Supplementary Appendix

Supplement to: Loomba R, Sanyal AJ, Kowdley KV, et al. Randomized, controlled trial of the FGF21 analogue pegozafermin in NASH. N Engl J Med 2022;387:998-1008. DOI: 10.1056/NEJMoa2304286

This appendix has been provided by the authors to give readers additional information about the work.

Supplementary Appendix

Table of Contents

List of Investigators

Madhavi Rudraraju	Pinnacle Clinical Research – San Antonio
Stephen Harrison	Pinnacle Clinical Research
Guy Neff	Covenant Research and Clinics, LLC
Rashmee Patil	South Texas Research Institute
Naim Alkhouri	Arizona Liver Health
Shekhar Challa	Kansas Medical Clinic PA
Gary Reiss	Tandem Clinical Research
Eric Lawitz	American Research Corporation at the Texas Liver Institute
Michael Waters	Velocity Clinical Research
Mark Kipnes	Diabetes and Glandular Disease Clinic, P.A.
Humberto Aguilar	Louisiana Research Center, LLC
Rogelio Machuca	The Machuca Foundation, Inc.
Zeid Kayali	Inland Empire Clinical Trials, LLC
Na Li	Ohio State University
Carmen Landaverde	American Research Corporation
Senthil Raghavan	Arcare Center for Clinical Research
Anjali Morey	DSI Research (Digestive Specialists Inc.)
Tomohiro Tanaka	University of Iowa Hospitals & Clinics
Jason Lockette	North Alabama Health Research, LLC
Ravi Patel	Digestive Research Alliance of Michiana
Vinay Patel	Northeast GI Research Division
Donald Lazas	Digestive Health Research
Saeid Goshtasbi	Digestive Health Research of Southern California
Carl Wallach	AIG Digestive Disease Research
Robert Barish	Ocala GI Research
Raja Mohi-ud-din	Mid-Atlantic GI Research
Michael Fuchs	McGuire VA Medical Center
Abdullah Mubarak	Liver Center of Texas
Harry E. Sarles	GI Alliance
Apurva Modi	Texas Digestive Disease Consultants
Robert Jenders	National Research Institute
Stanley Hsia	National Research Insitute
Mark Leibowitz	National Research Institute
William Sanchez	Florian Clinical Research, LLC
John Lowe	Advanced Research Institute
Anita Kohli	Arizona Liver Health - Chandler
Abdul Jabbar	Gastroenterology Health Partners
Alex White	Progressive Medical Research
Ann Moore	The Institute for Liver Health dba Arizona Liver Health
Bassel Kisso	Del Sol Research Management, LLC
Kris Kowdley	Liver Institute Northwest
Patrick Weston	Synergy Healthcare
Joseph Galati	Mt.Olympus Medical Research
James Andersen	Accel Research Sites-Lakeland

Mousab Tabbaa	CRIOH, LLC
Ben Thomas	WR-Mount Vernon Clinical Research, LLC
Marcelo Kugelmas	South Denver Gastroenterology, PC
Nabil Andrawis	Manassas Clinical Research Center
Colby Grossman	Palmetto Clinical Research
Cassandra Steimle	DSI Research Northridge
Omer Khalid	GI Select Health Research
Roger Estevez	Clinical Research of South Nevada
Adil Fatakia	Tandem Clinical Research GI, LLC
Rosemary Laird	ClinCloud, LLC
Nadege Gunn	Impact Research Institute
Mirel Sanchez	Sanchez Clinical Research, Inc
Jeffrey Williams	Summit Clinical Research
Kenolisa Onwueme	Woodholme Gastroenterology Associates
Robert Morin, Jr.	Quality Research Inc.
Hanumantha Ancha	Digestive Health Research of Central Texas
Charles Dasher	Birmingham Digestive Health Research

Supplementary Methods

Trial Registration

This study is registered at ClinicalTrials.gov (NCT04929483).

As per the 42 CFR Part 11 regulation, the trial was registered within 21 calendar days after enrolling the first patient. The first patient was screened on June 4, 2021. The first release on ClinicalTrials.gov was on June 10, 2021 and PRS posted on June 16, 2021. The first patient was randomized on September 28, 2021.

Inclusion and Exclusion Criteria

Inclusion Criteria

Patients are eligible to be included in the study only if all of the following criteria apply:

Age and Sex

1. Patients must be 21 to 75 years of age inclusive, at the time of signing the informed consent form (ICF)
2. Male or female

Type of Patient and Disease Characteristics

3. Biopsy-confirmed nonalcoholic steatohepatitis (NASH) with fibrosis stage F2, or F3 per NASH Clinical Research Network (CRN) system and Nonalcoholic fatty liver disease Activity Score (NAS) ≥4, with a score of at least 1 in each of steatosis, ballooning degeneration, and lobular inflammation, either through a historical biopsy or a biopsy at screening. A historical biopsy should be obtained within 6 months prior to first day of Screening (i.e., day ICF is signed) that is deemed suitable for interpretation by a central reader if the patient had no significant change in metabolic status (control of diabetes, hyperlipidemia or >5% weight loss or gain)

Pregnancy and Contraception

Contraceptive use by men or women should be consistent with local regulations regarding the methods of contraception for those participating in clinical studies.

4. All patients (male or female) who are of childbearing potential must agree to use highly effective, double contraception (both male and female partners) during the study. Use of a condom with spermicide in a male patient who underwent vasectomy is also acceptable as double contraception. Use of highly effective, double contraception must continue for 30 days after the last dose of IP. Female patients should not donate oocytes during this time. Male patients must not donate sperm during this time. Rhythm methods are not considered as highly effective methods of birth control. Patient abstinence for the duration of the study and 30 days after the last dose of investigational product (IP) is acceptable if it is the patient's regular practice
5. Females of childbearing potential must have a negative serum pregnancy test at Screening and a negative urine pregnancy test on Day 1. Females of childbearing potential must agree to undergo a pregnancy test prior to dosing at the timepoints specified in the schedule of activities (SoA)

6. Sexually active male patients whose female partner is pregnant must agree to use a condom

Informed Consent and Study Requirements

7. Capable of giving signed informed consent, which includes compliance with the requirements and restrictions listed in the ICF and in this protocol
8. Patients must not participate in any other interventional studies throughout the duration of this study. COVID-19 protocols may be excepted with Medical Monitor (or designee) approval

Exclusion Criteria

Patients are excluded from the study if any of the following criteria apply:

Medical Conditions

Liver Disease

1. History of a liver disorder other than NASH or clinical suspicion of a liver disorder other than NASH, including but not limited to hepatitis B and hepatitis C, autoimmune hepatitis, hemochromatosis, alcoholic liver disease, primary sclerosing cholangitis, primary biliary cirrhosis/cholangitis, alpha-1 antitrypsin deficiency, untreated celiac disease, or Wilson's disease
   Serology testing will be performed at screening. Patients positive for hepatitis B surface antigen (HBsAg) will be excluded. Patients positive for hepatitis C virus antibody (anti HCV) will undergo reflex polymerase chain reaction (PCR) for HCV RNA, and will only be eligible if the following conditions are met:
   a. Patients with spontaneous clearance of HCV infection (positive serology for HCV infection with documented negative PCR for HCV RNA and no history of acute HCV infection within 3 years prior to Screening)
   b. Patients who were previously diagnosed with chronic HCV infection who achieved documented sustained viral response (SVR) following treatment at least 2 years prior to Screening
2. Planned or history of liver transplantation
3. History or evidence of cirrhosis (NASH CRN Fibrosis Stage 4 on biopsy) or clinical indicators of hepatic decompensation including ascites, hepatic encephalopathy, splenomegaly, or variceal bleeding

Other Medical Conditions

4. Presence of any chronic medical condition that, in the opinion of the Investigator, might pose additional risk to the patient, make the patient unable to comply with the protocol requirements, or confound the results of the study. Individual cases in which the Investigator deems the patient appropriate for inclusion despite a clinically significant chronic medical condition should be discussed with and approved by the Medical Monitor (or designee)
5. Hospitalization due to COVID-19 within 3 months prior to Screening. A positive COVID-19 test or COVID-19 diagnosis after signing consent is not exclusionary
6. Human immunodeficiency virus (HIV)-1 or HIV-2 infection
7. Unstable or clinically significant cardiovascular or cerebrovascular disease:
   a. Unstable angina, myocardial infarction, coronary artery bypass graft (CABG) surgery, percutaneous coronary intervention (PCI), transient ischemic attack (TIA) or cerebrovascular accident (CVA) within 6 months prior to Screening

    b. Symptomatic valvular or other structural heart disease
    c. Symptomatic congestive heart failure
    d. Symptomatic, uncontrolled or high-risk arrhythmia or genetic predisposition to high-risk arrhythmia in the patient or a first degree relative
    e. Implanted defibrillator or pacemaker
    f. High risk abdominal aortic aneurysm, uncontrolled peripheral vascular disease, or symptomatic carotid stenosis
8. Uncontrolled or newly diagnosed (<2 months since diagnosis at time of Screening) hypertension. Patients with well controlled hypertension who are clinically stable may enroll if they have been on a stable dose of antihypertensive medications for at least 2 months before Screening
9. Uncontrolled or newly diagnosed thyroid disease. Patients with treated thyroid disease may be enrolled if they are considered stable on treatment for at least 3 months by the Investigator. Modest dose adjustments per standard of care are allowed
10. Uncontrolled or newly diagnosed (≤ 3 months since diagnosis) type 2 diabetes mellitus (T2DM) (patients with newly diagnosed T2DM may be rescreened if considered stable after 3 months):
    a. Patients must have glycated hemoglobin (HbA1c) level ≤ 9.5% at screening
    b. Patients must have been on a stable antidiabetic regimen for at least 3 months (for insulin and dipeptidyl peptidase IV [DPP-IV] antagonists) or 6 months (for glucagon-like peptide 1 [GLP-1] agonists and sodium glucose co-transporter 2 [SGLT2] inhibitors) prior to biopsy (historical or screening) and remains stable up to randomization. Stable regimen is defined as no addition or discontinuation of antidiabetic medications, but dose adjustments or switching to another medication in the same class at the same relative dose per standard of care are allowed. Thiazolidinediones are not allowed. Patients on any other antidiabetic regimen not specified above should be on stable treatment for at least 3 months prior to their qualifying biopsy. Consult with the Medical Monitor if further clarification is needed
11. Type 1 Diabetes Mellitus
12. Weight change of more than 5% within 3 months prior to on-study screening liver biopsy or more than 10% within 6 months prior to on-study screening liver biopsy or planning to start a new weight loss program, training for a marathon, or taking weight loss medication. However, in patients with a historical biopsy, weight change of no more than 5% is allowed between the historical biopsy and first day of Screening
13. History of bariatric surgery within the 5 years prior to Screening or plan to have bariatric surgery during conduct of study. Reversible procedures, such as lap banding, are allowed if they have been removed at least 12 months prior to Screening. Note: Removal of intra-gastric balloon or unsuccessful surgery more than 2 years prior to screening is acceptable
14. History of bone trauma, bone fracture, or bone surgery within 2 months of screening or other bone disorders that may have a clinically meaningful impact on bone formation or bone remodeling (such as osteoporosis, osteomalacia) or known, untreated severe vitamin D deficiency (serum 25-hydroxy-vitamin D ≤5 ng/mL; severe vitamin D deficiency that is being treated is not exclusionary). Joint or connective tissue disorders (such as arthritis) are not exclusionary
15. History of malignancy diagnosed or treated within 2 years of screening (recent localized treatment of squamous or noninvasive basal cell skin cancers is permitted; any carcinoma in situ is allowed if appropriately treated within 2 years prior to the

Screening biopsy); patients under evaluation for malignancy are not eligible. Any history of hepatocellular carcinoma is exclusionary

16. Current or history of significant alcohol consumption for a period of more than 3 consecutive months within 1 year prior to Screening. Defined as more than 14 units/week for females (>1 drink per day) and more than 21 units/week for males (>2 drinks per day) on average, where one unit of alcohol is equivalent to a 12-oz beer, 4-ounce glass of wine, or 1-ounce shot of hard liquor
17. History of substance use disorder, or any other substance dependence (with the exception of caffeine or nicotine) as defined by the latest edition of the Diagnostic and Statistical Manual of Mental Disorders in the past 2 years prior to Screening. A positive urine drug screen is not exclusionary. Patients who have a positive test during Screening, including patients without a history of substance use disorder or patients who have been prescribed medication (e.g., opiates, benzodiazepines) will be considered for enrolment at Investigator's discretion. Cannabis and cannabidiol (CBD) products are not exclusionary

Diagnostic Assessments

18. Clinically significant laboratory abnormality at Screening. Repeat tests may be allowed for each laboratory parameter at the discretion of the Investigator. The presence of one or more of the following laboratory abnormalities should lead to exclusion of the patient from participating in the study:
    a. alanine aminotransferase (ALT) or aspartate aminotransferase (AST) ≥ 250 U/L
    b. b. Alkaline Phosphatase >2-fold higher than upper limit of normal (ULN)
    c. Elevation of total bilirubin (TB) >1.30 mg/dL. Patients with isolated indirect hyperbilirubinemia (normal direct bilirubin) secondary to medically documented Gilbert's syndrome may be enrolled
    d. Triglycerides >1000 mg/dL
    e. International normalized ratio (INR) >1.30 unless due to anti-coagulant therapy. Patients on anti-coagulant therapy may require their treatment withheld according to local guidelines prior to liver biopsy
    f. Glomerular filtration rate (eGFR) ≤50 mL/min/1.73 m^2 as estimated by chronic kidney disease-epidemiology (CKD-EPI) Creatinine equation
    g. Platelet count <100,000/µL
    h. Greater than 40% increase in ALT or AST between 2 screening assessments, to be done at least 2 weeks apart between the 1st and 2nd assessment, as per the table below. A 3rd assessment, if required, will be collected via unscheduled visit, and performed at least 1 week apart from the 2nd assessment:

ALT and AST Screening Assessments			**Eligibility Status**
Assessment 1	**Assessment 2**	**Assessment 3 (if applicable)**	
Normal	Normal	Not applicable	Eligible
Normal	Abnormal and ≤40% increase from Assessment 1	Not applicable	Eligible
Normal	Abnormal and >40% increase from Assessment 1	Normal or ≤40% increase from Assessment 1	Eligible

		Abnormal and >40% increase from Assessment 1	Excluded
Abnormal	≤40% increase from Assessment 1	Not applicable	Eligible
Abnormal	>40% increase from Assessment 1	≤40% increase from Assessment 1	Eligible
		>40% increase from Assessment 1	Excluded

Abbreviations: ALT, alanine aminotransferase; AST, aspartate aminotransferase

Normal is defined as ≤ULN; abnormal is defined as >ULN.

