Denifanstat for the treatment of metabolic dysfunction-associated steatohepatitis: a multicentre, double-blind, randomised, placebo-controlled, phase 2b trial

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See Comment page 1066

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Summary

Background Denifanstat, an oral fatty acid synthase (FASN) inhibitor, blocks de-novo lipogenesis, a key pathway driving progressive lipotoxicity, inflammation, and fibrosis in metabolic dysfunction-associated steatohepatitis (MASH). This study aimed to examine the safety and efficacy of denifanstat for improving liver histology in individuals with MASH and moderate to advanced fibrosis.

Methods This multicentre, double-blind, randomised, placebo-controlled, phase 2b trial was conducted at 100 clinical sites in the USA, Canada, and Poland. After a screening period of up to 90 days, participants aged 18 years and older with biopsy-confirmed MASH and stage F2 or F3 fibrosis were randomly assigned (2:1) to receive either 50 mg oral denifanstat or placebo once per day for 52 weeks. Participants were dynamically allocated to treatment groups via a centrally administered interactive web-based response system and stratified by type 2 diabetes, region, and fibrosis stage. Investigators, patients, and the sponsor were masked to group allocation until database lock. The primary efficacy endpoints were a 2-point or greater improvement in non-alcoholic fatty liver disease activity score (NAS) without a worsening of fibrosis or MASH resolution with a 2-point or greater improvement in NAS without a worsening of fibrosis at week 52, assessed by intention to treat. Safety was assessed in all participants who received at least one dose of study drug. This trial is registered with ClinicalTrials.gov, NCT04906421, and is closed for enrolment.

Findings Of the 1087 individuals screened between June 2, 2021, and June 28, 2022, 168 eligible participants were randomly assigned to receive a dose of 50 mg denifanstat once per day (n=112) or placebo (n=56). All 168 participants (100 female, 68 male) received at least one dose of study treatment. In the ITT population, 42 (38%) of 112 participants in the denifanstat group had a 2-point or greater improvement in NAS without a worsening of fibrosis versus nine (16%) of 56 participants in the placebo group (common risk difference 21·0%, 95% CI 8·1–33·9; p=0·0035). 29 (26%) of 112 participants in the denifanstat group showed MASH resolution with a 2-point or greater improvement in NAS without a worsening of fibrosis compared with six (11%) of 56 participants in the placebo group (common risk difference 13·0%, 0·7–25·3; p=0·0173). The most common treatment-emergent adverse events were COVID-19 (19 [17%] of 112 in the denifanstat group *vs* six [11%] of 56) in the placebo group, dry eye symptoms (ten [9%] of 112 *vs* eight [14%] of 56), and alopecia (21 [19%] of 112 *vs* two [4%] of 56). All adverse events considered to be related to the study drug were of grade 1 or grade 2. None of the serious adverse events (13 [12%] of 112 participants in the denifanstat group *vs* three [5%] of 56 in the placebo group) were considered drug-related.

Interpretation Treatment with denifanstat resulted in statistically significant and clinically meaningful improvements in disease activity, MASH resolution, and fibrosis. The results of this phase 2b trial support the advancement of denifanstat to phase 3 development.

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Introduction

5–14% of adults in the USA are estimated as having metabolic dysfunction-associated steatohepatitis (MASH), putting over 9 million US individuals at increased risk of cardiac-related and liver-related morbidity and mortality.[1–4] Metabolic diseases, particularly obesity and type 2 diabetes, are strong independent risk factors for excess liver fat deposition and progressive liver disease in individuals with MASH.[5] Lipotoxins and cellular stresses in conjunction with increased de-novo lipogenesis drive inflammation, which leads to progressive fibrosis, cirrhosis, and hepatocellular carcinoma among people with MASH.[6]

A substantial portion of excess liver fat in MASH results from an inflow of abundant dietary simple carbohydrates, especially fructose, leading to increased de-novo lipogenesis. The action of the central enzyme in the de-novo lipogenesis pathway, fatty acid synthase (FASN), converts

Research in context

Evidence before this study

Metabolic dysfunction-associated steatohepatitis (MASH), formerly known as non-alcoholic steatohepatitis (NASH), is a progressive liver disease resulting in lipotoxic and cellular stress from increased de-novo lipogenesis (DNL), which drives progressive inflammation and fibrosis in the liver. PubMed was searched on April 24, 2024, for articles published between 2010 and 2021 (inclusive) with terms including "FASN", "NASH", and "DNL". Preclinical studies published in this set of 259 results showed that fatty acid synthase (FASN) inhibition could directly reduce inflammation in isolated human immune cells and reduce fibrosis in hepatic stellate cells. The only controlled trial of a FASN inhibitor was a randomised, controlled study of denifanstat in individuals with MASH given placebo, 25 mg denifanstat, or 50 mg denifanstat daily for 12 weeks. This proof-of-concept study with non-invasive methods showed that denifanstat was well tolerated, significantly reduced liver fat, and improved multiple biomarkers associated with the disease, including reductions of alanine aminotransferase, LDL cholesterol, and cytokeratin-18.

Added value of this study

The mechanism of action of the novel molecule denifanstat directly targets liver steatosis, inflammation, and fibrosis (the three main drivers of liver injury) in individuals with MASH. This study is the first clinical trial with a FASN inhibitor and biopsy-based histological endpoints to evaluate the potential of denifanstat and its unique mechanism of action to improve liver disease. 50 mg oral doses of denifanstat per day for 52 weeks resulted in histologically documented, statistically significant improvements in non-alcoholic fatty liver disease activity score, MASH resolution, and fibrosis in participants with MASH and stage 2 to stage 3 fibrosis, including individuals at higher risk with diabetes and more advanced fibrosis. The proportion of participants with fibrosis improvement and the extent of the improvement shown by individuals with two or more stages of improvement compares favourably with other oral drugs at this stage of development. Denifanstat also increased the level of polyunsaturated fatty acids in triglycerides and reduced LDL cholesterol, suggesting it might have beneficial cardiometabolic effects, and was generally well tolerated.

Implications of all the available evidence

These results show the importance of targeting liver inflammation and fibrosis directly. Phase 3 studies of denifanstat in patients with MASH and stage 2 to stage 3 fibrosis are planned to further characterise the safety and efficacy of this drug in a larger number of patients across multiple countries and assess its impact on longer term outcomes. These studies will pave the way to potentially make this drug available to patients with MASH with moderate to advanced fibrosis.

acetyl-coenzyme A and malonyl-coenzyme A to the fatty acid palmitate.[7] Palmitate, a saturated fatty acid, and its derivatives accumulate in hepatocytes, causing steatosis, followed by activation of the NLRP3 inflammasome and ultimately pyroptotic cell death.[8,9] This process releases signalling molecules, leading to immune cell infiltration and activation, the release of damaging cytokines, and the differentiation of pro-inflammatory T cells in the liver. This inflamed, lipotoxic setting activates hepatic stellate cells, promoting the development of hepatic fibrosis.[8–11] Multiple studies have shown that the pro-inflammatory and fibrotic processes in MASH are dependent on the activity of endogenous FASN in hepatic immune and stellate cells. In addition to blocking liver fat build-up (the initiating event in MASH), the inhibition of FASN directly reduces damaging pro-inflammatory and fibrotic pathways in MASH.[12–14]

In the phase 2a clinical study, FASCINATE-1,[10] treatment with denifanstat for 12 weeks reduced liver fat and improved multiple biomarkers of inflammation and fibrosis in participants with MASH in a dose-dependent manner and was generally well tolerated. These clinical results (in combination with preclinical data) suggested that denifanstat could improve MASH with moderate-to-advanced fibrosis.

