ORIGINAL ARTICLE

Efruxifermin in Compensated Liver Cirrhosis Caused by MASH

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ABSTRACT

BACKGROUND

In phase 2 trials involving patients with stage 2 or 3 fibrosis caused by metabolic dysfunction–associated steatohepatitis (MASH), efruxifermin, a bivalent fibroblast growth factor 21 (FGF21) analogue, reduced fibrosis and resolved MASH. Data are needed on the efficacy and safety of efruxifermin in patients with compensated cirrhosis (stage 4 fibrosis) caused by MASH.

METHODS

In this phase 2b, randomized, placebo-controlled, double-blind trial, we assigned patients with MASH who had biopsy-confirmed compensated cirrhosis (stage 4 fibrosis) to receive subcutaneous efruxifermin (at a dose of 28 mg or 50 mg once daily) or placebo. The primary outcome was a reduction of at least one stage of fibrosis without worsening of MASH at week 36. Secondary outcomes included the same criterion at week 96.

RESULTS

A total of 181 patients underwent randomization and received at least one dose of efruxifermin or placebo. Of these patients, liver biopsy was performed in 154 patients at 36 weeks and in 134 patients at 96 weeks. At 36 weeks, a reduction in fibrosis without worsening of MASH occurred in 8 of 61 patients (13%) in the placebo group, in 10 of 57 patients (18%) in the 28-mg efruxifermin group (difference from placebo after adjustment for stratification factors, 3 percentage points; 95% confidence interval [CI], –11 to 17; P=0.62), and in 12 of 63 patients (19%) in the 50-mg efruxifermin group (difference from placebo, 4 percentage points; 95% CI, –10 to 18; P=0.52). At week 96, a reduction in fibrosis without worsening of MASH occurred in 7 of 61 patients (11%) in the placebo group, in 12 of 57 patients (21%) in the 28-mg efruxifermin group (difference from placebo, 10 percentage points; 95% CI, –4 to 24), and in 18 of 63 patients (29%) in the 50-mg efruxifermin group (difference from placebo, 16 percentage points; 95% CI, 2 to 30). Gastrointestinal adverse events were more common with efruxifermin; most events were mild or moderate.

CONCLUSIONS

In patients with compensated cirrhosis caused by MASH, efruxifermin did not significantly reduce fibrosis at 36 weeks. (Funded by Akero Therapeutics; SYMMETRY ClinicalTrials.gov number, NCT05039450.)

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Metabolic dysfunction–associated steatohepatitis (MASH) — previously called nonalcoholic steatohepatitis (NASH) — is characterized by liver steatosis and inflammation that can lead to cirrhosis (stage 4 fibrosis).[1-3] Patients with cirrhosis caused by MASH have a poor prognosis owing to a high risk of hepatic decompensation, hepatocellular carcinoma, cardiovascular events, and death.[1,4] In the United States, at least 1.3 million persons are living with cirrhosis caused by MASH, which is also a leading cause of liver transplantation.[5-7] Pharmacologic treatments for MASH-associated cirrhosis are urgently needed.

Cirrhosis is characterized histologically by regenerative nodules surrounded by fibrous tissue, leading to portal hypertension and impaired liver function.[8-10] Although cirrhosis was previously thought to be irreversible, a reduction in fibrosis has been observed in cirrhosis caused by viral hepatitis. However, such a reduction can be delayed by as much as 5 years after the viral infection has been eliminated.[10-12] In a post hoc analysis of trials involving patients with cirrhosis caused by MASH, a reduction in fibrosis was associated with improved liver-related outcomes,[13] regardless of whether patients received treatment with an investigational drug (e.g., simtuzumab and selonsertib) or received placebo. However, trials of therapies that target metabolic dysregulation, inflammation, and fibrosis in patients with MASH cirrhosis thus far have not resulted in a reduction in fibrosis.[14-20]

Fibroblast growth factor 21 (FGF21) is a hormone that regulates glucose and lipid metabolism, insulin sensitivity, and protein homeostasis.[21] FGF21 analogues appear to have direct antifibrotic actions as well as indirect actions that reduce fibrogenesis by protecting hepatocytes against cellular stressors.[21] Efruxifermin is an FGF21 analogue in development for the treatment of advanced fibrosis and cirrhosis caused by MASH. It features a bivalent configuration consisting of two modified human FGF21 polypeptides fused to each fragment crystallizable (Fc) domain of homodimeric human immunoglobulin G1 (IgG1), which extends both pharmacokinetic and pharmacodynamic half-lives.[22,23] In phase 2 trials involving patients with stage 2 or 3 fibrosis caused by MASH, efruxifermin reduced fibrosis and resolved MASH.[24-26] Extending efruxifermin treatment from 24 to 96 weeks resulted in additional fibrosis regression, particularly in stage 3 fibrosis.[27] In the SYMMETRY trial, we evaluated the efficacy and safety of efruxifermin for up to 96 weeks in patients with compensated cirrhosis caused by MASH.

