NICE National Institute for Health and Care Excellence

Single Technology Appraisal

Obeticholic acid for treating primary biliary cholangitis [ID785]

Committee papers

Any information supplied to NICE which has been marked as confidential, has been redacted. All personal information has also been redacted.

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

SINGLE TECHNOLOGY APPRAISAL

Obeticholic acid for treating primary biliary cholangitis [ID785]

Contents:

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Pre-meeting briefing Obeticholic acid for treating primary biliary cirrhosis

This slide set is the pre-meeting briefing for this appraisal. It has been prepared by the technical team with input from the committee lead team and the committee chair. It is sent to the appraisal committee before the committee meeting as part of the committee papers. It summarises:

- the key evidence and views submitted by the company, the consultees and their nominated clinical experts and patient experts and
- the Evidence Review Group (ERG) report.

It highlights key issues for discussion at the first appraisal committee meeting and should be read with the full supporting documents for this appraisal.

Please note that this document includes information from the ERG before the company has checked the ERG report for factual inaccuracies.

The lead team may use, or amend, some of these slides for their presentation at the Committee meeting.

Key decision points

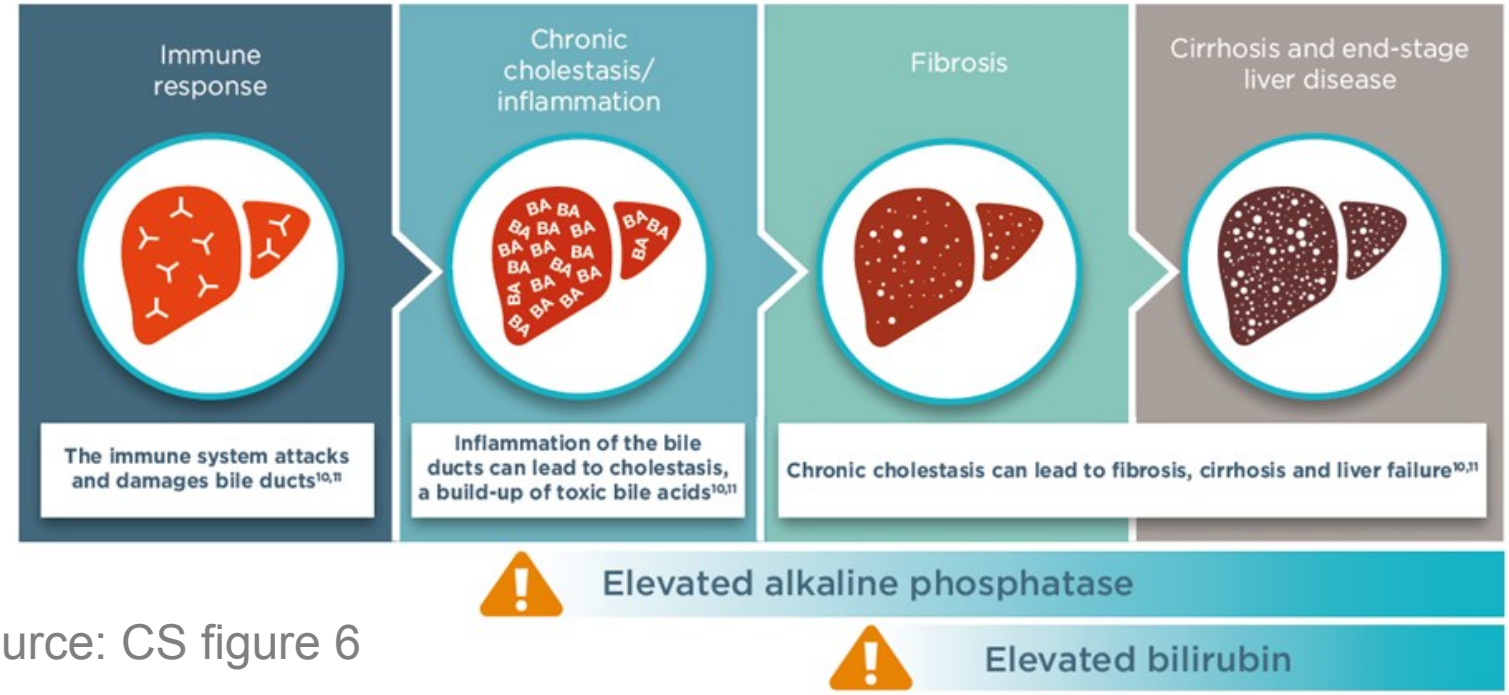
- Is there high unmet medical need? What is standard of care for people intolerant to/ have inadequate response to UCDA?
- Are fibrates relevant comparators?
- What is the natural history of people with low ALP? Can ALP be maintained at this level and will it prevent progression of PBC?
- How generalisable is the clinical trial in terms of
  - the proportion of people with moderate and severe PBC?
  - the proportion of people on OCA monotherapy (n=11)
  - the value of the composite primary outcome in clinical practice (is there a strong enough relationship between the surrogate and improved long term liver outcomes)?
- How is OCA used in clinical practice (is it titrated)?
- How severe is the pruritus associated with OCA?
- Utility values for PMB/Liver health states – appropriate?

Primary biliary cirrhosis (PBC)

- Also known as primary biliary cholangitis is rare, progressive, autoimmune, non-viral disease of the liver that gradually destroys the interlobular bile ducts. This causes accumulation of cytotoxic bile acids in the liver, which leads to inflammation, liver fibrosis, cirrhosis, and ultimately liver failure.
- Estimated prevalence in the UK is ~ 3.9 per 10,000 population, equating to ~ 19,175 people in England.
- Incidence is 0.58 per 10,000 population.
- ~ 90% of people with the condition are women, and age of diagnosis is typically between 30 and 65 years
- ~ 60–80% of patients are asymptomatic at diagnosis. The diagnosis in asymptomatic patients is usually established after the chance finding of an elevated ALP level during the course of an unrelated illness.

PBC progression and association with alkaline phosphatase and total bilirubin level

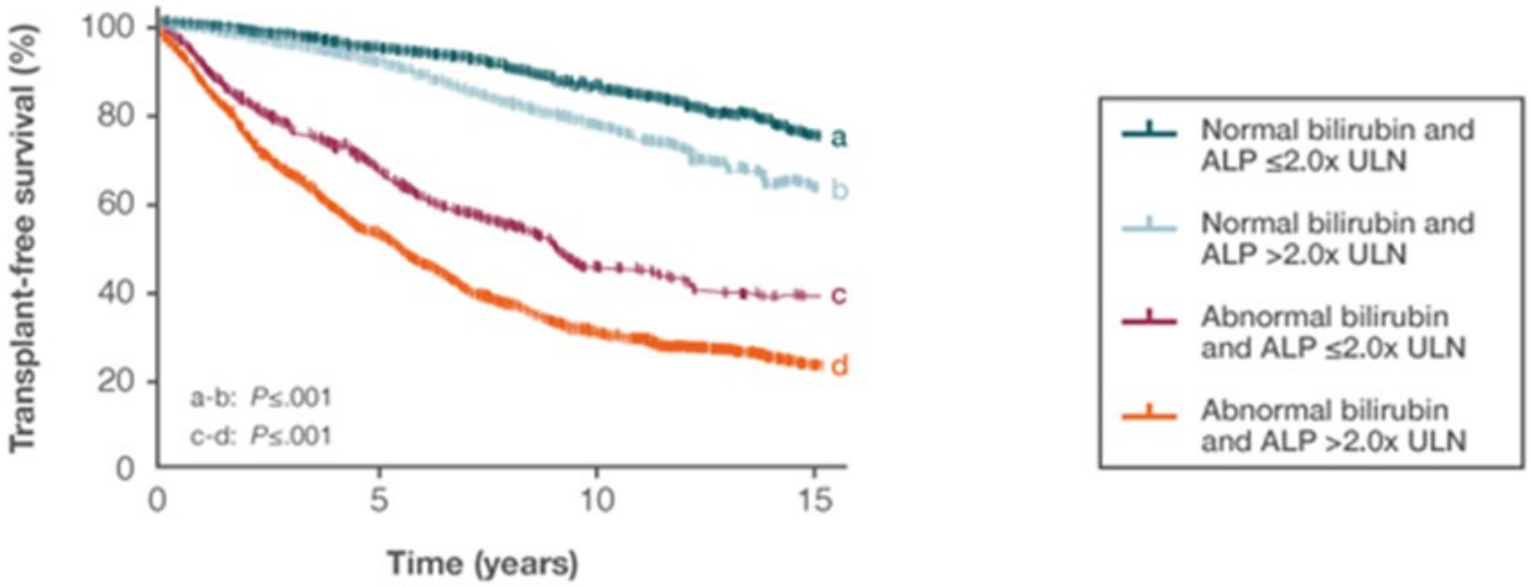
- The presence of AMA and elevated ALP levels are two early characteristic markers of PBC. It is important to treat patients when their ALP levels >1.67x ULN, equivalent to 200 U/L.
- An increase in serum bilirubin is detected only when significant liver damage has occurred, with a sharp increase occurring in the terminal phase. A rise in bilirubin to as low as 0.5 x ULN, is a significant change in the course of the disease



Source: CS figure 6

ALP and bilirubin level correlation with death and liver transplantation

- The company stated that serum ALP along with bilirubin are used to manage patients, test the efficacy of novel therapies in clinical studies, and gauge the risk of long-term adverse clinical outcomes.



Source: CS figure 7, p.35

Current management

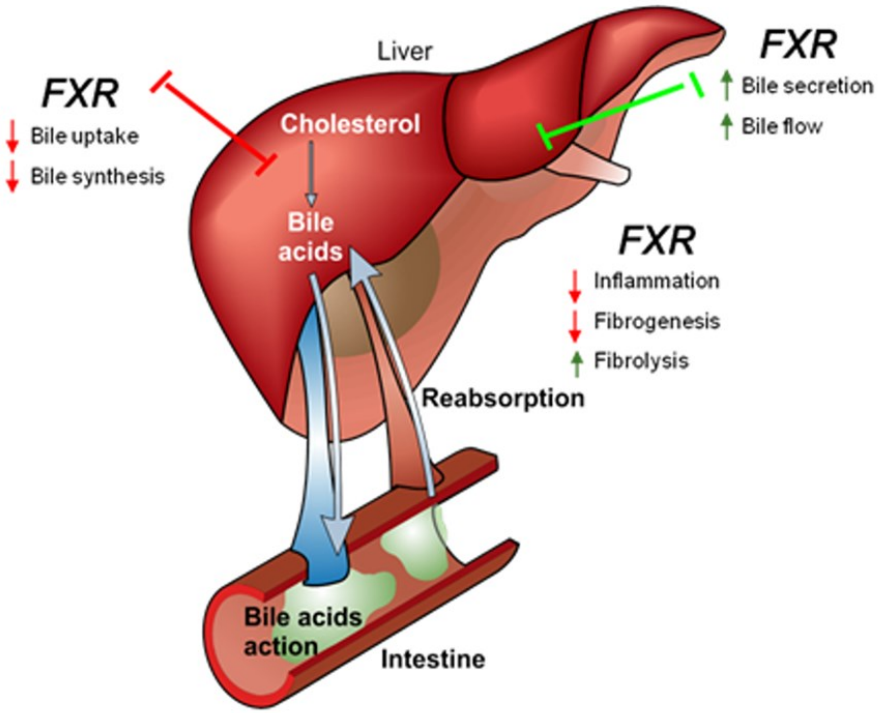
- First choice treatment: ursodeoxycholic acid (UDCA)
- Inadequate response to UDCA in up to 70% of people
- For people who are unable to tolerate, or whose disease responds inadequately to, UDCA – no licensed or effective treatments
- Immunosuppressive therapy no longer used for primary biliary cirrhosis. No benefit, severe side effects, not recommended in guidelines.
- Liver transplant is an option only for people with end stage liver disease or decompensated cirrhosis (10% of these people have disease recurrence)

Obeticholic acid (OCA)

Conditional marketing authorisation	Granted on 12 December 2016
	“primary biliary cholangitis (also known as primary biliary cirrhosis) in combination with ursodeoxycholic acid (UDCA) in adults with an inadequate response to UDCA or as monotherapy in adults unable to tolerate UDCA”
	Conditional on follow up studies to demonstrate clinical benefits of reduced alkaline phosphatase and bilirubin levels e.g. delayed liver fibrosis, cirrhosis, liver transplant, death
Administration & dosage	Oral tablet (5 mg or 10 mg) Start on 5 mg/day, increase to 10 mg/day after 6 months
Duration of treatment	As long as person continues to benefit (dose reduced/interrupted for severe intolerability due to pruritis)
Cost	£2,384.04 for 30 tablets (list price) → £29,005.78/year A confidential patient access scheme has been approved

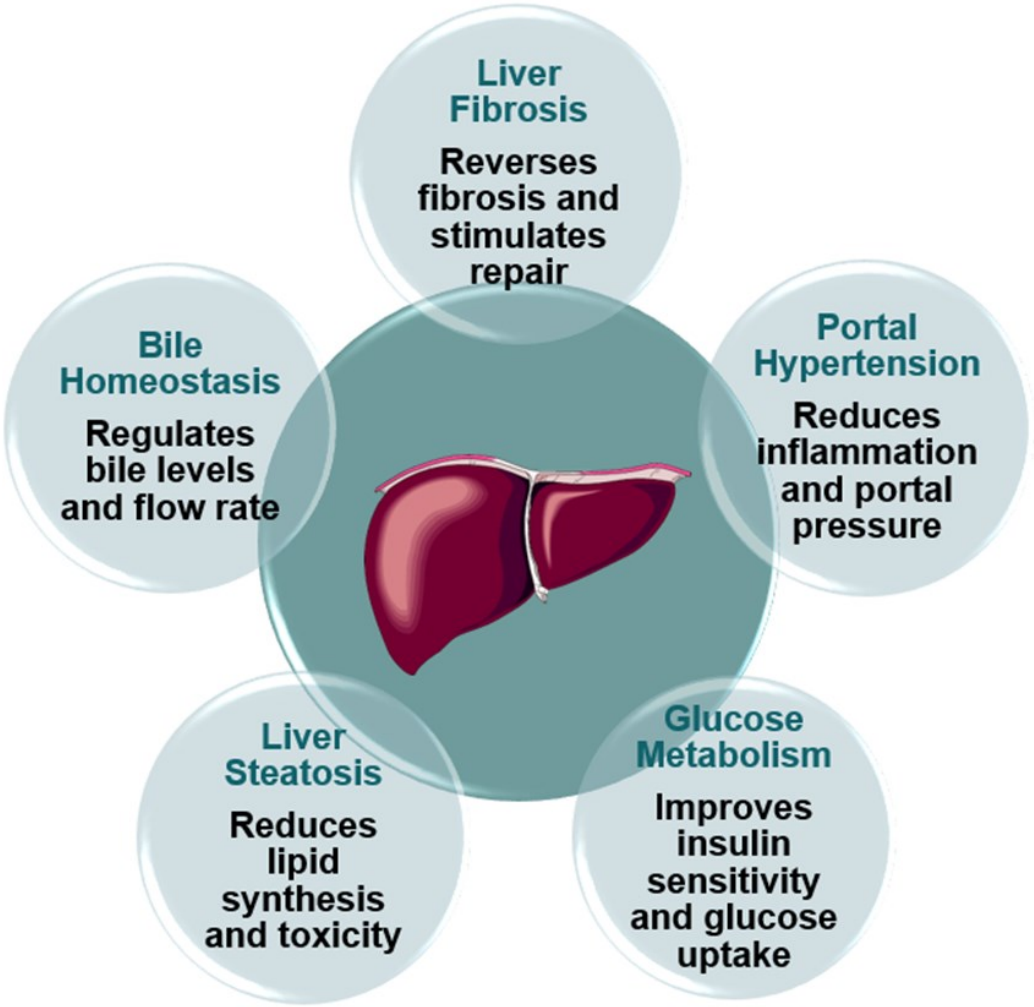
OCA mechanism of action

- OCA is farnesoid X receptor (FXR) agonist which:
  - ↓ bile acid synthesis
  - ↓ uptake and ↑ secretion of bile acids in and out of liver cells
  - mediates anti-inflammatory and anti-fibrotic pathways



Source: CS Figure 1

FXR regulation of biological pathways



Source: CS Figure 2

Patient perspective - the PBC Foundation

- Living with PBC has been described as “Living on an emotional and physical rollercoaster”.
- Symptoms vary from week to week and day to day, patients (and carers) never know what PBC will bring on a day to day basis.
- The main symptoms include: chronic fatigue (with the linked symptom of cognitive impairment), pruritus, joint/muscle/bone pain, and nausea
- The symptoms, just themselves, can have an enormously detrimental effect on quality of life which leads to social isolation and reinforces negative quality of life issues.
- The diagnosis of an incurable, progressive disease, particularly one with such a foreboding outline can lead to an insurmountable emotional burden.
- Patients experience a lack of knowledge and understanding within medical communities, particularly in primary care and district hospital levels. It is widely anticipated that a successful novel therapy for PBC will provide opportunity for much needed education of medics about the PBC.

Decision problem (final scope)

Population	People with primary biliary cirrhosis whose disease has an inadequate response to, or who are unable to tolerate, ursodeoxycholic acid (UDCA)
Intervention	OCA alone or in combination with UDCA
Comparators	For people whose disease has an inadequate response to UDCA: • UDCA alone or in combination with fibrates For people who are unable to tolerate UDCA: • Fibrates • No additional treatment
Outcomes	• Mortality • Liver function based on markers of liver biochemistry • Symptoms, including pruritus, fatigue and abdominal pain • Time to liver transplantation • Primary biliary cirrhosis related events, including ascites, varices, encephalopathy and HCC • Adverse effects of treatment • Health-related quality of life

Company deviations from the scope (1): comparators

Company submission did not include fibrates, with the rationale that fibrates:

- do not have a marketing authorisation for primary biliary cirrhosis in the UK
- not standard of care
- contraindicated in primary biliary cirrhosis
- rarely used: [redacted]% of patients in the UK-PBC cohort ([redacted]/2,245) have ever taken fibrates for any condition (not necessarily for PBC)
- do not have proven efficacy; there only a limited number of studies of fibrates in primary biliary cirrhosis, with the following challenges:
  - small patient numbers
  - all except 1 study was conducted in Japanese patients
  - poor trial quality and high risk of bias
  - significant safety concerns

Clinical effectiveness evidence

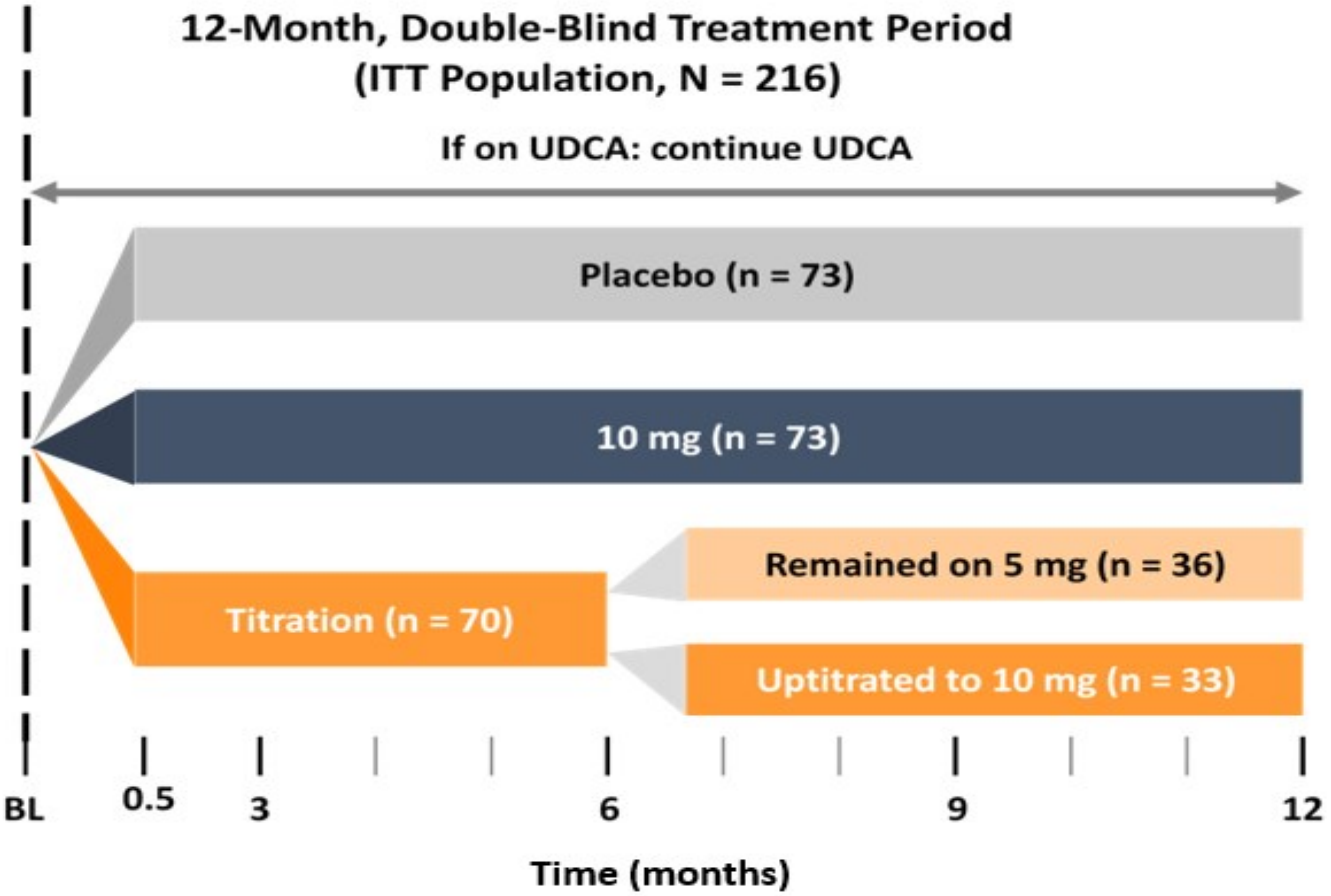
POISE trial

- Phase 3, randomised double-blind, placebo-controlled, parallel group trial. Stratified randomisation according to:
  - higher risk of developing clinical outcomes
  - intolerance to UDCA
  - presence or absence of biochemical response to UDCA treatment
- 59 sites in 13 countries including 7 sites in England and 2 sites in Scotland
- Intervention: OCA 10 mg, OCA titration, placebo with or without UDCA
- Primary outcomes:
  - percentage of participants at 12 month achieving the composite endpoint: ALP <1.67x ULN, **and** total bilirubin ≤ULN, **and** ALP decrease ≥15% from baseline
- Secondary outcomes:
  - percentage of patients having the primary endpoint in the OCA titration group at Month 12,
  - percentage of patients reaching the endpoint at Week 2, Month 3, Month 6 and Month 9, and comparing the 10 mg OCA fixed dose group with the OCA titration group at Month 6.
- The primary variable for the long-term safety extension phase was the percentage of patients having the composite endpoint based on previous treatment in the double-blind phase

POISE trial

- Patients were stratified by the presence or absence of the following biochemical response criteria and tolerance to UDCA treatment:
  - ALP >3x ULN and/or AST >2x ULN and/or bilirubin >ULN, and intolerant to UDCA or currently taking UDCA
  - ALP >3x ULN and/or AST >2x ULN and/or bilirubin >ULN, and currently taking UDCA or currently taking UDCA
- A request for titration to OCA 10 mg for the remainder of the double-blind phase (Months 6-12) could be made by the investigator for patients who met any of the following criteria at the Month 6 assessment:
  - ALP ≥1.67x ULN, and/or
  - Total bilirubin >ULN, or
  - <15% ALP reduction at month versus the mean pre-treatment value, and
- Provided AEs did not limit the administration of the higher dose of OCA.

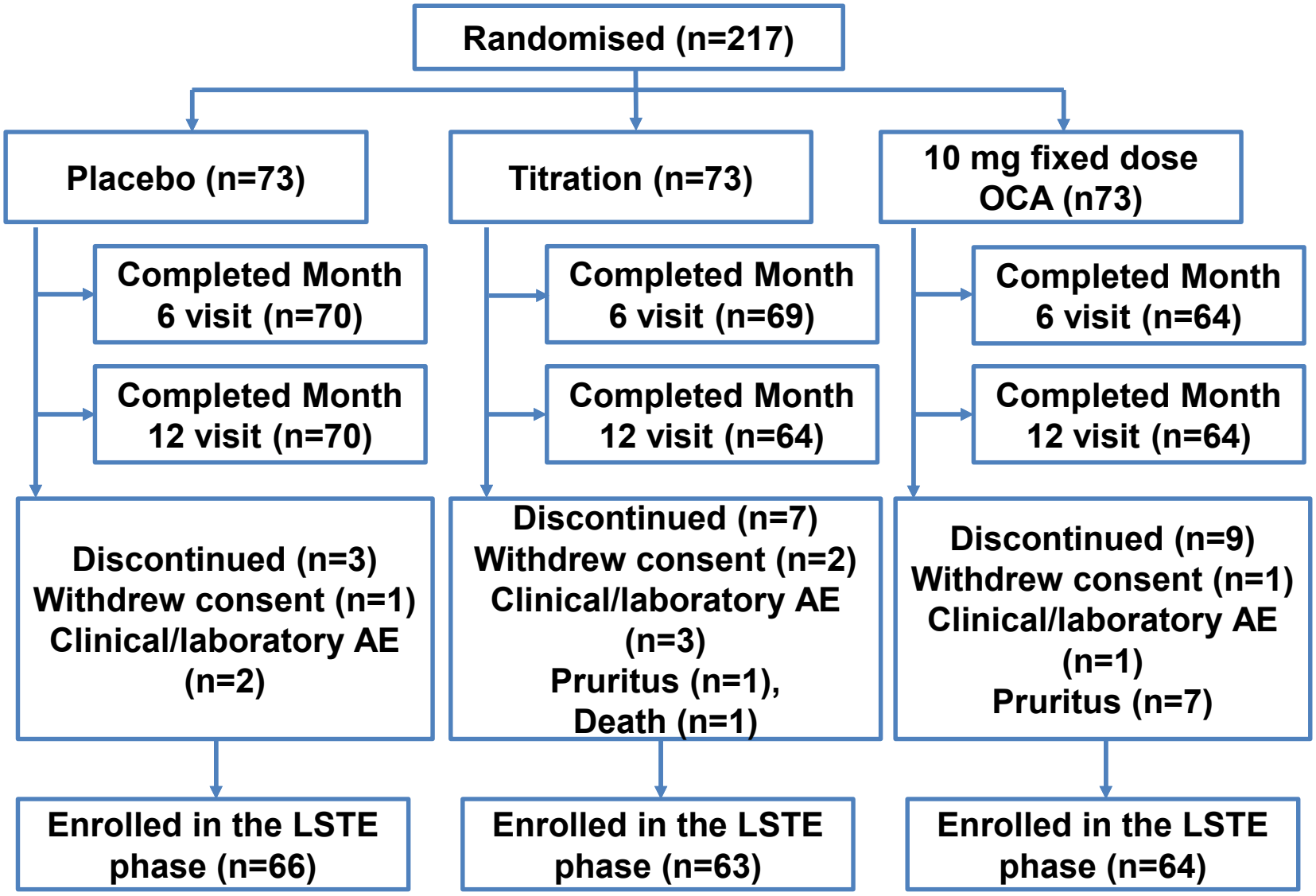
Design of the POISE trial



Source: CS p.49

BL – baseline, UDCA – ursodeoxycolic acid

Overview of POISE trial



Source: CS Figure 11

POISE baseline characteristics

- 81% of patients were younger than 65 years old.
- 91% female
- 11 patients were UDCA intolerant

	Placebo (n=73)	OCA titration (n=70)	OCA 10 mg (n=73)
Mean age, years (SD)	55.5 (10.0)	55.8 (10.5)	56.2 (11.0)
BMI<30 kg/m^2	79%	83%	84%
Pre-treatment liver biopsy	10%	19%	12%
UDCA use at baseline	93%	93%	92%
Baseline liver parameters, ITT population			
ALP >3x ULN	32%	27%	27%
Total bilirubin >ULN	10%	6%	10%

ALP, alkaline phosphatase; BMI, body mass index; OCA, obeticholic acid; SD, standard deviation; UDCA, ursodeoxycholic acid; ULN, upper limit of normal

Source: Tables 20, 22 CS.

POISE results

Primary outcomes	**Responders at Month 12**	
	Placebo (n=73)	10%
	10 mg OCA (n=73)	47%
	Titration OCA (n=70)	46%
	Titration subgroup	
	Remained at 5 mg OCA for 12 months (n=36)	53%
	Titrated to 10 mg OCA at Month 6 (n=33)	39%
Secondary outcomes	**ALP reduction from baseline ≥40% at Month 12**	
	Placebo (n=73)	1%
	10 mg OCA (n=73)	34%
	Titration OCA (n=70)	30%
	Mean total bilirubin levels at Month 12	
	Placebo (n=73)	13.2 (SE 1.0)
	10 mg OCA (n=73)	9.7 (SE 0,6)
	Titration OCA (n=70)	9.9 (SE 0.6)

Source: CS table 23 and ERG report p. 49

Adverse events

Participants, n (%)	Placebo n=73	OCA titration n=70	OCA 10 mg n=73
Any TEAE	66 (90)	65 (93)	69 (95)
Any treatment-related AE	38 (52)	42 (60)	54 (74)
Any SAEs	3 (4)	11 (16)	8 (11)
Mild TEAEs	29 (40)	16 (23)	19 (26)
Moderate TEAEs	28 (38)	27 (39)	29 (40)
Severe TEAEs	9 (12)	22 (31)	21 (29)
Any TEAE leading to discontinuation	2 (3)	5 (7)	8 (11)
Pruritus	27 (37)	35 (50)	48 (66)
Fatigue	8 (11)	6 (9)	6 (8)
Nausea	4 (5)	3 (4)	4 (5)
Discontinuation due to pruritus	0 (0)	1 (1)	7 (10)
Number of deaths	0 (0)	1 (1)	0 (0)

AE, adverse event; SAE, serious adverse event; TEAE, treatment-emergent adverse event

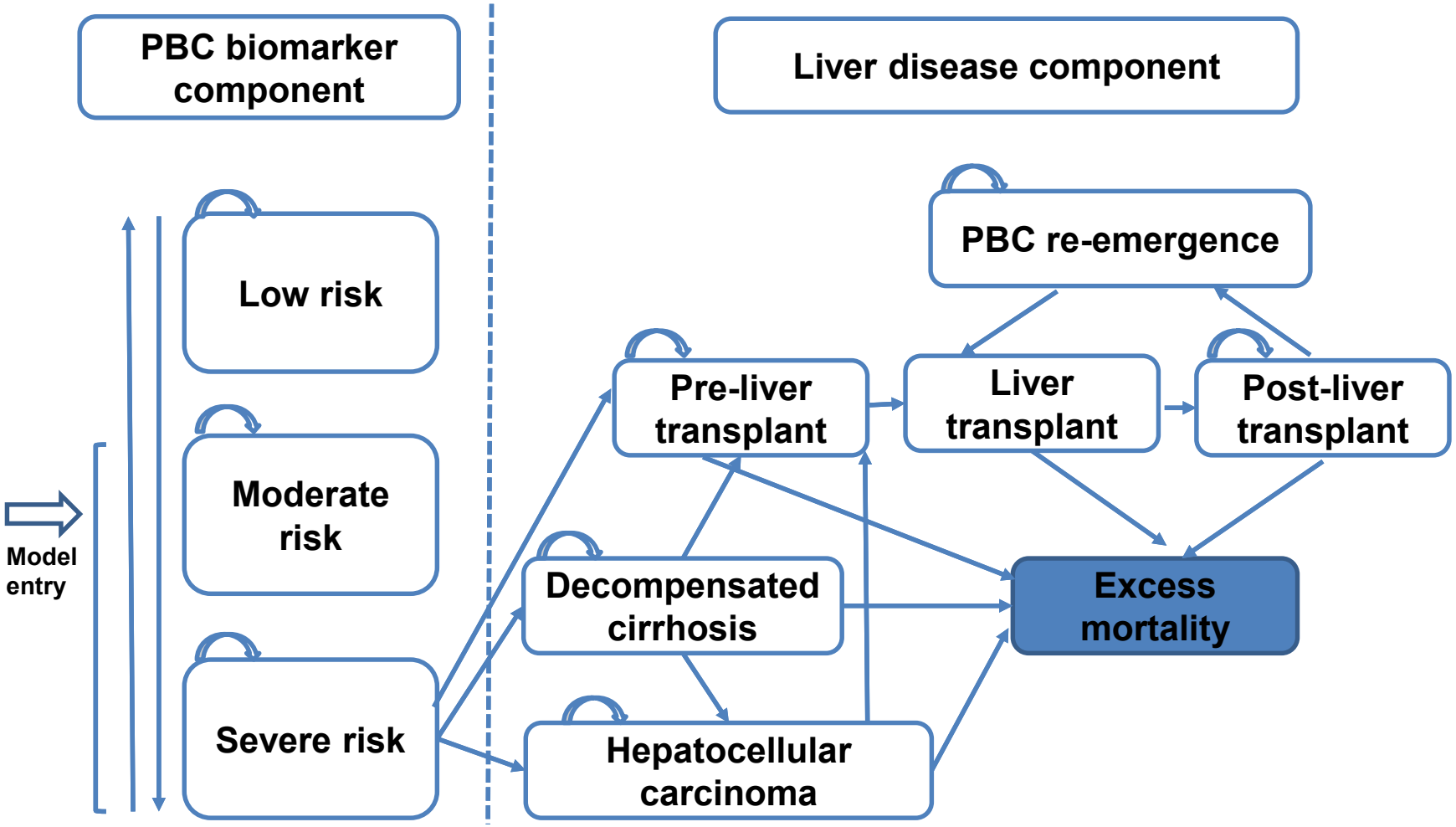
Source: CS table 37

ERG comments

- No trials comparing OCA with fibrates were identified.
- The group receiving OCA as monotherapy is underrepresented in the POISE trial (11 patients).
- The majority of patients in POISE appeared to be at an earlier stage of disease so the effects on those with more advanced disease are less clear.
- The POISE trial only examined surrogate outcomes; OCA showed positive effects on surrogate endpoints, and there is some evidence that surrogate endpoints are related to relevant outcomes. However, the size of the relationship is unclear.
- Two extension studies to POISE trial were not similar enough to be pooled with POISE trial. Clinical outcomes await the publication of the COBALT trial which is estimated to be in 2022.

Cost effectiveness evidence

Model structure



Source: CS Figure 24

Model details

- De novo model, lifetime horizon, 3.5% discount for utilities and costs; 3 month cycle length
- Model comprises 2 parts:
  - biomarker component based on surrogate outcomes of ALP and bilirubin biomarkers in three different health states based on the expected risk of disease progression:
    - low risk (ALP ≤ 1.67 x ULN [ALP ≤ 200 units/L]);
    - moderate risk (ALP > 1.67 x ULN and total bilirubin; TB ≤ 1.0 x ULN)
    - severe risk (TB > 1.0 x ULN [TB > 20 µmol/L] or compensated cirrhosis);
  - liver disease component based on clinical endpoints:
    - pre-liver transplant,
    - decompensated cirrhosis,
    - hepatocellular carcinoma (HCC),
    - liver transplant,
    - post-liver transplant state,
    - potential PBC re-emergence and death.

Clinical data used in the model

- Data from the POISE trial and literature was used to estimate transition probabilities between the health states in the biomarker component of the model.
- The literature was used to estimate and extrapolate the transition probabilities for the health states in the liver disease component of the model.

Transition probabilities

TPs between health states in the PBC-specific component of the model

- In its base case, the company used different methods to derive TPs for each treatment arm in the PBC-specific component of the model: trial data for OCA and published literature for comparators
  - **OCA monotherapy and combination with UDCA:** patient-level data from POISE (TPs for OCA monotherapy were based on data from patients who received OCA with UDCA)
    - Rationale: insufficient data from POISE for OCA monotherapy
  - **No treatment (for people who cannot tolerate UDCA):** TPs from published literature (Corpechot 2000 study of UDCA vs. no active treatment in PBC)
    - Rationale: insufficient data from POISE (n=5) and not appropriate to assume the same TPs for UDCA-intolerant population and UDCA inadequate-responders (who continue to benefit from UDCA)
  - **UDCA (for people whose disease responded inadequately to UDCA):** TPs based on patient-level POISE data, adjusted using published literature (GLOBE and UK risk scores)
    - Rationale: The company expected UDCA inadequate responders to get worse after the end of the trial but TPs were not available for the full time horizon.

TPs from the PBC-specific health state ("abnormal bilirubin and rising, or compensated cirrhosis") to the more severe liver-specific health states

- Derived from published literature (see table 54 of the company submission)

Use of HRQoL data in the model

- HRQoL is assumed to be constant in each of the biochemistry states, (the utility for patients in a certain health state does not change over time).
- HRQoL worsens as patients proceed from the biochemistry component to the liver disease component of the model.
- Utility values used in the cost-effectiveness analysis have been adjusted.
- The following health states in the liver disease component of the model had their corresponding utility values decreased by [redacted] to simulate the worsened HRQoL experienced by PBC patients in comparison to HBV/HCV patients, as an interpretation of KOL feedback by the company:
  - decompensated cirrhosis,
  - pre-transplant at listing, 3 and 6 months after listing health states
  - 3, 6, 12 and 24 months post liver transplant health states
- Clinical experts verified company's assumptions that PBC patients are likely to have worse utility values than HCV/HBV patients despite being in the same health state except of patients with hepatocellular carcinoma.

Utilities

State	Utility	Primary source
Low risk	0.84	Younossi et al. 2001
Moderate risk	0.84	Younossi et al. 2001
Severe risk	0.55	Wright et al. 2006
Decompensated cirrhosis	[redacted]	Wright et al. 2006
Hepatocellular carcinoma	0.45	Wright et al. 2006
Pre-transplant: utility at listing	[redacted]	Wright et al. 2006
Pre-transplant: 3 months after listing	[redacted]	Wright et al. 2006
Pre-transplant: 6 months after listing	[redacted]	Wright et al. 2006
Liver transplant: 3 months post-transplant	[redacted]	Wright et al. 2006
Liver transplant: 6 months post-transplant	[redacted]	Wright et al. 2006
Liver transplant: 12 months post-transplant	[redacted]	Wright et al. 2006
Liver transplant: 24 months post-transplant	[redacted]	Wright et al. 2006
Re-emergence of PBC	[redacted]	Wright et al. 2006

ALP, alkaline phosphatase; Bili, bilirubin; CC, compensated cirrhosis; CS, company submission; PBC, primary biliary cholangitis/cirrhosis

Source: CS Table 61

Health-state costs and resource use

Health states	Value
Low risk ALP: ≤ 200 U/L and Bili: Normal	Staff: £221 (1x Outpatient appointment, 1x outpatient follow-up)
	Hospital costs: £27 (3 blood tests, 3 times per year, at a cost of £3)
	Total: £248
Moderate risk ALP: > 200 U/L and Bili: Normal	Staff: £345 (1x Outpatient appointment, 2x outpatient follow-up appointments)
	Hospital costs: £27 (3 blood tests, 3 times per year, at a cost of £3)
	Total: £496
Severe risk	Total: £6,254
Decompensated cirrhosis	Total: £12,509
Hepatocellular carcinoma	Total: £11,147
Pre-transplant (end stage)	Total: £18,217
Re-emergence of PBC	Total: £248
Liver transplant	Total: £65,029
Follow-up 1 year after liver transplantation	Total for 2 years divided by 2: £18,166
Follow-up 2 years after liver transplantation	Total for 2 years divided by 2: £18,166

Source: CS table 66

Company's base case deterministic results

UDCA intolerant population, using the PAS price of OCA

	Total			ICER
	Costs	LYG	QALYs	
No treatment (placebo)	£103,233	11.30	6.61	–
OCA titration	£251,671	16.68	13.56	£21,351

UDCA inadequate responder population, using the PAS price of OCA

	Total			ICER
	Costs	LYG	QALYs	
UDCA + placebo	£96,977	12.35	7.85	–
OCA titration + UDCA	£261,791	16.78	13.68	£28,281

ICER, incremental cost-effectiveness ratio; LYG, life years gained; OCA, obeticholic acid; QALY, quality-adjusted life year; UDCA, ursodeoxycholic acid.

Source: CS tables 23, 24 (erratum PAS price)

Company's deterministic sensitivity analyses

- The following parameters was investigated through one way deterministic sensitivity analysis:
  - Discontinuation probabilities
  - Probabilities of experiencing an adverse event
  - Utility weights
  - Transition probabilities
  - Discounting
  - The probability of death for the general population
  - Adverse events costs and disease management costs (i.e. health state costs)
- In patients whose disease has inadequate response to UDCA and UDCA intolerant patients, the most influential parameters on the cost effectiveness results were the health states utility values for the health states of the biomarker component of the model and the transition probabilities between these health states.

Company scenario 1
Use of original HCV utility values

Scenario 1 analysis: UDCA intolerant patients

Technologies	Total			Incremental			ICER
	Costs	LYG	QALYs	Costs	LYG	QALYs	
No treatment (placebo)	£103,233	11.30	6.91	–	–	–	–
OCA titration	£251,671	16.68	13.61	£148,439	5.38	6.70	£22,160

Scenario 1 analysis: UDCA inadequate responders

Technologies	Total			Incremental			ICER
	Costs	LYG	QALYs	Costs	LYG	QALYs	
UDCA + placebo	£96,977	12.35	8.11	–	–	–	–
OCA titration + UDCA	£261,791	16.78	13.72	£164,814	4.43	5.61	£29,374

ICER, incremental cost-effectiveness ratio; LYG, life years gained; OCA, obeticholic acid; QALY, quality-adjusted life year; UDCA, ursodeoxycholic acid.

Source: Table 35 and 36, CS erratum PAS price

Company scenario 2
Use of alternative transition probabilities

Scenario 2 analysis: UDCA intolerant patients

Technologies	Total			Incremental			ICER
	Costs	LYG	QALYs	Costs	LYG	QALYs	
No treatment (placebo)	£94,717	10.89	6.39	–	–	–	–
OCA titration	£250,303	16.61	13.52	£155,586	5.73	7.13	£21,824

Scenario 2 analysis: UDCA inadequate patients

Technologies	Total			Incremental			ICER
	Costs	LYG	QALYs	Costs	LYG	QALYs	
UDCA + placebo	£89,666	12.00	7.67	–	–	–	–
OCA titration + UDCA	£260,540	16.72	13.65	£170,874	4.72	5.98	£28,596

ICER, incremental cost-effectiveness ratio; LYG, life years gained; OCA, obeticholic acid; QALY, quality-adjusted life year; UDCA, ursodeoxycholic acid.

Source: Table 37 and 38, CS erratum PAS price

ERG comments

- The decision to exclude fibrates as a comparator is inconsistent with the scope and may not be appropriate.
- There is an ongoing study on PBC patients treated with fibrates and that treatment with fibrates may present a viable comparator in the future.
- Improvements in surrogate outcomes were not reflected in the disease specific quality of life tool (PBC-40) over the 12 month period.

ERG comments

- Concerns regarding the model structure:
  - **Biomarker component:**
    - Aggregation of two different health states into one (compensated cirrhosis and abnormal total billirubin count)
    - Patients receiving OCA treatment and who are in the low and moderate risk biomarker component health states at the end of the first year remain there for the remainder of their lives. This holds for UDCA but may not hold for OCA. The ERG conducted the exploratory analysis (please see more in the next slides)
  - **Liver disease component:**
    - Company's model diverges from those used in other liver diseases in that an additional pre-liver transplant health state was introduced (compared to, for instance, TA 330). It groups patients together that came from different health states (HCC, DCC, severe risk) and who may experience different HRQoL.

ERG comments

- Population
  - Patients enter the biomarker component of the mode in the moderate (76.85%) and severe risk (23.15%) health states which is not reflective of the proportion of patients entering the POISE study in the severe risk health state (8.42%). This leads to more patients in the model remaining in the severe risk health state and moving to more severe disease (the liver disease component in the model). This in turn would potentially bias model outcomes in favour of OCA
  - The ERG considers that the proportions of patients entering the model in the moderate and severe risk health states should be based on data from POISE. Although the company state that the proportions entering the model are derived from POISE, it is not clear how this was done.

ERG comment on transition probabilities

- The ERG's concerns with estimating transition probabilities in the biomarker component are:
  1. Discrepancy between the transition probabilities reported in company submission Table 49 and those used in the economic model.
  2. Assumption of no discontinuation beyond 12 months
  3. Usage of unclear calibration methods based on the literature instead of the POISE trial for the non-OCA regimen for inadequate responders to UDCA;

ERG exploratory analyses

1. Used transition probabilities in the company submission for biomarker component because of a discrepancy with the numbers used in the model
2. Used unadjusted transition probabilities from POISE for the non-OCA regimen (for biomarker component of the model)
3. Proportions in the starting health states from POISE
4. NHS reference costs for outpatient visits
5. Health state costs of £1,561 for compensated cirrhosis consistent with TA330 for the severe risk health state in the biomarker component) (instead of £6,254)
6. Used age-dependent utilities (from the UK general population) for the low and moderate risk health states in the biomarker component of the model
7. Removed the [redacted] HRQoL decrements (in the liver disease component of the model)

ERG base case

UDCA **inadequate responders** – OCA PAS price

	Incremental results		
	ΔQALY	ΔCosts	ICER
Company base-case (deterministic)*	5.79	£164,551	£28,425
1. Fixing discrepancies between transition probabilities[1]	5.83	£164,806	£28,280
2. Use transition probabilities from POISE for the non-OCA regimen	5.20	£171,036	£32,897
3. POISE trial proportion in starting health states	5.55	£170,482	£30,736
4. Use NHS reference costs for outpatient visits	5.83	£165,453	£28,394
5. Use health state costs consistent with TA330	5.83	£180,737	£31,017
6. Use UK age-dependent utility values	4.93	£164,808	£33,458
7. Remove [redacted] utility decrement	5.61	£164,808	£29,377
ERG base-case (deterministic)	4.17	£189,968	£45,541
ERG base-case (probabilistic)	4.22	£189,706	£44,945

ICER, incremental cost-effectiveness ratio; NHS, National Health Services; OCA, obeticholic acid; QALYs, quality-adjusted life years; UDCA, ursodeoxycholic acid

Source: ERG report PAS appendix, table 3

ERG base case

UDCA **intolerant patients** – OCA PAS price

	Incremental results		
	ΔQALY	ΔCosts	ICER
Company base-case (deterministic)	6.91	£148,210	£21,438
1. Fixing discrepancies between transition probabilities[1]	6.95	£148,438	£21,351
2. Use transition probabilities from POISE for the non-OCA regimen	6.56	£151,875	£23,152
3. POISE trial proportion in starting health states	6.89	£152,275	£22,111
4. Use NHS reference costs for outpatient visits	6.95	£149,461	£21,500
5. Use health state costs consistent with TA330	6.95	£166,622	£23,969
6. Use UK age-dependent utility values	5.92	£148,441	£25,085
7. Remove [redacted] utility decrement	6.70	£148,441	£22,162
ERG base-case (deterministic)	5.38	£173,399	£32,217
ERG base-case (probabilistic)	5.46	£173,001	£31,682

ERG, Evidence Review group; ICER, incremental cost-effectiveness ratio; NHS, National Health Services; OCA, obeticholic acid; QALYs, quality-adjusted life years; UDCA, ursodeoxycholic acid

Source: ERG report PAS appendix table 4

ERG exploratory analyses

UDCA **inadequate responders** – OCA PAS price

	Incremental results		
	ΔQALY	ΔCosts	ICER
ERG base-case (deterministic)	4.17	£189,968	£45,541
ERG base-case (probabilistic)	4.22	£189,706	£44,945
1. Use transition probabilities and model structure from TA330	3.80	£221,832	£58,412
2. Using transition probabilities based on the POISE trial after 12 months for the non-OCA treatment arms	2.59	£206,182	£79,668
3. Assume that transition probabilities between biomarkers health states of the OCA arm are >0%	3.75	£185,078	£49,294
4. Use alternative costs for liver transplant	4.17	£191,025	£45,794

ICER, incremental cost-effectiveness ratio; OCA, obeticholic acid; QALYs, quality-adjusted life years; UDCA, ursodeoxycholic acid

Source: ERG report PAS appendix, table 9

ERG exploratory analyses

UDCA **intolerant patients** – OCA PAS price

	Incremental results		
	ΔQALY	ΔCosts	ICER
ERG base-case (deterministic)	5.38	£173,399	£32,217
ERG base-case (probabilistic)	5.46	£173,001	£31,682
1. Use transition probabilities and model structure from TA330	4.91	£214,417	£43,686
2. Using transition probabilities based on the POISE trial after 12 months for the non-OCA treatment arms	2.61	£202,848	£77,715
3. Assume that transition probabilities between biomarkers health states of the OCA arm are >0%	4.97	£168,979	£34,031
4. Use alternative costs for liver transplant	5.38	£174,703	£32,459

ICER, incremental cost-effectiveness ratio; OCA, obeticholic acid; QALYs, quality-adjusted life years; UDCA, ursodeoxycholic acid

Source: ERG report PAS appendix, table 10

Innovation

- OCA is a rationally designed FXR agonist that is the first to provide a novel, innovative therapy for patients with PBC.
- OCA has the potential to make a substantial and meaningful improvement in the quality and quantity of life for patients with PBC by providing an alternative or additional efficacious treatment option that will reduce the risk of, delay, or prevent the need for liver transplant.
- OCA offers a unique therapeutic modality, providing both hepatoprotective effects and potent and selective FXR-mediated effects, to patients who are currently at continued risk of hepatocellular carcinoma, fibrosis, cirrhosis and progression to liver transplantation or death.
- Anti-inflammatory effects of OCA may also contribute to the prevention of bile duct loss
- It would the only effective drug for patients who do not have an adequate response to, or who are intolerant to, UDCA.

Equality issues

- People with PBC face stigma in society because of the negative connotations of the term ‘cirrhosis’ and the association with alcoholism and drug abuse. This is one of the reasons that PBC has recently undergone a name change to primary biliary cholangitis
- PBC is a rare disease and it is essential that patients have the same opportunities to gain access to new treatments
- PBC mainly affects women, which itself presents a challenge with diagnosis since the early symptoms of PBC are often wrongly dismissed as menopausal symptoms or depression

Key issues for consideration: cost effectiveness

- Are primary outcome used in the POISE trial appropriate for modelling lifetime impact of OCA on liver outcomes?
- Do the health states in the model for low, medium and high risk PBC reflect how patients are categorised in clinical practice?
- Is it plausible to assume that patients remain in the same state while on OCA?
- Is it appropriate to apply a relative [redacted] reduction in utility for some liver health states for people with PBC compared with Hepatitis B/C?
- Is OCA an innovative transformative treatment for PBC in people who don't respond or an intolerant to UDCA?
- Does the committee consider structure and transition probabilities used in the company model or ERG exploratory analysis to best represent the progression of PMB?

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- Use the format painter to highlight commercial in confidence information like this

Confidential

Authors

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  Technical Lead
- **Eleanor Donegan**
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  with input from the Lead Team (Ian Bernstein, Stephen Sharp, Pamela Rees)

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Single Technology Appraisal

Obeticholic acid for treating primary biliary cirrhosis

Final scope

Remit/appraisal objective

To appraise the clinical and cost effectiveness of obeticholic acid within its marketing authorisation for treating primary biliary cirrhosis.

Background

Primary biliary cirrhosis (PBC), sometimes known as primary biliary cholangitis, is a progressive autoimmune disease that affects the liver and biliary system and destroys the small interlobular bile ducts. This prevents bile flowing from the liver to the small intestine (cholestasis) and leads to a build-up of bile in the liver cells, which damages the liver. PBC causes the formation of excess fibrous connective tissue (fibrosis) and eventually may lead to scarring of the liver (cirrhosis). The exact cause of PBC is not known, although it is thought a combination of environmental and genetic factors may play a part. The most common symptoms of PBC are itchy skin (pruritus) and fatigue, however, up to half of people with PBC do not have any symptoms until extensive liver damage occurs.

The estimated prevalence of PBC in England is approximately 18,900 people based on 35 people per 100,000 being diagnosed with PBC[1, 2]. In 2013 there were 131 deaths from PBC in England and Wales[3]. Most people with PBC are aged between 30 and 65 years, and around 90% of people with the condition are women.

Treatment for PBC aims to alleviate symptoms and slow disease progression. Ursodeoxycholic acid is the only current treatment available for primary biliary cirrhosis. The estimated proportion of people whose disease have an inadequate response to ursodeoxycholic acid ranges between 20% and 70%[1,4]. Fibrates have been used in clinical practice alone and in combination with ursodeoxycholic acid for people whose disease has an inadequate response to, or are unable to tolerate ursodeoxycholic acid. Symptomatic treatment of pruritus related to PBC includes the use of cholestyramine, rifampicin or naltrexone. Liver transplantation is the only treatment that can improve prognosis for people with PBC who have end-stage liver disease, however, the disease can recur following transplantation.

The technology

Obeticholic acid (brand name unknown, Intercept Pharmaceuticals) is a farnesoid-X receptor agonist and modified bile acid derived from the endogenous human bile acid chenodeoxycholic acid. It is administered orally.

Obeticholic acid does not currently have a marketing authorisation in the UK for primary biliary cirrhosis. It is being studied in clinical trials alone and in combination with ursodeoxycholic acid compared with placebo alone or in combination with ursodeoxycholic acid in adults whose disease had an inadequate response to ursodeoxycholic acid or who were unable to tolerate ursodeoxycholic acid.

Intervention(s)	Obeticholic acid alone or in combination with ursodeoxycholic acid
Population(s)	People with primary biliary cirrhosis whose disease has an inadequate response to, or who are unable to tolerate, ursodeoxycholic acid.
Comparators	For people whose disease has an inadequate response to ursodeoxycholic acid: • Ursodeoxycholic acid alone or in combination with fibrates For people who are unable to tolerate ursodeoxycholic acid: • Fibrates • No additional treatment
Outcomes	The outcome measures to be considered include: • mortality • liver function based on markers of liver biochemistry • symptoms, including pruritus, fatigue and abdominal pain • time to liver transplantation • primary biliary cirrhosis related events, including ascites, varices, encephalopathy and hepatic cell carcinoma • adverse effects of treatment • health-related quality of life.

Economic analysis	The reference case stipulates that the cost effectiveness of treatments should be expressed in terms of incremental cost per quality-adjusted life year. The reference case stipulates that the time horizon for estimating clinical and cost effectiveness should be sufficiently long to reflect any differences in costs or outcomes between the technologies being compared. Costs will be considered from an NHS and Personal Social Services perspective.
Other considerations	Guidance will only be issued in accordance with the marketing authorisation. Where the wording of the therapeutic indication does not include specific treatment combinations, guidance will be issued only in the context of the evidence that has underpinned the marketing authorisation granted by the regulator.
Related NICE recommendations and NICE Pathways	Related Guidelines: Clinical Guideline in Preparation, 'Assessment and management of cirrhosis'. Earliest anticipated date of publication May 2016. Related NICE Pathways: NICE Pathway: Liver conditions, Pathway created: Mar 2014. http://pathways.nice.org.uk/pathways/liver-conditions
Related National Policy	NHS England commissions specialist services for Primary Biliary Cirrhosis under its policy for Liver transplantation services in adults and children. Source: Manual for prescribed specialised services Page 161 Department of Health (2013) NHS Outcomes Framework 2014-2015, Domains 1, 2, 4 and 5

References

1. UK-PBC http://www.uk-pbc.com/about/aboutpbc/. Accessed July 2015
2. Office for National statistics (2013) Population Estimates for UK, England and Wales, Scotland and Northern Ireland, Mid-2013. Accessed July 2015
3. Office for National Statistics (2013) Mortality Statistics: Deaths Registered in England and Wales. Accessed February 2015
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NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Single Technology Appraisal

Obeticholic acid for treating primary biliary cirrhosis [ID785]

Matrix of consultees and commentators

Consultees	**Commentators (no right to submit or appeal)**
Company Intercept Pharmaceuticals (obeticholic acid) Patient/carer group • Addenbrookes Liver Transplant Association • Black Health Agency • British Liver Trust • Liver4Life • Muslim Council of Britain • South Asian Health Foundation • Specialised Healthcare Alliance • The PBC Foundation Professional groups • British Association for the Study of the Liver • British Geriatrics Society • British Liver Nurses Forum • British Society of Gastroenterology • CORE – Digestive Disorders Foundation • ESPRIT • Royal College of Anaesthetists • Royal College of General Practitioners • Royal College of Nursing • Royal College of Pathologists • Royal College of Physicians • Royal College of Surgeons • Royal Pharmaceutical Society • Royal Society of Medicine • UK Clinical Pharmacy Association Others • Department of Health • NHS England • NHS Herts Valleys CCG (West)	General • Allied Health Professionals Federation • Board of Community Health Councils in Wales • British National Formulary • Care Quality Commission • Department of Health, Social Services and Public Safety for Northern Ireland • Healthcare Improvement Scotland • Medicines and Healthcare Products Regulatory Agency • National Association of Primary Care • National Pharmacy Association • NHS Alliance • NHS Commercial Medicines Unit • NHS Confederation • Scottish Medicines Consortium • Welsh Association of Gastroenterology and Endoscopy (WAGE) Comparator companies • AAH Pharmaceuticals (bezafibrate, ciprofibrate, gemfibrozil) • Actavis UK (bezafibrate, • Alliance Healthcare (bezafibrate, ciprofibrate, ,gemfibrozil) • DE Pharmaceuticals (bezafibrate, ciprofibrate, gemfibrozil) • Dr Falk Pharma UK (ursodeoxycholic acid) • Mawdsley Brooks& Company (bezafibrate, gemfibrozil) • Mylan (bezafibrate) • Norgine (ursodeoxycholic acid) • Pfizer (gemfibrozil) • Phoenix Healthcare Distribution (bezafibrate, ciprofibrate, gemfibrozil) • Primegen (ciprofibrate)

Consultees	**Commentators (no right to submit or appeal)**
• NHS North Norfolk CCG • Welsh Government	• Sandoz (bezafibrate) • Sigma Pharmaceuticals (bezafibrate, ciprofibrate, gemfibrozil) • Teva UK (bezafibrate, gemfibrozil) • Tillomed Laboratories (gemfibrozil) • Waymade Healthcare (bezafibrate, gemfibrozil) • Wockhardt UK (ursodeoxycholic acid) <u>Relevant research groups</u> • Cochrane Hepato-Biliary Group • Foundation for Liver Research • MRC Clinical Trials Unit • National Institute for Health Research <u>Associated Public Health Groups</u> • Public Health England • Public Health Wales

NICE is committed to promoting equality, eliminating unlawful discrimination and fostering good relations between people who share a protected characteristic and those who do share it. Please let us know if we have missed any important organisations from the lists in the matrix, and which organisations we should include that have a particular focus on relevant equality issues.

PTO FOR DEFINITIONS OF CONSULTEES AND COMMENTATORS

Definitions:

Consultees

Organisations that accept an invitation to participate in the appraisal; the company that markets the technology; national professional organisations; national patient organisations; the Department of Health and the Welsh Government and relevant NHS organisations in England.

The company that markets the technology is invited to make an evidence submission, respond to consultations, nominate clinical specialists and has the right to appeal against the Final Appraisal Determination (FAD).

All non-company consultees are invited to submit a statement[1], respond to consultations, nominate clinical specialists or patient experts and have the right to appeal against the Final Appraisal Determination (FAD).

Commentators

Organisations that engage in the appraisal process but that are not asked to prepare an evidence submission or statement, are able to respond to consultations and they receive the FAD for information only, without right of appeal. These organisations are: companies that markets comparator technologies; Healthcare Improvement Scotland; other related research groups where appropriate (for example, the Medical Research Council [MRC], National Cancer Research Institute); other groups (for example, the NHS Confederation, NHS Alliance and NHS Commercial Medicines Unit, and the *British National Formulary*.

All non-company commentators are invited to nominate clinical specialists or patient experts.

[1]Non-company consultees are invited to submit statements relevant to the group they are representing.

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Single technology appraisal (STA)

Biliary cirrhosis (primary) – obeticholic acid [ID785]

Company evidence submission

26th October 2016

Contents

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Abbreviations

AASLD	American Association for the Study of Liver Disease
AB	Abnormal bilirubin
AE	Adverse event
ALD	Alcoholic liver disease
ALP	Alkaline phosphatase
ALT	Alanine aminotransferase
AMA	Anti-mitochondrial antibody
ANCOVA	Analysis of covariance
AST	Aspartate aminotransferase
ATC	Anatomical Therapeutic Chemical
BAS	Bile acid sequestrants
BMI	Body mass index
BNF	British National Formulary
BP	Bodily pain
BSG	British Society of Gastroenterology
CA	Cholic acid
CC	Compensated cirrhosis
CDCA	Chenodeoxycholic acid
CETP	Cholesterol ester transfer protein
CHB	Chronic hepatitis B
CHC	Chronic hepatitis C
CHMP	Committee for Medicinal Products for Human Use
CI	Confidence interval
CK-18	Cytokeratin-18
CLD	Chronic cholestatic liver disease
CLDQ	Chronic liver disease questionnaire
CMH	Cochran-Mantel-Haenszel
CONSORT	Consolidated Standards of Reporting Trials
CRP	C-reactive protein
CSR	Clinical study report
DARE	Database of abstracts of reviews and effects
DC	Decompensated cirrhosis
DCA	Deoxycholic acid

DCC	Decompensated cirrhosis
DEXA	Dual-emission x-ray absorptiometry
DM	Disease management
DSA	Deterministic sensitivity analysis
DSU	Decision Support Unit
EASL	European Association for the Study of Liver
ECDCA	Ethyl-chenodeoxycholic acid
eCRF	Electronic case report form
EE	Efficacy evaluable
ELF	Enhanced liver fibrosis
EMA	European Medicines Agency
EMEA	European Medicines Evaluation Agency
EOT	End of treatment
EU	European Union
FDA	Food and Drug Administration
FGF-19	Fibroblast growth factor-19
FXR	Farnesoid X receptor
GGT	Gamma-glutamyl transferase
GH	General health
GP	General practitioner
HA	Hyaluronic acid
HBV	Hepatitis B virus
HCC	Hepatocellular carcinoma
HCHS	Hospital & Community Health Services
HCV	Hepatitis C virus
HDL	High-density lipoprotein
HDLc	High-density lipoprotein cholesterol
HIV	Human immunodeficiency virus
HRQoL	Health-related quality of life
HUI	Health utility index
ICER	Incremental cost-effectiveness ratio
ICU	Intensive care unit
IL	Interleukin
INR	International standardised ration
IQR	Interquartile range

ITT	Intention-to-treat
IWRS	Interactive web response system
KOL	Key opinion leader
LA	Lysophosphatidic acid
LCA	Lithocholic acid
LCAT	Lecithin-cholesterol acyltransferase
LDL	Low density lipoprotein
LDLc	Low-density lipoprotein cholesterol
LDLT	Living donor liver transplantation
LLN	Lower limit of normal
LP	lipoprotein
LS	Least squares
LT	Liver transplantation
LTSE	Long-term safety extension
LYG	Life years gained
MCID	Minimal clinically important difference
MCS	Mental component summary
MELD	Model for End Stage Liver Disease
MH	Mental health
MRS	Mayo risk score
NB	Normal bilirubin
NCPE	National Centre for Pharmacoeconomics
NHS	National Health Service
OCA	Obeticholic acid
OD	Once daily
OPTN	Organ procurement and transplantation network
PAS	Patient access scheme
PASLU	Patient access schemes liaison unit
PBC	Primary biliary cholangitis/cirrhosis
PCS	Physical component summary
PF	Physical functioning
PK	Pharmacokinetics
PSA	Probabilistic sensitivity analysis
PSC	Primary sclerosing cholangitis
PT	Prothrombin time

PYE	Patient years of exposure
QALY(s)	Quality adjusted life year(s)
RCT	Randomised controlled trial
RE	Role emotional
REML	Restricted maximum likelihood
RMSE	Root mean square error
RP	Role physical
SAE	Serious adverse event
SD	Standard deviation
SE	Standard error
SF	Social functioning
SLR	Systematic literature review
SMC	Scottish Medicines Consortium
SOC	System organ class
SmPC	Summary of product characteristics
SVR	Sustained viral response
TB	Total bilirubin
TE	Transient elastography
TEAE	Treatment-emergent adverse event
TGF	Transforming growth factor
TIMP	Tissue inhibitor of metalloproteinase
TNF	Tumour necrosis factor
TP	Transition probability
UDCA	Ursodeoxycholic acid
ULN	Upper limit of normal
VAS	Visual analogue scale
VLDL	Very low density lipoprotein
VT	Vitality
WADD	Weighted average daily dose

1 Executive summary

Primary biliary cholangitis (PBC), previously known as primary biliary cirrhosis, is a rare, progressive, debilitating autoimmune liver disease that follows an unpredictable course and that, if inadequately controlled, leads to complications (including ascites, varices and portal hypertension), liver transplant, and death. The course of the disease involves bile duct loss, which leads to the accumulation of toxic bile acids in the liver, resulting in inflammation, fibrosis and cirrhosis. There is currently no predictor to indicate which patients will progress slowly or rapidly, although patients with earlier age of onset and/or male sex often have more aggressive disease that is refractory to existing treatment (1).

There are considerable healthcare costs associated with PBC. In 2014/15, there were 707 hospital admissions in England for PBC, 963 consultant episodes, 3,767 bed days, and at least 45 liver transplants (2, 3). The cost of PBC increases with the stage of the disease, with a liver transplant itself reported to cost £64,452 in 2014 (4). Whilst the demand for liver transplantation is increasing, supply is stable. PBC is one of the most frequent indications for liver transplantation in Europe (5, 6), although, due to the rapid decline of PBC patients, once they qualify for inclusion on the transplant waiting list they are more likely to die before transplant than patients with other liver diseases (for example hepatitis C, alcoholic liver disease, and hepatitis B) (7).

PBC is significantly more prevalent in women, with age of diagnosis typically between 30 and 65 years (8). At the point of diagnosis patients will have lived with symptoms of the disease for a median of 5.6 years. In POISE (the pivotal Phase 3 trial for obeticholic acid [OCA]), 91% of patients were female with a mean age of 55.8 years and mean age at diagnosis of 47.3 years. These patients will have spent additional time uncontrolled on ursodeoxycholic acid (UDCA) experiencing disease progression before being eligible for the trial. The majority of patients are of working age in the UK (81% of patients in POISE were <65 years old. Therefore, PBC is also likely to have an impact on societal costs, due to lower productivity and the inability to work. In addition, patients diagnosed at a young age are more likely to have more rapidly progressing disease, which can have a devastating effect on their families.

The current management of PBC focuses on reducing biochemical markers, initially alkaline phosphatase (ALP) levels, and in the more severe stages, bilirubin, in order to minimise the risk of long-term progression (9). Currently, the only licensed treatment for PBC is UDCA, which has been shown to be effective in increasing transplant-free survival (10). However, up to 74% of patients have an inadequate response to, or are unable to tolerate, UDCA (1, 11-14), and there are currently no available treatment options for these patients. Therefore, they are at significantly increased risk of clinical complications, the requirement of liver transplant, hepatocellular carcinoma (HCC), or death (1, 11-13, 15-19).

OCA is a novel, rationally designed drug, targeting the farnesoid X receptor (FXR), which represents a step-change in the treatment of PBC. It is the first treatment to provide a novel, innovative mechanism of action for patients with PBC, and is the first drug to be developed for patients with PBC in nearly 20 years. It is used in combination with UDCA as adjunct therapy in those patients with PBC who have an incomplete response to UDCA, and where ALP is already significantly elevated, to prevent disease progression.

It is also intended to be used as monotherapy in those who are intolerant to UDCA. OCA received orphan drug designation by the EMA for the treatment of PBC in July 2010 (20). FXR activation leads to a reduction in toxic bile acids in the liver by decreasing their synthesis and facilitating their transportation from the liver (21). OCA is a once-daily tablet that has been shown to clinically and statistically significantly reduce the clinically relevant biomarkers (alkaline phosphatase [ALP] and bilirubin), the underlying immune response as indicated by TNF alpha and IgG and downstream indicators of liver damage (hepatocellular transaminases) in patients who have an inadequate response to, or who are intolerant to, UDCA. It has been shown that achieving ALP <1.67x ULN, which equates to 200 U/L, and bilirubin ≤1 mg/dL is the most discriminating algorithm for predicting clinical outcomes such as varices, ascites, death or liver transplantation (17). Therefore, POISE assessed response by looking to demonstrate clinically and statistically meaningful reductions in ALP and bilirubin:

- ALP <1.67x ULN, which equates to 200 U/L, and
- Total bilirubin <ULN, which equates to 20 µmol/L (1.17 mg/dL), and
- A 15% decrease from baseline in ALP so that patients who had only a small change from slightly above 200 U/L at baseline were excluded.

This aggressive responder criteria will mean that patients who experience a clinically relevant improvement may not be classified as a responder as their ALP does not fall below 200 U/L.

In conclusion, there are both high clinical and patient unmet needs in PBC, with no treatment options for patients who have an inadequate response to, or are intolerant to, UDCA. These patients are at increased risk of complications, the requirement of a liver transplant, HCC, and death (1, 11-13, 15-19). OCA provides a novel and innovative treatment option for these patients, showing clinically and statistically significant benefits in terms of reductions in inflammatory markers compared with placebo (with or without UDCA, depending on tolerability). Treatment with OCA should therefore prevent or slow the progression of the disease, providing benefit to the patient as well as avoiding costly downstream outcomes, e.g. ascites, and liver transplantation. OCA provides a long-awaited treatment option for PBC, and is a cost-effective use of NHS resources (see Section 1.4).

1.1 *Statement of the decision problem*

Table 1: The decision problem

	Final scope issued by NICE	Decision problem addressed in the company submission	Rationale if different from the final NICE scope
Population	People with primary biliary cirrhosis† whose disease has an inadequate response to, or who are unable to tolerate, ursodeoxycholic acid	As per scope	Not applicable
Intervention	OCA alone or in combination with UDCA	As per scope	OCA is taken in combination with UDCA for people whose disease has an inadequate response to UDCA, and as monotherapy in people who are unable to tolerate UDCA
Comparator(s)	For people whose disease has an inadequate response to UDCA: • UDCA alone or in combination with fibrates For people who are unable to tolerate UDCA: • Fibrates • No additional treatment	For people whose disease has an inadequate response to UDCA, the following comparators were considered: • UDCA For people who are unable to tolerate UDCA, the following interventions were considered: • Placebo	Fibrates are not licensed in the UK, nor are they standard of care, and they are contraindicated in PBC (22, 23). They are rarely used, with only [redacted] of patients in the UK-PBC cohort having ever taken fibrates for any condition (not necessarily for PBC) (24). Their efficacy is yet to be proven, with only a limited number of studies reporting results for the use of fibrates in PBC (25-29), with the following challenges: • The studies were investigator-initiated and only had small patient numbers • All but one study were conducted in Japanese patients • In addition, there are significant

	Final scope issued by NICE	Decision problem addressed in the company submission	Rationale if different from the final NICE scope
			safety concerns with the use of fibrates in PBC, with one study (28) reporting three deaths in 13 patients in the UDCA + fibrates arm compared with no deaths in 14 patients in the UDCA monotherapy arm. In addition, one patient developed HCC in the fibrates + UDCA arm, compared with none in the UDCA monotherapy arm (28).
Outcomes	The outcome measures to be considered include: • Mortality • Liver function based on markers of liver biochemistry • Symptoms, including pruritus, fatigue and abdominal pain • Time to liver transplantation • PBC-related events, including ascites, varices, encephalopathy and HCC • Adverse effects of treatment • HRQoL	Surrogate efficacy outcomes are included in POISE: • Liver function biomarkers (ALP and bilirubin) • Other biomarkers relevant to PBC (GGT, AST, ALT, FGF-19, CK-18 and bile acids) • Inflammation biomarkers (CRP, TNF-α, TGF-β and IL-6) • Non-invasive evaluations of fibrosis (ELF and FibroScan® TE)	Due to the rare and chronic nature of PBC and the slow progression in most patients, a long-term trial is required to capture clinical outcomes such as mortality, transplant-free survival, and the incidence of complications. The primary outcome measured in POISE related to combined ALP and bilirubin levels, which have both been shown to be strongly correlated with disease prognosis (15, 17, 18). Other biomarkers relevant to PBC, inflammation biomarkers, and non-invasive evaluations of fibrosis have been included to further support changes in disease progression. There is currently a long-term Phase 3b trial ongoing, COBALT (see Section 4.14), that aims to capture clinical outcomes and should support

	Final scope issued by NICE	Decision problem addressed in the company submission	Rationale if different from the final NICE scope
			the longer-term impact of OCA on PBC already shown in POISE.
Economic analysis	The reference case stipulates that the cost effectiveness of treatments should be expressed in terms of incremental cost per quality-adjusted life year. The reference case stipulates that the time horizon for estimating clinical and cost effectiveness should be sufficiently long to reflect any differences in costs or outcomes between the technologies being compared. Costs will be considered from an NHS and personal social services perspective.	As per scope	Not applicable
Subgroups to be considered	Not applicable	Not applicable	Not applicable
Special considerations including issues related to equity or equality	Guidance will only be issued in accordance with the marketing authorisation. Where the wording of the therapeutic indication does not include specific treatment combinations, guidance will be issued only in the context of the evidence that has underpinned the marketing authorisation granted by the regulator.	Equality document	People with PBC face stigma in society because of the negative connotations of the term 'cirrhosis' and the association with alcoholism and drug abuse (30). In addition, PBC is a rare disease affecting mainly women, and it is essential that patients have the same opportunities to gain access to new treatments.

Abbreviations: ALP, alkaline phosphatase; ALT, alanine transaminase; AST, aspartate transaminase; CK-18, cytokeratin-18; CRP, C-reactive protein; ELF, enhanced liver fibrosis; FGF-19, fibroblast growth factor-19; GGT, gamma-glutamyl transpeptidase; HRQol, health-related quality of life; HCC, hepatocellular carcinoma; IL-6, interleukin-6; NHS, National Health Service; NICE, National Institute for Health and Care Excellence; OCA, obeticholic acid; OD, once daily; PBC, primary biliary cholangitis/cirrhosis; TE, transient elastography; TGF; transforming growth factor; TNF, tumour necrosis factor; UDCA, ursodeoxycholic acid.

[†]Note that primary biliary cirrhosis has recently undergone a name change to primary biliary cholangitis. At the time of consultation with NICE, the official name was primary biliary cirrhosis and, as such, this is reflected in this table.

1.2 *Description of the technology being appraised*

Table 2: Technology being appraised

UK approved name and brand name	Obeticholic acid (OCALIVA®)
Marketing authorisation/CE mark status	Awaiting European marketing approval. CHMP positive opinion is expected on 14th October 2016, with EMEA marketing authorisation expected mid-December 2016.
Indications and any restriction(s) as described in the summary of product characteristics	Indication: 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. Contraindications: • Complete biliary obstruction • Hypersensitivity to the active substance or to any of the following excipients: microcrystalline cellulose; sodium starch glycolate (Type A); magnesium stearate; poly(vinyl alcohol), partially hydrolysed (E1203); titanium dioxide (E171); macrogol 3350 (E1521); talc (E553b); iron oxide yellow (E172).
Method of administration and dosage	Provided as a film-coated tablet containing 5 mg or 10 mg OCA. The recommended starting dose is 5 mg taken orally, once daily. Based on the assessment of tolerability after 6 months, the dose should be increased to 10 mg once daily to achieve optimal response.

Abbreviations: CHMP, Committee for Medicinal Products for Human Use; PBC, primary biliary cholangitis; UDCA, ursodeoxycholic acid.

1.3 *Summary of the clinical effectiveness analysis*

The clinical study programme for OCA includes one pivotal Phase 3 study (POISE), which forms the main efficacy evidence for OCA, and two phase 2 studies (and extensions) providing supportive evidence.

The double-blind phase of POISE was a 12-month, international, multicentre, Phase 3, placebo-controlled study with a double-blind, randomised, parallel-group design in subjects aged ≥18 years with PBC who had previously failed treatment with UDCA or are intolerant to UDCA. The study is the largest PBC clinical trial to date, and was designed with input from the UK and global PBC group to assess the efficacy, safety, and tolerability of OCA. The primary efficacy endpoint was achieved.

Treatment with OCA resulted in clinically and statistically significant improvements from placebo as assessed by a composite ALP and total bilirubin endpoint (ALP <1.67x ULN [200 U/L], bilirubin ≤ULN [20 µmol/L] and ≥15% decrease from baseline in ALP). ALP is a key biochemical marker for the progress of PBC, and elevated bilirubin is more indicative of end-stage disease. The reduction of both has been shown to translate into reduced risks of complications, liver transplantation, and death (17). Furthermore, as secondary endpoints, the effect of OCA on several other independent biochemical response criteria (i.e. Paris I, Paris II, Toronto II, and Mayo II), all of which are shown

to correlate with improved prognostic outcomes, were supportive of the potential effect of OCA in inhibiting the progression of PBC and improving clinical outcomes.

Other secondary endpoints, including several biochemical markers of cholestasis, inflammation, hepatobiliary injury, fibrosis, and apoptosis, demonstrated clinically and statistically significant improvements compared with placebo that were sustained during the 12-month period. These improvements in IgM, CRP, and CK-18 values, paralleled by the improvement in liver biochemistry due to FXR-mediated effects on bile acid homeostasis, are further supportive of a beneficial disease-modifying effect of FXR activation over at least a 12-month period.

Subgroup analyses demonstrated that the effect of OCA on achieving the primary composite endpoint and changes in ALP and total bilirubin were independent of age at diagnosis, duration of PBC, and baseline ALP. In general, the baseline and demographic subgroup analyses were consistent with the observed effect in the overall population, in that OCA-treated subjects had more favourable outcomes than subjects receiving placebo. For subjects receiving BAS, efficacy was modestly attenuated in subjects receiving OCA 5 mg but was not affected in subjects receiving OCA 10 mg.

Based on the clinical response and adverse event profile, initiating subjects on OCA 5 mg and titrating to 10 mg is the optimal dosing strategy. For some subjects, the composite endpoint was achieved with 5 mg OCA, however, an additional incremental benefit was gained by titrating to 10 mg OCA in those that failed to achieve an optimal response within 6 months of initiating treatment, and this is therefore the recommended dosing strategy for all patients according to the summary of product characteristics (SmPC). It is important to note that the benefit of up-titrating is not fully captured in POISE, since patients in the titration arm who reached the primary endpoint criteria did not up-titrate at 6 months and therefore did not receive any additional benefit from a higher (10 mg) dose for the second 6 months.

An ongoing long-term safety extension (LTSE) of POISE has shown continuing efficacy of OCA in terms of ALP and bilirubin levels. Evidence from two Phase 2 studies and their LTSEs provide further support for the efficacy of OCA observed in POISE.

OCA was generally well tolerated, with pruritus being the most commonly reported adverse reaction. However, it is important to consider that pruritus is a common side effect of PBC; 63% of patients in POISE had a history of pruritus. Therefore, patients and their clinicians are typically familiar with the condition and its management.

In conclusion, OCA for the treatment of adults with PBC who have had an inadequate response with UDCA or are intolerant to UDCA is an effective and a generally well tolerated treatment option. OCA (5 mg and 10 mg) resulted in clinically and statistically significant improvements in a range of evidence-based disease-related prognostic factors, which is expected to result in a significant reduction in the need for liver transplant and/or death from PBC.

1.4 *Summary of the cost-effectiveness analysis*

Results in this submission are based on the list price of OCA. However, OCA will be offered under a patient access scheme (PAS) and so the results presented in this submission are for guidance only. Results of the economic analyses using the PAS price are presented in the accompanying PAS template, as requested by NICE, and are more reflective of the true cost-effectiveness of OCA.

The model presented for OCA is a decision-analytic model that reports cost-effectiveness in terms of incremental cost per QALY. The model evaluates the economic consequences of OCA 5-10 mg (titrated dose) alone (in the case of UDCA intolerant PBC patients) and adding OCA 5-10 mg OD to 15.4 mg/kg UDCA (in the case of UDCA inadequate responders). In other words, the model examines the cost-effectiveness of OCA titration versus placebo in UDCA intolerant patients, and OCA + UDCA titration versus UDCA monotherapy in UDCA tolerant patients.

Model inputs for health utilities are based on utility scores derived from literature. Where PBC-specific utility values were not available, HBV/HCV utility values were used instead; following key opinion leader interviews, utility values for the more severe health states (i.e. decompensated cirrhosis, pre-transplant and post-transplant) had a [redacted] decrement applied to them to reflect the worse outcomes and accelerated disease progression of PBC patients compared to HBV/HCV patients.

The base case results for UDCA-intolerant patients using the list price are shown in Table 3, and for UDCA inadequate responders in Table 4. Results using the PAS are presented in the accompanying PAS template. In addition, patients treated with OCA were found to have an 84% lower chance of undergoing liver transplant compared with patients treated with UDCA.

Table 3: Incremental cost-effectiveness results: UDCA-intolerant patients

Technologies	Total			Incremental			ICER (£)	ICER (£)
	Costs (£)	LYG	QALYs	Costs (£)	LYG	QALYs	versus baseline	incremental
No treatment (Placebo)	£103,233	11.30	6.61	-	-	-	-	-
OCA titration	[redacted]	16.65	13.52	[redacted]	5.35	6.91	[redacted]	[redacted]

Abbreviations: ICER, incremental cost-effectiveness ratio; LYG, life-years gained; QALYs, quality-adjusted life years; OCA, obeticholic acid.

Table 4: Incremental cost-effectiveness results: UDCA inadequate responder patients

Technologies	Total			Incremental			ICER (£)	ICER (£)
	Costs (£)	LYG	QALYs	Costs (£)	LYG	QALYs	versus baseline	incremental
UDCA + Placebo	£96,977	12.35	7.85	-	-	-	-	-
OCA titration + UDCA	[redacted]	16.75	13.64	[redacted]	4.40	5.79	[redacted]	[redacted]

Abbreviations: ICER, incremental cost-effectiveness ratio; LYG, life-years gained; QALYs, quality-adjusted life years; OCA, obeticholic acid; UDCA, ursodeoxycholic acid.

2 The technology

Summary

- OCA is a novel, rationally designed drug targeting the FXR receptor
- It is the first treatment to provide a novel, innovative mechanism of action for patients with PBC, and is the first drug to be developed for PBC in nearly 20 years. It provides the first effective therapy for patients who have an inadequate response to UDCA who would otherwise face progression of their disease
- FXR activation leads to a reduction of up to 60% in the levels of toxic bile acids in the liver by decreasing their synthesis and facilitating their transportation from the liver
- OCA demonstrates clinically and statistically meaningful reductions in ALP and bilirubin, the main accepted markers of response in PBC
- In addition, FXR mediates other anti-inflammatory and anti-fibrotic pathways, which are expected to prevent injury to hepatocytes, improve liver function, and reduce the risk of, delay, and/or prevent the need for liver transplant in a cholestatic liver disease such as PBC
- OCA is a once-daily tablet that has been shown to clinically and statistically significantly reduce the most important biomarkers of PBC (alkaline phosphatase [ALP] and bilirubin)
- OCA received orphan drug designation by the EMA in July 2010

2.1 *Description of the technology*

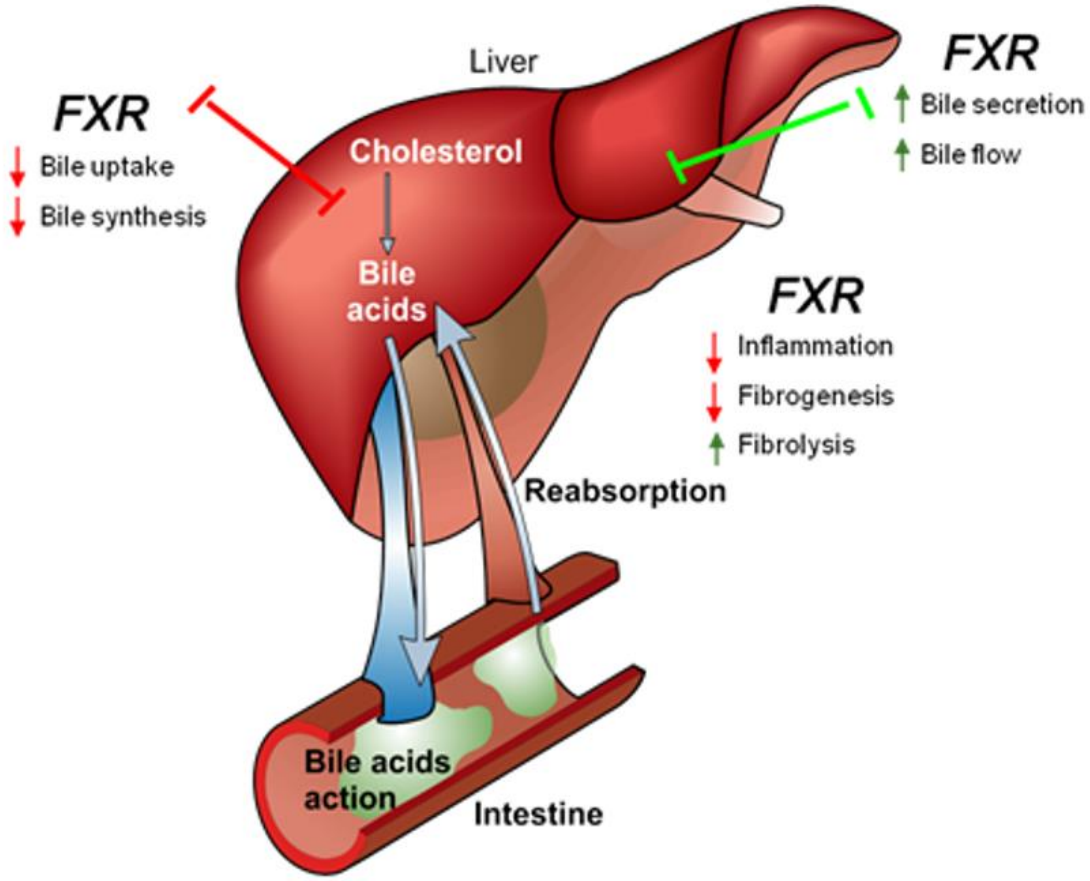
Brand name: OCALIVA®

UK approved name: Obeticholic acid

Therapeutic class: Bile acid preparations (ATC code (A05AA04)

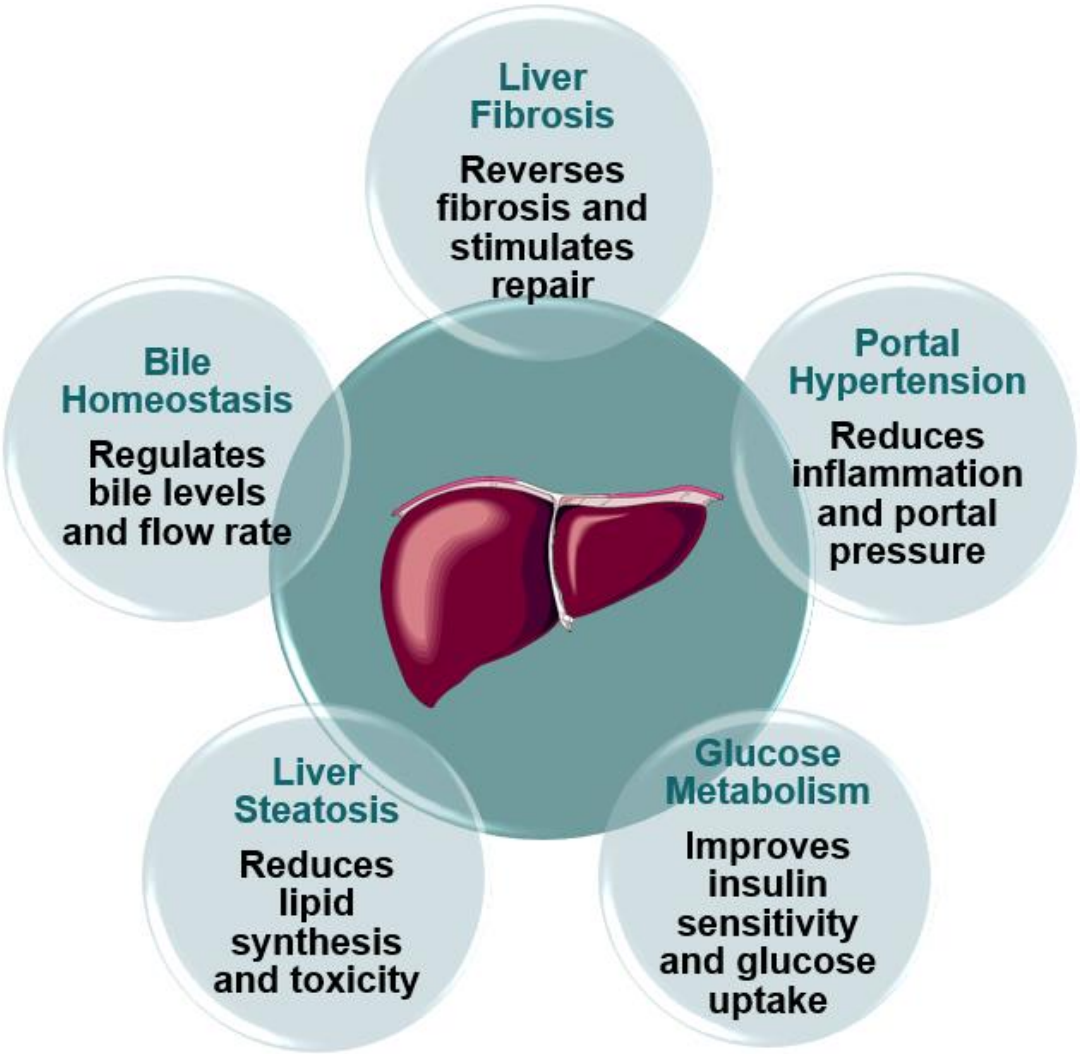
Mechanism of action: OCA is a novel selective and potent agonist for the farnesoid X receptor (FXR), a nuclear receptor expressed at high levels in the liver and intestine. FXR is a key regulator of bile acid, inflammatory, fibrotic, and metabolic pathways (see Figure 1 and Figure 2). OCA reduces the accumulation of bile acids in the liver and protects hepatocytes from bile acid toxicity by activating FXR. This decreases the concentration of bile acids by reducing their synthesis from cholesterol and by facilitating their transport out of hepatocytes (21). In addition, FXR mediates other anti-inflammatory and anti-fibrotic pathways (31).

Figure 1: FXR is a nuclear receptor expressed in the liver



Abbreviations: FXR, farnesoid X receptor.

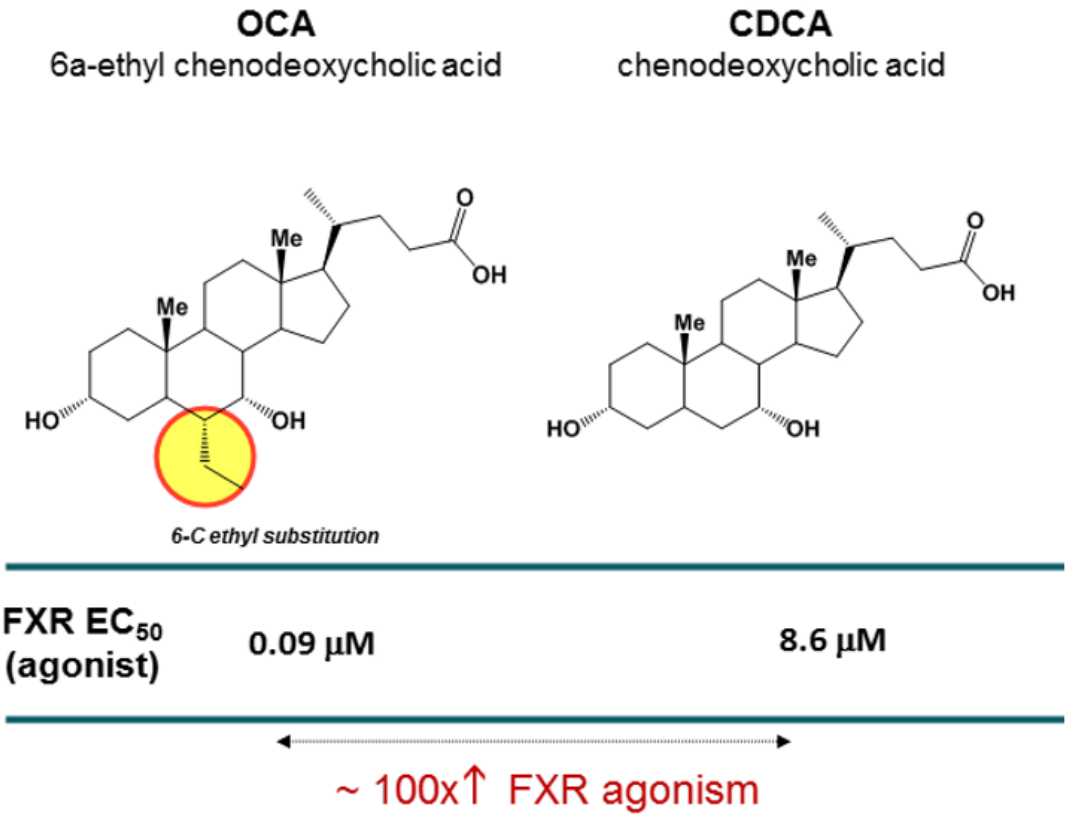
Figure 2: FXR regulation of biological pathways



Abbreviations: FXR, farnesoid X receptor.

Chenodeoxycholic acid (CDCA) is a natural bile acid that was identified as the most active physiological ligand for FXR. In structure-activity studies, it was found that the introduction of an alkyl group at the 6α position increased the activity and specificity of CDCA to FXR (32). A series of alkylated bile acid analogues were subsequently designed and studied, and it was found that the most highly potent and specific FXR agonist was OCA, which includes an ethyl group at the C6α position (Figure 3) and has approximately 100 times the potency of CDCA.

Figure 3: The molecular structure of OCA and CDCA



Abbreviations: CDCA, chenodeoxycholic acid; EC_{50}, half-maximal effective concentration; FXR, farnesoid X receptor; OCA, obeticholic acid.

In addition to its effects on bile acids, OCA has hepatoprotective effects, including its choleretic, anti-inflammatory, and anti-fibrotic properties. These are expected to prevent injury to hepatocytes, improve liver function, and reduce, delay, and/or prevent the need for liver transplant in a cholestatic liver disease such as PBC. OCA is the first new and effective treatment for PBC in almost 20 years.

2.2 *Marketing authorisation/CE marking and health technology assessment*

2.2.1 *Marketing authorisation/CE marking*

For the indication covered in this submission:

- Regulatory submission to EMA: June 2015
- CHMP positive opinion: expected 14th October 2016
- Marketing authorisation: expected mid-December 2016

2.2.2 *(Anticipated) indication(s) in the UK*

OCA is anticipated to be indicated 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.

2.2.3 *(Anticipated) restrictions or contraindications*

2.2.3.1 Contraindications

The contraindications listed in the draft SmPC are:

- Complete biliary obstruction
- Hypersensitivity to the active substance(s) or to any of the following excipients: microcrystalline cellulose; sodium starch glycolate (Type A); magnesium stearate; poly(vinyl alcohol), partially hydrolysed (E1203); titanium dioxide (E171); macrogol 3350 (E1521); talc (E553b); iron oxide yellow (E172).

2.2.3.2 Special warnings and precautions

Liver-related adverse events

Elevations in alanine aminotransferase (ALT) and aspartate aminotransferase (AST) have been observed in patients taking OCA. Clinical signs and symptoms of hepatic decompensation have also been observed. These events have occurred as early as within the first month of treatment. Liver-related adverse events have primarily been observed at doses higher than the maximum recommended dose of 10 mg once daily. Patients should be monitored during treatment with OCA for elevations in liver biochemical tests and for the development of liver-related adverse reactions.

Severe pruritus

Severe pruritus was reported in 23% of patients whose starting dose was OCA 10 mg once daily, 19% of patients on OCA titration (starting dose of 5 mg with up-titration to 10 mg) and in 7% of placebo patients. The median time to onset of severe pruritus was 11 days for patients on OCA 10 mg, 158 days for patients who were titrated at 6 months, and 75 days for patients in the arm that did not receive OCA. Management strategies include the addition of bile acid sequestrants or antihistamines, dose reduction, reduced dosing frequency, and/or temporary dose interruption (see Section 2.3).

2.2.4 *SmPC*

The draft SmPC is provided in Appendix 1.

2.2.5 *(Draft) assessment report*

The draft assessment report is currently not available.

2.2.6 *Main issues discussed by regulatory authorities*

The draft assessment report is currently not available.

2.2.7 *Anticipated date of availability in the UK*

OCA will be available in the UK from December 2016 and launched in January 2017.

2.2.8 *Regulatory approval outside the UK*

The US Food and Drug Administration (FDA) granted accelerated approval of OCA for the treatment of PBC in combination with UDCA in adults with an inadequate response to UDCA, or as a single therapy in adults unable to tolerate UDCA on 27 May 2016.

2.2.9 *Ongoing HTAs in the rest of the UK*

Submission to the SMC and the NCPE are anticipated to be made in Q4, 2016.

2.3 *Administration and costs of the technology*

The administration and costs of the technology are summarised in Table 5.

Table 5: Costs of the technology being appraised

	Information	Source
Pharmaceutical formulation	Film-coated tablet, each containing 5 mg (round tablet) or 10 mg (triangular tablet) of OCA. Yellow tablet debossed with INT on one side and 5 or 10 on the opposite side (representing 5 mg and 10 mg variations, respectively).	SmPC (21)
Acquisition cost (excluding VAT)†	List price: • OCA 5 mg, pack of 30 tablets: £2,384.04 • OCA 10 mg, pack of 30 tablets: £2,384.04 • This corresponds to a price per year of £29,005.78 (with either 5 mg or 10 mg being taken once daily)	
Method of administration	The tablet should be taken orally with or without food.	SmPC (21)
Doses	Each film-coated tablet contains either 5 mg or 10 mg of OCA.	SmPC (21)
Dosing frequency	The recommended starting dose is 5 mg OD. Based on the assessment of tolerability after 6 months, the dose should be increased to 10 mg OD to achieve optimal response.	SmPC (21)
Average length of a course of treatment	Patients should continue to take OCA for as long as the patient continues to benefit from treatment.	
Average cost of a course of treatment	Not applicable – patients are expected to take the treatment continuously	
Anticipated average interval between courses of treatments	Not applicable – the treatment is a once daily dose.	

	Information	Source
Anticipated number of repeat courses of treatments	Not applicable – patients are expected to take the treatment continuously until they have stopped responding.	

Dose adjustments	The recommended starting dose is 5 mg OD. Based on the assessment of tolerability after 6 months, the dose should be increased to 10 mg OD to achieve optimal response.
	For patients experiencing severe intolerability due to pruritus, consider one of the following:
	• Reducing the dosage of OCA to:
	  ○ 5 mg every other day, for patients intolerant to 5 mg OD
	  ○ 5 mg OD, for patients intolerant to 10 mg OD
	• Temporarily interrupting OCA dosing for up to 2 weeks followed by re-starting at a reduced dosage
	• Continue to increase the dosage to 10 mg once daily, as tolerated, to achieve optimal response
	• Consider discontinuing treatment with OCA for patients who continue to experience persistent intolerable pruritus.
	For patients with hepatic impairment:
	• The recommended starting dosage for moderate (Child-Pugh Class B) and severe (Child-Pugh Class C) hepatic impairment is 5 mg once weekly
	• If an adequate reduction in alkaline phosphatase and/or total bilirubin has not been achieved after 3 months of OCA 5 mg once weekly, and the patient is tolerating the medicinal product, the dose of OCA should be increased to 5 mg twice weekly (at least 3 days apart) and subsequently to 10 mg twice weekly (at least 3 days apart) depending on response and tolerability
	• No dose adjustment is needed for mild hepatic impairment (Child-Pugh Class A).
		SmPC (21)

Anticipated care setting	Secondary care.	

Abbreviations: OCA, obeticholic acid; OD, once daily; SmPC, summary of product characteristics; UDCA, ursodeoxycholic acid.

2.3.1 *Patient access scheme*

For the purpose of this submission, Intercept have submitted an accompanying PAS template, as requested by NICE, with a proposed PAS price for OCA. As such, the results of the economic analysis presented in this submission use the list price for OCA, and are provided for illustrative purposes only to provide contextual results for the cost-effectiveness. The economic analyses using the PAS price are more reflective of the true cost-effectiveness of OCA.

2.4 *Changes in service provision and management*

2.4.1 *Additional tests or investigations*

No additional tests or investigations are required for OCA treatment.

2.4.2 *Main resource use to the NHS associated with the technology*

OCA treatment will be initiated by specialists in the treatment of PBC.

2.4.3 *Additional infrastructure requirements*

No additional infrastructure will be required to facilitate treatment with OCA.

2.4.4 *Patient monitoring requirements*

Patients will be required to undergo a consultation 6 months after treatment initiation to assess tolerability and determine if the dose should be increased to 10 mg to achieve optimal response.

2.4.5 *Concomitant therapies*

OCA is indicated for the treatment of PBC in combination with UDCA in adult patients with an inadequate response to, or intolerant to, UDCA. No dose adjustment of UDCA is required.

Concomitant medication used to treat pruritus associated with PBC is often required. Guidelines from the European Association for the Study of the Liver (33) and the American Association for the Study of Liver Diseases (34) both have the same recommendations for the management of pruritus. Treatment with cholestyramine, a bile acid sequestrant, should be initiated as first-line therapy. A dose of 4 g up to four times daily is recommended, with doses spaced at least 4 hours apart from the time of administration of UDCA. For patients that do not benefit from cholestyramine treatment or who are intolerant to therapy, rifampicin should be taken as second-line treatment, at 150–600 mg daily. As third-line treatment for patients who do not benefit from or are intolerant to rifampicin, naltrexone, an oral opiate antagonist, should be started at 25 mg daily, increasing to 50 mg. The final treatment option for pruritus is sertraline (75–100 mg daily), after which invasive physical approaches, such as extracorporeal albumin dialysis, plasmapheresis and bile duct drainage, or liver transplantation should be considered.

The draft BSG/UK-PBC guidelines (35) include similar recommendations for the management of pruritus. Cholestyramine 4–16 g per day (as tolerated) is recommended as first-line treatment taken 2–4 hours before or after UDCA; [redacted].

[redacted] Rifampicin 300–600 mg per day should be taken as second-line therapy, with oral naltrexone 50 mg per day or parenteral naloxone as third-line treatment. Care should be taken with rifampicin to monitor hepatotoxicity, and naltrexone should be titrated slowly to avoid opiate withdrawal-like symptoms. Gabapentin and the selective serotonin reuptake inhibitor sertraline are also used; however, it is noted that a small trial with gabapentin failed to show benefit over placebo (37), and further evaluation is recommended.

Another common symptom of fatigue, experienced by up to 78% of patients, has been shown to improve with treatment with modafinil at a dose of 100–200 mg/day, although the EASL and AASLD do not recommend therapy for fatigue resulting from PBC (33, 34). The draft BSG/UK-PBC guidelines (35) recommending treating direct contributing factors, such as nocturnal pruritus, associated autoimmune disease and age-related conditions, modifying exacerbating processes, such as depression, autonomic dysfunction and sleep disturbance, as well as assisting with lifestyle adjustments, coping mechanisms and support. Modafinil is mentioned as a possible treatment for severe daytime somnolence.

2.5 *Innovation*

PBC is a rare disease with high clinical and patient unmet need with no new drugs developed in nearly 20 years. OCA is a rationally designed FXR agonist that is the first to provide a novel, innovative therapy for patients with PBC. There has been a long scientific history of in vitro and in vivo studies of the FXR axis, and OCA has finally provided an opportunity to use this mechanism of action to benefit patients with no other currently available treatment options. OCA received orphan drug designation by the EMA for the treatment of PBC in July 2010 (20). Intercept is currently pursuing a Promising Innovative Medicines (PIM) application for current and future indications for OCA.

There is a large unmet need in the area of PBC to provide a therapy for patients who have an inadequate response to or are intolerant to UDCA (up to 74% of UDCA-treated patients with PBC have a sub-optimal or absent response and are at significantly increased risk of clinical complications, the requirement of a liver transplant, and death (1, 11-14)). Patients who do not respond to or are intolerant to UDCA and show clear progression must live with the knowledge that their health is deteriorating and that their only treatment option is a liver transplant at some point in the future. Living with this knowledge, the fear of complications associated with liver transplant, and the uncertainty surrounding whether a donor liver will be available, are all likely to have a substantial detriment on mental health and quality of life. In addition, PBC progresses extremely rapidly in the latter stages of the disease, and so transplantation is sometimes not possible in time, since once patients are unwell enough to qualify for inclusion on the transplant list, it is often too late.

A recent study of a US database found that 16.5% of patients with PBC died while on the liver transplant waiting list, and 8% were removed from the list due to being too ill (7). It was also found that patients with PBC were more likely to die on the transplant waiting list than patients with other liver diseases, such as hepatitis C, alcoholic liver disease,

and hepatitis B (7). The organ donation and transplantation activity report for the UK states that only 51% of patients on the liver transplant list received a transplant between 1 April 2015 and 31 March 2016, while 5% died and 10% were removed from the list (38). In the economic analysis in Section 5, patients are only removed from the transplant waiting list if they die, so removing patients who are too ill is not captured in the health-related quality of life calculations. In addition, PBC patients are disadvantaged when it comes to allocating donor livers for transplant, since the current method for prioritising patients is based on the UK Model for End Stage Liver Disease (UKELD) score, which doesn't accurately predict the survival of patients with PBC (14). Even after transplant, up to 43% of patients will have a recurrence of PBC within 15 years (39) and only 8% of patients return to work (14). OCA has the potential to make a substantial and meaningful improvement in the quality and quantity of life for patients with PBC by providing an alternative or additional efficacious treatment option that will reduce the risk of, delay, or prevent the need for liver transplant. Another aspect of PBC that has a significant detrimental impact on a patient's quality of life is fatigue, which can lead to social isolation (35), since patients find it more difficult to lead a normal active life. This can affect both the patient's mental and physical health.

OCA offers a unique therapeutic modality, providing both hepatoprotective effects and potent and selective FXR-mediated effects, to patients who are currently at continued risk of hepatocellular carcinoma (HCC), fibrosis, cirrhosis and progression to liver transplantation or death. FXR activation not only reduces bile acid synthesis and promotes choleresis, but also mediates other anti-inflammatory and anti-fibrotic pathways. Recent evidence has emerged to suggest that inflammation in PBC may result in the senescence of bile duct epithelial cells, which show very slow or no division and may contribute to further injury and the irreversible loss of bile duct (40). Therefore, it is possible that the anti-inflammatory effects of OCA may also contribute to the prevention of bile duct loss.

OCA represents a step-change in the treatment of PBC. There are currently no drugs other than UDCA approved for this disease, and no drugs that are licensed or effective in this setting (for patients who do not have an adequate response to, or who are intolerant to, UDCA). Given the lack of emerging therapeutic options in the last 20 years, other treatments have been trialled for use in PBC, including budesonide and fibrates (which are contraindicated in PBC (22, 23)). However, limited efficacy has been observed in these other treatments.

OCA has been shown to be both clinically effective and to have a favourable safety and tolerability profile. In addition, it is likely that the clinical benefit of OCA is underestimated in POISE (a Phase 3 trial in OCA described in Section 4), since the trial design dictated that patients in the titration group were not up-titrated from 5 mg once daily at 6 months if they met the trial primary endpoint (ALP <1.67x ULN [equivalent to 200 U/L], total bilirubin ≤ULN [equivalent to 20 µmol/L], and ALP decrease ≥15% from baseline). In clinical practice, the up-titration of these patients to 10 mg based on tolerability to achieve optimal response would likely produce further benefit by generating further reductions in ALP and bilirubin levels.

3 Health condition and position of the technology in the treatment pathway

Summary

- PBC is a rare, progressive, debilitating autoimmune liver disease that follows an unpredictable course and that, if inadequately controlled, leads to complications (including ascites, varices and portal hypertension), liver transplant, and death
  - The course of this ductopenic disease involves bile duct loss, which leads to the accumulation of toxic bile acids in the liver, resulting in inflammation, fibrosis and cirrhosis
  - Unlike inflammatory liver diseases (such as hepatitis), PBC can progress extremely rapidly in the latter stages of the disease, and so transplantation is sometimes not possible as patients may be too unwell
- There are considerable healthcare costs associated with PBC
  - In 2014/15 in England for PBC there were:
    - 707 hospital admissions
    - 963 consultant episodes
    - 3,767 bed days
    - 45 liver transplants
  - The cost of PBC increases with the stage of disease
    - Liver transplant was reported to cost £64,452 in 2014
- PBC is significantly more prevalent in women, with age of diagnosis typically between 30 and 65 years
  - In POISE (the pivotal Phase 3 trial for obeticholic acid [OCA] described in Section 4), 91% of patients were female, with a mean age of 55.8 years
    - This is of working age in the UK, and therefore PBC is likely to have an impact on societal costs
  - Patients diagnosed at a young age are more likely to have rapidly progressing disease
    - This can have a devastating effect on the wellbeing of families
- Current management of PBC focuses on reducing ALP levels
  - The only licensed treatment for PBC is ursodeoxycholic acid (UDCA)
  - However, up to 74% of patients have an incomplete response to UDCA, and there are currently no available licensed or effective treatment options for these patients
  - Patients who have an inadequate response to UDCA are at significantly increased risk of clinical complications, the requirement of liver transplant, HCC, or death

3.1 *Disease overview*

Primary biliary cholangitis (PBC), recently renamed from primary biliary cirrhosis, is a rare, progressive, autoimmune, non-viral disease of the liver that gradually destroys the interlobular bile ducts. This causes an accumulation of cytotoxic bile acids in the liver, which leads to inflammation, liver fibrosis, cirrhosis, and ultimately liver failure. Complications of PBC include portal hypertension, ascites, peripheral oedema, bleeding varices, osteoporosis, and hepatocellular carcinoma (HCC). The final stages of PBC – cirrhosis and hepatic decompensation – is terminal unless a liver transplant is performed.

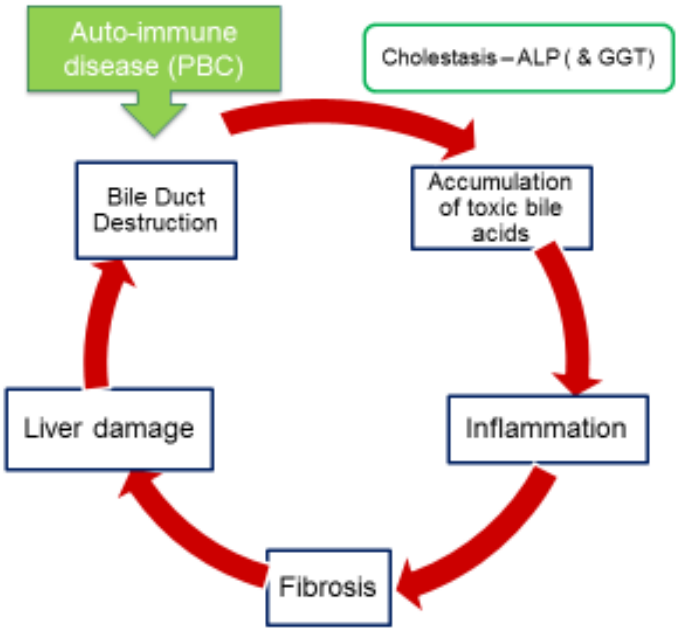
Liver transplant is a major operation that carries a risk of rejection and potentially serious complications, and even after transplant, up to 43% of patients will have a recurrence of PBC within 15 years (41). Whilst liver failure is the usual cause of death in most patients, other causes include a bleed from the oesophagus or stomach and hepatocellular carcinoma.

The destructive cycle of PBC is initiated by an immune response that results in inflammation targeting the intrahepatic bile ducts. As the disease progresses, the liver suffers from bile duct loss (ductopenia), leading to the impairment of bile flow from the liver to the intestine, resulting in increased hepatocellular bile acid concentrations (cholestasis) (42). Bile acids are natural detergents, and abnormally elevated hepatocellular concentrations are damaging to the liver, leading to inflammation, fibrosis and liver damage, which in turn causes further bile duct loss. Eventually PBC leads to cirrhosis and hepatic decompensation.

The serologic hallmark of PBC is the presence of anti-mitochondrial antibodies (AMA), which are present in 90–95% of patients with PBC but less than 1% of healthy controls (34). The course of the disease follows a cholestatic pattern, with rising levels of alkaline phosphatase (ALP) and elevated serum bilirubin in the late stages of the disease.

The destructive cycle of PBC is shown in Figure 4.

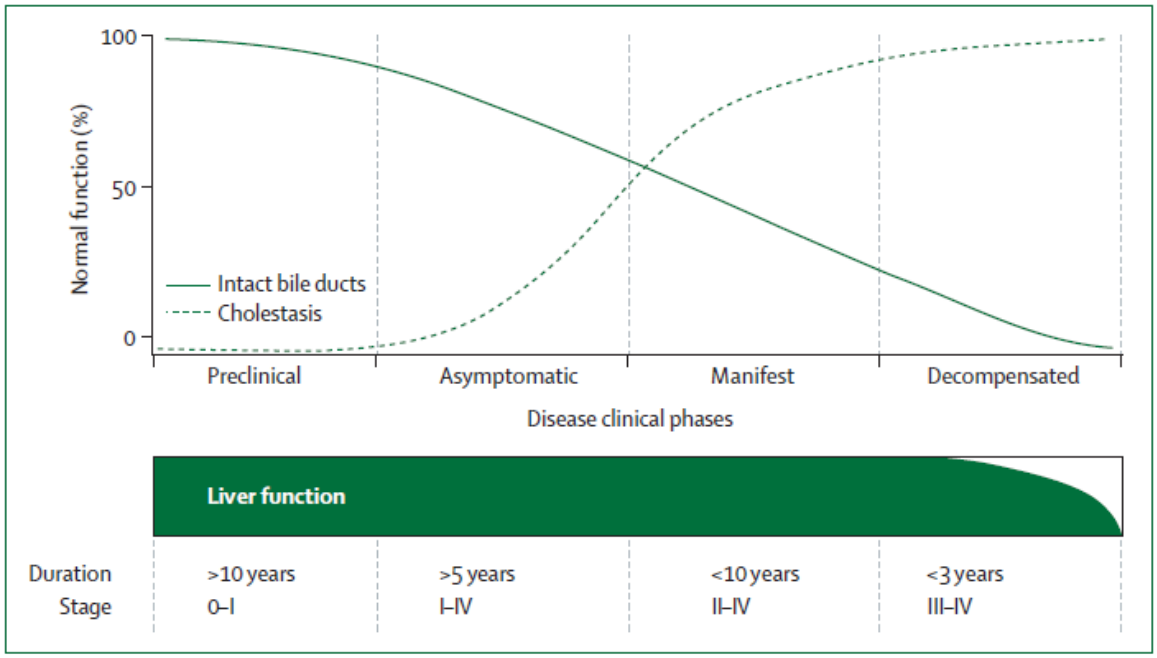
Figure 4: The destructive cycle of PBC



Abbreviations: ALP, alkaline phosphatase; GGT, gamma-glutamyl transpeptidase; PBC, primary biliary cholangitis/cirrhosis.

On an individual basis, the course of the disease is unpredictable and its prognosis varies greatly (43), and there is currently no predictor to indicate which patients will progress slowly or rapidly, although patients with earlier age of onset and/or of male sex often have more aggressive disease that is refractory to existing treatment (1). Figure 5 shows the pattern of disease for PBC.

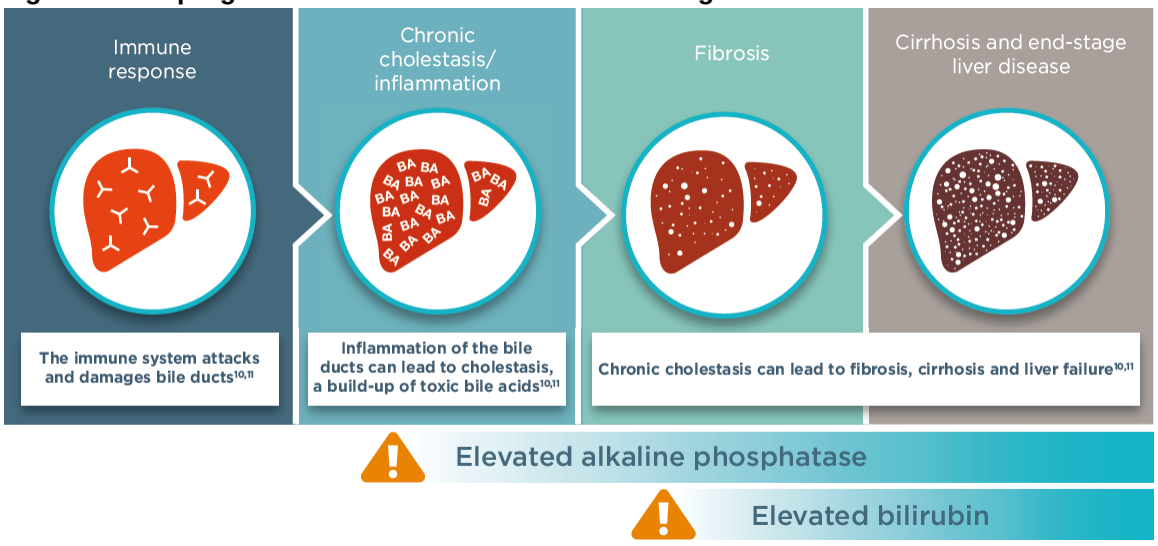
Figure 5: Pattern of ductopenia and cholestasis in PBC



Abbreviations: PBC, primary biliary cholangitis.
Source: Selmi 2011 (44).

The presence of AMA and elevated ALP levels are two early characteristic markers of PBC, with concurrent hepatocellular damage (inflammation) resulting in increased levels of AST, ALT, and GGT (34, 42, 45). It is important to treat patients when their ALP levels >1.67x ULN, equivalent to 200 U/L. An increase in serum bilirubin is detected only when significant liver damage has occurred, with a sharp increase occurring in the terminal phase (45, 46). Therefore, a rise in bilirubin to as low as 0.5x ULN, is a significant change in the course of the disease (47). An overview of disease progression and the associated changes in biochemical markers is shown in Figure 6.

Figure 6: The progression of PBC and associated changes in biochemical markers



European guidelines from EASL outline the following diagnostic criteria for PBC (33):

- Biochemical evidence of cholestasis based on ALP elevation for ≥6 months; and
- Positive AMA titre (≥1:40) in serum or if AMA are absent, antibodies against AMA-M2 (anti-PDC-E2) and/or PBC-specific antibodies (anti-Sp100 and anti Gp210); or
- In the absence of PBC antibodies, liver biopsy consistent with PBC

PBC can be diagnosed providing two of the above three criteria are met, typically ALP and AMA. A liver biopsy can be used to further substantiate the diagnosis if needed.

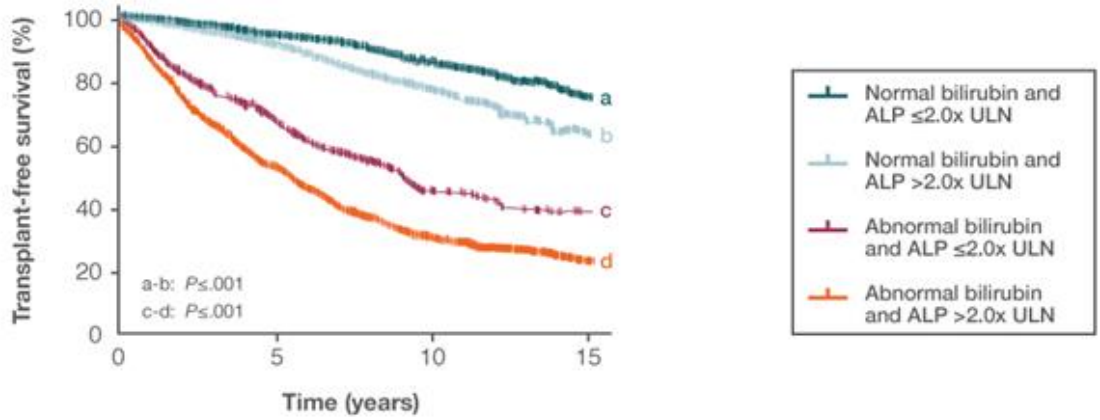
The more recent draft BSG/UK-PBC guidelines (35) assess PBC by:

- Cholestatic liver biochemistry (elevation in serum ALP and GGT; elevation in bilirubin and fall in serum albumin are features of advanced disease and are important prognostic markers)
- AMA or other PBC-specific autoantibody at a titre of >1/40 (there is evidence to suggest that PBC-linked antinuclear antibody [ANA] may be associated with more rapidly progressive disease and disease that is less responsive to UDCA therapy)
- Diagnostic or supportive liver histology.

The presence of all three of these factors indicates definite PBC, whereas two out of the three indicates the presence of probable PBC.

In addition, serum ALP along with other biochemical parameters such as bilirubin are used to manage patients, test the efficacy of novel therapies in clinical studies, and gauge the risk of long-term adverse clinical outcomes (17, 48). Analysis from a large research group (the Global PBC study group) shows that in patients with PBC, ALP and bilirubin levels strongly correlate with death and liver transplantation, with a combination of both variables improving prognostic prediction for patients (15). The lower the ALP and bilirubin levels, the better the transplant-free survival, as shown in Figure 7.

Figure 7: Bilirubin and ALP at 1-year follow-up



Abbreviations: ALP, alkaline phosphatase; ULN, upper limit of normal.
Source: Lammers et al, 2014 (15).

The estimated prevalence of PBC in the UK is approximately 3.9 per 10,000 population (46), equating to approximately 19,175 people in England (49) and making it a rare disease. The incidence of PBC is 0.58 per 10,000 population (50). Approximately 90% of people with the condition are women, and age of diagnosis is typically between 30 and

65 years (8). Whilst the cause of the disease is not known, genetic predispositions and environmental factors (exposure to chemicals) have been described (42, 51, 52).

Approximately 60–80% of patients with PBC are asymptomatic at diagnosis (53). The diagnosis of PBC in asymptomatic patients is usually established after the chance finding of an elevated ALP level during the course of an unrelated illness (43, 53).

There is an urgency to diagnose and treat patients early in the course of the disease to prevent/slow progression and to avoid/delay the latter stage complications of PBC. When treatment is delayed until PBC has progressed, survival is significantly worse than in the general population. In a Dutch prospective cohort study (13), it was found that survival for patients with early initiation of treatment (with UDCA) was comparable to the survival of the overall Dutch population (p=0.254). However, for patients with moderately advanced PBC before treatment initiation, survival was significantly worse (p<0.001). In addition, an analysis (10) combining individual data from three studies in which patients were either treated for 4 years (with UDCA), or received placebo for 2 years and UDCA for the following 2 years, showed that the probability of survival free of liver transplantation was significantly greater in the patients treated for 4 years (p<0.001; relative risk 1.92; 95% CI 1.30, 2.82).

The most common symptoms of PBC are pruritus and fatigue. The severity of cholestatic pruritus is not related to the prognosis or severity of the disease (48, 54, 55). Pruritus frequently subsides spontaneously when cirrhosis and hepatic decompensation develop, suggesting the pruritogen is synthesised in the liver (56, 57). Neither the exact pruritogen nor the underlying mechanisms for the cause of cholestatic pruritus have been completely elucidated (58). Fatigue, which can be severe, is related to autonomic dysfunction in the brainstem (59). This study also showed that fatigue was an independent predictor of mortality, particularly cardiac death.

3.2 *Burden to patients, carers and society*

PBC has a substantial detrimental impact on quality of life, and HRQoL impairment is correlated with the severity of the disease (60-65). In a study of 2,353 patients in the UK (54), 35% reported impairment of HRQoL compared with 6% of healthy controls (p<0.001), and 46% rated their overall health as ‘fair’ or ‘poor’ compared with 15% of healthy controls (p<0.0001).

Physical quality of life scores have been shown to be consistently lower in patients with PBC compared with the general population (64, 66-69), as measured by the SF-36, a widely used, validated, 36-item patient-reported survey of patient health (Table 6). The differences between patients with PBC and the general population were found to be statistically significant and clinically important, as measured by a minimal clinically important difference (MCID) of 5 points (70).

Table 6: SF-36 PCS scores in the PBC population and the general population

	PBC population		General population		
Study	**Mean**	**SD**	**Mean**	**SD**	**Significance**
Younossi et al (2000)	39	Not stated	50	Not stated	Not stated

Sogolow et al (2008)	39	9.61	47	11.18	p<0.05
Montagnese et al (2010)	41	31	47	9	p<0.0001
Montagnese et al (2013)	38.61	9.61	46.79	11.18	p<0.0001
Lasker et al (2011)	40.5	10	46.79	11.18	p<0.0001

Abbreviations: PBC, primary biliary cholangitis/cirrhosis; PCS, physical component summary; SD, standard deviation.

The mental quality of life in patients with PBC was also consistently lower than the general population across trials (64, 66-69). One aspect of PBC that may contribute to the detriment in mental quality of life is the uncertainty associated with the disease. Once diagnosed, patients may remain in a fairly stable disease state for a number of years, with uncertainty as to when their health may deteriorate further and what the outcomes may be.

PBC follows an unpredictable course, and the lack of treatment options for patients who do not have an adequate response to, or are intolerant to, UDCA will result in a more rapid disease progression. Inadequate response to UDCA has been shown to be associated with an increased risk of death, need for liver transplantation and the development of HCC (1, 11-13, 15-19).

The main symptoms to have a detrimental impact on quality of life for people with PBC are chronic fatigue (54, 63, 71-76) and pruritus (76), both of which can be severe. These symptoms frequently contribute to anxiety and depression (71).

A case-control study in the US that matched 1,032 patients with PBC with 1041 controls (77) found that a significantly larger percentage of patients with PBC needed help with routine aspects of daily living than controls (13% vs 10%, respectively; p=0.008), with difficulty in performing household chores (28% vs 21%, respectively; p=0.039), having limitations in the type of professional work that they could perform (36% vs 22%, respectively; p<0.001), having to change jobs because of health (39% vs 26%, respectively; p<0.001), having limitations in the performance of housework (31% vs 19%, respectively; p<0.001) and difficulty in accomplishing everyday activities (41% vs 30%, respectively; p<0.001) being reported significantly more frequently. The same study found that patients with PBC were significantly less likely to participate in sports, physical exercise and hobbies.

PBC is also associated with considerable healthcare costs. In 2014/15, there were 707 hospital admissions in England for PBC (ICD10 K74.3), accounting for 963 consultant episodes and 3,767 bed days (2).

In most patients, the management of complications such as ascites, oesophageal varices, variceal bleeding, encephalopathy, and liver transplantation accounts for the majority of resource use in patients with PBC (78). In Norway, costs for initial hospitalisation in 2005 ranged from €3,059 for ascites and encephalopathy to €8,156 for variceal bleeding, with follow-up costs for each event of over €2,000 per year (79).

PBC is one of the most frequent indications for liver transplantation in Europe (5, 6). There were 621 elective liver transplants performed in the UK in 2014/2015, of which at least 7% were for PBC (3). Overall, the number of patients waiting for a liver transplant

has steadily increased since 2007/8 and recent data found that PBC patients on the transplant waiting list were more likely to die before transplant compared to patients with other liver diseases (7). Singh et al reported a cost of £64,452 for a liver transplant in 2014 (4).

As the majority of cases of PBC affect patients of working age, lost productivity is likely to contribute to the burden on society. The mean age of patients in the POISE trial (discussed in Section 4) is 55.8 years, which is well below the age of retirement in the UK. The population enrolled in POISE has been validated as representative of patients with PBC in the UK by clinical expert opinion.

3.3 *Clinical pathway of care*

Patients are commonly asymptomatic at diagnosis, and are referred to secondary care on discovering abnormal liver function and/or positive autoantibody by blood tests at a GP visit for an unrelated illness (43, 53). Occasionally patients are referred internally, most commonly from a rheumatologist. Rarely, patients are referred due to pruritus, abnormal ultrasound, or decompensation (ascites). A hepatology specialist will perform a liver screen, including tests for AMA and immunoglobulin, an ultrasound, and a FibroScan® to identify fibrosis. A liver biopsy can be performed to confirm diagnosis, although this varies between centres.

On diagnosis of PBC, UDCA is prescribed at 13–15 mg/kg/day. Patients are monitored at 3–4 months for tolerability, and at 6 and 12 months to gauge response and compliance to therapy. There are currently no licensed or effective therapeutic options to treat patients with PBC who have an inadequate response to, or are intolerant to, UDCA.

Patients are referred to the liver transplant list if their UKELD score ≥49 or if they have decompensated disease. UKELD score is a measure of disease severity for end-stage liver disease, and is calculated using the patient's INR, serum creatinine, serum bilirubin, and serum sodium using the following formula:

$$(5.395 \times \ln(INR)) + (1.485 \times \ln(creatinine)) + (3.13 \times \ln(bilirubin) - (81.565 \times \ln(Na)) + 435$$

3.4 *Life expectancy*

Despite a number of studies investigating overall survival in PBC, life expectancy is difficult to determine, in part due to the intrinsic variability of the disease itself, but also due to the variability in study design and the time period over which these studies have taken place. A total of 130 deaths (113 female and 17 male) from PBC were registered in England and Wales during 2014 (80).

Life expectancy can be influenced by a number of factors, including the stage of disease at diagnosis, patient age at diagnosis, the rate of progression in the individual, and which, if any, treatments have been received (81). The estimated average time from first appearance of AMA to death is approximately 20–22 years without treatment (82, 83).

The natural history of untreated PBC is one of unpredictable progression through four phases: preclinical, asymptomatic, symptomatic (including systemic and portal hypertensive), and liver insufficiency. The duration of each phase varies but as this is a

ductopenic disease, the latter stages of the disease are non-linear and patients can experience rapid progression. Published data relating to each phase of PBC are reported in Table 7.

Table 7: Duration of different phases of PBC

Disease phase	Outcome	N	Time to outcome	Reference
Pre-clinical	Time from first detection of AMA to persistently abnormal ALP	28	Median 5.6 years	Metcalf 1996 (83)
Asymptomatic	Percentage of patients developing symptoms	37 (untreated)	89% developed symptoms within 2–4 years	Balasubramaniam 1990 (84)
		36 (untreated)	67% symptomatic at median follow-up of 12.1 years	Mahl 1994 (85)
		91 (24% UDCA treated)	36% symptomatic at a median follow-up of 5 years	Springer 1999 (86)
Symptomatic	Mean time from development of portal hypertensive symptoms to death	111 (ascites), 32 (peripheral oedema)	3.1 years	Chan 2005 (87)
Liver insufficiency	Mean time from development of persistently elevated bilirubin	55	4.1 years (bilirubin >34 µmol/L)	Shapiro 1979 (88)
			2.1 years (bilirubin >102 µmol/L)	
			1.4 years (bilirubin >170 µmol/L)	

Abbreviations: ALP, alkaline phosphatase; AMA, anti-mitochondrial antibodies; PBC, primary biliary cholangitis/cirrhosis; UDCA, ursodeoxycholic acid.

3.5 *Relevant NICE guidance, pathways or commissioning guides*

NICE have published guidance on the assessment and management of cirrhosis in over 16s (89). This guidance is primarily designed to address the diagnosis and management of the complications of cirrhosis, although PBC is not specifically discussed. No other relevant NICE guidance or NICE pathway is available.

There are currently no commissioning guides for the treatment of PBC.

3.6 *Clinical guidelines*

EASL guidelines provide current recommendations for the management of PBC in Europe (33). In addition, the British Society of Gastroenterology (BSG) and the UK-PBC have recently compiled a set of draft guidelines for PBC (35), which are now in a late stage of development and will be published shortly.

3.6.1 *First-line treatment*

The EASL guidelines recommend UDCA as first-line treatment for PBC and state that it is the only drug licensed to treat PBC that demonstrates any long-term efficacy. It is recommended that all patients with PBC, including those who present asymptomatically, receive UDCA at a dose of 13-15 mg/kg/day for long-term treatment, and that response to treatment should be evaluated after 1 year using either the Paris I criteria or the Barcelona criteria (see Table 8) (33).

Table 8: Biochemical treatment response criteria

Disease severity criteria	Responder criteria
Paris I† (11)	ALP ≤3x ULN and AST ≤2x ULN and total bilirubin ≤1 mg/dL (17 µmol/L)
Barcelona (16)	ALP ≤1 x ULN or decrease in ALP >40%

Abbreviations: ALP, Alkaline phosphatase; AST, Aspartate aminotransferase; ULN, upper limit of normal.

Although not yet published, Intercept have been allowed access to the BSG/UK-PBC draft guidelines for the purpose of this appraisal. These draft guidelines also recommend UDCA for all patients at a dose of 13–15 mg/kg/day (35). This can be given as a single daily dose or divided doses if tolerability is an issue, and if tolerated, treatment should be lifelong.

There are several response criteria that have been proposed to define non-response/progression (some of which are described in Section 4.3.6.2); however, there is no consensus as to which of these criteria should be used. It has been shown that attaining an ALP <1.67x ULN is associated with a statistically significantly reduced risk of disease progression over the subsequent 10 years (18). In addition, in a later study it was found that combining ALP and bilirubin (ALP <1.67x ULN and bilirubin ≤1 mg/dL) was the most discriminating algorithm for predicting clinical outcomes such as varices, ascites, death, or liver transplantation (17). Therefore, the POISE study in OCA used response criteria of:

- ALP <1.67x ULN, which equates to 200 U/L, and
- Total bilirubin <ULN, which equates to 20 µmol/L (1.17 mg/dL), and
- A 15% decrease from baseline in ALP, which was incorporated as a conservative estimate so that patients were excluded who had only a small change in ALP from slightly above 200 U/L at baseline to slightly below this level. This ensured that only subjects with a relevant clinical effect were judged to have a successful response in terms of trial endpoints.

3.6.2 *Second-line treatment*

There are no licensed or effective drugs approved for second-line treatment for the management of patients with an inadequate response to, or intolerance to, UDCA. Given the lack of emerging therapeutic options in the last 20 years, other treatments have been trialled for use in PBC, including budesonide and fibrates (which are contraindicated in PBC (22, 23)). However, limited efficacy has been observed in these other treatments.

The BSG/UK-PBC guidelines (35) stress that inadequate response to UDCA is associated with an increased risk of liver transplantation, development of HCC, and death (1, 11-13, 15-19) and that there are currently no licensed second-line treatments in

the UK. It is recommended that patients who do not respond to UDCA should participate in a clinical trial.

Further studies in second-line treatment for PBC are warranted.

3.6.3 *Liver transplantation*

Liver transplantation is the only treatment for patients with late-stage PBC, where UDCA has limited efficacy (33). The BSG/UK-PBC draft guidelines recommend that liver transplantation should be considered in all patients with bilirubin >50 µmol/L or evidence of decompensated liver disease. In addition, due to the variable nature of PBC, transplantation should be considered for all patients with advanced disease, as evidenced by jaundice, portal hypertension, or signs of early decompensation (e.g. ascites, encephalopathy, sarcopenia). Pruritus refractory to all medical therapy is also an indication for liver transplantation regardless of the stage of disease; however, due to limited organ availability, patients with a high UKELD score are currently prioritised, which would often not include patients with uncontrolled pruritus.

The EASL guidelines (33) recommend transplantation for patients with:

- Decompensated cirrhosis with an unacceptable quality of life, or
- Anticipated death within a year due to treatment-resistant ascites and spontaneous bacterial peritonitis, recurrent variceal bleeding, encephalopathy, or hepatocellular carcinoma

While the EASL guidelines state that liver transplant has dramatically improved survival in patients with late-stage PBC (33), it is important to note that there are risks associated with having a transplant, which can occur up to several years after the procedure. Risks associated with transplant include (90):

- Rejection of the new liver;
- Bleeding;
- The new liver not working, requiring a new transplant to be carried out immediately;
- An increased risk of infection;
- Loss of kidney function;
- Problems with blood flow to and from the liver; and
- An increased risk of certain types of cancer, particularly skin cancer.

After liver transplant it is necessary for patients to take immunosuppressants for the rest of their lives. Side effects from these include headaches, high blood pressure, tremors, an increased risk of infections, kidney failure, mood swings, muscle weakness, increased appetite and weight gain, and changes to your mental state, such as confusion, hallucinations and suicidal thoughts (91).

In addition, donated livers are scarce, and a recent study of a US database found that 16.5% of patients with PBC died while on the liver transplant waiting list, and 8% were removed from the list due to being too sick (7).

3.7 *Issues relating to current clinical practice*

Current clinical practice relies on the only licensed drug for PBC, UDCA. There are no licensed drugs approved for treatment of patients with an inadequate response to UDCA. Given the lack of emerging therapeutic options in the last 20 years, other treatments have been trialled for use in PBC, including budesonide and fibrates (which are contraindicated in PBC). However, limited efficacy has been observed. This leaves patients without any further treatment options if they are unable to tolerate or have an inadequate response to UDCA, which is common with PBC; up to 74% of UDCA-treated patients with PBC have a sub-optimal or absent response (1, 11-14) and are at significantly increased risk of clinical complications, the requirement of a liver transplant, HCC, or death (1, 11-13, 15-19).

3.8 *Equality*

People with PBC face stigma in society because of the negative connotations of the term ‘cirrhosis’ and the association with alcoholism and drug abuse (30). This is one of the reasons that PBC has recently undergone a name change to primary biliary cholangitis; however, this change is likely to take time to be adopted universally. In addition, PBC is also a rare disease and it is essential that patients have the same opportunities to gain access to new treatments. PBC mainly affects women, which itself presents a challenge with diagnosis since the early symptoms of PBC are often wrongly dismissed as menopausal symptoms or depression (92). This can lead to delays in treatment and corresponding worse outcomes, as well as frustration and distress to the patient.

4 Clinical effectiveness

Summary

- POISE, a 12-month randomised, double-blind, placebo-controlled Phase 3 study, is the largest PBC clinical trial to date designed with input from the UK and global PBC groups to assess the efficacy, safety and tolerability of OCA
  - Subjects who were taking UDCA before the trial (93% of subjects) continued to take UDCA throughout the trial
  - Arms were:
    - Placebo (with or without UDCA)
    - 10 mg OCA fixed dose (with or without UDCA)
    - OCA titration group (with or without UDCA)
  - Clinical expert opinion validated that the patient population in POISE is representative of the population with PBC in the UK
- Almost five times as many patients in the OCA 10 mg (47% of subjects) and OCA titration (46% of subjects) groups met the primary endpoint compared with the control arm (10% of subjects; $p<0.0001$) at 12 months
- Other important secondary endpoints, such as hepatocellular transaminases, markers of cholestasis, inflammation, hepatobiliary injury, fibrosis, and apoptosis, demonstrated clinically and statistically significant improvements compared with placebo that were sustained during the 12-month double-blind period. OCA demonstrates a complete biochemical improvement across the range of all the standard markers of cholestatic disease
- Subgroup analysis demonstrated that the effect of OCA on achieving the primary composite endpoint and changes in ALP and total bilirubin were independent of age at diagnosis, duration of PBC, and baseline ALP
- An ongoing long-term safety extension (LTSE) of POISE has shown continuing efficacy of OCA in controlling ALP and bilirubin levels to a degree which should halt progression of disease
- Evidence from two Phase 2 studies and their LTSEs provide further support for the efficacy of OCA observed in POISE
- OCA was generally well tolerated, with pruritus being the most commonly reported adverse event
  - However, it is important to consider that pruritus is a common symptom of PBC
    - 63% of patients in POISE had a history of pruritus
    - Therefore, patients and their clinicians are typically familiar with the condition and its management

4.1 *Identification and selection of relevant studies*

A systematic review was conducted to identify all relevant evidence for the efficacy and safety of interventions used to treat PBC. All randomised controlled trials investigating an intervention to treat PBC were included. The initial review was conducted in September 2014, followed by two updates in September 2015 and June 2016.

4.1.1 *Review question*

The PICOS (population, interventions, comparators, outcomes and study type) principle was applied to define the following review questions:

- "What is the clinical efficacy and safety of interventions used to treat primary biliary cirrhosis?"

4.1.2 *Search methodology*

Studies of interest were identified by searching the electronic databases shown in Table 9, with no restrictions on date of publication. Searches were conducted using the following interfaces:

- EMBASE (which covers Embase, Medline and Medline (R) In-Process)
- The Cochrane Library (which covers the Cochrane Database of Systematic Reviews, Database of Abstract of Reviews of Effects, and Cochrane Central Register of Controlled Trials).

Table 9: Databases searched and interfaces used in the systematic reviews for evidence relating to interventions for primary biliary cirrhosis†

Database	Interface
Embase	EMBASE
Medline	EMBASE
Medline (R) In-Process	EMBASE
Cochrane Database of Systematic Reviews	The Cochrane Library
Database of Abstracts of Reviews of Effects	The Cochrane Library
The Cochrane Central Register of Controlled Trials (CENTRAL)*	The Cochrane Library

†The term primary biliary cirrhosis was included in all searches; however, in the 2016 update search, the term 'primary biliary cholangitis' was also included due to the recent name change of the disease.

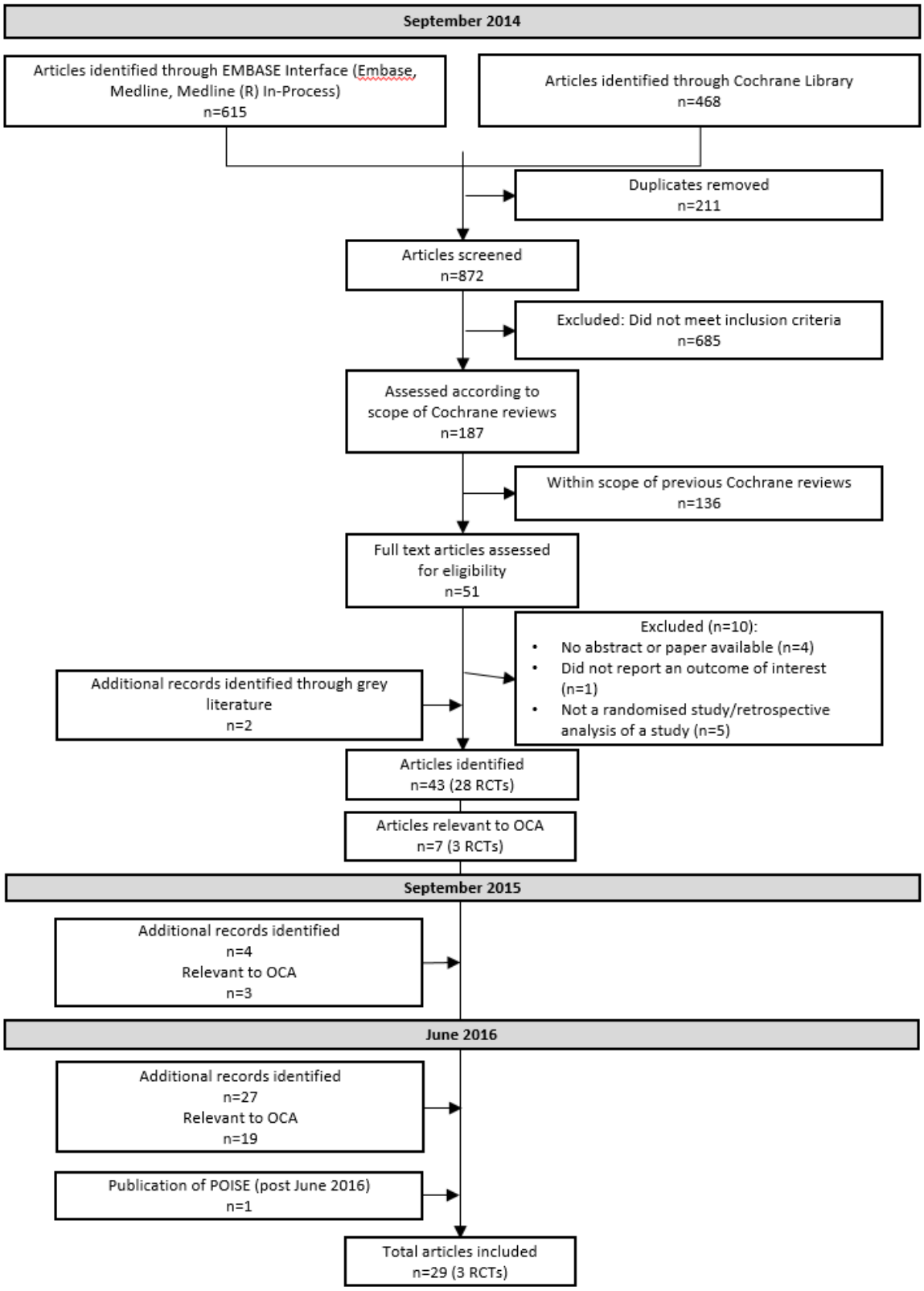
The search strategy is included in more detail in Appendix 2.

