NICE National Institute for Health and Care Excellence

Single Technology Appraisal

Elafibranor for treating primary biliary cholangitis [ID6331]

Committee Papers

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

SINGLE TECHNOLOGY APPRAISAL

Elafibranor for treating primary biliary cholangitis [ID6331]

Contents:

The following documents are made available to stakeholders:

Access the **final scope and final stakeholder list** on the NICE website.

1. **Company submission** from Ipsen:
   a. Full submission
   b. Summary of Information for Patients (SIP)

2. **Clarification questions and company responses**

3. **Patient group, professional group, and NHS organisation submission** from:
   a. British Liver Trust
   b. Liver4Life
   c. PBC Foundation
   d. British Association for the Study of the Liver (BASL)
   e. British Hepatology Pharmacy Group
   f. NHSE – written by commissioning expert Yasmin Stammers

4. **Expert personal perspectives** from:
   a. Prof. David Jones, Professor of Liver Immunology & Hon Consultant Hepatologist – clinical expert, nominated by Ipsen
   b. Mo Christie – patient expert, nominated by the PBC Foundation
   c. Lisa Woodcock – patient expert, nominated by British Liver Trust
   d. Yasmin Stammers, Head of Internal Medicine, Specialised Commissioning & Senior Commissioner, Hepatobiliary and Pancreas Clinical Reference Group – commissioning expert, nominated by NHSE

5. **External Assessment Report** prepared by Newcastle TAR Team

6. **External Assessment Group response to factual accuracy check of EAR**

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

Elafibranor for treating primary biliary cholangitis [ID6331]

Document B

Company evidence submission

April 2024

File name	Version	Contains confidential information	Date
ID6331 Elafibranor company evidence submission document B_redacted.docx	V1.0	**Yes**	12th April 2024

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Abbreviations

5’ NT	5-nucleotidase
µmol/L	Micromole per litre
AASLD	American Association for the Study of Liver Diseases
ADL	Activities of daily living
AE	Adverse event
AIH	Autoimmune hepatitis
ALB	Albumin
ALD	Adrenoleukodystrophy
ALP	Alkaline phosphatase
ALT	Alanine aminotransferase
AMA	Anti-mitochondrial antibodies
ANA	Antinuclear antibodies
AST	Aspartate aminotransferase
BASL	British Association for the Study of the Liver
BCL-6	B-cell lymphoma 6
BNF	British National Formulary
BSG	British Society of Gastroenterology
CI	Confidence interval
CMH	Cochran-Mantel-Haenszel
CPK	Creatine phosphokinase
CrI	Credible interval
CS	Clinically significant (itch)
DB	Double-blind
DDI	Drug-drug interactions
DCC	Decompensated cirrhosis
DSU	Decision support unit
EASL	European Association for the Study of the Liver
ELF	Enhanced liver fibrosis
EMA	European Medicines Agency
EQ-5D	EuroQol 5 dimensions
FDA	US Food and Drugs Administration
FXR	Farnesoid X receptor
GGT	Gamma- glutamyl transferase
GLOBE	Global-PBC Study Group
HAV	Hepatitis A
HBV	Hepatitis B
HCC	Hepatocellular carcinoma
HCV	Hepatitis C
HDL	High-density lipoprotein
hHSC	Human primary hepatic stellate cells
HRQoL	Health-related quality-of-life
ICE	Intercurrent events
iADL	Instrumental activities of daily living
IgG	Immunoglobin G
IgM	Immunoglobin M
IQR	Interquartile range
ITT	Intention-to-treat
kg	kilogram
kPa	kilopascal
LDL	Low-density lipoprotein
LS	Least squares

LSM	Liver stiffness measure
LLN	Lower limit of normal
LTE	Long-term extension
MAA	Marketing authorisation application
MDT	Multi-disciplinary team
MHRA	Medicines and Healthcare products Regulatory Agency
mg	milligram
MMRM	Mixed model for repeated measures
N/A	Not applicable
NASH	Non-alcoholic steatohepatitis
NICE	National Institute of Health and Care Excellence
NHS	National Health Service
NHSBT	National Health Service Blood and Transplant
NMA	Network meta-analysis
NMB	Net Monetary Benefit
NORS	National Organ Retrieval Service
OCA	Obeticholic acid
OLE	Open-label extension
OR	Odds ratio
PAS	Patient Access Scheme
PBC	Primary biliary cholangitis
PKS	Pharmacokinetics analysis set
PP	Per protocol
PPAR	Peroxisome proliferator-activated receptors
PSC	Primary sclerosing cholangitis
RCT	Randomised controlled trial
SAS	Safety analysis set
SD	Standard deviation
SLR	Systematic literature review
SmPC	Summary of product characteristics
TB	Total bilirubin
TG	Triglycerides
TE	Transient elastography
TEAE	Treatment-emergent adverse event
TSD	Technical support document
UDCA	Ursodeoxycholic acid
U/L	Units per litre
ULN	Upper limit of normal
UK	United Kingdom
US	United States
UTI	Urinary Tract Infection
VLDL	Very low-density lipoprotein
WI-NRS	Worst Itch Numeric Rating Scale

B.1 Decision problem, description of the technology and clinical care pathway

B.1.1 Decision problem

The submission covers the technology's full marketing authorisation for this indication. The decision problem for this appraisal is presented in Table 1.

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	Adults with primary biliary cholangitis (PBC) whose disease has an inadequate response to, or who are unable to tolerate, ursodeoxycholic acid (UDCA).	As per the final scope	N/A
Intervention	Elafibranor alone or in combination with UDCA.	As per the final scope	Elafibranor treatment with and without UDCA (determined according to tolerability to UDCA) are not considered separately in the company submission as the ELATIVE trial population is representative of the distribution of patients treated with and without UDCA in clinical practice.
Comparator(s)	For people whose disease has an inadequate response to UDCA: • Obeticholic acid (OCA) in combination with UDCA • UDCA monotherapy For people who are unable to tolerate UDCA: • OCA monotherapy • Best supportive care	As per the final scope	As stated above, subgroups according to patient response to UDCA and/or tolerability to UDCA are not considered separately in the company submission as the ELATIVE trial population is representative of the distribution of patients treated with and without UDCA in clinical practice. Thus, the comparators presented are UDCA and OCA 5-10mg dose with UDCA (where a proportion of both arms do not receive UDCA, which represents the cohorts receiving OCA only and no treatment). To note, only approximately 5% of patients are unable to tolerate UDCA, as reflected in the proportions of patients in the elafibranor and OCA trials.[1–4] Any best supportive care treatment other than OCA 5-10 mg has not been recommended by NICE and therefore will not be considered in the submission.
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	As per the final scope	All outcomes have been addressed throughout the company submission, as follows: • As outcomes of the ELATIVE trial, including outcomes based on liver function biomarkers, occurrence of pruritus symptoms and adverse events, and health-related quality-of-life (Section B.2.3 and B.2.6).

	• PBC-related events, including ascites, varices, encephalopathy, and hepatic cell carcinoma • adverse effects of treatment • health-related quality-of-life		• As outcomes of the cost-effectiveness model, which captures patient mortality, outcomes according to liver function biomarkers, pruritus, adverse events, liver transplantation, health-related quality-of-life, and PBC disease-specific health states, including hepatocellular carcinoma and decompensated cirrhosis [including PBC-related events such as ascites, varices, encephalopathy] (Section B.3.3).
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. If the technology is likely to provide similar or greater health benefits at similar or lower cost than technologies recommended in published NICE technology appraisal guidance for the same indication, a cost comparison may be carried out. 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 the final scope	N/A
Subgroups to be considered	None	None	As stated above, subgroups according to patient response to UDCA and/or tolerability to UDCA are not considered separately in the company submission as the ELATIVE trial population is representative of the distribution of patients treated with and without UDCA in clinical practice.
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.	As per the final scope	N/A

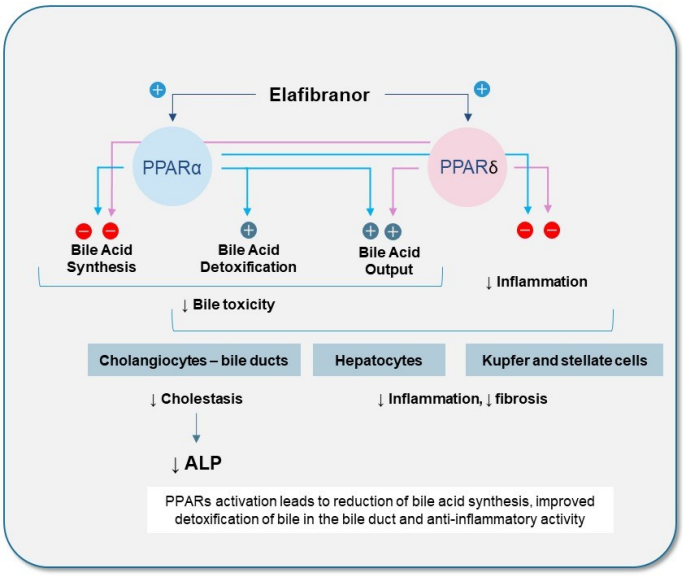
Abbreviations: NHS – National Health Service; NICE – National Institute of Health and Care Excellence; OCA – obeticholic acid; PBC – primary biliary cholangitis; UDCA – ursodeoxycholic acid

B.1.2 Description of the technology being appraised

A description of elafibranor is presented in Table 2. The current draft summary of product characteristics (SmPC) is provided in **Appendix C**. The elafibranor European and UK Public Assessment Report (EPAR) will be provided once available.

Table 2: Technology being appraised

UK approved name and brand name	Elafibranor (IQIRVO™)
Mechanism of action	Elafibranor is a peroxisome proliferator-activated receptor (PPAR) agonist, targeting primary biliary cholangitis (PBC) pathogenesis by combining the effects of PPARα and PPARδ activation to make elafibranor a possible valuable therapeutic tool in PBC via potentially additive or synergistic effects on bile output, bile toxicity, inflammation, and fibrosis to reduce cholestasis. Elafibranor is the only treatment under development for PBC which targets both PPARα and PPARδ.[5] PPARα is mostly expressed in the liver and its activation detoxifies, excretes bile acids and promotes bile acid synthesis inhibition.[6,7] Targeting PPARα results in the reduction of bile acid concentration in the liver and thereby induces a reduction in hepatic damage due to cholestasis in PBC patients.[6] PPARδ reduces bile acid synthesis by downregulating the expression of the rate-limiting enzyme cytochrome P450 (CYP) 7A1.[5,8] PPARδ is also involved in the activation of anti-inflammatory (M2) macrophages through transcription factor B-cell lymphoma 6 (BCL-6)-mediated pathways in the liver, which results in the reduction of hepatic inflammation.[5,8] By activating PPAR α and δ selectively, elafibranor is expected to confer additional therapeutic benefits compared with treatments which agonise only a single PPAR, while avoiding the side effects associated with PPARy activation (including weight gain, fluid retention, and heart failure).[9,10] Anti-fibrotic properties of elafibranor were demonstrated in human primary hepatic stellate cells (hHSCs), pivotal for fibrogenesis in the liver.[11] Figure 1 presents an overview of the mechanism of action of elafibranor.

	Figure 1: Elafibranor mechanism of action and potential impact on PBC  Abbreviations: ALP - alkaline phosphatase; PPAR - peroxisome proliferator-activated receptors Source: Modified from Schattenberg 2021[5]
Marketing authorisation/CE mark status	The national MAA submission to MHRA for elafibranor was submitted on [redacted]. The MHRA regulatory approval is expected in [redacted] 2024 (working assumption).
Indications and any restriction(s) as described in the SmPC	Elafibranor is 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. Restrictions for use: <u>Contraindications:</u> Elafibranor is not contraindicated in any medical condition, however, patients with hypersensitivity to the active substance or any of the excipients should not take elafibranor.[11] <u>Precautions for use:</u> Elafibranor is not recommended for patients with severe hepatic impairment (Child-Pugh C). If increases in liver biochemical tests and/or liver dysfunction are observed, prompt investigation of the cause is recommended and interruption of elafibranor treatment should be considered.[11] Observed increase in CPK or unexplained signs and symptoms of muscle injury; prompt investigation of the cause is recommended and interruption of elafibranor treatment should be considered.[11] During pregnancy or in women of childbearing potential not using effective contraception.[11] During breastfeeding; women who are breastfeeding should not breastfeed for at least three weeks following cessation of elafibranor.[11]

	Drug-drug interactions (DDIs): Clinical DDI studies showed no clinically significant effects when administering elafibranor as a DDI perpetrator with simvastatin, warfarin, atorvastatin or sitagliptin.[11] Elafibranor may therefore be safely administered with statins, with substrates of CYP3A, CYP2C9, OATP1B1, OATP1B3 and BCRP, as well as inhibitors of PTGR1.[11]
Method of administration and dosage	Pharmaceutical form: 80 mg film-coated tablets.[11,12] Administration: oral, once daily, with or without food.[11,12] Pack size: 30 film-coated tablets.[11,12] No dose adjustments are necessary in patients older than 65 years of age or those with renal impairment. No dose adjustment is necessary in patients with mild (Child-Pugh A) or moderate (Child-Pugh B) hepatic impairment. No relevant use of elafibranor in the paediatric population for PBC.[12,13]
Additional tests or investigations	Clinical and laboratory assessment of liver function should be done prior to initiation of elafibranor treatment and thereafter according to routine patient management.[11] CPK should be evaluated prior to initiation of elafibranor treatment and thereafter according to routine patient management.[11]
List price and average cost of a course of treatment	Packs are available in an 80 mg dose at £[redacted] per 30 tablet pack. The cost of elafibranor is £[redacted] per day.
Patient access scheme (if applicable)	A confidential simple patient access scheme has been applied. The pack price under this scheme is £[redacted]. The cost of elafibranor under this scheme is £[redacted] per day.

Abbreviations: CPK – creatine phosphokinase; DDI – drug-drug interactions; MAA – marketing authorisation application; MHRA – Medicines and Healthcare products Regulatory Agency; mg – milligrams; N/A – not applicable; PBC – primary biliary cholangitis; SmPC – summary of product characteristics; UDCA – ursodeoxycholic acid

B.1.3 Health condition and position of the technology in the treatment pathway

Summary:

- PBC is a rare, progressive, chronic autoimmune liver disease, characterised by loss of small intrahepatic bile ducts.[14,15] Progression of PBC is driven by a destructive cycle between immune responses and cholestasis.[14]
- PBC disproportionately affects females compared to males, with a nearly tenfold higher incidence in females (a ratio of 9:1).[16] PBC predominately affects individuals aged 40 years or older and is associated with a range of symptoms, including pruritus (itching) and fatigue, that accumulate as the disease progresses.[14,16–18] While both prevalence and incidence of PBC vary depending on geographical region, rates of PBC are increasing worldwide for both sexes.[16]
- Delayed diagnosis, which occurs in approximately 25% of PBC cases, and young age at diagnosis negatively impact PBC prognosis.[19,20]
- Patients with PBC experience a substantial clinical burden, with disease progression associated with an accumulation of symptoms, comorbidities and life-threatening liver-related complications such as cirrhosis and hepatocellular carcinoma (HCC).[21,22]
- Treatments for PBC aim to slow disease progression and prevent end-stage liver disease complications, while also providing symptom management.[17] While liver transplant offers a treatment option for patients with advanced-stage disease, it is a last resort for not having adequately managed cholestasis; it is not always curative and PBC can re-emerge. Additionally, liver transplants are a burdensome procedure for patients and has long waiting times, during which patients may further deteriorate.[23,24]
- Other treatment options for PBC are limited and associated with significant limitations, including lack of clinical response, potential adverse events (AEs), and limited impact on disease symptoms such as pruritus.[2,25] Furthermore, the current treatment options for PBC are associated with a considerable clinical burden, health-related quality-of-life (HRQoL) burden and cost burden.[21,22,26,27]
- PBC is also associated with substantial healthcare costs and indirect costs, which increase with disease progression and after the development of complications.[27]
- While UDCA is the only licensed first-line of treatment, 25-50% of patients with PBC do not have a sufficient response to UDCA treatment to prevent progressive liver disease,[28,29] with UK-PBC reporting that 40% of patients have an inadequate response to UDCA.[30] In addition to burden associated with liver transplants, second-line treatment options are necessary to effectively slow disease progression, avoid the need for liver transplant, and address the key symptoms of PBC.[17]
- Despite the availability of OCA as a licensed second-line therapy for PBC, patients with the disease still experience significant disease burden. While OCA is an effective second-line treatment, with similar response rates as UDCA, it does not improve pruritus (a common condition associated with PBC) and, in many patients, it exacerbates it. In the POISE trial, treatment-emergent adverse events (TEAEs) of pruritus were reported in 55.7% of patients in the OCA 5-10 mg treatment arm compared to 38.4% of patients in the placebo arm. Moreover, 34.3% of patients required additional intervention for pruritus management in the OCA 5-10 mg treatment arm compared to 19.2% in the placebo arm.[2] Therefore, there is a considerable unmet need for a novel treatment option that slows disease progression and address the symptoms of PBC, with a more tolerable AE profile to reduce the burden treatment for PBC.

- Elafibranor is a treatment option for the patients who have not responded to or are intolerant to UDCA, instead of OCA 5-10 mg, which is NICE recommended.

Abbreviations: AE – adverse event; HCC – hepatocellular carcinoma; HRQoL – health-related quality-of-life; OCA – obeticholic acid; PBC – primary biliary cholangitis; TEAE – treatment-emergent adverse events

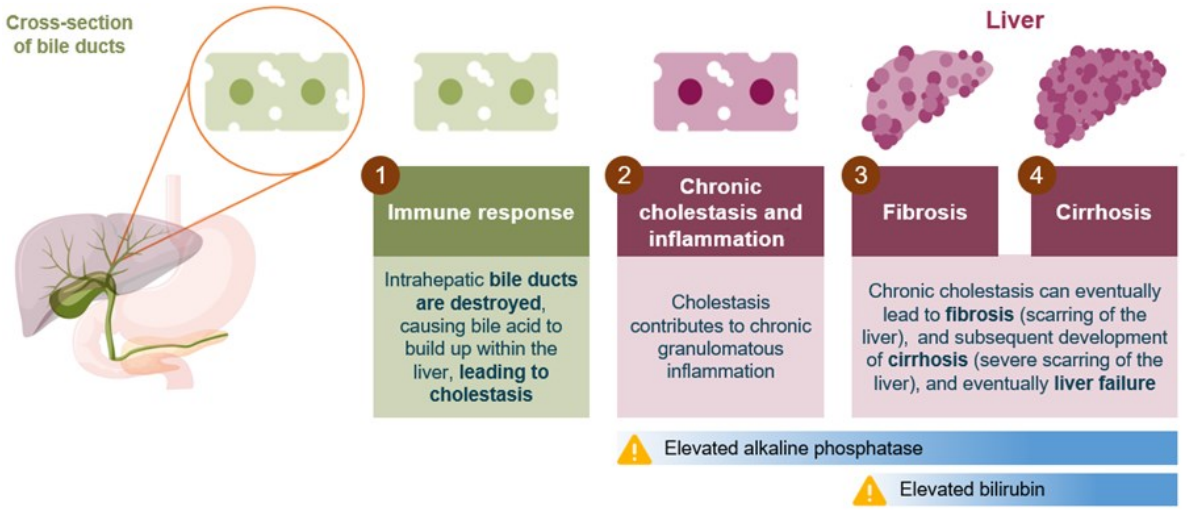
B.1.3.1 Disease overview

Primary biliary cholangitis (PBC) is a rare, progressive, chronic autoimmune liver disease, characterised by the destruction of small intrahepatic bile ducts.[14,15] Destruction of bile ducts leads to a build-up of toxic bile acids in the liver (cholestasis), resulting in inflammation and scarring of the liver (fibrosis).[14] If uncontrolled, the disease can progress to severe scarring (cirrhosis), liver failure, other complications (including ascites, varices, portal hypertension and hepatocellular carcinoma (HCC) and death.[14, 22,31]

Progression of PBC is driven by a destructive cycle between immune responses and cholestasis.[14] Bile acids are detergent molecules that are required to break down fats and vitamins for absorption and metabolism in the liver.[32,33] These bile acids accumulate as bile ducts become blocked and destroyed, causing cholestasis-mediated tissue damage, inflammation and further blockage of remaining biliary ducts. Anti-mitochondrial antibodies (AMA) also play a key role in this process, with AMA found in 90-95% of PBC patients compared with less than 1% of healthy individuals.[34]

The progression of PBC from the initial immune response is shown in Figure 2.

Figure 2: The progression of PBC and associated change in biochemical markers



Abbreviations: PBC – primary biliary cholangitis
Source: Galoosian 2020[16] Montano-Loza 2021[31]

B.1.3.1.1 Epidemiology

The exact cause of PBC is currently not well understood. Genetic factors, autoimmune causes and inflammatory pathways are likely to play a key role in initiating the immune response which drives the initial liver injury.[35,36] Additionally, environmental factors, such as geographical latitude, socioeconomic status and smoking, have been implicated in PBC pathogenesis and may trigger PBC in individuals with an underlying genetic predisposition.[37–39]

Patients are typically asymptomatic at presentation and picked up in the context of abnormal liver biochemistry. In those with symptoms, patients with PBC most commonly present with itching (pruritus) and fatigue, which can affect up to 70% and 80% of patients, respectively.[16, 18,40] Throughout the progression of PBC, patients may accumulate further symptoms associated with liver function impairment, including abdominal pain, progressive jaundice, malnutrition, portal hypertension, and liver failure, which can lead to premature death in the absence of a liver transplant or effective treatment.[14,31] Patient surveys have also reported restless legs, sleeplessness, depression and cognitive dysfunction.[14–16] See section B.1.3.2.1 for further details on the clinical burden of PBC.

Although PBC is a rare disease, its prevalence and incidence have been increasing in recent years.[41] The estimated UK prevalence of PBC is approximately 33.5 per 100,000 population according to UK-PBC based on the study by James *et al.* (1999),[42] equal to approximately 20,000 PBC patients in the UK.[43] The estimated annual incidence of PBC in the UK is 2.5 per 100,000 population (2021),[38] with other sources reporting higher annual incidence in the UK of 4.5 per 100,000 population (McNally *et al.* [2014]).[44]

PBC occurs more commonly in females than males, with more new cases in the UK in females (4.2 per 100,000 population) than in males (0.7 per 100,000 population).[38] Conversely, male patients tend to have more advanced disease at diagnosis, likely due to delayed presentation.[14,17] Most patients present with PBC between the age of 40 to 60 years, however, cases have been reported in individuals as young as 15 years. The disease tends to be more aggressive in these younger patients and the majority of patients needing transplantation had disease onset at a younger age.[16,45]

B.1.3.1.2 Diagnosis

Diagnosis of PBC is based primarily on serological markers with biochemical indicators of disease, as more than 50% of patients with PBC are asymptomatic at diagnosis.[15,16] Because the condition affects mostly women, with many experiencing symptoms around the time of menopause, some symptoms such as itch and depression may be dismissed by their general practitioner.[46] Often, PBC is only identified through routine laboratory testing or upon investigation for an unrelated disorder.[15,16] Abnormal liver function tests and a history of autoimmune disease may prompt clinicians to investigate a suspected diagnosis of PBC, which is then confirmed based on AMA titre, alkaline phosphatase (ALP) levels (elevated levels of which are both a diagnostic and prognostic marker for PBC), and liver histology.[14,31]

The European Association for the Study of the Liver (EASL) 2017, British Society of Gastroenterology/UK-PBC (BSG/UK-PBC) 2018, and American Association for the Study of Liver Diseases (AASLD) 2019 outline the following diagnostic criteria for PBC:[14,15,47]

- Biochemical evidence of cholestasis based on ALP elevation (≥2x the upper limit of normal [ULN])
- Presence of AMA at a titre of >1:40
- Histologic evidence of nonsuppurative cholangitis and destruction of interlobular bile ducts identified via liver biopsy

A diagnosis of PBC can be confirmed when two of these three criteria are met, typically ALP and presence of AMA.[47] A liver biopsy can be used to confirm the diagnosis, if needed. BSG-UK-PBC guidelines state that in clinical practice, the vast majority of patients are appropriately

and confidently diagnosed without a liver biopsy and in today's setting, biopsy confirmation is rare in practice.[47]

Delayed diagnosis, which occurs in approximately 25% of PBC cases, negatively impacts PBC prognosis, as patients with a delayed diagnosis are likely to have later-stage PBC that is more difficult to treat.[47] In particular, male patients with PBC are more commonly diagnosed at a later disease stage than female patients, possibly as males appear to experience fewer symptoms compared to females.[19]

Young age at diagnosis is also associated with PBC severity and prognosis, with symptom onset in patients with PBC under the age of 50 being associated with more severe and progressive disease, as well as poor treatment response, compared with patients over the age of 50 at diagnosis ($p<0.0001$).[20]

B.1.3.1.3 PBC treatment

The overall aim of treatment for PBC is to alter the natural progression of disease, thereby slowing disease progression and preventing end-stage liver disease complications, including the need for liver transplant, while also providing symptom management.[14,17] Liver transplant is the only potentially curative treatment for PBC, but is typically only available for patients with complications of cirrhosis, severe disease (indicated by progressively rising bilirubin levels), or severe medically-resistant pruritus.[14] The recurrence of PBC has been reported to occur in 21-37% of patients at 10 years after liver transplant, with a median time to recurrence of 3-5.5 years.[48] Thus, in addition to only being available for patients with severe PBC, liver transplant may not be curative in all cases.[47]

Current treatment options for patients with PBC are limited, with only two licensed, recommended therapies in the UK: UDCA and OCA (see section B.1.3.3). UDCA is the only licensed first-line treatment for PBC, and is universally recommended for the treatment of PBC in UK and international guidelines.[14,15,47] Despite improving patient outcomes, 25-50% of patients with PBC do not have a sufficient biochemical response to UDCA treatment to prevent progressive liver disease,[28,29] with UK-PBC reporting 40% of patients that have an inadequate response.[30] Patients who do not have an adequate response to UDCA are at greater risk of developing disease complications.[49] Up to 5% of patients are intolerant to UDCA, meaning they are unable to use the recommended first-line treatment.[3] Patients with an inadequate response or intolerance to UDCA are at an increased risk of disease progression, and should therefore be considered for second-line therapy.[31]

OCA is the only licensed second-line therapy for patients with PBC.[50] In the 12-month Phase III trial (POISE) of OCA in patients with PBC who did not respond to UDCA treatment (POISE; N=216), fewer than 50% of patients receiving OCA met the primary efficacy endpoint of biochemical cholestasis response, defined as ALP <1.67x ULN, with a reduction of ≥15% from baseline, and total bilirubin ≤ULN.[2] In addition, OCA does not improve pruritus, with patients experiencing an exacerbation in pruritus. In the POISE trial, treatment-emergent adverse events (TEAEs) of pruritus were reported in 55.7% of patients in the OCA 5-10 mg treatment arm compared to 38.4% of patients in the placebo arm. Moreover, 34.3% of patients required additional intervention for pruritus management in the OCA 5-10 mg treatment arm compared to 19.2% in the placebo arm. Therefore, achieving a cholestasis response might be outweighed by some patients' intolerability of OCA. Together, this demonstrates that a considerable proportion of patients treated with OCA do not respond to treatment, and response may be outweighed by tolerability amongst those who do respond.

Overall, the limited number of PBC-specific treatments and lack of innovation in this disease area (the most recent being the licensing of OCA in 2016 by the European Medicines Agency [EMA]) means that patients continue to experience a significant disease burden.[50] This burden includes various symptoms that significantly affect health-related quality-of-life (HRQoL), particularly pruritus and fatigue, which result in additional treatment and care management for patients with PBC.

B.1.3.1.4 Surrogate endpoints as biomarkers of disease progression

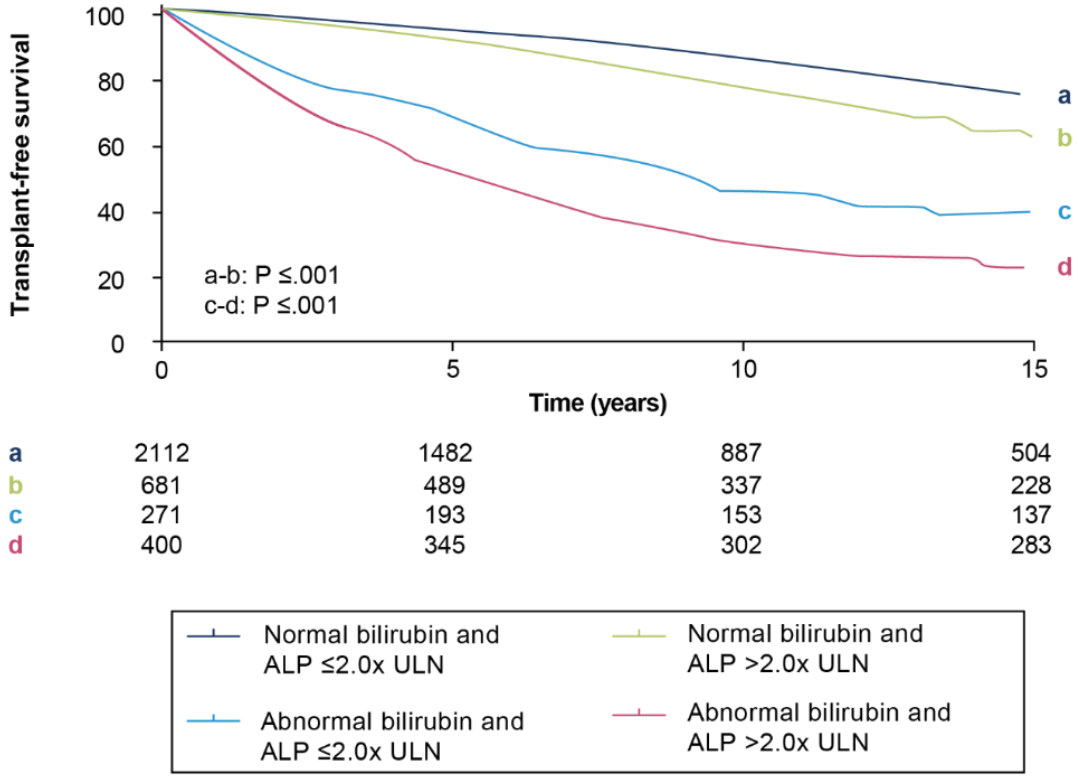
Surrogate endpoints, in particular the biomarkers of progression, ALP and bilirubin, can be used to predict the long-term clinical benefit of PBC treatment:

- **ALP** is the only disease marker used throughout the disease course from suspicion of PBC through to assessing a patient's treatment response and risk of disease progression.[14] ALP is an enzyme mostly found in the liver and bones. High levels of ALP in the blood may indicate a liver damage, with concentration of ALP correlating with the extent of damage.[17,51]
- **Bilirubin** is a yellow pigment produced during the breakdown of red blood cells. Bilirubin levels increase as PBC progresses, with high levels of bilirubin indicating cholestatic liver damage, cirrhosis, jaundice and decreased survival in PBC patients, making bilirubin a key marker of disease severity.[15,18,46]

Serum levels of ALP and bilirubin are frequently used as primary efficacy endpoints in clinical trials and in clinical practice to assess treatment response and disease progression in PBC.[2,4] They are also reliable surrogate markers of disease progression and powerful predictors of cholestatic injury and liver function, transplant-free survival and the rate of PBC progression when assessed in combination.[51]

Lammers *et al.* (2014) investigated ALP and bilirubin as surrogate endpoints in PBC, using data from 4,845 patients primarily treated with UDCA across North America and Europe, with a median follow-up of 7.3 years.[51] This study demonstrated that levels of both ALP and bilirubin, measured at study enrolment and each year for five years, are strongly associated with clinical outcomes. The combined assessment of both ALP and bilirubin levels was the strongest predictor of transplant-free survival duration, as shown in Figure 3.[51]

Figure 3: ALP and bilirubin levels are predictors of transplant-free survival in PBC

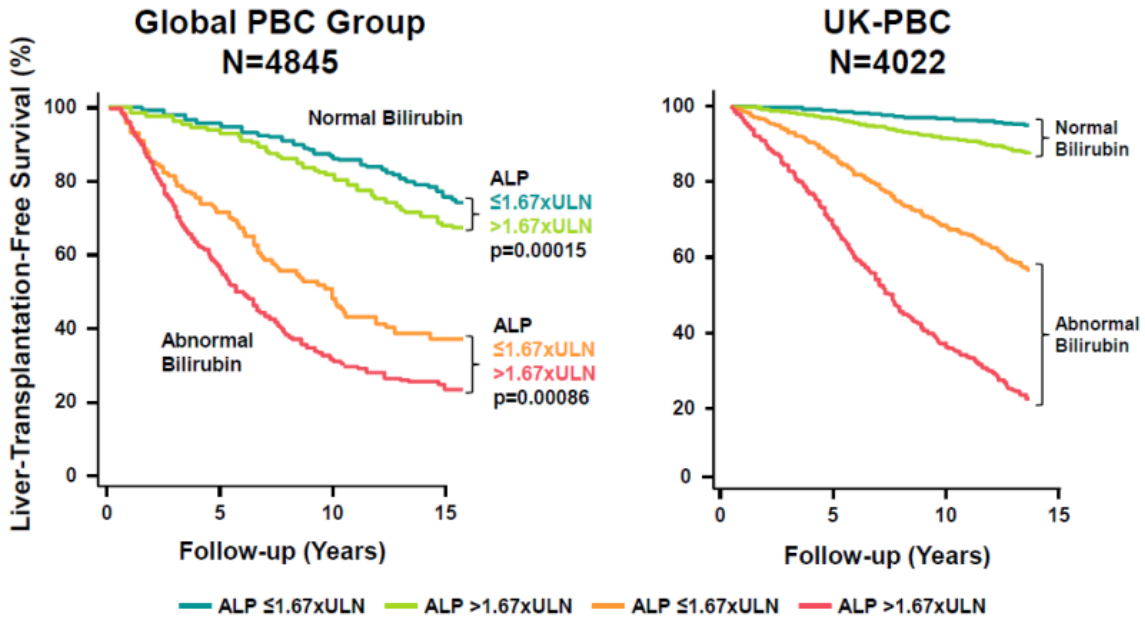


Abbreviations: ALP – alkaline phosphatase; PBC – primary biliary cholangitis; ULN – upper limit of normal
Source: Lammers 2014[51]

In the same study, ALP and bilirubin were also shown to be individually predictive of transplant-free survival: 84% of patients with ALP ≤2.0 x ULN at 12 months post-study enrolment survived transplant-free after a 10-year follow-up, compared with 62% of patients with ALP >2.0 x ULN (p<0.0001).[51] Similarly, 86% patients with bilirubin ≤1.0 x ULN one year post-study enrolment survived to 10 years, compared with 41% of patients over this bilirubin threshold (p<0.0001).[51]

Data from the Global-PBC and UK-PBC group also illustrate the impact of the relationship between ALP level and bilirubin levels using 1.67 x ULN as the cut-off for ALP and a normal/abnormal levels threshold for bilirubin (see Figure 4).

Figure 4: Global-PBC and UK-PBC data for 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 cholangitis; ULN – upper limit of normal
Source: NICE TA443[1]

Due to their value as prognostic biomarkers, ALP and bilirubin have been routinely used in composite endpoints to assess patients' biochemical response to treatment for PBC.[51] Slow progression of PBC has been observed in patients with normal bilirubin and ALP <1.67x ULN, whereas fast progression of PBC has been observed in patients with abnormal bilirubin and ALP ≥1.67x ULN.[52]

Due to the evolving scientific environment, specific cut-offs for initiating treatment can vary but the 2018 BSG UK-PBC guidelines recommend that those intolerant to treatment with UDCA or those with high risk disease as evidenced by UDCA treatment failure (frequently reflected in trial and clinical practice as an ALP >1.67× ULN and/or elevated TB) should be considered for second-line therapy.[47]

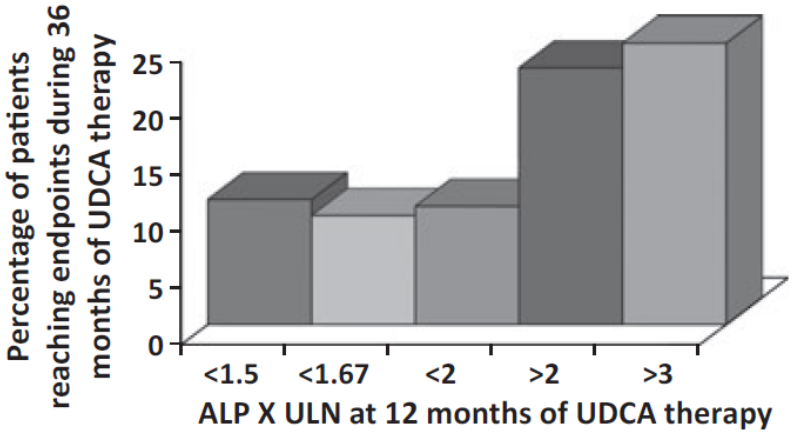
Studies have also shown ALP ≥1.67 x ULN and an ALP threshold of <1.67 x ULN combined with TB ≤1 ULN predict lower likelihood of adverse outcomes.[51,53,54] Momah *et al.* (2012) performed a retrospective review of 73 patients with PBC treated with UDCA followed over 36 months who reached the following clinical endpoints:[54]

- Varices and ascites by 24 months
- Hepatic encephalopathy by 24 months
- Ascites by 36 months
- Liver transplant and ascites by 36 months
- Varices by 24 months
- Hepatic encephalopathy and death by 24 months
- Varices by 36 months
- Ascites by 36 months; hepatic encephalopathy

- Varices by 24 months
- Ascites at entry; hepatic encephalopathy and death by 24 months
- Varices by 24 months
- Hepatic encephalopathy by 24 months

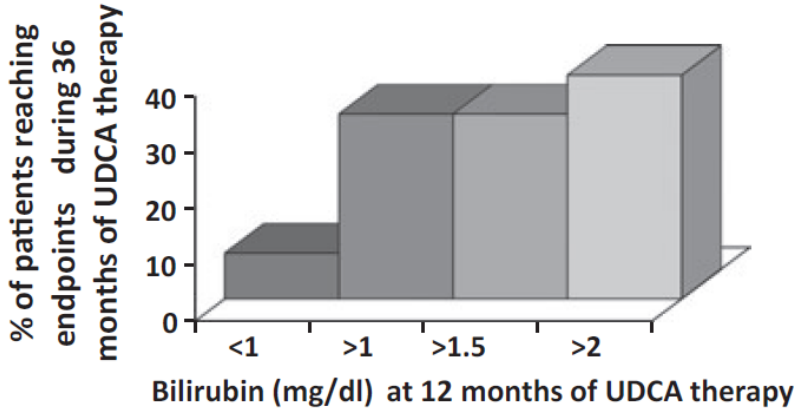
It was suggested that in patients enrolled in adjunctive therapy trials based on these criteria, ALP ≤1.67 x ULN and bilirubin ≤ 1 mg/dl are possible parameters to define treatment success as illustrated in Figure 5 and Figure 6.

Figure 5: Histogram representation of percentage of patients having varying levels of elevations of ALP x ULN at 12 months of UDCA therapy, who reached clinical endpoints within 36 months of UDCA therapy



Abbreviations: ALP – alkaline phosphatase; UDCA - ursodeoxycholic acid; ULN – upper limit of normal
Source: Momah et al 2012[54]

Figure 6: Histogram representation of percentage of patients with varying levels of elevation of bilirubin at 12 months of UDCA therapy, who reached clinical endpoints within 36 months of UDCA therapy



Abbreviations: ALP – alkaline phosphatase; UDCA - ursodeoxycholic acid; ULN – upper limit of normal
Source: Momah et al 2012[54]

In alignment with these findings, cholestasis response, defined as ALP <1.67 x ULN, TB ≤ULN and ALP decrease from baseline of ≥15%, has been recognised as a relevant surrogate marker in PBC clinical trials. It previously formed the primary endpoint in the POISE trial, for the conditional approval of OCA, and has been used in the pivotal elafibranor ELATIVE trial.[2,4] The addition of a minimum ALP reduction of ≥15% from baseline was included as part of the composite endpoint in these trials as a conservative threshold so that patients who only had

a small change in ALP from 1.67 x ULN were excluded. This ensured that only subjects with a relevant clinical effect were judged to have a successful response.

There is no consensus definition for an 'inadequate response' to UDCA: this depends on the scoring system being used and broadly refers to persistently elevated ALP values along with TB despite treatment. Different criteria for an inadequate response to UDCA have been reported in medical literature.[14] These criteria (Table 3) are based on the improvement of biochemical markers of the disease (ALP, gamma-GT, albumin, bilirubin) after 6-24 months of treatment. All studies agree that the response to UDCA, whatever the definition, represents an independent prognostic factor of disease progression. Therefore, the percentage of patients who are non-responders to UDCA changes according to the chosen marker.

Table 3: Defining Treatment Response in PBC

Scoring system	Time (months)	Scoring parameters
Qualitative binary definitions		**Criteria for inadequate response**
Rochester	6	ALP ≥2 x ULN or Mayo score ≥4.5
Barcelona	12	Decrease in ALP ≤40% and ALP ≥1 x ULN
Paris-I	12	ALP ≥3 x ULN or AST ≥2 x ULN or bilirubin >1 mg/dl
Rotterdam	12	Bilirubin ≥1 x ULN and/or albumin <1 x ULN
Toronto	24	ALP >1.67 x ULN
Paris-II	12	ALP ≥ 1.5 x ULN or AST ≥ 1.5 x ULN or bilirubin >1 mg/dl
Ehime	6	Decrease in GGT ≤70% and GGT ≥1 x ULN
Continuous scoring systems		**Scoring Parameters**
UK-PBC	12	Bilirubin, ALP and AST (or alanine aminotransferase [ALT]) at 12 months Albumin and platelet count at baseline
GLOBE	12	Bilirubin, ALP, albumin and platelet count at 12 months Age at baseline

Abbreviations: ALP – alkaline phosphatase; ALT – alanine aminotransferase; AST – aspartate aminotransferase; GGT – gamma- glutamyl transferase; ULN – upper limit of normal.
Source: EASL 2017[14]

All models that have been proposed to define the lack of response to UDCA (see Table 3) are easy to use but also dichotomous, namely they are able to define only two levels of risk (responder and non-responder). Conversely, these models are not able to provide intermediate levels of risk and do not measure risk over time. That is, they do not predict the likelihood that a patient will undergo transplant after 1-5 years.

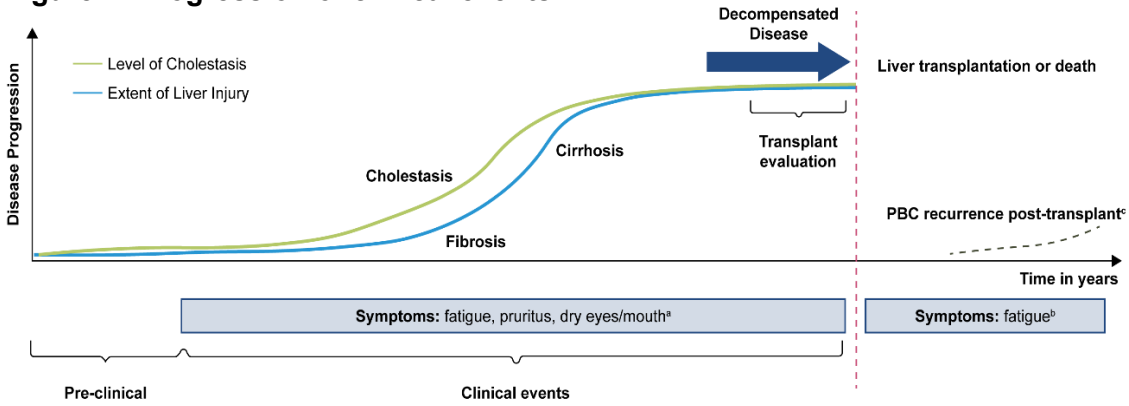
Ideally, to drive decisions on patient management, it is necessary to provide continuous models (indices, scores) with the power to measure the level of risk for each single patient in each disease stage and, above all, to quantify risk over time. Two scoring systems developed by the UK-PBC Consortium (UK-PBC risk scores) and Global-PBC Study Group (the GLOBE risk scores) use clinical and biochemical variables to continuously predict prognostic outcomes in patients with PBC, and typically generate similar results.[55,56] Using such models it is possible to quantify the risk of developing liver failure requiring transplant or liver and non-liver-related mortality over a specific timeframe (5,10 and 15 years) in single patients. A 2021 multi-centre trial of patients with PBC (N=1,100) reported that UK-PBC and GLOBE risk scores demonstrated comparable high accuracy in predicting risk of liver transplant or death at one year of UDCA treatment (concordance statistic: UK-PBC 0.68; 95% confidence interval [CI]: 0.64, 0.72; GLOBE 0.80; 95% CI: 0.76, 0.84).[57]

B.1.3.2 Burden of PBC

B.1.3.2.1 Clinical burden

Patients with PBC experience a substantial clinical burden, with disease progression associated with an accumulation of symptoms, comorbidities and life-threatening liver-related complications, such as cirrhosis and HCC.[21,22] Clinical presentation of PBC is highly variable and patients diagnosed with PBC can experience a range of symptoms, including pruritus, fatigue, progressive jaundice, malnutrition and portal hypertension, that increase their risk of complications and liver failure.[15,16,31] The progression of PBC from early to end-stage disease is shown in Figure 7.

Figure 7: Progression of clinical events in PBC



Abbreviations: PBC – primary biliary cholangitis
Footnotes: [a] Symptoms do not correlate with the disease stage and can occur at any point. [b] Fatigue may persist after liver transplant. [c] The frequency of post-transplant PBC is highly variable among studies.
Source: Trivella 2023[58]

Early-stage PBC, which may last for decades, is generally asymptomatic and is associated with immunologic and biochemical indicators of disease rather than clinical symptoms. However, around half of patients with PBC may experience some degree of itch or fatigue, although these symptoms may not always be recognised or inquired about during assessments.[14,31] Consequently, diagnosis of PBC is usually indicated through immunologic and biochemical markers investigated for an unrelated disorder.[14,31] While a diagnosis is usually made in primary care, disease management is usually shared between secondary care gastroenterologists and hepatologists, with tertiary care input for specialist treatment, such as transplantation or clinical trial enrolment, if necessary.[17]

During moderate-stage PBC, patients may accumulate a range of symptoms and comorbidities, with examples and estimates of prevalence compared to healthy individuals shown in Figure 8. Moderate-stage PBC can last for up to 10 years and is characterised by biochemical and clinical symptoms associated with cholestasis, ductopenia and then fibrosis.[31] The most commonly reported symptoms in moderate-stage PBC are pruritus and fatigue, occurring in 29.0-69.3% and 25.0-76.4% of patients with PBC at diagnosis, respectively.[18,40]

Pruritus has a significant negative impact on patients' day-to-day lives, as it is detrimental to sleep, impacts patients' social lives, housework and work.[59] Patients with PBC and pruritus also have a significantly higher prevalence of other symptoms and comorbidities including fatigue, depression, anxiety and sleep-related issues compared to patients with PBC without

pruritus.[60] Perspectives from PBC patients experiencing pruritus symptoms have been reported as follows:

> *"At night-time, pretty much as soon as I get home and sit down for the evening and at night when I'm trying to sleep, it's extremely severe. I mean, it's to the point where literally my skin opens up and bleeds because I'm scratching that much."* - a patient describing pruritus.[61]

> *"There's no escape from it [itching]…It can put you into a dark state of mind because it gets so overwhelmingly maddening. Because like it always happens for me at night-time, and I'm so tired, and I just want to sleep and I can't."* – a patient describing the impact of pruritus.[61]

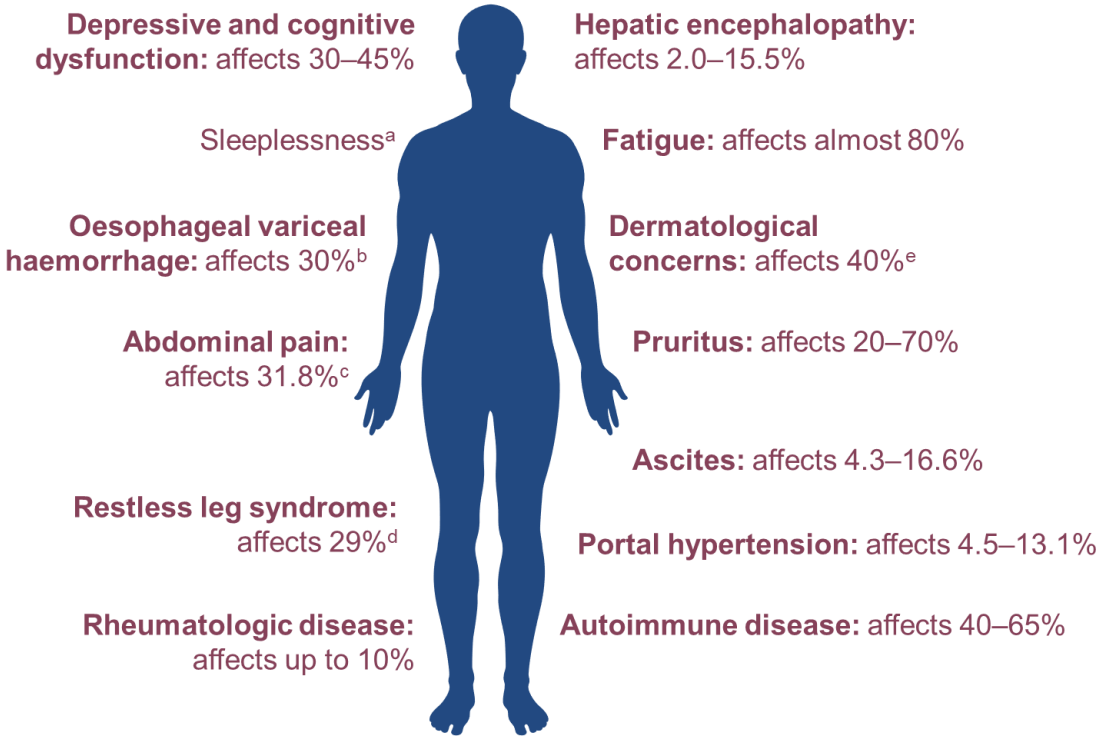
> *"The patients are embarrassed, and other people are telling them, "Stop itching. Stop scratching," as if they could control it. So that leads to social isolation…they're exhausted because they didn't sleep so that adds to their fatigue. That leads to depression."* – a clinician describing the impact of pruritus.[61]

Fatigue has a significant negative impact on patients' day-to-day lives, with patients reporting their fatigue resulting in brain fog, mental confusion, dizziness, memory problems, difficulty focussing and attention problems, all which contribute to sleep problems (95%).[61] Fatigue affects up to 80% of patients with PBC and one in five patients who have fatigue describe it as "significant" or "life altering".[62] A 2021 study of the UK-PBC cohort focussing on patients awaiting liver transplant (N=2,022), found that fatigue was reported in 63.4% of pre-liver transplant patients with PBC.[63] A PBC patient experiencing fatigue symptoms reported the burden as follows:

> *"One of the worst parts with PBC is the fatigue. People, including your family and your employers, don't understand. They think you're tired, you're lazy…I have fatigue at 7 AM before I even get off my bed. I am so tired that I literally cannot move."* – a patient describing fatigue.[64]

During late-stage PBC, patients can develop additional symptoms as their disease progresses, including progressive jaundice, malnutrition, portal hypertension and liver failure. Other symptoms in late-stage PBC include ascites (accumulation of fluid in the abdomen), hepatic encephalopathy (brain and nervous system disorder), oesophageal variceal haemorrhage (bleeding in the oesophagus), sicca complex (dry eyes and throat), and joint or bone pain.[17,65] Patients can also accumulate comorbidities, including osteoporosis, rheumatoid arthritis, thyroid disorders and other autoimmune disorders.[47,66] Late-stage PBC generally lasts two to four years before liver-related premature death or the need for a liver transplant.[31]

Figure 8: Symptoms and comorbidities of PBC



Abbreviations: PBC – primary biliary cholangitis
Footnotes: [a] specific incidence/prevalence figures for sleeplessness in PBC were not found; however, it is noted that patients with PBC frequently describe sleep problems and somnolence because of fatigue.[61] [b] oesophageal varices occur in approximately one-third of patients with PBC; of these patients, almost 40% experience one or more episodes of variceal bleeding within three years. [c] Up to 61.1% of patients with PBC and small intestinal bacterial overgrowth. [d] reported for primary biliary cirrhosis (based on cohort of 42 patients with early PBC). [e] includes dry skin, hyperpigmentation, xanthelasma, xanthomas, jaundice, dermatographism and fungal infection of the feet.
Source: Anderson 2013[67] (restless leg syndrome), Galoosian 2020[16] (fatigue, pruritus, rheumatologic disease, autoimmune disease), Gao 2017[68] (oesophageal variceal haemorrhage), Lindor 2019[15], Liu Chen Kiow 2019[69] (abdominal pain), Pandit 2023[70] (dermatological concerns), Sayiner 2019[71] (ascites; hepatic encephalopathy; portal hypertension), Shaheen 2018[72] (depressive and cognitive dysfunction)

It is important to diagnose and treat patients early to slow disease progression and to prevent the complications of late-stage PBC. The biological processes of the disease are more responsive to therapy early in their pathways – cholestasis and inflammation are inherently more treatable than duct injury or fibrosis, whilst the end-state of ductopenia and cirrhosis are not treatable.[14,47] When treatment is delayed, survival is significantly worse than in the general population.[19,73] Progression of PBC can result in liver cirrhosis if the disease remains uncontrolled by treatment, creating substantial clinical burden. Five-year survival and transplant-free survival has been shown to be lower in patients with cirrhosis compared with those without (80% vs. 93%, [p=0.003] and 80% vs. 93%, [p=0.002], respectively).[21] This study also found that patients with cirrhosis have a three-fold higher death risk than those without cirrhosis, demonstrating the significant impact of cirrhosis on patient prognosis.[21]

HCC is an aggressive cancer that frequently occurs in advanced stages of PBC and is associated with a faster PBC disease progression.[22] There is currently a limited number of effective treatments against HCC at an advanced-stage to improve survival, therefore HCC imposes a significant clinical burden in PBC. The majority of patients experiencing HCC also suffer from cirrhosis.[47] A 2021 meta-analysis of 29 cohort studies that reported the incidence of HCC in patients with cirrhotic PBC as 15.7 per 1,000 patient-years (n=22,615), compared with 2.68 per 1,000 patient-years in patients with non-cirrhotic PBC.[47,74] This study also

showed an incidence rate of PBC advancing to HCC three times higher in men than women (9.82 vs 3.82 per 1000 person-years; no p-value reported), further evidence that men with PBC often have worse outcomes compared to women.[74]

Liver transplant is required for patients who do not adequately respond to currently available treatments and progress to cirrhosis and its life-threatening complications, or suffer with severe medically-resistant pruritus.[17] While liver transplant offers a treatment option for patients with advanced-stage disease, it is a last resort for not having adequately managed cholestasis; it is not always curative and PBC can re-emerge.[47]

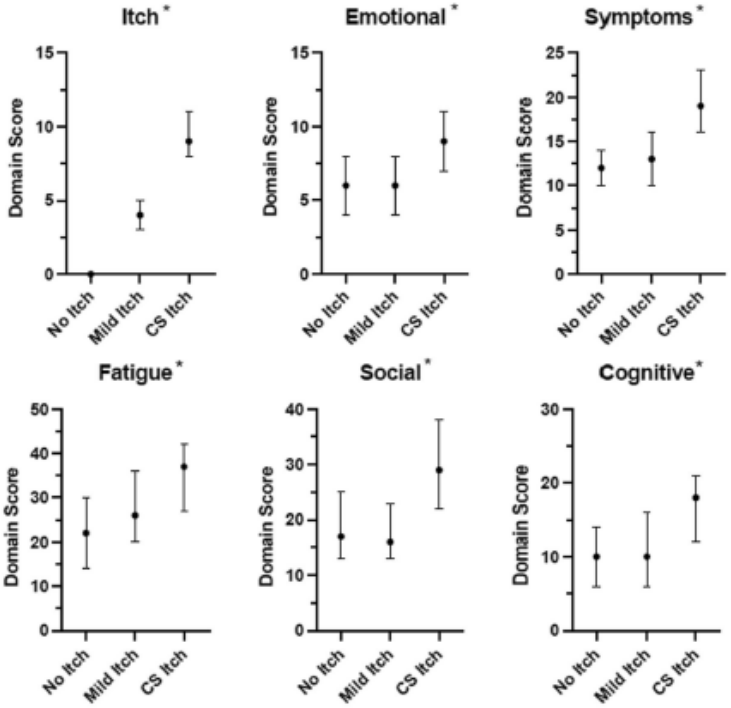
Liver transplant is also associated with significant wait times, as organ availability will impact the timing and indication for surgery; in the UK, average liver transplant waiting times are reported at 3-4 months.[75] As most patients with PBC are middle-aged and may be younger than other individuals on transplant lists, they can experience much longer waiting times for transplant. This is because the current liver transplant algorithm (Transplant Benefit Score) gives priority to those with alcohol-induced liver damage and/or elderly, instead of younger people who may have a longer term benefit.[76,77] PBC is one of the most frequent indications for liver transplantation in Europe, with patients on the liver transplant waiting list more likely to die while waiting for a transplant, due to deterioration of symptoms or serious liver complications, compared to patients with other liver disease, such as hepatitis C, alcoholic liver disease, and hepatitis B.[78–80]

Liver transplant itself is a challenging and resource-intensive procedure, and carries substantial risks for patients, including bleeding, blood clots, infection, mental confusion, seizures, and rejection of the donor liver. Side effects associated with anti-rejection medications, which are required for the lifetime of the individual following liver transplant, include: bone thinning, diabetes, headaches, susceptibility to infections and high blood pressure and high cholesterol.[23] While symptoms of PBC generally improve after transplant, many patients continue to experience symptoms such as fatigue and osteopenia (low bone density) after transplant or frequently experience post-transplant PBC re-emergence.[20] There is therefore an increasing clinical unmet need for effective treatments that slow disease progression and address PBC symptoms thus reducing the clinical burden associated with PBC and reducing the likelihood of a liver transplant referral or PBC re-emergence (see Section B.1.3.4).

