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

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OBJECTIVE

This study compared the efficacy and safety of dual add-on of saxagliptin plus dapagliflozin versus saxagliptin and dapagliflozin added on alone in patients with type 2 diabetes poorly controlled with metformin.

RESEARCH DESIGN AND METHODS

This was a double-blind trial in adults with HbA_{1c} ≥8.0% and ≤12.0% (64–108 mmol/mol), randomized to saxagliptin (SAXA) (5 mg/day) plus dapagliflozin (DAPA) (10 mg/day; *n* = 179), or SAXA (5 mg/day) and placebo (*n* = 176), or DAPA (10 mg/day) and placebo (*n* = 179) on background metformin extended release (MET) ≥1,500 mg/day. Primary objective compared changes from baseline in HbA_{1c} with SAXA+DAPA+MET versus SAXA+MET and DAPA+MET.

RESULTS

Patients had a mean baseline HbA_{1c} of 8.9% (74 mmol/mol), diabetes duration of 7.6 years, and a BMI of 32 kg/m^2. At week 24, the adjusted mean change from the baseline HbA_{1c} was −1.5% (−16.1 mmol/mol) with SAXA+DAPA+MET versus −0.9% (−9.6 mmol/mol) with SAXA+MET (difference −0.59% [−6.4 mmol/mol], $P < 0.0001$) and −1.2% (−13.1 mmol/mol) with DAPA+MET (difference −0.27% [3.0 mmol/mol], $P < 0.02$). The proportion of patients achieving HbA_{1c} <7% (53 mmol/mol) was 41% with SAXA+DAPA+MET versus 18% with SAXA+MET and 22% with DAPA+MET. Urinary and genital infections occurred in ≤1% of patients receiving SAXA+DAPA+MET. Hypoglycemia was infrequent, with no episodes of major hypoglycemia.

CONCLUSIONS

In this first report of adding a well-tolerated combination of saxagliptin plus dapagliflozin to background metformin therapy in patients poorly controlled with metformin, greater improvements in glycemic control were obtained with triple therapy by the dual addition of saxagliptin and dapagliflozin than dual therapy with the addition of saxagliptin or dapagliflozin alone.

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Patients with type 2 diabetes often require multiple antidiabetic agents to achieve and maintain glycemic control (1) because of the progressive nature of the disease (2). Most patients receive traditional stepped-up therapy with metformin as the initial therapy, followed by the sequential addition of single oral antidiabetic drugs (OADs) as glycemic control worsens (1). The number of antihyperglycemic agents has increased markedly, and the availability of multiple pharmacologic options is instrumental for treatment to target, which is a well-recognized strategy for the prevention of diabetes complications. Several guidelines recommend the use of dual or triple therapy based on glycated hemoglobin (HbA_{1c}) levels, but clinical trial evidence defining the optimal use of available pharmacologic options, especially in dual or triple combinations, based on the degree of glycemic control is limited (3–5).

Further evidence-based treatment guidance may be especially helpful for almost half of the adults in the U.S. with diabetes who do not meet the recommended goals for diabetes care despite the availability of these multiple therapeutic options (6). Clinical inertia with substantial delay in advancing therapy despite inadequate glycemic control is a major barrier in clinical practice (7). Adding or initiating a single therapy when HbA_{1c} levels are substantially elevated may not achieve glycemic goals. Thus, exploring new and more proactive therapeutic approaches to get more patients to goal without the increased risk of hypoglycemia or weight gain is needed. Here we report clinical trial evidence with one example of a therapeutic approach with dual combination treatment consisting of a dipeptidyl peptidase-4 (DPP-4) inhibitor, saxagliptin, and a sodium–glucose cotransporter 2 (SGLT2) inhibitor, dapagliflozin, added together to metformin as triple therapy compared with the addition of these individual components singly to metformin as dual therapy.

Saxagliptin increases the postprandial concentration of GLP-1 and (8) potentiates its action of increasing glucose-dependent insulin secretion and suppressing glucagon secretion (8). Dapagliflozin reduces plasma glucose concentrations independently of insulin secretion or action by increasing the renal excretion of glucose (9). The mechanisms of action of saxagliptin and dapagliflozin are complementary to that of metformin, and both have a low risk of hypoglycemia and are weight neutral (saxagliptin) or produce reductions in body weight (dapagliflozin) (9,10). In previous studies in patients with type 2 diabetes, saxagliptin and dapagliflozin improved glycemic control and were well tolerated when used as monotherapy (11–13) or as add-on therapy to commonly used OADs (14–20) and insulin (21,22).

The objective of this study was to assess the efficacy and safety of triple therapy with the novel combination of dual add-on with saxagliptin plus dapagliflozin to metformin compared with saxagliptin add-on alone or dapagliflozin add-on alone to metformin in patients with poorly controlled type 2 diabetes receiving metformin monotherapy. The entrance criterion of HbA_{1c} $\geq$8.0% and $\leq$12.0% (64–108 mmol/mol) in patients on metformin monotherapy was selected to be representative of patient populations encountered in clinical practice and to provide evidence to assist the decision-making process for selecting dual or triple therapy in a poorly controlled patient population.

RESEARCH DESIGN AND METHODS

Study Design

This was a 24-week, multicenter, randomized, double-blind, active-controlled, parallel-group phase 3 study (clinical trial reg. no. NCT01606007, clinicaltrials.gov). It was designed and monitored in accordance with the ethical principles of Good Clinical Practice as defined by the International Conference on Harmonisation 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.

