



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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Diabetes Care 2015;38:376–383 | DOI: 10.2337/dc14-1142

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} $\geq 8.0\%$ and $\leq 12.0\%$ (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) $\geq 1,500$ 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/m². 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 $\leq 1\%$ 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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Received 5 May 2014 and accepted 22 September 2014.

Clinical trial reg. no. NCT01606007, clinicaltrials.gov.

This article contains Supplementary Data online at <http://care.diabetesjournals.org/lookup/suppl/doi:10.2337/dc14-1142/-/DC1>.

A slide set summarizing this article is available online.

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See accompanying articles, pp. 352, 355, 365, 373, 384, 394, 403, 412, 420, 429, and 431.

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/m² 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 m² 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. 1A).

Table 1—Demographics and baseline characteristics

	SAXA+DAPA+MET <i>n</i> = 179	SAXA+MET <i>n</i> = 176	DAPA+MET <i>n</i> = 179	Total <i>N</i> = 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 (\pm SE) reductions from baseline in HbA_{1c} at 24 weeks ($-1.47 \pm 0.08\%$ [-16.1 ± 0.9 mmol/mol]) than did therapy with SAXA+MET ($-0.88 \pm 0.08\%$ [-9.6 ± 0.9 mmol/mol]) or DAPA+MET ($-1.20 \pm 0.08\%$ [-13.1 ± 0.9 mmol/mol]) (Fig. 1B 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;

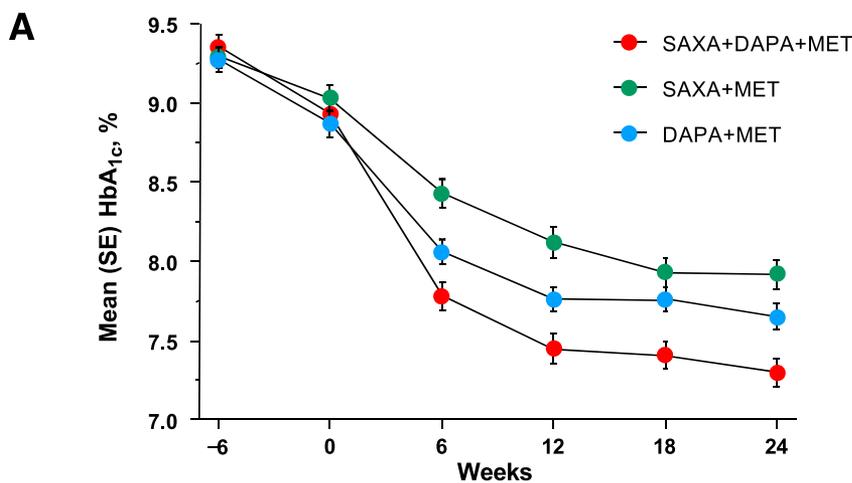
$P < 0.0001$) and versus DAPA+MET was -0.27% (-0.48% , -0.05% ; -3.0 [-5.2 , -0.5] mmol/mol; $P = 0.0166$). Thus, the primary end point of statistical superiority of SAXA+DAPA add-on to MET versus SAXA add-on to MET and DAPA add-on to MET was met.

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 $\geq 9\%$ (≥ 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} $\geq 9\%$ (≥ 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 (\pm 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 (\pm SE) proportion of patients achieving HbA_{1c} $<7\%$ (53 mmol/mol) at week 24 with SAXA+DAPA+MET ($41 \pm 3.5\%$) was nearly double that seen in the SAXA+MET ($18 \pm 2.7\%$) and DAPA+MET ($22 \pm 3.1\%$) groups. The proportions of patients achieving HbA_{1c} $<7\%$ (53 mmol/mol) with SAXA+DAPA+MET with baseline HbA_{1c} $<8\%$ (64 mmol/mol), $\geq 8\%$ to $<9\%$ (≥ 64 to 75 mmol/mol), and $\geq 9\%$ (≥ 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} $\geq 8\%$ to $<9\%$ (≥ 64 to 75 mmol/mol) were 39% (24.5% , 53.9%)



