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ORIGINAL ARTICLE

Long-term effects of dapagliflozin plus saxagliptin versus glimepiride on a background of metformin in patients with type 2 diabetes: Results of a 104-week extension to a 52-week randomized, phase 3 study and liver fat MRI substudy

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Abstract

Aim: To report the results of a 104-week extension to a 52-week study in which dapagliflozin plus saxagliptin (DAPA+SAXA) improved glycaemic control, liver fat and metabolic variables compared with glimepiride (GLIM) in participants with type 2 diabetes (T2D) receiving background metformin.

Materials and methods: This extension to a 52-week global, multicentre, parallel-group, active-controlled, double-blind study (NCT02419612) continued randomized participants (1:1) on DAPA+SAXA (10/5 mg) plus placebo, or GLIM (1-6 mg) plus placebo, once daily. Eligible participants were aged ≥18 years, had T2D (glycated haemoglobin [HbA1c] 58.5-91.3 mmol/mol [7.5%-10.5%]), and a body mass index of 20.0 to 45.0 kg/m^2, and were receiving metformin (MET; ≥1500 mg/d). Key outcomes were: requirement for treatment intensification, based on HbA1c ≥53 mmol/mol (7%); achieving therapeutic glycaemic response; and changes in adipose tissue and liver fat on magnetic resonance imaging in a substudy.

Results: Overall, 382 participants entered and 338 completed the 104-week extension period (MRI substudy, n = 82). The need for treatment intensification during the 156-week period was lower for DAPA+SAXA+MET (37.0%) than GLIM+MET (55.6%; hazard ratio 0.52, 95% confidence interval [CI] 0.39-0.68; $P < 0.001$). At week 156, 21.4% of DAPA+SAXA+MET versus 11.7% of GLIM+MET participants achieved therapeutic glycaemic response (HbA1c <53 mmol/mol; odds ratio 2.1, 95% CI 1.23-3.42; $P = 0.006$). DAPA+SAXA+MET led to greater adjusted mean reductions from baseline in liver fat and visceral and subcutaneous adipose tissue volumes versus GLIM+MET at week 122 (least-squares mean difference from GLIM+MET −4.89%, −0.41 L and −0.44 L, respectively; nominal P values ≤ 0.008). Safety was consistent with that of the monocomponents.

Conclusions: Overall, glycaemic control, metabolic benefits and efficacy were better maintained with DAPA+SAXA+MET than with GLIM+MET in T2D.

KEYWORDS
dapagliflozin, DPP-4 inhibitor, liver, phase III study, sulphonylureas, type 2 diabetes

1 | INTRODUCTION

Despite the availability of multiple classes of glucose-lowering drugs, the progressive nature of type 2 diabetes (T2D) makes maintenance of glycaemic control difficult.[1] Metformin (MET) is the preferred initial pharmacological treatment, with stepwise addition of glucose-lowering drugs recommended if glycaemic targets are not acheived.[2] Because clinical inertia often leads to delays in achieving glycaemic goals, therapies that provide rapid control with durability over time are needed. Moreover, T2D is associated with nonalcoholic fatty liver disease (NAFLD)[3]; therefore, assessing the effect of treatment on liver fat and other metabolic variables, in addition to glycaemic control, is of considerable interest.

American Diabetes Association (ADA) guidance advocates consideration of initial combination therapy for patients with significantly elevated glycated haemoglobin (HbA1c) levels (1.5%-2% above target).[2] Sodium-glucose cotransporter-2 (SGLT2) inhibitors and dipeptidyl peptidase-4 (DPP-4) inhibitors are recommended as second-line therapies for T2D management.[2] The ADA also recommends SGLT2 inhibitors irrespective of HbA1c levels in patients with established atherosclerotic cardiovascular disease, kidney disease or heart failure.[2] Dapagliflozin (DAPA), a selective SGLT2 inhibitor, reduces fasting plasma glucose (FPG) levels, HbA1c levels, systolic blood pressure (SBP) and body weight in patients with T2D.[4] Saxagliptin (SAXA), a selective DPP-4 inhibitor, reduces HbA1c levels, with neutral effects on body weight.[4] Both drugs also have a low risk of causing hypoglycaemia, especially when compared with sulphonylureas.[4] The addition of DAPA in combination with SAXA to MET has been shown to have superior efficacy to that of either of the individual medications plus MET from 24 to 52 weeks of treatment.[5-9]

The optimal pharmacological approach for achieving and maintaining glycaemic targets is currently unknown, but some evidence suggests that early intensive treatment with a combination of a DPP-4 inhibitor and MET may be more beneficial than sequential addition of a DPP-4 inhibitor when MET monotherapy fails to maintain glycaemic control.[10] However, more evidence is needed to help determine whether the durability of glycaemic response and metabolic benefits can be maintained over the long term. Add-on therapy with a sulphonylurea can be considered for stepwise treatment intensification, particularly in patients for whom medication cost is a concern, although disadvantages include weight gain, increased risk of hypoglycaemia[11] and poor durability of glycaemic response.[12]

