Safety and efficacy of weekly pemvidutide versus placebo for metabolic dysfunction-associated steatohepatitis (IMPACT): 24-week results from a multicentre, randomised, double-blind, phase 2b study

Mazen Noureddin, Stephen A Harrison, Rohit Loomba, Naim Alkhouri, Naga Chalasani, Muhammad Y Sheikh, Shaheen Tomah, Julio A Gutierrez, Silvia Urbina, John J Suschak, Randy Brown, Ozioma Odili, Jay Yang, Stephine Keeton, Guy Neff, Edward Mena, M Scot Roberts, Sarah K Browne, M Scott Harris

Summary

Background GLP-1–glucagon dual receptor agonists such as pemvidutide have shown promise in treating metabolic dysfunction-associated steatohepatitis (MASH). The aim of this trial was to assess the effects of pemvidutide on MASH resolution and fibrosis improvement in patients with liver fibrosis stage F2 or F3 MASH at 24 weeks of treatment.

Methods IMPACT is an ongoing 48-week international, randomised, double-blind, placebo-controlled, phase 2b trial in patients with biopsy-confirmed MASH and fibrosis stage F2 or F3. Patients from 83 sites in the USA and Australia were randomly assigned 1:2:2 to receive once-weekly subcutaneous pemvidutide (1·2 mg or 1·8 mg), administered without dose titration, or placebo. The dual primary endpoints were MASH resolution without worsening of fibrosis or at least one stage liver fibrosis improvement without worsening of MASH at 24 weeks in the intention-to-treat population. This trial was registered with ClinicalTrials.gov, NCT05989711.

Findings From July 27, 2023, to April 29, 2025, 1557 patients were screened and 212 patients were randomly assigned. MASH resolution without fibrosis worsening was observed in 18 (20%) of 86 patients in the placebo group, 24 (58%) of 41 patients in the 1·2 mg pemvidutide group (difference of 38% [95% CI 21–56]; p<0·0001), and 45 (52%) of 85 patients in the 1·8 mg pemvidutide group (difference of 32% [95% CI 19–46]; p<0·0001). Fibrosis improvement without worsening of MASH was observed in 24 (28%) of 86 patients in the placebo group, 13 (33%) of 41 patients in the 1·2 mg pemvidutide group (difference of 5% [95% CI –13 to 22]; p=0·59), and 30 (36%) of 85 patients in the 1·8 mg pemvidutide group (difference of 8% [95% CI –6 to 22]; p=0·27). Adverse events were reported in 32 (78%) of 41 patients receiving 1·2 mg pemvidutide, 69 (81%) of 85 patients receiving 1·8 mg pemvidutide, and 58 (67%) of 86 patients receiving placebo, the majority of which were mild or moderate in severity. Pemvidutide was well tolerated, with discontinuations due to adverse events in none of 41 patients in the 1·2 mg pemvidutide group, one (1%) of 85 patients in the 1·8 mg pemvidutide group, and two (2%) of 86 patients in the placebo group.

Interpretation Pemvidutide treatment met the primary endpoint of MASH resolution without worsening of fibrosis at 24 weeks but did not meet the other primary endpoint of fibrosis improvement without worsening of MASH at this timepoint. Additional trials of longer duration are planned.

Funding Altimmune.

Published Online November 11, 2025 https://doi.org/10.1016/S0140-6736(25)02114-2

Houston Methodist Hospital, Houston, TX, USA (Prof M Noureddin MD); **Houston Research Institute, Houston, TX, USA** (Prof M Noureddin); **Pinnacle Clinical Research, San Antonio, TX, USA** (S A Harrison* MD); **MASLD Research Center, Division of Gastroenterology and Hepatology, University of California at San Diego, La Jolla, California, USA** (Prof R Loomba MD); **Summit Clinical Research, San Antonio, TX, USA** (N Alkhouri MD); **Clinical Research Institute of Ohio, Westlake, OH, USA** (N Alkhouri); **Indiana University School of Medicine, Indianapolis, IN, USA** (Prof N Chalasani MD); **Fresno Clinical Research Center, Fresno, CA, USA** (M Y Sheikh MD); **Altimmune, Gaithersburg, MD, USA** (S Tomah MD, J A Gutierrez MD, S Urbina MD, J J Suschak PhD, R Brown MSc, O Odili PharmD, J Yang PhD, S Keeton PhD, M S Roberts PhD, S K Browne MD, M S Harris MD MS); **Scripps Clinic, La Jolla, CA, USA** (J A Gutierrez); **Covenant Metabolic Specialists, Fort Myers, FL, USA** (G Neff MD); **California Liver Research Institute, Pasadena, CA, USA** (E Mena MD)

*Deceased

Correspondence to: Prof Mazen Noureddin, Houston Methodist Hospital, Houston, TX 77030, USA **mnoureddin@houstonmethodist.org**

Introduction

Metabolic dysfunction-associated steatotic liver disease (MASLD) is a growing public health threat, affecting up to 38% of the population globally.[1,2] In the liver, metabolic syndrome can lead to MASLD in up to 80% of patients with obesity.[3] Steatosis can lead to inflammation (steatohepatitis) and hepatocyte ballooning with or without fibrosis, with up to 20–30% of patients with MASLD progressing to metabolic dysfunction-associated steatohepatitis (MASH).[4,5] MASH is associated with high morbidity, including a higher prevalence of poor cardiovascular, oncological, and hepatic outcomes and associated mortality.[6] Notably, many of the primary drivers of mortality in non-cirrhotic MASH patients are obesity-related.[2]

Resmetirom, the first US Food and Drug Administration-approved therapy for MASH, was approved in 2024 based on improvements in MASH resolution without worsening of fibrosis, and fibrosis improvement without worsening of MASH, but treatment was not associated with weight loss greater than that achieved with lifestyle counselling on nutrition

Research in context

Evidence before this study

Pemvidutide is a dual GLP-1 and glucagon receptor agonist being evaluated for the treatment of metabolic dysfunction-associated steatohepatitis (MASH). A PubMed search of results from clinical trials published before Sept 24, 2025 with the search terms ("GLP-1" OR "glucagon-like peptide") AND ("glucagon") AND ("MASH" OR "NASH") AND ("phase 2" OR "phase 3") identified five randomised clinical trials evaluating an incretin-based agent in patients with biopsy-confirmed MASH, including one phase 3 trial. Each of these studies evaluated treatment regimens of 48 weeks or longer. The phase 2 trials included a 48-week trial of the GLP-1–glucagon dual receptor agonist survodutide. Each of the phase 2 studies showed MASH resolution or improvement without worsening of fibrosis, although none of these trials showed significant fibrosis improvement without worsening of MASH by use of statistical standards by which patients with missing data due to missing biopsies or treatment discontinuations were treated as non-responders.

Added value of this study

Treatment with pemvidutide for 24 weeks led to a significant proportion of patients achieving MASH resolution without worsening of fibrosis at a shorter time interval than previous phase 2 studies of incretin therapies. Further, this study is, we believe, the first incretin-based study in MASH to show significant clinical activity and good tolerability in the absence of dose titration.

Implications of all the available evidence

The body of evidence highlights the utility of dual GLP-1–glucagon receptor agonists for the treatment of MASH. The efficacy and safety of pemvidutide in larger cohorts and over longer time periods is yet to be established. The findings here, and in other studies, support the continued investigation of pemvidutide in patients with MASH.

and exercise.[7] Semaglutide, a GLP-1 receptor agonist, was approved for the treatment of MASH on the basis of positive results on MASH resolution and fibrosis improvement, and although patients had significant weight loss, 72 weeks of treatment was required.[8] Although both approved monotherapies were found effective in the treatment of MASH, it is possible that a combined therapeutic approach could provide both rapid effects on MASH and reductions in bodyweight.

