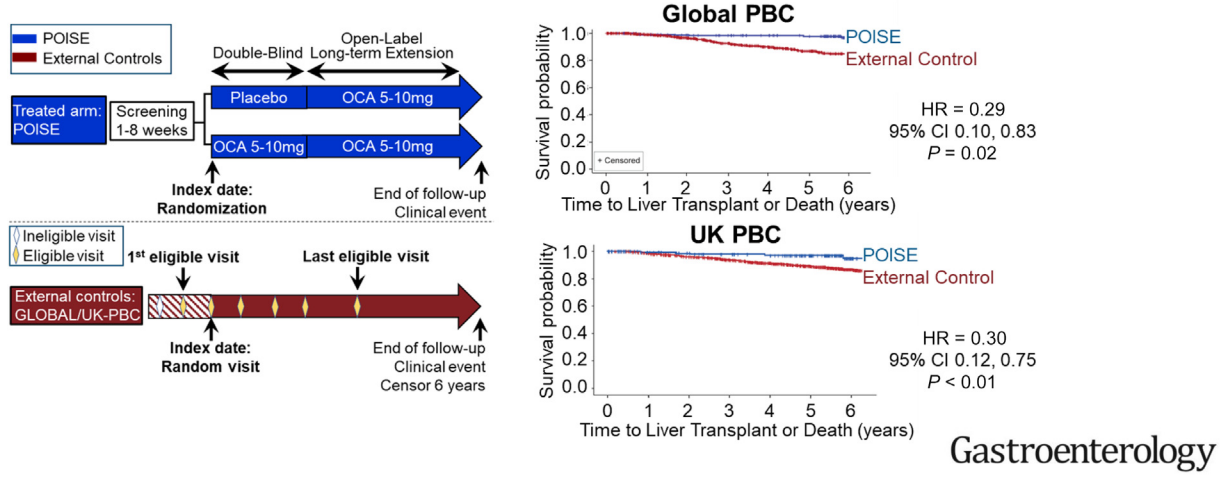
Gastroenterology 2022;163:1630–1642

HEPATOBILIARY

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

C. Fiorella Murillo Perez,[1,*] **Holly Fisher**,[2,*] Shaun Hiu,[2] Dorcas Kareithi,[2] Femi Adekunle,[3] Tracy Mayne,[3] Elizabeth Malecha,[3] Erik Ness,[3] Adriaan J. van der Meer,[4] Willem J. Lammers,[4] Palak J. Trivedi,[5] Pier Maria Battezzati,[6] Frederik Nevens,[7] Kris V. Kowdley,[8] Tony Bruns,[9] Nora Cazzagon,[10] Annarosa Floreani,[10] Andrew L. Mason,[11] Albert Parés,[12,13] Maria-Carlota Londoño,[12,13] Pietro Invernizzi,[13,14,15] Marco Carbone,[16] Ana Lleo,[17,18] Marlyn J. Mayo,[19] George N. Dalekos,[13,20] Nikolaos K. Gatselis,[13,20] Douglas Thorburn,[21] Xavier Verhelst,[22] Aliya Gulamhusein,[1] Harry L. A. Janssen,[1,4] Rachel Smith,[23] Steve Flack,[24] Victoria Mulcahy,[24] Michael Trauner,[25] Christopher L. Bowlus,[26] Keith D. Lindor,[27] Christophe Corpechot,[28] David Jones,[2] George Mells,[29] Gideon M. Hirschfield,[1] James Wason,[30,§] and Bettina E. Hansen,[1,31,32,§] on behalf of GLOBAL PBC Study Group and the members of the UK-PBC Consortium

[1]Toronto Centre for Liver Disease, Toronto General Hospital, University of Toronto, Toronto, Ontario, Canada; [2]Newcastle University, Newcastle upon Tyne, United Kingdom; [3]Intercept Pharmaceuticals, Morristown, New Jersey; [4]Department of Gastroenterology and Hepatology, Erasmus MC University Medical Center Rotterdam, Rotterdam, The Netherlands; [5]University of Birmingham, Birmingham, United Kingdom; [6]Università degli Studi di Milano, Milan, Italy; [7]University Hospital Katholieke Universiteit Leuven, Leuven, Belgium; [8]Liver Institute Northwest, Seattle, Washington; [9]Department of Gastroenterology and Hepatology, University Hospital Rheinisch-Westfälische Technische Hochschule Aachen University, Aachen, Germany; [10]University of Padova, Padova, Italy; [11]Department of Medicine, University of Alberta, Edmonton, Alberta, Canada; [12]Department of Medicine, Liver Unit, Hospital Clínic, University of Barcelona, The August Pi i Sunyer Biomedical Research Institute, Biomedical Research Networking Center in Hepatic and Digestive Diseases, Barcelona, Spain; [13]European Reference Network on Hepatological Diseases, Barcelona, Spain; [14]Division of Gastroenterology, Center for Autoimmune Liver Diseases, Department of Medicine and Surgery, University of Milano-Bicocca, Monza, Italy; [15]San Gerardo Hospital, Monza, Italy; [16]University of Milano-Bicocca, Monza, Italy; [17]Department of Biomedical Sciences, Humanitas University, Pieve Emanuele, Milan, Italy; [18]IRCCS Humanitas Research Hospital, Rozzano, Milan, Italy; [19]Department of Medicine, Division of Digestive and Liver Disease, University of Texas, Southwestern Medical Center, Dallas, Texas; [20]Department of Medicine and Research Laboratory of Internal Medicine, National Expertise Center of Greece in Autoimmune Liver Diseases, General University Hospital of Larissa, Larissa, Greece; [21]Royal Free London National Health Service Foundation Trust, London, United Kingdom; [22]Department of Hepatology, Ghent University Hospital, Ghent, Belgium; [23]Cambridge Liver Unit, Cambridge University Hospitals National Health Service Foundation Trust, Cambridge, United Kingdom; [24]Academic Department of Medical Genetics, University of Cambridge, Cambridge, United Kingdom; [25]Medical University of Vienna, Vienna, Austria; [26]University of California Davis, Sacramento, California; [27]Mayo Clinic, Scottsdale, Arizona; [28]Saint-Antoine University Hospital, Paris, France; [29]Addenbrooke's Hospital, Cambridge, United Kingdom; [30]Department of Biostatistics, Newcastle University, Newcastle upon Tyne, United Kingdom; [31]Department of Epidemiology & Biostatistics, Erasmus MC, Rotterdam, the Netherlands; and [32]IHPME, University of Toronto, Toronto, Ontario, Canada



See editorial on page 1491.

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.

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 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.

