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Exenatide and dapagliflozin combination improves markers of liver steatosis and fibrosis in patients with type 2 diabetes

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Abstract

Aim: To assess the efficacy of exenatide (EXE) once weekly + dapagliflozin once daily (DAPA) versus each drug alone in reducing biomarkers of fatty liver/steatosis and fibrosis in a *post hoc* analysis of DURATION-8, a 104-week study in 695 patients with type 2 diabetes uncontrolled by metformin monotherapy.

Materials and methods: We evaluated the impact of the study treatments on non-invasive markers of hepatic steatosis (fatty liver index [FLI] and non-alcoholic fatty liver disease [NAFLD] liver fat score), fibrosis (fibrosis-4 index [FIB-4]) and severe fibrosis (NAFLD fibrosis score), along with liver enzymes and insulin resistance, at weeks 28 and 52. All outcomes in this analysis were exploratory, with nominal *P* values reported.

Results: At week 28, biomarkers of fatty liver/steatosis and fibrosis were reduced from baseline in all treatment groups. At week 28, EXE once weekly + DAPA effects for decrease in FLI were stronger than those of EXE once weekly + placebo (PLB; −2.92, 95% confidence interval [CI] −5.11, −0.73; $P = 0.0092$) or DAPA+PLB (−2.77 [95% CI −4.93, −0.62]; $P = 0.0119$), and stronger than those of EXE once weekly + PLB at week 52 (−3.23 [95% CI −5.79, −0.68]; $P = 0.0134$). FIB-4 showed reduction versus baseline only in the EXE once weekly + DAPA group at both week 28 (−0.06 [95% CI −0.11, −0.01]; $P = 0.0135$) and week 52 (−0.05 [95% CI −0.09, −0.004]; $P = 0.0308$).

Conclusions: The EXE once weekly + DAPA combination showed stronger effects than EXE once weekly + PLB or DAPA + PLB in ameliorating markers of hepatic steatosis and fibrosis in patients with type 2 diabetes. Prospective trials are needed to validate these findings.

KEYWORDS

dapagliflozin, exenatide, liver, type 2 diabetes

1 | INTRODUCTION

Type 2 diabetes is associated with an increased risk of non-alcoholic fatty liver disease (NAFLD) as a result of factors including obesity and insulin resistance.[1,2] It has been estimated that 50% of people with type 2 diabetes have NAFLD despite exhibiting liver enzymes within normal ranges.[1] People with type 2 diabetes and NAFLD are at an increased risk of disease progression to non-alcoholic steatohepatitis (NASH), fibrosis, cirrhosis and hepatocellular carcinoma.[2] Moreover, NAFLD is independently associated with both prevalent and incident

cardiovascular disease,[2,3] and mortality risk increases exponentially with the severity of NAFLD.[4] The most recent American Diabetes Association guidelines recommend that people with type 2 diabetes or prediabetes with elevated liver enzymes or fatty liver should be evaluated for the presence of NASH and fibrosis, with non-invasive biomarkers used to assess the risk of fibrosis.[5] Despite this, less than 5% of diabetes specialists correctly assess the prevalence and severity of advanced fibrotic NAFLD in patients with type 1 or type 2 diabetes.[6]

For the screening/diagnosis of NAFLD, imaging techniques are expensive and are recommended only after an initial diagnosis of NAFLD is made using non-invasive biomarkers.[2,7] Non-invasive, clinically validated biomarkers that combine metabolic and hepatic parameters routinely measured in clinical practice have been developed and approved by the European Association for the Study of the Liver, the European Association for the Study of Diabetes (EASD) and the European Association for the Study of Obesity.[2] These include the fatty liver index (FLI)[8] and the NAFLD liver fat score (NLFS)[9] for the diagnosis of NAFLD, and the NAFLD fibrosis score (NFS)[10] and the fibrosis-4 index (FIB-4)[11] for the diagnosis of liver fibrosis.

Early diagnosis, assessment and intervention are important to stop the progression of NAFLD, because no pharmacotherapies are currently approved by the US Food and Drug Administration for the treatment of the more advanced stage NASH.[2] Glucose-lowering agents have been shown to improve NAFLD, but their direct, long-term impact remains to be fully explored.[12] Pioglitazone has demonstrated reductions in fatty liver content and has provided some resolution of NASH in patients with type 2 diabetes, but with the side effect of significant weight gain.[2,13] Evidence indicates that glucagon-like peptide-1 receptor agonists (GLP-1RAs) and sodium-glucose co-transporter-2 (SGLT2) inhibitors have some benefits in patients with type 2 diabetes and NAFLD/NASH.[14-19] For example, in a phase 2 study, 48 weeks of liraglutide treatment led to biopsy-confirmed resolution of NASH in 39% of overweight patients with or without type 2 diabetes.[14] Furthermore, semaglutide treatment reduced markers of NAFLD (ie, alanine aminotransferase [ALT] and high-sensitivity C-reactive protein) in patients with obesity and/or type 2 diabetes.[15] With regard to SGLT2 inhibitors, a 24-week, open-label, randomized trial of dapagliflozin (DAPA) monotherapy in patients with type 2 diabetes and NAFLD reported overall improvements in hepatic steatosis, along with attenuation of fibrosis in a subset of patients with significant fibrosis.[16] Additionally, 24 weeks of canagliflozin treatment demonstrated improvements in the individual histological components of NASH (eg, steatosis, lobular inflammation and ballooning) in patients with type 2 diabetes and NAFLD.[17] Building on these results, the GLP-1RA and SGLT2 inhibitor combination could have a synergistic effect on improving steatosis, steatohepatitis and/or fibrosis in patients with type 2 diabetes and NAFLD; however, this remains to be examined in a randomized controlled trial.

DURATION-8 (NCT02229396) was a multicentre, double-blind, randomized, active-controlled, phase 3 trial that evaluated the effects of exenatide (EXE) once weekly plus DAPA once daily (EXE once weekly + DAPA) compared with EXE once weekly plus placebo (PLB; EXE once weekly + PLB) and DAPA + PLB in people with type 2 diabetes (n = 695) and poor glycaemic control despite metformin monotherapy.[20-22] At 28 weeks, treatment with EXE once weekly + DAPA, compared with each drug alone, significantly reduced glycated haemoglobin (HbA1c) from baseline, along with body weight and systolic blood pressure,[20] with improvements maintained at 52 and 104 weeks.[21,22] In the present study, we conducted a *post hoc* analysis to evaluate the change from baseline to weeks 28 and 52 in non-invasive biomarkers of fatty liver/steatosis and fibrosis in the three treatment groups.

