Efficacy and safety of zalfermin co-administered with semaglutide in participants with fibrosis and cirrhosis due to metabolic dysfunction-associated steatohepatitis: a phase 2, dose-ranging, double-blind, randomised controlled trial

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Summary

Background This phase 2 study evaluated once-weekly zalfermin and semaglutide for efficacy and safety in patients with metabolic dysfunction-associated steatohepatitis and clinically significant fibrosis, including patients with compensated cirrhosis (F4c).

Methods This proof-of-concept, phase 2, dose-ranging, double-blind, randomised controlled trial was done in 187 clinical trial sites in Australia, Belgium, Bulgaria, Canada, Czech Republic, Denmark, France, Germany, Greece, India, Italy, Japan, Malaysia, Poland, Portugal, Russia, Singapore, South Korea, Spain, Taiwan, Türkiye, and the USA. Eligible participants were aged 18 years or older with histological confirmation of steatohepatitis on liver biopsy (baseline or historical within 180 days). Eligible participants had clinically significant fibrosis (stage F2–F4c) in the absence of decompensation. Eligible participants were randomly assigned to receive subcutaneous zalfermin 7·5 mg plus subcutaneous semaglutide 2·4 mg, zalfermin 15 mg plus semaglutide 2·4 mg, zalfermin 30 mg plus semaglutide 2·4 mg, zalfermin 30 mg, semaglutide 2·4 mg, cagrilintide 2·4 mg plus semaglutide 2·4 mg, or placebo only once a week for 52 weeks. The primary endpoint was improvement in liver fibrosis on the NASH CRN fibrosis scale of at least one stage and no worsening of metabolic dysfunction-associated steatohepatitis at week 52. Efficacy was assessed in the full analysis set (all randomly assigned participants) and safety was analysed in all participants who were randomly assigned and received at least one dose of trial product or placebo. The trial is registered with ClinicalTrials.gov, NCT05016882, and is completed.

Findings Between Aug 31, 2021, and March 14, 2025, 2420 people were screened for inclusion. 178 withdrew before random assignment and 1544 were disqualified. 698 participants were enrolled and randomly assigned to zalfermin 7·5 mg plus semaglutide 2·4 mg (n=99), zalfermin 15 mg plus semaglutide 2·4 mg (n=100), zalfermin 30 mg plus semaglutide 2·4 mg (n=99), zalfermin 30 mg (n=101), semaglutide 2·4 mg (n=100), cagrilintide 2·4 mg plus semaglutide 2·4 mg (n=99), or placebo (n=100). 441 (63%) of 698 participants were female and 257 (37%) were male. 484 (69%) of 698 participants were White and 172 (25%) were Asian. At week 52, the proportion of participants who had an improvement in liver fibrosis and no worsening of metabolic dysfunction-associated steatohepatitis with zalfermin 30 mg plus semaglutide 2·4 mg was not significantly greater than with placebo (24 [24%] of 99 participants in the combination group *vs* 16 [16%] of 100 participants in the placebo group; estimated difference in responder proportions [EDP] 7·98, 95% CI –3·82 to 19·79; p=0·19). A nominally significantly greater proportion of participants in the semaglutide 2·4 mg group achieved this endpoint than in the placebo group (30 [30%] of 100 participants in the semaglutide group; EDP 14·05, 95% CI 1·88 to 26·23; p=0·024), but not in the zalfermin 30 mg group versus placebo (22 [22%] of 101 participants in the zalfermin group; 4·99, –6·51 to 16·49; p=0·39). Similarly, the proportions of participants achieving this endpoint in the two groups that combined lower doses of zalfermin with semaglutide 2·4 mg and in the exploratory group combining cagrilintide 2·4 mg with semaglutide 2·4 mg were not substantially different than with placebo. Adverse events were mostly non-serious and mild to moderate in severity. The most frequent adverse events were gastrointestinal, reported in 79 (80%) of 99 participants in the zalfermin 30 mg plus semaglutide 2·4 mg group, 61 (60%) of 101 participants in the zalfermin 30 mg group, 73 (73%) of 100 participants in the semaglutide 2·4 mg group, and 51 (51%) of 100 participants in the placebo group. Serious adverse events were reported in seven (7%) participants in the zalfermin 30 mg plus semaglutide 2·4 mg group, 13 (13%) participants in the zalfermin 30 mg group, ten (10%) participants in the semaglutide 2·4 mg group, and five (5%) participants in the placebo group. Five deaths were reported in the trial, one of which was assessed as possibly related to study drug (heart failure, zalfermin 30 mg group).

Interpretation In participants with metabolic dysfunction-associated steatohepatitis and clinically significant fibrosis, the combination of zalfermin 30 mg plus semaglutide 2·4 mg did not significantly increase the proportion of participants who had an improvement in liver fibrosis and no worsening of metabolic dysfunction-associated

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steatohepatitis compared with placebo by week 52. However, a nominally significant treatment effect was observed for semaglutide 2·4 mg versus placebo. Semaglutide might be considered for further clinical assessment as a potential disease-modifying therapy in the F4c population.

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Introduction

Metabolic dysfunction-associated steatohepatitis is a progressive disorder characterised by steatosis, hepatocyte damage, and inflammation.[1] Steatohepatitis is a key driver of progression at all stages of the disease, with clinically significant fibrosis (stage 2 [F2] or higher) placing patients at risk of cirrhosis and hepatocellular carcinoma[2] and incurring a significantly greater risk of liver-related and all-cause mortality.[1,3] In particular, advanced fibrosis (stage 3 [F3]) and compensated cirrhosis [F4c]) are associated with an increased risk of mortality or liver transplantation (hazard ratio for stage 4 versus no fibrosis 10·9 [95% CI 6·06–19·62]).[4]

The GLP-1 receptor agonist semaglutide and the THRβ agonist resmetirom have been approved in adults with metabolic dysfunction-associated steatohepatitis consistent with F2–F3 fibrosis by the US Food and Drug Administration accelerated approval pathway based on positive phase 3 results.[3,5–7] In the ESSENCE trial, a regression of at least one stage in liver fibrosis without

Research in context

Evidence before this study

We searched PubMed, Embase, and Web of Science from database inception to March 1, 2026, for studies, randomised controlled trials, and meta-analyses of pharmacological treatments for metabolic dysfunction-associated steatohepatitis, with titles in the English language, focusing on GLP-1 receptor agonists and FGF21 analogues. Keywords were "GLP-1 receptor agonist", "semaglutide", "FGF21 analogue(s)", "nonalcoholic steatohepatitis", "NASH", "metabolic dysfunction-associated steatohepatitis", "MASH", "fibrosis", "liver histology", "randomised controlled trial", and "placebo-controlled". Preclinical studies support dual-pathway targeting of the GLP-1/FGF21 axis in disease models of metabolic dysfunction-associated steatohepatitis, due to complementary mechanisms targeting the liver and metabolism. However, no published randomised controlled trial has directly assessed the combination of an FGF21 analogue plus a GLP-1 receptor agonist in patients with metabolic dysfunction-associated steatohepatitis with moderate to advanced fibrosis (fibrosis stages F2–F4c).

Added value of this study

This is the first randomised controlled trial examining combination therapy with an FGF21 analogue (zalfermin) plus a GLP-1 receptor agonist (semaglutide) in patients with metabolic dysfunction-associated steatohepatitis and moderate to advanced fibrosis including compensated cirrhosis. Although responder proportions were numerically greater across all treatment groups versus placebo for the primary endpoint of improvement in liver fibrosis and no worsening of metabolic dysfunction-associated steatohepatitis, these differences were not significant, apart from nominally significant treatment effects for semaglutide 2·4 mg versus placebo (although not statistically confirmatory). For the confirmatory secondary endpoint of resolution of metabolic dysfunction-associated steatohepatitis and no worsening of liver fibrosis, nominally significant differences for all treatment groups versus placebo were found. However, combination treatment with zalfermin plus semaglutide did not produce an additive benefit beyond each agent alone, challenging the preclinical hypothesis of synergistic benefit from dual semaglutide and zalfermin treatment in metabolic dysfunction-associated steatohepatitis over the 52-week duration used in the trial. Of note, we found a nominally significant treatment effect for semaglutide 2·4 mg versus placebo for resolution of metabolic dysfunction-associated steatohepatitis and no worsening of liver fibrosis in the subgroup of patients with compensated cirrhosis (F4c), which suggests that semaglutide could be considered for further clinical assessment as a potential disease-modifying therapy in this population.

Implications of all the available evidence

The current scientific evidence base supports GLP-1 receptor agonists and FGF21 analogues as promising therapeutic strategies for metabolic dysfunction-associated steatohepatitis, capable of improving histological endpoints including fibrosis along with non-invasive biomarkers of metabolic dysfunction-associated steatohepatitis- and fibrosis-related activity. However, the findings of this study suggest that combining zalfermin and semaglutide does not confer additional histological benefit in patients with moderate to advanced fibrosis. Nonetheless, other FGF21 analogues with different structures and receptor-binding profiles, when paired with GLP-1 receptor agonist therapies, could elicit a different response and this warrants further assessment, along with lower doses of semaglutide. The study does, however, provide some evidence of the therapeutic benefit of semaglutide on fibrosis in patients with metabolic dysfunction-associated steatohepatitis-related cirrhosis, which should be investigated further in future studies.

worsening of steatohepatitis was reported in 36·8% of patients in the semaglutide group versus 22·4% in the placebo group (treatment difference of 14·4 percentage points; p<0·001).[5] In the MAESTRO-NASH trial, significantly more patients receiving resmetirom 100 mg had liver fibrosis regression versus placebo (treatment difference of 11·8 percentage points; p<0·001).[8] Despite being encouraging, these results imply an unmet need for further treatment options for all patients with metabolic dysfunction-associated steatohepatitis, including those with advanced fibrosis. Owing to the complex pathophysiology of metabolic dysfunction-associated steatohepatitis, it is expected that the use of combination therapies with differing modes of action could increase efficacy compared with monotherapy.[6,9]

