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Triple therapy with low-dose dapagliflozin plus saxagliptin versus dual therapy with each monocomponent, all added to metformin, in uncontrolled type 2 diabetes

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Abstract

Aim: To evaluate the efficacy and safety of triple therapy with low-dose dapagliflozin plus saxagliptin added to metformin in uncontrolled type 2 diabetes.

Materials and methods: This 24-week, double-blind trial (NCT02681094) randomized 883 patients (glycated haemoglobin [HbA1c] 7.5-10.0%) on metformin ≥1500 mg/d to add-on dapagliflozin 5 mg/d plus saxagliptin 5 mg/d or to add-on of either monocomponent. The primary endpoint was change in HbA1c from baseline.

Results: Baseline mean ± SD patient characteristics were: age 56.7 ± 10.5 years; HbA1c 8.2 ± 0.9%; and diabetes duration 7.6 ± 6.1 years. Triple therapy significantly decreased HbA1c versus dual therapy (−1.03% vs. −0.63% [dapagliflozin] vs. −0.69% [saxagliptin]; $P < .0001$). More patients achieved HbA1c <7.0% with triple versus dual therapy (41.6% vs. 21.8% [dapagliflozin; $P < .0001$] vs. 29.8% [saxagliptin; $P = .0018$]). Triple therapy significantly decreased fasting plasma glucose (−1.5 mmol/L vs. −1.1 mmol/L [dapagliflozin; $P = .0135$] vs. −0.7 mmol/L [saxagliptin; $P < .0001$]) and body weight (−2.0 kg vs. −0.4 kg [saxagliptin; $P < .0001$]), and β-hydroxybutyrate levels were lower than with dapagliflozin plus metformin (mean difference −0.51; $P = .0009$). Urinary tract/genital infections and hypoglycaemia occurred in <5.0% and 5.8% of patients, respectively, with triple therapy.

Conclusions: Triple therapy with once-daily dapagliflozin 5 mg, saxagliptin 5 mg and metformin significantly improved glycaemic control versus dual therapy with either agent added to metformin in uncontrolled type 2 diabetes, and was generally well tolerated.

KEYWORDS

dapagliflozin, metformin, phase III study, randomized trial, SGLT2 inhibitor, type 2 diabetes

1 | INTRODUCTION

Although achievement of optimal glycaemic control is an important aim of type 2 diabetes treatment, available data indicate poor attainment of glycaemic targets in clinical practice.[1,2] Clinical inertia, defined as failure to intensify anti-hyperglycaemic therapy in a timely manner,[3] has been proposed as one explanation for these findings when sequential therapy is used. Although many factors contribute to

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clinical inertia,[4] this traditional sequential treatment paradigm for type 2 diabetes, comprising stepwise addition of anti-hyperglycaemic agents to initial metformin monotherapy in response to increased glycated haemoglobin (HbA1c) levels, may be a major reason why some patients experience delays in reaching their glycaemic goals.[5-7]

An alternative approach to type 2 diabetes treatment is simultaneous combination therapy with anti-hyperglycaemic agents that have complementary mechanisms of action, and therefore target multiple physiological defects. Several studies have shown that first-line dual therapy, combining anti-hyperglycaemic agents, had greater efficacy than the components as monotherapies,[8-11] without increasing the risk of hypoglycaemia. In a 24-week study in patients with baseline HbA1c 8.0% to 12.0% and in whom metformin failed, triple therapy achieved by concomitant dual addition of the sodium-glucose co-transporter-2 (SGLT2) inhibitor dapagliflozin (highest dose of 10 mg/d) and the dipeptidyl peptidase-4 (DPP-4) inhibitor saxagliptin (5 mg/d) led to greater HbA1c reductions than the addition of either agent alone to metformin.[12] In addition, a recent 24-week trial demonstrated that the same triple therapy combination had greater glucose-lowering efficacy, and was associated with substantially lower incidence of hypoglycaemia, than glimepiride, a sulphonylurea, added on to metformin.[13]

Initiating simultaneous combination therapy at early stages of the disease, rather than by the sequential stepwise approach, may permit earlier achievement of glycaemic goals, more durable efficacy, and better preservation of β-cell function than gradual treatment intensification,[14-17] and might also enable a greater proportion of patients to meet their glycaemic targets than at present. However, there is still no clear consensus on whether the benefit-risk profile of this more proactive approach is superior to the sequential approach, or on for which patients early combination therapy would be most appropriate. Indeed, clinical guidelines differ in terms of the HbA1c level at which initial combination therapy is recommended. A recent Consensus Report by the American Diabetes Association (ADA) and the European Association for the Study of Diabetes (EASD) recommends the use of combination therapy in patients who present with an HbA1c level that is >1.5% above an individualized HbA1c target, based on the knowledge that most oral glucose-lowering therapies do not result in HbA1c reductions of >1.0% when given as monotherapies.[18] By contrast, guidelines from the American Association of Clinical Endocrinologists (AACE) recommend the use of initial combination therapy in patients with an HbA1c level ≥ 7.5%.[7]

The aim of the present study was to evaluate the efficacy and safety of triple oral therapy using the lower dapagliflozin dose of 5 mg/d plus saxagliptin 5 mg/d plus metformin ≥1500 mg/d, versus dual therapy with each monocomponent (low-dose dapagliflozin 5 mg/d or saxagliptin 5 mg/d plus metformin ≥1500 mg/d) in patients with uncontrolled type 2 diabetes (HbA1c 7.5-10.0%).[12] Dapagliflozin 5 mg, a lower dose than was used in previous studies of this triple therapy combination,[12,13] was chosen for this study because it is the recommended starting dose in the USA[19] and because entry criteria for HbA1c levels were lower than those in the previous studies.