2 | MATERIALS AND METHODS

The study design of DURATION-8 has been previously described.[20,21] In brief, the multicentre study (118 sites) enrolled adults aged ≥18 years with type 2 diabetes and poor glycaemic control (HbA1c 64–108 mmol/mol [8.0%–12.0%]) despite stable metformin monotherapy at ≥1500 mg/d for at least 2 months before screening. Participants (n = 695) were randomized (1:1:1) to receive EXE once weekly 2 mg plus oral DAPA 10 mg once daily, EXE once weekly 2 mg plus DAPA-matched oral PLB or DAPA 10 mg once daily plus EXE once weekly-matched PLB injections for 104 weeks (28-week initial treatment period followed by a 24-week, double-blind first extension period and a 52-week, second double-blind extension period; Figure S1).[20-22] Baseline characteristics of patients have been previously reported[20,21] and were broadly similar across treatment groups (Table 1).

The primary endpoint of DURATION-8 was change in HbA1c from baseline to week 28.[20] The main objective of the present *post hoc* analysis was to assess the effects of EXE once weekly + DAPA, EXE once weekly + PLB and DAPA + PLB treatments on change from baseline to weeks 28 and 52 in guideline-approved[2] biomarkers of fatty liver/steatosis (FLI and NLFS)[8,9] and fibrosis (NFS and FIB-4[10,11]; Table S1). In brief, the FLI comprises body mass index (BMI), waist circumference and serum levels of triglycerides and gamma-glutamyltransferase (GGT); a cut-off score of ≥60 rules-in hepatic steatosis as detected by ultrasonography.[8] The NLFS includes presence of metabolic syndrome and type 2 diabetes, fasting serum insulin concentration, aspartate aminotransferase (AST) and AST:ALT ratio; a cut-off score of > − 0.640 has good sensitivity to predict increased liver fat.[9] The NFS is based on age, BMI, the presence of type 2 diabetes or impaired fasting glucose, platelet count, albumin and AST:ALT ratio.[10] The FIB-4 comprises age, AST, ALT and platelet count.[11] A FIB-4 ≥ 1.3 cut-off score has high sensitivity and specificity for the diagnosis of fibrosis, whilst the NFS cut-off score of >0.676 is used for the diagnosis of severe fibrosis (stages F3 and F4).[10,11] Additional details of the constituent elements of the biomarkers used in the present study, including their scoring criteria and cut-offs, can be found in Table S1.

Changes from baseline to weeks 28 and 52 in ALT, AST, AST:ALT ratio and GGT were assessed, along with the proportion of participants with positive biomarker scores at weeks 28 and 52 versus baseline. Additional metabolic variables evaluated were changes from baseline to weeks 28 and 52 in homeostatic model assessment of insulin resistance (HOMA-IR), adipose tissue insulin resistance (Adipo-IR), HbA1c, body weight, triglycerides and fasting plasma insulin (FPI). HOMA-IR was calculated with the HOMA2 Calculator, based on fasting plasma glucose

TABLE 1 Key demographics and baseline characteristics (intention-to-treat population)

Characteristics	EXE once weekly + DAPA (n = 228)	EXE once weekly + PLB (n = 227)	DAPA + PLB (n = 230)
Age, years	53.8 ± 9.8	54.2 ± 9.6	54.5 ± 9.2
Women, n (%)	126 (55)	111 (49)	120 (52)
Weight, kg	91.8 ± 22.2	89.8 ± 20.2	91.1 ± 19.7
BMI, kg/m^2	33.2 ± 6.8	32.0 ± 5.9	33.0 ± 6.1
Waist circumference, cm	108.7 ± 16.6	107.1 ± 16.2	109.0 ± 15.6
Diabetes duration, years	7.6 ± 6.0	7.4 ± 5.5	7.1 ± 5.5
Fasting plasma insulin, pmol/L	81.5 ± 66.6	82.6 ± 114.8	83.8 ± 82.8
HbA1c, %	9.3 ± 1.1	9.3 ± 1.1	9.3 ± 1.0
Triglycerides, mmol/L	2.1 ± 1.2	2.2 ± 1.3	2.1 ± 1.3
ALT, U/L	26.4 ± 16.8	30.2 ± 19.7	28.1 ± 17.3
AST, U/L	21.3 ± 11.6	23.3 ± 13.2	22.7 ± 11.4
AST:ALT ratio	0.9 ± 0.3	0.9 ± 0.3	0.9 ± 0.2
GGT, U/L	40.0 ± 36.4	41.5 ± 38.0	38.0 ± 27.2
Albumin, g/L	44.0 ± 2.6	44.7 ± 2.8	44.0 ± 2.8
Platelet count, ×10^3/μL	256.3 ± 70.5	254.0 ± 65.4	260.9 ± 72.3
HOMA-IR	2.0 ± 1.8	1.6 ± 0.9	1.9 ± 1.2
Adipo-IR	44.6 ± 31.7	47.4 ± 57.4	40.3 ± 36.1
FFA, mmol/L	0.6 ± 0.2	0.6 ± 0.2	0.5 ± 0.2
NAFLD biomarkers, mean ± SD (n [%])			
FLI overall	78.1 ± 22.8 (190 [100])	76.2 ± 24.3 (180 [100])	78.5 ± 22.2 (190 [100])
FLI ≥60	87.4 ± 11.8 (153 [81])	86.4 ± 11.1 (145 [81])	87.2 ± 11.2 (156 [82])
NLFS overall	1.0 ± 1.7 (179 [100])	1.0 ± 2.0 (167 [100])	1.1 ± 2.1 (180 [100])
NLFS > −0.64	1.2 ± 1.6 (168 [94])	1.2 ± 2.0 (153 [92])	1.2 ± 2.1 (168 [93])
NFS overall	−0.8 ± 1.2 (224 [100])	−0.9 ± 1.1 (225 [100])	−0.9 ± 1.2 (227 [100])
NFS >0.676	1.3 ± 0.5 (25 [11])	1.3 ± 0.7 (16 [7])	1.2 ± 0.5 (21 [9])
FIB-4 overall	1.0 ± 0.6 (224 [100])	1.0 ± 0.9 (225 [100])	1.0 ± 0.5 (227 [100])
FIB-4 ≥ 1.3	1.8 ± 0.9 (39 [17])	1.9 ± 1.5 (46 [20])	1.7 ± 0.4 (50 [22])

Abbreviations: Adipo-IR, adipose tissue insulin resistance; ALT, alanine aminotransferase; AST, aspartate aminotransferase; BMI, body mass index; DAPA, dapagliflozin; EXE, exenatide; FFA, free fatty acids; FIB-4, fibrosis-4 index; FLI, fatty liver index; GGT, gamma-glutamyltransferase; HbA1c, glycated haemoglobin; HOMA-IR, homeostatic model assessment of insulin resistance; n, number of patients; NAFLD, non-alcoholic fatty liver disease; NFS, NAFLD fibrosis score; NLFS, NAFLD liver fat score; PLB, placebo; SD, standard deviation; SE, standard error.
Data are mean ± SD or geometric mean ± SE, unless specified otherwise.

and FPI.[23] Adipo-IR was calculated as the product of fasting plasma non-esterified fatty acids (NEFA) and FPI (Adipo-IR = NEFA × FPI). As increased Adipo-IR is a characteristic of patients with NAFLD,[24-27] we assessed the correlations between change in Adipo-IR and changes in biomarkers of fatty liver/steatosis and fibrosis at week 28.

