

ORIGINAL ARTICLE

Dapagliflozin plus saxagliptin add-on to metformin reduces liver fat and adipose tissue volume in patients with type 2 diabetes

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Abstract

Aim: To assess the effects of dapagliflozin plus saxagliptin plus metformin versus glimepiride plus metformin on liver fat (proton density fat fraction) and visceral and subcutaneous adipose tissue volumes over 52 weeks of treatment.

Materials and methods: This was a magnetic resonance imaging substudy of a 52-week, multicentre, randomized, double-blind, parallel-group trial that evaluated the efficacy and safety of dapagliflozin 10 mg/day plus saxagliptin 5 mg/day versus titrated glimepiride 1–6 mg (1, 2, 3, 4 or 6 mg) in 82 patients with type 2 diabetes (HbA1c 7.5%–10.5%) on metformin \geq 1500 mg/day background. Analyses were exploratory and not controlled for multiplicity; *P*-values are nominal.

Results: Magnetic resonance imaging was performed on 59 patients; liver fat and adipose tissue volumes were analysed for 59 and 57 patients, respectively. There was a significant >30% reduction from baseline in liver fat (*P* = 0.007) and >10% reduction in adipose tissue volumes (*P* < 0.01) with dapagliflozin plus saxagliptin plus metformin at week 52 versus glimepiride plus metformin. In the full-study population, dapagliflozin plus saxagliptin plus metformin decreased body weight and serum alanine aminotransferase and aspartate aminotransferase levels over 52 weeks.

Conclusions: Dapagliflozin plus saxagliptin significantly decreased liver fat and adipose tissue volume versus glimepiride, and reduced serum liver enzyme levels, indicating a favourable metabolic profile of dapagliflozin plus saxagliptin in patients with type 2 diabetes on metformin therapy.

KEYWORDS

dapagliflozin, ectopic fat, fixed-dose combination, glimepiride, liver fat, magnetic resonance imaging-estimated proton density fat fraction, metformin, nonalcoholic fatty liver disease, saxagliptin, sodium-glucose co-transporter-2 inhibitors

1 | INTRODUCTION

In patients with type 2 diabetes (T2D), weight loss is associated with improvement in glycaemic control and reduction in cardiovascular (CV) risk factors.¹ T2D is a risk factor for nonalcoholic fatty liver disease (NAFLD), which can progress to nonalcoholic steatohepatitis (NASH) and ultimately cirrhosis and/or liver cancer.² NAFLD has been defined by $\geq 5\%$ macrovesicular hepatocyte steatosis in the absence of significant alcohol use, and is the most common cause of liver enzyme increases.³ Almost three quarters of patients with T2D have NAFLD.^{4,5} Body weight reduction is one of the few measures that may prevent liver dysfunction.^{6,7} Given the well-known contribution of some commonly used T2D drugs, such as sulfonylureas, to weight gain,⁸ alternative drug therapies are desirable in patients with T2D with or at risk of concomitant liver disease.

Ectopic fat accumulation, including that of the liver, is related to increased insulin resistance.⁹ Weight loss results in a reduction in liver fat content.⁷ Reducing liver fat content in addition to weight loss may therefore help prevent liver disease progression in patients with T2D. Dapagliflozin is a sodium-glucose co-transporter-2 (SGLT2) inhibitor that reduces hyperglycaemia independent of insulin and also results in weight loss and moderate blood pressure reduction in patients with T2D.^{10,11} Most of the weight loss associated with dapagliflozin has been shown to be because of reductions in total body fat mass, abdominal visceral adipose tissue (VAT) volume and subcutaneous adipose tissue (SAT) volume.¹²