B.1.3.2.2 HRQoL

As mentioned in B.1.3.2.1, patients with PBC experience a range of symptoms, which can significantly impact patient HRQoL. Among these symptoms, pruritus has a large negative impact on HRQoL of patients with PBC during their disease course. It has been reported that, prior to specific treatment for pruritus, patients with mild or moderate pruritus have similar EQ-5D scores (0.75 and 0.76 respectively) to the general population (0.80), whereas patients with severe pruritus report notably worse utility scores (0.49), similar to that of Parkinson's Disease, compared to the general population.[81] This is because pruritus is detrimental to patients' sleep, social life, housework, and work, as shown in Figure 9 which shows significantly worse scores in patients with clinically significant (CS) itch (defined as ≥ 7 points from a maximum of 15 on the itch domain) compared to those with no or mild itch (defined as 0 points or ≥ 1 and < 7 out of 15 on the itch domain, respectively) across all patient reported outcomes domains evaluated.[59]

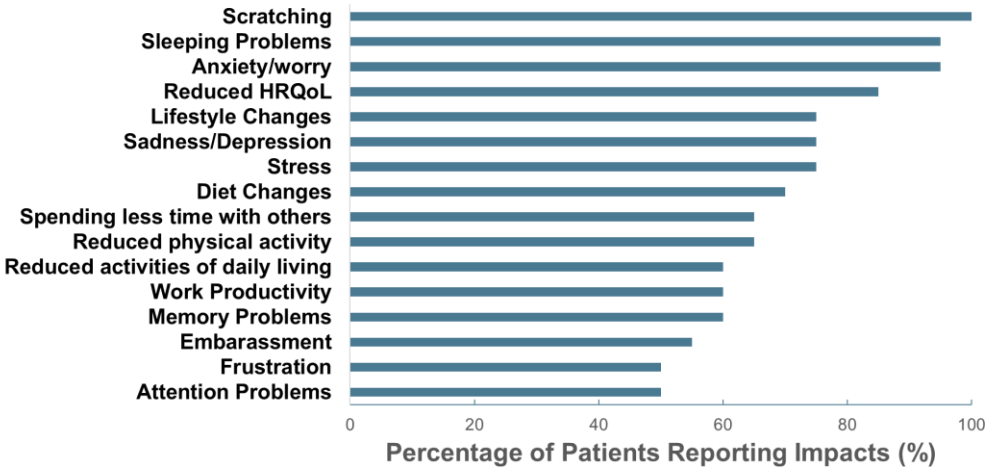
Figure 9: Median PBC-40 domain scores by itch severity



Abbreviations: CS – clinically significant; PBC – primary biliary cholangitis
*p-value <0.0001
Domain score ranges from each domain are: Itch (0-15); Emotional (3-14); Symptoms (6-33); Fatigue (11-54); Social (8-47); and Cognitive (6-29)
Source: Mayo 2023[59]

Qualitative interviews with clinicians (N=4) and patients with PBC who suffer from pruritus (N=20) demonstrated the impact of pruritus on HRQoL for patients with PBC.[61] Patients with pruritus reported scratching (100%), sleep problems (95%) and anxiety/worry (95%) leading to mental and physical fatigue and significant social and emotional disturbance of this symptom.[61] The impacts of PBC reported by >40% of patients with PBC and pruritus in this study is shown in Figure 10.

Figure 10: Impacts of PBC reported by >40% of patients with PBC and pruritus



Abbreviations: HRQoL – health-related quality-of-life; PBC – primary biliary cholangitis
Source: Levy 2023[61]

The UK-PBC cohort symptoms dataset is a UK-wide comprehensive cohort of PBC patients (N=2,055) with detailed symptom and HRQoL data. Between 2008-2011, most patients in the dataset were female (91%), receiving UDCA therapy (79%), with a median age at presentation of 55 years (interquartile range [IQR]: 48-63).[82] In a 2013 analysis of the dataset (N=2,353), 35% of patients with PBC reported perceived significant HRQoL impairment and 46% rated their health status as 'fair or poor', compared with 6% and 15%, respectively, in age- and sex-matched healthy individuals ($p<0.0001$ for both).[83] A 2016 extended analysis of the same dataset, focused on patients with recorded age at disease presentation (N=2,055), found that younger age at presentation was associated with poorer perceived HRQoL, with symptom domains relating to social isolation, fatigue, anxiety and depression being important predictors of poor self-perceived HRQoL (all $p<0.05$).[82] In a 2021 study of the same dataset (N=2,222), data associated with PBC-related characteristics, including fatigue, bone ache, liver discomfort, ascites, and memory and concentration problems, were analysed. It was reported that fatigue and bone ache were reported in 63.4% and 43.1% of patients with PBC, representing a significant reduction in HRQoL due to symptom burden.[63]

The negative impact of fatigue on HRQoL has been consistently reported across studies.[20, 63,83,84] For example, one study reported that up to 80% of patients with PBC experience fatigue, with one in five of those patients who have fatigue describing it as "significant" or "life altering".[62] In qualitative interviews of 20 patients with PBC and pruritus, patients reported their fatigue resulted in brain fog, mental confusion, dizziness, memory problems, difficulty focussing and attention problems; fatigue also resulted in 95% of patients experiencing sleep problems.[61]

A case-control study that matched 1,032 patients with PBC with 1,041 controls found that a significantly larger percentage of patients with PBC are significantly more likely to experience limitations to daily living and social functioning compared to matched healthy individuals (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.[85] The same study found that patients with PBC were significantly less likely to participate in sports, physical exercise and hobbies.[85]

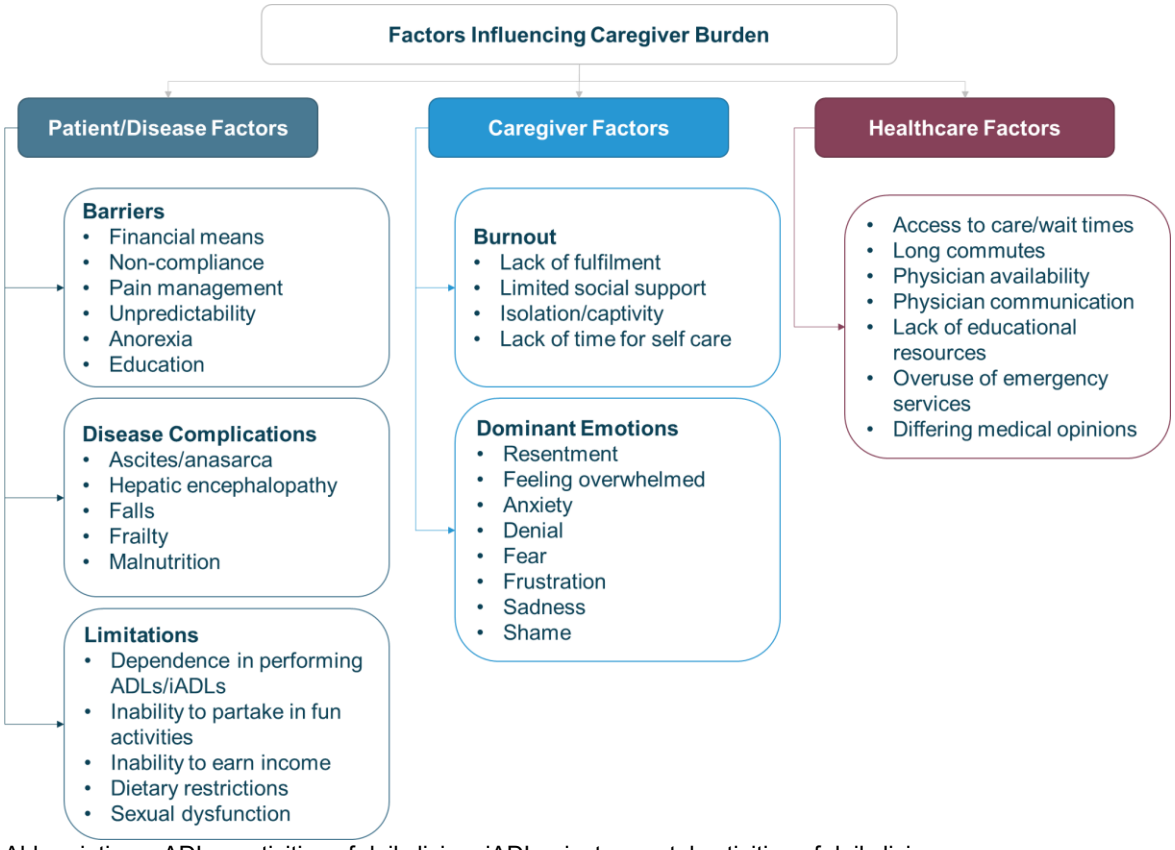
B.1.3.2.3 Caregiver burden

Caregivers are vital in disease management as patients often struggle to complete day-to-day activities without support. The supportive role caregivers play for patients impacts their HRQoL, including their mental and physical health. The burden of caring for patients with liver disease brings emotional strain, including anxiety, guilt, fear, and resentment, as well as a lack of time for their own self-care, frustrations with medical professionals and disease-related restrictions for carers.[86] Additionally, it is reported that patients with PBC have increased sick leave compared to matched controls,[87] which may contribute further to the carer burden as the support patients with PBC during acute illness. A study on family and friends' responses for people with PBC showed that the severity of illness is a major predictor of the strain caregivers experience.[88] A behavioural, cognitive and emotional impact of PBC on their daily life was reported by 69% of caregivers, including husbands, female family and friends.[88] Caregivers that reported no impact on daily life still needed to find their ways of dealing with

the situation, suggesting that the percentage of caregivers affected by PBC may be higher. The study also identified a relationship between gender and caregiving among patients, indicating that women experience greater emotional impact from illness compared to men.[88]

Factors influencing caregiver burden, demonstrating how the supportive role caregivers play for patients with cirrhosis impacts their HRQoL, as well as their mental and physical health, are shown in Figure 11.

Figure 11: Factors influencing burden experienced by caregivers of patients with cirrhosis



Abbreviations: ADL – activities of daily living; iADL – instrumental activities of daily living
Source: Saleh 2022[86]

Due to the high cost of paid care in the UK,[89] unpaid caregivers, such as family members, often need to care for patients. These individuals are likely to experience economic setback due to lost work and wages, which impacts their HRQoL.[86]

B.1.3.2.4 Economic burden

PBC is associated with substantial direct healthcare costs, which increase significantly with disease progression and after the development of complications.[27] Costs associated with inpatient treatment in particular account for a large proportion of direct costs associated with PBC. This is primarily driven by the management of the complications themselves, as well as their associated screening costs even in people who don't develop them.[27, 63,71] Moreover, the cost of inpatient treatment of PBC patients is large as care needs always to be personalised to the patient. Patients undergo various immunologic and biochemical tests of the liver for a clinical diagnosis of PBC, with subsequent disease staging tests and extensive management of the various symptoms and comorbidities of PBC (as further discussed in Section B.1.3.3).

Increasing disease severity and symptom burden are associated with greater healthcare resource use and costs. While PBC symptoms, such as pruritus, may initially be managed in primary care using prescription treatments, patients with PBC may require referral to inpatient care in specialist treatment centres as their disease progresses and symptoms become more severe.[47] Patients with severe PBC symptoms may also require more intensive or costly treatments than those with mild symptoms. A 2021 UK study of the UK-PBC cohort (N=2,222) demonstrated that PBC complications were associated with substantial economic burden, with varices (£2,504; 95% CI: £1,311, £3,696) and hepatic encephalopathy (£823; 95% CI: £148, £1,498) presenting the greatest annual costs to the NHS.[63]

By far the biggest cost to the NHS is liver transplant. The NICE evaluation of OCA (TA443) used data from an earlier report by Singh and Longworth in HCV patients where mean total costs were £18,055 pre-transplantation, £64,452 during the transplant phase and £36,009 in two years post-transplant.[90] The average cost per transplanted patient with HCV from assessment to two years post-transplant was calculated as £111,810. These costs were inflated to 2016 prices in TA443. More recently Singh and Longworth compared four approaches used to estimate current costs when good quality contemporary data are not available using liver transplantation.[91] This research focused on hepatitis B and C patients, but expert opinion obtained by Ipsen suggests that these costs would be applicable to PBC patients undergoing liver transplant. The authors found that data on resource use from National Health Service Blood and Transplant (NHSBT) are the most accurate reflection of cost estimates for transplantation and liver transplant follow-up of two years; however, given lack of NHSBT data for pre-transplant phase and given the changes in clinical practice, expert elicitation for pre-transplant was added to give a total cost of £121,211.

A highly specialised technology appraisal (HST17) also reported costs for pre-transplant phase (£19,699), transplant procedure (£70,320), transplant follow-up within two years (£39,287) taken from TA443, in addition to the costs for the organ (£17,861), and organ retrieval (£24,614) which were sourced from the NHSBT and data from the National Organ Retrieval Service (NORS) in the UK.[92–94] The HST17 appraisal also included costs associated with immunosuppression therapies (azathioprine, tacrolimus and prednisolone).[95–97] As mentioned in section B.1.3.1.3, 21-37% of patients will have a recurrence of PBC within 10 years, with only 8% of patients returning to work.[48,98]

In a Swedish population, patients with PBC had higher odds of sick leave (OR 2.50; 95% CI 1.69–3.70) than matched controls from the general population. Untreated patients were more likely to be on sick leave (OR 3.22; 95% CI 1.12–9.25) two years after diagnosis than UDCA responders.[87]

Caregiver costs, and the impact of PBC on caregivers, also contribute to the economic and societal impact of PBC. As the burden of symptoms progresses, it is more likely that paid help is needed, contributing to the costs of disease management.[99] As the average cost of hiring a private carer in the UK is approximately £20 per hour, many patients cannot afford paid care on the ongoing basis required as PBC is a chronic condition.[89] Therefore, unpaid caregivers, such as family members, often need to care for patients, and these individuals are then likely to experience economic setback themselves due to lost work and wages.

The key to generating the most cost savings in all liver diseases come from avoiding cirrhosis development and thus effective management of cholestasis will enable this.

B.1.3.2.5 Treatment-related burden

Existing treatments for patients with PBC are associated with important limitations and may add to the clinical burden experienced by patients.

UDCA is the only available first-line treatment for PBC. However, 25-50% of patients do not adequately respond to UDCA treatment, leaving them at increased risk of disease progression and further complications.[28,29] Moreover, patients who are younger or have aggressive disease are less likely to respond, demonstrating a greater unmet need in patients with most severe disease.[20] Additionally, while the treatment is well tolerated, with few side effects at its recommended dose, it has little impact on disease symptoms, such as pruritus, bleeding varices and hepatic encephalopathy, suggesting that treatment with UDCA alone does not adequately address patient burden.[14,47]

For patients who have an inadequate response to, or are unable to tolerate UDCA, second-line treatment with OCA is used. OCA is currently licensed as a 5-10 mg dose, which involves patients starting treatment on the 5 mg dose and subsequently receiving dose escalation to 10 mg.[50] In the POISE study (the pivotal trial for OCA), patients were also randomised to start treatment on the 10 mg dose instead of escalating, but this dose regimen is not currently licensed in the UK.[2]

OCA is not effective at controlling disease symptoms in any patients and is associated with significant side effects, including dose-dependent exacerbation in pruritus.[2] The exacerbation of pruritus brings additional burden on the patient by worsening sleep and fatigue, requiring add-on medication, follow-up visits, and dosage monitoring. Severe pruritus, defined as intense or widespread itching, interfering with daily activities and requiring medical intervention, was reported in patients treated with OCA in the POISE trial, with a median time of onset of pruritus at 11 days after initiation of treatment.[2] In the POISE trial, TEAEs of pruritus were reported in 55.7% of patients in the OCA 5-10 mg treatment arm (n=39/70) compared to 38.4% of patients in the placebo arm (n=28/73) with 72% (n=138/193) of patients on OCA reporting pruritus as an adverse event (AE) in the long-term open-label extension phase of the study.[2] One patient in the OCA 5-10 mg treatment arm withdrew from the study due to pruritus, compared to zero patients in the placebo arm. Moreover, 34.3% of patients required additional intervention for pruritus management in the OCA 5-10 mg treatment arm (n=24/70) compared to 19.2% in the placebo arm (n=14/73).[2]

In terms of treatment-related symptoms, qualitative interviews with patients with PBC and pruritus (N=20) suggest that many patients attribute several symptoms affecting their HRQoL specifically to their PBC treatment. In patients receiving either UDCA (100%), OCA (30%), and/or other treatments targeting key symptoms (50%), several treatment-related symptoms were reported, including:[61]

- Gastrointestinal symptoms: diarrhoea, vomiting, constipation, nausea, abdominal bloating, flatulence, indigestion/heartburn, changes in appetite, cramps, urgency in bowel movements
- Temperature sensitivity
- Headache
- Hypertension
- Hair thinning / hair loss
- Urine frequency change

Due to the chronic, life-long nature of PBC, UK patients receiving UDCA treatment have been reported to incur on average £989 (95% CI; £722, £1,257) in health service costs annually due to medication and hospital visit costs, regardless of response status.[63] As 25-50% of patients do not adequately respond to UDCA[28,29], patients requiring second-line treatment may also incur similar treatment costs associated with OCA.[25,100]

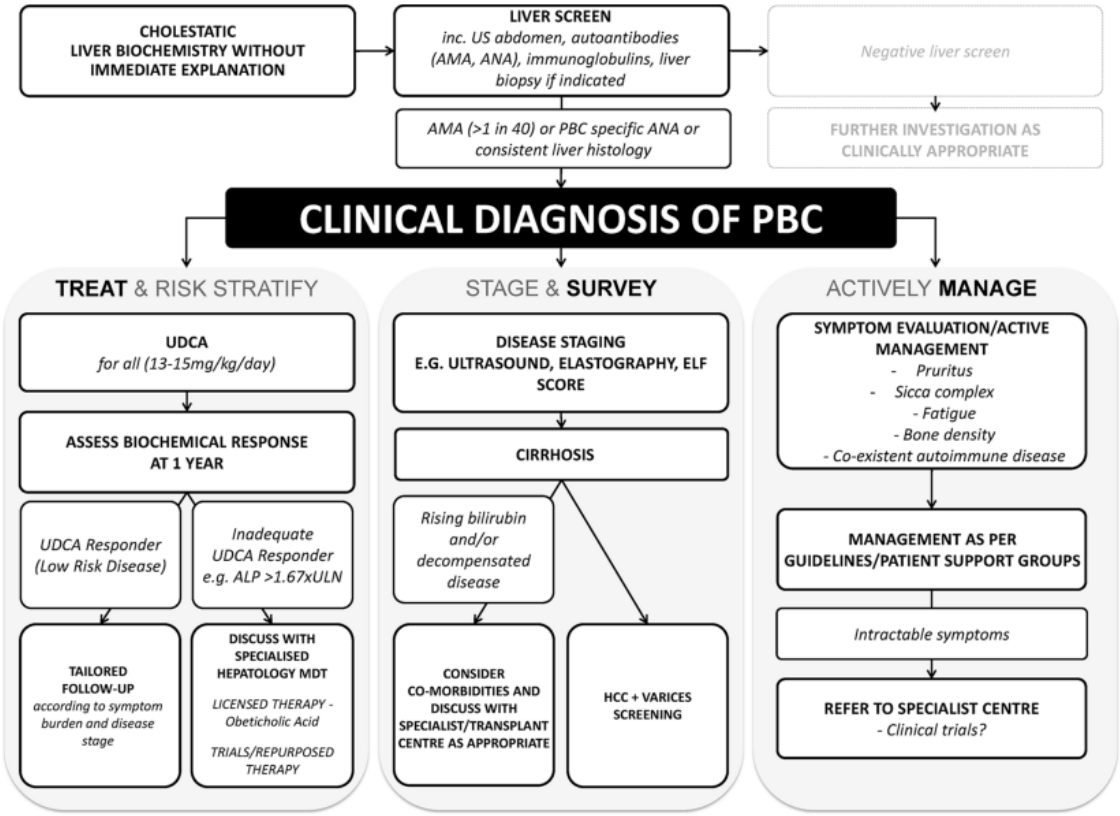
B.1.3.3 Current treatment pathway

Currently, care remains predominantly led by secondary and tertiary care physicians, who confirm diagnosis, initiate therapy and coordinate ongoing follow-up.[47] The impact for patients living with PBC reflects the risk of development of advanced cirrhotic and portal hypertensive liver disease as well as marked effects on quality-of-life (QoL) from associated symptoms.

NHS England commissions specialist services for PBC under its policy for liver transplantation services in adults and children.[101] Related technology appraisals include 'Obeticholic acid for treating primary biliary cholangitis' (2017) NICE technology appraisal guidance 443.[1] Related NICE guidelines include 'Cirrhosis in over 16s: assessment and management (2016) NICE guideline NG50'.[102]

Figure 12 shows the British Society of Gastroenterology/UK-PBC group primary biliary cholangitis treatment and management guidelines which are reflective of the EASL guidelines.[14,47] The BSG/UK-PBC guidelines state that while care always needs to be personalised to the patient, there are consensus pathways that are important for standardisation of care for PBC patients, which encompass the 'pillars' of care (as shown in the Figure 12 below) that are believed to provide optimal management of disease and its complications.

Figure 12: BSG/UK-PBC guidelines for PBC (2018)



Abbreviations: ALP – alkaline phosphatase; AMA – anti-mitochondrial antibody; ANA – antinuclear antibodies; BSG – British Society of Gastroenterology; ELF – enhanced liver fibrosis; HCC – hepatocellular carcinoma; PBC – primary biliary cholangitis; UDCA – ursodeoxycholic acid; US – ultrasound
Source: BSG/UK-PBC[47]

The frequency of follow-up appointments depends on patient's response to treatment and ongoing risk stratification, which is continually assessed throughout the disease course.[17] At minimum, the EASL 2017 guidelines suggest that patients undergo annual disease assessment, but once patients reach cirrhosis or show signs of decompensation blood tests may be required as frequently as once a month.[14,17] The British Society of Gastroenterology/UK-PBC primary biliary cholangitis treatment and management 2018 guidelines are the most accurate representation of detailed advice and recommendations on the best approaches of PBC management currently in the UK.[47]

In England, patients eligible for second-line therapy should be referred to a regional multi-disciplinary team (MDT), located in a specialist hepatobiliary centre ('specialist centre') that is networked to neighbouring, non-specialist hospitals. The specialist centre is responsible for the approval of second-line therapy and the prescription of OCA. In Wales and Northern Ireland, second-line therapy is decided by a national MDT. However there is an underlying issue of failure in recognition of the requirement of second-line therapy for patients based on a UK-wide audit (see Section B.1.3.4).[103]

Specialist centres generally have reported better performance than non-specialist centres, implying that familiarity with PBC is important for guidance adherence. However, no single centre has yet reached target performance across all domains of PBC care in the NHS (see section B.1.3.4, Figure 13) and specialist centres haven't managed the disease in a fully adequate manner.[103] Note that in the UK, the use of the BSG/British Association for the Study

of the Liver (BASL) Decompensated Cirrhosis Care Bundle improved standards of care in patients with decompensated cirrhosis within the first 24 hours of hospital admission.[103]

The decision to manage PBC in either primary or secondary care depends on the outcome of a risk stratification assessment, which determines disease severity based on biochemical indicators of liver function and fibrosis evidence, as well as response to UDCA.[17] Patients who respond to UDCA, with no evidence of cirrhosis and minimal symptom burden (low risk) can be managed by primary care professionals, whereas patients who are intolerant to or have an inadequate response to UDCA will have cirrhosis or complex symptom management by hospital specialists.[47]

UDCA is recommended for use in PBC by the EASL and BSG/UK-PBC guidelines for long-term efficacy.[14,47] The BSG/UK-PBC guidelines also recommend a dose of UDCA for all patients of 13-15 mg/kg/day, and this can be administered as a single dose or divided dose in case of tolerability issues.[47] NICE guidance on the management of PBC recommends UDCA as an effective first-line treatment, as it slows disease progression, however the effect on overall survival is uncertain.[104] The guidance also states that liver transplantation can be considered in patients with advanced PBC.[104]

Although UDCA has a well-characterised safety profile and is effective in reducing histological progression of disease, studies have shown that UDCA does not improve outcomes such as all-cause mortality, liver transplantation, or serious complications or comorbidities.[17, 49,105]

Stratification by biochemistry has now been reproduced widely across cohorts and is recommended for all patients after one year of UDCA therapy. This is in order to identify those high risk patients who are predicted to have reduced survival and are considered likely to benefit from new disease-modifying therapy trials. In addition to stratification by biochemistry, large-scale studies have been able to confirm clinical observations that age at presentation and gender also stratify risk. It is currently unclear as to which risk/response criteria are optimal for use in clinical practice.[47] In clinical practice, the expert group for the UK BSG/UK-PBC guidelines noted that criteria applied to recruitment into clinical trials were the ones seemingly used in widespread practice in the UK that is focused around an ALP >1.67 x ULN.[47]

Few recommended treatment options are currently available for patients with inadequate response to first-line therapy. For individuals who do not respond to or who are intolerant of UDCA, currently the only licensed second-line therapy for PBC; OCA is recommended for use by the EASL, AASLD and BSG/UK-PBC guidelines.[14,15,47] OCA is a semi-synthetic bile acid and selective farnesoid X receptor (FXR) agonist, that acts partly via suppression of NFκB. Through its activity at FXR, OCA targets bile acid production as well as anti-inflammatory and anti-fibrotic pathways.[31] In addition to limitations in its efficacy (see section B.1.3.1.3), OCA has a significant side effect burden, increasing both pruritus and fatigue in patients with PBC in the POISE trial.[2] Limited efficacy has been reported in patients treated with alternative second-line therapies compared to OCA, thus establishing it as a main comparator to elafibranor. In TA443 (2017), NICE recommended OCA, within its marketing authorisation, as an option for treating PBC in combination with UDCA for people whose disease has responded inadequately to UDCA or as monotherapy for people who cannot tolerate UDCA.[1]

Further guidelines specific to PBC are limited, and so understanding of the treatment pathway relies on existing EASL/BSG/UK-PBC guidelines and clinicians' opinions.

B.1.3.4 Unmet need for effective treatment in PBC

The limited PBC-specific treatments and lack of innovation in this disease area means patients are continuing to experience a significant disease burden. PBC is associated with various symptoms that impact QoL, including pruritus and fatigue, comorbidities such as other autoimmune diseases, and life-threatening liver-related complications due to disease progression such as cirrhosis and HCC; these conditions result in a significant treatment and care burden for PBC patients.

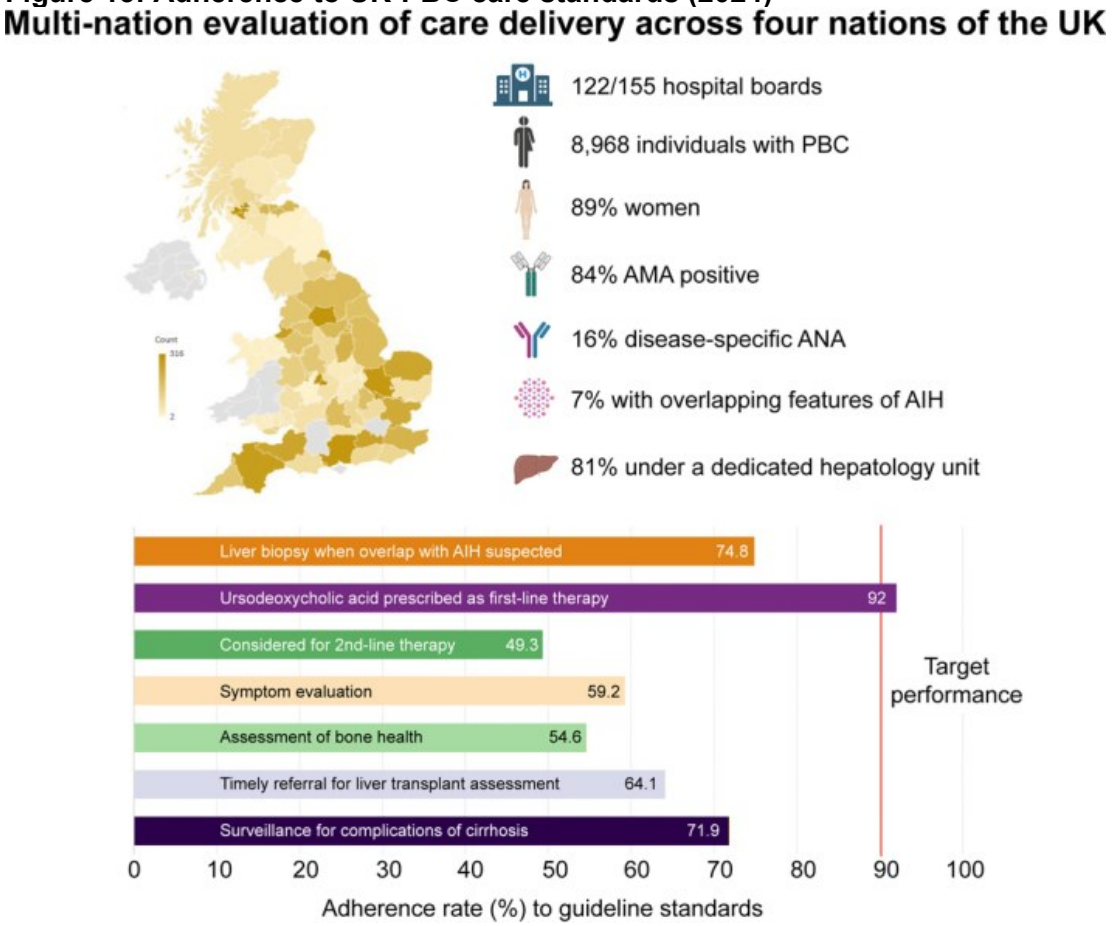
Current first-line treatment of PBC does not effectively halt progression of disease in many patients, including those who have the highest risk from PBC (see Section B.1.3.1), so patients with PBC continue to deteriorate and acquire more symptoms, leading to substantial morbidity and often eventually require liver transplant.[73,105,106] Prior to administration, a number of existing PBC treatments also require multiple screening tests, blood tests and follow-ups, adding to treatment costs and reducing clinical benefits. Additionally, the existing first-line treatment has side effects which significantly contribute to patients' clinical burden (see Section B.1.3.2.1 and 0). While liver transplant offers a treatment option for patients with advanced-stage disease, it is a burdensome procedure for patients and has long waiting times, during which patients may further deteriorate.[23] For this reason, there is a need for new treatments to effectively slow disease progression, avoid the need for liver transplant, and address the key symptoms of PBC.

Furthermore, currently available licensed treatments do not substantially improve pruritus, a common side effect associated with OCA treatment, in patients with PBC. Additionally, OCA does not improve fatigue, which, along with pruritus, have a profound impact on HRQoL.[2, 47,100] Fatigue, also associated with OCA, does not appear to be adequately addressed by liver transplantation, with over 40% of patients continuing to experience fatigue post-transplant. Therefore, there is a need for treatments for patients with an intolerance or inadequate response to UDCA which will improve the symptom burden of PBC while slowing disease progression, with a particular focus on pruritus and fatigue.

From a UK perspective there is a clear unmet need for novel treatments in the second-line setting in the UK. This is well illustrated from a recently published (2024) population-based evaluation of clinical care delivery, data was accrued from nearly 9,000 patients with PBC in the UK (Figure 13).[103] The scope and standards of the audit were adopted from the service standards listed in the 2018 BSG PBC guidelines, the 2016 NICE guidelines on cirrhosis management (NG50), and the 2015 BSG guidelines on varices in cirrhosis.[47, 102,107]

Except for using UDCA as first-line therapy, where adherence to the standard was 92%, adherence to guideline standards was poor in every assessed domain. Less than 50% and 65% of patients meeting the criteria for second-line treatment or liver transplant assessment, respectively, were appropriately referred. In England, Wales, and Northern Ireland, nearly three-quarters of these patients had not been referred to an MDT, suggesting that the underlying problem is a failure to recognise when second-line therapy is needed.[103] This potentially indicates to a degree that current treatment options for second-line therapy are either ineffective, difficult to implement or cannot be accessed. The authors proposed implementation of a dedicated PBC care bundle that aims to minimise heterogeneity in clinical practice and maximise adherence to key guideline standards.

Figure 13: Adherence to UK-PBC care standards (2024)



Abbreviations: AIH – autoimmune hepatitis; AMA – anti-mitochondrial antibody; ANA – antinuclear antibodies; PBC – primary biliary cholangitis; UDCA – ursodeoxycholic acid; UK – United Kingdom
Source : Abbas *et al.* 2024[103]

PBC patients experience a significant humanistic burden from diagnosis through to end-stage disease (see Section B.1.3.2.2). A PBC diagnosis often leads to emotional distress, including feelings of anger, fear, and depression. Current therapies do not sufficiently address the symptom burden associated with PBC which can significantly impact patients' HRQoL.

Management of PBC is also associated with substantial costs, which increase with disease progression and after the development of complications.[27] End-stage disease, in particular, is often associated with a need for inpatient care, which leads to significant healthcare resource use and cost burden.[99,108] Current PBC treatment options are ineffective at delaying progression. Therefore, this creates a considerable cost burden and demonstrates an unmet need for a novel treatment able to delay PBC progression to reduce these downstream costs and overall economic burden (see Section B.1.3.2.4).

Overall, current treatment options for PBC are associated with a considerable clinical burden, HRQoL burden and cost burden and there is an unmet need for a novel treatment option with greater efficacy, a more tolerable adverse event (AE) profile and a greater beneficial impact on PBC symptoms to reduce the economic burden treatment for PBC. Novel treatments, including elafibranor, could assist in bridging the gap in unmet need of current second-line treatment.

B.1.3.5 Proposed positioning of elafibranor in the PBC treatment pathway

Elafibranor has demonstrated substantial efficacy in a Phase II and pivotal Phase III trial of PBC patients with an inadequate response or intolerance to UDCA.[4,5] Based on the results of the Phase II trial, the potential that elafibranor has to help patients with PBC was recognised by the EMA and US Food and Drugs Administration (FDA) with Breakthrough Therapy and Orphan Drug Designations being granted in 2019.[109–111]

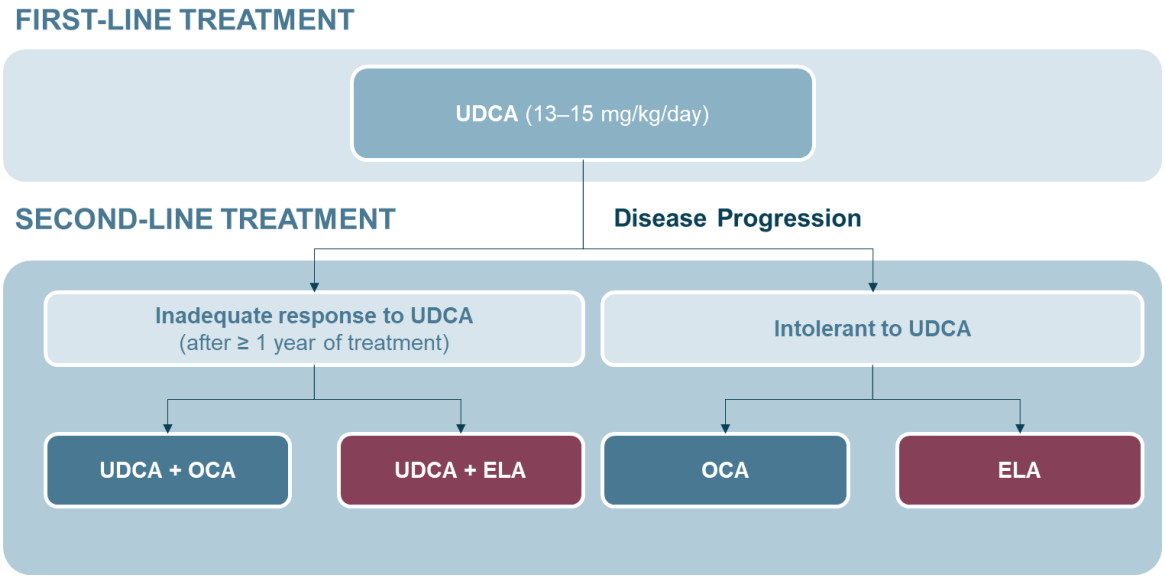
In the pivotal Phase III trial (ELATIVE) the primary endpoint, biochemical cholestasis response, was met with 50.9% of patients treated with elafibranor achieving it at Week 52, compared with 3.8% in the placebo group, resulting in a statistically significant improvement in cholestasis response (defined as ALP <1.67 x ULN, TB ≤ULN and ALP decrease from baseline of ≥15%; odds ratio [OR]: 37.6; 95% CI: 7.6; 302.2; p<0.0001).[4] Importantly, cholestasis response has been recognised as a relevant surrogate marker in PBC clinical studies (defined in Section B.1.3.1). Furthermore, treatment with elafibranor led to a statistically significant higher proportion of patients achieving the key secondary endpoint of ALP normalisation at Week 52 compared with placebo. The improvement in ALP with elafibranor treatment was rapid, occurring within four weeks, and was sustained over the study duration.[4]

A benefit of elafibranor over existing PBC treatments is its safe administration with statins as well as inhibitors of PTGR1.[11] Additionally, contrary to existing PBC therapies, the dose of elafibranor does not need to be adjusted for patients with renal impairment, which decreases the need for follow-up kidney function testing.[11] This could position elafibranor as a more convenient and cost saving treatment to patients.

In addition to the benefits that elafibranor demonstrates to clinical biomarkers, a positive trend in pruritus improvement from baseline through Week 52 on the PBC Worst Itch Numeric Rating Scale (WI-NRS) score for patients with moderate-to-severe pruritus at baseline (Pruritus intention-to-treat [ITT] Analysis Set) was seen in the elafibranor group compared to the placebo group and was further supported by a marked, statistically significant, improvement in pruritus according to the PBC-40 Itch and 5-D Itch measures.[4,112] Additionally, elafibranor was well tolerated in the ELATIVE trial, consistent with the wider clinical development programme in which approximately 2,500 patients have received elafibranor.[4,112] Most TEAEs were mild or moderate in severity and assessed to be unrelated to study treatment. Of note, patients treated with elafibranor experienced fewer TEAEs of pruritus and fatigue compared with placebo in the ELATIVE trial, and none were of severe intensity. Most of the patients enrolled in the trial (85.7%) continued the trial into the 5-year open-label LTE.[112]

The impact of elafibranor from the ELATIVE Phase III trial on clinical biomarker endpoints, pruritus and fatigue demonstrates that elafibranor potentially fulfils an unmet medical need as an efficacious and well tolerated treatment in individuals with PBC who have experienced an inadequate response or intolerance to UDCA.[4] In line with the eligibility criteria for the ELATIVE trial, it is anticipated that elafibranor will be indicated for the treatment of PBC as a second-line therapy for patients with PBC with an inadequate response or intolerant to UDCA (see Figure 14).

Figure 14: Proposed positioning of elafibranor in the PBC treatment sequence



Abbreviations: ELA – elafibranor; kg – kilograms; mg – milligrams; OCA – obeticholic acid; PBC – primary biliary cholangitis; UDCA – ursodeoxycholic acid
Source: Adapted from EASL 2017[14]

B.1.4 Equality considerations

PBC is much more common in women than men, with global estimates suggesting that 1 in 1,000 females aged over 40 years are living with PBC.[14,113] Lv *et al.* 2021 also found that the pooled overall prevalence and annual incidence rates of PBC in female individuals are six and five times that of male individuals, respectively.[41] As mentioned in Section B.1.3.1, there are more reported PBC cases in the UK in females (4.24 per 100,000 population) than in males (0.66 per 100,000 population).[15,18,38] The lower incidence in males compared to females may be explained by male patients often being diagnosed at advanced stages of disease, meaning early-stage PBC may be missed in males and therefore not factored into prevalence and incidence figures. X chromosome loss also occurs more frequently and preferentially in female patients with PBC, compared with age-matched healthy and liver disease control individuals, suggesting critical involvement of the X chromosome in PBC.[114] This may explain the significant female predominance in the PBC patient population, with recent epidemiological studies suggesting a 9:1 female to male ratio worldwide.[14,16] Additionally, the natural history of PBC suggests a potential role for oestrogen hormones in the clinical course of PBC, as clinical presentation typically occurs in the peri- and post-menopausal period in female patients.[113]

Though the majority of PBC patients present symptoms between the age of 40 to 60 years, cases have been reported in individuals as young as 15 years.[16,45] Individuals diagnosed with PBC under the age of 50 experience more severe and progressive disease and poor treatment response compared with patients over the age of 50 at diagnosis ($p<0.0001$),[20] with the majority of patients needing transplantation having disease onset at a younger age.[16,45]

Liver transplant is associated with significant wait times, as organ availability impacts the timing and indication for surgery; in the UK, average liver transplant waiting times are reported at 3-4 months.[75] The current liver transplant algorithm (Transplant Benefit Score) gives priority to those people with alcohol-induced liver damage and/or who are elderly, instead of younger

people who may be able to benefit from transplant for longer.[76,77] PBC is one of the most frequent indications for liver transplantation in Europe, with patients on the liver transplant waiting list more likely to die while waiting for a transplant due to deterioration of symptoms or serious liver complications, compared to patients with other liver disease, such as hepatitis C, alcoholic liver disease, and hepatitis B.[78–80] Additionally, referral for transplant assessment varies across England and Wales, with patients who live near a transplant centre more likely to be referred.[103] Having access to treatment options that avoid liver transplant therefore will help address some of these equality challenges.

Data on the association of smoking with PBC are conflicting; a 2021 retrospective study based in the UK (N=1,134) found that PBC was more frequent in smokers (3.4/100,000; 95% CI: 3.0, 3.8) than non-smokers (2.0/100,000; 95% CI: 1.8, 2.1; no p-value reported), while a 2014 population-based study in the Netherlands found no significant association for current or past smoking history.[38,39] It has been suggested that smoking may stimulate T-cell cytokine response seen in PBC, but the importance of smoking as a risk factor for PBC still remains unclear. Other environmental factors linked to PBC include the use of nail polish, hair dyes or reproductive hormone replacement, and exposure to toxic waste sites.[103]

Several of the risk factors described above are also related to prognosis for PBC patients. Firstly, men are at greater risk for more advanced disease at diagnosis and poor treatment response compared with female patients.[14, 17, 38,116] Young age at diagnosis is also associated with PBC severity and prognosis.[20]

B.2 Clinical effectiveness

Summary:

- ELATIVE is a 12-month, randomised, double-blind, Phase III trial evaluating the efficacy and safety of elafibranor in patients with PBC. The key inclusion criteria were adult patients with ALP ≤1.67 x ULN and TB ≤2 x ULN (41 µmol per litre).
- The trial included two treatment arms: elafibranor 80 mg once daily (N=108) and placebo once daily (N=53). Patients in both treatment arms were allowed to continue ursodeoxycholic acid (UDCA) treatment concomitantly.
- The primary endpoint of the trial was cholestasis response defined as: ALP ≤1.67 x ULN, TB ≤ULN, and ALP decrease ≥15% at 52 weeks.
  - Of the 161 patients who were randomised, 55 (50.9%) and 2 (3.8%) achieved cholestasis response for the elafibranor and placebo arms, respectively (p<0.0001).
- Key secondary endpoints included normalisation of ALP at Week 52 and a change in pruritus intensity from baseline through Week 52 and through Week 24, assessed with the use of the Worst Itch Numeric Rating Scale (WI-NRS) in the Pruritus ITT population (patients with moderate-to-severe pruritus at baseline defined as a WI-NRS score of ≥4).
  - Normalisation of ALP occurred in 14.8% of patients in the elafibranor arm and 0.0% in the placebo arm (p=0.002) by Week 52.
  - The least squares mean change in the WI-NRS score demonstrated as positive trend in improvement in pruritus but did not differ significantly between the elafibranor and placebo groups of the Pruritus ITT population at Week 52.

Additional endpoints for pruritus assessment included the PBC-40 Itch domain and 5-D itch scale.

Due to a lack of head-to-head trial data comparing elafibranor and OCA, the key comparator of elafibranor, a systematic literature review (SLR) was performed to identify relevant clinical evidence for elafibranor and obeticholic acid for use in an indirect treatment comparison (ITC).

- The NMA led to better results for the cholestasis response and ALP normalisation outcomes for elafibranor compared to the licensed dose of OCA (5-10 mg, i.e. 5 mg once daily for 6 months followed by an increase to 10 mg once daily in patients who have not achieved an adequate reduction in ALP and/or TB and who are tolerating OCA).
  - Patients treated with elafibranor 80 mg showed greater odds of achieving cholestasis response at Week 52 when compared to OCA 5-10 mg (median OR [95% credible interval (CrI)]: [redacted]).
  - Additionally, patients treated with elafibranor 80 mg exhibited greater odds of achieving ALP normalisation at Week 52 when compared to OCA 5-10 mg (median OR [95% CrI]: [redacted]).
- Pruritus is a focal point for HRQoL for patients with PBC due to its severe and life impacting burden to patients. It is known that OCA can exacerbate pruritus symptoms. The results of the NMA demonstrated favourable outcomes for elafibranor compared with OCA when assessing pruritus outcomes in the trials.
  - Patients in the ITT populations treated with elafibranor 80 mg exhibited a greater reduction in pruritus from baseline compared to OCA 5-10 mg, as measured by the PBC-40 scale and 5-D Itch scale at Week 52 (median difference in mean change from baseline [95% CrI]: -1.87 [redacted] and [redacted], respectively).

Abbreviations: µmol – micromole; ALP – alkaline phosphatase; CrI – credible interval; ITT – intention-to-treat; mg – milligram; NMA – network meta-analysis; OCA – obeticholic acid; OR – odds ratio; PBC – primary biliary cholangitis; TB – total bilirubin; UDCA – ursodeoxycholic acid; ULN – upper limit of normal; WI-NRS – Worst Itch Numeric Rating Scale

B.2.1 Identification and selection of relevant studies

An SLR was conducted up to 05 December 2023 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.

Please see **Appendix D** for more information regarding the identification and selection of relevant studies.

B.2.2 List of relevant clinical effectiveness evidence

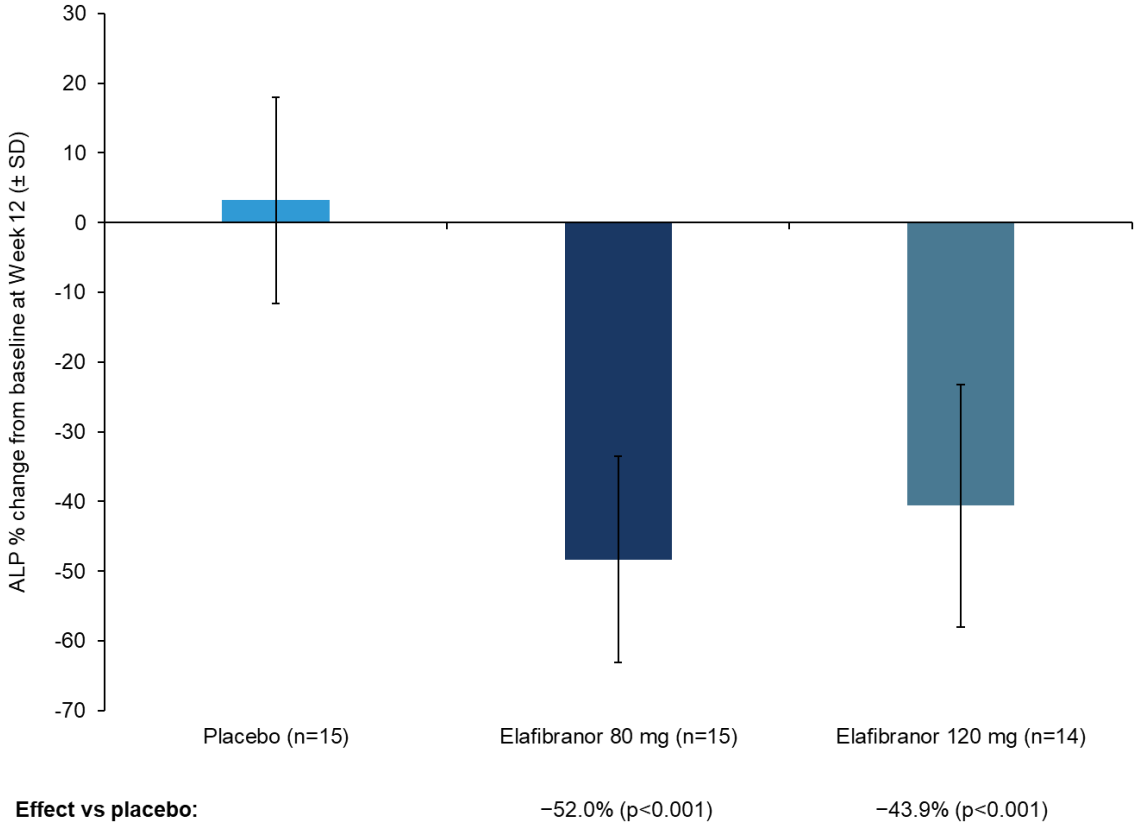
B.2.2.1 Elafibranor studies

The SLR identified two randomised controlled trials (RCTs) for elafibranor: a phase III trial, ELATIVE and a phase II trial, Schattenberg *et al.* (2021).[4,5] Schattenberg *et al.* (2021) was a 12-week, double-blind, randomised, placebo-controlled Phase II study of elafibranor and was conducted in 45 patients with non-cirrhotic PBC with an incomplete response to UDCA across Europe and the USA. Patients were randomised 1:1:1 to receive placebo, 80 mg elafibranor, or 120 mg elafibranor once daily for 12 weeks.[5] The primary endpoint was the relative change in serum ALP levels from baseline at week 12. Secondary endpoints included two main composite response definitions:

- ALP ≤1.67xULN and TB <ULN and ALP reduction >15%, and
- ALP <1.5xULN and TB <ULN and ALP reduction >40%.[5]

The trial met its primary endpoint; at 12 weeks, serum ALP was significantly reduced in patients treated with elafibranor (80 mg or 120 mg) compared with placebo (both p<0.001).[5] The results suggested that 80 mg elafibranor is equipotent to 120 mg elafibranor, and both doses had a tolerable safety profile.[5] The composite endpoint of ALP <1.67 x ULN, TB<ULN, and decrease of ALP >15% was achieved in 66.7% of patients receiving 80 mg elafibranor and 78.6% of patients receiving 120 mg elafibranor, compared with 6.7% of patients receiving placebo (p<0.001, Figure 15).[5] While the data reported by Schattenberg *et al.* (2021) is generalisable to PBC patients, and the licensed population of elafibranor, the low number of participants (15 in each treatment arm), the short time frame of the trial (12 weeks vs. 52 weeks for ELATIVE), and the limited additional insights it provides when compared to ELATIVE meant that further consideration as submission evidence was not considered appropriate.

