Randomized, Double-Blind, Phase 3 Trial of Triple Therapy With Dapagliflozin Add-on to Saxagliptin Plus Metformin in Type 2 Diabetes

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OBJECTIVE

To compare the efficacy and safety of treatment with dapagliflozin versus that with placebo add-on to saxagliptin plus metformin in patients whose type 2 diabetes is inadequately controlled with saxagliptin plus metformin treatment.

RESEARCH DESIGN AND METHODS

Patients receiving treatment with stable metformin (stratum A) (screening HbA_{1c} level 8.0–11.5% [64–102 mmol/mol]) or stable metformin and a dipeptidyl peptidase-4 (DPP-4) inhibitor (stratum B) (HbA_{1c} 7.5–10.5% [58–91 mmol/mol]) for ≥8 weeks received open-label saxagliptin 5 mg/day and metformin for 16 weeks (stratum A) or 8 weeks (stratum B) (saxagliptin replaced any DPP-4 inhibitor). Patients with inadequate glycemic control (HbA_{1c} 7–10.5% [53–91 mmol/mol]) were randomized to receive placebo or dapagliflozin 10 mg/day plus saxagliptin and metformin. The primary end point was the change in HbA_{1c} from baseline to week 24. Secondary end points included fasting plasma glucose (FPG) level, 2-h postprandial glucose (PPG) level, body weight, and proportion of patients achieving an HbA_{1c} level of <7% (53 mmol/mol).

RESULTS

Treatment with dapagliflozin add-on to saxagliptin plus metformin resulted in a greater mean HbA_{1c} reduction than placebo (−0.82 vs. −0.10% [−9 vs. −1.1 mmol/mol], $P < 0.0001$). Significantly greater reductions in FPG level, 2-h PPG level, and body weight were observed, and more patients achieved an HbA_{1c} level of <7% (53 mmol/mol) with treatment with dapagliflozin versus placebo. Adverse events were similar across treatment groups, with a low overall risk of hypoglycemia (~1%). Genital infections developed in more patients with dapagliflozin treatment (5%) than with placebo (0.6%).

CONCLUSIONS

Triple therapy with dapagliflozin add-on to saxagliptin plus metformin improves glycemic control and is well tolerated in patients whose type 2 diabetes is inadequately controlled with saxagliptin plus metformin therapy.

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Type 2 diabetes is a complex, chronic disease characterized by hyperglycemia (1) and an increased risk of microvascular and macrovascular complications (2). Because of the progressive nature of type 2 diabetes (3), achieving and maintaining glycemic treatment goals may be challenging (4,5). Metformin, if tolerated and not contraindicated, is generally considered the drug of choice for initiating oral therapy in patients with type 2 diabetes (6–8). As glycemic control worsens over time, other classes of antidiabetes medications with different mechanisms of action are typically added to metformin in a stepwise manner as dual or triple therapy as recommended by current treatment guidelines (6–8).

Clinical practice guidelines recommend a patient-centered approach when selecting add-on therapy for patients whose blood glucose levels are not controlled with metformin therapy (6–8). Among these options are dipeptidyl peptidase-4 (DPP-4) inhibitors and sodium–glucose cotransporter 2 (SGLT2) inhibitors (6,7). Saxagliptin, a DPP-4 inhibitor, enhances glucose-mediated insulin secretion and suppresses glucagon secretion by inhibiting the rapid degradation of glucagon-like peptide-1 (9). Dapagliflozin, an SGLT2 inhibitor, acts independently of insulin and inhibits renal glucose reabsorption, thus increasing urinary glucose excretion and reducing plasma glucose concentrations (10). By acting on distinct and separate pathways that affect different defects involved in the pathophysiology of type 2 diabetes, saxagliptin and dapagliflozin provide a treatment option that has a complementary mechanism of action when added to metformin (11).

Saxagliptin and dapagliflozin, when used as monotherapy or as an add-on to metformin therapy in patients with type 2 diabetes, improve glycemic control, and have favorable safety and tolerability profiles (12–16). Moreover, both agents have a low propensity for hypoglycemia and are weight neutral (saxagliptin) (13,15,16) or cause weight reduction of 2–3 kg (dapagliflozin) (12,17). Thus, the addition of dapagliflozin to saxagliptin and metformin results in a triple combination therapy that includes components with complementary mechanisms of action, a low risk of hypoglycemia, and the potential for weight reduction. This phase 3 study was designed to compare the safety and efficacy of dapagliflozin therapy versus placebo add-on to saxagliptin plus metformin therapy in patients with type 2 diabetes who had inadequate glycemic control with saxagliptin plus metformin therapy.