2 | MATERIALS AND METHODS

2.1 | Study design

This was a 24-week, multicentre, randomized, parallel-group, double-blind, active-controlled phase III study (NCT02681094), conducted at 119 centres in Canada, the Czech Republic, Germany, Mexico, Russia, and the USA. Local regulatory authorities and the responsible ethics committees/institutional review boards of the participating centres approved the study protocol, and all participants provided written informed consent. 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 Harmonization.

2.1.1 | Participants

Patients were eligible for inclusion in the study if they fulfilled the following criteria: age ≥ 18 years; diagnosis of type 2 diabetes; stable metformin dose (≥1500 mg/d) for ≥8 weeks before enrolment; body mass index ≤45 kg/m^2; fasting plasma glucose (FPG) ≤15 mmol/L (≤270 mg/dL); and HbA1c 7.5% to 10.0%. Major exclusion criteria included: a cardiovascular event in the 3 months before enrolment; moderate or severe impairment of renal function (estimated glomerular filtration rate [eGFR] of <60 mL/min/1.73 m^2 or serum creatinine ≥1.5 mg/dL for men, or ≥ 1.4 mg/dL for women]); presence or history of severe (New York Heart Association class III and IV) congestive heart failure; and/or unstable or acute congestive heart failure.

2.1.2 | Treatments

The study comprised screening and enrolment visits, after which participants completed a randomization visit, followed by a 24-week, double-blind treatment phase (Figure 1A). At the randomization visit, participants were randomized (1:1:1) to one of three treatment arms using an interactive voice response system: (a) dapagliflozin 5 mg plus saxagliptin 5 mg, (b) dapagliflozin 5 mg plus saxagliptin placebo, or (c) saxagliptin 5 mg plus dapagliflozin placebo, each added on to the patient's existing metformin treatment. Participants, investigators, and study site personnel were blinded to treatment assignment throughout the study. Participants were eligible for open-label rescue with dapagliflozin 10 mg/d plus saxagliptin 5 mg/d, or with insulin (the dose administered was at the investigator's discretion and based on the participant's need), from week 6 of the study onwards. The criteria for rescue medication were as follows: week 6, FPG >15.0 mmol/L (270 mg/dL); weeks 6 to 12, FPG >13.3 mmol/L (240 mg/dL); weeks 12 to 24, FPG >11.1 mmol/L (200 mg/dL).

2.2 | Endpoints and assessments

The primary efficacy endpoint was the mean change in HbA1c from baseline to week 24. Secondary endpoints included: the proportion of participants achieving a therapeutic glycaemic response, defined as

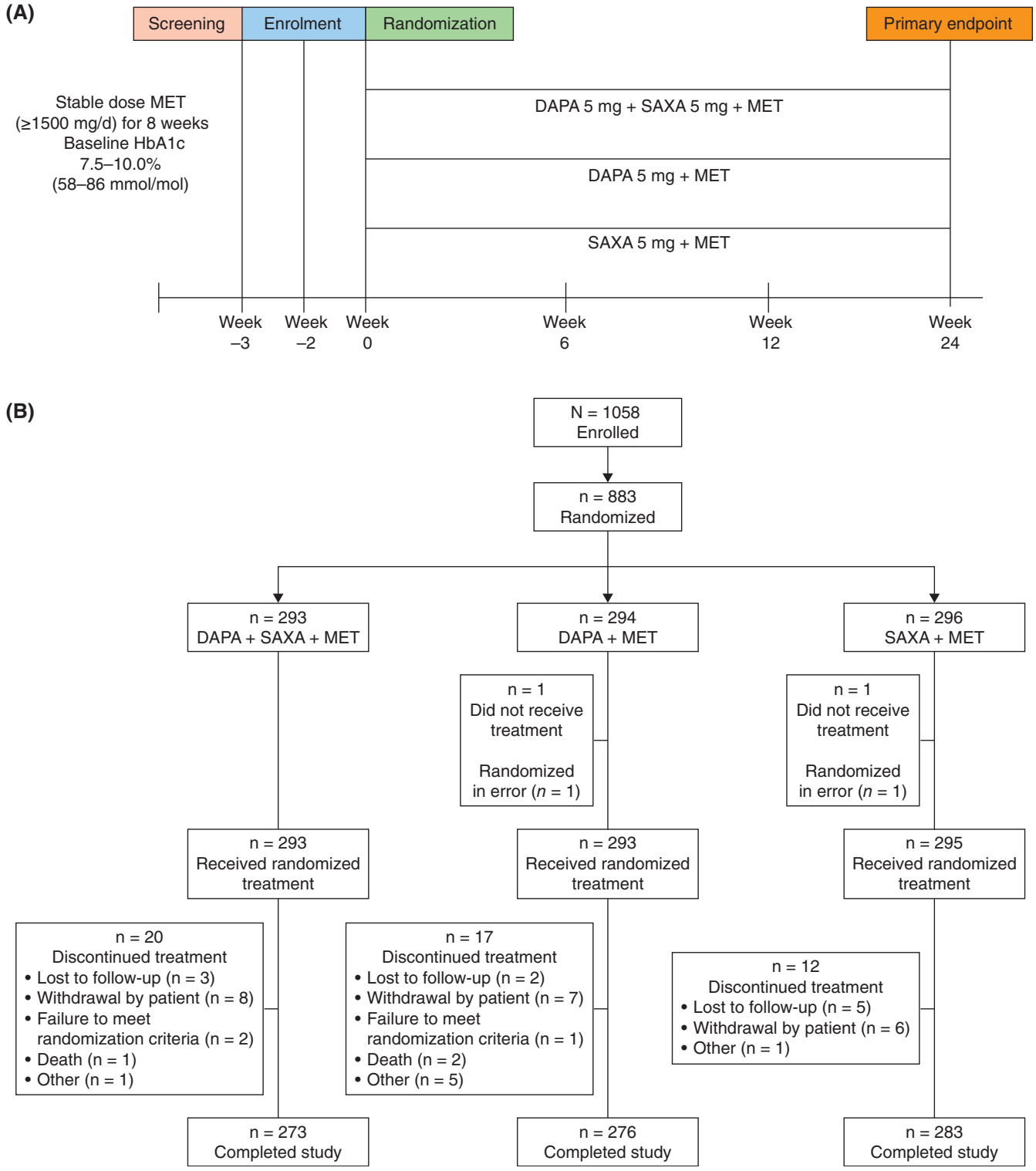

FIGURE 1 A, Study design and B, participant disposition. DAPA, dapagliflozin; HbA1c, glycated haemoglobin; MET, metformin; SAXA, saxagliptin

