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Clinical trial: Effects of pegozafermin on the liver and on metabolic comorbidities in subjects with biopsy-confirmed nonalcoholic steatohepatitis

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Summary

Background: An approved therapy for nonalcoholic steatohepatitis (NASH) and fibrosis remains a major unmet medical need.

Aim: To investigate the histological and metabolic benefits of pegozafermin, a glyco-PEGylated FGF21 analogue, in subjects with biopsy-confirmed NASH.

Methods: This proof-of-concept, open-label, single-cohort study, part 2 of a phase 1b/2a clinical trial, was conducted at 16 centres in the United States. Adults (age 21–75 years) with NASH (stage 2 or 3 fibrosis, NAS≥4) and magnetic resonance imaging proton density fat fraction (MRI-PDFF) ≥8% received subcutaneous pegozafermin 27 mg once weekly for 20 weeks. Primary outcomes were improvements in liver histology, and safety and tolerability.

Results: Of 20 enrolled subjects, 19 completed the study. Twelve subjects (63%) met the primary endpoint of ≥2-point improvement in NAFLD activity score with ≥1-point improvement in ballooning or lobular inflammation and no worsening of fibrosis. Improvement of fibrosis without worsening of NASH was observed in 26% of subjects, and NASH resolution without worsening of fibrosis in 32%. Least-squares mean relative change from baseline in MRI-PDFF was −64.7% (95% CI: −71.7, −57.7; $p < 0.0001$). Significant improvements from baseline were also seen in serum aminotransferases, noninvasive fibrosis tests, serum lipids, glycaemic control and body weight. Adverse events (AEs) were reported in 18 subjects (90%). The most frequently reported AEs were mild/moderate nausea and diarrhoea. There were no serious AEs, discontinuations due to AEs, or deaths.

Conclusions: Pegozafermin treatment for 20 weeks had beneficial effects on hepatic and metabolic parameters and was well tolerated in subjects with NASH. ClinicalTrials.gov: NCT04048135.

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1 | INTRODUCTION

Nonalcoholic fatty liver disease (NAFLD) is a common metabolic disease, affecting approximately 30% of adults worldwide, and is typically associated with obesity, insulin resistance, type 2 diabetes (T2D) and dyslipidaemia.[1] Nonalcoholic steatohepatitis (NASH), the progressive form of NAFLD, is characterised by steatosis, hepatocyte degeneration and lobular inflammation, with or without fibrosis.[2] Approximately 12%–14% of middle-aged Americans have NASH, and the prevalence of NASH in the United States is increasing.[3–5] Patients with NASH are at risk of cirrhosis and hepatocellular carcinoma, with progression of fibrosis being a key predictor of clinical outcomes.[2,6] In 2015 it was estimated that 20% of patients with NASH develop fibrosis and cirrhosis and 45% of patients with cirrhosis progress to decompensated cirrhosis within 10 years.[7] By 2030, 29% of patients with NASH in the United States are predicted to have stage 3 or 4 fibrosis or advanced liver disease, representing a substantial burden on healthcare systems.[5] Despite the high unmet medical need,[8] there are no approved pharmacological therapies for NASH, and diet and lifestyle modification are the recommended strategy for disease management.[9]

Pegozafermin is a long-acting glycoPEGylated analogue of fibroblast growth factor 21 (FGF21) in development for the treatment of patients with NASH and severe hypertriglyceridaemia.[10,11] FGF21 is a metabolic hormone, primarily secreted by the liver, that functions as a master regulator for energy expenditure and carbohydrate and lipid metabolism.[12] Consistent with a protective role in restoring metabolic homoeostasis, exogenous administration of FGF21 in patients with NASH has been associated with pleiotropic effects on liver health and whole-body metabolism.[13]

The safety, pharmacokinetics and pharmacodynamics of escalating doses of pegozafermin in 81 subjects with NASH or NAFLD with high risk of developing NASH were investigated in a randomised controlled phase 1b/2a study.[11] Pegozafermin administered once weekly or every 2 weeks for 12 weeks was well tolerated, with a low incidence of adverse events (AEs), and led to robust and clinically meaningful reductions versus placebo in liver fat, biomarkers of liver function and circulating lipids. In subjects receiving pegozafermin 27 mg once weekly, 86% had ≥30% reduction in hepatic fat fraction (magnetic resonance imaging proton density fat fraction [MRI-PDFF]).[11] Previous studies have shown that MRI-PDFF changes of this magnitude are associated with histological improvements and reduced progression of fibrosis.[14,15]

Here we present the findings of part 2 of the phase 1b/2a study, which aimed to investigate the potential histological and metabolic benefits of pegozafermin in a cohort of subjects with biopsy-confirmed NASH and fibrosis, to inform the design of the placebo-controlled, phase 2b ENLIVEN study.[16]

2 | METHODS

2.1 | Study design

This open-label, single-cohort, multicentre, proof-of-concept study was conducted at 16 specialist centres in the United States (ClinicalTrials.gov: NCT04048135). The primary objectives were to evaluate the safety and tolerability of once-weekly treatment with pegozafermin 27 mg (dose selected based on cumulative safety data from previous studies) for 20 weeks and to characterise the effects of pegozafermin on liver histology. The study included a screening period, a 20-week treatment period (days 1–140), during which pegozafermin was administered via subcutaneous injection in the abdomen by qualified study personnel, and a follow-up period (4 weeks post final dose). At the end of treatment, participants underwent a liver biopsy.