The initial systematic review identified 28 randomised controlled trials relating to interventions for primary biliary cirrhosis, three of which included OCA therapy. The first update identified a further four articles, three of which included OCA therapy; and the second update identified a further 27 articles (mostly conference abstracts), 19 of which included OCA therapy. Since the systematic literature search was performed, results from POISE have been published by Nevens et al (31). The systematic review schematic is shown in Figure 8.

Searches of the Cochrane database of systematic reviews and the database of abstracts of reviews of effects (DARE) identified 57 publications. Of these, nine were Cochrane systematic literature reviews that had previously been performed to identify RCTs for interventions in PBC. The search strategies and scopes for these reviews were closely aligned to that of this systematic review, and therefore publications were removed from

this review if they had previously been captured and reviewed by the Cochrane reviews, to avoid duplication.

Figure 8: PRISMA diagram for the systematic review of clinical evidence



4.2 *List of relevant randomised controlled trials*

The included articles that were relevant to OCA relate to three RCTs, one Phase 3 (POISE) (Table 10) and two Phase 2 studies (747-201 and 747-202) (described in Section 4.7.2.2). All trials had long-term safety extension phases, the results of which are summarised in Section 4.7.2.

Table 10: List of relevant Phase 3 RCTs

Trial no. (acronym)	Population	Intervention	Comparator	Primary study ref(s)	Is study excluded from further discussion? If yes state rationale
747-301 (POISE); NCT01473524	Patients diagnosed with PBC with ALP ≥1.67x ULN and/or total bilirubin >ULN but <2x ULN who fail to respond to or are intolerant to treatment with UDCA.	Oral OCA (5 mg or 10 mg) taken OD.	Placebo	Clinical study report (93)	No
LTSE to POISE	All subjects who completed the 12-month double-blind phase of POISE and who were willing to enrol in the 5-year LTSE phase of the study.	Oral OCA (5–25 mg[†]) taken OD	N/A	Interim clinical study report (94)	No

Abbreviations: ALP, alkaline phosphatase; LTSE, long-term safety extension; OCA, obeticholic acid; OD, once daily; PBC, primary biliary cholangitis; UDCA, ursodeoxycholic acid; ULN, upper limit of normal.
[†]All subjects initiated OCA at 5 mg OD; daily dose could be up-titrated if a satisfactory response was not achieved in 5 mg increments to a total dose of 25 mg OD (one increment per 3 months permitted), depending on tolerability.

Summaries of the included publications are shown in Table 11, Table 12, Table 13 and Table 14.

Table 11: Included articles relating to the Phase 2 study 747-201

Citation details	Objective
Hirschfield (2012) (95) Conference poster	Presents efficacy/safety results from the open-label long-term extension phase
Kowdley (2011) (96) Conference abstract	Presents efficacy/safety data of 12-week double-blind treatment phase
Kowdley (2011b) (97) Conference abstract	Presents efficacy/safety data of 12-week double-blind treatment phase
Kowdley (2014) (98) Conference abstract	Presents efficacy/safety results from the open-label long-term extension phase
Kowdley (2015) (99) Conference abstract	Presents efficacy/safety results from the open-label long-term extension phase

Table 12: Included articles relating to the Phase 2 study 747-202

Citation details	Objective
Hirschfield (2011) (100) Slide deck	Presents efficacy/safety results from the open-label long-term extension phase
Hirschfield (2012) (95) Conference poster	Presents efficacy/safety results from the open-label long-term extension phase
Hirschfield (2015) (101) Full publication	Presents efficacy/safety data from the 12-week double-blind treatment phase and open label extension phase
Marschall (2010) (102) Conference abstract	Presents efficacy/safety data of 12-week double-blind treatment phase
Mason (2010) (103) Conference abstract	Presents efficacy/safety data of 12-week double-blind treatment phase

Table 13: Included articles relating to the Phase 3 study POISE

Citation details	Objective
Kowdley (2014) (98) Conference abstract	Presents results from the open-label long-term extension phase
Andreone (2016) (104) Conference abstract	Subgroup analysis of Italian patients enrolled in POISE
Edwards (2016) (105) Conference abstract	Analysis of relationship between plasma total OCA exposure and changes in alkaline phosphatase and bilirubin
Malecha (2016) (106) Conference abstract	Analysis of baseline factors associated with pruritus
Mayne (2015) (107) Conference abstract	Analysis of validated methods to quantify pruritus
Mayo (2016) (108) Conference abstract	Analysis of strategies to mitigate pruritus
Nevens (2014) (109) Conference abstract	Presents efficacy/safety data from the 1-year double-blind treatment phase
Nevens (2016) (31) Full publication	Presents efficacy/safety data from the 1-year double-blind treatment phase and 2-year open label extension phase
Pares (2015) (110) Conference abstract	Analysis of effect of OCA on bone mineral density
Pencek (2015) (111) Conference abstract	Analysis to support early up-titration (<6 months) from 5 to 10 mg OCA/day
Peters (2015) (112) Conference abstract	Presents safety results from the open-label long-term extension phase
Peters (2016) (113) Conference abstract	Presents safety results from the open-label long-term extension phase

Citation details	Objective
Trauner (2015) (114) Conference abstract	Presents data on markers of cholestasis from the open-label long-term extension phase
Trauner (2016) (115) Conference abstract	Presents data on markers of cholestasis from the open-label long-term extension phase in patients treated with <10 mg OCA/day

Table 14: Included articles with integrated analyses

Citation details	Objective
Invernizzi (2015) (116) Conference abstract	Integrated analysis from the two phase II and Phase III POISE RCTs in patients treated with OCA <10 mg/day
Jones (2015) (117) Conference abstract	Integrated analysis from the two phase II and Phase III POISE RCTs restricted to patients with elevated bilirubin
Lutz (2016) (118) Conference abstract	Integrated analysis from the two phase II and Phase III POISE RCTs according to baseline disease severity
Mayne (2015) (119) Conference abstract	Integrated analysis from the OCA 10 mg treatment arm of the two phase II and Phase III POISE RCTs according to baseline alkaline phosphatase levels
Pencek (2015b) (120) Conference abstract	Integrated analysis from the two phase II and Phase III POISE RCTs based on age and gender
Pencek (2016) (121) Conference abstract	Integrated analysis from the two phase II and Phase III POISE RCTs based on age and gender

4.3 *Summary of methodology of the relevant randomised controlled trials*

The clinical study programme for OCA includes two Phase 2 studies (Study 747-201 (96, 97, 122) and 747-202 (101, 123, 124)) and one pivotal Phase 3 study (Study 747-301 - POISE (93, 109)), all of which had long-term safety extensions (LTSEs). The double-blind phases of these trials are completed, and the results from the double-blind phase of POISE are presented as the main efficacy evidence in Section 4.7.1, and of the two Phase 2 studies in Section 4.7.2 as supporting evidence. The LTSE phases of POISE and 747-201 are ongoing and the LTSE phase of 747-202 is completed. Interim/final results (as applicable) of these LTSEs are summarised as supporting evidence in Section 4.7.2.

4.3.1 *Study objectives*

The primary objectives of POISE were to assess the effects of OCA in subjects with PBC on serum ALP and total bilirubin (composite endpoint) and to evaluate the safety profile of OCA.

The secondary objectives were to evaluate the effects of OCA in subjects with PBC on:

- Hepatocellular injury and liver function, including histology (inflammatory, structural [portal, parenchymal], and fibrotic assessments)

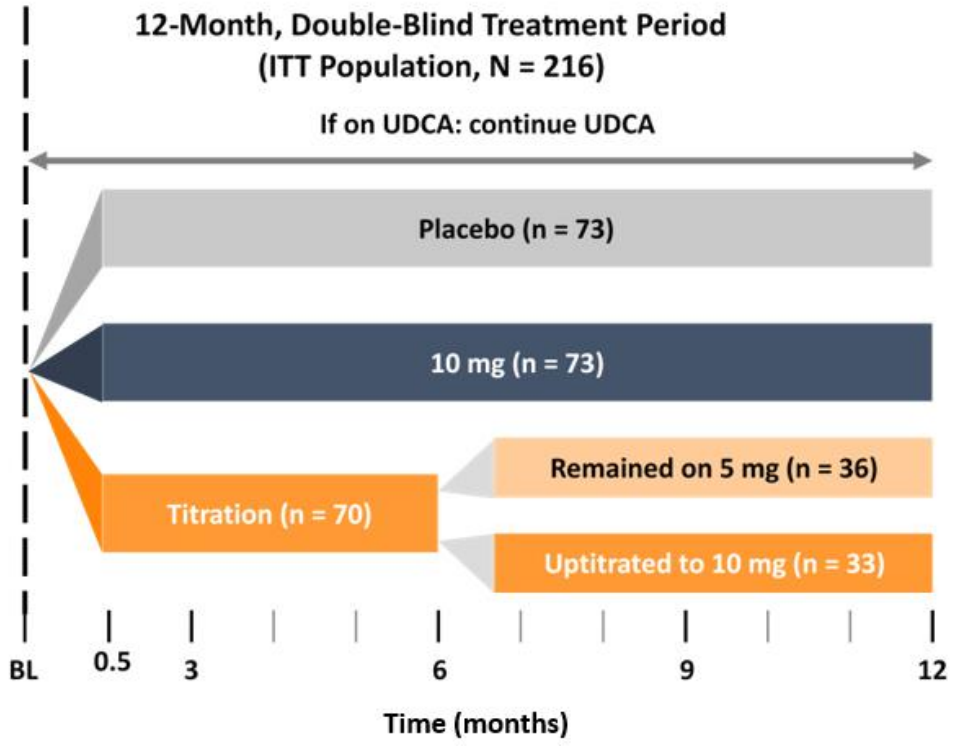
- Disease-specific symptoms
- Biomarkers and non-invasive assessments of liver fibrosis
- Bile acids
- Other exploratory evaluations

The objectives of the LTSE phase of the study were the same as for the double-blind phase.

4.3.2 *Study design*

POISE was a 12-month international, multi-centre, Phase 3, randomised, double-blind, placebo-controlled, parallel group study in subjects aged ≥18 years with PBC. The study was designed to assess the efficacy, safety, and tolerability of OCA by evaluating a titration group and a fixed dose group. In the titration group, subjects initiated treatment on 5 mg OCA once daily (OD), increasing to 10 mg OCA at 6 months if they met defined criteria (see Section 4.3.2.2). Subjects in the fixed dose group received a fixed dose of 10 mg OCA OD. Subjects who were taking UDCA at the time of randomisation continued to do so at prescribed doses and frequency for the study duration, and those who were intolerant to UDCA took only study drug or placebo. All subjects were screened for eligibility during an 8-week screening period prior to entering the study to allow for collection of repeat serum chemistry samples (at least 2 weeks apart), if necessary, to confirm pre-treatment ALP and total bilirubin values.

Figure 9: Study design



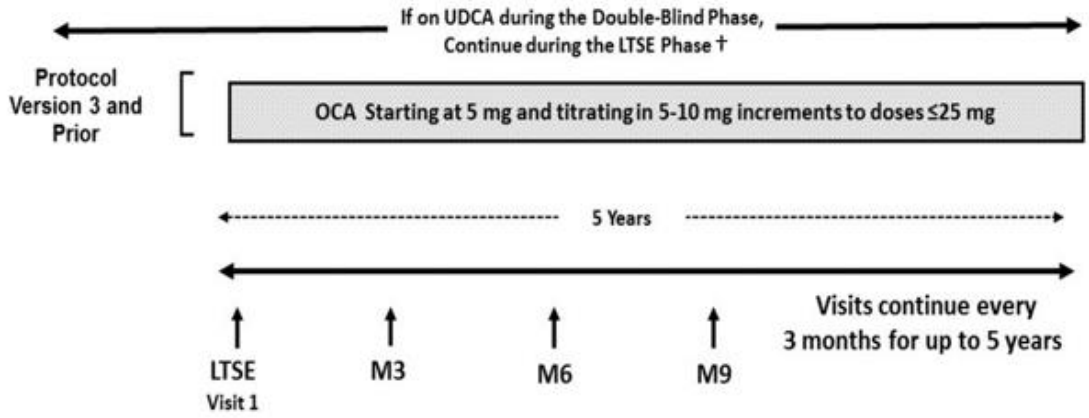
Abbreviations: BL, baseline; ITT, intention-to-treat; UDCA, ursodeoxycholic acid; W, week.
[†]If patients were on UDCA at screening, they were to continue on UDCA throughout the study. A small proportion of subjects in the study did not receive UDCA (7%), and therefore received OCA as monotherapy.

Following completion of the 12-month double-blind phase, subjects, including those who received placebo, were given the opportunity to enrol in the open-label LTSE phase of the study. The Month 12 visit from the double-blind phase served as the Day 1 visit of the LTSE phase. To preserve blinding for the double-blind phase, subject treatment allocation in the double-blind phase was not made available until all the double-blind data were final and a 'clean' database was locked, which was more than 12 months for the first subjects who enrolled in the study.

Because subjects were unaware of previous treatment (placebo/5 mg OCA/10 mg OCA), all subjects in the LTSE started at an initial dose of 5 mg OCA. Doses could be up-titrated or down-titrated as described in Section 4.3.2.2. Subjects who received study drug (OCA or placebo) in combination with UDCA during the double-blind phase were to continue taking UDCA during the LTSE phase. However, any subject who had a clinically significant therapeutic response during the LTSE phase was able to have their UDCA withdrawn if determined clinically appropriate by the investigator. Subjects who received study drug as monotherapy in the double-blind phase were to receive OCA monotherapy in the LTSE phase.

The study design of the LTSE phase is presented in Figure 10. Subjects were contacted by study site staff 2 weeks after starting the LTSE phase to ensure compliance and record any AEs. Clinic visits for study procedures and clinical laboratory evaluations occurred every 3 months. If a subject withdrew from the study early, all of the end-of-treatment evaluations were performed at the time of withdrawal. Additionally, the subject returned for a follow-up visit 4 weeks after their final dose of OCA.

Figure 10: LTSE phase study design



Abbreviations: LTSE, long-term safety extension; M, month; OCA, obeticholic acid; UDCA, ursodeoxycholic acid.
† Subjects who had a clinically significant therapeutic response during the open-label LTSE phase could have their UDCA withdrawn if determined clinically appropriate by the investigator.

4.3.2.1 Randomisation and stratification

In the double-blind phase, subjects were randomised in a 1:1:1 ratio via an interactive web response system (IWRS) to the placebo group, the OCA titration group, or the OCA 10 mg fixed dose group.

Randomisation was stratified according to pre-identified criteria:

- a group at higher risk of developing clinical outcomes based on ALP, AST, and total bilirubin levels, i.e. Paris I criteria (ALP >3x ULN and AST >2x ULN and total bilirubin >ULN) (11); and
- the small group of subjects who could not tolerate UDCA therapy.

In addition, subjects were stratified by the presence or absence of the following biochemical response criteria and tolerance to UDCA treatment:

- ALP >3x ULN and/or AST >2x ULN and/or bilirubin >ULN, and intolerant to UDCA
- ALP ≤3x ULN and/or AST ≤2x ULN and/or bilirubin ≤ULN, and intolerant to UDCA
- ALP >3x ULN and/or AST >2x ULN and/or bilirubin >ULN, and currently taking UDCA
- ALP ≤3x ULN and/or AST ≤2x ULN and/or bilirubin ≤ULN, and currently taking UDCA

4.3.2.2 Study drugs

In the double-blind phase, subjects randomised to the fixed dose group received 10 mg OCA OD throughout the double-blind phase. Subjects randomised to the titration group received OCA 5 mg OD for the initial 6-month period. A request for titration to OCA 10 mg OD for the remainder of the double-blind phase (Months 6-12) could be made by the investigator via the IWRS for subjects who met any of the following criteria at the Month 6 assessment:

- ALP ≥1.67x ULN, and/or
- Total bilirubin >ULN, or
- <15% ALP reduction at month versus the mean pre-treatment value, and
- Provided AEs (e.g. severe pruritus) did not limit the administration of the higher dose of OCA.

Both the investigator and the subject remained unaware whether or not titration had occurred.

At the start of the LTSE phase, subjects were unaware of previous treatment (placebo/5 mg OCA/10 mg OCA) in order to preserve blinding for the double-blind phase. Therefore, all subjects in the LTSE started at an initial dose of 5 mg OCA. Doses could be up-titrated in 5 mg increments not more than once every 3 months following discussion with and approval by the sponsor, to a maximum of 25 mg, if the subject met the same criteria as for up-titration in the double-blind phase.

Based on the investigator's clinical judgement, subjects could be titrated to lower doses. As down-titration was likely to occur due to an AE, the investigator was to determine whether to gradually down-titrate in 5 mg increments or whether to down-titrate directly to the new intended dose, e.g. directly from 25 mg to 15 mg.

4.3.2.3 Selection of doses used

In the Phase 2 studies 747-201 (OCA 10 mg and 50 mg) and 747-202 (OCA 10 mg, 25 mg, and 50 mg) (see Section 4.7.2), OCA significantly reduced ALP levels in subjects with PBC, and no dose-relationship was observed (i.e. OCA 10 mg was as effective as OCA 50 mg). However, a dose-related increase in the incidence and severity of pruritus was observed across the dose range evaluated. It therefore appears that a lower dose of

OCA is associated with a lower incidence of pruritus without compromising effectiveness. Therefore, POISE was designed to assess the efficacy, safety, and tolerability of a lower dose of OCA (5 mg) and a 10 mg dose. This also corresponds to the proposed licensed indication, whereby patients initiate treatment with 5 mg OCA and titrate to 10 mg OCA.

4.3.2.4 Blinding

Blinding was employed in the double-blind phase. Tablets of 5 mg OCA, 10 mg OCA and placebo were visually identical, thus ensuring the double-blind nature of the study. Investigational product bottles were not labelled with either a subject randomisation number or tablet strength.

Access to randomisation codes and the corresponding treatment assignment was made available through IWRS to the appropriate Sponsor designee(s) who were responsible for reporting SAEs to the regulatory authorities. This information could be accessed only in the event of a medical emergency. No other Sponsor personnel or vendor/clinical research organisation had access to blinded subject treatment codes until all study data had been entered into the study database, validated, and the database locked.

4.3.3 *Eligibility criteria*

Key inclusion and exclusion criteria are shown in Table 15.

Table 15: Key inclusion and exclusion criteria

Key inclusion criteria	Key exclusion criteria

• Male or female aged ≥18 years
• Definite/probable PBC diagnosis† as demonstrated by the presence of ≥2 of the following:
  ○ Elevated ALP levels for at least 6 months
  ○ Positive AMA titer or if AMA negative and/or low titer (<1:80) PBC specific antibodies (anti-GP210 and/or anti-SP100) and/or antibodies against the major M2 components (PDC-E2, 2-oxo-glutaric acid dehydrogenase complex)
  ○ Liver biopsy result consistent with PBC
• ALP ≥1.67x ULN and/or total bilirubin >ULN but <2x ULN
• Taking UDCA for ≥12 months prior to randomisation with a stable dose for ≥3 months, or no UDCA for ≥3 months prior to randomisation if unable to tolerate UDCA
• Female subjects to be post-menopausal, surgically sterile, or prepared to use ≥1 effective method of contraception during the study period and for 30 days after end of trial
	• History or presence of other concomitant liver disease§
	• Clinical complications of PBC or clinically significant hepatic decompensation¶
	• Severe pruritus or pruritus requiring systemic treatment (e.g. with BAS or rifampicin) within 2 months prior to randomisation
	• Administration within 6 months prior to randomisation and throughout the study of azathioprine, colchicine, cyclosporine, methotrexate, mycophenolate mofetil, pentoxifylline; fenofibrate or other fibrates; budesonide and other systemic corticosteroids; potentially hepatotoxic drugs (including α-methyl-dopa, sodium valproic acid, isoniazide, or nitrofurantoin)
	• Administration within 12 months prior to randomisation and throughout the study of antibodies or immunotherapy directed against interleukins or other cytokines or chemokines
	• Previous participation in a clinical trial using OCA
	• History or presence of clinically concerning cardiac arrhythmias, or prolongation of QT or QTc interval (>500 ms)
	• Pregnancy or lactating

Key inclusion criteria	Key exclusion criteria
	• History of HIV infection • Presence of any disease or condition that interferes with the absorption, distribution, metabolism, or excretion of drugs including bile salt metabolism in the intestine. Patients with inflammatory bowel disease or who have undergone gastric bypass procedures will be excluded (gastric lap band is acceptable) • Medical conditions that could cause non-hepatic increases in ALP (e.g. Paget's disease) or that could diminish life expectancy to <2 years, including known cancers • History of alcohol‡ or other substance abuse within 1 year prior to randomisation • Blood or plasma donation within 30 days prior to randomisation • Mentally unable to complete a signed consent form

Abbreviations: AASLD, American Association for the Study of Liver Disease; ALP, alkaline phosphatase; AMA, anti-mitochondrial antibody; BAS, bile acid sequestrants; EASL, European Association for the Study of Liver; HIV, human immunodeficiency virus; MELD, Model for End Stage Liver Disease; OCA, obeticholic acid; PBC, primary biliary cholangitis; UDCA, ursodeoxycholic acid; ULN, upper limit of normal. †Consistent with AASLD and EASL Practice Guidelines (33, 34). §Hepatitis C virus infection, primary sclerosing cholangitis, alcoholic liver disease, definite autoimmune liver disease, overlap hepatitis, non-alcoholic steatohepatitis, or Gilbert's syndrome. Subjects with hepatitis B virus were also excluded; however, subjects who had seroconverted could be included following consultation with the medical monitor. ¶Includes history of liver transplantation, current placement on a liver transplant list, current MELD score ≥15 (MELD is a scoring system for assessing the severity of chronic liver disease, where the higher the score, the more severe the disease), portal hypertension with complications, cirrhosis with complications, hepatorenal syndrome (type I or II), or screening serum creatinine >2 mg/dL. ‡Defined as consumption of more than 210 mL of alcohol per week (i.e., the equivalent of 14 4-ounce (125 mL) glasses of wine or 14 12-ounce cans/bottles of beer).

4.3.4 *Location*

The double-blind phase of the study was conducted in 59 sites in 13 countries in different geographical regions. Locations included the US (15 sites), Germany (10 sites), UK (9 sites), Poland (5 sites), the Netherlands (4 sites), Italy (4 sites), Australia (3 sites), Canada (2 sites), Spain (2 sites), Austria (2 sites), Belgium (1 site), France (1 site), and Sweden (1 site). The sites in the UK included 7 sites in England (London, Oxford, Newcastle-Upon-Tyne, Birmingham, Nottingham, Bristol, and Manchester) and 2 sites in Scotland (Larbert and Dundee).

The LTSE phase was conducted in the same sites as the double-blind phase of the study, with the exception of the US, where there were 14 sites in the LTSE phase compared with 15 sites in the double-blind phase.

4.3.5 *Prior and concomitant therapy*

Prohibited medication is listed as part of the trial exclusion criteria in Table 15.

Administration of the following medications was permitted as specified below:

- Topical or inhaled corticosteroids
- Herbal supplements or botanical preparations that are purported to affect the liver (e.g. milk thistle), provided that the dose and treatment regimen of these agents was kept constant during the double-blind phase.
- UDCA treatment for those patients who were taking UDCA at study entry
- Bile acid sequestrants (BAS) or aluminium hydroxide or smectite-containing antacids. Subjects were instructed to stagger their dosing of investigational product (and UDCA if taking) and BAS and/or antacids, ensuring at least 4 hours between doses of the BAS and/or antacids and investigational product (and UDCA if taking).
- Hormonal contraceptives

Concomitant medications were to be kept at a stable dose prior to randomisation. Investigators endeavoured to keep the doses of all concomitant medications the same during the course of the study, where medically appropriate. Subjects with other concomitant conditions that were not well controlled or whose medication needs were anticipated to change during the study were not enrolled in the study.

4.3.6 *Study endpoints*

4.3.6.1 Primary endpoint

The primary endpoint for the double-blind phase of the trial was the percentage of subjects achieving a composite endpoint of:

- ALP <1.67x ULN, and
- total bilirubin ≤ULN, and
- ALP decrease ≥15% from baseline

in the 10 mg OCA fixed dose group at Month 12.

Secondary analyses of the primary endpoint included the percentage of subjects achieving the primary endpoint in the OCA titration group at Month 12, the percentage of subjects reaching the endpoint at Week 2, Month 3, Month 6 and Month 9, and comparing the 10 mg OCA fixed dose group with the OCA titration group at Month 6.

The primary variable for the LTSE phase was the percentage of subjects achieving the composite endpoint based on previous treatment in the double-blind phase (i.e. 5 mg OCA, 10 mg OCA, or placebo).

Justification for the use of a composite surrogate endpoint

ALP is a key biochemical marker of PBC disease, and elevated bilirubin is indicative of end-stage disease. Both ALP and bilirubin are commonly used in an array of algorithms to predict survival and transplant outcomes in patients with PBC (11-13, 16, 125, 126). A patient-level meta-analysis study by Lammers et al demonstrated the significant prognostic value of ALP and bilirubin levels on long-term clinical outcomes in patients with PBC (15). The study demonstrated that lower levels of ALP and bilirubin strongly correlated with a longer transplant-free survival in a log linear manner. Of patients with ALP ≤2.0x ULN, 84% survived for 10 years compared with 63% of those with levels

>2.0x ULN, and of patients with bilirubin ≤1.0x ULN, 86% survived for 10 years versus just 41% in patients with bilirubin >1.0x ULN (15). When evaluating ALP alone, attaining an ALP <1.67x ULN is associated with a statistically significantly reduced risk of disease progression over the subsequent 10 years, and is therefore a key clinical goal when evaluating the effectiveness of treatment in patients with PBC (18).

In addition, bilirubin is an independent predictor of PBC prognosis and disease progression, and was used as an endpoint to support the approval of UDCA in the EU. Importantly, changes in ALP and bilirubin occur during different stages of PBC disease progression, with ALP changes occurring during the early/asymptomatic stages whereas changes in bilirubin occur during the later/decompensated stages of the disease. Therefore, the prognostic value of these surrogate markers is significantly increased when combined and evaluated together (15). Momah et al from the Mayo clinic evaluated different biochemical thresholds versus a combination of clinical outcomes such as varices, ascites, death, or liver transplantation in a cohort of UDCA-treated patients, and concluded that combining ALP and bilirubin (ALP <1.67x ULN and bilirubin ≤1 mg/dL) was the most discriminating of the algorithms they evaluated (17).

The validity of the combined surrogate endpoint proposed by Momah et al has since been supported by a meta-analysis of patient-level data from the Global PBC study (15). The Global PBC study comprised data from 4,845 patients from 15 centres in North America and Europe, and is the largest international database of PBC patients to date. The Global PBC study demonstrated that the combined use of ALP and bilirubin levels provided greater prognostic predictability versus either component alone (15). Therefore, the use of both ALP and bilirubin for evaluating patients with PBC represents an evidence-based, clinically meaningful surrogate endpoint for use in clinical studies (15).

Consistent with the data presented above for the combined prognostic value of ALP and bilirubin, a composite endpoint of ALP <1.67x ULN (200 U/L) and bilirubin ≤ULN (20 µmol/L) was used in POISE. In addition, a minimum ALP reduction of ≥15% from baseline was also included as part of the composite endpoint. This was incorporated as a conservative estimate so that patients were excluded who had only a small change in ALP from slightly above 200 U/L at baseline to slightly below this level. This ensured that only subjects with a relevant clinical effect were judged to have a successful response.

Due to the rarity, slow rate of progression in most patients, and chronic nature of PBC, it is a challenge to design studies based on absolute clinical long-term outcomes such as transplant-free survival and mortality. Therefore, there is a need to consider the use of surrogate endpoints to predict clinical benefit. As described above, ALP and bilirubin strongly predict the prognosis of PBC. In addition, NICE have previously accepted surrogate endpoints in the appraisals of other treatments, such as diabetes (127) and idiopathic pulmonary fibrosis (128).

4.3.6.2 Secondary endpoints for the double-blind phase of POISE

ALP response rates

Secondary efficacy endpoints relating to ALP levels were:

- Absolute and percentage change from baseline in ALP at Month 6 and Month 12
- Percentage of subjects with a decrease in ALP from baseline of ≥10%, ≥15%, ≥20%, and ≥40% at Week 2, Month 3, Month 6, Month 9 and Month 12, summarised by treatment group
- Percentage of subjects with ALP ≤ULN, summarised by treatment at all post-baseline assessments

Consistent with the log linear relationship between outcomes and ALP, the Global PBC study found that reductions in ALP were associated with increased survival with a favourable hazard ratio for all categorical percentage reductions. Statistical significance was achieved with reductions of 20–30% and >40% (15).

Biochemical treatment response criteria

The percentage of subjects meeting the Paris I, Paris II, Mayo II, Toronto II, or Rotterdam response criteria were summarised by treatment group at Week 2, Month 3, Month 6, Month 9, and Month 12. The analysis was repeated for the subgroups of subjects who met and did not meet the requirement of a responder at baseline for the endpoint analysed. The different response criteria are defined in Table 16.

Table 16: Biochemical treatment response criteria

Disease severity criteria	Responder criteria
Paris I† (11)	ALP ≤3x ULN and AST ≤2x ULN and total bilirubin ≤ULN
Paris II (12)	ALP ≤1.5x ULN and AST ≤1.5x ULN and total bilirubin ≤ULN
Toronto II (18)	ALP ≤1.76x ULN
Mayo II† (17)	ALP ≤1.67x ULN and total bilirubin ≤ULN
Rotterdam (13)	Normal bilirubin (≤ULN) and normal albumin (≥LLN) after treatment when one or both parameters were abnormal before treatment

Abbreviations: ALP, alkaline phosphatase; AST aspartate aminotransferase; LLN, lower limit of normal; ULN, upper limit of normal.
†Deviation from Paris I and Mayo II incorporates total bilirubin ≤ULN instead of ≤1 mg/dL of normal total bilirubin levels.

In addition, the number and percentage of subjects with:

- Normal bilirubin (≤ULN) and normal albumin (≥LLN),
- Moderate (bilirubin >ULN or albumin <LLN), and
- Severe (bilirubin >ULN and albumin <LLN)

were summarised by treatment group at baseline, Week 2, Month 3, Month 6, Month 9 and Month 12.

Clinical laboratory values

The absolute and percentage change from baseline in ALP, GGT, ALT, AST, total and conjugated (direct) bilirubin, albumin, and prothrombin time (PT) and international standardised ratio (INR) (both measure to determine the clotting tendency of blood) were summarised by treatment group and visit.

The majority of patients display abnormal liver function tests and typically include elevated ALP, GGT, and mild elevations of AST. During the later stages of the disease, elevations of bilirubin, PT and INR are typically observed (33, 34, 43). Changes in liver function tests relate to the stage of the disease and the severity of any underlying histological lesions (34).

Questionnaires

PBC-40

The PBC-40 is a PBC-specific, validated questionnaire that has significantly greater relevance to problems specifically associated with PBC as opposed to other frequently used health-related quality of life (HRQoL) measures (129). The absolute change from baseline in six domains (cognitive, social, emotional function, fatigue, itch, and general symptoms) were summarised by treatment using descriptive statistics at Week 2, Month 3, Month 6, Month 9, and Month 12.

Patient research questionnaire

A simple patient research questionnaire was administered at Month 12, or at termination if the subject withdrew from the study prior to this, to request feedback about the subjects' perception of the study.

Biomarkers and non-invasive assessments of liver fibrosis

The absolute change from baseline was measured for:

- Markers of hepatic fibrosis, inflammation and other disease relevant biomarkers, including CRP, tumour necrosis factor-α (TNF-α), transforming growth factor-β (TGF-β), fibroblast growth factor-19 (FGF-19), Interleukin-6 (IL-6), CK-18, autotaxin, and lysophosphatidic acid (LA), at Month 6 and Month 12
- Enhanced liver fibrosis (ELF) score and its components hyaluronic acid (HA), procollagen-3 N-terminal peptide (P3NP), and tissue inhibitor of metalloproteinase 1 (TIMP-1) at Month 6 and Month 12
- Hepatic stiffness measurements (at selected study sites) at Month 12, assessed by transient elastography (TE).

Bile acids

The absolute values and the change from baseline were summarised by treatment group for the following at Month 6 and Month 12:

- Total bile acids, total endogenous bile acids, and totals for the individual bile acids (UDCA, chenodeoxycholic acid [CDCA], deoxycholic acid [DCA], cholic acid [CA] and lithocholic acid [LCA]) and their respective conjugates
- Proportion of each of the individual bile acids relative to total bile acids

Subjects taking UDCA and subjects not taking UDCA were analysed separately. Only samples from subjects who had a confirmed fasting of approximately 8 hours or more prior to their visit were included in the analysis.

OCA PK analysis

The values at Month 6 and Month 12 for OCA (unconjugated), glyco-OCA, tauro-OCA, and total OCA were summarised by active treatment group. Only samples from subjects who had a confirmed fasting (based on the eCRF) of approximately 8 hours or more prior to their visit were included in the analysis.

The effect of BAS on OCA and total bile acid concentration, as well as the percentage change in ALP, were explored as part of the PK analysis. Relationships between plasma total OCA concentrations (unconjugated and conjugated) and FGF-19 concentrations, endogenous bile acid concentrations, ALP and liver enzyme levels, and severity of pruritus were explored, as appropriate.

Safety

Treatment-emergent adverse events (TEAEs) were defined as any adverse events (AEs) that newly appeared, increased in frequency, or worsened in severity following initiation of investigational product. The incidence of TEAEs were recorded by treatment group.

Pruritus is considered an AE of special interest because it is both the most common symptom of PBC and the most frequently reported AE in the Phase 2 PBC studies for OCA. The 5-D pruritus questionnaire and a pruritus VAS were used at Week 2, Month 3, Month 6, Month 9 and Month 12, and results and changes from baseline were summarised at all time points.

Clinical laboratory evaluations

Physical examination, vital signs (blood pressure, heart rate and temperature), body weight and BMI, electrocardiogram, Dual-emission x-ray absorptiometry (DEXA) scan of the femoral neck and lumbar spine (to measure bone mineral density), Mayo Risk Score (MRS, a scoring system to assess survival) and MELD score (a scoring system for assessing the severity of chronic liver disease) were assessed at Week 2, Month 3, Month 6, Month 9 and Month12.

4.3.6.3 Secondary endpoints for the LTSE phase of POISE

Clinical laboratory values

The absolute and percentage change from baseline in ALP, GGT, ALT, AST, total and conjugated bilirubin, albumin, PT and INR were measured.

ALP response rates

The percentage of subjects with the following were measured:

- Decrease from baseline in ALP of ≥15% and ≥40%
- ALP ≤ULN
- ALP ≤2x ULN (15)
- ALP ≤1.76x ULN (18)
- ALP ≤1.67x ULN (18)

Biochemical treatment response criteria

The percentage of subjects meeting the Paris I (11), Paris II (12) and Mayo II (17) response criteria were measured. Definitions of these criteria can be found in Section 4.3.6.2.

Disease-specific symptoms

The absolute change from baseline in disease-specific symptoms were assessed using the HRQoL PBC-40 domain scores (general symptoms, itch, fatigue, cognitive function, social, emotional).

Biomarkers and non-invasive assessments of liver fibrosis

The following were measured:

- Absolute change from baseline in ELF score and its components HA, P3NP and TIMP-1
- Absolute change from baseline in hepatic stiffness (at selected study sites)
- Absolute and percentage change from baseline in other markers of hepatic fibrosis, inflammation, and other disease-relevant biomarkers, including CRP, TNF-α, TGF-β, FGF-19, IL-6, and CK-18

Antibodies

The absolute change from baseline in PBC antibodies (IgA, IgG and IgM) and other cytokines and interleukins (IL-12 and IL-23) were measured.

Pharmacokinetics and pharmacodynamics

The change from baseline in OCA and bile acids were summarised, including descriptive statistics of OCA plasma concentrations and the extent of BAS exposure. Initial evaluations of the effects of BAS on OCA, total bile acid concentrations and ALP were performed.

Safety

Safety endpoints included the following:

- TEAEs, serious adverse events (SAEs), severe AEs, related AEs, AEs leading to study drug withdrawal or study discontinuation, and AEs leading to death
- AEs of special interest: pruritus, hepatic disorders, dyslipidaemia, and cardiovascular disorders
- Physical examination
- Body weight and BMI
- Vital sign measurements
- 12-lead electrocardiograms
- DEXA scans
- Patient questionnaires: 5-D pruritus and Pruritus visual analogue scale (VAS)
- Clinical laboratory evaluations: haematology, serum chemistry, urine chemistry, and lipoprotein analytes
- MRS and MELD score

4.4 *Statistical analysis and definition of study groups in POISE*

4.4.1 *Analysis populations*

Intention-to-treat (ITT) population: All randomised subjects who received at least one dose of investigational product, with treatment assignment based on the randomised treatment. The ITT population was used for the summary of baseline characteristics and summaries and analyses of efficacy data in the double-blind phase.

Completer population: For the double-blind phase, the completer population consisted of all randomised subjects who received at least one dose of investigational product and participated through the duration of the double-blind phase (12 months), with treatment assignment based on the randomised treatment. For the LTSE phase, the completer population included all subjects who were exposed to OCA for at least a specified time, allowing for interim annual data cut-offs updated each year to include an additional year of completed minimum exposure time. The completer population was used to summarise specified baseline characteristics and additional analyses of efficacy data

Efficacy evaluable (EE) population: The EE population was only used in the double-blind phase, and included all subjects in the completer population who did not have any major protocol deviations that could potentially affect the efficacy of the investigational product. The EE population was used in the double-blind phase for the summary of baseline characteristics and summaries and analyses of efficacy data, unless the exclusion of subjects from the completer population was less than 10%.

Pharmacokinetic (PK) population: All subjects who had at least one confirmed fasting analysable sample at the Month 6 or Month 12 visit, and who did not have any major protocol deviations that could potentially affect exposure levels. The PK population was used for the bile acid and OCA PK analyses.

Safety population: All subjects who received at least one dose of investigational product, with treatment assignment based on the treatment actually received. The safety population was used for the analysis of all safety data in the double-blind phase and for the analysis of all safety and efficacy data in the LTSE phase.

4.4.2 *Primary hypothesis*

The null hypothesis for the primary efficacy endpoint in the double-blind phase was that the response rates to the primary efficacy analysis at 12 months are equal between the placebo and OCA 10 mg fixed dose treatment groups.

4.4.3 *Determination of sample size*

In the double-blind phase, the planned sample size was approximately 180 subjects (60 in each group). A previous Phase 2 study found that 9% of subjects receiving placebo and 40% of subjects receiving OCA 10 mg achieved a positive response to this study's endpoint. Assuming slightly more conservative response rates of 14% and 40%, respectively, and based on the use of a two-sided test of equality of binomial proportions at the 5% level of significance, a sample size of 60 subjects per group would provide 90% power to detect a difference between the 10 mg fixed dose OCA group and the placebo group.

Due to a screening window of up to 8 weeks, some subjects had already successfully completed screening procedures, met all inclusion criteria, and had been scheduled for randomisation after the planned sample size of 180 subjects had been met. These subjects proceeded to be randomised upon approval by the Sponsor.

No formal sample size calculations were performed for the LTSE phase of the study, since all subjects who completed treatment during the double-blind phase were eligible to continue into the LTSE phase.

4.4.4 *Statistical analyses*

Statistical analyses of the primary and secondary outcomes in the double-blind phase, including sensitivity analyses, are summarised in Table 17.

Table 17: Statistical analyses

Endpoint	Statistical analyses
Primary endpoint	
Primary efficacy analysis	Completed using a CMH test stratified by the randomisation stratification factor. Missing values were considered a non-response. Statistical significance was declared if the p-value was ≤0.05.
Secondary analyses of the primary endpoint	The same statistical methods described for the primary endpoint were used.
Secondary endpoints	
ALP response rates	The same statistical methods described for the primary endpoint were used.
Biochemical treatment response criteria	The same statistical methods described for the primary endpoint were used for the percentage of subjects meeting the response criteria. Only descriptive statistics were provided for the subgroup of subjects who met the criteria of a responder at baseline.
Clinical laboratory values	Analyses of observed laboratory values were performed using an ANCOVA model at each visit, with absolute change from baseline as the dependent variable, including treatment group and randomisation stratification factor as fixed effects and baseline value as a covariate. The same analysis was performed using percentage change from baseline as the dependent variable. The results, as well as estimates of LS means, SE, and 95% CIs, were presented by treatment group. Estimates of the mean difference between each OCA group and placebo, the SE of the difference, and 95% CI of the difference were also presented.
Questionnaires	PBC-40 results were summarised using descriptive statistics for each domain score. The change from baseline for each domain score was analysed using the same ANCOVA model described for the analysis of clinical laboratory values. Results from the patient research questionnaire were presented as frequency counts of the responses.
Biomarkers and non-invasive assessments of liver fibrosis	Hepatic stiffness and the ELF score and its components were summarised using descriptive statistics. The absolute change from baseline was analysed using the same ANCOVA model described for the analysis of clinical laboratory values.
Bile acids	The absolute values and the change from baseline were summarised using descriptive statistics. For total UDCA and total endogenous bile acid, the change from baseline concentrations within each treatment group was compared using a paired t-test.
OCA PK analysis	Values for OCA (unconjugated), glyco-OCA, tauro-OCA, and total OCA, and the extent of BAS exposure were summarised using descriptive statistics. Initial evaluation of the effects of BAS on OCA and total bile acid concentration, as well as on ALP, was performed using correlation analysis (bile acid concentrations and ALP versus the extent of BAS exposure prior to Month 6 and Month 12 endpoints). For total bile acids, the regression analysis was performed on

Endpoint	Statistical analyses
	absolute values as well as absolute and percentage change from baseline by treatment group. For OCA, the regression analysis was performed on absolute values by active treatment group (OCA titration and OCA 10 mg fixed dose). For ALP, the regression analysis was based on the percentage change from baseline values by treatment group. For Month 12 assessments, separate summaries were provided for subjects in the OCA titration group who remained at 5 mg, and for those who titrated to 10 mg. The correlation coefficient and the estimated regression equation were included in the correlation plots.
Safety	Investigational product exposure, average daily dose, study drug compliance and TEAEs were summarised with descriptive statistics. For pruritus (AE of special interest), Kaplan-Meier (product-limit) estimates were calculated by treatment group. The quartiles, including the median time-to-event and their respective two-sided 95% CIs were presented. The OCA treatment groups compared with placebo were summarised using a stratified log-rank test controlling for the randomisation stratification factor. Kaplan-Meier estimates were plotted as a 'survival curve' for each treatment group. Results from the 5-D pruritus questionnaire were summarised using descriptive statistics. Pruritus VAS and the change from baseline VAS were summarised using descriptive statistics, and the change from baseline was also analysed using the same ANCOVA model described for the analysis for clinical laboratory values.
Clinical laboratory evaluations	Clinical laboratory evaluations were summarised using descriptive statistics.

Abbreviations: ALP, alkaline phosphatase; ALT, alanine aminotransferase; ANCOVA, analysis of covariance; AST, aspartate aminotransferase; BAS, bile acid sequestrants; CI, confidence interval; CMH, Cochran-Mantel-Haenszel; ELF, enhanced liver fibrosis; GGT, gamma-glutamyl transferase; INR, international normalised ratio; LS, least squares; OCA, obeticholic acid; PBC, primary biliary cholangitis; PT, prothrombin time; SE, standard error; TE, transient elastography; TEAE, treatment-emergent adverse event; UDCA, ursodeoxycholic acid; ULN, upper limit of normal; VAS, visual analogue scale.

4.5 *Participant flow in the relevant randomised controlled trials*

4.5.1 *Patient disposition*

In total, 217 subjects were randomised. Of these, 144 were randomised to receive treatment with OCA, and 73 were randomised to receive placebo. Of those randomised to OCA treatment, 71 were randomised to the titration group (with a starting dose of 5 mg OCA), and the remaining 73 were randomised to the 10 mg fixed dose OCA treatment group. In total, 216 subjects received at least one dose of study drug. Patients were then stratified by biochemical status (see Table 18). A total of 94% and 91% of randomised subjects completed 6 months and 12 months of the study, respectively. There was one subject in the OCA titration group who withdrew consent after randomisation and prior to the first dose of investigational product, leaving 70 subjects in the ITT group (Table 19).

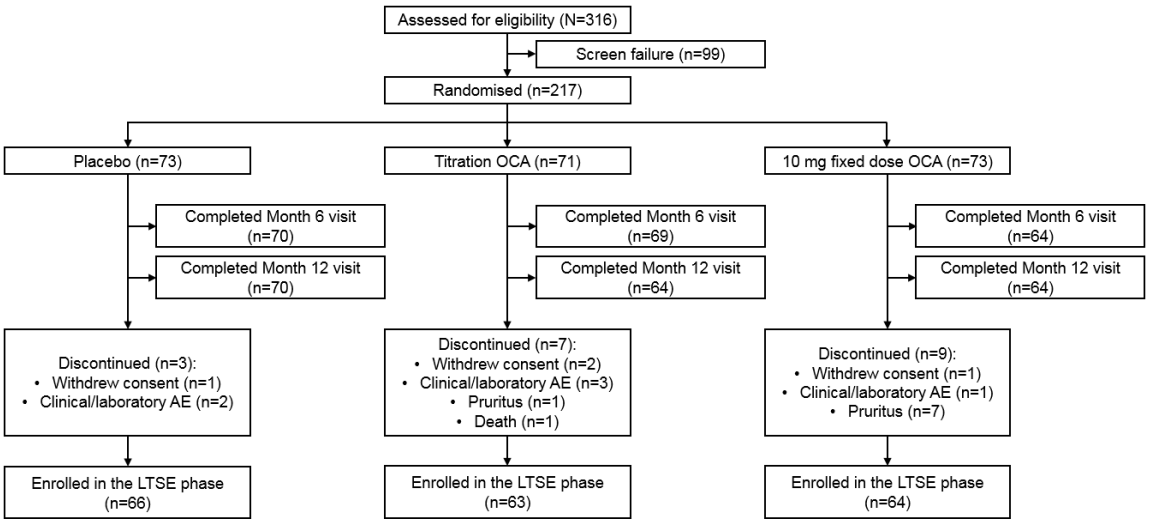
Table 18: Subject stratification†

Strata	Placebo, n (%)	OCA titration n (%)	10 mg fixed dose OCA, n (%)	Total, n (%)
Total	73 (100)	71 (100)	73 (100)	217
ALP >3x ULN and/or AST >2x ULN and/or bilirubin >ULN, intolerant to UDCA	3 (4)	3 (4)	3 (4)	9 (4)
ALP ≤3x ULN and/or AST ≤2x ULN and/or bilirubin ≤ULN, intolerant to UDCA	2 (3)	2 (3)	2 (3)	6 (3)
ALP >3x ULN and/or AST >2x ULN and/or bilirubin >ULN, currently taking UDCA	23 (32)	22 (31)	23 (32)	68 (31)
ALP ≤3x ULN and/or AST ≤2x ULN and/or bilirubin <ULN, currently taking UDCA	45 (62)	44 (62)	45 (62)	134 (62)

Abbreviations: ALP, alkaline phosphatase; AST, aspartate aminotransferase; OCA, obeticholic acid; UDCA, ursodeoxycholic acid; ULN, upper limit of normal. †Columns may not add due to rounding.

A CONSORT flow diagram for POISE is presented in Figure 11 and analysis populations are presented in Table 19.

Figure 11: CONSORT diagram for POISE trial



Abbreviations: AE, adverse event; LTSE, long-term safety extension; OCA, obeticholic acid.

Table 19: Analysis populations

	Number of subjects, n (%)			
	Placebo	**OCA titration**	**OCA 10 mg fixed dose**	**Total**
Enrolled/randomised	73 (100)	71 (100)	73 (100)	217 (100)
ITT population[§]	73 (100)	70[†] (99)	73 (100)	216 (<100)
Completer population[¶]	70 (96)	64 (90)	64 (88)	198 (91)
EE population[‡]	67 (92)	63 (89)	62 (85)	192 (88)
PK population[††]	0 (0)	66 (93)	60 (82)	126 (58)
Safety population[§§]	73 (100)	70 (99)	73 (100)	216 (<100)

Abbreviations EE, efficacy evaluable; ITT, intention-to-treat; OCA, obeticholic acid; PK, pharmacokinetics. [†]There was one subject in the OCA titration group who withdrew after randomisation, leaving 70 subjects in the ITT group; [§]All randomised subjects who received at least one dose of investigational product. Treatment assignment is based on the randomised treatment; [¶]All randomised subjects who received at least one dose of investigational product and participated through the end of the double-blind phase (12 months). Treatment assignment is based on the randomised treatment; [‡]All subjects in the completer population who did not have any major protocol deviations that could have potentially affected the efficacy of the investigational product. Treatment assignment is based on the randomised treatment; [††]All randomised subjects who received at least one dose of OCA who have at least one confirmed fasting sample at Month 6 and Month 12 visits (subjects must have been fasting for approximately 8 hours prior to the visit) and who did not have any major protocol deviations that could have potentially affected exposure levels; [§§]All subjects who received at least one dose of study drug. Treatment assignment is based on the treatment actually received.

4.5.2 *Baseline characteristics and demographics*

4.5.2.1 Baseline patient demographics

Key demographic and baseline characteristics are summarised in Table 20. Treatment groups were well balanced for each key demographic and baseline variable. For the overall population, mean age was 55.8 years, with a range from 29 to 86 years, and a total of 81% of subjects were <65 years of age. As expected with PBC, the study population was predominantly female (91%) and white (94%). The majority of the

population was European (67%), followed by North American (29%), and Australian (4%). The mean body weight and BMI were 69.8 kg and 26.0 kg/m^2, respectively, with 82% of subjects having a BMI <30 kg/m^2. Clinical expert opinion has validated that the patient population in POISE is representative of the population with PBC in the UK.

The majority (93%) of the population were taking UDCA at baseline. A small subset of patients (n=11) were unable to tolerate UDCA and received OCA as monotherapy. Efficacy results for this patient subgroup are presented in Section 4.8.4.3 but should be interpreted with caution due to low patient numbers.

Table 20: Baseline patient demographics

	Placebo (n=73)	OCA titration (n=70)	OCA 10 mg fixed dose (n=73)	Total (n=216)
Age, years				
Mean (SD)	55.5 (10.0)	55.8 (10.5)	56.2 (11.0)	55.8 (10.5)
Median	55.0	54.5	56.0	55.0
Min, max	35, 78	29, 83	30, 86	29, 86
Age subgroups, n (%)				
<65 years	60 (82)	60 (86)	56 (77)	176 (81)
≥65 years	13 (18)	10 (14)	17 (23)	40 (19)
Gender, n (%)				
Male	5 (7)	5 (7)	10 (14)	20 (9)
Female	68 (93)	65 (93)	63 (86)	196 (91)
Race/ethnicity, n (%)				
White	66 (90)	67 (96)	70 (96)	203 (94)
Non-white	7 (10)	3 (4)	3 (4)	13 (6)
Body weight, kg				
Mean (SD)	70.2 (13.3)	68.2 (13.1)	71.0 (15.3)	69.8 (13.9)
Median	70.5	65.2	67.6	67.5
Min, max	41.0, 106.0	46.7, 101.8	50.8, 134.0	41.0, 134.0
Region, n (%)				
Europe	49 (67)	45 (64)	51 (70)	145 (67)
North America	21 (29)	20 (29)	21 (29)	62 (29)
Australia	3 (4)	5 (7)	1 (1)	9 (4)
BMI, kg/m^2				
Mean (SD)	26.2 (4.4)	25.8 (4.9)	26.3 (5.1)	26.0 (4.8)
Median	25.9	24.5	25.1	25.0
Min, max	16.4, 37.6	17.7, 40.7	20.4, 49.2	16.4, 49.2
BMI subgroups, n (%)				
<30 kg/m^2	58 (79)	58 (83)	61 (84)	177 (82)
≥30 kg/m^2	15 (21)	11 (16)	12 (16)	38 (18)

	Placebo (n=73)	OCA titration (n=70)	OCA 10 mg fixed dose (n=73)	Total (n=216)
Pre-treatment liver biopsy, n (%)				
Yes	7 (10)	13 (19)	9 (12)	29 (13)
No	66 (90)	57 (81)	64 (88)	187 (87)
UDCA use at baseline, n (%)				
Yes	68 (93)	65 (93)	67 (92)	200 (93)
No	5 (7)	5 (7)	6 (8)	16 (7)

Abbreviations: BMI, body mass index; OCA, obeticholic acid; SD, standard deviation; UDCA, ursodeoxycholic acid.

4.5.2.2 Baseline disease characteristics

PBC baseline disease characteristics are summarised in Table 21. In general, each variable was well balanced across treatment groups. Overall, the mean age at time of diagnosis was 47.3 years with a mean duration of PBC of 8.6 years, and there was a comparable percentage of subjects with a duration of PBC ≤7.5 years versus >7.5 years. There were slightly more subjects <50 years of age at PBC diagnosis (58%) compared with ≥50 years of age.

Patients were comparable between groups based on a history of pruritus, but the overall incidence of pruritus at baseline was slightly higher for subjects in the placebo treatment group (64%) and OCA 10 mg fixed dose group (60%) than in the OCA titration group (53%).Overall severity of pruritus at baseline was assessed by the investigator as mild (43%), moderate (15%), or severe (1%).

A total of 128 (59%) subjects reported a history of fatigue prior to entering the study, with the most recent fatigue events being mild for 34% of patients, moderate for 19% of patients, and severe for 5% of patients. The overall incidence of fatigue was slightly higher for subjects in the placebo treatment group (67%) than in the OCA titration and OCA 10 mg fixed dose groups (54% and 56%, respectively).

Table 21: Baseline PBC disease characteristics: ITT population

Disease characteristic	Placebo (n=73)	OCA titration (n=70)	OCA 10 mg fixed dose (n=73)	Total (n=216)
History of pruritus, n (%)				
Yes	47 (64)	45 (64)	45 (62)	137 (63)
No	26 (36)	25 (36)	28 (38)	79 (37)
Severity of most recent pruritus event for subjects who had history of pruritus, n (%)				
Mild	31 (66)	29 (64)	34 (76)	94 (69)
Moderate	14 (30)	13 (29)	8 (18)	35 (26)
Severe	1 (2)	2 (4)	3 (7)	6 (4)
Unknown	1 (2)	1 (2)	0 (0)	2 (1)

Disease characteristic	Placebo (n=73)	OCA titration (n=70)	OCA 10 mg fixed dose (n=73)	Total (n=216)
Pruritus at baseline, n (%)				
Yes	47 (64)	37 (53)	44 (60)	128 (59)
Mild	32 (44)	27 (39)	33 (45)	92 (43)
Moderate	13 (18)	10 (14)	10 (14)	33 (15)
Severe	2 (3)	0 (0)	1 (1)	3 (1)
No	26 (36)	33 (47)	29 (40)	88 (41)
History of fatigue, n (%)				
Yes	49 (67)	38 (54)	41 (56)	128 (59)
No	24 (33)	32 (46)	32 (44)	88 (41)
Overall severity of PBC-related fatigue, n (%)				
Mild	28 (38)	17 (24)	29 (40)	74 (34)
Moderate	16 (22)	16 (23)	8 (11)	40 (19)
Severe	3 (4)	5 (7)	3 (4)	11 (5)
Age at PBC diagnosis, years				
Mean (SD)	47.3 (9.3)	47.6 (11.7)	47.1 (10.6)	47.3 (10.5)
Median	48.0	48.0	47.0	47.5
Min, Max	31, 74	25, 82	24, 78	24, 82
Age at PBC diagnosis subgroups, n (%)				
<50 years	45 (62)	38 (54)	42 (58)	125 (58)
≥50 years	28 (38)	32 (46)	31 (42)	91 (42)
Mean duration of PBC, years				
Mean (SD)	8.3 (5.4)	8.3 (5.8)	9.2 (6.9)	8.6 (6.0)
Median	7.4	7.2	8.5	7.8
Min, max	0.9, 21.8	0.3, 27.0	0.0, 32.3	0.0, 32.3
Duration of PBC subgroups, n (%)				
≤7.5 years	39 (53)	36 (51)	30 (41)	105 (49)
>7.5 years	34 (47)	34 (49)	43 (59)	111 (51)

Abbreviations: OCA, obeticholic acid; ITT, intention-to-treat; PBC, primary biliary cholangitis; SD, standard deviation.

4.5.2.3 Baseline liver laboratory parameters

Key baseline laboratory variables indicative of intrahepatic cholestasis, hepatocellular injury, and synthetic hepatic function are summarised in Table 22. In general, mean

baseline values were well balanced across treatment groups. These baseline data were consistent with the protocol inclusion criterion for subjects with PBC with either ALP ≥1.67x ULN[a] or total bilirubin >ULN but <2x ULN, and the exclusion of subjects with clinically significant hepatic decompensation. Mean baseline albumin values were predominantly (81– 89%) ≥LLN. In addition, the majority (94–99%) of subjects had a baseline INR ≤1.3, indicative of a population in an early stage of disease progression. Conjugated bilirubin is widely accepted as an early sign of hepatobiliary damage. The mean conjugated bilirubin levels at baseline were approximately 1.5–2.0x ULN, indicating evidence of hepatic dysfunction in the study population.

Mean baseline ALP values were well balanced across treatment groups, with 29% of subjects having a baseline ALP >3x ULN. Mean baseline total bilirubin values ranged from 10.3 µmol/L to 11.8 µmol/L across treatment groups, with 92% of subjects within normal range. Therefore, the majority of subjects met the inclusion criterion of ALP ≥1.67x ULN rather than the total bilirubin criterion >ULN but <2x ULN.

As expected in this patient population with intrahepatic cholestasis, GGT was substantially elevated across all three treatment groups (approximately 9–12x ULN). Mean baseline GGT levels were slightly higher in the placebo group than in the OCA groups; however, it should be noted the placebo group had a larger degree of variability than the OCA groups.

Hepatocellular transaminases (ALT and AST) were also elevated across all treatment groups, albeit to a much smaller magnitude (approximately 2x ULN) than GGT. This was not unexpected, given that PBC is often associated with mild and less consistent elevations of ALT and AST, which are typically more indicative of liver damage rather than intrahepatic cholestasis (34).

Table 22: Baseline liver parameters: ITT population

	Placebo (n=73)	OCA titration (n=70)	OCA 10 mg fixed dose (n=73)
ALP, U/L			
Mean (SD)	327.5 (115.0)	325.9 (116.2)	316.3 (103.9)
Min, max	143.8, 745.9	186.8, 811.0	207.1, 619.5
≤3x ULN, n (%)	50 (68)	51 (73)	53 (73)
>3x ULN, n (%)	23 (32)	19 (27)	20 (27)

[a] ALP ULN=118.3 U/L (female) and 124.2 U/L (male); total bilirubin ULN=19.32 µmol/L (female) and 25.48 µmol/L (male).

	Placebo (n=73)	OCA titration (n=70)	OCA 10 mg fixed dose (n=73)
Total bilirubin, µmol/L			
Mean (SD)	11.8 (7.4)	10.3 (5.5)	11.3 (6.7)
Min, max	2.3, 39.3	2.1, 36.4	1.6, 34.4
≤ULN, n (%)	66 (90)	66 (94)	66 (90)
>ULN, n (%)	7 (10)	4 (6)	7 (10)
Conjugated bilirubin, µmol/L			
Mean (SD)	5.5 (6.0)	4.5 (4.5)	4.9 (4.4)
Min, max	1.5, 31.3	1.5, 35.2	1.5, 23.9
≤ULN, n (%)	37 (51)	37 (53)	35 (48)
>ULN, n (%)	36 (49)	33 (47)	38 (52)
GGT, U/L			
Mean (SD)	309.6 (449.4)	252.8 (167.0)	261.1 (207.4)
Min, max	45.2, 3263.5	43.1, 727.8	48.2, 1084.0
ALT, U/L			
Mean (SD)	56.0 (30.3)	61.6 (39.0)	56.3 (39.7)
Min, max	17.1, 174.9	17.1, 245.5	16.3, 240.2
AST, U/L			
Mean (SD)	48.8 (22.4)	52.3 (25.3)	50.5 (31.1)
Min, max	20.6, 156.5	20.1, 173.4	23.3, 186.5
Albumin, g/L			
Mean (SD)	42.8 (3.1)	43.0 (3.1)	43.7 (2.7)
Min, max	32.5, 48.0	33.0, 50.5	36.5, 49.5
<LLN, n (%)	14 (19)	8 (11)	8 (11)
≥LLN, n (%)	59 (81)	62 (89)	65 (89)
INR†			
Mean (SD)	0.98 (0.1)	1.07 (0.4)	1.02 (0.3)
Min, max	0.7, 1.2	0.9, 3.5	0.8, 3.5
≤1.3	72 (99)	66 (94)	69 (95)
>1.3	0 (0)	3 (4)	2 (3)

Abbreviations: ALP, alkaline phosphatase; ALT, alanine aminotransferase; AST, aspartate aminotransferase; GGT, gamma-glutamyl transferase; INR, international standardised ratio; ITT, intention-to-treat; LLN, lower limit of normal; OCA, obeticholic acid; SD, standard deviation; ULN, upper limit of normal.
†Placebo n=72, OCA titration n=69, and OCA 10 mg fixed dose n=71.

4.6 *Quality assessment of the relevant randomised controlled trials*

A complete quality assessment for POISE is provided in Appendix 3.

4.7 *Clinical effectiveness results*

4.7.1 *POISE*

4.7.1.1 Primary efficacy endpoint at 12 months

The primary efficacy endpoint (superiority of 10 mg OCA fixed dose vs placebo, measured by the percentage of subjects with ALP <1.67x ULN and total bilirubin ≤ULN and ALP decrease ≥15% from baseline at 12 months) was met (see Table 23 and Figure 12). Almost five times as many patients (47% of subjects) in the OCA 10 mg fixed dose group achieved the primary endpoint at 12 months than in the placebo group (10% of subjects; p<0.0001). The primary efficacy analysis was repeated using the EE population and Completer populations, which were numerically comparable with the ITT population and statistically significant compared with placebo (p<0.0001).

The key secondary analysis of the primary endpoint demonstrated that 46% of subjects in the OCA titration group also achieved the primary endpoint after 12 months of OCA treatment (p<0.0001 vs placebo) (Figure 12). It is worth noting that those subjects who failed to respond to treatment with 5 mg OCA at Month 6 in the titration group had their dose increased to 10 mg OCA until Month 12. As such, there was an increase in the percentage of responders in those who titrated when comparing Month 6 data with Month 12 data. The increase in responders in this subgroup of patients is responsible for the overall increase in responders in the OCA titration group. On the other hand, patients who met the primary endpoint at Month 6 did not up-titrate, despite the fact that they may have experienced further benefit from the increased dose. Indeed, some patients who remained at 5 mg OCA were responders at Month 6 but not at Month 12. This is one of the reasons that the SmPC recommends all patients to up-titrate from 5 mg to 10 mg after 6 months, if OCA is tolerated.

Table 23: Summary of primary efficacy endpoint analyses

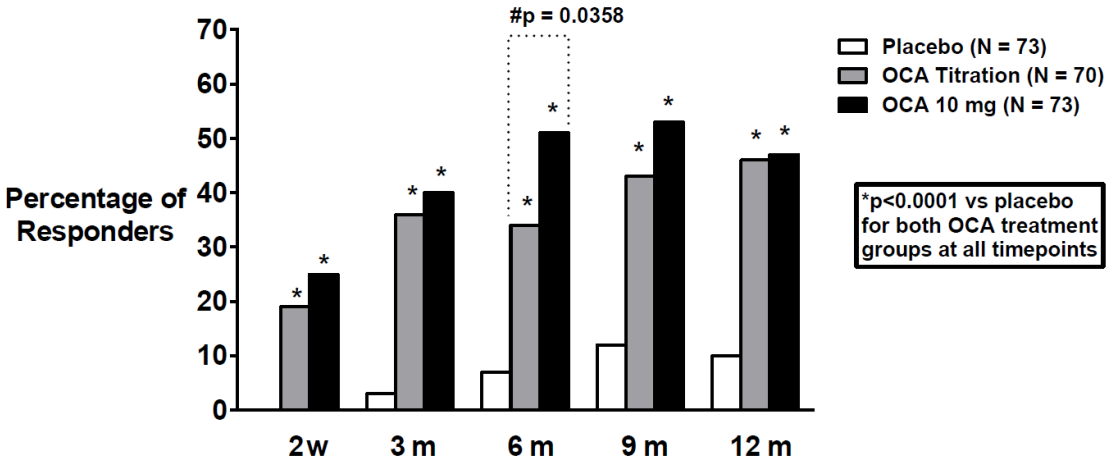
	Responders (%)	
	Month 6	**Month 12**
Placebo (n=73)	7%	10%
10 mg OCA (n=73)	51%	47%
Titration OCA (n=70)	34%	46%
Titration subgroup[†]		
Remained at 5 mg OCA for 12 months (n=36)	67%[§]	53%
Titrated to 10 mg OCA at Month 6 (n=33)	0%	39%

Abbreviations: ALP, alkaline phosphatase; OCA, obeticholic acid.
[†]There was one subject who withdrew from the trial due to an AE after 8 days of study medication, and

therefore there were no data for this subject at Month 6 and Month 12. §Of the 12 subjects who did not respond but did not up-titrate, nine did not increase their dose due to adverse events, and three recorded their reason as 'other'.

Other secondary analyses of the primary endpoint included the percentage of subjects achieving the endpoint at 2 weeks, and at 3, 6, 9 and 12 months (Figure 12). Both OCA treatment groups were superior to placebo in achieving the composite endpoint at all time points across the 12-month treatment period (p<0.0001 versus placebo). At Month 6, a higher percentage of subjects in the OCA 10 mg group (51%) achieved the composite endpoint compared with the OCA titration group (34%), which was statistically significant (p=0.0358). However, this is not surprising given the dose response of OCA since at this point, all patients in the OCA titration group had been receiving 5 mg per day for 6 months compared with 10 mg per day in the OCA 10 mg fixed dose group.

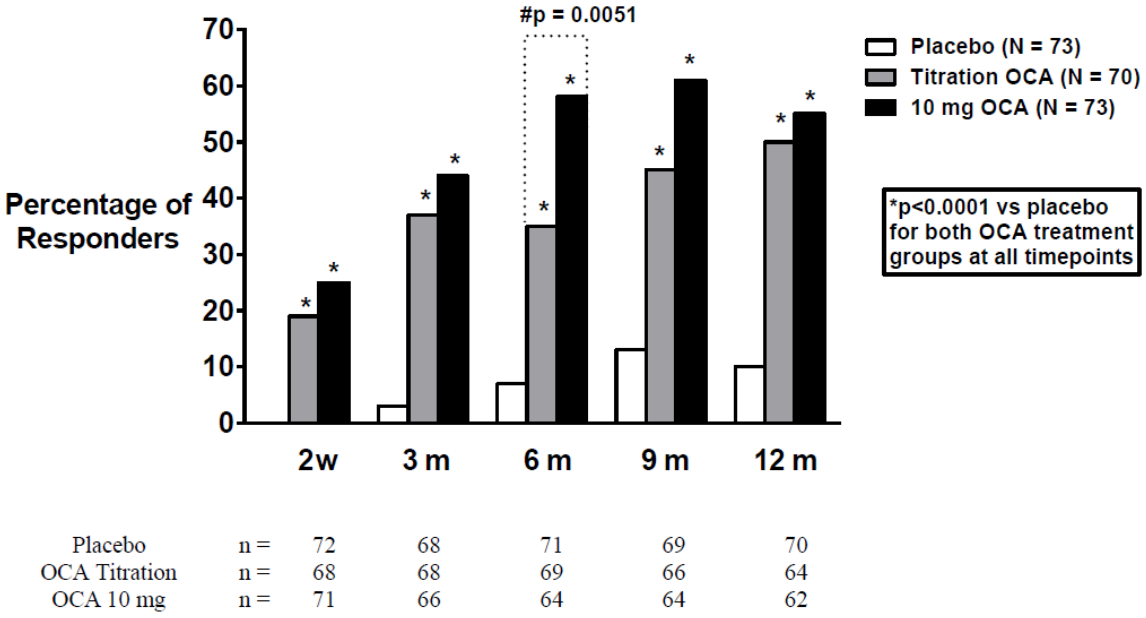
Figure 12: Secondary analyses: percentage of subjects achieving the primary endpoint at other time points



Abbreviations: OCA, obeticholic acid.
* p-value for treatment group versus placebo; # p-value for the between treatment group comparison at Month 6 of OCA titration (5 mg) and OCA 10 mg. P-values obtained using Cochran-Mantel-Haenszel tests stratified by randomization strata factor. Missing values were considered a non-response.

In sensitivity analyses of the primary endpoint, using observed data only, both OCA treatment groups were superior to placebo at all time points, with statistically significant differences apparent as early as Week 2 (p<0.0001). Statistically significantly (p=0.0051) more subjects in the OCA 10 mg group achieved the endpoint at 6 months compared with those in the titration group (Figure 13). Between Month 6 and Month 12, the percentage of subjects achieving the endpoint increased from 35% to 50% for the OCA titration group and was maintained for the OCA 10 mg fixed dose group (58% at Month 6 and 55% at Month 12). As with the primary endpoint, the increase observed from Month 6 to Month 12 in the OCA titration group is attributable to the group that titrated to 10 mg following the Month 6 visit versus those that remained on OCA 5 mg.

Figure 13 Sensitivity analysis of primary endpoint using observed data only



Placebo	n =	72	68	71	69	70
OCA Titration	n =	68	68	69	66	64
OCA 10 mg	n =	71	66	64	64	62

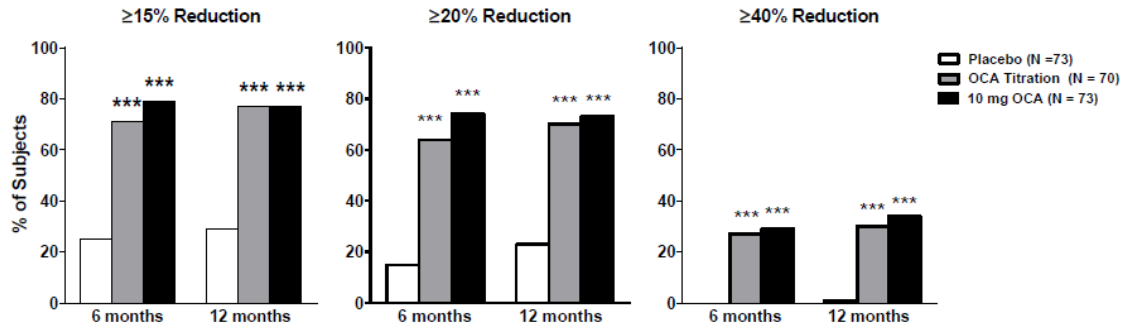
Abbreviations: OCA, obeticholic acid.
*p<0.0001; #p=0.0051 for the between treatment group comparison at Month 6 of OCA titration (5 mg) and OCA 10 mg. p-value obtained using Cochran-Mantel-Haenszel test stratified by randomisation strata factor.

4.7.1.2 Secondary efficacy endpoints

Responders based on ALP

The percentages of subjects achieving ALP reductions of ≥15%, ≥20%, and ≥40% at 6 months and 12 months are summarised in Figure 14. The odds ratios of achieving each respective reduction for both OCA groups vs placebo are summarised in Table 24. At both time points and for each ALP category, a statistically significantly higher percentage of OCA-treated subjects achieved the reduction in ALP compared with placebo (p<0.0001 vs placebo for both OCA treatment groups). At 12 months, 21 (30%) and 25 (34%) subjects from the OCA titration and OCA 10 mg fixed dose groups, respectively, achieved an ALP reduction from baseline ≥40% compared with 1 (1%) subject in the placebo group.

Figure 14: Percentage reduction from baseline in ALP



p-values versus placebo obtained using the Cochran-Mantel-Haenszel test stratified by randomisation strata factor. ***p<0.0001.

Table 24: Odds ratio of percentage reduction in ALP from baseline: ITT population

Odds ratio	≥15% reduction		≥20 reduction		≥40% reduction	
	OCA titration	OCA 10 mg	OCA titration	OCA 10 mg	OCA titration	OCA 10 mg
Month 6	7.8 (3.7, 16.5)	12.1 (5.5, 26.5)	10.2 (4.5, 22.8)	16.1 (7.0, 36.8)	NA†	NA†
p-value for treatment ratio (OCA vs placebo)†	<0.0001	<0.0001	<0.0001	<0.0001	NA†	NA†
Month 12	8.4 (4.0, 17.9)	8.2 (3.9, 17.3)	7.8 (3.7, 16.4)	8.8 (4.2, 18.7)	34.7 (4.4, 271.3)	43.0 (5.5, 334.9)
p-value for treatment ratio (OCA vs placebo)‡	<0.0001	<0.0001	<0.0001	<0.0001	0.0007	0.0003

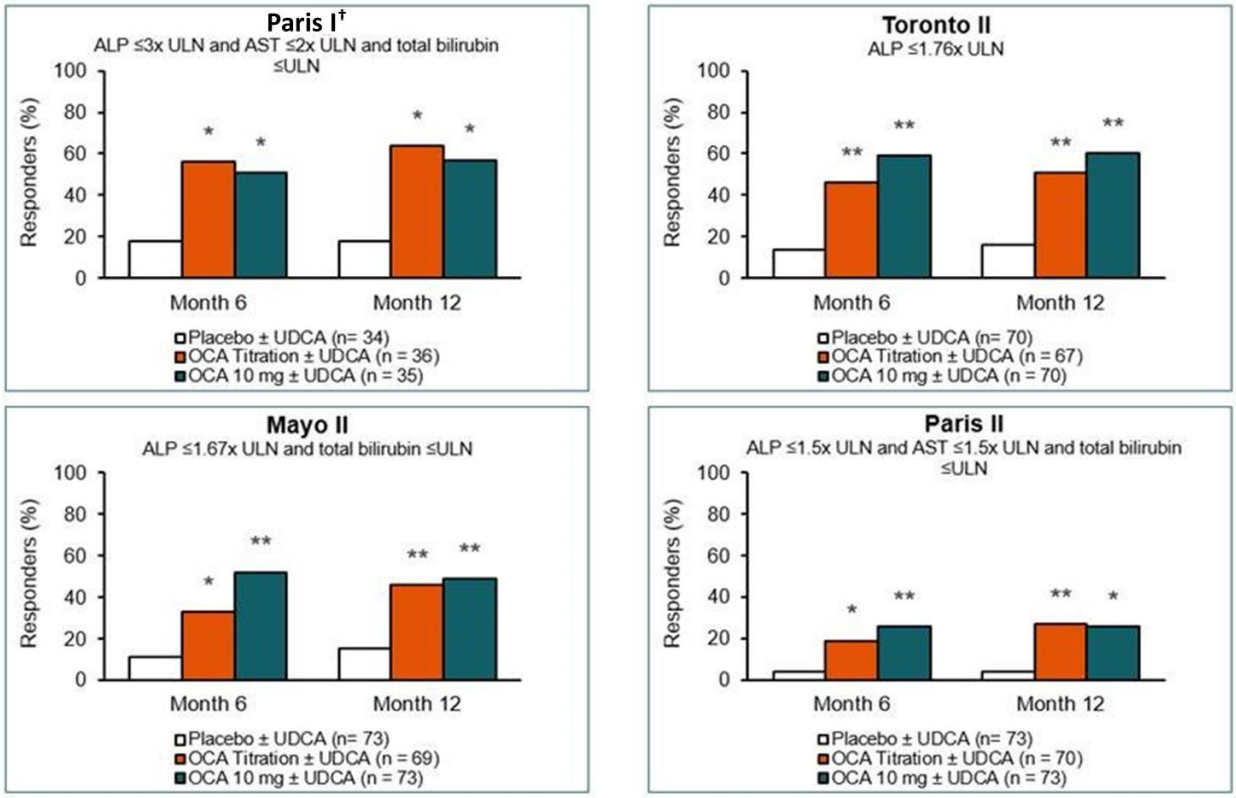
† Not applicable (NA) since zero subjects from the placebo group achieved ≥40% reduction from Baseline at Month 6. ‡p-values obtained using a logistic regression model with terms for treatment and the randomisation strata factor.

Responders based on the biochemical response criteria

Percentage of non-responders at baseline who responded at Month 6 and Month 12

Figure 15 and Table 25 summarise the percentage of non-responders at baseline who became responders at Month 6 and Month 12 for each of the biochemical treatment response criteria. A higher percentage of OCA-treated subjects (both in the titration group and the 10 mg fixed dose group) responded to each of the criteria at both Month 6 and Month 12 compared with placebo-treated subjects. The difference between placebo and each OCA treatment group was statistically significant at both time points for all criteria, with the exception of the Rotterdam criteria where the number of subjects who were non-responders at baseline was low.

Figure 15: Percentage of responders based on Paris I†, Toronto II, Mayo II and Paris II biochemical treatment response criteria: ITT population



Abbreviations: ALP, alkaline phosphatase; AST, aspartate aminotransferase; OCA, obeticholic acid; UDCA, ursodeoxycholic acid; ULN, upper limit of normal.
† Deviation from Paris I: incorporation of total bilirubin ≤ULN instead of ≤1 mg/dL of normal total bilirubin levels; **p-value <0.01; ***p-value ≤0.0001 for comparing treatments using Cochran-Mantel-Haenszel General Association test were stratified by randomisation strata factor.

Table 25: Percentage of responders and odds ratios based on biochemical treatment response criteria: ITT population

Endpoint, n (%)	Placebo		OCA titration		OCA 10 mg fixed dose	
	Month 6	Month 12	Month 6	Month 12	Month 6	Month 12
Paris I: ALP ≤3x ULN and AST ≤2x ULN and total bilirubin ≤ULN						
Non-responders at baseline	34		36		35	
Responders	6 (18)	6 (18)	20 (56)	23 (64)	18 (51)	20 (57)
p-value	–	–	0.0013	0.0002	0.0025	0.0007
Odds ratio vs placebo (95% CI)	–	–	6.0 (1.9, 18.6)	9.4 (2.8, 31.0)	5.2 (1.7, 16.0)	7.2 (2.2, 23.7)
p-value	–	–	0.0019	0.0002	0.0045	0.0011
Paris II: ALP ≤1.5x ULN and AST ≤1.5x ULN and total bilirubin ≤ULN						
Non-responders at baseline	73		70		73	
Responders	3 (4)	3 (4)	13 (19)	19 (27)	19 (26)	19 (26)
p-value	–	–	0.0055	0.0001	0.0001	0.0002
Odds ratio vs placebo (95% CI)	–	–	5.8 (1.5, 21.9)	9.1 (2.5, 32.6)	9.4 (2.6, 34.5)	8.5 (2.4, 30.6)
p-value	–	–	0.0095	0.0007	0.0007	0.0010
Mayo II: ALP ≤1.67x ULN and total bilirubin ≤ULN						
Non-responders at baseline	73		69		73	
Responders	8 (11)	11 (15)	23 (33)	32 (46)	38 (52)	36 (49)
p-value	–	–	0.0010	<0.0001	<0.0001	<0.0001
Odds ratio vs placebo (95% CI)	–	–	4.5 (1.8, 11.2)	5.7 (2.5, 13.1)	10.7 (4.3, 26.5)	6.4 (2.8, 14.7)
p-value	–	–	0.0013	<0.0001	<0.0001	<0.0001

Endpoint, n (%)	Placebo		OCA titration		OCA 10 mg fixed dose	
	Month 6	Month 12	Month 6	Month 12	Month 6	Month 12
Toronto II: ALP ≤1.76x ULN						
Non-responders at baseline	70		67		70	
Responders	10 (14)	11 (16)	31 (46)	34 (51)	41 (59)	42 (60)
p-value	–	–	<0.0001	<0.0001	<0.0001	<0.0001
Odds ratio vs placebo (95% CI)	–	–	6.5 (2.7, 15.5)	7.2 (3.0, 17.2)	11.9 (4.9, 29.0)	11.5 (4.7, 27.7)
p-value	–	–	<0.0001	<0.0001	<0.0001	<0.0001
Rotterdam (normal range): total bilirubin ≤ULN and albumin ≥LLN						
Non-responders at baseline	17		12		13	
Responders	2 (12)	1 (6)	3 (25)	2 (17)	3 (23)	3 (23)
p-value	–	–	0.4170	0.3537	0.3412	0.0992
Odds ratio vs placebo (95% CI)	–	–	3.0 (0.4, 23.2)	4.3 (0.3, 58.8)	2.7 (0.4, 20.3)	6.2 (0.5, 72.0)
p-value	–	–	0.2980	0.2704	0.3239	0.1429

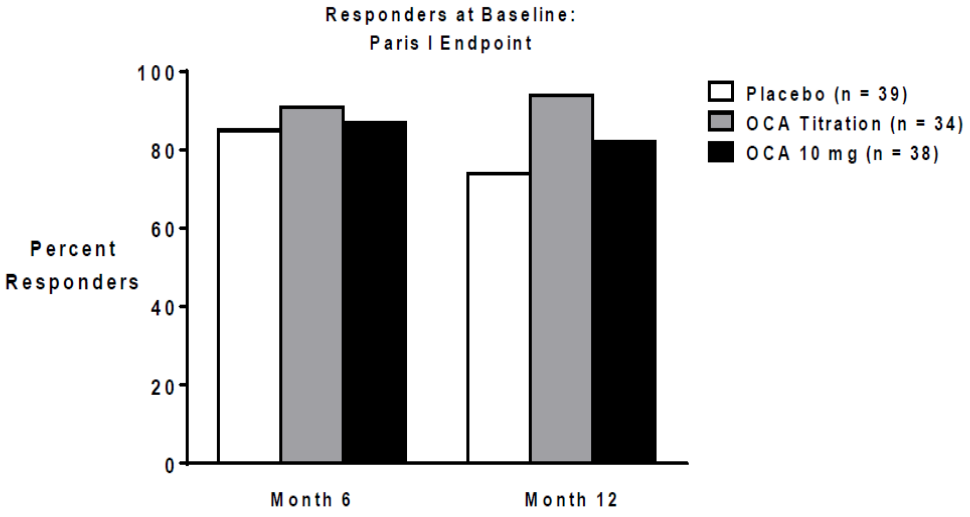
Abbreviations: ALP, alkaline phosphatase; AST, aspartate aminotransferase; CI, confidence interval; LLN, lower limit of normal' OCA, obeticholic acid; ULN upper limit of normal.

Maintenance of response in subjects who were responders at baseline

A separate analysis for those subjects that met the responder criteria at baseline for each of the pre-defined criteria was performed for each outcome, to assess the maintenance of response during the 12-month treatment period. Given that the majority (>95%) of subjects were non-responders at baseline for most endpoint criteria, data are presented only for the Paris I endpoint where approximately 50% of the subjects were responders at baseline.

In OCA-treated subjects who met the Paris I criteria of responder at baseline (ALP ≤3x ULN and AST ≤2x ULN and total bilirubin ≤ULN), the response was sustained at Month 6 and Month 12 (Figure 16).

Figure 16 Percentage responders at baseline to Paris I criteria at Month 6 and Month 12

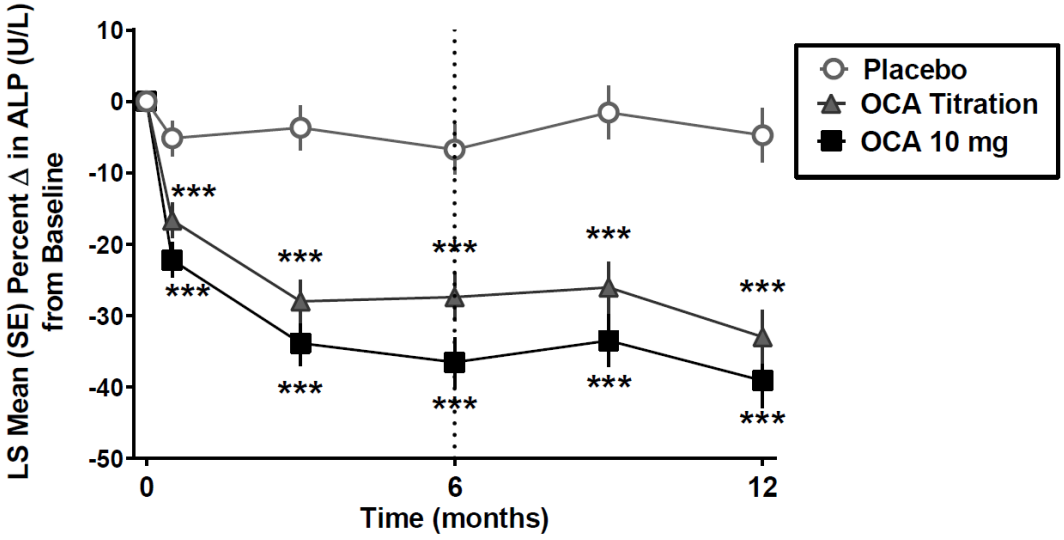


Abbreviations: OCA, obeticholic acid. Per statistical analysis plan, only descriptive statistics were provided.

Absolute and percentage change in ALP

Within 2 weeks, there was a rapid, statistically significant reduction in ALP in both OCA treatment groups when compared with placebo, which was maintained for the duration of the study (Figure 17). Table 26 summarises the least squares (LS) mean of the absolute and percentage change from baseline in ALP at Month 6 and Month 12 for the ITT population. For both OCA treatment groups, clinically and statistically significant improvements from baseline were observed at both Month 6 and Month 12, compared with placebo ($p<0.0001$ for both OCA treatment groups). At Month 12, the LS mean percentage change from baseline was –33% and –39% for the OCA titration and 10 mg fixed dose groups, respectively, compared with only –5% for the placebo group. ALP is the key biomarker for PBC, and a reduction in ALP is the main objective of treatment with PBC and has been shown to correlate with reduced risks of complications, liver transplantation, and death (15, 17, 18).

Figure 17: Change in ALP from baseline over time: ITT population



Abbreviations: ALP, alkaline phosphatase; ITT, intention-to-treat; OCA, obeticholic acid; UDCA, ursodeoxycholic acid.
*** p<0.0001 vs placebo.

Table 26: Change in ALP from baseline at Month 6 and Month 12: ITT population

Mean ALP, U/L (SE)	Placebo	OCA titration	OCA 10 mg fixed dose
Baseline†	327.5 (13.5)	325.9 (13.9)	316.3 (12.2)
Month 6			
Mean	311.1 (14.4)	239.3 (13.2)	196.1 (8.4)
LS mean change	–21.7 (13.2)	–91.2 (12.9)	–121.5 (13.2)
OCA vs placebo	–	–69.6 (11.7)	–99.9 (12.0)
p-value‡	–	<0.0001	<0.0001
LS mean % change	–6.8 (3.5)	–27.4 (3.4)	–36.5 (3.5)
OCA vs placebo	–	–20.7 (3.1)	–29.8 (3.2)
p-value‡	–	<0.0001	<0.0001
Month 12			
Mean	321.3 (17.1)	219.5 (12.5)	192.3 (7.8)
LS mean change	–14.4 (14.7)	–112.5 (14.4)	–129.9 (14.6)
OCA vs placebo	–	–98.1 (13.1)	–115.5 (13.2)
p-value‡	–	<0.0001	<0.0001
LS mean % change	–4.8 (3.8)	–33.0 (3.7)	–39.1 (3.8)
OCA vs placebo	–	–28.2 (3.4)	–34.4 (3.4)
p-value‡	–	<0.0001	<0.0001

Abbreviations: ALP, alkaline phosphatase; ANCOVA, analysis of covariance; ITT, intention-to-treat; LS, least squares; OCA, obeticholic acid.
† Baseline is defined as the mean of all available evaluations prior to treatment; ‡p-values obtained using an ANCOVA model with baseline value as a covariate, and treatment and randomisation strata factor as fixed effects.

Similar data were observed for the completer and EE populations. Sensitivity analyses demonstrated comparable clinically and statistically significant improvements for both OCA treatment groups compared with placebo at all time points (p <0.0001 versus placebo).

Absolute and percentage change in total and conjugated bilirubin

For the ITT population, the baseline mean total bilirubin was below the ULN for all treatment groups. Decreases in the absolute change from baseline in total bilirubin were observed for both OCA treatment groups, compared with an increase for the placebo treatment group. This is particularly important as it clearly shows improvement in the OCA treatment groups but disease progression in the placebo group, 93% of which were taking UDCA during the trial. An increase in bilirubin levels is associated with an increased risk of liver transplantation and death, and this risk starts at levels >0.5x ULN (10 µmol/L) (47). At 12 months, mean bilirubin levels in both OCA treatment groups are <10 µmol/L, whereas the mean level in the placebo group is 13.2 µmol/L. This reinforces the fact that without an additional treatment option, patients who do not respond to, or are intolerant to, UDCA are at increased risk of disease progression.

The difference in the absolute change from baseline in total bilirubin between placebo and each respective OCA treatment group was statistically significant (p <0.01) as early as Month 3, and at all subsequent time points with the exception of the OCA titration group at Month 9 (Table 27 and Figure 18).

Baseline conjugated bilirubin was elevated across treatment groups, which is consistent with intrahepatic obstruction with hepatobiliary damage observed in PBC. Mean baseline conjugated bilirubin was 5.5, 4.5, and 4.9 µmol/L, for the placebo, OCA titration, and OCA 10 mg fixed dose treatment groups, respectively. Both OCA treatment groups decreased and approached the ULN for conjugated bilirubin, while placebo increased from baseline at all time points, indicating ongoing cellular damage. For both OCA treatment groups, statistically significant differences (p<0.05) in both the absolute and percentage change from baseline relative to placebo were observed at Month 3 and at all subsequent time points. At Month 12, p-values were <0.0001 for each OCA treatment group versus placebo (Table 28 and Figure 18).

Table 27: Change in total bilirubin from baseline at Month 6 and Month 12: ITT population

Total bilirubin (µmol/L)	Placebo	OCA titration	OCA 10 mg fixed dose
Baseline†	11.8 (0.9)	10.3 (0.7)	11.3 (0.8)
Month 6			
Mean (SE)	12.3 (0.9)	9.7 (0.7)	9.7 (0.5)
LS mean change	1.1 (0.6)	–0.4 (0.6)	–0.8 (0.6)
OCA vs placebo, treatment difference	–	–1.5 (0.6)	–1.9 (0.6)
p-value‡	–	0.0089	0.0011

Total bilirubin (µmol/L)	Placebo	OCA titration	OCA 10 mg fixed dose
LS mean % change	13.8 (8.8)	–3.0 (8.6)	7.4 (8.9)
OCA vs placebo, treatment difference	–	–16.8 (8.1)	–6.5 (8.2)
p-value‡	–	0.0381	0.4307
Month 12			
Mean (SE)	13.2 (1.0)	9.9 (0.6)	9.7 (0.6)
LS mean change	1.9 (0.7)	–0.4 (0.7)	–1.0 (0.7)
OCA vs placebo, treatment difference	–	–2.3 (0.6)	–2.9 (0.7)
p-value‡	–	0.0004	<0.0001
LS mean % change (SE)	19.5 (6.8)	1.2 (6.7)	–0.2 (6.9)
OCA vs placebo, treatment difference	–	–18.3 (6.3)	–19.8 (6.3)
p-value‡	–	0.0039	0.0020

Abbreviations: ANCOVA, analysis of covariance; ITT, intention-to-treat; LS, least squares; OCA, obeticholic acid; SE, standard error.
†Baseline is defined as the mean of all available evaluations prior to treatment; ‡p-values obtained using an ANCOVA model with baseline value as a covariate and fixed effects for treatment and randomisation strata factor.

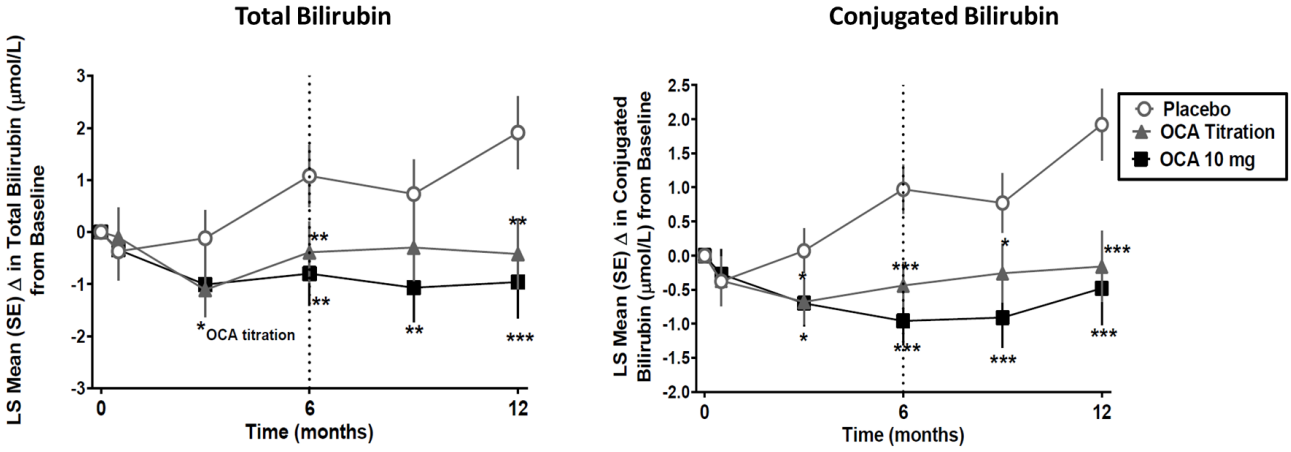
Table 28: Change in conjugated bilirubin from baseline at Month 6 and Month 12: ITT population

Conjugated bilirubin (µmol/L)	Placebo	OCA titration	OCA 10 mg fixed dose
Baseline†	5.5 (0.7)	4.5 (0.5)	4.9 (0.5)
Month 6			
Mean	6.2 (0.8)	4.0 (0.4)	3.5 (0.3)
LS mean change	1.0 (0.4)	–0.4 (0.4)	–1.0 (0.4)
OCA vs placebo, treatment difference	–	–1.4 (0.3)	–1.9 (0.3)
p-value‡	–	<0.0001	<0.0001
LS mean % change	23.0 (6.0)	–1.0 (6.0)	–6.0 (7.0)
OCA vs placebo	–	–24.0 (6.0)	–28.0 (6.0)
p-value‡	–	0.0001	<0.0001

Conjugated bilirubin (µmol/L)	Placebo	OCA titration	OCA 10 mg fixed dose
Month 12			
Mean	6.9 (0.9)	4.2 (0.4)	3.8 (0.3)
LS mean change	1.9 (0.5)	–0.2 (0.5)	–0.5 (0.5)
OCA vs placebo, treatment difference	–	–2.1 (0.5)	–2.4 (0.5)
p-value‡	–	<0.0001	<0.0001
LS mean % change	39.0 (7.0)	12.0 (7.0)	5.0 (7.0)
OCA vs placebo, treatment difference	–	–27.0 (7.0)	–34.0 (7.0)
p-value‡	–	<0.0001	<0.0001

Abbreviations: ANCOVA, analysis of covariance; ITT, intention-to-treat; LS, least squares; OCA, obeticholic acid.
†Baseline is defined as the mean of all available evaluations prior to treatment; ‡p-values obtained using an ANCOVA model with baseline value as a covariate and fixed effects for treatment and randomisation strata factor.

Figure 18: Summary of change in total and conjugated bilirubin



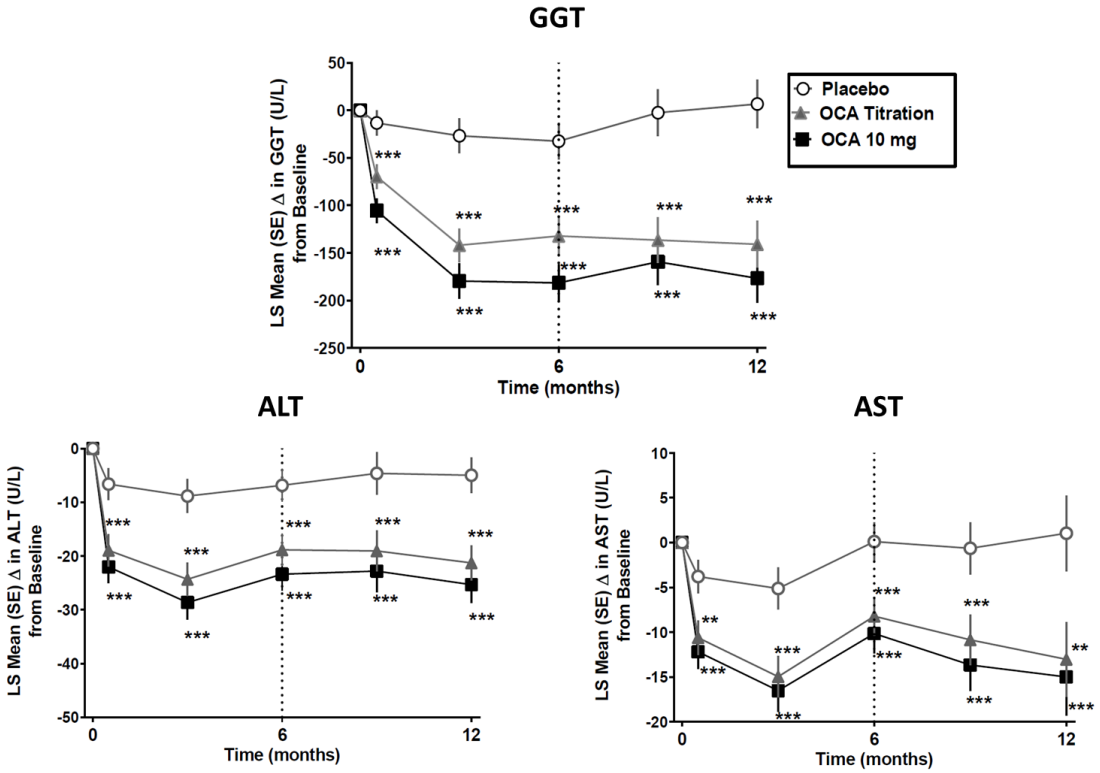
Abbreviations: ANCOVA, analysis of covariance; LS, least squares; OCA, obeticholic acid; SE, standard error. *p<0.05, **p<0.01, ***p<0.0001 vs placebo; p-values for comparing OCA treatments to placebo were obtained using an ANCOVA model with baseline value as a covariate and fixed effects for treatment and randomization strata factor.

Absolute and percentage change in GGT, ALT and AST

Results for GGT, ALT, and AST values at Month 6 and Month 12 are summarised in Table 29. As expected, GGT, ALT, and AST values were all elevated at baseline. Treatment with OCA resulted in a clinically and statistically significant improvement from baseline in all three parameters. Improvements were observed as early as 2 weeks, with the largest response generally observed at 3 months. For both OCA treatment groups and across all three parameters, the differences compared with placebo in LS mean reductions from baseline were statistically significant at all time points (Figure 19). The statistically significant reductions in these biochemical markers support the evidence

from ALP and bilirubin that OCA is slowing disease progression and improving liver function.

Figure 19 GGT, ALT, and AST change from baseline over time



Abbreviations: ALT, alanine aminotransferase; ANCOVA, analysis of covariance; AST aspartate aminotransferase; GGT, gamma-glutamyl transferase; OCA, obeticholic acid.

**p<0.01; ***p≤0.0001; p-values for comparing OCA treatments to placebo were obtained using an ANCOVA model with baseline value as a covariate and fixed effects for treatment and randomization strata factor.

Table 29: Change in GGT, ALT, and AST from baseline at Month 6 and 12: ITT population

	GGT (U/L)			ALT (U/L)			AST (U/L)		
Endpoint mean (SE)	**Placebo**	**OCA titration**	**OCA 10 mg fixed dose**	**Placebo**	**OCA titration**	**OCA 10 mg fixed dose**	**Placebo**	**OCA titration**	**OCA 10 mg fixed dose**
Baseline†	309.6 (52.6)	252.8 (20.0)	261.1 (24.3)	56.0 (3.5)	61.6 (4.7)	56.3 (4.7)	48.8 (2.6)	52.3 (3.0)	50.5 (3.6)
Month 6									
Mean (SE)	270.7 (41.0)	136.4 (12.3)	95.2 (11.4)	49.7 (3.0)	40.7 (3.8)	32.7 (2.2)	46.7 (2.5)	40.6 (2.7)	36.8 (2.1)
LS mean change from baseline	–32.4 (19.3)	–132.1 (18.8)	–181.5 (19.6)	–6.8 (3.0)	–18.8 (3.0)	–23.4 (3.1)	0.1 (2.2)	–8.2 (2.1)	–10.2 (2.2)
OCA vs placebo, treatment difference	–	–99.8 (17.5)	–149.2 (17.8)	–	–12.0 (2.8)	–16.5 (2.8)	–	–8.3 (2.0)	–10.3 (2.0)
p-value‡	–	<0.0001	<0.0001	–	<0.0001	<0.0001	–	<0.0001	<0.0001
LS mean % change from baseline	–9.0 (5.0)	–44.0 (4.8)	–64.1 (5.1)	–9.3 (3.8)	–31.1 (3.8)	–36.2 (3.9)	2.1 (3.5)	–15.4 (3.5)	–15.4 (3.6)
OCA vs placebo, treatment difference	–	–35.0 (4.5)	–55.1 (4.6)	–	–21.9 (3.5)	–26.9 (3.5)	–	–17.5 (3.2)	–17.5 (3.2)
p-value‡	–	<0.0001	<0.0001	–	<0.0001	<0.0001	–	<0.0001	<0.0001

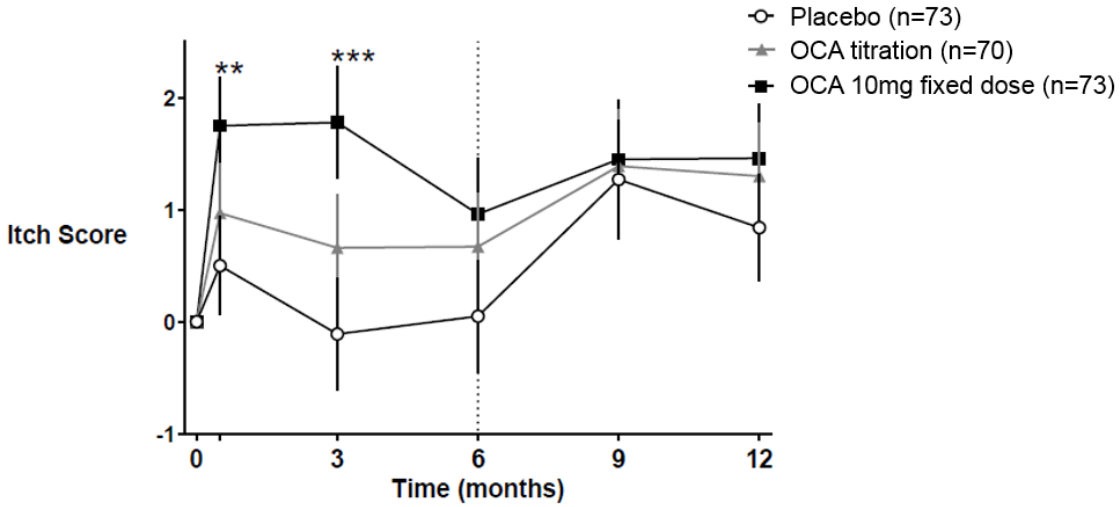
	GGT (U/L)			ALT (U/L)			AST (U/L)		
Endpoint mean (SE)	**Placebo**	**OCA titration**	**OCA 10 mg fixed dose**	**Placebo**	**OCA titration**	**OCA 10 mg fixed dose**	**Placebo**	**OCA titration**	**OCA 10 mg fixed dose**
Month 12									
Mean	301.8 (51.1)	114.2 (12.5)	91.9 (10.2)	52.8 (3.4)	39.0 (4.2)	32.1 (2.6)	51.6 (4.7)	39.5 (3.1)	36.4 (2.4)
LS mean change from baseline	6.7 (25.6)	–140.8 (24.7)	–176.7 (25.6)	–5.0 (3.3)	–21.3 (3.3)	–25.3 (3.4)	1.0 (4.2)	–13.0 (4.2)	–15.0 (4.3)
OCA vs placebo, treatment difference	–	–147.5 (23.1)	–183.4 (23.3)	–	–16.3 (3.0)	–20.4 (3.1)	–	–14.1 (3.8)	–16.0 (3.9)
p-value‡	–	<0.0001	<0.0001	–	<0.0001	<0.0001	–	0.0003	<0.0001
LS mean % change from baseline	0.8 (5.7)	–50.3 (5.5)	–63.7 (5.2)	–4.7 (5.0)	–35.5 (4.9)	–41.7 (5.0)	7.7 (8.8)	–21.9 (8.7)	–23.7 (8.9)
OCA vs placebo, treatment difference	–	–51.1 (5.1)	–64.5 (5.2)	–	–30.9 (4.5)	37.0 (4.6)	–	–29.6 (8.0)	–31.4 (8.1)
p-value‡	–	<0.0001	<0.0001	–	<0.0001	<0.0001	–	0.0003	0.0001

Abbreviations: ALT, alanine aminotransferase; ANCOVA, analysis of covariance; AST, aspartate aminotransferase; GGT, gamma glutamyl transferase; ITT, intention-to-treat; LS, least squares; OCA, obeticholic acid; SE, standard error.
†Baseline is defined as the mean of all available evaluations prior to treatment; ‡p-values obtained using an ANCOVA model with baseline value as a covariate and fixed effects for treatment and randomisation strata factor.

Absolute change in disease-specific symptoms (measured by change in PBC-40 and domain scores)

The disease-specific measure for PBC showed no clinically significant differences compared with placebo for the global score or individual scores of general symptoms, fatigue, cognitive function, and emotional/social domains. However, a difference was observed in itch scores. During the initial 3 months of treatment, the largest LS mean increase in itch was observed for the OCA 10 mg group, followed by the OCA titration group (Figure 20). The LS mean difference in itch score between the OCA 10 mg group and placebo group was statistically significant at both Week 2 (p= 0.0048) and Month 3 (p<0.0001) but not at any subsequent time points.

Figure 20: LS mean change from baseline in PBC-40 itch score: ITT population



Abbreviations: LS, least squares; OCA, obeticholic acid; PBC, primary biliary cholangitis/cirrhosis; SE, standard error; UDCA, ursodeoxycholic acid.
*p=0.0048; ***p<0.0001

Other relevant biomarkers and non-invasive assessments of liver fibrosis

Enhanced liver fibrosis (ELF) score

Baseline and Month 12 ELF data were available for 84% of subjects and are summarised in Table 30. Baseline ELF scores were slightly higher in the placebo group than in the OCA treatment groups, and were indicative of the upper end of moderate fibrosis to the lower end of severe fibrosis. At Month 12, the magnitude of the increase in total ELF score was lower in the OCA treatment groups than in the placebo group, although the treatment difference vs placebo was not significant for either OCA treatment group.

Table 30: ELF score using observed data: ITT population

ELF score†	Placebo		OCA titration		OCA 10 mg fixed dose	
	n	Mean (SE)	n	Mean (SE)	n	Mean (SE)
Baseline‡	70	10.03 (0.15)	65	9.76 (0.13)	71	9.81 (0.14)
Month 6						
Mean	69	10.00 (0.14)	67	9.83 (0.14)	60	9.83 (0.15)
Absolute change	67	0.09 (0.06)	63	0.13 (0.08)	59	0.14 (0.07)
LS mean absolute change	67	0.04 (0.11)	63	0.06 (0.11)	59	0.09 (0.11)
Treatment difference vs placebo	–		0.03 (0.10)		0.05 (0.10)	
p-value§	–		0.7811		0.6209	
Month 12						
Mean	66	10.12 (0.16)	61	9.73 (0.13)	64	9.77 (0.15)
Absolute change	64	0.17 (0.08)	55	0.15 (0.08)	63	0.08 (0.07)
LS mean absolute change	64	0.33 (0.13)	55	0.24 (0.12)	63	0.20 (0.12)
Treatment difference vs placebo	–		–0.08 (0.11)		–0.13 (0.11)	
p-value§	–		0.4718		0.2324	

Abbreviations: ANCOVA, analysis of covariance; ELF, enhanced liver fibrosis; ITT, intention-to-treat; LS, least squares; OCA, obeticholic acid; SE, standard error.
†ELF score ranges: 7.7 for a high sensitivity exclusion of fibrosis, 9.8 for a high specificity identification of fibrosis (sensitivity 69%, specificity 98% for moderate fibrosis), and 11.3 to discriminate cirrhosis (sensitivity 83%, specificity 97%); ‡Baseline is defined as the day 0 evaluation prior to treatment; §p-values comparing OCA treatments to placebo were obtained using an ANCOVA model with baseline value as a covariate and fixed effects for treatment and randomisation strata factor.

Hepatic stiffness

Mean and median baseline hepatic stiffness values using FibroScan®Fibroscan transient elastography were generally in the advanced fibrosis range (130). After 12 months of treatment, there was a general increase in hepatic stiffness across all three treatment groups, with the lowest increase occurring in the OCA treatment groups. However, there were no statistically significant differences between the placebo group and either OCA treatment groups.

Fibroblast growth factor-19 (FGF-19)

The median difference in absolute change and percentage change from baseline between the placebo and each OCA treatment group was statistically significant at Month 6 ($p<0.0001$) and Month 12 ($p=0.0002$ for the OCA titration group and $p<0.0001$ OCA 10 mg fixed dose group).

Cytokeratin-18 (CK-18)

Considerable inter-subject variability was shown across all three treatment groups for baseline CK-18 levels, with the median >ULN. During the study period, there was a statistically significant reduction at 6 months in the OCA titration and OCA 10 mg fixed

dose groups (p=0.0012 and 0.0077, respectively) and at 12 months (p=0.0003 and <0.0001, respectively).

Total bile acids

Total bile acid concentrations were similar at baseline across all three treatment groups, and there were no significant differences at Month 6 or Month 12 between the OCA titration and OCA 10 mg fixed dose treatment groups.

Total endogenous bile acid

Bile acid retention and cholestasis are key factors influencing the progressive loss of liver function in PBC, therefore a reduction in total endogenous bile will have a significant clinical benefit for the patient. OCA has a unique mode of action mediated through FXR receptor activation, leading to the reduction of endogenous bile acids demonstrated below.

The mean baseline levels of total endogenous bile acids were similar in the placebo group and the OCA titration group at baseline (6.63 vs 7.06 µmol, respectively), but was higher in the OCA 10 mg fixed dose treatment group (9.48 µmol). At Month 6, there was an overall decrease of –1.41 µmol and –5.72 µmol in the OCA titration and OCA 10 mg fixed dose groups, respectively, and an increase of 2.24 µmol in the placebo group. This corresponds to a 34% increase from baseline in the placebo group, but a 20% reduction in the OCA titration group and a 60% reduction in the OCA 10 mg fixed dose group.

By Month 12, the mean total endogenous bile acid levels had increased to 14.59 µmol in the placebo treatment group, but had decreased to 3.77 µmol in the OCA titration group and 3.86 µmol in the OCA 10 mg fixed dose group. When compared with baseline, bile acid levels had more than doubled in the placebo group (an increase of 220%), but had decreased by 47% and 59% in the OCA titration and 10 mg fixed dose groups, respectively. This represents a statistically significant reduction by Month 12 in the OCA titration and OCA 10 mg fixed dose groups (p=0.0010 and 0.0037, respectively).

Importantly, LCA – a toxic secondary bile acid – remained stable across all treatment groups when compared with baseline.

Inflammatory indirect markers

C-reactive protein (CRP)

Clinically and statistically significant decreases in CRP values were observed at Month 6 and Month 12 for both OCA treatment groups. The median change at Month 12 was −0.5 mg/L for the OCA titration group (p=0.0005 vs placebo) and −0.6 mg/L for the OCA 10 mg fixed dose group (p=0.0022 vs placebo), compared with an increase of 0.35 mg/L for the placebo group. Consistent with other efficacy parameters, the median change at Month 6 was smaller for subjects receiving OCA 5 mg compared with those receiving OCA 10 mg.

Tumour necrosis factor-α (TNF-α)

Baseline median levels were >ULN for TNF-α across all three treatment groups and slightly higher in subjects treated with placebo vs those treated with OCA. The OCA titration group had smaller increases at Month 6 and Month 12 compared with placebo, while the OCA 10 mg fixed dose group achieved a statistically significant reduction at Month 6 and Month 12 versus placebo (p=0.0002 and 0.0077, respectively).

Transforming growth factor-β (TGF-β) and interleukin-6 (IL-6)

Both parameters were within normal limits at baseline, and no significant changes were observed for TGF-β and IL-6 at Month 6 and Month 12 versus placebo.

Drug dose, drug concentration, and relationship to response

There was higher systemic exposure to OCA in the OCA 10 mg fixed dose treatment group than in the titration group. A dose relationship was observed, with 35% and 58% of subjects in the OCA titration and 10 mg fixed dose treatment groups, respectively, achieving the primary endpoint at Month 6. The magnitude of the LS mean reduction was larger for ALP, total bilirubin, and conjugated bilirubin at Month 6 in subjects that received 10 mg OCA versus those that received 5 mg OCA.

Effect of bile acid sequestrants (BAS) on the exposure and efficacy of OCA

For the OCA 10 mg fixed dose group, the use of BAS did not affect the change from baseline for ALP, total bilirubin, and conjugated bilirubin at Month 6 or Month 12, and therefore did not alter the efficacy of OCA.

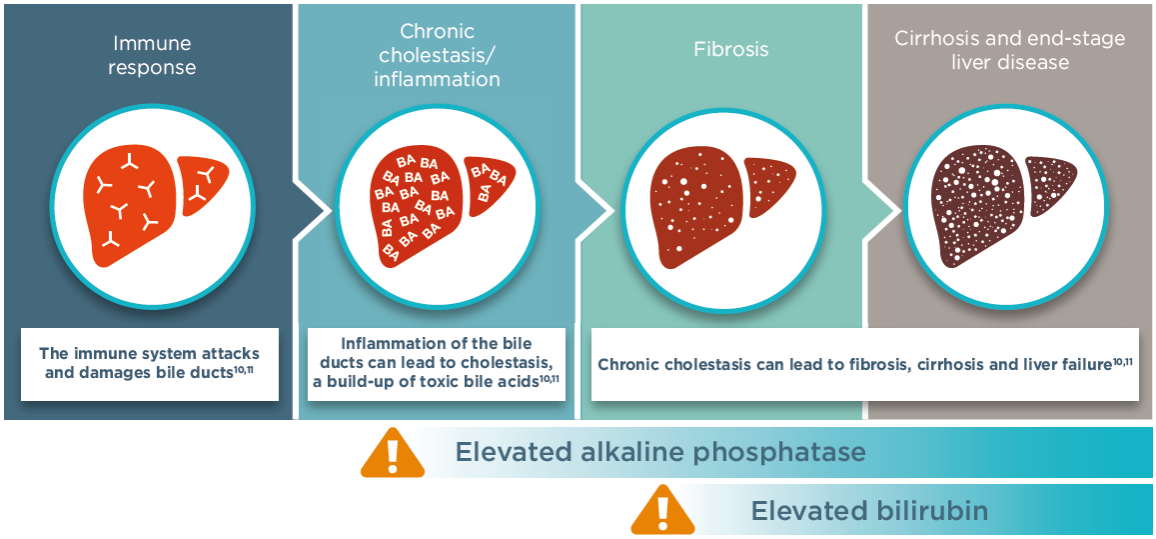
For the OCA titration group, the use of BAS appeared to modestly attenuate the effect of OCA on ALP and bilirubin from baseline to Month 6 and Month 12. This supports a dose-relationship response and may suggest that 5 mg is the minimally efficacious level.

Since BAS are used to control pruritus, the small to no effect on OCA efficacy is important, meaning that pruritus as a symptom of PBC and OCA treatment can be managed without affecting OCA activity.

4.7.1.3 Conclusion

Increases in ALP, bilirubin, GGT, ALT and AST are associated with disease progression (Figure 21). In POISE, all of these, as well as other relevant biomarkers (FGF-19, CK-18 and bile acids), inflammation biomarkers (CRP, TNF-α, TGF-β and IL-6), and assessments of liver fibrosis, indicate that OCA slows, halts or even reverses disease progression in patients with an inadequate response to, or who are intolerant to, UDCA.

Figure 21: The progression of PBC and associated changes in biochemical markers



These are important results for these patients, who currently have no available licensed or effective treatment options, and face the inevitability of disease progression to complications, the need for liver transplant, HCC, and death. Further evidence is needed to show that these reductions in biomarkers translate into a benefit in clinical outcomes, e.g. transplant-free survival. COBALT is an ongoing long-term study that seeks to evaluate the effect of OCA on clinical outcomes. It is described in Section 4.14.

4.7.2 *Supporting evidence*

4.7.2.1 Long-term safety extension of POISE

A total of 198 subjects completed the 12-month double-blind phase of the POISE trial, of which 193 subjects (97%) opted to continue into the LTSE phase. Of the five subjects who did not opt into the LTSE phase, four were in the placebo group in the double-blind phase of the trial, and one was in the OCA titration group for the double-blind phase. All 64 subjects who were randomised to 10 mg OCA and completed the double-blind phase chose to enter the LTSE phase of the study.

A total of 77% of subjects had a weighted average daily dose of >5 mg (i.e. up-titrated during the LTSE phase). This is in contrast to the double-blind phase, where only 48% of subjects in the titration group increased their dose to 10 mg. In the titration group in the double-blind phase, 35% of patients did not up-titrate because they had reached the criteria for response and were therefore not eligible for an increased dose (as per the protocol), and 13% did not up-titrate due to adverse events. The remaining 4% recorded their reason for not up-titrating as ‘other’.

Primary efficacy endpoint

- The percentage of subjects achieving the key primary endpoint in the double-blind phase was sustained over the subsequent 12-month open-label period (52% and 44% in the OCA titration group and OCA 10 mg group, respectively).
- There was a decrease from month 12 of the double-blind phase to month 3 of the LTSE phase in the percentage of subjects achieved the primary endpoint for subjects previously treated with 10 mg OCA. This was expected due to the down-

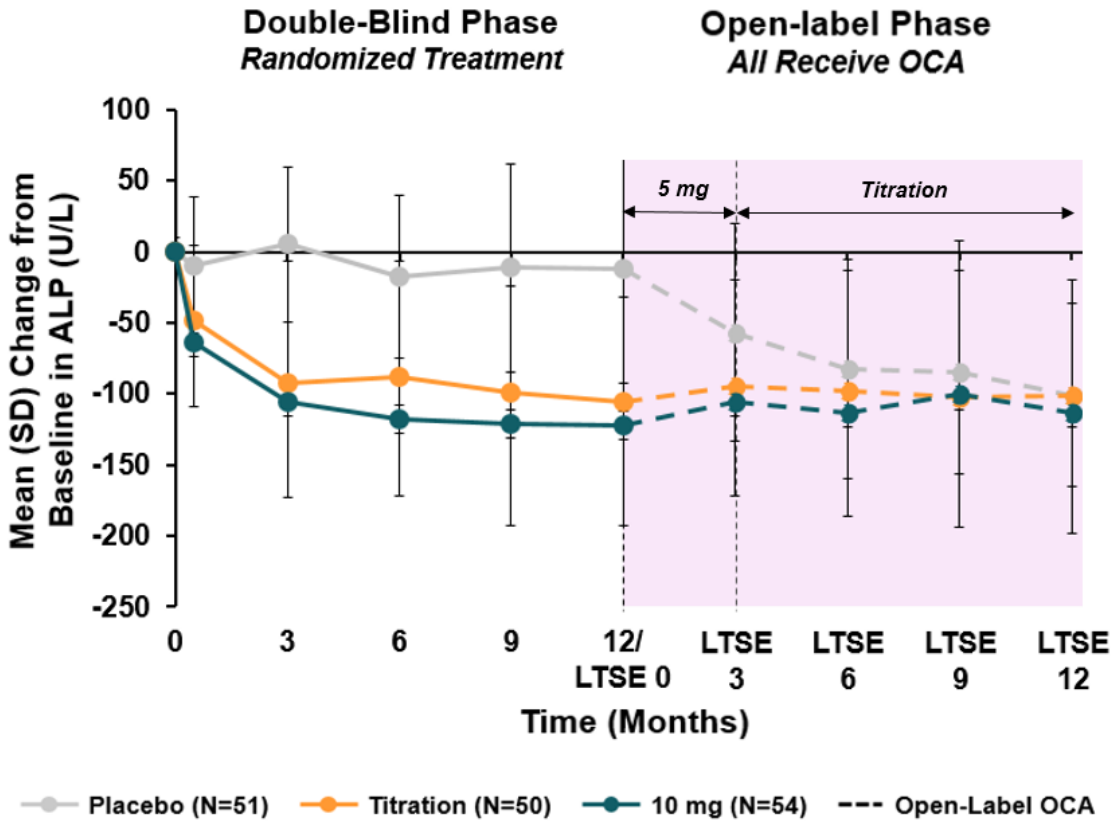
titration from 10 mg OCA to 5 mg OCA, however, the response rate was improved at month 6.

- For subjects who previously received placebo in the 12-month double-blind phase but subsequently entered the LTSE phase of the study and initiated treatment with 5 mg OCA, there was a robust response in the percentage of subjects who achieved the primary endpoint between Month 12 of the double-blind phase to Month 9 of the LTSE phase (9% vs 34%, respectively). Subjects were able to up-titrate in 5 mg increments not more than once every three months if the response criteria were not met and AEs did not limit the administration of the higher dose of OCA, and results in this group of patients are similar to the results seen in the OCA titration group in the double-blind phase.
- Similar consistent, clinically relevant percentages of subjects achieving the primary endpoint were also observed for the 2-year completer population.

ALP

- Mean improvements in ALP values for subjects randomised to OCA treatment in the double-blind phase were sustained over the subsequent open-label period, notably, absolute mean ALP approached 1.67x ULN.
- There was a slight increase in ALP at Month 3 in subjects who previously received 10 mg OCA.
- ALP levels decreased in the LTSE subjects who received placebo in the double-blind phase to levels almost equal to those in the OCA treatment groups (Figure 22).

Figure 22: ALP levels over time by treatment in the double-blind phase



Abbreviations: ALP, alkaline phosphatase; LTSE, long-term safety extension; OCA, obeticholic acid; SD, standard deviation.

Bilirubin

- Following initiation of OCA in the LTSE, mean total bilirubin levels decreased and were comparable to or below the double-blind baseline values.
- For those that received OCA during the double-blind phase, continued OCA treatment maintained total bilirubin concentrations at or below baseline.

GGT, ALT, and AST

- The clinically and statistically significant reductions from baseline GGT, ALT, and AST observed in OCA-treated subjects during the 12-month double-blind phase were sustained during the LTSE.
- For subjects who received placebo during the double-blind phase, similar statistically significant reductions from the double-blind baseline were observed for all three parameters at month 3 of the LTSE.

Summary

In summary, the efficacy associated with continued treatment with OCA was durable and consistent with the effects observed in the double-blind phase of the POISE study. For subjects originally randomised to OCA, continued treatment was associated with sustained improvements in liver chemistry. For subjects originally randomised to placebo, there were clinically significant improvements in liver chemistry following initiation of OCA treatment. Importantly, the tendency towards a deterioration in total bilirubin in placebo subjects was reversed following initiation of OCA treatment.

4.7.2.2 Phase 2 studies

There are two Phase 2 supporting studies, 747-201 and 747-202. The studies evaluated the efficacy, safety, and tolerability of OCA with UDCA (study 747-202) or without UDCA (study 747-201) vs placebo. The studies both included a 10 mg OCA treatment arm and other treatment arms at higher doses. In this section, key efficacy and safety results were summarised only for subjects who received 10 mg OCA, since this is the upper limit for the licensed indication of OCA. Both studies included a double-blind phase and an open-label long-term safety extension phase. Results from study 747-201 are summarised in Table 31 (double-blind phase) and Table 32 (interim results from the long-term extension phase), and results from study 747-202 are summarised in Table 33 (double-blind phase) and Table 34 (long-term extension phase).

Table 31: Study 747-201 (double-blind phase)

Title	**A study of INT-747-201 (6-ECDCA; OCA) monotherapy in patients with primary biliary cirrhosis†**
Study design	A 3-month international, multi-centre, randomised, double-blind, placebo-controlled, multi-dose, Phase II parallel group study of OCA monotherapy in subjects with a proven or likely diagnosis of PBC.
Location	18 centres in 6 countries (UK [5 sites], USA [4 sites], Canada [3 sites], Germany [4 sites], France [1 site], Spain [1 site]).

Primary objectives	To assess the effects of OCA in subjects with proven or likely PBC on: • Serum ALP levels • Safety.
Secondary objectives	To assess the effects of OCA in subjects with proven or likely PBC on: • Hepatocellular injury and liver function • Disease-specific and general health symptoms • Biomarkers of hepatic inflammation and fibrosis • Plasma trough concentrations of OCA and its major known conjugates.
Interventions	Eligible subjects were randomised (1:1:1) to placebo, OCA 10 mg, or OCA 50 mg
Sample size and power calculation	A total of 71 subjects were screened, 60 were randomised, and 59 received investigational product: placebo (n=23), OCA 10 mg (n=20), and OCA 50 mg (n=16). Approximately 20 subjects per group resulted in 49% power to detect an effect size of 0.6466 for the difference in the primary efficacy endpoint (change in serum ALP) between treatment arms and placebo using a Wilcoxon-Mann-Whitney rank-sum test with a 0.05, two-sided significance level.
Key inclusion/ exclusion criteria	• Proven or likely PBC • Aged 18–70 years (18–75 years in the UK) • Both male and female subjects had to use one method of contraception unless surgically sterile (males and females) or postmenopausal (females)
Primary outcome	• Percentage change in serum ALP from baseline to end of study
Secondary outcomes	• Absolute changes in serum ALP levels from baseline to Day 15, Day 29, Day 57, Day 85/end of treatment and Day 99/follow-up • Percentage of subjects meeting PBC responder criteria per the Paris I, Toronto I, Toronto II, Toronto III, Toronto IV, Mayo II, and Barcelona disease prognostic risk criteria at Day 85/end of treatment • Absolute and percentage change in serum AST, ALT, GGT, and conjugated (direct) bilirubin values from baseline to Day 15, Day 29, Day 57, Day 85/end of treatment and Day 99/follow-up • Safety
Other efficacy endpoints	• PBC-40 QoL Questionnaire: Change from Baseline to Day 29, Day 57, and Day 85/end of treatment for each domain
Statistical methods	A hierarchical testing strategy (131) was planned for the comparison of OCA treatment groups versus placebo. The statistical significance was to be evaluated in order as follows: if statistical significance at α=0.05 was observed for the OCA 10 mg group versus placebo, then the statistical significance at α = 0.05 for the OCA 50 mg versus placebo was to be performed. If no statistical significance was observed at α=0.05 at the first step, then the subsequent comparisons were not considered statistically significant, regardless of the p-value. For secondary endpoints, pairwise comparisons for placebo versus both OCA treatment groups at each on-treatment visit were performed using Wilcoxon-Mann-Whitney, chi-squared (with continuity correction) or Fisher's exact test.
Results for OCA 10 mg vs placebo	
Patient population	Baseline and demographic characteristics were generally well-balanced across the treatment groups.

Primary endpoint	There was a clinically and statistically significant improvement in ALP levels from baseline to end of study with OCA 10 mg versus placebo (p<0.0001). The mean (SD) percentage change in ALP levels was –44.5% (24.4) for the OCA 10 mg group versus +0.4% (15.3) for placebo.
Secondary endpoints	**Efficacy:** • Results for the absolute change in ALP were supportive of the primary endpoint analyses at Day 15, 29, 57, 85/end of treatment, and 99/follow-up. There was a statistically significant two-fold decrease in ALP from 461.6 U/L at baseline to 228.1 U/L at Day 85/end of treatment (p<0.0001) • Percentages of OCA-treated subjects meeting PBC responder criteria at Day 85/end of treatment were significantly greater with OCA 10 mg than with placebo across all disease prognostic criteria apart from the Paris I criterion and the Toronto III criterion • Treatment with OCA 10 mg resulted in a statistically significantly greater proportion of subjects achieving ALP <1.67x ULN and total bilirubin ≤ULN and ALP decrease ≥15% from baseline when compared with placebo (44% vs 4%, respectively) • Improvements in other markers of liver injury were supported by decreases in GGT, ALT, and AST • There was a statistically significantly greater decrease in conjugated bilirubin levels between baseline and Day 85/end of treatment in the OCA 10 mg group vs the placebo group (p=0.0184) • There were no statistically significant changes between baseline and end of treatment in the SF-36 survey, or in the general symptoms, cognitive function, and emotional/social domains of the PBC-40 questionnaire • Mean levels of endogenous bile acids decreased by 10% from baseline to Day 85/end of treatment in the OCA 10 mg group compared with a 52% increase in the placebo group. **Safety:** • AEs were reported by 90% and 91% of subjects treated with OCA 10 mg and placebo, respectively • The majority of AEs were mild or moderate in severity • The most commonly reported AE across groups was pruritus • There were no deaths • There was one reported SAE (rash); it occurred in the placebo group.
Conclusion	OCA monotherapy at 10 mg was highly effective in mitigating key clinical laboratory indicators of PBC disease, including significantly reducing serum ALP levels, increasing the percentage of responders, and reducing markers of liver injury (i.e. GGT, AST, and ALT levels). OCA treatment was well tolerated, with pruritus, a known side effect of PBC, being the most common adverse event with OCA.
Publications	Kowdley 2011 (96)

Abbreviations: AE, adverse event; ALP, alkaline phosphatase; ALT, alanine aminotransferase; AST, aspartate aminotransferase; 6-ECDCA, 6alpha-ethyl-chenodeoxycholic acid; ET, early termination; GGT, gamma-glutamyl transferase; OCA, obeticholic acid; PBC, primary biliary cholangitis/cirrhosis; SAE, serious adverse event; QOL, quality of life; ULN, upper limit of normal. †Note that primary biliary cirrhosis has recently undergone a name change to primary biliary cholangitis. At the time of the design of the protocol of this study, the official name was primary biliary cirrhosis and, as such, this is reflected in this table.

Table 32: Study 747-201 (interim results from the long-term safety extension phase)

Title	A study of INT-747-201 (6-ECDCA; OCA) monotherapy in patients with primary biliary cirrhosis†
Study design	A 72-month, open-label, long-term safety extension to provide further evaluation of the long-term safety and efficacy of OCA in doses up to 50 mg OD in subjects with PBC. Subjects who completed the 3-month, double-blind phase of Study 747-201 had the option to enrol in the LTSE.
Location	UK (3 sites). US (3 sites), Canada (3 sites) and Spain (1 site).
Primary objectives	• Safety
Secondary objectives	• ALP levels, as an assessment of efficacy • Hepatocellular injury and liver function • Disease-specific and general health symptoms
Interventions	OCA. The starting dose of OCA was based on the dose of OCA or placebo received in the double-blind phase, or on the timing of entry into the LTSE phase: • Placebo subjects: Start on 10 mg OCA OD • Active treatment subjects: Resume the same randomised dose of OCA, provided that the OCA dose was well tolerated during the double-blind phase • Double-blind completed subjects: If the last dose of OCA was taken >1 month before the start of the LTSE phase, start on 10 mg OCA OD • Subjects with significant pruritus or other AEs: Must not have received OCA for at least 1 month before starting the LTSE phase, start on a maximum dose of 10 mg OCA OD OCA was to be titrated from 10 mg to 25 mg to 50 mg OD no faster than at 8-week intervals, until one of the following occurred: • ALP was in the normal range • The Investigator considered that an adequate therapeutic response was obtained • AEs limited the administration of higher doses Exceptions were allowed, e.g. titration could have been performed more slowly and with smaller increments, and subjects could be titrated to doses above 50 mg OD if OCA 50 mg was well tolerated for ≥3 months.
Sample size and power calculation	All subjects who completed treatment during the double-blind phase were eligible to continue into the LTSE phase at selected study sites. No formal sample size calculations were performed.
Key inclusion/ exclusion criteria	• Completion or participation (including early termination subjects) of treatment during the double-blind phase of the study
Primary efficacy endpoint	• None
Secondary efficacy outcomes	• Absolute and percentage change from baseline in ALP at each 3-month visit • Absolute and percentage change from baseline in AST, ALT, GGT, and total and conjugated bilirubin at each 3-month visit • Absolute change from baseline in SF-36 scores and summary measures to last available visit

	• Absolute change from baseline in PBC-40 domains at 6-month visits
Other efficacy endpoints	• Percentage of subjects that meet disease response criteria: Paris I, Paris II, Toronto I, Toronto III, Mayo II, and Barcelona • Percentage of subjects with ALP within normal range and a decrease from baseline of 10%, 15%, 20% and 40% at each 3-month visit • Percentage of subjects with ALP <1.0, 1.25, 1.5, 1.67, 1.76, 2.0 and 3.0x ULN who had ≥the respective value at double-blind baseline, at each 3-month visit • Percentage of subjects with ALP <1.67x ULN, total bilirubin ≤ULN, and ≥15% decrease in ALP who had ALP ≥1.67x ULN or total bilirubin >ULN at baseline, at each 3-month visit • Absolute and percentage change from baseline in ELF score and its components (HA, P3NP and TIMP-1) at 6-month visits • Absolute change from baseline in biomarkers of hepatic inflammation and fibrosis (CRP, TNF-α, TGF-β, and IgM) at 6-month visits • Titration effects on ALP, AST, ALT and GGT • Absolute change from baseline for pruritus 5-D and VAS scores at 3-month visits
Primary safety endpoints	• Pruritus (AEs) • TEAEs
Secondary safety endpoints	• Vital signs • Physical examinations • 12-lead electrocardiograms • Laboratory results
Statistical methods	As dose modifications (both up- and down-titration) were allowed, treatment groups were defined in two ways: weighted average daily dose (WADD) and dose for 80% duration. WADD was presented to account for the flexibility of dose adjustments, titration, and frequency as specified by the protocol. Dose for 80% duration was presented regardless of subject non-compliant investigational product interruptions, Investigator-prescribed drug holidays, or dosing frequency. WADD and dose for 80% duration were categorised into the following treatment dose groups in summary tables as applicable: • ≤10 mg • >10 mg to ≤25 mg • >25 mg • Total OCA (combining all dose groups)
Results	
Patient population	A total of 28 subjects participated in the LTSE phase, with 23 (82%) participating for at least 1 year [redacted]
Efficacy results	Long-term treatment with OCA was associated with sustained reductions in ALP that were consistent with the observed effect of OCA in the double-blind phase of the study, showing the consistency and durability of OCA treatment. The apparent further decrease in ALP in the LTSE was due to the transitioning of placebo subjects to OCA treatment, which further decreased mean ALP of the entire cohort. Similar to ALP, sustained mean reductions in AST, ALT, GGT, and total bilirubin were observed at most LTSE time points. Changes in conjugated bilirubin tended to be more variable; however, values generally remained

	comparable to baseline.
Safety results	Long-term treatment with OCA was generally well tolerated. Consistent with the double-blind phase of the study and PBC, pruritus was the most common TEAE. Most pruritus events were mild to moderate in severity, with three subjects discontinuing the study due to pruritus. Other TEAEs with an exposure-adjusted incidence >10 events per 100 PYE included nausea, fatigue and arthralgia. In total seven subjects discontinued the study due to an AE or clinical laboratory value, eight subjects experienced a total of 19 serious AEs, and there was no clear dose relationship or system organ class grouping. There were no deaths in this study.
Conclusion	Long-term treatment with OCA is effective and well tolerated.
Publications	Hirschfield 2012 (95) Kowdley 2014 (98) Kowdley 2015 (99)

Abbreviations: AE, adverse event; ALP, alkaline phosphatase; ALT, alanine transaminase; AST, aspartate transaminase; CRP, C-reactive protein; 6-ECDCA, 6-alpha-ethyl-chenodeoxycholic acid; ELF, enhanced liver fibrosis; GGT, gamma-glutamyl transpeptidase; HA, hyaluronic acid; IgM, immunoglobulin M; LTSE, long-term safety extension; OCA, obeticholic acid; OD, once daily; PBC, primary biliary cholangitis/cirrhosis; P3NP, procollagen III N-peptide; PYE, patient years of exposure; TEAE, treatment-emergent adverse event; TGF-β, transforming growth factor-beta; TIMP-1, tissue inhibitor of metalloproteinase-1; TNF-α, tumour necrosis factor-alpha; ULN, upper limit of normal; VAS, visual analogue scale; WADD, weighted average daily dose. †Note that primary biliary cirrhosis has recently undergone a name change to primary biliary cholangitis. At the time of the design of the protocol of this study, the official name was primary biliary cirrhosis and, as such, this is reflected in this table.

Table 33: Study 747-202 (double-blind phase)

Title	**A study of INT-747 (6-ECDCA; OCA) in combination with ursodeoxycholic acid (UDCA) in subjects with primary biliary cirrhosis¶**
Study design	A 3-month, international, multi-centre, randomised, double-blind, placebo-controlled, multi-dose, Phase II parallel group study of OCA in combination with UDCA in subjects with a proven or likely diagnosis of PBC.
Location	30 centres in 8 countries (USA [11 sites], Canada [6 sites], Germany [4 sites], UK [4 sites], The Netherlands [2 sites], Austria [1 site], France [1 site], Spain [1 site])
Primary objectives	To assess the effect of OCA in combination with UDCA in subjects with proven or likely PBC on: • ALP levels • Safety.
Secondary objectives	To assess the effect of OCA in subjects with proven or likely PBC on: • Hepatocellular injury and liver function • Disease-specific and general health symptoms • Biomarkers of hepatic inflammation and fibrosis • Plasma trough concentrations of OCA and its major known conjugates.
Interventions	Eligible subjects were randomised (1:1:1:1) to placebo, OCA 10 mg, OCA 25 mg or OCA 50 mg
Sample size and power calculation	A total of 222 subjects were screened and 165 randomised: placebo (n=38), OCA 10 mg (n=38), OCA 25 mg (n=48), and OCA 50 mg (n=41). With 35 patients per group, there was 80% power to detect an effect

	size of 0.70, which translates to approximately a 10% mean greater reduction in ALP levels between groups.
Key inclusion/ exclusion criteria	• Proven or likely PBC • Aged 18–70 years (18–75 years in the UK) • Both male and female subjects had to use one method of contraception unless surgically sterile (males and females) or postmenopausal (females)
Primary outcome	• Percentage change in serum ALP from baseline to end of study
Secondary outcomes	• Changes in serum ALP levels from baseline to Day 15, Day 29, Day 57, Day 85/end of treatment and Day 99/follow-up • Responder analyses of ALP response • Change in serum AST, ALT, GGT, serum albumin and conjugated (direct) bilirubin values from baseline to Day 15, Day 29, Day 57, Day 85/end of treatment and Day 99/follow-up • Changes in CRP, non-esterified fatty acid, TNF-α & β, TGF-β, bile acids, glutathione, IgM, and osteopontin from Baseline to Day 85/end of treatment • SF-36 and PBC-40 QoL questionnaires • Bile acid analysis and change in FGF-19 from baseline to Day 85/end of treatment • Safety
Statistical methods	The percentage change from baseline to end of study was described with summary statistics. The two-sided Wilcoxon-Mann-Whitney test at the 5% level of significance was used for the primary endpoint. A hierarchical testing strategy (131) was proposed to account for multiple comparisons. The order of evaluation of statistical significance was as reported for study 747-201 in Table 31.
Results for 10 mg OCA vs placebo	
Patient population	Baseline and demographic characteristics were generally well-balanced across the treatment groups.
Primary endpoint	There was a clinically and statistically significant reduction in percentage change in ALP levels from baseline with OCA 10 mg compared with placebo ($p<0.0001$). The mean (SD) percentage change in ALP levels was –23.7 (17.8) U/L with OCA 10 mg versus –2.6 (12.5) U/L with placebo.
Secondary endpoints	• There was a statistically significantly ($p<0.0001$) greater reduction in ALP from baseline to end of treatment relative to placebo in the ITT, completer[†], and mITT[§] populations. • There were statistically significantly higher proportions of subjects who met the responder criteria (10, 20 and 40% reduction in ALP from baseline) in the OCA 10 mg treatment group compared with placebo • Improvement in other markers of liver injury was supported by statistically significant decreases in GGT ($p<0.0001$), ALT ($p<0.0001$), and AST ($p=0.0031$) from baseline to EOT • Conjugated bilirubin levels were all within normal ranges at Baseline and all subsequent time points • Only two scores were clinically significant in the SF-36 survey, however, there were no consistent patterns or indication of dose-response relationships in any domain • Overall, there were no changes observed in the PBC-40

	questionnaire for general symptoms, cognitive function, and emotional/social domains • Significant reductions in the median total endogenous bile acids were observed in all OCA treatment groups from Baseline to ET compared with no change in the placebo group • AEs were reported by 89% and 84% of subjects in the OCA 10 mg and placebo groups, respectively. Most AEs were mild or moderate in severity • There were no deaths. Pruritus was the most common AE leading to study withdrawal, which occurred only with OCA, not with placebo • AEs other than pruritus resulting in discontinuation that occurred in two or more OCA treated subjects were nausea, peripheral oedema, increased ALT, and rash.
Conclusion	Treatment with OCA in subjects with PBC who have an inadequate response to UDCA resulted in clinically and statistically significant improvements from placebo as assessed by changes in serum ALP, markers of cholestasis, inflammation, and hepatobiliary injury, such as bilirubin, GGT, ALT, and AST. Further, OCA treatment resulted in significantly higher rates of response which is shown to correlate with improved transplant-free survival. OCA treatment was safe and general well tolerated. These data provide a proof of concept that OCA may be a viable therapy for PBC.
Publications	Hirschfield et al, 2015 (101)

Abbreviations: AE, adverse event; ALP, alkaline phosphatase; ALT, alanine aminotransferase; AST, aspartate aminotransferase; BL, baseline; CRP, C-reactive protein; 6-ECDCA, 6alpha-ethyl-chenodeoxycholic acid; EOT, end of treatment; FGF, fibroblast growth factor; GGT, gamma-glutamyl transferase; Ig, immunoglobulin; ITT, intention-to-treat; mITT, modified intention-to-treat; OCA, obeticholic acid; PBC, primary biliary cholangitis/cirrhosis; QoL, quality of life; TGF, tumour growth factor; TNF, tumour necrosis factor.
[†]The completer population (n=136) included all randomised subjects who received at least one dose of investigational product based on the treatment group assignment and participated until the end of the 3-month, double-blind treatment period (i.e. Day 85). [§]The modified intention-to-treat (mITT) population (n=161) included all randomised subjects who received at least one dose of investigational product and had at least one post-baseline ALP evaluation taken ≤7 days after their last dose of investigational product. Subjects were analysed according to the treatment group to which they were randomized. The primary efficacy analysis was based on the mITT population. [¶]Note that primary biliary cirrhosis has recently undergone a name change to primary biliary cholangitis. At the time of the design of the protocol of this study, the official name was primary biliary cirrhosis and, as such, this is reflected in this table.