In a 52-week study, DAPA in combination with SAXA was previously evaluated as an add-on to MET in comparison with the sulphonylurea glimepiride (GLIM) plus MET in participants with T2D inadequately controlled on MET monotherapy.[13] DAPA+SAXA+MET (compared with GLIM+MET) was associated with significantly greater adjusted mean reductions from baseline at week 52 in HbA1c (least-squares [LS] mean change −1.35%, 95% confidence interval [CI] −1.49, −1.22 vs. −0.98%, 95% CI −1.12, −0.84), body weight and SBP, with 1.5 times greater odds of achieving a therapeutic glycaemic response of HbA1c <53.0 mmol/mol (7.0%) at 52 weeks, and with a lower proportion of participants requiring treatment intensification (addition of insulin or other glucose-lowering drug for rescue therapy, or discontinuation for lack of glycaemic control – defined as an HbA1c level ≥ 53.0 mmol/mol [7.0%]) during the 52-week treatment period.[13] A magnetic resonance imaging (MRI) substudy found greater adjusted mean decreases in liver fat and adipose tissue volumes from baseline at week 52 with DAPA+SAXA+MET versus GLIM+MET treatment.[14]

In the present paper, we report the results of the 104-week extension to the 52-week study, as well as the 122-week results of the MRI substudy.

2 | METHODS

2.1 | Study design and participants

This was a 52-week, global, multicentre, randomized, parallel-group, double-blind, active-controlled, phase 3b study,[13,14] with a site- and participant-blinded 104-week extension period (Figure S1). The study was conducted from August 2015 to September 2019 at 88 centres in 10 countries (United States, Hungary, Romania, Poland, Mexico, Russia, the Czech Republic, Sweden, Germany and the United Kingdom).

Eligible participants entered a 2-week screening and a 2-week lead-in period. Men and women (aged ≥18 years) with T2D, HbA1c levels of 58.5 to 91.3 mmol/mol (7.5%-10.5%; inclusive) and body mass index (BMI) of 20.0 to 45.0 kg/m^2 (inclusive) at the enrolment visit, who were currently treated with MET and on a stable dose (≥1500 mg/d) for ≥8 weeks before enrolment, were eligible for inclusion. Additional inclusion/exclusion criteria information can be found in Appendix S1 and in the the 52-week data publications.[13,14]

2.2 | Ethics

The study followed regulatory requirements, including the sponsor's policy on bioethics, and was performed in accordance with the Declaration of Helsinki and the International Council for Harmonisation Good Clinical Practice guidelines. The local independent ethics

committees/institutional review boards approved the final protocol and any amendments. All participants provided written informed consent prior to inclusion in the study and MRI substudy.

2.3 | Randomization and masking

Participants receiving MET were randomized in a 1:1 ratio to receive double-blinded once-daily DAPA 10 mg plus once-daily SAXA 5 mg plus placebo or once-daily titratable GLIM 1 to 6 mg (starting at 1 mg and titrated at 3-week intervals up to week 12 to a maximum of 6 mg using stepwise doses of 2, 3, 4 and 6 mg) plus placebo. GLIM could be downtitrated in case of hypoglycaemia. Randomization, stratified by site, was performed via an interactive voice response system that assigned each participant a unique, sequential five-digit number. Treatment with thiazolidinediones, glucagon-like peptide-1 receptor agonists, sulphonylureas and DPP-4 inhibitors or SGLT2 inhibitors other than the investigational drugs was not allowed.

Participants were rescued for hyperglycaemia with open-label insulin or, if not appropriate, other drugs except a DPP-4 inhibitor, SGLT2 inhibitor or sulphonylurea. Up-to-week-52 rescue criteria were based on FPG values,[13] whereas after-week-52 rescue was undertaken if the HbA1c level was >58.5 mmol/mol (7.5%).

2.4 | MRI substudy

As previously reported,[14] the MRI substudy included participants from the full study who had a BMI of 20.0 to 40.0 kg/m^2 (inclusive) at enrolment, a maximum weight of 140 kg to accommodate MRI scanning and no other contraindications to MRI scanning.

Participants assigned to the MRI substudy had an ad hoc visit to the imaging site within 2 weeks prior to the randomization visit, within ±2 weeks of the week-52 visit and within ±4 weeks of the week-122 visit. Visceral adipose tissue (VAT) and subcutaneous adipose tissue (SAT) volumes were assessed using abdominal MRI. Liver fat content was assessed using MRI-estimated proton density fat fraction (PDFF).

2.5 | Study objectives and assessments

Secondary endpoints for the overall 156-week study were: time to treatment intensification during the 156-week treatment period, and proportion of participants achieving a therapeutic glycaemic response at week 156.

All other objectives were exploratory and included mean changes from baseline in HbA1c, FPG, SBP, total body weight and serum alanine aminotransferase (ALT) and aspartate aminotransferase (AST) levels for all participants assessed at week 156. Other exploratory endpoints included the mean time spent at or below HbA1c 53.0 mmol/mol (7.0%) over 156 weeks, the proportion of participants achieving a therapeutic glycaemic response without any hypoglycaemia at week 156 and the proportion of participants achieving a therapeutic glycaemic response without any hypoglycaemia and without any weight gain at week 156. Participants rescued or discontinued prior to and participants with missing measurements at the specified timepoint were treated as nonresponders.

In the MRI substudy, endpoints included mean changes from baseline in liver fat percentage and SAT and VAT volumes at weeks 52 and 122. Post hoc analyses of mean changes from baseline for HbA1c, serum ALT and AST levels, body weight, and fibrosis-4 (FIB-4) scores were assessed over the 156-week treatment period for this substudy.

