Sustained 52-week efficacy and safety of triple therapy with dapagliflozin plus saxagliptin versus dual therapy with sitagliptin added to metformin in patients with uncontrolled type 2 diabetes

Yehuda Handelsman MD | Chantal Mathieu MD | Stefano Del Prato MD | Eva Johnsson MD | Raisa Kurlyandskaya MD | Nayyar Iqbal MD | Ricardo Garcia-Sanchez MD | Julio Rosenstock MD

1Metabolic Institute of America, Tarzana, California
2Clinical and Experimental Endocrinology, University Hospital Gasthuisberg, Leuven, Belgium
3Department of Clinical and Experimental Medicine, University of Pisa, Pisa, Italy
4AstraZeneca Gothenburg, Mölndal, Sweden
5AstraZeneca, Gaithersburg, Maryland
6Dallas Diabetes Research Center at Medical City, Dallas, Texas

Aims: To compare the efficacy and safety of an intensification strategy of early triple combination therapy with dapagliflozin (DAPA) plus saxagliptin (SAXA) to a dual therapy strategy with sitagliptin (SITA) in patients with type 2 diabetes who are inadequately controlled with metformin (MET) monotherapy.

Materials and methods: This multinational, active-controlled, parallel-group phase 3b trial randomized 461 patients, at least 18 years of age, with glycated haemoglobin (HbA1c) of 8%–10.5% (64–91 mmol/mol), to either DAPA plus SAXA or SITA, added to MET, for a 26-week double-blind treatment period and an extension of a 26-week blinded treatment period.

Results: Mean (± SD) baseline HbA1c was 8.8% ± 0.9% (73.0 ± 9.3 mmol/mol). DAPA plus SAXA (n = 232) provided a greater reduction from baseline in HbA1c at Weeks 26 and 52 compared with SITA (n = 229) (adjusted mean (± SE) change, Week 26: −1.41 ± 0.07% vs −1.07 ± 0.07% [−15.4 ± 0.8 mmol/mol vs 11.7 ± 0.8 mmol/mol]; P = 0.0008; Week 52: −1.29 ± 0.08% vs −0.81 ± 0.09% [14.1 ± 0.9 mmol/mol vs 8.9 ± 1.0 mmol/mol]). The between-group difference in adjusted mean (95% CI) change from baseline in HbA1c increased from −0.34 (−0.54, −0.14) at Week 26 to −0.48 (−0.71, −0.25) at Week 52. DAPA plus SAXA was generally well tolerated and the incidence of adverse events was similar in both treatment arms.

Conclusions: Early intensification to triple therapy with DAPA plus SAXA results in better, more durable glycaemic control than addition of SITA only (dual therapy) in patients with high HbA1c levels who are uncontrolled with MET monotherapy.

KEYWORDS
dapagliflozin, DPP-IV inhibitor, GLP-1, saxagliptin, SGLT2 inhibitor, type 2 diabetes

1 | INTRODUCTION

Clinical guidelines recommend the use of metformin (MET) monotherapy as first-line anti-hyperglycaemic therapy for the majority of patients with type 2 diabetes, but treatment intensification will probably be required to maintain glycaemic control as the disease progresses. However, the addition of individual oral therapies to MET may be inadequate to reach glycaemic targets in patients with very high levels of glycated haemoglobin (HbA1c) because of the complex multi-system pathophysiology of type 2 diabetes, which requires a multi-faceted treatment approach. Simultaneous intensification with two therapies that have different mechanisms of action has the...
potential to provide more rapid, greater and sustained reductions in HbA1c; however, it is not known whether this form of therapy increases the risk of adverse events. Simultaneous intensification with two therapies may have benefits, such as improved adherence, reduced clinical inertia and increased durability, but the safety of such an approach is yet to be established.

In the present study, we report results from a randomized, double-blind, active-controlled trial evaluating the efficacy and safety of triple therapy, with the addition of the sodium-glucose cotransporter 2 (SGLT2) inhibitor dapagliflozin (DAPA) plus the dipeptidyl peptidase-4 (DPP-4) inhibitor saxagliptin (SAXA), vs dual therapy, with the addition of the DPP-4 inhibitor sitagliptin (SITA) alone, in patients with type 2 diabetes who are inadequately controlled with MET monotherapy. The objective of this study, which included a short-term 26-week treatment period and a further 26-week extension treatment period, was to assess the efficacy, safety and long-term sustained control of a strategy of adding an early combination of two drugs to MET (triple therapy), compared with the commonly used strategy of adding only one drug (dual therapy).