HbA1c <7.0% at week 24; the change from baseline to week 24 in FPG; and the change from baseline to week 24 in total body weight. Exploratory endpoints included: mean change from baseline to week 24 in blood levels of ketones, specifically β-hydroxybutyrate, as SGLT2 inhibitors have been associated with a small but significant risk of ketoacidosis[19]; and mean changes from baseline in systolic (SBP) and diastolic blood pressure (DBP) at week 24.

Safety endpoints included the incidence of adverse events (AEs) and hypoglycaemia, as well as findings from physical examinations and clinical laboratory evaluations. Hypoglycaemic events were

classified in accordance with the 2013 ADA criteria[20] as follows: severe hypoglycaemia, defined as an event requiring assistance of another person to administer carbohydrate, glucagon, or other resuscitative actions actively; documented symptomatic hypoglycaemia, defined as typical symptoms of hypoglycaemia accompanied by a measured plasma glucose concentration of ≤3.9 mmol/L (70 mg/dL); and asymptomatic hypoglycaemia, defined as an event not accompanied by typical symptoms of hypoglycaemia but with a measured plasma glucose concentration of ≤3.9 mmol/L (70 mg/dL). Hypoglycaemic events could fall under more than one category.

2.3 | Statistical methods

The sample size was determined assuming a 0.3% difference in the mean change in HbA1c from baseline to week 24 for triple therapy with dapagliflozin plus saxagliptin plus metformin, versus the monocomponents added to metformin. Calculations used a common SD of 1.0%, a two-sided significance level of 0.05 for the comparison, and an assumed non-evaluability rate of 3.0%. A total of 300 randomized participants per group were required to provide at least 90% power for the comparison among the treatment groups.

All efficacy analyses were conducted on the full analysis set, which comprised all randomized patients who received at least one dose of study medication during the double-blind treatment period and who had a baseline HbA_{1c} measurement. Unless specified, analyses included values before rescue or treatment discontinuation.

The primary efficacy endpoint was analysed using a longitudinal repeated measures model, adjusted for treatment, week, baseline HbA1c, treatment-by-week interaction, and baseline HbA1c-by-week interaction. Sensitivity analyses were conducted for the primary endpoint using data up until the date of rescue medication or treatment discontinuation. Treatment-by-subgroup interactions were tested for the following variables: sex, region, baseline HbA1c, and age.

The proportion of participants achieving a therapeutic glycaemic response at week 24 was compared between treatment groups using the methodology of Zhang et al[21] and Tsiatis et al.[22] The analysis of change from baseline in FPG and total body weight was performed using the same model as for the primary endpoint. To protect the overall type 1 error rate, secondary endpoints were assessed for significance using a stepwise testing procedure. The order of testing was as follows: proportion of participants achieving a therapeutic glycaemic response; mean change from baseline in FPG at week 24; and mean change in total body weight at week 24. For each endpoint, dapagliflozin plus saxagliptin plus metformin was compared with the dapagliflozin plus metformin treatment group, before comparison with the saxagliptin plus metformin group. Exploratory efficacy endpoints were analysed using a similar model as for the primary and secondary endpoints. Exploratory endpoints were not included in the stepwise testing procedure; however, nominal *P* values are reported. All safety analyses were performed on the safety analysis dataset, which consisted of participants who received at least one dose of study medication; safety data were summarized using descriptive statistics.

3 | RESULTS

3.1 | Participant characteristics

The first participant was enrolled on 26 February 2016 and the last completed the study on 15 July 2017. The participant disposition flow diagram for this study is shown in Figure 1B. In total, 1058 participants were enrolled in the study, and 883 were randomized, of whom 832 (94.2%) completed the study. In all treatment groups, the main reason for study discontinuation was participant withdrawal (dapagliflozin plus saxagliptin plus metformin, 2.7%; dapagliflozin plus metformin, 2.4%; saxagliptin plus metformin, 2.0%).

Baseline demographic and diabetes characteristics were balanced across treatment groups (Table 1). Overall, 51.8% of participants were men, most (89.7%) were white, and the mean ± SD patient age and body mass index were 56.7 ± 10.5 years and 31.9 ± 5.4 kg/m^2, respectively. The mean ± SD duration of type 2 diabetes, HbA1c concentration, and FPG concentration were 7.6 ± 6.1 years, 8.2 ± 0.9%, and 9.8 ± 2.5 mmol/L, respectively.

3.2 | Extent of exposure

During the 24-week study period, the mean duration of treatment exposure was similar across treatment groups (range 155-156 days). Overall, only 4.4% of all patients required rescue therapy, but the proportion was substantially less with dapagliflozin plus saxagliptin (1.4%) than with dapagliflozin (3.1%) or saxagliptin (8.8%) individually, and none of these participants required further rescue with insulin.

