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

Stephan Matthaei,[1] Doina Catrinoiu,[2] Aleksander Celiński,[3] Ella Ekholm,[4] William Cook,[5] Boaz Hirshberg,[6] Hungta Chen,[5] Nayyar Iqbal,[7] and Lars Hansen[7]

Diabetes Care 2015;38:2018–2024 | DOI: 10.2337/dc15-0811

OBJECTIVE

The objective of this study was to assess the efficacy and safety of triple therapy with saxagliptin add-on versus placebo add-on to dapagliflozin plus metformin in adults with type 2 diabetes.

RESEARCH DESIGN AND METHODS

Patients on stable metformin (≥1,500 mg/day) for ≥8 weeks with glycated hemoglobin (HbA_{1c}) 8.0–11.5% (64–102 mmol/mol) at screening received open-label dapagliflozin (10 mg/day) plus metformin immediate release (IR) for 16 weeks. Patients with inadequate glycemic control (HbA_{1c} 7–10.5% [53–91 mmol/mol]) were then randomized to receive placebo (*n* = 153) or saxagliptin 5 mg/day (*n* = 162) in addition to background dapagliflozin plus metformin IR. The primary efficacy end point was change in HbA_{1c} from baseline to week 24.

RESULTS

There was a significantly greater reduction in HbA_{1c} at 24 weeks with saxagliptin add-on (–0.51% [–5.6 mmol/mol]) versus placebo (–0.16% [–1.7 mmol/mol]) add-on to dapagliflozin plus metformin (difference, –0.35% [95% CI –0.52% to –0.18%] and –3.8 [–5.7 to –2.0 mmol/mol], respectively; $P < 0.0001$). Reductions in fasting plasma glucose and 2-h postprandial glucose were similar between treatment arms. A larger proportion of patients achieved HbA_{1c} <7% (53 mmol/mol) with saxagliptin add-on (35.3%) versus placebo add-on (23.1%) to dapagliflozin plus metformin. Adverse events were similar between treatment groups. Episodes of hypoglycemia were infrequent in both treatment arms, and there were no episodes of major hypoglycemia.

CONCLUSIONS

Triple therapy with the addition of saxagliptin to dapagliflozin plus metformin was well tolerated and produced significant improvements in HbA_{1c} in patients with type 2 diabetes inadequately controlled with dapagliflozin plus metformin.

[1]Diabetes-Zentrum, Quakenbrück, Germany
[2]Spitalul Clinic Judetean de Urgenta Constanta, Constanta, Romania
[3]CenterMed–Centrum Badań Klinicznych, Kraków, Poland
[4]AstraZenenca, Mölndal, Sweden
[5]AstraZeneca, Gaithersburg, MD
[6]MedImmune, Gaithersburg, MD
[7]Bristol-Myers Squibb, Princeton, NJ

Corresponding author: Stephan Matthaei, s.matthaei@ckq-gmbh.de.

Received 16 April 2015 and accepted 28 July 2015.

Clinical trial reg. no. NCT01619059, clinicaltrials.gov.

This article contains Supplementary Data online at http://care.diabetesjournals.org/lookup/suppl/doi:10.2337/dc15-0811/-/DC1.

N.I. is currently affiliated with AstraZeneca, Gaithersburg, MD.

In most patients with type 2 diabetes, metformin is recommended as initial therapy to improve glycemic control and reduce the risk of diabetes-related complications (1–3). When metformin fails to maintain glycemic control, addition of antihyperglycemic medications with mechanisms of action complementary to that of metformin should be considered (2,3). Dipeptidyl peptidase-4 (DPP-4) inhibitors and sodium-glucose cotransporter 2 (SGLT2) inhibitors are recognized as add-on options for dual or triple therapy with metformin (2,3).

DPP-4 inhibitors reduce blood glucose concentrations in patients with type 2 diabetes by inhibiting the degradation of GLP-1, thereby stimulating insulin secretion and inhibiting glucagon secretion (4). Because the action of GLP-1 on insulin secretion is glucose-dependent (4), DPP-4 inhibitors are associated with a low risk of hypoglycemia. SGLT2 inhibitors are the newest class of U.S. Food and Drug Administration– and European Medicines Agency–approved oral antidiabetes drugs that reduce plasma glucose concentrations by inhibiting renal glucose reabsorption, resulting in increased renal glucose excretion (5). The mechanism of action of SGLT2 inhibitors is independent of insulin and therefore is associated with a low risk of hypoglycemia. SGLT2 inhibitors have been shown to be effective in patients at various stages of type 2 diabetes (6). SGLT2 inhibitors also have the added benefit of weight reduction because of caloric loss in the urine (200–340 kcal/day) (5,7). Thus, DPP-4 inhibitors and SGLT2 inhibitors have mechanisms of action that are complementary to metformin.

Saxagliptin, a DPP-4 inhibitor, and dapagliflozin, an SGLT2 inhibitor, have demonstrated favorable safety and tolerability profiles and improve glycemic control as monotherapy (8–10), as add-on therapy to metformin (11,12), as add-on to metformin plus a sulfonylurea (13,14), and together as dual add-ons to metformin (15) in patients with type 2 diabetes. This study assessed the efficacy and safety of saxagliptin as an add-on to dapagliflozin plus metformin in patients with type 2 diabetes and inadequate glycemic control with dapagliflozin plus metformin.

