ORIGINAL ARTICLE

Efficacy and Safety of Elafibranor in Primary Biliary Cholangitis

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ABSTRACT

BACKGROUND

Primary biliary cholangitis is a rare, chronic cholestatic liver disease characterized by the destruction of interlobular bile ducts, leading to cholestasis and liver fibrosis. Whether elafibranor, an oral, dual peroxisome proliferator-activated receptor (PPAR) α and δ agonist, may have benefit as a treatment for primary biliary cholangitis is unknown.

METHODS

In this multinational, phase 3, double-blind, placebo-controlled trial, we randomly assigned (in a 2:1 ratio) patients with primary biliary cholangitis who had had an inadequate response to or unacceptable side effects with ursodeoxycholic acid to receive once-daily elafibranor, at a dose of 80 mg, or placebo. The primary end point was a biochemical response (defined as an alkaline phosphatase level of <1.67 times the upper limit of the normal range, with a reduction of ≥15% from baseline, and normal total bilirubin levels) at week 52. Key secondary end points were normalization of the alkaline phosphatase level at week 52 and a change in pruritus intensity from baseline through week 52 and through week 24, as measured on the Worst Itch Numeric Rating Scale (WI-NRS; scores range from 0 [no itch] to 10 [worst itch imaginable]).

RESULTS

A total of 161 patients underwent randomization. A biochemical response (the primary end point) was observed in 51% of the patients (55 of 108) who received elafibranor and in 4% (2 of 53) who received placebo, for a difference of 47 percentage points (95% confidence interval [CI], 32 to 57; P<0.001). The alkaline phosphatase level normalized in 15% of the patients in the elafibranor group and in none of the patients in the placebo group at week 52 (difference, 15 percentage points; 95% CI, 6 to 23; P=0.002). Among patients who had moderate-to-severe pruritus (44 patients in the elafibranor group and 22 in the placebo group), the least-squares mean change from baseline through week 52 on the WI-NRS did not differ significantly between the groups (–1.93 vs. –1.15; difference, –0.78; 95% CI, –1.99 to 0.42; P=0.20). Adverse events that occurred more frequently with elafibranor than with placebo included abdominal pain, diarrhea, nausea, and vomiting.

CONCLUSIONS

Treatment with elafibranor resulted in significantly greater improvements in relevant biochemical indicators of cholestasis than placebo. (Funded by GENFIT and Ipsen; ELATIVE ClinicalTrials.gov number, NCT04526665.)

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Primary biliary cholangitis is a rare, chronic cholestatic liver disease with increasing prevalence worldwide that occurs predominantly in women 40 years of age or older.[1,2] The disease is characterized by the destruction of interlobular bile ducts, which leads to cholestasis and liver fibrosis.[1] If left untreated, primary biliary cholangitis can progress to cirrhosis, the need for liver transplantation, and premature death.[1] A higher risk of these adverse outcomes is correlated with elevated levels of alkaline phosphatase and bilirubin, and elevated levels are used as prognostic indicators of disease progression.[3]

The only approved first-line therapy for patients with primary biliary cholangitis is ursodeoxycholic acid, a tertiary hydrophilic bile acid.[1,4,5] Up to 40% of patients have an inadequate response to this treatment,[6,7] and 3 to 5% of patients have unacceptable adverse events.[7] Obeticholic acid, a selective farnesoid X receptor agonist,[4] is the only approved second-line treatment[1]; however, fewer than 50% of patients have a biochemical response, and pruritus may be exacerbated.[8] Although off-label treatment with fibrates as second-line therapy has shown potential for an improved biochemical response and decreased pruritus in patients with primary biliary cholangitis,[9-12] an efficacious and safe long-term treatment remains an unmet need.

Elafibranor is an oral, dual peroxisome proliferator-activated receptor (PPAR) α and δ agonist that decreases the toxic effects of bile acid and inflammation through downstream modulation of the nuclear receptor targets of PPAR-α and PPAR-δ.[13] In a 12-week, phase 2 trial involving patients with primary biliary cholangitis, treatment with elafibranor significantly reduced biomarkers of disease activity, and no safety concerns were identified.[13] Here, the results from ELATIVE, a phase 3 trial evaluating the efficacy and safety of elafibranor in patients with primary biliary cholangitis, are presented.