2.6 | Statistical analyses

Sample size calculations and other statistical analysis details can be found in the 52-week study and MRI substudy publications.[13,14]

Efficacy analyses during the 156-week treatment period included two secondary endpoints (part of sequential statistical testing[13]) and exploratory endpoints. Time to treatment intensification was tested before the proportion of participants achieving a therapeutic glycaemic response and was analysed using a Cox proportional hazards model and censored at 156 weeks if treatment intensification had not occurred by this timepoint. Participants rescued at the end of the treatment period were counted as having an event. The proportion of participants achieving a therapeutic glycaemic response at week 156 was analysed using logistic regression adjusting for baseline HbA1c. Participants rescued, discontinued prior to or with missed measurements at week 156 were considered as not achieving a glycaemic response (ie, nonresponders).

Exploratory change-from-baseline endpoints used a mixed model of repeated measures, which assumes that data are missing at random, including terms for treatment, baseline result, visit, treatment-by-visit interaction and baseline result-by-visit interaction, with no multiplicity adjustments and nominal *P* values presented. Efficacy results were summarized prior to rescue and treatment discontinuation (plus a tolerance window after the last dose). For HbA1c and body weight, assessments collected after initiation of rescue medication or collected >8 days after the last dose in the 156-week treatment period were excluded from the analysis. For lipids and SBP, >4 days was used, whereas for FPG >1 day was used.

Time spent at or below the HbA1c target (HbA1c ≤53 mmol/mol [7.0%]) over the 156-week treatment period was calculated for each participant using linear interpolation and analysed using an analysis of covariance model including terms for treatment and baseline HbA1c.

Safety data were summarized descriptively regardless of rescue medication (hypoglycaemic events summarized prior to rescue medication), and results >4 days after the last dose were excluded (30 days for serious adverse events [AEs] and liver function tests).

Statistical analyses were performed with SAS version 9.4 (SAS Institute Inc.).

3 | RESULTS

In the main 52-week study, 444 participants were randomized (443 received treatment) and 385 completed the double-blind

TABLE 1 Demographics and baseline disease characteristics (randomized analysis set)

	DAPA+SAXA+MET (N = 227)	GLIM+MET (N = 216)	Total (N = 443)
Age, years	56.1 (10.1)	56.1 (9.2)	56.1 (9.7)
Female, n (%)	110 (48.5)	115 (53.2)	225 (50.8)
Weight, kg	91.0 (19.8)	88.4 (17.1)	89.7 (18.5)
BMI, kg/m^2	32.4 (5.3)	32.2 (5.1)	32.3 (5.2)
BMI group, n (%)			
<25 kg/m^2	13 (5.7)	14 (6.5)	27 (6.1)
≥25 kg/m^2	214 (94.3)	202 (93.5)	416 (93.9)
≥27 kg/m^2	191 (84.1)	186 (86.1)	377 (85.1)
≥30 kg/m^2	145 (63.9)	136 (63.0)	281 (63.4)
Race, n (%)			
White	206 (90.7)	196 (90.7)	402 (90.7)
Black or African American	4 (1.8)	5 (2.3)	9 (2.0)
American Indian or Alaska Native	11 (4.8)	10 (4.6)	21 (4.7)
Other[a]	6 (2.6)	5 (2.3)	11 (2.5)
Region, n (%)			
North America	57 (25.1)	55 (25.5)	112 (25.3)
Latin America	39 (17.2)	37 (17.1)	76 (17.2)
Europe	131 (57.7)	124 (57.4)	255 (57.6)
Duration of T2D, years	7.7 (6.4)	7.9 (6.5)	7.8 (6.4)
HbA1c, %	8.4 (0.8)	8.5 (0.8)	8.5 (0.8)
FPG, mg/dL	172.9 (41.5)	176.5 (42.4)	174.7 (41.9)

Note: The randomized analysis set comprised all randomized participants who received ≥1 dose of the double-blinded study drug during the 52-week treatment period. Participants were included in the treatment group to which they were randomized at the start of the 52-week treatment period. Data are mean (SD), unless otherwise indicated.

Abbreviations: BMI, body mass index; DAPA, dapagliflozin; FPG, fasting plasma glucose; GLIM, glimepiride; HbA1c, glycated haemoglobin; MET, metformin; SAXA, saxagliptin; SD, standard deviation; T2D, type 2 diabetes.

[a]Includes Asian, Native Hawaiian or other Pacific Islander and Other.

treatment period.[13] Overall, 382 participants entered the 104-week long-term extension period, of whom 338 completed the extension period and 318 completed treatment during the extension period (Figure S2). A total of 82 participants who gave consent to have MRI performed were included in the randomized MRI substudy (46 in the DAPA+SAXA+MET group and 36 in the GLIM+MET group).

Treatment groups for the full study (Table 1) and the MRI substudy (Table S1) were proportionally well balanced with regard to demographics, participant characteristics and disease characteristics. Mean treatment compliance during the 156-week treatment period was ~99% in both groups.