2 | MATERIALS AND METHODS

2.1 | Study design

This multinational, randomized, double-blind, active-controlled, double-dummy parallel-group phase 3b trial (ClinicalTrials.gov Identifier: NCT02284893) was conducted in Hungary, Mexico, Poland, Romania, South Africa and the USA, in accordance with the principles of the Declaration of Helsinki. The protocol and its amendments were reviewed and approved by an Independent Ethics Committee or Institutional Review Board at each study site, and all patients provided written informed consent.

The study comprised a 2-week screening period, a 2-week lead-in period, an initial 26-week randomized, double-blind treatment period, and an extension 26-week site-blind and patient-blind treatment period (Figure S1). During the lead-in period, patients continued to receive background MET medication (≥1500 mg/d). After completing the lead-in period, eligible patients were randomized (1:1) using an interactive voice-response system to receive a combination of DAPA (10 mg/d) and SAXA (5 mg/d) or SITA (100 mg/d), in addition to their regular MET dose for 26 weeks. After completing the 26-week double-blind treatment period, patients entered the extension 26-week site- and patient-blind treatment period, during which they received the same blinded study treatment as during the initial 26-week period in addition to their regular MET dose. Study sites and patients were blinded to the treatment during the extension period, but the study sponsor’s delegate, Bristol-Myers Squibb, was unblinded.

2.2 | Patients

Men and women at least 18 years of age, with inadequately controlled type 2 diabetes, defined as HbA1c of 8%-10.5% (64-91 mmol/mol) at screening were eligible for inclusion in the study if they had undergone stable MET therapy for at least 8 weeks prior to enrolment (≥1500 mg/d) and had received no other anti-diabetes agent for more than 14 days during the 12 weeks prior to screening. Other inclusion criteria included having a body mass index (BMI) greater than 20 kg/m² at the enrolment visit and a fasting plasma glucose (FPG) level of at least 270 mg/dL (≥15 mmol/L) at randomization. Exclusion criteria included diagnosis of type 1 diabetes, history of cardiovascular disease within 3 months of screening, hepatic insufficiency, medical history of diabetic ketoacidosis, 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), history of acute pancreatitis and haemoglobinopathy.

Treatment compliance was assessed through patient interview and by counting returned tablets. Patients were strongly advised to adhere to both a diet and exercise programme and to the schedule of study assessments and procedures. Any concomitant use of a new prescription or over-the-counter or herbal/nutritional therapies was discussed with the investigator to avoid any alterations to glycaemic control; medications that were not included in the prohibited medications list were authorized at the discretion of the investigator. Patients meeting the criterion for rescue medication at any time (FPG > 270 mg/dL [≥15.0 mmol/L] before Week 6; FPG > 240 mg/dL [≥13.3 mmol/L] during Weeks 7-11; FPG > 200 mg/dL [≥11.1 mmol/L] during Weeks 12-26; and HbA1c > 8% [≥64 mmol/mol] during Weeks 27-51) received basal insulin or other anti-diabetes agents, with the exception of glucagon-like peptide-1 receptor agonists, other DPP-4 or SGLT2 inhibitors and MET, at the investigator’s discretion.

2.3 | Study assessments

The primary efficacy end point was mean change in HbA1c from baseline to Week 26. Secondary efficacy measures were the proportion of patients with HbA1c less than 7% (<53 mmol/mol) at Week 26 and mean changes in FPG and body weight from baseline to Week 26.

Efficacy end points assessed at 52 weeks were all considered exploratory and included mean change in HbA1c from baseline, proportion of patients achieving glycaemic control (HbA1c < 7% [≤53 mmol/mol]), mean change from baseline in total body weight and FPG level, proportion of patients requiring treatment intensification and time to intensification, mean change from baseline in seated systolic blood pressure, change from baseline in biomarkers, including high-sensitivity C-reactive protein (hsCRP) and B-type natriuretic protein (BNP), and mean change from baseline in urinary glucose: creatinine ratio at each time point.

Safety assessments at 52 weeks included proportion of patients experiencing adverse events (AEs) or serious AEs (SAEs), changes in selected safety clinical laboratory measures and confirmed hypoglycaemia, defined as plasma blood glucose of at least 70 mg/dL (≥3.9 mmol/L) or signs/symptoms of hypoglycaemia with self-monitored blood glucose of at least 70 mg/dL (≥3.9 mmol/L), and percentage change from baseline in fasting serum lipids (total cholesterol, low-density lipoprotein [LDL] cholesterol, high-density lipoprotein [HDL] cholesterol and triglycerides).
AEs of special interest included genital infections and urinary tract infections (UTIs), pancreatitis and pancreatic cancer, worsening renal function, decreased thrombocyte and lymphocyte counts, hypersensitivity reactions, severe cutaneous adverse reactions, bladder and breast neoplasms, and volume depletion.