Note: Clinical judgment should be used for patients with isolated AST increases in whom there is suggestion of another cause of AST increase (e.g., muscle injury as evident by concurrent creatine phosphokinase elevation).

19. Electrocardiogram (ECG) abnormality by central reader that may, in the opinion of the Investigator, interfere with study participation. Resting Fredericia corrected QT interval in ECG (QTcF) interval of ≥450 msec for males or ≥470 msec for females (by central reader)
20. Body mass index (BMI) at Screening <25.0 or >50.0 kg/m^2.

Prior/Concomitant Therapy

21. Patient report of use of medications historically associated with secondary NAFLD for more than 2 consecutive weeks in the 12 months prior to screening (e.g., amiodarone, methotrexate, systemic glucocorticoids, tetracyclines, tamoxifen, estrogens or anabolic steroids at doses greater than those used for hormone replacement, valproic acid, and other medications with known hepatotoxicity). Inhaled corticosteroids are allowed
22. Any prior exposure to a fibroblast growth factor 21 (FGF21) analog (e.g., including but not limited to pegozafermin, LY2405319, LY3025876, BMS986036, BMS986171, PF05231023, PF-06645849, AKR-001) or fibroblast growth factor receptor 1 (FGFR1) activating product, if known
23. Any investigational drug small molecule (new chemical entity) within 30 days and large molecule (biologics) within 90 days, or 5 half-lives, whichever is longer, prior to Day 1, if known
24. Patients taking vitamin E (>400 IU/day) must be on a stable dose for at least 6 months prior to screening

Prior/Concurrent Clinical Study Experience

25. Currently participating in or have participated in a study of an investigational agent or has used an investigational device within 30 days prior to the first dose of IP. Note: study participants will not be allowed to participate in other interventional trials for FGF21 analog (e.g., including but not limited to pegozafermin, LY2405319, LY3025876, BMS986036, BMS986171, PF05231023, PF-06645849, AKR 001) or FGFR1 activating products, during the immunogenicity follow up period

Other Exclusions

26. Inability to undergo a liver biopsy safely for any reason
27. Patient who cannot undergo magnetic resonance imaging (MRI) for any reason (e.g., contraindication, claustrophobia not controlled by anxiolytic, excessive weight or body size for MRI machine)
28. Patient who cannot fast for study procedures for any reason. Specifically, patients with T2DM who have a history of clinically significant, symptomatic hypoglycemia or past issues with fasting will be excluded. Patients with T2DM may need to consult their treating physician about the optimal timing to take their medications to enable them to fast safely for study procedures
29. Any abnormality of the skin or abdominal wall that would impede subcutaneous (SC) administration to the abdominal area
30. Known hypersensitivity to the components of the IP, or history of a severe hypersensitivity reaction that, in the opinion of the Investigator, might place the patient at risk to receive IP
31. Pregnant or breastfeeding or planning to become pregnant or breastfeed while enrolled in the study or within 30 days after last dose of IP
32. An employee of the investigational center or has a family member who is involved with the conduct of this study
33. Any other clinically significant findings (including incidental findings during Screening), disorders or prior therapy that, in the opinion of the Investigator or Medical Monitor (or designee), would make the patient unsuitable for the study or unable to comply with the dosing and protocol requirements

Rationale for Adjustment of Randomization Ratio

The sponsor conducted an open-label study with pegozafermin 27 mg once weekly in patients with NASH and fibrosis stage F2 or F3. After 20 weeks of treatment, follow-up biopsies showed encouraging responses on both fibrosis improvement and NASH resolution. The present study was already ongoing at the time these other data became available. Based on the responses observed from the open-label study, the sponsor concluded that the 15 mg once weekly dose was likely to result in sub-optimal efficacy. A protocol amendment was issued to change the randomization scheme and decrease the allocation of patients to the 15 mg once weekly cohort.

Study Drug Administration

Pegozafermin and placebo were supplied in Type 1 vials that were identical in appearance and were administered subcutaneously in the abdomen by qualified personnel at the study site or, after appropriate training, by the patient or their caregiver at home.

Protocol-Specified Guidance on Diet and Exercise

Diet and exercise guidance were provided by site staff at each study visit. Patients were encouraged to limit energy intake from total fats and sugars, increase consumption of fruit and vegetables, as well as legumes, whole grains, and nuts, and engage in at least 150 minutes of moderate-intensity aerobic physical activity throughout the week, or to do at least 75 minutes of vigorous-intensity aerobic physical activity throughout the week, or an

equivalent combination of moderate- and vigorous-intensity activity. Management of comorbidities was done at the investigator's discretion.

Consensus-Panel Read for Biopsy Scoring

A consensus charter approach that was aligned with current approaches in consensus reading methodology in NASH clinical trials,[1,2] was used for biopsy scoring to reduce the impact of individual reader bias and inter-reader variability. Digital biopsy slides were scored independently by three expert NASH pathologists, who were blinded to patient, treatment and sequence, using the NASH CRN fibrosis staging system and the NAS. A panel of three readers was selected to meet current FDA expectations of biopsy reading in NASH clinical trials by at least two pathologists, using an odd number of pathologists to facilitate achievement of modes or medians to minimize the need for social interaction between the pathologists (e.g. in consensus calls) that may jeopardize objectivity of biopsy reading, and taking into account practical considerations related to clinical trial conduct, the absence of clear evidence to indicate an advantage for a panel of a different size, and data indicating good concordance between consensus reads of two panels of this size.[1] Each pathologist underwent protocol-defined training before and during the trial to improve concordance among the readers. No formal testing of consistency and accuracy was performed.

The consensus score was derived using an algorithm from the independent scores submitted by each reader (Figure S1). If there was agreement between all pathologists, the agreed score was recorded as the consensus score. If there was no agreement between the three pathologists, the consensus score was determined by the mode (agreement between two of the pathologists). In the absence of a mode, the median score was used or, if that was not possible, a consensus phone call was held. The process was outlined in a consensus charter.

The three-reader consensus methodology was introduced when the trial had already started. Biopsies that were initially read by one of two central readers (the original reading methodology) were re-read and scored by all three panel pathologists.

Protocol-Specified Reasons for Study Discontinuation, Withdrawal or Interruption

In some instances, it may be necessary for a patient to permanently discontinue IP. Temporary IP interruption may be allowed if Investigator and Medical Monitor (or designee) assess that IP rechallenge is safe and appropriate.

Permanent discontinuation of IP at any time during the study does not mean withdrawal from the study, and the patient will be encouraged to remain in the study, complete the Early Termination (ET) visit at the time of IP discontinuation and continue to complete remaining study period during the Main Study or the Extension Study as appropriate (i.e., patients who ET before Week 24 may complete study visits through Week 24 and patients who ET after Week 24 may complete visits through Week 48). Procedures for the remaining visits will include assessment of AEs and updating concomitant medications. Patients who permanently discontinue IP at or after Week 16 and before Week 24 of the Main study will be requested to provide a liver biopsy at ET visit.

Patients who experience clinically significant TEAEs that are assessed as a potential risk to patient safety will be discontinued from IP and undergo an ET visit as specified in the SoA. The decision to discontinue IP will be made by the Investigator and should be discussed with

the Medical Monitor (or designee). If any Patient experiences a Grade 3 TEAE that is considered related to IP, the Investigator should discuss treatment discontinuation with the Medical Monitor (or designee).

Patients have the right to withdraw from the study at any time and for any reason without prejudice to their future medical care by the Investigator or at the institution. The reason for patient withdrawal from the study will be recorded in the eCRF. At the time of withdrawal from the study, the ET visit should be conducted as shown in the SoA. A patient may discontinue IP or withdraw from the study for the following reasons:

- Adverse event
- Death
- Lack of efficacy
- Lost to follow-up
- Non-compliance with study drug
- Physician decision
- Pregnancy
- Protocol deviation
- Site terminated by Sponsor
- Study terminated by Sponsor
- Withdrawal by Patient
- Randomized by mistake
- Evidence of hepatic decompensation including ascites, hepatic encephalopathy, splenomegaly, or variceal bleeding as assessed by the Investigator (for F4 patients only)
- Model for end-stage liver disease (MELD) Na^+ score >12 (for F4 patients only)

Monitoring and Discontinuation for Suspected Drug-induced Liver Injury (DILI)

Liver chemistry will be evaluated as specified in the SoA.

Per FDA recommendations, the following criteria for elevations in liver transaminases or bilirubin will be used for closely monitoring, discontinuing, or temporarily interrupting IP.

Definition of baseline ALT and AST values

Baseline value is defined as an average of ALT and AST values performed during Screening and the Baseline (Day 1) visit, as follows:

ALT/AST Screening Assessments			**Day 1 ALT/AST Assessment**	**Baseline Value**
Assessment 1	**Assessment 2**	**Assessment 3 (if applicable)**		
Normal	Normal	Not applicable	Any	Average of Assessment 1, Assessment 2 and Day 1 (3 tests)
Normal	Abnormal and ≤ 40% increase from Assessment 1	Not applicable	Any	Average of Assessment 1, Assessment 2 and Day 1 (3 tests)

Normal	Abnormal and >40% increase from Assessment 1	Normal or ≤40% increase from Assessment 1	Any	Average of Assessment 1, Assessment 2, Assessment 3 and Day 1 (4 tests)
		Abnormal and >40% increase from Assessment 1	Not applicable, Patient excluded	Not applicable, Patient excluded
Abnormal	≤40% increase from Assessment 1	Not applicable	Any	Average of Assessment 1, Assessment 2 and Day 1 (3 tests)
Abnormal	>40% increase from Assessment 1	≤40% increase from Assessment 1	Any	Average of Assessment 1, Assessment 2, Assessment 3 and Day 1 (4 tests)
		>40% increase from Assessment 1	Not applicable, Patient excluded	Not applicable, Patient excluded

Abbreviations: ALT, alanine aminotransferase; AST, aspartate aminotransferase

New transaminase elevations in patients with baseline value within the normal range:

For new elevations in transaminases to greater than 2x ULN, repeat measurement should be performed within 48–72 hours (in cases of isolated AST elevation to the indicated threshold, with a clear non-hepatic source for AST elevation [e.g., evidence of significant concurrent creatine phosphokinase elevation), decision regarding need to proceed with DILI work-up will be based on Investigator judgement.]) of receipt of laboratory results. If elevations persist, patients should be evaluated for other causes of transaminase elevations and with tests of hepatic function. If no other cause is identified, then the patients need to be monitored closely (see below), and discontinuation of the IP should be considered.

IP should be discontinued, and the Patient followed until resolution of symptoms or signs in the following situations:

- ALT or AST >8x ULN
- ALT or AST >5x ULN for more than 2 weeks
- ALT or AST >3x ULN and (TB [in patients with Gilbert's syndrome, Direct bilirubin >2x ULN] >2x ULN or INR >1.50 [patients on anti-coagulation therapy must be assessed individually, as INR criterion will not apply])
- ALT or AST >3x ULN with the appearance of fatigue, nausea, vomiting, right upper quadrant pain or tenderness, fever, rash, jaundice (not attributable to Gilbert's syndrome), and/or eosinophilia (>5.0%)

New transaminase elevations in patients with baseline ALT or AST >ULN

For new elevations in transaminases to greater than 2x baseline value or total bilirubin >1.5x ULN, repeat measurement should be performed within 48–72 hours (in patients with Gilbert's syndrome, Direct bilirubin >2x ULN) of receipt of laboratory results. If elevations

persist, patients should be evaluated for other causes of transaminase elevations and with tests of hepatic function. If no other cause is identified, then the patients need to be monitored closely (see below), and discontinuation of the IP should be considered.

IP should be discontinued, and the Patient followed until resolution of symptoms or signs in the following situations:

Baseline Value of ALT/AST	**Criteria to Discontinue IP**
<2x ULN	if ALT or AST increases to >5x baseline value
≥2x ULN but <5x ULN if ALT or AST increases to >3x baseline value	
≥5x ULN if ALT or AST increases to >2x baseline value	
Other	if ALT or AST increase to >2x baseline value AND the increase is accompanied by a concomitant total bilirubin increase to >2x ULN OR the INR concomitantly increases by >0.2
	if ALT or AST increase to >2x baseline value in the presence of signs and symptom(s) such as fatigue, nausea, vomiting, right upper quadrant pain or tenderness, fever, rash, jaundice (not attributable to Gilbert's syndrome) and/or eosinophil (>5%)

Abbreviations: ALT, alanine aminotransferase; AST, aspartate aminotransferase; INR, normalized ratio; ULN, upper limit of normal

Close Monitoring for Suspected DILI:

- Repeating liver enzymes, serum bilirubin, hematology panel (for eosinophil count), and INR tests two or three times weekly. Frequency of repeat testing can decrease to once a week or less if abnormalities stabilize or the IP has been discontinued and the patient is asymptomatic
- Obtaining a more detailed history of symptoms and prior or concurrent diseases
- Obtaining a history of concomitant drug use (including nonprescription medications and herbal and dietary supplement preparations), alcohol use, recreational drug use, and special diets
- Ruling out acute viral hepatitis types A, B, C, D, and E; autoimmune or alcoholic hepatitis; hypoxic/ischemic hepatopathy; and biliary tract disease
- Obtaining a history of exposure to environmental chemical agents
- Obtaining additional tests to evaluate liver function, as appropriate (e.g., INR, direct bilirubin)
- Considering gastroenterology or hepatology consultations

Note: If a visit to the clinic is not feasible, laboratory testing can be performed by home health and sent to the central laboratory, or locally and the results should be promptly communicated to the Investigator site.

