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Obeticholic Acid for the Treatment of Primary Biliary Cholangitis: Comparative Clinical Effectiveness and Value

Draft Evidence Report

May 25, 2016

Institute for Clinical and Economic Review

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We would also like to thank Erin Lawler, MA and Shanshan Liu, MS, MPH for their contributions to this report.

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Stakeholder Input

The following stakeholders provided input and feedback that helped guide the ICER team as we shaped our scope and report. None of these stakeholders is responsible for the final contents of this report or should be assumed to support any part of this report, which is solely the work of the ICER team and its affiliated researchers.

Stakeholders

Harvard Pilgrim HealthCare
Indiana University School of Medicine
Intercept Pharmaceuticals
Massachusetts General Hospital
Mayo Clinic

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List of Acronyms Used in this Report

AE	Adverse event
ALP	Alkaline phosphatase
ALT	Alanine aminotransferase
AST	Aspartate aminotransferase
AMA	Antimitochondrial antibodies
DB	Double-blind
FDA	Food and Drug Administration
GGT	Gamma-glutamyl transferase
HCC	Hepatocellular carcinoma
ITT	Intent-to-treat
LTSE	Long-term safety extension
mITT	Modified intent-to-treat
OCA	Obeticholic acid
PBC	Primary biliary cholangitis, also known as primary biliary cirrhosis
RCT	Randomized controlled trial
SAE	Serious adverse event
TB	Total bilirubin
UDCA	Ursodeoxycholic acid
ULN	Upper limit of normal
US	United States
USPSTF	United States Preventive Services Task Force

Executive Summary

Background

An executive summary will be provided as part of the full Evidence Report.

1. Background

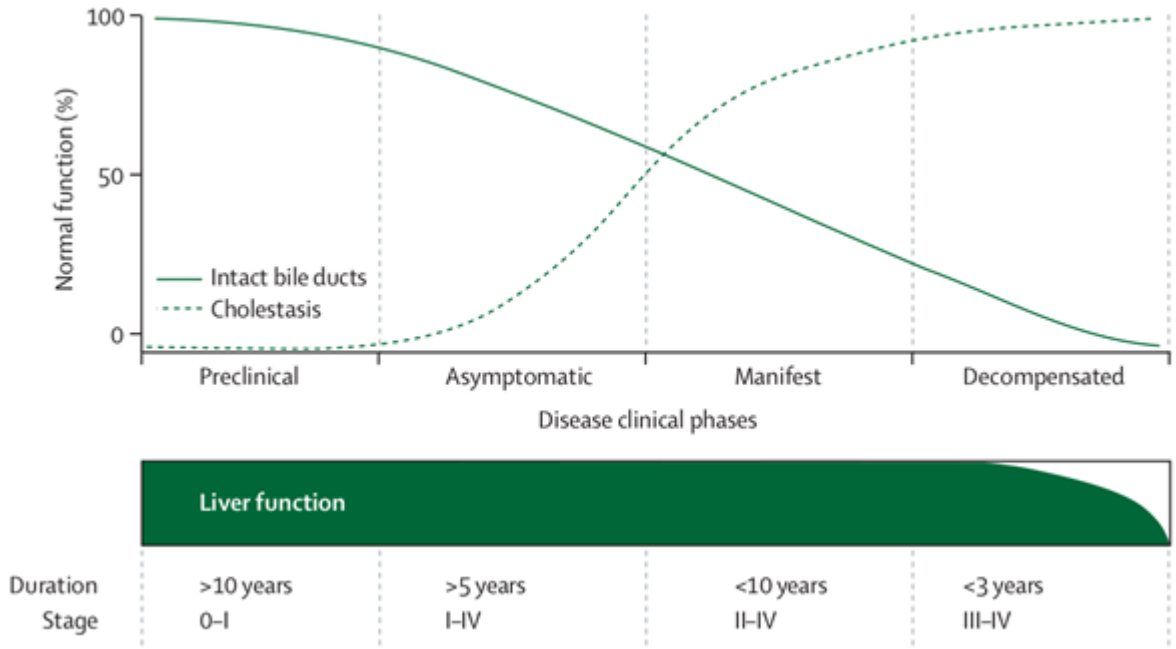
1.1 Introduction

Background

Primary biliary cholangitis (PBC), which has until recently been referred to as primary biliary cirrhosis,[1] is a rare, chronic, progressive autoimmune liver disease that mainly affects middle-aged women.[2] The prevalence varies between different countries and regions;[3] in the US, up to 130,000 individuals are estimated to have PBC.[4] Diagnosis is increasingly occurring in up to 60% of asymptomatic patients,[5] triggered through an investigation of increased levels of alkaline phosphatase (ALP) on routine blood tests. The presence of antimitochondrial antibodies (AMAs) confirms the diagnosis. AMAs are highly sensitive and specific, being present in 95% of patients and with specificity close to 100% when tested with recombinant antigens.[6] A liver biopsy can be used to further substantiate the diagnosis if needed, but is typically not required.

The disease process starts with autoimmune damage to small intrahepatic bile ducts, resulting in chronic cholestasis, portal inflammation, and fibrosis that can lead to cirrhosis and, ultimately, liver failure.[6] On a biochemical level, the disease can be divided into early stage disease with an elevated alkaline phosphatase (ALP) and normal total bilirubin (TB), moderately advanced disease with either low albumin or high TB, and advanced disease with both low albumin and high TB.[7] Figure 1 represents the natural history of PBC over time.

Figure 1. Natural History of PBC[6]



Fatigue and pruritus are the most common symptoms of PBC, and both can be debilitating in some patients, especially fatigue.[8] Among patients who are diagnosed once symptomatic, median survival has been estimated to range from 6-10 years without liver transplant.[8] In contrast, in a cohort of 29 patients who were asymptomatic at diagnosis, none developed cirrhosis during a median follow-up of 17.8 years.[9] An elevation in the levels of ALP and TB are predictive of average time to liver transplantation.[10] Hepatocellular carcinoma (HCC) is an infrequent yet critical consequence of PBC, especially in male patients and those who do not respond adequately to standard treatment.[11] Osteoporosis occurs in up to one-third of patients with PBC, but is usually asymptomatic and does not present an increased risk for fractures.[5,12]

Obeticholic acid (OCA) is a novel bile acid analogue that has shown positive effects on biochemical markers of liver function in two Phase II trials (NCT00550862 and NCT00570765) and in the one-year double-blind (DB) POISE Phase III trial that measured the impact of OCA on levels of ALP and TB (NCT02308111). OCA has received orphan drug designation in both the United States (US) and Europe for the treatment of PBC, and a priority review has been granted by the Food and Drug Administration (FDA). At a meeting of the FDA Gastrointestinal Drugs Advisory Committee Meeting on April, 7th, 2016, the committee unanimously agreed (17 to 0) that based on its effect on ALP, there is substantial evidence to support accelerated approval of OCA for the treatment of PBC in combination with ursodeoxycholic acid (UDCA) in adults with an inadequate response to UDCA, or as monotherapy in adults unable to tolerate UDCA.[13] The expected date for the FDA to take action under the Prescription Drug User Fee Act is May 29th, 2016.

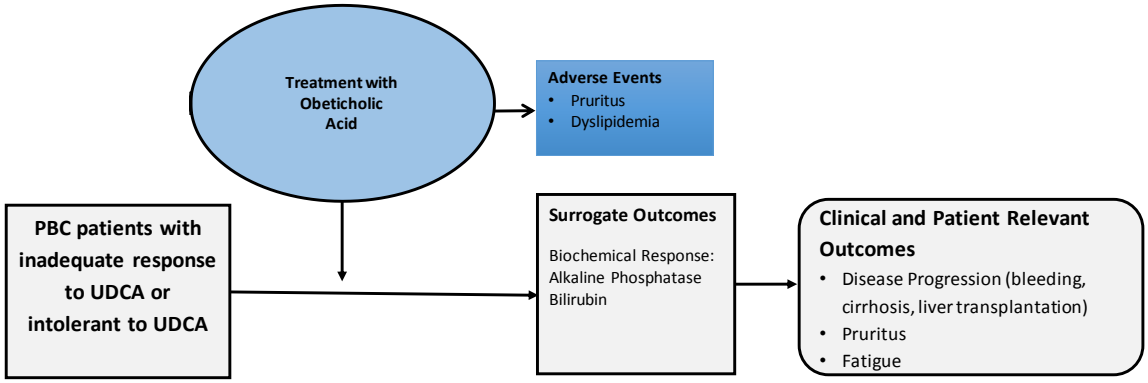
Scope of the Assessment

This assessment evaluates the health and economic outcomes of OCA as a second-line treatment of PBC in combination with UDCA in adults with an inadequate response to UDCA or as monotherapy in adults unable to tolerate UDCA. The scope is described using the PICOTS (Population, Intervention, Comparators, Outcomes, Timing, and Settings) framework.[14]

Analytic Framework

The analytic framework for this assessment is depicted in Figure 2.

Figure 2. Analytic Framework



Populations

The population of focus for the review included adults with PBC ages 18 years and older who have had an inadequate response to UDCA or who are unable to tolerate UDCA.

Interventions

The intervention of interest was OCA added to UDCA for patients with inadequate response to UDCA, or as a monotherapy for patients unable to tolerate UDCA.

Comparators

Comparators included continued use of UDCA in patients able to tolerate such therapy and usual care for patients intolerant to UDCA.

Outcomes

This review examined key clinical outcomes related to PBC and its treatment, including surrogate outcomes in available clinical trials. Outcomes of interest included:

- Biochemical response (e.g., ALP, bilirubin)
- Other markers of liver function (e.g., alanine aminotransferase [ALT], aspartate aminotransferase [AST], gamma-glutamyl transpeptidase [GGT])
- Measures of liver fibrosis
- Bleeding from portal hypertension
- Cirrhosis
- Liver transplantation
- Survival
- Health-related quality of life
- Adverse events (e.g., pruritus, fatigue, effects on cholesterol)

Timing

Evidence on intervention effectiveness and harms was derived from studies of any duration.

Settings

All relevant settings were considered, including inpatient, clinic, and office settings.

2. The Topic in Context

A relatively small number of patients have PBC, and it can take more than a decade for this chronic liver disease to progress from the early, typically asymptomatic stage to liver failure and need for liver transplantation. Both of these factors are major obstacles for the development of new therapeutic approaches.

Regulatory authorities have developed programs to advance the evaluation and development of therapeutic products for diagnosis and treatment of rare diseases or conditions. According to the US Orphan Drug Act, a rare disease is defined as any disease which affects less than 200,000 persons in the US.[15] With an estimate of 130,000 patients in the US, PBC is considered a rare disease and the manufacturer has received an orphan drug designation for OCA.[16]

The different disease stages from autoimmune damage to cholestasis, portal inflammation, and fibrosis could constitute targets for specific therapeutic interventions. For the early autoimmune stage, trials with most immunosuppressive agents have been inconclusive; the use of budesonide is currently being investigated in a large randomized controlled trial (RCT) (NCT00746486). UDCA, the only drug approved by the FDA for the treatment of PBC, mainly acts by decreasing cholestasis and protecting hepatocytes from the toxic effects of the bile acids. Specific antifibrotic agents could be of interest, but the cholestatic conditions seem to limit their potential.[17]

UDCA is a bile acid that is present in human bile at a concentration of approximately 3%. In patients with PBC, a daily dose of 13–15 mg/kg increases the percentage of UDCA in bile to about 40-50%.[18] At this dose it has been shown to improve hepatic biochemistry, including ALP and TB, slow histological progression to fibrosis, delay and reverse portal hypertension (which develops prior to cirrhosis in PBC), and delay the requirement for liver transplantation.[8,19] Lifetime treatment is recommended for all patients with PBC. Patients with early stage disease treated with UDCA have an overall survival similar to the general population. For patients with moderate to severe disease, UDCA treatment significantly improves average time to requirement for liver transplantation.[20] However, treatment with UDCA does not improve fatigue and pruritus, and around 40% of patients with PBC do not achieve adequate improvement in biochemical measures of liver function.[8] The introduction of UDCA has had other positive effects. PBC was the leading indication for liver transplantation in the US in the mid-1980s, but due to treatment with UDCA the number of patients with PBC requiring transplant has declined by 20% and it now ranks sixth.[5]

UDCA has minimal side effects.[5] The most frequently reported adverse events (AEs) of the drug include loose stool (2–9%), headache, and mild weight gain, but these rarely lead to discontinuation.[8] Patients who experience diarrhea should try to take the total daily dose in more frequent, smaller doses.[21] Beyond a certain level of discomfort patients may decide to discontinue

UDCA. This level of intolerance does not seem to be documented in the scientific literature, but according to Intercept market research, around 3% of patients are intolerant to UDCA.[4]

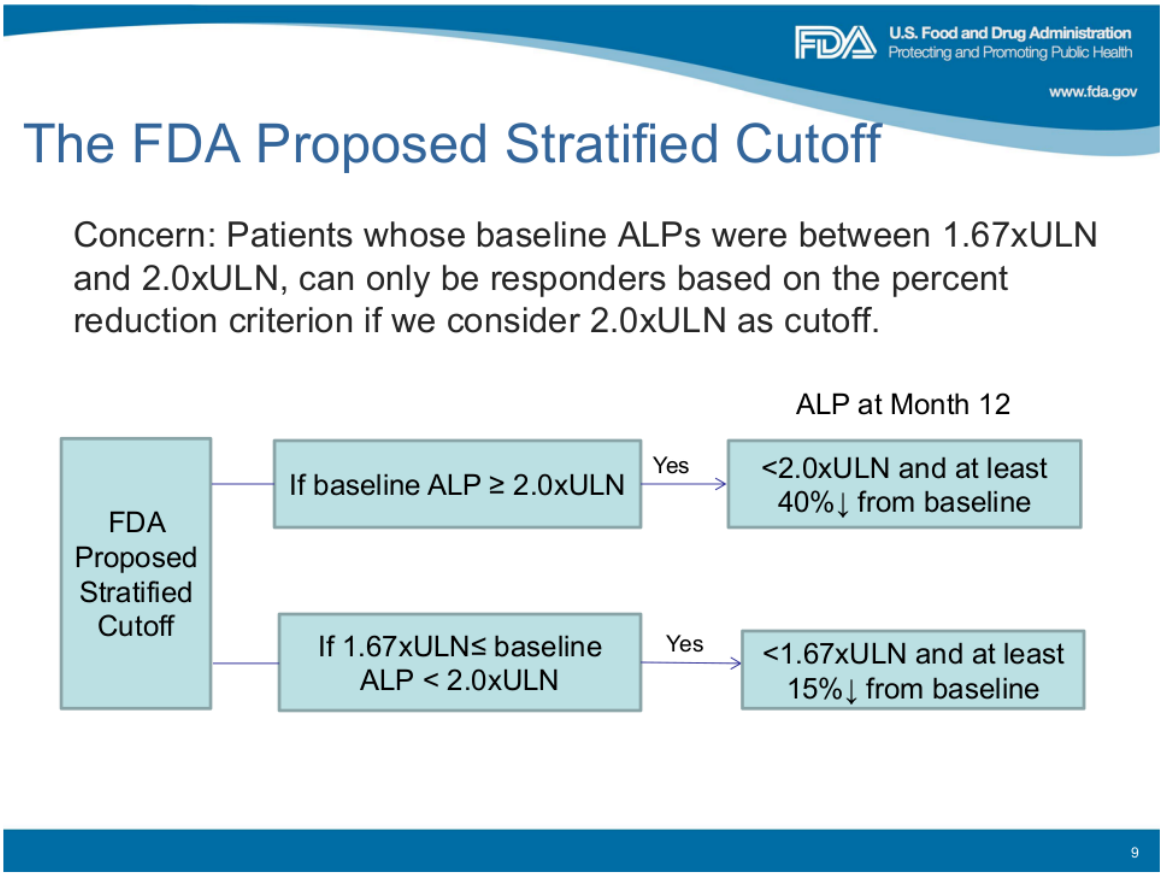
Improvement in ALP levels usually starts within a few weeks on UDCA and 90% of improvement occurs within six to nine months. For some patients, the treatment effect does not appear until up to five years on UDCA.[5]. Different criteria have been proposed to define biochemical response to UDCA, with six criteria being referred to most often. The cut-off points in time vary between six months for the Mayo Clinic criteria and two years for the Toronto criteria. The other four biochemical response criteria (Barcelona, Paris I and II, Rotterdam) use a cut-off point of 12 months to define inadequate response to UDCA.[8]

Overall, patients with an inadequate response to UDCA are at a higher risk of disease progression compared to those who show improvement.[8] In one study of 192 patients treated with UDCA over 1.5 to 14 years, applying the Barcelona criteria of response as normalization or 40% decrease in ALP levels after one year, patients without biochemical response had a relative risk of death or liver transplantation of 5.51 (95% CI, 1.70 to 15.99) compared to those with a response.[22] According to the different biochemical response criteria in UDCA-treated PBC patients, the reported nonresponse rates vary between 24% and 79%,[23] but a rate of approximately 40% of patients with an inadequate response to treatment with UDCA seems to be considered an appropriate estimation.[8]

At a meeting of the FDA Gastrointestinal Drugs Advisory Committee Meeting on April 7, 2016, the committee unanimously agreed there is substantial evidence to support the effect of OCA on ALP as a surrogate outcome for the treatment of PBC in combination with UDCA in adults with an inadequate response to UDCA or as monotherapy in adults unable to tolerate UDCA. However, "the majority of the committee agreed that the data are limited on the use of OCA in moderately advanced stage PBC patients, and absent in advanced stage PBC patients, to support the use of OCA in moderately advanced and advanced stages of PBC."[13] For treatment of advanced stage patients, the FDA suggests a reduction to the dosing regimen proposed by the manufacturer.[13]

For the Phase III trial of OCA, also known as POISE, response was defined as ALP less than 1.67 times the upper limit of normal (ULN), at least a 15% decrease in ALP, and normalization of TB after 12 months of treatment with OCA in combination with UDCA (NCT02308111). The Global PBC Study Group is an international non-profit collaboration between medical centers that was established to search for reliable surrogate endpoints for PBC.[24] Using a statistical analysis of this database, the FDA recommends the following definition of response after 12 months of treatment:

Figure 3. FDA Proposed Stratified Cutoff for PBC Patients Indicated for OCA[13]



The FDA analysts estimate that the above cutoff criteria for defining treatment response improve the validity of a treatment effect on ALP as a surrogate outcome for clinical benefit in PBC. The validity of using ALP as a surrogate outcome for clinical benefit can be different across disease stages. As discussed in Section 4, 92% of the patient population in the Phase III trial for OCA were in the early stage of their disease.