FGF21 belongs to the endocrine FGF family, which consists of FGF19, FGF21, and FGF23. These FGFs enter circulation, facilitate interorgan communication, and regulate key bile acid (FGF19); amino acid, lipid, and glucose (FGF21); and phosphate and vitamin D (FGF23) metabolic pathways. FGF21 is a hepatokine released from the liver in response to metabolic stressors (eg, high glucose, alcohol, and low protein); it is directly involved in clearance of systemic glucose and lipids, insulin sensitivity, energy expenditure, and regulation of food preferences.[10] The FGF21 receptor complex (FGFR1c, FGFR2c, and FGFR3c), which includes the obligate co-receptor beta-klotho, is expressed in the liver (hepatocytes and cholangiocytes) and adipocytes but importantly also in areas of the CNS that regulate energy balance and food intake, including the hypothalamus and hindbrain.[11] The novel FGF21 analogue zalfermin (formerly NNC0194-0499), a potent FGF21 receptor agonist, is modified in position 180 with C18 fatty diacid alkylation, making it albumin bound and preventing proteolytic cleavage of the C-terminal.[12] The plasma half-life of zalfermin is approximately 120 h, making it compatible with once-weekly dosing.[13,14] In a preclinical study, treatment with low-dose zalfermin and semaglutide in combination reduced hepatic steatosis, inflammation, liver biochemical endpoints, and gene expression markers of fibrosis to an equal or greater degree than high-dose monotherapies.[15] In human single-dose and multiple-ascending-dose trials, participants treated with zalfermin had significant improvement in plasma lipids, with an acceptable safety profile, indicating promise for the treatment of a range of cardiometabolic diseases, including metabolic dysfunction-associated steatohepatitis.[13,14]

In this study, we evaluated the combination of zalfermin and semaglutide for efficacy and safety in patients with metabolic dysfunction-associated steatohepatitis and F2–F4c.

Methods

Study design

This proof-of-concept, phase 2, dose-ranging, double-blind, randomised controlled trial was done at 187 clinical trial sites in Australia, Belgium, Bulgaria, Canada, Czech Republic, Denmark, France, Germany, Greece, India, Italy, Japan, Malaysia, Poland, Portugal, Russia, Singapore, South Korea, Spain, Taiwan, Türkiye, and the USA. The trial was conducted in accordance with the principles of the Declaration of Helsinki and International Conference on Harmonisation Good Clinical Practice guidelines. The trial was approved by local ethics committees and institutional review boards. There was no patient nor public involvement in the trial design. This trial is registered with ClinicalTrials.gov, NCT05016882, and is completed.

Participants

Eligible participants were aged 18 years or older with histological confirmation of metabolic dysfunction-associated steatohepatitis on liver biopsy (baseline or historical within 180 days). Per the NASH Clinical Research Network (NASH CRN) classification,[16] participants had clinically significant fibrosis or cirrhosis in the absence of decompensation (stage F2–F4c). Participants were required to have a non-alcoholic fatty liver disease activity score (NAS) of at least 4 for F2–F3, or at least 3 for F4c, and a score of at least 1 in steatosis, lobular inflammation, and ballooning. Sex was self-reported by participants from the options male or female. Participants could receive concomitant medication at randomisation and initiate concomitant medication during the trial. Participants were excluded if treated with vitamin E (≥800 IU/day), pioglitazone, any approved metabolic dysfunction-associated steatohepatitis medication, glucose-lowering agents other than GLP-1 receptor agonists, lipid-lowering medication, or weight loss medication that had not been stable, in the investigator's opinion, during the 90 days before screening. For participants with a historical liver biopsy obtained more than 90 days before screening, such treatment also had to remain stable from the time of biopsy until screening. Participants were also excluded if they had received GLP-1 receptor agonists within 90 days before screening or, for those with a historical liver biopsy obtained more than 90 days before screening, between biopsy and screening. A complete list of inclusion and exclusion criteria is reported in the appendix (p 16). A detailed screening process followed a stepwise approach over multiple visits: review the participant's metabolic dysfunction-associated steatotic liver disease history, with liver biopsy within 180 days of screening and available for central evaluation; blood sample to demonstrate fibrosis-4 (FIB-4) index of at least 1·3; screening assessments; and liver biopsy for final confirmation of eligibility (if no historical biopsy within 180 days of screening was available). Further information on the screening process is available in the appendix (p 13).

See Online for appendix

No changes were made to eligibility criteria after trial commencement. Patients provided written, informed consent before participating in the trial.

Randomisation and masking

The trial was designed to have ten randomised treatment groups (six active treatment groups and four placebo groups to blind the different treatment groups). Participants were randomly assigned in a 6:1:6:1:6:6:6:3:6:1 ratio to receive active treatment and/or placebo; six out of every seven participants were allocated to receive at least one active drug, with the remaining one participant assigned to receive two placebo injections. Participants were randomly assigned to receive zalfermin 7·5 mg plus semaglutide 2·4 mg or placebo plus semaglutide placebo in a 6:1 ratio; zalfermin 15 mg plus semaglutide 2·4 mg or placebo plus semaglutide placebo in a 6:1 ratio; zalfermin 30 mg plus semaglutide 2·4 mg, zalfermin 30 mg plus semaglutide placebo, placebo plus semaglutide 2·4 mg, or placebo plus semaglutide placebo in a 6:6:6:3 ratio; or cagrilintide 2·4 mg plus semaglutide 2·4 mg or cagrilintide placebo plus semaglutide placebo in a 6:1 ratio. The group containing the combination of the long-acting amylin analogue cagrilintide[17] 2·4 mg and semaglutide 2·4 mg was an exploratory treatment group (appendix p 14). Randomisation was stratified by region (Japan and rest of world) and within the rest of world stratum by fibrosis stage (F2/F3 and F4c).

All participants were centrally randomised using a central interactive web response system (IWRS). The randomisation sequence was computer-generated and the allocation ratio across treatment groups followed a sub-block structure (total block size 42, divided into six sub blocks) to maintain balance. Allocation concealment was ensured through the central IWRS, in which the prespecified randomisation schedule was inaccessible to masked site personnel before randomisation. At allocation, the IWRS assigned treatment and displayed only blinded pack information to masked users. All vials, devices, and injection guidance were identical. Participants, investigators, site staff involved in treatment administration and study conduct, and outcome assessors remained masked to treatment assignment.

Procedures

Participants received two subcutaneous injections per week (active drugs, drug plus placebo, or two placebos; at the same time, with different injection sites). Zalfermin or placebo was administered with a NovoPen 4 with a 3 mL underfilled cartridge (1 mL solution) and semaglutide or placebo was administered with a 3 mL prefilled PDS290 pen-injector. Semaglutide and cagrilintide doses were escalated every 4 weeks until the randomised dose was reached after 16 weeks. Zalfermin dose was not titrated within each treatment group.

The total trial duration for each individual participant was up to 81 weeks. This included a screening period of up to approximately 10 weeks, a 52-week treatment period, a 7-week follow-up period after the end of treatment, and an additional 12-week follow-up period to investigate potential antibody resolution (appendix p 14).

Two liver biopsies were used to assess the primary endpoint: one during the screening period, to assess the eligibility of a participant to enter the trial and to establish a baseline, unless the participant had a historical biopsy that fulfilled the eligibility criteria obtained within 180 days before the first screening visit, and one at week 52 to assess treatment effect. Central reading was done on all biopsy samples by expert liver pathologists with extensive experience with metabolic dysfunction-associated steatotic liver disease or metabolic dysfunction-associated steatohepatitis. To prevent bias and subjectivity in scoring the histology parameters, biopsy samples were assessed independently by one out of four pairs of pathologists who remained masked to the participant's treatment; each pair should have agreed on readings. If no agreement was obtained, a third pathologist took the final decision. For imaging assessments, participants fasted for at least 2 h before FibroScan assessment, except at screening. FibroScan assessments were done at sites where FibroScan equipment was available. The same equipment and software (± SmartExam) were used for all measurements throughout the trial. FibroScan assessments were done 2 weeks or less before the scheduled visit (weeks 12, 28, and 52).

Laboratory assessments were done at screening, randomisation, and weeks 4, 8, 12, 16, 20, 28, 36, 44, 52, 59, and 71. Adverse events were assessed at every study visit. Participants could withdraw consent at any time for any or no reason. Withdrawal was also allowed for other reasons such as loss to follow-up and death. Premature trial product discontinuation could occur due to adverse events, protocol deviations, investigator discretion, or pregnancy.

Dose reductions were not allowed for zalfermin or its matching placebo. For semaglutide and cagrilintide, dose escalation could be delayed, participants could remain at a lower dose, or doses could be reduced in response to unacceptable adverse events, as judged by the investigator. Escalation could be delayed by 1 week for rapid weight loss or poor tolerability, with cumulative delays of up to 4 weeks; the dose reached at the end of escalation was the maximum dose for the remainder of treatment. During maintenance, dose reduction could be considered for continued weight loss at a BMI of <22·5 kg/m², rapid excessive weight loss, lack of desire for further weight loss, or poor tolerability. Reductions followed the reverse escalation schedule, and for semaglutide plus cagrilintide, both doses were reduced simultaneously with re-escalation considered after recovery.

Outcomes

The primary endpoint was the proportion of participants with an improvement in liver fibrosis, defined as

improvement on the NASH CRN fibrosis scale of at least one stage,[16] and no worsening of metabolic dysfunction-associated steatohepatitis,[16] defined as no increase from baseline in NAS for ballooning, inflammation, or steatosis, from baseline to week 52 (appendix p 17). The confirmatory secondary endpoint was the proportion of participants with resolution of metabolic dysfunction-associated steatohepatitis and no worsening of liver fibrosis from baseline to week 52. Resolution of metabolic dysfunction-associated steatohepatitis was defined as a NAS of 0–1 for inflammation, 0 for ballooning, and any value for steatosis, according to NASH CRN.[16] Fibrosis was graded from 0 to 4 on the NASH CRN fibrosis scale. The primary objective of the trial was evaluation of improvement in liver fibrosis and no worsening of metabolic dysfunction-associated steatohepatitis with zalfermin 30 mg plus semaglutide 2·4 mg versus placebo; other doses and combinations were considered secondary objectives.