A path analysis hypothesizing a direct treatment effect on weight change, changes in triglycerides, AST:ALT ratio and Adipo-IR, and an indirect treatment effect mediated by weight loss on changes in triglycerides, AST:ALT ratio and Adipo-IR, was built to provide estimates of the magnitude and significance of these potentially causal connections.[28]

2.1 | Statistical analyses

Analyses were conducted on the intention-to-treat population, which included all randomized participants who received ≥1 dose of study medication and had ≥1 post-baseline HbA1c assessment. Changes in HbA1c and body weight from baseline to weeks 28 and 52 were analysed using a mixed-effects model with repeated measures.[20,21] Clinical indices of fatty liver/steatosis and fibrosis were calculated and scored in accordance with published methodologies (-Table S1).[8-11] Changes from baseline in least squares mean, or geometric mean ratio (HOMA-IR), to weeks 28 and 52 were analysed using analysis of covariance (ANCOVA) with the last observation carried forward (LOCF) method. The ANCOVA model included the following factors: treatment, region, baseline HbA1c stratum and baseline value of the dependent variable as a covariate. In the LOCF method, the last post-baseline measurement was carried forward to impute the missing value at weeks 28 and 52. HOMA-IR values were log-transformed and the log (endpoint/baseline) was analysed (eg, log[y2]−log[y1] = log[y2/y1]). All outcomes except HbA1c and body weight change at week 28 were exploratory and therefore nominal

TABLE 2 Changes from baseline in biomarkers of fatty liver/steatosis and fibrosis at weeks 28 and 52

	EXE once weekly + DAPA	EXE once weekly + PLB	DAPA + PLB	EXE once weekly + DAPA vs. EXE once weekly + PLB	EXE once weekly + DAPA vs. DAPA + PLB
FLI					
N	190	180	190	-	
Change from baseline at week 28	−6.81 (−8.52, −5.10); $P < 0.0001$	−3.90 (−5.70, −2.09); $P < 0.0001$	−4.04 (−5.77, −2.32); $P < 0.0001$	−2.92 (−5.11, −0.73); $P = 0.0092$ [$P = 0.0080$]	−2.77 (−4.93, −0.62); $P = 0.0119$ [$P = 0.0162$]
N	190	180	190		
Change from baseline at week 52	−6.23 (−8.23, −4.24); $P < 0.0001$	−3.00 (−5.11, −0.88); $P = 0.0055$	−4.58 (−6.60, −2.56); $P < 0.0001$	−3.23 (−5.79, −0.68); $P = 0.0134$ [$P = 0.0036$]	−1.65 (−4.17, 0.87); $P = 0.1981$ [$P = 0.1012$]
FLI ≥ 60					
N	153	145	156		
Change from baseline at week 28	−7.06 (−8.93, −5.19); $P < 0.0001$	−5.13 (−7.11, −3.16); $P < 0.0001$	−4.67 (−6.54, −2.79); $P < 0.0001$	−1.93 (−4.32, 0.47); $P = 0.1149$ [$P = 0.1353$]	−2.39 (−4.74, −0.05); $P = 0.0458$ [$P = 0.0401$]
N	153	145	156		
Change from baseline at week 52	−6.29 (−8.45, −4.12); $P < 0.0001$	−4.46 (−6.75, −2.18); $P = 0.0001$	−5.79 (−7.96, −3.62); $P < 0.0001$	−1.82 (−4.60, 0.95); $P = 0.1969$ [$P = 0.0982$]	−0.49 (−3.21, 2.22); $P = 0.7209$ [$P = 0.4663$]
NLFS					
N	179	167	180		
Change from baseline at week 28	−0.32 (−0.53, −0.120); $P = 0.0017$	−0.03 (−0.25, 0.18); $P = 0.7740$	−0.36 (−0.57, −0.16); $P = 0.0005$	−0.29 (−0.55, −0.03); $P = 0.0271$ [$P = 0.0006$]	0.04 (−0.21, 0.29); $P = 0.7557$ [$P = 0.6825$]
N	179	167	180		
Change from baseline at week 52	−0.31 (−0.52, −0.11); $P = 0.0026$	0.01 (−0.20, 0.23); $P = 0.8926$	−0.41 (−0.62, −0.21); $P < 0.0001$	−0.33 (−0.59, −0.07); $P = 0.0141$ [$P = 0.0002$]	0.10 (−0.16, 0.36); $P = 0.4447$ [$P = 0.8473$]
NLFS > −0.640					
N	168	153	168		
Change from baseline at week 28	−0.40 (−0.64, −0.16); $P = 0.0012$	−0.16 (−0.41, 0.10); $P = 0.2201$	−0.40 (−0.64, −0.16); $P = 0.0011$	−0.24 (−0.54, 0.06); $P = 0.1167$ [$P = 0.0023$]	0.00 (−0.29, 0.30); $P = 0.9788$ [$P = 0.6403$]
N	168	153	168		
Change from baseline at week 52	−0.41 (−0.65, −0.17); $P = 0.0008$	−0.10 (−0.35, 0.16); $P = 0.4547$	−0.45 (−0.69, −0.21); $P = 0.0002$	−0.31 (−0.61, −0.02); $P = 0.0389$ [$P = 0.0004$]	0.04 (−0.25, 0.33); $P = 0.7824$ [$P = 0.9355$]
NFS					
N	224	225	227		
Change from baseline at week 28	−0.17 (−0.27, −0.07); $P = 0.0008$	−0.20 (−0.31, −0.01); $P = 0.0001$	−0.13 (−0.23, −0.03); $P = 0.0113$	0.03 (−0.1, 0.16); $P = 0.6544$ [$P = 0.7861$]	−0.04 (−0.17, 0.08); $P = 0.4956$ [$P = 0.3641$]
N	224	225	227		
Change from baseline at week 52	−0.17 (−0.27, −0.07); $P = 0.0007$	−0.12 (−0.22, −0.02); $P = 0.0201$	−0.11 (−0.21, −0.02); $P = 0.0217$	−0.05 (−0.17, 0.07); $P = 0.4160$ [$P = 0.1009$]	−0.06 (−0.18, 0.07); $P = 0.3718$ [$P = 0.1436$]
NFS > 0.676					
N	25	16	21		
Change from baseline at week 28	−0.11 (−0.56, 0.35); $P = 0.6451$	−0.37 (−0.79, 0.05); $P = 0.0851$	−0.20 (−0.67, 0.27); $P = 0.3912$	0.26 (−0.21, 0.73); $P = 0.2691$ [$P = 1.0000$]	0.10 (−0.32, 0.51); $P = 0.6503$ [$P = 0.9912$]
N	25	16	21		

