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CLINICAL—LIVER

Efficacy of Obeticholic Acid in Patients With Primary Biliary Cirrhosis and Inadequate Response to Ursodeoxycholic Acid

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See Covering the Cover synopsis on page 669; see editorial on page 704.

BACKGROUND & AIMS: We evaluated the efficacy and safety of obeticholic acid (OCA, α-ethylchenodeoxycholic acid) in a randomized controlled trial of patients with primary biliary cirrhosis who had an inadequate response to ursodeoxycholic acid therapy. **METHODS:** We performed a double-blind study of 165 patients with primary biliary cirrhosis (95% women) and levels of alkaline phosphatase (ALP) 1.5- to 10-fold the upper limit of normal. Patients were randomly assigned to groups given 10 mg, 25 mg, or 50 mg doses of OCA or placebo, once daily for 3 months. Patients maintained their existing dose of ursodeoxycholic acid throughout the study. The primary outcome was change in level of ALP from baseline (day 0) until the end of the study (day 85 or early termination). We also performed an open-label extension of the trial in which 78 patients were enrolled and 61 completed the first year. **RESULTS:** OCA was superior to placebo in achieving the primary end point. Subjects given OCA had statistically significant relative reductions in mean ALP from baseline to the end of the study ($P < .0001$ all OCA groups vs placebo). Levels of ALP decreased 21%–25% on average from baseline in the OCA groups and 3% in the placebo group. Sixty-nine percent (68 of 99) of patients given OCA had at least a 20% reduction in ALP compared with 8% (3 of 37) of patients given placebo ($P < .0003$). Among secondary end points, levels of γ-glutamyl transpeptidase decreased 48%–63%, on average, among subjects given OCA, vs a 7% decrease in the group given placebo; levels of alanine aminotransferase decreased 21%–35% on average among subjects given OCA vs none of the patients given placebo. Pruritus was the principal adverse event; incidence values in the OCA 10 mg, 25 mg, and 50 mg groups were 47% (not significantly different), 87% ($P < .0003$), and 80% ($P < .006$), respectively, vs 50% in the placebo group. In the extension study, levels of ALP continued to decrease to a mean level of 202 ± 11 U/L after 12 months vs 285 ± 15 U/L at baseline. **CONCLUSIONS:** Daily doses of OCA, ranging from 10 to 50 mg, significantly reduced levels of ALP, γ-glutamyl transpeptidase, and alanine aminotransferase, compared with placebo, in patients with primary biliary cirrhosis who had inadequate responses to ursodeoxycholic acid. The incidence and severity of pruritus were lowest among patients who received 10 mg/d OCA. Biochemical responses to OCA were maintained in a 12-month open-label extension trial. ClinicalTrials.gov ID: NCT00550862.

Keywords: Cholestasis; Bile Acids; FXR; Dose Study.

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Primary biliary cirrhosis (PBC) is a chronic, progressive autoimmune cholestatic liver disease that impacts quality of life and is associated with increased mortality.[1] PBC is characterized by lymphocytic cholangitis

Abbreviations used in this paper: **AE, adverse event; ALP, alkaline phosphatase; ALT, alanine aminotransferase; AST, aspartate aminotransferase; BA, bile acid; C4, BA precursor C4 (7α-hydroxy-4-cholesten-3-one); CDCA, chenodeoxycholic acid; DCA, deoxycholic acid; FGF19, fibroblast growth factor 19; FXR, farnesoid x receptor; GGT, γ-glutamyl transferase; HDL, high-density lipoprotein; mITT, modified intent-to-treat; OCA, α-ethyl-chenodeoxycholic acid; PBC, primary biliary cirrhosis; UDCA, ursodeoxycholic acid; ULN, upper limit of normal.**

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and intralobular bile duct destruction leading to development of fibrosis, cirrhosis, and liver failure. Consistent with US and European guidelines, the current diagnosis of PBC is typically made on the basis of elevated alkaline phosphatase (ALP) values and positive anti-mitochondrial antibody reactivity[2] and, in keeping with this, the use of liver biopsy for diagnosis and staging has decreased significantly. PBC is increasingly diagnosed at earlier stages.[3–5] The only approved drug to treat patients with PBC is ursodeoxycholic acid (UDCA), a hydrophilic, noncytotoxic bile acid (BA) that is widely used.[1,6,7] However, up to 40% of UDCA-treated patients have an inadequate biochemical response, depending on the criteria used, and such patients have significantly worse transplant-free survival rates than UDCA-responsive patients.[8–11] Accordingly, there is a significant medical need for new therapies for the treatment of PBC.[12–19]

Obeticholic acid (OCA, INT-747) is a semi-synthetic analogue of the primary BA chenodeoxycholic acid (CDCA), which selectively activates the nuclear hormone receptor farnesoid X receptor (FXR).[20,21] CDCA is the endogenous FXR agonist; the 6-α ethyl substitution on OCA imparts a nearly 100-fold greater FXR-activating potency.[21] UDCA is an epimer of CDCA, but lacks meaningful FXR activity. OCA has shown anti-cholestatic, anti-inflammatory, and anti-fibrotic effects mediated by FXR activation in preclinical and clinical studies.[20–23] Therefore, we reasoned that a more potent FXR agonist would have a positive impact in patients with PBC. In this article, we report findings from a 3-month, placebo-controlled, dose–response trial of OCA added to UDCA in patients with PBC with an inadequate UDCA response. We also report results from patients on OCA treatment followed through 12 months in an open-label extension trial.

Materials and Methods

Patients

Patients, 18 to 75 years of age with PBC,[24] on a stable dose of UDCA for at least 6 months before screening, were enrolled. PBC was diagnosed by at least 2 of the following: history of increased ALP levels for at least 6 months; positive anti-mitochondrial antibody titer (>1:40 titer on immunofluorescence or M2 positive by enzyme-linked immunoabsorbant assay) or PBC-specific antinuclear antibodies; or liver biopsy consistent with PBC. Patients were required to have a mean baseline ALP value between 1.5 and 10× the upper limit of normal range (ULN = 117 U/L for women; 129 U/L for men). Key exclusion criteria were elevated plasma aspartate aminotransferase (AST) or alanine aminotransferase (ALT) levels >5× ULN; bilirubin >2× ULN; serum creatinine >1.5 mg/dL (133 μmol/L); use of colchicine, methotrexate, azathioprine, or systemic corticosteroids at any time during the 3 months before screening; and history or presence of hepatic decompensation. Patients with other concomitant liver diseases, including autoimmune hepatitis overlap, were also excluded. Patients maintained their existing dose of UDCA throughout the study.

The study protocol and subsequent amendments were reviewed and approved by the appropriate Ethics Committees or Institutional Review Boards at each site. The trial was preregistered (www.clinicaltrials.gov; NCT00550862 and www.controlled-trials.com; ISRCTN67465025). The study protocol is available on request. All authors had access to complete datasets. GMH, LA, CS, TB-J, EC, OB, and DS finalized analysis and data presentation. GMH, LA, and DS had final responsibility to submit the manuscript after all authors reviewed and approved the manuscript.

Sample Size

The study sample size was calculated in terms of effect size; 35 patients per group provided 80% power to detect an effect size of 0.70, which translates to approximately a 10% mean greater reduction in ALP levels between groups (see Supplementary Table 1).

Randomization and Masking

Eligible patients were randomly assigned (1:1:1:1) to 1 of 4 treatment groups for 85 days (3 months): OCA 10 mg, OCA 25 mg, OCA 50 mg, or a matching placebo administered once daily. The computerized randomization schedule used a block size of 4 at each center.

Recruitment and the double-blind study phase occurred between November 2007 and May 2009. Study assessment visits were performed on days 0 (randomization), 15, 29, 57, and 85 (ie, 3 months or end of treatment). Patients had a follow-up visit (off drug therapy) 14 days later. ALP and liver enzymes levels were determined at each visit by a central laboratory. Safety assessments included adverse events (AEs), pruritus, physical examinations, vital signs, clinical laboratory testing including lipids, and electrocardiograms. Blood samples for BAs, fibroblast growth factor-19 (FGF19), BA precursor C4 (7α-hydroxy-4-cholesten-3-one) (C4), C-reactive protein, and IgM assays were obtained at days 0 and 85 or at end of treatment, if earlier.

Open-label OCA therapy was offered to patients completing the double-blind portion of the study at 13 centers. These patients were dosed for at least an additional 12 months (unless they discontinued earlier). Patients were restarted on OCA 10-mg once-daily dosing or the dose assigned during the double-blind phase and allowed to titrate up or down at the discretion of the investigator based on individual ALP response and tolerability. Mean daily OCA doses of <10 mg, typically to manage pruritus, were achieved by alternate or every third day dosing of a 10-mg tablet.

For the double-blind and open-label extension, pruritus was managed with dose reduction, medication interruption, use of other medications (eg, antihistamines or BA sequestrants), or discontinuation, as deemed appropriate.

Primary Efficacy End Point

The primary end point was the relative (percent) change in ALP values from baseline (day 0) to end of study (day 85) in each of the OCA groups compared with placebo in the modified intent-to-treat (mITT) population.