3.3 | Efficacy

3.3.1 | Primary efficacy variable

The adjusted mean ± SE change from baseline in HbA1c at 24 weeks was significantly greater with dapagliflozin plus saxagliptin plus metformin than with either dapagliflozin or saxagliptin plus metformin (−1.03 ± 0.06% vs. −0.63 ± 0.06% vs. −0.69 ± 0.06%; $P < .0001$ for both comparisons [Figure 2A and Table 2]). Changes in HbA1c after 6 and 12 weeks of treatment were nominally significantly greater with dapagliflozin plus saxagliptin plus metformin than with either dapagliflozin or saxagliptin plus metformin (Figure 2B). The final mean HbA1c values in each group were 7.1 ± 0.9%, 7.6 ± 1.0%, and 7.6 ± 1.1%, respectively. There was no evidence of effects of sex, region, baseline HbA1c, or age on these results, as indicated by non-significant *P* values at the .05 level in analyses of treatment-by-subgroup interactions (sex, $P = .73$; region, $P = .73$; baseline HbA1c, $P = .59$; age, $P = .68$).

3.3.2 | Secondary efficacy variables

The proportion of participants who achieved HbA1c levels of <7.0% was significantly greater with dapagliflozin plus saxagliptin plus metformin than with dapagliflozin or saxagliptin plus metformin (adjusted response rate 41.6% [95% CI 36.0, 47.1] vs. 21.8% [95% CI 17.2,

TABLE 1 Participant demographics and baseline characteristics (full analysis set)

Variable	DAPA + SAXA + MET (N = 290)	DAPA + MET (N = 289)	SAXA + MET (N = 291)	Total (N = 870)
Sex, n (%)				
Women	148 (51.0)	137 (47.4)	134 (46.0)	419 (48.2)
Men	142 (49.0)	152 (52.6)	157 (54.0)	451 (51.8)
Ethnicity, n (%)				
White	265 (91.4)	257 (88.9)	258 (88.7)	780 (89.7)
Black/African American	10 (3.4)	17 (5.9)	24 (8.2)	51 (5.9)
Asian	9 (3.1)	9 (3.1)	6 (2.1)	24 (2.8)
Native American/Alaskan native	1 (0.3)	3 (1.0)	0	4 (0.5)
Other	5 (1.7)	3 (1.0)	3 (1.0)	11 (1.3)
Age, mean ± SD, years	57.2 ± 10.7	55.9 ± 10.9	57.0 ± 9.9	56.7 ± 10.5
Weight, mean ± SD, kg	87.2 ± 18.7	89.5 ± 17.8	92.3 ± 18.7	89.6 ± 18.5
BMI, mean ± SD, kg/m^2	31.5 ± 5.5	31.8 ± 5.2	32.4 ± 5.5	31.9 ± 5.4
Duration of type 2 diabetes, mean ± SD, years	7.5 ± 6.3	7.6 ± 6.3	7.8 ± 5.8	7.6 ± 6.1
SBP, mean ± SD, mmHg[a]	130.0 ± 12.6	130.2 ± 13.3	130.8 ± 12.7	–
HbA1c, mean ± SD, %	8.1 ± 0.9	8.2 ± 0.9	8.3 ± 1.0	8.2 ± 0.9
HbA1c category, n (%)				
≤8.0%	140 (48.3)	136 (47.1)	129 (44.3)	405 (46.6)
>8.0%	150 (51.7)	153 (52.9)	162 (55.7)	465 (53.4)
FPG level, mean ± SD, mmol/L	9.5 ± 2.4	9.8 ± 2.5	10.0 ± 2.6	9.8 ± 2.5

Abbreviations: BMI, body mass index; DAPA, dapagliflozin; FPG, fasting plasma glucose; HbA1c, glycated haemoglobin; MET, metformin; SAXA, saxagliptin; SBP, systolic blood pressure.
[a]Values are for the safety analysis set.

26.4] vs. 29.8% [95% CI 24.9, 34.8]; $P < .0001$ and $P = .0018$ for comparisons vs. dapagliflozin plus metformin and saxagliptin plus metformin, respectively [Table 2]). Reductions in FPG from baseline were significantly greater with dapagliflozin plus saxagliptin plus metformin than with dapagliflozin or saxagliptin plus metformin (adjusted mean ± SE change, −1.5 ± 0.1 mmol/L vs. −1.1 ± 0.1 mmol/L vs. −0.7 ± 0.1 mmol/L; $P = .0135$ and $P < .0001$ for comparisons vs. dapagliflozin plus metformin and saxagliptin plus metformin, respectively; Table 2). Reductions in total body weight from baseline were significantly greater with dapagliflozin plus saxagliptin plus metformin than with saxagliptin plus metformin (adjusted mean ± SE change −2.0 ± 0.2 kg vs. −0.4 ± 0.2 kg; $P < .0001$ [Table 2 and Figure 2C]). Changes in body weight after 6 and 12 weeks of treatment were nominally significantly greater with dapagliflozin plus saxagliptin plus metformin than with saxagliptin plus metformin (Figure 2D).

3.3.3 | Exploratory efficacy variables

Treatment with saxagliptin plus metformin had a negligible impact on blood β-hydroxybutyrate levels (adjusted mean ± SE increase of 0.10 ± 0.10 mg/dL from baseline), whereas dapagliflozin plus metformin induced a mean increase of 0.64 ± 0.11 mg/dL that was prevented with addition of saxagliptin (mean ± SE change in blood β-hydroxybutyrate levels with dapagliflozin plus saxagliptin plus metformin: 0.13 ± 0.11 mg/dL [Table 2 and Figure S1]). The combination of dapagliflozin, saxagliptin and metformin was associated with significantly lower β-hydroxybutyrate levels than dapagliflozin plus metformin (least-squares mean difference − 0.51 [95% CI −0.81, −0.21]; $P = .0009$).

At week 24, SBP decreased in all treatment groups, with no significant difference in the mean change from baseline between groups (Table 2). The mean change from baseline in DBP was significantly greater with dapagliflozin plus saxagliptin plus metformin than with saxagliptin plus metformin (nominal $P = .0025$). The mean changes from baseline in DBP did not differ significantly between dapagliflozin plus saxagliptin plus metformin and dapagliflozin plus metformin.