Methods

Patients

Patients 18 to 75 years of age were enrolled in the trial if they had received a diagnosis of primary biliary cholangitis and had had an inadequate response to or unacceptable side effects with ursodeoxycholic acid, as defined in the protocol, available with the full text of this article at NEJM.org. The trial was conducted at 82 sites in 14 countries. Key inclusion criteria were an alkaline phosphatase level at least 1.67 times the upper limit of the normal range (ULN) (174 U per liter for women and 215 U per liter for men) and a total bilirubin level no more than 2 times the ULN (41 μmol per liter). Among the exclusion criteria were autoimmune hepatitis or primary biliary cirrhosis–autoimmune hepatitis overlap and evidence of clinically significant hepatic decompensation, as defined in the protocol. Detailed inclusion and exclusion criteria are provided in Table S1 in the Supplementary Appendix (available at NEJM.org).

Trial Design and Oversight

In this multinational, phase 3, double-blind, placebo-controlled trial, patients were randomly assigned (in a 2:1 ratio) to receive once-daily elafibranor, at a dose of 80 mg, or placebo. Randomization was stratified according to an alkaline phosphatase level greater than 3 times the ULN or a total bilirubin level above the ULN (yes or no), and a score on the Worst Itch Numeric Rating Scale (WI-NRS; scores range from 0 [no itch] to 10 [worst itch imaginable])[14] greater than or equal to 4 (yes or no). Patients who were receiving a stable dose of ursodeoxycholic acid were permitted to continue this treatment throughout the trial. The overall double-blind period comprised two parts. In part one, patients were randomly assigned to receive elafibranor or placebo in a double-blind manner for at least 52 weeks. In part two, patients continued their assigned regimen after week 52 until all patients had completed their week 52 assessment or for a maximum of 104 weeks, whichever came first. The database lock occurred after the last patient completed the week 52 visit. At the end of the double-blind period, patients could enter an open-label extension period and receive elafibranor for up to 5 additional years.

The trial was designed by a steering group of clinical experts and representatives from the sponsors (GENFIT and Ipsen). The investigators gathered the data, and data analyses were performed by the sponsors. The trial was conducted in accordance with the International Council for Harmonisation Good Clinical Practice guidelines, applicable regulatory requirements, and the principles of the Declaration of Helsinki.[15,16] All patients

provided written informed consent. The authors vouch for the completeness and accuracy of the data and for the fidelity of the trial to the protocol. The initial manuscript draft was prepared by medical writers, funded by Ipsen. Subsequent revisions, and the final decision to submit the manuscript, were made by members of the publication working group under the direction of the first author. Additional details on trial design and oversight are provided in the Supplementary Appendix.

TRIAL END POINTS

The primary end point was a biochemical response at week 52 (defined as an alkaline phosphatase level <1.67 times the ULN, with a reduction of ≥15% from baseline, and total bilirubin at or below the ULN). Key secondary end points were normalization of the alkaline phosphatase level at week 52 and a change in pruritus intensity from baseline through week 52 and through week 24, assessed with the use of the WI-NRS among patients with moderate-to-severe pruritus (defined as a WI-NRS score of ≥4 at baseline).

Other secondary end points included changes from baseline to week 52 in patient-reported outcomes related to pruritus, as assessed with the primary biliary cirrhosis–40 (PBC-40) questionnaire (scores range from 1 [or 0 in some items for itch, social function, and symptoms] to 5 for each of the 40 items, with higher scores indicating worse quality of life) and the 5-D itch scale, which measures the degree, duration, direction (improvement or worsening), disability (effect on daily activities), and distribution of itching (total scores range from 5 to 25, with higher scores indicating worse itch-related quality of life).[17,18] Secondary end points also included the change from baseline to week 52 in the levels of alkaline phosphatase, total bilirubin, albumin, γ-glutamyltransferase, alanine aminotransferase, aspartate aminotransferase, IgG, and IgM; the international normalized ratio; the enhanced liver fibrosis score (calculated according to three markers of liver fibrosis [hyaluronic acid, procollagen type III amino-terminal peptide, and tissue inhibitor of matrix metalloproteinase-1]; a score <7.7 indicates no-to-mild fibrosis); liver stiffness (as measured by transient elastography [FibroScan, Echosens[19]]; scores range from 2 to 75 kPa, with higher values indicating greater liver stiffness); biomarkers of bile acid synthesis (7α-hydroxy-4-cholesten-3-one and fibroblast growth factor 19); and lipid variables (total cholesterol, low-density lipoprotein [LDL] cholesterol, high-density lipoprotein [HDL] cholesterol, very-low-density lipoprotein [VLDL] cholesterol, and triglycerides) (Table S2).