In this Article, we report the results of FASCINATE-2, a phase 2b trial that aimed to assess the safety and efficacy of 50 mg oral denifanstat once per day in participants with biopsy-confirmed MASH and stage 2 or 3 fibrosis.

Methods

Study design and participants

FASCINATE-2 (SB2640-CLIN-007), an international, multicentre, double-blind, randomised, placebo-controlled, phase 2b trial, enrolled participants at 68 sites in the USA (n=65), Canada (n=2), and Poland (n=1). The trial enrolled men and women aged 18 years and older with biopsy-confirmed MASH during screening, a non-alcoholic fatty liver disease (NAFLD) activity score (NAS) of 4 or higher, and at least a score of 1 in each of the categories steatosis, lobular inflammation, and hepatocyte ballooning, and stage 2 or 3 (F2 or F3) fibrosis.[15] For inclusion, patients were required to have a BMI of 23 kg/m² or higher if they were Asian or a BMI of 25 kg/m² or higher if they were another race, a liver stiffness measurement of 8·5 kPa or higher and a controlled attenuation parameter score of 280 dB/m or higher as measured by FibroScan during the screening period. Key exclusion criteria included having clinically acute or chronic liver disease unrelated to MASH, a history or presence of cirrhosis, weight gain or loss of more than 5% in the 6 months before baseline or weight loss of more than 10% in the 12 months before screening,

a history of harmful alcohol intake for a period of more than 3 consecutive months within 1 year before screening, uncontrolled diabetes (ie, haemoglobin A_{1c} (HbA_{1c}) >9·5% at screening), or liver enzyme concentrations more than five times the upper limit of typical. Individuals on stable doses of medications for at least 6 months before screening, including doses of pioglitazone, vitamin E, sodium-glucose transport protein 2, and GLP-1 receptor agonists (RAs) were eligible for inclusion; individuals taking obeticholic acid were excluded. A full list of the inclusion and exclusion criteria is provided in the appendix (pp 1–4). The study was conducted in accordance with the principles of the Declaration of Helsinki, International Council for Harmonisation Good Clinical Practice guidance, and all applicable regulatory requirements. Written informed consent was obtained from all participants before any study-related activities were conducted. This trial is registered with ClinicalTrials.gov, NCT04906421.

See Online for appendix

Randomisation and masking

Participants were randomly assigned (2:1) to receive 50 mg oral denifanstat once per day or identical matched placebo. Participants were dynamically allocated to treatment groups via a centrally administered interactive web-based response system and stratified by type 2 diabetes (yes or no), region (North America or not North America), and fibrosis stage (F2 [moderate] or F3 [advanced]). An independent study statistician generated the allocation sequence and a randomisation reconciliation plan was used to ensure correct kit assignment and balance between groups and stratification factors. The study team, including investigators, patients, and the sponsor, remained masked until database lock.

Procedures

After a screening period of up to 90 days, the study treatment was administered for up to 52 weeks. Instructions in the study protocol allowed dose modification, including interruption, for participants who experienced an on-target adverse event (AE) that was considered to be treatment-related and would lead to study or treatment discontinuation. To preserve the study masking, the number of administered tablets remained the same for both the study drug and the matching placebo. Participants were seen at baseline and weeks 4, 8, 13, 26, 39, and 52 during the dosing period in addition to a visit at either week 56 for follow-up or at early termination. Vital signs, symptom-directed physical exams, and blood samples for safety evaluation were collected at each visit. A full physical examination was performed during screening and again at week 56 or the early termination visit.

Baseline values for the assessment of histological endpoints were derived either from a biopsy taken during screening or a biopsy obtained within 180 days before screening (ie, a historical biopsy); a second biopsy was performed at the end of treatment. Liver biopsies were sectioned and stained with either haematoxylin and eosin or trichrome, and images were digitised. Biopsies were first evaluated by a single central expert pathologist (PB) for quality as the specimen needed to exceed a minimum threshold of size and fragmentation, otherwise new sections were cut and processed for evaluation. This single central pathologist then calculated the NAS and established the fibrosis stage according to the Non-Alcoholic Steatohepatitis Clinical Research Network (NASH CRN) histological scoring system. The pathologist was masked to the trial group assignment and clinical data and processed biopsies as they became available. A separate unstained slide was evaluated by second harmonic generation microscopy to visualise collagen and quantitated with imaging-based artificial intelligence (AI)-assisted digital pathology to produce the quantitative index of the architectural, morphological, and spatial distribution of collagen fibers referred to as the qFibrosis value (HistoIndex).[16] Participants had their proton density liver fat fraction mapped with MRI (MRI-PDFF), as available, before being randomly assigned (during screening or at baseline) and at weeks 26 and 52 or during an early termination visit.

Blood was collected for metabolic and lipid panels and for measuring MASH-related biomarkers at weeks 4, 8, 13, 26, 39, and 52. Lipidomic analyses were performed with ultra high-performance liquid chromatography analysing methanol and chloroform or methanol extracts.

Outcomes

This study had two primary endpoints, assessed at week 52 of treatment: histological improvement of 2 points or more in NAS (with 1 point or more of improvement in ballooning or inflammation) and without worsening of fibrosis (by NASH CRN fibrosis score); and MASH resolution (defined as the absence of fatty liver disease or isolated or simple steatosis without steatohepatitis and a score of either 0 or 1 for inflammation, 0 for ballooning, and any value for steatosis) and no worsening of liver fibrosis (by NASH CRN fibrosis score) and 2 points or more of improvement in NAS.

Secondary endpoints included both fibrosis improvement without worsening of steatohepatitis and MASH resolution without worsening of fibrosis as described in the US Food and Drug Administration (FDA) draft guidance for phase 3 endpoints for accelerated approval in patients with non-cirrhotic MASH.[17] Several other secondary endpoints were evaluated, including change in liver fat by MRI-PDFF and changes in the quantitative architectural, morphological, and spatial distribution of collagen fibres (the qFibrosis score) with AI-assisted digital pathology. All secondary endpoints are listed in the appendix (pp 11–13). Exploratory objectives included evaluation of the FibroScan-AST (FAST) score and changes in liver injury, lipidomic, and fibrosis

biomarkers. All exploratory objectives are provided in the protocol. AEs were coded following the Medical Dictionary for Regulatory Activities (MedDRA). Incidence of treatment-emergent AEs was summarised by MedDRA system organ class and preferred term by severity and causal relationship to study drug. The severity of treatment-emergent AEs was graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events version 5.0.