Table 34: Study 747-202 (long-term safety extension phase)

Title	**A study of INT-747 (6-ECDCA; OCA) in combination with ursodeoxycholic acid (UDCA) in subjects with primary biliary cirrhosis[†]**
Study design	A multi-centre, open-label study to assess the long-term treatment effects of OCA in subjects with PBC. Any subject who continued to meet the protocol requirements, regardless of the treatment group to which they were assigned during the double-blind phase, was eligible to participate in the study, including subjects who had not completed the double-blind phase.
Location	UK (2 sites), US (6 sites), Canada (3 sites), Spain (1 site), and Austria (1 site).
Primary objectives	• Safety

Secondary objectives	• ALP levels as an assessment of efficacy • Hepatocellular injury and liver function • Disease-specific and general health symptoms
Interventions	OCA. The starting dose of OCA was based on the dose of OCA or placebo received in the double-blind phase, or on the timing of entry into the LTSE phase: • Placebo subjects: Start on 10 mg OCA OD • Active treatment subjects: Resume the same randomised dose of OCA, provided that the OCA dose was well tolerated during the double-blind phase • Double-blind completed subjects: If the last dose of OCA was taken >1 month before the start of the LTSE phase, start on 10 mg OCA OD • Subjects with significant pruritus or other AEs: Must not have received OCA for at least 1 month before starting the LTSE phase, start on a maximum dose of 10 mg OCA OD OCA was to be titrated from 10 mg to 25 mg to 50 mg OD no faster than at 8-week intervals, until one of the following occurred: • ALP was in the normal range • The Investigator considered that an adequate therapeutic response was obtained • AEs limited the administration of higher doses Exceptions were allowed, e.g. titration could have been performed more slowly and with smaller increments, and subjects could be titrated to doses above 50 mg OD if OCA 50 mg was well tolerated for ≥3 months.
Sample size and power calculation	No formal sample size calculation was performed, since any subject who continued to meet the protocol requirements of the double-blind phase was eligible to participate in the LTSE phase.
Key inclusion/ exclusion criteria	• Completion or participation (including early termination subjects) of treatment during the double-blind phase of the study
Primary efficacy outcome	• None
Secondary efficacy outcomes	• Absolute and percentage change from baseline in ALP at 3-month visits • Absolute and percentage change from baseline in AST, ALT, GGT, and total and conjugated bilirubin at 3-month visits • Absolute change from double-blind baseline to study completion for scale scores and summary measures • Absolute change from double-blind baseline for PBC-40 domains at 6-month visits and study completion
Other efficacy variables	• Percentage of subjects that met response criteria Paris I, Pairs II, Toronto I, Toronto III and Mayo II at 6-month visits and study completion • Percentage of subjects with ALP within normal range and with a reduction from double-blind baseline by 10%, 20% and 40% at 6-month visits and study completion • Percentage of subjects with ALP values <1.0, 1.25, 1.5, 1.67, 1.76, 2.0 and 3.0x ULN who had ≥ the respective ALP value at double-blind baseline, at 6-month visits and study completion • Percentage of subjects with ALP <1.67x ULN, total bilirubin ≤ULN and ≥15% decrease in ALP who had ≥1.67x ULN or total bilirubin <ULN at baseline, at

	6-month visits and study completion • Absolute and percentage change from double-blind baseline of ELF score and its components (HA, P3NP and TIMP-1) at 6-month visits and study completion • Absolute and percentage changes from double-blind baseline in biomarkers of hepatic inflammation and fibrosis (CRP, TGF-β and IgM) at 6-month visits and study completion • Titration effects on ALP, AST, ALT, GGT and pruritus, measured by the change and percentage change from the pre-titration to the post-titration value (measured by VAS and 5-D scores for pruritus)
Primary safety variables	• Pruritus (AEs and clinically significant interventions) • TEAEs, including: o Overall incidence o Severity o Relationship to investigational product o Action taken o Outcome
Secondary safety variable	• Vital signs • Physical examinations • Electrocardiogram • Laboratory results
Other safety variable of interest	• Study duration, exposure and titration • Compliance of investigational product • Status at the end of study, reasons for withdrawal • Other concomitant medications • Titration effects on pruritus
Statistical methods	All safety and efficacy analyses were performed on the safety population. No algorithm for missing data imputation was employed. For AEs, if causality was missing, it was assumed to be probably related to investigational product. Missing severity was not imputed
Results	
[redacted]	[redacted]
Key efficacy endpoints	• ALP was lower at Month 3 and the reduced levels were maintained out to 1 year of LTSE dosing, suggesting a durable effect of OCA • AST and ALT levels remained within normal range; there was a decrease at 3 months, which was maintained out to 1 year of LTSE dosing • GGT levels were reduced by 52.4% at Month 3 and 60.4% at Month 12 compared with baseline • Total and conjugated bilirubin were within normal range and did not increase over 12 months of LTSE dosing [redacted]

	• [redacted]
Key safety endpoints	• SAEs were experienced by five subjects, none of which were considered related to investigational product. None of the subjects discontinued due to the SAE and all but one of the SAEs resolved without sequelae • [redacted] • The most frequently reported TEAE was pruritus, which was experienced by 87% of subjects during LTSE treatment, and fatigue, insomnia and upper respiratory tract infection were each reported by 13% of subjects
[redacted]	[redacted]
Publications	Hirschfield 2015 (101)

Abbreviations: AE, adverse event; ALP, alkaline phosphatase; ALT, alanine transaminase; AST, aspartate transaminase; CRP, C-reactive protein; 6-ECDCA, 6alpha-ethyl-chenodeoxycholic acid; ELF, enhanced liver fibrosis; GGT, gamma-glutamyl transpeptidase; HA, hyaluronic acid; IgM, immunoglobulin M; LTSE, long-term safety extension; OCA, obeticholic acid; OD, once daily; PBC, primary biliary cholangitis/cirrhosis; P3NP, procollagen III N-peptide; SAE, serious adverse event; TEAE, treatment-emergent adverse event; TGF-β, transforming growth factor-beta; TIMP-1, tissue inhibitor of metalloproteinase-1; UDCA, ursodeoxycholic acid; ULN, upper limit of normal; VAS, visual analogue scale. †Note that primary biliary cirrhosis has recently undergone a name change to primary biliary cholangitis. At the time of the design of the protocol of this study, the official name was primary biliary cirrhosis and, as such, this is reflected in this table.

4.8 *Subgroup analysis*

4.8.1 *Methodology and rationale*

Subgroups based on demographics (age, age at diagnosis, gender, race, and geographical site) and baseline characteristics (baseline BMI group, ALP category, total bilirubin level, years since diagnosis, and UDCA use) were evaluated. Analyses were performed on the percentage of subjects achieving the primary endpoint, as well as two secondary efficacy endpoints: change from baseline in ALP and total bilirubin at Month 12. The analyses were performed on the ITT population.

Age, age at diagnosis, years since diagnosis at baseline, and gender were parameters of interest based on findings from a large cross-sectional study (UK-PBC cohort) with a total of 2,353 subjects with PBC (n=2,132 females, n=221 males). This study highlighted that PBC is not a uniform disease with uniform risks and impact, but a disease with high- and low-risk patients (1). The primary efficacy endpoint, ALP and total bilirubin, were evaluated based on these parameters of interest (1). The patient population randomised to POISE was diagnosed early (median age at diagnosis was 47.5 years) and, as such, was classified as a high-risk population who are more likely to suffer a more severe form of the disease compared with patients diagnosed later in life (1).

In addition, subgroup analyses were performed to evaluate any differences in patient demographics, disease characteristics, and efficacy results in subjects in the OCA titration group who titrated from 5 mg OCA to 10 mg OCA versus those that remained on 5 mg OCA following the Month 6 visit (Section 4.8.4.2). These analyses were performed predominately to determine the efficacy of OCA at both 5 mg and 10 mg, since the licensed dose is 5 mg OCA, with titration to 10 mg if required.

Results are also presented for the small subgroup of patients that took OCA as monotherapy (Section 4.8.4.3).

4.8.2 *Patient characteristics*

A total of 69 (97%) subjects from the OCA titration group completed 6 months of the study. Of these, 36 (52%) remained at 5 mg for the duration of the 12-month treatment period, and 33 (48%) did not meet the primary composite endpoint but tolerated investigational product and titrated to 10 mg for the last 6 months of the 12-month period.

Demographic and baseline characteristics for subjects from the two OCA titration subgroups who completed the Month 6 visit are summarised in Table 35.

Table 35: Demographic and baseline characteristics by OCA titration subgroups: subset of ITT population

Characteristic	OCA titration subgroups	
	Remained at 5 mg n=36	Titrated to 10 mg n=33
Age, years		
Mean (SD)	55.4 (10.7)	55.6 (10.2)
Min, max	30, 81	29, 83
<65 years, n (%)	31 (86)	29 (88)
≥65 years, n (%)	5 (14)	4 (12)
Sex, n (%)		
Male	4 (11)	1 (3)
Female	32 (89)	32 (97)
Race/ethnicity, n (%)		
White	36 (100)	30 (91)
Non-white	0 (0)	3 (9)
Region, n (%)		
Europe	22 (61)	23 (70)
North America	12 (33)	7 (21)
Australia	2 (6)	3 (9)
BMI, kg/m^2		
Mean (SD)	25.5 (4.3)	26.0 (5.6)
Min, max	18, 37	18, 41
<30 kg/m^2, n (%)	31 (86)	26 (79)
≥30 kg/m^2, n (%)	5 (14)	7 (21)
UDCA use at baseline, n (%)		
Yes	32 (89)	32 (97)
No	4 (11)	1 (3)
Baseline ALP, U/L		
Mean (SD)	306.7 (121.9)	348.1 (109.1)

Characteristic	OCA titration subgroups	
	Remained at 5 mg n=36	Titrated to 10 mg n=33
Min, max	187, 811	212, 566
≤3x ULN, n (%)	28 (78)	22 (67)
>3x ULN, n (%)	8 (22)	11 (33)
Baseline total bilirubin, µmol/L		
Mean (SD)	9.6 (6.2)	11.1 (4.6)
Min, max	2, 36	4, 22
≤ULN, n (%)	35 (97)	30 (91)
>ULN, n (%)	1 (3)	3 (9)
Baseline conjugated bilirubin, µmol/L		
Mean (SD)	4.9 (6.0)	4.2 (2.2)
Min, max	1.5, 35.2	1.5, 9.6
Baseline albumin, g/L		
Mean (SD)	42.8 (3.0)	43.4 (3.1)
Min, max	34, 49	33, 51
≥LLN, n (%)	30 (83)	31 (94)
<LLN, n (%)	6 (17)	2 (6)
Baseline INR		
N	36	32
Mean (SD)	1.0 (0.4)	1.1 (0.5)
Min, max	0.9, 3.3	0.9, 3.5
≤1.3, n (%)	35 (97)	30 (91)
>1.3, n (%)	1 (3)	2 (6)

Abbreviations: ALP, alkaline phosphatase; BMI, body mass index; INR, International standardised ratio; ITT, intention-to-treat; LLN, lower limit of normal; OCA, obeticholic acid; SD, standard deviation; UDCA, ursodeoxycholic acid; ULN, upper limit of normal.

4.8.3 *Statistical information*

The primary efficacy endpoint, the absolute and percentage change in ALP and bilirubin from baseline, and TEAEs were descriptively analysed for several subgroup populations. The ITT population was used for the efficacy endpoints, and the safety population for AEs. The cut-off for these analyses was either consistent with appropriate regulatory guidelines (e.g. age, gender, geographical region) or represented clinically meaningful divisions. Subgroup outcomes were calculated only if there were greater than 5 subjects per group at baseline.

Baseline subgroups of interest were:

- Age: <65 years, ≥65 years
- Age at diagnosis: <50 years, ≥50 years
- Sex: male, female

- Race: white, non-white
- BMI: <30 kg/m^2, ≥30 kg/m^2
- ALP level: ≤3x ULN, >3x ULN
- ALP level: tertile (only for the absolute and percentage change in ALP)
- Bilirubin level: >ULN, ≤ULN
- Use of UDCA: Yes, No
- Years since diagnosis: ≤7.5 years, >7.5 years
- Geographic region: Europe, North America/Australia

Additional subgroup analyses were performed on the primary efficacy endpoint, absolute and percentage change in ALP from baseline, and the incidence of treatment-emergent pruritus using the following subgroups:

- Subjects in the OCA titration group who completed the Month 6 titration visit: Subjects who remained at OCA 5 mg, Subjects who titrated from OCA 5 mg to OCA 10 mg

4.8.4 *Results*

4.8.4.1 Analysis of the primary endpoint

In general, results from the subgroups were consistent with the observed effect in the overall ITT population in that greater and statistically significant improvements were observed in OCA-treated subjects compared with placebo-treated subjects. In terms of the primary composite endpoint, the effect of OCA was consistent independent of age at diagnosis, duration of PBC, or years since diagnosis. While the analyses according to sex were confounded by an imbalance in sample size with more females than males, a numerically better response in OCA-treated subjects was consistently demonstrated versus those receiving placebo.

Detailed results are provided in Appendix 4; however, a summary of the key results are listed below.

- **ALP and total bilirubin:** A larger proportion of subjects with lower baseline ALP or total bilirubin achieved the primary endpoint.
- **BMI:** Modestly lower responses in the composite endpoint and ALP were observed in subjects with a BMI ≥30 kg/m^2 compared with subjects with a BMI <30 kg/m^2.
- **UDCA treatment:** When evaluating only those subjects who were not taking UDCA treatment, there was a statistically significantly higher response for OCA-treated subjects compared with placebo-treated subjects.
- **Geographical region:**
  - There was a statistically significantly greater percentage of subjects treated with OCA at the European sites who met the primary endpoint versus placebo-treated subjects. There was no statistically significant difference between subjects treated with OCA versus those receiving placebo for the North America/Australia sites.
  - The apparent diminished efficacy in North America/Australia in terms of the primary endpoint was caused by a notable mean reduction from baseline in ALP in the North America/Australia placebo group. This will diminish the response in the OCA groups compared with placebo. Post hoc sensitivity analyses using the

last measurement prior to first dose instead of the average of all measurements prior to Day 0 demonstrated a statistically significantly higher percentage of subjects achieving the primary composite endpoint across the 12-month period with OCA vs placebo. Taking these limitations into account, no discernible qualitative differences were observed in any of the demographic subgroup categories for the primary composite endpoint, ALP, or total bilirubin analyses.

4.8.4.2 Subgroup analyses – 5 mg versus 10 mg OCA

Patients in the POISE trial were diagnosed with PBC relatively early in their life and, as such, present a more at-risk patient population (1). Therefore, it is likely that a proportion of subjects will not meet the definition of a responder (ALP <1.67x ULN and total bilirubin ≤ULN and ALP decrease ≥15%) after 6 months of treatment with 5 mg OCA, and thus will require their dose to be titrated to 10 mg for the remaining 6 months of the study. Therefore, the subgroup analyses evaluated and compared subjects that remained on 5 mg OCA compared with those that titrated to 10 mg OCA.

Demographics and baseline characteristics

The majority of demographic categories were similar between subjects who remained on OCA 5 mg versus subjects who titrated to OCA 10 mg. There were some key differences, however, which are listed below:

- A lower percentage of subjects who remained at 5 mg had a BMI ≥30 kg/m^2 compared with those who titrated to OCA 10 mg
- In the North American sites, a greater percentage of subjects remained at 5 mg, while a larger percentage of subjects titrated to 10 mg in the European sites
- Baseline ALP and total bilirubin levels were lower in subjects who remained at 5 mg OCA vs those who titrated to 10 mg.

PBC disease characteristics

A similar percentage of subjects had a history of pruritus, and the severity of the most recent pruritus event prior to randomisation was generally similar between the two subgroups. However, there were some key differences in disease characteristics at baseline between the subgroups:

- A greater percentage of subjects who remained at 5 mg (62%) had pruritus ongoing at baseline compared with subjects who titrated to 10 mg (42%)
- Of those who had pruritus at baseline, the severity of the baseline pruritus was greater for subjects who remained at 5 mg compared with those who titrated to 10 mg (moderate pruritus was 39% and 7%, respectively)
- A two-fold greater percentage of subjects in the 5 mg subgroup had a history of fatigue, compared with those subjects who titrated to 10 mg (70% versus 36%, respectively).

Efficacy

Primary endpoint: At Month 12, a greater proportion of subjects who remained at 5 mg OCA achieved the primary endpoint versus those that titrated to 10 mg OCA (53% vs 39%, respectively). However, since those that were titrated from 5 mg OCA to 10 mg OCA at Month 6 had previously failed to meet the primary endpoint, i.e. 0% of these

patients had met the primary endpoint at Month 6, an increase to 39% demonstrates that a significant incremental benefit can be gained with titration of OCA. In addition, it is likely that the benefit of OCA is underestimated in the group who did not up-titrate at Month 6. The SmPC advises all patients to up-titrate from 5 mg to 10 mg, if tolerated. Therefore, in clinical practice it is likely that patients will benefit further from the higher dose of OCA.

ALP, total bilirubin, and conjugated bilirubin: Absolute and percentage reductions from baseline in ALP were highly statistically significant for both OCA titration subgroups. These results support the results for the primary endpoint, in that for some subjects 5 mg OCA is sufficient for a clinically and statistically significant response, but for those subjects whose response is suboptimal following 6 months of treatment at 5 mg OCA, additional efficacy can be achieved by titrating to 10 mg. However, the absolute and percentage reductions in ALP were greater at Month 12 for subjects who titrated to 10 mg OCA compared with those who remained on 5 mg OCA.

The absolute mean reduction from baseline in total bilirubin was statistically significant at both Month 6 and Month 12 for subjects who titrated to 10 mg OCA but not for subjects who remained at 5 mg OCA. Baseline conjugated bilirubin was slightly higher in subjects who remained at 5 mg OCA compared with subjects who titrated to 10 mg OCA. Conjugated bilirubin levels were reduced from baseline for both subgroups at Month 6 and Month 12, with the absolute reduction at Month 6 for subjects who titrated to 10 mg OCA being statistically significant (p=0.0378).

4.8.4.3 Subgroup analyses – Subjects not taking UDCA

Only 11 subjects took OCA as monotherapy (five in the OCA titration group and six in the OCA 10 mg fixed dose group) and five subjects took placebo without UDCA. Of these, two subjects (40%) achieved the primary composite endpoint at Month 12 in the OCA titration group and one (17%) in the OCA 10 mg fixed dose group (Table 36). ALP levels decreased from baseline to Month 12 in both groups, and bilirubin levels decreased slightly in the OCA titration group but increased slightly in the OCA 10 mg fixed dose group. None of the results were statistically significant for either group vs placebo, which is not surprising given the small patient numbers in this analysis.

Table 36: Results for subjects not taking UDCA

	Placebo group (n=5)	OCA titration group (n=5)		OCA 10 mg fixed dose group (n=6)	
	Endpoint	Endpoint	p-value vs placebo	Endpoint	p-value vs placebo
Achieving the primary composite endpoint, n (%)	0 (0)	2 (40)	0.0833	1 (17)	0.3173
Change from baseline to Month 12 in ALP, LS mean (SE)	21.3 (98.4)	–59.5 (76.2)	0.4702	–175.8 (71.5)	0.0895
Change from baseline to Month 12 in total bilirubin, LS mean (SE)	–1.2 (3.0)	–0.5 (2.1)	0.8505	1.4 (1.8)	0.4521

Abbreviations: LS, least squares; OCA, obeticholic acid; SE, standard error; UDCA, ursodeoxycholic acid.

4.9 *Meta-analysis*

There was only one relevant Phase III trial providing data for the efficacy of OCA in PBC, therefore a meta-analysis was not conducted.

4.10 *Indirect and mixed treatment comparisons*

Indirect and mixed treatment comparisons were not conducted. The pivotal trial provides direct evidence of the effect of OCA compared with UDCA in patients who had an inadequate response to UDCA of OCA compared with no additional treatment for people who are unable to tolerate UDCA.

4.11 *Non-randomised and non-controlled evidence*

There are no non-RCTs relevant to this submission.

4.12 *Adverse reactions*

All safety data reported in this section are derived from the pivotal Phase 3 study, POISE, the methodology for which is described in Section 4.3. Supporting safety data were obtained from two Phase 2 trials, 747-201 and 747-202. The methodologies for these trials are described in Section 4.7.2 and they are summarised in Section 4.7.2.

4.12.1 *Summary of adverse events reported in POISE*

POISE included 216 subjects in the safety population who had PBC and were randomised to receive OCA 5 mg, OCA 10 mg, or placebo as described in detail in Section 4.3.

A summary of the AEs, based on the number of events occurring in ≥5% of patients in either treatment group are detailed in Table 37 and Table 38, and a summary of pruritus-related AEs is detailed in Appendix 5.

Table 37: Overview of adverse events: safety population (POISE)

Subjects, n (%)	Placebo n=73	OCA titration n=70	OCA 10 mg n=73
Any TEAE	66 (90)	65 (93)	69 (95)
Total number of TEAEs	452	471	467
Any treatment-related AE†	38 (52)	42 (60)	54 (74)
Any SEAs	3 (4)	11 (16)	8 (11)
Total number of SAEs	8	15	11
TEAEs by severity			
Mild	29 (40)	16 (23)	19 (26)
Moderate	28 (38)	27 (39)	29 (40)
Severe	9 (12)	22 (31)	21 (29)

Subjects, n (%)	Placebo n=73	OCA titration n=70	OCA 10 mg n=73
Any TEAE leading to discontinuation	2 (3)‡	5 (7)§	8 (11)¶
Discontinuation due to pruritus	0 (0)	1 (1)	7 (10)
Number of deaths	0 (0)	1 (1)	0 (0)

Abbreviations: AE, adverse event; CI, confidence interval; eCRF, electronic case report form; SAE, serious adverse event; TEAE, treatment-emergent adverse event.
† Includes any events determined to be "possibly", "probably", and "definitely" related. ‡One subject was discontinued from study due to withdrawal of consent; §No subjects withdrew who titrated to OCA 10 mg. ¶One subject experienced a TEAE of fatigue, which was recorded as a discontinuation on the AE eCRF; however, the subject remained in the study and study drug was not changed.

Table 38: Summary of TEAEs, severity of AEs, and treatment-related AEs occurring in ≥5% of subjects in either OCA treatment group

SOC/preferred term, n (%)†	Placebo N=73	OCA titration N=70	OCA 10 mg N=73
TEAEs occurring in ≥5% of subjects in either OCA treatment group‡			
Skin and subcutaneous tissue disorders			
Pruritus	28 (38)	39 (56)	50 (68)
Rash	3 (4)	3 (4)	4 (5)
Eczema	0	4 (6)	2 (3)
General disorders and administration site conditions			
Fatigue	10 (14)	11 (16)	17 (23)
Oedema peripheral	2 (3)	2 (3)	5 (7)
Pyrexia	1 (1)	0	5 (7)
Infections and infestations			
Nasopharyngitis	13 (18)	17 (24)	13 (18)
Upper respiratory tract infection	8 (11)	4 (6)	4 (5)
Urinary tract infection	8 (11)	4 (6)	4 (5)
Influenza	4 (5)	5 (7)	4 (5)
Bronchitis	0	4 (6)	1 (1)
Sinusitis	0	1 (1)	4 (5)
Gastrointestinal disorders			
Nausea	9 (12)	4 (6)	8 (11)
Diarrhoea	8 (11)	2 (3)	8 (11)
Constipation	4 (5)	5 (7)	5 (7)
Abdominal pain upper	5 (7)	5 (7)	4 (5)

SOC/preferred term, n (%)†	Placebo N=73	OCA titration N=70	OCA 10 mg N=73
Gastroesophageal reflux disease	4 (5)	2 (3)	4 (5)
Dyspepsia	8 (11)	4 (6)	0
Abdominal discomfort	1 (1)	5 (7)	0
Musculoskeletal and connective tissue disorders			
Arthralgia	3 (4)	4 (6)	7 (10)
Back pain	8 (11)	4 (6)	4 (5)
Nervous system disorders			
Headache	13 (18)	12 (17)	6 (8)
Respiratory, thoracic, and mediastinal disorders			
Cough	5 (7)	4 (6)	6 (8)
Oropharyngeal pain	1 (1)	5 (7)	6 (8)
Injury, poisoning, and procedural complications			
Procedural pain	1 (1)	4 (6)	1 (1)
Fractures	3 (4)	2 (3)	4 (5)
Cardiac disorders			
Palpitations	1 (1)	2 (3)	5 (7)
Eye disorders			
Dry eye	4 (5)	2 (3)	4 (5)
Endocrine disorders			
Hypothyroidism	1 (1)	4 (6)	1 (1)
Incidence of TEAE by maximum severity, n (%)			
Mild	29 (40)	16 (23)	19 (26)
Moderate	28 (38)	27 (39)	29 (40)
Severe	9 (12)	22 (31)	21 (29)
Treatment-related AEs in ≥5% of subjects in any OCA treatment group, n (%)§			
Skin and subcutaneous tissue disorders			
Pruritus	27 (37)	35 (50)	48 (66)
General disorders and administration site conditions			
Fatigue	8 (11)	6 (9)	6 (8)
Gastrointestinal disorders			
Nausea	4 (5)	3 (4)	4 (5)

Abbreviations: AE, adverse event; N, total number of subjects; n, number of subjects experiencing an event, OCA, obeticholic acid; SOC, systems organ class; TEAE, treatment-emergent adverse event.
† At each level of summation, subjects reporting >1 AE are counted only once.
‡ a TEAE is defined as any event that newly appeared, increased in frequency, or worsened in severity following initiation of investigational product. At each level of summation, subjects reporting >1 AE are counted only once using the highest severity.
§ treatment-related AEs include all events reported as “possible”, “probable”, or “definite” relationship to study drug.

4.12.2 *Safety overview*

4.12.2.1 Summary of key safety

OCA treatment was safe and generally well tolerated. Pruritus was the most common TEAE with a higher incidence reported in OCA treatment groups (OCA titration [56%] and OCA 10 mg [68%] versus the placebo [38%]). While pruritus was the most commonly reported TEAE, pruritus is a symptom of the disease, and therefore OCA may transiently exacerbate this feature of the disease, but patients will already be familiar with the adverse event. However, based on the rate of treatment discontinuations due to pruritus, treatment was better tolerated in subjects treated with OCA who initiated treatment at 5 mg and titrated up to 10 mg after 6 months based on clinical response. Additionally, the severity of pruritus was mitigated by this dosing strategy compared to starting at OCA 10 mg. There were no discontinuations due to pruritus in the placebo group, and in the majority of subjects who experienced pruritus in this group, the maximum severity of pruritus was mild or moderate. The incidence of TEAEs assessed as related, severe, serious, or leading to study discontinuation was higher in subjects treated with OCA, compared with placebo. With the exception of SAEs, these imbalances were predominantly attributed to pruritus.

Total TEAEs

The overall incidence of TEAEs was generally similar between OCA and placebo treatment groups. A total of 66 subjects (90%) from the placebo group reported 452 TEAEs, 65 subjects (93%) from the OCA titration group reported 471 TEAEs, and 69 subjects (95%) from the OCA 10 mg group reported a total of 467 TEAEs.

TEAEs occurring in ≥5% of subjects in either of the OCA groups

TEAEs that occurred with an incidence of ≥5% and were reported more frequently in either of the OCA treatment groups compared with placebo included pruritus, rash, eczema, fatigue, pyrexia, peripheral oedema, nasopharyngitis, influenza, bronchitis, sinusitis, diarrhoea, constipation, abdominal discomfort, arthralgia, cough, oropharyngeal pain, procedural pain, fractures, palpitations, and hypothyroidism.

TEAEs that occurred at an incidence of ≥5% and were reported with an incidence of >3% more frequently in subjects receiving OCA compared with placebo were limited to pruritus, fatigue, hypothyroidism, procedural pain, oropharyngeal pain, arthralgia, abdominal discomfort, sinusitis, peripheral oedema, pyrexia, palpitations, eczema, bronchitis, and nasopharyngitis.

Treatment-related AEs

As expected based on prior experience with OCA treatment in patients with PBC, the most common related TEAE was pruritus. In all treatment groups, the majority of pruritus AEs were considered related to investigational product. The incidence and number of subjects with related TEAEs of pruritus was 27 subjects (37%) in the placebo group, 35 subjects (50%) in the OCA titration group, and 48 subjects (66%) in the OCA 10 mg group. Fatigue and nausea were the only other related TEAE that occurred at an incidence ≥5%; however, these events were balanced between placebo and OCA treatment groups.

4.12.2.2 Safety parameters of special interest

Pruritus

A higher incidence of pruritus was observed in the OCA titration and OCA 10 mg groups when compared with placebo (60%, 74%, and 37%, respectively). Most pruritus events were of mild or moderate severity and resolved during the treatment period. Starting at OCA 5 mg and titrating to 10 mg OCA was associated with improved tolerability versus starting at 10 mg OCA. In the majority of cases, subjects remained in the study despite varying pruritus severity.

Hepatic-related effects

There was no dose-dependent trend in the incidence of hepatic-related events. In agreement with the improvements in hepatic indices, hepatic safety was maintained during the course of the study in both OCA treatment arms.

Lipid-related effects

There was an early decrease in high-density lipoprotein cholesterol (HDLc), which later stabilised, and all values remained within the normal range. In addition, there was a modest and transient increase in low-density lipoprotein cholesterol (LDLc) in OCA-treated subjects; however, there were no differences between groups after 12 months of treatment and hypercholesterolemia doesn't appear to increase the risk of cardiovascular disease in PBC patients (47). There was a greater number of subjects in the 10 mg OCA groups that experienced a shift from normal HDLc at baseline to a lower level after 12 months when compared with placebo. However, there were no treatment differences for lipid-related AEs.

Cardiovascular-related TEAEs

There were no treatment differences observed for cardiovascular-related AEs or SAEs.

Deaths and other SAEs

One death occurred during the double-blind phase (cardiac failure) in a subject from the OCA titration group who had an extensive history of cardiovascular conditions including cardiac failure. In total, three subjects (4%), 11 subjects (16%), and 8 subjects (11%) experienced SAEs in the placebo, OCA titration, and OCA 10 mg groups, respectively. None of the SAEs were considered to be related to study drug.

AEs leading to study discontinuation

A greater proportion of subjects in the OCA titration and OCA 10 mg groups experienced TEAEs which lead to study discontinuation when compared with placebo (7%, 11%, and 3%, respectively). The majority of these were attributed to pruritus and occurred in the OCA 10 mg group (10%). One subject (1%) discontinued due to pruritus in the OCA titration group versus none in the placebo group.

Safety laboratory parameters

No clinically meaningful differences between treatment groups were observed for any safety laboratory parameters.

4.12.2.3 Other safety evaluations

- As may be expected, minimal changes in MRS and MELD scores were observed in either treatment group indicating overall stable disease state over the course of the 12-month treatment period.
- Generally, reductions in DEXA scans results were observed from baseline to month 12 in all treatment groups. However, the decrease in mean femoral neck T-score from baseline to month 12 was significantly less in the OCA-treated groups compared with placebo. No significant differences from baseline or between treatment groups were seen in lumbar or femoral Z-scores.
- Overall, no clinically meaningful mean changes from Baseline to Month 12 in body weight or BMI were observed in any of the treatment groups and no clinically meaningful differences in vital signs or ECGs were noted.

4.12.3 *Interim safety results from the long-term safety extension of POISE (Study 747-301)*

Currently, there is an ongoing 5-year LTSE of the Phase 3 POISE study. As such, interim results are provided for the first 12 months of this study. For full study details, see Section 4.7.2.1.

Overall, continued treatment with OCA was safe and generally well tolerated with longer term treatment. During the LTSE, 10 subjects in the safety population discontinued from the study, 4 (2%) of these discontinuations were due to TEAEs, which was a comparable rate to that observed in the double-blind period.

The AE profile observed during the LTSE was consistent with that observed for OCA treatment in the double-blind period. Consistent with the double-blind period and the disease state in general, pruritus was the most common TEAE as assessed by crude and exposure adjusted incidence. Most pruritus events were mild to moderate in severity, with an increase in the occurrence of severe pruritus, as assessed by exposure adjusted incidence noted with increasing OCA dose with the highest rates observed in subjects who titrated to >10 mg OCA.

In the double blind phase, the use of a titration strategy mitigated subject discontinuations due to pruritus. The use of a titration strategy was similarly beneficial in the LTSE phase, with only one subject who enrolled in the LTSE discontinuing due to pruritus.

All SAEs occurring to date in the LTSE were considered unrelated or unlikely to be related to OCA. With the exception of one SAE that was fatal, all SAEs resolved with or without sequelae. There was no dose related trend or system organ class grouping of SAEs.

Lipid effects in the LTSE were consistent with the double-blind period. With continued OCA treatment, there was no change from baseline in LDL while the decrease in HDL was sustained.

4.13 *Interpretation of clinical effectiveness and safety evidence*

4.13.1 *Principal (interim) findings from the clinical evidence highlighting the clinical benefits and harms of the technology*

The double-blind phase of POISE assessed the efficacy, safety, and tolerability of OCA with or without UDCA (depending on tolerability) compared with placebo with or without UDCA (depending on tolerability) in patients with an adequate response to, or who are intolerant to, UDCA. Of 316 patients screened, 217 were randomised and 216 were included in the ITT population. The patient population was representative of patients with PBC in the UK, and baseline characteristics were generally well balanced across treatment arms.

The primary endpoint of POISE was met. Treatment with OCA resulted in clinically and statistically significant improvements from placebo as assessed by a composite ALP and total bilirubin endpoint (ALP <1.67x ULN [200 U/L], bilirubin ≤ULN [20 µmol/L] and ≥15% decrease from baseline in ALP). Almost five times as many patients had response to treatment in the OCA groups 47% and 46% of patients in the 10 mg OCA fixed dose and the OCA titration groups, respectively) than in the placebo group (10% of subjects; p<0.0001). Furthermore, as secondary endpoints, the effect of OCA on several other independent biochemical response criteria incorporating ALP, AST, bilirubin and albumin (i.e. Paris I, Paris II, Toronto II, and Mayo II), all of which are shown to correlate with improved prognostic outcomes, were supportive of the potential effect of OCA in inhibiting the progression of PBC and improving clinical outcomes.

Patients treated with OCA were over 30 times more likely to achieve a reduction in ALP ≥40% over 12 months compared with placebo (odds ratios of 34.7 and 43.0 for the OCA titration and OCA 10 mg fixed dose groups, respectively). Mean ALP was statistically significantly reduced from as early as 3 months compared with placebo, which maintained stable ALP. Total and conjugated bilirubin levels increased with placebo, but decreased or remained stable for both OCA treatment groups, and the results were statistically significant at 6 and 12 months. In addition, GGT, ALT and AST were statistically significantly reduced with OCA compared with placebo, which maintained or increased levels.

Other secondary endpoints, including several biochemical markers of FGF-19, CK-18, total endogenous bile acid, CRP, and TNF-α demonstrated clinically and statistically significant improvements compared with placebo that were sustained during the 12-month period. These improvements, paralleled by the improvement in liver biochemistry due to FXR-mediated effects on bile acid homeostasis, are further supportive of a beneficial disease-modifying effect of FXR activation over at least a 12-month period.

Subgroup analyses demonstrated that the effect of OCA on achieving the primary composite endpoint and changes in ALP and total bilirubin were independent of age at diagnosis, duration of PBC, and baseline ALP. In general, the baseline and demographic subgroup analyses were consistent with the observed effect in the overall population, in that OCA-treated subjects had more favourable outcomes than subjects receiving

placebo. For subjects receiving BAS, efficacy was modestly attenuated in subjects receiving OCA 5 mg but was not affected in subjects receiving OCA 10 mg.

Based on the clinical response and adverse event profile, initiating subjects on OCA 5 mg and titrating to 10 mg appears to be an appropriate dosing strategy. For some subjects, the composite endpoint was achieved with 5 mg OCA, however, an additional incremental benefit was gained by titrating to 10 mg OCA in those that failed to achieve an optimal response within 6 months of initiating treatment, and this is therefore the recommended dosing strategy for all patients according to the summary of product characteristics (SmPC).

An ongoing long-term safety extension (LTSE) of POISE has shown continuing efficacy of OCA out to a further 12 months in terms of ALP and bilirubin levels. Evidence from two Phase 2 studies and their LTSEs provide further support for the efficacy of OCA observed in POISE.

OCA was generally well tolerated, with pruritus being the most commonly reported AE. However, it is important to consider that pruritus is a common symptom of PBC; 63% of patients in POISE had a history of pruritus. Therefore, patients and their clinicians are typically familiar with the condition and its management.

In conclusion, OCA for the treatment of adults with PBC who have failed treatment with or are intolerant to UDCA is an effective and tolerable treatment option. OCA (5 mg and 10 mg) resulted in clinically and statistically significant improvements in a range of evidence-based disease-related prognostic factors, which is expected based on predictive modelling to lead to a reduced risk of liver transplant and/or death. In addition, markers of inflammation and liver dysfunction were reduced.

4.13.2 *Strengths and limitations of the clinical evidence base for the technology*

4.13.2.1 Strengths

1. Design features of POISE

    - POISE was a high-quality, multi-centre, multi-national randomised, controlled, double-blind study
    - It is the largest clinical trial in PBC to date, including 216 patients

2. Representativeness of patient population and generalisability to UK clinical practice

    - The patient population in POISE was validated as representative of the population with PBC in the UK by clinical expert opinion
    - It included nine sites in the UK:
        - Seven in England (London, Oxford, Newcastle-Upon-Tyne, Birmingham, Nottingham, Bristol, and Manchester)
        - Two in Scotland (Larbert and Dundee)

3. Value of clinical outcomes observed with OCA

- There is currently no licensed or effective treatment option for patients who have an inadequate response to, or are intolerant to, UDCA
    - These patients are at significantly increased risk of complications, the requirement of liver transplantation, HCC and death
    - Therefore, an effective treatment option for these patients is likely to make a substantial difference to the patients' health and quality of life, and also is likely to avoid the costly downstream events in PBC such as the management of complications and liver transplant
- OCA is the first new and effective treatment for PBC in almost 20 years, and provides a novel, innovative mechanism of action targeting the FXR receptor
- ALP is the key biomarker of PBC, with elevated bilirubin indicative of end-stage disease
    - Mean ALP decreased significantly with OCA (in both treatment groups), but remained stable at >1.67x ULN (200 U/L) in the placebo group
        - A patient-level meta-analysis (15) found that attaining an ALP <1.67x ULN is associated with a statistically significantly reduced risk of disease progression over the subsequent 10 years
    - Mean bilirubin decreased or remained stable with OCA (in both treatment groups), but increased in the placebo group to >0.5x ULN (20 µmol/L)
        - An increase in risk for liver transplantation or death starts at levels of bilirubin >0.5x ULN (47)
    - Since the vast majority (93%) of patients were taking UDCA in the placebo group, this shows clear progression of disease in these patients on the only currently licensed treatment option for PBC, correlating to an increased risk of complications, the requirement for liver transplantation, HCC and death
        - There is a substantial unmet need for an effective treatment option for these patients
- It is likely that the clinical benefit of OCA is actually underestimated in the OCA titration group of POISE compared with that proposed for clinical practice
    - It is recommended that patients initiate treatment at 5 mg and up-titrate to 10 mg at 6 months if tolerated
    - However, in POISE, patients in the OCA titration group were only up-titrated from 5 mg to 10 mg OCA if they did not reach the primary endpoint criteria for response
    - Therefore, further benefit in terms of efficacy is likely to be seen in clinical practice in this patient group due to the higher dose of OCA

4.13.2.2 Limitations

The main limitation of POISE was the necessity to use surrogate endpoints. This is due to the rarity, slow rate of progression in most patients, and chronic nature of PBC.

However, ALP and bilirubin levels are key factors for determining patients' prognoses and are included in a wide range of PBC patient scoring systems. Elevated ALP levels

are used as a marker for cholestasis in patients with PBC throughout the progression of the condition and are a key component used in the diagnosis of PBC in European guidelines (33).

Both ALP and bilirubin are commonly used in an array of algorithms to predict survival and transplant outcomes in patients with PBC (11-13, 16, 125, 126). Data demonstrates that in patients with PBC who receive treatment with UDCA, a reduction in ALP is associated with a general reduction in the risk of death and an increase in transplant-free survival (16, 125, 126). For example, Kuiper et al demonstrated that the normalisation of ALP and/or bilirubin was associated with an overall increase in survival outcomes, irrespective of the degree of disease severity (13). More recently, a patient-level meta-analysis study by Lammers et al demonstrated the significant prognostic value of ALP and bilirubin levels on long-term clinical outcomes in patients with PBC (15). Generally, the study demonstrated that lower levels of ALP and bilirubin strongly correlated with a longer transplant-free survival in a log linear manner. Of patients with ALP ≤2.0x ULN, 84% survived for 10 years compared with 63% of those with levels >2.0x ULN, and of patients with bilirubin ≤1.0x ULN, 86% survived for 10 years versus just 41% in patients with bilirubin >1.0x ULN (15). When evaluating ALP alone, attaining an ALP <1.67x ULN is associated with a statistically significantly reduced risk of disease progression over the subsequent 10 years, and is therefore a key clinical goal when evaluating the effectiveness of treatment in patients with PBC (18).

In addition, bilirubin is an independent predictor of PBC prognosis and disease progression, and was used as an endpoint to support the marketing authorisation application of UDCA in the EU. Many PBC studies have shown that increased bilirubin levels are an independent predictor of a poor prognosis (13, 88, 132-136), with increased survival associated with levels <ULN. As noted in the American Association for the Study of Liver Disease (AASLD) Endpoints Conference (137) bilirubin levels are an important serum marker of survival and are also a key criterion of the Model for End Stage Liver Disease (MELD) score that is used to manage US liver transplant programs and others globally (138).

Importantly, changes in ALP and bilirubin occur during different stages of PBC disease progression, with ALP changes occurring during the early/asymptomatic stages whereas changes in bilirubin occur during the later/decompensated stages of the disease. Therefore, the prognostic value of these surrogate markers is significantly increased when combined and evaluated together (15). Momah et al from the Mayo clinic evaluated different biochemical thresholds versus a combination of clinical outcomes such as varices, ascites, death, or liver transplantation in a cohort of UDCA-treated patients, and concluded that combining ALP and bilirubin (ALP <1.67x ULN and bilirubin ≤1 mg/dL) was the most discriminating of the algorithms they evaluated (17).

The validity of the combined surrogate endpoint proposed by Momah et al has since been supported by a meta-analysis of patient-level data from the Global PBC study (15). The Global PBC study comprised data from 4,845 patients from 15 centres in North America and Europe, and is the largest international database of PBC patients to date. The Global PBC study demonstrated that the combined use of ALP and bilirubin levels provided greater prognostic predictability versus either component alone (15). Therefore,

the use of both ALP and bilirubin for evaluating patients with PBC represents an evidence-based, clinically meaningful surrogate endpoint for use in clinical studies (15).

4.14 *Other ongoing studies*

There is a long-term phase 3b study (747-302, COBALT) currently recruiting participants, details of which are summarised in Table 39. Results of COBALT will establish whether OCA has an impact on long-term clinical outcomes and to what degree, and results are expected to validate the surrogate endpoints used in POISE.

There is also an ongoing phase 2 study that is summarised in Table 40. In addition, the long-term safety extension of the phase 2 study 747-201 (as described in Section 4.7.2.2) is ongoing, with a planned maximum exposure time of approximately 6 years and 3 months.

Table 39: Details of the ongoing trial 747-302 (COBALT)

Title	**Phase 3 study of obeticholic acid evaluating clinical outcomes in patients with primary biliary cirrhosis[§] (COBALT)**
Trial numbers	747-302, NCT02308111
Trial design	Phase 3b, double-blind, randomised, placebo-controlled, multi-centre study evaluating the effect of obeticholic acid on clinical outcomes in patients with PBC
Location	Up to 170 sites internationally, in Argentina, Australia, Austria, Belgium, Bulgaria, Canada, Chile, Denmark, Estonia, Finland, Former Serbia and Montenegro, France, Germany, Hungary, Israel, Italy, Lithuania, Mexico, Netherlands, New Zealand, Poland, Republic of Korea, Spain, Sweden, Switzerland, Turkey, the UK and the US
Estimated enrolment	350
Duration	Time to accrue approximately 121 primary endpoint events, estimated to be approximately 8 years, with an expected minimum follow-up time of approximately 6 years
Interventions	Subjects will be randomised 1:1 (stratified by standard treatment with UDCA [yes/no] and baseline liver function) to either: • OCA 5 mg OD for 3 months and then titrating up to 10 mg OD for the remainder of the trial, based on tolerability; or • Placebo OD
Primary outcome measures	Composite endpoint of any of the following: • Death • Liver transplant • MELD[†] score ≥15 • Uncontrolled ascites, defined as diuretic resistant ascites requiring therapeutic paracentesis at a frequency of at least twice in a month • Hepatocellular carcinoma confirmed by two complementary imaging modalities • Hospitalisation (defined as a stay of ≥24 hours) for new onset or recurrence of any of the following:

	○ Variceal bleed ○ Encephalopathy, as defined by a West Haven score of ≥2 ○ Spontaneous bacterial peritonitis confirmed by diagnostic paracentesis
Secondary outcome measures	• First occurrence of each of the following: ○ Death ○ Liver transplant ○ MELD score >15 ○ Uncontrolled ascites (defined as diuretic resistant ascites requiring therapeutic paracentesis at a frequency of at least twice in a month) ○ Hepatocellular carcinoma confirmed by two complementary imaging modalities ○ Hospitalisation (defined as a stay of ≥24 hours) for new onset or recurrence of any of the following: ▪ Variceal bleed ▪ Encephalopathy, as defined by a West Haven score of ≥2 ▪ Spontaneous bacterial peritonitis confirmed by diagnostic paracentesis • Changes from baseline in bilirubin, AST, ALT, ALP and GGT as markers of liver biochemistry • Changes from baseline in IgM, CRP, TNF-α and FGF-19 as markers of inflammation • Changes in CK-18, ELF test, and transient elastography as markers of liver fibrosis
Key eligibility criteria	• Aged ≥8 years • Definite or probable PBC diagnosis, as demonstrated by the presence of ≥2 of the following diagnostic factors: ○ History of elevated ALP levels for at least 6 months prior to Day 0 ○ Positive anti-mitochondrial antibody titer or if negative or in low titer (<1:80) PBC-specific antibodies ○ Liver biopsy consistent with PBC • Mean total bilirubin >ULN and ≤3x ULN or an ALP >5x ULN

Abbreviations: ALP, alkaline phosphatase; ALT, alanine aminotransferase; AST, aspartate aminotransferase; CK-18, cytokeratin-18; CRP, C-reactive protein; ELF, enhance liver fibrosis; FGF-19, fibroblast growth factor-19; GGT, gamma-glutamyl transferase; IgM, immunoglobulin M; MELD, Model for End-Stage Liver Disease; OCA, obeticholic acid; OD, once daily; PBC, primary biliary cholangitis/cirrhosis; TNF-α, tumour necrosis factor-α; UDCA, ursodeoxycholic acid; ULN, upper limit of normal.
[†]MELD is a scoring system for assessing the severity of chronic liver disease, where the higher the score, the more severe the disease. [§]Note that primary biliary cirrhosis has recently undergone a name change to primary biliary cholangitis. At the time of the design of the protocol of this study, the official name was primary biliary cirrhosis and, as such, this is reflected in this table.

In addition, a Phase 2 study is ongoing, which is summarised in Table 40.

Table 40: Details of the ongoing trial 747-205

Title	Phase 2 study on effects of OCA on lipoprotein metabolism in subjects with PBC
Trial numbers	747-205, NCT01865812
Trial design	Phase 2, open-label, single-arm, multi-centre study
Location	6 sites in the US
Estimated enrolment	25
Duration	8 weeks
Interventions	OCA 10 mg OD
Primary outcome measures	• Change from baseline in HDL metabolism, assessed by measuring HDL cholesterol concentration, HDL particle size and number
Secondary outcome measures	• Change from baseline in lipoprotein metabolism, assessed by measuring: o Concentrations of total cholesterol and triglycerides o LDL and VLDL cholesterol concentrations, particle size and number o Concentrations of ApoA, ApoB, ApoE and LP(a) • Change from baseline in reverse cholesterol transport, assessed by measuring: o HDL capacity to accept cholesterol measured by LCAT and CETP activity o Pre-β1 HDL concentration o Macrophage cholesterol efflux • Pharmacokinetic parameters of OCA and OCA conjugates
Other outcome measures	• Fasting levels of OCA and conjugates • Change from baseline in FGF-19 • Change from baseline in lipoprotein X • Markers of inflammation including CRP, GlycA and GlycB
Key eligibility criteria	• Aged ≥8 years • Definite or probable PBC diagnosis as demonstrated by the presence of ≥2 of the following diagnostic factors: o History of elevated ALP levels for at least 6 months o A positive anti-mitochondrial antibody titer or if negative or in low titer (<1:80) PBC antibodies o Liver biopsy consistent with PBC

Abbreviations: ALP, alkaline phosphatase; Apo, apolipoprotein; CETP, cholesterol ester transfer protein; CRP, C-reactive protein; FGF-19, fibroblast growth factor-19; HDL, high density lipoprotein; LCAT, lecithin-cholesterol acyltransferase; LDL, low density lipoprotein; LP, lipoprotein; OCA, obeticholic acid; OD, once daily; PBC, primary biliary cholangitis/cirrhosis; VLDL, very low density lipoprotein.

5 Cost effectiveness

Summary

- The model presented for OCA is a decision-analytic model that reports cost-effectiveness in terms of incremental cost per QALY.
- The model evaluates the economic consequences of OCA 5–10 mg (titrated dose) alone (in the case of UDCA intolerant PBC patients) and adding OCA 5–10 mg OD to 15.4 mg/kg UDCA (in the case of UDCA inadequate responders). In other words, the model examines the cost-effectiveness of OCA titration versus placebo in UDCA intolerant patients, and OCA + UDCA titration versus UDCA monotherapy in UDCA tolerant patients.
- The results presented in this submission use the list price of OCA. However, OCA will be offered with a PAS, which will reduce the price. Results of economic analyses using the PAS price are presented in the accompanying PAS template, as requested by NICE, and are more reflective of the true cost-effectiveness of OCA.
- The base case results using the list price of OCA gave an ICER of [redacted] in UDCA-intolerant patients, and an ICER of [redacted].16 in patients with an inadequate response to UDCA.
- Patients treated with OCA were found to have an 84% lower chance of undergoing liver transplant compared with patients treated with UDCA, which approaches the risk observed in the general population.

5.1 *Published cost-effectiveness studies*

5.1.1 *Identification of studies*

5.1.1.1 Overview and review question

A systematic review was conducted to identify all relevant PBC studies relating to cost effectiveness. The specific review question was:

- "What modelling techniques have been used previously to conduct economic evaluations for the treatment of PBC?"

5.1.1.2 Search methodology

Studies of interest were identified by simultaneously searching the electronic databases shown in Table 41 with no restrictions on date or language of publication. Searches were conducted in September 2014 using the following interfaces:

- EMBASE (which also covers Medline® and Medline® In-Process)
- The Cochrane Library (which covers the Cochrane Database of Systematic Reviews, Database of Abstracts of Reviews of Effects, Health Technology Assessment, NHS Economic Evaluation Database)
- EBSCO host (which covers EconLit, Health Economic Evaluations Database)

Table 41: Databases searched and interfaces used in the cost effectiveness systematic review

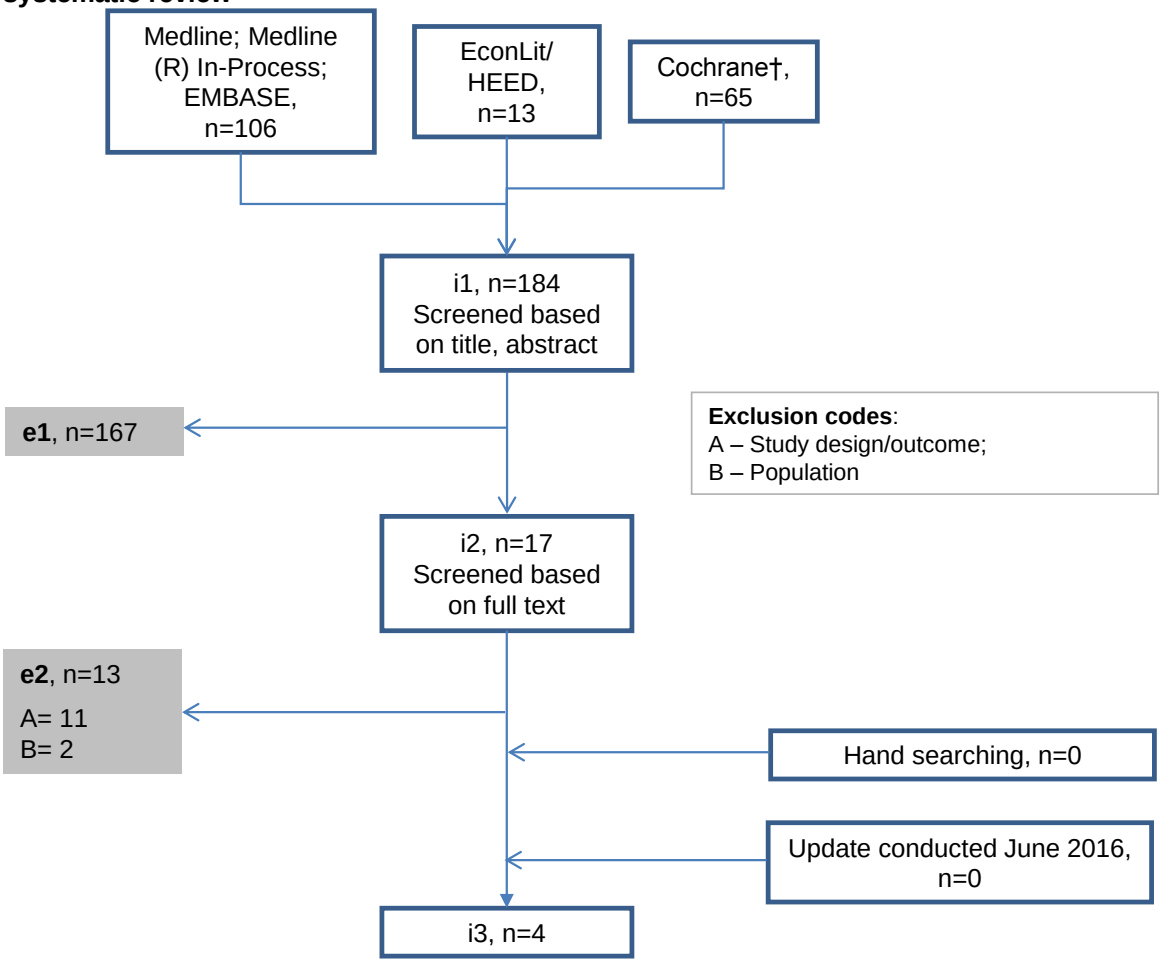
Database	Interface
Embase 1966 to 2014	Embase
Medline 1966 to 2014	Embase
Medline® In-Process 1966 to 2014	Embase
Cochrane Database of Systematic Reviews 1996 to 2014	The Cochrane Library
Database of Abstracts of Reviews of Effects 1994 to 2014	The Cochrane Library
Health Technology Assessment 1989 to 2014	The Cochrane Library
NHS Economic Evaluation Database 1968 to 2014	The Cochrane Library
EconLIT with Full Text 1961 to 2014	EBSCO host
Health Economic Evaluations Database 1990 to 2014	EBSCO host

Appendix 6 shows the complete search strategies used. The searches included terms for free text and keywords (Medical Subject Heading [MeSH] and Emtree terms) through the use of Boolean combination techniques. Searches were not restricted by study intervention or comparator to ensure all studies in this population were identified. The Cochrane Library and EBSCO host interfaces were searched using terms for the population only to broaden the results.

A grey literature search was performed to include additional studies that had not been identified by the search strategy. References included for the review had to meet the pre-specified inclusion/exclusion criteria shown as a PICOS table in Appendix 6.

The search identified 184 titles/abstracts. After screening, 167 references were excluded, leaving 17 references for full-text evaluation. Two further studies were identified from the review of grey literature. Following full-text evaluation, four references met the inclusion criteria. All of these four studies were deemed relevant to the review and to be used for data extraction. The PRISMA diagram for the systematic review is shown in Figure 23.

Figure 23: PRISMA diagram illustrating the flow of the cost and healthcare resource use systematic review



5.1.2 *Description of identified studies*

5.1.2.1 Overview of all included studies

The four relevant cost-utility analyses are summarised in Table 46. When comparing the four identified economic evaluations, the following salient points are noted:

- None of the analyses are economic evaluations of OCA.
- All identified economic evaluations incorporated liver transplant and death as key outcomes, with Boberg et al (79) and Ratcliffe et al (139) also allowing the possibility of re-transplantation in their patient pathway.
- In contrast to the other included papers, Boberg et al (79) was the only analysis identified to capture long-term outcomes. In addition to differences in liver transplant and death, their analysis also incorporated long-term changes in complications associated with PBC, e.g. ascites. The remaining papers focused on short-term horizons ranging from 27 months to 12 years, typically investigating outcomes associated with treatment strategies administered around the time when transplant may be required.

- Of the four economic evaluations included for review, three of these (Ratcliffe et al, Longworth et al, and Boberg et al) applied modelling techniques. The remaining article estimated costs and outcomes based on observed data. The three modelling studies applied varied techniques. The value of the complex discrete event simulation applied by Ratcliffe et al (139) is unclear, as the analysis for patients who did not receive transplants incorporated outcomes for patients who may not be eligible for transplantation. The approach taken by Longworth et al (140) estimated outcomes in the active treatment arm using observed data, with the comparator arm modelled using relative effect data. Boberg et al (79) simulated outcomes in the non-UDCA arm in a similar fashion; however, they simulated outcomes beyond those observed in data. This extrapolation beyond observed outcomes was conducted through the application of parametric survival analysis; however, details of curve fit and justification behind the selection of the Weibull curve are not reported.
- Only one of the identified papers reported QALYs (Longworth et al), with all other papers expressing effectiveness in real units. QoL analyses reported by Longworth et al (140) aligned with the NICE reference case for derivation of utility estimates.
- Studies typically undertook detailed costing analyses; however, the extent of reporting varied between studies. The costs included in analyses appear to be limited to direct costs. Reporting by Pasha et al (78) indicates that societal costs may have been included; however, their incorporation is unclear.
- Whilst analyses differ in their methods, those that compared UDCA or liver transplant to placebo each found the active therapy to dominate placebo, i.e. reducing costs and improving health outcomes.

5.1.2.2 Individual study summaries

BOBERG ET AL 2013 (Norway)

Reason for inclusion

Boberg et al (79) conducted a cost-consequence analysis in the treatment of PBC, comparing UDCA to a control strategy in which UDCA was not administered. Whilst the study was a cost-consequence analysis, the authors also presented results using a cost-effectiveness approach (incremental cost per life year gained); accordingly, this study was included for review.

Model overview

The authors simulated outcomes using a semi-Markov model, with patients transitioning between three health states:

- Alive (starting state)
- Alive after transplant
- Dead

UDCA was applied as the baseline treatment in the analysis. The probability of transitioning between the three health states whilst receiving UDCA were derived from registry data. Long-term survival data (up to 11.5 years) for PBC subjects treated with UDCA were available from a Norwegian registry. Weibull distributions were fitted to these data to estimate the following transitions:

- 'Alive' to 'Alive after transplant' – Patients who died prior to transplant were censored from this analysis
- 'Alive' to 'Dead' – patients who received transplant prior to death were censored from this analysis

The probability of transitioning to death from the post-transplantation state was taken from the Nordic Liver Transplant Registry, which estimated the relative risk of death following liver transplant compared with the general population. This relative risk was applied to baseline mortality rates observed in the general population to estimate the higher risk of death following liver transplant in this population. The probability of further surgery was derived from registry data; it is unclear from the report how further surgery was applied in the model.

The relative effect of not receiving UDCA was estimated from placebo data from a single trial (78). The separate hazard ratios for both transplant and death from the initial health state were estimated and applied to the baseline risk of progression to simulate outcomes in this patient group. The following hazard ratios were applied in the model:

- Mortality – Hazard ratio of 1.54 for control relative to UDCA
- Transplantation – Hazard ratio of 2.03 for control relative UDCA

Whilst these hazard ratios have been reported, the maturity of the data on which these estimates are based is not reported, nor are the associated significance levels.

In both arms, patients were at risk of experiencing major adverse events, which contributed to the cost profile of the simulated patients. Similar rates of adverse events were applied for both UDCA treatment and the non-UDCA PBC control strategy.

Costs were derived for each model health state and adverse event. Costs comprised regular physician visits, cost of major events, and treatment costs. No societal costs were considered. All costs were reported in 2005 Euros. A discount rate of 4% was used for both future costs and life-years.

Primary outcomes of the analysis were survival rates and adverse events, including variceal bleeding, ascites, encephalopathy, and liver transplantation.

It was not specified whether patients had previously been on treatment for PBC. Baseline characteristics of patients in the model were reported as shown in Table 42.

Table 42: Characteristics of PBC patients at start of UDCA- or non-UDCA treatment

Variable	UDCA Norwegian patients (n=182)	UDCA Canadian patients (n=111)	Placebo Canadian patients[§] (n=111)	Placebo patients from Mayo study[†] (n=91)
Gender; females, n (%)	163 (90)	101 (91)	105 (95)	79 (87)
Age; years, mean (SD)	56.3 (8.9)	57.3	55.4	52.0 (9)
Body weight; kg, mean (SD)	66.3 (11.9)			
Dose UDCA; mg/kg/day, median (range)	20.2 (17–23)		0	0
Symptoms before start, n (%)				
Pruritus, n (%)	91 (50)	87 (78)	79 (71)	
Fatigue, n (%)	99 (54)	87 (78)	83 (75)	
Jaundice, n (%)	12 (7)			
Ascites (clinical finding), n (%)	3 (2)	2 (1.8)	4 (3.6)	
Pruritus + fatigue, n (%)	65 (36)			
Encephalopathy, n (%)	3 (2)			
Asymptomatic, n (%)	56 (31)	13 (12)	14 (13)	
AMA titre, median (range)[‡]	1024 (0–2048)		79 (71)	
Bilirubin, mean (SD) (3–26 µmol/L)	19.4 (18.3)	40 (64)	31 (39)	31 (39)
ALP, mean (SD) (70–230 U/L)	980 (636)	588 (418)	549 (339)	1,252 (712)
ALT, mean (SD) (10–50 U/L)	110 (70)	110 (63)	109 (62)	
Albumin, mean (SD) (35–45 g/L)	40.0 (3.6)			33 (4.0)
INR, mean (SD) (0.8–1.2)	1.2 (0.2)			
IgM, mean (SD) (0.4–2.1 g/L)	5.23 (3.72)	5.9 (4.5)	5.9 (3.5)	
Hepatomegaly, n (%)	54 (30)			
Splenomegaly, n (%)	14 (8)			
Mayo risk score at inclusion[¶], mean (SD)	4.38 (0.88)	4.6 (1.3)	4.4 (1.2)	5.1 (1.1)

Abbreviations: ALT, amino transaminase; AMA,anti-mitochondrial antibody; INR, international normalised ratio; IgM, immunoglobulin M; SD, standard deviation; UDCA, ursodeoxycholic acid.[§]Data obtained from Pasha et al (78). [†]Data obtained from Lindor et al and Pasha et al (34, 78). [‡]Titer available in 150 patients. [¶]Based on 173 patients with complete set of variables in the Mayo risk score at inclusion.

Results

UDCA was found to dominate the control treatment. Life years gained were estimated to be superior (11.97 years vs. 10.78 years) in the UDCA arm, whilst costs were estimated to be lower in the UDCA arm (€151,403 vs. €157,741). Results by clinical outcome are reported below in Table 43.

Table 43: Incidence (per 100 person-years) of major events over time among Norwegian PBC patients (*n* = 182) treated with UDCA during the first 5 years.

Total number of events	First year	Second year	Third year	Fourth year	Fifth year
Variceal bleeding (n=16)	1.72	1.20	3.13*	1.94	1.82*
Ascites (de novo) (n=9)	1.15	1.20	1.88	0	1.21
Encephalopathy (de novo) (n=4)	0.57	0.60	0.63	0.65	0
Liver transplantation (n=3)	0.57	0	0.63	0	0.61
Death (n=16)	1.10	1.81	1.88	1.30	3.64

*Including one death.

LONGWORTH ET AL 2003 (UK)

Reason for inclusion

Longworth et al (140) conducted an economic evaluation investigating the mid-term (27 months) cost-utility of liver transplantation programs in England and Wales. The cost-effectiveness of the liver transplant program in PBC was reported in isolation to other conditions included in the analysis and was included on this basis (i.e. separate reporting of data and results for PBC patients).

Analysis overview

The analysis estimated outcomes for two groups:

- Patients that underwent liver transplant for PBC
- Patients that did not undergo liver transplant for PBC

The same cohort of patients entered into each arm of the analysis (i.e. there were no differences in baseline patient characteristics in each arm). Outcomes for patients undergoing liver transplantation were estimated from observed data collected across six UK liver transplant centres. Both survival and quality of life data for these patients were collected over a maximum of a 27-month period. Since this aligned with the chosen time horizon of the analysis, no modelling was required in this arm. The study reported demographics for patients who were assessed for, or underwent, liver transplantation (see Table 44).

Table 44: Demographic details of patients assessed for liver transplantation and patients who underwent transplantation

	PBC	ALD	PSC
Patients assessed for transplantation	N = 122	N = 155	N = 70
Men, n (%)	14 (11.4)	114 (73.6)	48 (68.6)
Age, median	57	51	50
Age, IQR	51-62	46-57	38-56
Listed for a liver transplant, *n* (%)	94 (77.0)	100 (64.5)	53 (75.7)
Patients who underwent a liver transplantation	N = 81	N = 82	N = 45
Patients who underwent a liver transplantation, men, n (%)	8 (9.9)	67 (81.7)	31 (68.9)

	PBC	ALD	PSC
Patients who underwent a liver transplantation, age, median	56	50	49
Patients who underwent a liver transplantation, age, IQR	51–62	45–57	38–56
Emergency cases, *n* (%)	1 (1.2)	0	0
Retransplantation, *n* (%)	9 (11.1)	6 (7.3)	7 (15.6)
Survival to 2 years posttransplantation, *n* (%)	69 (85.2)	67 (81.7)	36 (80.0)
Bilirubin (µmol / L), median	97	47	116
Bilirubin (µmol / L), IQR	42–176	25–94	46–265
MELD score, N*	74	66	41
MELD score, median	8	10	10
MELD score, IQR	5-13	6-15	6-16

Abbreviations: ALD, alcoholic liver disease; MELD, model of end stage liver disease; PBC, primary biliary cholangitis/cirrhosis; PSC, primary sclerosing cholangitis; IQR, inter-quartile range, *MELD scores were not available for all patients.

Outcomes for patients not undergoing liver transplant were estimated from published prognostic models. Baseline data for patients that underwent liver transplant were entered into the prognostic model, to estimate the survival probability of these patients had they not undergone surgery.

Utility estimates for patients with PBC were taken from patients enrolled in the observational study using the EuroQol 5 Dimension questionnaire. Estimates were reported from point of listing on the transplant list through to 24 months post-transplantation. HRQoL was captured directly for all patients that underwent transplantation. In the scenario in which transplant was not administered, patient utility was set equal to the last pre-surgery utility value captured in the observed dataset.

Costs for patients undergoing liver transplant were collected prospectively in the observational dataset, these were valued using the mean unit cost for each resource observed over the six centres. Costs in the no transplant arm were estimated on the assumption that the final pre-transplant cost remained constant over the remainder of the analysis. The cost year was not specified.

Results

Transplantation was found to increase costs relative to no transplantation (£52,525 vs £37,301). This increase in costs was associated with an increase in QALYs equal to 0.54. This resulted in an incremental cost-effectiveness ratio (ICER) of £29,000 per QALY gained. This result was found to be robust under PSA, with the authors noting that cost-effectiveness would likely improve should the time horizon be extended.

PASHA ET AL 1999 (US)

Reason for inclusion

Pasha et al (78) conducted an economic evaluation comparing UDCA to a scenario in which UDCA was not administered. All PICOS criteria specified in this review were met and the analysis was included on this basis.

Analysis overview

The costs and health outcomes of the two scenarios were estimated over a period of four years. All outcomes were based on results observed in two clinical trials comparing UDCA to placebo, and no extrapolation of the outcomes was conducted. The economic analysis combined results from these two studies to estimate the following outcomes:

- Survival
- Adverse events (ascites, varices, variceal bleed, encephalopathy)
- Liver transplantation

Survival was estimated as the area under the curve from observed Kaplan-Meier data. Incidence of adverse events was estimated as the total number of events in each arm divided by the total years of follow-up.

Patient characteristics are presented below in Table 45.

Table 45: Patient characteristics in Mayo and Canadian UDCA-PBC trials

	Mayo study		Canadian study	
	UDCA	Placebo	UDCA	Placebo
N	89	91	111	111
Age (yr)	54 ± 9	52 ± 9	57.3	55.4
Gender (F/M)	81/8	79/12	101/10	105/6
Histological stage				
1 and 2	31	26	50	47
3 and 4	58	65	57	60
Mayo risk score	5.2 ± 1.1	5.2 ± 1.1	4.6 ± 1.3	4.4 ± 1.2

Abbreviations: PBC, primary biliary cholangitis/cirrhosis; UDCA, ursodeoxycholic acid.

Only direct costs were incorporated in the analysis. Whilst a societal perspective was adopted, it is unclear from the reporting of the study which estimates were included as those incurred by the payer and those incurred by broader society. The costs utilised were 1995 wholesale prices.

Results

Treatment with UDCA was found to dominate placebo, as it increased survival and reduced the incidence of all major events (liver transplant and adverse events). A total increase in survival equal to 0.18 years was estimated in the UDCA arm relative to the placebo arm, with costs reducing from $7,993 in the control arm to $6,621 in the scenario in which UDCA was used.

RATCLIFFE ET AL 2001 (UK)

Reason for inclusion

The analysis presented by Ratcliffe et al (139) evaluates the cost-effectiveness strategies for the prioritisation of liver transplants in the UK. Two possible causes for liver transplantation are included in the analysis: PBC and alcoholic liver disease (ALD). The

analysis evaluates a scenario in which PBC patients are prioritised for liver transplant. The results of the analysis evaluating this priority setting were deemed relevant to the current review and were included.

Analysis overview

Ratcliffe et al developed a discrete event simulation to evaluate the cost-effectiveness of various transplant prioritisation scenarios. A single patient is evaluated at a time (i.e. a patient-level simulation approach was applied), with a total of 1,000 patients per simulation.

Patients entered the analysis and were assessed for suitability for transplantation. If they were accepted for transplant, the patient entered onto the waiting list for liver transplant. Whilst on this waiting list patients were at risk of death and complications. If patients survived to receive a liver transplant, they entered into a post-transplant state where they were retained unless requiring further transplantation. Those who were not listed for transplant entered into a separate model that simulated the care pathway for management of their ongoing liver disease. The analysis simulated outcomes over a 10-year time horizon. Costs used were in 1999 GBP. Patient characteristics and demographics were not reported.

Results

Incremental results were presented for two groups:

- Those who underwent transplant
- Those who did not receive any transplant

Since the analysis of those that did not receive transplant incorporated outcomes for those that may not be eligible for transplantation, there may be differences between the populations for which outcomes are compared. The impact this had on outcomes is unclear.

Regardless, the authors concluded that the prioritisation of PBC patients for liver transplant results in patients gaining an additional 4.01 life years, whilst those that did not receive liver transplant experienced 1.03 life years. Costs were equal to £59,610 in the transplant arm and £24,358 in the non-transplant arm. This resulted in an ICER of £11,830.

Table 46: Summary list of published cost-effectiveness evaluations

Study, Year, Country	Summary of model	Intervention/ comparator	Patient population (average age in years)	Time horizon	QALYs (intervention, comparator)	Costs (currency) (intervention, comparator)	ICER (per QALY gained)
Boberg et al 2013 (79), Norway	Markov model comprising the following health states: • Alive (starting state) • Alive after transplant • Dead These health states were used to simulate disease progression from point of initiating therapy to death. Within each health state patients were at risk of ascites, variceal bleeding, and encephalopathy. Survival analysis was conducted to estimate mortality and liver transplant probability over time in the UDCA arm. Patients that underwent liver transplant were censored from mortality estimates. Treatment effect attributable to a scenario in which patients did not receive UDCA was incorporated through application of hazard ratios.	UDCA versus placebo	PBC population with an average age of 56	44 years (to 100 years of age)	Expressed as life years gained: UDCA - 11.97 years; Untreated population - 10.78 years	UDCA - €151,403 Untreated - €157,741	UDCA found to dominate a strategy of no treatment. This result was found to be robust when undertaking probabilistic sensitivity analysis, with 82% of iterations resulting in UDCA dominating a strategy of no UDCA.
Longworth et al 2003 (140), UK	Two interventions – transplant administered versus no transplant. Outcomes in the transplant group	Liver transplantation versus no liver transplantation	The cohort of 122 PBC patients consisted of patients who presented for a	27 months	Underwent transplant – 1.30 QALYs No transplant –	Underwent transplant – £52,525 No transplant -	Transplant was associated with an ICER equal to £28,716/ QALY

Study, Year, Country	Summary of model	Intervention/ comparator	Patient population (average age in years)	Time horizon	QALYs (intervention, comparator)	Costs (currency) (intervention, comparator)	ICER (per QALY gained)
	were estimated from observed data. Transplant outcomes data were taken from a planned data capture over a 27-month period, i.e. no modelling was conducted for this arm. This included the capture of disease outcomes, quality of life (QoL) outcomes, and cost outcomes. The baseline characteristics of the transplant patients were assumed for the non-transplanted population. These baseline characteristics were applied in a published prognostic model, which estimated outcomes for patients in the absence of transplantation. Patients in this group were assumed to have a constant level of utility.		liver transplant in the UK between December 1995 and December 1996. The PBC group median age was 57, with patients undergoing liver transplant having a median age of 56		0.76 QALYs	£37,301	compared to no transplant. Approximately 60% of iterations are found to result in ICERs of £30,000 or less when considering results of probabilistic sensitivity analysis.
Pasha et al 1999 (78), USA	A within-trial analysis was conducted, i.e. no extrapolation beyond study outcomes was undertaken in either study arm. Two trials evaluating UDCA vs placebo informed the model outcomes. The results of these trials were combined, resulting in a total of 200 patients in the UDCA arm and 202 patients in the placebo arm.	UDCA versus placebo	Patients had an average age of 55, and 91% of subjects were female	4 years.	Outcomes were expressed as the incidence of adverse events, survival free of liver transplantation, and average life years in	Annual cost of treatment including cost of adverse events: UDCA - $6,621 Placebo - $7,993	UDCA was found to dominate placebo.

Study, Year, Country	Summary of model	Intervention/ comparator	Patient population (average age in years)	Time horizon	QALYs (intervention, comparator)	Costs (currency) (intervention, comparator)	ICER (per QALY gained)
	Major outcomes in each of the UDCA and placebo arms were estimated, including: • Death • Liver transplantation • Ascites • Development of varices • Development of variceal bleeding • Encephalopathy				each arm. No absolute estimates of life years in each arm were reported.		
Ratcliffe et al 2001 (139), UK	A discrete event simulation was built to simulate patient outcomes with end-stage liver disease, caused by either ALD or PBC (the analysis was conducted in a mixed pool of ALD/PBC; however, costs under a scenario in which PBC patients were prioritised was reported). Patients entered the model and underwent assessment for liver transplant. If a patient was selected for transplant they entered onto the waiting list. Providing the patient survived the waiting period they underwent surgery. Following surgery, patients were tracked until death unless requiring re-transplantation, at which point	Prioritisation of transplant versus no prioritisation of transplant	Age was not stated by the authors. 46% of the cohort had PBC.	10 years.	Outcomes were expressed in terms of life years. Prioritising transplant in the PBC group led to 4.01 life years gained. Under this scenario, patients that did not receive transplant survived for 1.03 years.	Costs in the PBC prioritisation scenario were equal to £59,610 for those that received transplant and £24,358 for those that did not.	Prioritisation of patients in the PBC group led to an ICER of £11,830.

Study, Year, Country	Summary of model	Intervention/ comparator	Patient population (average age in years)	Time horizon	QALYs (intervention, comparator)	Costs (currency) (intervention, comparator)	ICER (per QALY gained)
	they were re-assessed for suitability and entered into the same transplant pathway. Patients deemed unsuitable for transplant entered into a separate patient pathway capturing outcomes from the management of their underlying liver disease.						

Abbreviations: ALD, alcoholic liver disease; ICER, incremental cost-effectiveness ratio; PBC, primary biliary cholangitis/cirrhosis; QALY(s), quality-adjusted life year(s); QoL, quality of life; UDCA, ursodeoxycholic acid.

5.1.3 *Quality assessment of identified studies*

Quality assessments for all included studies are provided in Appendix 7.

5.1.4 *Update of systematic review*

The systematic review was updated by a supplementary review, which was conducted in March 2016. Full details of the search strategy and inclusion/exclusion criteria are provided in Appendix 6.

5.1.4.1 Results of updated systematic review

After screening, one publication was included. The publication in question was a poster of a systematic review of cost-effectiveness of current therapies in PBC, which identified two previous studies on the cost-effectiveness of UDCA(141). The authors concluded that a PBC model informed by recent advances in disease understanding is required to accurately estimate the economic burden of PBC.

5.2 *De novo analysis*

5.2.1 *Patient population*

The population considered for this economic model is patients with PBC who have failed to show adequate control with UDCA, including both UDCA-intolerant patients and patients who have previously had an inadequate response to UDCA. This reflects the population specified in the NICE scope and the anticipated marketing authorisation. The two main patient subgroups from POISE are considered:

- UDCA-intolerant patients
- UDCA inadequate responders

5.2.2 *Model structure*

A Markov state-transition model was developed to describe the progression of PBC over a lifetime horizon. The model comprises 10 health states with a three-month cycle length. Figure 24 shows a diagram of the model structure. The model captures two components of the natural history of PBC: the liver disease component showing the progression of PBC based on ALP and bilirubin biomarkers; and the clinical endpoint component once patients start progressing to decompensated cirrhosis, hepatocellular carcinoma (HCC), or are added on the liver transplantation waiting list.

A Markov structure was used as it is consistent with other approaches for liver disease modelling, for example, for hepatitis C (142). The main events and changes in the health of a PBC patient, NHS costs, and the risk of other clinical events (e.g. progression to decompensated cirrhosis) are captured by the Markov health states that have been selected.

The model includes three PBC health states contingent on their level of ALP and bilirubin at baseline as defined below:

- Low risk of PBC disease progression: ALP level ≤ threshold of 200 units / L (i.e. 1.67 x ULN) and normal bilirubin (i.e. total bilirubin [TB] ≤ 20 µmol / L)
- Progressive PBC: ALP > threshold and normal bilirubin
- Progressive PBC leading to liver failure: Abnormal bilirubin (TB > 20 µmol / L and rising, or compensated cirrhosis)

The three health states were classified as “low risk” (ALP ≤ threshold and normal bilirubin), “progressive PBC” (ALP > threshold and normal bilirubin) and “Progressive PBC leading to liver failure” (abnormal bilirubin and rising; includes patients with compensated cirrhosis) to reflect the degree of risk of progression for patients in each category. Patients in the first health state have stable ALP and bilirubin and a low risk of progression (15, 34). In the “progressive PBC” state, patients are at moderate risk of developing complications. Finally, the “progressive PBC leading to liver failure” health state combines both compensated cirrhotic patients and those with abnormal bilirubin. The increased risk of progression of patients with abnormal bilirubin has been documented in the literature. In a recent poster by Harms et al, it was shown that patients would either undergo liver transplant or die from liver-related causes within 19 months once total bilirubin reached 1.6 x ULN (141). From that point onward, the level of total bilirubin was shown to rise exponentially. On the other hand, the histological status of PBC patients is rarely documented in clinical practice, since monitoring is based on biochemical values, and liver biopsy is only considered in specific cases (e.g. disease staging, enrolment in randomised clinical trials, or differential diagnosis) (34, 44, 143).

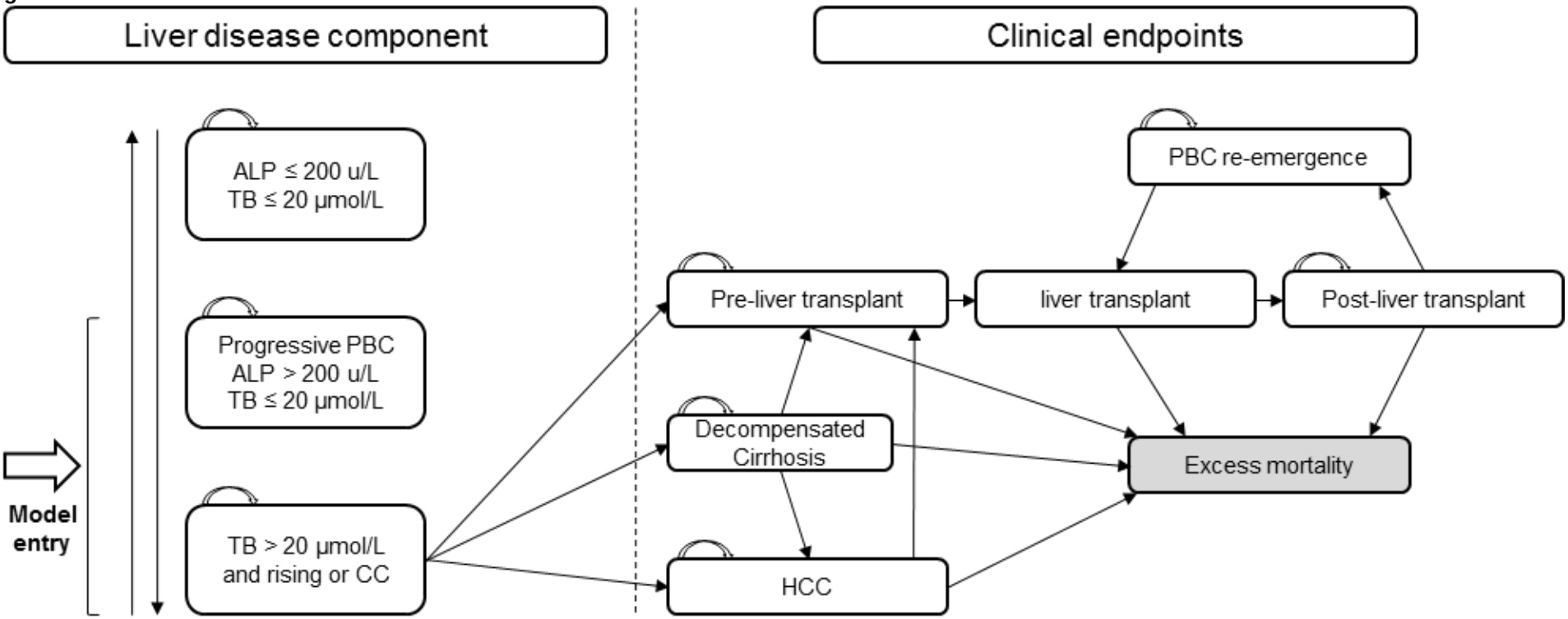
Given the lack of data on histological progression among PBC patients, patients with abnormal bilirubin and those with compensated cirrhosis were combined into one health state. This was to reflect the risk for PBC patients of developing compensated cirrhosis prior to decompensated cirrhosis, whilst also reflecting the risk of progression to hepatocellular carcinoma or to be added to the liver transplant waiting list based on their bilirubin level. Only patients in the moderate and high risk categories are deemed eligible to receive OCA, as these patients have had PBC for approximately 9 years with ALP ≥ 200 units / L despite treatment with UDCA, and have a moderate to high risk of progressing to more severe states of PBC.

In the OCA arm, patients can move through the different health states based on the biochemistry data available from POISE, while in the UDCA arm, patients inadequately controlled with UDCA can only progress from their initial pre-severe PBC health state to the severe PBC health state, as they have no effective treatment option to slow or prevent progression of PBC. Patients in the “high risk PBC” health state can progress to liver transplant, decompensated cirrhosis, or HCC, with their associated costs and health-related quality of life (HRQoL). It was assumed that patients in that health state would be in a worse condition than patients with compensated cirrhosis alone. In the decompensated health states, patients can either stay in that state, move to HCC, or progress to liver transplantation. Patients with HCC can either remain in that state, progress to liver transplantation, or die. Following liver transplantation, patients face a probability of dying or moving to the post-transplantation phase. The possibility of PBC recurring after transplant is included in the model, and after re-emergence, patients are at risk of needing a second liver transplantation.

Although not represented on the transition diagram, age- and gender-specific general population mortality rates are applied to each health state in the model. The risk of death is, however, highest in the last and most severe states (i.e. decompensated cirrhosis, HCC, pre-liver transplantation, liver transplant and post-liver transplantation). The excess mortality associated with these health states is depicted by the black coloured arrows in Figure 24. Excess mortality represents the disease-specific mortality associated with having decompensated cirrhosis, liver transplant or hepatocellular carcinoma. Dashed arrows represent health state transitions that can be investigated in sensitivity analysis.

A cohort of 1,000 patients entered the model to simulate the costs and outcomes associated with each of the treatment strategies that are considered. The option to apply a half-cycle correction is included, and is enabled by default.

Figure 24: Overview of model structure



Patients can die in each health state. The grey health state 'excess mortality' represents the disease-specific mortality associated with having decompensated cirrhosis, liver transplant or hepatocellular carcinoma.
TB, total bilirubin.

Abbreviations: ALP, alkaline phosphatase; CC, compensated cirrhosis; HCC, hepatocellular carcinoma; PBC, primary biliary cholangitis/cirrhosis; TB, total bilirubin.

5.2.2.1 Key features of the de novo analysis

Table 47: Features of the de novo analysis

Factor	Chosen values	Justification
Time horizon	Lifetime horizon, i.e. 50 years or a maximum age of 100 years	Consistent with the NICE reference case, which requires costs and effects to be measured over a sufficient time horizon to fully capture the relative costs and benefits. The average age of PBC patients included in the POISE trial is 56.2 years. A lifetime horizon (100 years old) was considered to be able to fully estimate the long-term impacts on costs and outcomes.
Were health effects measured in QALYs; if not, what was used?	Health effects were measured in QALYs	As per the NICE reference case. Life years, as well as the number of high-risk PBC, decompensated cirrhosis, HCC, liver transplants and deaths avoided, were also estimated.
Discount of 3.5% for utilities and costs	Selected by default	As per the NICE reference case.
Perspective (Payer – NHS)	Selected by default	As per the NICE reference case.

Abbreviations: NHS, National Health Service; PBC, primary biliary cholangitis/cirrhosis; QALYs, quality-adjusted life years.

5.2.3 *Intervention technology and comparators*

5.2.3.1 Intervention and comparators

The interventions considered in this submission depend on the population selected.

For UDCA-intolerant patients the following interventions are considered:

- OCA dose titration (as defined for the titration group in POISE)
- Placebo

For UDCA inadequate responders, the following interventions are considered:

- OCA dose titration (as defined for the titration group in POISE; 5 mg for the first six months of treatment, followed by 10 mg for the subsequent months) + UDCA
- UDCA monotherapy with placebo.

All UDCA doses are implemented in the model according to its UK marketing authorisation, which are also the same as those used in the POISE trial.

5.3 *Clinical parameters and variables*

5.3.1 *How are clinical data incorporated into the model?*

The POISE study (detailed in Sections 4.3, 4.4, 4.5, 4.6, 4.7, 4.8 and 4.12) is the principal source of evidence for the economic model, informing key clinical events and outcomes, including transitions to disease states, HRQoL, discontinuation, and adverse events.

The use of surrogate markers such as ALP and bilirubin levels is necessary to predict long-term clinical outcomes in patients with PBC (15, 34, 137, 141, 144). Biochemical response criteria are useful and generally accepted management tools used for stratification purposes and identifying patients in need of additional treatment; the FDA have accepted the validity of the use of ALP and bilirubin levels as surrogate markers for disease severity and progression (145). The COBALT phase III study on outcomes in PBC treated with OCA also included ALP and bilirubin levels as secondary outcomes. Numerous definitions of optimal biochemical response have been proposed in the literature (see Table 48). Although many of the response criteria are based on an assessment at 1 year or even 2 years of initial therapy, a recent study showed that assessment as early as 6 months can be used to identify high risk patients with poor prognosis and who are therefore in need of additional therapy (146).

Table 48: Biochemical criteria of optimal response to UDCA in PBC

Criteria	Evaluation Time	Biochemical response	Responder survival
Mayo (125)	6 months	ALP <2x ULN	Not reported
Barcelona (16)	1 year	ALP ≤1x ULN or decrease in ALP >40%	No significant difference between UDCA responders and the standardised general population (p=0.15)
Paris I (11)	1 year	ALP <3x ULN or AST <2x ULN or bilirubin ≤1 mg/dL	No significant difference between UDCA responders and the standardised general population (p=0.8)
Paris II (12)	1 year	ALP ≤1.5x ULN or AST ≤1.5x ULN or bilirubin ≤1 mg/dL	In early PBC, defined either histologically or biochemically, survival without adverse event† was significantly longer in responders compared with non-responders (p<0.001 and <0.05 respectively). Patients with histologically defined early disease who respond to treatment with UDCA experienced no progression of their disease over an average of 7 years.
Rotterdam (13)	1 year	Normal bilirubin (values ≤ULN) and/or normal albumin (values ≥LLN	Survival is significantly longer in UDCA responders vs non responders.
Toronto II (15, 18)	2 years	ALP ≤1.67x ULN	Not reported. Those who did not respond at 2 years had a five-fold greater risk of histological progression compared with responders (0.03).
Ehime (147, 148)	6 months	≥70% decrease of GGT	Transplant-free survival was significantly longer in UDCA responders compared with non-responders (p=0.01).
Mayo II (17)	1 year	ALP ≤1.67 and bilirubin ≤1mg/dL	Not reported

Abbreviations: ALP, alkaline phosphatase; AST, aspartate aminotransferase; GGT, gamma-glutamyl transferase; LLN, lower limit of normal; PBC, primary biliary cholangitis/cirrhosis; UDCA, ursodeoxycholic acid; ULN, upper limit of normal.

†Adverse event defined as liver-related death, liver transplantation or referral to transplant unit, complication of cirrhosis, or histological evidence of cirrhosis development.

5.3.1.1 Overview of analyses

Patient-level data analyses of POISE were used to inform:

- Baseline characteristics
- Base distribution of patients according to ALP or bilirubin state
- Adverse event rates
- Transition probabilities (for biochemistry states)

These analyses were performed and reported in accordance with NICE Decision Support Unit (DSU) methodologies where relevant (149) which are reported in the relevant sections in this submission. All analyses were based on the ITT population of POISE (216 patients).

5.3.1.2 Mortality

The base case analysis models all-cause mortality data from POISE (no deaths were reported in the POISE trial).

5.3.2 *Transition probabilities*

5.3.2.1 Biochemistry transition matrices (OCA)

Patient-level data from POISE was used to follow the progression of patients across the biochemical health states, i.e. either based on an ALP threshold of 200 units / L, and Table 49 presents the biochemistry data used to populate the transition matrices over the first year for the two OCA-based regimens. Given the low number of patients who received monotherapy, the same transition matrices were used for the OCA titration regimen with or without UDCA. This is a rather conservative method as in clinical practice, OCA patients would be expected to have lower transition probabilities to the more severe disease states.

Table 49: Biochemical transitions during the first year – OCA titration (POISE trial)

	0-3 months					3-6 months				6-9 months				9-12 months			
From/To:	**1**	**2**	**3**	**Disc.**	**N**	**1**	**2**	**3**	**N**	**1**	**2**	**3**	**N**	**1**	**2**	**3**	**N**
ALP threshold 200 units / L																	
1	[redacted]																
2	[redacted]																
3	[redacted]																
Probabilities																	
1	[redacted]				**1.0**	[redacted]			**1.0**	[redacted]			**1.0**	[redacted]			**1.0**
2	[redacted]				**1.0**	[redacted]			**1.0**	[redacted]			**1.0**	[redacted]			**1.0**
3	[redacted]				**1.0**	[redacted]			**1.0**	[redacted]			**1.0**	[redacted]			**1.0**

Health state 1: ALP ≤ 200 units / L and NB; 2: ALP > 200 units / L and NB; 3: (ALP > 200 units / L) and AB; Disc.: Discontinuation.
Source: Ad-hoc table ALP and BILI shift (Data on file). Analyses for other threshold are presented in Appendix 12.

5.3.2.2 PBC-specific component (literature)

UDCA inadequate responders

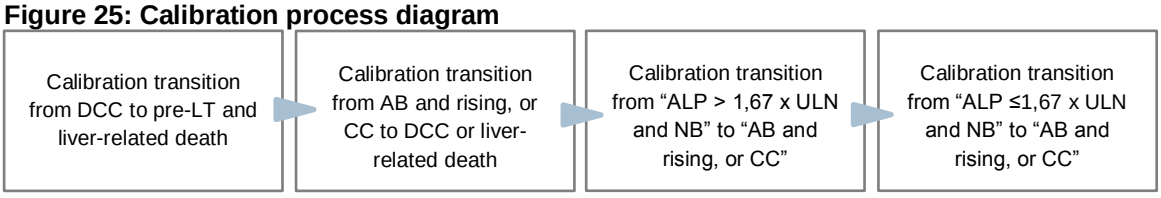
Whilst OCA-based regimens rely on POISE patient-level data during the first year, the transition probabilities used to reflect progression whilst on UDCA alone, or no treatment, are based on data from various literature sources identified in the previously discussed SLRs and hand searching of data. These transition probabilities are specific to PBC where available. Where no data were available in the literature, transition probabilities were calibrated so that the risks of liver transplantation and/or death reflected those observed in POISE.

At EASL 2016, Harms et al presented a poster showing the change in risk of live transplant and / or death in POISE patients treated with UDCA and OCA. The authors demonstrated that after one year the risk of transplant and / or death was greater in patients treated with UDCA versus patients treated with OCA. Data published from the global and UK PBC groups and an ad-hoc analysis carried out based on POISE patient-level data using the GLOBE and UK risk score were used to calibrate six transition probabilities, i.e.:

- Transition from “ALP ≤ 200 units / Lx ULN and bilirubin ≤ 20 µmol / L” to “bilirubin > 20 µmol / L and rising, or compensated cirrhosis”
- Transition from “ALP > 200 units / L x ULN and bilirubin ≤ 20 µmol / L” to “abnormal bilirubin and rising, or compensated cirrhosis”
- Transition from “abnormal bilirubin and rising, or compensated cirrhosis” to either “decompensated cirrhosis” or “Pre-LT” (liver transplant waiting list)
- Transition from “decompensated cirrhosis” to “Pre-LT” or liver-related death

The calibration process followed the process shown in Figure 25 below. A more detailed explanation of the calibration process is provided in Appendix 10.

Figure 25: Calibration process diagram



Abbreviations: AB, abnormal bilirubin (total bilirubin >1.0 x ULN); ALP, alkaline phosphatase; CC, compensated cirrhosis; DCC decompensated cirrhosis; LT, liver transplantation; NB, normal bilirubin (total bilirubin ≤1.0 x ULN); ULN, upper limit of normal.

Table 50: PBC component: Transition probabilities to "abnormal bilirubin and rising, or compensated cirrhosis" and decompensated cirrhosis

From:	To:	Probability	Time period (years)	Quarterly rate	Quarterly *probability
ALP threshold 200 units / L					
ALP ≤ 200 units / L and NB	AB and rising, or CC	0.05	1.0	0.01	0.01
ALP > 200 units /	AB and rising, or	0.12	1.0	0.03	0.03

From:	To:	Probability	Time period (years)	Quarterly rate	Quarterly *probability
L and NB	CC				
To decompensated cirrhosis (DCC)					
AB and rising, or CC	DCC	0.10	1.0	0.03	0.03

Abbreviations: AB, abnormal bilirubin; CC, compensated cirrhosis; DCC, decompensated cirrhosis; NB, normal bilirubin. * Obtained by converting quarterly rates to quarterly probabilities, using the formula p = 1–exp(–rt), where p = probability, r = rate, and t = time.

UDCA-intolerant patients

UDCA-intolerant patients can either receive OCA monotherapy (as a titrated dose) or no treatment. Given the limited number of patients not on UDCA, there is a lack of data in the literature looking at the natural history of PBC without active treatment since the launch of UDCA. Thus, to reflect the progression of patients who did not receive any active treatment, assumptions were made based on Corpechot et al. (2000), who assessed the effect of UDCA therapy on liver fibrosis progression compared with no treatment in PBC patients(150). The study was based on a French randomised, double-blind, placebo-controlled trial in which 146 patients were randomised to receive either 13-15 mg/kg/day of UDCA or a placebo for 2 years (150). After 2 years, placebo patients crossed over to UDCA for a further 2 years, whilst patients already on UDCA remained on UDCA. Paired liver biopsies were available for 103 patients (53 UDCA and 50 placebo) during the two-year blinded period.

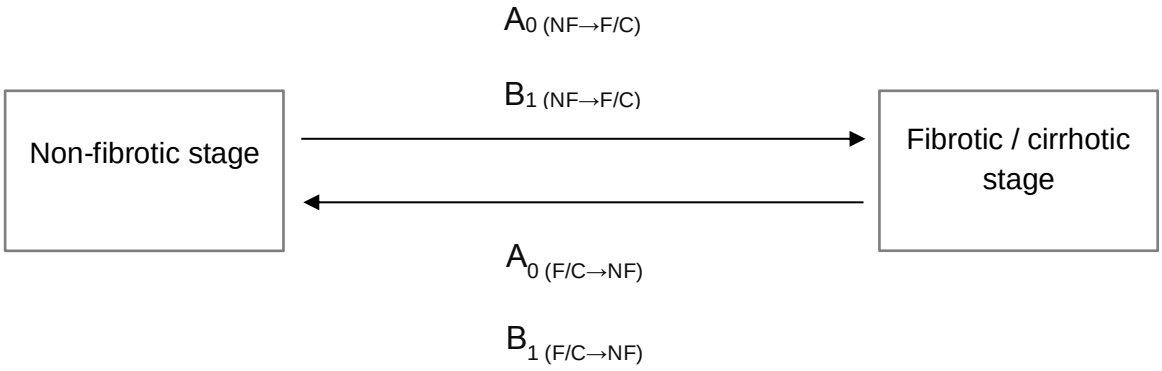
Corpechot et al. (2000) modelled the progression from two histologic stages (Figure 26):

- Non-fibrotic stage, defined by the presence of portal and periportal lesions without extensive fibrosis
- Fibrotic/cirrhotic stage, defined by the presence of numerous septa, bridging fibrosis or nodular cirrhotic formation.

The description provided by Corpechot et al for fibrotic and cirrhotic stages would contain compensated cirrhotic patients according to the METAVIR criteria (METAVIR stages F3 / F4 (151).

Progression between states was informed by the paired biopsy data. The authors of this study assumed that all patients in a given state and at a given time would have the same prognosis. Two transition rates were estimated to inform the model, i.e. the baseline transition rate α_0 and the regression coefficient for treatment β_t. The relationship between both parameters were expressed as follows: $\alpha_u = \alpha_0 * \exp(\beta_t \times U)$ where U=0 for placebo and 1 for UDCA.

Figure 26: Two-stage Markov model (150)



Based on the simplified model parameters (detailed in Table 51), it was possible to estimate the annual probability of progressing over time in the placebo group. Probabilities for patients to transition to the fibrotic/cirrhotic stage were calibrated to estimate the number of cirrhotic patients over time without the probability of moving backwards by minimising the root mean square error (RMSE), leading to a quarterly probability of progression to severe PBC of 0.079. The same transition was assumed between “abnormal bilirubin or compensated cirrhosis” and “decompensated cirrhosis” as for UDCA non-responders.

Whilst these histologic stages do not necessarily directly reflect compensated cirrhosis and decompensated cirrhosis, they essentially represent two different fibrotic or cirrhotic stages. This is the only publication which reflects the natural history of PBC without treatment, and allows estimation of the rate of disease progression for untreated patients.

Table 51: Simplified model - progression parameters (150)

Parameter	From/to	Estimate	SE
α0	NF to F/C	0.34	0.09
βt	NF to F/C	-1.55	0.49
α0	F/C to NF	0.03	0.01
βt	F/C to NF	0.00	0

Table 52: PBC components (UDCA intolerant): Transition probabilities to severe PBC and decompensated cirrhosis

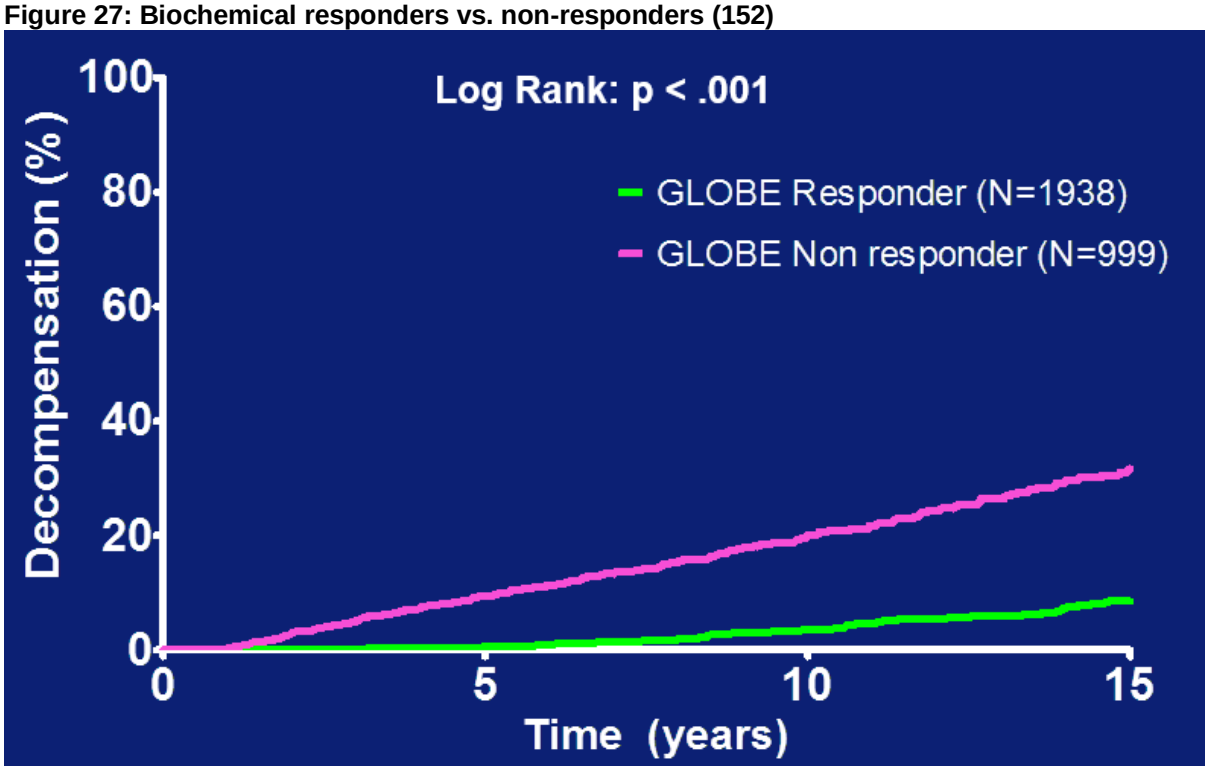
From:	To:	Probability	Time period (year)	Quarterly rate	Quarterly probability*
ALP threshold 200 units / L					
ALP ≤ 200 units / L and bilirubin ≤ 20 µmol / L	AB and rising, or CC	0.25	1.0	0.07	0.07
ALP > 200 units / L and bilirubin ≤ 20 µmol / L	AB and rising, or CC	0.25	1.0	0.07	0.07
To decompensated cirrhosis (DCC)					
Bilirubin > 20 µmol / L and rising, or CC	DCC	0.10	1.0	0.03	0.03

Abbreviations: AB, abnormal bilirubin; CC, compensated cirrhosis; DCC, decompensated cirrhosis. * Obtained by converting quarterly rates to quarterly probabilities, using the formula p = 1–exp(–rt), where p = probability, r = rate, and t = time.

OCA patients

For OCA, results from the long-term safety extension study showed sustained response in patients remaining on OCA for up to five years post initiation of treatment (115). For this reason, we have not assumed any additional progression to move from “ALP ≤ 200 units / L and normal bilirubin” or “ALP > 200 units / L and normal bilirubin” to “abnormal bilirubin and rising, or compensated cirrhosis” in the OCA arms after the first year. This assumption was based on the decompensation rate observed in UDCA responders presented by Harms et al in the PBC subgroup (152). The objectives of the study were to estimate the time to a decompensating cirrhotic event (i.e. the presentation of ascites, variceal bleeding or hepatic encephalopathy), as well as to identify factors predicting the occurrence of decompensating events and related outcomes (i.e. liver transplant-free survival). There were 2,938 of the 3,030 UDCA-treated patients included. The authors investigated the decompensation rate over 15 years for patients who had successfully responded to UDCA and those who had not responded, using the GLOBE score. The authors showed that the risk of developing decompensated cirrhosis was much greater in UDCA non-responders (15-year risk of ~32%) than in UDCA responders (15-year risk of ~9%) (Figure 27). It was assumed that OCA patients would follow a similar general trend to the UDCA patients in terms of their risk of developing DCC in the event of non-response. This is a conservative approach, as recent data shows that in patients with raised bilirubin the progression to advanced PBC is much more rapid, and with a greater quarterly probability than is shown in the base case scenario (Intercept data on file).

Figure 27: Biochemical responders vs. non-responders (152)



GLOBE-score: 0.044378 × age at start of UDCA therapy + 0.939820 × LN(bilirubin*ULN at 1 year follow-up) + 0.335648 × LN(alkaline phosphatase *ULN at 1 year follow-up) − 2.266708 × albumin*LLN at 1 year follow-up − 0.002581 × platelet count per 109/L at 1 year follow-up + 1.216865.

Table 53: PBC component: Transition probabilities to severe PBC (OCA)

From:	To:	Decompensation probability	Time (years)	Quarterly rate	Quarterly probability*
"ALP ≤ 200 units / L and NB" or "ALP > 200 units / L and NB"	AB and rising, or CC	0.25	1	0.07	6.80%

Abbreviations: AB, abnormal bilirubin; CC, compensated cirrhosis; ALP, alkaline phosphatase; ULN, upper limit of normal; NB, normal bilirubin. *Obtained by converting 15-year probability into quarterly rates, using the formula r = -LN(1-p)/t and quarterly rates to quarterly probabilities, using the formula p = 1-exp(-rt), where p = probability, r = rate, and t = time.

5.3.2.3 Liver disease-specific component

Transition probabilities from "abnormal bilirubin and rising, or compensated cirrhosis" to the more severe liver-specific health states were derived from the literature as shown in Table 54.

Table 54: Liver disease component: transition probabilities

From:	To:	Probability	Time (years)	Quarterly rate	Quarterly prob.	Source
AB and rising, or CC	HCC	0.01	1	0.00	0.35%	Assumed similar transition as between DC and HCC
	Pre-LT	0.04	1	0.01	1.02%	Calibrated (see Appendix 10)
DCC	Pre-LT	0.06	1	0.02	1.53%	Calibrated (see Appendix

						10)
	Death	0.17	1	0.05	3.98%	Calibrated (see Appendix 10)
	HCC	0.01	1	0.00	0.35%	Trivedi et al 2006 (153)
HCC	Pre-LT	0.04	1	0.01	1.02%	Wright et al 2006 (154), used by: STA330 (142)
	Death	0.43	1	0.14	13.11%	Wright et al 2006 (154), used by: STA330 (142)
Pre-LT	LT	0.35	1	0.11	10.21%	Kim et al 2016 (155)
	Death	0.09	1	0.02	2.33%	Kim et al 2016 (155)
LT	Death	0.21	1	0.06	5.72%	Wright et al 2006 (154), used by: STA330, Table 68 (142)
Post-LT	PBC recurrence	0.23	10	0.01	0.64%	Lindor, 2009 (34)
	Death	0.06	1	0.02	1.46%	Wright et al 2006 (154), used by: STA330, Table 68(142)
	LT	0.01	13	0.00	0.01%	Neuberger, 2003 (156)
PBC recurrence	LT	0.01	13	0.00	0.01%	Assumption

Abbreviations: AB, abnormal bilirubin; CC, compensated cirrhosis; DC, decompensated cirrhosis; HCC, hepatocellular carcinoma; LT, liver transplant; PBC, primary biliary cholangitis/cirrhosis.
*Obtained by converting 15-year probability into quarterly rates, using the formula r = –LN(1–p)/t and quarterly rates to quarterly probabilities, using the formula p = 1–exp(–rt), where p = probability, r = rate, and t = time.

Based on the transition probabilities presented in this section, the model predicts the mean times to events shown in Table 55.

Table 55: Mean time to event for liver-related death

	UDCA intolerant patients		UDCA inadequate responders	
	No treatment (Placebo)	**OCA titration**	**UDCA + Placebo**	**OCA + UDCA titration**
Annual rate of liver-related death	0.047	0.004	0.039	0.004
Mean liver-related death free survival (years)*	19.365	44.605	21.637	44.893
Years lost to liver-related death†	30.635	5.395	28.363	5.107
Median time to liver-related death (years)‡	14.750	N/A	17.500	N/A

*Area under the Kaplan Meier curve. †Area above the Kaplan Meier curve. ‡Using the total population as done with transplant free survival.

5.3.3 *Clinical expert assessment of applicability of clinical parameters*

UK expert opinion was sought via a series of interviews, to provide validation of proposed methods and statistical models, and to elicit estimates of utility values for PBC-specific health states. An overview of the information provided to experts is given in Appendix 11. Each interview was conducted by at least two health economists, with

audio recordings used to ensure all relevant details were captured. These interviews were supplemented by follow-up emails to clarify any further points that were raised.

Name in document	Date held	External Attendees†	Topics of discussion
OCA for PBC interview 1	17/6/16	1 x UK PBC specialist physician, 1x Health Economist	Model methods, health state utilities
OCA for PBC interview 2	14/7/16	1 x UK PBC specialist physician	Model methods, health state utilities, health state costs
OCA for PBC interview 2	25/7/16	1 x UK PBC specialist physician	Model methods, health state utilities, health state costs

†Attendees who were neither direct employees of Intercept nor direct employees of an Intercept-commissioned vendor.

5.4 *Measurement and valuation of health effects*

5.4.1 *Health-related quality-of-life data from clinical trials*

Health-related quality-of-life data were not gathered in the POISE trial, so the literature was searched for health state utilities.

5.4.2 *Health-related quality-of-life studies*

5.4.2.1 Overview and review question

A systematic review was conducted to identify HRQoL studies from the published literature relevant to the decision problem. In particular, EQ-5D health state utility values (in line with the NICE preferred method) relating to HRQoL in PBC-specific disease states were sought. The following specific review question was explored:

- "What evidence exists reporting the quality of life in patients with PBC?"

5.4.2.2 Search methodology

Studies of interest were identified by simultaneously searching the electronic databases shown in Table 56, with no restrictions on date or language of publication. Searches were conducted in September 2014 using the following interfaces:

- EMBASE (which also covers Medline® and Medline® In-Process)
- The Cochrane Library (which covers the Cochrane Database of Systematic Reviews, Database of Abstracts of Reviews of Effects, Health Technology Assessment, NHS Economic Evaluation Database)
- EBSCO host (which covers EconLit, Health Economic Evaluations Database).

Full details of the search are provided in Appendix 8.

Table 56: Databases searched and interfaces used in the quality of life systematic review

Database	Interface
Embase 1966 to 2014	Embase
Medline 1966 to 2014	Embase

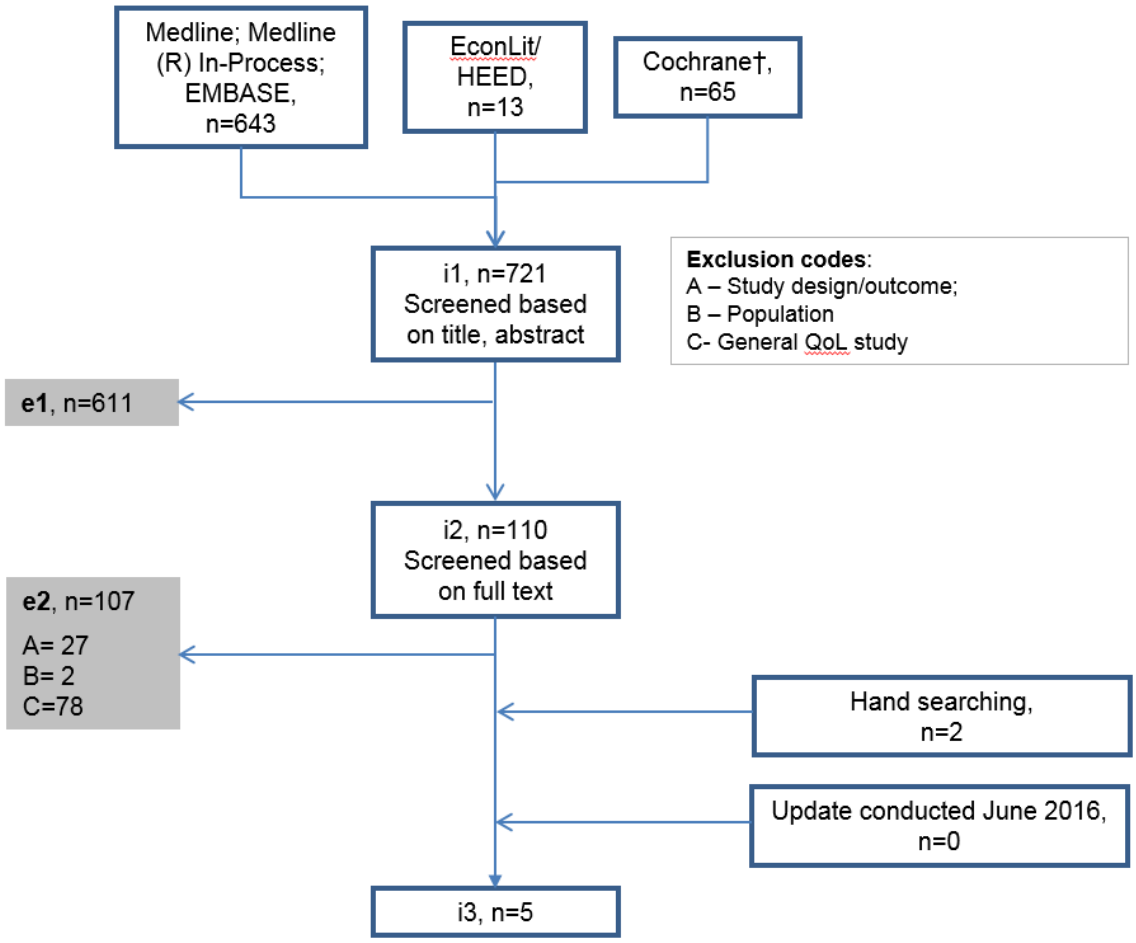
Medline® In-Process 1966 to 2014	Embase
Cochrane Database of Systematic Reviews 1996 to 2014	The Cochrane Library
Database of Abstracts of Reviews of Effects 1994 to 2014	The Cochrane Library
Health Technology Assessment 1989 to 2014	The Cochrane Library
NHS Economic Evaluation Database 1968 to 2014	The Cochrane Library
EconLIT with Full Text 1961 to 2014	EBSCO host
Health Economic Evaluations Database 1990 to 2014	EBSCO host

The searches included terms for free text and keywords (Medical Subject Heading (MeSH) and Emtree terms) through the use of Boolean combination techniques. Searches were not restricted by study intervention or comparator, to ensure studies reporting HRQoL in this population were identified. The Cochrane Library and EBSCO host interfaces were searched using terms for the population only, in order to broaden the results.

A grey literature search was performed to include additional studies that had not been identified by the search strategy. References included for the review had to meet the pre-specified inclusion/exclusion criteria shown as a PICOS table in Appendix 8.

The search identified 721 titles/abstracts. After screening, 611 were excluded, leaving 110 full texts. After the second round of screening, 107 studies were excluded, and relevant data were extracted from the remaining publications. The PRISMA diagram for the systematic review, including the March 2016 systematic review update, is shown in Figure 28.

Figure 28: PRISMA diagram illustrating the flow of the HRQoL systematic review



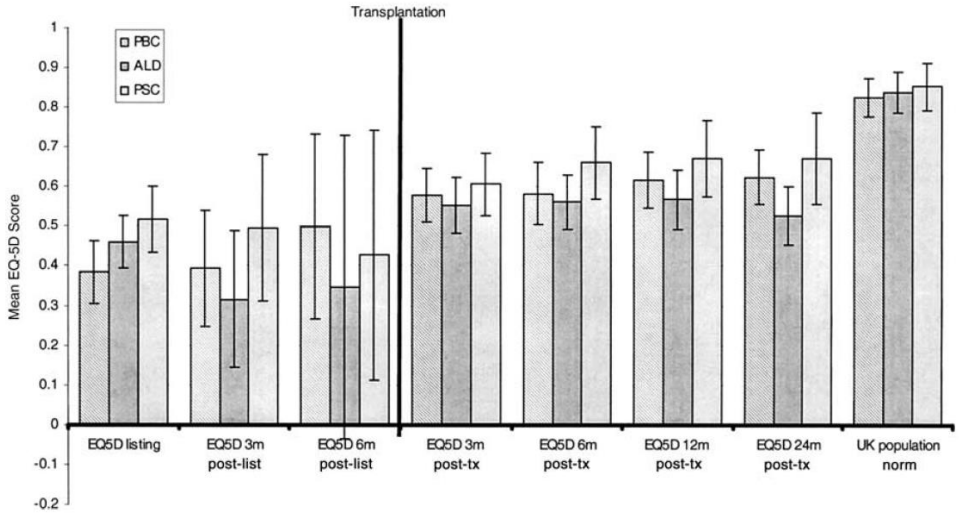
Five studies were found to report utility values (6, 140, 154, 157). Aberg et al evaluated the quality of life of Finnish adult patients having undergone liver transplantation between 1982 and 2007 using the 15D questionnaire, including 72 PBC patients.(6) This questionnaire is composed of 15 dimensions (mobility, vision, hearing, breathing, sleeping, eating, excretion, usual activities, mental function, discomfort, symptoms, depression, distress, vitality, and sexual activity) each assessed over five levels. PBC patients were mainly female (89%) and were an average of 52 years old at the time of transplantation and 63 years old at the time of the study. The mean time between liver disease diagnosis and transplantation was 9 years. After adjustment for age at the time of the study (covariate evaluated at age 55), patients with PBC were shown to have a similar 15D score (0.882) to other diseases and be statistically significantly lower than the general population (0.914).

Bondini et al carried out a study that aimed to compare the impact of chronic hepatitis B (CHB) on quality of life, and compared the results to patients suffering from chronic hepatitis C (CHC), PBC and healthy controls (157). The authors used three health-related quality of life questionnaires, the chronic liver disease questionnaire (CLDQ), SF-36 and the Health Utility Index (HUI Mark-2). Only 18 PBC patients were included in the study. PBC patients were shown to have a similar overall summary score to CHC patients (4.4 for CLDQ overall), and SF-36 (about 45 for MCS and 41 for PCS respectively). On the other hand, the health utility scores as estimated by HUI Mark-2

differed between CHC and PBC patients with a utility value more similar to CHB patients (0.81 for PBC, 0.55 for CHC and 0.78 for CHB patients, respectively). The authors stated that the presence of cirrhosis explained 24% of the variance in terms of the HUI Mark-2 values reported. One of the major limitations of this study is the very small sample size of the PBC group, preventing an accurate assessment of the quality of life in this population. Only HUI Mark-2 was used, although other scoring methods could have been used such as EQ-5D or converting SF-36 into SF-6D.

Longworth et al carried out a study assessing the cost-effectiveness of the liver transplantation program of England and Wales for three disease groups, including PBC (140). The quality of life of patients before and after transplantation were based on the EQ-5D questionnaire that was administered at time of listing and then every 3 months until transplantation, and then at 3, 6, 12 and 24 months after transplantation. Values and extrapolated values are shown in Figure 29 and Table 57, respectively.

Figure 29: Mean EQ-5D scores of transplantation patients before and after transplantation, including UK population norm EQ-5D scores(140)



Error bars depicts 95% bootstrap confidence intervals. Values of zero are included for patients who died post-transplantation

Table 57: Utility values extrapolated from Longworth et al (2003)

Time	Mean	95% lower CI	95% upper CI
At listing	0.384	0.305	0.463
3-month after listing	0.394	0.248	0.539
6-month after listing	0.500	0.266	0.731
3-month post-transplant	0.581	0.512	0.646
6-month post-transplant	0.583	0.504	0.661
12-month post-transplant	0.619	0.548	0.687
24-month post-transplant	0.623	0.546	0.693

Abbreviations: CI, confidence interval.

Wright et al carried out a study assessing the health benefits of antiviral therapy for mild chronic hepatitis C, including an economic evaluation (154). Some of these health states are similar to those experienced in PBC patients, including cirrhosis, HCC, post-liver transplantation and decompensated cirrhosis. A summary of the utility values observed are presented in

Table 58. All utility values are reported using the EQ-5D scale.

Table 58: Mean HRQoL for each disease stage as reported in Wright et al 2006 (154)

Health state	Utility value
Mild disease	0.77
Moderate disease	0.66
Cirrhosis	0.55
HCC	0.45
Treatment for mild disease	0.65
Treatment for moderate disease	0.55
Decompensated cirrhosis	0.45
Post-liver transplantation	0.67
SVR after mild disease	0.82
SVR after moderate disease	0.72

Abbreviations: HCC, HRQoL, health-related quality of life; hepatocellular carcinoma; SVR, sustained virologic response.

Younossi et al carried out a study which aimed to assess the utility and HRQoL of chronic liver disease patients, including chronic viral hepatitis and chronic cholestatic liver disease (CLD) (which includes both PBC and PSC patients) (64). The authors reported a utility value of 0.84 ± 0.15 for CLD patients.

5.4.2.3 Update of systematic review

An update of the systematic review was performed in March 2016. Full details of the search strategy and inclusion/exclusion criteria are provided in Appendix 8. No additional studies were identified as a result of the systematic literature review update.

5.4.2.4 Intercept clinical trial

An earlier phase II double-blind, placebo-controlled study (747-202) investigated the efficacy and safety of OCA 10, 25 and 50 mg doses compared with placebo in combination with UDCA, as described in Section 4.7.2.2 (158). The generic health-related quality of life questionnaire SF-36 was included as part of the information collected during the trial. The questionnaire was administered at baseline and at Day 85 or at the early termination (ET) visit. The SF-36 is a survey measuring eight domains (physical functioning, role limitations due to physical health, bodily pain, general health perceptions, vitality, social functioning, role limitations due to emotional problems, and mental health). It yields total scores for each of the domains as well as two component summary measures (physical and mental component summary [PCS and MCS]) (159).

Table 59: SF-36 dimensions scores at baseline (N=165) (747-202 CSR)

Dimensions	Mean	SD
Physical functioning	76.9	23.9
Role physical	71.7	29.5
Bodily pain	70.4	24.6
General health	57.7	23.2
Vitality	53.2	52.7
Social functioning	80.9	24.3
Role emotional	83.2	82.0
Mental health	75.8	74.5
PCS	**45.9**	**46.2**
MCS	**49.8**	**48.9**

Abbreviations: CSR, clinical study report; MCS, mental component summary; PCS, physical component summary; SD, standard deviations;

Table 60: Included HRQoL studies

Study, Country	Population	Study type	Metric	Result
Aberg et al 2012 (6)	72 PBC patients following liver transplant Sub-group of wider population	Observational	15D instrument	Utility value for entire PBC population following liver transplant: 0.882 Result found to be consistent regardless of aetiology
Bondini et al 2007 (157)	18 PBC patients	Observational	Chronic Liver Disease Questionnaire (CLDQ) SF-36 Health Utility Index (HUI Mark-2 and Mark-3)	18 patients in PBC group led to limited analysis in this population SF-36, CLDQ and HUI values reported HUI utility value reported as 0.81 (SD=0.1) in PBC population
Longworth et al 2003 (140)	122 PBC patients assessed for transplantation and followed up for a maximum of 24 months post-surgery	Observational	EQ-5D	Full results reported in Table 57
Wright et al 2006 (154)	204 chronic mild hepatitis C patients	Observational	EQ-5D	HRQoL results reported in Table 58.
Younossi et al 2001 (64)	120 patients with chronic liver disease, with 30% of patients suffering chronic cholestatic liver disease, including PBC and PSC patients	Observational	SF-36 CLDQ HUI	The study reported an HUI utility value of 0.84 ± 0.15 for patients with cholestatic liver disease.

Abbreviations: CLDQ, chronic liver disease questionnaire; EQ-5D, EuroQOL-5 dimensions, HRQoL, health-related quality of life; HUI, health utility index; PBC, primary biliary cholangitis/cirrhosis; PSC, primary sclerosing cholangitis; SF-36, short form-36 dimensions;

Each paper derived utility values using different measures. Aberg et al evaluated the utility of patients with PBC using the 15D survey, and estimated the utility of patients following liver transplant (6). Bondini et al reported utility derived using the Health Utilities Index; these estimates were reported for a general PBC population (157). Longworth et al reported utility values using the EQ-5D, for patients both pre- and post-liver transplant (Table 57) (140). Finally, Younossi et al reported utility values using the HUI and the CLDQ (64). The values reported in Longworth et al were substantially lower than those reported using the alternative instruments incorporated by Aberg et al , Bondini et al and Younossi et al. There was a substantial improvement in QoL following liver transplant in the population reported by Longworth et al, with utility rising from 0.384 at listing for transplant to 0.623 two years after treatment. None of the identified papers explicitly reported utility values in a population that were in the early stages of PBC, although values reported by Bondini et al and Younossi et al may incorporate such patients (6, 140, 157).

5.4.3 *Key differences*

As no HRQoL data were gathered in POISE, no comparison could be made to values derived from the literature search.

5.4.4 *Adverse reactions*

In the POISE trial, treatment-emergent adverse events (TEAEs) were defined as any adverse event (AE) that newly appeared, increased in frequency, or worsened in severity following initiation of investigational product; related TEAEs include all events reported having a possible, probable or definite relationship with the investigational product. Since pruritus and fatigue are two of the most common symptoms observed in PBC patients, their occurrence was expected. The most frequently reported related TEAEs in the POISE trial were included to account for the possible increase in any TEAE related to all active treatments (i.e. OCA or UDCA). In all arms, the most commonly reported TEAE was pruritus followed by fatigue and nausea. Since the number of patients not taking UDCA was limited (5 [6.8%] in the placebo, 5 [7.1%] in the OCA titration and 6 [8.2%] in the OCA 10 mg arms respectively), the incidence of TEAEs was assumed to be the same for the two indications. For UDCA-intolerant patients receiving no treatment, no adverse events were considered.

Adverse events are not explicitly modelled, and their impact is captured as part of the disease health state utility values. For the purposes of calculating adverse event cost, overall adverse event rates were used for fatigue, pruritus and nausea, and were applied to each comparator (93).

5.4.5 *Health-related quality-of-life data used in cost-effectiveness analysis*

In this analysis, a patient's HRQoL is assumed to be a function of:

- Their baseline characteristics (including their baseline ALP / bilirubin state)
- Risk of adverse events.

HRQoL is assumed to be constant in each of the biochemistry states, i.e. the utility for patients in a certain health state does not change over time. HRQoL worsens as patients

proceed from the biochemistry component of the model to the liver disease component of the model.

Utility values used in the cost-effectiveness analysis have been adjusted. The following health states in the liver disease component of the model had their corresponding utility values decreased by [redacted] to simulate the worsened HRQoL experienced by PBC patients in comparison to HBV/HCV patients, as an interpretation of KOL feedback by Intercept:

- Decompensated cirrhosis
- Pre-transplant: utility at listing
- Pre-transplant: 3 months after listing
- Pre-transplant: 6 months after listing
- Liver transplant: 3 months post-transplant
- Liver transplant: 6 months post-transplant
- Liver transplant: 12 months post-transplant
- Liver transplant: 24 months post-transplant.

Table 61: Summary of utility values for cost-effectiveness analysis

State	Utility value	Reference in submission (section and page number)	Justification
ALP: ≤ 200 u/L and Bili: Normal	0.84	Table 60, page 155	Cholestatic disease utility reported in Younossi 2001(64)
ALP: > 200 u/L and Bili: Normal	0.84	Table 60, page 155	Cholestatic disease utility reported in Younossi 2001(64)
Bili: Abnormal and rising, or CC	0.55	Table 58, page 153	Previously reported value for compensated cirrhosis (TA330)(142)
Decompensated cirrhosis	[redacted]	Table 58, page 153	Previously reported value for decompensated cirrhosis (TA330); decrement of [redacted] applied (142)
Hepatocellular carcinoma	0.45	Table 58, page 153	Previously reported value for HCC (TA330); KOL opinion (142)
Pre-transplant: utility at listing	[redacted]	Table 58, page 153	Previously reported value for pre-transplant (TA330); decrement of [redacted] applied (142)
Pre-transplant: 3 months after listing	[redacted]	Table 58, page 153	Previously reported value for pre-transplant (TA330); decrement of [redacted] applied (142)
Pre-transplant: 6 months after listing	[redacted]	Table 58, page 153	Previously reported value for pre-transplant (TA330); decrement of [redacted] applied (142)
Liver transplant: 3 months post-transplant	[redacted]	Table 58, page 153	Previously reported value for post liver transplant (TA330); decrement of [redacted] applied (142)

State	Utility value	Reference in submission (section and page number)	Justification
Liver transplant: 6 months post-transplant	[redacted]	Table 58, page 153	Previously reported value for post liver transplant (TA330); decrement of [redacted] applied (142)
Liver transplant: 12 months post-transplant	[redacted]	Table 58, page 153	Previously reported value for post liver transplant (TA330); decrement of [redacted] applied (142)
Liver transplant: 24 months post-transplant	[redacted]	Table 58, page 153	Previously reported value for post liver transplant (TA330); decrement of [redacted] applied (142)
Re-emergence of PBC	[redacted]	Table 58, page 153	Assumed equivalent to liver transplant 24-months post-transplant, without utility decrement provided according to KOL feedback. (TA330) (142)

Abbreviations: ALP, alkaline phosphatase; Bili, bilirubin; CC, compensated cirrhosis; PBC, primary biliary cholangitis/cirrhosis. [redacted].

5.4.5.1 Clinical expert assessment of applicability of health state utility values

Expert opinion was sought to determine whether the use of utility values specific to HCV/HBV was appropriate within the context of PBC. All experts agreed that it is inappropriate to use HCV/HBV-specific utility values, since PBC patients are likely to have worse utility values despite being in the same health state, e.g. HRQoL for PBC patients who are awaiting liver transplant are likely to be worse than for hepatitis patients awaiting liver transplant. An exception is made in the case of hepatocellular carcinoma, where clinical experts agreed that utility values are broadly similar between HCV/HBV patients and PBC patients, as HRQoL in HCC is mainly driven by the treatment of HCC, and the underlying cause of the disease (e.g. PBC or HCV) is no longer the main factor to explain the quality of life experienced by patients in this health state. In order to address this, all utility values for HCV/HBV were decreased by [redacted] to approximate the worse outcomes for PBC patients. The details of this process have been described previously in Section 5.3.3.

5.5 *Cost and healthcare resource use identification, measurement and valuation*

5.5.1 *Resource identification, measurement and valuation studies*

5.5.1.1 Overview and review question

A systematic review was conducted to identify all relevant PBC unit cost and resource use studies from the published literature relevant to the decision problem. The following specific review question was explored:

- "What are the costs and resource use associated with the management of PBC?"

5.5.1.2 Search methodology

Studies of interest were identified by simultaneously searching the electronic databases shown in Table 62, with no restrictions on date or language of publication. Searches were conducted in September 2014 using the following interfaces:

- EMBASE (which also covers Medline® and Medline® In-Process)
- The Cochrane Library (which covers the Cochrane Database of Systematic Reviews, Database of Abstracts of Reviews of Effects, Health Technology Assessment, NHS Economic Evaluation Database)
- EBSCO host (which covers EconLit, Health Economic Evaluations Database).

Full details of the search are provided in Appendix 9.

Table 62: Databases searched and interfaces used in the quality of life systematic review

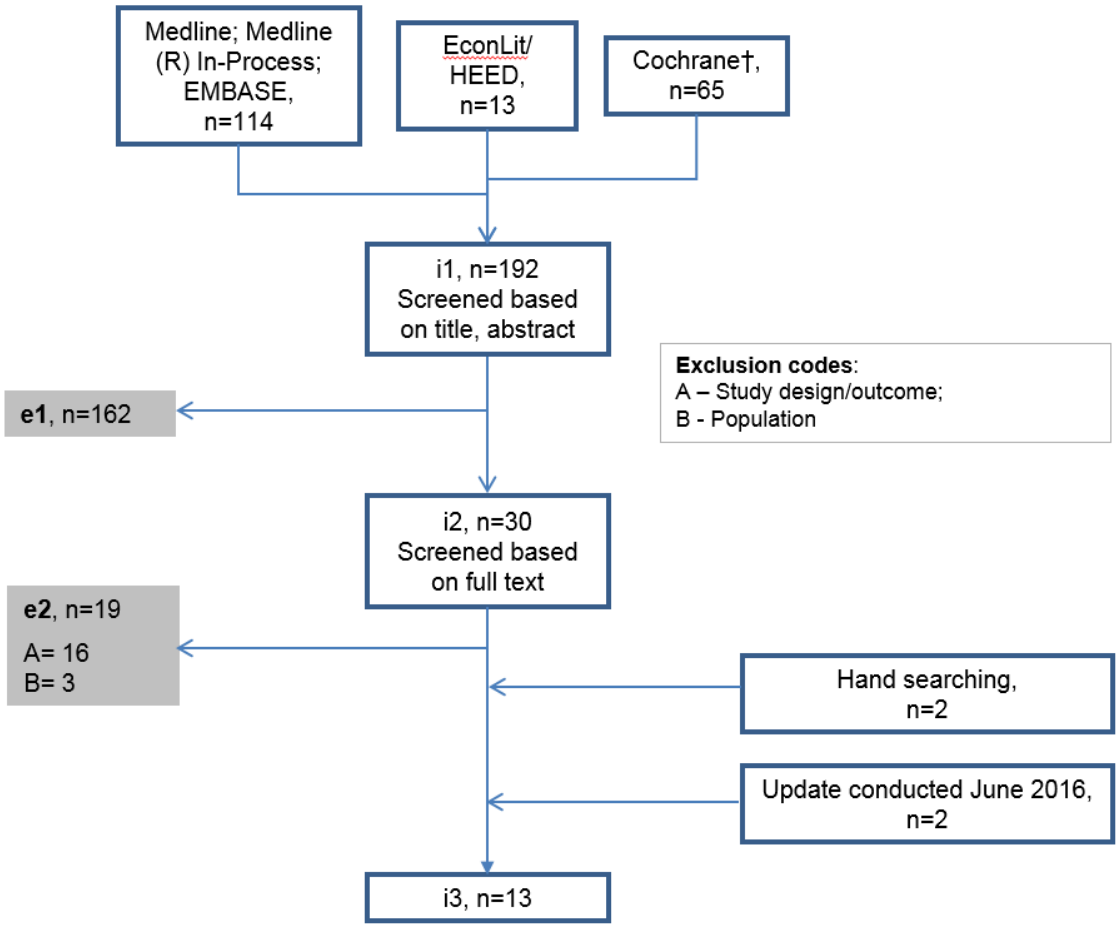
Database	Interface
Embase 1966 to 2014	Embase
Medline 1966 to 2014	Embase
Medline® In-Process 1966 to 2014	Embase
Cochrane Database of Systematic Reviews 1996 to 2014	The Cochrane Library
Database of Abstracts of Reviews of Effects 1994 to 2014	The Cochrane Library
Health Technology Assessment 1989 to 2014	The Cochrane Library
NHS Economic Evaluation Database 1968 to 2014	The Cochrane Library
EconLIT with Full Text 1961 to 2014	EBSCO host
Health Economic Evaluations Database 1990 to 2014	EBSCO host

The searches included terms for free text and keywords (Medical Subject Heading (MeSH) and Emtree terms) through the use of Boolean combination techniques. Searches were not restricted by study intervention or comparator to ensure studies reporting costs and resource use in this population were identified. The Cochrane Library and EBSCO host interfaces were searched using terms for the population only, in order to broaden the results.

A grey literature search was also performed to include additional studies that had not been identified by the search strategy. References included for the review had to meet the pre-specified inclusion/exclusion criteria shown as a PICOS table in Appendix 9.

The search identified 192 titles/abstracts. After screening, 162 references were excluded, leaving 30 references included for full-text evaluation. No further studies were identified from the review of grey literature. A total of 11 references met the inclusion/exclusion criteria following full-text evaluation. Of these 11 references, all studies were deemed relevant to the review. The PRISMA diagram for the systematic review is shown in Figure 30.

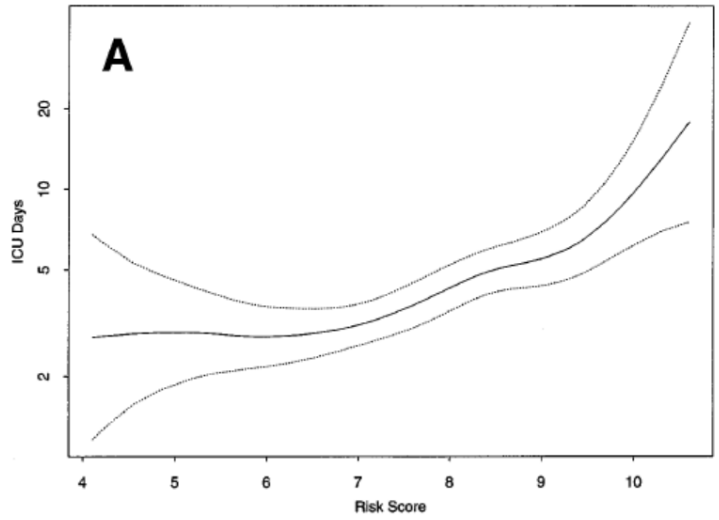
Figure 30: PRISMA diagram illustrating the flow of the cost and healthcare resource use systematic review

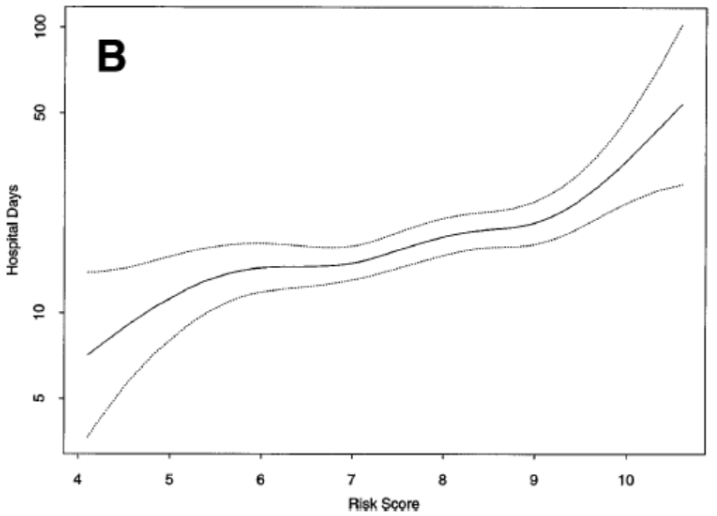


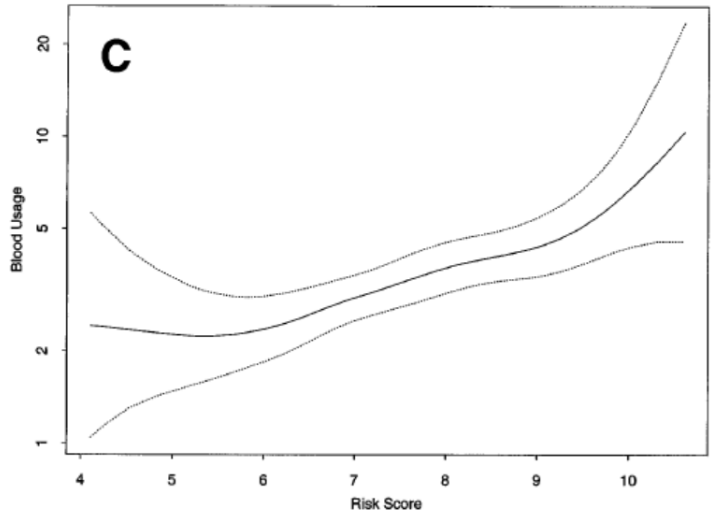
Details of the 11 included studies are shown in Table 63.

Table 63: Studies reporting resource data (original SLR and hand-searched publications)

Study, Year, Country	Cost and resource use data
Boberg et al (79)	• Costs were valued in Norwegian kroner (NOK), inflated to 2005 costs using the consumer price index and then converted to 2005 Euros • A cost of €132,903 was assigned to liver transplantation, which included donor organ harvesting and initial hospital stay
Horizon Scanning Centre (8)	• It has been identified that there were 777 hospital admissions in England due to PBC (ICD10 K74.3) in 2011 to 2012. This included 1,142 consultant episodes and 4,956 bed days • A pack of 100 x 250 mg tablets of ursodeoxycholic acid (Ursofalk) costs £31.88. Therefore, one year of treatment with 12–16 mg/kg would cost between £478 and £574
Lemos et al (160)	• The annual cost of treatment with UDCA was reported as $2,239.24 with the dose of 8 mg/kg; $3,168.97 with the dose of 12 mg/kg; and $4,098.71 with the dose of 15 mg/kg
Kogure et al (161)	• Kogure and colleagues acknowledge that the model for end-stage liver disease (MELD) score is useful for predicting medical expenses in living donor liver transplantation (LDLT) • Costs were valued in Japanese yen and then converted to US dollars using the rate of $1.00 = ¥110.0
Longworth et al (140)	• Longworth and colleagues report the number of patients that, following transplant assessment, were listed for transplant. Of those listed, the number that went on to receive a liver transplant is also given • Resource use was evaluated from the point of assessment for transplantation. Resource use included the following: all subsequent inpatient stays, outpatient visits, high-cost/high-volume drugs, blood products, nutrition, physiotherapy sessions, dietician sessions, tests, treatments, and the length of the transplant operation provided at the transplant centre • 1998–1999 GBP prices were used to value resources. These were derived by obtaining mean costs from the 6 UK liver transplant centres and weighting by number of transplantations performed • Based on data from the Royal College of Surgeons and Engineering and Physical Sciences Research Council an average cost per successful liver procurement is estimated at just over £7,200 • The average cost for a patient with PBC (from point of assessment for transplant) was reported as £52,525 for a 27-month period
Gilroy et al(162)	• Resource use was measured for length of stay in ICU, period of ventilation after the liver transplantation procedure, intraoperative blood product use, surgical time and duration of hospital stay • Gilroy and colleagues reported that patients with a Mayo risk score greater than 7.8 used almost twice the resources of patients with a risk score less than 7.8.
Ratcliffe et al (139)	• Costs were calculated (In 1999 GBP) for liver transplants and waiting list costs in a variety of scenarios which model different

	organ allocation policies • Costs were measured in terms of net life expectancy, average net costs and overall cost-effectiveness • The ICER for the base case allocation policy was determined to be £11,557 • The ICER for a transplant allocation policy based upon age (lowest age first) was £10,424 • The ICER for a transplant allocation policy based upon the severity of the pre-transplant condition of the patient (with most severely ill patients given a lower priority) was £9,077
Pasha et al (78)	• Within this analysis, only direct costs were included and were presented in 1995 US dollars • $2,543 was reported as the annual cost of UDCA
Kim et al (163)	• The figures below illustrate the relationship between pre-transplantation risk score and resource use following transplant, measured by days in ICU (A), hospital length of stay (B), and intraoperative blood transfusion requirements (amount of red blood cells transfused in litres [C]). • These three resource components had previously been identified as contributing over 90% of the cost burden in the post-transplant phase 


B
Hospital Days
100
50
10
5
4
5
6
7
8
9
10
Risk Score


C
Blood Usage
20
10
5
2
1
4
5
6
7
8
9
10
Risk Score

Kim et al(164)	• The majority of data reported by Kim and colleagues was not extracted on the basis that it did not relate to a PBC population. However, results of a multivariate regression analysis were reported, which captured the impact that certain variables had on non-fixed PBC costs.
Kankaanpa et al(165)	• Kankaanpaa and colleagues report the economic costs of liver transplantations for PBC patients, in 1986 US dollars.
Wright et al (154)	• Wright et al reported the costs of chronic hepatitis C. • Some of the costs could be applied to PBC as some hepatitis C health states are similar to PBC health states, including: o Cirrhosis (compensated cirrhosis) (£1,138 per annum) o Decompensated cirrhosis (£9,120 per annum) o Hepatocellular carcinoma (£8,127 per annum)
Singh et al (4)	• Singh et al estimated the costs of liver transplantation in patients diagnosed with chronic hepatitis C and B in the UK • The authors updated and analysed historical summary data from the original cohort study to generate updated cost estimates for liver transplantation, via conducting semi-structured interviews. • The authors estimated a cost of £18,055 pre-transplantation (waiting list), £64,452 during the transplant phase, and £36,009 in two-years post-transplant. • The authors did not specify the year for which costs were calculated.

GBP, Great British Pounds; ICER, incremental cost-effectiveness ratio; ICU, intensive care unit; LDLT, living donor liver transplantation; MELD, model of end-stage liver disease; NOK, Norwegian Kroner; PBC, primary biliary cholangitis/cirrhosis; UDCA, ursodeoxycholic acid.

5.5.1.3 Update of systematic review

The systematic review was updated by a supplementary review, which was conducted in March 2016. Full details of the search strategy and inclusion/exclusion criteria are provided in Appendix 9.

Two additional conference abstracts were identified (155, 166). These publications are detailed below in Table 64.

Table 64: Studies reporting cost data (SLR update)

Study, Year, Country	Cost and resource use data
Kim 2015 (155)	• Resource use for PBC and associated comorbidities including hyperlipidemia, hypothyroidism and extrahepatic autoimmune diseases were determined for South Korea • The nationwide total direct medical cost was $8.5 million (2013 USD) at a cost of $950 per patient • Epidemiological data were also reported
Pells 2015 (166)	• Resource savings for UDCA were reported, although it is not clear what comparators were identified. • The authors concluded that savings due to UDCA ranged between $1,372 USD per annum (cost year not reported) to an extrapolated disease lifetime saving of €6,338 EUR (cost year not reported) per patient. • Both studies assessed cost from a direct hospital-based perspective only, and QoL and primary care costs were not considered.

