmol/L] (95% CI)						
24	Adjusted mean change	-0.5 (-5.1 to 4.0) [0.0 (-0.3 to 0.2)]	-1.7 (-8.0 to 4.7) [-0.1 (-0.4 to 0.3)]	-25.7 (-31.1 to -20.3) [-1.4 (-1.7 to -1.1)]	-0.3 (-7.0 to 6.3) [0.0 (-0.4 to 0.4)]	-23.2 (-29.1 to -17.3) [-1.3 (-1.6 to -1.0)]
	Placebo-corrected change	-23.4 (-29.5 to -17.4) [-1.3 (-1.6 to -1.0)]		-24.0 (-32.3 to -15.8) [-1.3 (-1.8 to -0.9)]		-22.9 (-31.7 to -14.0) [-1.3 (-1.8 to -0.8)]
48	Adjusted mean change	13.5 (6.8 to 20.2) [0.8 (0.4 to 1.1)]	25.9 (12.8 to 39.0) [1.4 (0.7 to 2.2)]	-14.0 (-23.6 to -4.3) [-0.8 (-1.3 to -0.2)]	6.3 (-1.0 to 13.7) [0.4 (-0.1 to 0.8)]	-23.7 (-29.6 to -17.7) [-1.3 (-1.6 to -1.0)]
	Placebo-corrected change	-33.2 (-41.6 to -24.7) [-1.8 (-2.3 to -1.4)]		-39.9 (-56.0 to -23.7) [-2.2 (-3.1 to -1.3)]		-30.0 (-39.4 to -20.6) [-1.7 (-2.2 to -1.1)]
Seated SBP in patients with baseline seated SBP ≥130 mmHg (95% CI)						
24	Adjusted mean change	-4.0 (-6.9 to -1.2)	-4.0 (-7.3 to -0.8)	-7.1 (-10.5 to -3.8)	-2.4 (-5.7 to 0.9)	-6.0 (-9.5 to -2.5)
	Placebo-corrected change	-1.7 (-5.5 to 2.2)		-3.1 (-7.7 to 1.5)		-3.6 (-8.4 to 1.2)
48	Adjusted mean change	-5.2 (-8.8 to -1.6)	-2.9 (-6.0 to 0.2)	-7.0 (-10.1 to -3.8)	-5.6 (-8.9 to -2.4)	-3.5 (-6.8 to -0.3)
	Placebo-corrected change	-0.2 (-4.8 to 4.4)		-4.1 (-8.5 to 0.4)		2.1 (-2.6 to 6.8)
2-h postliquid meal glucose, mg/dL [mmol/L] (95% CI)						
24	Adjusted mean change	-18.0 (-25.1 to -10.9) [-1.0 (-1.4 to -0.6)]	-44.2 (-50.1 to -38.4) [-0.7 (-1.2 to -0.1)]	-44.5 (-52.4 to -36.5) [-2.5 (-2.9 to -2.0)]	-24.1 (-34.6 to -13.6) [-1.3 (-1.9 to -0.8)]	-44.5 (-53.1 to -35.9) [-2.5 (-3.0 to -2.0)]
	Placebo-corrected change	(n = 114)	(n = 166)	(n = 78)	(n = 59)	(n = 88)
48	Adjusted mean change	-12.1 (-21.4 to -2.8) [-0.7 (-1.2 to -0.2)]	-43.0 (-49.9 to -36.0) [-2.4 (-2.8 to -2.0)]	-32.6 (-45.0 to -20.2) [-1.8 (-2.5 to -1.1)]	-18.6 (-29.1 to -8.1) [-1.0 (-1.6 to -0.5)]	-20.5 (-34.1 to -6.9) [-1.1 (-1.9 to -0.4)]
	Placebo-corrected change	(n = 77)	(n = 138)	(n = 60)	(n = 46)	(n = 78)
	Placebo-corrected change	-30.9 (-42.5 to -19.2) [-1.7 (-2.4 to -1.1)]		-33.8 (-55.0 to -12.6) [-1.9 (-3.1 to -0.7)]		-28.6 (-42.0 to -15.3) [-1.6 (-2.3 to -0.9)]

