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DOI:
10.1056/NEJMoa1509840

Document Version
Publisher's PDF, also known as Version of record

Citation for published version (Harvard):
Nevens, F, Andreone, P, Mazzella, G, Strasser, SI, Bowlus, C, Invernizzi, P, Drenth, JPH, Pockros, PJ, Regula, J, Beuers, U, Trauner, M, Jones, DE, Floreani, A, Hohenester, S, Luketic, V, Shiffman, M, van Erpecum, KJ, Vargas, V, Vincent, C, Hirschfield, GM, Shah, H, Hansen, B, Lindor, KD, Marschall, H-U, Kowdley, KV, Hooshmand-Rad, R, Marmon, T, Sheeron, S, Pencek, R, MacConell, L, Pruzanski, M, Shapiro, D & POISE Study Group 2016, 'A Placebo-Controlled Trial of Obeticholic Acid in Primary Biliary Cholangitis', *The New England Journal of Medicine*, vol. 375, no. 7, pp. 631-43. https://doi.org/10.1056/NEJMoa1509840

ORIGINAL ARTICLE

A Placebo-Controlled Trial of Obeticholic Acid in Primary Biliary Cholangitis

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ABSTRACT

BACKGROUND

Primary biliary cholangitis (formerly called primary biliary cirrhosis) can progress to cirrhosis and death despite ursodiol therapy. Alkaline phosphatase and bilirubin levels correlate with the risk of liver transplantation or death. Obeticholic acid, a farnesoid X receptor agonist, has shown potential benefit in patients with this disease.

METHODS

In this 12-month, double-blind, placebo-controlled, phase 3 trial, we randomly assigned 217 patients who had an inadequate response to ursodiol or who found the side effects of ursodiol unacceptable to receive obeticholic acid at a dose of 10 mg (the 10-mg group), obeticholic acid at a dose of 5 mg with adjustment to 10 mg if applicable (the 5–10-mg group), or placebo. The primary end point was an alkaline phosphatase level of less than 1.67 times the upper limit of the normal range, with a reduction of at least 15% from baseline, and a normal total bilirubin level.

RESULTS

Of 216 patients who underwent randomization and received at least one dose of obeticholic acid or placebo, 93% received ursodiol as background therapy. The primary end point occurred in more patients in the 5–10-mg group (46%) and the 10-mg group (47%) than in the placebo group (10%; P<0.001 for both comparisons). Patients in the 5–10-mg group and those in the 10-mg group had greater decreases than those in the placebo group in the alkaline phosphatase level (least-squares mean, –113 and –130 U per liter, respectively, vs. –14 U per liter; P<0.001 for both comparisons) and total bilirubin level (–0.02 and –0.05 mg per deciliter [–0.3 and –0.9 μmol per liter], respectively, vs. 0.12 mg per deciliter [2.0 μmol per liter]; P<0.001 for both comparisons). Changes in noninvasive measures of liver fibrosis did not differ significantly between either treatment group and the placebo group at 12 months. Pruritus was more common with obeticholic acid than with placebo (56% of patients in the 5–10-mg group and 68% of those in the 10-mg group vs. 38% in the placebo group). The rate of serious adverse events was 16% in the 5–10-mg group, 11% in the 10-mg group, and 4% in the placebo group.

CONCLUSIONS

Obeticholic acid administered with ursodiol or as monotherapy for 12 months in patients with primary biliary cholangitis resulted in decreases from baseline in alkaline phosphatase and total bilirubin levels that differed significantly from the changes observed with placebo. There were more serious adverse events with obeticholic acid. (Funded by Intercept Pharmaceuticals; POISE ClinicalTrials.gov number, NCT01473524; Current Controlled Trials number, ISRCTN89514817.)

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*A complete list of members of the PBC OCA International Study of Efficacy (POISE) Study Group is provided in the Supplementary Appendix, available at NEJM.org.

This article was updated on August 18, 2016, at NEJM.org.

N Engl J Med 2016;375:631-43.
DOI: 10.1056/NEJMoa1509840

Primary biliary cholangitis, formerly called primary biliary cirrhosis,[1-5] is a rare autoimmune liver disease (prevalence of approximately 20 to 40 cases per 100,000 persons) that predominantly affects women.[6-8] It is characterized by inflammation and progressive destruction of interlobular bile ductules, cholestasis that provokes debilitating fatigue and itch, eventual cirrhosis, end-stage liver disease, and death.[7] Elevated alkaline phosphatase and γ-glutamyltransferase (GGT) levels are early biochemical signs of primary biliary cholangitis; the bilirubin level increases with advanced disease.[7] Higher levels of alkaline phosphatase and bilirubin levels correlate with disease progression, and lower levels are predictive of survival without the need for liver transplantation.[9,10] In a large, international cohort analysis involving patients with primary biliary cholangitis, elevations in the alkaline phosphatase level were independently associated with a risk of liver transplantation or death that was 2.0 to 2.5 times as high as the risk associated with normal levels.[10] An abnormally elevated bilirubin level, which occurs later in disease progression, was a stronger predictor of outcomes, with a risk of liver transplantation or death that was 5.1 to 10.7 times the risk associated with normal levels; however, even increased values within the normal range were associated with a risk of disease progression.[10]

The only approved treatment for primary biliary cholangitis was ursodiol, which decreases liver biochemical values and delays the time to liver transplantation.[7,8] However, an abnormally elevated level of alkaline phosphatase persists in many patients, and mortality is significantly higher among these patients than in the general population; therefore, there is an unmet need for additional therapeutic options for patients with primary biliary cholangitis.[9]

Obeticholic acid is a selective farnesoid X receptor (FXR) agonist that is derived from the bile acid chenodeoxycholic acid, the endogenous FXR ligand. Obeticholic acid has approximately 100 times greater potency in activating FXR than chenodeoxycholic acid.[11] FXR signaling protects hepatocytes against bile acid toxicity by impairing bile acid synthesis and stimulating choleresis by means of up-regulation of bile acid transporters.[12] In addition, FXR regulates other pathways with direct antiinflammatory and antifibrotic effects.[13-15]

In two 12-week phase 2 studies, daily doses of up to 50 mg of obeticholic acid resulted in reductions from baseline in levels of alkaline phosphatase and bilirubin that were significantly greater than those with placebo.[16] However, dose-related increases in the incidence and severity of pruritus were evident, particularly at doses of more than 10 mg. The aim of our phase 3 trial was to assess the longer-term efficacy, safety, and adverse-event profile of obeticholic acid in patients with primary biliary cholangitis who were receiving daily doses of 5 mg or 10 mg.

