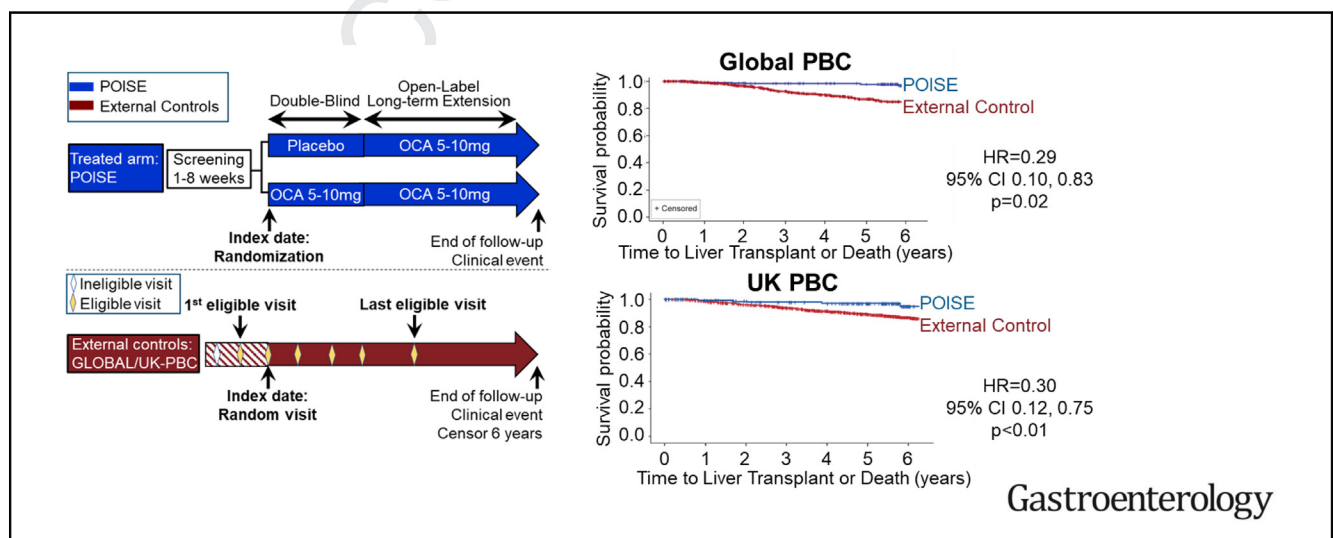


# Greater Transplant-Free Survival in Patients Receiving Obeticholic Acid for Primary Biliary Cholangitis in a Clinical Trial Setting Compared to Real-World External Controls

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**BACKGROUND & AIMS:** The Primary Biliary Cholangitis (PBC) Obeticholic Acid (OCA) International Study of Efficacy (POISE) randomized double-blind, placebo-controlled trial demonstrated that OCA reduced biomarkers associated with adverse clinical outcomes (ie, alkaline phosphatase, bilirubin, aspartate aminotransferase, and alanine aminotransferase) in patients with PBC. The objective of this study was to evaluate time to first occurrence of liver transplantation or death in patients with OCA in the POISE trial and open-label extension vs comparable non-OCA-treated external controls. **METHODS:** Propensity scores were generated for external control patients meeting POISE eligibility criteria from 2 registry studies (Global PBC and UK-PBC) using an index date selected randomly between the first and last date (inclusive) on which eligibility criteria were met. Cox proportional hazards models weighted by inverse probability of treatment assessed time to death or liver transplantation. Additional analyses (Global PBC only) added hepatic decompensation to the composite end point and assessed efficacy in patients with or without cirrhosis. **RESULTS:** During the 6-year follow-up, there were 5 deaths or liver transplantations in 209 subjects in the POISE cohort (2.4%), 135 of 1381 patients in the Global PBC control (10.0%), and 281 of 2135 patients in the UK-PBC control (13.2%). The hazard ratios (HRs) for the primary outcome were 0.29 (95% CI, 0.10–0.83) for POISE vs Global PBC and 0.30 (95% CI, 0.12–0.75) for POISE vs UK-PBC. In the Global PBC study, HR was 0.20 (95% CI, 0.03–1.22) for patients with cirrhosis and 0.31 (95% CI, 0.09–1.04) for those without cirrhosis; HR was 0.42 (95% CI, 0.21–0.85) including hepatic decompensation. **CONCLUSIONS:** Patients treated with OCA in a trial setting had significantly greater transplant-free survival than comparable external control patients.

**Keywords:** Obeticholic Acid; Global PBC; UK-PBC; Transplant-Free Survival; Propensity Score.

Primary biliary cholangitis (PBC) is a rare autoimmune cholestatic liver disease predominantly affecting women over the age of 40 years (approximately 6 in 1000).<sup>1,2</sup> It is characterized by progressive destruction of the intrahepatic bile ducts, leading to cholestasis, inflammation, and fibrosis. Without treatment, patients can progress to end-stage cirrhosis, resulting in hepatic decompensation and, without transplantation, death.<sup>3</sup>

Abnormal elevations in alkaline phosphatase (ALP) and bilirubin have been found to be independently associated with an increased risk of liver transplantation or death in patients with PBC.<sup>4</sup>

First-line therapy for PBC is ursodeoxycholic acid (UDCA), a bile acid found to improve ALP and bilirubin levels and, in recent real-world analyses, to improve transplant-free survival.<sup>3,5,6</sup> However, upwards of 40% of patients prescribed UDCA experience an inadequate response and require second-line therapy.<sup>7</sup> Inadequate response to UDCA is a strong predictor of hepatic complications and poor outcomes. A large international cohort study of more than 3000 patients with PBC on UDCA therapy reported a 10-year cumulative incidence of first hepatic

## WHAT YOU NEED TO KNOW

### BACKGROUND AND CONTEXT

Obeticholic acid (OCA), approved for use in ursodeoxycholic acid-intolerant or inadequate responders, has been shown to reduce alkaline phosphatase and other liver enzymes associated with adverse hepatic outcomes in patients with primary biliary cholangitis (PBC).

### NEW FINDINGS

Patients treated with OCA in the POISE double-blind, placebo-controlled trial and open-label extension experienced fewer liver transplantations and deaths vs comparable external controls from the Global PBC and UK-PBC registries.

### LIMITATIONS

The study compared patients treated with OCA treated in a clinical trial with external controls. We attempted to limit bias, but unobserved bias cannot be completely ruled out.

### IMPACT

Beyond improving biomarkers predictive of outcomes in PBC, these data provide evidence that OCA treatment improves transplant-free survival, increasing confidence in approving new therapies on the basis of surrogate markers for patients living with rare diseases.

complications of 32.4% in inadequate responders, as opposed to 6.2% in biochemical responders.<sup>8</sup> The only approved second-line therapy for PBC is obeticholic acid (OCA). Although there is evidence supporting the efficacy of peroxisome proliferator-activated receptor agonists, such as fibrates (eg, bezafibrate), their use remains off label.<sup>9–12</sup>

OCA received accelerated approval in the United States in June 2016, and conditional regulatory approval in the European Union in December 2016, for the treatment of patients with PBC who have an inadequate response to, or are intolerant of, UDCA. These initial approvals were based on results from the phase 3, randomized, double-blind (DB), placebo-controlled PBC OCA International Study of Efficacy (POISE) trial, which demonstrated a significant, sustained reduction in ALP. However, full approval of OCA was contingent on a post-approval requirement to confirm benefit by assessing the effect of OCA on clinical outcomes, such as hepatic decompensation, liver transplantation, and death.<sup>13,14</sup>

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**Abbreviations used in this paper:** ALP, alkaline phosphatase; ALT, alanine transaminase; AST, aspartate aminotransferase; CRF, case report form; DB, double blind; HR, hazard ratio; IPTW, inverse probability of treatment weights; IQR, interquartile range; OCA, obeticholic acid; OLE, open-label extension; POISE, Primary Biliary Cholangitis Obeticholic Acid International Study of Efficacy; PBC, primary biliary cholangitis; UDCA, ursodeoxycholic acid; ULN, upper limit of normal.

