Research Article
NAFLD and Alcohol-Related Liver Diseases

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A phase IIa active-comparator-controlled study to evaluate the efficacy and safety of efinopegdutide in patients with non-alcoholic fatty liver disease

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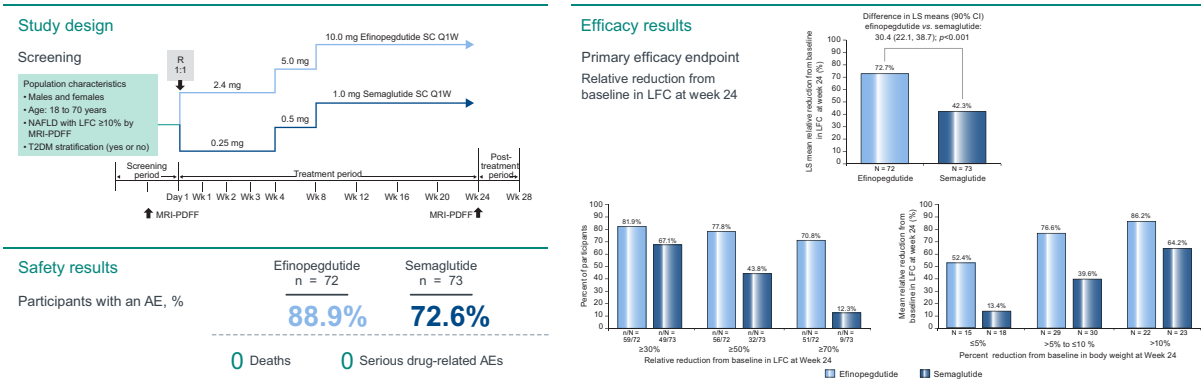
Graphical abstract



Highlights

- There are no approved therapies for fatty liver disease.
- Dual glucagon/glucagon-like peptide-1 receptor agonism may be beneficial.
- Efinopegdutide (dual agonist) improved liver fat content compared with semaglutide.
- Efinopegdutide's tolerability profile was similar to that of semaglutide.
- Efinopegdutide may be an effective treatment for fatty liver disease.

Impact and implications

Currently, there are no approved therapies for non-alcoholic steatohepatitis (NASH). The weight loss associated with glucagon-like peptide-1 (GLP-1) receptor agonists has been shown to decrease hepatic inflammation in patients with NASH. In addition to reducing liver fat content (LFC) indirectly through weight loss, glucagon receptor agonism may also reduce LFC by acting on the liver directly to stimulate fatty acid oxidation and reduce lipogenesis. This study demonstrated that treatment of patients with non-alcoholic fatty liver disease with the GLP-1/glucagon receptor co-agonist efinopegdutide (10 mg weekly) led to a significantly greater reduction in LFC compared to treatment with the GLP-1 receptor agonist semaglutide (1 mg weekly), suggesting that efinopegdutide may be an effective treatment for NASH.

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A phase IIa active-comparator-controlled study to evaluate the efficacy and safety of efinopegdutide in patients with non-alcoholic fatty liver disease

Manuel Romero-Gómez[1], Eric Lawitz[2], R. Ravi Shankar[3], Eirum Chaudhri[3], Jie Liu[3], Raymond L.H. Lam[3], Keith D. Kaufman[3], Samuel S. Engel [3,*], for the MK-6024 P001 Study Group[†]

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Background & Aims: This study assessed the effects of the glucagon-like peptide-1 (GLP-1)/glucagon receptor co-agonist efinopegdutide relative to the selective GLP-1 receptor agonist semaglutide on liver fat content (LFC) in patients with non-alcoholic fatty liver disease (NAFLD).
Methods: This was a phase IIa, randomized, active-comparator-controlled, parallel-group, open-label study. A magnetic resonance imaging-estimated proton density fat fraction assessment was performed to determine LFC at screening and Week 24. Participants with an LFC of ≥10% at screening were randomized 1:1 to efinopegdutide 10 mg or semaglutide 1 mg, both administered subcutaneously once weekly for 24 weeks. Participants were stratified according to the concurrent diagnosis of type 2 diabetes mellitus (T2DM). Both drugs were titrated to the target dose over an 8-week time period. The primary efficacy endpoint was relative reduction from baseline in LFC (%) after 24 weeks of treatment.
Results: Among 145 randomized participants (efinopegdutide n = 72, semaglutide n = 73), 33.1% had T2DM. At baseline, mean BMI was 34.3 kg/m^2 and mean LFC was 20.3%. The least squares (LS) mean relative reduction from baseline in LFC at Week 24 was significantly (p <0.001) greater with efinopegdutide (72.7% [90% CI 66.8–78.7]) than with semaglutide (42.3% [90% CI 36.5–48.1]). Both treatment groups had an LS mean percent reduction from baseline in body weight at Week 24 (efinopegdutide 8.5% *vs*. semaglutide 7.1%; p = 0.085). Slightly higher incidences of adverse events and drug-related adverse events were observed in the efinopegdutide group compared with the semaglutide group, primarily related to an imbalance in gastrointestinal adverse events.
Conclusions: In patients with NAFLD, treatment with efinopegdutide 10 mg weekly led to a significantly greater reduction in LFC than semaglutide 1 mg weekly.
Clinical Trial Number: EudraCT: 2020-005136-30; NCT: 04944992.

Introduction

Non-alcoholic fatty liver disease (NAFLD), a condition associated with increased accumulation of triglycerides in the liver, is estimated to affect approximately 30% of the global adult population.[1] NAFLD encompasses a broad spectrum of fatty liver disease, ranging from simple steatosis to non-alcoholic steatohepatitis (NASH), a form of fatty liver disease that is associated with chronic inflammation described histologically as steatohepatitis with or without fibrosis.[2] Approximately 20% of the NASH population will progress to cirrhosis, which is associated with increases in rates of hepatocellular carcinoma and all-cause and liver-related mortality.[3] NAFLD is increasingly being recognized as the hepatic manifestation of underlying metabolic dysregulation and is considered a consequence of obesity-related insulin resistance, resulting in increased trafficking of fatty acids from adipose tissue to the liver and *de novo* hepatic lipogenesis.[4,5] Overweight and obesity are considered the primary pathological drivers of metabolic disease, NAFLD and, by extension, NASH.[5]

Currently, there are no approved therapies for the treatment of NASH. Management of NAFLD/NASH is focused on lifestyle modification such as diet and exercise, directed mainly at weight loss. Pioglitazone and high-dose vitamin E (800 IU/day) have been recommended as pharmacotherapies for biopsy-proven NASH, with pioglitazone recommended in those with type 2 diabetes mellitus (T2DM) and vitamin E recommended in those without diabetes.[6]