Figure 15: ALP change from baseline at Week 12 (Phase II results)



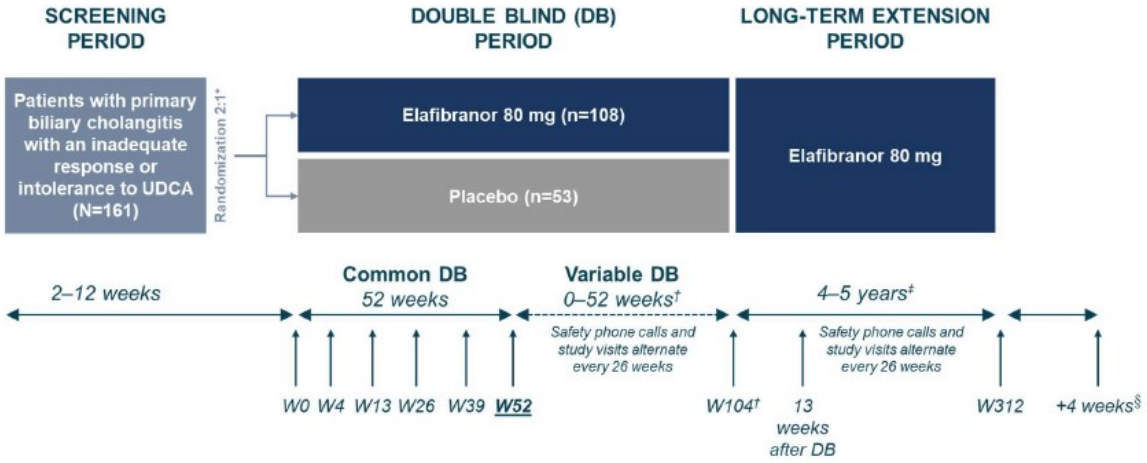
Effect vs placebo:		−52.0% (p<0.001)	−43.9% (p<0.001)

Abbreviations: ALP: alkaline phosphatase; SD: standard deviation.
Sources: Schattenberg 2021[5]

ELATIVE

ELATIVE was a Phase III, multinational, double-blind, placebo-controlled RCT. It assessed adult patients with PBC who have had an inadequate response to or were unable to tolerate UDCA. The objective of the trial was to investigate the efficacy and safety of elafibranor in patients with PBC over a 52-week time period. There were 161 patients randomised in a 2:1 ratio to elafibranor 80 mg (N=108) or placebo (N=53). The primary endpoint was cholestasis response defined as ALP ≤1.67xULN, TB ≤ULN, and ALP reduction ≥15% at Week 52. Key secondary endpoints were normalisation of ALP levels at Week 52 and change in pruritus intensity from baseline at Week 52 and 24 as measured using the Worst Itch Numeric Rating Scale (WI-NRS) in the Pruritus ITT population.[4] At the end of the double-blind period, patients could enter an open-label extension period and receive elafibranor for up to 5 additional years. An overview of the trial design is shown below (Figure 16).

Figure 16: Overview of ELATIVE trial design



*Patients receiving ursodeoxycholic acid at randomisation were encouraged to continue treatment throughout trial participation.
†Patients continued to receive double-blind treatment beyond Week 52 in a variable treatment period until all patients had completed their Week 52 assessment, or until a maximum treatment duration of 104 weeks, whichever came first, to further collect safety and clinical outcomes data in a double-blind manner.
‡Patients could optionally enter an open-label extension where they would receive elafibranor 80 mg for up to five years.
§Safety follow-up 4 weeks after the last dose of the study drug.
Source : Kowdley *et al.* 2023 Appendix[4]

The trial demonstrated that patients treated with elafibranor had a greater rate of response versus patients treated with placebo (50.9% versus 3.8%, respectively), with a difference of 47.2% favouring elafibranor (95% CI: [32.0%, 57.0%]; p<0.0001). The results also showed that ALP was normalised in 14.8% of the patients in the elafibranor group compared to none of the patients in the placebo group at Week 52, with a percentage difference of 14.8% (95% CI: [9.3%, 22.7%]; p = 0.0019).

Least squares (LS) mean change through Week 52 in PBC WI-NRS score was -1.9 in the elafibranor group and -1.1 in the placebo group, demonstrating a trend towards greater reduction in pruritus with elafibranor treatment compared with placebo. The LS means difference between elafibranor and placebo (Pruritus ITT Analysis Set) at Week 52 was -0.8 (95% CI: -2.0; 0.4; p=0.1970).[4,112]

Reductions from baseline in both ALP and TB levels were sustained throughout the 52-week trial period. At Week 4, the mean percent change from baseline in ALP was -36.5% in the elafibranor group, which further decreased to -38.9% by Week 52. In contrast, the mean percentage change in the placebo group was 0.2% (standard deviation [SD]: ±18.2%) and 1.7% (SD: ±18.5%) at Weeks 4 and 52, respectively. When considering TB, results for elafibranor were similar with a sustained decrease from baseline throughout the 52-week trial period. At Week 4, the mean change from baseline in TB was -0.9 µmol/L in the elafibranor group. By Week 13 it had stabilised at -0.6 µmol/L and was maintained to -0.7 µmol/L by Week 52. In contrast, the mean change in the placebo group was -0.3 µmol/L and 0.9 µmol/L at Weeks 4 and 52, respectively.

As the pivotal trial for elafibranor, ELATIVE is the trial of interest when assessing the efficacy and safety of elafibranor.

Table 4: Clinical effectiveness evidence: ELATIVE

Study	ELATIVE				
Study design	Phase III, multinational, multi-centre, randomised, double-blind, placebo-controlled.				
Population	Adult patients with PBC who had an inadequate response to or were unable to tolerate ursodeoxycholic acid.				
Intervention(s)	Elafibranor 80 mg				
Comparator(s)	Placebo				
Indicate if trial supports application for marketing authorisation	Yes	x	**Indicate if trial used in the economic model**	Yes	x
	No			No	
Rationale for use/non-use in the model	ELATIVE is the pivotal Phase III study assessing the efficacy and safety of elafibranor compared to placebo in adult patients with PBC who have had an inadequate response to or who are intolerant to UDCA. This aligns with the intended licensing population for elafibranor of second-line PBC patients.				
Reported outcomes specified in the decision problem	The outcome measures to be considered include: • mortality • liver function based on markers of liver biochemistry • symptoms including pruritus, fatigue and abdominal pain • adverse effects of treatment • HRQoL.				
All other reported outcomes	• N/A				

Abbreviations: HRQoL – health-related quality-of-life; mg – milligram; PBC – primary biliary cholangitis; UDCA – ursodeoxycholic acid

Table 5: Publications reporting data from the elafibranor clinical study

Study	Title	Citation	Presented in submission
ELATIVE	Efficacy and Safety of Elafibranor in Primary Biliary Cholangitis	Kowdley *et al.* 2023[4]	Yes

B.2.2.2 Comparator studies

A clinical SLR was conducted to identify all relevant efficacy and safety data for elafibranor and other therapies as treatment for patients with PBC. For details of the SLR, see Appendix D. Following the review process, one relevant RCT called POISE, for the comparator of OCA in the final scope was included for evidence synthesis with ELATIVE.

POISE was a 12-month international, multi-centre, Phase III, randomised, double-blind, placebo-controlled trial to assess efficacy and safety of OCA in patients with PBC.[2] It assessed adult patients with PBC who had inadequate response to, or were unable to tolerate, UDCA. There were 216 patients that underwent randomisation to three treatment arms: placebo (N=73), OCA 5-10 mg (the licensed dose) (N=70) and OCA 10 mg (unlicensed in the UK) (N=73).[2] The primary endpoint was cholestasis response defined as ALP <1.67xULN and TB ≤ULN and ALP reduction ≥15%, which was the same as the ELATIVE trial.[2,4] Secondary endpoints focused on the levels of liver biochemistry markers associated with PBC such as alanine aminotransferase (ALT), aspartate aminotransferase (AST) and gamma-glutamyl transferase (GGT).[2] The trial concluded that OCA treatment for patients with PBC was effective. Results showed a higher response rate in the OCA 5-10 mg (the licensed dose) and

OCA 10 mg arm than placebo at 12 months (46%, 47% and 10%, respectively, p < 0.001) and, for the secondary endpoints, levels of GGT, ALT, AST and conjugated bilirubin all decreased from baseline at month 12 for each OCA arm with significant differences from placebo observed for each.[2] It was also noted, however, that more serious AEs were observed in patients treated with OCA than placebo, specifically increases in pruritus. [2]

B.2.3 Summary of methodology of the relevant clinical effectiveness evidence

B.2.3.1 Study methodology

The ELATIVE clinical trial was a Phase III, randomised, double-blind, placebo-controlled, multi-centre study, investigating the efficacy and safety of elafibranor compared with placebo in patients with PBC and an inadequate response or intolerance to UDCA.

Detailed information regarding study design of ELATIVE is presented below in Table 6. For more detailed inclusion and exclusion criteria, please refer to Appendix D.

Table 6: ELATIVE Study Design

Trial number (acronym)	ELATIVE, NCT04526665, Kowdley *et al.* 2023[4,112]
Trial design and duration	• Multinational, randomised, Phase III, double-blind, placebo-controlled. • 52-week trial consisting of 6 visits at weeks 0, 4, 13, 26, 39 and 52.

Participants (Summary of main inclusion criteria)	• Informed consent
	• Males or females age of 18 to 75 years inclusive
	• PBC diagnosis as demonstrated by at least 2 of 3 diagnostic factors:
	  o ALP elevated for ≥6 months prior to randomisation
	  o Positive AMA titre or presence of PBC-specific ANA
	  o Liver biopsy consistent with PBC
	• UDCA for at least 12 months prior and at stable dose for ≥3 months, or unable to tolerate UDCA treatment.
	• ALP ≥1.67 x ULN (ULN = 104 U/L for females, 129 U/L for males).
	• TB ≤2 x ULN.
	• Females must be of non-childbearing potential or must be using highly effective contraception for the full duration of the study and for 1 month after the last drug intake.

Participants (Summary of main exclusion criteria)	• History or presence of other concomitant liver disease, including: HAV, HBV, HCV, AIH, PSC, ALD, NASH, Gilbert's syndrome or alpha-1-antitrypsin deficiency
	• History of:
	  o Liver transplant, or current placement on liver transplant list
	  o MELD-Na score ≥12
	  o Signs and symptoms of cirrhosis/portal hypertension
	  o Hepatorenal syndrome
	• Markers of liver damage, such as:
	  o ALT and/or AST >5 x ULN
	  o Platelet count <150 x 10^3/μL
	  o Albumin <3.0 g/dL
	  o Known pregnancy or lactating (female patients)
	  o Severely advanced patients according to Rotterdam criteria (TB >ULN and albumin <LLN)

	• Prohibited medications:
	  ○ Fibrates and glitazones (2 months prior to screening)
	  ○ OCA, azathioprine, colchicine, cyclosporine, methotrexate, mycophenolate mofetil, pentoxifylline, budesonide and other systemic corticosteroids (3 months prior to screening)
	  ○ Immunotherapy directed against interleukins or other cytokines or chemokines (12 months prior to screening)

Settings and location where data were collected	Multinational trial including the following study centre locations: United States of America, Argentina, Belgium, Brazil, Canada, Chile, France, Germany, Italy, South Africa, Spain, Switzerland, Turkey, and the United Kingdom.
Trial drugs (the interventions for each group with sufficient details to allow replication, including how and when they were administered) **Intervention(s) (n=[x]) and comparator(s) (n=[x])** **Permitted and disallowed concomitant medication**	• Elafibranor 80mg (N=108): Study subjects will take 1 tablet per day orally before breakfast with a glass of water each morning. • Placebo (N=53): Study subjects will take 1 tablet per day orally before breakfast with a glass of water each morning. • Concomitant UDCA use was permitted in the trial with patients allowed to continue their current UDCA usage at the time of trial commencement given they had been on a stable dose for ≥3 months prior to commencement. • Other medications that were not permitted are detailed in the exclusion criteria.
Primary outcomes (including scoring methods and timings of assessments)	Cholestasis response (defined as an ALP level of ≤1.67 times the ULN range, with a reduction of ≥15% from baseline, and normal TB levels) at Week 52.
Other outcomes used in the economic model/specified in the scope	Outcomes that were included within the model include the following: • Change from baseline in ALP at 52 weeks. • Change from baseline in TB at 52 weeks. • Change from baseline in liver stiffness at 52 weeks. • Change from baseline in pruritus using the PBC-40 Itch domain at 52 weeks. • Occurrence of pruritus TEAE. • TEAEs related to study treatment. • All-cause discontinuation.
Pre-planned subgroups	• Exploratory analyses of the primary endpoint and the three key secondary endpoints was performed for the following subgroups: • Age at randomisation. • 3 x ULN (Yes/No). • Sex (Female, Male). • Race (White, Others defined by American Indian or Alaska Native, Asian, Black or African American, Native Hawaiian or Other Pacific Islander or Others). • UDCA treatment at baseline (Yes/No). • Prior OCA treatment (Yes/No). • ALP level at baseline >3 x ULN (Yes/No). • TB at baseline >ULN (Yes/No). • TB at baseline >ULN or albumin (ALB) at baseline <LLN (Yes/No). • TB at baseline >0.6 x ULN (Yes/No).

	• Geographic region: Europe, North America, Latin America, Other (including Turkey and South Africa). • ALP >3 x ULN or TB >ULN at baseline (Yes/No). In case of mis-stratification during the randomisation, the true screening value was used. • PBC WI-NRS score ≥4 at baseline (averaged over the 14 days preceding randomisation) (Yes/No). In case of mis-stratification during the randomisation, the true screening value was used. • Cirrhotic defined by liver stiffness at baseline ≥16.9 kPa by TE (Yes/No) and/or cirrhosis on histology. • Advanced disease stage defined as liver stiffness at baseline >10 kPa by TE and/or bridging fibrosis or cirrhosis on histology.

Abbreviations: AIH – autoimmune hepatitis; ALB – albumin; AMA – anti-mitochondrial antibody; ANA – antinuclear antibodies; ALD – adrenoleukodystrophy; ALB – albumin; ALP – alkaline phosphatase; AST – aspartate aminotransferase; ALT – alanine aminotransferase; HAV – hepatitis A virus; HBV – hepatitis B virus; HCV – hepatitis C virus; kPa – kilo Pascal; LLN – lower limit of normal; NASH – non-alcoholic steatohepatitis; OCA – obeticholic acid; PBC – primary biliary cholangitis; PSC – primary sclerosing cholangitis; TB – total bilirubin; TE – transient elastography; TEAE – treatment-emergent adverse event; U/L – units per litre; UDCA – ursodeoxycholic acid; ULN – upper limit of normal; WI-NRS – Worst Itch Numeric Rating Scale.
Source : Kowdley *et al.* (2023)[4]; Ipsen Data on File 2023 (ELATIVE Clinical Study Report).[112]

B.2.3.2 Baseline characteristics

Key demographic and baseline characteristics of the ELATIVE trial population are summarised in Table 7. Treatment arms were well balanced for each key demographic and baseline variable. Across the entire trial population, the mean (SD) age was 57.1 (±8.7) with 95.7% being female and 91.3% being white. Most of the population was below 65 (78.3%) with an average time since diagnosis of 8.0 (±6.2) years. The majority (95.0%) of patients were taking UDCA at baseline.

Generally, disease characteristics were well balanced across treatment arms. Mean ALP values at baseline were well balanced with both arms reporting values of approximately 320 U/L. Additionally, across both treatment arms, 37.7%-39.8% of patients were reported to have >3 x ULN for baseline ALP and TB of 9.41-9.71 µmol/L, indicating similar disease severity in both the elafibranor and placebo arm.

Table 7: Baseline characteristics of patients in the ELATIVE trial

Baseline characteristic	Elafibranor 80 mg (N=108)	Placebo + UDCA (N=53)
Age and duration of disease		
Time since diagnosis, years	7.9 ± 5.9	8.3 ± 6.8
Age, years	57.5 ± 8.4	56.4 ± 9.3
Sex – n (%)		
Male – n (%)	6 (5.6)	1 (1.9)
Female – n (%)	102 (94.4)	52 (98.1)
Race – n (%)		
White	101 (93.5)	46 (86.8)
Black or African American	2 (1.9)	0 (0.0)
Asian	1 (0.9)	3 (5.7)
American Indian or Alaska Native	0 (0.0)	1 (1.9)
Other	3 (2.8)	2 (3.8)
Not reported	1 (0.9)	1 (1.9)

ALP		
Mean (U/L)	321.3 ± 121.9	323.1 ± 198.6
> 1.67 x ULN – n (%)	105 (97.2)	50 (94.3)
> 3 x ULN – n (%) ‡	43 (39.8)	20 (37.7)
Liver laboratory parameters		
TB (µmol/L) §	9.71 ±5.1	9.41 ± 5.0
AST (U/L)	45.0 ±24.2	47.2 ± 32.8
ALT (U/L)	49.3 ±29.4	50.3 ± 38.7
GGT (U/L)	213.3 ±186.1	220.0 ± 220.3
UDCA usage		
Concomitant ursodeoxycholic acid – n (%)	102 (94.4)	51 (96.2)
WI-NRS score¶		
Mean	3.3 ± 2.8	3.2 ± 2.9
≥4 – n (%) ‖	44 (40.7)	22 (41.5)
Liver stiffness		
Mean (kPa)	9.9 ± 7.8	10.7 ± 8.9
>10.0 kPa – n (%)	32 (30.8)	18 (36.0)
Bridging fibrosis or cirrhosis – n/total n (%) ††	12/31 (38.7)	8/16 (50.0)
Liver stiffness >10.0 kPa or bridging fibrosis (or both) or cirrhosis – n/total n**††	35/104 (33.7)	19/50 (38.0)

Abbreviations: µmol/L – micromole per litre; ALP – alkaline phosphatase; ALT – alanine aminotransferase; AST – aspartate aminotransferase; GGT – gamma-glutamyl transferase; kPa – kilo Pascal; mg – milligram; SD – standard deviation; TB – total bilirubin; U/L – units per litre; ULN – upper limit of normal; WI-NRS – Worst Itch Numeric Rating Scale

* Plus–minus values are means ±SD.

‡ The upper limit of the normal range (ULN) for the ALP level is 104 U per litre for women and 129 U per litre for men.

§ The ULN for the TB level is 20.5 μmol per litre for men and women.

¶ Shown are the mean baseline scores for intensity of itch (scores range from 0 [no itch] to 10 [worst itch imaginable]) as assessed on the Worst Itch Numeric Rating Scale (WI-NRS) reported over the 14 days preceding randomisation.

‖ Moderate-to-severe pruritus was defined as a score of ≥4 on the WI-NRS.

†† The presence or absence of bridging fibrosis or cirrhosis was determined by histologic findings in the patients who underwent a liver biopsy.

** Liver stiffness was assessed by means of vibration-controlled transient elastography; scores range from 2 to 75 kPa, with higher values indicating greater liver stiffness.

Source : Kowdley *et al.* (2023)[4]; Ipsen Data on File 2023 (ELATIVE Clinical Study Report).[112]

B.2.3.3 Participant flow in the relevant RCTs

B.2.3.3.1 Patient disposition

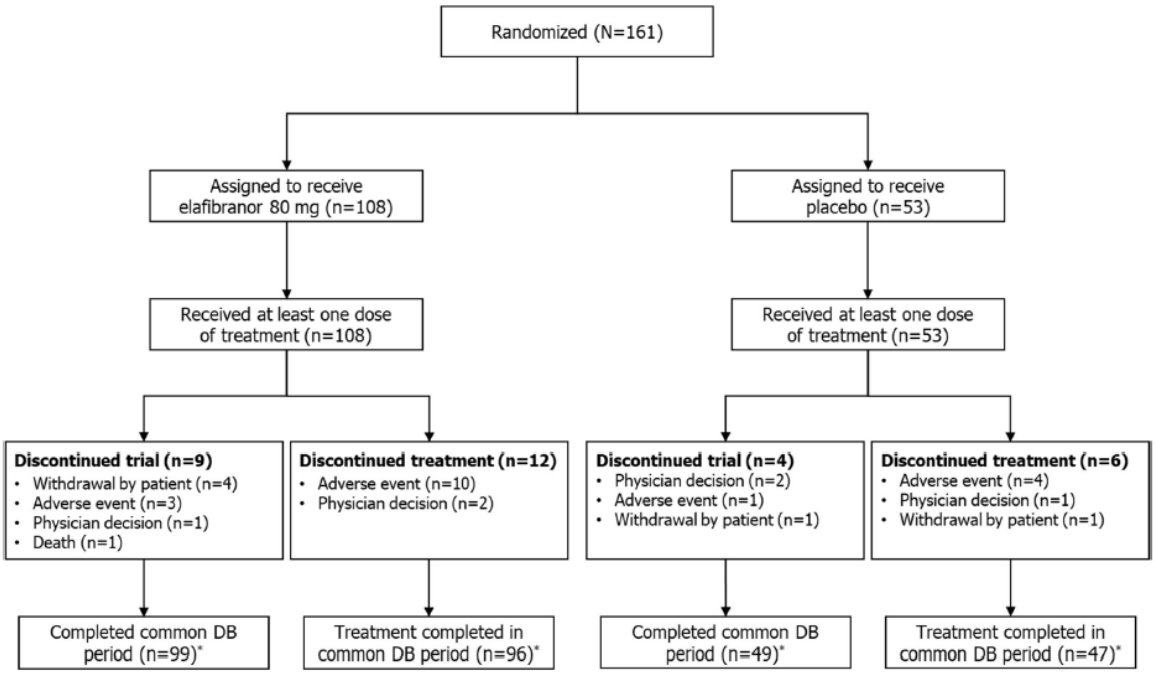
The common double-blind (DB) treatment period was defined as the first 52 weeks of the ELATIVE trial; the overall DB period included a treatment period of variable length beyond Week 52, during which patients continued to receive elafibranor or placebo until all patients completed their Week 52 visit (Visit 6) or until a maximum blinded treatment duration of 104 weeks (Visit 8), whichever came first. The data cut-off was after the last patient completed their end of study visit in the DB period on 01 June 2023.[112]

Overall, 244 patients were screened and 161 were randomised to elafibranor (N=108) or placebo (N=53) treatment. In total, 143 (88.8%) patients completed study treatment in the Company evidence submission for elafibranor for treating primary biliary cholangitis [ID6331]

common DB period (up to Week 52), 96 (88.9%) in the elafibranor group and 47 (88.7%) in the placebo group. Of these, 138 (87.5%) patients completed the overall DB period (up to Week 104); 93 (86.1%) in the elafibranor group and 45 (84.9%) in the placebo group.

Discontinuation of treatment rates were similar for both groups, at 11.1% (n=12) for the elafibranor group and 11.3% (n=6) for the placebo group. Reasons for patient discontinuation during the overall DB period across all patients in the ITT set were AEs (n=14 [8.7%]), physician decision (n=3 [1.9%]) and withdrawal by patient (n=1 [0.6%]).[4] A CONSORT flow diagram for ELATIVE is presented in Figure 17.

Figure 17: CONSORT diagram for ELATIVE trial



*The common DB period is defined as the time between study visit 1 (first study drug dispensation) and the visit 6/week 52 visit
Source: Kowdley *et al.* (2023)[4]

B.2.3.3.2 Analysis sets

The different analysis sets used in the ELATIVE trial are described below.

ITT Analysis Set: All randomised participants.

Pruritus ITT Analysis Set: All participants from the ITT Analysis Set with baseline PBC Worst Itch NRS score ≥4.

Per Protocol (PP) Analysis Set: All participants from the ITT Analysis Set without any major protocol deviation or event affecting the primary efficacy endpoint.

Pruritus PP Analysis Set: All participants from the Pruritus ITT Analysis Set without any major protocol deviation or event affecting the primary efficacy endpoint and/or the second and third key secondary endpoints.

Safety Analysis Set (SAS): All participants who were administered at least one dose of DB study drug irrespective of the treatment received. Participants were analysed according to the treatment received. Participants who received any amount of active treatment, even by mistake and for one intake, were assigned to the active treatment group.

Pharmacokinetics Analysis Set (PKS): All participants who were administered at least one dose of elafibranor and have at least one post dose PK sample. Participants of the PKS must have data for time of dosing, time of sampling and amount of product administered. Whereas all participants are sampled in order to maintain the blind, the PKS only included participants under elafibranor.

Exploratory (Histological) Analysis Set: All participants from the ITT Analysis Set who consented to have liver biopsy samples collected at baseline and/or Week 52. Participants were analysed according to randomised treatment.

The distribution of patients across the analysis sets is presented in Table 8.

Table 8: Analysis populations

Analysis set	Number of subjects, N (%)		
	Elafibranor 80 mg	Placebo	Total
Enrolled/randomised	108 (100.0)	53 (100.0)	161 (100.0)
ITT	108 (100.0)	53 (100.0)	161 (100.0)
Pruritus ITT	44 (40.7)	22 (41.5)	66 (41.0)
Safety	108 (100.0)	53 (100.0)	161 (100.0)
PP	91 (84.3)	44 (83.0)	135 (83.9)
Pruritus PP	40 (37.0)	18 (34.0)	58 (36.0)
Pharmacokinetics	105 (97.2)	0 (0.0)	105 (65.2)
Histological	39 (36.1)	18 (33.9)	57 (35.4)

Abbreviations: ITT – intention-to-treat; PP – per protocol.
Source: Ipsen Data on File 2023 (ELATIVE Clinical Study Report).[112]

B.2.4 Statistical analysis and definition of study groups in the relevant clinical effectiveness evidence

For a summary of statistical analyses please see Table 9.

Table 9: Summary of statistical analyses

Trial number (acronym)	Hypothesis objective	Statistical analysis	Sample size, power calculation	Data management, patient withdrawals
NCT04526665 (ELATIVE)	The null hypothesis for response to treatment based on the primary endpoint is that there is no difference in response rates between the elafibranor and the placebo groups. The alternative hypothesis is that there is a difference in response rates	The response rates at Week 52 were compared between the treatment groups using the exact Cochran-Mantel-Haenszel (CMH) test stratified by the randomisation strata. The estimate of the OR and the corresponding 95% exact CI and exact p-value were provided.	A sample size of 150 patients was required to achieve at least 90% power to detect a statistically significant difference of 35% in response rates between the elafibranor and placebo groups at Week 52, using a two-sided alpha of 0.05 and an exact Fisher test.	Discontinued participants who received the study drug were not replaced.

	between both groups.			

Abbreviations: CI – confidence interval; CMH – Cochran-Mantel-Haenszel; OR – odds ratio

B.2.4.1 Determination of sample size

Sample size was estimated assuming an expected response rate in the placebo group slightly higher than that in the POISE trial for OCA (10%) and an expected response rate in the elafibranor group similar or better compared to OCA in the POISE trial (47%).[2,112]

Overall, a sample size of 150 patients was required to achieve at least 90% power to detect a statistically significant difference of 35% in response rates between the elafibranor and placebo groups at Week 52, using a two-sided alpha of 0.05 and an exact Fisher test.[112]

Assuming 1/50 patients in the placebo group reached the key secondary endpoint (ALP normalisation at Week 52), a 150 sample size provided at least 80% power to detect a statistically significant between-group difference of 20.0% in this endpoint at a two-sided 0.05 alpha level.[112]

Assuming a pooled SD of 2.3 points, 60 participants (40 elafibranor and 20 placebo) with baseline PBC Worst Itch NRS score ≥4 provided approximately 80% power to detect a statistically significant between-group difference of 1.8 points in mean change from baseline in PBC Worst Itch NRS score (second key secondary endpoint) at a two-sided 0.05 alpha level. It is assumed that the same assumptions would apply to the two key secondary endpoints for pruritus (through Week 52 and through Week 24).[112]

B.2.4.2 Main analyses

The main analysis was conducted using the ITT Analysis Set and was repeated on the PP Analysis Set. The primary estimand was defined as the OR between treatment groups, from all randomised participants, achieving response at Week 52, and not stopping the study treatment prematurely nor using rescue therapy for PBC.

In case of missing data at Week 52 (visit 6) for participants without intercurrent event, the closest non-missing assessment from the DB treatment period before or after the theoretical visit 6 date was considered.

The null hypothesis for response to treatment based on the primary endpoint is that there is no difference in response rates between the elafibranor and the placebo groups. The alternative hypothesis is that there is a difference in response rates between both groups. The null hypothesis was tested at a two-sided alpha of 0.05.

B.2.4.2.1 Primary efficacy endpoint

The response rates at Week 52 were compared between the treatment groups using the exact CMH test stratified by the randomisation strata. The estimate of the OR and the corresponding 95% exact CI and exact p-value were provided. In addition, the difference between the treatment groups and 95% CI were calculated using the Newcombe method stratified by randomisation strata. For consistency, the Wilson score 95% CI for single proportion was provided for within group description.

B.2.4.2.2 Key secondary efficacy endpoint

The response to elafibranor 80 mg compared to placebo on cholestasis was evaluated considering the response to treatment in terms of normalisation of ALP at Week 52.

The null hypothesis for response to treatment based on the first key secondary endpoint is that there is no difference in response rates between the elafibranor and the placebo group. The alternative hypothesis is that there is a difference in response rates between both groups. The null hypothesis was tested at a two-sided alpha of 0.05, only if the primary endpoint is statistically significant. The analysis of the first key secondary efficacy endpoint was conducted similarly to the primary endpoint including strategies to handle the intercurrent events and missing values.

B.2.4.2.3 Second and third key efficacy endpoint

The second and third key secondary efficacy endpoints are change in pruritus from baseline at Week 52 and Week 24 on PBC Worst Itch NRS in participants with baseline PBC Worst Itch NRS score ≥4, respectively.

The response to elafibranor 80 mg compared to placebo on pruritus was evaluated using the Pruritus ITT Analysis Set. The null hypothesis for response to treatment based on the second key secondary endpoints is that there is no difference in mean change from baseline through Week 52 of PBC Worst Itch NRS score in participants with baseline PBC Worst Itch NRS score ≥4 between the elafibranor and the placebo groups. The alternative hypothesis is that there is a difference in mean change from baseline through Week 52 and Week 24 of PBC Worst Itch NRS score in participants with baseline PBC Worst Itch NRS score ≥4 between both groups. The null hypothesis was tested at two-sided alpha of 0.05, only if the primary endpoint and the first key secondary endpoint are statistically significant. PBC Worst Itch NRS scores for participants who stopped prematurely the study treatment or took a rescue therapy for pruritus prior to Week 52 assessment were considered as missing.

The analysis of the second key secondary efficacy endpoint was conducted modelling the change from baseline values over the entire duration between baseline and Week 52 via a mixed model for repeated measures (MMRM). The 4-week periods were considered as a repeated variable within a participant.

Missing values were handled within the analysis itself with the assumption that the model specification is correct and that the data will be missing at random.

B.2.4.2.4 General methods

The primary and first key secondary efficacy analyses were performed primarily on the ITT Analysis Set, while only the main analyses of the primary and first key secondary endpoints were replicated on the PP Analysis Set.

The second and third key secondary analyses were performed primarily on the Pruritus ITT Analysis Set, while only the main analyses of the second and third key secondary endpoints were replicated on the Pruritus PP Analysis Set.

Each efficacy endpoint was evaluated up to Week 52 (except the third key efficacy endpoint at Week 24). For participants who completed additional visits during the double-blind period, descriptive statistics were presented up to the end of the DB period.

The SAS was the primary analysis set for the analysis of safety endpoints such as the occurrence of AEs, treatment-related AEs and AEs of special interest. If both ITT and SASs are the same, meaning that all randomised participants took at least one study treatment dose and none were reallocated to a different treatment group compared to randomisation, the

replicated analysis planned on the SAS for demographics, screening and baseline characteristics was not done.

For definitions of analysis sets, refer to B.2.3.3.2. Further details of statistical analyses for the ELATIVE trial is provided in Appendix D.

B.2.4.2.5 Handling of missing data

Discontinued participants who received the study drug were not replaced. Over the DB period, follow-up of the participants who discontinued the study drug early continued until the end of the DB period (visit 8 or until the last visit 6 was performed). To limit the occurrence of intercurrent events (ICEs) such as study treatment discontinuations and/or use of rescue medication such as OCA, the treatment allocation as well as values of ALP, GGT and 5-nucleotidase (5' NT) remained blinded for the investigator and for the participant up to the DB database lock. Rescue therapy for PBC and pruritus were identified during the Blind Data Review Meetings. Use of PBC rescue therapies and pruritus rescue therapies were handled as intercurrent events for the primary endpoint, first key secondary endpoint, and second and third key secondary endpoints, respectively. The final list was provided and approved at the last Blind Data Review Meetings.

B.2.5 Quality assessment of the relevant clinical effectiveness evidence

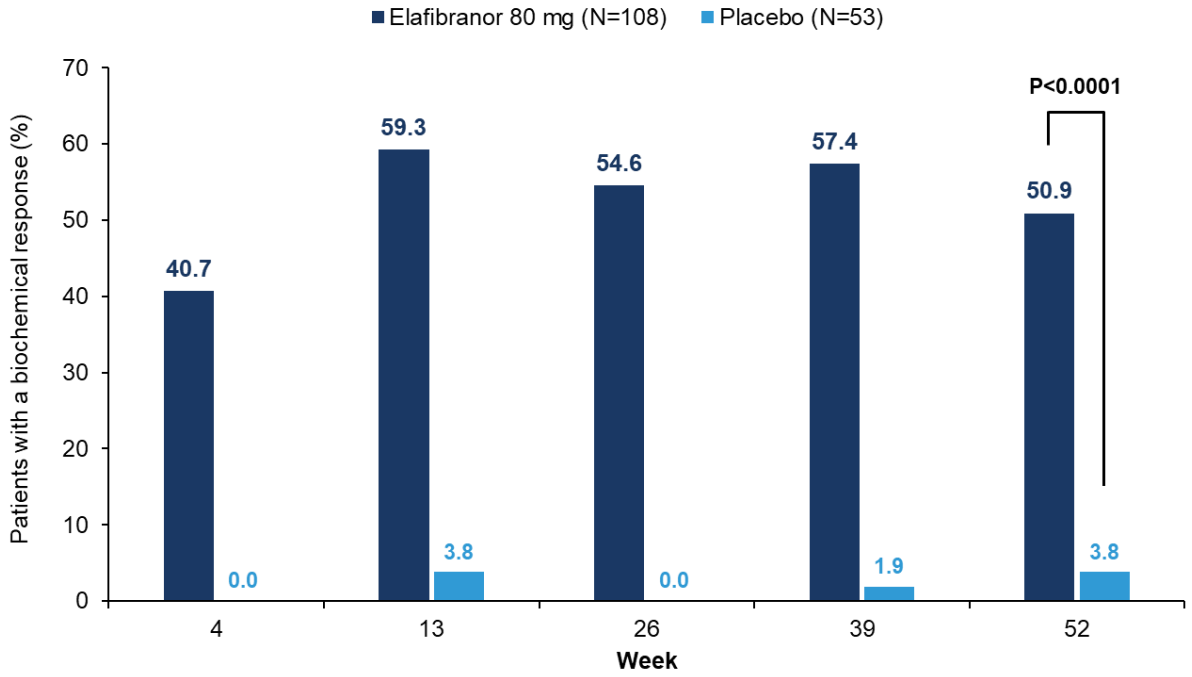
A complete quality assessment for ELATIVE is provided in Appendix D.

B.2.6 Clinical effectiveness results of the relevant trials

B.2.6.1.1 Primary efficacy endpoint: Cholestasis response

The primary endpoint of the ELATIVE study was the response to treatment based on cholestasis response at Week 52. Participants who prematurely discontinued the study treatment or used rescue therapy for PBC prior to the Week 52 visit (intercurrent events) were considered as non-responders. At Week 52, the proportion of patients with cholestasis response was 55/108 for the elafibranor arm and 2/53 in the placebo arm (50.9% and 3.8%, respectively). The odds ratio for elafibranor versus placebo was statistically significant in favour of elafibranor (OR of 37.6; 95% CI: 7.6, 302.2; $p<0.0001$). The analysis was carried out using the exact CMH test stratified by the randomisation strata. Results for the primary endpoint (ITT Analysis Set) are presented below in Figure 18.

Figure 18: Percentage of patients with cholestasis response[a] at Week 52 (ITT Analysis Set)



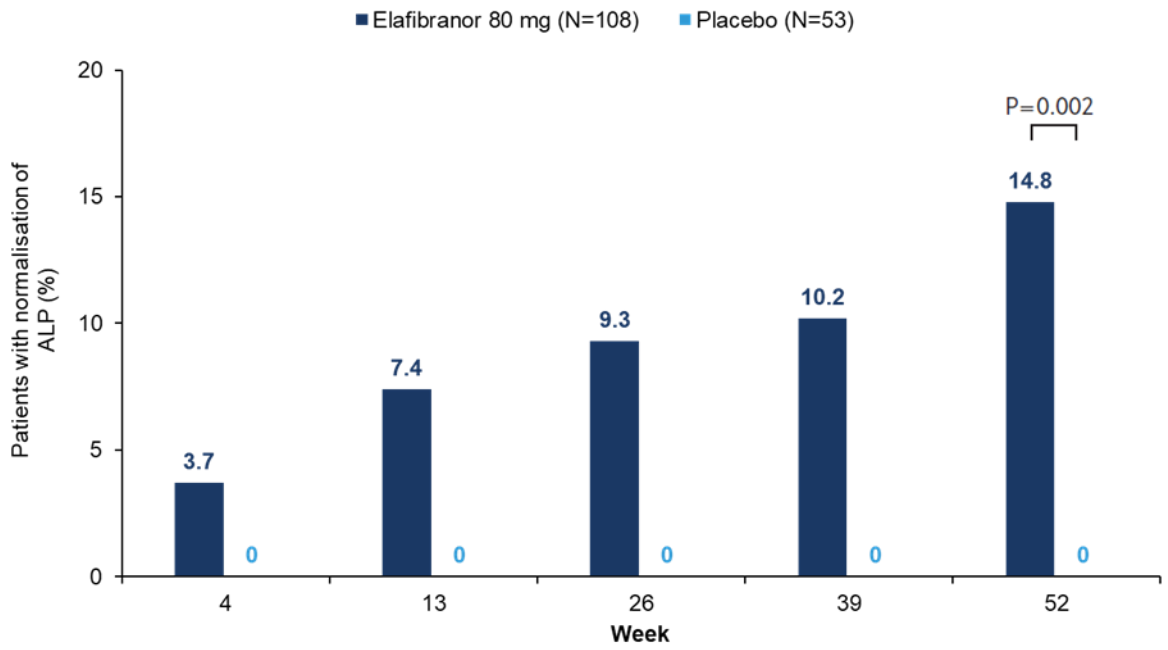
Abbreviations: ITT – intention-to-treat
[a] Cholestasis response was defined as ALP <1.67 x ULN, TB ≤ULN, and ALP decrease ≥15%.
Abbreviations: ITT – intent-to-treat.
Source : Kowdley *et al.* (2023)[4]; Ipsen Data on File 2023 (ELATIVE Clinical Study Report).[112]

B.2.6.1.2 Key secondary efficacy endpoints

B.2.6.1.2.1 ALP normalisation

ALP normalisation was defined as ALP ≤ULN, at Week 52. Participants who prematurely discontinued the study treatment or used rescue therapy for PBC prior to the Week 52 assessment were considered as non-responders. The proportion of responders was greater in the elafibranor group (n=16/108; [14.8%]) than in the placebo group (n=0/53 [0.0%] patients), resulting in a difference of 14.8% (95% CI: 6.1, 22.7) favouring the elafibranor group. The OR was statistically significant in favour of elafibranor (OR: infinity; 95% CI: 2.8, infinity; p=0.002). The results of the key secondary endpoint are shown below in Figure 19.

Figure 19: Percentage of patients achieving ALP normalisation at Week 52 (ITT Analysis Set)



Abbreviations: ALP – alkaline phosphatase; ITT – intent-to-treat
Source : Kowdley *et al.* (2023)[4]; Ipsen Data on File 2023 (ELATIVE Clinical Study Report).[112]

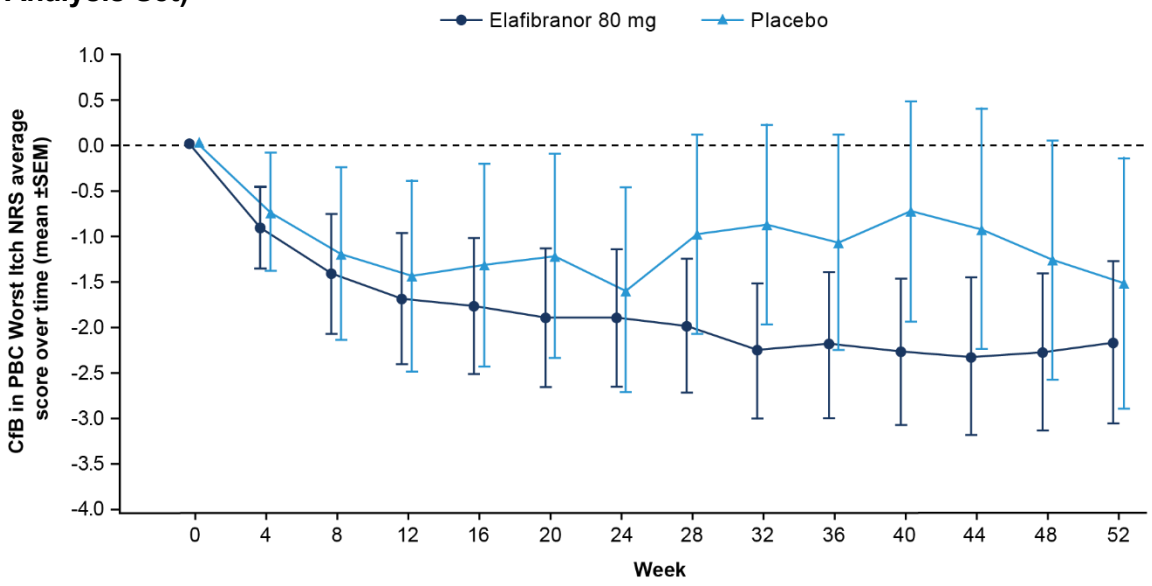
B.2.6.1.2.2 Change from baseline in Pruritus

The second and third key secondary endpoints were the change in pruritus from baseline through Week 52 and 24, respectively, assessed via PBC WI-NRS score in patients with baseline PBC WI-NRS score ≥4. These results were assessed in the Pruritus ITT Analysis Set and are summarised in Figure 20. Within this analysis, the outcome value for patients who prematurely discontinued the study treatment or used rescue therapy for pruritus was set to missing after such intercurrent events.[4,112]

The mean baseline PBC WI-NRS score in the Pruritus ITT population was 6.2 (SD: ±1.5) for the elafibranor group and 6.3 (SD: ±1.2) for the placebo group. In patients with moderate-to-severe pruritus, the LS mean change in the WI-NRS score demonstrated a trend towards greater reduction in pruritus with elafibranor treatment compared with placebo but did not differ significantly from baseline through Week 52 (-1.9 vs. -1.1; difference, -0.8; 95% CI: -2.0, 0.4; p=0.1970) and from baseline through Week 24 (-1.6 vs. -1.3; difference: -0.3; 95% CI: -1.5, 0.8, p=0.5522).[4,112]

Although the difference between treatments was not statistically significant, there was a clear trend for a greater improvement in pruritus for patients treated with elafibranor compared with placebo, seen as early as Week 1 and increasingly apparent from Week 24 onwards.

Figure 20: Change in PBC Worst Itch NRS score from baseline to Week 52 (Pruritus ITT Analysis Set)



No. of Patients														
Elafibranor 80 mg	44	41	40	39	40	38	37	34	35	34	32	34	35	32
Placebo	22	21	19	18	18	17	16	15	15	16	15	14	13	12

Abbreviations: CfB – change from baseline; CI – confidence interval; ITT – intent-to-treat; LS – least squares; mg – milligram; NRS – numeric rating scale; SEM – standard error of mean; PBC – primary biliary cholangitis.
Source: Kowdley *et al.* (2023)[4]; Ipsen Data on File 2023 (ELATIVE Clinical Study Report).[112]

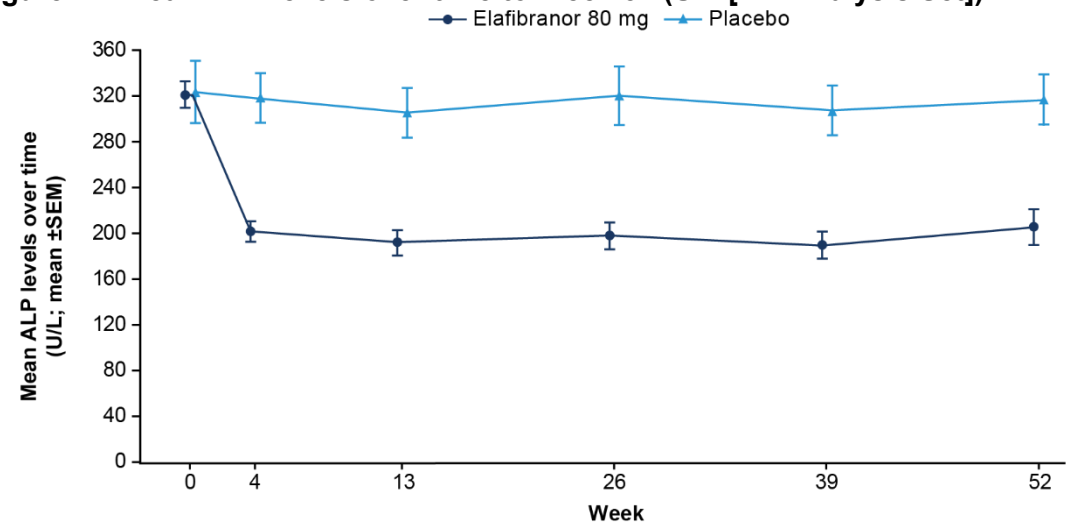
B.2.6.1.3 Other secondary endpoints

B.2.6.1.3.1 Change from baseline in ALP at 4, 13, 26, 39 and 52 weeks

The change from baseline in ALP at Weeks 4, 13, 26, 39, and 52 was assessed as a secondary endpoint. Patients treated with elafibranor demonstrated a rapid reduction in ALP as early as Week 4 that was sustained over 52 weeks of treatment compared with patients who received placebo, as shown by the mean absolute (Figure 21) and percentage change (Figure 23) from baseline. At Week 4, the mean change from baseline in ALP was -115.8 U/L (95% CI: -126.7, -105.0) in the elafibranor group, which further decreased to -117.0 U/L (95% CI: -134.4, -99.6) by Week 52. In contrast, the mean change in the placebo group was -10.4 U/L (95% CI: -26.0, 5.2) and -5.3 U/L (95% CI: -30.4, 19.7) at Weeks 4 and 52, respectively (Figure 21). This translated to a statistically significant reduction in ALP compared with placebo at both time points, with a LS means difference between groups of -105.4 U/L (95% CI: -124.2, -86.7; p<0.001) at Week 4 and -111.7 U/L (95% CI: -142.0, -81.3; p<0.001) at Week 52.[4,112]

At Week 4, the mean percent change from baseline in ALP was -36.5% (SD: ±13.2%) in the elafibranor group, which further decreased to -38.9% (SD: ±24.8%) by Week 52 (Figure 23). In contrast, the mean percentage change in the placebo group was 0.2% (SD: ±18.2%) and 1.7% (SD: ±18.5%) at Weeks 4 and 52, respectively. Elafibranor treatment resulted in a statistically significant reduction in ALP compared with placebo, with a treatment estimate of -40.6% (95% CI: -47.8, -33.5, p<0.0001) between groups in favour of elafibranor.[4,112]

Figure 21: Mean ALP levels over time to Week 52 (U/L [ITT Analysis Set])



No. of Patients						
Elafibranor 80 mg	108	104	107	104	102	94
Placebo	53	48	49	49	49	49

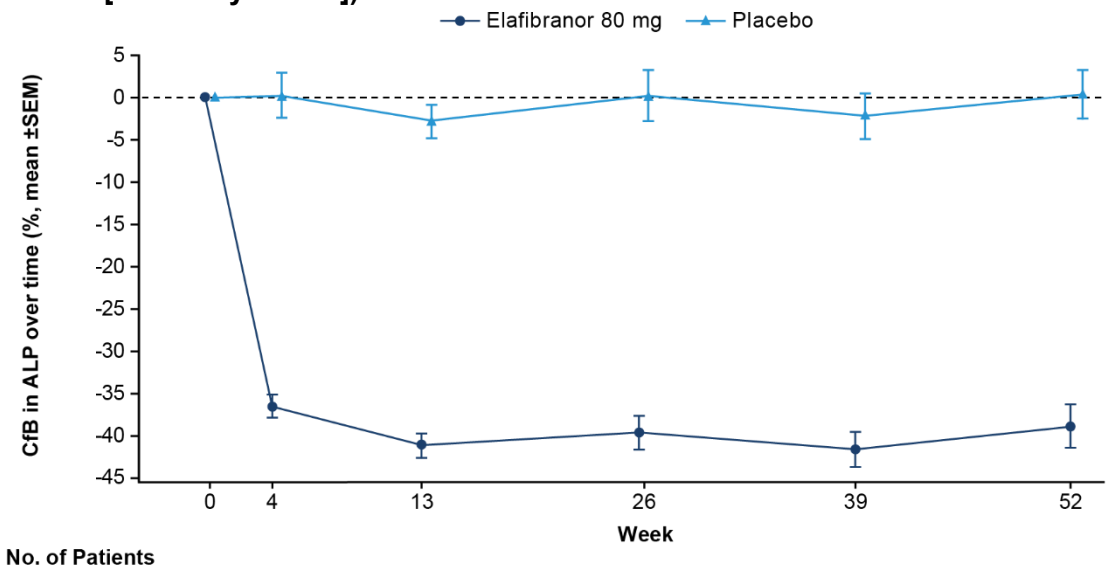
Abbreviations: ALP – alkaline phosphatase, ITT – intention-to-treat; mg – milligram; U/L – units per litre
Source: Kowdley *et al.* (2023)[4]; Ipsen Data on File 2023 (ELATIVE Clinical Study Report).[112]

Figure 22 provides some additional long-term data at Week 78 and Week 104 for the mean change in ALP from baseline although this sample size is currently smaller at these time points.

Figure 22: Mean ALP levels over time, including Week 78 and Week 104 (ITT Analysis Set)

Abbreviations: ALP – alkaline phosphatase, ITT – intention-to-treat; U/L – units per litreSource: Ipsen Data on File 2023 (ELATIVE Clinical Study Report).112

Figure 23: Mean percentage change from baseline in ALP levels (U/L over time to Week 52 [ITT Analysis Set])



No. of Patients						
Elafibranor 80 mg	108	104	107	104	102	94
Placebo	53	48	49	49	49	49

Abbreviations: ALP – alkaline phosphatase; CfB – change from baseline; mg – milligram; U/L – units per litre
Source: Kowdley *et al.* (2023)[4]; Ipsen Data on File 2023 (ELATIVE Clinical Study Report).[112]

B.2.6.1.3.2 Mean change from baseline in TB levels

In alignment with the ALP levels, participants on elafibranor 80 mg compared to placebo had greater decreases in TB levels from baseline at Week 52 (LS means difference from placebo) in TB (-1.3 µmol/L; 95% CI: -2.8, 0.2, p=0.0978); reduction in TB in the elafibranor 80 mg group was evident from Week 4 onwards and was sustained at subsequent timepoints and up to Week 52. The reduction in TB was further sustained throughout the variable DB period of the trial up to Week 104. Results for TB levels throughout the 52-week DB period and up to Week 104 are presented in Figure 24.

