Research Article
MASLD and Alcohol-Related Liver Diseases

JOURNAL OF HEPATOLOGY

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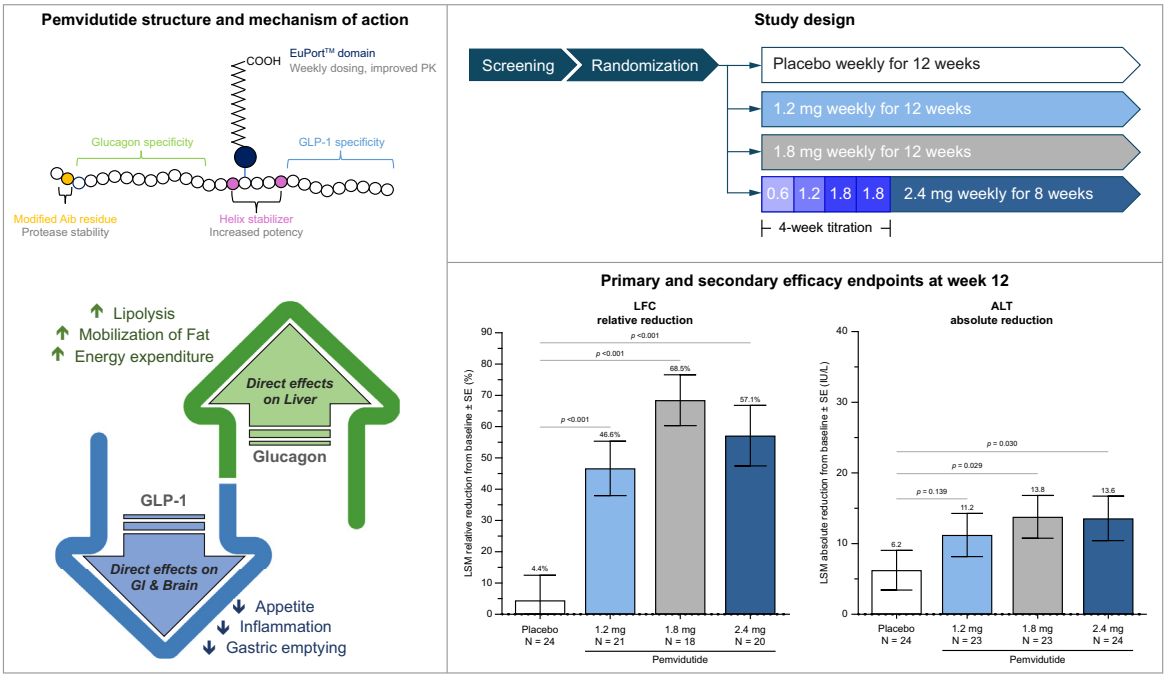
Graphical abstract



Highlights

- Pemvidutide is a GLP-1/glucagon dual receptor agonist.
- Pemvidutide treatment significantly reduced liver fat content compared to placebo.
- Pemvidutide treatment significantly reduced non-invasive biomarkers of liver inflammation.
- Pemvidutide treatment significantly reduced body weight.
- Pemvidutide may be an effective treatment for MASH.

Impact and implications

Metabolic dysfunction-associated steatotic liver disease, and its progressive form steatohepatitis, are strongly associated with overweight/obesity and it is believed that the excess liver fat associated with obesity is an important driver of these diseases. Glucagon-like peptide-1 receptor (GLP-1R) agonists elicit weight loss through centrally and peripherally mediated effects on appetite. Unlike GLP-1R agonists, glucagon receptor agonists act directly on the liver to stimulate fatty acid oxidation and inhibit lipogenesis, potentially providing a more potent mechanism for liver fat content reduction than weight loss alone. This study demonstrated the ability of once-weekly treatment with pemvidutide, a dual GLP-1R/glucagon receptor agonist, to significantly reduce liver fat content, hepatic inflammatory activity, and body weight, suggesting that pemvidutide may be an effective treatment for both metabolic dysfunction-associated steatohepatitis and obesity.

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Effect of pemvidutide, a GLP-1/glucagon dual receptor agonist, on MASLD: A randomized, double-blind, placebo-controlled study

Stephen A. Harrison[1], Sarah K. Browne[2], John J. Suschak[2,*], Shaheen Tomah[2], Julio A. Gutierrez[2,3], Jay Yang[2], M. Scot Roberts[2], M. Scott Harris[2]

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Background & Aims: This was a randomized, double-blind, placebo-controlled study to assess the effects of pemvidutide, a glucagon-like peptide-1 (GLP-1)/glucagon dual receptor agonist, on liver fat content (LFC) in individuals with metabolic dysfunction-associated steatotic liver disease (MASLD).

Methods: Patients with a BMI ≥28.0 kg/m^2 and LFC ≥10% by magnetic resonance imaging-proton density fat fraction were randomized 1:1:1:1 to pemvidutide at 1.2 mg, 1.8 mg, or 2.4 mg, or placebo administered subcutaneously once weekly for 12 weeks. Participants were stratified according to a diagnosis of type 2 diabetes mellitus. The primary efficacy endpoint was relative reduction (%) from baseline in LFC after 12 weeks of treatment.

Results: Ninety-four patients were randomized and dosed. Median baseline BMI and LFC across the study population were 36.2 kg/m^2 and 20.6%; 29% of patients had type 2 diabetes mellitus. At week 12, relative reductions in LFC from baseline were 46.6% (95% CI -63.7 to -29.6), 68.5% (95% CI -84.4 to -52.5), and 57.1% (95% CI -76.1 to -38.1) for the pemvidutide 1.2 mg, 1.8 mg, and 2.4 mg groups, respectively, *vs.* 4.4% (95% CI -20.2 to 11.3) for the placebo group (p <0.001 *vs.* placebo, all treatment groups), with 94.4% and 72.2% of patients achieving 30% and 50% reductions in LFC and 55.6% achieving normalization (≤5% LFC) at the 1.8 mg dose. Maximal responses for weight loss (-4.3%; p <0.001), alanine aminotransferase (-13.8 IU/L; p = 0.029), and corrected cT1 (-75.9 ms; p = 0.002) were all observed at the 1.8 mg dose. Pemvidutide was well-tolerated at all doses with no severe or serious adverse events.

Conclusions: In patients with MASLD, weekly pemvidutide treatment yielded significant reductions in LFC, markers of hepatic inflammation, and body weight compared to placebo.

Clinical Trial Number: NCT05006885.

Introduction

Metabolic dysfunction-associated steatotic liver disease (MASLD), formerly known as non-alcoholic fatty liver disease (NAFLD),[1] is estimated to affect 25% of adults globally.[2] MASLD is characterized by the presence of steatosis in 5% or more of the liver by volume in patients with no-to-minimal alcohol use. MASLD is the hepatic manifestation of metabolic syndrome and is integrally associated with obesity, insulin resistance, and type 2 diabetes mellitus (T2DM).[3,4] Between 20% and 30% of patients with MASLD progress to metabolic dysfunction-associated steatohepatitis (MASH), formerly known as non-alcoholic steatohepatitis (NASH), which is characterized by steatosis, inflammation, and hepatocyte ballooning, with or without fibrosis.[5,6] An estimated 20% of patients with MASH will further progress to end-stage liver disease and may require liver transplantation; however, cardiovascular disease and extrahepatic malignancy remain the leading causes of death in patients with MASH, emphasizing the importance of addressing these comorbidities in the treatment of the disease.[7] As little as 3-5% weight loss improves MASLD while 10% weight loss or more is associated with MASH resolution and fibrosis regression, underscoring the central role obesity plays in the development of these diseases.[8]

Glucagon-like peptide-1 receptor (GLP-1R) agonist-based approaches achieved weight loss in excess of 10% and resulted in resolution of MASH without an improvement in fibrosis.[9–11] As there is no GLP-1R expression in the liver, the

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effects of GLP-1R agonism on liver fat content (LFC), believed to be the principal driver of MASH and liver fibrosis,[12] are passive and follow the general reduction in adiposity associated with weight loss.