Keywords: efinopegdutide; semaglutide; nonalcoholic fatty liver disease; liver fat content.
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Glucagon-like peptide-1 (GLP-1) agonism is associated with reductions in serum glucose and weight loss. GLP-1 receptor agonists enhance glucose-stimulated insulin secretion and have become useful treatments for T2DM. At doses that have been developed for diabetes indications (*e.g.*, liraglutide up to 1.8 mg daily, semaglutide up to 2 mg weekly), GLP-1 receptor agonists are associated with weight loss of approximately 3% to 5%, generally attributed to reductions in food intake. More recently, higher dose administration of GLP-1 receptor agonists has been pursued for weight loss indications. At the approved doses for weight loss, liraglutide 3 mg subcutaneously (SC) daily over 56 weeks resulted in weight loss of approximately 7.4%,[7] while semaglutide 2.4 mg SC once weekly over 68 weeks resulted in approximately 15% weight loss.[8] The weight loss associated with GLP-1 agonists has been shown to be associated with decreased hepatic inflammation in patients with NASH. The Liraglutide Efficacy and Action in NASH (LEAN) phase II study showed that 39% (9/23) of participants who received liraglutide 1.8 mg SC daily and who underwent an end of treatment liver biopsy after 48 weeks had resolution of NASH compared with 9% (2/22) in the placebo group.[9] A phase IIb study with semaglutide at 0.1 mg, 0.2 mg, or 0.4 mg SC once daily (total weekly dose of 0.7 mg to 2.8 mg) showed histologic resolution of NASH without worsening of fibrosis in 40.4% to 58.9% of participants compared to placebo (17.2%) after 72 weeks of dosing, albeit without significant improvement in fibrosis.[10]

Glucagon receptor activation has a number of effects that may complement the beneficial effects of GLP-1 receptor agonism for the treatment of NASH.[11] Glucagon has been shown to induce weight loss by reducing food intake and increasing energy expenditure. In addition to reducing liver fat content (LFC) indirectly through weight loss, glucagon agonism may also reduce LFC by acting on the liver directly to stimulate fatty acid oxidation and reduce lipogenesis.[12]

Efinopegdutide (MK-6024) is a synthetic peptide of oxyntomodulin conjugated to the constant region of human IgG4 that acts as a dual GLP-1 receptor and glucagon receptor agonist, with a GLP-1 receptor:glucagon receptor relative potency of approximately 2:1. Oxyntomodulin, a 37 amino acid peptide product of the proglucagon gene released from L-cells of the small intestine in response to food ingestion, has been shown to decrease appetite and body weight in overweight and obese individuals.[13,14] The effects of efinopegdutide on weight loss were studied in two phase II dose-ranging studies in obese patients with and without T2DM.[15,16] In both studies, treatment with efinopegdutide resulted in a significant, dose-dependent reduction in body weight.[15,16] The present phase IIa study was conducted to compare the efficacy and safety of GLP-1 and glucagon receptor co-agonism with efinopegdutide to GLP-1 agonism alone with semaglutide in patients with NAFLD with and without T2DM, and to generate data on the potential of efinopegdutide as a novel therapy for NASH.

Patients and methods

Participant selection

This study enrolled males and females aged 18 to 70 years. Inclusion criteria included NAFLD based on an LFC of ≥10% as assessed by magnetic resonance imaging-estimated proton density fat fraction (MRI-PDFF), BMI ≥25 kg/m^2 and ≤50 kg/m^2, stable body weight (based on self-reporting) defined as ≤5% gain or loss of body weight for at least 3 months before screening, and either no history of T2DM or a history of T2DM with glycated hemoglobin (HbA1c) ≤8.5% at screening and controlled by diet and/or a stable dose of metformin for the 3 months before screening. Antihyperglycemic agents other than metformin were not permitted.

Key exclusion criteria included history or evidence of chronic liver disease other than NAFLD or NASH; known history of cirrhosis (fibrosis stage >3 based on a historical liver biopsy or a liver stiffness score >14 kPa based on a historical FibroScan® assessment; decompensated liver disease including, but not limited to, history of ascites, esophageal or gastric variceal bleeding, hepatocellular carcinoma, hepatic encephalopathy, splenomegaly, or spontaneous bacterial peritonitis; treatment with any GLP-1 receptor agonist or investigational GLP-1/glucagon receptor co-agonist within 6 months before screening; treatment with thiazolidinediones (*i.e.*, pioglitazone, rosiglitazone) within 6 months before screening; previous or current use of prescription weight-management medications or over-the-counter weight-loss medications or therapies within the 3 months before screening; treatment with an antihyperlipidemic therapy that was not at a stable dose for at least 1 month before screening; or treatment with >100 IU/day of vitamin E at a dose that was not stable for at least 3 months before screening.

Study design

This was a phase IIa, randomized, active-comparator-controlled (semaglutide; Ozempic®), parallel-group, multi-site, open-label study of efinopegdutide in participants with NAFLD (protocol 001; EudraCT: 2020-005136-30; NCT: 04944992). The study protocol was approved by the institutional review board or independent ethics committee at each investigational site and was conducted in accordance with applicable regulations and the ethical principles of Good Clinical Practice as defined by the International Conference on Harmonization and Declaration of Helsinki. Written informed consent was obtained from all participants.

The study design is shown in Fig. 1. The duration of the study was approximately 32 weeks, which included a staged screening period of approximately 4 weeks, a 24-week active-comparator-controlled treatment period, and a post-treatment period follow-up visit at approximately 5 weeks after the last dose of study intervention.

During the screening period, an MRI-PDFF was performed on all participants who met other screening eligibility requirements. If a participant had an LFC as assessed by MRI-PDFF of ≥10% as determined by blinded independent central review and all other eligibility criteria had been met, the participant proceeded to randomization.

At baseline (Day 1), participants who met eligibility criteria were randomly assigned in a 1:1 ratio to efinopegdutide 10 mg SC once weekly or semaglutide 1 mg SC once weekly, stratified according to concurrent diagnosis of T2DM at the time of randomization.

Participants randomized to efinopegdutide 10 mg once weekly or semaglutide 1 mg once weekly followed a 3-step dose-escalation regimen to achieve the planned study dose. Participants randomized to the efinopegdutide 10 mg once

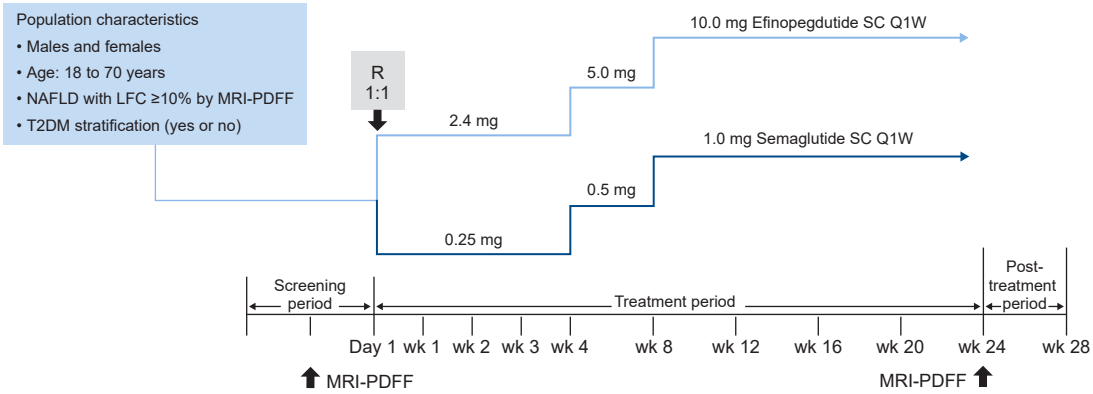

Fig. 1. Study design. LFC, liver fat content; MRI-PDFF, magnetic resonance imaging-estimated proton density fat fraction; NAFLD, non-alcoholic fatty liver disease; R, randomization; T2DM, type 2 diabetes mellitus.