Abbreviations: EUR, Euros; PBC, primary biliary cholangitis/cirrhosis; QoL, quality of life; UDCA, ursodeoxycholic acid; USD, United States Dollars;

5.5.1.4 Appropriateness of NHS Ref costs/PbR tariffs

Unit costs for UDCA were determined using the British National Formulary (2016) and market share data, to calculate a weighted average cost per pack (167). In the base case analysis, the daily cost of UDCA is based on the observed UDCA dose as defined in the POISE trial protocol (15.4 mg/kg) (93).

NHS reference costs were used to determine the cost of outpatient appointments (average of consultant-led and non-consultant-led episodes) and costs for blood diagnostic tests.

5.5.1.5 Clinical expert assessment of applicability of cost and healthcare resource use values

The details of this process have been described previously in Section 5.3.3.

5.5.2 *Intervention and comparators' costs and resource use*

Results in this submission are based on the list price of OCA. However, OCA will be offered under a patient access scheme (PAS) and so the results presented in this section are for guidance only. Results of the economic analyses using the PAS price are presented in the accompanying PAS template, as requested by NICE, and are more reflective of the true cost-effectiveness of OCA.

Table 65: Unit costs associated with the technology in the economic model

Items	OCA (confidence interval)	Reference to section in submission	UDCA (confidence interval)	Reference to section in submission
Technology cost (list price)	£2,384.04 / 30 tablets	N/A	Weighted average of tablet formulations detailed in NHS Prescription Cost Analysis (167)	N/A
Total annual cost (based on list price)	£29,005.78	N/A	£655.33	N/A

Abbreviations: OCA, obeticholic acid; N/A, not applicable; UDCA, ursodeoxycholic acid.

5.5.3 *Health-state costs and resource use*

All costs were inflated to 2016 costs using the Hospital & Community Health Services (HCHS) index (168).

Table 66: List of health states and associated costs in the economic model

Health states	Items	Value	Source	Reference to section in submission
ALP: ≤ 200 U/L and Bili: Normal	Staff	£221.00 (1x Outpatient appointment, 1x outpatient follow-up)	KOL opinion	N/A
	Hospital costs	£27.00 (3 blood tests, 3 times per year, at a cost of £3)	NHS Schedule of Reference Costs – DAPS05	N/A
	Total	**£248.00**		
ALP: > 200 U/L and Bili: Normal	Staff	£345.00 (1x Outpatient appointment, 2x outpatient follow-up appointments)	KOL opinion	N/A
	Hospital costs	£27.00 (3 blood tests, 3 times per year, at a cost of £3)	NHS Schedule of Reference Costs – DAPS05	N/A
	Total	**£496.00**		
Bili: Abnormal and rising, or CC	Total	**£6,254.00**	KOL opinion: half the costs of DCC identified in Wright et al (2006)(154)	Table 63, page 161

Health states	Items	Value	Source	Reference to section in submission
DCC	Total	**£12,509.00**	Wright et al (2006)(154)	Table 63, page 161
HCC	Total	**£11,147.00**	Wright et al (2006)(154)	Table 63, page 161
Pre-transplant (end stage)	Total	**£18,217.00**	Singh et al (2014)(4)	Table 63, page 161
Re-emergence of PBC	Total	**£248.00**	Assumed identical to ALP: ≤ 200 u/L and Bili: Normal	Table 63, page 161
Liver transplant	Total	**£65,029.00**	Singh et al (2014)(4)	Table 63, page 161
Follow-up 1 year after liver transplantation	Total for 2 years divided by 2	**£18,166.00**	Singh et al (2014)(4)	Table 63, page 161
Follow-up 2 years after liver transplantation	Total for 2 years divided by 2	**£18,166.00**	Singh et al (2014)(4)	Table 63, page 161

Abbreviations: ALP, alkaline phosphatase; Bili, bilirubin; CC, compensated cirrhosis; DCC, decompensated cirrhosis; HCC, hepatocellular carcinoma; KOL, key opinion leader; PBC, primary biliary cholangitis/cirrhosis.

5.5.4 *Adverse reaction unit costs and resource use*

Of the three most frequent adverse events reported in POISE (pruritus, fatigue and nausea), only pruritus is treated in routine clinical practice. Therefore, only pruritus incurs a cost within the model (Table 67).

Table 67: List of adverse reactions and summary of costs included in the economic model

Adverse events	Items	Percentage of patients cost applies to	Value	Reference to section in submission
Pruritus	Staff (GP visit)	100%**	£54.00*	KOL input
	Cholestyramine cost / 327.10 days†	85%**	£105.59‡	KOL input
	Rifampicin cost / 327.10 days†	15%**	£191.77‡	KOL input
	Naltrexone cost / 327.10 days†	5%**	£228.39‡	KOL input
	Total (weighted average + staff costs)	N/A	£177.75	KOL input

Abbreviations: GP, general practitioner. *Sourced from BNF, 2016. **Sourced from KOL opinion. †Mean duration of treatment for UDCA and OCA therapies. ‡Sourced from NHS Schedule of Reference Costs.

5.5.5 *Miscellaneous unit costs and resource use*

The de novo cost-effectiveness analysis does not include any further miscellaneous costs or resource use.

5.6 *Summary of base-case de novo analysis inputs and assumptions*

5.6.1 *Summary of base-case de novo analysis inputs*

Patient utility data are reported in Table 61, and transition probabilities are reported in Table 50, Table 52 and Table 54. Costs for the intervention and comparators are reported in Table 65, and health state-specific costs are reported in Table 66. A summary of the remaining variables used in the economic analysis is provided in Table 68.

Table 68: Summary of variables applied in the economic model

Variable	Value	CI (distribution)	Reference
Percentage of patients starting in state: ALP ≤ 200 u/L and Bili: Normal	0.00%	–	Data on file
Percentage of patients starting in state: ALP > 200 u/L and Bili: Normal	76.85%	–	Data on file
Percentage of patients starting in state: Bili: abnormal and rising, or CC	23.15%	–	Data on file
Discount rate – cost	3.5%	–	NICE DSU (149)
Discount rate – outcomes	3.5%	–	NICE DSU (149)

Abbreviations: ALP, alkaline phosphatase; Bili, bilirubin; CC, compensated cirrhosis; CI, confidence interval; PBC, primary biliary cholangitis/cirrhosis.

5.6.2 *Assumptions*

Several assumptions were made in the model, following consultation and approval by KOLs:

- In the absence of PBC-specific inputs, hepatitis C virus (HCV) data were used as proxy for health state costs and utility values (discussed further in Sections 5.4.5 and 5.5.2)
- In the first year, patients can progress freely between the three PBC health states, as observed in the POISE OCA regimen arms. Afterwards, patients remain in the health state they are in at 12 months to reflect the sustained reduction in ALP and bilirubin demonstrated in the preliminary results from the long-term safety extension (LTSE) phase. In sensitivity analysis, OCA patients might progress from the “moderate risk PBC” state to the “high risk PBC” state with a low probability based on the literature, assuming they would follow a similar decompensation rate as UDCA GLOBE responders (152).
- UDCA patients can progress between PBC health states based on transition probabilities estimated based on the POISE patient-level data using both the

GLOBE and UK risk score, calibrated to reflect the liver transplant-free survivals (152)

- Patients suffering from decompensated cirrhosis have serious symptoms and complications from cirrhosis, such as ascites, hepatic encephalopathy or portal hypertension. This model followed previously published liver disease models that collapsed all the aforementioned states into a single state.(169, 170) The advantage of collapsing these states into a single state is to allow a patient to have several complications simultaneously, as occurs in practice
- A proportion of patients from the “high risk PBC” group is assumed to be eligible for liver transplant and added to the waiting list
- All patients in the decompensated cirrhosis health state are assumed to be candidates for liver transplantation
- Patients suffering from HCC are also candidates for liver transplantation
- Background mortality is assumed to be the same as the general population
- A probability of having a re-transplantation after recurrence of PBC has been included in the model
- Utility values reported for the following health states were decreased by [redacted] to reflect poorer outcomes in PBC patients versus HCV / HBV patients, according to interpretation of KOL input by Intercept:
    - Decompensated cirrhosis
    - Pre transplant: utility at listing
    - Pre transplant: 3 months after listing
    - Pre transplant: 6 months after listing
    - Post-transplant: 3 months after transplant
    - Post-transplant: 6 months after transplant
    - Post-transplant: 12 months after transplant
    - Post-transplant: 24 months after transplant

5.7 *Base-case results*

5.7.1 *Base-case incremental cost effectiveness analysis results*

All analyses presented in this submission are based on the list price of OCA. However, OCA will be offered under a patient access scheme (PAS) and so the results in this submission are for guidance only. It is important to note that the relative cost-effectiveness and associated interpretation of the model results change significantly with the application of the proposed PAS price for OCA. Results of the economic analyses using the PAS price are presented in the accompanying PAS template, as requested by NICE, and are more reflective of the true cost-effectiveness of OCA.

Base-case results using the list price of OCA for the UDCA-intolerant population are presented in Table 69, which shows that OCA dose titration therapy is associated with incremental costs of [redacted] and incremental QALYs of 6.91 compared with placebo, resulting in an ICER of [redacted]. The results for the UDCA inadequate responder population are presented in Table 70. This table presents the results of the primary analysis of OCA dose titration in combination with UDCA vs UDCA monotherapy in UDCA inadequate responders. OCA dose titration + UDCA is associated with incremental costs of [redacted] and incremental QALYs of 5.79, resulting in an ICER of [redacted]

Table 69: Base-case results for UDCA-intolerant patients, using the list price of OCA

Technologies	Total			Incremental			ICER (£)	ICER (£)
	Costs (£)	LYG	QALYs	Costs (£)	LYG	QALYs	versus baseline	incremental
No treatment (Placebo)	£103,233	11.30	6.61					
OCA titration	[redacted]	16.65	13.52	[redacted]	5.35	6.91	[redacted]	[redacted]

Abbreviations: ICER, incremental cost-effectiveness ratio; LYG, life years gained; OCA, obeticholic acid; QALYs, quality-adjusted life years; UDCA, ursodeoxycholic acid

Table 70: Base-case results for UDCA inadequate responders, using the list price of OCA

Technologies	Total			Incremental			ICER (£)	ICER (£)
	Costs (£)	LYG	QALYs	Costs (£)	LYG	QALYs	versus baseline	incremental
UDCA + Placebo	£96,977	12.35	7.85					
OCA titration + UDCA	[redacted]	16.75	13.64	[redacted]	4.40	5.79	[redacted]	[redacted]

Abbreviations: ICER, incremental cost-effectiveness ratio; LYG, life years gained; OCA, obeticholic acid; QALYs, quality-adjusted life years; UDCA, ursodeoxycholic acid.

5.7.2 *Clinical outcomes from the model*

Table 71 presents the model outcomes for both therapies for UDCA-intolerant patients. The results show a lower number of patients with abnormal bilirubin, cases of decompensated cirrhosis, liver transplants and liver-related deaths in the OCA-treated group.

Table 71 Summary of model outcomes for UDCA-intolerant population

Outcome	OCA titration	No treatment (placebo)	Incremental
Total number of cases of Bili: abnormal and rising, or CC per 1,000 patients	[redacted]	[redacted]	[redacted]
Total number of cases of decompensated cirrhosis per 1,000 patients	[redacted]	[redacted]	[redacted]
Total liver transplants per 1,000 patients	[redacted]	[redacted]	[redacted]
Total liver related deaths per 1,000 patients	[redacted]	[redacted]	[redacted]

Abbreviations: Bili, bilirubin; CC, compensated cirrhosis; OCA, obeticholic acid; UDCA, ursodeoxycholic acid.

Table 72 presents the model outcomes for both therapies for UDCA inadequate responders. As with the UDCA-intolerant population, the results show a lower number of patients with abnormal bilirubin, cases of decompensated cirrhosis, liver transplants and liver-related deaths in the OCA-treated group.

Table 72: Summary of model outcomes for UDCA inadequate responder population

Outcome	OCA titration + UDCA	UDCA + Placebo	Incremental
Total number of cases of Bili: abnormal and rising, or CC per 1,000 patients	[redacted]	[redacted]	[redacted]
Total number of cases of decompensated cirrhosis per 1,000 patients	[redacted]	[redacted]	[redacted]
Total liver transplants per 1,000 patients	[redacted]	[redacted]	[redacted]
Total liver related deaths per 1,000 patients	[redacted]	[redacted]	[redacted]

Abbreviations: Bili, bilirubin; CC, compensated cirrhosis; OCA, obeticholic acid; UDCA, ursodeoxycholic acid.

5.7.3 *Disaggregated results of the base case incremental cost effectiveness analysis*

The disaggregated results show overall superiority of OCA over its comparator in both UDCA-intolerant and UDCA inadequate responder populations.

Table 73: Summary of QALY gain by health state for UDCA-intolerant population

Health state	OCA Titration	No treatment (Placebo)	Increment	Absolute increment
ALP: ≤ 200 u/L and Bili: Normal	5.981	0.000	-5.981	5.981
ALP: > 200 u/L and Bili: Normal	6.796	2.044	-4.752	4.752
Bili: Abnormal and rising, or CC	0.394	2.515	2.121	2.121
Discontinuation	0.009	0.000	-0.009	0.009
Decompensated cirrhosis	0.106	0.651	0.544	0.544
HCC	0.011	0.065	0.055	0.055
Pre transplant (end stage)	0.034	0.208	0.174	0.174
Liver transplant	0.005	0.031	0.026	0.026
Post liver transplant	0.136	0.822	0.686	0.686
Re-emergence of PBC	0.046	0.270	0.223	0.223
Total	13.520	6.606	-6.913	14.572

Abbreviations: ALP, alkaline phosphatase; Bili, bilirubin; CC, compensated cirrhosis; HCC, hepatocellular carcinoma; OCA, obeticholic acid; PBC, primary biliary cholangitis/cirrhosis; QALY, quality-adjusted life year; UDCA, ursodeoxycholic acid; ULN, upper limit of normal.

Table 74: Summary of QALY gain by health state for UDCA inadequate responders

Health state	QALY OCA + UDCA titration	QALY UDCA + Placebo	Increment	Absolute increment
ALP: ≤ 200 u/L and Bili: Normal	5.981	0.000	-5.981	5.981
ALP: > 200 u/L and Bili: Normal	6.974	3.867	-3.107	3.107
Bili: Abnormal and rising, or CC	0.365	2.222	1.857	1.857
Discontinuation	0.009	0.004	-0.006	0.006
Decompensated cirrhosis	0.098	0.569	0.471	0.471
HCC	0.010	0.057	0.048	0.048
Pre transplant (end stage)	0.031	0.182	0.151	0.151
Liver transplant	0.005	0.027	0.023	0.023
Post liver transplant	0.125	0.701	0.577	0.577
Re-emergence of PBC	0.042	0.222	0.180	0.180
Total	13.641	7.852	-5.789	12.399

Abbreviations: ALP, alkaline phosphatase; Bili, bilirubin; CC, compensated cirrhosis; HCC, hepatocellular carcinoma; OCA, obeticholic acid; PBC, primary biliary cholangitis/cirrhosis; QALY, quality-adjusted life year; UDCA, ursodeoxycholic acid; ULN, upper limit of normal.

Table 75: Summary of costs by health state for UDCA-intolerant population

Health state	OCA Titration	No treatment (Placebo)	Increment	Absolute increment
ALP: ≤ 200 u/L and bili: Normal	[redacted]	£0.00	[redacted]	[redacted]
ALP: > 200 u/L and bili: Normal	[redacted]	£1,207.08	[redacted]	[redacted]
Bili: Abnormal and rising, or CC	[redacted]	£28,597.68	[redacted]	[redacted]
Discontinuation	[redacted]	£0.00	[redacted]	[redacted]
Decompensated cirrhosis	[redacted]	£21,284.77	[redacted]	[redacted]
HCC	[redacted]	£1,620.43	[redacted]	[redacted]
Pre transplant (end stage)	[redacted]	£9,890.90	[redacted]	[redacted]
Liver transplant	[redacted]	£14,310.87	[redacted]	[redacted]
Post liver transplant	[redacted]	£26,221.30	[redacted]	[redacted]
Re-emergence of PBC	[redacted]	£99.80	[redacted]	[redacted]
Total	[redacted]	£103,232.81	[redacted]	[redacted]

Abbreviations: ALP, alkaline phosphatase; Bili, bilirubin; CC, compensated cirrhosis; HCC, hepatocellular carcinoma; OCA, obeticholic acid; PBC, primary biliary cholangitis/cirrhosis; QALY, quality-adjusted life year; UDCA, ursodeoxycholic acid; ULN, upper limit of normal.

Table 76: Summary of costs by health state for UDCA inadequate responders

Health state	OCA + UDCA titration	UDCA + Placebo	Increment	Absolute increment
ALP: ≤ 200 u/L and Bili: Normal	[redacted]	£0.00	[redacted]	[redacted]
ALP: > 200 u/L and Bili: Normal	[redacted]	£5,349.00	[redacted]	[redacted]
Bili: Abnormal and rising, or CC	[redacted]	£27,926.48	[redacted]	[redacted]
Discontinuation	[redacted]	£14.48	[redacted]	[redacted]
Decompensated cirrhosis	[redacted]	£18,619.88	[redacted]	[redacted]
HCC	[redacted]	£1,422.13	[redacted]	[redacted]
Pre transplant (end stage)	[redacted]	£8,665.20	[redacted]	[redacted]
Liver transplant	[redacted]	£12,526.26	[redacted]	[redacted]
Post liver transplant	[redacted]	£22,371.06	[redacted]	[redacted]
Re-emergence of PBC	[redacted]	£82.10	[redacted]	[redacted]
Total	[redacted]	£96,976.58	[redacted]	[redacted]

Abbreviations: ALP, alkaline phosphatase; Bili, bilirubin; CC, compensated cirrhosis; HCC, hepatocellular carcinoma; OCA, obeticholic acid; PBC, primary biliary cholangitis/cirrhosis; QALY, quality-adjusted life year; UDCA, ursodeoxycholic acid; ULN, upper limit of normal.

5.8 *Sensitivity analyses*

5.8.1 *Probabilistic sensitivity analysis*

5.8.1.1 Inputs

Patient characteristics (i.e. weight and baseline health state distribution) were included in the PSA alongside all other generic inputs (transition probabilities, clinical inputs and quality of life). Baseline distribution across the four PBC-specific health states were assumed to follow a Dirichlet distribution. The four variables were drawn from independent Gamma or Normal distributions contingent on whether the sample size of each category was below 340 or not, respectively. Then the required four probabilities were re-estimated dividing the sampled patient number in each category by the total sampled population. Quality of life parameters were assumed to follow a Beta distribution, costs a Gamma distribution and other continuous parameters a Normal distribution. The Gamma distribution parameters to use for the disease management costs were derived from Wright et al (154). The mean cost and standard errors reported by the authors were inflated from 2002/2003 to 2014/2015 and the parameters were estimated based on the newly inflated inputs as described below in Table 77. Where the variance was unknown, the lower and upper confidence intervals were estimated assuming a 20% variability around the mean. The PSA was performed by running 1,000 Monte Carlo simulations.

Table 77: Generic PSA inputs: UDCA-intolerant population

Parameter	Distribution and parameters	Expected value	Source/Comments
Baseline health state distribution – 200 units / L ALP threshold			
ALP ≤ 200 units / L and NB	Dirichlet	0.0%	POISE trial (93)
ALP > 200 units / L and NB	Dirichlet	76.85%	POISE trial (93)
(ALP ≤ or > 200 units / L) and AB	Dirichlet	23.15%	POISE trial (93)
Patient characteristics			
Weight (kg)	Normal: μ = 69.8, δ = 13.9	69.8	POISE trial (93)
Discontinuation probabilities			
No treatment (Placebo)	Beta: α = 3, β = 70	0.00%	POISE trial (93)
OCA titration	Beta: α = 7, β = 64	9.86%	POISE trial (93)
Adverse events			
No treatment (Placebo)			
Fatigue	Beta: α = 8, β = 65	0.00%	POISE trial (93)
Pruritus	Beta: α = 27, β = 46	0.00%	POISE trial (93)
Nausea	Beta: α = 4, β = 69	0.00%	POISE trial (93)
OCA titration			(93)
Fatigue	Beta: α = 6, β = 64	8.57%	POISE trial (93)
Pruritus	Beta: α = 35, β = 35	50.0%	POISE trial (93)
Nausea	Beta: α = 3, β = 67	4.29%	POISE trial (93)
Utility parameters			
ALP ≤ 200 units / L and NB	Beta: α=202.37, β=38.55	0.84	Younossi et al. (2001) (64)
ALP > 200 units / L and NB	Beta: α=202.37, β=38.55	0.84	Younossi et al. (2001) (64)
(ALP ≤ or > 200 units / L) and AB	Beta: α=47, β=39	0.55	Wright et al. (2006) (154)

Parameter	Distribution and parameters	Expected value	Source/Comments
Decompensated cirrhosis	[redacted]	[redacted]	Wright et al. (2006) (154) and assumed decrement of [redacted]
Hepatocellular carcinoma	Beta: α=124, β=151	0.45	Wright et al. (2006) (154)
Liver transplant	[redacted]	[redacted]	Wright et al. (2006) (154) and assumed decrement of [redacted]
Post-liver transplant	[redacted]	[redacted]	Wright et al. (2006) (154) and assumed decrement of [redacted]
Re-emergence of PBC	Beta: α=265.98, β=131.00	0.67	KOL input
Transition probabilities			
From ALP ≤ 200 units / L and NB to Bili: Abnormal and rising, or CC	Beta: α=89.44, β=1,225.60	6.80%	Assumption based on 20% variance
From ALP > 200 units / L and NB to Bili: Abnormal and rising, or CC	Beta: α=89.44, β=1,225.60	6.80%	Assumption based on 20% variance
From Bili: Abnormal and rising, or CC to decompensated cirrhosis	Beta: α=93.51, β=3,503.69	2.6%	Assumption based on 20% variance
From Bili: Abnormal and rising, or CC to HCC	Beta: α=2, β=136	0.35%	STA 330(142)
From decompensated cirrhosis to pre-liver transplant	Beta: α=94.55, β=6064.94	1.53%	Assumption based on 20% variance
From decompensated cirrhosis to death	Beta: α=92.17, β=2222.83	3.98%	Assumption based on 20% variance
From decompensated cirrhosis to HCC	Beta: α=2, β=136	0.35%	STA 330 (142)
From HCC to death	Beta: α=83.31, β=552.18	13.11%	STA 330 (142)
From pre-LT to LT	Beta: α=86.13, β=757.45	10.21%	Data on file
From pre-LT to death	Beta: α=93.78, β=3930.59	2.33%	Data on file

Parameter	Distribution and parameters	Expected value	Source/Comments
From LT to death	Beta: α=16, β=61	5.72%	STA 330(142)
From post-LT to re-emergence of PBC	Uniform: α=0.20, β=0.25	0.64%	Assumption based on 20% variance
From post-LT to LT	Beta: α=3, β=483	0.01%	Neuberger et al. (2003) (156)
From post-LT to death	Beta: α=23, β=379	1.46%	STA 330 (142)
From re-emergence of PBC to LT	Beta: α=3, β=483	0.01%	Neuberger et al. (2003) (156)
Disease management costs			
DM costs: ALP: ≤ 200 units / L and Bili: Normal	Gamma, α=96.04, β=2.58	£248.00	KOL input
DM costs: ALP: > 200 units / L and Bili: Normal	Gamma, α=96.04, β=5.16	£496.00	KOL input
DM costs: Bili: Abnormal and rising, or CC	Gamma, α=96.04, β=65.12	£6,254.00	KOL opinion: half the costs of DCC identified in Wright et al (2006)(154)
DM costs: Decompensated cirrhosis	Gamma, α=96.04, β=130.25	£12,509.00	Wright et al (2006)(154)
DM costs: HCC	Gamma, α=96.04, β=116.07	£11,147.00	Wright et al (2006)(154)
DM costs: Pre transplant (end stage)	Gamma, α=96.04, β=189.69	£18,217.00	Singh et al (2014)(4)
DM costs: Re-emergence of PBC	Gamma, α=96.04, β=2.58	£248.00	KOL input
Liver transplant costs	Gamma, α=96.04, β=677.13	£65,029.00	Singh et al (2014)(4)
Post-liver transplant costs: Year 1	Gamma, α=96.04, β=189.16	£18,166.00	Singh et al (2014)(4)
Post-liver transplant costs: Year 2	Gamma, α=96.04, β=189.16	£18,166.00	Singh et al (2014)(4)
Adverse event costs			
Adverse event costs: pruritus	Gamma, α=96.04, β=1.85	£177.75	KOL input

Table 78: Generic PSA inputs: UDCA inadequate responder population

Parameter	Distribution and parameters	Expected value	Source/Comments
Baseline health state distribution – 200 units / L ALP threshold			
ALP ≤ 200 units / L and NB	Dirichlet	0.0%	POISE trial (93)
ALP > 200 units / L and NB	Dirichlet	76.85%	POISE trial (93)
(ALP ≤ or > 200 units / L) and AB	Dirichlet	23.15%	POISE trial (93)
Patient characteristics			
Weight (kg)	Normal: μ = 69.8, δ = 13.9	69.8	POISE trial (93)
Discontinuation probabilities			
UDCA + Placebo	Beta: α = 3, β = 70	4.11%	POISE trial (93)
OCA + UDCA titration	Beta: α = 7, β = 64	9.86%	POISE trial (93)
Adverse events			
UDCA + Placebo			
Fatigue	Beta: α = 8, β = 65	10.96%	POISE trial (93)
Pruritus	Beta: α = 27, β = 46	36.99%	POISE trial (93)
Nausea	Beta: α = 4, β = 69	5.48%	POISE trial (93)
OCA + UDCA titration			
Fatigue	Beta: α = 6, β = 64	8.57%	POISE trial (93)
Pruritus	Beta: α = 35, β = 35	50.0%	POISE trial (93)
Nausea	Beta: α = 3, β = 67	4.29%	POISE trial (93)
Utility parameters			
ALP ≤ 200 units / L and NB	Beta: α=202.37, β=38.55	0.84	Younossi et al. (2001) (64)
ALP > 200 units / L and NB	Beta: α=202.37, β=38.55	0.84	Younossi et al. (2001) (64)

Parameter	Distribution and parameters	Expected value	Source/Comments
(ALP ≤ or > 200 units / L) and AB	Beta: α=47, β=39	0.55	Wright et al. (2006) (154)
Decompensated cirrhosis	[redacted]	[redacted]	Wright et al. (2006) (154) and assumed decrement of [redacted]
Hepatocellular carcinoma	Beta: α=124, β=151	0.45	Wright et al. (2006) (154)
Liver transplant	[redacted]	[redacted]	Wright et al. (2006) (154) and assumed decrement of [redacted]
Post-liver transplant	[redacted]	[redacted]	Wright et al. (2006) (154) and assumed decrement of [redacted]
Re-emergence of PBC	Beta: α=265.98, β=131.00	0.67	KOL input
Transition probabilities			
From ALP ≤ 200 units / L and NB to Bili: Abnormal and rising, or CC	Beta: α=94.80, β=7345.49	1.27%	Assumption based on 20% variance
From ALP > 200 units / L and NB to Bili: Abnormal and rising, or CC	Beta: α=92.98, β=2863.30	3.15%	Assumption based on 20% variance
From Bili: Abnormal and rising, or CC to decompensated cirrhosis	Beta: α=93.51, β=3503.69	2.6%	Assumption based on 20% variance
From Bili: Abnormal and rising, or CC to HCCd	Beta: α=2, β=136	0.35%	STA 330(142)
From decompensated cirrhosis to pre-liver transplant	Beta: α=94.55, β=6064.94	1.53%	Assumption based on 20% variance
From decompensated cirrhosis to death	Beta: α=92.17, β=2222.83	3.98%	Assumption based on 20% variance
From decompensated cirrhosis to HCC	Beta: α=2, β=136	0.35%	STA 330 (142)
From HCC to death	Beta: α=83.31, β=552.18	13.11%	STA 330 (142)
From pre-LT to LT	Beta: α=86.13, β=757.45	10.21%	Data on file
From pre-LT to death	Beta: α=93.78, β=3930.59	2.33%	Data on file
From LT to death	Beta: α=16, β=61	5.72%	STA 330(142)
From post-LT to re-emergence of PBC	Uniform: α=0.20, β=0.25	0.64%	Assumption based on 20% variance
From post-LT to LT	Beta: α=3, β=483	0.01%	Neuberger et al. (2003) (156)

Parameter	Distribution and parameters	Expected value	Source/Comments
From post-LT to death	Beta: α=23, β=379	1.46%	STA 330 (142)
From re-emergence of PBC to LT	Beta: α=3, β=483	0.01%	Neuberger et al. (2003) (156)
Disease management costs			
DM costs: ALP: ≤ 200 units / L and Bili: Normal	Gamma, α=96.04, β=2.58	£248.00	KOL input
DM costs: ALP: > 200 units / L and Bili: Normal	Gamma, α=96.04, β=5.16	£496.00	KOL input
DM costs: Bili: Abnormal and rising, or CC	Gamma, α=96.04, β=65.12	£6,254.00	KOL opinion: half the costs of DCC identified in Wright et al (2006)(154)
DM costs: Decompensated cirrhosis	Gamma, α=96.04, β=130.25	£12,509.00	Wright et al (2006)(154)
DM costs: HCC	Gamma, α=96.04, β=116.07	£11,147.00	Wright et al (2006)(154)
DM costs: Pre transplant (end stage)	Gamma, α=96.04, β=189.69	£18,217.00	Singh et al (2014)(4)
DM costs: Re-emergence of PBC	Gamma, α=96.04, β=2.58	£248.00	KOL input
Liver transplant costs	Gamma, α=96.04, β=677.13	£65,029.00	Singh et al (2014)(4)
Post-liver transplant costs: Year 1	Gamma, α=96.04, β=189.16	£18,166.00	Singh et al (2014)(4)
Post-liver transplant costs: Year 2	Gamma, α=96.04, β=189.16	£18,166.00	Singh et al (2014)(4)
Adverse event costs			
Adverse event costs: pruritus	Gamma, α=96.04, β=1.85	£177.75	KOL input

Table 79: Incremental cost effectiveness results of PSA for the UDCA intolerant population, using the list price of OCA

Technologies	Total			Incremental			ICER (£)	ICER (£)
	Costs (£)	LYG	QALYs	Costs (£)	LYG	QALYs	versus baseline	incremental
PSA results								
No treatment (placebo)	£103,439	11.33	6.77	-	-	-	-	-
OCA Titration	[redacted]	16.64	13.52	[redacted]	5.31	6.75	[redacted]	[redacted]
Base case deterministic results								
No treatment (placebo)	£103,233	11.30	6.61	-	-	-	-	-
OCA titration	[redacted]	16.65	13.52	[redacted]	5.35	6.91	[redacted]	[redacted]

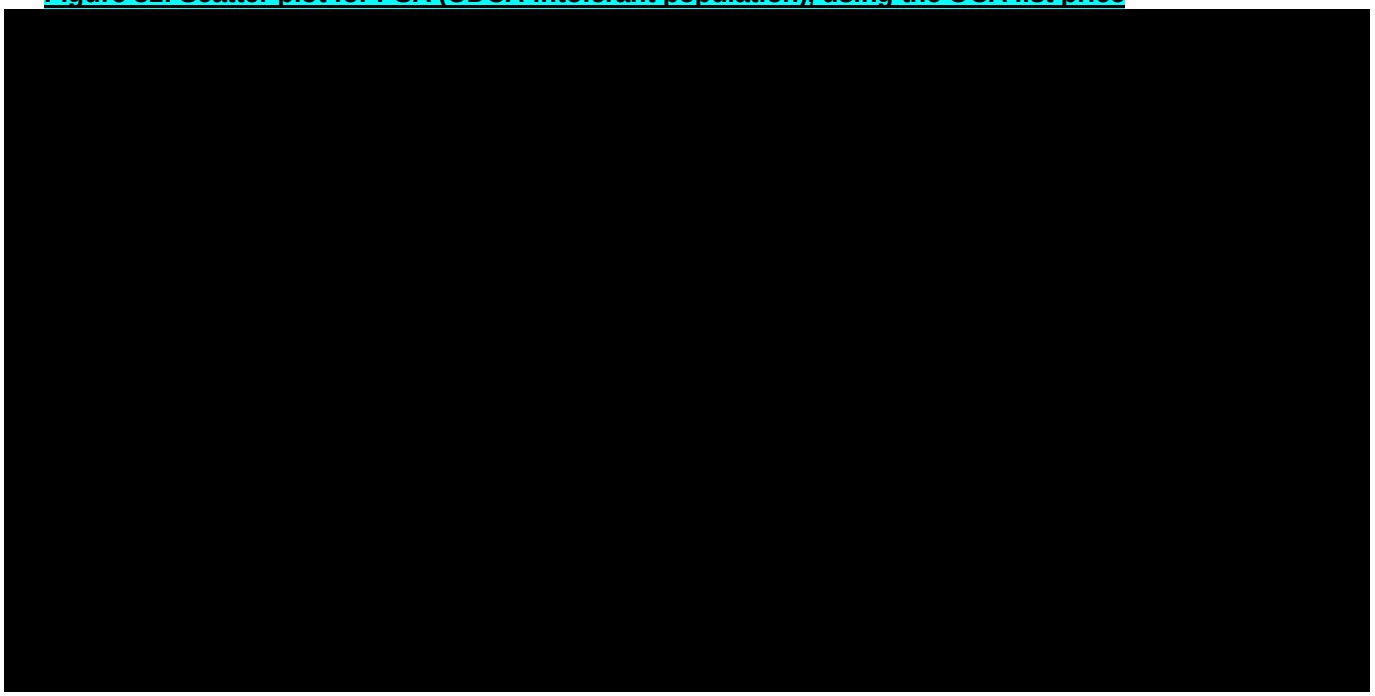
Abbreviations: ICER, incremental cost-effectiveness ratio; LYG, life years gained; PSA, probabilistic sensitivity analysis; QALY, quality-adjusted life year; OCA, obeticholic acid; UDCA, ursodeoxycholic acid.

Table 80: Incremental cost effectiveness results of PSA for the UDCA inadequate responder population, using the list price of OCA

Technologies	Total			Incremental			ICER (£)	ICER (£)
	Costs (£)	LYG	QALYs	Costs (£)	LYG	QALYs	versus baseline	incremental
PSA results								
UDCA + placebo	£97,044	12.38	7.88	-	-	-	-	-
OCA + UDCA titration	[redacted]	16.75	13.65	[redacted]	4.37	5.77	[redacted]	[redacted]
Base case deterministic results								
UDCA + placebo	£96,977	12.35	7.85	-	-	-	-	-
OCA + UDCA titration	[redacted]	16.75	13.64	[redacted]	4.40	5.79	[redacted]	[redacted]

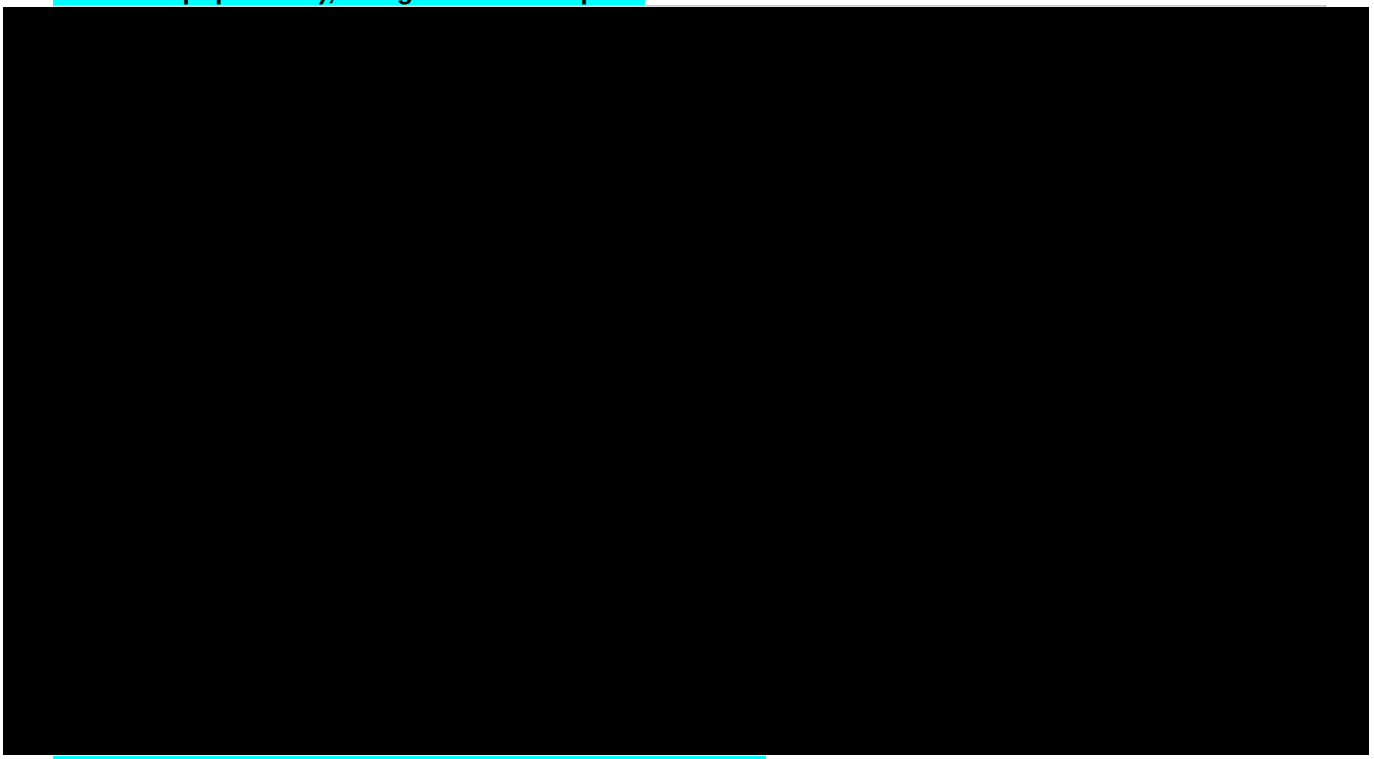
Abbreviations: ICER, incremental cost-effectiveness ratio; LYG, life years gained; OCA, obeticholic acid; PSA, probabilistic sensitivity analysis; QALY, quality-adjusted life year; UDCA, ursodeoxycholic acid.

Figure 31: Scatter plot for PSA (UDCA-intolerant population), using the OCA list price



Abbreviations: OCA, obeticholic acid; PSA, probabilistic sensitivity analysis; QALY, quality-adjusted life year; UDCA, ursodeoxycholic acid.

Figure 32: Cost-effectiveness acceptability curve for OCA titration versus placebo (UDCA-intolerant population), using the OCA list price



Abbreviations: OCA, obeticholic acid; UDCA, ursodeoxycholic acid.

Figure 33: Scatter plot for PSA (UDCA inadequate responders population), using the OCA list price

Abbreviations: OCA, obeticholic acid; PSA, probabilistic sensitivity analysis; QALY, quality-adjusted life year; UDCA, ursodeoxycholic acid.

Figure 34: Cost-effectiveness acceptability curve for OCA + UDCA titration versus UDCA + placebo (UDCA inadequate responders population), using the OCA list price

Abbreviations: OCA, obeticholic acid; UDCA, ursodeoxycholic acid.

5.8.1.2 Discussion of variation between base case and PSA results

The PSA shows that the model is linear and there is little variation between the results of the base case deterministic results and the probabilistic results. The deterministic results can reliably be used to generate scenarios.

5.8.2 *Deterministic sensitivity analysis*

5.8.2.1 Inputs

The generic inputs that are varied in the DSA are the discontinuation probabilities, probabilities of having an adverse event, utility weights, transition probabilities, discounting, and the probability of death for the general population.

The model also allows the user to run scenario analyses by assuming that all patients enter the model in each of the four PBC-specific health state at a time.

Table 81: Generic DSA inputs: UDCA-intolerant population

Parameter	Base case	Min	Max	Source
Discontinuation probabilities				
No treatment (Placebo)	0.0%	0.0%	0.0%	No variance is considered for this parameter
OCA titration	9.86%	4.12%	17.73%	POISE trial; LB and UB are limits of 95% CI estimated assuming a BETA distribution (93)
Adverse events				
No treatment (Placebo)				
Pruritus	0.0%	0.0%	0.0%	No variance is considered for this parameter
OCA titration				
Pruritus	50.0%	38.4%	61.6%	POISE trial; LB and UB are limits of 95% CI estimated assuming a BETA distribution (93)
Utility parameters				
ALP ≤ 200 units / L and NB	0.84	0.79	0.88	Younossi et al. (2001) (64); LB and UB are limits of 95% CI estimated assuming a BETA distribution
ALP > 200 units / L and NB	0.84	0.79	0.88	Younossi et al. (2001) (64); LB and UB are limits of 95% CI estimated assuming a BETA distribution
(ALP ≤ or > 200 units / L) and AB	0.55	0.44	0.65	Wright et al. (2006) (154); LB and UB are limits of 95% CI estimated assuming a BETA distribution
Decompensated cirrhosis	[redacted]	[redacted]	[redacted]	Wright et al. (2006) (154); [redacted] decrement; LB and UB assumed equal to +/- 20% of the base case
Hepatocellular carcinoma	0.45	0.39	0.51	Wright et al. (2006) (154); LB and UB are limits of 95% CI estimated assuming a BETA distribution
Liver transplant	[redacted]	[redacted]	[redacted]	Wright et al. (2006) (154); [redacted] decrement; LB and UB assumed equal to +/- 20% of the base case
Post-liver transplant	[redacted]	[redacted]	[redacted]	Wright et al. (2006) (154); [redacted] decrement; LB and UB assumed equal to +/- 20% of the base case
Re-emergence of PBC	0.67	0.62	0.72	Wright et al. (2006) (154); LB and UB are limits of 95%

Parameter	Base case	Min	Max	Source
				CI estimated assuming a BETA distribution
Transition probabilities				
From ALP ≤ 200 units / L and NB to Bili: Abnormal and rising, or CC	6.8%	5.4%	8.2%	20% variance assumed; LB and UB are limits of 95% CI estimated assuming a BETA distribution
From ALP > 200 units / L and NB to Bili: Abnormal and rising, or CC	6.8%	5.4%	8.2%	20% variance assumed; LB and UB are limits of 95% CI estimated assuming a BETA distribution
From Bili: Abnormal and rising, or CC to decompensated cirrhosis	2.6%	2.08%	3.12%	20% variance assumed; LB and UB are limits of 95% CI estimated assuming a BETA distribution
From severe PBC to HCC	0.35%	0.04%	1.02%	20% variance assumed; LB and UB are limits of 95% CI estimated assuming a BETA distribution
From decompensated cirrhosis to transplant	1.53%	1.23%	1.84%	20% variance assumed; LB and UB are limits of 95% CI estimated assuming a BETA distribution
From decompensated cirrhosis to death	3.98%	3.19%	4.78%	20% variance assumed; LB and UB are limits of 95% CI estimated assuming a BETA distribution
From decompensated cirrhosis to HCC	0.35%	0.0%	1.02%	20% variance assumed; LB and UB are limits of 95% CI estimated assuming a BETA distribution
From HCC to death	13.11%	10.49%	15.73%	20% variance assumed; LB and UB are limits of 95% CI estimated assuming a BETA distribution
From pre-LT to LT	10.21%	8.17%	12.25%	20% variance assumed; LB and UB are limits of 95% CI estimated assuming a BETA distribution
From pre-LT to death	2.33%	1.86%	2.80%	20% variance assumed; LB and UB are limits of 95% CI estimated assuming a BETA distribution
From LT to death	5.72%	3.29%	8.68%	20% variance assumed; LB and UB are limits of 95% CI estimated assuming a BETA distribution
From post-LT to re-emergence of PBC	0.64%	0.56%	0.72%	20% variance assumed; LB and UB are limits of 95% CI estimated assuming a Uniform distribution
From post-LT to LT	0.01%	0.00%	0.03%	20% variance assumed; LB and UB are limits of 95% CI estimated assuming a BETA distribution
From post-LT to death	1.46%	0.93%	2.11%	20% variance assumed; LB and UB are limits of 95% CI estimated assuming a BETA distribution

Parameter	Base case	Min	Max	Source
From re-emergence of PBC to LT	0.01%	0.00%	0.03%	20% variance assumed; LB and UB are limits of 95% CI estimated assuming a BETA distribution
Discount rates				
Discount rates – outcomes	3.5%	0.0%	6.0%	NICE - Guide to the methods of technology appraisal (171)
Discount rates – costs	3.5%	0.0%	6.0%	NICE - Guide to the methods of technology appraisal (171)
AE management costs				
Pruritus costs	£177.75	£142.20	£213.30	Calculation; LB and UB assumed equal to +/-20% of the base case
Disease management costs				
ALP ≤ 200 units / L and NB	£248.00	£198.40	£297.60	Calculation; LB and UB based on the CI from Gamma distribution
ALP > 200 units / L and NB	£496.00	£396.80	£595.20	Calculation; LB and UB based on the CI from Gamma distribution
(ALP ≤ or > 200 units / L) and AB	£6,254.00	£5,003.20	£7,504.80	Calculation; LB and UB based on the CI from Gamma distribution and assuming ½ variance of DCC
Decompensated cirrhosis	£12,509.00	£10,007.20	£15,010.80	Calculation; LB and UB based on the CI from Gamma distribution
HCC	£11,147.00	£8,917.60	£13,376.40	Calculation; LB and UB based on the CI from Gamma distribution
Pre transplant (end stage)	£18,217.00	£14,573.60	£21,860.40	Calculation; LB and UB assumed equal to +/-20% of the base case
Liver transplant	£65,029.00	£198.40	£297.60	Calculation; LB and UB assumed equal to +/-20% of the base case
Post-liver transplant - Year 1	£18,166.00	£52,023.20	£78,034.80	Calculation; LB and UB assumed equal to +/-20% of the base case
Post-liver transplant - Year 2	£18,166.00	£14,532.80	£21,799.20	Calculation; LB and UB assumed equal to +/-20% of the base case

Parameter	Base case	Min	Max	Source
Re-emergence of PBC	£248.00	£198.40	£297.60	Calculation; LB and UB based on the CI from Gamma distribution

Table 82: Generic DSA inputs: UDCA inadequate responder population

Parameter	Base case	Min	Max	Source
Discontinuation probabilities				
UDCA + Placebo	4.11%	0.87%	9.68%	POISE trial; LB and UB are limits of 95% CI estimated assuming a BETA distribution (93)
OCA + UDCA titration	9.86%	4.12%	17.73%	POISE trial; LB and UB are limits of 95% CI estimated assuming a BETA distribution (93)
Adverse events				
UDCA + Placebo				
Pruritus	36.99%	26.36%	48.29%	No variance is considered for this parameter
OCA + UDCA titration				
Pruritus	50.0%	38.4%	61.6%	POISE trial; LB and UB are limits of 95% CI estimated assuming a BETA distribution (93)
Utility parameters				
ALP ≤ 200 units / L and NB	0.84	0.79	0.88	Younossi et al. (2001) (64); LB and UB are limits of 95% CI estimated assuming a BETA distribution
ALP > 200 units / L and NB	0.84	0.79	0.88	Younossi et al. (2001) (64); LB and UB are limits of 95% CI estimated assuming a BETA distribution
(ALP ≤ or > 200 units / L) and AB	0.55	0.44	0.65	Wright et al. (2006) (154); LB and UB are limits of 95% CI estimated assuming a BETA distribution
Decompensated cirrhosis	[redacted]	[redacted]	[redacted]	Wright et al. (2006) (154); [redacted] decrement; LB and UB assumed equal to +/- 20% of the base case
Hepatocellular carcinoma	0.45	0.39	0.51	Wright et al. (2006) (154); LB and UB are limits of 95% CI estimated assuming a BETA distribution
Liver transplant	[redacted]	[redacted]	[redacted]	Wright et al. (2006) (154); [redacted] decrement; LB and UB

Parameter	Base case	Min	Max	Source
				assumed equal to +/- 20% of the base case
Post-liver transplant	[redacted]	[redacted]	[redacted]	Wright et al. (2006) (154); [redacted] decrement; LB and UB assumed equal to +/- 20% of the base case
Re-emergence of PBC	0.67	0.62	0.72	Wright et al. (2006) (154); LB and UB are limits of 95% CI estimated assuming a BETA distribution
Transition probabilities				
From ALP ≤ 200 units / L and NB to Bili: Abnormal and rising, or CC	6.8%	5.4%	8.2%	20% variance assumed; LB and UB are limits of 95% CI estimated assuming a BETA distribution
From ALP > 200 units / L and NB to Bili: Abnormal and rising, or CC	6.8%	5.4%	8.2%	20% variance assumed; LB and UB are limits of 95% CI estimated assuming a BETA distribution
From Bili: Abnormal and rising, or CC to decompensated cirrhosis	2.6%	2.08%	3.12%	20% variance assumed; LB and UB are limits of 95% CI estimated assuming a BETA distribution
From severe PBC to HCC	0.35%	0.04%	1.02%	20% variance assumed; LB and UB are limits of 95% CI estimated assuming a BETA distribution
From decompensated cirrhosis to transplant	1.53%	1.23%	1.84%	20% variance assumed; LB and UB are limits of 95% CI estimated assuming a BETA distribution
From decompensated cirrhosis to death	3.98%	3.19%	4.78%	20% variance assumed; LB and UB are limits of 95% CI estimated assuming a BETA distribution
From decompensated cirrhosis to HCC	0.35%	0.0%	1.02%	20% variance assumed; LB and UB are limits of 95% CI estimated assuming a BETA distribution
From HCC to death	13.11%	10.49%	15.73%	20% variance assumed; LB and UB are limits of 95% CI estimated assuming a BETA distribution
From pre-LT to LT	10.21%	8.17%	12.25%	20% variance assumed; LB and UB are limits of 95% CI estimated assuming a BETA distribution
From pre-LT to death	2.33%	1.86%	2.80%	20% variance assumed; LB and UB are limits of 95% CI estimated assuming a BETA distribution
From LT to death	5.72%	3.29%	8.68%	20% variance assumed; LB and UB are limits of 95% CI estimated assuming a BETA distribution
From post-LT to re-emergence of PBC	0.64%	0.56%	0.72%	20% variance assumed; LB and UB are limits of 95% CI estimated assuming a Uniform distribution

Parameter	Base case	Min	Max	Source
From post-LT to LT	0.01%	0.00%	0.03%	20% variance assumed; LB and UB are limits of 95% CI estimated assuming a BETA distribution
From post-LT to death	1.46%	0.93%	2.11%	20% variance assumed; LB and UB are limits of 95% CI estimated assuming a BETA distribution
From re-emergence of PBC to LT	0.01%	0.00%	0.03%	20% variance assumed; LB and UB are limits of 95% CI estimated assuming a BETA distribution
Discount rates				
Discount rates – outcomes	3.5%	0.0%	6.0%	NICE - Guide to the methods of technology appraisal (171)
Discount rates – costs	3.5%	0.0%	6.0%	NICE - Guide to the methods of technology appraisal (171)
AE management costs				
Pruritus costs	£177.75	£142.20	£213.30	Calculation; LB and UB assumed equal to +/-20% of the base case
Disease management costs				
ALP ≤ 200 units / L and NB	£248.00	£198.40	£297.60	Calculation; LB and UB based on the CI from Gamma distribution
ALP > 200 units / L and NB	£496.00	£396.80	£595.20	Calculation; LB and UB based on the CI from Gamma distribution
(ALP ≤ or > 200 units / L) and AB	£6,254.00	£5,003.20	£7,504.80	Calculation; LB and UB based on the CI from Gamma distribution and assuming ½ variance of DCC
Decompensated cirrhosis	£12,509.00	£10,007.20	£15,010.80	Calculation; LB and UB based on the CI from Gamma distribution
HCC	£11,147.00	£8,917.60	£13,376.40	Calculation; LB and UB based on the CI from Gamma distribution
Pre transplant (end stage)	£18,217.00	£14,573.60	£21,860.40	Calculation; LB and UB assumed equal to +/-20% of the base case
Liver transplant	£65,029.00	£198.40	£297.60	Calculation; LB and UB assumed equal to +/-20% of the base case

Parameter	Base case	Min	Max	Source
Post-liver transplant - Year 1	£18,166.00	£52,023.20	£78,034.80	Calculation; LB and UB assumed equal to +/-20% of the base case
Post-liver transplant - Year 2	£18,166.00	£14,532.80	£21,799.20	Calculation; LB and UB assumed equal to +/-20% of the base case
Re-emergence of PBC	£248.00	£198.40	£297.60	Calculation; LB and UB based on the CI from Gamma distribution

5.8.2.2 Results

All sensitivity analyses were performed at the list price of OCA (£29,005.78). Analyses using the PAS price, which are more reflective of the true cost-effectiveness of OCA, are presented in the accompanying PAS template.

Figure 35: Tornado diagram for OCA titration versus no treatment (placebo) in the UDCA intolerant population, using the list price of OCA

[redacted]

Figure 36: Tornado diagram for OCA + UDCA titration versus UDCA + placebo in the UDCA inadequate responder population, using the list price of OCA

[redacted]

5.8.3 *Scenario analysis*

5.8.3.1 Scenario 1: use of original HCV utility values

A scenario analysis was performed where all utility values that had been decremented from their previously reported values were set to their (HBV/HCV-specific) original values. The values changed are shown in Table 83. The results are presented in Table 84 and Table 85. OCA is still cost-effective despite using the more conservative HBV/HCV – specific utility values.

Table 83: Parameters changed for scenario 1

State	Base case utility value	Scenario utility value	Justification
Decompensated cirrhosis	0.38	0.45	Previously reported value for decompensated cirrhosis (TA330) (142)
Pre-transplant: utility at listing	0.38	0.45	Previously reported value for decompensated cirrhosis (TA330) (142)
Pre-transplant: 3 months after listing	0.38	0.45	Previously reported value for decompensated cirrhosis (TA330) (142)
Pre-transplant: 6 months after listing	0.38	0.45	Previously reported value for decompensated cirrhosis (TA330) (142)
Liver transplant: 3 months post-transplant	0.57	0.67	Previously reported value for decompensated cirrhosis (TA330) (142)
Liver transplant: 6 months post-transplant	0.57	0.67	Previously reported value for decompensated cirrhosis (TA330) (142)
Liver transplant: 12 months post-transplant	0.57	0.67	Previously reported value for decompensated cirrhosis (TA330) (142)
Liver transplant: 24 months post-transplant	0.57	0.67	Previously reported value for decompensated cirrhosis (TA330) (142)

Table 84: Scenario 1 results for UDCA intolerant patients, using the list price of OCA

Technologies	Total			Incremental			ICER (£)	ICER (£)
	Costs (£)	LYG	QALYs	Costs (£)	LYG	QALYs	versus baseline	incremental
No treatment (Placebo)	£103,233	11.30	6.64	-	-	-	-	-
OCA titration	[redacted]	16.65	13.52	[redacted]	5.35	6.88	[redacted]	[redacted]

Table 85: Scenario 1 results for UDCA inadequate responders, using the list price of OCA

Technologies	Total			Incremental			ICER (£)	ICER (£)
	Costs (£)	LYG	QALYs	Costs (£)	LYG	QALYs	versus baseline	incremental
UDCA + Placebo	£96,977	12.35	8.11	-	-	-	-	-
OCA + UDCA titration	[redacted]	16.75	13.64	[redacted]	4.40	5.75	[redacted]	[redacted]

5.8.3.2 Scenario 2: use of alternative transition probabilities

This scenario utilises alternative transition probabilities for pre-liver transplant to liver transplant, and pre-liver transplant to death, gathered from an ad-hoc analysis of PBC-specific data from OPTN (data on file).

Table 86: Parameters changed for scenario 2

Transition probability	Base case TP	Scenario TP	Justification
Pre-LT to LT	0.35	0.44	Based on ad-hoc data analysis of OPTN PBC data
Pre-LT to death	0.09	0.21	Based on ad-hoc data analysis of OPTN PBC data

Table 87: Scenario 2 results for UDCA intolerant patients, using the list price of OCA

Technologies	Total			Incremental			ICER (£)	ICER (£)
	Costs (£)	LYG	QALYs	Costs (£)	LYG	QALYs	versus baseline	incremental
No treatment (Placebo)	£95,697	10.93	6.56	-	-	-	-	-
OCA titration	[redacted]	16.59	13.51	[redacted]	5.66	6.95	[redacted]	[redacted]

Table 88: Scenario 2 results for UDCA inadequate responders, using the list price of OCA

Technologies	Total			Incremental			ICER (£)	ICER (£)
	Costs (£)	LYG	QALYs	Costs (£)	LYG	QALYs	versus baseline	incremental
UDCA + Placebo	£90,516	12.04	7.82	-	-	-	-	-
OCA + UDCA titration	[redacted]	16.69	13.63	[redacted]	4.66	5.82	[redacted]	[redacted]

5.8.4 *Summary of sensitivity analyses results*

The model was generally insensitive to changes in individual inputs. The primary drivers of the cost-effectiveness results (excluding discounting rates and OCA price) were:

- UDCA-intolerant population:
    - Transition probability for ALP > 200 u/L and Bili: normal to Bili: abnormal and rising, or CC
    - Utility value for Bili: abnormal and rising or CC
    - Utility: ALP ≤ 200 u/L and Bili: normal
- UDCA inadequate responder population:
    - Transition probability for ALP > 200 u/L and Bili: normal to Bili: abnormal and rising, or CC
    - Utility value for Bili: abnormal and rising or CC
    - Utility: ALP ≤ 200 u/L and Bili: normal

5.9 *Subgroup analysis*

No subgroups of patients were considered for this analysis.

5.10 *Validation*

5.10.1 *Validation of de novo cost-effectiveness analysis*

Internal verification of calculations was performed by the primary modeller in the first instance and checked by a second modeller involved with the model development (internal peer review). The economic model was also examined by two modellers external to the technical model development process (external peer review) (172). Verification techniques included:

- Face validity: testing that the model meets expectations based on simple calculations
- Model behaviour: testing whether varying model inputs has the expected directional effect
- Internal consistency: model outputs were compared against POISE
- Cell-by-cell checks of calculations: manual inspection of formulae
- Use of logical scenario checks and the rebuilding of important parts of the model
- A complete cross-check of inputs, sources, and supporting documentation.

The model produces outcomes at multiple time points to allow comparison against published sources.

5.11 *Interpretation and conclusions of economic evidence*

Results in this submission are based on the list price of OCA. However, OCA will be offered under a patient access scheme (PAS) and so the results presented in this submission are for guidance only. It is important to note that the relative cost-effectiveness and associated interpretation of the model results change significantly with the application of the proposed PAS price for OCA. Results of the economic analyses using the PAS price are presented in the accompanying PAS template, as requested by NICE, and are more reflective of the true cost-effectiveness of OCA.

The results of the economic analysis using the list price of OCA give an ICER of [redacted] for UDCA-intolerant patients and an ICER of [redacted] in UDCA inadequate responders. For both patient groups, the decrease in the number of liver transplants required for PBC patients is 84% when patients are treated with OCA.

The key limitation of this analysis is the absence of PBC-specific utility data. This was addressed by incorporating HBV/HCV utility data instead in similar health states, for example, pre-transplant stages where both hepatitis and PBC patients would be in advanced health states with comparatively poor quality of life. To reflect the generally worse outcomes and more rapid disease progression of PBC patients compared to HBV/HCV patients, utilities for disease states (excluding HCC and the re-emergence of PBC) were decremented by [redacted]

The deterministic sensitivity analysis shows that the model is fairly insensitive to individual variable changes, and is robust in that no single factor can easily alter the ICER.

6 Assessment of factors relevant to the NHS and other parties

6.1 *Population: people eligible for treatment*

All patients with PBC who have had an inadequate response to UDCA or who are unable to tolerate UDCA are eligible for treatment with OCA. An estimation of the number of patients who are eligible for treatment with OCA is shown in Table 89, and is calculated from the following parameters:

1. Total England + Wales populations (mid-2015 data).
2. Prevalence of PBC in England
3. PBC patients diagnosed
4. PBC patients under treater care
5. PBC patients eligible for treatment

As there are currently no other treatments available for this indication, no displacement of other medicines is assumed.

Table 89: Estimation of number of patients eligible for treatment with OCA

	Year 1	Year 2	Year 3	Year 4	Year 5
Population, England and Wales	57,885,400	57,885,400	57,885,400	57,885,400	57,885,400
Current prevalence, %	0.04%	0.04%	0.04%	0.04%	0.04%
Prevalent population	22,691	22,691	22,691	22,691	22,691
Patients diagnosed, %	52.00%	52.00%	52.00%	52.00%	52.00%
Patients diagnosed	11,799	11,799	11,799	11,799	11,799
Patients under treater care, %	92.00%	92.00%	92.00%	92.00%	92.00%
Patients under treater care	10,855	10,855	10,855	10,855	10,855
Patients eligible for treatment, %	35.00%	35.00%	35.00%	35.00%	35.00%
Patients eligible for treatment	3,799	3,799	3,799	3,799	3,799
Discontinuation rate	30%	30%	30%	30%	30%
Patients eligible for treatment minus patients who would be anticipated to discontinue	2,660	2,660	2,660	2,660	2,660
Proportion of eligible patients treated with new medicine	9.08%	30.32%	40.94%	49.59%	58.51%
Number of patients treated in each year	241	806	1,089	1,319	1,556

6.2 *Costs included*

The following costs were taken into account within budget impact calculations:

- Technology costs
    - OCA
    - UDCA (for UDCA – tolerant patients who have had an inadequate response to UDCA alone- 92.59% of the eligible PBC patient population)

Details of unit costs for the above are presented in Section 5.5.

6.3 *Resource savings*

Resource savings were not included as they were best presented as part of the cost-utility analysis where they would be captured within the extended time horizon. It is likely that were will be some costs savings related to a decreased number of liver transplants in PBC patients.

100% of the eligible patient population were assumed to be treated with OCA. No medicines were displaced by OCA as no other medicines exist for the specified indications.

6.4 *Budget impact*

OCA is expected to have a positive budget impact of [redacted] over five years in England for patients with PBC. Key drivers for this budget impact are:

- No other comparators existing for the specific indication, which means that no savings can be made by displacing cheaper medicines
- Potential cost saving aspects including decreased number of transplants not being taken into consideration (these are better considered as part of the cost-utility analysis).

Table 90: Budget impact of OCA

	Year 1	Year 2	Year 3	Year 4	Year 5
Uptake, %	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Patients treated with OCA, n	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Medicine acquisition cost per patient per annum	£29,005.78	£29,005.78	£29,005.78	£29,005.78	£29,005.78
Supportive medicines cost per patient per annum*	£620.71	£620.71	£620.71	£620.71	£620.71
Gross additional medicines cost per patient per annum	£29,626.49	£29,626.49	£29,626.49	£29,626.49	£29,626.49
Budget impact	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Cumulative budget impact	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

6.5 *Additional factors not included in analysis*

Yearly incidence rates for PBC were not used due to the incident population being a small proportion of the population. Adverse event costs were not included in the analysis.

6.6 *Limitations of the analysis*

It is important to note that the budget impact analysis only considers medicine acquisition costs, and without a comparator treatment to OCA there are no savings made due to treatment displacement. Also, the short time horizon of the budget impact analysis fails to capture savings caused by avoiding more severe health states that take a longer time to occur, such as decompensated cirrhosis, HCC and liver transplants. The impact of a

significant reduction in liver transplants will have both financial and medical implications given the high demand for donated livers.

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8 Appendices

Appendix 1: SmPC

Appendix 2: Search strategy for relevant studies for efficacy and safety

Appendix 3: Quality assessments of RCTs

Appendix 4: Subgroup analyses (POISE)

Appendix 5: Safety and adverse reactions (POISE)

Appendix 6: Search strategy for cost-effectiveness studies

Appendix 7: Quality assessment of cost-effectiveness studies

Appendix 8: Search strategy for measurement and valuation of health effects

Appendix 9: Cost and healthcare resource identification, measurement and valuation studies

Appendix 10: Calibration of transition probabilities

Appendix 11: Information and questions provided to experts

Appendix 12: POISE transition probabilities for ALP 1.5x ULN, ALP 2.0x ULN

Appendix 13: Checklist of confidential information

Single technology appraisal

Obeticholic acid for primary biliary cirrhosis [ID785]

Erratum to Intercept's responses to ERG questions

21st November 2016

Erratum preface

The company would like to bring to the ERG's attention that there was an error in the original submission regarding patient numbers used in the economic model.

The effects of this change are outlined in detail in this erratum. The erratum contains full deterministic and probabilistic sensitivity analyses of the new base case, including updated versions of the scenario analyses provided in the original submission. The overall effect on the ICERs for both the UDCA-intolerant and UDCA inadequate responder patient populations is minimal, as shown in Table 1 and Table 2. The ICER for the UDCA-intolerant population has decreased by £158.00/QALY, and the ICER for the UDCA inadequate responder population has decreased by £269.00/QALY.

Table 1: Comparison of the incremental cost-effectiveness results included in the original submission versus the updated base case results submitted in this erratum document for the UDCA-intolerant population, using the list price of OCA

Technologies	Total			Incremental			ICER (cost/QALY)	ICER (cost/QALY)
	Costs	LYG	QALYs	Costs	LYG	QALYs	versus baseline	Incremental
Base case results included in original submission								
No treatment (placebo)	£103,233	11.30	6.61	–	–	–	–	–
OCA titration	[redacted]	16.65	13.52	[redacted]	5.35	6.91	[redacted]	[redacted]
Updated base case results submitted in erratum								
No treatment (placebo)	£103,233	11.30	6.61	–	–	–	–	–
OCA titration	[redacted]	16.68	13.56	[redacted]	5.38	6.95	[redacted]	[redacted]

Abbreviations: ICER, incremental cost-effectiveness ratio; LYG, life years gained; OCA, obeticholic acid; QALYs, quality-adjusted life years; UDCA, ursodeoxycholic acid

Table 2: Comparison of the incremental cost-effectiveness results included in the original submission versus the updated base case results submitted in this erratum document for the UDCA inadequate responder population, using the list price of OCA

Technologies	Total			Incremental			ICER (cost/QALY)	ICER (cost/QALY)
	Costs	LYG	QALYs	Costs	LYG	QALYs	versus baseline	incremental
Base case results included in original submission								
UDCA + placebo	£96,977	12.35	7.85	–	–	–	–	–
OCA titration + UDCA	[redacted]	16.75	13.64	[redacted]	4.40	5.79	[redacted]	[redacted]
Updated base case results submitted in erratum								
UDCA + placebo	£96,977	12.35	7.85	–	–	–	–	–
OCA titration + UDCA	[redacted]	16.78	13.68	[redacted]	4.43	5.83	[redacted]	[redacted]

Abbreviations: ICER, incremental cost-effectiveness ratio; LYG, life years gained; OCA, obeticholic acid; QALYs, quality-adjusted life years; UDCA, ursodeoxycholic acid

The company would like to apologise for this error and the inconvenience caused. We would also like to thank the ERG for spotting the error in patient numbers and for requesting further clarification in their question B12b.

Changes to the cost-utility model

The revised cost-utility model has two changes to the originally submitted model:

- Patient-level data from the POISE CSR have been added for UDCA + no treatment (placebo) patients, and a switch to use these data has been included (as requested by NICE)
- Patient-level data for regimens containing OCA have been updated with the final data from the POISE CSR.

The addition of patient-level data for UDCA + no treatment (placebo) patients warranted minor structural changes to the model to allow the option of using patient-level data or not.

Incorporation of UDCA patient-level data

As described in the previous set of clarification responses (sent to NICE on 18/11/2016), the option to use patient-level UDCA data from POISE has been included in the model.

The majority of changes to the model were made in the 'Transition matrices' worksheet. All of the changes were made in the range L316:HL371 on this worksheet. A switch to enable or disable the use of UDCA patient-level data has been added in cell C10 on the 'Clinical inputs' worksheet. If the switch is activated, patient-level UDCA data from POISE is used to generate transition probabilities for that population.

Patient-level population numbers (added in the cells highlighted in yellow on the 'Transition matrices' worksheet) are included, along with their transition probability calculations (presented alongside). The calculations for how transition probabilities are derived are presented as formulae within the transition probability cells; for example, the patient numbers for UDCA + no treatment (placebo) patients with a recorded ALP threshold of >1.67x ULN (equating to 200 U/L) are located in the range X330:AF338. The transition probability calculations corresponding to this set of patient numbers are located in the range M330:V330. This method was used to derive all patient-level UDCA transition probability data for the first four cycles of the model.

Update of OCA patient-level data

The original submitted model contained data from an analysis of patient numbers according to an early version of the POISE patient-level dataset. Updated patient numbers have since been provided by the Intercept biostatistics team.

The model has now been updated to include the correct patient numbers. These have the effect of changing some transition probabilities used in the first four cycles of the economic model. This has had a downstream effect of changing the QALYs and costs generated for the OCA-treated patient groups.

The specific values changed were patient numbers in the transition matrices for the following treatment regimens:

- OCA titration
- OCA titration + UDCA
- OCA 10 mg (not relevant for this submission)
- OCA 10 mg + UDCA (not relevant for this submission)

Tables of all patient numbers that have been changed, their previous values, and their updated values, are presented below (Table 3, Table 4, Table 5, and Table 6). The cell references provided in the final column of the tables refer to the 'Transition matrices' worksheet of the model.

The different patient numbers have changed the corresponding transition probabilities. For example, on the 'Transition matrices' worksheet of the model, changes to patient numbers in

the range Y121:AF128 will have an impact on the transition probabilities calculated in the range N121:U128 (note that discontinuation is also applied to this specific transition matrix).

Table 3: OCA regimen patient numbers corrected from the original submission for the 0–3 month model cycle

Transition		Cycle: 0–3 months		
From:	**To:**	**Previous value**	**Updated value**	**Cell reference**
ALP: ≤ 2 ULN and Bili: Normal	ALP: ≤ 2 ULN and Bili: Normal	15	16	Y121
ALP: > 1.67 ULN and Bili: Normal	ALP: ≤ 1.67 ULN and Bili: Normal	31	32	Y134
ALP: > 1.5 ULN and Bili: Normal	ALP: > 1.5 ULN and Bili: Normal	39	40	Z146
ALP: ≤ 2 ULN and Bili: Normal	ALP: ≤ 2 ULN and Bili: Normal	13	14	Y170
ALP: > 2 ULN and Bili: Normal	ALP: ≤ 2 ULN and Bili: Normal	23	25	Y171
ALP: > 1.67 ULN and Bili: Normal	ALP: ≤ 1.67 ULN and Bili: Normal	22	24	Y183
ALP: > 1.67 ULN and Bili: Normal	ALP: > 1.67 ULN and Bili: Normal	38	39	Z183
ALP: > 1.5 ULN and Bili: Normal	ALP: ≤ 1.5 ULN and Bili: Normal	12	14	Y195
ALP: > 1.5 ULN and Bili: Normal	ALP: > 1.5 ULN and Bili: Normal	49	50	Z195
ALP: ≤ 2 ULN and Bili: Normal	ALP: ≤ 2 ULN and Bili: Normal	15	16	Y219
ALP: > 1.67 ULN and Bili: Normal	ALP: ≤ 1.67 ULN and Bili: Normal	31	32	Y232
ALP: > 1.5 ULN and Bili: Normal	ALP: > 1.5 ULN and Bili: Normal	39	40	Z244
ALP: ≤ 2 ULN and Bili: Normal	ALP: ≤ 2 ULN and Bili: Normal	13	14	Y268
ALP: > 2 ULN and Bili: Normal	ALP: ≤ 2 ULN and Bili: Normal	23	25	Y269
ALP: > 1.67 ULN and Bili: Normal	ALP: ≤ 1.67 ULN and Bili: Normal	22	24	Y281
ALP: > 1.67 ULN and Bili: Normal	ALP: > 1.67 ULN and Bili: Normal	38	39	Z281
ALP: > 1.5 ULN and Bili: Normal	ALP: ≤ 1.5 ULN and Bili: Normal	12	14	Y293
ALP: > 1.5 ULN and Bili: Normal	ALP: > 1.5 ULN and Bili: Normal	49	50	Z293

Abbreviations: ALP, alkaline phosphatase; Bili, bilirubin; OCA, obeticholic acid; ULN, upper limit of normal.

Table 4: OCA regimen patient numbers corrected from the original submission for the 3–6 month model cycle

Transition		Cycle: 3–6 months		
From	**To**	**Previous value**	**Updated value**	**Cell reference**
ALP: ≤ 2 ULN and Bili: Normal	ALP: > 2 ULN and Bili: Normal	0	1	CJ121
Bili: Abnormal and rising, or CC: Bili: Abnormal	ALP: ≤ 2 ULN and Bili: Normal	3	4	CI124
ALP: ≤ 2 ULN and Bili: Normal	ALP: > 2 ULN and Bili: Normal	2	3	CJ133
Bili: Abnormal and rising, or CC: Bili: Abnormal	ALP: ≤ 2 ULN and Bili: Normal	1	2	CI136
ALP: > 1.5 ULN and Bili: Normal	ALP: > 1.5 ULN and Bili: Normal	32	33	CJ146
Bili: Abnormal and rising, or CC: Bili: Abnormal	ALP: > 1.5 ULN and Bili: Normal	2	3	CJ148
ALP: ≤ 2 ULN and Bili: Normal	ALP: ≤ 2 ULN and Bili: Normal	30	35	CI170
ALP: > 2 ULN and Bili: Normal	ALP: > 2 ULN and Bili: Normal	21	22	CJ171
ALP: ≤ 1.67 ULN and Bili: Normal	ALP: ≤ 1.67 ULN and Bili: Normal	14	17	CI182
ALP: ≤ 1.67 ULN and Bili: Normal	ALP: > 1.67 ULN and Bili: Normal	6	7	CJ182
ALP: > 1.67 ULN and Bili: Normal	ALP: > 1.67 ULN and Bili: Normal	33	35	CJ183
ALP: ≤ 1.5 ULN and Bili: Normal	ALP: ≤ 1.5 ULN and Bili: Normal	11	12	CI194
ALP: ≤ 1.5 ULN and Bili: Normal	ALP: > 1.5 ULN and Bili: Normal	1	2	CJ194
ALP: > 1.5 ULN and Bili: Normal	ALP: ≤ 1.5 ULN and Bili: Normal	2	4	CI195
ALP: > 1.5 ULN and Bili: Normal	ALP: > 1.5 ULN and Bili: Normal	45	47	CJ195
ALP: ≤ 2 ULN and Bili: Normal	ALP: > 2 ULN and Bili: Normal	0	1	CJ219
Bili: Abnormal and rising, or CC: Bili: Abnormal	ALP: ≤ 2 ULN and Bili: Normal	3	4	CI222
ALP: ≤ 2 ULN and Bili: Normal	ALP: > 2 ULN and Bili: Normal	2	3	CJ231
Bili: Abnormal and rising, or CC: Bili: Abnormal	ALP: ≤ 2 ULN and Bili: Normal	1	2	CI234
ALP: > 1.5 ULN and Bili: Normal	ALP: > 1.5 ULN and Bili: Normal	32	33	CJ244
Bili: Abnormal and rising, or CC: Bili: Abnormal	ALP: > 1.5 ULN and Bili: Normal	2	3	CJ246

Transition		Cycle: 3–6 months		
From	**To**	**Previous value**	**Updated value**	**Cell reference**
ALP: ≤ 2 ULN and Bili: Normal	ALP: ≤ 2 ULN and Bili: Normal	30	35	CI268
ALP: > 2 ULN and Bili: Normal	ALP: > 2 ULN and Bili: Normal	21	22	CJ269
ALP: ≤ 1.67 ULN and Bili: Normal	ALP: ≤ 1.67 ULN and Bili: Normal	14	17	CI280
ALP: ≤ 1.67 ULN and Bili: Normal	ALP: > 1.67 ULN and Bili: Normal	6	7	CJ280
ALP: > 1.67 ULN and Bili: Normal	35.000	33	35	CJ281
ALP: ≤ 1.5 ULN and Bili: Normal	ALP: ≤ 1.5 ULN and Bili: Normal	11	12	CI292
ALP: ≤ 1.5 ULN and Bili: Normal	ALP: > 1.5 ULN and Bili: Normal	1	2	CJ292
ALP: > 1.5 ULN and Bili: Normal	ALP: ≤ 1.5 ULN and Bili: Normal	2	4	CI293
ALP: > 1.5 ULN and Bili: Normal	ALP: > 1.5 ULN and Bili: Normal	45	47	CJ293

Abbreviations: ALP, alkaline phosphatase; Bili, bilirubin; OCA, obeticholic acid; ULN, upper limit of normal.

Table 5: OCA regimen patient numbers corrected from the original submission for the 6–9 month model cycle

Transition		Cycle: 6–9 months		
From	**To**	**Previous value**	**Updated value**	**Cell reference**
ALP: ≤ 2 ULN and Bili: Normal	ALP: ≤ 2 ULN and Bili: Normal	44	46	ES121
ALP: ≤ 2 ULN and Bili: Normal	Bili: Abnormal and rising, or CC	0	1	EV121
ALP: > 2 ULN and Bili: Normal	ALP: > 2 ULN and Bili: Normal	7	8	ET122
ALP: ≤ 2 ULN and Bili: Normal	ALP: ≤ 2 ULN and Bili: Normal	31	33	ES133
ALP: ≤ 2 ULN and Bili: Normal	Bili: Abnormal and rising, or CC	0	1	EV133
ALP: > 2 ULN and Bili: Normal	ALP: > 2 ULN and Bili: Normal	19	20	ET134
ALP: ≤ 1.5 ULN and Bili: Normal	ALP: ≤ 1.5 ULN and Bili: Normal	19	20	ES145
ALP: > 1.5 ULN and Bili: Normal	ALP: ≤ 1.5 ULN and Bili: Normal	9	10	ES146
ALP: > 1.5 ULN and Bili: Normal	ALP: > 1.5 ULN and Bili: Normal	26	27	ET146

Transition		Cycle: 6–9 months		
From	**To**	**Previous value**	**Updated value**	**Cell reference**
ALP: > 1.5 ULN and Bili: Normal	Bili: Abnormal and rising, or CC: Bili: Abnormal	0	1	EV146
ALP: ≤ 2 ULN and Bili: Normal	ALP: ≤ 2 ULN and Bili: Normal	34	38	ES170
ALP: > 2 ULN and Bili: Normal	ALP: ≤ 2 ULN and Bili: Normal	3	5	ES171
ALP: > 2 ULN and Bili: Normal	ALP: > 2 ULN and Bili: Normal	14	17	ET171
ALP: ≤ 2 ULN and Bili: Normal	ALP: ≤ 2 ULN and Bili: Normal	16	18	ES182
ALP: > 2 ULN and Bili: Normal	ALP: ≤ 2 ULN and Bili: Normal	8	12	ES183
ALP: > 2 ULN and Bili: Normal	ALP: > 2 ULN and Bili: Normal	23	26	ET183
ALP: ≤ 1.5 ULN and Bili: Normal	ALP: ≤ 1.5 ULN and Bili: Normal	12	13	ES194
ALP: ≤ 1.5 ULN and Bili: Normal	ALP: > 1.5 ULN and Bili: Normal	3	4	ET194
ALP: > 1.5 ULN and Bili: Normal	ALP: ≤ 1.5 ULN and Bili: Normal	6	7	ES195
ALP: > 1.5 ULN and Bili: Normal	ALP: > 1.5 ULN and Bili: Normal	31	37	ET195
ALP: ≤ 2 ULN and Bili: Normal	ALP: ≤ 2 ULN and Bili: Normal	44	46	ES219
ALP: ≤ 2 ULN and Bili: Normal	Bili: Abnormal and rising, or CC	0	1	EV219
ALP: > 2 ULN and Bili: Normal	ALP: > 2 ULN and Bili: Normal	7	8	ET220
ALP: ≤ 2 ULN and Bili: Normal	ALP: ≤ 2 ULN and Bili: Normal	31	33	ES231
ALP: ≤ 2 ULN and Bili: Normal	Bili: Abnormal and rising, or CC	0	1	EV231
ALP: > 2 ULN and Bili: Normal	ALP: > 2 ULN and Bili: Normal	19	20	ET232
ALP: ≤ 1.5 ULN and Bili: Normal	ALP: ≤ 1.5 ULN and Bili: Normal	19	20	ES243
ALP: > 1.5 ULN and Bili: Normal	ALP: ≤ 1.5 ULN and Bili: Normal	9	10	ES244
ALP: > 1.5 ULN and Bili: Normal	ALP: > 1.5 ULN and Bili: Normal	26	27	ET244
ALP: > 1.5 ULN and Bili: Normal	Bili: Abnormal and rising, or CC: Bili: Abnormal	0	1	EV244
ALP: ≤ 2 ULN and Bili: Normal	ALP: ≤ 2 ULN and Bili: Normal	34	38	ES268

Transition		Cycle: 6–9 months		
From	**To**	**Previous value**	**Updated value**	**Cell reference**
ALP: > 2 ULN and Bili: Normal	ALP: ≤ 2 ULN and Bili: Normal	3	5	ES269
ALP: > 2 ULN and Bili: Normal	ALP: > 2 ULN and Bili: Normal	14	17	ET269
ALP: ≤ 2 ULN and Bili: Normal	ALP: ≤ 2 ULN and Bili: Normal	16	18	ES280
ALP: > 2 ULN and Bili: Normal	ALP: ≤ 2 ULN and Bili: Normal	8	12	ES281
ALP: > 2 ULN and Bili: Normal	ALP: > 2 ULN and Bili: Normal	23	26	ET281
ALP: ≤ 1.5 ULN and Bili: Normal	ALP: ≤ 1.5 ULN and Bili: Normal	12	13	ES292
ALP: ≤ 1.5 ULN and Bili: Normal	ALP: > 1.5 ULN and Bili: Normal	3	4	ET292
ALP: > 1.5 ULN and Bili: Normal	ALP: ≤ 1.5 ULN and Bili: Normal	6	7	ES293
ALP: > 1.5 ULN and Bili: Normal	ALP: > 1.5 ULN and Bili: Normal	31	37	ET293

Abbreviations: ALP, alkaline phosphatase; Bili, bilirubin; OCA, obeticholic acid; ULN, upper limit of normal.

Table 6: OCA regimen patient numbers corrected from the original submission for the 9–12 month model cycle

Transition		Cycle: 9–12 months		
From	**To**	**Previous value**	**Updated value**	**Cell reference**
ALP: ≤ 2 ULN and Bili: Normal	ALP: ≤ 2 ULN and Bili: Normal	41	44	HC121
ALP: ≤ 1.67 ULN and Bili: Normal	ALP: ≤ 1.67 ULN and Bili: Normal	29	31	HC133
ALP: > 1.67 ULN and Bili: Normal	ALP: ≤ 1.67 ULN and Bili: Normal	3	4	HC134
ALP: ≤ 1.5 ULN and Bili: Normal	ALP: ≤ 1.5 ULN and Bili: Normal	18	20	HC145
ALP: > 1.5 ULN and Bili: Normal	ALP: > 1.5 ULN and Bili: Normal	25	26	HD146
ALP: ≤ 2 ULN and Bili: Normal	ALP: ≤ 2 ULN and Bili: Normal	38	41	HC170
ALP: > 2 ULN and Bili: Normal	ALP: ≤ 2 ULN and Bili: Normal	2	3	HC171
ALP: > 2 ULN and Bili: Normal	ALP: > 2 ULN and Bili: Normal	12	15	HD171
ALP: ≤ 1.67 ULN and Bili: Normal	ALP: ≤ 1.67 ULN and Bili: Normal	25	28	HC182

Transition		Cycle: 9–12 months		
From	**To**	**Previous value**	**Updated value**	**Cell reference**
ALP: > 1.67 ULN and Bili: Normal	ALP: > 1.67 ULN and Bili: Normal	21	25	HD183
ALP: ≤ 1.5 ULN and Bili: Normal	ALP: ≤ 1.5 ULN and Bili: Normal	17	18	HC194
ALP: > 1.5 ULN and Bili: Normal	ALP: > 1.5 ULN and Bili: Normal	29	34	HD195
ALP: ≤ 2 ULN and Bili: Normal	ALP: ≤ 2 ULN and Bili: Normal	41	44	HC219
ALP: ≤ 1.67 ULN and Bili: Normal	ALP: ≤ 1.67 ULN and Bili: Normal	29	31	HC231
ALP: > 1.67 ULN and Bili: Normal	ALP: ≤ 1.67 ULN and Bili: Normal	3	4	HC232
ALP: ≤ 1.5 ULN and Bili: Normal	ALP: ≤ 1.5 ULN and Bili: Normal	18	20	HC243
ALP: > 1.5 ULN and Bili: Normal	ALP: > 1.5 ULN and Bili: Normal	25	26	HD244
ALP: ≤ 2 ULN and Bili: Normal	ALP: ≤ 2 ULN and Bili: Normal	38	41	HC268
ALP: > 2 ULN and Bili: Normal	ALP: ≤ 2 ULN and Bili: Normal	2	3	HC269
ALP: > 2 ULN and Bili: Normal	ALP: > 2 ULN and Bili: Normal	12	15	HD269
ALP: ≤ 1.67 ULN and Bili: Normal	ALP: ≤ 1.67 ULN and Bili: Normal	25	28	HC280
ALP: > 1.67 ULN and Bili: Normal	ALP: > 1.67 ULN and Bili: Normal	21	25	HD281
ALP: ≤ 1.5 ULN and Bili: Normal	ALP: ≤ 1.5 ULN and Bili: Normal	17	18	HC292
ALP: > 1.5 ULN and Bili: Normal	ALP: > 1.5 ULN and Bili: Normal	29	34	HD293

Abbreviations: ALP, alkaline phosphatase; Bili, bilirubin; OCA, obeticholic acid; ULN, upper limit of normal.

Base case results

Base case deterministic results

Table 7: Base-case results for the UDCA-intolerant population, using the list price of OCA

Technologies	Total			Incremental			ICER (cost/QALY)	ICER (cost/QALY)
	Costs	LYG	QALYs	Costs	LYG	QALYs	versus baseline	incremental
No treatment (placebo)	£103,233	11.30	6.61	–	–	–	–	–
OCA titration	[redacted]	16.68	13.56	[redacted]	5.38	6.95	[redacted]	[redacted]

Abbreviations: ICER, incremental cost-effectiveness ratio; LYG, life years gained; OCA, obeticholic acid; QALYs, quality-adjusted life years; UDCA, ursodeoxycholic acid.

Table 8: Base-case results for the UDCA inadequate responder population, using the list price of OCA

Technologies	Total			Incremental			ICER (cost/QALY)	ICER (cost/QALY)
	Costs	LYG	QALYs	Costs	LYG	QALYs	versus baseline	incremental
UDCA + placebo	£96,977	12.35	7.85	–	–	–	–	–
OCA titration + UDCA	[redacted]	16.78	13.68	[redacted]	4.43	5.83	[redacted]	[redacted]

Abbreviations: ICER, incremental cost-effectiveness ratio; LYG, life years gained; OCA, obeticholic acid; QALYs, quality-adjusted life years; UDCA, ursodeoxycholic acid.

Clinical outcomes from the model

Table 9: Summary of model outcomes for the UDCA-intolerant population

Outcome	OCA titration	No treatment (placebo)	Incremental
Total number of cases of Bili: abnormal and rising, or CC per 1,000 patients	[redacted]	[redacted]	[redacted]
Total number of cases of decompensated cirrhosis per 1,000 patients	[redacted]	[redacted]	[redacted]
Total liver transplants per 1,000 patients	[redacted]	[redacted]	[redacted]
Total liver-related deaths per 1,000 patients	[redacted]	[redacted]	[redacted]

Abbreviations: Bili, bilirubin; CC, compensated cirrhosis; OCA, obeticholic acid; UDCA, ursodeoxycholic acid.

Table 10: Summary of model outcomes for the UDCA inadequate responder population

Outcome	OCA titration + UDCA	UDCA + placebo	Incremental
Total number of cases of Bili: abnormal and rising, or CC per 1,000 patients	[redacted]	[redacted]	[redacted]
Total number of cases of decompensated cirrhosis per 1,000 patients	[redacted]	[redacted]	[redacted]
Total liver transplants per 1,000 patients	[redacted]	[redacted]	[redacted]
Total liver-related deaths per 1,000 patients	[redacted]	[redacted]	[redacted]

Abbreviations: Bili, bilirubin; CC, compensated cirrhosis; OCA, obeticholic acid; UDCA, ursodeoxycholic acid.

Results by health state

Table 11: Summary of QALY gain by health state for the UDCA-intolerant population

Health state	OCA titration	No treatment (placebo)	Incremental
ALP: ≤200 U/L and Bili: Normal	6.322	0.000	–6.322
ALP: >200 U/L and Bili: Normal	6.515	2.044	–4.470
Bili: Abnormal and rising, or CC	0.383	2.515	2.132
Discontinuation	0.009	0.000	–0.009
Decompensated cirrhosis	0.103	0.651	0.547
HCC	0.010	0.065	0.055
Pre transplant (end stage)	0.033	0.208	0.175
Liver transplant	0.005	0.031	0.026
Post liver transplant	0.133	0.822	0.689
Re-emergence of PBC	0.045	0.270	0.225
Total	13.558	6.606	–6.952

Abbreviations: ALP, alkaline phosphatase; Bili, bilirubin; CC, compensated cirrhosis; HCC, hepatocellular carcinoma; OCA, obeticholic acid; PBC, primary biliary cholangitis/cirrhosis; QALY, quality-adjusted life year; UDCA, ursodeoxycholic acid.

Table 12: Summary of QALY gain by health state for the UDCA inadequate responder population

Health state	OCA titration + UDCA	UDCA + placebo	Incremental
ALP: ≤200 U/L and Bili: Normal	6.322	0.000	–6.322
ALP: >200 U/L and Bili: Normal	6.693	3.867	–2.826
Bili: Abnormal and rising, or CC	0.354	2.222	1.868
Discontinuation	0.009	0.004	–0.006
Decompensated cirrhosis	0.095	0.569	0.474

Health state	OCA titration + UDCA	UDCA + placebo	Incremental
HCC	0.010	0.057	0.048
Pre transplant (end stage)	0.030	0.182	0.151
Liver transplant	0.005	0.027	0.023
Post liver transplant	0.121	0.701	0.580
Re-emergence of PBC	0.040	0.222	0.181
Total	13.680	7.852	–5.828

Abbreviations: ALP, alkaline phosphatase; Bili, bilirubin; CC, compensated cirrhosis; HCC, hepatocellular carcinoma; OCA, obeticholic acid; PBC, primary biliary cholangitis/cirrhosis; QALY, quality-adjusted life year; UDCA, ursodeoxycholic acid.

Table 13: Summary of life years gained by health state for the UDCA-intolerant population

Health state	OCA titration	No treatment (placebo)	Incremental
ALP: ≤200 U/L and Bili: Normal	7.527	0.000	7.527
ALP: >200 U/L and Bili: Normal	7.755	2.434	5.322
Bili: Abnormal and rising, or CC	0.696	4.573	–3.877
Discontinuation	0.012	0.000	0.012
Decompensated cirrhosis	0.270	1.702	–1.431
HCC	0.023	0.145	–0.122
Pre transplant (end stage)	0.086	0.543	–0.457
Liver transplant	0.009	0.055	–0.046
Post liver transplant	0.233	1.443	–1.211
Re-emergence of PBC	0.067	0.402	–0.335
Total	16.679	11.297	5.382

Abbreviations: ALP, alkaline phosphatase; Bili, bilirubin; CC, compensated cirrhosis; HCC, hepatocellular carcinoma; OCA, obeticholic acid; PBC, primary biliary cholangitis/cirrhosis; UDCA, ursodeoxycholic acid.

Table 14: Summary of life years gained by health state for the UDCA inadequate responder population

Health state	OCA titration + UDCA	UDCA + placebo	Incremental
ALP: ≤200 U/L and Bili: Normal	7.527	0.000	7.527
ALP: >200 U/L and Bili: Normal	7.967	4.604	3.364
Bili: Abnormal and rising, or CC	0.644	4.040	-3.396
Discontinuation	0.012	0.005	0.007
Decompensated cirrhosis	0.250	1.489	-1.239
HCC	0.021	0.128	-0.106
Pre transplant (end stage)	0.080	0.476	-0.396
Liver transplant	0.008	0.048	-0.040
Post liver transplant	0.212	1.231	-1.019

Health state	OCA titration + UDCA	UDCA + placebo	Incremental
Re-emergence of PBC	0.060	0.331	-0.271
Total	16.781	12.351	4.430

Abbreviations: ALP, alkaline phosphatase; Bili, bilirubin; CC, compensated cirrhosis; HCC, hepatocellular carcinoma; OCA, obeticholic acid; PBC, primary biliary cholangitis/cirrhosis; UDCA, ursodeoxycholic acid.

Table 15: Summary of costs by health state for the UDCA-intolerant population

Health state	OCA titration	No treatment (placebo)	Incremental
ALP: ≤200 U/L and Bili: Normal	[redacted]	£0.00	[redacted]
ALP: >200 U/L and Bili: Normal	[redacted]	£1,207.08	[redacted]
Bili: Abnormal and rising, or CC	[redacted]	£28,597.68	[redacted]
Discontinuation	[redacted]	£0.00	[redacted]
Decompensated cirrhosis	[redacted]	£21,284.77	[redacted]
HCC	[redacted]	£1,620.43	[redacted]
Pre transplant (end stage)	[redacted]	£9,890.90	[redacted]
Liver transplant	[redacted]	£14,310.87	[redacted]
Post liver transplant	[redacted]	£26,221.30	[redacted]
Re-emergence of PBC	[redacted]	£99.80	[redacted]
Total	[redacted]	£103,232.81	[redacted]

Abbreviations: ALP, alkaline phosphatase; Bili, bilirubin; CC, compensated cirrhosis; HCC, hepatocellular carcinoma; OCA, obeticholic acid; PBC, primary biliary cholangitis/cirrhosis; UDCA, ursodeoxycholic acid.

Table 16: Summary of costs by health state for the UDCA inadequate responder population

Health state	OCA titration + UDCA	UDCA + placebo	Incremental
ALP: ≤200 U/L and Bili: Normal	[redacted]	£0.00	[redacted]
ALP: >200 U/L and Bili: Normal	[redacted]	£5,349.00	[redacted]
Bili: Abnormal and rising, or CC	[redacted]	£27,926.48	[redacted]
Discontinuation	[redacted]	£14.48	[redacted]
Decompensated cirrhosis	[redacted]	£18,619.88	[redacted]
HCC	[redacted]	£1,422.13	[redacted]
Pre transplant (end stage)	[redacted]	£8,665.20	[redacted]
Liver transplant	[redacted]	£12,526.26	[redacted]
Post liver transplant	[redacted]	£22,371.06	[redacted]
Re-emergence of PBC	[redacted]	£82.10	[redacted]
Total	[redacted]	£96,976.58	[redacted]

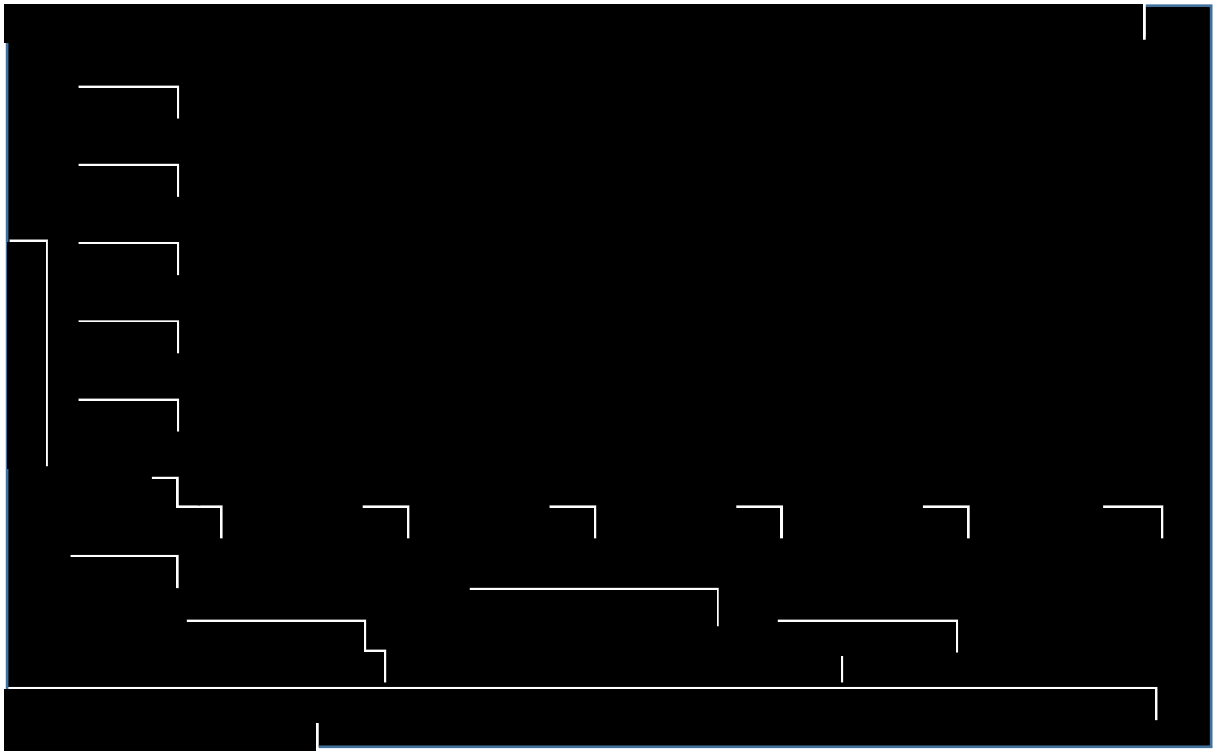
Abbreviations: ALP, alkaline phosphatase; Bili, bilirubin; CC, compensated cirrhosis; HCC, hepatocellular carcinoma; OCA, obeticholic acid; PBC, primary biliary cholangitis/cirrhosis; UDCA, ursodeoxycholic acid.

Probabilistic sensitivity analysis (PSA) results

Table 17: Incremental cost-effectiveness results of PSA for the UDCA-intolerant population, using the list price of OCA

Technologies	Total			Incremental			ICER (cost/QALY)	ICER (cost/QALY)
	Costs	LYG	QALYs	Costs	LYG	QALYs	versus baseline	incremental
PSA results								
No treatment (placebo)	£103,500	11.32	6.60	–	–	–	–	–
OCA titration	[redacted]	16.67	13.55	[redacted]	5.34	6.95	[redacted]	[redacted]
Base case deterministic results								
No treatment (placebo)	£103,233	11.30	6.61	–	–	–	–	–
OCA titration	[redacted]	16.68	13.56	[redacted]	5.38	6.95	[redacted]	[redacted]

Abbreviations: ICER, incremental cost-effectiveness ratio; LYG, life years gained; OCA, obeticholic acid; PSA, probabilistic sensitivity analysis; QALY, quality-adjusted life year; UDCA, ursodeoxycholic acid.



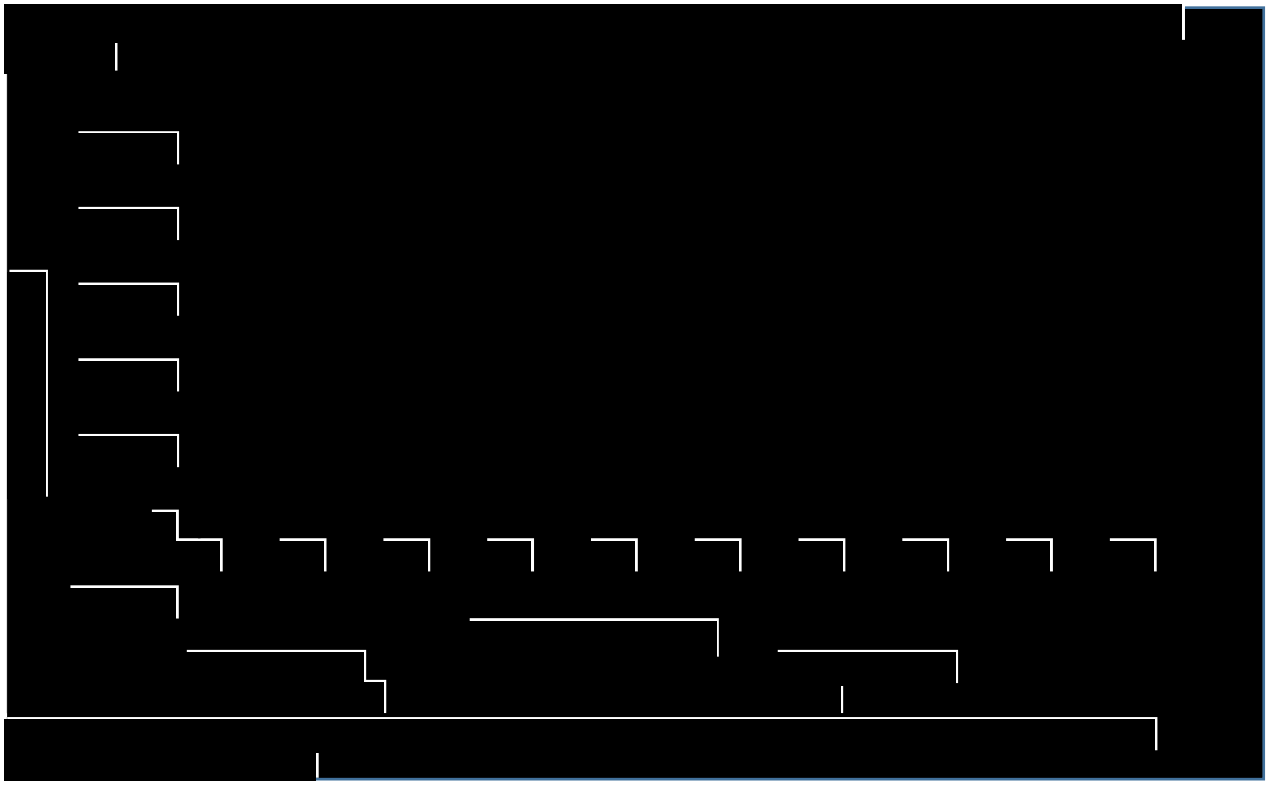
[redacted]

The probability that OCA is cost-effective vs placebo at a willingness-to-pay threshold of £30,000 is 0.0%.

Table 18: Incremental cost-effectiveness results of PSA for the UDCA inadequate responder population, using the list price of OCA

Technologies	Total			Incremental			ICER (cost/QALY)	ICER (cost/QALY)
	Costs	LYG	QALYs	Costs	LYG	QALYs	versus baseline	incremental
PSA results								
UDCA + placebo	£96,865	12.39	7.87	–	–	–	–	–
OCA titration + UDCA	[redacted]	16.77	13.66	[redacted]	4.38	5.79	[redacted]	[redacted]
Base case deterministic results								
UDCA + placebo	£96,977	12.35	7.85	–	–	–	–	–
OCA titration + UDCA	[redacted]	16.78	13.68	[redacted]	4.43	5.83	[redacted]	[redacted]

Abbreviations: ICER, incremental cost-effectiveness ratio; LYG, life years gained; OCA, obeticholic acid; PSA, probabilistic sensitivity analysis; QALY, quality-adjusted life year; UDCA, ursodeoxycholic acid.



Deterministic sensitivity analysis

[redacted]

Scenario 1: use of original HCV utility values

Table 19: Scenario 1 results for the UDCA-intolerant population, using the list price of OCA

Technologies	Total			Incremental			ICER (cost/QALY)	ICER (cost/QALY)
	Costs	LYG	QALYs	Costs	LYG	QALYs	versus baseline	Incremental
No treatment (placebo)	£103,233	11.30	6.91	–	–	–	–	–
OCA titration	[redacted]	16.68	13.61	[redacted]	5.38	6.70	[redacted]	[redacted]

Abbreviations: ICER, incremental cost-effectiveness ratio; LYG, life years gained; OCA, obeticholic acid; PSA, probabilistic sensitivity analysis; QALY, quality-adjusted life year; UDCA, ursodeoxycholic acid.

Table 20: Scenario 1 results for the UDCA inadequate responder population, using the list price of OCA

Technologies	Total			Incremental			ICER (cost/QALY)	ICER (cost/QALY)
	Costs	LYG	QALYs	Costs	LYG	QALYs	versus baseline	Incremental
UDCA + placebo	£96,977	12.35	8.11	–	–	–	–	–
OCA titration + UDCA	[redacted]	16.78	13.72	[redacted]	4.43	5.61	[redacted]	[redacted]

Abbreviations: ICER, incremental cost-effectiveness ratio; LYG, life years gained; OCA, obeticholic acid; PSA, probabilistic sensitivity analysis; QALY, quality-adjusted life year; UDCA, ursodeoxycholic acid.

Scenario 2: use of alternative transition probabilities

Table 21: Scenario 2 results for the UDCA-intolerant population, using the list price of OCA

Technologies	Total			Incremental			ICER (cost/QALY)	ICER (cost/QALY)
	Costs	LYG	QALYs	Costs	LYG	QALYs	versus baseline	incremental
No treatment (placebo)	£95,697	10.93	6.43	–	–	–	–	–
OCA titration	[redacted]	16.62	13.53	[redacted]	5.69	7.10	[redacted]	[redacted]

Abbreviations: ICER, incremental cost-effectiveness ratio; LYG, life years gained; OCA, obeticholic acid; PSA, probabilistic sensitivity analysis; QALY, quality-adjusted life year; UDCA, ursodeoxycholic acid.

Table 22: Scenario 1 results for UDCA inadequate responders, using the list price of OCA

Technologies	Total			Incremental			ICER (cost/QALY)	ICER (cost/QALY)
	Costs	LYG	QALYs	Costs	LYG	QALYs	versus baseline	incremental
UDCA + placebo	£90,516	12.04	7.70	–	–	–	–	–
OCA titration + UDCA	[redacted]	16.73	13.65	[redacted]	4.69	5.95	[redacted]	[redacted]

Abbreviations: ICER, incremental cost-effectiveness ratio; LYG, life years gained; OCA, obeticholic acid; PSA, probabilistic sensitivity analysis; QALY, quality-adjusted life year; UDCA, ursodeoxycholic acid.

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Technology appraisals

Patient access scheme submission template

October 2009

1 Introduction

The 2009 Pharmaceutical Price Regulation Scheme (PPRS) (www.dh.gov.uk/en/Healthcare/Medicinespharmacyandindustry/Pharmaceuticalpriceregulationscheme/2009PPRS) is a non-contractual scheme between the Department of Health and the Association of the British Pharmaceutical Industry. The purpose of the 2009 PPRS is to ensure that safe and cost-effective medicines are available on reasonable terms to the NHS in England and Wales. One of the features of the 2009 PPRS is to improve patients' access to medicines at prices that better reflect their value through patient access schemes.

Patient access schemes are arrangements which may be used on an exceptional basis for the acquisition of medicines for the NHS in England and Wales. Patient access schemes propose either a discount or rebate that may be linked to the number, type or response of patients, or a change in the list price of a medicine linked to the collection of new evidence (outcomes). These schemes help to improve the cost effectiveness of a medicine and therefore allow the National Institute for Health and Care Excellence (NICE) to recommend treatments which it would otherwise not have found to be cost effective. More information on the framework for patient access schemes is provided in the 2009 PPRS (www.dh.gov.uk/en/Healthcare/Medicinespharmacyandindustry/Pharmaceuticalpriceregulationscheme/2009PPRS.

Patient access schemes are proposed by a pharmaceutical company and agreed with the Department of Health, with input from the Patient Access Schemes Liaison Unit (PASLU) within the Centre for Health Technology Evaluation at NICE.

2 Instructions for manufacturers and sponsors

This document is the patient access scheme submission template for technology appraisals. If manufacturers and sponsors want the National Institute for Health and Care Excellence (NICE) to consider a patient access scheme as part of a technology appraisal, they should use this template. NICE can only consider a patient access scheme after formal referral from the Department of Health.

The template contains the information NICE requires to assess the impact of a patient access scheme on the clinical and cost effectiveness of a technology, in the context of a technology appraisal, and explains the way in which background information (evidence) should be presented. If you are unable to follow this format, you must state your reasons clearly. You should insert 'N/A' against sections that you do not consider relevant, and give a reason for this response.

Please refer to the following documents when completing the template:

- 'Guide to the methods of technology appraisal' https://www.nice.org.uk/process/pmg9/chapter/1-foreword
- 'Specification for manufacturer/sponsor submission of evidence' (http://www.nice.org.uk/aboutnice/howwework/devnicetech/singletechnologyappraisalsubmissiontemplates.jsp) and
- Pharmaceutical Price Regulation Scheme 2009 (www.dh.gov.uk/en/Healthcare/Medicinespharmacyandindustry/Pharmaceuticalpriceregulationscheme/2009PPRS).

For further details on the technology appraisal process, please see NICE's 'Guide to the single technology appraisal (STA) process' and 'Guide to the multiple technology appraisal (MTA) process' (https://www.nice.org.uk/process/pmg19/chapter/1-acknowledgements). The 'Specification for manufacturer/sponsor submission of evidence' provides details on disclosure of information and equality issues.

Make the submission as brief and informative as possible. Only mark information as confidential when absolutely necessary. Sufficient information must be publicly available for stakeholders to comment on the full content of the technology appraisal, including details of the proposed patient access scheme. Send submissions electronically to NICE in Word or a compatible format, not as a PDF file.

Appendices may be used to include additional information that is considered relevant to the submission. Do not include information in the appendices that has been requested in the template. Appendices should be clearly referenced in the main submission.

When making a patient access scheme submission, include:

- an updated version of the checklist of confidential information, if necessary an economic model with the patient access scheme incorporated, in accordance with the 'Guide to the methods of technology appraisal' (https://www.nice.org.uk/process/pmg9/chapter/1-foreword)

If you are submitting the patient access scheme at the end of the appraisal process, you should update the economic model to reflect the assumptions that the Appraisal Committee considered to be most plausible. No other changes should be made to the model.

3 Details of the patient access scheme

3.1 Please give the name of the technology and the disease area to which the patient access scheme applies.

Obeticholic acid (Ocaliva®) for the treatment of primary biliary cholangitis

3.2 Please outline the rationale for developing the patient access scheme.

The Pharmaceutical Price Regulation Scheme 2014 makes provisions for manufacturers and sponsors to submit proposals for patient access schemes to the Department of Health. These schemes involve innovative pricing agreements designed to improve cost effectiveness and facilitate patient access to specific drugs or other technologies. Intercept would like to take advantage of this flexibility to offer the best possible value to the NHS, without impacting on the international pricing reference point of the UK

3.3 Please describe the type of patient access scheme, as defined by the PPRS.

Simple discount scheme - percentage discount from the UK list price

3.4 Please provide specific details of the patient population to which the patient access scheme applies. Does the scheme apply to the whole licensed population or only to a specific subgroup (for example, type of tumour, location of tumour)? If so:

- How is the subgroup defined?
- If certain criteria have been used to select patients, why have these have been chosen?
- How are the criteria measured and why have the measures been chosen?

The patient access scheme will apply to the final NICE approved population

3.5 Please provide details of when the scheme will apply to the population specified in 3.4. Is the scheme dependent on certain

criteria, for example, degree of response, response by a certain time point, number of injections? If so:

- Why have the criteria been chosen?
- How are the criteria measured and why have the measures been chosen.

The scheme is not dependent on any other criteria

3.6 What proportion of the patient population (specified in 3.4) is expected to meet the scheme criteria (specified in 3.5)?

All patients specified in 3.4 are expected to meet the scheme criteria

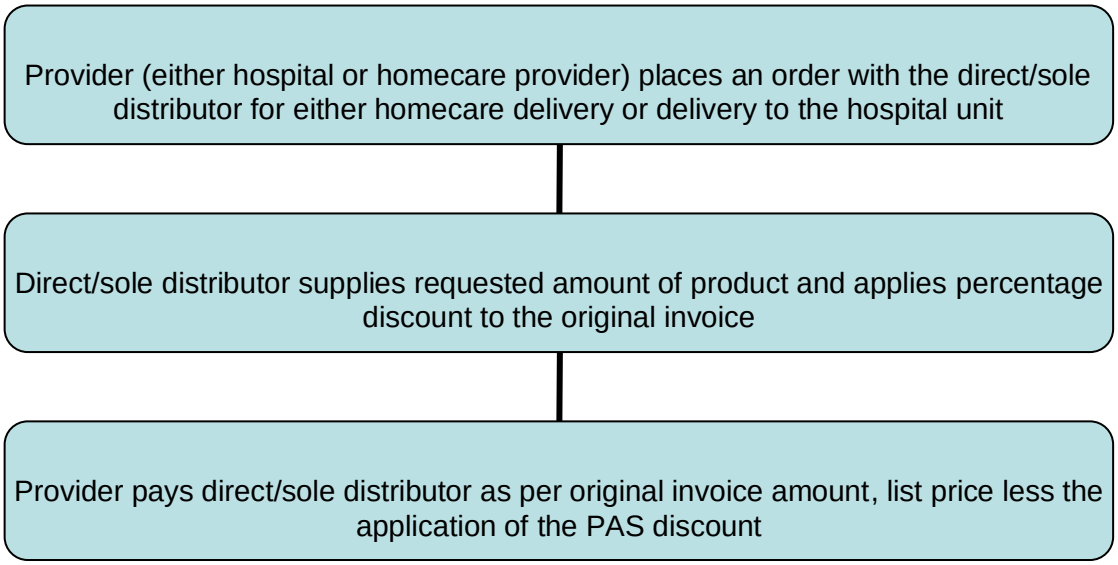
3.7 Please explain in detail the financial aspects of the scheme. How will any rebates be calculated and paid?

There will be no rebate required as the discount will be applied at the point of purchase

3.8 Please provide details of how the scheme will be administered. Please specify whether any additional information will need to be collected, explaining when this will be done and by whom.

The discount will be shown on the original invoice from either the sole distributor or the homecare company to the purchasing organisation (e.g. the prescribing hospital unit)

3.9 Please provide a flow diagram that clearly shows how the scheme will operate. Any funding flows must be clearly demonstrated.



3.10 Please provide details of the duration of the scheme.

The scheme will be in place for the life of the NICE technology appraisal guidance if the product is recommended for use

3.11 Are there any equity or equalities issues relating to the scheme, taking into account current legislation and, if applicable, any concerns identified during the course of the appraisal? If so, how have these been addressed?

No issues relating to equity or equalities have been identified

3.12 If available, please list any scheme agreement forms, patient registration forms, pharmacy claim forms/rebate forms, guides for pharmacists and physicians and patient information documents. Please include copies in the appendices.

None available at this time

3.13 In the exceptional case that you are submitting an outcome-based scheme, as defined by the PPRS, please also refer to appendix B.

4 Cost effectiveness

4.1 If the population to whom the scheme applies (as described in sections 3.4 and 3.5) has not been presented in the main manufacturer/sponsor submission of evidence for the technology appraisal (for example, the population is different as there has been a change in clinical outcomes or a new continuation rule), please (re-)submit the relevant sections from the 'Specification for manufacturer/sponsor submission of evidence' (particularly sections 5.5, 6.7 and 6.9). You should complete those sections both with and without the patient access scheme. You must also complete the rest of this template.

Not applicable. The population has been presented in the technology appraisal

4.2 If you are submitting the patient access scheme at the end of the technology appraisal process, you should update the economic model to reflect the assumptions that the Appraisal Committee considered to be most plausible. No other changes should be made to the model.

Not applicable. The PAS has not been submitted at the end of the technology appraisal process

4.3 Please provide details of how the patient access scheme has been incorporated into the economic model. If applicable, please also provide details of any changes made to the model to reflect the assumptions that the Appraisal Committee considered most plausible.

In the model the PAS has been implemented as a straight discount off the list price

4.4 Please provide the clinical effectiveness data resulting from the evidence synthesis and used in the economic model which includes the patient access scheme.

Not applicable. The PAS has been implemented as a straight discount off the list price

4.5 Please list any costs associated with the implementation and operation of the patient access scheme (for example, additional pharmacy time for stock management or rebate calculations). A suggested format is presented in table 1. Please give the reference source of these costs. Please refer to section 6.5 of the 'Specification for manufacturer/sponsor submission of evidence'.

As the PAS is implemented as a straight discount off the list price, there are no additional costs associated with the implementation and operation of the PAS.

4.6 Please provide details of any additional treatment-related costs incurred by implementing the patient access scheme. A suggested format is presented in table 2. The costs should be provided for the intervention both with and without the patient access scheme. Please give the reference source of these costs.

Not applicable. The PAS has been implemented as a straight discount off the list price. There are no additional treatment-related costs incurred with or without the PAS.

Summary results

Base-case analysis

4.7 Please present in separate tables the cost-effectiveness results as follows.[1]

- the results for the intervention without the patient access scheme
- the results for the intervention with the patient access scheme.

A suggested format is shown below (table 3).

Table 1: Base case cost-effectiveness results without PAS

Variable	UDCA intolerant population		UDCA inadequate responder population	
	No treatment (placebo)	OCA titration	Placebo + UDCA	OCA titration + UDCA
Total costs	£103,233	[redacted]	£96,977	[redacted]
Difference in total costs	–	[redacted]	–	[redacted]
LYG	11.30	16.65	12.35	16.75
LYG difference	–	5.35	–	4.40
QALYs	6.61	13.52	7.85	13.64
QALY difference	–	6.91	–	5.79
ICER (cost/QALY)	–	[redacted]	–	[redacted]

Abbreviations: ICER, incremental cost-effectiveness ratio; LYG, life-year gained; OCA, obeticholic acid; PAS, patient access scheme; QALY, quality-adjusted life-year; UDCA, ursodeoxycholic acid.

[1] For outcome-based schemes, please see section 5.2.8 in appendix B.

Table 2: Base case cost-effectiveness results with PAS

Variable	UDCA intolerant population		UDCA inadequate responder population	
	No treatment (placebo)	OCA titration	Placebo + UDCA	OCA titration + UDCA
Total costs	£103,233	£251,443	£96,977	£261,527
Difference in total costs	–	£148,210	–	£164,551
LYG	11.30	16.65	12.35	16.75
LYG difference	–	5.35	–	4.40
QALYs	6.61	13.52	7.85	13.64
QALY difference	–	6.91	–	5.79
ICER (cost/QALY)	–	£21,438	–	£28,425

Abbreviations: ICER, incremental cost-effectiveness ratio; LYG, life-year gained; OCA, obeticholic acid; PAS, patient access scheme; QALY, quality-adjusted life-year; UDCA, ursodeoxycholic acid.

4.8 Please present in separate tables the incremental results as follows. [2]

- the results for the intervention without the patient access scheme
- the results for the intervention with the patient access scheme.

List the interventions and comparator(s) from least to most expensive. Present the incremental cost-effectiveness ratios (ICERs) in comparison with baseline (usually standard care), and the incremental analysis ranking technologies in terms of dominance and extended dominance. A suggested format is presented in table 4.

[2] For outcome-based schemes, please see section 5.2.9 in appendix B.

Table 3: Base case incremental results for the UDCA intolerant population, without PAS

Technologies	Total			Incremental			ICER versus baseline (cost/QALY)	ICER incremental (cost/QALY)
	Costs	LYG	QALYs	Costs	LYG	QALYs		
No treatment (placebo)	£103,233	11.30	6.61	–	–	–	–	–
OCA titration	[redacted]	16.65	13.52	[redacted]	5.35	6.91	[redacted]	[redacted]

Abbreviations: ICER, incremental cost-effectiveness ratio; LYG, life-year gained; OCA, obeticholic acid; PAS, patient access scheme; QALY, quality-adjusted life-year; UDCA, ursodeoxycholic acid.

Table 4: Base case incremental results for the UDCA intolerant population, with PAS

Technologies	Total			Incremental			ICER versus baseline (cost/QALY)	ICER incremental (cost/QALY)
	Costs	LYG	QALYs	Costs	LYG	QALYs		
No treatment (placebo)	£103,233	11.30	6.61	–	–	–	–	–
OCA titration	£251,443	16.65	13.52	£148,210	5.35	6.91	£21,438	£21,438

Abbreviations: ICER, incremental cost-effectiveness ratio; LYG, life-year gained; OCA, obeticholic acid; PAS, patient access scheme; QALY, quality-adjusted life-year; UDCA, ursodeoxycholic acid.

Table 5: Base case incremental results for the UDCA inadequate responder population, without PAS

Technologies	Total			Incremental			ICER versus baseline (cost/QALY)	ICER incremental (cost/QALY)
	Costs	LYG	QALYs	Costs	LYG	QALYs		
Placebo + UDCA	£96,977	12.35	7.85					
OCA titration + UDCA	[redacted]	16.75	13.64	[redacted]	4.40	5.79	[redacted]	[redacted]

Abbreviations: ICER, incremental cost-effectiveness ratio; LYG, life-year gained; OCA, obeticholic acid; PAS, patient access scheme; QALY, quality-adjusted life-year; UDCA, ursodeoxycholic acid

Table 4: Base case incremental results for the UDCA inadequate responder population, with PAS

Technologies	Total			Incremental			ICER versus baseline (cost/QALY)	ICER incremental (cost/QALY)
	Costs	LYG	QALYs	Costs	LYG	QALYs		
Placebo + UDCA	£96,977	12.35	7.85	–	–	–	–	–
OCA titration + UDCA	£261,527	16.75	13.64	£164,551	4.40	5.79	£28,425	£28,425

Abbreviations: ICER, incremental cost-effectiveness ratio LYG, life-year gained; OCA, obeticholic acid; PAS, patient access scheme; QALY, quality-adjusted life-year; UDCA, ursodeoxycholic acid.

Sensitivity analyses

4.9 Please present deterministic sensitivity analysis results as described for the main manufacturer/sponsor submission of

evidence for the technology appraisal. Consider using tornado diagrams.

The generic inputs that are varied in the deterministic sensitivity analysis (DSA) are the discontinuation probabilities, probabilities of having an adverse event, utility weights, transition probabilities, discounting, and the probability of death for the general population.

The model also allows the user to run scenario analyses by assuming that all patients enter the model in each of the four PBC-specific health states at a time.

The results of the DSA are presented below in Figure 1, Figure 2, Figure 3, and Figure 4.

Figure 1: Tornado diagram for OCA titration versus no treatment (placebo) for the UDCA intolerant population, without PAS

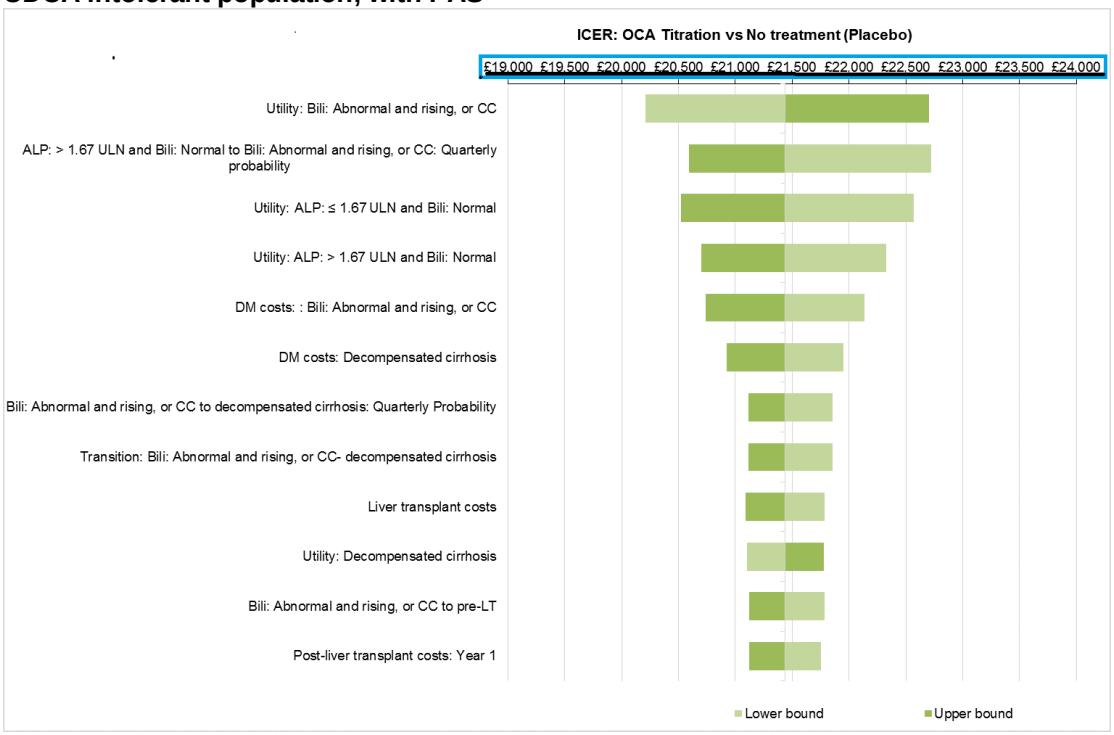
Abbreviations: ALP, alkaline phosphatase; bili, bilirubin; CC, compensated cirrhosis; DM, disease management; HCC, hepatocellular carcinoma; ICER, incremental cost-effectiveness ratio; LT, liver transplant; OCA, obeticholic acid; PAS, patient access scheme; UDCA, ursodeoxycholic acid; ULN, upper limit of normal.

Figure 2: Tornado diagram for UDCA + OCA titration versus UDCA + placebo for the UDCA inadequate responder population, without PAS

[redacted]

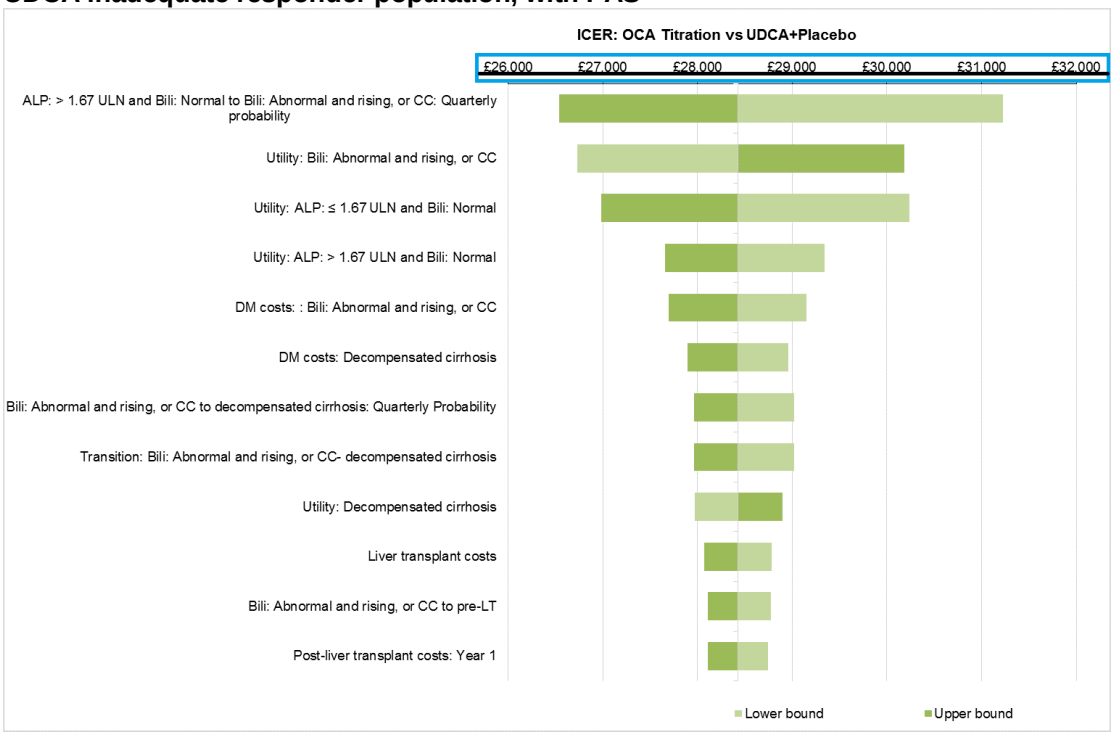
Abbreviations: ALP, alkaline phosphatase; bili, bilirubin; CC, compensated cirrhosis; DM, disease management; HCC, hepatocellular carcinoma; ICER, incremental cost-effectiveness ratio; LT, liver transplant; OCA, obeticholic acid; PAS, patient access scheme; UDCA, ursodeoxycholic acid; ULN, upper limit of normal.

Figure 3: Tornado diagram for OCA titration versus no treatment (placebo) for the UDCA intolerant population, with PAS



Abbreviations: ALP, alkaline phosphatase; bili, bilirubin; CC, compensated cirrhosis; DM, disease management; ICER, incremental cost-effectiveness ratio; LT, liver transplant; OCA, obeticholic acid; PAS, patient access scheme; UDCA, ursodeoxycholic acid; ULN, upper limit of normal;.

Figure 4: Tornado diagram for UDCA + OCA titration versus UDCA + placebo for the UDCA inadequate responder population, with PAS



Abbreviations: ALP, alkaline phosphatase; bili, bilirubin; CC, compensated cirrhosis; DM, disease management; ICER, incremental cost-effectiveness ratio; LT, liver transplant; OCA, obeticholic acid; PAS, patient access scheme; UDCA, ursodeoxycholic acid; ULN, upper limit of normal.

4.10 Please present any probabilistic sensitivity analysis results, and include scatter plots and cost-effectiveness acceptability curves.

Patient characteristics (i.e. weight and baseline health state distribution) were included in the PSA alongside all other generic inputs (transition probabilities, clinical inputs and quality of life). Data including confidence intervals and distributions were sourced from the literature. Where the variance was unknown, the lower and upper confidence intervals were estimated assuming a 20% variability around the mean. The PSA was performed by running 1,000 Monte Carlo simulations.

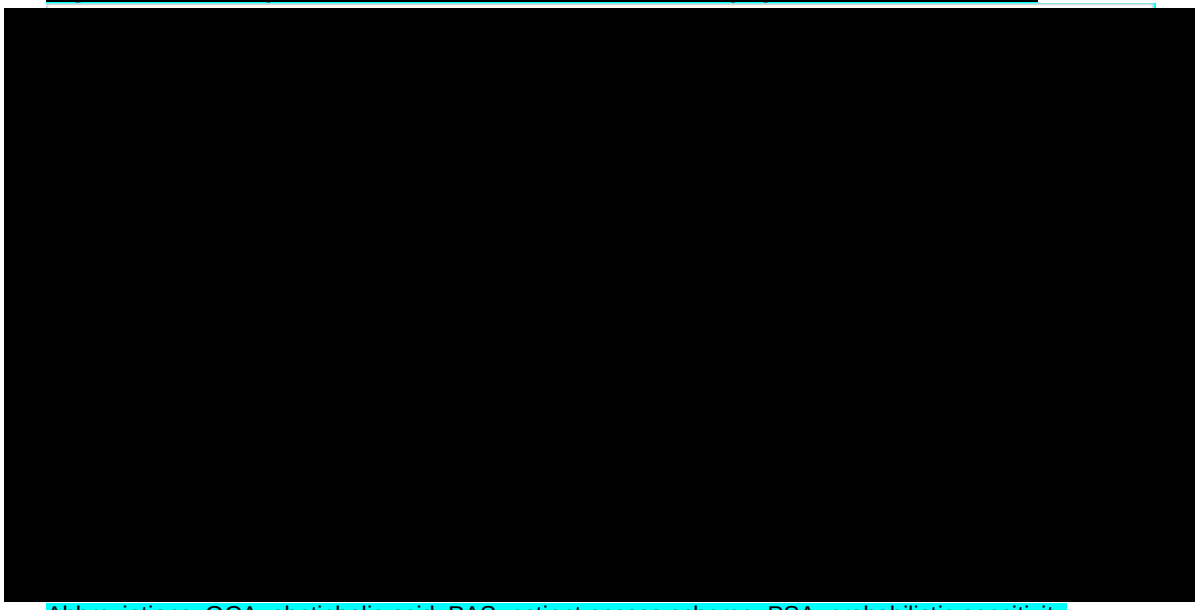
The results without the implementation of the PAS are presented below in Table 5 and Table 6. The results with the implementation of the PAS are presented in Table 7 and Table 8.

Table 5: Incremental cost-effectiveness results of PSA for the UDCA intolerant population, without PAS

Technologies	Total			Incremental			ICER versus baseline (cost/QALY)	ICER incremental (cost/QALY)
	Costs	LYG	QALYs	Costs	LYG	QALYs		
PSA results								
No treatment (placebo)	£103,439	11.33	6.77	-	-	-	-	-
OCA titration	[redacted]	16.64	13.52	[redacted]	5.31	6.75	[redacted]	[redacted]
Base case deterministic results								
No treatment (placebo)	£103,233	11.30	6.61	-	-	-	-	-
OCA titration	[redacted]	16.65	13.52	[redacted]	5.35	6.91	[redacted]	[redacted]

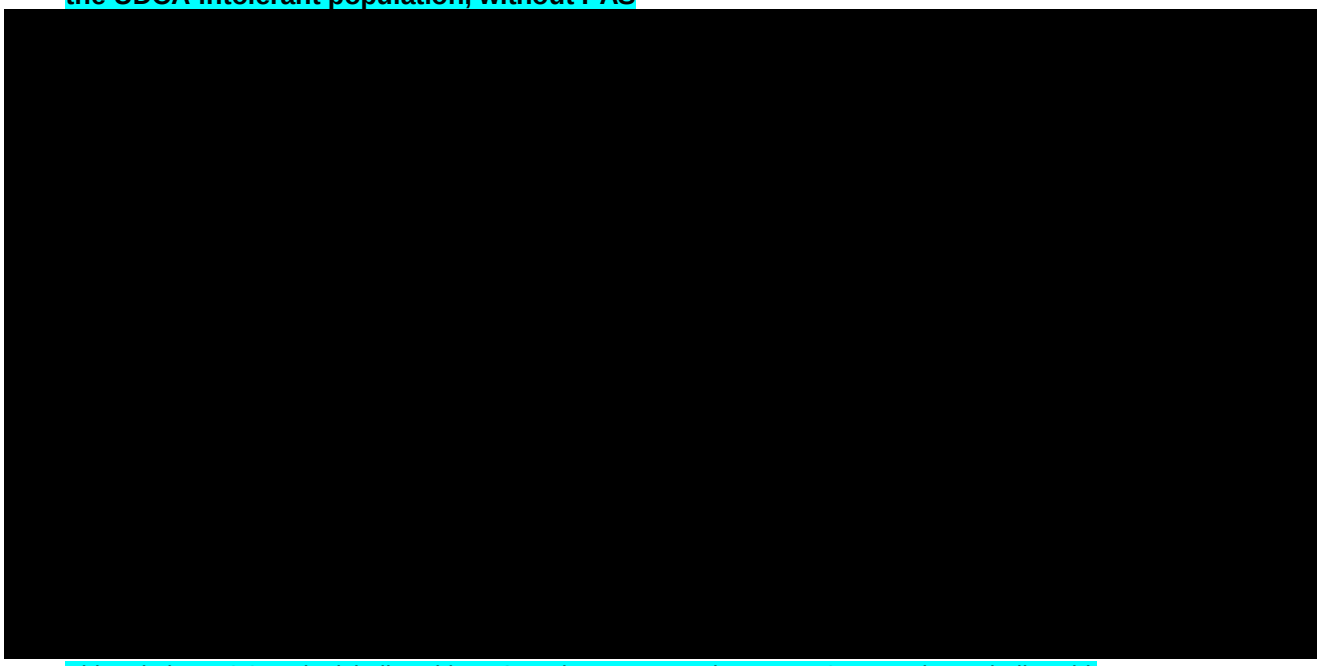
Abbreviations: ICER, incremental cost-effectiveness ratio; LYG, life-year gained; OCA, obeticholic acid; PAS, patient access scheme; PSA, probabilistic sensitivity analysis; QALY, quality-adjusted life-year; UDCA, ursodeoxycholic acid.

Figure 5: Scatter plot for PSA for the UDCA intolerant population, without PAS



Abbreviations: OCA, obeticholic acid; PAS, patient access scheme; PSA, probabilistic sensitivity analysis; QALY, quality-adjusted life year; UDCA, ursodeoxycholic acid.

Figure 6: Cost-effectiveness acceptability curve for OCA titration versus placebo for the UDCA-intolerant population, without PAS



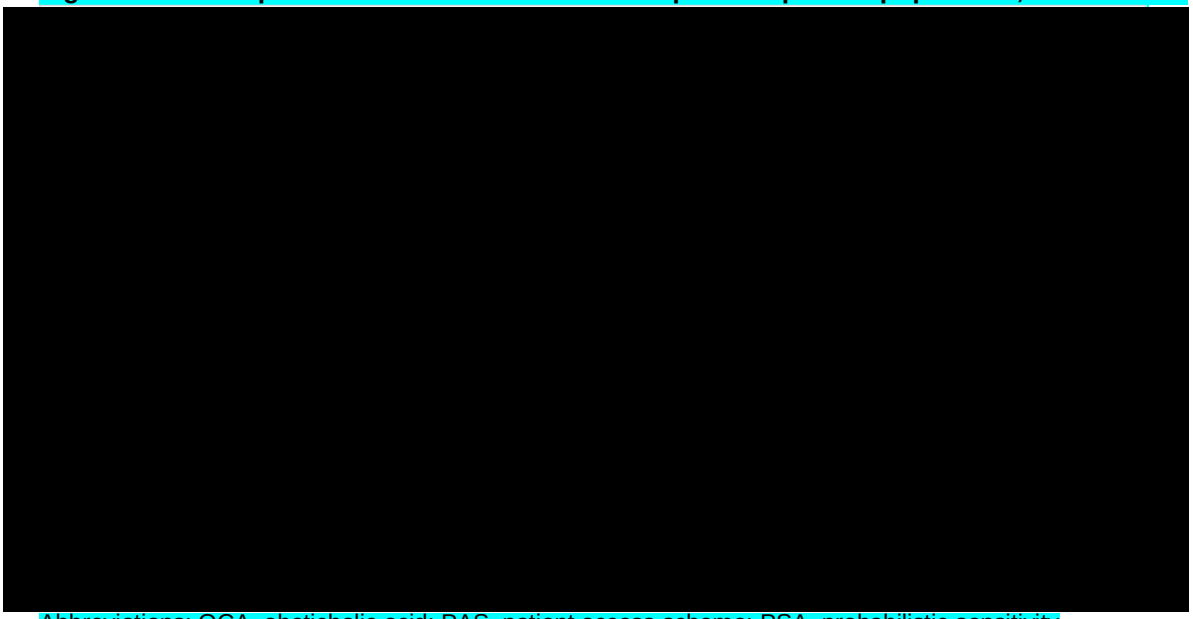
Abbreviations: OCA, obeticholic acid; PAS, patient access scheme; UDCA, ursodeoxycholic acid.

Table 6: Incremental cost-effectiveness results of PSA for the UDCA inadequate responder population, without PAS

Technologies	Total			Incremental			ICER versus baseline (cost/QALY)	ICER incremental (cost/QALY)
	Costs	LYG	QALYs	Costs	LYG	QALYs		
PSA results								
UDCA + placebo	£97,044	12.38	7.88	-	-	-	-	-
OCA + UDCA titration	[redacted]	16.75	13.65	[redacted]	4.37	5.77	[redacted]	[redacted]
Base case deterministic results								
UDCA + placebo	£96,977	12.35	7.85	-	-	-	-	-
OCA + UDCA titration	[redacted]	16.75	13.64	[redacted]	4.40	5.79	[redacted]	[redacted]

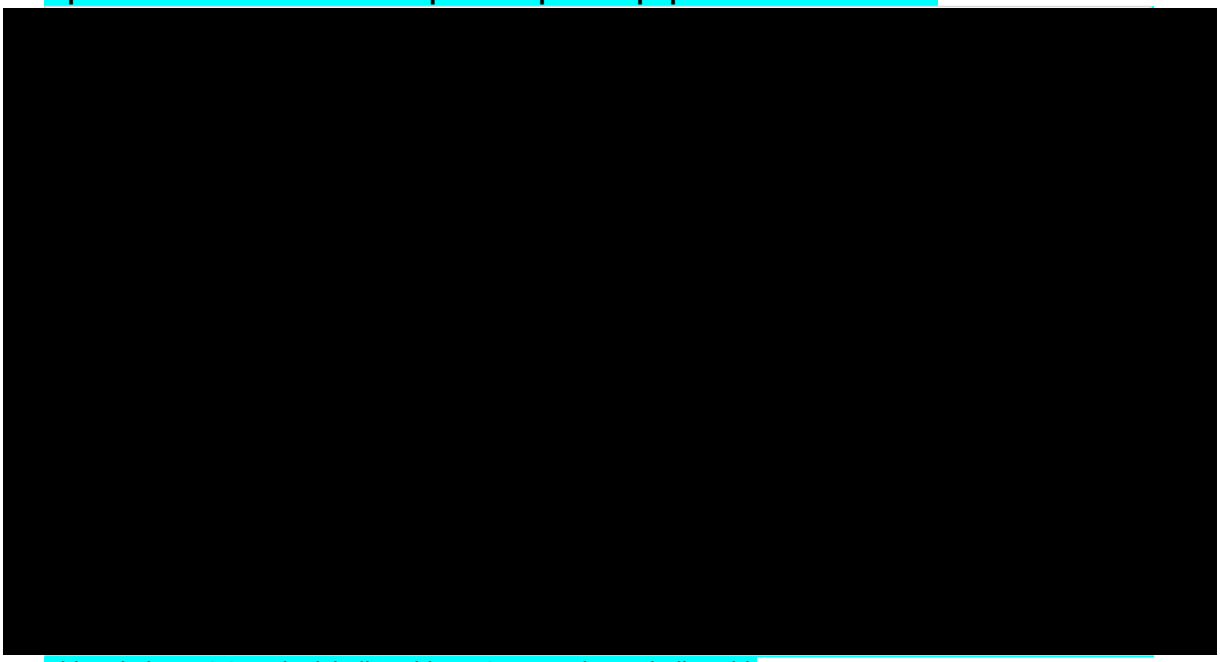
Abbreviations: ICER, incremental cost-effectiveness ratio; LYG, life-year gained; OCA, obeticholic acid; PAS, patient access scheme; PSA, probabilistic sensitivity analysis; QALY, quality-adjusted life-year; UDCA ursodeoxycholic acid.

Figure 7: Scatter plot for PSA for the UDCA inadequate responder population, without PAS



Abbreviations: OCA, obeticholic acid; PAS, patient access scheme; PSA, probabilistic sensitivity analysis; QALY, quality-adjusted life year; UDCA, ursodeoxycholic acid.

Figure 8: Cost-effectiveness acceptability curve for OCA + UDCA titration versus UDCA + placebo for the UDCA inadequate responder population without PAS



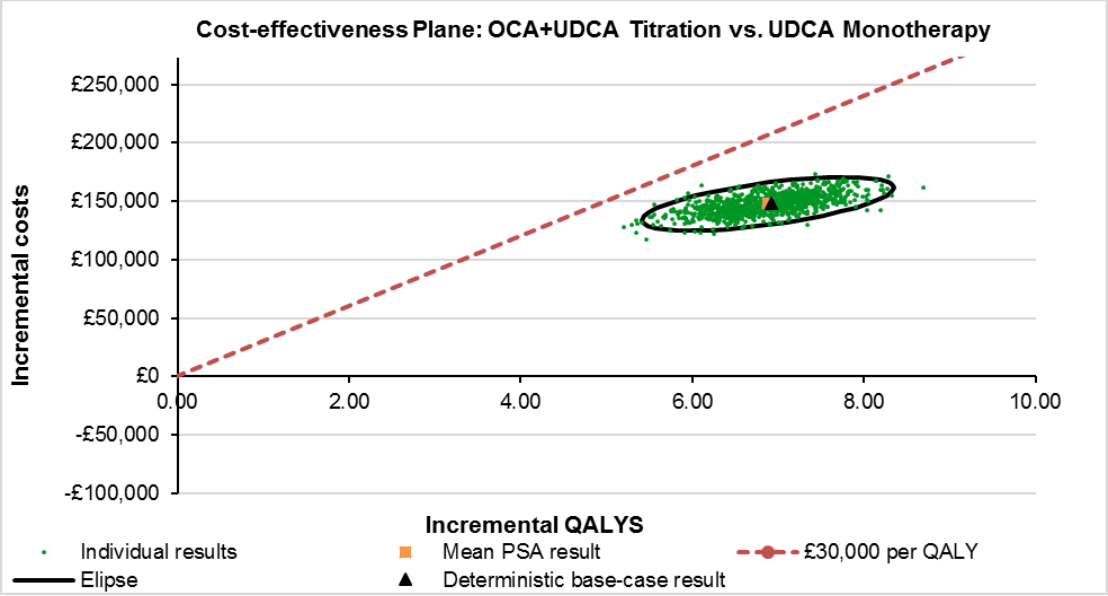
Abbreviations: OCA, obeticholic acid; UDCA, ursodeoxycholic acid.