Supportive secondary endpoints from baseline to week 52 were the proportion of participants with at least a two-point improvement in metabolic dysfunction-associated steatohepatitis NAS and no worsening of fibrosis; resolution of metabolic dysfunction-associated steatohepatitis and improvement in liver fibrosis; improvement in liver fibrosis; progression of liver fibrosis; worsening of steatohepatitis; improvement in ballooning, improvement in inflammation; and improvement in steatosis. Change from baseline to week 52 in histology-assessed liver collagen proportionate area, alanine aminotransferase, aspartate aminotransferase, inflammation assessed by high-sensitivity C-reactive protein, triglycerides, free fatty acids, LDL cholesterol, and HDL cholesterol (ratio to baseline) were also supportive secondary endpoints. Additional supportive secondary endpoints were change from baseline to week 52 in Enhanced Liver Fibrosis (ELF) score (logarithm), HbA_{1c} (percentage points), bodyweight (%), SF-36 bodily pain (points), NASH-CHECK pain score (points), and PROMIS fatigue score (points). Other analyses that were prespecified in the statistical analysis plan, and are reported here, were change from baseline to week 52 in FIB-4, liver steatosis (controlled attenuation parameter), released N-terminal propeptide C3, liver stiffness, and adiponectin.

Safety was primarily assessed on the basis of adverse events from baseline to week 59 presented by system organ class and preferred term. Adverse events were defined as abnormal laboratory test results or safety assessments considered clinically significant in the medical and scientific judgment of the investigator, including events that had worsened at the time of reporting. The investigator recorded all relevant adverse event information in the case report form.

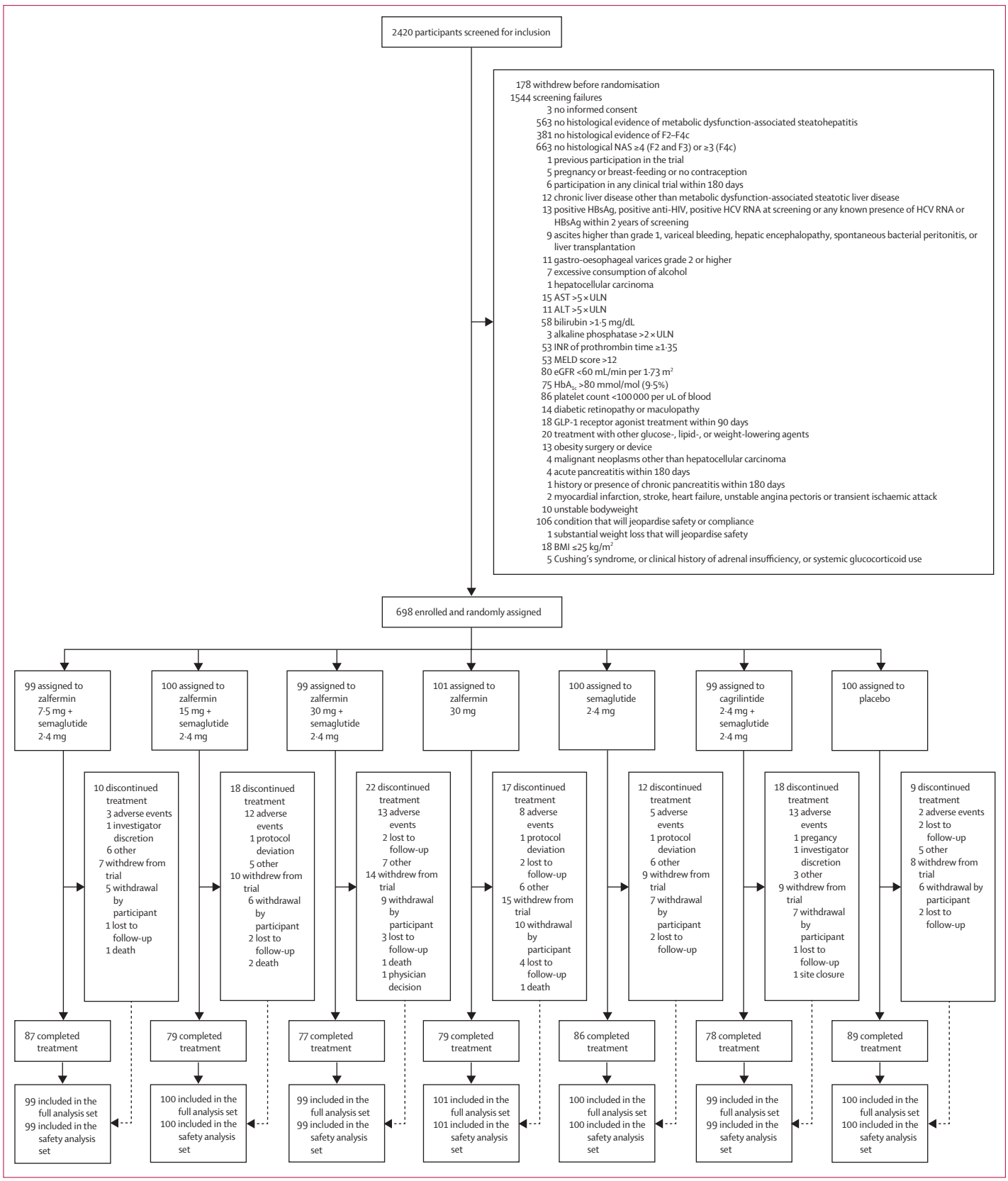
Here, we focus on reporting data for the zalfermin 30 mg plus semaglutide 2·4 mg, zalfermin 30 mg, semaglutide 2·4 mg, and pooled placebo groups; data for the additional treatment groups are reported in the appendix. Outcomes are reported for the overall population (F2–F4c), with the primary and confirmatory secondary histology endpoints also reported by fibrosis stage subgroup (F2–F3 and F4c; prespecified analysis).

Statistical analysis

All analyses were completed with SAS version 9.4 (TS1M5). For sample size determination, calculations used a Pearson's χ^2 test with normal approximation and 1:1 randomisation, consistent with the primary analysis pooling placebo groups. It was assumed that 15% of participants receiving placebo and 35% of those receiving zalfermin 30 mg monotherapy would have liver fibrosis improvement at week 52, corresponding to a 20 percentage point estimated difference in responder proportions (EDP) and 90% power. Sample size calculation is reported in the appendix (p 11). Ten confirmatory statistical tests were planned for the primary and confirmatory secondary endpoint (appendix p 12). For the primary objective of the trial, both a primary estimand and an additional estimand were defined according to the ICH E9(R1) guideline. Further information on trial estimands is reported in the appendix (pp 11–12).

The primary and confirmatory secondary endpoints were analysed separately for each comparison using a Cochran–Mantel–Haenszel (CMH) test in two strata defined by baseline fibrosis stage (F2–F3 or F4c). The analysis was based on the full analysis set and the in-trial observation period. The response data consisted of outcomes of the week 52 biopsy including assessments taken after premature discontinuation of trial product. Missing response data in any treatment group were handled by reference-based imputation; missing data occurred if participants withdrew consent, became lost to follow-up, or continued to be followed up without being ascertained for the endpoint in scope. Participants who had a hepatic decompensation event, died, or had liver transplantation before week 52 were handled as non-responders. Responder counts are model-based estimates rather than observed counts. Percentages are based on the unrounded model estimates. Subgroup analysis by fibrosis stage used a CMH test stratified by fibrosis stage and the same imputed values as the primary analysis. Continuous endpoints (changes from baseline to week 52) were assessed by ANCOVA, with multiple reference-based imputation used for missing values.

The four placebo groups were pooled in the statistical analyses. The pooling was based on the assumption that there was no substantial effect of different placebo volumes on the efficacy and safety endpoints. Sensitivity analyses were done to investigate the sensitivity of the results in the primary analysis with regard to the handling of missing data (appendix p 11). The full analysis set was defined as all randomly assigned participants, and the safety analysis set was defined as all participants assigned to trial treatment who took at least one dose of trial product.


2420 participants screened for inclusion
178 withdrew before randomisation
1544 screening failures
3 no informed consent
563 no histological evidence of metabolic dysfunction-associated steatohepatitis
381 no histological evidence of F2–F4c
663 no histological NAS ≥4 (F2 and F3) or ≥3 (F4c)
1 previous participation in the trial
5 pregnancy or breast-feeding or no contraception
6 participation in any clinical trial within 180 days
12 chronic liver disease other than metabolic dysfunction-associated steatotic liver disease
13 positive HBsAg, positive anti-HIV, positive HCV RNA at screening or any known presence of HCV RNA or HBsAg within 2 years of screening
9 ascites higher than grade 1, variceal bleeding, hepatic encephalopathy, spontaneous bacterial peritonitis, or liver transplantation
11 gastro-oesophageal varices grade 2 or higher
7 excessive consumption of alcohol
1 hepatocellular carcinoma
15 AST >5 × ULN
11 ALT >5 × ULN
58 bilirubin >1·5 mg/dL
3 alkaline phosphatase >2 × ULN
53 INR of prothrombin time ≥1·35
53 MELD score >12
80 eGFR <60 mL/min per 1·73 m²
75 HbA1c >80 mmol/mol (9·5%)
86 platelet count <100 000 per uL of blood
14 diabetic retinopathy or maculopathy
18 GLP-1 receptor agonist treatment within 90 days
20 treatment with other glucose-, lipid-, or weight-lowering agents
13 obesity surgery or device
4 malignant neoplasms other than hepatocellular carcinoma
4 acute pancreatitis within 180 days
1 history or presence of chronic pancreatitis within 180 days
2 myocardial infarction, stroke, heart failure, unstable angina pectoris or transient ischaemic attack
10 unstable bodyweight
106 condition that will jeopardise safety or compliance
1 substantial weight loss that will jeopardise safety
18 BMI ≤25 kg/m²
5 Cushing's syndrome, or clinical history of adrenal insufficiency, or systemic glucocorticoid use
698 enrolled and randomly assigned
99 assigned to zalfermin 7·5 mg + semaglutide 2·4 mg
100 assigned to zalfermin 15 mg + semaglutide 2·4 mg
99 assigned to zalfermin 30 mg + semaglutide 2·4 mg
101 assigned to zalfermin 30 mg
100 assigned to semaglutide 2·4 mg
99 assigned to cagrilintide 2·4 mg + semaglutide 2·4 mg
100 assigned to placebo
10 discontinued treatment
3 adverse events
1 investigator discretion
6 other
7 withdrew from trial
5 withdrawal by participant
1 lost to follow-up
1 death
18 discontinued treatment
12 adverse events
1 protocol deviation
5 other
10 withdrew from trial
6 withdrawal by participant
2 lost to follow-up
2 death
22 discontinued treatment
13 adverse events
2 lost to follow-up
7 other
14 withdrew from trial
9 withdrawal by participant
3 lost to follow-up
1 death
1 physician decision
17 discontinued treatment
8 adverse events
1 protocol deviation
2 lost to follow-up
6 other
15 withdrew from trial
10 withdrawal by participant
4 lost to follow-up
1 death
12 discontinued treatment
5 adverse events
1 protocol deviation
6 other
9 withdrew from trial
7 withdrawal by participant
2 lost to follow-up
18 discontinued treatment
13 adverse events
1 pregancy
1 investigator discretion
3 other
9 withdrew from trial
7 withdrawal by participant
1 lost to follow-up
1 site closure
9 discontinued treatment
2 adverse events
2 lost to follow-up
5 other
8 withdrew from trial
6 withdrawal by participant
2 lost to follow-up
87 completed treatment
79 completed treatment
77 completed treatment
79 completed treatment
86 completed treatment
78 completed treatment
89 completed treatment
99 included in the full analysis set
99 included in the safety analysis set
100 included in the full analysis set
100 included in the safety analysis set
99 included in the full analysis set
99 included in the safety analysis set
101 included in the full analysis set
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100 included in the safety analysis set