weekly group were started at a dose of 2.4 mg once weekly from Day 1 to Week 4; the dose was increased to 5 mg once weekly from Week 4 up to Week 8 and then to 10 mg once weekly from Week 8 to Week 24. Participants who could not tolerate the efinopegdutide 10 mg once weekly dose could continue in the study on the efinopegdutide 5 mg once weekly dose. Down-titration below the 5 mg once weekly dose for efinopegdutide was not permitted; study treatment was discontinued in participants unable to tolerate at least the 5 mg once weekly efinopegdutide dose. Participants randomized to the semaglutide 1 mg once weekly treatment group were started at a dose of 0.25 mg once weekly from Day 1 to Week 4; the dose was increased to 0.5 mg once weekly from Week 4 to Week 8 and then to 1 mg once weekly from Week 8 to Week 24. Participants who could not tolerate the semaglutide 1 mg once weekly dose could continue in the study on the semaglutide 0.5 mg once weekly dose. Down-titration below the 0.5 mg once weekly dose for semaglutide was not permitted; study treatment was discontinued in participants unable to tolerate at least the 0.5 mg once weekly semaglutide dose.

All participants received dietary and activity counseling at the randomization visit from a qualified health care professional, using diet and activity guidance sheets. At subsequent visits, the site staff reviewed the diet and activity guidance sheets with the participants.

Efficacy endpoints

The primary efficacy endpoint was the relative reduction from baseline in LFC measured by MRI-PDFF (evaluated by blinded independent central review) after 24 weeks of treatment. Secondary efficacy endpoints included the percent change from baseline in body weight and fasting lipid levels (total cholesterol, high-density lipoprotein cholesterol, low-density lipoprotein cholesterol, and triglycerides) after 24 weeks of treatment. The following exploratory endpoints supported the primary efficacy endpoint: the proportions of participants with relative reductions from baseline in LFC of ≥30%, ≥50% and ≥70%; the proportion of participants who had achieved normal LFC (<5%); and the mean relative reduction from baseline in LFC by weight-loss categories (percent reductions from baseline in body weight of ≤5%, >5% to ≤10%, and >10%). Exploratory fibrosis biomarkers included change from baseline at Week 24 in pro-peptide of type III collagen (Pro-C3) and enhanced liver fibrosis (ELF) and a *post hoc* analysis of change from baseline at Week 24 in fibrosis-4 index (FIB-4). Because the study population included a broad range of participants with NAFLD, many of whom may have had no or minimal fibrosis, the results of these analyses of fibrosis biomarkers should be interpreted with caution.

Safety assessments

Safety and tolerability were monitored throughout the study by clinical evaluation of adverse events and inspection of other study parameters including physical examinations, 12-lead electrocardiograms, vital signs, and laboratory safety tests.

Statistical analysis

The efficacy analysis population included all randomized participants who received at least one dose of study intervention and had at least one assessment. The primary efficacy analysis compared the efficacy of efinopegdutide to semaglutide in the relative reduction from baseline in LFC at Week 24. The difference (efinopegdutide minus semaglutide) in means and the associated 90% CI and p values were provided based on a longitudinal data analysis model.[17] Efinopegdutide was considered superior to semaglutide if the one-sided p value was <0.05. The model-based least squares (LS) mean change from baseline for each treatment group and difference (with CI) between treatment groups at the Week 24 post-baseline time point were summarized.

Percent changes in body weight and fasting lipid levels were analyzed using the same longitudinal data analysis model as described for the primary endpoint. The changes from baseline in Pro-C3, ELF, and FIB-4 at Week 24 were summarized descriptively.

The safety analysis population consisted of all randomized participants who received at least one dose of study intervention.

A sample size of 65 participants per arm provided approximately 99% power to establish that efinopegdutide was superior to semaglutide with respect to the mean relative reduction from baseline in LFC at Week 24, with a one-sided $\alpha = 0.05$, assuming a true treatment difference of approximately 19.4%, a common SD of 20%, and 10% missing Week 24 data. A sample size of 65 participants per arm provided 80%

power to establish that efinopegdutide was superior to semaglutide by 10% or more with respect to the mean relative reduction from baseline in LFC after 24 weeks.

Results

This study was performed from 4 August 2021 to 19 October 2022 across 79 centers in 16 countries (Argentina, Australia, Canada, France, Israel, Italy, Mexico, New Zealand, Poland, Russia, South Korea, Spain, Taiwan, Turkiye, Ukraine, and United States). The disposition of participants is shown in Fig. 2. A total of 145 participants were randomized to treatment, of whom 135 completed the study. In the efinopegdutide group, seven participants did not tolerate the target dose of 10 mg once weekly; of those, six down-titrated to and completed the study on a dose of 5 mg once weekly, and one down-titrated to 5 mg once weekly but subsequently discontinued study medication. In the semaglutide group, one participant attempted to up-titrate to the target dose of 1 mg once weekly, but had to down-titrate, and completed the study on a dose of semaglutide 0.5 mg once weekly. One other participant who could not tolerate 0.5 mg once weekly discontinued study medication.

Demographics and baseline characteristics

The two treatment groups had similar demographics and baseline characteristics (Table 1). Among 145 randomized participants (efinopegdutide, n = 72; semaglutide, n = 73), the majority (55.2%) of participants were male, mean age was 49.5 years, mean BMI was 34.3 kg/m^2, mean body weight was 97.3 kg, 33.1% of participants had T2DM, and mean LFC was 20.3%.

Efficacy

At Week 24, treatment with efinopegdutide led to a significantly (p <0.001) greater relative reduction from baseline in LFC compared to semaglutide; the LS mean relative reduction from baseline in LFC was 72.7% (90% CI 66.8–78.7) with efinopegdutide and 42.3% (90% CI 36.5–48.1) with semaglutide (Fig. 3A, Table 2). The difference in the LS mean relative reduction from baseline in LFC at Week 24 in the efinopegdutide group compared to the semaglutide group was 30.4% (90% CI 22.1–38.7; p <0.001) (Fig. 3A, Table 2). The mean relative reduction from baseline in LFC at Week 24 in the efinopegdutide group was superior by 10% or more to that observed in the semaglutide group. Median relative reductions from baseline in LFC at Week 24 were 83.8% with efinopegdutide and 44.4% with semaglutide. A greater proportion of participants achieved a normal LFC level (<5%) at Week 24 with efinopegdutide (66.7%) compared with semaglutide (17.8%). Greater proportions of participants had relative reductions from baseline in LFC at Week 24 of ≥30%, ≥50% and ≥70% with efinopegdutide (81.9%, 77.8%, and 70.8%, respectively) compared with semaglutide (67.1%, 43.8%, and 12.3%, respectively) (Fig. 3B).