METHODS

PARTICIPANTS

Patients 18 years of age or older who had received a diagnosis of primary biliary cholangitis[7,8] were recruited at 59 sites in 13 countries (see the Supplementary Appendix, available with the full text of this article at NEJM.org). Entry criteria were an alkaline phosphatase level of at least 1.67 times the upper limit of the normal range or an abnormal total bilirubin level of less than 2 times the upper limit of the normal range. The first patient was enrolled in March 2012, and the last patient completed the double-blind phase in December 2013.

TRIAL DESIGN

The PBC OCA International Study of Efficacy (POISE) was a randomized, double-blind, placebo-controlled, parallel-group, 12-month phase 3 trial. Patients were randomly assigned, in a 1:1:1 ratio, to receive once-daily oral placebo, obeticholic acid at an initial dose of 5 mg with adjustment to 10 mg if applicable (the 5–10-mg group), or obeticholic acid at a dose of 10 mg (the 10-mg group), all of which were added to standard-of-care ursodiol (at a daily dose of 13 to 15 mg per kilogram of body weight) or administered alone in patients who had unacceptable side effects from ursodiol (patients who were not receiving ursodiol had to have not received ursodiol for ≥3 months before enrollment). Randomization was stratified according to Paris 1 risk criteria (an alkaline phosphatase level >3 times the upper limit of the normal range, an aspartate aminotransferase level >2 times the upper limit of the normal range, or a bilirubin level above the upper limit of the normal range)[17] and according to the use or nonuse of ursodiol. Patients who were assigned to the 5–10-mg group initially received obeticholic acid at a dose of 5 mg for 6 months, after which time the dose was

increased to 10 mg on the basis of the side-effect profile and biochemical response; if patients had adverse events such as severe pruritus or had already met the primary composite end point, their dose was not increased. All patients who entered the 5-year open-label extension phase after completing the double-blind phase received obeticholic acid at a dose of 5 mg (including those who been taking 10 mg in the double-blind phase) for the first 3 months, after which time dose could be increased.

TRIAL OVERSIGHT

The protocol, available at NEJM.org, was approved by appropriate local and national ethics and regulatory agencies and was conducted in accordance with Good Clinical Practice guidelines and the Declaration of Helsinki (Seoul, South Korea, October 2008 amendment). All the patients provided written informed consent. Details regarding trial oversight and author contributions are provided in the Supplementary Appendix. The authors vouch for the accuracy and completeness of the data and analyses reported and for the fidelity of this report to the protocol. Employees of the funder (Intercept Pharmaceuticals) assisted with the writing and internal review of the manuscript. The funder participated in each of the tasks outlined above in collaboration with the academic investigators (Section 2.1 of the Supplementary Appendix). The final decision to submit the manuscript was made by the members of the publication steering committee, which included the last author, who is an employee of the funder.

PRIMARY, SECONDARY, AND EXPLORATORY END POINTS

The primary composite end point was an alkaline phosphatase level of less than 1.67 times the upper limit of the normal range, with a reduction of at least 15% from baseline, and a total bilirubin level at or below the upper limit of the normal range at 12 months. Secondary efficacy end points included levels of alkaline phosphatase, GGT, alanine aminotransferase, aspartate aminotransferase, total and conjugated bilirubin, and albumin; prothrombin time; international normalized ratio; plasma bile acid levels; level of fibroblast growth factor 19 (FGF-19), an enterokine released after FXR activation; inflammation, as assessed by high-sensitivity C-reactive protein (CRP) and tumor necrosis factor α (TNF-α) levels; interleukin-6 level; transforming growth factor β (TGF-β) level; liver apoptosis, as assessed by the cleaved cytokeratin 18 level; serum autotaxin level; and noninvasive measures of fibrosis, such as transient elastography[18] and the enhanced liver fibrosis score[19] (including the components of levels of hyaluronic acid, procollagen type III N-terminal peptide [P3NP], and tissue inhibitor of metalloproteinase 1 [TIMP-1]). Other secondary end points included results of categorical analyses of alkaline phosphatase levels and biochemical-response criteria; symptoms, as assessed by the primary biliary cirrhosis–40 (PBC-40) questionnaire (a disease-specific quality-of-life questionnaire)[20]; and a patient-research questionnaire. For patients who had undergone liver biopsy at baseline, a repeat biopsy is planned to be performed after 3 years of treatment with obeticholic acid.

Additional secondary analyses focused on the pharmacokinetics and pharmacodynamics of obeticholic acid, the effect on the bile acid pool, and the effect of bile acid sequestrants (data not reported here). Exploratory end points included IgA, IgG, IgM, interleukin-12, and interleukin-23 levels. A genetics study is planned in a subgroup of patients after they receive obeticholic acid for 3 years. Assessments of safety and side effects included adverse events, laboratory variables, a visual-analogue scale for pruritus,[21] the 5-D pruritus questionnaire (measuring the degree, duration, direction [improvement or worsening], disability [effect on daily activities], and distribution of itching),[22] dual energy x-ray absorptiometry (DEXA), electrocardiography, physical examination, and vital signs. A post hoc analysis to assess the correlation between the autotaxin level and the severity of patient-reported pruritus was also performed. Relevant methods and domain ranges are summarized in the Supplementary Appendix.