Efficacy Assessed by Published Response Criteria

The proportion of patients meeting the various previously published "nonresponse" criteria at the start of the study were also evaluated (eg, Paris I,[8] II,[9] Toronto criteria[25,26]), in

addition to 2 additional criteria[27] that also incorporated normal bilirubin levels.

Secondary End Points

Secondary and exploratory end points were evaluated in the ITT population and included changes in other liver enzymes (AST, ALT, γ-glutamyl transferase [GGT]), conjugated bilirubin, and albumin values expressed as both absolute values, change from baseline, and proportional changes. Other evaluations included assessment of lipids, free fatty acids, C-reactive protein, and IgM. Changes were measured in blood serum concentrations of total endogenous BAs and the individual BAs: UDCA, CDCA, cholic acid, lithocholic acid, and deoxycholic acid (DCA). Changes in C4 and FGF19, a marker of FXR activation, were also assessed. Serum levels of unconjugated and glycine- or taurine-conjugated OCA and other BAs were determined by liquid chromatography tandem mass spectrometry.[28] FGF19 concentrations were assayed using the solid-phase enzyme-linked immunoabsorbant assay Quantikine FGF19 Immunoassay (R&D Systems, Minneapolis, MN). Serum C4 levels were determined by high-performance liquid chromatography.[29]

Statistical Analysis

Three analysis populations were evaluated: an ITT population (N = 165) of randomized patients who received at least one dose of OCA; an mITT population (N = 161) of patients who received at least one dose of OCA and had at least one post-baseline ALP evaluation <7 days after their last dose of OCA; and a completer population (N = 136) of patients who had completed 85 days of treatment were also defined.

A hierarchical testing strategy[30] was used to account for multiple comparisons; statistical significance was evaluated at $\alpha = .05$ for 10 mg vs placebo, at $\alpha = .05$ for 25 mg vs placebo, then at $\alpha = .05$ for 50 mg vs placebo. The last observation carried forward method was used for missing data (Supplementary Table 2). Primary analyses were performed on the mITT population. All secondary analyses were performed on the ITT dataset only. Additional ALP evaluations over time were analyzed for the completer population. Pair-wise comparisons for OCA treatment groups vs placebo changes used the 2-sided Wilcoxon Mann-Whitney test at a 5% significance level. Safety variables were summarized by treatment group with descriptive statistics. Disease severity criteria were assessed by Fisher's exact test and the response analysis by χ^2 test.

Results

Study Patients

One hundred and sixty-five patients from 41 North American and European centers were randomized in a 1:1:1:1 fashion to placebo or 1 of 3 once-daily doses of OCA, 10 mg, 25 mg, and 50 mg (Supplementary Figure 1 for patient disposition). Nearly all enrolled patients were women (95%), Caucasian (96%), and had a positive anti-mitochondrial

Table 1. Demographic and Baseline Characteristics of Primary Biliary Cirrhosis Patients

Characteristics	Placebo (n = 38)	OCA, 10 mg (n = 38)	OCA, 25 mg (n = 48)	OCA, 50 mg (n = 41)
Sex, n (%)				
Male	2 (5)	0 (0)	3 (6)	3 (7)
Women	36 (95)	38 (100)	45 (94)	38 (93)
Age, *y*				
Mean (SD)	54.8 (8.5)	55.6 (9.3)	55.9 (8.0)	54.0 (9.7)
Range	36.0–72.0	37.0–71.0	35.0–69.0	37.0–71.0
Body weight, *kg*				
Mean (SD)	74.3 (15.9)	73.6 (13.6)	72.7 (13.4)	70.9 (17.1)
Range	44.0–107.6	50.0–99.2	45.4–101.3	46.2–116.0
Body mass index, kg/m^2				
Mean (SD)	27.4 (5.2)	27.8 (4.7)	27.4 (5.1)	26.4 (6.2)
Range	19.1-38.6	19.9–37.5	18.9–39.6	17.6–45.3
Laboratory markers, mean (SD)				
ALP, *U/L*	275.2 (102.7)	294.4 (149.4)	290.0 (123.6)	286.9 (106.2)
Bilirubin, *mg/dL*	0.2 (0.2)	0.2 (0.2)	0.2 (0.1)	0.3 (0.2)
Albumin, *g/dL*	4.2 (0.3)	4 (0.5)	4.1 (0.4)	4.2 (0.3)
Platelets, $10^3/\mu L$	281 (106)	272 (96)	275 (92)	244 (92)
INR	1.00 (0.06)	1.01 (0.07)	1.02 (0.13)	1.05 (0.27)
PBC inclusion criteria, n (%)				
History of increased ALP	37 (97)	36 (95)	46 (96)	39 (95)
Positive AMA titer	33 (87)	28 (74)	40 (83)	33 (80)
Liver biopsy	33 (87)	35 (92)	43 (90)	34 (83)
Total UDCA daily dose at study entry, *mg/kg*				
Mean (SD)	15.9 (4.4)	15.9 (4.1)	15.6 (3.7)	16.3 (5.2)
Range	8.8–26.9	7.2–25.4	8.4–24.7	6.6–35.0
1^{st}–3^{rd} quartile	13–17.8	13.5–18.3	13–17.2	13.5–17.6

AMA, anti-mitochondrial antibody; INR, international normalized ratio; SD, standard deviation.

antibody test (81%). Baseline demographics and clinical characteristics were similar at baseline between the groups (Table 1). The mean daily dose of UDCA at study entry was 15.6–16.3 mg/kg across all treatment groups (recommended dosing range 13–15 mg/kg/d). Most patients (82%) completed the study; pruritus was the principal reason for discontinuation (10%). The mITT population of 161 patients was evaluated for the primary end point.

Primary Efficacy End Point

The primary end point in the study, relative (percent) change in mean ALP levels in the mITT group from day 0 to day 85 compared with placebo, was met across all OCA dose groups with statistical significance ($P < .0001$, Figure 1*A*). Specifically, mean relative change in ALP from baseline from day 0 to day 85 was a decrease of 24% (95% confidence interval [CI]: −30% to −18%), 25% (95% CI: −30% to −20%), and 21% (95% CI: −30% to −12%) for the 10 mg, 25 mg, and 50 mg OCA groups, respectively, compared with a 3% decrease in the placebo group (95% CI: −7% to 2%) (Figure 1*A*). The results were virtually identical when the primary end point was applied to the ITT and completer populations ($P < .0001$ for all OCA doses). The maximum decreases in ALP values in the completer population (Figure 2*A* and *B*) occurred on day 85 (3 months) for all OCA dose groups. However, statistically significant ALP reductions were observed as early as the 2-week study visit, and the vast majority of the effect was seen at 1 month.

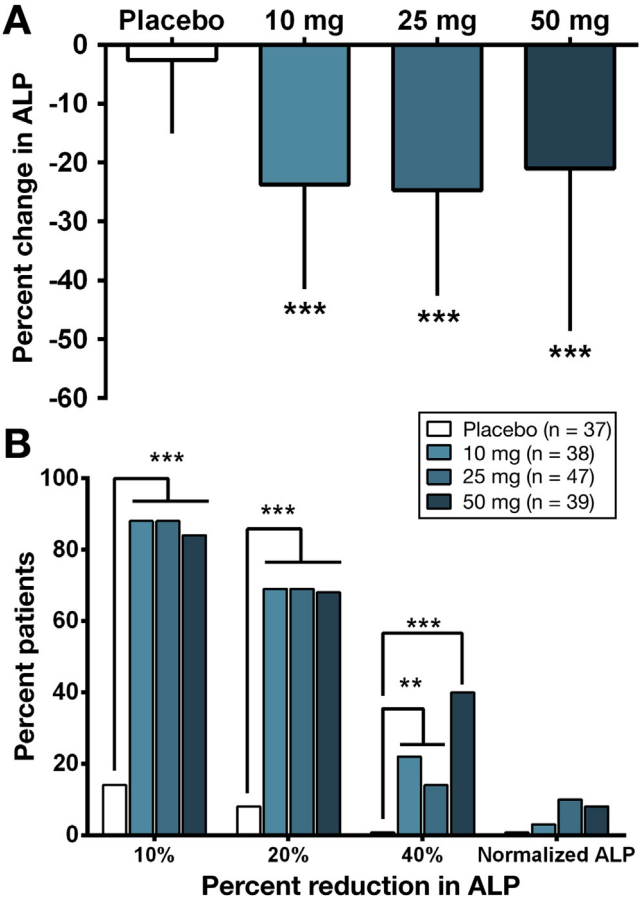

Figure 1. (*A*) Mean ± SD ALP relative change from baseline to end of study in the mITT (last observation carried forward) population. $P < .0001$ pair-wise comparison for all treatment groups. (*B*) Percent decrease in ALP values in the completer population. Pairwise comparisons for 10%, 20% and 40% cutoff, respectively: 10 mg $P < .0001$, $P < .0001$, $P = .0031$; 25 mg $P < .0001$, $P < .0001$, $P = .0272$; 50 mg $P < .000l$ for all cutoffs, respectively. *P* value: Comparison of proportion of patients with a 10%, 20%, 40%, or complete response for OCA dose groups with placebo group using the likelihood ratio χ^2 test. $^{**}P < .05$; $^{***}P < .0001$.