SAFETY

Safety was assessed at each visit by means of clinical assessments, evaluations that were processed at a central laboratory (including hematologic measures, blood chemical tests, and urinalysis), and reported adverse events. Adverse events were summarized according to the system organ class and preferred terms in the *Medical Dictionary for Regulatory Activities* (MedDRA), version 26.0.

STATISTICAL ANALYSIS

We calculated that enrollment of 150 patients (100 patients in the elafibranor group and 50 in the placebo group) would provide a power of at least 90%, at a two-sided alpha level of 0.05, to detect a between-group difference of 35 percentage points in the proportion of patients with a biochemical response at week 52. The primary analysis was based on data from the double-blind period, with efficacy end points assessed at week 52; safety analyses included data up to 104 weeks. The primary end point (biochemical response at week 52) and key secondary end points (normalization of alkaline phosphatase at week 52, and the change from baseline in the WI-NRS score through week 52 and through week 24) were assessed with the use of a prespecified fixed-sequence testing approach, at a two-sided alpha of 0.05, until a nonsignificant result was encountered. Other secondary end points are reported as point estimates and 95% confidence intervals, which were not adjusted for multiple testing and should not be used in place of hypothesis testing or to infer definitive treatment effects.

Analyses of the primary end point and the key secondary end point of normalization of the alkaline phosphatase level at week 52 were performed in the intention-to-treat population with the use of the exact Cochran–Mantel–Haenszel test, stratified according to the randomization factors. For these two binary end points, a composite strategy of imputation of nonresponse among patients who had intercurrent events (discontinuation of the trial regimen or use of rescue therapy for primary biliary cholangitis) before week 52 was applied. Response data for patients who did

not have intercurrent events and had missing data at week 52 were imputed with data from the closest nonmissing assessment from the double-blind period before or after the date of the theoretical week 52 visit. Details of supplementary analyses for the primary end point, including different approaches for handling missing data or intercurrent events (or both), are included in the Supplementary Appendix.

The change from baseline in the WI-NRS score through week 52 and through week 24 in patients with moderate-to-severe pruritus was compared with the use of a mixed model for repeated measures. In this model, a hypothetical strategy was applied in which any outcomes after the occurrence of intercurrent events (discontinuation of the trial regimen or the use of rescue therapy for pruritus) were considered to be missing data and handled within the model under the assumption that the patient continued the trial regimen. Missing data not related to the occurrence of an intercurrent event were similarly handled under a missing-at-random assumption.

RESULTS

TRIAL POPULATION

From September 2020 through June 2022, a total of 161 patients were randomly assigned to receive elafibranor (108 patients) or placebo (53 patients); these patients made up the intention-to-treat and safety populations (Fig. S1). The intention-to-treat population of patients with moderate-to-severe pruritus at baseline included 66 patients (44 in the elafibranor group and 22 in the placebo group). Patient demographics and clinical characteristics at baseline were similar in the elafibranor and placebo groups (Table 1). The representativeness of the trial population is shown in Table S3. Overall, 96% of the patients were women, the mean (±SD) age was 57±9 years, and the baseline mean alkaline phosphatase level was 321.9±150.9 U per liter.

PRIMARY END POINT

At week 52, a biochemical response was observed in a greater percentage of patients in the elafibranor group than in the placebo group (51% vs. 4%) — a difference of 47 percentage points (95% confidence interval [CI], 32 to 57; P<0.001). A response to elafibranor appeared to occur within 4 weeks after initiation of treatment and was maintained through 52 weeks (Fig. 1A). The results of supplementary analyses were consistent with these results (Table S4). Results of all subgroup analyses of the primary end point are shown in Figure S2.

KEY SECONDARY END POINTS

Normalization of Alkaline Phosphatase Level

Normalization of the alkaline phosphatase level at week 52 occurred in 15% of patients in the elafibranor group and in 0% of patients in the placebo group, for a difference of 15 percentage points (95% CI, 6 to 23; P=0.002). The percentage of patients with normalization of the alkaline phosphatase level was consistently higher in the elafibranor group through week 52 than in the placebo group (Fig. 1B). The results for all subgroup analyses of the normalization of the alkaline phosphatase level are presented in Figure S3.

Change from Baseline in WI-NRS Score

In patients with moderate-to-severe pruritus, the least-squares mean change in the WI-NRS score did not differ significantly between the elafibranor group and the placebo group from baseline through week 52 (–1.93 vs. –1.15; difference, –0.78; 95% CI, –1.99 to 0.42; P=0.20) and from baseline through week 24 (–1.60 vs. –1.26; difference, –0.34; 95% CI, –1.49 to 0.80) (Fig. 1C).