HEPATOBILIARY

Primary biliary cholangitis (PBC) is a rare autoimmune cholestatic liver disease predominantly affecting women over the age of 40 years (approximately 6 in 1000).[1,2] 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.[3]

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.[4]

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.[3,5,6] However, upward of 40% of patients prescribed UDCA experience an inadequate response and require second-line therapy.[7] 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 receiving UDCA therapy reported a 10-year cumulative incidence of first hepatic complications of 32.4% in inadequate responders, as opposed to 6.2% in biochemical responders.[8] 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.[9–12]

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

* Authors share co-first authorship; § Authors share co-senior authorship.

Femi Adekunle's current affiliation is Advanz, London, United Kingdom.

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.

Most current article

0016-5085
https://doi.org/10.1053/j.gastro.2022.08.054

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.[13,14]

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.[15,16] 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.[17]

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.[18,19] 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[4] and UK-PBC[20] 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 level $>1.67\times$ 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 level $<1.67\times$ ULN with a $\geq$15% reduction from baseline ALP level and bilirubin level $\leq 1\times$ 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.[15]

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 were 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, alanine transaminase [ALT], aspartate aminotransferase [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 arrythmias).

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

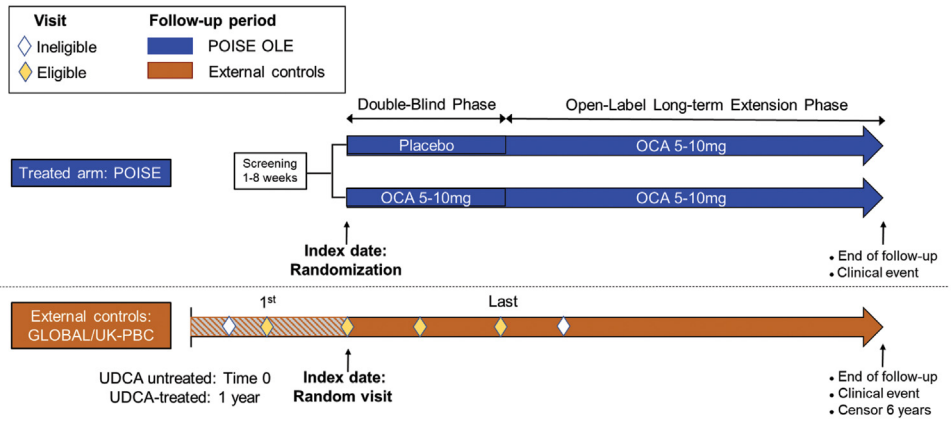


Figure 1. Schematic of index date selection. Each qualifying patient visit (*diamond*) was examined to determine whether the patient met eligibility criteria at that visit (*yellow diamond*) or did not meet criteria (*white diamond*). An eligibility period was established between the first visit that 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.

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 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.[21] The boundaries due to extreme values (>10) were reduced,[22] 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 ±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).[23] 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 the presence of 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.[24,25] 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 $<140{,}000/mm^3$ with persistent decrease in serum albumin or total bilirubin $>2\times$ 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 levels 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 2*A*) and between POISE and UK-PBC (Figure 2*B*) 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

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)[a]	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 (IQR)	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.
[a]UDCA baseline dose data were available for 1169 patients in Global PBC and 201 patients in UK-PBC.

(Figure 3*A*) and UK-PBC (Figure 3*B*). The curves begin 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 prespecified 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 the first qualifying visit and slightly lower for the 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 with evidence of cirrhosis, the CIs were widely overlapping,

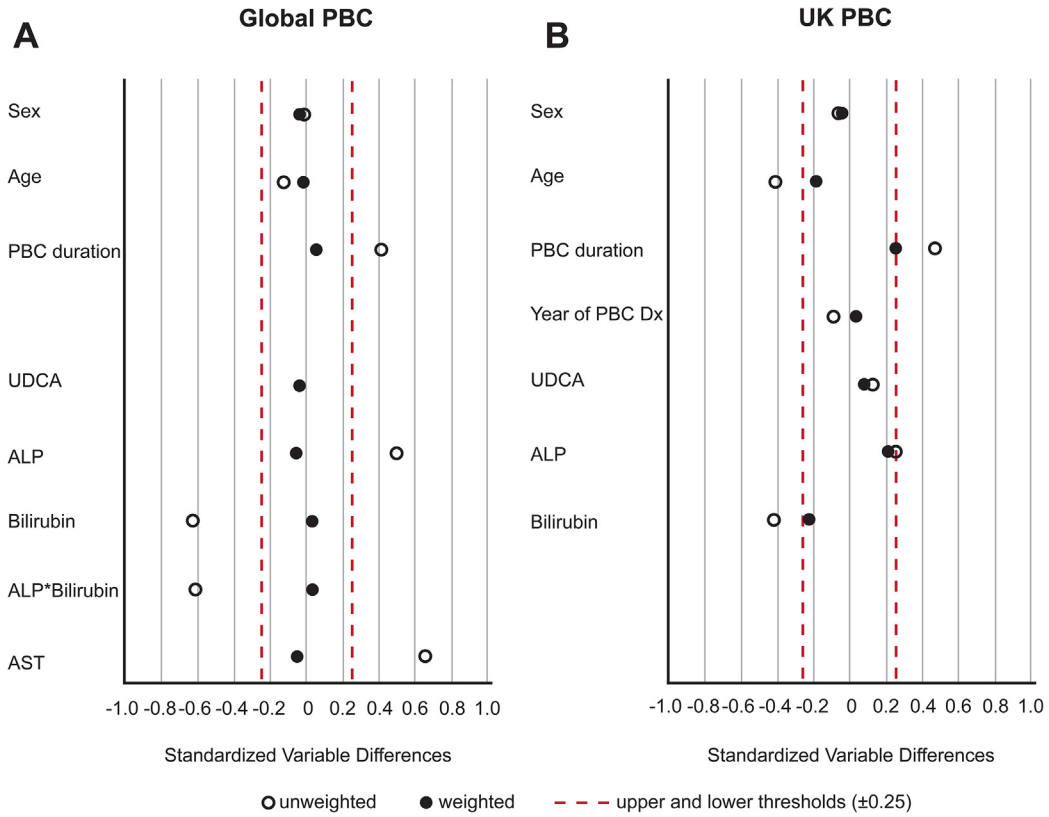


Figure 2. Standard variable differences for POISE vs Global PBC (*A*) and POISE vs UK-PBC (*B*) for unadjusted and adjusted baseline variables included in logistic regression and propensity score. The balance of baseline variable differences following propensity score application is shown. (*A*) An additional ALP–bilirubin interaction term was added due to the high correlation between baseline variables in the dataset. All variables were in the prespecified range (±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.