Monitoring and Study Continuation of patients with NASH Fibrosis Stage F1 or F4

The initial protocol allowed patients to be included based on the biopsy read by one of the 2 expert pathologists. Version 3 Amendment #2 (March 11, 2022) changed the biopsy reading

methodology to a central panel of 3 independent pathologists. This change in methodology resulted in a change in fibrosis stage at baseline for some patients (from F2 or F3 to either F1 or F4). These patients and patients evaluated as F4 during the study will be managed as follows:

1. Patients with baseline fibrosis stage F1 as determined by a consensus of 3 central pathologists may continue all phases of the study and will be analyzed separately as an exploratory population
2. Patients with baseline fibrosis stage F4 (cirrhotic) as determined by a consensus panel of 3 central pathologists (as described above) will participate in all phases of the study as an exploratory population and will be analyzed separately provided:
    a. Their liver disease is considered well compensated as assessed by Child-Pugh Class A criteria, and
    b. There is no evidence of hepatic decompensation (i.e., hepatic encephalopathy, ascites, or bleeding varices) as assessed by the Principal Investigator according to usual standard of care, and
    c. There is no evidence of hepatocellular carcinoma as assessed by local standard of care (e.g., ultrasound, computer tomography [CT] scan, or MRI imaging methods and/or central alpha feto-protein [AFP] measurement). Central AFP measurement will be performed at every scheduled visit and may be done locally if applicable
    d. Their MELD Na+ score is ≤ 12. The MELD Na+ score can be calculated by the Investigator, if applicable
3. Patients who complete the Main Study and have Week 24 biopsy results evaluated as F4 (cirrhotic) will complete all remaining study periods, provided they continue to meet the criteria in 2a–d above
4. Consistent with these requirements, patients who are F4 (cirrhotic) and have evidence of decompensation at any time during the study will be discontinued per discontinuation criteria above

Pregnancy

A female patient must permanently discontinue IP if she becomes pregnant. If a male patient's partner becomes pregnant, the male patient must agree to use condoms with spermicide to prevent potential fetal exposure. See the SoA for data to be collected at the time of IP discontinuation (ET visit).

Sample Size Calculation

The sample size was planned to be approximately 184 patients, based on the assumption that 15% of patients receiving placebo would have NASH resolution without worsening of fibrosis and 20% would have improvement of fibrosis of at least one stage without worsening of NASH, as reported in previous studies.[3-5] The treatment effect of pegozafermin was expected to be 30% for both histological primary end points. Therefore, response rates with pegozafermin were assumed to be 45% for NASH resolution and 50% for fibrosis improvement. The dropout rate was assumed to be 15%. Under these assumptions, a sample size of 64 patients for the pegozafermin 30 mg once weekly group and the pooled placebo groups would provide 94% power to detect treatment differences in NASH resolution and 92% power in fibrosis improvement at a two-sided significance level of 0.05. A sample size of 40 patients for the pegozafermin 44 mg once every 2 weeks group would

provide 87% power to detect treatment differences in NASH resolution and 83% in fibrosis improvement when compared with the pooled placebo group.

Multiple Imputation Strategy and Cochran–Mantel–Haenszel Method

Standard multiple imputation strategies for handling missing data were employed in this study. Missing outcomes were imputed 100 times via a logistic regression model with selected baseline covariates. For each individual completed dataset, a stratified Cochran–Mantel–Haenszel method was used to compare the differences in proportions of patients who met histological response criteria at week 24 between each pegozafermin group and placebo. Results from the individual completed datasets were then combined using Rubin's rule to produce a single inferential result.

In the main analysis, missing outcomes for efficacy end points were imputed under the assumption of missing at random (MAR). The imputation strategies accounted for the relevant intercurrent events (ICEs), namely: 1. discontinuation of treatment due to an adverse event and 2. all other events (e.g, protocol deviation).

The missing outcomes for all patients were imputed assuming an imputation model informed by observed outcomes from similar patients. The imputation model was based on a logistic regression model and included the following covariates: treatment arm, stratification factors, baseline NAS score, sex and age. The final inferences were performed based on the multiply imputed datasets using Rubin's combination rules.

	Pooled placebo (N=61)	**Pegozafermin 15 mg QW (N=14)**	**Pegozafermin 30 mg QW (N=66)**	**Pegozafermin 44 mg Q2W (N=51)**
Number of patients with ICE	5	0	12	5
Type 2	1	0	6	1
Type 3	4	0	6	4
Number of patients without ICE	56	14	54	46
Number of patients with missing outcomes not due to ICE	2	0	1	3

Additional analyses were performed to assess the robustness of the conclusions (i.e. their sensitivity to the MAR assumption). This included standard sensitivity analyses introducing missing-not-at-random assumptions. For example, a 'control-based' hypothetical strategy was utilized for the first ICE. This strategy assumed that patients with this ICE would have switched to placebo starting after the ICE and the missing outcomes were imputed using the placebo arm alone. For the second ICE, a hypothetical strategy that assumes that patients would have continued their assigned treatment after the ICE was applied. The missing outcomes were imputed using the same imputation model as above but fitted for treated patients without the first ICE only.

Mixed Model Repeated Measures Analysis for Continuous End Points

The model included treatment group, week and treatment-by-week interactions as the main effects and baseline measurement and stratifications (type 2 diabetes status and fibrosis stage) as covariates. The observed means of the continuous covariates were used when computing the least squares (LS) means. For the two categorical variables, type 2 diabetes status (yes and no) and fibrosis stage (F2 and F3), equal coefficients (i.e., 0.5) were assumed for each category when calculating the LS means. The following table lists the observed means of the baseline covariates.

Baseline variable	Observed baseline mean*
Hepatic fat fraction by magnetic resonance imaging – proton density fat fraction (MRI-PDFF)	16.53%
Alanine aminotransferase (ALT)	54.87 U/L
N-terminal type III collagen propeptide (Pro-C3)	52.35 ng/mL
Adiponectin	4.94 µg/mL
Serum triglycerides	171.64 mg/dL
High density lipoprotein cholesterol (HDL-C)	45.45 mg/dL
Non-HDL-C	128.88 mg/dL
Low density lipoprotein-cholesterol (LDL-C)	95.33 mg/dL
Glycated hemoglobin (HbA1c)	6.64%

*Based on the patients included in the model.

Supplementary Results

Adverse Events Reported After Data Cut

The study database remains open during the extension study, allowing investigators to report additional adverse events for the main study period. The date of data cut for the manuscript was February 14, 2023. As of April 24, 2023, in addition to the data shown in Table 3, one additional case of COVID-19 was reported in the placebo group and one additional case of vomiting was reported in the pegozafermin 30 mg once weekly group.

Supplementary Figures

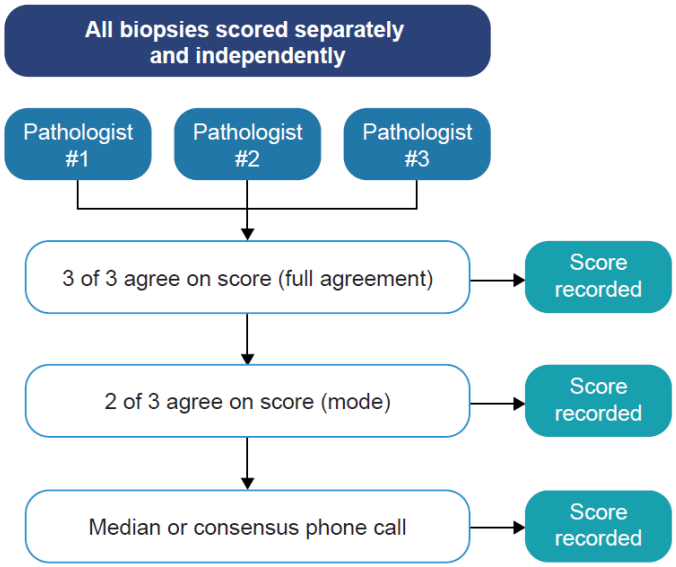

Figure S1. Consensus Process for Biopsy Scoring. Proportions of scores based on full agreement, mode, median, and consensus call are presented in Table S3.

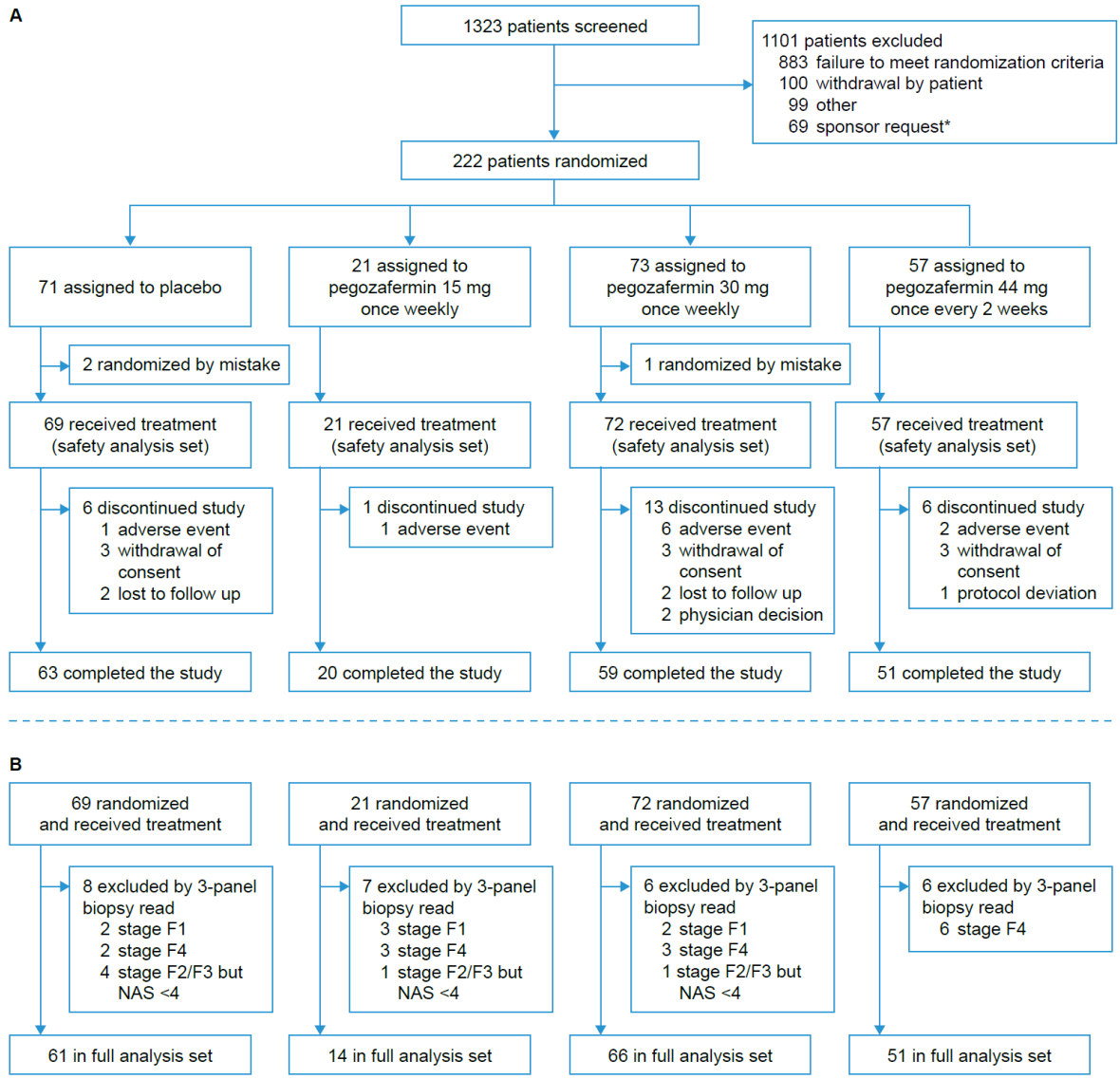

Figure S2. Patient Flow (A) and Patient Flow From Safety Analysis Set (Randomized and Received Treatment) to Full Analysis Set (F2/F3 Fibrosis and NAS ≥4) (B).
* Sponsor request was related to closure of screening. The patients who discontinued from the study discontinued study drug for the same reasons. No other patients discontinued treatment. NAS, Nonalcoholic fatty liver disease Activity Score.

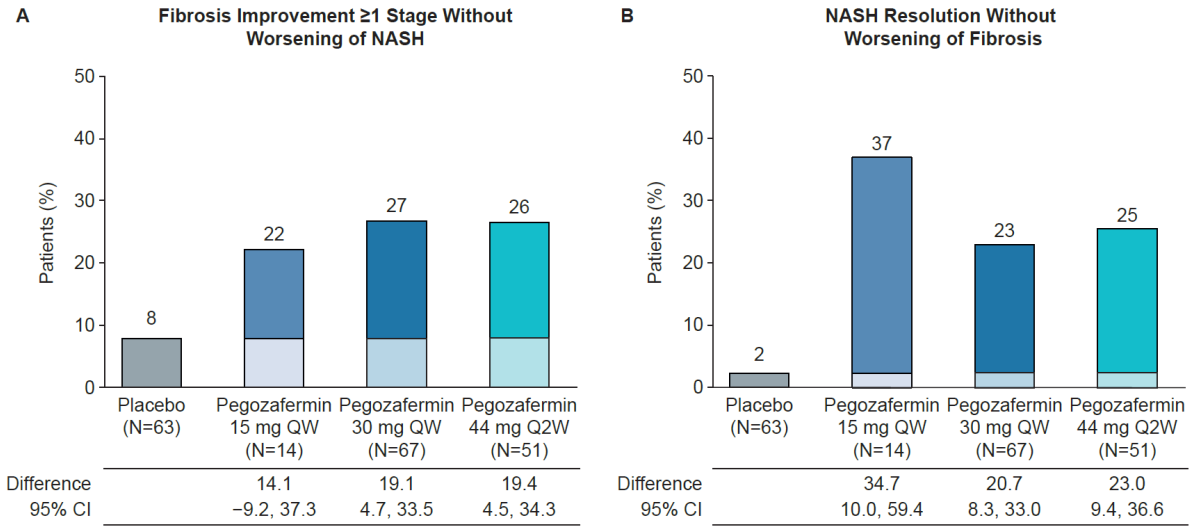

Figure S3. Primary End Points at Week 24 (Full Analysis Set Plus 3 Non-Treated Patients with F2/F3 Fibrosis; N=195). The lighter shading in each bar represents the level of response in the placebo group. Data analyzed using a Cochran–Mantel–Haenszel method with adjustment for baseline stratification factors (type 2 diabetes status and fibrosis stage). Missing outcome data (N=31) were imputed using multiple imputation via logistic regression with all collected outcomes. The full analysis set included all enrolled patients with confirmed fibrosis stage F2 or F3 and NAS ≥4 at baseline per independent review by a three-pathologist panel who were randomized to treatment and received at least one dose of study drug. The widths of the confidence intervals have not been adjusted for multiplicity. Thus, the confidence intervals should not be used to reject or not reject treatment effects. NAS, Nonalcoholic fatty liver disease Activity Score; NASH, nonalcoholic steatohepatitis; Q2W, every 2 weeks; QW, once weekly.