Dual GLP-1–glucagon receptor agonists are unimolecular peptide molecules that combine activity on both the GLP-1 and glucagon receptors, addressing the pathophysiology of MASH directly via glucagon effects in the liver and through reductions in bodyweight and anti-inflammatory effects mediated by GLP-1.[9] A phase 2 trial of the GLP-1–glucagon dual agonist survodutide has shown promising effects in improving liver histology in MASH patients at 48 weeks of treatment. However, patient discontinuations due to drug-related adverse events were observed despite the inclusion of a lengthy dose titration scheme.[10]

See Online for appendix

Pemvidutide is a 29-amino acid GLP-1–glucagon dual receptor agonist peptide developed for the treatment of MASH. In contrast to the GLP-1-biased activity of survodutide and other GLP-1–glucagon dual agonists, pemvidutide has 1:1 agonist potency at both receptors.[11] Further, on an equimolar basis, pemvidutide displays slower kinetics of entry into the bloodstream and reduced peak plasma concentrations while maintaining overall exposure that is similar to most GLP-1 based agents, possibly due to the EuPort glycolipid surfactant conjugation used to increase the plasma half-life of the peptide.[11] These pharmacokinetic properties might eliminate the need for dose titration, since gastrointestinal side-effects with GLP-1-based agents are related to peak concentration.[12] A previous phase 1 study showed promising effects on liver fat and bodyweight in MASLD after up to 24 weeks of use.[13]

Here, we report the primary efficacy outcomes after 24 weeks of treatment in the IMPACT phase 2b study of pemvidutide in patients with biopsy-proven MASH (NCT05989711).

Methods

Study design

The IMPACT trial is a randomised, double-blind, placebo-controlled, dose-finding, phase 2b trial done at 83 sites in the USA and Australia. A prespecified analysis of the primary histological endpoints was done when all patients reached week 24, with on-treatment follow-up to 48 weeks for assessment of safety and non-invasive biomarker response. The protocol (appendix p 20) was conducted in accordance with Declaration of Helsinki, International Council for Harmonisation guidelines and Good Clinical Practice principles, and applicable regulations. All enrolled patients provided written informed consent. The sponsor (Altimmune) designed the trial, without patient or public involvement, and was responsible for data collection and analysis. Institutional review board approval was provided by WCG IRB (approval number 20231239) in the USA and St Vincent's Hospital Melbourne HREC (approval number 287/23) in Australia.

Participants

Eligible patients were aged 18–75 years with biopsy-confirmed MASH with a non-alcoholic fatty liver disease activity score (NAS)[14] of at least 4 (scale of 0–8, with higher scores reflecting more severe disease) with at least 1 point in each subcomponent. The subcomponents are steatosis (0–3 points), inflammation (0–3 points), and

hepatocyte ballooning (0–2 points). In addition, patients were required to have confirmed F2 or F3 fibrosis following non-alcoholic steatohepatitis (NASH) Clinical Research Network (CRN) conventions.[14] Biopsies, taken at the time of screening or within 6 months before screening, if historical, served as the baseline for histological measures. Notable other inclusion criteria included BMI at least 27·0 kg/m^2, magnetic resonance imaging proton density fat fraction (MRI-PDFF) at least 8%, and liver stiffness measurement (LSM) at least 8·5 kPa. Key exclusion criteria included non-MASH chronic liver disease, consuming more than 14 (females) or more than 21 (males) alcohol units per week, and medications that might induce steatosis or steatohepatitis. A complete list of inclusion and exclusion criteria is located in the appendix (pp 2–7).

Randomisation and masking

Patients were randomly assigned in a 1:2:2 ratio to receive 1·2 mg or 1·8 mg pemvidutide or placebo via once-weekly subcutaneous injection for 48 weeks. Dose titration was not used at either pemvidutide dose. Patients, investigators, central reviewers, and other study personnel were unaware of study group assignments. Randomisation was done via an interactive web response system following a list drawn up by an independent statistician. Randomisation was stratified by fibrosis stage at baseline (F2 or F3) and the presence or absence of type 2 diabetes.

Procedures

A post-treatment liver biopsy was planned at week 24 to measure primary efficacy (appendix p 10), with follow-up for safety, weight loss, and non-invasive tests at 48 weeks. Biopsies were scored independently by three pathologists masked to patient, treatment, and sampling sequence (appendix p 10).

Outcomes

The study had two dual primary endpoints established by histological assessment of liver biopsy samples, both measured at 24 weeks. The first dual endpoint was the proportion of patients achieving MASH resolution, defined as at least a 2-point reduction in NAS with no hepatocyte ballooning and a score of 0 or 1 in the lobular inflammation component of NAS, without worsening of fibrosis stage. The second dual primary endpoint was fibrosis improvement, defined as the proportion of patients achieving at least a one-stage improvement in liver fibrosis (per NASH CRN criteria) without worsening of NAS score at 24 weeks.

Secondary endpoints at 24 weeks included the proportion of patients achieving both MASH resolution and at least a one-stage improvement in liver fibrosis, relative change from baseline in liver fat content established by MRI-PDFF, the proportion of patients achieving 30%, 40%, or 50% reduction in liver fat content from baseline per MRI-PDFF, and normalisation of liver fat content (≤5%) per MRI-PDFF. Other secondary endpoints included the absolute change from baseline in corrected T1 (cT1) relaxation time, the proportion of patients with an 80 ms decrease in cT1 relaxation time, the absolute change from baseline in alanine aminotransferase (ALT), the proportion of patients with a 17 international units (IU)/L decrease in ALT relative to baseline, the absolute changes from baseline in the Enhanced Liver Fibrosis (ELF) score, FibroScan-aspartate aminotransferase (FAST) score, N-terminal type III collagen propeptide (Pro-C3), fibrosis (FIB)-4 index, and the proportion of patients with a 0·5 decrease in ELF score.

In a post-hoc analysis, liver biopsies were also read for the proportionate area of fibrosis by the Liver Explore (PathAI, Boston, MA, USA) artificial intelligence (AI)-based algorithm to quantify the magnitude of fibrosis in each biopsy specimen.[15]

A full list of endpoints is provided in the appendix (p 8).

Statistical analysis

Based on previous trials of pemvidutide in patients with MASLD,[13] a sample size of 190 patients was estimated to provide 90% power to show a significant difference in MASH resolution at 24 weeks between the 1·8 mg pemvidutide and placebo groups, and 80% power to show a significant difference in fibrosis improvement between the 1·8 mg pemvidutide and placebo groups at 24 weeks with a two-sided significance of 0·05. For the

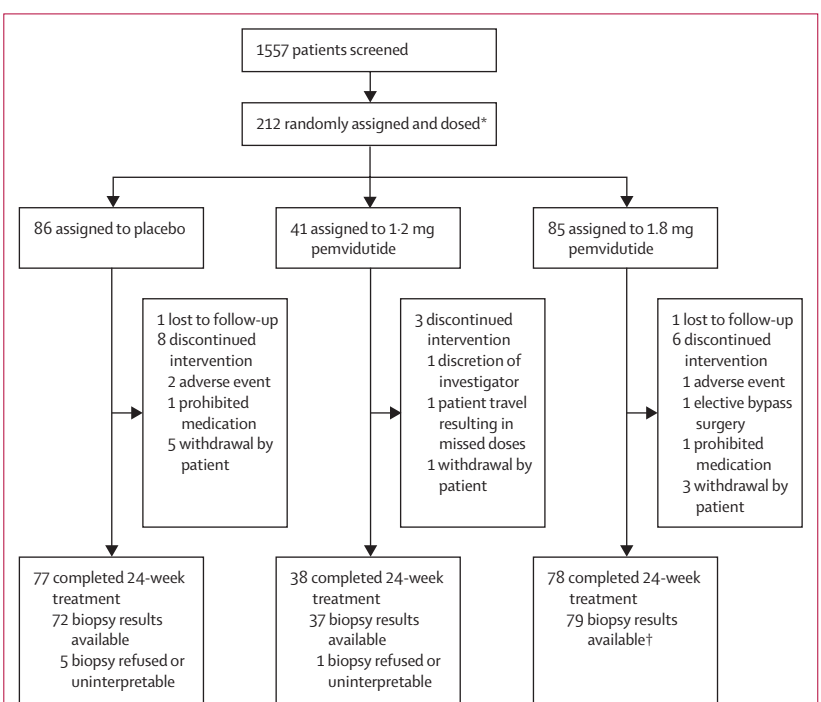

Figure 1: **Trial profile**
*One patient randomly assigned to receive placebo received 1·2 mg pemvidutide. †One patient did not complete 24 weeks of treatment but underwent biopsy.

endpoint of MASH resolution, the power calculation assumed a response rate of 45% in the 1·8 mg group and 20% in the placebo group. The fibrosis improvement endpoint assumed 42% response in the 1·8 mg group and 20% response in the placebo group.