(Continues)

TABLE 2 (Continued)

	EXE once weekly + DAPA	EXE once weekly + PLB	DAPA + PLB	EXE once weekly + DAPA vs. EXE once weekly + PLB	EXE once weekly + DAPA vs. DAPA + PLB
Change from baseline at week 52	−0.32 (−0.74, 0.10); *P* = 0.1336	−0.44 (−0.83, −0.05); *P* = 0.0271	−0.58 (−1.02, −0.15); *P* = 0.0089	0.12 (−0.32, 0.56); *P* = 0.5842 [*P* = 0.9574]	0.26 (−0.13, 0.65); *P* = 0.1798 [*P* = 0.2654]
FIB-4					
N	224	225	227		
Change from baseline at week 28	−0.06 (−0.11, −0.01); *P* = 0.0135	−0.03 (−0.08, 0.02); *P* = 0.2264	−0.04 (−0.09, 0.003); *P* = 0.0697	−0.03 (−0.09, 0.03); *P* = 0.3184 [*P* = 0.9038]	−0.02 (−0.08, 0.04); *P* = 0.5848 [*P* = 0.5447]
N	224	225	227		
Change from baseline at week 52	−0.05 (−0.09, −0.004); *P* = 0.0308	−0.02 (−0.07, 0.02); *P* = 0.3214	−0.04 (−0.08, 0.003); *P* = 0.0669	−0.03 (−0.08, 0.03); *P* = 0.3551 [*P* = 0.4564]	−0.01 (−0.06, 0.05); *P* = 0.7792 [*P* = 0.5979]
FIB-4 ≥ 1.3					
N	39	46	50		
Change from baseline at week 28	−0.03 (−0.45, 0.39); *P* = 0.8902	−0.15 (−0.54, 0.25); *P* = 0.4613	−0.15 (−0.58, 0.27); *P* = 0.4746	0.12 (−0.26, 0.50); *P* = 0.5428 [*P* = 0.3364]	0.12 (−0.25, 0.50); *P* = 0.5124 [*P* = 0.4225]
N	39	46	50		
Change from baseline at week 52	0.11 (−0.55, 0.78); *P* = 0.7424	−0.43 (−1.05, 0.19); *P* = 0.1739	−0.27 (−0.94, 0.40); *P* = 0.4203	0.54 (−0.06, 1.14); *P* = 0.0778 [*P* = 0.2137]	0.38 (−0.21, 0.97); *P* = 0.2001 [*P* = 0.2899]

Abbreviations: CI, confidence interval; DAPA, dapagliflozin; EXE, exenatide; FIB-4, fibrosis-4 index; FLI, fatty liver index; LS, least squares; NAFLD, non-alcoholic fatty liver disease; NFS, NAFLD fibrosis score; NLFS, NAFLD liver fat score; PLB, placebo.
Change from baseline in biomarker score data are LS mean (95% CI). Between group comparison *P* values in parentheses are derived from the Wilcoxon rank-sum test.

P values were reported for these variables. Data were first checked for normality of distribution and, as the calculated NAFLD biomarkers either did not follow a log-normal distribution or had negative values that were invalid for log-transformation, additional *P* values based on non-parametric Wilcoxon rank-sum tests for the between-treatment group comparisons were reported as supportive evidence. Pearson's correlation coefficients were used to assess the association between change in Adipo-IR and biomarkers of fatty liver/steatosis and fibrosis at week 28. Path analysis was conducted to examine correlations among variables for interpretation of direct and indirect effects; standardized path coefficients were calculated for the path diagram to quantify the contribution (effect) from different paths. All statistical analyses were conducted using SAS version 9.2 or higher (SAS Institute Inc., Cary, North Carolina).

3 | RESULTS

3.1 | Baseline characteristics

The intention-to-treat population comprised 685 participants: EXE once weekly + DAPA, n = 228; EXE once weekly + PLB, n = 227; and DAPA + PLB, n = 230 (Table 1). The mean BMI was 32.7 kg/m^2, the mean HbA1c was 78 mmol/mol (9.3%) and the mean duration of type 2 diabetes was 7.4 years.[20,21] At baseline, liver enzymes and biomarker scores were similar across the three groups (Table 1). In participants with available data at baseline, 81.3% and 93.0% had altered biomarker scores indicating the presence of fatty liver/steatosis (FLI ≥60 and NLFS > − 0.640 cut-offs, respectively) and 19.9% and 9.0% had biomarker scores suggestive of fibrosis and severe fibrosis (ie, stages F3 and F4; FIB-4 ≥ 1.3 and NFS >0.676 cut-offs [Table 1]).

3.2 | Effects of treatment at weeks 28 and 52

At week 28, indices of fatty liver/steatosis (FLI overall, FLI in participants with baseline cut-off of ≥60, NLFS overall and NLFS in participants with baseline cut-off of > − 0.640) decreased from baseline in all three treatment groups (Table 2). At week 28, the proportions of participants with biomarker scores suggestive of fatty liver/steatosis (ie, FLI ≥60 and NLFS > − 0.640) were reduced by 10.5% and 6.1%, respectively, with EXE once weekly + DAPA. At weeks 28 and 52, changes in FLI and NLFS in the EXE once weekly + DAPA group were larger than the corresponding changes in the EXE once weekly + PLB group; change in FLI was also larger with EXE once weekly + DAPA versus DAPA + PLB at week 28 (Figure 1). Regarding the