3.4 | Safety and tolerability

The proportions of participants reporting at least one AE were 41.3%, 42.0%, and 39.3% for dapagliflozin plus saxagliptin plus metformin, dapagliflozin plus metformin, and saxagliptin plus metformin,

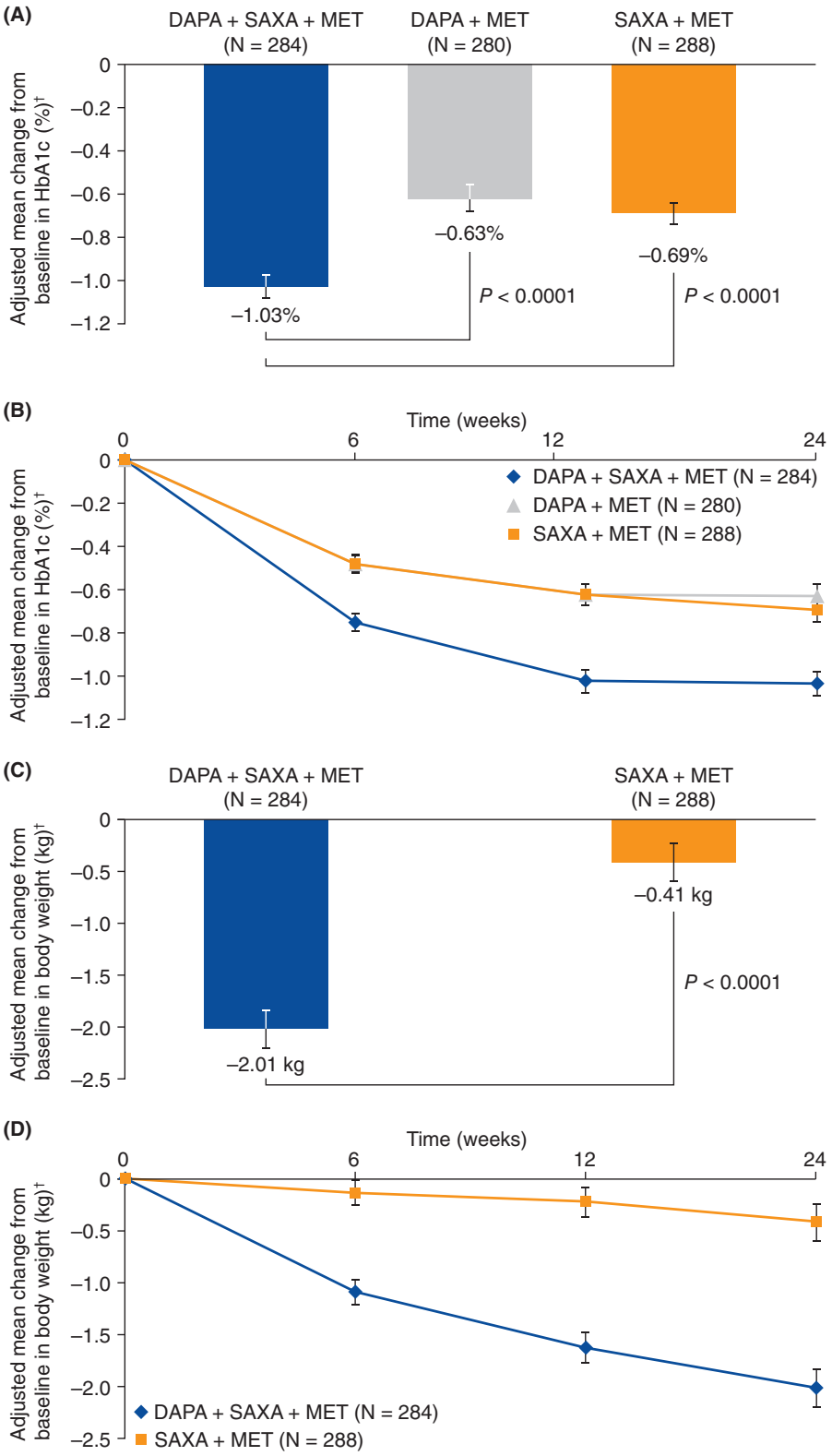

FIGURE 2 Adjusted mean change in glycated HbA1c levels A, over time and B, from baseline to week 24 and adjusted mean change in body weight C, over time and D, from baseline to week 24 (full analysis set). †All values are least-squares mean ± SE. The mixed model of repeated measures includes fixed effects for treatment, week, baseline value, treatment-by-week interaction, and baseline-by-week interaction. DAPA, dapagliflozin; HbA1c, glycated haemoglobin; MET, metformin; SAXA, saxagliptin

respectively (Table 3). The most commonly reported AEs with dapagliflozin plus saxagliptin plus metformin were decreased eGFR (4.1%), urinary tract infection (UTI; 2.4%), and pollakiuria (2.4%). With dapagliflozin plus metformin, the most commonly reported AEs were decreased eGFR (3.8%), viral upper respiratory tract infection (3.1%), and influenza (3.1%). With saxagliptin plus metformin, viral or non-viral upper respiratory tract infections (2.7% and 2.0%) were the most commonly reported AEs (Table 3).