Figure 24: Mean TB Change from Baseline Over Time up to Week 104

[redacted]

Abbreviations: µmol/L – micromole per litre; mg – milligram; SE – standard error; TB – total bilirubin
Source: Ipsen Data on File 2023 (ELATIVE Clinical Study Report).[112]

B.2.6.1.3.3 Mean change from baseline in liver-related variables

Patients treated with elafibranor had a greater decrease from baseline at Week 52 in GGT (LS mean difference: -30.2 U/L; 95% CI: -65.1, 4.8); and 5' NT (LS mean difference: -1.9 U/L; 95% CI: -3.9, 0.2).Greater reductions in immunoglobin G (IgG) and immunoglobin M (IgM) were observed at Week 52 in patients treated with elafibranor compared with those receiving placebo (ITT Analysis Set).[4,112] At Week 52, the LS mean change from baseline in IgG was -0.4 g/L in the elafibranor group and 0.3 g/L in the placebo group. The LS mean difference between groups was -0.7 (95% CI: -1.2, -0.2; p=0.0088). For IgM, the LS mean change from baseline at Week 52 was -0.6 g/L in the elafibranor group and 0.0 g/L in the placebo group; the LS mean difference between groups was -0.6 (95% CI: -0.9, -0.3; p<0.001).[4,112]

At Week 52, levels of 7α-hydroxy-4-cholesten-3-one and fibroblast growth factor-19 appeared to be lower in patients who received elafibranor than in those who received placebo.[4]

Changes from baseline to Week 52 in liver-related variables and immunoglobulins are shown in Table 10 below.

Table 10: Changes from Baseline through Week 52 in Laboratory Data and Non-invasive Markers of Fibrosis*

Variable	Elafibranor 80 mg (N=108)		Placebo (N=53)		Difference (95% CI)
	LS mean change from baseline (95% CI)	No. of patients with data (%)	LS mean change from baseline (95% CI)	No. of patients with data (%)	
ALP – U/litre	-117.0 (-134.4, -99.6)	94 (87.0)	-5.3 (-30.4, 19.7)	47 (88.7)	-111.7 (-142.0, -81.3)
TB – µmol/litre	-0.1 (-1.0, 0.7)	93 (86.1)	1.1 (-0.1, 2.4)	47 (88.7)	-1.3 (-2.8, 0.2)
ALB – g/litre	0.7 (0.1, 1.2)	94 (87.0)	-0.9 (-1.7, -0.1)	47 (88.7)	1.6 (0.7, 2.6)
INR	0.04 (0.01, 0.06)	95 (88.0)	0.02 (-0.02, 0.06)	46 (86.8)	0.01 (-0.03, 0.06)
GGT – U/litre	-47.6 (-67.5, -27.7)	94 (87.0)	-17.4 (-46.3, 11.5)	47 (88.7)	-30.2 (-65.1, 4.8)
5’ NT	-3.7 (-4.9, -2.5)	82 (79.6)	-1.9 (-3.5, -0.2)	43 (81.1)	-1.9 (-3.9, 0.2)
ALT – U/litre	-9.3 (-13.4, -5.1)	94 (87.0)	-5.4 (-11.4, 0.5)	47 (88.7)	-3.8 (-11.0, 3.4)
AST – U/litre	-1.3 (-5.1, 2.5)	94 (87.0)	-3.2 (-8.6, 2.2)	47 (88.7)	1.9 (-4.6, 8.5)
IgG – g/litre	-0.4 (-0.7, -0.1)	95 (88.0)	0.3 (-0.1, 0.8)	46 (86.8)	-0.7 (-1.2, -0.2)
IgM – g/litre	-0.6 (-0.7, -0.4)	95 (88.0)	0.0 (-0.2, 0.3)	46 (86.8)	-0.6 (-0.9, -0.3)
7-α-Hydroxy-4-cholesten-3-one – µg/ml	-7.2 (-10.1, -4.2)	61 (56.5)	-2.0 (-6.2, 2.3)	30 (56.6)	-5.2 (-10.3, -0.1)
Fibroblast growth factor-19 – pg/ml	-22.8 (-70.8, 25.2)	73 (67.6)	64.2 (-4.3, 132.6)	36 (67.9)	-87.0 (-170.4, -3.5)
Enhanced liver fibrosis score†	0.1 (-0.1, 0.2)	89 (82.4)	0.2 (0.0, 0.3)	44 (83.0)	-0.1 (-0.3, 0.1)
Liver stiffness – kPa	0.2 (-0.9, 1.3)	90 (83.3)	0.3 (-1.4, 1.9)	44 (83.0)	-0.1 (-2.1, 1.9)

Abbreviations: µmol – micromole; ABL – albumin; ALP – Alkaline phosphatase; ALT – alanine aminotransferase; AST – aspartate aminotransferase; CI – confidence interval; GGT – gamma-glutamyl transferase; IgG – immunoglobin G; IgM – immunoglobin M; INT – internal normalised ratio; kPa – kilopascal; LS – least squares; pg/ml – picograms per millilitre; TB – total bilirubin

* Analyses were performed with the use of a MMRM, with treatment, visits (until Week 52), and treatment-by-visit interaction as fixed factors and with adjustment for baseline values and stratification factors.

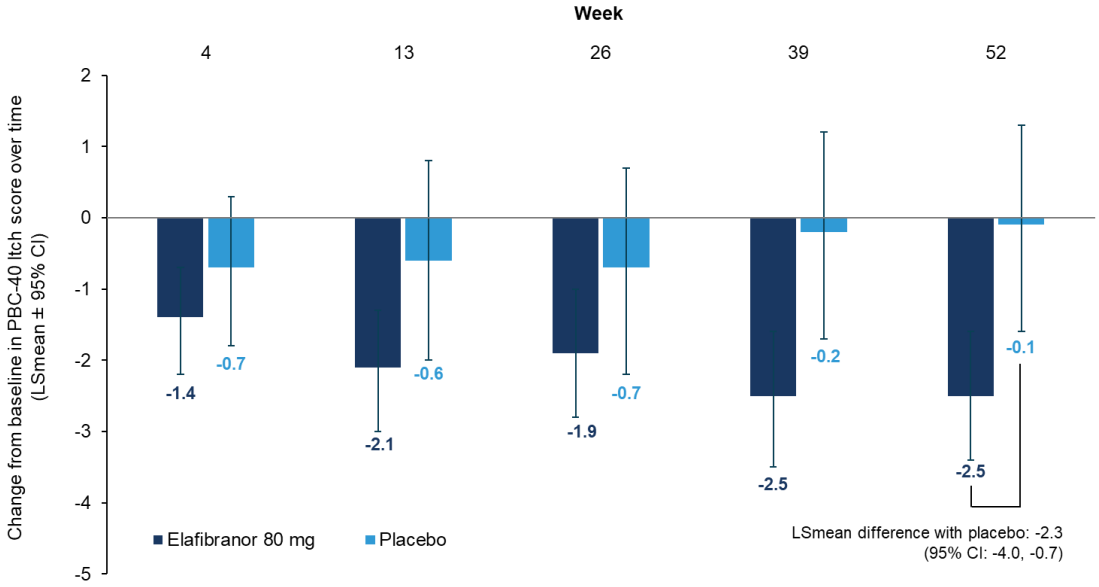
† The enhanced liver fibrosis score was calculated according to three markers of liver fibrosis (hyaluronic acid, procollagen type III amino-terminal peptide, and tissue inhibitor of matrix metalloproteinase-1). An enhanced liver fibrosis score of less than 7.7 indicates no-to-mild fibrosis.

Source: Kowdley *et al.* 2023[4]

B.2.6.1.3.4 Change from baseline in PBC-40 Itch domain

Treatment with elafibranor led to an improvement in symptom burden in the itch domain of the PBC-40 questionnaire compared with treatment with placebo. Improvement in pruritus was seen in the Pruritus ITT Analysis Set, with an LS mean change from baseline to Week 52 of -2.5 in the elafibranor group and -0.1 in the placebo group. The LS means difference from placebo was -2.3 (95% CI: -4.0, -0.7; nominal p=0.0070). This improvement was also observed in the ITT Analysis Set, indicating a trend towards elafibranor alleviating the pruritus burden associated with PBC (Figure 25).[4,112]

Figure 25: Change from baseline in the PBC-40 Itch score over time in patients with moderate-to-severe pruritus (Pruritus ITT Analysis Set)



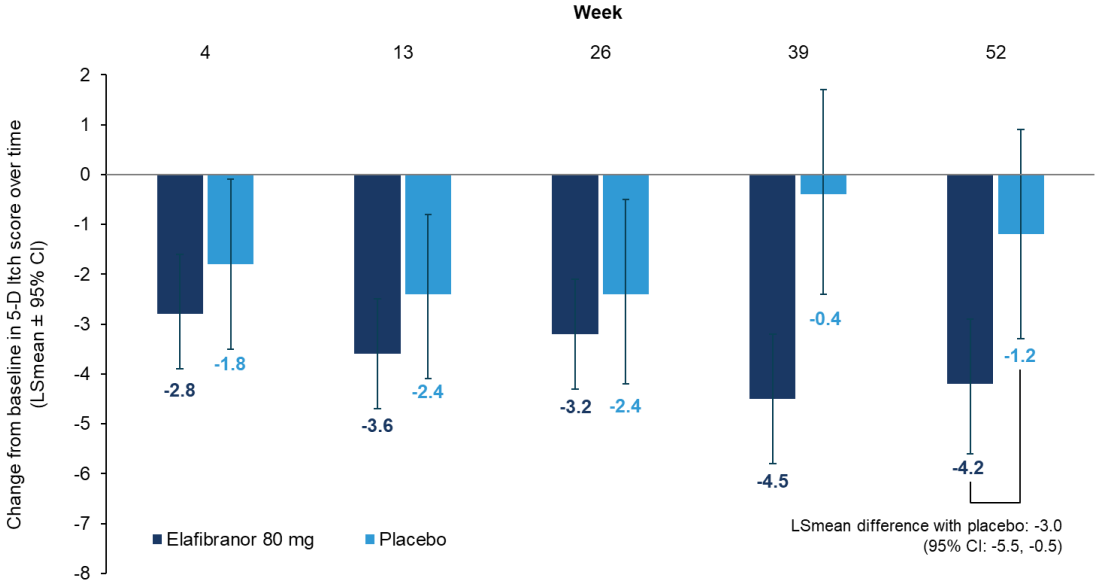
No. of Patients					
Elafibranor 80 mg	43	42	43	42	42
Placebo	20	17	15	16	16

Abbreviations: CI – confidence interval; LS – least squares; PBC – primary biliary cholangitis.
Source: Kowdley *et al.* (2023)[4]; Ipsen Data on File 2023 (ELATIVE Clinical Study Report).[112]

B.2.6.1.3.5 Change from baseline in 5-D Itch score

Treatment with elafibranor led to a significant improvement in pruritus as measured by the 5-D Itch scale in the Pruritus ITT Analysis Set (Figure 26). At Week 52, there was an LS mean change from baseline of -4.2 in the elafibranor group and -1.2 in the placebo group; resulting in an LS means difference of -3.0 (95% CI: -5.5, -0.5; nominal p=0.0199), favouring elafibranor. This trend was also supported by similar results in the ITT Analysis Set.[4,112]

Figure 26: Change from baseline in the 5-D Itch score over time in patients with moderate-to-severe pruritus (Pruritus ITT Analysis Set)



No. of Patients					
Elafibranor 80 mg	43	42	43	42	42
Placebo	20	17	15	16	16

Abbreviations: CI – confidence interval; LS – least squares; PBC – primary biliary cholangitis.
Source: Kowdley *et al.* (2023)[4]; Ipsen Data on File 2023 (ELATIVE Clinical Study Report).[112]

B.2.6.1.3.6 Change from baseline in lipid parameters

Treatment with elafibranor was associated with a beneficial anti-lipidemic effect for patients in the ELATIVE trial through to Week 52. The change from baseline in lipid parameters, including triglycerides (TG), total cholesterol, very low-density lipoprotein (VLDL)-cholesterol, low-density lipoprotein-cholesterol (LDL-C) and high-density lipoprotein-cholesterol (HDL-C), was measured over the study period. In the ITT Analysis Set, statistically greater decreases in TG and VLDL-C were observed for patients treated with elafibranor compared with patients who received placebo from baseline through to Week 52 (p<0.001); differences in other lipid measures were also observed but these did not reach statistical significance. Levels of high-density lipoprotein (HDL)-C remained stable with elafibranor treatment over the study period (see Table 11 and see also the figures in the Kowdley *et al.* (2023) publication).[4,112]

Table 11: Change from baseline in lipid parameters at Week 52 (ITT Analysis Set)

	Change from Baseline LS Mean (95% CI)		Difference Between Groups	
Parameter	**Elafibranor 80 mg (N=108)**	**Placebo (N=53)**	**LS mean (95% CI)**	**p-value**
Triglycerides (mmol/L)				
Triglycerides	N=92	N=47	–	–
	-0.2 (-0.3, -0.2)	0.0 (-0.1, 0.1)	-0. 3 (-0.4, -0.1)	<0.001
Total cholesterol (mmol/L)				
Total cholesterol	N=94	N=47	–	–
	-0.5 (-0.7, -0.4)	-0.3 (-0.5, -0.0)	-0.3 (-0.6, 0.1)	0.1069
VLDL-cholesterol (mmol/L)				

	Change from Baseline LS Mean (95% CI)		Difference Between Groups	
Parameter	**Elafibranor 80 mg (N=108)**	**Placebo (N=53)**	**LS mean (95% CI)**	**p-value**
VLDL-cholesterol	N=91	N=47	–	–
	-0.1 (-0.1, -0.1)	0.0 (-0.0, 0.1)	-0.1 (-0.2, -0.1)	<0.001
LDL-cholesterol (mmol/L)				
LDL-cholesterol	N=91	N=47	–	–
	-0.4 (-0.6, -0.3)	-0.2 (-0.5, -0.0)	-0.2 (-0.4, 0.1)	0.1891
HDL-cholesterol (mmol/L)				
HDL-cholesterol	N=95	N=47	–	–
	0.0 (-0.1, 0.1)	-0.0 (-0.1, 0.1)	0.0 (-0.1, 0.2)	0.5491

Abbreviations: CI – confidence interval; HDL – high-density lipoprotein; ITT – intent-to-treat; LDL – low-density lipoprotein; LS – least squares; mg – milligram; mmol/L – millimoles per litre; N – total number of patients in a group; VLDL – very low-density lipoprotein.
Source: Ipsen Data on File 2023 (ELATIVE Clinical Study Report).[112]

B.2.6.1.3.7 Change from baseline in PROMIS Fatigue Short Form 7a score

At Week 52, the LS means change from baseline in PROMIS scores for the ITT Analysis Set were [redacted] (95% CI: [redacted], [redacted]) for the elafibranor group and [redacted] (95% CI: [redacted], [redacted]) for the placebo group. The LS means difference from placebo was [redacted] (95% CI: [redacted], [redacted]; p=[redacted]).[112] In the Pruritus ITT set, the LS mean changes from baseline were [redacted] for the elafibranor group and [redacted] for the placebo group and the LS mean difference between elafibranor and placebo was [redacted] (95% CI: [redacted], [redacted]; p=[redacted]). Overall, these data indicate a trend towards improvement of fatigue at Week 52 in patients treated with elafibranor, particularly for patients with moderate-to-severe pruritus.[112]

Post-hoc analyses/supportive information

Open-label extension (OLE) data is not yet available for ELATIVE with the long-term extension not expecting to be complete until December of 2028. The long-term study ELFIDENCE is not expected to complete until October 2030 and therefore data is not available. [redacted]

B.2.7 Subgroup analysis

Pre-planned subgroup analyses were performed in each subgroup separately. Cholestasis response and ALP normalisation were analysed within subgroups using the exact CMH with the composite strategy using the ITT Analysis Set, stratified by the randomisation strata. The subgroup analyses of second and third key secondary endpoints was conducted on the Pruritus ITT Analysis Set and with the model for the change from baseline values over the entire duration between baseline and Week 52 and analysed using the MMRM.

Within each subgroup, the treatment effect was analysed comparing elafibranor to placebo by presenting the estimate of the risk difference, OR/overall contrast and their corresponding 95% Cis. For subgroup analyses, if the subgroup at baseline included less than 20 participants across treatment groups or less than 5 participants for a treatment group, the analysis was omitted.

The characteristics considered for each subgroup are as follows:

- Age at randomisation (<65 years, ≥65 years).
- Sex (Female, Male).
- Race (White, Others defined by American Indian or Alaska Native, Asian, Black or African American, Native Hawaiian or Other Pacific Islander or Others).
- UDCA treatment at baseline (Yes/No).
- Prior OCA treatment (Yes/No).
- ALP level at baseline >3 x ULN (Yes/No).
- TB at baseline >ULN (Yes/No).
- TB at baseline >ULN or ALB at baseline <LLN (Yes/No).
- TB at baseline >0.6 x ULN (Yes/No).
- Geographic region: Europe, North America, Latin America, Other (including Turkey and South Africa).
- ALP >3 x ULN or TB >ULN at baseline (Yes/No). In case of mis-stratification during the randomisation, the true screening value was used.
- PBC Worst Itch NRS score ≥4 at baseline (averaged over the 14 days preceding randomisation) (Yes/No). In case of mis-stratification during the randomisation, the true screening value was used.
- Cirrhotic defined by liver stiffness at baseline ≥16.9 kPa by TE (Yes/No) and/or cirrhosis on histology.
- Advanced disease stage defined as liver stiffness at baseline >10 kPa by TE and/or bridging fibrosis or cirrhosis on histology.

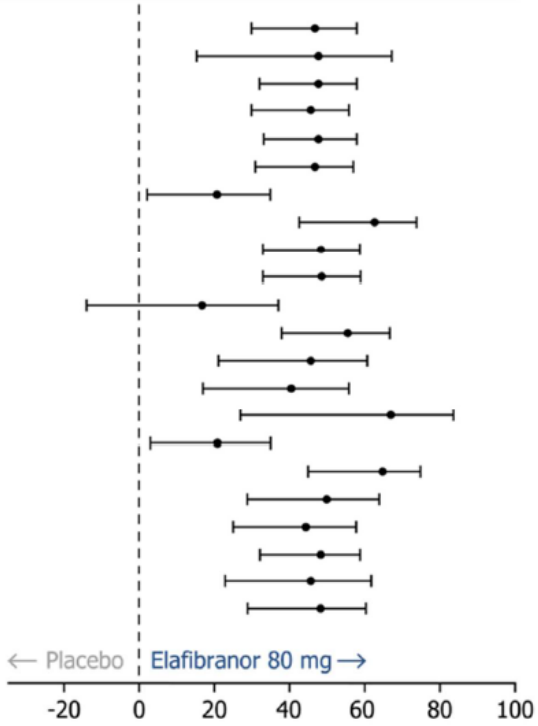
Forest plots of the results of the subgroup analyses on both the primary and secondary endpoint are shown in Figure 27 and Figure 28 respectively.[4] For the primary endpoint, results showed favourable results for elafibranor over placebo for all subgroup analyses conducted. Cholestasis response was more likely in patients treated with elafibranor than placebo across various subgroup populations including participants with ALP >3 x ULN, TB >0.6 x ULN, advanced fibrosis, without prior OCA treatment, concurrent UDCA treatment, PBC WI-NRS score ≥4, by age, and geographical region.[4]

For the key secondary endpoint, there were no responders in the placebo arm of the trial, resulting in favourable results for elafibranor for all subgroup analyses conducted. The results of these subgroup analyses demonstrated a consistent treatment effect in favour of elafibranor among various participant subgroups that were generally consistent with subgroup analyses performed on the primary endpoint.[4]

Note that the decision problem does not consider any subgroup analysis and therefore should not be considered for decision making in this submission.

Figure 27: Subgroup analyses for the primary endpoint

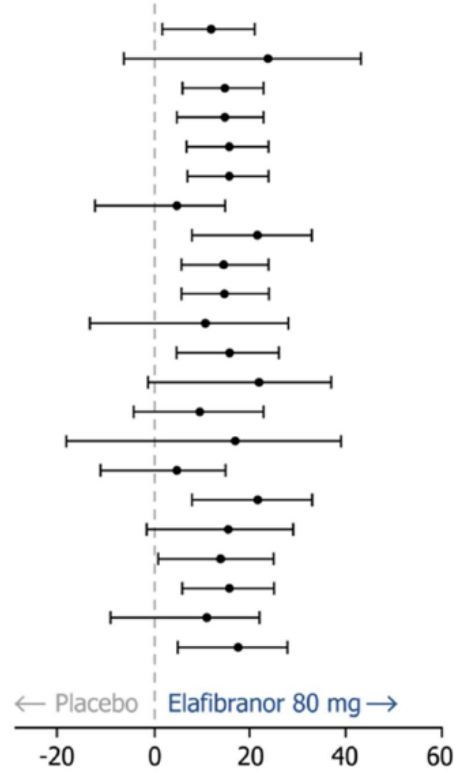
Subgroup	Elafibranor, n	Placebo, n	Risk difference [95% CI]
Age <65 years	83	43	47 [30; 58]
Age ≥65 years	25	10	48 [15; 67]
Female	102	52	48 [32; 58]
White	101	46	46 [30; 56]
Ursodeoxycholic acid treatment at baseline (Yes)	102	51	48 [33; 58]
Prior obeticholic acid treatment (No)	100	48	47 [31; 57]
Alkaline phosphatase level at baseline >3x ULN (Yes)	43	20	21 [2; 35]
Alkaline phosphatase level at baseline >3x ULN (No)	65	33	63 [43; 74]
Total bilirubin at baseline >ULN (No)	104	51	49 [33; 59]
Total bilirubin at baseline >ULN or albumin at baseline <LLN (No)	104	51	49 [33; 59]
Total bilirubin at baseline >0.6x ULN (Yes)	27	13	17 [−14; 37]
Total bilirubin at baseline >0.6x ULN (No)	81	40	56 [38; 67]
Europe	41	15	46 [21; 61]
North America	41	28	41 [17; 56]
Latin America	18	8	67 [27; 84]
Alkaline phosphatase level >3x ULN or total bilirubin >ULN at baseline (Yes)	43	21	21 [3; 35]
Alkaline phosphatase level >3x ULN or total bilirubin >ULN at baseline (No)	65	32	65 [45; 75]
WI-NRS score ≥4 at baseline (Yes)	44	22	50 [29; 64]
WI-NRS score ≥4 at baseline (No)	64	31	45 [25; 58]
Cirrhotic at baseline (No)	99	46	49 [32; 59]
Advanced disease stage* (Yes)	35	19	46 [23; 62]
Advanced disease stage* (No)	73	34	49 [29; 61]



Abbreviations: CI – confidence interval; ULN – upper limit of normal; WI-NRS – Worst Itch Numeric Rating Scale
Risk difference corresponds to difference (%) in response (elafibranor versus placebo). If the subgroup at baseline included fewer than 20 patients across treatment groups or fewer than 5 patients for a treatment group, the subgroup was omitted.
*Defined as liver stiffness at baseline >10.0 kPa and/or bridging fibrosis or cirrhosis on histology.
Source: Kowdley *et al.* (2023)[4]

Figure 28: Subgroup analyses for normalisation of ALP at Week 52

Subgroup	Elafibranor, n	Placebo, n	Risk difference [95% CI]
Age <65 years	83	43	12 [2; 21]
Age ≥65 years	25	10	24 [−6, 43]
Female	102	52	15 [6; 23]
White	101	46	15 [5; 23]
Ursodeoxycholic acid treatment at baseline (Yes)	102	51	16 [7; 24]
Prior obeticholic acid treatment (No)	100	48	16 [7; 24]
Alkaline phosphatase level at baseline >3x ULN (Yes)	43	20	5 [−12; 15]
Alkaline phosphatase level at baseline >3x ULN (No)	65	33	22 [8; 33]
Total bilirubin at baseline >ULN (No)	104	51	15 [6; 24]
Total bilirubin at baseline >ULN or albumin at baseline <LLN (No)	104	51	15 [6; 24]
Total bilirubin at baseline >0.6x ULN (Yes)	27	13	11 [−13; 28]
Total bilirubin at baseline >0.6x ULN (No)	81	40	16 [5; 26]
Europe	41	15	22 [−1; 37]
North America	41	28	10 [−4; 23]
Latin America	18	8	17 [−18; 39]
Alkaline phosphatase level >3x ULN or total bilirubin >ULN at baseline (Yes)	43	21	5 [−11; 15]
Alkaline phosphatase level >3x ULN or total bilirubin >ULN at baseline (No)	65	32	22 [8; 33]
WI-NRS score ≥4 at baseline (Yes)	44	22	16 [−1; 29]
WI-NRS score ≥4 at baseline (No)	64	31	14 [1; 25]
Cirrhotic at baseline (No)	99	46	16 [6; 25]
Advanced disease stage* (Yes)	35	19	9 [−9; 22]
Advanced disease stage* (No)	73	34	18 [5; 28]



Abbreviations: ALP – alkaline phosphatase; CI – confidence interval; ULN – upper limit of normal; WI-NRS – Worst Itch Numeric Rating Scale
Risk difference corresponds to difference (%) in response (elafibranor versus placebo). If the subgroup at baseline included fewer than 20 patients across treatment groups or fewer than 5 patients for a treatment group, the subgroup was omitted.
*Defined as liver stiffness at baseline >10.0 kPa and/or bridging fibrosis or cirrhosis on histology.
Source: Kowdley *et al.* (2023)[4]

B.2.8 Meta-analysis

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

B.2.9 Indirect and mixed treatment comparisons

Due to the lack of head-to-head data assessing the comparative efficacy of elafibranor and OCA, it was necessary to perform an ITC. This involved conducting an SLR to identify relevant clinical evidence, followed by a feasibility assessment. The feasibility assessment aimed to confirm which of the identified clinical trials were feasible to include and determine the optimal methodology for conducting the ITC. Following the SLR, it was determined that POISE was the only relevant trial for the comparison of elafibranor and OCA.

Trial design, study type, interventions of interest, comparators, patient population and outcomes measured were all considered to assess homogeneity between trials. The feasibility assessment confirmed that the ELATIVE and POISE trials were sufficiently homogeneous for an NMA to be performed. While only the OCA 5-10 mg dose is licensed for use in PBC, the ITC considered both the OCA 5-10 mg and OCA 10 mg arms of the POISE trial to assess the maximum possible treatment effect of OCA under the highest dose of 10 mg. Results for both arms are included in the ITC outcomes. Use of outcomes within the economic model, is based on the licensed dose of 5-10 mg to ensure the model best reflects current clinical practice and licensed therapies in England and Wales. For a summary of the trial included within the analysis see Table 12.

A statistical analysis plan was developed to present the data to be used in the ITCs along with the methodology. For details on the identification and selection of the relevant studies that were included in the ITC, please see Appendix D.

Table 12: Summary of the trials used to carry out the indirect or mixed treatment comparison

References of trial	Elafibranor 80 mg + UDCA	Placebo + UDCA	OCA 5-10 mg + UDCA	OCA 10 mg + UDCA
ELATIVE, Kowdley *et al.* 2023[4]	Yes	Yes		
POISE, Nevens *et al.* 2016[2]		Yes	Yes	Yes

Abbreviations: mg – milligram; OR – odds ratio; UDCA – ursodeoxycholic acid

B.2.9.1 Network meta-analysis

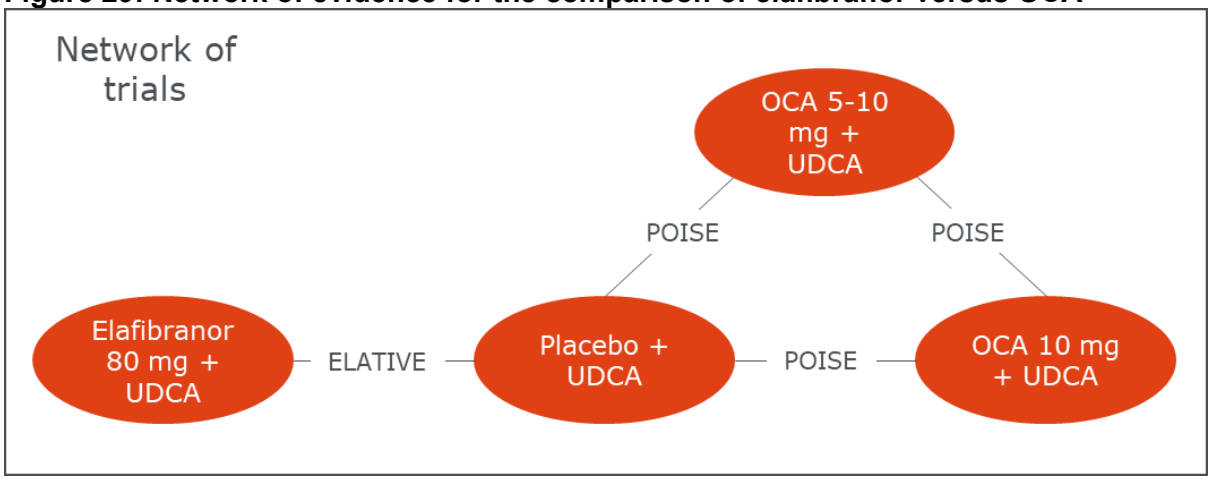
An NMA of the following outcomes were performed:[2,4]

- Cholestasis response, defined by ALP ≤1.67 x ULN, TB ≤ULN and ALP decrease ≥15%, at 52 weeks (binary endpoint)
- Change from baseline in ALP levels (IU/L) at 52 weeks (continuous endpoint)
- ALP normalisation, defined by ALP ≤1.0 x ULN at 52 weeks (binary endpoint)

- Change from baseline in pruritus according to the 5-D Itch score questionnaire at 52 weeks (continuous endpoint)
- Change from baseline in pruritus according to the 5-D Itch score questionnaire using the earliest reported data after commencement of treatment (Week 2 and Week 4 data for POISE and ELATIVE, respectively; continuous endpoint)
- Change from baseline in pruritus according to the PBC-40 Itch dimension score at 52 weeks (continuous endpoint)
- Change from baseline in pruritus according to the PBC-40 Itch dimension score using the earliest reported data after commencement of treatment (Week 2 and Week 4 data for POISE and ELATIVE, respectively; continuous endpoint)
- Occurrence of pruritus of any severity as a TEAE within 52 weeks (binary endpoint)
- Discontinuation due to pruritus within 52 weeks (binary endpoint)
- All-cause discontinuation within 52 weeks (binary endpoint)
- Change from baseline in HDL-cholesterol at 52 weeks (continuous endpoint)

Figure 29 shows the network of evidence that was used to carry out the analyses listed above. Analyses were carried out using both a random effects (base-case) model as well as a fixed effects (sensitivity analyses) model. Additionally, analyses were carried out to calculate the posterior probabilities for each outcome. The fixed effect results are presented in Appendix D.

Figure 29: Network of evidence for the comparison of elafibranor versus OCA



Abbreviations: mg – milligram; OCA – obeticholic acid; UDCA – ursodeoxycholic acid

B.2.9.1.1 Odds of achieving cholestasis response at 12 months

Results in Figure 30 show that patients treated with elafibranor 80 mg had greater odds of achieving response when compared to placebo, OCA 5-10 mg and OCA 10 mg (median OR [95% credible interval (CrI)]: [redacted] [redacted], [redacted], [redacted] [redacted], [redacted] and [redacted] [redacted], [redacted], respectively). The odds of cholestasis response with elafibranor 80 mg were statistically significantly higher than placebo. However, no statistically significant differences in the odds of cholestasis response were observed between elafibranor 80 mg and either OCA 5-10 mg or OCA 10 mg. Nonetheless, assessments of the median ORs for cholestasis response indicate a numerical inclination towards elafibranor 80 mg over both OCA treatment alternatives. Posterior probabilities demonstrated that the probability that the odds of cholestasis response with elafibranor 80 mg was greater than placebo, OCA 5-10 mg and OCA 10 mg ([redacted], [redacted] and [redacted], respectively [Table 13]).

The between-study standard deviation (τ = [redacted]) indicated a moderate level of heterogeneity among the effects observed in the analyses, which suggested that the relative treatment effects were mostly consistent across the studies considered. Additionally, the total residual difference ([redacted]) indicated that the predicated values did not deviate far from actual values to a great extent. The sample sizes for the ELATIVE trial were 108 and 53 for the elafibranor and placebo groups, respectively. In the POISE trial, sample sizes were 73, 70 and 73 for the placebo, OCA 5-10 mg, and OCA 10 mg groups, respectively.

Figure 30: Forest plot – OR of achieving cholestasis response at 12 months

Abbreviations: CrI – credible interval; mg – milligram; OCA – obeticholic acid
Analysis details: Burn-in: 150,000; Number of iterations: 500,000; Thinning interval: 10.

Table 13: Posterior probabilities of elafibranor having greater odds of achieving cholestasis response than each of the comparators at 12 months (random effects model)

Comparisons	Posterior probabilities
Elafibranor 80 mg vs placebo	[redacted]
Elafibranor 80 mg vs OCA 5-10 mg	[redacted]
Elafibranor 80 mg vs OCA 10 mg	[redacted]

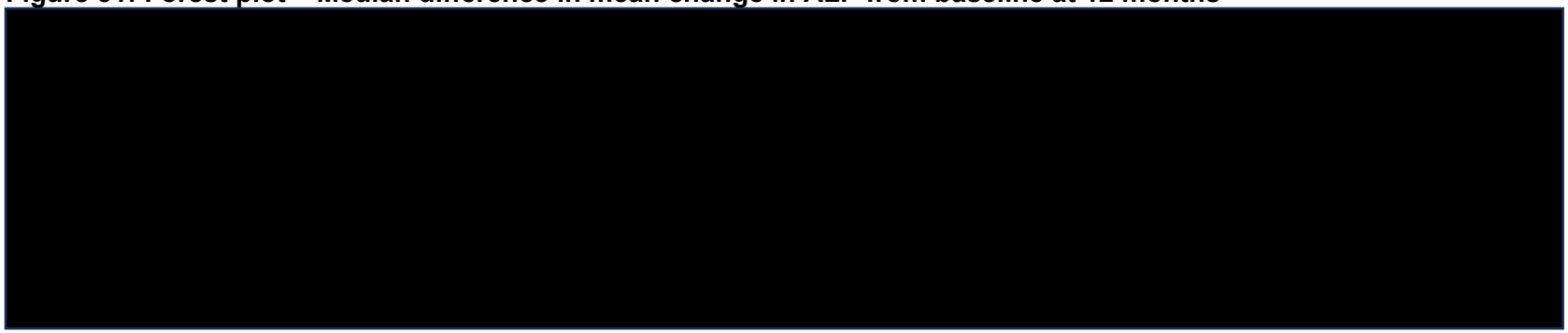
Abbreviations: mg – milligram; OCA – obeticholic acid

B.2.9.1.2 Mean change in ALP from baseline at 12 months

Results in Figure 31 show that patients treated with elafibranor 80 mg had a greater reduction in ALP levels from baseline when compared to placebo (median difference in mean change from baseline [95% CrI]: [redacted] [redacted], [redacted]). Elafibranor 80 mg was associated with a nominally greater change from baseline in ALP levels than OCA 5-10 mg ([redacted] [redacted], [redacted]) and nominally lower change from baseline in ALP than OCA 10 mg ([redacted] [redacted], [redacted]). The change from baseline in ALP with elafibranor 80 mg was statistically significantly greater than with placebo, whereas statistically significant differences in the change from baseline in ALP with elafibranor 80 mg compared to OCA 5-10 mg and OCA 10 mg could not be concluded. Posterior probabilities demonstrated that the probability that change from baseline in ALP with elafibranor 80 mg was greater than placebo and OCA 5-10 mg ([redacted] and [redacted], respectively [Table 14]).

After adjusting the between-study standard deviation ($\tau =$ [redacted]) to the standardised mean difference scale (i.e., dividing τ by the SD seen for the outcome in ELATIVE), the between-study SD on the standardised mean difference scale ($\tau_{SMD} =$ [redacted]) indicated a moderate level of heterogeneity among the effects observed in the analyses, which suggested that the relative treatment effects were mostly consistent across the studies considered. Additionally, the total residual difference ([redacted]) indicated that there was a moderate difference between the difference in change from baseline of ALP estimated via the NMA compared to the values observed in the trials. The sample sizes for the ELATIVE trial were 94 and 47 for the elafibranor and placebo groups, respectively. In the POISE trial, sample sizes were 70, 64 and 62 for the placebo, OCA 5-10 mg, and OCA 10 mg groups, respectively.

Figure 31: Forest plot – Median difference in mean change in ALP from baseline at 12 months



Abbreviations: ALP – alkaline phosphatase; CrI – credible interval; mg – milligram; OCA – obeticholic acid
Analysis details: Burn-in: 80,000; Number of iterations: 100,000; Thinning interval: 10.

Table 14: Posterior probabilities of elafibranor having a greater mean reduction in ALP from baseline than each of the comparators at 12 months (random effects model)

Comparisons	Posterior probabilities
Elafibranor 80 mg vs placebo	
Elafibranor 80 mg vs OCA 5-10 mg	
Elafibranor 80 mg vs OCA 10 mg	

Abbreviations: ALP – alkaline phosphatase; mg – milligram; OCA – obeticholic acid

B.2.9.1.3 Odds of achieving ALP normalisation at 12 months

Results in Figure 32 show that patients treated with elafibranor 80 mg had greater odds of achieving ALP normalisation when compared to placebo, OCA 5-10 mg and OCA 10 mg (median OR [95% CrI]: [,], [,] and [,], respectively). The odds of ALP normalisation with elafibranor 80 mg were statistically significantly higher than with placebo, whereas statistically significant differences in the odds of ALP normalisation with elafibranor 80 mg compared to OCA 5-10 mg and OCA 10 mg could not be concluded. Comparisons of the median ORs of ALP normalisation with elafibranor 80 mg relative to both OCA treatment options does suggest numerical preference for elafibranor 80 mg. Posterior probabilities demonstrated that the odds of ALP normalisation with elafibranor 80 mg was greater than placebo, OCA 5-10 mg and OCA 10 mg (, and , respectively [Table 15]).

The between-study standard deviation ($\tau =$) indicated a moderate level of heterogeneity among the effects observed in the analyses, which suggested that the relative treatment effects were mostly consistent across the studies considered. Additionally, the total residual difference

([redacted]) indicated that the predicated values did not deviate far from actual values to a great extent. The sample sizes for the ELATIVE trial were 108 and 53 for the elafibranor and placebo groups, respectively. In the POISE trial, sample sizes were 73, 70 and 73 for the placebo, OCA 5-10 mg, and OCA 10 mg groups, respectively.

Figure 32: Forest plot – OR of achieving ALP normalisation at 12 months

Abbreviations: ALP – alkaline phosphatase; CrI – credible interval; mg – milligram; OCA – obeticholic acid; OR – odds ratio
Analysis details: Burn-in: 500,000; Number of iterations: 700,000; Thinning interval: 10.

Table 15: Posterior probabilities of elafibranor having greater odds of achieving ALP normalisation than each of the comparators at 12 months (random effects model)

Comparisons	Posterior probabilities
Elafibranor 80 mg vs placebo	[redacted]
Elafibranor 80 mg vs OCA 5-10 mg	[redacted]
Elafibranor 80 mg vs OCA 10 mg	[redacted]

Abbreviations: ALP – alkaline phosphatase; mg – milligram; OCA – obeticholic acid

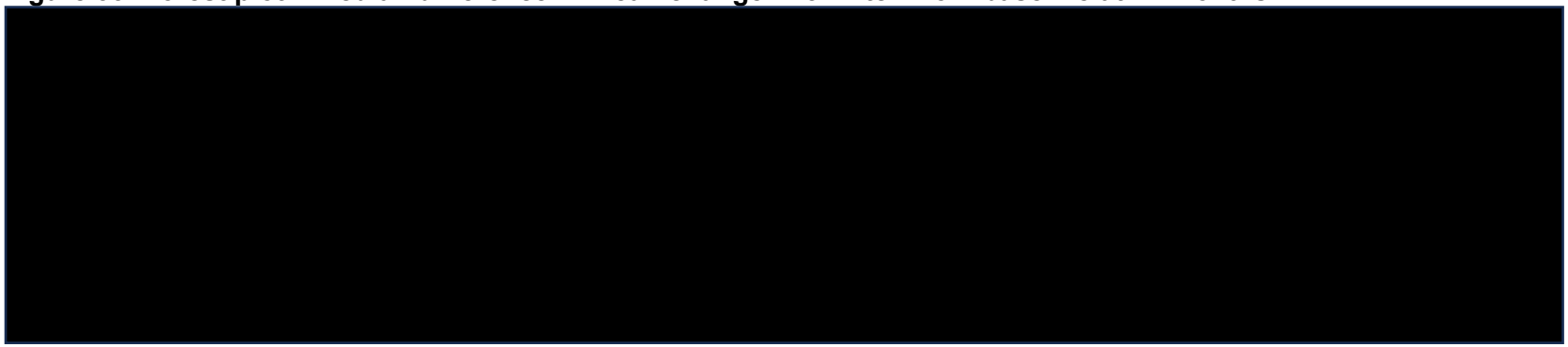
B.2.9.1.4 Mean change in pruritus (5-D Itch) from baseline at 12 months

Results in Figure 33 show that patients treated with elafibranor 80 mg had a greater reduction in pruritus, measured using the 5-D Itch scale at 12 months, when compared to placebo, OCA 5-10 mg and OCA 10 mg (median difference in mean change from baseline [95% CrI]: [redacted] [redacted], [redacted]], [redacted] [redacted], [redacted]] and [redacted] [redacted], [redacted]], respectively). However, it could not be determined that there were statistically significant differences in the change from baseline in 5-D Itch with elafibranor 80 mg compared to placebo, OCA 5-10 mg, and OCA 10 mg. Posterior

probabilities demonstrated that the probability that change from baseline in pruritus (5-D Itch) at 12 months with elafibranor 80 mg was greater than placebo, OCA 5-10 mg and OCA 10 mg ([redacted], [redacted] and [redacted], respectively [Table 16]).

After adjusting the between-study standard deviation ($\tau =$ [redacted]) to the standardised mean difference scale (i.e., dividing τ by the SD seen for the outcome in ELATIVE), the between-study SD on the standardised mean difference scale ($\tau_{SMD} =$ [redacted]) indicated a moderate level of heterogeneity among the effects observed in the analyses, which suggested that the relative treatment effects were mostly consistent across the studies considered. Additionally, the total residual difference ([redacted]) indicated that there was a small difference between the difference in change from baseline of pruritus estimated via the NMA compared to the values observed in the trials. The sample sizes for the ELATIVE trial were 95 and 48 for the elafibranor and placebo groups, respectively. In the POISE trial, sample sizes were 73, 70 and 73 for the placebo, OCA 5-10 mg, and OCA 10 mg groups, respectively.

Figure 33: Forest plot – Median difference in mean change in 5-D Itch from baseline at 12 months



Abbreviations: CrI – credible interval; mg – milligram; OCA – obeticholic acid
Analysis details: Burn-in: 100,000; Number of iterations: 200,000; Thinning interval: 10.

Table 16: Posterior probabilities of elafibranor having greater mean reduction in 5-D Itch from baseline than each of the comparators at 12 months (random effects model)

Comparisons	Posterior probabilities
Elafibranor 80 mg vs placebo	[redacted]
Elafibranor 80 mg vs OCA 5-10 mg	[redacted]
Elafibranor 80 mg vs OCA 10 mg	[redacted]

Abbreviations: mg – milligram; OCA – obeticholic acid

B.2.9.1.5 Mean change in pruritus (5-D Itch) from baseline using the earliest reported data after commencement of treatment (2-4 weeks)

Results in Figure 34 show that patients treated with elafibranor 80 mg had a greater reduction in pruritus, measured using the 5-D Itch scale at 2-4 weeks, when compared to placebo, OCA 5-10 mg and OCA 10 mg (median difference in mean change from baseline [95% CrI]: [redacted] [redacted], [redacted], [redacted] [redacted], [redacted] and [redacted] [redacted], [redacted], respectively). The change from baseline in 5-D Itch with elafibranor 80 mg was statistically significantly greater than with OCA 10 mg, whereas statistically significant differences in the change from baseline in 5-D Itch with elafibranor 80 mg compared to placebo and OCA 5-10 mg could not be concluded. Posterior probabilities demonstrated that the probability that change from baseline in pruritus (5-D Itch) at 2-4 weeks with elafibranor 80 mg was greater than placebo, OCA 5-10 mg and OCA 10 mg ([redacted], [redacted] and [redacted], respectively [Table 17).

After adjusting the between-study standard deviation (τ= [redacted]) to the standardised mean difference scale (i.e., dividing τ by the SD seen for the outcome in ELATIVE), the between-study SD on the standardised mean difference scale ($\tau_{SMD} =$ [redacted]) indicated a moderate level of heterogeneity among the effects observed in the analyses, which suggested that the relative treatment effects were mostly consistent across the studies considered. Additionally, the total residual difference ([redacted]) indicated that there was a small difference between the difference in change from baseline of pruritus estimated via the NMA compared to the values observed in the trials. The sample sizes for the ELATIVE trial were 105 and 50 for the elafibranor and placebo groups, respectively. In the POISE trial, sample sizes were 73, 70 and 73 for the placebo, OCA 5-10 mg, and OCA 10 mg groups, respectively.

Figure 34: Forest plot – Median difference in mean change in 5-D Itch from baseline using the earliest reported data after commencement of treatment (2-4 weeks)

Abbreviations: CrI – credible interval; mg – milligram; OCA – obeticholic acid
Analysis details: Burn-in: 200,000; Number of iterations: 300,000; Thinning interval: 10.

Table 17: Posterior probabilities of elafibranor having greater mean reduction in 5-D Itch from baseline than each of the comparators using the earliest reported data after commencement of treatment (2-4 weeks; random effects model)

Comparisons	Posterior probabilities
Elafibranor 80 mg vs placebo	[redacted]
Elafibranor 80 mg vs OCA 5-10 mg	[redacted]
Elafibranor 80 mg vs OCA 10 mg	[redacted]

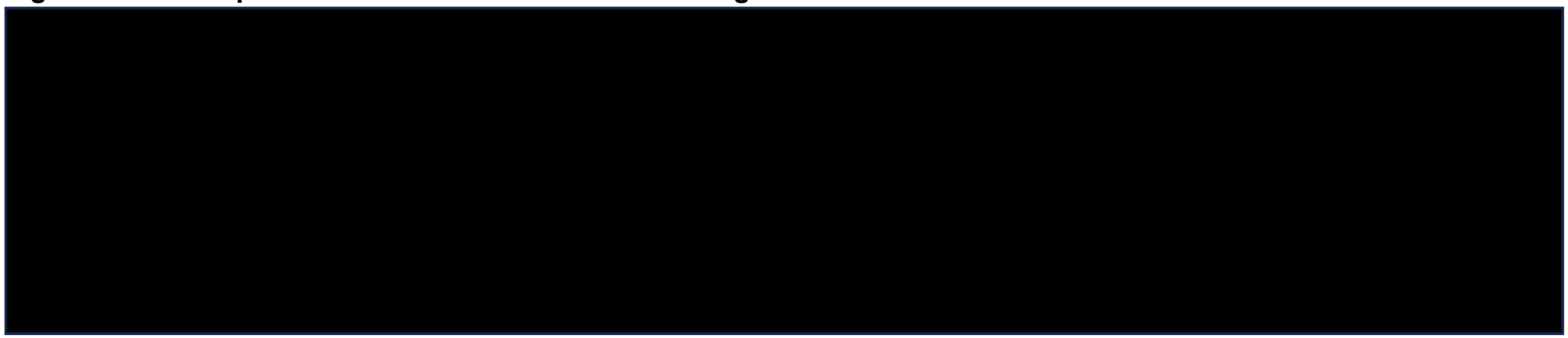
Abbreviations: mg – milligram; OCA – obeticholic acid

B.2.9.1.6 Mean change in pruritus (PBC-40 Itch) from baseline at 12 months

Results in Figure 35 show that patients treated with elafibranor 80 mg had a greater reduction in pruritus, measured using PBC-40 Itch at 12 months, when compared to placebo, OCA 5-10 mg and OCA 10 mg (median difference in mean change from baseline [95% CrI]: [redacted] [redacted], [redacted], [redacted] [redacted], [redacted] and [redacted] [redacted], [redacted], respectively). The change from baseline in PBC-40 Itch with elafibranor 80 mg was statistically significantly greater than with placebo and OCA 10 mg, whereas statistically significant differences in the change from baseline in PBC-40 Itch with elafibranor 80 mg compared to OCA 5-10 mg could not be concluded. Posterior probabilities demonstrated that the probability that change from baseline in pruritus (PBC-40 Itch) at 12 months with elafibranor 80 mg was greater than placebo, OCA 5-10 mg and OCA 10 mg ([redacted], [redacted] and [redacted], respectively [Table 18]).

After adjusting the between-study standard deviation (τ=[redacted]) to the standardised mean difference scale (i.e., dividing τ by the SD seen for the outcome in ELATIVE), the between-study SD on the standardised mean difference scale (τ_{SMD} = [redacted]) indicated a moderate level of heterogeneity among the effects observed in the analyses, which suggested that the relative treatment effects were mostly consistent across the studies considered. Additionally, the total residual difference (4.357) indicated that there was a small difference between the difference in change from baseline of pruritus estimated via the NMA compared to the values observed in the trials. The sample sizes for the ELATIVE trial were 95 and 48 for the elafibranor and placebo groups, respectively. In the POISE trial, sample sizes were 73, 70 and 73 for the placebo, OCA 5-10 mg, and OCA 10 mg groups, respectively.

Figure 35: Forest plot – Median difference in mean change in PBC-40 Itch from baseline at 12 months



Abbreviations: CrI – credible interval; mg – milligram; OCA – obeticholic acid
Analysis details: Burn-in: 500,000; Number of iterations: 600,000; Thinning interval: 10.

Table 18: Posterior probabilities of elafibranor having greater mean reduction in PBC-40 Itch from baseline than each of the comparators at 12 months (random effects model)

Comparisons	Posterior probabilities
Elafibranor 80 mg vs placebo	[redacted]
Elafibranor 80 mg vs OCA 5-10 mg	[redacted]
Elafibranor 80 mg vs OCA 10 mg	[redacted]

Abbreviations: mg – milligram; OCA – obeticholic acid

B.2.9.1.7 Mean change in pruritus (PBC-40 Itch) from baseline using the earliest reported data after commencement of treatment (2-4 weeks)

Results in Figure 36 show that patients treated with elafibranor 80 mg had a greater reduction in pruritus, measured using PBC-40 Itch at 2-4 weeks, when compared to placebo, OCA 5-10 mg and OCA 10 mg (median difference in mean change from baseline [95% CrI]: [redacted] [redacted], [redacted], [redacted] [redacted], [redacted] and [redacted] [redacted], [redacted], respectively). The change from baseline in PBC-40 Itch with elafibranor 80 mg was statistically significantly greater than with OCA 10 mg, whereas statistically significant differences in the change from baseline in PBC-40 Itch with elafibranor 80 mg compared to placebo and OCA 5-10 mg could not be concluded. Posterior probabilities demonstrated that the probability that change from baseline in pruritus (PBC-40 Itch) at 2-4 weeks with elafibranor 80 mg was greater than placebo, OCA 5-10 mg and OCA 10 mg ([redacted], [redacted] and [redacted], respectively [Table 19]).

After adjusting the between-study standard deviation (τ=[redacted]) to the standardised mean difference scale (i.e., dividing τ by the SD seen for the outcome in ELATIVE), the between-study SD on the standardised mean difference scale ($\tau_{SMD} =$ [redacted]) indicated a moderate level of heterogeneity among the effects observed in the analyses, which suggested that the relative treatment effects were mostly consistent across the studies considered. Additionally, the total residual difference ([redacted]) indicated that there was a small difference between the difference in change from baseline of pruritus estimated via the NMA compared to the values observed in the trials. The sample sizes for the ELATIVE trial were 105 and 50 for the elafibranor and placebo groups, respectively. In the POISE trial, sample sizes were 73, 70 and 73 for the placebo, OCA 5-10 mg, and OCA 10 mg groups, respectively.

Figure 36: Forest plot – Median difference in mean change in PBC-40 Itch from baseline using the earliest reported data after commencement of treatment (2-4 weeks)

Abbreviations: CrI – credible interval; mg – milligram; OCA – obeticholic acid
Analysis details: Burn-in: 500,000; Number of iterations: 600,000; Thinning interval: 10.