Methods

Trial Design and Oversight

The SYMMETRY trial was a phase 2b, randomized, double-blind, placebo-controlled trial conducted at 45 sites in the United States, Puerto Rico, and Mexico (see the Supplementary Appendix, available with the full text of this article at NEJM.org). The protocol (available at NEJM.org) was approved by the institutional review board and independent ethics committee at each participating site.

The trial was conducted in accordance with the principles of the Declaration of Helsinki, the International Council for Harmonisation Good Clinical Practice guidelines, and applicable laws and regulations. All the patients provided written informed consent.

The sponsor (Akero Therapeutics) designed the trial in collaboration with three of the academic authors. The sponsor performed site monitoring, data collection, and data analysis. The first draft of the manuscript was written by a medical writer funded by the sponsor under guidance from the authors. All the authors had access to the data, participated in data interpretation, and provided critical review of the manuscript; they vouch for the accuracy and completeness of the data and for the fidelity of the trial to the protocol.

Patients

Eligible patients were 18 to 75 years of age, had liver histologic features consistent with MASH, and had compensated cirrhosis, which was defined as stage 4 fibrosis with a Child–Pugh score of 5 or 6 (class A, the mildest stage of chronic liver disease) on a scale ranging from 5 to 15. The patients also had type 2 diabetes or two components of metabolic syndrome (obesity, dyslipidemia, elevated blood pressure, and elevated fasting glucose level). Approximately 80% of the patients had biopsy-confirmed MASH.[28] The presence of cryptogenic cirrhosis attributed to MASH (so-called burnt-out MASH)[28] was limited to approximately 20% of the patients (Table S1 in the Supplementary Appendix). Biopsy-confirmed

MASH was defined as a nonalcoholic fatty liver disease (NAFLD) activity score (NAS) of 3 or more, with at least 1 point each for steatosis, hepatocellular ballooning, and lobular inflammation. Among the exclusion criteria were a history of or current hepatic decompensation, liver transplantation, hepatocellular carcinoma, alcohol consumption in excess of 2 drinks per day for men or 1 drink per day for women, or other causes of liver disease. Full eligibility criteria are provided in the Supplementary Appendix.

PROCEDURES

The patients were randomly assigned in a 1:1:1 ratio by means of an interactive-response system to receive 28 mg or 50 mg of efruxifermin or matching placebo, administered subcutaneously once weekly. The patients were stratified according to whether they had type 2 diabetes (yes or no) and their MASH diagnosis (biopsy-confirmed MASH or cryptogenic cirrhosis attributed to MASH) (Fig. S1). Liver biopsies were performed at weeks 36 and 96. The investigators, patients, and staff members remained unaware of trial-group assignments for the duration of the 96-week trial. The week 36 analysis was performed in a prespecified unblinded manner by members of the study team who were not involved in subsequent trial conduct (as described in the Methods section in the Supplementary Appendix).

Liver-biopsy samples were scanned and images scored independently by two pathologists who were unaware of trial-group assignments or sequence (Fig. S2). To mask the sequence of visits, a prespecified percentage of baseline liver-biopsy samples were randomly shuffled into samples being read at weeks 36 and 96. If there was disagreement, the pathologists met to reach consensus; adjudication by a third pathologist was available in case of lack of consensus. Biopsy samples were evaluated according to the NASH Clinical Research Network (CRN) grading and fibrosis-staging system.[29] Screening biopsy samples were scored at enrollment.

END POINTS

The primary end point was a reduction in fibrosis without a worsening of MASH on the basis of liver histologic testing at week 36 (Table S2). Selected secondary end points were a reduction in fibrosis without a worsening of MASH at week 96 and MASH resolution at weeks 36 and 96. Fibrosis was graded on the NASH CRN fibrosis scale from 0 to 4, with a reduction in fibrosis defined as a decrease of at least one stage.[29] MASH worsening was defined as an increase from baseline in any of the NAS subscores of ballooning, inflammation, or steatosis. MASH resolution, which was defined as an inflammation score of 0 or 1 and ballooning score of 0, was evaluated in the subgroup of patients who had biopsy-confirmed MASH at baseline.

Additional secondary end points were the change from baseline in noninvasive markers of fibrosis (e.g., enhanced liver fibrosis [ELF] test score,[30] N-terminal type III collagen propeptide (Pro-C3) level, and liver-stiffness measurement by vibration-controlled transient elastography [FibroScan]), along with lipoprotein levels, markers of glycemic control, body weight, and markers of liver injury. Safety evaluations included adverse events, clinical and laboratory assessments, and bone mineral density by dual-energy x-ray absorptiometry. Clinical-outcome events were hepatic decompensation, liver transplantation or qualification for liver transplantation, and death from any cause.