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Table 3—Continued

Weeks	Entire primary analysis cohort		Sitagliptin monotherapy		Sitagliptin plus metformin	
	Placebo (N = 224)	Dapagliflozin 10 mg (N = 223)	Placebo (N = 111)	Dapagliflozin 10 mg (N = 110)	Placebo (N = 113)	Dapagliflozin 10 mg (N = 113)
24	13.1 (8.7 to 17.5)	29.6 (23.7 to 35.5)	14.5 (7.9 to 21.0)	37.1 (28.3 to 45.9)	11.8 (5.9 to 17.6)	22.3 (14.7 to 30.0)
	Adjusted mean decrease in HbA <sub>1c</sub> ≥0.7% (95% CI)	16.5 (9.2 to 23.9)	4.5 (0.7 to 8.4)	22.6 (11.6 to 33.6)	5.4 (1.3 to 9.5)	10.6 (0.9 to 20.3)
48	5.0 (2.1 to 7.8)	25.9 (20.2 to 31.6)	21.0 (14.6 to 27.3)	26.0 (18.0 to 34.0)	20.5 (11.5 to 29.5)	25.9 (17.8 to 33.9)
	Adjusted mean decrease in HbA <sub>1c</sub> ≥0.7% (95% CI)	21.0 (14.6 to 27.3)	21.5 (12.6 to 30.4)	21.5 (12.6 to 30.4)	21.5 (12.6 to 30.4)	21.5 (12.6 to 30.4)

N is the number of subjects in the FAS. ND, not determined. n is the number of subjects in the FAS with nonmissing baseline and week 24 or 48 value.

patients achieving a therapeutic response (reduction in HbA<sub>1c</sub> ≥0.7%) because of their position in the sequential testing hierarchy. However, numerical improvements in the two variables were observed at 24 weeks, consistent with the significant findings of the glycemic variables that occurred earlier in the hierarchy. These improvements in PPG and therapeutic response were maintained through to 48 weeks (Table 3). The placebo-corrected change in glucose values from baseline to 2 h was −14.8 mg/dL (0.82 mmol/L) in the overall population, −16.7 mg/dL (0.93 mmol/L) in stratum 1, and −12.6 mg/dL (0.70 mmol/L) in stratum 2.

#### Exploratory End Points

A higher proportion of subjects achieved a therapeutic glycemic response, defined as achieving HbA<sub>1c</sub> levels <7.0% with dapagliflozin compared with placebo (week 24, 27.8 and 17.9%, respectively; week 48, 22.1 and 12.0%, respectively) (Supplementary Table 1). A mean decrease in seated SBP from baseline to week 24 (LOCF) was observed with dapagliflozin, with no meaningful mean change in seated SBP with placebo. Analyses including and excluding data after rescue showed similar decreases in seated SBP in the dapagliflozin group (−1.8 and −2.1 mmHg, respectively) and no meaningful mean change in seated SBP in the placebo group (0.8 and −0.3, respectively; nominal *P* value <0.05, including data after rescue).

Patients receiving dapagliflozin showed small increases from baseline to week 24 (placebo subtracted [95% CI]) in total cholesterol (3.6% [0.6–6.7]) and HDL (4.6% [1.8–7.4]). A small increase from baseline to week 24 was observed in LDL cholesterol with dapagliflozin compared with placebo (placebo subtracted 3.6% [−1.3 to 8.8]), and a small reduction was observed in triglyceride levels from baseline to week 24 (placebo subtracted −1.9% [−8.2 to 4.8]). Results were generally similar at 48 weeks (Supplementary Table 1).

