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A Randomized, Controlled Trial of the Pan-PPAR Agonist Lanifibranor in NASH

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ABSTRACT

BACKGROUND

Management of nonalcoholic steatohepatitis (NASH) is an unmet clinical need. Lanifibranor is a pan-PPAR (peroxisome proliferator–activated receptor) agonist that modulates key metabolic, inflammatory, and fibrogenic pathways in the pathogenesis of NASH.

METHODS

In this phase 2b, double-blind, randomized, placebo-controlled trial, patients with noncirrhotic, highly active NASH were randomly assigned in a 1:1:1 ratio to receive 1200 mg or 800 mg of lanifibranor or placebo once daily for 24 weeks. The primary end point was a decrease of at least 2 points in the SAF-A score (the activity part of the Steatosis, Activity, Fibrosis [SAF] scoring system that incorporates scores for ballooning and inflammation) without worsening of fibrosis; SAF-A scores range from 0 to 4, with higher scores indicating more-severe disease activity. Secondary end points included resolution of NASH and regression of fibrosis.

RESULTS

A total of 247 patients underwent randomization, of whom 103 (42%) had type 2 diabetes mellitus and 188 (76%) had significant (moderate) or advanced fibrosis. The percentage of patients who had a decrease of at least 2 points in the SAF-A score without worsening of fibrosis was significantly higher among those who received the 1200-mg dose, but not among those who received the 800-mg dose, of lanifibranor than among those who received placebo (1200-mg dose vs. placebo, 55% vs. 33%, P=0.007; 800-mg dose vs. placebo, 48% vs. 33%, P=0.07). The results favored both the 1200-mg and 800-mg doses of lanifibranor over placebo for resolution of NASH without worsening of fibrosis (49% and 39%, respectively, vs. 22%), improvement in fibrosis stage of at least 1 without worsening of NASH (48% and 34%, respectively, vs. 29%), and resolution of NASH plus improvement in fibrosis stage of at least 1 (35% and 25%, respectively, vs. 9%). Liver enzyme levels decreased and the levels of the majority of lipid, inflammatory, and fibrosis biomarkers improved in the lanifibranor groups. The dropout rate for adverse events was less than 5% and was similar across the trial groups. Diarrhea, nausea, peripheral edema, anemia, and weight gain occurred more frequently with lanifibranor than with placebo.

CONCLUSIONS

In this phase 2b trial involving patients with active NASH, the percentage of patients who had a decrease of at least 2 points in the SAF-A score without worsening of fibrosis was significantly higher with the 1200-mg dose of lanifibranor than with placebo. These findings support further assessment of lanifibranor in phase 3 trials. (Funded by Inventiva Pharma; NATIVE ClinicalTrials.gov number, NCT03008070.)

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*A full list of the investigators in the NATIVE study group is provided in the Supplementary Appendix, available at NEJM.org.

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A Quick Take is available at NEJM.org

Nonalcoholic steatohepatitis (NASH), a condition that results from a combination of adipose-tissue insulin resistance, adipocytokine imbalance, and systemic inflammation, is currently a major worldwide cause of chronic liver disease, contributing to cirrhotic morbidity, hepatocellular carcinoma and liver transplantation, worsening cardiovascular disease, and metabolic dysfunction.[1-3] Peroxisome proliferator–activated receptors (PPARs) are nuclear receptors with key regulatory functions in metabolism, inflammation, and fibrogenesis.[4,5] In preclinical models, the indole sulfonamide lanifibranor (IVA337), a pan-PPAR agonist, improved insulin sensitivity and macrophage activation and reduced liver fibrosis and inflammatory gene expression with higher efficacy than single or dual PPAR agonists.[6,7] Resolution of NASH and regression of fibrosis are currently considered to be likely surrogate outcomes for the prevention of progression to cirrhosis and associated complications.[8] Here, we report the results of the NASH Trial to Validate IVA337 Efficacy (NATIVE), a phase 2b, double-blind, randomized, placebo-controlled trial evaluating the efficacy and safety of lanifibranor in patients with biopsy-proven, noncirrhotic NASH with severe disease activity.

Methods

Trial Oversight

NATIVE was approved by independent ethics committees and the appropriate authorities in 16 countries where at least one patient underwent randomization (Table S1 in the Supplementary Appendix, available with the full text of this article at NEJM.org). The trial was conducted in accordance with the principles of the Declaration of Helsinki, the International Council for Harmonisation Good Clinical Practice guidelines, and all relevant regulations. Written informed consent was obtained from all participants. The sponsor (Inventiva Pharma) designed the trial and monitored the trial sites, collected the data, and analyzed the data. All the authors had access to the data and reviewed the manuscript. The first and last authors and four of the authors employed by Inventiva Pharma participated in the analysis and interpretation of the data and vouch for the accuracy and completeness of the data and for the fidelity of the trial to the protocol, available at NEJM.org. An earlier version of the manuscript was drafted with the assistance of a medical writer (funded by the sponsor) under the guidance of the authors.