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0016-5085

<https://doi.org/10.1053/j.gastro.2022.08.054>

There are numerous challenges to conducting outcomes studies in PBC. As a rare disease, recruitment is difficult, especially when there are multiple trials competing for a small pool of qualifying patients. In trials for slow-progressing diseases, retention is difficult, as patients must remain in the trial for years in order to accumulate a sufficient number of clinical events. During this time, patients and treating physicians may choose to withdraw from the trial in favor of active treatment if hepatic function is declining and they conclude the patient has been randomized to placebo. In fact, questions have been raised broadly concerning the ethics of continuing a patient in a clinical trial when active therapy is an option.<sup>15,16</sup> Recent US Food and Drug Administration guidance recommends the use of real-world evidence from disease registries and other sources to fulfill post-marketing requirements in rare disease.<sup>17</sup>

In POISE, after the 12-month, randomized, placebo-controlled, DB phase of the trial, patients were rolled over into the open-label extension (OLE). Patients in the placebo arm were crossed over to OCA treatment and those in the OCA arm were maintained on therapy and followed for up to an additional 5 years.<sup>18,19</sup> The POISE study with DB and OLE phases provides a cohort of OCA-treated patients followed long term for safety. In order to use those data to evaluate clinical efficacy, a comparable non-OCA-treated comparator group was required (ie, an external control for a single-arm, open-label study). The Global PBC<sup>4</sup> and UK-PBC<sup>20</sup> registries provide a rich repository of longitudinal real-world information on more than 13,000 patients with PBC, an ideal source of data from which to construct external control groups for comparison with the treatment arm of the POISE study to evaluate OCA's effect on outcomes.

The objective of this study was to evaluate the long-term efficacy of OCA, comparing time to first occurrence of liver transplantation or death among patients treated with OCA in the POISE trial DB and OLE phases (hereafter referred to as the POISE study) with comparable non-OCA-treated external controls inadequately responding to UDCA from the Global PBC and UK-PBC disease registries.

## Methods

### Data Sources

Data from the following 3 sources were leveraged for the study: POISE DB and OLE, the Global PBC Registry, and the UK-PBC Registry. Each is described briefly.

**Primary Biliary Cholangitis Obeticholic Acid International Study of Efficacy double-blind and open-label extension.** POISE DB was a 12-month randomized, DB, placebo-controlled, phase 3 trial. Patients intolerant to, or with an inadequate response (defined as an ALP  $>1.67 \times$  upper limit of normal [ULN]) to, UDCA were recruited from 59 sites in 13 countries and randomized into 1 of the following 3 groups: OCA 10 mg; OCA 5 mg with titration to 10 mg; or placebo. The primary end point was ALP  $<1.67 \times$  ULN with a  $\geq 15\%$  reduction from baseline ALP and bilirubin  $\leq 1 \times$  ULN. Of the 216 patients randomized, 198 (92%) completed the 12-month placebo-controlled phase. Of the 193 patients who transferred to the OLE, 158 (82%) completed 4 years of OCA treatment and

116 (60%) completed 5 years. The primary reason for early OLE discontinuation was administrative study termination.<sup>15</sup>

**Global Primary Biliary Cholangitis Registry.** The Global PBC registry includes 6484 non-OCA-treated patients with PBC recruited from 17 liver centers across 8 countries in Europe and North America between September 2012 and August 2016. PBC diagnosis was based on 2 or 3 of the following criteria: cholestatic liver biochemistry, compatible or diagnostic liver histology, and antimitochondrial antibody at a titer  $>1:40$ . Detailed information on demographics, date of first PBC diagnosis, disease history, treatment history, histology (if available), and comorbidities was collected at baseline. Treatment, disease progression, and clinical outcomes were collected at regular follow-up intervals (between 6 and 12 months, depending on site).

**United Kingdom Primary Biliary Cholangitis Registry.** The UK-PBC registry includes more than 6900 non-OCA-treated patients with PBC recruited from 161 UK centers between February 2008 and December 2020. PBC diagnosis was confirmed using the same approach as the Global PBC registry. Detailed clinical information was collected at enrollment and at site-specific follow-up intervals, with a fixed study-wide update in 2016. Data collection included date of first presentation with PBC; patient self-reported age at diagnosis; antimitochondrial antibody status; liver biochemistry (ALP, bilirubin, ALT, AST, and albumin); liver histology-reported compatibility with PBC diagnosis (if biopsy had been performed); and patient self-reported therapy for PBC.

### Index Date

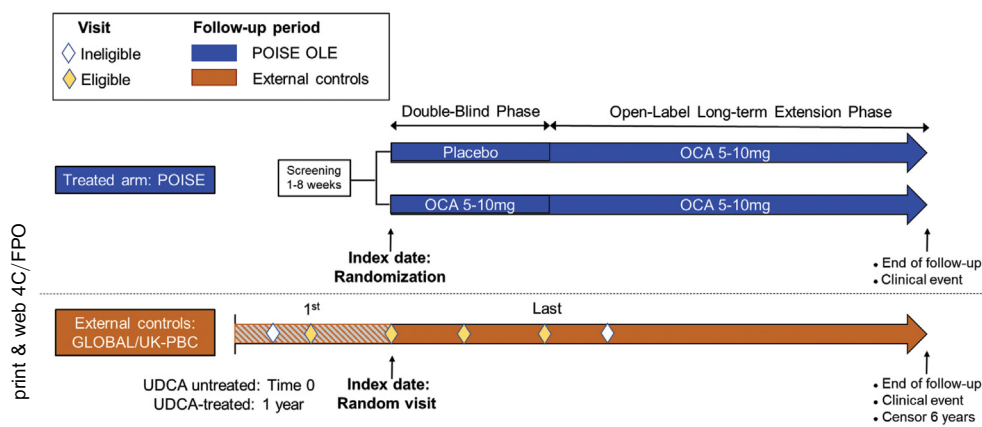
The index date was used to define the point at which follow-up observation for clinical end points begins. A schematic of the process to assign index date is shown in Figure 1. For patients randomized to receive OCA in POISE (in blue), the index date was the date of randomization. For patients initially randomized to receive placebo, the follow-up included an initial 12 months of non-OCA treatment.

For external controls, the index emulated the date of randomization to the degree possible. A qualifying visit was defined by meeting POISE inclusion criteria, including UDCA failure. All POISE exclusion criteria also had to be met, excepting 4 areas not assessed in the registries (ie, pregnancy; severe pruritus; concomitant medications; and specific comorbidities of Gilbert's syndrome, nonalcoholic steatohepatitis, human immunodeficiency virus, and cardiac arrhythmias).

In order to define an index date comparable with randomization date, each qualifying patient visit (represented by a diamond in Figure 1) was examined to determine whether the patient met eligibility criteria at that visit (yellow diamond) or did not (white diamond). From this, an eligibility period was established between the first visit that each control patient met POISE inclusion/exclusion criteria, and the last visit the patient met criteria. To emulate POISE randomization date, a random visit was selected between those dates (inclusive) to serve as the index date. Sensitivity analyses, using first and last eligible dates, were conducted to determine the degree to which this selection procedure affected study outcomes.