RESEARCH DESIGN AND METHODS

Study Design

This was a multicenter, randomized, double-blind, placebo-controlled, parallel-group, phase 3 study (ClinicalTrials.gov identifier NCT01619059). 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 period and an open-label treatment period before randomization and a short-term (24 weeks), double-blind treatment period (Supplementary Fig. 1). Patients could then enter a long-term (28 weeks) extension, for a total of 52 weeks of triple-therapy treatment. Patients with type 2 diabetes with glycated hemoglobin (HbA_{1c}) 8.0–11.5% (64–102 mmol/mol) at screening and taking stable metformin immediate release (IR) or extended release (XR) ($\geq$1,500 mg/day) for $\geq$8 weeks before screening were included. Eligible patients also had to have a C-peptide concentration $\geq$1.0 ng/mL and BMI $\leq$45.0 kg/m^2. At the end of the screening period, patients were switched to 16 weeks of open-label treatment with the nearest multiple of metformin IR 500 mg and dapagliflozin (10 mg/day).

Major exclusion criteria for screening and the open-label treatment period included pregnancy, cardiovascular disease within 3 months of screening, estimated glomerular filtration rate $<$60 mL/min/1.73 m^2, or serum creatinine $\geq$1.5 mg/dL in men or $\geq$1.4 mg/dL in women, microscopic hematuria with no known cause in men, and significant hepatic disease. Patients also were excluded if they received any antidiabetic medication other than metformin for more than 14 days during the 12 weeks before screening. Patients with uncontrolled hypertension (systolic blood pressure $\geq$160 mmHg and/or diastolic blood pressure $\geq$100 mmHg) could enter the open-label period provided that their antihypertensive therapy was adjusted as appropriate. If their blood pressure remained at or above these limits, however, they could not be considered for randomization to double-blind treatment.

The number of patients enrolled into the open-label treatment period, beginning at week $-$16 of the study, with HbA_{1c} values in the lower range (8.0–9.0% [64–75 mmol/mol]) was limited to approximately 50% of the patients. The remainder of the patients had HbA_{1c} $>$9.0% to 11.5% (75–102 mmol/mol). At weeks 10 and 2, if fasting plasma glucose (FPG) was $>$270 mg/dL, a patient could not be randomized and was discontinued from the study.

For inclusion into the randomized, 24-week, double-blind treatment period, patients had to have an HbA_{1c} 7.0–10.5% (53–91 mmol/mol) at week 2 of the open-label treatment period. Following the open-label period, eligible patients were randomized 1:1 using a centralized blocked randomization schedule and received placebo or saxagliptin 5 mg/day in addition to open-label dapagliflozin 10 mg/day and metformin IR for 24 weeks. Patients completing the double-blind period could enter the 28-week long-term extension, the results of which will be presented in a separate report.

Efficacy End Points

The primary end point was the mean change from baseline in HbA_{1c} after 24 weeks of double-blind treatment with a saxagliptin versus a placebo add-on to dapagliflozin plus metformin. Secondary end points were mean change from baseline at 24 weeks in 2-hour postprandial glucose (PPG) following a liquid meal tolerance test (MTT), mean change from baseline at 24 weeks in FPG, and the proportion of patients achieving a therapeutic glycemic response, defined as HbA_{1c} $<$7.0% (53 mmol/mol), at 24 weeks. Other end points included the proportion of patients rescued or discontinued from the study for lack of efficacy, change from baseline in PPG area under the concentration–time curve from time 0 to 180 min change in serum lipids from baseline, and change in body weight from baseline.

The composition of the liquid MTT was dependent on the investigational site and consisted of 360–375 kcal: protein, 14.0–28.2 g; fat, 10.5–14.0 g; carbohydrates 42–45 g; sugars (as a component of carbohydrates), 16.8–22.0 g. The MTT was performed at baseline (day 1) and at week 24. Blood was obtained for measurement of plasma glucose concentration 0, 30, 60, 120, and 180 min after administering the liquid MTT.

Safety

Safety was evaluated based on adverse events (AEs), hypoglycemia, laboratory

abnormalities, and vital signs. Hypoglycemic episodes were classified as minor (symptomatic or asymptomatic, with plasma glucose concentration <63 mg/dL, regardless of need for external assistance); major (symptomatic, requiring third-party assistance because of severe impairment in consciousness or behavior, with or without plasma glucose concentration <54 mg/dL, and prompt recovery after glucose or glucagon administration); and other (a suggestive episode not meeting the criteria for major or minor). Prespecified AEs of special interest included severe cutaneous events, decreased lymphocyte count, decreased thrombocyte count, opportunistic infection, pancreatitis, fracture, 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 an independent committee managed by the Montreal Heart Institute. Reported liver injury AEs were blindly adjudicated by an independent hepatic adjudication committee that determined the probability of drug-induced liver injury as the cause of reported liver-related abnormalities.