RESEARCH DESIGN AND METHODS

Study Design

This was a multicenter, randomized, double-blind, placebo-controlled, parallel-group, phase 3 study (clinical trial reg. no. NCT01646320). It was designed and monitored in accordance with the ethical principles of Good Clinical Practice as defined by the International Conference on Harmonization and the Declaration of Helsinki. Institutional review boards or ethics committees at each study site approved the protocol, and all patients gave written informed consent.

The study design consisted of a screening and open-label treatment period followed by a randomized, 24-week, short-term, double-blind treatment period (Supplementary Fig. 1); this was followed with a long-term extension of an additional 28 weeks for a total of 52 weeks of triple therapy. The results of the long-term extension will be presented in a subsequent report. Two groups of patients (≥18 years of age) with type 2 diabetes and inadequate glycemic control were included in the open-label treatment period based on DPP-4 inhibitor use. Patients in stratum A had a glycated hemoglobin (HbA_{1c}) level of 8.0–11.5% (64–102 mmol/mol) at screening and were receiving stable metformin therapy (immediate release [IR] or extended release [XR] ≥1,500 mg/day) for at least 8 weeks before screening. These patients were switched to the nearest lower or higher multiple of metformin IR 500-mg tablets and saxagliptin 5 mg/day for 16 weeks of open-label treatment. Patients in stratum B had an HbA_{1c} level of 7.5–10.5% (58–91 mmol/mol) and were receiving stable metformin (IR or XR ≥1,500 mg/day) and a DPP-4 inhibitor at the maximum approved dose for at least 8 weeks before the screening visit. These patients were switched to the nearest lower or higher multiple of metformin IR 500-mg tablets, and any DPP-4 inhibitor was replaced by saxagliptin 5 mg/day. They received 8 weeks of open-label treatment with this regimen.

Major exclusion criteria for screening and the open-label treatment period included pregnancy, cardiovascular events within 3 months of screening, an estimated glomerular filtration rate of <60 mL/min/1.73 m^2 or a serum creatinine level of ≥1.5 mg/dL in men or ≥1.4 mg/dL in women, microscopic hematuria with no known cause in men, and significant hepatic disease. Patients were also excluded if they received any antidiabetes medication, other than metformin and DPP-4 inhibitors, for >14 days during the 12 weeks before screening. Patients with uncontrolled hypertension (systolic blood pressure ≥160 mmHg and/or diastolic blood pressure ≥100 mmHg) were allowed to enter the open-label period provided that their antihypertensive therapy was adjusted appropriately; if their blood pressure fell below these limits, they could be considered for randomization to double-blind treatment.

For the open-label period, the enrollment of patients with an HbA_{1c} level at the lower end of the inclusion range (8–9% [64–75 mmol/mol] for patients in stratum A, 7.5–8.5% [58–69 mmol/mol] for patients in stratum B) was limited to ~50%. The other ~50% of patients had an HbA_{1c} level of >9–11.5% (75–102 mmol/mol) (stratum A) or >8.5–10.5% (69–91 mmol/mol) (stratum B). At week −10 and week −2, if the fasting plasma glucose (FPG) level was >270 mg/dL, the patient could not be randomized and was discontinued from the study.

For inclusion in the 24-week double-blind treatment period, patients in both stratum A and B had to have an HbA_{1c} level of 7.0–10.5% (53–91 mmol/mol) when assessed at week −2. Following the open-label period, eligible patients were randomly assigned by an interactive voice response system in a centrally blocked 1:1 ratio within each stratum to double-blind treatment with placebo or dapagliflozin 10 mg/day for 24 weeks. Patients completing the 24-week, short-term, double-blind period could enter a 28-week long-term extension.

Efficacy End Points

The primary end point was the mean change from baseline in HbA_{1c} level

after 24 weeks of double-blind treatment with dapagliflozin versus placebo add-on to saxagliptin plus metformin. Secondary end points were the mean change from baseline at 24 weeks in FPG level, 2-h postprandial glucose (PPG) level following a liquid meal tolerance test (MTT), and body weight and the mean proportion of patients achieving a therapeutic glycemic response, defined as an HbA_{1c} level of <7.0% (53 mmol/mol), after 24 weeks. The composition of the liquid MTT was dependent on the investigational site and consisted of 360–375 kcal, 14.0–28.2 g of protein, 10.5–14.0 g of fat, and 42–45 g of carbohydrates; 16.8–22.0 g of sugars as a component of carbohydrates. Other end points included the proportion of patients rescued or discontinued from the study for lack of efficacy, the change from baseline in the PPG area under the concentration-time curve from 0 to 180 min ($AUC_{0–180\ min}$) during a liquid MTT, and the change from baseline in serum lipid levels.