A partial database lock was done at the end of the follow-up period for all participants. The database was updated after the partial database lock to include remaining anti-zalfermin antibody data collected at week 71 and any additional safety information collected in that period. There were no stopping guidelines for the trial.

Role of the funding source

The sponsor was responsible for the trial design, preparing the trial protocol and the statistical analysis plan, performing the statistical analyses, and interpretation of the results.

Results

Between Aug 31, 2021, and March 14, 2025, 2420 people were screened for inclusion. 178 withdrew before random assignment and 1544 were disqualified. 698 participants were enrolled and randomly assigned to zalfermin 7·5 mg plus semaglutide 2·4 mg (n=99), zalfermin 15 mg plus semaglutide 2·4 mg (n=100), zalfermin 30 mg plus semaglutide 2·4 mg (n=99), zalfermin 30 mg (n=101), semaglutide 2·4 mg (n=100), cagrilintide 2·4 mg plus semaglutide 2·4 mg (n=99), or placebo (n=100; figure 1). Both the full analysis set and safety analysis set contained 698 participants. 441 (63%) of 698 participants were female and 257 (37%) were male. 484 (69%) of 698 participants were White and 172 (25%) were Asian. F4c was the most common fibrosis stage observed in 301 (43%) of 698 participants. 384 (55%) of 698 participants had type 2 diabetes.

Among the 400 patients in the zalfermin 30 mg plus semaglutide 2·4 mg, zalfermin 30 mg, semaglutide 2·4 mg, and placebo groups, the mean age of participants ranged from 55·5 (SD 12·9) to 58·2 (9·8) years (table 1). At baseline, 175 (44%) of 400 participants were in receipt of concomitant medication and 211 (53%) of 400 participants commenced concomitant medication during the trial, at similar levels between groups (56 [57%] of 99 participants in the zalfermin 30 mg plus semaglutide 2·4 mg group, 58 [57%] of 101 participants in the zalfermin 30 mg group, 47 [47%] of 100 participants in the semaglutide 2·4 mg group, and 50 [50%] of 100 participants in the placebo group). Baseline characteristics for the additional treatment groups are reported in the appendix (p 18).

All participants received at least one dose of study drug or placebo. 58 (59%) of 99 participants in the zalfermin 30 mg plus semaglutide 2·4 mg group received the maximum dose of semaglutide at week 52, compared with 76 (77%) of 99 participants in the zalfermin 7·5 mg plus semaglutide 2·4 mg group and 70 (70%) of 100 participants in the zalfermin 15 mg plus semaglutide 2·4 mg group.

	Zalfermin 30 mg + semaglutide 2·4 mg (n=99)	Zalfermin 30 mg (n=101)	Semaglutide 2·4 mg (n=100)	Placebo (n=100)
Age, years	58·2 (9·8)	55·5 (12·9)	57·8 (10·4)	57·7 (11·0)
Sex				
Male	30 (30%)	40 (40%)	36 (36%)	37 (37%)
Female	69 (70%)	61 (60%)	64 (64%)	63 (63%)
Ethnicity				
Hispanic or Latino	23 (23%)	19 (19%)	11 (11%)	18 (18%)
Not Hispanic or Latino	73 (74%)	80 (79%)	89 (89%)	79 (79%)
Missing	3 (3%)	2 (2%)	0	3 (3%)
Race				
American Indian or Alaska Native	0	0	1 (1%)	0
Asian	22 (22%)	23 (23%)	18 (18%)	27 (27%)
Black or African American	1 (1%)	0	1 (1%)	0
Native Hawaiian or other Pacific Islander	0	0	0	0
White	70 (71%)	73 (72%)	78 (78%)	65 (65%)
Other	4 (4%)	3 (3%)	2 (2%)	6 (6%)
Missing	2 (2%)	2 (2%)	0	2 (2%)
Bodyweight, kg	95·3 (23·2)	98·6 (21·6)	97·2 (21·3)	96·4 (23·3)
BMI, kg/m²	35·0 (7·2)	35·2 (6·8)	34·9 (5·9)	35·0 (6·9)
Type 2 diabetes	44 (44%)	65 (64%)	57 (57%)	59 (59%)
Fibrosis stage				
F2	23 (23%)	24 (24%)	22 (22%)	19 (19%)
F3	34 (34%)	37 (37%)	36 (36%)	37 (37%)
F4c	42 (42%)	40 (40%)	42 (42%)	44 (44%)
NAS				
3	10 (10%)	11 (11%)	11 (11%)	7 (7%)
4	37 (37%)	36 (36%)	31 (31%)	45 (45%)
5	24 (24%)	31 (31%)	41 (41%)	33 (33%)
6	23 (23%)	15 (15%)	14 (14%)	11 (11%)
7	5 (5%)	8 (8%)	3 (3%)	4 (4%)
FIB-4 index	2·19 (1·18)	2·20 (1·24)	2·06 (1·17)	2·15 (1·22)
ELF score	10·36 (1·03)	10·36 (0·95)	10·17 (1·06)	10·27 (1·06)
ALT, U/L	68·4 (46·7)	72·1 (41·7)	63·9 (40·7)	61·5 (37·7)
AST, U/L	54·4 (34·1)	62·8 (36·4)	53·0 (27·0)	51·7 (25·7)
VCTE LSM, kPa	18·2 (10·3)	16·7 (8·9)	16·2 (8·5)	16·0 (7·7)
VCTE CAP, dB/m	324 (43)	323 (54)	327 (46)	318 (55)
PRO-C3, ng/mL	52·8 (19·3)	54·0 (19·6)	49·7 (20·0)	52·6 (22·4)
Triglycerides, mmol/L	1·75 (0·83)	1·86 (1·03)	1·70 (0·81)	1·58 (0·73)
HDL cholesterol, mmol/L	1·17 (0·29)	1·14 (0·27)	1·18 (0·29)	1·22 (0·32)
LDL cholesterol, mmol/L	2·92 (1·07)	3·16 (1·08)	2·83 (1·12)	3·01 (1·13)
HbA_{1c}, %	6·3 (0·9)	6·7 (1·2)	6·6 (1·0)	6·6 (1·1)
Albumin, g/dL	4·3 (0·3)	4·3 (0·3)	4·4 (0·3)	4·4 (0·3)
Concomitant medication	45 (46%)	42 (42%)	46 (46%)	42 (42%)

Data are mean (SD) or n (%). Placebo data are pooled. ALT=alanine aminotransferase. AST=aspartate aminotransferase. CAP=controlled attenuation parameter. ELF=Enhanced Liver Fibrosis. FIB-4=fibrosis-4. LSM=liver stiffness measurement. NAS=non-alcoholic fatty liver disease activity score. PRO-C3=released N-terminal propeptide C3. VCTE=vibration-controlled transient elastography.

Table 1: **Baseline demographics and characteristics**

Figure 1: **Trial profile**
Screening failure reasons may overlap. ALT=alanine aminotransferase. AST=aspartate aminotransferase. F2=fibrosis stage 2. F3=fibrosis stage 3. F4c=fibrosis stage 4c. HCV=hepatitis C virus. INR=international normalised ratio. MELD=Model for End-stage Liver Disease. NAS=non-alcoholic fatty liver disease activity score. ULN=upper limit of normal.

The median in-trial observation period was 71·1 weeks (IQR 71·1–71·6). At week 52, 17 of 99 participants in the zalfermin 30 mg plus semaglutide 2·4 mg group had imputed data, compared with 15 of 101 participants in the zalfermin 30 mg group, 13 of 100 participants in the semaglutide 2·4 mg group, and 14 of 100 participants in the placebo group, in the analysis of the primary and confirmatory secondary endpoint.