Alkaline Phosphatase Completer Analysis

There were also statistically significant ALP reductions of 10%, 20%, and 40% in patients completing therapy in all OCA groups vs placebo (Figure 1*B*). Specifically, 87% (86 of 99) of OCA-treated patients completing therapy achieved at least a 10% ALP reduction, compared with 14% of placebo patients (5 of 37). Similarly, 69% (68 of 99) of OCA-treated patients showed at least a 20% reduction in ALP compared with 8% (3 of 37) of placebo-treated patients. ALP normalization was only achieved in 7% (7 of 99) of OCA-treated patients, but in no placebo patients.

Efficacy Assessed by Published Response Criteria

The efficacy of OCA was also evaluated using 5 major published PBC biochemical algorithms that describe criteria shown to be predictive of adverse clinical outcomes (liver transplant or death): Paris I,[8] Paris II,[9] Toronto I,[25] Toronto II,[26] and Mayo II.[27] Although these criteria differ in their definition of biochemical response with respect to the key liver enzymes assessed and their threshold levels, all algorithms include an ALP criterion, the level of which varies (range, ≤1.5–3× ULN). Some algorithms employ other liver tests, such as bilirubin (≤1 mg/dL) or AST (≤1.5–2× ULN).[8,9] Regardless of the algorithm used, OCA-treated patients always had higher rates of response than placebo-treated patients (Table 2).

ALP Assessment of Open-Label Extension Therapy

After the double-blind portion of the study, 78 patients at select centers were enrolled into an open-label extension study. The biochemical results at 3, 6, 9, and 12 months are presented (Figure 2*C* and *D*, Supplementary Figure 2). The biochemical improvements observed in the 3-month double-blind phase were maintained during the open-label extension (12 months or more) (Supplemental Figure 3). Mean ALP for all 3 cohorts after 3 months in the open-label extension was 210 ± 12 U/L and after 12 months had further decreased to 202 ± 11 U/L.

Secondary End Points

Other liver biochemistry. Significant reductions in values of GGT (48% to 63%) and ALT (21% to 35%) were observed for all OCA treatment groups compared with

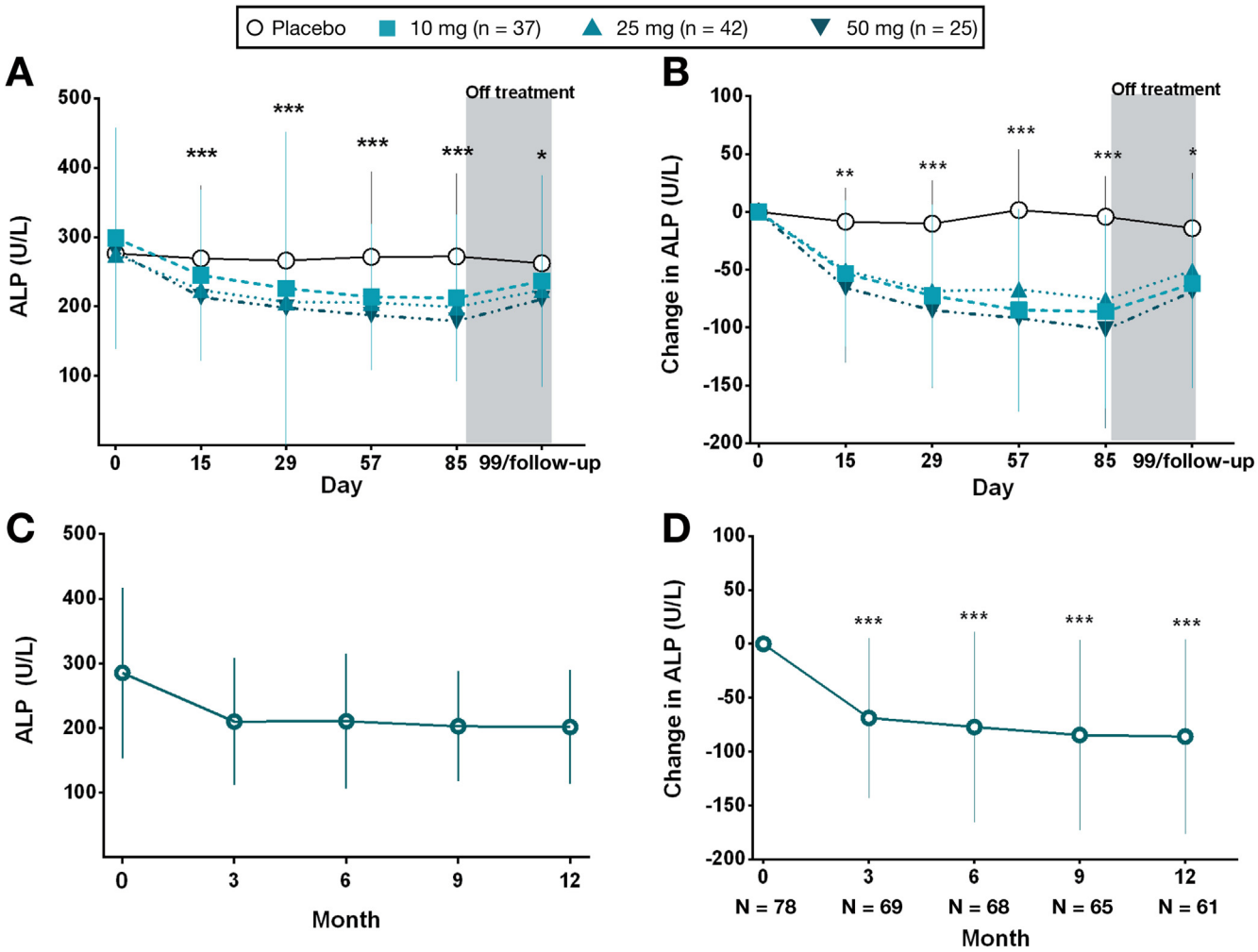

Figure 2. OCA treatment decreases serum ALP levels in patients with PBC in the double-blind (DB) trial and the open-label extension. (*A*) Decreases in ALP values during the DB phase were significant for all OCA dose groups vs placebo at all the study day visits ($P < .0001$). After OCA withdrawal on day 85, mean ALP values started to increase, but 2 weeks later had not reached mean baseline ALP values and remained statistically lower compared with the placebo group. ALP values in the completer population in the DB trial. $P < .0001$ for all OCA dose groups vs placebo. (*B*) Change in ALP values in the completer population in the DB trial. $P < .0001$ for all OCA dose groups vs placebo. (*C*) Decreases in ALP values during the open-label extension trial were significant for all OCA dose groups vs placebo at all the study day visits ($P < .0001$). (*D*) Change in ALP values during the open-label extension trial for the completer population. $P < .0001$ for all OCA dose groups vs placebo at all the study day visits. $^{*}P < .01$; $^{**}P < .001$; $^{***}P < .0001$.

placebo from baseline to end of treatment (Table 3). Placebo-treated patients experienced essentially no change in these analytes from baseline to day 85. OCA was also associated with significant reductions in AST values (9% to 17%) for all dose groups compared with placebo. Although mean conjugated bilirubin levels were in the normal range in all treatment groups at baseline, reductions in the median values were seen in the OCA treatment groups compared with a small increase in the placebo group (Table 3).

Inflammatory markers. C-reactive protein and IgM values also showed significant reductions from baseline at the end of the study with OCA treatment. Median C-reactive protein values decreased 21%, 42%, and 33% ($P = .0595$ for 10 mg; $P = .0009$ for 25 mg, and not significant for 50 mg compared with baseline values) in all 3 OCA treatment groups in comparison with a 10% increase for placebo. Median IgM values decreased by 14%, 21%, and 18% at 10 mg, 25 mg, and 50 mg OCA ($P = .0003$ for 10 mg; $P < .0001$ for 25 and 50 mg compared with baseline), respectively, vs a 19% increase in the placebo group.