Patients ($\geq$18 years) with type 2 diabetes and inadequate glycemic control, defined as HbA_{1c} $\geq$8.0% and $\leq$12.0% (64–108 mmol/mol) at screening, were eligible. Patients had to be on stable metformin therapy ($\geq$1,500 mg/day) for $\geq$8 weeks before screening and have C-peptide concentrations $\geq$1.0 ng/mL and BMI $\leq$45.0 kg/m^2 at screening. Major exclusion criteria included pregnancy, uncontrolled hypertension (systolic blood pressure $\geq$160 mmHg and diastolic blood pressure $\geq$100 mmHg) at randomization, fasting plasma glucose (FPG) $\geq$270 mg/dL during the 4-week lead-in period, cardiovascular disease within 3 months of screening, congestive heart failure (New York Heart Association functional class IV), estimated glomerular filtration rate (eGFR) $<$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, and significant hepatic disease. Also excluded were patients who received any antidiabetic medication, other than metformin, for more than 14 days during the 12 weeks before screening.

At the beginning of a 4-week lead-in period, patients who had been on stable metformin therapy for at least 8 weeks before screening were switched to the nearest metformin extended release (MET) dose (1,500–2,000 mg/day) for the lead-in period and for the duration of the 24-week double-blind treatment period. Patients were then randomized 1:1:1 using a centralized blocked randomization schedule to receive saxagliptin (5 mg/day) and dapagliflozin (10 mg/day) plus MET (SAXA+DAPA+MET), saxagliptin (5 mg/day) and placebo plus MET (SAXA+MET), or dapagliflozin (10 mg/day) and placebo plus MET (DAPA+MET) for 24 weeks. Other antidiabetic medications (except for open-label rescue medications) were prohibited during the screening and treatment periods. Open-label rescue medication, including insulin or other antidiabetic medications, except metformin, GLP-1 receptor agonists, and other DPP-4 inhibitors or SGLT2 inhibitors, was given to patients with FPG $>$270 mg/dL up to week 6; FPG $>$240 mg/dL at weeks 6–12; or FPG $>$200 mg/dL at weeks 12–24.

Efficacy End Points

The primary end point was the adjusted mean change from baseline in HbA_{1c} after 24 weeks of double-blind treatment. Secondary end points were adjusted mean change from baseline at 24 weeks in 2-h postprandial glucose (PPG), adjusted mean change from baseline at 24 weeks in FPG, adjusted mean proportion of patients achieving a therapeutic glycemic response, defined as HbA_{1c} $<$7.0% (53 mmol/mol), after 24 weeks, and the adjusted mean change from baseline in body weight. PPG was assessed after the administration of a liquid meal (360–375 kcal; protein, 14–28.2 g; fat, 10.5–14 g; carbohydrates 42–45 g; sugars, 16.8–22 g, investigational site dependent) before study medication administration

at randomization (day 1) and at 24 weeks 1 h after study medication administration. Exploratory end points included adjusted mean changes from baseline at 24 weeks in fasting serum lipids.

Safety

Safety assessments included 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 due 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). Event categories for AEs of special interest included severe cutaneous events, decreased lymphocyte count, decreased thrombocyte count, opportunistic infection, pancreatitis, hepatic AEs, fracture, hypersensitivity, worsening renal function, genital infections, urinary tract infections, bladder neoplasm, and breast neoplasm. Blood pressure was recorded as a safety assessment, and investigators were allowed to adjust antihypertensive therapy as needed.

Statistical Analysis

With 163 patients per treatment group, there was 90% power to detect a difference in mean HbA_{1c} of 0.4% (4.4 mmol/mol) between the SAXA+DAPA+MET group and each of the monotherapy add-on groups, assuming a SD of 1.0%. Assuming that 5% of patients would not have a postbaseline assessment, ~516 patients needed to be randomized (172 patients per treatment arm).

The primary efficacy data set included all randomized patients who received at least one dose of a study medication during the double-blind treatment period. The approach of Laska and Meisner (23) was used to test the simultaneous addition of SAXA+DAPA to MET versus each of the individual add-on components plus placebo. Statistical significance of the primary end point required that the *P* values for both comparisons were significant at the two-sided, 0.05 significance level. Analysis of the primary efficacy end point, change from baseline at week 24 in HbA_{1c}, was performed 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 observations 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.

To protect the overall type I error rate, the interpretation of the statistical significance of treatment comparisons for each secondary efficacy end point was performed using a step-wise procedure. The analysis of the mean change from baseline at week 24 for 2-h PPG was based on an ANCOVA (last observation carried forward [LOCF]) with terms for treatment group and baseline value. Analyses of the mean change from baseline at week 24 for FPG and total body weight were performed using the same longitudinal repeated-measures model as for the primary efficacy end point. The analysis of total body weight compared the SAXA+DAPA+MET treatment group versus the SAXA+MET group only. 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 (24,25).

RESULTS

Patients

The first patient visit for this study occurred on 5 June 2012 and the last patient visit on 17 January 2014. The disposition of patients is shown in Supplementary Fig. 1. Of the 1,282 enrolled patients, 639 entered the 4-week lead-in period, and 534 were randomized and received at least one dose of double-blind medication during the double-blind treatment period: SAXA+DAPA+MET, *n* = 179; SAXA+MET, *n* = 176; or DAPA+MET, *n* = 179. At least 89% of patients in each treatment group completed the 24-week treatment period. Patient demographics and baseline characteristics were balanced across treatment groups (Table 1). Equal numbers of men and women were randomized, and patients were predominately white, with a mean age of 54 years. Mean duration of type 2 diabetes was ~7.6 years, and mean baseline HbA_{1c} was 8.94% (74 mmol/mol).

