Dapagliflozin Plus Saxagliptin Add-on Therapy Compared With Insulin in Patients With Type 2 Diabetes Poorly Controlled by Metformin With or Without Sulfonylurea Therapy: A Randomized Clinical Trial

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OBJECTIVE

This study evaluated whether an oral combination of a sodium–glucose cotransporter 2 inhibitor and a dipeptidyl peptidase 4 inhibitor achieved glycemic control similar to basal insulin in patients with type 2 diabetes, poorly controlled with metformin, without increasing hypoglycemia or body weight.

RESEARCH DESIGN AND METHODS

In a multinational, open-label, randomized, phase 3 trial (ClinicalTrials.gov reg. no. NCT02551874), adults with type 2 diabetes inadequately controlled on metformin, with or without sulfonylurea, were randomized (1:1) to receive dapagliflozin (DAPA) plus saxagliptin (SAXA) or titrated insulin glargine (INS). The primary end point was change in glycated hemoglobin A_{1c} (HbA_{1c}) from baseline to week 24. DAPA + SAXA treatment was tested for noninferiority versus INS.

RESULTS

The efficacy data set included 643 patients (mean ± SD HbA_{1c}, 9.1 ± 1.0% [75 ± 11 mmol/mol]). At week 24, DAPA + SAXA treatment versus INS resulted in noninferior reductions in HbA_{1c} (adjusted mean ± SE change, −1.7 ± 0.1% vs. −1.5 ± 0.1% [18.3 ± 0.7 mmol/mol vs. 16.8 ± 0.7 mmol/mol]; $P = 0.118$), significantly different body weight change (between-group difference, −3.64 kg [95% CI −4.20 to −3.09]; $P < 0.001$), fewer patients with confirmed hypoglycemia (21.3% vs. 38.4%, $P < 0.001$), more patients achieving HbA_{1c} <7.0% (53 mmol/mol) without hypoglycemia (20.9% vs. 13.1%, $P = 0.008$), and a similar proportion of patients achieving HbA_{1c} <7.0% (33.2% vs. 33.5%, $P = 0.924$). Mean reductions in 24-h glucose measurements from baseline to week 2 were greater with DAPA + SAXA than with INS ($P < 0.0001$). No patients in the DAPA + SAXA group and three patients (0.9%) in the INS group experienced severe hypoglycemia.

CONCLUSIONS

Adding DAPA + SAXA to insulin-naive patients with poorly controlled type 2 diabetes achieved similar glycemic control, a lower risk of hypoglycemia, and a clinically relevant body weight difference compared with basal INS.

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Most patients with type 2 diabetes are treated with metformin as a first-line glucose-lowering monotherapy, as recommended by treatment guidelines (1,2). However, patients receiving metformin monotherapy often require the subsequent addition of one or more further glucose-lowering agents to achieve and maintain glycemic control as the disease progresses (2). Sulfonylureas are the most commonly prescribed drug after metformin, although treatment with this drug class is associated with an increased risk of hypoglycemia and weight gain (2).

An ideal therapy should be efficacious, achieve glycated hemoglobin A_{1c} (HbA_{1c}) targets without hypoglycemia through complementary mechanisms of actions, and result in weight reduction. Sodium–glucose cotransporter 2 (SGLT2) inhibitors, glucagon-like peptide 1 receptor agonists (GLP-1RAs), and dipeptidyl peptidase 4 inhibitors (DPP-4is) are glucose-lowering drugs that are recommended by international guidelines for use in combination with metformin (3). SGLT2 inhibitors promote urinary excretion of excess glucose by inhibiting renal glucose reabsorption and act independently of insulin (4), whereas DPP-4is and GLP-1RAs enhance glucose-dependent insulin secretion and suppress glucagon secretion (5). GLP-1RAs are generally recommended by clinical guidelines as the first injectable medication for patients with type 2 diabetes (6).

The SGLT2 inhibitor dapagliflozin (DAPA) and the DPP-4i saxagliptin (SAXA) improve glycemic control in patients with type 2 diabetes when used as monotherapies (7–9) or in combination with metformin (10,11). Moreover, dual addition of DAPA plus SAXA to metformin resulted in greater reductions in HbA_{1c} than either agent added to metformin alone (12). DAPA plus SAXA add-on to metformin is also associated with body weight reduction and a low risk of hypoglycemia and produces a similar safety profile to that reported in previous studies of these agents as monotherapy (7–9) or as add-on therapy (10–12).

Insulin is an effective glucose-lowering agent for patients with type 2 diabetes and is recommended as one of several options for second- or third-line glucose-lowering therapy by many clinical guidelines. However, insulin may be associated with undesirable adverse effects, including an increased risk of hypoglycemia and body weight gain, which may reduce patient compliance (13). Furthermore, insulin is administered by injection, and titration is mandatory to obtain acceptable glycemic control. Many patients are reluctant to use insulin owing to psychological barriers, and health care providers must have specialist knowledge and resources to initiate and guide patients in the use of insulin therapy. It is likely that many clinicians perceive insulin to be more efficacious than oral therapies in patients with high HbA_{1c} levels, because studies comparing insulin with oral agents have generally excluded these patients. No studies to date have evaluated whether an oral combination of two modern glucose-lowering agents may achieve a glucose reduction similar to initiation and titration of a once-daily basal insulin analog in patients with type 2 diabetes inadequately controlled with metformin.