The study was conducted in accordance with the Declaration of Helsinki, the International Council for Harmonisation guidelines for Good Clinical Practice and applicable laws and regulations. The study protocol and other study-related documents were reviewed and approved by an Institutional Review Board.

2.2 | Participants

All participants provided written informed consent. Eligible participants were adults (age 21–75 years) at increased metabolic risk with biopsy-confirmed NASH and fibrosis. Participants had to either undergo a liver biopsy during screening or have had a recent liver biopsy (≤24 weeks before day 1). Key inclusion criteria were NAFLD activity score (NAS) ≥4 (≥1 score in each of steatosis, ballooning and lobular inflammation) and NASH Clinical Research Network (NASH CRN) stage 2 or 3 fibrosis (or F1 with high risk). In subjects without an eligible biopsy obtained within 24 weeks of baseline, evidence of fibrosis (FibroScan vibration-controlled transient elastography [VCTE] score ≥8.5 kPa and aspartate transaminase [AST] >20 U/L for males or >17 U/L for females; or a historical liver biopsy with F1/F2/F3 fibrosis), MRI-PDFF ≥8% and FibroScan controlled attenuation parameter score ≥280 dB/m were required. Individuals with history or evidence of cirrhosis, evidence of liver disease other than NASH or glycated haemoglobin (HbA1c) ≥9.5% were excluded. Participants with T2D were allowed to be on a stable dose of a glucagon-like peptide 1 receptor agonist and/or a sodium-glucose cotransporter-2 inhibitor at baseline; thiazolidinedione therapy was not allowed. Full inclusion and exclusion criteria are shown in Tables S1 and S2.

2.3 | Outcomes

Biopsies were read centrally by a single expert pathologist and scored using the NASH CRN scoring system. The primary efficacy

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endpoint was ≥2-point improvement in NAS with ≥1-point improvement in ballooning or lobular inflammation and no worsening of fibrosis. Secondary endpoints included improvement of fibrosis (≥1 stage) without worsening of NASH, NASH resolution (total absence of ballooning and absent or mild inflammation) without worsening of fibrosis (≥1-stage increase), and changes from baseline to week 20 in liver function tests (alanine transaminase [ALT] and AST), liver fat fraction (MRI-PDFF), triglycerides, high-density lipoprotein cholesterol (HDL-C), low-density lipoprotein cholesterol (LDL-C), non-HDL cholesterol (non-HDL-C), body weight, HbA1c, adiponectin and N-terminal propeptide of type III collagen (Pro-C3). Trough concentration of pegozafermin in serum was a secondary endpoint. The primary safety endpoint was frequency of treatment-emergent AEs and serious AEs (Medical Dictionary for Regulatory Activities version 23.1). Other safety assessments included vital signs, physical examination findings, electrocardiogram (ECG) data, clinical laboratory measurements and the presence of anti-drug antibodies (ADAs).

2.4 | Statistical analyses

A sample size of 20 subjects was planned, based on preliminary data from part 1 of the clinical trial. The full analysis set included all enrolled subjects who received at least one dose of pegozafermin. The histology biopsy and MRI analysis sets included all subjects in the full analysis set who had both baseline and post-baseline biopsies or measurable post-baseline MRI data respectively. Data were summarised using descriptive statistics and all analyses were performed using SAS software, version 9.4 or higher. A mixed-model repeated measures analysis was used for changes from baseline in secondary endpoints, with baseline as a covariate, subjects as a random effect for repeated visits and a compound symmetric covariance structure. There were no adjustments for multiplicity.

2.5 | Post hoc exploratory analysis

Three additional expert pathologists evaluated the baseline and end-of-treatment liver biopsies separately and independently, without a consensus process, to assess the impact of inter-reader variability on histological endpoints. Pathologists were blinded to the time point.

3 | RESULTS

3.1 | Subject disposition and baseline characteristics

The study was conducted between 29 December 2020 and 19 January 2022. In total, 104 patients were screened, 20 subjects were enrolled and received treatment with pegozafermin (full analysis set) and 19 subjects (95%) completed the study. One subject discontinued treatment owing to withdrawal of consent. Most participants were female (75%) and had a history of T2D (85%) (Table 1). Mean (standard deviation [SD]) NAS at baseline was 5.3 (1.2) and all participants had stage 2 (35%) or stage 3 fibrosis (65%). Overall, 17 subjects (85%)

TABLE 1 Baseline demographics and characteristics.