Primary and secondary endpoints were analysed in the intention-to-treat population comprised of all randomly assigned patients, all of whom also received at least one dose of pemvidutide or placebo. Statistical analysis of the primary endpoints involved dual binary outcomes indicating successful response to treatment (MASH resolution or fibrosis improvement) employing a sequential hierarchal testing procedure, with MASH resolution preceding fibrosis improvement. The

	Placebo (n=86)	Pemvidutide 1·2 mg (n=41)	Pemvidutide 1·8 mg (n=85)	Total (n=212)
Age, years	52·5 (12·2)	55·2 (13·0)	53·4 (12·4)	53·4 (12·4)
Self-reported sex				
Female	48 (56%)	25 (61%)	50 (59%)	123 (58%)
Male	38 (44%)	16 (39%)	35 (41%)	89 (42%)
Race*				
American Indian or Alaska Native	0	0	2 (2%)	2 (1%)
Asian	1 (1%)	1 (2%)	3 (4%)	5 (2%)
Black	3 (3%)	0	0	3 (1%)
Native Hawaiian or Pacific Islander	1 (1%)	0	1 (1%)	2 (1%)
White	78 (91%)	37 (90%)	76 (89%)	191 (90%)
Unknown	0	1 (2%)	1 (1%)	2 (1%)
Other	3 (3%)	2 (5%)	2 (2%)	7 (3%)
Ethnicity*				
Hispanic or Latinx	38 (44%)	18 (44%)	43 (51%)	99 (47%)
Not Hispanic or Latinx	48 (56%)	23 (56%)	41 (48%)	112 (53%)
Not reported	0	0	1 (1%)	1 (<1%)
Bodyweight, kg	109·7 (28·0)	110·7 (26·3)	107·7 (21·3)	109·1 (25·1)
Waist circumference, cm	118·8 (18·8)	123·5 (16·9)	119·1 (14·3)	119·8 (16·8)
BMI, kg/m^2	38·3 (8·4)	39·2 (8·4)	38·7 (6·9)	38·7 (7·8)
Liver fat content, %	19·6% (6·4)	20·0% (7·1)	19·0% (6·8)	19·4% (6·7)
Alanine aminotransferase, IU/L	56·6 (32·7)	67·6 (54·6)	67·6 (43·0)	63·2 (42·0)
Aspartate aminotransferase, IU/L	44·9 (20·8)	50·8 (26·8)	51·0 (29·4)	48·5 (25·8)
Type 2 diabetes	37 (43%)	19 (46%)	36 (42%)	92 (43%)
Fasting glucose, mg/dL	123·4 (38·5)	121·6 (42·2)	126·7 (44·9)	124·4 (41·7)
Glycated haemoglobin, %	6·4% (1·0)	6·3% (1·1)	6·5% (1·2)	6·4% (1·1)
Total cholesterol, mmol/L	4·7 (1·2)	5·0 (1·1)	4·7 (1·1)	4·7 (1·1)
High-density lipoprotein, mmol/L	1·2 (0·4)	1·1 (0·3)	1·2 (0·3)	1·2 (0·4)
Low-density lipoprotein, mmol/L	2·6 (1·0)	3·0 (1·1)	2·6 (1·0)	2·7 (1·0)
Triglycerides, mmol/L	1·9 (1·0)	1·9 (0·7)	1·9 (1·0)	1·9 (1·0)
Blood pressure, mm Hg				
Systolic	125·7 (13·0)	125·3 (13·7)	124·2 (13·4)	125·0 (13·3)
Diastolic	79·4 (7·3)	76·1 (8·4)	78·9 (7·8)	78·5 (7·8)
Non-alcoholic fatty liver disease activity score†	5·2 (0·9)	5·1 (1·0)	5·2 (1·0)	5·2 (1·0)
Controlled attenuation parameter, dB/m	342·5 (33·2)	336·5 (35·1)	342·9 (33·0)	341·6 (33·3)
Enhanced Liver Fibrosis score	9·7 (0·8)	10·0 (0·8)	9·9 (1·0)	9·9 (0·9)
Liver stiffness, kPa	12·5 (4·4)	12·3 (3·6)	12·8 (4·4)	12·6 (4·2)
Corrected T1 relaxation time, ms	984·7 (132·7)	976·1 (159·3)	969·4 (123·5)	977·0 (133·6)
Liver fibrosis stage				
F2	46 (53%)	24 (59%)	46 (54%)	116 (55%)
F3	40 (47%)	17 (41%)	39 (46%)	96 (45%)

Data are presented as n (%) or mean (SD). Percentages might not total 100 owing to rounding. *Self-reported by patients. †The non-alcoholic fatty liver disease activity score (scale of 0 to 8; high scores indicate more severe disease) characterised by the NASH Clinical Research Network incorporates scores for steatosis (0–3 points), lobular inflammation (0–3 points), and hepatocellular ballooning. NASH=non-alcoholic steatohepatitis.

Table 1: **Baseline characteristics**

specified order of statistical testing was MASH resolution at 1·8 mg, fibrosis improvement at 1·8 mg, MASH resolution at 1·2 mg, and fibrosis improvement at 1·2 mg. An intention-to-treat treatment policy estimand was applied, as described in the statistical analysis plan, with missing outcomes due either to missing biopsies or treatment discontinuations treated as non-responders (composite estimand). Logistic regression analyses were used to calculate the difference in proportions, with corresponding 95% CIs between the pemvidutide groups and placebo. For the primary efficacy analyses, p values were obtained by use of the χ^2-test at a two-sided significance level of 0·05. Secondary endpoint analyses of continuous variables limited to one or two pretreatment and post-treatment measurements, including changes from baseline in liver fat content, cT1 relaxation time, and fibrosis markers were compared between pemvidutide and placebo by use of statistical tests based on ANCOVA. Continuous measures with multiple measurements, such as weekly changes in bodyweight, waist circumference, serum ALT, blood pressure, and heart rate, were analysed by use of a mixed model for repeated measures. Point estimates were presented as least-squares means. The Cochran–Mantel–Haenszel test was applied to secondary endpoints that were categorical in nature. Adverse events were analysed in the safety population, comprised of patients receiving at least one dose of pemvidutide or placebo and reported with descriptive statistics. Patients were analysed by the treatment to which they were randomly assigned. Statistical analyses were done with SAS version 9.4. The full statistical analysis plan is presented in the appendix (p 118). The safety of patients was monitored by an independent Data Monitoring Committee.

Role of the funding source

The funder had a role in the study design, data collection, data analysis, data interpretation, and writing of the report.

Results

Between July 27, 2023, the date at which the first patient was screened, and April 29, 2025, the date at which the last patient completed 24 weeks of treatment, 1557 potential patients were screened for eligibility, of which 212 patients were randomly assigned to 1·2 mg pemvidutide (41 patients), 1·8 mg pemvidutide (85 patients), or placebo (86 patients; figure 1). Of those patients, 193 (91%) completed week 24 of the trial and 188 (89%) had interpretable 24-week biopsy results. The reasons for ineligibility on screening are presented in the appendix (p 12). One patient randomly assigned to the placebo group received 1·2 mg pemvidutide but was included in the placebo group for the intention-to-treat analysis.

Demographic and clinical characteristics, which were similar across groups, are presented in table 1 and the appendix (p 13). 123 (58%) patients were female. The NAS at baseline was 4 (31%) in 66 patients, 5 (33%) in 71 patients, 6 (25%) in 53 patients, and 7 (10%) in 22 patients. Baseline biopsies revealed F2 fibrosis in 116 (55%) of 212 patients and F3 fibrosis in 96 (45%) patients.