### Design of External Control Groups

The validity of a single-arm trial with external control hinges on the comparability of the trial arm and real-world study groups in terms of observed and unobserved baseline



**Figure 1.** Schematic of index date selection. Each qualifying patient visit (*diamond*) was examined to determine whether the patient met eligibility criteria at that visit (*yellow diamond*) or did not meet criteria (*white diamond*). An eligibility period was established between the first visit that each control patient met POISE inclusion/exclusion criteria, and the last visit the patient met criteria. A random visit was selected between those dates (inclusive), which served as the index date.

patient characteristics. As patients are not randomized to treatment or control, we employed a 2-step procedure to help ensure comparability. First, patients in the Global PBC and UK-PBC registries who met POISE inclusion/exclusion criteria at 1 or more visits were selected (Supplementary Table 1). The second step derived inverse probability of treatment weights (IPTW). Two logistic regressions were performed, 1 for each external cohort. The dichotomous outcome variable was treatment group (POISE arm vs each external control group). Predictor variables included age at baseline, sex, time in months since diagnosis (duration of disease), calendar year of diagnosis, liver biochemistry at baseline (ALP, bilirubin, AST, or ALT), and UDCA treatment at baseline.

The IPTW was estimated with the use of the propensity scores.<sup>21</sup> The boundaries due to extreme values ( $>10$ ) were reduced,<sup>22</sup> and the distribution of the weights based on the propensity scores were stabilized. The standardized mean difference and variance ratios for each covariate were calculated and tolerability was set at  $\pm 0.25$  standardized mean difference.

### Primary End Points

**All-cause death.** In the POISE study, all adverse events with a fatal outcome were reported as serious adverse events, including date of death. In the Global PBC and UK-PBC registries, sites reported death and date of death via case report form (CRF).

**Liver transplantation.** In the POISE study, liver transplantation was not recorded as an adverse event but as a surgical procedure, with the adverse events causing the subject to require a liver transplantation captured in the adverse event CRF. To assess liver transplantation, all POISE libraries (ie, raw data, clinical study report listings, analysis data model, and study data tabulation model) for both the DB and OLE phases were programmatically searched for the strings “liver” AND “trans.” The search was conducted by 2 investigators and results were reconciled (after initial results reporting).<sup>23</sup> Two liver transplantations were identified, both of which occurred before the end of study and were included in the primary analysis. In the Global PBC and UK-PBC registries, liver transplantation and date of transplantation were reported on the CRF.

### Secondary End Point

A secondary outcomes analysis was conducted adding hepatic decompensation to the composite end point. In the POISE study,

hepatic decompensation was defined via CRF as any of the following decompensating events: bleeding, spontaneous bacterial peritonitis, uncontrolled or diuretic-resistant ascites, and hepatic encephalopathy. Date of diagnosis for each condition was recorded.

Hepatic decompensating events were systematically collected in the Global PBC registry but, although collected, are not complete in the UK-PBC registry. Therefore, analyses including hepatic decompensation were only conducted using the Global PBC external control. The Global PBC CRF defined ascites as “ascitic fluid confirmed by abdominal imaging or in the event of prescribed diuretic treatment for clinically obvious ascites.” Hepatic encephalopathy was defined as “expert (physician) opinion.” Variceal bleeding was defined as “hematemesis or melena due to endoscopically documented haemorrhage originating from gastro-oesophageal varices.” Spontaneous bacterial peritonitis was reported if “confirmed by diagnostic paracentesis.”

### Primary Outcome Analysis

The primary outcome was time to first occurrence of liver transplantation or death, also referred to as “transplant-free survival.” In both groups, patients with events in the first 6 months were excluded per protocol, as this was assumed to reflect disease state and not treatment effect. Follow-up was censored at 6 years for external controls to match the maximum follow-up in the POISE study. Weighted Kaplan-Meier estimates (using the stabilized IPTWs) of the distribution of the time to event were tabulated and graphed by treatment group. Cox proportional hazards models were run to establish the hazard ratio (HR) and 95% CI (using the model-based SE) and a Wald test of cohort effect performed using the stabilized IPTWs comparing patients treated with OCA from the POISE OLE with external controls on the composite end point, applying a Firth correction due to the small number of events in the treatment arm.<sup>24,25</sup> Additional models included univariate, unweighted multivariable (adjusting for the same predictors used in the propensity score, see Supplementary Table 2); and the above weighted analyses. Variables not suitably balanced through propensity score were included as covariates in all outcomes analyses.

### Secondary Outcome Analysis

The secondary outcome—time to first occurrence of liver transplantation or death or hepatic decompensation—was

conducted using the Global PBC external control only, as hepatic decompensation was not systematically collected in the UK-PBC registry. As in the primary analysis, follow-up was censored at 6 years for external controls; weighted Kaplan-Meier estimates (using the stabilized IPTWs) of the distribution of the time to event were tabulated and graphed by treatment arm and control group. Cox proportional hazards models were run to establish the HR and 95% CI (using the model-based SE) and a Wald test of cohort effect was performed using the stabilized IPTWs comparing patients treated with OCA from the POISE OLE with external controls, applying a Firth correction due to the small number of events in the treatment arm.

### Sensitivity Analyses

Three sensitivity analyses were performed. The first examined the impact of index date on outcomes. Cox proportional hazards and Wald test of cohort effect on time to first occurrence of liver transplantation or death were performed using first and last qualifying visit as index date in both the UK-PBC and Global PBC databases.

The second sensitivity analysis was a subgroup analysis in patients with and without cirrhosis in the Global PBC dataset (cirrhosis was not consistently quantified in the UK-PBC registry). In both the POISE study and Global PBC, cirrhosis was defined as 1 or more of the following: biopsy stage 4; transient elastography  $\geq 16.9$  kPa; radiological evidence (eg, nodular liver or enlargement of portal vein plus splenomegaly); clinical features of portal hypertension, defined as platelet count  $< 140,000/\text{mm}^3$  with persistent decrease in serum albumin or total bilirubin  $> 2 \times \text{ULN}$ ; or prothrombin time/international normalized ratio greater than ULN (not due to antithrombotic use).

The third sensitivity analysis, conducted using both the Global PBC and UK-PBC external controls, tested the hypothesis that there was residual, unmeasured selection bias, in which POISE study investigators selected healthier patients for the trial, and that any effect observed was due to the external controls representing patients with more progressed disease. To test this hypothesis, POISE patients randomized to receive placebo during their first year (ie, not treated with OCA) were compared with non-OCA-treated Global PBC external controls during their first year of observation, examining change in ALP, bilirubin, and AST from baseline to 12 months. If external controls represented a sicker population, it was anticipated that biomarkers would deteriorate and be worse at 12 months vs the non-OCA-treated placebo patients in POISE, indicating faster disease progression.

As sensitivity analyses were conducted to explore potential bias, point and variance estimates were calculated, but formal statistical testing with *P* values was not performed.

## Results

### Subject Selection and Propensity Score

Of the 4922 patients in the Global PBC registry, 1381 met POISE inclusion criteria, with 6702 qualifying visits. Of the 6543 patients in the UK-PBC registry, 2135 patients met POISE inclusion criteria, with 8331 qualifying visits. A full waterfall diagram is included in [Supplementary Figure 1](#). Of

the 216 patients in the POISE DB trial, 7 patients who were randomized to receive placebo and did not cross over to active treatment were excluded from the analysis, leaving a final sample of 209 patients. No patients in Global PBC were treated with OCA or fibrates. In UK-PBC, 32 patients were treated with fibrates and 54 with OCA,  $< 4\%$  of the sample. As this was an intent-to-treat analysis, these patients were not censored.

The baseline characteristics of each cohort before propensity score application are shown in [Table 1](#). The samples were closely aligned on baseline characteristics before propensity scoring, reflecting the epidemiology of patients with PBC as predominantly female, diagnosed in their 50s and 60s, with the majority receiving UDCA therapy between 900 and 1000 mg/d for 3.5–4 years at index. Year of index visit was earlier for the Global PBC cohort, while duration of disease was higher for the POISE group. Both variables were included in the propensity score.