STATISTICAL ANALYSIS

The sample size calculation was based on data from patients with MASH and stage 2 or 3 fibrosis and limited data from a small cohort of patients with cirrhosis (stage 4).[24,31] We estimated that a reduction of at least one fibrosis stage without worsening of MASH would occur in 12% of the patients receiving placebo and in 42% of those receiving either dose of efruxifermin at week 36. On the basis of a withdrawal rate of 10%, we estimated that enrollment of 45 patients in each group would provide at least 90% power to show the superiority of each efruxifermin dose to placebo at a two-sided significance level of 0.05. Because of the high unmet medical need of patients with this condition, the trial rapidly overenrolled patients beyond the planned sample size (to ≤60 patients per group), which prompted a protocol modification before the week 36 analysis.

The primary efficacy outcome was assessed in an intention-to-treat analysis of all the patients who had undergone randomization and had received at least one dose of efruxifermin or placebo; missing data were imputed as nonresponse. A prespecified complete case on-treatment analysis was assessed in patients who had liver-biopsy

results both at baseline and at a trial end point (week 36 or 96). Safety outcomes were assessed in all the patients in the intention-to-treat population. Additional details are provided in the Supplementary Methods.

The primary statistical analysis of liver histologic end points was based on the Cochran–Mantel–Haenszel test at a type I error rate of 0.05 (two-sided), after adjustment for stratification factors. Point estimates and 95% confidence intervals were constructed by means of the Miettinen–Nurminen method. Continuous efficacy end points were analyzed by mixed-model repeated-measures analysis with fixed effects of treatment, stratification factors, postbaseline visit, treatment-by-visit interaction, and baseline value.

A two-sided P value is reported for analysis of the primary end point for comparison of the two doses of efruxifermin against placebo at week 36. There was no prespecified plan to adjust for multiple comparisons. Secondary end points are reported with the use of 95% confidence intervals that have not been adjusted for multiple comparisons and should not be used to infer definitive treatment effects. Further details are provided in the statistical analysis plan, available with the protocol. All analyses were performed with the use of SAS software, version 9.4 (SAS Institute).

RESULTS

PATIENTS

From December 21, 2021, through December 16, 2022, a total of 182 patients underwent randomization. Of these patients, 181 received efruxifermin or placebo and were included in the intention-to-treat and safety analyses (Fig. S3). Overall, liver-biopsy data were available for 154 patients at week 36 and for 134 patients at week 96.

The patients' demographic and clinical characteristics are shown in Table 1 and Table S3. A total of 142 patients (78%) had biopsy-confirmed MASH, and 39 (22%) had cryptogenic cirrhosis attributed to MASH. Although trial-group assignment was stratified according to the presence or absence of cryptogenic cirrhosis, there was an imbalance in this factor across groups. The baseline characteristics of the patients indicate that they were largely representative of the general population with compensated cirrhosis caused by MASH (Table S4). In findings that were consistent with advanced disease, type 2 diabetes and hypertension were prevalent (both in 80% of the population), and both the mean baseline body-mass index (the weight in kilograms divided by the square of the height in meters) of 36 and the mean liver-stiffness measurement (24 kPa) were elevated.

EFFICACY

At 36 weeks, a reduction in fibrosis without worsening of MASH (the primary outcome) occurred in 8 of 61 patients (13%) in the placebo group, in 10 of 57 patients (18%) in the 28-mg efruxifermin group (difference from placebo after adjustment for stratification factors, 3 percentage points; 95% confidence interval [CI], –11 to 17; P=0.62), and in 12 of 63 patients (19%) in the 50-mg efruxifermin group (difference from placebo, 4 percentage points; 95% CI, –10 to 18; P=0.52) (Fig. 1A). At week 96, a reduction in fibrosis without worsening of MASH (a secondary outcome) occurred in 7 of 61 patients (11%) in the placebo group, in 12 of 57 patients (21%) in the 28-mg efruxifermin group (difference from placebo, 10 percentage points; 95% CI, –4 to 24), and in 18 of 63 patients (29%) in the 50-mg efruxifermin group (difference from placebo, 16 percentage points; 95% CI, 2 to 30) (Fig. 1B).

In an analysis involving the 134 patients for whom liver-biopsy data were available at week 96 without imputation of missing data, the percentage of those with a reduction in fibrosis without MASH worsening was 29% (in 12 of 41 patients) with 28 mg of efruxifermin, 39% (in 18 of 46 patients) with 50 mg of efruxifermin, and 15% (in 7 of 47 patients) with placebo (Fig. S4). Figure S8 shows the results of a prespecified analyses of fibrosis reduction without MASH worsening at 36 weeks according to subgroup and baseline status. A post hoc analysis of fibrosis reduction according to subgroup and baseline status at week 96 is shown in Figure S9. In an exploratory analysis involving patients who had a primary-outcome response at weeks 36 and 96, most of those in the efruxifermin groups who had a response at week 36 sustained their response at week 96. In addition, some patients without a response at week 36 had a response by week 96, particularly in the 50-mg dose group (Table S8). The fibrosis response was similar among the patients with cryptogenic cirrhosis and those with biopsy-confirmed MASH (Table S9).