Table 7: Incremental cost effectiveness results of PSA for the UDCA intolerant population, with PAS

Technologies	Total			Incremental			ICER versus baseline (cost/QALY)	ICER incremental (cost/QALY)
	Costs	LYG	QALYs	Costs	LYG	QALYs		
PSA results								
No treatment (placebo)	£103,607	11.32	6.59	–	–	–	–	–
OCA titration	£251,856	16.66	13.54	£148,249	5.34	6.95	£21,339	£21,339
Base case deterministic results								
No treatment (placebo)	£103,233	11.30	6.61	–	–	–	–	–
OCA titration	£251,443	16.65	13.52	£148,210	5.35	6.91	£21,438	£21,438

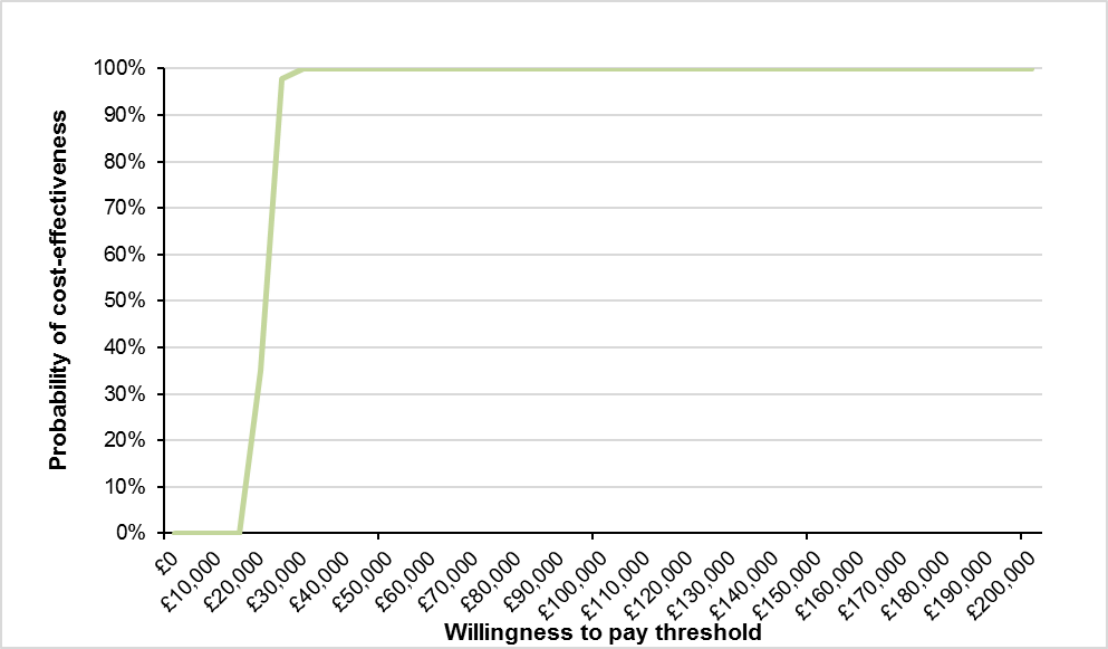
Abbreviations: ICER, incremental cost-effectiveness ratio; LYG, life-year gained; OCA, obeticholic acid; PAS, patient access scheme; PSA, probabilistic sensitivity analysis; QALY, quality-adjusted life-year; UDCA, ursodeoxycholic acid.

Figure 9: Scatter plot for PSA for the UDCA intolerant population, with PAS



Abbreviations: OCA, obeticholic acid; PAS, patient access scheme; PSA, probabilistic sensitivity analysis; QALY, quality-adjusted life year; UDCA, ursodeoxycholic acid.

Figure 10: Cost-effectiveness acceptability curve for OCA titration versus placebo for the UDCA intolerant population, with PAS



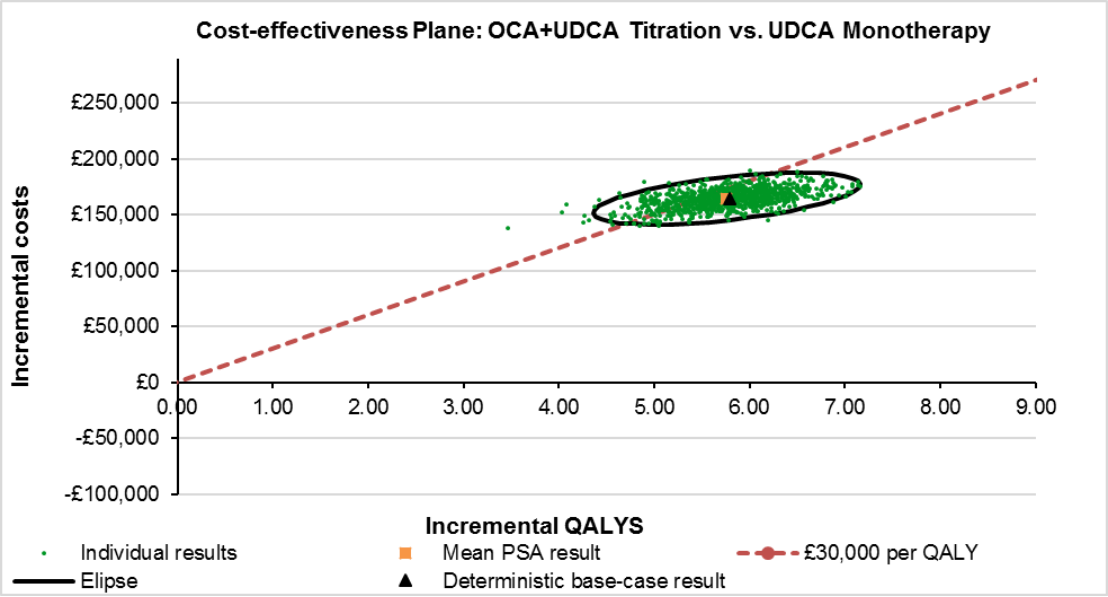
Abbreviations: OCA, obeticholic acid; PAS, patient access scheme; UDCA, ursodeoxycholic acid.

Table 8: Incremental cost effectiveness results of PSA for the UDCA inadequate responder population, with PAS

Technologies	Total			Incremental			ICER versus baseline (cost/QALY)	ICER incremental (cost/QALY)
	Costs	LYG	QALYs	Costs	LYG	QALYs		
PSA results								
Placebo + UDCA	£96,840	12.38	7.87	–	–	–	–	–
OCA titration + UDCA	£261,193	16.74	13.63	£164,353	4.36	5.76	£28,526	£28,526
Base case deterministic results								
Placebo + UDCA	£96,977	12.35	7.85	–	–	–	–	–
OCA titration + UDCA	£261,527	16.75	13.64	£164,551	4.40	5.79	£28,425	£28,425

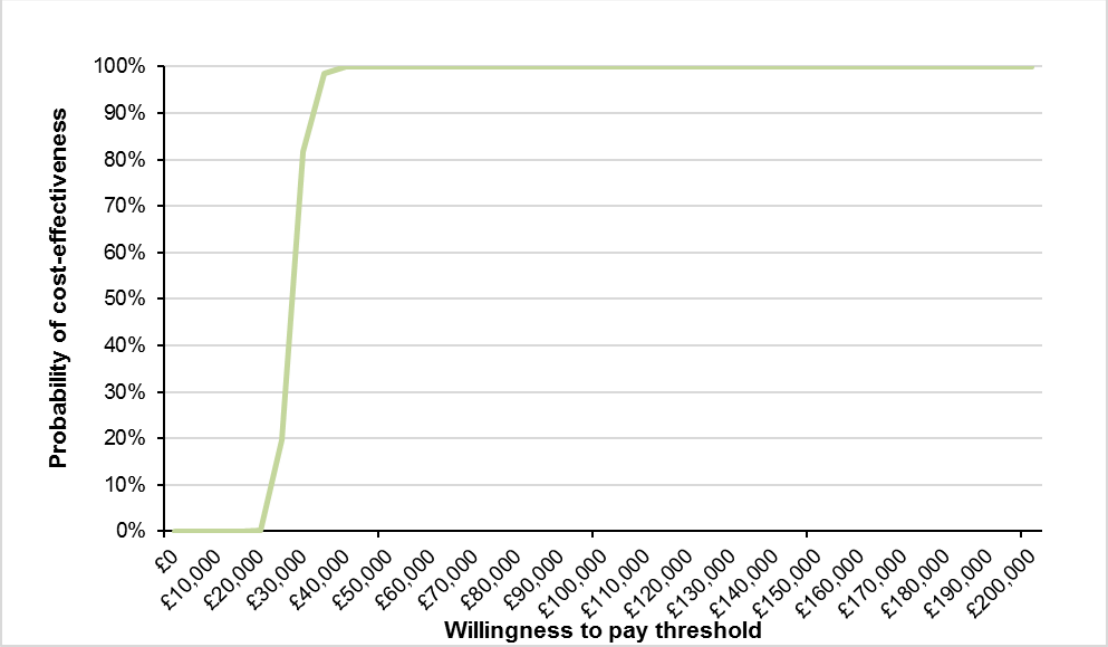
Abbreviations: ICER, incremental cost-effectiveness ratio; LYG, life-year gained; OCA, obeticholic acid; PAS, patient access scheme; PSA, probabilistic sensitivity analysis; QALY, quality-adjusted life-year; UDCA, ursodeoxycholic acid.

Figure 11: Scatter plot for PSA for the UDCA inadequate responder population, with PAS



Abbreviations: OCA, obeticholic acid; PAS, patient access scheme; PSA, probabilistic sensitivity analysis; UDCA, QALY, quality-adjusted life year; ursodeoxycholic acid.

Figure 12: Cost-effectiveness acceptability curve for OCA + UDCA titration versus UDCA + placebo for the UDCA inadequate responder population, with PAS



Abbreviations: OCA, obeticholic acid; PAS, patient access scheme; UDCA, ursodeoxycholic acid.

4.11 Please present scenario analysis results as described for the main manufacturer/sponsor submission of evidence for the technology appraisal.

Scenario 2: use of original HCV utility values

A scenario analysis was performed where all utility values that had been decremented from their previously reported values were set to their original values, which were hepatitis B/hepatitis C-specific). The values changed are shown in Table 9. The non-PAS results are presented in Table 10 and Table 11. The results with the implementation of the PAS are presented in Table 12 and Table 13.

Table 9: Parameters changed for scenario 2

State	Base case utility value	Scenario utility value	Justification
Decompensated cirrhosis	0.38	0.45	Previously reported value for decompensated cirrhosis (TA330) (143)
Pre-transplant: utility at listing	0.38	0.45	Previously reported value for decompensated cirrhosis (TA330) (143)
Pre-transplant: 3 months after listing	0.38	0.45	Previously reported value for decompensated cirrhosis (TA330) (143)
Pre-transplant: 6 months after listing	0.38	0.45	Previously reported value for decompensated cirrhosis (TA330) (143)
Liver transplant: 3 months post-transplant	0.57	0.67	Previously reported value for decompensated cirrhosis (TA330) (143)
Liver transplant: 6 months post-transplant	0.57	0.67	Previously reported value for decompensated cirrhosis (TA330) (143)
Liver transplant: 12 months post-transplant	0.57	0.67	Previously reported value for decompensated cirrhosis (TA330) (143)
Liver transplant: 24 months post-transplant	0.57	0.67	Previously reported value for decompensated cirrhosis (TA330) (143)

Table 10: Scenario 2 results for the UDCA intolerant population, without PAS

Technologies	Total			Incremental			ICER versus baseline (cost/QALY)	ICER incremental (cost/QALY)
	Costs	LYG	QALYs	Costs	LYG	QALYs		
No treatment (placebo)	£103,233	11.30	6.64	-	-	-	-	-
OCA titration	[redacted]	16.65	13.52	[redacted]	5.35	6.88	[redacted]	[redacted]

Abbreviations: ICER, incremental cost-effectiveness ratio; LYG, life-year gained; OCA, obeticholic acid; PAS, patient access scheme; QALY, quality-adjusted life-year; UDCA, ursodeoxycholic acid.

Table 11: Scenario 2 results for the UDCA inadequate responder population, without PAS

Technologies	Total			Incremental			ICER versus baseline (cost/QALY)	ICER incremental (cost/QALY)
	Costs	LYG	QALYs	Costs	LYG	QALYs		
Placebo + UDCA	£96,977	12.35	8.11	-	-	-	-	-
OCA titration + UDCA	[redacted]	16.75	13.64	[redacted]	4.40	5.75	[redacted]	[redacted]

Abbreviations: ICER, incremental cost-effectiveness ratio; LYG, life-year gained; OCA, obeticholic acid; PAS, patient access scheme; QALY, quality-adjusted life-year; UDCA, ursodeoxycholic acid.

Table 12: Scenario 2 results for the UDCA intolerant population, with PAS

Technologies	Total			Incremental			ICER versus baseline (cost/QALY)	ICER incremental (cost/QALY)
	Costs	LYG	QALYs	Costs	LYG	QALYs		
No treatment (placebo)	£103,233	11.30	6.91	–	–	–	–	–
OCA titration	£251,443	16.65	13.57	£148,210	5.35	6.66	£22,250	£22,250

Abbreviations: ICER, incremental cost-effectiveness ratio; LYG, life-year gained; OCA, obeticholic acid; PAS, patient access scheme; QALY, quality-adjusted life-year; UDCA, ursodeoxycholic acid.

Table 13: Scenario 2 results for the UDCA inadequate responder population, with PAS

Technologies	Total			Incremental			ICER versus baseline (cost/QALY)	ICER incremental (cost/QALY)
	Costs	LYG	QALYs	Costs	LYG	QALYs		
Placebo + UDCA	£96,977	12.35	8.11	–	–	–	–	–
OCA titration + UDCA	£261,527	16.75	13.69	£164,551	4.40	5.57	£29,524	£29,524

Abbreviations: ICER, incremental cost-effectiveness ratio; LYG, life-year gained; OCA, obeticholic acid; PAS, patient access scheme; QALY, quality-adjusted life-year; UDCA, ursodeoxycholic acid.

Scenario 3: use of alternative transition probabilities

This scenario utilises alternative transition probabilities for pre-liver transplant to liver transplant, and pre-liver transplant to death, gathered from an ad-hoc analysis of PBC-specific data from the Organ Procurement and Transplantation Network (OPTN) (data on file). The parameters changed are shown in Table 14. Results without the PAS are shown in Table 15 and Table

16. Results with the implementation of the PAS are shown in Table 17 and Table 18.

Table 14: Parameters changed for scenario 3

Transition probability	Base case TP	Scenario TP	Justification
Pre-LT to LT	0.35	0.44	Based on ad-hoc data analysis of OPTN PBC data
Pre-LT to death	0.09	0.21	Based on ad-hoc data analysis of OPTN PBC data

Abbreviations: LT, liver transplant; OPTN, Organ Procurement and Transplantation Network; PBC, primary biliary cholangitis/cirrhosis; TP, transition probability.

Table 15: 3 results for the UDCA intolerant population, without PAS

Technologies	Total			Incremental			ICER versus baseline (cost/QALY)	ICER incremental (cost/QALY)
	Costs	LYG	QALYs	Costs	LYG	QALYs		
No treatment (Placebo)	£95,697	10.93	6.56	-	-	-	-	-
OCA titration	[redacted]	16.59	13.51	[redacted]	5.66	6.95	[redacted]	[redacted]

Abbreviations: ICER, incremental cost-effectiveness ratio; LYG, life-year gained; OCA, obeticholic acid; PAS, patient access scheme; QALY, quality-adjusted life-year; UDCA, ursodeoxycholic acid.

Table 16: Scenario 3 results for the UDCA inadequate responder population, without PAS

Technologies	Total			Incremental			ICER versus baseline (cost/QALY)	ICER incremental (cost/QALY)
	Costs	LYG	QALYs	Costs	LYG	QALYs		
UDCA + Placebo	£90,516	12.04	7.82	-	-	-	-	-
OCA + UDCA titration	[redacted]	16.69	13.63	[redacted]	4.66	5.82	[redacted]	[redacted]

Abbreviations: ICER, incremental cost-effectiveness ratio; LYG, life-year gained; OCA, obeticholic acid; PAS, patient access scheme; QALY, quality-adjusted life-year; UDCA, ursodeoxycholic acid.

Table 17: Scenario 3 results for the UDCA intolerant population, with PAS

Technologies	Total			Incremental			ICER versus baseline (cost/QALY)	ICER incremental (cost/QALY)
	Costs	LYG	QALYs	Costs	LYG	QALYs		
No treatment (placebo)	£95,697	10.93	6.43	–	–	–	–	–
OCA titration	£250,197	16.59	13.49	£154,499	5.66	7.06	£21,874	£21,874

Abbreviations: ICER, incremental cost-effectiveness ratio; LYG, life-year gained; OCA, obeticholic acid; PAS, patient access scheme; QALY, quality-adjusted life-year; UDCA, ursodeoxycholic acid.

Table 18: Scenario 3 results for the UDCA inadequate responder population, with PAS

Technologies	Total			Incremental			ICER versus baseline (cost/QALY)	ICER incremental (cost/QALY)
	Costs (£)	LYG	QALYs	Costs (£)	LYG	QALYs		
Placebo + UDCA	£90,516	12.04	7.70	–	–	–	–	–
OCA titration + UDCA	£260,386	16.69	13.61	£169,870	4.66	5.91	£28,724	£28,724

Abbreviations: ICER, incremental cost-effectiveness ratio; LYG, life-year gained; OCA, obeticholic acid; PAS, patient access scheme; QALY, quality-adjusted life-year; UDCA, ursodeoxycholic acid.

4.12 If any of the criteria on which the patient access scheme depends are clinical variable (for example, choice of response measure, level of response, duration of treatment), sensitivity analyses around the individual criteria should be provided, so that the Appraisal Committee can determine which criteria are the most appropriate to use.

The PAS functions as a direct discount, so this section is not applicable.

Impact of patient access scheme on ICERs

4.13 For financially based schemes, please present the results showing the impact of the patient access scheme on the ICERs for the base-case and any scenario analyses. A suggested format is shown below (see table 5). If you are submitting the patient access scheme at the end of the appraisal process, you must include the scenario with the assumptions that the Appraisal Committee considered to be most plausible.

Table 19: Results showing the impact of PAS on ICERs

	UDCA intolerant population (OCA titration vs placebo)		UDCA inadequate responder population (UDCA + OCA titration vs UDCA + placebo)	
	Without PAS	With PAS	Without PAS	With PAS
Scenario 1 (base case)	[redacted]	£21,438	[redacted]	£28,425
Scenario 2 (alternative utilities)	[redacted]	£22,250	[redacted]	£29,524
Scenario 3 (alternative TPs)	[redacted]	£21,874	[redacted]	£28,724

Abbreviations: ICER, incremental cost-effectiveness ratio; OCA, obeticholic acid; PAS, patient access scheme, TPs, transition probabilities; UDCA, ursodeoxycholic acid.

5 Appendices

5.1 Appendix A: Additional documents

5.1.1 If available, please include copies of patient access scheme agreement forms, patient registration forms, pharmacy claim forms/rebate forms, guides for pharmacists and physicians, patient information documents.

Response

5.2 Appendix B: Details of outcome-based schemes

5.2.1 If you are submitting a proven value: price increase scheme, as defined in the PPRS, please provide the following information:

- the current price of the intervention
- the proposed higher price of the intervention, which will be supported by the collection of new evidence
- a suggested date for when NICE should consider the additional evidence.

Response

5.2.2 If you are submitting an expected value: rebate scheme, as defined in the PPRS, please provide the following details:

- the current price of the intervention (the price that will be supported by the collection of new evidence)
- the planned lower price of the intervention in the event that the additional evidence does not support the current price
- a suggested date for when NICE should consider the additional evidence.

Response

5.2.3 If you are submitting a risk-sharing scheme, as defined in the PPRS, please provide the following details:

- the current price of the intervention (the price that will be supported by the collection of new evidence)
- the proposed relationship between future price changes and the evidence to be collected.

Response

5.2.4 For outcome-based schemes, as defined in the PPRS, please provide the full details of the new information (evidence) planned to be collected, who will collect it and who will carry the cost associated with this planned data collection. Details of the new information (evidence) may include:

- design of the new study
- patient population of the new study
- outcomes of the new study
- expected duration of data collection
- planned statistical analysis, definition of study groups and reporting (including uncertainty)
- expected results of the new study
- planned evidence synthesis/pooling of data (if applicable)
- expected results of the evidence synthesis/pooling of data (if applicable).

Response

5.2.5 If you are submitting a risk-sharing scheme, please specify the period between the time points when the additional evidence will be considered.

Response

5.2.6 Please provide the clinical effectiveness data resulting from the evidence synthesis and used in the economic modelling of the

patient access scheme at the different time points when the additional evidence is to be considered.

Response

5.2.7 Please provide the other data used in the economic modelling of the patient access scheme at the different time points when the additional evidence is to be considered. These data could include cost/resource use, health-related quality of life and utilities.

Response

5.2.8 Please present the cost-effectiveness results as follows.

- For proven value: price increase schemes, please summarise in separate tables:
  - the results based on current evidence and current price
  - the anticipated results based on the expected new evidence and the proposed higher price.
- For expected value: rebate schemes, please summarise in separate tables:
  - the results based on the expected new evidence and the current price (which will be supported by the additional evidence collection)
  - the results based on the current evidence and the lower price (if the new evidence is not forthcoming).
- For risk-sharing schemes, please summarise in separate tables:
  - the results based on current evidence and current price
  - the results based on the expected new evidence and the current price (which will be supported by the additional evidence collection)
  - the results based on the current evidence and the lower price (if the new evidence is not forthcoming)
  - the anticipated results based on the expected new evidence and the proposed higher price.

A suggested format is shown in table 3, section 4.7.

5.2.9 Please present in separate tables the incremental results for the different scenarios as described above in section 5.2.8 for the type of outcome-based scheme being submitted.

List the interventions and comparator(s) from least to most expensive. Present the incremental cost-effectiveness ratios (ICERs) in comparison with baseline (usually standard care), and the incremental analysis ranking technologies in terms of dominance and extended dominance. A suggested format is presented in table 4, section 4.8.

Single technology appraisal

Obeticholic acid for primary biliary cirrhosis [ID785]

Erratum to Intercept's responses to ERG questions

21st November 2016

Erratum preface

The company would like to bring to the ERG's attention that there was an error in the original submission regarding patient numbers used in the economic model.

The effects of this change are outlined in detail in this erratum. The erratum contains full deterministic and probabilistic sensitivity analyses of the new base case, including updated versions of the scenario analyses provided in the original submission. The overall effect on the ICERs for both the UDCA-intolerant and UDCA inadequate responder patient populations is minimal, as shown in Table 1 and Table 2. The ICER for the UDCA-intolerant population has decreased by £158.00/QALY, and the ICER for the UDCA inadequate responder population has decreased by £269.00/QALY.Appendix 1.

Table 1: Comparison of the incremental cost-effectiveness results included in the original submission versus the updated base case results submitted in this erratum document for the UDCA-intolerant population, using the list price of OCA

Technologies	Total			Incremental			ICER (cost/QALY)	ICER (cost/QALY)
	Costs	LYG	QALYs	Costs	LYG	QALYs	versus baseline	Incremental
Base case results included in original submission								
No treatment (placebo)	£103,233	11.30	6.61	–	–	–	–	–
OCA titration	[redacted]	16.65	13.52	[redacted]	5.35	6.91	[redacted]	[redacted]
Updated base case results submitted in erratum								
No treatment (placebo)	£103,233	11.30	6.61	–	–	–	–	–
OCA titration	[redacted]	16.68	13.56	[redacted]	5.38	6.95	[redacted]	[redacted]

Abbreviations: ICER, incremental cost-effectiveness ratio; LYG, life years gained; OCA, obeticholic acid; QALYs, quality-adjusted life years; UDCA, ursodeoxycholic acid

Table 2: Comparison of the incremental cost-effectiveness results included in the original submission versus the updated base case results submitted in this erratum document for the UDCA inadequate responder population, using the list price of OCA

Technologies	Total			Incremental			ICER (cost/QALY)	ICER (cost/QALY)
	Costs	LYG	QALYs	Costs	LYG	QALYs	versus baseline	Incremental
Base case results included in original submission								
UDCA + placebo	£96,977	12.35	7.85	–	–	–	–	–
OCA titration + UDCA	[redacted]	16.75	13.64	[redacted]	4.40	5.79	[redacted]	[redacted]
Updated base case results submitted in erratum								
UDCA + placebo	£96,977	12.35	7.85	–	–	–	–	–
OCA titration + UDCA	[redacted]	16.78	13.68	[redacted]	4.43	5.83	[redacted]	[redacted]

Abbreviations: ICER, incremental cost-effectiveness ratio; LYG, life years gained; OCA, obeticholic acid; QALYs, quality-adjusted life years; UDCA, ursodeoxycholic acid

The company would like to apologise for this error and the inconvenience caused. We would also like to thank the ERG for spotting the error in patient numbers and for requesting further clarification in their question B12b.

Changes to the cost-utility model

The revised cost-utility model has two changes to the originally submitted model:

- Patient-level data from the POISE CSR have been added for UDCA + no treatment (placebo) patients, and a switch to use these data has been included (as requested by NICE)
- Patient-level data for regimens containing OCA have been updated with the final data from the POISE CSR.

The addition of patient-level data for UDCA + no treatment (placebo) patients warranted minor structural changes to the model to allow the option of using patient-level data or not.

Incorporation of UDCA patient-level data

As described in the previous set of clarification responses (sent to NICE on 18/11/2016), the option to use patient-level UDCA data from POISE has been included in the model.

The majority of changes to the model were made in the 'Transition matrices' worksheet. All of the changes were made in the range L316:HL371 on this worksheet. A switch to enable or disable the use of UDCA patient-level data has been added in cell C10 on the 'Clinical inputs' worksheet. If the switch is activated, patient-level UDCA data from POISE is used to generate transition probabilities for that population.

Patient-level population numbers (added in the cells highlighted in yellow on the 'Transition matrices' worksheet) are included, along with their transition probability calculations (presented alongside). The calculations for how transition probabilities are derived are presented as formulae within the transition probability cells; for example, the patient

numbers for UDCA + no treatment (placebo) patients with a recorded ALP threshold of >1.67x ULN (equating to 200 U/L) are located in the range X330:AF338. The transition probability calculations corresponding to this set of patient numbers are located in the range M330:V330. This method was used to derive all patient-level UDCA transition probability data for the first four cycles of the model.

Update of OCA patient-level data

The original submitted model contained data from an analysis of patient numbers according to an early version of the POISE patient-level dataset. Updated patient numbers have since been provided by the Intercept biostatistics team.

The model has now been updated to include the correct patient numbers. These have the effect of changing some transition probabilities used in the first four cycles of the economic model. This has had a downstream effect of changing the QALYs and costs generated for the OCA-treated patient groups.

The specific values changed were patient numbers in the transition matrices for the following treatment regimens:

- OCA titration
- OCA titration + UDCA
- OCA 10 mg (not relevant for this submission)
- OCA 10 mg + UDCA (not relevant for this submission)

Tables of all patient numbers that have been changed, their previous values, and their updated values, are presented below (Table 3, Table 4, Table 5, and Table 6). The cell references provided in the final column of the tables refer to the 'Transition matrices' worksheet of the model.

The different patient numbers have changed the corresponding transition probabilities. For example, on the 'Transition matrices' worksheet of the model, changes to patient numbers in the range Y121:AF128 will have an impact on the transition probabilities calculated in the range N121:U128 (note that discontinuation is also applied to this specific transition matrix).

Table 3: OCA regimen patient numbers corrected from the original submission for the 0–3 month model cycle

Transition		Cycle: 0–3 months		
From:	**To:**	**Previous value**	**Updated value**	**Cell reference**
ALP: ≤ 2 ULN and Bili: Normal	ALP: ≤ 2 ULN and Bili: Normal	15	16	Y121
ALP: > 1.67 ULN and Bili: Normal	ALP: ≤ 1.67 ULN and Bili: Normal	31	32	Y134
ALP: > 1.5 ULN and Bili: Normal	ALP: > 1.5 ULN and Bili: Normal	39	40	Z146
ALP: ≤ 2 ULN and Bili: Normal	ALP: ≤ 2 ULN and Bili: Normal	13	14	Y170
ALP: > 2 ULN and Bili: Normal	ALP: ≤ 2 ULN and Bili: Normal	23	25	Y171

ALP: > 1.67 ULN and Bili: Normal	ALP: ≤ 1.67 ULN and Bili: Normal	22	24	Y183
ALP: > 1.67 ULN and Bili: Normal	ALP: > 1.67 ULN and Bili: Normal	38	39	Z183
ALP: > 1.5 ULN and Bili: Normal	ALP: ≤ 1.5 ULN and Bili: Normal	12	14	Y195
ALP: > 1.5 ULN and Bili: Normal	ALP: > 1.5 ULN and Bili: Normal	49	50	Z195
ALP: ≤ 2 ULN and Bili: Normal	ALP: ≤ 2 ULN and Bili: Normal	15	16	Y219
ALP: > 1.67 ULN and Bili: Normal	ALP: ≤ 1.67 ULN and Bili: Normal	31	32	Y232
ALP: > 1.5 ULN and Bili: Normal	ALP: > 1.5 ULN and Bili: Normal	39	40	Z244
ALP: ≤ 2 ULN and Bili: Normal	ALP: ≤ 2 ULN and Bili: Normal	13	14	Y268
ALP: > 2 ULN and Bili: Normal	ALP: ≤ 2 ULN and Bili: Normal	23	25	Y269
ALP: > 1.67 ULN and Bili: Normal	ALP: ≤ 1.67 ULN and Bili: Normal	22	24	Y281
ALP: > 1.67 ULN and Bili: Normal	ALP: > 1.67 ULN and Bili: Normal	38	39	Z281
ALP: > 1.5 ULN and Bili: Normal	ALP: ≤ 1.5 ULN and Bili: Normal	12	14	Y293
ALP: > 1.5 ULN and Bili: Normal	ALP: > 1.5 ULN and Bili: Normal	49	50	Z293

Abbreviations: ALP, alkaline phosphatase; Bili, bilirubin; OCA, obeticholic acid; ULN, upper limit of normal.

Table 4: OCA regimen patient numbers corrected from the original submission for the 3–6 month model cycle

Transition		Cycle: 3–6 months		
From	**To**	**Previous value**	**Updated value**	**Cell reference**
ALP: ≤ 2 ULN and Bili: Normal	ALP: > 2 ULN and Bili: Normal	0	1	CJ121
Bili: Abnormal and rising, or CC: Bili: Abnormal	ALP: ≤ 2 ULN and Bili: Normal	3	4	CI124
ALP: ≤ 2 ULN and Bili: Normal	ALP: > 2 ULN and Bili: Normal	2	3	CJ133
Bili: Abnormal and rising, or CC: Bili: Abnormal	ALP: ≤ 2 ULN and Bili: Normal	1	2	CI136
ALP: > 1.5 ULN and Bili: Normal	ALP: > 1.5 ULN and Bili: Normal	32	33	CJ146
Bili: Abnormal and rising, or CC: Bili: Abnormal	ALP: > 1.5 ULN and Bili: Normal	2	3	CJ148
ALP: ≤ 2 ULN and Bili: Normal	ALP: ≤ 2 ULN and Bili: Normal	30	35	CI170

Transition		Cycle: 3–6 months		
From	**To**	**Previous value**	**Updated value**	**Cell reference**
ALP: > 2 ULN and Bili: Normal	ALP: > 2 ULN and Bili: Normal	21	22	CJ171
ALP: ≤ 1.67 ULN and Bili: Normal	ALP: ≤ 1.67 ULN and Bili: Normal	14	17	CI182
ALP: ≤ 1.67 ULN and Bili: Normal	ALP: > 1.67 ULN and Bili: Normal	6	7	CJ182
ALP: > 1.67 ULN and Bili: Normal	ALP: > 1.67 ULN and Bili: Normal	33	35	CJ183
ALP: ≤ 1.5 ULN and Bili: Normal	ALP: ≤ 1.5 ULN and Bili: Normal	11	12	CI194
ALP: ≤ 1.5 ULN and Bili: Normal	ALP: > 1.5 ULN and Bili: Normal	1	2	CJ194
ALP: > 1.5 ULN and Bili: Normal	ALP: ≤ 1.5 ULN and Bili: Normal	2	4	CI195
ALP: > 1.5 ULN and Bili: Normal	ALP: > 1.5 ULN and Bili: Normal	45	47	CJ195
ALP: ≤ 2 ULN and Bili: Normal	ALP: > 2 ULN and Bili: Normal	0	1	CJ219
Bili: Abnormal and rising, or CC: Bili: Abnormal	ALP: ≤ 2 ULN and Bili: Normal	3	4	CI222
ALP: ≤ 2 ULN and Bili: Normal	ALP: > 2 ULN and Bili: Normal	2	3	CJ231
Bili: Abnormal and rising, or CC: Bili: Abnormal	ALP: ≤ 2 ULN and Bili: Normal	1	2	CI234
ALP: > 1.5 ULN and Bili: Normal	ALP: > 1.5 ULN and Bili: Normal	32	33	CJ244
Bili: Abnormal and rising, or CC: Bili: Abnormal	ALP: > 1.5 ULN and Bili: Normal	2	3	CJ246
ALP: ≤ 2 ULN and Bili: Normal	ALP: ≤ 2 ULN and Bili: Normal	30	35	CI268
ALP: > 2 ULN and Bili: Normal	ALP: > 2 ULN and Bili: Normal	21	22	CJ269
ALP: ≤ 1.67 ULN and Bili: Normal	ALP: ≤ 1.67 ULN and Bili: Normal	14	17	CI280
ALP: ≤ 1.67 ULN and Bili: Normal	ALP: > 1.67 ULN and Bili: Normal	6	7	CJ280
ALP: > 1.67 ULN and Bili: Normal	35.000	33	35	CJ281
ALP: ≤ 1.5 ULN and Bili: Normal	ALP: ≤ 1.5 ULN and Bili: Normal	11	12	CI292
ALP: ≤ 1.5 ULN and Bili: Normal	ALP: > 1.5 ULN and Bili: Normal	1	2	CJ292
ALP: > 1.5 ULN and Bili: Normal	ALP: ≤ 1.5 ULN and Bili: Normal	2	4	CI293

Transition		Cycle: 3–6 months		
From	**To**	**Previous value**	**Updated value**	**Cell reference**
ALP: > 1.5 ULN and Bili: Normal	ALP: > 1.5 ULN and Bili: Normal	45	47	CJ293

Abbreviations: ALP, alkaline phosphatase; Bili, bilirubin; OCA, obeticholic acid; ULN, upper limit of normal.

Table 5: OCA regimen patient numbers corrected from the original submission for the 6–9 month model cycle

Transition		Cycle: 6–9 months		
From	**To**	**Previous value**	**Updated value**	**Cell reference**
ALP: ≤ 2 ULN and Bili: Normal	ALP: ≤ 2 ULN and Bili: Normal	44	46	ES121
ALP: ≤ 2 ULN and Bili: Normal	Bili: Abnormal and rising, or CC	0	1	EV121
ALP: > 2 ULN and Bili: Normal	ALP: > 2 ULN and Bili: Normal	7	8	ET122
ALP: ≤ 2 ULN and Bili: Normal	ALP: ≤ 2 ULN and Bili: Normal	31	33	ES133
ALP: ≤ 2 ULN and Bili: Normal	Bili: Abnormal and rising, or CC	0	1	EV133
ALP: > 2 ULN and Bili: Normal	ALP: > 2 ULN and Bili: Normal	19	20	ET134
ALP: ≤ 1.5 ULN and Bili: Normal	ALP: ≤ 1.5 ULN and Bili: Normal	19	20	ES145
ALP: > 1.5 ULN and Bili: Normal	ALP: ≤ 1.5 ULN and Bili: Normal	9	10	ES146
ALP: > 1.5 ULN and Bili: Normal	ALP: > 1.5 ULN and Bili: Normal	26	27	ET146
ALP: > 1.5 ULN and Bili: Normal	Bili: Abnormal and rising, or CC: Bili: Abnormal	0	1	EV146
ALP: ≤ 2 ULN and Bili: Normal	ALP: ≤ 2 ULN and Bili: Normal	34	38	ES170
ALP: > 2 ULN and Bili: Normal	ALP: ≤ 2 ULN and Bili: Normal	3	5	ES171
ALP: > 2 ULN and Bili: Normal	ALP: > 2 ULN and Bili: Normal	14	17	ET171
ALP: ≤ 2 ULN and Bili: Normal	ALP: ≤ 2 ULN and Bili: Normal	16	18	ES182
ALP: > 2 ULN and Bili: Normal	ALP: ≤ 2 ULN and Bili: Normal	8	12	ES183
ALP: > 2 ULN and Bili: Normal	ALP: > 2 ULN and Bili: Normal	23	26	ET183
ALP: ≤ 1.5 ULN and Bili: Normal	ALP: ≤ 1.5 ULN and Bili: Normal	12	13	ES194

Transition		Cycle: 6–9 months		
From	**To**	**Previous value**	**Updated value**	**Cell reference**
ALP: ≤ 1.5 ULN and Bili: Normal	ALP: > 1.5 ULN and Bili: Normal	3	4	ET194
ALP: > 1.5 ULN and Bili: Normal	ALP: ≤ 1.5 ULN and Bili: Normal	6	7	ES195
ALP: > 1.5 ULN and Bili: Normal	ALP: > 1.5 ULN and Bili: Normal	31	37	ET195
ALP: ≤ 2 ULN and Bili: Normal	ALP: ≤ 2 ULN and Bili: Normal	44	46	ES219
ALP: ≤ 2 ULN and Bili: Normal	Bili: Abnormal and rising, or CC	0	1	EV219
ALP: > 2 ULN and Bili: Normal	ALP: > 2 ULN and Bili: Normal	7	8	ET220
ALP: ≤ 2 ULN and Bili: Normal	ALP: ≤ 2 ULN and Bili: Normal	31	33	ES231
ALP: ≤ 2 ULN and Bili: Normal	Bili: Abnormal and rising, or CC	0	1	EV231
ALP: > 2 ULN and Bili: Normal	ALP: > 2 ULN and Bili: Normal	19	20	ET232
ALP: ≤ 1.5 ULN and Bili: Normal	ALP: ≤ 1.5 ULN and Bili: Normal	19	20	ES243
ALP: > 1.5 ULN and Bili: Normal	ALP: ≤ 1.5 ULN and Bili: Normal	9	10	ES244
ALP: > 1.5 ULN and Bili: Normal	ALP: > 1.5 ULN and Bili: Normal	26	27	ET244
ALP: > 1.5 ULN and Bili: Normal	Bili: Abnormal and rising, or CC: Bili: Abnormal	0	1	EV244
ALP: ≤ 2 ULN and Bili: Normal	ALP: ≤ 2 ULN and Bili: Normal	34	38	ES268
ALP: > 2 ULN and Bili: Normal	ALP: ≤ 2 ULN and Bili: Normal	3	5	ES269
ALP: > 2 ULN and Bili: Normal	ALP: > 2 ULN and Bili: Normal	14	17	ET269
ALP: ≤ 2 ULN and Bili: Normal	ALP: ≤ 2 ULN and Bili: Normal	16	18	ES280
ALP: > 2 ULN and Bili: Normal	ALP: ≤ 2 ULN and Bili: Normal	8	12	ES281
ALP: > 2 ULN and Bili: Normal	ALP: > 2 ULN and Bili: Normal	23	26	ET281
ALP: ≤ 1.5 ULN and Bili: Normal	ALP: ≤ 1.5 ULN and Bili: Normal	12	13	ES292
ALP: ≤ 1.5 ULN and Bili: Normal	ALP: > 1.5 ULN and Bili: Normal	3	4	ET292
ALP: > 1.5 ULN and Bili: Normal	ALP: ≤ 1.5 ULN and Bili: Normal	6	7	ES293

Transition		Cycle: 6–9 months		
From	**To**	**Previous value**	**Updated value**	**Cell reference**
ALP: > 1.5 ULN and Bili: Normal	ALP: > 1.5 ULN and Bili: Normal	31	37	ET293

Abbreviations: ALP, alkaline phosphatase; Bili, bilirubin; OCA, obeticholic acid; ULN, upper limit of normal.

Table 6: OCA regimen patient numbers corrected from the original submission for the 9–12 month model cycle

Transition		Cycle: 9–12 months		
From	**To**	**Previous value**	**Updated value**	**Cell reference**
ALP: ≤ 2 ULN and Bili: Normal	ALP: ≤ 2 ULN and Bili: Normal	41	44	HC121
ALP: ≤ 1.67 ULN and Bili: Normal	ALP: ≤ 1.67 ULN and Bili: Normal	29	31	HC133
ALP: > 1.67 ULN and Bili: Normal	ALP: ≤ 1.67 ULN and Bili: Normal	3	4	HC134
ALP: ≤ 1.5 ULN and Bili: Normal	ALP: ≤ 1.5 ULN and Bili: Normal	18	20	HC145
ALP: > 1.5 ULN and Bili: Normal	ALP: > 1.5 ULN and Bili: Normal	25	26	HD146
ALP: ≤ 2 ULN and Bili: Normal	ALP: ≤ 2 ULN and Bili: Normal	38	41	HC170
ALP: > 2 ULN and Bili: Normal	ALP: ≤ 2 ULN and Bili: Normal	2	3	HC171
ALP: > 2 ULN and Bili: Normal	ALP: > 2 ULN and Bili: Normal	12	15	HD171
ALP: ≤ 1.67 ULN and Bili: Normal	ALP: ≤ 1.67 ULN and Bili: Normal	25	28	HC182
ALP: > 1.67 ULN and Bili: Normal	ALP: > 1.67 ULN and Bili: Normal	21	25	HD183
ALP: ≤ 1.5 ULN and Bili: Normal	ALP: ≤ 1.5 ULN and Bili: Normal	17	18	HC194
ALP: > 1.5 ULN and Bili: Normal	ALP: > 1.5 ULN and Bili: Normal	29	34	HD195
ALP: ≤ 2 ULN and Bili: Normal	ALP: ≤ 2 ULN and Bili: Normal	41	44	HC219
ALP: ≤ 1.67 ULN and Bili: Normal	ALP: ≤ 1.67 ULN and Bili: Normal	29	31	HC231
ALP: > 1.67 ULN and Bili: Normal	ALP: ≤ 1.67 ULN and Bili: Normal	3	4	HC232
ALP: ≤ 1.5 ULN and Bili: Normal	ALP: ≤ 1.5 ULN and Bili: Normal	18	20	HC243
ALP: > 1.5 ULN and Bili: Normal	ALP: > 1.5 ULN and Bili: Normal	25	26	HD244

Transition		Cycle: 9–12 months		
From	**To**	**Previous value**	**Updated value**	**Cell reference**
ALP: ≤ 2 ULN and Bili: Normal	ALP: ≤ 2 ULN and Bili: Normal	38	41	HC268
ALP: > 2 ULN and Bili: Normal	ALP: ≤ 2 ULN and Bili: Normal	2	3	HC269
ALP: > 2 ULN and Bili: Normal	ALP: > 2 ULN and Bili: Normal	12	15	HD269
ALP: ≤ 1.67 ULN and Bili: Normal	ALP: ≤ 1.67 ULN and Bili: Normal	25	28	HC280
ALP: > 1.67 ULN and Bili: Normal	ALP: > 1.67 ULN and Bili: Normal	21	25	HD281
ALP: ≤ 1.5 ULN and Bili: Normal	ALP: ≤ 1.5 ULN and Bili: Normal	17	18	HC292
ALP: > 1.5 ULN and Bili: Normal	ALP: > 1.5 ULN and Bili: Normal	29	34	HD293

Abbreviations: ALP, alkaline phosphatase; Bili, bilirubin; OCA, obeticholic acid; ULN, upper limit of normal.

Appendix 1: Results using the patient access scheme (PAS) price of OCA

Base case deterministic results

Table 7: Base-case results for the UDCA-intolerant population, using the PAS price of OCA

Technologies	Total			Incremental			ICER (cost/QALY)	ICER (cost/QALY)
	Costs	LYG	QALYs	Costs	LYG	QALYs	versus baseline	incremental
No treatment (placebo)	£103,233	11.30	6.61	–	–	–	–	–
OCA titration	£251,671	16.68	13.56	£148,439	5.38	6.95	£21,351	£21,351

Abbreviations: ICER, incremental cost-effectiveness ratio; LYG, life years gained; OCA, obeticholic acid; PAS, patient access scheme; QALYs, quality-adjusted life years; UDCA, ursodeoxycholic acid

Table 8: Base-case results for the UDCA inadequate responder population, using the PAS price of OCA

Technologies	Total			Incremental			ICER (cost/QALY)	ICER (cost/QALY)
	Costs	LYG	QALYs	Costs	LYG	QALYs	versus baseline	incremental
UDCA + placebo	£96,977	12.35	7.85	–	–	–	–	–
OCA titration + UDCA	£261,791	16.78	13.68	£164,814	4.43	5.83	£28,281	£28,281

Abbreviations: ICER, incremental cost-effectiveness ratio; LYG, life years gained; OCA, obeticholic acid; PAS, patient access scheme; QALYs, quality-adjusted life years; UDCA, ursodeoxycholic acid

Clinical outcomes from the model

Table 9: Summary of model outcomes for the UDCA-intolerant population

Outcome	OCA titration	No treatment (placebo)	Incremental
Total number of cases of Bili: abnormal and rising, or CC per 1,000 patients	[redacted]	[redacted]	[redacted]
Total number of cases of decompensated cirrhosis per 1,000 patients	[redacted]	[redacted]	[redacted]
Total liver transplants per 1,000 patients	[redacted]	[redacted]	[redacted]
Total liver-related deaths per 1,000 patients	[redacted]	[redacted]	[redacted]

Abbreviations: Bili, bilirubin; CC, compensated cirrhosis; OCA, obeticholic acid; UDCA, ursodeoxycholic acid.

Table 10: Summary of model outcomes for the UDCA inadequate responder population

Outcome	OCA titration + UDCA	UDCA + placebo	Incremental
Total number of cases of Bili: abnormal and rising, or CC per 1,000 patients	[redacted]	[redacted]	[redacted]
Total number of cases of decompensated cirrhosis per 1,000 patients	[redacted]	[redacted]	[redacted]
Total liver transplants per 1,000 patients	[redacted]	[redacted]	[redacted]
Total liver-related deaths per 1,000 patients	[redacted]	[redacted]	[redacted]

Abbreviations: Bili, bilirubin; CC, compensated cirrhosis; OCA, obeticholic acid; UDCA, ursodeoxycholic acid.

Results by health state

Table 11: Summary of QALY gain by health state for the UDCA-intolerant population

Health state	OCA titration	No treatment (placebo)	Incremental
ALP: ≤200 U/L and Bili: Normal	6.322	0.000	–6.322
ALP: >200 U/L and Bili: Normal	6.515	2.044	–4.470
Bili: Abnormal and rising, or CC	0.383	2.515	2.132
Discontinuation	0.009	0.000	–0.009
Decompensated cirrhosis	0.103	0.651	0.547
HCC	0.010	0.065	0.055
Pre transplant (end stage)	0.033	0.208	0.175
Liver transplant	0.005	0.031	0.026
Post liver transplant	0.133	0.822	0.689
Re-emergence of PBC	0.045	0.270	0.225
Total	13.558	6.606	–6.952

Abbreviations: ALP, alkaline phosphatase; Bili, bilirubin; CC, compensated cirrhosis; HCC, hepatocellular carcinoma; OCA, obeticholic acid; PBC, primary biliary cholangitis/cirrhosis; QALY, quality-adjusted life year; UDCA, ursodeoxycholic acid.

Table 12: Summary of QALY gain by health state for the UDCA inadequate responder population

Health state	OCA titration + UDCA	UDCA + placebo	Incremental
ALP: ≤200 U/L and Bili: Normal	6.322	0.000	–6.322
ALP: >200 U/L and Bili: Normal	6.693	3.867	–2.826
Bili: Abnormal and rising, or CC	0.354	2.222	1.868
Discontinuation	0.009	0.004	–0.006
Decompensated cirrhosis	0.095	0.569	0.474
HCC	0.010	0.057	0.048
Pre transplant (end stage)	0.030	0.182	0.151
Liver transplant	0.005	0.027	0.023
Post liver transplant	0.121	0.701	0.580
Re-emergence of PBC	0.040	0.222	0.181
Total	13.680	7.852	–5.828

Abbreviations: ALP, alkaline phosphatase; Bili, bilirubin; CC, compensated cirrhosis; HCC, hepatocellular carcinoma; OCA, obeticholic acid; PBC, primary biliary cholangitis/cirrhosis; QALY, quality-adjusted life year; UDCA, ursodeoxycholic acid.

Table 13: Summary of life years gained by health state for the UDCA-intolerant population

Health state	OCA titration	No treatment (placebo)	Incremental
ALP: ≤200 U/L and Bili: Normal	7.527	0.000	7.527
ALP: >200 U/L and Bili: Normal	7.755	2.434	5.322
Bili: Abnormal and rising, or CC	0.696	4.573	–3.877
Discontinuation	0.012	0.000	0.012
Decompensated cirrhosis	0.270	1.702	–1.431
HCC	0.023	0.145	–0.122
Pre transplant (end stage)	0.086	0.543	–0.457
Liver transplant	0.009	0.055	–0.046
Post liver transplant	0.233	1.443	–1.211
Re-emergence of PBC	0.067	0.402	–0.335
Total	16.679	11.297	5.382

Abbreviations: ALP, alkaline phosphatase; Bili, bilirubin; CC, compensated cirrhosis; HCC, hepatocellular carcinoma; OCA, obeticholic acid; PBC, primary biliary cholangitis/cirrhosis; UDCA, ursodeoxycholic acid.

Table 14: Summary of life years gained by health state for the UDCA inadequate responder population

Health state	OCA titration + UDCA	UDCA + placebo	Incremental
ALP: ≤200 U/L and Bili: Normal	7.527	0.000	7.527
ALP: >200 U/L and Bili: Normal	7.967	4.604	3.364
Bili: Abnormal and rising, or CC	0.644	4.040	–3.396
Discontinuation	0.012	0.005	0.007
Decompensated cirrhosis	0.250	1.489	–1.239
HCC	0.021	0.128	–0.106
Pre transplant (end stage)	0.080	0.476	–0.396
Liver transplant	0.008	0.048	–0.040
Post liver transplant	0.212	1.231	–1.019
Re-emergence of PBC	0.060	0.331	–0.271
Total	16.781	12.351	4.430

Abbreviations: ALP, alkaline phosphatase; Bili, bilirubin; CC, compensated cirrhosis; HCC, hepatocellular carcinoma; OCA, obeticholic acid; PBC, primary biliary cholangitis/cirrhosis; UDCA, ursodeoxycholic acid.

Table 15: Summary of costs by health state for the UDCA-intolerant population

Health state	OCA titration	No treatment (placebo)	Incremental
ALP: ≤200 U/L and Bili: Normal	[redacted]	£0.00	[redacted]
ALP: >200 U/L and Bili: Normal	[redacted]	£1,207.08	[redacted]
Bili: Abnormal and rising, or CC	[redacted]	£28,597.68	[redacted]
Discontinuation	[redacted]	£0.00	[redacted]
Decompensated cirrhosis	[redacted]	£21,284.77	[redacted]
HCC	[redacted]	£1,620.43	[redacted]
Pre transplant (end stage)	[redacted]	£9,890.90	[redacted]
Liver transplant	[redacted]	£14,310.87	[redacted]
Post liver transplant	[redacted]	£26,221.30	[redacted]
Re-emergence of PBC	[redacted]	£99.80	[redacted]
Total	[redacted]	£103,232.81	[redacted]

Abbreviations: ALP, alkaline phosphatase; Bili, bilirubin; CC, compensated cirrhosis; HCC, hepatocellular carcinoma; OCA, obeticholic acid; PBC, primary biliary cholangitis/cirrhosis; UDCA, ursodeoxycholic acid.

Table 16: Summary of costs by health state for the UDCA inadequate responder population

Health state	OCA titration + UDCA	UDCA + placebo	Incremental
ALP: ≤200 U/L and Bili: Normal	[redacted]	£0.00	[redacted]
ALP: >200 U/L and Bili: Normal	[redacted]	£5,349.00	[redacted]
Bili: Abnormal and rising, or CC	[redacted]	£27,926.48	[redacted]
Discontinuation	[redacted]	£14.48	[redacted]
Decompensated cirrhosis	[redacted]	£18,619.88	[redacted]
HCC	[redacted]	£1,422.13	[redacted]
Pre transplant (end stage)	[redacted]	£8,665.20	[redacted]
Liver transplant	[redacted]	£12,526.26	[redacted]
Post liver transplant	[redacted]	£22,371.06	[redacted]
Re-emergence of PBC	[redacted]	£82.10	[redacted]
Total	[redacted]	£96,976.58	[redacted]

Abbreviations: ALP, alkaline phosphatase; Bili, bilirubin; CC, compensated cirrhosis; HCC, hepatocellular carcinoma; OCA, obeticholic acid; PBC, primary biliary cholangitis/cirrhosis; UDCA, ursodeoxycholic acid.

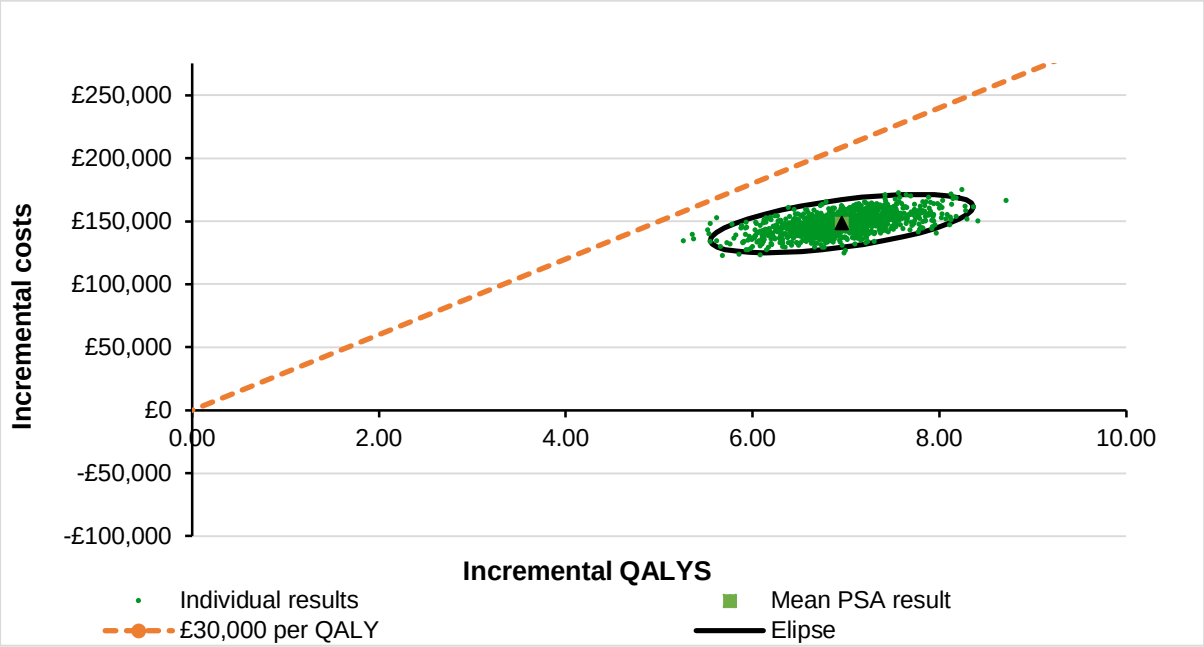
PSA results

Table 17: Incremental cost-effectiveness results of PSA for the UDCA intolerant population, using the PAS price of OCA

Technologies	Total			Incremental			ICER (cost/QALY)	ICER (cost/QALY)
	Costs	LYG	QALYs	Costs	LYG	QALYs	versus baseline	incremental
PSA results								
No treatment (placebo)	£103,252	11.31	6.60	–	–	–	–	–
OCA titration	£251,440	16.67	13.56	£148,188	5.36	6.95	£21,309	£21,309
Base case deterministic results								
No treatment (placebo)	£103,233	11.30	6.61	–	–	–	–	–
OCA titration	£251,671	16.68	13.56	£148,439	5.38	6.95	£21,351	£21,351

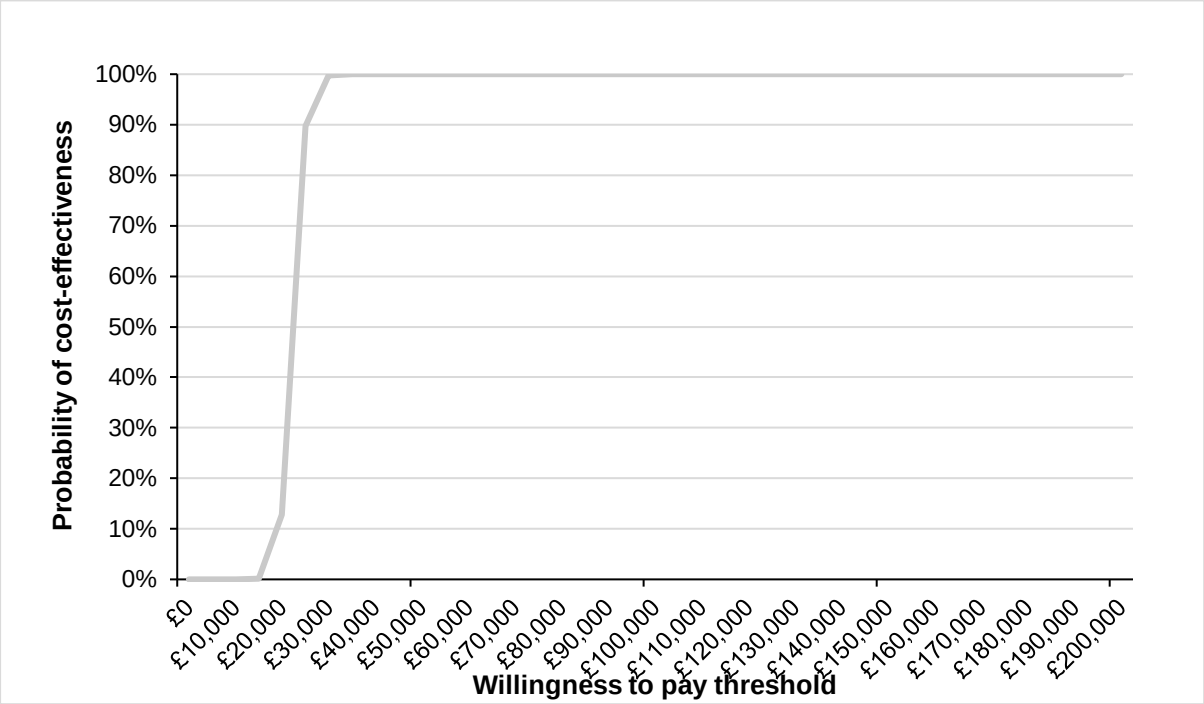
Abbreviations: ICER, incremental cost-effectiveness ratio; LYG, life years gained; OCA, obeticholic acid; PAS, patient access scheme; PSA, probabilistic sensitivity analysis; QALY, quality-adjusted life year; UDCA, ursodeoxycholic acid.

Figure 1: Scatter plot for PSA for the UDCA-intolerant population, using the PAS price of OCA



Abbreviations: OCA, obeticholic acid; PAS, patient access scheme; PSA, probabilistic sensitivity analysis; QALY, quality-adjusted life year; UDCA, ursodeoxycholic acid.

Figure 2: Cost-effectiveness acceptability curve for the UDCA-intolerant population, using the OCA PAS price



Abbreviations: OCA, obeticholic acid; **PAS, patient access scheme;** UDCA, ursodeoxycholic acid.

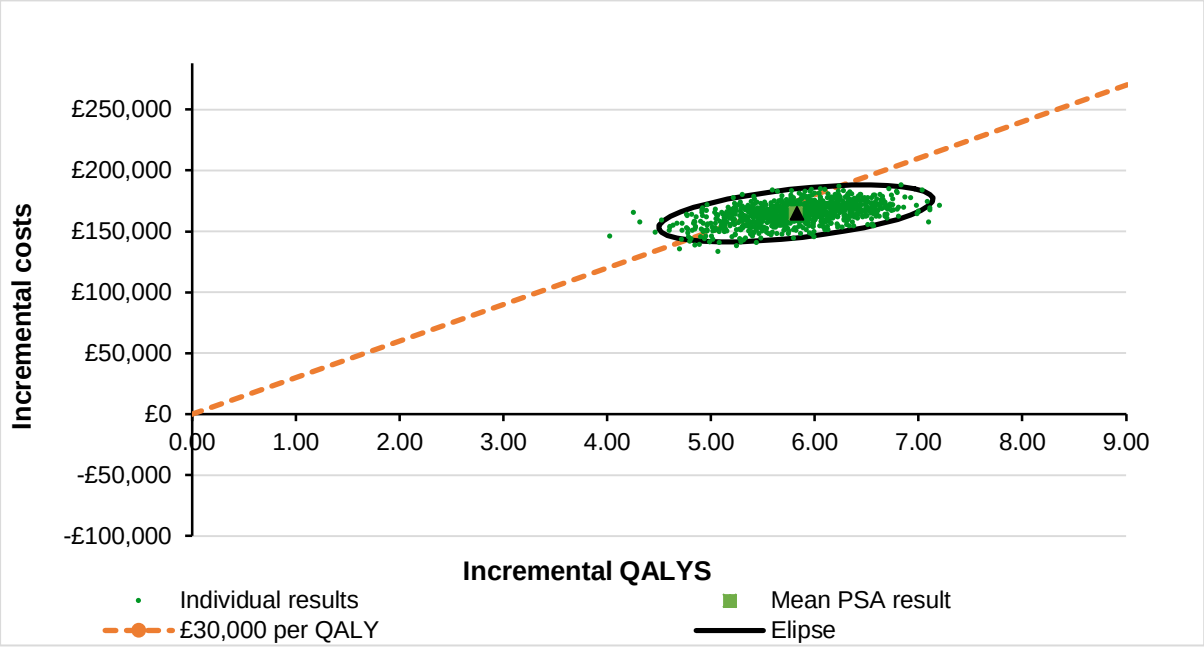
The probability that OCA is cost-effective vs placebo at a willingness-to-pay threshold of £30,000 is 99.8%.

Table 18: Incremental cost-effectiveness results of PSA for the UDCA inadequate responder population, using the PAS price of OCA

Technologies	Total			Incremental			ICER (costs / QALY)	ICER (costs / QALY)
	Costs	LYG	QALYs	Costs	LYG	QALYs	versus baseline	Incremental
PSA results								
UDCA + placebo	£96,928	12.37	7.84	–	–	–	–	–
OCA titration + UDCA	£261,641	16.77	13.65	£164,712	4.40	5.82	£28,321	£28,321
Base case deterministic results								
UDCA + placebo	£96,977	12.35	7.85	–	–	–	–	–
OCA titration + UDCA	£261,791	16.78	13.68	£164,814	4.43	5.83	£28,281	£28,281

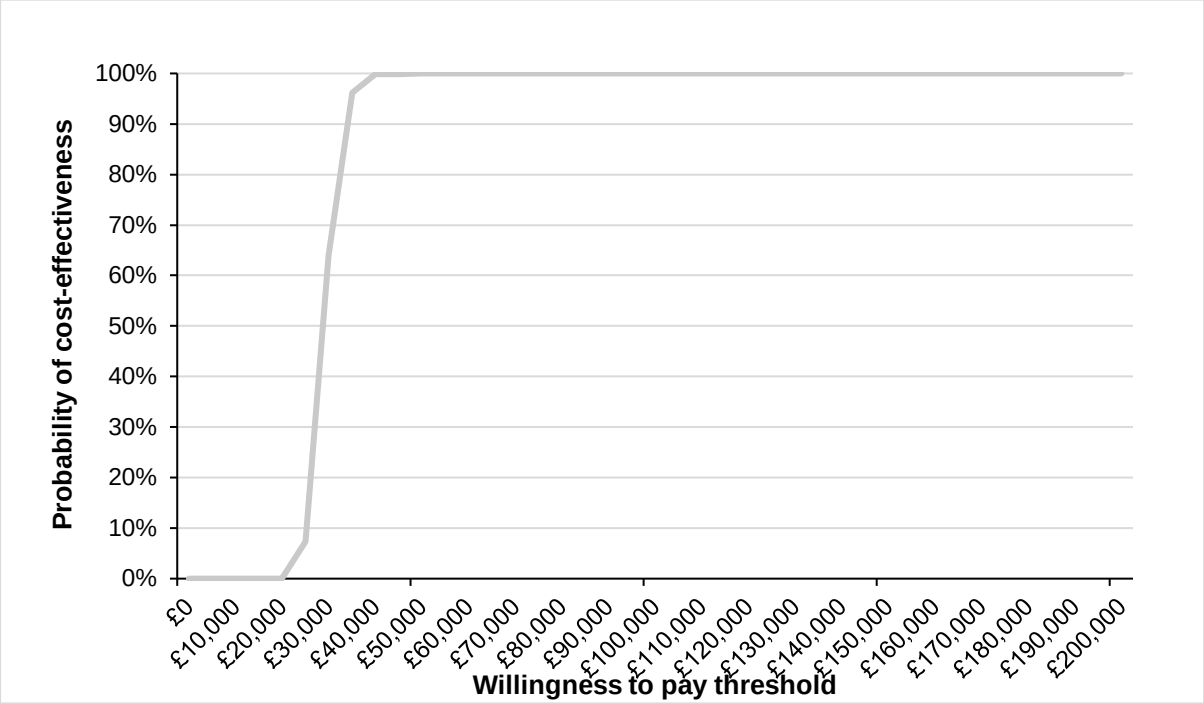
Abbreviations: ICER, incremental cost-effectiveness ratio; LYG, life years gained; OCA, obeticholic acid; PAS, patient access scheme; PSA, probabilistic sensitivity analysis; QALY, quality-adjusted life year; UDCA, ursodeoxycholic acid.

Figure 3: Scatter plot for PSA for the UDCA inadequate responder population, using the PAS price of OCA



Abbreviations: OCA, obeticholic acid; PAS, patient access scheme; PSA, probabilistic sensitivity analysis; QALY, quality-adjusted life year; UDCA, ursodeoxycholic acid.

Figure 4: Cost-effectiveness acceptability curve for the UDCA inadequate responder population, using the PAS price of OCA

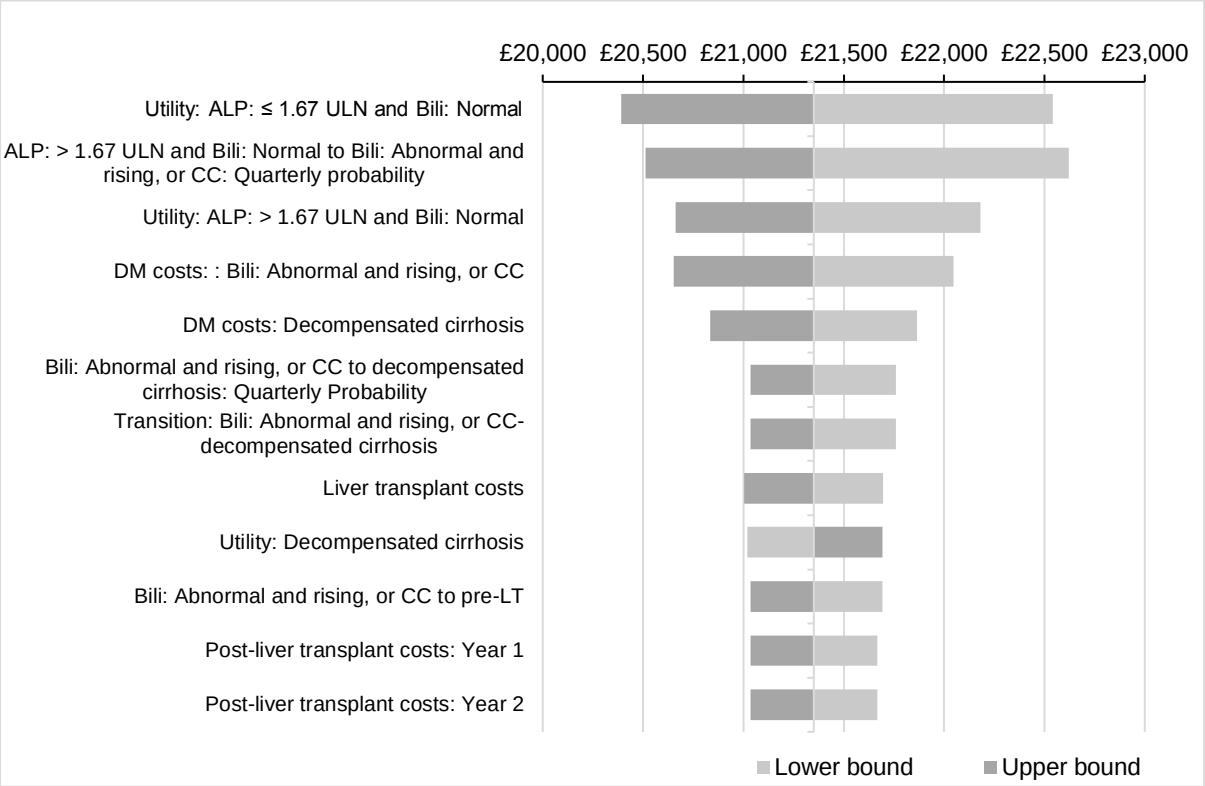


Abbreviations: OCA, obeticholic acid; PAS, patient access scheme; UDCA, ursodeoxycholic acid.

The probability that OCA titration + UDCA is cost-effective vs UDCA + placebo at a willingness-to-pay threshold of £30,000 is 64.0%.

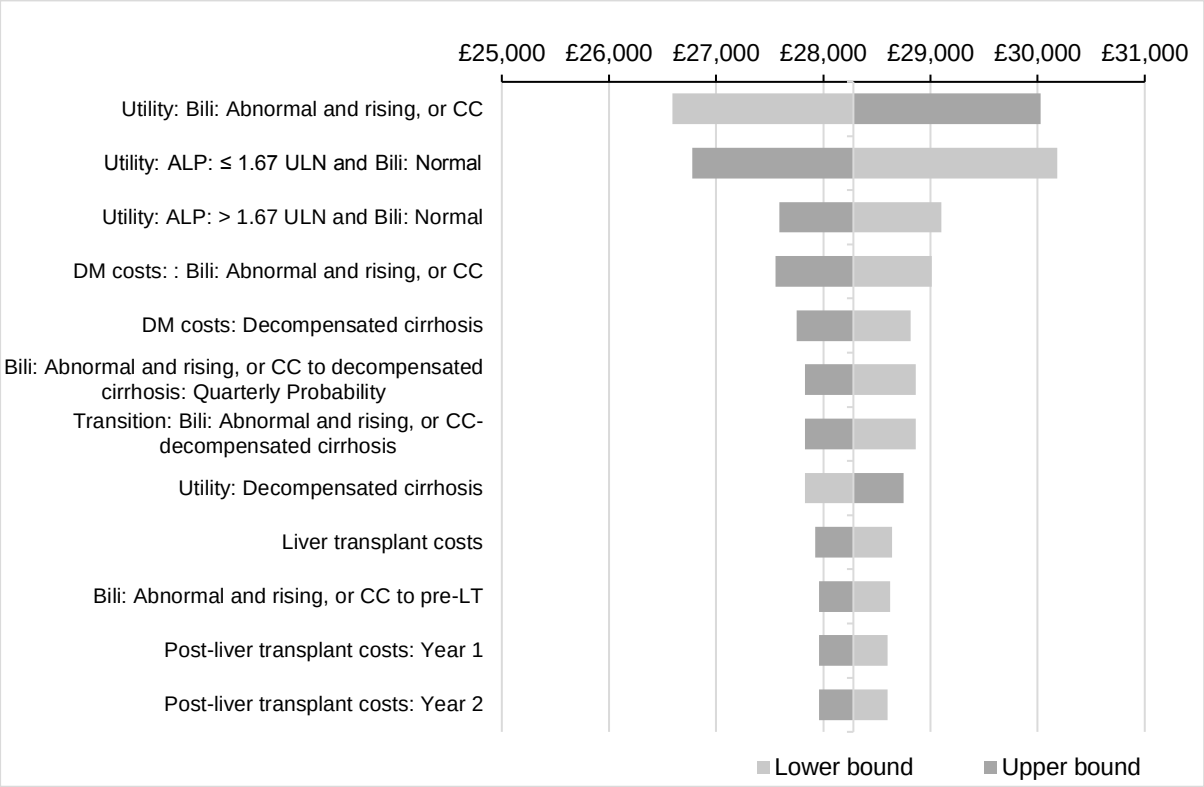
Deterministic sensitivity analysis

Figure 5: Tornado diagram for the UDCA-intolerant population, using the PAS price of OCA



Abbreviations: ALP, alkaline phosphatase; Bili, bilirubin; CC, compensated cirrhosis; DM, disease management; LT, liver transplant; OCA, obeticholic acid; PAS, patient access scheme; UDCA, ursodeoxycholic acid; ULN, upper limit of normal.

Figure 6: Tornado diagram for the UDCA inadequate responder population, using the PAS price of OCA



Abbreviations: ALP, alkaline phosphatase; Bili, bilirubin; CC, compensated cirrhosis; DM, disease management; LT, liver transplant; OCA, obeticholic acid; PAS, patient access scheme; UDCA, ursodeoxycholic acid; ULN, upper limit of normal.

Scenario 1: use of original HCV utility values

Table 19: Scenario 1 results for the UDCA-intolerant population, using the PAS price of OCA

Technologies	Total			Incremental			ICER (cost/QALY)	ICER (cost/QALY)
	Costs	LYG	QALYs	Costs	LYG	QALYs	versus baseline	Incremental
No treatment (placebo)	£103,233	11.30	6.91	–	–	–	–	–
OCA titration	£251,671	16.68	13.61	£148,439	5.38	6.70	£22,160	£22,160

Abbreviations: ICER, incremental cost-effectiveness ratio; LYG, life years gained; OCA, obeticholic acid; PAS, patient access scheme; QALY, quality-adjusted life year; UDCA, ursodeoxycholic acid.

Table 20: Scenario 1 results for the UDCA inadequate responder population, using the PAS price of OCA

Technologies	Total			Incremental			ICER (cost/QALY)	ICER (cost/QALY)
	Costs	LYG	QALYs	Costs	LYG	QALYs	versus baseline	Incremental
UDCA + placebo	£96,977	12.35	8.11	–	–	–	–	–
OCA titration + UDCA	£261,791	16.78	13.72	£164,814	4.43	5.61	£29,374	£29,374

Abbreviations: ICER, incremental cost-effectiveness ratio; LYG, life years gained; OCA, obeticholic acid; PAS, patient access scheme; QALY, quality-adjusted life year; UDCA, ursodeoxycholic acid.

Scenario 2: use of alternative transition probabilities

Table 21: Scenario 2 results for the UDCA-intolerant population, using the PAS price of OCA

Technologies	Total			Incremental			ICER (cost/QALY)	ICER (cost/QALY)
	Costs	LYG	QALYs	Costs	LYG	QALYs	versus baseline	Incremental
No treatment (placebo)	£94,717	10.89	6.39	–	–	–	–	–
OCA titration	£250,303	16.61	13.52	£155,586	5.73	7.13	£21,824	£21,824

Abbreviations: ICER, incremental cost-effectiveness ratio; LYG, life years gained; OCA, obeticholic acid; PAS, patient access scheme; QALY, quality-adjusted life year; UDCA, ursodeoxycholic acid.

Table 22: Scenario 2 results for the UDCA inadequate responder population, using the PAS price of OCA

Technologies	Total			Incremental			ICER (cost/QALY)	ICER (cost/QALY)
	Costs	LYG	QALYs	Costs	LYG	QALYs	versus baseline	Incremental
UDCA + placebo	£89,666	12.00	7.67	–	–	–	–	–
OCA titration + UDCA	£260,540	16.72	13.65	£170,874	4.72	5.98	£28,596	£28,596

Abbreviations: ICER, incremental cost-effectiveness ratio; LYG, life years gained; OCA, obeticholic acid; PAS, patient access scheme; QALY, quality-adjusted life year; UDCA, ursodeoxycholic acid.

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Single technology appraisal

Obeticholic acid for primary biliary cirrhosis [ID785]

Dear Intercept,

The Evidence Review Group, Kleijnen Systematic Reviews, and the technical team at NICE have looked at the submission received on 30 September 2016 from Intercept. In general they felt that it is well presented and clear. However, the ERG and the NICE technical team would like further clarification on the clinical and cost effectiveness data (see questions listed at end of letter).

The ERG and the technical team at NICE will be addressing these issues in their reports.

Please provide your written response to the clarification questions by **5pm** on **4 November 2016**. Your response and any supporting documents should be uploaded to NICE Docs/Appraisals **https://appraisals.nice.org.uk/request/20103**

Two versions of your written response should be submitted; one with academic/commercial-in-confidence information clearly marked and one with this information removed.

Please underline all confidential information, and separately highlight information that is submitted as commercial in confidence in turquoise, and all information submitted as academic in confidence in yellow.

If you present data that are not already referenced in the main body of your submission and that are academic/commercial in confidence, please complete the attached checklist for confidential information.

Please do not embed documents (PDFs or spreadsheets) in your response because this may result in them being lost or unreadable.

If you have any queries on the technical issues raised in this letter, please contact [redacted] Technical Lead [redacted] Any procedural questions should be addressed to [redacted] Project Manager [redacted]

Yours sincerely

Eleanor Donegan
Technical Adviser – Appraisals
Centre for Health Technology Evaluation

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Encl. checklist for confidential information

Section A: Clarification on effectiveness data

Literature searching (all searches)

A1. Please confirm the host for the following resources:

- **Priority question:** Regarding the Embase strategy reported for the 2014/2015 searches: the company submission states "Embase (platform covers Medline and Medline ® In-Process)" (table 2 Appendix 2). Was this a single search conducted simultaneously over the 3 separate databases? Or a single search of Embase (which now contains all records from Medline and Medline in Process)?

- Regarding the Embase/Medline/Medline in Process 2014 and 2015 searches: please clarify whether "Embase" refers to Embase.com or Embase via Ovid or EBSCO. Regarding the Embase 2016 searches: please confirm that this used the Ovid platform (as stated for both the Medline and Medline in Process searches). Regarding the Cochrane Library 2014 and 2015 searches: please confirm that this used the Wiley interface.

A2. Were the date ranges used to identify clinical evidence the same as those reported in the cost effectiveness and health-related quality of life (HRQoL) sections?

Literature searching (clinical evidence)

A3. **Priority question:** Section 4.1 and Appendix 2 of the company submission describe a systematic review of studies of the efficacy and safety of interventions for primary biliary cirrhosis/cholangitis (PBC). Please clarify the following in relation to the selection and identification of studies.

- The eligibility criteria for the systematic review of trials specified 'All randomised controlled trials investigating an intervention to treat PBC were included' (company submission page 44). A post-hoc decision was made to exclude all randomised controlled trials (RCTs) that did not include at least one obeticholic acid (OCA) treatment arm (monotherapy or combination) (Appendix 2). Please explain the rationale for this decision.

- Please confirm that studies of mixed populations of PBC and patients with other conditions were excluded even if data were available for patients with PBC separately?

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A4. **Priority question:** Please provide a list of studies excluded from the review and reasons for exclusion. This list should include as a minimum the 136 articles excluded because they were within the scope of previous Cochrane reviews. It should also include the 36 articles (25 RCTS) excluded based on having no OCA treatment arm. These numbers have been derived from the PRISMA flow chart on page 46 of the company submission.

A5. Section 4.10 of the company submission states that 'indirect and mixed treatment comparisons were not conducted'. Was this decision made a priori or as a result of a lack of evidence? No mention is made of any searches, however page 44 of the clinical effectiveness states that "all randomised controlled trials investigating an intervention to treat PBC were included" and the strategies reported in Appendix 2 combine terms for PBC with an RCT filter. Please confirm if these searches were also screened to inform section 4.10.

A6. Section 4.11 of the company submission states that 'There are no non-RCTs relevant to this submission.' However the systematic review specifies RCTs as an inclusion criterion for study design. Please clarify if any searches were conducted to identify non-RCTS (to inform this section or adverse event estimates in the model) and provide full search strategies.

A7. Section 4.12 of the company submission states that all safety data reported in this section were derived from the POISE study, with supporting safety data obtained from two phase 2 trials. No searches for adverse events were reported. Please confirm whether any searches were conducted and if yes, provide full search strategies.

A8. Please provide search dates for the grey literature searches reported on page 8 of Appendix 2.

The POISE Trial

A9. **Priority question:** The POISE trial is based on surrogate outcomes. Tools exist to predict long-term outcomes from these surrogate outcomes. The ERG have identified a paper by Carbone et al (UK-PBC Risk Scores).[1] Please produce risk scores according to this paper for each intervention group at baseline and at 12 months follow-up, using patient level data from the POISE trial. Please calculate risk scores (5 years, 10 years and 15 years) for each patient at baseline and calculate the average for all patients in each treatment arm at baseline, and do the same for 12 months follow-up.

A10. **Priority question:** The POISE trial was restricted to patients with a relatively early stage of disease. What is the evidence for safety and effectiveness of OCA in more advanced stages of PBC?

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A11. The company submission lists 7 study centres in England (page 54). Please state the number of patients recruited in England.

A12. In the long-term extension to POISE patients were permitted to titrate to lower doses. Was this permitted in the double-blind phase of the trial in any of the treatment arms?

The COBALT Trial

A13. The ongoing COBALT RCT is mentioned on page 119 of the company submission. The ERG notes that the study start date is December 2014 and that the estimated study completion date is April 2023. Are there any interim data available from this trial?

Other

A14. Page 30 of the company submission mentions a sub-optimal response to ursodeoxycholic acid (UDCA). Please define sub-optimal response, inadequate response and absence of response to UDCA. How many people with PBC in England have disease with A) sub-optimal B) inadequate and C) no response to UDCA, respectively?

Section B: Clarification on cost-effectiveness data

Literature searching (cost, healthcare resource use and health-related quality of life)

B1. The PRISMA chart on page 124 of the company submission (figure 23) reports that 11 studies were excluded for study design/outcome and 2 for population after review of full text. Please list individual studies that were excluded at the full text stage and the reasons for exclusion.

B2. The strategy reported for the 2014 Embase healthcare resource use identification search (Table 40, Appendix 9) appears to be a duplicate copy of the HRQoL Embase strategy (Table 33, Appendix 8) and does not reflect the resource use terminology utilised in the update search run in June 2016 (Tables 43 & 44, Appendix 9). If this has been included in error, please provide details of the correct strategy.

B3. Pages 123, 153 and 162 state that a grey literature search was conducted to inform the sections on cost effectiveness, HRQoL and healthcare resource use identification. However, no further details or strategies are provided. Please confirm whether these statements refer to the grey literature search reported on page 8 of Appendix 2 for Clinical Effectiveness? If not, please provide full strategies for each search.

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Model structure and population

B4. **Priority question:** Page 138 of the company submission states that patients with abnormal bilirubin and those with compensated cirrhosis were combined into one health state (see also figure 24).

a. Please confirm the definition of abnormal bilirubin and justify this definition.

i. Is abnormal defined as total bilirubin >20 µmol/L and rising? Or, does total bilirubin >20 µmol/L indicate that bilirubin levels are abnormal and also rising?

b. Please provide a clinical rationale for combining abnormal bilirubin and compensated cirrhosis into one health state. Is abnormal bilirubin assumed to be equivalent to having compensated cirrhosis?

c. Are the transitions from and to this health state reflective of this combination of health states (people with abnormal bilirubin **and** people with compensated cirrhosis).

d. Please provide the working definition of compensated cirrhosis, particularly in terms of total bilirubin?

B5. **Priority question:** The model structure considers thresholds based on ALP and total bilirubin.

a. Figure 24 of the company submission states thresholds of 200 u/L for ALP and 20 µmol/L for total bilirubin. Different thresholds have been used in the economic model submitted in Excel (ALP; 1.67 ULN and TB of 1.0 x ULN). Table 49 of the company submission does not include a threshold for total bilirubin. Please clarify what threshold is used in the company's base-case results and provide all Tables, Figures and results using this threshold.

b. Please justify why the Metavir fibrosis score is not used (F0-F4) in the model structure.

B6. **Priority question:** The liver disease component of the model assumes that patients treated with OCA (monotherapy or combined with UDCA) can move to an improved health state (e.g. to ALP ≤ 200 u/L and TB ≤ 20 µmol/L), while patients not treated with OCA cannot. Please justify this assumption.

B7. The model seems to imply that demographics (in terms of age, gender and weight) are similar for both UDCA-intolerant patients and UCDA inadequate responders (see model settings). However, the company submission states "patients with earlier age of onset and/or male sex often have more aggressive disease that is refractory to

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existing treatment". Please explain how the model accounts for different demographic profiles for UDCA intolerant patients and UCDA inadequate responders.

B8. In the first year of the model (liver disease component), the transition probabilities for the OCA treatment arm seem to be based on the OCA arms of the POISE RCT. Patients then remain in the health state they were in at 12 months, to reflect the sustained reduction in ALP and bilirubin demonstrated in the preliminary results from the long-term safety extension phase. Please confirm.

B9. The model includes a health state for recurrence of PBC (PBC re-emerge). It is unclear what this health state exactly entails (e.g. is it a re-infection of liver disease; or re-emergence of specifically PBC)

a. Please provide a precise definition of the PBC re-emerge health state.

b. Please clarify whether this health state considers the re-administration of OCA and/or UDCA for the treatment of PBC? Please justify why.

Comparators

B10. **Priority question:** Fibrates have been excluded as a comparator on the basis that "Fibrates are not licensed in the UK, nor are they standard of care, and they are contraindicated in PBC. They are rarely used, with only [redacted] of patients in the UK-PBC cohort having ever taken fibrates for any condition (not necessarily for PBC)" (table 1 of the company submission). The usage of fibrates in the UK was referenced to a personal communication with George Mells. Given that fibrates are a comparator in the scope:

a. Please provide details of the personal communication with George Mells (and response)?

b. Is there any other corroborating evidence in support of the personal communication? Please comment on the clinical trial evidence for fibrates in PBC (ideally this evidence would be sourced systematically, but it is acknowledged that this might not be feasible in the timeframe).

c. Please provide details of the number of patients (by country) who were excluded from the POISE trial because of use of fibrates (a medication which was prohibited in the trial).

d. In addition, please provide reasons for exclusion for the 99 screen failures mentioned in the CONSORT patient-flow diagram (company submission, Figure 11).

e. Please include fibrates in the economic model and present the results.

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B11. The company have suggested that placebo is a comparator for people who are unable to tolerate UDCA. Please confirm that this refers to 'no additional treatment' in the final scope and describe the management of disease in patients who cannot tolerate UDCA.

Treatment effectiveness and adverse events

B12. **Priority question:** Table 49 of the company submission appears to describe the transition probabilities for the OCA comparator. The table is unclear:

a. Please provide the primary source(s) of the numbers used in the upper part of the table.

b. Please explain how probabilities are obtained from the upper part of the table.

c. Please provide the methods (calculations) and results.

d. Please explain how these numbers are used in the model and how discontinuation is handled in the model.

e. Please explain why discontinuation is only included in the first 3 months of the year.

f. Please provide results of a sensitivity analysis including discontinuation in the later months (i.e. months 3-6, 6-9, 9-12).

B13. **Priority question:** For the comparators in the model, transition probabilities are primarily obtained from the literature.

a. Please justify why transition probabilities for the PBC-specific component of the model are not based on POISE for all treatment arms.

b. Please provide the results of a sensitivity analysis using the clinical data from POISE to inform the transition probabilities for all comparators for the PBC-specific component of the model. Provide details of the methods used.

B14. **Priority question:** Please explain the following concerning Table 50 of the company submission:

a. Please provide the primary source(s) on which the transition probabilities are based.

b. Please detail the characteristics of patients included in this/these primary source(s).

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c. Please provide an overview of the data extracted from this/these primary source(s) to calculate the transition probabilities.

d. In addition to Appendix 10, please provide a detailed explanation of the methods and sources used for calibration after data extraction (i.e. provide the calculations for the quarterly transition probabilities) and an Excel sheet containing these calculations.

B15. **Priority question:** Please explain the following concerning Table 52 of the company submission:

a. Please provide the primary source(s) on which the transition probabilities are based.

b. Please detail the characteristics of patients included in this/these primary source(s).

c. Please provide an overview of the data extracted from this/these primary source(s) to calculate the transition probabilities

d. Please explain how Table 51 of the company submission should be used to obtain the estimates in Table 52.

B16. **Priority question:** Please provide an overview of all transition probabilities used for all comparators and all time points (if time-dependent) for the PBC-specific component, incorporating:

a. the estimated probability

b. standard error

c. primary source

d. justification for source

e. method of calculation if applicable.

B17. Please provide an overview of adverse event proportions for fatigue, pruritus and nausea (stratified by treatment).

Health related quality of life

B18. **Priority question:** A recent publication (Dyson et al 2016[2]) suggested that……"The majority of patients with primary biliary cholangitis do not feel their QoL is impaired, although impairment is reported by a sizeable minority".

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a. Please justify the primary sources used for quality of life estimates.

b. Please justify the high utility values for PBC, considering the general population utility (age-dependent).

c. Please clarify why the utilities from a hepatitis B/C population are appropriate (with or without the reduction of [redacted]), and justify that these health state utility values are based on the most appropriate source(s). Please explain the rationale for reducing the hepatitis values by [redacted].

B19. The impact of adverse events on health-related quality of life is not included in the cost-effectiveness model. Please provide a sensitivity analysis including the influence of adverse events on quality of life.

Resource use and costs

B20. It is unclear how the technology cost is used to obtain the total annual technology costs (company submission Table 65). Please clarify and justify the calculation of total annual technology costs.

B21. Costs of transplant and follow up costs are derived from the literature.

a. Please explain the relevance of using transplant-related cost assumptions based on Hepatitis C and B patients (Wright et al. 2006[3] and Singh 2014[4]). Explain why NHS reference costs were not used.

b. Please provide the results of a sensitivity analysis using reference cost estimates for liver transplant.

B22. Outpatient appointment costs are based on expert opinion.

a. Please justify why outpatient appointment costs are based on expert opinion and not NHS reference costs (Table 66).

b. Please provide a cost estimate for outpatient appointments based on NHS reference costs. Provide the results of a sensitivity analysis using this estimate.

B23. Please justify why the health state cost for 'Abnormal/Total bilirubin> 20 µmol/L and rising, or CC' is half the 'DCC' health state cost.

Results and validation

B24. Please provide an overview of disaggregated life years gained, as provided for QALYs gained in Tables 73 and 74 of the company submission.

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B25. Please provide the outcomes of expert opinion meetings (i.e. individual answers on all of the questions provided in Appendix 11).

B26. No cross and external validations have been performed and no results of the validation steps described in Section 5.10.1 of the company submission are provided.

a. Please perform cross and external validations (for instance, by using the following tool: http://www.uk-pbc.com/resources/tools/riskcalculator/).

b. Please provide the results of other validation steps as described in Section 5.10.1 (e.g. comparison of model results with POISE data).

References

[1] Carbone M, Sharp SJ, Flack S, Paximadas D, Spiess K, Adgey C, et al. The UK-PBC risk scores: derivation and validation of a scoring system for long-term prediction of end-stage liver disease in primary biliary cholangitis. *Hepatology* 2016;63(3):930-50.

[2] Dyson JK, Wilkinson N, Jopson L, Mells G, Bathgate A, Heneghan MA, et al. The inter-relationship of symptom severity and quality of life in 2055 patients with primary biliary cholangitis. *Aliment Pharmacol Ther* 2016:Epub 2016 Sep 19.

[3] Wright M, Grieve R, Roberts J, Main J, Thomas HC. Health benefits of antiviral therapy for mild chronic hepatitis C: randomised controlled trial and economic evaluation. *Health Technol Assess* 2006;10(21):1-113, iii.

[4] Singh J, Longworth L. Estimating the cost of liver transplantation in patients diagnosed with chronic hepatitis C and B in the Uk [Abstr PGI33]. Paper presented at ISPOR 17th Annual European Congress; 8-12 Nov 2014; Amsterdam: The Netherlands *Value Health* 2014;17(7):A368.

Single technology appraisal

Obeticholic acid for primary biliary cirrhosis [ID785]

Intercept's responses to ERG questions

04 November 2016

Section A: Clarification on effectiveness data

Literature searching (all searches)

A1. Please confirm the host for the following resources:

- **Priority question:** Regarding the Embase strategy reported for the 2014/2015 searches: the company submission states "Embase (platform covers Medline and Medline ® In-Process)" (table 2 Appendix 2). Was this a single search conducted simultaneously over the 3 separate databases? Or a single search of Embase (which now contains all records from Medline and Medline in Process)?

A single search of Embase, which contains all records from Medline and Medline in-Process, was performed.

- Regarding the Embase/Medline/Medline in Process 2014 and 2015 searches: please clarify whether "Embase" refers to Embase.com or Embase via Ovid or EBSCO. Regarding the Embase 2016 searches: please confirm that this used the Ovid platform (as stated for both the Medline and Medline in Process searches). Regarding the Cochrane Library 2014 and 2015 searches: please confirm that this used the Wiley interface.

The Embase searches in 2014 and 2015 used Embase.com, and the Embase 2016 search used the Ovid platform.

The Cochrane library searches in 2014 and 2015 used the Wiley interface.

A2. Were the date ranges used to identify clinical evidence the same as those reported in the cost effectiveness and health-related quality of life (HRQoL) sections?

The date ranges of all searches conducted in 2014 were from database creation as reported in the cost-effectiveness and HRQoL searches (e.g. 1966 for Embase) to 2014. Subsequent update searches were from date of previous search to date of current search, e.g. the 2015 update searched from 2014 to 2015.

Literature searching (clinical evidence)

A3. **Priority question:** Section 4.1 and Appendix 2 of the company submission describe a systematic review of studies of the efficacy and safety of interventions for primary biliary cirrhosis/cholangitis (PBC). Please clarify the following in relation to the selection and identification of studies.

- The eligibility criteria for the systematic review of trials specified 'All randomised controlled trials investigating an intervention to treat PBC were included' (company submission page 44). A post-hoc decision was made to exclude all randomised controlled trials (RCTs) that did not include at least one obeticholic acid (OCA) treatment arm (monotherapy or combination) (Appendix 2). Please explain the rationale for this decision.

When the protocol for the systematic literature review was designed, the strategy was to keep the criteria as broad as possible. However, for the current submission, it was clear that there were no other treatments licensed or being used in the UK for patients with an inadequate response to or intolerance to UDCA. Therefore, only RCTs that included at least one OCA arm were relevant for this submission.

- Please confirm that studies of mixed populations of PBC and patients with other conditions were excluded even if data were available for patients with PBC separately?

Studies of mixed populations of PBC and patients with other conditions were excluded, even if data were available for patients with PBC separately.

A4. **Priority question:** Please provide a list of studies excluded from the review and reasons for exclusion. This list should include as a minimum the 136 articles excluded because they were within the scope of previous Cochrane reviews. It should also include the 36 articles (25 RCTS) excluded based on having no OCA treatment arm. These numbers have been derived from the PRISMA flow chart on page 46 of the company submission.

A total of 136 publications were removed at second pass because they fell within the scope of the Cochrane reviews. The relevant publications are listed in Appendix 1 at the end of this document.

The 36 publications excluded based on having no OCA treatment arm are listed in Appendix 2 at the end of this document.

A5. Section 4.10 of the company submission states that 'indirect and mixed treatment comparisons were not conducted'. Was this decision made a priori or as a result of a lack of evidence? No mention is made of any searches, however page 44 of the clinical effectiveness states that "all randomised controlled trials investigating an intervention to treat PBC were included" and the strategies reported in Appendix 2

combine terms for PBC with an RCT filter. Please confirm if these searches were also screened to inform section 4.10.

It was identified that there were no treatments licensed or being used in the UK for patients with an inadequate response or intolerance to UDCA, and therefore there was no relevant comparator to OCA other than UDCA, which has been compared head to head in POISE. Therefore, an indirect or mixed treatment comparison was not necessary. The reason for including any intervention to treat PBC in the systematic literature review, and the subsequent post-hoc decision to only include publications with an OCA treatment arm, is explained in the answer to question A3.

A6. Section 4.11 of the company submission states that 'There are no non-RCTs relevant to this submission.' However the systematic review specifies RCTs as an inclusion criterion for study design. Please clarify if any searches were conducted to identify non-RCTS (to inform this section or adverse event estimates in the model) and provide full search strategies.

No non-RCT searches were conducted, since head-to-head RCT data (more robust than non-RCT data) were available for OCA vs UDCA in POISE.

A7. Section 4.12 of the company submission states that all safety data reported in this section were derived from the POISE study, with supporting safety data obtained from two phase 2 trials. No searches for adverse events were reported. Please confirm whether any searches were conducted and if yes, provide full search strategies.

No separate searches for adverse events were conducted, since adverse events and any safety data for OCA would be included in the evidence identified in the clinical systematic literature review.

A8. Please provide search dates for the grey literature searches reported on page 8 of Appendix 2.

Grey literature searches were conducted on the same dates as the relevant database searches.

The POISE Trial

A9. **Priority question:** The POISE trial is based on surrogate outcomes. Tools exist to predict long-term outcomes from these surrogate outcomes. The ERG have identified a paper by Carbone et al (UK-PBC Risk Scores). Please produce risk scores according to this paper for each intervention group at baseline and at 12 months follow-up, using patient level data from the POISE trial. Please calculate risk scores (5 years, 10 years and 15 years) for each patient at baseline and calculate the average for all patients in each treatment arm at baseline, and do the same for 12 months follow-up.

Another recent publication by Carbone et al investigated the risk of end-stage liver disease (ESLD) in POISE patients (1). The authors aimed to assess the change in the predicted risk of ESLD with the UK-PBC algorithm in patients who initially received placebo ± UDCA in the double-blind phase of the trial, then switched to OCA ± UDCA during the open-label extension stage of the trial.

After 1 year of continued standard-of-care treatment, patients on placebo ±UDCA experienced an increase in their predicted risk of ESLD (using the UK-PBC model), due to worsening liver biochemistry (Table 1). After 1 year of OCA treatment, the predicted risk of ESLD was reduced at 5, 10 and 15 years.

Table 1: Predicted risk of ESLD in patients with PBC before and after OCA treatment

	Baseline Placebo ± UDCA (n=73)	Month 12 DB Placebo ± UDCA (n=68)	Month 12 OLE Placebo ± UDCA (n=58)
Median (IQR) 5-year risk, %	1.9 (1.1, 3.5)	2.3 (1.1, 4.4)	1.4 (0.8, 3.3)*
Median (IQR) 10-year risk, %	6.4 (3.8, 11.3)	7.5 (3.6, 14.0)	4.7 (2.7, 10.6)*
Median (IQR) 15-year risk, %	11.5 (6.9, 19.9)	13.5 (6.6, 24.4)	8.5 (5.0, 18.8)*

Abbreviations: DB, double blind; ESLD, end-stage liver disease; IQR, interquartile range; OCA, obeticholic acid; OLE, open label extension; PBC, primary biliary cirrhosis/cholangitis; UDCA, ursodeoxycholic acid.
*p<0.05; p-value for within-group comparison using Wilcoxon Signed Rank test comparing Month 12 DB and Month 12 OLE.
Source: Carbone 2016 (1)

A10. **Priority question:** The POISE trial was restricted to patients with a relatively early stage of disease. What is the evidence for safety and effectiveness of OCA in more advanced stages of PBC?

Two analyses have been performed to assess the safety and efficacy of OCA in more advanced stages of PBC.

The safety of OCA was evaluated in a more advanced disease population using several definitions to approximate severe disease, including a clinical composite definition (based on biochemical criteria, non-invasive measures of fibrosis, biopsies, and/or medical history of decompensation) and presence of cirrhosis. Using the clinical composite definition, 72 patients (30, 22, and 20 patients in the placebo, OCA titration, and OCA 10 mg treatment arms, respectively) were identified with evidence of advanced disease.

Albeit a small sample size, based on the entirety of data, there was not an increased risk in patients with advanced disease. All clinical hepatic AEs in POISE occurred in four patients with advanced disease per the clinical composite criteria (one in the placebo arm, two in the OCA titration arm, and one in the OCA 10 mg arm), and are likely related to disease progression as part of the natural history of PBC.

A post-hoc analysis was also performed (2) to assess the efficacy and safety of OCA in the subset of patients in POISE with cirrhosis, as defined by biopsy-proven cirrhosis, transient elastography of ≥16.9 kPa, or history of cirrhosis. It was found that 13 patients in the placebo arm, 13 patients in the OCA titration arm, and 10 patients in the OCA 10 mg arm had cirrhosis. ALP levels were significantly more reduced over 12 months in the OCA treatment

groups than the placebo groups, and bilirubin increased in the placebo group but remained stable in the OCA treatment groups (). The primary composite endpoint in POISE (ALP <1.67x ULN and bilirubin ≤ULN and ≥15% reduction in ALP from baseline) was met by 8% of subjects in the placebo arm, 54% of subjects in the OCA titration arm, and 40% of subjects in the OCA 10 mg arm after 12 months.

Table 2: Effect on ALP and total bilirubin on patients with cirrhosis in POISE

	Placebo ± UDCA (n=13)	OCA titration ± UDCA (n=13)	OCA 10 mg ± UDCA (n=10)
Mean baseline ALP (SD), U/L	322.5 (138.9)	352.0 (173.6)	305.7 (91.6)
LS mean change from baseline at Month 12 in ALP (SE), U/L	–24.3 (50.6)	–157.9 (48.8)**	–176.2 (56.5)**
Mean baseline total bilirubin (SD), µmol/L	13.0 (7.8)	14.2 (7.7)	16.5 (7.7)
LS mean change from baseline at Month 12 in total bilirubin (SE), µmol/L	4.7 (1.8)	0.6 (1.6)*	–0.5 (2.1)*

Abbreviations: ALP, alkaline phosphatase; LS, least squares; SD, standard deviation; SE, standard error; UDCA, ursodeoxycholic acid.

In terms of safety in patients with cirrhosis, there were no additional concerns compared with the overall patient population in POISE. However, pruritus was experienced by a greater proportion of patients with cirrhosis than the general population in the OCA treatment groups (69% vs 56%, respectively, in the OCA titration group, and 80% vs 68%, respectively, in the OCA 10 mg group).

The long-term clinical benefit and safety of OCA is currently being investigated in an ongoing double-blind, placebo-controlled confirmatory study (747-302; COBALT), which includes patients with more advanced stages of PBC.

A11. The company submission lists 7 study centres in England (page 54). Please state the number of patients recruited in England.

There were 16 patients recruited in England that were randomised into the trial.

A12. In the long-term extension to POISE patients were permitted to titrate to lower doses. Was this permitted in the double-blind phase of the trial in any of the treatment arms?

Patients were not permitted to titrate to lower doses of OCA in the double-blind phase of POISE. All patients initiated the LTSE phase of POISE at 5 mg once daily, and so this assessed the effect of down-titration on the patients in the OCA 10 mg fixed dose arm of the double-blind phase and patients in the titration arm who had up-titrated to 10 mg OCA for months 6–12 in the double-blind phase.

The COBALT Trial

A13. The ongoing COBALT RCT is mentioned on page 119 of the company submission. The ERG notes that the study start date is December 2014 and that the estimated

study completion date is April 2023. Are there any interim data available from this trial?

No, there are no interim data available and no interim analysis is planned since COBALT is an events-driven trial and 121 primary endpoint events need to have occurred before the trial will report and analyses will be performed.

Other

A14. Page 30 of the company submission mentions a sub-optimal response to ursodeoxycholic acid (UDCA). Please define sub-optimal response, inadequate response and absence of response to UDCA. How many people with PBC in England have disease with A) sub-optimal B) inadequate and C) no response to UDCA, respectively?

For the purpose of this submission, a suboptimal response is the same as an inadequate response. A complete lack of response to UDCA has not been documented in the literature, and is likely included in the definition of suboptimal or inadequate response. Therefore, it is not possible to split people into the three separate categories specified in the question. Nearly 40% of patients with PBC exhibit inadequate response to UDCA (3).

Section B: Clarification on cost-effectiveness data

Literature searching (cost, healthcare resource use and health-related quality of life)

B1. The PRISMA chart on page 124 of the company submission (figure 23) reports that 11 studies were excluded for study design/outcome and 2 for population after review of full text. Please list individual studies that were excluded at the full text stage and the reasons for exclusion.

The articles that were excluded for study design/outcome are listed in Appendix 3 and those excluded for population are listed in Appendix 4, both of which are at the end of this document.

B2. The strategy reported for the 2014 Embase healthcare resource use identification search (Table 40, Appendix 9) appears to be a duplicate copy of the HRQoL Embase strategy (Table 33, Appendix 8) and does not reflect the resource use terminology utilised in the update search run in June 2016 (Tables 43 & 44, Appendix 9). If this has been included in error, please provide details of the correct strategy.

This was an error. A corrected version of the appendix is included below.

Appendix 9: Cost and healthcare resource identification, measurement and valuation studies

Databases searched and service provider

- Embase 1966 to 2014
- Medline 1966 to 2014
- Medline (R) In-Process 1966 to 2014
- Cochrane Database of Systematic Reviews 1996 to 2014
- Database of Abstracts of Reviews of Effects 1994 to 2014
- Health Technology Assessment 1989 to 2014
- NHS Economic Evaluation Database 1968 to 2014
- EconLIT with Full Text 1961 to 2014
- Health Economic Evaluations Database 1990 to 2014

Dates of searches

The searches were conducted in September 2014. The update was conducted in February 2016.

Search strategy

Table 3: Embase cost and resource use utilization search strategy

Embase (platform covers Medline and Medline® In-Process)			
Index	Description	Search terms	Hits
1	Terms for population	'primary biliary cirrhosis'/exp OR 'primary biliary cirrhosis'	10,402
2	Cost-effectiveness filter	socioeconomics'/exp OR 'cost benefit analysis'/exp OR 'cost effectiveness analysis'/exp OR 'cost of illness'/exp OR 'economic evaluation'/exp OR 'cost utility'/exp OR 'cost control'/exp OR 'economic aspect'/exp OR 'financial management'/exp OR 'health care cost'/exp OR 'health care financing'/exp OR 'health economics'/exp OR 'hospital cost'/exp OR fiscal:ab,ti OR financial:ab,ti OR finance:ab,ti OR funding:ab,ti OR 'cost minimization analysis'/exp OR 'cost estimate':ab:ti OR 'cost variable':ab:ti OR 'unit cost':ab:ti	1,183,117
3	Resource use / societal cost filter	'resource use' OR 'resource utilisation' OR 'resource utilization' OR 'productivity'/exp OR 'absenteeism'/exp OR presenteeism OR 'work disability' OR 'work capacity'/exp OR 'caregiver'/exp OR 'caregiver	108,882

Embase (platform covers Medline and Medline® In-Process)			
		burden'/exp OR 'caregiver support'/exp OR 'indirect cost'	
6	Combine searches	#1 AND (#2 OR #3) NOT ('animal'/exp NOT 'human'/exp) NOT (letter:it OR editorial:it OR note:it)	114

Table 4: Cochrane Library cost and resource use utilization search strategy

The Cochrane Library (this platform covers Cochrane Database of Systematic Reviews, Database of Abstract of Reviews of Effects, Health Technology Assessment, NHS Economic Evaluation Database)			
Index	Description	Search terms	Hits
1	Terms for population	MeSH descriptor: [Liver Cirrhosis, Biliary] explode all trees	236
		"primary biliary cirrhosis"	523
2	Combine searches	#1 OR #2 in Cochrane Reviews (Reviews and Protocols), Other Reviews, Technology Assessments and Economic Evaluations	65

Table 5: EBSCO cost and resource use utilization search strategy

EBSCO host (this platform covers EconLit with Full Text, Health Economic Evaluations Database)			
Index	Description	Search terms	Hits
1	Terms for population	Primary biliary cirrhosis	13

Additional searches

Table 6: Cost and healthcare resource identification systematic review update search strategy- EMBASE

Embase 1980 to 2016 Week 13: accessed June 13th 2016		
#	**Searches**	**Results**
1	exp primary biliary cirrhosis/	8269
2	(primary biliary adj3 (cholangitis or cirrhosis)).mp. [mp=title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword]	11214
3	pbc.mp.	6111
4	exp socioeconomics/	204548
5	exp "cost benefit analysis"/	71339
6	exp "cost effectiveness analysis"/	114497

Embase 1980 to 2016 Week 13: accessed June 13th 2016		
#	**Searches**	**Results**
7	exp "cost of illness"/	16409
8	exp economic evaluation/	242514
9	exp "cost utility analysis"/	6759
10	exp "cost control"/	55630
11	exp economic aspect/	1260488
12	exp financial management/	342101
13	exp "health care cost"/	232855
14	exp health care financing/	12030
15	exp health economics/	690164
16	exp "hospital cost"/	29031
17	fiscal.ti,ab.	7541
18	financial.ti,ab.	75875
19	finance.ti,ab.	4859
20	funding.ti,ab.	43301
21	exp "cost minimization analysis"/	2810
22	cost estimate.ti,ab.	275
23	cost variable.ti,ab.	50
24	unit cost.ti,ab.	1114
25	4 or 5 or 6 or 7 or 8 or 9 or 10 or 11 or 12 or 13 or 14 or 15 or 16 or 17 or 18 or 19 or 20 or 21 or 22 or 23 or 24	1310899
26	1 or 2 or 3	13078
27	'resource use'.ti,ab.	8401
28	'resource utili?ation'.ti,ab.	10980
29	exp productivity/	29789

Embase 1980 to 2016 Week 13: accessed June 13th 2016		
#	**Searches**	**Results**
30	exp absenteeism/	14129
31	presenteeism.ti,ab.	1103
32	work disability.ti,ab.	1925
33	exp work capacity/	10237
34	exp caregiver burden/ or exp caregiver/	53866
35	exp caregiver support/	1937
36	indirect cost*.ti,ab.	6527
37	27 or 28 or 29 or 30 or 31 or 32 or 33 or 34 or 35 or 36	128789
38	25 or 37	1395559
39	26 and 38	221
40	limit 39 to yr="2014 -Current"	41

Table 7: Cost and healthcare resource identification systematic review update search strategy-MEDLINE

Ovid MEDLINE(R) In-Process & Other Non-Indexed Citations and Ovid MEDLINE(R) 1946 to Present: accessed June 13th 2016		
#	**Searches**	**Results**
1	(primary biliary adj3 (cholangitis or cirrhosis)).mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier]	7343
2	pbc.mp.	4127
3	exp Liver Cirrhosis, Biliary/	7480
4	exp Cost-Benefit Analysis/	66406

5	exp "Cost of Illness"/	20694
6	exp "Cost Control"/	30556
7	exp Financial Management/	82454
8	exp Health Care Costs/	52500
9	exp Hospital Costs/	8906
10	fiscal.ti,ab.	6486
11	financial.ti,ab.	58421
12	finance.ti,ab.	4025
13	funding.ti,ab.	36742
14	cost estimate.ti,ab.	189
15	cost variable.ti,ab.	37
16	unit cost.ti,ab.	773
17	4 or 5 or 6 or 7 or 8 or 9 or 10 or 11 or 12 or 13 or 14 or 15 or 16	304288
18	'resource use'.ti,ab.	5795
19	'resource utili?ation'.ti,ab.	6434
20	exp Efficiency/	12239
21	exp Absenteeism/	7964
22	exp Presenteeism/	31

23	exp Work Capacity Evaluation/	5444
24	exp Caregivers/	25418
25	'work disability'.ti,ab.	1572
26	(caregiver adj2 (support or burden)).ti,ab.	2720
27	indirect cost*.ti,ab.	4399
28	18 or 19 or 20 or 21 or 22 or 23 or 24 or 25 or 26 or 27	67320
29	17 or 28	357642
30	1 or 2 or 3	10644
31	30 and 29	58
32	limit 31 to yr="2014 -Current"	1

Table 8: Cost and healthcare resource identification systematic review update search strategy-EconLit

Econlit 1886 to February 2016: accessed March 24th 2016		
#	**Searches**	**Results**
1	(primary biliary adj3 (cholangitis or cirrhosis)).mp. [mp=heading words, abstract, title, country as subject]	1
2	pbc.mp. [mp=heading words, abstract, title, country as subject]	73
3	1 or 2	74
4	limit 3 to yr="2014 -Current"	12

Table 9: Cost and healthcare resource identification systematic review update search strategy- EBM Reviews

EBM Reviews - Cochrane Central Register of Controlled Trials February 2016, EBM Reviews - Cochrane Database of Systematic Reviews 2005 to March 23, 2016, EBM Reviews - Database of Abstracts of Reviews of Effects 1st Quarter 2016, EBM Reviews - Health Technology Assessment 1st Quarter 2016, EBM Reviews - NHS Economic Evaluation Database 1st Quarter 2016: accessed June 13th 2016		
#	**Searches**	**Results**
1	(primary biliary adj3 (cholangitis or cirrhosis)).mp. [mp=ti, ot, ab, sh, hw, kw, tx, ct]	569
2	pbc.mp.	303
3	exp Liver Cirrhosis, Biliary/	227
4	exp Cost-Benefit Analysis/	17067
5	exp "Cost of Illness"/	1227
6	exp "Cost Control"/	1226
7	exp Financial Management/	285
8	exp Health Care Costs/	6961
9	exp Hospital Costs/	1436
10	fiscal.ti,ab.	68
11	financial.ti,ab.	1948
12	finance.ti,ab.	42
13	funding.ti,ab.	2759

EBM Reviews - Cochrane Central Register of Controlled Trials February 2016, EBM Reviews - Cochrane Database of Systematic Reviews 2005 to March 23, 2016, EBM Reviews - Database of Abstracts of Reviews of Effects 1st Quarter 2016, EBM Reviews - Health Technology Assessment 1st Quarter 2016, EBM Reviews - NHS Economic Evaluation Database 1st Quarter 2016: accessed June 13th 2016		
#	**Searches**	**Results**
14	cost estimate.ti,ab.	16
15	cost variable.ti,ab.	2
16	unit cost.ti,ab.	86
17	4 or 5 or 6 or 7 or 8 or 9 or 10 or 11 or 12 or 13 or 14 or 15 or 16	25365
18	'resource use'.ti,ab.	3910
19	'resource utili?ation'.ti,ab.	750
20	exp Efficiency/	309
21	exp Absenteeism/	457
22	exp Presenteeism/	0
23	exp Work Capacity Evaluation/	195
24	exp Caregivers/	1326
25	'work disability'.ti,ab.	134
26	(caregiver adj2 (support or burden)).ti,ab.	407
27	indirect cost*.ti,ab.	408
28	18 or 19 or 20 or 21 or 22 or 23 or 24 or 25 or 26 or 27	6815

EBM Reviews - Cochrane Central Register of Controlled Trials February 2016, EBM Reviews - Cochrane Database of Systematic Reviews 2005 to March 23, 2016, EBM Reviews - Database of Abstracts of Reviews of Effects 1st Quarter 2016, EBM Reviews - Health Technology Assessment 1st Quarter 2016, EBM Reviews - NHS Economic Evaluation Database 1st Quarter 2016: accessed June 13th 2016		
#	Searches	Results
29	17 or 28	30648
30	1 or 2 or 3	668
31	30 and 29	11
32	limit 31 to yr="2014 -Current" [Limit not valid in DARE; records were retained]	0

Data abstraction strategy

Identified studies were independently assessed by two reviewers in order to ascertain they met the pre-defined inclusion/exclusion criteria and any discrepancies were resolved by a third party. Relevant information was extracted into the STA template/into a pre-defined Microsoft Excel spreadsheet by a reviewer. A second reviewer checked the data extraction and any inconsistencies were resolved through discussion.

B3. Pages 123, 153 and 162 state that a grey literature search was conducted to inform the sections on cost effectiveness, HRQoL and healthcare resource use identification. However, no further details or strategies are provided. Please confirm whether these statements refer to the grey literature search reported on page 8 of Appendix 2 for Clinical Effectiveness? If not, please provide full strategies for each search.

The grey literature searches were performed on the following websites for the cost-effectiveness, HRQoL, and healthcare resource use systematic literature reviews:

- American Association for the Study of Liver Diseases (AASLD) http://www.aasld.org/Pages/Default.aspx
- European Association for the Study of the Liver (EASL) http://www.easl.eu/
- American College of Gastroenterology (ACG) http://gi.org/
- Digestive Disease Week (DDW) http://www.ddw.org/
- United European Gastroenterology Week (UEGW) http://www.ueg.eu/

- Canadian Digestive Disease Week http://www.cag-acg.org/
- Japan Digestive Disease Week http://www.jddw.jp/english/index.html
- Liver Foundation UK http://www.liverfoundation.org.uk/
- The Foundation for Liver Research http://www.liver-research.org.uk/
- American Liver Foundation http://www.liverfoundation.org/
- Canadian Liver Foundation http://www.liver.ca/
- British Liver Trust http://www.britishlivertrust.org.uk/
- The British Library http://www.bl.uk
- National Institute for Health Research http://www.hta.ac.uk/
- National Institute for Health and Care Excellence (NICE) http://www.nice.org.uk/
- Scottish Medicines Consortium (SMC) http://www.scottishmedicines.org.uk/Home
- National Centre for Pharmacoeconomics (NCPE) Ireland http://www.ncpe.ie/submission-processs/hta-guidelines/
- All Wales Medicines Strategy Group (AWMSG) http://www.wales.nhs.uk/sites3/home.cfm?orgid=371
- Institute for Quality and Efficiency in Health Care (IQWiG) https://www.iqwig.de/en/home.2724.html
- Haute Autorité de Santé (HAS) http://www.has-sante.fr/portail/jcms/j_5/home
- Italian Medicines Agency (AIFA) http://www.agenziafarmaco.gov.it/en
- Agencia de Evaluación de Tecnologías Sanitarias (AETS) http://www.isciii.es/
- Canadian Agency for Drugs and Technologies in Health (CADTH) http://www.cadth.ca/
- Pharmaceutical Benefits Advisory Committee (PBAC) http://www.pbs.gov.au/info/industry/listing/participants/pbac
- Search Engine (Google) http://www.google.co.uk

Search terms, where applicable, were 'primary biliary cirrhosis', as well as 'primary biliary cholangitis' in the update searches, due to the recent name change of the disease.

Model structure and population

B4. **Priority question:** Page 138 of the company submission states that patients with abnormal bilirubin and those with compensated cirrhosis were combined into one health state (see also figure 24).

a. Please confirm the definition of abnormal bilirubin and justify this definition.

In POISE, abnormal bilirubin is considered to be anything >ULN, also commonly defined as 1.2 mg/dL or 20 µmol/L. Total bilirubin is a well-established and independent predictor of prognosis in PBC, regardless of treatment (4-6), and is incorporated into most scoring systems and prediction models of clinical outcomes for PBC and other liver diseases,

including the Mayo Risk Score for PBC (7), MELD (8), and Child-Turcotte-Pugh (9, 10). Lammers et al conducted a meta-analysis of data from 4,119 patients with PBC (11) that demonstrated that after one year of UDCA treatment, a bilirubin level >ULN was associated with a higher risk of liver transplant or death compared with a bilirubin level <ULN (hazard ratio 3.215; 95% CI: 2.903, 3.562). The stratification of risk using bilirubin <ULN or >ULN to determine prognostic risk is common.

i. Is abnormal defined as total bilirubin >20 µmol/L and rising? Or, does total bilirubin >20 µmol/L indicate that bilirubin levels are abnormal and also rising?

As described above, abnormal bilirubin is defined as total bilirubin >ULN, which corresponds to 20 µmol/L. The interplay with rising bilirubin levels is an added component that increases risk beyond abnormal bilirubin levels in the model.

b. Please provide a clinical rationale for combining abnormal bilirubin and compensated cirrhosis into one health state. Is abnormal bilirubin assumed to be equivalent to having compensated cirrhosis?

In previous chronic liver disease models (12-15), patients were followed up in terms of their fibrotic stage progression, with all patients progressing to compensated cirrhosis before being at risk of developing decompensated cirrhosis, hepatocellular carcinoma (HCC), or being eligible to be added to the liver transplant waiting list.

In PBC, this is not possible and therefore certain assumptions had to be made. Firstly, the increased risk of progression of patients with abnormal bilirubin has been documented in the literature. In a recent poster by Harms et al, it was shown that patients would either undergo liver transplant or die from liver-related causes within 19 months once total bilirubin had reached 1.6x ULN, and the total bilirubin level increased exponentially from that point (16). Secondly, the histological status of patients with PBC is rarely documented in clinical practice, since disease monitoring is based on biochemical values (e.g. ALP and bilirubin) and liver biopsy is only considered in very specific cases (e.g. enrolment in clinical trials) (17-19). However, as shown in previous economic models, it is not possible for patients to progress to more severe chronic liver health sates, especially decompensated cirrhosis, without having developed advanced fibrosis such as compensated cirrhosis.

Given the lack of data on histological progression among patients with PBC and to account for the advancement of fibrosis before patients can progress to HCC or decompensated cirrhosis, patients with abnormal and rising bilirubin were combined with those with compensated cirrhosis to reflect the severity of the disease from either a biochemical or histological level.

c. Are the transitions from and to this health state reflective of this combination of health states (people with abnormal bilirubin **and** people with compensated cirrhosis).

Since patient histological status is rarely documented, it was not possible to inform transition probabilities based on the histological status of the patients before they reached

decompensated cirrhosis or HCC. Therefore, data based only on elevated and rising bilirubin levels were used to estimate the transition probabilities to and from this health state.

d. Please provide the working definition of compensated cirrhosis, particularly in terms of total bilirubin?

Patients with compensated cirrhosis do not have symptoms related to their cirrhosis, but may have asymptomatic oesophageal or gastric varices. Patients with decompensated cirrhosis have symptomatic complications, including those related to hepatic insufficiency (jaundice) and those related to portal hypertension (ascites, variceal haemorrhage, or hepatic encephalopathy).

Patients with cirrhosis can be sub-categorised into four stages, with stages 1 and 2 classified as compensated cirrhosis and stages 3 and 4 as decompensated cirrhosis (Table 10).

Table 10: Stages of cirrhosis

	Compensated cirrhosis		**Decompensated cirrhosis**	
Stage	1	2	3	4
Clinical parameters	No varices, no ascites	Varices, no ascites	Ascites ± varices	Bleeding ± ascites

Source: D'Amico 2006 (20).

The Child-Turcotte-Pugh classification system () utilised two clinical parameters (encephalopathy and ascites) and three laboratory values (bilirubin, albumin and international normalised ratio). Patients are classified as class A, B or C based on their total points. Based on this system, compensated cirrhosis is classified as class A.

Table 11: Child-Turcotte-Pugh classification for severity of cirrhosis

	Points per parameter		
	1	**2**	**3**
Encephalopathy	None	Grade 1–2 (or precipitant induced)	Grade 3–4 (or chronic)
Ascites	None	Mild to moderate (diuretic responsive)	Severe (diuretic refractrory)
Bilirubin, mg/dL	<2	2–3	>3
Albumin, g/dL	>3.5	2.8–3.5	<2.8
INR	<1.7	1.7–2.3	>2.3
Total score	Class (severity of cirrhosis)		
5–6 points	Class A		
7–9 points	Class B		
10–15 points	Class C		

Abbreviations: INR, international normalised ratio.

B5. **Priority question:** The model structure considers thresholds based on ALP and total bilirubin.

a. Figure 24 of the company submission states thresholds of 200 u/L for ALP and 20 µmol/L for total bilirubin. Different thresholds have been used in the economic model submitted in Excel (ALP; 1.67 ULN and TB of 1.0 x ULN). Table 49 of the company submission does not include a threshold for total bilirubin. Please clarify what threshold is used in the company's base-case results and provide all Tables, Figures and results using this threshold.

As POISE is a global trial, there were variations in the definition of ULN for ALP. The eligibility criteria state that patients must have ALP >1.67x ULN for inclusion, and the average ALP for women in the trial was 197.561. As a result, 1.67x ULN is assumed to be 200 U/L. The ULN for total bilirubin is commonly defined as 1.2 mg/dL (20 µmol/L), and so was assumed to be 20 µmol/L.

b. Please justify why the Metavir fibrosis score is not used (F0-F4) in the model structure.

PBC is primarily a ductopenic disease, and therefore ALP and bilirubin levels alone will give a clear outline of the risk of a serious event in PBC. Biopsy is not used in clinical practice and staging of fibrosis through biopsy has limited clinical value. The current management of PBC focuses on reducing biochemical markers, initially ALP levels, and in the more severe stages bilirubin, in order to minimise the risk of long-term progression (21).

B6. **Priority question:** The liver disease component of the model assumes that patients treated with OCA (monotherapy or combined with UDCA) can move to an improved health state (e.g. to ALP ≤ 200 u/L and TB ≤ 20 µmol/L), while patients not treated with OCA cannot. Please justify this assumption.

Patients who are taking UDCA can only progress to more severe PBC health states based on transition probabilities calibrated to reflect the 10-year liver transplant-free survivals estimated based on POISE patient-level data using GLOBE and UK risk scores (1, 22). This assumption was made to account for the fact that in POISE, patients had similar ALP levels over the duration of the 12-month study period but had increasing bilirubin levels, thus worsening their risk of end-stage liver disease, liver transplant, or death.

Patients who were intolerant to UDCA were assumed to not receive any additional treatment for PBC. They progress to more severe health states based on transition probabilities obtained from the literature.

B7. The model seems to imply that demographics (in terms of age, gender and weight) are similar for both UDCA-intolerant patients and UCDA inadequate responders (see model settings). However, the company submission states "patients with earlier age of onset and/or male sex often have more aggressive disease that is refractory to existing treatment". Please explain how the model accounts for different demographic profiles for UDCA intolerant patients and UCDA inadequate responders.

The demographics used in the model are indeed similar in terms of age, gender and weight for both UDCA intolerant patients and UDCA inadequate responders and were based on the POISE overall population. This was due to the fact that only 16 patients (7.4%) did not receive UDCA during the trial, which prevented the observation of any differences in terms of age, gender and weight between the two groups.

While the model considers the same demographic profiles in both populations in the model, it is possible to change it in the 'model settings' worksheet. Given the lack of data published in PBC, especially in patients with earlier age of onset and male patients, it was not feasible to include any correcting factor to show the impact of their more aggressive disease on the transition probabilities included in the model. More research in these patients is needed.

B8. In the first year of the model (liver disease component), the transition probabilities for the OCA treatment arm seem to be based on the OCA arms of the POISE RCT. Patients then remain in the health state they were in at 12 months, to reflect the sustained reduction in ALP and bilirubin demonstrated in the preliminary results from the long-term safety extension phase. Please confirm.

In the first year, patients can progress freely between the three PBC health states as observed in the POISE OCA regimen arms. Afterwards, patients remain in the health state they are in at 12 months to reflect the sustained reduction/stabilisation of ALP and bilirubin demonstrated in the preliminary results from the LTSE phase of POISE. In sensitivity analysis, OCA patients might progress from the 'moderate risk PBC' state to the 'high risk PBC' state with a low probability based on the literature, assuming they would follow a similar decompensation rate as UDCA GLOBE responders (23).

B9. The model includes a health state for recurrence of PBC (PBC re-emerge). It is unclear what this health state exactly entails (e.g. is it a re-infection of liver disease; or re-emergence of specifically PBC)

a. Please provide a precise definition of the PBC re-emerge health state.

A re-emergence of PBC is defined as the re-emergence of PBC (specifically) following a successful liver transplant. PBC is an autoimmune disease, and will not be cured by liver transplantation; 43% of patients who have a liver transplant as treatment for PBC will develop PBC again within 15 years (24).

b. Please clarify whether this health state considers the re-administration of OCA and/or UDCA for the treatment of PBC? Please justify why.

Patients experiencing recurrence of PBC will not start treatment again and can only receive a second liver transplant or die from liver-related cause.

Comparators

B10. **Priority question:** Fibrates have been excluded as a comparator on the basis that "Fibrates are not licensed in the UK, nor are they standard of care, and they are

contraindicated in PBC. They are rarely used, with only [redacted] of patients in the UK-PBC cohort having ever taken fibrates for any condition (not necessarily for PBC)" (table 1 of the company submission). The usage of fibrates in the UK was referenced to a personal communication with George Mells. Given that fibrates are a comparator in the scope:

a. Please provide details of the personal communication with George Mells (and response)?

Dr Mells is a member of the UK PBC Consortium and manages the patient database. Following a request to the Consortium, Dr Mells reported that from a sample of 2,245 patients in the database, [redacted] are listed as "ever having used fibrates". A subsequent reanalysis of the database identified that [redacted] patients were currently taking fibrates from a cohort of 2,353 sampled from the database (a level of [redacted]

b. Is there any other corroborating evidence in support of the personal communication? Please comment on the clinical trial evidence for fibrates in PBC (ideally this evidence would be sourced systematically, but it is acknowledged that this might not be feasible in the timeframe).

A major factor to note regarding the use of fibrates in PBC is that they are actually contraindicated. Bezafibrate has a contraindication for significant hepatic disease (25), and fenofibrate is contraindicated in hepatic insufficiency including biliary cirrhosis (26).

A Cochrane Collaboration review in 2012 (27) identified only six RCTs comparing bezafibrate with UDCA treatment, either in comparison or in combination with UDCA. All trials were conducted in Japan. There was some effect on ALP seen in the trials, but all suffered from poor trial quality, low patient numbers, and had a high risk of bias. The Cochrane collaboration concluded "treatment of primary biliary cirrhosis with bezafibrate can neither be supported nor refuted based on the best current evidence available ensuing from trials in Japanese patients".

In addition, there are significant safety concerns with the use of fibrates in PBC, with one study (28) reporting three deaths in 13 patients in the UDCA + fibrates arm compared with no deaths in 14 patients in the UDCA monotherapy arm. In addition, one patient developed HCC in the fibrates + UDCA arm, compared with none in the UDCA monotherapy arm (28).

c. Please provide details of the number of patients (by country) who were excluded from the POISE trial because of use of fibrates (a medication which was prohibited in the trial).

As the use of fibrates was an exclusion criterion for POISE, patients would not be entered into screening if they were currently being treated with fibrates. A patient will only sign a consent form to allow data capture after they have been considered for screening, so it was not possible under Good Clinical Practice to capture information on patients who did not progress to screening because of the use of fibrates. There were 13 of 316 patients who were excluded due to criteria relating to prohibited medicines, which included azathioprine, colchicine, cyclosporine, methotrexate, mycophenolate mofetil, pentoxifylline, fenofibrate or other fibrates, budesonide and other systemic corticosteroids, potentially hepatotoxic drugs

(including α-methyl-dopa, sodium valproic acid, isoniazide, or nitrofurantoin), antibodies, and immunotherapy directed against interleukins or other cytokines or chemokines. However, which treatment led to the exclusion was not captured, and so it is not possible to say which, if any, patients were excluded due to the use of fibrates.

d. In addition, please provide reasons for exclusion for the 99 screen failures mentioned in the CONSORT patient-flow diagram (company submission, Figure 11).

Reasons for screening failures are provided in Table 12.

Table 12: Reasons for screening failures in POISE

Fail category	Category details	Number of patients based on highest category
Failed inclusion category 2	ALP and/or bilirubin levels not documented	63
Failed inclusion category 1	At least two confirmatory symptoms of PBC not documented	5
Failed inclusion category 4	Stable UDCA dose or intolerance to UDCA not confirmed)	4
Failed inclusion category 5	Use of contraception not confirmed	1
Exclusion category 4	Patient has received a prohibited medication in previous 6 months	8
Exclusion category 9	Patient has a condition affecting the absorption of drugs (IBD)	2
Exclusion category 2	Patient suffers significant complications of PBC	2
Exclusion category 3	Patient suffers severe pruritus	2
Exclusion category 11	Patient has uncontrolled significant medical conditions	2
Other	Other exclusions	10

Abbreviations: ALP, alkaline phosphatase; IBD, inflammatory bowel disease; PBC, primary biliary cirrhosis/cholangitis; UDCA, ursodeoxycholic acid.

e. Please include fibrates in the economic model and present the results.

Fibrates are not licenced or used in the UK, and are contraindicated in PBC. In addition, the available clinical evidence for fibrates in the form of acceptable quality RCTs and underlying safety concerns does not allow a meaningful comparison. Fibrates were not included as a comparator in the company submission for these reasons.

B11. The company have suggested that placebo is a comparator for people who are unable to tolerate UDCA. Please confirm that this refers to 'no additional treatment' in the final scope and describe the management of disease in patients who cannot tolerate UDCA.

Yes, this is correct.

Treatment effectiveness and adverse events

B12. **Priority question:** Table 49 of the company submission appears to describe the transition probabilities for the OCA comparator. The table is unclear:

a. Please provide the primary source(s) of the numbers used in the upper part of the table.

The primary source for the numbers in the upper part of the table is the POISE CSR. The numbers indicate the number of patients in each of the listed biochemical states at each given timepoint:

- State 1: ALP ≤ 200 U/L and normal bilirubin
- State 2: ALP > 200 U/L and normal bilirubin
- State 3: abnormal bilirubin and rising, or compensated cirrhosis.

b. Please explain how probabilities are obtained from the upper part of the table.

Probabilities were generated by converting the number of patients in a given state into a percentage value, by the following formula:

$$\frac{n_x}{N} = p$$

Where n_x is the number of patients in a given state, N is the total number of patients who initiated that three-month cycle in a given state, and p is the transition probability. For example, in the 3-6 month columns, of the 25 patients starting out in state 1, 17 remained in state 1, whilst 7 transitioned to state 2, and 1 patient transitioned to state 3. To calculate the probability of a patient remaining in state 1, the following calculation would be performed:

$$\frac{17}{25} = 0.68$$

To give a quarterly probability of 0.68 to remain in state 1.

In months 0-3, discontinuation is considered. This is factored in by the following method:

$$\left(\frac{n_x}{N}\right) - \left(d\left(\frac{n_x}{N}\right)\right) = p$$

Where *d* is the rate of discontinuation, n_x is the number of patients in a given state, *N* is the total number of patients who initiated that three-month cycle in a given state, and *p* is the transition probability. For example, in the 0-3 month columns, of the 63 patients starting out in state 2, 24 patients remained in state 1, 39 patients transitioned to state 2, and no patients transitioned to state 3. To calculate the probability of a patient remaining in state 1, the following calculation would be performed:

$$\left(\frac{24}{63}\right) - (0.099\left(\frac{24}{N63}\right)) = 0.343$$

To give a quarterly probability of 0.343 to remain in state 1.

c. Please provide the methods (calculations) and results.

The original table (Table 49 in the original submission) is shown below (Table 13). A comparison table, with Excel formulae shown, shows the calculations that were performed (Table 14). Column and row numbers are shown to allow identification of the calculations that were performed. Table 13 should be used as a reference when reviewing Table 14Table 14.

Table 13: Transition probabilities calculated from POISE

	B	C	D	E	F	G	H	I	J	K	L	M	N	O	P	Q	R	S
15		0-3 months					3-6 months				6-9 months				9-12 months			
16	From/To:	1	2	3	Disc.	N	1	2	3	N	1	2	3	N	1	2	3	N
17	ALP threshold 200 units / L																	
18	1																	
19	2																	
20	3																	
21	Probabilities																	
22	1					1				1				1				1
23	2					1				1				1				1
24	3					1				1				1				1

Abbreviations: ALP, alkaline phosphatase; Disc, discontinuation rate.

Table 14: Transition probabilities calculated from POISE (calculations shown)

	0-3 months					3-6 months				6-9 months				9-12 months			
From/ To:	1	2	3	Disc.	N	1	2	3	N	1	2	3	N	1	2	3	N
Probabilities																	
1					1				1				1				1
2					1				1				1				1
3					1				1				1				1

d. Please explain how these numbers are used in the model and how discontinuation is handled in the model.

The POISE data are used to determine the transition probabilities for all patients in the first year of treatment. Different transition matrices were utilised for different patient populations; the full tables of transition probabilities are available in the model on the sheet 'Transition matrices' between rows 119 and 312.

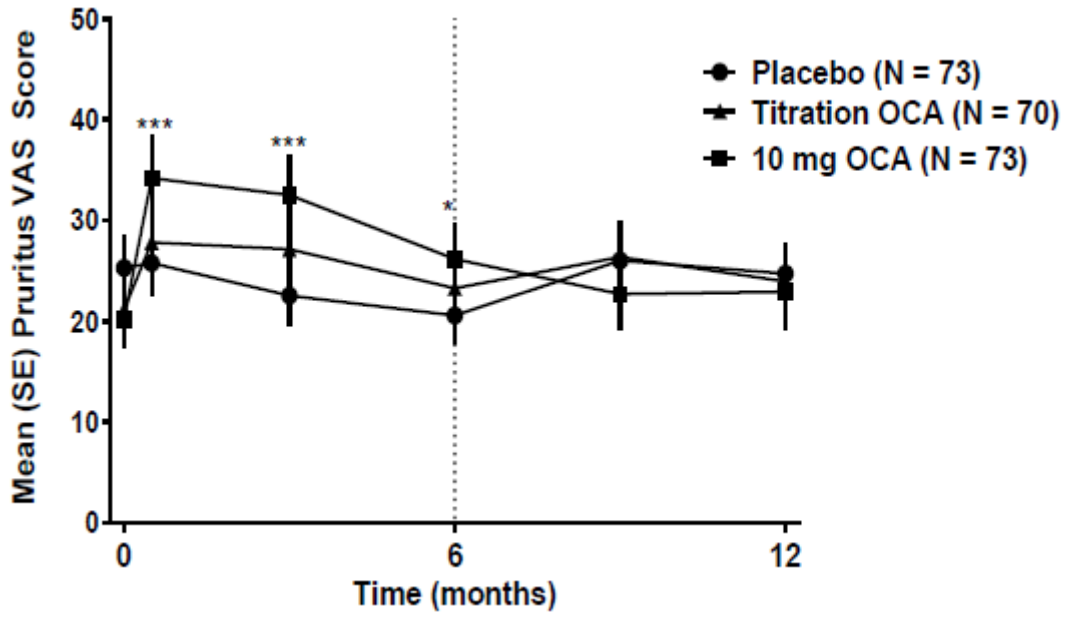
Discontinuation is only considered during the first three months of the model. Patients who discontinue stay in their treatment arm, but use transition probabilities for patients treated with placebo.

e. Please explain why discontinuation is only included in the first 3 months of the year.

The exact time point for each discontinuation event within POISE is not known. With this in mind, it was assumed that patients would discontinue during the first three months of treatment. This was based on the following assumptions:

- Patients who experience adverse events would be more likely to discontinue earlier in their treatment course rather than later, as they would be more likely to experience adverse events immediately after starting treatment
- Following an initial increase in pruritus severity (as reported by the pruritus VAS from POISE), severity of pruritus decreases over the duration of treatment (Figure 1) (29). As pruritus is a strong driver for discontinuation, it can therefore be assumed that a decrease in pruritus would cause a corresponding decrease in treatment discontinuation over the course of OCA treatment.

Figure 1: Pruritus VAS scores over time using observed data



Abbreviations: OCA, obeticholic acid; SE, standard error; VAS, visual analogue scale.

f. Please provide results of a sensitivity analysis including discontinuation in the later months (i.e. months 3-6, 6-9, 9-12).

This analysis is not possible, as the time of discontinuation cannot specifically be set beyond 0 to 3 months, and a restructure of how discontinuation is handled in the model would be required. The impact of discontinuation on the overall ICER is negligible. To illustrate the small impact of discontinuation, a sensitivity analysis is included below where the discontinuation rate has been set to 0% for all treatment arms.

Table 15: Deterministic results for UDCA-intolerant patients with discontinuation rates set to 0% for all treatments (using the list price of OCA)

Technologies	Total			Incremental			ICER (cost/QALY) versus baseline	ICER (cost/QALY) incremental
	Costs	LYG	QALYs	Costs	LYG	QALYs		
No treatment (placebo)	£103,233	11.30	6.76	–	–	–	–	–
OCA Titration	[redacted]	17.22	14.28	[redacted]	5.93	7.52	[redacted]	[redacted]

Abbreviations: ICER, incremental cost-effectiveness ratio; LYG, life-years gained; OCA, obeticholic acid; QALY, quality-adjusted life year; UDCA, ursodeoxychoic acid.

Table 16: Deterministic results for UDCA inadequate responders with discontinuation rates set to 0% for all treatments (using the list price of OCA)

Technologies	Total			Incremental			ICER (cost/QALY) versus baseline	ICER (cost/QALY) incremental
	Costs	LYG	QALYs	Costs	LYG	QALYs		
UDCA + placebo	£96,977	12.35	7.98	–	–	–	–	–
OCA titration + UDCA	[redacted]	17.22	14.28	[redacted]	4.87	6.30	[redacted]	[redacted]

Abbreviations: ICER, incremental cost-effectiveness ratio; LYG, life-years gained; OCA, obeticholic acid; QALY, quality-adjusted life year; UDCA, ursodeoxycholic acid.

The ICER for UDCA-intolerant patients is 0.1% lower than the base case ([redacted]/QALY versus [redacted]/QALY in the base case), whereas the ICER for UDCA inadequate responder is 1% greater than the base case ([redacted]/QALY versus [redacted]/QALY in the base case).

B13. **Priority question:** For the comparators in the model, transition probabilities are primarily obtained from the literature.

a. Please justify why transition probabilities for the PBC-specific component of the model are not based on POISE for all treatment arms.

As stated in the answer to question B6, patients' progression in the placebo arm was based on transitions reflecting their liver transplant-free survival rates at 10 years, based on patient-level data from POISE using both GLOBE and UK risk scores (1, 22). Patients in the UDCA arm were assumed to progress only to more severe health states to reflect the fact that their ALP levels remained similar to baseline throughout the 12-month treatment period and bilirubin levels increased at all time points in POISE.

b. Please provide the results of a sensitivity analysis using the clinical data from POISE to inform the transition probabilities for all comparators for the PBC-specific component of the model. Provide details of the methods used.

In the base case, the risk of end-stage liver disease associated with the UDCA arm from POISE was captured, as well as the fact that patients had similar ALP but increasing bilirubin over the 12-month study period, thus worsening their risk of end-stage liver disease, liver transplant, or death. Since the transitions reflect the data from POISE, the proposed scenario is not necessary.

B14. **Priority question:** Please explain the following concerning Table 50 of the company submission:

a. Please provide the primary source(s) on which the transition probabilities are based.

UDCA inadequate responders
Transition probabilities from POISE were used where possible, however transition probabilities were not available for all health states, nor were they available for the full time horizon of the model. The OCA titration regimen relies on POISE patient-level data to generate transition probabilities; transition probabilities for UDCA-based, or placebo regimens, are based on data sourced from the literature.

Calibration of transition probabilities was carried out in four steps. These were:

- Transition from “decompensated cirrhosis” to “pre-liver transplant” and “liver-related death”
- Transition from “abnormal bilirubin and rising, or compensated cirrhosis” to “decompensated cirrhosis” or “liver-related death”
- Transition from “ALP > 200 U/L and normal bilirubin” to “abnormal bilirubin and rising, or compensated cirrhosis”
- Transition from “ALP ≤ 200 U/L and normal bilirubin” to “abnormal bilirubin and rising, or compensated cirrhosis”.