Statistical analysis

We estimated that a sample of 162 randomly assigned (2:1) participants had a power of at least 80% to detect a 20% treatment effect with a 20% placebo rate, assuming a discontinuation rate of 18·5%. These rate assumptions were extrapolated from previous studies of denifanstat and other studies in the field.[10,18] The covariance matrix included fibrosis stage (F2 or F3) and type 2 diabetes status (yes or no) at randomisation. The primary hypotheses in the protocol are the superiority of a 50 mg dose of denifanstat over placebo based on each of these two endpoints. Biopsy data were analysed with two-sided p values from the Cochran–Mantel–Haenszel test stratified by type 2 diabetes status at baseline (yes or no) and the amount of fibrosis at baseline (F2 or F3); region (ie, North America or not North America) was not used during analysis since only one participant was enrolled outside of North America (in Poland). Estimates of treatment effect are reported as the common risk difference with Miettinen Nurminen 95% CIs adjusted for the stratification factors diabetes status (yes or no) and amount of fibrosis at baseline (F2 or F3). No adjustment for multiplicity for the two primary efficacy tests was performed. Two-sided 0·05 significance-level tests were used for the efficacy endpoints and two-sided p values are reported unless otherwise indicated.

The primary efficacy analysis was by intention-to-treat (ITT). For the ITT population, participants with missing end-of-study biopsies were considered to have not had a response. An additional efficacy analysis was by modified ITT (mITT). The mITT population included patients who had paired pretreatment and end-of-treatment biopsies and a minimum of 42 weeks of treatment. For all biomarkers (including MRI-PDFF), participants were included only when they had both a pretreatment and post-treatment sample; missing values were not imputed. Prespecified subpopulations were defined for primary and secondary histological analyses on the basis of baseline criteria of fibrosis stage (F2 or F3), GLP-1 usage (yes or no), or type 2 diabetes status (yes or no). The safety analysis population included all participants who received at least one dose of denifanstat or placebo. For most analyses of laboratory-based parameters, least-squares mean estimates were based on the linear mixed-effects model for repeated measures with fixed effects for type 2 diabetes status at baseline (yes or no), fibrosis stage at baseline (F2 or F3), treatment group, visit, and treatment-by-visit interaction as the fixed effects, and baseline value as a covariate. Analyses were preplanned unless otherwise stated. Analyses were performed with SAS version 9.4. An independent data monitoring committee provided review and assessment of study data and monitored the overall study conduct in a systematic manner to safeguard the safety of the study participants.

Role of the funding source

The sponsor (along with expert consultants in the field) was responsible for the trial design, protocol, and development of the statistical analysis plan. The sponsor, its contractors, and the investigators were responsible for the study conduct and data collection. The sponsor had responsibility for the data analysis, data interpretation, and submission of the results for publication, and had a role in the writing of the report.

Results

Among the 1087 individuals screened between June 2, 2021, and June 28, 2022, 168 eligible participants were randomly assigned to receive a dose of 50 mg denifanstat once per day (n=112) or placebo (n=56); these participants comprised the ITT population (figure 1). All

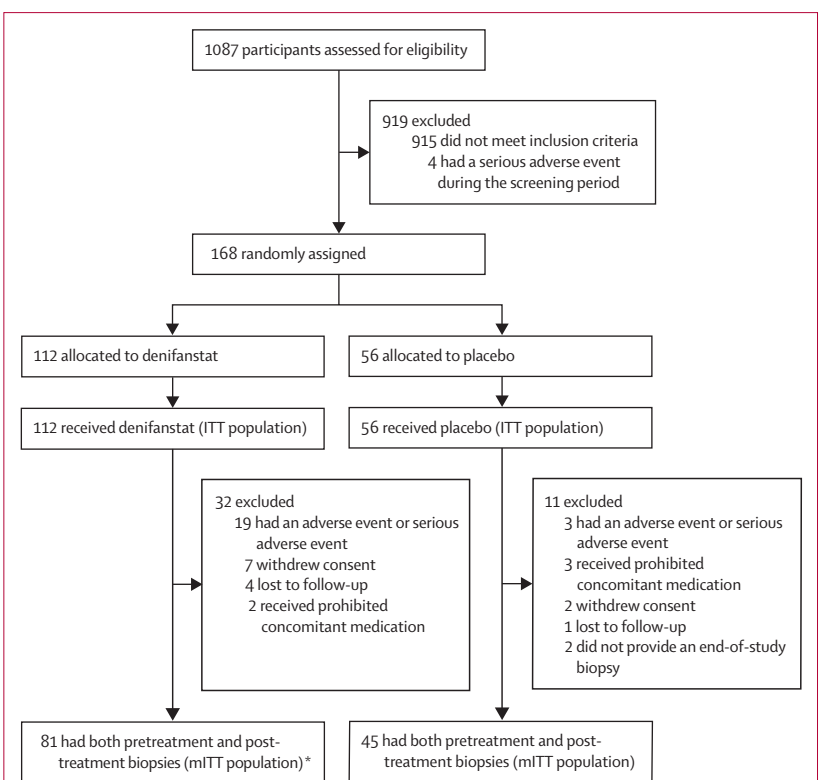

Figure 1: **Trial profile**
ITT=intention-to-treat. mITT=modified ITT. *One participant of the 32 participants who did not complete the study consented to have an end-of-treatment biopsy that qualified for the mITT population per the protocol, resulting in 81 participants in the denifanstat mITT.

	50 mg denifanstat (n=112)	Placebo (n=56)	Total (N=168)
Age, years	56·3 (10·5)	58·4 (11·9)	57·0 (11·0)
Sex			
Male	46 (41%)	22 (39%)	68 (41%)
Female	66 (59%)	24 (61%)	100 (60%)
White race*	100 (89%)	50 (89%)	150 (89%)
Hispanic or Latino ethnic group*	34 (30%)	21 (38%)	55 (33%)
Bodyweight, kg	97·4 (18·8)	99·9 (20·2)	98·2 (19·2)
BMI, kg/m²	34·4 (5·8)	36·2 (6·6)	35·0 (6·1)
Statin use	58 (52%)	28 (50%)	86 (51%)
GLP-1 receptor agonist use	17 (15%)	6 (11%)	23 (14%)
Type 2 diabetes	69 (62%)	34 (61%)	103 (61%)
Glycated haemoglobin, %	6·8% (1·1)	6·6% (0·9)	6·7% (1·1)
Alanine aminotransferase, U/L	50·5 (25·1)	64·5 (35·4)	55·2 (29·6)
Aspartate aminotransferase, U/L	41·9 (22·7)	51·8 (30·8)	45·2 (26·0)
Liver biopsy findings			
NASH CRN fibrosis stage†			
F2	48 (43%)	27 (48%)	75 (45%)
F3	64 (57%)	29 (52%)	93 (55%)
NAS‡			
4–5	61 (55%)	35 (63%)	96 (57%)
6–8	51 (46%)	21 (38%)	72 (43%)
Liver fat (MRI-PDFF), %	16·8% (7·2)	18·8% (6·9)	17·5% (7·2)
Liver fat (FibroScan CAP)	336·5 (36·4)	344·9 (35·7)	339·3 (36·3)
Liver stiffness, kPa§	11·2 (3·9)	12·2 (4·6)	11·6 (4·2)
FibroScan-AST score	0·6 (0·2)	0·6 (0·2)	0·6 (0·2)
qFibrosis score	2·6 (0·8)	2·5 (0·6)	2·6 (0·7)
Enhanced liver fibrosis	9·6 (0·8)	9·7 (0·9)	9·6 (0·8)
LDL cholesterol, mg/dL	93·3 (37·9)	103·1 (38·9)	96·5 (38·4)
Triglycerides, mg/mL	170·2 (82·9)	176·6 (152·2)	172·3 (110·4)
Polyunsaturated fatty acid to saturated triglyceride ratio	4·2 (3·4)	3·6 (2·8)	4·0 (3·2)
Tripalmitin, mg/mL	6·3 (5·1)	6·7 (5·6)	6·5 (5·2)
Cytokeratin-18 (M30), U/L	475·1 (328·5)	542·7 (405·7)	498·2 (357·0)
Cytokeratin-18 (M65), U/L	702·0 (563·0)	757·6 (516·0)	721·0 (546·5)
Insulin, pmol/L	271·8 (177·5)	307·5 (166·2)	283·7 (174·0)