Unlike GLP-1R, the liver is dense with glucagon receptors (GCGRs).[13] The direct effects of glucagon on the liver are well established and include the stimulation of hepatic β-oxidation of fatty acids and a reduction of *de novo* lipogenesis.[14] It was hypothesized that combining GLP-1R and GCGR agonism in the same molecule, a so-called dual agonist, could achieve levels of liver fat reduction greater than those achievable by GLP-1-based agents alone. GLP-1R and GCGR agonism may also lead to better weight loss than GLP-1R agonism alone as GLP-1 is recognized to reduce food consumption through anorectic effects while glucagon has been shown to stimulate energy expenditure, potentially mimicking the effects of diet and exercise.[15–18] Consequently, GLP-1R/GCGR dual agonists may provide mechanisms for further reducing both LFC and body weight beyond GLP-1 monotherapy.

We recently reported on the design of pemvidutide (formerly ALT-801), a unimolecular, 29 amino acid peptide-based GLP-1R/GCGR dual agonist with equal potency against the GLP-1 and GCGRs.[19] A previous study of GLP-1R/GCGR dual agonists showed that balanced (1:1) agonism was associated with greater body weight loss and improved regulation of metabolic effects compared to GLP-1R/GCGR dual agonists with biased agonism towards either GLP-1 or glucagon.[20] In preclinical testing, pemvidutide demonstrated significant reductions in liver fat, inflammation, and fibrosis in addition to significant weight loss.[21] An 18 carbon diacid alkyl chain attached to the peptide through a novel glycosidic linkage provides for albumin binding and increases the plasma half-life of pemvidutide, allowing for weekly dosing. The surfactant-like properties of this side chain may slow entry of the compound into the bloodstream, prolonging T_{max}, and reducing C_{max}, which may be associated with lower rates of gastrointestinal intolerability.[22]

In a 12-week randomized, double-blind, placebo-controlled phase I clinical trial, pemvidutide-treated patients exhibited statistically significant reductions in body weight, BMI, serum lipids, and in patients with steatosis, a reduction in LFC.[23] In the current study, we present the results of a 12-week randomized, double-blind, placebo-controlled clinical trial of pemvidutide in patients with overweight/obesity and MASLD (NCT05006885).

Materials and methods

Study design and patient selection

This was a multicenter, randomized, double-blind, placebo-controlled study to assess the safety of pemvidutide in patients with MASLD. The trial was conducted in accordance with the principles of the Declaration of Helsinki and the International Conference on Harmonization Good Clinical Practice. The trial protocol and amendments were approved by the relevant institutional review boards and/or ethics committees at each study site. All participants provided written informed consent prior to participation in the study.

To be eligible for study participation, participants were required to be 18-65 years of age and have a BMI ≥28.0 kg/m^2 and LFC by magnetic resonance imaging-proton density fat fraction (MRI-PDFF) ≥10%. Participants with T2DM were permitted in the study if they had an HbA1c (glycated hemoglobin) <9.5% and were on a stable regimen of one or more of the following for at least 3 months prior to screening: diet and exercise, metformin with no more than mild gastrointestinal symptoms (nausea, vomiting or diarrhea), and/or sodium glucose transporter-2 inhibitor therapy. Participants with significantly elevated serum alanine aminotransferase (ALT) levels, defined as >75 IU/L, or significant hepatic fibrosis, defined as FibroScan® liver stiffness measurement of 10 kPa or greater, were excluded. Use of insulin or GLP-1R-based therapies was also excluded.

Study procedures

Participants were randomized by interactive web response system 1:1:1:1 to receive either 1.2 mg pemvidutide, 1.8 mg pemvidutide, 2.4 mg pemvidutide, or placebo (normal saline) administered weekly by subcutaneous injection for 12 weeks, stratified by presence or absence of T2DM at baseline. The randomization list was generated by an independent statistician. The investigator, patient, and study staff remained blinded throughout the study, and saline placebo was matched for volume based on the dose and volume of pemvidutide administered in that cohort. No dose titration was used with 1.2 mg or 1.8 mg dose groups. In the 2.4 mg dose group, a 4-week dose titration was employed (0.6 mg at week 1, 1.2 mg at week 2, 1.8 mg at weeks 3 and 4) to reach the target dose of 2.4 mg for 8 weeks. Participants were instructed to maintain their normal diet and activities during screening and throughout study participation, without diet or exercise interventions. Changes in hepatic inflammation were assessed by serum ALT levels in all participants; 32 patients participated in a sub-study of MRI-based corrected T1 (cT1) imaging to assess the effects of pemvidutide on this additional marker of hepatic inflammation.

Efficacy endpoints

The primary efficacy endpoints were the absolute and relative (percent, %) reductions in LFC from baseline by MRI-PDFF. Secondary efficacy endpoints included absolute changes in serum ALT and percent change from baseline in body weight. Additional endpoints included liver volume by MRI-PDFF, FibroScan controlled attenuation parameter score, FibroScan vibration-controlled transient elastography, fibrosis biomarkers (ELF [enhanced liver fibrosis] and Pro-C3 [pro-peptide of type III collagen]), and lipid metabolism (total cholesterol, LDL, HDL, and triglycerides). A sub-study to measure relaxation time for iron-corrected T1 (cT1) MRI imaging was also conducted. Secondary endpoint analyses and sub-analyses were conducted *post hoc*. Responder analyses included the proportions of patients achieving 30% or 50% relative reductions in LFC or normalization, defined as LFC ≤5%, and the proportion of patients with a ≥80 ms reduction in cT1 relaxation time. Safety endpoints included adverse events (AEs), electrocardiograms, vital signs (systolic blood pressure [BP], diastolic BP, heart rate, rate pressure product [equal to the product of systolic BP x heart rate]), and glucose homeostasis as assessed by fasting serum glucose and HbA1c.

Statistical analysis

The efficacy analysis population included all randomized participants who received at least one dose of study medication and completed at least one post-baseline assessment. Continuous variables limited to a single pre- and post-treatment measurement, including changes from baseline in LFC, cT1 relaxation time, fibrosis markers, inflammation markers, and lipids, were compared between pemvidutide and placebo using statistical tests based on analysis of covariance (ANCOVA), with the treatment arm as a factor and stratification for presence or absence of T2DM and the corresponding baseline demographic characteristics (gender, race, BMI) as covariates. Continuous measures with multiple measurements, such as weekly changes in body weight, serum ALT, BP, and heart rate, were analyzed using mixed model of repeated measures with the same covariates as ANCOVA under the assumption of missing values at random, employing a pattern mixture model under the assumption of missing not at random as a sensitivity analysis. The results of ANCOVA and mixed model of repeated measures analyses were expressed as least-squares mean. The Cochrane-Mantel-Haenszel test was applied to secondary endpoints that were categorical in nature, while considering the stratification of presence or absence of T2DM, at a one-sided significance level of 0.025. Only non-missing values were included in these analyses. The numbers of participants experiencing treatment-emergent AEs were summarized by Medical Dictionary for Regulatory Activities System Organ Class, Preferred Term, seriousness, severity, and relationship to study medication. All statistical analyses refer to the respective treatment group *vs.* placebo unless otherwise stated.

The sample size of 95 participants is consistent with phase I studies, which are typically designed to enable a qualitative evaluation for safety imbalances between placebo and study drug recipients and supports adequate descriptive statistical analyses of pharmacodynamic parameters (*i.e.*, efficacy endpoints).

Results

Study participants

Between November 2021, and May 2022, 271 individuals at 13 investigative sites in the United States were screened for eligibility, of whom 95 were enrolled. The disposition of study participants is shown in Fig. 1. Eighty-three (83) individuals completed the study and 11 discontinued before the completion of treatment.

The baseline characteristics of study participants are provided in Table 1. The mean ages of study participants across the four treatment groups ranged from 47.9 to 50.3 years. The majority of study participants were female with an imbalance towards males at the 1.2 mg dose. Across all study groups, 29% of study participants had T2DM at baseline and over 75% of study participants were of Hispanic ethnicity. Mean body weight ranged from 98.2 to 105.1 kg, and mean BMI ranged from 35.3 to 36.9 kg/m^2. Mean baseline LFC ranged from 20.2% to 23.8%, and baseline ALT means ranged from 32.4 IU/L to 39.5 IU/L.