Safety

Safety and tolerability were evaluated based on adverse events (AEs), hypoglycemia, laboratory abnormalities, and vital signs. Hypoglycemia episodes were classified as minor (symptomatic or asymptomatic with plasma glucose concentration of <63 mg/dL, regardless of the need for external assistance), major (symptomatic requiring third-party assistance because of severe impairment in consciousness or behavior with or without a plasma glucose concentration of <54 mg/dL and prompt recovery after glucose or glucagon administration), and other (suggestive episode not meeting the criteria for major or minor). AEs of special interest included severe cutaneous events, decreased lymphocyte count, decreased thrombocyte count, opportunistic infection, pancreatitis, pancreatic cancer, fracture, severe hypersensitivity, worsening renal function, genital infections, urinary tract infections, bladder neoplasm, breast neoplasm, volume depletion, and heart failure. Suspected cardiovascular AEs were blindly adjudicated by a clinical event committee managed by the Montreal Heart Institute. Reported liver injury AEs were blindly adjudicated by an independent hepatic adjudication committee who determined the probability of drug-induced liver injury as the cause for liver-related abnormalities.

Statistical Analysis

With 133 patients per treatment group, there was 90% power to detect a difference in the mean changes from baseline in HbA_{1c} level at 24 weeks of 0.4% (4.4 mmol/mol) between the dapagliflozin plus saxagliptin plus metformin treatment group and the placebo plus saxagliptin plus metformin treatment group, assuming an SD of 1.0%. Assuming that 5% of patients would not have a post-baseline assessment, a total of ~280 patients (140 patients per treatment arm) needed to be randomized. Because patients in stratum B were assumed to have better glycemic control based on their prior exposure to dual therapy, ~33% of randomized patients were expected to be from stratum B.

The primary efficacy data set included all randomized patients who received one or more doses of study medication during the double-blind treatment period. The primary efficacy analysis was performed using a longitudinal repeated-measures analysis with terms for baseline value, treatment group, time, stratum, the interaction of treatment group and time, and the interaction of baseline value and time, including only observations made before rescue. Point estimates and 95% CIs were calculated for the adjusted mean changes within each treatment group and for the differences in adjusted mean changes between treatment groups.

The interpretation of the statistical significance of treatment comparisons for each secondary efficacy end point was performed using a stepwise procedure to protect the overall type I error rate. Analysis of the mean change from baseline at week 24 for FPG level and body weight was performed using the same longitudinal repeated-measures model as for the primary efficacy end point. The analysis of the mean change from baseline at week 24 for 2-h PPG level during a liquid MTT was based on an ANCOVA model using last observation carried forward methodology with terms for treatment group, stratum, and baseline value in the model. The proportion of patients achieving an HbA_{1c} level of <7.0% (<53 mmol/mol) at 24 weeks was summarized by treatment group and analyzed using previously published methods (18,19).

RESULTS

Patients

For the 24-week short-term phase of this study, the first patient visit occurred on 21 September 2012, and the last patient visit occurred on 7 August 2014. Of the 818 enrolled patients, 483 entered the open-label period, and 83% (402) completed this period (Supplementary Fig. 2). Three hundred twenty patients (219 from stratum A and 101 from stratum B) were eligible for randomization and entered the 24-week, double-blind treatment period, and 94.1% (301) completed the short-term period of the study. Patient demographics and baseline characteristics were balanced across treatment groups (Table 1). Most patients (93%) were white, and 54% were women. The mean age was 55 years. The mean duration of diabetes was 7.6 years, the mean HbA_{1c} level was 8.2% (66 mmol/mol), and the mean FPG level was 178 mg/dL at baseline. The proportion of patients from each stratum was also balanced in the two treatment groups. The baseline HbA_{1c} level at randomization was similar between the two treatment groups (8.17% [66 mmol/mol] and 8.24% [67 mmol/mol]) (Table 1).

Efficacy

The addition of dapagliflozin to saxagliptin plus metformin therapy resulted in a significantly greater adjusted mean ± SE reduction from baseline in HbA_{1c} level at 24 weeks (−0.82 ± 0.07% [−9.0 ± 0.8 mmol/mol]) compared with placebo (−0.10 ± 0.07% [−1.1 ± 0.8 mmol/mol]) (Fig. 1*A*, Table 2). The difference (95% CI) in change from baseline in HbA_{1c} level between dapagliflozin and placebo add-on to saxagliptin plus metformin therapy was −0.72% ([95% CI −0.91, −0.53]) (−7.9 mmol/mol [95% CI −9.9, −5.8], $P < 0.0001$). Thus, the primary end point of statistical superiority of dapagliflozin add-on to saxagliptin plus metformin therapy versus placebo add-on to saxagliptin plus metformin therapy was met. A clear separation in HbA_{1c} level was observed between the treatment groups starting at week 6, the earliest time point assessed, and continuing to the end of the study (Fig. 1*B*).