Patients with an inadequate response should receive a second-line treatment after monotherapy with UDCA, and there are several agents besides OCA that are currently being investigated for this purpose. Budesonide, fibrates, and OCA are currently considered as the most promising second-line treatments to be used in addition to UDCA.[17] Both budesonide (NCT00746486) and bezafibrate (NCT01654731) are currently being studied in Phase III trials in Europe. Budesonide is recommended by European experts as a valid add-on to UDCA for patients with early stage disease and inadequate response to UDCA.[17] According to clinical experts consulted, budesonide is rarely used as a second line treatment in the US. Bezafibrate, the fibrate most studied as a second-line treatment in PBC, is not licensed for sale in the US. In addition, on March 31, 2016 Genfit

announced plans for a Phase II trial evaluating a new agent, elafibranor, as a second-line treatment for PBC patients with an inadequate response to UDCA, and is set to start before the end of 2016.[25]

3. Summary of Coverage Policies

OCA

FDA approval for OCA is pending at the time of this report. This section will be updated as coverage policies become available.

UDCA

UDCA is widely covered by most public and private payers in the New England region and nationally. Many insurers cover both generic and brand name formulations, with brand names falling into higher tiers and sometimes requiring prior authorization.

4. Comparative Clinical Effectiveness

4.1 Overview

To inform our analysis of the comparative clinical effectiveness of OCA as a second-line treatment for PBC, we abstracted evidence from available clinical studies, whether in published, unpublished, or abstract form. Regimens of interest included:

- OCA taken once daily in combination with UDCA for patients with an inadequate response to UDCA; and
- OCA taken once daily as monotherapy in patients unable to tolerate UDCA

As described previously in the Background section, the comparators of interest included continued use of UDCA in patients able to tolerate such therapy and usual supportive care for patients intolerant to UDCA. Our review focused on surrogate markers of clinical benefit (i.e., biochemical response, other markers of liver function) as well as potential harms (drug-related AEs). The outcomes we addressed in detail are as follows:

- Clinical Benefits
    - Changes in ALP
    - Treatment response (based on composite endpoints of ALP and other liver biomarkers)
    - Other measures of liver function (GGT, AST, ALT, and bilirubin)
- Harms
    - Pruritus
    - Dyslipidemia
    - Other adverse events (e.g., hepatic decompensation)

4.2 Methods

We included evidence from Phase II and III RCTs and supplemented our review of published studies with data from conference proceedings, regulatory documents, information submitted by the manufacturer, and other grey literature that met ICER standards for review (for more information, see http://icer-review.org/methodology/icers-methods/icer-value-assessment-framework/grey-literature-policy/).

Data Sources and Searches

Procedures for the systematic literature review assessing the evidence on OCA with or without UDCA followed established best methods used in systematic review research.[26] We conducted the review in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines.[27] The PRISMA guidelines include a checklist of 27 items, further detail of which is available in Appendix Table A1.

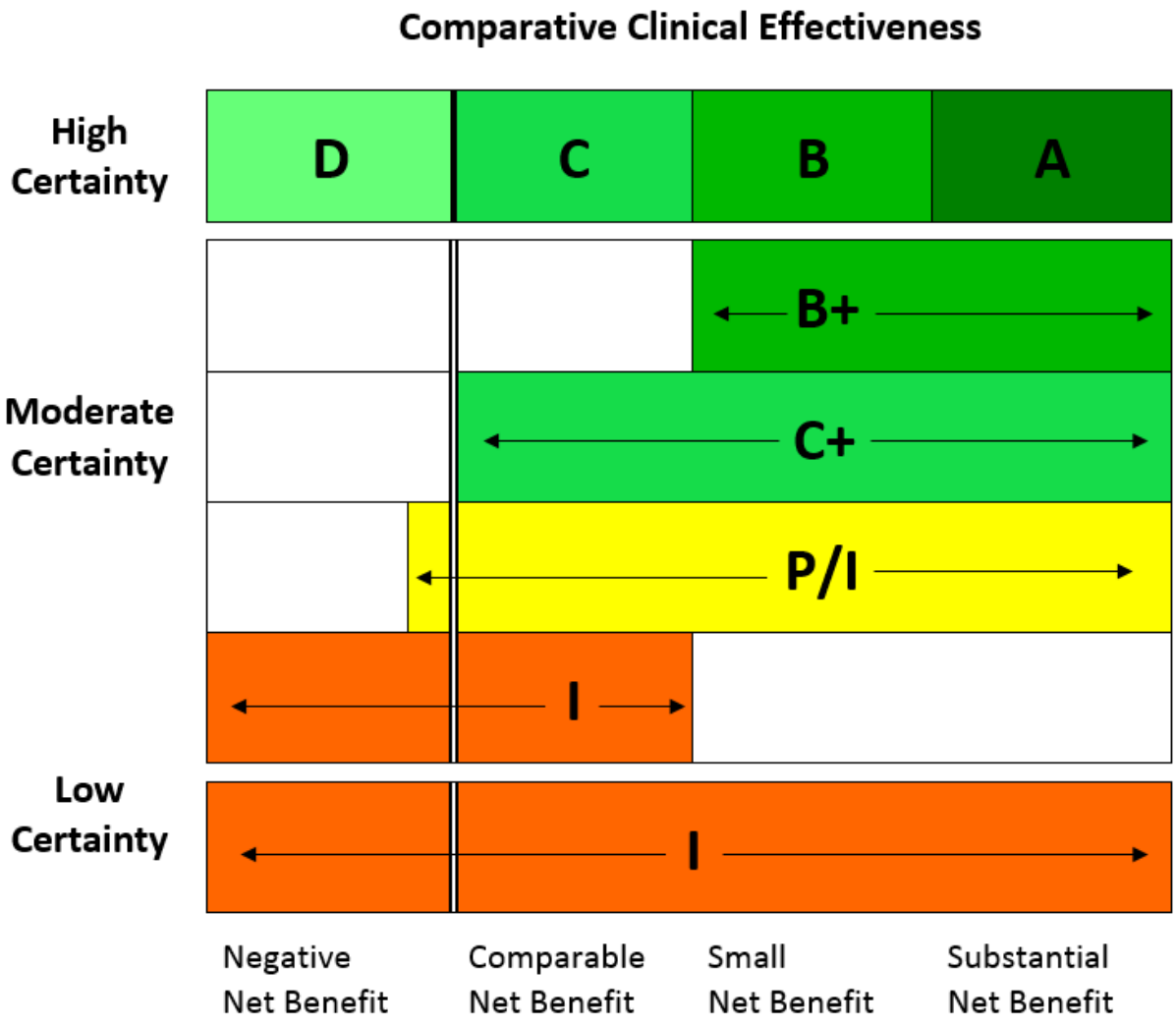
The timeframe for our search spanned the period from January 1996 to April 12, 2016 and focused on MEDLINE, EMBASE, and Cochrane-indexed articles. We limited each search to studies of human subjects and excluded articles indexed as guidelines, letters, editorials, narrative reviews, case reports, or news items. To supplement the above searches and ensure optimal and complete literature retrieval, we performed a manual check of the references of recent relevant reviews and meta-analyses. Other grey literature sources included data submissions from the manufacturer of OCA that were not otherwise publically available. Further details on the search algorithms, methods for study selection, data extraction, quality assessment, assessment for publication bias, and our approach to meta-analyses of the data are available in Appendix A.

Assessment of Level of Certainty in Evidence

We used the ICER Evidence Rating Matrix (see Figure 2) to evaluate the evidence for a variety of outcomes. The evidence rating reflects a joint judgment of two critical components:

The **magnitude** of the difference between a therapeutic agent and its comparator in "net health benefit" – the balance between clinical benefits and risks and/or adverse effects AND
The level of **certainty** in the best point estimate of net health benefit.[28]

Figure 4. ICER Evidence Rating Matrix



A = "Superior" **-** High certainty of a substantial (moderate-large) net health benefit
B = "Incremental" **-** High certainty of a small net health benefit
C = "Comparable"- High certainty of a comparable net health benefit
D="Negative"- High certainty of an inferior net health benefit
B+="Incremental or Better" **–** Moderate certainty of a small net health benefit, with high certainty of at least incremental net health benefit
C+="Comparable or Better" **-** Moderate certainty of a comparable net health benefit, with high certainty of at least comparable net health benefit
P/I = "Promising but Inconclusive" - Moderate certainty of a small or substantial net health benefit, small (but nonzero) likelihood of a negative net health benefit
I = "Insufficient" **–** Either moderate certainty that the best point estimate of comparative net health benefit is comparable or inferior; or any situation in which the level of certainty in the evidence is low

4.3 Results

Study Selection

Our literature search identified 103 potentially relevant references, of which 14 met our inclusion criteria. Only one published study[29] was available from our survey of the literature, with 13 additional conference abstracts and poster presentations; these references were related to three individual DB RCTs. Primary reasons for exclusion included: not a population of interest (i.e., not PBC patients), pharmacokinetic studies of OCA, abstracts/posters which contained duplicative data, or inappropriate study type (e.g., comment/opinion or review). We prioritized the reporting of information we identified as part of our literature search, and supplemented our presentation of the evidence with data available from regulatory documents. Details of the included references are described in Appendix B, and the three key trials are summarized in Table 1.

Key Studies

We identified only one published study reporting on outcomes from the Phase II RCT (Study 202) of OCA in combination with UDCA for patients with inadequate response to UDCA.[29] Given the limited information available in the peer-reviewed literature, we included summaries of the other key RCTs (Study 202 and 301) below. All trials included patients with elevated ALP (≥1.5xULN) and excluded patients with a history or presence of hepatic decompensation and bilirubin greater than twice the ULN.

Study 301 (POISE)[30,31]

The only Phase III trial we identified included 216 patients (mean age 56, 91% female, mean ALP 323.2 U/L, mean UDCA dose 15.4 mg/day) with ALP ≥1.67xULN or bilirubin <2xULN who were randomized to placebo, OCA 10 mg, or an OCA titration group who received 5 mg at the beginning of treatment and were titrated based on response after six months to a maximum dose of 10 mg. Most of the participants had been on UDCA for at least 12 months and were on a stable dose for at least three months prior to enrollment; 7% were UDCA intolerant and received OCA as monotherapy, and 92% had normal bilirubin at baseline. The primary endpoint was treatment response based on the proportion of patients achieving the Global PBC Study Group's definition of response that has been shown to be correlated with clinical benefit (ALP <1.67xULN with a ≥15% ALP reduction and normal bilirubin). Safety measures were also assessed, and a long-term safety extension (LTSE) phase is ongoing for patients who completed the one-year DB phase (n=193).

Study 202[29]

A Phase II trial evaluated three dosing regimens of OCA (10 mg, 25 mg, 50 mg) compared to placebo in 161 adults (mean age 55, 95% female, mean ALP 286.8 U/L, mean UDCA dose 15.9 mg/day) on a

stable dose of UDCA (≥6 months) with ALP 1.5-10xULN over 85 days. Most of the participants (96%) who enrolled had mean bilirubin levels in the normal range across all treatment groups. The primary endpoint was reduction in ALP in the modified intent-to-treat (mITT) population (n=161) who received at least one OCA dose; secondary endpoints were based on changes in liver chemistry in the intent-to-treat (ITT) population (n=165), including AST, ALT, GGT, conjugated bilirubin, and blood serum levels. The authors also evaluated these effects for the proportion of patients meeting five published definitions of response criteria based on surrogate outcomes (e.g., ALP and TB levels above ULN), which have been shown to predict the risk of progression. An open-label safety extension trial was also conducted up to a year following enrollment, with 78 patients from the DB trial restarting treatment at a maximum 10 mg dose of OCA and titrating based on response.

***Study 201*[32,33]**

Another Phase II trial was conducted in 59 adult patients who received OCA as monotherapy in 10 mg and 50 mg doses compared to placebo over 12 weeks, followed by an off-treatment phase (day 86-99). This study was conducted subsequent to another Phase II trial (Study 202) evaluating the use of OCA taken concomitantly with UDCA to determine if the treatment effect of OCA was independent of UDCA. Included participants (mean age 55, 85% female, mean ALP 432.6 U/L) had ALP levels between 1.5-10xULN and had not been taking UDCA for at least six months prior to enrollment. Outcome measures included changes in biochemical response from baseline, mean reduction in ALP above the ULN, and harms. At the end of the DB phase of the trial, 28 patients (mean age 60, 84% female) enrolled in the LTSE and were followed up to 4.5 years; 43% of patients were taking a maximum 10 mg dose of OCA and eight eventually added UDCA.

Table 1. Key Trials

RCT	Study 201	Study 202 Hirschfield et al.	Study 301 (POISE)
Patient Characteristics	N=59 (ITT) Mean age: 55 years Female: 85% Mean ALP: 432.6 U/L	N=161 (ITT, N=165) Mean age: 55 years Female: 95% Mean ALP: 286.9 U/L Mean UDCA dose: 15.9 mg/day	N=216 (ITT, N=217) Mean age: 56 years Female: 91% Mean ALP: 323.2 U/L Mean UDCA dose: 15.4 mg/day
Interventions/Comparators	OCA 10 mg OCA 50 mg Placebo	OCA 10 mg OCA 25 mg OCA 50 mg Placebo	OCA 5-10 mg OCA 10 mg Placebo
Duration	DB: 3 months LTSE: Up to 4.5 years	DB: 3 months LTSE: 1 year	DB: 1 year LTSE: 5 years (ongoing)
Inclusion criteria	OCA as monotherapy for patients not on UDCA for ≥3 months ALP 1.5-10xULN	OCA+UDCA for patients with inadequate response to UDCA (stable dose ≥6 months) ALP 1.5-10xULN	OCA±UDCA for patients with inadequate response to UDCA (on UDCA for ≥12 months and stable dose ≥3 months), or intolerant to UDCA (7%) ALP ≥1.67xULN **or** bilirubin >1xULN but <2xULN
% Change in ALP	OCA 10 mg: -44.5 OCA 50 mg: -37.6 Placebo: +11.7 All OCA groups from baseline, p<0.0001	OCA 10 mg: -23.7 OCA 25 mg: -24.7 OCA 50 mg: -21.0 Placebo: -3.1 All OCA groups from baseline, p<0.0001	OCA 5-10 mg: -33.0 OCA 10 mg: -39.1 Placebo: -4.8 All OCA groups vs. placebo, p<0.0001

Quality of Individual Studies

Using criteria from U.S. Preventive Services Task Force (USPSTF),[34] we rated the one published RCT identified for this review to be of good quality.[29] We judged this report to be of good quality because study arms were comparable at baseline, the authors used valid instruments to evaluate outcomes, and no differential attrition was observed. We did not assign a quality rating to the remaining 13 documents, which included results from the Phase II trial (Study 201) evaluating the use of OCA as monotherapy, and the Phase III trial (Study 301) evaluating the use of titrating the OCA dose (5-10 mg) in combination with UDCA, as well as pooled analyses from all three trials, because they were obtained from conference proceedings and regulatory packages rather than peer-reviewed publications.

Clinical Benefits

A detailed review of each outcome of interest is presented in the sections that follow. All trials were designed primarily to measure changes in ALP, including percentage or absolute mean reductions in ALP from baseline, as well as ALP normalization. Other liver biomarkers, including, AST, ALT, GGT and bilirubin, were also measured in all studies; these tests indicate liver function and are used by clinicians to follow the disease process. Treatment response was compared to different published risk models (e.g., ALP <1.67xULN and TB <ULN) that may reasonably predict important clinical outcomes for PBC patients (e.g., transplant-free survival and mortality). We also described the most frequently-reported harms as reported in the trials, with a particular focus on drug-related AEs (e.g., pruritus). Importantly, the outcomes reported from Study 202 were primarily based on the Hirschfield publication, while results from the other two key trials of OCA for PBC (Study 201 and 301) were only available in the grey literature.

Changes in ALP

The RCT publication for the Phase II trial evaluating OCA taken concomitantly with UDCA evaluated mean reduction in ALP levels from baseline to day 85 in the mITT group as the primary endpoint.[29] Among those receiving OCA, there were ALP reductions of 24%, 25%, and 21% in the 10 mg, 25 mg, and 50 mg groups, respectively, while the placebo group saw a 3% reduction; these results were also statistically significant for the ITT and completer populations over three months, and these improvements were sustained during the nine month open-label extension period (OCA groups vs. baseline, p<0.0001). Overall, more OCA-treated patients saw at least a 10% reduction (87% vs. 14% for placebo) or at least a 20% reduction (69% vs. 8% for placebo) compared to placebo (both outcomes, p<0.0001). While only 7% of patients in the OCA-treated groups achieved ALP normalization, no patients in the placebo group did. A greater number of patients in the 25 mg group achieved ALP normalization (12%) than either the 50 mg (11%) or 10 mg (3%) groups, but these results were not evaluated statistically.[29]

Findings from Grey Literature

Similarly, at the end of the one-year DB phase of the POISE study, there was a statistically significant mean percent reduction in ALP from baseline for the OCA-treated groups (-33.0% and -39.1% vs. -4.8% for 5-10 mg, 10 mg, and placebo, respectively), coinciding with a statistically significant mean absolute ALP reduction (-106 U/L and -127 U/L vs. -6 U/L for 5-10 mg, 10 mg, and placebo, respectively) compared to placebo (both outcomes, p<0.0001).[35] Notably, the OCA 10 mg group had a greater effect in the Phase II trial when taken as monotherapy (-44.5%) than for the Phase III trial evaluating UDCA combination therapy (-39.1%), which may in part be due to higher baseline ALP in monotherapy patients.

At the end of Study 201, patients in the OCA monotherapy groups experienced a statistically significant mean absolute reduction (10 mg, -233.5 U/L; 50 mg, -161.3 U/L) and mean percent reduction (10 mg, -44.5%; 50 mg, -37.6%) in ALP from baseline (all outcomes, p<0.0001), while ALP increased for placebo (+11.7 U/L, +0.4%). ALP also decreased from a mean 3.9xULN to 1.9xULN in the 10 mg group. Differences between groups were not evaluated statistically.[32] In the open-label LTSE trial, OCA monotherapy patients (43% on ≤10 mg OCA) completing 4.5 years of follow-up (n=11) sustained a statistically significant mean absolute reduction in ALP from baseline (-182 U/L, p=0.0105). When including those patients who added UDCA (n=19), the mean absolute reduction in ALP was larger (-244 U/L, p=0.0034).[33]

Treatment Response

In Study 202, treatment response was evaluated against several published criteria, which differed according to specific thresholds of biochemical response.[29] Although the 25 mg OCA group saw statistically significant response rates across all algorithms (all p<0.05), the 10 mg and 50 mg groups did not demonstrate a statistically significant difference against placebo on two of the six criteria being evaluated; these included Paris I (ALP ≤3xULN, AST ≤2xULN, and TB ≤1 mg/dL), and a modified version of the Toronto I criteria that required normalization of bilirubin as well as ALP levels ≤1.67xULN.[29]

Findings from Grey Literature

The Phase III POISE trial evaluated the proportion of patients achieving the primary endpoint (i.e., a mean ALP <1.67xULN with ≥15% reduction, and normal bilirubin), as well as the proportion of patients meeting varied definitions of biochemical response according to published predictive risk models.[30] Statistically significantly more patients in the OCA-treated groups achieved the primary endpoint (46% and 47% vs. 10% in the 5-10 mg, 10 mg, and placebo groups, respectively; p<0.0001).