The LS mean percent reduction from baseline in body weight at Week 24 was 8.5% in the efinopegdutide group compared with 7.1% in the semaglutide group (p = 0.085) (Table 2). Similar percent reductions from baseline in mean body weight were observed in the two treatment groups over time (Fig. 4A). The relative reductions from baseline in LFC at Week 24 by weight-loss category (≤5%, >5% to ≤10%, and >10% reduction in body weight from baseline) were greater in the efinopegdutide group (52.4%, 76.6%, and 86.2%, respectively) than in the semaglutide group (13.4%, 39.6%, and 64.2%, respectively) (Fig. 3C).

In the efinopegdutide group, LS mean percent reductions from baseline at Week 24 were observed in total cholesterol, high-density lipoprotein cholesterol, low-density lipoprotein cholesterol, and triglycerides of 15.2%, 8.1%, 13.0%, and 30.9%, respectively (Table 2). In the semaglutide group, LS mean percent reductions from baseline in total cholesterol, low-

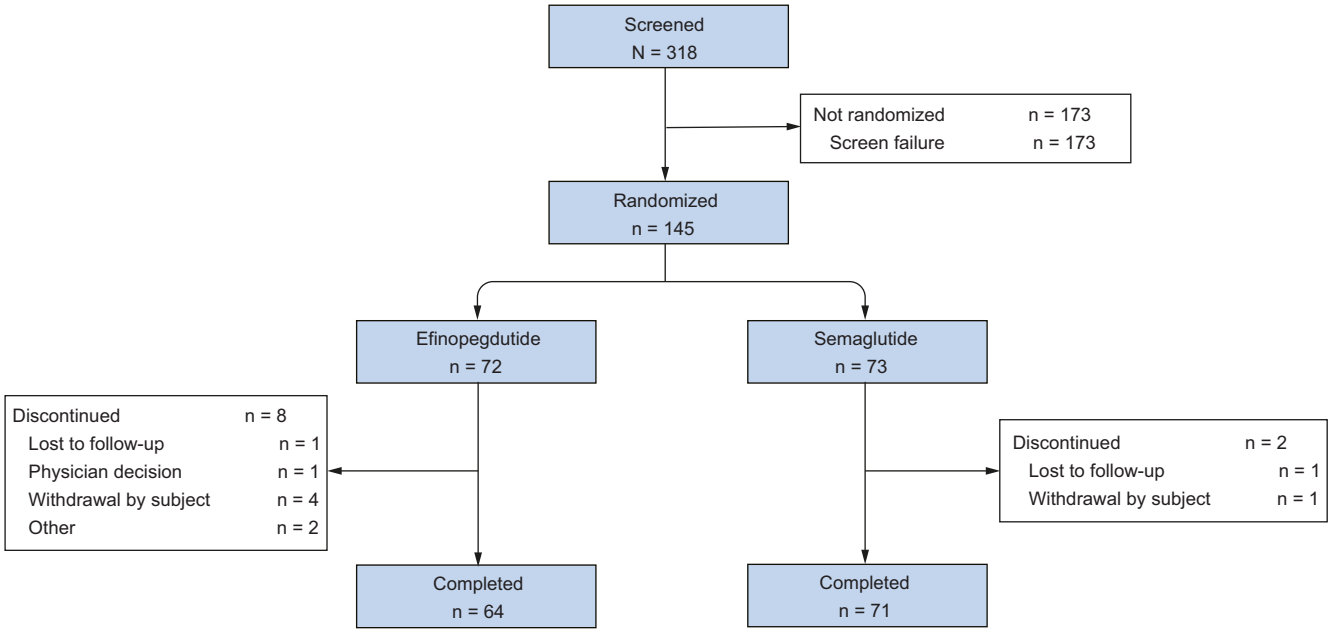

Fig. 2. Disposition of participants.

Table 1. Demographics and baseline characteristics.

Parameter	Efinopegdutide n= 72	Semaglutide n= 73
Sex		
Male	39 (54.2)	41 (56.2)
Female	33 (45.8)	32 (43.8)
Age, years	48.1 [11.0]	50.9 [10.9]
Race		
American Indian or Alaska Native	3 (4.2)	2 (2.7)
Asian	7 (9.7)	7 (9.6)
Black	0	1 (1.4)
White	62 (86.1)	63 (86.3)
Ethnicity		
Hispanic or Latino	25 (34.7)	26 (35.6)
Not Hispanic or Latino	46 (63.9)	47 (64.4)
Unknown	1 (1.4)	0
BMI, kg/m^2	35.2 [5.7]	33.5 [5.0]
Body weight, kg	100.2 [18.8]	94.5 [18.9]
T2DM (stratification)		
Yes	24 (33.3)	24 (32.9)
No	48 (66.7)	49 (67.1)
With T2DM		
HbA1c %	6.3 [0.7]	6.5 [0.8]
FPG, mg/dl	121.9 [33.0]	122.3 [31.0]
Without T2DM		
HbA1c, %	5.7 [0.3]	5.6 [0.4]
FPG, mg/dl	101.6 [13.0]	99.1 [11.4]
LFC, %	21.1 [8.1]	19.4 [8.1]
ALT, IU/L	61.9 [45.4]	54.2 [32.7]
AST, IU/L	35.6 [18.9]	36.6 [19.3]
Total cholesterol, mmol/L	5.3 [1.1]	5.3 [1.2]
High-density lipoprotein cholesterol, mmol/L	1.2 [0.3]	1.2 [0.4]
Low-density lipoprotein cholesterol, mmol/L	3.3 [0.9]	3.2 [1.1]
Triglycerides, mmol/L	2.0 [0.9]	2.0 [1.0]
WBC, 10^9/L	6.6 [1.6]	6.6 [1.6]
Platelet count, 10^9/L	258.6 [58.8]	256.8 [70.4]
Hemoglobin, mmol/L	9.1 [0.8]	9.0 [0.9]
Pro-C3, µg/L	53.2 [16.7]	55.9 [16.7]
ELF	8.8 [0.9]	9.1 [0.9]

Data are presented as n (%) for categorical variables and mean [SD] for continuous variables.
ALT, alanine aminotransferase; AST, aspartate aminotransferase; ELF, enhanced liver fibrosis; FPG, fasting plasma glucose; LFC, liver fat content; Pro-C3, pro-peptide of type III collagen; T2DM, type 2 diabetes mellitus; WBC, white blood cell count.