At week 52, 24 (24%) of 99 participants in the zalfermin 30 mg plus semaglutide 2·4 mg group had an improvement in liver fibrosis and no worsening of metabolic dysfunction-associated steatohepatitis, compared with 16 (16%) of 100 participants in the placebo group. The EDP for zalfermin 30 mg plus semaglutide 2·4 mg versus placebo for improvement in liver fibrosis and no worsening of metabolic dysfunction-associated steatohepatitis was 7·98 (95% CI −3·82 to 19·79, p=0·19; figure 2A). The relative risk ratio (RR) for zalfermin 30 mg plus semaglutide 2·4 mg versus placebo for improvement in liver fibrosis and no worsening of metabolic dysfunction-associated steatohepatitis was 1·49 (95% CI 0·82 to 2·71, p=0·19). As the first comparison failed to reach the prespecified one-sided significance threshold of 2·5, the trial did not provide confirmatory evidence for the predefined hierarchical set of hypotheses. Therefore, the remaining comparisons

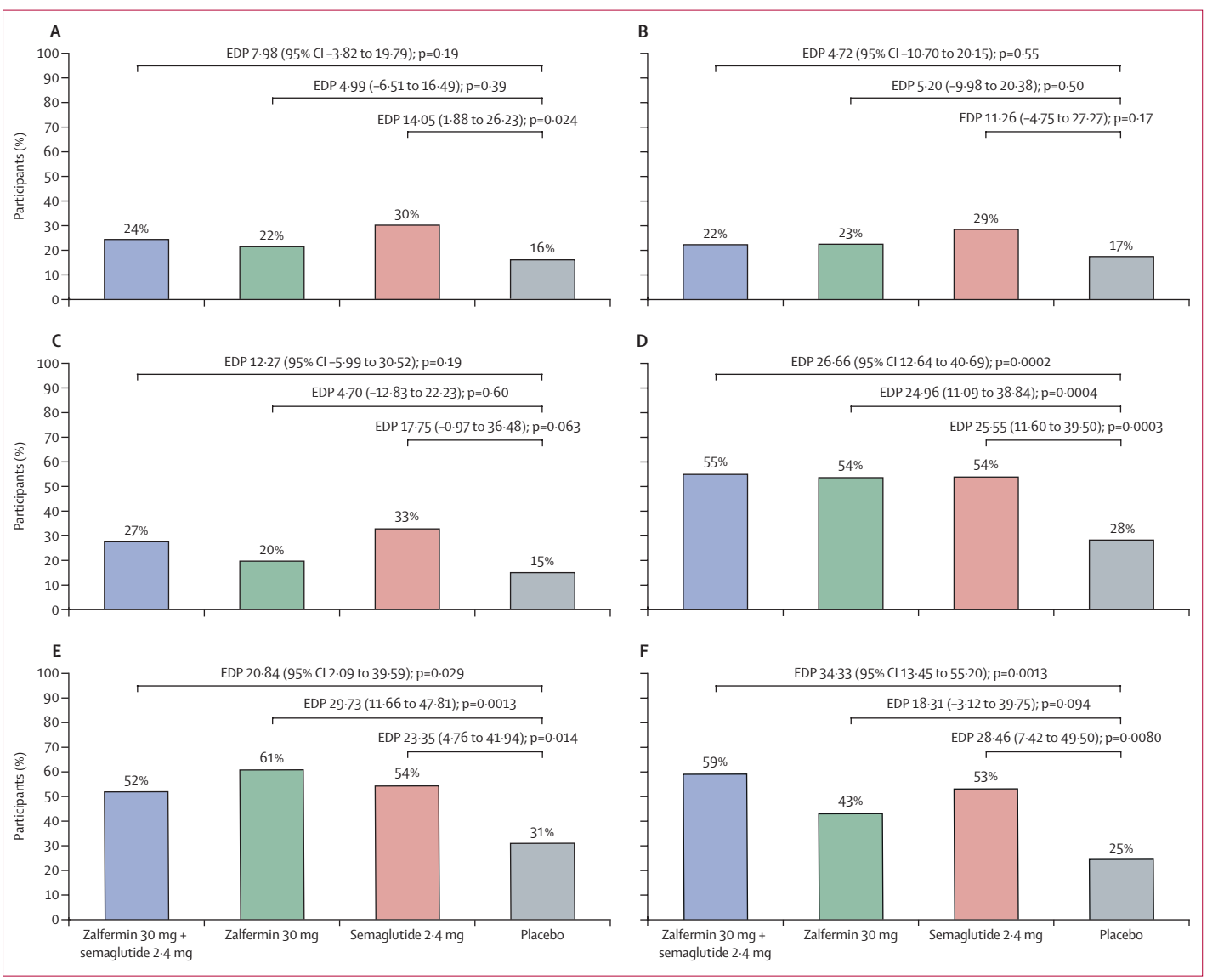

Figure 2: **Improvement in liver fibrosis and resolution of metabolic dysfunction-associated steatohepatitis from baseline to week 52**
Improvement in liver fibrosis and no worsening of metabolic dysfunction-associated steatohepatitis in the (A) overall population, (B) F2 and F3 subgroup, and (C) F4c subgroup. Resolution of metabolic dysfunction-associated steatohepatitis and no worsening of liver fibrosis in the (D) overall population, (E) F2 and F3 subgroup, and (F) F4c subgroup. Cochran–Mantel–Haenszel test stratified by baseline fibrosis stage. As the first comparison failed to reach the prespecified significance threshold, the trial did not provide confirmatory evidence for the predefined heirarchical set of of hypotheses. Responder counts are model-based estimates rather than observed counts. Percentages are based on the unrounded model estimates. EDP=estimated difference in responder proportions.

were not considered statistically confirmatory, and superiority cannot be claimed; their results are hypothesis-generating only.

30 (30%) of 100 participants in the semaglutide 2·4 mg group had an improvement in liver fibrosis and no worsening of metabolic dysfunction-associated steatohepatitis; the EDP compared with placebo was 14·05 (95% CI 1·88 to 26·23, p=0·024) and RR of 1·86 (95% CI 1·06 to 3·28, p=0·031). 22 (22%) of 101 participants in the zalfermin 30 mg group had an improvement in liver fibrosis and no worsening of metabolic dysfunction-associated steatohepatitis, with an EDP versus placebo of 4·99 (–6·51 to 16·49; p=0·39). Results for the primary endpoint in the other groups are shown in the appendix (p 15).

In the F2 and F3 subgroup (397 of 698 participants), 13 (22%) of 57 participants in the zalfermin 30 mg plus semaglutide 2·4 mg group, 17 (29%) of 58 in the semaglutide 2·4 mg group, 14 (23%) of 61 in the zalfermin 30 mg group, and ten (17%) of 56 in the placebo group had an improvement in liver fibrosis and no worsening of metabolic dysfunction-associated steatohepatitis (figure 2B). The EDP for zalfermin 30 mg plus semaglutide 2·4 mg versus placebo for improvement in liver fibrosis and no worsening of metabolic dysfunction-associated steatohepatitis was 4·72 (–10·70 to 20·15, p=0·55) and RR was 1·27 (0·58 to 2·79, p=0·56). For semaglutide 2·4 mg versus placebo, the EDP was 11·26 (–4·75 to 27·27, p=0·17; figure 2B) and RR was 1·65 (0·79 to 3·43, p=0·18). For zalfermin 30 mg versus placebo, the EDP was 5·20 (–9·98 to 20·38, p=0·50) and RR was 1·30 (0·60 to 2·81, p=0·50).

In the F4c subgroup (301 of 698 participants), 11 (27%) of 42 participants in the zalfermin 30 mg plus semaglutide 2·4 mg group, 14 (33%) of 42 in the semaglutide 2·4 mg group, eight (20%) of 40 in the zalfermin 30 mg group, and seven (15%) of 44 in the placebo group had an improvement in liver fibrosis and no worsening of metabolic dysfunction-associated steatohepatitis (figure 2C). The EDP for zalfermin 30 mg plus semaglutide 2·4 mg versus placebo for improvement in liver fibrosis and no worsening of metabolic dysfunction-associated steatohepatitis was 12·27 (–5·99 to 30·52, p=0·19) and RR was 1·84 (0·72 to 4·72, p=0·21). For semaglutide 2·4 mg versus placebo, the EDP was 17·75 (–0·97 to 36·48, p=0·063; figure 2C) and RR was 2·21 (0·89 to 5·47, p=0·087). For zalfermin 30 mg versus placebo, the EDP was 4·70 (–12·83 to 22·23, p=0·60) and RR was 1·32 (0·47 to 3·71, p=0·59).

At week 52, 54 (55%) of 99 participants in the zalfermin 30 mg plus semaglutide 2·4 mg group had resolution of metabolic dysfunction-associated steatohepatitis and no worsening of liver fibrosis, compared with 28 (28%) of 100 participants in the placebo group. The EDP for zalfermin 30 mg plus semaglutide 2·4 mg versus placebo for resolution of metabolic dysfunction-associated steatohepatitis and no worsening of liver fibrosis was 26·66 (95% CI 12·64 to 40·69, p=0·0002; figure 2D) and RR was 1·95 (95% CI 1·33 to 2·86, p=0·0007). Resolution of metabolic dysfunction-associated steatohepatitis and no worsening of liver fibrosis was achieved by was achieved by 54 [54%] of 100 participants in the semaglutide 2·4 mg group [EDP 25·55, 95% CI 11·60 to 39·50; p=0·0003 and RR 1·91, 1·30 to 2·80; p=0·0010] and 54 [54%] of 101 participants in the zalfermin 30 mg group [EDP 24·96, 11·09 to 38·84; p=0·0004 and RR 1·88, 1·28 to 2·76; p=0·0012, figure 2D). Results for the additional treatment groups are reported in the appendix (p 15).

Results were consistent in the F2 and F3 subgroup (397 of 698 participants). 30 (52%) of 57 participants in the zalfermin 30 mg plus semaglutide 2·4 mg group, 32 (54%) of 58 in the semaglutide 2·4 mg group, 37 (61%) of 61 in the zalfermin 30 mg group, and 17 (31%) of 56 in the placebo group had resolution of metabolic dysfunction-associated steatohepatitis and no worsening of liver fibrosis (figure 2E). The EDP for zalfermin 30 mg plus semaglutide 2·4 mg versus placebo was 20·84 (95% CI 2·09 to 39·59, p=0·029) and RR was 1·67 (95% CI 1·03 to 2·72, p=0·038). For semaglutide 2·4 mg versus placebo, the EDP was 23·35 (4·76 to 41·94, p=0·014) and RR was 1·76 (1·09 to 2·84, p=0·022). For zalfermin 30 mg versus placebo, the EDP was 29·73 (11·66 to 47·81, p=0·0013) and RR was 1·76 (1·09 to 2·84, p=0·020).