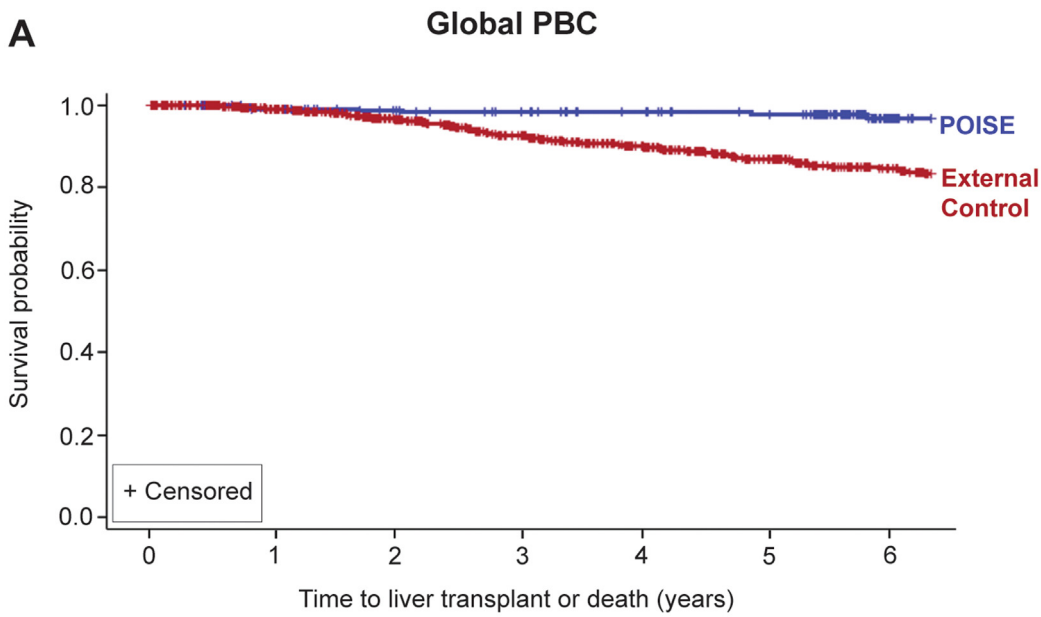
indicating no significant difference between patients with or without cirrhosis.

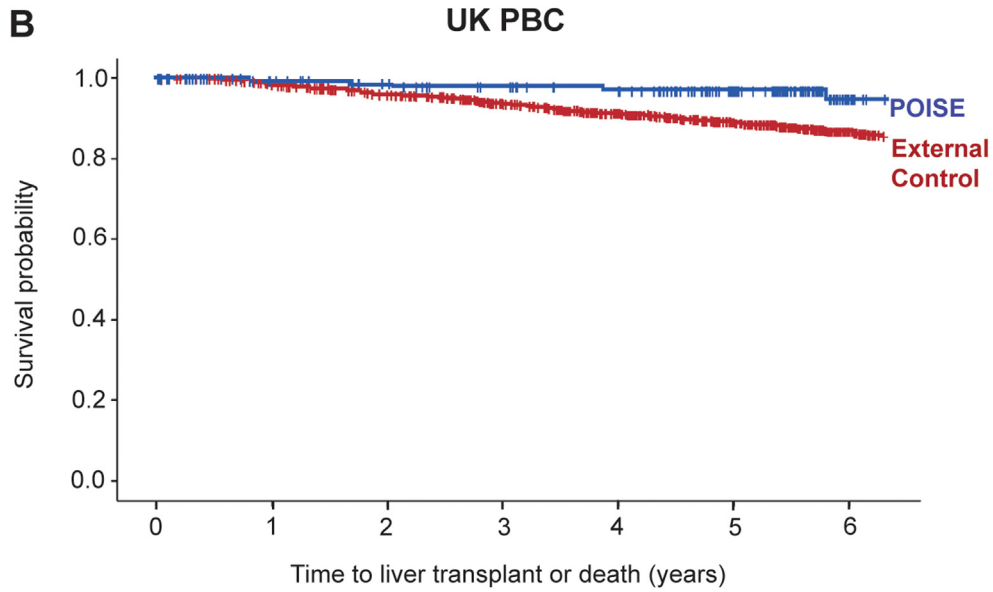
The third sensitivity analysis assessed the possibility that there was positive but unmeasured selection bias, resulting in a healthier cohort in the POISE study vs the Global PBC and UK-PBC external controls. Table 2 shows change from baseline to 12 months for ALP, bilirubin, and AST/ALT (expressed 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 there were 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 to an accumulating body of real-world evidence showing





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.

a positive effect of OCA treatment on hepatic biomarkers, fibrosis, and PBC risk scores,[1,2,26–28] and support current guidance, which recommends initiation of second-line therapy if UDCA is not tolerated or if there is an inadequate response at 6–12 months after starting UDCA.[29,30]

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 surrogate biomarkers can accelerate bringing needed therapies to market, once approved it is challenging to carry out long-term, placebo-controlled outcomes trials.