Data are mean (SD) or n (%). ITT=intention-to-treat. MRI-PDFF=proton density liver fat fraction mapped with MRI. NAS=non-alcoholic fatty liver disease activity score. NASH CRN=Nonalcoholic Steatohepatitis Clinical Research Network. *Race and ethnic group data were self-reported by participants; individuals could be recorded as both White and Hispanic or Latino. †The fibrosis stages according to NASH CRN in participants with non-alcoholic steatohepatitis are as follows: F2 moderate (perisinusoidal and portal or periportal) fibrosis and F3 severe (bridging) fibrosis. ‡NAS is assessed on a scale of 0 to 8, with higher scores indicating more severe disease; the components of this measure are steatosis (assessed on a scale of 0 to 3), lobular inflammation (assessed on a scale of 0 to 3), and hepatocellular ballooning (assessed on a scale of 0 to 2). §Liver stiffness was assessed by means of vibration-controlled transient elastography (FibroScan); higher liver stiffness scores as assessed with the use of vibration-controlled transient elastography indicate a higher risk of advanced fibrosis.

Table 1: **Baseline characteristics of the ITT population**

participants received at least one dose of study treatment and could be included in the safety analysis population. Nine patients in the placebo group and 32 patients in the denifanstat group did not complete treatment. 45 patients in the placebo group and 81 patients in the denifanstat group had post-treatment biopsies and were included in the mITT population. The demographic and clinical characteristics of the two groups were similar at baseline. The majority of trial participants were female, White, and had stage 3 fibrosis, type 2 diabetes, and elevated liver enzymes—characteristics consistent with moderate-to-advanced high-risk MASH (table 1). Common background medications included statins (86 [51%] of 168 participants) and GLP-1 RAs (23 [14%] of 168). The most common reason for withdrawal from the study was an AE (19 [17%] of 112 for denifanstat *vs* three [5%] of 56 participants for placebo), followed by withdrawal of consent (seven [6%] *vs* two [4%]), loss to follow-up (four [4%] *vs* one [2%]), and use of prohibited concomitant medications (two [2%] *vs* three [5%]).

Analysis of the 168 patients in the ITT population showed that 42 (38%) of 112 participants who received denifanstat met the primary endpoint of improvement in NAS by 2 points or more without worsening of fibrosis compared with nine (16%) of 56 participants who received placebo (common risk difference 21·0%, 95% CI 8·1–33·9; p=0·0035; figure 2A). In the ITT population, 29 (26%) of 112 participants who received denifanstat met the other primary endpoint of MASH resolution and a 2-point or more improvement in NAS without worsening of fibrosis compared with six (11%) of 56 participants who received placebo (common risk difference 13·0%, 0·7–25·3; p=0·0173; figure 2B).

In the mITT population, 42 (52%) of 81 participants in the denifanstat group had a 2-point or greater improvement in their NAS without worsening of fibrosis compared with nine (20%) of 45 participants in the placebo group (common risk difference 30·9%, 15·7–46·1; p=0·0003). 29 (36%) of 81 participants in the denifanstat group had MASH resolution with no worsening of fibrosis and a 2-point or more improvement in NAS compared with six (13%) of 45 participants in the placebo group (common risk difference 20·2%, 5·2–35·2; p=0·0044).

Improvement of fibrosis by one stage or more (according to the NASH CRN score) without worsening of steatohepatitis was attained in 33 (41%) of 81 participants in the denifanstat group in the mITT population compared with eight (18%) of the 45 participants in the placebo group (common risk difference 20·1%, 4·5 to 35·7; p=0·0102; figure 3A). In the ITT population, 33 (30%) of 112 participants in the denifanstat group had improved fibrosis by one stage or more according to their NASH CRN score without worsening of steatohepatitis compared with eight (14%) of 56 participants in the placebo group (common risk difference 11·8%, –1·3 to 24·8; p=0·040; figure 3B).

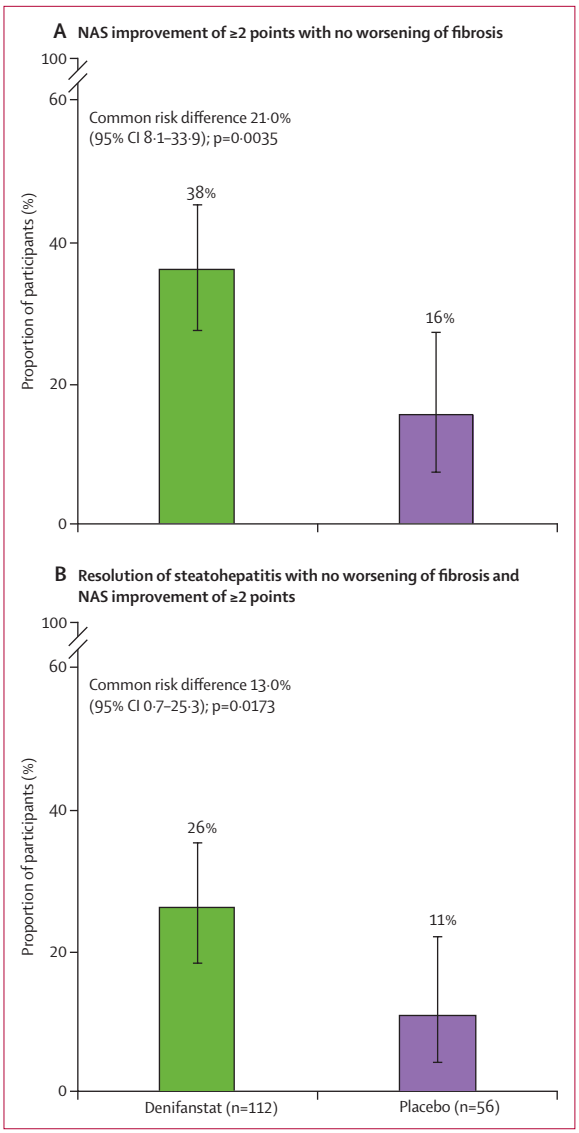

Figure 2: **Primary endpoints at week 52 in the ITT population**
(A) Proportion of participants with the co-primary endpoint of a 2-point or greater improvement in NAS (with a 1-point or greater improvement in ballooning or inflammation) at week 52 without worsening fibrosis. (B) The proportion of participants with the other co-primary endpoint of resolution of steatohepatitis and no worsening of liver fibrosis according to NASH CRN fibrosis score and histological improvement in NAS (ie, 2 points or more of improvement in NAS). Resolution of steatohepatitis was defined as the absence of fatty liver disease or isolated or simple steatosis without steatohepatitis and a NAS of 0 or 1 for inflammation, 0 for ballooning, and any value for steatosis. ITT=intention-to-treat. NAS=non-alcoholic fatty liver disease activity score. NASH CRN=Nonalcoholic Steatohepatitis Clinical Research Network.