Efficacy

The primary efficacy endpoints for this study of absolute and relative reductions in LFC, by MRI-PDFF, were achieved. By treatment week 12, all pemvidutide-treated cohorts achieved statistically significant reductions in LFC compared to placebo. Absolute reductions in LFC for pemvidutide-treated groups were (least-squares mean [95% CI; *p* value *vs.* placebo]) 8.9% [-12.4 to -5.4; p <0.001], 14.7% [-18.0 to -11.4; p <0.001], and 11.3% [-15.3 to -7.4; p <0.001] for pemvidutide 1.2 mg, 1.8 mg, and 2.4 mg, respectively, compared to 0.2% [-3.4 to 3.1] in those receiving placebo (Fig. 2A). Relative reductions of LFC were 46.6% [-63.7 to -29.6; p <0.001], 68.5% [-84.4 to -52.5; p <0.001], and 57.1% [-76.1 to -38.1; p <0.001] for pemvidutide 1.2 mg, 1.8 mg, and 2.4 mg, respectively, *vs.* 4.4% [-20.2 to 11.3] in those receiving placebo (Fig. 2B). Responder analyses showed the proportions of individuals with a ≥30% relative reduction in LFC at week 12 were 65.0%, 94.4%, and 85.0% for pemvidutide 1.2 mg, 1.8 mg, and 2.4 mg, respectively, *vs.* 4.2% in placebo (p <0.0001 *vs*. placebo, respectively). Furthermore, 40.0% (p = 0.001), 72.2% (p <0.0001), and 70.0% (p <0.0001) of patients achieved a ≥50% reduction in liver fat at the 1.2 mg, 1.8 mg, and 2.4 mg doses of pemvidutide, respectively, compared to none of the individuals receiving placebo. Normalization of liver fat, defined as a post-treatment liver fat fraction of 5% or less, was achieved in 20.0% (p = 0.0266), 55.6% (p <0.0001), and 50.0% (p = 0.0003) of patients at the 1.2 mg, 1.8 mg, and 2.4 mg doses of pemvidutide, respectively, compared to none of the individuals receiving placebo (Fig. 2C). Changes in LFC correlated with relative reductions in liver volume of 9.3% [-14.9 to -3.7; p <0.001], 17.9% [-23.1 to -12.7; p <0.001], and 13.7% [-19.8 to -7.6; p <0.001] at the 1.2 mg, 1.8 mg, and 2.4 mg doses of pemvidutide, respectively, compared to a 1.4% [-3.8 to 6.5] relative increase in liver volume in those receiving placebo (Fig. S1). Pemvidutide treatment also resulted in significant decreases in controlled attenuation parameter score *vs.* placebo at all doses (Table 2). As expected for this MASLD study population, significant changes in hepatic fibrosis and systemic inflammation measurements were not observed (Table 2).

Pemvidutide-treated patients also exhibited significant improvements in non-invasive biomarkers of hepatic inflammation. At week 12, ALT levels were reduced in all pemvidutide groups and were significantly reduced in the 1.8 mg (-13.8 IU/L [-19.7 to -7.9; p = 0.029]) and 2.4 mg (-13.6 IU/L [-19.8 to -7.4; p = 0.030]) groups compared to placebo (-6.2 IU/L [-11.7 to -0.7]) (Fig. 3A). In a sub-analysis of patients with baseline ALT levels ≥30 IU/L, pemvidutide treatment reduced ALT by at least 17 IU/L in all pemvidutide treatment groups (Fig. 3B). In the 32 patients analyzed by cT1, absolute changes in cT1 relaxation time across pemvidutide treatment groups were -57.4 ms [-114.9 to 0.1; p = 0.006], -75.9 ms [-136.1 to -15.8; p = 0.002], and -55.4 ms [-117.8 to 7.0; p = 0.012] at the 1.2 mg, 1.8 mg, and 2.4 mg doses of pemvidutide, respectively, *vs.* an increase of 10.2 ms [-34.1 to 54.5] in placebo (Fig. 4A). In these same pemvidutide treatment groups, 87.5% [47.3 to 99.7; p = 0.0002], 83.3% [35.9 to 99.6; p = 0.0019], and 85.7% [42.1 to 99.6; p = 0.0004] of patients achieved ≥80 ms reductions by week 12 at the 1.2 mg, 1.8 mg, and 2.4 mg doses of pemvidutide, respectively. No patients [0.0 to 28.5] in the placebo cohort achieved an 80 ms reduction in cT1 relaxation time (Fig. 4B).

Significant weight loss compared to placebo was observed in all pemvidutide dose groups at week 12 (Fig. 5A). Reductions

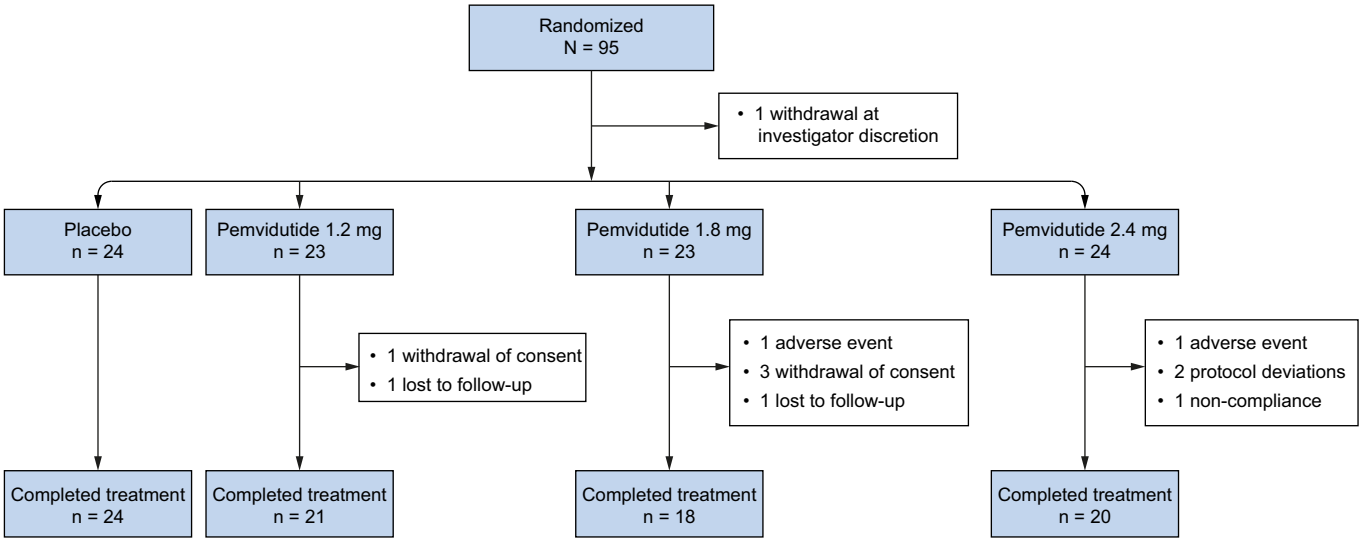

Fig. 1. CONSORT diagram.

Table 1. Patient demographics and baseline characteristics (safety population).