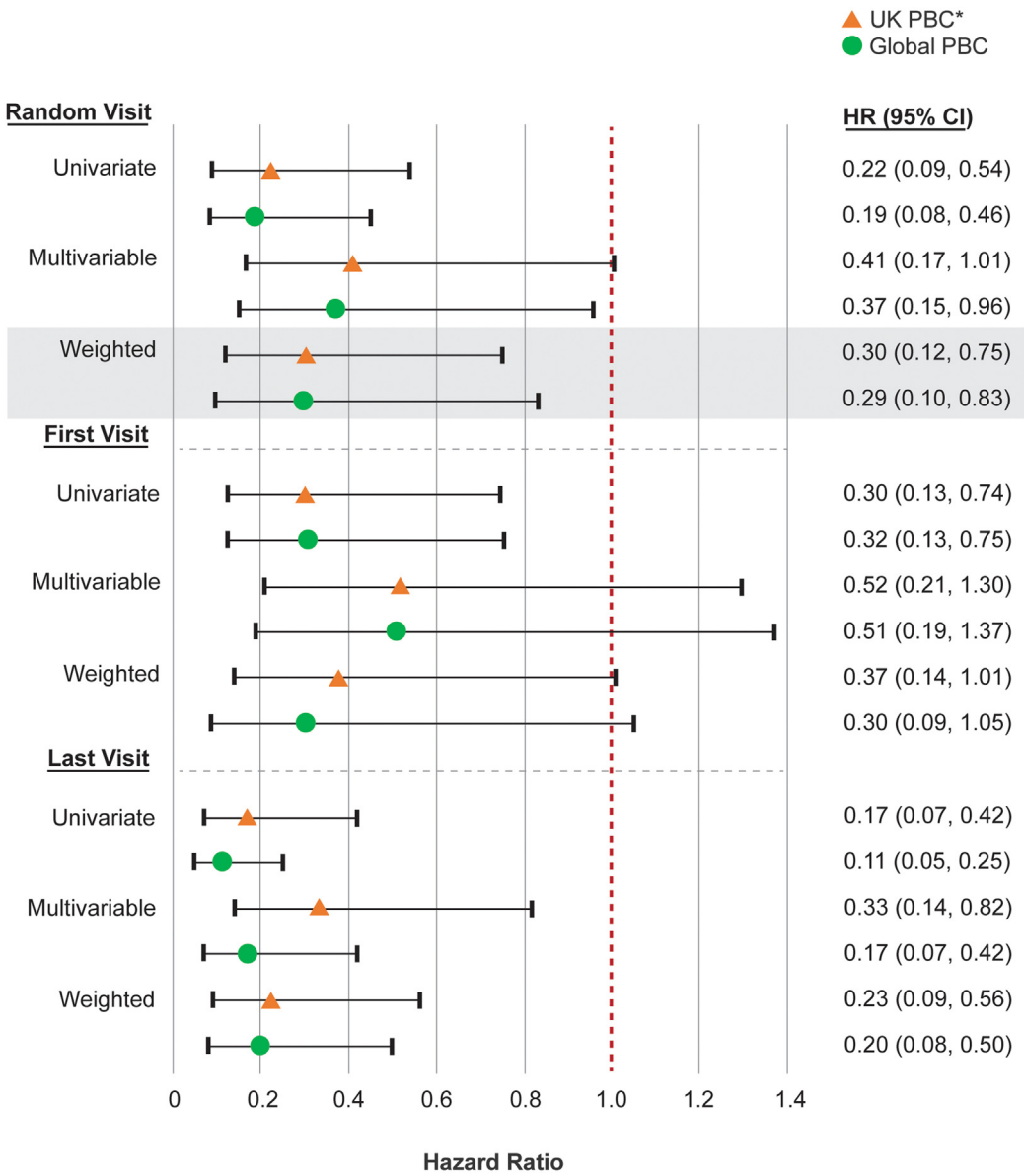
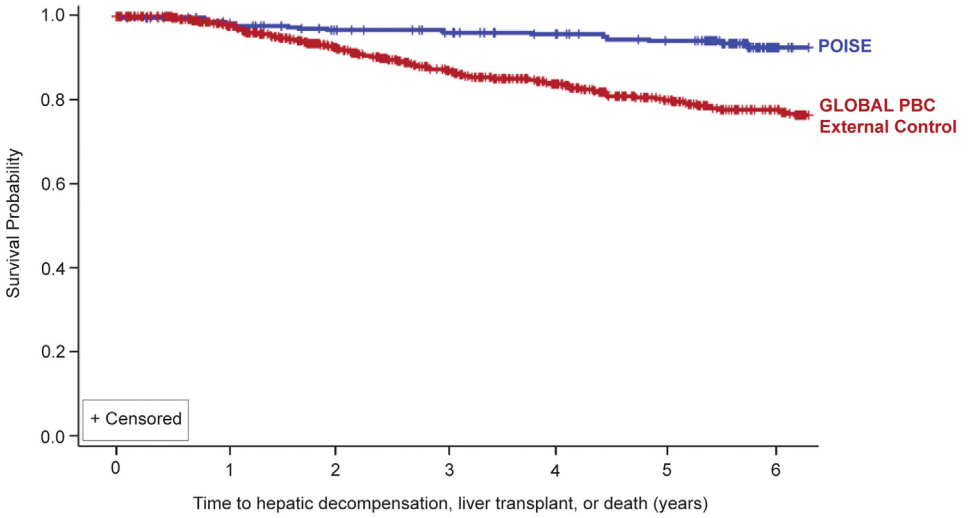


Figure 4. HRs for death or liver transplantation for POISE vs Global PBC and UK-PBC in univariate, multivariable, and weighted Cox regressions for random index date, first qualifying visit date, and last qualifying visit date. *UK-PBC: ALT included as a covariate. Predictor variables in multivariable 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.

Real-world data can be used to demonstrate clinical efficacy, as it did for UDCA.[6] 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 composite end point. The results are also similar to results modeled from the POISE trial based on biochemical response.[31]



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; $P = .02$).

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 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

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

	Change from baseline to 12 mo (in ULN), mean (95% CI)		
Variable	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.

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.[15,28,32] Pharmacologically lowering these biomarkers with UDCA has been found to reduce clinical events.[6] 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, and at https://doi.org/10.1053/j.gastro.2022.08.054.