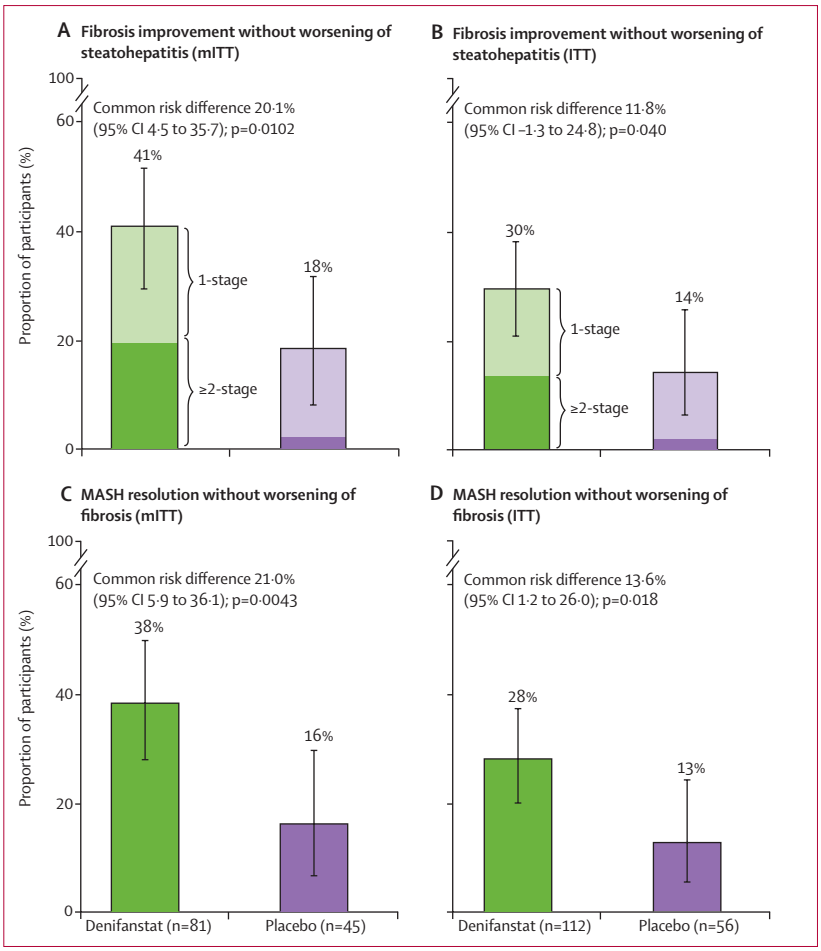

Figure 3: **Secondary histological endpoints at week 52 in the mITT and ITT populations**
Proportion of participants with improvement of fibrosis by one stage without a worsening of steatohepatitis (hatched box) or by two or more stages without a worsening of steatohepatitis (solid box) in the mITT (A) and ITT (B) populations. Proportion of participants with MASH resolution without a worsening of fibrosis in the mITT (C) and ITT (D) populations. MASH resolution was defined as the absence of fatty liver disease or isolated or simple steatosis without steatohepatitis and a NAS of 0 or 1 for inflammation, 0 for ballooning, and any value for steatosis. ITT=intention-to-treat. MASH=metabolic dysfunction-associated steatohepatitis. mITT=modified ITT.

In the mITT population, more participants in the denifanstat group improved by two or more stages of fibrosis without worsening of steatohepatitis than in the placebo group (table 2). Several prespecified subpopulation analyses in the mITT population assessed the effect of denifanstat on the improvement of fibrosis by one stage or more without worsening of steatohepatitis (table 2 and appendix p 5). 23 (49%) of 47 participants with F3 fibrosis in the denifanstat group showed improved fibrosis compared with three (13%) of 23 participants with F3 fibrosis in the placebo group. In participants with type 2 diabetes, 22 (40%) of 55 participants in the denifanstat group showed improved fibrosis compared with five (19%) of 27 participants in the placebo group. In the 12 participants taking both GLP-1 RAs and denifanstat, five (42%) had a fibrosis response (appendix p 5); however, none of the four participants in the placebo group who were on stable GLP-1 RA therapy had improvement of fibrosis.

Compared with baseline, qFibrosis score decreased significantly by 6·1% (95% CI –11·5 to –0·77) in participants in the denifanstat group, whereas there was a 4·6% (–2·27 to 11·55) increase in the qFibrosis score of participants in the placebo group (least-squares mean difference –10·8%, 95% CI –19·36 to –2·2; p=0·014; table 2).

In the mITT population, 31 (38%) of 81 participants in the denifanstat group showed MASH resolution without worsening of fibrosis compared with seven (16%) of 45 participants in the placebo group (common risk difference 21·0%, 95% CI 5·9–36·1; p=0·0043; figure 3C). In the ITT population, 31 (28%) of 112 participants in the denifanstat group showed MASH resolution without worsening of fibrosis compared with seven (13%) of 56 participants in the placebo group (common risk difference 13·6%, 1·2–26·0; p=0·018; figure 3D).

In the mITT population, MASH resolution with fibrosis improvement and without worsening of steatohepatitis