The proportion of participants reporting AEs of UTIs or genital infections overall was slightly higher with dapagliflozin plus saxagliptin plus metformin (UTIs 3.1%, genital infections 3.4%) than with dapagliflozin plus metformin (UTIs 2.0%, genital infections 1.7%) or

TABLE 2 Efficacy endpoints at 24 weeks before rescue (full analysis set)

Efficacy endpoint at week 24	DAPA + SAXA + MET (N = 290)	DAPA + MET (N = 289)	SAXA + MET (N = 291)
HbA1c			
Baseline mean ± SD, %	8.1 ± 0.9	8.2 ± 0.9	8.3 ± 1.0
Week 24 mean ± SD, %	7.1 ± 0.9	7.6 ± 1.0	7.6 ± 1.1
Adjusted mean change from baseline ± SE, %[a]	N = 284 −1.03 ± 0.06	N = 280 −0.63 ± 0.06	N = 288 −0.69 ± 0.06
Difference vs. DAPA + SAXA + MET (95% CI)	–	−0.40 (−0.55, −0.24)	−0.34 (−0.50, −0.19)
P value vs. DAPA + SAXA + MET	–	< 0.0001	< 0.0001
Patients achieving HbA1c <7.0%			
Number of responders	124	63	83
Adjusted response rate, % (95% CI)[b]	41.6 (36.0, 47.1)	21.8 (17.2, 26.4)	29.8 (24.9, 34.8)
Difference vs. DAPA + SAXA + MET (95% CI), %	–	19.8 (12.7, 26.9)	11.8 (4.4, 19.1)
P value vs. DAPA + SAXA + MET	–	< 0.0001	0.0018
FPG level			
Adjusted mean change from baseline ± SE, mmol/L[a]	N = 284 −1.5 ± 0.1	N = 278 −1.1 ± 0.1	N = 287 −0.7 ± 0.1
Difference vs. DAPA + SAXA + MET (95% CI), mmol/L	–	−0.4 (−0.8, −0.1)	−0.8 (−1.2, −0.5)
P value vs. DAPA + SAXA + MET	–	0.0135	< 0.0001
Total body weight			
Adjusted mean change from baseline ± SE, kg[a]	N = 284 −2.0 ± 0.2	–[c]	N = 288 −0.4 ± 0.2
Difference vs. DAPA + SAXA + MET (95% CI), kg	–	–	−1.6 (−2.1, −1.1)
P value vs. DAPA + SAXA + MET	–	–	< 0.0001
Ketone (β-hydroxybutyrate) level			
Adjusted mean change from baseline ± SE, mg/dL[d]	N = 142 0.13 ± 0.11	N = 137 0.64 ± 0.11	N = 150 0.10 ± 0.10
Difference vs. DAPA + MET or SAXA + MET (95% CI), mg/dL	DAPA + MET: −0.51 (−0.81, −0.21) SAXA + MET: 0.03 (−0.26, −0.33)	–	–
P value vs. DAPA + MET or SAXA + MET	DAPA + MET: 0.0009 SAXA + MET: 0.8200	–	–
SBP			
Adjusted mean change from baseline ± SE, mmHg[a]	−2.36 ± 0.64	−1.80 ± 0.64	−0.79 ± 0.63
Difference vs. DAPA + SAXA + MET (95% CI), mmHg	–	−0.56 (−2.33, 1.21)	−1.57 (−3.33, 0.19)
P value vs. DAPA + SAXA + MET	–	0.5376	0.0800
DBP			
Adjusted mean change from baseline ± SE, mmHg[a]	−2.20 ± 0.42	−1.36 ± 0.42	−0.41 ± 0.42
Difference vs. DAPA + SAXA + MET (95% CI), mmHg	–	−0.84 (−2.01, 0.33)	−1.79 (−2.95, −0.63)
P value vs. DAPA + SAXA + MET	–	0.1589	0.0025

Abbreviations: CI, confidence interval; DAPA, dapagliflozin; DBP, diastolic blood pressure; FPG, fasting plasma glucose; HbA1c, glycated haemoglobin; LS, least squares; MET, metformin; MMRM, mixed model of repeated measures; SAXA, saxagliptin; SBP, systolic blood pressure.

[a]Values are LS mean estimates. The MMRM includes fixed effects for treatment, week, baseline value, treatment-by-week interaction, and baseline-by-week interaction.

[b]Comparison between treatment groups was performed using the methodology of Zhang et al.[21]

[c]Difference in the change in total body weight between DAPA + SAXA + MET and DAPA + MET was not a prespecified analysis in this study.

[d]Values are LS mean estimates. The MMRM includes fixed effects for treatment, week, and baseline β-hydroxybutyrate value.

TABLE 3 Treatment-emergent adverse events (safety analysis set)

AE category	DAPA + SAXA + MET (N = 293)	DAPA + MET (N = 293)	SAXA + MET (N = 295)
Patients with ≥1 AE, n (%)	121 (41.3)	123 (42.0)	116 (39.3)
Patients with ≥1 treatment-related AE, n (%)	39 (13.3)	32 (10.9)	14 (4.7)
Patients with an AE leading to discontinuation of study medication, n (%)	19 (6.5)	15 (5.1)	6 (2.0)
Patients with ≥1 SAE, n (%)	7 (2.4)	8 (2.7)	7 (2.4)
Patients with ≥1 treatment-related SAE, n (%)	0	0	0
Most common AEs by preferred term (frequency of ≥2% of patients)			
Decreased eGFR, n (%)	12 (4.1)	11 (3.8)	5 (1.7)
UTI, n (%)	7 (2.4)	3 (1.0)	5 (1.7)
Pollakiuria, n (%)	7 (2.4)	1 (0.3)	0
Nausea, n (%)	6 (2.0)	5 (1.7)	3 (1.0)
Viral upper respiratory tract infection, n (%)	5 (1.7)	9 (3.1)	8 (2.7)
Influenza, n (%)	3 (1.0)	9 (3.1)	3 (1.0)
Upper respiratory tract infection, n (%)	3 (1.0)	4 (1.4)	6 (2.0)
AEs of special interest[a]			
Renal impairment or failure, n (%)	16 (5.5)	12 (4.1)	6 (2.0)
UTI (overall analysis), n (%)	9 (3.1)	6 (2.0)	7 (2.4)
Women	7 (4.7)	5 (1.4)	7 (5.1)
Men	2 (1.4)	1 (0.6)	0
Genital infection (overall analysis), n (%)	10 (3.4)	5 (1.7)	0
Women	6 (4.1)	1 (0.7)	0
Men	4 (2.8)	4 (2.6)	0
Hypoglycaemia events[b]			
Any, n (%)	17 (5.8)	8 (2.7)	10 (3.4)
Severe, n (%)	1 (0.3)	1 (0.3)	0
Documented symptomatic, n (%)	6 (2.0)	1 (0.3)	4 (1.4)
Asymptomatic, n (%)	6 (2.0)	7 (2.4)	6 (2.0)

Abbreviations: AE, adverse event; DAPA, dapagliflozin; eGFR, estimated glomerular filtration rate; MET, metformin; SAE, serious adverse event; SAXA, saxagliptin; UTI, urinary tract infection.