Here, we report the results from a randomized, open-label, 24-week, phase 3 trial evaluating the efficacy and safety of DAPA plus SAXA add-on therapy versus titrated insulin in patients with type 2 diabetes inadequately controlled by metformin with or without sulfonylurea therapy. The primary objective of this study was to determine whether DAPA plus SAXA treatment was noninferior to titrated insulin in reducing HbA_{1c}. Secondary objectives included effects on hypoglycemia and body weight.

RESEARCH DESIGN AND METHODS

Study Design

This international, multicenter, randomized, open-label, active-controlled, parallel-group, 24-week phase 3b trial (ClinicalTrials.gov identifier: NCT02551874) was conducted at 112 centers in 11 countries (Czech Republic, Denmark, Germany, Hungary, Mexico, Poland, Romania, South Africa, Spain, Sweden, and the U.S.). It consisted of a 2-week lead-in period, during which participants received instruction on diet, exercise, and self-monitoring of glucose levels, followed by a 24-week treatment period.

The study was conducted in accordance with the ethical principles outlined in the Declaration of Helsinki and Good Clinical Practice guidelines of the International Conference on Harmonisation. The study protocol, including any amendments, and the participant informed consent form were both reviewed by the relevant institutional review board or independent ethics committee before initiation of the study.

Participants and Eligibility Criteria

Adults (≥18 years) with type 2 diabetes and inadequate glycemic control (HbA_{1c} 8.0–12.0% [64–108 mmol/mol]), who had been receiving a stable dose of metformin (≥1,500 mg/day), with or without a stable dose of sulfonylurea (≥50% maximum dose) for at least 8 weeks before screening, were eligible for enrollment. Participants were required to have a maximum BMI of 45.0 kg/m^2 at screening and a maximum fasting plasma glucose (FPG) measurement of 270 mg/dL at baseline. All participants provided written, informed consent.

Key exclusion criteria were type 1 diabetes, cardiovascular disease (including myocardial infarction; cardiac surgery or revascularizations; valvular disease or repair; unstable angina; unstable congestive heart failure; transient ischemic attack or significant cerebrovascular disease; unstable or previously undiagnosed arrhythmia; congestive heart failure defined as New York Heart Association Functional Classification III and IV; unstable or acute congestive heart failure; and/or known left ventricular ejection fraction of ≤40%) within 3 months of screening, severe hepatic insufficiency, and a medical history of diabetic ketoacidosis or renal impairment (defined as creatinine clearance <60 mL/min or serum creatinine ≥1.5 mg/dL in men or ≥1.4 mg/dL in women).

Randomization

Participants were randomized 1:1 using an interactive voice response system to receive DAPA plus SAXA or titrated insulin glargine (INS), stratified by use of sulfonylurea with background metformin treatment, for 24 weeks (Supplementary Fig. 1). Randomization schedules were generated and kept by Bristol-Myers Squibb.

Interventions

DAPA, 10 mg/day (Bristol-Myers Squibb, New Brunswick, NJ), and SAXA, 5 mg/day (Bristol-Myers Squibb, Mount Vernon, IN), were administered orally in tablet form, and INS U100 (Sanofi, Laval, Quebec, Canada) was administered by subcutaneous injection. All patients continued to receive their previous dose regimen of

metformin (with or without sulfonylurea) throughout the study. INS treatment was initiated at a dose of 0.2 units/kg body weight or at least 10 units/day, and patients self-titrated their dose in 2-unit increments every 3 days until week 8 of the study, based on daily glucose monitoring and an FPG target of 100 mg/dL. At week 12, investigators could decide whether to increase the daily INS dose for individual patients to help them achieve target levels. During the first 8 weeks, investigators could also increase the fixed dosing titration steps to optimize INS titration for the individual patient. The goal was to reach an acceptable and stable INS dose at week 12. If hypoglycemic events occurred (plasma glucose ≤70 mg/dL during the previous 3 days), the INS dose would not be uptitrated. Patients with FPG values >200 mg/dL were eligible for open-label rescue medication. In a subset of participants (planned as 125 patients in each treatment arm), a masked continuous glucose monitoring (CGM) sensor (Medtronic iPro2 CGM system) was inserted subcutaneously for 7 consecutive days from the beginning of the lead-in period (before receiving study medication), week 2, week 11, and week 23.

Outcome Measures

The primary efficacy end point was mean change in HbA_{1c} from baseline to week 24 and was centrally assessed. Secondary efficacy end points included mean change from baseline in weight at week 24, the proportion of patients with confirmed hypoglycemia (plasma glucose ≤70 mg/dL or symptoms of hypoglycemia with self-monitored blood glucose ≤70 mg/dL) at week 24, the proportion of patients achieving a therapeutic glycemic response (HbA_{1c} <7.0% [<53 mmol/mol]) without any reported hypoglycemia at week 24, change from baseline in the mean value of 24-h glucose readings measured by CGM at week 2 (in a subset of patients), and the proportion of patients achieving a therapeutic glycemic response (HbA_{1c} <7.0% [<53 mmol/mol]) at week 24. An ad hoc analysis was performed for an additional efficacy end point: the proportion of patients achieving a therapeutic glycemic response (HbA_{1c} <7.0% [<53 mmol/mol]) without hypoglycemia or weight gain at week 24.