Trial Design

The trial rationale and design have been described previously.[9] Patients were eligible for inclusion if they were 18 years of age or older and had noncirrhotic NASH (the diagnosis of which required a Steatosis, Activity, Fibrosis [SAF] grade of 1 or higher for steatosis [range, 0 to 3], hepatocellular ballooning [range, 0 to 2], and lobular inflammation [range, 0 to 2] on liver biopsy); higher grades indicate more-severe disease activity.[10] The diagnosis was confirmed by a centrally read biopsy sample obtained at screening or in the preceding 6 months (patients whose diagnosis was not confirmed at screening had to have a stable body weight, defined as no more than a 5% loss of initial body weight between the time of biopsy and screening). Patients with stage F4 fibrosis, classified according to the criteria of both the SAF and NASH Clinical Research Network (NASH CRN) (stages range from F0 [no fibrosis] to F4 [cirrhosis]),[10,11] were excluded. A score of 3 or higher on the SAF-A (the activity part of the SAF scoring system that incorporates the scores for hepatocellular ballooning and lobular inflammation) was also a criterion for eligibility.[10] Steatosis was assessed separately because it does not reflect liver-cell damage and inflammation per se, outcomes that are included in the SAF concept of "activity" (Fig. S1). Additional details of the inclusion and exclusion criteria are provided in the Supplementary Appendix.

Trial End Points

The primary end point was a decrease of at least 2 points from baseline to week 24 in the SAF-A score and no worsening of fibrosis (i.e., no increase in fibrosis stage based on SAF–NASH CRN criteria). Secondary histologic end points included resolution of NASH (defined as a ballooning grade of 0 and a lobular inflammation grade of ≤1) and no worsening of fibrosis; improvement in fibrosis stage of at least 1 and no worsening of NASH (i.e., no worsening in either steatosis, ballooning, or lobular inflammation); Nonalcoholic Fatty Liver Disease Activity Score (NAS) improvement (defined as a decrease of ≥2 points from baseline to week 24 in the NAS,

which is the sum of the scores for steatosis [range, 0 to 3], ballooning [range, 0 to 2], and lobular inflammation [range, 0 to 3], with higher scores indicating greater disease activity) and no worsening of fibrosis[12]; resolution of NASH and an improvement in fibrosis stage of at least 1 (a composite end point); change in scores for the components of the SAF and NASH CRN scoring system (steatosis, activity, inflammation, ballooning, and fibrosis); and change in the modified Ishak score. All biopsy samples were read serially by one pathologist who was unaware of the time at which the samples were obtained (baseline or end of assigned regimen), the trial-group assignment, and the identity of the person who assessed the adequacy of the samples.

Nonhistologic secondary end points included changes in liver enzyme levels (alanine aminotransferase, aspartate aminotransferase, and γ-glutamyltransferase); changes in measures of glucose metabolism (fasting levels of glucose, insulin, and glycated hemoglobin and homeostatic model assessment of insulin resistance [HOMA-IR] index score); changes in lipid levels (total cholesterol, high-density lipoprotein [HDL] cholesterol, low-density lipoprotein [LDL] cholesterol, triglycerides, and apolipoprotein A1); change in adiponectin level; and changes in inflammatory markers (fibrinogen, high-sensitivity C-reactive protein, α2-macroglobulin, and haptoglobin). Exploratory end points included change in the apoptosis marker cytokeratin 18 M30; changes in serum markers of fibrosis and collagen turnover (ratio of tissue inhibitor of metalloproteinase 1 to matrix metalloproteinase 2, N-terminal type III collagen propeptide [Pro-C3] level, and scores on the Enhanced Liver Fibrosis test and Fibrosis-4 index); changes in other lipid levels (apolipoprotein B and C3); changes on transient elastography (FibroScan, Echosens) with controlled attenuation parameter; and change in quality of life.

RANDOMIZATION

Patients were randomly assigned in a 1:1:1 ratio to receive 1200 mg or 800 mg of oral lanifibranor or placebo once daily for 24 weeks; randomization was stratified according to diabetic status (absence or presence). The full analysis population included all patients who underwent randomization and received at least one dose of the assigned regimen and was identical to the safety analysis population. All patients who had undergone randomization received at least one dose of the assigned regimen, and no patient was excluded from the full analysis population. The per-protocol population included all patients who had biopsy data available at the end of the treatment period and no major protocol deviations.

STATISTICAL ANALYSIS

The sample-size calculation is described in the Supplementary Methods section of the Supplementary Appendix. For statistical tests, the type I error risk was set at 5% (two-sided) in accordance with the protocol. Adjustments for multiplicity testing in the primary analysis were performed with the use of the Hochberg procedure; each active-treatment group was compared with the placebo group. No multiplicity adjustments for the secondary and exploratory end points were defined. Therefore, only point estimates and 95% confidence intervals are provided. The confidence intervals have not been adjusted for multiple comparisons and should not be used to infer definitive treatment effects.

Comparisons of histologic responses among the trial groups were performed with the use of the Cochran–Mantel–Haenszel test stratified according to diabetic status at baseline. The risk ratios that were calculated with this test are reported with the corresponding 95% confidence intervals. The primary analyses that we report here were performed in the full analysis population with the use of multiple imputation for missing data, including missing or inadequate biopsy data at the end of the treatment period (see the Supplementary Appendix). We also report the analyses that were performed with the use of single imputation to treat missing data as nonresponses, as specified in the statistical analysis plan. In addition, sensitivity analyses were conducted on the basis of complete cases (i.e., those with biopsy samples available at both baseline and the end of assigned regimen), as specified in the statistical analysis plan. Other analyses were performed in the per-protocol population and in the subgroups defined according to significant (moderate) or advanced fibrosis and diabetic status. Comparisons of quantitative secondary end points among the trial groups were assessed with the use of mixed

models for repeated measures, with the absolute change in the value of the continuous variable from baseline as the end point; the time, trial group, diabetic status, trial-group–by–time interaction, and baseline value of the variable as fixed effects; a time-repeated effect within each subject; and an unstructured variance–covariance matrix.