Saxagliptin, a selective dipeptidyl peptidase-4 (DPP-4) inhibitor, also reduces HbA1c regardless of T2D stage, although with no clinically significant effects on body weight.¹³ The fixed-dose combination of dapagliflozin and saxagliptin was approved by the United States Food and Drug Administration on February 28, 2017, for improving glycaemic control in adults with T2D as an adjunct to diet and exercise for those who have inadequate control with dapagliflozin or who are already being treated with dapagliflozin and saxagliptin.¹⁴ Evidence from phase 3 studies of dapagliflozin plus saxagliptin indicates that weight loss observed with concomitant administration of dapagliflozin and saxagliptin is similar to that of dapagliflozin alone.^{15,16} A global phase 3b study (NCT02419612) found better efficacy (as shown by a significantly decreased HbA1c) for dapagliflozin plus saxagliptin versus the sulfonylurea glimepiride, both groups on metformin background, in patients with T2D who had inadequate glycaemic control on metformin

alone.¹⁷ Safety profiles were similar between the two groups, although the incidence of hypoglycaemia was lower in the dapagliflozin plus saxagliptin group.¹⁷ Here, we report a substudy of this trial that used magnetic resonance imaging (MRI) to determine liver fat deposition via assessment of proton density fat fraction (PDFF), VAT volume and SAT volume over 52 weeks of treatment.

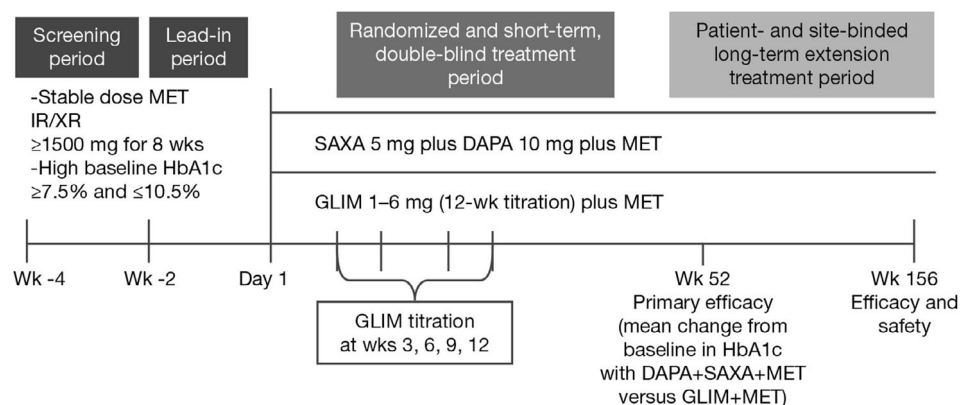
2 | MATERIALS AND METHODS

2.1 | Study design and patients

This was a 52-week, international, multicentre, randomized, double-blind, active-controlled, parallel-group, phase 3b study, with a patient- and site-blinded, 104-week, long-term extension period (Figure 1). At week 52, the least-squares mean change (95% confidence interval [CI]) in HbA1c was -1.35% (-1.49 , -1.22) for the dapagliflozin plus saxagliptin group, and -0.98% (-1.12 , -0.84) for the glimepiride group, with similar rates of adverse events between groups.¹⁷

The study was conducted at 87 centres in 10 countries beginning on August 14, 2015 and comprised a 2-week screening period and a 2-week lead-in period. The study enrolled male or female patients (aged ≥ 18 years) with T2D, with HbA1c from $\geq 7.5\%$ (58.5 mmol/mol) to $\leq 10.5\%$ (91.3 mmol/mol), with a body mass index (BMI) of 20.0 – 45.0 kg/m² (inclusive) at enrolment, and on the same daily dose of metformin ≥ 1500 mg for at least 8 weeks before enrolment. Key exclusion criteria comprised clinical diagnosis of type 1 diabetes, malignancy within 5 years of the screening visit (with the exception of treated basal cell or treated squamous cell carcinoma), pregnancy, history of diabetic ketoacidosis and history of CV/vascular disease within 3 months of enrolment, including transient ischaemic attack or significant cerebrovascular disease, and unstable or previously undiagnosed arrhythmia. Patients with impaired renal function (creatinine clearance < 60 mL/min/1.73m² [estimated by Cockcroft–Gault] or serum creatinine ≥ 1.5 mg/dL [132.6 μ mol/L] in males or ≥ 1.4 mg/dL [123.8 μ mol/L] in females), severe hepatic insufficiency and/or significant abnormal liver function (aspartate aminotransferase [AST] $> 3 \times$ upper limit of normal [ULN] and/or alanine aminotransferase [ALT] $> 3 \times$ ULN),