STATISTICAL ANALYSIS

An analysis of the primary end point was performed in the phase 2 trial, in which obeticholic acid was added to ursodiol therapy[16]: 9% of the patients in the placebo group and 40% of those who were assigned to receive 10 mg of obeticholic acid had a positive response. We then calculated the sample size using more conservative numbers. Assuming a rate of response of 14% in the placebo group and of 40% in the group that received 10 mg of obeticholic acid, on the basis of a two-sided test of equality of binomial proportions at an alpha

level of 5%, we calculated that a sample of 60 patients per group would provide the trial with 90% power to detect a significant difference between the 10-mg group and the placebo group.

Statistical testing was two-sided and was performed at the 0.05 alpha level. The analyses of the composite end point and of response were performed with the use of a Cochran–Mantel–Haenszel test that was stratified according to the randomization stratification factors for the intention-to-treat population. Missing values were considered in the analyses as nonresponse. For the primary end point, multiple comparisons were accounted for with the use of a sequential closed gatekeeping method; if the P value was less than 0.05 for the primary comparison between the 10-mg group and the placebo group, testing of the 5–10-mg group would be considered to be confirmatory. There was no prespecified plan for the adjustment for multiple comparisons in the analyses of secondary outcomes.

Results of laboratory tests, transient elastography, enhanced liver fibrosis tests, and the PBC-40 questionnaire were compared between the obeticholic acid groups and the placebo group with the use of an analysis of covariance (ANCOVA) model with changes from baseline as the dependent variable, treatment group and randomization stratification factors as fixed effects, and baseline value as a covariate. Markers of immunity, inflammation, apoptosis, and the FGF-19 level were not normally distributed; differences between the trial groups were therefore compared with the use of a Wilcoxon rank-sum test and Hodges–Lehmann estimates of median differences between the treatment groups and the placebo group.

Adverse events were summarized according to the *Medical Dictionary for Regulatory Activities* (MedDRA) System Organ Class, the MedDRA preferred term, severity (as defined in the protocol), and causal relationship (as assessed by the individual investigators). DEXA scans were obtained at baseline and at month 12. Other safety and side-effect assessments were summarized with the use of descriptive statistics at baseline and at each visit. The visual-analogue scale and the 5-D questionnaires were analyzed with the use of an ANCOVA model, as described above. Details of additional statistical analyses and sample-size and power calculations are provided in the Supplementary Appendix.

RESULTS

TRIAL POPULATIONS

A total of 316 persons were screened for participation, of whom 217 underwent randomization; 73 patients were randomly assigned to the placebo group, 71 to the group that received obeticholic acid at an initial dose of 5 mg with adjustment to 10 mg if applicable (5–10-mg group), and 73 to the group that received 10 mg of obeticholic acid (10-mg group) (Fig. S1 and Table S1 in the Supplementary Appendix). The intention-to-treat population and the safety population included all patients who underwent randomization and received at least one dose of obeticholic acid or placebo (216 patients; 1 patient from the 5–10-mg group withdrew).

The trial groups were balanced at baseline. As is typical of the demographic characteristics of patients with primary biliary cholangitis, 91% of the participants were female and 94% were white; the mean age of the patients was 56 years (Table 1). A total of 93% of the patients took ursodiol at baseline and throughout the trial. A total of 63% of the patients had a history of disease-related pruritus, and 59% reported pruritus at baseline. Approximately 20% of the patients who underwent transient elastography had a value that was indicative of cirrhosis (≥16.9 kPa).[18]

PRIMARY END POINT

On a background of standard of care, the rate of the primary end point was higher in the 5–10-mg group (46%) and in the 10-mg group (47%) than in the placebo group (10%) at month 12 (P<0.001 for both comparisons) (Fig. 1). Response to obeticholic acid was rapid, with a significant difference observed between each obeticholic acid group and the placebo group by week 2 and at each time point thereafter in the double-blind phase (P<0.001 for all comparisons) (Fig. 1).

SECONDARY END POINTS

The reduction in the alkaline phosphatase level was greater in each obeticholic acid group than in the placebo group at all visits, with significantly greater reductions from baseline at 12 months (least-squares mean [±SE] reduction, –113±14 U per liter in the 5–10-mg group and –130±15 U per liter in the 10-mg group vs. –14±15 U per liter in the placebo group; P<0.001 for both comparisons)

