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Supplementary appendix

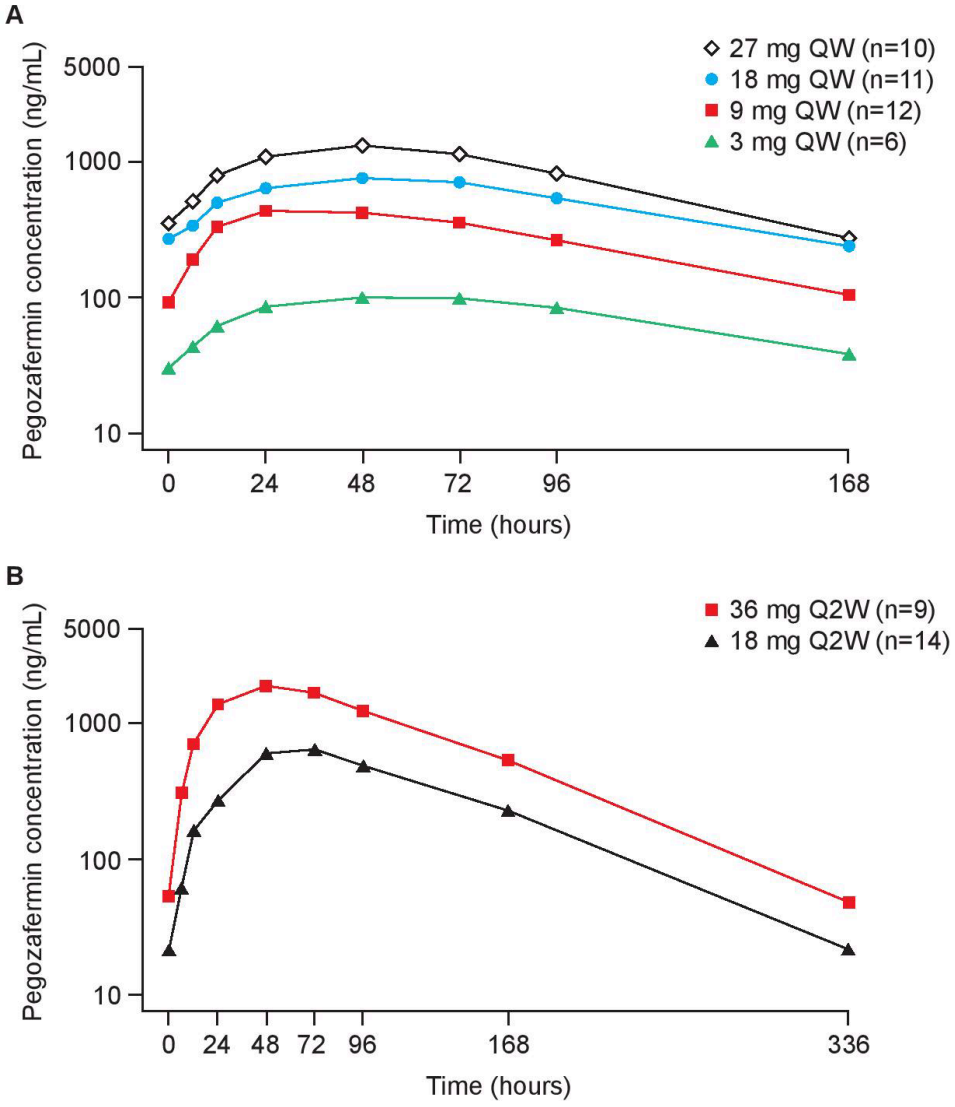
This appendix formed part of the original submission and has been peer reviewed. We post it as supplied by the authors.

Supplement to: Loomba R, Lawitz EJ, Frias JP, et al. Safety, pharmacokinetics, and pharmacodynamics of pegozafermin in patients with non-alcoholic steatohepatitis: a randomised, double-blind, placebo-controlled, phase 1b/2a multiple-ascending-dose study. *Lancet Gastroenterol Hepatol* 2022; published online Dec 12. https://doi.org/10.1016/S2468-1253(22)00347-8.

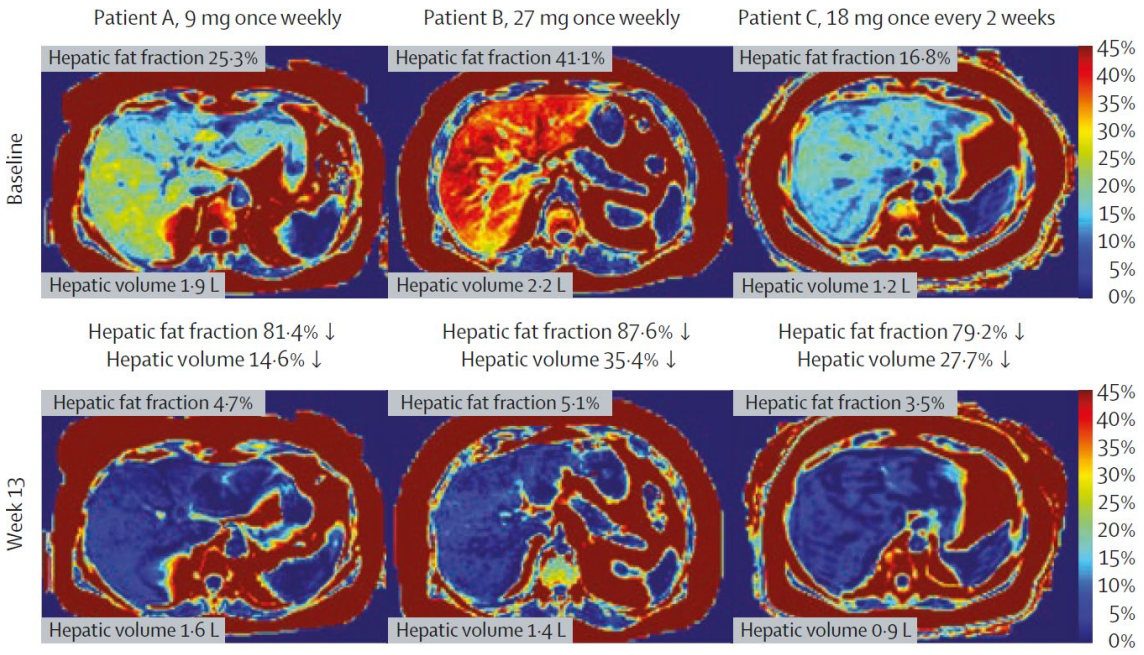
SUPPLEMENTARY MATERIALS

CONTENTS

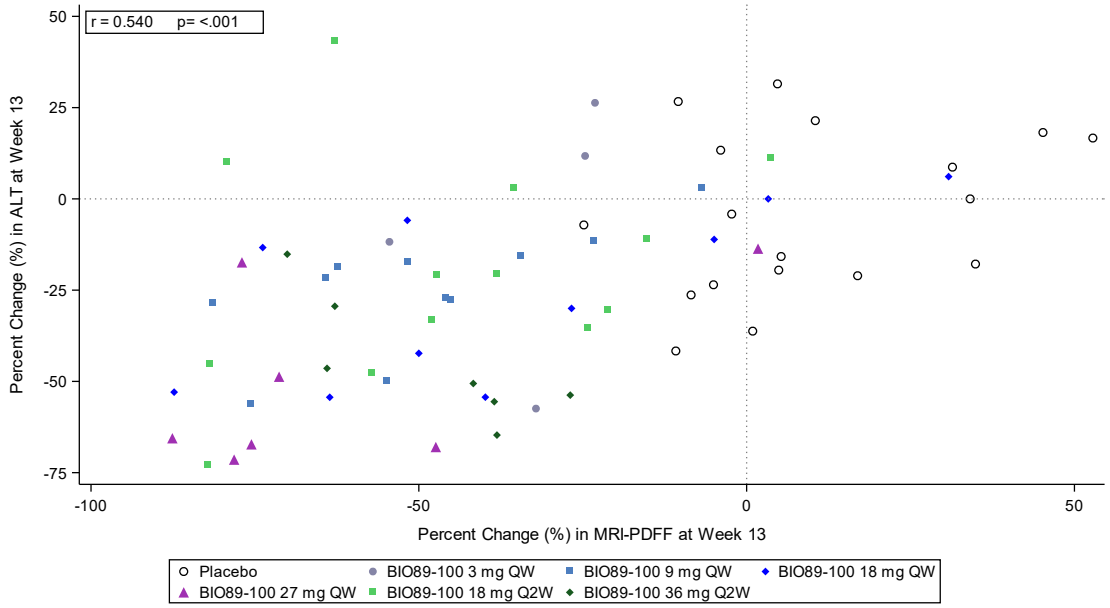
Supplementary figure 1: **Arithmetic mean pegozafermin serum concentration–time profiles across dose regimens.** Shown are steady-state values on day 29 for the QW (A) and Q2W (B) regimens. Note: day 57 concentrations (ie, 336 hours after the day 43 dose rather than the day 29 dose) were used as equivalent trough values for the Q2W regimen (B). Q2W=once every 2 weeks. QW=once per week.



Supplementary figure 2: **Changes in hepatic fat fraction and hepatic volume in three participants after 12 weeks of treatment with pegozafermin**



Supplementary figure 3: **Correlation of percentage change from baseline in ALT levels at week 13 with percentage change in MRI-PDFF at week 13.** ALT=alanine aminotransferase. BIO89-100=pegozafermin. MRI-PDFF=magnetic resonance imaging proton-density fat fraction. Q2W=once every 2 weeks. QW=once every week.



Supplementary table 1: **Responder analysis of hepatic steatosis as assessed by MRI-PDFF (Pharmacodynamics–MRI population) and ALT concentrations (Pharmacodynamics population)**

		Pegozafermin						
	Placebo (n=18)	**3 mg QW (n=5)**	**9 mg QW (n=11)**	**18 mg QW (n=10)**	**27 mg QW (n=7)**	**18 mg Q2W (n=13)**	**36 mg Q2W (n=8)**	**Pooled (n=54)**
≥30% relative reduction from baseline in MRI-PDFF hepatic fat fraction at week 13								
n (%)	0 (0·0)	3 (60·0)	9 (81·8)	6 (60·0)	6 (85·7)	9 (69·2)	7 (87·5)	40 (74·1)
95% CI[a]	··	(22·6, 88·5)	(51·8, 95·0)	(30·9, 83·5)	(47·9, 97·5)	(42·0, 87·5)	(52·2, 97·8)	(54·8, 83·9)
p value[b]	··	0·0056	<0·0001	0·0006	<0·0001	<0·0001	<0·0001	<0·0001
≥50% relative reduction from baseline in MRI-PDFF hepatic fat fraction at week 13								
n (%)	0 (0·0)	1 (20·0)	6 (54·5)	5 (50·0)	5 (71·4)	5 (38·5)	4 (50·0)	26 (48·1)
95% CI[a]	··	(−1·10, 63·2)	(27·7, 79·0)	(23·3, 76·7)	(35·3, 92·0)	(16·7, 64·8)	(21·1, 78·9)	(28·8, 61·2)
p value[b]	··	0·22	0·0010	0·0026	0·0004	0·0076	0·0047	0·0001
MRI-PDFF hepatic fat fraction <5% (normalised) at week 13								
n (%)	0 (0·0)	0 (0·0)	2 (18·2)	2 (20·0)	3 (42·9)	2 (15·4)	2 (25·0)	11 (20·4)
95% CI[a]	··	··	(−19·8, 48·2)	(−46·0, 51·5)	(15·5, 75·4)	(−4.3, 42·7)	(3·73, 59·7)	(1·69, 33·0)
p value[b]	··	··	0·1355	0·1190	0·0152	0·1677	0·0862	0·0548
	Placebo (n=19)	**3 mg QW (n=6)**	**9 mg QW (n=12)**	**18 mg QW (n=11)**	**27 mg QW (n=10)**	**18 mg Q2W (n=14)**	**36 mg Q2W (n=9)**	**Pooled (n=62)**
≥30% relative reduction from baseline in ALT concentration at week 13								
n/n (%)	2/18 (11·1)	1/4 (25·0)	2/11 (18·2)	5/10 (50·0)	5/7 (71·4)	6/13 (46·2)	5/7 (71·4)	24/52 (46·2)
95% CI[a]	··	(−17·7, 61·8)	(−19·6, 39·3)	(4·7, 68·6)	(19·0, 84·8)	(3·4, 63·0)	(19·0, 84·8)	(10·1, 52·0)
p value[b]	··	0·4701	0·6221	0·0627	0·0069	0·0429	0·0069	0·0101
≥17 U/L absolute reduction from baseline in ALT concentration at week 13								
n/n (%)	3/18 (16·7)	1/4 (25·0)	1/11 (9·1)	2/10 (20·0)	5/7 (71·4)	2/13 (15·4)	4/7 (57·1)	15/52 (28·8)
95% CI[a]	··	(−24·7, 57·2)	(−33·0, 24·4)	(−25·2, 38·1)	(12·3, 81·0)	(−28·1, 29·2)	(0·4, 72·4)	(−13·1, 30·5)
p value[b]	··	1·0000	1·0000	1·0000	0·0169	1·0000	0·0664	0·3669

ALT=alanine aminotransferase. CI=confidence interval. MRI=magnetic resonance imaging. MRI-PDFF=magnetic resonance imaging proton-density fat fraction. Q2W=once every 2 weeks. QW=once per week.

[a]Score (Miettinen–Nurminen) 95% CI.

[b]p value versus placebo from Fisher's exact test.

Supplementary table 2: **Summary of protocol amendments**

Amendment No. (Date of Approval (reference: MOD00633021)	**Key Details of the Amendment**
Amendment No. 1.0, 29 June 2019	• Objectives/endpoints relating to PD assessments were modified in Section 1.1 Synopsis and the Section 3 Objectives and Endpoints. • Cohort 3 (18 mg weekly) was added in Section 1.1 Synopsis, Section 4 Study Design, Section 6.1 Study Intervention Administered, and as a global change. • Sample size was updated in the Section 1.1 Synopsis, Section 4 Study Design, and Section 9.2 Sample Size Determination. • Stratification by biopsy-confirmed NASH with fibrosis status of F1, F2, and F3 in the 18 mg QW and 18 mg Q2W cohorts was added in the Section 1.1 Synopsis, Section 4 Study Design, and Section 6.4 Measures to Minimize Bias: Randomisation. • Clarification that endogenous FGF21 levels were to be collected at Baseline for all subjects and were to be repeated only in ADA-positive subjects at 3-5 months after EOS for potential analysis in Section 1.2 Synopsis, Section 1.3 SOA, Section 2 Study Design, and Section 8.6.1 Immunogenicity Assessments. • Each domicile period was shortened to a 2 overnight stay in Section 1.2 SOA. Prior errors and formatting were corrected. • Emerging data from the SAD study and recent publications were included in Section 2.2.3 Background and Section 2.3.1 Risk Assessment. • Repeat screening measurements were added and the eligibility criterion for ALT/AST was refined in Section 5.2 Exclusion Criteria. • Section 6.7.1 on monitoring suspected DILI was revised. • Text related to secondary objectives on selected markers in Section 9.1 Statistical Hypotheses was revised. • Formatting, style, typos, and glossary, were updated, and consistency was checked to align across protocol sections as global changes.
Administrative Letter #1, 19 July 2019	• The glucose drink given to subjects was amended from a 75-gram, 7.5 oz. size to a 75-gram, 10 oz size.
Administrative Letter #2, 19 July 2019	• The SOA was changed to include an “X” for IGF-1 on Day 50 for Cohorts 5 and 6.
Amendment No. 2,	• Follow-up procedures for subjects who tested positive for neutralizing antibodies to BIO89-100 were clarified in Section 2.3.1.1 Potential Risk: Immunogenicity and Section 8.6.1 Immunogenicity Assessments.

Amendment No. (Date of Approval (reference: MOD00633021)	Key Details of the Amendment
09 February 2020	• Neutralizing immunogenicity was added to ADA objectives/endpoints and corresponding analysis in Section 1.1 Synopsis, Section 3 Objectives and Endpoints and Section 9.4.3 Immunogenicity Analyses. • Optional percutaneous liver biopsy, a clarified definition of T2DM and central obesity, and a revision of pregnancy and contraception inclusion criterion number 5 were added to Section 5.1 Inclusion Criteria. • Section 5.2 Exclusion Criteria were clarified. • The use of CYP3A during the study was clarified in Section 6.6 Concomitant Therapy. • Sampling collection procedures for urine drug tests on Day -1 were clarified, and tests previously missing were added to Appendix 2 Clinical Laboratory Tests. • The definition of women who were not of childbearing potential (NCBP) was clarified and pregnancy was clarified as a mandatory criterion for permanent discontinuation of study intervention in Appendix 4 Contraception Guidance and Section 7.2 Subject Discontinuation/Withdrawal from Study. • Section 1.2 SOA and corresponding footnotes were updated to align with changes in the protocol. • Editorial, consistency, and formatting changes were made as global changes.
Administrative Letter #3, 19 March 2020	• Contraceptive requirements for presumptive fertile male subjects who were partnered with women who were NCBP, either post-menopausal or through sterilization or other surgical procedures, were clarified as follows: o Men were to confirm that their partners were determined to be sterile or post-menopausal based on medical judgment; this could be confirmed either by statement or medical records, if presented by the subject. o Men were not required to use other contraceptives when sexually active with a sterile or post-menopausal partner. o Men who were sexually active with fertile women needed to confirm that they would use 2 forms of contraceptives as per protocol.
Amendment No. 3.0, 25 March 2020	• Actions were added to address the potential disruptions to the study due to the COVID-19 pandemic in Section 1.1 Synopsis and Section 4 Study Design. • Fibroscan assessments were added to Day 50 and Day 92/ET study visits in Section 1.2 SOA and Section 8.6.2 Pharmacodynamics. • Fibroscan CAP score and Fibroscan VCTE score were added as exploratory endpoints in Section 3 Objectives and Endpoints. • Inclusion criterion #7 (Section 5.1, Appendix 4) was clarified to state that male subjects who were sexually active with female partners who were not of a childbearing potential (postmenopausal or surgically sterile) were to confirm that their partner had been medically confirmed to be sterile. • Exclusion criterion #2 (Section 5.2) was clarified to exclude subjects with clinically significant infectious disorders, including subjects who tested positive for COVID-19, even if they were asymptomatic. • Exclusion criterion #10 (Section 5.2) was clarified to state that subjects with stage 4 fibrosis based on VCTE or FIB-4 but who had a liver biopsy within

Amendment No. (Date of Approval (reference: MOD00633021)	Key Details of the Amendment
	12 months of screening and reported fibrosis stage of F0-F3 were to be considered eligible based on the liver biopsy result. • Exclusion criterion #18 (Section 5.2) was clarified to state that presumptive fertile, sexually active male subjects whose female partner was pregnant were excluded. • Clarification that IP could be administered by a home health care worker on a case-by-case basis if circumstances related to the COVID-19 pandemic precluded dosing at the study site was added to Section 6.2 Administration Instruction and Section 6.3 Preparation/Handling/Storage/Accountability. • The procedure for visit adjustment in case of dosing outside of window was clarified in Section 6.5 Study Intervention Compliance. • Clarification that the COVID-19 vaccine was allowed, if available, and that COVID-19 treatment was to be discussed with the Medical Monitor on a case-by-case basis was added to Section 6.6.1 Prohibited Medications/Therapies. • Stopping Rules and Dose Modifications (Section 6.7) were clarified to add that the Sponsor could suspend or terminate the study in the event of external circumstances that did not enable the study to be properly conducted including potential circumstances related to the COVID-19 pandemic. • Study Assessments and Procedures (Section 8) were clarified to indicate that any situation at the site level with potential impact on subject safety or study conduct, including situations related to COVID-19 infection or control measures, should have been discussed with the Sponsor immediately upon occurrence or awareness to determine potential impact on study subject(s) or study conduct. • Statistical Analyses (Section 9.4) were clarified to state that subjects with dose interruptions impacted by the COVID-19 pandemic were to be noted in the listings, and that subgroups including and excluding subjects with dose interruptions due to the COVID-19 pandemic may have been considered for efficacy and safety analyses if appropriate. • Clarification that some or all monitoring activities (Section 10.6.1 Data Quality Assurance) may be halted or performed remotely due to the COVID-19 pandemic, and in such a case details of the changes made to the monitoring strategy would be described in the Monitoring Plan. • The glossary was updated.