OTHER SECONDARY END POINTS

Among the patients with moderate-to-severe pruritus at baseline, the changes from baseline to week 52 appeared to favor elafibranor over placebo for the itch domain of the PBC-40 quality-of-life questionnaire (least-squares mean difference, –2.3; 95% CI, –4.0 to –0.7) and for the total score on the 5-D itch scale (least-squares mean difference, –3.0; 95% CI, –5.5 to –0.5). The changes in other domains of the PBC-40 questionnaire over 52 weeks were similar in the two groups (Figs. S5 and S6).

Reductions from baseline in alkaline phosphatase levels were observed in the elafibranor group within 4 weeks after initiation of treatment and appeared to be sustained at levels lower than those in the placebo group through week 52, with a between-group estimated percentage-point difference of –40.6±5.3 (95% CI, –47.8 to –33.5) (Fig. 1D and Fig. S4). Changes from baseline to week 52 in liver-related variables and immunoglobulins are shown in Table 2.

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

Characteristic	Elafibranor Group (N=108)	Placebo Group (N=53)	Total (N=161)
Age — yr	57.5±8.4	56.4±9.3	57.1±8.7
Female sex — no. (%)	102 (94)	52 (98)	154 (96)
White race — no. (%)†	101 (94)	46 (87)	147 (91)
Time since diagnosis — yr	7.9±5.9	8.3±6.8	8.0±6.2
Alkaline phosphatase			
Mean — U/liter	321.3±121.9	323.1±198.6	321.9±150.9
>3× ULN — no. (%)‡	43 (40)	20 (38)	63 (39)
Total bilirubin — μmol/liter§	9.7±5.1	9.4±5.0	9.6±5.1
Aspartate aminotransferase — U/liter	45.0±24.2	47.2±32.8	45.7±27.2
Alanine aminotransferase — U/liter	49.3±29.4	50.3±38.7	49.6±32.6
γ-Glutamyltransferase — U/liter	213.3±186.1	220.0±220.3	215.5±197.4
Concurrent ursodeoxycholic acid — no. (%)	102 (94)	51 (96)	153 (95)
WI-NRS score¶			
Mean	3.3±2.8	3.2±2.9	3.3±2.8
Moderate-to-severe pruritus — no. (%)‖	44 (41)	22 (42)	66 (41)
Liver stiffness**			
Mean — kPa	9.9±7.8	10.7±8.9	10.1±8.2
>10.0 kPa — no./total no. (%)	31/104 (30)	17/50 (34)	48/154 (31)
Bridging fibrosis or cirrhosis — no./total no. (%)††	12/31 (39)	8/16 (50)	20/47 (43)
Liver stiffness >10 kPa or bridging fibrosis (or both) or cirrhosis — no./total no. (%)**††	35/104 (34)	19/50 (38)	54/154 (35)

* Plus–minus values are means ±SD.
† Race was reported by the patients. All countries and sites used the same categories to determine race.
‡ The upper limit of the normal range (ULN) for the alkaline phosphatase level is 104 U per liter for women and 129 U per liter for men.
§ The ULN for the total bilirubin level is 20.5 μmol per liter for men and women.
¶ Shown are the mean baseline scores for intensity of itch (scores range from 0 [no itch] to 10 [worst itch imaginable]) as assessed on the Worst Itch Numeric Rating Scale (WI-NRS) reported over the 14 days preceding randomization.
‖ Moderate-to-severe pruritus was defined as a score of greater than or equal to 4 on the WI-NRS.
** Liver stiffness was assessed by means of vibration-controlled transient elastography; scores range from 2 to 75 kPa, with higher values indicating greater liver stiffness.
†† The presence or absence of bridging fibrosis or cirrhosis was determined by histologic findings in the patients who underwent a liver biopsy.

At week 52, levels of 7α-hydroxy-4-cholesten-3-one and fibroblast growth factor-19 appeared to be lower in patients who received elafibranor than in those who received placebo (Table 2). The levels of total cholesterol, LDL cholesterol, VLDL cholesterol, and triglycerides were lower in patients who received elafibranor than in those who received placebo within 4 weeks after baseline (Fig. S7). Lower levels of triglycerides and VLDL cholesterol with elafibranor than with placebo were sustained through week 52. HDL cholesterol levels remained stable with elafibranor treatment from baseline through week 52.