Table 19: Posterior probabilities of elafibranor having greater mean reduction in PBC-40 Itch from baseline than each of the comparators using the earliest reported data after commencement of treatment (2-4 weeks; random effects model)

Comparisons	Posterior probabilities
Elafibranor 80 mg vs placebo	
Elafibranor 80 mg vs OCA 5-10 mg	
Elafibranor 80 mg vs OCA 10 mg	

Abbreviations: mg – milligram; OCA – obeticholic acid

B.2.9.1.8 Odds of occurrence of pruritus TEAE of any severity within 12 months

Results in Figure 37 show that patients treated with elafibranor 80 mg had lower odds of occurrence of pruritus TEAE of any severity when compared to placebo, OCA 5-10 mg and OCA 10 mg (median OR [95% CrI]: [,], [,] and [,], respectively). The odds of pruritus TEAEs of any severity with elafibranor 80 mg were statistically significantly lower than with OCA 10 mg, whereas statistically significant differences in the odds of pruritus TEAEs of any severity with elafibranor 80 mg compared to placebo and OCA 5-10 mg could not be concluded. Comparisons of the median ORs of pruritus TEAEs of any severity with elafibranor 80 mg relative to both placebo and OCA 5-10 mg did suggest numerical preference for elafibranor 80 mg. Posterior probabilities demonstrated that the probability that the odds of pruritus TEAEs of any severity with elafibranor 80 mg was lower than placebo, OCA 5-10 mg and OCA 10 mg (and and , respectively [Table 20]).

The between-study standard deviation ($\tau =$ [redacted]) indicated a moderate level of heterogeneity among the effects observed in the analyses, which suggested that the relative treatment effects were mostly consistent across the studies considered. Additionally, the total residual difference ([redacted]) indicated that the predicated values did not deviate far from actual values to a great extent. The sample sizes for the ELATIVE trial were 108 and 53 for the elafibranor and placebo groups, respectively. In the POISE trial, sample sizes were 73, 70 and 73 for the placebo, OCA 5-10 mg, and OCA 10 mg groups, respectively.

Figure 37: Forest plot – OR of occurrence of pruritus TEAE of any severity

Abbreviations: CrI – credible interval; mg – milligram; OCA – obeticholic acid
Analysis details: Burn-in: 400,000; Number of iterations: 500,000; Thinning interval: 10.

Table 20: Posterior probabilities of elafibranor having lower odds of occurrence of pruritus TEAE of any severity than each of the comparators (random effects model)

Comparisons	Posterior probabilities
Elafibranor 80 mg vs placebo	[redacted]
Elafibranor 80 mg vs OCA 5-10 mg	[redacted]
Elafibranor 80 mg vs OCA 10 mg	[redacted]

Abbreviations: mg – milligram; OCA – obeticholic acid

B.2.9.1.9 Odds of discontinuation due to pruritus within 12 months

Results in Figure 38 show that patients treated with elafibranor 80 mg had lower odds of discontinuation of treatment due to pruritus when compared to placebo, OCA 5-10 mg and OCA 10 mg (median OR [95% CrI]: [redacted] [redacted], [redacted], [redacted] [redacted], [redacted] and [redacted] [redacted], [redacted], respectively). Statistically significant differences in the odds of discontinuation due to pruritus with elafibranor 80 mg compared to placebo, OCA

5-10 mg and OCA 10 mg could not be concluded. Comparisons of the median ORs of discontinuation due to pruritus with elafibranor 80 mg relative to both placebo, OCA 5-10 mg and OCA 10 mg did suggest numerical preference for elafibranor 80 mg. Posterior probabilities demonstrated that the probability the odds of discontinuation due to pruritus TEAEs with elafibranor 80 mg was lower than placebo, OCA 5-10 mg and OCA 10 mg ([redacted], [redacted] and [redacted], respectively [Table 21]).

The between-study standard deviation ($\tau =$[redacted]) indicated a moderate level of heterogeneity among the effects observed in the analyses, which suggested that the relative treatment effects were mostly consistent across the studies considered. Additionally, the total residual difference ([redacted]) indicated that the predicated values did not deviate far from actual values to a great extent. The sample sizes for the ELATIVE trial were 108 and 53 for the elafibranor and placebo groups, respectively. In the POISE trial, sample sizes were 73 (74 when including a continuity correction due to zero events), 70 and 73 for the placebo, OCA 5-10 mg, and OCA 10 mg groups, respectively.

Figure 38: Forest plot – OR of discontinuation due to pruritus

Abbreviations: CrI – credible interval; mg – milligram; OCA – obeticholic acid
Analysis details: Burn-in: 700,000; Number of iterations: 800,000; Thinning interval: 30.

Table 21: Posterior probabilities of elafibranor having lower odds of discontinuation due to pruritus (random effects model)

Comparisons	Posterior probabilities
Elafibranor 80 mg vs placebo	[redacted]
Elafibranor 80 mg vs OCA 5-10 mg	[redacted]
Elafibranor 80 mg vs OCA 10 mg	[redacted]

Abbreviations: mg – milligram; OCA – obeticholic acid

B.2.9.1.10 Odds of discontinuation (all-cause) within 12 months

Results in Figure 39 show that patients treated with elafibranor 80 mg had lower odds of discontinuation of treatment due to any reason when compared to OCA 5-10 mg and OCA 10 mg (median OR [95% CrI]: [redacted] [redacted] and [redacted] respectively). When compared to placebo, results showed that patients treated with elafibranor 80 mg displayed almost identical odds of discontinuation of treatment due to all-cause events (median OR [95% CrI]: [redacted]). Statistically significant differences in the odds of discontinuation due to all-cause events with elafibranor 80 mg compared to placebo, OCA 5-10 mg and OCA 10 mg could not be concluded. However, comparisons of the median ORs of discontinuation due to all-cause events with elafibranor 80 mg relative to both OCA 5-10 mg and OCA 10 mg did indicate a numerical preference for elafibranor 80 mg. Posterior probabilities demonstrated that the probability the odds of discontinuation due to all-cause events with elafibranor 80 mg was lower than OCA 5-10 mg and OCA 10 mg ([redacted] and [redacted], respectively [Table 22]).

The between-study standard deviation ($\tau =$[redacted]) indicated a moderate level of heterogeneity among the effects observed in the analyses, which suggested that the relative treatment effects were mostly consistent across the studies considered. Additionally, the total residual difference ([redacted]) indicated that the predicated values did not deviate far from actual values to a great extent. The sample sizes for the ELATIVE trial were 108 and 53 for the elafibranor and placebo groups, respectively. In the POISE trial, sample sizes were 73, 71 and 73 for the placebo, OCA 5-10 mg, and OCA 10 mg groups, respectively.

Figure 39: Forest plot – OR of discontinuation all-cause

Abbreviations: CrI – credible interval; mg – milligram; OCA – obeticholic acid
Analysis details: Burn-in: 350,000; Number of iterations: 100,000; Thinning interval: 30.

Table 22: Posterior probabilities of elafibranor having lower odds of discontinuation all-cause (random effects model)

Comparisons	Posterior probabilities
Elafibranor 80 mg vs placebo	[redacted]

Elafibranor 80 mg vs OCA 5-10 mg	[redacted]
Elafibranor 80 mg vs OCA 10 mg	[redacted]

Abbreviations: mg – milligram; OCA – obeticholic acid

B.2.9.1.11 Mean change in HDL-cholesterol from baseline at 12 months

Results in Figure 40 show that patients treated with elafibranor 80 mg had a greater increase in HDL-cholesterol levels from baseline when compared to placebo, OCA 5-10 mg and OCA 10 mg (median difference in mean change from baseline [95% CrI]: [redacted] [redacted], [redacted] [redacted], [redacted] and [redacted] [redacted], respectively). The difference in the change from baseline in HDL-cholesterol with elafibranor 80 mg was statistically significantly greater than OCA 5-10 mg. Posterior probabilities demonstrated that the probability that change from baseline in HDL-cholesterol with elafibranor 80 mg was greater than placebo, OCA 5-10 mg and OCA 10 mg ([redacted], [redacted] and [redacted], respectively [Table 23]).

After adjusting the between-study standard deviation (τ=[redacted]) to the standardised mean difference scale (i.e., dividing τ by the SD seen for the outcome in ELATIVE), the between-study SD on the standardised mean difference scale (τ_{SMD} = [redacted]) indicated a moderate level of heterogeneity among the effects observed in the analyses, which suggested that the relative treatment effects were mostly consistent across the studies considered. Additionally, the total residual difference ([redacted]) indicated that there was a moderate difference between the difference in change from baseline of ALP estimated via the NMA compared to the values observed in the trials. The sample sizes for the ELATIVE trial were 94 and 47 for the elafibranor and placebo groups, respectively. In the POISE trial, sample sizes were 73, 70 and 73 for the placebo, OCA 5-10 mg, and OCA 10 mg groups, respectively.

Figure 40: Forest plot – Median difference in mean change in HDL-cholesterol from baseline at 12 months


[redacted]

Abbreviations: CrI – credible interval; mg – milligram; OCA – obeticholic acid
Analysis details: Burn-in: 250,000; Number of iterations: 350,000; Thinning interval: 10.

Table 23: Posterior probabilities of elafibranor having greater mean change in HDL-cholesterol from baseline at 12 months (random effects model)

Comparisons	Posterior probabilities
Elafibranor 80 mg vs placebo	[redacted]
Elafibranor 80 mg vs OCA 5-10 mg	[redacted]
Elafibranor 80 mg vs OCA 10 mg	[redacted]

Abbreviations: mg – milligram; OCA – obeticholic acid

B.2.9.2 Uncertainties in the indirect treatment comparisons

When evaluating baseline characteristics of patients during the feasibility assessment, the distribution of patients in POISE and ELATIVE was considered to be sufficiently similar when both intra- and inter-study comparisons were made.[2,4] Both studies reported ALP levels at baseline, and age at diagnosis and were confirmed to be sufficiently similar across both studies. The proportion of female patients across both ELATIVE and POISE were also similar reporting values of 95.7% and 90.7% respectively. The ULN of ALP definitions differed between studies with ELATIVE using a lower ULN value for females than POISE. The lower threshold for ULN of females in ELATIVE would require patients to have greater reductions in ALP before they would meet response criteria than if they were in POISE. Consequently, participants in the POISE trial might find it comparatively easier to achieve a response to OCA than participants receiving elafibranor in the ELATIVE trial. Additionally, in POISE 29.0% of patients had ALP > x3 ULN at baseline, whilst in ELATIVE 39.1% of patients had ALP > x3 ULN at baseline.[50,112] This suggests that while the average ALP values at baseline are consistent across ELATIVE and POISE, there is a greater proportion of patients in ELATIVE that have a more severe state of illness which also reduces their likelihood of achieving cholestasis response. As a result, the relative probability of achieving cholestasis response with OCA compared to elafibranor may be exaggerated.

Patients with TB < ULN are more likely to meet the criteria of achieving cholestasis response than those with TB > ULN. Overall, both the POISE and ELATIVE trials had a similar proportion of patients with TB < ULN (91.7% and 96.3%, respectively).[2,4] Despite the slight difference, patient baseline characteristics of both ELATIVE and POISE trials were deemed to be homogeneous and comparable by clinical experts.

At the time of the feasibility assessment, it was not possible to compare rates of cirrhosis at baseline between trials as limited ELATIVE baseline characteristics were available. Since final analysis of the DB period of ELATIVE is now complete, a comparison with POISE can be made. In ELATIVE, mean liver stiffness at baseline was 9.9 kPa and 10.7 kPa for the elafibranor 80 mg and placebo arms, respectively. In POISE, liver stiffness at baseline was reported to be 12.7 kPa, 10.7 kPa and 11.4 kPa for placebo, OCA 5-10 mg and OCA 10 mg, respectively, demonstrating a higher range. This was also reflected by a greater proportion of patients with liver stiffness ≥16.9 kPa in POISE compared to ELATIVE (range of 17.9% to 20.0% and [redacted] to [redacted], respectively). As such, there are more patients with cirrhosis in POISE than ELATIVE although liver stiffness data were missing for 46.6%, 50.0% and 56.1% of placebo, OCA 5-10 mg and OCA 10 mg patients, respectively, compared to <5% in the ELATIVE trial. Cirrhosis is associated with the later stages of PBC, and is a prognostic factor of disease severity.[70] Since the patient population of POISE demonstrated a higher rate of cirrhosis than that of ELATIVE, this could be indicative of a generally less healthy population. This heterogeneity between-study populations is a limitation of the analysis and may introduce uncertainty into the results of the ITC. It is worth noting, however, that upon clinical validation, the baseline values for liver stiffness for patients in both ELATIVE and POISE can be considered equivalent.[117] Differences observed between the two patient populations, as well as treatment arms, is within the margin of error of liver stiffness tests and so should not be considered meaningful.[117]

Over a 52-week period, no patients in the placebo arms of the ELATIVE and POISE trials achieved ALP normalisation.[2,4] The zero-value events can lead to mathematical problems in

the calculation of ratios, leading to OR and variance estimates of infinite values. However, to handle the zero event rate for placebo, in line with recommendations from NICE DSU TSD 2, a continuity correction was applied.[118] These corrections were carried out by adding 1 to the number of patients in the given arm for which a zero-value event occurred, and by adding 0.5 to the frequency of the given event. This, however, does generates bias in the estimates of effect size as the event frequency has been artificially increased and, as such, the difference between treatment arms will differ from uncorrected results.[118] Therefore, the variability in the estimate of the OR of ALP normalisation with elafibranor 80 mg compared to OCA 5-10 mg is likely overestimated to a degree.

For outcomes assessing mean change in pruritus from baseline, several considerations must be made. Presence of pruritus at baseline was reported in POISE.[2] A similar definition of pruritus was not reported in ELATIVE and so comparisons of the presence of pruritus at baseline could not be assessed between the two studies. ELATIVE did, however, report the number of patients at baseline who recorded a PBC WI-NRS score of ≥ 4 threshold which was used to define the number of patients with moderate-to-severe pruritus.[4] The elafibranor and placebo arms had 40.7% and 41.5% of patients with a score of ≥ 4, respectively. Conversely, in POISE, 15.3% of patients were reported to have moderate pruritus at baseline and only 1.4% were reported to have severe pruritus at baseline, though the definition to ascertain pruritus at baseline was different.[50] While rates of moderate-to-severe pruritus are lower in the POISE patient population than in the ELATIVE population, comparisons of the baseline values are uncertain due to the varying definitions used by each trial. Whilst this is a limitation of the NMA, all other aspects of the patient populations were deemed similar by clinical experts and therefore it was considered suitable for an NMA to be the ITC methodology of choice. Homogeneity across other baseline characteristics suggests that the patient populations are very similar. It could therefore be assumed that any heterogeneity that may be present when assessing baseline pruritus would be small. Additionally, it is worth noting that the analysis of change from baseline reduces the effect of baseline pruritus when compared to analysis of pruritus directly.

To capture the acute effect of pruritus, analysis was conducted on data from the earliest timepoint available for both POISE and ELATIVE. For POISE this was 2 weeks, whereas for ELATIVE this was 4 weeks.[2,112] The use of data from varying timepoints does introduce a high level of uncertainty within the results and should be considered when interpreting results.

Finally, when considering the validity of the NMA methodology, the small sample size of studies (n=2) meant that study population heterogeneity could not be accounted for, and the homogeneity of the populations had to be assumed. Moreover, because of the small network and small patient sample sizes, point estimates resulted in wide confidence and credible intervals, leading to a greater level of uncertainty in the relative treatment effects. Based on the limitations of the data available and potential unobserved biases, all results of the ITC comparing elafibranor with OCA should be considered conservative.

B.2.10 Safety, tolerability, and adverse reactions

B.2.10.1 Overview of TEAEs

Similar percentages of patients in the two groups had AEs, AEs considered to be related to the trial regimen, severe or serious adverse events (SAEs), or AEs leading to discontinuation

of elafibranor or placebo. The frequency of AEs occurring in more than 10% of patients, and more frequently in patients receiving elafibranor than in those receiving placebo, were predominantly gastrointestinal in nature, including abdominal pain, diarrhoea, nausea, and vomiting (Table 24).

Table 24: Summary of AEs and AEs Occurring in More than 10% of Patients in Either Group

Event	Elafibranor (N=108), n (%)	Placebo (N=53), n (%)
Any AEs that emerged during treatment period*	104 (96.3)	48 (90.6)
Covid-19	31 (28.7)	20 (37.7)
Pruritus	22 (20.4)	14 (26.4)
Abnormal weight gain	21 (19.4)	10 (18.9)
Abdominal pain, including upper and lower abdomen	12 (11.1)	3 (5.7)
Diarrhoea	12 (11.1)	5 (9.4)
Nausea	12 (11.1)	3 (5.7)
Urinary tract infection	12 (11.1)	10 (18.9)
Vomiting	12 (11.1)	1 (1.9)
Fatigue	10 (9.3)	7 (13.2)
Headache	9 (8.3)	6 (11.3)
Back pain	4 (3.7)	6 (11.3)
Any severe AEs†	12 (11.1)	6 (11.3)
Any AEs attributed to the trial regimen that emerged during treatment period‡	42 (38.9)	21 (39.6)
Any SAE that emerged during treatment period§	11 (10.2)	7 (13.2)
Any AEs leading to discontinuation of the trial regimen that emerged during treatment period	11 (10.2)	5 (9.4)
Any fatal AE	2 (1.9)	0 (0.0)

Abbreviations: AE – adverse event; SAE – serious adverse event
* AEs that emerged during the treatment period were defined as any adverse event with an onset on or after the date of the first administration of elafibranor or placebo and up to the date of the last DB data collection for patients who completed the DB period and continued in the long-term extension period, and up to 30 days after the date of the last dose of elafibranor or placebo was received among the patients who discontinued the trial regimen during the DB period; or any event with a start date before the first dose of elafibranor or placebo was administered for which the severity worsened in intensity on or after the date of the first dose and up to the date of the last DB data collection among patients who completed the DB period and continued in the long-term extension period, and up to 30 days after the date of the last dose of elafibranor or placebo was received among the patients who discontinued their trial regimen during the DB period.
† Severe AEs were defined as AEs that caused an interruption in normal activities of daily living and generally required systemic drug therapy or other treatment; these AEs were usually incapacitating.
‡ AEs attributed to the trial regimen that emerged during the treatment period included any AEs that were determined by the investigator to be “possibly related” or “related” to elafibranor or placebo, or in cases for which relatedness to the trial regimen was either not assessable or missing.
§ SAEs that emerged during the treatment period were defined as any untoward medical occurrence that at any dose resulted in death, was life-threatening, required inpatient hospitalisation or prolongation of existing hospitalisation, resulted in persistent or significant disability or incapacity, or was determined to be a congenital anomaly or birth defect.
Source: Kowdley *et al.* (2023)[4]

Most AEs were of mild or moderate intensity, and no patients receiving elafibranor had severe pruritus. All AEs occurring 1% more frequently in patients receiving elafibranor than in those receiving placebo and all SAEs are shown in Table 25 and Table 26, respectively.

Table 25: Summary of TEAEs* occurring >1% more frequently in the elafibranor group versus placebo System Organ Class Preferred Term

System Organ Class Preferred Term	Elafibranor (N=108), n (%)	Placebo (N=53), n (%)
Infections and infestations	68 (63.0)	31 (58.5)
Upper respiratory tract infection	7 (6.5)	2 (3.8)
Sinusitis	5 (4.6)	2 (3.8)
Gastroenteritis	4 (3.7)	1 (1.9)
Nasopharyngitis	4 (3.7)	1 (1.9)
Influenza	4 (3.7)	1 (1.9)
Herpes zoster	3 (2.8)	0 (0.0)
Bacteriuria	3 (2.8)	0 (0.0)
Pneumonia	3 (2.8)	0 (0.0)
Acarodermatitis	2 (1.9)	0 (0.0)
Acute sinusitis	2 (1.9)	0 (0.0)
Wound infection	2 (1.9)	0 (0.0)
Gastrointestinal disorders	55 (50.9)	16 (30.2)
Diarrhoea	12 (11.1)	5 (9.4)
Nausea	12 (11.1)	3 (5.7)
Vomiting	12 (11.1)	1 (1.9)
Abdominal pain (including upper and lower abdomen)	12 (11.1)	3 (5.7)
Constipation	9 (8.3)	1 (1.9)
Gastroesophageal reflux disease	7 (6.5)	1 (1.9)
Dry mouth	5 (4.6)	1 (1.9)
Abdominal distension	3 (2.8)	0 (0.0)
Flatulence	3 (2.8)	0 (0.0)
Faeces pale	2 (1.9)	0 (0.0)
Abnormal faeces	2 (1.9)	0 (0.0)
Gastritis	2 (1.9)	0 (0.0)
Musculoskeletal and connective tissue disorders	34 (31.5)	17 (32.1)
Arthralgia	9 (8.3)	2 (3.8)
Osteoporosis	5 (4.6)	1 (1.9)
Myalgia	3 (2.8)	0 (0.0)
Osteoarthritis	3 (2.8)	0 (0.0)
Fibromyalgia	2 (1.9)	0 (0.0)
Tendon disorder	2 (1.9)	0 (0.0)
Skin and subcutaneous tissue disorders	33 (30.6)	20 (37.7)
Hyperhidrosis	3 (2.8)	0 (0.0)
Metabolism and nutrition disorders	33 (30.6)	12 (22.6)
Abnormal loss of weight	5 (4.6)	0 (0.0)
Iron deficiency	3 (2.8)	0 (0.0)
Hypomagnesemia	2 (1.9)	0 (0.0)
Investigations	29 (26.9)	9 (17.0)
Blood creatine phosphokinase increased	4 (3.7)	0 (0.0)

System Organ Class Preferred Term	Elafibranor (N=108), n (%)	Placebo (N=53), n (%)
Weight increased	4 (3.7)	1 (1.9)
C-reactive protein increased	2 (1.9)	0 (0.0)
Glomerular filtration rate decreased	2 (1.9)	0 (0.0)
White blood cell count decreased	2 (1.9)	0 (0.0)
General disorders and administration site conditions	26 (24.1)	13 (24.5)
Influenza-like illness	4 (3.7)	1 (1.9)
Malaise	2 (1.9)	0 (0.0)
Pyrexia	2 (1.9)	0 (0.0)
Nervous system disorders	24 (22.2)	15 (28.3)
Dizziness	4 (3.7)	1 (1.9)
Sciatica	2 (1.9)	0 (0.0)
Injury, poisoning, and procedural complications	21 (19.4)	9 (17.0)
Ligament sprain	3 (2.8)	0 (0.0)
Hip fracture	2 (1.9)	0 (0.0)
Wrist fracture	2 (1.9)	0 (0.0)
Respiratory, thoracic, and mediastinal disorders	14 (13.0)	6 (11.3)
Oropharyngeal pain	4 (3.7)	0 (0.0)
Rhinorrhoea	2 (1.9)	0 (0.0)
Renal and urinary disorders	12 (11.1)	1 (1.9)
Dysuria	2 (1.9)	0 (0.0)
Pollakiuria	2 (1.9)	0 (0.0)
Urine odour abnormal	2 (1.9)	0 (0.0)
Blood and lymphatic system disorders	8 (7.4)	3 (5.7)
Neutropenia	2 (1.9)	0 (0.0)
Hepatobiliary disorders	8 (7.4)	1 (1.9)
Cholelithiasis	3 (2.8)	0 (0.0)
Vascular disorders	8 (7.4)	3 (5.7)
Hot flush	2 (1.9)	0 (0.0)
Ear and labyrinth disorders	6 (5.6)	2 (3.8)
Cerumen impaction	2 (1.9)	0 (0.0)
Tinnitus	2 (1.9)	0 (0.0)

*Treatment-emergent was defined as any AEs with onset on or after the date of first administration of study treatment and up to the date of the last DB data collection for patients who completed the DB period and continued in the long-term extension, and up to 30 days after the date of the last study treatment for the patients that discontinued the study treatment during DB period; or any event with start date prior to first dose of treatment whose severity worsened in intensity on or after the date of first dose of study treatment and up to the date of the last DB data collection for patients who completed the DB period and continued in the long-term extension, and up to 30 days after the date of the last study treatment for the patients that discontinued the study treatment during DB period.
†If a patient had more than one event in a given category, the patient was counted only once in that category.
Source: Kowdley *et al.* (2023)[4]

Table 26: Summary of all serious TEAEs*

Preferred Term	Elafibranor (N=108), n (%)	Placebo (N=53), n (%)

Acute kidney injury	3 (2.8)	1 (1.9)
Hip fracture	2 (1.9)	0 (0.0)
Abdominal hernia	1 (0.9)	0 (0.0)
Appendicitis	1 (0.9)	0 (0.0)
Ascites	1 (0.9)	0 (0.0)
Asthma	1 (0.9)	0 (0.0)
Biliary sepsis	1 (0.9)	0 (0.0)
Blood bilirubin increased	1 (0.9)	0 (0.0)
Cardiac arrest	1 (0.9)	0 (0.0)
Cardiac failure	1 (0.9)	0 (0.0)
Cholecystitis acute	1 (0.9)	0 (0.0)
Crohn's disease	1 (0.9)	0 (0.0)
Oedema peripheral	1 (0.9)	0 (0.0)
Haemorrhagic stroke	1 (0.9)	0 (0.0)
Hypervolemia	1 (0.9)	0 (0.0)
Multiple fractures	1 (0.9)	0 (0.0)
Multiple organ dysfunction syndrome	1 (0.9)	0 (0.0)
Osteonecrosis	1 (0.9)	0 (0.0)
Parkinsonism	1 (0.9)	0 (0.0)
Pneumonia	1 (0.9)	0 (0.0)
Pulmonary embolism	1 (0.9)	0 (0.0)
Pulseless electrical activity	1 (0.9)	0 (0.0)
Rhabdomyolysis	1 (0.9)	0 (0.0)
Retroperitoneal hematoma	1 (0.9)	0 (0.0)
Sudden hearing loss	1 (0.9)	0 (0.0)
Tremor	1 (0.9)	0 (0.0)
Anxiety	0 (0)	1 (1.9)
Cataract	0 (0)	1 (1.9)
COVID-19	0 (0)	1 (1.9)
Invasive ductal breasts carcinoma	0 (0)	1 (1.9)
Pain	0 (0)	1 (1.9)
Papillary thyroid cancer	0 (0)	1 (1.9)
Procedural pain	0 (0)	1 (1.9)
Syncope	0 (0)	1 (1.9)
Urinary tract infection	0 (0)	1 (1.9)

Abbreviations: TEAE – treatment-emergent adverse event
*Defined as any untoward medical occurrence that at any dose resulted in death, was life-threatening, required inpatient hospitalisation or prolongation of existing hospitalisation, resulted in persistent or significant disability/incapacity, or was a congenital anomaly/birth defect.
†If a patient had more than one event in a given category, the patient was counted only once in that category.
Source: Kowdley *et al.* (2023)[4]

Elevated creatine phosphokinase (CPK) levels and muscle injury were more common in patients receiving elafibranor than in those receiving placebo. Elevated levels of CPK (>5 times the ULN with or without associated symptoms, or >3 times the ULN in the presence of associated symptoms) led to permanent discontinuation of the trial regimen (in accordance with protocol requirements) in four patients (3.7%) in the elafibranor group, as compared with no patients in the placebo group. Among the four patients who discontinued treatment with

elafibranor, two were receiving concomitant statin therapy, one had coexisting chronic kidney disease, and one had coexisting autoimmune thyroiditis. The elevations were associated with myalgia in two patients. An additional patient who had advanced cirrhosis and was receiving elafibranor and concomitant atorvastatin at a dose of 40 mg once daily had a serious case of rhabdomyolysis. One patient in the elafibranor group (0.9%) and two patients in the placebo group (3.8%) had elevated levels of aminotransferases (>3 times the baseline value if baseline was elevated or >3 times or 5 times the ULN if the baseline value was normal) or bilirubin (>2 times the ULN), or both, that met the protocol-defined thresholds for consideration of potential drug-induced liver injury and for report to the clinical events committee. The event in the elafibranor group was adjudicated as a possible drug-induced liver injury, and the events in the placebo group were adjudicated as probable drug-induced liver injuries. Elevated levels of aminotransferases led to permanent discontinuation in accordance with protocol requirements in two patients (one in each group). All cases of elevated aminotransferases levels were reversible, and the levels returned to or trended toward baseline levels after discontinuation of the trial regimen.[4] Table 27 shows the results of a customised group of MedDRA queries for preferred terms related to hepatic injury.

Table 27: Customised MedDRA query search for Preferred Terms related to hepatic injury

Custom Hepatic Query Preferred Term	Elafibranor 80 mg N=108, n (%)	Placebo N=53, n (%)
Hepatic injury	8 (7.4)	5 (9.4)
Blood bilirubin increased	3 (2.8)	1 (1.9)
Alanine aminotransferase increased	1 (0.9)	1 (1.9)
Ascites	1 (0.9)	1 (1.9)
Aspartate aminotransferase increased	1 (0.9)	0 (0.0)
Hepatic failure	1 (0.9)	0 (0.0)
Liver function test increased	1 (0.9)	0 (0.0)
Liver scan abnormal	1 (0.9)	1 (1.9)
Model for end-stage liver disease score abnormal	1 (0.9)	0 (0.0)
Model for end-stage liver disease score increased	1 (0.9)	0 (0.0)
Portal hypertension	1 (0.9)	0 (0.0)
Hepatomegaly	0 (0.0)	1 (1.9)
Transaminase increased	0 (0.0)	1 (1.9)
Varices oesophageal	0 (0.0)	1 (1.9)

Abbreviations: mg – milligram
Source: Kowdley *et al.* (2023)[4]

The mean change from baseline through Week 52 in the serum creatinine level was −0.01 (SD: ±8.0) µmol per litre in patients receiving elafibranor and −0.7 (SD: ±7.6) µmol per litre in those receiving placebo. Increases in serum creatinine levels of 25% above baseline values were observed in 11 patients receiving elafibranor (10.2%) and in 4 patients receiving placebo (7.5%); these increases were not associated with corresponding changes in cystatin C or estimated glomerular filtration rate, which was calculated with the use of the Chronic Kidney Disease Epidemiology Collaboration cystatin C formula. Acute kidney injury was reported in 3 patients receiving elafibranor (2.8%) and in 1 receiving placebo (1.9%). Fatal AEs occurred in 2 patients receiving elafibranor (1.9%); 1 patient died from postoperative complications after elective surgery for an abdominal hernia repair, and 1 patient who had end-stage liver disease

died from biliary sepsis and acute kidney injury. Neither event was considered by the investigators or an independent clinical events committee to be related to treatment.[4]

In summary, the safety profile of elafibranor in this trial was consistent with that observed in the wider clinical development program, in approximately 2,500 patients with chronic liver diseases have received elafibranor.[5, 7,119] Four patients discontinued treatment with elafibranor because of increased creatine phosphokinase levels. Pharmacokinetic exposure to atorvastatin is 11 times as high in patients with Child-Pugh class B liver cirrhosis as in those with less advanced cirrhosis,[120] which increases the risk of rhabdomyolysis associated with statin exposure,[121] as was observed in 1 patient with cirrhosis who received elafibranor and concomitant atorvastatin with no dose adjustments made on the basis of hepatic function.[122] No clinically meaningful changes in renal function were observed.

B.2.10.2 TEAEs leading to discontinuation

Eleven (10.2%) patients in the elafibranor group and 5 (9.4%) patients in the placebo group experienced TEAEs that led to treatment discontinuation.[4]

B.2.11 Ongoing studies

There is an ongoing long-term extension (LTE) of ELATIVE. It is an OLE and is expected to be completed in December of 2028, evaluating the same outcome as ELATIVE (the efficacy and safety of elafibranor 80 mg in patients with PBC with inadequate response or intolerance to ursodeoxycholic acid). The study design of ELATIVE and the associated OLE is presented in Figure 16 in section B.2.2.[4]

There is also a long-term, Phase III, randomised, double-blind, placebo-controlled study currently ongoing to evaluate the efficacy and safety of elafibranor on long-term clinical outcomes in adult patients with PBC. The trial is known as ELFIDENCE and consists of two treatment arms, elafibranor 80 mg and placebo. Details of ELFIDENCE are presented below in **Error! Reference source not found.**.[123]

Table 28: Details of the ongoing ELFIDENCE trial[123]

Title	A Long-Term Study of Elafibranor in Adult Participants with Primary Biliary Cholangitis (ELFIDENCE).
Trial numbers/identifier	NCT06016842
Trial design	A Phase III Randomised, Parallel-Group, Double-Blind, Placebo-Controlled, Two-Arm Study to Evaluate the Efficacy and Safety of Elafibranor 80 mg on Long-Term Clinical Outcomes in Adult Participants with PBC.
Location	United States
Estimated enrolment	450
Duration	Each participant will be in the study up to about 7 years.
Interventions	Elafibranor 80 mg
Primary outcome measures	Event-free survival [Time Frame: From baseline until 4 weeks after the end of treatment (maximum duration of 7 years)]. Event-free survival is defined as the time from start of treatment to either adjudicated disease progression or death, whichever occurs first.

Secondary outcome measures	• Percentage of participants experiencing TEAEs, treatment-related TEAEs, Serious Adverse Events (SAEs), and Adverse Events of Special Interests (AESIs). • Percentage of participants developing clinically significant changes in physical examination findings. • Percentage of participants developing clinically significant changes in vital signs. • Percentage of participants developing clinically significant changes in Electrocardiogram (ECG) readings. • Percentage of participants with clinically significant changes in laboratory parameters (blood chemistry, haematology, coagulation and urinalysis). • Change from baseline in ALP. • Change from baseline in TB. • Percentage of participants with ALP≤ 1.67x ULN and TB≤ ULN. • Percentage of participants with complete biochemical response. • Percentage of participants with normalisation of TB and ALP. • Percentage of participants with stabilisation in TB (i.e. no increase). • Percentage of participants with a response based on albumin normalisation. • Change from baseline in liver stiffness measurement. • Change from baseline in PBC risk scores based in Global-PBC Study Group (GLOBE) score. • Change from baseline in PBC risk scores based on United Kingdom (UK)-PBC score. • Percentage of participants with LSM ≥15 kPa. • Change in serum levels of Aspartate aminotransferase (AST), ALT and GGT compared to the baseline. • Change from baseline in hepatic function: Conjugated bilirubin, international normalised ratio (INR) and fractionated ALP. • Change in serum levels of Albumin compared to the baseline. • Percentage of participants with no worsening of LSM. • Percentage of participants with ALP reduction of 40%. • Percentage of participants with ALP <1.5x ULN, ALP decrease ≥15% and TB ≤ULN. • Percentage of participants with ALP <1.5x ULN, ALP decrease ≥40% and TB ≤ULN. • Percentage of participants with ALP <1.67x ULN, ALP decrease ≥15% and TB ≤ULN. • Percentage of participants with ALP <3x ULN, AST <2x ULN and TB ≤1 mg/dL (Paris-I). • Percentage of participants with ALP ≤1.5x ULN, AST ≤1.5x ULN and TB ≤1 mg/dL (Paris-II criteria). • Percentage of participants with normalisation of abnormal TB. • Percentage of participants with normalisation of abnormal TB and albumin (Rotterdam criteria). • Percentage of participants with reduction in TB to ≤0.6x ULN in participants with TB >0.6x ULN at baseline. • Change from baseline in lipid parameters.

	• Percentage of participants with a response in PBC Worst Itch NRS score. • Percentage of participants with a response in PBC Worst Itch NRS. • Change from baseline in pruritus (5D-Itch scale, PBC-40 score and PBC Worst Itch Numeric Rating Scale). • Change from baseline inpatient Reported Outcome Measurement Information System (PROMIS) Fatigue Short Form 7a. • Change from baseline in the Epworth Sleepiness Scale. • Change from baseline in EuroQol 5-dimensional 5-level questionnaire (EQ-5D-5L).
Key eligibility criteria	• Male or female participants must be ≥18 years of age at the time of signing the informed consent. • Participants with a definite or probable diagnosis of PBC. • Participants taking ursodeoxycholic acid (UDCA) for at least 12 months (at a stable dose for ≥3 months) prior to screening period and expected to remain on stable dose during the study, or unable to tolerate UDCA treatment (no UDCA for ≥3 months) prior to screening period (per country standard-of-care dosing). • Participants taking medications for management of pruritus (e.g. cholestyramine, rifampin, naltrexone, sertraline or colchicine) must be on a stable dose for ≥3 months prior to screening period. • Contraceptive use by men or women should be consistent with local regulations regarding the methods of contraception for those participating in clinical studies. • Capable of giving signed informed consent which includes compliance with the requirements and restrictions listed in the informed consent form and in this protocol.

Key exclusion criteria	• History or presence of other concomitant liver disease, including HBV, HCV, AIH, PSC, ALD, NASH, Gilbert's syndrome or alpha-1-antitrypsin deficiency
	• History of:
	  ○ Liver transplant, or current placement on liver transplant list
	  ○ MELD-Na score ≥12
	  ○ Signs and symptoms of cirrhosis/portal hypertension
	  ○ Hepatorenal syndrome
	• Markers of liver damage, such as:
	  ○ ALT and/or AST >5 x ULN
	  ○ Platelet count <75 x 10^3/μL
	  ○ Known pregnancy or lactating (female patients)
	• Prohibited medications:
	  ○ 3 months prior to screening period: fibrates, seladelpar, glitazones, OCA, azathioprine, cyclosporine, methotrexate, mycophenolate, pentoxifylline, budesonide and other systemic corticosteroids (parenteral and oral chronic administration only); potentially hepatotoxic drugs (including α-methyl-dopa, sodium valproic acid, isoniazid or nitrofurantoin).

Abbreviations: AE – adverse event; AESIs – adverse events of special interests; AIH – autoimmune hepatitis; ALP – alkaline phosphatase; ALT – alanine aminotransferase; AST – aspartate aminotransferase; CT – computerised tomography; ECG – electrocardiogram; GGT – gamma-glutamyl transferase; HbcAb – hepatitis B core antibody; HbsAg – hepatitis B surface antigen; HCV – hepatitis C virus; HIV – human immunodeficiency virus; INR – international normalised ratio; LLN – lower limit of normal; LSM – liver stiffness measure; MELD – model for end-stage liver disease; MRI – magnetic resonance imaging; NASH – non-alcoholic steatohepatitis; NRS – numeric rating scale; OCA – obeticholic acid; PBC – Primary Biliary Cholangitis; QTcF – QT corrected by

Fridericia's formula; RNA – ribonucleic acid; SAEs – serious adverse events; TB – total bilirubin; TEAEs – treatment-emergent adverse events; UDCA – ursodeoxycholic acid; ULN – upper limit of normal; VAS – visual analogue scale; VCTE – vibration-controlled transient elastography.
Source: ClinicalTrials.gov[123]

B.2.12 Interpretation of clinical effectiveness and safety evidence

B.2.12.1 Key findings of the clinical evidence

The ELATIVE trial is a Phase III, randomised, double-blind, placebo-controlled, multi-centre study, investigating elafibranor compared with placebo in patients with PBC and an inadequate response or intolerance to UDCA.[4] During the 52-week DB phase, patients were randomised to receive either elafibranor 80 mg (N=108) or placebo (N=53) in a 2:1 ratio. The study will include a 5-year, open-label LTE after the completion of the initial DB phase.[12]

ELATIVE met its primary outcome for cholestasis response (defined as ALP ≤1.67xULN, TB ≤ULN, and ALP reduction ≥15% at Week 52) and the first key secondary outcome (ALP normalisation). After 52 weeks, cholestasis response was observed in 50.9% (n=55/108) of patients in the elafibranor group and in 3.8% (n=2/53) of patients in the placebo group (p<0.0001). Results from the trial demonstrated rapid and sustained reductions in both ALP and TB levels for patients receiving elafibranor. Normalisation of ALP, which has been associated with improved transplantation-free survival, also occurred in a greater proportion of patients who received elafibranor than in those who received placebo (14.8% and 0% respectively, p=0.002).[4,112] Reduction in ALP was demonstrated by the first visit after treatment commencement and was sustained through to the end of the trial at Week 52. Reduction in TB levels was similar with a drop at Week 4 which was sustained through the remainder of the trial.

Pruritus affects up to 75% of patients with PBC during their disease course, and has a significant negative impact on QoL.[59,82] In the ELATIVE trial, analyses of secondary endpoints showed reductions in moderate-to-severe pruritus. Although the WI-NRS questionnaire suggested a trend towards greater pruritus improvement in patients treated with elafibranor compared to those receiving placebo, this trend did not reach statistical significance. This difference was apparent early into the trial and became greater as the trial progressed, especially from Week 24 onwards. On the other hand, when evaluating the PBC-40 questionnaire and the 5-D itch scale, elafibranor demonstrated statistically significant improvements after 52 weeks.[4,112] When considering PBC-40, an instrument specifically designed and validated for the PBC patient population, progressive improvement in pruritus was seen in the Pruritus ITT Analysis Set, with an LS mean change from baseline to Week 52 of -2.5 in the elafibranor group and -0.1 in the placebo group. The LS means difference from placebo was -2.3 (95% CI: -4.0, -0.7; nominal p=0.0070). Similarly, for 5D-Itch, in the Pruritus ITT Analysis Set, there was an LS mean change from baseline at Week 52 of -4.2 in the Y group and -1.2 in the placebo group; LS means difference from placebo was -3.0 ([95% CI: -5.5; -0.5]; nominal p=0.0199).[4,112] These findings contrast with those of OCA, which has been shown to exacerbate pruritus with treatment-emergent pruritus reported in 55.7% of patients in the OCA 5-10 mg treatment arm compared to 38.4% of patients in the placebo arm and 71.5% of OCA treated patients reporting pruritus as an AEs in the OLE of the POISE trial. Moreover, 34.3% of patients required additional intervention for pruritus management in the

OCA 5-10 mg treatment arm compared to 19.2% in the placebo arm (B.1.3.1.3).[2] In the ELATIVE trial pruritus was reported as an AEs in 20% of patients in the elafibranor arm and 26% of patients in the placebo arm.[4]

Dyslipidaemia is prevalent among patients with PBC, with an estimated >75% of patients presenting elevated cholesterol levels.[36,124] In patients treated with elafibranor, reduced levels of triglycerides and VLDL-cholesterol and stable levels of LDL-cholesterol and HDL-cholesterol were observed. A statistically significantly greater decrease was seen in TG and VLDL-cholesterol for patients treated with elafibranor compared to those who received placebo ($p<0.001$). In contrast, among patients treated with OCA, increases in the levels of total cholesterol and LDL-cholesterol and decreases in the level of HDL-cholesterol have been observed.[125] This was also reflected in POISE where HDL-cholesterol levels decreased in patients treated with OCA when compared to placebo and LDL-cholesterol levels increased in patients treated with OCA when compared to placebo.[2]

Elafibranor was generally well tolerated in the ELATIVE trial, with 85.7% of patients continuing in the 5-year OLE Most patients reported at least one TEAE during the study (96.3% treated with elafibranor 80 mg and 90.6% treated with placebo). However, TEAEs were mostly mild or moderate in intensity and assessed to be unrelated to study treatment, with only one severe TEAE reported by more than one patient in the elafibranor group (acute kidney injury, two patients). Of note, patients treated with elafibranor experienced fewer TEAEs of pruritus and fatigue compared with placebo, and none were of severe intensity. Severe AEs were reported for 12 (11.1%) patients in the elafibranor group and 6 (11.3%) patients in the placebo group. Discontinuation rates due to TEAEs were similar being 10.2% patients in the elafibranor group and 9.4% patients in the placebo group.[4]

Subgroup analyses were carried out on the primary and key secondary endpoint assessing the following groups: age, sex, race, UDCA treatment at baseline, prior OCA treatment, ALP level at baseline >3 x ULN, TB at baseline >ULN, TB at baseline >ULN or ALB at baseline <LLN, TB at baseline >0.6 x ULN, geographic region, ALP >3 x ULN or TB >ULN at baseline, PBC WI-NRS score ≥4 at baseline, cirrhosis, and advanced disease stage. The results are favourable for elafibranor compared to placebo for all subgroups analysed. Subgroup analyses demonstrated a consistent cholestatic response in favour of elafibranor compared with placebo among various subgroups, including participants with ALP >3 x ULN, TB >0.6 x ULN, advanced fibrosis, without prior OCA treatment, concurrent UDCA treatment, PBC Worst Itch NRS score ≥4, by age, and geographical region. The results of the secondary endpoint subgroup analyses demonstrated a consistent treatment effect in favour of elafibranor among various participant subgroups that were generally consistent with subgroup analyses performed on the primary endpoint.

The NMA provided favourable results for elafibranor 80 mg compared to placebo and OCA 5-10 mg for the likelihood of cholestasis response, ALP normalisation, mean change in pruritus (5-D Itch and PBC-40 Itch) from baseline at 52 weeks and 2-4 weeks, the likelihood of pruritus TEAEs of any severity, the likelihood of discontinuing due to pruritus, the likelihood of all-cause discontinuation, and change from baseline in HDL-cholesterol. The probability that elafibranor 80 mg was more effective than OCA, and less likely to lead to pruritus events, remained high across all analyses. In its entirety, the NMA demonstrated elafibranor 80 mg as an effective second-line treatment option for PBC that has a favourable profile relating to pruritus complications compared to OCA.

Overall, the positive impact of elafibranor in patients with PBC was demonstrated by the totality of the evidence in the ELATIVE trial, across multiple secondary endpoints, including biochemical markers of liver function such as ALP levels and lipid parameters, as well as pruritus symptoms and QoL measures.[4,112] Collectively, these results demonstrate that elafibranor fulfils an unmet medical need as an efficacious and well tolerated treatment in individuals with PBC who have experienced an inadequate response or intolerance to UDCA.[4,112]

B.2.12.2 Strengths and limitations of the clinical evidence base

ELATIVE was designed to evaluate the efficacy and safety of elafibranor at a dose of 80 mg once daily in participants with PBC with inadequate response or intolerance to UDCA. The demographic characteristics of the population enrolled in this study were consistent with the characteristics of the general patient population with PBC and was considered consistent with the anticipated patient population of England and Wales. This was validated by clinical experts. Most participants were female, and the mean age was 57.1 years. Most participants were receiving concurrent UDCA at baseline, consistent with treatment guideline recommendations for the dose of UDCA and the reported low incidence of patients with PBC who do not tolerate UDCA. It is important to note that response to UDCA is dependent on factors including age and disease severity with younger patients and those with a greater severity of disease less likely to respond to UDCA. As such, the benefit of UDCA treatment is often over estimated as it offers a greater benefit to patients whose disease has not progressed to a severe stage and those who are older. UDCA fails to benefit younger patients with greater disease severity to the same extent as older patients with less severe disease. This over estimation of UDCA may underestimate the relative efficacy of elafibranor especially when considering patients who have progressed to a more severe disease state.

The primary endpoint of cholestasis response for this study has been recognised as a relevant surrogate marker in PBC clinical studies and improvement in survival in patients (see section B.1.3.1.4). Normalisation of ALP, the first key secondary endpoint, has been associated with further improvement in survival in patients compared to ALP cut-offs above the ULN. As pruritus is one of the most common symptoms in patients with PBC, with an important impact on HRQoL (see section B.1.3.2.2), change in pruritus according to the PBC Worst Itch NRS score was evaluated as an additional key secondary endpoint. Two other patient reported outcome measures assessed pruritus as additional secondary endpoints: the itch domain of the PBC-40, an instrument specifically designed and validated for the PBC patient population, and the 5-D Itch total score. When assessing these outcomes *via* an NMA, results were favourable for elafibranor across multiple outcomes including cholestasis response, reduction in ALP levels from baseline, ALP normalisation, pruritus outcomes across multiple timepoints and HDL levels. Safety outcomes also demonstrated favourable results for elafibranor. Patients who were treated with elafibranor were less likely to discontinue treatment due to all-cause events compared to OCA.

Limitations of the clinical evidence base include the short duration of the ELATIVE trial, especially when considering that PBC is a long-term liver disease, and the lack of a head-to-head comparison with OCA. Complications associated with PBC progression, such as cirrhosis and liver failure, may take a long time to develop, and clinical trials of novel PBC therapies would require a prolonged follow-up period to demonstrate a reduction in these outcomes.[126] Whilst the complications surrounding liver failure and potential transplant are not

captured here, the ongoing OLE of ELATIVE as well as the 5-year ELFIDENCE trials have the potential to capture these complications in the future.

It is also worth noting the difficulty to recruit a large enough study population of patients with advanced PBC (a subgroup of an already small patient population) that would provide sufficient statistical power for a clinical trial.[51,126] The small patient population also limited the NMA leading to wide CrIs.

B.2.12.3 End of life criteria

Elafibranor does not meet the criteria for 'life-extending treatment at the end of life'.

B.3 Cost-effectiveness

B.3.1 Published cost-effectiveness studies

An SLR was conducted in November 2022, and updated in December 2023, to identify studies reporting economic evaluations associated with PBC. Eight economic evaluations studies were found and are presented in Table 29.

Of the economic evaluations identified, four are health technology assessment (HTA) appraisals of OCA and one a published manuscript assessing the cost-effectiveness of OCA.[1, 52,127–129] The four HTA appraisals all use the same model structure with a lifetime time horizon and three-monthly cycles: a Markov cohort model with health states defined according to risk of progression from PBC biomarker defined health states to liver disease.[1,127–129] The manuscript is a microsimulation model which assesses disease progression according to the Ludwig scoring system.[52]

Of the three remaining economic evaluations, one is a Markov cohort model with health states defined according to the presence or absence of liver transplant.[130] The other two evaluations do not clearly report the model structure used.[131,132]

Given that the consistency in the structure followed in the HTA appraisals,[1, 52,127–129] the model used for OCA was adapted for this appraisal.