Supplementary table 3: **Additional supporting text for methods**

Methods section	**Supporting text**
Study design and participants	**Exclusion Criteria** **Medical Conditions** 1. History of, or current symptoms of, cardiovascular disease or cerebrovascular disease including clinical congestive heart failure (CHF), symptomatic coronary artery disease (CAD), peripheral arterial disease, and/or abdominal aortic aneurysm (AAA), history of transient ischemic attack (TIA), peripheral vascular disease (PVD), or symptomatic carotid stenosis. 2. Clinically significant respiratory, hepatic (other than NAFLD or NASH), renal, gastrointestinal, neurological, immunological, hematologic, infectious, or psychiatric disorder(s) (e.g., schizophrenia, generalized anxiety disorder, panic disorder), or a history of any illness that, in the opinion of the Investigator, might have confounded the results of the study or posed additional risk to the subject by participation in the study. Individual cases in which the Investigator deemed the subject appropriate for inclusion despite a chronic medical condition should have been discussed with and approved by the Medical Monitor. Subjects who were known to have tested positive for COVID-19 were excluded, even if they were asymptomatic. The following conditions were **NOT EXCLUDED**: • **Hypertension**: Subjects with a history of hypertension, whose hypertension was controlled and were clinically stable, may have been enrolled if they had been on a stable dose of no more than 2 antihypertensive medications at least 2 months before Screening. • **Dyslipidemia:** Subjects with dyslipidemia who were clinically stable may have been enrolled, including subjects who had been on a stable statin dose at least 2 months before Screening. • **T2DM:** Subjects with T2DM may have been enrolled if their HbA1c level did not exceed 9.5%, there were no known macrovascular or clinically significant microvascular complications, and they had been on a stable dose of antidiabetic medications in the 6 months before Screening (for GLP-1 agonists or DPP-IV antagonists), or 3 months for other oral or injectable treatments. Subjects treated with thiazolidinediones or insulin were excluded from this study. • **Depression**: Subjects with stable, controlled depression who had not been hospitalized in the past for depression and had been on a stable dose of no more than one antidepressant in the 2 months before Screening may have been enrolled. 3. Greater than 40% increase in ALT or AST between 2 Screening assessments, to be

done at least 2 weeks apart, as per the table below:

ALT/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**

Normal was defined as ≤ upper limit of normal (ULN); abnormal was defined as >ULN.
Note: Clinical judgment was used for subjects with isolated AST increases in whom there was suggestion of another cause of AST increase (e.g., muscle injury as evident by concurrent creatine phosphokinase elevation).

4. A personal or family history of arrhythmia, sudden unexplained death at a young age (before 40 years) in a first-degree relative, or long QT syndrome.
5. History of bariatric surgery or planned to have bariatric surgery during conduct of study.
6. History of type 1 diabetes mellitus (T1DM).
7. Weight loss of more than 5% within 3 months prior to Day -1, or more than 10% within 6 months prior to Day -1 or had planned to try to lose weight during conduct of study.
8. 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 (PSC), primary biliary cirrhosis (PBC), or Wilson's disease.
9. History of liver transplantation.
10. History of cirrhosis or evidence of cirrhosis (clinical, imaging-liver appearance or splenomegaly), advanced fibrosis (F4) on biopsy, VCTE-based Fibroscan >12.5 kPa or Fibrosis-4 (FIB-4) index >3.25 (FIB-4 score = Age × AST [IU/L/platelet count [x 10^9/L] × √ALT [IU/L]). In cases in which a patient was determined to have stage 4 fibrosis based on VCTE or FIB-4 but had a liver biopsy within 12 months of Screening and reported to show fibrosis stage F0, F1, F2, or F3, the subject was considered to be eligible based on the liver biopsy result.
11. Major trauma or surgery in the 2 months before Screening or at any time between

	Screening and Day -1. 12. Recent clinically significant acute illness (within 4 weeks of Screening) unless per the Investigator's clinical discretion a full recovery was apparent. 13. History of bone trauma, fracture, or surgery within 2 months of Screening. 14. Had any known malignancy or history of malignancy, except for basal cell skin cancer that had been treated with no evidence of recurrence for at least 3 months prior to Day -1. In specific circumstances in which there was basis to consider the subject as cured from cancer, exceptions may have been considered. Any exception needed to be approved in advance by the Sponsor's Medical Monitor. 15. History of alcohol use disorder (per Diagnostic and Statistical Manual of Mental Disorders fifth edition [DSM-5]) or risky drinking (defined as alcohol intake >14 standard drink units per week or 4 standard drinks on a single occasion in men; and alcohol intake >7 standard drink units per week or 3 standard drinks on a single occasion in women) within the 24 months before Day -1, or had a positive alcohol test at Screening and/or check-in. A unit of alcohol was defined as 14 grams, or as 355 mL of beer (5%), 1 glass of wine (150 mL; 12%), or 1 shot of hard liquor (45 mL; 40%). During the study, subjects were encouraged to abstain from alcohol. Alcohol intake was limited to 2 drinks per day for men and 1 drink per day for women. 16. History of drug abuse, or any other substance dependence (with the exception of caffeine) as defined by the Diagnostic and Statistical Manual of Mental Disorders IV – Text Revision (DSM-IV-TR) in the past 2 years prior to Screening or a positive test for drugs of abuse (i.e., amphetamines, barbiturates, benzodiazepines, cannabinoids, cocaine metabolites, opiates, and phencyclidine) at Screening and/or Day -1. 17. Daily use of more than 10 cigarettes/day, or 2 cigars/day, or equivalent use of any tobacco product within 6 weeks prior to Screening. E-cigarettes or other vaping devices should not have delivered more than 15 mg of nicotine/day. 18. Pregnant or breastfeeding, or planning to become pregnant or breastfeed, while enrolled in the study, or within 30 days or 5 half-lives (whichever was longer) after last dose of study intervention. Presumptive fertile, sexually active male subjects whose female partner was pregnant, were excluded. **Prior/Concomitant Therapy** 19. Subject 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 at doses greater than those used for hormone replacement, anabolic steroids, valproic acid, and other medications with known hepatotoxicity). 20. Any prior exposure to an FGF21 analog (e.g., BIO89-100, LY2405319, LY3025876, BMS-986036, BMS-986171, PF-05231023, PF-06645849, AKR-

001) or FGFR1 activating product, if known.

21. Any previous long-term (>4 weeks) use of systemic steroid (glucocorticoid) medications such as prednisone.

22. Vitamin E supplementation beyond Recommended Dietary Allowance (22.4 IU/day) within 6 months before Screening.

23. Any systemic medications, including over-the-counter (OTC) medications, prescription drugs, biologics, vaccines, herbal preparations, used within 14 days, or 5 half-lives, whichever was longer, before Day -1 and throughout the study with the FOLLOWING EXCEPTIONS:

    a. Acetaminophen (up to 4 g/day, use as indicated in the label).
    b. Ibuprofen (up to 1.2 g/day, use as indicated in the label).
    c. Aspirin (up to 81 mg/day).
    d. Antihypertensive medications (no more than 2 agents) on stable dose for at least 2 months prior to Screening.
    e. Antidiabetic medications: stable dose for 6 months prior to Screening for GLP-1 analogs or DPP-IV antagonists; 3 months prior to Screening for oral or other injectable medications. Thiazolidinediones and insulin were not allowed in this study.
    f. Statins on stable dose for at least 2 months.
    g. Asthma treatment with exception of oral corticosteroids.
    h. Anti-depressants (no more than 1 agent) on stable dose for at least 2 months.
    i. Other exceptions must have been approved by the Medical Monitor.
    j. Vitamins (other than vitamin E at a dose greater than recommended dietary allowance) and food supplements were allowed if the subject had been taking a stable regimen for at least 2 months before Screening.

Prior/Concurrent Clinical Study Experience

24. Any investigational drug small molecule (new chemical entity) within 30 days and large molecule (biologics) within 90 days, or 5 half-lives, whichever was longer, prior to Day -1, if known.

Diagnostic Assessments

25. Any history of suicidal behavior or suicidal ideation with plan and intent based upon clinical history. A “yes” response to any of the suicidal ideation or suicidal behavior questions in the Columbia-Suicide Severity Rating Scale (C-SSRS) on Day -1.

26. Any clinically significant laboratory abnormality at Screening. One repeat test may have been allowed at the discretion of the Investigator. The presence of one or more of the following laboratory abnormalities would have led to exclusion of the subject from participating in the study:

    a. ALT or AST ≥200 U/L.
    b. Elevation of total bilirubin (TB) > ULN.
    c. International normalized ratio (INR) > ULN.
    d. Alkaline phosphatase at Screening >1.25x ULN.
    e. Glomerular filtration rate (eGFR) ≤60 mL/min/1.73 m^2 as estimated by Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) Creatinine equation.
    f. Serum total TG ≥1000 mg/dL.

	g. HbA1c ≥9.5%. 27. ECG abnormality that may have, in the opinion of the Investigator, interfered with study participation, including intraventricular conduction delays (QRS interval ≥120 msec or PR interval >200 msec; 220 msec in individuals with a heart rate <70 beats per minute; and resting QTcF interval of ≤320 msec and/or ≥450 msec for males or ≥470 msec for females). 28. Vital sign abnormalities on Screening including having a supine systolic blood pressure <90 or >150 mmHg; diastolic blood pressure (following at least a 5-minute rest) <50 or >95 mmHg; or resting heart rate <50 or >100 beats per minute. 29. BMI at Screening <25 or ≥45 kg/m^2. **Other Exclusions** 30. Known allergy or sensitivity to injected proteins, or any component of the formulation, or had a history of allergies (including food allergies) requiring acute or chronic treatment (except for seasonal allergic rhinitis). 31. Donated or received any blood or blood products (e.g., white blood cells, platelets) within the 60 days prior to Screening, or had donated blood or blood products at least twice within the 6 months prior to Screening, or the subject had donated plasma within 7 days of the Screening visit or had planned donations during the 56 days or 5 half-lives following the last day of study intervention administration, whichever was longer. 32. Any abnormality of the skin or abdominal wall that would have affected SC administration to the abdominal area or any tattoos or scars in the intended injection area. 33. An employee of the investigational center or had a family member who was involved with the conduct of this study. 34. Subject who could not undergo MRI for any reason (e.g., contraindication, claustrophobia, excessive weight, or body size for MRI machine). 35. Subject who could not fast for study procedures for any reason. Specifically, subjects with T2DM who had had one or more episodes of hypoglycemia or past issues with fasting were excluded. Subjects with T2DM who were treated by insulin secretagogues needed to consult their treating physician about the optimal timing to take these medications to enable them to fast safely for study procedures.
Randomisation and masking	The randomisation ratios were as follows: 3:1 (pegozafermin:placebo) for cohorts 1 (n=8), 4 (n=12) and 6 (n=12), 4:1 for cohort 2 (n=15), and a 7:2 split into 3:1 and 4:1 for cohorts 3 (n=18) and 5 (n=18). Cohorts 3 and 5 were stratified by BC-NASH with fibrosis status of F1, F2, and F3 (Yes/No) to minimise bias (Amendment No. 1.0, 29 June 2019) (supplementary table 2). Block sizes were as follows: 4 for cohorts 1, 4 and 6, 5 for cohort 2, and 9 split into 4 and 5 for cohorts 3 and 5.
Procedures	Patient discontinuation or withdrawal was allowed for the following reasons: investigator decision, adverse event (AE) or intercurrent illness, non-compliance with protocol requirements, subject withdrawal of consent, pregnancy, sponsor termination or suspension

	of the study, or lost to follow-up As a result of the COVID-19 pandemic, the study protocol was amended to allow interruption in dosing and study procedures for up to 4 weeks due to COVID-related circumstances, and to define COVID-related circumstances for the analyses (Amendment No. 3.0, 25 March 2020) (supplementary table 2).

Supplementary table 4: **Dosing and assessment schedule for cohorts 1 to 4**

	Screening period		Treatment period																	Follow-up period	
Study visit	**1**	**2**	**3**			**4**	**5**	**6**	**7**	**8**	**9**	**10**			**11**	**12**	**13**	**14–20**	**21**	**22**	**23**
Study day	**−59 to −8**	**−7 to −3**	**−1**	**1**	**2**	**3**	**4**	**5**	**8**	**15**	**22**	**28**	**29**	**30**	**31**	**32**	**33**	**36, 43, 50, 57, 64, 71, 78**	**85**	**92/ET[a]**	**113/EOS**
Informed consent	X																				
Medical history/demographics	X																				
Percutaneous liver biopsy (optional)[b]	X																				
Prior medications	X																				
Inclusion and exclusion criteria	X		X																		
Complete physical exam[c]	X													X						X	X
Symptom-directed physical exam[d]			X	B	P				B	B	B		B					B	B		
Body weight[e]	X			B					B	B	B		B					B	B		
Waist and hip measurements	X			B									B					B D50		X	X
Fibroscan[f]	X																	D50		X	
12-lead ECG (single)[g]	X			B	X				B	B	B		B	X					B	X	X
Urine drug screen and alcohol breath test	X		X[h]																		
Clinical laboratory tests[i]	X	X		B	X				B	B	B		B	X				B at D36, D50, and D71	B	X	X
Cortisol (24-h urine collection)[j]	X																	D50		X	
Urinalysis	X		X											X				B at D50		X	X
HbA_{1c}	X		X															B at D50		X	X
Serology[k]	X																				
TSH	X																				
Pregnancy test in WOCBP only[l]	X(S)		X						B	B	B		B					B	B	X	X
Vital signs[m]	X		X	X	P	X	X	X	X	X	X	X	X	P	X	X	X	X	X	X	X
Columbia Suicide Severity Rating Scale			X															D50		X	
Randomisation			X																		
Study intervention administration[n]				X					X	X	X		X					X	X		
PK blood collection[o]				X	X	X	X	X	B	B	B		X	X	X	X	X	B at D36, D50, D57, and D71	B	X	

	Screening period		Treatment period																		Follow-up period	
Study visit	**1**	**2**	**3**			**4**	**5**	**6**	**7**	**8**	**9**	**10**			**11**	**12**	**13**	**14–20**		**21**	**22**	**23**
Study day	**−59 to −8**	**−7 to −3**	**−1**	**1**	**2**	**3**	**4**	**5**	**8**	**15**	**22**	**28**	**29**	**30**	**31**	**32**	**33**	**36, 43, 50, 57, 64, 71, 78**		**85**	**92/ET[a]**	**113/EOS**
PD and biomarker blood sampling																						
IGF1, total				B					B	B			B					B at D50			X	
Adiponectin				B					B				B					B at D50			X	X
CK18, ELF panel, and PRO-C3				B									B					B at D50			X	PRO-C3 only
Free fatty acid				B					B				B					B at D50			X	X
OGTT[p]			X																		X	
Insulin (not part of OGTT)				B					B				B					B at D50				X
HOMA-IR calculation				X														B at D50			X	X
MRI-PDFF, visceral fat, and subcutaneous fat[q]	X																	D50			X	
Plasma sample for potential future bone biomarkers analysis[r]			X															B at D50			X	X
Pharmacogenomic (DNA) blood sampling			X																			
Exploratory biomarker analysis[s]			X															B at D50			X	X
Immunogenicity[t]				B						B			B					B at D50			X[u]	X
Endogenous FGF21[v]				B																		
Adverse event monitoring[w]	X	X	X	←==========																→	X	X
Concomitant medication	X	X	X	←==========																→	X	X
Domiciled[x]			X	X	X							X	X	X								

All outpatient visits were to have a study window of ±1 day. The dosing days for the cohorts are indicated in pink.
ADA=anti-drug antibody. ALT=alanine aminotransferase. AST=aspartate aminotransferase. B=pre-dose. CK18=cytokeratin 18. CTX=carboxy-terminal collagen crosslinks. D=day. ECG=electrocardiogram. ELF=enhanced liver fibrosis. EOS=end of study. ET=early termination. FGF21=fibroblast growth factor 21. FSH=follicle stimulating hormone. HbA_{1c}=glycated haemoglobin. HOMA-IR= homeostatic model assessment of insulin resistance. IGF1=insulin-like growth factor 1. MRI=magnetic resonance imaging. MRI-PDFF=magnetic resonance imaging proton-density fat fraction. OGTT=oral glucose tolerance test. P=pre-discharge. P1NP=*N*-terminal propeptide of type I collagen. PD=pharmacodynamic. PK=pharmacokinetic. PRO-C3=*N*-terminal propeptide of type III collagen. S=serum. TSH=thyroid stimulating hormone. WOCBP=women of childbearing potential.
[a]For any participant who withdrew before completion of the study, an ET visit was conducted, if possible, with the same assessments as the D92 visit.
[b]Optional liver biopsy may have been performed for participants who did not have a medical contraindication for a liver biopsy and did not have a liver biopsy in the 24 months before screening. For participants who underwent a previous liver biopsy >24 months before screening who would not have qualified for the study based on results of the initial biopsy, there should have been sound clinical basis to expect different findings in a repeat biopsy based on medical judgement. Any biopsy needed to be approved in advance by the sponsor and only after the participant had met all other inclusion and exclusion criteria.