Safety assessments included monitoring of adverse events (AEs) and frequency and American Diabetes Association classification of hypoglycemia events (14), as well as changes in clinical laboratory parameters, physical examinations, vital signs, and electrocardiographic findings.

Statistical Analysis

Efficacy analyses included all randomized patients who received at least one dose of study medication (intention-to-treat population) and who had a baseline assessment and at least one postbaseline assessment. Efficacy analyses were based on all data before rescue or treatment discontinuation.

A sample size of 299 patients per group was determined a priori to yield ~90% power to demonstrate a noninferiority margin for difference in mean HbA_{1c} change from baseline (primary efficacy end point) between the two groups of 0.3% (3.3 mmol/mol), at a one-sided significance level of 0.025 and assuming an SD of 1.1% and a 5% dropout rate.

Analysis of the primary efficacy end point was performed using a direct likelihood longitudinal repeated-measures analysis including the fixed categorical effects of treatment, week, randomization stratification factor (metformin, with or without sulfonylurea background medication), treatment-by-week interaction, and the continuous fixed covariates of baseline measurement and baseline measurement-by-week interaction. Point estimates and 95% CIs were calculated for the differences in mean changes between treatment groups. The primary efficacy end point was considered noninferior if the upper limit of the 95% CI of the difference between groups was <0.3%.

The proportions of patients achieving a therapeutic glycemic response (HbA_{1c} <7.0% [<53 mmol/mol]), achieving HbA_{1c} <7.0% (<53 mmol/mol) without hypoglycemia, and achieving HbA_{1c} <7.0% (<53 mmol/mol) without hypoglycemia or weight gain were compared between treatment groups using a logistic regression analysis, as previously described (15,16). The change from baseline in mean 24-h glucose and the proportion of patients achieving HbA_{1c} <7.0% (<53 mmol/mol) were tested for noninferiority with margins of 12.0 mg/dL (0.7 mmol/L) and 10% (86 mmol/mol), respectively. In addition to point estimates and 95% CIs, *P* values were calculated for all continuous secondary end points using the same mixed statistical model as for the primary end point.

Safety analyses included all randomized patients who received at least one dose of the study medication (safety set), including data after rescue. No formal statistical testing was performed. Statistical analyses for efficacy end points were performed using SAS 9.4 software. The SAS procedure PROC MIXED was used for analysis of the primary efficacy end point. Data were monitored by Bristol-Myers Squibb centrally to assess data quality and the integrity of the study.

RESULTS

Patient Disposition and Baseline Characteristics

Participants were enrolled between 20 October 2015 and 19 October 2016. Enrolled patients, patients entering the lead-in period, and randomized patients are shown in Supplementary Fig. 2. Of the 643 randomized patients who received treatment, 584 (90.8%; DAPA + SAXA, *n* = 298; INS, *n* = 286) completed the 24-week treatment period. The most common reason for study discontinuation was loss to follow-up (DAPA + SAXA, *n* = 8; INS, *n* = 11). There were 16 patients who required rescue medication or discontinued owing to lack of glycemic control (DAPA + SAXA, *n* = 11; INS, *n* = 5; *P* = 0.165).

Patient demographics and characteristics at baseline were similar across treatment groups (Table 1). At baseline, mean ± SD duration of type 2 diabetes was 9.4 ± 6.3 years, and HbA_{1c} was 9.1 ± 1.0% (76.0 ± 10.9 mmol/mol). In total, 51.5% of patients were receiving sulfonylurea treatment (DAPA + SAXA, 51.2%; INS, 51.7%). Of the 643 randomized patients who received treatment, 307 had a masked CGM sensor inserted subcutaneously at baseline for the measurement of 24-h glucose readings. A total of 283 of these patients (DAPA + SAXA, *n* = 141; INS, *n* = 142) had an evaluable CGM baseline value and qualified for the CGM substudy. In insulin-treated patients, the mean INS dose was 35.6 and 36.5 units at weeks 12 and 24, respectively.

Efficacy

The addition of DAPA plus SAXA resulted in noninferior reductions in HbA_{1c} from baseline versus INS at week 24 (adjusted