Fibroblast growth factor 19, bile acid precursor C4 (7α-hydroxy-4-cholesten-3-one), and endogenous bile acids levels analysis. Consistent with FXR agonist effects, significant increases in FGF19 from baseline to end of treatment were observed for 10-mg and 25-mg OCA dose groups compared with placebo (Figure 3*A*). Significant reductions in C4 (Figure 3*B*) and total endogenous BAs (Figure 3*C*) were observed in all OCA dose groups compared with an increase in the placebo group. Endogenous BA (ie, BAs excluding UDCA and OCA) showed a significant dose-related decrease compared with placebo. Mean values and SD of the individual and total BAs measured at baseline and at the end of the study (UDCA, CDCA, cholic acid, lithocholic acid, DCA, and OCA) are

Table 2. Biochemical Treatment Response Criteria: Baseline and Day 85 Response

Treatment groups/criterion	Placebo (n = 38)	OCA, 10 mg (n = 38)	OCA, 25 mg (n = 48)	OCA, 50 mg (n = 41)
ALP ≤3× ULN and AST ≤2× ULN and tBili ≤1 mg/dL[a]				
Baseline (biochemical nonresponse), n	5	11	10	10
Day 85 (biochemical nonresponse), n	5	7	3	5
Day 85 Baseline nonresponders with treatment effect, %	0	36	**70**	50
P value		.2445	**.0256**	.1009
ALP ≤1.5× ULN and AST ≤1.5× ULN and tBili ≤1 mg/dL[b]				
Baseline (biochemical nonresponse), n	34	34	46	40
Day 85 (biochemical nonresponse), n	30	22	30	25
Day 85 baseline nonresponders with treatment effect, %	12	**35**	**35**	**35**
P value		**.0433**	**.0210**	**.0280**
ALP ≤1.67× ULN[c]				
Baseline (biochemical nonresponse), n	32	30	39	35
Day 85 (biochemical nonresponse), n	28	17	22	19
Day 85 baseline nonresponders with treatment effect, %	13	**43**	**44**	**43**
P value		**.0099**	**.0047**	**.0063**
ALP ≤1.76× ULN[d]				
Baseline (biochemical nonresponse), n	29	28	38	30
Day 85 (biochemical nonresponse), n	24	17	20	14
Day 85 baseline nonresponders with treatment effect, %	17	39	**47**	**50**
P value		**.0819**	**.0184**	**.0119**
ALP ≤1.67× ULN and tBili ≤1 mg/dL[e]				
Baseline (biochemical nonresponse), n	33	30	39	37
Day 85 (biochemical nonresponse), n	28	18	22	21
Day 85 baseline nonresponders with treatment effect, %	15	**40**	**44**	**41**
P value		**.0452**	**.0110**	**.0185**
ALP ≤1.67× ULN and tBili ≤ULN[f]				
Baseline (biochemical nonresponse), n	21	22	30	25
Day 85 (biochemical nonresponse), n	19	17	18	17
Day 85 baseline nonresponders with treatment effect, %	10	23	**40**	28
P value		.4121	**.0248**	.1430

NOTE. Bold type indicates significant values. Treatment groups were compared using Fisher exact test.
tBili, total bilirubin.
The evaluation of the treatment groups for various published algorithm ([a]Paris I; [b]Paris II; [c]Toronto I; [d]Toronto II) and [e,f]deviations of Toronto I with the incorporation of normal bilirubin levels.

provided in Supplementary Table 3. At baseline, BA concentrations were similar for placebo and OCA-treated patients (Supplementary Table 4). The majority of total baseline BA concentration (63%–65%) was UDCA (consistent with the mean 16 mg/kg dose being taken by the patients), followed by CDCA (11%–15%), cholic acid (11%–12%), and DCA (5%–7%). Lithocholic acid composed <1% of total BA concentrations. In treated patients, OCA constituted <2% of total plasma BAs.

Adverse Events

Overall, 84% (32 of 38) of the placebo-treated and 96% (122 of 127) of OCA-treated patients experienced at least one AE (Supplementary Tables 5 and 6). Apart from pruritus, only mild or moderate nausea was reported more frequently in all 3 OCA groups than in the placebo group. Severe AEs were primarily due to pruritus, and of 37, 30 patients with severe AEs were pruritus related.

Pruritus. Although pruritus was no more common in the OCA 10-mg group compared with the placebo group, the severity appeared to be worse at this dose, and both the incidence and severity were worse in the 2 higher-dosing groups. The incidence of pruritus in the OCA 10-mg, 25-mg, and 50-mg groups were 47% (not significant), 85% ($P < .0003$), and 80% ($P < .006$) vs 50% in the placebo group (Figure 4*A*, Supplementary Table 6). Severe pruritus was reported in 16% (6 of 38) of the patients in the 10-mg group, 24% (9 of 37) of the patients in the 25-mg group, and 37% (15 of 41) of the patients in the 50-mg group of patients, respectively. Overall, severe pruritus was less commonly reported during the open-label extension trial (Figure 4*B*) and although 87% (68 of 78) of patients experienced some pruritus, only 13% (10 of 78) discontinued OCA treatment as a result (Supplementary Table 7).

Lipid changes. Across all treatment groups, patients at baseline had elevated levels of total cholesterol (median, 218–239 mg/dL), low-density lipoprotein cholesterol (median, 123–133 mg/dL), and high-density lipoprotein (HDL) cholesterol (median, 65–70 mg/dL), and normal to low levels of triglycerides (median, 113–119 mg/dL). A dose-related decrease in total cholesterol of 3%, 5%, and 13% was noted for OCA 10-mg, 25-mg, and 50-mg groups, respectively, mediated by a decrease in HDL levels (Table 3

Table 3. Liver Chemistry, Immunologic Markers, and Lipids

	Placebo (n = 38)		OCA, 10 mg (n = 38)			OCA, 25 mg (n = 48)			OCA, 50 mg (n = 41)		
	Day 0	Day 85	Day 0	Day 85	*P* value	Day 0	Day 85	*P* value	Day 0	Day 85	*P* value
Liver chemistry											
ALT, *U/L*	41 (28–53)	40 (26–63)	45 (30–60)	27 (22–41)	<.0001	39 (30–59)	24 (19–38)	<.0001	40 (33–70)	27 (21–43)	.0018
AST, *U/L*	38 (30–49)	36 (27–48)	43 (32–57)	33 (27–40)	.0031	39 (30–47)	29 (24–42)	.0026	43 (31–55)	33 (27–48)	.0636
GGT, *U/L*	142 (118–291)	141 (100–311)	154 (101–241)	62 (39–122)	<.0001	177 (92–373)	45 (24–124)	<.0001	178 (118–312)	55 (30–140)	<.0001
Conjugated bilirubin, *mg/dL*	0.15 (0.10–0.25)	0.19 (0.10–0.20)	0.20 (0.10–0.30)	0.19 (0.10–0.30)	.4117	0.20 (0.15–0.25)	0.12 (0.10–0.20)	.0030	0.25 (0.15–0.30)	0.20 (0.10–0.30)	.0218
Immunologic											
CRP, *mg/L*	3.4 (1.6–7.9)	5.5 (1.4–8.1)	5.5 (3.1–9.5)	4.7 (2.8–6.4)	.0595	6.1 (2.8–8.9)	2.4 (1.4–4.7)	.0009	3.7 (1.5–6.3)	2.1 (1.0–6.4)	.1674
IgM, *mg/dL*	260 (170–440)	260 (170–450)	390 (290–520)	350 (240–490)	.0003	260 (180–380)	230 (150–290)	<.0001	320 (210–420)	270 (170–350)	<.0001
Lipids											
Cholesterol, *mg/dL*	239 (201–258)	246 (204–268)	218 (190–251)	206 (179–244)	.0055	231 (196–272)	208 (184–259)	.0014	239 (193–258)	199 (160–230)	<.0001
LDL, *mg/dL*	133 (104–162)	137 (113–160)	130 (104–159)	128 (107–172)	.4607	133 (105–157)	139 (108–165)	.8893	123 (94–150)	123 (92–157)	.6613
HDL, *mg/dL*	70 (55–86)	72 (61–87)	65 (54–80)	57 (42–68)	<.0001	67 (59–81)	56 (45–74)	<.0001	67 (62–88)	56 (46–71)	<.0001
Triglycerides, *mg/dL*	119 (101–154)	106 (85–137)	113 (81–148)	108 (86–139)	.4030	114 (83–150)	97 (76–130)	.8415	115 (76–143)	93 (73–134)	.6242

NOTE. *P* values are for changes from baseline to end of treatment. Medians (quartiles 1st–3rd); Clinical laboratory reference range: ALT: 10–40 U/L; AST: 20–48 U/L; GGT: 0–30 U/L; conjugated bilirubin: 0.2 mg/dL; CRP: <0.80 mg/L; IgM: 54–222 mg/dL; cholesterol: 70–232 mg/dL; LDL: ≤162 mg/dL; HDL: ≥35 mg/dL; triglycerides: ≤199 mg/dL. CRP, C-reactive protein; LDL, low-density lipoprotein.

Figure 3. OCA treatment increases FGF19 and decreases C4 and endogenous BA plasma levels. Increased FGF19 (*A*), associated with decreased C4 (*B*), and endogenous BA (*C*) plasma levels in PBC patients after OCA treatment. Data are presented as median (*line in middle of box*), interquartile range (*top and bottom of box*), minimum and maximum (outliers denoted by *diamonds*). Statistical significance is based on the change from baseline to end of treatment. After treatments with 10 mg, 25 mg, and 50 mg OCA, changes in FGF19 levels ($P = .0007$; $P < .0001$; $P = .002$), C4 ($P = .0275$; $P < .0001$; $P < .0003$), and BA ($P = .0093$; $P < .0001$; $P < .0001$) were all respectively significant.

and Supplementary Figure 4). Other lipids and triglycerides were not meaningfully changed. HDL levels remained stable after the early decline at each follow-up visit in OCA treated subjects.