SAFETY AND ADVERSE EVENTS

Similar percentages of patients in the two groups had adverse events, adverse events considered to be related to the trial regimen, severe or serious adverse events, or adverse events leading to discontinuation of elafibranor or placebo. Adverse events occurring in more than 10% of patients and more frequently in patients receiving elafibranor than in those receiving placebo were predominantly gastrointestinal in nature, including abdominal pain, diarrhea, nausea, and vomiting (Table 3). The majority of adverse events were of mild or moderate intensity, and no patients re-

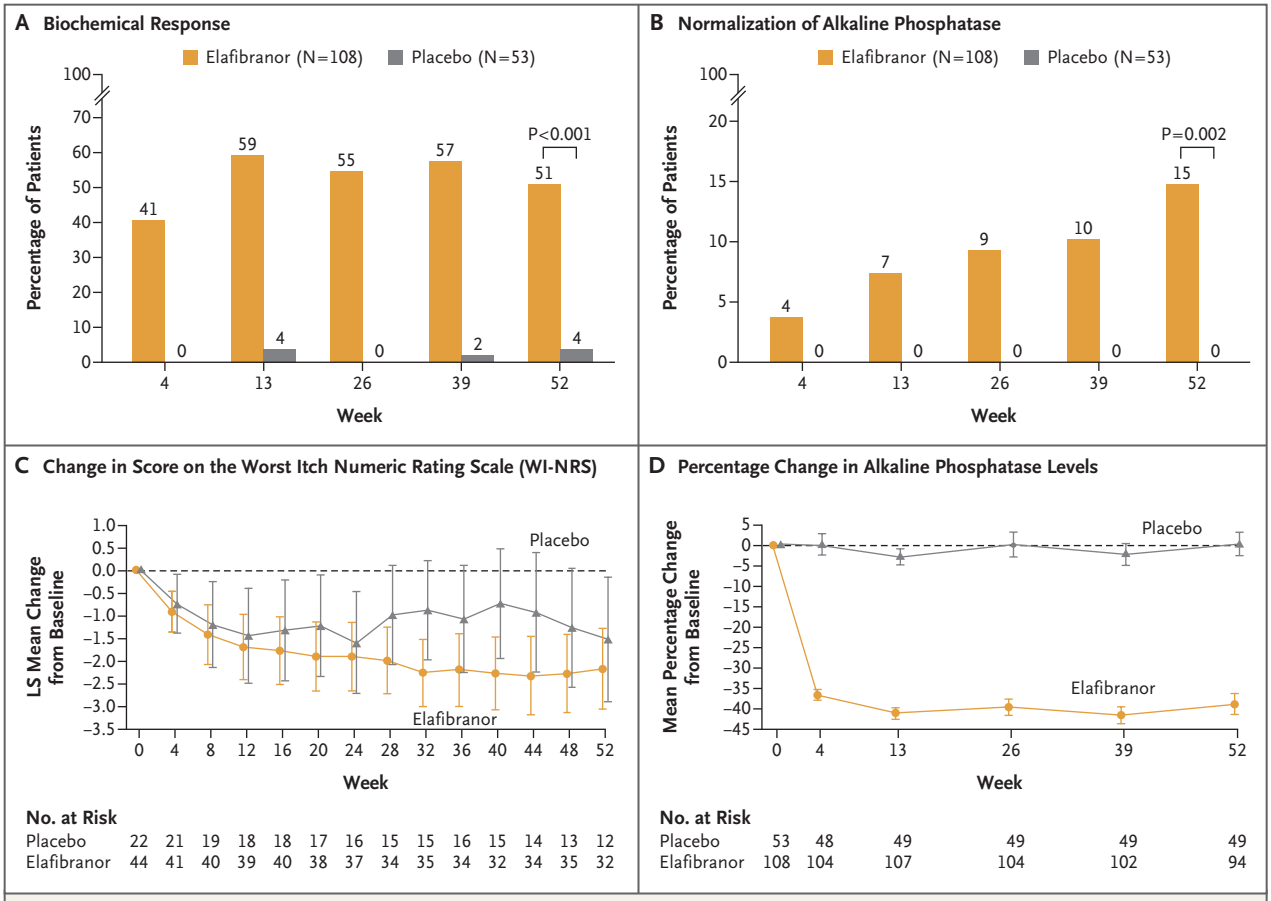

Figure 1. Primary and Secondary End Points.