Although Study 201 did not evaluate outcomes against a prescriptive definition of treatment response, a secondary analysis evaluated the proportion of patients achieving the POISE primary endpoint at 12 weeks across all three available trials.[36] Table 2 shows that for the OCA 10 mg group in each trial, as well as the pooled results for all OCA groups, the proportion of patients in the OCA-treated cohorts achieving the POISE definition of treatment response was statistically significantly greater compared to placebo.

Table 2. Proportion of Trial Patients Achieving the POISE Primary Endpoint[36]

% of Patients	Study 201, n=43	Study 202, n=76	Study 301, n=146	Pooled, n=306
Placebo	4	8	10	8
OCA 10 mg	40	42	47	45 (all OCA groups)
p-value	p=0.0026	p=0.0002	p<0.0001	p<0.0001

Other Measures of Liver Function

In Study 202, improvements in other measures of liver function were statistically significant, including GGT (range: -48% to -63%) and ALT (-9% to -17%), across all OCA groups compared to the placebo group which experienced a negligible change at day 85 (all outcomes, $p<0.05$).[29] However, the OCA 50 mg group did not produce a statistically significant reduction in AST, nor did the OCA 10 mg group produce a statistically significant reduction in conjugated bilirubin. The authors reported that three patients discontinued the DB trial per the mandated protocol as a result of elevated conjugated bilirubin (>2x average predose value),[29] one in the 10 mg and two in the 50 mg groups.[37]

Findings from Grey Literature

Results from the Phase III POISE trial demonstrated statistically significant improvements for the 5-10 mg and 10 mg groups on ALT (-35.5% and -41.7% vs. -4.7% for placebo, respectively) and GGT (-50.3% and -63.7% vs. 0.8% for placebo, respectively) compared to placebo, with greater reductions in the 10 mg group (all outcomes, $p<0.0001$).[35] TB was also statistically significantly better than placebo for the OCA groups (1.2% and -0.2% vs. 19.5% for the 5-10 mg, 10 mg, and placebo groups, respectively; $p<0.005$).[35] Finally, absolute changes in AST were statistically significantly improved from baseline for both OCA groups, but were not compared statistically to placebo (-13 U/L and -15 U/L vs. 1 U/L for 5-10 mg, 10 mg, and placebo, respectively, $p<0.0001$).[37]

For Study 201, other measures of liver function in the 10 mg OCA and 50 mg OCA groups were statistically significantly improved from baseline at the end of the DB phase, including ALT (-38% and -35%, respectively) and GGT (-73% and -65%, respectively), with overall greater reductions for the 10 mg group (all outcomes, $p<0.0001$).[32] Changes from baseline continued to be statistically significantly improved in the LTSE phase (mean 4.5 years of follow-up) for the combined OCA-treated groups (ALT: -54%, GGT: -70%, AST: -29%, $p<0.01$). However, mean change in TB was not statistically significantly at 4.5 years, and differences between groups were not compared statistically at any point.[33]

Harms

Treatment-related adverse effects were generally mild to moderate in nature, and primarily related to pruritus. The main reason for discontinuation in the trials was severe pruritus, with increased frequency in patients receiving higher doses. Changes in lipid levels, mostly due to reductions in HDL, were also common in all OCA-treated patients. Although treatment-related reductions are concerning given the protective nature of HDL against cardiovascular morbidity, it is unclear if these changes represent clinical significance. Other serious adverse events (SAEs) occurred with much less frequency and included hepatic decompensation, gastrointestinal disorders, and hyperbilirubinemia; questions remain as to whether these events were correlated with OCA or manifested independently as a result of progressing disease. With the exception of some pruritus

outcomes in the Hirschfield trial, these events were not evaluated statistically, likely due to the overall limited occurrence.

Pruritus

Although pruritus is a symptom of PBC, the available evidence suggests there is increased frequency and severity of pruritus due to OCA treatment, particularly at higher doses. In the Hirschfield RCT, the incidence of pruritus was 85% ($p<0.0003$) and 80% ($p<0.006$) in the 25 mg and 50 mg OCA groups, respectively, compared to 50% in the placebo group. In the OCA 10 mg group, the incidence of pruritus was numerically lower than in the placebo group (47%), but the difference was not statistically significant.[29]

Severe pruritus, which was the primary reason for trial discontinuation, occurred in 16%, 24%, and 37% of the 10 mg, 25 mg, and 50 mg cohorts, respectively, compared to no patients in the placebo group. Overall, 10% of the OCA-treated population discontinued the DB phase due to pruritus. Although the authors reported that incidence of severe pruritus in the open-label LTSE phase was lower, 10 patients (13%) discontinued the trial due to severe pruritus.[29] No additional details on the distribution of pruritus severity or trial discontinuation across treatment groups from the open-label LTSE phase were available, however.

Findings from Grey Literature

The POISE trial demonstrated similar dosing effects of OCA related to pruritus. In the DB phase, pruritus occurred more frequently in the OCA-treated groups relative to placebo, with 38%, 56%, and 68% in the placebo, 5-10 mg, and 10 mg groups, respectively.[38] However, pruritus was generally well-managed using bile acid sequestrants and/or antihistamines, with 13% in the titration group and 20% in the 10 mg group requiring a change in their dosing schedule.[39] Pruritus was less severe in the titration group, with only 1% (1 patient) discontinuing due to pruritus compared to 10% (7 patients) in the 10 mg group.[31,38] Overall, less than six percent of patients discontinued due to pruritus.[30] With up to two years of follow-up in the LTSE phase, new incidence of pruritus was lower than in the DB trial, occurring at the rate of 15% in the 5-10 mg group and 21% in the 10 mg group, with a discontinuation rate of less than 1%.[31,38]

In Study 201, incidence of pruritus occurred at a rate of 30%, 70%, and 94% in the placebo, 10 mg, and 50 mg groups, respectively.[32] These cases were generally mild to moderate; three patients (15%) in the 10 mg arm and six patients (38%) in the 50 mg arm discontinued due to pruritus in the DB trial.[40] After 4.5 years of follow-up, three (10%) of the 28 remaining patients in the trial discontinued due to pruritus.[33]

Dyslipidemia

Hirschfield et al. reported that changes in lipid levels were dose-related and mainly due to a reduction in HDL levels. While total cholesterol decreased 3-13% across all OCA-treated groups, with incrementally greater reductions correlated with higher doses, all OCA groups experienced a drop in HDL while the placebo group remained relatively stable over time.[29] Mean reductions in HDL levels ranged from a 0.47 mmol/L in the 50 mg group, to 0.25 mmol/L in the 10 mg group.[40] During the off-treatment phase of the DB study (day 86-99), HDL levels increased for all OCA-treated groups, suggesting an OCA-induced effect. With the exception of the 50 mg treatment arm, mean LDL levels were similar for all groups at the end of the study,[29] and one patient in the 10 mg group had a clinically significant reduction in LDL.[40]

Findings from Grey Literature

HDL effects were also observed in the POISE trial, with reductions of 16% in the 5-10 mg group, 26% in the 10 mg group, and 3% in the placebo group.[35,40] The mean percent increases in LDL were 4%, 1%, and 2% in the 5-10 mg, 10 mg, and placebo arms, respectively.[40] Additionally, of those patients that had normal HDL at baseline, seven in the 10 mg group compared to four in the placebo group had below normal HDL by the end of the study.[40] After two years of treatment, the HDL decrease that occurred during the DB trial was unchanged, while LDL returned to baseline levels in all groups.[31]

Although all groups in Study 201 had modest changes in serum lipids, HDL levels decreased by 0.16 mmol/L, 0.09 mmol/L, and 0.14 mmol/L in the 10 mg, 50 mg and placebo groups, respectively. The reduction was noticeably less in the 50 mg group than in the placebo groups, but the investigators noted that this was likely due to the high dropout rate due to pruritus. There were also corresponding increases in LDL levels in the 10 mg (0.10 mmol/L) and 50 mg (0.23 mmol/L) arms, while there was a decrease in the placebo arm (0.08 mmol/L).[40] The principal investigators did not consider these changes to be clinically meaningful.[33]

Other Adverse Events

Other commonly-reported adverse effects of treatment include skin and subcutaneous tissue disorders (e.g., rash and gastrointestinal issues), infections (e.g., headache), and respiratory disorders. Table 3 lists the three most frequently reported AEs (other than pruritus) across the treatment groups in the DB study.[29]

Table 3. Top 3 Most Frequently Reported AEs in Hirschfield et al.[29]

Incidence of AEs	Placebo n, %	OCA, 10 mg n, %	OCA, 25 mg n, %	OCA, 50 mg n, %
Fatigue	5, 13	7, 18	3, 6	5, 12
Headache	4, 11	3, 8	5, 10	11, 27
Gastrointestinal disorders	10, 26	17, 45	17, 35	17, 41

Overall, 23 patients (14%) discontinued the trial after experiencing an AE of which more than half were in the OCA 50 mg arm.[29] Serious AEs occurred in seven patients (4%) (of which five were in the OCA 50 mg cohort), including dyspnea, salivary gland neoplasm, angina pectoris and angioedema. Two hepatic events occurred in two subjects, requiring discontinuation: one had a GI hemorrhage (gastrointestinal bleed related to esophageal varices that were present prior to treatment), and the other on the 50 mg dose of OCA had advanced PBC with cirrhosis and developed jaundice.[29,40]

In the open-label extension trial, fatigue, insomnia, and upper respiratory infection were most common and reported with the same frequency across the OCA-treated groups (13%), but only 3 patients (4%) discontinued the trial due to an AE.[29]

Findings from Grey Literature

The Phase III trial of OCA (POISE) reported a higher proportion of patients experiencing treatment-related AEs across OCA-treated groups during the first 12 months (39%, 51%, and 28% for 5-10 mg, 10 mg, and placebo, respectively).[39] Overall, 22 patients (10%) experienced a serious AE;[30] 15 events occurred in 11 patients in the titration group, two of which were hepatic-related; five events occurred in eight patients in the 10 mg group, one of which was hepatic-related.[40] Eight patients experienced cardiovascular-related AEs, most of which were palpitations and occurred with more frequency in the OCA-treated groups; one patient died of cardiac failure but this was likely unrelated to treatment.[40] Bone fractures were also more common in the OCA-treated groups (3 vs. 1 in the placebo group); a subgroup analysis was performed to determine whether this was related to treatment, the details of which are presented in the section below.[40]

In the DB phase of the trial for OCA monotherapy patients (Study 201), placebo patients experienced the same rate of adverse events as the OCA-treated groups; only one patient in the placebo group experienced a SAE, and no deaths occurred.[32,40] A total of eight patients experienced 20 events in the long-term extension phase,[33] of which four OCA-treated subjects that had serious hepatic-related AEs, including jaundice, liver decompensation, esophageal variceal hemorrhage, and hyperbilirubinemia.[40]

Subgroup Analyses

We identified five conference abstracts and poster presentations evaluating subgroup analyses for the available trials, three of which pooled data from all three RCTs. Two of three pooled analyses stratified patients according to disease severity with one evaluating those patients within ALP ranges above the ULN, and another for those patients with abnormal bilirubin levels;[41,42] a third analysis evaluated subpopulations based on age at diagnosis of PBC, age, and gender.[43] The final two analyses evaluated subgroups of patients in the POISE trial based on those remaining on 5 mg versus those who titrated to 10 mg in the titration treatment arm, and the proportion of patients who had dual-emission x-ray absorptiometry (DEXA) scans to determine the effect of OCA on bone mineral density (BMD).[44,45]

In a pooled analysis of the three available RCTs, those patients with abnormal bilirubin at baseline (n=46, mean age 53, 83% female) achieved statistically significant reductions in ALP for the OCA 10 mg and all OCA-treated groups relative to placebo at three months of follow-up (-212 U/L and -189 U/L vs. -31 U/L, in 10 mg, all-OCA, and placebo cohorts, respectively; p<0.005); these changes were also statistically significant at month 12 (-110 U/L and -120 U/L vs. -20 U/L, in 10 mg, all-OCA, and placebo cohorts, respectively; p<0.05).[41] Although mean reduction in bilirubin was not statistically significant at three months, for patients that had follow-up at month 12 (n=21) there was a statistically significantly greater effect of OCA compared to placebo on TB levels (-8.9 µmol/L vs. -0.7 µmol/L, p<0.05). As with patients with normal bilirubin, there was a dose-related increase for the incidence of pruritus (86% and 73% vs. 30% in 10 mg, all OCA, and placebo cohorts, respectively). Hepatic events were lower in the 10 mg group (7%) compared to the all-OCA (14%) and placebo (10%) cohorts, but the number of patients in these groups were too small to determine any association with treatment.[41]

In a similar subgroup analysis that patients stratified by ranges of ALP above the ULN, a linear regression model adjusting for UDCA dose at baseline indicated that patients receiving a 10 mg dose across the three trials (n=114, mean age 56, 88% female) who were within the ALP ranges of 1-2xULN, >2-3xULN, >3-4x ULN, and >4xULN had a statistically significant (p<0.0001) ALP reduction of 23%, 29%, 44%, and 45%, respectively, from baseline which corresponded to a statistically significant decrease of 3.5% for every incremental level above ULN (p=0.0046).[42] Finally, there was a statistically significant incremental effect on TB levels, with a greater reduction for higher ALP ranges (-4%, -5%, -6%, and -17%; p<0.05). Harms associated with these ALP ranges were not reported.[42]

The third subgroup analysis evaluating the potential differential effect of OCA according to age at PBC diagnosis (<50 or ≥50 years), age (<65 or ≥65 years), and gender (male or female) on outcomes found that all groups experienced similar reductions in ALP and a comparable proportion of patients

meeting the POISE primary endpoint based on three-month results pooled across the three trials for patients taking a maximum 10 mg dose of OCA; incidence of pruritus was also similar.[43]

For those patients in the titration arm of the POISE trial, a fourth subgroup analysis evaluated whether efficacy and tolerability were comparable for those who remained at 5 mg (n=33) relative to those who titrated to 10 mg (n=36) after six months if the composite endpoint was not met.[44] Patients in both groups had similar response rates (with an additional 13 responders who titrated to 10 mg), reductions in ALP, and incidence of pruritus; however, differences between the two subgroups were not evaluated statistically.[44]

The final subgroup analysis assessed those patients in the POISE trial (n=122, 85% female, 52% postmenopausal) who had DEXA scans at baseline and study end to determine the effect of OCA on BMD.[45] While the 10 mg and placebo groups had statistically significant decreases in femoral T-scores (p=0.01 and p=0.03, respectively), OCA-treated participants had statistically significantly smaller decreases compared to placebo (-0.06 g/cm² and -0.07g/cm² vs. -0.33g/cm² for 5-10 mg, 10 mg, and placebo groups, respectively, $p<0.05$) suggesting a possible beneficial effect of OCA on BMD.[45]

Controversies and Uncertainties

Several limitations in the body of evidence reduce our ability to make judgments regarding the comparative net health benefits of OCA. First, data on clinically-relevant outcomes, including transplant-free survival and mortality, are not yet available. Surrogate endpoints, such as reduction in ALP, have not been previously adopted by the FDA as acceptable criteria for regulatory approval of new PBC regimens. As discussed at the FDA Advisory Committee meeting, there remains some uncertainty surrounding the appropriate definition of treatment response (and specifically the cut-off points used in POISE) for PBC patients, particularly for those patients with elevated ALP and normal bilirubin, as well as the clinical significance of treatment-related reductions in HDL. Although the committee voted unanimously to recommend approval of the drug, FDA authorization would set a precedent for the use of ALP reduction alone as a measure of improvement in PBC patients before a correlation between changes in liver biomarkers and clinically-relevant outcomes across the disease spectrum has been corroborated; only long-term studies will validate this association.

Our certainty in the efficacy of OCA is also hampered by the lack of peer-reviewed data of the dose regimens selected for marketing approval. For example, only one Phase III trial (POISE) evaluated a starting dose of 5 mg titrating to a maximum of 10 mg based on response, which is the regimen suggested by the manufacturer to reduce discontinuation due to pruritus. Although interim data of this trial is available in the grey literature, such information not yet been subject to the adjudication process employed for journal publications.

Yet another area of uncertainty is the use of OCA as monotherapy. Although pooled data demonstrated similar efficacy to patients on combination therapy with regards to reduction in ALP (38% vs. 41% for OCA+UDCA),[40] data on the use of OCA without concomitant use of UDCA is primarily limited to results from two trials in conference abstracts and regulatory documents. Additionally, baseline values of ALP were higher for the Phase II monotherapy cohort, and only 16 patients from the POISE trial were considered intolerant to UDCA and taking OCA alone. Some experts suggest that patients taking UDCA with inadequate response may see additional benefits of the drug for up to five years of ongoing treatment.[5] Given that no head-to-head trial has been conducted, the true effect of OCA relative to UDCA is uncertain. However, because there were no additional safety concerns in these patients even after 4.5 years of follow-up, it is unlikely that OCA taken as monotherapy would represent a unique issue for patients intolerant to UDCA, particularly since there is no other available treatment option for these patients in the US.[33]

Perhaps the greatest amount of uncertainty in comparative net health benefit lies in the lack of data available for patients in later stages of their disease. Across the three trials of PBC, only 46 patients (11%) had abnormal bilirubin at baseline. Although a subgroup analysis of these patients demonstrated a statistically significant reduction in ALP and other liver biomarkers for OCA-treated patients compared to placebo at one year, less than half of these patients completed the studies (n=21).[41] In addition, because those patients with higher bilirubin at baseline tended to experience more SAEs, there may be a safety concern for moderately advanced patients that would warrant a reduced dosing schedule.[40] Therefore, further study should elucidate OCA's performance at different points during the disease course.

Summary

As previously mentioned, no trial has yet assessed clinically-meaningful outcomes associated with OCA as a second-line treatment. Therefore, we assigned ICER evidence ratings based on the reporting of improvements on surrogate endpoints (e.g., ALP reductions) balanced with treatment-related incidence and severity of AEs. Given the potential variabilities in outcomes for different patient populations (i.e., early vs. moderate-advanced disease) and regimens (i.e., monotherapy vs. combination therapy) being studied in the clinical trials of OCA for PBC, our ratings are based on the evidence for these distinguishing factors.

Because only a small minority (11%) of patients included in clinical trials of OCA for PBC had moderate disease based on elevated bilirubin, and no patients had advanced disease, we judge the evidence to be "insufficient" ("I") for both patient populations. Although a pooled subgroup analysis demonstrated statistically significant improvements in biochemical response for those patients with elevated bilirubin at baseline, questions remain regarding the safety profile of OCA in patients who are in the later stages of their disease course.