Table 1—Patient demographics and baseline characteristics

Variable	DAPA + SAXA + MET *n* = 324	INS + MET *n* = 319	Total *N* = 643
Age, years	55.7 ± 9.52	55.3 ± 9.6	55.5 ± 9.6
Age categories			
<65 years	265 (81.8)	260 (81.5)	525 (81.6)
≥65 to <75 years	55 (17.0)	54 (16.9)	109 (17.0)
≥75 years	4 (1.2)	5 (1.6)	9 (1.4)
Sex			
Men	176 (54.3)	171 (53.6)	347 (54.0)
Women	148 (45.7)	148 (46.4)	296 (46.0)
Race			
White	263 (81.2)	254 (79.6)	517 (80.4)
Black or African American	28 (8.6)	35 (11.0)	63 (9.8)
Asian	12 (3.7)	12 (3.8)	24 (3.7)
Other*	21 (6.5)	18 (5.6)	39 (6.1)
Geographic region			
North America	168 (51.9)	168 (52.7)	336 (52.3)
Latin America	45 (13.9)	34 (10.7)	79 (12.3)
Europe or South Africa	111 (34.3)	117 (36.7)	228 (35.5)
BMI, kg/m^2	32.5 ± 5.3	32.0 ± 5.4	32.2 ± 5.3
Body weight, kg	89.8 ± 17.7	89.4 ± 18.4	89.6 ± 18.0
Duration of type 2 diabetes, years	9.6 ± 6.5	9.3 ± 6.2	9.4 ± 6.3
Duration of type 2 diabetes categories			
<3 years	47 (14.5)	49 (15.4)	96 (14.9)
≥3 to ≤10 years	137 (42.3)	145 (45.5)	282 (43.9)
>10 years	140 (43.2)	125 (39.2)	265 (41.2)
HbA_{1c}, %	9.0 ± 1.0	9.1 ± 1.1	9.1 ± 1.0
HbA_{1c}, mmol/mol	75 ± 11	75 ± 12	75 ± 11)
HbA_{1c} categories			
<8%	44 (13.6)	48 (15.0)	92 (14.3)
≥8% to <9%	124 (38.3)	112 (35.1)	236 (36.7)
≥9%	156 (48.1)	159 (49.8)	315 (49.0)
FPG, mg/dL	189.5 ± 55.5	188.6 ± 53.8	189.0 ± 54.6
FPG, mmol/L	10.5 ± 3.1	10.5 ± 3.0	10.5 ± 3.0
Estimated glomerular filtration rate, mL/min/1.73 m^2	94.6 ± 23.6	97.3 ± 21.7	95.9 ± 22.7
Proportion of patients receiving sulfonylurea	166 (51.2)	165 (51.7)	331 (51.5)
Specific disease history			
Dyslipidemia	94 (29.0)	100 (31.3)	194 (30.2)
Hyperlipidemia	137 (42.3)	131 (41.1)	268 (41.7)
Recent vascular history†	32 (9.9)	31 (9.7)	63 (9.8)
Coronary artery bypass grafting	5 (1.5)	4 (1.3)	9 (1.4)
Carotid endarterectomy or stenting	7 (2.2)	5 (1.6)	12 (1.9)
Cerebrovascular accident	5 (1.5)	6 (1.9)	11 (1.7)
Congestive heart failure	6 (1.9)	4 (1.3)	10 (1.6)
Hospitalization for unstable angina	2 (0.6)	2 (0.6)	4 (0.6)
Percutaneous coronary intervention	8 (2.5)	10 (3.1)	18 (2.8)
Peripheral vascular surgery	0	3 (0.9)	3 (0.5)
Previous myocardial infarction	10 (3.1)	13 (4.1)	23 (3.6)
Transient ischemic attack	5 (1.5)	2 (0.6)	7 (1.1)
Concomitant medications			
Diuretics			
ACE inhibitors and diuretics	15 (4.6)	15 (4.7)	30 (4.7)
Angiotensin II antagonists and diuretics	12 (3.7)	7 (2.2)	19 (3.0)
Low-ceiling diuretics and potassium-sparing agents	2 (0.6)	5 (1.6)	7 (1.1)
β-Blocking agents, selective, and other diuretics	1 (0.3)	0	1 (0.2)
High-ceiling diuretics and potassium-sparing agents	0	1 (0.3)	1 (0.2)

Data are mean ± SD or *n* (%). MET, metformin. *Includes American Indian or Alaska Native, Native Hawaiian or other Pacific Islander, or other. †Cardiovascular/vascular diseases within 3 months of the screening visit.

mean ± SE change, −1.67 ± 0.06% [−18.3 ± 0.7 mmol/mol] vs. −1.54 ± 0.06% [−16.8 ± 0.7 mmol/mol]) (Fig. 1*A*). The adjusted between-group difference (95% CI) was −0.13% (−0.30 to 0.03) (−1.4 mmol/mol [−3.3 to 0.3]; P = 0.118). In patients receiving background sulfonylurea treatment, reductions in HbA_{1c} were significantly greater with the addition of DAPA plus SAXA than with INS, with an adjusted mean ± SE change from baseline of −1.76 ± 0.08% (−19.2 ± 0.9 mmol/mol) vs. −1.43 ± 0.08% (−15.6 ± 0.9 mmol/mol) and an adjusted between-group difference (95% CI) of −0.34% (−0.57 to −0.10%) (−3.7 mmol/mol [−6.2 to −1.1]; P = 0.005). Reductions in HbA_{1c} were similar between treatment groups in patients not receiving sulfonylurea, with an adjusted between-group difference (95% CI) of 0.08% (−0.16% to 0.32%) (0.9 mmol/mol [−1.7 to 3.5]; P = 0.501). The treatment-by-stratification factor interaction was statistically significant (P = 0.014).