	Treatment			
Characteristic	**Placebo (n = 24)**	**1.2 mg pemvidutide (n = 23)**	**1.8 mg pemvidutide (n = 23)**	**2.4 mg pemvidutide (n = 24)**
Age, mean years	47.9 (14)	48.6 (11)	50.3 (9)	48.8 (8)
Sex, n (%)				
Female	14 (58.3)	9 (39.1)	12 (52.2)	15 (62.5)
Ethnicity, n (%)				
Hispanic	14 (58.3)	20 (87.0)	19 (82.6)	18 (75.0)
Non-Hispanic	10 (41.7)	3 (13.0)	4 (17.4)	6 (25.0)
Body weight, kg (SD)	105.1 (20.8)	102.4 (14.6)	98.9 (19.7)	98.2 (18.9)
BMI, kg/m^2 (SD)	36.9 (4.7)	36.3 (5.6)	35.4 (3.9)	35.3 (5.0)
Liver fat content, % (SD)	23.8 (9.2)	21.6 (7.3)	21.8 (8.0)	20.2 (7.0)
ALT, IU/L (SD)	39.5 (21.4)	32.4 (13.8)	36.4 (15.6)	37.8 (24.4)
AST, IU/L (SD)	23.8 (10.0)	25.4 (7.5)	24.6 (7.2)	27.2 (13.9)
Diabetes status, n (%)				
Non-diabetes	18 (75.0)	16 (69.6)	16 (69.6)	17 (70.8)
Non-diabetes				
Fasting glucose, mg/dl (SD)	99.9 (13.6)	99.4 (12.4)	95.1 (10.3)	97.9 (13.6)
HbA1c, % (SD)	5.8 (0.2)	5.7 (0.3)	5.7 (0.3)	5.6 (0.4)
Diabetes				
Fasting glucose, mg/dl (SD)	114.0 (18.1)	124.4 (26.1)	117.3 (134.7)	166.1 (49.6)
HbA1c, % (SD)	6.2 (0.6)	6.6 (1.4)	6.4 (0.5)	7.5 (1.3)
Baseline Lipids, mg/dl (SD)				
Triglycerides	169.3 (90.1)	224.9 (119.1)	192.2 (114.9)	220.0 (169.3)
Total cholesterol	181.4 (39.0)	186.9 (44.8)	200.0 (35.2)	182.2 (39.7)
LDL cholesterol	100.0 (38.2)	100.2 (34.3)	116.6 (33.6)	101.3 (33.0)
HDL cholesterol	47.5 (6.8)	42.6 (9.1)	47.0 (9.9)	45.3 (7.3)
Blood pressure, mmHg (SD)				
Systolic	122.8 (11.4)	129.1 (14.7)	123.3 (15.9)	125.9 (12.4)
Diastolic	79.6 (6.0)	79.2 (9.2)	78.1 (10.4)	80.8 (8.5)
Heart rate, bpm (SD)	69.1 (9.0)	71.2 (10.5)	68.1 (10.2)	72.3(9.7)
RPP (SD)	8,475.3 (1,294.3)	9,187.7 (1,703.4)	8,458.3 (1,981.4)	9,130.7 (1,641.5)
CAP score, dB/m (SD)	343.8 (30.4)	331.3 (28.3)	324.7 (70.4)	329.3 (40.7)
Pro-C3, (SD)	37.3 (6.6)	36.6 (7.5)	36.5 (6.7)	33.6 (6.8)
ELF score, (SD)	8.6 (0.9)	8.8 (0.6)	8.8 (0.8)	8.7 (1.3)
FibroScan VCTE, kPa (SD)	6.5 (1.2)	6.9 (2.0)	6.3 (1.3)	6.3 (1.9)
hs-CRP, mg/L (SD)	6.8 (5.4)	5.5 (4.9)	4.3 (4.8)	7.0 (7.6)
cT1, ms (SD)[a]	943.4 (94.3)	916.7 (101.2)	894.7 (161.3)	927.6 (18.3)

ALT, alanine aminotransferase; AST, aspartate aminotransferase; CAP, controlled attenuation parameter; cT1, corrected T1; ELF, enhanced liver fibrosis; HbA1c, hemoglobin A1C; HDL, high-density lipoprotein; hs-CRP, high sensitivity C reactive protein; LDL, low-density lipoprotein; Pro-C3, pro-peptide of type III collagen; RPP, rate pressure product; VCTE, vibration-controlled transient elastography.

Data are presented as n (%) for categorical variables and mean (SD) for continuous variables.

[a]Sub-study of randomized participants. Baseline participant numbers: placebo (n = 12), 1.2 mg (n = 9), 1.8 mg (n = 7), 2.4 mg (n = 7).

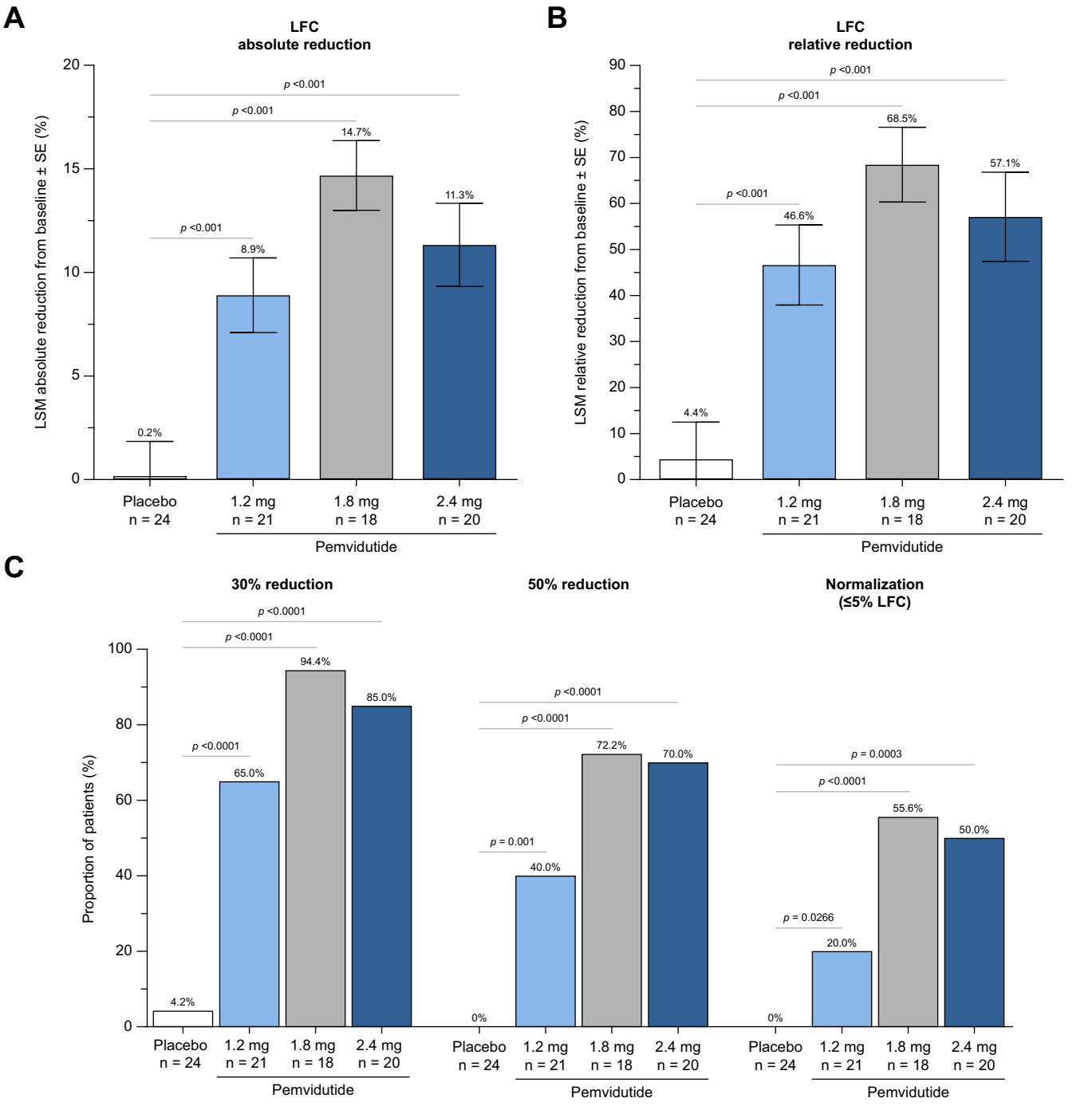

Fig. 2. Primary efficacy endpoint at week 12. (A) LSM (SE) absolute reduction from baseline in LFC; (B) LSM (SE) relative reduction from baseline in LFC; (C) proportion of patients with relative reductions from baseline in LFC of ≥30%, ≥50%, or normalization (≤5%). Statistical significance in (A) and (B) was assessed by analysis of covariance. Statistical significance in (C) was assessed by Cochran-Mantel-Haenszel analysis. All *p* values displayed are nominal. LFC, liver fat content; LSM, least squares mean.

in body weight from baseline to week 12 were 3.4% [-4.7 to -2.0; *p* <0.001], 4.3% [-5.6 to -3.0; *p* <0.001], and 3.7% [-5.1 to -2.3; *p* <0.001] for the 1.2 mg, 1.8 mg, and 2.4 mg cohorts, respectively, compared with 0.2% [-1.5 to 1.1] for those receiving placebo. Weight losses were greater in those without diabetes, in whom changes of 3.4% [-5.0 to -1.9; *p* <0.001], 4.9% [-6.4 to -3.4; *p* <0.001], and 3.5% [-5.1 to -2.0; *p* <0.001] were observed or the 1.2 mg, 1.8 mg, and 2.4 mg arms, respectively, compared with 0.2% [-1.6 to 1.2] in the placebo arm. Weight loss trajectories suggested that weight loss would continue beyond 12 weeks of treatment (Fig. 5B).