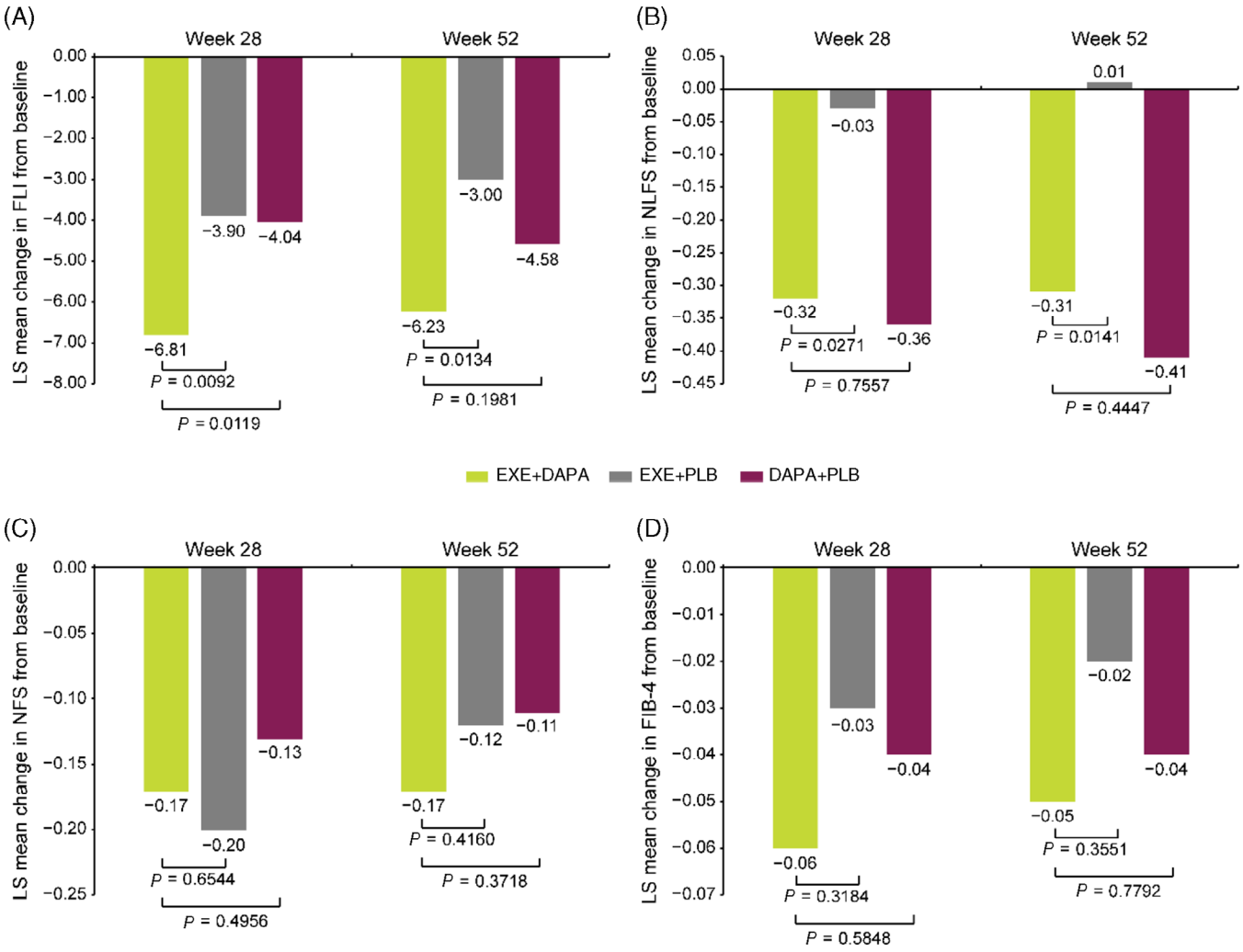

FIGURE 1 Least squares (LS) mean change in **A,** fatty liver index (FLI), **B**, non-alcoholic fatty liver disease (NAFLD) liver fat score (NLFS), **C,** NAFLD fibrosis score (NFS) and **D,** fibrosis-4 index (FIB-4) from baseline to weeks 28 and 52. DAPA, dapagliflozin; EXE, exenatide; PLB, placebo

indices of fibrosis and severe fibrosis at weeks 28 and 52, FIB-4 showed a reduction versus baseline in the EXE once weekly + DAPA group only and NFS was reduced in all treatment groups versus baseline (Table 2). Changes in NFS and FIB-4 were similar in all treatment groups (Figure 1). At week 28, the proportions of participants with biomarker scores suggestive of fibrosis and severe fibrosis (ie, FIB-4 ≥ 1.3 and NFS >0.676) were reduced by 2.8% and 4.1%, respectively, with EXE once weekly + DAPA.

Levels of ALT decreased from baseline to weeks 28 and 52 in the EXE once weekly + DAPA (P = 0.0026 vs. EXE once weekly + PLB) and the DAPA + PLB group. AST decreased from baseline to week 28 in the EXE once weekly + DAPA group (P = 0.0052 vs. EXE once weekly + PLB) and the DAPA + PLB group, and at week 52 in the EXE once weekly + DAPA group (Table 3).Triglyceride concentration decreased in the EXE once weekly + DAPA group at weeks 28 and 52 (P < 0.0500 vs. DAPA + PLB), and in the EXE once weekly + PLB group at week 28 (Table 2). GGT levels decreased at weeks 28 and 52 in the EXE once weekly + DAPA group, and at week 28 in the DAPA + PLB group (data not shown).

Regarding the indices of insulin resistance, HOMA-IR improved similarly in the EXE once weekly + DAPA and DAPA + PLB groups at weeks 28 and 52, with the effect observed in the EXE once weekly + DAPA group being larger than that in the EXE once weekly + PLB group (Table 3). Adipo-IR improved in the EXE once weekly + DAPA and the DAPA + PLB groups at week 52, with the change in the EXE once weekly + DAPA group being no different from those in the individual drug groups (Table 3). In the EXE once weekly + DAPA group, changes in Adipo-IR were mainly associated with improvements in biomarkers of fatty liver/steatosis (FLI and NLFS) compared with biomarkers of fibrosis (NFS and FIB-4; Figure 2).

By path analysis, weight loss had a significant (P < 0.05) direct effect on AST:ALT ratio (β = −0.12) and Adipo-IR (β = 0.16), but not on triglycerides (β = 0.06; Figure S2). There were significant (P < 0.05) indirect treatment effects on AST:ALT ratio and Adipo-IR with EXE once weekly + DAPA (ie, mediated by weight loss) versus EXE once weekly + PLB (β = 0.29) and DAPA + PLB (β = 0.19; Figure S2).