2.4 Statistical analysis

A sample size of 210 patients per group was determined a priori to yield approximately 89% power to detect a difference in mean HbA1c of 0.35% (3.8 mmol/mol) between the two groups at a two-sided significance level of 0.05 and assuming a standard deviation (SD) of 1.1% and a 5% dropout rate. Efficacy analyses included all randomized patients who received at least one dose of study medication during the full double-blind treatment period (intention-to-treat population). The DAPA plus SAXA plus MET group was tested against the SITA plus MET group for the primary efficacy end point at a two-sided 5% level. Analysis of the primary efficacy end point was performed using a longitudinal repeated-measures analysis with the factors of baseline value, treatment group, time, interaction between treatment group and time, and interaction between baseline value and time, including observations made prior to rescue medication until treatment discontinuation. Point estimates and 95% CIs were calculated for adjusted mean changes within each treatment group, as well as for differences in adjusted mean (± standard error [SE]) changes between treatment groups. Secondary efficacy end points were tested sequentially at a two-sided 5% α level. To limit the overall type I error rate, interpretation of the statistical significance of treatment comparisons for each secondary efficacy end point was tested using a stepwise procedure. For the long-term 52-week extension period, no statistical hypothesis tests were performed and no P values were calculated because all efficacy end points for this period were considered exploratory. Mean changes in HbA1c from baseline until Week 52 were compared between treatment groups using the same longitudinal repeated-measures analysis as described above. The proportion of patients achieving HbA1c less than 7% (<53 mmol/mol) at Weeks 26 and 52 were compared as described above. The proportion of patients achieving HbA1c less than 7% (<53 mmol/mol) at Weeks 26 and 52 were compared between treatment groups using previously published methods.5,6

3 RESULTS

3.1 Patient disposition and baseline characteristics

The first patient visit for this study took place 22 December 2014 and the last patient visit took place 26 October 2016. The number of patients enrolled was 861; of these, 487 entered the lead-in period and 461 were randomized to receive at least one dose of medication during the double-blind treatment period (DAPA plus SAXA, n = 232; SITA, n = 229) (Figure S2). Of the 461 patients randomized, 411 (89.2%) completed the short-term 26-week treatment period, 402 (87.2%) entered the long-term 26-week extension period and 378 (82.0%) (DAPA plus SAXA, n = 198; SITA, n = 180) completed the study. Patient demographics and characteristics at baseline were similar across treatment groups (Table 1). Mean (±SD) baseline HbA1c was 8.8 ± 0.9% (73.0 ± 9.3 mmol/mol). More than 99% of patients in both treatment groups were compliant with the study medication (patients received ≥80% and ≤120% of planned drug doses).

3.2 Efficacy

Patients receiving DAPA plus SAXA add-on therapy showed a greater reduction from baseline in HbA1c at both Week 26 and Week 52 compared with those receiving SITA add-on therapy (adjusted mean ± SE change, Week 26: −1.41 ± 0.07% vs −1.07 ± 0.07% [15.4 ± 0.8 mmol/mol vs 11.7 ± 0.8 mmol/mol]; P = 0.0008; Week 52: −1.29 ± 0.08% vs −0.81 ± 0.09% [14.1 ± 0.9 mmol/mol vs 8.9 ± 1.0 mmol/mol]) (Figure 1A). The between-group difference in adjusted mean (95% CI) change in HbA1c from baseline increased from −0.34 (−0.54, −0.14) at Week 26 to −0.48 (−0.71, −0.25) at Week 52. More patients achieved HbA1c less than 7% with DAPA plus SAXA add-on therapy than did patients who received SITA add-on therapy at Weeks 26 and 52 (adjusted mean percentage ± SE, Week 26: 37.3 ± 3.2% vs 25.1 ± 2.9%; P = 0.0034; Week 52: 33.0 ± 3.1% vs 19.5 ± 2.6%). At Week 52, the adjusted difference (95% CI) between treatment groups was 13.5% (5.6, 21.4) (Figure 1B).