Body weight in the two treatment arms diverged from baseline (Fig. 1*B*), decreasing and then stabilizing at week 12 in the DAPA plus SAXA group and increasing in the INS group. At week 24, the adjusted mean ± SE change in body weight was −1.50 ± 0.20 kg and +2.14 ± 0.20 kg for the DAPA plus SAXA group and INS group, respectively (difference between treatment groups −3.64 kg [95% CI −4.20 to −3.09]; $P < 0.001$) (Table 2).

A lower proportion of patients had confirmed hypoglycemia in the DAPA plus SAXA group than in the INS group at week 24 (adjusted percentages, 21.3% vs. 38.4%; odds ratio 0.4 [95% CI 0.30–0.62]; $P < 0.001$) (Fig. 1*C*). A greater proportion of patients achieved HbA_{1c} <7.0% (<53 mmol/mol) without hypoglycemia in the DAPA plus SAXA group than in the INS group at week 24 (adjusted percentages, 20.9% [95% CI 16.7–25.8] vs. 13.1% [9.7–17.3]; odds ratio 1.8 [95% CI 1.2–2.7]; P = 0.008).

Mean reductions in 24-h glucose measurements from baseline to week 2 were greater with DAPA plus SAXA treatment than with INS (adjusted mean ± SE change, −48.5 ± 2.5 mg/dL vs. −28.5 ± 2.5 mg/dL; $P < 0.0001$).

The proportion of patients achieving HbA_{1c} <7.0% (<53 mmol/mol) in the DAPA plus SAXA group was similar and noninferior to that in the INS group (adjusted percentages [95% CI], 33.2% [28.0–38.8] vs. 33.5% [28.3–39.3]; odds ratio 1.0 [95% CI 0.70–1.38]; P = 0.924).

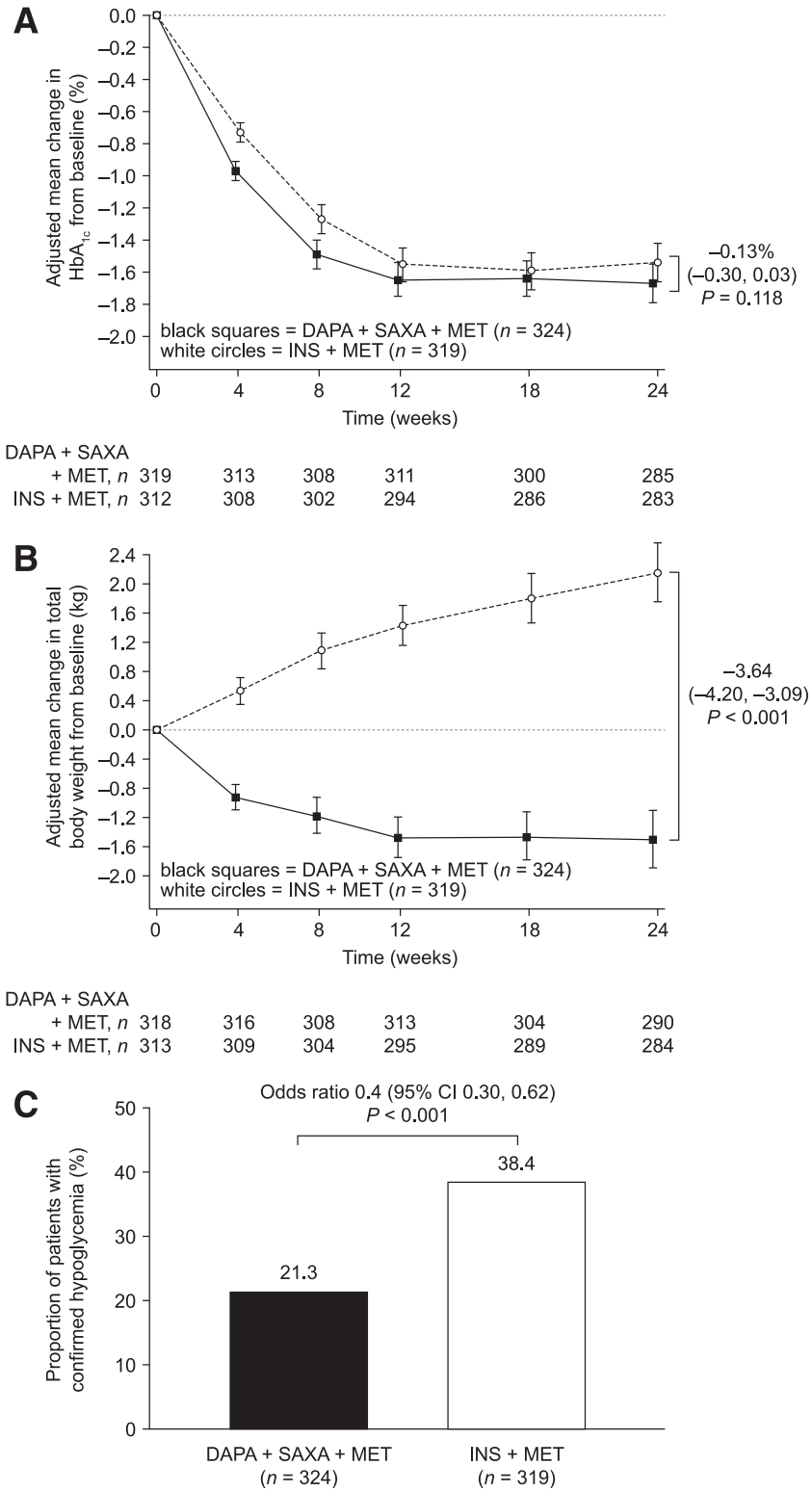

Figure 1—Adjusted mean change from baseline over the 24-week treatment period in HbA_{1c} (*A*) and total body weight (*B*). The error bars show the 95% CIs. *C*: Proportion of patients with confirmed hypoglycemia at week 24, defined as plasma glucose ≤70 mg/dL or symptoms of hypoglycemia with self-monitored blood glucose ≤70 mg/dL. MET, metformin.