For patients with early disease, we have moderate certainty that OCA with or without UDCA provides an incremental or better net health benefit ("B+"). All three RCTs of OCA for PBC, of which a large majority were early stage PBC patients, demonstrated statistically significant ALP reductions from baseline and compared to placebo for all doses under investigation. Although incidence and severity of pruritus increased while taking OCA, these outcomes appeared to be mostly associated with higher doses, and were reduced in patients on a titration regimen (5-10 mg).

Table 4. ICER Evidence Ratings by Regimen

Regimen	Comparators	Evidence Rating
OCA as monotherapy	Placebo	P/I
OCA plus UDCA	Placebo plus UDCA	B+

For OCA taken as monotherapy, we judge the evidence to be "promising but inconclusive." Across two clinical trials, only 75 patients (17%) received OCA as monotherapy, and outcomes for these patients are only available in the grey literature. Nevertheless, results from conference abstracts and regulatory documents suggest a statistically significant improvement from baseline and compared to placebo on most liver biomarkers. In addition, in a pooled analysis of OCA 10 mg monotherapy patients from the two RCTs, reductions in ALP were similar to those patients who were also taking UDCA, and no additional safety concerns arose over 4.5 years of follow-up.

Finally, we have moderate certainty of an incremental or better net health benefit for OCA used as combination therapy with UDCA. The one published RCT evaluating patients on a stable dose of UDCA plus OCA demonstrated statistically significant improvements in ALP levels on all liver biomarkers compared to UDCA alone, with the exception of bilirubin. Taking into consideration an increased incidence of treatment-related pruritus, we assign the evidence a "B+" rating.

5. Other Benefits or Disadvantages

Our reviews seek to provide information on other benefits or disadvantages offered by the intervention to the individual patient, caregivers, the delivery system, other patients, or the public that would not have been considered as part of the evidence on comparative clinical effectiveness. Examples include but are not limited to:

1. Methods of administration that improve or diminish patient acceptability and adherence
2. A public health benefit, e.g., reducing new infections
3. Treatment outcomes that reduce disparities across various patient groups
4. More rapid return to work or other positive effects on productivity (if not considered a benefit as part of comparative clinical effectiveness)
5. New mechanisms of action for treatments of clinical conditions for which the response to currently available treatments vary significantly among patients for unknown reasons (substantial heterogeneity of treatment effect)

As previously discussed, UDCA is currently the only other FDA-approved treatment for PBC, on which an estimated 40% of patients have inadequate response to therapy; these patients are at an increased risk of liver transplant and death.[8] Although not yet demonstrated in clinical trials, OCA has the potential to improve clinically-relevant outcomes, particularly for patients with no other treatment option (i.e., patients with inadequate response or intolerant to UDCA).

6. Comparative Value

6.1 Overview

The primary aim of this analysis was to estimate the cost-effectiveness of OCA treatment for patients with PBC who have an inadequate response to conventional (i.e., UDCA) treatment. We conducted a cost-effectiveness analysis by developing a microsimulation model that simulated the long-term outcomes of patients receiving OCA in addition to UDCA as observed in the Phase III POISE study; as a comparator, we also simulated the placebo (±UDCA) arm of the trial. Model parameters were estimated from published studies and calibrated when assumptions were required. The outcomes of the model included total costs, quality-adjusted life years (QALY), incremental cost-effectiveness ratios, transplant-free survival, and cumulative incidence of advanced disease stages.

6.2 Prior Published Evidence on Costs and Cost-Effectiveness of Obeticholic Acid

We did not identify any published articles or public presentations pertaining to the cost and/or cost-effectiveness of OCA. To the best of our knowledge, this report is the first publicly available analysis that estimates the cost-effectiveness and long-term impact of OCA for the treatment of patients with PBC.

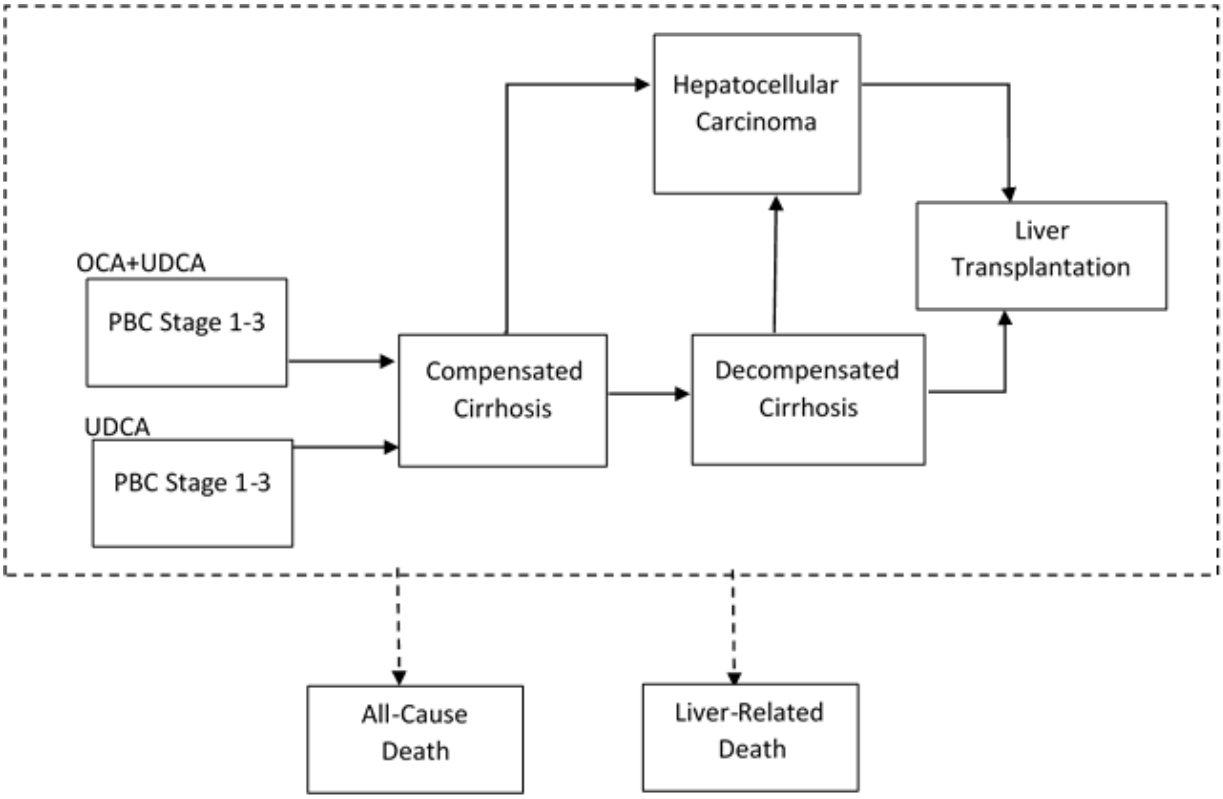
6.3 Incremental Costs per Outcome Achieved

Cost-Effectiveness Model: Methods

Model Structure

We developed a microsimulation model (individual-level state transition model) using Java, a general purpose programming language. Figure 5 describes the model structure. For each treatment regimen, a hypothetical patient population begins the model in the PBC health state (defined as PBC stage 1–3), where they remain until they experience either: (a) disease progression or (b) death from all-cause or liver-related mortality. Patients who transition from the PBC stage 1–3 to compensated cirrhosis state remain there until they transition to another advanced liver disease health state or die from liver-related mortality or from other causes. Patient survival, quality-adjusted survival, and health care costs were estimated for each model cycle and then summarized over the entire time horizon for each treatment option. We used an annual cycle length in the model.

Figure 5. Model Structure for the Natural History of PBC



Target Population

The population of focus for the review was adults with PBC whose disease has not adequately responded to UDCA treatment (i.e., is refractory). Demographic characteristics for the modeled cohort were selected to match those of patients in the POISE study. The mean age of patients was 55.8, and 91% were female. At the beginning of the model simulation, 90% of the cohort started in stages 1–3 and 10% started with compensated cirrhosis (Table 5).

Table 5. Model Cohort Characteristics

	Value	Primary Source
Mean age	55.8	POISE study
PBC stage distribution		POISE study
Stage 1-3	90%	
Stage 4 (cirrhosis)	10%	
Sex: Female / male	91% / 9%	POISE study

Treatment Strategies

The interventions of interest were OCA plus UDCA compared to UDCA monotherapy. The 12-month Phase III trial of OCA included a 10 mg arm and a titration arm; for patients in the titration arm, the dose was initiated at 5 mg once daily and increased to 10 mg once daily if they had not yet achieved the primary composite endpoint and were tolerating treatment. As the titration arm included fewer discontinuations due to adverse events, we chose to use the titration arm to model the "OCA plus UDCA" intervention in our analysis, which is consistent with our conversations with PBC experts.

Key Model Choices and Assumptions

- Health states in the model include PBC, compensated cirrhosis (CC), decompensated cirrhosis (DC), hepatocellular carcinoma (HCC), liver transplant (LT), liver-related death, and death from other causes.
- The model primarily utilized data from one Phase III trial of OCA in patients with PBC. We derived estimates of the proportion of patients in each of the following categories at baseline and at 12 months: normal bilirubin, ALP ≤ 1.67 x ULN; normal bilirubin, ALP > 1.67xULN; abnormal bilirubin, ALP ≤ 1.67xULN; and abnormal bilirubin, ALP > 1.67xULN. These criteria have been clinically validated as predictors of disease progress.
- We also derived estimates of the proportion of patients experiencing pruritus.
- Survival was weighted by health state utilities to estimate quality-adjusted life years (QALYs).
- The model also included a disutility for pruritus; however, we assumed pruritus would resolve in all patients after the first year of treatment.
- We assumed that treatment effects persisted after 12 months, i.e., if a patient moves from the "normal bilirubin, ALP **>** 1.67xULN" group to the "normal bilirubin, ALP ≤ 1.67xULN" group, then the patient will continue to follow the disease progress for an individual in the "normal bilirubin, ALP ≤ 1.67xULN" group for the rest of his/her life.
- Patients who discontinued OCA, either because of pruritus or lack of adherence, entered the comparator arm of the model (i.e., the UDCA arm).
- All future quality-adjusted life years and health care costs were discounted at 3% per year.

Clinical Inputs

Levels of ALP and bilirubin will be used as reported in the clinical trial. Table 6 below summarizes the proportion of patients in different categories after 12 months of treatment. Levels of ALP and bilirubin are correlated with disease course in patients with PBC.

Table 6. Efficacy of OCA versus placebo (UDCA) after 12 months

Primary Endpoint	OCA + UDCA	UDCA
Normal Bilirubin & ALP ≤ 1.67xULN	45.7%	9.6%
Normal Bilirubin & ALP > 1.67xULN	50.0%	69.9%
Abnormal Bilirubin & ALP ≤ 1.67xULN	2.1%	2.5%
Abnormal Bilirubin & ALP > 1.67xULN	2.2%	18.0%

Source: POISE study (Intercept)

Adverse Events

The model includes pruritus of varying severity, classified as mild, moderate, or severe. Table 7 provides the percentage of patients who experienced mild, moderate and severe pruritus in the OCA and placebo (±UDCA) arms of the trial. The overall probability of pruritus was derived from the POISE trial, to which we applied the distribution of pruritus severity (i.e., whether pruritus was mild, moderate, or severe) for doses of 10 mg or less using data from the Phase II trial by Hirschfield et al.

Table 7. Adverse Event Inputs

	Value (%)	Reference
***Pruritus with UDCA*[29]**		
Mild	28%	Figure 4A (placebo)
Moderate	10%	Figure 4A (placebo)
Severe	0%	Figure 4A (placebo)
***Pruritus with OCA plus UDCA*[29]**		
Mild	29%	Figure 4B (≤10mg dose)
Moderate	18%	Figure 4B (≤10mg dose)
Severe	9%	Figure 4B (≤10mg dose)

Costs

Health state costs associated with advanced stages of disease were based on reported costs in hepatitis C patients.[46] The cost of care for early stage PBC was assumed to be similar to that of hepatitis C patients with moderate fibrosis. Table 8 summarizes the costs associated with each health state. All costs were converted to a 2015 baseline using the medical care component of the Consumer Price Index.

For patients who have pruritus, we assumed there will be additional costs associated with two primary care visits; these costs are based on the fees associated with HCPCS code 99213 (equivalent to a 15-minute established patient office visit) in the physician fee schedule.[47] We also applied the cost of one year of hydroxyzine treatment, based on the Red Book value for a 25 mg dose three times per day for one year.[48]

The annual cost of UDCA was estimated using an average UDCA dosage of 16 mg/kg/day, as well as an average BMI of 26 kg/m^2 and height of 164.3 cm, as reported in the Phase II data currently available to us.[29] Accordingly, the average daily dose for patients in the model was 1,123 mg. We assumed that patients in the trial were taking doses of either 1,000 mg (two 500 mg capsules) or 1,250 mg (two 500 mg capsules and one 250 mg capsule). Through this line of reasoning, we determined that the cost of UDCA treatment was $8.66/day or $3,163/year (assuming 365.25 days/year), using Red Book wholesale acquisition costs.

Table 8. Cost Inputs Associated with Health States and Management of Adverse Events

Parameter	Values
Early stage PBC	$737
Compensated cirrhosis	$5,752
Decompensated cirrhosis	$40,141
Hepatocellular carcinoma	$88,383
Liver transplant-1st year	$179,080
Liver transplant-subsequent year	$44,074
Cost of OCA	Assumption
Cost of UDCA	$3,163
Cost of Pruritus (doctor's office visit)	$103
Cost of Pruritus (ongoing hydroxyzine treatment)	$712

Utilities

We assigned health-related quality-of-life (QoL) utilities to each individual in our model, with 0 denoting death and 1 denoting perfect health. Health utilities were adjusted by age and sex to accurately reflect comorbidities occurring with aging as well as differences by sex. Health state utilities from publicly available literature (Table 9), with consistent health state utility values across treatments, were used in the model. Because PBC-specific utilities by different stages of disease were not available, we used utilities of health states for patients with hepatitis C virus infection. Specifically, we used health-state specific utility weights from a previously published study using the EuroQol-5D instrument,[49,50] and adjusted these weights to the U.S. population norm (Table 10).[51] We also applied a disutility for patients who experience pruritus; to determine the overall utility for a patient with pruritus, we took the product of each health state utility and the pruritus utility.

Table 9. Utilities for Health States and Adverse Events

Health State	Base Case
Health States[49]	
PBC (UDCA+OCA)	0.93
PBC (UDCA)	0.93
Compensated cirrhosis	0.90
Decompensated cirrhosis	0.80
Hepatocellular carcinoma	0.79
Transplant-first year	0.84
Transplant-subsequent year	0.93
Adverse events (multiplicative factor)[52]	
Pruritus – mild	0.93
Pruritus – moderate	0.87
Pruritus – severe	0.79

Table 10. Health-Related Quality of Life Utilities for the US Population

Age Group	Male	Female
20–29	0.928	0.913
30–39	0.918	0.893
40–49	0.887	0.863
50–59	0.861	0.837
60–69	0.84	0.811
70–79	0.802	0.771
80–89	0.782	0.724

Source: Hammer et al.[51]

Transition Probabilities

The transition probabilities between advanced disease states (i.e., compensated cirrhosis, decompensated cirrhosis, hepatocellular carcinoma, and liver transplant) are derived from the natural history of patients with hepatitis C virus infection (Table 8). We took this approach because there are limited data on the natural history of PBC in advanced stages of the disease. In addition, clinical evidence indicates that the risk of hepatocellular carcinoma in PBC patients with cirrhosis is similar to that in patients with hepatitis C, which was confirmed with communications with clinical experts. We also believe that this approach is biologically appropriate.[53,54] Therefore, we used transition probabilities from a published cost-effectiveness model of hepatitis C.[55] Transition probabilities from early stages of PBC (stages 1–3) to compensated cirrhosis, compensated cirrhosis to decompensated cirrhosis, compensated cirrhosis to hepatocellular carcinoma, and liver-related death in PBC stages 1–3 and compensated cirrhosis were calibrated such that the predicted 15-year transplant-free survival from the model matches the reported values based on patients' levels of

ALP and bilirubin at 12 months, as reported by the Global PBC study.[10] We also incorporated age- and sex-specific background mortality using U.S. life tables.[56]

Disease progression from PBC stages 1–3 to compensated cirrhosis and liver-related death, and from compensated cirrhosis to decompensated cirrhosis and liver-related death, was dependent on the response to OCA (i.e., bilirubin and ALP levels after 12 months of treatment).

Specifically, we converted the bilirubin and ALP levels into meaningful clinical endpoints using a meta-analysis that links liver function tests to the likelihood of liver transplantation or death.[10] This meta-analysis describes the 15-year transplant-free survival of patients who have not responded to UDCA treatment compared to those who achieved improvements in ALP or bilirubin. For each response category, we estimated the corresponding hazard ratio that would result in a 15-year transplant-free survival as reported by the Global PBC study and adjusted transition probabilities based for each response category (Table 11). The hazard ratio was used to adjust transition probabilities to account for slower disease progression because of ALP reduction or an improvement in bilirubin levels. Figures 6–9 show the 15-year transplant free survival from our model and Global PBC study.