RESULTS

PATIENTS

From February 2017 through July 2019, a total of 868 patients underwent screening, and 247 patients were randomly assigned in a 1:1:1 ratio to receive 1200 mg of lanifibranor (83 patients), 800 mg of lanifibranor (83 patients), or placebo (81 patients) orally once daily for 6 months (Fig. S3). Baseline characteristics of the patients who underwent randomization are shown in Table 1. The mean age of the patients was 54 years, and the mean body-mass index (the weight in kilograms divided by the square of the height in meters) was 33; 144 (58%) were female, 232 (94%) were White, and 103 (42%) had type 2 diabetes mellitus. Significant or advanced fibrosis (stages F2 and F3, respectively) was present in 188 patients (76%), and most patients had highly active NASH (the mean [±SD] SAF-A score was 3.3±0.5, and 73% had an NAS of ≥6, which indicates high disease activity). The median duration between screening biopsy and randomization was 2.3 months (range, 0.5 to 9.2). The histologic characteristics of screening biopsy samples according to SAF-A scores are shown in Table S2.

Among the 247 patients in the full analysis population, 228 completed the trial (77 patients in each lanifibranor group and 74 in the placebo group). Reasons for discontinuation of the trial regimen are shown in Figure S3. Major protocol deviations occurred in 53 patients (34 did not have biopsy data available at the end of the treatment period and 19 had other major protocol deviations), who were not included in the per-protocol population, which comprised 194 patients (Table S3).

PRIMARY END POINT

In the full analysis population in which missing data were handled with multiple imputation, the percentage of patients who had a decrease of at least 2 points in the SAF-A score without worsening of fibrosis (the primary end point) was significantly higher among those who received the 1200-mg dose (55%), but not among those who received the 800-mg dose (48%), of lanifibranor than among those who received placebo (33%) (risk ratio for a response in the 1200-mg lanifibranor group vs. the placebo group, 1.7; 95% confidence interval [CI], 1.2 to 2.3; P=0.007; risk ratio in the 800-mg lanifibranor group vs. the placebo group, 1.5; 95% CI, 1.0 to 2.1; P=0.07) (Fig. 1). Results were similar in the prespecified analyses in which missing data were imputed as nonresponses and in the complete-case analyses (Fig. S9 and Tables S4 and S5). The results were also similar in the per-protocol population and among 188 patients with significant or advanced fibrosis.

SECONDARY END POINTS

Resolution of NASH without worsening of fibrosis at week 24 from baseline was observed in 49% of patients who received the 1200-mg dose of lanifibranor, in 39% of patients who received the 800-mg dose, and in 22% of patients who received placebo (risk ratio for a response in the 1200-mg lanifibranor group vs. the placebo group, 2.2; 95% CI, 1.5 to 3.3; and risk ratio in the 800-mg lanifibranor group vs. the placebo group, 1.7; 95% CI, 1.1 to 2.7) (Fig. 1 and Table S5). Improvement in fibrosis stage of at least 1 without worsening of NASH was observed in 48% of patients in the 1200-mg lanifibranor group, in 34% of patients in the 800-mg lanifibranor group, and in 29% of patients in the placebo group (risk ratio in the 1200-mg lanifibranor group vs. the placebo group, 1.7; 95% CI, 1.2 to 2.5; and risk ratio in the 800-mg lanifibranor group vs. the placebo group, 1.2; 95% CI, 0.7 to 1.9) (Fig. 1). Among patients with significant or advanced fibrosis, the results were also better in the lanifibranor groups than in the placebo group. Resolution of NASH and improvement in fibrosis stage of at least 1 (composite end point) was observed in 35% of patients in the 1200-mg lanifibranor group, in 25% of patients in the 800-mg lanifibranor group, and in 9% of patients in the placebo group (risk ratio in the 1200-mg lanifibranor group vs. the placebo group, 4.0; 95% CI, 2.0 to 7.7; and risk ratio in the 800-mg lanifibranor group vs. the placebo group, 2.6; 95% CI, 1.2 to 5.5) (Fig. 1). The re-

Table 1. Demographic and Clinical Characteristics of the Patients at Baseline (Full Analysis Population).*