[c]Complete physical exam done at screening included recording height, weight, and calculating body mass index.
[d]Symptom-directed physical exam was done pre-dose and pre-discharge from the phase 1 unit on domiciled dosing visits (first and fifth doses), and pre-dose on ambulatory dosing visits. Additional physical examinations were performed if clinically indicated.
[e]On domiciled and ambulatory visits, body weight was measured pre-dose.
[f]Fibroscan (Echosens, Waltham, MA, USA) was performed during screening, before MRI for all participants.
[g]12-lead safety ECGs were recorded as single bedside measurements; on domiciled dosing visits (first and fifth doses), ECGs were measured pre-dose and 24 h post dose. On ambulatory dosing visits, ECG was measured pre-dose. Additional ECGs were conducted if clinically indicated.
[h]On D−1, urine drug screen could have been done at a local laboratory. However, a sample should also have been collected for central laboratory evaluation.
[i]Clinical laboratory tests included biochemistry, haematology, coagulation, and FSH for determination of postmenopausal status; on domiciled dosing visits (first and fifth doses), clinical laboratory samples were collected pre-dose and 24 h post dose; on ambulatory visits, clinical laboratory samples were collected pre-dose. For all participants, ALT and AST samples were collected twice during the screening period (≥2 weeks apart), with the second assessment collected at D−7 to D−3. A third sample, if required, was collected via an unscheduled visit.
[j]Ambulatory 24-h urine collection for cortisol was done within 14 days from baseline, on D50 and D92/ET. It was recommended that participants collect urine for the 24 h before the D−7 to D−3 visit and bring the container with them to this visit. Alternatively, urine could have been collected for the 24 h before the randomisation visit (D−1) and brought to the site on D−1 (the result was not required for eligibility confirmation). For D50 and D92/ET, the participant started collection 24 h before coming into the clinic and brought the sample to the visit.
[k]Serology tests included hepatitis B surface antigen, hepatitis C virus, and HIV 1 and 2 antibodies.
[l]The serum urine pregnancy test was conducted at screening; at all other time points, a urine pregnancy test was done to guide clinical decisions to dose on dosing days. Before the first dosing, the baseline urine pregnancy test was performed on D−1 to allow for randomisation on that day. If the urine test was positive, a confirmatory serum pregnancy test was conducted.
[m]Vital signs included supine blood pressure, pulse, body temperature, and respiratory rate. Vital signs were measured pre-dose (before scheduled blood draws and study intervention administration), 1, 12, and 24 h post dose, and pre-discharge on domiciled dosing visits (first and fifth doses). On dosing ambulatory visits, vital signs were measured pre-dose (before scheduled blood draws and study intervention administration) and pre-discharge. On non-dosing visits, vital signs were measured before scheduled blood draws. Starting from randomisation, blood pressure and pulse were measured in duplicate; the first measurement was taken up to 15 min before the indicated time point. Additional vital signs measurements may have been done if clinically indicated. Participants were in a supine or semi-erect/seated position and resting for ≥5 min before measurements.
[n]Study intervention was administered subcutaneously to the abdomen region by qualified study personnel.
[o]Additional blood samples for PK analysis may have been collected if clinically indicated (eg, in the case of a serious adverse event).
[p]Blood samples for the OGTT were collected under fasting conditions (10 h) at the following time points: 0 (just before ingesting glucose), 30, 60, 90, 120, and 180 min. On D92/ET, the insulin was captured from the OGTT.
[q]At screening, MRI-PDFF was done within 35 days of baseline (D1). On D50 and D92, MRI-PDFF was done within ±2 days of the planned visit date. If outside the window, MRI-PDFF was performed as close to the target day as possible and protocol deviation was recorded.
[r]Samples for CTX and P1NP were obtained at the designated time points for storage and potential future analysis. The D42 sample was obtained pre-dose.
[s]Samples for RNA as well as plasma and serum samples were collected for potential future exploratory assessments to increase understanding of pegozafermin biological activity and identify potential existing and/or emerging biomarkers.
[t]Participants who tested positive for neutralising antibodies to pegozafermin at the EOS visit (or at the ET visit if withdrawn from study) were asked to return for additional follow-up testing. This testing occurred approximately every 3 months starting from when the site was notified of the positive result until: (1) neutralising antibodies were no longer detectable; or (2) the participant had been followed up for a period of ≥1 year (±4 weeks). More frequent testing (eg, every month) or testing for a longer period may have been requested in the event of safety-related concerns. Follow-up testing was not required if it was established that the participant did not receive pegozafermin. All follow-up results, both positive and negative, were to be communicated to the sites. A blood sample for

ADA assessment was also to be collected upon observation of any severe hypersensitivity reaction (eg, anaphylaxis). Participants who tested positive for binding, non-neutralising antibodies and had clinical sequelae that were considered potentially related to an anti-pegozafermin antibody response may also have been asked to return for additional follow-up testing.

[u]Immunogenicity sample on D92/ET was only collected for participants who terminated early from the study.

[v]Baseline samples of endogenous FGF21 were analysed; sample(s) were also obtained from neutralising ADA+ participants with additional follow-up visit(s) for potential future analysis.

[w]The sites may have taken non-personally identifying photographs of potential injection-site reactions (optional).

[x]Participants in cohorts 1 to 4 were to be domiciled at the clinic from 1 day before dosing until 24 h after the first and fifth doses. Other study visits were ambulatory. On D8, 15, and 22 (ambulatory dosing visits), participants remained at the site for observation for ≥2 h after dosing.

Supplementary table 5: **Dosing and assessment schedule for cohorts 5 and 6**

	Screening period		Treatment period																	Follow-up period	
Study visit	**1**	**2**	**3**			**4**	**5**	**6**	**7**	**8**	**9**	**10**			**11**	**12**	**13, 14**	**15**	**16**	**17–19[a]**	**20**	**21**
Study day	**−59 to −8**	**−7 to −3**	**−1**	**1**	**2**	**3**	**4**	**5**	**8**	**15**	**22**	**28**	**29**	**30**	**31**	**32**	**33, 36**	**43**	**50**	**57, 71, 85**	**92/ET[b]**	**113/EOS**
Informed consent	X																					
Medical history/demographics	X																					
Percutaneous liver biopsy (optional)[c]	X																					
Prior medications	X																					
Inclusion and exclusion criteria	X		X																			
Complete physical exam[d]	X													X							X	X
Symptom-directed physical exam[e]			X	B	P				X	B	X		B					B		B		
Body weight[f]	X			B					X	B	X		B				D36	B		B		
Waist and hip measurements	X			B									B						X		X	X
Fibroscan[g]	X																		X		X	
12-lead ECG (single)[h]	X			B	X				X	B			B	X						B (D85)	X	X
Urine drug screen and alcohol breath test	X		X[i]																			
Clinical laboratory tests[j]	X	X		B	X				X	B	X		B	X			D36		X	B (D71, D85)	X	X
Cortisol (24-h urine collection)[k]	X																		X		X	
Urinalysis	X		X											X					X		X	X
HbA_{1c}	X		X																X		X	X
Serology[l]	X																					
TSH	X																					
Pregnancy test in WOCBP only[m]	X (S)		X							B			B					B		B	X	X
Vital signs[n]	X		X	X	P	X	X	X	X	X	X	X	X	P	X	X	X	X	X	X	X	X
Columbia Suicide Severity Rating Scale			X																X		X	
Randomisation			X																			
Study intervention administration[o]				X						X			X					X		X		
PK blood collection[p]				X	X	X	X	X	X	B	X		X	X	X	X	X		X	B (D57, D71, D85)	X	
PD and biomarker blood sampling																						

	Screening period		Treatment period																		Follow-up period	
Study visit	**1**	**2**	**3**			**4**	**5**	**6**	**7**	**8**	**9**	**10**			**11**	**12**	**13, 14**	**15**	**16**	**17–19[a]**	**20**	**21**
Study day	**−59 to −8**	**−7 to −3**	**−1**	**1**	**2**	**3**	**4**	**5**	**8**	**15**	**22**	**28**	**29**	**30**	**31**	**32**	**33, 36**	**43**	**50**	**57, 71, 85**	**92/ET[b]**	**113/EOS**
IGF1, total				B					X	B			B								X	
Adiponectin				B					X				B						X		X	X
CK18, ELF panel, and PRO-C3				B									B						X		X	PRO-C3 only
Free fatty acid				B					X				B						X		X	X
OGTT[q]			X																		X	
Insulin (not part of OGTT)				B					X				B						X			X
HOMA-IR calculation				X															X		X	X
MRI-PDFF, visceral fat, and subcutaneous fat[r]	X																		X		X	
Plasma sample for potential future bone biomarkers analysis[s]			X																X		X	X
Pharmacogenomic (DNA) blood sampling			X																			
Exploratory biomarker analysis[t]			X																X		X	X
Immunogenicity[u]				B						B			B						X		X[v]	X
Endogenous FGF21[w]				B																n		
Adverse event monitoring[x]	X	X	X	←═══																	X	X
Concomitant medication	X	X	X	←═══																	X	X
Domiciled[y]			X	X	X							X	X	X								

All outpatient visits were to have a study window of ±1 day. The dosing days for the cohorts are indicated in pink.
ADA=anti-drug antibody. ALT=alanine aminotransferase. AST=aspartate aminotransferase. B=pre-dose. CK18=cytokeratin 18. CTX=carboxy-terminal collagen crosslinks. D=day. ECG=electrocardiogram. ELF=enhanced liver fibrosis. EOS=end of study. ET=early termination. FGF21=fibroblast growth factor 21. FSH=follicle stimulating hormone. HbA_{1c}=glycated haemoglobin. HOMA-IR= homeostatic model assessment of insulin resistance. IGF1=insulin-like growth factor 1. MRI=magnetic resonance imaging. MRI-PDFF=magnetic resonance imaging proton-density fat fraction. OGTT=oral glucose tolerance test. P=pre-discharge. P1NP=*N*-terminal propeptide of type I collagen. PD=pharmacodynamic. PK=pharmacokinetic. PRO-C3=*N*-terminal propeptide of type III collagen. S=serum; TSH=thyroid stimulating hormone. WOCBP=women of childbearing potential.
[a]Between visits 17 and 19, on D64 and D78, participants were contacted by phone to inquire about adverse events and concomitant medications.
[b]For any participant who withdrew before completion of the study, an ET visit was conducted, if possible, with the same assessments as the D92 visit.
[c]Optional liver biopsy may have been performed for participants who did not have a medical contraindication for a liver biopsy and did not have a liver biopsy in the 24 months before screening. For participants who underwent a previous liver biopsy >24 months before screening who would not have qualified for the study based on results of the initial biopsy, there should have been a sound clinical basis to expect different findings in a repeat biopsy based on medical judgement. Any biopsy needed to be approved in advance by the sponsor and only after the participant had met all other inclusion and exclusion criteria.

[d]Complete physical exam done at screening included recording height, weight, and calculating body mass index.
[e]Symptom-directed physical exam was done pre-dose and pre-discharge from the phase 1 unit on domiciled dosing visits (first and third dose), and pre-dose on ambulatory dosing visits. Additional physical examinations were also performed if clinically indicated.
[f]On domiciled and ambulatory visits, body weight was measured pre-dose.
[g]Fibroscan (Echosens, Waltham, MA, USA) was performed during screening, before MRI for all participants.
[h]12-lead safety ECGs were recorded as single bedside measurements. On domiciled dosing visits (first and third doses), ECGs were measured pre-dose and 24 h post dose; on ambulatory dosing visits, ECG was measured pre-dose. Additional ECGs were conducted if clinically indicated.
[i]On D−1, urine drug screen could have been done at a local laboratory, however, a sample should also have been collected for central laboratory evaluation.
[j]Clinical laboratory tests included biochemistry, haematology, coagulation, and FSH for determination of postmenopausal status; on domiciled dosing visits (first and third doses), clinical laboratory samples were collected pre-dose and 24 h post dose; on ambulatory visits, clinical laboratory samples were collected pre-dose. For all participants, ALT and AST samples were collected twice during the screening period (≥2 weeks apart), with the second assessment to be collected at D−7 to D−3. A third sample, if required, was collected via an unscheduled visit.
[k]Ambulatory 24-h urine collection for cortisol was done within 14 days from baseline, on D50 and D92/ET. It was recommended that participants collected urine for the 24 h before the D−7 to D−3 visit and brought the container with them to this visit. Alternatively, urine could have been collected for the 24 h before the randomisation visit (D−1) and brought to the site on D−1 (the result was not required for eligibility confirmation). For D50 and D92/ET, the participant started collection 24 h before coming into the clinic and brought the sample to the visit.
[l]Serology tests included hepatitis B surface antigen, hepatitis C virus, and HIV 1 and 2 antibodies.
[m]The serum urine pregnancy test was conducted at screening; at all other time points, a urine pregnancy test was done to guide clinical decisions to dose on dosing days. Before the first dosing, the baseline urine pregnancy test was performed on D−1 to allow for randomisation on that day. If the urine test was positive, a confirmatory serum pregnancy test was conducted.
[n]Vital signs included supine blood pressure, pulse, body temperature, and respiratory rate. Vital signs were measured pre-dose (before scheduled blood draws and study intervention administration), 1, 12, and 24 h post dose, and pre-discharge on domiciled dosing visits (first and third doses). On dosing ambulatory visits, vital signs were measured pre-dose (before scheduled blood draws and study intervention administration) and pre-discharge. On non-dosing visits, vital signs were measured before scheduled blood draws. Starting from randomisation, blood pressure and pulse were measured in duplicate; the first measurement was taken up to 15 min before the indicated time point. Additional vital signs measurements may have been done if clinically indicated. Participants were in a supine or semi-erect/seated position and resting for ≥5 min before measurements.
[o]Study intervention was administered subcutaneously to the abdomen region by qualified study personnel.
[p]Additional blood samples for PK analysis may have been collected if clinically indicated (eg, in the case of a serious adverse event).
[q]Blood samples for the OGTT were collected under fasting conditions (10 h) at the following time points: 0 (just before ingesting glucose), 30, 60, 90, 120, and 180 min. On D92/ET the insulin was captured from the OGTT.
[r]At screening, MRI-PDFF was done within 35 days of baseline (D1). On D50 and D92, MRI-PDFF was done within ±2 days of the planned visit date. If outside the window, MRI-PDFF was performed as close to the target day as possible and protocol deviation was recorded.
[s]Samples for CTX and P1NP were obtained at the designated time points for storage and potential future analysis. The D42 sample was obtained pre-dose.
[t]Samples for RNA as well as plasma and serum samples were collected for potential future exploratory assessments to increase understanding of pegozafermin biological activity and identify potential existing and/or emerging biomarkers.
[u]Participants who tested positive for neutralising antibodies to pegozafermin at the EOS visit (or at the ET visit if withdrawn from study) were asked to return for additional follow-up testing. This testing occurred approximately every 3 months starting from when the site was notified of the positive result until: (1) neutralising antibodies were no longer detectable; or (2) the participant had been followed up for a period of ≥1 year (±4 weeks). More frequent testing (eg, every month) or testing for a longer period may have been requested in the event of safety-related concerns. Follow-up testing was not required if it was established that the participant did not receive pegozafermin. All follow-up results, both positive and negative, were to be communicated to the sites. A blood sample for

ADA assessment was also to be collected upon observation of any severe hypersensitivity reaction (eg, anaphylaxis). Participants who tested positive for binding, non-neutralising antibodies and had clinical sequelae that were considered potentially related to an anti-pegozafermin antibody response may also have been asked to return for additional follow-up testing.

[v]Immunogenicity sample on D92/ET was only to be collected for participants who terminated early from the study.

[w]Baseline samples of endogenous FGF21 were analysed; sample(s) were also obtained from neutralising ADA+ participants with additional follow-up visit(s) for potential future analysis.

[x]The sites may have taken non-personally identifying photographs of potential injection-site reactions (optional).

[y]Participants in cohorts 5 and 6 were domiciled at the clinic from 1 day before dosing until 24 h after the first dose and 24 h after the third dose; other study visits were ambulatory. On the D15 ambulatory dosing visit, participants remained at the study site for observation for ≥2 h after dosing.

Supplementary table 6: **Population analysis sets**

	Placebo (n=19)	Pegozafermin						
		3 mg QW (n=6)	9 mg QW (n=12)	18 mg QW (n=11)	27 mg QW (n=10)	18 mg Q2W (n=14)	36 mg Q2W (n=9)	Pooled (n=62)
Screened[a]	..	..	..	..	..	..	..	275
Randomised[b]	19	6	12	11	10	14	9	81
Safety[c]	19	6	12	11	10	14	9	81
Pharmacokinetics[d]	0	6	12	11	10	14	9	62
Pharmacodynamics[e]	19	6	12	11	10	14	9	81
Pharmacodynamics–MRI[f]	18	6	11	10	8	14	8	75

MRI=magnetic resonance imaging. Q2W=once every 2 weeks. QW=once per week.

[a]All individuals who signed informed consent and underwent screening.
[b]All randomised participants who received at least one dose of study drug. One participant was planned for placebo treatment, but actually received pegozafermin 3 mg QW.
[c]All screened analysis set participants who were assigned a randomisation number in the study. The safety analysis set row was summarised based on planned treatment.
[d]All participants in the safety analysis set who received at least one dose of study drug and had at least one on-study pharmacokinetic measurement.
[e]All participants in the safety analysis set who had measurable post-baseline pharmacodynamic data.
[f]All participants in the safety analysis set who had measurable post-baseline MRI assessments.