Table 29: Summary list of published cost-effectiveness studies

Study	Year	Summary of model	Patient population (average age in years)	QALYs (intervention, comparator)	Costs (currency) (intervention, comparator)	ICER (per QALY gained)
Boberg[130]	**2013**	• Type of model and rationale: Markov model, no explicit rationale provided • Model health states: 3 health states: (1) alive without liver transplantation; (2) alive after liver transplantation; and (3) death • Intervention and comparators modelled: UDCA (intervention) vs placebo (comparator) • Time horizon and cycle lengths, plus rationale: Lifetime time horizon, with starting age set at 56 years (based on the average age of the population). Transitions are on an annual basis	UDCA-treated adult PBC patients	No QALYs were reported	*(Cost is reported in euros.)* • Cost per year for a patient on UDCA: 2,329 • Cost per year for a control patient: 1,188 • Cost of liver transplantation: 132,903 • Total lifetime costs for a patient on UDCA: 151,403 (discounted: 102,912) • Total lifetime costs for a control patient: 157,741 (discounted: 115,031) • Cost-saving for a patient on UDCA: 6,338 (discounted: 12,119) • Cost per year for a patient on UDCA: 2,329	N/A

CADTH[127]	**2017**	• Type of model and rationale: Markov state-transition model, no explicit rationale provided • Model health states: 10 health states with transitions taking place every 3 months, capturing progression. The health states were 3 PBC-specific disease states (low, moderate and high risk), decompensated cirrhosis, HCC, pre-liver transplant, liver transplant, post-liver transplant, PBC re-emergence, and excess mortality. Initial transition probabilities and natural history data were based on the POISE study. After year 1, data from the Global and UK-PBC study cohorts were used to calculate health state transitions • Interventions and comparators modelled: For UDCA-tolerant patients, UDCA + OCA (intervention) vs UDCA alone (comparator); for UDCA-intolerant patients, OCA alone (intervention) vs no treatment (comparator)	• Adult PBC patients with an inadequate response to UDCA (UDCA-tolerant) • Adult PBC patients who are unable to tolerate UDCA (UDCA-intolerant)	**Total QALYs results of the base-case analysis** • UDCA-tolerant population: – UDCA: 9.95 – OCA plus UDCA: 17.06 • UDCA-intolerant population: – No treatment: 7.72 – OCA alone: 16.94 **Total QALYs results of the manufacturer scenario analysis of OCA 10 mg vs UDCA** • UDCA-tolerant population: – UDCA: 9.95 – OCA plus UDCA: 16.72 • UDCA-intolerant population: – No treatment: 7.72 – OCA alone: 16.56	*(Cost is reported in Canadian dollars.)* **Total costs results of the base-case analysis** • UDCA-tolerant population: – UDCA: 115,452 – OCA plus UDCA: 705,334 • UDCA-intolerant population: – No treatment: 116,310 – OCA alone: 681,721 **Total costs results of the manufacturer scenario analysis of OCA 10 mg vs UDCA (Canadian Dollar)** • UDCA-tolerant population: – UDCA: 115,452 – OCA plus UDCA: 622,144 • UDCA-intolerant population: – No treatment: 116,310	**ICER result of the base-case analysis** • UDCA-tolerant population: – UDCA: - – OCA plus UDCA: 82,921 • UDCA-intolerant population: – No treatment: - – OCA alone: 61,365 **Total QALYS results of the manufacturer scenario analysis of OCA 10 mg vs UDCA** • UDCA-tolerant population: – UDCA: - – OCA plus UDCA: 74,819 • UDCA-intolerant population: – No treatment: - – OCA alone: 54,984

		• Time horizon and cycle lengths, plus rationale: Lifetime (50-year) time horizon, 3-month cycle. No explicit rationale provided			– OCA alone: 602,426	
Longworth[131]	**2003**	• Type of model and rationale: NR • Model health states: NR • Interventions and comparators modelled: Liver transplantation and absence of liver transplantation • Time horizon and cycle lengths, plus rationale: 27 months (2 years post-transplantation + 3 months spent on the transplant waiting list) • Treatment sequencing: NR	• PBC, ALD, and PSC patients aged 16 and older listed for an isolated liver transplant in six liver transplant centres in England	Mean QALYs (95% CI) – measured over 27 months from date of listing (results for PBC patients) • Observed (in patients who underwent transplantation): 1.30 (1.18–1.43) • Shadow (estimated, in absence of transplantation): 0.76 (0.65–0.91)	*(Cost is reported in British pound sterling.)* Mean cost (95% CI), GBP- measured over 27 months from date of listing, including cost of assessment (results for PBC patients) • Observed (in patients who underwent transplantation): 1.30 (1.18–1.43) • Shadow (estimated, in absence of transplantation): 0.76 (0.65–0.91)	ICER (95% CI): 28,716 (1,000–59,000)
NCPE[128]	**2017**	• Type of model and rationale: Markov state-transition model, no explicit rationale provided. • Model health states: The model included 10 health states with transitions every 3 months. 3 health states represented progression of PBC based	• Adults with an inadequate response to, or unable to tolerate UDCA	• OCA dose titration therapy (UDCA inadequate responder population): 3.096 • OCA dose titration therapy (UDCA-intolerant population): 3.9	*(Cost is reported in euros.)* • OCA dose titration therapy (UDCA inadequate responder population): 454,067 • OCA dose titration therapy (UDCA-	• OCA dose titration therapy (UDCA inadequate responder population): 146,659 • OCA dose titration therapy (UDCA-intolerant population): 108,094

		on ALP and bilirubin biomarkers, and 7 health states represented liver disease clinical outcomes which is entered once patients progress to decompensated cirrhosis or HCC. • Interventions and comparators modelled: Intervention: OCA dose titration (5 mg for the first six months of treatment, followed by 10 mg for the subsequent months). Comparator in the UDCA inadequate responder group: oral UDCA at 13 mg/kg/day to 15mg/kg/day. Comparator in the UDCA-intolerant group: placebo (no treatment). • Time horizon and cycle lengths, plus rationale: Three-month cycle length, lifetime time horizon of 50 years. No explicit rationale for this time horizon is given.			intolerant population): 108,094	
NICE[1]	**2017**	• Type of model and rationale: Markov state-transition model, no explicit rationale provided • Model health states: The model is split into two components, biomarkers	• Adult PBC patients with an inadequate response to UDCA (UDCA-tolerant)	**Total QALYs results for the UDCA-intolerant population, using the PAS price of OCA**	*(Cost is reported in British pound sterling.)* **Total costs results for the UDCA-intolerant population, using**	**ICER results for the UDCA-intolerant population, using the PAS price of OCA** • UDCA-intolerant population

		and liver disease. The biomarker part of the model had three health states: low, moderate and severe. The liver disease part of the model included significant liver disease, including decompensated cirrhosis, hepatocellular carcinoma, pre-transplant state, transplantation, re-emergence of PBC and death • Interventions and comparators modelled: • In UDCA-intolerant patients, the intervention 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) vs no treatment or fibrates as the comparator • For UDCA inadequate responders, the intervention is OCA (dose titration as per above in combination with UDCA) vs UDCA monotherapy or UDCA in combination with fibrates as the comparator	• Adult PBC patients who are unable to tolerate UDCA (UDCA-intolerant)	• UDCA-intolerant population – No treatment (placebo): 6.61 – OCA titration: 13.56 **Total QALYs results for the UDCA inadequate responder population, using the PAS price of OCA** • UDCA inadequate responder population: – No treatment (placebo): 7.85 – OCA titration: 13.68	**the PAS price of OCA** • UDCA-intolerant population – No treatment (placebo): 103,233 – OCA titration: 251,671 **Total costs results for the UDCA inadequate responder population, using the PAS price of OCA** • UDCA inadequate responder population: – No treatment (placebo): 96,977 – OCA titration: 261,791	– No treatment (placebo): - – OCA titration: 21,351 **ICER results for the UDCA inadequate responder population, using the PAS price of OCA** • UDCA inadequate responder population: – No treatment (placebo): - – OCA titration: 28,281

		• Time horizon and cycle lengths, plus rationale: Four-week cycle length used over a time horizon of 50 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.				
Pasha[132]	**1999**	• Type of model and rationale: NR • Model health states: Unclear, but major events included ascites, varices, variceal bleeds, encephalopathy, liver transplantation, and death • Interventions and comparators modelled: UDCA, placebo • Time horizon and cycle lengths, plus rationale: The time frame of the analysis was 4 years after the start of the trials; cycle length NR	• Patients with PBC from the Mayo and Canadian UDCA trials	N/A	N/A	No ICER was reported, however, UDCA was the preferable and dominant strategy, with a gain in life expectancy of 4 years of 0.18 (i.e. treating 100 PBC patients with UDCA for 4 years would result in a gain of 18 years of life compared with the placebo group) and reduces morbidity, whilst saving money (USD 7,883 – USD 6,621 = USD 1,372)

Samur[52]	**2017**	• Type of model and rationale: microsimulation (individual level state-transition) model • Model health states: PBC stages 1-3, as defined by the Ludwig scoring system, and compensated cirrhosis. Patient characteristics were based on the POISE study • Interventions and comparators modelled: UDCA monotherapy versus OCA plus UDCA • Time horizon and cycle lengths, plus rationale: Lifetime horizon, no explicit rationale	• Adults with PBC who were not adequately responding to UDCA monotherapy	• Total QALYs results of OCA plus UDCA treatment: – UDCA: 10.74 – OCA + UDCA: 11.78 • Total QALYs results of OCA plus UDCA treatment for cirrhotic patients: – UDCA: 9.64 – OCA + UDCA: 10.98 • Total QALYs results of OCA plus UDCA treatment for early-stage PBC patients: – UDCA: 10.87 – OCA + UDCA: 11.87	*(Cost is reported in US dollars.)* • Total costs results of OCA plus UDCA treatment: – UDCA: 142,300 – OCA + UDCA: 633,900 • Total costs results of OCA plus UDCA treatment for cirrhotic patients: – UDCA: 184,750 – OCA + UDCA: 688,454 • Total costs results of OCA plus UDCA treatment for early-stage PBC patients: – UDCA: 137,754 – OCA + UDCA: 626,334	• ICER results of OCA plus UDCA treatment: – UDCA: - – OCA + UDCA: 473,400 • ICER results of OCA plus UDCA treatment for cirrhotic patients: – UDCA: - – OCA + UDCA: 374,672 • ICER results of OCA plus UDCA treatment for early-stage PBC patients: – UDCA: - – OCA + UDCA: 488,117
SMC[129]	**2017**	• Type of model and rationale: Markov state-transition model • Model health states: Patients entered the model in either a PBC moderate or high risk of liver disease	• Adult PBC patients with an inadequate response to UDCA • Adult PBC patients who are	**Total QALYs results with PAS for OCA** – OCA (vs UDCA) in UDCA	*(Cost is reported in British pound sterling.)* **Total cost results with PAS for OCA**	**ICER results with PAS for OCA** – OCA (vs UDCA) in UDCA inadequate: 28,821

		health state, with high risk state also covering compensated cirrhosis • Interventions and comparators modelled: For patients with inadequate response to UDCA: OCA + UDCA vs. UDCA alone; for patients intolerant to UDCA: OCA vs. placebo • Time horizon and cycle lengths, plus rationale: lifetime horizon (44 years), 3-monthly cycles • Treatment sequencing: OCA tablets titrated from 5 mg to 10 mg, given daily	intolerant to UDCA	inadequate: 5.50 – OCA (vs UDCA) in UDCA-intolerant patients: 6.59	– OCA (vs UDCA) in UDCA inadequate: 158,000 – OCA (vs UDCA) in UDCA-intolerant patients: 143,000	– OCA (vs UDCA) in UDCA-intolerant patients: 21,695

Abbreviations: ICER – incremental cost-effectiveness ratio; kg – kilograms; mg – milligrams; NR – not reported; OCA – obeticholic acid; PAS – patient access scheme; QALYs – quality-adjusted life years; UDCA – ursodeoxycholic acid; US – United States

B.3.2 Economic analysis

B.3.2.1 Patient population

The population entering the cost-effectiveness model (CEM) is aligned with the inclusion criteria of the ELATIVE trial and its licensed indication: adult patients with PBC whose disease has an inadequate response to, or who are unable to tolerate, UDCA.[4,11] This positions elafibranor as a second-line therapy and is also in line with the anticipated marketing authorisation for the licensed indication and the final NICE scope.[133] Elafibranor treatment with and without UDCA is not considered separately in the CEM as the ELATIVE trial population is representative of the distribution of patients treated with and without UDCA in clinical practice.

The baseline characteristics of the CEM population, as summarised in Table 30, are informed by the ELATIVE trial intention-to-treat (ITT) analysis set, which includes all randomised participants.[112] The ELATIVE trial comprised a total of 161 patients randomly assigned to receive elafibranor (N=108) or placebo (N=53). Demographics and clinical characteristics at baseline were similar between the elafibranor and placebo groups. These patient characteristics align with the expected population in clinical practice.

Table 30: Baseline population characteristics in the CEM based on the ELATIVE trial[112]

Baseline characteristic	Impact on the model
Mean age	Baseline age is a key parameter for the CEM as patient's age is directly linked with their survival prognosis. Furthermore, baseline age will drive decisions on the model time horizon.
Sex distribution	Required for mortality calculations.
Severity of pruritus	Pruritus is a key outcome experienced by most patients with PBC. The proportion of patients with no itch, mild itch, and CS itch baseline is required for accurate calculations of costs and utilities.
Health state distribution	To inform the starting health state distribution for the population entering the model.

Abbreviations: CEM – cost-effectiveness model; CS – clinically significant; PBC – primary biliary cholangitis

B.3.2.2 Model structure

A Markov cohort structure was developed to describe the progression of PBC over the lifetime time horizon of the CEM. This model structure is consistent with other approaches for liver disease-related modelling, for example, for hepatitis C.[134] The main events and changes in the health of a PBC patient, and costs are captured by the health states.

The model structure aligns with the model structure used in the OCA NICE technology appraisal (TA443) and consists of 10 health states divided into two components: the PBC biomarker component and the liver disease component.[1] The PBC biomarker component stratifies patients according to their risk of progression to liver disease. The liver disease component contains patients who have progressed to liver disease. The death health state is absorbing.

The PBC biomarker component uses the following definitions of mild, moderate, and high risk of disease progression, respectively, which are aligned with the definitions of health states in the TA443 model:

- Mild risk: ALP ≤ 200 u/L and TB ≤ 20 µmol/L;
- Moderate risk: ALP > 200 u/L and TB ≤ 20 µmol/L;
- High risk: TB > 20 µmol/L or compensated cirrhosis (defined as kPa >15).

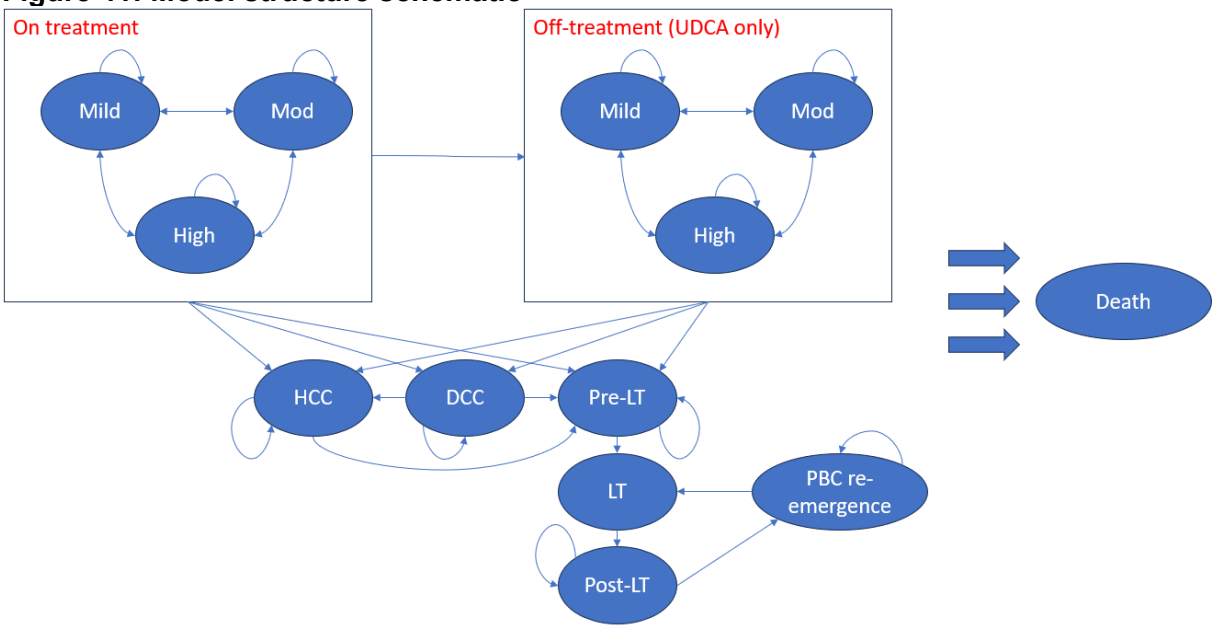
This is aligned with the approach in the TA443 submission with the criteria to define compensated cirrhosis added by using a liver stiffness score (as measured by transient elastography) of > 15 kPA to consider histological progression for the high risk biomarker health state. This cut-off value has been also validated through consultation with clinical experts and corroborating literature sources. [117,135] In TA443, it was cited that there was a lack of data on histological progression among PBC patients for the composite criteria for the high risk biomarker health state.[1] Therefore, this has been addressed in this submission.

The liver disease component of the model includes the following health states: decompensated cirrhosis (DCC), HCC, pre-liver transplant (LT), LT, post-LT and PBC re-emergence.

A visual representation of the model structure is presented in Figure 41. Patients enter the CEM on treatment in the PBC biomarker component. Within the PBC biomarker component, patients are categorised into mild, moderate, or high risk of disease progression and they can transition between these three health states. From the PBC biomarker component of the model, patients can transition from the moderate or high risk of disease progression health states to the liver disease component into either the DCC, HCC, or pre-LT health states or discontinuing treatment. Patients in the DCC health state can remain in the DCC health state or transition to the HCC or pre-LT health states. Patients in the HCC health state can remain in the HCC state or transition into the DCC or pre-LT health states. Once in the pre-LT health state, patients can either remain in the pre-LT health state, where they await LT, or they transition to the LT health state. In the LT health state, patients undergo a LT and transition to the post-LT health state in the next cycle. Patients in the post-LT health state may remain in that state, or transition to PBC re-emergence. In the PBC re-emergence health state, patients can either remain or return to the LT health state for another LT. Patients can transition into the death health state from any other health state, where they remain for the rest of the model time horizon.

If a patient discontinues second-line therapy whilst in one of the PBC biomarker health states, it is assumed that patients remain in the PBC biomarker component of the model ‘off-treatment’ and follow the UDCA arm transition probabilities from the cycle of discontinuation. Whilst off-treatment, the patients continue to receive treatment with UDCA and accumulate the costs and outcomes associated with UDCA treatment. As for patients on treatment, patients off-treatment can progress to the liver disease health states if they are at moderate or high risk of disease progression.

Figure 41: Model structure schematic



Abbreviations: DCC – decompensated cirrhosis; HCC – hepatocellular carcinoma; LT – liver transplant, PBC – primary biliary cholangitis; UDCA – ursodeoxycholic acid

The core model structure follows that of TA443. Table 31 shows the issues identified by NICE and the evidence assessment group (EAG) in TA443 and details how these issues have been addressed in the elafibranor submission. Several additional modifications have been implemented in the CEM in an attempt to comprehensively capture the value proposition of elafibranor. These changes are listed in Table 32.

Table 31: NICE questions for the committee and EAG preferred base-case assumptions in TA443

NICE questions in TA443 for the committee[136]	TA443 – Committee preferred assumptions[137]	How addressed in the elafibranor CEM	Comments
Limited clinical evidence underpinning the cost-effectiveness analysis of the UDCA-intolerant group (makes up 5% of the study and real-life population) separate to patients with inadequate response to UDCA.	Trial data would be preferred.	UDCA inadequate responders and intolerant patients are not separated, and trial data is used directly.	Only ~5% of patients enrolled in the ELATIVE trial are intolerant to UDCA. Therefore, there are insufficient patient numbers to present the two groups separately.
Suitability of model for decision making (it includes a pre-transplant health state which was not in previous models in	The committee concluded that the structure of the model was suitable for decision making and further considered some of the key assumptions within the model	The model structure that was used in TA443 is adopted.	Limitations of the model have been addressed where possible, including omission of pruritus and

liver disease [e.g. TA330]).	where it agreed that the EAG had raised valid issues for further consideration.		transitions from the moderate risk health state to liver disease health states.
Should longer term literature or POISE data be used for the natural history of PBC for patients on UDCA?	The EAG noted that the way transition probabilities were calibrated in the UDCA arm was not transparent, and for consistency it would be better to derive them from trial data. The committee concluded that there is uncertainty about whether the transition probabilities used in the UDCA arm are the most appropriate.	Trial data used to derive UDCA transition probabilities.	None.
Is it reasonable to assume that if people in the mild or moderate state on OCA and UDCA stay in that state for a year they will not progress to the severe state?	The committee considered whether the assumption of no progression from the low or moderate risk state to the severe risk state after 12 months was plausible. The committee noted that clinical advice to the EAG was that this assumption was reasonable, since existing data on UDCA showed that an ALP ≤ 1.67 X ULN (which corresponds to the mild risk health state in the PBC biomarker component) was associated with an excellent long-term prognosis with no overall effect on life expectancy.	Patients treated with UDCA can continue to progress. Patients treated with elafibranor and OCA remain in their PBC biomarker health state and do not move between them. However, patients in the moderate and severe risk health states can move into the liver disease health states.	Consulted with clinicians to identify the trajectory of disease following the trial phase to appropriately extrapolate.
Is a utility value of 0.84 for mild and moderate health states reasonable despite it being above the UK age adjusted utility?	The committee noted that the utility values were derived from published sources and that patients with PBC may be asymptomatic. The committee acknowledged the uncertainty associated with the utility values but accepted that they had been derived from published sources. They agreed that an age-related decrement over time should have been incorporated into the model.	The same published sources have been used but age-adjustment applied in the CEM to ensure QoL remains in line with population norms over the model time horizon.	None.
Is it appropriate to apply a relative reduction to utilities	The committee considered whether the confidential decrement applied to the	Not applied as the confidential	None

for hepatitis B/C patients to estimate utilities for PBC patients?	DCC, pre-LT and LT health states based on clinical advice to the company was appropriate. The committee heard from the clinical experts that they considered it reasonable to consider a lower utility for some of the advanced liver disease states in PBC compared with hepatitis because of the additional morbidity related to having cholestasis as well as fibrosis.	decrement is not in the public domain.	
Model includes at baseline a higher proportion of people in the severe health state than in POISE – is this reasonable?	The committee concluded that the results of POISE are generalisable to the intended use of OCA in clinical practice in England.	Distribution of patients at baseline is aligned with the ELATIVE study.	None
Are health state costs reasonable?	The committee did not consider costs a key area of uncertainty.	As costs were not considered a key area of uncertainty, they are aligned to TA443.	None.

Abbreviations: DCC – decompensated cirrhosis; CEM – cost-effectiveness model; EAG – evidence assessment group; LT – liver transplant; OCA – obeticholic acid; PBC – primary biliary cholangitis; QoL – quality-of-life; TA – technology appraisal; UDCA – ursodeoxycholic acid; UK – United Kingdom

Table 32: Changes applied in the elafibranor health economic model compared to TA443

Changes to the elafibranor CEM	Rationale
Liver stiffness score included in the definition of high risk in the PBC biomarker component	Definition of compensated cirrhosis not given in TA443; the definition of ≥ 15 kPa was validated with clinical experts.[135]
All-cause discontinuation applied across the entire time horizon	Patients may discontinue treatment over time for many reasons (such as AEs, loss of efficacy or lack of compliance). Therefore, it is appropriate to capture the relevant time on treatment.
End of life costs applied to DCC and HCC liver health states	For patients with DCC and HCC, care at end of life can be costly. Therefore, it is included in the CEM to adequately describe all costs associated with PBC.
Pruritus included	Pruritus is included in the model given its substantial impact on HRQoL. Including pruritus allows for a more comprehensive capturing of disease management costs and QoL impact.
Excess mortality applied to high risk health state (in the PBC biomarker component)	Excess mortality is included in the model following clinical validation, which indicated a higher mortality rate for patients in the high risk health state. This addition ensures a more accurate representation of the disease progression and its associated outcomes.

Utilities from ELATIVE included for the low and moderate risk health state (in the PBC biomarker component)	These are included in the model for the purpose of scenario analysis to address uncertainty regarding face validity.
Whole patient population presented – not split into inadequate responder and intolerant UDCA sub-populations	The trial population reflects the anticipated distribution of patients in clinical practice and so cost-effectiveness estimates from the overall cohort will be generalisable to the patients with PBC in the UK. Moreover, the proportion of patients who are intolerant to UDCA is insufficient to suitably inform transition data.
UDCA-treated patients cannot improve after 12 months	As patients eligible for treatment with elafibranor either have inadequate response to, or are intolerant of UDCA, it would not be appropriate for patients treated with UDCA only (or indeed no treatment in patients unable to tolerate UDCA) to continue deriving benefit. This is supported by trial data from ELATIVE which suggests stability of ALP and increases in TB over the trial time horizon for patients treated with placebo. This was supported by clinical expert opinion.[117]
The last UDCA transition is extrapolated across the time horizon	In line with the above, the trial data from ELATIVE demonstrates a trend of increasing TB for patients treated with placebo, which supports a trajectory of deterioration for patients treated with UDCA or patients not receiving treatment. This was supported by clinical expert opinion.[117]

Abbreviations: AE – adverse event; ALP – alkaline phosphatase; CEM – cost-effectiveness model; HRQoL – health-related quality-of-life; kPa – kilopascals; PBC – primary biliary cholangitis; QoL – quality-of-life; TA – technology appraisal; TB – total bilirubin; UDCA – ursodeoxycholic acid

The NICE reference case states that the time horizon for estimating clinical and cost-effectiveness should be sufficiently long to reflect any difference in costs or outcomes between the medicines being compared.[138] Consequently, a lifetime time horizon was adopted to estimate the life-long impacts on costs and outcomes of PBC. This was reflected in a 43-year time horizon, based on the mean age of the ELATIVE trial randomised patients' ITT population (57.1 years), with the assumption that no patient can live beyond 100 years.[4]

Over the time horizon, the cohort accrues the costs and outcomes faced when patients transition between the health states. A cycle length of three months is applied with a half-cycle correction applied, assuming patients enter/exit health states mid-way through a cycle.

For each cycle, total costs and QALYs are calculated based on the distribution of patients across all health states. These are accumulated over the model time horizon to calculate total costs and QALYs for the cohorts from which incremental results and the incremental cost-effectiveness ratio (ICER) per QALY are determined. Costs and outcomes are discounted at 3.5% per annum in line with the NICE reference case.[138]

The model adopts a UK NHS and Personal Social Services (PSS) perspective on costs, in line with the NICE reference case.[138] The perspective on outcomes considers all direct health effects for patients, in line with the NICE reference case.[138]

Table 33 summarises the main features of the economics analysis.

Table 33: Features of the economic analysis

Previous appraisals		Current appraisal	
Factor	**TA443 (OCA)**[139]	**Chosen values**	**Justification**
Time horizon	Lifetime	Lifetime	Due to the chronic nature of the condition, a lifetime time horizon is chosen to sufficiently capture all relevant differences in the future costs and outcomes associated with the interventions being compared.
Cycle length	Three months	Three months	The cycle length aligns with the time interval between visits in the ELATIVE trial and sufficiently captures meaningful differences in disease progression over time.
Discount rate	3.5% discount for utilities and costs	3.5% discount for utilities and costs	As per NICE reference case.[138]
Perspective (NHS/PSS)	NHS and PSS	NHS and PSS	As per NICE reference case.[138]
Treatment waning effect?	No	No	There is no evidence of a waning of treatment effect for elafibranor.
Source of utilities	Calculated based on literature data	Sourced from literature	The literature sources are appropriate to define health state utility values in the model.
Source of costs	BNF, literature, expert opinion, assumption, NHS reference costs	BNF, eMIT, literature, assumption, NHS reference costs	These are the most appropriate sources to define costs and resource use in the model.

Abbreviations: BNF – British National Formulary; eMIT – electronic market information tool; NHS – National Health Service; PSS – Personal Social Services; OCA – obeticholic acid; TA – technology appraisal

B.3.2.3 Intervention technology and comparators

The intervention considered in the economic analysis is elafibranor. Clinical effectiveness of elafibranor is derived from the ELATIVE trial, representing patients with inadequate response or intolerance to UDCA.[112] This includes patients receiving elafibranor 80 mg in combination with UDCA and patients receiving elafibranor 80 mg monotherapy. It was modelled as a single intervention, reflecting the general population's distribution of concomitant UDCA use.

Current treatment options for patients with PBC are limited to only two therapies: UDCA and OCA.[50] For individuals who do not respond to or who are intolerant to UDCA, currently the only licensed second-line therapy for PBC, also recommended for use by the EASL, AASLD and BSG/UK-PBC guidelines, is OCA.[14,15,47] OCA is licensed in combination with UDCA as a second-line therapy for those whose disease has responded inadequately to UDCA, or as monotherapy for those who cannot tolerate UDCA.[50] In 2017, NICE recommended OCA for treatment of PBC patients according to its licensed indication.[1]

B.3.3 Clinical parameters and variables

B.3.3.1 Baseline characteristics

Patient demographics at baseline from the ELATIVE trial were used to inform the characteristics of the population entering the model, as outlined in Table 34. The mean age of randomised patients forming the ITT population was 57.1 years old.[4]

Table 34: Baseline characteristics of patients entering the model

Baseline characteristics	Value	Reference
Age (years), mean (SD)	57.1 (8.7)	Kowdley *et al*. (2023)[4]
Male, n (%)	7 (4.3)	Kowdley *et al*. (2023)[4]
Low risk health state, %	11.0	ELATIVE trial[140]
Moderate risk health state, %	74.8	ELATIVE trial
High risk health state, %	14.2	ELATIVE trial[140]
No itch, %	6.5	ELATIVE trial[140]
Mild itch, %	56.5	ELATIVE trial[140]
CS itch, %	37.0	ELATIVE trial[140]

Abbreviations: CS – clinically significant; n – number; SD – standard deviation

B.3.3.2 Transition probabilities

B.3.3.2.1 PBC biomarker health states: elafibranor and UDCA

The transition probabilities for health states in the PBC biomarker component of the model of the elafibranor and UDCA treatment arms were calculated using the proportion of patients in the mild, moderate, and severe risk health states (according to ALP, TB and liver stiffness) in the ELATIVE trial for patients treated with elafibranor and placebo, respectively. In line with the model cycle length, movement between the health states was captured at five time points:

- Baseline (Visit 1), the beginning of cycle 1
- Visit 3, the end of cycle 1
- Visit 4, the end of cycle 2
- Visit 5, the end of cycle 3
- Visit 6, the end of cycle 4

At each timepoint, patients' ALP, TB and kPa (liver stiffness) levels were recorded. Patient level data was used to assign patients to the mild, moderate or severe health state at each time point, as defined in Section B.3.2.2. As kPa was measured at baseline, Visit 4, and Visit 6 only, missing kPa observations were imputed using the last observation carried forward (LOCF) approach for Visits 3 and 5. For each cycle and health state, transition probabilities were then calculated as the proportion of patients remaining within the same health state or moving into either of the alternative PBC biomarker health states.

For transitions after cycle 4 in the PBC biomarker component, patients receiving elafibranor were assumed to remain in their health state for the remainder of the lifetime time horizon. This

assumption was applied to OCA and accepted in TA443. Patients who discontinue elafibranor were assumed to return to their health state at baseline. To capture the worsening condition of patients who are treated with UDCA only, the LOCF assumption was implemented by continuing to apply to transition probabilities from cycle 3 to cycle 4 for the remainder of the time horizon.

[redacted]

Figure 42: Mean ALP levels over time in ELATIVE, including the OLE

Abbreviations: ALP – alkaline phosphatase; mg – milligram; OLE – open-label extension

Figure 43: Mean TB levels over time in ELATIVE, including the OLE
Abbreviations: mg – milligram; OLE – open-label extension; TB – total bilirubin

B.3.3.2.2 PBC biomarker health states: OCA

A NMA assessing the relative likelihood of achieving cholestasis response compared to elafibranor was used to inform the efficacy of OCA (see section B.2.9.1.1). The odds ratio from this analysis (OR [95% CrI]: [redacted] [redacted], [redacted]) was used to derive the OCA transition probabilities, by converting the odds ratio to a risk ratio and applying this to the elafibranor transition probabilities. The OR was used for the transitions from moderate and high risk to the low risk health state. From the moderate and high risk health states, the transitions to the moderate and high risk health states were redistributed so that the sum of all transitions from a single health state summed to 100%. The transitions from the low risk health state were assumed equivalent to elafibranor as there was no evidence to suggesting a difference in the maintenance of cholestasis response for patients treated with elafibranor or OCA.

Similarly to elafibranor, it is assumed that patients treated with OCA remain in state after cycle 4 whilst on treatment. This aligns with the assumption in TA443 for OCA. At the point of discontinuation, which can happen in any cycle, patients return to their baseline health state and are treated with UDCA only; after discontinuation patients follow the UDCA transition matrices.

B.3.3.2.3 Liver disease health states

To inform the transition probabilities in the liver disease component of the CEM, the transition probabilities reported in the NICE submission of OCA were used (Table 35).[1] These transition probabilities were originally sourced from published literature. The chosen transition probabilities were presented to health economics and outcomes research (HEOR) and clinical experts, who agreed them to be appropriate to use in the elafibranor CEM. In validation of the transition probabilities, clinical experts also advised of the probabilities of moving from the moderate risk health state to the liver disease component. The transitions from moderate risk to liver disease health states have been included in the adaption of the TA443 model to accurately capture the disease trajectory of patients with moderate risk of progression based

on clinical expert feedback. Additionally, the EAG of TA443 criticised that patients with moderate risk of disease progression would remain in the moderate risk health state for the remainder of the time horizon, highlighting this as a weakness of the OCA model.[137]

Table 35: Liver disease component transition probabilities

From (health state)	To (health state)	Transition probability per cycle	Source
Moderate risk of PBC disease progression	DCC	0.02%	Clinician, 2023[142]
	HCC	0.02%	Clinician, 2023[142]
	Pre-LT	0.06%	Clinician, 2023[142]
High risk of PBC disease progression	DCC	0.25%	Assumption
	HCC	0.25%	TA443, 2017[1]
	Pre-LT	1.02%	TA443, 2017[1]
DCC	HCC	0.25%	TA443, 2017[1]
	Pre-LT	1.53%	TA443, 2017[1]
HCC	Pre-LT	1.02%	TA443, 2017[1]
Pre-LT	LT	10.21%	TA443, 2017[1]
Post-LT	LT	0.02%	TA443, 2017[1]
	Re-emergence of PBC	0.58%	TA443, 2017[1]
Re-emergence of PBC	LT	0.02%	TA443, 2017[1]

Abbreviations: DCC – decompensated cirrhosis; HCC – hepatocellular carcinoma; LT – liver transplant; PBC – primary biliary cholangitis; TA – technology appraisal

B.3.3.3 Pruritus

Pruritus is a common outcome experienced by patients with PBC, with 41% and 59% of patients experiencing pruritus at baseline in the ELATIVE and POISE trials, respectively.[2,4] Therefore, it is considered an outcome of interest in the CEM. The CEM considers the impact of pruritus by modelling the severity of pruritus over time. The patient population is stratified into the three itch severity categories (no itch, mild itch, and CS itch). The thresholds of itch severity were developed by creators of the PBC-40 Itch instrument, which is the only validated instrument for PBC which includes an itch domain, as presented in Mayo *et al*. (2023):[59]

- No itch: PBC-40 Itch domain score = 0
- Mild itch: PBC-40 Itch domain score ≥ 1 to < 7
- CS itch: PBC-40 Itch domain score ≥ 7

For elafibranor and UDCA, the change in the distribution of pruritus severity over time is informed by patient level data of PBC-40 Itch scores from the ELATIVE trial (Table 36).[140] The distribution of itch severity was parameterised using recorded PBC-40 Itch scores from baseline, Visit 1, and Visits 3 to 6 of the ELATIVE trial. From Month 12 onwards, the distribution of itch severity was assumed to remain constant as a conservative extrapolation assumption.

Table 36: Distribution of PBC-40 Itch over time (elafibranor and UDCA)

Timepoint	Elafibranor			UDCA		
	No itch	Mild itch	CS itch	No itch	Mild itch	CS itch
Month 3	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Month 6	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Month 9	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Month 12+	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: CS – clinically significant; UDCA – ursodeoxycholic acid

An NMA was performed to assess the difference in change from baseline in PBC-40 Itch scores between elafibranor and OCA (see sections B.2.9.1.6 and B.2.9.1.7) at Weeks 2 to 4 and Week 52 (i.e., Month 1 and 12 [Table 37]). As patients were not treated at baseline, all patients share the same distribution of itch severity. To calculate the distribution of itch severity over time for patients treated with OCA, the median difference in change from baseline in PBC-40 Itch scores at Month 1 and Month 12 was applied to patient level PBC-40 Itch scores for patients in the elafibranor arm of the ELATIVE trial: the median difference at Month 1 was applied to itch severity distributions at Month 3 in order to catch the maximal difference in pruritus when treatments are introduced to manage itch worsening, the median difference at Month 12 was applied to itch severity distributions at Months 6, 9 and 12+. These values were then stratified by itch severity as per the Mayo *et al*. (2023) criteria.[59] The distribution of PBC-40 Itch severity over time for OCA are shown in Table 38.

Table 37: Median difference of OCA to elafibranor in mean change in pruritus from baseline at Month 3 and Month 12

Timepoint in the CEM	Median difference with elafibranor (95% CrI or CI)
Month 3	[redacted]
Month 12	[redacted]

Abbreviations: CI – confidence interval; CrI – credible interval; mg – milligram; OCA – obeticholic acid

Table 38: Distribution of PBC-40 Itch over time for OCA

Timepoint	OCA		
	No itch	Mild itch	CS itch
Baseline	[redacted]	[redacted]	[redacted]
Month 3	[redacted]	[redacted]	[redacted]
Month 6	[redacted]	[redacted]	[redacted]
Month 9	[redacted]	[redacted]	[redacted]
Month 12+	[redacted]	[redacted]	[redacted]

Abbreviations: CS – clinically significant; OCA – obeticholic acid

B.3.3.4 Discontinuation

The model accounts for treatment discontinuation to capture the number of patients remaining on treatment each cycle. This varies to the assumptions applied in TA443, whereby discontinuation was only considered in the first year of treatment.[1] All-cause discontinuation is assumed in the base-case and applied across the entire time horizon for elafibranor and OCA in the model. Parametric distributions were used to extrapolate the all-cause time to

discontinuation (TTD) of elafibranor treatment during and beyond the ELATIVE study duration. Estimates from the extrapolations beyond the ELATIVE study period were used to model the movement of patients between the on and off-treatment PBC biomarker health states.[140]

For patients receiving elafibranor, parametric distributions were fitted to the Kaplan Meier all-cause TTD data, in line with NICE guidance.[143] Table 39 shows all estimated distributions, along with their respective Akaike Information Criterion (AIC) and Bayesian Information Criterion (BIC) statistics for both treatment arms. Lower AIC and BIC values indicate a better statistical fit of the curves to the Kaplan Meier. Thus, the exponential curve is considered the best fit to the data. As the AIC of exponential, Weibull, Gompertz and log-logistic curves are all within 2 points, they may be considered equally good statistical fits.[144] However, the Gompertz curve predicts unrealistically high retention to treatment over the long-term, and so has been discounted based on clinical implausibility.

Table 39: AIC and BIC statistics from all-cause TTD parametric distributions

Distribution	AIC	BIC
Exponential	258.84	261.51
Weibull	260.81	266.16
Gompertz	260.56	265.90
Log-logistic	260.69	266.04
Lognormal	260.88	266.23
Generalised Gamma	262.96	270.98

Abbreviations: AIC – Akaike Information Criterion; BIC – Bayesian Information Criterion; TTD – time to discontinuation

Figure 44 shows all parametric distributions and the Kaplan Meier curve. According to expert clinical opinion, the most clinically plausible parametric distribution to reflect treatment duration of elafibranor in practice is the flattest curve compared to other distributions.[117]

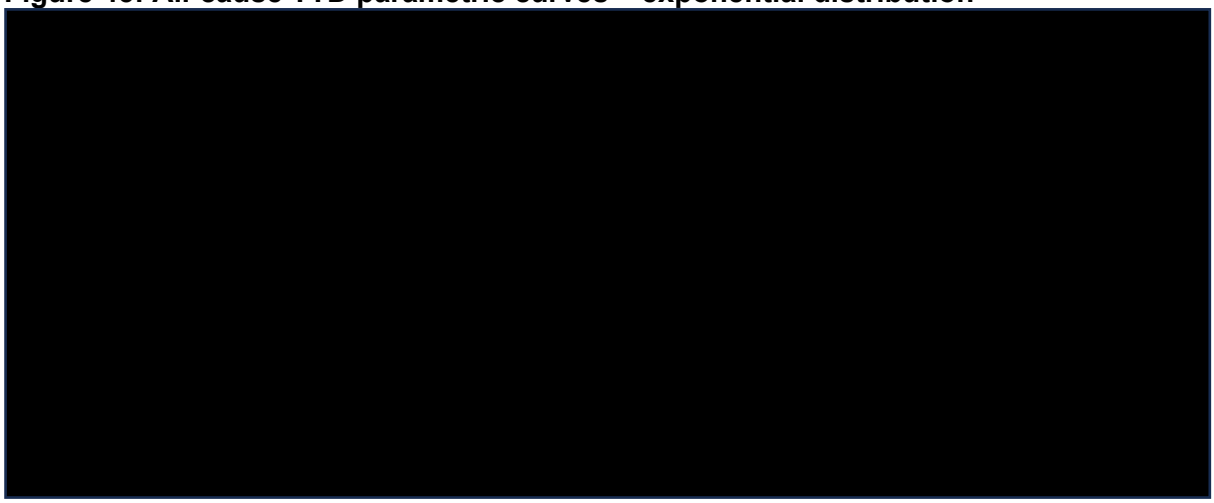
Figure 44: All-cause TTD parametric curves - all distributions

Abbreviations: TTD – time to discontinuation

Considering the AIC and BIC values, the exponential distribution is chosen as the best fit to the Kaplan Meier data for all-cause TTD (see Figure 45). As shown in Table 39, the exponential distribution gives the lowest AIC and BIC values (AIC = 258.84; BIC = 261.51) and the

treatment retention curve is consistent with the treatment duration observed in the ELATIVE trial study (~89% of patient retention after 12 months).[4]

Figure 45: All-cause TTD parametric curves – exponential distribution



Abbreviations: TTD – time to discontinuation

The TTD extrapolation for OCA was derived by applying the OR of all-cause discontinuation within a 12-month period for patients treated with OCA relative to elafibranor to the selected TTD curve for elafibranor (see section B.2.9.1.10). Results from the NMA showed that patients treated with elafibranor had a lower likelihood of discontinuation for any reason within 12 months compared with OCA (OR [95% CI]: [redacted] [redacted]). It was assumed that the relative likelihood of discontinuing treatment with OCA compared to elafibranor was maintained over the time horizon of the model. The resulting TTD applied for OCA is presented in Figure 46.

Figure 46: TTD (exponential distribution) – elafibranor and OCA

Abbreviations: OCA – obeticholic acid; TTD – time to discontinuation

B.3.3.5 Mortality

Age- and sex-specific general population mortality rates sourced from the Office for National Statistics (ONS) National Life Tables for England and Wales were applied to all patients in the model.[145] With exception of the high risk health state (upon advice from clinical experts), the biomarker component health states had mortality rates equal to the general population. Excess mortality for health states in the liver disease component of the model were sourced from the NICE submission for OCA and applied throughout the liver disease component of the model.[1] The excess mortality rates applied in the CEM are shown in Table 40.

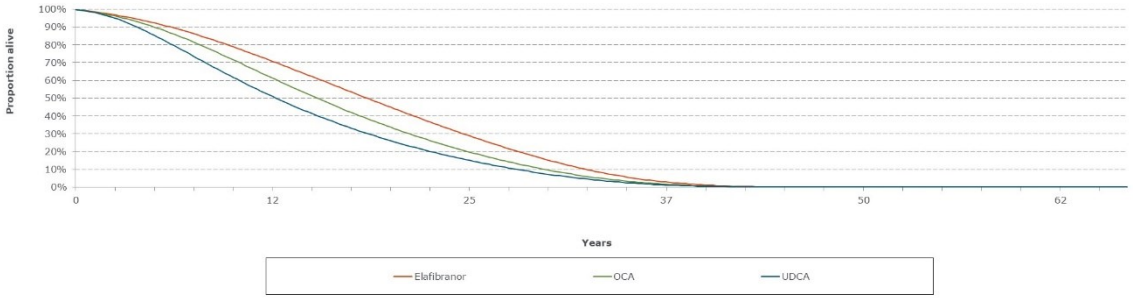
Table 40: Excess mortality applied in the CEM

Health state	Annual excess mortality	Source
Mild	0.0%	TA443, 2017[1] and Clinician, 2023[142]
Moderate	0.0%	TA443, 2017[1] and Clinician, 2023[142]
High	1.2%	Clinician, 2023[142]
DCC	4.2%	TA443, 2017[1]
HCC	10.2%	TA443, 2017[1]
Pre-LT	2.2%	TA443, 2017[1]
LT	18.9%	TA443, 2017[1]
Post-LT	1.5%	TA443, 2017[1]
Re-emergence of PBC	2.2%	TA443, 2017[1]

Abbreviations: CEM – cost-effectiveness model; DCC – decompensated cirrhosis; HCC – hepatocellular carcinoma; LT – liver transplant; PBC – primary biliary cholangitis; TA – technology appraisal

The resulting survival curves applied in the model are illustrated in Figure 47.

Figure 47: Proportion of patients alive over lifetime time horizon



Abbreviations: OCA – obeticholic acid; UDCA - ursodeoxycholic acid

B.3.3.6 Safety

Standard practice for cost-effectiveness analyses and existing NICE appraisals (such as NICE TA443) is to include any grade 3+ AE reported in ≥5% of one arm of the study population. However, as no grade 3+ AEs occurred in ≥ 5% of one arm of the study population in ELATIVE, the threshold was reduced such that any grade 2+ AEs reported in ≥ 5% of one arm of the study population were considered.[112] The resulting AEs considered in the CEM are presented below in Table 41. Despite grade 2+ COVID-19 being an AE that occurred in ≥ 5% of one arm of the study population, it was excluded, as supported by clinical expert validation, given the timing of the trial coinciding with the COVID-19 pandemic and that it is not expected to occur at this frequency in clinical practice on an ongoing basis.[117]

Table 41: Grade 2+ AEs included in the CEM – elafibranor and UDCA

Adverse event	Elafibranor	UDCA
Pruritus	12.8%	14.2%
Urinary tract infections	5.8%	1.9%
Fatigue	4.7%	5.9%

Abbreviations: AE – adverse event; CEM – cost-effectiveness model; UDCA – ursodeoxycholic acid

For OCA, it was assumed only that the occurrence of pruritus would vary across treatments, while all other AEs were assumed to occur at the same rate as for elafibranor. Thus, an NMA was conducted to assess the relative likelihood of pruritus as a TEAE compared to elafibranor (Section B.2.9.1.8). The odds ratio from this analysis (OR [95% CrI]: [redacted] [redacted], [redacted]) was converted to a risk ratio and applied to the elafibranor probabilities to derive the expected frequency of pruritus as an AE for OCA. OCA treatment-related AEs are presented in Table 42.

Table 42: Grade 2+ AEs included in the CEM - OCA

Adverse event	OCA
Pruritus	29.5%
Urinary tract infections	5.8%
Fatigue	4.7%

Abbreviations: AE – adverse event; CEM – cost-effectiveness model; OCA – obeticholic acid

Treatment-related grade 2+ AEs were incorporated as one-off events and the impact was attributed to the first cycle of treatment for patients entering the CEM, assuming that AEs are likely to occur close to treatment initiation and require acute care.

B.3.4 Measurement and valuation of health effects

B.3.4.1 Health-related quality-of-life data from clinical trials

During the ELATIVE study, patients completed the EQ-5D-5L and EQ-5D-5L-VAS at multiple time points across the study. In the study protocol, it was specified for EQ-5D-VAS and EQ-5D-5L domain scores to be summarised according to study arm, and this is presented herein.

Overall, HRQoL as measured by EQ-5D-5L remained high and stable throughout the study period, with no meaningful differences observed between groups (Table 43). Baseline EQ-5D-5L scores were [redacted] (SD: [redacted]) for the elafibranor group and [redacted] (SD: [redacted]) for the placebo group. The LS means change from baseline to Week 52 was [redacted] in the elafibranor group and [redacted] in the placebo groups; the LS means difference from placebo was [redacted] ([95% CI: [redacted]; [redacted]]; p=[redacted]).

Table 43: EQ-5D-5L-VAS scores in the ELATIVE study

Timepoint	Mean EQ-5D-5L-VAS scores (SD)	
	Elafibranor 80 mg	Placebo
Baseline	[redacted]	[redacted]
Week 52	[redacted]	[redacted]
LS mean change from baseline	[redacted]	[redacted]
LS mean difference with placebo (95% CI; p-value)	[redacted]	[redacted]

Abbreviations: CI – confidence interval; EQ-5D-5L – EuroQol-five dimensions-five level; LS – least squares; mg – milligrams, SD – standard deviation; VAS – visual analogue scale

EQ-5D-5L domain scores at baseline (on the lefthand side) and after Week 52 (on the righthand side) of the ELATIVE study for elafibranor and placebo are presented in Figure 48 and Figure 49, respectively. Patients treated with elafibranor and placebo had a large

proportion of patients with no problems at baseline in the mobility and self-care domains. The most impacted domains were the pain/discomfort and anxiety/depression domains. For patients treated with elafibranor, there was a small increase in the proportion of patients reporting no or slight problems in the usual activities and anxiety/depression domains at Week 52 compared to baseline. For patients treated with placebo, there were limited improvements observed.

Figure 48: Distribution of EQ-5D-5L domains for elafibranor at baseline and Week 52

Abbreviations: EQ-5D-5L – EuroQol-five dimensions-five level

Figure 49: Distribution of EQ-5D-5L domains for placebo at baseline and Week 52

Abbreviations: EQ-5D-5L – EuroQol-five dimensions-five level

B.3.4.2 Mapping

A utility mapping analysis was performed on the ELATIVE trial data to identify differences in utility values according to risk of progression to liver disease and the severity of pruritus.

To conduct the mapping analysis EQ-5D-5L domain responses, ALP levels, bilirubin levels and kPa levels were collected at Visit 1, Visit 3, Visit 4, Visit 5, and Visit 6, of patients treated with both elafibranor and placebo in the ELATIVE study. Then, the Hernandez-Alava mapping was performed on the EQ-5D-5L domain responses in R, using the code provided by the NICE decision support unit (DSU).[146] Pruritus was also included as a covariate in the utility analyses, to determine whether severity of pruritus also predicts HRQoL in combination with the risk of disease progression. To identify data collected for patients in each itch category (No itch, Mild itch, and CS itch, see

Table 44), the severity of itch for each patient was identified from the ELATIVE trial IPD.[140]

A linear mixed effect model for repeated measures was used to estimate the utility values of each PBC biomarker health state and itch severity, to account for correlations between repeated measurements within each patient.[147] This model contained both fixed effects and random effects; patient ID was fitted as a random effect component whilst progression status and itch severity were fixed effect components. Following this, the mean utility within each health state was estimated. The analysis was performed using the lme4 package in R.[148]

The results of the linear mixed effects regression analysis of the EQ-5D-3L utilities obtained using the mapping algorithm by Hernandez-Alava *et al*. (2020)[149] are presented in

Table 44.

Table 44: Results of the regression analysis of the EQ-5D-3L utilities for the overall population

	Estimate	SE	P-value
(Intercept)	[redacted]	[redacted]	[redacted]
Moderate biomarker risk	[redacted]	[redacted]	[redacted]
High biomarker risk	[redacted]	[redacted]	[redacted]
Mild itch	[redacted]	[redacted]	[redacted]
CS itch	[redacted]	[redacted]	[redacted]

Abbreviations: CS – clinically significant; EQ-5D-3L – EuroQol-five dimensions-three level; SE – standard error

From the final mixed effects regression models, the final health state utility values (HSUVs) were derived. Table 45 presents the HSUVs derived from the regression analysis based on the EQ-5D-5L from ELATIVE using the Hernandez-Alava *et al*. (2020) algorithm.[149] The HSUV for the low risk state is higher than for the moderate and high biomarker risk HSUVs, and the HSUV for the moderate risk health state is higher than for the high risk state. The disutility values for mild and CS itch derived from the regression analyses are also presented in Table 45. The disutility values demonstrate a greater reduction in utility for patients with CS itch compared to mild itch, relative to patients with no itch.

Table 45: HSUVs derived from the regression analysis

HSUV	
Low biomarker risk	[redacted]

Moderate biomarker risk	[redacted]
High biomarker risk	[redacted]
Itch severity disutility value	
No itch	[redacted]
Mild itch	[redacted]
CS itch	[redacted]

Abbreviations: CS – clinically significant; HSUV – health state utility value

The incremental difference in utility between the moderate and high risk health states is lower than expected from the regression analysis. This is hypothesised to be driven by the low sample size in the high risk state (N=78 observations in the utility analysis, 10.3% of the overall sample), which reduces the reliability of the utility estimates as lower sample sizes reduces the statistical power of the analyses. Therefore, the HSUVs derived from the regression analysis, using the Hernandez-Alava *et al*. (2020) mapping algorithm, are not used in the CEM in the base-case. [149] However, the mild and moderate biomarker risk state values from ELATIVE are presented as a scenario of the value of 0.84 for these health states was flagged as an issue by the EAG in TA443. As the analysis was sufficiently powered to detect disutility according to severity of pruritus, the regression informs the disutility of pruritus in the CEM.

B.3.4.3 Health-related quality-of-life studies

An SLR was conducted in November 2022, and updated in December 2023, to identify studies reporting HRQoL data associated with PBC. In total, 11 articles reporting utility data on six unique studies were identified; the six studies are presented

Table 46. Three studies reported average utility values in a cohort of patients with PBC.[150–152] Two studies reported on the utility values of patients with PBC according to additional symptoms, such as pruritus, sleep interference and depression.[63,81] One remaining study reported utility values before and after liver transplantation.[131] The studies identified were collectively insufficient to parametrise HSUVs in the CEM, so alternative sources were sought.