Table 11. Estimates of Transition Probabilities

Parameters	Annual Transition Probability
Disease progression with Normal Bilirubin & ALP ≤ 1.67xULN (*calibrated*)	
PBC stages 1–3 to F4	0.0220
PBC stages 1–3 to liver-related death	0.0016
Compensated cirrhosis to decompensated cirrhosis	0.0063
Compensated cirrhosis to HCC	0.0023
Compensated cirrhosis to liver-related death	0.0032
Disease progression with Normal Bilirubin & ALP > 1.67xULN (*calibrated*)	
PBC stages 1–3 to F4	0.0673
PBC stages 1–3 to liver-related death	0.0050
Compensated cirrhosis to decompensated cirrhosis	0.0197
Compensated cirrhosis to HCC	0.0070
Compensated cirrhosis to liver-related death	0.0101
Disease progression with Abnormal Bilirubin & ALP ≤ 1.67xULN (*calibrated*)	
PBC stages 1–3 to F4	0.1420
PBC stages 1–3 to liver-related death	0.0277
Compensated cirrhosis to decompensated cirrhosis	0.0428
Compensated cirrhosis to HCC	0.0154
Compensated cirrhosis to liver-related death	0.0550
Disease progression with Abnormal Bilirubin & ALP > 1.67xULN (*calibrated*)	
PBC stages 1–3 to F4	0.1828
PBC stages 1–3 to liver-related death	0.0490
Compensated cirrhosis to decompensated cirrhosis	0.0561
Compensated cirrhosis to HCC	0.0202
Compensated cirrhosis to liver-related death	0.0961
Decompensated cirrhosis to HCC (*Planas et al.)*[57]	0.068
Decompensated cirrhosis to transplantation (*Davis et al., Thuluvath et al*.)[58,59]	0.023
Decompensated cirrhosis (first year) to liver-related death (*Planas et al.)*[57]	0.182
Decompensated cirrhosis (subsequent year) to liver-related death (*Planas et al.)*[57]	0.112
HCC to liver transplant (*Lang et al., Saab et al.)*[46,60]	0.040
HCC to liver-related death (*Fattovich et al*.)[61]	0.427
Liver transplant (first year) to liver-related death (*Wolfe et al.)*[62]	0.116
Post-liver transplant to liver-related death (*Wolfe et al.)* [62]	0.044

Figure 6. Transplant-free Survival in Patients with Normal Bilirubin and ALP ≤ 1.67xULN

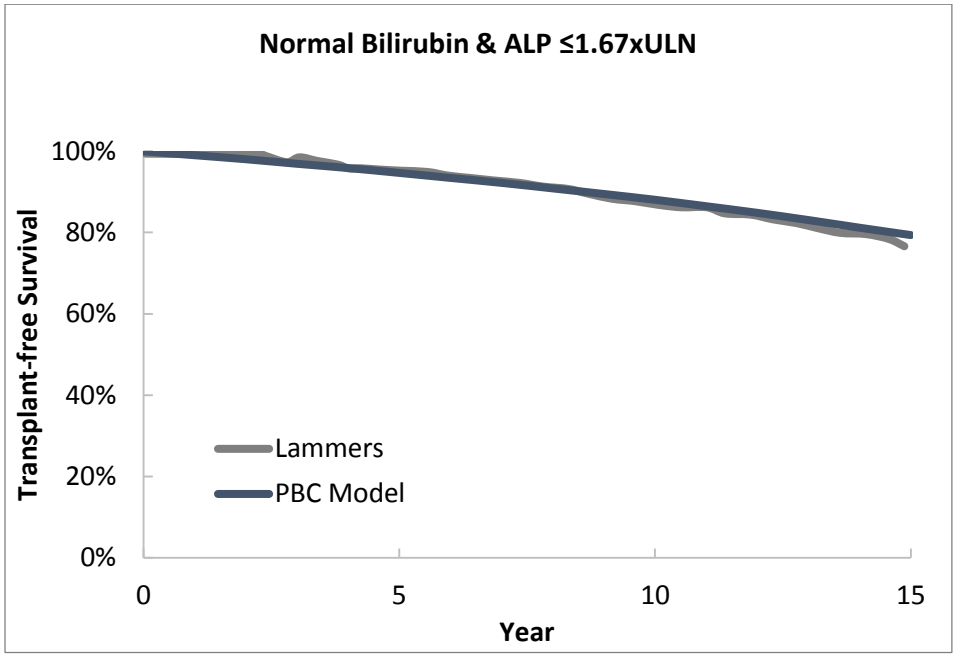


Figure 7. Transplant-free Survival in Patients with Normal Bilirubin and ALP > 1.67xULN

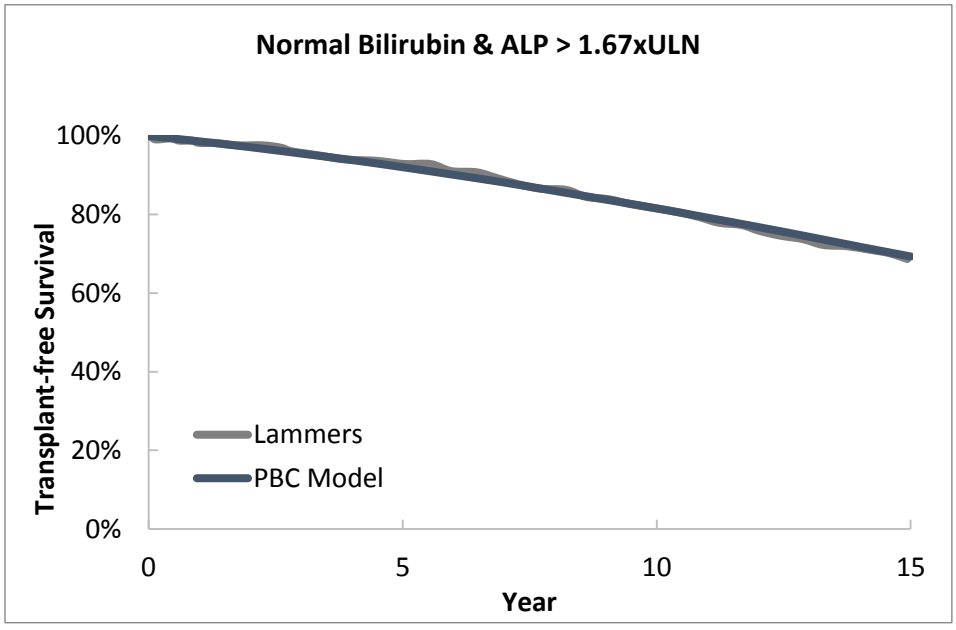


Figure 8. Transplant-free Survival in Patients with Abnormal Bilirubin and ALP ≤ 1.67xULN

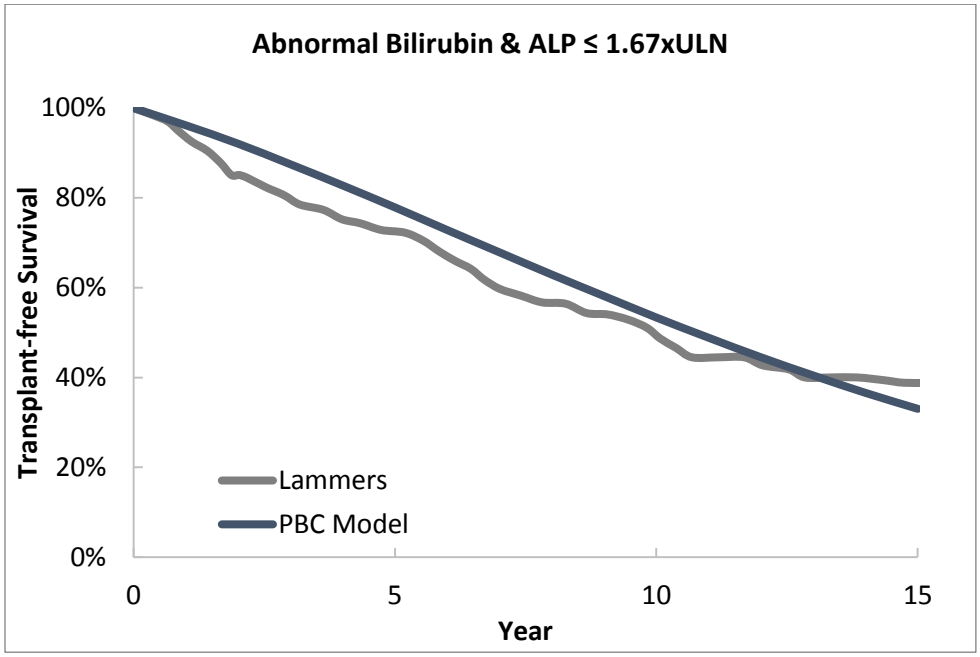
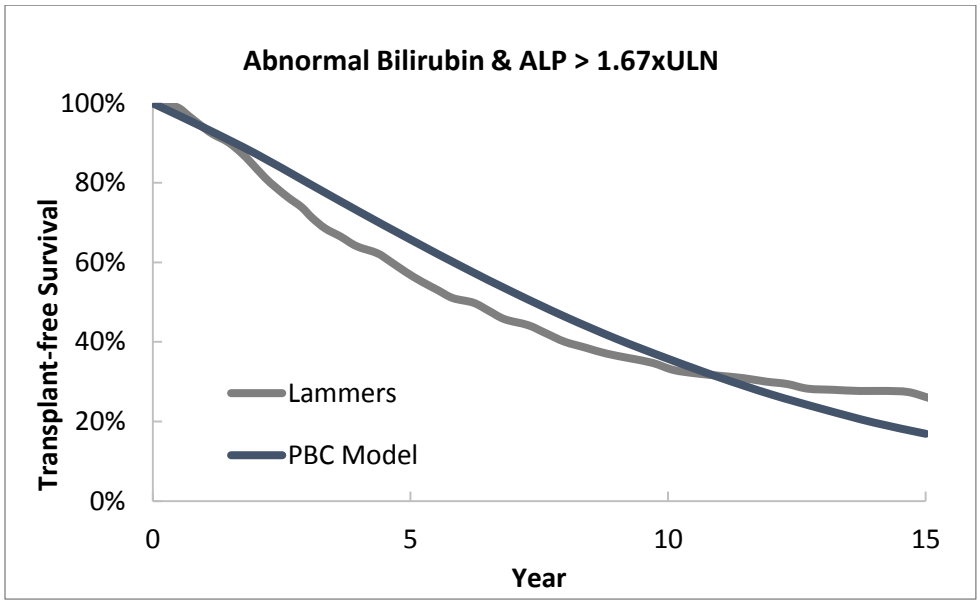


Figure 9. Transplant-free Survival in Patients with Abnormal Bilirubin and ALP > 1.67xULN



Sensitivity Analyses

We performed one-way sensitivity analyses to identify the key drivers of model outcomes. In addition, probabilistic sensitivity analysis was also performed by simultaneously varying all model

parameters over 100,000 simulations, then calculating 95% credible range estimates for each model outcome based on the results. We also performed threshold analyses to identify drug prices necessary to achieve a range of incremental cost-effectiveness ratios, from $50,000 to $150,000 per QALY.

Cost-Effectiveness Model: Results

Figures 10-13 show 15-year cumulative incidence of decompensated cirrhosis, hepatocellular carcinoma, liver transplants, and liver-related deaths in the simulated cohort of patients treated with OCA plus UDCA versus UDCA only. In patients who had an inadequate response to UDCA, treatment with OCA would decrease the 15-year cumulative incidence of decompensated cirrhosis from 5% to 2%, hepatocellular carcinoma from 4% to 2%, liver transplant from 0.6% to 0.2%, and liver-related deaths from 26.6% to 11.1%, respectively. In addition, treatment with OCA increased 15-year transplant-free survival from 60% to 72% (Figure 10). Compared with the UDCA strategy, treating 10,000 patients using OCA plus UDCA could prevent 300 cases of decompensated cirrhosis, 200 cases of hepatocellular carcinoma, 40 liver transplants and 1,550 liver-related deaths.