TABLE 3 Change from baseline in metabolic and liver biomarkers at weeks 28 and 52

	EXE once weekly + DAPA (n = 228)	EXE once weekly + PLB (n = 227)	DAPA + PLB (n = 230)	EXE once weekly + DAPA vs. EXE once weekly + PLB	EXE once weekly + DAPA vs. DAPA + PLB
Body weight, kg					
Change from baseline at week 28	−3.55 (−4.12, −2.99); $P < 0.05$	−1.56 (−2.13, −0.98); $P < 0.05$	−2.22 (−2.78, −1.66); $P < 0.05$	−2.00 (−2.79, −1.20); $P < 0.001$	−1.33 (−2.12, −0.55); $P < 0.001$
Change from baseline at week 52	−3.31 (−4.05, −2.57); $P < 0.05$	−1.51 (−2.28, −0.73); $P < 0.05$	−2.28 (−3.05, −1.52); $P < 0.05$	−1.80 (−2.87, −0.73); $P < 0.001$	−1.02 (−2.08, 0.03); $P = 0.057$
Fasting plasma insulin, pmol/L					
Change from baseline at week 28	−5.46 (−20.4, 9.49); $P = 0.4736$	12.03 (−3.67, 27.73); $P = 0.1329$	−11.6 (−26.4, 3.25); $P = 0.1257$	−17.5 (−36.5, 1.52); $P = 0.0713$	6.10 (−12.4, 24.64); $P = 0.5185$
Change from baseline at week 52	−8.58 (−18.7, 1.53); $P = 0.0959$	4.76 (−5.82, 15.34); $P = 0.3771$	−14.4 (−24.4, −4.39); $P = 0.0049$	−13.3 (−26.2, −0.45); $P = 0.0426$	5.82 (−6.74, 18.39); $P = 0.3631$
HbA1c, %					
Change from baseline at week 28	−1.98 (−2.16, −1.79); $P < 0.05$	−1.60 (−1.79, −1.41); $P < 0.05$	−1.39 (−1.57, −1.21); $P < 0.05$	−0.38 (−0.63, −0.13); $P = 0.003$	−0.59 (−0.84, −0.34); $P < 0.001$
Change from baseline at week 52	−1.75 (−1.94, −1.56); $P < 0.05$	−1.38 (−1.57, −1.18); $P < 0.05$	−1.23 (−1.42, −1.04); $P < 0.05$	−0.37 (−0.64, −0.11); $P = 0.006$	−0.52 (−0.79, −0.26); $P < 0.001$
Triglycerides, mmol/L					
Change from baseline at week 28	−0.31 (−0.47, −0.16); $P < 0.0001$	−0.18 (−0.34, −0.02); $P = 0.0237$	−0.11 (−0.26, 0.04); $P = 0.1448$	−0.13 (−0.32, 0.06); $P = 0.1813$	−0.20 (−0.39, −0.01); $P = 0.0364$
Change from baseline at week 52	−0.24 (−0.43, −0.05); $P = 0.0143$	−0.07 (−0.27, 0.13); $P = 0.4748$	0.00 (−0.19, 0.19); $P = 0.9695$	−0.16 (−0.41, 0.08); $P = 0.1804$	−0.27 (−0.48, 0.00); $P = 0.0463$
ALT, U/L					
Change from baseline at week 28	−5.68 (−7.74, −3.62); $P < 0.0001$	−1.72 (−3.81, 0.37); $P = 0.1072$	−4.56 (−6.61, −2.52); $P < 0.0001$	−3.96 (−6.54, −1.39); $P = 0.0026$	−1.12 (−3.68, 1.44); $P = 0.3915$
Change from baseline at week 52	−4.44 (−6.75, −2.14); $P = 0.0002$	−0.02 (−2.36, 2.32); $P = 0.9865$	−3.13 (−5.42, −0.85); $P = 0.0072$	−4.42 (−7.30, −1.55); $P = 0.0026$	−1.31 (−4.17, 1.55); $P = 0.3688$
AST, U/L					
Change from baseline at week 28	−3.44 (−5.00, −1.87); $P < 0.0001$	−0.65 (−2.24, 0.93); $P = 0.4186$	−2.75 (−4.30, −1.20); $P = 0.0005$	−2.78 (−4.73, −0.83); $P = 0.0052$	−0.69 (−2.63, 1.26); $P = 0.4875$
Change from baseline at week 52	−2.31 (−4.06, −0.56); $P = 0.0096$	−0.18 (−1.95, 1.60); $P = 0.8441$	−1.48 (−3.22, 0.25); $P = 0.0934$	−2.13 (−4.31, 0.05); $P = 0.0551$	−0.83 (−3.00, 1.34); $P = 0.4541$
AST:ALT ratio					
Change from baseline at week 28	0.07 (0.04, 0.10); $P < 0.001$	0.04 (0.00, 0.07); $P = 0.027$	0.03 (0.00, 0.06); $P = 0.038$	0.03 (−0.01, 0.07); $P = 0.087$	0.04 (−0.00, 0.08); $P = 0.061$
Change from baseline at week 52	0.06 (0.03, 0.09); $P = 0.001$	0.02 (−0.02, 0.05); $P = 0.311$	0.03 (−0.00, 0.06); $P = 0.058$	0.04 (0.00, 0.08); $P = 0.048$	0.03 (−0.01, 0.07); $P = 0.195$
HOMA-IR					
Change from baseline at week 28	0.81 (0.75, 0.88); $P < 0.0001$	1.00 (0.92, 1.08); $P = 0.9344$	0.75 (0.70, 0.81); $P < 0.0001$	0.81 (0.74, 0.90); $P < 0.0001$	1.08 (0.98, 1.18); $P = 0.1116$

(Continues)

TABLE 3 (Continued)

	EXE once weekly + DAPA (n = 228)	EXE once weekly + PLB (n = 227)	DAPA + PLB (n = 230)	EXE once weekly + DAPA vs. EXE once weekly + PLB	EXE once weekly + DAPA vs. DAPA + PLB
Change from baseline at week 52	0.80 (0.74, 0.87); $P < 0.0001$	1.00 (0.93, 1.09); $P = 0.9672$	0.77 (0.71, 0.83); $P < 0.0001$	0.80 (0.73, 0.88); $P < 0.0001$	1.04 (0.95, 1.15); $P = 0.3972$
Adipo-IR					
Change from baseline at week 28	−4.32 (−12.4, 3.72); $P = 0.2919$	5.36 (−2.95, 13.67); $P = 0.2054$	−4.68 (−12.4, 3.07); $P = 0.2360$	−9.68 (−19.9, 0.54); $P = 0.0632$	0.36 (−9.49, 10.21); $P = 0.9425$
Change from baseline at week 52	−6.92 (−12.5, −1.36); $P = 0.0148$	−2.33 (−8.23, 3.58); $P = 0.4386$	−7.35 (−12.7, −1.99); $P = 0.0073$	−4.59 (−11.8, 2.66); $P = 0.2142$	0.44 (−6.53, 7.40); $P = 0.9022$

Abbreviations: Adipo-IR, adipose tissue insulin resistance; ALT, alanine aminotransferase; AST, aspartate aminotransferase; CI, confidence interval; DAPA, dapagliflozin; EXE, exenatide; HbA1c, glycated haemoglobin; HOMA-IR, homeostatic model assessment-insulin resistance; LS, least squares; n, number of patients; PLB, placebo.