Statistical Analysis

Assuming an SD of 1.0%, with 133 patients per treatment group there was 90% power to detect a difference in mean change in HbA_{1c} from baseline of 0.4% (4.4 mmol/mol) between the saxagliptin add-on to dapagliflozin plus metformin treatment group and the placebo add-on to dapagliflozin plus metformin treatment group. Assuming that 5% of the patients would not have a measurement after baseline, a total of approximately 280 patients (140 patients per treatment arm) needed to be randomized.

The primary efficacy data set included all randomized patients who received at least one dose of study medication during the double-blind treatment period. The primary efficacy end point was analyzed using a longitudinal repeated-measures analysis with terms for baseline value, treatment group, time, the interaction of treatment group and time, and the interaction of baseline value and time, including only observations before rescue. Point estimates and 95% CIs were calculated for the adjusted mean changes within each treatment group as well as for the differences in adjusted mean changes between treatment groups. If the primary efficacy comparison was significant at the 0.05 level, then the secondary efficacy end points were statistically tested using a hierarchical closed testing procedure.

The analysis of the mean change from baseline at week 24 for 2-h PPG during a liquid MTT was based on an ANCOVA model using the last observation carried forward method, with terms for treatment group and baseline value in the model. The mean change from baseline at week 24 for FPG was analyzed using the same longitudinal repeated-measures model as for the primary efficacy end point. The proportion of patients achieving HbA_{1c} <7.0% (53 mmol/mol) at 24 weeks was summarized by treatment group and analyzed using previously published methods (16,17).

RESULTS

Patients

The first patient visit for the 24-week short-term study period occurred on 29 June 2012 and the last patient visit on 18 June 2014. Of the 857 enrolled patients, 482 entered and received treatment during the open-label period, and 431 (89.4%) completed this period (Supplementary Fig. 2). A total of 315 were randomized and entered the 24-week, double-blind treatment period, and 94.6% (298) completed the short-term period of the study. Patient demographics and baseline characteristics were balanced across treatment groups (Table 1). Most patients (87.9%) were white, and 52.7% were female. Mean age was 54.6 years. Mean duration of diabetes was 7.7 years, and mean baseline HbA_{1c} was 7.91% (63 mmol/mol). Baseline HbA_{1c} at randomization was similar in the placebo (7.86% [62 mmol/mol])

Table 1—Demographics and baseline characteristics at randomization

	Placebo add-on to dapagliflozin plus metformin (*n* = 162)	Saxagliptin add-on to dapagliflozin plus metformin (*n* = 153)	Total population (*N* = 315)
Age, years	54.5 ± 9.3	54.7 ± 9.8	54.6 ± 9.6
Women	86 (53.1)	80 (52.3)	166 (52.7)
Race			
White	141 (87.0)	136 (88.9)	277 (87.9)
Black	9 (5.6)	11 (7.2)	20 (6.3)
Asian	8 (4.9)	5 (3.3)	13 (4.1)
Other	4 (2.5)	1 (0.7)	5 (1.6)
BMI, kg/m^2	31.4 ± 5.3	31.4 ± 5.2	31.4 ± 5.3
Duration of diabetes, years	7.4 ± 5.8	8.1 ± 7.0	7.7 ± 6.4
HbA_{1c}, % (mmol/mol)	7.86 ± 0.93 (62 ± 10.2)	7.97 ± 0.83 (64 ± 9.1)	7.91 ± 0.88 (63 ± 9.6)
HbA_{1c} category			
<8% (64 mmol/mol)	99 (61.1)	85 (55.6)	184 (58.4)
8–<9% (64–<75 mmol/mol)	42 (25.9)	50 (32.7)	92 (29.2)
≥9% (75 mmol/mol)	21 (13.0)	18 (11.8)	39 (12.4)
FPG, mg/dL	158 ± 34.6	164 ± 34.4	161 ± 34.6
2-h PPG, mg/dL	206 ± 53.1	209 ± 50.1	207 ± 51.6
Fasting C-peptide, ng/mL	2.6 ± 1.2	2.4 ± 1.0	2.5 ± 1.1
eGFR, mL/min/1.73 m^2	93.9 ± 20.6	92.8 ± 21.6	93.4 ± 21.1

Data are mean ± SD or *n* (%). eGFR, estimated glomerular filtration rate (calculated by the Modification of Diet in Renal Disease formula).

and saxagliptin (7.97% [64 mmol/mol]) groups (Table 1).