Table 46: Summary of the results of utility studies included in the economic SLR

<table>
<tr><th>Source (study/ publication, publication year)</th><th>Utility values and uncertainty around values</th></tr>
<tr><td>Cortesi 2020[150]</td><td>EQ-5D-3L utility outcomes*
<table><tr><th>Variable</th><th>PBC (N=66)</th></tr><tr><td>Mean (SD)</td><td>0.872 (0.112)</td></tr><tr><td>Median (IQR)</td><td>0.887 (0.827–0.915)</td></tr></table>*Additional data in the study details the number of responses by individual dimension of the EQ-5D-3L, but data have not been extracted</td></tr>
<tr><td>Longworth 2003[131]</td><td>• Mean EQ-5D scores of transplantation patients before and after transplantation were reported in a graph with no extractable data
• The EQ-5D scores were used to weigh survival and form QALYs in this study</td></tr>
<tr><td>Rice 2021[63]</td><td><u>EQ-5D utility index</u>
<table><tr><th rowspan="2">Health state</th><th colspan="2">EQ-5D index (95% CI)</th></tr><tr><th>Pre-liver transplant</th><th>Post-liver transplant</th></tr><tr><td>No symptoms or complications</td><td>0.917 (0.901–0.933)</td><td>0.838 (0.791–0.886)</td></tr><tr><td>Itching, no complications</td><td>0.899 (0.880–0.917)</td><td>0.897 (0.761–1.034)</td></tr><tr><td>Fatigue, no complications</td><td>0.842 (0.820–0.865)</td><td>0.644 (0.538–0.749)</td></tr><tr><td>Bone ache, no complications</td><td>0.756 (0.725–0.787)</td><td>0.697 (0.591–0.802)</td></tr><tr><td>Other symptoms, no complications</td><td>0.832 (0.806–0.858)</td><td>0.833 (0.719–0.946)</td></tr><tr><td>⩾1 symptom, no complications</td><td>0.721 (0.708–0.735)</td><td>0.600 (0.537–0.664)</td></tr><tr><td>⩾1 symptom, varices</td><td>0.727 (0.686–0.767)</td><td>-</td></tr></table></td></tr>
</table>

<table>
<tr><th>Source (study/ publication, publication year)</th><th>Utility values and uncertainty around values</th></tr>
<tr><td></td><td>
<table>
<tr><td>⩾1 symptom, ascites</td><td>0.596 (0.550–0.642)</td><td>-</td></tr>
<tr><td>⩾1 symptom, hepatic encephalopathy</td><td>0.694 (0.658–0.731)</td><td>-</td></tr>
<tr><td>⩾1 symptom, liver cancer</td><td>0.778 (0.689–0.868)</td><td>-</td></tr>
<tr><td>⩾1 symptom, ⩾1 complication</td><td>0.663 (0.638–0.688)</td><td>-</td></tr>
</table>
</td></tr>
<tr><td>Skat-Rørdam 2023[152]</td><td>EQ-5D-5L utility outcomes
<table>
<tr><th>Characteristic</th><th></th></tr>
<tr><td>Mean index value</td><td>0.7945</td></tr>
</table>
</td></tr>
<tr><td>Smith 2022[81]</td><td>EQ-5D-5L utility
<table>
<tr><th>Cohort</th><th>Baseline utility value, mean (SD)</th></tr>
<tr><td>All cohorts</td><td>0.69 (0.23)</td></tr>
<tr><td>Mild pruritus</td><td>0.75 (0.17)</td></tr>
<tr><td>Moderate pruritus</td><td>0.76 (0.17)</td></tr>
<tr><td>Severe pruritus</td><td>0.49 (0.28)</td></tr>
</table>
Over the course of the study, health utility declined in the placebo group (-0.01) and increased across all linerixibat arms (0.04–0.05)
Health utility score depending on pruritus level and sleep interference level
<table>
<tr><th>Cohort</th><th>Utility value, mean (SD)</th></tr>
<tr><td>Severe sleep interference</td><td>0.52 (0.303)</td></tr>
<tr><td>Severe pruritus and severe sleep interference</td><td>0.47 (0.309)</td></tr>
</table>
</td></tr>
</table>

<table>
<tr><th>Source (study/ publication, publication year)</th><th>Utility values and uncertainty around values</th></tr>
<tr><td></td><td>
Mean EQ-5D-5L utility score versus weekly sleep score, by pruritus severity, at baseline were reported in a graph with no extractable data
Health utility score depending on depression severity
<table>
<tr><th>Depression level</th><th>Utility value, mean (SD)</th></tr>
<tr><td>No/minimal depression</td><td>0.78 (0.171)</td></tr>
<tr><td>Severe depression</td><td>0.40 (0.291)</td></tr>
</table>
Overall, mean (SD) health utility scores decreased with worsening depression
Health utility score based on pruritis and depression severity
<table>
<tr><th>Pruritus level</th><th>Depression level</th><th>Utility value, mean (SD)</th></tr>
<tr><td rowspan="3">Severe pruritus</td><td>Mild depression</td><td>0.28 (0.132)</td></tr>
<tr><td>Moderate depression</td><td>0.29 (0.166)</td></tr>
<tr><td>Severe depression</td><td>0.30 (0.249)</td></tr>
</table>
Mean EQ-5D-5L utility score versus pruritus severity, by depression severity, at baseline were reported in a graph with no extractable data
</td></tr>
<tr><td>Wunsch 2022[151]</td><td>
Mean EQ-5D utility index for patients with PBC (N=386)
<table>
<tr><th>Characteristic</th><th>Utility value (SD)</th></tr>
<tr><td>EQ-5D-5L
•</td><td>0.73 (0.2)</td></tr>
</table>
</td></tr>
</table>

Abbreviations: CLD – chronic liver disease; EQ-5D – EuroQoL-five dimension; EQ-5D-3L – EuroQoL-five dimension-three level; EQ-5D-5L – EuroQoL-five dimension-five level; HRQoL – health-related quality-of-life; IQR – interquartile range; PBC – primary biliary cholangitis; NHS – National Health Service; QALY – quality-adjusted life year; SD – standard deviation; SLR – systematic literature review; UK – United Kingdom

B.3.4.4 Adverse events

Pruritus, urinary tract infections and fatigue were the AEs considered in the CEM. The disutility associated with pruritus as a TEAE was informed by clinician opinion during the CEM development. The disutility of urinary tract infections and fatigue were sourced from literature. As AEs are assumed to occur in the first cycle as a one-off, the disutility of these events was assumed to last for the duration of one cycle. A summary of the disutilities and sources applied in the CEM are provided in Table 47.

Table 47: Disutility of AEs applied in the model

Adverse event	Disutility value	Source
Pruritus	0.11	Clinician, 2023[142]
Urinary tract infection	0.06	Abrahamian, 2011[153]
Fatigue	0.07	TA779, 2021[154]

Abbreviations: AE – adverse event; TA – technology appraisal

B.3.4.5 Disutility of pruritus

Pruritus was considered as an outcome of interest in the CEM. For this reason, the disutility associated with pruritus was considered separate to pruritus as a TEAE and the HSUVs.

As described in Section B.3.4.2, pruritus was included in a regression of EQ-5D data collected during the ELATIVE study. The disutility of pruritus according to its severity was sourced from this regression and applied in the CEM. Patients with no pruritus have no disutility applied. As the distribution of severity of pruritus is considered throughout all time in the CEM, the disutility is applied throughout time and is considered distinct to the disutility of pruritus as a TEAE, which occurs only in the first cycle of treatment. As such, any double counting of the disutility associated with pruritus as an outcome and as a TEAE is minimised. The disutilities applied for pruritus over the model time horizon are reported in Table 48.

Table 48: Disutility of pruritus applied in the model

Severity of pruritus	Disutility value
Mild itch	[redacted]
CS itch	[redacted]

Abbreviations: CS – clinically significant

B.3.4.6 Health-related quality-of-life data used in the cost-effectiveness analysis

B.3.4.6.1 Health state utility values

HSUVs used in the CEM were primarily identified from the NICE submission of OCA, which were originally sourced from Wright *et al*., (2006) and published values in TA330, as shown in Table 49 below.[134,155]

These utility values were used in the OCA NICE submission (TA443) and were also validated by a UK clinical expert.[1,117] It was noted that utility values associated with DCC, pre-LT, LT, and post-LT were given a redacted decrement in TA443 to ensure the HSUVs were reflective of someone with PBC. Therefore, the utility values used in this submission have no decrement

applied. It was also noted that the utility value source for DCC was not focused on cholestatic disease and is too high. Alternative utility values for DCC will be considered, including McPhail *et al*. (2021) which gives a utility value of 0.62 from a HRQoL study in Australian cirrhosis patients.[156]

Table 49: Summary of utility values for cost-effectiveness analysis

State	Utility value: mean (SE)	95% confidence interval	Reference in TA443 submission (section and page number)	Justification
Mild	0.84 (0.17)	0.39 - 1.00	Table 61, page 157	Cholestatic disease utility reported in Younossi 2001[157]
Moderate	0.84 (0.17)	0.39 - 1.00	Table 61, page 157	Cholestatic disease utility reported in Younossi 2001[157]
High	0.55 (0.11)	0.33 - 0.76	Table 61, page 157	Previously reported value for compensated cirrhosis (TA330)[134]
DCC	0.38 (0.08)	0.24 - 0.53	Table 83, page 194	Previously reported value for DCC (TA330); redacted utility decrement not applied[134]
HCC	0.45 (0.09)	0.28 - 0.63	Table 61, page 157	Previously reported value for HCC (TA330)[134]
Pre-LT	0.38 (0.08)	0.24 - 0.53	Table 83, page 194	Previously reported value for pre-LT (TA330); redacted utility decrement not applied[134]
LT	0.57 (0.11)	0.34 - 0.78	Table 83, page 194	Previously reported value for LT (TA330); redacted utility decrement not applied[134]
Post-LT	0.67 (0.13)	0.39 - 0.90	Table 83, page 194	Previously reported value for post-LT (TA330)[134]
Re-emergence of PBC	0.67 (0.13)	0.39 - 0.90	Table 61, page 157	Assumed equivalent to post-LT, without utility decrement provided according to KOL feedback. (TA330)[134]

Abbreviations: AR – adverse reaction; DCC – decompensated cirrhosis; HCC – hepatocellular carcinoma; HS – health state; KOL – key opinion leader; LT – liver transplant; PBC – primary biliary cholangitis; SE – standard error; TA – technology appraisal

B.3.4.6.2 Disutilities

As summarised in Sections B.3.4.2 and B.1.1.1, disutilities for AEs and pruritus are included in the CEM. The disutilities applied in the model are summarised in Table 50.

Table 50: Disutilities applied in the model

Cause	Disutility	Source
Pruritus as a TEAE	0.11	Clinician opinion[117]
Urinary tract infection	0.06	Abrahamian *et al*. 2011[153]
Fatigue	0.07	TA779[154]

Mild itch	[redacted]	ELATIVE trial[140]
CS itch	[redacted]	ELATIVE trial[140]

Abbreviations: CS – clinically significant; TEAE – treatment-emergent adverse event; TA – technology appraisal

B.3.4.6.3 Carer disutilities

Carer disutilities are not applied in the CEM due to a lack of published literature informing of the HRQoL burden to carers of patients with PBC and liver disease. However, as described in Section B.1.3.2.3, the carer burden of PBC is substantial. In particular, there is a substantial burden to caregivers in the liver disease health state. The caregiver burden brings emotional strain, including anxiety, guilt, fear, and resentment, as well as a lack of time for their own self-care, frustrations with medical professionals and disease-related restrictions for carers.[86] A study on family and friends' responses for people with PBC showed that the severity of illness is a major predictor of the strain caregivers experience.[88] B.1.3.2.3, the carer burden of PBC is substantial. In particular, there is a substantial burden to caregivers in the liver disease health state. The caregiver burden brings emotional strain, including anxiety, guilt, fear, and resentment, as well as a lack of time for their own self-care, frustrations with medical professionals and disease-related restrictions for carers.[86] A study on family and friends' responses for people with PBC showed that the severity of illness is a major predictor of the strain caregivers experience.[88]

B.3.5 Cost and healthcare resource use identification, measurement, and valuation

The model includes the following direct cost categories:

- Treatment acquisition costs
- Health state costs
- AEs costs
- Pruritus costs

Where possible, unit costs were obtained for the 2022/23 cost year. If 2022/23 cost data were not available, then costs were sourced from earlier sources and were inflated to 2022/23 cost year using the Personal Social Services Research Unit (PSSRU).[158]

B.3.5.1 Treatment acquisition costs

The unit drug costs for OCA and UDCA were sourced from the British National Formulary (BNF) and eMIT, respectively, in line with the NICE methods manual and are presented in Table 51.[159,160] Ipsen have proposed a confidential simple discount patient access scheme (PAS) for elafibranor. This results in a net price of £[redacted] per pack.

Table 51: Unit drug costs

Drug	Formulation	Unit size (mg)	Price per pack (GBP) (with PAS)	Units per pack	Source
Elafibranor	Tablet	80	[redacted]	30	Data on file

OCA 5-10 mg	Tablet	5	2,384.04	30	NICE BNF[159]
		10	2,384.04	30	
UDCA	Capsule	250	6.72	60	eMIT[160]

Abbreviations: BNF – British National Formulary, eMIT – electronic market information tool; GBP – British Pound Sterling; mg – milligrams, NICE – National Institute for Health and Care Excellence, OCA – obeticholic acid, PAS – patient access scheme, UDCA – ursodeoxycholic acid

The dosing schedule for elafibranor was aligned with the dosing schedule from the ELATIVE trial: patients receive one 80 mg tablet of elafibranor orally once daily. The dosing schedule is also aligned with its draft SmPC.[11]

The dosing schedule for concomitant UDCA was based on the total daily dose received at baseline for patients enrolled in the ELATIVE trial.[112] Throughout the time horizon of the model, the dosing schedule for UDCA (whether received concomitantly or as monotherapy) was assumed equal across all treatments. The dosing regimen for OCA were sourced from the NICE BNF. All dosing data to inform the model is reported in Table 52.

Table 52: Dosing regimen of interventions and comparators

Drug	Dosing regimen
Elafibranor	Single elafibranor oral tablet of 80 mg/day.[11]
OCA	Start on single OCA oral tablet of 5 mg/day followed by 10 mg/day from 6 months.[159]
UDCA	UDCA dose of 991.2 mg/day, based on the average daily dose of UDCA received at baseline in the ELATIVE trial.[112]

Abbreviations: mg – milligram; OCA – obeticholic acid; UDCA – ursodeoxycholic acid

The treatment acquisition cost per cycle for all treatments are presented in Table 53. To derive the treatment cost per cycle, the number of tablets administered per cycle was calculated by dividing the pack price by the number of tablets per pack. The number of tablets per cycle was then multiplied by price per tablet to derive the treatment acquisition cost per cycle. As OCA have the same price per tablet regardless of dose, it was not necessary to calculate a cost dependent on dose.

As all treatments are orally administered, no administration costs were applied in the model. Wastage costs were not applied in the economic analysis as it was assumed patients would receive their medication in full tablets. A compliance rate of [redacted]% (sourced from the ELATIVE study) was applied to the treatment acquisition cost of elafibranor and assumed equal to OCA.[112] As the average dose per day of UDCA was obtained from patients at baseline in the ELATIVE study, it was not necessary to consider compliance in addition to this.

Table 53: Treatment acquisition cost per cycle

Drug	Cycle	Price per tablet (GBP)	Number of tablets per cycle	Total cost per cycle (GBP)
Elafibranor	All cycles	[redacted]	91	[redacted]
OCA	Up to cycle 2	79.47	91	7,256.42
	Cycle 3+	79.47	91	7,256.42
UDCA	All cycles	0.11	362	40.55

Abbreviations: GBP – British pounds; mg – milligram; OCA – obeticholic acid

It is assumed that 95% of patients receive concomitant UDCA or UDCA monotherapy, as informed by the ELATIVE trial.[4] The average cost per patient per cycle of UDCA is £38.52 (see Table 54).

Table 54: UDCA costs

Intervention/comparator	Proportion of patients receiving UDCA per cycle	Average cost per patient per cycle of UDCA (GBP)
Elafibranor	95.0%	38.52
OCA	95.0%	38.52
UDCA	95.0%	38.52

Abbreviations: GBP – British pound; OCA – obeticholic acid; UDCA – ursodeoxycholic acid

B.3.5.2 Health state costs

Costs associated with the management and monitoring of patients with PBC were captured over the lifetime time horizon of the CEM. Health care resource use (HCRU) for the low, moderate and high risk health states in the PBC biomarker component were sourced from the NICE TA443 submission for OCA.[1] Similarly, HCRU for the liver disease component health states (except pre- and post-LT) was sourced from the Wright *et al*. (2006) study.[155] Clinical opinion in the TA443 submission suggested that the health state costs for patients in the high risk health state would be 50% of the health state costs accrued per cycle in the DCC health state. Thus, HCRU for patients in the high risk health state was assumed to be 50% of the HCRU associated with DCC. To quantify the costs associated with the identified HCRU, unit costs were sourced from NHS reference costs and PSSRU costs.[158,161]

Total costs associated with pre-LT, LT, and post-LT health states were inflated to 2022/23 values using data reported by the PSSRU 2022 where necessary.[158] In order to provide a comprehensive disaggregation of the costs associated with LT, costs were sourced from NICE Highly Specialised Technology (HST) HST17.[94] The HST17 appraisal used costs associated with pre-LT, LT, and post-LT health states from the TA443 appraisal,[139] but also included costs for the organ, organ retrieval, and LT follow-up for 2 years.[94] Though HST17 focuses on a paediatric population, the costs reported in HST17 were not paediatric-specific and so are relevant for adult patients with PBC. As the pre-LT costs were reported as an annual cost, they were adjusted to a per cycle cost by dividing through by 4 (to align with the three-month cycle length). All costs associated with the LT and first two years following the LT were applied in the cycle in which the LT occurred as a one-off cost since patients reside in the LT health state for one cycle only.[94]

Post-LT (i.e. after 2 years) costs were also sourced from Rice *et al*. (2021) submission to capture the long-term costs post-LT.[63] Similar to the pre-LT health state, resource use in the post-LT health state were adjusted to a per cycle cost by dividing through by 4 (to align with the three-month cycle length). Immunosuppression resource use post-LT transplant (azathioprine, tacrolimus and prednisolone) are applied to patients in the LT and post-LT health states for the first year and then all subsequent years following LT (see Table 55). The immunosuppressants used following LT were also sourced from HST17, but as the dose was applicable to a paediatric population, the doses were sourced from the BNF; costs were also sourced from the BNF.[95, 97,162]

A scenario is performed where the total cost per year associated with pre-LT health state care, LT health state (including procedure and LT follow-up for 2 years only) were sourced from the TA443 NICE submission for OCA.[1] In the scenario, immunosuppression costs for first and subsequent years are not included. This scenario aligns with the LT sources applied in the TA443 submission, however, the HST17 source is considered in the base-case as it provides a more comprehensive disaggregation of the costs associated with LT.

Table 55: Liver transplant immunosuppression costs

Drug	Month*	Dose per day (mg/kg) †	Unit size (mg)†	Units per pack †	Cost per pack (GBP) †	Annual cost - year 1 (GBP)	Annual cost - subsequent years (GBP)
Azathioprine	All months	1.00	25.00	28.00	1.16	42.85	42.85
Tacrolimus	All months	0.0010	1.00	50.00	55.69	28.80	28.80
Prednisolone	All months	Not indicated following LT in adults	50.00	28.00	23.00	0.00	0.00
Total						71.66	71.66

Abbreviations: mg – Milligram; kg – Kilogram; GBP – British Pound Sterling
* Sourced from HST17
† Sourced from BNF

Due to limited data for the costs associated with re-emergence of PBC, the resource use per cycle in the re-emergence of PBC is assumed to be the same as patients in the high risk health state.

A list of health states and associated costs in the economic model are presented in Table 56.

Table 56: List of health states and associated costs in the economic model

Health state	Resource	Cost per unit (GBP)	Resource use per cycle	Source
Mild	Outpatient visits - Doctor (consultant-led)	220.17	0.25	NHS reference costs 2021/22; TA443[1,161]
	Blood tests	1.59	2.25	NHS reference costs 2021/22; TA443[1,161]
	Outpatient follow-up visit (nurse led)	192.20	0.25	NHS reference costs 2021/22; TA443[1,161]
	Total cost per cycle (GBP)	**106.67**		
Moderate	Outpatient visits - Doctor (consultant-led)	220.17	0.25	NHS reference costs 2021/22; TA443[1,161]

	Blood tests	1.59	2.25	NHS reference costs 2021/22; TA443[1,161]
	Outpatient follow-up visit (nurse led)	192.20	0.50	NHS reference costs 2021/22; TA443[1,161]
	Total cost per cycle (GBP)	**154.72**		
High	Inpatient days - ICU	1,110.65	0.03	NHS reference costs 2021/22; TA443[1,161]
	Inpatient days - HDU	737.30	0.03	NHS reference costs 2021/22; TA443[1,161]
	Inpatient days - Liver unit	776.22	1.68	NHS reference costs 2021/22; TA443[1,161]
	Inpatient days - General ward	415.61	0.39	NHS reference costs 2021/22; TA443[1,161]
	TIPPS	4,035.84	0.02	NHS reference costs 2021/22; TA443[1,161]
	Hepatic angiographies (pre- and post-contrast)	268.34	0.02	NHS reference costs 2021/22; TA443[1,161]
	Endoscopies	1,108.18	0.28	NHS reference costs 2021/22; TA443[1,161]
	Liver biopsies	934.85	0.01	NHS reference costs 2021/22; TA443[1,161]
	Outpatient visits - Doctor (consultant-led)	220.17	0.67	TA443[1]
	Outpatient visits- Nurse (non-consultant led)	204.52	0.05	TA443[1]
	Total cost per cycle (GBP)	**2,080.52**		
DCC	Inpatient days - ICU	1,110.65	0.06	NHS reference costs 2021/22; Wright *et al*. 2006[155,161]
	Inpatient days - HDU	737.30	0.06	NHS reference costs 2021/22; Wright *et al*. 2006[155,161]
	Inpatient days - Liver unit	776.22	3.35	NHS reference costs 2021/22; Wright *et al*. 2006[155,161]
	Inpatient days - General ward	415.61	0.78	NHS reference costs 2021/22; Wright *et al*. 2006[155,161]
	TIPPS	4,034.84	0.04	NHS reference costs 2021/22; Wright *et al*. 2006[155,161]
	Hepatic angiographies (pre- and post-contrast)	268.34	0.05	NHS reference costs 2021/22; Wright *et al*. 2006[148,154]

	Endoscopies	1,108.18	0.57	NHS reference costs 2021/22; Wright *et al*. 2006[155,161]
	Liver biopsies	934.85	0.02	NHS reference costs 2021/22; Wright *et al*. 2006[155,161]
	Outpatient visits - Doctor (consultant-led)	220.17	1.34	NHS reference costs 2021/22; Wright *et al*. 2006[155,161]
	Outpatient visits- Nurse (non-consultant led)	204.52	0.10	NHS reference costs 2021/22; Wright *et al*. 2006[155,161]
	Total cost per cycle (GBP)	**4,161.05**		
HCC	Inpatient days - Liver unit	776.22	2.72	NHS reference costs 2021/22; Wright *et al*. 2006[155,161]
	Inpatient days - General ward	415.61	0.93	NHS reference costs 2021/22; Wright *et al*. 2006[155,161]
	Hepatic angiographies (pre- and post-contrast)	268.34	0.16	NHS reference costs 2021/22; Wright *et al*. 2006[155,161]
	Endoscopies	1,108.18	0.12	NHS reference costs 2021/22; Wright *et al*. 2006[155,161]
	Liver biopsies	934.85	0.08	NHS reference costs 2021/22; Wright *et al*. 2006[155,161]
	Outpatient visits - Doctor (consultant-led)	220.17	1.34	NHS reference costs 2021/22; Wright *et al*. 2006[155,161]
	Outpatient visits- Nurse (non-consultant led)	204.52	0.10	NHS reference costs 2021/22; Wright *et al*. 2006[155,161]
	Total cost per cycle (GBP)	**3,053.32**		
Pre-LT	Pre-LT (annual cost)	21,186.63	0.25	HST17[94]
	Total cost per cycle (GBP)	**5,296.66**		
LT	LT (procedure)	75,630.42	1.00	HST17[94]
	LT (organ)	19,209.83	1.00	HST17[94]
	LT (organ retrieval)	26,472.80	1.00	HST17[94]
	Post-LT (first 2 years)	42,253.87	1.00	HST17[94]
	LT immunosuppression cost (first year)	71.66	1.00	BNF[95, 97,162]

	Total cost per cycle (GBP)	**163,638.57**		
Post-LT	LT immunosuppression cost (subsequent years)	71.66	0.25	BNF[95, 97,162]
	Post-LT (annual cost)	3,606.63	0.25	Rice *et al.* (2021).[63]
	Total cost per cycle (GBP)	**919.57**		
Re-emergence of PBC	Assumed equal to healthcare resource use of high risk health state			
	Total cost per cycle (GBP)	**2,080.52**		

Abbreviations: DCC – decompensated cirrhosis; GBP – British Pound Sterling; HCC – hepatocellular carcinoma; HDU – high dependency unit; ICU – intensive care unit; LT – liver transplant; NHS – National Health Service; PBC – primary biliary cholangitis; TA – technology appraisal; TIPPS – transjugular intrahepatic portosystemic shunt

B.3.5.3 Adverse events costs

In line with the NICE appraisal for OCA, it was assumed that each AE is only experienced once per patient, and the cost of each AE will be applied within the first cycle of the CEM for elafibranor and other included comparators. Costs were multiplied by the frequency of AEs to evaluate the total costs associated with AEs by treatment, as shown in Table 57.

The cost of pruritus was sourced from the NICE TA443 submission and inflated using PSSRU 2022.[1,154]

The cost of the urinary tract infection (UTI) was sourced from an NHS report evaluating treatment of UTIs in women under 65 and inflated using PSSRU 2022.[158,163] The model assumes costs associated with fatigue equal to the cost of outpatient visits (non-consultant led) sourced from NHS 2021/22 reference costs, as no drug treatment is recommended for fatigue according to PBC guidelines.[161]

Table 57: Adverse event unit costs

Adverse event	Unit cost (GBP)
Pruritus	200.75
Urinary Tract Infection	46.43
Fatigue	204.52

Abbreviations: GBP – British Pound Sterling

B.3.5.4 Pruritus costs

The percentage of patients who are prescribed medicines for pruritus when treated with OCA or UDCA was based on clinical expert opinion and is presented in Table 58.[117] As patients treated with elafibranor would not receive bezafibrate to manage pruritus, the share of bezafibrate was excluded and re-apportioned to the alternative treatments for patients treated with elafibranor.

Table 58: Percentage of patients who receive medicines for pruritus (based on clinical expert opinion[117])

Drug	Percentage of patients cost applies to for patients treated with elafibranor	Percentage of patients cost applies to for patients treated with OCA or UDCA
Cholestyramine	35%	30%
Rifampicin	35%	30%
Bezafibrate	0%	20%
Gabapentin	20%	15%
Naltrexone	10%	5%

Abbreviations: OCA – obeticholic acid; UDCA – ursodeoxycholic acid

Resources associated with monitoring pruritus were sourced from the OCA NICE appraisal. It is assumed that resource use for CS itch is twice that of mild itch, and this assumption was validated by a clinical expert.[117] The pruritus monitoring and drug resource use was validated with a UK clinical expert and are presented in Table 59 and Table 60, respectively. [117] A scenario assuming equal resource use for both mild and CS itch has been explored.

Table 59: Pruritus monitoring resource use

Item		Resource use per year	Resource use per cycle: all cycles	Source
Mild itch	Outpatient visits (doctor)	1.00	0.25	Clinical expert opinion[117]
	Outpatient visits follow-up (doctor)	2.00	0.50	Clinical expert opinion[117]
	Blood test monitoring	2.00	0.50	TA443[1]
CS itch	Outpatient visits (doctor)	2.00	0.50	Clinical expert opinion[117]
	Outpatient visits follow-up (doctor)	4.00	1.00	Clinical expert opinion[117]
	Blood test monitoring	4.00	1.00	TA443[1]

Abbreviations: CS – clinically significant; TA – technology appraisal

Table 60: Pruritus drug resource use

Drug	Frequency	Proportion of patients receiving treatment for pruritus when treated with elafibranor	Proportion of patients receiving treatment for pruritus when treated with OCA or UDCA	Source
Cholestyramine	Once daily	35%	30%	Clinical expert opinion[117]
Rifampicin	Once daily	35%	30%	Clinical expert opinion[117]
Bezafibrate	Once daily	0%	20%	Clinical expert opinion[117]
Gabapentin	Three times a day	20%	15%	Clinical expert opinion[117]

Naltrexone	Once daily	10%	5%	Clinical expert opinion[117]

Abbreviations: OCA – obeticholic acid; UDCA – ursodeoxycholic acid

The unit costs of resource use were sourced from the National Reference Costs Collection Publication, BNF, and validated with clinical experts. The related cost data are presented in Table 61.

Table 61: Unit costs of resource use for pruritus

Item		Unit cost (GBP)	Cost per cycle for mild itch (GBP)	Cost per cycle for CS itch (GBP)	Source
Monitoring	Outpatient visits (doctor)	220.17	55.04	110.09	NHS reference costs 2021/22[161]
	Outpatient visits follow-up (doctor)	178.80	89.40	178.80	NHS reference costs 2021/22[161]
	Blood test monitoring	1.59	0.80	1.59	NHS reference costs 2021/22[161]
Drug	Cholestyramine	1.05	96.04	96.04	BNF, 2023[164]
	Rifampicin	1.44	131.73	131.73	BNF, 2023[165]
	Bezafibrate	0.25	23.22	23.22	BNF, 2023[166]
	Gabapentin	0.03	6.96	6.96	BNF, 2023[167]
	Naltrexone	2.65	242.01	242.01	BNF, 2023[96]

Abbreviations: BNF – British National Formulary; CS – clinically significant; GBP – British Pound Sterling; NHS – National Health Service

For elafibranor, the total mild pruritus cost per cycle was £296.66, and the total CS pruritus cost per cycle was £441.90. For OCA and UDCA, the total mild pruritus cost per cycle was £270.88, and the total CS pruritus cost per cycle was £416.12. Pruritus cost per cycle is both elafibranor and OCA are presented in Table 62.

Table 62: Pruritus cost per cycle for elafibranor, OCA and UDCA

Pruritus severity	Cost per cycle for elafibranor (GBP)	Cost per cycle for OCA and UDCA (GBP)
Mild itch	296.66	270.88
CS itch	441.90	416.12

Abbreviations: CS – clinically significant; GBP – British Pound Sterling; OCA – obeticholic acid; UDCA – ursodeoxycholic acid

B.3.5.5 Miscellaneous unit costs and resource use

The economic model includes end of life costs for patients who die in health states where there is expected to be palliative care. End of life costs are included for patients who die in the DCC and HCC health states and were sourced from published literature; they are presented in

Table 63.

Table 63: End of life costs considered in the CEM

Health state	End of life cost	Source
DCC	10,901.52	Gola *et al.* (2015)[168]
HCC	8,804.62	NICE TA666[169]

Abbreviations: DCC – decompensated cirrhosis; HCC – hepatocellular carcinoma

B.3.6 Severity

The QALY shortfall calculations have been assessed for a cohort with an average age of 57 and a female proportion of 96% as per the ELATIVE trial (see section B.2.3.2). The results indicate that the elafibranor does not meet the criteria for a QALY weighting.

B.3.7 Uncertainty

As mentioned in section B.1.3.1.3, complications associated with PBC progression, such as cirrhosis and liver failure, may take a long time to develop, and clinical trials of novel PBC therapies would require a prolonged follow-up period to demonstrate a reduction in these outcomes. It is also difficult to recruit a large enough study population of patients with advanced PBC (a subgroup of an already small patient population) that would provide sufficient statistical power for a clinical trial.[50,51]

The ELATIVE trial reported clinical outcomes for a 52 week period, from which the clinical inputs to the economic model were derived. This means that complications associated with advanced stages of PBC, such as cirrhosis and liver failure, may not be fully realised in the model. Therefore, there is uncertainty of the economic benefit of elafibranor for the entire PBC population, including those with advanced-stage disease, in England and Wales. However, despite there being limited long-term data, the model made use of ALP and TB levels that have been well validated as surrogate endpoints for long-term outcomes of patients.

B.3.8 Summary of base-case analysis inputs and assumptions

B.3.8.1 Summary of base-case analysis inputs

A summary of the base-case analysis inputs can be found in Appendix J.

B.3.8.2 Assumptions

Several assumptions were made in the model and are presented in Table 64.

Table 64: Assumptions underpinning CEM

Variable	Assumed value	Justification
Time horizon	Lifetime	Due to the chronic nature of the condition, a lifetime time horizon is chosen to sufficiently capture all relevant differences in the future costs and outcomes associated with the interventions being compared.[129,139]

Cycle length	Three months	A three-month cycle length is considered sufficiently short enough to capture meaningful differences in disease progression over time. Aligns with the NICE reference case and OCA NICE submission.[139,170]
Half-cycle correction applied	Yes	Half-cycle correction means that patients may transition at any point during the cycle. Transitions are assumed to occur at the midpoint of the cycle to reflect the continuous nature of transitions between states, in line with the NICE reference case.[17]
Health states	• Low risk: ALP ≤ 200 u/L and TB ≤ 20 µmol/L • Moderate risk: ALP > 200 u/L and TB ≤ 20 µmol/L • High risk: TB > 20 µmol/L or compensated cirrhosis (defined as liver stiffness > 15 kPa) • Decompensated cirrhosis • Hepatocellular carcinoma • Pre-LT • LT • Post-LT • PBC re-emergence	Aligned with the model structure of the obeticholic acid NICE submission (TA443) where significance was achieved.[1] The aggregation of compensated cirrhosis and abnormal TB into one high risk health state was considered appropriate as in PBC patients because liver histology is rarely known. Furthermore, all transition probabilities leading to and coming out of this combined health state were estimated based on data on elevated and rising bilirubin levels.
Model approach	Markov cohort structure	Consistent with other approaches for liver disease modelling, for example, for hepatitis C.[134] 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.
Transitions for PBC biomarker health states: elafibranor and UDCA	Patients can move between the mild, moderate, and high risk health states.	Based on transition probabilities estimated based on the ELATIVE trial patient level data.
Extrapolation of treatment effect for elafibranor and OCA in the PBC biomarker phase	Patients treated with elafibranor and OCA will remain in state after cycle 4 for the remainder of the time horizon unless they discontinue treatment or progress to liver disease from the moderate and severe risk of disease progression health states.	Trial data from ELATIVE supports the conclusion that ALP and TB levels are stabilised within 12 months of treatment. This is line with the assumptions applied for OCA in TA443.
Extrapolation of treatment effect	After cycle 4, patients treated with UDCA will continue to	Trial data from ELATIVE supports the conclusion that TB levels continue to

for UDCA in the PBC biomarker phase	transition to worse health states at the rate observed in the last cycle of data in ELATIVE. It is also assumed that patients cannot move to better health states.	increase when patients are treated with UDCA only. This conclusion was supported by clinical expert opinion.
Disease trajectory on discontinuation of elafibranor and OCA	On discontinuation, patients will return to baseline and follow the disease trajectory of UDCA.	There is no evidence to suggest that treatment benefit is maintained after discontinuation. This conclusion was supported by clinical expert opinion.
Transitions for PBC biomarker health states: comparators	Calculated using odds ratios derived from ITCs.	Required in the absence of direct clinical data comparisons.
Transitions for liver disease states	Patients transition from moderate and high risk health states to the liver disease health states, and between liver disease health states as disease progresses.	Based on published transition probabilities, as presented in Section B.3.3.2.
TTD extrapolation for elafibranor	Exponential distribution was the best fit to the Kaplan Meier data for all-cause TTD beyond trial duration.	• The exponential distribution was the best statistically fit. • The exponential distribution was also consistent with treatment duration observed in the ELATIVE trial studies (~89% of patient retention after 12 months).[171]
TTD extrapolation for OCA	The OR for all-cause discontinuation with OCA relative to elafibranor is applied to the elafibranor TTD.	In the absence of direct head-to-head data, it is most appropriate to use NMA data to inform the relative likelihood of treatment retention.
HSUVs for the PBC biomarker health states	Sourced from TA443.	Whilst the ELATIVE trial collected EQ-5D data, there were insufficient observations in the high risk health state to reliably inform utility values across all PBC biomarker health states.
HSUVs for the liver disease health states	Sourced from TA443.	Aligned with the obeticholic acid NICE submission (TA443) which was acknowledged by the committee.[1] The utility values have also been validated by clinical experts.[117]

Abbreviations: ALP – alkaline phosphatase; CEM – cost-effectiveness model; EQ-5D – EuroQol-five dimension; HSUV – health state utility value; ITC – indirect treatment comparison; kPa – kilopascal; LT – liver transplant; NHS – National Health Service; NICE – National Institute for Health and Care Excellence; NMA – network meta-analysis; OCA – obeticholic acid; OR – odds ratio; PBC – primary biliary cholangitis; TA – technology appraisal; TB – total bilirubin; TTD – time-to-treatment discontinuation; UDCA – ursodeoxycholic acid; ULN – upper limit of normal; µmol – micromole

B.3.9 Base-case results

B.3.9.1 Base-case incremental cost-effectiveness analysis results

The base-case cost-effectiveness analysis results are presented in Table 65. The base-case results are based on the price of elafibranor offered under the PAS.

Table 65: Base-case results for elafibranor vs OCA and elafibranor vs UDCA, using the PAS price of elafibranor

Treatment	Total			Incremental			ICER (£) versus baseline
	Costs (£)	LYG	QALYs	Costs (£)	LYG	QALYs	
Elafibranor	[redacted]	[redacted]	[redacted]	-	-	-	-
OCA	203,726	11.997	7.558	[redacted]	[redacted]	[redacted]	Dominating
UDCA	104,283	10.808	6.383	[redacted]	[redacted]	[redacted]	31,762

Abbreviations: ICER – incremental cost-effectiveness ratio; LYG – life years gained; PAS – patient access scheme; OCA – obeticholic acid; QALYs – quality-adjusted life years; UDCA – ursodeoxycholic acid

B.3.9.2 Disaggregated results

Disaggregated life years, QALYs and costs by health state are presented in Table 66, Table 67 and Table 68, respectively.

Table 66: LY gain by health state

Health state	LYG elafibranor	LYG OCA	LYG UDCA	Increment elafibranor vs OCA	Increment elafibranor vs UDCA
Mild	[redacted]	1.560	0.356	[redacted]	[redacted]
Moderate	[redacted]	3.866	2.864	[redacted]	[redacted]
High	[redacted]	4.830	5.558	[redacted]	[redacted]
DCC	[redacted]	0.179	0.206	[redacted]	[redacted]
HCC	[redacted]	0.108	0.123	[redacted]	[redacted]
Pre-LT	[redacted]	0.417	0.475	[redacted]	[redacted]
LT	[redacted]	0.041	0.047	[redacted]	[redacted]
Post-LT	[redacted]	0.882	1.040	[redacted]	[redacted]
Re-emergence of PBC	[redacted]	0.114	0.139	[redacted]	[redacted]
Total LYs	[redacted]	11.997	10.808	[redacted]	[redacted]

Abbreviations: DCC – decompensated cirrhosis; HCC – hepatocellular carcinoma; LT – liver transplant; LY – life years gained; OCA – obeticholic acid; PBC – primary biliary cholangitis; UDCA – ursodeoxycholic acid

Table 67: QALY gain by health state

Health state	QALY elafibranor	QALY OCA	QALY UDCA	Increment elafibranor vs OCA	Increment elafibranor vs UDCA
Mild	[redacted]	1.243	0.287	[redacted]	[redacted]
Moderate	[redacted]	3.057	2.288	[redacted]	[redacted]
High	[redacted]	2.375	2.765	[redacted]	[redacted]
DCC	[redacted]	0.064	0.074	[redacted]	[redacted]
HCC	[redacted]	0.046	0.053	[redacted]	[redacted]
Pre-LT	[redacted]	0.149	0.171	[redacted]	[redacted]
LT	[redacted]	0.022	0.025	[redacted]	[redacted]
Post-LT	[redacted]	0.536	0.638	[redacted]	[redacted]
Re-emergence of PBC	[redacted]	0.068	0.083	[redacted]	[redacted]
Total QALYs	[redacted]	7.558	6.383	[redacted]	[redacted]

Abbreviations: DCC – decompensated cirrhosis; HCC – hepatocellular carcinoma; LT – liver transplant; OCA – obeticholic acid; PBC – primary biliary cholangitis; QALYs – quality-adjusted life years; UDCA – ursodeoxycholic acid

Table 68: Costs by health state, using the PAS price of elafibranor

Health state	Cost elafibranor (£)	Cost OCA (£)	Cost UDCA (£)	Increment elafibranor vs OCA (£)	Increment elafibranor vs UDCA (£)
Mild	[redacted]	43,569	312	[redacted]	[redacted]
Moderate	[redacted]	59,097	3,037	[redacted]	[redacted]
High	[redacted]	55,405	48,745	[redacted]	[redacted]
DCC	[redacted]	2,994	3,434	[redacted]	[redacted]
HCC	[redacted]	1,323	1,509	[redacted]	[redacted]
Pre-LT	[redacted]	8,845	10,080	[redacted]	[redacted]
LT	[redacted]	27,046	30,858	[redacted]	[redacted]
Post-LT	[redacted]	3,250	3,835	[redacted]	[redacted]
Re-emergence of PBC	[redacted]	953	1,162	[redacted]	[redacted]
Death	[redacted]	1,242	1,310	[redacted]	[redacted]
Total costs	[redacted]	203,726	104,283	[redacted]	[redacted]

Abbreviations: DCC – decompensated cirrhosis; HCC – hepatocellular carcinoma; LT – liver transplant; OCA – obeticholic acid; PAS – patient access scheme; PBC – primary biliary cholangitis; UDCA – ursodeoxycholic acid

B.3.10 Exploring uncertainty

B.3.10.1 Probabilistic sensitivity analysis

A probabilistic sensitivity analysis (PSA) was used to assess the effect of parameter uncertainty on the ICER. The following distributions were assumed for parameters: Dirichlet for transitions matrices; gamma for costs; beta for probabilities and utilities; lognormal for odds ratios. The PSA works by drawing a value for each parameter from their assumed probability distributions 500 times and evaluating the ICER obtained with each iteration. Where the standard errors for the parameters are unknown, they are assumed to be 20% of the parameter value for the purposes of defining the distributions for each parameter. Mean incremental results were recorded and illustrated through an incremental cost-effectiveness plane (ICEP). The mean PSA results are presented in Table 69. The ICEP, CEAC and cost-effectiveness acceptability frontier (CEAF) are presented in Figure 50, Figure 51, and Abbreviations: GBP – British Pound Sterling; OCA – obeticholic acid; UDCA – ursodeoxycholic acid

Figure 52, respectively. The PSA results are based on the price of elafibranor offered under the PAS.

Table 69: PSA results for elafibranor vs OCA and elafibranor vs UDCA, using the PAS price of elafibranor

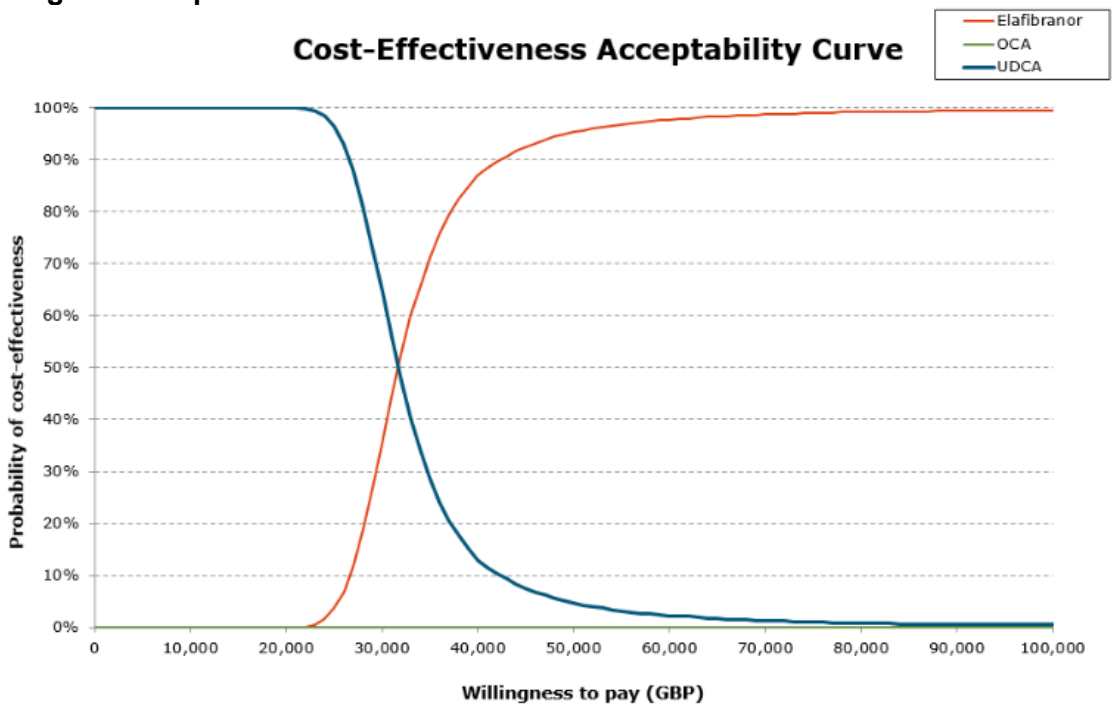
Treatment	Total costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs	ICER of elafibranor (£)
Elafibranor	[redacted]	[redacted]	-	-	-
OCA	202,233	7.575	[redacted]	[redacted]	Dominating
UDCA	103,015	6.493	[redacted]	[redacted]	32,628

Abbreviations: ICER – incremental cost-effectiveness ratio; OCA – obeticholic acid; QALY – quality-adjusted life year; UDCA – ursodeoxycholic acid

Figure 50: ICEP for elafibranor vs OCA and elafibranor vs UDCA (10,000 iterations), using the PAS price of elafibranor

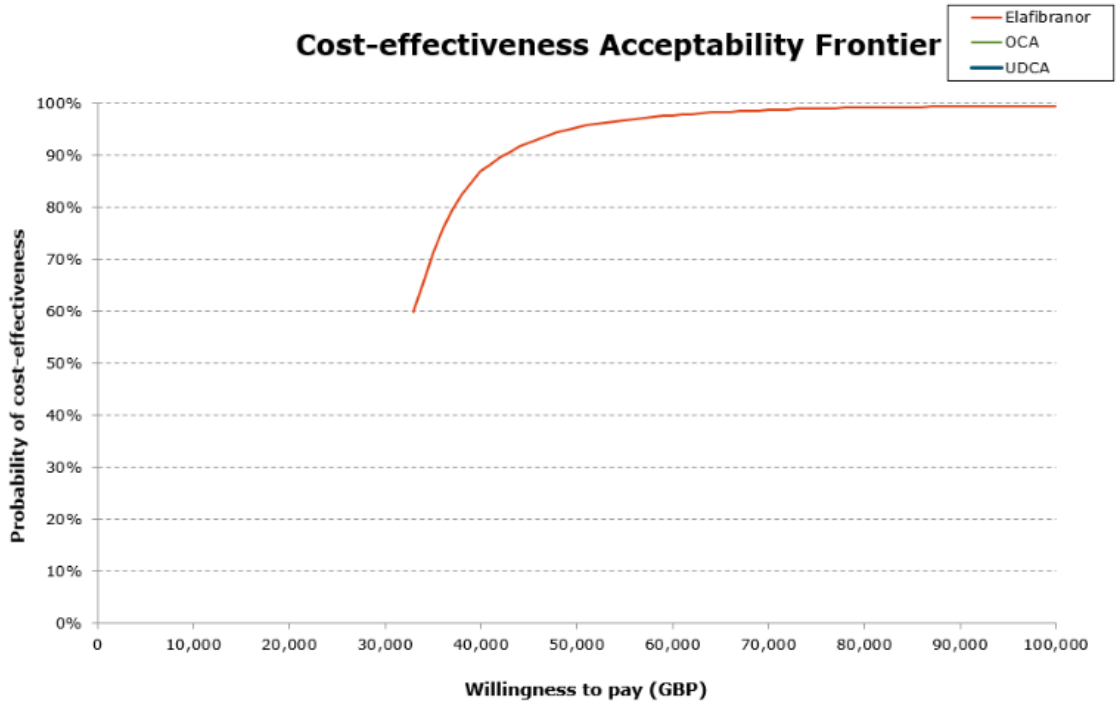
Abbreviations: OCA – obeticholic acid; UDCA – ursodeoxycholic acid

Figure 51: CEAC for elafibranor vs OCA and elafibranor vs UDCA (10,000 iterations) , using the PAS price of elafibranor



Abbreviations: GBP – British Pound Sterling; OCA – obeticholic acid; UDCA – ursodeoxycholic acid

Figure 52: CEAF for elafibranor vs OCA and elafibranor vs UDCA (10,000 iterations)



Abbreviations: GBP – British Pound Sterling; OCA – obeticholic acid; UDCA – ursodeoxycholic acid

B.3.10.2 One-way sensitivity analysis

The one-way sensitivity analysis (OWSA) for elafibranor versus OCA results are presented in Table 70. The NMB is most sensitive to the OCA cost per cycle parameters, with a difference in NMB of £75,579 and £10,947, respectively. The results are also sensitive to health state costs in the high and LT health states, with a difference in NMB of £6,171 and £4,291, respectively.

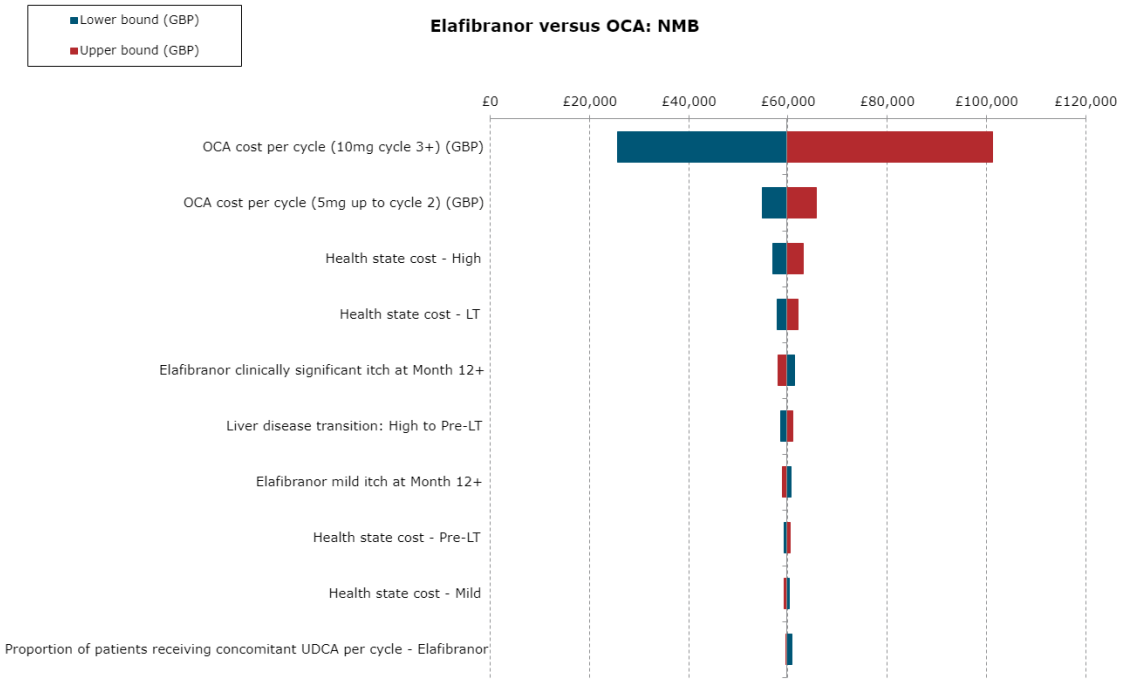
Table 70: OWSA results for elafibranor versus OCA (top 10 most sensitive parameters only)*

Parameter	Lower bound (£)	Upper bound (£)	Difference (£)
OCA cost per cycle (10mg cycle 3+) (GBP)	£25,631	£101,210	£75,579
OCA cost per cycle (5mg up to cycle 2) (GBP)	£54,822	£65,769	£10,947
Health state cost - High	£56,979	£63,150	£6,171
Health state cost - LT	£57,828	£62,119	£4,291
Elafibranor CS itch at Month 12+	£61,339	£57,968	£3,372
Liver disease transition: High to Pre-LT	£58,506	£60,981	£2,475
Elafibranor mild itch at Month 12+	£60,657	£58,952	£1,705
Health state cost - Pre-LT	£59,136	£60,531	£1,395
Health state cost - Mild	£60,250	£59,179	£1,071

Proportion of patients receiving concomitant UDCA per cycle - Elafibranor	£60,746	£59,709	£1,037

Abbreviations: CS – clinically significant; GBP – British Pound Sterling; LT – liver transplant; mg – milligrams; OCA – obeticholic acid; OWSA – one-way sensitivity analysis; UDCA – ursodeoxycholic acid
*Note: The OWSA vs. OCA uses net monetary benefit (NMB) because elafibranor was dominating

Figure 53: OWSA tornado diagram for elafibranor versus OCA



Abbreviations: GBP – British Pound Sterling; LT – liver transplant; mg – milligrams; OCA – obeticholic acid; OWSA – one-way sensitivity analysis; UDCA – ursodeoxycholic acid

The result of the deterministic sensitivity analysis for elafibranor versus UDCA are presented in Table 71. The ICER is most sensitive to health state costs in the high and LT health states, with a difference in NMB of £4,321 and £2,878, respectively.

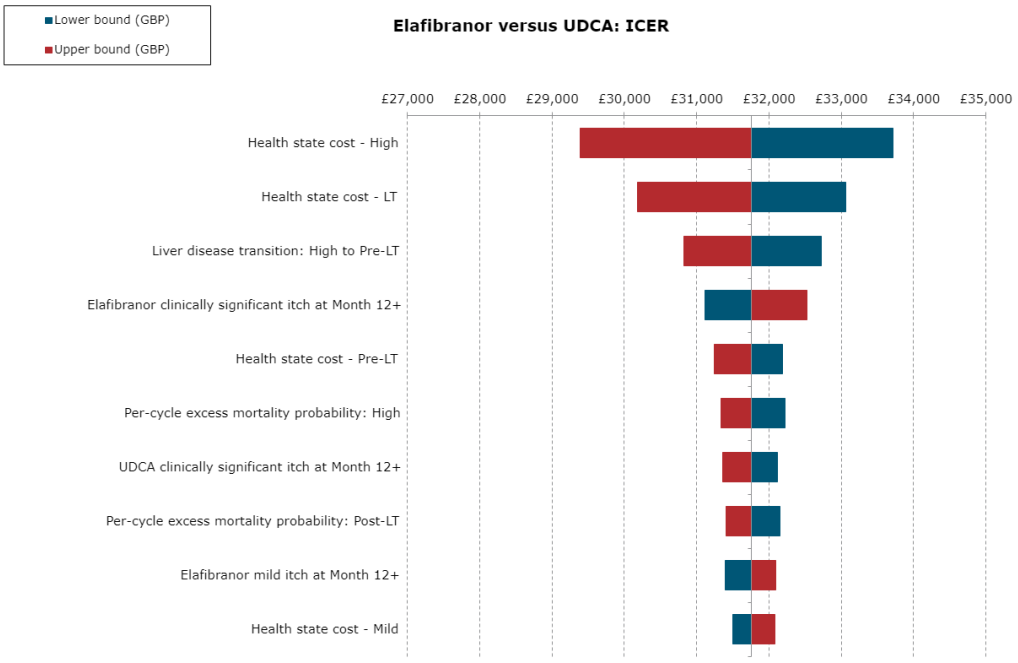
Table 71: OWSA results for elafibranor versus UCDA (top 10 most sensitive parameters only)

Parameter	Lower bound (£)	Upper bound (£)	Difference (£)
Health state cost - High	£33,713	£29,392	£4,321
Health state cost - LT	£33,061	£30,184	£2,878
Liver disease transition: High to Pre-LT	£32,720	£30,827	£1,894
Elafibranor CS itch at Month 12+	£31,119	£32,524	£1,405
Health state cost - Pre-LT	£32,184	£31,249	£935
Per-cycle excess mortality probability: High	£32,221	£31,337	£884
UDCA CS itch at Month 12+	£32,123	£31,364	£759
Per-cycle excess mortality probability: Post-LT	£32,158	£31,403	£755

Elafibranor mild itch at Month 12+	£31,401	£32,095	£695
Health state cost - Mild	£31,498	£32,082	£583

Abbreviations: CS – clinically significant; LT – liver transplant; UDCA – ursodeoxycholic acid; OWSA – one-way sensitivity analysis

Figure 54: OWSA tornado diagram for elafibranor versus UCDA



Abbreviations: LT – liver transplant; UDCA – ursodeoxycholic acid; OWSA – one-way sensitivity analysis

B.3.10.3 Scenario analysis

The scenario analyses performed are summarised in Table 72.