	Pegozafermin 27 mg QW (*n* = 20)
Age, years	58.4 (9.1)
Female, *n* (%)	15 (75)
White, *n* (%)	20 (100)
Hispanic or Latino, *n* (%)	5 (25)
Body weight, kg	104.6 (17.7)
BMI, kg/m^2	37.0 (4.7)
History of type 2 diabetes, *n* (%)	17 (85)
HbA1c, %	6.6 (1.1)
NAFLD Activity Score (NAS)	5.3 (1.2)
NAS category, *n* (%)	
4	6 (30)
5	7 (35)
6	3 (15)
7	3 (15)
8	1 (5)
NASH CRN fibrosis stage, *n* (%)	
F2	7 (35)
F3	13 (65)
ALT,[a] U/L	47.1 (16.2)
AST,[a] U/L	36.1 (10.9)
MRI-PDFF, %	21.1 (9.1)
FibroScan CAP score, dB/m	358.6 (32.3)
FibroScan VCTE score, kPa	14.3 (5.6)
FAST score	0.6 (0.2)
FIB-4 score	1.4 (0.5)
Pro-C3, ng/mL	19.3 (4.9)
Triglycerides, mg/dL	170.0 (55.7)
Non-HDL-C, mg/dL	125.9 (27.2)
LDL-C, mg/dL	92.0 (28.3)
HDL-C, mg/dL	43.4 (11.1)
Adiponectin, μg/dL	3.6 (1.7)

Note: Data are shown as mean (SD) unless otherwise indicated.

Abbreviations: ALT, alanine transaminase; AST, aspartate transaminase; BMI, body mass index; CAP, controlled attenuation parameter; FAST, FibroScan-AST; FIB-4, Fibrosis-4; HbA1c, glycated haemoglobin; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; MRI-PDFF, magnetic resonance imaging proton density fat fraction; NAFLD, nonalcoholic fatty liver disease; NASH CRN, Nonalcoholic Steatohepatitis Clinical Research Network; Pro-C3, N-terminal propeptide of type III collagen; QW, once weekly; SD, standard deviation; VCTE, vibration-controlled transient elastography.

[a]Baseline values calculated as the average of all values recorded during screening and study day 1.

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were receiving medication for diabetes, 14 (70%) were receiving antihypertensives and 11 (55%) were receiving statins.

3.2 | Effects of 20 weeks of pegozafermin treatment on the liver

At week 20, 12/19 subjects (63%) met the primary endpoint of ≥2-point improvement in NAS with ≥1-point improvement in ballooning or lobular inflammation and no worsening of fibrosis. Overall, pegozafermin treatment was associated with a robust improvement in all NAS components (Figure 1A). A 2-point improvement in NAS (with ≥1-point improvement in ballooning or lobular inflammation) was observed for 14 subjects (74%). Improvement of fibrosis without worsening of NASH was observed in five subjects (26%), and six subjects (32%) had NASH resolution without worsening of fibrosis (Figure 1B).

Least-squares (LS) mean (standard error [SE]) relative change from baseline in liver aminotransferases was −45.8% (3.9%) for ALT ($p < 0.0001$) and −47.3% (3.5%) for AST ($p < 0.0001$) (Table 2 and Figure 2). Overall, 11/19 subjects (58%) had an absolute reduction in ALT of ≥17 U/L. In subjects with elevated ALT at baseline (≥40 U/L in males and ≥30 U/L in females; $n = 14$ with available week 20 results), 10 (71%) had a reduction in ALT ≥17 U/L and 11 (79%) had a reduction to normal levels (<40 U/L in males and <30 U/L in females).

LS mean (SE) relative change from baseline in liver fat (MRI-PDFF) was −64.7% (3.4%) ($p < 0.0001$; Table 2). Overall, 19/19 subjects (100%) had ≥30% reduction in liver fat, 15 (79%) had ≥50% reduction, and eight (42%) had normal liver fat (<5%) at week 20.

Scores in noninvasive tests (NITs) for fibrosis significantly decreased from baseline (Table 2 and Figure S1). Responder rates at week 20, based on clinically relevant thresholds, were 72% for