The list of variables included in the logistic regression and propensity score are shown in [Supplementary Table 2](#). For Global PBC, an additional ALP–bilirubin interaction term was added to the model due to the high correlation between these baseline variables in this dataset. [Figure 2](#) shows the balance of baseline variables, in standardized variable differences, between POISE and Global PBC ([Figure 2A](#)) and between POISE and UK-PBC ([Figure 2B](#)) before and after propensity score application. All variables were within the prespecified range ( $\pm 0.25$  standardized variable difference).

In the UK-PBC cohort, ALT remained unbalanced and was removed from the propensity scoring and weighting and was instead included as a covariate in outcomes analyses. Although PBC duration was slightly outside the prespecified range (standardized variable difference = 0.259), it was retained in the propensity score and weighting and was not added as a separate covariate in the outcomes model.

Using reverse Kaplan-Meier on the weighted sample, median follow-up in the Global PBC analysis was 5.7 years in POISE and 4.1 years in the Global PBC—a difference of 1.6 years more follow-up in the POISE cohort. In the UK-PBC analysis, median follow-up in POISE was 5.4 years and 6.3 years in the UK-PBC—a difference of 0.9 more years in the UK-PBC cohort. During follow-up, median OCA exposure in the POISE cohort was 65 months (interquartile range [IQR], 50.0–70.0 months). Median weighted OCA daily dose was 8.3 mg (IQR, 5.7–9.8 mg). In Global PBC, there was no permanent discontinuation of UDCA during follow-up, and median dose during follow-up was 900 mg (IQR, 900–1200 mg), indicating dose was stable from index throughout follow-up. In UK-PBC, of the 1739 patients treated with UDCA at the random index visit for whom UDCA follow-up data were available, 293 (16.8%) discontinued UDCA during follow-up. Dose stability was not characterized.

### Primary Outcome: Liver Transplantation or Death

[Figure 3](#) presents the Kaplan-Meier curves for transplant-free survival comparing POISE with Global PBC ([Figure 3A](#)) and UK-PBC ([Figure 3B](#)). The curves begin

**Table 1.** Baseline (Unmatched) Characteristics of the POISE Open-Label Extension, Global PBC, and UK-PBC Cohorts

Characteristic	POISE OLE (n = 209)	Global PBC (n = 1381)	UK-PBC (n = 2135)
Female, n (%)	190 (90.9)	1253 (90.7)	1907 (89.3)
UDCA, n (%)	197 (94.3)	1265 (91.6)	1849 (86.6)
UDCA dose, mg, median (IQR) <sup>a</sup>	1000 (900–1250)	900 (750–1050)	1000 (750–1000)
Duration of UDCA treatment, mo, median (IQR)	46 (20–95)	40 (16–90)	48 (12–89)
Year of diagnosis, median (IQR)	2005 (2000–2009)	1999 (1994–2003)	2004 (2000–2009)
Year of visit, median (IQR)	2012 (2012–2012)	2005 (2000–2009)	2011 (2006–2015)
Age, y, mean (SD)	55.7 (10.6)	56.9 (12.3)	60.55 (11.6)
Duration of disease, y, median (range)	7.8 (3.6–12.6)	4.5 (2.1–7.9)	4.5 (1.7–9.1)
ALP, ×ULN, median (range)	2.41 (2.00–3.15)	2.08 (1.75–2.81)	2.16 (1.78–3.03)
Bilirubin, ×ULN, median (range)	0.47 (0.34–0.67)	0.67 (0.45–1.09)	0.57 (0.40–1.00)
AST, ×ULN, median (range)	1.68 (1.20–2.36)	1.20 (0.88–1.78)	—
ALT, ×ULN, median (range)	2.09 (1.44–3.02)	—	1.16 (0.74–1.84)
Cirrhosis at inclusion, n (%)	36 (17.2)	197 (14.3)	—

NOTE. The samples were closely aligned on baseline characteristics before propensity scoring. Year of index visit was earlier for the Global PBC cohort and duration of disease was higher for the POISE group. Both variables were included in the propensity score.

<sup>a</sup>UDCA baseline dose data were available for 1169 patients in Global PBC and 201 patients in UK-PBC.

separating at 12–18 months. During the 6-year follow-up period, there were 5 composite events (2 liver transplantations and 3 deaths) in 209 subjects in the POISE study (2.4%), 135 events (51 liver transplantations and 84 deaths) in 1381 patients in the Global PBC external control group (10.0%), and 281 events (119 liver transplantations and 162 deaths) in 2135 patients in the UK-PBC control group (13.2%). Figure 4 presents the Cox regression HRs and 95% CIs for POISE vs Global PBC and UK-PBC, including univariate, multivariable, and weighted analyses for random index date and first and last qualifying visit. The pre-specified primary analysis using IPTW for the random index date yielded HRs of 0.29 (95% CI, 0.10–0.83;  $P = .02$ ) for POISE vs Global PBC and 0.30 (95% CI, 0.12–0.75;  $P < .01$ ) for POISE vs UK-PBC, indicating that patients treated with OCA in a trial setting had significantly greater transplant-free survival than patients in either external control group. All analyses for the random index date, including univariate and multivariable, produced similar point estimates. When events that occurred in the first 6 months after index were not excluded, the results for Global PBC (HR, 0.26; 95% CI, 0.09–0.74;  $P = .01$ ) and UK-PBC (HR, 0.25; 95% CI, 0.10–0.60;  $P = .02$ ) did not differ meaningfully and remained statistically significant.

### Secondary Outcome: Decompensation, Liver Transplantation, or Death

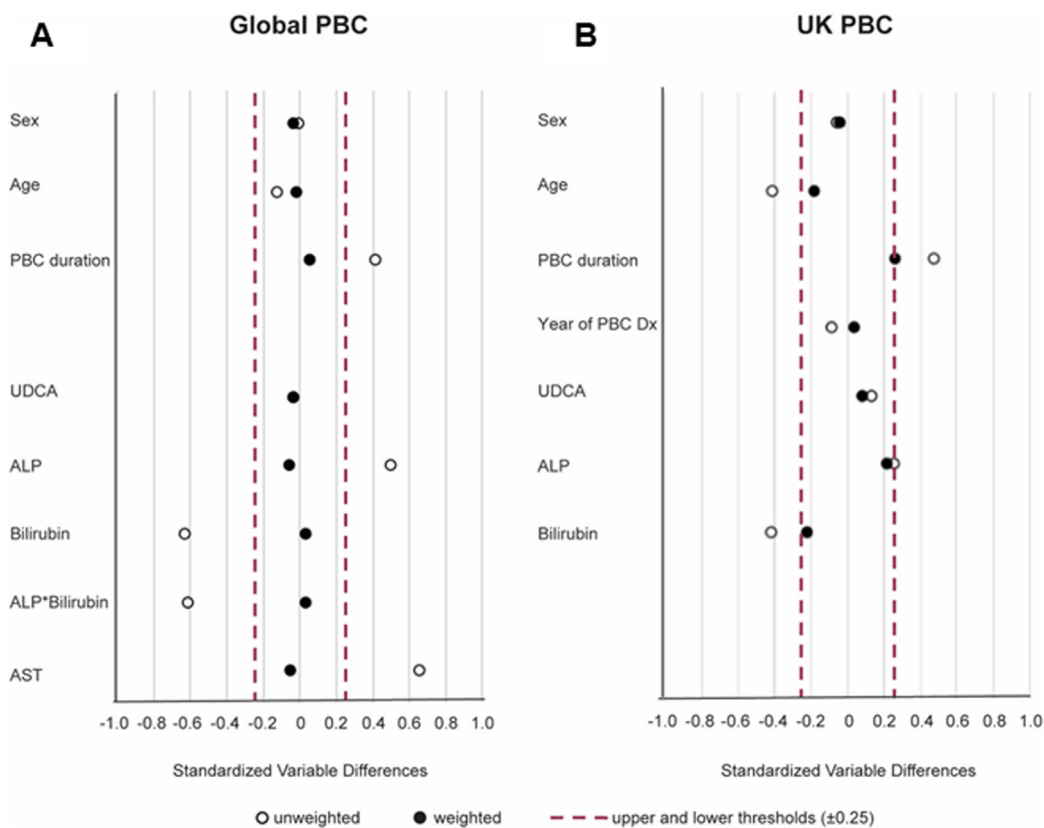
During the 6-year follow-up period, there were 16 events of death, liver transplantations, or hepatic