Table 1. Demographic and Clinical Characteristics of the Patients at Baseline.*

Characteristic	Efruxifermin, 28 mg (N=57)	Efruxifermin, 50 mg (N=63)	Placebo (N=61)	All Patients (N=181)
Demographic				
Age — yr	61.7±8.3	59.4±8.8	61±7.5	60.7±8.2
Female sex — no. (%)	39 (68)	44 (70)	38 (62)	121 (67)
Clinical				
Body-mass index†	36.1±7.1	34.5±5.9	36.7±6.8	35.8±6.6
Type 2 diabetes — no. (%)	46 (81)	49 (78)	50 (82)	145 (80)
Use of GLP-1 receptor agonist — no. (%)	11 (19)	21 (33)	16 (26)	48 (27)
MASH — no. (%)	45 (79)	52 (83)	45 (74)	142 (78)
Cryptogenic cirrhosis — no. (%)	12 (21)	11 (17)	16 (26)	39 (22)
Testing results				
NAFLD activity score‡	3.9±1.6	4.1±1.5	3.7±1.6	3.9±1.6
Liver-stiffness measurement — kPa§	24.1±12.4	24.5±13.4	24.7±14.2	24.4±13.3
Enhanced liver fibrosis test score¶	10.6±0.8	10.5±0.8	10.4±0.8	10.5±0.8
Child–Pugh score of 5 — no. (%)‖	56 (98)	61 (97)	60 (98)	177 (98)
Laboratory measure				
Pro-C3 — μg/liter	141.8±66.3	146.9±77.0	131.7±61.9	140.1±68.7
Alanine aminotransferase — U/liter	40.1±22.9	38.4±20.8	40.3±22.3	39.6±21.8
Aspartate aminotransferase — U/liter	37.1±18.2	37.5±19.3	35.5±17.0	36.7±18.1
Triglycerides — mg/dl	148.4±71.0	159.3±78.6	143.3±60.1	150.5±70.3
Glycated hemoglobin — %	6.8±1.1	6.6±1.1	6.8±1.2	6.7±1.1

* Plus–minus values are means ±SD. To convert the values for triglycerides to millimoles per liter, multiply by 0.01129. GLP-1 denotes glucagon-like peptide 1, MASH metabolic dysfunction–associated steatohepatitis, and Pro-C3 N-terminal type III collagen propeptide.
† The body-mass index is the weight in kilograms divided by the square of the height in meters.
‡ The nonalcoholic fatty liver disease (NAFLD) activity score (ranging from 0 to 8) is the sum of the subscores for steatosis (on a scale of 0 to 3), lobular inflammation (on a scale of 0 to 3), and hepatocellular ballooning (on a scale of 0 to 2), with higher scores indicating more severe disease.
§ The liver-stiffness measurement was assessed by transient elastography (FibroScan).
¶ The enhanced liver fibrosis test consists of a panel of three serum biomarkers associated with extracellular matrix turnover: hyaluronic acid, tissue inhibitor of metalloproteinase 1, and type III procollagen peptide. Advanced fibrosis is considered unlikely if the value is less than 7.7 and likely if the value is 9.8 or more.
‖ The Child–Pugh score ranges from 5 to 15, with higher scores indicating greater disease severity.

In a prespecified analysis involving 142 patients who had biopsy-confirmed MASH at baseline (i.e., the intention-to-treat population who had missing values imputed as no response), MASH resolution at week 96 occurred in 42% of the patients in the two efruxifermin dose groups and in 13% of those in the placebo group at week 96 (Fig. S5). Among the patients who had liver-biopsy data at week 96 without imputation of missing data, MASH resolution occurred in 55 to 59% of those in the efruxifermin groups and in 18% of those in the placebo group.