Using HOMA-2 analysis methodology (16), subjects receiving dapagliflozin showed a 24.9% increase in  $\beta$ -cell function from baseline (mean [SD]: 72.3 [37.3] index points) to week 24 (97.6 [45.8] index points) versus a 5.2%

increase with placebo from baseline (76.8 [39.1] index points) to week 24 (81.6 [43.6] index points) that was maintained to week 48 (Supplementary Table 1). No meaningful difference in insulin resistance from baseline (mean [SD]: placebo, 2.82 [1.31] index points; dapagliflozin, 2.84 [1.27] index points) was observed in subjects receiving dapagliflozin to week 24 or 48 (−0.1 and 0.1 index points, respectively) compared with placebo (−0.1 and 0.3 index points).

#### Safety and Tolerability

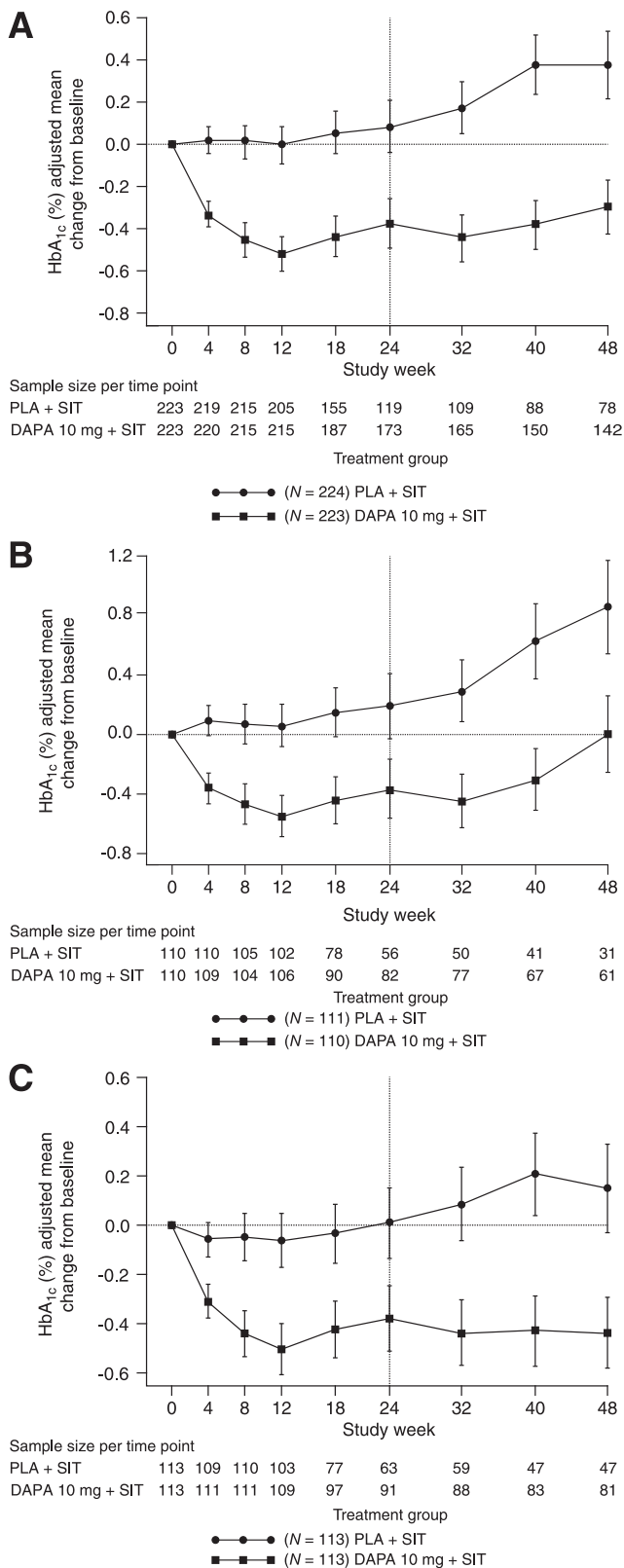
In the overall safety set, the proportion of patients reporting at least one AE was slightly higher in the dapagliflozin group (24 weeks, 119/225 [52.9%]; 48 weeks, 149/225 [66.2%]) versus the placebo (24 weeks, 109/226 [48.2%]; 48 weeks, 138/226 [61.1%]) group.