decompensation in 209 subjects in the POISE study and 212 events in 1381 patients in the Global PBC external control group. The IPTW HR was 0.42 (95% CI, 0.21–0.85;  $P = .02$ ), indicating that patients treated with OCA in a trial setting had significantly greater event-free survival than patients in the Global PBC control group. The Kaplan-Meier curve is shown in Figure 5.

### Sensitivity Analyses

Three sets of sensitivity analyses were conducted. The first assessed the effect of varying the index date for the control groups on the HR estimates in both the Global PBC and UK-PBC databases. Figure 4 shows the HRs for death or liver transplantation for POISE vs Global PBC and UK-PBC in univariate, multivariable, and weighted Cox regressions for the random index date (primary analysis), first qualifying visit date, and last qualifying visit date. The HRs were all  $\leq 0.52$ , and overall slightly higher for first qualifying visit and slightly lower for last qualifying visit. The 95% CIs all overlapped.

The second sensitivity analysis was a subgroup analysis examining event rates for patients with or without cirrhosis in the POISE patients treated with OCA vs external controls from Global PBC. Using the random index date, the HR for death or liver transplantation among patients with evidence of cirrhosis for patients treated with OCA in POISE vs Global PBC controls was 0.20 (95% CI, 0.03–1.22). For patients without cirrhosis, HR was 0.31 (95% CI, 0.09–1.04). Thus, although the effect size was somewhat larger in the patients



**Figure 2.** Standard variable differences for POISE vs Global PBC (A) and POISE vs UK-PBC (B) for unadjusted and adjusted baseline variables included in logistic regression and propensity score. The balance of baseline variable differences following propensity score application is shown. (A) An additional ALP–bilirubin interaction term was added due to the high correlation between baseline variables in the dataset. All variables were in the prespecified range ( $\pm 0.25$  standardized variable difference). (B) ALT remained unbalanced in the UK-PBC control and was thus included as a covariate in the outcomes analyses. PBC duration was slightly outside the prespecified range, but was retained in the propensity score weighting and not added as a separate covariate in the model. DX, diagnosis.

with evidence of cirrhosis, the CIs were widely overlapping, indicating no significant difference between patients with or without cirrhosis.

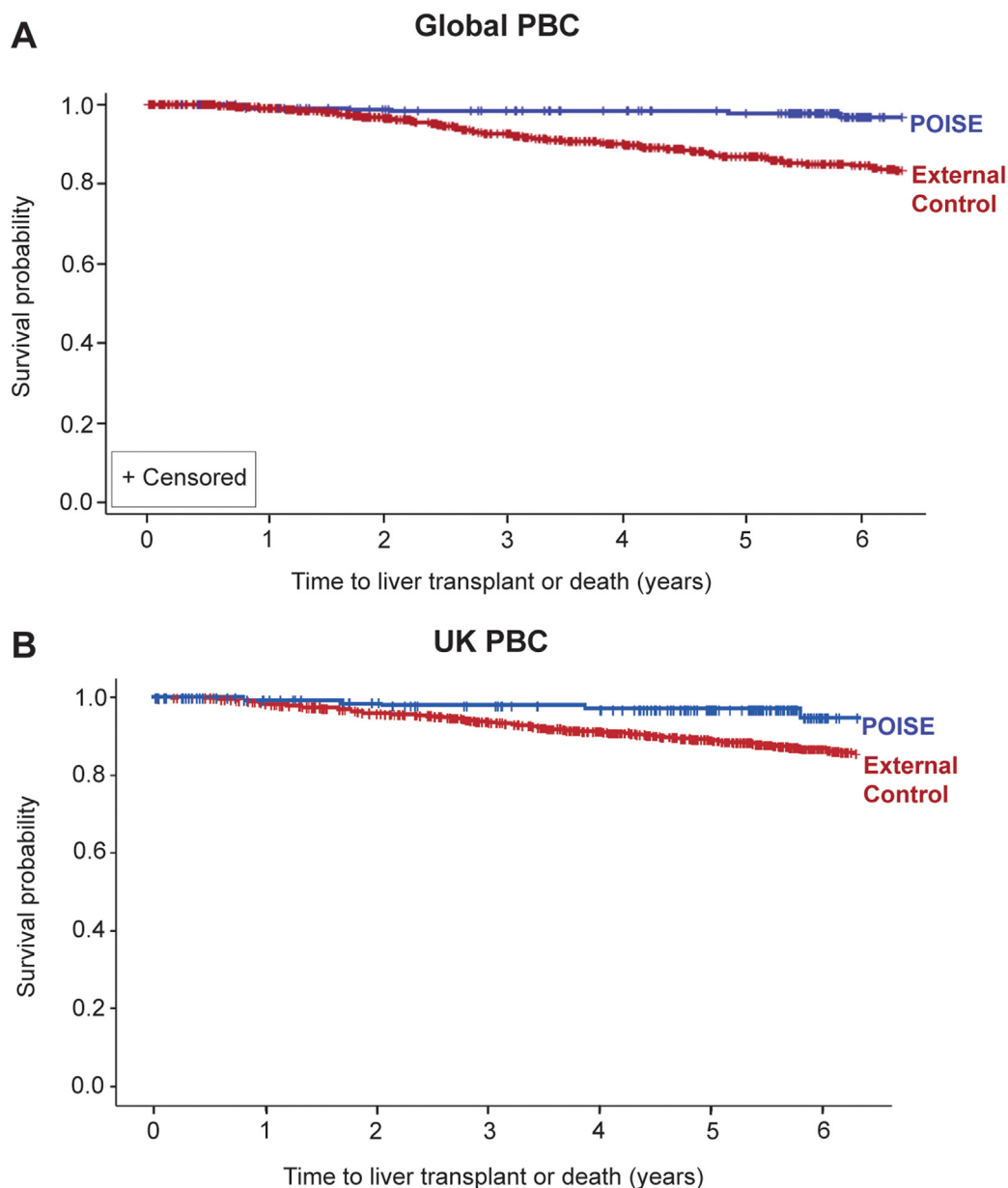
The third sensitivity analysis assessed the possibility that there was positive but unmeasured selection bias, resulting in a healthier cohort in the POISE study vs the Global PBC and UK-PBC external controls. Table 2 shows change from baseline to 12 months for ALP, bilirubin, and AST/ALT (expressed in ULN) for the patients randomized to placebo in the POISE DB (non-OCA-treated) compared with the patients in Global PBC and UK-PBC external controls (non-OCA-treated). Both external control groups showed improvement in ALP ( $-0.26$  ULN and  $-0.29$  ULN) vs a small decrease ( $-0.08$  ULN) or small increase ( $0.07$  ULN) in the OCA placebo group. There was a slight increase in bilirubin in the POISE placebo group ( $0.07$  ULN) vs no change in the Global PBC external control, and small increases in bilirubin in both POISE placebo ( $0.04$  ULN) and UK-PBC ( $0.10$  ULN) groups. There were small decreases in AST for both POISE placebo ( $-0.04$  ULN) and Global PBC ( $-0.08$  ULN). There was improvement in ALT in the UK-PBC control ( $-0.23$  ULN) vs a small decrease in the POISE placebo group ( $-0.10$  ULN). With the exception of bilirubin in the UK-PBC control, which showed a slightly greater increase vs POISE placebo (an

absolute difference of  $0.06$  ULN), all changes in biomarkers from baseline to 12 months favored the external control groups numerically.