Changes from baseline for selected secondary end points at week 96 are shown in Table 2 and Table S6; changes at week 36 are shown in Table S5. The patients in the efruxifermin groups had lower postbaseline levels of alanine aminotransferase and aspartate aminotransferase (markers of liver injury) than those in the placebo group; these lower levels were sustained through week 96 (Fig. 2). Efruxifermin was also associated with improvements in noninvasive markers of fibrosis, including ELF test scores, liver-stiffness measurements (Fig. S6), and Pro-C3 levels (Table 2

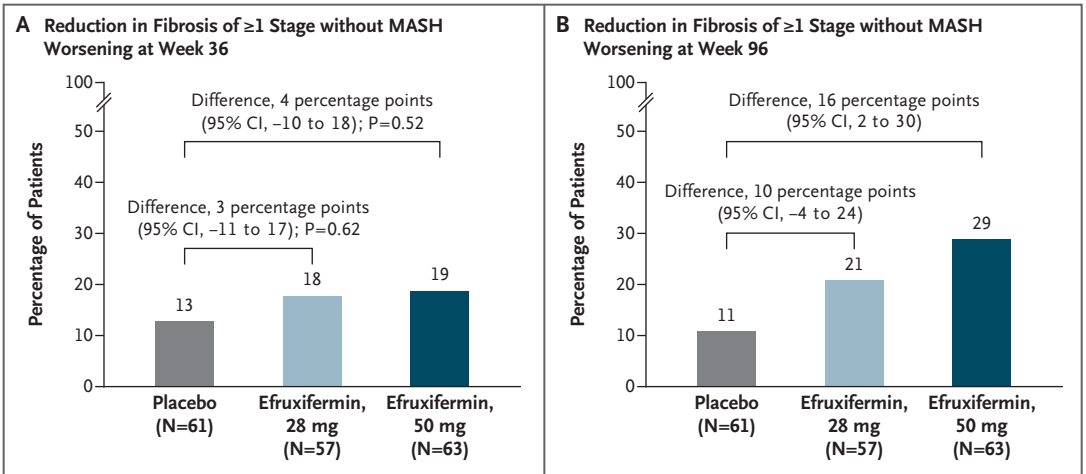

Figure 1. Reduction in Fibrosis without Worsening of MASH.

Shown is the percentage of patients with a reduction in fibrosis without a worsening of metabolic dysfunction–associated steatohepatitis (MASH) at week 36 (primary outcome) (Panel A) and at week 96 (a secondary outcome) (Panel B). MASH worsening was defined as an increase from baseline in any of the subscores of the nonalcoholic fatty liver disease (NAFLD) activity score (NAS): ballooning, inflammation, and steatosis. Data are provided as the mean for the trial group and least-squares-mean difference for the comparison between efruxifermin and placebo with a 95% confidence interval (CI). Confidence intervals have not been adjusted for multiple comparisons and should not be used to infer definitive effects of efruxifermin.

and Table S5). Patients who met the thresholds for a reduction in the ELF test score of at least 0.5 or a reduction of at least 25% in the liver-stiffness measurement are shown in Table 2 and Figures S10 and S11.

At week 96, efruxifermin appeared to be associated with greater improvements than placebo in levels of lipids — triglycerides, non–high-density-lipoprotein (HDL) cholesterol, and HDL cholesterol — and markers of insulin sensitivity (homeostasis model assessment for insulin resistance [HOMA-IR] index and levels of C-peptide and adiponectin) (Table 2 and Table S6). Changes in markers of liver injury and function are shown in Table S7 and Figure S7.

SAFETY

Adverse events were reported by 99% of the patients who received efruxifermin and 97% of those who received placebo (Table 3). Adverse events that were more common with efruxifermin than with placebo were primarily gastrointestinal (diarrhea, nausea, and increased appetite) as well as administration-site reactions (erythema). Most adverse events were mild or moderate in severity. The most common adverse event leading to discontinuation of efruxifermin was diarrhea (in 7 patients); most of these patients were in the 50-mg efruxifermin group, and most discontinuations occurred before week 36. Serious adverse events occurred in 25% of the patients who received efruxifermin and in 18% of those who received placebo; none of these events were considered by the investigators to be related to efruxifermin or placebo (Table 3 and Table S10).

Four clinical-outcome events were reported: one death in the placebo group (from pneumonia), one hepatic-decompensation event in the 28-mg efruxifermin group (ascites), and two hepatic-decompensation events in the 50-mg efruxifermin group (one case of ascites and one case of hepatic encephalopathy) (Table S11). Of the three patients with hepatic decompensation, two had evidence of advanced disease at baseline. Both patients had an elevated ELF test score and liver-stiffness measurement at baseline, and one also had reduced baseline platelet and albumin levels, together with increased bilirubin and international normalized ratio values.