In the F4c subgroup (301 of 698 participants), 25 (59%) of 42 participants in the zalfermin 30 mg plus semaglutide 2·4 mg group, 22 (53%) of 42 in the semaglutide 2·4 mg group, 17 (43%) of 40 in the zalfermin 30 mg group, and 11 (25%) of 44 in the placebo group had resolution of metabolic dysfunction-associated steatohepatitis and no worsening of liver fibrosis (figure 2F). The EDP for zalfermin 30 mg plus semaglutide 2·4 mg versus placebo was 34·33 (13·45 to 55·20, p=0·0013) and RR was 2·41 (1·28 to 4·53, p=0·0065). For semaglutide 2·4 mg versus placebo, the EDP was 28·46 (7·42 to 49·50, p=0·0080) and RR was 2·17 (1·13 to 4·13, p=0·019). For zalfermin 30 mg versus placebo, the EDP was 18·31 (–3·12 to 39·75, p=0·094) and RR was 1·75 (0·88 to 3·49, p=0·11).

Results of the sensitivity analysis supported the robustness of the conclusions for the histology endpoints (appendix p 19). Additional secondary endpoints are reported in the appendix (pp 20–23).

Changes from baseline in alanine aminotransferase, aspartate aminotransferase, liver stiffness, and ELF score for the overall population are shown in figure 3. Nominally significant and clinically meaningful reductions in non-invasive markers of metabolic dysfunction-associated steatohepatitis disease activity (controlled attenuation parameter, alanine aminotransferase, and aspartate aminotransferase) and liver fibrosis (eg, ELF, liver stiffness, FIB-4, and released N-terminal propeptide C3) were observed across all treatment groups versus placebo (figure 3; appendix pp 20–23). For

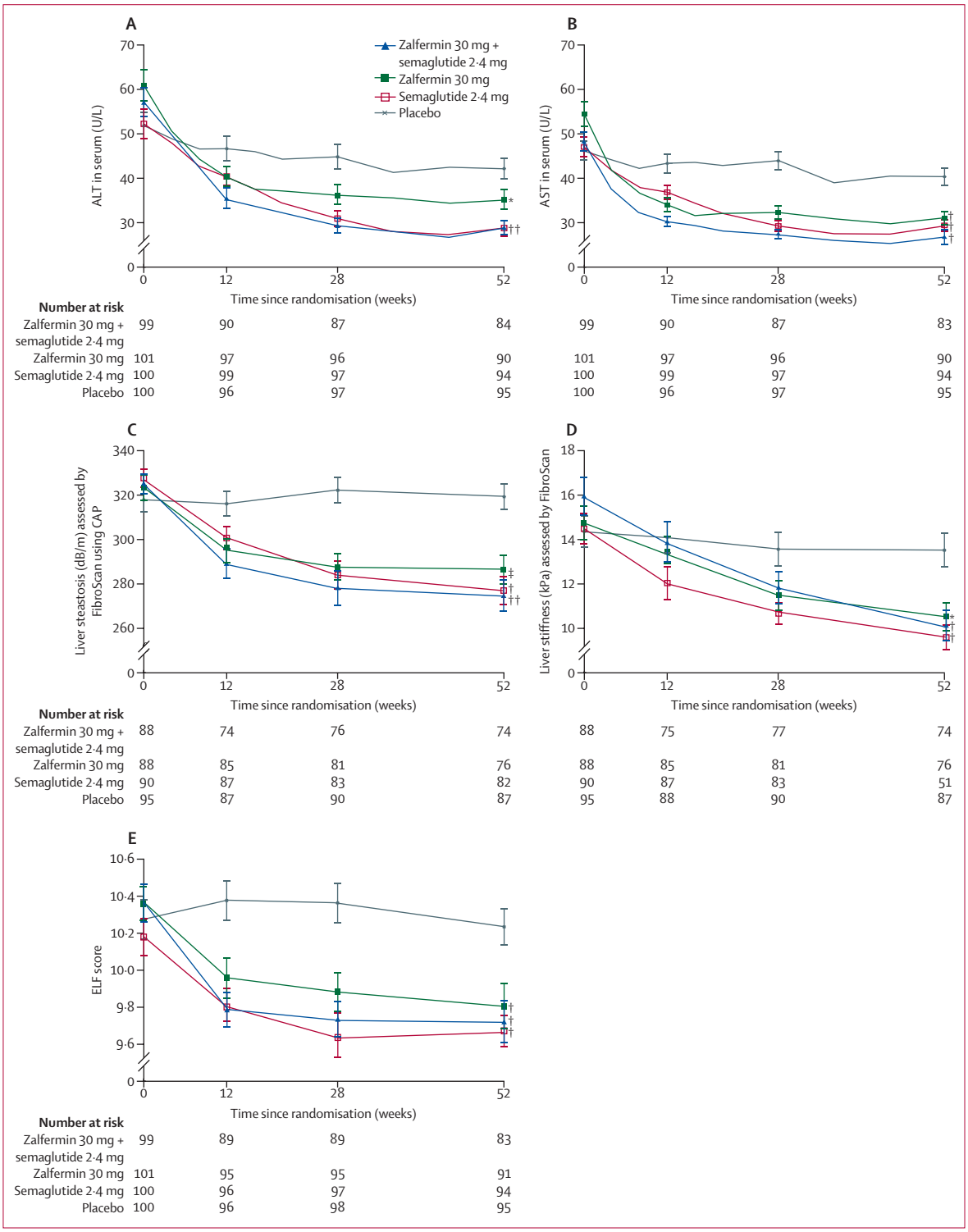

Figure 3: **Mean change in non-invasive tests by time since randomisation**
(A) ALT. (B) AST. (C) VCTE CAP. (D) VCTE LSM. (E) ELF score. Error bars indicate standard error. VCTE data are from sites with available measurements. ALT=alanine aminotransferase. AST=aspartate aminotransferase. CAP=controlled attenuation parameter. ELF=Enhanced Liver Fibrosis. LSM=liver stiffness measurement. VCTE=vibration-controlled transient elastography. *p=0·0006 versus placebo. †p<0·0001 versus placebo. ‡p=0·0002 versus placebo.

bodyweight, triglycerides, and adiponectin, nominally significant improvements versus placebo were observed for all treatment groups, except for bodyweight in the zalfermin 30 mg group (mean relative change from baseline of –3·11% in the zalfermin 30 mg group compared with –1·15% in the placebo group and –11·02% and –10·95% in the semaglutide 2·4 mg and zalfermin 30 mg plus semaglutide 2·4 mg groups, respectively; appendix pp 20–23).

No unexpected safety concerns were identified and adverse events were mostly non-serious and mild to moderate in severity (table 2; appendix p 24). The most frequent adverse events were gastrointestinal (79 [80%] of 99 participants in the zalfermin 30 mg plus semaglutide

	Zalfermin 30 mg + semaglutide 2·4 mg (n=99)	Zalfermin 30 mg (n=101)	Semaglutide 2·4 mg (n=100)	Placebo (n=100)
Any adverse event	89 (90%) [808]	85 (84%) [698]	96 (96%) [594]	81 (81%) [488]
Severe	10 (10%) [23]	10 (10%) [14]	3 (3%) [3]	5 (5%) [7]
Moderate	61 (62%) [184]	49 (49%) [152]	55 (55%) [142]	46 (46%) [113]
Mild	84 (85%) [598]	83 (82%) [531]	80 (80%) [449]	78 (78%) [368]
Adverse events by SOC or preferred term				
Gastrointestinal disorders	79 (80%) [308]	61 (60%) [165]	73 (73%) [246]	51 (51%) [127]
Nausea	60 (61%) [122]	34 (34%) [45]	41 (41%) [91]	22 (22%) [26]
Diarrhoea	23 (23%) [35]	27 (27%) [39]	26 (26%) [44]	13 (13%) [16]
Vomiting	29 (29%) [57]	14 (14%) [19]	21 (21%) [25]	4 (4%) [4]
Infections and infestations	42 (42%) [98]	53 (53%) [99]	39 (39%) [64]	41 (41%) [59]
General disorders and administration site conditions	40 (40%) [141]	43 (43%) [135]	25 (25%) [50]	26 (26%) [47]
Injection site reactions	11 (11%) [18]	17 (17%) [65]	4 (4%) [4]	2 (2%) [2]
Nervous system disorders	22 (22%) [38]	25 (25%) [38]	31 (31%) [55]	27 (27%) [34]
Metabolism and nutrition disorders	27 (27%) [43]	21 (21%) [24]	19 (19%) [23]	18 (18%) [25]
Injury, poisoning, and procedural complications	27 (27%) [37]	25 (25%) [34]	18 (18%) [26]	24 (24%) [32]
Musculoskeletal and connective tissue disorders	17 (17%) [22]	24 (24%) [36]	18 (18%) [27]	27 (27%) [40]
Skin and subcutaneous tissue disorders	24 (24%) [35]	29 (29%) [47]	17 (17%) [22]	16 (16%) [18]
Investigations	17 (17%) [28]	13 (13%) [19]	18 (18%) [23]	14 (14%) [20]
Respiratory, thoracic, and mediastinal disorders	7 (7%) [9]	16 (16%) [32]	10 (10%) [12]	12 (12%) [17]
Eye disorders	2 (2%) [2]	12 (12%) [16]	7 (7%) [8]	10 (10%) [12]
Vascular disorders	7 (7%) [7]	6 (6%) [7]	3 (3%) [5]	5 (5%) [6]
Psychiatric disorders	8 (8%) [9]	8 (8%) [15]	4 (4%) [5]	4 (4%) [8]
Renal and urinary disorders	7 (7%) [11]	2 (2%) [2]	4 (4%) [6]	6 (6%) [6]
Cardiac disorders	1 (1%) [1]	6 (6%) [7]	2 (2%) [3]	6 (6%) [8]
Hepatobiliary disorders	4 (4%) [4]	3 (3%) [3]	3 (3%) [3]	6 (6%) [7]
Ear and labyrinth disorders	4 (4%) [4]	4 (4%) [4]	3 (3%) [4]	5 (5%) [6]
Reproductive system and breast disorders	1 (1%) [2]	4 (4%) [5]	3 (3%) [4]	4 (4%) [4]
Neoplasms benign, malignant, and unspecified	2 (2%) [2]	4 (4%) [4]	3 (3%) [4]	1 (1%) [2]
Blood and lymphatic system disorders	1 (1%) [1]	3 (3%) [3]	1 (1%) [1]	3 (3%) [5]
Immune system disorders	3 (3%) [3]	1 (1%) [1]	0	2 (2%) [2]
Endocrine disorders	3 (3%) [3]	0	3 (3%) [3]	1 (1%) [1]
Congenital, familial, and genetic disorders	0	1 (1%) [1]	0	1 (1%) [1]
Surgical and medical procedures	0	1 (1%) [1]	0	0
Pregnancy, puerperium, and perinatal conditions	0	0	0	0
Social circumstances	0	0	0	1 (1%) [1]
Adverse events leading to dose reduction*	18 (18%) [43]	4 (4%) [4]	13 (13%) [23]	2 (2%) [2]
Adverse events leading to premature discontinuation of zalfermin	13 (13%) [13]	8 (8%) [8]	5 (5%) [5]	0
Fatal adverse events	1 (1%) [1]	1 (1%) [1]	0	0
Treatment-related adverse events	82 (83%) [535]	69 (68%) [344]	71 (71%) [333]	47 (47%) [171]
Serious adverse events	7 (7%) [9]	13 (13%) [18]	10 (10%) [15]	5 (5%) [10]