Efficacy

At 24 weeks, the adjusted mean (95% CI) change from baseline in HbA_{1c} was significantly greater with saxagliptin (–0.51% [–0.63 to –0.39]; –5.6 mmol/mol [–6.9 to –4.3]) compared with placebo (–0.16% [–0.28 to –0.04]; –1.7 mmol/mol [–3.1 to –0.4]) add-on to dapagliflozin plus metformin (difference –0.35% [–0.52 to –0.18]; –3.8 mmol/mol [–5.7 to –2.0]; $P < 0.0001$) (Fig. 1*A*, Table 2). A clear separation in HbA_{1c} was observed between the treatment groups at the earliest time point assessed (6 weeks), which continued to the end of the study (Fig. 1*B*). Saxagliptin add-on to dapagliflozin plus metformin treatment was associated with a larger reduction in HbA_{1c} from baseline than placebo add-on to dapagliflozin plus metformin, irrespective of baseline HbA_{1c} (Supplementary Table 1). Adjusted mean reductions in HbA_{1c} from baseline to 24 weeks were largest in patients with baseline HbA_{1c} ≥9% (≥75 mmol/mol): –1.21% (–13.2 mmol/mol) for saxagliptin add-on to dapagliflozin plus metformin versus –0.26% (–2.8 mmol/mol) for placebo add-on to dapagliflozin plus metformin. Reductions in 2-h PPG and FPG were similar between treatment arms (Table 2). A larger proportion of patients achieved HbA_{1c} <7% (53 mmol/mol) with saxagliptin add-on to dapagliflozin plus metformin (35.3%) compared with placebo add-on to dapagliflozin plus metformin (23.1%; Table 2).

Few patients were rescued or discontinued for lack of glycemic control in the saxagliptin add-on to dapagliflozin plus metformin group (4 of 153) or the placebo add-on to dapagliflozin plus metformin group (7 of 162). The adjusted mean (95% CI) change from baseline in PPG area under the concentration–time curve from time 0 to 180 min at week 24 was numerically greater with saxagliptin add-on to dapagliflozin plus metformin (–6,211 mg/dL · min [–7,231 to –5,191]) than with placebo add-on to dapagliflozin plus metformin (–5,258 mg/dL · min [–6,236 to –4,279]). The mean percentage changes in fasting serum lipids from baseline at week 24 were small and similar between the 2 treatment groups (Supplementary Table 2). There were similar small reductions in body weight over the 24-week treatment period with saxagliptin (–0.53 kg) and placebo (–0.51 kg) add-on to dapagliflozin plus metformin.

Safety

The proportion of patients with AEs was similar between treatment groups (Table 3). Few patients discontinued, and there were no deaths. The most common AEs (≥5% of patients) were nasopharyngitis and urinary tract infections. The proportion of patients with serious AEs was small and similar in both treatment groups. Discontinuations as a result of AEs were higher with the placebo add-on (1.9%) than with the saxagliptin add-on (0.7%) to dapagliflozin plus metformin. Hypoglycemic episodes were infrequent, and there were no cases of major hypoglycemia or discontinuations due to hypoglycemia. There were no AEs of decreased lymphocyte or thrombocyte counts, pancreatitis, opportunistic infections, kidney infections, bladder or breast neoplasms, or pancreatic cancer.

During the 24-week double-blind treatment period, one patient (0.6%) in the placebo add-on to dapagliflozin plus metformin group and one patient (0.7%) in the saxagliptin add-on to dapagliflozin plus metformin group had cardiovascular events (atrial fibrillation with placebo and pulmonary embolism with saxagliptin) that were confirmed upon adjudication. Neither event was considered