Supplementary table 7: **Change in hepatic fat fraction (Pharmacodynamics–MRI population)**

	Placebo (n=18)	Pegozafermin					
		3 mg QW (n=6)	9 mg QW (n=11)	18 mg QW (n=10)	27 mg QW (n=8)	18 mg Q2W (n=14)	36 mg Q2W (n=8)
MRI-PDFF hepatic fat fraction, %							
Baseline							
Mean (SD)	20·84 (8·35)	22·43 (8·47)	21·23 (6·57)	18·54 (6·07)	22·16 (10·37)	21·57 (8·93)	21·48 (10·06)
Change from baseline to day 92							
n, unstructured	18	5	11	10	7	13	8
LS mean (SE)	1·42 (1·42)	–7·50 (2·56)	–10·04 (1·81)	–7·50 (1·91)	–13·51 (2·19)	–9·00 (1·63)	–9·68 (2·12)
90% CI of LS mean	(–0·94, 3·79)	(–11·76, –3·24)	(–13·07, –7·02)	(–10·68, –4·31)	(–17·16, –9·86)	(–11·72, –6·27)	(–13·22, –6·13)
95% CI of LS mean	(–1·40, 4·25)	(–12·60, –2·40)	(–13·66, –6·42)	(–11·30, –3·69)	(–17·87, –9·14)	(–12·25, –5·74)	(–13·92, –5·43)
p value[a]	0·3182	0·0045	<0·0001	0·0002	<0·0001	<0·0001	<0·0001
LS mean difference compared with placebo[b]	··	–8·93 (2·92)	–11·47 (2·30)	–8·92 (2·37)	–14·93 (2·61)	–10·42 (2·16)	–11·10 (2·55)
90% CI of LS mean difference	··	(–13·80, –4·05)	(–15·30, –7·63)	(–12·88, –4·96)	(–19·28, –10·59)	(–14·03, –6·82)	(–15·36, –6·84)
95% CI of LS mean difference	··	(–14·76, –3·09)	(–16·06, –6·87)	(–13·66, –4·18)	(–20·13, –9·73)	(–14·74, –6·11)	(–16·20, –6·00)
p value[c]	··	0·0032	<0·0001	0·0004	<0·0001	<0·0001	<0·0001
Percent change from baseline to day 92							
n, unstructured	18	5	11	10	7	13	8
LS mean (SE)	9·77 (6·04)	–36·94 (11·01)	–49·62 (7·73)	–36·11 (8·14)	–60·39 (9·40)	–43·19 (6·99)	–50·39 (9·07)
90% CI of LS mean	(–0·32, 19·86)	(–55·30, –18·59)	(–62·52, –36·71)	(–49·69, –22·52)	(–76·06, –44·73)	(–54·85, –31·54)	(–65·53, –35·26)
95% CI of LS mean	(–2·30, 21·84)	(–58·90, –14·99)	(–65·06, –34·17)	(–52·37, –19·85)	(–79·14, –41·65)	(–57·14, –29·25)	(–68·51, –32·28)
p value[a]	0·1108	0·0013	<0·0001	<0·0001	<0·0001	<0·0001	<0·0001
LS mean difference compared with placebo[b]	··	–46·72 (12·56)	–59·39 (9·82)	–45·88 (10·14)	–70·16 (11·17)	–52·96 (9·24)	–60·16 (10·90)
90% CI of LS mean difference	··	(–67·66, –25·77)	(–75·77, –43·01)	(–62·80, –28·96)	(–88·80, –51·53)	(–68·38, –37·55)	(–78·35, –41·98)
95% CI of LS mean difference	··	(–71·77, –21·66)	(–78·99, –39·78)	(–66·13, –25·63)	(–92·46, –47·87)	(–71·41, –34·52)	(–81·93, –38·40)
p value[c]	··	0·0004	<0·0001	<0·0001	<0·0001	<0·0001	<0·0001

Mixed-model repeated measures analysis was used to analyse the change from baseline and the percent change from baseline in MRI parameters. The model included baseline as a covariate, and treatment group, visit and the interaction between treatment group and visit as factors.

CI=confidence interval. LS=least-squares. MRI=magnetic resonance imaging. MRI-PDFF=magnetic resonance imaging proton-density fat fraction. Q2W=once every 2 weeks. QW=once per week. SD=standard deviation. SE=standard error.

[a]p value of the within-group treatment difference.

[b]The difference between treatment and placebo.

[c]p value of the between-group and placebo treatment difference.

Supplementary table 8: **Change in hepatic volume (Pharmacodynamics population)**

	Placebo (n=18)	Pegozafermin					
		3 mg QW (n=6)	9 mg QW (n=11)	18 mg QW (n=10)	27 mg QW (n=8)	18 mg Q2W (n=14)	36 mg Q2W (n=8)
Liver volume, L							
Baseline							
Mean (SD)	2·10 (0·44)	1·98 (0·65)	2·03 (0·41)	2·11 (0·66)	2·33 (0·70)	2·05 (0·61)	2·40 (0·35)
Change from baseline to day 92							
n, unstructured	17	5	11	10	7	12	8
LS mean (SE)	0·01 (0·05)	–0·29 (0·09)	–0·19 (0·06)	–0·10 (0·07)	–0·33 (0·08)	–0·22 (0·06)	–0·24 (0·08)
90% CI of LS mean	(–0·08, 0·09)	(–0·44, –0·14)	(–0·30, –0·08)	(–0·21, 0·01)	(–0·46, –0·20)	(–0·32, –0·12)	(–0·37, –0·12)
95% CI of LS mean	(–0·10, 0·11)	(–0·47, –0·11)	(–0·32, –0·06)	(–0·23, 0·03)	(–0·48, –0·17)	(–0·34, –0·10)	(–0·40, –0·09)
p value[a]	0·8948	0·0024	0·0041	0·1346	<0·0001	0·0005	0·0020
LS mean difference compared with placebo[b]	··	–0·29 (0·10)	–0·20 (0·08)	–0·11 (0·08)	–0·33 (0·09)	–0·22 (0·08)	–0·25 (0·09)
90% CI of LS mean difference	··	(–0·47, –0·12)	(–0·33, –0·06)	(–0·25, 0·03)	(–0·49, –0·18)	(–0·35, –0·09)	(–0·40, –0·10)
95% CI of LS mean difference	··	(–0·50, –0·09)	(–0·36, –0·03)	(–0·28, 0·06)	(–0·52, –0·15)	(–0·38, –0·07)	(–0·43, –0·07)
p value[c]	··	0·0064	0·0191	0·2040	0·0007	0·0055	0·0079
Percent change from baseline to day 92							
n, unstructured	17	5	11	10	7	12	8
LS mean (SE)	1·19 (2·32)	–15·32 (4·12)	–8·85 (2·89)	–5·66 (3·03)	–15·18 (3·53)	–10·71 (2·68)	–10·84 (3·42)
90% CI of LS mean	(–2·69, 5·07)	(–22·19, –8·44)	(–13·68, –4·03)	(–10·71, –0·60)	(–21·07, –9·28)	(–15·17, –6·25)	(–16·55, –5·12)
95% CI of LS mean	(–3·45, 5·83)	(–23·55, –7·09)	(–14·63, –3·07)	(–11·71, 0·39)	(–22·23, –8·13)	(–16·05, –5·37)	(–17·67, –4·00)
p value[a]	0·6101	0·0004	0·0032	0·0663	<0·0001	0·0002	0·0024
LS mean difference compared with placebo[b]	··	–16·51 (4·73)	–10·04 (3·71)	–6·85 (3·81)	–16·37 (4·23)	–11·90 (3·54)	–12·03 (4·14)
90% CI of LS mean difference	··	(–24·40, –8·62)	(–16·23, –3·86)	(–13·22, –0·48)	(–23·43, –9·31)	(–17·81, –5·99)	(–18·94, –5·11)
95% CI of LS mean difference	··	(–25·95, –7·06)	(–17·45, –2·64)	(–14·47, 0·78)	(–24·82, –7·92)	(–18·97, –4·83)	(–20·30, –3·75)
p value[c]	··	0·0009	0·0087	0·0775	0·0003	0·0013	0·0051

Mixed-model repeated measures analysis was used to analyse the change from baseline and the percent change from baseline in MRI parameters. The model included baseline as a covariate, and treatment group, visit and the interaction between treatment group and visit as factors.
CI=confidence interval. LS=least-squares. MRI=magnetic resonance imaging. Q2W=once every 2 weeks. QW=once per week. SD=standard deviation. SE=standard error.
[a]p value of the within-group treatment difference.
[b]The difference between treatment and placebo.

[c]P value of the between-group and placebo treatment difference.

Supplementary table 9: **Change in ALT levels (Pharmacodynamics population)**

	Placebo (n=19)	Pegozafermin					
		3 mg QW (n=6)	9 mg QW (n=12)	18 mg QW (n=11)	27 mg QW (n=10)	18 mg Q2W (n=14)	36 mg Q2W (n=9)
ALT, U/L							
Baseline[a]							
Mean (SD)	38·8 (21·8)	45·0 (26·8)	32·8 (16·7)	38·4 (25·3)	53·3 (46·8)	39·1 (17·4)	50·4 (27·3)
Change from baseline to day 92							
n, unstructured	18	4	11	10	7	13	7
LS mean (SE)	–3·4 (3·4)	–10·4 (6·3)	–9·9 (4·3)	–10·9 (4·5)	–30·0 (5·3)	–9·6 (3·9)	–22·4 (5·1)
90% CI of LS mean	(–9·1, 2·2)	(–21·0, 0·1)	(–17·0, –2·8)	(–18·5, –3·3)	(–38·9, –21·2)	(–16·1, –3·0)	(–30·9, –13·9)
95% CI of LS mean	(–10·2, 3·3)	(–23·1, 2·2)	(–18·4, –1·3)	(–20·0, –1·8)	(–40·7, –19·4)	(–17·4, –1·7)	(–32·6, –12·2)
p value[b]	0·3118	0·1038	0·0241	0·0200	<0·0001	0·0175	<0·0001
LS mean difference compared with placebo[c]	··	–7·0 (7·2)	–6·4 (5·4)	–7·4 (5·6)	–26·6 (6·3)	–6·1 (5·2)	–18·9 (6·1)
90% CI of LS mean difference	··	(–19·0, 5·0)	(–15·5, 2·7)	(–16·9, 2·0)	(–37·1, –16·0)	(–14·8, 2·5)	(–29·2, –8·7)
95% CI of LS mean difference	··	(–21·3, 7·4)	(–17·3, 4·5)	(–18·8, 3·9)	(–39·2, –13·9)	(–16·5, 4·2)	(–31·2, –6·7)
p value[d]	··	0·3337	0·2412	0·1937	<0·0001	0·2402	0·0030
Percent change from baseline to day 92							
n, unstructured	18	4	11	10	7	13	7
LS mean (SE)	–4·18 (5·47)	–16·87 (10·62)	–26·65 (6·99)	–26·73 (7·40)	–43·69 (8·55)	–18·83 (6·38)	–39·84 (8·42)
90% CI of LS mean	(–13·32, 4·96)	(–34·57, 0·83)	(–38·32, –14·97)	(–39·09, –14·37)	(–57·95, –29·44)	(–29·48, –8·17)	(–53·88, –25·79)
95% CI of LS mean	(–15·12, 6·76)	(–38·05, 4·30)	(–40·62, –12·68)	(–41·53, –11·93)	(–60·75, –26·64)	(–31·59, –6·07)	(–56·65, –23·03)
p value[b]	0·4479	0·1165	0·0003	0·0006	<0·0001	0·0045	<0·0001
LS mean difference compared with placebo[c]	··	–12·69 (11·96)	–22·47 (8·86)	–22·55 (9·19)	–39·51 (10·19)	–14·65 (8·40)	–35·66 (10·07)
90% CI of LS mean difference	··	(–32·63, 7·24)	(–37·25, –7·68)	(–37·90, –7·20)	(–56·51, –22·52)	(–28·68, –0·62)	(–52·45, –18·86)
95% CI of LS mean difference	··	(–36·54, 11·16)	(–40·17, –4·77)	(–40·93, –4·17)	(–59·85, –19·17)	(–31·44, 2·15)	(–55·76, –15·55)
p value[d]	··	0·2922	0·0137	0·0171	0·0002	0·0863	0·0007

Mixed-model repeated measures analysis was used to analyse the change from baseline and the percent change from baseline in liver parameters. The model included baseline as a covariate, and treatment group, visit and the interaction between treatment group and visit as factors.
ALT=alanine aminotransferase. CI=confidence interval. LS=least-squares. MRI=magnetic resonance imaging. Q2W=once every 2 weeks. QW=once per week. SD=standard deviation. SE=standard error.

[a]Baseline values are for the Randomised population.
[b]p value of the within-group treatment difference.
[c]The difference between treatment and placebo.
[d]p value of the between-group and placebo treatment difference.

Supplementary table 10: **Change in ALT levels in patients with baseline ALT levels >45 U/L (Pharmacodynamics population)**

	Placebo (n=6)	**Pooled pegozafermin (n=22)**
ALT, U/L		
Change from baseline to day 92		
n, unstructured	5	17
LS mean (SE)	–10·3 (9·9)	–34·6 (5·1)
90% CI of LS mean	(–27·5, 6·9)	(–43·3, –25·8)
95% CI of LS mean	(–31·1, 10·6)	(–45·1, –24·0)
p value[a]	0·3140	<0·0001
LS mean difference compared with placebo[b]	··	–24·3 (11·1)
90% CI of LS mean difference	··	(–43·6, –5·0)
95% CI of LS mean difference	··	(–47·6, –0·9)
p value[c]	··	0·0426
Percent change from baseline to day 92		
n, unstructured	5	17
LS mean (SE)	–10·08 (12·37)	–47·20 (6·42)
90% CI of LS mean	(–31·35, 11·19)	(–58·22, –36·19)
95% CI of LS mean	(–35·79, 15·62)	(–60·50, –33·90)
p value[a]	0·4240	<0·0001
LS mean difference compared with placebo[b]	··	–37·12 (13·94)
90% CI of LS mean difference	··	(–61·08, –13·16)
95% CI of LS mean difference	··	(–66·07, –8·17)
p value[c]	··	0·0144

Mixed-model repeated measures analysis was used to analyse the change from baseline and the percent change from baseline in liver parameters. The model included baseline as a covariate, and treatment group, visit and the interaction between treatment group and visit as factors.
ALT=alanine aminotransferase. CI=confidence interval. LS=least-squares. SE=standard error.
[a]p value of the within group treatment difference.
[b]The difference between treatment and placebo.
[c]p value of the between group and placebo treatment difference.

Supplementary table 11: **Change in AST levels (Pharmacodynamics population)**

	Placebo (n=19)	Pegozafermin					
		3 mg QW (n=6)	9 mg QW (n=12)	18 mg QW (n=11)	27 mg QW (n=10)	18 mg Q2W (n=14)	36 mg Q2W (n=9)
AST, U/L							
Baseline[a]							
Mean (SD)	29·0 (16·7)	34·5 (29·2)	22·8 (7·2)	30·9 (19·3)	39·0 (25·6)	28·8 (11·3)	38·1 (36·5)
Change from baseline to day 92							
n, unstructured	18	4	11	10	7	13	7
LS mean (SE)	–5·2 (2·0)	–13·4 (3·8)	–8·9 (2·5)	–6·1 (2·7)	–14·5 (3·2)	–6·3 (2·3)	–14·1 (3·0)
90% CI of LS mean	(–8·5, –1·9)	(–19·7, –7·1)	(–13·2, –4·7)	(–10·6, –1·6)	(–19·8, –9·2)	(–10·2, –2·4)	(–19·1, –9·0)
95% CI of LS mean	(–9·2, –1·2)	(–21·0, –5·8)	(–14·0, –3·8)	(–11·5, –0·7)	(–20·8, –8·2)	(–10·9, –1·6)	(–20·1, –8·0)
p value[b]	0·0117	0·0008	0·0008	0·0265	<0·0001	0·0089	<0·0001
LS mean difference compared with placebo[c]	··	–8·2 (4·3)	–3·7 (3·2)	–0·9 (3·3)	–9·3 (3·8)	–1·1 (3·1)	–8·9 (3·6)
90% CI of LS mean difference	··	(–15·4, –1·0)	(–9·1, 1·7)	(–6·5, 4·7)	(–15·6, –3·0)	(–6·2, 4·0)	(–15·0, –2·8)
95% CI of LS mean difference	··	(–16·8, 0·4)	(–10·2, 2·7)	(–7·6, 5·8)	(16·8, –1·8)	(–7·2, 5·0)	(–16·2, –1·6)
p value[d]	··	0·0604	0·2519	0·7880	0·0158	0·7221	0·0179
Percent change from baseline to day 92							
n, unstructured	18	4	11	10	7	13	7
LS mean (SE)	–4·40 (4·85)	–29·36 (9·47)	–19·90 (6·15)	–15·10 (6·52)	–37·88 (7·52)	–11·41 (5·63)	–25·32 (7·43)
90% CI of LS mean	(–12·52, 3·72)	(–45·17, –13·56)	(–30·19, –9·60)	(–26·02, –4·18)	(–50·45, –25·32)	(–20·84, –1·98)	(–37·73, –12·91)
95% CI of LS mean	(–14·13, 5·33)	(–48·28, –10·45)	(–32·23, –7·56)	(–28·19, –2·02)	(–52·93, –22·84)	(–22·70, –0·11)	(–40·18, –10·46)
p value[b]	0·3682	0·0029	0·0021	0·0246	<0·0001	0·0478	0·0012
LS mean difference compared with placebo[c]	··	–24·96 (10·64)	–15·49 (7·82)	–10·70 (8·12)	–33·48 (8·97)	–7·01 (7·43)	–20·92 (8·89)
90% CI of LS mean difference	··	(–42·74, –7·19)	(–28·58, –2·41)	(–24·30, 2·91)	(–48·47, –18·49)	(–19·44, 5·43)	(–35·77, –6·07)
95% CI of LS mean difference	··	(–46·24, –3·69)	(–31·17, 0·19)	(–27·00, 5·60)	(–51·43, –15·54)	(–21·91, 7·89)	(–38·70, –3·13)
p value[d]	··	0·0222	0·0527	0·1936	0·0004	0·3498	0·0220

Mixed-model repeated measures analysis was used to analyse the change from baseline and the percent change from baseline in liver parameters. The model included baseline as a covariate, and treatment group, visit and the interaction between treatment group and visit as factors.

AST=aspartate aminotransferase. CI=confidence interval. LS=least-squares. Q2W=once every 2 weeks. QW=once per week. SD=standard deviation. SE=standard error.
[a]Baseline values are for the Randomised population.
[b]p value of the within-group treatment difference.
[c]The difference between treatment and placebo.
[d]p value of the between-group and placebo treatment difference.