Markers of liver function and hemostasis generally remained stable or appeared to show improvement in the efruxifermin groups. There were no reports of drug-induced liver injury. Small reductions in bone mineral density in the lumbar spine

Table 2. Change from Baseline to Week 96 in Selected Secondary End Points.*

End Point	Efruxifermin, 28 mg (N=57)	Efruxifermin, 50 mg (N=63)	Placebo (N=61)
Enhanced liver fibrosis test score			
Absolute change			
Value	–0.3 (–0.6 to –0.1)	–0.5 (–0.8 to –0.3)	0.2 (0.0 to 0.4)
Difference from placebo (95% CI)	–0.6 (–0.9 to –0.2)	–0.8 (–1.1 to –0.4)	
Decrease of ≥0.5			
Percentage of patients	56	60	14
Difference from placebo (95% CI)	39.2 (22.7 to 55.7)	38.4 (21.9 to 54.9)	
Liver-stiffness measurement — kPa†			
Absolute change	–6.3 (–8.7 to –3.9)	–7.1 (–9.5 to –4.8)	–4.4 (–6.7 to –2.1)
Difference from placebo (95% CI)	–1.9 (–4.9 to –1.2)	–2.7 (–5.6 to 0.2)	
Triglycerides — mg/dl			
Absolute change	–26.9 (–44.5 to –9.3)	–32.6 (–49.3 to –15.9)	–3.3 (–19.3 to 12.7)
Difference from placebo (95% CI)	–23.6 (–47.0 to –0.2)	–29.3 (–52.1 to –6.5)	
HDL cholesterol — mg/dl			
Absolute change	5.5 (2.0 to 9.0)	9.0 (5.8 to 12.3)	–1.8 (–5.0 to 1.3)
Difference from placebo (95% CI)	7.3 (2.8 to 11.9)	10.9 (6.4 to 15.3)	
LDL cholesterol — mg/dl			
Absolute change	–14.4 (–22.0 to –6.7)	–13.4 (–20.7 to –6.2)	–9.5 (–16.4 to –2.7)
Difference from placebo (95% CI)	–4.8 (–14.8 to 5.2)	–3.9 (–13.6 to 5.8)	
Adiponectin — percent change			
Value	31.7 (9.1 to 54.3)	69.1 (47.3 to 90.9)	8.4 (–12.3 to 29.0)
Difference from placebo (95% CI)	23.3 (–4.9 to 51.5)	60.7 (33.2 to 88.2)	
C-peptide — percent change			
Value	–12.8 (–23.6 to –1.9)	–18.1 (–28.6 to –7.6)	–1.4 (–11.4 to 8.6)
Difference from placebo (95% CI)	–11.4 (–25.6 to 2.9)	–16.7 (–30.6 to –2.8)	
HOMA-IR index‡			
Absolute change	–3.4 (–6.5 to –0.3)	–4.1 (–7.1 to –1.2)	1.6 (–1.3 to 4.4)
Difference from placebo (95% CI)	–5.0 (–9.0 to –0.9)	–5.7 (–9.6 to –1.7)	

* Values are estimates of the least-squares mean with the 95% confidence interval (CI) for the change from baseline to week 96 (with indication of absolute or percent change) and least-squares mean estimates for the difference from placebo with the 95% confidence interval. Confidence intervals have not been adjusted for multiple comparisons and should not be used to infer definitive effects of efruxifermin. HDL denotes high-density lipoprotein, and LDL low-density lipoprotein.

† Included in the liver-stiffness measure are patients for whom data at baseline and at week 96 were available and valid (39 patients in the 28-mg efruxifermin group, 46 patients in the 50-mg efruxifermin group, and 45 patients in the placebo group). Liver-stiffness measurements were considered to be valid if the interquartile range divided by the median value of the readings was 30% or less.

‡ In the homeostasis model assessment for insulin resistance (HOMA-IR), values of 2.0 to 2.5 suggest an increased risk of type 2 diabetes.