Figure 10. Cumulative Incidence of Decompensated Cirrhosis

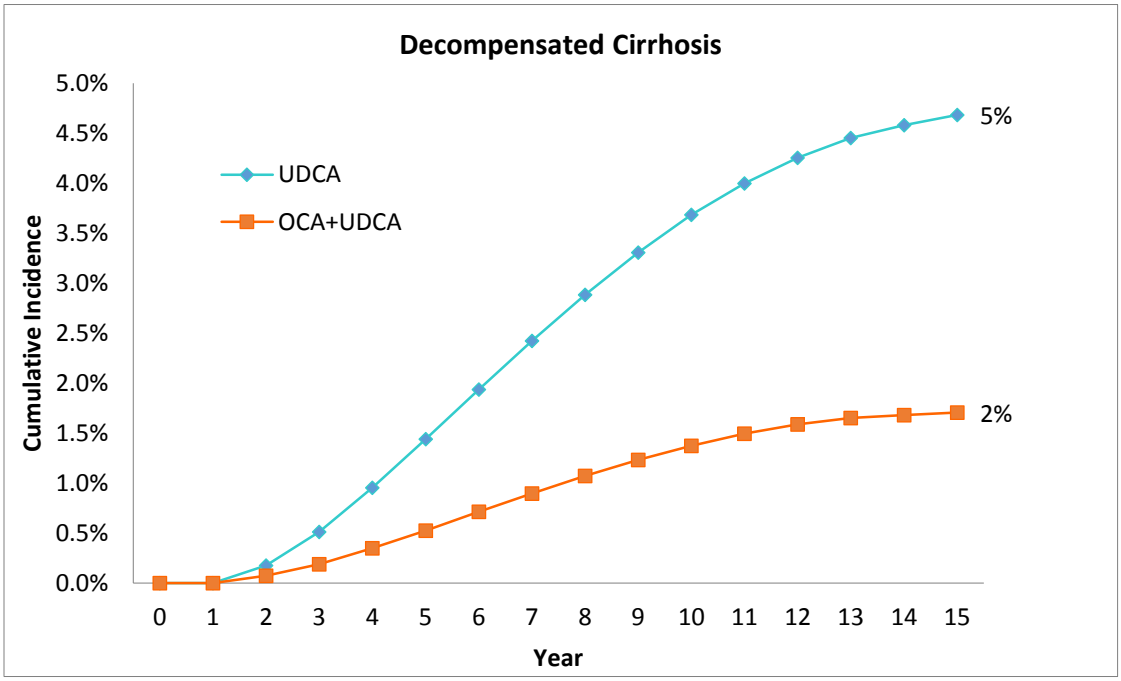


Figure 11. Cumulative Incidence of Hepatocellular Carcinoma

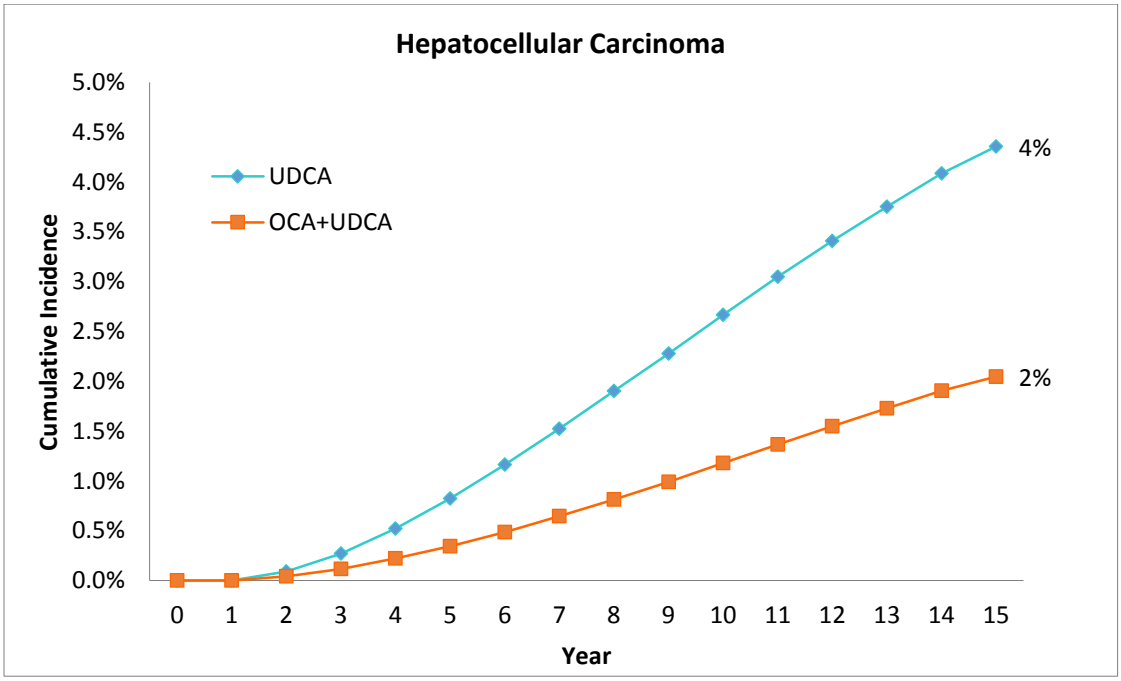


Figure 12. Cumulative Incidence of Liver Transplants in PBC Patients

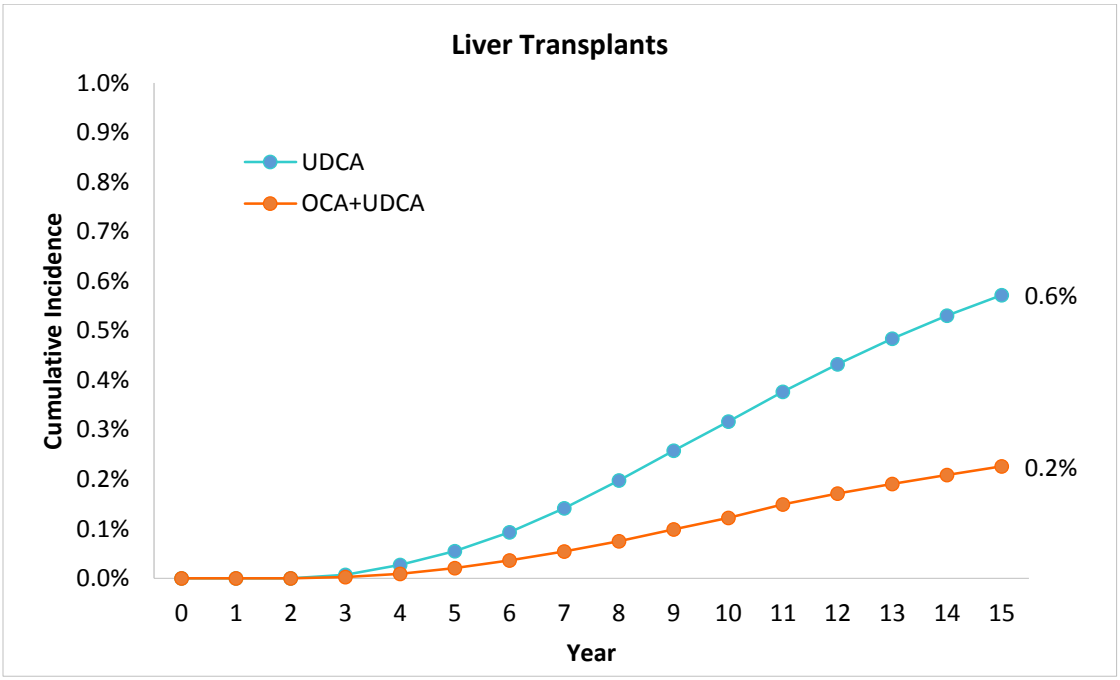


Figure 13. Cumulative Incidence of Liver-related Deaths in PBC Patients

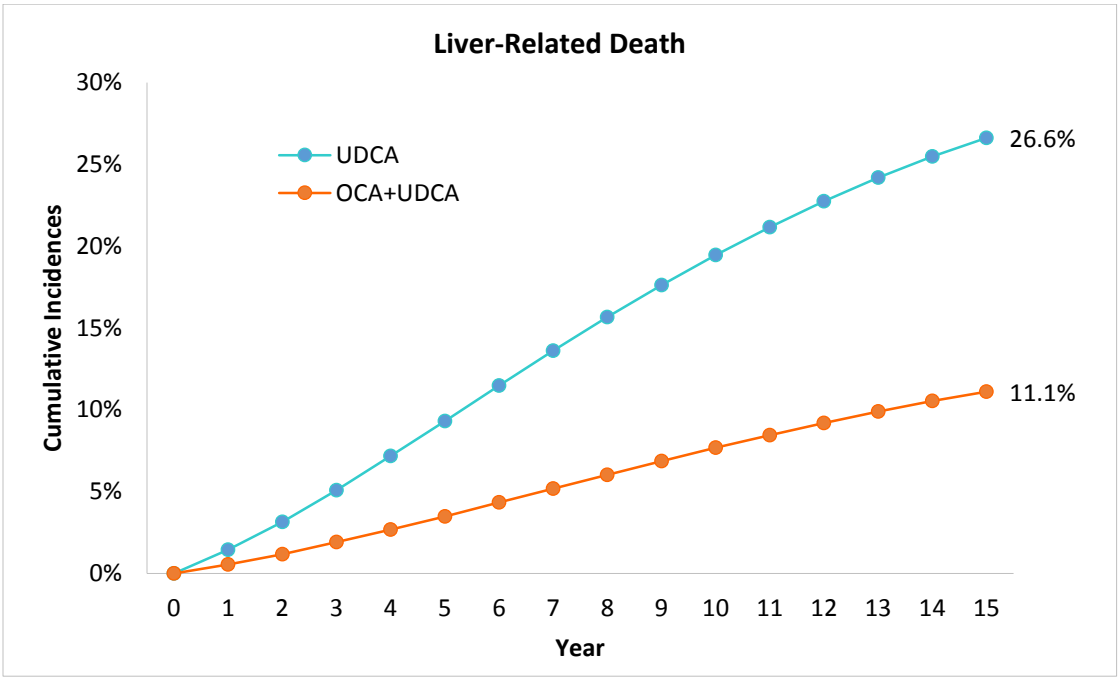
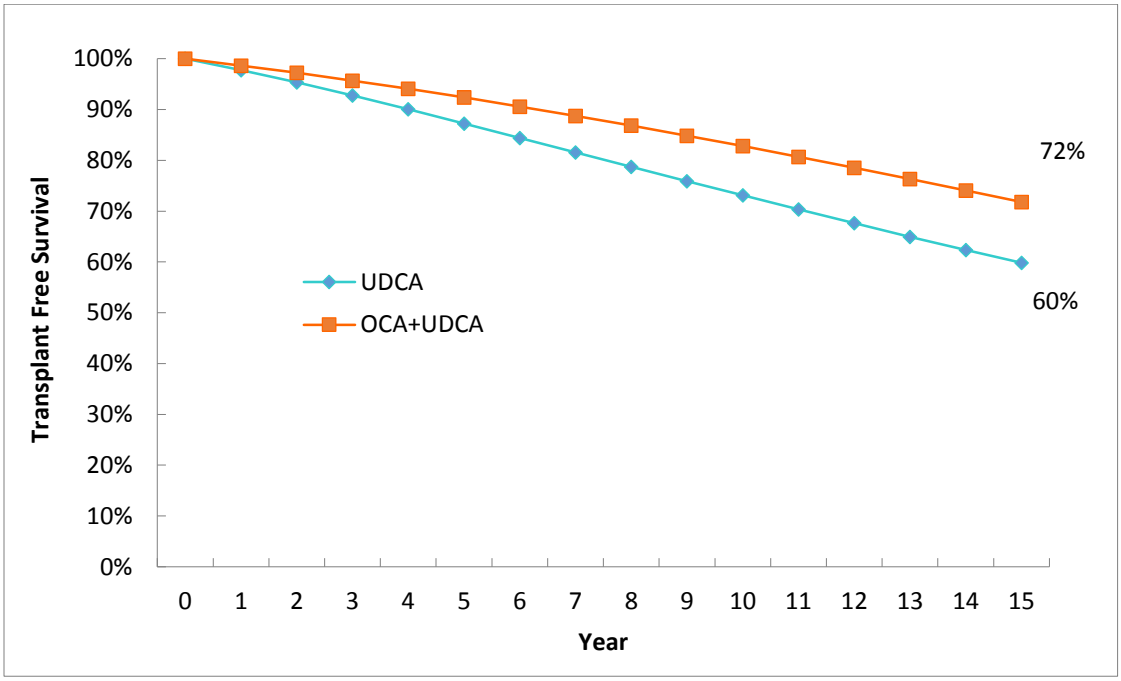


Figure 14. Transplant-free Survival in PBC Patients who had Inadequate Response to UDCA



The average life years per patient treated with UDCA versus OCA plus UDCA were 19.28 and 22.20, respectively (increment = 2.92 years). The corresponding average discounted QALYs gained were 10.42 and 11.73, respectively (increment = 1.31 years). The average lifetime discounted cost per patient treated with UDCA was $97,208. Assuming that the price of OCA is $65,000/year, average

lifetime cost of OCA plus UDCA was $587,700 (an increment of $490,500). The incremental cost-effectiveness of OCA plus UDCA was approximately $374,200 per QALY (Table 12). Using the willingness to pay threshold of $100,000 per QALY, OCA at a $65,000/year price is not a cost-effective option in PBC patients who have inadequate response to UDCA.

Table 12. Cost-effectiveness of OCA when the Annual Cost of OCA is $65,000 per Year

	UDCA*	OCA + UDCA
Undiscounted Life Years	19.28	22.20
Discounted QALYs	10.42	11.73
Discounted Total Cost ($)	97,208	587,707
ICER ($/QALY)		374,220

*Results correspond to inadequate response to UDCA, as observed in POISE study

If the annual price of OCA were assumed to be $15,000/year, the average lifetime cost of the OCA plus UDCA strategy was reduced to approximately $205,300 and the incremental cost-effectiveness to $82,600 per QALY (Table 13). At this reduced price, OCA would be cost-effective using a $100,000 per QALY threshold.

Table 13. Cost-effectiveness of OCA when the Annual Cost of OCA is $15,000 per Year

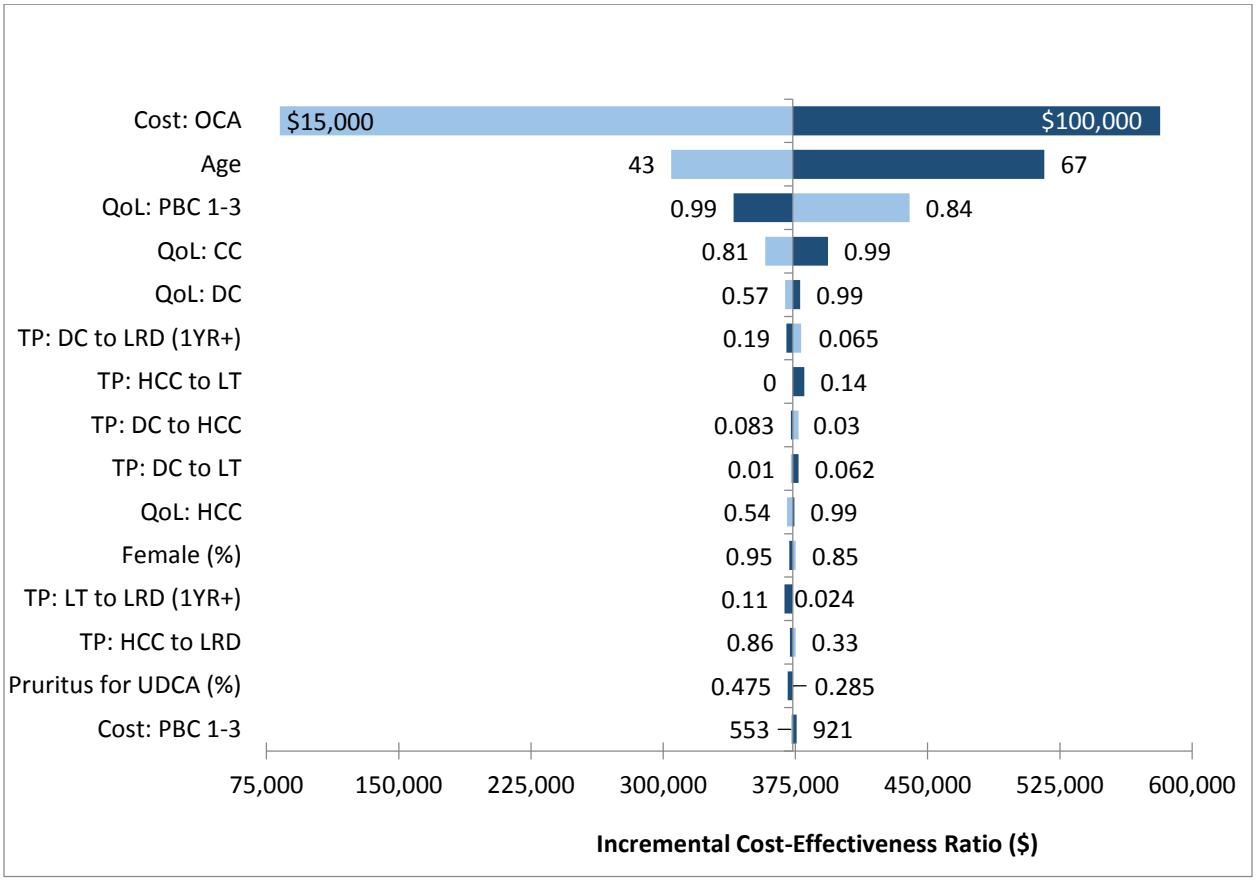
	UDCA*	OCA + UDCA
Undiscounted Life Years	19.28	22.20
Discounted QALYs	10.42	11.73
Discounted Total Cost	$97,028	$205,280
ICER ($/QALY)		$82,596

*Results correspond to inadequate response to UDCA, as observed in POISE study

Sensitivity Analyses

We conducted one-way sensitivity analyses to identify the parameters to which the model was most sensitive. We have plotted a tornado diagram showing the 15 most sensitive parameters (Figure 15). We found that the incremental cost-effectiveness ratios were most sensitive to the cost of OCA. For all other parameters, the ICERs remained above $100,000 / QALY when the annual cost of OCA was assumed to be $65,000.

Figure 15. Tornado Diagram Showing 15 Most Sensitive Model Parameters



6.4 Potential Budget Impact

We also used the cost-effectiveness model to estimate the potential total budgetary impact of OCA for PBC patients, based on assumed patterns of product uptake.

Potential Budget Impact Model: Methods

We used results from the same model employed for the cost-effectiveness analyses to estimate total potential budget impact. Potential budget impact was defined as the total incremental cost of the OCA therapy for the treated population, calculated as incremental health care costs (including drug costs) minus any offsets in these costs from averted disease progression. All costs were undiscounted and estimated over one- and five-year time horizons. The five-year timeframe was of primary interest, given the potential for cost offsets to accrue over time.

The potential budget impact analysis included the entire candidate population for treatment, which was considered to be adults with PBC who have either inadequate response to UDCA or are unable to tolerate UDCA. To estimate the size of the potential candidate population for OCA, we first

applied the estimated prevalence of PBC in the US. We located one estimate of PBC prevalence in the US. Kim et al.[63] used the Rochester Epidemiology Project diagnostic indexes to estimate an age- and sex-adjusted prevalence in Olmsted County, Minnesota, of 40.2 per 100,000. Applying this prevalence to the projected 2016 US population would imply approximately 130,000 individuals with PBC. The Kim at al. study also reported that 43.5% of PBC patients had received UDCA treatment. We assumed that 40% of the treated population with PBC would have inadequate response to UDCA therapy,[64] and that another 3% would be unable to tolerate UDCA.[4] Applying these percentages resulted in a candidate population size of approximately 24,350 individuals in the US.

ICER's methods for estimating potential budget impact and calculating value-based benchmark prices are described in detail elsewhere. Briefly, our calculations assume that the utilization of new drugs occurs without any payer, provider group, or pharmacy benefit management controls in place, to provide an estimate of "unmanaged" drug uptake by five years after launch.

In general, we examine six characteristics of the drug or device and the marketplace to estimate "unmanaged" uptake. These characteristics are listed below:

- Magnitude of improvement in clinical safety and/or effectiveness
- Patient-level burden of illness
- Patient preference (ease of administration)
- Proportion of eligible patients currently being treated
- Primary care versus specialty clinician prescribing/use
- Presence or emergence of competing treatments of equal or superior effectiveness

Based on our assessment of these criteria, we assign a new drug or device to one of four categories of unmanaged drug uptake patterns: 1) very high (75% uptake by year 5); 2) high (50% uptake by year 5); 3) intermediate (25% uptake by year 5); and 4) low (10% uptake by year 5). In this analysis, we assumed a 25% uptake pattern for OCA in PBC patients. We assumed that uptake would be high for this drug because of the lack of therapeutic alternatives for PBC patients with inadequate response or intolerance to UDCA.

Using this approach to estimate potential budget impact, we then compared our estimates to a budget impact threshold that represents a potential trigger for policy mechanisms to improve affordability, such as changes to pricing, payment, or patient eligibility. As described in ICER's methods presentation, this threshold is based on an underlying assumption that health care costs should not grow much faster than growth in the overall national economy. From this foundational assumption, our potential budget impact threshold is derived using an estimate of growth in US gross domestic product (GDP) +1%, the average number of new drug approvals by the FDA each

year, and the contribution of spending on retail and facility-based drugs to total health care spending. Calculations are performed as shown in Table 14.

For 2015-16, therefore, the five-year annualized potential budget impact threshold that should trigger policy actions to manage affordability is calculated to total approximately $904 million per year for new drugs.

Table 14. Calculation of Potential Budget Impact Threshold

Item	Parameter	Estimate	Source
1	Growth in US GDP, 2015-2016 (est.) +1%	3.75%	World Bank, 2015
2	Total health care spending ($)	$3.08 trillion	CMS NHE, 2014
3	Contribution of drug spending to total health care spending (%)	13.3%	CMS National Health Expenditures (NHE), Altarum Institute, 2014
4	Contribution of drug spending to total health care spending ($) (Row 2 x Row 3)	$410 billion	Calculation
5	Annual threshold for net health care cost growth for ALL new drugs (Row 1 x Row 4)	$15.4 billion	Calculation
6	Average annual number of new molecular entity approvals, 2013-2014	34	FDA, 2014
7	Annual threshold for average cost growth per individual new molecular entity (Row 5 ÷ Row 6)	$452 million	Calculation
8	Annual threshold for estimated potential budget impact for each individual new molecular entity (doubling of Row 7)	$904 million	Calculation

Potential Budget Impact Model: Results

Table 10 below presents the potential budget impact of one year and five years of OCA in the candidate population, assuming the uptake patterns previously described. (Undiscounted costs per patient for years 1 through 5 are provided in Appendix Table G1.) Results are presented for both one-year and five-year time horizons.

Results from the potential budget impact model showed that, with the uptake pattern assumptions mentioned above, an estimated 2,440 individuals would receive OCA in the first year. After one year of treatment, with net annual costs of approximately $65,100 per patient, one-year budget impact is estimated to be $158.6 million.

Over the entire five-year time horizon, we estimate that "unmanaged" uptake would lead to approximately 12,200 persons taking OCA. Across the full five-year time horizon, the weighted potential budgetary impact (i.e., adjusted for differing periods of drug utilization and associated cost-offsets) is approximately $122,500 per patient. Total potential budgetary impact over five

years is approximately $1.5 billion, with an average budget impact per year of approximately $298.4 million. This annualized potential budget impact is 33% of the budget impact threshold of $904 million for a new drug.

Table 15. Estimated Total Potential Budget Impact (BI) of OCA

		Analytic Horizon = 1 Year			Analytic Horizon = 5 Years		
	Eligible Population	Number Treated	Annual BI per Patient*	Total BI (millions)	Number Treated	Weighted BI per Patient*	Average BI per year (millions)
OCA	24,350	2,440	$65,100	$158.6	12,200	$122,500	$298.4

*Weighted budget impact calculated by subtracting cost offsets from drug costs for one-year horizon. For five-year horizon, drug costs and cost offsets apportioned assuming 20% of patients in uptake target initiate therapy each year. Those initiating in year 1 receive full drug costs and cost offsets, those initiating in year 2 receive 80% of drug costs and cost offsets, etc.

Figure 16 provides findings of multiple analyses that give perspective on the relationship between varying possible drug prices, cost-effectiveness ratios, uptake patterns, and potential budget impact. The vertical axis shows the annualized budget impact, and the horizontal axis represents the percentage of eligible patients treated over a five-year period. The colored lines demonstrate how quickly the annual budget impact increases with increasing percentages of patients treated at four different prices: those at which the cost/QALY = $50,000, $100,000, and $150,000; and the list price used in this analysis (i.e., $65,000 annually for OCA).

6.5 Draft Value-based Benchmark Prices

Value-based price benchmarks will be provided as part of the full Evidence Report.

6.6 Summary and Comment

We conducted a cost-effectiveness analysis by developing a microsimulation model that simulated the long-term outcomes of PBC patients with an inadequate response to UDCA receiving OCA (in addition to UDCA) compared to UDCA alone. We estimated that, in patients who had an inadequate response to UDCA, treatment with OCA would decrease the 15-year cumulative incidence of decompensated cirrhosis from 5% to 2%, hepatocellular carcinoma from 4% to 2%, liver transplant from 0.6% to 0.2%, and liver-related deaths from 26.6% to 11.1%. Assuming that the price of OCA is $65,000/year, the incremental cost-effectiveness of OCA plus UDCA was estimated to be approximately $374,200 per QALY.

We also used the cost-effectiveness model to estimate the potential total budgetary impact of OCA for PBC patients over five years. Assuming that “unmanaged” uptake would lead to 50% of eligible patients (or approximately 12,200 persons) taking OCA, total potential budgetary impact over five

years is approximately $1.5 billion, with an average budget impact per year of approximately $298.4 million. This annualized potential budget impact is 33% of the budget impact threshold of $904 million for a new drug.

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This is the first ICER review of obeticholic acid for PBC.

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APPENDICES

Appendix A. Evidence Review Methods and PRISMA

Table A1. PRISMA 2009 Checklist

	#	Checklist item
TITLE		
Title	1	Identify the report as a systematic review, meta-analysis, or both.
ABSTRACT		
Structured summary	2	Provide a structured summary including, as applicable: background; objectives; data sources; study eligibility criteria, participants, and interventions; study appraisal and synthesis methods; results; limitations; conclusions and implications of key findings; systematic review registration number.
INTRODUCTION		
Rationale	3	Describe the rationale for the review in the context of what is already known.
Objectives	4	Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS).
METHODS		
Protocol and registration	5	Indicate if a review protocol exists, if and where it can be accessed (e.g., Web address), and, if available, provide registration information including registration number.
Eligibility criteria	6	Specify study characteristics (e.g., PICOS, length of follow-up) and report characteristics (e.g., years considered, language, publication status) used as criteria for eligibility, giving rationale.
Information sources	7	Describe all information sources (e.g., databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched.
Search	8	Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated.
Study selection	9	State the process for selecting studies (i.e., screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis).
Data collection process	10	Describe method of data extraction from reports (e.g., piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators.
Data items	11	List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made.