Data are number of participants (%) [number of events] from the in-trial observation period. Coded with MedDRA v27.1. Placebo data are pooled. SOC=system organ class.
*There were no events that led to a dose reduction of zalfermin.

Table 2: **Safety outcomes**

2·4 mg group, 61 [60%] of 101 participants in the zalfermin 30 mg group, 73 [73%] of 100 participants in the semaglutide 2·4 mg group, and 51 [51%] of 100 participants in the placebo group), including nausea, diarrhoea, and vomiting, and mainly occurred upon treatment initiation, with an additive effect observed for zalfermin 30 mg plus semaglutide 2·4 mg for nausea and vomiting. Dose-dependent injection site reaction adverse events were observed with zalfermin (11 [11%] of 99 participants with zalfermin 30 mg plus semaglutide 2·4 mg, four [4%] of 99 participants in the zalfermin 7·5 mg plus semaglutide 2·4 mg group, and eight [8%] of 100 participants in the zalfermin 15 mg plus semaglutide 2·4 mg group). There was a higher proportion of adverse events possibly or probably related to treatment with zalfermin 30 mg plus semaglutide 2·4 mg (82 [83%] of 99 participants) versus zalfermin 30 mg (69 [68%] of 101 participants), semaglutide 2·4 mg (71 [71%] of 100 participants), and placebo (47 [47%] of 100 participants). Serious adverse events were reported in seven (7%) of 99 participants in the zalfermin 30 mg plus semaglutide 2·4 mg group, 13 (13%) of 101 participants in the zalfermin 30 mg group, ten (10%) of 100 participants in the semaglutide 2·4 mg group, and five (5%) of 100 participants in the placebo group (table 2). Adverse events led to dose reduction in 18 (18%) of 99 participants and discontinuation of treatment in 13 (13%) in the zalfermin 30 mg plus semaglutide 2·4 mg group (table 2).

Five deaths were reported. Two deaths were reported in the zalfermin 15 mg plus semaglutide 2·4 mg group (one case of abdominal pain, dizziness, and nausea; and one case of multi-system organ failure), one in the zalfermin 7·5 mg plus semaglutide 2·4 mg group (adenocarcinoma), one in the zalfermin 30 mg plus semaglutide 2·4 mg group (gastrointestinal ileus), and one in the zalfermin 30 mg group (heart failure). The fatal heart failure in the zalfermin 30 mg group was assessed by the investigator as possibly related to study drugs and all other deaths were assessed as not related to study drugs.

Discussion

There is an unmet need in patients with advanced fibrosis for treatment approaches to regress the disease or avoid liver-related outcomes. In this phase 2 study, although responder proportions were numerically greater across all treatment groups versus placebo for improvement in liver fibrosis and no worsening of metabolic dysfunction-associated steatohepatitis in participants with F2–F4c, these differences were not statistically significant, apart from for semaglutide 2·4 mg versus placebo (but this was not statistically confirmatory due to break of hierarchy). For resolution of metabolic dysfunction-associated steatohepatitis and no worsening of liver fibrosis, nominally significant differences in responder proportions were observed for all treatment groups versus placebo. Sensitivity analyses supported the primary analyses with consistent results.

Semaglutide showed a similar antifibrotic effect to that seen in the ESSENCE trial,[5] and a stronger antifibrotic effect in F4c versus a previous phase 2 study.[18,19] In the previous phase 2 study, once-weekly semaglutide 2·4 mg did not significantly improve fibrosis or achievement of metabolic dysfunction-associated steatohepatitis resolution versus placebo in patients with metabolic dysfunction-associated steatohepatitis and F4c (n=71).[18] The more pronounced antifibrotic effect of semaglutide observed in this study might be due to the longer trial duration, along with differences in placebo response and study populations. Although the semaglutide 2·4 mg versus placebo treatment difference for improvement in liver fibrosis and no worsening of metabolic dysfunction-associated steatohepatitis was nominally significant in the overall trial population, it was not in the F2 and F3 nor F4c subgroups. This might be due to the smaller sample size and reduced precision in the subgroups versus the overall population.

Given the different modes of action of zalfermin and semaglutide, with effects on the brain, liver, and adipose tissue, an additive effect was hypothesised in line with preclinical data.[15] However, we observed no additive effect for the combination of zalfermin and semaglutide on fibrosis and metabolic dysfunction-associated steatohepatitis, thus this study did not confirm the effect that has been observed in rodents. Notably, a lower number of participants were in receipt of the 2·4 mg dose of semaglutide at the end of treatment in the zalfermin 30 mg combination group, which might affect the interpretation of these results and could have diluted the treatment effect. In preclinical studies, FGF21 analogues induce bodyweight loss and show a synergistic bodyweight-lowering effect with GLP-1,[20] which has yet to be shown in humans, therefore challenging the translational value of the existing preclinical evidence base.

This study is the first to show a nominally significant treatment effect for semaglutide 2·4 mg versus placebo for resolution of metabolic dysfunction-associated steatohepatitis and no worsening of liver fibrosis in the F4c population. However, this result should be interpreted cautiously as it arises from a secondary endpoint evaluated within a subgroup after breaking of the statistical heirarchy. Despite previous negative phase 2 findings,[18] our results might suggest that semaglutide could be considered for further clinical assessment as a potential disease-modifying therapy in this population. Broadly, although nominally significant treatment effects were observed for resolution of metabolic dysfunction-associated steatohepatitis and no worsening of liver fibrosis, effects were less pronounced for improvement in liver fibrosis and no worsening of metabolic dysfunction-associated steatohepatitis. Mechanistically, despite both FGF21 analogues and GLP-1 receptor agonists targeting the metabolic and inflammatory drivers of metabolic dysfunction-associated steatohepatitis, fibrosis regression is a slower process typically beginning in the first year and

continuing up to 5 years.[21] Resolution of metabolic dysfunction-associated steatohepatitis also strongly predicts fibrosis regression at 72 and 96 weeks.[22] Therefore, a longer treatment duration, such as the 72-week treatment period in part 1 of the ESSENCE trial,[5] might have been required to fully observe significant antifibrotic effects.

For non-invasive tests (NITs) related to metabolic dysfunction-associated steatohepatitis disease activity and liver fibrosis, clinically meaningful and nominally significant treatment differences were observed for all treatment groups versus placebo. Compared with categorical biopsy endpoints, NITs reflected larger changes, suggesting they might be more sensitive to the early effects of zalfermin and semaglutide over a 52-week treatment period. These results support previous studies demonstrating that FGF21 analogues significantly improve metabolic dysfunction-associated steatohepatitis- and fibrosis-related biomarkers in patients with metabolic dysfunction-associated steatohepatitis.[23–25] NITs could offer value in real-world clinical practice settings in which liver biopsy presents logistical challenges.

There are structural differences across FGF21 analogues that might influence their efficacy in people with metabolic dysfunction-associated steatohepatitis and the use of zalfermin in our study might have affected the outcome. Efruxifermin is a bivalent Fc-FGF21 fusion whereas zalfermin is a modified FGF21 variant with no Fc fusion.[12] Direct CNS penetration of FGF21 analogues remains unclear. However, zalfermin might have a more pronounced CNS activity than efruxifermin due to its smaller molecular size. Broadly, the FGF21 analogue class remains promising for the treatment of metabolic dysfunction-associated steatohepatitis. In phase 2 studies, efruxifermin has shown dual efficacy on liver histology and metabolic markers in people with metabolic dysfunction-associated steatohepatitis and significant fibrosis (≥F2),[24,26] including a significant treatment effect versus placebo for improvement in liver fibrosis (decrease of one stage or more) without worsening of metabolic dysfunction-associated steatohepatitis (efruxifermin 50 mg *vs* placebo difference: 31 percentage points, 95% CI 12–49; p=0·0030).[24] Notably, efruxifermin was the first FGF21 analogue to show fibrosis improvement in the F4c population, with 33% of patients achieving fibrosis improvement of at least one stage without worsening of metabolic dysfunction-associated steatohepatitis.[23] Moreover, the tolerability profile of efruxifermin added to a low-dose GLP-1 receptor agonist used at stable doses was similar to that of either drug alone and significantly reduced hepatic fat fraction and fibrosis-related NITs in patients with metabolic dysfunction-associated steatohepatitis, and type 2 diabetes.[27] The combination of efruxifermin and semaglutide might be an efficacious treatment option for patients with metabolic dysfunction-associated steatohepatitis; however, future studies are needed to evaluate this. Additionally, the FGF21 analogue pegozafermin at doses of 30 mg once weekly and 44 mg every 2 weeks for 24 weeks led to significant improvements in fibrosis (decrease of one stage or more) without worsening of metabolic dysfunction-associated steatohepatitis versus placebo (pegozafermin 30 mg *vs* placebo difference: 19 percentage points, 95% CI 5–32; p=0·009) in patients with F2 or F3 metabolic dysfunction-associated steatohepatitis.[25]