Efficacy

For patients who were later randomized, mean ± SE HbA_{1c} was 9.30 ± 0.05% (78 ± 0.5 mmol/mol) at screening (week –6) and was 8.94 ± 0.05% (74 ± 0.5 mmol/mol) at randomization (Fig. 1*A*).

Table 1—Demographics and baseline characteristics

	SAXA+DAPA+MET *n* = 179	SAXA+MET *n* = 176	DAPA+MET *n* = 179	Total *N* = 534
Age, years	53 ± 10	55 ± 10	54 ± 10	54 ± 10
Women	94 (53)	82 (47)	90 (50)	266 (50)
Race				
White	120 (67)	121 (69)	131 (73)	372 (70)
African American	22 (12)	22 (13)	16 (9)	60 (11)
Asian	12 (7)	11 (6)	10 (6)	33 (6)
Other	25 (14)	22 (13)	22 (12)	69 (13)
BMI, kg/m^2	31.8 ± 4.8	31.8 ± 5.1	31.5 ± 5.3	31.7 ± 5.1
Duration of diabetes, years	7.1 ± 5.0	8.2 ± 5.5	7.4 ± 5.4	7.6 ± 5.3
HbA_{1c}, %	8.92 ± 1.18	9.03 ± 1.05	8.87 ± 1.16	8.94 ± 1.13
HbA_{1c}, mmol/mol	74 ± 12.9	75 ± 11.5	73 ± 12.7	74 ± 12.4
HbA_{1c} category				
<8% (64 mmol/mol)	41 (23)	30 (17)	41 (23)	112 (21)
≥8% and <9% (≥64 and <75 mmol/mol)	59 (33)	62 (35)	61 (34)	182 (34)
≥9% (75 mmol/mol)	79 (44)	84 (48)	77 (43)	240 (45)
FPG, mg/dL	180 ± 45.5	192 ± 45.3	185 ± 48.4	186 ± 46.6
PPG, mg/dL	242 ± 54.6	256 ± 62.1	246 ± 59.4	248 ± 58.9
Fasting C-peptide, ng/mL	2.2 ± 1.0	2.1 ± 0.90	2.2 ± 1.03	2.2 ± 0.98
eGFR,* mL/min/1.73 m^2	96.6 ± 19.6	92.5 ± 19.5	93.9 ± 19.9	94.4 ± 19.7

Data are mean ± SD or *n* (%). *Calculated by MDRD formula.

The addition of SAXA+DAPA to MET therapy resulted in significantly greater adjusted mean (± SE) reductions from baseline in HbA_{1c} at 24 weeks (–1.47 ± 0.08% [–16.1 ± 0.9 mmol/mol]) than did therapy with SAXA+MET (–0.88 ± 0.08% [–9.6 ± 0.9 mmol/mol]) or DAPA+MET (–1.20 ± 0.08% [–13.1 ± 0.9 mmol/mol]) (Fig. 1*B* and Table 2). The difference (95% CI) in change from baseline in HbA_{1c} between SAXA+DAPA+MET versus SAXA+MET was –0.59% (–0.81%, –0.37%; –6.4 [–8.9, –4.0] mmol/mol; $P < 0.0001$) and versus DAPA+MET was –0.27% (–0.48%, –0.05%; –3.0 [–5.2, –0.5] mmol/mol; $P = 0.0166$). Thus, the primary end point of statistical superiority of SAXA+DAPA add-on to MET versus SAXA add-on to MET and DAPA add-on to MET was met.

SAXA+DAPA+MET produced greater reductions from baseline in HbA_{1c} than did SAXA+MET and DAPA+MET in patients with baseline HbA_{1c} <8% (<64 mmol/mol) (difference [95% CI], –0.10% [–0.60%, 0.39%] {–1 [–6.6, 4.3] mmol/mol}; –0.35% [–0.81%, 0.11%] {–4 [–8.9, 1.2] mmol/mol}; ≥8 to <9% (≥64 to 75 mmol/mol) (–0.66% [–1.03%, –0.28%] {7 [–11.3, –3.1] mmol/mol}; –0.33% [–0.71%, 0.05%] {–4 [–7.8, 0.5] mmol/mol}, and ≥9% (≥75 mmol/mol) (–0.71% [–1.04%, –0.38%) {–8 [–11.4, –4.2] mmol/mol}; –0.16% [–0.50%, 0.17%] {–2 [–5.5, 1.9] mmol/mol}) (Supplementary Table 1). As expected, adjusted mean reductions from baseline in HbA_{1c} at 24 weeks were greatest in patients with baseline HbA_{1c} ≥9% (≥75 mmol/mol), at –2.03% (–22 mmol/mol) for SAXA+DAPA+MET, –1.32% (–14 mmol/mol) for SAXA+MET, and –1.87% (–20 mmol/mol) for DAPA+MET. Greater reductions in HbA_{1c} with SAXA+DAPA+MET versus SAXA+MET and DAPA+MET were also seen in patients aged <65 years (–0.63%, [–0.86%, –0.39%] {–7 [–9.4, –4.3] mmol/mol}; –0.26% [–0.49%, –0.02%] {–3 [–5.4, –0.2] mmol/mol}) and ≥65 years (–0.37% [–0.97%, 0.24%] {–4 [–10.6, 2.6] mmol/mol}; –0.35% [–1.00%, 0.30%] [–4 [–10.9, 3.3] mmol/mol}) (Supplementary Table 2).