HEPATOBILIARY

References

1. Lleo A, Wang GQ, Gershwin ME, et al. Primary biliary cholangitis. Lancet 2020;396(10266):1915–1926.
2. Trivedi PJ, Hirschfield GM. Recent advances in clinical practice: epidemiology of autoimmune liver diseases. Gut 2021;70:1989–2003.
3. Hohenester S, Oude-Elferink RP, Beuers U. Primary biliary cirrhosis. Semin Immunopathol 2009;31:283–307.
4. Lammers WJ, van Buuren HR, Hirschfield GM, et al. Levels of alkaline phosphatase and bilirubin are surrogate end points of outcomes of patients with primary biliary cirrhosis: an international follow-up study. Gastroenterology 2014;147:1338–1349. e1335; quiz e1315.
5. Poupon RE, Balkau B, Eschwège E, et al. A multicenter, controlled trial of ursodiol for the treatment of primary biliary cirrhosis. UDCA-PBC Study Group. N Engl J Med 1991;324:1548–1554.
6. Harms MH, van Buuren HR, Corpechot C, et al. Ursodeoxycholic acid therapy and liver transplant-free survival in patients with primary biliary cholangitis. J Hepatol 2019;71:357–365.
7. Shah RA, Kowdley KV. Current and potential treatments for primary biliary cholangitis. Lancet Gastroenterol Hepatol 2020;5:306–315.
8. Harms MH, Lammers WJ, Thorburn D, et al. Major hepatic complications in ursodeoxycholic acid-treated patients with primary biliary cholangitis: risk factors and time trends in incidence and outcome. Am J Gastroenterol 2018;113:254–264.
9. Corpechot C. The role of fibrates in primary biliary cholangitis. Curr Hepatol Rep 2019;18:107–114.
10. Phase 4 Study of Obeticholic Acid Evaluating Clinical Outcomes in Patients With Primary Biliary Cholangitis (COBALT). Clinicaltrials.gov. Accessed December 8, 2021. https://clinicaltrials.gov/ct2/show/NCT02308111?term=obeticholic+acid+COBALT&draw=2&rank=1.
11. Honda A, Tanaka A, Kaneko T, et al. Bezafibrate improves GLOBE and UK-PBC scores and long-term outcomes in patients with primary biliary cholangitis. Hepatology 2019;70:2035–2046.
12. Corpechot C, Chazouillères O, Rousseau A, et al. A placebo-controlled trial of bezafibrate in primary biliary cholangitis. N Engl J Med 2018;378:2171–2181.
13. OCALIVA [package insert]. Incercept Pharmaceuticals, Inc.; 2021.
14. Ocaliva. European Medicines Agency. Accessed December 2, 2021. https://www.ema.europa.eu/en/medicines/human/EPAR/ocaliva.
15. Wolinsky H. The battle of Helsinki: two troublesome paragraphs in the Declaration of Helsinki are causing a furor over medical research ethics. EMBO Rep 2006;7:670–672.
16. Cheah PY, Steinkamp N, von Seidlein L, et al. The ethics of using placebo in randomised controlled trials: a case study of a Plasmodium vivax antirelapse trial. BMC Med Ethics 2018;19(19):1–5.
17. US Food and Drug Administration. Real-World Data: Assessing Electronic Health Records and Medical Claims Data to Support Regulatory Decision Making for Drug and Biological Products. Guidance for Industry. Published September 2021. Accessed September 22, 2022. https://www.fda.gov/regulatory-information/search-fda-guidance-documents/real-world-data-assessing-electronic-health-records-and-medical-claims-data-support-regulatory.
18. Nevens F, Andreone P, Mazzella G, et al. A placebo-controlled trial of obeticholic acid in primary biliary cholangitis. N Engl J Med 2016;375:631–643.
19. Trauner M, Nevens F, Shiffman ML, et al. Long-term efficacy and safety of obeticholic acid for patients with primary biliary cholangitis: 3-year results of an international open-label extension study. Lancet Gastroenterol Hepatol 2019;4:445–453.
20. Carbone M, Sharp SJ, Flack S, et al. The UK-PBC risk scores: derivation and validation of a scoring system for long-term prediction of end-stage liver disease in primary biliary cholangitis. Hepatology 2016;63:930–950.
21. Allan V, Ramagopalan SV, Mardekian J, et al. Propensity score matching and inverse probability of treatment weighting to address confounding by indication in comparative effectiveness research of oral anticoagulants. J Comp Eff Res 2020;9:603–614.
22. Xu S, Ross C, Raebel MA, et al. Use of stabilized inverse propensity scores as weights to directly estimate relative risk and its confidence intervals. Value Health 2010;13:273–277.
23. **Perez CFM, Fisher H,** Hiu S, et al. Patients with primary biliary cholangitis treated with long-term obeticholic acid in a trial-setting demonstrate better transplant-free survival than external controls from the Global PBC and UK-

PBC study groups. Presented at the American Association for the Study of Liver Diseases Meeting November 12–15, 2021.
24. Firth D. Bias reduction of maximum likelihood estimates. Biometrika 1993;80:27–38.
25. Firth D. Amendments and corrections: bias reduction of maximum likelihood estimates. Biometrika 1995;82:667.
26. Gomez E, Garcia Buey L, Molina E, et al. Effectiveness and safety of obeticholic acid in a Southern European multicentre cohort of patients with primary biliary cholangitis and suboptimal response to ursodeoxycholic acid. Aliment Pharmacol Ther 2021;53:519–530.
27. Harms MH, Hirschfield GM, Floreani A, et al. Obeticholic acid is associated with improvements in AST-to-platelet ratio index and GLOBE score in patients with primary biliary cholangitis. JHEP Rep 2021;3(1):100191.
28. Roberts SB, Ismail M, Kanagalingam G, et al. Real-world effectiveness of obeticholic acid in patients with primary biliary cholangitis. Hepatol Commun 2020;4:1332–1345.
29. Lindor KD, Bowlus CL, Boyer J, et al. Primary biliary cholangitis: 2018 practice guidance from the American Association for the Study of Liver Diseases. Hepatology 2019;69:394–419.
30. EASL Clinical Practice Guidelines. The diagnosis and management of patients with primary biliary cholangitis. J Hepatol 2017;67:145–172.
31. Samur S, Klebanoff M, Banken R, et al. Long-term clinical impact and cost-effectiveness of obeticholic acid for the treatment of primary biliary cholangitis. Hepatology 2017;65:920–928.
32. Leoni MC, Amelung L, Lieveld FI, et al. Adherence to ursodeoxycholic acid therapy in patients with cholestatic and autoimmune liver disease. Clin Res Hepatol Gastroenterol 2019;43:37–44.

Author names in bold designate shared co-first authorship.

Received March 4, 2022. Accepted August 30, 2022.

Correspondence
Address correspondence to: Bettina Hansen, PhD, Erasmus University Medical Center Rotterdam, Dr. Molewaterplein 50, 3015 GE Rotterdam, Postbus 2040, 3000 CA Rotterdam, The Netherlands. e-mail: b.hansen@erasmusmc.nl.