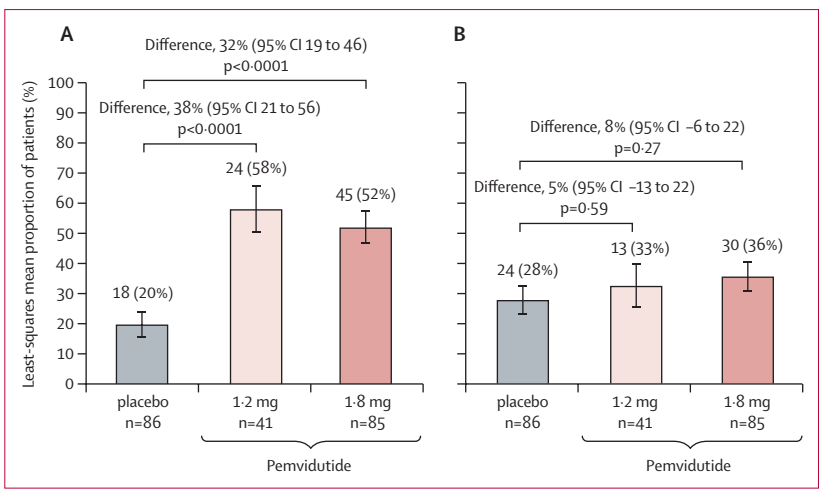

Figure 2: **Primary endpoints**
(A) The least-squares mean proportion of patients with resolution of MASH without worsening of fibrosis after 24 weeks of treatment; error bars represent SE; MASH resolution was defined as at least a 2-point reduction in NAS (scale of 0 to 8, with higher scores indicating more severe disease), no hepatocyte ballooning, and a score of 0 or 1 in the lobular inflammation component of the score, without worsening fibrosis. (B) The least-squares mean proportion of patients with liver fibrosis improvement without worsening of MASH after 24 weeks of treatment, defined as the proportion of patients achieving at least a one-stage improvement in liver fibrosis without worsening of NAS; error bars represent SE. A composite strategy was employed that considered patients with missing outcomes due either to missing biopsies or treatment discontinuations as non-responders. Data were analysed with the use of the chi-square test. MASH=metabolic dysfunction-associated steatohepatitis. NAS=non-alcoholic fatty liver disease activity score.

In the intention-to-treat analysis employing the composite estimand strategy, with missing outcomes owing either to missing biopsies or treatment discontinuations treated as non-responders, the primary endpoint of MASH resolution without worsening of fibrosis at week 24 was statistically higher with 1·2 mg pemvidutide compared with placebo (24 [58%] of 41 *vs* 18 [20%] of 86; difference of 38% [95% CI 21 to 56]; p<0·0001) and with 1·8 mg pemvidutide versus placebo (45 [52%] of 85 *vs* 18 [20%] of 86; difference of 32% [95% CI 19 to 46]; p<0·0001; figure 2A). There was no statistical difference in the proportion of patients who had fibrosis improvement without worsening of MASH at week 24 between the 1·2 mg pemvidutide group and placebo (13 [33%] of 41 *vs* 24 [28%] of 86; difference of 5% [95% CI −13 to 22]; p=0·59) nor the 1·8 mg pemvidutide group and placebo (30 [36%] of 85 *vs* 24 [28%] of 86; difference of 8% [95% CI −6 to 22]; p=0·27; figure 2B). The secondary endpoint of the proportion of patients with combined MASH resolution and ≥1 stage fibrosis improvement was seen in ten (24%) of 41 patients in the 1·2 mg pemvidutide group, 21 (24%) of 85 patients in the 1·8 mg group, and 13 (14%) of 86 patients in the placebo group (appendix p 15). A

	Placebo (n=86)	Pemvidutide 1·2 mg (n=41)	Pemvidutide 1·8 mg (n=85)
Non-alcoholic fatty liver disease activity score			
Absolute change from baseline	−1·3 (0·1)	−2·9 (0·2)	−2·6 (0·1)
Least-squares mean difference from placebo (95% CI)	..	−1·6 (−2·1 to −1·1)	−1·4 (−1·8 to −1·0)
p value	..	<0·001	<0·001
Liver fat reduction			
Relative change			
Value	−11·4 (3·0)	−52·0 (4·2)	−57·7 (3·0)
Least-squares mean difference from placebo (95% CI)	..	−40·6 (−50·9 to −30·4)	−46·3 (−54·6 to −38·0)
p value	..	<0·001	<0·001
Decrease of ≥30%, percentage of patients	15/76 (20%)	32/39 (82%)	66/79 (84%)
p value	..	<0·0001	<0·0001
Decrease of ≥40%, percentage of patients	12/76 (16%)	29/39 (74%)	63/79 (80%)
p value	..	<0·0001	<0·0001
Decrease of ≥50%, percentage of patients	8/76 (11%)	24/39 (62%)	57/79 (72%)
p value	..	<0·0001	<0·0001
Liver fat content normalisation, percentage of patients	3/76 (4%)	12/39 (31%)	35/79 (44%)
p value	..	<0·0001	<0·0001
Corrected T1 relaxation time, ms			
Absolute change	−14·7 (11·9)	−124·6 (16·1)	−134·7 (11·9)
Least-squares mean difference from placebo (95% CI)	..	−109·9 (−142·0 to −77·8)	−120·0 (−144·4 to −95·6)
p value	..	<0·001	<0·001
Decrease of 80 ms from baseline, percentage of patients	18/64 (28%)	21/27 (78%)	49/66 (74%)
p value	..	<0·0001	<0·0001
Alanine aminotransferase, IU/L			
Absolute change	−10·3 (2·4)	−34·6 (3·3)	−34·4 (2·3)
Least-squares mean difference from placebo (95% CI)	..	−24·3 (−32·3 to −16·3)	−24·1 (−30·6 to −17·6)
p value	..	<0·001	<0·001
Decrease of ≥17 IU/L, percentage of patients	17/74 (23%)	22/39 (56%)	52/78 (67%)
p value	..	0·0003	<0·0001
Aspartate aminotransferase, IU/L			
Absolute change	−6·9 (1·8)	−23·7 (2·5)	−25·0 (1·8)
Least-squares mean difference from placebo (95% CI)	..	−16·8 (−22·9 to −10·7)	−18·0 (−23·1 to −13·0)
p value	..	<0·001	<0·001
Enhanced Liver Fibrosis score			
Absolute change	0·03 (0·1)	−0·6 (0·1)	−0·5 (0·1)
Least-squares mean difference from placebo (95% CI)	..	−0·6 (−0·8 to −0·4)	−0·5 (−0·7 to −0·3)
p value	..	<0·001	<0·001
Decrease of ≥0·5 points, percentage of patients	14/74 (19%)	18/39 (46%)	39/76 (51%)
p value	..	0·0021	<0·0001
FibroScan-aspartate aminotransferase score			
Absolute change	−0·08 (0·02)	−0·38 (0·04)	−0·36 (0·02)
Least-squares mean difference from placebo (95% CI)	..	−0·30 (−0·38 to −0·21)	−0·27 (−0·34 to −0·21)
p value	..	<0·001	<0·001
Bodyweight, kg			
Percentage change	−0·5% (0·3)	−4·8% (0·5)	−5·8% (0·3)
Least-squares mean difference from placebo (95% CI)	..	−4·3 (−5·4 to −3·2)	−5·2 (−6·1 to −4·3)
p value	..	<0·001	<0·001
Waist circumference, cm			
Percentage change	0·9% (1·1)	−3·2% (1·5)	−3·5% (1·1)
Least-squares mean difference from placebo (95% CI)	..	−4·1 (−7·7 to −0·4)	−4·4 (−7·3 to −1·4)
p value	..	0·029	0·003

(Table 2 continues on next page)