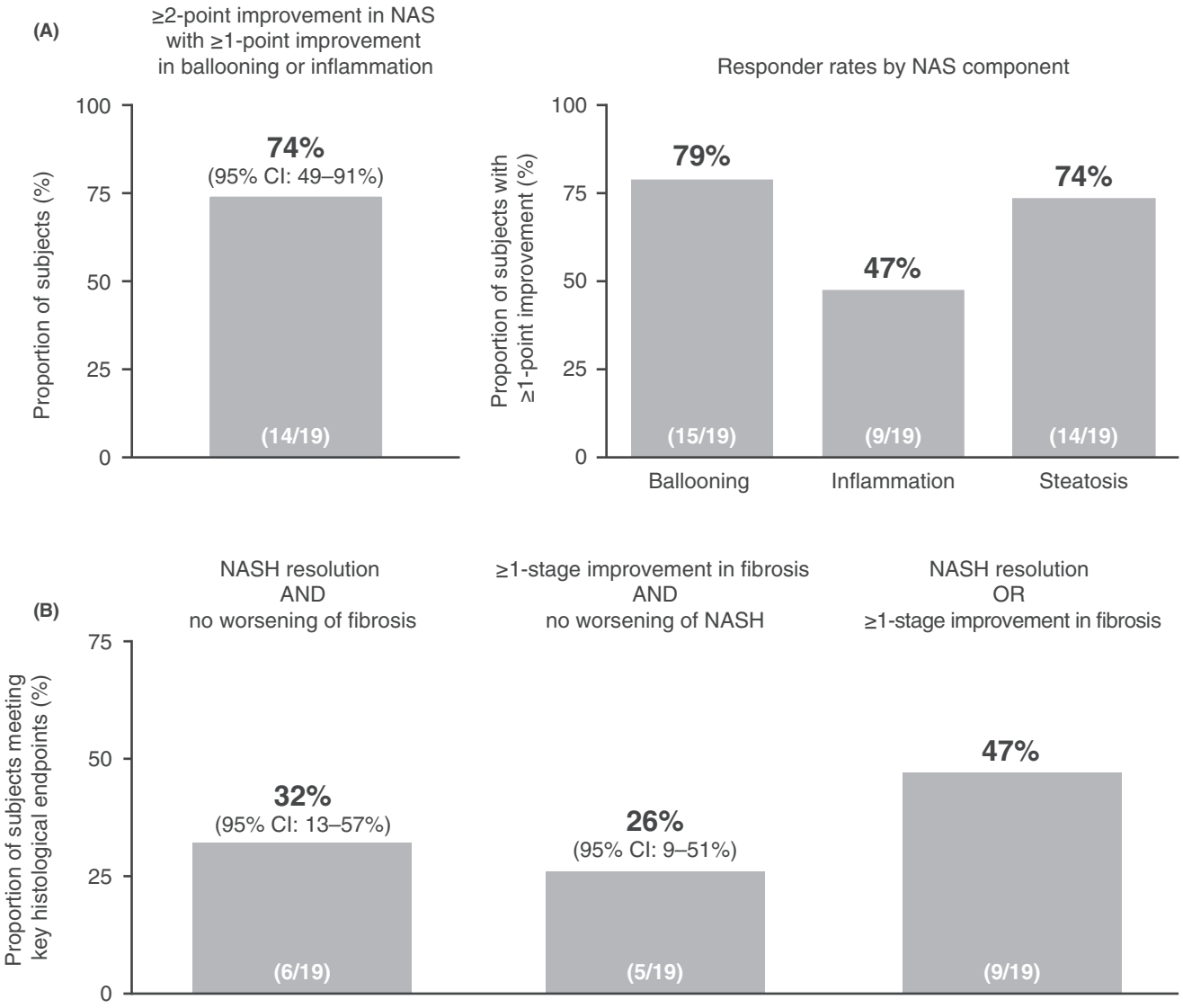

FIGURE 1 Effects of pegozafermin on liver histology. CI, confidence interval; NAS, nonalcoholic fatty liver disease activity score; NASH, nonalcoholic steatohepatitis.

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TABLE 2 Changes from baseline to week 20 in liver parameters.

	LS mean (SE)	95% CI	*p* value
ALT, U/L			
Absolute change	−23.1 (1.8)	−26.6, −19.6	<0.0001
Percentage change	−45.8 (3.9)	−53.6, −38.0	<0.0001
ALT in subjects with elevated ALT at baseline,[a] U/L			
Absolute change	−27.7 (2.2)	−32.2, −23.1	<0.0001
Percentage change	−49.9 (4.2)	−58.3, −41.4	<0.0001
AST, U/L			
Absolute change	−18.0 (1.3)	−20.6, −15.4	<0.0001
Percentage change	−47.3 (3.5)	−54.4, −40.1	<0.0001
AST in subjects with elevated ALT at baseline,[a] U/L			
Absolute change	−21.0 (1.7)	−24.4, −17.6	<0.0001
Percentage change	−50.8 (4.3)	−59.6, −42.1	<0.0001
MRI-PDFF, %			
Absolute change	−13.7 (0.8)	−15.3, −12.1	<0.0001
Percentage change	−64.7 (3.4)	−71.7, −57.7	<0.0001
FibroScan VCTE score, kPa			
Absolute change	−4.2 (0.7)	−5.7, −2.6	<0.0001
Percentage change	−28.3 (4.8)	−38.5, −18.1	<0.0001
FAST score			
Absolute change	−0.5 (0.0)	−0.5, −0.4	<0.0001
Percentage change	−76.5 (4.6)	−86.2, −66.9	<0.0001
FIB-4 score			
Absolute change	−0.3 (0.1)	−0.4, −0.1	0.0004
Percentage change	−18.0 (5.3)	−28.7, −7.3	0.0016
Pro-C3, ng/mL			
Absolute change	−4.3 (0.6)	−5.6, −3.0	<0.0001
Percentage change	−19.5 (3.3)	−26.2, −12.9	<0.0001