FIGURE 1 Study design (NCT02419612). DAPA, dapagliflozin; GLIM, glimepiride; IR, instant release; MET, metformin; SAXA, saxagliptin; XR, extended release



positive serologic evidence of current infectious liver disease, including patients who were positive for hepatitis B viral antibody immunoglobulin M, hepatitis B surface antigen and hepatitis C antibody, and/or history of current, acute or chronic pancreatitis were also excluded. Further details are in the primary study article.¹⁷

2.2 | Interventions

Patients on metformin were randomly assigned, based on a randomization schedule stratified by site and using an interactive voice response system, to the following double-blinded treatment groups in a 1:1 ratio: dapagliflozin 10 mg plus saxagliptin 5 mg plus placebo, each administered orally once daily (QD), or glimepiride 1–6 mg (specifically 1, 2, 3, 4 or 6 mg) plus placebo, each administered orally QD. A fasting plasma glucose level of ≤ 270 mg/dL (15.0 mmol/L) was required at randomization. The starting dose for glimepiride was 1 mg QD, and was titrated stepwise using doses of 2, 3, 4 and 6 mg QD at 3-week intervals to a maximum of 6 mg QD. In patients for whom titration was not medically indicated at week 3, reassessment for titration occurred at weeks 6, 9 and 12. Glimepiride could be downtitrated in the event of hypoglycaemia.

2.3 | MRI substudy

The MRI substudy included patients from the full study who provided informed consent, had no contraindications to MRI scanning, and had a BMI of 20.0–40.0 kg/m² (inclusive) at enrolment and a maximum weight of 140 kg to accommodate MRI scanning. No other selection criteria were applied for participation in the substudy. The MRI substudy was conducted at nine MRI centres in Hungary, the Czech Republic, Poland, Russia and Sweden using GE HealthCare, Siemens or Philips 1.5 or 3 T MRI scanners. MRI centres were selected based on proximity to study sites willing to participate in the MRI substudy and ability to perform PDFF measurements. To qualify, at each site a healthy volunteer was scanned and PDFF values in adipose tissue and muscle were checked to test that the PDFF measurements gave reasonable results. No phantom was used because MRI-PDFF has been shown to have excellent linearity, bias and precision across different field strengths, imager manufacturers and reconstruction methods.^{18–20} The MRI substudy endpoint was 52 weeks. SAT and VAT volumes were assessed using abdominal MRIs of patients. Liver fat content was assessed using MRI-PDFF. This well-validated, noninvasive imaging technique exploits the difference in MRI chemical shift of triglyceride-based mobile protons from that of the water to enable accurate quantitative liver fat assessment over the entire liver.²¹ In adults with NAFLD, MRI-PDFF correlates highly with steatosis grade²² and is a useful method in NASH clinical trials.²¹ MRI is a comprehensive tool to quantify fat, able to differentiate between VAT and SAT with multidimensional images and to quantify ectopic fat safely and with minimal examination time.²³

2.4 | Assessments

The mean change from baseline in liver fat percentage by MRI-PDFF and VAT and SAT volumes was assessed by MRI in both treatment groups at week 52 in the subpopulation of patients in the MRI substudy.

2.5 | Statistical analyses

Efficacy analyses were performed using the randomized patient dataset (all randomized patients who received at least one dose of study medication) during the double-blind treatment period. Analysis for change in serum liver enzyme levels was conducted on the treated patient dataset (all patients who received at least one dose of study medication during the study treatment period) during the short-term double-blind treatment period. Analyses of change from baseline in liver fat percentage and VAT and SAT volumes in the MRI substudy were performed using the analysis of covariance (ANCOVA) model based on last observation carried forward (LOCF) data. MRI analyses were not controlled for multiplicity and nominal *P*-values are presented. Analysis of mean change from baseline in total body weight was performed using a longitudinal repeated measures model. All statistical analyses were performed using SAS version 9.4 (SAS Institute, Cary, NC).