At Weeks 26 and 52, patients in the DAPA plus SAXA group showed a greater reduction in FPG (adjusted mean ± SE change, week 26: −32 ± 3 vs −11 ± 3 mg/dL [−1.8 ± 0.1 vs −0.6 ± 0.1 mmol/L]; P < 0.0001; Week 52: −26 ± 3 vs −4 ± 4 mg/dL [−1.4 ± 0.2 mmol/L vs −0.2 ± 0.2 mmol/L]) (Figure S3A) and greater weight loss (adjusted mean ± SE change, Week 26: −1.9 ± 0.2 vs −0.5 ± 0.2 kg; P < 0.0001; Week 52: −2.3 ± 0.3 vs −0.8 ± 0.3 kg) (Figure S3B) than did those in the SITA group. The adjusted differences (95% CI) between treatment groups in FPG and weight loss were −22 mg/dL (−32, −12) and −1.6 kg (−2.4, −0.8), respectively, at Week 52.

The proportion of patients who discontinued the study because of a lack of glycaemic control or who were rescued because of failure to achieve pre-specified glycaemic targets are included in Table 2. By Week 52, 18.1% of patients in the DAPA plus SAXA group and 32.8% of patients in the SITA group had received rescue medication. The most commonly used rescue medication over the 52-week study period was glimepiride (used by 23 patients in the DAPA plus SAXA group and by 39 patients in the SITA group). Five patients in the
|                          | DAPA plus SAXA plus MET | SITA plus MET | Total N = 461 |
|--------------------------|--------------------------|---------------|--------------|
| **N**                   | 232                      | 229           | 461          |
| **Age, y**              |                          |               |              |
| Mean ± SD               | 55.9 ± 8.9               | 55.8 ± 9.6    | 55.9 ± 9.2   |
| **Age categories, n (%)**|                          |               |              |
| <65 y                   | 197 (84.9)               | 184 (80.3)    | 381 (82.6)   |
| ≥65 y                   | 35 (15.1)                | 45 (19.7)     | 80 (17.4)    |
| ≥75 y                   | 3 (1.3)                  | 6 (2.6)       | 9 (2.0)      |
| **Sex, n (%)**          |                          |               |              |
| Male                    | 100 (43.1)               | 110 (48.0)    | 210 (45.6)   |
| Female                  | 132 (56.9)               | 119 (52.0)    | 251 (54.4)   |
| **Race, n (%)**         |                          |               |              |
| White                   | 153 (65.9)               | 149 (65.1)    | 302 (65.5)   |
| Black or African-American| 34 (14.7)               | 32 (14.0)     | 66 (14.3)    |
| Asian                   | 8 (3.4)                  | 12 (5.2)      | 20 (4.3)     |
| Other                   | 37 (15.9)                | 36 (15.7)     | 73 (15.8)    |
| **Geographic region, n (%)**|                         |               |              |
| North America           | 114 (49.1)               | 113 (49.3)    | 227 (49.2)   |
| Latin America           | 46 (19.8)                | 42 (18.3)     | 88 (19.1)    |
| Europe                  | 72 (31.0)                | 74 (32.3)     | 146 (31.7)   |
| **BMI, kg/m²**          |                          |               |              |
| Mean ± SD               | 33.3 ± 6.1               | 32.8 ± 6.3    | 33.1 ± 6.2   |
| **BMI categories, n (%)**|                          |               |              |
| <25 kg/m²               | 14 (6.0)                 | 20 (8.7)      | 34 (7.4)     |
| ≥25 kg/m²               | 218 (94.0)               | 209 (91.3)    | 427 (92.6)   |
| ≥27 kg/m²               | 202 (87.1)               | 191 (83.4)    | 393 (85.2)   |
| ≥30 kg/m²               | 151 (65.1)               | 147 (64.2)    | 298 (64.6)   |
| **Duration of type 2 diabetes, years**|          |               |              |
| Mean ± SD               | 7.9 ± 5.7                | 8.2 ± 5.2     | 8.0 ± 5.4    |
| **Duration of type 2 diabetes categories, n (%)**| |               |              |
| <3 years                | 51 (22.0)                | 35 (15.3)     | 86 (18.7)    |
| 3-10 years              | 115 (49.6)               | 119 (52.0)    | 234 (50.8)   |
| >10 years               | 66 (28.4)                | 75 (32.8)     | 141 (30.6)   |
| **Recent history of congestive cardiac failure, n (%)**| |               |              |
| 2 (0.9)                 | 3 (1.3)                  | 5 (1.1)       |
| **HbA1c, Mean ± SD, %**  |                          |               |              |
|                       | 8.8 ± 0.8                | 8.9 ± 0.9     | 8.8 ± 0.9    |
|                       | 73.0 ± 9.2               | 74.0 ± 9.4    | 73.0 ± 9.3   |
| **HbA1c categories, n (%)**|                         |               |              |
| <8% [<64 mmol/mol]     | 33 (14.2)                | 27 (11.8)     | 60 (13.0)    |
| 8%-9% [64-74 mmol/mol] | 108 (46.6)               | 96 (41.9)     | 204 (44.3)   |
| ≥9% [≥75 mmol/mol]     | 91 (39.2)                | 106 (46.3)    | 197 (42.7)   |
| **Fasting plasma glucose**, Mean ± SD, mg/dL | |               |              |
|                       | 171.8 ± 42.3             | 175.0 ± 43.4  | 173.4 ± 42.9 |
|                       | 9.5 ± 2.4                | 9.7 ± 2.4     | 9.6 ± 2.4    |
| **eGFR, mL/min/1.73 m²**, Mean ± SD | |               |              |
|                       | 92.2 ± 20.2              | 92.9 ± 22.5   | 92.5 ± 21.3  |
| **eGFR categories, n (%)**|                         |               |              |
| <30 mL/min/1.73 m²     | 0                        | 0             | 0            |
| 30-59 mL/min/1.73 m²   | 9 (3.9)                  | 13 (5.7)      | 22 (4.8)     |
| 60-89 mL/min/1.73 m²   | 96 (41.4)                | 96 (41.9)     | 192 (41.6)   |
| ≥90 mL/min/1.73 m²     | 127 (54.7)               | 120 (52.4)    | 247 (53.6)   |
DAPA plus SAXA group and nine patients in the SITA group used basal insulin. No patient discontinued the study because of a lack of glycaemic control.