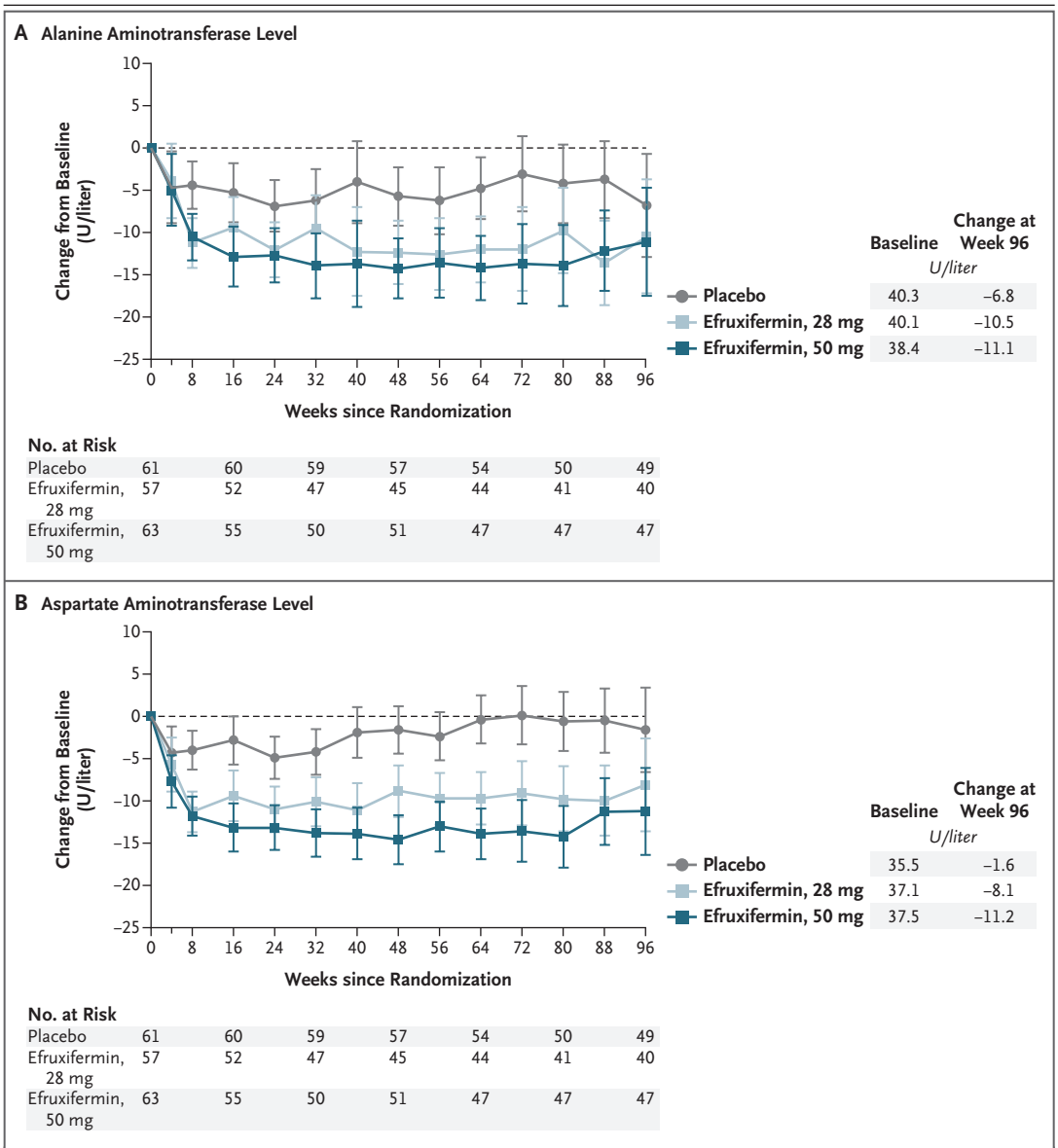

Figure 2. Change in Liver-Enzyme Levels at 96 Weeks.

Data are presented as the least-squares mean with a 95% confidence interval for the absolute change from baseline. Only patients for whom data were available at baseline and at specified visits were included in this analysis. Confidence intervals have not been adjusted for multiple comparisons and should not be used to infer definitive effects of efruxifermin.

and femoral neck were observed for efruxifermin as compared with placebo at week 96 (Table S12). The incidence of fracture was similar across the trial groups (four per group). The incidence and titer of antidrug antibodies were similar across efruxifermin doses and were consistent with values reported in previous studies.

DISCUSSION

In this phase 2b trial, the use of efruxifermin did not result in a significant reduction in fibrosis without worsening of MASH at week 36 (the primary outcome), as compared with placebo. No formal hypothesis testing of secondary outcomes

Table 3. Adverse Events (Safety Population).*

Event	Efruxifermin, 28 mg (N=57)	Efruxifermin, 50 mg (N=63)	Placebo (N=61)	All Patients (N=181)
	number of patients (percent)			
Any serious adverse event	15 (26)	15 (24)	11 (18)	41 (23)
Adverse event leading to discontinuation	6 (11)	11 (17)	2 (3)	19 (10)
Before week 36	5 (9)	9 (14)	2 (3)	16 (9)
Week 36 to week 96	1 (2)	2 (3)	0	3 (2)
Adverse event considered by the investigator to be related to assigned treatment	36 (63)	47 (75)	30 (49)	113 (62)
Adverse event in any system organ class†	56 (98)	63 (100)	59 (97)	178 (98)
Diarrhea	24 (42)	34 (54)	18 (30)	76 (42)
Nausea	17 (30)	29 (46)	18 (30)	64 (35)
Covid-19	13 (23)	14 (22)	18 (30)	45 (25)
Increased appetite	9 (16)	25 (40)	4 (7)	38 (21)
Vomiting	16 (28)	13 (21)	8 (13)	37 (20)
Injection-site bruising	11 (19)	13 (21)	12 (20)	36 (20)
Upper abdominal pain	9 (16)	5 (8)	7 (11)	21 (12)
Injection-site erythema	13 (23)	16 (25)	6 (10)	35 (19)
Arthralgia	9 (16)	12 (19)	13 (21)	34 (19)
Fatigue	11 (19)	10 (16)	12 (20)	33 (18)
Upper respiratory tract infection	10 (18)	10 (16)	12 (20)	32 (18)
Urinary tract infection	6 (11)	18 (29)	8 (13)	32 (18)
Headache	8 (14)	13 (21)	8 (13)	29 (16)
Hypoglycemia	7 (12)	12 (19)	8 (13)	27 (15)
Sinusitis	7 (12)	11 (17)	8 (13)	26 (14)
Diabetes mellitus‡	6 (11)	7 (11)	13 (21)	26 (14)
Hypertension‡	8 (14)	10 (16)	5 (8)	23 (13)
Nasopharyngitis	10 (18)	5 (8)	8 (13)	23 (13)
Procedural pain	9 (16)	5 (8)	9 (15)	23 (13)
Back pain	4 (7)	10 (16)	10 (16)	24 (13)