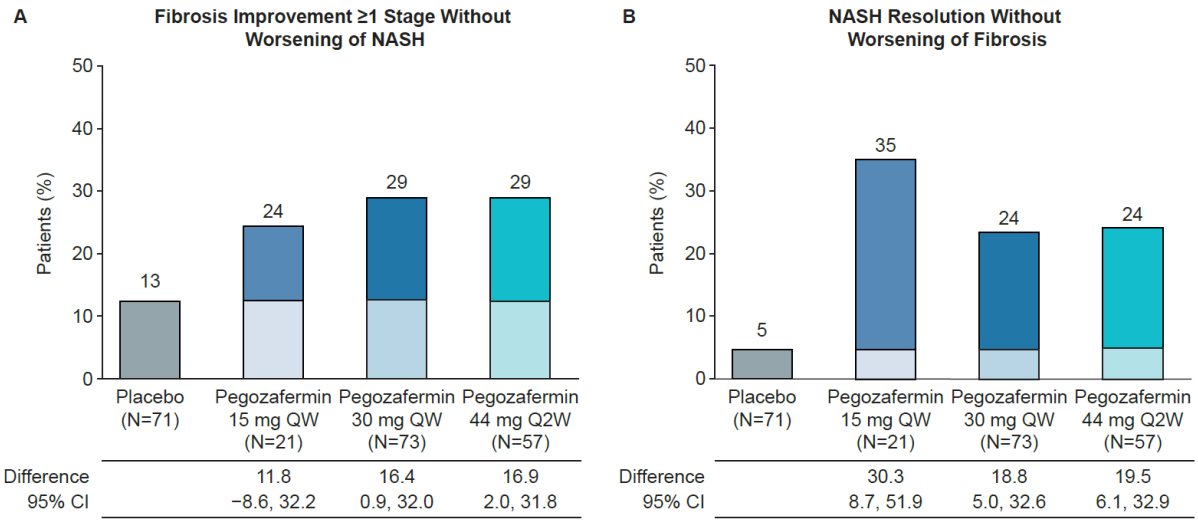

Figure S4. Primary End Points at Week 24 (Randomized Analysis Set; N=222). The lighter shading in each bar represents the level of response in the placebo group. Data analyzed using a Cochran–Mantel–Haenszel method with adjustment for baseline stratification factors (type 2 diabetes status and fibrosis stage). Missing outcome data (N=58) were imputed using multiple imputation via logistic regression with all collected outcomes. The widths of the confidence intervals have not been adjusted for multiplicity. Thus, the confidence intervals should not be used to reject or not reject treatment effects. NASH, nonalcoholic steatohepatitis; Q2W, every 2 weeks; QW, once weekly.

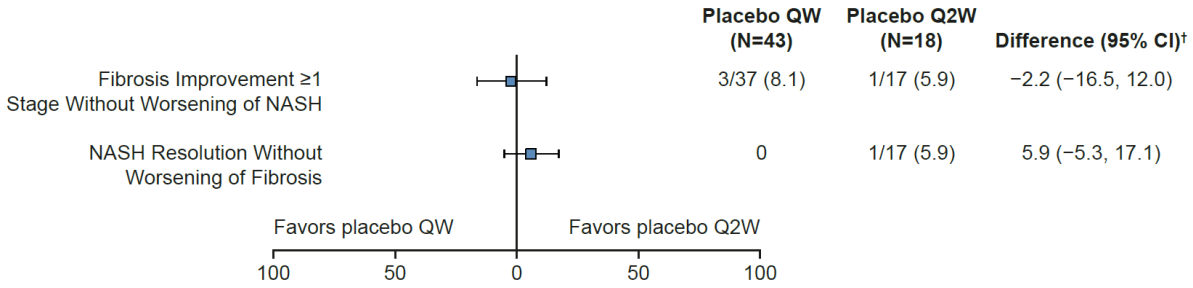

Figure S5. Differences in Proportions of Patients Achieving Primary End Points in the Placebo Groups* (Full Analysis Set; Post Hoc Analysis). * Based on observed data. † Placebo QW is the reference group. Placebo groups were pooled for all analyses in the absence of a clinical basis to expect a difference in response; this analysis was performed to confirm a lack of difference between the two groups. The full analysis set included all enrolled patients with confirmed fibrosis stage F2 or F3 and NAS ≥4 at baseline per independent review by a three-pathologist panel who were randomized to treatment and received at least one dose of study drug. NAS, Nonalcoholic fatty liver disease Activity Score; NASH, nonalcoholic steatohepatitis; Q2W, every 2 weeks; QW, once weekly.

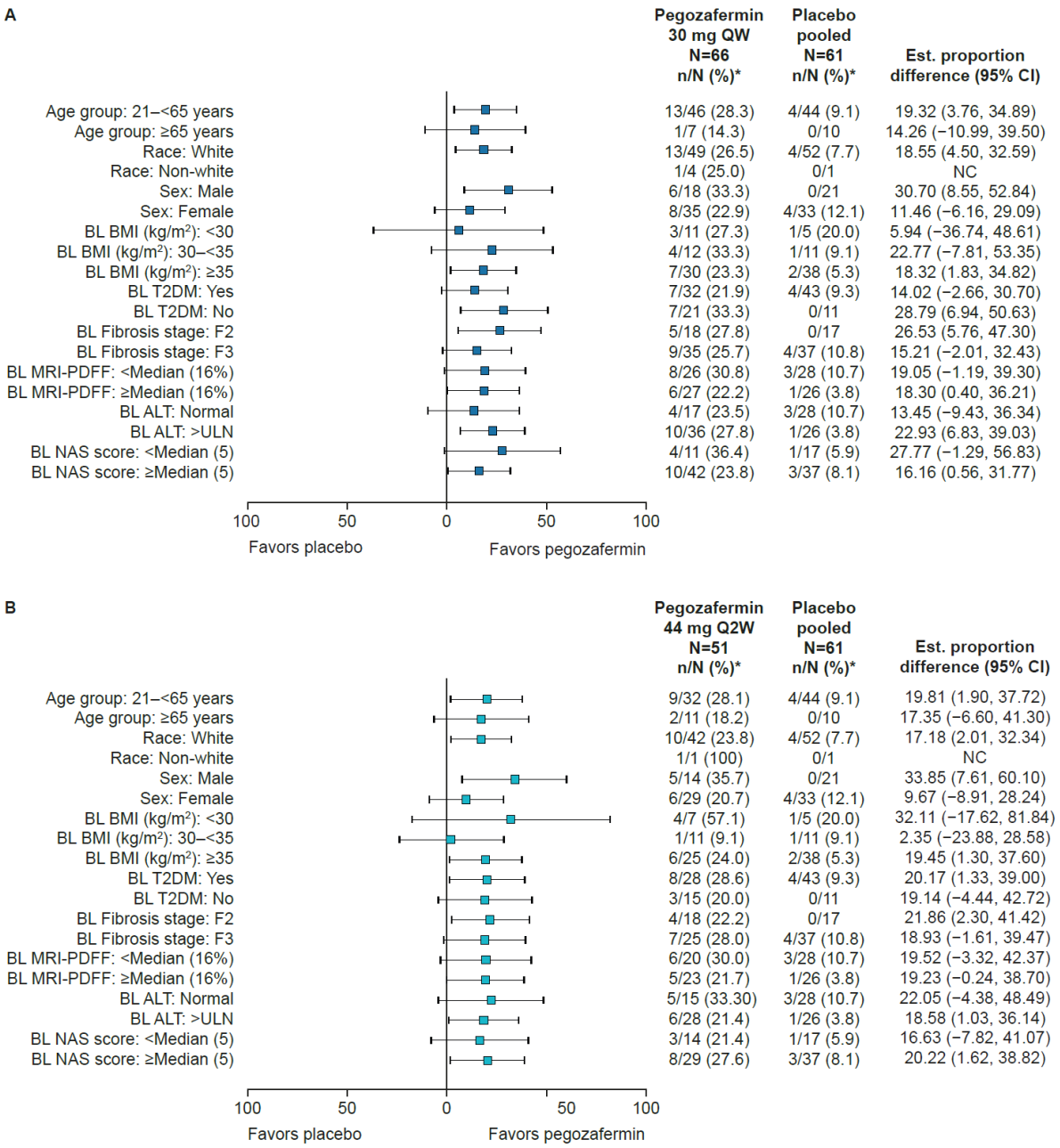

Figure S6. Differences in Proportions of Patients Achieving Fibrosis Improvement ≥1 Stage Without Worsening of NASH at Week 24 by Prespecified Subgroups. (Full Analysis Set). Panel A shows data for the 30 mg QW dose group and panel B shows data for the 44 mg Q2W dose group. The full analysis set included all enrolled patients with confirmed fibrosis stage F2 or F3 and NAS ≥4 at baseline per independent review by a three-pathologist panel who were randomized to treatment and received at least one dose of study drug. The widths of the confidence intervals have not been adjusted for multiplicity. Thus, the confidence intervals should not be used to reject or not reject treatment effects. ALT, alanine aminotransferase; BL, baseline; BMI, body mass index; MRI-PDFF, magnetic resonance imaging proton density fat fraction; NAS, Nonalcoholic fatty liver disease Activity Score; NASH, nonalcoholic steatohepatitis; Q2W, every 2 weeks; QW, once weekly; T2DM, type 2 diabetes mellitus; ULN, upper limit of normal.

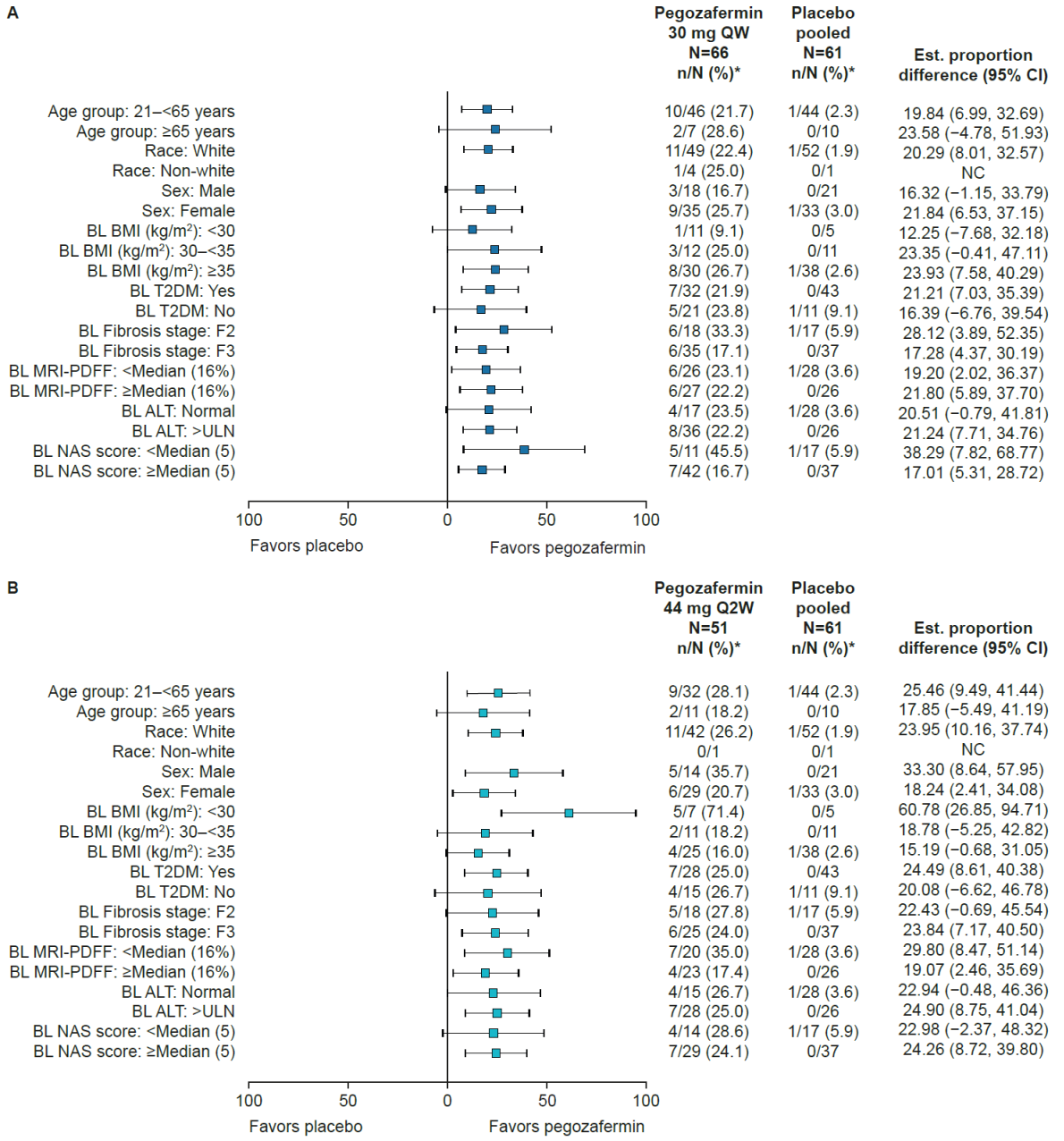

Figure S7. Differences in Proportions of Patients Achieving NASH Resolution Without Worsening of Fibrosis at Week 24 by Prespecified Subgroups. (Full Analysis Set). Panel A shows data for the 30 mg QW dose group and panel B shows data for the 44 mg Q2W dose group. The full analysis set included all enrolled patients with confirmed fibrosis stage F2 or F3 and NAS ≥4 at baseline per independent review by a three-pathologist panel who were randomized to treatment and received at least one dose of study drug. The widths of the confidence intervals have not been adjusted for multiplicity. Thus, the confidence intervals should not be used to reject or not reject treatment effects. ALT, alanine aminotransferase; BL, baseline; BMI, body mass index; MRI-PDFF, magnetic resonance imaging proton density fat fraction; NAS, Nonalcoholic fatty liver disease Activity Score; NASH, nonalcoholic steatohepatitis; Q2W, every 2 weeks; QW, once weekly; T2DM, type 2 diabetes mellitus; ULN, upper limit of normal.