The adjusted mean (± SE) reduction in FPG was greater in the SAXA+DAPA+MET group (–38 ± 2.8 mg/dL) than in the SAXA+MET group (–14 ± 2.9 mg/dL) but similar to the DAPA+MET group (–32 ± 2.8 mg/dL). SAXA+DAPA+MET also resulted in a significantly greater adjusted mean reduction from baseline in PPG versus SAXA+MET (difference [95% CI], –44 mg/dL [–53.7, –34.3], $P < 0.0001$) but not versus DAPA+MET (difference [95% CI], –9 mg/dL [–18.8, 0.5], $P = 0.06$) (Table 2).

The adjusted mean (± SE) proportion of patients achieving HbA_{1c} <7% (53 mmol/mol) at week 24 with SAXA+DAPA+MET (41 ± 3.5%) was nearly double that seen in the SAXA+MET (18 ± 2.7%) and DAPA+MET (22 ± 3.1%) groups. The proportions of patients achieving HbA_{1c} <7% (53 mmol/mol) with SAXA+DAPA+MET with baseline HbA_{1c} <8% (64 mmol/mol), ≥8% to <9% (≥64 to ≤75 mmol/mol), and ≥9% (≥75 mmol/mol) were 65%, 50%, and 24%, respectively (Supplementary Table 3). The differences (95% CI) between SAXA+DAPA+MET versus SAXA+MET and DAPA+MET for baseline HbA_{1c} of <8% (64 mmol/mol) were 7% (–15.3%, 29.4%) and 23% (2.4%, 43.7%), for baseline HbA_{1c} ≥8% to <9% (≥64 to ≤75 mmol/mol) were 39% (24.5%, 53.9%)

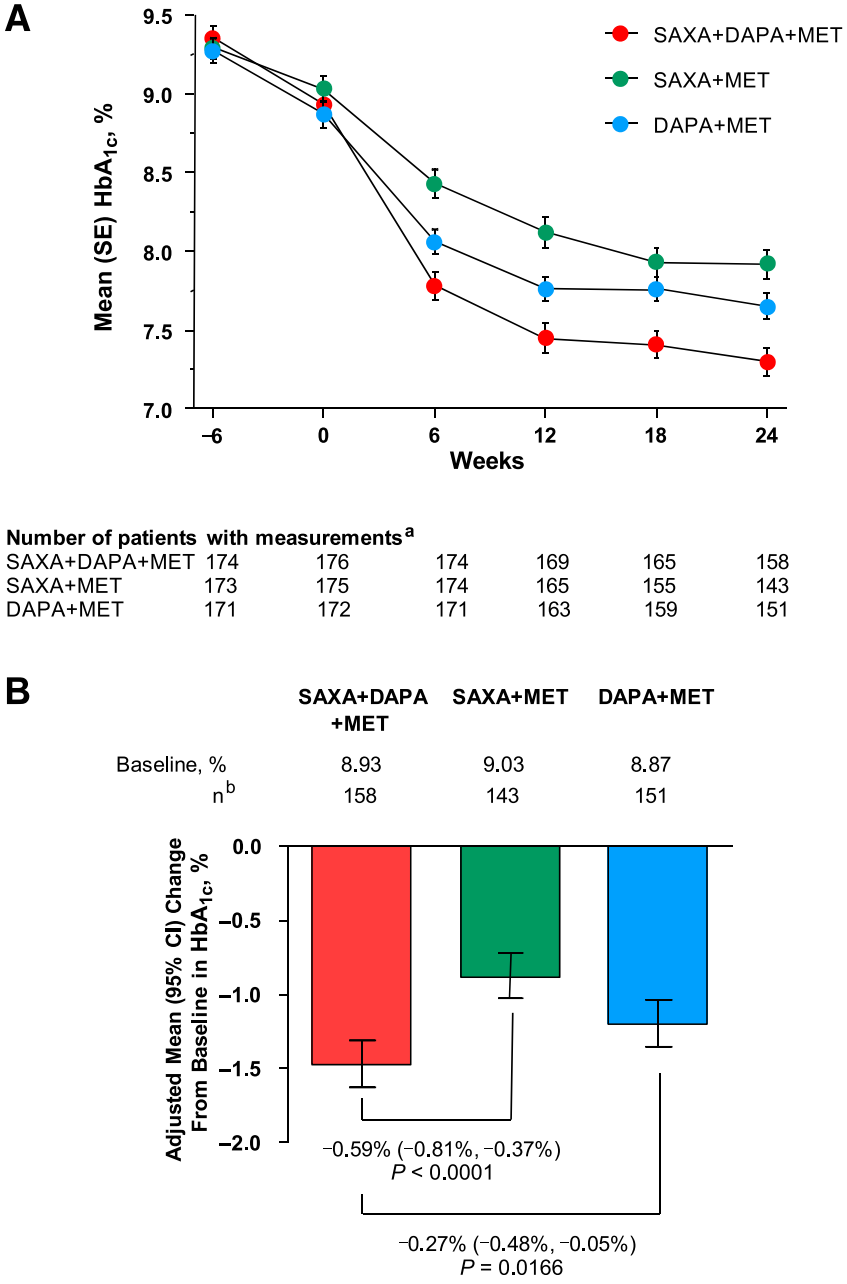

Figure 1—Mean (SE) HbA_{1c} over time (*A*) and adjusted mean change from baseline in HbA_{1c} at 24 weeks (*B*). [a]Observed values. [b]Number of randomized patients with nonmissing baseline values and week 24 values.