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

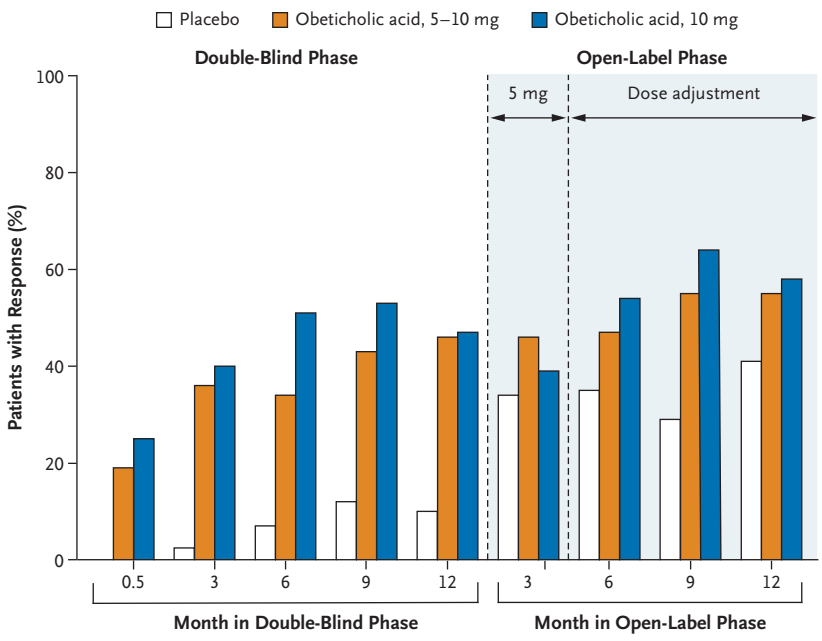
Characteristic	Placebo (N=73)	Obeticholic Acid, 5–10 mg (N=70)	Obeticholic Acid, 10 mg (N=73)
Age — yr	56±10	56±11	56±11
Female sex — no. (%)	68 (93)	65 (93)	63 (86)
White race — no. (%)†	66 (90)	67 (96)	70 (96)
Alkaline phosphatase			
Mean value — U/liter	327±115	326±116	316±104
≥1.67× ULN — no. (%)	72 (99)	69 (99)	73 (100)
Total bilirubin			
Mean value — mg/dl‡	0.69±0.42	0.60±0.33	0.66±0.39
>ULN — no. (%)	7 (10)	4 (6)	7 (10)
Ursodiol			
Use at baseline — no. (%)	68 (93)	65 (93)	67 (92)
Daily dose — mg/kg	15±4	17±5	16±5
Age at diagnosis — yr	47±9	48±12	47±11
Duration of disease — yr	8±5	8±6	9±7
Pruritus — no. (%)	47 (64)	37 (53)	44 (60)
Mayo Risk Score§	4.3±1.1	4.3±1.2	4.3±1.2
Liver stiffness¶			
Mean value — kPa	12.7±10.7	10.7±8.6	11.4±8.2
≥16.9 kPa — no./total no. (%)	7/39 (18)	7/35 (20)	6/32 (19)

* Plus–minus values are means ±SD. All patients were allowed to take ursodiol. There were no significant differences among the three groups at baseline. ULN denotes upper limit of the normal range.
† Race was self-reported.
‡ To convert values for total bilirubin to micromoles per liter, multiply by 17.1.
§ The Mayo Risk Score incorporates the patient's age, total levels of bilirubin and albumin, the prothrombin time, and the presence or absence of edema and ascites in order to estimate survival, with lower scores indicating longer survival. A score of 1.28 to 7.42 indicates a low risk of death, a score of 7.43 to 8.49 intermediate risk, a score of 8.50 to 9.09 high risk, and a score of 9.10 to 11.62 highest risk[23]; for example, a patient with a score of 10.2 has a 50% risk of death at 1 year (http://www.mayoclinic.org/medical-professionals/model-end-stage-liver-disease/updated-natural-history-model-for-primary-biliary-cirrhosis).
¶ Liver stiffness was assessed by means of transient elastography. On the basis of research by Corpechot et al.,[18] liver stiffness in patients with primary biliary cholangitis is assessed as follows: fibrosis stage F1 is associated with stiffness of 7.1 to 8.7 kPA, stage F2 with a stiffness of 8.8 to 10.6 kPA, stage F3 with a stiffness of 10.7 to 16.8 kPA, and stage F4 with a stiffness of 16.9 kPa or more. Data were missing for 34 patients in the placebo group, for 35 in the 5–10-mg group (initial dose of 5 mg, with adjustment to 10 mg, if applicable), and for 41 in the 10-mg group.

(Fig. 2A, and Table S2 in the Supplementary Appendix). In the 5–10-mg group, an incremental benefit was observed among patients who had dose adjustment from 5 mg to 10 mg at month 6, as compared with those who continued taking 5 mg (Fig. S2 in the Supplementary Appendix).

The percentage of patients who had a reduction of at least 15% from baseline in the alkaline phosphatase level was higher in the 5–10-mg group (77%) and in the 10-mg group (77%) than in the placebo group (29%) (P<0.001 for both comparisons). The total bilirubin level decreased in each treatment group, as compared with a progressive increase in the placebo group (least-squares mean, −0.02±0.04 mg per deciliter [−0.3±0.7 μmol per liter] in the 5–10-mg group and −0.05±0.04 mg per deciliter [−0.9±0.7 μmol per liter] in the 10-mg group vs. 0.12±0.04 mg per deciliter [2.0±0.7 μmol per liter] in the placebo group; P<0.001 for both comparisons) (Fig. 2B, and Table S2 in the Supplementary Appendix).

Most patients who were treated with obeticho-



No. of Patients									
Placebo	73	73	73	73	73	64	60	59	59
Obeticholic acid, 5–10 mg	70	70	70	70	70	63	62	62	60
Obeticholic acid, 10 mg	73	73	73	73	73	64	59	61	59

Figure 1. Primary Composite End Point in the Double-Blind and Open-Label Extension Phases, According to Trial Group.

The primary composite end point was an alkaline phosphatase level of less than 1.67 times the upper limit of the normal range, with a reduction of at least 15% from baseline, and a total bilirubin level at or below the upper limit of the normal range. Obeticholic acid was administered with standard-of-care ursodiol or as monotherapy (in patients who had unacceptable side effects from ursodiol). P values were calculated with the use of the Cochran–Mantel–Haenszel test, stratified according to the randomization stratification factor. P<0.001 for each obeticholic acid group versus placebo at each time point shown during the double-blind phase. All trial groups shown are those that were assigned at randomization in the double-blind phase. In the open-label extension phase, most patients initially received obeticholic acid at a dose of 5 mg; at 3 months, and every 3 months thereafter, patients had the option to increase the dose up to 10 mg.

lic acid had reductions in liver biochemical measurements even if they did not meet the criteria for the primary end point (Fig. S3 in the Supplementary Appendix). Both obeticholic acid groups had results that were superior to those in the placebo group with regard to all previously published composite biochemical-response criteria except one (total bilirubin level at or below the upper limit of the normal range and albumin level at or above the lower limit of the normal range)[24] (Fig. S4 in the Supplementary Appendix). The levels of GGT, alanine aminotransferase, aspartate aminotransferase, and conjugated bilirubin decreased from baseline in each obeticholic acid group; in each case, the changes with obeticholic acid differed significantly from the changes with placebo (P<0.001 for both comparisons) (Table S2 and Fig. S5 in the Supplementary Appendix). There were no significant differences between the treatment groups and the placebo group in the differences in change in the albumin level, prothrombin time, and the international normalized ratio from baseline to 12 months (Table S3 in the Supplementary Appendix).