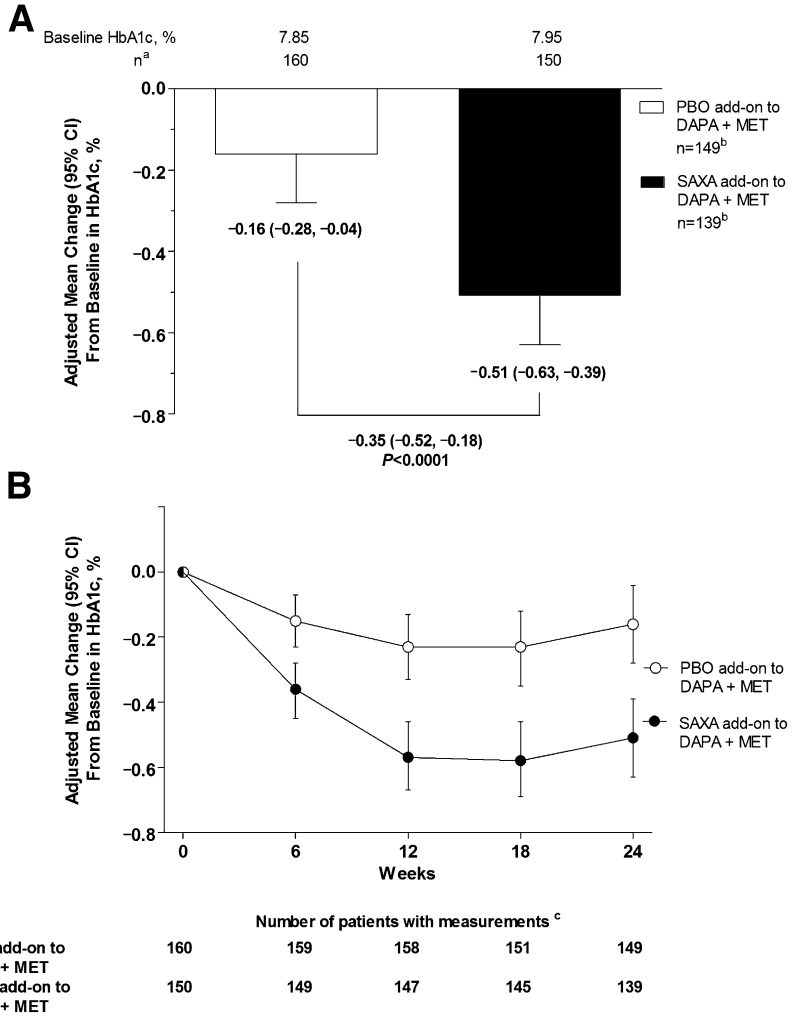

Figure 1—Change in HbA_{1c}. Adjusted mean change in HbA_{1c} from baseline to 24 weeks (*A*) and time course of adjusted mean change in HbA_{1c} from baseline (*B*). DAPA, dapagliflozin; MET, metformin; PBO, placebo; SAXA, saxagliptin. [a]Randomized patients with a baseline measurement and at least one measurement after baseline. [b]Randomized patients with a baseline measurement and a measurement at week 24. [c]Randomized patients who received at least one dose of double-blind medication.

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

	Placebo add-on to dapagliflozin plus metformin (n = 162)	Saxagliptin add-on to dapagliflozin plus metformin (n = 153)	P value
HbA_{1c}			
Baseline mean ± SD, % (mmol/mol)	7.85 ± 0.92 (62 ± 10.1)	7.95 ± 0.83 (63 ± 9.1)	
Change from baseline, %	−0.16 (–0.28 to –0.04)	−0.51 (–0.63 to –0.39)	
Change from baseline, mmol/mol	–1.7 (–3.1 to –0.4)	–5.6 (–6.9 to –4.3)	
Difference in saxagliptin vs. placebo, % (mmol/mol)	−0.35 (–0.52 to –0.18) (–3.8 [–5.7 to –2.0])		<0.0001
2-h PPG, mg/dL			
Baseline mean ± SD	204 ± 52.0	208 ± 50.6	
Change from baseline	−31 (–37.5 to –25.0)	−37 (–43.6 to –30.7)	
Difference saxagliptin vs. placebo	−6 (–14.9 to 3.1)		0.2014
FPG, mg/dL			
Baseline mean ± SD	157 ± 33.94	164 ± 34.3	
Change from baseline	−5 (–10.4 to –0.2)	−9 (–14.3 to –3.9)	
Difference saxagliptin vs. placebo	−4 (–11.0 to –3.6)		NT
Patients with HbA_{1c} <7% (53 mmol/mol)			
x/n*	39/160	51/150	
Adjusted %	23.1 (16.9 to 29.3)	35.3 (28.2 to 42.4)	
Difference vs. saxagliptin + metformin, %	12.2 (3.4 to 21.0)		NT

Data are adjusted mean change from baseline (95% CI) or as indicated. NT, not tested because of hierarchical testing procedure. *Number of responders/number of patients with nonmissing baseline values and week 24 values (last observation carried forward).

to be related to treatment. Two patients (1.2%) in the placebo add-on to dapagliflozin plus metformin group and one patient (0.7%) in the saxagliptin add-on to dapagliflozin plus metformin group had events of heart failure (worsening of heart failure and peripheral edema, and edema, respectively); none of the events were considered to be treatment related.

One patient in the saxagliptin add-on to dapagliflozin plus metformin group had a serious AE of hepatic cancer, and two patients in each treatment group had AEs of hepatic disorders that were adjudicated and confirmed; only one event in a patient receiving placebo (elevated alanine transaminase) was considered to be possibly related to treatment.

There were small changes (<1 mmHg) in systolic and diastolic blood pressure from baseline to 24 weeks in both treatment arms.

Table 3—AEs

AEs	Placebo add-on to dapagliflozin plus metformin (n = 162)	Saxagliptin add-on to dapagliflozin plus metformin (n = 153)
At least 1 AE	70 (43.2)	73 (47.7)
At least 1 SAE	5 (3.1)	5 (3.3)
AE leading to discontinuation	3 (1.9)	1 (0.7)
SAE leading to discontinuation	0 (0)	0 (0)
AEs of special interest		
Urinary tract infection	6 (3.7)	8 (5.2)
Genital infection	4 (2.5)	0 (0)
GFR decrease	2 (1.2)	0 (0)
Fracture	1 (0.6)	1 (0.7)
Heart failure	2 (1.2)	1 (0.7)
Severe cutaneous	1 (0.6)	0 (0)
Hypersensitivity	2 (1.2)	0 (0)
Hypotension, dehydration, hypovolemia	2 (1.2)	0 (0)
Hypoglycemia*	4 (2.5)	2 (1.3)
Major	0 (0)	0 (0)
Minor	2 (1.2)	1 (0.7)
Other	3 (1.9)	1 (0.7)
Adjudicated cardiovascular event	1 (0.6)	1 (0.7)
Adjudicated liver AE	2 (1.2)	2 (1.3)

Data are n (%). GFR, glomerular filtration rate; SAE, serious AE. *Hypoglycemic episodes were classified as minor (symptomatic or asymptomatic with plasma glucose concentration <63 mg/dL, regardless of need for external assistance); major (symptomatic requiring third-party assistance owing to severe impairment in consciousness or behavior, with or without 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).