Acknowledgments
UK-PBC Consortium: Christopher Healey,[1] Andrew Yeoman,[2] Anton Gunasekera,[3] Meera Kirby,[4] Kapil Kapur,[5] Yiannis Kallis,[6] Sambit Sen,[7] Roger McCorry,[8] Richard Evans,[9] Jaber Gasem,[9] Thiriloganathan Mathialahan,[9] David Ramanaden,[9] Emma Ward,[10] Mahesh Bhalme,[11] Paul Southern,[12] James Maggs,[13] Mohamed Yousif,[14] Richard Sandford,[15] Brijesh Srivastava,[16] Carole Collins,[17] Matthew Foxton,[17] David Elphick,[18] Yash Prasad,[19] Francisco Porras Perez,[20] Minesh Patel,[21] Tom Yapp,[21] Roland Ede,[22] Joanna Sayer,[23] Martyn Carter,[24] Konrad Koss,[25] Prayman Sattianayagam,[26] Jayshri Shah,[26] Charles Grimley,[27] Ian Gooding,[28] Abdul Mohsen,[28] Judith Tidbury,[29] Kuldeep Cheent,[30] Dina Mansour,[31] Matilda Beckley,[32] Coral Hollywood,[33] Harriet Gordon,[34] John Ramage,[34] Joanne Ridpath,[35] George Abouda,[36] Mark Narain,[37] Ian Rees,[37] Imroz Salam,[37] Paul Banim,[38] Debasish Das,[39] Michael Heneghan,[40] Helen Matthews,[41] Faiyaz Mohammed,[42] Rebecca Jones,[43] Tehreem Chaudhry,[44] Richard Sturgess,[44] George Bird,[45] Geeta Prasad,[46] Martin Prince,[46] Paul Kitchen,[47] Gary Bray,[48] Gavin Wright,[48] John Hutchinson,[49] Prakash Gupta,[50] Amir Shah,[51] Chris Evans,[52] Subrata Saha,[53] Katharine Pollock,[54] Timothy Heron,[55] Joanna Leithead,[55] Ashis Mukhopadhya,[56] Stephen Barclay,[57] Andrea Broad,[58] Natasha McDonald,[59] Andrew Bathgate,[60] Kelvin Palmer,[60] John Dillon,[61] Simon Rushbrook,[62] Robert Przemioslo,[63] Christopher Macdonald,[64] Andrew Millar,[65] Stephen Mitchell,[66] Udi Shmueli,[67] Asifabbas Naqvi,[68] Thomas Lee,[69] Stephen Ryder,[70] Jane Collier,[71] Richard Aspinall,[72] Jonathan Booth,[73] Hyder Hussaini,[74] John Christie,[75] Andrew Davis,[75] Steven Mann,[76] Douglas Thorburn,[76] Aftab Ala,[77] Julia Maltby,[78] Saket Singhal,[79] Barbara Hoeroldt,[80] Jeffrey Butterworth,[81] Emma Wesley,[82] Andrew Douglass,[83] Simon Panter,[84] Rohit Sinha,[84] Jeremy Shearman,[85] Michael Roberts,[86] Daniel Forton,[87] Nicola Taylor,[88] Wisam Jafar,[89] Matthew Cowan,[90] Chin Lye Ch'ng,[91] Mesbah Rahman,[91] Neil Fisher,[92] Bob Grover,[93] Jessica Dyson,[94] David Jones,[94] Debabrata Ghosh,[95] Christopher Corbett,[96] Keith George,[97] Aditya Mandal,[98] Sanjiv Jain,[98] Mark Wright,[99] Palak Trivedi,[100] Fiona Gordon,[101] Esther Unitt,[102] Earl Williams,[103] Andrew Austin,[104] Altaf Palejwala,[104] Vishwaraj Vemala,[105] Andrew Higham,[106] Matthew Cramp,[107] Jocelyn Fraser,[108] Andy Li,[108] Subramaniam Ramakrishnan,[109] Alistair King,[110] Simon Whalley,[111] Ian Gee,[112] Richard Keld,[113] Helen Fellows,[114] James Gotto,[115] and Charles Millson[116]

[1]Airedale NHS Foundation Trust; [2]Aneurin Bevan University Health Board; [3]Ashford and St. Peter's Hospitals NHS Foundation Trust; [4]Barking, Havering and Redbridge University Hospitals NHS Trust; [5]Barnsley Hospital NHS Foundation Trust; [6]Barts Health NHS Trust; [7]Bedfordshire Hospitals NHS Foundation Trust; [8]Belfast Health and Social Care Trust; [9]Betsi Cadwaladr University Health Board; [10]Blackpool Teaching Hospitals NHS Foundation Trust; [11]Bolton NHS Foundation Trust; [12]Bradford Teaching Hospitals NHS Foundation Trust; [13]Buckinghamshire Healthcare NHS Trust; [14]Calderdale and Huddersfield NHS Foundation Trust; [15]Cambridge University Hospitals NHS Foundation Trust; [16]Cardiff and Vale University Health Board; [17]Chelsea and Westminster Hospital NHS Foundation Trust; [18]Chesterfield Royal Hospital NHS Foundation Trust; [19]Countess of Chester Hospital NHS Foundation Trust; [20]County Durham and Darlington NHS Foundation Trust; [21]Cwm Taf Morgannwg University Health Board; [22]Dartford and Gravesham NHS Trust; [23]Doncaster and Bassetlaw Teaching Hospitals NHS Foundation Trust; [24]East and North Hertfordshire NHS Trust; [25]East Cheshire NHS Trust; [26]East Kent Hospitals University NHS Foundation Trust; [27]East Lancashire Hospitals NHS Trust; [28]East Suffolk and North Essex NHS Foundation Trust; [29]East Sussex Healthcare NHS Trust; [30]Frimley Health NHS Foundation Trust; [31]Gateshead Health NHS Foundation Trust; [32]George Eliot Hospital NHS Trust; [33]Gloucestershire Hospitals NHS Foundation Trust; [34]Hampshire Hospitals NHS Foundation Trust; [35]Harrogate and District NHS Foundation Trust; [36]Hull University Teaching Hospitals NHS Trust; [37]Hywel Dda University Health Board; [38]James Paget University Hospitals NHS Foundation Trust; [39]Kettering General Hospital NHS Foundation Trust; [40]King's College Hospital NHS Foundation Trust; [41]Kingston Hospital NHS Foundation Trust; [42]Lancashire Teaching Hospitals NHS Foundation Trust; [43]Leeds Teaching Hospitals NHS Trust; [44]Liverpool University Hospitals NHS Foundation Trust; [45]Maidstone and Tunbridge Wells NHS Trust; [46]Manchester University NHS Foundation Trust; [47]Medway NHS Foundation Trust; [48]Mid and South Essex NHS Foundation Trust; [49]Mid Yorkshire Hospitals NHS Trust; [50]Milton Keynes University Hospital NHS Foundation Trust; [51]NHS Ayrshire & Arran; [52]NHS Borders; [53]NHS Dumfries & Galloway; [54]NHS Fife; [55]NHS Forth Valley; [56]NHS Grampian; [57]NHS Greater Glasgow and Clyde; [58]NHS Highland; [59]NHS Lanarkshire; [60]NHS Lothian; [61]NHS Tayside; [62]Norfolk and Norwich University Hospitals NHS Foundation Trust; [63]North Bristol NHS Trust; [64]North Cumbria Integrated Care NHS Foundation Trust; [65]North Middlesex University Hospital NHS Trust; [66]North Tees and Hartlepool NHS Foundation Trust; [67]Northampton General Hospital NHS Trust; [68]Northern Lincolnshire and Goole NHS Foundation Trust; [69]Northumbria Healthcare NHS Foundation Trust; [70]Nottingham University Hospitals NHS Trust; [71]Oxford University Hospitals NHS Foundation Trust; [72]Portsmouth Hospitals NHS Trust; [73]Royal Berkshire NHS Foundation Trust; [74]Royal Cornwall Hospitals NHS Trust; [75]Royal Devon University Healthcare NHS Foundation Trust; [76]Royal Free London NHS Foundation Trust; [77]Royal Surrey NHS Foundation Trust; [78]Royal United Hospitals Bath NHS Foundation Trust; [79]Sandwell and West Birmingham Hospitals NHS Trust; [80]Sheffield Teaching Hospitals NHS Foundation Trust; [81]Shrewsbury and Telford Hospital NHS Trust; [82]Somerset NHS Foundation Trust; [83]South Tees Hospitals NHS Foundation Trust; [84]South Tyneside And Sunderland NHS Foundation Trust; [85]South Warwickshire University NHS Foundation Trust; [86]Southport and Ormskirk Hospital NHS Trust; [87]St George's University Hospitals NHS Foundation Trust; [88]St Helens and Knowsley Teaching Hospitals NHS Trust; [89]Stockport NHS Foundation Trust; [90]Surrey and Sussex Healthcare NHS Trust; [91]Swansea Bay University Health Board; [92]The Dudley Group NHS Foundation Trust; [93]The Hillingdon Hospitals NHS Foundation Trust; [94]The Newcastle upon Tyne Hospitals NHS Foundation Trust; [95]The Princess Alexandra Hospital NHS Trust; [96]The Royal Wolverhampton NHS Trust; [97]Torbay and South Devon NHS Foundation Trust; [98]United Lincolnshire Hospitals NHS Trust; [99]University Hospital Southampton NHS Foundation Trust; [100]University Hospitals Birmingham NHS Foundation Trust; [101]University Hospitals Bristol and Weston NHS Foundation Trust; [102]University Hospitals Coventry and Warwickshire NHS Trust; [103]University Hospitals Dorset NHS Foundation Trust; [104]University Hospitals of Derby and Burton NHS Foundation Trust; [105]University Hospitals Of Leicester NHS Trust; [106]University Hospitals of Morecambe Bay NHS Foundation Trust; [107]University Hospitals Plymouth NHS Trust; [108]University Hospitals Sussex NHS Foundation Trust; [109]Warrington and Halton Hospitals NHS Foundation Trust; [110]West Hertfordshire Teaching Hospitals NHS Trust; [111]West Suffolk NHS Foundation Trust; [112]Worcestershire Acute Hospitals NHS Trust; [113]Wrightington, Wigan and Leigh NHS Foundation Trust; [114]Wye Valley NHS