Safety

Pemvidutide was well-tolerated with no serious or severe AEs deemed related to study medication (Table 3). One patient each in the 1.8 mg and 2.4 mg pemvidutide dose groups

Table 2. LSM change from baseline to week 12 in key endpoints.

	LSM (95% CI)				LSM difference *vs.* placebo (95% CI; *p* value)		
Endpoint	placebo (n = 24)	1.2 mg pemvidutide (n = 23)	1.8 mg pemvidutide (n = 23)	2.4 mg pemvidutide (n = 24)	1.2 mg pemvidutide	1.8 mg pemvidutide	2.4 mg pemvidutide
LFC, % absolute[a]	-0.2 (-3.4 to 3.1)	-8.9 (-12.4 to -5.4)	-14.7 (-18.0 to -11.4)	-11.3 (-15.3 to -7.4)	-8.7 (-11.8 to -5.7; <0.001)	-14.5 (-17.6 to -11.4; <0.001)	-11.2 (-14.3 to -8.0; <0.001)
LFC, % relative[a]	-4.4 (-20.2 to 11.3)	-46.6 (-63.7 to -29.6)	-68.5 (-84.4 to -52.5)	-57.1 (-76.1 to -38.1)	-42.2 (-56.9 to -27.5; <0.001)	-64.0 (-78.9 to -49.2; <0.001)	-52.7 (-68.0 to -37.4; <0.001)
Weight loss, %[b]	-0.2 (-1.5 to 1.1)	-3.4 (-4.7 to -2.0)	-4.3 (-5.6 to -3.0)	-3.7 (-5.1 to -2.3)	-3.2 (-4.6 to -1.7; <0.001)	-4.1 (-5.5 to -2.6; <0.001)	-3.5 (-4.9 to -2.1; <0.001)
Non-diabetes							
Fasting glucose, mg/dl[a]	2.9 (-3.5 to 9.4)	1.0 (-6.4 to 8.5)	1.6 (-5.1 to 8.3)	3.8 (-3.9 to 11.4)	-1.9 (-8.6 to 4.8; 0.575)	-1.3 (-8.1 to 5.5; 0.703)	0.9 (-5.9 to 7.6; 0.800)
HbA1c, %[a]	0.1 (0.0 to 0.2)	0.2 (0.0 to 0.3)	0.0 (-0.2 to 0.1)	0.3 (0.2 to 0.4)	0.1 (-0.1 to 0.2; 0.399)	-0.1 (-0.3 to 0.1; 0.182)	0.2 (0.1 to 0.4; 0.010)
Diabetes							
Fasting glucose, mg/dl[a]	-10.1 (-84.4 to 64.2)	8.3 (-55.3 to 72.0)	8.9 (-61.3 to 79.2)	-11.6 (-86.0 to 62.8)	18.5 (-59.7 to 96.7; 0.627)	19.0 (-43.4 to 81.4; 0.531)	-1.5 (-73.0 to 70.0; 0.966)
HbA1c, %[a]	0.2 (-0.5 to 0.9)	-0.2 (-0.8 to 0.4)	0.6 (0.0 to 1.2)	0.2 (-0.4 to 0.9)	-0.4 (-1.3 to 0.5; 0.345)	0.4 (-0.5 to 1.3; 0.384)	0.0 (-1.0 to 1.0; 0.999)
Lipids							
Triglycerides, mg/dl[a]	-59.5 (-129.2 to 10.2)	-111.4 (-185.4 to -37.4)	-67.3 (-137.2 to 2.6)	-130.4 (-210.6 to -50.6)	-51.9 (-116.1 to 12.4; 0.112)	-7.8 (-73.2 to 57.6; 0.813)	-70.8 (-135.5 to -6.2; 0.032)
Total cholesterol, mg/dl[a]	-15.3 (-31.4 to 0.9)	-25.2 (-42.4 to -8.0)	-22.3 (-38.5 to -6.0)	-25.8 (-44.3 to -7.2)	-10.0 (-24.8 to 4.9; 0.184)	-7.0 (-22.4 to 8.3; 0.365)	-10.5 (-25.4 to 4.4; 0.164)
LDL cholesterol, mg/dl[a]	-4.4 (-18.9 to 10.2)	-6.5 (-22.1 to 9.0)	-2.5 (-17.1 to 12.2)	-4.7 (-22.1 to 12.7)	-2.2 (-15.7 to 11.3; 0.750)	1.9 (-12.3 to 16.1; 0.788)	-0.3 (-14.2 to 13.6; 0.967
HDL cholesterol, mg/dl[a]	-3.2 (-6.2 to -0.3)	-1.8 (-4.9 to 1.3)	-5.5 (-8.4 to -2.5)	-4.2 (-7.6 to -0.8)	1.4 (-1.3 to 4.1; 0.293)	-2.2 (-5.0 to 0.5; 0.112)	-0.9 (-3.6 to 1.8; 0.499
Blood pressure							
Systolic, mmHg[b]	2.4 (-2.4 to 7.2)	-6.0 (-11.2 to -0.8)	-4.0 (-9.3 to 1.3)	-10.4 (-15.8 to -5.0)	-8.4 (-14.6 to -2.2; 0.008)	-6.4 (-12.8 to 0.1; 0.053)	-12.7 (-19.0 to -6.5; <0.001)
Diastolic, mmHg[b]	3.1 (-0.3 to 6.5)	0.3 (-3.3 to 3.9)	-0.7 (-4.4 to 3.1)	-4.8 (-8.5 to -1.0)	-2.8 (-7.2 to 1.6; 0.210)	-3.8 (-8.4 to 0.8; 0.107)	-7.9. (-12.4 to -3.4; <0.001)
Heart rate, bpm[b]	0.6 (-2.6 to 3.8)	3.9 (0.5 to 7.3)	1.6 (-1.9 to 5.1)	2.6 (-1.0 to 6.1)	3.2 (-0.9 to 7.4; 0.127)	1.0 (-3.4 to 5.3; 0.658)	2.0 (-2.3 to -6.2; 0.365)
RPP[b]	292.6 (-243.1 to 828.3)	112.1 (-462.5 to 686.6)	-94.3 (-685.9 to 497.3)	-384.1 (-984.7 to 216.5)	-180.5 (-874.9 to 513.9; 0.610)	-387.0 (-1,107.7 to 333.8; 0.292)	-676.7 (-1,380.2 to 26.8; 0.059)
CAP score, dB/m[a]	-17.9 (-48.6 to 12.8)	-48.2 (-81.2 to -15.2)	-53.9 (-84.4 to -23.3)	-66.3 (-101.4 to -31.2)	-30.3 (-58.8 to -1.7; 0.038)	-35.9 (-63.8 to -8.0; 0.012)	-48.4 (-77.0 to -19.7; 0.001)
Pro-C3[a]	-3.7 (-7.5 to 0.1)	-6.2 (-10.3 to -2.2)	-7.4 (-11.2 to -3.6)	-6.7 (-11.0 to -2.4)	-2.5 (-6.0 to 1.0; 0.156)	-3.7 (-7.2 to -0.2; 0.038)	-3.0 (-6.6 to 0.6; 0.099)
ELF score[a]	-0.6 (-1.2 to 0.0)	-0.8 (-1.5 to -0.2)	-0.8 (-1.5 to -0.2)	-0.7 (-1.4 to -0.0)	-0.2 (-0.8 to 0.4; 0.440)	-0.3 (-0.8 to 0.3; 0.377)	-0.1 (-0.7 to 0.5; 0.653)
FibroScan VCTE, kPa[a]	-0.7 (-2.5 to 1.2)	-0.5 (-2.5 to 1.5)	-1.7 (-3.5 to 0.1)	-1.0 (-3.1 to 1.1)	0.2 (-1.6 to -2.0; 0.844)	-1.0 (-2.7 to -0.7; 0.239)	-0.3 (-2.1 to 1.5; 0.729)
hs-CRP, mg/L[a]	5.8 (2.6 to 8.9)	5.1 (1.7 to 8.5)	3.5 (0.4 to 6.7)	5.9 (2.3 to 9.5)	-0.6 (-3.6 to 2.3; 0.678)	-2.2 (-5.2 to 0.7; 0.135)	0.1 (-2.9 to 3.2; 0.933)