From baseline levels, systolic blood pressure decreased in the DAPA plus SAXA group and increased in the SITA group at Week 52 (adjusted mean/C6/SE change, −2.6/C6/0.9 vs +2.5/C6/1.0 mm Hg, respectively) (Table 2). The adjusted difference (95% CI) between treatment groups was −5.1 mm Hg (−7.7, −2.5).

The changes from baseline in hsCRP, BNP and urinary glucose: creatinine ratio are included in Table 2. Patients in the DAPA plus SAXA group showed a greater change from baseline in urinary glucose: creatinine ratio than did those in the SITA group (adjusted mean/C6/SE change, 40.1/C6/2.3 vs −1.1/C6/2.4).

Adjusted mean changes from baseline in fasting serum lipids (total cholesterol, LDL-cholesterol, HDL-cholesterol, and triglycerides) were small and no clinically meaningful differences between treatment groups were observed, with all lipid values remaining in the normal to borderline ranges up to Week 52 (Table 2).

### 3.3 Safety

Triple therapy with DAPA plus SAXA add-on to MET was generally well tolerated after 52 weeks of treatment; the incidence of AEs in patients receiving triple therapy was similar to that in patients receiving dual therapy with SITA add-on (Table 3). AEs that were determined by the investigator to be related to the study drug were reported by 22 (9.5%) patients in the DAPA plus SAXA group and by 17 (7.4%) patients in the SITA group. Few patients discontinued the study because of AEs (DAPA plus SAXA, 1.7%; SITA, 4.4%) and none of these discontinuations was because of hypoglycaemia. The proportion of patients who experienced SAEs was low in both treatment groups (DAPA plus SAXA, 3.9%; SITA, 5.7%). Of the SAEs reported, none was considered by the investigator to be related to DAPA plus SAXA treatment, and only one SAE, drug hypersensitivity, was reported to be related to SITA treatment. The most common SAEs were pneumonia, endometriosis and osteoarthritis, which were reported for two patients each in the SITA group; no other SAEs were reported more than once in either treatment group.

Confirmed hypoglycaemia was reported in similar numbers of patients in each treatment group after 26 weeks and after 52 weeks of treatment (26 weeks: DAPA plus SAXA, 9 [3.9%]; SITA, 6 [2.6%]; 52 weeks: DAPA plus SAXA, 12 [5.2%]; SITA, 9 [3.9%]; no major episodes were reported.

The proportion of patients experiencing genital infections was similar in the DAPA plus SAXA group and the SITA group (3.4% vs 2.2%, respectively). Vulvovaginal mycotic infection was the most common genital infection (DAPA plus SAXA, n = 5 women; SITA, n = 2 women). In the DAPA plus SAXA group, two women experienced vaginitis; one experienced vulvovaginitis and one experienced vulvovaginal candidiasis. In the SITA group, one woman experienced vulvitis and two men experienced balanoposthitis.