Results from the ad hoc analysis showed that a greater proportion of patients achieved HbA_{1c} <7.0% (<53 mmol/mol) without hypoglycemia or

Table 2—Secondary end points

Secondary end point	DAPA + SAXA + MET (*n* = 324)	INS + MET (*n* = 319)	Difference/odds ratio* (95% CI)	*P* value
Body weight, kg				
Baseline mean ± SD	*n* = 319	*n* = 313		
	89.93 ± 17.70	89.36 ± 18.38		
Week 24 mean ± SD	*n* = 290	*n* = 284		
	88.08 ± 17.52	91.81 ± 18.85		
Adjusted mean change from baseline ± SE	−1.50 ± 0.20	2.14 ± 0.20	−3.64 (−4.20 to −3.09)	<0.001
Proportion of patients with confirmed hypoglycemia† at week 24	*n* = 324	*n* = 319		
Patients, *n* (%)	76 (23.5)	127 (39.8)		
Adjusted percentage	21.3	38.4	0.4* (0.30–0.62)	<0.001
Proportion of patients with HbA_{1c} <7.0% without any hypoglycemia† at week 24	*n* = 324	*n* = 319		
Patients, *n* (%)	73 (22.5)	47 (14.7)		
Adjusted percentage	20.9	13.1	1.8* (1.2–2.7)	0.008
24-h glucose readings,‡ mg/dL				
Baseline mean ± SD	*n* = 133	*n* = 133		
	206.7 ± 47.8	200.4 ± 45.6		
Week 2 mean ± SD	*n* = 133	*n* = 133		
	156.9 ± 36.1	173.2 ± 39.4		
Adjusted mean change at week 2 ± SE	−48.6 ± 2.5	−28.5 ± 2.5	−20.0 (−27.0 to −13.0)	<0.0001
24-h glucose readings,‡ mmol/L				
Baseline mean ± SD	*n* = 133	*n* = 133		
	11.5 ± 2.7	11.1 ± 2.5		
Week 2 mean ± SD	*n* = 133	*n* = 133		
	8.7 ± 2.0	9.6 ± 2.2		
Adjusted mean change at week 2 ± SE	−2.7 ± 0.1	−1.6 ± 0.1	−1.1 (−1.5 to −0.7)	<0.0001
Proportion of patients with HbA_{1c} <7.0% at week 24	*n* = 324	*n* = 319		
Patients, *n* (%)	114 (35.2)	113 (35.4)		
Adjusted percentage	33.2	33.5	1.0* (0.70–1.38)	0.924

MET, metformin. *Odds ratio between treatment groups. †Confirmed hypoglycemia was defined as plasma glucose ≤70 mg/dL or symptoms of hypoglycemia with self-monitored blood glucose ≤70 mg/dL. ‡Measured by CGM.

weight gain in the DAPA plus SAXA group than in the INS group at week 24 (adjusted percentages [95% CI], 16.5% [12.7–21.2] vs. 3.2% [1.8–5.7]; odds ratio 6.0 [95% CI 3.1–11.4]; $P < 0.001$). The mean ± SD INS dose at week 24 was 36.6 ± 17.0 units, and mean changes in FPG from baseline are reported in Supplementary Table 1.

Safety

The proportions of patients experiencing AEs were similar in both treatment groups (Table 3). A greater proportion of patients experienced AEs that were determined by the investigator to be related to study drug in the DAPA plus SAXA group than in the INS group (9.6% vs. 3.4%), but none of these events in either treatment group were reported as serious. Few patients discontinued owing to AEs (DAPA + SAXA; 1.9%; INS, 0.3%), and none of these discontinuations were due to hypoglycemia.

Less than 3% of patients experienced serious AEs (SAEs) (DAPA + SAXA, 2.8%; INS, 1.6%). None of the SAEs reported were considered by the investigator to be related to study treatment. One patient in the DAPA plus SAXA group discontinued owing to an SAE.