As compared with the changes from baseline with placebo, significant decreases from baseline in bile acid levels and dose-dependent increases from baseline in the FGF-19 level were observed in each obeticholic acid group (P<0.01 for all comparisons), findings that are consistent with FXR activation (Fig. 3). In addition, as compared with the changes from baseline with placebo,

the high-sensitivity CRP level decreased significantly from baseline in each obeticholic acid group (P<0.01 for both comparisons) and the TNF-α level decreased significantly from baseline in the 10-mg obeticholic acid group (P=0.006) (Fig. S6 and Table S4 in the Supplementary Appendix). The cleaved cytokeratin 18 level decreased significantly from baseline in each obeticholic acid group, as compared with the change from baseline in the placebo group (P<0.001 for both comparisons). The changes in the levels of interleukin-6 and TGF-β did not differ significantly between each treatment group and the placebo group. The autotaxin level decreased significantly from baseline in the 10-mg group, as compared with the change from baseline in the placebo group (P=0.03); the difference with placebo was not significant in the 5–10-mg group. Details are provided in Table S4 in the Supplementary Appendix.

Obeticholic acid did not result in any significant abatement in symptoms as measured by the PBC-40 questionnaire. Patients in the 10-mg group had significantly worse scores than those in the placebo group on the itch domain of the PBC-40 questionnaire during the initial 3 months of the trial (P=0.005 at week 2 and P<0.001 at month 3) (Fig. S7 in the Supplementary Appendix). A patient-research questionnaire that was administered at month 12 showed that 85% of the patients in the placebo group, 87% of those in the 5–10-mg group, and 92% of those in the 10-mg group considered participation in the trial to be worthwhile (Table S5 in the Supplementary Appendix).

There were no significant differences in noninvasive measures of liver fibrosis between either treatment group and the placebo group. The change from baseline to 12 months in transient elastographic findings (as assessed at centers at which a FibroScan device was available) and in the enhanced liver fibrosis score did not differ significantly between either treatment group and the placebo group. The changes in the levels of hyaluronic acid and TIMP-1 (components of the enhanced liver fibrosis score) did not differ significantly between either treatment group and the placebo group; the P3NP level was significantly decreased from baseline at month 12 in the 10-mg group, as compared with the changes from baseline with placebo (P=0.04). Details are provided in Table S6 in the Supplementary Appendix.

EXPLORATORY END POINTS

The IgM level was elevated at baseline in all groups and was reduced to a greater extent in each obeticholic acid group than in the placebo group (P<0.001 for both comparisons). Reductions from baseline in the IgA and IgG levels were greater in the 10-mg group than in the placebo group (P<0.001 for both comparisons), and the reduction in the IgG level was greater in the 5–10-mg group than in the placebo group (P=0.02); the reduction in the IgA level did not differ significantly between the placebo group and the 5–10-mg group. The interleukin-12 level decreased significantly from baseline, as compared with placebo, in the 5–10-mg group (P=0.009) and in the 10-mg group (P=0.003). The change in the interleukin-23 level did not differ significantly between either treatment group and the placebo group. Details are provided in Figure S6 and Table S4 in the Supplementary Appendix.