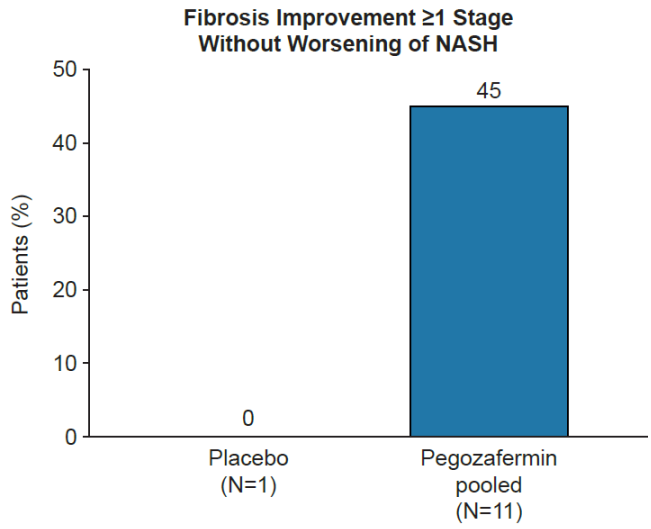

Figure S8. Fibrosis Improvement Without Worsening of NASH at Week 24 in Patients with F4 Fibrosis (Post Hoc Analysis). When the biopsy reading method was updated during the study, 14 patients were re-assessed as having F4 fibrosis at baseline by the three expert panel process (previously assessed as having F2/F3 fibrosis by a single central reader). Of these patients (who were excluded from the full analysis set), 12 had follow-up biopsies at week 24. Of these patients, 11 were treated with pegozafermin: seven had fibrosis improvement of ≥1 stage without worsening of ballooning or inflammation and five had fibrosis improvement of ≥1 stage without worsening of any component of the NAS. NAS, Nonalcoholic fatty liver disease Activity Score; NASH, nonalcoholic steatohepatitis.

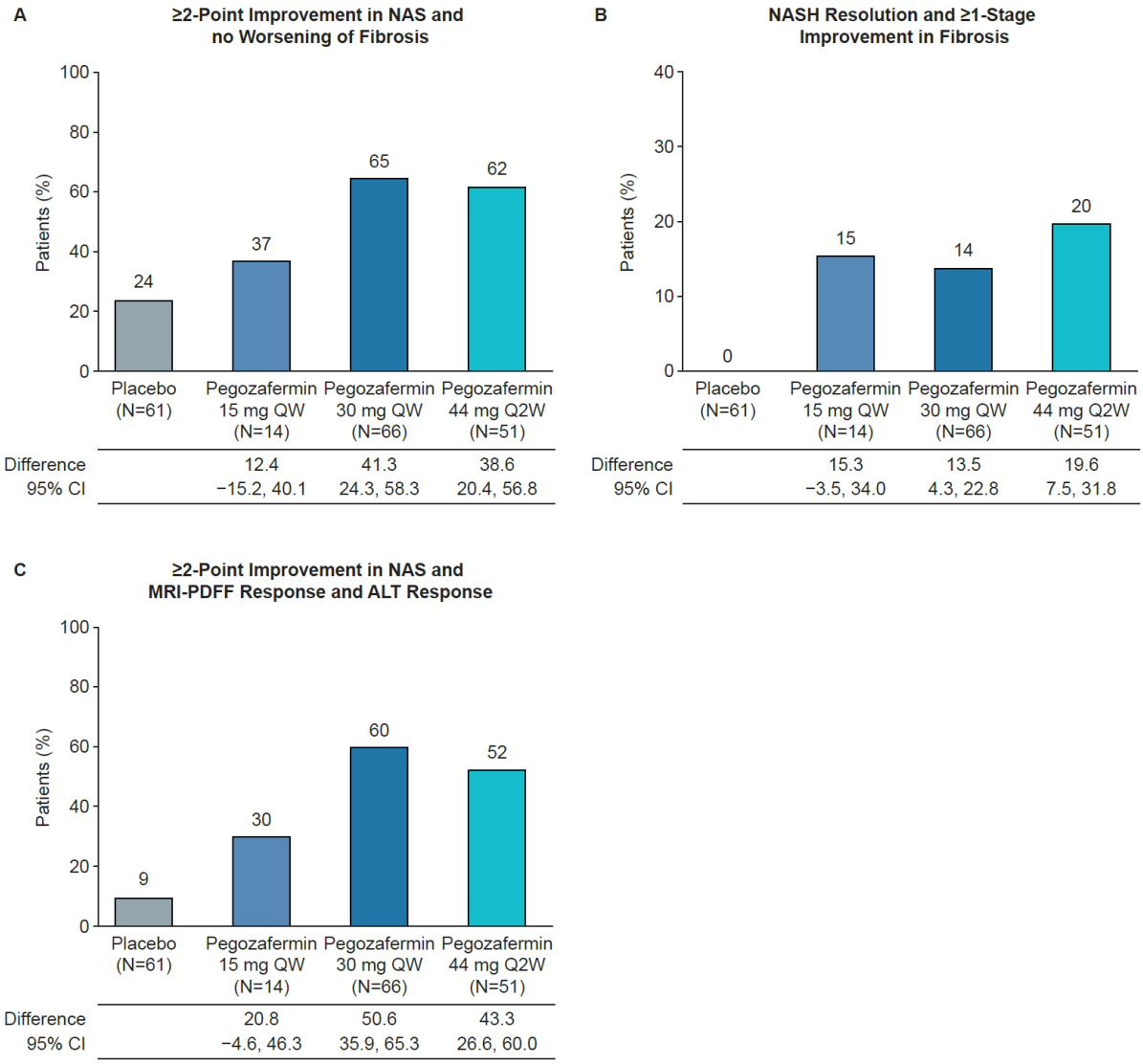

Figure S9. Key Secondary End Points at Week 24 (Full Analysis Set). MRI-PDFF response was defined as ≥30% reduction from baseline in liver fat by MRI-PDFF. ALT response was defined as ≥17 U/L or ≥30% reduction from baseline in ALT. Data analyzed using a Cochran–Mantel–Haenszel method with adjustment for baseline stratification factors (type 2 diabetes status and fibrosis stage). Missing outcome data (N=28) were imputed using multiple imputation via logistic regression with all collected outcomes. The full analysis set included all enrolled patients with confirmed fibrosis stage F2 or F3 and NAS ≥4 at baseline per independent review by a three-pathologist panel who were randomized to treatment and received at least one dose of study drug. The widths of the confidence intervals have not been adjusted for multiplicity. Thus, the confidence intervals should not be used to reject or not reject treatment effects. ALT, alanine aminotransferase; MRI-PDFF, magnetic resonance imaging proton density fat fraction; NAS, Nonalcoholic fatty liver disease Activity Score; NASH, nonalcoholic steatohepatitis; Q2W, every 2 weeks; QW, once weekly.

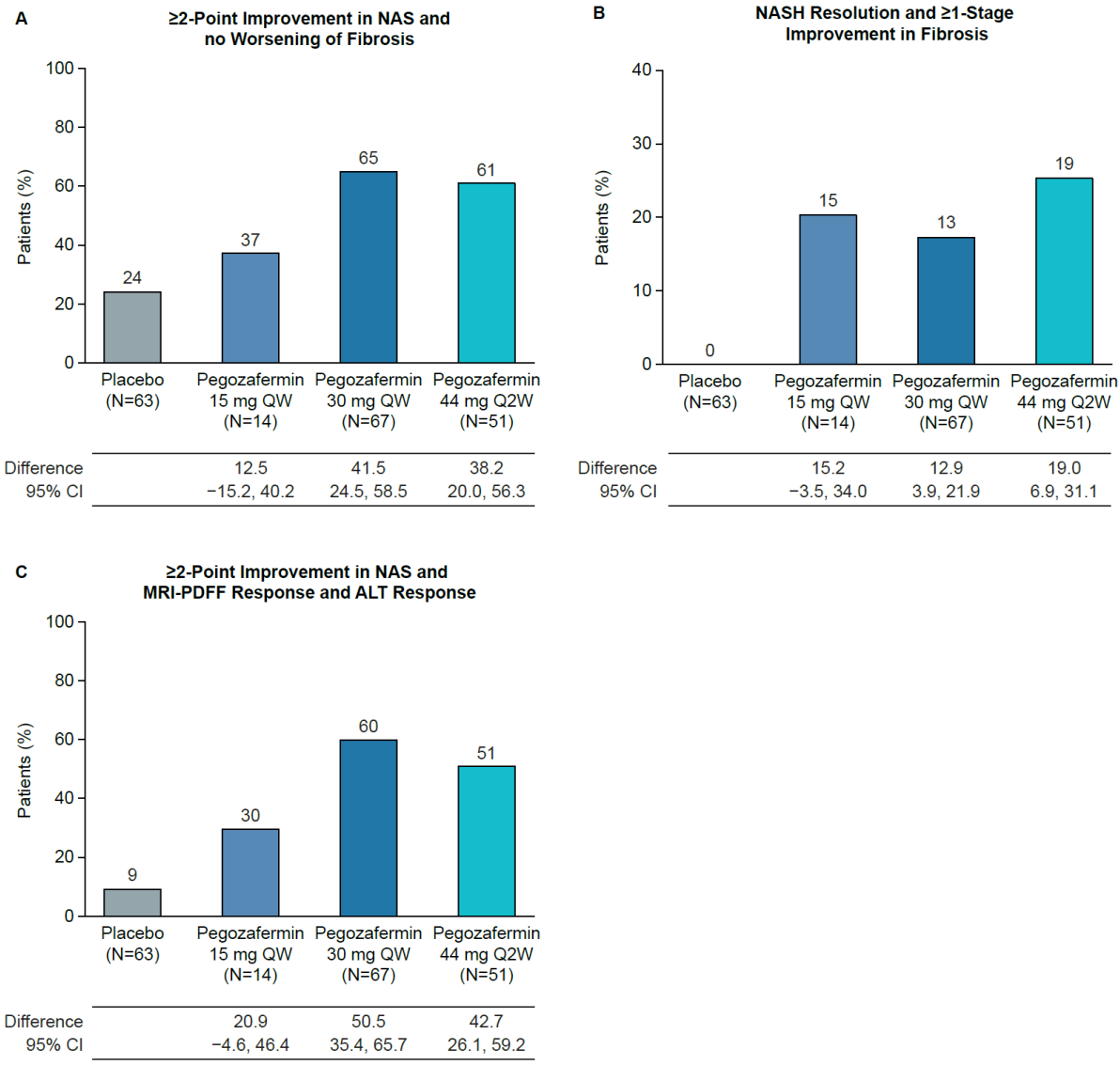

Figure S10. Key Secondary End Points at Week 24 (Full Analysis Set Plus 3 Non-Treated Patients with F2/F3 Fibrosis; N=195). MRI-PDFF response was defined as ≥30% reduction from baseline in liver fat by MRI-PDFF. ALT response was defined as ≥17 U/L or ≥30% reduction from baseline in ALT. Data analyzed using a Cochran–Mantel–Haenszel method with adjustment for baseline stratification factors (type 2 diabetes status and fibrosis stage). Missing outcome data (N=31) were imputed using multiple imputation via logistic regression with all collected outcomes. The full analysis set included all enrolled patients with confirmed fibrosis stage F2 or F3 and NAS ≥4 at baseline per independent review by a three-pathologist panel who were randomized to treatment and received at least one dose of study drug. The widths of the confidence intervals have not been adjusted for multiplicity. Thus, the confidence intervals should not be used to reject or not reject treatment effects. ALT, alanine aminotransferase; MRI-PDFF, magnetic resonance imaging proton density fat fraction; NAS, Nonalcoholic fatty liver disease Activity Score; NASH, nonalcoholic steatohepatitis; Q2W, every 2 weeks; QW, once weekly.