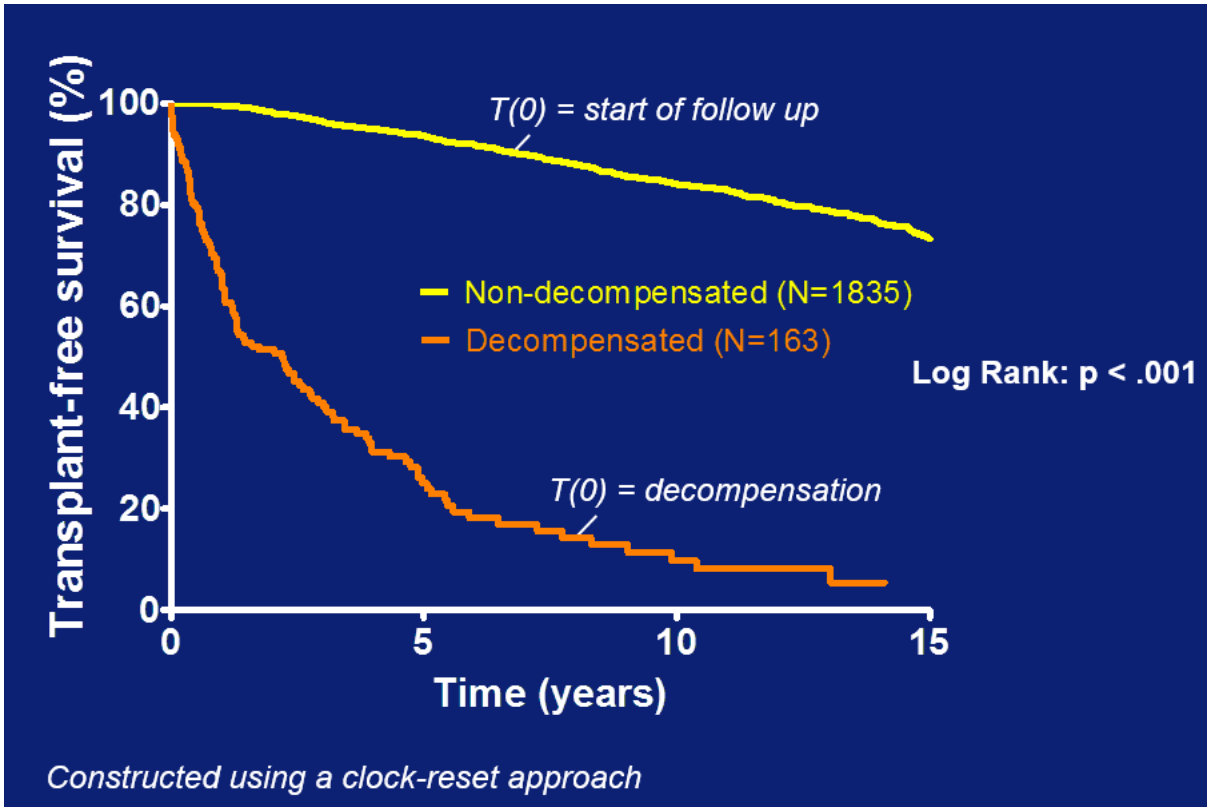
Step 1: Transition from “decompensated cirrhosis” to “pre-liver transplant” and “liver-related death”
The probabilities for this transition were calibrated to reflect the ten-year liver transplant-free survival (LTFS) reported by Harms et al. (2015) for PBC patients who had developed decompensated cirrhosis (23). In this study, decompensation was defined as the first instance of any of the following events, in a given patient:

- Ascites
- Variceal bleeding
- Hepatic encephalopathy

The study included 2,938 patients. 467 clinical events were reported; 136 liver transplantations (29.1%) and 331 deaths (70.9%). Survival data was presented for two patient groups:

- Patients who underwent decompensation
- Patients who did not undergo decompensation

Figure 2: Liver-transplant free survival of decompensated and non-decompensated patients with PBC



Transitions from decompensated cirrhosis to liver transplant waitlist and liver-related death were calibrated based on the 10-year liver-transplant free survival observed for decompensated PBC patients, while respecting the relative risk stating that patients have a 2.43-fold (i.e. 331/136) greater risk of dying than having a liver transplantation. In the calibration process, a simplified Markov model including 4 health states (i.e. decompensated cirrhosis, liver transplant waitlist, liver transplantation and death) was used. This is shown in the calibration spreadsheet for UDCA inadequate responders (see question B14 d).

To perform the calibration, Solver (an add-on module for Excel 2013) was use to estimate the transition probabilities from “decompensated cirrhosis” to “pre-liver transplant” which would result in a 10-year LFTS of 10% (as shown above in Figure 2). As shown in Table 17, patients who progress to liver transplant remain there to allow the calculation of the LTFS which captures time to first event (i.e. either liver transplant or death). The calibrated annual transitions from decompensated cirrhosis were as follows:

- To liver transplant waitlist: 7%
- To liver-related death: 17%

Table 17: Step 1 calibration results: Markov model – transitions from "decompensated cirrhosis"

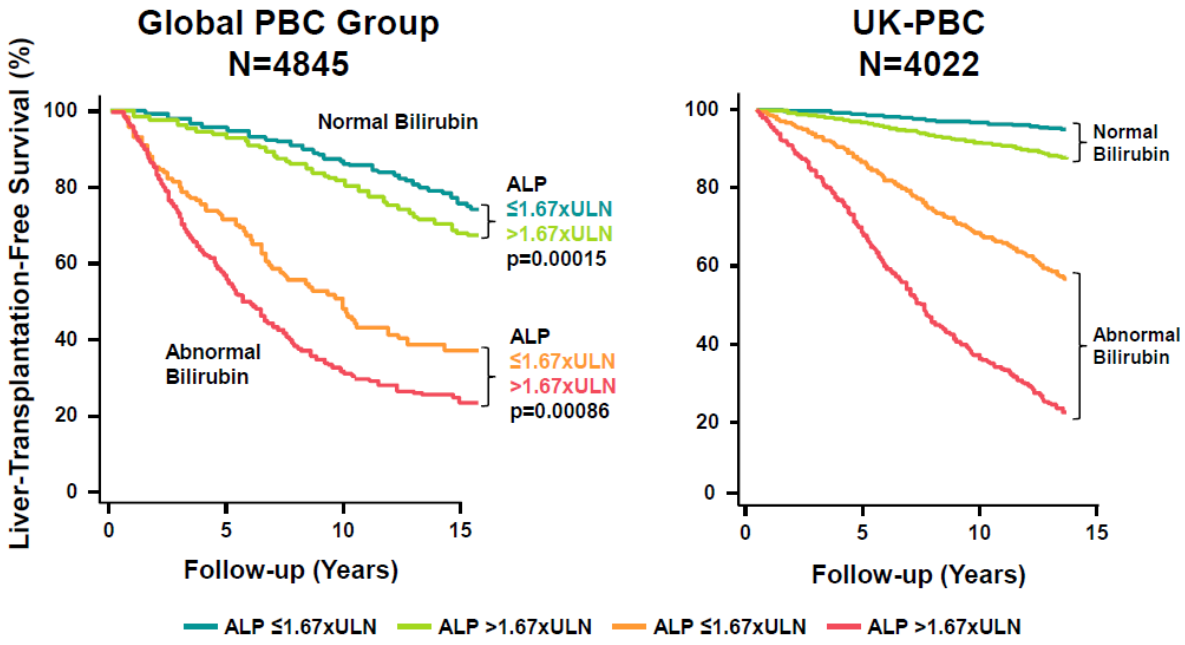
	DCC	Pre-LT (i.e. waiting list)	LT	Death
DCC	76%	**7%**	0.0%	**17%***
Pre-LT (i.e. waiting list)	0%	52%	*35%*	*9%*
LT	0%	0%	100%	0.0%
Death	0%	0%	0%	100%

Abbreviations: DCC: Decompensated cirrhosis; LT: liver transplantation.
Grey cell: Calculation – 1-sum(all other transitions).
* Transition to death is calculated as transition to pre-LT x 2.43 (231/331)
Source: Harms 2015 (23)

Step 2: Transitions from "abnormal bilirubin and rising, or compensated cirrhosis"

As data for transition probabilities were not available for specific histologic states of PBC patients, calibration was performed using groups of PBC patients who have abnormal bilirubin. Transitions to decompensated cirrhosis and liver-related deaths were calibrated based on the data shown in Figure 3 to replicate the 10-year liver-transplant survival observed in the GLOBE and UK PBC cohorts (the mean of the Global and UK cohorts was used). The transition probability for "abnormal bilirubin and rising" to "hepatocellular carcinoma" is 0.014, based on Trivedi et al. (2016) (30). The 10-year LTFS rate was estimated at 0.39 and 0.48, using the Global and UK PBC risk scores respectively. Lammers et al. (2014) was used to determine the numbers of patients who would have abnormal bilirubin after 12 months (31).

Figure 3: Liver-transplant free survival rates based on ALP and bilirubin thresholds



Liver transplant-free survival for Global PBC is based on all-cause mortality or liver transplant and the UKPBC is based on liver-related death or liver transplant. Courtesy of Global PBC Study Group and UK-PBC

Abbreviations: ALP, alkaline phosphatase; PBC, primary biliary cirrhosis/cholangitis; ULN, upper limit of normal.

The transition from “abnormal bilirubin and rising, or compensated cirrhosis” to “pre-liver transplant” was calibrated first. Based on data from the UNOS database, it was determined that 30-35% of new additions to the waitlist were added due to PBC, cirrhosis or HCC. (32) The transition was calibrated to ensure that 30% of patients would be on the liver transplant waitlist (“pre-liver transplant” health state) over the next 20 years, by assuming that patients who move to the “pre-liver transplant” state remain there (i.e. patients cannot leave the waitlist unless they die). Once the transition to the “pre-liver transplant” state was determined, the transition from to “abnormal bilirubin and rising, or compensated cirrhosis” to “decompensated cirrhosis” was calibrated to ensure that LTFS was 39% at 10 years.

Table 18: Step 2 calibration: Markov model – transitions from “abnormal bilirubin and rising, or compensated cirrhosis”

	AB and rising, or CC	DCC	HCC	Pre-LT (i.e. waiting list)	LT	Death
AB and rising, or CC	85%	10%	1%	4%*	0%	0%
DCC	0%	76%	0%	7%	0%	17%
HCC	0%	0%	53%	4%	0%	43%
Pre-LT (i.e. waiting list)	0%	0%	0%	52%	*35%*	*9%*
LT	0%	0%	0%	0%	100%	0%
Death	0%	0%	0%	0%	0%	100%

Abbreviations: AB, abnormal bilirubin (total bilirubin >ULN); CC, compensated cirrhosis; DCC, decompensated cirrhosis; LT, liver transplantation.
Grey cell: Calculation – 1-sum(all other transitions).
* Transition to pre-LT was calibrated first to reflect 30% of patients moving to waitlist over next 20 years (32)

Step 3: Transitions from “ALP > 200 U/L and normal bilirubin”

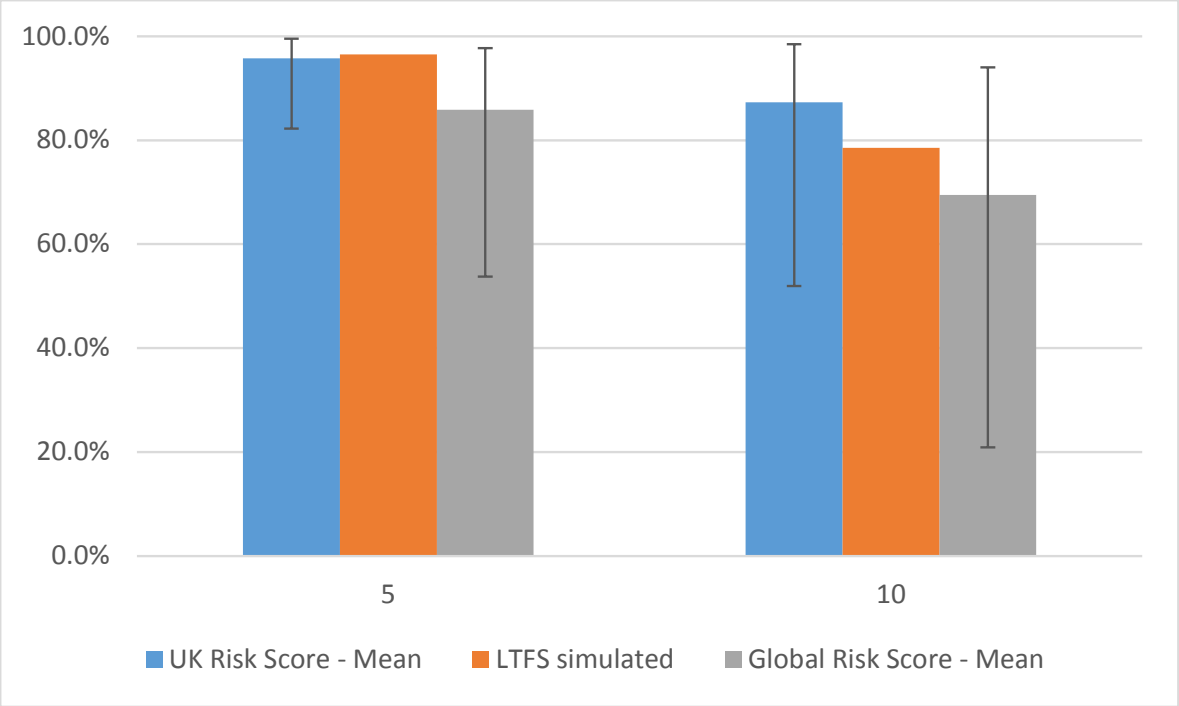
The transition from “ALP > 200 U/L and normal bilirubin” to “abnormal bilirubin and rising, or compensated cirrhosis” was calibrated to reflect the LTFS as estimated by the mean of the GLOBE and UK PBC risk score on the patient-level data from POISE (33) (31). The GLOBE and UK risk score both estimate LTFS over time. Whilst the GLOBE estimate includes the risk of all-cause death, including liver-related death, the UK risk score focuses on liver-related deaths only. As a result, whilst both estimates show a worsening prognosis for PBC patients on UDCA after 12 months, the magnitude of the change is lower when the UK PBC risk score is used. With wide confidence intervals around the survival rate estimates over time (see Figure 4), transitions were calibrated (again, using Solver) so that the 10-year LTFS was 78%, the mean of the UK and GLOBE estimates (87% and 69%). The calculated transition probabilities for this step of the process are shown in Table 19.

Table 19: Step 3 calibration: Markov model – transitions from "ALP >200 U/L and normal bilirubin"

	ALP >1.67x ULN and NB	AB and rising, or CC	DCC	HCC	Pre-LT (i.e. waiting list	LT	Death
ALP >1.67x ULN and NB	88%	**12%**	0%	0%	0%	0%	0%
AB and rising, or CC	0%	85%	10%	1%	4%*	0%	0%
DCC	0%	0%	76%	0%	7%	0%	17%
HCC	0%	0%	0%	53%	4%	0%	43%
Pre-LT (i.e. waiting list)	0%	0%	0%	0%	52%	*35%*	*9%*
LT	0%	0%	0%	0%	0%	100%	0%
Death	0%	0%	0%	0%	0%	0%	100%

Abbreviations: AB, abnormal bilirubin (total bilirubin <ULN); ALP, alkaline phosphatase; CC, compensated cirrhosis; DCC, decompensated cirrhosis; HCC, hepatocellular carcinoma; LT, liver transplantation; NB, normal bilirubin (total bilirubin ≤ULN); ULN, upper limit of normal.
Grey cell: Calculation – 1-sum(all other transitions).

Figure 4: Step 3 calibration: liver transplant-free survival rates at 5 and 10 years as estimated by GLOBE, UK risk score, and the result from the calibrated model



Abbreviations: LTFS, liver transplant-free survival.

Step 4: Transition from "ALP ≤ 200 U/L and normal bilirubin"

The transition from "ALP ≤ 200 U/L and normal bilirubin" to "abnormal bilirubin and rising, or compensated cirrhosis" was calibrated to reflect the liver-transplant free survival as shown in Figure 3 for patients with "ALP ≤ 1.67xULN and normal bilirubin" after 12 months on treatment. The transition was calibrated (using Solver, as previously done) so that the 10-

year LTFS was 91%, the mean of the UK and Global PBC group estimates (96% and 87%). The final table of calibrated transition probabilities is shown below in Table 20.

Table 20: Step 4 calibration: Markov model from ALP >1.67x ULN and normal bilirubin

	ALP ≤1.67x ULN and NB	ALP >1.67x ULN and NB	AB and rising, or CC	DCC	HCC	Pre-LT (i.e. waiting list)	LT	Death
ALP ≤1.67x ULN and NB	95%	0%	5%	0%	0%	0%	0%	0%
ALP >1.67x ULN and NB	0.0%	88.4%	11.6%	0%	0%	0%	0%	0%
AB and rising, or CC	0.0%	0.0%	84.9%	9.7%	1.4%	4.1%	0%	0%
DCC	0.0%	0.0%	0.0%	75.8%	0.0%	7.1%	0%	17.2%
HCC	0.0%	0.0%	0.0%	0.0%	53.0%	4.0%	0%	43.0%
Pre-LT (i.e. waiting list)	0.0%	0.0%	0.0%	0.0%	0.0%	55.3%	35%	9%
LT	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	100%	0%
Death	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	100%

Abbreviations: AB, abnormal bilirubin (total bilirubin >ULN); ALP, alkaline phosphatase; CC, compensated cirrhosis; DCC, decompensated cirrhosis; HCC, hepatic cellular carcinoma; LT, liver transplantation; NB, normal bilirubin (total bilirubin ≤ULN); ULN, upper limit of normal.
Grey cell: Calculation – 1-sum(all other transitions)

b. Please detail the characteristics of patients included in this/these primary source(s).

The following sources were used:

- GLOBE PBC cohort
- UK PBC cohort

The baseline demographics for each cohort are detailed below in Table 21 and Table 22.

Table 21: Global PBC cohort baseline characteristics

Characteristic	Global PBC Study Group (N=4845)
Age at entry (SD), years	54.5 (12.0)
Duration of PBC (SD), years	7.3 (3.6 – 11.5)
Female, n (%)	4348 (90)
UDCA-treated patients, n (%)	4119 (85)
Baseline ALP (IQR), x ULN	2.10 (1.31, 3.72)
Baseline ALP >3x ULN, n (%)	606 (16)
Baseline bilirubin (IQR), x ULN	0.67 (0.45 – 1.06)
Baseline bilirubin >ULN, n (%)	740 (20)
Biochemical disease stage, n (%):	
Early: bilirubin ≤ ULN and albumin ≥ LLN	2040 (67)
Moderately Advanced: abnormal bilirubin or albumin	730 (24)

Characteristic	Global PBC Study Group (N=4845)
Advanced: abnormal bilirubin and albumin	259 (9)

Abbreviations: ALP, alkaline phosphatase; IQR, interquartiler range; LLN, lower limit of normal; PBC, primary biliary cirrhosis/cholangitis; SD, standard deviation UDCA, ursodeoxycholic acid; ULN, upper limit of normal.

Table 22: UK PBC cohort baseline characteristics

Characteristic	Whole cohort (n=2353)	Female (n=2132)	Male (n=221)	P-value (female vs male)
Female, %	90.6	–	–	–
Age at diagnosis (range), years	55 (16–86)	55 (16–86)	60 (34–81)	<.0001
Age at study (range), years	65 (21–91)	65 (21–91)	67 (40–89)	<.0005
Length of follow-up period (range), years	8 (0–52)	8 (0–52)	6 (0–31)	<.01
UDCA use, % receiving	80	80	79	NS
Duration of reported UDCA therapy (range), years	3.7 (0.1–21.1)	3.8 (0.1–21.1)	3.6 (0.2–19.4)	NS
UDCA response in adequately treated patients, %	79	80	72	<.05
ALP, U/L	266 ± 262	267 ± 262 1.8	265 ± 249 1.8	NS
ALP (range), xULN	1.8 (0.3–23.3)	(0.3–23.3)	(0.3–21.4)	NS
ALT/AST, U/L	47.7 ± 45.5	47.4 ± 41.3	49.1 ± 43.8	NS
ALT/AST (range), ULN	1.1 (0.2–20.3)	1.1 (0.2–20.3)	1.2 (0.3–8.3)	NS
Bilirubin, µmol / L	11.2 ± 8.6	11.0 ± 8.6	13.8 ± 8.8	<.0001
Bilirubin (range), xULN	0.6 (0.1–10.5)	0.6 (0.1–10.3)	0.6 (0.1–5.0)	<.0001
Albumin, g/L	39.4 ± 8.5	39.4 ± 8.7	39.7 ± 7.3	NS
Albumin (range), xLLN	1.0 (0.5–1.5)	1.0 (0.5–1.5)	1.0 (0.7–1.3)	NS

Abbreviations: ALP, alkaline phosphatase; ALT, alanine aminotransferase; AST, aspartate aminotransferase; LLN, lower limit of normal; NS, not significant; PBC, primary biliary cirrhosis/cholangitis; UDCA, ursodeoxycholic acid; ULN, upper limit of normal.

c. Please provide an overview of the data extracted from this/these primary source(s) to calculate the transition probabilities.

The data extracted from these publications are detailed in the calibration calculations Excel workbook which will be submitted alongside this clarification letter.

d. In addition to Appendix 10, please provide a detailed explanation of the methods and sources used for calibration after data extraction (i.e. provide the calculations for the quarterly transition probabilities) and an Excel sheet containing these calculations.

A workbook containing clarifications has been submitted alongside this clarification letter.

B15. **Priority question:** Please explain the following concerning Table 52 of the company submission:

a. Please provide the primary source(s) on which the transition probabilities are based.

UDCA-intolerant patients

UDCA-intolerant patients can either receive OCA monotherapy (as a titrated dose) or no treatment. Given the limited number of patients not on UDCA, there is a lack of data in the literature looking at the natural history of PBC without active treatment since the launch of UDCA. Thus, to reflect the progression of patients who did not receive any active treatment, assumptions were made based on Corpechot et al. (2000), who assessed the effect of UDCA therapy on liver fibrosis progression compared with no treatment in PBC patients (34). The study was based on a French randomised, double-blind, placebo-controlled trial in which 146 patients were randomised to receive either 13-15 mg/kg/day of UDCA or a placebo for 2 years. After 2 years, placebo patients crossed over to UDCA for a further 2 years, whilst patients already on UDCA remained on UDCA. Paired liver biopsies were available for 103 patients (53 UDCA and 50 placebo) during the two-year blinded period.

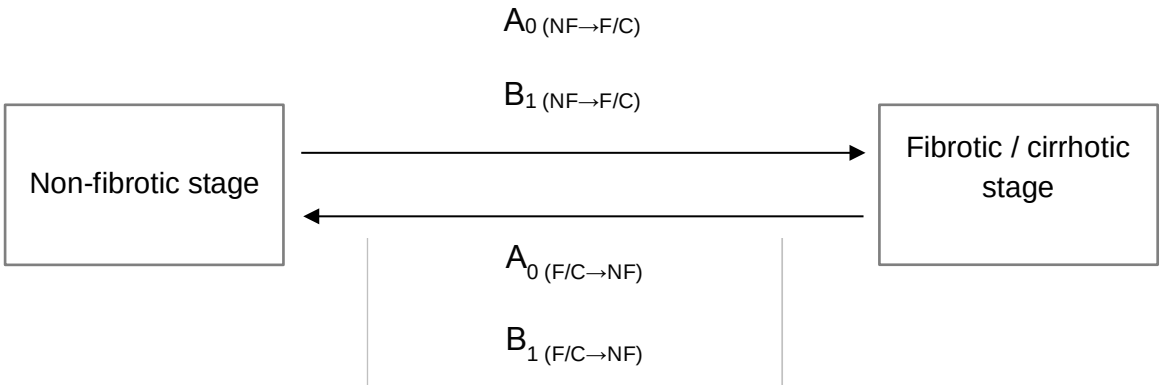
Corpechot et al. (2000) modelled the progression from two histologic stages:

- Non-fibrotic stage, defined by the presence of portal and periportal lesions without extensive fibrosis
- Fibrotic/cirrhotic stage, defined by the presence of numerous septa, bridging fibrosis or nodular cirrhotic formation.

The description provided by Corpechot et al for fibrotic and cirrhotic stages would contain compensated cirrhotic patients according to the METAVIR criteria (METAVIR stages F3 / F4) (35).

Progression between states was informed by the paired biopsy data. The authors of this study assumed that all patients in a given state and at a given time would have the same prognosis. Two transition rates were estimated to inform the model, i.e. the baseline transition rate α_0 and the regression coefficient for treatment β_t. The relationship between both parameters were expressed as follows: $\alpha_u = \alpha_0 * \exp(\beta_t \times U)$ where U=0 for placebo and 1 for UDCA.

Figure 5: Two-stage Markov model



Based on the simplified model parameters (detailed in Table 23) it was possible to estimate the annual probability of progressing over time in the placebo group. Probabilities for patients to transition to the fibrotic/cirrhotic stage were calibrated to estimate the number of cirrhotic patients over time without the probability of moving backwards by minimising the root mean square error (RMSE), leading to a quarterly probability of progression to severe PBC of 0.079. The same transition was assumed between "abnormal bilirubin or compensated cirrhosis" and "decompensated cirrhosis" as for UDCA non-responders.

Whilst these histologic stages do not necessarily directly reflect compensated cirrhosis and decompensated cirrhosis, they essentially represent two different fibrotic or cirrhotic stages. This is the only publication which reflects the natural history of PBC without treatment, and allows estimation of the rate of disease progression for untreated patients.

Table 23: Simplified model - progression parameters

Parameter	From/to	Estimate	SE
α0	NF to F/C	0.34	0.09
βt	NF to F/C	-1.55	0.49
α0	F/C to NF	0.03	0.01
βt	F/C to NF	0.00	0

Abbreviations: F/C, fibrotic/cirrhotic; NF, non-fibrotic; SE, standard error.
Source: Corpechot 2000 (34).

b. Please detail the characteristics of patients included in this/these primary source(s).

The Corpechot study utilised patient data from a French randomized, double-blind, placebo-controlled trial of UDCA therapy. The baseline characteristics of the patients are presented below in Table 24.

Table 24: Baseline characteristics of patients in the original study groups

Characteristic	UDCA*	Placebo*
No. of patients	72	73
Age, years	55 ± 1	57 ± 1

Characteristic	UDCA*	Placebo*
Female sex, n (%)	68 (94)	65 (89)
Months since diagnosis (range)	39 ± 4 (1–132)	43 ± 5 (0–240)
Bilirubin – mg/dl	1.25 ± 0.11	1.24 ± 0.15
ALP, x normal	5.61 ± 0.40	4.26 ± 0.27
ALT, x normal	2.69 ± 0.19	2.25 ± 0.13
Γ-Glutamyltransferase, x normal	13.1 ± 1.1	13.2 ± 1.1
Albumin, g/dl	3.90 ± 0.05	4.01 ± 0.05
Prothrombin time, %	96.0 ± 1.0	95.4 ± 1.1
IgM, x normal	2.56 ± 0.24	2.49 ± 0.27
Total bile acids, µg/ml	10.5 ± 1.2	11.5 ± 1.9
Hepatomegaly, n (%)	17 (24)	20 (27)
Splenomegaly, n (%)	11 (15)	15 (21)
Clinically overt disease, n (%)†	47 (65)	44 (60)
Mayo risk score	4.87 ± 0.11	4.80 ± 0.12
Histologic stage III or IV, n (%)	36 (50)	31 (42)

Abbreviations: ALP, alkaline phosphatase; ALT, alanine aminotransferase; IgM, immunoglobulin M; SE, standard error; UDCA, ursodeoxycholic acid.
*Plus-minus values are means ± SE. Enzyme activity and immunoglobulin levels are expressed as multiples of the upper limit of the normal value. These values were standardized by dividing the measured value by the reference value in the laboratory. To convert values for bilirubin to micromoles per litre, multiply by 17.1. To convert values for total bile acids to micromoles per litre, multiply by 2.547. †Clinically overt disease was defined by the presence of at least of the following signs or symptoms: jaundice, fatigue, pruritus, hepatomegaly, and splenomegaly.
Source: Poupon 1994 (36)

c. Please provide an overview of the data extracted from this/these primary source(s) to calculate the transition probabilities

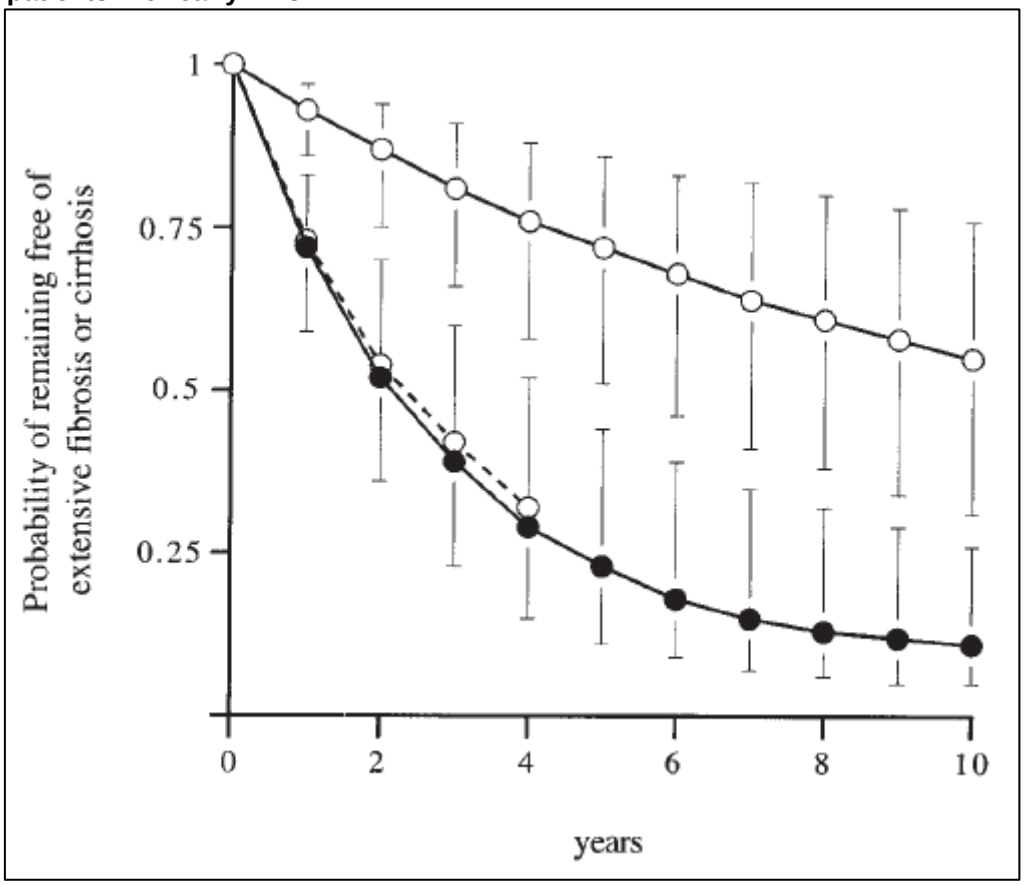
The authors constructed a Markov model to estimate the probability of progression to extensive fibrosis and cirrhosis from a non-fibrotic or cirrhotic state. The model closely replicated the results of the trial, which found that patients on UDCA therapy had a five-fold lower risk of developing liver fibrosis or cirrhosis compared to placebo controls (34). The model was found to replicate the results of the clinical trial closely, and those of Locke *et al*, a study on the spontaneous progression of PBC (37).

Table 25: Numbers of transitions of fibrosis stage: observed versus predicted

	Consecutive stage			
	UDCA		Placebo	
Initial stage	NF	F/C	NF	F/C
NF	38 (38.01)	6 (5.99)	15 (14.98)	14 (14.02)
F/C	4 (4.04)	64 (63.96)	1 (0.97)	20 (20.03)

Abbreviations: NF, nonfibrotic stage; F/C, fibrotic/cirrhotic stage; UDCA, ursodeoxycholic acid.
Note: each cell gives the number of observed and predicted (in parentheses) transitions from the stage in the row to the stage in the column. For example, the number of observed transitions under UDCA from NF to F/C is 6 and that predicted by the model is 5.99.

Figure 6: Probability of remaining free of extensive fibrosis or cirrhosis in UDCA and placebo-treated patients with early PBC.



Abbreviations: PBC, primary biliary cirrhosis/cholangitis; UDCA, ursodeoxycholic acid.
Empty circle with solid line: model predicted UDCA disease course; solid circle with solid line: model predicted placebo disease course; empty circle with dashed line: observed results of the spontaneous course of the disease.
Source: Locke 1996 (37).

d. Please explain how Table 51 of the company submission should be used to obtain the estimates in Table 52.

An Excel spreadsheet containing the calculations performed to reach the results shown in Table 52 of the submission has been attached with these clarification questions. The Markov model detailed by Corpechot *et al* was recreated and calibrated (as described in B14 a).

B16. **Priority question:** Please provide an overview of all transition probabilities used for all comparators and all time points (if time-dependent) for the PBC-specific component, incorporating:

a. the estimated probability

b. standard error

c. primary source

d. justification for source

e. method of calculation if applicable.

All transition probabilities used within the model, including their sources, can be found on the 'clinical inputs' page of the model, in the range E32:L61. Details of how calibration was performed can be found in the answers to questions B14 and B15.

B17. Please provide an overview of adverse event proportions for fatigue, pruritus and nausea (stratified by treatment).

The proportion of patients who experienced fatigue, pruritus and nausea, stratified by treatment, are reported below in Table 26 and Table 27. Note that adverse event incidence data were derived from the ITT population, and not for UDCA-intolerant / UDCA inadequate responder subpopulations.

Table 26: Proportions of patients who experienced adverse events, UDCA-intolerant patients

Treatment	Fatigue	Pruritus	Nausea
No treatment (placebo)	0.00%	0.00%	0.00%
OCA titration	8.57%	50.00%	4.29%

Abbreviations: OCA, obeticholic acid; UDCA, ursodeoxycholic acid.
Source: POISE (29)

Table 27: Proportions of patients who experienced adverse events, UDCA inadequate responders

Treatment	Fatigue	Pruritus	Nausea
UDCA + placebo	10.96%	36.99%	5.48%
OCA titration + UDCA	8.57%	50.00%	4.29%

Abbreviations: OCA, obeticholic acid; UDCA, ursodeoxycholic acid.
Source: POISE (29).

Health related quality of life

B18. **Priority question:** A recent publication (Dyson et al 2016) suggested that……"The majority of patients with primary biliary cholangitis do not feel their QoL is impaired, although impairment is reported by a sizeable minority".

a. Please justify the primary sources used for quality of life estimates.

The sources identified were selected because whilst the underlying cause of HCV / HBV differs, patients will often experience similar health states, for example decompensated cirrhosis. These data were used as there is no PBC-specific HRQoL data which uses a utility measure preferred by NICE, e.g. EQ-5D.

b. Please justify the high utility values for PBC, considering the general population utility (age-dependent).

The utility data used for the biochemistry states in the model uses data reported in Younossi *et al*, 2001 (38). The HRQoL for cholestatic liver disease (which includes PBC / PSC) was reported as 0.84. These are the only identified utility data for PBC patients.

c. Please clarify why the utilities from a hepatitis B/C population are appropriate (with or without the reduction of [redacted]), and justify that these health state utility values are based on the most appropriate source(s). Please explain the rationale for reducing the hepatitis values by [redacted].

KOL input stated that PBC patients are likely to have lower QoL than HCV / HBV patients in comparable health states. To reflect this, a [redacted] decrement was applied to all HCV / HBV – specific utility values, aside for HCC (according to KOL opinion, in HCC, the utility value is driven by the treatment for HCC rather than the disease itself).

The [redacted] decrement in utility was not applied to disease states where utility values which could be considered specific to PBC were identified, i.e. the biochemistry states relating to ALP threshold (38).

B19. The impact of adverse events on health-related quality of life is not included in the cost-effectiveness model. Please provide a sensitivity analysis including the influence of adverse events on quality of life.

According to input by KOLs, the only recorded adverse event with a meaningful impact on quality of life is pruritus, and this subsides within the first three months of treatment. If HRQoL was modelled, it would have a negligible impact on the overall QALY. The impact of The difference in the rate of pruritus between UDCA and OCA regimens is also small, further decreasing the impact that this change would have on the overall QALYs calculated.

In addition, data from the Phase 2 study 747-201 showed that there were no statistically significant changes between baseline and end of treatment in quality of life, as assessed by the SF-36 and PBC-40 health questionnaires (39).

To illustrate the minor impact of the costs of adverse events on the overall results, a sensitivity analysis has been included where the cost of adverse events has been set to £0.

Figure 7: Deterministic results for UDCA-intolerant patients with adverse event costs set to £0 (using the list price of OCA)

Technologies	Total			Incremental			ICER (cost/QALY)	ICER (cost/QALY)
	Costs	LYG	QALYs	Costs	LYG	QALYs	versus baseline	Incremental
No treatment (placebo)	£103,233	11.30	6.61	–	–	–	–	–
OCA titration	[redacted]	16.65	13.52	[redacted]	5.35	6.91	[redacted]	[redacted]

Abbreviations: ICER, incremental cost-effectiveness ratio; LYG, life-years gained; OCA, obeticholic acid; QALY, quality-adjusted life year; UDCA, ursodeoxycholic acid.

Table 28: Deterministic results for UDCA inadequate responders with adverse event costs set to £0 (using the list price of OCA)

Technologies	Total			Incremental			ICER (cost/QALY)	ICER (cost/QALY)
	Costs	LYG	QALYs	Costs	LYG	QALYs	versus baseline	incremental
UDCA + placebo	£96,911	12.35	7.85	–	–	–	–	–
OCA titration + UDCA	[redacted]	16.75	13.64	[redacted]	4.40	5.79	[redacted]	[redacted]

Abbreviations: ICER, incremental cost-effectiveness ratio; LYG, life-years gained; OCA, obeticholic acid; QALY, quality-adjusted life year; UDCA, ursodeoxycholic acid.

Omitting the cost of adverse events results in an ICER of [redacted] QALY in UDCA-intolerant patients. This is a decrease of 1.96% from the base case ICER for the same population ([redacted]). In UDCA inadequate responders, the ICER is [redacted]/QALY, and there is no difference between the ICERs for the sensitivity analysis and the base case result ([redacted]/QALY, <0.1% decrease). In summary, the impact of adverse events on model outcomes is minimal.

Resource use and costs

B20. It is unclear how the technology cost is used to obtain the total annual technology costs (company submission Table 65). Please clarify and justify the calculation of total annual technology costs.

The list price shown in table 65 is an error; the list price should read £29,005.78. The annual price is built up from the price per tablet assuming 365 days in the year ((£2,384.04/30)*365).

B21. Costs of transplant and follow up costs are derived from the literature.

a. Please explain the relevance of using transplant-related cost assumptions based on Hepatitis C and B patients (Wright et al. 2006 and Singh 2014). Explain why NHS reference costs were not used.

NHS reference costs were not used, as the cost for the liver transplant health state reported in Wright et al 2006 and Singh 2014 reflect the total annual mean resource use, however it was not clear exactly how the micro-costing for the resource use was performed in terms of procedure codes.

In addition, the costs reported in the publications have been used previously in NICE TA330: Sofosbuvir for the treatment of chronic hepatitis C (15). As there is precedence for the use of these data, and KOLs have stated that the costs of treating each of the HCV health states in question (decompensated cirrhosis, hepatocellular carcinoma, liver transplant, liver transplant follow-up) would be identical to PBC, the existing costs in the model should be appropriate.

b. Please provide the results of a sensitivity analysis using reference cost estimates for liver transplant.

For the reasons discussed in the answer to question B21 a, the NHS reference cost for a liver transplant does not capture the full extent of transplantation costs. The currency code for a liver transplant (GA01C) places the cost to the NHS at £17,746.82 per transplant, approximately 27% of that estimated by Wright *et al* when inflated to 2016 values (13).

This does not include the additional costs of supporting care which is necessary for liver transplant patients, as was captured in the cost estimates generated by Wright et al. Using the NHS reference cost for liver transplants would be likely to underestimate the true cost of liver transplantation and its associated care costs.

B22. Outpatient appointment costs are based on expert opinion.

a. Please justify why outpatient appointment costs are based on expert opinion and not NHS reference costs (Table 66).

The NHS National Tariff 2015/2016 was used to estimate the cost of outpatient appointments. KOL input informed the number of each type of appointment which patients would be expected to receive, and the number of blood test patients would be expected to undergo on an annual basis.

b. Please provide a cost estimate for outpatient appointments based on NHS reference costs. Provide the results of a sensitivity analysis using this estimate

A sensitivity analysis has been included below, where NHS reference costs for outpatient appointments have been included. The currency code and its respective cost are presented below in Table 29.

Table 29: Reference cost for hepatology outpatient appointment

Outpatient attendance type	Service code	Cost
Hepatology (total)	306	£220.08

Source: National Schedule of Reference Costs, Year 2014-15; 15 NHS trusts and NHS foundation trusts.

The usage of this new cost impacted the calculations for the health states “ALP ≤ 200 U/L and normal bilirubin”, and “ALP > 200 U/L and normal bilirubin”, as shown below in Table 30.

Table 30: Updated annual costs for health states " ALP ≤200 U/L and normal bilirubin”, and “ALP >200 U/L and normal bilirubin”

	ALP: ≤1.67x ULN and Bili: Normal	ALP: >1.67x ULN and Bili: Normal
Outpatient visit cost: first visit†	£220.08	£220.08
Outpatient visit cost: quantity / year*	1	1
Outpatient visit cost: follow up†	£0.00	£220.08
Outpatient visit cost: quantity / year*	1	2
Blood test cost†	£3	£3

Blood test quantity / year*	9	9
Total annual cost	**£247.08**	**£687.24**

Abbreviations: ALP, alkaline phosphatase; bili, bilirubin; ULN, upper limit of normal.
†Sourced from the National Schedule of Reference Costs, Year 2014-15; 15 NHS trusts and NHS foundation trusts. *Sourced from KOL opinion.

The following changes to the health state costs resulted in the following deterministic results:

Table 31: Deterministic results for UDCA-intolerant patients, using NHS reference costs for outpatient appointments (using the list price of OCA)

Technologies	Total			Incremental			ICER (cost/QALY) versus baseline	ICER (cost/QALY) Incremental
	Costs	LYG	QALYs	Costs	LYG	QALYs		
No treatment (placebo)	£103,698	11.30	6.61	–	–	–	–	–
OCA Titration	[redacted]	16.65	13.52	[redacted]	5.35	6.91	[redacted]	[redacted]

Abbreviations: ICER, incremental cost-effectiveness ratio; LYG, life-years gained; NHS, National Health Service; OCA, obeticholic acid; QALY, quality-adjusted life year; UDCA, ursodeoxycholic acid.

Table 32: Deterministic results for UDCA inadequate responders, using NHS reference costs for outpatient appointments (using the list price of OCA)

Technologies	Total			Incremental			ICER (cost/QALY) versus baseline	ICER (cost/QALY) incremental
	Costs	LYG	QALYs	Costs	LYG	QALYs		
UDCA + placebo	£97,858	12.35	7.85	–	–	–	–	–
OCA titration + UDCA	[redacted]	16.75	13.64	[redacted]	4.40	5.79	[redacted]	[redacted]

Abbreviations: ICER, incremental cost-effectiveness ratio; LYG, life-years gained; NHS, National Health Service; OCA, obeticholic acid; QALY, quality-adjusted life year; UDCA, ursodeoxycholic acid.

The use of NHS reference costs had minimal impact on the ICERs; the ICER for UDCA-intolerant patients was 1.7% lower compared to the base case ICER ([redacted]), and the ICER for UDCA inadequate responders ([redacted]) was 0.19% greater in this sensitivity analysis.

B23. Please justify why the health state cost for 'Abnormal/Total bilirubin> 20 µmol/L and rising, or CC' is half the 'DCC' health state cost.

The health state for 'abnormal total bilirubin >20 µmol/L and rising, or CC' has been assumed to half the cost of managing DCC based on expert recommendation. The rationale for this was that patients in this health state would have a higher healthcare resource used than patients with CC due to the health issues associated with rising levels of bilirubin, since this is viewed as a sign of disease progression and liver failure. This is also why liver transplantation can be considered at this stage.

Results and validation

B24. Please provide an overview of disaggregated life years gained, as provided for QALYs gained in Tables 73 and 74 of the company submission.

Table 33 and Table 34 show the disaggregated life years gained for both UDCA-intolerant patients and UDCA inadequate responders.

Table 33: Summary of life years gained by health state for UDCA-intolerant population

Health state	OCA titration	No treatment (placebo)	Increment
ALP: ≤ 200 U/L and Bili: Normal	7.120	0.000	7.120
ALP: > 200 U/L and Bili: Normal	8.091	2.434	5.657
Bili: Abnormal and rising, or CC	0.716	4.573	–3.856
Discontinuation	0.012	0.000	0.012
Decompensated cirrhosis	0.278	1.702	–1.423
HCC	0.024	0.145	–0.122
Pre transplant (end stage)	0.089	0.543	–0.454
Liver transplant	0.009	0.055	–0.046
Post liver transplant	0.240	1.443	–1.204
Re-emergence of PBC	0.069	0.402	–0.333
Total	16.648	11.297	5.351

Abbreviations: ALP, alkaline phosphatase; Bili, bilirubin; CC, compensated cirrhosis; HCC, hepatocellular carcinoma; OCA, obeticholic acid; PBC, primary biliary cholangitis/cirrhosis; UDCA, ursodeoxycholic acid.

Table 34: Summary of life years gained by health state for UDCA inadequate responders

Health state	OCA titration + UDCA	UDCA + placebo	Increment
ALP: ≤ 200 U/L and Bili: Normal	7.120	0.000	7.120
ALP: > 200 U/L and Bili: Normal	8.303	4.604	3.699
Bili: Abnormal and rising, or CC	0.664	4.040	–3.376
Discontinuation	0.012	0.005	0.007
Decompensated cirrhosis	0.257	1.489	–1.231
HCC	0.022	0.128	–0.106
Pre transplant (end stage)	0.082	0.476	–0.394
Liver transplant	0.008	0.048	–0.040
Post liver transplant	0.219	1.231	–1.013
Re-emergence of PBC	0.062	0.331	–0.269
Total	16.750	12.351	4.399

Abbreviations: ALP, alkaline phosphatase; Bili, bilirubin; CC, compensated cirrhosis; HCC, hepatocellular carcinoma; OCA, obeticholic acid; PBC, primary biliary cholangitis/cirrhosis; UDCA, ursodeoxycholic acid.

B25. Please provide the outcomes of expert opinion meetings (i.e. individual answers on all of the questions provided in Appendix 11).

The company are not authorised to release the details of all the conversations with external experts; however, we will happily answer any specific questions.

B26. No cross and external validations have been performed and no results of the validation steps described in Section 5.10.1 of the company submission are provided.

a. Please perform cross and external validations (for instance, by using the following tool: http://www.uk-pbc.com/resources/tools/riskcalculator/).

It is not possible to fulfil this request; the UK-PBC risk calculator tool is designed to handle patient-level data. In order to perform this analysis, a single mean biochemistry reading would need to be calculated for the entire patient cohort, which has the potential to introduce bias. However, question A9 (Table 1) shows the results of an analysis of ESLD risk using the UK-PBC risk score algorithm. Following one year of OCA treatment, patients had a lower risk of ESLD when they crossed over onto UDCA + placebo treatment (1). External validation with other models is also not possible, since this is the first cost-effectiveness model in PBC.

b. Please provide the results of other validation steps as described in Section 5.10.1 (e.g. comparison of model results with POISE data).

The model was not validated against POISE (this was stated in error). The model outputs were instead validated against the GLOBE and UK PBC cohort survival rates, shown in Harms *et al,* 2016 (22).

The model cannot be directly validated against POISE, as POISE was one year in length, whereas the cost-utility model has an effective time horizon of 44 years.

External validation against other models cannot be performed, as this analysis is the first cost-utility model in PBC.

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Appendix 3: Publications excluded due to study design/outcome

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Appendix 4: Publications excluded due to population

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Question B13b - It is not clear how the POISE effectiveness data is already reflected for the UDCA and no treatment comparators. In response to question B6 the company notes that they made assumptions based on POISE, but this is different than actually using the POISE data. In addition, the ERG are concerned that different methods were used to calculate the transition probabilities for different treatments. Using the same methodology for all comparators would ensure that the differences between the treatments considered is not due to the difference in methods.

The ERG strongly request that you provide the results of scenario analyses using transition probabilities based on POISE for all comparators, using the same methodology and assumptions for the UDCA monotherapy and the no treatment comparators as was used for the OCA-based regimens (i.e. using a similar Table for these comparators as CS Table 49 for the OCA-based regimens). The updated model and detail of the adjustments and methodology (including the formulae used to derive transition probabilities) should accompany these results.

Patients who are intolerant to UDCA would not receive active treatment in clinical practice. In POISE, only 5 patients did not receive UDCA at baseline (i.e. they were intolerant and not treated with UDCA) and none responded positively. Therefore assuming that patients intolerant to UDCA would have the same response and progression as the UDCA inadequate responders (who are still gaining benefit from treatment) was not considered appropriate as it would not reflect an accurate history and risk of progression over time. We would overstate the outcomes for this population. After discussion with key opinion leaders, and because this is an extremely small patient population, we based our transition probabilities on the literature in this population (Corpechot, 2000,J Hepatology, V32, 6, 1196-1199)

For patients with inadequate response to UDCA, patients with low ALP values at baseline were more likely to achieve the 15% criteria and fall below 1.67 threshold compared to patients with higher values; this is driven by natural variation in ALP and the lower baseline value. This outcome potentially overestimates the benefit of UDCA in patients who were close to the 1.67 threshold in the POISE trial. To account for this natural variation and expected risk of progression in this population, we considered in our base case, transition probabilities that would reflect the natural history expected for this specific population, based on the 10-year liver transplant free survival rates estimated on POISE UDCA patients.

Regarding the additional analysis requested as clarification to question B13b:

- **The ERG strongly request that you provide the results of scenario analyses using transition probabilities based on POISE for all comparators, using the same methodology and assumptions for the UDCA monotherapy and the no-treatment comparators as was used for the OCA-based regimens (I.e. using a similar table for these comparators as CS table 49 for the OCA-based regiments). The updated model and detail of the adjustments and methodology (including the formulae used to derive transition probabilities) should accompany these results**.

Please note: the following results were generated using updated patient-level data from POISE. The previous version of the model used an incorrect patient-level dataset from an earlier version of the POISE CSR. The updated patient numbers used in the model are now reflective of the CSR.

Methodology

The ability to use patient-level UDCA data from POISE has been added into the model. While the majority of changes to the model were made in the 'Transition matrices' worksheet, some of the formulas were also updated to reflect this new feature in the sheets 'Clinical inputs' and 'UDCA Markov Model'. All additional transitions to use for the first 4 cycles were added in the range L316:HL371 on this worksheet and the transition matrices to use after the first year in the range X9:AP27. A switch to enable or disable the use of UDCA patient-level data has been added in cell C10 on the 'Clinical inputs' worksheet. If the switch is activated, patient-level UDCA data from POISE is used to generate transition probabilities for that population.

The new patient-level population numbers (added in the cells highlighted in yellow on the 'Transition matrices' worksheet) are displayed along with their transition probability calculations (presented alongside). The calculations for how transition probabilities are derived are present as formulae within the transition probability cells; for example, the patient numbers for UDCA patients with a recorded ALP threshold of > 1.67 * ULN (200 u/L) are located in the range X330:AF338. The transition probability calculations corresponding to this set of patient numbers are located in the range M330:V330. This method was used to derive all patient-level UDCA transition probability data for the first four cycles of the model.

Results

Use of the patient-level UDCA transition data produced the following results:

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Table 1: Deterministic results for UDCA-intolerant patients, using the list price of OCA and UDCA patient-level data

Technologies	Total			Incremental			ICER (£)	ICER (£)
	Costs (£)	LYG	QALYs	Costs (£)	LYG	QALYs	versus baseline	incremental
No treatment (Placebo)	£103,233	11.30	6.61					
OCA titration	[redacted]	16.68	13.56	[redacted]	5.38	6.95	[redacted]	[redacted]

Abbreviations: ICER, incremental cost-effectiveness ratio; LYG, life years gained; OCA, obeticholic acid; QALYs, quality-adjusted life years; UDCA, ursodeoxycholic acid

Table 2: Base-case results for UDCA inadequate responders, using the list price of OCA, and UDCA patient-level data

Technologies	Total			Incremental			ICER (£)	ICER (£)
	Costs (£)	LYG	QALYs	Costs (£)	LYG	QALYs	versus baseline	incremental
UDCA+Placebo	£92,218	12.72	8.30					
OCA+UDCA Titration	[redacted]	16.78	13.68	[redacted]	4.06	5.38	[redacted]	[redacted]

Abbreviations: ICER, incremental cost-effectiveness ratio; LYG, life years gained; OCA, obeticholic acid; QALYs, quality-adjusted life years; UDCA, ursodeoxycholic acid

As no UDCA is considered for the UDCA-intolerant population, the results in Table 1 are identical to the updated base case model, i.e. corrected ICER of [redacted] (submitted alongside this document). Use of the patient-level UDCA transition data for the inadequate response patient population resulted in an ICER of [redacted], which is [redacted] greater than the corrected base case ICER of [redacted].

Question B12 section 3) *Please clarify why the number of patients in Table 13 add up to 68, while the number of patients in the trial arm is 70*

The answer to the difference in the numbers is patient discontinuation in the trial. 71 patients were randomized into the 5mg titration arm, 69 patients completed to month 6, and 64 patients completed the 12 months evaluation phase (defined as the Completer Population).

The table below (from our submission) illustrates the different analysis populations:

Table 3: Analysis populations

	Number of subjects, n (%)			
	Placebo	**OCA titration**	**OCA 10 mg fixed dose**	**Total**
Enrolled/randomised	73 (100)	71 (100)	73 (100)	217 (100)
ITT population[§]	73 (100)	70[†] (99)	73 (100)	216 (<100)
Completer population[¶]	70 (96)	64 (90)	64 (88)	198 (91)
EE population[‡]	67 (92)	63 (89)	62 (85)	192 (88)
PK population[††]	0 (0)	66 (93)	60 (82)	126 (58)
Safety population[§§]	73 (100)	70 (99)	73 (100)	216 (<100)

Abbreviations EE, efficacy evaluable; ITT, intention-to-treat; OCA, obeticholic acid; PK, pharmacokinetics.
[†]There was one subject in the OCA titration group who withdrew after randomisation, leaving 70 subjects in the ITT group; [§]All randomised subjects who received at least one dose of investigational product. Treatment assignment is based on the randomised treatment; [¶]All randomised subjects who received at least one dose of investigational product and participated through the end of the double-blind phase (12 months). Treatment assignment is based on the randomised treatment; [‡]All subjects in the completer population who did not have any major protocol deviations that could have potentially affected the efficacy of the investigational product. Treatment assignment is based on the randomised treatment; [††]All randomised subjects who received at least one dose of OCA who have at least one confirmed fasting sample at Month 6 and Month 12 visits (subjects must have been fasting for approximately 8 hours prior to the visit) and who did not have any major protocol deviations that could have potentially affected exposure levels; [§§]All subjects who received at least one dose of study drug. Treatment assignment is based on the treatment actually received.

The CONSORT diagram in figure 11 of our submission shows that 7 patients out of the 71 patients in the randomized population in the 5mg titration arm discontinued.

The reasons for discontinuation were (n):

Clinical / laboratory adverse event (3), withdrew consent (2), pruritus (1), death (1).

The difference in the numbers of patients reporting in each quarter is accounted for by discontinuation from the trial. Neither the death nor the adverse events were considered to be associated with the trial treatment. Pruritus as a known symptom of PBC and an established side effect of obeticholic acid.

Question B4b – Lack of data/evidence is not a clinical rationale for combining abnormal bilirubin (TB>20umol/L) and compensated cirrhosis into one health state. Please provide a clinical justification why combining abnormal bilirubin (TB>20umol/L) and compensated cirrhosis into one health state is appropriate. Why does the company believe that abnormal bilirubin (TB>20umol/L) can be assumed to be equivalent to having compensated cirrhosis?

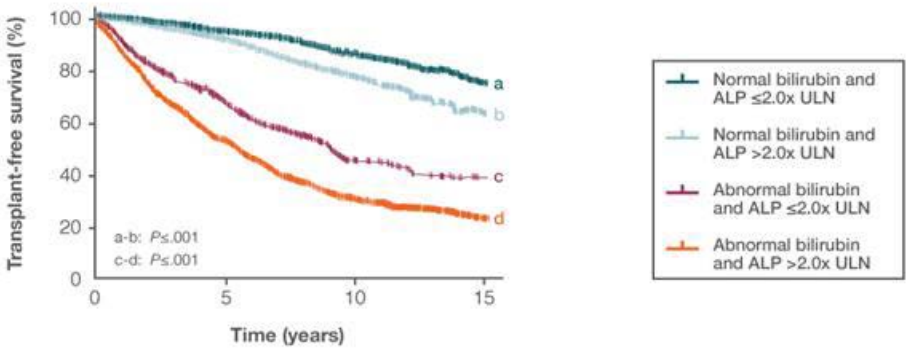
We have not combined the two groups into one health state because of a lack of evidence, but because the outcomes from these groups are clinically similar. PBC is a condition driven by progressive loss of bile ducts (ductopenia) leading to mechanical failure in the transport of bile from the liver (cholestasis), which then leads to the death (or senescence) of biliary epithelial cells. The condition is functionally different from other liver conditions such as HepC. As a result, fibrosis in itself is not considered to be the key clinical measure – whilst it is present in the later stages of the condition, the underlying ductopenia means that fibrosis progression is not a good measure of severity or response to treatment.

PBC therapeutic trials are challenging to conduct because of the slow course of the disease. The choice of selection criteria and primary endpoints is of critical importance. Because most patients are currently diagnosed and treated at an early stage, the use of hard endpoints, such as the occurrence of death or liver transplantation (LT), alone appears unsuitable as this can take up to 10 years from diagnosis. The use of additional endpoints, such as the occurrence of cirrhosis or of extensive fibrosis, seems undoubtedly more relevant in this condition, however more towards the end stages of the condition. The necessity to perform repeated liver biopsies remains a serious limitation to the utilization of such endpoints. *Liver biopsies are not routinely done in clinical practice and the soon to be published UK PBC guideline recommends that 'liver biopsy is not usually required in the diagnosis of PBC or for monitoring of disease progression out with clinical trial'.*

The previously referred to UK guideline recommends that "whilst there are a range of non-invasive tools to stage and monitor disease progression. There is no consensus as to what is the optimal strategy". There is a continued need for developing non-invasive methods of liver fibrosis assessment and monitoring. In this regard, transient elastography (TE) appears as one of the most promising methods. We have used TE in the POISE trial, but not all units have established this technology in clinical practice. As a result we only have a subgroup of patients who have been reviewed at baseline and at 12 months. The results have been included in the main submission.

The role of raised ALP and bilirubin is well established in the diagnosis and management of PBC (Corpechot) and the global support group (Lammers) has demonstrated that controlling the levels of both biochemical indicators improves outcomes. As a result, raised ALP and bilirubin are used to diagnose the condition and response to therapy is measured against reduction of ALP and bilirubin. The graph below demonstrates how abnormal bilirubin significantly reduces progression free survival, even where ALP levels are below 2X ULN. The Bowlus paper indicates

from a further analysis of the Global PBC study group that the risk starts to increase at 0.5xULN, i.e. even within the normal range.



Abnormal bilirubin is a lagging indicator of progressive liver deterioration in PBC. The Harms publication shows that bilirubin at 1.6x ULN will result in significant events with median time of 19 months to a major endpoint. As a result, PBC patients with abnormal bilirubin will have a similarly increased risk of an event to patients in the compensated cirrhosis state.

In summary, abnormal bilirubin is a clear indicator of progression with similar risk of events as patients in the compensated cirrhosis state, which is why, following guidance from the principal investigator in the UK PBC Consortium, we have combined the two states in the model.

References;

Bowlus,	Hepatic Medicine: Evidence and Research 2016:8 89-95
Lammers,	Journal of hepatology. 2013;58(S388)
BSG	UK PBC draft PBC guidelines
Corpechot,	Hepatology. 2008 Sep;48(3):871-7.
Harms	Poster SAT-351 presented at EASL 2016

Remaining response to ERG clarification questions

We would like to bring to the ERG's attention that there was an error in the original submission regarding patient numbers used in the economic model.

The original submitted model contained data from an analysis of patient numbers according to an early dataset version from POISE. A QC has since been performed on the patient numbers by the Intercept bio stats team and updated data provided.

The model has now been updated to include the correct patient numbers. These have the effect of changing some transition probabilities used in the first four cycles of the economic model. This has had a downstream effect of changing the QALYs and costs generated for the OCA treated patient groups.

The effect of this change will be outlined in detail in a forthcoming erratum. The erratum will contain a full deterministic and probabilistic analysis of the new base case, including updated versions of the scenario analyses provided in the original submission. The overall effect on the ICERs for both the intolerant and inadequate response patient populations is minimal (deterministic ICERs change by <£500).

We would like to apologise for this error and the inconvenience caused. We would also like to thank the ERG for spotting the issue with the patient numbers, and requesting further clarification in their question B12b.

The model submitted with this response is the corrected version of the model and we have used this version to respond to the ERG queries in this document.

Regarding the response to clarification questions B12b:

a. **Please explain how the numbers in Table 13 of the response are used in the economic model. Please provide cell references to the transition probabilities that are used in the Markov trace – for example what are the cell references for 0.343 and 0.558 (reported in Table 13)?**

We apologise for the lack of clarity in our previous answer. The data shown in Table 13 of the response are the entire ITT patient population from POISE for the OCA titration arm of the trial. The actual patient numbers used in the model were lower. This is because a given patient could only be used in transition matrices if we could track their progress through the different health states based on ALP and bilirubin every 3 months, i.e. :

1. Patients had their ALP and bilirubin levels recorded at their previous appointment (i.e. baseline, 3 months, 6 and 9 months)
2. Both ALP and bilirubin levels were recorded at the subsequent visit (i.e. 3, 6, 9 and 12 months respectively).

If a patient missed an appointment, or had only ALP or bilirubin levels recorded, they could not be used to generate transition probabilities, as the biochemistry state that the patient was previously in could not be determined. Patients were removed from the analysis if they did not meet the criteria for inclusion.

The transition matrices containing transition probabilities, and the patient numbers used to generate these probabilities, are located on the worksheet 'Transition matrices' in the accompanying updated model.

An example of a range containing an OCA-specific patient number matrix (on the 'transition matrices' sheet) is [redacted]. Its corresponding transition probability matrix is in [redacted]. The formulae for generating these transition probabilities are present in this range. Patient number values that have been updated from the previous base case version of the model have been highlighted in yellow.

The transition probabilities are used in each of the Markov engines for the involved comparators. These vary depending on the population selected (UDCA intolerant versus UDCA tolerant). The proportions of patients in each model state are tabulated on the 'Markov trace' worksheet. This table is then drawn visually as a Markov trace, which can be seen on the 'Clinical inputs' worksheet.

Due to the transition probabilities changing over time, the Markov trace is composed of a number of transition matrices, which are labelled in the 'Transition matrices' worksheet.

The specific cells which the Markov trace is referencing can be determined by selecting a data series on the Markov trace. In the formula bar, the range reference for that data series on the 'Markov trace' worksheet will be present.

b. How is the discontinuation in Table 13 calculated (i.e. how did the company derive the 0.099)?

The overall discontinuation rates for the trial were taken from patient-level data from POISE. All patients are assumed to discontinue within the first three months of treatment. The discontinuation rates used are shown in cells C23, C24 and C25 on the 'Clinical inputs' worksheet.

Reply to question received from NICE 12.22pm on the 18th of November 2016

In the sheet "UDCA Markov model", the information presented in the sheet "Transition matrices " range "L329:HL339" is reflected in the in the transitions displayed rows 54:61 of the sheet "transition matrices. When you switch, the data used in the UDCA markov sheet changes in the range "BK7:BN10" taking the patient-level data from the POISE UDCA arm into account

It is correct that the transitions in C10:T27 and Y10:AP27 are similar. This is due to the fact that we still allowed the patients to be able to progress to abnormal bilirubin during the first year. This can be removed by changing as follows the probabilities in cell F10:F11 as follows:

- Before: =IF('Model parameters'!C145="yes",'Model parameters'!$C150,0)
- New: =IF(UDCAPL="No", 'Model parameters'!$C150,0) and =IF(UDCAPL="No", 'Model parameters'!$C155,0) respectively

We have uploaded an updated model containing this specific feature

Question:

Dear Gordon

There seems to be an error in the model submitted with regards to the requested scenario analysis or the description in the accompanying document is unclear/incorrect.

To clarify this concern the ERG state:

- The UDCA Transition matrix is located in 'Transition matrices'!C$10:T$27; i.e. this is the matrix referred to in cells 'UDCA Markov model'!AR7:AU10

- According to the company's accompanying document, the transition matrices for this scenario analysis are located in 'Transition matrices'!L316:HL371; I think we can narrow this down to 'Transition matrices'!L329:HL339 for the company base-case

- If we would change the 'switch' variable indicated by the company to 'yes' ('Clinical inputs'!C10), the transition matrices in 'Transition matrices'!L329:HL339 are not reflected in 'Transition matrices'!C$10:T$27 and do not seem to be used in the for the UDCA Markov trace (in the 'UDCA Markov model' work sheet). Moreover,the transition matrix used in the UDCA Markov trace doesn't seem to differ between cycles 1-4 whereas those in 'Transition matrices'!L329:HL339 differ for cycles 1-4 (as I would expect as this is consistent with how it is done for the OCA-regimens).

Please can you clarify the above and if needed send us an updated/corrected version of the model.

Kind Regards

Technology Appraisals Administrator - Committee A

Appendix G - professional organisation submission template

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Single Technology Appraisal (STA)

Obeticholic acid for treating primary biliary cirrhosis [ID785]

Thank you for agreeing to make a submission on your organisation's view of the technology and the way it should be used in the NHS.

Healthcare professionals can provide a unique perspective on the technology within the context of current clinical practice which is not typically available from the published literature.

To help you in making your submission, we have provided a template. The questions are there as prompts to guide you. It is not essential that you answer all of them.

Please do not exceed the 8-page limit.

Your name: [redacted]

Name of your organisation: BASL

I am a specialist in the treatment of people with primary biliary cirrhosis.

I am also involved closely with UK-PBC, an MRC funded nationwide study group that has determined the natural history of PBC with careful genotyping and phenotyping. This study has emphasised the value of the serum alkaline phosphatase as a biomarker for clinical outcome. The early clinical response of the alkaline phosphatase to ursodeoxycholic acid therapy has allowed separation of patients into distinct clinical groups with eventual high and low mortality, but at an early point in the clinical course. Thus introducing a surrogate marker of efficacy in this condition, avoiding long-term mortality based studies.

I am also the (unpaid) president of the British Association for the study of the liver (BASL) an organisation that represents clinicians treating PBC.

I have no conflict of interest and do not accept any personal funding or personal support from the pharmaceutical industry.

Appendix G - professional organisation submission template

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Single Technology Appraisal (STA)

Obeticholic acid for treating primary biliary cirrhosis [ID785]

What is the expected place of the technology in current practice?

The long natural clinical course for patients with PBC, sometimes decades, has made trials of therapy in PBC difficult to conduct if based on mortality or the onset of liver failure. Ursodeoxycholic acid has been used predominantly to manage pruritus and the role of this agent as a disease modifier in the treatment of PBC was not accepted universally. However recent data based on both retrospective and prospective evidence in large groups has emphasised that patients can be stratified by the response to this agent (by a reduction in the alkaline phosphatase) into those with an excellent clinical outcome and those in whom the long-term prognosis is poor. The majority of patients in the UK and elsewhere are now being offered treatment with Ursodeoxycholic acid, encouraged by patient support groups. Recent data has encouraged physicians to use larger doses nearer that recommended with benefit in many patients. This agent is well tolerated. A number of other agents are offered to manage pruritus, a major issue in PBC, with variable success and without evidence that these modify the clinical course of disease or liver biochemistry. Thus, Ursodeoxycholic acid is inexpensive, effective and safe with a low incidence of side effects, but there is a distinct cohort, identified by an unchanged alkaline phosphatase with therapy, that do not respond to treatment.

There are only two prospective randomised controlled trials comparing Obeticholic acid (OBCA) with placebo in patients unresponsive to, or intolerant of Ursodeoxycholic acid and in both studies those on active therapy had a biochemical response with a fall in the alkaline phosphatase, the best early marker we have currently POISE study, NEJM, 2016 and Hirschfield et al Gastroenterology 2015). Based on the data from natural history studies it can be inferred that OBCA is a disease modifier but that cannot be regarded as certain while outcome data such as liver failure, death or a need for liver transplantation are years from accrual. The agent is not just ‘another bile acid’ but has broad biological activity based on FXR agonism, which might explain effects in those unresponsive to Ursodeoxycholic acid. However side effects are much more prominent than with Ursodeoxycholic acid and to an extent appear to be dose related.

There is no clear view on where such patients should be managed. However, it would be pragmatic if patients with a good long-term prognosis identified by the alkaline phosphatase and the response to Ursodeoxycholic acid were managed in secondary care (or in some cases primary care with clear guidance). Alternatively those with a poor outcome might be better managed in tertiary care centres.

Guidelines on managing PBC (via the BSG) are close to publication and are likely to be based on similar recommendations.

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Single Technology Appraisal (STA)

Obeticholic acid for treating primary biliary cirrhosis [ID785]

The advantages and disadvantages of the technology

The side effect profile is well described in the two randomised controlled clinical trials. The earlier study identified pruritus as an issue with this agent, which appears to be dose related. There is nothing in that profile to cause particular anxiety. The role of OBCA in de novo therapy for PBC is uncertain. However, many of those using OBCA have found pruritus to be difficult to manage and this may prove to be be an issue in 'real life' clinical practice.

Any additional sources of evidence

Implementation issues

I cannot se that implementation would be problematic for hepatology services. The patients are seen in clinic regularly in any case and many are enrolled in the national study. One model for ensuring responsible use would be to adopt the ODNs delivering antiviral therapy currently for patients with hepatitis C.

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Single Technology Appraisal (STA)

Obeticholic acid for treating primary biliary cirrhosis [ID785]

Equality
I cannot see that this will be an issue.

Appendix G - professional organisation submission template

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

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To help you in making your submission, we have provided a template. The questions are there as prompts to guide you. It is not essential that you answer all of them.

Please do not exceed the 8-page limit.

About you

Your name: [redacted]

Name of your organisation: British Society of Gastroenterology/Royal College of Physicians/University of Birmingham

Are you (tick all that apply):

- a specialist in the treatment of people with the condition for which NICE is considering this technology? **YES**
- a specialist in the clinical evidence base that is to support the technology (e.g. involved in clinical trials for the technology)? **YES**
- an employee of a healthcare professional organisation that represents clinicians treating the condition for which NICE is considering the technology? If so, what is your position in the organisation where appropriate (e.g. policy officer, trustee, member etc.)? **NO**
- other? (please specify) **Work Strand Lead for UK-PBC (User Interface; www.uk-pbc.com)**

Links with, or funding from the tobacco industry - please declare any direct or indirect links to, and receipt of funding from the tobacco industry: NONE

Appendix G - professional organisation submission template

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Single Technology Appraisal (STA)

Obeticholic acid for treating primary biliary cirrhosis [ID785]

What is the expected place of the technology in current practice?

Primary biliary cirrhosis (PBC; now referred to as primary biliary cholangitis) is a chronic autoimmune liver disease. Diagnosis is generally straight forward and care in the UK is overwhelmingly delivered by the NHS with the involvement of Gastroenterologists, Hepatologists and Primary Care. There are only a few specialist centres and most patients are looked after by Gastroenterologists. There is relative uniformity in practice, and estimated to be perhaps 15-20,000 patients in the UK: 1 in 1000 women over the age of 40 live with PBC. The current UK-PBC flow chart for management (Figure) is shown below and a) current recommended management is with oral Ursodeoxycholic acid (UDCA) at a dose of 13-15mg/kg/day. This is in keeping with UK (BSG/UK-PBC) guidance under review, European (EASL) and North American (AASLD) professional guidance. It is believed that the majority of patients with PBC diagnosed in the UK are now offered this therapy (pending the licencing of OCA in Europe, this is the only licenced therapy for patients with PBC). Efforts continue to optimise awareness that weight based dosing is recommended. The majority of patients tolerate therapy: UDCA intolerance is recognised in 5-10% of patients; b) There is no true geographical variation in practice: it is however recognised generally that there are variations in Hepatology services across the NHS and variation as a result of the presence of dedicated liver services, which have until late remained focused in large cities and around transplant programmes. This is being addressed over time by efforts from a number of organisations spanning professional and patient groups and increasingly every 'DGH' has a Hepatologist; c) There is consensus now that risk stratification is relevant to clinical practice and that biochemical indices are appropriate tools to stratify patients to low or high risk of disease progression; there are a number of biochemical markers that have been robustly identified and validated as appropriate surrogates of PBC outcome and there is recognition that there are strengths and weaknesses associated with individual scoring approaches (some are dichotomous others are continuous in nature). Furthermore there has been a consensus in Industry practice such that second line disease modifying clinical trials have sought patient inclusion based on a dichotomous stratifier of in essence an ALP of >1.67 x ULN after 1 year of UDCA therapy (OR elevated bilirubin values consistent with later stage disease). It is however also accepted that there is a log-linear association between ALP values and future risk of deleterious outcomes i.e. dichotomous stratification is good but response to a new therapy has potential to benefit more than just those who achieve a change in a dichotomous response criteria; d) There is no consensus as regards second line therapy for patients failing UDCA. In the UK it is not widespread practice to offer unlicensed therapies such as fibrates, methotrexate, colchicine, Budesonide, ciclosporin. Only occasional patients are offered such therapy and UK-PBC data suggests this is not widespread or adopted by the majority. For example UK-PBC data (personal communication Dr G Mells, University of Cambridge) shows that in a recent updated survey of a significant proportion of the overall cohort, only 58 patients out of 2245, had ever used a fibrate. Additionally it was not possible to ascertain if this was for hyperlipidaemia or PBC. It can thus be fairly concluded that it is not UK practice to offer any specific therapy for patients who do not respond to UDCA or who are intolerant. In this setting of non-response current practice is to either enrol into formal clinical trials, or refer to an expert centre. To that end it is notable that every NHS trust is represented in UK-PBC, a marker of interest in the UK delivering evidence based care not anecdote based care. Whilst an advantage to off-label drug use has been availability without restriction, significant disadvantages have limited this approach appropriately: namely a lack of evidence of benefit from randomised trials, a reluctance to use off-label therapy and a concern about toxicity that spans liver injury (e.g. fibrates are overtly contraindicated by the manufacturer in liver disease/PBC and hepatotoxicity is clearly documented) as well as infection risk, metabolic risk and renal/haematologic toxicity. BSG and UK-PBC guidelines therefore suggest that in

those patients stratified to high risk based on UDCA treatment failure that second line licenced therapy should be sought if available or alternatively patients offered access to approved clinical trials.

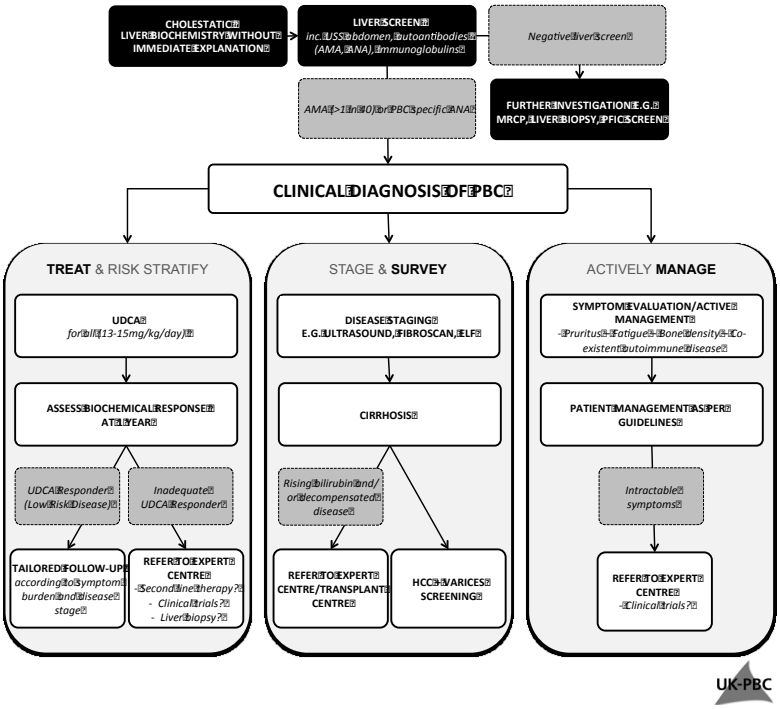


Figure: Overview of patient journey as per BSG/UK-PBC PBC guidelines under review

Subgroups:

This is addressed really by the concept of risk stratification by risk scores. This is a new technology designed as second line to UDCA because the concept is clear that there are patients treated with UDCA whose response to UDCA predicts a very low risk of progressive disease: these responders do not need new therapy. The 20-30% of patients who don't respond adequately to UDCA are the group this technology has the greatest impact on. Predictors of non-response include age at diagnosis, stage of disease at presentation, bilirubin values, and degree of ductopenia (if biopsied). Male patients may also be more likely to be UDCA non-responders. It is of note that whilst risk is relevant to patients of all ages with PBC, the UK-PBC database has shown that patients under the age of 50 have a 50% chance of being a non-responder. Data from UK Transplant has also suggested that despite widespread UDCA use, the age at transplant in the UK is unchanged over the last 20 years.

As with any liver disease it is unclear whether patients in the very late stages of liver disease with overt decompensation/indication for liver transplant would benefit from addition of second line therapy. Given the side effect profile of OCA (pruritus) it is also important to note that very symptomatic patients will need close attention as tolerability in this small subgroup is relevant, and will need a personalised approach.

Technology setting:

This new technology (Obeticholic acid) is an oral therapy that can be readily delivered to patients. However it is recommended that PBC stratified as high risk is managed in expert centres. It is envisaged that this encompasses Hospital based Hepatologists (or Gastroenterologists with an interest in Hepatology) who are supported by local and regional established Hepatology networks. There is a clear track record of delivering new therapies in

the Hepatology space (cf. Hepatitis C therapy) and evidence that the NHS is well placed to do so in a way that captures need and reports efficacy.

Technology availability presently:

This technology is presently only available as part of approved clinical trials. To my knowledge as yet no NHS patient has received Obeticholic acid outside of approved clinical trials.

*Relevant **clinical guidelines**:*

The BSG and UK-PBC have prepared, according to BSG/NICE guidance, treatment guidelines for the management of PBC. These are presently under review by the BSG and have been widely circulated for comment across multiple stakeholders. They have been developed under the auspices of a Cholestasis Guideline Development group according to BSG guidance, and with the intent of meeting NICE guidance on treatment guidelines. They have not evaluated non-licenced therapy. The methodology used has been appropriate and is fit for purpose. It should be noted that the BSG/UK-PBC guidelines (now under BSG review following formal drafting) will have the following recommendations relevant to evaluation of this new technology:

RECOMMENDATION 11: All patients with PBC should be offered structured lifelong follow-up, recognising that different patients have different disease courses. For most patients secondary care will manage disease (EL 4, strong).

RECOMMENDATION 12: Ursodeoxycholic acid at 13-15mg/kg/day is recommended as the first-line pharmaco-therapy in all patients with PBC. If tolerated treatment should be lifelong. (EL 1-, strong)

RECOMMENDATION 13: Individualised risk stratification using biochemical response indices is recommended following one year of UDCA therapy. (EL 2++, Strong)

RECOMMENDATION 14: Inadequate response to UDCA is robustly associated with a greater likelihood of future liver transplantation, development of hepatocellular carcinoma and death. For those patients, clinicians should consider discussion with a liver disease specialist and the opportunity for clinical trial participation, in the absence of access to licenced second line therapies. It is of note that current clinical trials focused on disease modification have used an inclusion criteria that stratifies based on ALP and Bilirubin (e.g. an ALP value of at least 1.67 times the upper limit of the normal range or an abnormal total bilirubin) (EL 4, strong)

RECOMMENDATION 15: All patients should be evaluated for the presence of symptoms, particularly fatigue and itch. Clinicians should recognise that severity of symptoms does not correlate with stage of disease. (EL 4, strong)

RECOMMENDATION 16: Cholestyramine is first-line therapy for pruritus and should be taken separately to UDCA to avoid interaction. (EL 2+, strong)

RECOMMENDATION 17: Rifampicin is the recommended second-line therapy for pruritus. (EL 1-, strong)

The advantages and disadvantages of the technology

Alternatives:

At present it is our opinion that there are no established alternative available therapies for patients failing UDCA therapy. This is supported by the practice of the major centres involved in UK-PBC, as well as the national level data from UK-PBC demonstrating very low uptake for non-licenced therapies. Therefore this new therapy will be an additional opportunity for patient benefit. Its use will not be overtly burdensome because it is a once daily oral therapy. However, as above, expert treaters will be appropriate, and liver disease management in the UK is appropriately engaged and set up to deliver this (e.g. successful implementation of Hepatitis C therapy across the NHS). There will be requirements on treatment to confirm benefit (a fall in ALP) as well as monitor for side effects (particularly in the rare population with decompensated liver disease), including pruritus. The management of pruritus will be according to standard practice but will need to be proactive. However the agents available for pruritus management are readily accessible and low cost (Cholestyramine and Rifampicin). The expectation is that Obeticholic acid will be delivered through established ambulatory Hepatology practices and the NHS will be well placed to safely implement this therapy without significant added cost beyond the drug itself.

Treatment rules:

The important underlying principal in developing new therapies for patients with PBC is the concept of UDCA treatment failure. It has become clear, and has been validated and extended by numerous academic efforts, that biochemical response in patients with PBC i) is associated with clinical outcomes; ii) there is a log-linear association between ALP values as relates to future clinical outcomes; iii) utilising risk stratification is an appropriate way to presently design clinical trials for second line therapy in PBC; iv) in the context of a rare and orphan disease with a slow clinical course, biochemical surrogates are reasonably likely to predict clinical outcome and benefits when evaluating new therapies; v) true clinical outcome studies of new therapies are desirable but very difficult to conduct. In this context clinical practice (see above) now recommends risk stratification using simple laboratory indices that are measured in routine clinical practice (i.e. there is no additional cost). With a variety of biochemical indices of high risk, there is no overwhelming evidence for one tool over another. Consensus has however rested on a criteria based in essence on ALP values >1.67xULN and/or bilirubin above ULN (in clinical trials often there is an upper limit added which encompasses safety parameters for trial conduct, more so than need) for trial inclusion and therefore this is likely to be the most appropriate rule for consideration of future new therapies in clinical practice. This applies to this new technology and it is the expectation that patients with ALP >1.67 x ULN and/or an elevated Bilirubin will be considered for therapy.

Effective response to therapy is based on biochemical indices as well. For the purposes of clinical trials this has been broadly defined as a fall in ALP alongside stabilisation of Bilirubin. In the context of this new agent the Phase 3 endpoint agreed after academic consultation, was that of ALP <1.67xULN, Normal Bilirubin, and fall in ALP of at least 15%. Such categorical response criteria are most valid in clinical trial settings, and it needs to be noted that there is a log-linear association between ALP values and outcome in particular, hence categorical classification of response under represents the true potential benefit to patients of therapy over prolonged use. Therefore at the present time it is clinical consensus that for new second line therapies categorical response criteria are not rigidly appropriate and broader definitions of clinical response based on overall evaluation of the patient and laboratory indices are more appropriate in the clinic e.g. ALP values fall by at least 15% persistently.

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Single Technology Appraisal (STA)

Obeticholic acid for treating primary biliary cirrhosis [ID785]

Criteria for Biochemical Response to UDCA

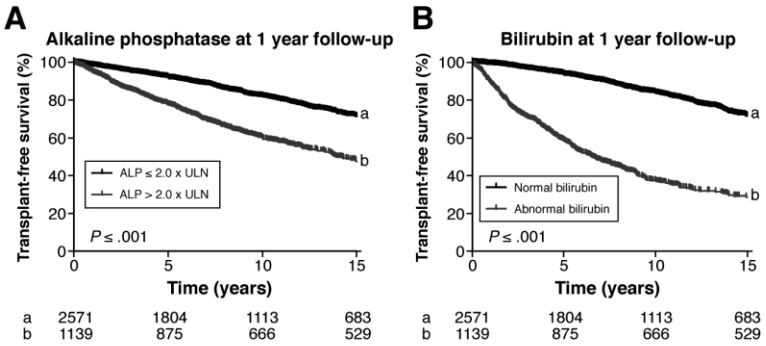
Barcelona	ALP ≤1 x ULN or decreased by ≥40%	At 1 year
Paris I	ALP ≤3 x ULN and AST ≤2 x ULN and bilirubin <1 mg/dL	At 1 year
Rotterdam	Normalisation of abnormal bilirubin and/or albumin	At 1 year
Toronto	ALP <1.67 x ULN	At 2 years
Paris II	ALP ≤1.5 x ULN and AST ≤1.5 x ULN and bilirubin <1 mg/dL	At 1 year
Beijing	Barcelona, Paris I, or Toronto criteria	At 6 months
Biochemical + APRI	Biochemical response (Barcelona, Paris I/II, or Toronto) and APRI ≤0.54	At 1 year
Globe Score	Prognostic index: baseline age, and bilirubin, ALP, albumin, and platelet count	At 1 year
UK-PBC Risk Score	Prognostic index: baseline albumin and platelet count, plus bilirubin, ALT or AST, and ALP	At 1 year

Evidence base:

For Obeticholic acid the clinical trials have been reflective of broad clinical practice relevant to the NHS. The trials were multi-centre, international, placebo controlled and included UK centres; trials included open label extensions mirroring standard clinical practice. Care was delivered in ambulatory settings in keeping with current care offered for patients with PBC. There is ready extrapolation to UK practice. The most important outcomes from the studies were a) consistent effects in improving the surrogate marker of outcome in PBC, namely ALP; b) demonstrable evidence of stabilisation of bilirubin values (noting that bilirubin values in the normal range do still predict outcomes in large studies and that in high risk disease it is evident that you do see slow rises in bilirubin over time); c) consistent improvement in other markers of liver injury alongside ALP- ALT, AST, GGT; d) improvements in IgM concentrations; e) falls in markers of inflammation e.g. CRP; f) overall meeting of primary endpoints.

Surrogates were used in this trial and published data strongly supports that surrogates markers of liver injury (ALP, Bilirubin in particular) are reasonably likely to predict clinical benefit. It is quite clear that there are caveats to this argument that are well rehearsed, but the use and utility of surrogates needs to be recognised in the context of the disease and its current clinical course, and ongoing rare nature. It is fair to state that clinicians accept the use of these surrogates as a route to demonstrating early markers of benefit, and with the expectation that true outcome data will take considerable time to establish.

Stratification of risk



Lammers WJ, van Buuren HR, Hirschfield GM, et al. *Gastroenterol.* 2014;147:1338-1349;

Side effects:

Pruritus: Pruritus is a common and fluctuant symptom in patients with PBC. Obeticholic acid is a FXR agonist (bile acid derived). It is a modification of chenodeoxycholic acid. In clinical practice it is already recognised that UDCA (ursodeoxycholic acid) can precipitate pruritus in around 1% of patients, presumably because of changes in bile acid compositions. Similarly it was not a surprise that pruritus was a clear side effect of both the Phase 2 and Phase 3 trials of OCA in patients with PBC. It would appear to be dose dependent and will be an important component of patient counselling, particularly as symptoms are of importance to patients with PBC. In this regard the relevant lessons learnt from the Phase 3 clinical trial were that i) whilst pruritus was a concern the high retention of patients into the open label long term safety extension suggests high acceptance of the therapy by patients; ii) dose titration, starting at 5mg and not going above 10mg of OCA was an effective means of mitigating pruritus and significantly reducing its impact; iii) pruritus appears to settle with ongoing use; iv) standard of care interventions such as cholestyramine and rifampicin were of utility; v) dose reduction of OCA was a final approach. It must be acknowledged that the Phase 3 patients may have been biased against those with pre-existing itch to some degree, and it is therefore an expectation as OCA is used that clinician and patient education addresses potential pruritus and its management.

Hyperlipidaemia: this is a common pre-existing feature of the cholestasis associated with PBC, wherein despite hyperlipidaemia there is no evidence that patients with PBC have elevated cardiovascular risk. This is a reflection most likely of the nature of hyperlipidaemia in cholestasis wherein unusual lipoprotein particles, such as lipoprotein X, may accumulate and levels of HDL cholesterol are typically elevated. FXR agonists are predicted to have complex effects on lipids and it is not surprising that in patients with PBC given OCA there was a slight increase in LDL and an overall small fall in HDL. There were no reported excess cardiac events in the trials to date, and it is probable that the changes reported for lipid results on treatment with OCA do not change cardiac risk. It remains an area for long term monitoring but no intervention is needed. It should also be noted that for those with risk factors beyond cholesterol values, that statins are safe in patients with PBC, including those on OCA.

Advanced liver disease: the phase 3 trials included some patients with Child Pugh A cirrhosis and in those included there were no clinical concerns. Response seemed equal. It is however noted that Child Pugh B and C patients were not studied and going forward additional information will be needed to ensure safe use in these patients with high risk, late stage liver disease.

Any additional sources of evidence

Additional evidence:

I believe that the evidence needed is readily available. A relevant bibliography of studies of note would include the following studies of merit/relevance to this response:

1: Nevens F et al. A Placebo-Controlled Trial of Obeticholic Acid in Primary Biliary Cholangitis. N Engl J Med. 2016 Aug 18;375(7):631-43.
2: Lammers WJ et al. Development and Validation of a Scoring System to Predict Outcomes of Patients With Primary Biliary Cirrhosis Receiving Ursodeoxycholic Acid Therapy. Gastroenterology. 2015 Dec;149(7):1804-1812.
3: Carbone M et al. The UK-PBC risk scores: Derivation and validation of a scoring system for long-term prediction of end-stage liver disease in primary biliary cholangitis. Hepatology. 2016 Mar;63(3):930-50.
4: Trivedi PJ et al. Stratification of hepatocellular carcinoma risk in primary biliary cirrhosis: a multicentre international study. Gut. 2016 Feb;65(2):321-9.
5: Hirschfield GM et al. Efficacy of obeticholic acid in patients with primary biliary cirrhosis and inadequate response to ursodeoxycholic acid. Gastroenterology. 2015 Apr;148(4):751-61.
6: Lammers WJ et al. Levels of alkaline phosphatase and bilirubin are surrogate end points of outcomes of patients with primary biliary cirrhosis: an international follow-up study. Gastroenterology. 2014 Dec;147(6):1338-49.
7: Mells GF et al. Impact of primary biliary cirrhosis on perceived quality of life: the UK-PBC national study. Hepatology. 2013 Jul;58(1):273-83.
8: Carbone M et al. Sex and age are determinants of the clinical phenotype of primary biliary cirrhosis and response to ursodeoxycholic acid. Gastroenterology. 2013 Mar;144(3):560-569.

Implementation issues

This is an oral therapy and there would need to be very limited additional education and training to implement this therapy, all of which could readily be delivered as part of existing efforts for improved care of PBC generally by UK-PBC. Therapy is delivered from routine out patient visits and no additional facilities are envisaged. To ensure adequate reach and the opportunity to ensure rapid and timely, but safe, delivery of this therapy, it is likely desirable that regional networks are evolved, and there is the opportunity to do so using existing infrastructure used to deliver other therapies in liver disease.

Equality

None relevant but evaluation of this technology must accept and acknowledge that PBC is a rare disease and as such the conduct of clinical trials with hard clinical outcomes has, and always will, remain very challenging. Surrogates are therefore an inevitable component of the evaluation of new therapies for patients with PBC.

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Patient/carer organisation submission (STA)

Obeticholic acid for treating primary biliary cirrhosis [ID785]

Thank you for agreeing to give us your views on this treatment that is being appraised by NICE and how it could be used in the NHS. Patients, carers and patient organisations can provide a unique perspective on conditions and their treatment that is not typically available from other sources. We are interested in hearing about:

- the experience of having the condition or caring for someone with the condition
- the experience of receiving NHS care for the condition
- the experience of having specific treatments for the condition
- the outcomes of treatment that are important to patients or carers (which might differ from those measured in clinical studies, and including health-related quality of life)
- the acceptability of different treatments and how they are given
- expectations about the risks and benefits of the treatment.

To help you give your views, we have provided a questionnaire. You do not have to answer every question — the questions are there as prompts to guide you. The length of your response should not normally exceed 10 pages.

1. About you and your organisation

Your name: [redacted]

Name of your organisation: The PBC Foundation

Your position in the organisation: Head of Education and Development

Brief description of the organisation:

The PBC Foundation is a UK based international charity that provides information, help and support to those affected by PBC: patients, carers and families. The Foundation provides a free service to those it supports. The Foundation has almost 10,000 registered service users in 71 countries around the world, some of whom are already benefitting from the appraised therapy.

Links with, or funding from the tobacco industry - please declare any direct or indirect links to, and receipt of funding from the tobacco industry: None

2. Living with the condition

What is it like to live with the condition or what do carers experience when caring for someone with the condition?

Living with PBC has been described as "Living on an emotional and physical rollercoaster." As symptoms vary from week to week and day to day, patients (and carers) never know what PBC will bring on a day to day basis. Chronic fatigue (with the linked symptom of cognitive impairment), pruritus, joint/muscle/bone pain, and nausea are just some of the symptoms PBC patients face.

The fatigue can be genuinely debilitating. Intractable itch can be an indication for liver transplantation. The symptoms, just themselves, can have an enormously detrimental effect on quality of life. This often leads to social isolation which reinforces negative quality of life issues, and so begins an all too familiar spiral.

Aside from the symptoms, which are not indicative of disease progression, there are other, even more devastating aspects of living with PBC. The diagnosis of an incurable, progressive disease, particularly one with such a foreboding outline (before the widespread use of UDCA, many studies predicted life expectancy of *up to* 7 years life expectancy after diagnosis, and many patients still find this information on the internet) can lead to an insurmountable emotional burden. One in three patients with PBC experience depression. For many patients, there is an experience of the grieving process, where one deals with the loss of their perceived life and comes to terms with a shorter life with reduced quality.

We now know that early intervention combined with response to UDCA leads to normal life expectancy. This information, in itself, is of enormous benefit to patients. Once armed with this information, and assuming UDCA response, these patients live

in a much improved paradigm with less fear and are better equipped to manage their symptoms on a daily basis.

However, whilst science doesn't agree on a figure, we know many, many patients who do not respond satisfactorily to UDCA. This leads to a very different and far more difficult paradigm. With patients facing life without hope, the combined challenges of emotional and physical self-management become too much, to devastating effect. Many give up work, becoming more and more inwards and reclusive: negatively affecting home and family life, also. The questions patients first ask at diagnosis- "How long will I live?"; "Will I see my children grow up?"; etc return with a much, much darker answer.

Another difficult cited by patients is a lack of knowledge and understanding within medical communities: particularly in primary care and district hospital levels. It is widely anticipated that a successful novel therapy for PBC will provide opportunity for much needed education of medics re PBC.

3. Current practice in treating the condition

Which treatment outcomes are important to patients or carers? (That is, what would patients or carers like treatment to achieve?) Which of these are most important? If possible, please explain why.

In an ideal world, patients would dearly love a cure to PBC. At present, the best we have is slower progression of liver damage for a number of patients. Patients' priorities are longevity of life, then symptom management. Many patients are holding out for a cure to the debilitating fatigue. UDCA can, and seems to, prolong life. All patients with PBC want this for themselves. To explain why would be difficult in such a small space but each of us, I am sure, understand and empathise with the hope of an equal chance of normal life expectancy.

What is your organisation's experience of currently available NHS care and of specific treatments for the condition? How acceptable are these treatments and which are preferred and why?

We know that UDCA is a safe, tolerable and successful treatment for many. The UK is renowned, unfortunately for good reason, within the international PBC community for poor treatment of PBC. In the UK, it has been proven that many patients do not have access to UDCA and many who do are not given the recommended dose. With a new medication available to those who do not respond to first line therapy, we believe very strongly that this will lead to more patients receiving first line therapy quicker, easier and in an appropriate dosage.

Liver transplantation is not a cure for PBC. It is an exchange of challenges. Even after transplant, most people with PBC experience a PBC attack upon the new liver.

We are aware of off-label use of fibrates but there is currently a dearth of peer-reviewed studies that we have seen that support wide-spread use in PBC for UDCA non-responders.

4. What do patients or carers consider to be the advantages of the treatment being appraised?

Benefits of a treatment might include its effect on:

- the course and/or outcome of the condition
- physical symptoms
- pain
- level of disability
- mental health
- quality of life (such as lifestyle and work)
- other people (for example, family, friends and employers)
- ease of use (for example, tablets rather than injection)
- where the treatment has to be used (for example, at home rather than in hospital)
- any other issues not listed above

Please list the benefits that patients or carers expect to gain from using the treatment being appraised.

Prolonged life expectancy
Improved quality of life (through improved mental health and decreased isolation)
Positive impact on home and family life for carers as well as patients
Less need for liver transplantation
Less deaths through unavailability of liver transplantation
Hope

Please explain any advantages that patients or carers think this treatment has over other NHS treatments in England.

OCA is a proposed second line therapy for PBC. As there is no current second line therapy for PBC, then this treatment is immeasurably advantageous.
Whilst liver transplantation is curative for end stage liver disease (often caused by PBC) and liver failure, it is not curative for PBC.

If you know of any differences in opinion between patients or carers about the benefits of the treatment being appraised, please tell us about them.

None

5. What do patients and/or carers consider to be the disadvantages of the treatment being appraised?

Disadvantages of a treatment might include:

- aspects of the condition that the treatment cannot help with or might make worse
- difficulties in taking or using the treatment (for example, injection rather than tablets)
- side effects (for example, type or number of problems, how often, for how long, how severe. Please describe which side effects patients might be willing to accept or tolerate and which would be difficult to accept or tolerate)
- where the treatment has to be used (for example, in hospital rather than at home)
- impact on others (for example, family, friends and employers)
- financial impact on the patient and/or their family (for example, the cost of travel to hospital or paying a carer)
- any other issues not listed above

Please list any concerns patients or carers have about current NHS treatments in England.

Both patients and carers are fearful of transplant:
Fear of the operation itself
Fear of being too ill but not "making the list"
Fear of not passing assessment
Fear of pasdsding assessment for there not to be a liver available
Fear of post-operation survival quality of life

Please list any concerns patients or carers have about the treatment being appraised.

Patients are aware of complications of pruritus with the appraised medication within clinical trials, yet anecdotal evidence from those currently prescribed with the medication is that itch normalises within a short timeframe.

If you know of any differences in opinion between patients or carers about the disadvantages of the treatment being appraised, please tell us about them.

None known.

6. Patient population

Are there any groups of patients who might benefit more from the treatment than others? If so, please describe them and explain why.

Any patient for whom treatment for their PBC has been ineffective might benefit from the appraised treatment. This may include UDCA non-responders and those intolerant of UDCA. This group of patients would benefit as there is no current second line therapy available to these patients.

Are there any groups of patients who might benefit less from the

treatment than others? If so, please describe them and explain why.

None known

7. Research evidence on patient or carer views of the treatment

Is your organisation familiar with the published research literature for the treatment?

☐x **Yes** ☐ No

If you answered 'no', please skip the rest of section 7 and move on to section 8.

Please comment on whether patients' experience of using the treatment as part of their routine NHS care reflects the experiences of patients in the clinical trials.

Do you think the clinical trials have captured outcomes that are important to patients? Are you aware of any limitations in how the treatment has been assessed in clinical trials?

If the treatment being appraised is already available in the NHS, are there any side effects that were not apparent in the clinical trials but have emerged during routine NHS care?

Are you aware of any relevant research on patient or carer views of the condition or existing treatments (for example, qualitative studies, surveys and polls)?

☐ Yes ☐ No

If yes, please provide references to the relevant studies.

8. Equality

NICE is committed to promoting equality of opportunity, eliminating unlawful discrimination and fostering good relations between people with particular protected characteristics and others. Protected characteristics are: age; being or becoming a transsexual person; being married or in a civil partnership;

being pregnant or having a child; disability; race including colour, nationality, ethnic or national origin; religion, belief or lack of religion/belief; sex; sexual orientation.

Please let us know if you think that recommendations from this appraisal could have an adverse impact on any particular groups of people, such as:

- excluding from full consideration any people protected by the equality legislation who fall within the patient population for which the treatment is/will be licensed;
- having a different impact on people protected by the equality legislation than on the wider population, e.g. by making it more difficult in practice for a specific group to access the treatment;
- any adverse impact on people with a particular disability or disabilities.

Please let us know if you think that there are any potential equality issues that should be considered in this appraisal.

Are there groups of patients who would have difficulties using the treatment or currently available treatments? Please tell us what evidence you think would help the Committee to identify and consider such impacts.

None known

9. Other issues

Do you consider the treatment to be innovative?

☐X **Yes** ☐ No

If yes, please explain what makes it significantly different from other treatments for the condition.

This treatment is innovative for many reasons:
Firstly, it is the first new therapy for PBC in over 20 years. Secondly, because it has a different mechanism, the dosage is fixed and not dependent on weight of patient, etc. This simplifies prescription and daily intake of medicine for those patients on this treatment. It also addresses the unmet need of a significant proportion of patients who do not respond to the only other medication available for PBC.

Are there any other issues that you would like the Appraisal Committee to consider?

10. Key messages

In no more than 5 bullet points, please summarise the key messages of your submission.

- Prolonged life expectancy
- Improved quality of live
- Reduced reliance on (and failure of) liver transplantation service
- Reduced social isolation, economic isolation, HCP burden
- Equity of service

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Single Technology Appraisal (STA)

Obeticholic acid for treating primary biliary cirrhosis [ID785]

Please sign and return via NICE Docs/Appraisals.

I confirm that:

- I agree with the content of the submission provided by BSG and RCP and consequently I will not be submitting a personal statement.

Name: ... .

Signed: .....

Date: .....22nd February 2017.....

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Single Technology Appraisal (STA)

Obeticholic acid for treating primary biliary cirrhosis [ID785*]*

Please sign and return via NICE Docs/Appraisals.

I confirm that:

- I agree with the content of the statement submitted by [The PBC Foundation] and consequently I will not be submitting a personal statement.

Name: ....[redacted].....

Signed: .....[redacted].....

Date: .....21st December 2016 .....

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Single Technology Appraisal (STA)

Obeticholic acid for treating primary biliary cirrhosis [ID785]

Please sign and return via NICE Docs/Appraisals.

I confirm that:

- I agree with the content of the submission provided by **British Association for Study of the Liver (BASL)** and consequently I will not be submitting a personal statement.

Name: GEORGE MELLS.

Signed: G. (Mells).

Date: 22/02/17.

in collaboration with:

ERASMUS UNIVERSITEIT ROTTERDAM
INSTITUTE OF HEALTH POLICY & MANAGEMENT

Maastricht University

Obeticholic acid for treating primary biliary cirrhosis

Produced by Kleijnen Systematic Reviews (KSR) Ltd. in collaboration with Erasmus University Rotterdam (EUR) and Maastricht University

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Declared competing interests of the authors

None.

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Dr Stephen Ryder, Consultant Hepatologist at Nottingham University Hospital Trust.

The clinical expert was not directly involved in writing the report and overall responsibility for the report remains with the ERG.

Commercial in confidence (CiC) data are highlighted in blue throughout the report.

Academic in confidence (AiC) data are highlighted in yellow throughout the report.

Rider on responsibility for report

The views expressed in this report are those of the authors and not necessarily those of the NIHR HTA Programme. Any errors are the responsibility of the authors.

This report should be referenced as follows:

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Contributions of authors

Debra Fayter acted as project lead and systematic reviewer on this assessment, critiqued the clinical effectiveness methods and evidence and contributed to the writing of the report. Bram Ramaekers acted as health economic project lead, critiqued the company's economic evaluation and contributed to the writing of the report. Xavier Pouwels, Sabine Grimm, Nigel Armstrong and Steve Ryder acted as health economists on this assessment, critiqued the company's economic evaluation and contributed to the writing of the report. Sonia Garcia, Rob Riemsma and Piet Portegijs acted as systematic reviewers, critiqued the clinical effectiveness methods and evidence and contributed to the writing of the report. Caro Noake critiqued the search methods in the submission and contributed to the writing of the report. Manuela Joore acted as health economist on this assessment, critiqued the company's economic evaluation, contributed to the writing of the report and provided general guidance. Jos Kleijnen critiqued the company's definition of the decision problem and their description of the underlying health problem and current service provision, contributed to the writing of the report and supervised the project.

Abbreviations

AASLD	American Association for the Study of Liver Disease
AB	Abnormal bilirubin
AE	Adverse event
ALD	Alcoholic liver disease
ALP	Alkaline phosphatase
ALT	Alanine aminotransferase
AMA	Anti-mitochondrial antibody
ANCOVA	Analysis of covariance
AST	Aspartate aminotransferase
ATC	Anatomical Therapeutic Chemical Classification System
BAS	Bile acid sequestrants
BASL	British Association for the Study of the Liver
BMI	Body mass index
BNF	British National Formulary
BSG	British Society of Gastroenterology
CA	Cholic acid
CC	Compensated cirrhosis
CDCA	Chenodeoxycholic acid
CE	Cost effectiveness
CEA	Cost effectiveness analysis
CEAC	Cost-effectiveness acceptability curve
CETP	Cholesterol ester transfer protein
CHB	Chronic hepatitis B
CHC	Chronic hepatitis C
CHMP	Committee for Medicinal Products for Human Use
CI	Confidence interval
CK-18	Cytokeratin-18
CLD	Chronic cholestatic liver disease
CLDQ	Chronic liver disease questionnaire
CMH	Cochran-Mantel-Haenszel
CONSORT	Consolidated Standards of Reporting Trials
CRD	Centre for Reviews and Dissemination
CRP	C-reactive protein
CS	Company submission
CSR	Clinical study report
DALY	Disability-adjusted life years
DARE	Database of abstracts of reviews and effects
DC	Decompensated cirrhosis
DCA	Deoxycholic acid

DCC	Decompensated cirrhosis
df	Degrees of freedom
DSA	Deterministic sensitivity analysis
DSU	Decision Support Unit
EASL	European Association for the Study of Liver
ECDCA	Ethyl-chenodeoxycholic acid
ELF	Enhanced liver fibrosis
EMA	European Medicines Agency
EMEA	European Medicines Evaluation Agency
EO	Expert opinion leader
EOT	End of treatment
ERG	Evidence Review group
EU	European Union
FDA	Food and Drug Administration
FGF-19	Fibroblast growth factor-19
FXR	Farnesoid X receptor
GGT	Gamma-glutamyl transferase
GH	General health
GP	General practitioner
HA	Hyaluronic acid
HBV	Hepatitis B virus
HCC	Hepatocellular carcinoma
HCHS	Hospital & Community Health Services
HCV	Hepatitis C virus
HDL	High-density lipoprotein
HDLc	High-density lipoprotein cholesterol
HIV	Human immunodeficiency virus
HRQoL	Health-related quality of life
HTA	Health Technology Assessment
HUI	Health utility index
ICER	Incremental cost-effectiveness ratio
ICU	Intensive care unit
IL	Interleukin
INR	International standardised ration
IQR	Interquartile range
ITT	Intention to treat
IWRS	Interactive web response system
KM	Kaplan-Meier
KSR	Kleijnen Systematic Reviews
LA	Lysophosphatidic acid

LCA	Lithocholic acid
LCAT	Lecithin-cholesterol acyltransferase
LDL	Low density lipoprotein
LDLc	Low-density lipoprotein cholesterol
LDLT	Living donor liver transplantation
LLN	Lower limit of normal
LP	lipoprotein
LS	Least squares
LT	Liver transplantation
LTSE	Long-term safety extension
LYG	Life years gained
MCID	Minimal clinically important difference
MCS	Mental component summary
MELD	Model for End Stage Liver Disease
MH	Mental health
MESH	Medical Subject Headings
mg	Milligrams
MHRA	Medicines and Healthcare Products Regulatory Agency
MRS	Mayo risk score
MRU	Medical resource utilisation
MTC	Mixed Treatment Comparison
NA	Not applicable
NB	Normal bilirubin
NCPE	National Centre for Pharmacoeconomics
NHS	National Health Service
NICE	National Institute for Health and Care Excellence
NIHR	National Institute for Health Research
NR	Not reported
OCA	Obeticholic acid
OD	Once daily
OPTN	Organ procurement and transplantation network
OR	Odds ratio
PAS	Patient access scheme
PASLU	Patient access schemes liaison unit
PBC	Primary biliary cirrhosis (recently renamed as ‘primary biliary cholangitis’)
PCS	Physical component summary
PF	Physical functioning
PK	Pharmacokinetics
PSA	Probabilistic sensitivity analysis
PSC	Primary sclerosing cholangitis

PRESS	Peer Review of Electronic Search Strategies
PT	Prothrombin time
PYE	Patient years of exposure
QALY(s)	Quality adjusted life year(s)
QoL	Quality of life
RCT	Randomised controlled trial
RE	Role emotional
REML	Restricted maximum likelihood
RMSE	Root mean square error
RP	Role physical
RR	Relative Risk; Risk Ratio
SAE	Serious adverse event
SD	Standard deviation
SE	Standard error
SF	Social functioning
SLR	Systematic literature review
SMC	Scottish Medicines Consortium
SOC	System organ class
SmPC	Summary of product characteristics
STA	Single Technology Appraisal
SVR	Sustained viral response
TB	Total bilirubin
TE	Transient elastography
TEAE	Treatment-emergent adverse event
TGF	Transforming growth factor
TIMP	Tissue inhibitor of metalloproteinase
TNF	Tumour necrosis factor
TP	Transition probability
UDCA	Ursodeoxycholic acid
UK	United Kingdom
ULN	Upper limit of normal
VAS	Visual analogue scale
VLDL	Very low density lipoprotein
VT	Vitality
WADD	Weighted average daily dose
WHO	World Health Organisation

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1. SUMMARY

1.1 Critique of the decision problem in the company's submission

The patient population described in the final scope issued by the National Institute for Health and Care Excellence (NICE) was '*People with primary biliary cirrhosis whose disease has an inadequate response to, or who are unable to tolerate, ursodeoxycholic acid*'. For patients whose disease has an inadequate response to ursodeoxycholic acid (UDCA), obeticholic acid (OCA) was to be compared to UDCA alone or in combination with fibrates. For patients who are unable to tolerate UDCA, comparators were fibrates or no additional treatment. Outcomes included mortality, liver function based on markers of liver biochemistry, symptoms, including pruritus, fatigue and abdominal pain, time to liver transplantation, primary biliary cirrhosis (PBC)-related events, adverse effects of treatment and health-related quality of life (HRQoL).

The decision problem in the company submission (CS) differed from the scope in a number of ways. Firstly, fibrates were not considered by the company to be a comparator to OCA. Secondly, the main evidence presented (the POISE trial) considered only surrogate outcomes. No data were available from the trial on long-term clinical outcomes outlined in the scope such as mortality and liver transplantation. Finally the number of patients in POISE receiving OCA as monotherapy (i.e. without UDCA) was very small (11 patients) so results for this group of patients should be treated with some caution.

1.2 Summary of clinical effectiveness evidence submitted by the company

The company conducted a systematic review to inform the submission. The aim of the systematic review was '*to identify all relevant evidence for the efficacy and safety of interventions used to treat PBC.'* A post-hoc decision was taken to include only trials with an OCA treatment arm.

The systematic review identified one main randomised controlled trial, POISE, and two supporting Phase 2 trials. The company did not pool the results of the trials.

POISE, was an international trial of 217 patients including patients from the UK. The trial compared UDCA and combined UDCA and OCA in patients with an inadequate response to UDCA and OCA and placebo in those who were intolerant to UDCA. Seventy-three patients received 10 mg OCA, 71 patients received 5 mg OCA rising to 10 mg during months 6 to 12 if they had an inadequate response to UDCA (the titration group).

The primary outcome of POISE was a composite one (percentage of participants with alkaline phosphatase (ALP) < 1.67 x upper limit of normal (ULN) and total bilirubin ≤ ULN and ALP ≥ decrease from baseline at 12 months). At 12 months 47% of participants in the OCA 10 mg group achieved the primary outcome, 46% in the titration group and 10% in the placebo group ($p < 0.0001$ for both comparisons). The results of other surrogate outcomes supported these findings. Incidence of adverse events (AEs) was similar across groups. Events occurring more frequently in treatment groups included pruritus. It was noted that 10% of patients discontinued treatment due to pruritus in the OCA 10 mg group which did not titrate based on tolerability.

The Phase 2 trials supported the positive findings of POISE on surrogate outcomes.

1.3 Summary of the ERG's critique of clinical effectiveness evidence submitted

The systematic review conducted by the company was broadly appropriate to the scope of this submission. The CS and response to clarification provided sufficient details for the ERG to appraise the searches. A broad range of databases were searched, and additional searches of conference proceedings and other relevant resources including trials databases, HTA agencies, specialist and organisational

websites were reported. The ERG is satisfied that the direct evidence comparing OCA and UDCA has been presented. However no evidence on fibrates as a comparator was presented.

The main evidence was based on POISE, a well-conducted international randomised controlled trial of 217 patients with a 12 month follow up. The ERG agrees that this trial could not be pooled with the two Phase 2 trials identified due to differences between the trials including OCA dosage and study duration.

The ERG identified some limitations in applying the results of the POISE trial to the NICE scope.

- The number of patients intolerant to UDCA and receiving OCA as monotherapy was limited to 11 patients (five [7%] in the OCA titration group and six [8%] in the OCA 10 mg group). Five patients received OCA placebo. As such the results for this group of patients should be considered with caution due to the low numbers.
- The ERG noted that the POISE trial included mainly patients at an early stage of PBC progression. The ERG asked the company to clarify how OCA would benefit patients with more advanced PBC. The company stated that two analyses were performed in more advanced stages of PBC. The brief results of these analyses were based on a subset of 72 patients classified as having advanced disease in particular 36 patients who had cirrhosis. The ongoing COBALT trial includes more advanced patients and should provide more definitive results for those patients with more advanced disease.
- In the POISE trial 73 patients were randomised to a fixed dose of 10 mg OCA and 73 patients received the placebo. Seventy-one patients were randomised to the titration group which reflects the recommended dosage of OCA. They received OCA 5mg OD for the initial six month period. The patients in POISE were only up-titrated to 10 mg OCA if they did not reach the primary endpoint criteria for response. The ERG draws to the attention of the committee that the evidence for obeticholic acid given at the recommended dosage is based on the 33 patients who actually up-titrated to 10 mg.
- The POISE trial present evidence using surrogate outcomes only. The ERG is satisfied that the company has demonstrated some evidence of correlation between the surrogate outcomes of interest and longer-term clinical outcomes. However the extent of the correlation and the optimal thresholds of surrogate outcomes to predict long-term disease is unclear.
- The definitive effects of obeticholic acid on clinical outcomes relevant to patients awaits the results of the ongoing COBALT trial

1.4 Summary of cost effectiveness submitted evidence by the company

The company conducted systematic reviews to identify relevant cost effectiveness studies, health-related quality of life studies, resource use and costs studies. The company did not identify any study investigating the cost effectiveness of OCA in the population of interest for the current decision problem, and hence developed a *de novo* model.

The cost effectiveness analysis described in the CS is considered by the ERG to partially meet the NICE reference case. The company developed a Markov state transition model to describe the progression of PBC over a lifetime horizon. The model is composed of two parts with a total of 10 health states. The first part of the model (referred to as the biomarker component) captures the surrogate outcomes of ALP and bilirubin biomarkers in three different health states based on the expected risk of disease progression: low risk (ALP ≤ 1.67 * ULN); moderate risk (ALP > 1.67 * ULN and TB ≤ 1.0 * ULN) and severe risk (TB > 1.0 * ULN or compensated cirrhosis; CC). The latter health state combined patients with CC and those with abnormal TB. In the second part of the model, the liver disease component, the following clinical endpoints are modelled: pre-liver transplant; decompensated cirrhosis

(DCC); hepatocellular carcinoma (HCC); liver transplant; a post-liver transplant state; potential PBC re-emergence; and death. Patients can move to the liver disease component of the model only coming from the severe risk health state of the biomarker component of the model. Regarding adverse events, only the costs in relation to pruritus were modelled, while the impact on HRQoL was not modelled. A four week cycle length was used over a time horizon of 50 years, which is effectively a life time perspective.

The economic evaluation considers PBC patients who are intolerant to or have inadequate response to treatment with UDCA. Only moderate and severe patients based on ALP and bilirubin levels, at model entry, were deemed eligible for OCA treatment in the model. This is in line with the final scope issued by NICE for this appraisal and is also in line with the study population of the pivotal POISE study.

The interventions and comparators in this model depend on the selected population. For UDCA-intolerant patients, the intervention considered in this economic evaluation is OCA dose titration based on a starting dose of 5 mg taken orally, once daily, which may be increased to 10 mg once daily based on the assessment of tolerability after six months, to achieve optimal response and the comparator is no treatment. For UDCA inadequate responders, the intervention is OCA dose titration as per above in combination with UDCA; and the comparator is UDCA monotherapy. UDCA doses implemented in the model were in line with its UK marketing authorisation, which are also the same as in the POISE trial. Fibrates, listed in the scope as a comparator, were not considered as a comparator. The company argued that fibrates are not licensed in the UK, nor are they standard care, and they are contraindicated in PBC. The company also argued that they are rarely used, with only [redacted] of patients in the UK-PBC cohort having ever taken fibrates for any condition (not necessarily for PBC).

For the health states in the biomarker component, transition probabilities for the OCA-based regimen relied on POISE patient-level data during the first year. Given the low number of patients who received OCA monotherapy, the same transition matrices were used for the OCA titration regimen with or without UDCA. The transition probabilities used to reflect progression whilst on UDCA alone, or no treatment, are based on data from various literature sources. Mortality in the biomarker component of the model was assumed to be equal to background mortality. The literature was used to inform transitions between the health states in the liver disease component of the model, in part relying on previous assessments (i.e. TA330).

HRQoL evidence was not collected through a generic preference elicitation instrument in the POISE trial, and was therefore obtained from the literature, and based on assumptions. The company did not provide a justification for the health state utility values used for the biomarker component of the model. The company applied a [redacted] decrement to the health state utility values found in the literature for the liver disease component of the model, except for the HCC health state. This decrement was based on expert opinion (further details on how the [redacted] was estimated were not provided by the company).

Resource use and costs included in the model were based on data from the British National Formulary (BNF), NHS reference costs, assumptions validated by expert opinion, and published sources identified in the literature review. The list price was used for OCA while drug acquisition costs for UDCA were determined from the BNF and market share data to calculate a weighted average. Health state costs were obtained from different sources: expert opinion, NHS reference costs and published studies. Finally, the costs of pruritus were based on expert opinion and the BNF.

In both populations, OCA (without and with UDCA) led to longer survival, a quality adjusted life year (QALY) gain, and higher costs than the comparators (i.e. no treatment for the UDCA-intolerant population and UDCA monotherapy for the UDCA inadequate responders). The main QALY gain of

OCA was accumulated in the low risk and moderate risk health states in the biomarker component. The same was observed for costs; more than half of the incremental cost was accrued in the low risk and moderate risk health states. The company base-case incremental cost effectiveness ratios (ICERs) (probabilistic) of OCA (without or with UDCA) versus no treatment and UDCA alone were [redacted] for UDCA intolerant patients and UDCA inadequate responders respectively. The one-way sensitivity analyses conducted by the company showed that the model results were most sensitive to the health states utility values for the health states of the biomarker component of the model and the transition probabilities between these health states. It should be noted though that the one-way sensitivity analyses were partly based on arbitrary estimates of the variance (i.e. using ±20% of the mean value).

1.5 Summary of the ERG's critique of cost effectiveness evidence submitted

The majority of searches in Appendices 6, 8 and 9 of the CS were well reported and easily reproducible. Searches covered a broad range of databases and grey literature resources. The ERG expressed some concerns regarding the use of study design filters. However, it is unlikely that this would have impacted on the overall recall of results. In terms of the *de novo* model, there are a number of areas of uncertainty regarding the biomarker component of the model that the ERG is concerned about. Firstly, the aggregation of two different health states (CC and abnormal TB) into one severe risk health state could be problematic, as the transition probability to the DCC state (based on the literature) may refer to CC patients only. The ERG consulted with a clinical expert who stated that the aggregation of these two health states was sensible in PBC patients because liver histology is rarely known. Secondly, the justification of no additional progression from low-risk or moderate risk to severe-risk after the first year is questionable. The company claims that this is consistent with experience with patients responding to UDCA treatment. Although the progression to DCC is higher for UDCA non-responders than for UDCA responders (which is the justification provided by the company), there is evidence for progression to DCC in both groups, so assuming no progression after 12 months might not be justified by these data. Moreover, the cited evidence stems from UDCA responders treated with UDCA, hence it might be questioned whether this would also be applicable to PBC patients who are intolerant to or have inadequate response to treatment with UDCA and are treated with OCA. Nevertheless, the clinical expert consulted by the ERG stated that this assumption was reasonable given that 'we know that patients with a response to UDCA and normal (or below 1.67x ULN ALP) have an excellent long term prognosis with no overall impact on life expectancy'. The liver disease component is similar to other assessments of liver disease treatments and seems appropriate for the current decision problem. However, the company introduced an additional health state, not typically considered in other liver disease models: the pre-liver transplant health state, without justifying why this was necessary. While the ERG acknowledges that the introduction of the pre-liver transplant health state has face validity as being a waiting list state, the ERG is concerned that it groups patients together that came from different health states (HCC, DCC, severe risk) and who therefore may experience different transition probabilities, health-related quality of life and/or costs.

The population represented in the cost effectiveness model seems to correspond to the expected licensed indication and the final scope issued by NICE for the current decision problem. However, the ERG considers that the proportion of patients entering the model in the moderate and severe risk health states should be based on data from POISE. In the company's model, the proportion of patients entering the model in the severe risk health state (23.15%) is much larger than the proportion of patients in the POISE study who are in the severe risk health state at baseline (8.42%). This could potentially bias model outcomes in favour of OCA treatment. Therefore, the ERG preferred to use the proportions obtained from the POISE study.

Regarding the estimation of treatment effectiveness in the biomarker component of the model, the main ERG concern is that the company uses the data from the POISE trial to estimate transition probabilities for the patients receiving OCA (OCA titration arm), but not for patients receiving UDCA only and no treatment. Moreover, the methods used by the company to estimate treatment effectiveness for the patients receiving UDCA only and no treatment are lacking transparency and justification and are unclear to the ERG. The ERG thinks very strong arguments must be presented to warrant favouring observational evidence over randomised evidence of comparative effectiveness (i.e. the POISE trial). Finally, the ERG noticed a discrepancy between the transition probabilities reported in the CS and those used in the economic model.

The company refers to TA330 for multiple transition probabilities. The ERG generally agrees with the approach used in TA330 for modelling liver disease. It should be noted that not all the transition probabilities of the liver disease component, used in the CS, are fully consistent with TA330. The company did not provide justifications for the sources that were used, nor for the deviations from the transition probabilities used in TA330. Therefore, the ERG prefers to use transition probabilities consistent with TA330 for the liver disease component of the model, this also entails excluding the pre liver transplant state. The only exception is the transition to HCC; here the source provided by the company was preferred as this was based on PBC patients.

Health state utility values for the low risk and moderate risk health states of the biomarker component of the model were estimated based on 35 patients who had either PBC or primary sclerosing cholangitis using the Health Utilities Index Mark 2 (HUI:2) The HUI:2 measurements were valued based on a sample of Canadian parents. This is not consistent with the NICE reference case and the representativeness of this estimate to the UK setting is uncertain. Given that a recent review reported that 34.1% of PBC patients have a 'poor' quality of life and that the current estimate is higher than the general population utility values for the age category 50-59, the ERG thinks that the utility values for these health states might be overestimated. In the absence of representative utility data specific to UK PBC patients, the ERG prefers to use the age-dependent utility values of the UK general population for these two health states in its base-case analysis. Based on expert opinion, the company applied a [redacted] utility decrement on the utility values of the liver disease component health states, except for the HCC health state. Given the lack of details, the ERG was not able to investigate the validity of this decrement. Younossi et al. 2001 report a lower utility value for chronic liver disease due to viral infection (e.g. HCV/HBV) than the utility value reported for chronic liver disease due to cholestatic disease (PBC and primary sclerosing cholangitis). This is contradictory to the company's reasoning that PBC patients have lower health state utility values than HCV/HBV patients. For these reasons, the ERG prefers to remove the [redacted] utility decrements.

The company used expert opinion for estimating costs associated with outpatient visits. The ERG prefers to use the NHS reference costs. The company assumed, without adequate justification, that the cost associated with the severe risk health state of abnormal TB and CC are half the costs of DCC. The ERG prefers to use the cost for CC used in TA 330. Finally, the ERG regarded the estimation of liver transplant costs uncertain, and explored alternative estimates in an exploratory analysis.

The lack of transparency, regarding the justification and detail of the methods used in the CS as well as regarding the economic model submitted by the company, is an area of concern. Given this lack of transparency, also after multiple requests from the ERG, the methods used by the company are still unclear. The ERG was therefore unable to assess the validity and appropriateness of these methods. Given the lack of transparency in the submission by the company, the ERG was unable to explore the whole economic model for programming errors (although the ERG was able to replicate the Markov trace) nor to assess whether all methods used by the company conformed to best practices. Therefore,

the cost effectiveness results (presented by both the company and the ERG) should be interpreted with caution.

1.6 ERG commentary on the robustness of evidence submitted by the company

1.6.1 Strengths

The company used systematic review methods to identify the evidence on obeticholic acid for primary biliary cirrhosis. The majority of searches in the CS were well documented and easily reproducible. Searches were carried out on a broad range of resources including those recommended in the NICE 2013 guide to the methods of technology appraisal. Supplementary searches of conference proceedings and other relevant resources including trials databases, HTA agencies, specialist and organisational websites, and the checking of references lists were undertaken by the company in order to identify additional studies not retrieved by the main searches.

The main evidence was based on a well-conducted international randomised controlled trial of 217 patients with a 12 month follow up.

1.6.2 Weaknesses and areas of uncertainty

The company reported that no separate adverse events searches were undertaken as the clinical effectiveness searches were used to inform the adverse events section. However these searches contained a methodological filter intended to limit the search to RCTs. Guidance by the Centre for Reviews and Dissemination (CRD) recommends that if searches have been limited by a study design filter, additional searches should be undertaken to ensure that adverse events that are long-term, rare or unanticipated are not missed.

The main limitation of the evidence identified is that the main trial POISE is based on surrogate outcomes. The ERG is satisfied that the company has demonstrated evidence of some correlation between the surrogate outcomes of interest and longer-term clinical outcomes. However the extent of the correlation and the optimal thresholds of surrogate outcomes to predict long-term disease is unclear. Furthermore, the relative efficacy of OCA and fibrates is unknown. The role of OCA as monotherapy in patients intolerant to UDCA and in those with more advanced disease is still unclear.

The lack of transparency, justification and details regarding the methods used in the CS are the main weaknesses in the cost effectiveness chapter and the model submitted by the company. Transparency is a key quality aspect of modelling. The lack of transparency hampered the validity check by the ERG. Additionally, the inability of external validation, relatively short trial follow-up using intermediate outcomes and reliance on non PBC sources in the model stress the uncertainty in the estimation of long-term outcomes.

1.7 Summary of exploratory and sensitivity analyses undertaken by the ERG

The main areas of ERG concern were not using POISE trial data directly for the non-OCA regimen, lack of transparency and justification regarding calibration methods, data and assumptions to extrapolate the POISE trial data beyond the time horizon of 12 months and to final outcomes, implausible high utility values in the biomarker component of the model and lack of justification for the [redacted] HRQoL decrement in the liver disease component of the model. The ERG has incorporated various adjustments to the company base-case. The ERG base-case resulted in ICERs (probabilistic) of [redacted] for UDCA inadequate responders and UDCA intolerant patients respectively. The most influential adjustments/corrections made by the ERG were estimating transition probabilities using data from the POISE trial for the non-OCA regimens, and using age dependent utilities for the low and moderate risk health states. The ERG base-case ICER can be regarded as a lower bound, as transition probabilities after 12 months and the

calibration method used by the company are still considered highly uncertain, and exploratory analyses showed that alternative assumptions resulted in substantially higher ICERs (ranging from [redacted] for UDCA inadequate responders and UDCA intolerant patients respectively).

As the methods used by the company to estimate and extrapolate treatment effectiveness are lacking transparency and justification, the ICERs (presented by both the company and the ERG) should be interpreted with caution. Given the lack of long-term results of the POISE trial, the ERG would generally agree with using a calibration approach (as adopted by the company), to extrapolate the POISE trial data beyond the time horizon of 12 months and to final outcomes. However, the assumptions, methods and data used should be documented in detail to avoid 'black box' criticism, and should be validated. This is particularly the case, considering that the use of alternative assumptions, methods and data resulted in substantially higher ICERs, as illustrated in the exploratory analyses by the ERG.

2. BACKGROUND

This report provides a review of the evidence submitted by Intercept Pharmaceuticals in support of obeticholic acid (trade name OCALIVA®) a bile acid preparation for the treatment of people with primary biliary cirrhosis (PBC) whose disease has an inadequate response to, or who are unable to tolerate, ursodeoxycholic acid. In addition to the main company submission (CS), the ERG received a submission from Professor Gideon Hirschfield on behalf of the British Society of Gastroenterology/Royal College of Physicians[1] and from Professor Graeme Alexander on behalf of the British Association for the Study of the Liver (BASL).[2]

The background section of this report by the Evidence Review Group (ERG) outlines and critiques the company's description of the underlying health problem and the overview of current service provision. The information is largely based on Section 3 of the CS with subsections referenced as appropriate.[3]

2.1 Critique of company's description of underlying health problem.

The underlying health problem is primary biliary cirrhosis (recently renamed as primary biliary cholangitis). Throughout this report we will refer to the disease as primary biliary cirrhosis as this is the terminology used in the scope issued by the National Institute for Health and Care Excellence (NICE)[4] and in the CS.[3]

Section 3.1 of the company submission describes primary biliary cirrhosis as a *'rare, progressive, autoimmune, non-viral disease of the liver that gradually destroys the interlobular bile ducts. This causes an accumulation of cytotoxic bile acids in the liver which leads to inflammation, liver fibrosis, cirrhosis, and ultimately liver failure.'*[3] The CS further states that *'The final stages of PBC – cirrhosis and hepatic decompensation – is terminal unless a liver transplant is performed.'*[3] The risks of liver transplantation are outlined and the CS states that *'up to 43% of patients will have a recurrence within 15 years.'*[3]

The CS states that *'The estimated prevalence of PBC in the UK is approximately 3.9 per 10,000 population, equating to approximately 19,175 people in England[5] and making it a rare disease.'*[3] The company further state that *'Approximately 90% of people with the condition are women, and age of diagnosis is typically between 30 and 65 years[6].'*

The company notes that *'Approximately 60–80% of patients with PBC are asymptomatic at diagnosis.[7] The diagnosis of PBC in asymptomatic patients is usually established after the chance finding of an elevated ALP level during the course of an unrelated illness[7, 8].'*[3]The CS notes the need for early diagnosis and prompt treatment of patients early in the course of the disease to help prevent or to slow progression and to avoid or delay later complications of PBC. The CS notes that *'When treatment is delayed until PBC has progressed, survival is significantly worse than in the general population.'*[3] This statement was supported by reference to a Dutch cohort study of patients receiving ursodeoxycholic acid (UDCA).[9]

The CS notes that prognosis of the disease is unpredictable and varies from patient to patient. They state that *'there is currently no predictor to indicate which patients will progress slowly or rapidly, although patients with earlier age of onset and/or of male sex often have more aggressive disease that is refractory to existing treatment.[10]'*[3] This statement was supported by reference to an observational study of the UK-PBC Research Cohort comprising 2,353 patients.[10]

However the CS states that *'Analysis from a large research group (the Global PBC study group) shows that in patients with PBC, ALP and bilirubin levels strongly correlate with death and liver transplantation, with a combination of both variables improving prognostic prediction for patients[11]'*[3]

The supporting study was a meta-analysis of 4,845 patients diagnosed with PBC from 1959 to 2012 with a median follow-up of 7.3 years. It included both UDCA treated and non-treated patients.[11]

The CS states that *'PBC has a substantial detrimental impact on quality of life, and HRQoL impairment is correlated with the severity of the disease.'*[3] They cite a number of studies including a UK cohort study of 2,353 patients[12] in which *'35% reported impairment of HRQoL compared with 6% of healthy controls (p<0.001), and 46% rated their overall health as 'fair' or 'poor' compared with 15% of healthy controls (p < 0.0001).[12]'*[3]

In addition to its impact on patients, the burden of the disease from the healthcare perspective is outlined. *'PBC is also associated with considerable healthcare costs. In 2014/15 there were 707 hospital admissions in England for PBC (ICD10 K74.3), accounting for 963 consultant episodes and 3,767 bed days[7].'*[3] They further note that *'PBC is one of the most frequent indications for liver transplantation in Europe….There were 621 elective liver transplants performed in the UK in 2014/2015, of which at least 7% were for PBC.[13]'*[3]

ERG comment:

- The references cited by the company were checked. The underlying health problem was considered to be appropriately described and appropriate references cited.
- The impact on patient quality of life was appropriately highlighted. The ERG notes that whilst the impact of PBC may be limited in early-diagnosed UDCA-responsive patients, among those who are unresponsive highly disabling symptoms such as fatigue and pruritus are common and patients face possible progression into cirrhosis and ultimately liver failure.

2.2 Critique of company's overview of current service provision

The company states that no NICE guidance or pathway specific to PBC is available.[3]

The CS states that *'Patients are commonly asymptomatic at diagnosis, and are referred to secondary care on discovering abnormal liver function and / or positive antibody by blood tests at a GP visit for an unrelated illness.[7, 8] Occasionally patients are referred internally, most commonly from a rheumatologist. Rarely, patients are referred due to pruritus, abnormal ultrasound, or decompensation (ascites).'*[3]

The company further state that *'The only licensed treatment for PBC is ursodeoxycholic acid ((UDCA).'*[3] The company states that '*On diagnosis of PBC, UDCA is prescribed at 13-15mg/kg/day. Patients are monitored at 3-4 months for tolerability, and at 6 and 12 months to gauge response and compliance to therapy.'*[3] The company cites two relevant clinical guidelines.[14, 15] Both recommend long-term therapy at this dosage of UDCA as a first line of treatment.[14, 15]

The company states that *'up to 74% of patients have an incomplete response to UDCA and there are currently no available licensed or effective treatment options for these patients.'*[3] The company states that *'There are several response criteria that have been proposed to define non-response / progression….; however, there is no consensus as to which of these criteria should be used.'*[3]

The indication for obeticholic acid is 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'* (Section 2.2.2 of the CS)[3] Therefore the place of obeticholic acid in the clinical pathway for PBC would be as a second-line treatment.

The CS states that '*There are no licensed or effective drugs approved for second-line treatment for second-line treatment for the management of patients with an inadequate response to, or intolerance to, UDCA.'*[3] They further state that *'other treatments have been trialled for use in PBC, including*

budesonide and fibrates (which are contraindicated in PBC).[CS refs 22,23] However, limited efficacy has been observed in these other treatments.'[3]

The CS states that *'Liver transplantation is the only treatment for patients with late-stage PBC, where UDCA has limited efficacy.[14]'* The CS outlines the challenges and risks of liver transplantation and notes that *'up to 43% of patients will have a recurrence of PBC within 15 years[16]. Draft guidance from the BSG note that there is no consensus on routine use of UDCA post-transplant.[15]'*

The CS states that '*No additional tests or investigations are required for OCA treatment.'*[3] Although OCA treatment is to be initiated by specialists in the treatment of PBC, the company states that no additional infrastructure will be required for treatment with OCA. However patients are required to undergo a consultation six months after treatment initiation to assess tolerability and determine if the dose should be increased to 10 mg to achieve optimal response.[3]

ERG comment:

- The company correctly states that there is no specific NICE guidance on PBC. The CS cites two clinical guidelines – by the European Association for the Study of the Liver (EASL) published in 2009[14] and the more up-to-date but as yet unpublished British Society of Gastroenterology (BSG) guidelines.[15] The CS correctly states that UDCA is the only licensed treatment at first line for PBC.
- Response rates to UDCA between 20 and 70% have been identified.[4] The company correctly highlight that determining response rates to UDCA depends on the specific criteria used to assess response. Several sets of criteria have been used across the research literature. We are advised by our clinical expert that in practice various systems may be used including simple clinical criteria.
- Clinical guidelines state that there are no second line agents when patients have failed to respond to UDCA.[14, 15] OCA would therefore be the only agent available at second line. The company mentions other agents that have been investigated (fibrates are most relevant to this submission). The statement *'limited efficacy has been observed'* in relation to other treatments was not supported by any references.[3] A further discussion of the role of fibrates as a comparator to OCA can be found in Section 3 of this report, the decision problem.

3. CRITIQUE OF COMPANY'S DEFINITION OF DECISION PROBLEM

The decision problem as presented in the CS is given in Table 3.1.

Table 3.1: Decision Problem

	Final scope issued by NICE	Decision problem addressed in the company submission	Rationale if different from the final NICE scope
Population	People with primary biliary cirrhosis† whose disease has an inadequate response to, or who are unable to tolerate, ursodeoxycholic acid	As per scope	Not applicable
Intervention	OCA alone or in combination with UDCA	As per scope	OCA is taken in combination with UDCA for people whose disease has an inadequate response to UDCA, and as monotherapy in people who are unable to tolerate UDCA
Comparator(s)	For people whose disease has an inadequate response to UDCA: • UDCA alone or in combination with fibrates For people who are unable to tolerate UDCA: • Fibrates • No additional treatment	For people whose disease has an inadequate response to UDCA, the following comparators were considered: • UDCA For people who are unable to tolerate UDCA, the following interventions were considered: • Placebo	Fibrates are not licensed in the UK, nor are they standard of care, and they are contraindicated in PBC[17, 18]. They are rarely used, with only [redacted] of patients in the UK-PBC cohort having ever taken fibrates for any condition (not necessarily for PBC).[CS24] Their efficacy is yet to be proven, with only a limited number of studies reporting results for the use of fibrates in PBC[19-23], with the following challenges: The studies were investigator-initiated and only had small patient numbers All but one study were conducted in Japanese patients In addition, there are significant safety concerns with the use of fibrates in PBC, with one study[22] reporting three deaths in

	Final scope issued by NICE	Decision problem addressed in the company submission	Rationale if different from the final NICE scope
			13 patients in the UDCA + fibrates arm compared with no deaths in 14 patients in the UDCA monotherapy arm. In addition, one patient developed HCC in the fibrates + UDCA arm, compared with none in the UDCA monotherapy arm[22].
Outcomes	The outcome measures to be considered include: • Mortality • Liver function based on markers of liver biochemistry • Symptoms, including pruritus, fatigue and abdominal pain • Time to liver transplantation • PBC-related events, including ascites, varices, encephalopathy and HCC • Adverse effects of treatment • HRQoL	Surrogate efficacy outcomes are included in POISE: • Liver function biomarkers (ALP and bilirubin) • Other biomarkers relevant to PBC (GGT, AST, ALT, FGF-19, CK-18 and bile acids) • Inflammation biomarkers (CRP, TNF-α, TGF-β and IL-6) • Non-invasive evaluations of fibrosis (ELF and FibroScan® TE)	Due to the rare and chronic nature of PBC and the slow progression in most patients, a long-term trial is required to capture clinical outcomes such as mortality, transplant-free survival, and the incidence of complications. The primary outcome measured in POISE related to combined ALP and bilirubin levels, which have both been shown to be strongly correlated with disease prognosis[11, 24, 25]. Other biomarkers relevant to PBC, inflammation biomarkers, and non-invasive evaluations of fibrosis have been included to further support changes in disease progression. There is currently a long-term Phase 3b trial ongoing, COBALT, that aims to capture clinical outcomes and should support the longer-term impact of OCA on PBC already shown in POISE.
Economic analysis	The reference case stipulates that the cost effectiveness of treatments should be expressed in terms of incremental cost per quality-adjusted life year. The reference case stipulates that the time horizon for estimating clinical and cost effectiveness should be sufficiently long to	As per scope	Not applicable

	Final scope issued by NICE	Decision problem addressed in the company submission	Rationale if different from the final NICE scope
	reflect any differences in costs or outcomes between the technologies being compared. Costs will be considered from an NHS and personal social services perspective.		
Subgroups to be considered	Not applicable	Not applicable	Not applicable
Special considerations including issues related to equity or equality	Guidance will only be issued in accordance with the marketing authorisation. Where the wording of the therapeutic indication does not include specific treatment combinations, guidance will be issued only in the context of the evidence that has underpinned the marketing authorisation granted by the regulator.	Equality document	People with PBC face stigma in society because of the negative connotations of the term 'cirrhosis' and the association with alcoholism and drug abuse[26]. In addition, PBC is a rare disease affecting mainly women, and it is essential that patients have the same opportunities to gain access to new treatments.

Source: Table 1 of the CS[3]

Footnote: †Note that primary biliary cirrhosis has recently undergone a name change to primary biliary cholangitis. At the time of consultation with NICE, the official name was primary biliary cirrhosis and, as such, this is reflected in the table.

ALP, alkaline phosphatase; ALT, alanine transaminase; AST, aspartate transaminase; CK-18, cytokeratin-18; CRP, C-reactive protein; ELF, enhanced liver fibrosis; FGF-19, fibroblast growth factor-19; GGT, gamma-glutamyl transpeptidase; HRQoL, health-related quality of life; HCC, hepatocellular carcinoma; IL-6, interleukin-6; NHS, National Health Service; NICE, National Institute for Health and Care Excellence; OCA, obeticholic acid; OD, once daily; PBC, primary biliary cholangitis/cirrhosis; TE, transient elastography; TGF, transforming growth factor; TNF, tumour necrosis factor; UDCA, ursodeoxycholic acid

3.1 Population

The population described in the scope issued by NICE was *'People with primary biliary cirrhosis whose disease has an inadequate response to, or who are unable to tolerate, ursodeoxycholic acid.'*[4]

ERG comment:

- The CS matches the scope. However it should be noted that the main evidence submitted by the company is the POISE randomised controlled trial.[27] This trial has 11 patients (7%) who are unable to tolerate ursodeoxycholic acid and who are receiving obeticholic acid alone. Hence it is not representative of this patient group and results may not be reliable for this group. However based on clinical advice we have received, the percentage of patients intolerant to UDCA in practice is low, approximately 5%.

3.2 Intervention

The intervention described in the scope was *'obeticholic acid alone or in combination with ursodeoxycholic acid'*.[4]

Obeticholic acid is a bile acid preparation (Anatomical Therapeutic Chemical Classification System (ATC) code A05AA04). By activating the farnesoid X receptor (FXR), OCA is expected to reduce the production of bile in the liver, thus reducing the exposure of the liver to toxic levels of bile acids. It is marketed as Ocaliva and was designated as an orphan medicinal product on 27 July 2010.

At the time of writing the submission, the company was awaiting European marketing approval for obeticholic acid. On 13 October 2016 the Committee for Medicinal Products for Human Use (CHMP) adopted a positive opinion.[28] The full indication was *'for the treatment of primary biliary cholangitis (also known as primary biliary cirrhosis) in combination with ursodeoxycholic acid (UDCA) in adults with an inadequate response to UDCA or as monotherapy in adults unable to tolerate UDCA.' The committee further noted 'The benefits with Ocaliva are its ability to reduce alkaline phosphatase and bilirubin levels in adults with primary biliary cholangitis. This is likely to lead to clinical benefits for the patient such as delayed development of liver fibrosis, cirrhosis liver transplant and death. However, this remains to be formally demonstrated by means of the post-authorisation follow up within this conditional marketing authorisation.'*.[28]

Obeticholic acid will be *'provided as a film-coated tablet containing 5 mg or 10 mg OCA. The recommended starting dose is 5 mg taken orally, once daily. Based on the assessment of tolerability after 6 months, the dose should be increased to 10 mg once daily to achieve optimal response.'*[3].

The CS states that *'Patients should continue to take OCA for as long as the patient continues to benefit from treatment'*. For patients experiencing severe intolerability due to pruritus the company advise dose reductions, dose interruptions for up to two weeks or gradual increase to achieve optimal response or discontinuation for those who continue to experience persistent intolerable pruritus (CS Table 5).[3].

For those taking UDCA concomitantly with obeticholic acid, the company state that no dose adjustment of UDCA is required.[3].

ERG comment:

- The CS matches the scope in that it evaluates OCA alone or in combination with UDCA.
- However, as stated above, the main efficacy trial POISE has just 11 patients (7%) who are taking obeticholic acid alone. The remaining 93% are taking it in combination with UDCA.[27] One of the two Phase 2 studies included in the submission as supporting evidence was a study of monotherapy including 49 patients, 20 of whom received 10 mg OCA and 23 received

placebo. The remainder received 50 mg OCA and were not relevant to the proposed dosage.[29] As stated above, the role of OCA monotherapy at the appropriate dosage has only been investigated in a small number of patients so results for this group of patients may not be reliable.

- In the POISE trial 73 patients were randomised to a fixed dose of 10 mg OCA and 73 patients received the placebo.[27] Seventy-one patients were randomised to the titration group which reflects the recommended dosage. They received OCA 5 mg OD for the initial six months period. The patients in POISE were only up-titrated to 10 mg OCA if they did not reach the primary endpoint criteria for response.[27] The ERG draws to the attention of the committee that the evidence for obeticholic acid given at the recommended dosage is based on the 33 patients who actually up-titrated to 10 mg.[27] The company notes that *'further benefit in terms of efficacy is likely to be seen in clinical practice in this patient group due to the higher dose of OCA.'*[3] This appears to be reasonable but is an assumption.