Other adverse events. Seven patients (4%; 7 of 165) experienced a serious AE during the study, including one

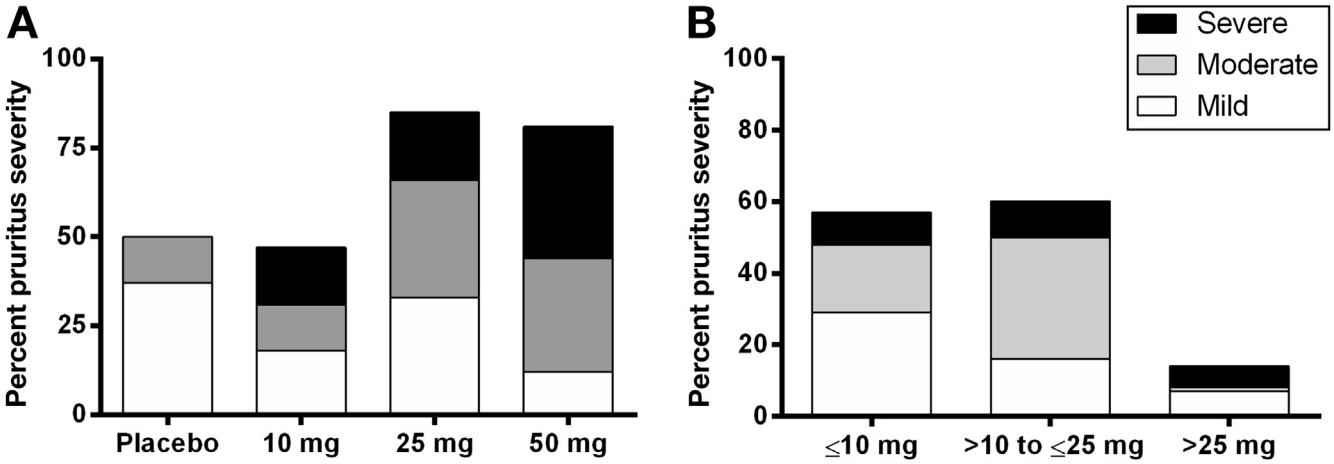

Figure 4. Pruritus severity in PBC patients expressed as percent of patients with mild, moderate, or severe pruritus. (*A*) Pruritus severity in the double-blind phase. (*B*) Pruritus severity in the open-label OCA therapy extension.

patient in the placebo arm (dyspnea) and one patient in the OCA 25-mg arm (resection of nonmalignant, pre-existent Warthin salivary gland tumor). Five patients in the OCA 50-mg group had 6 serious AEs; 3 had nonhepatic AEs (presumed gastroesophageal reflux disease and angioedema/angina pectoris due to a food allergy that did not reoccur with continuing OCA treatment) and 3 patients had gastrointestinal/hepatic AEs. One patient developed an upper gastrointestinal esophageal bleed approximately 1 week after therapy for pre-existing esophageal varices (that was not revealed to the investigator), 2 patients had significant increases in their bilirubin and aminotransferase levels that reverted to prestudy levels after OCA therapy was discontinued. OCA was restarted in one of these patients without an additional rise in her bilirubin or aminotransferases. In total, 27 patients discontinued the study: 23 patients due to an AE, 3 patients with elevated conjugated bilirubin, 1 patient with elevated AST/ALT; the majority of these patients (56%; 15 of 27) were receiving OCA at the highest dose of 50 mg (Supplementary Table 5).

Open-label extension over 1 year. Seventy-eight patients were enrolled in the open-label protocol after completion of the double-blind trial; 61 patients (78%; 61 of 78) completed 1 year of dosing. Nearly all patients were restarted at a mean daily OCA dose of ≤10 mg (75 patients [96%; 75 of 78]), and patients were allowed to titrate OCA dosing at the discretion of the treating physician based on ALP response and tolerability. OCA daily doses ranged from 3 mg to 60 mg daily throughout the trial. The mean final daily dose at 12 months was 20 mg. Although most patients (87%) reported some pruritus during the open-label phase of the trial, the pruritus was generally less severe than in the double-blind phase (Figure 4). Nineteen patients (24%; 19 of 78) discontinued the open-label extension trial: pruritus (13%; 10 of 78); other AEs (5%; 4/78; sleep–wake schedule disorder, rising blood glucose, left eye vitreous detachment, elevated conjugated bilirubin); consent withdrawal (3%, 2 of 78); major protocol violation (1%; 1 of 78); and other reasons (3%; 2 of 78) (see Supplementary Tables 7 and 8 for patient disposition and incidence of adverse events).

Discussion

This international, multicenter, placebo-controlled trial evaluated the utility of OCA across a range of doses for the treatment of PBC in patients with inadequate response to UDCA. OCA produced significant decreases in 2 biochemical, surrogate markers of PBC outcomes, ALP and bilirubin. In addition, OCA may improve underlying immunologic and inflammatory processes at play in PBC, as both C-reactive protein and IgM (the hallmark elevated immunoglobin in PBC) were significantly reduced. Pruritus, the most common symptom in PBC, was exacerbated with OCA treatment in a dose-related manner.

The study data strongly suggest OCA primarily mediates its effects in PBC via FXR agonism. Physiologically, a BA with FXR agonist properties would be expected to induce FGF19 production from gut enterocytes, which would, in turn, mediate (via induction of the nuclear receptor small heterodimer partner [SHP]) a decrease in endogenous BA synthesis, the postprandial signal to decrease BA synthesis.[31] Such effects were confirmed in this clinical study: serum FGF19 concentrations increased in a dose-related manner and both C4 (a BA precursor) and endogenous BA concentrations decreased. In contrast, UDCA is not an FXR agonist,[32] and is thought to mediate its beneficial effects in PBC by several mechanisms, including diluting toxic BAs and promoting their excretion, providing biliary tract protection by up-regulating the biliary bicarbonate "umbrella", and exerting immune-modulatory and anti-inflammatory effects.[33–35] UDCA has low detergent properties requiring administration of large doses (13–15 mg/kg/d) to be effective in PBC. Consequently, UDCA becomes the predominant BA comprising >60% of the BA pool. In contrast OCA, which comprised <2% of the serum BAs at the end of this study, appears to exert its effects at approximately 100-fold lower doses than UDCA. Considered together, these complementary mechanisms likely explain the significant additional efficacy seen when OCA was added to UDCA in this study. OCA monotherapy efficacy in patients with PBC has been documented in a separate study,[36] supporting the

hypothesis that OCA effects are independent of concomitant UDCA dosing (ClinicalTrials.gov ID: NCT00570765).

With the use of UDCA for the treatment of PBC, the prognostic utility of ALP and other biochemical markers as surrogates for the "hard" end points of death and liver transplantation continues to be evaluated.[8–10] Recently, 2 groups analyzing large PBC cohorts have shown that lower ALP alone and combined with other biochemical markers is associated with better transplant-free survival, both when assessed at discrete thresholds[11] and as a continual variable.[37] Our study shows that OCA produces significant reductions in ALP, GGT, and, to a lesser extent, the aminotransferases. Bilirubin, which has long been shown to be predictive of clinical outcomes in PBC,[38] decreased significantly in 2 of the OCA groups in the trial, even though the vast majority of patients had mean bilirubin levels within the normal range.

No clear differences were observed in biochemical end points across the 5-fold range of OCA doses studied, strongly suggesting that the dose range studied in this trial was too high. This finding is somewhat surprising, based on preclinical rodent studies that have consistently shown doses of 5–30 mg/kg are needed to elicit a therapeutic response in appropriate models.[21] The 10-mg dose of OCA represents approximately a 0.14-mg/kg dose in patients with PBC—nearly 10 times lower than the effective doses in the animal studies. A likely explanation for these interspecies differences is that CDCA (on which OCA is based) is the natural FXR ligand in man, but is not in rodents.

Pruritus was by far the most common AE in the study and was clearly OCA dose-related. Although the exact mediators of cholestatic pruritus remain to be elucidated, 2 mechanisms have been proposed: activation of the autotaxin pathway[39] and activation of TGR5.[40–42] Data from the current study are inconsistent with TGR5-induced pruritus; OCA is a weak TGR5 agonist and actually reduced levels of the endogenous human TGR5 agonist, DCA. Whether OCA activates the autotaxin pathway has yet to be determined. The incidence of pruritus in the 10-mg OCA group was no higher than that seen in the placebo patients (although the pruritus was more severe). Based on the dose-response related pruritus observed in this study, we believe that doses of OCA $<$10 mg will be better tolerated. A Phase 3 study of OCA is designed to address this issue (ClinicalTrials.gov ID: NCT01473524).

PBC patients with early disease have elevated HDL levels, however, altered risks of cardiovascular morbidity relative to the general population have not been clearly demonstrated.[10,43] In this study, OCA treatment was associated with decreases in total and HDL cholesterol. Adverse cardiovascular events are unlikely to be a concern during the 3-month double-blind or open-label extension, however, longer studies are ongoing to explore potential adverse effects of chronic FXR activation, particularly on lipid homeostasis (ClinicalTrials.gov ID: NCT01865812).

The mechanism by which OCA contributes to lowering HDL has not been established in humans, but the observation is consistent with the OCA-mediated effects of FXR in animals and could be related to up-regulation of reverse cholesterol transport through SR-B1 activation. Specifically, FXR knockout mice display hypercholesterolemia due to a marked increase in HDL driven by down-regulation of SR-B1, a key receptor for hepatic clearance of cholesterol from HDL.[44] Similarly, partial or complete knockout of SR-B1 results in elevations in HDL with marked increases in mature, lipid-rich HDL.[45] OCA has been shown in animal models to lower HDL driven by a decrease in mature, lipid-rich HDL.[46] In addition, atherogenic plaque formation was reduced by OCA in proatherogenic mice and led to a selective reduction of HDL2c or ApoAI in cynomolgus monkeys.[46,47] Nonetheless, the potential cardiovascular implication of these effects in humans needs to be established. Future studies will evaluate lipid profiles in patients with PBC to delineate HDL particle formation, maturation, and clearance, as well as macrophage cholesterol efflux before and after treatment with OCA (ClinicalTrials.gov ID: NCT01865812).