No unexpected safety concerns were identified with zalfermin and semaglutide. Adverse events were more common in the combination treatment groups; there was an additive effect with zalfermin 30 mg plus semaglutide 2·4 mg for nausea and vomiting, which could limit the clinical usefulness of this regimen. Notably, there were no safety or tolerability concerns with semaglutide, corroborating a previous phase 2 study in participants with F4c.[18]

Strengths of the study include the large sample size relative to other proof of concept phase 2 studies of FGF21 analogues in metabolic dysfunction-associated steatohepatitis. Additionally, this is the first study to show a nominally significant treatment effect for semaglutide 2·4 mg versus placebo for resolution of metabolic dysfunction-associated steatohepatitis and no worsening of liver fibrosis in the F4c population, and the study provides valuable efficacy and safety data for this population. Limitations include the predominantly White population, the preponderance of female participants that could have influenced the results,[28] and the inclusion of only one zalfermin monotherapy group. In our study, zalfermin was added during semaglutide uptitration; it is unknown whether adding zalfermin after semaglutide maintenance would change the response in MASH management. Our findings might have little generalisability to a broader real-world population of patients with metabolic dysfunction-associated steatohepatitis diagnosed without biopsy or with milder fibrosis.

In conclusion, there was no clear additive effect of combining zalfermin with semaglutide in this phase 2 study; however, nominally significant treatment effects were observed for semaglutide for improvement in liver fibrosis and no worsening of metabolic dysfunction-associated steatohepatitis in patients with advanced fibrosis.

Contributors

JOC and BA were involved in the study concept and design, and collection and analysis of data. RL, JG, LC, SF, EL, and LLG were investigators in the trial and were responsible for recruiting patients and collecting data. All authors had full access to the trial data and contributed to the drafting and critical revision of the manuscript, coordinated by the medical writer, and accept responsibility to submit the manuscript for publication. RL, AS, JOC, BA, and ABL had access to the raw data and verified the underlying data.

Declaration of interests

RL receives funding support from NCATS (5UL1TR001442) and NIDDK (U01DK061734, U01DK130190, R01DK106419, R01DK121378, R01DK124318, P30DK120515); serves as a consultant to Aardvark Therapeutics, Altimmune, Anylam/Regeneron, Amgen, Arrowhead

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Data sharing

An authorised researcher can request access to clinical trial data by submitting a research proposal for review and approval by Novo Nordisk and an internal independent review panel. Requests are usually considered after the research is finished and the main results have been published. If the research supports a regulatory application, requests will be considered after the product and its intended use are approved in both the EU and the USA. Participants' clinical data will be anonymised, following an approved internal process, before data are shared to external third parties. The statistical code used for the analysis is available in the statistical analysis plan. For details on how to request access to clinical data, visit novonordisk-trials.com.

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References

1 Loomba R, Friedman SL, Shulman GI. Mechanisms and disease consequences of nonalcoholic fatty liver disease. *Cell* 2021; **184:** 2537–64.
2 Gupta U, Ruli T, Buttar D, Shoreibah M, Gray M. Metabolic dysfunction associated steatotic liver disease: current practice, screening guidelines and management in the primary care setting. *Am J Med Sci* 2024; **367:** 77–88.
3 Taylor RS, Taylor RJ, Bayliss S, et al. Association between fibrosis stage and outcomes of patients with nonalcoholic fatty liver disease: a systematic review and meta-analysis. *Gastroenterology* 2020; **158:** 1611–25.
4 Angulo P, Kleiner DE, Dam-Larsen S, et al. Liver fibrosis, but no other histologic features, is associated with long-term outcomes of patients with nonalcoholic fatty liver disease. *Gastroenterology* 2015; **149:** 389–97.
5 Sanyal AJ, Newsome PN, Kliers I, et al. Phase 3 trial of semaglutide in metabolic dysfunction-associated steatohepatitis. *N Engl J Med* 2025; **392:** 2089–99.
6 Newsome PN, Loomba R. Therapeutic horizons in metabolic dysfunction-associated steatohepatitis. *J Clin Invest* 2025; **135:** e186425.
7 Li W, Alazawi W, Loomba R. Current and emerging therapeutic landscape for metabolic dysfunction-associated steatohepatitis. *Lancet Gastroenterol Hepatol* 2026; **11:** 150–62.
8 Harrison SA, Bedossa P, Guy CD, et al. A phase 3, randomized, controlled trial of resmetirom in NASH with liver fibrosis. *N Engl J Med* 2024; **390:** 497–509.
9 Schwabe RF, Tacke F, Sugimoto A, Friedman SL. Antifibrotic therapies for metabolic dysfunction-associated steatotic liver disease. *JHEP Rep* 2025; **7:** 101421.
10 Kilkenny DM, Rocheleau JV. The FGF21 receptor signaling complex: Klothoβ, FGFR1c, and other regulatory interactions. *Vitam Horm* 2016; **101:** 17–58.
11 Owen BM, Ding X, Morgan DA, et al. FGF21 acts centrally to induce sympathetic nerve activity, energy expenditure, and weight loss. *Cell Metab* 2014; **20:** 670–77.
12 Sass-Ørum K, Tagmose TM, Olsen J, et al. Development of zalfermin, a long-acting proteolytically stabilized FGF21 analog. *J Med Chem* 2024; **67:** 11769–88.
13 Dahl K, Friedrichsen MH, Ribel-Madsen R, et al. Safety, tolerability, pharmacokinetics, and pharmacodynamics of the novel long-acting FGF21 analog zalfermin: a multiple ascending dose study in healthy participants with overweight/obesity. *Endocrinol Diabetes Metab J* 2025; **9:** 1–12.
14 Dahl K, Friedrichsen MH, Ribel-Madsen R, et al. Safety, tolerability, pharmacokinetics, and pharmacodynamics of the novel long-acting FGF21 analog zalfermin. *Clin Transl Sci* 2025; **18:** e70435.
15 Norlin J, Dermit M, Sidiropoulos N, et al. The combination of zalfermin and semaglutide has additive therapeutic effects in a diet-induced obese and biopsy-confirmed mouse model of MASH. *PLoS One* 2025; **20:** e0331665.
16 Kleiner DE, Brunt EM, Van Natta M, et al. Design and validation of a histological scoring system for nonalcoholic fatty liver disease. *Hepatology* 2005; **41:** 1313–21.
17 Frias JP, Deenadayalan S, Erichsen L, et al. Efficacy and safety of co-administered once-weekly cagrilintide 2·4 mg with once-weekly semaglutide 2·4 mg in type 2 diabetes: a multicentre, randomised, double-blind, active-controlled, phase 2 trial. *Lancet* 2023; **402:** 720–30.
18 Loomba R, Abdelmalek MF, Armstrong MJ, et al. Semaglutide 2·4 mg once weekly in patients with non-alcoholic steatohepatitis-related cirrhosis: a randomised, placebo-controlled phase 2 trial. *Lancet Gastroenterol Hepatol* 2023; **8:** 511–22.
19 Newsome PN, Buchholtz K, Cusi K, et al. A placebo-controlled trial of subcutaneous semaglutide in nonalcoholic steatohepatitis. *N Engl J Med* 2021; **384:** 1113–24.
20 Pan Q, Lin S, Li Y, et al. A novel GLP-1 and FGF21 dual agonist has therapeutic potential for diabetes and non-alcoholic steatohepatitis. *EBioMedicine* 2021; **63:** 103202.

21 Lassailly G, Caiazzo R, Ntandja-Wandji L-C, et al. Bariatric surgery provides long-term resolution of nonalcoholic steatohepatitis and regression of fibrosis. *Gastroenterology* 2020; **159:** 1290–301.

22 Brunt EM, Kleiner DE, Wilson LA, Sanyal AJ, Neuschwander-Tetri BA. Improvements in histologic features and diagnosis associated with improvement in fibrosis in nonalcoholic steatohepatitis: results from the Nonalcoholic Steatohepatitis Clinical Research Network treatment trials. *Hepatology* 2019; **70:** 522–31.

23 Harrison SA, Ruane PJ, Freilich B, et al. A randomized, double-blind, placebo-controlled phase IIa trial of efruxifermin for patients with compensated NASH cirrhosis. *JHEP Rep* 2022; **5:** 100563.

24 Noureddin M, Frias JP, Neff GW, et al. Safety and efficacy of once-weekly efruxifermin versus placebo in metabolic dysfunction-associated steatohepatitis (HARMONY): 96-week results from a multicentre, randomised, double-blind, placebo-controlled, phase 2b trial. *Lancet* 2025; **406:** 719–30.

25 Loomba R, Sanyal AJ, Kowdley KV, et al. Randomized, controlled trial of the FGF21 analogue pegozafermin in NASH. *N Engl J Med* 2023; **389:** 998–1008.

26 Kamrul-Hasan ABM, Borozan S, Jena S, et al. Safety and efficacy of efruxifermin in metabolic dysfunction-associated steatohepatitis: a systematic review. *World J Gastrointest Pharmacol Ther* 2025; **16:** 110709.

27 Harrison SA, Frias JP, Lucas KJ, et al. Safety and efficacy of efruxifermin in combination with a GLP-1 receptor agonist in patients with NASH/MASH and type 2 diabetes in a randomized phase 2 study. *Clin Gastroenterol Hepatol* 2025; **23:** 103–13.

28 Penmetsa R, Kapil S, VanWagner LB. Sex and gender differences in metabolic dysfunction-associated liver disease. *Indian J Gastroenterol* 2026; **45:** 192–201.