Panel A shows the percentage of patients who had a biochemical response (the primary end point), defined as alkaline phosphatase levels of less than 1.67 times the upper limit of the normal range (ULN) (104 U per liter for women and 129 U per liter for men), with a reduction of at least 15% from baseline, and total bilirubin levels at or below the ULN, from week 4 through week 52. Panel B shows the percentage of patients with normalization of the alkaline phosphatase level from week 4 through week 52 (a key secondary end point). The P values in Panels A and B were calculated with the use of the Cochran–Mantel–Haenszel test, stratified according to the randomization factors. A composite strategy of imputation of nonresponse among patients who had intercurrent events (discontinuation of the trial regimen or use of rescue therapy for primary biliary cholangitis) before week 52 was applied. Missing responses that were not due to an intercurrent event were imputed with data from the closest nonmissing assessment from the double-blind period before or after the visit date. Panel C shows the least-squares (LS) mean change from baseline in the WI-NRS average score (scores range from 0 [no itch] to 10 [worst itch imaginable]) in patients with moderate-to-severe pruritus over time (a key secondary end point). Analyses were performed with the use of a mixed model for repeated measures, with terms for treatment, visits (4-week periods until week 52), and treatment-by-visit interaction as fixed factors and with adjustment for baseline WI-NRS values and the stratification factor of alkaline phosphatase greater than 3 times the ULN or total bilirubin above the ULN. An unstructured correlation matrix was used to model within-patient variability. The WI-NRS scores for patients who discontinued the trial regimen early or received a rescue therapy for pruritus were considered to be missing data and were handled within the model itself (missing-at-random assumption). I bars indicate 95% confidence intervals. Panel D shows the mean percentage change from baseline in alkaline phosphatase levels over time (a secondary end point); raw data are summarized here and are presented as collected data. I bars indicate standard errors.

ceiving elafibranor had severe pruritus. All adverse events occurring more frequently in patients receiving elafibranor than in those receiving placebo and all serious adverse events are shown in Tables S5 and S6, respectively.

Elevated creatine phosphokinase levels and muscle injury were more common in patients receiving elafibranor than in those receiving placebo. Elevated levels of creatine phosphokinase (>5 times the ULN with or without associated symptoms, or >3 times the ULN in the presence of associated symptoms) led to permanent dis-

Table 2. Changes from Baseline through Week 52 in Laboratory Data and Noninvasive Markers of Fibrosis.*

Variable	Elafibranor Group (N = 108)		Placebo Group (N = 53)		Difference (95% CI)
	LS Mean Change from Baseline (95% CI)	No. of Patients with Data (%)	LS Mean Change from Baseline (95% CI)	No. of Patients with Data (%)	
Alkaline phosphatase — U/liter	−117.0 (−134.4 to −99.6)	94 (87)	−5.3 (−30.4 to 19.7)	47 (89)	−111.7 (−142.0 to −81.3)
Total bilirubin — μmol/liter	−0.1 (−1.0 to 0.7)	93 (86)	1.1 (−0.1 to 2.4)	47 (89)	−1.3 (−2.8 to 0.2)
Albumin — g/liter	0.7 (0.1 to 1.2)	94 (87)	−0.9 (−1.7 to −0.1)	47 (89)	1.6 (0.7 to 2.6)
International normalized ratio	0.04 (0.01 to 0.06)	95 (88)	0.02 (−0.02 to 0.06)	46 (87)	0.01 (−0.03 to 0.06)
γ-Glutamyltransferase — U/liter	−47.6 (−67.5 to −27.7)	94 (87)	−17.4 (−46.3 to 11.5)	47 (89)	−30.2 (−65.1 to 4.8)
Alanine aminotransferase — U/liter	−9.3 (−13.4 to −5.1)	94 (87)	−5.4 (−11.4 to 0.5)	47 (89)	−3.8 (−11.0 to 3.4)
Aspartate aminotransferase — U/liter	−1.3 (−5.1 to 2.5)	94 (87)	−3.2 (−8.6 to 2.2)	47 (89)	1.9 (−4.6 to 8.5)
IgG — g/liter	−0.4 (−0.7 to −0.1)	95 (88)	0.3 (−0.1 to 0.8)	46 (87)	−0.7 (−1.2 to −0.2)
IgM — g/liter	−0.6 (−0.7 to −0.4)	95 (88)	0.03 (−0.2 to 0.3)	46 (87)	−0.6 (−0.9 to −0.3)
7-α-Hydroxy-4-cholesten-3-one — μg/ml	−7.2 (−10.1 to −4.2)	61 (56)	−2.0 (−6.2 to 2.3)	30 (57)	−5.2 (−10.3 to −0.1)
Fibroblast growth factor-19 — pg/ml	−22.8 (−70.8 to 25.2)	73 (68)	64.2 (−4.3 to 132.6)	36 (68)	−87.0 (−170.4 to −3.5)
Enhanced liver fibrosis score†	0.1 (−0.1 to 0.2)	89 (82)	0.2 (0.0 to 0.3)	44 (83)	−0.1 (−0.3 to 0.1)
Liver stiffness — kPa	0.2 (−0.9 to 1.3)	90 (83)	0.3 (−1.4 to 1.9)	44 (83)	−0.1 (−2.1 to 1.9)