Limitations of the trial include limited duration of the study, the dose range evaluated and the need for additional mechanistic studies focusing on pruritus and the lipid profile. Although biochemical surrogates are of clear value in PBC,[8,9,25–27,37] we acknowledge the challenges of applying any surrogate end point in the development and approval of new drugs.

In conclusion, we present randomized controlled clinical trial data demonstrating biochemical efficacy of OCA, a FXR agonist, when given to patients with PBC with an inadequate response to UDCA therapy. Across all doses tested, biochemical efficacy of OCA was evident; based on the balance of efficacy and tolerability, in this study 10-mg once daily dose of OCA was the most effective dose, and has formed the basis for additional studies of OCA in PBC. Evaluating the lower end of the dose–response relationship in treatment of PBC is merited, as is a strategy of titrating the dose of OCA based on an evaluation that includes biochemical markers and symptomatic response to low doses of the drug. Our trial, therefore, supports ongoing efforts to further evaluate the long-term safety and clinical efficacy of OCA as a new therapy for patients with PBC.

Supplementary Material

Note: To access the supplementary material accompanying this article, visit the online version of *Gastroenterology* at www.gastrojournal.org, and at http://dx.doi.org/10.1053/j.gastro.2014.12.005.

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The Data Safety Monitoring Committee: Edward Krawitt, MD, Chair; Helen Young, MD, Secretary; Tilman Oltersdorf, MD; Timothy Morgan, MD.

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Supplementary Material

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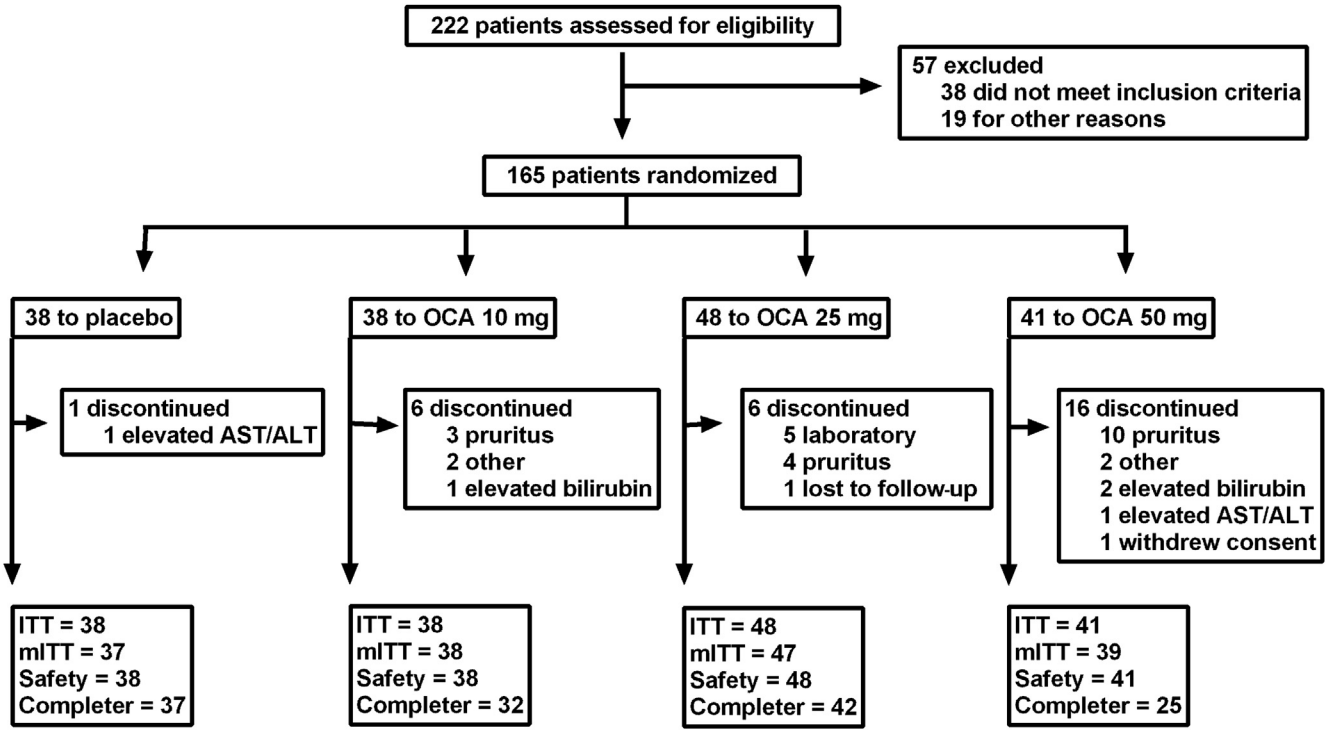
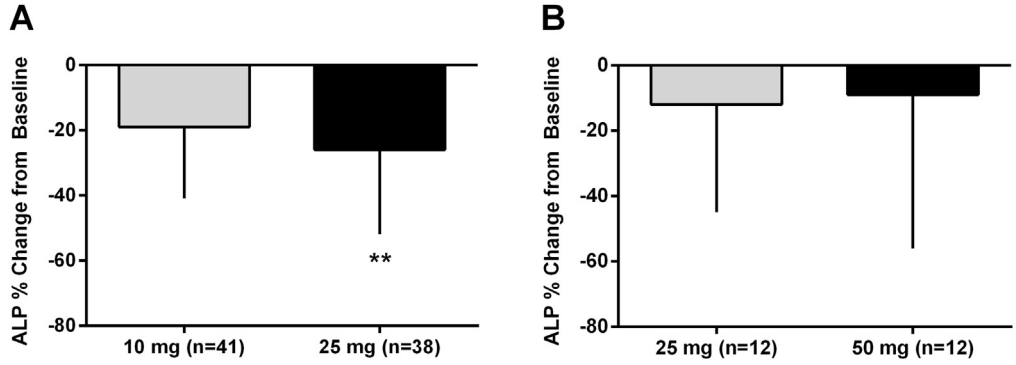
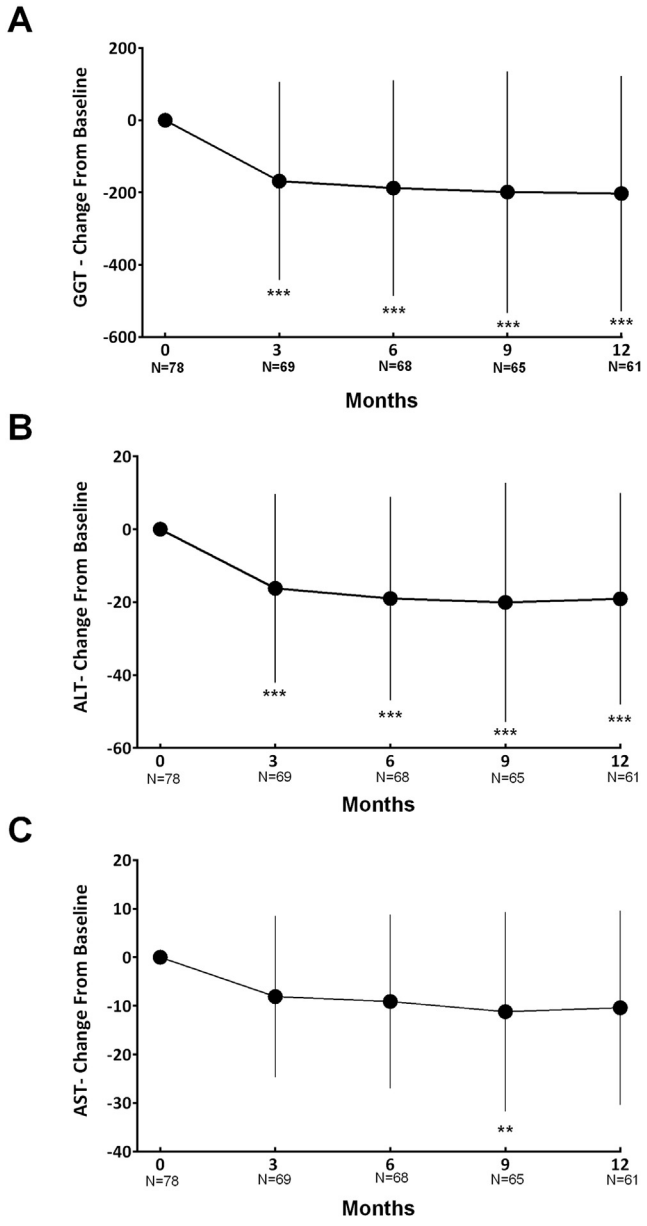