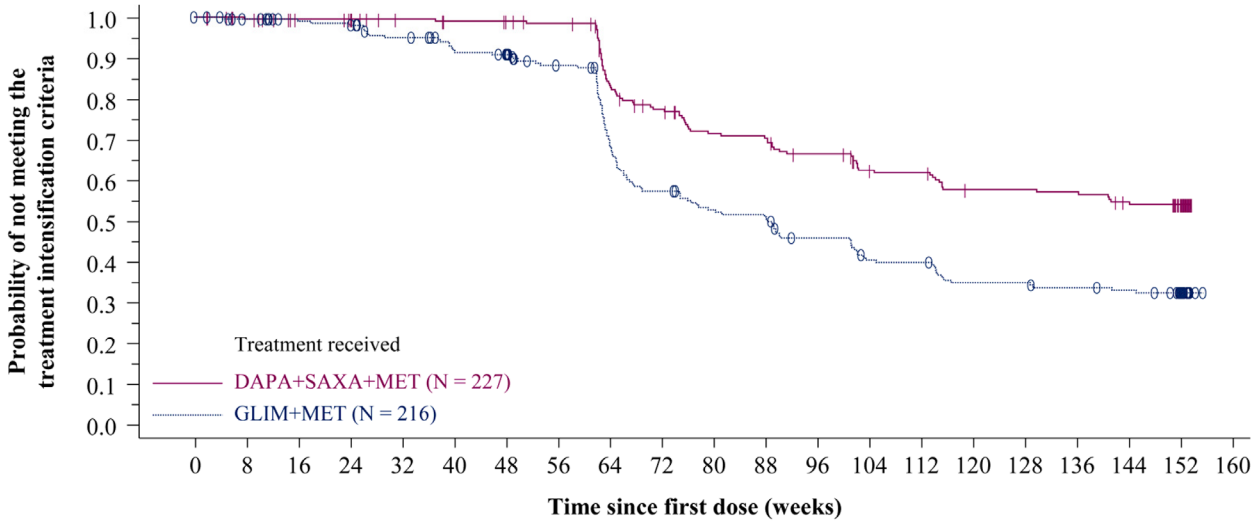
3.1 | Full study

There were 84/227 participants (37.0%) in the DAPA+SAXA+MET group and 120/216 participants (55.6%) in the GLIM+MET group who required treatment intensification by week 156. Figure 1 shows a Kaplan-Meier plot of the time to treatment intensification during the 156-week treatment period. There was a 48% decreased risk of treatment intensification during the 156-week treatment period for participants in the DAPA+SAXA+MET group compared with participants in the GLIM+MET group (hazard ratio 0.52 [95% CI 0.39, 0.68]; $P < 0.001$).

Table S2 shows the data for participants who were rescued during the 156-week treatment period and the rescue medications taken. The most common rescue treatment was insulin (49 participants [21.6%] in the DAPA+SAXA+MET group and 71 participants [32.9%] in the GLIM+MET group).

Table S3 shows the proportion of participants achieving a therapeutic glycaemic response (HbA1c <53.0 mmol/mol [7.0%]) at week 156. At week 156, 21.4% of participants in the DAPA+SAXA+MET group versus 11.7% of participants in the GLIM+MET group achieved a therapeutic glycaemic response (odds ratio 2.1 [95% CI 1.23, 3.42]; $P = 0.006$).

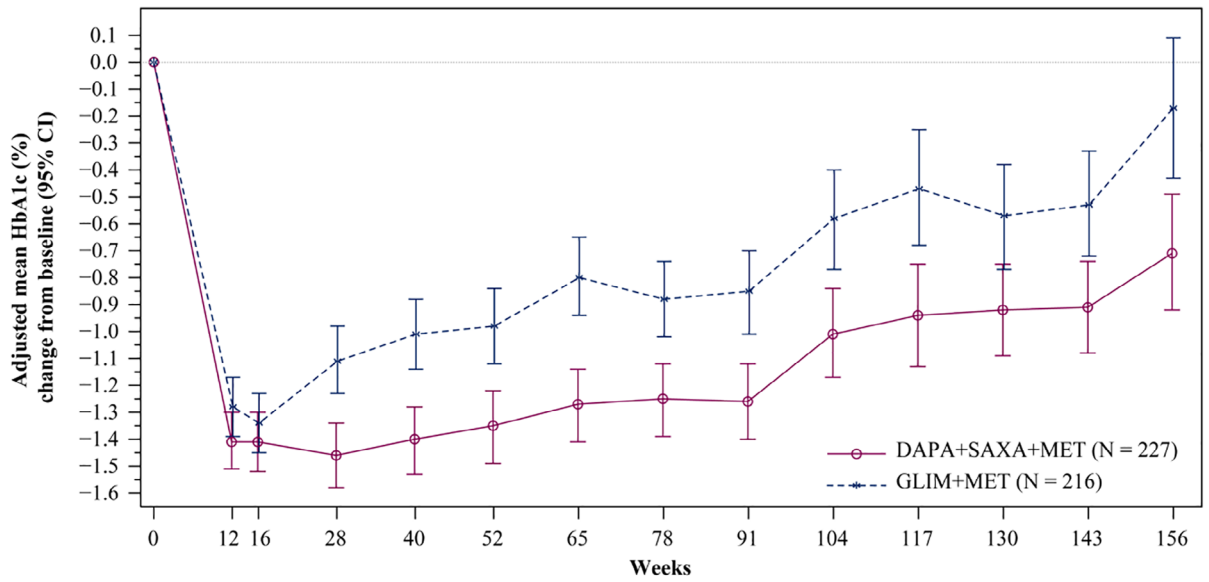
Figure 2 presents the adjusted mean change from baseline in HbA1c through to week 156. Table S4 shows additional exploratory efficacy analysis results for the 156-week treatment period. The proportion of participants in the DAPA+SAXA+MET group who achieved a therapeutic glycaemic response without any hypoglycaemia was