	50 mg denifanstat	Placebo	Common risk difference (95% CI)	p value
Histological or MRI-PDFF endpoint change from baseline				
Fibrosis improvement of one stage or more without worsening of steatohepatitis				
F2	10 (29%); N=34	5 (23%); N=22	4·4 (–19·1 to 27·9)	0·59
F3	23 (49%); N=47	3 (13%); N=23	32·6 (11·7 to 53·4)	0·0032
Type 2 diabetes	22 (40%); N=55	5 (19%); N=27	16·8 (–3·2 to 36·8)	0·076
Improvement by two or more stages without worsening of steatohepatitis	16 (20%); N=81	1 (2%); N=45	9·2 (–3·0 to 21·4)	0·0065
Non-alcoholic steatohepatitis resolution with no worsening of fibrosis	31 (38%); N=81	7 (16%); N=45	21·0 (5·9 to 36·1)	0·0043
Fibrosis improvement of 1 stage or more without worsening of steatohepatitis or non-alcoholic steatohepatitis resolution with no worsening of fibrosis	45 (56%); N=81	12 (27%); N=45	26·5 (10·4 to 42·6)	0·0018
Liver fat (MRI-PDFF 30% reduction or more)	45 (65%); N=69	8 (21%); N=39	36·0 (19·0 to 53·0)	<0·0001
Biomarkers				
Alanine aminotransferase				
Absolute change, U/L	–20·1 (–25·2 to –15·0); N=80	–13·9 (–20·7 to –7·0); N=43	–6·2 (–14·7 to 2·2)	0·15
Percent change, %	–30·6% (–38·3 to –22·8); N=80	–16·2% (–26·6 to –5·9); N=43	–14·3% (–27·2 to –1·5)	0·0295
Aspartate transferase				
Absolute change, U/L	–16·1 (–20·6 to –11·6); N=80	–10·0 (–16·0 to –4·0); N=43	–6·1 (–13·6 to 1·4)	0·11
Percent change, %	–26·8% (–34·8 to –19·0); N=80	–12·1% (–22·6 to –1·5); N=43	–14·8% (–27·9 to –1·7)	0·0272
Cytokeratin-18 (M30)				
Absolute change, U/L	–160·6 (–221·5 to –99·7); N=71	–67·1 (–143·6 to 9·4); N=44	–93·5 (–190·5 to 3·4)	0·0585
Percent change, %	–14·1% (–28·0 to –0·30); N=71	19·7% (2·3 to 37·2); N=44	–33·8% (–56·0 to –11·7)	0·0031
Cytokeratin-18 (M65)				
Absolute change, U/L	–302·5 (–377·2 to –227·9); N=72	–150·0 (–244·6 to –55·3); N=44	–152·5 (–272·0 to –33·1)	0·013
Percent change, %	–23·5% (–34·7 to –12·2); N=72	3·6% (–10·6 to 17·8); N=44	–27·1% (–45·0 to –9·1)	0·0034
FibroScan*†				
Absolute change, kPa	–1·8 (–3·2 to –0·4); N=76	–0·8 (–2·6 to 1·0); N=44	–1·0 (–3·3 to 1·2)	0·22
Percent change, %	–10·6% (–24·7 to 3·5); N=76	–5·3% (–23·6 to 13·0); N=44	–5·3% (–28·3 to 17·6)	0·35
FibroScan CAP*				
Absolute change, Db/m	–36·2 (–46·0 to –26·3); N=73	–4·1 (–17·0 to 8·8); N=41	–32·0 (–48·1 to –16·0)	0·0006
Percent change, %	–10·4% (–13·4 to –7·3); N=73	–0·6% (–4·6 to 3·3); N=41	–9·7% (–14·7 to –4·8)	0·0007
qFibrosis score				
Absolute change	–0·3 (–0·39 to –0·11); N=81	0·1 (–0·11 to 0·25); N=45	–0·3 (–0·54 to –0·10)	0·0047
Percent change, %	–6·1% (–11·5 to –0·77); N=81	4·6% (–2·27 to 11·55); N=45	–10·8% (–19·4 to –2·2)	0·0142
Enhanced liver fibrosis test score				
Absolute change	0·0 (–0·19 to 0·10); N=78	0·1 (–0·13 to 0·25); N=45	–0·1 (–0·34 to 0·13)	0·38
Percent change, %	–0·1% (–1·64 to 1·35); N=78	0·8% (–1·13 to 2·72); N=45	–0·9% (–3·4 to 1·5)	0·44
Enhanced liver fibrosis (baseline >9·8)§				
Absolute change	–0·4 (–0·69 to –0·16); N=30	–0·1 (–0·39 to 0·19); N=23	–0·3 (–0·71 to 0·06)	0·10
Percent change, %	–4·0% (–6·57 to –1·46); N=30	–1·0% (–3·76 to 1·80); N=23	–3·0% (–6·7 to 0·66)	0·11
LDL cholesterol				
Absolute change, mg/dL	–6·9 (–13·7 to –0·1); N=72	–0·5 (–9·3 to 8·4); N=43	–6·4 (–17·5 to 4·6)	0·25
Percent change, %	–2·3% (–9·9 to 7·9); N=72	2·2% (–7·7 to 12·2); N=43	–4·5% (–17·0 to 7·9)	0·47

(Table 2 continues on next page)

	50 mg denifanstat	Placebo	Common risk difference (95% CI)	p value
(Continued from previous page)				
LDL cholesterol (baseline >100 mg/dL)§				
Absolute change, mg/dL	–21·3 (–31·2 to –11·5); N=32	–9·0 (–19·7 to 1·7); N=27	–12·3 (–26·9 to 2·2)	0·095
Percent change, %	–15·2% (–22·8 to –7·5); N=32	–6·5% (–14·8 to 1·8); N=27	–8·7% (–20·0 to 2·7)	0·13
Triglyceride¶				
Absolute change, mg/dL	51 (24·4 to 77·7); N=80	–16·8 (–52·8 to 19·2); N=43	67·9 (23·2 to 112·5)	0·0032
Percent change, %	32·0 (18·4 to 45·6); N=80	–5·8 (–24·1 to 12·5); N=43	37·8 (15·1 to 60·6)	0·0013

Data are n (%) or least-squares mean (95% CI) unless otherwise indicated. The endpoints shown in this table were selected on the basis of interest for this type of trial involving participants with non-cirrhotic non-alcoholic steatohepatitis. The histological subpopulations of F2 fibrosis, F3 fibrosis, and type 2 diabetes, and the baseline cutoffs for LDL cholesterol of more than 100 mg/dL and an enhanced liver fibrosis test score of more than 9·8 were calculated post hoc. mITT=modified intention-to-treat. MRI-PDFF=proton density liver fat fraction mapped with MRI. NAS=non-alcoholic fatty liver disease activity score. NASH CRN=Nonalcoholic Steatohepatitis Clinical Research Network. *Data are least-squares mean (90% CI). †Liver stiffness was assessed with the use of vibration-controlled transient elastography; data were analysed with the use of analysis of covariance with trial group, baseline measurements, and stratifications (ie, type 2 diabetes status and fibrosis stage) as covariates. ‡Derived from an algorithm that combines hyaluronic acid, type 3 procollagen peptide, and a tissue inhibitor of matrix metalloproteinase 1; a score of less than 7·7 indicates no or mild fibrosis and a score of 11·3 or higher indicates cirrhosis. §Post-hoc analysis. ¶The triglyceride increase consisted of a statistically significant increase in polyunsaturated fatty acids relative to saturated content for participants in the denifanstat group versus participants in the placebo group (appendix p 9).

Table 2: **Changes from baseline in selected liver and metabolic endpoints in participants with pretreatment and post-treatment biopsies (ie, the mITT population)**

occurred in 19 (24%) of 81 participants in the denifanstat group compared with three (7%) of 45 participants in the placebo group (common risk difference 15·1%, 95% CI 1·2 to 29·0; p=0·013). 45 (56%) of 81 participants in the denifanstat group showed either fibrosis improvement by one stage or more without worsening of steatohepatitis or MASH resolution with no worsening of fibrosis compared with 12 (27%) of 45 participants in the placebo group (common risk difference 26·5%, 10·4 to 42·6; p=0·0018; table 2). In the ITT population, MASH resolution and fibrosis improvement occurred in 19 (17%) of 112 participants in the denifanstat group compared with three (5%) in the placebo group (common risk difference 8·9%, –2·4 to 20·2; p=0·033); 45 (40%) of 112 participants in the denifanstat group and 12 (21%) of 56 in the placebo group achieved one or other or both of these endpoints (common risk difference 16·7%, 3·0 to 30·5; p=0·016; appendix p 7). Based on the results in this study, the number needed to treat for either MASH resolution or fibrosis improvement is 6 in the ITT population and 4 in the mITT population.