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

	SAXA+DAPA+MET *n* = 179	SAXA+MET *n* = 176	DAPA+MET *n* = 179
HbA_{1c}, % (mmol/mol)			
n[a]	176	175	172
Baseline mean ± SD	8.93 ± 1.19 (74 ± 13.0)	9.03 ± 1.05 (75 ± 11.5)	8.87 ± 1.17 (73 ± 12.8)
n[b]	158	143	151
Change from baseline, % [mmol/mol]	−1.47 (–1.62, –1.31) [–16 (–17.7, –14.3)]	−0.88 (–1.03, –0.72) [–10 (–11.3, –7.9)]	−1.20 (–1.35, –1.04) [–13 (–14.8, –11.4)]
Difference vs. SAXA+MET, % [mmol/mol]		−0.59 (–0.81, –0.37) [–6 (–8.9, –4.0)] $P < 0.0001$	
Difference vs. DAPA+MET, % [mmol/mol]		−0.27 (–0.48, –0.05) [–3 (–5.2, –0.5)] $P = 0.0166$	
PPG, mg/dL			
n[b]	154	147	144
Baseline mean ± SD	243 ± 55.5	256 ± 64.3	247 ± 56.3
Change from baseline	−80 (–86.3, –72.8)	−36 (–42.5, –28.7)	−70 (–77.4, –63.5)
Difference vs. SAXA+MET		−44 (–53.7, –34.3) $P < 0.0001$	
Difference vs. DAPA+MET		−9 (–18.8, 0.5) $P = 0.06$	
FPG, mg/dL			
n[a]	176	175	172
Baseline mean ± SD	181 ± 45.5	192 ± 45.4	185 ± 47.6
n[b]	155	142	148
Change from baseline	−38 (–43.2, –32.3)	−14 (–19.6, –8.4)	−32 (–37.3, –26.2)
Difference vs. SAXA+MET		−24 (–31.6, –15.9) NT	
Difference vs. DAPA+MET		−6 (–13.8, 1.7) NT	
Patients with HbA_{1c} <7% (53 mmol/mol)			
x/*n*[c]	74/177	29/175	40/173
%	41 (34.5, 48.2)	18 (13.0, 23.5)	22 (16.1, 28.3)
Difference vs. SAXA+MET		23 (14.7, 31.5) NT	
Difference vs. DAPA+MET		19 (10.1, 28.1) NT	
Body weight, kg			
n[a]	176	175	172
Baseline mean ± SD	87.1 ± 18.0	88.0 ± 18.7	86.3 ± 18.6
n[b]	159	145	152
Change from baseline	−2.1 (–2.5, –1.6)	0 (–0.5, 0.5)	−2.4 (–2.9, –1.9)
Difference vs. SAXA+MET		−2.1 (–2.7, –1.4)	
Difference vs. DAPA+MET		NT	

NT, not tested under sequential testing procedure if previous tested end point was not statistically significant. Data are adjusted mean change from baseline (95% CI) or as indicated. [a]Number of randomized patients with nonmissing baseline values and at least one postbaseline value. [b]Number of randomized patients with nonmissing baseline values and week 24 values (LOCF). [c]Number of responders (x)/number of patients with nonmissing baseline values and week 24 values (LOCF).

and 31% (14.5%, 46.9%), and for baseline HbA_{1c} ≥9% (≥75 mmol/mol) were 15% (4.1%, 25.8%) and 9% (–3.2%, 21.0%).

Reduction in body weight of 2.1 kg (2.4%) was observed in the SAXA+DAPA+MET group and 2.4 kg (2.8%) in the DAPA+MET group compared with no change in the SAXA+MET group.

Patients receiving SAXA+DAPA+MET showed small increases from baseline to week 24 ([95% CI]) in HDL cholesterol (HDL-C) of 5.4% (3.0%, 7.8%), a nonsignificant increase in LDL cholesterol (LDL-C) of 3.7% (–0.9%, 8.6%), and a significant reduction in triglycerides of –10.8% (–16.0%, –5.4%) (Supplementary Table 4). No significant changes in fasting lipids were observed for patients receiving SAXA+MET (all 95% CIs included 0), whereas patients receiving DAPA+MET showed small increases in total cholesterol of 3.8% (1.5%, 6.3%) and HDL-C of 7.7% (5.2%, 10.2%) and a nonsignificant increase in LDL-C of 1.5% (–3.1%, 6.4%]). Compared with the dual-therapy regimens, SAXA+DAPA+MET produced greater increases in HDL-C versus SAXA+MET (4.4% [1.1%, 7.8%], $P = 0.009$), smaller increases in total cholesterol versus DAPA+MET (–3.3% [–6.4%, –0.2%], $P = 0.04$), and greater reductions in triglycerides versus DAPA+MET (–8.5% [–15.9%, –0.4%], $P = 0.04$).

Safety

The proportion of patients with AEs was similar across treatment groups (Table 3). Few patients discontinued, and there were no deaths. Despite large decreases in HbA_{1c}, hypoglycemic event rates were low and similar across treatment groups, at 1% each for SAXA+DAPA+MET,

Table 3—AEs

	SAXA+DAPA+MET *n* = 179	SAXA+MET *n* = 176	DAPA+MET *n* = 179
At least 1 AE	87 (49)	93 (53)	87 (49)
At least 1 serious AE	2 (1)	6 (3)	2 (1)
AE leading to discontinuation	1 (0.6)	0	1 (0.6)
Serious AE leading to discontinuation	0	0	0
AEs of special interest			
Urinary tract infections	1 (0.6)	9 (5)	7 (5)
Genital infections	0	1 (0.6)	10 (6)
GFR decrease	3 (2)	1 (0.6)	0
Fractures	0	2 (1)	1 (0.6)
Pancreatitis	1 (0.6)	0	0
Cutaneous	0	1 (0.6)	0
Hypoglycemia*	2 (1)	2 (1)†	2 (1)
Major	0	0	0
Minor	1 (0.6)	1 (0.6)	1 (0.6)
Other	1 (0.6)	2 (1)	1 (0.6)

Data are *n* (%). *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. †Patients with more than one type of hypoglycemic episode were counted within each category but only once for patients experiencing hypoglycemia.