[a]Based on a group of terms, rather than one preferred term.

[b]Severe hypoglycaemia, an event requiring assistance of another person to administer carbohydrate, glucagon, or other resuscitative actions actively; documented symptomatic hypoglycaemia, typical symptoms of hypoglycaemia accompanied by a measured plasma glucose concentration of ≤3.9 mmol/L (70 mg/dL); asymptomatic hypoglycaemia, an event not accompanied by typical symptoms of hypoglycaemia but with a measured plasma glucose concentration of ≤3.9 mmol/L (70 mg/dL). Events can fall under more than one category.

saxagliptin plus metformin (UTIs 2.4%, genital infections 0.0%). The incidences of both UTIs and genital infections were higher in women than in men with dapagliflozin plus saxagliptin plus metformin (Table 3).

The AEs of renal impairment or failure (including the preferred terms of decreased glomerular filtration rate [GFR], renal failure, abnormal GFR, renal impairment, increased blood creatinine, and chronic kidney disease) were more common in the dapagliflozin plus saxagliptin plus metformin group than in the monocomponent groups (5.5% vs. 4.1% [dapagliflozin plus metformin] vs. 2.0% [saxagliptin plus metformin]). One event of cardiac failure occurred in the dapagliflozin plus metformin treatment group, but this was considered to be unrelated to study treatment. Three participants reported AEs with evidence of ketonuria: one and two participants in the dapagliflozin plus saxagliptin plus metformin and the dapagliflozin plus metformin treatment groups, respectively. These events were captured in the Medical Dictionary for Regulatory Activities (MedDRA) as diabetic ketoacidosis; however, on subsequent clinical review, none of these participants had a confirmed diagnosis of diabetic ketoacidosis.

Incidences and types of serious AEs (SAEs) were balanced between treatment groups (Table 3), and no participant experienced SAEs that were considered related to treatment. Three participants died during the study treatment period: one participant in the triple therapy group died in a motorcycle accident, and two participants in the dapagliflozin plus metformin group died from a myocardial infarction and a ventricular arrhythmia, respectively. These deaths were all

considered to be unrelated to treatment. In general, values for haematological variables remained within normal ranges throughout the study period, and the frequency of marked laboratory abnormalities was low. There were no notable changes from baseline in heart rate during the study.

3.5 | Hypoglycaemic events

In the triple therapy group, 5.8% of participants experienced at least one hypoglycaemic event, compared with 2.7% and 3.4% in the dapagliflozin plus metformin and saxagliptin plus metformin groups, respectively (Table 3). Only two participants reported a severe hypoglycaemic event: one with dapagliflozin plus saxagliptin plus metformin and one with dapagliflozin plus metformin. No participant discontinued treatment owing to hypoglycaemia.

4 | DISCUSSION

The majority of participants with type 2 diabetes will eventually require combination therapy with multiple anti-hyperglycaemic agents to achieve and to maintain adequate glycaemic control. Although this approach is consistent with the premise that type 2 diabetes is a disease that is driven by diverse pathophysiological mechanisms,[15] the timing of combination therapy and the participant population to which it is administered remain topics of intense debate.

The present study compared the efficacy and safety of add-on low-dose dapagliflozin plus saxagliptin therapy, versus the addition of each monocomponent in metformin-treated people with uncontrolled type 2 diabetes. For the primary endpoint of change from baseline in HbA1c at week 24, triple therapy with dapagliflozin, saxagliptin and metformin clearly had higher efficacy than dual therapy with either dapagliflozin or saxagliptin plus metformin, as was expected. Triple therapy was also associated with more participants achieving a therapeutic glycaemic response (HbA1c <7.0%), as well as greater decreases from baseline in FPG and body weight than either dual therapy regimen, and a decrease in SBP from baseline.

The greater improvements in glycaemic control seen with triple therapy than with either dual therapy regimen are consistent with other clinical studies of combination therapies, as well as with a previous study of the combination of dapagliflozin plus saxagliptin plus metformin that used dapagliflozin at the higher dose of 10 mg in a patient population with poorer glycaemic control than in the present study.[23] As seen in previous studies of dapagliflozin, triple therapy was also associated with greater body weight loss than with dual therapy of saxagliptin plus metformin, with a clinically significant between-treatment difference of −1.6 kg. These findings exemplify the benefits of combining anti-hyperglycaemic therapies with different mechanisms of action and also show that the lower 5-mg dose of dapagliflozin was associated with similar body weight loss to previous studies of dapagliflozin 10 mg.[23] The decreases in SBP observed with triple therapy were not as pronounced as those seen previously,[12,13] which may relate to the relatively low baseline SBP values of participants in the present study.

An interesting finding from the present study was that addition of saxagliptin to dapagliflozin plus metformin appeared to prevent the increased production of β-hydroxybutyrate that was seen with dapagliflozin plus metformin. SGLT2 inhibitors directly and indirectly stimulate glucagon secretion, which promotes the β-oxidation of fatty acids and the formation of ketone bodies.[24] DPP-4 inhibitors have previously been shown to suppress SGLT2-inhibitor-induced glucagon secretion,[25] which may have prevented the dapagliflozin-mediated ketosis in the present study. Although this finding and the underlying mechanisms require further investigation, the present data are important. SGLT2 inhibitors are thought to be associated with a very small increase in the risk of diabetic ketoacidosis, based on testing in patients with type 1 diabetes, although reports of this serious event are very rare in patients with type 2 diabetes.[23] Notably, no participant in the present study had a confirmed diagnosis of diabetic ketoacidosis. Although three participants had AEs of urinary ketones, there were no additional signs or symptoms suggestive of this condition.