At risk

DAPA+SAXA+MET r =	227	220	213	208	202	200	196	191	190	147	134	129	120	119	105	97	96	95	94	88	0
GLIM+MET r =	216	213	204	199	189	187	176	162	158	104	97	90	78	77	66	57	56	53	52	49	0

FIGURE 1 Time to treatment intensification during the 156-week treatment period, Kaplan-Meier plot (randomized analysis set). Treatment intensification was defined as addition of insulin or other glucose-lowering agents for rescue therapy or discontinuation for lack of glycaemic control. Time to treatment intensification was censored at 156 weeks if treatment intensification had not occurred by then. Participants rescued at week 156 were counted as having an event for the analysis. "|" and "0" denote a censored observation. DAPA, dapagliflozin; GLIM, glimepiride; MET, metformin; N, number of participants in the treatment group; r, number of participants at risk at that timepoint; SAXA, saxagliptin



DAPA+SAXA+MET n =	218	217	211	207	197	195	192	148	128	117	104	95	94	88
GLIM+MET n =	212	210	204	197	185	171	163	103	90	76	65	56	53	49

FIGURE 2 Adjusted mean change from baseline in glycated haemoglobin (HbA1c) up to week 156, prior to rescue and treatment discontinuation (randomized analysis set). Repeated measures analysis, least-squares mean (95% confidence interval [CI]). Participants with nonmissing baseline assessment and ≥1 post-baseline assessment were included in the analysis. (DAPA+SAXA+MET, 218; GLIM+MET, 212). Week 0 refers to the baseline value. Baseline is defined as participants in the randomized analysis set with nonmissing baseline assessment and ≥1 post-baseline assessment. DAPA, dapagliflozin; GLIM, glimepiride; MET, metformin; N, number of participants in the treatment group; n, number of participants with observed result at a timepoint; SAXA, saxagliptin

TABLE 2 Selected AEs during the 156-week treatment period (treated participants dataset)

	DAPA+SAXA+MET (N = 227)	GLIM+MET (N = 216)
Regardless of rescue		
Total participants by AE category,[a] n (%)		
≥1 AE	180 (79.3)	179 (82.9)
≥1 hypoglycaemic event[b]	54 (23.8)	120 (55.6)
≥1 AE or hypoglycaemic event[b]	188 (82.8)	191 (88.4)
≥1 AE causally related to IP	41 (18.1)	20 (9.3)
Any AE with outcome of death	1 (0.4)	3 (1.4)
≥1 SAE	29 (12.8)	24 (11.1)
≥1 SAE causally related to IP	3 (1.3)	1 (0.5)
SAE leading to discontinuation of IP	2 (0.9)	8 (3.7)
AE leading to discontinuation of IP	13 (5.7)	13 (6.0)
Hypoglycaemia leading to discontinuation of IP	1 (0.4)	1 (0.5)
UTI AEs of special interest[c]		
Men		
N	117	101
Participants with any AE of UTI, n (%)	11 (9.4)	7 (6.9)
UTIs	7 (6.0)	7 (6.9)
Cystitis	3 (2.6)	0
Urethritis	1 (0.9)	0
Women		
N	110	115
Participants with any AE of UTI, n (%)	29 (26.4)	17 (14.8)
UTIs	25 (22.7)	14 (12.2)
Cystitis	2 (1.8)	4 (3.5)
Escherichia UTIs	1 (0.9)	0
Urogenital infection fungal	1 (0.9)	0
Prior to rescue		
Total participants with hypoglycaemic events, n (%)	51 (22.5)	103 (47.7)
Severe hypoglycaemia	0	3 (1.4)
Documented symptomatic hypoglycaemia	19 (8.4)	53 (24.5)
Asymptomatic hypoglycaemia	39 (17.2)	82 (38.0)
Probable symptomatic hypoglycaemia	4 (1.8)	7 (3.2)
Relative hypoglycaemia	4 (1.8)	9 (4.2)
Total number of hypoglycaemic events, n (%)	275	902
Severe hypoglycaemia	0	5 (0.6)
Documented symptomatic hypoglycaemia	65 (23.6)	292 (32.4)
Asymptomatic hypoglycaemia	190 (69.1)	581 (64.4)

TABLE 2 (Continued)

	DAPA+SAXA+MET (N = 227)	GLIM+MET (N = 216)
Probable symptomatic hypoglycaemia	4 (1.5)	12 (1.3)
Relative hypoglycaemia	11 (4.0)	16 (1.8)

Note: Safety was analysed according to the treated participants dataset, which comprised all participants who received ≥1 dose of the double-blinded study drug during the 52-week treatment period. Participants were included in the treatment group to which they were randomized, except if they received a different treatment for the entire course of participation in the treatment period. There were five events of hypoglycaemia episodes reported for the DAPA+SAXA+MET group, for which no symptoms or glucose level was recorded. Hypoglycaemic events were categorized using class of events following American Diabetes Association 2005 recommendations.[15] Percentages are based on the number of participants in the treated participants dataset, except for event level, where percentages are based on total events of hypoglycaemia.

Abbreviations: AE, adverse event; DAPA, dapagliflozin; GLIM, glimepiride; IP, investigational product; MET, metformin; N, number of participants in the treatment group; SAE, serious adverse event; SAXA, saxagliptin; UTI, urinary tract infection.