3.3 Comparators

For people whose disease has an inadequate response to UDCA the CS evaluates the use of UDCA alone as a comparator as per the final scope issued by NICE. For people who are unable to tolerate UDCA the CS (more specifically the POISE trial) compared obeticholic acid alone to placebo (representing no additional treatment as stated in the NICE scope). As stated above, 11 patients (7%) took obeticholic acid alone in POISE (five in the OCA titration group and six in the OCA 10 mg fixed dose group and five patients received a placebo alone). The CS presents results for this comparison but notes that these *'should be interpreted with caution due to low patient numbers.'*[3]

However the comparators addressed in the CS differ from those in the final scope issued by NICE in that fibrates have not been included as a comparator for people whose disease has an inadequate response to UDCA nor for those who are intolerant to UDCA. The company provide several justifications for this including: fibrates not being licensed for this indication in the UK, not being standard care, they are contraindicated in PBC, have been rarely used in the UK and efficacy is as yet unproven with a small number of limited studies with some safety concerns.[3]

ERG comment:

- As stated above, the role of OCA monotherapy compared to placebo (no treatment) has only been investigated in a small number of patients so results for this group may be less reliable than those taking obeticholic acid in combination with UDCA.
- The omission of fibrates from the comparators in the decision problem was investigated by the ERG in several ways. We consulted clinical experts and identified systematic reviews of fibrates as the most reliable source of up to date evidence. Our response to the omission of fibrates is given in the table below.

Table 3.2: Response to the omission of fibrates as a comparator in the submission

Assertion in the company submission	ERG comments
'Fibrates are not licensed in the UK, nor are they standard of care.' 'They are rarely used, with only [redacted] of patients in the UK-PBC cohort having ever taken fibrates for any condition (not necessarily for PBC)'[3]	Fibrates are not licensed for this indication. We are advised that fibrates are not routinely used in the UK for PBC.

Assertion in the company submission	ERG comments
'*Fibrates are……contraindicated in PBC*'[3]	The summary of product characteristics[17, 18] were checked. Some qualification of this statement is necessary. Hepatic insufficiency (including biliary cirrhosis) is mentioned as a contra-indication for fenofibrate, but the summary of product characteristics also states that patients with hepatic disease have not been studied. Significant hepatic disease is mentioned as a contraindication for bezafibrate, due to the fact that it alters the composition of bile, and that there have been isolated reports of the development of gallstones. The ERG judges that prevention of progressive disease might well outweigh the risk of gallstone disease, a risk that can be managed with cholecystectomy.
'Their efficacy is yet to be proven with only a limited number of studies reporting results for the use of fibrates in PBC[3, 19-23]	The ERG asked the company to '*comment on the clinical trial evidence for fibrates in PBC (ideally this evidence would be sourced systematically, but it is acknowledged that this might not be feasible in the timeframe).*'[30] The company referred us to a Cochrane review[31]that concluded '*treatment of primary biliary cirrhosis with bezafibrate can neither be supported nor refuted based on the best current evidence available ensuing from trials in Japanese patients*.'[32]. On examination of the review this conclusion related to the effect of fibrates on mortality, liver morbidity, adverse events, pruritus, and fatigue. The Cochrane review conclusion also stated: '*Bezafibrate seems to have an effect on decreasing the activity of serum alkaline phosphatase compared with no intervention or with UDCA in patients with primary biliary cirrhosis….*'[31] The ERG identified further systematic reviews of fibrates[33-35] including fenofibrates. We agree that the evidence for efficacy on hard clinical outcomes is limited. However improvements in surrogate outcomes have been noted across the reviews. We are aware of at least one ongoing trial in fibrates for PBC.[36*]
'*In addition, there are significant safety concerns with the use of fibrates in PBC*'	One study (a RCT) was cited as evidence of safety concerns regarding fibrates.[22] The safety concerns raised by this study are valid. However the ERG noted that evidence for the safety of fibrates in PBC was not gathered systematically.
Source: CS[3] Footnote: * This trial is due to complete data collection for the primary outcome in December 2016. One hundred patients were randomised to bezafibrate 400 mg/day or placebo, UDCA was continued. Primary outcome is complete biochemical response at 24 months and the normalisation of hepatic biochemical tests. (36) ERG, Evidence Review Group; PBC, primary biliary cirrhosis; RCT, randomised controlled trial; UDCA, ursodeoxycholic acid; UK, United Kingdom	

Overall, although fibrates may not be widely used across the UK, the ERG believes that the decision to exclude them as a comparator may not be appropriate.

3.4 Outcomes

The final scope issued by NICE specified patient outcomes including mortality, symptoms including pruritus, fatigue and abdominal pain, time to liver transplantation, PBC-related events, health-related quality of life and adverse effects of treatment.[4] However all efficacy outcomes in the POISE trial which forms the main evidence of the submission relate to surrogate outcomes.[3] These include a range of liver function biomarkers and other biomarkers related to PBC. Disease-specific quality of life based on the PBC-40 tool was collected in POISE but was not specifically mentioned as being addressed in the decision problem. Adverse events were also collected in POISE.[3]

The CS explains that '*due to the rare and chronic nature of PBC and the slow progression in most patients, a long-term trial is required to capture clinical outcomes such as mortality, transplant-free survival, and the incidence of complications.*'[3] The POISE trial is of 12 months' duration although there is an ongoing five year long-term safety extension (LTSE). The LTSE has data from 12 months but efficacy is still based on surrogate outcomes.[3] The company cite three references to provide evidence for the correlation of the primary outcome of POISE (combined alkaline phosphatise (ALP) and bilirubin levels) to disease prognosis.[11, 24, 25]

The company also note that there is an ongoing trial of obeticholic acid (COBALT) that measures clinical outcomes. Details of the COBALT trial are provided in Table 39 of the CS.[3] Briefly, this is a double-blind randomised, placebo-controlled trial of obeticholic acid on clinical outcomes in patients with PBC. The estimated enrolment is 350 across up to 170 international sites. Duration is estimated to be approximately eight years according to the time to accrue approximately 121 primary endpoint events. The primary outcome is a composite endpoint of clinical events. The start date of the trial was December 2014 and the study completion date is April 2023.[3]

ERG comment:

- The ERG draws the attention of the committee to the fact that the main evidence in the submission relates to surrogate outcomes. The ERG did not have the means to systematically review the validity of this correlation. Instead the ERG investigated the three references cited by the company as evidence of the correlation. The ERG observed that one of the references cited was a meta-analysis of individual patient data (4,845 patients) which concluded that *'Levels of alkaline phosphatase and bilirubin can predict outcomes (liver transplantation or death) of patients with PBC and might be used as surrogate end points in therapy trials.'*[11] This finding was supported by a retrospective review of 73 patients treated with UDCA over 36 months.[24] Biochemical response predicted histological progression, assessed with paired biopsies about 10 years apart, as well.[25] The ERG is satisfied that the company demonstrated evidence of some correlation between the surrogate outcomes of interest and longer-term clinical outcomes. However the extent of the correlation and the optimal thresholds of surrogate outcomes to predict long-term disease are unclear.
- The definitive effects of obeticholic acid on clinical outcomes relevant to patients awaits the results of the COBALT trial.[37]
- The ERG asked the company if any interim data were available from the COBALT trial which investigates clinical outcomes. The company confirmed that '*there are no interim data available and no interim analysis is planned since COBALT is an events-driven trial and 121 primary endpoint events need to have occurred before the trial will report and analyses will be performed*.'[32]

3.5 Other relevant factors

The company highlights that PBC is a rare disease affecting mainly women as a consideration relating to equity.[3] The company has offered a Patient Access Scheme (PAS) as part of this submission. Details of the scheme were not available in the submission.[3]

4. CLINICAL EFFECTIVENESS

4.1 Critique of the methods of review(s)

The CS states that *'A systematic review was conducted to identify all relevant evidence for the efficacy and safety of interventions used to treat PBC.'*[3] This systematic review is discussed in this section.

4.1.1 Searches

The following paragraphs contain summaries and critiques of all searches related to clinical effectiveness presented in the company submission. The Canadian Agency for Drugs and Technologies in Health (CADTH) evidence based checklist for the Peer Review of Electronic Search Strategies (PRESS), was used to inform this critique.[38] The submission was checked against the Single Technology Appraisal (STA) specification for company/sponsor submission of evidence.[39] The ERG has presented only the major limitations of each search strategy in the report.

Systematic literature review (CS Section 4.1.2)

The company submission stated that searches were originally undertaken in September 2014 and updated in September 2015 and June 2016. Searches were reported for Embase, MEDLINE, MEDLINE in-Process, Cochrane's CENTRAL, DARE and CDSR databases. An additional grey literature search was reported on the following resources: The trials registry, Clinical trials.gov. meeting and conference papers for the following: American Association for the study of Liver Diseases (AASLD), European Association for the Study of the Liver (EASL), American College of Gastroenterology (ACG), Digestive Disease Week (DDW), United European Gastroenterology Week (UEGW), Canadian Digestive Disease Week (CDDW) and the Japan Digestive Disease Week. As well as browsing websites for Liver Foundation UK, The Foundation for Liver Research, American Liver Foundation, Canadian Liver Foundation and the British Liver Trust. The bibliographies of selected articles were also checked to identify any further studies missed by the electronic searches or the Cochrane systematic literature reviews

The CS reported that searches were designed to retrieve RCTs for the population PBC, the study design filter was based on the BMJ Evidence Centre filter and the population terms were informed by those utilised in the Cochrane review of Ursodeoxycholic Acid in Primary Biliary Cirrhosis. The company reported that the terminology for PBC changed in 2015 when the name primary biliary cirrhosis was replaced by the term primary biliary cholangitis. This change was reflected in the 2016 update searches.

ERG comment: The database searches were clearly structured and documented. No language limits were applied. In their response to clarification the company confirmed that the date span for each resource was the same for those reported for the cost effectiveness and HRQoL searches. Searches were conducted over a broad range of bibliographic databases and grey literature resources, and a recognised RCT filter was referenced.

For the original 2014 systematic literature review (SLR) and 2015 update searches, the company conducted a single search of Embase.com on the understanding that it now contains all MEDLINE and MEDLINE In-Process content. This was replaced by separate searches of Embase and MEDLINE via the Ovid interface for the subsequent 2016 update. Whilst the ERG accepts this single approach as being adequate, the ERG considers it preferable to conduct a separate companion MEDLINE search in order to fully utilise the power of database specific study design filters developed to make the most of an individual databases subject headings. However given the searches of additional bibliographic databases and grey literature resources reported by company, it is unlikely that this omission would have impacted on the overall recall of results. The ERG noted that the same approach to the search of

Medline content via Embase.com was adopted for all of the original literature searches reported in Appendices 6, 8 and 9, therefore the same limitations will have applied.

Adverse Events

Section 4.12 of the company submission states that all safety data reported in this section were derived from the POISE study, with supporting safety data obtained from two Phase 2 trials. No searches for adverse events were reported.

ERG comment: The ERG queried this lack of searches in their points of clarification and the company confirmed *'No separate searches for adverse events were conducted, since adverse events and any safety data for OCA would be included in the evidence identified in the clinical systematic literature review'*[32] The clinical effectiveness searches incorporated a methodological filter intended to limit the search to specific study designs, namely RCTs. Guidance by the Centre for Reviews and Dissemination (CRD)[40] recommends that if searches have been limited by a study design filter, additional searches should be undertaken to ensure that adverse events that are long-term, rare or unanticipated are not missed. The ERG considered that it was possible that some relevant evidence may not have been identified as a consequence of the study design limits used. The ERG was unable to undertake independent adverse events searches and review the results within the STA timeline, as this would be outside of the ERG remit.

4.1.2 Inclusion criteria

The eligibility criteria for the systematic review of the efficacy and safety of interventions used to treat PBC is given in Table 4.1. It was stated that study selection was *'performed by two independent reviewers and discrepancies were resolved by a third independent reviewer'*[41]

Table 4.1: Eligibility criteria used in the clinical effectiveness and safety systematic review

	Inclusion	Exclusion
Population	Primary Biliary Cirrhosis (confirmed diagnosis as defined in international guidelines[42, 43]	Biliary Cirrhosis and any other liver condition Mixed populations of primary biliary cirrhosis and patients with other conditions
Interventions / comparators	Any intervention used to treat primary biliary cirrhosis	
Outcomes	• All-cause mortality • All-cause mortality or liver transplantation • Adverse events (serious and non-serious) • Quality of Life • Pruritus; number of patients with pruritus or pruritus score • Fatigue: number of patients with fatigue • Liver-related morbidity (number of patients who developed jaundice, portal hypertension, oesophageal varices, gastric varices, upper gastrointestinal haemorrhage, ascites, hepatic encephalopathy, hepato-renal syndrome). • Biochemical markers: serum bilirubin, serum alkaline phosphatases, serum gamma-	

	Inclusion	Exclusion
	glutamyltransferase, serum aspartate aminotransferase, serum alanine aminotransferase, serum albumin, total cholesterol, plasma immunoglobulins, prothrombin index. • Liver biopsy (or FibroScan®) findings: worsening of liver histological stage or score • Enhanced Liver Fibrosis (ELF) test • Transient Elastography (TE)	
Study design	Randomised controlled trials (RCTs; including extension studies of RCTs where found)	• Meta-analysis and reviews • Non-randomised controlled trials
Source: Table 2 of the CS Appendix 2[41] CS, company submission; ELF, Enhanced Liver Fibrosis; RCT, randomised controlled trial; TE, Transient Elastography		

ERG comment:

- The population, intervention, comparators and outcomes reported in the above table from the CS reflect the scope issued by NICE.[4] However the ERG had a number of concerns in relation to eligibility criteria for the review and the selection process used.
- The CS states that '*A systematic review was conducted to identify all relevant evidence for the efficacy and safety of interventions used to treat PBC. All randomised controlled trials investigating an intervention to treat PBC were included.*' [3] However according to Appendix 2 of the submission, a post-hoc decision was made to exclude all randomised trials (RCTs) that did not include at least one obeticholic acid (OCA) treatment arm (monotherapy or combination).[41] The ERG asked the company to explain the rationale for this decision.[30] The company responded '*When the protocol for the systematic literature review was designed, the strategy was to keep the criteria as broad as possible. However, for the current submission, it was clear that there were no other treatments licensed or being used in the UK for patients with an inadequate response to or intolerance to UDCA. Therefore, only RCTs that included at least one OCA arm were relevant for this submission.*'[41] The ERG identified from the flow chart (Figure 8 of the CS)[3] that 36 publications had been excluded on this basis and asked the company to provide bibliographic details of the 36 studies. The list provided by the company in response to the letter of clarification was checked.[41] and the ERG confirmed that studies including an obeticholic acid arm had been appropriately included. The decision to include only RCTs with at least one OCA arm meant that no indirect comparisons between OCA and fibrates could be made in the absence of direct evidence.
- The company identified nine Cochrane systematic literature reviews '*that had previously been performed to identify RCTs for interventions in PBC. The search strategies and scopes for these reviews were closely aligned to that of this systematic review, and therefore publications were removed from this review if they had previously been captured and reviewed by the Cochrane reviews to avoid duplication.*'[3] The ERG identified from the flow chart (Figure 8 of the CS) that 136 publications were rejected on the basis of being included in Cochrane reviews.[3] The company provided a list of these publications in the response to clarification document.[41] The list was checked and the ERG noted that no relevant direct evidence comparing obeticholic acid with one of the comparators in the NICE scope appeared to have been omitted.

- Section 4.11 of the CS states that '*There are no non-RCTs relevant to this submission.*'[3] As the systematic review inclusion criteria specified RCTs only, the ERG queried whether searches had been conducted separately to determine the lack of non-RCT evidence.[30] The company stated that '*No non-RCT searches were conducted, since head-to-head RCT data (more robust than non-RCT data) were available for OCA vs UDCA in POISE.*'[41] The statement that '*There are no non-RCTs relevant to this submission*' is not supported by a systematic review of the evidence. Therefore possibly relevant non-RCTs could have been missed in relation to effectiveness in the absence of direct evidence and in relation to safety.
- Section 4.12 of the CS states that '*all safety data reported in this section were derived from the POISE study, with supporting safety data obtained from two phase 2 trials*'.[3] The company confirmed that '*no separate searches for adverse events were conducted, since adverse events and any safety data for OCA would be included in the evidence identified in the clinical systematic literature review.*'[41] However the systematic review was limited to RCTs and, as stated above, the clinical effectiveness searches incorporated a methodological filter intended to limit the search to studies with this design. Guidance by the Centre for Reviews and Dissemination (CRD)[40] recommends that if searches have been limited by a study design filter, additional searches should be undertaken to ensure that adverse events that are long-term, rare or unanticipated are not missed. The ERG considered that it was possible that some relevant evidence on adverse events may not have been identified as a consequence of the study design limits used.
- The ERG asked the company to confirm that studies of mixed populations of PBC and patients with other conditions were excluded even if data were available for patients with PBC separately[30]The company confirmed that '*Studies of mixed populations of PBC and patients with other conditions were excluded, even if data were available for patients with PBC separately.*'[41] This exclusion criterion could have led to relevant data being omitted.
- Within the constraints of conducting the evaluation of the CS in a short timeframe, the ERG could not carry out further reviews of the evidence and search for missing studies. Overall the ERG is satisfied that the company has identified the RCTs directly comparing OCA with other treatments outlined in the scope issued by NICE.[4] However this could have been supplemented by indirect evidence on fibrates to inform the NICE scope as no direct evidence is presented for this comparator and by searching for adverse events beyond the RCT literature.

4.1.3 Critique of data extraction

No specific details were provided in the CS regarding methods of data extraction of studies for the review of clinical effectiveness. It was unclear if more than one reviewer was involved in this process.

ERG comment: It is good practice to include details of methods of data extraction when reporting a systematic review, in order to ascertain that the review was carried out appropriately. As study selection was performed by two independent reviewers with discrepancies resolved by a third independent reviewer, it may be reasonable to assume that such procedures were followed for data extraction.

4.1.4 Quality assessment

Quality assessment of the three RCTs included in the submission was given in Appendix 3 of the CS.[41] Elements assessed were randomisation procedures, allocation concealment, comparability of groups, blinding of care providers, patients and outcome assessors and drop out, selective reporting of outcomes and use of intention to treat analysis and appropriate methods for dealing with missing data.[41]

No specific details were provided in the CS regarding methods of quality assessment of studies for the review of effectiveness. It was unclear if more than one reviewer was involved in this process.

ERG comment: Study quality appeared to have been assessed using appropriate tools. However it is good practice to include details of methods of quality assessment when reporting a systematic review, in order to ascertain that the review was carried out appropriately. As study selection was performed by two independent reviewers with discrepancies resolved by a third independent reviewer, it may be reasonable to assume that such procedures were followed for quality assessment. The quality of the included trial, POISE, is discussed in Section 4.2.3.

4.1.5 Evidence synthesis

The CS states that '*There was only one relevant Phase III trial providing data for the efficacy of OCA in PBC, therefore a meta-analysis was not conducted.*'[3]

The CS also states in Section 4.10 of the submission that '*indirect and mixed treatment comparisons were not conducted*'.[3]

ERG comment:

- The ERG acknowledges that two Phase 2 trials were included as supporting evidence in the submission[29, 44] but agrees that not pooling these with the main trial data from POISE[27] is reasonable. Both Phase 2 studies were of three months' duration only and not all patients received OCA at the licensed dose.[29, 44] Results relevant to the licensed dose are presented in the CS for both trials.[3]
- The ERG queried whether the decision not to conduct indirect or mixed treatment comparisons was made a priori or as a result of a lack of evidence from the systematic review.[30] The company reiterated that '*there were no treatments licensed or being used in the UK for patients with an inadequate response or intolerance to UDCA, and therefore there was no relevant comparator to OCA other than UDCA, which has been compared head to head in POISE. Therefore, an indirect or mixed treatment comparison was not necessary.*'[41]
- The ERG draws to the attention of the committee that the decision not to perform indirect comparisons appears appropriate given the direct evidence comparing OCA and UDCA. However there is no direct evidence comparing OCA and fibrates.

4.2 Critique of trials of the technology of interest, their analysis and interpretation (and any standard meta-analyses of these)

4.2.1 Overview of the evidence in the submission

The evidence base for the clinical efficacy of obeticholic acid (OCA) for primary biliary cirrhosis, consists of one Phase 3 randomised controlled trial (RCT), POISE,[45] and two Phase 2 RCTs, [29, 44] as identified by the systematic literature review. POISE provides the main evidence with the two Phase 2 trials treated as supporting evidence.

The POISE trial was a 12-month, international, multicentre, placebo-controlled study with a randomised, parallel-group design in patients aged ≥18 years with PBC who had previously failed to respond to treatment with ursodeoxycholic acid (UDCA) or were intolerant to UDCA.[45] The double-blind phase of the POISE trial lasted 12 months. A five-year extension phase of this trial was offered to participants of POISE willing to enrol.

The two Phase 2 supporting studies, 747-201 and 747-202 evaluated the efficacy, safety, and tolerability of OCA with UDCA (study 747-202) [29] or without UDCA (study 747-201) [44] versus placebo. Both studies included a double-blind phase and an open-label long-term safety extension phase. The double-blind phases have been completed. With regards to the intervention in both these studies, the CS states that they '*included a 10mg OCA and an arm at higher doses […] key efficacy and safety results were*

summarised only for subjects who received 10 mg OCA, since this is the upper limit for the licensed indication of OCA.'[3]

An additional trial, COBALT (NCT02308111) is mentioned in the CS (Section 4.14 of the submission).[3] This trial seeks to evaluate the effect on OCA on clinical outcomes such as transplant-free survival. The ERG can confirm that the trial is still ongoing and that no interim data has been made available.[37] Please see Section 3.4 of this report for a discussion relating to COBALT. In addition to this trial, another Phase 2 study (747-205) is currently ongoing in the US that includes patients from 8eightyears of age and aims to investigate the change from baseline in HDL metabolism.[3]

As stated in the CS, '*the results from the double-blind phase of POISE are presented as the main efficacy evidence and the two Phase 2 studies as supporting evidence*'. [3] In this regard, this report follows the same structure. More detail will be provided on the double blind phase of POISE with a briefer summary of the Phase 2 trials.

ERG comment:

- The ERG agrees that the POISE trial provides the main evidence for the comparison with UDCA or placebo and that the two Phase 2 trials represent supporting evidence.
- The ERG is satisfied that no data from the ongoing COBALT trial could have been used to inform the CS.
- The included trials did not compare OCA to fibrates as outlined in the scope.[4]

4.2.2 Overview of the POISE trial

An overview of the POISE trial and its extension study is presented in Table 4.2.

Table 4.2: Summary of the POISE trial and its extension study

Trial no. (acronym)	Population	Intervention	Comparator
747-301 (POISE); NCT01473524	Patients diagnosed with PBC with ALP ≥1.67x ULN and/or total bilirubin >ULN but <2x ULN who fail to respond to or are intolerant to treatment with UDCA.	Oral OCA (5 mg or 10 mg) taken OD.	Placebo
LTSE to POISE	All participants who completed the 12-month double-blind phase of POISE and who were willing to enrol in the 5-year LTSE phase of the study.	Oral OCA (5–25 mg[a]) taken OD	N/A

Source: CS
Footnote: a) All patients initiated OCA at 5 mg OD; daily dose could be up-titrated if a satisfactory response was not achieved in 5 mg increments to a total dose of 25 mg OD (one increment per 3 months permitted), depending on tolerability
ALP, alkaline phosphatase; LTSE, long-term safety extension; OCA, Obeticholic acid; OD, once daily; PBC, primary biliary cholangitis; UDCA, ursodeoxycholic acid; ULN, upper limit of normal.

The main methodological features of the double-blind phase of the POISE trial are summarised in Table 4.3.

Table 4.3: Overview of POISE trial

Trial Design	Phase 3, randomised double-blind, placebo-controlled, parallel group trial. Stratified randomisation according to: - higher risk of developing clinical outcomes i.e. Paris I criteria* - intolerance to UDCA - presence or absence of biochemical response to UDCA treatment
Setting	59 sites in 13 countries. (7 sites in England and 2 sites in Scotland)
Participants	217 were randomised (216 gave consent)
Interventions	3 arms: Placebo (with or without UDCA) (n = 73) 10 mg OCA, with or without UDCA (n = 73) Titration (5mg OCA rising to 10 mg during months 6 to 12 if inadequate response to UDCA), with or without UDCA) (n = 71)
Follow-up	12 months
Primary Outcome	Percentage of participants in the 10 mg OCA fixed dose group at 12 month achieving the composite endpoint: - ALP <1.67x ULN, and - total bilirubin ≤ULN, and - ALP decrease ≥15% from baseline
Source CS[3] Footnote: * Paris I criteria defined as ALP ≤3x ULN and AST ≤2x ULN and total bilirubin ≤1 mg/dL (17 μmol/l) ALP, alkaline phosphatase; CS, company submission; TEAEs, Treatment-emergent adverse events; ULN, upper limit of normal	

Table 4.4 details the secondary endpoints of the POISE trial and their definitions.

Table 4.4: Summary of secondary endpoints of the double-blind phase of POISE

Study outcome	Definition
ALP response rates	Absolute and percentage change from baseline in ALP at Month 6 and Month 12 Percentage of participants with a decrease in ALP from baseline of ≥10%, ≥15%, ≥20%, and ≥40% at Week 2, Month 3, Month 6, Month 9 and Month 12, Percentage of participants with ALP ≤ULN, summarised by treatment at all post-baseline assessments
Biochemical treatment response criteria	Percentage of participants meeting the Paris I, Paris II, Mayo II, Toronto II, or Rotterdam response criteria* at Week 2, Month 3, Month 6, Month 9, and Month 12. The analysis was repeated for subgroups of participants who met and did not meet the requirement of a responder at baseline for the endpoint analysed. Number and percentage of participants with: • Normal bilirubin (≤ULN) and normal albumin (≥LLN), • Moderate (bilirubin >ULN or albumin <LLN), and • Severe (bilirubin >ULN and albumin <LLN) at baseline, Week 2, Month 3, Month 6, Month 9 and Month 12.
Clinical laboratory values	Defined as the absolute and percentage change from baseline in ALP, GGT, ALT, AST, total and conjugated (direct) bilirubin, albumin, and prothrombin time (PT) and international standardised ratio (INR) summarised by treatment group and visit.

Study outcome	Definition
Questionnaire PBC-40	Absolute change from baseline in six domains (cognitive, social, emotional function, fatigue, itch, and general symptoms) were summarised by treatment using descriptive statistics at Week 2, Month 3, Month 6, Month 9, and Month 12. A total score was not calculated.
Patient Research Questionnaire	'A simple patient research questionnaire was administered at Month 12, or at termination if the subject withdrew from the study prior to this, to request feedback about the subjects' perception of the study.'[3]
Biomarkers and non-invasive assessments of liver fibrosis	Absolute change from baseline in the following markers: Markers of hepatic fibrosis, inflammation and other disease relevant biomarkers, including CRP, tumour necrosis factor-α (TNF-α), transforming growth factor β (TGF-β), fibroblast growth factor-19 (FGF-19), Interleukin-6 (IL-6), CK-18, autotaxin, and lysophosphatidic acid (LA), at Month 6 and Month 12 Enhanced liver fibrosis (ELF) score and its components hyaluronic acid (HA), procollagen-3 N-terminal peptide (P3NP), and tissue inhibitor of metalloproteinase 1 (TIMP-1) at Month 6 and Month 12 Hepatic stiffness measurements (at selected study sites) at Month 12, assessed by transient elastography (TE).
Bile acids	Absolute values and change from baseline by treatment group at 6 and 12 months' follow-up in the following: Total bile acids, total endogenous bile acids, and totals for the individual bile acids (UDCA, chenodeoxycholic acid [CDCA], deoxycholic acid [DCA], cholic acid [CA] and lithocholic acid [LCA]) and their respective conjugates Proportion of each of the individual bile acids relative to total bile acids
OCA Pharmacokinetics analysis	Values at Month 6 and Month 12 for OCA (unconjugated), glyco-OCA, tauro-OCA, and total OCA from participants who had a confirmed fasting of approximately 8 hours or more prior to their visit were included in the analysis. The effect of BAS on OCA and total bile acid concentration, as well as the percentage change in ALP, were explored as part of the PK analysis. Relationships between plasma total OCA concentrations (unconjugated and conjugated) and FGF-19 concentrations, endogenous bile acid concentrations, ALP and liver enzyme levels, and severity of pruritus were explored.
Safety	TEAEs defined as any adverse events (AEs) that newly appeared, increased in frequency, or worsened in severity following initiation of investigational product. Additionally, Pruritus was measured by using the 5-D pruritus questionnaire and a VAS score at week 2, months 3, 6, 9 and 12.
Clinical laboratory evaluations	Physical examinations, vital signs, body weight and BMI, electrocardiongram, dual-emission x-ray absorptioametry (DEXA) scan of the femoral neck and lumbar spine, Mayo Risk Score to assess survival and MELD score to assess the severity of chronic liver disease were assessed at week 2, months 3, 6, 9, and 12.

Source: Section 4.3.6 of CS[3]

Footnote: *Different response criteria studied in POISE are reported in Table 16 of the CS.

BAS, bile acids sequestrants; CS, company submission; TEAEs, Treatment-emergent adverse events

Assessment of clinical outcomes

The company stated in the clinical study report (CSR) that '*The incidence rate of clinical outcomes during the 12 month double-blind phase of Study 747-301 was expected to be low given the relatively early stages of disease in the enrolled patient population (total bilirubin <2x ULN). However, for completeness, the incidence of such events was retrospectively assessed based on the occurrence of pre-defined MedDRA Preferred Terms and the incidence of reaching a MELD score >15 (with a baseline MELD of <15'*.[46]

The pre-determined preferred terms, which were used to define a clinical outcome included the following: death (all-cause); liver transplant; model of end stage liver disease (MELD) score ≥15; hospitalisation (as defined by a stay of 24 hours or greater) for new onset or recurrence of: variceal bleed, encephalopathy (as defined by a West Haven score of ≥2), spontaneous bacterial peritonitis (confirmed by diagnostic paracentesis, uncontrolled ascites (diuretic resistant ascites requiring therapeutic paracentesis at a frequency of at least twice in a month) and hepatocellular carcinoma confirmed by two complementary imaging modalities. [46]

The company further stated that '*These events were not adjudicated by an independent committee as is standard for clinical outcomes trials that prospectively collect clinical outcomes*.'[46]

The incidence of these events is reported in Section 4.2.4 of this report.

Table 4.5 describes the eligibility criteria for the POISE trial.

Table 4.5: POISE inclusion and exclusion criteria

Inclusion criteria	Exclusion criteria
Male or female aged ≥18 years Definite/probable PBC diagnosis[†] as demonstrated by the presence of ≥2 of the following: • Elevated ALP levels for at least 6 months • Positive AMA titer or if AMA negative and/or low titer (<1:80) PBC specific antibodies (anti-GP210 and/or anti-SP100) and/or antibodies against the major M2 components (PDC-E2, 2-oxo-glutaric acid dehydrogenase complex) • Liver biopsy result consistent with PBC ALP ≥1.67x ULN and/or total bilirubin >ULN but <2x ULN Taking UDCA for ≥12 months prior to randomisation with a stable dose for ≥3 months, or no UDCA for ≥3 months prior to randomisation if unable to tolerate UDCA Female participants to be post-menopausal, surgically sterile, or prepared to use ≥1 effective method of contraception during the study period and for 30 days after end of trial	History or presence of other concomitant liver disease[§] Clinical complications of PBC or clinically significant hepatic decompensation[¶] Severe pruritus or pruritus requiring systemic treatment (e.g. with BAS or rifampicin) within 2 months prior to randomisation Administration within 6 months prior to randomisation and throughout the study of azathioprine, colchicine, cyclosporine, methotrexate, mycophenolate mofetil, pentoxifylline; fenofibrate or other fibrates; budesonide and other systemic corticosteroids; potentially hepatotoxic drugs (including α-methyl-dopa, sodium valproic acid, isoniazide, or nitrofurantoin) Administration within 12 months prior to randomisation and throughout the study of antibodies or immunotherapy directed against interleukins or other cytokines or chemokines Previous participation in a clinical trial using OCA History or presence of clinically concerning cardiac arrhythmias, or prolongation of QT or QTc interval (>500 ms) Pregnancy or lactating History of HIV infection Presence of any disease or condition that interferes with the absorption, distribution, metabolism, or excretion of drugs including bile salt metabolism in the intestine. Patients with inflammatory bowel disease or who have undergone gastric bypass procedures will be excluded (gastric lap band is acceptable) Medical conditions that could cause non-hepatic increases in ALP (e.g. Paget's disease) or that could diminish life expectancy to <2 years, including known cancers History of alcohol[‡] or other substance abuse within 1 year prior to randomisation Blood or plasma donation within 30 days prior to randomisation Mentally unable to complete a signed consent form
Source: Table 15 of the CS[3] Footnotes: [†]Consistent with AASLD and EASL Practice Guidelines; [§]Hepatitis C virus infection, primary sclerosing cholangitis, alcoholic liver disease, definite autoimmune liver disease, overlap hepatitis, non-alcoholic steatohepatitis, or Gilbert's syndrome. Subjects with hepatitis B virus were also excluded; however, subjects who had seroconverted could be included following consultation with the medical monitor; [¶]Includes history of liver transplantation, current placement on a liver transplant list, current MELD score ≥15 (MELD is a scoring system for assessing the severity of chronic liver disease, where the higher the score, the more severe the disease), portal	

hypertension with complications, cirrhosis with complications, hepatorenal syndrome (type I or II), or screening serum creatinine >2 mg/dl; ‡Defined as consumption of more than 210 mL of alcohol per week (i.e., the equivalent of 14 4-ounce (125 mL) glasses of wine or 14 12-ounce cans/bottles of beer).
AASLD, American Association for the Study of Liver Disease; ALP, alkaline phosphatase; AMA, anti-mitochondrial antibody; BAS, bile acid sequestrants; CS, company submission; EASL, European Association for the Study of Liver; HIV, human immunodeficiency virus; MELD, Model for End Stage Liver Disease; OCA, obeticholic acid; PBC, primary biliary cholangitis; UDCA, ursodeoxycholic acid; ULN, upper limit of normal

The baseline patient characteristics of POISE are reproduced in Table 4.6.

Table 4.6: POISE Trial: Baseline patient demographics

	Placebo (n=73)	OCA titration (n=70)	OCA 10 mg fixed dose (n=73)	Total (n=216)
Age, years				
Mean (SD)	55.5 (10.0)	55.8 (10.5)	56.2 (11.0)	55.8 (10.5)
Median	55.0	54.5	56.0	55.0
Min, max	35, 78	29, 83	30, 86	29, 86
Age subgroups, n (%)				
<65 years	60 (82)	60 (86)	56 (77)	176 (81)
≥65 years	13 (18)	10 (14)	17 (23)	40 (19)
Gender, n (%)				
Male	5 (7)	5 (7)	10 (14)	20 (9)
Female	68 (93)	65 (93)	63 (86)	196 (91)
Race/ethnicity, n (%)				
White	66 (90)	67 (96)	70 (96)	203 (94)
Non-white	7 (10)	3 (4)	3 (4)	13 (6)
Body weight, kg				
Mean (SD)	70.2 (13.3)	68.2 (13.1)	71.0 (15.3)	69.8 (13.9)
Median	70.5	65.2	67.6	67.5
Min, max	41.0, 106.0	46.7, 101.8	50.8, 134.0	41.0, 134.0
Region, n (%)				
Europe	49 (67)	45 (64)	51 (70)	145 (67)
North America	21 (29)	20 (29)	21 (29)	62 (29)
Australia	3 (4)	5 (7)	1 (1)	9 (4)
BMI, kg/m^2				
Mean (SD)	26.2 (4.4)	25.8 (4.9)	26.3 (5.1)	26.0 (4.8)
Median	25.9	24.5	25.1	25.0
Min, max	16.4, 37.6	17.7, 40.7	20.4, 49.2	16.4, 49.2
BMI subgroups, n (%)				
<30 kg/m^2	58 (79)	58 (83)	61 (84)	177 (82)
≥30 kg/m^2	15 (21)	11 (16)	12 (16)	38 (18)
Pre-treatment liver biopsy, n (%)				
Yes	7 (10)	13 (19)	9 (12)	29 (13)
No	66 (90)	57 (81)	64 (88)	187 (87)
UDCA use at baseline, n (%)				
Yes	68 (93)	65 (93)	67 (92)	200 (93)
No	5 (7)	5 (7)	6 (8)	16 (7)

Source: Table 20 in the CS.[3] BMI, body mass index; CS, company submission; OCA, obeticholic acid; SD, standard deviation; UDCA, ursodeoxycholic acid

The company states that *'treatment groups were well balanced for each key demographic and baseline variable. For the overall population, mean age was 55.8 years, with a range from 29 to 86 years, and a total of 81% of subjects were <65 years of age'.*[3] The study population was composed mainly of women (91%) of white ethnic background (94%). The majority of the population was European (67%), followed by North American (29%) and Australian (4%). The company stated that *'clinical expert opinion has validated that the patient population in POISE is representative of the population with PBC in the UK'*[3]

The table below summarises the disease characteristics of the intention to treat (ITT) population included in the double-blind phase of POISE.

Table 4.7: POISE Trial: Baseline disease characteristics

Disease characteristic	Placebo (n=73)	OCA titration (n=70)	OCA 10 mg fixed dose (n=73)	Total (n=216)
History of pruritus, n (%)				
Yes	47 (64)	45 (64)	45 (62)	137 (63)
No	26 (36)	25 (36)	28 (38)	79 (37)
Severity of most recent pruritus event for subjects who had history of pruritus, n (%)				
Mild	31 (66)	29 (64)	34 (76)	94 (69)
Moderate	14 (30)	13 (29)	8 (18)	35 (26)
Severe	1 (2)	2 (4)	3 (7)	6 (4)
Unknown	1 (2)	1 (2)	0 (0)	2 (1)
Pruritus at baseline, n (%)				
Yes	47 (64)	37 (53)	44 (60)	128 (59)
Mild	32 (44)	27 (39)	33 (45)	92 (43)
Moderate	13 (18)	10 (14)	10 (14)	33 (15)
Severe	2 (3)	0 (0)	1 (1)	3 (1)
No	26 (36)	33 (47)	29 (40)	88 (41)
History of fatigue, n (%)				
Yes	49 (67)	38 (54)	41 (56)	128 (59)
No	24 (33)	32 (46)	32 (44)	88 (41)
Overall severity of PBC-related fatigue, n (%)				
Mild	28 (38)	17 (24)	29 (40)	74 (34)
Moderate	16 (22)	16 (23)	8 (11)	40 (19)
Severe	3 (4)	5 (7)	3 (4)	11 (5)
Age at PBC diagnosis, years				
Mean (SD)	47.3 (9.3)	47.6 (11.7)	47.1 (10.6)	47.3 (10.5)
Median	48.0	48.0	47.0	47.5
Min, Max	31, 74	25, 82	24, 78	24, 82
Age at PBC diagnosis subgroups, n (%)				
<50 years	45 (62)	38 (54)	42 (58)	125 (58)
≥50 years	28 (38)	32 (46)	31 (42)	91 (42)

Disease characteristic	Placebo (n=73)	OCA titration (n=70)	OCA 10 mg fixed dose (n=73)	Total (n=216)
Mean duration of PBC, years				
Mean (SD)	8.3 (5.4)	8.3 (5.8)	9.2 (6.9)	8.6 (6.0)
Median	7.4	7.2	8.5	7.8
Min, max	0.9, 21.8	0.3, 27.0	0.0, 32.3	0.0, 32.3
Duration of PBC subgroups, n (%)				
≤7.5 years	39 (53)	36 (51)	30 (41)	105 (49)
>7.5 years	34 (47)	34 (49)	43 (59)	111 (51)
Source: Table 21 of CS[3]				

The CS states that '*the mean age at time of diagnosis was 47.3 years with a mean duration of PBC of 8.6 years*' and that '*There were slightly more subjects <50 years of age at PBC diagnosis (58%) compared with ≥50 years of age.*' Fifty-nine percent of patients had pruritus at baseline (43% mild, 15% moderate and 1% severe) and 59% had a history of fatigue. The CS notes that '*the majority (94–99%) of subjects had a baseline INR ≤1.3, indicative of a population in an early stage of disease progression'*.

The CS notes that '*In general, each variable was well balanced across treatment groups.' However 'the overall incidence of pruritus at baseline was slightly higher for subjects in the placebo treatment group (64% and OCA 10mg fixed dose group (60%) than in the OCA titration group (53%).....The overall incidence of fatigue was slightly higher for subjects in the placebo treatment group (67%) than in the OCA titration and OCA 10mg fixed dose groups (54% and 56%, respectively).*'

ERG comments on POISE:

POISE, has several strengths and matches the NICE scope in several ways:

- It is a randomised controlled trial in a PBC population relevant to England and Wales.
- It is a multicentre international trial with 217 participants comparing OCA to UDCA alone in patients with an inadequate response to UDCA and comparing OCA to no treatment in patients intolerant to UDCA.
- Follow-up is of 12 months' duration covering an extensive range of surrogate outcomes.

There are a number of limitations in applying the results of the trial to the NICE scope:

- The number of patients intolerant to UDCA and receiving OCA as monotherapy was limited to 11 patients (five [7%] in the OCA titration group and six [8%] in the OCA 10 mg group). Five patients received OCA placebo. As such the results for this group of patients should be considered with caution due to the low numbers.
- The ERG noted that the POISE trial included patients at an early state of PBC progression as stated in Section 4.5.2.3 of the CS '*the majority (94–99%) of subjects had a baseline INR ≤1.3, indicative of a population in an early stage of disease progression'*.[3] The ERG asked the company to clarify how OCA would benefit patients with more advanced PBC. In the response to clarification letter, the company stated that two analyses were performed in more advanced stages of PBC. Several definitions were used to approximate severity of the disease including a clinical composite definition and presence of cirrhosis. The results of these analyses are provided in Section 4.2.4. It should be noted that these are based on a subset of 72 patients

classified as having advanced disease and 36 who had cirrhosis.[32]The ongoing COBALT trial includes more advanced patients and should provide more definitive results for these patients.

- Although stratified on several important variables, the POISE trial had differences between treatment groups at baseline. In particular the placebo group had a higher incidence of pruritus and fatigue which should be borne in mind particularly when interpreting results of adverse events.
- In the POISE trial 73 patients were randomised to a fixed dose of 10 mg OCA and 73 patients received the placebo.[27] Seventy-one patients were randomised to the titration group which reflects the recommended dosage. They received OCA 5 mg OD for the initial six month period. The patients in POISE were only up-titrated to 10 mg OCA if they did not reach the primary endpoint criteria for response.[27] The ERG draws to the attention of the committee that the evidence for obeticholic acid given at the recommended dosage is based on the 33 patients who actually up-titrated to 10 mg.[27] The company notes that '*further benefit in terms of efficacy is likely to be seen in clinical practice in this patient group due to the higher dose of OCA.*'[3] This appears to be reasonable but is an assumption.
- The POISE trial presents evidence using surrogate outcomes only for clinical effectiveness. As stated in Section 3.4, the ERG is satisfied that the company has demonstrated evidence of some correlation between the surrogate outcomes of interest and longer-term clinical outcomes. However the extent of the correlation and the optimal thresholds of surrogate outcomes to predict long-term disease is unclear.
- In the POISE CSR some early clinical outcomes were retrospectively gathered.[46] Although these are presented in Section 4.2.5, the time scale of the trial (12 months) does not allow conclusions to be drawn based on this early long-term evidence. The definitive effects of obeticholic acid on clinical outcomes relevant to patients awaits the results of the COBALT trial.[37]
- As stated in the NICE scope for Obeticholic acid, the HRQoL of PBC patients is relevant for this submission.[4] The company used a disease-specific questionnaire PBC-40 that assesses symptoms across several domains: fatigue, emotional and social, cognitive function, general symptoms and itch.[47] Brief results as presented in the CSR are given in Section 4.2.4 of the report.

4.2.3 Quality assessment of POISE

We reproduce the company's quality assessment of the POISE trial[3] alongside the ERG's views on the quality of the trial.

Table 4.8: Quality assessment of POISE

Study question	How is the question addressed in the study?	Company Grade (yes/no/not clear/NA)	ERG Grade (yes/no/not clear/NA)
Was randomisation carried out appropriately?	Subjects were randomised via an IWRS based on a pre-defined randomisation code with stratification criteria to ensure subjects were randomised equally within each sub-group.	Yes	Yes
Was the concealment of treatment allocation adequate?	The IWRS served as an investigational product inventory and management system. All investigational product was visually identical for both OCA treatment arms and for the placebo group. Investigational product bottles were not labelled with either a subject randomisation number or tablet strength, to ensure that neither subject nor Investigator was unblinded. Access to randomisation codes and corresponding treatment assignment was made available to the appropriate Sponsor designee(s) in the event of a medical emergence. No other Sponsor personnel or vendor/CRO had access to blinded subject treatment codes until all study data were entered into the study database, validated, and the database locked.	Yes	Yes
Were the groups similar at the outset of the study in terms of prognostic factors, for example severity of disease?	Baseline characteristics were similar between treatment arms	Yes	Yes

Study question	How is the question addressed in the study?	Company Grade (yes/no/not clear/NA)	ERG Grade (yes/no/not clear/NA)
Were the care providers, participants and outcome assessors blind to treatment allocation? If any of these people were not blinded, what might be the likely impact on the risk of bias (for each outcome)?	All investigational product was visually identical for both OCA treatment arms and for the placebo group. Investigational product bottles were not labelled with either a subject randomisation number or tablet strength, to ensure that neither subject nor Investigator was unblinded. Access to randomisation codes and corresponding treatment assignment was made available to the appropriate Sponsor designee(s) in the event of a medical emergence. No other Sponsor personnel or vendor/CRO had access to blinded subject treatment codes until all study data were entered into the study database, validated, and the database locked.	Yes	Yes
Were there any unexpected imbalances in drop-outs between groups? If so, were they explained or adjusted for?	Slightly more patients withdrew from the OCA treatment groups (10% in the titration group and 12% in the 10 mg group) than the placebo group (4%). This was mainly due to pruritus.	Yes	Yes
Is there any evidence to suggest that the authors measured more outcomes than they reported?	Results are reported for all outcomes specified in the methodology.	No	No
Did the analysis include an intention-to-treat analysis? If so, was this appropriate and were appropriate methods used to account for missing data?	An ITT population was used where appropriate. Missing values were considered a non-response.	Yes	Yes
Source: CS, Appendix 3[41] Abbreviations: ITT, intention to treat; IWRS, interactive web response system			

ERG comment: It can be seen that the ERG agrees with the company's assessment and finds that the trial has been well conducted with appropriate procedures for randomisation, allocation concealment, blinding and outcome assessment.

4.2.4 POISE: Efficacy results

The primary efficacy endpoint (percentage of participants with ALP < 1.67 x ULN and total bilirubin ≤ ULN and ALP decrease from baseline at 12 months) is detailed in Table 4.9 below.

Table 4.9: Summary of primary efficacy outcome in POISE

	Responders (%)
	Month 12
Placebo (n=73)	10%
10 mg OCA (n=73)	47%
Titration OCA (n=70)	46%
Titration subgroup[†]	
Remained at 5 mg OCA for 12 months (n=36)	53%
Titrated to 10 mg OCA at Month 6 (n=33)	39%

Source: Table 23 CS[3]
Footnote: [†]There was one participant who withdrew from the trial due to an AE after 8 days of study medication, and therefore there were no data for this participant at Month 6 and Month 12. §Of the 12 participants who did not respond but did not up-titrate, nine did not increase their dose due to adverse events, and three recorded their reason as 'other'
ALP, alkaline phosphatase; CS, company submission; OCA, obeticholic acid.

It can be seen from the table above that at 12 months 47% of participants in the 10mg group achieved the primary outcome, 46% in the titration group and 10% in the placebo group ($p < 0.0001$ for both comparisons).

Secondary outcomes

For the two main surrogate outcomes relevant to the primary composite outcome in POISE, namely ALP and total bilirubin levels, the company reports that at 12 months, 25 (34%) and 21 (30%) of participants from the OCA 10 mg fixed dose and OCA titration groups respectively achieved an ALP reduction from baseline ≥40% compared with 1% in the placebo group.[3] For the total bilirubin outcome, decreases in the absolute change from baseline were observed for both OCA treatment groups compared with an increase for the placebo treatment group. At 12 months, mean bilirubin levels in the OCA 10 mg group were 9.7 (SE 0.6), 9.9 (SE 0.6) in the OCA titration group and 13.2 (1.0) in the placebo group.[3]

The CSR states that '*The disease-specific measure for PBC showed no clinically significant improvements in comparison to placebo for the global score or individual scores of general symptoms, fatigue, cognitive function, and emotional/social domains; however, a difference was observed in itch scores in the earlier treatment months*.'[46] The CSR further states that '*During the initial 3 months of treatment, the largest LS mean increase in itch was observed for the OCA 10 mg group, followed by the OCA titration group…. The LS mean difference in itch score between the OCA 10 mg group and placebo group was statistically significant at both Week 2 (p = 0.0048) and Month 3 (p <0.0001) but not at any subsequent time points.*' [46]

Retrospective assessment of clinical outcomes

The results of the retrospective assessment of pre-defined clinical outcomes during the 12 month double-blind phase is given in Table 4.10.[46]

Table 4.10: All-cause mortality and clinical complications: safety population (N = 216)

Outcomes[a]	No of patients	Treatment at the time of event	Preferred term Score	Time to onset from Day 0
All cause mortality	1	OCA 5 mg	Cardiac failure[b]	257
Clinical complications				
Oesophageal / bleeding varices	1	Placebo	Upper GI haemorrhage[c] Varices oesophageal Varices oesophageal	75 92 134
Ascites / Diuretic-Resistant Ascites	1	OCA 5 mg	Ascites	360
Hepatic encephalopathy	1	OCA 5 mg	Hepatic encephalopathy Hepatic encephalopathy	360 378

Source: CSR 747-301[46]

Footnotes: a) No clinical outcome events were reported in liver-related mortality, hepatic cellular carcinoma (HCC), spontaneous bacterial peritonitis, or hepatorenal syndrome or hepatopulmonary syndromes.

b The event qualified as a clinical endpoint due to fatal outcome.

c The gastrointestinal haemorrhage was considered due to variceal bleeding.

The incidence of reaching a MELD score >15 (with a baseline MELD of <15) is given in Table 4.11.[46]

Table 4.11: Clinical Outcomes – Transplant (MELD Score): Safety Population (N = 216)

No of patients	Treatment	Baseline MELD score	Score	Visit
1	Placebo	6.4	15.8 17.1 21.7	Week 2 Month 3 Month 6
1	Placebo	6.4	21.7 17.1 17.6 20.1	Week 2 Month 6 Month 9 Month 12
1	Placebo	8.5	23.6	Month 9
1	Placebo	6.8	20.8	Month 6
1	OCA 5 mg	8.8	16.6	Month 3
1	OCA 5 mg	6.4	17.5	Week 2
1	OCA 10 mg	6.7	18.0	Unscheduled[a]
1	OCA 10 mg	11.3	16.0	EOT[b]

Source: CSR 747-301[46]

Footnotes: a) Unscheduled visit occurred approximately 4.5 months post-Baseline; b) End of treatment (EOT) occurred 185 days post-Baseline. Participant early terminated due to pruritus

CSR, clinical study report; MELD, Model for End Stage Liver Disease

Subgroup of patients with advanced disease

A total of 72 participants (30, 22 and 20 in the placebo, OCA titration and OCA 10 mg respectively) were classified as having advanced disease using a clinical composite definition that included biochemical criteria (not specified), non-invasive measures of fibrosis, biopsies and/or medical history of decompensation and presence of cirrhosis.[32] The company concluded that '*there was not an increased risk (of adverse events) in patients with advanced disease*'.[32] No efficacy data were presented for these patients. A post-hoc analysis of efficacy and safety of 36 patients with cirrhosis (13 in the placebo arm, 13 in the OCA titration arm and 10 in the OCA 10 mg arm) was conducted. The company stated that '*ALP levels were significantly more reduced over 12 months in the OCA treatment groups than the placebo groups and bilirubin increased in the placebo group but remained stable in the OCA treatment group. The primary composite outcome in POISE ….was met by 8% of subjects in the placebo arm, 54% in the OCA titration arm and 40% in the OCA 10 mg arm after 12 months.*'[32]

ERG comment:

- The ERG notes the improvements shown in the OCA treatment groups in terms of the combined efficacy endpoint (percentage of participants with ALP < 1.67 x ULN and total bilirubin ≤ ULN and ALP decrease from baseline at 12 months). This is supported by improvements in other surrogate markers. However no firm data on clinical outcomes are available. It is too early to draw conclusions on long-term clinical outcomes and the need for transplant based on the retrospective data available.
- The ERG notes that improvements in surrogate outcomes were not reflected in the disease specific quality of life tool (PBC-40) over the 12 month period.
- The improvements seen in patients with more advanced disease (briefly reported) are based on lower patient numbers as the majority of patients in POISE had earlier stage disease.
- As few patients used OCA as monotherapy it is unclear if results accurately reflect this patient group.

4.2.5 POISE: Safety results

A summary of the adverse events as described in the CS [3] is detailed in Table 4.12.

Table 4.12: Overview of adverse events: safety population (POISE)

Participants, n (%)	**Placebo n=73**	**OCA titration n=70**	**OCA 10 mg n=73**
Any TEAE	66 (90)	65 (93)	69 (95)
Total number of TEAEs	452	471	467
Any treatment-related AE[†]	38 (52)	42 (60)	54 (74)
Any SAEs	3 (4)	11 (16)	8 (11)
Total number of SAEs	8	15	11
TEAEs by severity			
Mild	29 (40)	16 (23)	19 (26)
Moderate	28 (38)	27 (39)	29 (40)
Severe	9 (12)	22 (31)	21 (29)
Any TEAE leading to discontinuation	2 (3)[‡]	5 (7)[§]	8 (11)[¶]
Discontinuation due to pruritus	0 (0)	1 (1)	7 (10)
Number of deaths	0 (0)	1 (1)	0 (0)

Participants, n (%)	Placebo n=73	OCA titration n=70	OCA 10 mg n=73
Source: Table 37 CS[3] Footnotes: † Includes any events determined to be 'possibly', 'probably', and 'definitely' related. ‡One participant was discontinued from study due to withdrawal of consent; §No participants withdrew who titrated to OCA 10 mg. ¶ One participant experienced a TEAE of fatigue, which was recorded as a discontinuation on the AE eCRF; however, the participant remained in the study and study drug was not changed AE, adverse event; CI, confidence interval; CS, company submission; eCRF, electronic case report form; SAE, serious adverse event; TEAE, treatment-emergent adverse event			

Over 90% of patients across the trial experienced an adverse event. Occurrence of any AE was comparable across treatment groups. However a larger number of events were rated as severe in the OCA treatment groups (OCA 10 mg 29%, OCA titration 31% and placebo 12%). Of note, 10% of patients in the OCA 10 mg group discontinued due to pruritus.

The company stated that '*TEAEs that occurred with an incidence of ≥5% and were reported more frequently in either of the OCA treatment groups compared with placebo included pruritus, rash, eczema, fatigue, pyrexia, peripheral oedema, nasopharangitis, influenza, bronchitis, sinusitis, diarrhoea, constipation, abdominal discomfort, arthralgia, cough, oropharyngeal pain, procedural pain, fractures, palpitations and hypothyroidism.*'[3] Full details of specific adverse events are given in Table 4.13.

Table 4.13: Summary of TEAEs, severity of AEs, and treatment-related AEs occurring in ≥5% of participants in either OCA treatment group

SOC/preferred term, n (%)†	Placebo N=73	OCA titration N=70	OCA 10 mg N=73
TEAEs occurring in ≥5% of participants in either OCA treatment group‡			
Skin and subcutaneous tissue disorders			
Pruritus	28 (38)	39 (56)	50 (68)
Rash	3 (4)	3 (4)	4 (5)
Eczema	0	4 (6)	2 (3)
General disorders and administration site conditions			
Fatigue	10 (14)	11 (16)	17 (23)
Oedema peripheral	2 (3)	2 (3)	5 (7)
Pyrexia	1 (1)	0	5 (7)
Infections and infestations			
Nasopharyngitis	13 (18)	17 (24)	13 (18)
Upper respiratory tract infection	8 (11)	4 (6)	4 (5)
Urinary tract infection	8 (11)	4 (6)	4 (5)
Influenza	4 (5)	5 (7)	4 (5)
Bronchitis	0	4 (6)	1 (1)
Sinusitis	0	1 (1)	4 (5)
Gastrointestinal disorders			
Nausea	9 (12)	4 (6)	8 (11)
Diarrhoea	8 (11)	2 (3)	8 (11)
Constipation	4 (5)	5 (7)	5 (7)

SOC/preferred term, n (%)[†]	Placebo N=73	OCA titration N=70	OCA 10 mg N=73
Abdominal pain upper	5 (7)	5 (7)	4 (5)
Gastroesophageal reflux disease	4 (5)	2 (3)	4 (5)
Dyspepsia	8 (11)	4 (6)	0
Abdominal discomfort	1 (1)	5 (7)	0
Musculoskeletal and connective tissue disorders			
Arthralgia	3 (4)	4 (6)	7 (10)
Back pain	8 (11)	4 (6)	4 (5)
Nervous system disorders			
Headache	13 (18)	12 (17)	6 (8)
Respiratory, thoracic, and mediastinal disorders			
Cough	5 (7)	4 (6)	6 (8)
Oropharyngeal pain	1 (1)	5 (7)	6 (8)
Injury, poisoning, and procedural complications			
Procedural pain	1 (1)	4 (6)	1 (1)
Fractures	3 (4)	2 (3)	4 (5)
Cardiac disorders			
Palpitations	1 (1)	2 (3)	5 (7)
Eye disorders			
Dry eye	4 (5)	2 (3)	4 (5)
Endocrine disorders			
Hypothyroidism	1 (1)	4 (6)	1 (1)
Incidence of TEAE by maximum severity, n (%)			
Mild	29 (40)	16 (23)	19 (26)
Moderate	28 (38)	27 (39)	29 (40)
Severe	9 (12)	22 (31)	21 (29)
Treatment-related AEs in ≥5% of participants in any OCA treatment group, n (%)[§]			
Skin and subcutaneous tissue disorders			
Pruritus	27 (37)	35 (50)	48 (66)
General disorders and administration site conditions			
Fatigue	8 (11)	6 (9)	6 (8)
Gastrointestinal disorders			
Nausea	4 (5)	3 (4)	4 (5)

Source: Table 38 CS[3]. Footnotes: [†] At each level of summation, participants reporting >1 AE are counted only once; [‡] a TEAE is defined as any event that newly appeared, increased in frequency, or worsened in severity following initiation of investigational product. At each level of summation, participants reporting >1 AE are counted only once using the highest severity; [§] treatment-related AEs include all events reported as 'possible', 'probable', or 'definite' relationship to study drug. AE, adverse event; CS, company submission; N, total number of participants; n, number of participants experiencing an event, OCA, obeticholic acid; SOC, systems organ class; TEAE, treatment-emergent adverse event

Pruritus was the most commonly occurring TEAE with higher incidence in the OCA arms (OCA 10 mg [68%], OCA titration [56%] and placebo [38%]). The company stated that '*Most pruritus events were of mild or moderate severity and resolved during the treatment period. Starting at OCA 5 mg and titrating to 10 mg OCA was associated with improved tolerability versus starting at 10 mg OCA.*'[3]

The company also state that '*Fatigue and nausea were the only other related TEAE that occurred at an incidence ≥5%; however, these events were balanced between placebo and OCA treatment arms.*'[3]

ERG comment:

- Adverse events overall appear broadly comparable in OCA and placebo groups. However a larger number in the OCA group appear to be rated severe.
- Ten percent of patients discontinued treatment due to pruritus in the OCA 10 mg group (1% in the titration group, 0 in the placebo group). Pruritus was more common in the OCA groups than in placebo groups. The company's comments on the benefits of titration of dose in relation to pruritus appear to be appropriate.

4.2.6 Overview of the supporting Phase 2 trials (747-201 and 747-202):

The Phase 2 trials evaluated the efficacy, safety, and tolerability of OCA with UDCA (study 747-202) or without UDCA (study 747-201) vs. placebo. Both included a 10 mg OCA treatment arm and other treatment arms at higher doses. In the CS, key efficacy and safety results were summarised only for patients who received 10 mg OCA, since this is the upper limit for the licensed indication of OCA. Both studies included a double-blind phase and an open-label long-term safety extension phase. Table 4.14 includes the study design characteristics of the double-blind phase.

Table 4.14: Summary of Phase 2 study characteristics (double-blind phase)

Trial number	Study 747-201	Study 747-202
Settings and locations	18 centres in 6 countries (UK, USA, Canada, Germany, France, Spain)	30 centres in 8 countries (USA, Canada, Germany, UK, The Netherlands, Austria, France, Spain)
Duration of trial	3 months	3 months
Trial design	Multi-centre, randomised, double-blind, placebo-controlled, multi-dose, Phase 2 parallel group study of OCA monotherapy in participants with a proven or likely diagnosis of PBC	Multi-centre, randomised, double-blind, placebo-controlled, multi-dose, Phase 2 parallel group study of OCA in with UDCA in participants with a proven or likely diagnosis of PBC.
Eligibility criteria for participants	Proven or likely PBC Aged 18–70 years (18–75 years in the UK)	Proven or likely PBC Aged 18–70 years (18–75 years in the UK)
Number randomised	60 were randomised, 59 participated (23 placebo, 20 OCA 10 mg, 16 OCA 50 mg)	165 were randomised (38 to placebo, 38 to OCA 10 mg, 48 to OCA 25 mg, 41 to OCA 50 mg)
Number of arms	3 arms (placebo, OCA 10 mg and OCA 50 mg)	4 arms (placebo, OCA 10 mg, OCA 25 mg, OCA 50 mg)
Primary endpoint	Percentage change in serum ALP from baseline to end of study	Percentage change in serum ALP from baseline to end of study
Secondary endpoints	Absolute changes in serum ALP levels from baseline to Day 15, Day 29, Day 57, Day 85/end of treatment and Day 99/follow-up Percentage of participants meeting PBC responder criteria as per the Paris I, Toronto I, Toronto II, Toronto III, Toronto IV, Mayo II, and Barcelona disease prognostic risk criteria at Day 85/end of treatment Absolute and percentage change in serum AST, ALT, GGT, and conjugated (direct) bilirubin values from baseline to Day 15, Day 29, Day 57, Day 85/end of treatment and Day 99/follow-up Safety	Changes in serum ALP levels from baseline to Day 15, Day 29, Day 57, Day 85/end of treatment and Day 99/follow-up Responder analyses of ALP response Change in serum AST, ALT, GGT, serum albumin and conjugated (direct) bilirubin values from baseline to Day 15, Day 29, Day 57, Day 85/end of treatment and Day 99/follow-up Changes in CRP, non-esterified fatty acid, TNF-α & β, TGF-β, bile acids, glutathione, IgM, and osteopontin from Baseline to Day 85/end of treatment SF-36 and PBC-40 QoL questionnaires Bile acid analysis and change in FGF-19 from baseline to Day 85/end of treatment Safety

Source: CS[3]

ALP, alkaline phosphatase; AST, aspartate aminotransferase; CRP, C-reactive protein; GGT, gamma-glutamyl transferase; TGF, transforming growth factor; TNF, tumour necrosis factor, UDCA, ursodeoxycholic acid

In summary, both studies found a statistically significant effect of OCA 10 mg on ALP levels from baseline to end of study versus placebo. In study 747-201 (monotherapy) the mean (SD) percentage change in ALP levels was –44.5% (24.4) for the OCA 10 mg group versus +0.4% (15.3) for placebo. Study 747-202 reported mean (SD) percentage change in ALP levels was –44.5% (24.4) for the OCA 10 mg group versus +0.4% (15.3) for placebo. Both results were statistically significant at $p<0.0001$.

ERG comment: The Phase two trials lend support to the findings of POISE on the benefits of OCA on surrogate outcomes for patients with PBC. However both trials were of a short-term duration (three months) and a variety of doses were used limiting the comparability of the trials to POISE and the possibility of pooling results.

4.3 Critique of trials identified and included in the indirect comparison and/or multiple treatment comparison

Not applicable as there was no indirect comparison or multiple treatment comparison in the CS.

4.4 Critique of the indirect comparison and/or multiple treatment comparison

Not applicable as there was no indirect comparison or multiple treatment comparison in the CS.

4.5 Additional work on clinical effectiveness undertaken by the ERG

Not applicable.

4.6 Conclusions of the clinical effectiveness section

The company conducted a systematic review to identify studies comparing OCA to the comparators outlined in the NICE scope.[4] Overall the ERG is satisfied that the relevant direct evidence comparing OCA and UDCA has been presented. However no trials comparing OCA to fibrates were identified.

One Phase 3 trial, POISE, with 217 patients was presented as the main source of evidence.[27] The trial compared UDCA and combined UDCA and OCA in patients with an inadequate response to UDCA and OCA and placebo in those who were intolerant to UDCA. However the group receiving OCA as monotherapy is underrepresented in this trial (11 patients). Additionally, the majority of patients in POISE appeared to be at an earlier stage of disease so the effects on those with more advanced disease are less clear.

The POISE trial was well-conducted. However it only examined surrogate outcomes. These were justified by the company based on previously published research. In POISE, OCA shows positive effects on surrogate endpoints, and there is some evidence that surrogate endpoints are related to relevant outcomes. However, the size of the relationship is unclear.

The primary outcome of POISE was a composite one (percentage of participants with ALP < 1.67 x ULN and total bilirubin ≤ ULN and ALP decrease from baseline at 12 months). At 12 months 47% of participants in the OCA 10 mg group achieved the primary outcome, 46% in the titration group and 10% in the placebo group ($p < 0.0001$ for both comparisons). The results of other surrogate outcomes supported these findings. Incidence of adverse events was similar across groups. Events occurring more frequently in treatment groups were noted. The most notable was pruritus and it was noted that 10% of patients discontinued treatment due to pruritus in the OCA 10 mg group which did not titrate based on tolerability.

Two supporting Phase 2 trials were presented (including one of OCA monotherapy and one of OCA in combination with UDCA). These were not similar enough to be pooled with POISE but added support to the positive findings on surrogate outcomes. Clinical outcomes await the publication of the COBALT trial.[37]

5. COST EFFECTIVENESS

5.1 ERG comment on company's review of cost effectiveness evidence

The following section includes searches for the cost effectiveness analysis review, measurement and evaluation of health effects as well as for cost and healthcare resource identification, measurement and valuation. Moreover, the review of cost effectiveness analysis studies is considered

5.1.1 Searches performed for cost effectiveness section

The following paragraphs contain summaries and critiques of all searches related to cost effectiveness presented in the company submission.

Objective and searches for cost effectiveness analysis review

A systematic review was conducted to identify all relevant PBC studies relating to cost effectiveness. More specifically, the review question was: what modelling techniques have been used previously to conduct economic evaluations for the treatment of PBC?

The CS reported that searches were carried out in September 2014 and updated in 2016. The original searches were not limited by date or language. Searches were carried out on a broad range of databases including those recommended in the NICE 2013 guide to the methods of technology appraisal Sections 5.2.2 and 5.2.4.[48] A supplementary grey literature search was reported in Section 5.1.1.2, but no further details were provided in the appendices.

ERG comment: The majority of searches in Appendix 6 were well reported and easily reproducible. The ERG queried the lack of further information regarding the grey literature searches in their request for clarification.[30] In their response the company reported that where applicable the following resources were searched using the terms 'primary biliary cirrhosis' and primary biliary cholangitis' in order to inform the cost effectiveness, HRQoL and healthcare resource use literature reviews:

- American Association for the Study of Liver Diseases (AASLD) http://www.aasld.org/Pages/Default.aspx
- European Association for the Study of the Liver (EASL) http://www.easl.eu/
- American College of Gastroenterology (ACG) http://gi.org/
- Digestive Disease Week (DDW) http://www.ddw.org/
- United European Gastroenterology Week (UEGW) http://www.ueg.eu/
- Canadian Digestive Disease Week http://www.cag-acg.org/
- Japan Digestive Disease Week http://www.jddw.jp/english/index.html
- Liver Foundation UK http://www.liverfoundation.org.uk/
- www.nice.org.uk
- The Foundation for Liver Research http://www.liver-research.org.uk/
- American Liver Foundation http://www.liverfoundation.org/
- Canadian Liver Foundation http://www.liver.ca/
- British Liver Trust http://www.britishlivertrust.org.uk/
- The British Library http://www.bl.uk
- National Institute for Health Research http://www.hta.ac.uk/
- National Institute for Health and Care Excellence (NICE) http://www.nice.org.uk/
- Scottish Medicines Consortium (SMC) http://www.scottishmedicines.org.uk/Home
- National Centre for Pharmacoeconomics (NCPE) Ireland http://www.ncpe.ie/submission-processs/hta-guidelines/

- All Wales Medicines Strategy Group (AWMSG) http://www.wales.nhs.uk/sites3/home.cfm?orgid=371
- Institute for Quality and Efficiency in Health Care (IQWiG) https://www.iqwig.de/en/home.2724.html
- Haute Autorité de Santé (HAS) http://www.has-sante.fr/portail/jcms/j_5/home
- Italian Medicines Agency (AIFA) http://www.agenziafarmaco.gov.it/en
- Agencia de Evaluación de Tecnologías Sanitarias (AETS) http://www.isciii.es/
- Canadian Agency for Drugs and Technologies in Health (CADTH) http://www.cadth.ca/
- Pharmaceutical Benefits Advisory Committee (PBAC) http://www.pbs.gov.au/info/industry/listing/participants/pbac
- Search Engine (Google) http://www.google.co.uk[32]

The ERG noted a disparity in the date reported for the 2016 update searches, Section 6.2 (Appendix 6)[41] stated that these were carried out in February 2016, but individual strategies carry a search date of June 2016. This error was also present in Section 9.2 (Appendix 9).[41] Although not explicitly stated the cost effectiveness filter used in the Embase and MEDLINE strategies reported in Tables 20, 23 and 24 (Appendix 6) appeared to be based on the pragmatic filter developed by the Scottish Intercollegiate Guidelines Network (SIGN)[49] to identify Economic studies.[41] Although some attempt had been made to translate the Embase filter in the 2016 MEDLINE update search, the MEDLINE version of the filter created by SIGN, which contains additional relevant MeSH had not been used, therefore potentially useful records may have been missed. However given the searches of additional bibliographic databases and the above list of grey literature resources, it is unlikely that this would have impacted on the overall recall of results. The ERG noted that an economics filter was included in the update of the NHS EED search. As this is an economics database the ERG believes it is not necessary to include this facet, as this may result in unnecessarily restricting the results retrieved. However given the breadth of the searches reported this is unlikely to have impacted on the overall recall of results.

Objective and searches for measurement and valuation of health effects

A systematic review was conducted to identify HRQoL studies from the published literature relevant to the decision problem. In particular, EQ-5D health state utility values (in line with the NICE preferred method) relating to HRQoL in PBC-specific disease states were sought. More specifically, the review question was: what evidence exists reporting the quality of life in patients with PBC?

Searches were carried out on a broad range of databases including those recommended in the NICE 2013 guide to the methods of technology appraisal Sections 5.2.2 and 5.2.4.[48] No date or language limits were applied. Supplementary searches of conference proceedings and other relevant resources including HTA agencies and organisational websites were reported, for further details of the grey literature searches please see the company's response to clarification above.

ERG comment: Searches were well reported and easily reproducible. The HRQoL filters contained a good combination of relevant subject heading terms and free text terms. As with the previous search the ERG noted that the HRQoL filter was included in the update of the NHS EED search, as stated above this is unlikely to have been consequential but the same limitations will apply. As with the section above a disparity was noted in the date reported for the update searches, Section 8.2 (Appendix 8) stated that these were carried out in February 2016, but individual strategies carry a search date of May 2016.

Objective and searches for cost and healthcare resource identification, measurement and valuation

A systematic review was conducted to identify all relevant PBC unit cost and resource use studies from the published literature relevant to the decision problem. More specifically, the review question was: what are the costs and resource use associated with the management of PBC?

Searches were carried out on a broad range of databases including those recommended in the NICE 2013 guide to the methods of technology appraisal Sections 5.2.2 and 5.2.4.[48] No date or language limits were applied. Supplementary searches of conference proceedings and other relevant resources including HTA agencies and organisational websites were reported, for further details of the grey literature searches please see the company's response to clarification above.

ERG comment: The ERG noted that the strategy reported for the 2014 Embase healthcare resource use identification search (Table 40, Appendix 9) appeared to be a duplicate copy of the HRQoL Embase strategy (Table 33, Appendix 8) and did not reflect the resource use terminology utilised in the update search run in June 2016 (Tables 43 & 44, Appendix 9). The company confirmed that this had been included in error and provided full details of the correct strategy, which included a resource use/societal cost filter which contained a combination of relevant subject heading and free text terms.

5.1.2 Inclusion/exclusion criteria used in the study selection

The pre-specified inclusion/exclusion criteria are shown as a PICOS table in Appendix 6 of the CS (Tables 27 and 28).[41]

ERG comment: The eligibility criteria used by the company seem appropriate to the ERG.

5.1.3 Included/excluded studies in the cost effectiveness review

The search identified 184 titles/abstracts. After screening, 167 references were excluded, leaving 17 references for full-text evaluation. Two further studies were identified from the review of grey literature. Following full-text evaluation, four references met the inclusion criteria.[50-53] All of these four studies were deemed relevant to the review and to be used for data extraction.

Based on these four studies, the company noted that:

- None of the analyses are economic evaluations of OCA.
- Three studies[50-52] applied modelling techniques, and one study[51] considered long-term outcomes.
- All identified economic evaluations incorporated liver transplant and death as key outcomes, (while two also allowed the possibility of re-transplantation in their patient pathway).
- Only one of the identified papers[50] reported QALYs, this study aligned with the NICE reference case for derivation of utility estimates.
- Studies typically undertook detailed costing analyses; however, the extent of reporting varied between studies. The costs included in analyses appear to be limited to direct costs.
- Whilst analyses differed in their methods, those that compared UDCA or liver transplant to placebo each found the active therapy to dominate placebo, i.e. reducing costs and improving health outcomes.

5.1.4 Conclusions of the cost effectiveness review

The CS provides an overview of the included studies but no specific conclusion regarding the cost effectiveness of OCA is formulated.

ERG comment: Since the identified studies did not consider all relevant costs and outcomes (i.e. only considered the short-term) and/or did not consider the intervention of interest, the ERG agrees that no specific conclusion from the review could be formulated.

5.2 Summary and critique of company's submitted economic evaluation by the ERG

Table 5.1: Summary of the company's economic evaluation (with signposts to CS)

	Approach	Source / Justification	Signpost (location in CS)
Model	A semi-Markov state transition model was constructed to evaluate the cost effectiveness of OCA compared with placebo in treating patients with PBC who have failed to show adequate control with UDCA treatment, i.e. UDCA-intolerant patients or patients who had inadequate response to UDCA.		5.2.2
States and events	In the first year, the model comprises of the following liver disease component health states, or death: • Low risk of disease progression: ALP ≤ 1.67 * ULN • Progressive PBC: ALP > 1.67 * ULN and TB ≤ 1.0 * ULN • Progressive PBC: TB > 1.0 * ULN or compensated cirrhosis (CC) In the following periods, patients can progress to: • Pre-liver transplant • decompensated cirrhosis, • hepatocellular carcinoma (HCC) and from there can move on to: • liver transplant, with a post-liver transplant state and potential PBC re-emergence • excess mortality	A Markov structure was used as it was consistent with other approaches for liver disease modelling. Patients with abnormal bilirubin and CC were combined into one health state due to lack of data and to reflect the risk of patients developing CC prior to DCC and also the risk of progressing to HCC or liver transplant waiting list based on bilirubin levels.	5.2.2

	Approach	Source / Justification	Signpost (location in CS)
Comparators	• No treatment (in UDCA-intolerant patients) • UDCA monotherapy (in patients with inadequate response to UDCA)	Fibrates were not used as a comparator in the company's model because fibrates are not licensed in the UK, nor are they standard of care, and they are contraindicated in PBC. They are rarely used, with only [redacted] of patients in the UK-PBC cohort having ever taken fibrates for any condition (not necessarily for PBC). The efficacy of fibrates in treating PBC is yet to be proven.	5.2.3, 1.1
Population	• Patients who have failed to show adequate control with UDCA treatment, i.e. UDCA-intolerant patients • Patients who had inadequate response to UDCA		5.2.1
Treatment effectiveness	Film-coated tablet containing 5 mg or 10 mg OCA. The recommended starting dose is 5 mg taken orally, once daily. Based on the assessment of tolerability after 6 months, the dose should be increased to 10 mg once daily to achieve optimal response (titration dose). The POISE study is the principal source of evidence on treatment effectiveness. Effectiveness is measured by the decrease in risk of moving to the progressive PBC states in the first year.	This is the dose stated in the marketing authorisation and used in the POISE study.	5.3.1, 1.2, 5.3.2
Adverse events	The following adverse events were identified: fatigue, pruritus and nausea. The health care cost consequences of pruritus only were incorporated in the model.		5.4.4
Health related QoL	Health related quality of life data were sourced from the literature. These quality of life data were used to calculate health state utility values.	Literature	5.4

	Approach	Source / Justification	Signpost (location in CS)
Resource utilisation and costs	Treatment costs, health state costs and adverse event costs were taken into account in the economic model. Treatment costs were based on OCA list price and equalled £2,384.04 per 30 tablets, and on BNF data for UDCA. Health state costs and adverse event costs were based on NHS reference costs, assumptions validated by expert opinion, and literature.	BNF, literature, expert opinion, assumption, NHS reference cost	5.5
Discount rates	Discount of 3.5% for utilities and costs	As per NICE scope	5.2.2.1
Sub groups	No subgroups were considered. There are, however, two populations (as stated above).		5.2.1
Sensitivity analysis	Both DSA and PSA were performed as well as two scenario analyses. The model was the most sensitive to the choice of utility values for the liver disease component health states.		5.8

Source: CS[3]

ALP = Alkaline phosphatase; BNF = British National Formulary; CC = compensated cirrhosis; CS = company submission; DSA = deterministic sensitivity analysis; HCC = hepatocellular carcinoma; NHS = National Health Service; NICE = National Institute for Health and Care Excellence; OCA = obeticholic acid; PBC = primary biliary cirrhosis; PSA = probabilistic sensitivity analysis; TB = total bilirubin; TTD = time to treatment discontinuation; UDCA = ursodeoxycholic acid; UK = United Kingdom; ULN = upper limit of normal

5.2.1 NICE reference case checklist (TABLE ONLY)

Table 5.2: NICE reference case checklist

Elements of the economic evaluation	Reference Case	Included in submission	Comment on whether *de novo* evaluation meets requirements of NICE reference case
Population	As per NICE scope	Yes	As per NICE reference case
Comparator(s)	Therapies routinely used in the NHS, including technologies regarded as current best practice	Yes	UDCA and no treatment are used as comparators. Fibrates are excluded from the analysis but the company argues that these are not routinely used in the NHS.

Elements of the economic evaluation	Reference Case	Included in submission	Comment on whether *de novo* evaluation meets requirements of NICE reference case
Type of economic evaluation	Cost effectiveness analysis	Yes	As per NICE reference case
Perspective on costs	NHS and PSS	Yes	As per NICE reference case
Perspective on outcomes	All health effects on individuals	Partly	Disutilities of adverse events are not considered.
Time horizon	Lifetime horizon, i.e. 50 years or a maximum age of 100 years	Yes	As per NICE reference case.
Synthesis of evidence in outcomes	Systematic review	Yes	As per NICE reference case partially. Evidence of effectiveness came primarily from the POISE trial but also from other sources and unclear calibration methods.
Measure of health effects	Quality adjusted life years (QALYs)	Yes	As per NICE reference case partially. Utility decrements applied to published utility values lacked justification.
Source of data for measurement HRQoL	Described using a standardised and validated instrument	Yes	The EQ-5D-3L and HUI utility values are derived from the literature, expert opinion and decrements are applied to some health state specific utility values.
Source of preference data for valuation of changes in HRQoL	Visual analogue scale (VAS), and time-trade off (TTO)	Partly	The UK TTO valuations have been used as a default for the EQ-5D-3L questionnaire and VAS/SG from a sample of Canadian parents for the HUI questionnaire.
Discount rate	An annual rate of 3.5% on both costs and health effects	Yes	As per NICE reference case
Equity weighting	An additional QALY has the same weight regardless of the other characteristics of the individuals receiving the health benefit	Yes	As per NICE reference case
Sensitivity analysis	Probabilistic modelling	Yes	As per NICE reference case

EQ-5D-3L = European Quality of Life-5 Dimensions, 3 Levels; HRQoL = health-related quality of life; NHS = National Health Service; HUI = health Utility index; NICE = National Institute for Health and Clinical Excellence; PSA = probabilistic sensitivity analysis; quality-adjusted life years; PSS = Personal Social Services; QALY = quality-adjusted life year; TTO = Time trade off; UDCA = ursodeoxycholic acid; UK = United Kingdom; VAS = visual analogue scale

5.2.2 Model structure

The company developed a Markov state transition model to describe the progression of PBC over a lifetime horizon.[3] The model comprises two parts with a total of 10 health states. In the first part, the model captures the biomarker component based on the surrogate outcomes of alkaline phosphatase (ALP) and bilirubin biomarkers in three different health states based on the expected risk of disease progression: low risk (ALP ≤ 1.67 * upper limit of normal; ULN); moderate risk (ALP > 1.67 * ULN and total bilirubin; TB ≤ 1.0 * ULN) and severe risk (TB > 1.0 * ULN or compensated cirrhosis; CC). The latter health state combined both patients with compensated cirrhosis (CC) and those with abnormal and rising TB. The company acknowledged that CC preceded decompensated cirrhosis (DCC) but that data to confirm if patients with PBC had CC were sparse. In clinical practice, the histological status of PBC patients is rarely documented, and hence the risk of patients moving from CC to DCC is unknown. Moreover, in response to a request for further clarification,[54] the company argued that progression to DCC can occur without the fibrosis that typically characterises CC:

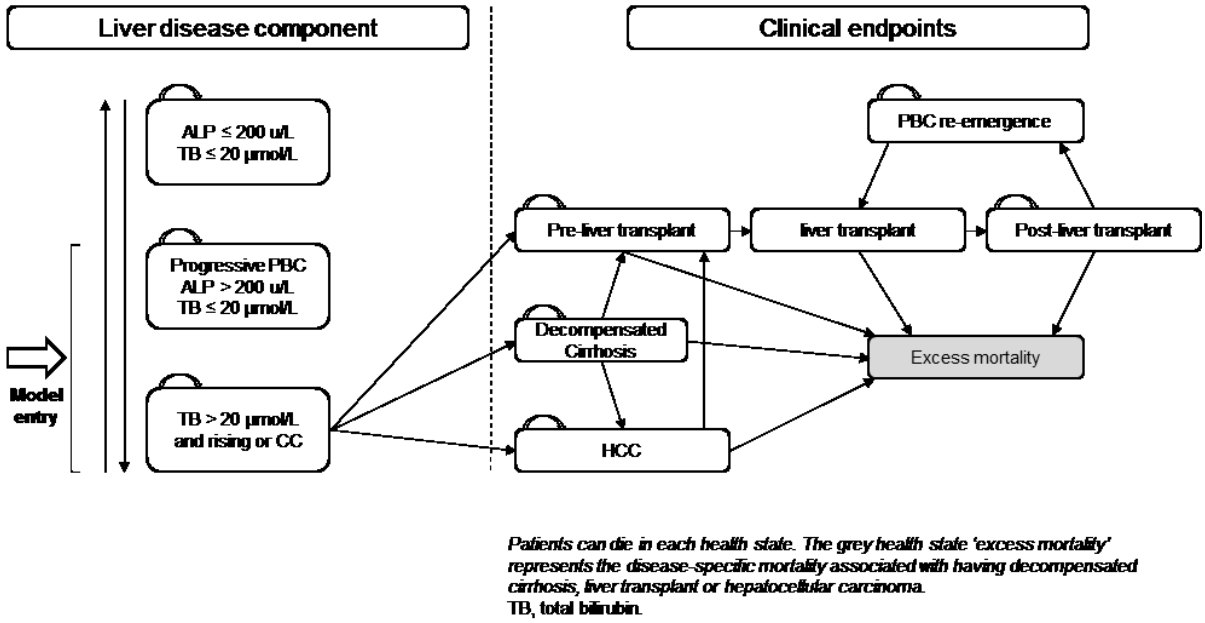
'PBC is a condition driven by progressive loss of bile ducts (ductopenia) leading to mechanical failure in the transport of bile from the liver (cholestasis), which then leads to the death (or senescence) of biliary epithelial cells. The condition is functionally different from other liver conditions such as HepC. As a result, fibrosis in itself is not considered to be the key clinical measure – whilst it is present in the later stages of the condition, the underlying ductopenia means that fibrosis progression is not a good measure of severity or response to treatment.'

The company therefore combined CC and abnormal bilirubin in one health state to reflect that patients with abnormal TB, as those with CC, were documented to exhibit higher mortality or undergo liver transplant. CC and abnormal bilirubin were thus assumed to be equivalent health states. In the first year, patients on OCA treatment can move from low, to moderate, to severe, and vice versa in the biomarker component. Patients in the comparator arm can only progress from low or moderate risk to the severe risk health state directly in the first year.

In the second part of the model, here called the liver disease component, the following clinical endpoints are modelled: pre-liver transplant; DCC; HCC; liver transplant; a post-liver transplant state; potential PBC re-emergence; and death. Patients can move to the liver disease component of the model only coming from the severe risk health state in the biomarker component. Patients can move to pre-liver transplant or HCC directly, or they can move to DCC first and from there to pre-liver transplant or HCC. From HCC they can also move on to pre-liver transplant. After liver transplant, patients move to the post-liver transplant health state, from which PBC can re-emerge. The model structure is shown in Figure 5.1.

Costs and health-related utilities associated with each health state were calculated per cycle. Relevant adverse events identified by the company were fatigue, pruritus and nausea, but costs were only modelled in relation to pruritus, and the impact on health-related quality of life (HRQoL) was not modelled. A three months cycle length was used. The model was programmed in Excel.[55]

Figure 5.1: Model structure



Source: CS Figure 24[3]

ERG comment:

The biomarker component

The biomarker component of the model is unique to the present decision problem and the condition. There are a number of areas of uncertainty that the ERG is concerned about:

1. The aggregation of two different health states into one (CC and abnormal TB count) to form the severe risk state could be problematic, as the transition probability (TP) to the DCC state may refer to CC patients only. The company claimed in the response to the clarification letter that all TPs leading to and coming out of this combined health state were estimated based on data on elevated and rising bilirubin levels. The ERG consulted with a clinical expert who stated that the aggregation of these two health states was reasonable in PBC patients because elevated bilirubin is deemed the best short term predictor of adverse outcomes in PBC. The clinical expert stated that a caveat was the assumption that the elevated bilirubin was not due to other causes (Gilberts disease primarily) but considered this a minor confounder with no significant impact on the model. The ERG concludes that, while it appears reasonable to group elevated and rising bilirubin and CC in one health state in PBC, there remains significant uncertainty surrounding the TP with which patients transition from the severe risk health state to the DCC health state.
2. Patients receiving OCA treatment and who are in the low and moderate risk biomarker component health states at the end of the first year are assumed to remain there for the remainder of their lives. The company claims that this is consistent with experience with patients responding to UDCA treatment. The ERG consulted a clinical expert who backed the company's claim, stating that patients with a response to UDCA and normal (or below 1.67x ULN ALP) have an excellent long term prognosis with no overall impact on life expectancy. The ERG remains concerned that 1) the long term prognosis for OCA responders may not be equivalent to that of UDCA responders, and that 2) even if there is only a very small proportion of patients that lose response, this may have an effect on model outcomes. The ERG therefore performed exploratory analyses relaxing this assumption.

3. The assumption that patients in the comparator arm can only transit from the low risk health state to the severe risk health state directly, without the possibility of moving to the moderate risk health state, may lack plausibility because patients in the low risk state are not treated with OCA and there should therefore be no difference between the TPs in both treatment arms. The company, in response to the clarification letter,[32] however, claimed that this assumption was made to account for the fact that in POISE, patients not receiving OCA had similar ALP levels over the duration of the 12 month study period but had increasing bilirubin levels, thus worsening their risk of end-stage liver disease, liver transplant, or death. The ERG considers that the same TP should be applied to patients moving from low to moderate or severe risk for consistency between OCA and the comparator arm. When using the company's assumption of none of the patients starting in a low risk health state, this assumption has no impact on the model outcomes.

The liver disease component

The model structure for this component is similar to other assessments of liver disease treatments and the ERG is satisfied that it is appropriate for the current decision problem. According to the company, the use of a Markov structure for the liver disease component of the model was consistent with other approaches to modelling liver diseases. However, the company's model diverges from those used in other liver diseases in that an additional pre-liver transplant health state was introduced (compared to, for instance, Technology Appraisal (TA) 330,[56] in which this state does not exist). No justification was provided for the introduction of the pre-liver transplant health state and it does not appear to be typically considered in other liver disease models. While the ERG acknowledges that the introduction of the pre-liver transplant health state has face validity as being a waiting list state with its own costs associated with it, the ERG is concerned that it groups patients together that came from different health states (HCC, DCC, severe risk) and who therefore may experience different health-related quality of life. The ERG therefore uses the liver disease component model structure and transition probabilities from TA 330 in its base-case.[56] The ERG furthermore notes that in the model, it is possible for patients to move from the post-liver transplant state back to the liver transplant state, without going through PBC re-emergence. This is inconsistent with the company's model structure in Figure 5.1 and no justification was provided for this.

5.2.3 Population

The economic evaluation considers patients with PBC who are intolerant to or have inadequate response to treatment with UDCA. Only moderate and severe patients based on ALP and TB levels, at model entry, were deemed eligible to receive OCA treatment in the model. This is in line with the final scope issued by NICE for this appraisal and is also in line with the study population of the pivotal POISE study. Patients enter the model in the moderate (76.85%) and severe risk (23.15%) health states in the biomarker component of the model, according to ALP and bilirubin levels. These proportions of patients starting the model were not justified and apparently not in line with the distribution of patients in the POISE study: the distribution there was 91.58% in the moderate and 8.42% in the severe risk health state, based on Table 49 in the CS for the OCA titration arm,[3] the company's model for the OCA treatment arm[3] and the second clarification excel file for the UDCA arm and OCA arms.[32]

ERG comment: The population represented in the cost effectiveness model corresponds to the expected licensed indication and the final scope issued by NICE for the current decision problem. However, the ERG considers that the proportions of patients entering the model in the moderate and severe risk health states should be based on data from POISE, and, although the company claims that the used proportions are derived from POISE, it is not clear how this was done. In the company's model, the proportion of patients entering the model in the severe risk health state is much larger than the

proportion of patients entering the POISE study in the severe risk health state (23.15% in the company's model compared to 8.42%). This leads to more patients remaining in the severe risk health state and moving to more severe disease (i.e. the liver disease component in the model). This in turn would potentially bias model outcomes in favour of OCA or OCA titration treatment. The ERG therefore uses the proportions of patients starting in the moderate and severe health states derived from the POISE OCA, OCA titration and UDCA treatment arms, as described above.

5.2.4 Interventions and comparators

The interventions and comparators in this model depend on the selected population. For UDCA-intolerant patients, the intervention considered in this economic evaluation is OCA dose titration based on a starting dose of 5 mg taken orally, once daily, which may be increased to 10 mg once daily based on the assessment of tolerability after six months, to achieve optimal response (as was done in the titration arm of the POISE study); and the comparator is no treatment. For UDCA inadequate responders, the intervention is OCA dose titration as per above in combination with UDCA; and the comparator is UDCA monotherapy. Only patients in the moderate and severe risk categories were deemed eligible to receive OCA. UDCA doses implemented in the model were in line with its UK marketing authorisation, which are also the same as in the POISE trial. Fibrates were not considered as a comparator in the CS because fibrates are not licensed in the UK, nor are they standard of care, and they are contraindicated in PBC. According to the company, they are rarely used, with only [redacted] of patients in the UK-PBC cohort ever having taken fibrates for any condition (not necessarily for PBC).[3] See Section 3.3 for more details.

ERG comment: Despite the low patient numbers that would have been treated with fibrates and the lack of evidence on fibrates, the decision to exclude fibrates as a comparator is inconsistent with the scope and may not be appropriate. See Section 3.3 for more details. The ERG also notes that there is an ongoing study on PBC patients treated with fibrates and that treatment with fibrates may present a viable comparator in the future.

5.2.5 Perspective, time horizon and discounting

The analysis was conducted from the perspective of the payer, i.e. the NHS England and Wales, over a time horizon of 50 years. Costs and outcomes were discounted by 3.5%.

ERG comment: This is in line with the NICE reference case.

5.2.6 Treatment effectiveness and extrapolation

Data from the POISE trial and various literature sources were used to estimate TPs between the health states in the biomarker component of the model (based on surrogate markers, i.e. ALP and bilirubin levels). The literature was used to estimate and extrapolate TPs for the health states in the liver disease component of the model.

Treatment effectiveness for health states in the biomarker component

Mortality in the biomarker component of the model was assumed to be equal to background mortality (National Life Tables, United Kingdom, 2012-2014; Office for National Statistics).[57] In addition, treatment discontinuation was assumed to only occur within the first three months of treatment. The company claimed that it was not possible to model treatment discontinuation beyond the first three months. Moreover, for discontinued patients, the TPs for UDCA or no treatment were assumed (independently of initial treatment) for UDCA non-responders and UDCA intolerant patients respectively.

Obeticholic acid with and without UDCA for inadequate UDCA responders and UDCA intolerant patients, respectively

For OCA, the transition probabilities during the first year between the biomarker component health states as well as treatment discontinuation (not shown in model structure Figure in CS; Figure 5.1) were based on the POISE trial (see Table 5.3). Here the company assumed that patients would only discontinue during the first three months of treatment given that the exact time of discontinuation in the POISE trial is unknown.

Given the low number of patients who received OCA monotherapy, the same transition matrices were used for the OCA titration regimen with or without UDCA (i.e. to UDCA tolerant and intolerant patients). The company states that this is reasonable as 'in clinical practice, OCA patients would be expected to have lower TPs to the more severe disease states'.

The company assumed no progression from low-risk or moderate risk to severe-risk after the first year. This assumption was, according to the company, justified based on the low decompensation rate observed in UDCA responders presented by Harms et al. (2015) in the PBC subgroup.[58] This study (details obtained from an oral presentation) included a total of 3,030 patients, of which 2,938 were UDCA-treated and showed that the risk of developing DCC was greater in UDCA non-responders (15-year risk of ~32%) than in UDCA responders (15-year risk of ~9%) (CS Figure 27).[3]

Table 5.3: Transitions between health states of the biomarker component – OCA titration

		0-3 months (N=68)			
		To			
		Low-risk	Moderate risk	Severe risk	Discontinuation
From	Low-risk	[redacted]	[redacted]	[redacted]	[redacted]
	Moderate risk	[redacted]	[redacted]	[redacted]	[redacted]
	Severe risk	[redacted]	[redacted]	[redacted]	[redacted]
		3-6 months (N=68)			
		To			
		Low-risk	Moderate risk	Severe risk	Discontinuation
From	Low-risk	[redacted]	[redacted]	[redacted]	NA
	Moderate risk	[redacted]	[redacted]	[redacted]	NA
	Severe risk	[redacted]	[redacted]	[redacted]	NA
		6-9 months (N=68)			
		To			
		Low-risk	Moderate risk	Severe risk	Discontinuation
From	Low-risk	[redacted]	[redacted]	[redacted]	NA
	Moderate risk	[redacted]	[redacted]	[redacted]	NA
	Severe risk	[redacted]	[redacted]	[redacted]	NA
		9-12 months (N=68)			
		To			
		Low-risk	Moderate risk	Severe risk	Discontinuation
From	Low-risk	[redacted]	[redacted]	[redacted]	NA
	Moderate risk	[redacted]	[redacted]	[redacted]	NA
	Severe risk	[redacted]	[redacted]	[redacted]	NA

		12 months+ (assumption)			
		To			
		Low-risk	Moderate risk	Severe risk	Discontinuation
From	Low-risk	1.000	0.000	0.000	NA
	Moderate risk	0.000	1.000	0.000	NA
	Severe risk	0.000	0.000	1.000	NA

Source: CS Table 49[3]
Footnote: Note that low risk corresponds to ALP ≤ 200 u/lL and TB ≤ 20 µmol/l; moderate risk corresponds to ALP > 200 u/L and TB ≤ 20 µmol/l and; severe risk corresponds to TB > 20 µmol/l
NA, not applicable

UDCA alone and no treatment for inadequate UDCA responders and UDCA intolerant patient respectively

For UDCA inadequate responders, the company did not estimate TPs using POISE trial data but opted instead for calibrating TPs (Table 5.4) based on PBC specific data from the literature considering 10 year liver transplant-free survival estimated using GLOBE and UK risk scores.[59] The justification for using a calibration approach was that transition probabilities were not available from POISE for all health states nor over the full time horizon of the model. The company did not provide a detailed account of their calibration method in the CS. In the response to the clarification letter,[32] the company provided more detail and an Excel spreadsheet used for the calibration, which was done in four steps: The company calibrated 1) the transition from DCC to the pre-liver transplant health state and liver-related death; 2) transitions from the severe risk health state to the liver disease component health states; 3) transitions from the moderate risk health state to the severe risk health state and other liver disease component states and; 4) transitions from the low risk health state to the severe risk health state and other liver disease component states. There is little detail on the methods, the estimates used and the sources of data.

Given the limited number of patients not on UDCA (i.e. patients receiving no treatment), there is a lack of evidence on the natural history of PBC without active treatment since the launch of UDCA. Therefore, to reflect the progression of patients who did not receive any active treatment, the company made assumptions based on Corpechot et al. 2000,[60] who assessed the effect of UDCA therapy on liver fibrosis progression compared with no treatment in PBC patients (see Table 5.4).

Table 5.4: Transitions between health states of the biomarker component – UDCA alone

		UDCA alone (for UDCA inadequate responders)			
		To			
		Low-risk	Moderate risk	Severe risk	Discontinuation
From	Low-risk	NA[a]	NA[a]	NA[a]	NA
	Moderate risk	0.000	0.969	0.031	NA
	Severe risk	0.000	0.000	1.00	NA
		No treatment (for UDCA-intolerant patients)			
		To			
		Low-risk	Moderate risk	Severe risk	Discontinuation
From	Low-risk	NA[a]	NA[a]	NA[a]	NA
	Moderate risk	0.000	0.932	0.068	NA
	Severe risk	0.000	0.000	1.000	NA

Source: CS Tables 50, 52 and 53[3]
Footnote: [a]No patients will transit to (or start in) the low-risk health state, hence these transition probabilities are not applicable.
Note that low risk corresponds to ALP ≤ 200 u/l and TB ≤ 20 µmol/l; moderate risk corresponds to ALP > 200 u/l and TB ≤ 20 µmol/l and; severe risk corresponds to TB > 20 µmol/l
NA, not applicable (or not reported in the CS)

ERG comment: The ERG's concerns regarding the estimation of treatment effectiveness for health states in the biomarker component are: 1) the usage of unclear calibration methods based on the literature instead of the POISE trial for the non-OCA regimen; 2) not exploring different ALP and TB thresholds for defining the health states; 3) assumption of no additional progression from low-risk or moderate risk to severe-risk after the first year in patients receiving OCA as well as no additional treatment discontinuation after the first year and; 4) discrepancy between the TPs reported in CS Table 49 and those used in the economic model.[55]

Regarding the first 12 months in the model, the ERG considers the rationale provided by the company for not using the data from the POISE trial to estimate treatment effectiveness for the patients receiving UDCA only or no treatment as insufficient and inconsistent. The lack of long-term data in the POISE trial is not only an issue for the UDCA arm but as much so for the OCA treatment arm. The ERG thinks that very strong arguments must be present to neglect randomised evidence of comparative effectiveness in favour of observational evidence. Randomisation renders groups comparable not only in respect of known prognostic factors, but also with regard to unknown factors; hence observed differences in outcomes can be attributed to the treatment. The company did not however provide a justification for using the literature instead of the POISE patient-level data for modelling the effectiveness of UDCA and no treatment. Therefore, the ERG requested an analysis using the data from the POISE trial for UDCA and no treatment.[30] The company provided this analysis after further requests (post-clarification letter response). The ERG adopted this analysis in the ERG base-case (i.e. the POISE trial). See Table 5.5 for the TPs (assuming equal TPs for the UDCA and no treatment between the biomarker health states, as is done for the OCA regimen).

Considering the TPs after 12 months, the methods used by the company to estimate treatment effectiveness for the patients receiving UDCA only and no treatment are lacking transparency and justification (i.e. the calibration process described in CS Appendix 10 and in response to clarification question B14, as well as the estimation process described in response to clarification question B15). The additional Excel file provided by the company did not provide the necessary clarity as the values of interest are hard copied into the cells without the formulae to derive these. Moreover, the exact 10 year liver transplant-free survival used to calibrate the TPs is unclear to the ERG (in response to clarification question B14, the company mentions multiple probabilities; 10%, 78% and 91% without appropriate referencing). The methods and data used are poorly documented: the principal references are abstracts to posters without any data available. Furthermore, the company does not use the POISE comparator data where it is available for the start of the calibration process: instead of calibrating the POISE patient proportions with abnormal TB after one year of follow-up (10% in the UDCA and OCA treatment arms, and 6% in the OCA titration arm) on the 10 year liver transplant free survival (LTFS) data, the company uses patient proportions from another study, without justification.[11] Upon checking the reference, it does not appear that these patient proportions were available from the publication, but two year follow-up data suggest that 21% of patients had abnormal TB in that study. It is therefore unclear what estimate the company derived from this study and why evidence from the POISE study was not used. Without the necessary data and detailed description of methods that would have allowed verifying the methods and data used by the company for the long-term extrapolation, the ERG attempted to verify outcomes by cross-checking the model prediction with long-term survival in PBC patients

based on Lammers et al. 2015.[61] The ERG notes a relatively poor match between the number of deaths predicted by the company's model with the 10 year LTFS study[61]18.7% of tolerant patients in the UDCA treatment arm would have died after 7.8 years in the former, while 14.8% of patients were reported to have died at 7.8 years of follow-up in the latter. The ERG agrees in principle with the approach to calibrate the TPs based on external sources in this specific case where there is lack of long-term evidence. However, according to the ERG the company has failed to provide proper justification for their calibration method, to demonstrate that it is conducted correctly and that it results in plausible TPs. Therefore, with the exception of the TPs in the biomarker component that could be based on reported POISE trial results (i.e. for the first 12 months), the calibrated TPs are maintained in the ERG base-case although the ERG considers the approach a 'black box'. To show the impact of alternative assumptions, exploratory scenario analyses are provided by the ERG (this includes using TPs from TA330 in the liver component of the model).

Table 5.5: Transitions between health states of the biomarker component – non-OCA regimen

		0-3 months (N=68) - inadequate UDCA responders			
		To			
		Low-risk	Moderate risk	Severe risk	Discontinuation
From	Low-risk	[redacted]	[redacted]	[redacted]	[redacted]
	Moderate risk	[redacted]	[redacted]	[redacted]	[redacted]
	Severe risk	[redacted]	[redacted]	[redacted]	[redacted]
		0-3 months (N=68) - UDCA intolerant patients			
		To			
		Low-risk	Moderate risk	Severe risk	Discontinuation
From	Low-risk	[redacted]	[redacted]	[redacted]	NA
	Moderate risk	[redacted]	[redacted]	[redacted]	NA
	Severe risk	[redacted]	[redacted]	[redacted]	NA
		3-6 months (N=68) - equal for both comparators			
		To			
		Low-risk	Moderate risk	Severe risk	Discontinuation
From	Low-risk	[redacted]	[redacted]	[redacted]	NA
	Moderate risk	[redacted]	[redacted]	[redacted]	NA
	Severe risk	[redacted]	[redacted]	[redacted]	NA
		6-9 months (N=69) - equal for both comparators			
		To			
		Low-risk	Moderate risk	Severe risk	Discontinuation
From	Low-risk	[redacted]	[redacted]	[redacted]	NA
	Moderate risk	[redacted]	[redacted]	[redacted]	NA
	Severe risk	[redacted]	[redacted]	[redacted]	NA
		9-12 months (N=69) - equal for both comparators			
		To			
		Low-risk	Moderate risk	Severe risk	Discontinuation
From	Low-risk	[redacted]	[redacted]	[redacted]	NA
	Moderate risk	[redacted]	[redacted]	[redacted]	NA

	Severe risk	[redacted]	[redacted]	[redacted]	NA
		12 months+ - inadequate UDCA responders based on calibration			
		To			
		Low-risk	Moderate risk	Severe risk	Discontinuation
From	Low-risk	[redacted]	[redacted]	[redacted]	NA
	Moderate risk	[redacted]	[redacted]	[redacted]	NA
	Severe risk	[redacted]	[redacted]	[redacted]	NA
		12 months+ - UDCA intolerant patients based on calibration			
		To			
		Low-risk	Moderate risk	Severe risk	Discontinuation
From	Low-risk	[redacted]	[redacted]	[redacted]	NA
	Moderate risk	[redacted]	[redacted]	[redacted]	NA
	Severe risk	[redacted]	[redacted]	[redacted]	NA

Source: CS Table 49 and economic model submitted by the company[55]
Footnote: Note that low risk corresponds to ALP ≤ 200 u/l and TB ≤ 20 µmol/l; moderate risk corresponds to ALP > 200 u/l and TB ≤ 20 µmol/l and; severe risk corresponds to TB > 20 µmol/l
NA, not applicable

The company did not explore the impact of different thresholds for ALP and TB on the estimated cost effectiveness. It is unclear to the ERG what the impact would be of using different ALP and TB thresholds to define the health states in the biomarker component of the model.

For the OCA regimen, the justification for no additional progression from low-risk or moderate risk to severe-risk after the first year is questionable. Although the progression to DCC is higher for UDCA non-responders than for UDCA responders (which is the justification provided by the company), in both groups there is progression to DCC so assuming no progression (fixed, with life long duration) might not be justified by these data. Moreover, this is observed in UDCA responders treated with UDCA, hence it might be questioned whether this would also be applicable to PBC patients who were intolerant to or had inadequate response to treatment with UDCA and are now treated with OCA. In fact, it could be argued that POISE captures patients at varying stages of their disease. The TPs shown in Table 5.5 suggest that patients continue to move between health states even at 9-12 months. This is not surprising given that patients in the POISE trial had the condition for an average of eight years at the time they were enrolled in the trial and given that their treatment would not have changed. The ERG therefore considers there to be no strong justification to assume patients stop moving between the biomarker states after one year. Nevertheless, the clinical expert consulted by the ERG stated that this assumption was reasonable given that 'we know that patients with a response to UDCA and normal (or below 1.67x ULN) ALP have an excellent long term prognosis with no overall impact on life expectancy'. For OCA, the ERG therefore considers the possibility of patients continuing to move between the biomarker states as observed in the POISE study beyond the initial 12 months in an exploratory analysis (based on the abovementioned 15-year risk of DCC of ~9%). Similarly, the ERG also considers that the assumption of no treatment discontinuation after 12 months is questionable. Moreover, it is unclear how the company calculated/retrieved the proportion (e.g. the [redacted] reported in Table 5.3) of discontinued patients and why this was only considered in the first three months of the model. This is not appropriately justified. However, the company stated that the impact of treatment discontinuation is expected to be minor (see company response to clarification question B12f).

Finally, the ERG noticed that there was a discrepancy between the TPs reported in CS Table 49 and those used in the economic model. The adjusted TPs used in the economic model correspond to CS Table 49 (i.e. Table 5.3 above).

Treatment effectiveness for health states in the liver disease component

The TPs for the liver disease component of the model were equal for all comparators and mainly based on the literature (see Table 5.6). The company argued that it used the model structure from TA330[62] to be consistent with other approaches for modelling the liver disease component. The company also refers to TA330[62] for multiple TPs. These TPs are derived from patients with HCV. Only the TP from DCC to HCC was based on PBC patients.[63] The same calibration (described above for TPs for UDCA and no treatment in the biomarker component) was used for TPs from severe risk in the biomarker component to DCC, HCC and pre-LT, and DCC to pre-LT and death. This calibration aimed to reflect the 10-year liver transplant-free survival estimated based on POISE patient-level data using GLOBE and UK risk scores. No justification was provided by the company for the sources or methods used to derive these TPs.

Table 5.6: Transitions between health states of the liver disease component

From:	To:	Probability	Time (years)	Quarterly probability	Source
Severe risk	DCC	0.10	1	0.0260	Calibrated (CS Appendix 10)
	HCC	0.01	1	0.0035	Assumption
	Pre-LT	0.04	1	0.0102	Calibrated (CS Appendix 10)
DCC	Pre-LT	0.06	1	0.0153	Calibrated (CS Appendix 10)
	Death	0.17	1	0.0398	Calibrated (CS Appendix 10)
	HCC	0.01	1	0.0035	Trivedi et al. 2006[63]
HCC	Pre-LT	0.04	1	0.0102	Wright et al. 2006[64]
	Death	0.43	1	0.1311	Wright et al. 2006 [64]
Pre-LT	LT	0.35	1	0.1021	Kim et al. 2016[65]
	Death	0.09	1	0.0233	Kim et al. 2016[65]
LT	Death	0.21	1	0.0572	Wright et al. 2006[64]
Post-LT	PBC recurrence	0.23	10	0.0064	Lindor, 2009[66]
	Death	0.06	1	0.0146	Wright et al. 2006[64]
	LT	0.01	13	0.0001	Neuberger, 2003[67]
PBC recurrence	LT	0.01	13	0.0001	Assumption

Source: CS Tables 50, 52 and 54[3]
CC, compensated cirrhosis; CS, company submission; DCC, decompensated cirrhosis; HCC, hepatocellular carcinoma; LT, liver transplant; PBC, primary biliary cholangitis/cirrhosis; TB, total bilirubin

ERG comment: The ERG generally agrees with the approach used in TA330[62]for modelling liver disease in patients with HCV.[62] It should be noted that neither the model structure of the liver disease component (see Section 5.2.2) nor the TPs of the liver disease component, used in the CS, are fully

consistent with TA330.[62] The company did not provide any justifications for the sources that were used (if not based on the calibration approach). Moreover, for the TP from severe risk and DCC, the abovementioned ERG comments regarding the calibration also apply for the TPs in the liver disease component of the model. Therefore, the ERG used TPs consistent with TA330[62] in an exploratory analysis (Table 5.7). This also entailed excluding the pre liver transplant state as discussed in Section 5.2.2. The only exception is the transition from DCC to HCC; this was based on the source provided by the company[63] instead of the source that was used in TA330[62] (that is based on a study by Cardoso et al[68] based on hepatitis C (HBC) patients) as the source provided by the company was based on PBC patients.

Table 5.7: Transitions between health states of the liver disease component based on TA330

From:	To:	Quarterly probability CS	Quarterly probability ERG exploratory scenario	ERG source
Severe risk	DCC	**0.0260**	**0.0104**	Cardoso[68]
	HCC	0.0035	0.0035	Assumption
	Pre-LT	**0.0102**	**NA**	
DCC	Pre-LT	**0.0153**	**NA**	
	Death	**0.0398**	**0.0663**[b]	Riemsma et al. 2016[56c]
	HCC	0.0035	0.0035	Trivedi et al..2009[63]
	LT	**NA**	**0.0055**	Siebert et al. 2005[69]
HCC	Pre-LT	**0.0102**	**NA**	
	Death	0.1311	0.1311	Fattovich et al. 1997[70] Shepherd et al. 2007[71]
	LT	NA	NA[a]	
Pre-LT	LT	**0.1021**	**NA**	
	Death	**0.0233**	**NA**	
LT	Death	0.0572	0.0572	Fattovich et al. 1997[70] Shepherd[71]
Post-LT	PBC recurrence	0.0064	0.0064	Lindor[66]
	Death	0.0146	0.0146	Fattovich et al. 1997[70] Shepherd et al. 2007[71]
	LT	0.0001	0.0001[b]	Neuberger, 2003[67]
PBC recurrence	LT	0.0001	0.0001	Assumption

Footnotes: Note that the discrepant transitions are printed in **bold**.
[a]No transition was assumed between HCC and LT in TA330[62]
[b]The ERG was unable to reproduce this number from the original source / the source provided by the company.

From:	To:	Quarterly probability CS	Quarterly probability ERG exploratory scenario	ERG source
[c]Original citation in the CS[62] and ERG report of TA330[56] was: 'Cheung M, Foster G, Irving W, Walker A, Hudson B, Verma S. Antiviral treatment in patients with advanced HCV cirrhosis using sofosbuvir and ledipasvir/ daclatasvir, with or without ribavirin – outcomes compared to untreated patients and long term outcomes. Presented at the European Association for the Study of the Liver (EASL); Barcelona. 13-17 April 2016; Barcelona, Spain [PowerPoint Presentation].'				
CC, compensated cirrhosis; DCC, decompensated cirrhosis; HCC, hepatocellular carcinoma; LT, liver transplant; NA, not applicable; PBC, primary biliary cholangitis/cirrhosis TB, total bilirubin				

5.2.7 Adverse events

The most commonly reported treatment-emergent adverse events in the POISE trial were pruritus followed by fatigue and nausea (Table 5.8). The company did not explicitly model the impact of these adverse events on health-related quality of life, as it was assumed by the company that their impact is captured as part of the health state utility values. Only the adverse event cost of pruritus were considered, because, according to the company, this is treated in routine clinical practice.

Table 5.8: Incidence of AE

	Fatigue	Pruritus	Nausea
No treatment	0.0000	0.0000	0.0000
UDCA	0.1096	0.3699	0.0548
OCA Titration	0.0857	0.5000	0.0429
Source: economic model submitted by the company[55]			

ERG comment: The economic impact of pruritus only was considered in the company's cost effectiveness model. The differential impact of adverse events on health-related quality of life was not considered by the company. This is not in line with best modelling practices. In the clarification letter (question B19), the ERG requested that the company incorporate the differential impact of adverse events on health-related quality of life. However, the company did not provide these analyses and stated that the impact of this scenario would be negligible. The company did not support this statement with a scenario analysis wherein the differential impact of adverse events on health-related quality of life was incorporated. Hence, the impact of this assumption on the cost effectiveness remains uncertain.

5.2.8 Health-related quality of life

HRQoL evidence was not collected through a generic preference elicitation instrument in the POISE trial[45] and was therefore obtained from the literature.

Results of the literature review of HRQoL evidence

The company performed a systematic literature review to identify relevant HRQoL evidence for the current decision problem. Five studies were identified after abstract and full text screening (Figure 28 of the CS).[50, 64, 72-74] Table 5.9 provides an overview of the included studies. A description of the search strategy is provided in Section 5.1.1.

Table 5.9: Included HRQoL studies

Study, Country	Population	Study type	Metric	Result
Aberg et al. 2012[72]	72 PBC patients following liver transplant Sub-group of wider population	Observational	15D instrument	Utility value for entire PBC population following liver transplant: 0.882 Result found to be consistent regardless of aetiology
Bondini et al. 2007[73]	18 PBC patients	Observational	Chronic Liver Disease Questionnaire (CLDQ) SF-36 Health Utility Index (HUI Mark-2 and Mark-3)	18 patients in PBC group led to limited analysis in this population SF-36, CLDQ and HUI values reported HUI utility value reported as 0.81 (SD=0.1) in PBC population
Longworth et al. 2003[50]	122 PBC patients assessed for transplantation and followed up for a maximum of 24 months post-surgery	Observational	EQ-5D	Full results reported in Table 57 of the CS[3]
Wright et al. 2006[64]	204 chronic mild hepatitis C patients	Observational	EQ-5D	HRQoL results reported in Table 58 of the CS[3]
Younossi et al. 2001[74]	120 patients with chronic liver disease, with 30% of patients suffering chronic cholestatic liver disease, including PBC and PSC patients	Observational	SF-36 CLDQ HUI	The study reported an HUI utility value of 0.84 ± 0.15 for patients with cholestatic liver disease.

Source: Table 60 of the CS[3]

CLDQ, chronic liver disease questionnaire; EQ-5D, EuroQOL-5 dimensions, HRQoL, health-related quality of life; HUI, health utility index; PBC, primary biliary cholangitis/cirrhosis; PSC, primary sclerosing cholangitis; SF-36, short form-36 dimensions.

HRQoL evidence used in the cost effectiveness model

In the company's cost effectiveness model, health state utility values have been obtained from the literature. Younossi et al. 2001[74] report utility values for patients having chronic liver disease due to viral infection(e.g. hepatitis B/C patients (HBV/HCV), cholestatic liver disease (i.e. PBC and primary sclerosing cholangitis patients) or other causes. Thirty-five patients with cholestatic disease were included in that study which provided the utility values for the low risk and moderate risk health states from the biomarker component of the model. No justification supported the use of this source in the CS. Wright et al. 2006[64] report utility values for chronic liver disease health states in hepatitis C patients, and was used for the remaining health states in the model (consistent with TA330[62]). Moreover, a [redacted] decrement was applied to the health state utility values found in the literature for all health states of the model, except for the three PBC health states and the HCC health state (Table 5.10). This decrement was based on expert opinion. In the CS it was stated that experts agreed that *'it is inappropriate to use [hepatitis C and B] HCV/HBV-specific utility values, since PBC patients are likely to have worse utility values despite being in the same health state'*.[3] No further details were provided regarding the identification of experts and the estimation of the [redacted] decrement.

Table 5.10: Health state utility values used in the company's cost effectiveness model

State	Utility value	Primary source[#]
Low risk[a]	0.84	Younossi et al. 2001[74, 75]
Moderate risk[b]	0.84	Younossi et al. 2001[74]
Severe risk[c]	0.55	Wright et al. 2006[64]
Decompensated cirrhosis	[redacted]	Wright et al. 2006[64]
Hepatocellular carcinoma	0.45	Wright et al. 2006[64]
Pre-transplant: utility at listing	[redacted]	Wright et al. 2006[64]
Pre-transplant: 3 months after listing	[redacted]	Wright et al. 2006[64]
Pre-transplant: 6 months after listing	[redacted]	Wright et al. 2006[64]
Liver transplant: 3 months post-transplant	[redacted]	Wright et al. 2006[64]
Liver transplant: 6 months post-transplant	[redacted]	Wright et al. 2006[64]
Liver transplant: 12 months post-transplant	[redacted]	Wright et al. 2006[64]
Liver transplant: 24 months post-transplant	[redacted]	Wright et al. 2006[64]
Re-emergence of PBC	[redacted][d]	Wright et al. 2006[64]

Source: Table 61 of the CS[3]

[a] referred as 'ALP: ≤ 200 u/L and Bili: Normal' in the CS[3]

[b] referred as 'ALP: > 200 u/L and Bili: Normal' in the CS[3]

[c] referred as 'Bili: Abnormal and rising, or CC' in the CS[3]

[d] Assumed equivalent to liver transplant 24 months post-transplant, without [redacted] utility decrement provided according expert opinion feedback

[#] Wright et al. 2006[64] is referred as TA 330 in the CS[3]

[redacted] expert opinion [redacted].

ALP, alkaline phosphatase; Bili, bilirubin; CC, compensated cirrhosis; CS, company submission; PBC, primary biliary cholangitis/cirrhosis

Impact of adverse events on HRQoL

The most frequent adverse events (AEs) were pruritus, fatigue and nausea. Their impact on HRQoL was not explicitly modelled in the company's cost effectiveness model because, according to the company, the impact was captured in the health state utility values.

ERG comment: The ERG's main concerns around HRQoL estimates are the appropriateness of Younossi et al. 2001[74] to inform the health state utility values for the low and moderate risk health states in the biomarker component, the validity of the [redacted] utility decrement applied to the health state utility values found in the literature for all health states in the liver component of the model, except for the HCC health state, and the omission of including AEs impact on HRQoL.

The ERG asked for justification of the use of Younossi et al. 2001[74] to inform the utility values for the low and moderate risk health states in the biomarker component of the model. In its response to Clarification Question B18b, the company explained that this was the only study reporting utility data for PBC patients.[32] However, the ERG notes that this estimate is based on 35 patients who have either PBC or primary sclerosing cholangitis and that the study does not provide information on the number of PBC patients, PBC patients' demographic characteristics, treatment and treatment response. Due to the small number of patients on which the utility estimate is based and the impossibility to assess whether patients from this study are comparable to patients included in the current assessment, uncertainty remains about the health state utility values for the low risk and moderate risk health states. Furthermore, this study used the valuation set from Torrance et al. 1996[76] in order to value the Health Utilities Index Mark 2 (HUI:2) measurements. This valuation set is based on a sample of parents from Canada. This is not consistent with the NICE reference case and the representativeness of this estimate to the UK setting is uncertain. Given that a recent review from Dyson et al. 2016[77] reported that 34.1% of PBC patients have a 'poor' quality of life and that the current estimate is higher than the general population utility values for the age category 50-59 (the starting age of the population in the model being 55.8 years)[78], the ERG thinks that the current utility values for these health states might be overestimated. In absence of utility data specific to PBC patients which is representative of the UK setting, the ERG will use the age-dependent utility values of the UK general population for these two health states in its base-case analysis.[78] An additional concern is that the low risk and moderate risk health states were valued though the HUI:2 while the remaining health states were valued through the EQ-5D. This leads to inconsistencies in the valuation of health state utility values in the model. Using UK general population utility values will remove this concern.

The company applied a [redacted] utility decrement to the health state utility values found in the literature for all health states in the liver component of the model, except for the HCC health state. This decrement was based on expert opinion. Appendix 11 of the CS contains the interview guide used to elicit expert opinion but it does not contain (a summary of) answers provided by experts on the different questions.[41] The ERG requested these answers, but the company replied it was not authorised to share this information (Clarification Question B25).[32] The ERG was consequently not able to investigate the validity of this decrement applied on the utility values from Wright et al.2006[64] (e.g. how the experts were selected, whether the clinical experts agreed on applying a decrement on the utility values obtained from the literature and whether experts agreed on the potential magnitude of the decrement). In addition, Younossi et al. 2001[74] report lower utility value for chronic liver disease due to viral infection (e.g. HCV/HBV) than the utility value reported for chronic liver disease due to cholestatic disease (PBC and primary sclerosing cholangitis patients). This is contradictory to the company's reasoning that PBC patients have lower health state utility values than HCV/HBV patients. For these reasons, the ERG removed the [redacted] utility decrements in the ERG base-case.

The ERG requested the company to provide a sensitivity analysis including the impact of AEs on HRQoL. The company did not meet this request but provided a sensitivity analysis in which the costs of AEs were set to £0. According to the company, this underlined the minor impact of AEs on the cost effectiveness results (Clarification Question B19).[32] The ERG thinks this approach does not represent the impact of AEs on HRQoL. Given the little differences in AEs occurrence between treatments (Section 5.2.7), the little influence this implementation will have on the cost effectiveness results and time constraints, the ERG will not include AEs' impact on HRQoL in its base-case analysis.

5.2.9 Resources and costs

Resource use and costs included in the CS model were based on data from the British National Formulary (BNF) 2016,[79] NHS reference costs, assumptions validated by expert opinion, and published sources identified in the systematic literature review (SLR).

Resource identification, measurement and valuation studies

The company performed a SLR to identify relevant costs and resource use evidence for the current decision problem. After abstract and full text screening, the SLR identified a total of 13 studies reporting cost and resource use data in Section 5.5.1.2 of the CS.[3] All of these studies were deemed relevant to the decision problem. In the absence of any additional sources of evidence, assumptions were made for both cost and resource inputs included in the model, where necessary, and were validated by expert clinical opinion.

ERG comment: The ERG notes small inconsistencies in the numbers of studies identified in the different phases of the SLR[3] but is satisfied that relevant literature has been identified.

Intervention and comparators' costs and resource use

Drug acquisition costs for UDCA were determined from the BNF 2016[79] and market share data to calculate a weighted average cost per pack. The daily cost of UDCA was based on the observed UDCA dose as defined in the POISE trial protocol. The company used the list price of OCA in the cost-effectiveness model. The outcomes in the CS were presented only based on the list price, analyses using the proposed PAS will be submitted in a separate appendix. The dosing frequency of OCA and UDCA used in the base-case analysis was based on the dosing schedule from the POISE trial for OCA (titration dose) and the marketing authorisation of UDCA.

The annual costs of drug administration for OCA and UDCA included in the model are presented in Section 5.5.2 of the CS,[3] Table 65 (reproduced below in Table 5.11). OCA and UDCA are both administered orally.

Table 5.11: Unit costs associated with the technology in the economic model

Items	OCA	UDCA
Technology cost (list price)	£2,384.04 / 30 tablets	Weighted average of tablet formulations detailed in NHS Prescription Cost Analysis
Total annual cost (based on list price, 1 tablet per day)	£29,005.78	£655.33
Source: CS, Table 65[3]		

Health state costs and resource use

Data on health state costs and resource use were obtained from different sources and all costs are detailed in Table 5.12. All costs were inflated to 2016 costs using the Hospital & Community Health Services (HCHS) index[80].

Table 5.12: List of health states and associated annual costs in the economic model

Health states	Items	Value	Source
ALP: ≤ 200 U/l and Bili: Normal	Staff	£221.00 (1x Outpatient appointment, 1x outpatient follow-up)	EO
	Hospital costs	£27.00 (3 blood tests, 3 times per year, at a cost of £3)	NHS Schedule of Reference Costs – DAPS05[81]
	Total	£248.00	
ALP: > 200 U/l and Bili: Normal	Staff	£345.00 (1x Outpatient appointment, 2x outpatient follow-up appointments)	EO
	Hospital costs	£27.00 (3 blood tests, 3 times per year, at a cost of £3)	NHS Schedule of Reference Costs – DAPS05[81]
	Total	£496.00	
Bili: Abnormal and rising, or CC	Total	£6,254.00	EO: half the costs of DCC identified in Wright et al. 2006[64]
DCC	Total	£12,509.00	Wright et al. 2006[64]
HCC	Total	£11,147.00	Wright et al. 2006[64]
Pre-transplant (end stage)	Total	£18,217.00	Singh et al. 2014[42]
Re-emergence of PBC	Total	£248.00	Assumed identical to ALP: ≤ 200 u/L and Bili: Normal
Liver transplant	Total	£65,029.00	Singh et al. 2014[42]
Follow-up 1 year after liver transplantation	Total for 2 years divided by 2	£18,166.00	Singh et al. 2014[42]
Follow-up 2 years after liver transplantation	Total for 2 years divided by 2	£18,166.00	Singh et al. 2014[42]

Source: CS, Table 66[3]

ALP, alkaline phosphatase; Bili, bilirubin; CC, compensated cirrhosis; CS, company submission; DCC, decompensated cirrhosis; EO, expert opinion; HCC, hepatocellular carcinoma; PBC, primary biliary cholangitis/cirrhosis

Costs associated with the liver disease component were based on expert opinion, the literature and NHS reference costs. Costs for outpatient visits were based on expert opinion rather than on NHS reference costs.

Costs associated with the severe risk biomarker health state of abnormal TB or CC was estimated by an expert to be half of the cost of DCC (reported in Wright et al. 2006[64]). The company justified this by stating that rising bilirubin levels would cause use of more health care resources.

The cost of liver transplant was derived from Singh et al. 2014[42], which, the company claimed, was in line with TA 330[56]. Furthermore, the company claimed that using NHS reference costs for an estimate

of liver transplant costs would under-estimate the cost of liver transplant, because it would not include the additional cost of supporting care.

Adverse reaction unit costs and resource use

The company considered costs associated with pruritus only and excluded costs of fatigue and nausea from their analysis. The company justified this by claiming that only pruritus was routinely treated in clinical practice. An overview of costs associated with pruritus care is shown in Table 5.13.

Table 5.13: List of adverse reactions and summary of costs included in the economic model

Adverse events	Items	Percentage of patients cost applies to	Value	Reference to section in submission
Pruritus	Staff (GP visit)	100%**	£54.00*	EO
	Cholestyramine cost / 327.10 days†	85%**	£105.59‡	EO
	Rifampicin cost / 327.10 days†	15%**	£191.77‡	EO
	Naltrexone cost / 327.10 days†	5%**	£228.39‡	EO
	Total (weighted average + staff costs)	N/A	£177.75	EO

Source: CS, Table 67[3]

Footnotes: * Sourced from BNF, 2016. **Sourced from EO, Mean duration of treatment for UDCA and OCA therapies; ‡ Sourced from NHS Schedule of Reference Costs

CS, company submission; EO, expert opinion; GP, general practitioner.

ERG comment: In their original model, the company had used expert opinion for estimating costs associated with outpatient visits. The company then provided a scenario analysis where NHS reference costs were used instead. The ERG was satisfied that the use of NHS reference costs had only a small effect on model outcomes. The ERG uses NHS reference costs for its base case.

The company did not provide adequate justification how the cost associated with the severe risk health state of abnormal TB and CC was estimated. The ERG is concerned that the assumption of halving the cost of DCC is arbitrary. The ERG therefore uses the cost for CC used in TA 330[62], which was £1,561 instead of £6,254 used by the company[56] in its base case.

The company's estimate of liver transplant related costs was based on cost data in patients with hepatitis C[42]. Costs of liver transplant in the PBC population also exist (Longworth et al. 2003) [50]. If these costs based on PBC were inflated to 2015 values, costs would be similar to those used by the company (approximately £66,000 compared with £65,029 used by company). However, there is reason to believe that liver transplant costs for PBC patients should be lower than those for hepatitis C patients (Longworth et al. 2003)[42]. Furthermore, as the number of liver transplants has increased, the impact of scale economies as considered likely by Habka et al. 2015[82] suggest that a lower inflation uplift may be more appropriate. The ERG therefore explores alternative costs of liver transplant in an exploratory analysis.

5.2.10 Cost effectiveness results

In both populations, OCA (with or without UDCA) led to longer survival, a QALY gain, and higher costs than the comparators (i.e. no treatment for the UDCA-intolerant population and UDCA alone for

the UDCA inadequate responders). The company provided disaggregated results for QALYs (Tables 5.14 and 5.15) and costs by health state (Tables 5.16 and 5.17). The low risk and moderate risk health states contribute to 74% and 73% of the absolute incremental QALY gained for the UDCA-intolerant population and UDCA inadequate responders. The incremental costs per health state follow the same trend as the incremental QALYs gained per health state. The low risk and moderate risk health states account for 85% and 87% of the incremental costs for the UDCA-intolerant population and UDCA inadequate responders. Disaggregated results were not provided for life years (LYs) gained. At list price, OCA was associated with an incremental cost effectiveness ratio (ICER) of [redacted] per additional QALY gained in the UDCA-intolerant patients population and an ICER of [redacted] in the UDCA inadequate responder patients population (Tables 5.18 and 5.19).

Table 5.14: Summary of QALY gain by health state for UDCA-intolerant population

Health state	OCA Titration	No treatment	Increment	Absolute increment	Absolute increment (in %)*
Low risk[a]	5.981	0.000	-5.981	5.981	41%
Moderate risk[b]	6.796	2.044	-4.752	4.752	33%
Severe risk[c]	0.394	2.515	2.121	2.121	15%
Discontinuation	0.009	0.000	-0.009	0.009	0%
Decompensated cirrhosis	0.106	0.651	0.544	0.544	4%
HCC	0.011	0.065	0.055	0.055	0%
Pre transplant (end stage)	0.034	0.208	0.174	0.174	1%
Liver transplant	0.005	0.031	0.026	0.026	0%
Post liver transplant	0.136	0.822	0.686	0.686	5%
Re-emergence of PBC	0.046	0.270	0.223	0.223	2%
Total	**13.520**	**6.606**	**-6.913**	**14.572**	**100%**

Source: Table 73 of the CS[3]

Footnotes: [a] referred as 'ALP: ≤ 200 u/L and Bili: Normal' in the CS[3]; [b] referred as 'ALP: > 200 u/L and Bili: Normal' in the CS[3]; [c] referred as 'Bili: Abnormal and rising, or CC' in the CS[3]; * Calculated by the ERG

ALP, alkaline phosphatase; Bili, bilirubin; CC, compensated cirrhosis; CS, company submission; ERG, Evidence Review Group; HCC, hepatocellular carcinoma; OCA, obeticholic acid; PBC, primary biliary cholangitis/cirrhosis; QALY, quality-adjusted life year; UDCA, ursodeoxycholic acid; ULN, upper limit of normal

Table 5.15: Summary of QALY gain by health state for UDCA inadequate responders

Health state	OCA + UDCA titration	UDCA + No treatment	Increment	Absolute increment	Absolute increment (in %)*
Low risk[a]	5.981	0.000	-5.981	5.981	48%
Moderate risk[b]	6.974	3.867	-3.107	3.107	25%
Severe risk[c]	0.365	2.222	1.857	1.857	15%
Discontinuation	0.009	0.004	-0.006	0.006	0%
Decompensated cirrhosis	0.098	0.569	0.471	0.471	4%

Health state	OCA + UDCA titration	UDCA + No treatment	Increment	Absolute increment	Absolute increment (in %)*
HCC	0.010	0.057	0.048	0.048	0%
Pre transplant (end stage)	0.031	0.182	0.151	0.151	1%
Liver transplant	0.005	0.027	0.023	0.023	0%
Post liver transplant	0.125	0.701	0.577	0.577	5%
Re-emergence of PBC	0.042	0.222	0.180	0.180	1%
Total	**13.641**	**7.852**	**-5.789**	**12.399**	**100%**

Source: Table 74 of the CS[3]

Footnotes: [a] referred as 'ALP: ≤ 200 u/L and Bili: Normal' in the CS[3]; [b] referred as 'ALP: > 200 u/L and Bili: Normal' in the CS[3]; [c] referred as 'Bili: Abnormal and rising, or CC' in the CS[3]; * Calculated by the ERG

ALP, alkaline phosphatase; Bili, bilirubin; CC, compensated cirrhosis; CS, company submission; ERG, Evidence Review Group; HCC, hepatocellular carcinoma; OCA, obeticholic acid; PBC, primary biliary cholangitis/cirrhosis; QALY, quality-adjusted life year; UDCA, ursodeoxycholic acid; ULN, upper limit of normal

Table 5.16: Summary of costs by health state for UDCA-intolerant population

Health state	OCA Titration	No treatment	Increment	Absolute increment	Absolute increment (in %)*
Low risk[a]	[redacted]	£0.00	[redacted]	[redacted]	[redacted]
Moderate risk[b]	[redacted]	£1,207.08	[redacted]	[redacted]	[redacted]
Severe risk[c]	[redacted]	£28,597.68	[redacted]	[redacted]	[redacted]
Discontinuation	[redacted]	£0.00	[redacted]	[redacted]	[redacted]
Decompensated cirrhosis	[redacted]	£21,284.77	[redacted]	[redacted]	[redacted]
HCC	[redacted]	£1,620.43	[redacted]	[redacted]	[redacted]
Pre transplant (end stage)	[redacted]	£9,890.90	[redacted]	[redacted]	[redacted]
Liver transplant	[redacted]	£14,310.87	[redacted]	[redacted]	[redacted]
Post liver transplant	[redacted]	£26,221.30	[redacted]	[redacted]	[redacted]
Re-emergence of PBC	[redacted]	£99.80	[redacted]	[redacted]	[redacted]
Total	[redacted]	**£103,232.81**	[redacted]	[redacted]	[redacted]

Source: Table 75 of the CS[3]

Footnotes: [a] referred as 'ALP: ≤ 200 u/L and Bili: Normal' in the CS[3]; [b] referred as 'ALP: > 200 u/L and Bili: Normal' in the CS[3]; [c] referred as 'Bili: Abnormal and rising, or CC' in the CS[3]; * Calculated by the ERG

ALP, alkaline phosphatase; Bili, bilirubin; CC, compensated cirrhosis; CS, company submission; ERG, Evidence Review Group; HCC, hepatocellular carcinoma; OCA, obeticholic acid; PBC, primary biliary cholangitis/cirrhosis; QALY, quality-adjusted life year; UDCA, ursodeoxycholic acid; ULN, upper limit of normal

Table 5.17: Summary of costs by health state for UDCA inadequate responders

Health state	OCA + UDCA titration	UDCA + No treatment	Increment	Absolute increment	Absolute increment (in %)*
Low risk[a]	[redacted]	£0.00	[redacted]	[redacted]	[redacted]
Moderate risk[b]	[redacted]	£5,349.00	[redacted]	[redacted]	[redacted]
Severe risk[c]	[redacted]	£27,926.48	[redacted]	[redacted]	[redacted]
Discontinuation	[redacted]	£14.48	[redacted]	[redacted]	[redacted]
Decompensated cirrhosis	[redacted]	£18,619.88	[redacted]	[redacted]	[redacted]
HCC	[redacted]	£1,422.13	[redacted]	[redacted]	[redacted]
Pre transplant (end stage)	[redacted]	£8,665.20	[redacted]	[redacted]	[redacted]
Liver transplant	[redacted]	£12,526.26	[redacted]	[redacted]	[redacted]
Post liver transplant	[redacted]	£22,371.06	[redacted]	[redacted]	[redacted]
Re-emergence of PBC	[redacted]	£82.10	[redacted]	[redacted]	[redacted]
Total	[redacted]	**£96,976.58**	[redacted]	[redacted]	[redacted]

Source: Table 76 of the CS[3]

Footnotes: [a] referred as 'ALP: ≤ 200 u/L and Bili: Normal' in the CS[3]; [b] referred as 'ALP: > 200 u/L and Bili: Normal' in the CS[3]; [c] referred as 'Bili: Abnormal and rising, or CC' in the CS[3]; * Calculated by the ERG

ALP, alkaline phosphatase; Bili, bilirubin; CC, compensated cirrhosis; CS, company submission; ERG, Evidence Review Group; HCC, hepatocellular carcinoma; OCA, obeticholic acid; PBC, primary biliary cholangitis/cirrhosis; QALY, quality-adjusted life year; UDCA, ursodeoxycholic acid; ULN, upper limit of normal

Table 5.18: Deterministic base-case results for UDCA-intolerant patients, using the list price for OCA

Technologies	Total			Incremental			ICER (£)	ICER (£)
	Costs (£)	LYG	QALYs	Costs (£)	LYG	QALYs	versus baseline	incremental
No treatment	£103,233	11.30	6.61					
OCA titration	[redacted]	16.65	13.52	[redacted]	5.35	6.91	[redacted]	[redacted]

Source: Table 69 of the CS[3]

CS, company submission; ICER, incremental cost-effectiveness ratio; LYG, life years gained; OCA, obeticholic acid; QALYs, quality-adjusted life years; UDCA, ursodeoxycholic acid

Table 5.19: Deterministic base-case results for UDCA inadequate responders, using the list price for OCA

Technologies	Total			Incremental			ICER (£)	ICER (£)
	Costs (£)	LYG	QALYs	Costs (£)	LYG	QALYs	versus baseline	incremental
UDCA	£96,977	12.35	7.85					
OCA titration + UDCA	[redacted]	16.75	13.64	[redacted]	4.40	5.79	[redacted]	[redacted]

Source: Table 70 of the CS[3]
CS, company submission; ICER, incremental cost-effectiveness ratio; LYG, life years gained; OCA, obeticholic acid; QALYs, quality-adjusted life years; UDCA, ursodeoxycholic acid

ERG comment: Upon request from the ERG, the company provided the disaggregated LYs gained per health state (Tables 5.20 and 5.21). As for the disaggregated QALYs gained and disaggregated costs per health state, the incremental LYs gained in the low risk health state are the same in both population. In addition, the low risk and the moderate risk health states contribute to more than half of the absolute increment in LYs gained, as expected when examining the incremental QALYs gained (respectively 63% and 62% of the incremental LY for the UDCA-intolerant population and UDCA inadequate responders).

The cost effectiveness results reported in the current report are potentially not representative of the true value for money of OCA (with or without UDCA) for treating PBC patients if OCA will be provided under a patient access scheme (PAS).

Table 5.20: Summary of life years gained by health state for UDCA-intolerant population

Health state	OCA titration	No treatment	Increment	Absolute increment*	Absolute increment (in %)*
Low risk[a]	7.120	0.000	7.120	7.120	35%
Moderate risk[b]	8.091	2.434	5.657	5.657	28%
Severe risk[c]	0.716	4.573	–3.856	3.856	19%
Discontinuation	0.012	0.000	0.012	0.012	0%
Decompensated cirrhosis	0.278	1.702	–1.423	1.423	7%
HCC	0.024	0.145	–0.122	0.122	1%
Pre transplant (end stage)	0.089	0.543	–0.454	0.454	2%
Liver transplant	0.009	0.055	–0.046	0.046	0%
Post liver transplant	0.240	1.443	–1.204	1.204	6%
Re-emergence of PBC	0.069	0.402	–0.333	0.333	2%
Total	**16.648**	**11.297**	**5.351**	**20.227**	**100%**

Health state	OCA titration	No treatment	Increment	Absolute increment*	Absolute increment (in %)*
Source: Table 33 of the response to the clarification letter[32] Footnotes: [a] referred as 'ALP: ≤ 200 u/L and Bili: Normal' in the CS[3]; [b] referred as 'ALP: > 200 u/L and Bili: Normal' in the CS[3]; [c] referred as 'Bili: Abnormal and rising, or CC' in the CS[3]; * Calculated by the ERG ALP, alkaline phosphatase; Bili, bilirubin; CC, compensated cirrhosis; CS, company submission; ERG, Evidence Review Group; HCC, hepatocellular carcinoma; OCA, obeticholic acid; PBC, primary biliary cholangitis/cirrhosis; QALY, quality-adjusted life year; UDCA, ursodeoxycholic acid; ULN, upper limit of normal					

Table 5.21: Summary of life years gained by health state for UDCA inadequate responders

Health state	OCA titration + UDCA	UDCA + No treatment	Increment	Absolute increment*	Absolute increment (in %)*
Low risk[a]	7.120	0.000	7.120	7.120	41%
Moderate risk[b]	8.303	4.604	3.699	3.699	21%
Severe risk[c]	0.664	4.040	–3.376	3.376	20%
Discontinuation	0.012	0.005	0.007	0.007	0%
Decompensated cirrhosis	0.257	1.489	–1.231	1.231	7%
HCC	0.022	0.128	–0.106	0.106	1%
Pre transplant (end stage)	0.082	0.476	–0.394	0.394	2%
Liver transplant	0.008	0.048	–0.040	0.04	0%
Post liver transplant	0.219	1.231	–1.013	1.013	6%
Re-emergence of PBC	0.062	0.331	–0.269	0.269	2%
Total	**16.750**	**12.351**	**4.399**	**17.255**	**100%**
Source: Table 34 of the response to the clarification letter[32] Footnotes: [a] referred as 'ALP: ≤ 200 u/L and Bili: Normal' in the CS[3]; [b] referred as 'ALP: > 200 u/L and Bili: Normal' in the CS[3]; [c] referred as 'Bili: Abnormal and rising, or CC' in the CS[3]; * Calculated by the ERG ALP, alkaline phosphatase; Bili, bilirubin; CC, compensated cirrhosis; CS, company submission; ERG, Evidence Review Group; HCC, hepatocellular carcinoma; OCA, obeticholic acid; PBC, primary biliary cholangitis/cirrhosis; QALY, quality-adjusted life year; UDCA, ursodeoxycholic acid; ULN, upper limit of normal					

5.2.11 Sensitivity analyses

Probabilistic sensitivity analysis

The company performed a probabilistic sensitivity analysis (PSA) on the following parameters:

- Baseline distribution of patients in the 'ALP > 200 units / L and Normal Bilirubin' and '(ALP ≤ or > 200 units / L) and Abnormal Bilirubin' health states
- Patients' mean weight
- Discontinuation probabilities
- Adverse event rates
- Utilities
- TPs

- Disease management costs
- Adverse event costs

To perform the PSA, the minimum and maximum values of several parameters were assumed to be +/- 20% of the mean estimate. This is the case for the health state utility values decreased by the [redacted] decrement, disease management costs and the following TPs: from the severe risk health state to DCC health state, from the sever risk health state to HCC, from HCC to death, from Pre-LT to LT and from Pre-LT to death. Results of the PSA for both populations (UDCA-intolerant patients and UDCA inadequate responders) compared to the deterministic results are provided in Tables 5.22 and 5.23. At list price, the probability for OCA of being cost effective at a willing-to-pay threshold of £30,000 was [redacted] in both populations. Appendix 3 provides the scatter plots and cost effectiveness acceptability curves for both populations.