	Placebo (n=86)	Pemvidutide 1·2 mg (n=41)	Pemvidutide 1·8 mg (n=85)
(Continued from previous page)			
Glycated haemoglobin, %			
Absolute change	0·03% (0·1)	−0·14% (0·1)	0·03% (0·1)
Least-squares mean difference from placebo (95% CI)	..	−0·17 (−0·4 to 0·1)	0·0 (−0·2 to 0·2)
p value	..	0·17	0·97
Liver stiffness measurement, kPa			
Absolute change	−0·7 (0·5)	−3·7 (0·7)	−2·2 (0·5)
Least-squares mean difference from placebo (95% CI)	..	−3·0 (−4·6 to −1·4)	−1·5 (−2·8 to −0·3)
p value	..	<0·001	0·02
Decrease of ≥25%, percentage of patients	16/76 (21%)	26/37 (70%)	33/78 (42%)
p value	..	<0·0001	0·0049
<10 kPa at week 24, percentage of patients	18/51 (35%)	19/25 (76%)	24/56 (43%)
p value	..	0·001	0·31
N-terminal type III collagen propeptide, µg/L			
Absolute change	−2·4 (1·6)	−15·3 (2·2)	−14·7 (1·5)
Least-squares mean difference from placebo (95% CI)	..	−12·9 (−18·2 to −7·7)	−12·3 (−16·7 to −8·0)
p value	..	<0·001	<0·001
Fibrosis-4 (FIB-4) score			
Absolute change	−0·06 (0·05)	−0·34 (0·06)	−0·31 (0·04)
Least-squares mean difference from placebo (95% CI)	..	−0·28 (−0·43 to −0·13)	−0·25 (−0·37 to −0·13)
p value	..	<0·001	<0·001
Enhanced Liver Fibrosis score and liver stiffness measurement			
0·5 reduction in Enhanced Liver Fibrosis score + 25% reduction in liver stiffness measurement, percentage of patients	5/70 (7%)	16/37 (43%)	17/73 (23%)
p value	..	<0·0001	0·008
Total cholesterol, mmol/L			
Percentage change	−2·0% (1·8)	−8·0% (2·5)	−6·4% (1·8)
Least-squares mean difference from placebo (95% CI)	..	−6·0 (−12·1 to 0·1)	−4·4 (−9·3 to 0·6)
p value	..	0·055	0·08
High-density lipoprotein, mmol/L			
Percentage change	2·5% (1·7)	−2·4% (2·4)	1·0% (1·7)
Least-squares mean difference from placebo (95% CI)	..	−4·9 (−10·7 to 0·8)	−1·5 (−6·2 to 3·1)
p value	..	0·093	0·52
Low-density lipoprotein, mmol/L			
Percentage change	−2·2% (3·3)	−7·0% (4·7)	−3·6% (3·4)
Least-squares mean difference from placebo (95% CI)	..	−4·8 (−16·2 to 6·6)	−1·4 (−10·7 to 7·8)
p value	..	0·41	0·76
Triglycerides, mmol/L			
Percentage change	−0·7% (3·3)	−10·8% (4·6)	−12·9% (3·3)
Least-squares mean difference from placebo (95% CI)	..	−10·0 (−21·2 to 1·1)	−12·2 (−21·3 to −3·2)
p value	..	0·076	0·009
Blood pressure, mm Hg			
Systolic Absolute change	0·6 (1·2)	−4·8 (1·7)	−4·2 (1·2)
Least-squares mean difference from placebo (95% CI)	..	−5·3 (−9·4 to −1·3)	−4·8 (−8·0 to −1·5)
p value	..	0·01	0·005
Diastolic Absolute change	0·1 (0·7)	−1·1 (1·1)	−1·6 (0·7)
Least-squares mean difference from placebo (95% CI)	..	−1·2 (−3·7 to −1·3)	−1·7 (−3·8 to 0·3)
p value	..	0·35	0·10

(Table 2 continues on next page)

	Placebo (n=86)	Pemvidutide 1·2 mg (n=41)	Pemvidutide 1·8 mg (n=85)
(Continued from previous page)			
Heart rate, beats per min			
Absolute change	0·4 (0·9)	−0·8 (1·3)	1·0 (0·9)
Least-squares mean difference from placebo (95% CI)	..	−1·2 (−4·3 to 1·9)	0·6 (−1·9 to 3·0)
p value	..	0·44	0·65

Data are presented as mean (SE) unless indicated otherwise. Comparisons versus placebo were made using mixed models for repeated measures for endpoints measured at multiple timepoints and analysis of covariance for endpoints measured at baseline and week 24. The Cochran–Mantel–Haenszel test was applied to endpoints that were categorical in nature. p values are nominal and calculated without adjustment for multiplicity.

Table 2: **Change from baseline to week 24 in secondary efficacy endpoints**

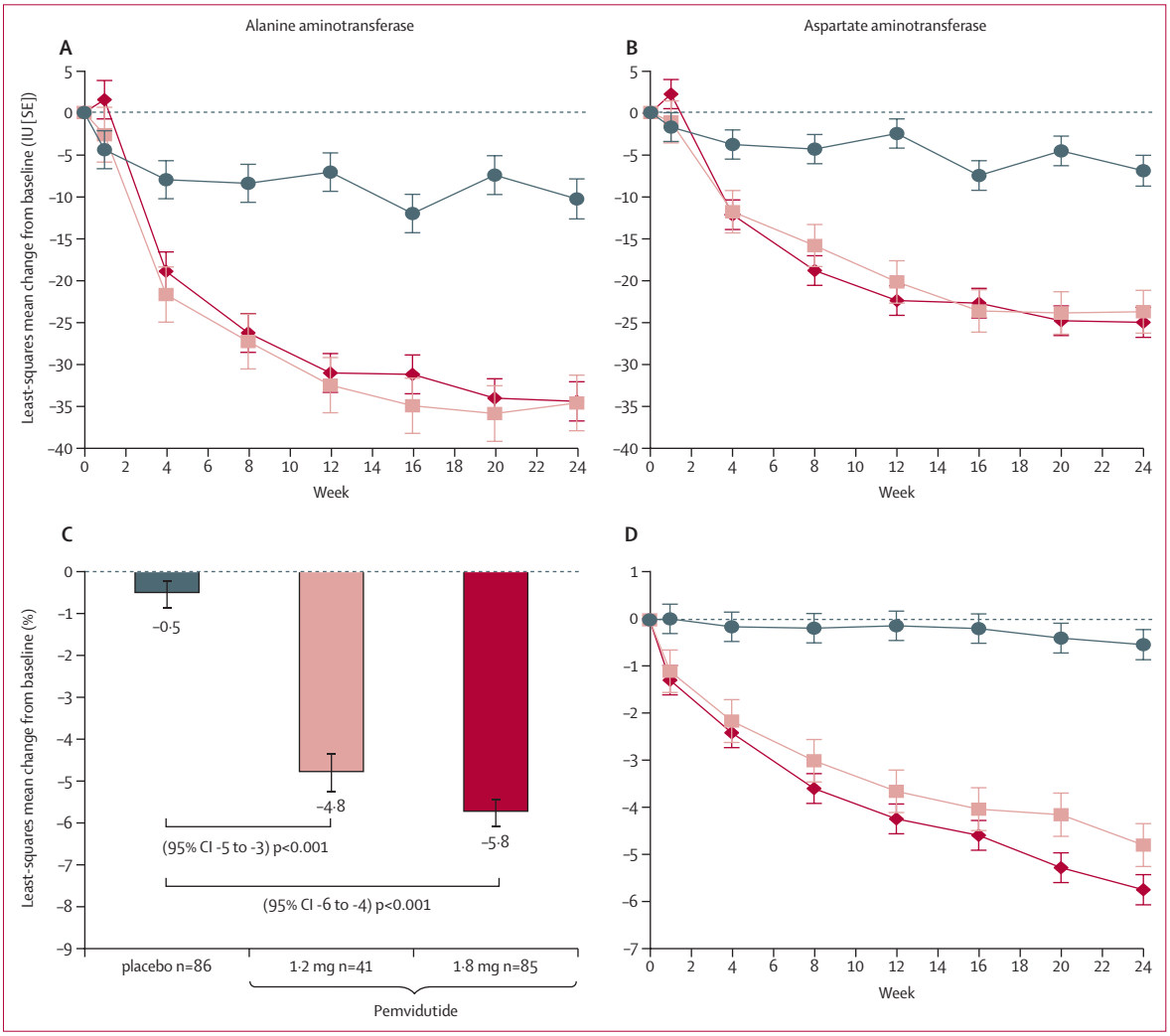

Figure 3: **Secondary endpoints**

(A) Absolute changes in alanine aminotransferase over the course of the trial. (B) Absolute changes in aspartate aminotransferase over the course of the trial. (C) The relative change in weight from baseline at 24 weeks. (D) Relative changes in weight from baseline over the course of the trial. Change is shown as least-squares mean change from baseline; error bars represent SE. Data were analysed with the use of the mixed model for repeated measures. p values are nominal and calculated without adjustment for multiplicity.

post-hoc AI-based pathology assessment of biopsy slides identified consistent and substantial decreases in the proportionate area of pathological fibrosis with pemvidutide treatment, including a reduction of at least 50% in up to 30 (35% of 85) of the 1·8 mg group (appendix p 16).