CONCLUSIONS

In the United States, only 52% of adults with diagnosed diabetes have HbA_{1c} <7.0% (53 mmol/mol) (18). Thus there is a need for new therapeutic approaches that get more patients to their individual glycemic goal without increased risk of hypoglycemia or weight gain. Failure to escalate treatment when blood glucose becomes uncontrolled is common (19) and exposes patients to needless periods of hyperglycemia (20,21). In accordance with clinical treatment guidelines, most patients receive initial therapy with metformin followed by the stepwise addition of other oral antidiabetes drugs as glycemic control worsens (2,3). DPP-4 inhibitors and SGLT2 inhibitors are recommended as options for add-on therapy to metformin in patients inadequately controlled with metformin monotherapy (2,3). Addition of a DPP-4 inhibitor to a combination of an SGLT2 inhibitor and metformin results in a triple drug combination that works in a complementary manner and targets several of the pathologic defects present in type 2 diabetes (22) without the increased risks of hypoglycemia and weight gain, which are common with other

antidiabetes agents such as sulfonylureas and insulin (23,24).

In this study we assessed the efficacy and safety of triple therapy with saxagliptin compared with placebo as an add-on to dapagliflozin plus metformin in patients with advanced disease in whom, after 16 weeks of open-label treatment with dapagliflozin added to metformin monotherapy, HbA_{1c} remained at 7–10.5% (53–91 mmol/mol) and the glycemic goal of $HbA_{1c} < 7\%$ (53 mmol/mol) had not been reached. The addition of saxagliptin to dapagliflozin plus metformin resulted in a significantly greater reduction in HbA_{1c} compared with placebo (–0.35% [–3.8 mmol/mol]). The proportion of patients achieving a glycemic goal of $HbA_{1c} < 7\%$ (53 mmol/mol) with saxagliptin as triple therapy with dapagliflozin plus metformin (35.3%) after 24 weeks was in the same range as the 30.7% that was previously observed with saxagliptin as triple therapy with a sulfonylurea plus metformin (14), but without the increased risk of hypoglycemia associated with sulfonylureas. Thus, the efficacy of saxagliptin is retained across different combination therapy regimens.

Triple therapy of saxagliptin added to dapagliflozin plus metformin was well tolerated. The overall safety of saxagliptin added to dapagliflozin plus metformin was similar to that seen in a study of a dual add-on of saxagliptin and dapagliflozin to metformin in patients with type 2 diabetes that was poorly controlled with metformin alone (15). The proportion of patients experiencing an AE was similar between treatment groups. AEs of special interest occurred infrequently in both treatment arms, although urinary tract infections were more frequent with saxagliptin compared with placebo. SGLT2 inhibitors have been associated with an increased risk of genital infections (25,26). In this study, however, no patients in the saxagliptin add-on to dapagliflozin plus metformin group reported genital infections, compared with four patients (2.5%) in the placebo add-on to dapagliflozin plus metformin group. A lower rate of genital infections when a DPP-4 inhibitor is added to an SGLT2 inhibitor compared with the SGLT2 inhibitor alone has also been observed in other studies (15,27) and leads to speculation that DPP-4 inhibitors may, by an unknown mechanism, protect against SGLT2 inhibitor–induced genital infections.

In patients with type 2 diabetes, hypoglycemia is associated with increased morbidity and mortality (28,29), whereas body weight reduction is associated with improved glycemic control and a reduction in cardiovascular risk factors (30,31). Thus hypoglycemic potential and effects on body weight, among other factors, are important attributes to be considered when choosing a drug as an add-on to dual therapy, as highlighted in clinical treatment guidelines (1–3). Both saxagliptin and dapagliflozin are associated with a low rate of hypoglycemia when used in combination with metformin (11,12), and they either are weight neutral (saxagliptin) (9,10,12,32) or reduce body weight (dapagliflozin) (11,33–35). The findings of this study of triple therapy of a saxagliptin add-on to dapagliflozin plus metformin are generally consistent with the mechanisms of action of saxagliptin and dapagliflozin and with the results from previous clinical studies investigating the efficacy and safety of these agents as monotherapy (8–10) and add-on therapy (11,12,32–36) and when used together as a dual add-on to metformin (15). Moreover, saxagliptin was effective in patients with advanced disease whose hyperglycemia was poorly controlled despite receiving metformin and dapagliflozin.

In summary, this study demonstrated that triple therapy using a combination of a DPP-4 inhibitor as an add-on to a background SGLT2 inhibitor plus metformin therapy in patients with advanced type 2 diabetes who were not at target for glycemic control was well tolerated and resulted in significant reductions in HbA_{1c}, with a greater proportion of patients achieving $HbA_{1c} < 7\%$ (53 mmol/mol) compared with dual therapy of dapagliflozin plus metformin. Importantly, the improvements in glycemic control with a saxagliptin add-on to dapagliflozin plus metformin were achieved without any increased risk of hypoglycemia and were not associated with an increase in body weight. Thus, saxagliptin added to dapagliflozin plus metformin therapy provides an effective and well-tolerated treatment option of triple oral therapy in patients with advanced disease that is poorly controlled with dapagliflozin plus metformin. The 52-week long-term extension of this study is ongoing and will provide additional data on the durability and long-term safety of triple therapy with saxagliptin added to dapagliflozin plus metformin.