Characteristic	Lanifibranor, 1200 mg (N=83)	Lanifibranor, 800 mg (N=83)	Placebo (N=81)	Overall (N=247)
Female sex — no. (%)	49 (59)	54 (65)	41 (51)	144 (58)
Age — yr	52.2±13.8	55.0±10.4	53.4±13.1	53.6±12.5
White race — no. (%)†	78 (94)	80 (96)	74 (91)	232 (94)
Weight — kg	93.0±19.9	91.6±19.3	95.1±17.3	93.2±18.9
Body-mass index	33.3±5.5	32.5±5.5	32.8±5.1	32.9±5.4
Type 2 diabetes mellitus — no. (%)	35 (42)	33 (40)	35 (43)	103 (42)
Median time between screening biopsy and randomization (range) — mo	2.4 (0.5–7.0)	2.6 (0.5–9.2)	2.0 (0.5–7.4)	2.3 (0.5–9.2)
Steatosis grade‡	2.6±0.6	2.6±0.7	2.5±0.7	2.5±0.7
Lobular inflammation grade§	1.5±0.5	1.5±0.5	1.5±0.5	1.5±0.5
Ballooning grade¶	1.8±0.4	1.7±0.4	1.8±0.4	1.8±0.4
Fibrosis stage‖	2.1±0.8	2.1±0.8	2.0±0.9	2.1±0.8
Fibrosis stage F2 or F3 — no. (%)	63 (76)	68 (82)	57 (70)	188 (76)
SAF-A score**	3.3±0.5	3.2±0.5	3.3±0.5	3.3±0.5
NAS††	5.9±0.9	5.9±1.0	5.9±1.1	5.9±1.0
NAS ≥6 — no. (%)	61 (73)	63 (76)	56 (69)	180 (73)
Alanine aminotransferase level — IU/liter	63.6±43.4	64.1±41.4	56.9±31.6	61.6±39.2
Aspartate aminotransferase level — IU/liter	43.9±24.8	53.9±43.4	43.3±24.1	47.1±32.3
γ-Glutamyltransferase level — IU/liter	67.1±93.1	101.6±146.1	67.9±80.4	78.9±111.2
Fasting HDL cholesterol level — mmol/liter	1.2±0.3	1.3±0.3	1.2±0.3	1.2±0.3
Fasting triglyceride level — mmol/liter	2.0±0.9	1.9±0.9	2.0±0.8	2.0±0.9
Fasting glucose level — mmol/liter	5.9±1.1	6.2±1.8	6.0±1.6	6.0±1.5
Glycated hemoglobin level — %	6.1±0.7	6.1±0.8	6.0±0.7	6.0±0.7
Fasting insulin level — pmol/liter	274.7±321.2	231.9±191.9	234.0±254.6	246.9±260.7

* Plus–minus signs are means ±SD. To convert the values for high-density lipoprotein (HDL) cholesterol to milligrams per deciliter, divide by 0.02586. To convert the values for triglycerides to milligrams per deciliter, divide by 0.01129. To convert the values for glucose to milligrams per deciliter, divide by 0.01129. To convert the values for insulin to micrograms per liter, divide by 172.2.

† Race or ethnic group is reported according to the record in the electronic case-report form, which included American Indian or Alaskan, Asian, Black or African American, Native Hawaiian or other Pacific Islander, White, or other.

‡ Steatosis was assessed as the percentage of hepatocytes containing large and medium-sized intracytoplasmic lipid droplets (but not foamy microvesicles) and graded as 0 (<5%), 1 (5 to 33%), 2 (34 to 66%), or 3 (≥67%), according to the Steatosis, Activity, Fibrosis (SAF) scoring system. Patients with grade 0 steatosis were excluded from the trial.

§ Lobular inflammation was classified as grade 1 (two small foci of inflammatory cells) or grade 2 (more than two foci of inflammatory cells), according to the SAF scoring system.

¶ Ballooning was classified as grade 1 (round hepatocytes with pale cytoplasm and size similar to that of normal hepatocytes) or grade 2 (presence of enlarged hepatocytes with a diameter at least twice that of normal hepatocytes in a background of clear and round hepatocytes), according to the Nonalcoholic Steatohepatitis Clinical Research Network (NASH CRN) grading system.

‖ Fibrosis was classified as stage F0 (no fibrosis), stage F1 (mild fibrosis), stage F2 (significant [moderate] fibrosis), stage F3 (advanced fibrosis), or stage F4 (cirrhosis), according to the SAF–NASH CRN staging system. Patients with stage F4 fibrosis were excluded from the trial.

** The SAF-Activity (SAF-A) score ranges from 0 to 4; with higher scores indicating more-severe disease activity.

†† The Nonalcoholic Fatty Liver Disease Activity Score (NAS) ranges from 0 to 8. A score of 2 or less indicates "not NASH"; a score of 3 or 4, "borderline NASH," and a score of 5 to 8, "definite NASH."

sults of analyses in which missing data were imputed as nonresponses, per-protocol analyses, and complete-case analyses are provided in Tables S4 and S5. The effects on the individual histologic features of NASH are provided in Table S6.