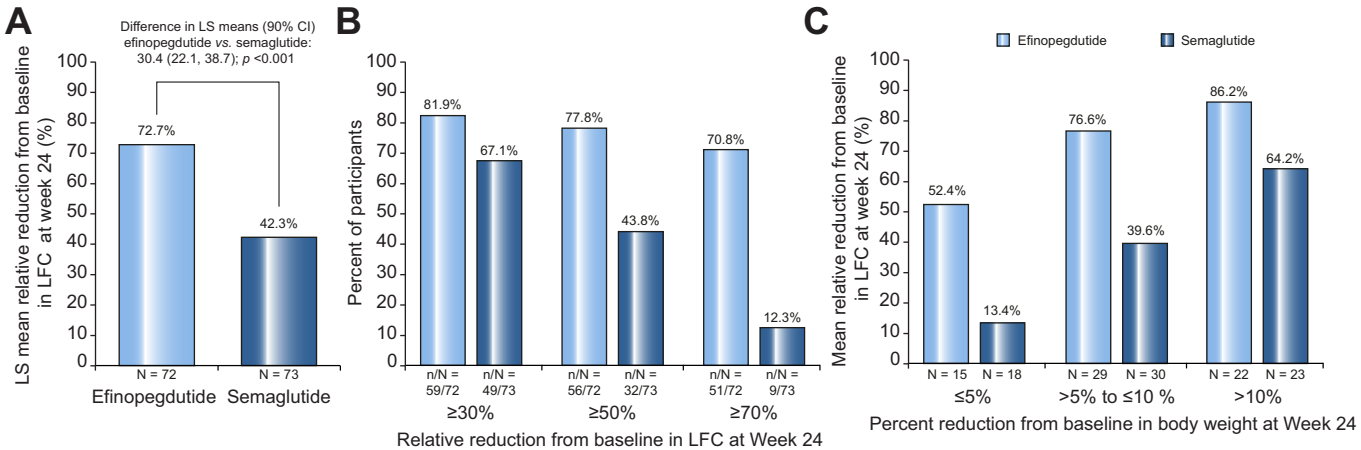

Fig. 3. Primary efficacy endpoint. (A) LS mean relative reduction from baseline at Week 24 in LFC, derived from a longitudinal data analysis; (B) proportions of participants with relative reductions from baseline in LFC at Week 24 of ≥30%, ≥50%, and ≥70%; (C) mean relative reductions from baseline in LFC at Week 24 by weight-loss category (≤5%, >5% to ≤10%, and >10% reduction in body weight from baseline). LFC, liver fat content; LS, least squares.

density lipoprotein cholesterol, and triglycerides of 8.0%, 6.9%, and 23.3%, respectively, and an LS mean percent increase from baseline in high-density lipoprotein cholesterol of 3.6%, were observed at Week 24 (Table 2).

Safety

Slightly higher incidences of adverse events and drug-related adverse events were observed in the efinopegdutide group, primarily related to an imbalance in gastrointestinal adverse

Table 2. Efficacy results.

					Percent change from baseline at Week 24			
Parameter	n	Baseline mean (SD)	n	Week 24 mean (SD)	n	Mean (SD)	LS mean (90% CI)[a]	Difference in LS means (90% CI) efinopegdutide *vs.* semaglutide[a]; *p* value[b]
LFC, %								
Efinopegdutide	72	21.1 (8.1)	65	4.6 (4.5)	72	−74.6 (28.0)	−72.7 (−78.7 to −66.8)	−30.4 (−38.7 to −22.1); <0.001
Semaglutide	73	19.4 (8.1)	72	11.4 (7.2)	73	−40.9 (27.9)	−42.3 (−48.1 to −36.5)	
Body weight, kg								
Efinopegdutide	72	100.2 (18.8)	66	91.6 (19.5)	72	−8.7 (5.2)	−8.5 (−9.5 to −7.5)	−1.4 (−2.7 to −0.1); 0.085
Semaglutide	73	94.5 (18.9)	71	87.4 (19.0)	73	−7.5 (4.3)	−7.1 (−8.1 to −6.2)	
Total cholesterol, mmol/L								
Efinopegdutide	72	5.3 (1.1)	65	4.4 (1.0)	72	−16.4 (14.8)	−15.2 (−18.2 to −12.2)	−7.2 (−11.2 to −3.1)
Semaglutide	73	5.3 (1.2)	69	4.7 (1.0)	73	−8.6 (15.3)	−8.0 (−11.0 to −5.0)	
High-density lipoprotein cholesterol, mmol/L								
Efinopegdutide	72	1.2 (0.3)	65	1.1 (0.3)	72	−8.5 (15.3)	−8.1 (−11.2 to −5.1)	−11.7 (−15.8 to −7.7)
Semaglutide	73	1.2 (0.4)	68	1.2 (0.3)	73	2.0 (15.0)	3.6 (0.6 to 6.6)	
Low-density lipoprotein cholesterol, mmol/L								
Efinopegdutide	71	3.3 (0.9)	65	2.7 (0.8)	72	−14.9 (19.5)	−13.0 (−17.4 to −8.6)	−6.1 (−12.0 to −0.1)
Semaglutide	73	3.2 (1.1)	67	2.8 (0.9)	73	−8.3 (22.9)	−6.9 (−11.3 to −2.6)	
Triglycerides, mmol/L								
Efinopegdutide	72	2.0 (0.9)	65	1.3 (0.5)	72	−26.1 (26.0)	−30.9 (−35.6 to −25.8)	−7.6 (−14.3 to −0.9)
Semaglutide	73	2.0 (1.0)	68	1.5 (0.6)	73	−18.6 (27.3)	−23.3 (−28.5 to −17.7)	

For baseline and Week 24, n is the number of participants with non-missing assessments at the specific timepoint. For percent change from baseline, n is the number of randomized participants.
LFC, liver fat content; LS, least squares.
[a]Based on a constrained longitudinal data analysis model including terms for treatment, time, stratum (T2DM), and the interactions of treatment by stratum, time by treatment, and time by stratum.
[b]*p* value not computed for total cholesterol, high-density lipoprotein cholesterol, low-density lipoprotein cholesterol, and triglycerides.