	-6	0	6	12	18	24
SAXA+DAPA+MET	174	176	174	169	165	158
SAXA+MET	173	175	174	165	155	143
DAPA+MET	171	172	171	163	159	151

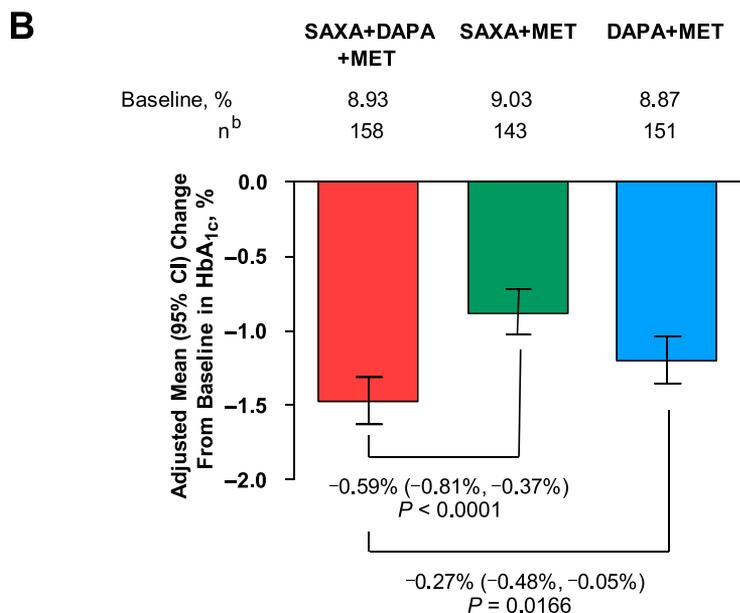


Figure 1—Mean (SE) HbA_{1c} over time (A) and adjusted mean change from baseline in HbA_{1c} at 24 weeks (B). ^aObserved values. ^bNumber of randomized patients with nonmissing baseline values and week 24 values.

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

	SAXA+DAPA+MET <i>n</i> = 179	SAXA+MET <i>n</i> = 176	DAPA+MET <i>n</i> = 179
HbA_{1c}, % (mmol/mol)			
<i>n</i> ^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)
<i>n</i> ^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)]	
Difference vs. DAPA+MET, % [mmol/mol]		−0.27 (−0.48, −0.05) [−3 (−5.2, −0.5)]	
		<i>P</i> < 0.0001	
		<i>P</i> = 0.0166	
PPG, mg/dL			
<i>n</i> ^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)	
Difference vs. DAPA+MET		−9 (−18.8, 0.5)	
		<i>P</i> < 0.0001	
		<i>P</i> = 0.06	
FPG, mg/dL			
<i>n</i> ^a	176	175	172
Baseline mean ± SD	181 ± 45.5	192 ± 45.4	185 ± 47.6
<i>n</i> ^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)	
Difference vs. DAPA+MET		−6 (−13.8, 1.7)	
		NT	
		NT	
Patients with HbA_{1c} <7% (53 mmol/mol)			
<i>x/n</i> ^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)	
Difference vs. DAPA+MET		19 (10.1, 28.1)	
		NT	
Body weight, kg			
<i>n</i> ^a	176	175	172
Baseline mean ± SD	87.1 ± 18.0	88.0 ± 18.7	86.3 ± 18.6
<i>n</i> ^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. ^aNumber of randomized patients with nonmissing baseline values and at least one postbaseline value. ^bNumber of randomized patients with nonmissing baseline values and week 24 values (LOCF). ^cNumber 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 <i>n</i> = 179	SAXA+MET <i>n</i> = 176	DAPA+MET <i>n</i> = 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*			
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 m² and was discontinued from the study because of an eGFR <60 mL/min/1.73m² for >12–16 weeks. eGFR after discontinuation was 57 mL/min/1.73m². 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 non-insulin 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 proglucagonogenic 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.

Acknowledgments. 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), with funding from Bristol-Myers Squibb and AstraZeneca.

Duality of Interest. This study was funded by Bristol-Myers Squibb and AstraZeneca. None of the authors received any financial or monetary transfer of value for their participation in the writing of the manuscript.

J.R. has served on scientific advisory boards and received honoraria or consulting fees from Sanofi, Novo Nordisk, Eli Lilly, GlaxoSmithKline, Takeda, Merck, Daiichi Sankyo, Janssen, Novartis, Boehringer Ingelheim, MannKind, Halozyne, Intarcia, and Lexicon and grants/research support from Merck, Pfizer, Sanofi, Novo Nordisk, Roche, Bristol-Myers Squibb, Eli Lilly, GlaxoSmithKline, Takeda, Novartis, AstraZeneca, Amylin, Janssen, Daiichi Sankyo, MannKind, Boehringer Ingelheim, Intarcia, and Lexicon. L.H., P.Z., and N.I. are full-time employees of Bristol-Myers Squibb. Y.L., W.C., and B.H. are full-time employees of AstraZeneca. No other potential conflicts of interest relevant to this article were reported.

Author Contributions. J.R., W.C., and N.I. wrote, reviewed, and edited the manuscript and contributed to the discussion of the manuscript. L.H. researched data; wrote, reviewed, and edited the manuscript; and contributed to the discussion of the manuscript. P.Z. reviewed and edited the manuscript. Y.L. performed statistical analysis and reviewed and edited the manuscript. B.H. reviewed and edited the manuscript and contributed to the discussion of the manuscript. J.R. 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.

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