3 | RESULTS

3.1 | Patient disposition

Overall, 823 patients were enrolled. Of these, 444 entered the double-blind treatment period; 227 were randomized to dapagliflozin plus saxagliptin plus metformin and 217 were randomized to glimepiride plus metformin (Figure S1). A total of 82 patients provided informed consent to participate in the MRI substudy, of whom 46 were in the dapagliflozin plus saxagliptin plus metformin treatment group and 36 were in the glimepiride plus metformin treatment group.

3.2 | Baseline demographics

Key baseline characteristics of the MRI substudy patients were well balanced between the groups (Table 1).

3.3 | MRI substudy

MRI was performed on 59 patients and liver fat and adipose tissue volume were analysed for 59 and 57 patients, respectively. There was a significant >30% reduction from baseline in liver fat ($P = 0.007$) and a >10% reduction in VAT volume ($P < 0.001$) and SAT volume

TABLE 1 Demographics and baseline disease characteristics (randomized patient dataset) for the MRI substudy

Characteristic	DAPA+SAXA+MET (n = 46)	GLIM+MET (n = 36)	Total (N = 82)
Age, years	58.9 (8.2)	56.9 (10.0)	58.0 (9.0)
Female, n (%)	22 (47.8)	19 (52.8)	41 (50.0)
Weight, kg	94.4 (16.5)	90.9 (17.3)	92.9 (16.8)
BMI, kg/m ²	32.9 (4.7)	32.3 (5.1)	32.6 (4.9)
BMI group, kg/m ² , n (%)			
<25	1 (2.2)	3 (8.3)	4 (4.9)
≥25– <27	4 (8.7)	1 (2.8)	5 (6.1)
≥27– <30	11 (23.9)	8 (22.2)	19 (23.2)
≥30	30 (65.2)	24 (66.7)	54 (65.9)
Race, n (%)			
White	46 (100.0)	36 (100.0)	82 (100.0)
Region, n (%)			
Europe	46 (100.0)	36 (100.0)	82 (100.0)
Duration of T2D, years	6.4 (5.8)	6.5 (6.4)	6.4 (6.0)
HbA1c, %	8.4 (0.8)	8.6 (0.9)	8.5 (0.9)
FPG, mg/dL	10.2 (3.1)	10.5 (2.6)	10.4 (2.8)

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

All data are reported as mean (SD) unless specified otherwise. Includes all patients who consented to be in the MRI substudy.

($P = 0.006$) with dapagliflozin plus saxagliptin plus metformin at week 52 versus glimepiride plus metformin (Table 2 and Figure 2).

3.4 | Full study

For patients in the dapagliflozin plus saxagliptin plus metformin treatment group, body weight (mean \pm standard deviation [SD]) reduced from 90.8 ± 19.7 kg at baseline to 88.4 ± 18.1 kg at week 52. Patients in the glimepiride plus metformin treatment group experienced weight gain (mean \pm SD) from 88.4 ± 17.0 kg at baseline to 90.6 ± 17.4 kg at week 52. The decrease in mean total body weight from baseline to week 52 in the dapagliflozin plus saxagliptin plus metformin treatment group was significantly different from that in the glimepiride plus metformin treatment group (difference [95% CI], -4.1 kg [-4.8 , -3.3]; $P < 0.001$). The difference in body weight between treatment groups was evident at week 3 (difference [95% CI], -1.1 kg [-1.4 , -0.9]; $P < 0.001$; Figure 3).

At week 52, there was a decrease from baseline in the serum levels of both ALT and AST in the dapagliflozin plus saxagliptin plus metformin treatment group. Although ALT and AST levels decreased they remained within the normal range. By contrast, enzyme levels increased in the glimepiride plus metformin treatment group (Figure S2).