AEs were mostly mild or moderate. Rates of serious AEs (SAEs) were balanced between the groups (entire cohort 24 weeks: dapagliflozin, 10/225 [4.4%]; placebo, 9/226 [4.0%]; 48 weeks: dapagliflozin, 15/225 [6.7%]; placebo, 18/226 [8.0%]).

Discontinuations due to AEs were few, with rates balanced across treatments (entire cohort 24 weeks: dapagliflozin, 7/225 [3.1%]; placebo, 5/226 [2.2%]; 48 weeks: dapagliflozin, 7/225 [3.1%]; placebo, 7/226 [3.1%]).

One death occurred in the placebo group throughout the 24-week short-term and 24-week extension periods. A 65-year-old female Caucasian subject died of metastatic squamous cell carcinoma on study day 117. The subject received placebo plus sitagliptin 100 mg in combination with metformin 2,000 mg. The SAE was assessed as not related to the study medication.

Few events of hypoglycemia were reported, and none led to treatment discontinuation. Similar numbers of patients reported one or more hypoglycemic events in both groups (dapagliflozin 24 weeks 6/225 [2.7%], 48 weeks 12/225 [5.3%]; placebo 24 weeks 4/226 [1.8%], 48 weeks 14/226 [6.2%]). Over the 48 weeks, one event of major hypoglycemia was reported in the dapagliflozin group and one SAE of hypoglycemia in the placebo group.



**Figure 1**—Adjusted mean change from baseline in HbA<sub>1c</sub> over time; 24-week short-term double-blind treatment period and 24-week extension period, excluding data after rescue for entire patient population (A), sitagliptin alone (B), and sitagliptin plus metformin (C). Black circles, placebo plus sitagliptin; black squares, dapagliflozin plus sitagliptin.

Signs, symptoms, and events suggestive of vulvovaginitis/balanitis or urinary tract infection (UTI) were captured based on a list of predefined Medical Dictionary for Regulatory Activities (MedDRA) terms. Signs, symptoms, and events suggestive of genital infection (safety analysis set) were reported more frequently in the dapagliflozin group (24 weeks, 19/225 [8.4%]; 48 weeks, 22/225 [9.8%]) compared with placebo (24 weeks, 1/226 [0.4%]; 48 weeks, 1/226 [0.4%]). None were assessed as serious. One subject in the dapagliflozin group was discontinued from treatment due to a vulvovaginal mycotic infection. Three-quarters of the subjects in the dapagliflozin group experiencing at least one event suggestive of genital infection or at least one AE of genital infection were female. The majority responded to one course of treatment; however, one event required additional treatment due to an inadequate response to the initial course.

Whereas the incidence of signs, symptoms, and events suggestive of UTI was balanced between dapagliflozin (24 weeks, 11/225 [4.9%]; 48 weeks, 15/225 [6.7%]) and placebo (24 weeks, 9/226 [4.0%]; 48 weeks, 14/226 [6.2%]), the number of diagnosed events of UTI was greater with dapagliflozin (24 weeks, 8/225 [3.6%]; 48 weeks, 13/225 [5.8%]) compared with placebo (24 weeks, 3/226 [1.3%]; 48 weeks, 8/226 [3.5%]). This imbalance in events of UTI was only observed in women. No AEs in the category of “kidney infections” were reported throughout the duration of the study and the 24-week extension period.

Events of hypotension/dehydration/hypovolemia were balanced across treatment groups over the 48-week treatment period (three events in the dapagliflozin group vs. two in the placebo group). There were eight events (3.6%) of renal laboratory parameters, reported as AEs of renal impairment, in the dapagliflozin group versus four events (1.8%) in the placebo group over the 48-week treatment period; this imbalance was due to more events of “decreased renal creatinine clearance” in the dapagliflozin (four subjects) than in the placebo group (one subject) and reflected strict protocol-mandated



testing requirements that were based on renal laboratory parameters. AEs of renal impairment in the dapagliflozin group were due to transient, reversible changes in laboratory parameters that did not require treatment, consistent with a mild diuretic effect. There was no SAE of renal impairment, and AEs leading to discontinuation were balanced across the two treatment groups (two with dapagliflozin and three with placebo).