When considering liver fat content by volume as established by MRI-PDFF, the 1·2 mg pemvidutide group had a 52% relative reduction and the 1·8 mg pemvidutide group had a 58% relative reduction in liver fat from baseline, compared with an 11% relative reduction in the placebo group (table 2). A relative decrease in liver fat content of at least 30% was seen in 32 (82%) of 39 patients in the 1·2 mg pemvidutide group, 66 (84%) of 79 patients in the 1·8 mg pemvidutide group, and 15 (20%) of 76 patients in the placebo group. Relative reductions in liver fat of at least 50% were seen in 24 (62%) patients in the 1·2 mg pemvidutide group, 57 (72%) patients in the 1·8 mg pemvidutide group, and eight (11%) patients in the placebo group. In the 1·2 mg pemvidutide group, 12 (31%) patients had normalisation of liver fat content to less than 5% at week 24, versus 35 (44%) in the 1·8 mg pemvidutide group, and three (4%) in the placebo group.

Mean absolute changes in cT1 relaxation time were –124·6 ms in the 1·2 mg pemvidutide group, –134·7 ms in the 1·8 mg group, and –14·7 ms in the placebo group (table 2). The number of patients achieving at least 80 ms decrease in cT1 from baseline at 24 weeks was 21 (78%) of 27 in the 1·2 mg pemvidutide group, 49 (74%) of 66 patients in the 1·8 mg group, and 18 (28%) of 64 patients in the placebo group.

The absolute changes in ALT at 24 weeks were –34·6 IU/L in the 1·2 mg and –34·4 IU/L in the 1·8 mg pemvidutide groups compared with –10·3 IU/L in the placebo group (table 2). The numbers of patients with at least 17 IU/L decrease in ALT were 22 (56%) of 39 patients in the 1·2 mg pemvidutide group, 52 (67%) of 78 patients in the 1·8 mg group, and 17 (23%) of 74 patients in the placebo group. At 24 weeks, the mean absolute changes in aspartate aminotransferase (AST) were –23·7 IU/L in the 1·2 mg group, –25·0 IU/L in the 1·8 mg group, and –6·9 IU/L in the placebo group (table 2). The time courses of these changes are shown in figure 3A and B.

Pemvidutide was associated with a –0·6 change in ELF score at 24 weeks in the 1·2 mg group and a –0·5 change in the 1·8 mg group, compared with a +0·03 change in the placebo group (table 2). In the 1·2 mg group, 18 (46%) of 39 patients had an ELF score decrease of at least 0·5 points, compared with 39 (51%) of 76 patients in the 1·8 mg group, and 14 (19%) of 74 patients in the placebo group. From baseline to 24 weeks, the mean decrease in FAST score was 0·38 in the 1·2 mg group, 0·36 in the 1·8 mg group, and 0·08 in the placebo group (table 2). The mean change in Pro-C3 was –15·3 µg/L in the 1·2 mg group, –14·7 µg/L in the 1·8 mg group, and –2·4 µg/L in the placebo group (table 2; appendix p 17). FIB-4 scores decreased from baseline to 24 weeks, with larger decreases in the pemvidutide groups than placebo (table 2; appendix p 18). The combination of a 0·5-point reduction in ELF and a 25% reduction in LSM occurred in 16 (43%) of 37 patients in the 1·2 mg pemvidutide group, 17 (23%) of 73 patients in the 1·8 mg group, and five (7%) of 70 patients in the placebo group (table 2).

	Placebo (n=86)	Pemvidutide 1·2 mg (n=41)	Pemvidutide 1·8 mg (n=85)
Any adverse event	58 (67%)	32 (78%)	69 (81%)
Adverse event considered by the investigator to be related to assigned treatment	21 (24%)	19 (46%)	50 (59%)
Any serious adverse event	3 (3%)	1 (2%)	3 (4%)
Serious adverse event considered by the investigator to be related to assigned treatment	0	0	0
Adverse event leading to the discontinuation of treatment	2 (2%)	0	1 (1%)
Adverse event from any system organ class			
Nausea	12 (14%)	9 (22%)	35 (41%)
Mild	8 (9%)	8 (20%)	28 (33%)
Moderate	4 (5%)	1 (2%)	7 (8%)
Diarrhoea	7 (8%)	4 (10%)	18 (21%)
Mild	7 (8%)	4 (10%)	14 (16%)
Moderate	0	0	4 (5%)
Constipation	8 (9%)	5 (12%)	11 (13%)
Mild	7 (8%)	5 (12%)	10 (12%)
Moderate	1 (1%)	0	1 (1%)
Hyperglycaemia adverse events	7 (8%)	2 (5%)	12 (14%)
Mild	6 (7%)	1 (2%)	6 (7%)
Moderate	1 (1%)	1 (2%)	6 (7%)
Urinary tract infection	2 (2%)	3 (7%)	14 (16%)
Mild	2 (2%)	1 (2%)	10 (12%)
Moderate	0	2 (5%)	4 (5%)
Headache	6 (7%)	3 (7%)	9 (11%)
Mild	5 (6%)	3 (7%)	7 (8%)
Moderate	1 (1%)	0	2 (2%)
Nasopharyngitis	2 (2%)	5 (12%)	3 (4%)
Mild	2 (2%)	4 (10%)	1 (1%)
Moderate	0	1 (2%)	2 (2%)

Data are n (%). Shown are adverse events with an incidence of at least 10% in any trial group, according to the preferred term in the Medical Dictionary for Regulatory Activities. No severe adverse events were reported for any adverse events listed.

Table 3: **Adverse events**

The relative change in bodyweight at 24 weeks was –4·8% in the 1·2 mg pemvidutide group, –5·8% in the 1·8 mg group, and –0·5% in the placebo group (table 2), with weight loss appearing to continue at the end of treatment (figure 3C, D). Waist circumference decreased by 3·2% in the 1·2 mg group, 3·5% in the 1·8 mg group and increased 0·9% in the placebo group (table 2).

Over 24 weeks, adverse events were reported in 32 (78%) of 41 patients receiving 1·2 mg pemvidutide, 69 (81%) of 85 patients receiving 1·8 mg pemvidutide, and 58 (67%) of 86 patients receiving placebo (table 3). Discontinuation from the trial due to adverse events occurred in one (1%) patient in the pemvidutide groups and two (2%) patients in the placebo group. Gastrointestinal disorders were the most common adverse events, with 98 (46%) of 212 reporting

gastrointestinal events, including nausea, diarrhoea, and constipation. No severe gastrointestinal events were reported. Seven (3%) of 212 patients across the pemvidutide and placebo groups reported serious adverse events, and none were assessed as treatment related. Details on serious adverse events are provided in the appendix (p 14).

Changes in HbA_{1c} at 24 weeks were –0·14, 0·03, and 0·03 in the 1·2 mg, 1·8 mg, and placebo groups, respectively (table 2). Hyperglycaemic adverse events, although higher in the 1·8 mg group, were generally mild, episodic, did not require treatment, and did not result in treatment discontinuation. Urinary tract infections (UTIs) were reported in 19 (9%) of 212 total patients across the three treatment groups. The urinary tract infections were predominantly mild and asymptomatic, with no severe events reported. There was no association of urinary tract infection and hyperglycaemia events; only two patients who had a urinary tract infection also had a hyperglycaemia event. The UTIs were considered unrelated to study drug in all patients, and none of the events resulted in study drug discontinuation. Systolic blood pressure decreased by 4·8 mm Hg in the 1·2 mg group and 4·2 mm Hg in the 1·8 mg group, versus a 0·6 mm Hg increase in the placebo group, whereas diastolic blood pressure decreased by 1·1 mm Hg and 1·6 mm Hg, and increased by 0·1 mm Hg, respectively. The effects on heart rate (–0·8, 1·0, and 0·4 beats per min in 1·2 mg, 1·8 mg, and placebo, respectively), were similar across treatment groups.