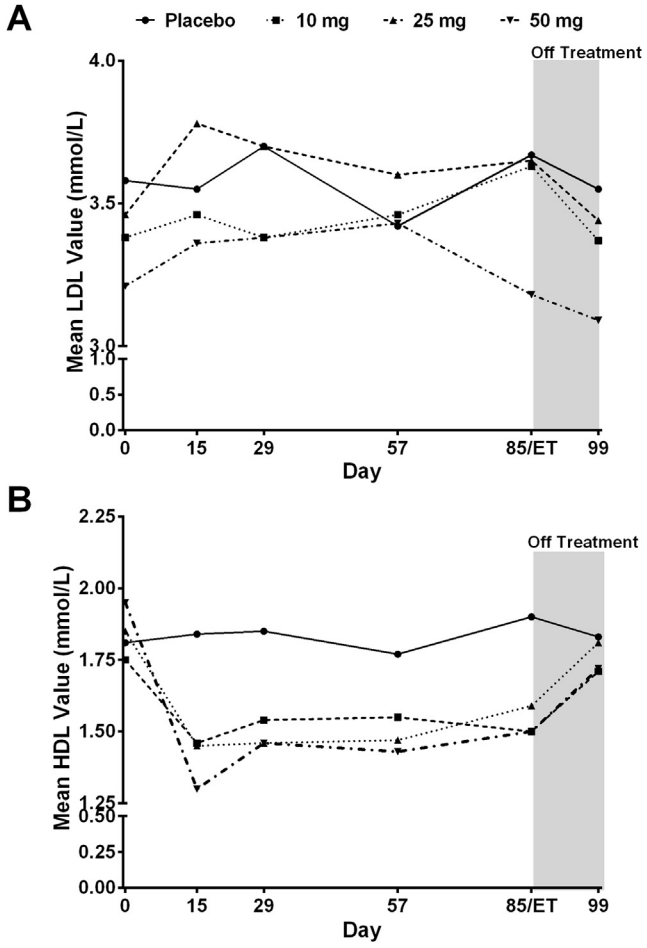
Supplementary Figure 1. Patient disposition.



Supplementary Figure 2. Dose-titration effect of OCA therapy in the open-label extension. *Panel A* compares the effect of OCA at 10 mg and 25 mg daily; *panel B* compares the effect of OCA at 25 mg and 50 mg daily. ALP values are presented as mean ± SD percent change from baseline after a 30-day pre-titration (*gray bars*) and 30-day post-titration (*black bars*) dosing. $^{**}P = .01$ for relative change from baseline compared with placebo.



Supplementary Figure 3. Safety population. Persistent biochemical response in PBC patients after OCA therapy in the open-label extension. Patients on OCA therapy in the OLE demonstrated sustained reduction compared with baseline in GGT (*A*), ALT (*B*), and AST (*C*) levels 1 year after treatment initiation. ** $P < .001$ and *** $P < .0001$ (transaminases and GGT, all time points) vs time 0. Data are mean ± SD.



Supplementary Figure 4. Mean absolute levels of (*A*) low-density lipoprotein (LDL) and (*B*) high-density lipoprotein (HDL) and over time. Data are mean values for safety population.

Supplementary Table 1. Study Power Calculations

	Assumed numbers[a] (for sample size calculation)			Observed numbers[b]		
				10 mg	25 mg	50 mg
$Mean_{placebo}$, %	−1	−3.5	−6	−2.6	−2.6	2.6
$Mean_{active}$, %	−8	−13	−20	−23.7	−24.7	21.0
Difference ($mean_{placebo}$ – $mean_{active}$), %	7	10.5	14	21.1	22.1	18.4
SD, %	10	15	20	15.4[c]	15.8[c]	21.6[c]
Effect size	0.7	0.7	0.7	1.37	1.40	0.85
Power, %	80	80	80	99	99	95
n (per group)	35	35	35	37[d]	42[d]	38[d]

NOTE. The difference of means and standard deviation (SD) are to be set for the estimation of the effect size, which is calculated as ($mean_{active}$ − $mean_{placebo}$)/SD. The listed mean values are examples that could result in the specified difference of means.
[a]Leading to an effect size of 0.7.
[b]mITT; percent change from baseline.
[c]Common SD calculated using observed SDs from treatment groups.
[d]Mean number of observed patients in both treatment groups.

Supplementary Table 2. Missing Data From the Double-Blind Trial

	Treatment group				
No. of subjects analysis by time point for:	Placebo (n = 38)	OCA 10 mg (n = 38)	OCA 25 mg (n = 48)	OCA 50 mg (n = 41)	Total (n = 165), n (%)
ALP, ALT, AST, GGT, conjugated bilirubin, cholesterol, LDL, HDL, and TG					
Baseline	38	38	48	41	165
Day 15	36	38	46	33	153 (93)
Day 29	37	35	43	27	142 (86)
Day 57	36	33	41	26	136 (82)
Day 85/ET	38	38	48	40	164 (99)
Day 99	38	35	43	34	150 (91)
CRP					
Baseline	32	36	41	35	
Day 85/ET	31	28	36	30	
Change from baseline, n (%)	28 (74)	28 (74)	31 (65)	27 (66)	
IgM					
Baseline	32	35	41	35	
Day 85/ET	33	29	38	31	
Change from baseline, n (%)	30 (79)	28 (74)	33 (69)	28 (68)	
FGF19/Total BA					
Baseline	32	32	42	34	
Day 85/ET	35	29	40	33	
Change from baseline, n (%)	30 (79)	26 (68)	38 (79)	30 (73)	

CRP, C-reactive protein; ET, end of therapy; LDL, low-density lipoprotein; TG, triglyceride.

Supplementary Table 3. Bile Acid Levels at Baseline and Month 3 in the Intent-to-Treat Population During the Double-Blind Trial

BA analytes	Treatment group			
	Placebo (n = 32)	OCA, 10 mg (n = 32)	OCA, 25 mg (n = 42)	OCA, 50 mg (n = 34)
Total BA, *μmol/L*				
Baseline, mean (SD)	18.8 (24.3)	33.9 (27.0)	28.4 (30.5)	37.8 (56.2)
Month 3, mean (SD)	23.2 (25.5)	30.6 (42.9)	24.1 (35.8)	72.6 (142.2)
Mean (SD) change from baseline to month 3	0.53 (19.2)	-4.5 (34.3)	-3.0 (29.9)	33.5 (153.2)
Median change from baseline to month 3	−1.27	−5.95	−4.36	−4.17
P values[a]	NA	.1549	.1946	.2903
Total UDCA, *μmol/L*				
Baseline, mean (SD)	12.4 (15.6)	22.9 (20.0)	18.4 (19.9)	21.8 (30.7)
Month 3, mean (SD)	14.4 (15.0)	20.8 (31.5)	17.8 (21.9)	47.2 (87.8)
Mean (SD) change from baseline to month 3	−0.08 (12.9)	−2.32 (27.6)	−0.07 (20.4)	24.0 (98.6)
Median change from baseline to month 3	−0.72	−2.55	−0.23	−1.96
P values[a]	NA	.2381	.7662	.6408
Total CDCA, *μmol/L*				
Baseline, mean (SD)	2.40 (3.75)	4.71 (4.13)	4.22 (5.46)	7.21 (14.65)
Month 3, mean (SD)	3.53 (4.51)	4.96 (7.67)	2.54 (5.15)	15.81 (37.95)
Mean (SD) change from baseline to month 3	0.34 (3.20)	0.13 (4.62)	-1.35 (4.09)	9.01 (37.01)
Median change from baseline to month 3	0.194	−0.736	−0.564	−0.898
P values[a]	NA	.0542	.0005	.0189
Total CA, *μmol/L*				
Baseline, mean (SD)	2.46 (3.64)	4.20 (4.30)	3.91 (5.87)	6.21 (11.96)
Month 3, mean (SD)	3.46 (5.34)	3.13 (6.18)	2.88 (10.80)	6.54 (16.31)
Mean (SD) change from baseline to month 3	0.45 (3.26)	−1.70 (4.66)	−0.79 (8.24)	0.26 (17.23)
Median change from baseline to month 3	0.04	−0.68	−1.09	−1.00
P values[a]	NA	.0030	.0003	.0044
Total DCA, *μmol/L*				
Baseline, mean (SD)	1.27 (2.35)	1.81 (1.76)	1.65 (2.07)	2.33 (2.59)
Month 3, mean (SD)	1.60 (1.99)	1.10 (2.44)	0.36 (0.71)	1.28 (2.99)
Mean (SD) change from baseline to month 3	−0.13 (1.70)	−0.87 (1.98)	−1.16 (1.66)	−1.25 (4.22)
Median change from baseline to month 3	0.000	−0.31	−0.64	−1.02
P values[a]	NA	.0021	<.0001	<.0001
Total LCA, *μmol/L*				
Baseline, mean (SD)	0.194 (0.320)	0.282 (0.363)	0.227 (0.398)	0.305 (0.445)
Month 3, mean (SD)	0.196 (0.291)	0.321 (0.492)	0.167 (0.226)	0.305 (0.396)
Mean (SD) change from baseline to month 3	−0.034 (0.185)	0.001 (0.326)	−0.030 (0.222)	−0.055 (0.529)
Median change from baseline to month 3	0.000	0.000	−0.021	0.000
P values[a]	NA	.3782	.3245	.6839
Total endogenous bile acids, *μmol/L*				
Baseline, mean (SD)	6.35 (9.54)	11.0 (9.07)	10.0 (12.9)	16.0 (28.3)
Month 3, mean (SD)	8.80 (11.6)	9.52 (14.9)	5.95 (15.6)	23.9 (54.4)
Mean (SD) change from baseline to month 3	0.6 (7.6)	−2.4 (9.8)	−3.3 (12.0)	8.0 (54.4)
Median change from baseline to month 3	0.0	−2.3	−3.1	−3.7
P values[a]	NA	.0108	.0001	.0071
Total OCA, *μmol/L*				
Baseline, mean (SD)	0.000	0.000	0.000	0.003 (0.018)
Month 3, mean (SD)	0.000	0.252 (0.410)	0.371 (0.525)	1.552 (5.202)

NA, not applicable; SD, standard deviation.
[a]*P* values: Comparison of OCA dose group with placebo group using Wilcoxon Mann-Whitney test.