An ad hoc sensitivity analysis was conducted in which events that occurred in the first 6 months after index were not excluded. The results for Global PBC (HR,  $0.26$ ; 95% CI,  $0.09$ – $0.74$ ;  $P = .01$ ) and UK-PBC (HR,  $0.25$ ; 95% CI,  $0.10$ – $0.60$ ;  $P = .02$ ) did not differ meaningfully and remained statistically significant.

## Discussion

PBC is a rare disease with limited treatment options. With up to 40% of patients not responding adequately to first-line UDCA therapy, the approval of OCA as second-line treatment represented an important therapeutic advance. However, regulatory approval was based on improvement in ALP and other biomarkers predictive of outcomes, such as hepatic decompensation, liver transplantation, and death. The goal of therapy in patients with PBC is to prevent progression to these events, and this is the first study to demonstrate that treatment with OCA is associated with a reduction in death, liver transplantation, and hepatic decompensation. These data add



Total Number of Events	POISE (n=5)	Global PBC (n=135)	UK PBC (n=281)
Liver transplantation	2	51	119
Death	3	84	162

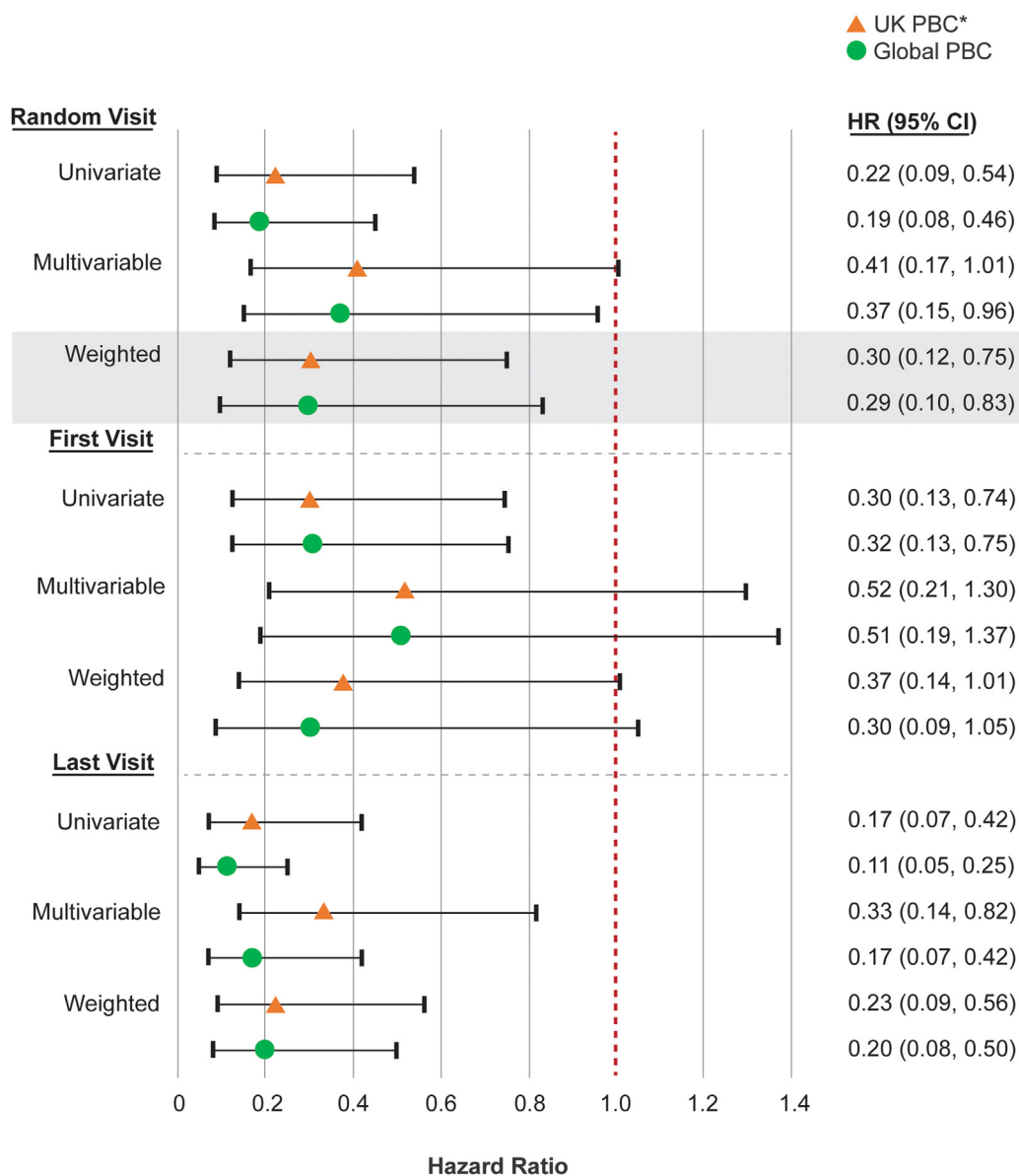
**Figure 3.** Kaplan-Meier curves for transplant-free survival comparing POISE with Global PBC (A) and UK-PBC (B) external controls. \*UK-PBC: ALT included as a covariate. Kaplan-Meier curves for transplant-free survival comparing POISE with Global PBC (A) and UK-PBC (B) begin separating at 12–18 months. During the 6-year follow-up period, there were 5 composite events in 209 subjects in the POISE study, 135 events in 1381 patients in the Global PBC external control group, and 281 events in 2135 patients in the UK-PBC control group.

to an accumulating body of real-world evidence showing a positive effect of OCA treatment on hepatic biomarkers, fibrosis, and PBC risk scores,<sup>1,2,26–28</sup> and support current guidance, which recommend initiation of second-line therapy if UDCA is not tolerated or if there is an

inadequate response at 6–12 months after starting UDCA.<sup>29,30</sup>

Both the strengths and limitations of this study lie in the use of real-world data to assess drug efficacy. PBC has a long natural history and, although drug approval on the basis of

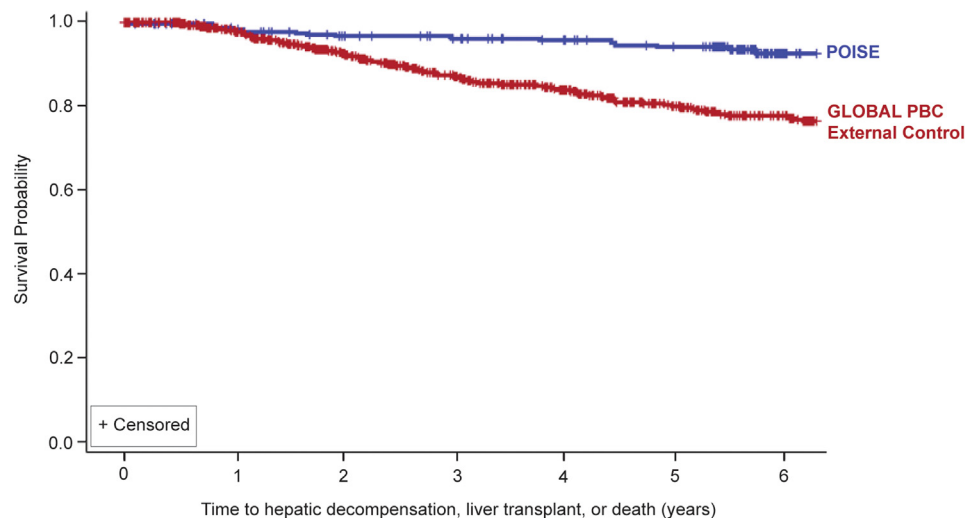




**Figure 4.** HRs for death or liver transplantation for POISE vs Global PBC and UK-PBC in univariate, multivariable, and weighted Cox regressions for random index date, first qualifying visit date, and last qualifying visit date. \*UK-PBC: ALT included as a covariate. Predictor variables in multivariable analyses included age at baseline, sex, time in months since diagnosis (duration of disease), calendar year of diagnosis, liver biochemistry at baseline (ALP, bilirubin, AST, or ALT), and UDCA treatment at baseline. Patients treated with OCA in a trial setting had significantly greater transplant-free survival than patients in external control groups. All analyses for the random index date produced similar point estimates.