[a]Participants with multiple events in the same category are counted only once in that category. Participants with events in more than one category are counted once in each of those categories.

[b]Events recorded by the investigators are included in this category. All other categories exclude hypoglycaemic events not reported as SAEs.

[c]AEs coded using the Medical Dictionary for Regulatory Activities version 22.0.

34.8% at week 52[13] and 16.7% at week 156; corresponding values for participants in the GLIM+MET group were 14.8% at week 52 and 3.2% at week 156.

The mean (standard deviation) duration of exposure throughout the 156-week treatment period regardless of rescue was 902.0 (344.5) days in the DAPA+SAXA+MET group and 903.0 (338.5) days in the GLIM+MET group.

Table 2 summarizes the AEs, hypoglycaemic events and urinary tract infection AEs of special interest during the 156-week treatment period. None of the participants had any confirmed diabetic ketoacidosis AEs.

A greater percentage of participants with any urinary tract infection AE were in the DAPA+SAXA+MET group (17.6%) than in the GLIM+MET group (11.1%), and such AEs were more common in women than in men, regardless of group. Table S5 shows the most common AEs reported with a frequency of ≥5% in either group.

3.2 | MRI substudy

Baseline mean results for liver fat, VAT and SAT were similar for participants in the DAPA+SAXA+MET group (14.30%, 3.64 L and 4.71 L, respectively) compared with the GLIM+MET group (13.71%, 2.92 L and 4.14 L, respectively). At week 122, treatment with DAPA+SAXA +MET was associated with greater adjusted mean reductions from baseline in liver fat and VAT and SAT volumes (adjusting for baseline value) than treatment with GLIM+MET (LS mean difference from GLIM+MET −4.89%, −0.41 L and −0.44 L, respectively; nominal *P* values ≤ 0.008 [Figure 3A-C]). The mean liver fat and VAT and SAT volumes at week 122 had relative reductions from baseline of 32%, 10% and 9%, respectively, in the DAPA+SAXA+MET group, determined as follows: (mean week-122 result − mean baseline result)/mean baseline result. MRI results at week 122 were consistent with those at week 52.[14] Of the 35 participants in the DAPA+SAXA+MET group and the 24 participants in the GLIM+MET group with baseline and week-52 liver fat results, 18 (51.4%) and six (25%), respectively, were considered responders at week 52 (ie, had relative liver fat reduction from baseline of at least 30% at week 52).

Mean baseline ALT and AST levels, respectively, were 27.2 and 20.5 U/L in the DAPA+SAXA+MET group, and 29.8 and 23.6 U/L in the GLIM+MET group (Table S1). LS mean body weight and mean ALT level reductions from baseline observed at week 52 (−4.50 kg [n = 46]; −5.55 U/L [n = 44]) were sustained to week 156 (−4.36 kg [n = 46]; −7.34 U/L [n = 41]) in the DAPA+SAXA+MET group. Participants in the DAPA+SAXA+MET group had greater adjusted mean decreases from baseline at weeks 52 and 156 in total body weight (Figure 3D) and at week 52 in HbA1c (Figure S3) compared with patients in the GLIM+MET group. Mean baseline FIB-4 scores were <1.45 in both groups, indicative of an absence of advanced fibrosis, and mean FIB-4 scores were consistent throughout 156 weeks. Mean changes from baseline in ALT and AST levels over 156 weeks for DAPA+SAXA+MET and GLIM+MET are shown in Figure S4.

Figure S5 shows pre- and post-treatment liver fat (PDFF) images from two patients (one patient from each group).

4 | DISCUSSION

At 156 weeks in this 104-week extension to a 52-week study, there were greater reductions in HbA1c, body weight and liver enzymes and greater maintenance of glycaemic control with DAPA+SAXA +MET than with GLIM+MET. Additionally, a higher adjusted mean weight gain from baseline at week 156 and a higher proportion of participants with hypoglycaemia during the 156-week treatment period were observed in the GLIM+MET group than in the DAPA+SAXA +MET group.

In the MRI substudy, there were greater adjusted mean reductions from baseline in liver fat and adipose tissue volume at 122 weeks with DAPA+SAXA+MET than with GLIM+MET. These data provide evidence of the long-term durability of treatment