Table 5.22: Incremental cost effectiveness results of PSA for the UDCA intolerant population, using the list price of OCA

Technologies	Total			Incremental			ICER (£) versus baseline	ICER (£) incremental
	Costs (£)	LYG	QALYs	Costs (£)	LYG	QALYs		
PSA results								
No treatment	£103,439	11.33	6.77	-	-	-	-	-
OCA Titration	[redacted]	16.64	13.52	[redacted]	5.31	6.75	[redacted]	[redacted]
Base case deterministic results								
No treatment	£103,233	11.30	6.61	-	-	-	-	-
OCA titration	[redacted]	16.65	13.52	[redacted]	5.35	6.91	[redacted]	[redacted]

Source: Table 79 of the CS[3]
CS, company submission; ICER, incremental cost-effectiveness ratio; LYG, life years gained; PSA, probabilistic sensitivity analysis; QALY, quality-adjusted life year; OCA, obeticholic acid; UDCA, ursodeoxycholic acid

Table 5.23: Incremental cost effectiveness results of PSA for the UDCA inadequate responder population, using the list price of OCA

Technologies	Total			Incremental			ICER (£) versus baseline	ICER (£) incremental
	Costs (£)	LYG	QALYs	Costs (£)	LYG	QALYs		
PSA results								
UDCA	£97,044	12.38	7.88	-	-	-	-	-
OCA + UDCA titration	[redacted]	16.75	13.65	[redacted]	4.37	5.77	[redacted]	[redacted]
Base case deterministic results								
UDCA	£96,977	12.35	7.85	-	-	-	-	-
OCA + UDCA titration	[redacted]	16.75	13.64	[redacted]	4.40	5.79	[redacted]	[redacted]

Technologies	Total			Incremental			ICER (£)	ICER (£)
	Costs (£)	LYG	QALYs	Costs (£)	LYG	QALYs	versus baseline	incremental
Source: Table 80 of the CS[3] CS, company submission; ICER, incremental cost-effectiveness ratio; LYG, life years gained; PSA, probabilistic sensitivity analysis; QALY, quality-adjusted life year; OCA, obeticholic acid; UDCA, ursodeoxycholic acid								

Deterministic sensitivity analyses

The influence of varying the following parameters was investigated through one-way deterministic sensitivity analyses (DSA):

- Discontinuation probabilities
- Probabilities of experiencing an AE
- Utility weights
- TPs
- Discounting
- The probability of death for the general population
- AEs costs and disease management costs (i.e. health state costs)

Tables 81 and 82 of the CS provide an overview of the variation in each model parameter used during the DSA for the UDCA-intolerant population and the UDCA inadequate responders population.[3] In both populations, the most influential parameters on the cost effectiveness results were the health states utility values for the health states of the biomarker component of the model and the TPs between these health states. Tornado diagrams were provided in the CS (Appendix 2).[41]

In the DSA, the following parameters were varied by +/- 20%:

- AEs costs and disease management costs
- Utility weights decreased by the [redacted] decrements
- TPs concerning the biomarker component of the model
- The following TPs from the liver disease component of the model: DCC to LT, DCC to death, DCC to HCC, severe risk to DCC, severe risk to HCC, HCC to death, Pre-LT to LT, Pre-LT to death, LT to death, Post LT to re-emergence of PBC, Post LT to LT, Post LT to death, Re-emergence of PBC to LT, HCC to LT.

ERG comment: The variation around a substantial number of parameters is based on a +/-20% variation around the mean which does not reflect the parameter uncertainty around these parameter estimates. Furthermore, using an arbitrary variation around the mean is not in line with international modelling guidelines.[83] Empirical evidence should have been used to determine the variation around the estimates for the DSA.

Scenario analyses

The company performed two scenario analyses. In the first scenario analysis, the original HCV utility values (without [redacted] decrease) were used for the health states of the liver disease component of the model. This resulted in ICERs of [redacted] for the UDCA-intolerant patients and the UDCA inadequate responder respectively. In the second scenario analysis, the TPs from the pre-LT health state to the LT health state, and from the pre-LT health state to death were based on PBC-specific data from the Organ procurement and transplantation network (OPTN) (data on file).[3] The TPs were changed in 0.44 and 0.21 instead of 0.35 and 0.09, respectively. This resulted in ICERs of [redacted]

[redacted] for the UDCA intolerant patients and the UDCA inadequate responders respectively.

ERG comment: In response to the ERG requests, the company provided the results of three additional scenario analyses. The first additional scenario analysis concerns the discontinuation rate and the second concerns the implementation of the HRQoL impact of AEs in the cost effectiveness model. The third additional sensitivity analysis presented by the company included NHS reference costs for outpatients visits.[32] These additional sensitivity analyses are discussed in Sections 5.2.6, 5.2.8 and 5.2.9 respectively.

Upon the ERG's request, the company provided an additional analysis in which the TPs of all comparators in the first year of the model were based on the patient-level data from POISE. This approach is considered more consistent by the ERG and results in ICERs of [redacted] for the UDCA-intolerant patients and the UDCA inadequate responders respectively (Tables 5.24 and 5.25).

Table 5.24: Deterministic results for UDCA-intolerant patients, using the list price of OCA and UDCA patient-level data

Technologies	Total			Incremental			ICER (£) versus baseline	ICER (£) incremental
	Costs (£)	LY	QALYs	Costs (£)	LYG	QALYs		
No treatment	£103,233	11.30	6.61					
OCA titration	[redacted]	16.68	13.56	[redacted]	5.38	6.95	[redacted]	[redacted]

CS, company submission; ICER, incremental cost-effectiveness ratio; LYG, life years gained; OCA, obeticholic acid; QALYs, quality-adjusted life years; UDCA, ursodeoxycholic acid

Table 5.25: Base-case results for UDCA inadequate responders, using the list price of OCA, and UDCA patient-level data

Technologies	Total			Incremental			ICER (£) versus baseline	ICER (£) incremental
	Costs (£)	LY	QALYs	Costs (£)	LYG	QALYs		
UDCA	£92,218	12.72	8.30					
OCA+UDCA Titration	[redacted]	16.78	13.68	[redacted]	4.06	5.38	[redacted]	[redacted]

CS, company submission; ICER, incremental cost-effectiveness ratio; LYG, life years gained; OCA, obeticholic acid; QALYs, quality-adjusted life years; UDCA, ursodeoxycholic acid

5.2.12 Model validation and face validity check

The company described that the model had been internally checked by two modellers who were involved in the model development (internal peer review) and that an external peer review took place (performed by two modellers who were not involved in the development of the model). The company stated that the following verification techniques were performed during these peer reviews:

- *'Face validity: testing that the model meets expectations based on simple calculations*
- *Model behaviour: testing whether varying model inputs has the expected directional effect*
- *Internal consistency: model outputs were compared against POISE*
- *Cell-by-cell checks of calculations: manual inspection of formulae*

- *Use of logical scenario checks and the rebuilding of important parts of the model*
- *A complete cross-check of inputs, sources, and supporting documentation.'*[3]

The company provided the clinical outcomes of the cost effectiveness model (Tables 5.26 to 5.28), but did not compare them to any external source.

Table 5.26: Mean time to event for liver-related death

	UDCA intolerant patients		UDCA inadequate responders	
	No treatment	**OCA titration**	**UDCA + No treatment**	**OCA + UDCA titration**
Annual rate of liver-related death	0.047	0.004	0.039	0.004
Mean liver-related death free survival (years)*	19.365	44.605	21.637	44.893
Years lost to liver-related death†	30.635	5.395	28.363	5.107
Median time to liver-related death (years)‡	14.750	N/A	17.500	N/A

Source:Table 55 of CS[3]

Footnotes: *Area under the Kaplan Meier curve; † Area above the Kaplan Meier curve; ‡ Using the total population as done with transplant free survival

Table 5.27: Summary of model outcomes for UDCA-intolerant population

Outcome	OCA titration	No treatment	Incremental
Total number of cases of Bili: abnormal and rising, or CC per 1,000 patients	[redacted]	[redacted]	[redacted]
Total number of cases of decompensated cirrhosis per 1,000 patients	[redacted]	[redacted]	[redacted]
Total liver transplants per 1,000 patients	[redacted]	[redacted]	[redacted]
Total liver related deaths per 1,000 patients	[redacted]	[redacted]	[redacted]

Source: Table 71 of the CS[3]

Bili, bilirubin; CC, compensated cirrhosis; CS, company submission; OCA, obeticholic acid; UDCA, ursodeoxycholic acid

Table 5.28: Summary of model outcomes for UDCA inadequate responder population

Outcome	OCA titration + UDCA	UDCA	Incremental
Total number of cases of Bili: abnormal and rising, or CC per 1,000 patients	[redacted]	[redacted]	[redacted]
Total number of cases of decompensated cirrhosis per 1,000 patients	[redacted]	[redacted]	[redacted]
Total liver transplants per 1,000 patients	[redacted]	[redacted]	[redacted]
Total liver related deaths per 1,000 patients	[redacted]	[redacted]	[redacted]

Source: Table 72 of the CS[3]
Bili, bilirubin; CC, compensated cirrhosis; CS, company submission; OCA, obeticholic acid; UDCA, ursodeoxycholic acid

ERG comment: The results of the validation steps were not described in the CS and were not provided in response to the clarification letter upon the ERG's request. Furthermore, the ERG requested the company to perform cross and external validation (for example, by using the UK-PBC Risk Score Calculator[84]). Validation against the UK-PBC Risk Score was not performed. The company stated that it required patient-level data and calculating mean ALP or bilirubin levels per group would potentially introduce bias. The company deemed cross validation impossible in the absence of other cost utility models for PBC.[32] The ERG does not agree with this, because the cost effectiveness review identified four studies focussing on PBC treatment. The ERG believes that other outcomes of the model (e.g. UDCA costs, LY for the No treatment and UDCA arms) could have been validated against these sources. If the company considered comparisons with these models inappropriate, justifications should have been provided for not performing cross validation (or why it was deemed inappropriate).

The company claimed to have validated model outputs against the GLOBE and UK PBC cohort survival rates, shown in Harms et al. 2016,[59] but did not provide the results of this validation.[32] The lack of information concerning validation efforts (both in the CS and the response to the clarification letter) is a violation of good modelling practices[85] and it hampered the ERG's efforts to assess whether adequate validation efforts have been performed by the company.

Moreover, given the lack of transparency regarding the methods used by the company (e.g. concerning the calibration process described in Section 5.2.6), even after requests from the ERG (Clarification Questions B12, B14, B15 and B16[30]), the methods used by the company are still unclear. The ERG was therefore unable to assess the validity and appropriateness of these methods.

5.3 Exploratory and sensitivity analyses undertaken by the ERG

Based on all considerations from Section 5.2, the ERG defined a new base-case. This base-case included multiple adjustments to the original base-case presented in the CS. These adjustments were subdivided into three categories (derived from Kaltenthaler 2016[86]):

- Fixing errors (correcting the model were the company's submitted model was unequivocally wrong)
- Fixing violations (correcting the model where the ERG considered that the NICE reference case, scope or best practice had not been adhered to)

- Matters of judgement (amending the model were the ERG considers that reasonable alternative assumptions are preferred)

Additionally, multiple exploratory sensitivity analyses (see Section 5.3.2) were performed by the ERG to examine the potential impact of alternative assumptions on the cost effectiveness estimates.

Fixing errors

1. Fixing discrepancy between TPs reported in the CS and used in the economic model (for biomarker component of the model; see Section 5.2.6 for more details). To fix this error, the ERG used the TPs reported in the CS.

Fixing violations

2. Use TPs from POISE for the non-OCA regimen (for biomarker component of the model; see Section 5.2.6 for more details).
3. Use proportions in the starting health states as derived from the POISE trial (see Section 5.2.3 for more details).
4. Use NHS reference costs for outpatient visits (see Section 5.2.9 for more details).
5. Use health state costs of £1,561 for CC (severe risk health state in the biomarker component) (instead of £6,254, consistent with TA330 (see Section 5.2.9 for more details)
6. Use age-dependent utilities (from the UK general population) for the low and moderate risk health states in the biomarker component of the model (see Section 5.2.8 for more details).

Matters of judgment

7. Remove the [redacted] HRQoL decrements (for health states in the liver disease component of the model; see Section 5.2.9 for more details).

5.3.1 Probabilistic sensitivity analysis (ERG base-case)

The ERG performed a PSA to obtain the ERG base-case incorporating all abovementioned adjustments. This resulted in ICERs (probabilistic) for OCA versus UDCA or no treatment of [redacted] for UDCA inadequate responders and UDCA intolerant patients respectively.

The PSA showed that OCA has a [redacted] probability of being cost-effective at thresholds below £30,000 per QALY gained (Figure 5.2).

Table 5.29: ERG base-case for UDCA inadequate responders

	OCA titration+UDCA			UDCA			Incremental results				
	QALYs	LYs	Costs	QALYs	LYs	Costs	ΔQALY	ΔLY	ΔCosts	ICER LY	ICER QALY
ERG base-case (deterministic)	12.57	16.98	[redacted]	8.39	13.11	£72,332	4.17	3.88	[redacted]	[redacted]	[redacted]
ERG base-case (probabilistic)	12.51	16.95	[redacted]	8.29	13.13	£72,266	4.22	3.82	[redacted]	[redacted]	[redacted]

ERG, Evidence Review group; ICER, incremental cost-effectiveness ratio; OCA, obeticholic acid; QALYs, quality-adjusted life years; TPs, Transition probabilities; UDCA, ursodeoxycholic acid

Table 5.30: ERG base-case for UDCA intolerant patients

	OCA titration			No treatment			Incremental results				
	QALYs	LYs	Costs	QALYs	LYs	Costs	ΔQALY	ΔLY	ΔCosts	ICER LY	ICER QALY
ERG base-case (deterministic)	12.44	16.86	[redacted]	7.05	11.79	£78,461	5.38	5.07	[redacted]	[redacted]	[redacted]
ERG base-case (probabilistic)	12.40	16.84	[redacted]	6.93	11.81	£78,541	5.47	5.03	[redacted]	[redacted]	[redacted]

ERG, Evidence Review group; ICER, incremental cost-effectiveness ratio; OCA, obeticholic acid; QALYs, quality-adjusted life years; TPs, Transition probabilities; UDCA, ursodeoxycholic acid

Figure 5.2: Incremental cost effectiveness planes for ERG base-case

UDCA inadequate responders

UDCA intolerant patients

5.3.2 Additional exploratory and threshold analyses performed based on the ERG base-case

Four additional exploratory sensitivity analyses were performed by the ERG to examine the potential impact of alternative assumptions on the cost effectiveness estimates. These analyses were performed on the ERG base-case and investigated the impact of the following adjustments:

8. Use TPs from TA330 (for liver disease component) and accordingly exclude pre-liver disease health state and update health sate costs for liver transplant

9. Assume that for the non-OCA regimen, after 12 months, the TPs in the biomarker component of the model are based on the POISE trial (using the average TPs over the first 12 months).
10. Assume that for the OCA regimen, after 12 months, the TPs between the health states in the biomarker component of the model are 0.16% per quarter based on the progression observed in UDCA responders (instead of assuming no additional progression from low-risk or moderate risk to severe-risk after the first year).
11. Use alternative costs for liver transplant (£57,777 instead of £65,029).

The exploratory analysis all resulted in increased ICERs (Tables 6.3 and 6.4). The use of the TPs from TA330 resulted in ICERs of [redacted] for UDCA inadequate responders and UDCA intolerant patients respectively. Assuming alternative TPs for the non-OCA regimen after 12 months, resulted in ICERs of [redacted] for UDCA inadequate responders and UDCA intolerant patients respectively. Adding progression in the biomarker component of the model for the OCA regimen resulted in ICERs of [redacted] for UDCA inadequate responders and UDCA intolerant patients respectively. Finally, lowering the liver transplant costs resulted in a minor increase in ICERs to [redacted] for UDCA inadequate responders and UDCA intolerant patients respectively.

5.4 Conclusions of the cost effectiveness section

The majority of searches in Appendix 6, 8 and 9 were well reported and easily reproducible. Searches covered a broad range of databases and grey literature resources. The ERG expressed some concerns regarding the use of study design filters. However, it is unlikely that this would have impacted on the overall recall of results.

Reviewing the overall evidence, the ERG confirmed that there was no existing cost effectiveness model for OCA for the current indication, and thus that development of a *de novo* model was necessary. The economic model described in the CS is considered by the ERG to partially meet the NICE reference case. The company developed a Markov state transition model to describe the progression of PBC over a lifetime horizon. The model comprises two parts with a total of 10 health states. The first part of the model (referred as the biomarker component) captures the surrogate outcomes of ALP and bilirubin biomarkers in three different health states based on the expected risk of disease progression: low risk (ALP ≤ 1.67 * ULN); moderate risk (ALP > 1.67 * ULN and TB ≤ 1.0 * ULN) and severe risk (TB > 1.0 * ULN or compensated cirrhosis; CC). The latter health state combined both patients with compensated cirrhosis and those with abnormal bilirubin. In the second part of the model, the liver disease component, the following clinical endpoints are modelled: pre-liver transplant; DCC; HCC; liver transplant; a post-liver transplant state; potential PBC re-emergence; and death. Patients can move to the liver disease component of the model only coming from the severe risk health state in the biomarker component of the model. Furthermore, relevant adverse events identified by the company were fatigue, pruritus and nausea, but costs were only modelled in relation to pruritus, and the differential impact on health-related HRQoL was not modelled.

The company base-case ICERs (probabilistic) of OCA (without or with UDCA) versus no treatment and UDCA monotherapy were [redacted] for UDCA intolerant patients and UDCA inadequate responders respectively. The one-way sensitivity analyses conducted by the company showed that the model results were most sensitive to the health states utility values for the health states of the biomarker component of the model and the TPs between these health states. It should be noted though that the one-way sensitivity analyses were often based on arbitrary estimates of the variance (i.e. using ±20% of the mean value).

The main areas of ERG concern were the fact that the company did not use the POISE trial data directly for the non-OCA regimen, the lack of transparency and justification regarding methods and data to extrapolate the POISE trial data beyond the time horizon of 12 months and to final outcomes, the implausible high utility values in the biomarker component of the model and the lack of justification for the [redacted] HRQoL decrement for the health states of the liver disease component of the model. The ERG has incorporated various adjustments to the company base-case. The ERG base-case resulted in ICERs (probabilistic) of [redacted] for UDCA inadequate responders and UDCA intolerant patients respectively. The most influential adjustments/corrections made by the ERG were using TPs from the POISE trial for the non-OCA regimens and using age-dependent utilities for the low and moderate risk health states. However, the ERG base-case ICER should be regarded as a lower bound as the exploratory analysis showed that alternative assumptions, for the TPs after 12 months and the non-transparent calibration method used by the company, resulted in substantially higher ICERs (ranging from [redacted] for UDCA inadequate responders and UDCA intolerant patients respectively).

As the methods used by the company to extrapolate treatment effectiveness are lacking transparency and justification, the ICERs (presented by both the company and the ERG) should be interpreted with caution. Given the lack of long-term results of the POISE trial, the ERG would generally agree with using a calibration approach (as adopted by the company), to extrapolate the POISE trial data beyond the time horizon of 12 months and to final outcomes. However, the assumptions, methods and data used should be validated and documented in detail to avoid 'black box' criticism and obtain credible results. This includes the assumption of no progression after 12 months when the ALP and bilirubin levels are within normal range due to treatment. Particularly, considering the impact of the usage of alternative assumptions, methods and data will potentially result in substantially higher ICERs as illustrated in the exploratory analysis by the ERG.

6. IMPACT ON THE ICER OF ADDITIONAL CLINICAL AND ECONOMIC ANALYSES UNDERTAKEN BY THE ERG

In Section 5.3 the ERG base-case was presented, which was based on various changes compared to the company base-case. Tables 6.1 and 6.2 show how each individual change impacts the ICER plus the combined effect of all changes simultaneously. The analyses numbers in Tables 6.1 and 6.2 correspond to the analyses numbers reported in Section 5.3. Also, the exploratory analyses are presented in Tables 6.3 and 6.4 (conditional on the ERG base-case). Appendix 2 contains technical details on the analyses performed by the ERG.

Table 6.1: ERG base-case - UDCA inadequate responders

	OCA titration+UDCA		UDCA		Incremental results		
	QALYs	Costs	QALYs	Costs	ΔQALY	ΔCosts	ICER
Company base-case (deterministic) *	13.64	[redacted]	7.85	£96,977	5.79	[redacted]	[redacted]
1. Fixing discrepancies between TPs[1]	13.68	[redacted]	7.85	£96,968	5.83	[redacted]	[redacted]
2. Use transition probabilities from POISE for the non-OCA regimen	13.68	[redacted]	8.48	£90,740	5.20	[redacted]	[redacted]
3. POISE trial proportion in starting health states	13.92	[redacted]	8.37	£92,834	5.55	[redacted]	[redacted]
4. Use NHS reference costs for outpatient visits	13.68	[redacted]	7.85	£97,849	5.83	[redacted]	[redacted]
5. Use health state costs consistent with TA330	13.68	[redacted]	7.85	£78,004	5.83	[redacted]	[redacted]
6. Use UK age-dependent utility values	12.32	[redacted]	7.39	£96,968	4.93	[redacted]	[redacted]
7. Remove [redacted] utility decrement	13.72	[redacted]	8.11	£96,968	5.61	[redacted]	[redacted]
ERG base-case (deterministic)	12.57	[redacted]	8.39	£72,332	4.17	[redacted]	[redacted]
ERG base-case (probabilistic)	12.51	[redacted]	8.29	£72,266	4.22	[redacted]	[redacted]

Footnotes: * The ERG was not able to reproduce these results based on the last version of the model sent by the company: FINAL_ID785 Obeticholic acid Cost utility model_list_price v0.4_UDCA New patient data STC 211116 MM (ACIC); [1] These errors were also corrected in the erratum submitted by the company[3, 87]

	OCA titration+UDCA		UDCA		Incremental results		
	QALYs	Costs	QALYs	Costs	ΔQALY	ΔCosts	ICER
ERG, Evidence Review group; ICER, incremental cost-effectiveness ratio; NHS, National Health Services; OCA, obeticholic acid; QALYs, quality-adjusted life years; TPs, Transition probabilities; UDCA, ursodeoxycholic acid							

Table 6.2: ERG base-case - UDCA intolerant patients

	OCA titration		No treatment		Incremental results		
	QALYs	Costs	QALYs	Costs	ΔQALY	ΔCosts	ICER
Company base-case (deterministic) *	13.52	[redacted]	6.61	£103,233	6.91	[redacted]	[redacted]
1. Fixing discrepancies between TPs[1]	13.56	[redacted]	6.61	£103,233	6.95	[redacted]	[redacted]
2. Use transition probabilities from POISE for the non-OCA regimen	13.56	[redacted]	7.00	£99,799	6.56	[redacted]	[redacted]
3. POISE trial proportion in starting health states	13.78	[redacted]	6.89	£100,942	6.89	[redacted]	[redacted]
4. Use NHS reference costs for outpatient visits	13.56	[redacted]	6.61	£103,698	6.95	[redacted]	[redacted]
5. Use health state costs consistent with TA330	13.56	[redacted]	6.61	£81,773	6.95	[redacted]	[redacted]
6. Use UK age-dependent utility values	12.20	[redacted]	6.29	£103,233	5.92	[redacted]	[redacted]
7. Remove [redacted] utility decrement	13.61	[redacted]	6.91	£103,233	6.70	[redacted]	[redacted]
ERG base-case (deterministic)	12.44	[redacted]	7.05	£78,461	5.38	[redacted]	[redacted]
ERG base-case (probabilistic)	12.40	[redacted]	6.93	£78,541	5.47	[redacted]	[redacted]

Footnotes: * The ERG was not able to reproduce these results based on the last version of the model sent by the company: FINAL_ID785 Obeticholic acid Cost utility model_list_price v0.4_UDCA New patient data STC 211116 MM (ACIC); [1] These errors were also corrected in the erratum submitted by the company[87]

ERG, Evidence Review group; ICER, incremental cost-effectiveness ratio; NHS, National Health Services; OCA, obeticholic acid; QALYs, quality-adjusted life years; TPs, Transition probabilities; UDCA, ursodeoxycholic acid

Table 6.3: ERG exploratory analysis - UDCA inadequate responders

	OCA titration		No treatment		Incremental results		
	QALYs	Costs	QALYs	Costs	ΔQALY	ΔCosts	ICER
1. Use TPs and model structure from TA330	12.67	[redacted]	8.87	£38,094	3.80	[redacted]	[redacted]
2. Using TPs based on the	12.79	[redacted]	10.20	£54,015	2.59	[redacted]	[redacted]

	OCA titration		No treatment		Incremental results		
	QALYs	Costs	QALYs	Costs	ΔQALY	ΔCosts	ICER
POISE trial after 12months for the non-OCA treatment arms							
3. Assume that TPs between biomarkers health states of the OCA arm are >0%	12.15	[redacted]	8.39	£72,332	3.75	[redacted]	[redacted]
4. Use alternative costs for liver transplant	12.57	[redacted]	8.39	£71,083	4.17	[redacted]	[redacted]
ERG, Evidence Review group; ICER, incremental cost-effectiveness ratio; NHS, National Health Services; OCA, obeticholic acid; QALYs, quality-adjusted life years; TPs, Transition probabilities; UDCA, ursodeoxycholic acid							

Table 6.4: ERG exploratory analysis - UDCA intolerant patients

	OCA titration		No treatment		Incremental results		
	QALYs	Costs	QALYs	Costs	ΔQALY	ΔCosts	ICER
1. Use TPs and model structure from TA330	12.55	[redacted]	7.64	£34,009	4.91	[redacted]	[redacted]
2. Using TPs based on the POISE trial after 12months for the non-OCA treatment arms	12.79	[redacted]	10.18	£45,639	2.61	[redacted]	[redacted]
3. Assume that TPs between biomarkers health states of the OCA arm are >0%	12.02	[redacted]	7.05	£78,461	4.97	[redacted]	[redacted]
4. Use alternative costs for liver transplant	12.44	[redacted]	7.05	£76,942	5.38	[redacted]	[redacted]
ERG, Evidence Review group; ICER, incremental cost-effectiveness ratio; NHS, National Health Services; OCA, obeticholic acid; QALYs, quality-adjusted life years; TPs, Transition probabilities; UDCA, ursodeoxycholic acid							

7. END OF LIFE

Not relevant.

8. OVERALL CONCLUSIONS

8.1 Statement of principal findings

Overall the ERG is satisfied that the relevant direct evidence comparing OCA and UDCA has been presented. However no trials comparing OCA to fibrates were identified.

One Phase 3 trial, POISE, with 217 patients was presented as the main source of evidence.[27] The trial compared UDCA and combined UDCA and OCA in patients with an inadequate response to UDCA and OCA and placebo in those who were intolerant to UDCA. However the group receiving OCA as monotherapy is underrepresented in this trial (11 patients). Additionally, the majority of patients in POISE appeared to be at an earlier stage of disease so the effects on those with more advanced disease are less clear.

The POISE trial was well-conducted. However it only examined surrogate outcomes. These were justified by the company based on previously published research. In POISE, OCA shows positive effects on surrogate endpoints, and there is some evidence that surrogate endpoints are related to relevant outcomes. However, the size of the relationship is unclear.

The primary outcome of POISE was a composite one (percentage of participants with ALP < 1.67 x ULN and total bilirubin ≤ ULN and ALP decrease from baseline at 12 months). At 12 months 47% of participants in the OCA 10 mg group achieved the primary outcome, 46% in the titration group and 10% in the placebo group ($p < 0.0001$ for both comparisons). The results of other surrogate outcomes supported these findings. Incidence of adverse events was similar across groups. Events occurring more frequently in treatment groups were noted. The most notable was pruritus and it was noted that 10% of patients discontinued treatment due to pruritus in the OCA 10 mg group which did not titrate based on tolerability.

Two supporting Phase 2 trials were presented (including one of OCA monotherapy and one of OCA in combination with UDCA). These were not similar enough to be pooled with POISE but added support to the positive findings on surrogate outcomes. Clinical outcomes await the publication of the COBALT trial.[37]

The main areas of ERG concern were the fact that the company did not use the POISE trial data directly for the non-OCA regimen, the lack of transparency and justification regarding methods and data to extrapolate the POISE trial data beyond the time horizon of 12 months and to final outcomes, the implausible high utility values in the biomarker component of the model and the lack of justification for [redacted] HRQoL decrement for the health states of the liver disease component of the model, except HCC. The ERG has incorporated various adjustments to the company base-case. The ERG base-case resulted in ICERs (probabilistic) of [redacted] for UDCA inadequate responders and UDCA intolerant patients respectively. The most influential adjustments/corrections made by the ERG were using TPs from the POISE trial for the non-OCA regimens and using age dependent utilities for the low and moderate risk health states. However, the ERG base-case ICER should be regarded as a lower bound as the exploratory analysis showed that alternative assumptions, for the TPs after 12 months and the non-transparent calibration method used by the company, resulted in substantially higher ICERs (ranging from [redacted] and from [redacted] for UDCA inadequate responders and UDCA intolerant patients respectively).

As the methods used by the company to estimate and extrapolate treatment effectiveness are lacking transparency and justification, the ICERs (presented by both the company and the ERG) should be interpreted with caution. Given the lack of long-term results of the POISE trial, the ERG would generally agree with using a calibration approach (as adopted by the company), to extrapolate the

POISE trial data beyond the time horizon of 12 months and to final outcomes. However, the assumptions, methods and data used should be validated and documented in detail to avoid 'black box' criticism and obtain credible results. This includes the assumptions of no progression after 12 months. Particularly, considering the impact of the usage of alternative assumptions, methods and data will potentially result in substantially higher ICERs as illustrated in the exploratory analysis by the ERG.

8.2 Strengths and limitations of the assessment

The company used systematic review methods to identify the evidence on obeticholic acid for primary biliary cirrhosis. The majority of searches in the CS were well documented and easily reproducible. Searches were carried out on a broad range of resources. However no evidence was provided relating to fibrates, one of the comparators in the NICE scope. The company identified evidence comparing OCA to UDCA or placebo. The main evidence was based on a well-conducted international randomised controlled trial of 217 patients with a 12 month follow-up.

The main limitation of the evidence identified is that the main trial POISE is based on surrogate outcomes. The ERG is satisfied that the company has demonstrated some evidence of correlation between the surrogate outcomes of interest and longer-term clinical outcomes. However the extent of the correlation and the optimal thresholds of surrogate outcomes to predict long-term disease is unclear. The role of OCA as monotherapy in patients intolerant to UDCA was investigated in a small number of patients so results may not be reliable. POISE included mainly patients at an early stage of disease progression so the role of OCA in more advanced disease is less clear.

The lack of transparency, justification and details regarding the methods used in the CS are the main weaknesses in the cost effectiveness chapter and the model submitted by the company. Transparency is a key quality aspect of modelling. The lack of transparency hampered the validity check by the ERG. Additionally, the inability of performing external validation, the relatively short trial follow-up using intermediate outcomes and the reliance on non PBC sources in the model stress the uncertainty in the estimation of long-term outcomes.

8.3 Suggested research priorities

The main research priority is to identify the role of OCA on clinical outcomes such as those highlighted in the NICE scope[4] as current evidence relies on surrogate outcomes. The COBALT trial which investigates clinical outcomes is ongoing.[37] Duration is estimated to be approximately 8 years according to the time to accrue approximately 121 primary endpoint events. The start date of the trial was December 2014.[3]

There is also a need to compare OCA with other potential second line treatments including fibrates. There appear to be no ongoing trials comparing the two treatments. However we note the ongoing research into fibrates for PBC.[36]

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APPENDIX 1: DETAILS OF ERG ANALYSES (FOR VALIDATION PURPOSES)

Altered cells are printed in *italics*.

Fixing errors

1. Fixing discrepancy between TPs reported in the CS and used in the economic model (for biomarker component of the model; see Section 5.2.6 for more details). To fix this error, the ERG used the TPs reported in the CS.
   Transition matrices Y121,134,170,171,183,195,219,232,268,269,281,293, Z146,183,195,244,281,293

Fixing violations

2. Use TPs from POISE for the non-OCA regimen (for biomarker component of the model; see Section 5.2.6 for more details).
   Clinical inputs C10
3. Use proportions in the starting health states (for biomarker component) as derived from the POISE trial (see Section 5.2.3 for more details).
   Model settings C25,27, Defaults D46,
4. Use NHS reference costs for outpatient visits (see Section 5.2.9 for more details).
   F46Disease management costs D6:D7, D17, Defaults D286:D287
5. Use health state costs of £1,561 for CC (instead of £6,254) consistent with TA330 (for liver disease component of the model; see Section 5.2.9 for more details)
   Disease management costs D9, Defaults K289
6. Use age-dependent utilities (from the UK general population) for the low and moderate risk health states (for biomarker component of the model; see Section 5.2.8 for more details).
   Quality of life inputs D6:D7, Model parameters I115:116, Defaults D346:D347, UDCA Markov model DN24:206, OCA+UDCA Titration Markov model DN24:206

Matters of judgment

Remove the [redacted] HRQoL decrement (for liver disease component of the model; see Section 5.2.9 for more details).
Quality of life inputs D13, D20:D23, Defaults D353, D356:D358

A2 APPENDIX 2: SCATTER PLOTS AND COST EFFECTIVENESS ACCEPTABILITY CURVES OF OCA (WITH OR WITHOUT UDCA) VERSUS COMPARATORS IN BOTH POPULATIONS.

Figure A2.1: Scatter plot for PSA (UDCA-intolerant population), using the OCA list price

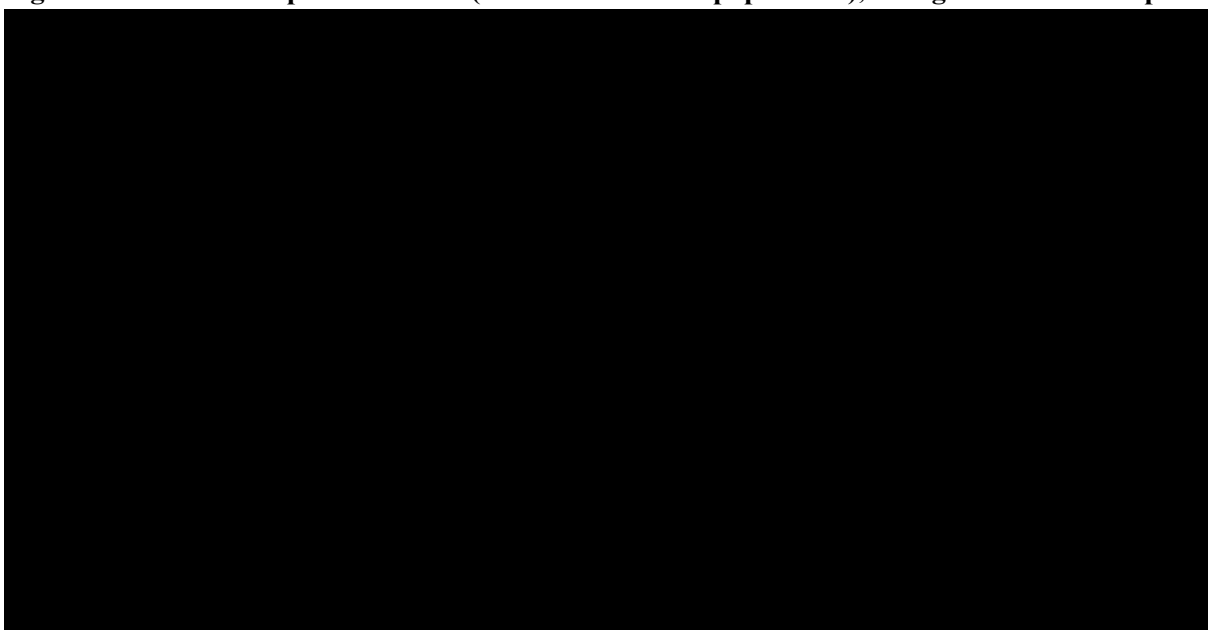


Figure A2.1: Cost effectiveness acceptability curve for OCA titration versus no treatment (UDCA-intolerant population), using the OCA list price

Source: Figure 32 of the CS[3]
OCA, obeticholic acid; UDCA, ursodeoxycholic acid

Figure A2.3: Scatter plot for PSA (UDCA inadequate responders population), using the OCA list price

Source: Figure 32 of the CS[3]
OCA, obeticholic acid; UDCA, ursodeoxycholic acid

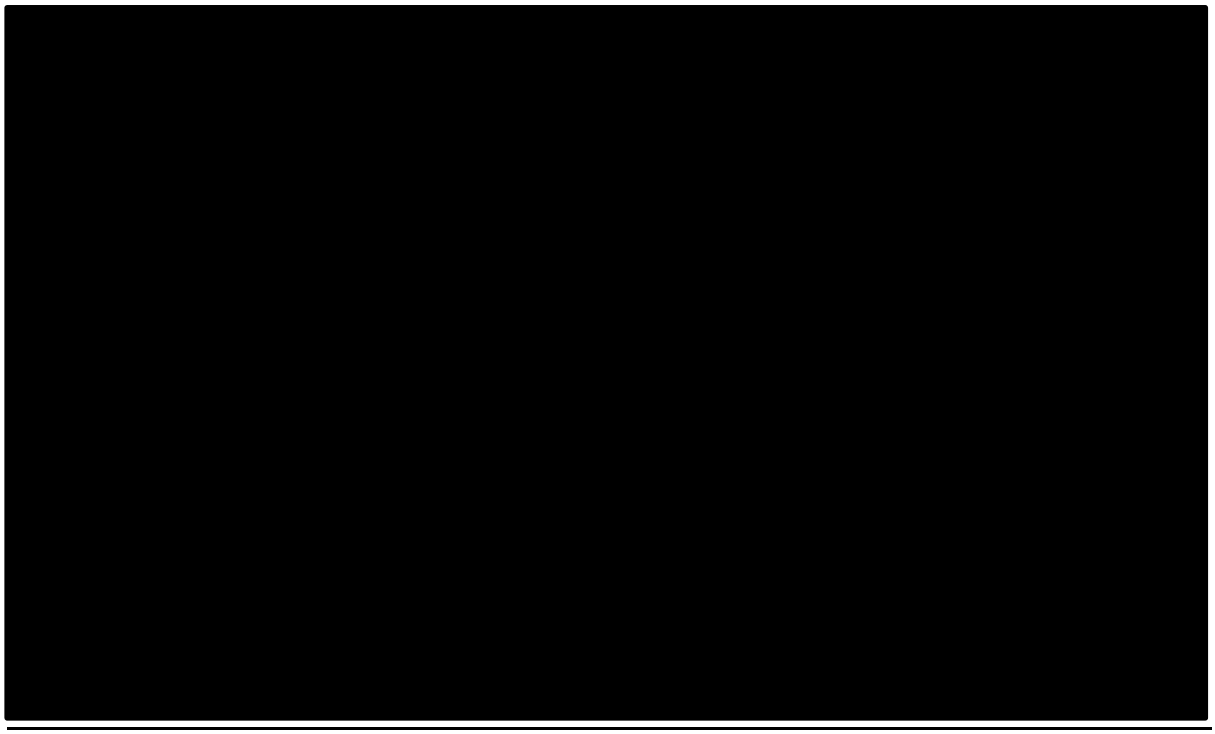
Figure A2.2: Cost effectiveness acceptability curve for OCA + UDCA titration versus UDCA (UDCA inadequate responders population), using the OCA list price

Source: Figure 34 of the CS[3]
OCA, obeticholic acid; UDCA, ursodeoxycholic acid

APPENDIX 3: TORNADO DIAGRAMS OF THE DSA FOR BOTH POPULATIONS.

Figure A3.1: Tornado diagram for OCA titration versus no treatment in the UDCA intolerant population, using the list price of OCA

Figure A3.1: Tornado diagram for OCA + UDCA titration versus UDCA in the UDCA inadequate responder population, using the list price of OCA



Source: Figure 36 of the CS[3]

in collaboration with:

ERASMUS UNIVERSITEIT ROTTERDAM
INSTITUTE OF HEALTH POLICY & MANAGEMENT

Maastricht University

Obeticholic acid for treating primary biliary cirrhosis

Confidential Appendix

Produced by Kleijnen Systematic Reviews (KSR) Ltd. in collaboration with Erasmus University Rotterdam (EUR) and Maastricht University

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In this confidential appendix, the patient access scheme (PAS) price of Obeticholic acid (OCA) has been implemented in all company's and ERG's analyses. The PAS price has been communicated by the company through the patient access scheme submission template on the 1st of December 2016.[1] The PAS price is implemented as a simple price discount of [redacted]% on the list price, which lowers the pack price of OCA from £2,384.04 to [redacted] (annual prices are respectively £29,005 and [redacted]).

In order to conduct these analyses, the ERG adjusted the following cells (for the ERG base-case analyses, these adjustments were added to the ERG base-case adjustments described in Appendix 4 of the ERG report):

'Treatment cost'!D8

'Default'!C230

These analyses are performed for the company base-case and the ERG base-case analyses. Results provided in the current confidential appendix concern OCA Titration (PAS price) versus UDCA in the UDCA inadequate responder population and OCA Titration (PAS price) versus 'No treatment' in the UDCA intolerant population.

Company's cost effectiveness results

In both populations, OCA (with or without UDCA) led to longer survival, a QALY gain, and higher costs than the comparators (i.e. no treatment for the UDCA-intolerant population and UDCA alone for the UDCA inadequate responders). The company provided disaggregated results for QALYs (Tables 5.14 and 5.15 of the ERG report)[2] and costs by health state (Tables 1 and 2). The low risk and moderate risk health states contribute to 74% and 73% of the absolute incremental QALY gained for the UDCA-intolerant population and UDCA inadequate responders. The disaggregated results are not reproduced in this confidential appendix since the PAS price does not influence the QALY results.

In the company base-case analysis, OCA (PAS price) versus UDCA resulted in an incremental cost effectiveness ratio (ICER) of £28,425 per additional QALY gained (deterministic results) in the UDCA inadequate responder population. OCA (PAS price) versus 'No treatment' was associated with an ICER of £21,438 per additional QALY gained (deterministic results) (Tables 3 and 4).

Tables 5 and 6 present the results of the first scenario analysis performed by the company for the UDCA intolerant and UDCA inadequate populations respectively (Scenario 1). In this analysis, the PAS price of OCA is used and the [redacted] utility decrement (ERG report Section 5.2.8) is removed. Tables 7 and 8 present the results of the second sensitivity analysis performed by the company, using the PAS price of OCA (Scenario 2). In this analysis, alternative transition probabilities are used from the pre-liver transplant to the liver transplant health states and from the pre-liver transplant to death health states. Results of these analyses were provided in the CS sent to the ERG on the 4th of October 2016.[3]

ERG's cost effectiveness results

The ERG base-case analyses results in an ICER of £44,945 per additional QALY gained for OCA versus UDCA in the UDCA inadequate responder patient population (probabilistic results). OCA versus 'No treatment' in the UDCA intolerant patient population was associated with an ICER of £31,682 per QALY gained (probabilistic results). In the UDCA inadequate responder population, OCA has a 0.0% and 0.1% probability of being cost effective at a willingness to pay of £20,000 and £30,000 per QALY, respectively. In the UDCA intolerant population, OCA has a 0% and 16.2% probability of being cost effective at a willingness to pay of £20,000 and £30,000 per QALY, respectively. Scatter plots and cost

effectiveness acceptability curves for the ERG base-case are presented in Figures 1 and 2 for the UDCA inadequate responders and in Figures 3 and 4 for the UDCA intolerant population.

Tables 9 and 10 provide the cost effectiveness results of the exploratory analyses performed by the ERG. These exploratory analyses all resulted in increased ICERs. The ERG base-case ICER should be regarded as a lower bound and it should be noted that the usage of alternative assumptions, methods and data will potentially result in substantially higher ICERs.

Table 1: Summary of costs by health state for UDCA inadequate responders – company's base-case

Health state	OCA Titration	No treatment	Increment	Absolute increment	Absolute increment (in %)*
Low risk[a]	[redacted]	[redacted]	[redacted]	[redacted]	37%
Moderate risk[b]	[redacted]	[redacted]	[redacted]	[redacted]	40%
Severe risk[c]	[redacted]	[redacted]	[redacted]	[redacted]	6%
Discontinuation	[redacted]	[redacted]	[redacted]	[redacted]	0%
Decompensated cirrhosis	[redacted]	[redacted]	[redacted]	[redacted]	5%
HCC	[redacted]	[redacted]	[redacted]	[redacted]	0%
Pre transplant (end stage)	[redacted]	[redacted]	[redacted]	[redacted]	2%
Liver transplant	[redacted]	[redacted]	[redacted]	[redacted]	3%
Post liver transplant	[redacted]	[redacted]	[redacted]	[redacted]	6%
Re-emergence of PBC	[redacted]	[redacted]	[redacted]	[redacted]	0%
Total	[redacted]	[redacted]	[redacted]	[redacted]	100%

Source: Table 76 of the CS provided by the company on the 4th of October 2016, in which the PAS price was already applied to OCA.[3]

Footnotes: [a] referred as 'ALP: ≤ 200 u/L and Bili: Normal' in the CS[4]; [b] referred as 'ALP: > 200 u/L and Bili: Normal' in the CS[3]; [c] referred as 'Bili: Abnormal and rising, or CC' in the CS[3]; * Calculated by the ERG

ALP, alkaline phosphatase; Bili, bilirubin; CC, compensated cirrhosis; CS, company submission; ERG, Evidence Review Group; HCC, hepatocellular carcinoma; OCA, obeticholic acid; PBC, primary biliary cholangitis/cirrhosis; QALY, quality-adjusted life year; UDCA, ursodeoxycholic acid; ULN, upper limit of normal

Table 2: Summary of costs by health state for UDCA-intolerant population – company's base-case

Health state	OCA + UDCA titration	UDCA + No treatment	Increment	Absolute increment	Absolute increment (in %)*
Low risk[a]	[redacted]	[redacted]	[redacted]	[redacted]	35%
Moderate risk[b]	[redacted]	[redacted]	[redacted]	[redacted]	39%
Severe risk[c]	[redacted]	[redacted]	[redacted]	[redacted]	6%
Discontinuation	[redacted]	[redacted]	[redacted]	[redacted]	0%
Decompensated cirrhosis	[redacted]	[redacted]	[redacted]	[redacted]	6%
HCC	[redacted]	[redacted]	[redacted]	[redacted]	0%
Pre transplant (end stage)	[redacted]	[redacted]	[redacted]	[redacted]	3%
Liver transplant	[redacted]	[redacted]	[redacted]	[redacted]	4%
Post liver transplant	[redacted]	[redacted]	[redacted]	[redacted]	7%
Re-emergence of PBC	[redacted]	[redacted]	[redacted]	[redacted]	0%
Total	[redacted]	[redacted]	[redacted]	[redacted]	100%

Source: Table 75 of the CS provided by the company on the 4th of October 2016, in which the PAS price was already applied to OCA.[3]

Footnotes: [a] referred as 'ALP: ≤ 200 u/L and Bili: Normal' in the CS[4]; [b] referred as 'ALP: > 200 u/L and Bili: Normal' in the CS[3]; [c] referred as 'Bili: Abnormal and rising, or CC' in the CS[3]; * Calculated by the ERG

ALP, alkaline phosphatase; Bili, bilirubin; CC, compensated cirrhosis; CS, company submission; ERG, Evidence Review Group; HCC, hepatocellular carcinoma; OCA, obeticholic acid; PBC, primary biliary cholangitis/cirrhosis; QALY, quality-adjusted life year; UDCA, ursodeoxycholic acid; ULN, upper limit of normal

Table 3: ERG base-case - UDCA inadequate responders – OCA PAS price

	OCA titration+UDCA		UDCA		Incremental results		
	QALYs	**Costs**	**QALYs**	**Costs**	**ΔQALY**	**ΔCosts**	**ICER**
Company base-case (deterministic)*	13.64	£261,527	7.85	£96,977	5.79	£164,551	£28,425
1. Fixing discrepancies between TPs[1]	13.68	£261,774	7.85	£96,968	5.83	£164,806	£28,280
2. Use transition probabilities from POISE for the non-OCA regimen	13.68	£261,776	8.48	£90,740	5.20	£171,036	£32,897
3. POISE trial proportion in starting health states	13.92	£263,317	8.37	£92,834	5.55	£170,482	£30,736
4. Use NHS reference costs for outpatient visits	13.68	£263,301	7.85	£97,849	5.83	£165,453	£28,394
5. Use health state costs consistent with TA330	13.68	£258,741	7.85	£78,004	5.83	£180,737	£31,017
6. Use UK age-dependent utility values	12.32	£261,776	7.39	£96,968	4.93	£164,808	£33,458
7. Remove [redacted] utility decrement	13.72	£261,776	8.11	£96,968	5.61	£164,808	£29,377
ERG base-case (deterministic)	12.57	£262,300	8.39	£72,332	4.17	£189,968	£45,541
ERG base-case (probabilistic)	12.53	£261,929	8.31	£72,223	4.22	£189,706	£44,945

Footnotes: * The ERG did not reproduce these results. These are based on the first version of the CS sent by the company on the 4th of October 2016[3]; [1] These errors were also corrected in the erratum submitted by the company[5]

ERG, Evidence Review group; ICER, incremental cost-effectiveness ratio; NHS, National Health Services; OCA, obeticholic acid; QALYs, quality-adjusted life years; TPs, Transition probabilities; UDCA, ursodeoxycholic acid

Figure 1: Scatterplot of the ERG base-case - UDCA inadequate responders – OCA PAS price

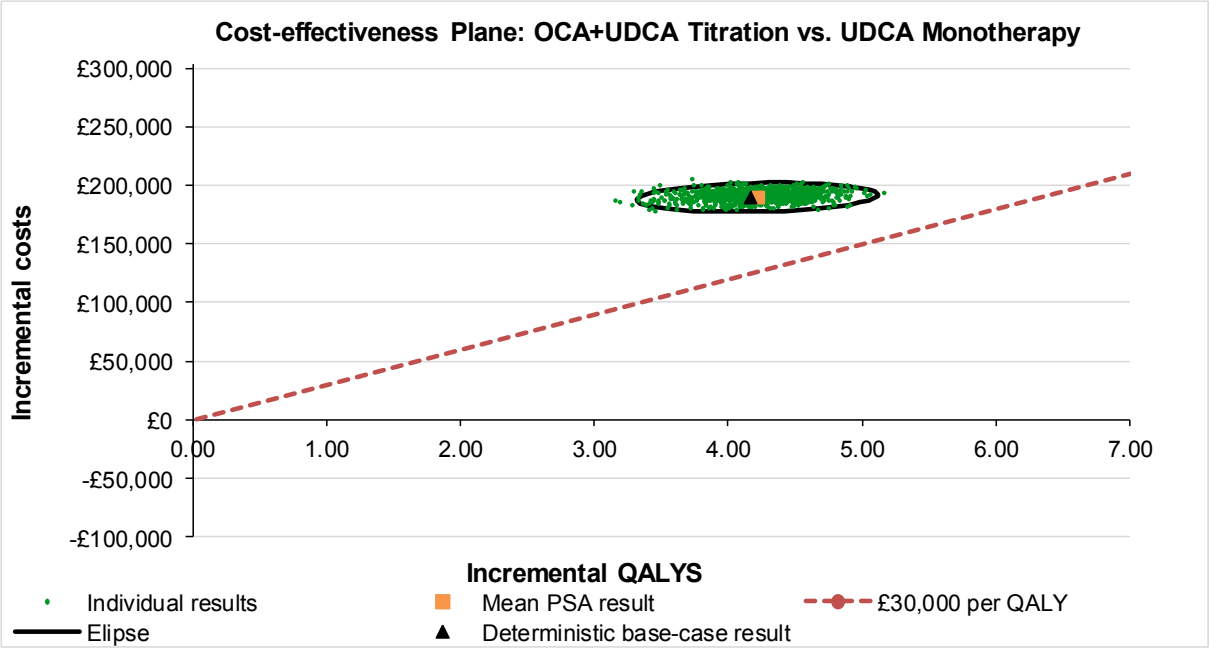


Figure 2: Cost effectiveness acceptability curve of the ERG base-case - UDCA inadequate responders – OCA PAS price

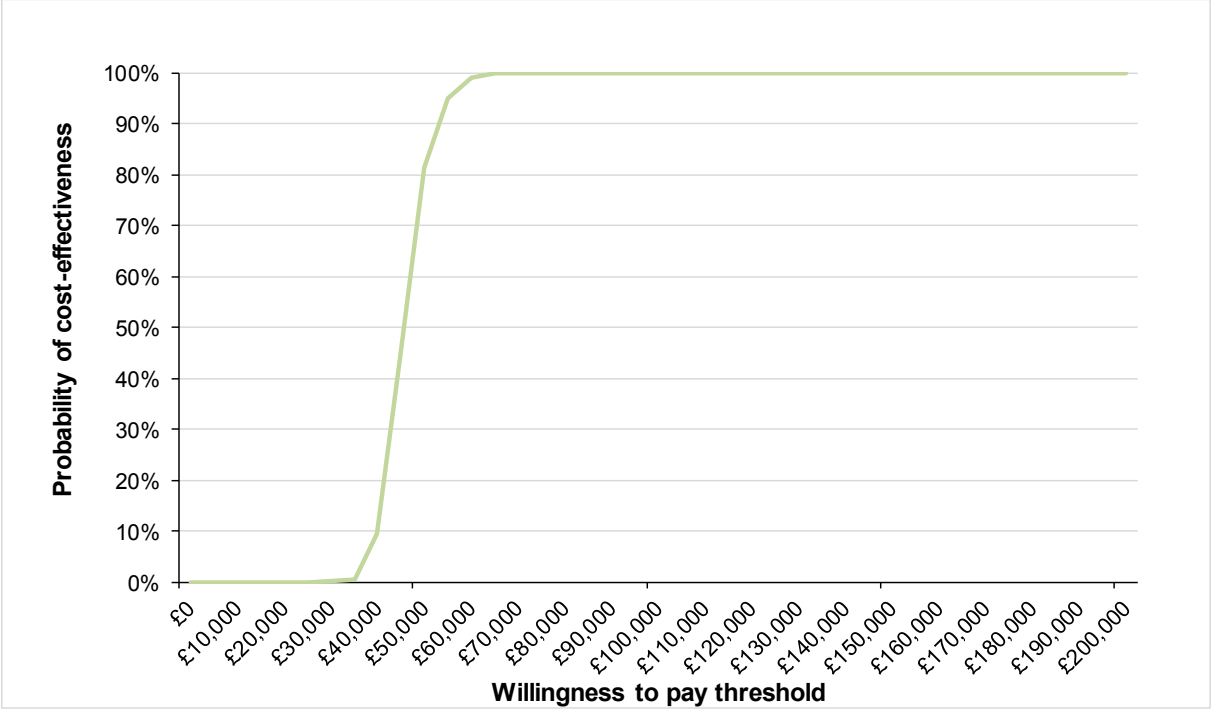


Table 4: ERG base-case - UDCA intolerant patients – OCA PAS price

	OCA titration		No treatment		Incremental results		
	QALYs	**Costs**	**QALYs**	**Costs**	**ΔQALY**	**ΔCosts**	**ICER**
Company base-case (deterministic)*	13.52	£251,443	6.61	£103,233	6.91	£148,210	£21,438
1. Fixing discrepancies between TPs[1]	13.56	£251,671	6.61	£103,233	6.95	£148,438	£21,351
2. Use transition probabilities from POISE for the non-OCA regimen	13.56	£251,674	7.00	£99,799	6.56	£151,875	£23,152
3. POISE trial proportion in starting health states	13.78	£253,217	6.89	£100,942	6.89	£152,275	£22,111
4. Use NHS reference costs for outpatient visits	13.56	£253,159	6.61	£103,698	6.95	£149,461	£21,500
5. Use health state costs consistent with TA330	13.56	£248,395	6.61	£81,773	6.95	£166,622	£23,969
6. Use UK age-dependent utility values	12.20	£251,674	6.29	£103,233	5.92	£148,441	£25,085
7. Remove [redacted] utility decrement	13.61	£251,674	6.91	£103,233	6.70	£148,441	£22,162
ERG base-case (deterministic)	12.44	£251,860	7.05	£78,461	5.38	£173,399	£32,217
ERG base-case (probabilistic)	12.39	£251,478	6.92	£78,477	5.46	£173,001	£31,682

Footnotes: * The ERG did not reproduce these results. These are based on the first version of the CS sent by the company on the 4th of October 2016[3]; [1] These errors were also corrected in the erratum submitted by the company[5]

ERG, Evidence Review group; ICER, incremental cost-effectiveness ratio; NHS, National Health Services; OCA, obeticholic acid; QALYs, quality-adjusted life years; TPs, Transition probabilities; UDCA, ursodeoxycholic acid

Figure 3: Scatterplot of the ERG base-case - UDCA intolerant population – OCA PAS price

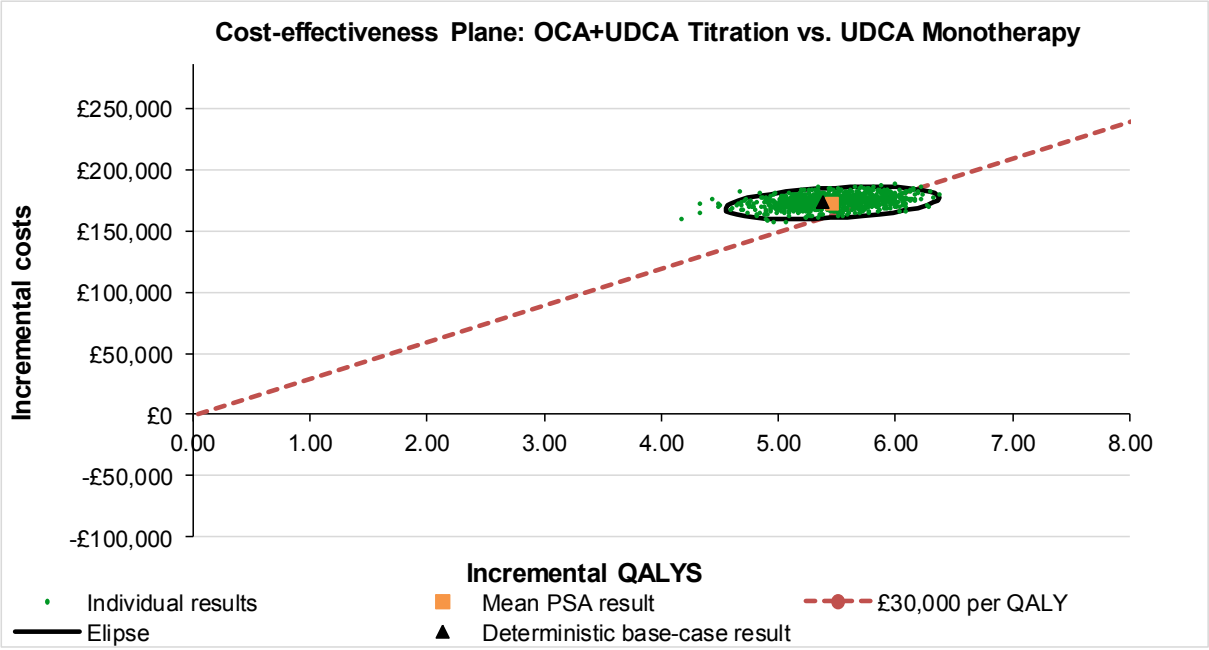
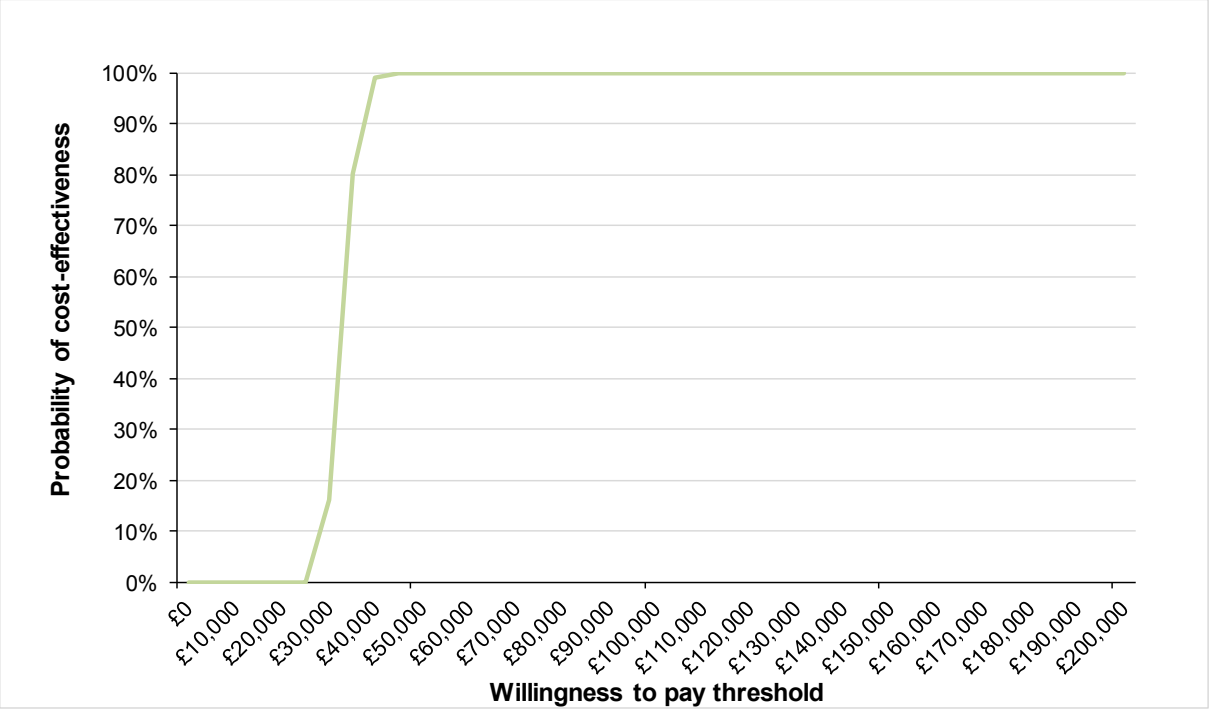


Figure 4: Cost effectiveness acceptability curve of the ERG base-case - UDCA intolerant population – OCA PAS price



Sensitivity / scenario analyses

Table 5: Company's scenario analysis 1 results: UDCA intolerant patients

Technologies	Total			Incremental			ICER (£)
	Costs (£)	LYG	QALYs	Costs (£)	LYG	QALYs	OCA versus No treatment
No treatment	£103,233	11.30	6.91	-	-	-	-
OCA titration	£251,443	16.65	13.57	£148,210	5.35	6.66	£22,250

Source: Table 84 of the CS submitted by the company on the 4th of October 2016.[3]

LYG: Life year gained; QALYs: Quality-adjusted life years; ICER: Incremental cost effectiveness ratio; OCA: Obeticholic acid.

Table 6: Company's scenario analysis 1 results: UDCA inadequate responders

Technologies	Total			Incremental			ICER (£)
	Costs (£)	LYG	QALYs	Costs (£)	LYG	QALYs	OCA + UDCA versus UDCA
UDCA	£96,977	12.35	8.11	-	-	-	-
OCA + UDCA titration	£261,527	16.75	13.69	£164,551	4.40	5.57	£29,524

Source: Table 85 of the CS submitted by the company on the 4th of October 2016.[3]

LYG: Life year gained; QALYs: Quality-adjusted life years; ICER: Incremental cost effectiveness ratio; OCA: Obeticholic acid; UDCA: ursodeoxycholic acid

Table 7: Company's scenario analysis 2 results: UDCA intolerant patients

Technologies	Total			Incremental			ICER (£)
	Costs (£)	LYG	QALYs	Costs (£)	LYG	QALYs	OCA versus No treatment
No treatment	£95,697	10.93	6.43	-	-	-	-
OCA titration	£250,197	16.59	13.49	£154,499	5.66	7.06	£21,874

Source: Table 87 of the CS submitted by the company on the 4th of October 2016.[3]

LYG: Life year gained; QALYs: Quality-adjusted life years; ICER: Incremental cost effectiveness ratio; OCA: Obeticholic acid.

Table 8: Company's scenario analysis 2 results: UDCA inadequate responders

Technologies	Total			Incremental			ICER (£)
	Costs (£)	LYG	QALYs	Costs (£)	LYG	QALYs	OCA+ UDCA versus UDCA
UDCA	£90,516	12.04	7.70	-	-	-	-
OCA + UDCA titration	£260,386	16.69	13.61	£169,870	4.66	5.91	£28,724

Source: Table 88 of the CS submitted by the company on the 4th of October 2016.[3]

LYG: Life year gained; QALYs: Quality-adjusted life years; ICER: Incremental cost effectiveness ratio; OCA: Obeticholic acid; UDCA: ursodeoxycholic acid

Table 9: ERG exploratory analysis - UDCA inadequate responders – OCA PAS price

	OCA titration		No treatment		Incremental results		
	QALYs	Costs	QALYs	Costs	ΔQALY	ΔCosts	ICER
1. Use TPs and model structure from TA330	12.67	£259,927	8.87	£38,094	3.80	£221,832	£58,412
2. Using TPs based on the POISE trial after 12months for the non-OCA treatment arms	12.79	£260,197	10.20	£54,015	2.59	£206,182	£79,668
3. Assume that TPs between biomarkers health states of the OCA arm are >0%	12.15	£257,410	8.39	£72,332	3.75	£185,078	£49,294
4. Use alternative costs for liver transplant	12.57	£262,108	8.39	£71,083	4.17	£191,025	£45,794

ERG, Evidence Review group; ICER, incremental cost-effectiveness ratio; NHS, National Health Services; OCA, obeticholic acid; QALYs, quality-adjusted life years; TPs, Transition probabilities; UDCA, ursodeoxycholic acid

Table 10: ERG exploratory analysis - UDCA intolerant patients – OCA PAS price

	OCA titration		No treatment		Incremental results		
	QALYs	Costs	QALYs	Costs	ΔQALY	ΔCosts	ICER
1. Use TPs and model structure from TA330	12.55	£248,426	7.64	£34,009	4.91	£214,417	£43,686
2. Using TPs based on the POISE trial after 12months for the non-OCA treatment arms	12.79	£248,486	10.18	£45,639	2.61	£202,848	£77,715
3. Assume that TPs between biomarkers health states of the OCA arm are >0%	12.02	£247,440	7.05	£78,461	4.97	£168,979	£34,031
4. Use alternative costs for liver transplant	12.44	£251,645	7.05	£76,942	5.38	£174,703	£32,459

ERG, Evidence Review group; ICER, incremental cost-effectiveness ratio; NHS, National Health Services; OCA, obeticholic acid; QALYs, quality-adjusted life years; TPs, Transition probabilities; UDCA, ursodeoxycholic acid

References

[1] Intercept Pharmaceuticals Inc. *Patient access scheme submission template (Biliary cirrhosis (primary) – obeticholic acid [ID:785]): Patient Access Scheme (PAS) appendix) [document provided by the company]*, October 2009 [accessed 7.12.16]. 30p.

[2] Fayter D, Ramaekers B, Grimm S, Pouwels X, Armstrong N, Ryder S, et al. *Obeticholic acid for treating primary biliary cirrhosis (Evidence Review Group report commissioned by the NIHR HTA Programme as project number STA 15/69/09) [Confidential until published]*. York: Kleijnen Systematic Reviews Ltd; Maastricht University, 30th November 2016. 115p.

[3] Intercept Pharmaceuticals Inc. *Biliary cirrhosis (primary) – obeticholic acid [ID:785]: Company evidence submission to National Institute of Health and Clinical Excellence. Single technology appraisal (STA)*, 30th September 2016. 216p.

[4] Intercept Pharmaceuticals Inc. *Biliary cirrhosis (primary) – obeticholic acid [ID:785]: Company evidence submission to National Institute of Health and Clinical Excellence. Single technology appraisal (STA)*, 26th October 2016 212p.

[5] Intercept Pharmaceuticals Inc. *Obeticholic acid for primary biliary cirrhosis [ID:785]: Erratum to Intercept's responses to ERG questions*, 21st November 2016 29p.

ERG appendix corrections page

The ERG appendix contains the results of the cost-effectiveness analysis, which includes the confidential patient access scheme discount based on the model in the original company submission. The company supplied an updated model that corrected an error regarding patient numbers used in the economic model. This correction page gives the cost-effectiveness results based on the updated company erratum and replaces the corresponding tables in the ERG appendix.

Sensitivity / scenario analyses

Table 1: Company's scenario analysis 1 results: UDCA intolerant patients

Technologies	Total			Incremental			ICER (£)
	Costs (£)	LYG	QALYs	Costs (£)	LYG	QALYs	OCA versus No treatment
No treatment (placebo)	£103,233	11.30	6.91	–	–	–	–
OCA titration	£251,671	16.68	13.61	£148,439	5.38	6.70	£22,160

Source: Table 35 of the Erratum submitted by the company on 20th December 2016.[1]

LYG: Life-year gained; QALYs: Quality-adjusted life years; ICER: Incremental cost-effectiveness ratio; OCA: Obeticholic acid

Table 2: Company's scenario analysis 1 results: UDCA inadequate responders

Technologies	Total			Incremental			ICER (£)
	Costs (£)	LYG	QALYs	Costs (£)	LYG	QALYs	OCA + UDCA versus UDCA
UDCA + placebo	£96,977	12.35	8.11	–	–	–	–
OCA titration + UDCA	£261,791	16.78	13.72	£164,814	4.43	5.61	£29,374

Source: Table 36 of the Erratum submitted by the company on 20th December 2016.[1]

LYG: Life-year gained; QALYs: Quality-adjusted life years; ICER: Incremental cost-effectiveness ratio; OCA: Obeticholic acid; UDCA: ursodeoxycholic acid

[1] Intercept Pharmaceuticals Inc. *Biliary cirrhosis (primary) – obeticholic acid [ID:785]: Erratum to Intercept's responses to ERG questions. Single technology appraisal (STA)*, 21st November 2016. 18-19p.

Table 3: Company's scenario analysis 2 results: UDCA intolerant patients

Technologies	Total			Incremental			ICER (£)
	Costs (£)	LYG	QALYs	Costs (£)	LYG	QALYs	OCA versus No treatment
No treatment (placebo)	£94,717	10.89	6.39	–	–	–	–
OCA titration	£250,303	16.61	13.52	£155,586	5.73	7.13	£21,824

Source: Table 37 of the Erratum submitted by the company on 20th December 2016.[1]

LYG: Life-year gained; QALYs: Quality-adjusted life years; ICER: Incremental cost-effectiveness ratio; OCA: Obeticholic acid

Table 4: Company's scenario analysis 2 results: UDCA inadequate responders

Technologies	Total			Incremental			ICER (£)
	Costs (£)	LYG	QALYs	Costs (£)	LYG	QALYs	OCA+ UDCA versus UDCA
UDCA + placebo	£89,666	12.00	7.67	–	–	–	–
OCA titration + UDCA	£260,540	16.72	13.65	£170,874	4.72	5.98	£28,596

Source: Table 38 of the Erratum submitted by the company on 20th December 2016.[1]

LYG: Life-year gained; QALYs: Quality-adjusted life years; ICER: Incremental cost-effectiveness ratio; OCA: Obeticholic acid; UDCA: ursodeoxycholic acid

in collaboration with:

ERASMUS UNIVERSITEIT ROTTERDAM
INSTITUTE OF HEALTH POLICY & MANAGEMENT

Maastricht University

Obeticholic acid for treating primary biliary cirrhosis

ERRATA

This document contains errata in respect of the ERG report in response to the company's factual accuracy check.

The table below lists the page to be replaced in the original document and the nature of the change:

Page nr:	**Change:**
12, 47,49,54,99	Percentage decrease in ALP was omitted from the primary composite outcome. 'This has been amended on all pages to 'percentage of participants with alkaline phosphatase (ALP) < 1.67 x upper limit of normal (ULN) and total bilirubin ≤ ULN and ALP ≥**15%** decrease from baseline at 12 months)'
20	Section 2.2, second paragraph 'antibody' replaced with 'autoantibody'.
20	In the final paragraph repeated words 'for second-line treatment' were deleted.
21	In the first full paragraph the sentence 'Draft guidance from the BSG note that there is no consensus on routine use of UDCA post-transplant.' has been removed.
26, 44	In the description of the POISE trial one sentence has been amended for clarity. 'The patients in POISE were only up-titrated to 10 mg OCA **at six months** if they did not reach the primary endpoint criteria for response.' One sentence has been added. 'The remaining patients in this arm responded to OCA treatment and so did not require up-titration, as per the protocol.'
28	Section 3.4 third paragraph was amended to: 'the **estimated** study completion date is April 2023.'
35	The first full paragraph has been amended to: 'In addition to this trial, another Phase 2 study (747-205) is currently ongoing in the US that includes patients from 18 years of age and aims to investigate the change from baseline in HDL metabolism as the primary outcome.'
36	Table 4.3 final bullet point has been amended to: 'Combinations of the presence or absence of biochemical response to UDCA treatment (yes/no) and intolerance to UDCA (yes/no)'
36	Table 4.3 footnote has been amended to 'Paris I criteria defined as ALP ≤3x ULN and AST ≤2x ULN and total bilirubin ≤ ULN'
37	Table 4.4 'Bile acids row' amended to: 'Absolute values and change from baseline by treatment group at 6 and 12 months' follow-up **from participants who had a confirmed fasting of approximately 8 hours or more prior to their visit** in the following:'
43	ERG comments second bullet point has been amended to: 'It is a multicentre international trial with 217 participants comparing OCA **in combination with** UDCA to UDCA alone in patients with an inadequate response to UDCA and comparing OCA to no treatment in patients intolerant to UDCA'
44	First bullet point amended: 'Although stratified on several important variables, the POISE trial had differences between treatment groups at baseline. In particular the placebo group and the OCA 10 mg fixed dose group had a slightly higher incidence of pruritus than the OCA titration group and the placebo group had a slightly higher incidence of fatigue compared with both OCA treatment groups, which should be borne in mind particularly when interpreting results of adverse events.'
54	In the first paragraph the following sentence has been amended to: 'Study 747-202 reported mean (SD) percentage change in ALP levels was –23.7% (17.8) for the OCA 10 mg group versus –2.6% (12.5) for placebo.'

1. SUMMARY

1.1 Critique of the decision problem in the company's submission

The patient population described in the final scope issued by the National Institute for Health and Care Excellence (NICE) was '*People with primary biliary cirrhosis whose disease has an inadequate response to, or who are unable to tolerate, ursodeoxycholic acid*'. For patients whose disease has an inadequate response to ursodeoxycholic acid (UDCA), obeticholic acid (OCA) was to be compared to UDCA alone or in combination with fibrates. For patients who are unable to tolerate UDCA, comparators were fibrates or no additional treatment. Outcomes included mortality, liver function based on markers of liver biochemistry, symptoms, including pruritus, fatigue and abdominal pain, time to liver transplantation, primary biliary cirrhosis (PBC)-related events, adverse effects of treatment and health-related quality of life (HRQoL).

The decision problem in the company submission (CS) differed from the scope in a number of ways. Firstly, fibrates were not considered by the company to be a comparator to OCA. Secondly, the main evidence presented (the POISE trial) considered only surrogate outcomes. No data were available from the trial on long-term clinical outcomes outlined in the scope such as mortality and liver transplantation. Finally the number of patients in POISE receiving OCA as monotherapy (i.e. without UDCA) was very small (11 patients) so results for this group of patients should be treated with some caution.

1.2 Summary of clinical effectiveness evidence submitted by the company

The company conducted a systematic review to inform the submission. The aim of the systematic review was '*to identify all relevant evidence for the efficacy and safety of interventions used to treat PBC.'* A post-hoc decision was taken to include only trials with an OCA treatment arm.

The systematic review identified one main randomised controlled trial, POISE, and two supporting Phase 2 trials. The company did not pool the results of the trials.

POISE, was an international trial of 217 patients including patients from the UK. The trial compared UDCA and combined UDCA and OCA in patients with an inadequate response to UDCA and OCA and placebo in those who were intolerant to UDCA. Seventy-three patients received 10 mg OCA, 71 patients received 5 mg OCA rising to 10 mg during months 6 to 12 if they had an inadequate response to UDCA (the titration group).

The primary outcome of POISE was a composite one (percentage of participants with alkaline phosphatase (ALP) < 1.67 x upper limit of normal (ULN) and total bilirubin ≤ ULN and ALP ≥ 15% decrease from baseline at 12 months). At 12 months 47% of participants in the OCA 10 mg group achieved the primary outcome, 46% in the titration group and 10% in the placebo group ($p < 0.0001$ for both comparisons). The results of other surrogate outcomes supported these findings. Incidence of adverse events (AEs) was similar across groups. Events occurring more frequently in treatment groups included pruritus. It was noted that 10% of patients discontinued treatment due to pruritus in the OCA 10 mg group which did not titrate based on tolerability.

The Phase 2 trials supported the positive findings of POISE on surrogate outcomes.

1.3 Summary of the ERG's critique of clinical effectiveness evidence submitted

The systematic review conducted by the company was broadly appropriate to the scope of this submission. The CS and response to clarification provided sufficient details for the ERG to appraise the searches. A broad range of databases were searched, and additional searches of conference proceedings and other relevant resources including trials databases, HTA agencies, specialist and organisational

The supporting study was a meta-analysis of 4,845 patients diagnosed with PBC from 1959 to 2012 with a median follow-up of 7.3 years. It included both UDCA treated and non-treated patients.[11]

The CS states that *'PBC has a substantial detrimental impact on quality of life, and HRQoL impairment is correlated with the severity of the disease.'*[3] They cite a number of studies including a UK cohort study of 2,353 patients[12] in which *'35% reported impairment of HRQoL compared with 6% of healthy controls (p<0.001), and 46% rated their overall health as 'fair' or 'poor' compared with 15% of healthy controls (p < 0.0001).[12]'*[3]

In addition to its impact on patients, the burden of the disease from the healthcare perspective is outlined. *'PBC is also associated with considerable healthcare costs. In 2014/15 there were 707 hospital admissions in England for PBC (ICD10 K74.3), accounting for 963 consultant episodes and 3,767 bed days[7,]'*[3] They further note that *'PBC is one of the most frequent indications for liver transplantation in Europe….There were 621 elective liver transplants performed in the UK in 2014/2015, of which at least 7% were for PBC.[13]'*[3]

ERG comment:

- The references cited by the company were checked. The underlying health problem was considered to be appropriately described and appropriate references cited.
- The impact on patient quality of life was appropriately highlighted. The ERG notes that whilst the impact of PBC may be limited in early-diagnosed UDCA-responsive patients, among those who are unresponsive highly disabling symptoms such as fatigue and pruritus are common and patients face possible progression into cirrhosis and ultimately liver failure.

2.2 Critique of company's overview of current service provision

The company states that no NICE guidance or pathway specific to PBC is available.[3]

The CS states that *'Patients are commonly asymptomatic at diagnosis, and are referred to secondary care on discovering abnormal liver function and / or positive autoantibody by blood tests at a GP visit for an unrelated illness.[7, 8] Occasionally patients are referred internally, most commonly from a rheumatologist. Rarely, patients are referred due to pruritus, abnormal ultrasound, or decompensation (ascites).'*[3]

The company further state that *'The only licensed treatment for PBC is ursodeoxycholic acid ((UDCA).'*[3] The company states that '*On diagnosis of PBC, UDCA is prescribed at 13-15mg/kg/day. Patients are monitored at 3-4 months for tolerability, and at 6 and 12 months to gauge response and compliance to therapy.'*[3] The company cites two relevant clinical guidelines.[14, 15] Both recommend long-term therapy at this dosage of UDCA as a first line of treatment.[14, 15]

The company states that *'up to 74% of patients have an incomplete response to UDCA and there are currently no available licensed or effective treatment options for these patients.'*[3] The company states that *'There are several response criteria that have been proposed to define non-response / progression….; however, there is no consensus as to which of these criteria should be used.'*[3]

The indication for obeticholic acid is 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'* (Section 2.2.2 of the CS) [3] Therefore the place of obeticholic acid in the clinical pathway for PBC would be as a second-line treatment.

The CS states that '*There are no licensed or effective drugs approved for second-line treatment for the management of patients with an inadequate response to, or intolerance to, UDCA.'*[3] They further state

that *'other treatments have been trialled for use in PBC, including budesonide and fibrates (which are contraindicated in PBC).[CS refs 22,23] However, limited efficacy has been observed in these other treatments.'*[3]

The CS states that *'Liver transplantation is the only treatment for patients with late-stage PBC, where UDCA has limited efficacy.[14]'* The CS outlines the challenges and risks of liver transplantation and notes that *'up to 43% of patients will have a recurrence of PBC within 15 years[16].'*

The CS states that '*No additional tests or investigations are required for OCA treatment.'*[3] Although OCA treatment is to be initiated by specialists in the treatment of PBC, the company states that no additional infrastructure will be required for treatment with OCA. However patients are required to undergo a consultation six months after treatment initiation to assess tolerability and determine if the dose should be increased to 10 mg to achieve optimal response.[3]

ERG comment:

- The company correctly states that there is no specific NICE guidance on PBC. The CS cites two clinical guidelines – by the European Association for the Study of the Liver (EASL) published in 2009[14] and the more up-to-date but as yet unpublished British Society of Gastroenterology (BSG) guidelines.[15] The CS correctly states that UDCA is the only licensed treatment at first line for PBC.
- Response rates to UDCA between 20 and 70% have been identified.[4] The company correctly highlight that determining response rates to UDCA depends on the specific criteria used to assess response. Several sets of criteria have been used across the research literature. We are advised by our clinical expert that in practice various systems may be used including simple clinical criteria.
- Clinical guidelines state that there are no second line agents when patients have failed to respond to UDCA.[14, 15] OCA would therefore be the only agent available at second line. The company mentions other agents that have been investigated (fibrates are most relevant to this submission). The statement *'limited efficacy has been observed'* in relation to other treatments was not supported by any references.[3] A further discussion of the role of fibrates as a comparator to OCA can be found in Section 3 of this report, the decision problem.

of monotherapy including 49 patients, 20 of whom received 10 mg OCA and 23 received placebo. The remainder received 50 mg OCA and were not relevant to the proposed dosage.[29] As stated above, the role of OCA monotherapy at the appropriate dosage has only been investigated in a small number of patients so results for this group of patients may not be reliable.

- In the POISE trial 73 patients were randomised to a fixed dose of 10 mg OCA and 73 patients received the placebo.[27] Seventy-one patients were randomised to the titration group which reflects the recommended dosage. They received OCA 5 mg OD for the initial six months period. The patients in POISE were only up-titrated to 10 mg OCA at six months if they did not reach the primary endpoint criteria for response.[27] The ERG draws to the attention of the committee that the evidence for obeticholic acid given at the recommended dosage is based on the 33 patients who actually up-titrated to 10 mg.[27] The remaining patients in this arm responded to OCA treatment and so did not require up-titration, as per the protocol. The company notes that *'further benefit in terms of efficacy is likely to be seen in clinical practice in this patient group due to the higher dose of OCA.'*[3] This appears to be reasonable but is an assumption.

3.3 Comparators

For people whose disease has an inadequate response to UDCA the CS evaluates the use of UDCA alone as a comparator as per the final scope issued by NICE. For people who are unable to tolerate UDCA the CS (more specifically the POISE trial) compared obeticholic acid alone to placebo (representing no additional treatment as stated in the NICE scope). As stated above, 11 patients (7%) took obeticholic acid alone in POISE (five in the OCA titration group and six in the OCA 10 mg fixed dose group and five patients received a placebo alone). The CS presents results for this comparison but notes that these *'should be interpreted with caution due to low patient numbers.'*[3]

However the comparators addressed in the CS differ from those in the final scope issued by NICE in that fibrates have not been included as a comparator for people whose disease has an inadequate response to UDCA nor for those who are intolerant to UDCA. The company provide several justifications for this including: fibrates not being licensed for this indication in the UK, not being standard care, they are contraindicated in PBC, have been rarely used in the UK and efficacy is as yet unproven with a small number of limited studies with some safety concerns.[3]

ERG comment:

- As stated above, the role of OCA monotherapy compared to placebo (no treatment) has only been investigated in a small number of patients so results for this group may be less reliable than those taking obeticholic acid in combination with UDCA.
- The omission of fibrates from the comparators in the decision problem was investigated by the ERG in several ways. We consulted clinical experts and identified systematic reviews of fibrates as the most reliable source of up to date evidence. Our response to the omission of fibrates is given in the table below.

Table 3.1: Response to the omission of fibrates as a comparator in the submission

Assertion in the company submission	ERG comments
'Fibrates are not licensed in the UK, nor are they standard of care.' 'They are rarely used, with only [redacted] of patients in the UK-PBC cohort having ever taken fibrates for any condition (not necessarily for PBC)'[3]	Fibrates are not licensed for this indication. We are advised that fibrates are not routinely used in the UK for PBC.

3.4 Outcomes

The final scope issued by NICE specified patient outcomes including mortality, symptoms including pruritus, fatigue and abdominal pain, time to liver transplantation, PBC-related events, health-related quality of life and adverse effects of treatment.[4] However all efficacy outcomes in the POISE trial which forms the main evidence of the submission relate to surrogate outcomes.[3] These include a range of liver function biomarkers and other biomarkers related to PBC. Disease-specific quality of life based on the PBC-40 tool was collected in POISE but was not specifically mentioned as being addressed in the decision problem. Adverse events were also collected in POISE.[3]

The CS explains that '*due to the rare and chronic nature of PBC and the slow progression in most patients, a long-term trial is required to capture clinical outcomes such as mortality, transplant-free survival, and the incidence of complications.*'[3] The POISE trial is of 12 months' duration although there is an ongoing five year long-term safety extension (LTSE). The LTSE has data from 12 months but efficacy is still based on surrogate outcomes.[3] The company cite three references to provide evidence for the correlation of the primary outcome of POISE (combined alkaline phosphatise (ALP) and bilirubin levels) to disease prognosis.[11, 24, 25]

The company also note that there is an ongoing trial of obeticholic acid (COBALT) that measures clinical outcomes. Details of the COBALT trial are provided in Table 39 of the CS.[3] Briefly, this is a double-blind randomised, placebo-controlled trial of obeticholic acid on clinical outcomes in patients with PBC. The estimated enrolment is 350 across up to 170 international sites. Duration is estimated to be approximately eight years according to the time to accrue approximately 121 primary endpoint events. The primary outcome is a composite endpoint of clinical events. The start date of the trial was December 2014 and the estimated study completion date is April 2023.[3]

ERG comment:

- The ERG draws the attention of the committee to the fact that the main evidence in the submission relates to surrogate outcomes. The ERG did not have the means to systematically review the validity of this correlation. Instead the ERG investigated the three references cited by the company as evidence of the correlation. The ERG observed that one of the references cited was a meta-analysis of individual patient data (4,845 patients) which concluded that *'Levels of alkaline phosphatase and bilirubin can predict outcomes (liver transplantation or death) of patients with PBC and might be used as surrogate end points in therapy trials.'*[11] This finding was supported by a retrospective review of 73 patients treated with UDCA over 36 months.[24] Biochemical response predicted histological progression, assessed with paired biopsies about 10 years apart, as well.[25] The ERG is satisfied that the company demonstrated evidence of some correlation between the surrogate outcomes of interest and longer-term clinical outcomes. However the extent of the correlation and the optimal thresholds of surrogate outcomes to predict long-term disease are unclear.
- The definitive effects of obeticholic acid on clinical outcomes relevant to patients awaits the results of the COBALT trial.[37]
- The ERG asked the company if any interim data were available from the COBALT trial which investigates clinical outcomes. The company confirmed that '*there are no interim data available and no interim analysis is planned since COBALT is an events-driven trial and 121 primary endpoint events need to have occurred before the trial will report and analyses will be performed*.'[32]

summarised only for subjects who received 10 mg OCA, since this is the upper limit for the licensed indication of OCA.'[3]

An additional trial, COBALT (NCT02308111) is mentioned in the CS (Section 4.14 of the submission).[3] This trial seeks to evaluate the effect on OCA on clinical outcomes such as transplant-free survival. The ERG can confirm that the trial is still ongoing and that no interim data has been made available.[37] Please see Section 3.4 of this report for a discussion relating to COBALT. In addition to this trial, another Phase 2 study (747-205) is currently ongoing in the US that includes patients from 18 years of age and aims to investigate the change from baseline in HDL metabolism as the primary outcome.[3]

As stated in the CS, '*the results from the double-blind phase of POISE are presented as the main efficacy evidence and the two Phase 2 studies as supporting evidence*'. [3] In this regard, this report follows the same structure. More detail will be provided on the double blind phase of POISE with a briefer summary of the Phase 2 trials.

ERG comment:

- The ERG agrees that the POISE trial provides the main evidence for the comparison with UDCA or placebo and that the two Phase 2 trials represent supporting evidence.
- The ERG is satisfied that no data from the ongoing COBALT trial could have been used to inform the CS.
- The included trials did not compare OCA to fibrates as outlined in the scope.[4]

4.2.2 Overview of the POISE trial

An overview of the POISE trial and its extension study is presented in Table 4.2.

Table 4.2: Summary of the POISE trial and its extension study

Trial no. (acronym)	Population	Intervention	Comparator
747-301 (POISE); NCT01473524	Patients diagnosed with PBC with ALP ≥1.67x ULN and/or total bilirubin >ULN but <2x ULN who fail to respond to or are intolerant to treatment with UDCA.	Oral OCA (5 mg or 10 mg) taken OD.	Placebo
LTSE to POISE	All participants who completed the 12-month double-blind phase of POISE and who were willing to enrol in the 5-year LTSE phase of the study.	Oral OCA (5–25 mg[a]) taken OD	N/A

Source: CS
Footnote: a) All patients initiated OCA at 5 mg OD; daily dose could be up-titrated if a satisfactory response was not achieved in 5 mg increments to a total dose of 25 mg OD (one increment per 3 months permitted), depending on tolerability
ALP, alkaline phosphatase; LTSE, long-term safety extension; OCA, Obeticholic acid; OD, once daily; PBC, primary biliary cholangitis; UDCA, ursodeoxycholic acid; ULN, upper limit of normal.

The main methodological features of the double-blind phase of the POISE trial are summarised in Table 4.3.

Table 4.3: Overview of POISE trial

Trial Design	Phase 3, randomised double-blind, placebo-controlled, parallel group trial. Stratified randomisation according to: - higher risk of developing clinical outcomes i.e. Paris I criteria* - intolerance to UDCA - Combinations of the presence or absence of biochemical response to UDCA treatment (yes/no) and intolerance to UDCA (yes/no)'
Setting	59 sites in 13 countries. (7 sites in England and 2 sites in Scotland)
Participants	217 were randomised (216 gave consent)
Interventions	3 arms: Placebo (with or without UDCA) (n = 73) 10 mg OCA, with or without UDCA (n = 73) Titration (5mg OCA rising to 10 mg during months 6 to 12 if inadequate response to UDCA), with or without UDCA) (n = 71)
Follow-up	12 months
Primary Outcome	Percentage of participants in the 10 mg OCA fixed dose group at 12 month achieving the composite endpoint: - ALP <1.67x ULN, and - total bilirubin ≤ULN, and - ALP decrease ≥15% from baseline
Source CS[3] Footnote: * Paris I criteria defined as ALP ≤3x ULN and AST ≤2x ULN and total bilirubin ≤ ULN ALP, alkaline phosphatase; CS, company submission; TEAEs, Treatment-emergent adverse events; ULN, upper limit of normal	

Table 4.4 details the secondary endpoints of the POISE trial and their definitions.

Table 4.4: Summary of secondary endpoints of the double-blind phase of POISE

Study outcome	Definition
ALP response rates	Absolute and percentage change from baseline in ALP at Month 6 and Month 12 Percentage of participants with a decrease in ALP from baseline of ≥10%, ≥15%, ≥20%, and ≥40% at Week 2, Month 3, Month 6, Month 9 and Month 12, Percentage of participants with ALP ≤ULN, summarised by treatment at all post-baseline assessments

Biochemical treatment response criteria	Percentage of participants meeting the Paris I, Paris II, Mayo II, Toronto II, or Rotterdam response criteria* at Week 2, Month 3, Month 6, Month 9, and Month 12. The analysis was repeated for subgroups of participants who met and did not meet the requirement of a responder at baseline for the endpoint analysed. Number and percentage of participants with: • Normal bilirubin (≤ULN) and normal albumin (≥LLN), • Moderate (bilirubin >ULN or albumin <LLN), and • Severe (bilirubin >ULN and albumin <LLN) at baseline, Week 2, Month 3, Month 6, Month 9 and Month 12.
Clinical laboratory values	Defined as the absolute and percentage change from baseline in ALP, GGT, ALT, AST, total and conjugated (direct) bilirubin, albumin, and prothrombin time (PT) and international standardised ratio (INR) summarised by treatment group and visit.
Questionnaire PBC-40	Absolute change from baseline in six domains (cognitive, social, emotional function, fatigue, itch, and general symptoms) were summarised by treatment using descriptive statistics at Week 2, Month 3, Month 6, Month 9, and Month 12. A total score was not calculated.
Patient Research Questionnaire	'A simple patient research questionnaire was administered at Month 12, or at termination if the subject withdrew from the study prior to this, to request feedback about the subjects' perception of the study.'[3]
Biomarkers and non-invasive assessments of liver fibrosis	Absolute change from baseline in the following markers: Markers of hepatic fibrosis, inflammation and other disease relevant biomarkers, including CRP, tumour necrosis factor-α (TNF-α), transforming growth factor β (TGF-β), fibroblast growth factor-19 (FGF-19), Interleukin-6 (IL-6), CK-18, autotaxin, and lysophosphatidic acid (LA), at Month 6 and Month 12 Enhanced liver fibrosis (ELF) score and its components hyaluronic acid (HA), procollagen-3 N-terminal peptide (P3NP), and tissue inhibitor of metalloproteinase 1 (TIMP-1) at Month 6 and Month 12 Hepatic stiffness measurements (at selected study sites) at Month 12, assessed by transient elastography (TE).
Bile acids	Absolute values and change from baseline by treatment group at 6 and 12 months' follow-up in the following from participants who had a confirmed fasting of approximately 8 hours or more prior to their visit in the following Total bile acids, total endogenous bile acids, and totals for the individual bile acids (UDCA, chenodeoxycholic acid [CDCA], deoxycholic acid [DCA], cholic acid [CA] and lithocholic acid [LCA]) and their respective conjugates Proportion of each of the individual bile acids relative to total bile acids
OCA Pharmacokinetics analysis	Values at Month 6 and Month 12 for OCA (unconjugated), glyco-OCA, tauro-OCA, and total OCA from participants who had a confirmed fasting of

	approximately 8 hours or more prior to their visit were included in the analysis. The effect of BAS on OCA and total bile acid concentration, as well as the percentage change in ALP, were explored as part of the PK analysis. Relationships between plasma total OCA concentrations (unconjugated and conjugated) and FGF-19 concentrations, endogenous bile acid concentrations, ALP and liver enzyme levels, and severity of pruritus were explored.
Safety	TEAEs defined as any adverse events (AEs) that newly appeared, increased in frequency, or worsened in severity following initiation of investigational product. Additionally, Pruritus was measured by using the 5-D pruritus questionnaire and a VAS score at week 2, months 3, 6, 9 and 12.
Clinical laboratory evaluations	Physical examinations, vital signs, body weight and BMI, electrocardiongram, dual-emission x-ray absorptioametry (DEXA) scan of the femoral neck and lumbar spine, Mayo Risk Score to assess survival and MELD score to assess the severity of chronic liver disease were assessed at week 2, months 3, 6, 9, and 12.
Source: Section 4.3.6 of CS[3] Footnote: *Different response criteria studied in POISE are reported in Table 16 of the CS. BAS, bile acids sequestrants; CS, company submission; TEAEs, Treatment-emergent adverse events	

Disease characteristic	Placebo (n=73)	OCA titration (n=70)	OCA 10 mg fixed dose (n=73)	Total (n=216)
Mean duration of PBC, years				
Mean (SD)	8.3 (5.4)	8.3 (5.8)	9.2 (6.9)	8.6 (6.0)
Median	7.4	7.2	8.5	7.8
Min, max	0.9, 21.8	0.3, 27.0	0.0, 32.3	0.0, 32.3
Duration of PBC subgroups, n (%)				
≤7.5 years	39 (53)	36 (51)	30 (41)	105 (49)
>7.5 years	34 (47)	34 (49)	43 (59)	111 (51)
Source: Table 21 of CS[3]				

The CS states that '*the mean age at time of diagnosis was 47.3 years with a mean duration of PBC of 8.6 years*' and that '*There were slightly more subjects <50 years of age at PBC diagnosis (58%) compared with ≥50 years of age.*' Fifty-nine percent of patients had pruritus at baseline (43% mild, 15% moderate and 1% severe) and 59% had a history of fatigue. The CS notes that '*the majority (94–99%) of subjects had a baseline INR ≤1.3, indicative of a population in an early stage of disease progression'*.

The CS notes that '*In general, each variable was well balanced across treatment groups.' However 'the overall incidence of pruritus at baseline was slightly higher for subjects in the placebo treatment group (64% and OCA 10mg fixed dose group (60%) than in the OCA titration group (53%).....The overall incidence of fatigue was slightly higher for subjects in the placebo treatment group (67%) than in the OCA titration and OCA 10mg fixed dose groups (54% and 56%, respectively).*'

ERG comments on POISE:
POISE, has several strengths and matches the NICE scope in several ways:

- It is a randomised controlled trial in a PBC population relevant to England and Wales.
- It is a multicentre international trial with 217 participants comparing OCA in combination with UDCA to UDCA alone in patients with an inadequate response to UDCA and comparing OCA to no treatment in patients intolerant to UDCA.
- Follow-up is of 12 months' duration covering an extensive range of surrogate outcomes.

There are a number of limitations in applying the results of the trial to the NICE scope:

- The number of patients intolerant to UDCA and receiving OCA as monotherapy was limited to 11 patients (five [7%] in the OCA titration group and six [8%] in the OCA 10 mg group). Five patients received OCA placebo. As such the results for this group of patients should be considered with caution due to the low numbers.

The ERG noted that the POISE trial included patients at an early state of PBC progression as stated in Section 4.5.2.3 of the CS '*the majority (94–99%) of subjects had a baseline INR ≤1.3, indicative of a population in an early stage of disease progression'*.[3] The ERG asked the company to clarify how OCA would benefit patients with more advanced PBC. In the response to clarification letter, the company stated that two analyses were performed in more advanced stages of PBC. Several definitions were used to approximate severity of the disease including a clinical composite definition and presence of cirrhosis. The results of these analyses are provided in Section 4.2.4. It should be noted that these are based on a subset of 72 patients

classified as having advanced disease and 36 who had cirrhosis.[32]The ongoing COBALT trial includes more advanced patients and should provide more definitive results for these patients.

- Although stratified on several important variables, the POISE trial had differences between treatment groups at baseline. In particular the placebo group and the OCA 10 mg fixed dose group had a slightly higher incidence of pruritus than the OCA titration group and the placebo group had a slightly higher incidence of fatigue compared with both OCA treatment groups, which should be borne in mind particularly when interpreting results of adverse events.
- In the POISE trial 73 patients were randomised to a fixed dose of 10 mg OCA and 73 patients received the placebo.[27] Seventy-one patients were randomised to the titration group which reflects the recommended dosage. They received OCA 5 mg OD for the initial six month period. The patients in POISE were only up-titrated to 10 mg OCA at six months if they did not reach the primary endpoint criteria for response.[27] The ERG draws to the attention of the committee that the evidence for obeticholic acid given at the recommended dosage is based on the 33 patients who actually up-titrated to 10 mg.[27] The remaining patients in this arm responded to OCA treatment and so did not require up-titration, as per the protocol.The company notes that '*further benefit in terms of efficacy is likely to be seen in clinical practice in this patient group due to the higher dose of OCA.*'[3] This appears to be reasonable but is an assumption.
- The POISE trial presents evidence using surrogate outcomes only for clinical effectiveness. As stated in Section 3.4, the ERG is satisfied that the company has demonstrated evidence of some correlation between the surrogate outcomes of interest and longer-term clinical outcomes. However the extent of the correlation and the optimal thresholds of surrogate outcomes to predict long-term disease is unclear.
- In the POISE CSR some early clinical outcomes were retrospectively gathered.[46] Although these are presented in Section 4.2.5, the time scale of the trial (12 months) does not allow conclusions to be drawn based on this early long-term evidence. The definitive effects of obeticholic acid on clinical outcomes relevant to patients awaits the results of the COBALT trial.[37]
- As stated in the NICE scope for Obeticholic acid, the HRQoL of PBC patients is relevant for this submission.[4] The company used a disease-specific questionnaire PBC-40 that assesses symptoms across several domains: fatigue, emotional and social, cognitive function, general symptoms and itch.[47] Brief results as presented in the CSR are given in Section 4.2.4 of the report.

4.2.3 Quality assessment of POISE

We reproduce the company's quality assessment of the POISE trial[3] alongside the ERG's views on the quality of the trial.

ERG comment: It can be seen that the ERG agrees with the company's assessment and finds that the trial has been well conducted with appropriate procedures for randomisation, allocation concealment, blinding and outcome assessment.

4.2.4 POISE: Efficacy results

The primary efficacy endpoint (percentage of participants with ALP < 1.67 x ULN and total bilirubin ≤ ULN and ALP ≥15% decrease from baseline at 12 months) is detailed in Table 4.9 below.

Table 4.5: Summary of primary efficacy outcome in POISE

	Responders (%)
	Month 12
Placebo (n=73)	10%
10 mg OCA (n=73)	47%
Titration OCA (n=70)	46%
Titration subgroup[†]	
Remained at 5 mg OCA for 12 months (n=36)	53%
Titrated to 10 mg OCA at Month 6 (n=33)	39%

Source: Table 23 CS[3]
Footnote: [†]There was one participant who withdrew from the trial due to an AE after 8 days of study medication, and therefore there were no data for this participant at Month 6 and Month 12. §Of the 12 participants who did not respond but did not up-titrate, nine did not increase their dose due to adverse events, and three recorded their reason as 'other'
ALP, alkaline phosphatase; CS, company submission; OCA, obeticholic acid.

It can be seen from the table above that at 12 months 47% of participants in the 10mg group achieved the primary outcome, 46% in the titration group and 10% in the placebo group ($p < 0.0001$ for both comparisons).

Secondary outcomes

For the two main surrogate outcomes relevant to the primary composite outcome in POISE, namely ALP and total bilirubin levels, the company reports that at 12 months, 25 (34%) and 21 (30%) of participants from the OCA 10 mg fixed dose and OCA titration groups respectively achieved an ALP reduction from baseline ≥40% compared with 1% in the placebo group.[3] For the total bilirubin outcome, decreases in the absolute change from baseline were observed for both OCA treatment groups compared with an increase for the placebo treatment group. At 12 months, mean bilirubin levels in the OCA 10 mg group were 9.7 (SE 0.6), 9.9 (SE 0.6) in the OCA titration group and 13.2 (1.0) in the placebo group.[3]

The CSR states that '*The disease-specific measure for PBC showed no clinically significant improvements in comparison to placebo for the global score or individual scores of general symptoms, fatigue, cognitive function, and emotional/social domains; however, a difference was observed in itch scores in the earlier treatment months*.'[46] The CSR further states that '*During the initial 3 months of treatment, the largest LS mean increase in itch was observed for the OCA 10 mg group, followed by the OCA titration group…. The LS mean difference in itch score between the OCA 10 mg group and placebo group was statistically significant at both Week 2 (p = 0.0048) and Month 3 (p <0.0001) but not at any subsequent time points.*' [46]

Subgroup of patients with advanced disease

A total of 72 participants (30, 22 and 20 in the placebo, OCA titration and OCA 10 mg respectively) were classified as having advanced disease using a clinical composite definition that included biochemical criteria (not specified), non-invasive measures of fibrosis, biopsies and/or medical history of decompensation and presence of cirrhosis.[32] The company concluded that '*there was not an increased risk (of adverse events) in patients with advanced disease*'.[32] No efficacy data were presented for these patients. A post-hoc analysis of efficacy and safety of 36 patients with cirrhosis (13 in the placebo arm, 13 in the OCA titration arm and 10 in the OCA 10 mg arm) was conducted. The company stated that '*ALP levels were significantly more reduced over 12 months in the OCA treatment groups than the placebo groups and bilirubin increased in the placebo group but remained stable in the OCA treatment group. The primary composite outcome in POISE ….was met by 8% of subjects in the placebo arm, 54% in the OCA titration arm and 40% in the OCA 10 mg arm after 12 months.*'[32]

ERG comment:

- The ERG notes the improvements shown in the OCA treatment groups in terms of the combined efficacy endpoint (percentage of participants with ALP < 1.67 x ULN and total bilirubin ≤ ULN and ALP ≥15% decrease from baseline at 12 months). This is supported by improvements in other surrogate markers. However no firm data on clinical outcomes are available. It is too early to draw conclusions on long-term clinical outcomes and the need for transplant based on the retrospective data available.
- The ERG notes that improvements in surrogate outcomes were not reflected in the disease specific quality of life tool (PBC-40) over the 12 month period.
- The improvements seen in patients with more advanced disease (briefly reported) are based on lower patient numbers as the majority of patients in POISE had earlier stage disease.
- As few patients used OCA as monotherapy it is unclear if results accurately reflect this patient group.

4.2.5 POISE: Safety results

A summary of the adverse events as described in the CS [3] is detailed in Table 4.12.

Table 4.6: Overview of adverse events: safety population (POISE)

Participants, n (%)	Placebo n=73	OCA titration n=70	OCA 10 mg n=73
Any TEAE	66 (90)	65 (93)	69 (95)
Total number of TEAEs	452	471	467
Any treatment-related AE[†]	38 (52)	42 (60)	54 (74)
Any SAEs	3 (4)	11 (16)	8 (11)
Total number of SAEs	8	15	11
TEAEs by severity			
Mild	29 (40)	16 (23)	19 (26)
Moderate	28 (38)	27 (39)	29 (40)
Severe	9 (12)	22 (31)	21 (29)
Any TEAE leading to discontinuation	2 (3)[‡]	5 (7)[§]	8 (11)[¶]
Discontinuation due to pruritus	0 (0)	1 (1)	7 (10)
Number of deaths	0 (0)	1 (1)	0 (0)

In summary, both studies found a statistically significant effect of OCA 10 mg on ALP levels from baseline to end of study versus placebo. In study 747-201 (monotherapy) the mean (SD) percentage change in ALP levels was –44.5% (24.4) for the OCA 10 mg group versus +0.4% (15.3) for placebo. Study 747-202 reported mean (SD) percentage change in ALP levels was –23.7% (17.8) for the OCA 10 mg group versus –2.6% (12.5) for placebo. Both results were statistically significant at $p<0.0001$.

ERG comment: The Phase two trials lend support to the findings of POISE on the benefits of OCA on surrogate outcomes for patients with PBC. However both trials were of a short-term duration (three months) and a variety of doses were used limiting the comparability of the trials to POISE and the possibility of pooling results.

4.3 Critique of trials identified and included in the indirect comparison and/or multiple treatment comparison

Not applicable as there was no indirect comparison or multiple treatment comparison in the CS.

4.4 Critique of the indirect comparison and/or multiple treatment comparison

Not applicable as there was no indirect comparison or multiple treatment comparison in the CS.

4.5 Additional work on clinical effectiveness undertaken by the ERG

Not applicable.

4.6 Conclusions of the clinical effectiveness section

The company conducted a systematic review to identify studies comparing OCA to the comparators outlined in the NICE scope.[4] Overall the ERG is satisfied that the relevant direct evidence comparing OCA and UDCA has been presented. However no trials comparing OCA to fibrates were identified.

One Phase 3 trial, POISE, with 217 patients was presented as the main source of evidence.[27] The trial compared UDCA and combined UDCA and OCA in patients with an inadequate response to UDCA and OCA and placebo in those who were intolerant to UDCA. However the group receiving OCA as monotherapy is underrepresented in this trial (11 patients). Additionally, the majority of patients in POISE appeared to be at an earlier stage of disease so the effects on those with more advanced disease are less clear.

The POISE trial was well-conducted. However it only examined surrogate outcomes. These were justified by the company based on previously published research. In POISE, OCA shows positive effects on surrogate endpoints, and there is some evidence that surrogate endpoints are related to relevant outcomes. However, the size of the relationship is unclear.

The primary outcome of POISE was a composite one (percentage of participants with ALP < 1.67 x ULN and total bilirubin ≤ ULN and ALP ≥15% decrease from baseline at 12 months). At 12 months 47% of participants in the OCA 10 mg group achieved the primary outcome, 46% in the titration group and 10% in the placebo group ($p < 0.0001$ for both comparisons). The results of other surrogate outcomes supported these findings. Incidence of adverse events was similar across groups. Events occurring more frequently in treatment groups were noted. The most notable was pruritus and it was noted that 10% of patients discontinued treatment due to pruritus in the OCA 10 mg group which did not titrate based on tolerability.

Two supporting Phase 2 trials were presented (including one of OCA monotherapy and one of OCA in combination with UDCA). These were not similar enough to be pooled with POISE but added support to the positive findings on surrogate outcomes. Clinical outcomes await the publication of the COBALT trial.[37]

8. OVERALL CONCLUSIONS

8.1 Statement of principal findings

Overall the ERG is satisfied that the relevant direct evidence comparing OCA and UDCA has been presented. However no trials comparing OCA to fibrates were identified.

One Phase 3 trial, POISE, with 217 patients was presented as the main source of evidence.[27] The trial compared UDCA and combined UDCA and OCA in patients with an inadequate response to UDCA and OCA and placebo in those who were intolerant to UDCA. However the group receiving OCA as monotherapy is underrepresented in this trial (11 patients). Additionally, the majority of patients in POISE appeared to be at an earlier stage of disease so the effects on those with more advanced disease are less clear.

The POISE trial was well-conducted. However it only examined surrogate outcomes. These were justified by the company based on previously published research. In POISE, OCA shows positive effects on surrogate endpoints, and there is some evidence that surrogate endpoints are related to relevant outcomes. However, the size of the relationship is unclear.

The primary outcome of POISE was a composite one (percentage of participants with ALP < 1.67 x ULN and total bilirubin ≤ ULN and ≥15% ALP decrease from baseline at 12 months). At 12 months 47% of participants in the OCA 10 mg group achieved the primary outcome, 46% in the titration group and 10% in the placebo group ($p < 0.0001$ for both comparisons). The results of other surrogate outcomes supported these findings. Incidence of adverse events was similar across groups. Events occurring more frequently in treatment groups were noted. The most notable was pruritus and it was noted that 10% of patients discontinued treatment due to pruritus in the OCA 10 mg group which did not titrate based on tolerability.

Two supporting Phase 2 trials were presented (including one of OCA monotherapy and one of OCA in combination with UDCA). These were not similar enough to be pooled with POISE but added support to the positive findings on surrogate outcomes. Clinical outcomes await the publication of the COBALT trial.[37]

The main areas of ERG concern were the fact that the company did not use the POISE trial data directly for the non-OCA regimen, the lack of transparency and justification regarding methods and data to extrapolate the POISE trial data beyond the time horizon of 12 months and to final outcomes, the implausible high utility values in the biomarker component of the model and the lack of justification for [redacted] HRQoL decrement for the health states of the liver disease component of the model, except HCC. The ERG has incorporated various adjustments to the company base-case. The ERG base-case resulted in ICERs (probabilistic) of £[redacted] and £[redacted] for UDCA inadequate responders and UDCA intolerant patients respectively. The most influential adjustments/corrections made by the ERG were using TPs from the POISE trial for the non-OCA regimens and using age dependent utilities for the low and moderate risk health states. However, the ERG base-case ICER should be regarded as a lower bound as the exploratory analysis showed that alternative assumptions, for the TPs after 12 months and the non-transparent calibration method used by the company, resulted in substantially higher ICERs (ranging from £[redacted] to £[redacted] and from £[redacted] to £[redacted] for UDCA inadequate responders and UDCA intolerant patients respectively).

As the methods used by the company to estimate and extrapolate treatment effectiveness are lacking transparency and justification, the ICERs (presented by both the company and the ERG) should be interpreted with caution. Given the lack of long-term results of the POISE trial, the ERG would generally agree with using a calibration approach (as adopted by the company), to extrapolate the

National Institute for Health and Care Excellence
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Pro-forma Response

ERG report

Obeticholic acid for treating primary biliary cirrhosis [ID785]

You are asked to check the ERG report from Klejinen Systematic Reviews Ltd to ensure there are no factual inaccuracies contained within it.

If you do identify any factual inaccuracies you must inform NICE by **5pm, 9 December 2016** using the below proforma comments table. All factual errors will be highlighted in a report and presented to the Appraisal Committee and will subsequently be published on the NICE website with the Evaluation report.

The proforma document should act as a method of detailing any inaccuracies found and how and why they should be corrected.

Issue 1 Error

Description of problem	Description of proposed amendment	Justification for amendment	ERG Response
Section 1.2, Page 12 First sentence in fourth paragraph of this section has an error: "The primary outcome of POISE was a composite one (percentage of participants with alkaline phosphatase (ALP) < 1.67 x upper limit of normal (ULN) and total bilirubin ≤ ULN and ALP ≥ decrease from baseline at 12 months)."	The sentence should be amended to: 'The primary outcome of POISE was a composite one (percentage of participants with alkaline phosphatase (ALP) < 1.67 x upper limit of normal (ULN) and total bilirubin ≤ ULN and ALP ≥**15%** decrease from baseline at 12 months).'	This is an error in describing the primary endpoint of POISE, the pivotal trial for OCA.	This has been corrected.

Issue 2 Error and further information required

Description of problem	Description of proposed amendment	Justification for amendment	ERG Response
Section 1.2, Page 12 Error and further information required for the last sentence of the fourth paragraph in this section: "It was noted that 10% of patients discontinued treatment due to pruritus in the OCA 10 mg group which did not titrate based on tolerability."	The sentence should be amended to: 'It was noted that 10% of patients discontinued treatment due to pruritus in the OCA 10 mg **fixed dose** group ~~which did not titrate based on tolerability.~~**, but only 1% discontinued due to pruritus in the OCA titration group that more closely represents the OCA dosing regimen recommended for use in clinical practice.**'	The percentage quoted in the original statement (10%) refers to the OCA 10 mg fixed dose group, within which there was no option to titrate the dose. In addition, Intercept believe that it is a fairer representation to also include the percentage discontinuing due to pruritus in the OCA titration group, since this more closely resembles the OCA dosing regimen recommended for use in clinical practice, and the lower rate of adverse events (including pruritus)	Not a factual error. See also issues 28 and 35.

		was one of the reasons that the titration regimen was proposed for use in clinical practice compared with the 10 mg fixed dose regimen.	

Issue 3 Further explanation required

Description of problem	Description of proposed amendment	Justification for amendment	ERG Response
Section 1.3, Page 13 Further explanation is required in the third bullet point in this section: "In the POISE trial 73 patients were randomised to a fixed dose of 10 mg OCA and 73 patients received the placebo. Seventy-one patients were randomised to the titration group which reflects the recommended dosage. They received OCA 5 mg OD for the initial six month period. The patients in POISE were only up-titrated to 10 mg OCA if they did not reach the primary endpoint criteria for response. The ERG draws to the attention of the committee that the evidence for obeticholic acid given at the recommended dosage is based on the 33 patients who actually up-titrated to 10 mg."	The bullet point should be amended to: 'In the POISE trial 73 patients were randomised to a fixed dose of 10 mg OCA and 73 patients received the placebo. Seventy-one patients were randomised to the titration group which reflects the recommended dosage. They received OCA 5 mg OD for the initial six month period. The patients in POISE were only up-titrated to 10 mg OCA **at six months** if they did not reach the primary endpoint criteria for response. ~~The ERG draws to the attention of the committee that the evidence for obeticholic acid given at the recommended dosage is based on the~~ **There were** 33 patients **in the OCA titration group** who actually up-titrated to 10 mg~~.~~**; the remaining patients in this arm responded to OCA treatment and so did not require up-titration, as per the protocol.** The company notes that '*further benefit in terms of efficacy is likely to be seen in clinical practice in this patient group due to the higher dose of OCA.*' This appears to be reasonable but is an assumption.'	Further explanation is required for context, and to explain that 'this patient group' in the quote from the company submission refers to the entire OCA titration group and not just to the 33 patients who up-titrated. It is important to note that, in terms of efficacy, results are likely to be underestimated due to the lower dose of OCA received (compared with clinical practice) for the patients who did not up-titrate.	Not a factual error. Extra detail not needed for the executive summary.

Issue 4 Misrepresentation

Description of problem	Description of proposed amendment	Justification for amendment	ERG Response
Section 1.5, Page 16 There is misrepresentation in the second sentence of the final paragraph of this page: "Given this lack of transparency, also after multiple requests from the ERG, the methods used by the company are still unclear."	The sentence point should be amended to: '~~Given this lack of transparency, also after multiple requests from the ERG, t~~**T**he methods used by the company are ~~still~~ unclear **to the ERG**.'	The methods and sources of data were explained both in the appendices of the company submission and in the workbook, and further explanation was provided to the ERG on request.	Not a factual inaccuracy. The methods to estimate treatment effectiveness for patients receiving UDCA only and no treatment are unclear to the ERG based on the company submission and clarification responses (see ERG comment in section 5.2.6 of the ERG report for more details). No correction needed.

Issue 5 Misquote of the company submission

Description of problem	Description of proposed amendment	Justification for amendment	ERG Response
Section 2.2, Page 20 There is a misquote in the first sentence of the second paragraph in this section: "The CS states that '*Patients are commonly asymptomatic at diagnosis, and are referred to secondary care on discovering abnormal liver function and / or positive antibody by blood tests at a GP visit for an unrelated illness*."	The sentence should be amended to: 'The CS states that '*Patients are commonly asymptomatic at diagnosis, and are referred to secondary care on discovering abnormal liver function and / or positive* ***auto****antibody by blood tests at a GP visit for an unrelated illness*.'	This is an error.	This has been corrected.

Issue 6 Typographical error

Description of problem	Description of proposed amendment	Justification for amendment	ERG Response
Section 2.2, Page 20 There is a typographical error in the first sentence of the sixth paragraph in this section: "The CS states that '*There are no licensed or effective drugs approved for second-line treatment for second-line treatment for the management of patients with an inadequate response to, or intolerance to, UDCA*.'"	The sentence should be amended to: 'The CS states that '*There are no licensed or effective drugs approved for second-line treatment ~~for second-line treatment~~ for the management of patients with an inadequate response to, or intolerance to, UDCA*.'	This is an error.	This has been corrected.

Issue 7 Misquote of the company submission

Description of problem	Description of proposed amendment	Justification for amendment	ERG Response
Section 2.2, Page 21 There is a misquote in seventh paragraph in this section: "The CS states that '*Liver transplantation is the only treatment for patients with late-stage PBC, where UDCA has limited efficacy*.' The CS outlines the challenges and risks of liver transplantation and notes that '*up to 43% of patients will have a recurrence of PBC within 15 years. Draft guidance from the*	The paragraph should be amended to: 'The CS states that '*Liver transplantation is the only treatment for patients with late-stage PBC, where UDCA has limited efficacy*.' The CS outlines the challenges and risks of liver transplantation and notes that '*up to 43% of patients will have a recurrence of PBC within 15 years. ~~Draft guidance from the BSG note that there is no consensus on routine use of UDCA post-transplant~~*.''	This is an error.	The sentence '*Draft guidance from the BSG note that there is no consensus on routine use of UDCA post-transplant*.' Has been removed.

BSG note that there is no consensus on routine use of UDCA post-transplant.'"			

Issue 8 Further explanation required

Description of problem	Description of proposed amendment	Justification for amendment	ERG Response
Section 3.2, Page 26 Further explanation is required in the final bullet point in this section: "In the POISE trial 73 patients were randomised to a fixed dose of 10 mg OCA and 73 patients received the placebo. Seventy-one patients were randomised to the titration group which reflects the recommended dosage. They received OCA 5 mg OD for the initial six months period. The patients in POISE were only up-titrated to 10 mg OCA if they did not reach the primary endpoint criteria for response. The ERG draws to the attention of the committee that the evidence for obeticholic acid given at the recommended dosage is based on the 33 patients who actually up-titrated to 10 mg. The company notes that '*further benefit in terms of efficacy is likely to be seen in clinical practice in this patient*	The bullet point should be amended to: 'In the POISE trial 73 patients were randomised to a fixed dose of 10 mg OCA and 73 patients received the placebo. Seventy-one patients were randomised to the titration group which reflects the recommended dosage. They received OCA 5 mg OD for the initial six months period. The patients in POISE were only up-titrated to 10 mg OCA **at six months** if they did not reach the primary endpoint criteria for response. ~~The ERG draws to the attention of the committee that the evidence for obeticholic acid given at the recommended dosage is based on the~~ **There were** 33 patients **in the OCA titration group** who actually up-titrated to 10 mg~~.~~**; the remaining patients in this arm responded to OCA treatment and so did not require up-titration, as per the protocol.** The company notes that '*further benefit in terms of efficacy is likely to be seen in clinical practice in this patient group due to the higher dose of OCA*.' This appears to be reasonable but is an assumption.'	Further explanation is required for context, and to explain that 'this patient group' in the quote from the company submission refers to the entire OCA titration group and not just to the 33 patients who up-titrated. It is important to note that, in terms of efficacy, results are likely to be underestimated due to the lower dose of OCA received (compared with clinical practice) for the patients who did not up-titrate.	One sentence has been amended for clarity. 'The patients in POISE were only up-titrated to 10 mg OCA at six months if they did not reach the primary endpoint criteria for response.' One sentence has been added. 'The remaining patients in this arm responded to OCA treatment and so did not require up-titration, as per the protocol.'

group due to the higher dose of OCA.' This appears to be reasonable but is an assumption."			

Issue 9 Error

Description of problem	Description of proposed amendment	Justification for amendment	ERG Response
Section 3.4, Page 28 There is an error in the final sentence of the third paragraph of this section: "The start date of the trial was December 2014 and the study completion date is April 2023."	The sentence should be amended to: 'The start date of the trial was December 2014 and the **estimated** study completion date is April 2023.'	The details of the trial that have been extracted by the ERG from clinicaltrials.gov refer to the estimated completion date.	This has been corrected.

Issue 10 Typographical error and further information required

Description of problem	Description of proposed amendment	Justification for amendment	ERG Response
Section 4.2.1, Page 35 There is a typographical error in the final sentence of the fourth paragraph of this section: "In addition to this trial, another Phase 2 study (747-205) is currently ongoing in the US that includes patients from 8eightyears of age and aims to investigate the change from baseline in HDL metabolism."	The sentence should be amended to: 'In addition to this trial, another Phase 2 study (747-205) is currently ongoing in the US that includes patients from ~~8eightyears~~ **18 years** of age and aims to investigate the change from baseline in HDL metabolism **as the primary outcome**.'	This was a typographical error in the company submission, and the sentence has been expanded to make clear that the investigation of HDL metabolism was the primary outcome, since other outcomes were measured in the trial as well as HDL metabolism as secondary outcomes.	This has been corrected.

Issue 11 Error

Description of problem	Description of proposed amendment	Justification for amendment	ERG Response
Table 4.3, Page 36 There is an error in the final bullet point in the 'Trial design' row: "presence or absence of biochemical response to UDCA treatment"	The bullet point should be amended to: **'Combinations of the** presence or absence of biochemical response to UDCA treatment **(yes/no) and intolerance to UDCA (yes/no)**'	The stratification criteria are not reflected correctly.	This has been corrected.

Issue 12 Error

Description of problem	Description of proposed amendment	Justification for amendment	ERG Response
Table 4.3, Page 36 There is an error in the footnote: "Paris I criteria defined as ALP ≤3x ULN and AST ≤2x ULN and total bilirubin ≤1 mg/dL (17 µmol/l)"	The footnote should be amended to: 'Paris I criteria defined as ALP ≤3x ULN and AST ≤2x ULN and total bilirubin ≤**ULN** ~~1 mg/dL (17 µmol/l)~~'	For the stratification criteria, total bilirubin in the response criteria was defined as ≤ULN, not ≤1 mg/dL.	This has been corrected.

Issue 13 Addition required

Description of problem	Description of proposed amendment	Justification for amendment	ERG Response
Table 4.4, Page 37 There is an addition required in the 'Bile acids' row: "Absolute values and change from baseline by treatment group at 6 and 12	The statement should be amended to: 'Absolute values and change from baseline by treatment group at 6 and 12 months' follow-up **from participants who had a confirmed fasting of approximately 8 hours or more prior to their visit** in the following:'	This has been highlighted in the 'OCA pharmacokinetics analysis' row, and so should also be included in the 'Bile acids' row for consistency.	This has been corrected.

months' follow-up in the following:"			

Issue 14 Addition required

Description of problem	Description of proposed amendment	Justification for amendment	ERG Response
Section 4.2.2, Page 43 There is an addition required in the second bullet point under the heading 'ERG comments on POISE': "It is a multicentre international trial with 217 participants comparing OCA to UDCA alone in patients with an inadequate response to UDCA and comparing OCA to no treatment in patients intolerant to UDCA"	The bullet point should be amended to: 'It is a multicentre international trial with 217 participants comparing OCA **in combination with UDCA** to UDCA alone in patients with an inadequate response to UDCA and comparing OCA to no treatment in patients intolerant to UDCA'	An addition is required to clarify that OCA was taken in combination with UDCA in patients with an inadequate response to UDCA.	This has been corrected.

Issue 15 Further explanation required

Description of problem	Description of proposed amendment	Justification for amendment	ERG Response
Section 4.2.2, Page 44 There is further explanation required in the first full bullet point on this page: "Although stratified on several important variables, the POISE trial had differences between treatment groups at baseline. In particular the placebo group had a higher	The bullet point should be amended to: 'Although stratified on several important variables, the POISE trial had differences between treatment groups at baseline. In particular the placebo group **and the OCA 10 mg fixed dose group** had a **slightly** higher incidence of pruritus **than the OCA titration group** and **the placebo group had a slightly higher incidence of** fatigue	Further explanation is required to fully reflect the results of POISE.	This has been corrected.

incidence of pruritus and fatigue which should be borne in mind particularly when interpreting results of adverse events."	**compared with both OCA treatment groups,** which should be borne in mind particularly when interpreting results of adverse events.'		

Issue 16 Further explanation required

Description of problem	Description of proposed amendment	Justification for amendment	ERG Response
Section 4.2.2, Page 44 There is further explanation required in the second full bullet point on this page: "In the POISE trial 73 patients were randomised to a fixed dose of 10 mg OCA and 73 patients received the placebo. Seventy-one patients were randomised to the titration group which reflects the recommended dosage. They received OCA 5 mg OD for the initial six month period. The patients in POISE were only up-titrated to 10 mg OCA if they did not reach the primary endpoint criteria for response. The ERG draws to the attention of the committee that the evidence for obeticholic acid given at the recommended dosage is based on the 33 patients who actually up-titrated to 10 mg. The company notes that *'further benefit in terms of efficacy is*	The bullet point should be amended to: 'In the POISE trial 73 patients were randomised to a fixed dose of 10 mg OCA and 73 patients received the placebo. Seventy-one patients were randomised to the titration group which reflects the recommended dosage. They received OCA 5 mg OD for the initial six month period. The patients in POISE were only up-titrated to 10 mg OCA **at six months** if they did not reach the primary endpoint criteria for response. ~~The ERG draws to the attention of the committee that the evidence for obeticholic acid given at the recommended dosage is based on the~~ **There were** 33 patients **in the OCA titration group** who actually up-titrated to 10 mg~~.~~**; the remaining patients in this arm responded to OCA treatment and so did not require up-titration, as per the protocol.** The company notes that *'further benefit in terms of efficacy is likely to be seen in clinical practice in this patient group due to the higher dose of OCA*.' This appears to be reasonable but is an assumption.'	Further explanation is required for context, and to explain that 'this patient group' in the quote from the company submission refers to the entire OCA titration group and not just to the 33 patients who up-titrated. It is important to note that, in terms of efficacy, results are likely to be underestimated due to the lower dose of OCA received (compared with clinical practice) for the patients who did not up-titrate.	One sentence has been amended for clarity. 'The patients in POISE were only up-titrated to 10 mg OCA at six months if they did not reach the primary endpoint criteria for response.' One sentence has been added. 'The remaining patients in this arm responded to OCA treatment and so did not require up-titration, as per the protocol.'

likely to be seen in clinical practice in this patient group due to the higher dose of OCA.' This appears to be reasonable but is an assumption."			

Issue 17 Typographical error

Description of problem	Description of proposed amendment	Justification for amendment	ERG Response
Table 4.8, Page 45 There is a typographical error in the penultimate sentence in the second row of the table on this page: "Access to randomisation codes and corresponding treatment assignment was made available to the appropriate Sponsor designee(s) in the event of a medical emergence."	The sentence should be amended to: 'Access to randomisation codes and corresponding treatment assignment was made available to the appropriate Sponsor designee(s) in the event of a medical emergenc~~e~~**y**.'	This was a typographical error in the company submission.	Correct, but the mistake was in the company submission, so no correction made.

Issue 18 Typographical error

Description of problem	Description of proposed amendment	Justification for amendment	ERG Response
Table 4.8, Page 46 There is a typographical error in the penultimate sentence in the first row of the table on this page: "Access to randomisation codes and corresponding treatment assignment was made available to the appropriate Sponsor	The sentence should be amended to: 'Access to randomisation codes and corresponding treatment assignment was made available to the appropriate Sponsor designee(s) in the event of a medical emergenc~~e~~**y**.'	This was a typographical error in the company submission.	Correct, but the mistake was in the company submission, so no correction made.

designee(s) in the event of a medical emergence."			

Issue 19 Error

Description of problem	Description of proposed amendment	Justification for amendment	ERG Response
Section 4.2.4, Page 47 There is an error/omission in the first sentence of this section: "The primary efficacy endpoint (percentage of participants with ALP < 1.67 x ULN and total bilirubin ≤ ULN and ALP decrease from baseline at 12 months) is detailed in Table 4.9 below."	The sentence should be amended to: 'The primary efficacy endpoint (percentage of participants with ALP < 1.67 x ULN and total bilirubin ≤ ULN and ALP **≥15%** decrease from baseline at 12 months) is detailed in Table 4.9 below.'	This is an error in describing the primary endpoint of POISE, the pivotal trial for OCA.	This has been corrected.

Issue 20 Error/omission

Description of problem	Description of proposed amendment	Justification for amendment	ERG Response
Section 4.2.4, Page 47 There is an error/omission in the first sentence under the heading 'Secondary outcomes' in this section: "For the two main surrogate outcomes relevant to the primary composite outcome in POISE, namely ALP and total bilirubin levels, the company reports that at 12 months, 25 (34%) and 21 (30%) of	The sentence should be amended to: 'For the two main surrogate outcomes relevant to the primary composite outcome in POISE, namely ALP and total bilirubin levels, the company reports that at 12 months, 25 (34%) and 21 (30%) ~~of~~ participants from the OCA 10 mg fixed dose and OCA titration groups respectively achieved an ALP reduction from baseline ≥40% compared with **1 (**1%**) participant** in the placebo group.'	This is an error/omission amended for consistency.	It is clear from the text what is meant here, so no correction needed.

participants from the OCA 10 mg fixed dose and OCA titration groups respectively achieved an ALP reduction from baseline ≥40% compared with 1% in the placebo group."			

Issue 21 Error

Description of problem	Description of proposed amendment	Justification for amendment	ERG Response
Section 4.2.4, Page 48 There is an error in the text above Table 4.11 in this section: "The incidence of reaching a MELD score >15 (with a baseline MELD of <15) is given in Table 4.11."	The sentence should be amended to: 'The incidence of reaching a MELD score >15 (with a baseline MELD of <**12**) is given in Table 4.11.'	This is an error, and should correspond with Table 41 (page 170) of the CSR. There is an error in the text of the CSR on page 168.	This was taken from the text of the CSR which was incorrect. No correction to the report.

Issue 22 Error

Description of problem	Description of proposed amendment	Justification for amendment	ERG Response
Section 4.2.4, Page 49 There is an error/omission in the first sentence of the first bullet point under the heading 'ERG comment' in this section: "The ERG notes the improvements shown in the OCA treatment groups in terms of the combined efficacy endpoint (percentage of participants with ALP < 1.67 x	The sentence should be amended to: 'The ERG notes the improvements shown in the OCA treatment groups in terms of the combined efficacy endpoint (percentage of participants with ALP < 1.67 x ULN and total bilirubin ≤ ULN and ALP **≥15%** decrease from baseline at 12 months).'	This is an error in describing the primary endpoint of POISE, the pivotal trial for OCA.	This has been corrected.

ULN and total bilirubin ≤ ULN and ALP decrease from baseline at 12 months)."			

Issue 23 Context

Description of problem	Description of proposed amendment	Justification for amendment	ERG Response
Section 4.2.4, Page 49 The final bullet point under the heading 'ERG comment' in this section is out of context: "As few patients used OCA as monotherapy it is unclear if results accurately reflect this patient group."	This bullet point should be removed.	Section 4.2.4 has not discussed the results of OCA monotherapy (vs OCA in combination with UDCA), and so this statement is not relevant here.	Not a factual error.

Issue 24 Context

Description of problem	Description of proposed amendment	Justification for amendment	ERG Response
Section 4.2.5, Page 52 The second paragraph on this page is out of context: "The company also state that '*Fatigue and nausea were the only other related TEAE that occurred at an incidence ≥5%; however, these events were balanced between placebo and OCA treatment arms*.'"	The paragraph should be amended to: 'The company also state that '***As expected based on prior experience with OCA treatment in patients with PBC, the most common related TEAE was pruritus. In all treatment groups, the majority of pruritus AEs were considered related to investigational product. The incidence and number of subjects with related TEAEs of pruritus was 27 subjects (37%) in the placebo group, 35 subjects (50%) in the OCA titration group, and 48 subjects (66%) in the OCA 10 mg***	The previous paragraph was related to TEAEs in general, whereas this paragraph concerns treatment-related TEAEs.	Not a factual error. No correction needed.

	group. *Fatigue and nausea were the only other related TEAE that occurred at an incidence ≥5%; however, these events were balanced between placebo and OCA treatment arms.*'		

Issue 25 Omission

Description of problem	Description of proposed amendment	Justification for amendment	ERG Response
Table 4.14, Page 53 There is an omission in the cell relating to trial design of study 747-202: "Multi-centre, randomised, double-blind, placebo-controlled, multi-dose, Phase 2 parallel group study of OCA in with UDCA in participants with a proven or likely diagnosis of PBC."	The cell should be amended to: 'Multi-centre, randomised, double-blind, placebo-controlled, multi-dose, Phase 2 parallel group study of OCA in **combination** with UDCA in participants with a proven or likely diagnosis of PBC.'	This is an omission.	It is clear from the text what is meant here, so no correction needed.

Issue 26 Error

Description of problem	Description of proposed amendment	Justification for amendment	ERG Response
Section 4.2.6, Page 54 There is an error in the penultimate sentence of the first paragraph on this page: "Study 747-202 reported mean (SD) percentage change in ALP levels was −44.5% (24.4) for the OCA	The sentence should be amended to: 'Study 747-202 reported mean (SD) percentage change in ALP levels was ~~−44.5% (24.4)~~ **–23.7% (17.8)** for the OCA 10 mg group versus ~~+0.4% (15.3)~~ **–2.6% (12.5)** for placebo.'	This is an error.	This has been corrected.

10 mg group versus +0.4% (15.3) for placebo.”			

Issue 27 Error

Description of problem	Description of proposed amendment	Justification for amendment	ERG Response
Section 4.6, Page 54 There is an error/omission in the first sentence of the fourth paragraph of this section: “The primary outcome of POISE was a composite one (percentage of participants with ALP < 1.67 x ULN and total bilirubin ≤ ULN and ALP decrease from baseline at 12 months).”	The sentence should be amended to: ‘The primary outcome of POISE was a composite one (percentage of participants with ALP < 1.67 x ULN and total bilirubin ≤ ULN and ALP **≥15%** decrease from baseline at 12 months).’	This is an error in describing the primary endpoint of POISE, the pivotal trial for OCA.	This has been corrected.

Issue 28 Error and further information required

Description of problem	Description of proposed amendment	Justification for amendment	ERG Response
Section 4.6, Page 54 Error and further information required for the last sentence of the fourth paragraph in this section: “The most notable was pruritus and it was noted that 10% of patients discontinued treatment due to pruritus in the OCA 10 mg group which did not titrate based on tolerability.”	The sentence should be amended to: ‘It was noted that 10% of patients discontinued treatment due to pruritus in the OCA 10 mg **fixed dose** group ~~which did not titrate based on tolerability.~~**, but only 1% discontinued due to pruritus in the OCA titration group that more closely represents the OCA dosing regimen recommended for use in clinical practice.**’	The percentage quoted in the original statement (10%) refers to the OCA 10 mg fixed dose group, within which there was no option to titrate the dose. In addition, Intercept believe that it is a fairer representation to also include the percentage discontinuing due to pruritus in the OCA titration group, since this more closely resembles the OCA dosing regimen	Not a factual error. See also issues 2 and 35.

		recommended for use in clinical practice, and the lower rate of adverse events (including pruritus) was one of the reasons that the titration regimen was proposed for use in clinical practice compared with the 10 mg fixed dose regimen.	

Issue 29 Misrepresentation

Description of problem	Description of proposed amendment	Justification for amendment	ERG Response
Section 5.2.1, Page 61: There is misrepresentation in the 'Synthesis of evidence in outcomes' row of Table 5.2: "Evidence of effectiveness came primarily from the POISE trial but also from other sources and unclear calibration methods."	'Evidence of effectiveness came primarily from the POISE trial but also from other sources and ~~unclear~~ calibration methods.'	The methods and sources of data were explained both in the appendices of the company submission and in the workbook. The calibration was carried out using Solver in Excel to estimate the transition probability to better fit all transition-free survival estimates used as the basis for the calibration. The model was then used to compare the liver transplant-free survival estimates from POISE to the ones calculated using the model to evaluate their validity.	Not a factual inaccuracy. The methods to estimate treatment effectiveness for patients receiving UDCA only and no treatment are unclear to the ERG based on the company submission and clarification responses (see ERG comment in section 5.2.6 of the ERG report for more details). No correction needed.

Issue 30 Error

Description of problem	Description of proposed amendment	Justification for amendment	ERG Response
Section 5.2.3, Page 64: There is an error in the first paragraph of this section: "Patients enter the model in the moderate (76.85%) and severe risk (23.15%) health states in the biomarker component of the model, according to ALP and bilirubin levels. These proportions of patients starting the model were not justified and apparently not in line with the distribution of patients in the POISE study: the distribution there was 91.58% in the moderate and 8.42% in the severe risk health state, based on Table 49 in the CS for the OCA titration arm, the company's model for the OCA treatment arm and the second clarification excel file for the UDCA arm and OCA arms."	'Patients enter the model in the moderate (76.85%) and severe risk (23.15%) health states in the biomarker component of the model, according to ALP and bilirubin levels as well as presence of compensated cirrhosis. ~~These proportions of patients starting the model were not justified and apparently not in line with the distribution of patients in the POISE study: the distribution there was 91.58% in the moderate and 8.42% in the severe risk health state, based on Table 49 in the CS for the OCA titration arm, the company's model for the OCA treatment arm and the second clarification excel file for the UDCA arm and OCA arms.~~'	The distribution of patients to the moderate (76.85%) and severe risk (23.15%) health states was intentional. The patient numbers in the model were different as only patients who had all ALP/bilirubin observations at all appointments could be used. The distribution of patients to the moderate and severe risk health states was taken directly from the POISE CSR. The ERG's suggestion (that the patient numbers used for transition probabilities used in the model should also be used for the initial patient distribution) does not take into account the patients that could not be included in the model analysis as well as patients with compensated cirrhosis.	Not a factual inaccuracy. The estimation of the proportions of patients starting in the moderate (76.85%) and severe risk (23.15%) health states is unclear to the ERG based on the company submission and clarification responses. No correction needed.

Issue 31 Misrepresentation

Description of problem	Description of proposed amendment	Justification for amendment	ERG Response
Section 5.2.6, Page 67: There is misrepresentation in the third sentence onwards of the first paragraph on this page: “The company did not provide a detailed account of their calibration method in the CS. In the response to the clarification letter, the company provided more detail and an Excel spreadsheet used for the calibration, which was done in four steps: The company calibrated 1) the transition from DCC to the pre-liver transplant health state and liver-related death; 2) transitions from the severe risk health state to the liver disease component health states; 3) transitions from the moderate risk health state to the severe risk health state and other liver disease component states and; 4) transitions from the low risk health state to the severe risk health state and other liver disease component states. There is little detail on the methods, the estimates used and the sources of data.”	This passage should be removed.	The methods and sources of data were explained both in the appendices of the company submission and in the workbook. The calibration was carried out using Solver in Excel to estimate the transition probability to better fit all transition-free survival estimates used as the basis for the calibration. The model was then used to compare the liver transplant-free survival estimates from POISE to the ones calculated using the model to evaluate their validity.	Not a factual inaccuracy. The methods to estimate treatment effectiveness for patients receiving UDCA only and no treatment are unclear to the ERG based on the company submission and clarification responses (see ERG comment in section 5.2.6 of the ERG report for more details). No correction needed.

Issue 32 Error

Description of problem	Description of proposed amendment	Justification for amendment	ERG Response
Section 5.2.12, Page 89: There is an error from the fourth sentence of the first paragraph of this page: “The company stated that it required patient-level data and calculating mean ALP or bilirubin levels per group would potentially introduce bias. The company deemed cross validation impossible in the absence of other cost utility models for PBC. The ERG does not agree with this, because the cost effectiveness review identified four studies focussing on PBC treatment.	‘The company stated that it required patient-level data and calculating mean ALP or bilirubin levels per group would potentially introduce bias. The company deemed cross validation impossible in the absence of other cost utility models for PBC. The ERG does not agree with this, because the cost effectiveness review identified four studies focussing on PBC treatment, **of which two may have been used for limited validation**.’	Two of the four publications stated would not have been appropriate to compare against. Longworth et al and Ratcliffe et al both focused on liver transplantation as a comparator and therefore it would have been inappropriate to compare results to a model that examined a different intervention. For the two remaining models (Boberg et al and Pasha et al), any validation performed would only be partial in scope – only life years for the no treatment and UDCA arms could be compared. Comparing UDCA costs would be of limited use as Boberg et al and Pasha et al do not elaborate on how the UDCA costs were calculated; the Boberg model took a Norwegian perspective so any comparison to the model used in the CS would have been of limited use due to the different costs of treatment between the UK and Norway. The Pasha et al model did include methods for how the cost of UDCA	Not a factual inaccuracy. This is only an addition to one sentence of the ERG report. No correction needed.

		were calculated, and broadly used the same methods as the model used in the company submission, albeit with different, US-specific costs.	

Issue 33 Misrepresentation

Description of problem	Description of proposed amendment	Justification for amendment	ERG Response
Section 5.2.12, Page 89: There is misrepresentation in the third paragraph on this page: "Moreover, given the lack of transparency regarding the methods used by the company (e.g. concerning the calibration process described in Section 5.2.6), even after requests from the ERG (Clarification Questions B12, B14, B15 and B16), the methods used by the company are still unclear."	This passage should be removed.	The methods and sources of data were explained both in the appendices of the company submission and in the workbook. The calibration was carried out using Solver in Excel to estimate the transition probability to better fit all transition-free survival estimates used as the basis for the calibration. The model was then used to compare the liver transplant-free survival estimates from POISE to the ones calculated using the model to evaluate their validity.	Not a factual inaccuracy. The methods to estimate treatment effectiveness for patients receiving UDCA only and no treatment are unclear to the ERG based on the company submission and clarification responses (see ERG comment in section 5.2.6 of the ERG report for more details). No correction needed.

Issue 34 Error

Description of problem	Description of proposed amendment	Justification for amendment	ERG Response
Section 8.1, Page 99 There is an error/omission in the first sentence of the fourth	The sentence should be amended to: 'The primary outcome of POISE was a composite one (percentage of participants with ALP <	This is an error in describing the primary endpoint of POISE, the pivotal trial for OCA.	This has been corrected.

paragraph of this section: “The primary outcome of POISE was a composite one (percentage of participants with ALP < 1.67 x ULN and total bilirubin ≤ ULN and ALP decrease from baseline at 12 months).”	1.67 x ULN and total bilirubin ≤ ULN and ALP **≥15%** decrease from baseline at 12 months).’		

Issue 35 Error and further information required

Description of problem	Description of proposed amendment	Justification for amendment	ERG Response
Section 8.1, Page 99 Error and further information required for the last sentence of the fourth paragraph in this section: “The most notable was pruritus and it was noted that 10% of patients discontinued treatment due to pruritus in the OCA 10 mg group which did not titrate based on tolerability.”	The sentence should be amended to: ‘It was noted that 10% of patients discontinued treatment due to pruritus in the OCA 10 mg **fixed dose** group ~~which did not titrate based on tolerability.~~**, but only 1% discontinued due to pruritus in the OCA titration group that more closely represents the OCA dosing regimen recommended for use in clinical practice.**’	The percentage quoted in the original statement (10%) refers to the OCA 10 mg fixed dose group, within which there was no option to titrate the dose. In addition, Intercept believe that it is a fairer representation to also include the percentage discontinuing due to pruritus in the OCA titration group, since this more closely resembles the OCA dosing regimen recommended for use in clinical practice, and the lower rate of adverse events (including pruritus) was one of the reasons that the titration regimen was proposed for use in clinical practice compared with the 10 mg fixed dose regimen.	Not a factual error. See also issues 2 and 28.