As seen previously, the combination of dapagliflozin, saxagliptin, and metformin was well tolerated, and there were no major differences in tolerability among the treatment groups.[26] As expected, UTIs and genital infections generally occurred more frequently in women than in men,[27] and the incidence of genital infections was higher with dapagliflozin-containing treatment regimens than with saxagliptin. Notably, the mitigation of genital infections that has been seen with the combination of dapagliflozin, saxagliptin, and metformin[23] was not seen with dapagliflozin 5 mg used in this study; however, genital infections were mostly mild and easily treated in all groups.

Although AEs of renal impairment or failure were more common with triple therapy than with dual therapy, these were mainly minor decreases in eGFR, and none of the events were considered serious. Notably, decreases in eGFR with SGLT2 inhibitors have been shown to be reversible, but might also be renoprotective, owing to the resultant decrease in intraglomerular pressure that ultimately decreases the rate of eGFR decline in people with type 2 diabetes, relative to those not taking SGLT2 inhibitors.[28,29] Findings from the DECLARE-TIMI randomized trial also suggest that long-term use of dapagliflozin is beneficial rather than detrimental to renal outcomes. In that trial, patients treated with dapagliflozin for a median of 4.2 years had lower rates of renal disease progression than those treated with placebo.[30]

The incidence of hypoglycaemia was generally low across groups, consistent with previous studies and the mechanisms of action of dapagliflozin and saxagliptin.[31,32] Although hypoglycaemic incidence was higher with dapagliflozin plus saxagliptin plus metformin than with addition of either monocomponent to metformin, these events were mild and easily managed. Only two cases of hypoglycaemia in the whole study met the ADA criteria for severe hypoglycaemic events (one in each of the dapagliflozin plus saxagliptin plus metformin and the dapagliflozin plus metformin treatment groups), and the glucose levels reported during these events were not consistent with levels typically associated with severe hypoglycaemia. Moreover, no

participant discontinued the study as a consequence of hypoglycaemia.

Current treatment guidelines offer differing perspectives on the most appropriate time to initiate and advance therapy with a combination of agents given simultaneously in participants with type 2 diabetes. Guidelines from the AACE recommend initiation of dual therapy as first-line treatment in patients with HbA1c ≥7.5% and triple therapy as first-line treatment in patients with HbA1c ≥9.0%,[7] whereas the recent consensus statement from the ADA and the EASD advises use of dual combination therapy if a patient is >1.5% above their target HbA1c level.[18] There is a growing argument that treating the disease more aggressively at earlier stages than is current practice may slow disease progression.[33] In the past, a less aggressive approach to treatment intensification might have been justified as avoiding the adverse consequences of hypoglycaemia with drugs such as sulphonylureas.[34] However, the risk of hypoglycaemia is very low with newer anti-hyperglycaemic drugs such as SGLT2 inhibitors and DPP-4 inhibitors, so safety would be less of a concern when these are used as part of combination treatment regimens.[35]

The similar efficacy and safety of dapagliflozin 5 mg to those of the 10-mg dose used previously suggest that dapagliflozin 5 mg may have utility in the treatment of people with type 2 diabetes who are early in the disease process. This approach may also minimize the risk of AEs occurring during treatment. A limitation of this study is that it reports 24-week results, thus not allowing a long-term assessment of the benefits of triple therapy compared with the dual therapy regimens. Prolonged benefits, however, have been observed with the same drug combinations when administered for 52 weeks.[36,37] Moreover, the study population was relatively homogenous, particularly in terms of ethnicity, so generalizability of the study findings cannot be assumed.

In summary, triple therapy consisting of concomitant addition of dapagliflozin 5 mg and saxagliptin 5 mg to metformin achieved greater improvements in glycaemic control, with the benefit of body weight loss, than dual therapy with addition of either monocomponent to metformin, and was generally well tolerated. These findings support the initiation of triple therapy with dapagliflozin 5 mg plus saxagliptin 5 mg added to metformin as a valid treatment option in people with uncontrolled type 2 diabetes.

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CONFLICT OF INTEREST

J.R. serves or has served on advisory panels for and has received honoraria from AstraZeneca, Boehringer Ingelheim, Eli Lilly & Company, Intarcia Therapeutics, Janssen Pharmaceuticals, Novo Nordisk, and Sanofi, and has received research support from AstraZeneca, Boehringer Ingelheim, Bristol-Myers Squibb, Eli Lilly & Company, Genentech, GlaxoSmithKline, Intarcia Therapeutics, Janssen Pharmaceuticals, Lexicon Pharmaceuticals, Merck, Novo Nordisk, and Pfizer. S.P., E.K.J., and R.G.-S. are employees of and stockholders in AstraZeneca. S.J. has received honoraria, research support, and consulting fees from Abbott, Amgen, AstraZeneca, Bayer, Berlin Chemie, Boehringer Ingelheim, Bristol-Myers Squibb, Daiichi Sankyo, Janssen, Johnson & Johnson, Lilly, Merck, Merck Sharp & Dohme, Novartis, Novo Nordisk, Orexigen, Pfizer, Roche, Sanofi-Aventis, and Servier.

AUTHOR CONTRIBUTIONS

J.R., S.P., E.J., and R.G.S. contributed to the study design. J.R., S.P., E.J., and S.J. contributed to the data collection. J.R., S.P., E.J., R.G.S., and S.J. contributed to the data analysis. All authors contributed to the writing of the manuscript.

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section at the end of this article.

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