Abbreviations: ALT, alanine transaminase; AST, aspartate transaminase; CI, confidence interval; FAST, FibroScan-AST; FIB-4, Fibrosis-4; LS, least-squares; MRI-PDFF, magnetic resonance imaging proton density fat fraction; Pro-C3, N-terminal propeptide of type III collagen; SE, standard error; VCTE, vibration-controlled transient elastography.

[a]≥40 U/L in males and ≥30 U/L in females ($n = 14$).

FibroScan VCTE score ($n = 13/18$; reduction of ≥20% from baseline), 89% for FibroScan-AST (FAST) score ($n = 16/18$; score ≤0.35), 58% for Fibrosis-4 (FIB-4) score ($n = 11/19$; score <1.3) and 63% for Pro-C3 ($n = 12/19$; ≥15% reduction from baseline); 9/18 (50%) of subjects had a reduction in ALT ≥17 U/L, a reduction in MRI-PDFF ≥30% and a reduction in Fibroscan VCTE score ≥20%.

3.3 | Extra-hepatic metabolic effects of 20 weeks of pegozafermin treatment

LS mean (SE) relative change from baseline in lipid parameters was −25.3% (5.7%) ($p < 0.0001$) for triglycerides, −12.4% (4.8%) ($p < 0.05$) for LDL-C, −17.1% (3.5%) ($p < 0.0001$) for non-HDL-C and +22.7% (5.6%) ($p < 0.001$) for HDL-C (Table 3). In a post hoc analysis, similar mean (SD) relative changes from baseline in serum lipids were seen in subjects receiving lipid-lowering therapies ($n = 12$; triglycerides, −28.3% [29.3%]; LDL-C, −17.2% [28.2%]; non-HDL-C, −22.3% [22.2%]; HDL-C, +34.4% [23.8%]).

LS mean (SE) absolute change from baseline in HbA1c was −0.52% (0.12%) ($p < 0.001$; Table 3). In subjects with baseline HbA1c of 6.5% or higher ($n = 11$; mean [SD] HbA1c 7.25% [1.05%]), mean (SD) HbA1c at week 20 was 6.44% (0.93%) and the LS mean (SE) absolute change in HbA1c was −0.87% (0.23%) ($p < 0.01$); on average these subjects were receiving two antidiabetic medications. LS mean (SE) relative change in adiponectin was +88.1% (13.2%) ($p < 0.0001$; Table 3). A significant reduction in body weight was observed, with a LS mean (SE) relative change from baseline of −3.8% (0.8%) ($p < 0.0001$; Table 3).

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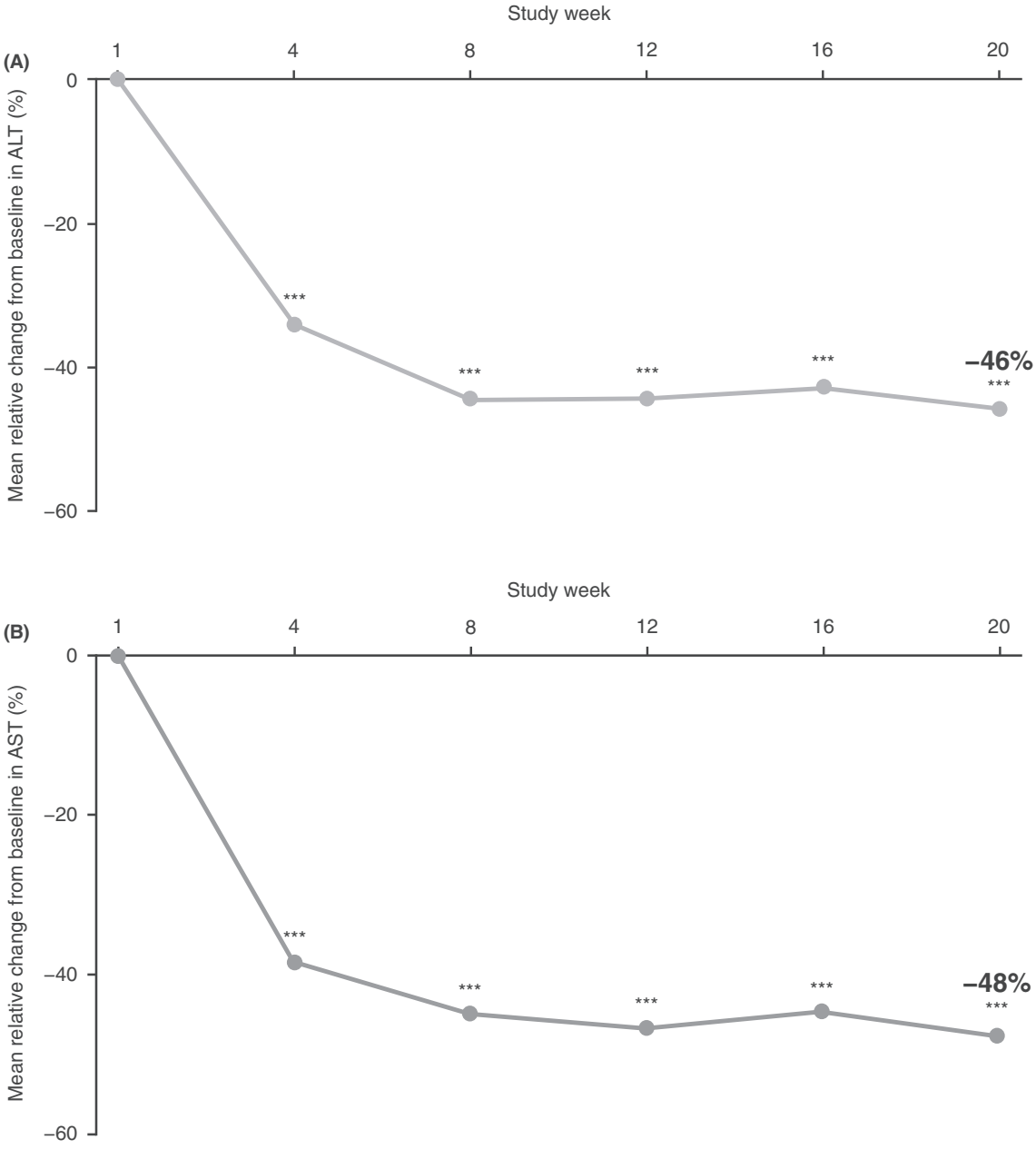