surrogate biomarkers can accelerate bringing needed therapies to market, once approved it is challenging to carry out long-term, placebo-controlled, outcomes trials. Real-world data can be used to demonstrate clinical efficacy, as it did for UDCA.<sup>6</sup> The strength of this study, a single-arm trial with external controls, is its novel and thorough approach to ensuring the treatment and control groups were as comparable as possible. From applying POISE inclusion/exclusion criteria, propensity scoring and inverse proportional treatment weighting, testing for unobserved bias by assessing various index dates, and comparing POISE placebo patients with untreated matched controls for potential selection bias, the

methodical approach provides confidence that the Global PBC and UK-PBC cohorts represented valid and comparable control comparators. The consistency of results across analyses also increases confidence in the observed outcomes. The effect sizes and variance estimates were remarkably similar between replicate external controls (Global PBC: HR, 0.29; 95% CI, 0.10–0.83; UK-PBC: HR, 0.30; 95% CI, 0.12–0.75), despite differences in the makeup of these 2 cohorts. The results were similar regardless of whether the analysis was univariate, multivariable, or weighted. The effect size was consistent in patients with and without cirrhosis. And the effect persisted when hepatic decomposition was added to the



FIRST EVENT	POISE (n=16)	Global PBC (n=212)
Decompensation	12	126
Liver Transplant*	1	23
Death	3	63

**Figure 5.** Kaplan-Meier curves for time to first occurrence of hepatic decompensation, liver transplantation, or death comparing POISE with Global PBC external controls (random visit). \*Of the 2 patients with liver transplantation in the primary outcomes analysis, 1 had hepatic decompensation before the transplantation in the secondary outcomes analysis. Patients treated with OCA in a trial setting had significantly greater event-free survival (composite end point of decompensation, liver transplantation, or death) than patients in the Global PBC external control group (HR, 0.42; 95% CI, 0.21–0.85;  $P = .02$ ).

composite end point. The results are also similar to results modeled from the POISE trial based on biochemical response.<sup>31</sup>

Real-world studies also have limitations. Despite a methodical approach to ensuring the treatment arm and external control groups were comparable at baseline, patients were not randomized and one cannot rule out unobserved bias. There remains the possibility that physicians avoided enrolling sicker patients in the POISE trial, and that this selection bias could not be adequately assessed examining differences in biomarkers between untreated placebo patients and external controls in the first year. The small number of deaths and liver transplantations in the POISE

treatment arm ( $n = 5$ ) in the primary analysis can raise legitimate questions as to the reliability of the observation, although the effect persisted when the events increased 3-fold with the addition of hepatic decompensation. Although baseline UDCA exposure was similar between groups, as was baseline dose (acknowledging limitations of available dosing data), there was limited information on dose stability in the UK-PBC cohort. So, although UDCA treatment continuation and dose stability are unlikely confounders in the Global PBC cohort, it is not possible to rule these out as potential confounders in the UK-PBC analysis. One can also question the generalizability of results to a broader population, given the relative health of patients

**Table 2.** Change in Alkaline Phosphatase, Bilirubin, and Aspartate Aminotransferase From Baseline to 12-Month for Patients Randomized to Placebo in the POISE Double-Blind and Patients in Global PBC and UK-PBC External Controls

Variable	Change from baseline to 12 mo (in ULN), mean (95% CI)		
	ALP	Bilirubin	AST
POISE placebo	-0.08 (-0.53 to 0.23)	0.07 (-0.04 to 0.16)	-0.04 (-0.28 to 0.26)
GLOBAL PBC	-0.26 (-0.72 to 0.12)	0.00 (-0.18 to 0.13)	-0.08 (-0.34 to 0.12)
Variable	ALP	Bilirubin	ALT
POISE placebo	0.07 (-0.34 to 0.48)	0.04 (-0.13 to 0.20)	-0.10 (-0.11 to 0.31)
UK-PBC	-0.29 (-0.9 to 0.80)	0.10 (0.03 to 0.16)	-0.23 (-0.31 to -0.15)

NOTE. All changes in biomarkers from baseline to 12 mo numerically favored the external control groups, with the exception of bilirubin in the UK-PBC control group.

enrolled in the POISE trial, although here again the consistency of effect in patients with and without cirrhosis is encouraging. And one can question specific methodologic choices, such as including platelet count as part of a definition of cirrhosis in a sensitivity analysis vs including it as a control variable in a propensity score.

Reductions in ALP, AST, ALT, and bilirubin are epidemiologically associated with improved hepatic outcomes in PBC, and in both clinical trials and real-world studies, treatment with OCA has been found to improve these biomarkers.<sup>15,28,32</sup> Pharmacologically lowering these biomarkers with UDCA has been found to reduce clinical events.<sup>6</sup> This study provides the first data indicating that OCA, beyond reducing cholestasis surrogate markers, is associated with improved transplant-free survival in patients with PBC who have an inadequate response to, or are intolerant of, UDCA. The results of this analysis support the continued use of long-term OCA therapy to optimize the prognosis of patients with PBC, as well as the use of surrogate markers to accelerate drug approval in rare disease.

## Supplementary Material

Note: To access the supplementary material accompanying this article, visit the online version of *Gastroenterology* at [www.gastrojournal.org](http://www.gastrojournal.org), and at <https://doi.org/10.1053/j.gastro.2022.08.054>.

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#### 1371 Acknowledgments

1372 UK-PBC Consortium: Richard Sturgess, Aintree University Hospitals National  
1373 Health Service (NHS) Foundation Trust; Christopher Healey, Airedale NHS  
1374 Foundation Trust; Andrew Yeoman, Aneurin Bevan University Health Board;  
1375 Anton Gunasekera, Ashford & St Peter's Hospitals NHS Foundation Trust;  
1376 Meera Kirby, Barking, Havering and Redbridge University Hospitals NHS  
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#### Data Availability Statement

All data supporting the findings of this analysis are available within the article and its [Supplementary Materials](#). Questions regarding additional data availability should be directed to the study sponsor through the corresponding author.