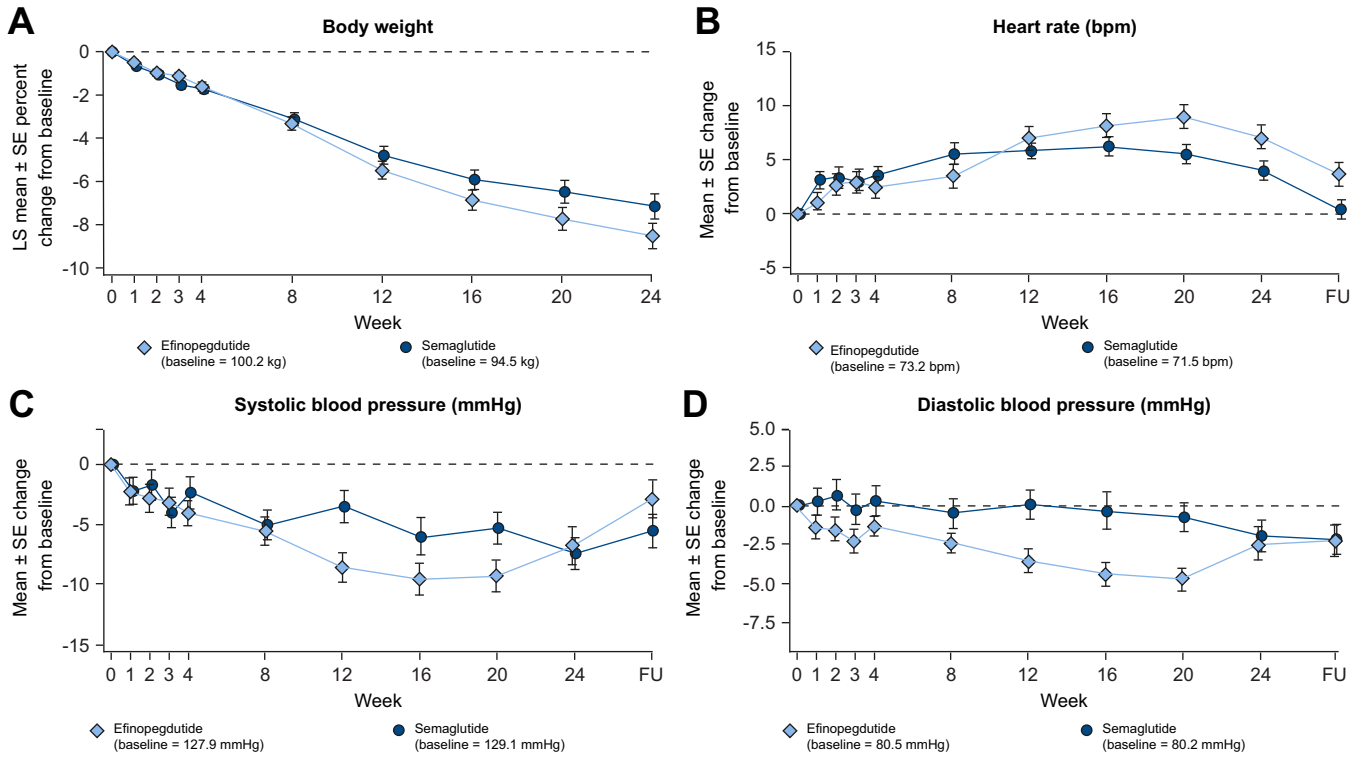

Fig. 4. Other endpoints. Mean (SE) percent change from baseline over time in (A) body weight and mean (SE) change from baseline over time in (B) heart rate, (C) systolic blood pressure, and (D) diastolic blood pressure. LS, least squares.

Table 3. Adverse events.

	Efinopegdutide n= 72		Semaglutide n= 73	
	n	(%)	n	(%)
Adverse events	64	(88.9)	53	(72.6)
Drug-related[a] adverse events	46	(63.9)	35	(47.9)
Serious adverse events	1	(1.4)	1	(1.4)
Serious drug-related adverse events	0		0	
Deaths	0	0	0	
Discontinued drug due to an adverse event	4	(5.6)	0	
Discontinued drug due to a drug-related adverse event	3	(4.2)	0	
Discontinued drug due to a serious adverse event	0		0	
Discontinued drug due to a serious drug-related adverse event	0		0	
Adverse events that occurred in ≥4 participants in either treatment group				
Gastrointestinal adverse events				
Abdominal distension	4	(5.6)	3	(4.1)
Abdominal pain	9	(12.5)	2	(2.7)
Abdominal pain upper	7	(9.7)	1	(1.4)
Constipation	12	(16.7)	4	(5.5)
Diarrhea	12	(16.7)	13	(17.8)
Dyspepsia	6	(8.3)	5	(6.8)
Flatulence	4	(5.6)	1	(1.4)
Gastroesophageal reflux disease	6	(8.3)	5	(6.8)
Nausea	20	(27.8)	23	(31.5)
Vomiting	12	(16.7)	11	(15.1)
General disorders and administration site conditions				
Fatigue	1	(1.4)	6	(8.2)
Infections and infestations				
COVID-19	8	(11.1)	10	(13.7)
Urinary tract infection	4	(5.6)	2	(2.7)
Investigations				
Alanine aminotransferase increased	4	(5.6)	0	
Lipase increased	4	(5.6)	3	(4.1)
Metabolism and nutrition disorders				
Decreased appetite	12	(16.7)	11	(15.1)
Nervous system disorders				
Dizziness	4	(5.6)	2	(2.7)
Headache	5	(6.9)	5	(6.8)

[a]Considered by the investigator to be related to the drug.

events (Table 3). There were otherwise no meaningful differences between the two treatment groups in the incidence of overall, serious, or drug-related adverse events, including adverse events that led to discontinuation (Table 3). The overall profile of adverse events reported by at least four participants was similar between the two treatment groups (Table 3). The incidences of nausea and of vomiting were similar between the two treatment groups (Table 3). Three specific adverse events in the gastrointestinal system organ class were reported at a higher incidence with efinopegdutide compared to semaglutide: abdominal pain (12.5% *vs.* 2.7%, respectively), abdominal pain upper (9.7% *vs.* 1.4%), and constipation (16.7% *vs.* 5.5%) (Table 3). An adverse event of a composite of abdominal pain terms (including terms for abdominal pain, abdominal pain upper, abdominal pain lower, or abdominal tenderness) was reported for 17 participants in the efinopegdutide group (23.6%); the majority (13/17) of these participants were reported to have a maximum toxicity grade of 1 while the remainder (4/17) had a maximum toxicity of grade 2. An adverse event of the same composite of abdominal pain terms was reported for three participants in the semaglutide group (4.1%); one of the three participants had a maximum toxicity grade of 2. Constipation was reported as an adverse event for 12 participants in the efinopegdutide group (16.7%) compared to four in the semaglutide group (5.5%). All of the adverse events of constipation were reported to have a toxicity grade of 1 and required a dose reduction in only one participant in the efinopegdutide group. All adverse events of abdominal pain and constipation resolved while participants remained on study treatment. A slightly greater increase from baseline in mean heart rate, and slightly greater reductions from baseline in both mean systolic and mean diastolic blood pressure, were observed with efinopegdutide compared to semaglutide (Fig. 4B-D). There was no notable imbalance in adverse events considered potentially related to changes in heart rate or blood pressure.