Supplementary table 12: **Change in PRO-C3 levels (Pharmacodynamics population)**

	Placebo (n=19)	**Pegozafermin**					
		3 mg QW (n=6)	**9 mg QW (n=12)**	**18 mg QW (n=11)**	**27 mg QW (n=10)**	**18 mg Q2W (n=14)**	**36 mg Q2W (n=9)**
PRO-C3, ng/mL							
Baseline[a]							
Mean (SD)	10·81 (3·57)	12·18 (4·48)	10·01 (4·42)	11·51 (2·72)	13·81 (3·58)	12·14 (2·53)	14·43 (2·94)
Change from baseline to day 92							
n, unstructured	18	4	11	10	7	13	7
LS mean (SE)	–0·29 (0·78)	–2·96 (1·63)	–2·03 (1·01)	0·06 (1·05)	–3·84 (1·25)	–1·56 (0·92)	–2·43 (1·25)
90% CI of LS mean	(–1·60, 1·02)	(–5·68, –0·24)	(–3·71, –0·36)	(–1·69, 1·81)	(–5·93, –1·75)	(–3·09, –0·03)	(–4·52, –0·34)
95% CI of LS mean	(–1·85, 1·28)	(–6·21, 0·30)	(–4·04, –0·03)	(–2·03, 2·16)	(–6·34, –1·34)	(–3·39, 0·27)	(–4·93, 0·07)
p value[b]	0·7149	0·0741	0·0472	0·9532	0·0032	0·0931	0·0565
LS mean difference compared with placebo[c]	··	–2·67 (1·81)	–1·75 (1·27)	0·35 (1·31)	–3·55 (1·48)	–1·27 (1·21)	–2·14 (1·48)
90% CI of LS mean difference	··	(–5·69, 0·35)	(–3·86, 0·37)	(–1·84, 2·53)	(–6·03, –1·08)	(–3·29, 0·74)	(–4·62, 0·33)
95% CI of LS mean difference	··	(–6·28, 0·94)	(–4·28, 0·79)	(–2·27, 2·96)	(–6·52, –0·59)	(–3·68, 1·14)	(–5·11, 0·82)
p value[d]	··	0·1446	0·1736	0·7904	0·0196	0·2948	0·1531
Percent change from baseline to day 92							
n, unstructured	18	4	11	10	7	13	7
LS mean (SE)	3·26 (7·02)	–19·71 (14·53)	–18·79 (9·02)	1·08 (9·38)	–22·67 (11·20)	–11·18 (8·19)	–12·76 (11·22)
90% CI of LS mean	(–8·45, 14·97)	(–43·93, 4·52)	(–33·84, –3·73)	(–14·58, 16·75)	(–46·35, –8·99)	(–24·86, 2·49)	(–31·47, 5·95)
95% CI of LS mean	(–10·75, 17·28)	(–48·70, 9·28)	(–36·81, –0·77)	(–17·67, 19·83)	(–50·02, –5·32)	(–27·55, 5·18)	(–35·15, 9·63)
p value[b]	0·6436	0·1794	0·0412	0·9085	0·0160	0·1771	0·2595
LS mean difference compared with placebo[c]	··	–22·97 (16·14)	–22·05 (11·38)	–2·18 (11·72)	–30·93 (13·26)	–14·44 (10·79)	–16·02 (13·29)
90% CI of LS mean difference	··	(–49·88, 3·94)	(–41·04, –3·06)	(–21·74, 17·38)	(–53·06, –8·81)	(–32·45, 3·56)	(–38·18, 6·14)
95% CI of LS mean	··	(–55·17, 9·23)	(–44·78, 0·68)	(–25·59, 21·23)	(–57·41, –4·46)	(–36·00, 7·11)	(–42·54, 10·50)

difference							
p value[d]	..	0·1592	0·0570	0·8531	0·0227	0·1854	0·2321

Mixed-model repeated measures analysis was used to analyse the change from baseline and the percent change from baseline in liver parameters. The model included baseline as a covariate, and treatment group, visit and the interaction between treatment group and visit as factors.
CI=confidence interval. LS=least-squares. PRO-C3=*N*-terminal propeptide of type III collagen. Q2W=once every 2 weeks. QW=once per week. SD=standard deviation. SE=standard error.
[a]Baseline values are for the Randomised population.
[b]p value of the within-group treatment difference.
[c]The difference between treatment and placebo.
[d]p value of the between-group and placebo treatment difference.

Supplementary table 13: **Change in triglyceride levels (Pharmacodynamics population)**

	Placebo (n=19)	**Pegozafermin**					
		3 mg QW (n=6)	**9 mg QW (n=12)**	**18 mg QW (n=11)**	**27 mg QW (n=10)**	**18 mg Q2W (n=14)**	**36 mg Q2W (n=9)**
Triglycerides, mg/dL							
Baseline[a]							
Mean (SD)	174·0 (47·8)	135·3 (41·8)	177·0 (77·5)	225·8 (143·3)	156·6 (76·5)	137·3 (59·3)	207·4 (105·6)
Change from baseline to day 92							
n, unstructured	17	5	11	10	7	9	7
LS mean (SE)	–14·1 (13·7)	–42·8 (25·4)	–50·8 (17·2)	–22·8 (18·1)	–47·5 (21·5)	–58·7 (18·9)	–53·1 (21·6)
90% CI of LS mean	(–37·2, 9·0)	(–85·5, –0·2)	(–79·7, –22·0)	(–53·2, 7·6)	(–83·6, –11·4)	(–90·4, –27·0)	(–89·2, –16·9)
95% CI of LS mean	(–41·8, 13·6)	(–94·0, 8·3)	(–85·4, –16·2)	(–59·3, 13·7)	(–90·8, –4·2)	(–96·6, –20·7)	(–96·4, –9·7)
p value[b]	0·3116	0·0986	0·0050	0·2141	0·0322	0·0031	0·0175
LS mean difference compared with placebo[c]	..	–28·8 (28·9)	–36·7 (22·0)	–8·7 (22·7)	–33·4 (25·5)	–44·6 (23·4)	–39·0 (25·6)
90% CI of LS mean difference	..	(–77·3, 19·7)	(–73·7, 0·2)	(–46·9, 29·5)	(–76·3, 9·4)	(–83·8, –5·4)	(–81·9, 3·9)
95% CI of LS mean difference	..	(–86·9, 29·4)	(–81·1, 7·6)	(–54·6, 37·1)	(–84·8, 17·9)	(–91·6, 2·3)	(–90·5, 12·5)
p value[d]	..	0·3247	0·1020	0·7026	0·1967	0·0621	0·1340
Percent change from baseline to day 92							
n, unstructured	17	5	11	10	7	9	7
LS mean (SE)	–2·21 (6·23)	–22·74 (11·53)	–23·95 (7·74)	–17·71 (8·20)	–27·63 (9·66)	–28·49 (8·62)	–20·71 (9·74)
90% CI of LS mean	(–12·62, 8·21)	(–42·00, –3·47)	(–36·89, –11·01)	(–31·41, –4·01)	(–43·78, –11·49)	(–42·88, –14·11)	(–36·98, –4·44)
95% CI of LS mean	(–14·68, 10·27)	(–45·80, 0·33)	(–39·45, –8·45)	(–34·12, –1·30)	(–46·96, –8·30)	(–45·71, –11·28)	(–40·19, –1·23)
p value[b]	0·7246	0·0532	0·0030	0·0349	0·0058	0·0016	0·0375
LS mean difference	..	–20·53 (13·10)	–21·74 (9·94)	–15·50 (10·30)	–25·43 (11·50)	–26·29 (10·63)	–18·50 (11·57)

compared with placebo[c]							
90% CI of LS mean difference	..	(–42·43, 1·36)	(–38·36, –5·13)	(–32·72, 1·72)	(–44·64, –6·22)	(–44·04, –8·54)	(–37·83, 0·82)
95% CI of LS mean difference	..	(–46·75, 5·68)	(–41·64, –1·85)	(–36·13, 5·12)	(–48·43, –2·43)	(–47·54, –5·04)	(–41·64, 4·63)
p value[d]	..	0·1224	0·0327	0·1379	0·0308	0·0162	0·1149

Mixed-model repeated measures analysis was used to analyse the change from baseline and the percent change from baseline in lipid parameters. The model included baseline as a covariate, and treatment group, visit and the interaction between treatment group and visit as factors.
CI=confidence interval. LS=least-squares. Q2W=once every 2 weeks. QW=once per week. SD=standard deviation. SE=standard error.
[a]Baseline values are for the Randomised population.
[b]p value of the within-group treatment difference.
[c]The difference between-treatment and placebo.
[d]p value of the between group and placebo treatment difference.

Supplementary table 14: **Change in LDL-C levels (Pharmacodynamics population)**

	Placebo (n=19)	**Pegozafermin**					
		3 mg QW (n=6)	**9 mg QW (n=12)**	**18 mg QW (n=11)**	**27 mg QW (n=10)**	**18 mg Q2W (n=14)**	**36 mg Q2W (n=9)**
LDL-C, mg/dL							
Baseline[a]							
Mean (SD)	112·2 (26·8)	98·1 (34·3)	143·3 (43·1)	112·2 (31·9)	99·4 (42·8)	106·3 (28·7)	116·6 (29·1)
Change from baseline to day 92							
n, unstructured	17	5	11	10	7	10	7
LS mean (SE)	–0·9 (4·4)	–11·5 (7·9)	–20·7 (5·6)	–2·8 (5·8)	–19·9 (6·8)	–7·4 (5·4)	–7·8 (6·6)
90% CI of LS mean	(–8·1, 6·4)	(–24·7, 1·7)	(–30·1, –11·3)	(–12·4, 6·9)	(–31·1, –8·6)	(–16·3, 1·6)	(–18·8, 3·2)
95% CI of LS mean	(–9·6, 7·8)	(–27·2, 4·2)	(–31·9, –9·4)	(–14·3, 8·8)	(–33·3, –6·4)	(–18·1, 3·4)	(–21·0, 5·4)
p value[b]	0·8450	0·1494	0·0005	0·6355	0·0045	0·1752	0·2423
LS mean difference compared with placebo[c]	..	–10·6 (9·0)	–19·8 (7·2)	–1·9 (7·2)	–19·0 (8·0)	–6·5 (6·9)	–6·9 (7·9)
90% CI of LS mean difference	..	(–25·7, 4·4)	(–31·7, –7·9)	(–14·0, 10·2)	(–32·4, –5·6)	(–18·0, 5·0)	(–20·1, 6·3)
95% CI of LS mean difference	..	(–28·6, 7·3)	(–34·1, –5·6)	(–16·4, 12·6)	(–35·0, –3·0)	(–20·3, 7·3)	(–22·7, 8·9)
p value[d]	..	0·2410	0·0072	0·7939	0·0209	0·3501	0·3840
Percent change from baseline to day 92							
n, unstructured	17	5	11	10	7	10	7
LS mean (SE)	1·15 (4·08)	–6·17 (7·38)	–13·45 (5·29)	2·59 (5·41)	–16·46 (6·34)	–5·02 (5·06)	–4·11 (6·20)
90% CI of LS mean	(–5·66, 7·97)	(–18·48, 6·15)	(–22·27, –4·62)	(–6·45, 11·62)	(–27·04, –5·89)	(–13·45, 3·40)	(–14·45, 6·23)

95% CI of LS mean	(–7·00, 9·31)	(–20·90, 8·57)	(–24·01, –2·89)	(–8·23, 13·41)	(–29·12, –3·81)	(–15·10, 5·06)	(–16·49, 8·26)
p value[b]	0·7786	0·4066	0·0134	0·6340	0·0116	0·3239	0·5094
LS mean difference compared with placebo[c]	··	–7·32 (8·43)	–14·60 (6·71)	1·44 (6·78)	–17·62 (7·54)	–6·18 (6·49)	–5·27 (7·43)
90% CI of LS mean difference	··	(–21·37, 6·74)	(–25·79, –3·41)	(–9·88, 12·75)	(–30·19, –5·05)	(–17·00, 4·65)	(–17·65, 7·12)
95% CI of LS mean difference		(–24·14, 9·50)	(–27·99, –1·21)	(–12·11, 14·98)	(–32·66, –2·57)	(–19·13, 6·78)	(–20·09, 9·56)
p value[d]	··	0·3882	0·0330	0·8328	0·0224	0·3447	0·4807

Mixed-model repeated measures analysis was used to analyse the change from baseline and the percent change from baseline in lipid parameters. The model included baseline as a covariate, and treatment group, visit and the interaction between treatment group and visit as factors.
CI=confidence interval. LDL-C=low-density lipoprotein cholesterol. LS=least-squares. Q2W=once every 2 weeks. QW=once per week. SD=standard deviation. SE=standard error.
[a]Baseline values are for the Randomised population.
[b]p value of the within-group treatment difference.
[c]The difference between treatment and placebo.
[d]p value of the between-group and placebo treatment difference.

Supplementary table 15: **Change in HDL-C levels (Pharmacodynamics population)**

	Placebo (n=19)	**Pegozafermin**					
		3 mg QW (n=6)	**9 mg QW (n=12)**	**18 mg QW (n=11)**	**27 mg QW (n=10)**	**18 mg Q2W (n=14)**	**36 mg Q2W (n=9)**
HDL-C, mg/dL							
Baseline[a]							
Mean (SD)	45·1 (8·9)	39·9 (9·3)	45·1 (13·9)	40·4 (8·8)	44·5 (8·7)	44·8 (8·8)	42·3 (14·1)
Change from baseline to day 92							
n, unstructured	17	5	11	10	7	10	7
LS mean (SE)	0·7 (1·4)	6·7 (2·5)	5·5 (1·7)	3·6 (1·8)	1·3 (2·1)	8·8 (1·7)	5·2 (2·1)
90% CI of LS mean	(–1·6, 3·0)	(2·6, 10·9)	(2·6, 8·3)	(0·5, 6·6)	(–2·2, 4·7)	(6·0, 11·7)	(1·7, 8·7)
95% CI of LS mean	(–2·0, 3·5)	(1·7, 11·7)	(2·0, 8·9)	(–0·1, 7·2)	(–2·8, 5·4)	(5·4, 12·3)	(1·0, 9·4)
p value[b]	0·6030	0·0092	0·0023	0·0558	0·5410	<0·0001	0·0155
LS mean difference compared with placebo[c]	··	6·0 (2·9)	4.8 (2·2)	2·9 (2·3)	0·5 (2·5)	8·1 (2·2)	4·5 (2·5)
90% CI of LS mean difference	··	(1·2, 10·8)	(1·1, 8·4)	(–1·0, 6·7)	(–3·6, 4·7)	(4·4, 11·8)	(0·3, 8·6)
95% CI of LS mean difference	··	(0·3, 11·7)	(0·4, 9·1)	(–1·8, 7·5)	(–4·4, 5·5)	(3·7, 12·5)	(–0·5, 9·5)
p value[d]	··	0·0401	0·0347	0·2196	0·8278	0·0005	0·0793

Percent change from baseline to day 92							
n, unstructured	17	5	11	10	7	10	7
LS mean (SE)	1·96 (2·97)	18·17 (5·43)	11·19 (3·68)	9·20 (3·92)	2·90 (4·50)	20·10 (3·76)	9·79 (4·53)
90% CI of LS mean	(–3·01, 6·92)	(9·12, 27·23)	(5·03, 17·34)	(2·65, 15·75)	(–4·60, 10·41)	(13·83, 26·38)	(2·22, 17·36)
95% CI of LS mean	(–3·99, 7·90)	(7·33, 29·02)	(3·81, 18·56)	(1·36, 17·05)	(–6·08, 11·89)	(12·60, 27·61)	(0·73, 18·85)
p value[b]	0·5124	0·0014	0·0036	0·0223	0·5206	<0·0001	0·0346
LS mean difference compared with placebo[c]	··	16·22 (6·20)	9·23 (4·73)	7·24 (4·93)	0·95 (5·39)	18·15 (4·79)	7·84 (5·43)
90% CI of LS mean difference	··	(5·86, 26·57)	(1·33, 17·13)	(–1·00, 15·49)	(–8·05, 9·94)	(10·16, 26·14)	(–1·23, 16·90)
95% CI of LS mean difference	··	(3·82, 28·61)	(–0·23, 18·69)	(–2·63, 17·12)	(–9·82, 11·71)	(8·58, 27·71)	(–3·01, 18·68)
p value[d]		0·0112	0·0557	0·1473	0·8612	0·0003	0·1538

Mixed-model repeated measures analysis was used to analyse the change from baseline and the percent change from baseline in lipid parameters. The model included baseline as a covariate, and treatment group, visit and the interaction between treatment group and visit as factors.
CI=confidence interval. HDL-C=high-density lipoprotein cholesterol. LS=least-squares. Q2W=once every 2 weeks. QW=once per week. SD=standard deviation. SE=standard error.
[a]Baseline values are for the Randomised population.
[b]p value of the within-group treatment difference.
[c]The difference between treatment and placebo.
[d]p value of the between-group and placebo treatment difference.

Supplementary table 16: **Change in non-HDL-C levels (Pharmacodynamics population)**

	Placebo (n=19)	**Pegozafermin**					
		3 mg QW (n=6)	**9 mg QW (n=12)**	**18 mg QW (n=11)**	**27 mg QW (n=10)**	**18 mg Q2W (n=14)**	**36 mg Q2W (n=9)**
Non-HDL-C, mg/dL							
Baseline[a]							
Mean (SD)	136·3 (28·6)	118·3 (34·2)	171·1 (46·8)	147·5 (45·1)	121·4 (45·5)	126·4 (29·4)	149·2 (38·1)
Change from baseline to day 92							
n, unstructured	17	5	11	10	7	10	7
LS mean (SE)	–1·3 (4·8)	–12·8 (8·8)	–24·1 (6·2)	–7·3 (6·4)	–25·8 (7·4)	–12·6 (5·9)	–12·8 (7·3)
90% CI of LS mean	(–9·3, 6·7)	(–27·3, 1·8)	(–34·5, –13·7)	(–18·0, 3·4)	(–38·2, –13·3)	(–22·5, –2·7)	(–25·0, –0·7)
95% CI of LS mean	(–10·9, 8·3)	(–30·2, 4·7)	(–36·5, –11·6)	(–20·1, 5·5)	(–40·6, –10·9)	(–24·4, –0·8)	(–27·4, 1·7)
p value[b]	0·7849	0·1493	0·0002	0·2577	0·0009	0·0368	0·0830
LS mean difference compared with placebo[c]	··	–11·4 (10·0)	–22·8 (7·9)	–6·0 (8·0)	–24·4 (8·9)	–11·3 (7·6)	–11·5 (8·8)
90% CI of LS mean	··	(–28·0, 5·2)	(–35·9, –9·6)	(–19·4, 7·4)	(–39·2, –9·7)	(–24·0, 1·4)	(–26·1, 3·1)

difference							
95% CI of LS mean difference	..	(–31·3, 8·4)	(–38·5, –7·0)	(–22·0, 10·0)	(–42·1, –6·8)	(–26·5, 3·9)	(–29·0, 5·9)
p value[d]	..	0·2546	0·0053	0·4571	0·0074	0·1423	0·1922
Percent change from baseline to day 92							
n, unstructured	17	5	11	10	7	10	7
LS mean (SE)	1·18 (3·56)	–6·31 (6·45)	–13·87 (4·61)	–1·92 (4·74)	–16·32 (5·51)	–7·75 (4·38)	–6·34 (5·39)
90% CI of LS mean	(–4·75, 7·12)	(–17·08, 4·45)	(–21·56, –6·19)	(–9·84, 5·99)	(–25·51, –7·13)	(–15·06, –0·44)	(–15·33, 2·66)
95% CI of LS mean	(–5·92, 8·29)	(–19·19, 6·57)	(–23·07, –4·67)	(–11·40, 7·55)	(–27·32, –5·33)	(–16·49, 0·99)	(–17·10, 4·43)
p value[b]	0·7403	0·3313	0·0037	0·6862	0·0042	0·0815	0·2442
LS mean difference compared with placebo[c]	..	–7·50 (7·35)	–15·06 (5·85)	–3·11 (5·93)	–17·51 (6·54)	–8·93 (5·63)	–7·52 (6·47)
90% CI of LS mean difference	..	(–19·76, 4·76)	(–24·82, –5·30)	(–13·01, 6·80)	(–28·43, –6·58)	(–18·32, 0·46)	(–18·31, 3·27)
95% CI of LS mean difference	..	(–22·17, 7·18)	(–26·74, –3·37)	(–14·96, 8·75)	(–30·58, –4·43)	(–20·17, 2·30)	(–20·44, 5·40)
p value[d]		0·3114	0·0123	0·6022	0·0095	0·1173	0·2491

Mixed-model repeated measures analysis was used to analyse the change from baseline and the percent change from baseline in lipid parameters. The model included baseline as a covariate, and treatment group, visit and the interaction between treatment group and visit as factors.
CI=confidence interval. HDL-C=high-density lipoprotein cholesterol. LS=least-squares. Q2W=once every 2 weeks. QW=once per week. SD=standard deviation. SE=standard error.
[a]Baseline values are for the Randomised population.
[b]p value of the within-group treatment difference.
[c]The difference between treatment and placebo.
[d]p value of the between-group and placebo treatment difference.