TABLE 2 Liver fat and adipose tissue volumes over the 52-week, double-blind treatment period for the magnetic resonance imaging (MRI) substudy

Variable	DAPA+SAXA+MET	GLIM+MET	P-value [†]
N	35	24	
Liver fat, PDFF%			
Baseline	14.3 (6.4)	13.7 (8.3)	
Week 52	9.9 (7.1)	12.9 (8.6)	0.007
N	34	23	
VAT, L			
Baseline	3.6 (1.1)	2.9 (1.1)	
Week 52	3.2 (1.1)	3.0 (1.1)	< 0.001
SAT, L			
Baseline	4.7 (2.2)	4.1 (1.8)	
Week 52	4.2 (2.0)	4.1 (1.7)	0.006

Abbreviations: ANCOVA, analysis of covariance; DAPA, dapagliflozin; GLIM, glimepiride; LOCF, last observation carried forward; LS, least squares; MET, metformin; PDFF, proton density fat fraction; SAT, subcutaneous adipose tissue; SAXA, saxagliptin; SD, standard deviation; VAT, visceral adipose tissue.

All data are reported as mean (SD) unless specified otherwise.

[†]Nominal P-value for LS mean difference in change from baseline to week 52 between groups. Analysis of mean change from baseline in total body weight was performed using a longitudinal repeated measures model.

Analyses of change from baseline in liver fat percentage and VAT and SAT volumes in the MRI substudy were performed using the ANCOVA model based on LOCF data.

4 | DISCUSSION

In this 52-week MRI substudy of a phase 3b, randomized, active-controlled study, the SGLT2 inhibitor dapagliflozin, co-administered with the DPP-4 inhibitor saxagliptin, significantly decreased liver fat content, adipose tissue volume and body weight versus the sulfonyl-urea glimepiride, with both groups on metformin background. Serum liver enzyme levels in the dapagliflozin group were lower than in the saxagliptin group, and although still in the normal range, did show a decreasing trend. Elevated ectopic fat is a significant contributor to the pathogenesis of T2D.²⁴ Because liver fat correlates with increased mortality from liver disease,²⁵ the significant reduction in liver fat content observed in this substudy indicates that the combination of dapagliflozin plus saxagliptin added to metformin could help prevent the progression of liver disease in patients with T2D.

Although the mechanisms by which liver fat reduction occurs with SGLT2 inhibition are not fully established, there are several possibilities. These include reduced hepatic lipogenesis, increased hepatic insulin extraction as seen with dapagliflozin,²⁶ improvements in insulin concentrations and/or resistance, and/or, as seen in some animal models, suppression of inflammatory cytokines and/or mitigation of oxidative stress.^{27–29} Additionally, dapagliflozin's possible role as an alpha cell secretagogue that has been shown to promote glucagon secretion³⁰ is consistent with its ability to reduce intrahepatic lipid content.