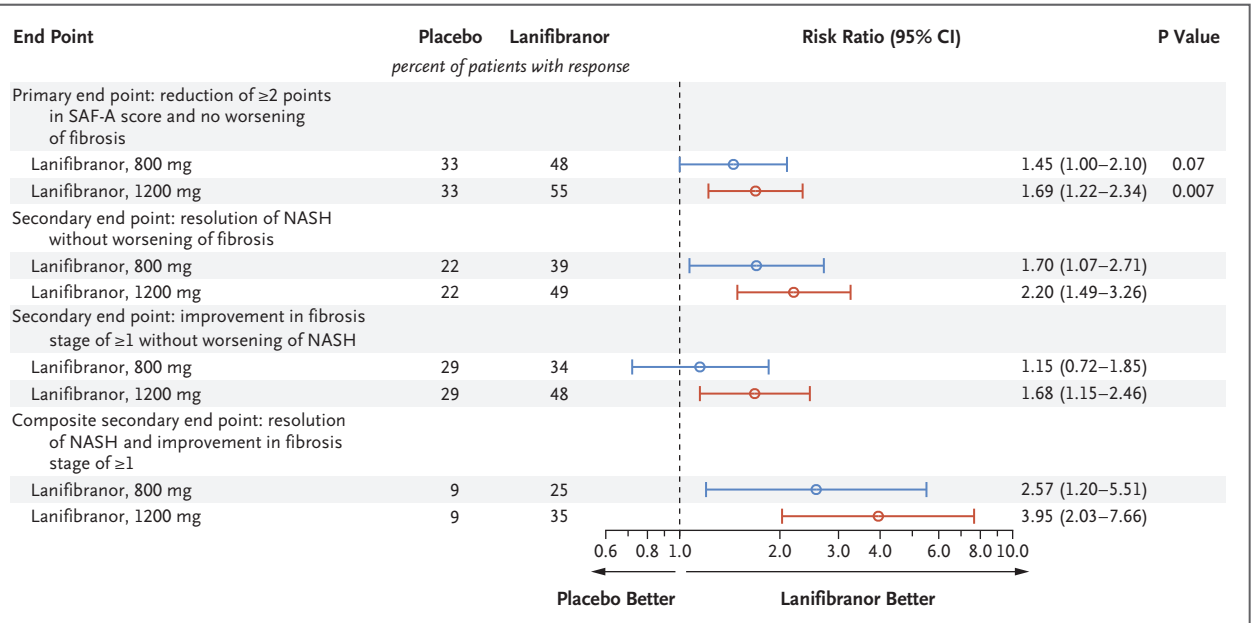

Figure 1. Response for Primary and Secondary Histologic End Points at Week 24.

Analyses were performed with multiple imputation of missing data. Risk ratios, 95% confidence intervals, and P values were calculated with the Cochran–Mantel–Haenszel test stratified according to diabetic status at baseline. In the analysis of the primary end point, an ascending Hochberg procedure was used to adjust for multiplicity testing (each dose of lanifibranor was compared with placebo). Missing data for the 34 patients in the full analysis population (11 in the 800-mg lanifibranor group, 9 in the 1200-mg lanifibranor group, and 14 in the placebo group had missing biopsy samples at week 24) were handled with multiple imputation (details are provided in the Supplementary Appendix). The Steatosis, Activity, Fibrosis–Activity (SAF-A) score represents the activity part of the SAF scoring system that incorporates the scores for hepatocellular ballooning and lobular inflammation; SAF-A scores range from 0 to 4, with higher scores indicating more-severe disease activity. NASH denotes nonalcoholic steatohepatitis.

Changes in the levels of aminotransferases, HDL and LDL cholesterol, and glycated hemoglobin are reported in Figure S6. The adjusted mean decrease in alanine aminotransferase level was 25 U per liter in the 1200-mg lanifibranor group, 26 U per liter in the 800-mg lanifibranor group, and 1 U per liter in the placebo group (Table 2). The decreases in the aspartate aminotransferase and γ-glutamyltransferase levels were in a similar direction, with greater decreases in the lanifibranor groups than in the placebo group. The adjusted mean change in glycated hemoglobin level was −0.4% in the 1200-mg lanifibranor group, −0.4% in the 800-mg lanifibranor group, and 0.1% in the placebo group. Changes in other secondary end points (serum adiponectin level; fasting levels of insulin, glucose, triglycerides, total cholesterol, LDL and HDL cholesterol, and apolipoprotein A1; fasting HOMA-IR index score; and inflammatory markers) are reported in Table 2.

EXPLORATORY EFFICACY ANALYSES

Changes in markers of apoptosis, fibrosis, and collagen turnover are reported in Table 2. Mean transient elastography values decreased by 1.7 in the 1200-mg lanifibranor group, 1.0 in the 800-mg lanifibranor group, and 0.7 in the placebo group. The results with respect to controlled attenuation parameter were in a similar direction, with greater decreases in the lanifibranor groups than in the placebo group (Table S9). With regard to quality of life, no substantial changes from baseline in the various dimensions of the Medical Outcomes Study 36-Item Short-Form Health Survey and the score on the Flinders Fatigue Scale were observed at week 24 (Table S10).

A total of 103 patients who underwent randomization had type 2 diabetes mellitus; the mean age of these patients was 56 years, the mean body-mass index was 33, 62 (60%) were women, 83 (81%) had significant or advanced fibrosis,

Table 2. Laboratory Measures at Week 24 among the Patients in the Full Analysis Population Who Completed the Trial.*