Change data are LS mean (95% CI) apart from change in HOMA-IR, which is reported as the geometric LS mean ratio (95% CI); HOMA-IR values <1 relate to a decrease, values >1 relate to an increase.

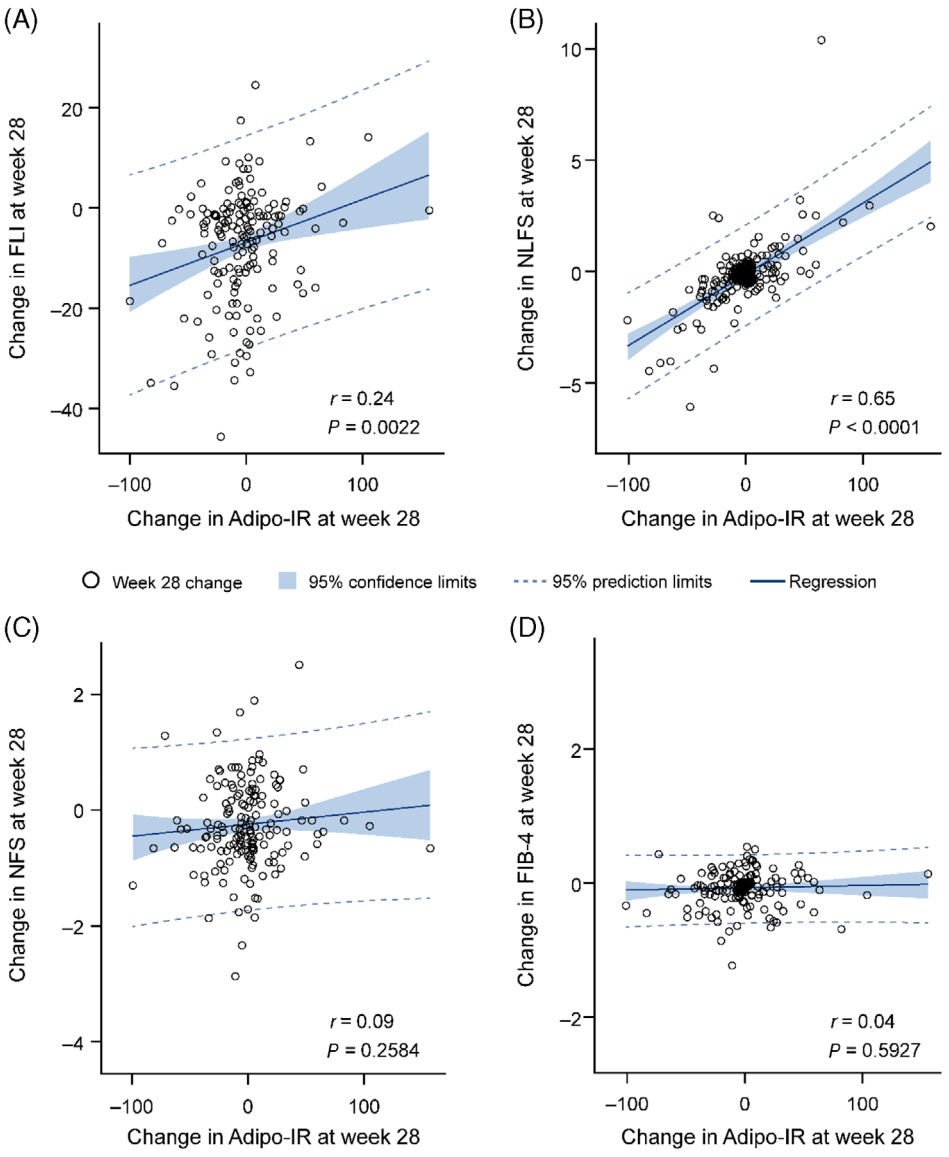

FIGURE 2 Pearson's correlations between changes in Adipo-IR and **A,** fatty liver index (FLI), **B**, non-alcoholic fatty liver disease (NAFLD) liver fat score (NLFS), **C,** NAFLD fibrosis score (NFS) and **D,** fibrosis-4 index (FIB-4) at week 28 in the exenatide (EXE) once weekly + dapagliflozin (DAPA) group. Adipo-IR, adipose tissue insulin resistance; r, Pearson's correlation coefficient

4 | DISCUSSION

DURATION-8 investigated the efficacy and safety of EXE once weekly + DAPA combination therapy compared with each individual drug plus PLB in people with type 2 diabetes inadequately controlled on metformin.[20,22] In the present *post hoc* analysis, we evaluated the effect of these treatments on liver enzymes and serum non-invasive biomarkers of fatty liver/steatosis and fibrosis.[8-11] EXE once weekly + DAPA showed improvements in liver enzymes and all biomarkers of fatty liver/steatosis and fibrosis versus baseline, with superior improvements observed for biomarkers of fatty liver/steatosis (the FLI and NLFS at week 28 and the FLI at week 52) compared with EXE once weekly + PLB and/or DAPA + PLB. All treatments reduced the NFS, a marker of severe fibrosis, from baseline; FIB-4 was reduced in the EXE once weekly + DAPA group only, but no difference was observed between the treatment groups. However, the number of participants with fibrosis or severe fibrosis was small, which affects the interpretability of these results. Extending recent data demonstrating the individual effects of GLP-1RAs or SGLT2 inhibitors on NAFLD,[14-19] the present results are the first to demonstrate the effect of this combination in reducing NAFLD biomarkers in people with type 2 diabetes, and indicate that combining these two agents may exert stronger beneficial effects on NAFLD than each drug alone. Moreover, as NAFLD is independently associated with cardiovascular disease,[2,3] and the cardiovascular benefits of GLP-1RAs and SGLT2 inhibitors are now well established,[5,29] the EXE once weekly + DAPA combination may confer a reduction in cardiovascular risk in patients with type 2 diabetes and NAFLD. However, this needs to be evaluated in a specific, prospective trial.