SAXA+MET, and DAPA+MET. There were no events of major hypoglycemia. Urinary tract infections were more common in the SAXA+MET (5%) and DAPA+MET (4%) groups than in the SAXA+DAPA+MET (0.6%) group. Genital infections occurred most commonly in the DAPA+MET (6%) group and were reported by no patients in the SAXA+DAPA+MET group and one patient in the SAXA+MET (0.6%) group. One patient in the triple-therapy group experienced a decrease in GFR that resulted in discontinuation from study treatment. This patient had an eGFR at enrollment of 66 mL/min/1.73 m^2 and was discontinued from the study because of an eGFR <60 mL/min/1.73m^2 for >12–16 weeks. eGFR after discontinuation was 57 mL/min/1.73m^2.There were no events of bladder or breast neoplasms, hypersensitivity, decreased lymphocyte or thrombocyte count, opportunistic infections, or worsening renal function.

Mean reductions in systolic blood pressure from baseline to 24 weeks occurred only in the SAXA+DAPA+MET and DAPA+MET groups (–1.9 and –3.5 mmHg, respectively) and smaller reductions in diastolic blood pressure across all groups (–1.0, –0.4, and –1.4 mmHg for SAXA+DAPA+MET, SAXA+MET, and DAPA+MET, respectively) were observed (Supplementary Table 4).

CONCLUSIONS

The American Diabetes Association/European Association for the Study of Diabetes (1) and the American Association of Clinical Endocrinologists (4) recommend that addition of a third noninsulin agent can be considered as a treatment option in some patients, taking into account the benefits and adverse effects of the additional medication. However, the addition of a third agent is often delayed until several trials of dual therapy, commonly single additions of different OADs to metformin, have been attempted. This approach often leads to long periods of hyperglycemia preceding any treatment intensification (26), which may contribute to microvascular and macrovascular complications (27) and glucotoxicity that in turn accelerates treatment failure. Dual addition of two OADs with complementary mechanisms of action to metformin may be an alternative strategy for patients with higher HbA_{1c} poorly controlled with metformin.

Triple antihyperglycemic therapy using a combination of a DPP-4 inhibitor and an SGLT2 inhibitor as dual add-on to metformin is an effective and well-tolerated novel intervention that has not been previously reported in uncontrolled type 2 diabetes. The primary objective of this study was to compare the change in HbA_{1c} achieved with the concurrent addition of SAXA+DAPA to MET therapy with the changes in HbA_{1c} obtained with the addition of SAXA+MET and DAPA+MET in patients with poorly controlled type 2 diabetes on metformin monotherapy. The combined addition of SAXA+DAPA to MET reduced HbA_{1c} to a significantly greater extent than did SAXA+MET or DAPA+MET therapy, and the proportion of patients achieving HbA_{1c} <7% (53 mmol/mol) at week 24 with SAXA+DAPA+MET was almost double that seen in the SAXA+MET and DAPA+MET groups. In addition, reductions in body weight of ~2 kg were noted in patients receiving SAXA+DAPA+MET and DAPA+MET therapy, whereas no change was observed in patients receiving SAXA+MET. Moreover, the addition of SAXA+DAPA to MET resulted in greater reductions in systolic blood pressure than SAXA+MET. These favorable effects of dapagliflozin on body weight and blood pressure are characteristic of SGLT2 inhibitors (28).

In the subgroup of patients with baseline HbA_{1c} ≥9%, the change in HbA_{1c} with SAXA+DAPA+MET was similar to that seen with DAPA+MET, suggesting that the contribution of saxagliptin to the reduction in HbA_{1c} in this subgroup may have been less than was noted for the HbA_{1c} <8% and HbA_{1c} >8%–9% subgroups. However, the number of patients was small and the analysis was not powered to make a definitive conclusion about this observation. SAXA+DAPA+MET was well tolerated, with the incidence of AEs similar to that reported for the SAXA+MET and DAPA+MET groups.

A preliminary report assessing the effects of the addition of empagliflozin (10 and 25 mg) and linagliptin (5 mg) to metformin in patients with baseline HbA_{1c} 7–10.5% (29) are in general agreement with our results. Empagliflozin + linagliptin + metformin produced a greater reduction in HbA_{1c} (–1.1% and –1.2% for empagliflozin, 10- and 25-mg doses, respectively) than empagliflozin + metformin (–0.6% and –0.7% for empagliflozin, 10- and 25-mg doses, respectively) or linagliptin + metformin (–0.7%). A reduction in body weight of ~2 kg was observed in the dual add-on and empagliflozin + metformin groups compared with the linagliptin + metformin group.

These findings for the novel triple therapy achieved by adding a dual combination of saxagliptin and dapagliflozin

to metformin are generally consistent with the mechanisms of action of saxagliptin and dapagliflozin and results from previous clinical studies investigating the efficacy and safety of these agents as monotherapy (11–13) or as add-on therapy (14–20). Both drugs are associated with a low rate of hypoglycemia (9,10), and dapagliflozin, owing to its ability to increase the renal excretion of glucose (calorie loss), produces reductions in body weight (30) and an increase in genital and urinary tract infections (31,32). In the current study, the incidence of genital and urinary tract infections was low in the triple-therapy group.