Laboratory parameters of interest

While there was a small imbalance in the number of participants with the adverse event of alanine aminotransferase (ALT) elevation, similar reductions from baseline in mean ALT and mean aspartate aminotransferase were observed in the two treatment groups, which had begun by Week 4 and continued throughout the 24-week treatment period (Fig. 5A,B). A *post hoc* analysis showed that 45.2% of participants in the efinopegdutide group achieved a reduction from baseline in ALT of ≥17 U/L at Week 24 compared with 44.1% of participants in the semaglutide group. The relative reductions from baseline in ALT at Week 24 by weight-loss category (≤5%, >5% to ≤10%,

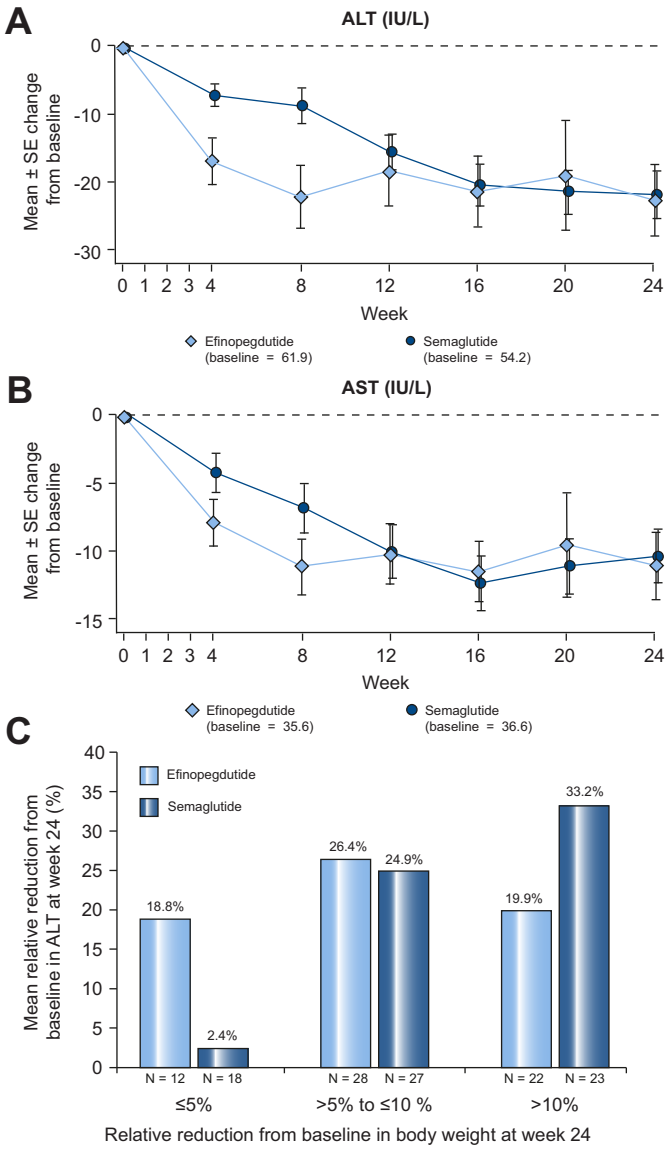

Fig. 5. Laboratory results. Mean (SE) change from baseline over time in (A) ALT and (B) AST; (C) mean relative reductions from baseline in ALT at Week 24 by weight-loss category (≤5%, >5% to ≤10%, and >10% reduction in body weight from baseline). ALT, alanine aminotransferase; AST, aspartate aminotransferase.

and >10% reduction in body weight from baseline) were 18.8%, 26.4%, and 19.9%, respectively, in the efinopegdutide group compared with 2.4%, 24.9%, and 33.2%, respectively, in the semaglutide group (Fig. 5C). At Week 24, treatment with efinopegdutide led to similar changes from baseline in Pro-C3, ELF, and FIB-4 compared to treatment with semaglutide (Table S1).

Treatment with efinopegdutide was associated with a mean increase from baseline in fasting plasma glucose of 0.01 mmol/L and a mean change from baseline in HbA1c of 0.0% at Week 24, compared to a mean decrease in fasting plasma glucose of 0.64 mmol/L and a mean decrease in HbA1c of 0.5% with semaglutide. Treatment with efinopegdutide and semaglutide was associated with a mean decrease from baseline in hemoglobin of 0.62 mmol/L and 0.12 mmol/L, respectively, at Week 24. There were no adverse events related to reductions in hemoglobin in either treatment group. There were no meaningful differences for other laboratory assessments.

Discussion

The present study compared the efficacy and safety of GLP-1 and glucagon receptor co-agonism with efinopegdutide to GLP-1 receptor agonism alone with semaglutide in patients with NAFLD. In this study, both active treatments produced clinically meaningful reductions from baseline in LFC, with efinopegdutide providing a significantly greater reduction in LFC than semaglutide. Treatment with efinopegdutide allowed two-thirds of participants to achieve a normal LFC level (<5%) compared with less than one-fifth of participants on semaglutide.

The significantly larger reduction in LFC with efinopegdutide (72.7%) than with semaglutide (42.3%) occurred in spite of both treatments producing similar reductions in body weight. This study was initiated prior to the availability of the higher dose (2.4 mg weekly) of semaglutide that is currently approved for the treatment of obesity and that is being evaluated in a phase III study as a potential therapeutic option for patients with NASH. While the greater magnitude of weight loss observed with higher doses of semaglutide may provide some additional antisteatotic efficacy compared to the dose used in this study, prior studies with higher doses of semaglutide have resulted in relative reductions of liver fat of 36% to 46% at 6 months.[18–20] Both treatments resulted in a majority of participants achieving at least a 30% reduction in LFC, which is generally regarded as the minimum threshold for histologic response in patients with NASH.[21] The substantial proportion of participants achieving over 50% and over 70% reduction in liver fat in the efinopegdutide treatment group, with approximately two-thirds of the population normalizing their liver fat concentration, suggests that robust effects on steatohepatitis may be achievable with co-agonists that target both the GLP-1 receptor and the glucagon receptor. Further studies are needed to evaluate the effects of efinopegdutide on histologic endpoints in patients with NAFLD/NASH.

Consistent with the experience with dietary,[22] pharmacologic,[23] and surgical therapies[24,25] for weight loss, participants in both treatment groups with larger body weight reductions had greater reductions in LFC. The relative reductions from baseline in LFC at Week 24 by specific weight-loss category (≤5%, >5% to ≤10%, and >10% reduction in body weight from baseline) were all greater in the efinopegdutide group than in the semaglutide group. Of particular note was the magnitude of LFC reduction in participants in the lowest weight-loss category. Among those with ≤5% weight loss from baseline, the reduction in LFC with efinopegdutide was 52.4% compared to a reduction of 13.4% in the semaglutide group. These findings suggest that other mechanisms, beyond those related to weight loss, contributed to the greater LFC-reducing effect with efinopegdutide compared to semaglutide. This difference is likely due to the glucagon receptor agonism of efinopegdutide directly stimulating fatty acid oxidation and reducing lipogenesis in the liver.[12]