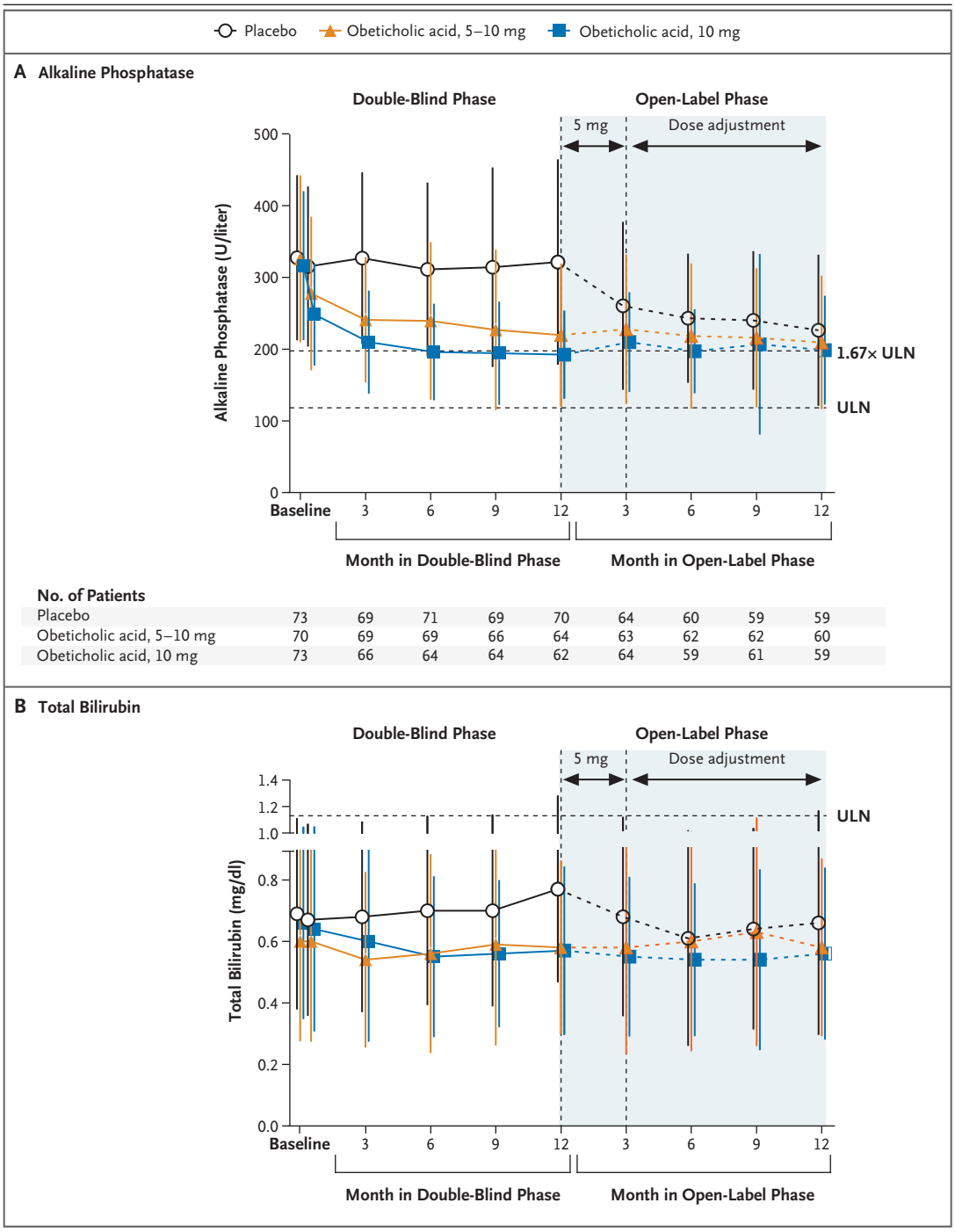
OPEN-LABEL EXTENSION

A total of 193 of 198 patients (97%) who completed the 12-month double-blind phase entered the open-label extension. Patients who had received obeticholic acid in the double-blind phase had sustained reductions in the alkaline phosphatase levels and total bilirubin levels, a finding that shows a durable response through 2 years of treatment (Fig. 2). Patients in the placebo group who initiated treatment with obeticholic acid in the open-label extension had similar efficacy to those who had received obeticholic acid in the double-blind phase, including a reversal of previous increases in the total bilirubin level to levels that were similar to baseline levels (Fig. 2, and Table S2 in the Supplementary Appendix).

SAFETY AND SIDE EFFECTS

A total of 198 of 217 patients (91%) who underwent randomization completed the double-blind phase (Fig. S1 and Table S1 in the Supplementary Appendix). Nineteen patients withdrew from the double-blind phase; 1 patient (<1%) died from an exacerbation of preexisting congestive heart failure and ischemic heart disease (as determined by hospital staff), 8 patients (4%) withdrew because of pruritus, 6 (3%) withdrew because of other adverse events, and 4 (2%) withdrew consent (Table S1 in the Supplementary Appendix).

Pruritus was the most common adverse event that occurred during the double-blind phase across



all groups, with a higher incidence reported in the 5–10-mg group (56%) and the 10-mg group (68%) than in the placebo group (38%) (Table 2). Changes from baseline in the visual-analogue scale score for pruritus and the 5-D questionnaire score were greater in the 10-mg group than in the placebo group (visual-analogue scale: P<0.001 at week 2, P=0.003 at month 3, and P=0.03 at month 6; 5-D questionnaire: P<0.001 at week 2 and P=0.005 at month 3). At month 12, the scores on the visual-analogue scale and the 5-D questionnaire did not differ significantly between either obeticholic acid group and the placebo group (Fig. S8 in the Supplementary Appendix).

Figure 2 (facing page). Alkaline Phosphatase and Total Bilirubin Levels in the Double-Blind and Open-Label Extension Phases, According to Trial Group.

Shown are the mean values of alkaline phosphatase (Panel A) and total bilirubin (Panel B) from baseline to month 12 in the open-label extension phase. Error bars indicate standard deviations. Treatment groups shown are those that were assigned at randomization in the double-blind period. All P values are for the comparison of each treatment group with placebo with respect to the least-squares mean change from baseline in the double-blind phase. In Panel A, $P<0.001$ for the comparison of each obeticholic acid group with placebo. In Panel B, $P=0.046$ for the comparison of the 5–10-mg group (initial dose at 5 mg with adjustment to 10 mg, if applicable) with placebo at month 3, $P=0.008$ for the comparison at month 6, and $P<0.001$ for the comparison at month 12; $P<0.001$ for the comparison of the 10-mg group with placebo at month 6, $P=0.003$ for the comparison at month 9, and $P<0.001$ at month 12. To convert total bilirubin values to micromoles per liter, multiply by 17.1. P values for the comparison of each treatment group with placebo with respect to the change from baseline were obtained with the use of an analysis of covariance model, with the baseline value as a covariate and with fixed effects for treatment and randomization stratification factor. ULN denotes upper limit of the normal range.

Autotaxin is the only variable that has so far been identified to correlate with the severity of cholestatic pruritus.[25] However, post hoc analysis showed no correlation between autotaxin activity and patient-reported measures of pruritus severity (according to the visual-analogue scale, 5-D questionnaire, or PBC-40 itch scores) (Fig. S9 in the Supplementary Appendix).

Among patients who reported pruritus during the double-blind phase (Table S7 in the Supplementary Appendix), the percentage of patients who received an intervention (mostly bile acid sequestrants) was similar across groups (range, 50 to 62%). Discontinuation of treatment owing to pruritus occurred in 7 patients (10%) in the 10-mg group and in 1 (1%) in the 5–10-mg group; no patient in the placebo group discontinued the trial regimen owing to pruritus.