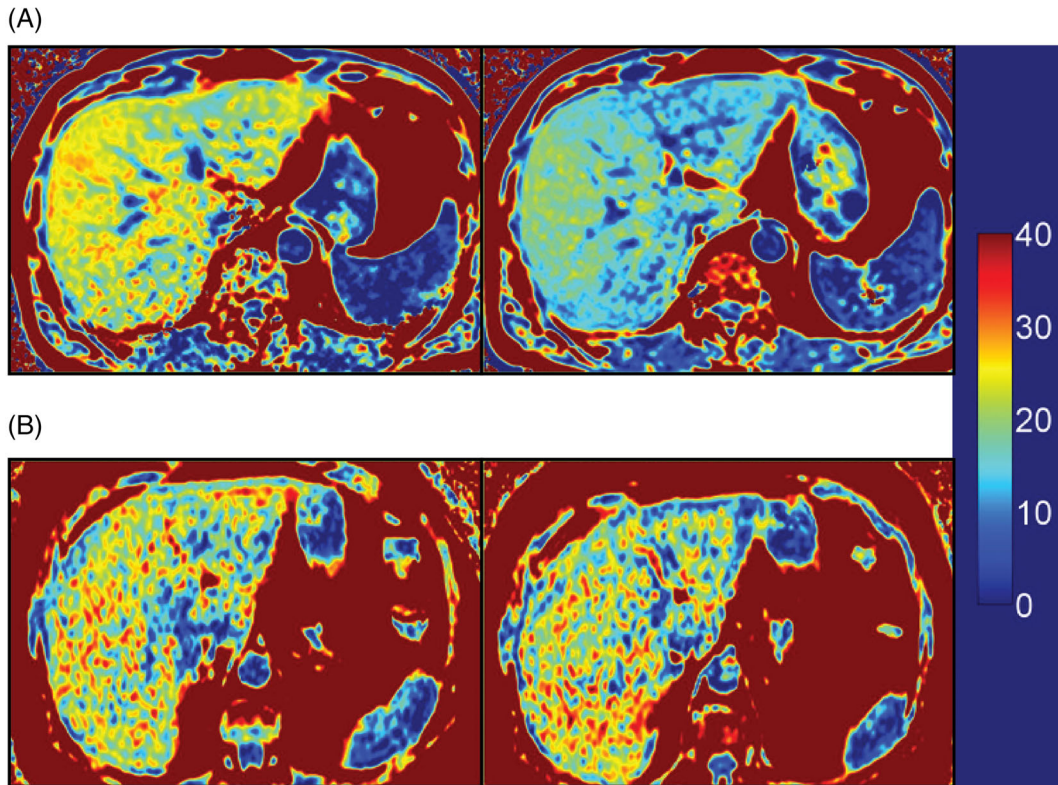


FIGURE 2 Representation of liver magnetic resonance imaging-estimated proton density fat fraction (MRI-PDFF) pre- and post-treatment. (A) Pre- and post-treatment MRI-PDFF for dapagliflozin plus saxagliptin plus metformin and (B) pre- and post-treatment MRI-PDFF for glimepiride plus metformin

There may also be several mechanisms by which reductions in liver fat content could lead to therapeutic benefit in patients with T2D. The strong association between VAT and liver fat content with hepatic insulin resistance in patients with T2D³¹ suggests one possibility. The liver fat reduction results we found are consistent with those of other studies of dapagliflozin. In a 12-week, randomized controlled study, dapagliflozin significantly reduced liver fat in patients with T2D and NAFLD.³² In a 6-month Japanese study, dapagliflozin

significantly reduced liver size and hepatic fat accumulation in patients with inadequately controlled T2D. However, the study's open-label and nonrandomized design precludes firm conclusions.²⁶ Liver enzymes were decreased with empagliflozin treatment in the EMPA-REG OUTCOME trial.³³

Although the direct contribution of each drug in the dapagliflozin plus saxagliptin combination to liver improvement could not be determined, a previous study with a DPP-4 inhibitor did not find a

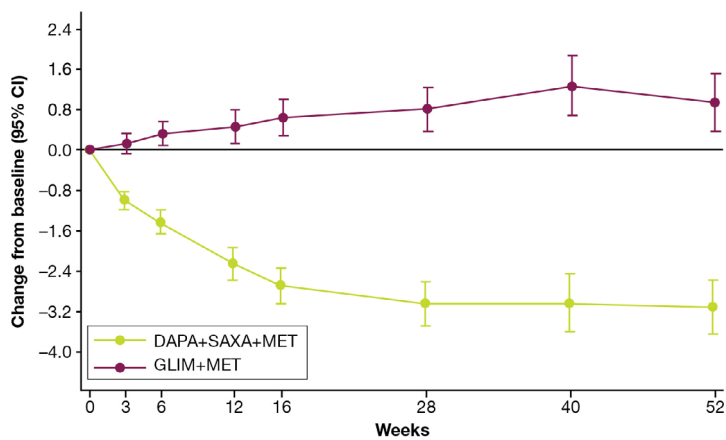


FIGURE 3 Adjusted mean change from baseline in total body weight during the 52-week, double-blind treatment period[†].