Denifanstat reduced liver fat measured by MRI-PDFF in the treatment group by 23·1% (SD 61·0) relative to baseline compared with a 2·7% (36·0) increase in participants in the placebo group after 26 weeks of treatment (least-squares mean difference denifanstat *vs* placebo –30·7% [95% CI –51·1 to –10·2]; p=0·0036). By week 52, liver fat was reduced by 31·0% (38·5) compared with baseline in the denifanstat group compared with a reduction of 10·0% (26·1) in the placebo group (least-squares mean difference denifanstat *vs* placebo –22·9% [95% CI –9·7 to –36·0]; p=0·0008). At week 52, 45 (65%) of 81 participants in the denifanstat group showing a reduction in liver fat of 30% or more compared with eight (21%) of 45 participants in the placebo group (common risk difference 36·0%, 19·0 to 53·0; p<0·0001).

Changes in liver enzymes and metabolic parameters are shown in table 2. Despite the concurrent use of statins in more than half of the study patients (28 [50%] of 56 participants in the placebo group and 58 [52%] of 112 participants in the denifanstat group; table 1), LDL cholesterol was reduced from baseline with denifanstat treatment, with larger relative decreases in the subgroup of participants with a baseline concentration of 100 mg/dL or higher, which was defined post hoc (table 2). Triglyceride concentrations were significantly increased in participants in the denifanstat group compared with the placebo group (table 2). Exploratory lipidomic analyses showed that the increase in triglycerides resulted from a higher content of polyunsaturated fatty acids in triglycerides in the denifanstat group compared with the placebo group (appendix p 9). The change from baseline in tripalmitin, a triglyceride in which the three acyl chains are fully saturated, was –2·4 mg/mL (95% CI –3·4 to –1·3) in the denifanstat group, and –0·2 mg/mL (–1·6 to 1·2) in the placebo group at week 13 (common risk difference –2·1 mg/mL, 95% CI –3·9 to –0·4; p=0·015; appendix p 9). These changes significantly increased the ratio of polyunsaturated fatty acid triglycerides to saturated triglycerides by 107% in participants in the denifanstat group; this ratio increased by 38% in the placebo group (appendix p 9).

Overall, denifanstat was generally well tolerated. All treatment-related AEs in the safety analysis population were of grades 1 or 2. All grade 3 or higher treatment-emergent AEs were deemed unrelated to the study drug by the investigators (table 3; appendix p 10). There were no treatment-related serious AEs and no deaths in the study. There were more treatment-related AEs and treatment-related AEs leading to discontinuation observed in participants in the denifanstat group than in the placebo group; none of the discontinuations due to an AE

	50 mg denifanstat (n=112)	Placebo (n=56)	Total (N=168)
Any AE	99 (88%)	46 (82%)	145 (86%)
Serious AE	13 (12%)	3 (5%)	16 (10%)
AE related to denifanstat or placebo	51 (46%)	20 (36%)	71 (42%)
Grade 1 or 2	51 (46%)	20 (36%)	71 (42%)
AE leading to the discontinuation of denifanstat or placebo by preferred term*	22 (20%)	3 (5%)	25 (15%)
Alopecia	11 (10%)	1 (2%)	12 (7%)
Dizziness	2 (2%)	0	2 (1%)
Dry eye	2 (2%)	1 (2%)	3 (2%)
Abdominal discomfort	1 (1%)	0	1 (1%)
Abdominal pain (upper)	1 (1%)	0	1 (1%)
Abscess	1 (1%)	0	1 (1%)
Cellulitis	1 (1%)	0	1 (1%)
Diarrhoea	1 (1%)	0	1 (1%)
Ductal adenocarcinoma of the pancreas	1 (1%)	0	1 (1%)
Erythema	1 (1%)	0	1 (1%)
Hallucination, visual	1 (1%)	0	1 (1%)
Haemoptysis	1 (1%)	0	1 (1%)
Hyperkeratosis	1 (1%)	0	1 (1%)
Memory impairment	1 (1%)	0	1 (1%)
Meningioma	1 (1%)	0	1 (1%)
Petechiae	1 (1%)	0	1 (1%)
Skin discoloration	0	1 (2%)	1 (1%)
Skin exfoliation	1 (1%)	0	1 (1%)
Skin lesion	1 (1%)	0	1 (1%)
Vertigo	1 (1%)	0	1 (1%)
AE related to denifanstat or placebo leading to discontinuation	18 (16%)	2 (4%)	20 (12%)
Most common AEs by system organ class and by preferred term			
COVID-19	19 (17%)	6 (11%)	25 (15%)
Dry eye	10 (9%)	8 (14%)	18 (11%)
Alopecia†	21 (19%)	2 (4%)	23 (14%)

Data are n (%). AEs that had an incidence of at least 10% are shown. The relatedness of AEs to denifanstat or placebo was established by the investigators. AE=adverse event. *A patient is counted only once for discontinuation and only once for any AE in a system organ class. †One participant inadvertently took twice the prescribed dose of denifanstat (ie, 100 mg) for 18 days.

Table 3: **AEs in the safety analysis population**

considered related to study drug were of grade 3 or higher. The leading cause of discontinuation in participants in the denifanstat group was hair thinning, accounting for 11 (50%) of 22 discontinuations; over half (six of 11) of these instances of hair thinning were evaluated as mild. The other 11 discontinuations were sporadic.

There was no weight change associated with the drug in most participants; 61 (75%) of 81 participants in the denifanstat group had a weight loss of less than 5 kg compared with 42 (93%) of 45 participants in the placebo group (appendix p 8). There were no notable changes in glycaemic parameters from baseline between the groups; the mean change in glucose was a 0·2 mmol/L (SD 4·0) increase in the denifanstat group compared with a 0·0 mmol/L (1·2) change in the placebo group (common risk difference 0·8 mmol/L [95% CI –0·21 to 1·9]; p=0.12). Similarly, mean HbA1c values increased by 0·1% (SD 1·3) from baseline in the denifanstat group compared with a 0.0% (0·6) change in the placebo group (common risk difference 0·1% [95% CI –0·3 to 0·5]; p=0·61).

The most common treatment-emergent AEs by preferred term (greater than 10% in either the denifanstat or the placebo group) were COVID-19 (19 [17%] of 112 participants in the denifanstat group *vs* six [11%] of 56 participants in the placebo group), hair thinning (21 [19%] of 112 participants in the denifanstat group *vs* two [4%] of 56 participants in the placebo group), and dry eye symptoms (ten [9%] of 112 participants in the denifanstat group *vs* eight [14%] of 56 participants in the placebo group; table 3). Over half (14 of 21) of the hair-thinning AEs were grade 1 (mild). The remaining seven hair-thinning AEs were grade 2. Hair thinning, typically located on the scalp, usually took several weeks of treatment to manifest and was managed by dose reduction or discontinuation, leading to reversal. Most participants (14 of 21) in this study experiencing hair thinning had one or more other factors associated with hair loss including use of GLP-1RAs (n=4) or levothyroxine (n=7), or recent infection with SARS-CoV-2 (n=5).