Table 1—Demographics and baseline characteristics at randomization

	Placebo add-on to saxagliptin plus metformin (*n* = 160)	Dapagliflozin add-on to saxagliptin plus metformin (*n* = 160)	Total (*n* = 320)
Age, years	55.0 ± 9.6	55.2 ± 8.6	55.1 ± 9.1
Women	84 (52.5)	90 (56.3)	174 (54.4)
Race			
White	147 (91.9)	150 (93.8)	297 (92.8)
African American	10 (6.3)	8 (5.0)	18 (5.6)
Asian	1 (0.6)	1 (0.6)	2 (0.6)
Other	2 (1.3)	1 (0.6)	3 (0.9)
BMI, kg/m^2	32.2 ± 5.3	31.2 ± 4.7	31.7 ± 5.1
Duration of diabetes, years	8.0 ± 6.6	7.2 ± 5.7	7.6 ± 6.1
HbA_{1c}			
%	8.17 ± 0.98	8.24 ± 0.96	8.20 ± 0.97
mmol/mol	66 ± 10.7	67 ± 10.5	66 ± 10.6
HbA_{1c} category			
<8% (64 mmol/mol)	75 (46.9)	69 (43.1)	144 (45.0)
≥8% and <9% (≥64 and <75 mmol/mol)	53 (33.1)	51 (31.9)	104 (32.5)
≥9% (75 mmol/mol)	32 (20.0)	40 (25.0)	72 (22.5)
FPG, mg/dL	177 ± 46.8	179 ± 48.9	178 ± 47.8
2-h PPG, mg/dL	243 ± 57.5 (*n* = 154)	242 ± 60.9 (*n* = 156)	242 ± 59.1 (*n* = 310)
Fasting C-peptide, ng/mL	2.6 ± 1.1	2.5 ± 1.1	2.6 ± 1.1
eGFR, mL/min/1.73 m^2	91.6 ± 23.2	93.5 ± 20.8	92.5 ± 22.0
Randomization stratification			
Stratum A	109 (68.1)	110 (68.8)	219 (68.4)
Stratum B	51 (31.9)	50 (31.3)	101 (31.6)

Data are mean ± SD or *n* (%), unless otherwise indicated. eGFR, estimated glomerular filtration rate calculated by MDRD formula.

There were statistically significantly larger reductions from baseline to week 24 in the dapagliflozin add-on to saxagliptin plus metformin group compared with the placebo add-on to saxagliptin plus metformin group in FPG level (difference for dapagliflozin vs. placebo add-on −28 mg/dL [95% CI −35.4, −19.6], $P < 0.0001$), 2-h PPG level (difference for dapagliflozin vs. placebo add-on −36 mg/dL [95% CI −46.3, −24.7], $P < 0.0001$), and body weight (difference for dapagliflozin vs. placebo add-on −1.5 kg [95% CI −2.12, −0.89], $P < 0.0001$) (Table 2). In addition, a statistically significantly higher proportion of patients in the dapagliflozin add-on to saxagliptin plus metformin group (38.0%) achieved an HbA_{1c} level of <7% at week 24 than in the placebo add-on to saxagliptin plus metformin group (12.4%) (Table 2).

Fewer patients were rescued or discontinued from the study for lack of glycemic control in the dapagliflozin add-on to saxagliptin plus metformin group (3 of 160 patients) compared with the placebo add-on to saxagliptin plus metformin group (24 of 160 patients; adjusted percent difference for dapagliflozin vs. placebo add-on −13.6% [95% CI −19.4, −7.7]). The adjusted mean (SE) change from baseline at week 24 in PPG $AUC_{0-180\ min}$ was greater with dapagliflozin add-on to saxagliptin plus metformin −11,353 mg/dL/min (676.3) than with placebo add-on to saxagliptin plus metformin −5,162 mg/dL/min (681.7) (difference for dapagliflozin vs. placebo, −6,191 mg/dL/min [95% CI −8,027.1, −4,354.6]). The mean percentage changes from baseline at week 24 in fasting serum lipids were small and similar in the two treatment groups (Supplementary Table 1).