Body weight assessments collected after initiation of rescue treatment or collected more than 8 days after the last dose in the short-term, double-blind treatment period were excluded from the analysis. [†]Patients from the randomized patient dataset with nonmissing baseline assessment at week 52 were included in this analysis. Baseline is defined as patients in the randomized patient dataset with nonmissing baseline assessment and at least one postbaseline assessment. DAPA, dapagliflozin; GLIM, glimepiride; MET, metformin; SAXA, saxagliptin

DAPA+SAXA+MET, n =	224	224	222	216	212	206	195	194
GLIM+MET, n =	214	214	213	209	205	197	187	172

reduction in hepatic fibrosis or steatosis in patients with T2D,³⁴ suggesting that the beneficial liver effects observed in the current study were a result of dapagliflozin. However, significant reductions in body weight, VAT volume and liver fat content assessed by MRI-PDF were found with 26-week DPP-4 inhibitor treatment in patients with T2D and NAFLD.³⁵ Baseline DPP-4 activity has been reported to be higher in insulin-resistant patients with NAFLD than in healthy controls,³⁶ and a small uncontrolled study reported a significant decrease in hepatic lipid content after 6 months of vildagliptin or sitagliptin treatment, although only in females.³⁷

Elevated ALT levels sometimes indicate the presence of NAFLD, and in NAFLD cases with normal liver enzyme levels, assessment of liver fibrosis markers is recommended.^{2,38} In the current study, ALT levels decreased in the dapagliflozin plus saxagliptin versus glimepiride treatment group. SGLT2 inhibitors have been shown to result in significantly greater reductions in ALT levels than incretin-based drugs in patients with T2D,³⁹ lending support to the notion that the ALT decreases observed in the current study were primarily attributable to dapagliflozin.

The weight loss observed with dapagliflozin plus saxagliptin was consistent with that observed in previous studies.¹⁶ The difference in weight loss between the treatment groups was evident by week 3, suggesting that the trend towards weight maintenance or decrease among patients receiving dapagliflozin plus saxagliptin versus those receiving glimepiride is rapid and sustainable. However, weight loss alone may not be sufficient to entail a reduction in liver fat content. This is supported by the fact that glucagon-like peptide-1 receptor agonism⁴⁰ and thiazolidinedione treatment⁴¹⁻⁴³ in patients with T2D have been shown to result in liver fat reductions independent of effects on body weight. In the current study, at least some of the reduction in liver fat content with dapagliflozin plus saxagliptin compared with glimepiride could have been because of a reduction in body weight; however, because glimepiride resulted in weight gain, it is not possible to compare the differential effects of the two treatment groups with respect to liver fat reduction. Although the reduction in liver fat in the current study was accompanied by overall weight loss, there is some evidence to suggest that reductions in liver fat with SGLT2 inhibition may be independent of SGLT2 inhibitors' effects on weight loss.⁴⁴ We did not, however, investigate if this was true for dapagliflozin.

In conclusion, dapagliflozin co-administered with saxagliptin significantly decreased liver fat and adipose tissue volume versus glimepiride. The decrease in liver fat and adipose tissue volume was accompanied by a significant reduction in body weight and a reduction in the levels of serum liver enzymes for patients in the full study in the dapagliflozin plus saxagliptin group. These results indicate a favourable metabolic profile of dapagliflozin plus saxagliptin versus glimepiride in patients with T2D.

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CONFLICT OF INTEREST

ND, JM and EJ are employees of AstraZeneca. RG-S was an employee of AstraZeneca at the time the work was conducted. PDH and LJ are employees of Antaros Medical AB, which received payment from AstraZeneca for conducting the study. LJ is a shareholder in Antaros Medical AB. JPHW, outside the submitted work, has grants, personal fees and consultancy fees (paid to his institution) from AstraZeneca, Novo Nordisk and Takeda; personal fees and consultancy fees (paid to his institution) from Boehringer Ingelheim, Janssen, Lilly, Mundipharma, Napp and Sanofi; and consultancy fees (paid to his institution) from Wilmington Healthcare.

AUTHOR CONTRIBUTIONS

JPHW contributed to data interpretation. PDH contributed to study conduct, data collection and data analysis. EJ and LJ contributed to study design, study conduct, data collection and data analysis. All authors contributed to critical review of the manuscript.

ETHICAL APPROVAL

All procedures involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Declaration of Helsinki and its later amendments or comparable ethical standards. The study was conducted in accordance with the International Council for Harmonisation Good Clinical Practice Guidelines, and followed applicable regulatory requirements, including AstraZeneca's policy on bioethics. The local Institutional Review Boards or Independent Ethics Committees approved the final protocol and amendment. All patients provided written informed consent. 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

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

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