Supplementary table 17: **Change in HOMA-IR levels (Pharmacodynamics population)**

	Placebo (n=19)	**Pegozafermin**					
		3 mg QW (n=6)	**9 mg QW (n=12)**	**18 mg QW (n=11)**	**27 mg QW (n=10)**	**18 mg Q2W (n=14)**	**36 mg Q2W (n=9)**
HOMA-IR							
Baseline[a]							
n	15	2	6	8	10	12	7
Mean (SD)	11·53 (5·90)	15·95 (10·82)	12·23 (7·86)	12·13 (7·63)	11·90 (6·75)	10·06 (4·10)	13·00 (7·63)
Change from baseline to day 92							
n, unstructured	11	1	3	6	7	11	5
LS mean (SE)	0·63 (1·75)	0·40 (6·07)	1·55 (3·24)	1·43 (2·47)	–4·23 (2·23)	–0·88 (1·80)	–5·81 (2·66)
90% CI of LS mean	(–2·38, 3·65)	(–10·14, 10·94)	(–3·96, 7·07)	(–2·85, 5·72)	(–8·09, –0·38)	(–4·00, 2·24)	(–10·39, –1·22)

95% CI of LS mean	(–3·01, 4·28)	(–12·38, 13·17)	(–5·09, 8·20)	(–3·76, 6·63)	(–8·90, 0·43)	(–4·66, 2·90)	(–11·35, –0·27)
p value[b]	0·7209	0·9486	0·6357	0·5688	0·0728	0·6314	0·0409
LS mean difference compared with placebo[c]	··	–0·24 (6·31)	0·92 (3·67)	0·80 (3·03)	–4·87 (2·84)	–1·51 (2·51)	–6·44 (3·21)
90% CI of LS mean difference	··	(–11·18, 10·71)	(–5·25, 7·18)	(–4·44, 6·04)	(–9·77, 0·03)	(–5·84, 2·81)	(–11·96, –0·92)
95% CI of LS mean difference	··	(–13·50, 13·03)	(–6·64, 8·47)	(–5·55, 7·15)	(–10·80, 1·06)	(–6·74, 3·71)	(–13·11, 0·23)
p value[d]	··	0·9703	0·8047	0·7948	0·1022	0·5522	0·0576
Percent change from baseline to day 92							
n, unstructured	11	1	3	6	7	11	5
LS mean (SE)	–0·09 (15·72)	10·37 (51·30)	7·40 (30·62)	37·07 (20·87)	–41·42 (19·48)	–4·57 (15·57)	–41·11 (23·39)
90% CI of LS mean	(–26·62, 26·44)	(–76·24, 97·08)	(–44·25, 59·06)	(1·79, 72·35)	(–74·33, –8·51)	(–30·88, 21·74)	(–80·62, –1·61)
95% CI of LS mean	(–31·96, 31·78)	(–93·83, 114·57)	(–54·64, 69·44)	(–5·33, 79·47)	(–80·96, –1·87)	(–36·18, 27·04)	(–88·58, 6·35)
p value[b]	0·9953	0·8410	0·8103	0·0846	0·0406	0·7709	0·0874
LS mean difference compared with placebo[c]	··	10·46 (53·52)	7·49 (34·21)	37·16 (26·13)	–41·33 (25·06)	–4·48 (22·01)	–41·02 (28·40)
90% CI of LS mean difference	··	(–80·00, 100·92)	(–50·25, 65·24)	(–6·99, 81·31)	(–83·65, 1·00)	(–41·65, 32·70)	(–88·96, 6·92)
95% CI of LS mean difference	··	(–98·24, 119·17)	(–61·87, 76·85)	(–15·89, 90·21)	(–82·17, 9·52)	(–49·14, 40·19)	(–98·61, 16·57)
p value[d]	··	0·8462	0·8279	0·1638	0·1079	0·8400	0·1573

Mixed-model repeated measures analysis was used to analyse the change from baseline and the percent change from baseline in metabolic parameters. The model included baseline as a covariate, and treatment group, visit and the interaction between treatment group and visit as factors.
CI=confidence interval. HOMA-IR= homeostatic model assessment of insulin resistance. LS=least-squares. Q2W=once every 2 weeks. QW=once per week. SD=standard deviation. SE=standard error.
[a]Baseline values are for the Randomised population.
[b]p value of the within-group treatment difference.
[c]The difference between treatment and placebo.
[d]p value of the between-group and placebo treatment difference.

Supplementary table 18: **Change in glucose levels (Pharmacodynamics population)**

	Placebo (n=19)	**Pegozafermin**					
		3 mg QW (n=6)	**9 mg QW (n=12)**	**18 mg QW (n=11)**	**27 mg QW (n=10)**	**18 mg Q2W (n=14)**	**36 mg Q2W (n=9)**
Glucose, mg/dL							
Baseline[a]							
Mean (SD)	147·6 (50·0)	156·3 (53·3)	133·7 (36·4)	135·3 (45·4)	128·6 (27·1)	107·7 (17·0)	118·6 (41·0)

Change from baseline to day 92							
n, unstructured	17	2	10	10	7	13	7
LS mean (SE)	10·0 (9·2)	51·0 (20·1)	12·7 (11·6)	–7·5 (12·2)	–9·7 (14·2)	6·9 (10·6)	5·9 (13·6)
90% CI of LS mean	(–5·6, 25·5)	(17·4, 84·5)	(–6·7, 32·2)	(–28·1, 13·0)	(–33·5, 14·1)	(–11·0, 24·7)	(–16·9, 28·7)
95% CI of LS mean	(–8·7, 28·6)	(10·8, 91·1)	(–10·6, 36·0)	(–32·2, 17·1)	(–38·2, 18·9)	(–14·6, 28·3)	(–21·4, 33·2)
p value[b]	0·2866	0·0137	0·2774	0·5396	0·4992	0·5217	0·6657
LS mean difference compared with placebo[c]	..	41·0 (22·1)	2·8 (14·8)	–17·5 (15·3)	–19·6 (17·0)	–3·1 (14·2)	–4·1 (16·5)
90% CI of LS mean difference	..	(4·1, 77·8)	(–22·1, 27·6)	(–43·2, 8·2)	(–48·1, 8·9)	(–27·0, 20·8)	(–31·7, 23·6)
95% CI of LS mean difference	..	(–3·1, 85·1)	(–27·0, 32·6)	(–48·4, 13·3)	(–53·8, 14·6)	(–31·7, 25·5)	(–37·2, 29·1)
p value[d]	..	0·0680	0·8532	0·2585	0·2537	0·8284	0·8063
Percent change from baseline to day 92							
n, unstructured	17	2	10	10	7	13	7
LS mean (SE)	7·94 (5·53)	38·90 (12·78)	11·92 (6·97)	–3·77 (7·27)	–7·18 (8·48)	4·35 (6·37)	3·80 (8·21)
90% CI of LS mean	(–1·33, 17·20)	(17·62, 60·18)	(0·25, 23·58)	(–15·97, 8·44)	(–21·39, 7·03)	(–6·33, 15·03)	(–9·93, 17·53)
95% CI of LS mean	(–3·17, 19·04)	(13·45, 64·35)	(–2·06, 25·90)	(–18·40, 10·87)	(–24·21, 9·84)	(–8·45, 17·14)	(–12·65, 20·25)
p value[b]	0·1574	0·0032	0·0930	0·6070	0·4010	0·4983	0·6454
LS mean difference compared with placebo[c]	..	30·96 (13·88)	3·98 (8·87)	–11·70 (9·13)	–15·12 (10·16)	–3·59 (8·52)	–4·14 (9·93)
90% CI of LS mean difference	..	(7·84, 54·08)	(–10·89, 18·85)	(–27·02, 3·61)	(–32·14, 1·90)	(–17·86, 10·68)	(–20·76, 12·48)
95% CI of LS mean difference	..	(3·31, 58·62)	(–13·84, 21·80)	(–30·06, 6·65)	(–35·51, 5·27)	(–20·69, 13·51)	(–24·05, 15·77)
p value[d]	..	0·0287	0·6556	0·2059	0·1428	0·6752	0·6783

Mixed-model repeated measures analysis was used to analyse the change from baseline and the percent change from baseline in metabolic parameters. The model included baseline as a covariate, and treatment group, visit and the interaction between treatment group and visit as factors.

CI=confidence interval. LS=least-squares. Q2W=once every 2 weeks. QW=once per week. SD=standard deviation. SE=standard error.

[a]Baseline values are for the Randomised population.

[b]p value of the within-group treatment difference.

[c]The difference between treatment and placebo.

[d]p value of the between-group and placebo treatment difference.

Supplementary table 19: **Change in HbA_{1c} levels (Pharmacodynamics population)**

	Placebo (n=19)	Pegozafermin					
		3 mg QW (n=6)	9 mg QW (n=12)	18 mg QW (n=11)	27 mg QW (n=10)	18 mg Q2W (n=14)	36 mg Q2W (n=9)
HbA_{1c} (%)							
Baseline[a]							
Mean (SD)	7·38 (1·43)	7·53 (1·61)	6·77 (1·26)	6·31 (1·45)	6·74 (1·27)	5·98 (0·70)	6·21 (0·91)
Change from baseline to day 92							
n, unstructured	18	5	11	10	7	13	7
LS mean (SE)	0·01 (0·16)	0·58 (0·29)	0·08 (0·20)	0·06 (0·22)	–0·26 (0·25)	–0·08 (0·19)	0·54 (0·25)
90% CI of LS mean	(–0·26, 0·29)	(0·10, 1·07)	(–0·26, 0·42)	(–0·30, 0·42)	(–0·67, 0·16)	(–0·39, 0·23)	(0·12, 0·95)
95% CI of LS mean	(–0·32, 0·34)	(0·00, 1·17)	(–0·33, 0·49)	(–0·37, 0·49)	(–0·75, 0·24)	(–0·46, 0·30)	(0·04, 1·03)
p value[b]	0·9339	0·0501	0·6945	0·7688	0·3046	0·6707	0·0343
LS mean difference compared with placebo[c]	··	0·57 (0·33)	0·07 (0·26)	0·05 (0·28)	–0·27 (0·30)	–0·09 (0·26)	0·53 (0·30)
90% CI of LS mean difference	··	(0·02, 1·12)	(–0·37, 0·50)	(–0·41, 0·51)	(–0·77, 0·23)	(–0·52, 0·33)	(0·02, 1·02)
95% CI of LS mean difference	··	(–0·09, 1·23)	(–0·45, 0·59)	(–0·50, 0·60)	(–0·87, 0·33)	(–0·61, 0·42)	(–0·08, 1·12)
p value[d]	··	0·0880	0·7979	0·8566	0·3711	0·7149	0·0875
Percent change from baseline to day 92							
n, unstructured	18	5	11	10	7	13	7
LS mean (SE)	0·61 (2·28)	7·36 (4·05)	1·80 (2·84)	3·05 (2·99)	–3·66 (3·42)	–1·85 (2·60)	6·89 (3·43)
90% CI of LS mean	(–3·19, 4·41)	(0·61, 14·11)	(–2·93, 6·54)	(–1·95, 8·04)	(–9·36, 2·05)	(–6·19, 2·49)	(1·17, 12·62)
95% CI of LS mean	(–3·94, 5·16)	(–0·72, 15·44)	(–3·86, 7·47)	(–2·93, 9·02)	(–10·48, 3·17)	(–7·05, 3·34)	(0·05, 13·74)
p value[b]	0·7890	0·0734	0·5270	0·3125	0·2893	0·4792	0·0485
LS mean difference compared with placebo[c]	··	6·75 (4·57)	1·19 (3·61)	2·43 (3·81)	–4·27 (4·14)	–2·47 (3·54)	6·28 (4·16)
90% CI of LS mean difference	··	(–0·87, 14·36)	(–4·84, 7·22)	(–3·93, 8·79)	(–11·17, 2·63)	(–8·37, 3·44)	(–0·66, 13·22)
95% CI of LS mean difference	··	(–2·36, 15·86)	(–6·03, 8·41)	(–5·18, 10·04)	(–12·52, 3·99)	(–9·53, 4·60)	(–2·02, 14·59)
p value[d]	··	0·1440	0·7425	0·5255	0·3059	0·4888	0·1357

Mixed-model repeated measures analysis was used to analyse the change from baseline and the percent change from baseline in metabolic parameters. The model included baseline as a covariate, and treatment group, visit and the interaction between treatment group and visit as factors.

CI=confidence interval. HbA_{1c}=glycated haemoglobin. LS=least-squares. Q2W=once every 2 weeks. QW=once per week. SD=standard deviation. SE=standard error.
[a]Baseline values are for the Randomised population.
[b]p value of the within-group treatment difference.
[c]The difference between treatment and placebo.
[d]p value of the between-group and placebo treatment difference.

Supplementary table 20: **Change in bodyweight (Pharmacodynamics population)**

	Placebo (n=19)	Pegozafermin					
		3 mg QW (n=6)	9 mg QW (n=12)	18 mg QW (n=11)	27 mg QW (n=10)	18 mg Q2W (n=14)	36 mg Q2W (n=9)
Bodyweight, kg							
Baseline[a]							
Mean (SD)	93·64 (15·26)	87·93 (23·40)	87·18 (17·33)	87·05 (17·14)	94·02 (11·00)	101·48 (18·75)	101·06 (19·80)
Change from baseline to day 85							
n, unstructured	18	5	11	10	7	13	8
LS mean (SE)	1·23 (0·83)	0·65 (1·45)	2·17 (1·03)	2·58 (1·11)	–0·54 (1·25)	2·35 (0·96)	3·18 (1·20)
90% CI of LS mean	(–0·16, 2·61)	(–1·77, 3·08)	(0·45, 3·89)	(0·72, 4·43)	(–2·63, 1·54)	(0·76, 3·95)	(1·17, 5·18)
95% CI of LS mean	(–0·43, 2·88)	(–2·25, 3·55)	(0·12, 4·23)	(0·35, 4·80)	(–3·03, 1·95)	(0·44, 4·26)	(0·78, 5·58)
p value[b]	0·1436	0·6548	0·0386	0·0238	0·6669	0·0165	0·0101
LS mean difference compared with placebo[c]	..	–0·57 (1·67)	0·95 (1·32)	1·35 (1·39)	–1·77 (1·50)	1·12 (1·27)	1·95 (1·46)
90% CI of LS mean difference	..	(–3·36, 2·21)	(–1·26, 3·15)	(–0·97, 3·66)	(–4·27, 0·73)	(–0·99, 3·24)	(–0·49, 4·39)
95% CI of LS mean difference	..	(–3·91, 2·76)	(–1·69, 3·58)	(–1·42, 4·12)	(–4·76, 1·22)	(–1·40, 3·65)	(–0·96, 4·87)
p value[d]	..	0·7322	0·4775	0·3354	0·2427	0·3783	0·1865
Percent change from baseline to day 85							
n, unstructured	18	5	11	10	7	13	8
LS mean (SE)	1·38 (0·59)	1·19 (1·06)	2·59 (0·74)	2·47 (0·79)	–0·80 (0·86)	2·11 (0·69)	2·64 (0·86)
90% CI of LS mean	(0·41, 2·36)	(–0·56, 2·93)	(1·36, 3·81)	(1·16, 3·79)	(–2·22, 0·62)	(0·97, 3·25)	(1·21, 4·06)
95% CI of LS mean	(0·22, 2·55)	(–0·90, 3·27)	(1·13, 4·04)	(0·91, 4·04)	(–2·50, 0·90)	(0·75, 3·47)	(0·94, 4·34)
p value[b]	0·0204	0·2636	0·0006	0·0022	0·3539	0·0026	0·0026
LS mean difference compared with placebo[c]	..	–0·20 (1·21)	1·20 (0·94)	1·09 (0·99)	–2·18 (1·04)	0·73 (0·90)	1·26 (1·04)
90% CI of LS mean difference	..	(–2·20, 1·81)	(–0·36, 2·77)	(–0·54, 2·73)	(–3·91, –0·46)	(–0·77, 2·23)	(–0·47, 2·98)
95% CI of LS mean	..	(–2·59, 2·20)	(–0·66, 3·07)	(–0·86, 3·04)	(–4·24, –0·12)	(–1·06, 2·52)	(–0·80, 3·32)

difference							
p value[d]	..	0·8718	0·2043	0·2710	0·0380	0·4223	0·2299

Mixed-model repeated measures analysis was used to analyse the change from baseline and the percent change from baseline in anthropomorphic parameters. The model included baseline as a covariate, and treatment group, visit and the interaction between treatment group and visit as factors.
CI=confidence interval. LS=least-squares. Q2W=once every 2 weeks. QW=once per week. SD=standard deviation. SE=standard error.
[a]Baseline values are for the Randomised population.
[b]p value of the within-group treatment difference.
[c]The difference between treatment and placebo.
[d]p value of the between-group and placebo treatment difference.