CAP, controlled attenuation parameter; ELF, enhanced liver fibrosis; HbA1c, hemoglobin A1C; HDL, high-density lipoprotein; hs-CRP, high sensitivity C reactive protein; LDL, low-density lipoprotein; LFC, liver fat content; LSM, least squares mean; PRO-C3, pro-peptide of type III collagen; RPP, rate pressure product; VCTE, vibration-controlled transient elastography.

[a]Based on analysis of covariance model; All *p* values displayed are nominal in nature.

[b]Based on mixed model of repeated measures; All *p* values displayed are nominal in nature.

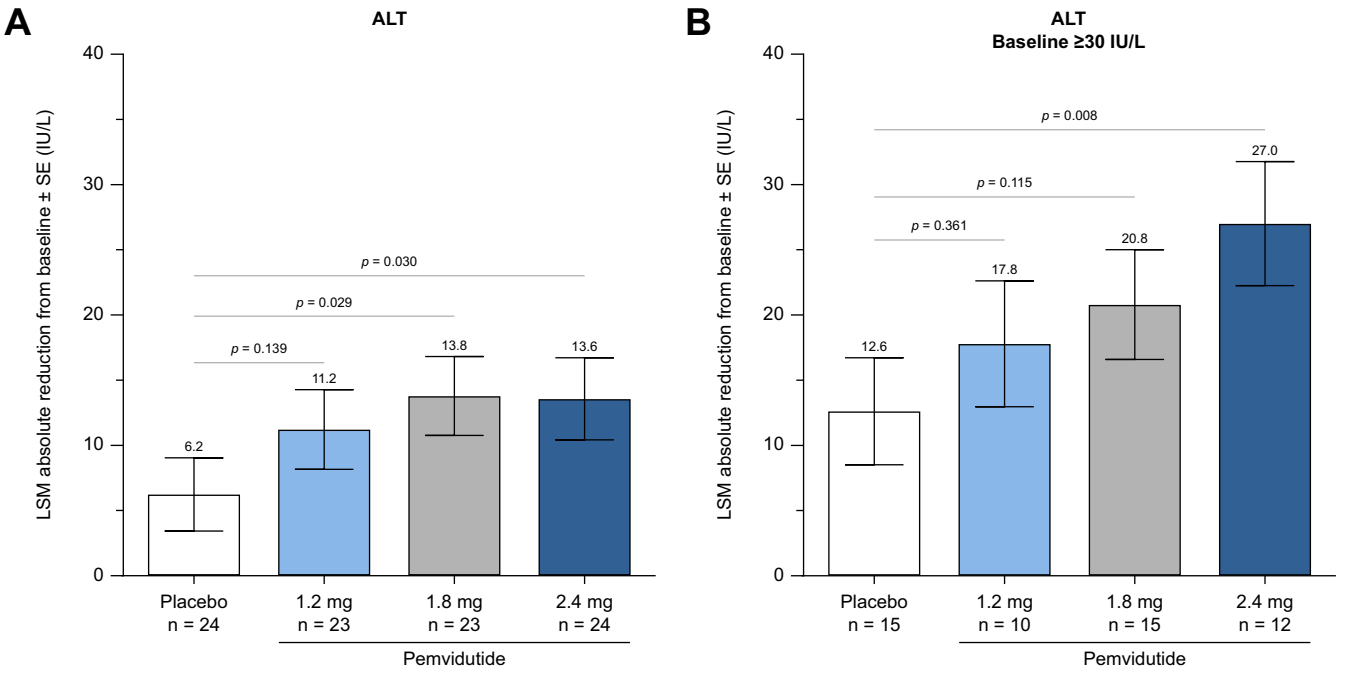

Fig. 3. Changes in serum ALT at week 12. (A) LSM (SE) absolute reduction from baseline in ALT; (B) LSM (SE) absolute ALT reduction in patients with a baseline ALT ≥30 IU/L; Statistical significance was assessed by mixed model of repeated measures. All *p* values displayed are nominal. ALT, alanine aminotransferase; LSM, least squares mean.

discontinued treatment due to AEs. The most common AE was nausea, which was observed in 35.7% of pemvidutide-treated individuals, with the majority of events being mild. A small number of patients reported vomiting, diarrhea, and/or constipation, but these events were almost entirely mild and resolved without treatment.

Pemvidutide treatment improved systolic and diastolic BP at all three dose levels (Table 2). Importantly, no significant

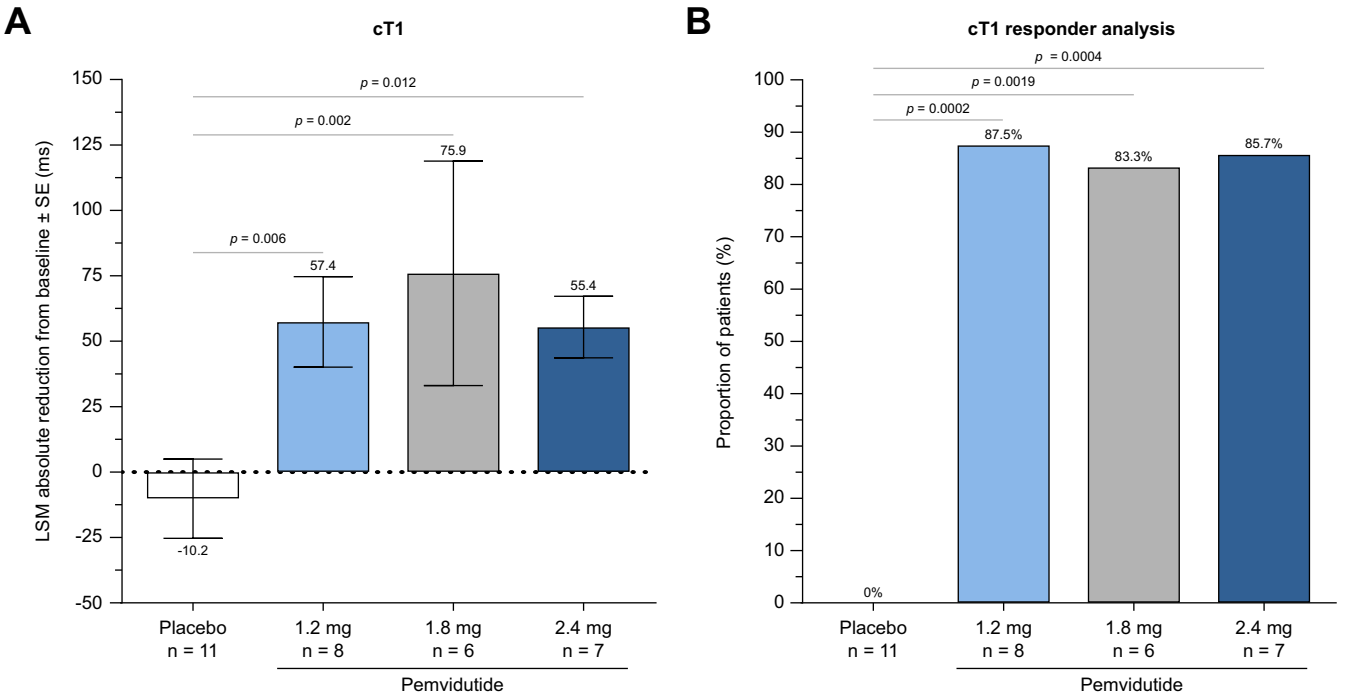

Fig. 4. Sub-analysis of cT1 at week 12. (A) LSM (SE) absolute reduction in cT1 relaxation time; (B) proportion of patients with ≥80 ms reduction in cT1 relaxation time. Statistical significance in (A) was assessed by analysis of covariance. Statistical significance in (B) was assessed by Cochran-Mantel-Haenszel analysis. All *p* values displayed are nominal. cT1, iron-corrected T1; LSM, least squares mean.