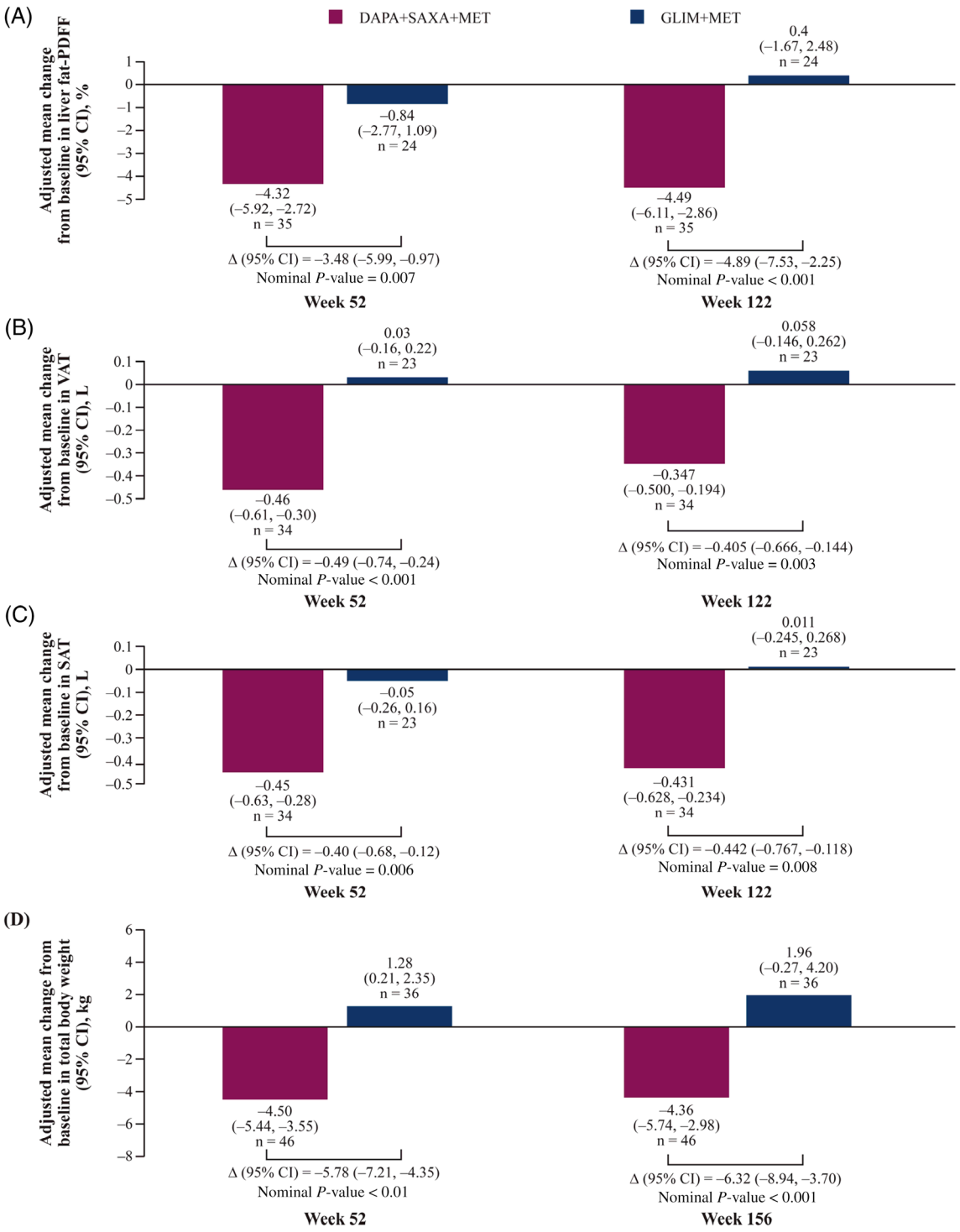


FIGURE 3 Adjusted mean change from baseline at weeks 52 and 122 in (A) liver fat (proton density fat fraction [PDFF]), (B) visceral adipose tissue (VAT) volume, (C) subcutaneous adipose tissue (SAT) volume and (D) adjusted mean change from baseline at weeks 52 and 156 in total body weight (randomized analysis set for magnetic resonance imaging substudy). Nominal *P* value for difference versus glimepiride (GLIM) plus metformin (MET) in least-squares mean change from baseline at weeks 52 (analysis of covariance [ANCOVA], except mixed model of repeated measures [MMRM] for total body weight) and 122 or 156 (MMRM), before rescue and treatment discontinuation, adjusting for baseline value. The mean liver fat and VAT and SAT volumes at week 122 had relative reductions from a baseline of 32%, 10% and 9%, respectively, in the dapagliflozin (DAPA)+ saxagliptin (SAXA)+MET group. The relative reductions are based on the unadjusted mean values at baseline and week 122. MMRM includes patients with both baseline value and ≥1 post-baseline value for the variable. ANCOVA includes patients with both baseline and week 52 results for the variable. Δ, least-squares mean difference from GLIM+MET; CI, confidence interval; n, number of patients included in the analysis

response in patients with T2D, showing that in addition to improving metabolic control, DAPA+SAXA+MET also reduces liver fat and associated markers of liver inflammation.

Many patients with poorly controlled T2D have steatosis or some degree of steatohepatitis.[16,17] Our MRI substudy results showed that treatment with DAPA+SAXA+MET was associated with greater adjusted mean decreases in liver fat (with 32% relative reduction in means) and SAT and VAT volumes from baseline at week 122 compared with treatment with GLIM+MET. Results were consistent with decreases at week 52. Other studies support the reduction in liver fat content with DAPA that we observed.[18,19] A study on body fat content and distribution (whole body, SAT, VAT and liver) that addressed effects of DAPA in combination with exenatide is largely consistent with the present data, although numeric reductions in liver fat percent units were not statistically significant.[20]

There is a strong association of NAFLD with T2D, and its presence increases the worsening of liver-related complications as well as hepatic insulin resistance.[21] Given that approximately 70% of patients with T2D have NAFLD,[16,22] interventions that can mitigate the risk, halt the progression or lessen the impact of liver disease would be valuable additions to the treatment regimens of most patients with T2D. NAFLD sometimes involves elevated ALT levels.[23] At 156 weeks in both the MRI substudy and main study, there were greater mean decreases from baseline in ALT levels in the DAPA+SAXA+MET group versus the GLIM+MET group.