Supplementary table 21: **Change in adiponectin levels (Pharmacodynamics population)**

	Placebo (n=19)	**Pegozafermin**					
		3 mg QW (n=6)	**9 mg QW (n=12)**	**18 mg QW (n=11)**	**27 mg QW (n=10)**	**18 mg Q2W (n=14)**	**36 mg Q2W (n=9)**
Adiponectin, ug/mL							
Baseline[a]							
Mean (SD)	4·921 (3·700)	3·083 (1·283)	5·033 (1·459)	4·864 (4·127)	4·750 (3·183)	4·893 (2·059)	4·600 (2·283)
Change from baseline to day 92							
n, unstructured	18	5	11	10	7	13	7
LS mean (SE)	–0·34 (0·43)	1·05 (0·79)	1·05 (0·79)	1·80 (0·58)	3·35 (0·66)	1·23 (0·50)	0·67 (0·66)
90% CI of LS mean	(–1·06, 0·38)	(–0·26, 2·36)	(0·20, 2·02)	(0·83, 2·77)	(2·25, 4·44)	(0·39, 2·06)	(–0·43, 1·77)
95% CI of LS mean	(–1·21, 0·52)	(–0·52, 2·62)	(0·02, 2·20)	(0·64, 2·95)	(2·03, 4·66)	(0·23, 2·22)	(–0·65, 1·99)
p value[b]	0·4323	0·1858	0·0466	0·0029	<0·0001	0·0169	0·3140
LS mean difference compared with placebo[c]	..	1·39 (0·90)	1·45 (0·70)	2·15 (0·72)	3·69 (0·79)	1·57 (0·66)	1·01 (0·79)
90% CI of LS mean difference	..	(–0·11, 2·89)	(0·29, 2·62)	(0·94, 3·35)	(2·37, 5·00)	(0·47, 2·67)	(–0·31, 2·33)
95% CI of LS mean difference	..	(–0·40, 3·19)	(0·06, 2·85)	(0·70, 3·59)	(2·11, 5·26)	(0·25, 2·89)	(–0·57, 2·59)
p value[d]	..	0·1258	0·0415	0·0044	<0·0001	0·0208	0·2045
Percent change from baseline to day 92							
n, unstructured	18	5	11	10	7	13	7
LS mean (SE)	–4·25 (7·80)	37·65 (14·48)	25·46 (9·88)	29·09 (10·47)	60·85 (12·00)	23·11 (9·07)	24·14 (12·10)
90% CI of LS mean	(–17·27, 8·77)	(13·51, 61·79)	(8·97, 41·94)	(11·62, 46·57)	(40·86, 80·85)	(7·98, 38·23)	(3·96, 44·31)
95% CI of LS mean	(–19·83, 11·33)	(8·76, 66·54)	(5·73, 45·19)	(8·18, 50·01)	(36·93, 84·77)	(5·01, 41·21)	(0·00, 48·28)
p value[b]	0·5877	0·0114	0·0122	0·0071	<0·0001	0·0131	0·0500
LS mean difference compared with placebo[c]	..	41·90 (16·47)	29·71 (12·59)	33·34 (13·05)	65·11 (14·31)	27·36 (11·96)	28·39 (14·40)

90% CI of LS mean difference	..	(14·44, 69·36)	(8·71, 50·71)	(11·56, 55·12)	(41·25, 88·96)	(7·41, 47·31)	(4·37, 52·50)
95% CI of LS mean difference	..	(9·04, 74·76)	(4·57, 54·84)	(7·27, 59·41)	(36·57, 93·65)	(3·48, 51·24)	(–0·35, 57·12)
p value[d]	..	0·0132	0·0213	0·0130	<0·0001	0·0254	0·0528

Mixed-model repeated measures analysis was used to analyse the change from baseline and the percent change from baseline in metabolic parameters. The model included baseline as a covariate, and treatment group, visit and the interaction between treatment group and visit as factors.
CI=confidence interval. LS=least-squares. Q2W=once every 2 weeks. QW=once per week. SD=standard deviation. SE=standard error.
[a]Baseline values are for the Randomised population.
[b]p value of the within group treatment difference.
[c]The difference between treatment and placebo.
[d]p value of the between group and placebo treatment difference.

Supplementary table 22: **Change in free fatty acid levels (Pharmacodynamics population)**

	Placebo (n=19)	**Pegozafermin**					
		3 mg QW (n=6)	**9 mg QW (n=12)**	**18 mg QW (n=11)**	**27 mg QW (n=10)**	**18 mg Q2W (n=14)**	**36 mg Q2W (n=9)**
Free Fatty Acid, mmol/L							
Baseline[a]							
n	18	6	8	11	10	12	9
Mean (SD)	0·47 (0·22)	0·50 (0·11)	0·34 (0·09)	0·39 (0·15)	0·53 (0·31)	0·41 (0·20)	0·35 (0·18)
Change from baseline to day 92							
n, unstructured	16	5	7	10	6	9	7
LS mean (SE)	0·06 (0·05)	0·15 (0·08)	0·12 (0·07)	0·03 (0·06)	0·14 (0·07)	0·12 (0·06)	0·09 (0·07)
90% CI of LS mean	(–0·02, 0·14)	(0·01, 0·28)	(0·01, 0·24)	(–0·07, 0·13)	(0·02, 0·27)	(0·02, 0·22)	(–0·02, 0·21)
95% CI of LS mean	(–0·03, 0·15)	(–0·02, 0·31)	(–0·02, 0·26)	(–0·09, 0·15)	(–0·01, 0·29)	(0·00, 0·24)	(–0·05, 0·23)
p value[b]	0·2124	0·0817	0·0794	0·6257	0·0590	0·0474	0·1878
LS mean difference compared with placebo[c]	..	0·09 (0·09)	0·07 (0·08)	–0·03 (0·07)	0·08 (0·09)	0·06 (0·08)	0·03 (0·08)
90% CI of LS mean difference	..	(–0·07, 0·25)	(–0·07, 0·21)	(–0·15, 0·10)	(–0·06, 0·23)	(–0·06, 0·19)	(–0·11, 0·17)
95% CI of LS mean difference	..	(–0·10, 0·28)	(–0·10, 0·23)	(–0·18, 0·12)	(–0·09, 0·26)	(–0·09, 0·22)	(–0·13, 0·20)
p value[d]	..	0·3554	0·4343	0·6949	0·3390	0·4020	0·6883
Percent change from baseline to day 92							
n, unstructured	16	5	7	10	6	9	7
LS mean (SE)	20·91 (13·96)	28·70 (24·68)	50·20 (21·05)	27·08 (17·76)	51·58 (22·08)	43·85 (18·17)	56·12 (20·81)
90% CI of LS mean	(–2·45, 44·26)	(–12·56, 69·96)	(15·00, 85·40)	(–2·64, 56·81)	(14·70, 88·46)	(13·50, 74·21)	(21·36, 90·89)

95% CI of LS mean	(–7·06, 48·88)	(–20·71, 78·12)	(8·05, 92·36)	(–8·52, 62·69)	(7·43, 95·73)	(7·51, 80·20)	(14·50, 97·75)
p value[b]	0·1399	0·2497	0·0205	0·1331	0·0228	0·0189	0·0091
LS mean difference compared with placebo[c]	··	7·79 (28·29)	29·29 (25·33)	6·18 (22·63)	30·67 (26·07)	22·95 (22·91)	35·22 (25·13)
90% CI of LS mean difference	··	(–39·51, 55·10)	(–13·06, 71·64)	(–31·69, 44·04)	(–12·89, 74·24)	(–15·36, 61·25)	(–6·78, 77·21)
95% CI of LS mean difference	··	(–48·86, 64·45)	(–21·43, 80·02)	(–39·18, 51·53)	(–21·49, 82·84)	(–22·92, 68·81)	(–15·07, 85·50)
p value[d]	··	0·7840	0·2523	0·7860	0·2441	0·3208	0·1663

Mixed-model repeated measures analysis was used to analyse the change from baseline and the percent change from baseline in metabolic parameters. The model included baseline as a covariate, and treatment group, visit and the interaction between treatment group and visit as factors.
CI=confidence interval. LS=least-squares. Q2W=once every 2 weeks. QW=once per week. SD=standard deviation. SE=standard error.
[a]Baseline values are for the Randomised population.
[b]p value of the within-group treatment difference.
[c]The difference between treatment and placebo.
[d]p value of the between-group and placebo treatment difference.

Supplementary table 23: **Change in Adipo-IR levels (Pharmacodynamics population)**

	Placebo (n=19)	**Pegozafermin**					
		3 mg QW (n=6)	**9 mg QW (n=12)**	**18 mg QW (n=11)**	**27 mg QW (n=10)**	**18 mg Q2W (n=14)**	**36 mg Q2W (n=9)**
Adipo-IR							
Baseline[a]							
n	18	6	7	8	10	11	7
Mean (SD)	13·43 (9·41)	11·55 (4·68)	8·84 (4·05)	15·16 (11·26)	17·41 (8·99)	17·33 (11·70)	14·37 (11·49)
Change from baseline to day 50							
n, unstructured	14	4	4	4	7	8	6
LS mean (SE)	–3·05 (2·58)	–2·84 (4·90)	0·24 (4·70)	–4·40 (4·72)	1·61 (3·68)	–6·13 (3·38)	–3·39 (4·00)
90% CI of LS mean	(–7·39, 1·29)	(–11·09, 5·41)	(–7·66, 8·14)	(–12·33, 3·53)	(–4·58, 7·80)	(–11·80, –0·45)	(–10·11, 3·33)
95% CI of LS mean	(–8·26, 2·16)	(–12·74, 7·06)	(–9·24, 9·72)	(–13·91, 5·11)	(–5·82, 9·03)	(–12·93, 0·68)	(–11·45, 4·68)
p value[b]	0·2440	0·5654	0·9598	0·3560	0·6643	0·0766	0·4013
LS mean difference compared with placebo[c]	··	0·21 (5·54)	3·29 (5·36)	–1·35 (5·38)	4·66 (4·50)	–3·08 (4·26)	–0·34 (4·76)
90% CI of LS mean difference	··	(–9·11, 9·52)	(–5·72, 12·29)	(–10·39, 7·68)	(–2·91, 12·22)	(–10·23, 4·07)	(–8·34, 7·66)
95% CI of LS mean difference	··	(–10·97, 11·39)	(–7·51, 14·09)	(–12·19, 9·49)	(–4·42, 13·73)	(–11·65, 5·50)	(–9·94, 9·26)
p value[d]	··	0·9702	0·5427	0·8027	0·3064	0·4735	0·9435

Percent change from baseline to day 50							
n, unstructured	14	4	4	4	7	8	6
LS mean (SE)	–15·82 (32·62)	–6·12 (61·71)	82·00 (59·79)	3·28 (60·01)	78·40 (46·41)	–25·96 (42·75)	–10·36 (50·33)
90% CI of LS mean	(–70·66, 39·01)	(–109·90, 97·66)	(–18·48, 182·47)	(–97·56, 104·13)	(0·39, 156·40)	(–97·79, 45·87)	(–95·00, 74·29)
95% CI of LS mean	(–81·61, 49·96)	(–130·63, 118·39)	(–38·52, 202·52)	(–117·68, 124·25)	(–15·18, 171·97)	(–112·11, 60·20)	(–111·91, 91·20)
p value[b]	0·6301	0·9215	0·1772	0·9566	0·0984	0·5469	0·8379
LS mean difference compared with placebo[c]	..	9·70 (69·79)	97·82 (68·09)	19·11 (68·29)	94·22 (56·74)	–10·13 (53·79)	5·47 (59·99)
90% CI of LS mean difference	..	(–107·65, 127·06)	(–16·60, 212·24)	(–95·66, 133·87)	(–1·16, 189·60)	(–100·52, 80·26)	(–95·40, 106·33)
95% CI of LS mean difference	..	(–131·09, 150·50)	(–39·43, 235·07)	(–118·55, 156·77)	(–20·19, 208·63)	(–118·55, 98·29)	(–115·55, 126·48)
p value[d]		0·8901	0·1579	0·7809	0·1041	0·8515	0·9278

Mixed-model repeated measures analysis was used to analyse the change from baseline and the percent change from baseline in metabolic parameters. The model included baseline as a covariate, and treatment group, visit and the interaction between treatment group and visit as factors.
Adipo-IR=adipose tissue insulin resistance which is derived from fasting insulin and free fatty acid. CI=confidence interval. LS=least-squares. Q2W=once every 2 weeks. QW=once per week. SD=standard deviation. SE=standard error.
[a]Baseline values are for the Randomised population.
[b]p value of the within-group treatment difference.
[c]The difference between treatment and placebo.
[d]p value of the between-group and placebo treatment difference.

Supplementary table 24: **Participant randomisation by site (Randomised population)**

		Pegozafermin						
	Placebo (n=19)	**3 mg QW (n=6)**	**9 mg QW (n=12)**	**18 mg QW (n=11)**	**27 mg QW (n=10)**	**18 mg Q2W (n=14)**	**36 mg Q2W (n=9)**	**Overall (N=81)**
Site								
1101	4	4	2	0	2	0	0	12
1102	0	0	0	0	0	0	0	0
1103	2	0	0	4	0	6	0	12
1104	5	2	9	3	1	0	4	24
1105	2	0	0	1	0	1	0	4
1106	0	0	0	0	0	0	0	0

	Placebo (n=19)	Pegozafermin						
		3 mg QW (n=6)	9 mg QW (n=12)	18 mg QW (n=11)	27 mg QW (n=10)	18 mg Q2W (n=14)	36 mg Q2W (n=9)	Overall (N=81)
1107	0	0	1	1	2	1	1	6
1108	1	0	0	0	0	5	0	6
1109	0	0	0	0	0	0	0	0
1110	2	0	0	0	1	1	1	5
1111	2	0	0	0	4	0	3	9
1112	0	0	0	0	0	0	0	0
1113	1	0	0	1	0	0	0	2
1114	0	0	0	1	0	0	0	1

Supplementary table 25: **Demographics and baseline characteristics of the BC-NASH and PNASH subpopulations (Randomised population)**

	BC-NASH[a] (n=15)	PNASH[b] (n=66)	Overall (n=81)
Age, mean, years	50·6	52·2	51·9
Male, %	20·0	42·4	38·3
Weight, mean, kg	99·3	92·3	93·6
BMI, mean, kg/m^2	35·4	34·4	34·6
T2DM, %	26·7	50·0	45·7
MRI-PDFF, %	21·2	21·4	21·3
ALT, mean, U/L	42·9	41·1	41·5
ALT >ULN,[c] %	26·7	36·4	34·6
AST, mean, U/L	34·9	30·0	31·0

ALT=alanine aminotransferase. AST=aspartate aminotransferase; BC-NASH=biopsy-confirmed non-alcoholic steatohepatitis. BMI=body mass index. MRI-PDFF=magnetic resonance imaging proton-density fat fraction. PNASH=phenotypic non-alcoholic steatohepatitis. T2DM=type 2 diabetes mellitus. ULN=upper limit of normal.

[a]Defined as NASH Clinical Research Network fibrosis stage 1, 2, or 3 based on biopsy performed in the 24 months before screening, or PNASH if biopsy was not available.

[b]Defined as: obesity (BMI >30 kg/m^2) with either T2DM (fasting plasma glucose ≥126 mg/dL, plasma glucose in a 75 g oral glucose tolerance test ≥200 mg/dL, or glycated haemoglobin ≥6·5 %); obesity with evidence of liver injury (increased ALT [≥40 U/L in men or ≥30 U/L in women]; and/or FibroScan (EchoSens, Waltham, MA, USA) vibration-controlled transient elastography score ≥7 kPa.

[c]ULN=45 U/L.

Supplementary table 26: **Demographics and baseline characteristics of participants who had a ≥30% relative reduction versus placebo in hepatic fat fraction (MRI-PDFF responders) versus those who did not (MRI-PDFF non-responders) (Pharmacodynamics–MRI population)**

	MRI-PDFF responder (n=40)	MRI-PDFF non-responder (n=14)
Age, years		
Mean (SD)	52·83 (8·335)	47·54 (13·603)
Median (IQR)	53·15 (46·40, 58·45)	51 (2·40, 56·70)
Female, n (%)	26 (65·0)	7 (50·0)
Race, n (%)		
Black or African American	2 (5·0)	2 (14·3)
White	37 (92·5)	12 (85·7)
Other	1 (2·5)	0
Ethnicity, n (%)		
Hispanic or Latino	39 (97·5)	11 (78·6)
Not Hispanic of Latino	1 (2·5)	3 (21·4)
Weight, kg		
Mean (SD)	89·908 (17·868)	104·454 (18·345)
Median (IQR)	87·55 (80·175, 97·050)	104·7 (92·100, 119·100)
BMI, kg/m^2		
Mean (SD)	33·95 (4·905)	37·33 (6·274)
Median (IQR)	33·65 (0·45, 37·40)	38·05 (31·30, 43·30)
T2DM history		
No	24 (60·0)	10 (71·4)
Yes	16 (40·0)	4 (28·6)
ALT, U/L		
Mean (SD)	42·8 (30·60)	40·4 (23·63)
Median (IQR)	33·5 (23·0, 52·5)	32·5 (26·0, 46·0)
AST, U/L		
Mean (SD)	33·0 (25·72)	26·9 (12·41)
Median (IQR)	24·5 (19·5, 32·0)	23·5 (21·0, 29·0)
MRI-PDFF, %		
Mean (SD)	20·60 (8·715)	22·14 (6·763)
Median (IQR)	18·6 (13·70, 26·20)	20·15 (18·20, 27·60)
≥1/5 high-risk NAFLD criteria,[a] n (%)	37 (92·5)	13 (92·9)
≥2/5 high-risk NAFLD criteria,[a] n (%)	24 (60·0)	10 (71·4)

ALT=alanine aminotransferase. AST=aspartate aminotransferase. BMI=body mass index. IQR=interquartile range. MRI=magnetic resonance imaging. MRI-PDFF=magnetic resonance imaging proton-density fat fraction. NAFLD=non-alcoholic fatty liver disease. SD=standard deviation. T2DM=type 2 diabetes mellitus.

[a]Baseline ALT >1×ULN; vibration-controlled transient elastography ≥7·0 kPa; enhanced liver fibrosis ≥7·7; PRO-C3 ≥14·71 ng/mL; and Fibrosis-4 index score >1·3.