* Analyses were performed with the use of a mixed model for repeated measures, with treatment, visits (until week 52), and treatment-by-visit interaction as fixed factors and with adjustment for baseline values and stratification factors. LS denotes least-squares.

† The enhanced liver fibrosis score was calculated according to three markers of liver fibrosis (hyaluronic acid, procollagen type III amino-terminal peptide, and tissue inhibitor of matrix metalloproteinase-1). An enhanced liver fibrosis score of less than 7.7 indicates no-to-mild fibrosis.

Table 3. Summary of Adverse Events and Adverse Events Occurring in More than 10% of Patients in Either Group.

Event	Elafibranor (N = 108)	Placebo (N = 53)
	no. of patients (%)	
Any adverse event that emerged during treatment period*	104 (96)	48 (91)
Covid-19	31 (29)	20 (38)
Pruritus	22 (20)	14 (26)
Abnormal weight gain	21 (19)	10 (19)
Abdominal pain, including upper and lower abdomen	12 (11)	3 (6)
Diarrhea	12 (11)	5 (9)
Nausea	12 (11)	3 (6)
Urinary tract infection	12 (11)	10 (19)
Vomiting	12 (11)	1 (2)
Fatigue	10 (9)	7 (13)
Headache	9 (8)	6 (11)
Back pain	4 (4)	6 (11)
Any severe adverse event†	12 (11)	6 (11)
Any adverse event attributed to the trial regimen that emerged during treatment period‡	42 (39)	21 (40)
Any serious adverse event that emerged during treatment period§	11 (10)	7 (13)
Any adverse event leading to discontinuation of the trial regimen that emerged during treatment period	11 (10)	5 (9)
Any fatal adverse event	2 (2)	0

* Adverse events that emerged during the treatment period were defined as any adverse event with an onset on or after the date of the first administration of elafibranor or placebo and up to the date of the last double-blind data collection for patients who completed the double-blind period and continued in the long-term extension period, and up to 30 days after the date of the last dose of elafibranor or placebo was received among the patients who discontinued the trial regimen during the double-blind period; or any event with a start date before the first dose of elafibranor or placebo was administered for which the severity worsened in intensity on or after the date of the first dose and up to the date of the last double-blind data collection among patients who completed the double-blind period and continued in the long-term extension period, and up to 30 days after the date of the last dose of elafibranor or placebo was received among the patients who discontinued their trial regimen during the double-blind period.

† Severe adverse events were defined as adverse events that caused an interruption in normal activities of daily living and generally required systemic drug therapy or other treatment; these adverse events were usually incapacitating.

‡ Adverse events attributed to the trial regimen that emerged during the treatment period included any adverse events that were determined by the investigator to be "possibly related" or "related" to elafibranor or placebo, or in cases for which relatedness to the trial regimen was either not assessable or missing.

§ Serious adverse events that emerged during the treatment period were defined as any untoward medical occurrence that at any dose resulted in death, was life-threatening, required in-patient hospitalization or prolongation of existing hospitalization, resulted in persistent or significant disability or incapacity, or was determined to be a congenital anomaly or birth defect.

continuation of the trial regimen (in accordance with protocol requirements) in four patients (3.7%) in the elafibranor group, as compared with no patients in the placebo group. Among the four patients who discontinued treatment with elafibranor, two were receiving concomitant statin therapy, one had coexisting chronic kidney disease, and one had coexisting autoimmune thyroiditis. The elevations were associated with myalgia in two patients. An additional patient who had advanced cirrhosis and was receiving elafibranor and concomitant atorvastatin at a dose of 40 mg once daily had a serious case of rhabdomyolysis.