FIGURE 2 Change in (A) alanine transaminase (ALT) and (B) aspartate transaminase (AST) over 20 weeks. ***$p < 0.001$.

3.4 | Pharmacokinetics

A time-independent pharmacokinetics of pegozafermin was observed following multiple dose administration. Mean pegozafermin serum trough concentrations were consistent after day 29, indicating that a steady state was reached by the fourth dose (Figure S2).

3.5 | Safety and tolerability

AEs were reported in 18/20 subjects (90%; Table 4). All AEs were mild or moderate in severity. The most frequently reported AEs were nausea and diarrhoea. No subjects discontinued treatment due to an AE and there were no serious AEs or deaths. Treatment-related AEs were reported in 14 subjects (70%; Table 4); the most common were nausea and diarrhoea. No tremors or hypersensitivity reactions were reported. No consistent or meaningful patterns were observed for changes in safety-related laboratory parameters and there were no clinically significant findings related to vital signs, ECG results or physical examinations. Overall, ADAs were detected in 16/20 subjects (80%). Two subjects had ADAs specific to PEG at baseline. Following pegozafermin treatment, 14 subjects (70%) developed ADAs. All ADAs were non-neutralising and there were no apparent effects on pegozafermin pharmacokinetics, pharmacodynamics (MRI-PDFF) or safety.

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TABLE 3 Changes from baseline to week 20 in extra-hepatic metabolic parameters.

	LS mean (SE)	95% CI	*p* value
Triglycerides, mg/dL			
Absolute change	−44.4 (9.3)	−63.1, −25.7	<0.0001
Percentage change	−25.3 (5.7)	−36.7, −13.9	<0.0001
LDL-C, mg/dL			
Absolute change	−10.7 (3.7)	−18.2, −3.1	0.0065
Percentage change	−12.4 (4.8)	−22.1, −2.7	0.0136
Non-HDL-C, mg/dL			
Absolute change	−19.6 (3.9)	−27.4, −11.7	<0.0001
Percentage change	−17.1 (3.5)	−24.2, −10.0	<0.0001
HDL-C, mg/dL			
Absolute change	8.8 (2.5)	3.7, 13.9	0.0013
Percentage change	22.7 (5.6)	11.4, 34.0	0.0002
HbA1c, %			
Absolute change	−0.5 (0.1)	−0.8, −0.3	0.0004
HbA1c in subjects ≥6.5% at baseline,[a] %			
Absolute change	−0.9 (0.2)	−1.4, −0.4	0.0029
Adiponectin, μg/mL			
Absolute change	3.2 (0.6)	1.9, 4.5	<0.0001
Percentage change	88.1 (13.2)	60.7, 115.5	<0.0001
Body weight, kg			
Absolute change	−3.7 (0.8)	−5.4, −2.0	<0.0001
Percentage change	−3.8 (0.8)	−5.5, −2.1	<0.0001

Abbreviations: CI, confidence interval; HbA1c, glycated haemoglobin; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; LS, least-squares; SE, standard error.