Discussion

This study marks the first incretin-based clinical trial in MASH to report on histological outcomes after 24 weeks of treatment. With respect to the dual primary efficacy endpoints of the trial, pemvidutide met the MASH resolution without worsening of the fibrosis endpoint at 24 weeks compared with placebo, but did not achieve a significant difference from placebo in the second dual primary endpoint of fibrosis improvement without worsening of MASH at this timepoint.

The magnitude of MASH resolution at this early 24-week timepoint was similar to or greater than the responses of other agents either approved or in development for MASH, including agents with longer treatment duration and at a shorter time interval than previous phase 2 studies of other incretins.[8,16] Pemvidutide was also associated with robust reductions and normalisation in liver fat as measured by MRI-PDFF, and reductions in the hepatic inflammation and injury markers ALT, AST, and cT1 relaxation time. The reduction in liver fat content was greater than that reported with semaglutide treatment at 24 weeks,[8,17,18] reflective of the recognised effects of glucagon on hepatic fat metabolism. With regard to the secondary endpoints, significant improvements in non-invasive markers of fibrosis activity, including ELF, LSM, and Pro-C3, are potentially indicative of an ongoing anti-fibrotic effect.

The post-hoc analyses of the proportionate area of pathological liver fibrosis by use of Liver Explore suggested significant improvement in fibrosis had occurred but that resolution of the architectural features that define F2 and F3 MASH, such as septal fibrosis, was incomplete, and that a categorical one-stage improvement in fibrosis might be achieved in a trial of longer duration.

Weight loss is central to the treatment of MASH as it addresses the risks of obesity-related morbidity and mortality. Obesity is a primary driver of MASH in most people and although liver-related mortality increases with fibrosis progression,[19] the most common cause of mortality in patients with MASH is cardiovascular disease.[2] Thus, treating both MASH and obesity might address multiple major causes of morbidity and mortality in these patients.

The safety profile for pemvidutide shown here is noteworthy, particularly as pemvidutide was administered without dose titration, unique among trials of the incretin-based class of agents. Despite having no dose titration phase, the adverse event discontinuation rate for pemvidutide was less than 1% and numerically lower than placebo, a result unseen in other reported incretin-based MASH studies.[8,10,16] Pemvidutide's tolerability might be related to the pharmacokinetics of pemvidutide, which is marked by a prolonged T_{max} and reduced C_{max} compared with other peptide incretins.[20–22] The absence of dose titration while maintaining good tolerability could be an important advantage in the treatment of MASH patients leading to improved retention of patients on therapy, as adherence in the treatment of obesity with incretin-based agents has been highlighted as a challenge.[23,24]

Limitations of this trial include the moderate sample size, which was typical of a phase 2 trial, and the reduced cohort size for the 1·2 mg pemvidutide, which might have complicated the establishment of a dose response. Likewise, a 24-week readout could give an incomplete interpretation of pemvidutide's effect on hepatic fibrosis, which might have been seen at a later timepoint typical of other trials with GLP-1 based agents.

This phase 2 trial of once-weekly pemvidutide met the primary endpoint of MASH resolution without worsening of fibrosis at 24 weeks of treatment but did not meet the second primary endpoint of fibrosis improvement. Improvements were seen in multiple non-invasive tests of fibrosis improvement and weight loss. Even at this early timepoint, the magnitude of MASH resolution was similar or greater than the responses of other agents either approved or in development for MASH, including agents with longer treatment duration.[8,16] The drug was administered without dose titration and was associated with a low rate of discontinuation due to drug-related events, supporting its potential as a treatment for MASH in patients with obesity. Larger and longer-duration trials are needed to further evaluate its effects on fibrosis and long-term outcomes.

Contributors

All authors had full access to all data in the study and final responsibility for deciding to submit this manuscript for publication. MN and MSH wrote the first draft of the manuscript with assistance from a medical writer and with input from JJS, SK, and MSR. MN, JY and SK have directly accessed and verified the data and statistical analyses

Declaration of interests

MN reports research support from Allergan, Altimmune, Akero, BI, BMS, Boston Pharma, Conatus, Corcept, Gilead, Galectin, Genfit, GSK, Kowa, Enanta, Madrigal, Eli Lilly, Merck, Novartis, Novo Nordisk, Rivus, Shire, Takeda, Terns, Viking and Zydus; consulting fees from Akero, Altimmune, Alligos, AstraZeneca, BI, Boston Pharma, Curve Bioscience, Cytodyn, GSK, Histoindex, Kryia, Eli Lilly, Madrigal, Merck, Novo Nordisk, OPKO, Rivus, Sagimet, Terns, and Takeda; speaking fees from Madrigal and Novo Nordisk; has leadership roles at the journal *Clinical Gastroenterology and Hepatology* (associate editor) and the American Association for the Study of Liver Diseases (chair of the metabolic dysfunction-associated steatotic liver disease special interest group); and stock in Rivus Pharma, OPKO, Kryia, and Akero. RL reports research support from Arrowhead Pharmaceuticals, AstraZeneca, Boehringer Ingelheim, Bristol Myers Squibb, Eli Lilly, Galectin Therapeutics, Gilead, Intercept, Hanmi, Inventiva, Ionis, Janssen, John C Martin Foundation, Madrigal Pharmaceuticals, Merck, US National Institutes of Health, Novo Nordisk, Pfizer, Sonic Incytes, and Terns Pharmaceuticals; consulting fees from Aardvark Therapeutics, Altimmune, Arrowhead Pharmaceuticals, AstraZeneca, Cascade Pharmaceuticals, Eli Lilly, Gilead, Glympse Bio, Inipharma, Intercept, Inventiva, Ionis, Janssen, Lipidio, Madrigal, Neurobo, Novo Nordisk, Merck, Pfizer, Sagimet, 89 bio, Takeda, Terns Pharmaceuticals, and Viking Therapeutics; is the co-founder of LipoNexus; and has stock in Sagimet Biosciences. NA reports research support from 89bio, Akero Therapeutics, Arbutus Biopharma, AstraZeneca, BioAge, Boehringer Ingelheim, Bristol Myers Squibb, Corcept Therapeutics, Galectin Therapeutics, Genentech, Gilead Sciences, Hepagene Therapeutics, Intercept Pharmaceuticals, Inventiva Pharma, Ionis Pharmaceuticals, Ipsen, Eli Lilly, Madrigal Pharmaceuticals, Merck, NGM Biopharmaceuticals, NorthSea Therapeutics, Novo Nordisk, Perspectum, Pfizer, PharmaIN, Poxel, Regeneron, Viking Therapeutics, and Zydus; consulting fees from 89bio, AbbVie, Akero, Boehringer Ingelheim, Echosens, Fibronostics, Gilead Sciences, HistoIndex, Intercept Pharmaceuticals, Ipsen, LiverRight, Madrigal Pharmaceuticals, NorthSea Therapeutics, Novo Nordisk, Perspectum, Pfizer, Regeneron, and Sonic Incytes; and speaking fees from AbbVie, AstraZeneca, Echosens, Gilead Sciences, Ipsen, Madrigal Pharmaceuticals, Novo Nordisk, and Perspectum. NC reports research funding from Madrigal, Exact Sciences, and Boehringer Ingelheim; consulting fees from Madrigal, GSK, Altimmune, Chugai, Insitro, Zydus, Eccogene, Biomea, and Ipsen; and stock in Heligenics and Avant Sante. MYS reports research support from Akero Therapeutics, Altimmune, Allergan, 89bio, Intercept Pharmaceuticals, Hanmi Pharmaceuticals, Salix Pharmaceuticals, Madrigal Pharmaceuticals, Viking Therapeutics, NGM Biopharmaceuticals, Eli Lilly, and Boston Pharmaceuticals; and speaking fees from Madrigal Pharmaceuticals, Salix Pharmaceuticals, and Gilead Sciences. ST is an employee of Altimmune; has a patent pending with Altimmune; and holds stock and stock options in Altimmune. JAG is an employee of Altimmune, has received consulting fees from Altimmune; has received speaking fees from Gilead and Madrigal; has participated in a data safety monitoring board or advisory board with Surrozen and Escient; and holds stock in Altimmune. SU is an employee of Altimmune. JJS is an employee of Altimmune; has received travel support from Altimmune; has a patent pending with Altimmune; and holds stock and stock options in Altimmune. RB is an employee of Altimmune; has received travel support from Altimmune; and holds stock and stock options in Altimmune. OO is an employee of Altimmune. JY is an employee of Altimmune. SK is an employee of Altimmune. GN reports consulting fees from Boehringer Ingelhelm, Boston Pharmaceuticals, and Echosens. EM reports speaking fees from Gilead, AbbVie, Madrigal Pharmaceuticals, and Ipsen; monitoring or advisory board participation with Gilead, Madrigal, and Ipsen; and board membership with HMRI non-profit and Salernis Collegium. MSR is an employee of Altimmune; has received travel support from Altimmune; and holds stock and stock options in Altimmune. SKB is an employee of Altimmune; holds stock in and has received travel support from Altimmune; has received speaking fees from Altimmune and is a lead for the Altimmune scientific advisory board. MSH is an employee of Altimmune; has received travel support from Altimmune; has a patent pending with Altimmune; is an Altimmune company officer, and holds stock and stock options in Altimmune. SAH is deceased and was unable to provide a competing interest statement; to the best of our knowledge he had no competing interests.