In a post hoc subgroup analysis of the change from baseline in HbA_{1c} level in the two strata, the difference in the adjusted mean change from baseline in HbA_{1c} level between dapagliflozin add-on to saxagliptin plus metformin therapy and placebo add-on to saxagliptin plus metformin therapy was identical (stratum A −0.72% [95% CI −0.94, −0.49], stratum B −0.72% [95% CI −1.06, −0.38]). However, the adjusted mean change (95% CI) from baseline in HbA_{1c} level with dapagliflozin add-on to saxagliptin plus metformin therapy was numerically greater (−0.96% [95% CI −1.19, −0.72]) in patients who received a DPP-4 inhibitor and metformin before screening (stratum B) than in those patients who received only metformin before screening (−0.75% [95% CI −0.94, −0.59]) (stratum A). A numerically greater change from baseline in HbA_{1c} level was also seen in the placebo group in stratum B (−0.24% [95% CI −0.48, 0.01]) compared with stratum A (−0.03% [95% CI −0.20, 0.13]).

Safety

The proportion of patients with AEs was similar across treatment groups (Table 3). Few patients were discontinued from the study, and there were no deaths. The most common AEs in both treatment groups (≥5% of patients) were headache, urinary tract infections, and influenza. The proportion of patients with serious AEs (SAEs) was small and similar in both treatment groups. Only one SAE (thrombocytopenia in the dapagliflozin add-on to saxagliptin plus metformin group) was considered by the investigators to be related to study medication. Discontinuations because

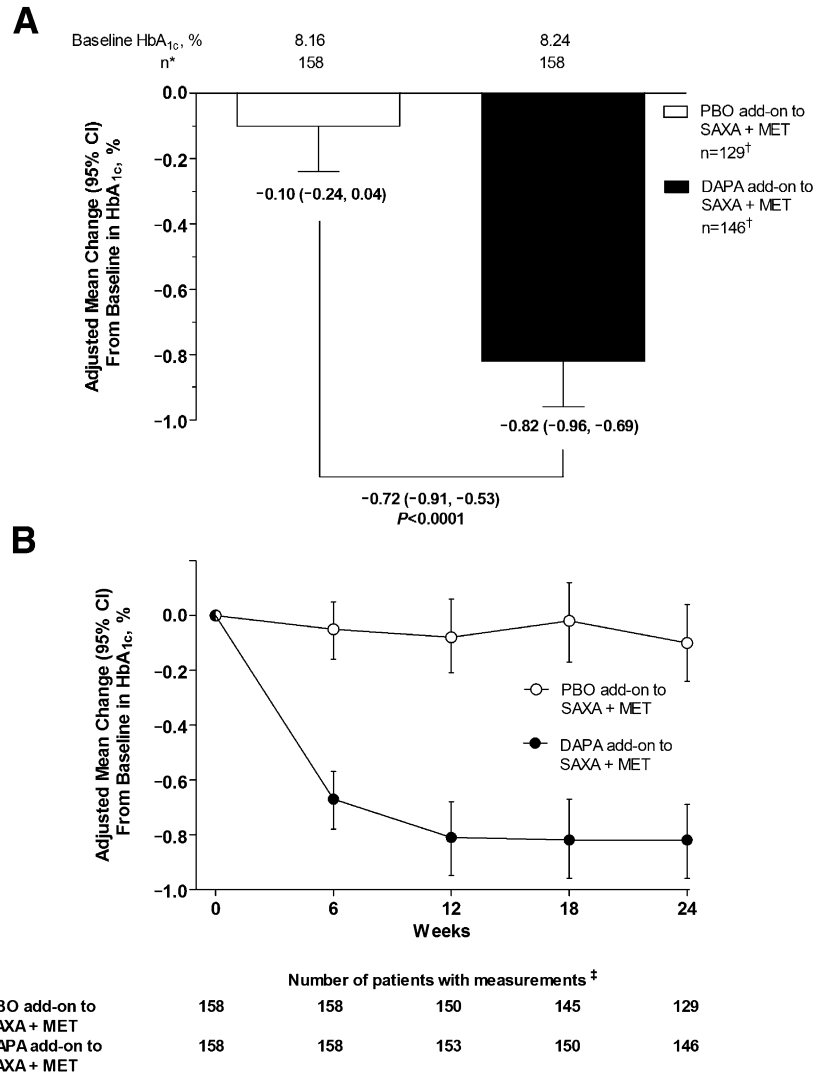

Figure 1—Change in HbA_{1c} level. Adjusted mean change in HbA_{1c} level from baseline to 24 weeks (*A*) and time course of adjusted mean change from baseline in HbA_{1c} level (*B*). *Randomized patients with baseline and one or more postbaseline measurements. †Randomized patients with baseline and week 24 measurement. ‡Randomized patients who received one or more doses of double-blind medication. DAPA, dapagliflozin; MET, metformin; PBO, placebo; SAXA, saxagliptin.