Trust; [115]Yeovil District Hospital NHS Foundation Trust; and [116]York and Scarborough Teaching Hospitals NHS Foundation Trust

Editing assistance was provided by Meg Franklin, PharmD, PhD.

CRediT Authorship Contributions

C. Fiorella Murillo Perez, MSc, PhD (Conceptualization: Lead; Data curation: Lead; Formal analysis: Lead; Methodology: Supporting; Validation: Lead; Writing – original draft: Equal; Writing – review & editing: Equal).

Holly Fisher, PhD (Data curation: Equal; Methodology: Equal; Writing – original draft: Equal; Writing – review & editing: Equal).

Shaun Hiu, PhD (Data curation: Equal; Methodology: Equal; Validation: Lead; Writing – original draft: Lead; Writing – review & editing: Equal).

Dorcas Kareithi, MSc (Data curation: Lead; Formal analysis: Lead; Validation: Lead; Writing – original draft: Equal; Writing – review & editing: Equal).

Femi Adekunle, MD (Conceptualization: Equal; Methodology: Equal; Visualization: Equal; Writing – original draft: Equal; Writing – review & editing: Equal).

Tracy Mayne, PhD (Formal analysis: Equal; Methodology: Equal; Validation: Equal; Writing – original draft: Equal; Writing – review & editing: Equal).

Elizabeth Malecha, PhD (Formal analysis: Lead; Writing – review & editing: Equal).

Erik Ness, MD (Formal analysis: Lead; Methodology: Lead; Writing – original draft: Equal; Writing – review & editing: Equal).

Adriaan J. van der Meer, MD (Writing – review & editing: Equal).

Willem J. Lammers, MD, PhD (Writing – original draft: Supporting; Writing – review & editing: Equal).

Palak J. Trivedi, BSc (Hons), MBBS, MRCP Gastro (UK), PhD (Writing – original draft: Supporting; Writing – review & editing: Equal).

Pier Maria Battezzati, MD (Writing – original draft: Supporting; Writing – review & editing: Supporting).

Frederik Nevens, MD, PhD (Methodology: Equal; Writing – original draft: Equal; Writing – review & editing: Equal).

Kris Kowdley, MD (Writing – original draft: Equal; Writing – review & editing: Equal).

Tony Bruns, MD (Writing – original draft: Supporting; Writing – review & editing: Equal).

Nora Cazzagon, MD, PhD (Writing – original draft: Equal; Writing – review & editing: Equal).

Annarosa Floreani, MD (Writing – original draft: Equal; Writing – review & editing: Equal).

Andrew L. Mason, MBBS, FRCPI, FAASLD (Writing – original draft: Equal; Writing – review & editing: Equal).

Albert Parés, MD, PhD, FAASLD (Writing – original draft: Supporting; Writing – review & editing: Supporting).

Maria-Carlota Londoño, MD (Writing – original draft: Supporting; Writing – review & editing: Supporting).

Pietro Invernizzi, MD, PhD (Writing – original draft: Supporting; Writing – review & editing: Equal).

Marco Carbone, MD (Writing – original draft: Equal; Writing – review & editing: Equal).

Ana Lleo, MD, PhD (Writing – original draft: Equal; Writing – review & editing: Equal).

Marlyn J. Mayo, MD (Writing – original draft: Equal; Writing – review & editing: Equal).

George N. Dalekos, MD, PhD, FEFIM (Writing – original draft: Equal; Writing – review & editing: Equal).

Nikolaos K. Gatselis, MD (Writing – original draft: Equal; Writing – review & editing: Equal).

Douglas Thorburn, MB, CHB, MD, FRCP (Writing – original draft: Equal; Writing – review & editing: Equal).

Xavier Verhelst, MD, PhD (Writing – original draft: Supporting; Writing – review & editing: Equal).

Aliya Gulamhusein, MD (Methodology: Supporting; Writing – original draft: Equal; Writing – review & editing: Equal).

Harry L. A. Janssen, MD, PhD (Writing – original draft: Equal; Writing – review & editing: Equal).