Funding and Duality of Interest. This study was funded by Bristol-Myers Squibb and AstraZeneca. Medical writing support for the preparation of the manuscript was provided by Richard Edwards, PhD, and Janet Matsuura, PhD, from Complete Healthcare Communications, Inc. (Chadds Ford, PA), supported by funding from Bristol-Myers Squibb and AstraZeneca.

S.M. is a member of the speakers bureau and advisory committees of AstraZeneca. E.E., W.C., B.H., and H.C. are employees of AstraZeneca. N.I. was an employee of Bristol-Myers Squibb at the time of the study. L.H. is an employee of Bristol-Myers Squibb.

Author Contributions. S.M., D.C., A.C., E.E., W.C., B.H., N.I., and L.H. interpreted the data, reviewed and edited the manuscript, and contributed to the discussion. H.C. reviewed the statistics and data, reviewed and edited the manuscript, and contributed to the discussion. All authors approved the final version of the manuscript. S.M. is the guarantor of this work and, as such, had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

References

1. Cheng AY; Canadian Diabetes Association Clinical Practice Guidelines Expert Committee. Canadian Diabetes Association 2013 clinical practice guidelines for the prevention and management of diabetes in Canada. Introduction. Can J Diabetes 2013;37(Suppl. 1):S1–S3

2. Garber AJ, Abrahamson MJ, Barzilay JI, et al.; American Association of Clinical Endocrinologists. AACE comprehensive diabetes management algorithm 2013. Endocr Pract 2013;19:327–336

3. American Diabetes Association. Standards of medical care in diabetes—2015. Diabetes Care 2015;38(Suppl. 1):S1–S93

4. Nauck MA, Vilsbøll T, Gallwitz B, Garber A, Madsbad S. Incretin-based therapies: viewpoints on the way to consensus. Diabetes Care 2009;32(Suppl. 2):S223–S231

5. Ferrannini E, Solini A. SGLT2 inhibition in diabetes mellitus: rationale and clinical prospects. Nat Rev Endocrinol 2012;8:495–502

6. Zhang L, Feng Y, List J, Kasichayanula S, Pfister M. Dapagliflozin treatment in patients with different stages of type 2 diabetes mellitus: effects on glycaemic control and body weight. Diabetes Obes Metab 2010;12:510–516

7. Bailey CJ, Day C. SGLT2 inhibitors: glucuretic treatment for type 2 diabetes. Br J Diabetes Vasc Dis 2010;10:193–199

8. Ferrannini E, Ramos SJ, Salsali A, Tang W, List JF. Dapagliflozin monotherapy in type 2 diabetic patients with inadequate glycemic control by diet and exercise: a randomized, double-blind, placebo-controlled, phase 3 trial. Diabetes Care 2010;33:2217–2224