A lower proportion of patients experienced at least one hypoglycemic event in the DAPA plus SAXA group than in the INS group (25.6% vs. 42.0%). Three patients in the INS group (0.9%) experienced severe hypoglycemia, two of whom were receiving treatment with sulfonylurea. Conversely, no patients in the DAPA plus SAXA group experienced severe hypoglycemia. Urinary tract infections occurred in 3.7% of patients in the DAPA plus SAXA group and in 3.4% of those in the INS group (men, 0.6% vs. 2.3%; women, 7.4% vs. 4.7%, respectively). More patients experienced AEs of genital infections in the DAPA plus SAXA group than in the INS group (3.4% vs. 0.3%); all AEs in the former group were experienced by women. AEs of renal impairment or renal failure were uncommon (DAPA plus SAXA, 1.9%; INS, 0.3%) and included events of increased blood creatinine, decreased estimated glomerular filtration rate, and decreased creatinine renal clearance. None of these events were reported as an SAE. There were no patients with confirmed adjudicated hospitalizations owing to cardiac failure or with adjudicated hepatic AEs and no clinically relevant changes from baseline in urinalysis, lipids, vital signs, electrocardiograms, or physical examinations (Supplementary Tables 2 and 3). AEs of increased or decreased blood pressure and increased heart rate were uncommon (≤0.6%), and no patients in either treatment group experienced an AE that was suggestive of diabetic ketoacidosis during the study period.

One patient in the DAPA plus SAXA group died during the study of respiratory

Table 3—Adverse events

AEs, *n* (%)	DAPA + SAXA + MET *n* = 324	INS + MET *n* = 319
Summary of AEs		
At least one AE	175 (54.0)	180 (56.4)
At least one SAE	9 (2.8)	5 (1.6)
At least one treatment-related AE	31 (9.6)	11 (3.4)
At least one treatment-related SAE	0	0
AE leading to study discontinuation	6 (1.9)	1 (0.3)
SAE leading to study discontinuation	1 (0.3)	0
Deaths	1 (0.3)	0
Hypoglycemia		
At least one event	83 (25.6)	134 (42.0)
At least one event		
During the first 12-week treatment period*†	61 (18.8)	96 (30.1)
During the second 12-week treatment period*†	49 (15.1)	105 (32.9)
At least one event and		
Plasma glucose concentration <54 mg/dL (3 mmol/L)*‡	19 (5.9)	47 (14.7)
A nonmissing plasma glucose concentration <54 mg/dL (3 mmol/L)*	14 (4.3)	38 (11.9)
Severe hypoglycemia	0	3 (0.9)
Hypoglycemia leading to study discontinuation	0	0
Most common AEs (≥2% of patients)		
Viral upper respiratory tract infection	21 (6.5)	15 (4.7)
Upper respiratory tract infection	13 (4.0)	16 (5.0)
Back pain	10 (3.1)	7 (2.2)
Headache	10 (3.1)	22 (6.9)
Urinary tract infection	8 (2.5)	8 (2.5)
Diarrhea	7 (2.2)	10 (3.1)
Dizziness	7 (2.2)	1 (0.3)
Arthralgia	4 (1.2)	9 (2.8)
Cough	3 (0.9)	7 (2.2)
Hypertension	0	7 (2.2)
AEs of special interest		
Genital infection	11 (3.4)	1 (0.3)
Urinary tract infection	12 (3.7)	11 (3.4)
Renal impairment, failure	6 (1.9)	1 (0.3)

Data are regardless of rescue. All data shown were collected during the 24-week treatment period, unless otherwise stated. MET, metformin. *Data from a post hoc analysis. †The sum of the number of patients with at least one hypoglycemic event during the first 12-week treatment period and the number of patients with at least one event during the second 12-week period is not necessarily equal to the number of patients with at least one event during the 24-week treatment period because patients could be counted in both the first 12-week period and the second 12-week period if they had events in both periods. ‡If a patient had a hypoglycemic event and a missing glucose value then the glucose value for that patient was assumed to be <54 mg/dL (3 mmol/L).

failure, which was not considered by the investigator to be related to study treatment.

CONCLUSIONS

This is the first study to evaluate the efficacy and safety of a combination of an SGLT2 inhibitor and a DPP-4i versus titrated insulin in insulin-naive patients with type 2 diabetes inadequately controlled with metformin, with or without sulfonylurea therapy. Oral combination therapy with DAPA (10 mg) and SAXA (5 mg) resulted in noninferior reductions in HbA_{1c} with a beneficial weight profile and a lower prevalence of hypoglycemia versus INS from baseline to week 24. Patients receiving background sulfonylurea therapy showed reductions in HbA_{1c} that were significantly greater with the addition of DAPA plus SAXA than with INS, whereas those not receiving a sulfonylurea showed similar reductions in HbA_{1c} between the treatment groups.

After 24 weeks of treatment, patients treated with DAPA plus SAXA had a clinically relevant and sustained body weight change from baseline that was significantly greater (by 3.64 kg) than that for patients in the INS group, indicating that DAPA plus SAXA treatment prevents body weight gain. This finding supports results from previous studies showing that treatment with DAPA alone or with SAXA is associated with body weight reduction, whereas INS treatment induces body weight gain (7,10,12,13), and is in line with the reported weight neutrality of SAXA and the weight-reducing effect of DAPA through reductions in total body fat mass, visceral adipose tissue, and subcutaneous adipose tissue (12,17).

Furthermore, fewer patients had confirmed hypoglycemia and experienced at least one hypoglycemic event, and more patients in the DAPA plus SAXA group had a therapeutic glycemic response (HbA_{1c} <7.0% [<53 mmol/mol]) without hypoglycemia than in the INS group from baseline to week 24. These findings corroborate previous evidence that, unlike insulin, treatment with DAPA and SAXA is associated with a low risk of hypoglycemia (7–12).