Recent studies have shown that the glucosuric effect of SGLT2 inhibitors improves insulin sensitivity and β-cell function in individuals with type 2 diabetes (33,34). However, these changes were accompanied by an increase in endogenous glucose production, possibly the result of an increase in plasma glucagon, which may partially offset the decrease in plasma glucose concentrations brought about by SGLT2 inhibitor-induced glucosuria (34). Because DPP-4 inhibitors reduce plasma glucagon concentrations (8), the combination of a DPP-4 inhibitor with an SGLT2 inhibitor may suppress the latter's proglucagogenic effects.

The patients enrolled in the current study had a high mean baseline HbA_{1c} of 8.9% (74 mmol/mol), with 45% having baseline $HbA_{1c} \geq 9.0\%$ (75 mmol/mol) and a mean duration of type 2 diabetes of 7.6 years. These characteristics suggest relatively advanced disease with significant β-cell loss or dysfunction in these patients and are representative of poorly controlled patients. Several recent studies examining the safety and efficacy of triple oral therapy enrolled patients with mean baseline HbA_{1c} in the range of 7.8–8.8% (62–73 mmol/mol) with mean disease durations of 5–10 years (20,35–41). Most of these studies examined a single-agent add-on to dual therapy and obtained placebo-corrected reductions in HbA_{1c} ranging from –0.4% to –0.9% (–4.4 to 9.8 mmol/mol). However, DeFronzo et al. (35) assessed the efficacy and tolerability of alogliptin combined with pioglitazone as add-on therapy in patients poorly controlled with metformin (baseline HbA_{1c} 8.5–8.6% [69–70 mmol/mol]) and diabetes duration of 6.2 years. The combination of alogliptin and pioglitazone add-on to metformin was more effective in reducing HbA_{1c} (–1.4% [15.3 mmol/mol], for both alogliptin 12.5 and 25 mg + pioglitazone [pooled 15, 30, and 45 mg/day]) than either pioglitazone or alogliptin add-on to metformin (both –0.9% [9.8 mmol/mol]). The current study complements that report and provides data supporting concurrent dual add-on of saxagliptin and dapagliflozin to metformin as an alternative option when oral triple-combination therapy is being considered, with the added benefit of weight loss rather than weight gain observed with pioglitazone.

The current study was limited by not having a placebo group. However, we concluded that administering a placebo in this population (patients with high baseline HbA_{1c} and metformin failure) would have been unethical. In addition, the 24-week duration of the current study precludes conclusions about the durability of the observed effects on glycemic control and possible long-term benefits or safety concerns.

This study produced an HbA_{1c} reduction in the dual add-on group that was less than the summation of the reductions seen in the monotherapy arms. Looking at previous studies that have had dual add-on arms versus individual components, including the above study of alogliptin plus pioglitazone (35) and initial combination therapies with saxagliptin and metformin (42) as well as dapagliflozin and metformin (43), this finding appears to be consistent even when the two agents used have theoretically complementary mechanisms.

To our knowledge, this is the first report demonstrating that triple therapy by the dual addition of a well-tolerated combination of a DPP-4 inhibitor and an SGLT2 inhibitor to background metformin therapy in patients with type 2 diabetes poorly controlled with metformin leads to greater reductions in HbA_{1c} and a greater proportion of patients achieving $HbA_{1c} < 7\%$ (53 mmol/mol) than the addition of each component alone. Importantly, the improvements in glycemic control with the dual add-on therapy were achieved without any increased risk of hypoglycemia and were associated with body weight reduction. Except in symptomatic patients with very high HbA_{1c} (>10%) and evidence of volume depletion and/or weight loss, where initiation of insulin therapy would still be considered standard of care, the new treatment paradigm consisting of triple therapy with dual add-on of saxagliptin and dapagliflozin to metformin appears to be an attractive therapeutic option to safely and effectively bring patients poorly controlled on metformin monotherapy to individualized glycemic goals.

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References

1. Inzucchi SE, Bergenstal RM, Buse JB, et al.; American Diabetes Association (ADA); European Association for the Study of Diabetes (EASD). Management of hyperglycemia in type 2 diabetes: a patient-centered approach: position statement of the American Diabetes Association (ADA) and the European Association for the Study of Diabetes (EASD). Diabetes Care 2012;35:1364–1379