[a]$n = 11$.

TABLE 4 Summary of treatment-emergent AEs.

	Pegozafermin 27 mg QW ($n = 20$)
Any AE	18 (90)
Grade 1 (mild)	8 (40)
Grade 2 (moderate)	10 (50)
Grade 3 (severe)	0
Serious AEs	0
AEs leading to discontinuation of study drug or study withdrawal	0
AEs leading to death	0
Treatment-related AEs	14 (70)
AEs reported in >10% of subjects	
Nausea	10 (50)
Diarrhoea	7 (35)
Abdominal pain (upper)	4 (20)
Fatigue	4 (20)
Vomiting	4 (20)
Decreased appetite	3 (15)
Treatment-related AEs reported in ≥10% of subjects	
Nausea	7 (35)
Diarrhoea	5 (25)
Vomiting	2 (10)
Decreased appetite	2 (10)
Injection-site bruising	2 (10)
Injection-site erythema	2 (10)

Note: Data are shown as *n* (%).

Abbreviations: AE, adverse event; QW, once weekly.

3.6 | Impact of inter-reader variability on histological endpoints

In a post hoc analysis of the liver biopsies, the proportion of subjects assessed as meeting histological endpoints varied among four pathologists (including the central reader), ranging between 68% and 79% for ≥2-point improvement in NAS, 12% and 42% for improvement in fibrosis without worsening of NASH and 26% and 47% for NASH resolution without worsening of fibrosis (Table S3). The three additional pathologists assessed fibrosis stage at baseline as more advanced than the central reader, with 6/19 subjects (32%) assessed as having stage 4 fibrosis, an exclusion criterion in this study, by at least two pathologists (Tables S4 and S5). All six subjects had well-compensated cirrhosis (Child–Pugh class A) and there were no clinical or laboratory findings suggestive of clinically significant portal hypertension or other complications of cirrhosis. When these subjects were excluded, the proportions of subjects who achieved histological endpoints as assessed by the central reader were higher than in the primary analysis (77% vs. 74% for ≥2-point improvement in NAS, 38% vs. 26% for improvement in fibrosis without worsening of NASH and 46% vs. 32% for NASH resolution without worsening of fibrosis). Notably, in the subjects assessed as having stage 4 fibrosis ($n = 5$–7 depending on pathologist), the proportions with fibrosis improvement without worsening of NASH and NASH resolution without worsening of fibrosis at week 20 ranged from 17%–57% and 20%–50% respectively. A marked improvement versus baseline in NITs, metabolic parameters and adiponectin was also observed in these subjects (Table S6).

4 | DISCUSSION

The development of an effective treatment for NASH represents a major unmet medical need.[8,14] In this study, once-weekly treatment with pegozafermin 27 mg for 20 weeks was associated with robust beneficial effects on liver histology in subjects with NASH and fibrosis. Overall, 63% of subjects met the primary endpoint, and clinically meaningful improvements were observed in regulatory-recommended histological endpoints. Improvement of fibrosis without worsening of NASH and NASH resolution without worsening

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of fibrosis were observed in 26% and 32% of subjects respectively. Significant changes in liver aminotransferases were most pronounced in patients with elevated ALT at baseline (≥40 U/L in males and ≥30 U/L in females). At week 20, 71% of these subjects met the 17 U/L threshold of reduction that has previously been correlated with favourable histological outcomes[17] and 79% had normal ALT levels. Liver fat was reduced to normal levels (<5%) in 42% of subjects. A reduction in liver fat of ≥30% was seen in all subjects at week 20 and 79% achieved a reduction of ≥50%, which is associated with NASH resolution.[14] There were also high responder rates for NITs for fibrosis, with clinically meaningful and significant improvements in FibroScan VCTE score,[18] FAST score,[19] FIB-4 score[20] and Pro-C3 levels.[21] The combination of ≥17 U/L reduction in ALT, ≥30% reduction in MRI-PDFF and ≥20% reduction in VCTE was observed in 50% of subjects. Although the small sample size does not enable meaningful conclusions to be drawn about the correlation of these NITs with histology, the favourable results of these tests, occurring in parallel with the histological improvements, demonstrate their utility in assessing treatment effects in subjects with NASH, and complement the histological findings.