End Point	Lanifibranor, 1200 mg (N=77)	Lanifibranor, 800 mg (N=77)	Placebo (N=74)
Change from baseline in secondary end points (95% CI)†			
Total cholesterol — mmol/liter	−0.07 (−0.22 to 0.07)	−0.02 (−0.17 to 0.13)	0.01 (−0.14 to 0.16)
Fasting HDL cholesterol — mmol/liter	0.11 (0.06 to 0.15)	0.16 (0.12 to 0.21)	0.01 (−0.04 to 0.05)
Fasting LDL cholesterol — mmol/liter	0.03 (−0.11 to 0.16)	0.03 (−0.11 to 0.16)	0.01 (−0.12 to 0.15)
Fasting triglycerides — mmol/liter	−0.44 (−0.61 to −0.27)	−0.49 (−0.66 to −0.31)	0.06 (−0.12 to 0.23)
Fasting apolipoprotein A1 — mg/dl	−4.39 (−8.64 to −0.13)	−0.29 (−4.61 to 4.04)	0.03 (−4.27 to 4.33)
Aspartate aminotransferase — U/liter	−12.04 (−18.29 to −5.79)	−15.11 (−21.43 to −8.80)	−0.08 (−6.43 to 6.26)
Alanine aminotransferase — U/liter	−24.54 (−32.06 to −17.01)	−26.08 (−33.67 to −18.50)	−1.40 (−9.04 to 6.25)
γ-Glutamyltransferase — U/liter	−27.87 (−38.88 to −16.86)	−43.38 (−54.46 to −32.29)	4.41 (−6.76 to 15.58)
Fasting glucose — mmol/liter	−0.60 (−0.83 to −0.37)	−0.78 (−1.01 to −0.55)	0.24 (0.01 to 0.47)
Glycated hemoglobin — %	−0.41 (−0.51 to −0.32)	−0.38 (−0.47 to −0.28)	0.07 (−0.02 to 0.17)
Fasting insulin — pmol/liter	−114.91 (−138.09 to −91.73)	−118.66 (−141.66 to −95.67)	−35.7 (−58.59 to −12.82)
Fasting HOMA-IR index score‡	−5.46 (−6.60 to −4.32)	−5.79 (−6.92 to −4.65)	−1.47 (−2.59 to −0.35)
Adiponectin — μg/ml	17.12 (14.29 to 19.96)	11.95 (8.97 to 14.94)	−0.35 (−3.20 to 2.50)
High-sensitivity CRP — mg/liter	−1.37 (−2.28 to −0.46)	−2.05 (−2.97 to −1.13)	0.11 (−0.81 to 1.03)
Fibrinogen — g/liter	−0.10 (−0.24 to 0.05)	−0.17 (−0.32 to −0.02)	0.02 (−0.12 to 0.17)
α2-Macroglobulin — g/liter	0.13 (0.04 to 0.22)	0.15 (0.06 to 0.24)	0.05 (−0.04 to 0.13)
Haptoglobin — g/liter	−0.07 (−0.13 to 0)	−0.05 (−0.12 to 0.01)	0.05 (−0.01 to 0.12)
Change from baseline in exploratory end points (95% CI)†			
Fasting apolipoprotein B — mg/dl	−11.61 (−15.64 to −7.57)	−11.51 (−15.61 to −7.41)	−1.85 (−5.79 to 2.09)
Fasting apolipoprotein C3 — μg/dl	−9.98 (−17.74 to −2.22)	−8.08 (−16.02 to −0.13)	10.31 (2.67 to 17.94)
Pro-C3 — μg/liter	−1.79 (−3.07 to −0.52)	−3.93 (−5.26 to −2.61)	−1.01 (−2.30 to 0.28)
TIMP-1 to MMP-2 ratio	−0.75 (−0.93 to −0.57)	−0.69 (−0.88 to −0.50)	−0.11 (−0.29 to 0.08)
Cytokeratin 18 M30 — pmol/liter	−315.55 (−441.55 to −189.55)	−331.71 (−463.78 to −199.65)	−105.03 (−232.86 to 22.80)
Enhanced Liver Fibrosis test score§	0.11 (−0.04 to 0.26)	−0.19 (−0.35 to −0.04)	−0.08 (−0.23 to 0.06)
Fibrosis-4 index score¶	0.03 (−0.13 to 0.19)	0 (−0.17 to 0.16)	−0.03 (−0.19 to 0.13)

* A total of 228 patients completed their week-24 visit. The analysis of each variable was conducted with data from approximately the same number of patients; there were some missing data from a small number of patients for certain variables. To convert the values for cholesterol to milligrams per deciliter, divide by 0.02586. To convert the values for fibrinogen to micromoles per liter, multiply by 2.94. CRP denotes C-reactive protein, LDL low-density lipoprotein, MMP-2 matrix metalloproteinase 2, Pro-C3 N-terminal type III collagen propeptide, and TIMP-1 tissue inhibitor of metalloproteinase 1.

† Adjusted mean absolute changes and 95% confidence intervals were derived with the use of mixed models for repeated measures, with the absolute change from baseline of the continuous outcome as the end point, the time, trial group, diabetic status, trial-group–by–time interaction, and baseline value of the outcome as fixed effects; a time repeated effect within each subject; and an unstructured variance–covariance matrix.

‡ The score on the homeostatic model assessment of insulin resistance (HOMA-IR) was calculated as follows: (fasting insulin [in micro–international units per milliliter]×fasting glucose [in milligrams per deciliter])/405. The conversion factor that was used for insulin was that 1 μU per milliliter was equal to 6.00 pmol per liter. Higher values indicate greater insulin resistance.

§ An Enhanced Liver Fibrosis test score of less than 7.7 indicates none to mild fibrosis, and a score of 11.3 or greater indicates cirrhosis.

¶ A Fibrosis-4 index score of less than 1.45 indicates low probability of stage F3 or F4 fibrosis, and a score greater than 3.25 indicates a high probability of stage F3 or F4 fibrosis.

and 84 (82%) had an NAS of 6 or greater. The diabetes regimens are reported in Table S8. The patients with diabetes had improvements in histologic features of NASH that were similar to those in the full analysis population, and they had more pronounced reductions in fasting levels

of glucose, insulin, and glycated hemoglobin than those observed in the full analysis population.