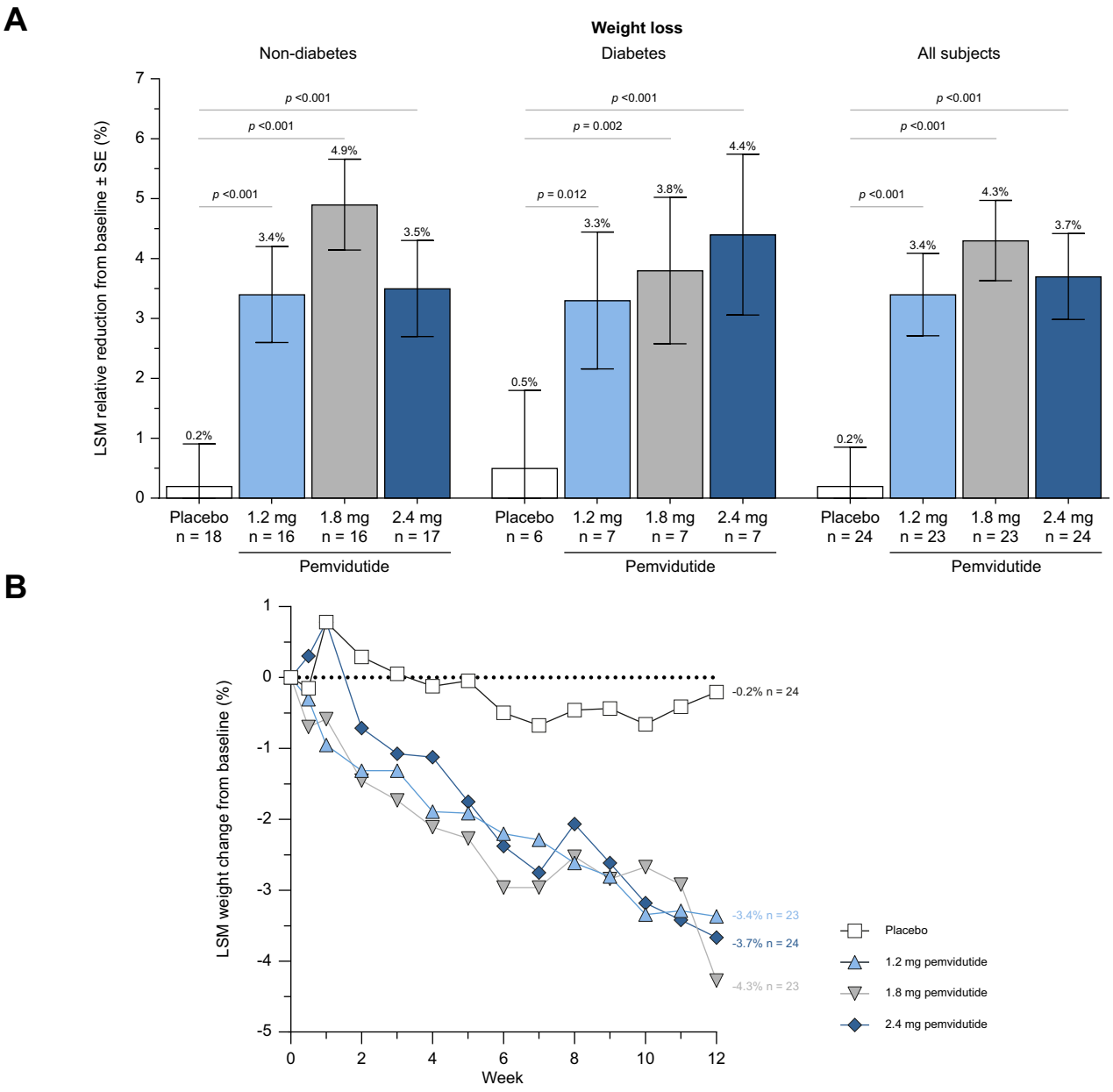

Fig. 5. Percent reduction in body weight. LSM (SE) percent reductions from baseline at (A) week 12 and (B) over time. Statistical significance in (A) was assessed by mixed model of repeated measures. All *p* values displayed are nominal. LSM, least squares mean.

changes in heart rate were observed, and the decreases in systolic BP were accompanied by decreases in rate pressure product when compared to the placebo group.

Discussion

This randomized, double-blind, placebo-controlled, clinical trial was conducted to evaluate the safety and efficacy of pemvidutide in adults with MASLD and overweight/obesity, with or without T2DM. In this study, treatment with pemvidutide led to rapid and significant reductions in LFC, hepatic inflammation (serum ALT, cT1 relaxation time), and body weight.

In individuals with confirmed MASLD, weekly subcutaneous doses of pemvidutide resulted in statistically significant reductions in hepatic fat compared to placebo, yielding up to a 68.5% relative reduction in LFC in only 12 weeks. Studies suggest that a 30% relative reduction in LFC correlates with a ≥2-point reduction in NAFLD activity score (NAS), while a ≥50% relative reduction in LFC correlates with MASH resolution (absence of ballooning with minimal-to-no lobular inflammation) and improvements in fibrosis.[24–26] The reductions in LFC following pemvidutide treatment are comparable to those observed after bariatric surgery, and surpass those seen with GLP-1R agonist-based compounds lacking glucagon.[10,11,27–29] While the significant weight loss achieved in this study presumably contributed to decreased LFC,[8,30] glucagon's direct effects on hepatic fatty acid β-oxidation and lipogenesis likely contributed to and accelerated the reduction in LFC. Given the

Table 3. Adverse events.

Adverse event	Placebo (n = 24)	1.2 mg pemvidutide (n = 23)	1.8 mg pemvidutide (n = 23)	2.4 mg pemvidutide (n = 24)
Severe AEs, n (%)	0	0	0	0
Serious AEs, n (%)	0	0	0	0
AEs leading to treatment discontinuation, n (%)	0	0	1 (4.3)	1 (4.2)
Nausea				
Mild, n (%)	3 (12.5)	3 (13.0)	6 (26.1)	6 (25.0)
Moderate, n (%)	0	1 (4.3)	6 (26.1)	3 (12.5)
Vomiting				
Mild, n (%)	0	3 (13.0)	2 (8.7)	2 (8.3)
Moderate, n (%)	0	0	0	0
Diarrhea				
Mild, n (%)	4 (16.7)	3 (13.0)	5 (21.7)	1 (4.2)
Moderate, n (%)	0	0	0	0
Constipation				
Mild, n (%)	0	3 (13.0)	4 (17.4)	1 (4.2)
Moderate, n (%)	0	1 (4.3)	0	0

potent effects of pemvidutide on LFC at 12 weeks, longer treatment may result in even greater LFC reduction and higher rates of liver fat normalization. With respect to the reduction in LFC, there was no clear dose effect between the 1.8 mg and 2.4 mg cohorts, possibly due to greater than 50% of participants in each cohort achieving LFC normalization within the 12 weeks. Conversely, the short dose titration utilized in the 2.4 mg cohort may have slowed the initial effects of pemvidutide on LFC. A longer trial with a larger study population may illustrate greater dose effects between the two groups.