Risk of bias in individual studies	12	Describe methods used for assessing risk of bias of individual studies (including specification of whether this was done at the study or outcome level), and how this information is to be used in any data synthesis.
Summary measures	13	State the principal summary measures (e.g., risk ratio, difference in means).
Synthesis of results	14	Describe the methods of handling data and combining results of studies, if done, including measures of consistency (e.g., I^2) for each meta-analysis.
Risk of bias across studies	15	Specify any assessment of risk of bias that may affect the cumulative evidence (e.g., publication bias, selective reporting within studies).
Additional analyses	16	Describe methods of additional analyses (e.g., sensitivity or subgroup analyses, meta-regression), if done, indicating which were pre-specified.
RESULTS		
Study selection	17	Give numbers of studies screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally with a flow diagram.
Study characteristics	18	For each study, present characteristics for which data were extracted (e.g., study size, PICOS, follow-up period) and provide the citations.
Risk of bias within studies	19	Present data on risk of bias of each study and, if available, any outcome level assessment (see item 12).
Results of individual studies	20	For all outcomes considered (benefits or harms), present, for each study: (a) simple summary data for each intervention group (b) effect estimates and confidence intervals, ideally with a forest plot.
Synthesis of results	21	Present results of each meta-analysis done, including confidence intervals and measures of consistency.
Risk of bias across studies	22	Present results of any assessment of risk of bias across studies (see Item 15).
Additional analysis	23	Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression [see Item 16]).
DISCUSSION		
Summary of evidence	24	Summarize the main findings including the strength of evidence for each main outcome; consider their relevance to key groups (e.g., healthcare providers, users, and policy makers).
Limitations	25	Discuss limitations at study and outcome level (e.g., risk of bias), and at review-level (e.g., incomplete retrieval of identified research, reporting bias).
Conclusions	26	Provide a general interpretation of the results in the context of other evidence, and implications for future research.
FUNDING		
Funding	27	Describe sources of funding for the systematic review and other support (e.g., supply of data); role of funders for the systematic review.

From: Moher D, Liberati A, Tetzlaff J, Altman DG. The PRISMA Group (2009). Preferred Reporting Items for Systematic Reviews and Meta-Analyses: The PRISMA Statement. PLoS Med 6(6): e1000097. doi:10.1371/journal.pmed1000097

Search Strategies

Table A2. Search Strategy of Medline 1996 to Present with Daily Update, EBM Reviews - Cochrane Database of Systematic Reviews, EBM Reviews - Cochrane Central Register of Controlled

1	exp Liver Cirrhosis, Biliary/	3,905
2	(primary biliary cirrhosis or primary biliary cholangitis or PBC).mp.	5,371
3	1 or 2	6,095
4	(obeticholic acid or OCA or INT-747).mp.	665
5	3 and 4	34
Date of Search: April 12, 2016		

Table A3: Search Strategy of Embase on April 12, 2016

#4	#3 AND [humans]/lim AND [english]/lim NOT [medline]/lim	69
#3	#1 AND #2	128
#2	'obeticholic acid' OR oca OR 'int 747'	2,774
#1	'primary biliary cirrhosis'/exp OR 'primary biliary cirrhosis' OR 'primary biliary cholangitis' OR pbc	26,047

Study Selection

We performed screening at both the abstract and full-text level. Two investigators screened abstracts identified through electronic searches according to the inclusion and exclusion criteria described earlier. All exclusions were validated by a third reviewer. We did not exclude any study at abstract-level screening due to insufficient information. For example, an abstract that did not report an outcome of interest would be accepted for further review in full text.

We retrieved the citations that were accepted during abstract-level screening for full text appraisal. Two investigators reviewed full papers and provided justification for exclusion of each excluded study; a third investigator resolved any discrepancies in selection as necessary.

Data Extraction and Quality Assessment

Summary tables of extracted data are available in Appendix E. We abstracted data from conference abstracts and posters affiliated with the clinical trials included in the evidence review. We used criteria published by the U.S. Preventive Services Task Force (USPSTF) to assess the quality of RCTs using the categories "good," "fair," or "poor."[34]

Guidance for quality ratings using these criteria is presented below.

Good: *Meets all criteria: Comparable groups are assembled initially and maintained throughout the study; reliable and valid measurement instruments are used and applied equally to the groups;*

interventions are spelled out clearly; all important outcomes are considered; and appropriate attention is paid to confounders in analysis. In addition, intention to treat analysis is used for RCTs.

Fair: *Studies were graded "fair" if any or all of the following problems occur, without the fatal flaws noted in the "poor" category below: Generally comparable groups are assembled initially but some question remains whether some (although not major) differences occurred with follow-up; measurement instruments are acceptable (although not the best) and generally applied equally; some but not all important outcomes are considered; and some but not all potential confounders are addressed. Intention to treat analysis is done for RCTs.*

Poor: *Studies were graded "poor" if any of the following fatal flaws exists: Groups assembled initially are not close to being comparable or maintained throughout the study; unreliable or invalid measurement instruments are used or not applied equally among groups (including not masking outcome assessment); and key confounders are given little or no attention. For RCTs, intention to treat analysis is lacking.*

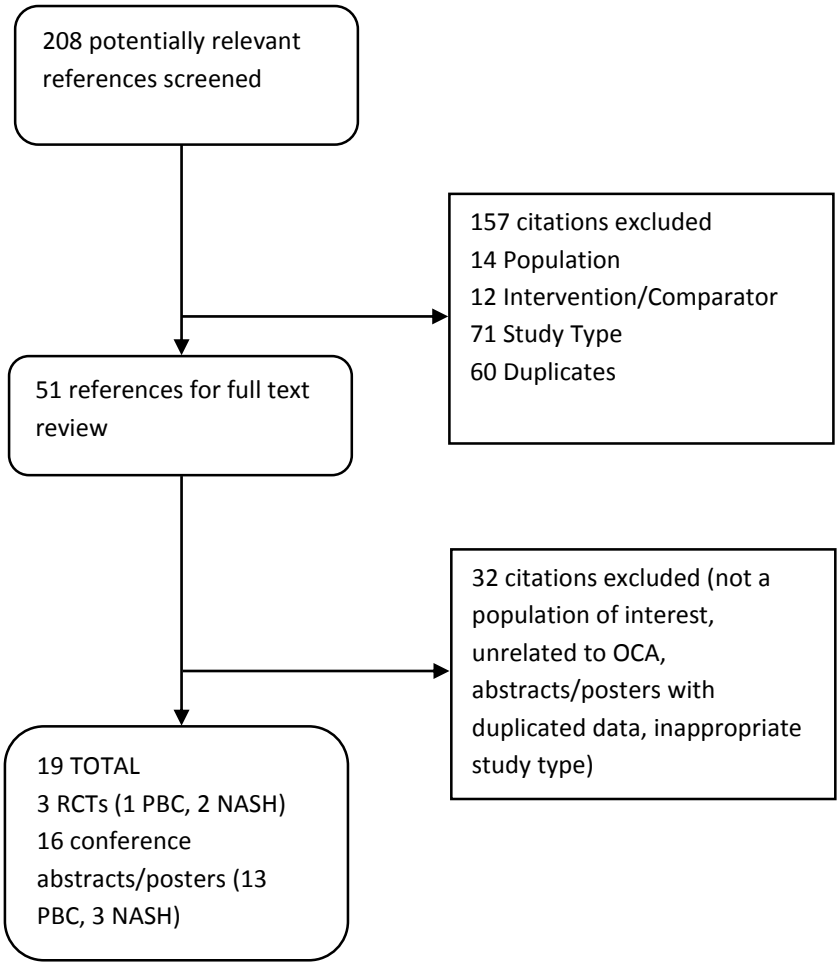
Assessment of Bias

As part of our quality assessment, we evaluated the evidence base for the presence of potential publication bias. Given the emerging nature of the evidence for newer treatments, we performed an assessment of publication bias using the clinicaltrials.gov database of trials. We scanned the site to identify studies completed more than two years ago that would have met our inclusion criteria and for which no findings have been published. No studies were identified using this criterion.

Data Synthesis and Statistical Analyses

Given the small numbers of relevant studies for OCA in PBC, we judged there to be no role for formal meta-analysis to generate pooled estimates of treatment effect.

Figure A1. PRISMA Flow Chart Showing Results of Literature Search for OCA in PBC and NASH.



Appendix B. Summary Evidence Table

<table>
<tr><th>Author & Year of Publication (Trial)</th><th>Study Design</th><th>Interventions (n) & Dosing Schedule</th><th>Inclusion and Exclusion Criteria</th><th>Patient Characteristics</th><th>Outcomes</th><th>Harms</th></tr>
<tr>
<td>Beuers, 2014

Abstract in Hepatology

(POISE)</td>
<td>See Luketic</td>
<td>See Luketic

Patients in the OCA, 5-10mg were titrated based on biochemical response and tolerability</td>
<td>See Luketic</td>
<td>See Luketic</td>
<td>See Luketic</td>
<td>
<table>
<tr><td>Pruritus Outcomes</td><td>1) n, %</td><td>2) n, %</td><td>3) n, %</td></tr>
<tr><td>Baseline Pruritus</td><td>47, 64</td><td>37, 53</td><td>44, 60</td></tr>
<tr><td>TE Pruritus</td><td>28, 38</td><td>39, 56</td><td>50, 68</td></tr>
<tr><td>0-6mo</td><td>11, 15</td><td>22, 31</td><td>38, 52</td></tr>
<tr><td>>6-12mo</td><td>8, 11</td><td>14, 20</td><td>9, 14</td></tr>
<tr><td>Pruritus discon’d</td><td>0, 0</td><td>1, 1</td><td>7, 10</td></tr>
<tr><td>Mean Baseline VAS, SD</td><td>25, 28</td><td>21, 26</td><td>20, 25</td></tr>
<tr><td>0-6mo</td><td>21, 23</td><td>23, 27</td><td>26, 29*</td></tr>
<tr><td>>6-12mo</td><td>25, 25</td><td>24, 27</td><td>23, 30</td></tr>
</table>
*p=0.0314; OCA 10mg vs. placebo (did not persist at 1 year)
</td>
</tr>
<tr>
<td>Bowlus, 2014

Abstract in Hepatology

(POISE)</td>
<td>See Luketic</td>
<td>See Luketic

Subgroup analysis for the titration arm (n=69)</td>
<td>See Luketic</td>
<td>See Luketic

7% UDCA intolerant</td>
<td>
<table>
<tr><td>Outcomes @ 12 mo</td><td>% responders</td><td>Change in ALP (U/L)</td></tr>
<tr><td>Remained @ 5mg (n=36)</td><td>53*</td><td>-80 (12)**</td></tr>
<tr><td>Titrated to 10mg (n=33)</td><td>39*</td><td>-126 (17)**</td></tr>
</table>
</td>
<td>
<table>
<tr><td>Outcomes @ 12 mo</td><td>Pruritus (%)</td></tr>
<tr><td>Remained @ 5mg (n=36)</td><td>58</td></tr>
<tr><td>Titrated to 10mg (n=33)</td><td>55</td></tr>
</table>
p=NR
</td>
</tr>
</table>

					*p<0.0001 for OCA vs. placebo from CMH test ** p<0.0001 for change from baseline from paired t-test Results reported at 6 months were also SS	1 subject discontinued due to pruritus in the 10mg arm between 0-6 months 4 subjects who were able to titrate did not due to pruritus
Hirschfield, 2015 **(747-202)** ***Publication in Gastro-enterology***	Phase II RCT 41 North American and European Centers	1) Placebo (38) 2) OCA, 10mg (38) 3) OCA, 25mg (48) 4) OCA, 50mg (41) All doses once daily for 3 months (in combination with UDCA)	*Inclusion:* -Adults aged 18-75 with PBC -Stable does of UDCA for 6 months before screening -Increased APL levels for 6 months -Mean ALP baseline value between 1.5-10x ULN *Exclusion:* -Elevated AST or ALT >5xULN -TB >2x -Serum creatinine >1.5mg/dl -Use of colchine, methotrexate, azathioprine, or systematic corticosteroids during 3	Sex (%): Male- 5 Female: 95 Age (years): 55 Total UDCA dose (mg/kg): 15.9 Weight (kg): 72.8 BMI, laboratory markers, and PBC inclusion criteria also reported No statistically significant differences between groups	*Mean ALP change:* <u>mITT</u>- 1) -3% (95% CI -7%, +2%) 2) -24% (95% CI -30%, -18%) 3) -25% (95% CI -30%, -20%) 4) -21% (95% CI -30%, -12%) p<0.001 for all OCA groups vs. placebo, and for ITT and completer populations *% achieving 10% ALP reduction*: OCA- 87% Placebo- 14% *% achieving 20% ALP reduction*: OCA- 69% Placebo-8% Both outcomes: p<0.001 ALP normalization: OCA- 7% Placebo- 0% p=NR For all algorithms, OCA had a higher response rate OCA results maintained in long-term extension: 210 U/L after 3 months 202 U/L after 12 months Daily mean dose of ≤10mg restarted (range 3-60mg)	Overall AEs: Placebo- 84% OCA- 96% Overall SAEs due to pruritus (n, %): 30/37, 81 Incidence of pruritus (%): 1) 50 2) 47 3) 85 4) 80 OCA 10mg vs. placebo- p=NS OCA 25mg vs. placebo- p<0.0003 OCA 50mg and 50mg- p<0.006 Incidence of severe pruritus (%): 1) NR 2) 16 3) 24 4) 37 p=NR Cholesterol reduction (%)*: 1) NR 2) -3% 3) -5% 4) -13%

<table>
<tr>
<td></td>
<td></td>
<td></td>
<td>months before screening
-Patients with concomitant liver diseases</td>
<td></td>
<td>Reductions in liver biochemistry:
GGT- 48-63%
ALT- 21-35%
AST- 9-17%
All SS vs. placebo

Bilirubin also significantly reduced in 25mg and 50mg groups (not in 10mg group)</td>
<td>*Due to HDL lowering

Other AEs:
7 patients, 4%

Discontinuation:
27 patients, 23 due to AEs
3 had elevated bilirubin
1 had elevated ALT/AST levels
15/27 (56% in the OCA 50mg group)

Long-term extension:
Pruritus- 87% (less severe)

Discontinuation:
19 patients, 24%

Due to pruritus: 10 patients, 13%</td>
</tr>
<tr>
<td>Jones, 2014

Abstract in Hepatology

Abstract and poster</td>
<td>Pooled analysis of all OCA trials (2 Phase II trials, and POISE)</td>
<td>1) Placebo + UDCA (10)
2) 10mg OCA ± UDCA (14)
3) Total OCA ± UDCA (22)</td>
<td>Patients with abnormal bilirubin pooled across 3 trials at 12 weeks</td>
<td>
<table>
<tr><th></th><th>Age (years)</th><th>Female (%)</th><th>White (%)</th></tr>
<tr><td>1)</td><td>50.2</td><td>100</td><td>90</td></tr>
<tr><td>2)</td><td>54.8</td><td>79</td><td>93</td></tr>
<tr><td>3)</td><td>53.6</td><td>77</td><td>95</td></tr>
</table>
Weighted Means
Age (years): 52.8
Female (%): 86.9
White (%): 92.2
Baseline ALP (U/L): 421.3
Baseline GGT (U/L): 551.0
Baseline ALT (U/L): 94.9
Baseline AST (U/L): 83.9
Baseline bilirubin (µmol/L): 28.8
1) 29.0
2) 28.9
</td>
<td>
<table>
<tr><th></th><th>ΔALP</th><th>ΔBilirubin</th><th>ΔAST</th><th>ΔALT</th><th>ΔGGT</th></tr>
<tr><td>1) 3 mths</td><td>-31</td><td>1.3</td><td>-1</td><td>-4</td><td>-90</td></tr>
<tr><td>1) 12 mths</td><td>-20</td><td>-0.1</td><td>10</td><td>-5</td><td>-110</td></tr>
<tr><td>2) 3 mths</td><td>-212**</td><td>-3.4</td><td>-25</td><td>-38</td><td>-425**</td></tr>
<tr><td>2) 12 mths</td><td>-140*</td><td>-13**</td><td>-33*</td><td>-4</td><td>-375*</td></tr>
<tr><td>3) 3 mths</td><td>-189**</td><td>-3.3</td><td>-10</td><td>-32</td><td>-400**</td></tr>
<tr><td>4) 12 mths</td><td>-100*</td><td>-9**</td><td>-15</td><td>-30</td><td>-300*</td></tr>
</table>
All absolute values
*p<0.05, **p<0.01 for comparing active treatment to placebo using ANCOVA model with baseline value as covariate and fixed effects for treatment

Patients with decreased bilirubin @ 12 months
<table>
<tr><td>Placebo</td><td>23/70</td></tr>
<tr><td>Titration OCA</td><td>34/64</td></tr>
<tr><td>10mg OCA</td><td>37/62</td></tr>
</table>
</td>
<td>All TEAEs (n, % [events]):
1) 9, 90
2) 13, 93
3) 21, 95

Pruritus (n, % [events]):
1) 3, 30
2) 12, 86
3) 16, 73

Fatigue (n, % [events]):
1) 2, 20
2) 1, 7
3) 3, 14

All serious TEAEs (n, % [events]):
1) 1, 10</td>
</tr>
</table>

<table>
<tr><td></td><td></td><td></td><td></td><td>3) 27.9</td><td></td><td>2) 1, 7
3) 3, 14

p=NR

Other AEs also reported, including more granular data for TEAEs</td></tr>
<tr><td>Kowdley
DB: 2011
LTSE: 2015

Abstracts in Hepatology

(747-201)</td><td>Phase II
RCT
Multicenter
Double-blinded (DB)

DB: 12 weeks f/u

LTSE: 4.5 years f/u</td><td>DB
1) Placebo (23)

2) OCA, 10mg (20)

3) OCA, 50mg (16)

LTSE: 28 enrolled and 19 completed f/u (8 added UDCA)</td><td>DB
-Patients who had not been taking UDCA for at least 6 months
-Mean ALP baseline value between 1.5-10x ULN

LTSE
43% taking ≤10mg OCA</td><td>DB
Age (years): 55
Female: 84%
Caucasian: 95%
AP: 433 U/L
GGT: 527 U/L
ALT: 81 U/L
AST: 68 U/L

LTSE
Age (years): 60
Female: 85%
All patients
ALP: 435 U/L
GGT: 455 U/L
ALT: 68.21U/L
AST: 60 U/L
Bilirubin: 13 µmol/L