One patient in the elafibranor group (0.9%) and two patients in the placebo group (3.8%) had elevated levels of aminotransferases (>3 times the baseline value if baseline was elevated or >3 times or 5 times the ULN if the baseline value was normal) or bilirubin (>2 times the ULN), or both, that met the protocol-defined thresholds

for consideration of potential drug-induced liver injury and for report to the clinical events committee. The event in the elafibranor group was adjudicated as a possible drug-induced liver injury, and the events in the placebo group were adjudicated as probable drug-induced liver injuries. Elevated levels of aminotransferases led to permanent discontinuation in accordance with protocol requirements in two patients (one in each group). All cases of elevated aminotransferases levels were reversible, and the levels returned to or trended toward baseline levels after discontinuation of the trial regimen. Table S7 shows the results of a customized group of MedDRA queries for preferred terms related to hepatic injury.

The mean change from baseline through week 52 in the serum creatinine level was −0.01±8.0 μmol per liter in patients receiving elafibranor and −0.7±7.6 μmol per liter in those receiving placebo. Increases in serum creatinine levels of 25% above baseline values were observed in 11 patients receiving elafibranor (10.2%) and in 4 patients receiving placebo (7.5%); these increases were not associated with corresponding changes in cystatin C or estimated glomerular filtration rate, which was calculated with the use of the Chronic Kidney Disease Epidemiology Collaboration cystatin C formula. Acute kidney injury was reported in 3 patients receiving elafibranor (2.8%) and in 1 receiving placebo (1.9%).

Fatal adverse events occurred in 2 patients receiving elafibranor (1.9%); 1 patient died from postoperative complications after elective surgery for an abdominal hernia repair, and 1 patient who had end-stage liver disease died from biliary sepsis and acute kidney injury. Neither event was considered by the investigators or an independent clinical events committee to be related to treatment.

DISCUSSION

Patients enrolled in the ELATIVE trial had primary biliary cholangitis and had had an inadequate response to or unacceptable side effects with ursodeoxycholic acid. Among these patients, 35% had a liver stiffness measurement of greater than 10 kPa and bridging fibrosis or cirrhosis (or both),[20] and 39% had an alkaline phosphatase level greater than 3 times the ULN at baseline. After 52 weeks, a biochemical response indicative of a reduction in cholestasis was observed in 51% of patients in the elafibranor group and in 4% of patients in the placebo group. The improvement in biochemical response is consistent with previous reports for other PPAR-targeting therapies in primary biliary cholangitis.[12,21-23] In this trial, rapid and sustained reductions in the alkaline phosphatase level were observed in patients receiving elafibranor. Normalization of alkaline phosphatase, which has been associated with improved transplantation-free survival,[24-26] also occurred in a significantly greater proportion of patients who received elafibranor than in those who received placebo.

Pruritus is among the most common symptoms reported by patients with primary biliary cholangitis and can negatively impact quality of life.[27,28] In the ELATIVE trial, the WI-NRS score did not differ significantly between the elafibranor group and the placebo group. Analyses of secondary end points showed possible reductions in moderate-to-severe pruritus, according to scores on the itch domain of the PBC-40 questionnaire and the 5-D itch scale, after 52 weeks of treatment with elafibranor. This finding is in contrast to that with obeticholic acid, which has been shown to exacerbate pruritus.[8] Dyslipidemia is also common among patients with primary biliary cholangitis.[29] In patients treated with elafibranor, reduced levels of triglycerides and VLDL cholesterol and stable levels of LDL cholesterol and HDL cholesterol were observed. In contrast, among patients treated with obeticholic acid, increases in the levels of total cholesterol and LDL cholesterol and decreases in the level of HDL cholesterol have been observed.[30]

The safety profile of elafibranor in this trial was consistent with that observed in the wider clinical development program, in which more than 1600 patients with chronic liver diseases have received elafibranor.[13,31,32] Four patients discontinued treatment with elafibranor because of increased creatine phosphokinase levels. Pharmacokinetic exposure to atorvastatin is 11 times as high in patients with Child–Pugh class B liver cirrhosis as in those with less advanced cirrhosis,[33] which increases the risk of rhabdomyolysis associated with statin exposure,[34] as was observed in 1 patient with cirrhosis who received elafibranor and concomitant atorvastatin with no dose adjustments made on the basis of hepatic function.[35] No clinically meaningful changes in renal function were observed.

The majority of patients enrolled in this trial were White, and although this feature aligns with the general epidemiology of the disease,[36] racial minorities appeared to be underrepresented and ethnicity was not recorded. The ongoing open-label extension and confirmatory phase 3 trial (ClinicalTrials.gov number, NCT06016842) are assessing additional data on the long-term safety of elafibranor and effects on clinical outcomes. The results of the current trial showed that elafibranor may provide an effective, new second-line treatment for patients with primary biliary cholangitis.

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APPENDIX

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