Rachel Smith, MD (Writing – original draft: Supporting; Writing – review & editing: Equal).

Steven Flack, none (Data curation: Supporting; Writing – original draft: Supporting; Writing – review & editing: Supporting).

Victoria Mulcahy, MD (Methodology: Equal; Validation: Equal; Writing – original draft: Equal; Writing – review & editing: Equal).

Michael Trauner, MD (Methodology: Equal; Writing – original draft: Equal; Writing – review & editing: Equal).

Christopher Bowlus, MD (Methodology: Equal; Visualization: Equal; Writing – original draft: Equal; Writing – review & editing: Equal).

Keith D. Lindor, MD (Writing – original draft: Equal; Writing – review & editing: Equal). Christophe Corpechot, MD (Writing – original draft: Equal; Writing – review & editing: Equal).

David E.J. Jones, MD, PhD (Conceptualization: Lead; Data curation: Equal; Formal analysis: Equal; Methodology: Lead; Resources: Equal; Validation: Equal; Writing – original draft: Lead; Writing – review & editing: Lead).

George Mells, MBBS, PhD, MRCP (Conceptualization: Equal; Data curation: Equal; Formal analysis: Equal; Methodology: Equal; Writing – original draft: Equal; Writing – review & editing: Equal).

Gideon M. Hirschfield, MD, PhD (Conceptualization: Lead; Data curation: Supporting; Formal analysis: Equal; Methodology: Lead; Resources: Lead; Supervision: Lead; Writing – original draft: Equal; Writing – review & editing: Equal).

James Wason, PhD (Conceptualization: Lead; Data curation: Lead; Formal analysis: Lead; Methodology: Lead; Validation: Lead; Writing – original draft: Equal; Writing – review & editing: Equal).

Bettina E. Hansen, PhD (Conceptualization: Lead; Data curation: Lead; Formal analysis: Lead; Methodology: Lead; Supervision: Lead; Validation: Lead; Writing – original draft: Lead; Writing – review & editing: Lead).

Data Availability

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.

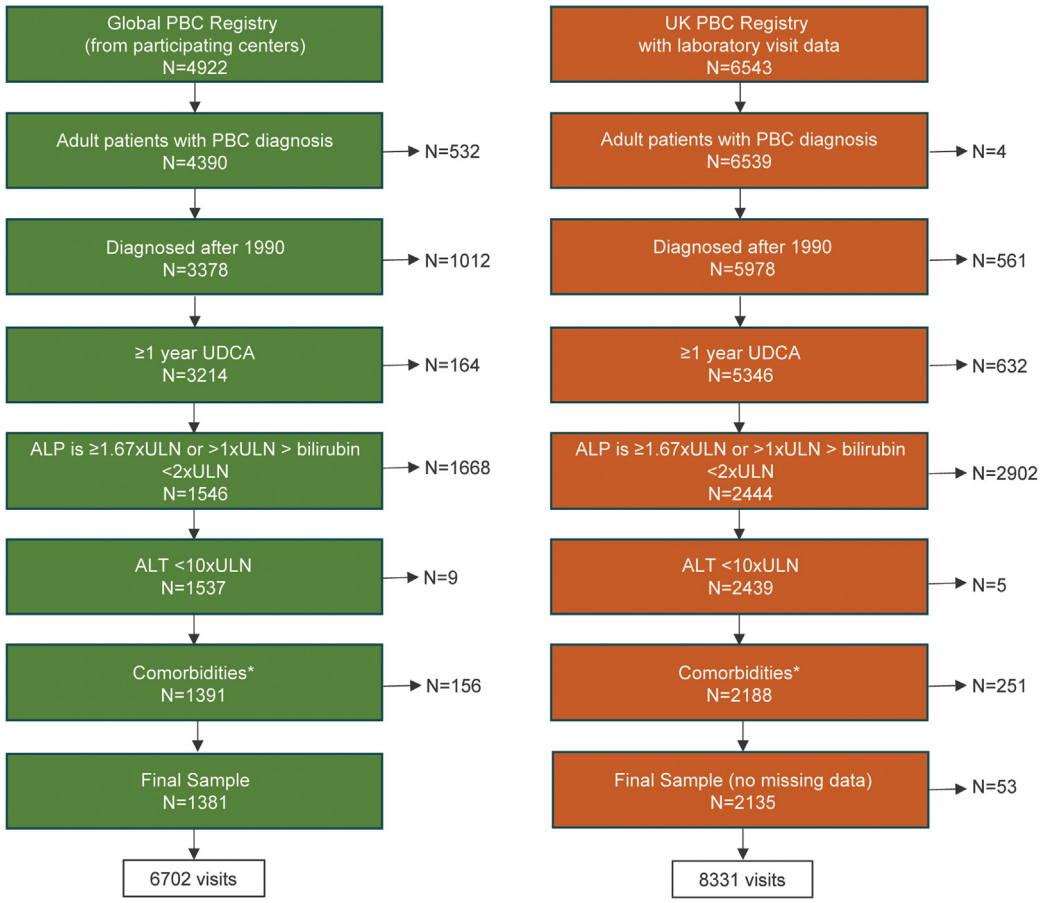
Conflicts of interest

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.

HEPATOBILIARY



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 of elevated ALP levels for at least 6 mo Positive AMA titer or PBC-specific antibodies Liver biopsy consistent with PBC	History or presence of other concomitant liver disease, including: Hepatitis C virus infection Active hepatitis B infection Primary sclerosing cholangitis Alcoholic liver disease Definite autoimmune liver disease or overlap hepatitis Nonalcoholic steatohepatitis (hepatic steatosis by ultrasound, CT, MRI, TE, or body mass index >30 kg/m^2)
1 or more of the following biochemistry values: ALP ≥1.67× ULN and total bilirubin <2× ULN Total bilirubin >ULN but <2× ULN	Insufficient follow-up: at least annually clinical assessment in the absence of cirrhosis, and a least every 6 mo in the presence of cirrhosis.
Age ≥18 y	Missing date of therapy initiation or clinical event
Taking UDCA for at least 12 mo without interruption before index date at a dose of 13–15 mg/kg, or;	Presence of clinical complications of PBC or clinically significant hepatic decompensation within the first 6 mo of follow-up, including: History of liver transplantation, current placement on a liver transplant list, or current MELD score ≥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
not treated with UDCA ≥3 mo before index date	ALT levels >10× ULN at baseline
Diagnosis year >1990	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.

Supplementary Table 2. Results of Propensity Score Logistic Regression

	Global PBC			UK PBC		
Parameter	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.