UTIs occurred in 6.5% of patients in the DAPA plus SAXA group and in 3.5% of patients in the SITA group (men, 4.0% vs 1.8%; women, 8.3% vs 5.0%, respectively). Unclassified UTIs were more common in women than in men (DAPA plus SAXA, n = 9 women, n = 1 man; SITA, n = 6 women, n = 1 man). In the DAPA plus SAXA group, one man experienced a fungal UTI, one man experienced prostatitis, one man experienced urethritis and two women experienced cystitis. In the SITA group, one man experienced cystitis.
The following conditions were reported as other AEs of special interest; definitions are based on preferred terms in the Standardised Medical Dictionary for Regulatory Activities Queries of cardiac failure. In the DAPA plus SAXA group, one patient reported an AE of syncope, one patient experienced adenocarcinoma of the colon, two patients reported an AE of peripheral oedema and three patients reported an AE of renal impairment/failure (\( n = 1 \), acute kidney injury; \( n = 1 \), decreased glomerular filtration rate; \( n = 1 \), increased blood creatinine); none of these AEs was deemed by the investigator to be related to the study drug. In the SITA group, seven patients experienced at least one cardiac event (\( n = 4 \), peripheral swelling; \( n = 2 \), peripheral oedema; \( n = 1 \), congestive cardiac failure; \( n = 1 \), chronic cardiac failure; \( n = 1 \), BNP increased); of these events, only one incidence of peripheral swelling was considered by the investigator to be related to the study drug. In addition, five patients in the SITA group reported AEs potentially related to hypotension, hypovolaemia or dehydration, and one
patient experienced a decreased glomerular filtration rate. Hypersensitivity AEs were reported in six patients (2.6%) in the DAPA plus SAXA group and in seven patients (3.1%) in the SITA group; the most common hypersensitivity AE was rash (DAPA plus SAXA, n = 2; SITA, n = 4). No other AEs of special interest were reported (ie, pancreatitis, pancreatic cancer, breast/bladder neoplasms, severe cutaneous adverse reactions, decreased thrombocyte or lymphocyte counts).

One patient in the SITA group requested to discontinue the study because of suspected diabetic ketoacidosis. No deaths were reported for patients who received treatment during the study.

After 52 weeks, no clinically meaningful differences were observed in adjusted mean percentage change from baseline in fasting serum lipids between treatment groups (Table 2).

### 4 | DISCUSSION

In this double-blind, double-dummy 52-week trial, we report that an intensification strategy of early triple combination therapy with the addition of DAPA plus SAXA provides significantly greater improvements in glycaemic control than a dual therapy strategy with the addition of SITA alone in patients with inadequately controlled MET-treated type 2 diabetes. These improvements were sustained after 52 weeks and were not associated with an increased risk of hypoglycaemia or other diabetes-specific events, and the overall incidence of AEs was low. Furthermore, the improvement in glycaemic control with DAPA plus SAXA treatment was accompanied by a greater reduction in body weight and systolic blood pressure compared with treatment with SITA.

Therapeutic guidelines recommend treatment intensification through addition of anti-diabetes agents for patients with inadequate glycaemic control with MET. However, dual add-on therapy is rarely used, despite the knowledge that glycaemic control is seldom achieved with single-agent add-ons. The use of single-agent add-ons often leads to long periods of hyperglycaemia, which are associated with increased morbidity. The objective of this study was to evaluate the strategy of adding two anti-hyperglycaemic agents (DAPA plus SAXA) simultaneously compared with the more common approach of adding one agent at a time (SITA) in patients with type 2 diabetes that is uncontrolled by MET. Adding two therapies simultaneously led to more rapid glucose control, which was sustained over 52 weeks, suggesting that there may be underlying improvements in insulin sensitivity and β-cell function. Treatment with DAPA plus SAXA add-on to MET provided greater reductions in HbA1c and FPG than treatment with SITA add-on, although, even with triple therapy, mean final HbA1c values were greater than 7% (53 mmol/mol), probably the result of the patients’ high baseline HbA1c levels. However, a significantly greater proportion of patients achieved HbA1c less than 7% (<53 mmol/mol) with DAPA plus SAXA add-on therapy than with SITA add-on after 26 and 52 weeks, despite high baseline HbA1c levels. Differences in adjusted mean change from baseline in both HbA1c and FPG between the two treatment groups increased from Week 26 to Week 52, and a lower proportion of patients in the DAPA