The number of subjects with reported events of neoplasms (benign, malignant, or unspecified) over the 24-week study and 24-week extension was lower in the dapagliflozin group (2/225) compared with placebo (7/226). One event of prostate neoplasm and one of thyroid neoplasm were reported in the dapagliflozin group (no definitive cytologic diagnosis was available for either of these patients). Three reports of basal cell carcinoma and one each of breast cancer, endometrial cancer, fibroma, lipoma, metastatic nevus, and metastatic squamous cell carcinoma were reported in the placebo group.

At week 48, an absolute increase from baseline in mean hematocrit was observed with dapagliflozin (2.2%) compared with placebo (−0.5%). Over 48 weeks, there was one case of alanine aminotransferase and/or aspartate aminotransferase  $>3 \times$  the upper limit of normal (ULN) in combination with total bilirubin  $>1.5 \times$  ULN in the placebo group and none in the dapagliflozin group. One case of alanine aminotransferase  $>5 \times$  ULN and one of aspartate aminotransferase  $>5 \times$  ULN was observed in each treatment group over 48 weeks. There were no clinically meaningful mean changes in serum levels of potassium, sodium, magnesium, calcium, parathyroid hormone, or creatinine.

There was a decrease in serum uric acid with dapagliflozin (mean [SE], including data after rescue: 24 weeks, −0.75 [0.06] mg/dL; 48 weeks, −0.76 [0.07] mg/dL) versus placebo (24 weeks, 0.03 [0.06] mg/dL; 48 weeks, 0.10 [0.07] mg/dL).

## CONCLUSIONS

Although there is no single approach to the treatment of type 2 diabetes, the overall goal is to maintain glycemic

targets over time and thereby reduce the risk of acute and chronic complications. Exercise and dietary modifications are the cornerstone of treatment. For most patients, however, lifestyle interventions alone are ineffective in achieving adequate glycemic control and pharmacologic intervention is required (19). Due to the progressive decline in  $\beta$ -cell function, OADs can lose efficacy with prolonged use and a progression from monotherapy to combination (dual or triple) therapies may be necessary (20). The use of injectable insulin as the third-line treatment in a triple combination therapy regimen is well established; however, there is a paucity of information surrounding the concomitant use of three OADs. Oral thiazolidinediones have been shown to be effective as part of a triple combination with a sulfonylurea and metformin (21,22). In addition, sitagliptin significantly improved glycemic control and  $\beta$ -cell function in patients with type 2 diabetes who had inadequate glycemic control with a sulfonylurea, with or without metformin (23).

The unique mechanism of action of dapagliflozin, involving the inhibition of SGLT2, is not dependent on the ability of the pancreatic  $\beta$ -cells to secrete insulin. Thus, dapagliflozin may be an appropriate choice for a wide range of patients at different stages of type 2 diabetes, including those in the advanced stages of the disease with significantly compromised  $\beta$ -cell function who are already receiving one or more OADs.

The results presented here indicate that the addition of dapagliflozin to ongoing therapy in patients with type 2 diabetes inadequately controlled with sitagliptin, with or without metformin, was well tolerated over 48 weeks. Glycemic parameters and body weight were significantly improved with dapagliflozin treatment and were maintained through the duration of the study compared with placebo. In stratum 2 (treatment added to metformin and sitagliptin), the HbA<sub>1c</sub> change was maintained over time in the dapagliflozin group compared with baseline, consistent with findings in

other dapagliflozin studies of 1 or more years' duration. In stratum 1 (treatment added to sitagliptin monotherapy), after an initial reduction, the HbA<sub>1c</sub> increased over time in the dapagliflozin group compared with baseline, although to a lesser extent than that observed in the placebo group; the placebo-subtracted change at 48 weeks in the dapagliflozin group was clinically significant at −0.9%.