The incidence of serious adverse events was greater in each obeticholic acid group than in the placebo group; no single serious adverse event occurred in both obeticholic acid groups, and all serious adverse events resolved without sequelae (Table S8 in the Supplementary Appendix). High-density lipoprotein (HDL) cholesterol levels decreased in patients in the two obeticholic acid groups but stabilized within the normal range and were similar to levels observed in patients in the placebo group after 12 months. At week 2, a sustained decrease from baseline in the triglyceride level and an increase from baseline in the level of low-density lipoprotein (LDL) cholesterol were observed, as compared with the changes from baseline with placebo (Fig. S10 in the Supplementary Appendix). Electrocardiographic results were similar in each treatment group and the placebo group (Table S9 in the Supplementary Appendix).

Although the rates of bone fracture were similar among the trial groups, DEXA revealed a smaller decrease in the femoral bone mineral density T score in each obeticholic acid group than in the placebo group ($P<0.05$ for both comparisons). The z score and the lumbar bone mineral density did not differ significantly between each treatment group and the placebo group (Table S10 in the Supplementary Appendix).

The safety profile that was observed with obeticholic acid during the open-label extension was similar to that in the double-blind phase (Table S8 in the Supplementary Appendix). Approximately 6 months after entering the open-label extension, one patient died (the death was attributed by hospital staff to sepsis complications related to endocarditis associated with a replacement valve). Mild-to-moderate pruritus was the most common adverse event in all the groups, although among patients who were originally randomly assigned to receive obeticholic acid, the severity and incidence were both lower in the open-label extension than in the double-blind phase. Lipid profiles were similar in the 12 month open-label extension and the double-blind phase. No incremental safety findings were observed during the open-label extension.

DISCUSSION

Obeticholic acid that was administered in addition to ursodiol or as monotherapy in patients with primary biliary cholangitis reduced alkaline phosphatase and total bilirubin levels, as well as most other evaluated markers of cholestasis, hepatocellular injury, immunity, inflammation, and apoptosis. Almost half the patients in each obeticholic acid group, as compared with 10% of those in the placebo group, met the criteria for

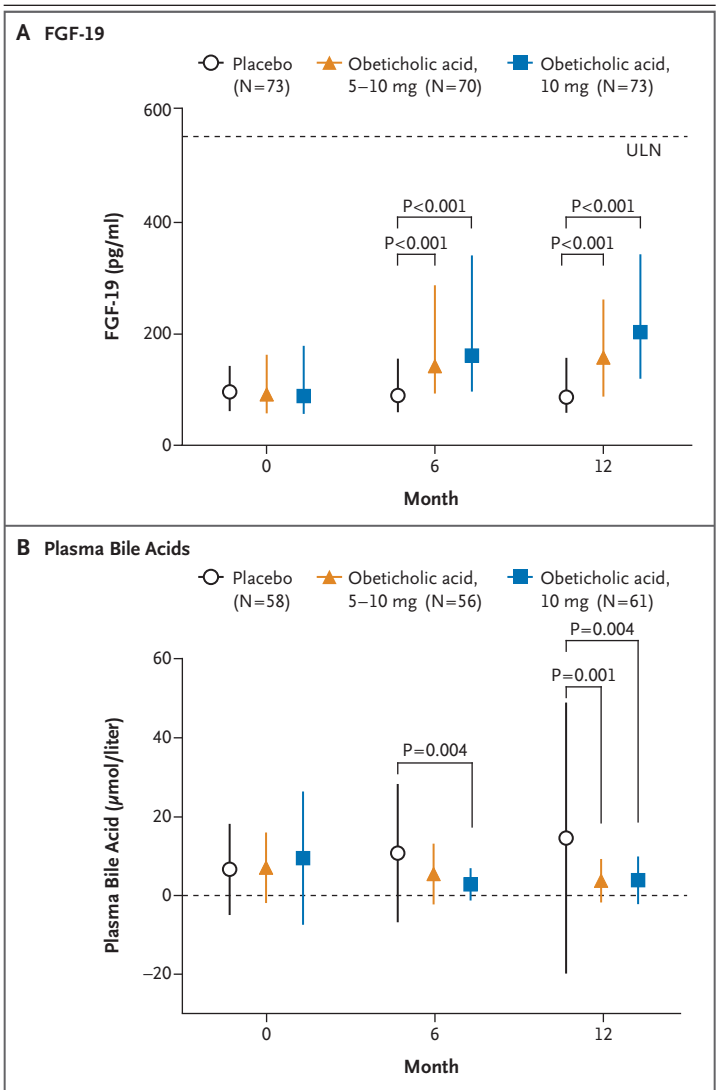


Figure 3. Farnesoid X Receptor Activation and Plasma Bile Acid Levels in the Double-Blind Phase, According to Trial Group.

The median values of fibroblast growth factor 19 (FGF-19) increased (Panel A), whereas the mean values for plasma bile acids decreased (Panel B) in the two obeticholic acid groups. Error bars in Panel A indicate the interquartile range, and those in Panel B standard deviations. For the total plasma bile acid levels, data are shown only for patients who were receiving ursodiol. P values for the comparison of each treatment group with the placebo group with respect to the change from baseline in the FGF-19 level were calculated with the use of the Wilcoxon rank-sum test. For the analysis of plasma bile acid levels, P values for the within-treatment group comparisons are from a paired Student's t-test.

the composite primary end point at the end of the double-blind phase. In the 5–10-mg group, approximately half the patients remained at the 5-mg dose level throughout the trial, and the remaining patients had doses adjusted to 10 mg after 6 months. Although the primary end point occurred at the lower dose in some patients, there was an incremental benefit observed with adjustment to the higher dose.

Liver biopsies are not routinely conducted to assess disease progression in patients with primary biliary cholangitis; therefore, noninvasive assessments of fibrosis were made in this trial with the use of transient elastography and enhanced liver fibrosis scores. Among the subgroup of patients who had transient elastography assessed (43%), obeticholic acid was not associated with significant reductions in this noninvasive measure of liver fibrosis at 12 months. Similarly, changes in the enhanced liver fibrosis scores did not differ between either obeticholic acid group and the placebo group.