Supplementary Table 4. Mean Relative Proportion of Individual Bile Acids to Total Bile Acid Concentration at Baseline and Month 3 in the Intent-to-Treat Population During the Double-Blind Trial

	Treatment group			
Laboratory analytes	Placebo (n = 38)	OCA, 10 mg (n = 38)	OCA, 25 mg (n = 48)	OCA 50 mg (n = 41)
Total UDCA				
Baseline	0.654	0.632	0.641	0.630
Month 3	0.634	0.685	0.794	0.752
Total CDCA				
Baseline	0.106	0.145	0.121	0.144
Month 3	0.133	0.140	0.069	0.092
Total CA				
Baseline	0.118	0.115	0.109	0.119
Month 3	0.112	0.070	0.051	0.056
Total DCA				
Baseline	0.051	0.051	0.069	0.051
Month 3	0.063	0.019	0.003	0.009
Total LCA				
Baseline	0.000	0.000	0.004	0.000
Month 3	0.003	0.000	0.002	0.009
Total OCA				
Month 3	NA	0.014	0.013	0.018

NOTE. Values are mean relative proportion.
NA, not applicable.

Supplementary Table 5. Summary of Treatment-Emergent Adverse Events by Treatment Group in the Double-Blind Trial

	Treatment group				
	Placebo (n = 38)	OCA, 10 mg (n = 38)	OCA, 25 mg (n = 48)	OCA, 50 mg (n = 41)	Total (n = 165)
Subjects with any AEs, n (%)	32 (84)	34 (89)	47 (98)	41 (100)	154 (93)
Subjects with treatment-related AE,[a] n (%)	22 (58)	28 (74)	45 (94)	38 (93)	133 (81)
Subjects with serious AE, n (%)	1 (3)	0 (0)	1 (2)	5 (12)	7 (4)
Subject deaths, n (%)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
Subjects who withdrew due to an AE,[b] n (%)	1 (3)	5 (13)	5 (10)	12 (29)	23 (14)
AE reports (entries), n	96	101	152	198	547
Mild	68	58	91	96	313
Moderate	21	35	50	76	182
Severe	7	8	11	26	52

[a]Related adverse events include "possibly" or "probably" relationship.
[b]Three additional subjects discontinued the study due to elevated conjugated bilirubin.

Supplementary Table 6. Incidence of All Adverse Events Occurring in ≥5% in Any Treatment Group During the Double-Blind Trial

System organ class/preferred term	Treatment group			
	Placebo (n = 38)	OCA, 10 mg (n = 38)	OCA, 25 mg (n = 48)	OCA, 50 mg (n = 41)
Subjects with any AEs	32 (84)	34 (89)	47 (98)	41 (100)
Skin and subcutaneous tissue disorders	21 (55)	19 (50)	43 (90)	36 (88)
Pruritus	19 (50)	18 (47)	41 (85)	33 (80)
Rash	0 (0)	0 (0)	1 (2)	2 (5)
Gastrointestinal disorders	10 (26)	17 (45)	17 (35)	17 (41)
Abdominal distension	1 (3)	2 (5)	0 (0)	4 (10)
Abdominal pain	2 (5)	1 (3)	2 (4)	2 (5)
Abdominal pain upper	1 (3)	0 (0)	2 (4)	2 (5)
Constipation	3 (8)	3 (8)	4 (8)	3 (7)
Diarrhea	3 (8)	3 (8)	4 (8)	3 (7)
Dyspepsia	0 (0)	2 (5)	2 (4)	2 (5)
Nausea	1 (3)	4 (11)	3 (6)	4 (10)
Vomiting	0 (0)	0 (0)	3 (6)	0 (0)
General disorders and administration site conditions	7 (18)	9 (24)	8 (17)	10 (24)
Chest pain	0 (0)	0 (0)	0 (0)	2 (5)
Chills	0 (0)	0 (0)	2 (4)	2 (5)
Fatigue	5 (13)	7 (18)	3 (6)	5 (12)
Edema peripheral	0 (0)	1 (3)	1 (2)	2 (5)
Pyrexia	0 (0)	3 (8)	0 (0)	0 (0)
Infections and infestations	10 (26)	8 (21)	5 (10)	11 (27)
Bronchitis	0 (0)	2 (5)	0 (0)	0 (0)
Gastroenteritis viral	0 (0)	0 (0)	0 (0)	2 (5)
Nasopharyngitis	1 (3)	2 (5)	1 (2)	0 (0)
Sinusitis	2 (5)	1 (3)	0 (0)	2 (5)
Tooth abscess	0 (0)	2 (5)	0 (0)	1 (2)
Upper respiratory tract infection	2 (5)	0 (0)	1 (2)	0 (0)
Urinary tract infection	3 (8)	0 (0)	0 (0)	0 (0)
Nervous system disorders	4 (11)	4 (11)	9 (19)	8 (20)
Headache	4 (11)	3 (8)	5 (10)	7 (17)
Hyperesthesia	0 (0)	0 (0)	0 (0)	2 (5)
Respiratory, thoracic and mediastinal disorders	6 (16)	3 (8)	4 (8)	11 (27)
Cough	1 (3)	1 (3)	0 (0)	2 (5)
Dyspnea	2 (5)	0 (0)	0 (0)	0 (0)
Oropharyngeal pain	1 (3)	2 (5)	4 (8)	0 (0)
Epistaxis	0 (0)	0 (0)	0 (0)	4 (10)
Musculoskeletal and connective tissue disorders	5 (13)	5 (13)	3 (6)	6 (15)
Arthralgia	1 (3)	2 (5)	2 (4)	0 (0)
Myalgia	2 (5)	1 (3)	0 (0)	0 (0)
Pain in extremity	0 (0)	0 (0)	1 (2)	4 (10)
Investigations	3 (8)	3 (8)	2 (4)	2 (5)
Metabolism and nutrition disorders	1 (3)	3 (8)	1 (2)	4 (10)
Hypokalemia	0 (0)	0 (0)	0 (0)	2 (5)
Psychiatric disorders	1 (3)	3 (8)	3 (6)	2 (5)
Insomnia	0 (0)	2 (5)	1 (2)	2 (5)
Ear and labyrinth disorders	2 (5)	1 (3)	3 (6)	2 (5)
Vertigo	2 (5)	0 (0)	0 (0)	0 (0)
Eye disorders	1 (3)	0 (0)	4 (8)	3 (7)
Dry eye	1 (3)	0 (0)	3 (6)	2 (5)
Injury, poisoning and procedural complications	1 (3)	1 (3)	1 (2)	2 (5)
Contusion	1 (3)	0 (0)	0 (0)	2 (5)
Hepatobiliary disorders	0 (0)	0 (0)	0 (0)	4 (10)
Renal and urinary disorders	1 (3)	2 (5)	1 (2)	0 (0)
Reproductive system and breast disorders	2 (5)	1 (3)	1 (2)	0 (0)
Cardiac disorders	2 (5)	0 (0)	0 (0)	1 (2)
Palpitations	2 (5)	0 (0)	0 (0)	0 (0)

NOTE. Values are n (%).

Supplementary Table 7. Patient Disposition in the Open-label Extension Trial

Reason for discontinuation	Patients (n = 78)
Pruritus	10 (13)
Other adverse event	3 (4)
Increased conjugated bilirubin	1 (1)
Protocol violation	1 (1)
Withdrew consent/lost	2 (3)
Other	2 (3)

NOTE. Values are n (%).

Supplementary Table 8. Incidence of All Adverse Events Occurring in ≥5% in Any Treatment Group in the Open-Label Extension Trial

Adverse event	Patients (n = 78)
Pruritus	68 (87)
Fatigue	10 (13)
Insomnia	10 (13)
Upper respiratory tract infection	10 (13)
Headache	8 (10)
Rash	8 (10)
Constipation	7 (9)
Abdominal distension	6 (8)
Nausea	4 (5)
Edema peripheral	5 (6)
Nasopharyngitis	7 (9)
Sinusitis	5 (6)
Excoriation	6 (8)
Arthralgia	5 (6)
Pain in extremity	5 (6)
Nasal congestion	4 (5)
Ecchymosis	5 (6)

NOTE. Values are n (%).