of AEs were higher with dapagliflozin add-on to saxagliptin plus metformin therapy (5.0%) than with placebo add-on to saxagliptin plus metformin therapy (1.3%). In the dapagliflozin add-on to saxagliptin plus metformin group, reasons for discontinuations were thrombocytopenia ($n = 1$), breast cancer ($n = 1$), heart failure ($n = 1$), recurrent vulvovaginal and urinary tract infections ($n = 1$), a decrease in glomerular filtration rate ($n = 1$), renal impairment ($n = 1$), and pollakiuria ($n = 2$). A higher proportion of patients, all of whom were women, receiving dapagliflozin add-on to saxagliptin plus metformin therapy had genital infections (5%) compared with those receiving placebo add-on to saxagliptin plus metformin therapy (0.6%); the occurrence of urinary tract infections was similar for the dapagliflozin add-on to saxagliptin plus metformin group (5%) and placebo add-on to saxagliptin plus metformin group (6.3%). Hypoglycemia episodes were infrequent, and there were no cases of major hypoglycemia. Two cardiovascular events confirmed by adjudication (ventricular tachycardia and heart failure) occurred in the dapagliflozin add-on to saxagliptin plus metformin group. One patient in the dapagliflozin add-on to saxagliptin plus metformin group had elevated alanine aminotransferase and/or aspartate aminotransferases. Three patients receiving placebo add-on to saxagliptin plus metformin therapy had elevated levels of alanine aminotransferase and/or aspartate aminotransferase. There were no AEs of pancreatitis, fracture, severe cutaneous events, opportunistic infection, hypersensitivity, bladder neoplasm, pancreatic cancer, decreased lymphocyte count, or hypotension, dehydration, and hypovolemia.

There were small decreases from baseline to week 24 in systolic blood pressure (adjusted mean change −1.9 vs. 2.0 mmHg; difference −3.9 [95% CI −6.6, −1.2], $P = 0.005$) and diastolic blood pressure (−1.7 vs. 0.3 mmHg; −2.0 [95% CI −3.7, −0.3], $P = 0.024$) with dapagliflozin add-on to saxagliptin plus metformin therapy compared with placebo add-on to saxagliptin plus metformin therapy.

CONCLUSIONS

Acknowledging the progressive nature of type 2 diabetes, with an underlying failure of β-cell function, current clinical guidelines (6,7) recommend combination therapies with glucose-lowering agents. In the absence of contraindications, metformin remains the drug of first choice in patients who can tolerate it. Treatment guidelines recommend a patient-centered approach when deciding what should be added when metformin monotherapy fails to achieve or sustain glycemic control (6,7). DPP-4 inhibitors are becoming a preferred second agent for many prescribers because of their low risk of hypoglycemia, lack of weight gain, and once-daily administration (20). However, mechanistically, in addition to their effect to inhibit glucagon secretion, DPP-4 inhibitors rely on residual β-cell function to lower hyperglycemia (9). Although some data suggest that these agents may have the ability to slow the deterioration of β-cell function (21), the progressive nature of diabetes will eventually lead to β-cell failure (3) and loss of glycemic control, regardless of which antidiabetes agent is used. Thus, further combinations with additional glucose-lowering therapies are needed to maintain glycemic control. Although combination injectable therapy with insulin with or without glucagon-like peptide 1 receptor agonist is recommended in patients with severe hyperglycemia (HbA_{1c} level ≥10%) (7), for patients with less severe disease, the

Table 2—Adjusted mean change from baseline at 24 weeks for primary and secondary efficacy end points

	Placebo add-on to saxagliptin plus metformin (*n* = 160)		Dapagliflozin add-on to saxagliptin plus metformin (*n* = 160)
HbA_{1c}			
Baseline, mean ± SD, % [mmol/mol]	8.16 ± 0.99 [66 ± 10.8]		8.24 ± 0.97 [67 ± 10.6]
Change from baseline, % [mmol/mol]	−0.10 (−0.24, 0.04) [−1.1 (−2.6, 0.4)]		−0.82 (−0.96, −0.69) [−9 (−10.5, −7.5)]
Difference dapagliflozin vs. placebo, % [mmol/mol]		−0.72 (−0.91, −0.53) [−7.9 (−9.9, −5.8)] $P < 0.0001$	
FPG, mg/dL			
Baseline, mean ± SD	177 ± 46.8		179 ± 48.7
Change from baseline	−5 (−11.1, 0.60)		−33 (−38.3, −27.2)
Difference dapagliflozin vs. placebo		−28 (−35.4, −19.6) $P < 0.0001$	
2-h PPG, mg/dL			
Baseline, mean ± SD	241 ± 57.1		240 ± 60.9
Change from baseline	−38 (−46.1, −29.9)		−74 (−81.5, −65.5)
Difference dapagliflozin vs. placebo		−36 (−46.3, −24.7) $P < 0.0001$	
Body weight, kg			
Baseline, mean ± SD	88.2 ± 18.1		85.8 ± 18.4
Change from baseline	−0.4 (−0.86, 0.04)		−1.9 (−2.34, −1.48)
Difference dapagliflozin vs. placebo		−1.5 (−2.12, −0.89) $P < 0.0001$	
Patients with HbA_{1c} <7% (53 mmol/mol)			
x/*n*	21/158		58/158
Adjusted %	12.4 (7.0, 17.9)		38.0 (30.9, 45.1)
Difference vs. saxagliptin plus metformin, %		25.5 (16.7, 34.4) $P < 0.0001$	