#### Conflicts of interest

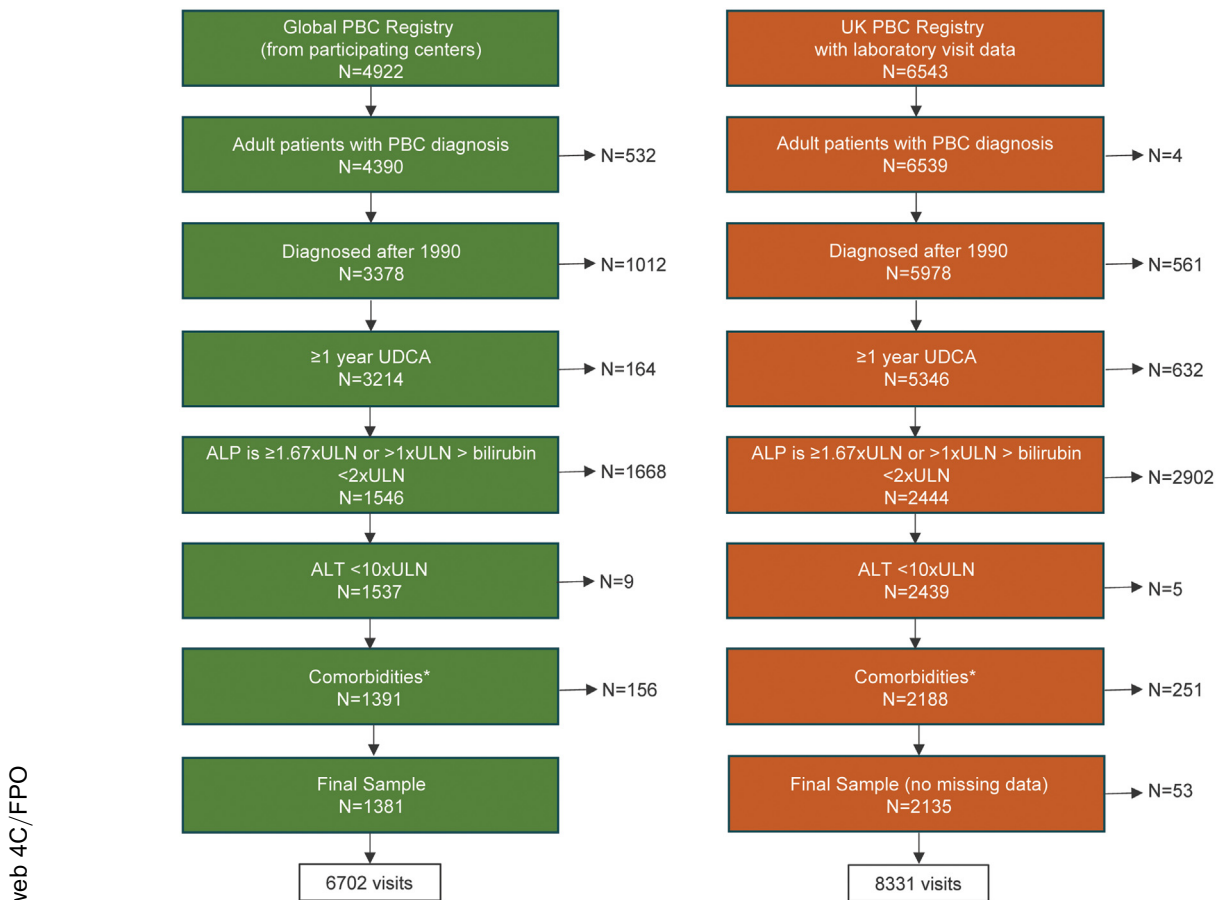
These authors disclose the following: Femi Adekunle, Elizabeth Malecha, Erik Ness, and Tracy Mayne are employees of Intercept Pharmaceuticals. Christopher Bowlus, Tony Bruns, Marco Carbone, Holly Fisher, Aliya Gulamhusein, Bettina Hansen, Gideon Hirschfield, Ana Lleo, Frederik Nevens, C. Fiorella Murillo Perez, Michael Trauner, Palak Trivedi, Adriaan van der Meer, and James Wason are consultants for Intercept Pharmaceuticals. Ana Lleo, Maria-Carlota Londoño, and Michael Trauner received honoraria from Intercept Pharmaceuticals. Kris Kowdley, Andrew Mason, and Michael Trauner received grant support from Intercept Pharmaceuticals. The remaining authors disclose no conflicts.

#### Funding

This study was funded through a collaborative research agreement with Intercept Pharmaceuticals.

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**Supplementary Figure 1.** Flow diagram of application of POISE inclusion and exclusion criteria to Global PBC and UK-PBC cohorts. \*History of spontaneous peritonitis, variceal bleeding, ascites, encephalopathy, or hepatocellular carcinoma within the first 6 mo.

**Supplementary Table 1.** POISE Criteria Used for Creation of External Control Arms

Inclusion criteria	Exclusion criteria
PBC diagnosis as demonstrated by the presence of 2 or more of the following 3 diagnostic factors:	History or presence of other concomitant liver disease, including:
History of elevated ALP levels for at least 6 mo	Hepatitis C virus infection
Positive AMA titer or PBC-specific antibodies	Active hepatitis B infection
Liver biopsy consistent with PBC	Primary sclerosing cholangitis
1 or more of the following biochemistry values:	Alcoholic liver disease
ALP $\geq 1.67 \times$ ULN and total bilirubin $< 2 \times$ ULN	Definite autoimmune liver disease or overlap hepatitis
Total bilirubin $> \text{ULN}$ but $< 2 \times$ ULN	Nonalcoholic steatohepatitis (hepatic steatosis by ultrasound, CT, MRI, TE, or body mass index $> 30 \text{ kg/m}^2$ )
Age $\geq 18$ y	Insufficient follow-up: at least annually clinical assessment in the absence of cirrhosis, and a least every 6 mo in the presence of cirrhosis.
Taking UDCA for at least 12 mo without interruption before index date at a dose of 13–15 mg/kg, or;	Missing date of therapy initiation or clinical event
not treated with UDCA $\geq 3$ mo before index date	Presence of clinical complications of PBC or clinically significant hepatic decompensation within the first 6 mo of follow-up, including:
Diagnosis year $> 1990$	History of liver transplantation, current placement on a liver transplant list, or current MELD score $\geq 15$ .
	Cirrhosis with complications, including history or presence of:
	Variceal bleed
	Refractory ascites (cannot be mobilized or the early recurrence of which cannot be prevented because of a lack of response to sodium restriction and diuretic treatment
	Hepatic encephalopathy
	Spontaneous bacterial peritonitis
	Known or suspected HCC
	ALT levels $> 10 \times$ ULN at baseline
	Known history of human immunodeficiency virus infection
	Medical conditions that may cause nonhepatic increases in ALP (eg, Paget's disease or fractures within 3 mo before day 0)
	Use of fibrates (POISE and Global PBC only)
	Participation in another investigational drug, biologic, or medical device trial within 30 d before screening

AMA, antimitochondrial antibody; CT, computed tomography; HCC, hepatocellular carcinoma; MELD, Model for End-Stage Liver Disease; MRI, magnetic resonance imaging; TE, transient elastography.

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**Supplementary Table 2.** Results of Propensity Score Logistic Regression

Parameter	Global PBC			UK PBC		
	Coefficient	SE	P value	Coefficient	SE	P value
Intercept	-3.7972	0.7362	<.01	57.556	31.4263	.07
Age	-0.00515	0.00757	.50	0.0563	0.00738	<.01
Sex (UK PBC: ref: female; Global PBC: ref: male)	-0.8174	0.2943	<.01	0.2022	0.1339	.13
LN (bilirubin, ×ULN)	-5.1106	0.8732	<.01	0.7712	0.1385	<.01
LN (ALP, ×ULN)	0.8513	0.5757	.14	-0.4365	0.1678	<.01
LN (AST, ×ULN)	3.8747	0.4702	<.01	NA	NA	NA
LN (ALP*bilirubin)	3.4616	1.9504	.08	NA	NA	NA
LN (duration of PBC in months)	1.4937	0.2577	<.01	-0.8234	0.1201	<.01
Calendar year of PBC diagnosis	—	—	—	-0.0271	0.0155	.08
UDCA (ref: no)	0.1146	0.3651	.75	-0.1526	0.1544	.32

LN, natural logarithm; NA, not applicable; ref, reference.