Treatment with efinopegdutide was generally well tolerated. Slightly higher incidences of adverse events and drug-related adverse events were observed in the efinopegdutide group, primarily related to an imbalance in gastrointestinal

adverse events. There were otherwise no meaningful differences between the two treatment groups in the incidence of overall, serious, or drug-related adverse events, including adverse events that led to discontinuation. Dose-dependent gastrointestinal adverse events (predominantly nausea and vomiting) were previously reported in two phase II dose-ranging studies with efinopegdutide in obese patients with and without T2DM[15,16] and have been well described for GLP-1 receptor agonists and other GLP-1R/GCG receptor co-agonists.[26] Notably, the two previous phase II dose-ranging studies with efinopegdutide did not employ a titration regimen.[15,16] Because the use of titration regimens to mitigate the occurrence of gastrointestinal adverse events has been successfully implemented for marketed GLP-1 receptor agonists, a titration strategy was used in the current study. The incidences of nausea and vomiting reported in the efinopegdutide group in the present study (27.8% and 16.7%, respectively) were similar to those reported in the semaglutide group (31.5% and 15.1%, respectively) and were notably lower than those reported with efinopegdutide 10 mg in the previous phase II dose-ranging studies (42.9–66.9% and 34.7–55.1%, respectively),[15,16] indicating that the titration strategy was effective in mitigating these adverse events. Effects of efinopegdutide on heart rate and blood pressure in the current study were slightly greater than those observed with semaglutide and were consistent with observations in prior studies with efinopegdutide; these hemodynamic changes did not appear to be mitigated by use of a titration strategy and likely reflect the combined effect of GLP-1 and glucagon receptor agonism.

Similar to observations on efinopegdutide in prior phase II studies,[15,16] in the present study there was no meaningful mean change from baseline in HbA1c or fasting plasma glucose in the efinopegdutide group at Week 24. This was likely due a balanced impact of GLP-1 and glucagon receptor co-agonism on glucose metabolism, resulting in a neutral glycemic effect. The reductions in serum lipids observed with efinopegdutide were also similar to those reported in the prior phase II studies.[15,16] Reductions in hemoglobin have not been reported with GLP-1 receptor agonists and are likely a pharmacologic effect of glucagon agonism. Glucagon has been shown to inhibit erythropoiesis[27] and to decrease heme production in rodent models,[28] and normochromic normocytic anemia is common (~35%) in patients with the glucagonoma syndrome.[29]

Limitations of the study include the absence of a placebo group; however, the use of an active comparator in this study and historical comparisons to placebo responses in prior trials of antisteatotic agents provide adequate context by which to assess the observed efficacy of efinopegdutide. Additionally, this study was conducted in a broad population of patients with NAFLD, and not restricted to patients with NASH. While the study excluded patients with a known history of cirrhosis, the comparison of the antisteatotic efficacy of the study treatments is unlikely to be affected by the stage of fibrosis. Further studies are needed to determine the effects of long-term treatment with efinopegdutide in patients with NASH, particularly on histologic endpoints and clinical outcomes.

In summary, treatment with efinopegdutide led to a significant improvement in LFC compared with semaglutide in patients with NAFLD. Treatment with efinopegdutide was also generally well tolerated, with a tolerability profile similar to that of semaglutide. The substantial benefit of therapy with efinopegdutide on reducing liver fat is likely due to the complementary dual mechanisms of action of GLP-1 and glucagon receptor agonism, which together lead to improvements in the core pathophysiologic defects associated with NAFLD.

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Abbreviations

ALT, alanine aminotransferase; ELF, enhanced liver fibrosis; FIB-4, fibrosis-4 index; GLP-1, glucagon-like peptide-1; HbA1c, glycated hemoglobin; LS, least squares; LFC, liver fat content; MRI-PDFF, magnetic resonance imaging-estimated proton density fat fraction; NAFLD, non-alcoholic fatty liver disease; NASH, non-alcoholic steatohepatitis; Pro-C3, pro-peptide of type III collagen; T2DM, type 2 diabetes mellitus.

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Conflict of interest

M. Romero-Gómez has the following conflicts of interest to declare: scientific advisor, consultant and/or speaker for AbbVie, Alpha-sigma, Allergan, AstraZeneca, Axcella, BMS, Boehringer-Ingelheim, Gilead, Intercept, Inventia, Kaleido, MSD, Novo-Nordisk, Pfizer, Prosciento, Rubió, Siemens, Shionogi, Sobi, and Zydus; received research grants from Gilead, Intercept, Siemens; co-inventor of Hepamet Fibrosis Score, DeMILI, and DeMILI 3.0. E. Lawitz has the following conflicts of interest to declare: researcher for 89Bio Inc., AbbVie, Akero Therapeutics, Allergan, Alnylam Pharmaceuticals Inc., Amgen, Ascelia Pharma, AstraZeneca, Axcella Health, Boehringer Ingelheim, Bristol-Myers Squibb, Conatus Pharmaceuticals, Cymabay Therapeutics, CytoDyn, DSM, Durect Corporation, Eli Lilly and Company, Enanta Pharmaceuticals, Enyo Pharma, Exalenz Bioscience, Galectin Therapeutics, Galmed Pharmaceuticals, Genfit, Genentech, Gilead Sciences, GlaxoSmithKline, Hanmi Pharmaceuticals, Hightide Biopharma, Intercept Pharmaceuticals, Inventiva, Janssen Pharmaceuticals, Laboratory for Advanced Medicine, Loxo Oncology, Madrigal Pharmaceuticals, Merck & Co., Inc., Metacrine, NGM Biopharmaceuticals Inc., Northsea Therapeutics, Novartis, Novo Nordisk Inc., Pfizer, Poxel Co., Roche, Sagimet Biosciences, Terns Pharmaceuticals, Viking Therapeutics, Zydus Pharmaceuticals; advisor for Akero, Boehringer Ingelheim, BMS, Intercept, Novo Nordisk, Metacrine, Sagimet, Terns; speaker for Abbvie, Gilead Sciences, Intercept. R.R Shankar, E. Chaudhri, J. Liu, R.L.H. Lam, K.D. Kaufman, and S.S. Engel are current or former employees of Merck Sharp & Dohme LLC, a subsidiary of Merck & Co., Inc., Rahway, NJ, USA, and may own stock/stock options in Merck & Co., Inc., Rahway, NJ, USA.

Please refer to the accompanying ICMJE disclosure forms for further details.

Authors' contributions

R.R Shankar, E. Chaudhri, J. Liu, R.L.H. Lam, K.D. Kaufman, and S.S. Engel contributed to the conception and design of the study. M. Romero-Gómez and E. Lawitz were investigators in the study and contributed to the acquisition of the data. All of the authors contributed to the analysis of the data and the interpretation of the results. All of the authors drafted and/or critically reviewed the manuscript and provided final approval of the manuscript for publication.

Data availability statement

The data sharing policy, including restrictions, of Merck Sharp & Dohme LLC, a subsidiary of Merck & Co., Inc., Rahway, NJ, USA, is available at http://engagezone.msd.com/ds_documentation.php. Requests for access to the clinical study data can be submitted through the EngageZone site or via email to dataaccess@merck.com.

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Supplementary data

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