Patients receiving DAPA plus SAXA treatment showed significantly greater

mean reductions in 24-h glucose readings measured by CGM than those receiving INS from baseline to week 2. This result suggests that DAPA plus SAXA reduces 24-h glucose readings rapidly compared with INS, although it should be noted that the INS dose was not optimized by this time point. However, this finding is of interest because some health care professionals may prefer to initiate insulin therapy in patients with high glucose levels and not feel confident to treat them with an oral combination therapy, but we show here that there is a more rapid initial decline in glucose levels in these patients with an oral combination. More extensive CGM data from this patient population will be presented in a subsequent publication.

There were no unexpected AEs or safety findings in the current study. The safety and tolerability profile of DAPA plus SAXA was consistent with that reported in previous studies (7–12). The proportions of patients experiencing AEs and SAEs were similar between treatment groups.

In a previous randomized, open-label trial, add-on therapy with the DPP-4i sitagliptin was compared with INS in insulin-naive patients with type 2 diabetes inadequately controlled with metformin (18). In contrast with the current study, the adjusted mean reduction in HbA_{1c} with sitagliptin after 24 weeks was inferior to that with INS (adjusted mean ± SE change, −1.13 ± 0.06% vs. −1.72 ± 0.06%; $P < 0.0001$). Like DAPA plus SAXA combination therapy, sitagliptin treatment resulted in a lower prevalence of hypoglycemia than insulin (sitagliptin, 13%; insulin, 46%) and a change in weight that was different from the change in weight with insulin (adjusted mean change ± SE from baseline: sitagliptin, −1.08 ± 0.20 kg; insulin, 0.44 ± 0.22 kg; $P < 0.0001$). However, the adjusted mean difference between treatment groups in the sitagliptin study was considerably less than in the current study (−1.51 kg vs. −3.64 kg). Taken together, results from these studies suggest that using DPP-4is in combination with SGLT2 inhibitors produces more favorable and clinically relevant reductions in HbA_{1c} that are comparable to insulin, and, as expected, greater reductions in body weight than using DPP-4is alone.

Overall, the current study shows that adding an oral combination therapy of DAPA plus SAXA to patients with type 2 diabetes poorly controlled with metformin, with or without sulfonylureas, achieves similar glycemic control to adding INS therapy by injection, with the added benefits of prevention of weight gain and a lower risk of hypoglycemia. These results are particularly promising because patients included in the study had very high baseline HbA_{1c} levels (mean ± SD, 9.1 ± 1.0% [76.0 ± 10.9 mmol/mol]); and, therefore, addition of a single oral glucose-lowering agent is unlikely to achieve sufficient reductions in HbA_{1c} levels. Hence, the oral treatment is efficient and a valid alternative to insulin for patients with very high glucose levels. A low prevalence of hypoglycemic AEs is associated with a low risk of cardiovascular disease and cognitive impairment and a greater quality of life (19,20). Results from recent randomized trials and observational studies indicate that SGLT2 inhibitors probably have a similarly, or more, beneficial cardiovascular disease protective effect than insulin (21–24). Patients place a high value on body weight loss when considering desirable health improvements associated with glucose-lowering therapies for the treatment of type 2 diabetes (25). Oral administration of glucose-lowering drugs is often preferred to injection by both patients and health care professionals because insulin injection is associated with psychological resistance from patients and the need for more resources from health care providers (25,26). These factors, together with results from the current study, support a treatment strategy for patients with uncontrolled type 2 diabetes of adding oral, noninsulin glucose-lowering drugs rather than basal insulin.

Important strengths of the current study include the randomized and multinational design. Limitations include that the study was not blinded, although it should be noted that both patient groups received active treatments, and was relatively short in duration. Another limitation was that INS was not titrated beyond 12 weeks, and therefore the titration regimen could have been made more aggressive. However, basal insulin dose titration in clinical practice is often delayed and not optimized, partly due to fear of hypoglycemia, an increase in body weight, failure to titrate in the absence of symptoms, and low patient motivation (27,28); therefore, it is unlikely that patients and health care professionals could follow a more strict protocol for titration than performed here. Moreover, the greater risks of hypoglycemia and weight gain found with the current insulin titration regimen would likely have been more prominent if the regimen had been more aggressive. Similar algorithms for INS titration have been used in other studies adding INS to patients treated with metformin plus sulfonylureas and have produced similar FPG levels as shown here (29). Other studies adding INS to oral therapies may have used somewhat less, as well as more, aggressive titration algorithms than the one used here (30,31).

In conclusion, adding an oral therapy with DAPA plus SAXA in patients with poorly controlled type 2 diabetes treated with metformin, with or without sulfonylureas, achieves similar glycemic control and a lower risk of hypoglycemia, and results in a clinically relevant weight difference compared with basal insulin. Hence, DAPA plus SAXA is a therapeutically valid alternative in insulin-naive patients for achieving HbA_{1c} targets. This combination therapy could therefore have a positive impact on patient care and clinical practice, compared with insulin, owing to easier administration, lower health care resource utilization, and increased patient well-being due to fewer hypoglycemic events and prevention of weight gain. The results of a long-term extension study, which are to be reported separately, will help to assess the durability of these effects.

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