### TABLE 2  Additional exploratory end points at week 52

| Study end point | DAPA plus SAXA plus MET | SITA plus MET | Difference (95% CI) |
|-----------------|-------------------------|--------------|---------------------|
| Proportion of patients discontinued because of a lack of glycaemic control or rescued for not achieving pre-specified glycaemic targets, % | n = 42<sup>b</sup> 18.6 ± 2.5 | n = 75<sup>b</sup> 32.3 ± 3.1 | −13.8 (−21.4, −6.1) |
| Seated SBP, mm Hg<sup>c</sup> | n = 157 −2.6 ± 0.9 | n = 112 2.5 ± 1.0 | −5.1 (−7.7, −2.5) |
| Change in biomarkers from baseline, SI units<sup>c</sup> | | | |
| hsCRP, mg/L | n = 195 0.43 ± 0.54 | n = 176 −0.09 ± 0.75 | −1.6 (−2.6, −0.6) |
| BNP, ng/L | n = 183 −1.39 ± 0.84 | n = 168 4.10 ± 3.61 | −1.3 (−3.3, 0.7) |
| Change in urine glucose: Creatinine ratio from baseline<sup>d</sup> | n = 186 40.1 ± 2.3 | n = 171 −1.1 ± 2.4 | 41.2 (34.7, 47.7) |
| Percentage change in fasting serum lipids from baseline, mg/dL (95% CI) | | | |
| Total cholesterol | n = 196 2.1 (−0.4, 4.7) | n = 177 3.0 (0.3, 5.8) | −0.9 (−4.4, 2.8) |
| LDL cholesterol | n = 196 2.2 (−2.0, 6.6) | n = 177 5.6 (1.0, 10.4) | −3.2 (−8.9, 2.9) |
| HDL cholesterol | n = 196 3.9 (1.8, 6.1) | n = 177 1.8 (−0.3, 4.0) | 2.0 (−0.9, 5.1) |
| Triglycerides | n = 196 −2.4 (−7.5, 3.0) | n = 177 −1.7 (−7.1, 3.9) | −0.7 (−8.1, 7.4) |

Values are adjusted mean ± SE unless otherwise specified. Abbreviations: BNP, B-type natriuretic protein; DAPA, dapagliflozin; hsCRP, HDL, high density lipoprotein; high-sensitivity C-reactive protein; LDL, low density lipoprotein; MET, metformin; SAXA, saxagliptin; SBP, systolic blood pressure; SE, standard error; SI units, international system of units; SITA, sitagliptin.

<sup>a</sup> Excluding data after rescue medication.

<sup>b</sup> Number of patients discontinued owing to lack of glycaemic control or rescued for not achieving pre-specified glycaemic targets.

<sup>c</sup> Including data after rescue medication.
TABLE 3  Summary of adverse events over 52 weeks of treatment (safety set)

| Adverse events, n (%) | DAPA plus SAXA plus MET N = 232 | SITA plus MET N = 229 |
|----------------------|----------------------------------|----------------------|
| **Overall summary**  |                                  |                      |
| At least one AE      | 133 (57.3)                       | 132 (57.6)           |
| At least one treatment-related AE | 22 (9.5) | 17 (7.4) |
| At least one SAE     | 9 (3.9)                          | 13 (5.7)             |
| At least one treatment-related SAE<sup>a</sup> | 0 (0.0) | 1 (0.4) |
| AE leading to discontinuation of study drug | 4 (1.7) | 10 (4.4) |
| SAE leading to discontinuation of study drug | 0 (0.0) | 4 (1.7) |
| **Hypoglycaemia<sup>b</sup>** | 29 (12.5) | 27 (11.8) |
| **Confirmed hypoglycaemia<sup>b</sup>** | 12 (5.2) | 9 (3.9) |
| **Hypoglycaemia leading to discontinuation of study drug** | 0 (0.0) | 0 (0.0) |
| Genital infections   | 8 (3.4)                          | 5 (2.2)              |
| Urinary tract infections | 15 (6.5) | 8 (3.5) |
| Deaths               | 0 (0.0)                          | 0 (0.0)              |
| **AEs occurring in ≥2% of treated patients in either treatment group** |                   |
| Nasopharyngitis      | 18 (7.8)                         | 12 (5.2)             |
| Headache             | 13 (5.6)                         | 10 (4.4)             |
| Urinary tract infection (unclassified) | 10 (4.3) | 7 (3.1) |
| Influenza            | 8 (3.4)                          | 11 (4.8)             |
| Bronchitis           | 8 (3.4)                          | 2 (0.9)              |
| Upper respiratory tract infection | 7 (3.0) | 8 (3.5) |
| Back pain            | 5 (2.2)                          | 9 (3.9)              |
| Dyslipidaemia        | 5 (2.2)                          | 3 (1.3)              |
| Arthralgia           | 5 (2.2)                          | 2 (0.9)              |
| Sinusitis            | 5 (2.2)                          | 2 (0.9)              |
| Vulvovaginal mycotic infection | 5 (2.2) | 2 (0.9) |
| Gastroesophageal reflux disease | 5 (2.2) | 1 (0.4) |
| Gastroenteritis      | 4 (1.7)                          | 5 (2.2)              |
| Hypertension         | 3 (1.3)                          | 8 (3.5)              |
| Cough                | 3 (1.3)                          | 7 (3.1)              |
| Pain in extremity    | 3 (1.3)                          | 6 (2.6)              |
| Diarrhoea            | 2 (0.9)                          | 6 (2.6)              |
| Anaemia              | 1 (0.4)                          | 7 (3.1)              |
| Atrial fibrillation  | 1 (0.4)                          | 5 (2.2)              |
| Gastritis            | 1 (0.4)                          | 5 (2.2)              |
| Hyperglycaemia       | 0 (0.0)                          | 5 (2.2)              |