* The safety analysis included all the adverse events that occurred in the patients who had undergone randomization and received at least one dose of efruxifermin or placebo. Covid-19 denotes coronavirus disease 2019.
† Shown are adverse events with an incidence of at least 15% in any trial group, according to the preferred term in the *Medical Dictionary for Regulatory Activities*. Data are shown according to descending frequency among all the patients.
‡ In this category, the adverse event could have had a new onset during the trial or represent the worsening of an existing condition.

was conducted, so no statistical conclusions can be drawn. However, the results suggest the possibility of benefit for the 50-mg dose of efruxifermin on fibrosis reduction at 96 weeks. Efruxifermin also appeared to be associated with improvements in MASH-related histologic findings, noninvasive markers of liver injury and fibrosis, and markers of glucose and lipid metabolism.

This trial included patients at high risk for hepatic decompensation, as evidenced by baseline liver-stiffness measurements of approximately 25 kPa[32] and the presence of cryptogenic cirrhosis in 22% of the patients.[33] At week 96, the magnitude of the placebo-adjusted treatment effects was similar in the intention-to-treat population and in the patients for whom liver-biopsy data were available at week 96 without imputa-

tion of missing data. The patients who had a reduction in fibrosis by week 36 appeared to maintain their response at week 96, whereas additional new responses were observed at week 96. Furthermore, histologic improvements were corroborated by noninvasive measures of fibrosis and of risk factors for disease progression, including the ELF test score and liver-stiffness measurements, as well as increased platelet counts, which may imply a clinically meaningful reduction in liver-related outcomes.[8,13,16,34]

A potential reduction in fibrosis is consistent with the results of previous trials of efruxifermin in patients with MASH and stage 2 or 3 fibrosis.[25,26] However, fibrosis regression in patients with cirrhosis appeared to occur more slowly than in patients with less advanced (stage 2 or stage 3) fibrosis.[8,14-18] This finding is consistent with observations in patients with cirrhosis caused by viral hepatitis, in whom a reduction of fibrosis was observed 5 years after successful antiviral treatment,[11,12] and probably reflects the longer duration needed to allow resorption of the extensive fibrotic structures associated with cirrhosis after removal of the underlying cause.[10]

Along with efruxifermin, four other FGF21 analogues have completed phase 2 trials involving patients with stage 2 or 3 fibrosis caused by MASH.[14,35-38] Of these trials, phase 2 results with pegozafermin and efimosfermin were positive, and both drugs are in development.[35,38] In a phase 2b trial, pegbelfermin was evaluated in patients with cirrhosis and MASH, but efficacy was not shown regarding fibrosis reduction (the primary outcome).[14]

The safety and side-effect profile of efruxifermin were consistent with the findings in previous trials.[24-26] Adverse events with efruxifermin were primarily gastrointestinal (e.g., diarrhea and nausea) or injection-site related; most events were mild or moderate and transient. Although more patients in the efruxifermin groups reported increased appetite, the mean body weight was unchanged from baseline levels. Reductions in bone mineral density were observed with efruxifermin, although the number of fractures was similar to that in the placebo group. Since patients with MASH and cirrhosis are at higher risk for osteoporosis and fractures owing to accelerated bone loss,[39] low vitamin D levels, and side effects of common concomitant medications (e.g., glucagon-like peptide-1 receptor agonists),[40] continued careful evaluation and potential mitigation strategies should be evaluated in the future. Three events of hepatic decompensation were reported in patients in the efruxifermin groups (two cases of ascites and one of hepatic encephalopathy). The effects on hepatic-decompensation events will be further assessed in phase 3 trials.

Cirrhosis caused by MASH remains a major unmet medical need for treatment. In this trial, efruxifermin did not have significant benefit regarding a reduction in fibrosis without a worsening of MASH at week 36. However, the trial duration of 96 weeks enabled identification of possible treatment effects that were not apparent at week 36. Longer studies in diverse populations will be necessary to evaluate clinical outcomes, safety, and generalizability of the findings and to assess benefits of longer-term treatment.

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