Data are adjusted mean change from baseline (95% CI), unless otherwise indicated. PPG, postprandial plasma glucose; *x*/*n*, number of responders/number of patients with nonmissing baseline and week 24 values; LOCF, last observation carried forward.

recently introduced class of SGLT2 inhibitors offers the advantage of reducing hyperglycemia independent of β-cell function and circulating insulin levels (22) and can thus, theoretically, be combined with all other glucose-lowering agents. In addition, adding an SGLT2 inhibitor to a combination therapy with metformin and a DPP-4 inhibitor results in a combination that works complementarily to address several of the pathologic defects of type 2 diabetes (11), leading to clinically relevant reductions in hyperglycemia in patients whose glycemic control has not been maintained with two oral agents and without the burden of hypoglycemia or weight gain that one would expect with sulfonylureas or insulins (23,24). Moreover, a DPP-4 inhibitor may reduce the increase in glucagon secretion induced by SGLT2 inhibitors (25).

Although major clinical practice guidelines recommend the use of such triple therapy based on HbA_{1c} levels, evidence from randomized clinical trials remains scarce (7,8). The purpose of this study was to assess the efficacy and safety of triple therapy with dapagliflozin add-on to saxagliptin plus metformin compared with placebo add-on to saxagliptin plus metformin in patients with type 2 diabetes who were not at a glycemic goal HbA_{1c} level of <7% (53 mmol/mol), had poor glycemic control, and remained in the HbA_{1c} range of 7–10.5% (53–91 mmol/mol) after open-label treatment with saxagliptin and metformin.

We demonstrate that treatment with dapagliflozin add-on to saxagliptin plus metformin improved all glycemic measures in this study (fasting and postprandial glycemia), resulting in a statistically significantly larger reduction in HbA_{1c} from baseline. This difference became apparent from the earliest time point at which HbA_{1c} was measured (6 weeks), and HbA_{1c} levels remained stable throughout the study. The degree of HbA_{1c} lowering observed in this study (placebo-corrected, −0.72% [−7.9 mmol/mol]) was greater than that seen in a similarly designed study (23) in a cohort of patients receiving treatment with dapagliflozin add-on to sitagliptin plus metformin (−0.4% [−4.4 mmol/mol]). However, the patients in the latter study had lower baseline HbA_{1c} levels (7.8–7.9% [62–63 mmol/mol]) than patients in the current study (8.2% [66 mmol/mol]), which may account for the greater HbA_{1c} response observed in this study.

Triple therapy with dapagliflozin add-on to saxagliptin plus metformin was well tolerated, and the proportion of patients with AEs was similar in the two treatment groups during the 24-week double-blind period. The overall safety observed in the current study was similar to that in the dapagliflozin add-on to sitagliptin with or without metformin study (23) and the dual add-on of dapagliflozin and saxagliptin to metformin study (26). This study confirms the increased risk for genital infections with dapagliflozin therapy (5.0% compared with 0.6% in placebo-treated patients) as observed in previous studies (14,17,27); however, no increased risk in urinary tract infections was observed (5.3% vs. 6.0% in placebo-treated patients).

These findings with triple therapy of dapagliflozin add-on to saxagliptin plus

Table 3—AEs

	Placebo add-on to saxagliptin plus metformin (n = 160)	Dapagliflozin add-on to saxagliptin plus metformin (n = 160)
At least 1 AE	94 (58.8)	90 (56.3)
At least 1 SAE	3 (1.9)	5 (3.1)
AE leading to discontinuation	2 (1.3)	8 (5.0)
SAE leading to discontinuation	2 (1.3)	3 (1.9)
Most common AEs (≥5% of patients)		
Headache	9 (5.6)	9 (5.6)
Influenza	8 (5.0)	8 (5.0)
Diarrhea	8 (5.0)	3 (1.9)
AEs of special interest		
Urinary tract infections	10 (6.3)	8 (5.0)
Genital infections	1 (0.6)	8 (5.0)
GFR decrease	0	2 (1.3)
Fractures	2 (1.3)	0
Decreased thrombocyte count	1 (0.6)	2 (1.3)
Breast neoplasms	0	1 (0.6)
Heart failure	0	2 (1.3)
Hypoglycemia*	0	2 (1.3)
Major	0	0
Minor	0	0
Other	0	2 (1.3)
Adjudicated cardiovascular events	0	2 (1.3)
Adjudicated liver AEs	3 (1.9)	1 (0.6)