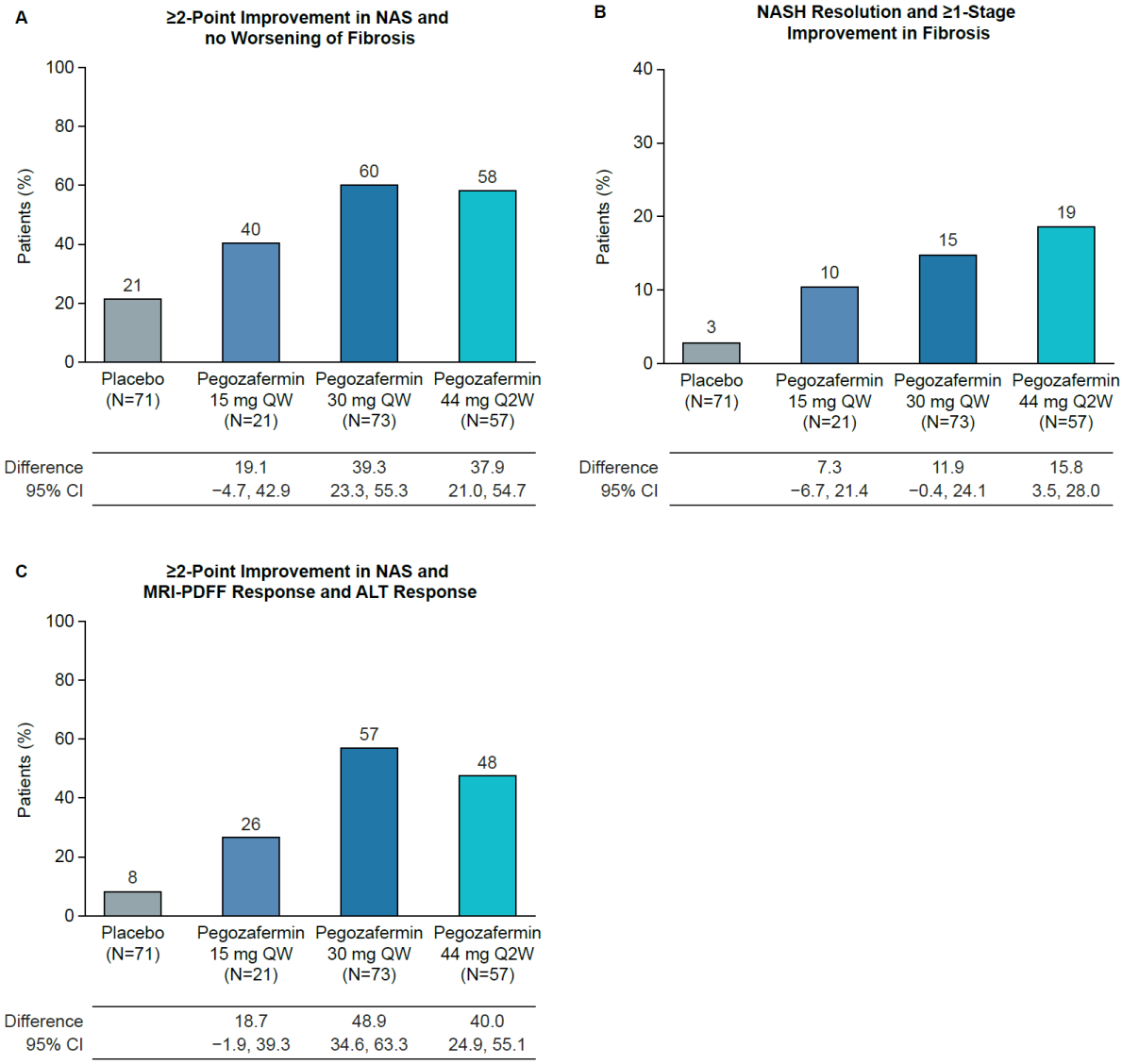

Figure S11. Key Secondary End Points at Week 24 (Randomized Analysis Set; N=222). MRI-PDFF response was defined as ≥30% reduction from baseline in liver fat by MRI-PDFF. ALT response was defined as ≥17 U/L or ≥30% reduction from baseline in ALT. Data analyzed using a Cochran–Mantel–Haenszel method with adjustment for baseline stratification factors (type 2 diabetes status and fibrosis stage). Missing outcome data (N=58) were imputed using multiple imputation via logistic regression with all collected outcomes. The widths of the confidence intervals have not been adjusted for multiplicity. Thus, the confidence intervals should not be used to reject or not reject treatment effects. ALT, alanine aminotransferase; MRI-PDFF, magnetic resonance imaging proton density fat fraction; NAS, Nonalcoholic fatty liver disease Activity Score; NASH, nonalcoholic steatohepatitis; Q2W, every 2 weeks; QW, once weekly.

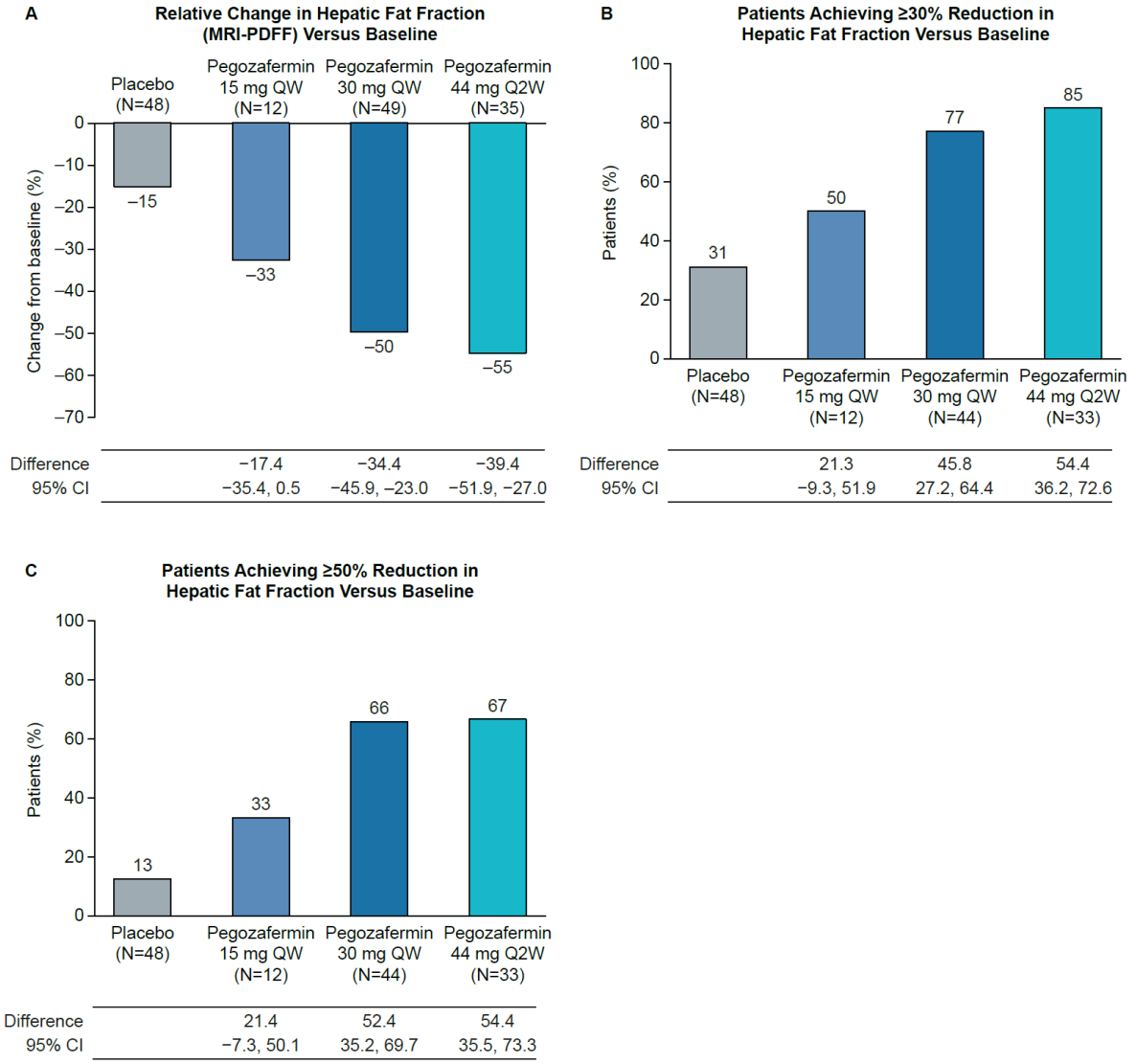

Figure S12. Liver Fat at Week 24 (MRI-PDFF Analysis Set with Baseline Values >10%; Post Hoc Analysis). Panel A shows least squares mean reductions analyzed using a mixed model with treatment group, week and treatment-by-week interactions as main effects and baseline measurements and stratifications (type 2 diabetes status and fibrosis stage) as covariates. Panels B and C shows percentage of patients analyzed using a Cochran–Mantel–Haenszel method with adjustment for baseline stratification factors. The MRI-PDFF analysis set included all patients in the full analysis set who had a baseline and at least one follow-up MRI-PDFF assessment. The widths of the confidence intervals have not been adjusted for multiplicity. Thus, the confidence intervals should not be used to reject or not reject treatment effects. MRI-PDFF, magnetic resonance imaging proton density fat fraction; Q2W, every 2 weeks; QW, once weekly.

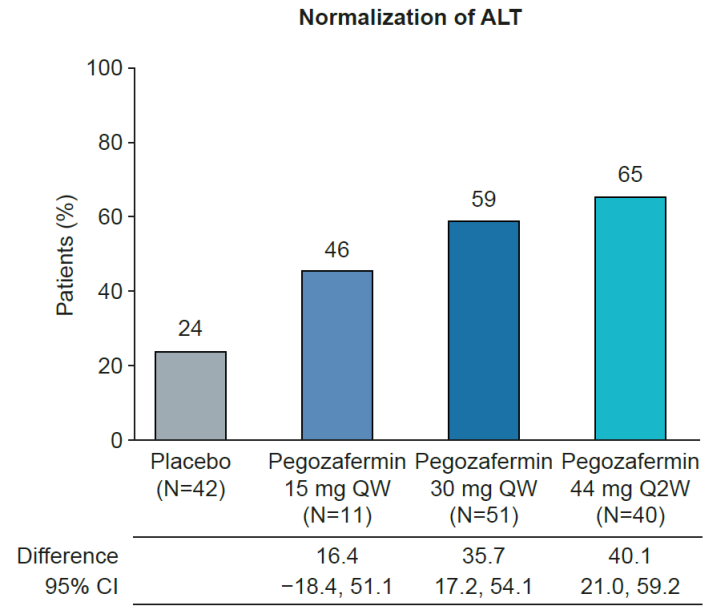

Figure S13. Proportion of Patients With Normalized Alanine Aminotransferase at Week 24 (Full Analysis Set with Baseline Values >30 U/L; Post Hoc Analysis). Normalization was defined as ≤30 U/L. Data analyzed using a Cochran–Mantel–Haenszel method with adjustment for baseline stratification factors (type 2 diabetes status and fibrosis stage). The full analysis set included all enrolled patients with confirmed fibrosis stage F2 or F3 and NAS ≥4 at baseline per independent review by a three-pathologist panel who were randomized to treatment and received at least one dose of study drug. The widths of the confidence intervals have not been adjusted for multiplicity. Thus, the confidence intervals should not be used to reject or not reject treatment effects. ALT, alanine aminotransferase; NAS, Nonalcoholic fatty liver disease Activity Score; Q2W, every 2 weeks; QW, once weekly.

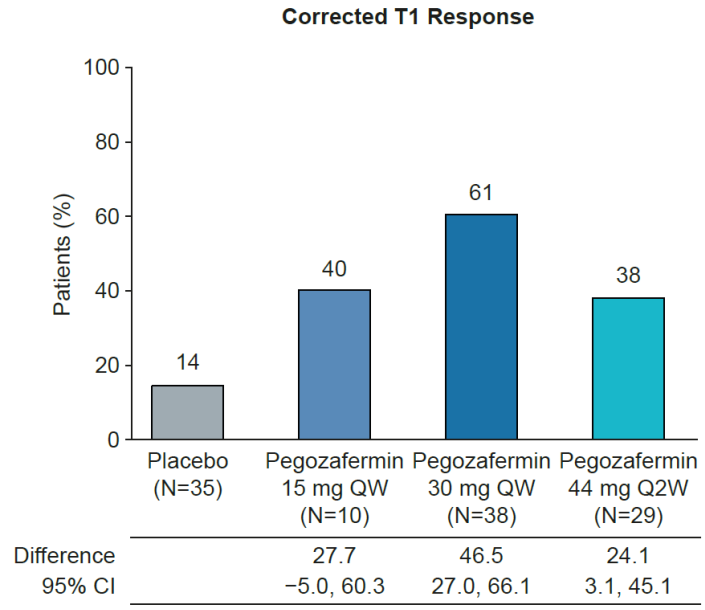

Figure S14. Proportion of Patients Achieving Corrected T1 Response at Week 24 (MRI-PDFF Analysis Set). Response was defined as ≥80 msec reduction in iron-corrected T1 imaging versus baseline; analysis was performed at sites where available. Data analyzed using a Cochran–Mantel–Haenszel method with adjustment for baseline stratification factors (type 2 diabetes status and fibrosis stage). The MRI-PDFF analysis set included all patients in the full analysis set who had a baseline and at least one follow-up MRI-PDFF assessment. The widths of the confidence intervals have not been adjusted for multiplicity. Thus, the confidence intervals should not be used to reject or not reject treatment effects. MRI-PDFF, magnetic resonance imaging proton density fat fraction; Q2W, every 2 weeks; QW, once weekly

Supplementary Tables

Table S1. Primary, Secondary and Safety End Points.