The post hoc analysis in this study highlighted the considerable inter-reader variability in biopsy scoring, which has been widely recognised.[22,23] Based on the analysis of the three additional pathologists, 32% of subjects had putative stage 4 fibrosis at baseline and would have failed screening. When these individuals, who had to improve to F2 to meet the guidance-defined fibrosis histological endpoint given their baseline assessment as F3 by the central reader, were excluded, a higher proportion of subjects met histological endpoints. These data emphasise the need for more objective, consensus-based methodologies for biopsy scoring in NASH clinical trials. A panel of three pathologists, each scoring and reading independently has been shown to reduce bias and improve sensitivity.[24] Use of more granular scoring systems, such as the Elucidating Pathways of Steatohepatitis (EPoS) staging system,[25] or automated artificial intelligence/machine learning-based methodologies for histological scoring may be additional approaches to reduce inter-reader variability.[26–28]

These findings also highlight an inherent weakness of threshold-defined endpoints, which can be met without significant histological change or not met despite significant histological change depending on within-stage baseline variability in the studied population. A concern that rapid de-fattening of the liver may lead to biopsy artefacts (i.e. architectural 'collapse' with crowding of collagen fibres or other biopsy elements) that can mask histological improvement is another challenge with current histological endpoints. This has been increasingly recognised with the recent availability of drugs that reduce liver fat rapidly and potently, and correction methods have been proposed.[29] Given the rapid and robust reduction in liver fat observed with pegozafermin, a possible impact of this on the histological results seen in this study cannot be excluded.

Interestingly, improvements in liver histology, noninvasive liver and metabolic markers and adiponectin were also observed in subjects with putative stage 4 fibrosis; however, the small sample size limits interpretation of these data.

Pegozafermin treatment was also associated with significant metabolic benefits in this study. Metabolic disorders are key drivers of NASH and significant risk factors for cardiovascular morbidity and mortality in patients with NASH.[1,30] Some other therapies in development for NASH may increase cardiovascular risk by exacerbating dyslipidaemia (farnesoid X receptor agonists and FGF19 agonists), increasing serum triglyceride levels (acetyl coenzyme A carboxylase inhibitors) or promoting weight gain (peroxisome proliferator-activated receptor agonists).[13] Clinically meaningful changes were observed in this study in lipid markers, glycaemic control and body weight, despite a high proportion of the subjects receiving background therapies for diabetes and hyperlipidaemia. Pegozafermin treatment also significantly increased adiponectin, which has been demonstrated in mouse studies to be a key downstream mediator of the pleiotropic effects of FGF21 on lipid and glucose homoeostasis and insulin sensitivity.[12]

Pegozafermin 27 mg once weekly was well tolerated and had a favourable safety profile, consistent with previous studies, with no reports of serious AEs, deaths or discontinuations due to AEs. The most common AEs were nausea and diarrhoea, consistent with other studies of FGF21 analogues in subjects with metabolic disease and NASH.[13,31,32]

Limitations of this study include the small sample size and lack of a comparator arm. Because it was designed as a proof-of-concept study to obtain preliminary data, a single cohort of 20 subjects was considered appropriate to provide an initial understanding of potential histological and metabolic benefits. The effects of pegozafermin on liver histology in subjects with biopsy-confirmed NASH have been further investigated in the randomised, controlled, phase 2b ENLIVEN study (NCT049483).[16] The use of a single central reader for liver biopsy analysis was also a limitation. Learnings from this study were incorporated in the ENLIVEN study, in which three expert NASH pathologists scored liver biopsies separately and independently, and a consensus score reached by an objective algorithm that minimised need for adjudication.[16,24]

In conclusion, pegozafermin had pleiotropic beneficial effects on hepatic and metabolic parameters and was well tolerated over 20 weeks. Learnings from this proof-of-concept study have been instrumental to inform the design of the recently published phase 2b ENLIVEN study,[16] including the introduction of an objective consensus reading methodology to reduce biopsy reading variability. These results add to the growing body of evidence for pegozafermin as a potential treatment for NASH.

AUTHOR CONTRIBUTIONS

Naim Alkhouri: Conceptualization (equal); investigation (equal); methodology (equal); writing – original draft (equal); writing – review and editing (equal). **Donald Lazas:** Investigation (equal); writing – review and editing (equal). **Rohit Loomba:** Conceptualization (equal); methodology (equal); writing – review and editing (equal). **Juan P. Frias:** Writing – review and editing (equal). **Shibao Feng:**

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Formal analysis (equal); methodology (equal); writing – review and editing (equal). **Leo Tseng:** Formal analysis (equal); methodology (equal); writing – review and editing (equal). **Kemal Balic:** Formal analysis (equal); methodology (equal); writing – review and editing (equal). **Germaine D. Agollah:** Formal analysis (equal); investigation (equal); methodology (equal); writing – review and editing (equal). **Tinna Kwan:** Investigation (equal); writing – review and editing (equal). **Janani S. Iyer:** Formal analysis (equal); investigation (equal); writing – review and editing (equal). **Linda Morrow:** Investigation (equal); writing – review and editing (equal). **Hank Mansbach:** Conceptualization (equal); methodology (equal); writing – review and editing (equal). **Maya Margalit:** Conceptualization (equal); investigation (equal); methodology (equal); writing – review and editing (equal). **Stephen A. Harrison:** Conceptualization (equal); investigation (equal); methodology (equal); writing – original draft (equal); writing – review and editing (equal).

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AUTHORSHIP

Guarantor of the article: Naim Alkhouri is the guarantor of the article.

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