Data are n (%). GFR, glomerular filtration rate. *Hypoglycemia includes minor (symptomatic or asymptomatic with plasma glucose concentration <63 mg/dL, regardless of need for external assistance), major (symptomatic requiring third-party assistance due to severe impairment in consciousness or behavior with plasma glucose concentration <54 mg/dL, and prompt recovery after glucose or glucagon administration), and other (suggestive episode not meeting the criteria for major or minor) episodes. Data after the receipt of rescue medication were excluded; one patient receiving placebo reported a minor hypoglycemia episode while receiving glimepiride rescue medication.

metformin are generally consistent with the mechanisms of action of dapagliflozin and saxagliptin and with results from previous clinical studies investigating the efficacy and safety of these agents as monotherapy (14–16), as add-on therapy to oral antidiabetes medications (12,13,27–30), or when used as triple therapy with dual add-on of saxagliptin and dapagliflozin to metformin (26).

Current treatment recommendations position triple therapy using metformin, a DPP-4 inhibitor, and an SGLT2 inhibitor as an alternative to metformin, plus a sulfonylurea, and a DPP-4 inhibitor or an SGLT2 inhibitor. The major issue when using a sulfonylurea in combination therapy is the risk of hypoglycemia (31). In addition, the use of DPP-4 inhibitors with sulfonylureas mechanistically relies on the residual β-cell function, whereas the SGLT2 inhibitors work complementarily with the action of DPP-4 inhibitors, reducing hyperglycemia through renal excretion of glucose independent of insulin secretion, resulting in a lessening of glucotoxicity (32,33) that relieves some of the burden on the failing β-cells. Previous studies (14–16) have demonstrated a low risk of hypoglycemia with saxagliptin or dapagliflozin therapy when studied individually. Likewise, in the current study, hypoglycemia events were infrequent in the dapagliflozin, saxagliptin, and metformin triple therapy group and occurred with a frequency similar to that in the placebo group. When comparing the current study to a previous one where dapagliflozin was added on to therapy with metformin plus a sulfonylurea, the mean reductions with dapagliflozin compared with placebo in HbA_{1c} levels, FPG levels, and body weight were similar, but the rates of hypoglycemia in the study with the sulfonylurea combination were much higher than those in the current study (24).

The results of the current study are in line with the results of several recent studies that have examined the safety and efficacy of DPP-4 inhibitors or SGLT2 inhibitors as a component of triple oral therapy, mainly as add-on to metformin plus a sulfonylurea. In these studies, placebo-corrected changes from baseline in HbA_{1c} level at 24–26 weeks were in the range of −0.59 to −0.93% (−6.4 to −10.2 mmol/mol). In another study (40) in patients whose conditions were inadequately controlled with therapy using metformin plus a sulfonylurea, the add-on of sitagliptin or canagliflozin produced reductions in HbA_{1c} levels at 52 weeks of −0.66% (−7.2 mmol/mol) and −1.03% (−11.3 mmol/mol), respectively. Finally, in patients whose conditions were inadequately controlled with therapy using metformin and pioglitazone, the addition of a DPP-4 inhibitor or SGLT2 inhibitor reduced HbA_{1c} levels by −0.48 to −0.77% (−5.2 to −8.4 mmol/mol) relative to placebo at 24–26 weeks (41–45).

In summary, this study demonstrated that triple therapy using a well-tolerated combination of dapagliflozin add-on to saxagliptin plus metformin in patients with type 2 diabetes who were not at their goal for glycemic control resulted in clinically meaningful reductions in HbA_{1c} level and in a greater proportion of patients achieving an HbA_{1c} level of <7% (53 mmol/mol) compared with those patients receiving placebo add-on to saxagliptin plus metformin therapy. The significantly improved glycemic control with dapagliflozin add-on to saxagliptin plus metformin therapy was achieved without an increased risk

of hypoglycemia and was associated with the additional benefit of body weight reduction. Taken together, dapagliflozin add-on to saxagliptin plus metformin therapy provides a new treatment option of triple oral therapy with weight reduction and low risk of hypoglycemia. The 28-week long-term extension of the study is currently ongoing and will provide further characterization regarding the long-term safety of triple therapy with dapagliflozin add-on to saxagliptin plus metformin.

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