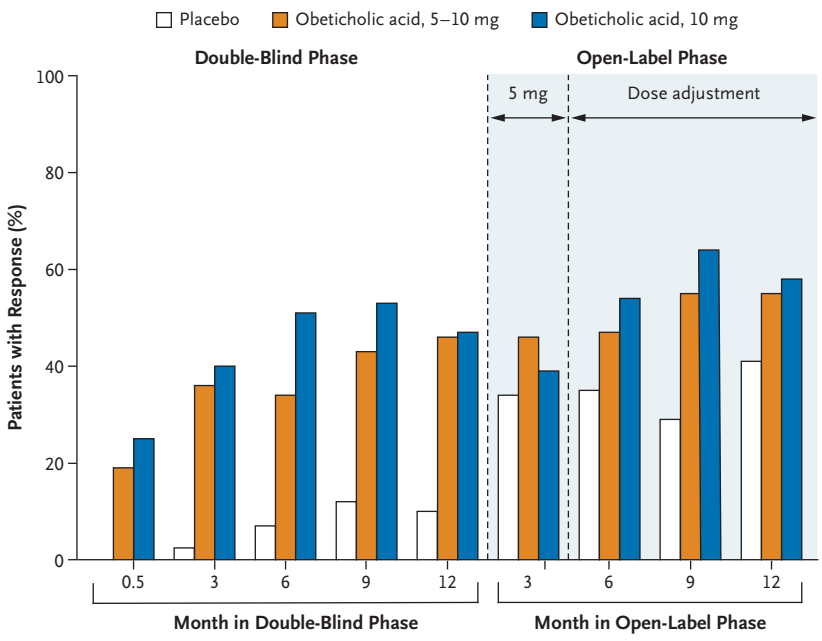

No. of Patients									
Placebo	73	73	73	73	73	64	60	59	59
Obeticholic acid, 5–10 mg	70	70	70	70	70	63	62	62	60
Obeticholic acid, 10 mg	73	73	73	73	73	64	59	61	59

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,