Abbreviations: AE, adverse event; DAPA, dapagliflozin; MET, metformin; SAE, serious adverse event; SAXA, saxagliptin; SITA, sitagliptin.

<sup>a</sup> Drug hypersensitivity.

<sup>b</sup> Excluding data after rescue medication.
of DAPA plus SAXA may result in better, more durable and well-tolerated glycaemic control than adding only a single drug (SITA) as a dual combination therapy in patients with high HbA1c levels.

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CONFLICTS OF INTEREST

Y. H. has received honoraria for consultancy from Amarin Pharmaceuticals, Amgen, AstraZeneca, Boehringer Ingelheim, Eisai, Intarcia Therapeutics, Eli Lilly & Company, Janssen Pharmaceuticals, Merck KGaA, Pfizer, Novo Nordisk, Regeneron Pharmaceuticals and Sanofi; has received research support from Amgen, AstraZeneca, Boehringer Ingelheim, Bristol-Myers Squibb, Lexicon Pharmaceuticals, Merck KGaA, Novo Nordisk and Sanofi; and serves or has served on speakers bureaus for Amarin Pharmaceuticals, Amgen, AstraZeneca, Boehringer Ingelheim, Eli Lilly & Company, Janssen Pharmaceuticals, Merck KGaA, Novo Nordisk, Regeneron Pharmaceuticals and Sanofi.

C. M. serves or has served on advisory panels for AstraZeneca, Boehringer Ingelheim, Bristol-Myers Squibb, Eli Lilly & Company, Hannmi Pharmaceuticals, Intrexon, Janssen Pharmaceuticals, Mannkind, Medtronic, Merck Sharp & Dohme, Novartis, Novo Nordisk, Pfizer, Roche Diagnostics, Sanofi and UCB; has received research support from Abbott, Eli Lilly & Company, Intrexon, Merck Sharp & Dohme, Novartis, Novo Nordisk, Roche Diagnostics and Sanofi; and serves or has served on speakers bureaus for AstraZeneca, Boehringer Ingelheim, Eli Lilly & Company, Janssen Pharmaceuticals, Merck KGaA, Novo Nordisk, Regeneron Pharmaceuticals and Sanofi.

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E. J., R. K., N. I. and R. G.-S. are employees of AstraZeneca.

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, Asahi Kasei Corporation, Boehringer Ingelheim, Bristol-Myers Squibb, Eli Lilly & Company, GlaxoSmithKline, Hannmi Pharmaceuticals, Intarcia Therapeutics, Janssen Pharmaceuticals, Lexicon Pharmaceuticals, Merck, Novartis, Novo Nordisk and Pfizer.

Author contributions

E. J., R. K., N. I. and R. G.-S. were involved in study design and conduct. All authors (Y. H., C. M., S. D. P., E. J., R. K., N. I., R. G.-S. and J. R.) had full access to study data and were involved in data interpretation and drafting and critically reviewing the manuscript. All authors approved the final version of the manuscript for submission.

ORCID

Yehuda Handelsman https://orcid.org/0000-0001-7830-0247
Chantal Mathieu https://orcid.org/0000-0002-4055-5233
Stefano Del Prato https://orcid.org/0000-0002-5388-0270
Julio Rosenstock https://orcid.org/0000-0001-8324-3275

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**SUPPORTING INFORMATION**

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