Serum ALT is an accepted method for assessing MASH response to treatment.[31,32] Here, the reductions in LFC were complemented by significant decreases in ALT at week 12, despite the relatively low baseline levels. Pemvidutide-treated patients with an elevated baseline ALT ≥30 IU/L exhibited clinically relevant reductions of at least 17 IU/L, which has been shown to be a positive predictor of histologic improvement.[33,34] Importantly, rapid defatting of the liver did not result in significant liver enzyme increases as no participants had a 3-fold elevation in ALT as has been reported elsewhere.[35]

In addition to significant reductions in LFC and ALT, a subset of pemvidutide-treated patients evaluated for cT1 response achieved clinically meaningful reductions in cT1 signal, with 85.7% of measured patients having a ≥80 ms reduction in cT1 relaxation time from baseline. As an indicator of regional tissue water content, cT1 measurements reflect the degree of hepatic inflammatory disease and a reduction of approximately 80 ms in cT1 relaxation time has been associated with a 2-point reduction in NAS.[36] The mean cT1 value at baseline for each group in this study was ≥894 ms with all pemvidutide-treated groups achieving values <800 ms by week 12. Importantly, an increased risk of major adverse cardiac events and major adverse liver outcomes are associated with cT1 levels above 800 ms independent of LFC.[37] Despite clear evidence of hepatic anti-inflammatory activity, pemvidutide did not lower high-sensitivity C reactive protein (hs-CRP) levels. Given the documented effect of glucagon on increasing hs-CRP expression in human hepatocytes, hs-CRP may not be an appropriate indicator of systemic inflammation following pemvidutide treatment.[38]

Finally, body weight loss has also been correlated with MASH improvement.[8] In this study, all pemvidutide-treated cohorts achieved statistically significant weight loss within 12 weeks without prescribed lifestyle or dietary modification. This is in contrast to many MASH therapeutics in development that do not elicit a clinically significant decrease in body weight or even cause weight gain.[39–41] Incretin-based approaches for MASH are the exception where weight loss is observed, but the reduction in LFC with some of these agents appears less robust than the data reported here.[9,10,29,42] The addition of glucagon agonism is likely to accelerate and augment the reduction in LFC in individuals with MASLD as noted in this study and results reported elsewhere.[42]

A limitation in the extrapolation of these data to a MASH population is that participants in this trial were unlikely to have advanced fibrosis, preventing direct investigation of pemvidutide's effect on this parameter. Further studies in a population with more advanced fibrosis are needed to determine pemvidutide's effect on this endpoint. A preponderance of participants from a Hispanic background may make these findings less generalizable to a broader ethnic population, and the exclusion of individuals with baseline serum ALT greater than 75 IU/L may have biased the study population to less advanced MASLD; despite this limitation, robust reductions were observed, especially in the sub-population of individuals with ALT ≥30 IU/L at baseline.

In conclusion, pemvidutide led to rapid and potent reductions in LFC, serum ALT, cT1, and body weight over 12 weeks of dosing. While this was a non-invasive study that was conducted in MASLD, the rapid and significant reductions in steatosis and hepatic inflammation observed in this study may be predictive of improvements in MASH, including its histopathological endpoints and associated comorbidities in late-phase clinical studies.

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Abbreviations

AE, adverse event; ALT, alanine aminotransferase; ANCOVA, analysis of covariance; BP, blood pressure; cT1, iron-corrected T1; GCGR, G-coupled glucagon receptor; GLP-1, glucagon-like peptide-1; GLP-1R, glucagon-like peptide-1 receptor; hs-CRP, high sensitivity C reactive protein; LFC, liver fat content; MASH, metabolic dysfunction-associated steatohepatitis; MASLD, metabolic dysfunction-associated steatotic liver disease; MRI-PDFF, magnetic resonance imaging estimated proton density fat fraction; NAS, NAFLD activity score; T2DM, type 2 diabetes mellitus.

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This study was funded by Altimmune, Inc. The authors (some of whom are Altimmune, Inc employees) designed, collected, analyzed, and interpreted the data. All authors had full access to the study data, and the corresponding author had final responsibility for publishing the manuscript.

Conflict of interest

S.A.H. and J.A.G. are paid consultants to Altimmune, Inc. S.K.B., J.J.S., S.T., J.Y., M.S.R., and M.S.H. are employees of Altimmune, Inc. and hold a financial interest in the company.

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

Authors' contributions

S.A.H. and M.S.H. designed the study. S.K.B., J.J.S., S.T., J.A.G., J.Y., M.S.R., and M.S.H. analyzed and interpreted data. All authors were involved in the development, review and editing of the manuscript.

Data availability statement

Aggregated data that supports the findings of this study may be available from the authors on reasonable request pending approval from Altimmune, Inc. Individual participant-level data containing confidential or identifiable subject information is covered by patient privacy and cannot be shared.

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Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.jhep.2024.07.006.

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Effect of pemvidutide, a GLP-1/glucagon dual receptor agonist, on MASLD: a randomized, double-blind, placebo-controlled study

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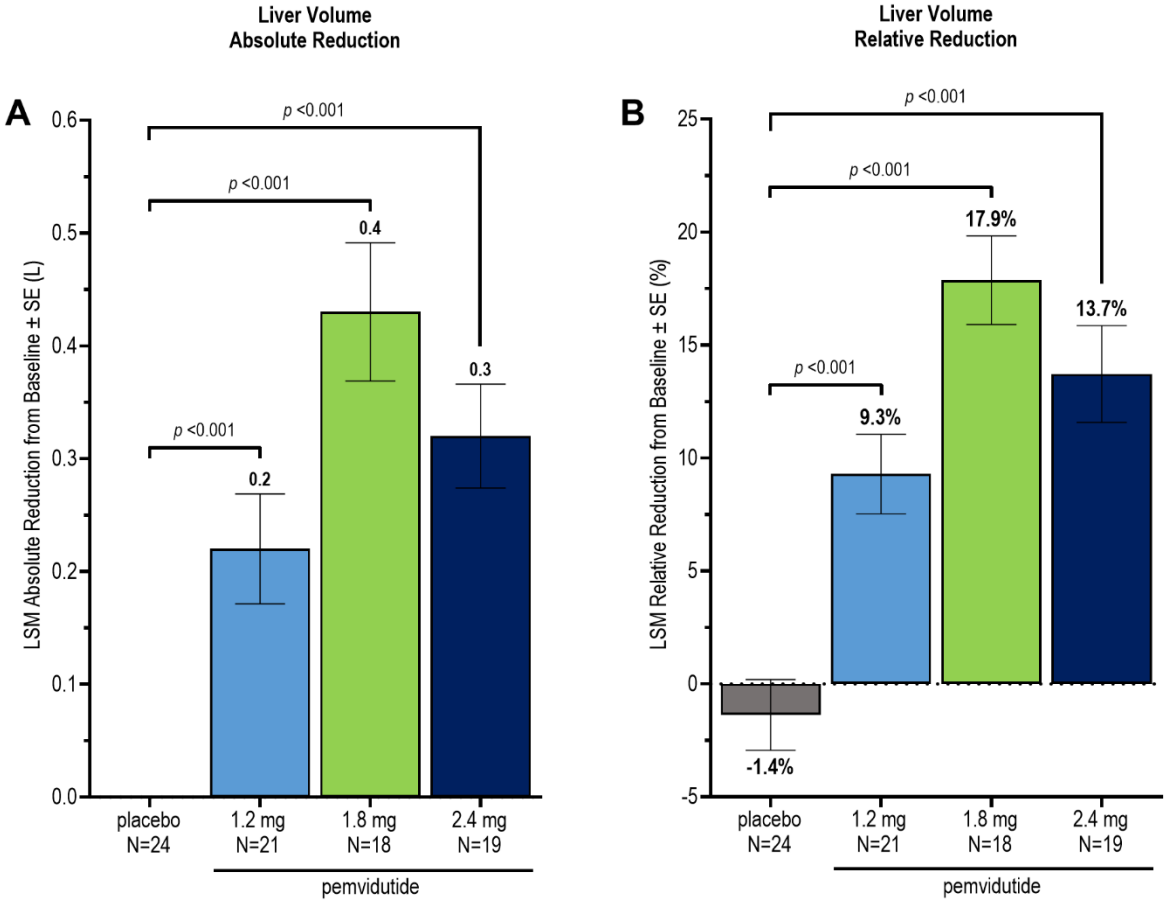
Table of Content



Supplementary Fig. 1. Changes in liver volume at Week 12. (A) LSM (SE) absolute reduction from baseline in liver volume; (B) LSM (SE) relative reduction from baseline in liver volume. Statistical significance was assessed by ANCOVA. All p-values displayed are nominal.