SAFETY

The assigned regimen was discontinued because of adverse events in three patients (4%) in the 1200-mg lanifibranor group, in four patients (5%) in the 800-mg lanifibranor group, and in three patients (4%) in the placebo group. Most adverse events were mild or moderate in severity (Table 3). In each trial group, three patients (4%) had a severe adverse event during the treatment period (defined as the period after the first dose up to 28 days after the last dose). There were two serious adverse events (mild heart failure and urticaria, both in the placebo group) that were determined by the investigator to be related to the placebo. Nausea, diarrhea, peripheral edema, anemia, and weight gain occurred more frequently with lanifibranor than with placebo. One patient in the 1200-mg lanifibranor group was reported by the investigator to have nontreatment-related mild heart failure that did not lead to further investigation or hospitalization. Peripheral edema that was assessed by the investigator as being related to the active drug or placebo occurred in four patients (2%) in the lanifibranor groups (two in each group) and in no patient in the placebo group during the treatment period. One patient had severe peripheral edema but recovered after discontinuing the 1200-mg regimen of lanifibranor for 12 days; treatment was resumed without reoccurrence of edema. A mean increase of 2.7 kg (3.1%) from baseline in body weight was observed among the patients in the 1200-mg lanifibranor group, and a mean increase of 2.4 kg (2.6%) was observed among the patients in the 800-mg lanifibranor group (Fig. S7). Anemia was reported in six patients (7%) in the 1200-mg lanifibranor group, with the hemoglobin levels returning to pretreatment values after either investigator-initiated iron supplementation or discontinuation of lanifibranor. A relative reduction in hemoglobin levels of 5 to 6% from baseline was observed in the lanifibranor groups, as compared with a 1% reduction in the placebo group (Fig. S8). Kidney function (markers included creatinine and urea levels and estimated glomerular filtration rate) (Table S11) and bone turnover (markers included osteocalcin level and beta-CrossLaps value [the level of β-isomer of the C-terminal telopeptide of type I collagen, as measured with a CrossLaps osteometer, Biotech]) (Table S12) were not impaired.

DISCUSSION

In this phase 2, placebo-controlled trial of lanifibranor in patients with highly active NASH and fibrosis, the percentage of patients who had a reduction in activity of steatohepatitis was significantly higher among those who received the 1200-mg dose, but not among those who received the 800-mg dose, of lanifibranor for 24 weeks than among those who received placebo. The results of this trial also support the potential for benefits with lanifibranor with respect to many secondary end points, including hepatic fibrosis, lipid profile, and glycemic control.

NASH is the primary predictor of progressive hepatic fibrosis.[13,14] Patients with significant (moderate) or advanced hepatic fibrosis are at increased risk of cirrhosis,[15,16] which justifies the need for pharmacotherapy in patients with NASH and advanced fibrosis. Resolution of NASH has been shown to be associated with regression of hepatic fibrosis.[13,17] In this trial, a dose-dependent improvement in SAF-A score and its individual components was noted with lanifibranor. Resolution of NASH without worsening of fibrosis , a secondary end point, was observed in 49% of patients who received the 1200-mg dose of lanifibranor, as compared with 22% of patients in the placebo group. When the analysis was restricted to patients with significant (stage F2) or advanced (stage F3) fibrosis (i.e., those who compose the target population for the treatment of noncirrhotic NASH according to regulatory guidance), similar results were obtained, a finding that supports the potential for benefits with lanifibranor as compared with placebo.

In this trial, other findings from the secondary end-point analyses suggest that the 1200-mg dose of lanifibranor may have led to a regression of fibrosis. Fibrosis is the primary predictor of medical complications and death in patients with NASH.[18] Regression of fibrosis in NASH is associated with decreased risk of liver-related events[19] and is a surrogate end point for regulatory approval.[8] Although regression of fibrosis can be indirectly accomplished with long-term therapy to control disease activity, the combination of therapy to control disease activity and fibrogenesis, the goals of which are reflected in the

composite end point of resolution of NASH and improvement in fibrosis stage of at least 1, could have a stronger and faster effect on disease progression.

Previous trials have also shown resolution of NASH with no worsening in fibrosis with other compounds.[20-23] Regression of fibrosis without worsening of NASH has been reported with a few other drugs.[24,25] None of these compounds were reported to have concomitant benefits with respect to both histologic end points.

The histologic results are supported by apparent improvements in several relevant metabolic, inflammatory, and fibrogenesis markers, including Pro-C3 and liver stiffness, but other markers of fibrosis (scores on the Enhanced Liver Fibrosis test and Fibrosis-4 index) did not improve. However, as changes in biomarkers are not fully validated as surrogates of histologic change, these results should be interpreted with caution, particularly in short-term trials.

There was a dose-dependent increase in serum adiponectin level, which suggests that there was an improvement in adipose-tissue function.[26,27] This improvement in adipose tissue function is most likely the main reason for the observed increase in body weight. Lanifibranor induced a histologic improvement despite this weight gain, which could be explained by the role of adipose-tissue dysfunction rather than overweight per se in the pathophysiology of NASH[28] and by a shift from visceral to metabolically healthy subcutaneous adipose tissue, a finding that was noted with other PPARγ agonists.[29]

NASH is a risk factor for type 2 diabetes mellitus, which is associated with a higher risk of more-advanced fibrosis.[30] Lanifibranor appeared to improve histologic features in patients regardless of diabetes status. Patients with diabetes who received lanifibranor had reductions in glycated hemoglobin level, a validated surrogate for improved outcomes,[31,32] and in other measures of glycemic control. Also, the patients who received lanifibranor had an increase in HDL cholesterol level and a decrease in serum triglyceride level, two major cardiovascular risk factors. Such metabolic improvements could be beneficial in a patient population at high risk for adverse cardiovascular outcomes.[3]