Type of end point	End point	Reported	Rationale
Primary	Proportion of patients achieving improvement of fibrosis ≥1 stage without worsening of NASH at Week 24 compared to baseline	Yes	N/A
Primary	Proportion of patients with NASH resolution without worsening of fibrosis at Week 24 compared to baseline	Yes	N/A
Key secondary	Proportion of patients with at least a 2-point improvement in NAS and no worsening of fibrosis at Week 24 compared to baseline	Yes	N/A
Key secondary	Proportion of patients with NASH resolution AND fibrosis improvement ≥1 stage at Week 24 compared to baseline	Yes	N/A
Key secondary	Proportion of patients with ≥ 2-point improvement in NAS score AND are MRI-PDFF responders AND ALT responders at Week 24 compared to baseline	Yes	N/A
Secondary	Absolute change and percentage change from baseline in: • Hepatic fat fraction by magnetic resonance imaging – proton density • fat fraction (MRI-PDFF) • Alanine aminotransferase (ALT) • N-terminal type III collagen propeptide (Pro-C3)	Yes	N/A
Secondary	Absolute and percent change from baseline in: • Adiponectin • Serum triglycerides • High density lipoprotein cholesterol (HDL-C) • Non-HDL-C • Low density lipoprotein-cholesterol (LDL-C) • Glycated hemoglobin (HbA1c)	Yes	N/A
Secondary	Trough concentration of pegozafermin	No	For internal use; not directly relevant to study interpretation
Safety	Frequency and severity of treatment emergent adverse events (TEAEs) and serious adverse events (SAEs)	Yes	N/A

Safety	Number of subjects who discontinued due to TEAEs and due to related TEAEs	Yes	N/A
Safety	Incidence and shifts of clinically significant physical examination findings, electrocardiogram (ECG) data and laboratory abnormalities; safety laboratory evaluations include hematology, blood biochemistry and urinalysis, serum, salivary, and urinary cortisol as appropriate	Yes	N/A
Safety	Change from baseline in: • Insulin-like growth factor 1 (IGF-1) • Bone biomarkers: Carboxy-terminal collagen crosslinks (CTX), N terminal propeptide of type 1 collagen (P1NP) and osteocalcin • Thyroid stimulating hormone (TSH)	Yes	N/A
Safety	Absolute and % change from baseline in lumbar spine, total hip, and femoral neck bone mineral density (BMD) as assessed by dual X-ray absorptiometry (DXA)	Yes	N/A
Safety	Incidence and characteristics of antidrug antibodies (ADA) and neutralizing antibody (NAb) after dosing (e.g., titer and binding specificity, to the FGF21 and polyethylene glycol [PEG] part of pegozafermin)	No	Data not yet available
Safety	Impact of the presence of ADAs on serum pegozafermin concentrations and clinical safety	No	Data not yet available

Table S2. Representativeness of Study Participants.

Category	Details
Disease	Nonalcoholic steatohepatitis (NASH)
Special considerations related to	
Sex and gender	Nonalcoholic fatty liver disease (NAFLD) is more common in men; however, NASH is more likely to develop in women with NAFLD than men with NAFLD (ratio 2:1)
Age	NASH is common in middle-aged individuals (45–64 years of age)
Race or ethnic group	In the USA, NASH is more common in Hispanics than Caucasians or African Americans
Geography	The highest global prevalence of NAFLD has been reported in Latin America, followed by North Africa and the Middle East, South Asia, South-East Asia, North America, East Asia, and Asia Pacific. Approximately 12–14% of middle-aged Americans have NASH
Other considerations	NASH is more common in people who have obesity or type 2 diabetes
Overall representativeness of this trial	The participants in the present trial demonstrate the expected age range and comorbidities. Approximately 60% of participants were women and 40% were Hispanic or Latino. The study was conducted in the USA and most of the patients were white, potentially limiting the generalizability of the data.

Table S3. Consensus Scoring for Biopsy Reads.*

	Fibrosis	Ballooning	Steatosis	Inflammation
Baseline (N=219)				
Consistent — no. (%)	97 (44)	90 (41)	87 (40)	97 (44)
Mode — no. (%)	114 (52)	117 (53)	126 (58)	118 (54)
Median — no. (%)	7 (3)	11 (5)	5 (2)	3 (1)
Consensus call — no. (%)	1 (1)	1 (1)	1 (1)	1 (1)
Week 24 (N=189)				
Consistent — no. (%)	94 (50)	85 (45)	84 (44)	114 (60)
Mode — no. (%)	77 (41)	103 (54)	104 (55)	69 (37)
Median — no. (%)	17 (9)	1 (1)	1 (1)	5 (3)
Consensus call — no. (%)	1 (1)	0	0	1 (1)

* If there was no consistent read among the three pathologists, the mode (agreement between two pathologists) was taken; if there was no mode, the median was used; if that was not possible, a consensus call took place.

Table S4. Relative Risks for Primary End Points (Full Analysis Set; Post-Hoc Analysis).

	Placebo (pooled) (N=61)	Pegozafermin 15 mg once weekly (N=14)	Pegozafermin 30 mg once weekly (N=66)	Pegozafermin 44 mg once every 2 weeks (N=51)
Fibrosis improvement ≥1 stage without worsening of NASH				
Relative risk versus placebo	1	2.88	3.67	4.12
95% CI		0.77, 10.84	1.24, 10.84	1.31, 12.94
NASH resolution without worsening of fibrosis				
Relative risk versus placebo	1	18.87	12.77	12.68
95% CI		3.15, 113.12	1.68, 97.12	1.90, 84.46

The full analysis set included all enrolled patients with confirmed fibrosis stage F2 or F3 and NAS ≥4 at baseline per independent review by a three-pathologist panel who were randomized to treatment and received at least one dose of study drug.
NASH, nonalcoholic steatohepatitis.

Table S5. Sensitivity Analysis for Fibrosis Improvement Without Worsening of NASH at Week 24.

	Placebo (pooled) (N=61)	Pegozafermin 15 mg once weekly (N=14)	Pegozafermin 30 mg once weekly (N=66)	Pegozafermin 44 mg once every 2 weeks (N=51)
Completer analysis				
Number of patients with biopsy data available at both baseline and week 24	54	14	53	43
Responders at week 24 — no. (%)	4 (7)	3 (21)	14 (26)	11 (26)
Difference in % versus placebo (95% CI)		14.3 (−9.0, 37.7)	19.3 (5.4, 33.1)	20.0 (5.4, 34.5)
Missing data = nonresponder				
Responders at week 24 — no. (%)	4 (7)	3 (21)	14 (21)	11 (22)
Difference in % versus placebo (95% CI)		15.1 (−8.0, 38.2)	14.8 (3.0, 26.6)	16.0 (3.2, 28.7)
Multiple imputation based on ICE type*				
Proportion of responders at week 24 — %	7.7	22.2	24.2	25.6
Difference in % versus placebo (95% CI)		14.1 (−9.1, 37.4)	16.8 (3.6, 30.1)	18.7 (3.9, 33.5)

* Patients who experienced ICE-1 had week 24 outcomes set to missing and were imputed using baseline data alone. Patients who experienced ICE-2 had week 24 outcomes set to missing and were imputed based on an imputation model informed by patients who did not experience any ICE using only data from the placebo arm. Patients who experienced ICE-3 had week 24 outcomes set to missing and were imputed based on an imputation model informed by patients who did not experience any ICE using only data from the respective randomized treatment arm.
Data analyzed using a Cochran Mantel-Haenszel method with adjustment for stratification factors (type 2 diabetes status and fibrosis stage). The widths of the confidence intervals have not been adjusted for multiplicity. Thus, the confidence intervals should not be used to reject or not reject treatment effects.
ICE, intercurrent event; NASH, nonalcoholic steatohepatitis.

Table S6. Sensitivity Analysis For NASH Resolution Without Worsening of Fibrosis at Week 24.

	Placebo (pooled) (N=61)	Pegozafermin 15 mg once weekly (N=14)	Pegozafermin 30 mg once weekly (N=66)	Pegozafermin 44 mg once every 2 weeks (N=51)
Completer analysis				
Number of patients with biopsy data available at both baseline and week 24	54	14	53	43
Responders at week 24 — no. (%)	1 (2)	5 (36)	12 (23)	11 (26)
Difference in % versus placebo (95% CI)		35.1 (10.6, 59.6)	21.4 (9.5, 33.2)	24.1 (10.6, 37.7)
Missing data = nonresponder				
Responders at week 24 — no. (%)	1 (2)	5 (36)	12 (18)	11 (22)
Difference in % versus placebo (95% CI)		34.9 (10.4, 59.4)	16.9 (7.1, 26.7)	19.7 (8.0, 31.4)
Multiple imputation based on ICE type*				
Proportion of responders at week 24 — %	2.0	36.7	20.8	24.6
Difference in % versus placebo (95% CI)		33.1 (8.2, 58.0)	18.9 (8.0, 29.7)	22.4 (9.3, 35.5)

* Patients who experienced ICE-1 had week 24 outcomes set to missing and were imputed using baseline data alone. Patients who experienced ICE-2 had week 24 outcomes set to missing and were imputed based on an imputation model informed by patients who did not experience any ICE using only data from the placebo arm. Patients who experienced ICE-3 had week 24 outcomes set to missing and were imputed based on an imputation model informed by patients who did not experience any ICE using only data from the respective randomized treatment arm.
Data analyzed using a Cochran Mantel-Haenszel method with adjustment for stratification factors (type 2 diabetes status and fibrosis stage). The widths of the confidence intervals have not been adjusted for multiplicity. Thus, the confidence intervals should not be used to reject or not reject treatment effects.
ICE, intercurrent event; NASH, nonalcoholic steatohepatitis.

Table S7. Changes From Baseline to Week 24 in Liver Parameters (Full Analysis Set).*

	Placebo (pooled) (N=61)	Pegozafermin 15 mg once weekly (N=14)	Pegozafermin 30 mg once weekly (N=66)	Pegozafermin 44 mg once every 2 weeks (N=51)
Secondary end points				
Liver fat content (MRI-PDFF)† — %				
LS mean absolute change	−1.5±0.7	−4.6±1.4	−8.1±0.7	−8.2±0.7
Difference versus placebo (95% CI)		−3.0 (−6.2, 0.1)	−6.6 (−8.5, −4.6)	−6.7 (−8.7, −4.6)
LS mean percentage change	−5.0±5.2	−27.1±10.3	−48.2±5.1	−41.9±5.6
Difference versus placebo (95% CI)		−22.0 (−44.3, 0.3)	−43.1 (−57.1, −29.1)	−36.9 (−51.6, −22.2)
Alanine aminotransferase — U/L				
LS mean absolute change	−8.8±2.5	−24.3±5.1	−26.3±2.4	−23.5±2.7
Difference versus placebo (95% CI)		−15.5 (−26.5, −4.3)	−17.5 (−24.2, −10.7)	−14.7 (−21.9, −7.6)
LS mean percentage change	−4.6±5.0	−37.7±10.1	−41.6±4.8	−31.8±5.4
Difference versus placebo (95% CI)		−33.1 (−55.1, −11.2)	−36.9 (−50.4, −23.5)	−27.2 (−41.4, −13.0)
Aspartate aminotransferase — U/L				
LS mean absolute change	−6.2±2.2	−21.4±4.5	−18.4±2.1	−19.1±2.4
Difference versus placebo (95% CI)		−15.2 (−25.0, −5.0)	−12.2 (−18.2, −6.3)	−12.9 (−19.2, −6.6)
LS mean percentage change	−4.6±4.8	−38.5±9.9	−39.3±4.7	−33.9±5.2
Difference versus placebo (95% CI)		−34.0 (−55.4, −12.5)	−34.7 (−47.8, −21.6)	−29.3 (−43.2, −15.5)
Pro-C3 — ng/mL				
LS mean absolute change	−1.2±1.8	−9.9±3.7	−13.8±1.8	−11.4±2.0
Difference versus placebo (95% CI)		−8.7 (−16.7, −0.7)	−12.6 (−17.5, −7.8)	−10.3 (−15.4, −5.1)
LS mean percentage change	6.4±4.1	−5.4±8.3	−18.1±4.0	−17.3±4.4
Difference versus placebo (95% CI)		−11.8 (−29.7, 6.1)	−24.5 (−35.5, −13.5)	−23.7 (−35.3, −12.1)

Exploratory end points				
Patients achieving ≥30% relative reduction in hepatic fat fraction† — no. (%)	16 (28)	7 (50)	43 (80)	34 (76)
Difference versus placebo (95% CI)		23.3 (−5.1, 51.7)	51.5 (35.3, 67.6)	48.4 (31.3, 65.5)
Patients achieving ≥50% relative reduction in hepatic fat fraction† — no. (%)	7 (12)	4 (29)	34 (63)	26 (58)
Difference versus placebo (95% CI)		17.1 (−8.5, 42.8)	49.7 (34.1, 65.4)	46.3 (29.4, 63.1)
Gamma-glutamyl transpeptidase — U/L				
LS mean absolute change	−0.5±4.0	−20.9±8.1	−18.2±3.9	−17.0±4.3
Difference versus placebo (95% CI)		−20.4 (−38.0, −2.9)	−17.7 (−28.5, −6.9)	−16.5 (−27.9, −5.1)
LS mean percentage change	6.7±6.0	−30.3±12.3	−27.2±5.9	−18.5±6.6
Difference versus placebo (95% CI)		−37.0 (−63.9, −10.2)	−33.9 (−50.4, −17.5)	−25.2 (−42.6, −7.8)
Fibrosis-4 index score‡				
LS mean absolute change	0.2±0.1	−0.5±0.2	−0.3±0.1	−0.4±0.1
Difference versus placebo (95% CI)		−0.5 (−0.9, −0.2)	−0.4 (−0.6, −0.2)	−0.4 (−0.6, −0.2)
Enhanced Liver Fibrosis test score§				
LS mean absolute change	0.2±0.1	−0.3±0.1	−0.3±0.1	−0.3±0.1
Difference versus placebo (95% CI)		−0.5 (−0.9, −0.2)	−0.5 (−0.7, −0.3)	−0.5 (−0.7, −0.3)
FAST score¶				
LS mean absolute change	−0.1±0.0	−0.2±0.1	−0.3±0.0	−0.3±0.0
Difference versus placebo (95% CI)		−0.2 (−0.3, −0.1)	−0.3 (−0.4, −0.2)	−0.3 (−0.4, −0.2)
LS mean percentage change	−5.6±6.7	−32.8±13.0	−56.2±6.2	−56.6±6.9
Difference versus placebo (95% CI)		−27.1 (−54.8, 0.6)	−50.6 (−67.7, −33.5)	−51.0 (−69.2, −32.7)
Liver stiffness (FibroScan VCTE)‖ — kPa				
LS mean absolute change	0.8±0.8	−1.4±1.5	−3.1±0.8	−2.4±0.9

Difference versus placebo (95% CI)		−2.2 (−5.6, 1.2)	−3.9 (−6.1, −1.7)	−3.1 (−5.4, −0.9)
Iron-corrected T1† — ms				
LS mean absolute change	−6.1±11.7	−46.7±21.3	−92.4±10.7	−69.8±12.3
Difference versus placebo (95% CI)		−40.6 (−87.8, 6.7)	−86.3 (−117.2, −55.4)	−63.6 (−96.6, −30.7)
Liver volume — L				
LS mean absolute change	−0.1±0.0	−0.1±0.1	−0.3±0.0	−0.2±0.0
Difference versus placebo (95% CI)		−0.1 (−0.2, 0.1)	−0.2 (−0.3, −0.1)	−0.2 (−0.3, −0.1)
LS mean percentage change	−2.5±1.5	−5.9±3.1	−12.5±1.5	−9.5±1.7
Difference versus placebo (95% CI)		−3.4 (−10.2, 3.3)	−10.0 (−14.1, −5.9)	−7.0 (−11.4, −2.6)
Spleen volume — L				
LS mean absolute change	0.0±0.0	−0.0±0.0	−0.0±0.0	−0.0±0.0
Difference versus placebo (95% CI)		−0.0 (−0.1, 0.0)	−0.0 (−0.1, −0.0)	−0.0 (−0.0, −0.0)
LS mean percentage change	1.3±1.7	−6.1±3.5	−9.8±1.7	−5.2±1.9
Difference versus placebo (95% CI)		−7.3 (−14.8, 0.1)	−11.1 (−15.8, −6.4)	−6.5 (−11.4, −1.5)

* Plus–minus signs are least squares (LS) means ±SE. The full analysis set included all enrolled patients with confirmed fibrosis stage F2 or F3 and NAS ≥4 at baseline per independent review by a three-pathologist panel who were randomized to treatment and received at least one dose of study drug. Data analyzed using a mixed model with treatment group, week and treatment-by-week interactions as main effects and baseline measurements and stratifications (type 2 diabetes status and fibrosis stage) as covariates. The widths of the confidence intervals have not been adjusted for multiplicity. Thus, the confidence intervals should not be used to reject or not reject treatment effects.