Data sharing

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

Acknowledgments

This study was funded by Altimmune. Elizabeth W Brombosz and Gražina Binkauskiene (Summit Clinical Research; paid by Altimmune) assisted with writing and preparing the manuscript for submission.

References

1 Ho GJK, Tan FXN, Sasikumar NA, et al. High global prevalence of steatotic liver disease and associated subtypes: a meta-analysis. *Clin Gastroenterol Hepatol* 2025; published online May 5. https://doi.org/10.1016/j.cgh.2025.02.006.

2 Younossi ZM, Kalligeros M, Henry L. Epidemiology of metabolic dysfunction-associated steatotic liver disease. *Clin Mol Hepatol* 2025; **31** (suppl)**:** S32–50.

3 Polyzos SA, Kountouras J, Mantzoros CS. Obesity and nonalcoholic fatty liver disease: From pathophysiology to therapeutics. *Metabolism* 2019; **92:** 82–97.

4 Diehl AM, Day C. Cause, pathogenesis, and treatment of nonalcoholic steatohepatitis. *N Engl J Med* 2017; **377:** 2063–72.

5 Singh S, Allen AM, Wang Z, Prokop LJ, Murad MH, Loomba R. Fibrosis progression in nonalcoholic fatty liver vs nonalcoholic steatohepatitis: a systematic review and meta-analysis of paired-biopsy studies. *Clin Gastroenterol Hepatol* 2015; **13**: 643–54.

6 Younossi ZM, Golabi P, Price JK, et al. The global epidemiology of nonalcoholic fatty liver disease and nonalcoholic steatohepatitis among patients with type 2 diabetes. *Clin Gastroenterol Hepatol* 2024; **22:** 1999–2010.e8.

7 Harrison SA, Bedossa P, Guy CD, et al, and the MAESTRO-NASH Investigators. A phase 3, randomized, controlled trial of resmetirom in NASH with liver fibrosis. *N Engl J Med* 2024; **390:** 497–509.

8 Sanyal AJ, Newsome PN, Kliers I, et al, and the ESSENCE Study Group. Phase 3 trial of semaglutide in metabolic dysfunction-associated steatohepatitis. *N Engl J Med* 2025; **392:** 2089–99.

9 Alkhouri N, Charlton M, Gray M, Noureddin M. The pleiotropic effects of glucagon-like peptide-1 receptor agonists in patients with metabolic dysfunction-associated steatohepatitis: a review for gastroenterologists. *Expert Opin Investig Drugs* 2025; **34:** 169–95.

10 Sanyal AJ, Bedossa P, Fraessdorf M, et al, and the 1404-0043 Trial Investigators. A phase 2 randomized trial of survodutide in MASH and fibrosis. *N Engl J Med* 2024; **391:** 311–19.

11 Nestor JJ, Zhang X, Jaw-Tsai S, Parkes DG, Becker CK. Design and characterization of a surfactant-conjugated, long-acting, balanced GLP-1/glucagon receptor dual agonist. *Pept Sci (Hoboken)* 2021; **113:** e24221.

12 Nauck MA, Niedereichholz U, Ettler R, et al. Glucagon-like peptide 1 inhibition of gastric emptying outweighs its insulinotropic effects in healthy humans. *Am J Physiol* 1997; **273:** E981–88.

13 Browne SK, Suschak JJ, Tomah S, et al. Safety and efficacy of 24 weeks of pemvidutide in metabolic dysfunction-associated steatotic liver disease: a randomized, controlled clinical trial. *JHEP Rep Innov Hepatol* 2025; **7:** 101483.

14 Kleiner DE, Brunt EM, Van Natta M, et al, and the Nonalcoholic Steatohepatitis Clinical Research Network. Design and validation of a histological scoring system for nonalcoholic fatty liver disease. *Hepatology* 2005; **41:** 1313–21.

15 Pulaski H, Harrison SA, Mehta SS, et al. Clinical validation of an AI-based pathology tool for scoring of metabolic dysfunction-associated steatohepatitis. *Nat Med* 2025; **31:** 315–22.

16 Loomba R, Hartman ML, Lawitz EJ, et al, and the SYNERGY-NASH Investigators. Tirzepatide for metabolic dysfunction-associated steatohepatitis with liver fibrosis. *N Engl J Med* 2024; **391:** 299–310.

17 Loomba R, Abdelmalek MF, Armstrong MJ, et al, and the NN9931-4492 investigators. Semaglutide 2·4 mg once weekly in patients with non-alcoholic steatohepatitis-related cirrhosis: a randomised, placebo-controlled phase 2 trial. *Lancet Gastroenterol Hepatol* 2023; **8:** 511–22.

18 Flint A, Andersen G, Hockings P, et al. Randomised clinical trial: semaglutide versus placebo reduced liver steatosis but not liver stiffness in subjects with non-alcoholic fatty liver disease assessed by magnetic resonance imaging. *Aliment Pharmacol Ther* 2021; **54:** 1150–61.

19 Ekstedt M, Hagström H, Nasr P, et al. Fibrosis stage is the strongest predictor for disease-specific mortality in NAFLD after up to 33 years of follow-up. *Hepatology* 2015; **61:** 1547–54.

20 Aroda VR. A review of GLP-1 receptor agonists: Evolution and advancement, through the lens of randomised controlled trials. *Diabetes Obes Metab* 2018; **20** (suppl 1)**:** 22–33.

21 Shi A, Xie P, Nielsen LL, Skjøth TV, He X, Haugaard SP. Pharmacokinetics, safety and tolerability of once-weekly subcutaneous semaglutide in healthy Chinese Subjects: a double-blind, phase 1, randomized controlled trial. *Adv Ther* 2021; **38:** 550–61.

22 Lawitz EJ, Fraessdorf M, Neff GW, et al, and the NCT05296733 Investigators. Efficacy, tolerability and pharmacokinetics of survodutide, a glucagon/glucagon-like peptide-1 receptor dual agonist, in cirrhosis. *J Hepatol* 2024; **81:** 837–46.

23 Rodriguez PJ, Zhang V, Gratzl S, et al. Discontinuation and reinitiation of dual-labeled glp-1 receptor agonists among US Adults with overweight or obesity. *JAMA Netw Open* 2025; **8:** e2457349.

24 Ladebo L, Ernst MT, Mailhac A, Dirksen C, Bojsen-Møller KN, Pottegård A. Real-world use of semaglutide for weight management: patient characteristics and dose titration—A Danish cohort study. *Diabetes Care* 2024; **47:** 1834–37.