Overall, our results demonstrate that DAPA+SAXA+MET offers several advantages over GLIM+MET because of greater overall glycaemic durability, HbA1c reduction, lower hypoglycaemia risk and improvement in metabolic profile as shown by weight loss and improvements in liver fat, adipose tissue volumes and liver enzyme levels over an extended time period.

Although there are no clinical studies showing the impact of liver fat and adipose tissue volume reductions on long-term metabolic health and clinical outcomes in patients with T2D, there is some clinical evidence suggesting that a reduction of >30% in liver fat at 72 weeks is associated with a statistically significant and clinically relevant histological response in patients with nonalcoholic steatohepatitis.[24,25] In a post hoc analysis of the present dataset for the MRI substudy, mean changes from baseline in HbA1c results were presented at several timepoints throughout the 156-week treatment period by responders and "less responders" for each group, where a responder was defined as a participant who had a relative reduction in liver fat (PDFF %) from baseline at week 52 of ≥30% and "less responders" had a relative reduction of <30%, no change or a relative increase. These results did not suggest a prediction of long-term glycaemic effects based on liver fat results (data not shown). Investigation of whether the improvements in indicators of liver health that we observed in the present study are associated with improvements in clinical outcomes would require larger and longer studies that are specifically designed to answer this question.

In a 4-year study, DAPA added to MET showed greater durability of glycaemic control than glipizide plus MET treatment, with less hypoglycaemia and greater reductions in body weight and SBP.[12] Combining drugs with complementary mechanisms of action has been postulated to possibly maintain long-term glycaemic control.[26] However, the results of the present study do not necessarily support that the combination per se of DAPA+SAXA+MET preserves β-cell function to any greater extent than the individual drugs, only that it offers benefits over GLIM+MET. Further studies would be needed to explore this possibility. A rationale for early combination therapy with DAPA+SAXA+MET derives from complementary mechanisms of action involving insulin-independent durable reductions in HbA1c, SBP and body weight with DAPA, glucose-dependent insulin secretion with SAXA[4] and insulin sensitization with MET.[27] Although there are adherence benefits to monotherapy,[28] aggressive early intervention with a fixed-dose combination[4] of DAPA and SAXA could improve adherence compared with administering these drugs separately.

Durable glycaemic control is a cornerstone of long-term T2D management. Our results demonstrate that more participants receiving DAPA+SAXA+MET were able to maintain durability of glycaemic response than those receiving GLIM+MET. In the short term, the difference between treatment groups in adjusted mean changes from baseline in HbA1c, particularly the increase between weeks 16 and 28 in the GLIM group, may have been attributable to hypoglycaemia and downtitration of GLIM. After week 28, the increases in adjusted mean changes from baseline in HbA1c appeared similar between the two study groups, which supports the progressive nature of T2D and the increased efficacy of the DAPA+SAXA combination versus GLIM. At week 156, DAPA+SAXA+MET was associated with greater mean reductions from baseline compared with GLIM+MET in HbA1c, body weight and serum liver enzyme levels.

The sudden increase in the number of participants in both treatment groups who required rescue therapy around week 56 was most likely protocol-driven, related to the change from FPG to HbA1c results at week 52 determining whether rescue medication should be given (ie, the requirement for rescue being more easily met after week 52).

Overall, the safety and tolerability profile of DAPA+SAXA+MET over 156 weeks was generally consistent with that observed over 52 weeks[13] and the established profiles of the individual components.[9,29]

The present study has several limitations. Although this study included participants of different races, 90% and 100% of the population were White in the study and the MRI substudy, respectively. A more diverse ethnic mix and populations comprising the elderly and those vulnerable to hypoglycaemia remains to be explored. Furthermore, GLIM was uptitrated only during the initial 12 weeks of the study to achieve a stable and maximum dose, but some participants could have benefited from further uptitration during the study. Finally, almost 12% of the participants who entered the 104-week extension period dropped out of the study and did not complete the extension period. Strengths of the study include the fact that it was long-term (3 years), with double-blinding that continued throughout the extension period, providing a comprehensive evaluation of liver fat and adipose tissue distribution over 122 weeks.

In conclusion, the present results indicate that glycaemic control and favourable metabolic benefits and efficacy are better maintained with DAPA+SAXA+MET compared with GLIM+MET in patients with T2D, with a safety profile consistent with that of the individual components.

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AUTHOR CONTRIBUTIONS

Juan P. Frías was an investigator in the study and contributed to interpretation of the results. Jill Maaske and Lisa Suchower contributed to statistical analysis and interpretation of results. Lars Johansson contributed to study design, study conduct, data collection and data analysis. Paul D. Hockings contributed to study conduct, data collection and data analysis. Nayyar Iqbal contributed to study conception, study conduct and interpretation of results. John P. H. Wilding contributed to the interpretation of the results. Juan P. Frías is the guarantor of this work and, as such, had full access to all data in the study and takes responsibility for the integrity of the data and accuracy of the data analysis. All authors contributed to critical review and revision of the manuscript and gave final approval of the version to be published.

CONFLICTS OF INTEREST

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DATA AVAILABILITY STATEMENT

Data underlying the findings described in this manuscript may be obtained in accordance with AstraZeneca's data sharing policy described at https://astrazenecagrouptrials.pharmacm.com/ST/Submission/Disclosure

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SUPPORTING INFORMATION

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