Discussion

In this study, denifanstat showed significant improvements in both primary endpoints in the ITT population, a 2-point or greater improvement in NAS without worsening of fibrosis and MASH resolution with a 2-point or greater improvement in NAS without worsening of fibrosis. This latter endpoint is similar to one outlined in the FDA's draft guidance on phase 3 endpoints;[17] however, this study and several other recent studies have added the criterion of a 2-point or greater improvement in NAS when assessing MASH resolution.[19,20] Denifanstat also significantly improved other important endpoints related to liver damage in patients with MASH and stage 2–3 fibrosis, notably those related to MASH resolution and fibrosis regression.[21] The mITT population (ie, participants who had both pre-treatment and post-treatment biopsies) provides evidence of the direct effect of denifanstat's mechanism of action on the liver in individuals with MASH. Based on the results in this study, the number needed to treat for either MASH resolution or fibrosis improvement is 6 in the ITT population and 4 in the mITT population. The magnitude of fibrosis improvement observed with traditional pathology and independent validation with AI-assisted digital pathology validates progression of denifanstat to a registrational trial.

Denifanstat directly targets three of the major pathways responsible for liver injury via direct inhibition of endogenous FASN activity in hepatocytes, immune cells, and stellate cells. The results of this study, notably an improvement in fibrosis without worsening of steatohepatitis in around 20% more participants in the denifanstat group than in the placebo group, show the potential impact this unique mechanism could have in treating MASH. Several other compounds in development focus on the reduction of hepatic fat, without regard for the inherent toxicity of the lipids being removed. For example, two clinical trials of semaglutide, a GLP-1 RA, in patient populations with F2–F4 MASH who were given treatment for 48–72 weeks,[22,23] showed significant reductions in hepatic fat but no improvement in liver fibrosis. This approach probably mimics observations from bariatric surgery in patients with MASH. Surgical manipulation substantially reduces overall fat burden, but fibrosis improvement can take up to 5 years to fully manifest.[24]

Most individuals with MASH have a poor cardiovascular risk profile, including increased saturated fatty acid levels in plasma triglycerides. Treatment with denifanstat for 52 weeks increased plasma triglyceride concentrations, driven by an increase in polyunsaturated fatty acids in triglycerides, suggesting that the increase in triglyceride concentrations is not accompanied by increased atherogenicity. This observation has been shown to be a direct consequence of FASN inhibition, which causes the incorporation of polyunsaturated fatty acids into plasma triglycerides.[25] The improvement in triglyceride composition combined with the lowering of LDL cholesterol observed in FASCINATE-2 suggest that denifanstat might confer a cardiovascular benefit.

The rate of alopecia observed in this study was higher than that reported for the 50 mg dose of denifanstat in a previous phase 2 trial in individuals with MASH.[10] This AE is related to a reduction in lipid synthesis in sebocytes in the hair follicle and is probably similar to other pathologies and therapies that reduce fat synthesis in structures supporting hair growth. The increased rate of alopecia observed in this study might be related to differences in other factors experienced by participants, including SARS-CoV-2 infection, GLP-1 RA drug use, or thyroid replacement therapy. Steps toward managing this rate in phase 3 trials are underway, including assessing baseline variables, concomitant medications, and therapeutic interventions (including but not limited to dose modification).

The extent of hepatic fibrosis strongly correlates to poorer outcomes in people with MASH[3] and people with type 2 diabetes progress faster than others. In this study, denifanstat was shown to provide significant improvements in fibrosis in participants with type 2 diabetes or F3 fibrosis. Therapies that deliver effective improvements in short periods of time are crucial for these patient populations.

The limitations of this study include the small number of participants and short treatment duration, which led to even smaller numbers for some subgroup analyses and did not enable long-term patient outcomes to be evaluated. In addition, this study was conducted during waves of COVID-19, which led to a large percentage of patients being infected. Despite these limitations, the placebo response rate was similar to that reported in a meta-analysis of a large number of MASH studies of varying sizes and timeframes before the emergence of COVID-19.[18] The majority of participants in this study were White, with approximately a third being of Hispanic heritage, thereby restricting conclusions for broader populations.

In summary, 52 weeks of oral treatment with denifanstat once per day was well tolerated with an acceptable adverse event profile. In participants with MASH and F2–F3 liver fibrosis, denifanstat showed significant improvement in all key histological features of the disease and met both the fibrosis improvement and MASH resolution endpoints described in the FDA draft guidance[17] in both the mITT and ITT populations. These results warrant further development of denifanstat in late-stage registrational trials.

Contributors

RL, PB, KG, MO'F, GK, EBM, WM, and SAH were involved in the study design and protocol development. RL, PB, KG, MO'F, GK, EBM, WM, W-WT, and SAH collected data and performed the analyses. JC, EL, and MR were the investigators in the trial responsible for patient recruitment, patient care, and data collection. All authors had full access to the trial data and were involved in the preparation and critical review of the manuscript. All authors had final responsibility for the decision to submit for publication. KG, MO'F, GK, EBM, WM, and W-WT had access to the raw data, and KG, MO'F, and W-WT verified the underlying data.

Declaration of interests

RL serves as a consultant to Aardvark Therapeutics, Altimmune, Arrowhead Pharmaceuticals, AstraZeneca, Cascade Pharmaceuticals, Eli Lilly, Gilead, Glympse Bio, Inipharma, Intercept, Inventiva, Ionis, Janssen, Lipidio, Madrigal, Neurobo, Novo Nordisk, Merck, Pfizer, Sagimet, 89Bio, Takeda, Terns Pharmaceuticals and Viking Therapeutics. RL has stock options in Sagimet Biosciences. In addition, his institution received research grants from Arrowhead Pharmaceuticals, AstraZeneca, Boehringer Ingelheim, Bristol Myers Squibb, Eli Lilly, Galectin Therapeutics, Gilead, Intercept, Hanmi, Inventiva, Ionis, Janssen, Madrigal Pharmaceuticals, Merck, Novo Nordisk, Pfizer, Sonic Incytes, and Terns Pharmaceuticals. He is a co-founder of LipoNexus. RL receives funding support from the National Institute of Diabetes and Digestive and Kidney Diseases (P30DK120515) and the John C Martin Foundation (RP124). KG, EBM, GK, MO'F, WM, and W-WT are current or former employees of Sagimet Biosciences and own or have options to purchase stock in the company. EL is a researcher for 89Bio, Akero Therapeutics, Alnylam Pharmaceuticals, Amgen, AstraZeneca, Boehringer Ingelheim, Bristol Myers Squibb, DSM, Eli Lilly, Enanta Pharmaceuticals, Enyo Pharma, Exalenz Bioscience, Galectin Therapeutics, Galmed Pharmaceuticals, Genfit, Gilead Sciences, GSK, Hanmi Pharmaceuticals, Hightide Biopharma, Intercept Pharmaceuticals, Inventiva, Janssen Pharmaceuticals, Madrigal Pharmaceuticals, Merck & Co, NGM Biopharmaceuticals, Northsea Therapeutics, Novartis, Novo Nordisk, Poxel, Sagimet Biosciences, Takeda, Terns Pharmaceuticals, Viking Therapeutics, and Zydus Pharmaceuticals. SAH was a scientific advisor or consultant for Akero, Aligos, Altimmune, Arrowhead, Auransa, Echosens, Galecto, Gilead, GSK, Hepion, Hepta Bio, HistoIndex, Humana, Inventiva,

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Data sharing

Data will be shared with researchers who submit a methodologically sound protocol to clinicaldatarequest@sagimet.com following the signing of a data access agreement. Data will be made available following first approval of denifanstat from the US Food and Drug Administration. The final trial protocol will be made available upon request to clinicaldatarequest@sagimet.com from 30 days following the publication of this study.

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