With regard to the potential mechanisms underlying the beneficial effects of EXE once weekly + DAPA treatment, weight loss and/or an improvement in hyperglycaemia, hyperinsulinaemia and resultant glucotoxicity may explain the present results. Weight loss was greater with EXE once weekly + DAPA versus the individual drugs at 28 and 52 weeks,[20,21] and the path analysis suggested that weight loss mediated the treatment effect of EXE once weekly + DAPA, versus the individual drugs, on AST:ALT ratio and Adipo-IR. Weight loss is the mainstay of NAFLD treatment,[2] and it has been previously demonstrated that the extent of weight loss achieved by patients is directly proportional to reduced NAFLD activity score, NASH resolution and fibrosis regression.[30] Moreover, the Diabetes Remission Clinical Trial (DiRECT) reported that a weight loss of ~15% in patients with type 2 diabetes was associated with a substantial decrease in liver fat content and recovery of β-cell function, suggesting that the normalization of liver fat may help put type 2 diabetes into remission.[31] However, in overweight, insulin-resistant patients without type 2 diabetes, it has been reported that 12 weeks of DAPA treatment had no impact on hepatic steatosis despite a mean weight loss of 4.4 kg.[32] Recent evidence suggests that DAPA reduces specific hepatocyte injury biomarkers, such as cytokeratin 18-M30 and plasma fibroblast growth factor 21, suggesting an intrinsic disease-modifying effect in NAFLD.[18] Regarding hyperglycaemia, excess dietary sugars can induce liver glucotoxicity by increasing hepatic steatosis, via *de novo* lipogenesis, and exacerbating insulin resistance and cellular demise, through mechanisms including the activation of oxidative and endoplasmic reticulum stress responses.[33] Recently, amelioration of hepatic dysfunction following at least 6 months of SGLT2 inhibitor treatment in patients with type 2 diabetes was mediated partly through an alleviation of hyperglycaemia, independent of weight loss.[34]

In the present study, we observed that EXE once weekly + DAPA combination therapy led to an improvement in insulin resistance, as measured by Adipo-IR and HOMA-IR. Adipo-IR (ie, the impaired suppression of lipolysis in the presence of high insulin levels) plays a key role in the pathogenesis of NAFLD.[24-27] Adipose tissue dysfunction affects both glucose and lipid metabolism by releasing proinflammatory adipokines and NEFA.[24,26] These have an impact on all tissues, including skeletal muscle, β cells and the liver, and modify inflammatory responses as well as glucose and lipid metabolism, thus contributing to metabolic abnormalities.[24,26,33] In patients with NAFLD, increased Adipo-IR is linked with deterioration of metabolic variables, in conjunction with increased liver insulin resistance and fibrosis.[25] Accordingly, improvement in Adipo-IR has been associated with a reduction in liver fat and associated necroinflammation following pioglitazone treatment in patients with NASH.[27] In the present study, we observed that correlations were stronger between improvement in Adipo-IR and reduction in biomarkers of fatty liver/steatosis versus biomarkers of fibrosis. However, as the proportion of participants with biomarker scores suggestive of fibrosis was considerably lower than fatty liver/steatosis, with less pronounced changes from baseline than the FLI and NLFS, the absence of a strong association between improvement in Adipo-IR and fibrosis is perhaps not surprising.

Although DURATION-8 was not primarily designed to investigate the beneficial effects of EXE once weekly + DAPA on NAFLD, the present results suggest that the combination could be effective in reducing liver steatosis, and may potentially improve NASH and fibrosis in patients with type 2 diabetes. Strengths of the study include the large number of participants enrolled, its double-blind, placebo-controlled design, and being the first to evaluate the effects of a GLP-1RA and SGLT2 inhibitor combination on biomarkers of fatty liver/steatosis and fibrosis in people with type 2 diabetes. There are also several limitations. For instance, DURATION-8 was not primarily powered to assess the effect of the EXE once weekly + DAPA combination on markers of fatty liver/steatosis and fibrosis, and these were exploratory outcomes. Further, the biomarkers that include type 2 diabetes in their formulae (ie, NLFS and NFS) may not be fully reliable in a solely diabetic population. Also, there was an imbalance between treatment groups in the number of participants with high FPI values, mainly in the EXE once weekly + PLB group. Further, the histological features of NASH were not assessed, and imaging tools were not available. However, when imaging tools are not available or feasible, clinical guidelines recommend the use of serum biomarkers as an acceptable alternative for the assessment of steatosis and fibrosis, particularly in large populations.[2] Indeed, the use of biomarkers can be particularly helpful in clinical practice to identify those individuals at risk of severe fibrosis who require an early management approach,[5] and improvement in NAFLD biomarkers has been shown to independently predict biopsy-confirmed

improvement in fibrosis after 1 year of lifestyle intervention in people with NASH.[35]

In conclusion, the present analysis is the first to describe improvements in biomarkers of fatty liver/steatosis and fibrosis in a large trial of GLP-1RAs plus SGLT2 inhibitor combination therapy in people with type 2 diabetes. This nascent evidence may inform future, specifically designed prospective clinical trials that will investigate the efficacy and long-term safety of the GLP-1RA and SGLT2 inhibitor combination for the treatment of NASH in people with or without type 2 diabetes.

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PRIOR ABSTRACT PUBLICATION

Parts of this study were presented at the 54th Annual Meeting of the EASD, Berlin, Germany, October 1–5, 2018; and at the 55th Annual Meeting of the EASD, Barcelona, Spain, September 16–20, 2019.

AUTHOR CONTRIBUTIONS

J.H. conducted the data analyses. All authors contributed to the conception and design of the study, interpretation of the data and made critical revisions to the manuscript. All authors read and approved the final version. All authors are the guarantors of this work and take responsibility for the integrity of the data and the accuracy of the data analysis.

CONFLICTS OF INTEREST

E.F. has participated in scientific advisory boards for Boehringer Ingelheim, Eli Lilly and Sanofi, has been an *ad hoc* consultant for Janssen, AstraZeneca and Mitsubishi Tanabe, has participated in occasional speaking engagements for AstraZeneca, Novo Nordisk, Sanofi, Mitsubishi Tanabe, Eli Lilly, Boehringer Ingelheim and Merck Sharp & Dohme (MSD), and has received research grant support from Boehringer Ingelheim and AstraZeneca. A.G. is a consultant for Eli Lilly, Genentech, Menarini, Inventiva and Gilead. C.G. has participated in scientific advisory boards and received consulting fees from AstraZeneca, Egis Pharmaceuticals, Eli Lilly, MSD, Novo Nordisk, Sanofi and Zentiva. E.R. and E.H. are employees of AstraZeneca. J.H. is a consultant with AstraZeneca. S.A.J. is a consultant with AstraZeneca, Eli Lilly and Janssen.

DATA SHARING AND ACCESSIBILITY

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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