Steatosis is a cardinal feature of NASH. The majority of patients with steatosis do not, however, show signs of liver damage.[33] While disease activity should reflect ongoing damage and inflammation, the inclusion of steatosis as part of a composite activity score introduces a risk that these outcomes may be overestimated. Moreover, although regression of steatosis was shown in conjunction with regression of NASH in several trials, the severity of steatosis can also decrease when disease progresses to cirrhosis.[34] We therefore used the SAF scoring system, which assesses steatosis separately from activity and accounts for necroinflammation without steatosis, in the selection of patients for the trial and to define the primary end point.[10] The use of the SAF-A score leads to a selection of patients with more-severe disease activity and fibrosis,[35] as was observed in the current trial, in which 76% of patients had significant or advanced fibrosis, despite the fact that no inclusion criterion with respect to fibrosis stage was set (except for the exclusion of patients with cirrhosis). The use of the SAF-A score enriched the trial with patients more likely to benefit from pharmacologic treatment. As for the other histologic end points, the validity of the use of the SAF-A score to define the primary end point as a surrogate for long-term outcomes warrants further study.

Lanifibranor is a first-in-class pan-PPAR agonist with the ability to activate the three PPAR isotypes.[6] The ability of lanifibranor to simultaneously improve pathways driving insulin resistance, reduce hepatic inflammation, and improve the fibrotic response suggests an effective multitargeted mechanism of action. The complex pathophysiology of NASH may require targeting multiple pathways, rather than a single pathway, for successful treatment.[36]

Gastrointestinal adverse events, peripheral edema, anemia, and weight gain occurred more frequently with lanifibranor than with placebo. A reduction in hemoglobin levels was observed in the lanifibranor groups, a finding that is consistent with those in previous reports of other compounds with PPARγ agonism; such a reduction has several potential underlying mechanisms.[37] No effect on kidney function or markers of bone turnover was observed.

The majority of patients in this 24-week trial were White. To assess whether longer treatment would result in similar efficacy and whether this efficacy would apply to other racial and ethnic groups, some of which have a greater predisposition to NASH than others, an appropriate

Table 3. Overview of Adverse Events That Occurred during the Treatment Period (Full Analysis Population).*

Event	Lanifibranor, 1200 mg (N=83)	Lanifibranor, 800 mg (N=83)	Placebo (N=81)
		number (percent)	
≥1 Adverse event	62 (75)	59 (71)	50 (62)
Mild	54 (65)	51 (61)	42 (52)
Moderate	28 (34)	20 (24)	22 (27)
Severe	3 (4)	3 (4)	3 (4)
Adverse event related to active drug or placebo, during the treatment period, as assessed by the investigator	23 (28)	25 (30)	19 (23)
Adverse event that led to permanent discontinuation of the trial regimen	3 (4)	4 (5)	3 (4)
Adverse event related to active drug or placebo that led to discontinuation of the trial regimen	2 (2)†	1 (1)‡	2 (2)
Serious adverse event	7 (8)	3 (4)	3 (4)
Death	0	0	0
Serious adverse event related to active drug or placebo	0	0	2 (2)§
Serious postprocedural condition linked to biopsy procedure	3 (4)	1 (1)	0
Other serious adverse event			
Wrist fracture	0	0	1 (1)
Unstable angina	1 (1)	0	0
Heart failure	0	0	1 (1)
Gastroenteritis	1 (1)	0	0
Pyelonephritis	1 (1)	0	0
Pancreatitis	0	1 (1)	0
Undifferentiated connective tissue disease	0	1 (1)	0
Urticaria	0	0	1 (1)
Foot operation	1 (1)	0	0
Most frequent adverse events¶			
Diarrhea	10 (12)	8 (10)	1 (1)
Fatigue‖	11 (13)	3 (4)	8 (10)
Nausea	7 (8)	8 (10)	3 (4)
Weight gain	7 (8)	8 (10)	0
Peripheral edema**	7 (8)	5 (6)	2 (2)
Headache	7 (8)	4 (5)	4 (5)
Abdominal pain††	5 (6)	4 (5)	4 (5)
Dizziness	6 (7)	2 (2)	3 (4)
Anemia‡‡	6 (7)	1 (1)	0
Constipation	5 (6)	3 (4)	6 (7)
Increase in aminotransferase level§§	3 (4)	5 (6)	1 (1)

* The treatment period was defined as the period after the first dose up to 28 days after the last dose.
† One patient had mild cardiac failure, and one patient had mild diarrhea, abdominal pain, and dizziness.
‡ One patient had moderate diarrhea.
§ There were two suspected unexpected serious adverse reactions; one patient had mild cardiac failure, and one patient had moderate urticaria.
¶ Adverse events are listed for those that occurred in more than 5% of patients in either lanifibranor group.
‖ Fatigue included asthenia.
** Cases of peripheral edema were assessed by the investigator as being drug-related in two patients (including one case of severe intensity) in the 1200-mg lanifibranor group and in two patients in the 800-mg lanifibranor group.
†† Abdominal pain included upper and lower abdominal pain.
‡‡ Anemia included iron deficiency anemia and decreased hemoglobin level.
§§ Increase in aminotransferase level included increased alanine aminotransferase level, increased aspartate aminotransferase level, or abnormal liver function test result.

phase 3 trial of longer duration and with more extensive assessments for efficacy and safety is needed.

In this phase 2b trial of patients with active NASH, the percentage of patients who had a decrease of at least 2 points in the SAF-A score without worsening of fibrosis was significantly higher with the 1200-mg once-daily dose of lanifibranor than with placebo.

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APPENDIX

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