2. Fonseca VA. Defining and characterizing the progression of type 2 diabetes. Diabetes Care 2009;32(Suppl. 2):S151–S156

3. Harper W, Clement M, Goldenberg R, et al.; Canadian Diabetes Association Clinical Practice

Guidelines Expert Committee. Canadian Diabetes Association 2013 clinical practice guidelines for the prevention and management of diabetes in Canada. Pharmacologic management of type 2 diabetes. Can J Diabetes 2013;37(Suppl. 1): S61–S68
4. Garber AJ, Abrahamson MJ, Barzilay JI, et al. American Association of Clinical Endocrinologists' comprehensive diabetes management algorithm 2013 consensus statement—executive summary. Endocr Pract 2013;19:536–557
5. Raz I, Riddle MC, Rosenstock J, et al. Personalized management of hyperglycemia in type 2 diabetes: reflections from a Diabetes Care Editors' Expert Forum. Diabetes Care 2013;36: 1779–1788
6. 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
7. 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
8. Drucker DJ, Nauck MA. The incretin system: glucagon-like peptide-1 receptor agonists and dipeptidyl peptidase-4 inhibitors in type 2 diabetes. Lancet 2006;368:1696–1705
9. Jabbour SA, Whaley JM, Tirmenstein M, et al. Targeting renal glucose reabsorption for the treatment of type 2 diabetes mellitus using the SGLT2 inhibitor dapagliflozin. Postgrad Med 2012;124:62–73
10. Schwartz SL. Saxagliptin for the treatment of type 2 diabetes mellitus: focus on recent studies. Ann Med 2012;44:157–169
11. 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
12. 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
13. 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
14. 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
15. 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
16. 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
17. 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
18. 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
19. 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
20. Jabbour SA, Hardy E, Sugg J, Parikh S; Study 10 Group. Dapagliflozin is effective as add-on therapy to sitagliptin with or without metformin: a 24-week, multicenter, randomized, double-blind, placebo-controlled study. Diabetes Care 2014;37:740–750
21. Barnett AH, Charbonnel B, Donovan M, Fleming D, Chen R. Effect of saxagliptin as add-on therapy in patients with poorly controlled type 2 diabetes on insulin alone or insulin combined with metformin. Curr Med Res Opin 2012;28: 513–523
22. Wilding JPH, Woo V, Soler NG, et al.; Dapagliflozin 006 Study Group. Long-term efficacy of dapagliflozin in patients with type 2 diabetes mellitus receiving high doses of insulin: a randomized trial. Ann Intern Med 2012;156:405–415
23. Laska EM, Meisner MJ. Testing whether an identified treatment is best. Biometrics 1989; 45:1139–1151
24. 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
25. Zhang M, Tsiatis AA, Davidian M. Improving efficiency of inferences in randomized clinical trials using auxiliary covariates. Biometrics 2008;64:707–715
26. Brown JB, Nichols GA, Perry A. The burden of treatment failure in type 2 diabetes. Diabetes Care 2004;27:1535–1540
27. Stratton IM, Adler AI, Neil HA, et al. Association of glycaemia with macrovascular and microvascular complications of type 2 diabetes (UKPDS 35): prospective observational study. BMJ 2000;321:405–412
28. 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
29. DeFronzo RA, Lewin A, Patel S, et al. Fixed-dose combinations of empagliflozin/linagliotin for 24 weeks as add-on to metformin in patients with type 2 diabetes (T2DM) (Abstract). Diabetes 2014;63(Suppl. 1A):LB33
30. Bolinder J, Ljunggren Ö, Kullberg J, et al. Effects of dapagliflozin on body weight, total fat mass, and regional adipose tissue distribution in patients with type 2 diabetes mellitus with inadequate glycemic control on metformin. J Clin Endocrinol Metab 2012;97:1020–1031
31. Johnsson KM, Ptaszynska A, Schmitz B, Sugg J, Parikh SJ, List JF. Urinary tract infections in patients with diabetes treated with dapagliflozin. J Diabetes Complications 2013;27:473–478
32. 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
33. Ferrannini E, Muscelli E, Frascerra S, et al. Metabolic response to sodium-glucose cotransporter 2 inhibition in type 2 diabetic patients. J Clin Invest 2014;124:499–508
34. Merovci A, Solis-Herrera C, Daniele G, et al. Dapagliflozin improves muscle insulin sensitivity but enhances endogenous glucose production. J Clin Invest 2014;124:509–514
35. DeFronzo RA, Burant CF, Fleck P, Wilson C, Mekki Q, Pratley RE. Efficacy and tolerability of the DPP-4 inhibitor alogliptin combined with pioglitazone, in metformin-treated patients with type 2 diabetes. J Clin Endocrinol Metab 2012;97:1615–1622
36. Fonseca V, Staels B, Morgan JD 2nd, et al. Efficacy and safety of sitagliptin added to ongoing metformin and pioglitazone combination therapy in a randomized, placebo-controlled, 26-week trial in patients with type 2 diabetes. J Diabetes Complications 2013;27:177–183
37. Owens DR, Swallow R, Dugi KA, Woerle HJ. Efficacy and safety of linagliptin in persons with type 2 diabetes inadequately controlled by a combination of metformin and sulphonylurea: a 24-week randomized study. Diabet Med 2011; 28:1352–1361
38. Hermansen K, Kipnes M, Luo E, Fanurik D, Khatami H, Stein P; Sitagliptin Study 035 Group. Efficacy and safety of the dipeptidyl peptidase-4 inhibitor, sitagliptin, in patients with type 2 diabetes mellitus inadequately controlled on glimepiride alone or on glimepiride and metformin. Diabetes Obes Metab 2007;9:733–745
39. Lukashevich V, Del Prato S, Araga M, Kothny W. Efficacy and safety of vildagliptin in patients with type 2 diabetes mellitus inadequately controlled with dual combination of metformin and sulphonylurea. Diabetes Obes Metab 2014;16: 403–409
40. 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 glycemic control on metformin plus a sulfonylurea. Diabetes Obes Metab 2014;16:443–450
41. Schernthaner G, Gross JL, Rosenstock J, et al. Canagliflozin compared with sitagliptin for patients with type 2 diabetes who do not have adequate glycemic control with metformin plus sulfonylurea: a 52-week randomized trial. Diabetes Care 2013;36:2508–2515
42. Jadzinsky M, Pfützner A, Paz-Pacheco E, Xu Z, Allen E, Chen R; CV181-039 Investigators. Saxagliptin given in combination with metformin as initial therapy improves glycaemic control in patients with type 2 diabetes compared with either monotherapy: a randomized controlled trial. Diabetes Obes Metab 2009;11:611–622
43. Henry RR, Murray AV, Marmolejo MH, Hennicken D, Ptaszynska A, List JF. Dapagliflozin, metformin XR, or both: initial pharmacotherapy for type 2 diabetes, a randomised controlled trial. Int J Clin Pract 2012;66:446–456