9. Frederich R, McNeill R, Berglind N, Fleming D, Chen R. The efficacy and safety of the dipeptidyl peptidase-4 inhibitor saxagliptin in treatment-naïve patients with type 2 diabetes mellitus: a randomized controlled trial. Diabetol Metab Syndr 2012;4:36
10. Rosenstock J, Aguilar-Salinas C, Klein E, Nepal S, List J, Chen R; CV181-011 Study Investigators. Effect of saxagliptin monotherapy in treatment-naïve patients with type 2 diabetes. Curr Med Res Opin 2009;25:2401–2411
11. Bailey CJ, Gross JL, Pieters A, Bastien A, List JF. Effect of dapagliflozin in patients with type 2 diabetes who have inadequate glycaemic control with metformin: a randomised, double-blind, placebo-controlled trial. Lancet 2010; 375:2223–2233
12. DeFronzo RA, Hissa MN, Garber AJ, et al.; Saxagliptin 014 Study Group. The efficacy and safety of saxagliptin when added to metformin therapy in patients with inadequately controlled type 2 diabetes with metformin alone. Diabetes Care 2009;32:1649–1655
13. Matthaei S, Bowering K, Rohwedder K, Grohl A, Parikh S; Study 05 Group. Dapagliflozin improves glycemic control and reduces body weight as add-on therapy to metformin plus sulfonylurea: a 24-week randomized, double-blind clinical trial. Diabetes Care 2015;38:365–372
14. Moses RG, Kalra S, Brook D, et al. A randomized controlled trial of the efficacy and safety of saxagliptin as add-on therapy in patients with type 2 diabetes and inadequate glycaemic control on metformin plus a sulphonylurea. Diabetes Obes Metab 2014;16:443–450
15. Rosenstock J, Hansen L, Zee P, et al. Dual add-on therapy in type 2 diabetes poorly controlled with metformin monotherapy: a randomized double-blind trial of saxagliptin plus dapagliflozin addition versus single addition of saxagliptin or dapagliflozin to metformin. Diabetes Care 2015; 38:376–383
16. Tsiatis AA, Davidian M, Zhang M, Lu X. Covariate adjustment for two-sample treatment comparisons in randomized clinical trials: a principled yet flexible approach. Stat Med 2008;27: 4658–4677
17. Zhang M, Tsiatis AA, Davidian M. Improving efficiency of inferences in randomized clinical trials using auxiliary covariates. Biometrics 2008;64:707–715
18. Ali MK, Bullard KM, Saaddine JB, Cowie CC, Imperatore G, Gregg EW. Achievement of goals in U.S. diabetes care, 1999–2010. N Engl J Med 2013;368:1613–1624
19. Shah BR, Hux JE, Laupacis A, Zinman B, van Walraven C. Clinical inertia in response to inadequate glycemic control: do specialists differ from primary care physicians? Diabetes Care 2005;28:600–606
20. Brown JB, Nichols GA, Perry A. The burden of treatment failure in type 2 diabetes. Diabetes Care 2004;27:1535–1540
21. Khunti K, Wolden ML, Thorsted BL, Andersen M, Davies MJ. Clinical inertia in people with type 2 diabetes: a retrospective cohort study of more than 80,000 people. Diabetes Care 2013;36:3411–3417
22. DeFronzo RA, Eldor R, Abdul-Ghani M. Pathophysiologic approach to therapy in patients with newly diagnosed type 2 diabetes. Diabetes Care 2013;36(Suppl. 2):S127–S138
23. Bennett WL, Maruthur NM, Singh S, et al. Comparative effectiveness and safety of medications for type 2 diabetes: an update including new drugs and 2-drug combinations. Ann Intern Med 2011;154:602–613
24. Vasilakou D, Karagiannis T, Athanasiadou E, et al. Sodium-glucose cotransporter 2 inhibitors for type 2 diabetes: a systematic review and meta-analysis. Ann Intern Med 2013;159:262–274
25. Johnsson KM, Ptaszynska A, Schmitz B, Sugg J, Parikh SJ, List JF. Vulvovaginitis and balanitis in patients with diabetes treated with dapagliflozin. J Diabetes Complications 2013;27:479–484
26. Nyirjesy P, Sobel JD, Fung A, et al. Genital mycotic infections with canagliflozin, a sodium glucose co-transporter 2 inhibitor, in patients with type 2 diabetes mellitus: a pooled analysis of clinical studies. Curr Med Res Opin 2014;30:1109–1119
27. DeFronzo RA, Lewin A, Patel S, et al. Combination of empagliflozin and linagliptin as second-line therapy in subjects with type 2 diabetes inadequately controlled on metformin. Diabetes Care 2015;38:384–393
28. Zoungas S, Patel A, Chalmers J, et al.; ADVANCE Collaborative Group. Severe hypoglycemia and risks of vascular events and death. N Engl J Med 2010;363:1410–1418
29. Johnston SS, Conner C, Aagren M, Smith DM, Bouchard J, Brett J. Evidence linking hypoglycemic events to an increased risk of acute cardiovascular events in patients with type 2 diabetes. Diabetes Care 2011;34:1164–1170
30. Horton ES, Silberman C, Davis KL, Berria R. Weight loss, glycemic control, and changes in cardiovascular biomarkers in patients with type 2 diabetes receiving incretin therapies or insulin in a large cohort database. Diabetes Care 2010;33:1759–1765
31. Wing RR, Bolin P, Brancati FL, et al.; Look AHEAD Research Group. Cardiovascular effects of intensive lifestyle intervention in type 2 diabetes. N Engl J Med 2013;369:145–154
32. Hollander P, Li J, Allen E, Chen R; CV181-013 Investigators. Saxagliptin added to a thiazolidinedione improves glycemic control in patients with type 2 diabetes and inadequate control on thiazolidinedione alone. J Clin Endocrinol Metab 2009;94:4810–4819
33. Nauck MA, Del Prato S, Meier JJ, et al. Dapagliflozin versus glipizide as add-on therapy in patients with type 2 diabetes who have inadequate glycemic control with metformin: a randomized, 52-week, double-blind, active-controlled noninferiority trial. Diabetes Care 2011;34:2015–2022
34. Rosenstock J, Vico M, Wei L, Salsali A, List JF. Effects of dapagliflozin, an SGLT2 inhibitor, on HbA(1c), body weight, and hypoglycemia risk in patients with type 2 diabetes inadequately controlled on pioglitazone monotherapy. Diabetes Care 2012;35:1473–1478
35. Strojek K, Yoon KH, Hruba V, Elze M, Langkilde AM, Parikh S. Effect of dapagliflozin in patients with type 2 diabetes who have inadequate glycaemic control with glimepiride: a randomized, 24-week, double-blind, placebo-controlled trial. Diabetes Obes Metab 2011;13: 928–938
36. Chacra AR, Tan GH, Apanovitch A, Ravichandran S, List J, Chen R; CV181-040 Investigators. Saxagliptin added to a submaximal dose of sulphonylurea improves glycaemic control compared with uptitration of sulphonylurea in patients with type 2 diabetes: a randomised controlled trial. Int J Clin Pract 2009;63:1395–1406