Although obeticholic acid and ursodiol are structurally similar, they have distinct but complementary pharmacologic properties. Obeticholic acid acts by means of the FXR-mediated transcriptional mechanisms (as shown by the FGF-19 and bile acid levels), whereas ursodiol acts mainly through post-transcriptional mechanisms.[15] Effective daily doses of ursodiol are 13 to 15 mg per kilogram (approximately 1 g per day), which makes this drug the primary constituent of the bile acid pool during long-term administration. In contrast, obeticholic acid is effective at considerably lower doses and constitutes less than 2% of the bile acid pool at steady-state concentrations.[16]

In addition to mediating the anticholestatic and antifibrotic effects of obeticholic acid, FXR also modulates immune response and inflammation.[26] Several immune and inflammatory mediators were evaluated in an exploratory manner, and the results showed that treatment with obeticholic acid was associated with decreases in the levels of IgM (which is classically elevated in patients with primary biliary cholangitis),[7,8] IgA, IgG, interleukin-12,[27] TNF-α,[28] and high-sensitivity CRP, findings that suggest potential disease modification, although no significant between-group differences were observed in the levels of interleukin-6, interleukin-23, or TGF-β.

Pruritus was the most common adverse event across all groups in the double-blind phase, with a higher incidence reported in the 5–10-mg group (56%) and the 10-mg (68%) group than in the placebo group (38%). Although pruritus is the most common symptom in patients with primary biliary cholangitis, neither its incidence nor its sever-

Table 2. Incidence of Adverse Events of 10% or More in any Treatment Group.*

Event	Double-Blind Phase			Open-Label Extension
	Placebo (N = 73)	Obeticholic Acid, 5–10 mg (N = 70)	Obeticholic Acid, 10 mg (N = 73)	Total Obeticholic Acid (N = 193)
	number of patients (percent)			
Pruritus	28 (38)	39 (56)	50 (68)	138 (72)
Nasopharyngitis	13 (18)	17 (24)	13 (18)	45 (23)
Headache	13 (18)	12 (17)	6 (8)	36 (19)
Fatigue	10 (14)	11 (16)	17 (23)	50 (26)
Nausea	9 (12)	4 (6)	8 (11)	28 (15)
Diarrhea	8 (11)	2 (3)	8 (11)	17 (9)
Back pain	8 (11)	4 (6)	4 (5)	24 (12)
Upper respiratory tract infection	8 (11)	4 (6)	4 (5)	20 (10)
Urinary tract infection	8 (11)	4 (6)	4 (5)	31 (16)
Dyspepsia	8 (11)	4 (6)	0	10 (5)
Arthralgia	3 (4)	4 (6)	7 (10)	32 (17)
Serious adverse event	3 (4)	11 (16)	8 (11)	27 (14)

* All patients were allowed to take ursodiol. Details regarding discontinuations due to adverse events and regarding all serious adverse events are provided in Tables S1 and S8, respectively, in the Supplementary Appendix.

ity correlates with disease stage.[29,30] However, the initiation of therapy with obeticholic acid at a dose of 5 mg, with adjustment up to 10 mg if appropriate, was associated with a lower rate of discontinuation owing to pruritus (one patient) than was starting at 10 mg (seven patients). The mechanism for obeticholic acid–related pruritus is unclear; although autotaxin has been shown to correlate with cholestatic pruritus,[25] there was no correlation in this trial. There were no other changes in quality of life, as assessed by the PBC-40 questionnaire, among patients who were treated with obeticholic acid.

Patients with primary biliary cholangitis typically have hyperlipidemia, with elevated levels of HDL cholesterol and LDL cholesterol; this profile is not associated with increased cardiovascular risk.[31] As in previous studies, treatment with obeticholic acid was associated with a reduction in the HDL cholesterol level. This finding may result from increased hepatic scavenger receptor B1 expression, which is up-regulated by FXR activation and stimulates hepatic uptake of cholesterol from HDL.[32] Treatment with obeticholic acid was associated with an initial increase in the LDL cholesterol level and persistent decreases in the triglyceride level, which remained stable during the open-label extension. The long-term significance of these findings is unclear.

This trial has several limitations. First, primary biliary cholangitis is a chronic liver disease, and the results reported here are for only 2 years of treatment with obeticholic acid. The focus of the trial was therefore limited to surrogate biomarkers, imaging, and symptom end points, with no statistical power to assess clinical outcomes. Second, multiplicity adjustments were made only for the primary end point and not for secondary or exploratory analyses.

In conclusion, 12 months of obeticholic acid, administered either with ursodiol or as monotherapy, in patients with primary biliary cholangitis resulted in improvements in the alkaline phosphatase level, the total bilirubin level, and other biochemical markers of disease. These effects were sustained for 2 years, and patients who crossed over from placebo to obeticholic acid had similar improvements after 1 year. Obeticholic acid dose-dependently increased the incidence of pruritus; the mechanism remains unknown. A multiyear study to assess the effects of obeticholic acid on clinical outcomes in patients with

primary biliary cholangitis who have more advanced liver disease (Clinical Outcomes with Obeticholic Acid in Liver Treatment [COBALT]) is currently enrolling patients (ClinicalTrials.gov number, NCT02308111).

Presented in part in abstract form at the annual meetings of the European Association for the Study of the Liver (London, April 2014) and the American Association for the Study of Liver Diseases (Boston, November 2014).

Supported by Intercept Pharmaceuticals.

Disclosure forms provided by the authors are available with the full text of this article at NEJM.org.

We thank the patients, without whom this trial would not have been possible; Luciano Adorini, of Intercept Pharmaceuticals, for critical review of an earlier version of the manuscript; and Julie Ellison, Karen Lutz, and Alexander Liberman, of Intercept Pharmaceuticals, for medical-writing assistance.

APPENDIX

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