The rescue rates observed over 48 weeks in both arms of this study were comparable to rates observed with other therapeutic agents when such strict rescue criteria, which included mandating rescue of all patients with HbA<sub>1c</sub>  $>8\%$  at week 12, were implemented (24,25). In this particular trial, 22% of patients receiving dapagliflozin achieved target glycemic goals of HbA<sub>1c</sub>  $<7\%$  as compared with 12% with placebo. Dapagliflozin causes excretion of glucose in proportion to hyperglycemia (and renal filtration), and as such, lower HbA<sub>1c</sub> is associated with less glucose excretion as HbA<sub>1c</sub> levels approach goal. This may also explain the low rate of hypoglycemia observed with this novel therapy.

Overall, the findings in this study support the value of this novel mechanism as a treatment for type 2 diabetes that is complementary to other agents and effective across different stages of disease.

This is the first published study evaluating the efficacy and safety of a triple oral combination therapy that includes dapagliflozin. Reductions in HbA<sub>1c</sub> and body weight with dapagliflozin were observed in patients receiving sitagliptin either alone or in combination with metformin. Slightly greater numerical reductions in HbA<sub>1c</sub> were observed in the sitagliptin monotherapy stratum than in the sitagliptin plus metformin stratum; this result was likely due to natural variability given the overlap in 95% CIs between comparable treatment groups. The slightly lower baseline HbA<sub>1c</sub> in the sitagliptin plus metformin stratum may also have contributed to the observed findings. In addition, a more advanced stage of disease may have been encountered in patients receiving both

sitagliptin and metformin and this may also have contributed to the slightly lower reductions in HbA<sub>1c</sub> observed in that patient population.

Although the efficacy of dapagliflozin has not been found to be affected by disease duration, it is affected by glomerular filtration rate, which may be lower in patients with more advanced disease.

Patients receiving dapagliflozin showed an increase in  $\beta$ -cell function compared with placebo and, although the use of HOMA methodology needs further validation for use with SGLT2 inhibitors, this change was comparable to results observed using euglycemic clamp methodology (26).

Dapagliflozin treatment was generally well tolerated over 48 weeks, whether added to sitagliptin with or without metformin. From a safety perspective, reports of signs, symptoms, and events suggestive of genital infections and reports of diagnosed UTIs were elevated in patients receiving dapagliflozin and were consistent with the known mechanism of action. A small imbalance in events of renal impairment was observed in this study, although such an imbalance was not observed in the general population in the overall dapagliflozin program. These events were due to transient, reversible, nonserious changes in laboratory parameters that did not require treatment, consistent with a mild diuretic effect. Small changes in total cholesterol, HDL cholesterol, LDL cholesterol, and triglycerides were observed with dapagliflozin compared with placebo that were unlikely to be clinically relevant.

In previously published trials, BP reductions consistent with diuretic effects of dapagliflozin have been observed with monotherapy and in combination with insulin sensitizers and metformin (7–11,13). In patients with baseline SBP  $\geq$ 130 mmHg, a decrease in mean seated SBP of  $\sim$ 5 mmHg was observed at 8 weeks in both the placebo and dapagliflozin groups. This population of patients, with a baseline SBP  $\geq$ 130 mmHg, was identified based on single BP measurements performed at baseline, and further

antihypertensive medication adjustment was allowed prior to randomization. As such, these patients are likely to exhibit regression to mean, with reductions in BP in both the dapagliflozin and placebo treatment arms that might mask modest BP lowering with dapagliflozin. In the overall study population, placebo-corrected changes from baseline in SBP of  $-2$  to  $-3$  mmHg were observed at 48 weeks and were consistent with findings observed across the dapagliflozin program.

In summary, this 24-week study with a 24-week extension period showed that once-daily treatment with dapagliflozin 10 mg, in dual combination with sitagliptin or in triple combination with sitagliptin plus metformin, was well tolerated and led to clinically meaningful reductions in glycemic parameters and body weight that were sustained through 48 weeks of treatment.

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