Monotherapy:
ALP: 435 U/L
GGT: 455 U/L
ALT: 68.21U/L
AST: 60 U/L
Bilirubin: 13 µmol/L</td><td>DB
<table><tr><td>Endpoint</td><td>1)</td><td>2)</td><td>3)</td></tr><tr><td>Δ% ALP</td><td>+0.4</td><td>-44.5*</td><td>-37.6*</td></tr><tr><td>Δ U/L ALP</td><td>+11.7</td><td>-233.5*</td><td>-161.3*</td></tr><tr><td>Δ% GGT</td><td>-3</td><td>-73*</td><td>-65*</td></tr><tr><td>Δ% ALT</td><td>-4</td><td>-37**</td><td>-35**</td></tr></table>Compared to baseline:
*p<0.0001; **p<0.01

LTSE (all OCA patients); n=19
<table><tr><td>Endpoint</td><td>Mean change</td><td>P value</td></tr><tr><td>Δ U/L ALP</td><td>-244</td><td>0.0034</td></tr><tr><td>Δ U/L GGT</td><td>-317</td><td>0.0019</td></tr><tr><td>Δ U/L ALT</td><td>-37</td><td>0.0010</td></tr><tr><td>Δ U/L AST</td><td>-22</td><td>0.0043</td></tr><tr><td>Δ µmol/L Bilirubin</td><td>-2</td><td>0.1314</td></tr></table>
LTSE (OCA monotherapy); n=11
<table><tr><td>Endpoint</td><td>Mean change</td><td>P value</td></tr><tr><td>Δ U/L ALP</td><td>-182</td><td>0.0105</td></tr><tr><td>Δ U/L GGT</td><td>-235</td><td>0.0188</td></tr><tr><td>Δ U/L ALT</td><td>-32</td><td>0.0049</td></tr><tr><td>Δ U/L AST</td><td>-17</td><td>0.0205</td></tr><tr><td>Δ µmol/L Bilirubin</td><td>-1</td><td>0.7990</td></tr></table></td><td>DB
Pruritus (%):
1) 30
2) 70
3) 94

Discontinued due to pruritus (%):
1) 0
2) 15
3) 38

LTSE
AEs: 8 patients (3 pruritus-related); 20 events

7 patients discontinued</td></tr>
<tr><td>Kowdley, 2015</td><td>Pooled analysis of all OCA trials (2</td><td>Reported elsewhere</td><td>Reported elsewhere</td><td>Reported elsewhere</td><td>ALP Change from BL (end of DB study):
<u>201 Study</u>-
Placebo (n=23): -19
OCA, 10mg (n=20): -251</td><td>Reported elsewhere</td></tr>
</table>

Abstract in Gastro-enterology	Phase II trials, and POISE)				202 Study- Placebo (n=38): 12 OCA, 10mg (n=38): -58 POISE (301) Study- Placebo (n=73): -0.06 OCA, 5-10mg (n=70): -98 OCA, 10mg (n=23): -110 Pooled (all 3 trials): Placebo (n=134): -26 OCA (all groups, n=306): -128 p<0.001 for OCA vs. placebo *% of patients achieving the POISE Composite Endpoint: normal bilirubin and ALP reduction <1.67 ULN and ≥15% reduction* 201 Study- Placebo (n=23): 4 OCA, 10mg (n=20): 40 p=0.0026 for OCA vs. placebo 202 Study- Placebo (n=38): 8 OCA, 10mg (n=38): 42 p=0.0002 for OCA vs. placebo Pooled (all 3 trials, including POISE)- Placebo (n=134): 8 OCA (all groups, n=306): 45 p<0.0001 for OCA vs. placebo	
Luketic, 2014 ***Abstract in Hepatology***	Phase III RCT Multicenter	1) Placebo (73) 2) OCA, 5-10mg (70)	Patients on a stable dose of UDCA with ALP ≥1.67xULN or	Age (years): 55.8 Female (%): 91 Caucasian (%): 94 Median UDCA dose: 15.4mg	<table><tr><td rowspan="2">Tx</td><td>POISE</td><td colspan="2">Paris I</td><td colspan="2">Paris II</td></tr><tr><td>1 yr</td><td>Baseline</td><td>1 yr</td><td>Baseline</td><td>1 yr</td></tr><tr><td>1)</td><td>10</td><td>53</td><td>48</td><td>0</td><td>4</td></tr><tr><td>2)</td><td>46*</td><td>49</td><td>79***</td><td>0</td><td>27**</td></tr><tr><td>3)</td><td>47*</td><td>52</td><td>70***</td><td>0</td><td>26**</td></tr></table>	AE incidence by group (%): 1) 90 2) 89 3) 86 p=NR

<table>
<tr>
<td>(POISE)</td>
<td>Double-blinded (DB)</td>
<td>3) OCA, 10mg (73)

1 year f/u

91% completed</td>
<td>bilirubin <2xULN</td>
<td></td>
<td>*p<0.0001, **p<0.0002, ***p<0.02
POISE Endpoint = normal bilirubin and ALP reduction <1.67 ULN and ≥15% reduction
Paris I Endpoint = ALP ≤3x ULN, AST≤3x ULN, and normal bilirubin
Paris II Endpoint = ALP ≤1.5x ULN, AST≤3xULN

No SS differences for Rotterdam criteria across all severity of illness (likely due to high % of patients with normal bilirubin)</td>
<td>Although most AEs were related to pruritus, <6% discontinued due to pruritus

Overall SAEs in 22 (10%) of patients

See Beuers for more detailed info on harms associated with pruritus</td>
</tr>
<tr>
<td>Mayne, 2014

Abstract in Hepatology

Abstract and poster</td>
<td>Pooled analysis of all OCA trials (2 Phase II trials, and POISE)</td>
<td>1) 1-2x ULN (39)
2) >2-3x ULN (44)
3) >3-4x ULN (17)
4) >4x ULN (14)</td>
<td>Patients receiving the 10mg dose across 3 trials at 12 weeks stratified by ALP</td>
<td>
<table>
<tr><th></th><th>Age (years)</th><th>Female (%)</th><th>White (%)</th></tr>
<tr><td>1)</td><td>57.5</td><td>77</td><td>95</td></tr>
<tr><td>2)</td><td>55.0</td><td>95</td><td>95</td></tr>
<tr><td>3)</td><td>54.1</td><td>82</td><td>94</td></tr>
<tr><td>4)</td><td>53.1</td><td>100</td><td>100</td></tr>
</table>
Weighted Means
Age (years): 55.5
Female (%): 87.5
White (%): 95.5
Baseline ALP (U/L): 314.7
</td>
<td>
<table>
<tr><th></th><th>ΔALP (%)</th><th>ΔBilirubin (%):</th><th>ΔAST (%):</th><th>ΔALT (%):</th><th>ΔGGT (%):</th></tr>
<tr><td>1)</td><td>-23*</td><td>-4</td><td>-18*</td><td>-30*</td><td>-60*</td></tr>
<tr><td>2)</td><td>-29*</td><td>-5</td><td>-19*</td><td>-32*</td><td>-56*</td></tr>
<tr><td>3)</td><td>-44*</td><td>-6</td><td>-25*</td><td>-46*</td><td>-66*</td></tr>
<tr><td>4)</td><td>-45*</td><td>-17**</td><td>-32*</td><td>-46*</td><td>-62*</td></tr>
</table>
*p<0.0001 from baseline; **p<0.05 from baseline

For each incremental increase 1x ULN increase in baselines ALP, there was an incremental 3.5% reduction in ALP in patients treated with 10mg (p=0.0046).
</td>
<td>Reported elsewhere</td>
</tr>
<tr>
<td>Mayo

Poster presented as the EASL: International Liver Congress, April 13-17, 2016

(POISE)</td>
<td>See Luketic

Analysis to study the effect of an OCA titration group on pruritus</td>
<td>See Luketic</td>
<td>See Luketic</td>
<td>See Luketic</td>
<td>Reported elsewhere</td>
<td>Patients reporting at least 1 TEAE (n, %):
1) 28, 38
2) 39, 56
3) 51, 70

Median time to first onset of pruritus (days):
1) 50.5
2) 24.0
3) 9.0
Results also reported for those experiencing severe pruritus

Discontinuations due to pruritus:
1) 0</td>
</tr>
</table>

<table>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>2) 1, 1
3) 7, 10

Pruritus events by maximum severity (n, %):
<u>Mild</u>
1) 16, 22
2) 11, 16
3) 15, 21

<u>Moderate</u>
1) 7, 10
2) 15, 21
3) 19, 26

<u>Severe</u>
1) 5, 7
2) 13, 19
3) 17, 23

Also reports % of patients receiving concomitant medication</td>
</tr>
<tr>
<td>Nevens, 2014

Abstract in Hepatology

(POISE)</td>
<td>See Luketic</td>
<td>See Luketic</td>
<td>See Luketic</td>
<td>See Luketic</td>
<td>
<table>
<tr><th>% Δ from baseline</th><th>ALP U/L</th><th>Bili µmoL</th><th>GGT U/L</th><th>ALT U/L</th></tr>
<tr><td>1)</td><td>-4.8</td><td>19.5</td><td>0.8</td><td>-4.7</td></tr>
<tr><td>2)</td><td>-33.0**</td><td>1.2*</td><td>-50.3**</td><td>-35.5**</td></tr>
<tr><td>3)</td><td>-39.1**</td><td>-0.2*</td><td>-63.7**</td><td>-41.7**</td></tr>
</table>
OCA vs. placebo: *p<0.005, **p<0.0001

Absolute values at baseline and 12 mo also reported
</td>
<td>HDL mean reduction (%):
1) NR
2) 16
3) 26
p=NR

Also see Luketic and Beuers for additional harms outcomes</td>
</tr>
<tr>
<td>Pares, 2015

Abstract in J Hepatology</td>
<td>See Luketic

Analysis to study the effect of</td>
<td>See Luketic

122 had DEXA scans</td>
<td>See Luketic</td>
<td>See Luketic</td>
<td>
<table>
<tr><th>BMD</th><th>Placebo Δ (SD)</th><th>OCA, 5-10mg Δ (SD)</th><th>OCA, 10mg Δ (SD)</th></tr>
<tr><td>Lumbar</td><td>-0.01</td><td>-0.01</td><td>-0.01</td></tr>
</table>
</td>
<td>Reported elsewhere</td>
</tr>
</table>

<table>
<tr>
<td>(POISE)</td>
<td>OCA vs. placebo on bone density</td>
<td>at baseline and at 12 mo</td>
<td></td>
<td></td>
<td>
<table>
<tr><td>L2-L4 (g/cm²)</td><td>(0.01)</td><td>(0.01)</td><td>(0.01)</td></tr>
<tr><td>Lumbar T-score (g/cm²)</td><td>-0.26 (0.14)</td><td>-0.01 (0.14)</td><td>-0.09 (0.14)</td></tr>
<tr><td>Femoral Neck</td><td>0.80 (0.12)</td><td>-0.01 (0.01)</td><td>-0.04 (0.01)</td></tr>
<tr><td>Femoral T-Score</td><td>-0.33* (0.11)</td><td>-0.06ǂ (0.11)</td><td>-0.07ǂ* *(0.11)</td></tr>
</table>
*p<0.05, OCA vs. placebo
ǂp<0.03 end of DB vs. DL
Baseline and study end scores also reported
</td>
<td></td>
</tr>
<tr>
<td>Pencek, 2014

Abstract in Hepatology</td>
<td>Pooled analysis of all OCA trials (2 Phase II trials, and POISE)</td>
<td>1) Placebo (134)
2) OCA ≤10mg (201)</td>
<td>Reported elsewhere</td>
<td>Reported elsewhere</td>
<td>
<table>
<tr><td>Age</td><td><65</td><td>≥65</td><td><50</td><td>≥50</td></tr>
<tr><td>BL ALP (U/L)</td><td>334</td><td>315</td><td>338</td><td>318</td></tr>
<tr><td>End of DB ΔALP (U/L)</td><td>-133*</td><td>-109*</td><td>-120*</td><td>-120*</td></tr>
<tr><td>Responders n, %</td><td>75, 47*</td><td>17, 41**</td><td>50, 42*</td><td>42, 51*</td></tr>
</table>
Outcomes for age (<65|≥65) and age at diagnosis (<50|≥50)
*p<0.0001, **p=0.0004 for OCA vs. placebo using ANCOVA model

<table>
<tr><td>Sex</td><td>Male</td><td>Female</td></tr>
<tr><td>BL ALP</td><td>294</td><td>334</td></tr>
<tr><td>End of DB ΔALP</td><td>-111**</td><td>-136*</td></tr>
<tr><td>Responders n, %</td><td>9, 43ǂ</td><td>83, 46*</td></tr>
</table>
Outcomes for sex
*p<0.0001, **p=0.0009; ǂp= 0.0131 for OCA vs. placebo using ANCOVA model
</td>
<td>Incidence of pruritus (%):
<u>Age</u>
<65: 63
≥65: 51

<u>Age at diagnosis</u>
<50: 62
≥50: 57

<u>Sex</u>
Male: 57
Female: 61</td>
</tr>
<tr>
<td>Peters, 2014

Abstract in Hepatology

(POISE)</td>
<td>See Luketic</td>
<td>See Luketic

Long-term safety extension trial</td>
<td>See Luketic</td>
<td>See Luketic</td>
<td>Reported elsewhere</td>
<td>Overall AE incidence rate (DB, %):
2) 56
3) 68

Overall AE incidence rate (LTSE, %):
2) 15</td>
</tr>
</table>

		outcomes up to 24 months (n=193)				3) 21 Discontinuation due to pruritus (DB, %): 1) 0 2) 1 3) 10 Discontinuation due to pruritus (LTSE, %): 3% overall LDL remained comparable to baseline; HDL lowering remained stable and unchanged Hepatic disorders (DB trial, n): 0 Hepatic disorders (LTSE trial, n): 2 Overall SAEs incidence (%): 1) NR 2) 7 3) 3 1 death occurred due to cardiac failure

Appendix C. Comparative Value Supplemental Information

Table C1. Undiscounted Budget Impact Cost per Patient from 1 to 5 Years: Payer Perspective

	OCA + UDCA		UDCA	
	Treatment Costs	Non-Treatment Costs	Treatment Costs	Non-Treatment Costs
1 year	$68,574	$1,241	$3,441	$1,240
2 years	$101,064	$2,719	$6,525	$2,934
3 years	$133,204	$4,431	$9,518	$5,100
4 years	$164,971	$6,364	$12,415	$7,704
5 years	$196,361	$8,488	$15,214	$10,672

Appendix D. Clinical Guidelines

The American Association for the Study of Liver Diseases (2009)

http://www.aasld.org/sites/default/files/guideline_documents/PrimaryBillaryCirrhosis2009.pdf

The AASLD recommends a daily 13-15mg/kg dose of UDCA for treatment of PBC. UDCA treatment should be continued indefinitely, with liver tests every three to six months. In addition, the AASLD notes that additional medications may be needed to aid in management of symptoms of PBC, including use of bile acid sequestrants for treatment of pruritus. For pruritis that does not respond to treatment with bile acid sequestrants, patients can try rifampicin, oral opiate antagonists, or Sertaline.

European Association for the Study of the Liver (2009)

http://www.easl.eu/medias/cpg/issue2/Report.pdf

Patients with PBC should be treated on a long-term basis with UDCA dosed at 13-15mg/kg per day. Biochemical response should be assessed after one year. If biochemical response is not optimal, there is no consensus on the next treatment options. One option may be adding budesonide to UDCA in patients without cirrhosis. Liver transplant should be considered for patients with advanced disease indicated by bilirubin over 6mg/dL or decompensated cirrhosis with an unacceptable quality of life or prognosis of less than one year of life without transplant.

Appendix E. Previous Systematic Reviews and Technology Assessments

Because the approval for obeticholic acid is pending at the time of this report, we were not able to identify any previous HTAs or systematic reviews on OCA for PBC. However, NICE has set forth plans of an appraisal on OCA for PBC, with expected publication in February 2017; more details on this report can be found here.

Appendix F. Ongoing Studies

Title/ Trial Sponsor	Study Design	Comparators	Patient Population	Primary Outcomes	Estimated Completion Date
A Phase 3 Double-Blind, Placebo Controlled Trial and Long-term Safety Extension of Obeticholic Acid in Patients with Primary Biliary Cirrhosis **(POISE)** **Sponsor: Intercept Pharmaceuticals**	Phase 3 double-blind RCT After completion of the 1-year double-blind study, subjects will be offered the opportunity to enter an open-label LTSE trial	• Obeticholic Acid (5-10 mg and 10mg doses) • Placebo	N=217 Inclusion criteria • Definite or probably PBC diagnosis • At least one of the following: ALP ≥1.67xULN, TB >ULN but <2xULN • Age ≥18 years • Taking UDCA ≥12 months (stable dose ≥3 months), or unable to tolerate UDCA prior to Day 0 • Females must be postmenopausal, surgically sterile, or if premenopausal, be prepared to take ≥1 contraceptive Exclusion criteria • History of presence of other concomitant liver diseases • Presence of complications of PBC or clinically significant hepatic decompensation • Patients with a history of severe pruritus or prior systematic treatment for pruritus	Primary • Composite endpoint of ALP <1.67ULN, ≥15% decrease in ALP, and normal TB Secondary • ALP response rates of 10, 20 and 40% change • ALP ≤3xULN and ≤2xULN • ALP ≤1.5xULN and aspartate aminotranserase ≤1.5xULN and normal TB • Bilirubin and albumin	June 2018

Title/ Trial Sponsor	Study Design	Comparators	Patient Population	Primary Outcomes	Estimated Completion Date
A Phase 3b Double-Blind, Randomized, Placebo-Controlled Multicenter Study Evaluating the Effect of Obeticholic Acid on Clinical Outcomes in Patients with Primary Biliary Cirrhosis **(COBALT)** **Sponsor: Intercept Pharmaceuticals**	Phase 3b double-blind RCT	• Obeticholic Acid (5-10 mg dose) • Placebo	N=350 Inclusion criteria • Definite or probably PBC diagnosis • A mean TB of >ULN and ≤3xULN • Age ≥18 years • Taking UDCA ≥12 months (stable dose ≥3 months), or unable to tolerate UDCA prior to Day 0 • Females must be postmenopausal, surgically sterile, or if premenopausal, be prepared to take ≥1 contraceptive Exclusion criteria • History of presence of other concomitant liver diseases • Presence of complications of PBC or clinically significant hepatic decompensation • Mean TB <3xULN	Primary • Composite endpoint of any of: death, liver transplant, MELD score ≥15, uncontrolled ascites, HCC, hospitalization for new onset or reoccurrence of variceal bleed, encephalopathy, spontaneous bacterial problems Secondary • First occurrence of any one of the above-mentioned for the primary endpoint • Changes from baseline on liver biomarkers	April 2023

Source: www.ClinicalTrials.gov (NOTE: studies listed on site include both clinical trials and observational studies)