Supplementary table 27: **Change in hepatic fat fraction in sub-group with BC-NASH (Pharmacodynamics–MRI population)**

	Placebo (n=4)	**Pegozafermin**	
		18 mg QW (n=4)	**18 mg Q2W (n=7)**
MRI-PDFF hepatic fat fraction, %			
Change from baseline to day 92			
n, unstructured	4	4	7
LS mean (SE)	–3·32 (3·81)	–7·05 (3·87)	–9·27 (2·89)
90% CI of LS mean	(–10·14, 3·50)	(–13·96, –0·15)	(–14·44, –4·10)
95% CI of LS mean	(–11·67, 5·02)	(–15·50, 1·40)	(–15·60, –2·94)
p value[a]	0·4009	0·0938	0·0079
LS mean difference compared with placebo[b]		–3·73 (5·45)	–5·95 (4·77)
90% CI of LS mean difference		(–13·46, 6·01)	(–14·49, 2·60)
95% CI of LS mean difference		(–15·64, 8·19)	(–16·41, 4·51)
p value[c]		0·5073	0·2378
Percent change from baseline to day 92			
n, unstructured	4	4	7
LS mean (SE)	–13·18 (16·39)	–27·16 (16·61)	–48·76 (12·44)
90% CI of LS mean	(–42·54, 16·18)	(–56·86, 2·53)	(–71·03, –26·50)
95% CI of LS mean	(–49·13, 22·77)	(–63·50, 9·18)	(–76·02, –21·50)
p value[a]	0·4380	0·1289	0·0022
LS mean difference compared with placebo[b]		–13·98 (23·42)	–35·58 (20·54)
90% CI of LS mean difference		(–55·87, 27·90)	(–72·37, 1·21)
95% CI of LS mean difference		(–65·25, 37·28)	(–80·63, 9·47)
p value[c]		0·5620	0·1103

Mixed-model repeated measures analysis was used to analyse the change from baseline and the percent change from baseline in MRI parameters. The model included baseline as a covariate, and treatment group, visit and the interaction between treatment group and visit as factors.

BC-NASH, biopsy-confirmed nonalcoholic steatohepatitis. CI=confidence interval. LS=least-squares. MRI=magnetic resonance imaging. MRI-PDFF=magnetic resonance imaging proton-density fat fraction. Q2W=once every 2 weeks. QW=once per week. SE=standard error.

[a]p value of the within-group treatment difference.

[b]The difference between treatment and placebo.

[c]p value of the between-group and placebo treatment difference.

Supplementary table 28: **Change in hepatic fat fraction in sub-group with PNASH[a] (Pharmacodynamics–MRI population)**

	Placebo (n=14)	Pegozafermin	
		18 mg QW (n=6)	18 mg Q2W (n=7)
MRI-PDFF hepatic fat fraction, %			
Change from baseline to day 92			
n, unstructured	14	6	6
LS mean (SE)	2·82 (1·49)	–8·45 (2·31)	–8·55 (2·17)
90% CI of LS mean	(0·33, 5·31)	(–12·32, –4·57)	(–12·18, –4·92)
95% CI of LS mean	(–0·16, 5·80)	(–13·09, –3·80)	(–12·89, –4·20)
p value[b]	0·0635	0·0006	0·0002
LS mean difference compared with placebo[c]		–11·27 (2·75)	–11·37 (2·63)
90% CI of LS mean difference		(–15·88, –6·66)	(–15·77, –6·96)
95% CI of LS mean difference		(–16·79, –5·74)	(–16·64, –6·09)
p value[d]		0·0002	<0·0001
Percent change from baseline to day 92			
n, unstructured	14	6	6
LS mean (SE)	16·47 (6·14)	–44·52 (9·60)	–36·54 (9·02)
90% CI of LS mean	(6·18, 26·76)	(–60·60, –28·45)	(–51·63, –21·45)
95% CI of LS mean	(4·14, 28·80)	(–63·79, –25·26)	(–54·62, –18·46)
p value[b]	0·0099	<·0001	0·0002
LS mean difference compared with placebo[c]		–60·99 (11·40)	–53·01 (10·91)
90% CI of LS mean difference		(–80·09, –41·89)	(–71·27, –34·75)
95% CI of LS mean difference		(–83·88, –38·10)	(–74·89, –31·13)
p value[d]		<0·0001	<0·0001

Mixed-model repeated measures analysis was used to analyse the change from baseline and the percent change from baseline in MRI parameters· The model included baseline as a covariate, and treatment group, visit and the interaction between treatment group and visit as factors.

BC-NASH, biopsy-confirmed nonalcoholic steatohepatitis. CI=confidence interval. LS=least-squares. MRI=magnetic resonance imaging. MRI-PDFF=magnetic resonance imaging proton-density fat fraction. PNASH, phenotypic nonalcoholic steatohepatitis. Q2W=once every 2 weeks. QW=once per week. SE=standard error.

[a]Only the 18 mg QW and Q2W cohorts included participants with BC-NASH. PNASH data are thus provided for these cohorts only to compare with BC-NASH.

[b]p value of the within-group treatment difference.

[c]The difference between treatment and placebo.

[d]p value of the between-group and placebo treatment difference.

Supplementary table 29: **Change in ALT levels in sub-group with BC-NASH (Pharmacodynamics population)**

	Placebo (n=4)	**Pegozafermin**	
		18 mg QW (n=4)	**18 mg Q2W (n=7)**
ALT, U/L			
Change from baseline to day 92			
n, compound symmetry	4	4	7
LS mean (SE)	–4·6 (9·4)	–9·4 (9·4)	–7·0 (7·2)
90% CI of LS mean	(–20·6, 11·3)	(–25·3, 6·4)	(–19·2, 5·2)
95% CI of LS mean	(–23·8, 14·5)	(–28·4, 9·6)	(–21·6, 7·7)
p value[a]	0·6262	0·3206	0·3401
LS mean difference compared with placebo[b]		–4·8 (13·1)	–2·3 (12·2)
90% CI of LS mean difference		(–26·8, 17·3)	(–22·9, 18·3)
95% CI of LS mean difference		(–31·3, 21·7)	(–27·1, 22·4)
p value[c]		0·7155	0·8486
Percent change from baseline to day 92			
n, compound symmetry	4	4	7
LS mean (SE)	–10·05 (22·07)	–26·41 (21·89)	–11·75 (16·89)
90% CI of LS mean	(–47·68, 27·58)	(–63·69, 10·88)	(–40·57, 17·08)
95% CI of LS mean	(–55·39, 35·29)	(–71·33, 18·52)	(–46·49, 22·99)
p value[a]	0·6526	0·2382	0·4930
LS mean difference compared with placebo[b]		–16·35 (30·47)	–1·70 (28·57)
90% CI of LS mean difference		(–68·20, 35·50)	(–50·52, 47·13)
95% CI of LS mean difference		(–78·80, 46·09)	(–60·57, 57·18)
p value[c]		0·5958	0·9531

Mixed-model repeated measures analysis was used to analyse the change from baseline and the percent change from baseline in liver parameters. The model included baseline as a covariate, and treatment group, visit and the interaction between treatment group and visit as factors.
ALT=alanine aminotransferase. BC-NASH, biopsy-confirmed nonalcoholic steatohepatitis. CI=confidence interval. LS=least-squares. MRI=magnetic resonance imaging. Q2W=once every 2 weeks. QW=once per week. SE=standard error.
[a]p value of the within-group treatment difference.
[b]The difference between treatment and placebo.
[c]p value of the between-group and placebo treatment difference.

Supplementary table 30: **Change in ALT levels in sub-group with PNASH[a] (Pharmacodynamics population)**

	Placebo (n=15)	Pegozafermin	
		18 mg QW (n=7)	18 mg Q2W (n=7)
ALT, U/L			
Change from baseline to day 92			
n, unstructured	14	6	6
LS mean (SE)	–7·0 (21·3)	–11·8 (32·7)	–23·5 (32·5)
90% CI of LS mean	(–42·8, 28·7)	(–66·7, 43·1)	(–78·0, 31·0)
95% CI of LS mean	(–49·9, 35·9)	(–77·6, 54·1)	(–88·8, 41·8)
p value[b]	0·7432	0·7204	0·4736
LS mean difference compared with placebo[c]		–4·8 (39·0)	–16·5 (38·9)
90% CI of LS mean difference		(–70·3, 60·8)	(–81·6, 48·7)
95% CI of LS mean difference		(–83·3, 73·8)	(–94·6, 61·7)
p value[d]		0·9036	0·6740
Percent change from baseline to day 92			
n, unstructured	14	6	6
LS mean (SE)	–8·06 (40·52)	–26·71 (62·17)	–41·46 (61·78)
90% CI of LS mean	(–76·0l, 59·90)	(–131·02, 77·60)	(–145·01, 62·09)
95% CI of LS mean	(–89·52, 73·41)	(–151·77, 98·35)	(–165·56, 82·64)
p value[b]	0·8432	0·6694	0·5053
LS mean difference compared with placebo[c]		–18·65 (74·19)	–33·40 (73·88)
90% CI of LS mean difference		(–143·11, 105·80)	(–157·26, 90·45)
95% CI of LS mean difference		(–167·86, 130·55)	(–181·85, 115·04)
p value[d]		0·8026	0·6532

Mixed–model repeated measures analysis was used to analyse the change from baseline and the percent change from baseline in liver parameters. The model included baseline as a covariate, and treatment group, visit and the interaction between treatment group and visit as factors.

ALT=alanine aminotransferase. BC-NASH, biopsy-confirmed nonalcoholic steatohepatitis. CI=confidence interval. LS=least–squares. MRI=magnetic resonance imaging. PNASH, phenotypic nonalcoholic steatohepatitis. Q2W=once every 2 weeks. QW=once per week. SE=standard error.

[a]Only the 18 mg QW and Q2W cohorts included participants with BC-NASH. PNASH data are thus provided for these cohorts only to compare with BC-NASH.

[b]p value of the within–group treatment difference.

[c]The difference between treatment and placebo.

[d]p value of the between–group and placebo treatment difference.

Supplementary table 31: **Change in AST levels in sub-group with BC-NASH (Pharmacodynamics population)**

	Placebo (n=4)	**Pegozafermin**	
		18 mg QW (n=4)	**18 mg Q2W (n=7)**
AST, U/L			
Change from baseline to day 92			
n, compound symmetry	4	4	7
LS mean (SE)	–11·4 (6·6)	–4·7 (6·5)	–6·8 (5·0)
90% CI of LS mean	(–22·4, –0·5)	(–15·6, 6·1)	(–15·1, 1·5)
95% CI of LS mean	(–24·5, 1·7)	(–17·7, 8·2)	(–16·7, 3·2)
p value[a]	0·0860	0·4702	0·1798
LS mean difference compared with placebo[b]		6·7 (9·2)	4·7 (8·4)
90% CI of LS mean difference		(–8·6, 22·0)	(–9·3, 18·6)
95% CI of LS mean difference		(–11·6, 25·0)	(–12·0, 21·3)
p value[c]		0·4687	0·5781
Percent change from baseline to day 92			
n, unstructured	4	4	7
LS mean (SE)	–25·25 (12·25)	–12·43 (12·13)	–10·29 (9·29)
90% CI of LS mean	(–47·07, –3·43)	(–34·07, 9·20)	(–26·83, 6·25)
95% CI of LS mean	(–51·92, 1·42)	(–38·89, 14·02)	(–30·51, 9·93)
p value[a]	0·0615	0·3258	0·2895
LS mean difference compared with placebo[b]		12·82 (17·11)	14·96 (15·60)
90% CI of LS mean difference		(–17·70, 43·33)	(–12·78, 42·70)
95% CI of LS mean difference		(–24·49, 50·13)	(–18·93, 48·85)
p value[c]		0·4683	0·3560

Mixed-model repeated measures analysis was used to analyse the change from baseline and the percent change from baseline in liver parameters. The model included baseline as a covariate, and treatment group, visit and the interaction between treatment group and visit as factors.
AST=aspartate aminotransferase. BC-NASH, biopsy-confirmed nonalcoholic steatohepatitis. CI=confidence interval. LS=least-squares. SE=standard error. Q2W=once every 2 weeks. QW=once per week.
[a]p value of the within-group treatment difference.
[b]The difference between treatment and placebo.
[c]p value of the between-group and placebo treatment difference.

Supplementary table 32: **Change in AST levels in sub-group with PNASH[a] (Pharmacodynamics population)**

	Placebo (n=15)	Pegozafermin	
		18 mg QW (n=7)	18 mg Q2W (n=7)
AST, U/L			
Change from baseline to day 92			
n, unstructured	14	6	6
LS mean (SE)	–5·7 (11·5)	–10·3 (17·6)	–6·9 (17·9)
90% CI of LS mean	(–25·0, 13·7)	(–39·9, 19·2)	(–36·9, 23·1)
95% CI of LS mean	(–28·9, 17·6)	(–45·8, 25·1)	(–42·8, 29·0)
p value[b]	0·6256	0·5598	0·7006
LS mean difference compared with placebo[c]		–4·7 (21·1)	–1·2 (21·3)
90% CI of LS mean difference		(–40·0, 30·7)	(–36·9, 34·4)
95% CI of LS mean difference		(–47·0, 37·7)	(–44·0, 41·5)
p value[d]		0·8252	0·9538
Percent change from baseline to day 92			
n, unstructured	14	6	6
LS mean (SE)	–l·03 (43·27)	–18·58 (66·13)	–16·14 (66·38)
90% CI of LS mean	(–73·59, 71·53)	(–129·49, 92·34)	(–127·39, 95·11)
95% CI of LS mean	(–88·01, 85·95)	(–151·54, 114·38)	(–149·47, 117·20)
p value[b]	0·9811	0·7800	0·8089
LS mean difference compared with placebo[c]		–17·55 (79·02)	–15·11 (79·24)
90% CI of LS mean difference		(–150·08, 114·98)	(–147·93, 117·71)
95% CI of LS mean difference		(–176·42, 141·32)	(–174·30, 144·08)
p value[d]		0·8252	0·8495

Mixed-model repeated measures analysis was used to analyse the change from baseline and the percent change from baseline in liver parameters. The model included baseline as a covariate, and treatment group, visit and the interaction between treatment group and visit as factors.
AST=aspartate aminotransferase. BC-NASH, biopsy-confirmed nonalcoholic steatohepatitis. CI=confidence interval. LS=least-squares. PNASH, phenotypic nonalcoholic steatohepatitis. SE=standard error. Q2W=once every 2 weeks. QW=once per week.
[a]Only the 18 mg QW and Q2W cohorts included participants with BC-NASH. PNASH data are thus provided for these cohorts only to compare with BC-NASH.
[b]p value of the within-group treatment difference.
[c]The difference between treatment and placebo.
[d]p value of the between-group and placebo treatment difference.

Supplementary table 33: **Change in PRO-C3 levels in sub-group with BC-NASH (Pharmacodynamics population)**

	Placebo (n=4)	**Pegozafermin**	
		18 mg QW (n=4)	**18 mg Q2W (n=7)**
PRO-C3, ng/mL			
Change from baseline to day 92			
n, unstructured	4	4	7
LS mean (SE)	–2·49 (2·06)	0·97 (2·05)	–0·40 (1·55)
90% CI of LS mean	(–6·15, 1·17)	(–2·69, 4·63)	(–3·17, 2·37)
95% CI of LS mean	(–6·97, 1·99)	(–3·51, 5·45)	(–3·79, 2·98)
p value[a]	0·2491	0·6450	0·7996
LS mean difference compared with placebo[b]		3·46 (2·91)	2·09 (2·58)
90% CI of LS mean difference		(–1·72, 8·64)	(–2·51, 6·68)
95% CI of LS mean difference		(–2.87, 9.80)	(–3.53, 7.70)
p value[c]		0.2568	0.4339
Percent change from baseline to day 92			
n, unstructured	4	4	7
LS mean (SE)	–20·21 (18·87)	8·86 (18·86)	–1·20 (14·26)
90% CI of LS mean	(–53·85, 13·43)	(–24·76, 42·49)	(–26·63, 24·22)
95% CI of LS mean	(–61·34, 20·92)	(–32·25, 49·97)	(–32·29, 29·88)
p value[a]	0·3053	0·6469	0·9341
LS mean difference compared with placebo[b]		29·07 (26·68)	19·00 (23·66)
90% CI of LS mean difference		(–18·50, 76·63)	(–23·18, 61·18)
95% CI of LS mean difference		(–29·08, 87·22)	(–32·56, 70·57)
p value[c]		0·2974	0·4375

Mixed-model repeated measures analysis was used to analyse the change from baseline and the percent change from baseline in liver parameters. The model included baseline as a covariate, and treatment group, visit and the interaction between treatment group and visit as factors.
BC-NASH, biopsy-confirmed nonalcoholic steatohepatitis. CI=confidence interval. LS=least-squares. PRO-C3=*N*-terminal propeptide of type III collagen. SE=standard error. Q2W=once every 2 weeks. QW=once per week.
[a]p value of the within-group treatment difference.
[b]The difference between treatment and placebo.
[c]p value of the between-group and placebo treatment difference.

Supplementary table 34: **Change in PRO-C3 levels in sub-group with PNASH[a] (Pharmacodynamics population)**

	Placebo (n=15)	Pegozafermin	
		18 mg QW (n=7)	18 mg Q2W (n=7)
PRO-C3, ng/mL			
Change from baseline to day 92			
n, unstructured	14	6	6
LS mean (SE)	0·36 (0·83)	–0·53 (1·25)	–2·80 (1·25)
90% CI of LS mean	(–1·02, 1·75)	(–2·64, 1·57)	(–4·89, –0·71)
95% CI of LS mean	(–1·29, 2·02)	(–3·05, 1·99)	(–5·31, –0·30)
p value[b]	0·6603	0·6720	0·0290
LS mean difference compared with placebo[c]		–0·90 (1·50)	–3·17 (1·50)
90% CI of LS mean difference		(–3·42,1·62)	(–5·68, –0·66)
95% CI of LS mean difference		(–3·92,2·12)	(–6·18, –0·16)
p value[d]		0·5521	0·0393
Percent change from baseline to day 92			
n, unstructured	14	6	6
LS mean (SE)	10·58 (7·19)	–4·09 (10·94)	–22·50 (10·89)
90% CI of LS mean	(–1·47, 22·63)	(–22·42, 14·25)	(–40·75, –4·26)
95% CI of LS mean	(–3·86, 25·03)	(–26·06, 17·89)	(–44·37, –0·64)
p value[b]	0·1474	0·7103	0·0439
LS mean difference compared with placebo[c]		–14·67 (13·09)	–33·09 (13·06)
90% CI of LS mean difference		(–36·61, 7·28)	(–54·97, –11·20)
95% CI of LS mean difference		(–40·97, 11·63)	(–59·32, –6·86)
p value[d]		0·2679	0·0145

Mixed-model repeated measures analysis was used to analyse the change from baseline and the percent change from baseline in liver parameters. The model included baseline as a covariate, and treatment group, visit and the interaction between treatment group and visit as factors.

BC-NASH, biopsy-confirmed nonalcoholic steatohepatitis. CI=confidence interval. LS=least-squares. PNASH, phenotypic nonalcoholic steatohepatitis. PRO-C3=*N*-terminal propeptide of type III collagen. SE=standard error. Q2W=once every 2 weeks. QW=once per week.

[a]Only the 18 mg QW and Q2W cohorts included participants with BC-NASH. PNASH data are thus provided for these cohorts only to compare with BC-NASH.

[b]p value of the within-group treatment difference.

[c]The difference between treatment and placebo.

[d]p value of the between-group and placebo treatment difference.