† MRI-PDFF analysis set: pooled placebo (N=57); pegozafermin 15 mg once weekly (N=14); pegozafermin 30 mg once weekly (N=61); pegozafermin 44 mg every 2 weeks (N=49). Data for proportions of patients achieving ≥30% or ≥50% relative reduction were analyzed using a Cochran–Mantel–Haenszel method with adjustment for baseline stratification factors (type 2 diabetes status and fibrosis stage).

‡ The Fibrosis-4 index score is calculated as = (age × AST) / (platelets x $\sqrt{}$(ALT)). A score of <1.45 indicates low probability of stage F3 or F4 fibrosis, and a score >3.25 indicates a high probability of stage F3 or F4 fibrosis.

§ The Enhanced Liver Fibrosis test score is derived from an algorithm that combines for hyaluronic acid, type III procollagen peptide, and tissue inhibitor of matrix metalloproteinase 1. A score of <7.7 indicates none to mild fibrosis, and a score of ≥11.3 indicates cirrhosis.

¶ The FAST score uses the FibroScan liver stiffness measurement and controlled attenuation parameter, combined with levels of AST to estimate risk of NASH. A score <0.35 indicate low risk of NASH, and a score ≥0.67 indicates high risk of NASH.

‖ VCTE analyzed using analysis of covariance with treatment group, baseline measurements and stratifications (type 2 diabetes status and fibrosis stage) as covariates.
ALT, alanine aminotransferase; AST, aspartate aminotransferase; FAST, FibroScan-aspartate transaminase; MRI-PDFF, magnetic resonance imaging proton density fat fraction; Pro-C3, N-terminal propeptide of type III collagen; VCTE, vibration-controlled transient elastography.

Table S8. Changes From Baseline to Week 24 in Metabolic Parameters (Full Analysis Set).*

	Placebo (pooled) (N=61)	Pegozafermin 15 mg once weekly (N=14)	Pegozafermin 30 mg once weekly (N=66)	Pegozafermin 44 mg once every 2 weeks (N=51)
Secondary end points				
Adiponectin — µg/mL				
LS mean absolute change	−0.6±0.4	1.1±0.7	1.1±0.3	1.2±0.4
Difference versus placebo (95% CI)		1.6 (0.1, 3.2)	1.7 (0.8, 2.6)	1.8 (0.8, 2.8)
LS mean percentage change	−7.2±5.9	20.6±11.9	30.0±5.6	27.7±6.1
Difference versus placebo (95% CI)		27.8 (2.4, 53.2)	37.2 (21.8, 52.5)	34.8 (18.7, 51.0)
Triglycerides† — mg/dL				
Median absolute change (Q1, Q3)	−7.5 (−29.0, 19.0)	−8.3 (−26.8, 10.3)	−40.5 (−73.0, −7.0)	−14.0 (−45.5, 7.0)
Median percentage change (Q1, Q3)	−6.4 (−17.8, 13.6)	−5.9 (−22.9, 6.4)	−26.6 (−39.7, −5.8)	−10.1 (−28.6, 3.5)
Difference versus placebo (95% CI)		−5.3 (−18.8, 9.8)	−21.7 (−30.8, −12.3)	−8.2 (−19.8, 2.7)
HDL-C† — mg/dL				
Median absolute change (Q1, Q3)	−1.5 (−4.0, 3.5)	1.0 (−1.0, 5.5)	6.0 (0.5, 13.0)	1.5 (−1.0, 7.5)
Median percentage change (Q1, Q3)	−3.9 (−9.7, 6.2)	2.8 (−1.8, 13.5)	13.4 (1.2, 29.6)	4.4 (−3.2, 19.5)
Difference versus placebo (95% CI)		6.6 (−2.6, 14.4)	16.3 (10.1, 23.0)	8.6 (2.4, 15.0)
Non-HDL-C† — mg/dL				
Median absolute change (Q1, Q3)	1.0 (−14.0, 11.5)	−8.0 (−19.8, 12.5)	−9.0 (−31.0, 3.0)	−11.5 (−23.0, 4.0)
Median percentage change (Q1, Q3)	0.7 (−9.3, 8.2)	−7.5 (−16.7, 15.1)	−7.6 (−21.6, 2.0)	−8.7 (−20.2, 3.1)
Difference versus placebo (95% CI)		−5.0 (−16.4, 9.6)	−7.5 (−14.8, −0.8)	−8.3 (−15.8, −1.1)
LDL-C† — mg/dL				
Median absolute change (Q1, Q3)	−0.3 (−12.5, 11.5)	−1.0 (−16.0, 18.0)	−2.0 (−21.5, 7.5)	−4.8 (−19.0, 2.3)
Median percentage change (Q1, Q3)	−0.2 (−14.3, 14.5)	−1.6 (−16.0, 32.4)	−3.3 (−19.2, 10.7)	−5.1 (−24.9, 3.5)

Difference versus placebo (95% CI)		4.0 (−15.9, 25.1)	−3.6 (−12.7, 5.5)	−7.4 (−17.0, 2.1)
HbA1c‡ — %				
LS mean absolute change	−0.0±0.1	−0.1±0.2	−0.3±0.1	−0.2±0.1
95% CI	−0.2, 0.2	−0.6, 0.3	−0.5, −0.1	−0.4, 0.1
HbA1c in patients ≥6.5% at baseline‡ — %				
N	31	8	32	25
LS mean absolute change	−0.0±0.2	−0.2±0.4	−0.5±0.2	−0.4±0.2
95% CI	−0.4, 0.4	−1.0, 0.5	−0.9, −0.1	−0.8, 0.1
Exploratory end points				
Body weight — kg				
LS mean absolute change	−0.7±0.6	−0.0±1.2	−1.2±0.6	0.2±0.7
Difference versus placebo (95% CI)		0.6 (−2.0, 3.3)	−0.6 (−2.2, 1.1)	0.9 (−0.9, 2.6)
LS mean percentage change	−0.7±0.6	−0.2±1.2	−1.2±0.6	0.3±0.6
Difference versus placebo (95% CI)		0.4 (−2.2, 3.0)	−0.5 (−2.2, 1.1)	1.0 (−0.7, 2.7)

* Plus–minus signs are least squares (LS) means ±SE. The full analysis set included all enrolled patients with confirmed fibrosis stage F2 or F3 and NAS ≥4 at baseline per independent review by a three-pathologist panel who were randomized to treatment and received at least one dose of study drug. Data analyzed using a mixed model with treatment group, week and treatment-by-week interactions as main effects and baseline measurements and stratifications (type 2 diabetes status and fibrosis stage) as covariates. The widths of the confidence intervals have not been adjusted for multiplicity. Thus, the confidence intervals should not be used to reject or not reject treatment effects.
† Analyzed using a van Elteren method; patients with missing week 24 values were excluded from the non-parametric analysis.
‡ 95% CI shown for HbA1c are for week 24 versus baseline.
HbA1c, glycated hemoglobin; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol.

Table S9. Serious Adverse Events (Safety Analysis Set).

Serious adverse events — no. (%)	Placebo (pooled) (N=69)	Pegozafermin 15 mg once weekly (N=21)	Pegozafermin 30 mg once weekly (N=72)	Pegozafermin 44 mg once every 2 weeks (N=57)
Patients with ≥1 serious adverse event*	3 (4)	1 (5)	3 (4)	6 (11)
Serious adverse events according to system organ class				
General disorders and administration site conditions	0	0	1 (1)	1 (2)
Hepatobiliary disorders	0	0	1 (1)	0
Neoplasms benign, malignant and unspecified (including cysts and polyps)	0	0	1 (1)	0
Cardiac disorders	1 (1)	0	0	1 (2)
Gastrointestinal disorders	0	1 (5)	0	1 (2)
Infections and infestations	0	0	0	1 (2)
Injury, poisoning and procedural complications	1 (1)	0	0	0
Musculoskeletal and connective tissue disorders	0	0	0	1 (2)
Nervous system disorders	0	0	0	2 (4)
Psychiatric disorders	0	0	0	1 (2)
Renal and urinary disorders	1 (1)	0	0	0

* All serious adverse events were considered not drug-related, with the exception of the pancreatitis case described in the main text.

Table S10. Changes From Baseline to Week 24 in Serum Albumin, Bilirubin, International Normalized Ratio and Platelets (Safety Analysis Set).*

	Placebo (pooled) (N=69)	Pegozafermin 15 mg once weekly (N=21)	Pegozafermin 30 mg once weekly (N=72)	Pegozafermin 44 mg once every 2 weeks (N=57)
Albumin — g/dL				
Baseline	4.3±0.3	4.7±0.3	4.4±0.3	4.5±0.4
Absolute change	−0.0±0.3	−0.4±0.3	−0.1±0.3	−0.2±0.3
Percentage change	−0.5±6.6	−9.0±5.3	−3.0±6.2	−4.2±6.8
Bilirubin — mg/dL				
Baseline	0.6±0.2	0.6±0.4	0.5±0.2	0.6±0.2
Absolute change	0.1±0.2	0.1±0.1	−0.0±0.2	0.0±0.2
Percentage change	14.0±38.0	21.5±30.5	6.5±32.4	8.5±35.1
International Normalized Ratio				
Baseline	1.1±0.1	1.1±0.1	1.1±0.1	1.1±0.3
Absolute change	0.0±0.1	−0.0±0.1	−0.0±0.1	−0.1±0.3
Percentage change	0.9±10.1	−1.3±7.5	−1.9±10.7	−2.9±12.1
Platelets — $10^3/\mu L$				
Baseline	236.5±63.0	239.7±62.5	250.0±66.9	247.3±82.4
Absolute change	−3.8±30.5	−12.6±26.9	−9.7±29.1	−14.4±44.3
Percentage change	−2.0±12.5	−4.3±13.1	−2.8±11.0	−3.7±16.1

* Plus–minus signs are means ±SD.

Table S11. Changes From Baseline to Week 24 in Bone Mineral Density (Safety Analysis Set).*

	Placebo (pooled) (N=69)	Pegozafermin 15 mg once weekly (N=21)	Pegozafermin 30 mg once weekly (N=72)	Pegozafermin 44 mg once every 2 weeks (N=57)
Femoral neck — g/cm^2				
Absolute change	−0.0±0.0	−0.0±0.1	−0.0±0.1	0.0±0.0
Percentage change	−0.5±3.8	−2.3±7.5	−0.3±6.2	1.1±4.7
L1–L4 — g/cm^2				
Absolute change	0.0±0.0	0.0±0.0	0.0±0.1	−0.0±0.1
Percentage change	0.7±3.8	1.4±4.1	0.1±5.2	−0.2±4.1
Hip — g/cm^2				
Absolute change	−0.0±0.0	−0.0±0.0	−0.0±0.0	−0.0±0.0
Percentage change	−0.4±3.6	−0.4±3.4	−1.4±3.3	−0.6±3.1

* Plus–minus signs are means ±SD. Bone mineral density was assessed using dual X-ray absorptiometry.

Supplementary References

1. Sanyal AJ, Loomba R, Anstee QM, et al. Minimizing variability and increasing concordance for NASH histological scoring in NASH clinical trials. Hepatology 2021;74:968A.

2. Sanyal AJ, Loomba R, Anstee QM, et al. Topline results from a new analysis of the REGENERATE trial of obeticholic acid for the treatment of nonalcoholic steatohepatitis. AASLD The Liver Meeting 2022:5008 (Abstract).

3. Drenth JPH, Schattenberg JM. The nonalcoholic steatohepatitis (NASH) drug development graveyard: established hurdles and planning for future success. Expert Opin Investig Drugs 2020;29:1365-75.

4. Han MAT, Altayar O, Hamdeh S, et al. Rates of and factors associated with placebo response in trials of pharmacotherapies for nonalcoholic steatohepatitis: systematic review and meta-analysis. Clin Gastroenterol Hepatol 2019;17:616-29.e26.

5. Nikoolenejad A, Brouwers B, Hartman ML. Predictive model for estimating placebo response of NASH resolution and fibrosis improvement in NASH clinical trials. Hepatology 2020;72:1044A.