Table 72: Summary of scenario analyses

#	Model aspect	Base-case	Scenario analysis
1	Time horizon	Lifetime	20 years
2	Discount rate	3.5% for costs and outcomes	0% for costs and outcomes
3			5% for costs and outcomes
4	OCA price per pack discount	0%	10%
5			20%
6			30%
7			40%
8			50%
9			[redacted]%
10	Source for LT costs	Singh and Longworth	HST17
11	AEs	Include	Exclude
12	Costs of pruritus	Mild and CS are different	Mild and CS are the same
13	UDCA extrapolations	Improvements not possible	Improvements possible
14	UDCA transition matrix extrapolation	Last observation carried forwards	Average of all transition matrices
15	Moderate risk to liver disease transitions	Include	Exclude
16	Duration of treatment effect of elafibranor relative to OCA on discontinuation	Lifetime	1 year
17	Treatment discontinuation distribution	Exponential	Weibull
18			Log-logistic
19			Lognormal
20			Gompertz
21	Disutility due to pruritus source	ELATIVE	Clinical opinion
22	Mild and moderate risk biomarker health states utilities	Younossi, 2000	ELATIVE
23	Utility values for DCC health state	0.38 (TA330)	0.62 (McPhail et al, 2021)

Abbreviations: AE – adverse event; CS – clinically significant; DCC – decompensated cirrhosis; HST – Highly Specialised Technologies; LT – liver transplant; OCA – obeticholic acid; TA – technology appraisal; UDCA – ursodeoxycholic acid

The results of scenario analyses conducted in the model are summarised below in Table 73. In the comparison of elafibranor and OCA, the scenario analysis found that the cost of OCA had a relatively high effect on the cost-effectiveness. In all other scenarios presented elafibranor dominates OCA exhibiting the lower total cost and higher QALY gain. In the

comparison of elafibranor and UDCA, the scenario analysis found that a discount rate of 0% had a moderate effect on cost-effectiveness. All other scenario analyses had a minimal to no effect on the cost-effectiveness, with all other scenarios producing an ICER below £35,000 (range between £27,659 and £34,306). These results indicate that the cost-effectiveness results presented in the base-case analysis are stable to variability of inputs for key variables in the economic model.

Table 73: Scenario analysis

Scenario	Total costs of elafibranor (GBP)	Total QALYs of elafibranor	Incremental costs to OCA (GBP)	Incremental QALYs to OCA	Incremental costs to UDCA (GBP)	Incremental QALYs to UDCA	ICER of elafibranor vs OCA	ICER of elafibranor vs UDCA
Base-case	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	Dominating	**31,762**
#1	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	Dominating	33,153
#2	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	Dominating	27,659
#3	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	Dominating	33,888
#4	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	Dominating	31,762
#5	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	31,762
#6	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	31,762
#7	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	31,762
#8	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	31,762
#9	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	31,762
#10	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	Dominating	31,762
#11	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	Dominating	31,763
#12	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	Dominating	31,693
#13	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	Dominating	33,648
#14	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	Dominating	33,895
#15	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	Dominating	31,650
#16	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	Dominating	31,762
#17	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	Dominating	31,588
#18	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	Dominating	31,253
#19	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	Dominating	30,880
#20	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	Dominating	30,749
#21	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	Dominating	34,306
#22	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	Dominating	33,893
#23	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	Dominating	31,952

Abbreviations: ICER – incremental cost-effectiveness ratio; LYG – life year gained; OCA – obeticholic acid; QALY – quality-adjusted life year; UCDA – ursodeoxycholic acid

B.3.11 Subgroup analysis

No subgroup analyses have been performed.

B.3.12 Benefits not captured in the QALY calculation

As described in Section B.3.4.6.3, there is a lack of data on the disutility to caregivers of patients with liver disease. Therefore, the direct impact to caregivers has not been included in the QALY calculation. As more patients treated with elafibranor are anticipated to achieve cholestasis response than patients treated with OCA or UDCA, it follows that fewer patients with PBC will progress to liver disease if treated with elafibranor than treated with UDCA or OCA. Therefore, omission of caregiver disutility will underestimate the incremental QALYs associated with elafibranor treatment compared to OCA and UDCA.

The ease of administration of elafibranor (i.e., dosing frequency of one tablet once daily) and no requirement for dose adjustments, simplifies dosing management for patients and their caregivers.[11] However, it is not possible to quantify this benefit in the QALY calculations as oral medications are not typically assigned any QALY benefit or decrement. Additionally, as described in section B.1.2, clinical DDI studies have shown no clinically significant effects from administering elafibranor as a DDI perpetrator with simvastatin, warfarin, atorvastatin or sitagliptin.[11] This means PBC patients are likely to have improved tolerability to elafibranor compared to other treatments, thereby increasing the likelihood of response for patients receiving elafibranor.

As described in section B.1.3, liver transplants are sometimes considered as a treatment option for those patients who have not responded to other treatments and with inadequate management of cholestasis. However, liver transplant is not always curative and PBC can re-emerge in some patients after transplant. The economic model does not capture the potential QALY decrement associated with liver transplant failure. This favours the currently available PBC therapies (i.e., OCA and UDCA) which the model predicts to have a higher rate of patients progressing to need liver transplant in the advance stages of PBC compared to elafibranor.

B.3.13 Validation

Validation of cost-effectiveness analysis

The model has undergone thorough internal and external validation. The model was developed internally by one health economist and checked for accuracy by a further two health economists.

Internal validation techniques included:

- Ease of use checks to ensure the model is transparent and user-friendly
- Review of all calculations to ensure accuracy
- Face validity checks that the model calculations and formulae are consistent and accurate
- Verifying inputs back to original source and documentation
- Test of results to check that varying model inputs has the anticipated effect on results and for internal consistency of model outputs compared to ELATIVE
- Re-performing sensitivity analysis and scenario analyses

Prior to the development of the CEM, a protocol was devised to outline the key modelling assumptions and inputs implemented. The model protocol was put forward to one clinical expert ([redacted]) with the following objectives:

- To ratify the appropriateness and suitability of the model structure
- To ratify the appropriateness of population and comparators
- To ratify assumptions on QoL and costs, including the cost categories that were implemented
- Validation and identification of data sources from the literature

The clinical expert agreed with the general approach and structure for the model. Basing the structure of the model on the model structure presented in the previously submitted TA443 was also considered appropriate by the clinical expert.

After validation of the model protocol and initial development of the model, two HEOR experts ([redacted] and [redacted]) as well as two clinical experts ([redacted] and [redacted]) were consulted. The objective of the clinical validation meetings was to validate clinical inputs within the model as well as any assumptions that were made during development which involved clinical aspects. HEOR experts were consulted to validate any assumptions that were made with regards to the overall model structure. The HEOR experts and clinicians agreed with our approach to the CEM. Input on transition probabilities, excess mortality, AEs, and discontinuation were also provided by the experts.

An external statistician ([redacted]), who sits on the EAG at Sheffield University, was consulted with to review the statistical analysis plan of the NMA which subsequently informed inputs in the CEM.

B.3.14 Interpretation and conclusions of economic evidence

Results in this submission are based on the PAS price of elafibranor. The cost-effectiveness analysis shows that, for patients with PBC, elafibranor is a cost-effective use of NHS resources when compared to UDCA. When compared to OCA, elafibranor is cost-effective when the confidential discount to OCA is below [redacted]%. The results from the base-case analysis show that elafibranor is associated with [redacted] QALYs at a cost of £[redacted]. In the base-case, elafibranor has an ICER of £31,762 compared to UDCA and dominates OCA.

In all scenario analyses, the ICER of elafibranor compared to UDCA remained below £35,000 per QALY. The results from the PSA confirm the deterministic results and show that elafibranor is cost-effective compared to OCA at its list price at all willingness-to-pay thresholds. It also showed that elafibranor is cost-effective compared to UDCA around the £30,000 per QALY willingness-to-pay threshold. In section 6.2.34 of the NICE Health Technology Evaluations manual, it is outlined that a higher degree of accepting uncertainty should be adopted in rare diseases due to the complexity inherent in gathering evidence.[170] Whilst PBC is a relatively rare disease, there is data available showing ALP and bilirubin liver function as surrogate markers linked to long-term outcomes. Despite the evidence supporting the relevance of ALP and bilirubin to long-term outcomes, there remains uncertainty due to the trial design. Specifically, the timeframe of trials may not allow for adequate progression of patients to cirrhosis and the development of complications associated with liver failure, thereby impacting the certainty of the link between biomarkers and subsequent liver disease. A reduction in these

longer term outcomes would therefore not be captured in the model directly from trial data due to the follow-up period of clinical trials of PBC therapies being too short (as mentioned in Section B.3.7). There has also been a lack of PBC-specific data published since the NICE appraisal of OCA, so limitations remain surrounding the use of data in hepatitis C to proxy liver disease following PBC. With regards to uncertainty, there is also an absence of direct head-to-head trial data comparing elafibranor and OCA. Therefore, the efficacy and safety of OCA relative to elafibranor has been determined via an ITC, which although established as a robust tool, ITCs may impose a level of uncertainty in results. As clinical trials are often powered only to detect differences between treatments within the trial population; greater patient numbers would be needed to detect treatment differences in NMA.

Overall, the methodology and results from the economic evaluation performed in the submission are consistent with published economic literature. The base-case assumptions used in the model are more closely aligned with the OCA NICE technology appraisal (TA443).[1] Although this model was adapted from the TA443, results in TA443 showed higher QALYs for OCA and UDCA compared to this model. Differences in the QALYs accrued for OCA and UDCA are likely due to discontinuation being assumed to only occur within the first year of treatment and assumption of no transitions from the moderate risk of disease progression into the liver disease component of the model of the TA443 model. In our evaluation, discontinuation was considered across the full time horizon, to accurately reflect time on treatment with elafibranor. Moreover, consultation with clinicians enabled a more accurate demonstration of the disease trajectory for patients treated with UDCA only and as such movement between the moderate and severe health states to liver disease was included. To ensure transparency in the calculation of UDCA transitions, only ELATIVE trial data were used.

Compared to the rest of the published cost-effectiveness studies, this model structure and time horizon aligns with that of the four HTA appraisals (NICE, CADTH, NCPE, SMC).[1,127–129] Differences in results were identified between the model and CADTH,[127] NICE,[1] and Samur[52] publications which reported higher total number of QALYs. The difference between this model and the Samur study can be attributed to the fact that the latter is a microsimulation model which assesses disease progression according to the Ludwig scoring system. Differences in health state-transition calculations between studies could also explain these results. Due to confidentiality issues, including the unknown PAS price of OCA, the ICER values between studies cannot be compared. Overall, the majority of differences in results between the evaluation and previous studies are attributed to the varied extrapolation assumptions.

This evaluation is relevant to all groups of patients with PBC, aligning with the proposed positioning and marketing authorisation of elafibranor (see Section B.1.3.5), the inclusion criteria of the ELATIVE trial and its licensed indication. Although the ELATIVE trial is multinational, the eligible population aligns with the eligible population with PBC in the UK, as verified by clinical opinion. To reflect the decision problem, only UDCA and OCA were presented as comparators. The selection of comparators ensured alignment with the ELATIVE trial population which represents the distribution of patients treated with and without UDCA in clinical practice. These selected comparators are reflective of the currently available and reimbursed therapies for patients with PBC. The model structure also represents the treatment pathway for patients with PBC and standardisation of PBC care, according to the BSG/UK-PBC and EASL guidelines. HEOR and clinical experts from England and Wales have also validated the comparators and structure of the model as relevant to UK practice.

In terms of clinical effectiveness, ALP and bilirubin have been proven to be reliable surrogate endpoints, biomarkers of disease progression and powerful predictors of cholestatic injury and

liver function, transplant-free survival and the rate of PBC progression when assessed in combination. Patient level data on these surrogate endpoints were used for elafibranor and UDCA to accurately predict the risk of liver disease progression. As pruritus is a symptom causing significant burden to patients with PBC and due to lack of explicit data in past published literature, patient level-data was used to capture the longer term outcomes of treatment with regards to pruritus symptoms, which more accurately reflects the QoL of patients. For OCA and the disease trajectory within the liver disease component of the model, data were sourced from relevant clinical trials for comparators as well as previous NICE submissions. Therefore, this model effectively captures outcomes for patients including mortality, outcomes according to liver function biomarkers, pruritus, AEs, liver transplantation, HRQoL, and PBC disease-specific health states (see Section B.3.3). Thus, results of the evaluation can accurately predict the long-term clinical benefit of elafibranor and how it fulfils an unmet medical need as a well tolerated treatment in individuals with PBC.

In terms of utility values, the HSUVs used in the evaluation are deemed appropriate as they have been used in previous appraisals, thus have been accepted for decision making. However, an important difference to highlight between this model and TA443 is the inclusion of age-adjustment in this model to ensure that QoL is in line with population norms over time.

With regards to costs, all unit costs have been appropriately sourced using NHS reference costs, PSSRU costs, the BNF or previous relevant NICE appraisals, ensuring relevance of results to UK practice. Health state costs in this model were also fully aligned with TA443. It is important to note that for the liver disease health state, costs associated with the LT procedure (which, though sourced for HST17 is based on TA443), organ, organ retrieval, LT follow-up for 2 years as well as immunosuppression costs for the LT and post-LT states, were also considered to comprehensively evaluate the full cost associated with LT. Importantly, a key limitation and point of uncertainty in this analysis is the absence of the confidential discount to OCA, which limits the interpretability of the results.

The sensitivity analyses performed demonstrate that the economic model is robust to parametrisation in that the ICER remains stable under probabilistic and deterministic sensitivity analyses. Although, these analyses were carried out in order to enhance the robustness of results, increasing the model parameters could allow for a more accurate estimation of elafibranor's cost-effectiveness in the future, and for exploration of more outcomes that would further investigate the efficiency of the technology in this disease area. Overall, the base-case results derived from this analysis can be considered reliable estimates of the cost-effectiveness of elafibranor.

Overall, the positive impact of elafibranor in patients with PBC was demonstrated by the totality of the evidence in the ELATIVE trial, across multiple secondary endpoints, including well validated biochemical markers of liver function for long-term outcomes such as ALP and bilirubin levels, as well as pruritus symptoms and quality of life (QoL) measures.[4,112] Collectively, these results demonstrate that elafibranor fulfils an unmet medical need as an efficacious and well tolerated treatment in individuals with PBC who have experienced an inadequate response or intolerance to UDCA.[4,112]

B.4 References

1. NICE. Obeticholic acid for treating primary biliary cholangitis (TA443) | Guidance | NICE. 2017. at <https://www.nice.org.uk/guidance/ta443>
2. Nevens F, Andreone P, Mazzella G, *et al.* A Placebo-Controlled Trial of Obeticholic Acid in Primary Biliary Cholangitis. *N Engl J Med* 2016. 375: 631–643.
3. Invernizzi P, Floreani A, Carbone M, *et al.* Primary Biliary Cholangitis: advances in management and treatment of the disease. *Dig Liver Dis* 2017. 49: 841–846.
4. Kowdley KV, Bowlus CL, Levy C, *et al.* Efficacy and Safety of Elafibranor in Primary Biliary Cholangitis. *N Engl J Med* 2023. doi:10.1056/NEJMoa2306185
5. Schattenberg JM, Pares A, Kowdley KV, *et al.* A randomized placebo-controlled trial of elafibranor in patients with primary biliary cholangitis and incomplete response to UDCA. *J Hepatol* 2021. 74: 1344–1354.
6. Ye X, Zhang T & Han H. PPARα: A potential therapeutic target of cholestasis. *Frontiers in Pharmacology* 2022. 13:
7. Ratziu V, Harrison SA, Francque S, *et al.* Elafibranor, an Agonist of the Peroxisome Proliferator-Activated Receptor-α and -δ, Induces Resolution of Nonalcoholic Steatohepatitis Without Fibrosis Worsening. *Gastroenterology* 2016. 150: 1147-1159.e5.
8. Lee C-H, Chawla A, Urbiztondo N, *et al.* Transcriptional repression of atherogenic inflammation: modulation by PPARdelta. *Science* 2003. 302: 453–457.
9. Cariou B & Staels B. GFT505 for the treatment of nonalcoholic steatohepatitis and type 2 diabetes. *Expert Opin Investig Drugs* 2014. 23: 1441–1448.
10. Hanf R, Millatt LJ, Cariou B, *et al.* The dual peroxisome proliferator-activated receptor alpha/delta agonist GFT505 exerts anti-diabetic effects in db/db mice without peroxisome proliferator-activated receptor gamma-associated adverse cardiac effects. *Diab Vasc Dis Res* 2014. 11: 440–447.
11. IPSEN. Draft Summary of Product Characteristics (SmPC). 2023.

12. IPSEN. Clinical Protocol - A double-blind, randomized, placebo-controlled study and open-label long-term extension to evaluate the efficacy and safety of elafibranor 80 mg in patients with primary biliary cholangitis with inadequate response or intolerance to ursodeoxycholic acid.Version 5.0; 2022.
13. IPSEN. Draft Company Core Data Sheet: Elafibranor 80 mg Film-Coated Tablets (Internal Reference: IPN60190). 2023.
14. EASL. EASL Clinical Practice Guidelines: The diagnosis and management of patients with primary biliary cholangitis. *J Hepatol* 2017. 67: 145–172.
15. Lindor KD, Bowlus CL, Boyer J, *et al.* Primary Biliary Cholangitis: 2018 Practice Guidance from the American Association for the Study of Liver Diseases. *Hepatology* 2019. 69: 394–419.
16. Galoosian A, Hanlon C, Zhang J, *et al.* Clinical Updates in Primary Biliary Cholangitis: Trends, Epidemiology, Diagnostics, and New Therapeutic Approaches. *J Clin Transl Hepatol* 2020. 8: 49–60.
17. Hirschfield GM, Chazouillères O, Cortez-Pinto H, *et al.* A consensus integrated care pathway for patients with primary biliary cholangitis: a guideline-based approach to clinical care of patients. *Expert Rev Gastroenterol Hepatol* 2021. 15: 929–939.
18. Jung HE, Jang JY, Jeong SW, *et al.* Prognostic indicators in primary biliary cirrhosis: significance of revised IAHG (International Autoimmune Hepatitis Group) score. *Clin Mol Hepatol* 2012. 18: 375–382.
19. Abdulkarim M, Zenouzi R, Sebode M, *et al.* Sex differences in clinical presentation and prognosis in patients with primary biliary cholangitis. *Scand J Gastroenterol* 2019. 54: 1391–1396.
20. Carbone M, Mells GF, Pells G, *et al.* Sex and age are determinants of the clinical phenotype of primary biliary cirrhosis and response to ursodeoxycholic acid. *Gastroenterology* 2013. 144: 560-569.e7; quiz e13-14.

21. Axley P, Mudumbi S, Sarker S, *et al.* Patients with stage 3 compared to stage 4 liver fibrosis have lower frequency of and longer time to liver disease complications. *PLOS ONE* 2018. 13: e0197117.
22. Trivedi PJ, Lammers WJ, van Buuren HR, *et al.* Stratification of hepatocellular carcinoma risk in primary biliary cirrhosis: a multicentre international study. *Gut* 2016. 65: 321–329.
23. Mayo Clinic. Liver transplant overview. 2023. at <https://www.mayoclinic.org/tests-procedures/liver-transplant/about/pac-20384842>
24. Silveira MG, Talwalkar JA, Lindor KD, *et al.* Recurrent primary biliary cirrhosis after liver transplantation. *Am J Transplant* 2010. 10: 720–726.
25. Corpechot C, Abenavoli L, Rabahi N, *et al.* Biochemical response to ursodeoxycholic acid and long-term prognosis in primary biliary cirrhosis. *Hepatology* 2008. 48: 871–877.
26. Living with PBC. Laurie's Story. at <https://www.livingwithpbc.com/pbc-patient-stories/laurie/>
27. Gerussi A, Restelli U, Croce D, *et al.* Cost of illness of Primary Biliary Cholangitis - a population-based study. *Dig Liver Dis* 2021. 53: 1167–1170.
28. Kuiper EMM, Hansen BE, de Vries RA, *et al.* Improved prognosis of patients with primary biliary cirrhosis that have a biochemical response to ursodeoxycholic acid. *Gastroenterology* 2009. 136: 1281–1287.
29. Zhang L-N, Shi T-Y, Shi X-H, *et al.* Early biochemical response to ursodeoxycholic acid and long-term prognosis of primary biliary cirrhosis: results of a 14-year cohort study. *Hepatology* 2013. 58: 264–272.
30. Treating PBC – UK-PBC. at <https://www.uk-pbc.com/about/aboutpbc/treating-pbc/>
31. Montano-Loza AJ & Corpechot C. Definition and Management of Patients With Primary Biliary Cholangitis and an Incomplete Response to Therapy. *Clin Gastroenterol Hepatol* 2021. 19: 2241-2251.e1.

32. Mitra V & Metcalf J. Metabolic functions of the liver. *Anaesthesia & Intensive Care Medicine* 2009. 10: 334–335.
33. Chiang JYL & Ferrell JM. Bile acid metabolism in liver pathobiology. *Gene Expr* 2018. 18: 71–87.
34. Oertelt S, Rieger R, Selmi C, *et al.* A sensitive bead assay for antimitochondrial antibodies: Chipping away at AMA-negative primary biliary cirrhosis. *Hepatology* 2007. 45: 659–665.
35. Kuś A, Grabowska MA, Szymański K, *et al.* Genetic Risk Factors for Autoimmune Thyroid Disease might Affect the Susceptibility to and Modulate the Progression of Primary Biliary Cholangitis. *Journal of Gastrointestinal and Liver Diseases* 2017. 26: 245–252.
36. Purohit T & Cappell MS. Primary biliary cirrhosis: Pathophysiology, clinical presentation and therapy. *World J Hepatol* 2015. 7: 926–941.
37. Murillo Perez CF, Gerussi A, Trivedi PJ, *et al.* Geographical region and clinical outcomes of patients with primary biliary cholangitis from Western Europe. *Eur J Gastroenterol Hepatol* 2023. 35: 112–119.
38. Webb GJ, Ryan RP, Marshall TP, *et al.* The Epidemiology of UK Autoimmune Liver Disease Varies With Geographic Latitude. *Clin Gastroenterol Hepatol* 2021. 19: 2587–2596.
39. Boonstra K, Kunst AE, Stadhouders PH, *et al.* Rising incidence and prevalence of primary biliary cirrhosis: a large population-based study. *Liver Int* 2014. 34: e31-38.
40. Milovanovic T, Popovic D, Stojkovic Lalosevic M, *et al.* Quality of Life in Patients with Primary Biliary Cholangitis: A Single-Center Experience in Serbia. *Digestive Diseases* 2020. 38: 515–521.
41. Lv T, Chen S, Li M, *et al.* Regional variation and temporal trend of primary biliary cholangitis epidemiology: A systematic review and meta-analysis. *J Gastroenterol Hepatol* 2021. 36: 1423–1434.

42. James OF, Bhopal R, Howel D, *et al.* Primary biliary cirrhosis once rare, now common in the United Kingdom? *Hepatology* 1999. 30: 390–394.
43. Epidemiology of PBC – UK-PBC. at <https://www.uk-pbc.com/about/aboutpbc/epidemiology-of-pbc/>
44. McNally RJQ, James PW, Ducker S, *et al.* No rise in incidence but geographical heterogeneity in the occurrence of primary biliary cirrhosis in North East England. *Am J Epidemiol* 2014. 179: 492–498.
45. Gazda J, Drazilova S, Janicko M, *et al.* The Epidemiology of Primary Biliary Cholangitis in European Countries: A Systematic Review and Meta-Analysis. *Can J Gastroenterol Hepatol* 2021. 2021: 9151525.
46. Michelle-Thain R. Associate Feature: Primary Biliary Cholangitis (PBC) – A hidden women's health issue. *Holyrood Website* 2024. at <https://www.holyrood.com/comment/view,associate-feature-primary-biliary-cholangitis-pbc-a-hidden-womens-health-issue>
47. Hirschfield GM, Dyson JK, Alexander GJM, *et al.* The British Society of Gastroenterology/UK-PBC primary biliary cholangitis treatment and management guidelines. *Gut* 2018. 67: 1568–1594.
48. Raczyńska J, Habior A, Pączek L, *et al.* Primary biliary cirrhosis in the era of liver transplantation. *Ann Transplant* 2014. 19: 488–493.
49. Setsu T, Yokoyama J, Takamura M, *et al.* Long-term prevalence of gastro-oesophageal varices in early primary biliary cholangitis patients with good response to treatment. *Journal of Hepatology* 2020. 73: S488.
50. EMA. Ocaliva | European Medicines Agency | SmPC. 2023. at <https://www.ema.europa.eu/en/medicines/human/EPAR/ocaliva>
51. Lammers WJ, van Buuren HR, Hirschfield GM, *et al.* Levels of alkaline phosphatase and bilirubin are surrogate end points of outcomes of patients with primary biliary

cirrhosis: an international follow-up study. *Gastroenterology* 2014. 147: 1338-1349.e5; quiz e15.

52. Samur S, Klebanoff M, Banken R, *et al.* Long-term clinical impact and cost-effectiveness of obeticholic acid for the treatment of primary biliary cholangitis. *Hepatology* 2017. 65: 920–928.
53. Kumagi T, Guindi M, Fischer SE, *et al.* Baseline ductopenia and treatment response predict long-term histological progression in primary biliary cirrhosis. *Official journal of the American College of Gastroenterology| ACG* 2010. 105: 2186–2194.
54. Momah N, Silveira MG, Jorgensen R, *et al.* Optimizing biochemical markers as endpoints for clinical trials in primary biliary cirrhosis. *Liver Int* 2012. 32: 790–795.
55. Carbone M, Sharp SJ, Flack S, *et al.* The UK-PBC risk scores: Derivation and validation of a scoring system for long-term prediction of end-stage liver disease in primary biliary cholangitis. *Hepatology* 2016. 63: 930–950.
56. Lammers WJ, Hirschfield GM, Corpechot C, *et al.* Development and Validation of a Scoring System to Predict Outcomes of Patients With Primary Biliary Cirrhosis Receiving Ursodeoxycholic Acid Therapy. *Gastroenterology* 2015. 149: 1804-1812.e4.
57. Goet JC, Harms MH, Carbone M, *et al.* Risk stratification and prognostic modelling in primary biliary cholangitis. *Best Pract Res Clin Gastroenterol* 2018. 34–35: 95–106.
58. Trivella J, John BV & Levy C. Primary biliary cholangitis: Epidemiology, prognosis, and treatment. *Hepatol Commun* 2023. 7: e0179.
59. Mayo MJ, Carey E, Smith HT, *et al.* Impact of Pruritus on Quality of Life and Current Treatment Patterns in Patients with Primary Biliary Cholangitis. *Dig Dis Sci* 2023. 68: 995–1005.
60. Gungabissoon U, Gibbons DC, Requena G, *et al.* Disease burden of primary biliary cholangitis and associated pruritus based on a cross-sectional US claims analysis. *BMJ Open Gastroenterol* 2022. 9: e000857.

61. Levy C, Williams B, Sowell F, *et al.* Understanding the Experience of Patients with Primary Biliary Cholangitis and Pruritus. Poster number: PCR34. Presented at ISPOR 2023. 2023. at <https://www.ispor.org/docs/default-source/intl2023/genfit-ipsenpatient-experience-with-pbcispor-posterfinal-pdf.pdf?sfvrsn=b6cc8c99_0>
62. Jopson L & Jones DEJ. Fatigue in Primary Biliary Cirrhosis: Prevalence, Pathogenesis and Management. *Dig Dis* 2015. 33 Suppl 2: 109–114.
63. Rice S, Albani V, Minos D, *et al.* Effects of Primary Biliary Cholangitis on Quality of Life and Health Care Costs in the United Kingdom. *Clin Gastroenterol Hepatol* 2021. 19: 768-776.e10.
64. Living with PBC. Patient Stories | Bel. at <https://www.livingwithpbc.com/pbc-patient-stories/bel/>
65. Kim K-A, Ki M, Choi HY, *et al.* Population-based epidemiology of primary biliary cirrhosis in South Korea. *Aliment Pharmacol Ther* 2016. 43: 154–162.
66. Parés A, Albillos A, Andrade RJ, *et al.* Primary biliary cholangitis in Spain. Results of a Delphi study of epidemiology, diagnosis, follow-up and treatment. *Rev Esp Enferm Dig* 2018. 110: 641–649.
67. Anderson K, Jones DEJ, Wilton K, *et al.* Restless leg syndrome is a treatable cause of sleep disturbance and fatigue in primary biliary cirrhosis. *Liver Int* 2013. 33: 239–243.
68. Gao L, Meng F, Cheng J, *et al.* Prediction of oesophageal varices in patients with primary biliary cirrhosis by non-invasive markers. *Arch Med Sci* 2017. 13: 370–376.
69. Liu Chen Kiow J, Sidani S, Vincent C, *et al.* A194 The prevalence of small intestinal bacterial overgrowth in primary biliary cholangitis. *Journal of the Canadian Association of Gastroenterology* 2019. 2: 381–382.
70. Pandit S & Samant H. in *StatPearls* (StatPearls Publishing, 2023). at <http://www.ncbi.nlm.nih.gov/books/NBK459209/>

71. Sayiner M, Golabi P, Stepanova M, *et al.* Primary Biliary Cholangitis in Medicare Population: The Impact on Mortality and Resource Use. *Hepatology* 2019. 69: 237–244.
72. Shaheen A-A, Kaplan GG, Almishri W, *et al.* The impact of depression and antidepressant usage on primary biliary cholangitis clinical outcomes. *PLoS One* 2018. 13: e0194839.
73. Prince M, Chetwynd A, Newman W, *et al.* Survival and symptom progression in a geographically based cohort of patients with primary biliary cirrhosis: follow-up for up to 28 years. *Gastroenterology* 2002. 123: 1044–1051.
74. Natarajan Y, Tansel A, Patel P, *et al.* Incidence of Hepatocellular Carcinoma in Primary Biliary Cholangitis: A Systematic Review and Meta-Analysis. *Dig Dis Sci* 2021. 66: 2439–2451.
75. How long is the wait for a liver? - Organ transplantation - NHS Blood and Transplant. at <https://www.nhsbt.nhs.uk/organ-transplantation/liver/receiving-a-liver/how-long-is-the-wait-for-a-liver/>
76. EASL Clinical Practice Guidelines: Liver transplantation. *Journal of Hepatology* 2016. 64: 433–485.
77. BBC. Young people wait four times longer for liver transplants. 2023. at <https://www.bbc.co.uk/news/health-66259618>
78. Adam R, Karam V, Delvart V, *et al.* Evolution of indications and results of liver transplantation in Europe. A report from the European Liver Transplant Registry (ELTR). *J Hepatol* 2012. 57: 675–688.
79. Aberg F, Mäkisalo H, Höckerstedt K, *et al.* Infectious complications more than 1 year after liver transplantation: a 3-decade nationwide experience. *Am J Transplant* 2011. 11: 287–295.
80. Singal AK, Fang X, Kaif M, *et al.* Primary biliary cirrhosis has high wait-list mortality among patients listed for liver transplantation. *Transpl Int* 2017. 30: 454–462.

81. Smith H, Fettiplace J, Von Maltzahn R, *et al.* More than just an itch: impact of cholestatic pruritus in primary biliary cholangitis (PBC) on health-related quality of life (HRQoL). *Journal of Hepatology* 2022. 77: S327–S328.
82. Dyson JK, Wilkinson N, Jopson L, *et al.* The inter-relationship of symptom severity and quality of life in 2055 patients with primary biliary cholangitis. *Aliment Pharmacol Ther* 2016. 44: 1039–1050.
83. Mells GF, Pells G, Newton JL, *et al.* Impact of primary biliary cirrhosis on perceived quality of life: the UK-PBC national study. *Hepatology* 2013. 58: 273–283.
84. Sogolow ED, Lasker JN & Short LM. Fatigue as a major predictor of quality of life in women with autoimmune liver disease: the case of primary biliary cirrhosis. *Womens Health Issues* 2008. 18: 336–342.
85. Selmi C, Gershwin ME, Lindor KD, *et al.* Quality of life and everyday activities in patients with primary biliary cirrhosis. *Hepatology* 2007. 46: 1836–1843.
86. Saleh ZM, Salim NE, Nikirk S, *et al.* The emotional burden of caregiving for patients with cirrhosis. *Hepatol Commun* 2022. 6: 2827–2835.
87. Henriksson I, Udumyan R, Nilsson E, *et al.* Clinical outcomes and sick leave in relation to UDCA treatment in Swedish patients with primary biliary cholangitis. *Scandinavian Journal of Gastroenterology* 2023. 58: 70–75.
88. Lasker J, Sogolow E & Sharim R. For Better and for Worse: Family and Friends' Responses to Chronic Liver Disease. *Illness Crisis and Loss* 2005. 13: 249–266.
89. NHS. Help at home from a paid carer - Social care and support guide. *nhs.uk* 2023. at <https://www.nhs.uk/conditions/social-care-and-support-guide/care-services-equipment-and-care-homes/homecare/>
90. Singh J & Longworth L. Estimating The Cost Of Liver Transplantation In Patients Diagnosed With Chronic Hepatitis C And B In The Uk. *Value Health* 2014. 17: A368.

91. Singh J & Longworth L. Comparison of methods for estimating comtemporary costs: an application to liver transplantation in the United Kingdom. *International Journal of Technology Assessment in Health Care* 2017. 33: 620–628.
92. Annual Activity Report - Section 8 Liver activity. *NHS Blood and Transplant* at <https://www.odt.nhs.uk/statistics-and-reports/annual-activity-report/>
93. National Organ Retrieval Services. *ODT Clinical - NHS Blood and Transplant* at <https://www.odt.nhs.uk/retrieval/national-organ-retrieval-services/>
94. NICE. Odevixibat for treating progressive familian intrahepatic cholestasis [ID1570, HST17]: Committee papers. 2021. Available at: https://www.nice.org.uk/guidance/hst17/documents/committee-papers. [Accessed: February 2024].
95. Medicinal forms | Azathioprine | Drugs | BNF content published by NICE. at <https://bnf.nice.org.uk/drugs/azathioprine/medicinal-forms/>
96. Medicinal forms | Naltrexone hydrochloride | Drugs | BNF content published by NICE. at <https://bnf.nice.org.uk/drugs/naltrexone-hydrochloride/medicinal-forms/>
97. Medicinal forms | Tacrolimus | Drugs | BNF content published by NICE. at <https://bnf.nice.org.uk/drugs/tacrolimus/medicinal-forms/>
98. Intercept Pharmaceuticals. UK-PBC study group.
99. Luk KM, Shaw FM, Zhang C, *et al.* The Annual Direct and Indirect Health Care Costs for Patients with Chronic Pruritus and their Determining Factors. *J Invest Dermatol* 2020. 140: 699-701.e5.
100. Corpechot C, Chazouillères O & Poupon R. Early primary biliary cirrhosis: biochemical response to treatment and prediction of long-term outcome. *J Hepatol* 2011. 55: 1361–1367.
101. NHS England » Prescribed specialised services manual. at <https://www.england.nhs.uk/publication/manual-for-prescribed-specialised-services/>

102. Overview | Cirrhosis in over 16s: assessment and management | Guidance | NICE. 2016. at <https://www.nice.org.uk/guidance/ng50>
103. Abbas N, Smith R, Flack S, *et al.* Critical shortfalls in the management of PBC: Results of a UK-wide, population-based evaluation of care delivery. *JHEP Rep* 2024. 6: 100931.
104. NICE. Primary biliary cholangitis | Treatment summaries | BNF content published by NICE. at <https://bnf.nice.org.uk/treatment-summaries/primary-biliary-cholangitis/>
105. Rudic JS, Poropat G, Krstic MN, *et al.* Ursodeoxycholic acid for primary biliary cirrhosis. *Cochrane Database Syst Rev* 2012. 12: CD000551.
106. Gatselis NK, Goet JC, Zachou K, *et al.* Factors Associated With Progression and Outcomes of Early Stage Primary Biliary Cholangitis. *Clin Gastroenterol Hepatol* 2020. 18: 684-692.e6.
107. Tripathi D, Stanley AJ, Hayes PC, *et al.* U.K. guidelines on the management of variceal haemorrhage in cirrhotic patients. *Gut* 2015. 64: 1680–1704.
108. Provision of unpaid cared - Census Maps, ONS. at <https://www.ons.gov.uk/census/maps/choropleth/health/provision-of-unpaid-cared/is-carer-5a/provides-no-unpaid-care>
109. EU/3/19/2182 - orphan designation for treatment of primary biliary cholangitis | European Medicines Agency. at <https://www.ema.europa.eu/en/medicines/human/orphan-designations/eu-3-19-2182>
110. GENFIT announces FDA Grant of Breakthrough Therapy Designation to Elafibranor for the Treatment of PBC | GENFIT. at <https://ir.genfit.com/news-releases/news-release-details/genfit-announces-fda-grant-breakthrough-therapy-designation/>
111. Search Orphan Drug Designations and Approvals. at <https://www.accessdata.fda.gov/scripts/opdlisting/oopd/detailedIndex.cfm?cfgridkey=693919>

112. IPSEN. Clinical Study Report: A Double-Blind, Randomized, Placebo-Controlled Study and Open-Label Long Term Extension to Evaluate the Efficacy and Safety of Elafibranor 80 Mg in Patients with Primary Biliary Cholangitis with Inadequate Response or Intolerance to Ursodeoxycholic Acid. 2023.
113. Alvaro D, Mancino MG, Onori P, *et al.* Estrogens and the pathophysiology of the biliary tree. *World J Gastroenterol* 2006. 12: 3537–3545.
114. Miozzo M, Selmi C, Gentilin B, *et al.* Preferential X chromosome loss but random inactivation characterize primary biliary cirrhosis. *Hepatology* 2007. 46: 456–462.
115. Onofrio FQ, Hirschfield GM & Gulamhusein AF. A Practical Review of Primary Biliary Cholangitis for the Gastroenterologist. *Gastroenterol Hepatol (N Y)* 2019. 15: 145–154.
116. French J, Simpson-Yap S, van der Mei I, *et al.* Identification of a Latitude Gradient in the Prevalence of Primary Biliary Cholangitis. *Clin Transl Gastroenterol* 2021. 12: e00357.
117. IPSEN. Clinical expert opinion | Ipsen data on file. 2024.
118. Decision Support Unit, NICE DSU Technical Support Document 2: A generalised linear modelling framework for pairwise and network meta-analysis of randomised controlled trials. (2016) Available at: http://scharr.dept.shef.ac.uk/nicedsu/wp-content/uploads/sites/7/2017/05/TSD2-General-meta-analysis-corrected-2Sep2016v2.pdf. [Last accessed: July 2017].
119. RESOLVE-IT Phase 3 of Elafibranor in NASH: Final Results of the Week 72 Interim Surrogate Efficacy Analysis. at <https://www.natap.org/2020/AASLD/AASLD_162.htm>
120. Food and Drug Administration. Lipitor highlights of prescribing information. at <https://www.accessdata.fda.gov/drugsatfda_docs/label/2019/020702s073lbl.pdf>
121. Graham DJ, Staffa JA, Shatin D, *et al.* Incidence of hospitalized rhabdomyolysis in patients treated with lipid-lowering drugs. *JAMA* 2004. 292: 2585–2590.
122. Wright AP, Adusumalli S & Corey KE. Statin therapy in patients with cirrhosis. *Frontline Gastroenterol* 2015. 6: 255–261.

123. Ipsen. *A Long-Term Study of Elafibranor in Adult Participants With Primary Biliary Cholangitis (ELFIDENCE)*. (clinicaltrials.gov, 2024). at <https://clinicaltrials.gov/study/NCT06016842>

124. Longo M, Crosignani A, Battezzati PM, *et al.* Hyperlipidaemic state and cardiovascular risk in primary biliary cirrhosis. *Gut* 2002. 51: 265–269.

125. Neuschwander-Tetri BA, Loomba R, Sanyal AJ, *et al.* Farnesoid X nuclear receptor ligand obeticholic acid for non-cirrhotic, non-alcoholic steatohepatitis (FLINT): a multicentre, randomised, placebo-controlled trial. *Lancet* 2015. 385: 956–965.

126. Bahar R, Wong KA, Liu CH, *et al.* Update on New Drugs and Those in Development for the Treatment of Primary Biliary Cholangitis. *Gastroenterol Hepatol (N Y)* 2018. 14: 154–163.

127. Anonymous. Pharmacoeconomic Review Report – Obeticholic Acid (Ocaliva). Canadian Agency for Drugs and Technologies in Health. CADTH Common Drug Reviews 2017;08:08.

128. NCPE. Cost-effectiveness of obeticholic acid (Ocaliva®) for the treatment of primary biliary cholangitis in combination with ursodeoxycholic acid (UDCA) in adults with an inadequate response to UDCA or as monotherapy in adults unable to tolerate UDCA. Available at: https://www.ncpe.ie/drugs/obeticholic-acid-ocaliva/. 2017.

129. SMC. Obeticholic acid (Ocaliva®). 2017. at <https://www.scottishmedicines.org.uk/medicines-advice/obeticholic-acid-ocaliva-fullsubmission-123217/. 2017.>

130. Boberg KM, Wisløff T, Kjøllesdal KS, *et al.* Cost and health consequences of treatment of primary biliary cirrhosis with ursodeoxycholic acid. *Aliment Pharmacol Ther* 2013. 38: 794–803.

131. Longworth L, Young T, Buxton MJ, *et al.* Midterm cost-effectiveness of the liver transplantation program of England and Wales for three disease groups. *Liver Transpl* 2003. 9: 1295–1307.

132. Pasha T, Heathcote J, Gabriel S, *et al.* Cost-effectiveness of ursodeoxycholic acid therapy in primary biliary cirrhosis. *Hepatology* 1999. 29: 21–26.
133. NICE. Final scope - elafibranor for treating primary biliary cholangitis. 2023. at <https://www.nice.org.uk/guidance/gid-ta11378/documents/final-scope>
134. NICE. Sofosbuvir for treating chronic hepatitis C. NICE technology appraisal guidance [TA330]. 2015. at <https://www.nice.org.uk/guidance/ta330>
135. Corpechot C, F C, F G, *et al.* Liver stiffness measurement by vibration-controlled transient elastography improves outcome prediction in primary biliary cholangitis. *J Hepatol* 2022. 77: 1545–1553.
136. NICE. Lead team presentation: Obeticholic acid for treating primary biliary cirrhosos - STA. 2017. Available at: https://www.nice.org.uk/guidance/ta443/documents/1-2.
137. NICE. Final appraisal determination: Obeticholic acid for treating primary biliary cholangitis. 2017. Available at: https://www.nice.org.uk/guidance/ta443/documents/final-appraisal-determination-document. [Date accessed: February 2024].
138. NICE. Guide to the methods of technology appraisal 2013: The reference case. Available at: https://www.nice.org.uk/process/pmg9/chapter/the-reference-case.
139. NICE. Obeticholic acid for treating primary biliary cholangitis [ID785] - Committee papers. 2017. at <https://www.nice.org.uk/guidance/ta443/documents/committee-papers>
140. IPSEN. ELATIVE Individual Patient Data. Data on File.
141. Clinicaltrials.gov. *Study of Elafibranor in Patients With Primary Biliary Cholangitis (PBC) (ELATIVE)*. (clinicaltrials.gov, 2023). at <https://clinicaltrials.gov/study/NCT04526665>
142. FIECON. Clinical validation summary slides (Ipsen FIECON_summary of clinician validation_ITC_August2023.ppt). 2023.
143. Nicholas Latimer. NICE DSU TECHNICAL SUPPORT DOCUMENT 14: SURVIVAL ANALYSIS FOR ECONOMIC EVALUATIONS ALONGSIDE CLINICAL TRIALS -

EXTRAPOLATION WITH PATIENT-LEVEL DATA. REPORT BY THE DECISION SUPPORT UNIT. 2011. at <https://www.sheffield.ac.uk/nice-dsu/tsds/survival-analysis>

144. Burnham KP & Anderson DR. Multimodel Inference: Understanding AIC and BIC in Model Selection. *Sociological Methods & Research* 2004. 33: 261–304.
145. National life tables: England and Wales - Office for National Statistics. at <https://www.ons.gov.uk/peoplepopulationandcommunity/birthsdeathsandmarriages/lifeexpectancies/datasets/nationallifetablesenglandandwalesreferencetables>
146. NICE DSU - Mapping EQ-5D-5L to 3L. at <https://nicedsu.sites.sheffield.ac.uk/methods-development/mapping-eq-5d-5l-to-3l>
147. Harrison XA, Donaldson L, Correa-Cano ME, *et al.* A brief introduction to mixed effects modelling and multi-model inference in ecology. *PeerJ* 2018. 6: e4794.
148. Bates D, Maechler M & Bolker. lme4: Linear Mixed-Effects Models using “Eigen” and S4. at <https://cran.r-project.org/web/packages/lme4/index.html>
149. Hernandez Alava M, Pudney S & Wailoo A. The EQ-5D-5L Value Set for England: Findings of a Quality Assurance Program. *Value in Health* 2020. 23: 642–648.
150. Cortesi PA, Conti S, Scalone L, *et al.* Health related quality of life in chronic liver diseases. *Liver Int* 2020. 40: 2630–2642.
151. Wunsch E, Krause L, Gevers TJ, *et al.* Confidence in treatment is contributing to quality of life in autoimmune liver diseases. The results of ERN RARE-LIVER online survey. *Liver Int* 2023. 43: 381–392.
152. Skat-Rørdam PA, Eliasson J, Skalshøi Kjær M, *et al.* Health-related quality of life in patients with primary biliary cholangitis: a cross-sectional study from a single centre in Denmark. *Minerva Gastroenterol (Torino)* 2023. doi:10.23736/S2724-5985.23.03206-0
153. Abrahamian FM, Krishnadasan A, Mower WR, *et al.* The association of antimicrobial resistance with cure and quality of life among women with acute uncomplicated cystitis. *Infection* 2011. 39: 507–514.

154. NICE. NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE SINGLE TECHNOLOGY APPRAISAL (STA) Dostarlimab for previously treated advanced or recurrent endometrial cancer with high microsatellite instability or mismatch repair deficiency [ID3802]. 2021.
155. Wright M, Grieve R, Roberts J, *et al.* Health benefits of antiviral therapy for mild chronic hepatitis C: randomised control trial and economic evaluation. *Health Technology Assessment* 2006. 10:
156. McPhail SM, Amarasena S, Stuart KA, *et al.* Assessment of health-related quality of life and health utilities in Australian patients with cirrhosis. *JGH Open* 2020. 5: 133–142.
157. Younossi ZM, Kiwi ML, Boparai N, *et al.* Cholestatic liver diseases and health-related quality of life. *Am J Gastroenterol* 2000. 95: 497–502.
158. PSSRU. Unit Costs of Health and Social Care 2022. 2022. at <https://www.pssru.ac.uk/pub/uc/uc2022/Unit_Costs_of_Health_and_Social_Care_2022.pdf>
159. Medicinal forms | Obeticholic acid | Drugs | BNF content published by NICE. at <https://bnf.nice.org.uk/drugs/obeticholic-acid/medicinal-forms/>
160. ONS. eMIT national database 2023. Available at: https://www.gov.uk/government/publications/drugs-and-pharmaceutical-electronic-market-information-emit [Date accessed: March 2024].
161. NHS England » 2021/22 National Cost Collection Data Publication. at <https://www.england.nhs.uk/publication/2021-22-national-cost-collection-data-publication/>
162. Medicinal forms | Prednisolone | Drugs | BNF content published by NICE. at <https://bnf.nice.org.uk/drugs/prednisolone/medicinal-forms/>
163. NHS Office for Life Sciences. Evaluation of the treatment of adult women under 65 years presenting with symptoms of uncomplicated urinary tract infections in community

pharmacy using home-based urinalysis testing. 2020. at <https://healthinnovation-em.org.uk/images/Digital_UTI_Pathway_Evaluation_-_Final_v270720.pdf>

164. Medicinal forms | Colestyramine | Drugs | BNF content published by NICE. at <https://bnf.nice.org.uk/drugs/colestyramine/medicinal-forms/>
165. Medicinal forms | Rifampicin | Drugs | BNF content published by NICE. at <https://bnf.nice.org.uk/drugs/rifampicin/medicinal-forms/>
166. Medicinal forms | Bezafibrate | Drugs | BNF content published by NICE. at <https://bnf.nice.org.uk/drugs/bezafibrate/medicinal-forms/>
167. Medicinal forms | Gabapentin | Drugs | BNF content published by NICE. at <https://bnf.nice.org.uk/drugs/gabapentin/medicinal-forms/>
168. Gola A, Davis S, Greenslade L, *et al.* Economic analysis of costs for patients with end stage liver disease over the last year of life. *BMJ supportive & palliative care* 2015. 5: 110.
169. NICE. Atezolizumab with bevacizumab for treating advanced or unresectable hepatocellular carcinoma - Committee papers. 2020. at <https://www.nice.org.uk/guidance/ta666/evidence/committee-papers-pdf-8954415181>
170. NICE health technology evaluations: the manual.
171. Trivedi PJ, Lammers WJ, van Buuren HR, *et al.* Stratification of hepatocellular carcinoma risk in primary biliary cirrhosis: a multicentre international study. *Gut* 2016. 65: 321–329.

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Single Technology Appraisal

Elafibranor for treating primary biliary cholangitis [ID6331]

Summary of Information for Patients (SIP)

April 2024

Template version	Date amended	Changes since previous version
2.0	Dec 2023	Clarifications made to guidance notes in section 3i regarding inclusion of statements on cost effectiveness.

File name	Version	Contains confidential information	Date
ID6331 Elafibranor vi. NICE SIP template [noCON]_v1.0 FINAL	**1.0**	**Yes**	**12/04/2024**

Summary of Information for Patients (SIP):

The pharmaceutical company perspective

What is the SIP?

The Summary of Information for Patients (SIP) is written by the company who is seeking approval from NICE for their treatment to be sold to the NHS for use in England. It is a plain English summary of their submission written for patients participating in the evaluation. It is not independently checked, although members of the public involvement team at NICE will have read it to double-check for marketing and promotional content before it is sent to you.

The **Summary of Information for Patients** template has been adapted for use at NICE from the Health Technology Assessment International – Patient & Citizens Involvement Group (HTAi PCIG). Information about the development is available in an open-access IJTAHC journal article

SECTION 1: Submission summary

Note to those filling out the template: Please complete the template using plain language, taking time to explain all scientific terminology. Do not delete the grey text included in each section of this template as you move through drafting because it might be a useful reference for patient reviewers. Additional prompts for the company have been in red text to further advise on the type of information which may be most relevant and the level of detail needed. You may delete the red text.

1a) Name of the medicine (generic and brand name):

Response:
Generic name – elafibranor (Brand name – IQIRVO®)

1b) Population this treatment will be used by. Please outline the main patient population that is being appraised by NICE:

Response:
Elafibranor will be used to treat adults with primary biliary cholangitis (PBC) whose disease has an inadequate response to, or who are unable to tolerate, ursodeoxycholic acid (UDCA).

1c) Authorisation: Please provide marketing authorisation information, date of approval and link to the regulatory agency approval. If the marketing authorisation is pending, please state this, and reference the section of the company submission with the anticipated dates for approval.

Response:
Ipsen submitted to the Medicines and Healthcare products Regulatory Agency (MHRA) last year (2023) and approval is pending. Anticipated dates for approval can be found in Section B.1.2 of the company submission.

1d) Disclosures. Please be transparent about any existing collaborations (or broader conflicts of interest) between the pharmaceutical company and patient groups relevant to the medicine. Please outline the reason and purpose for the engagement/activity and any financial support provided:

Response: Ipsen has an ongoing collaborative partnership with PBC Foundation, comprising various projects at a global and UK level. Additionally, we partner with the British Liver Trust and Liver4Life at a UK level across different activities.

SECTION 2: Current landscape

Note to authors: This SIP is intended to be drafted at a global level and typically contain global data. However, the submitting local organisation should include country-level information where needed to provide local country-level context.

Please focus this submission on the **main indication (condition and the population who would use the treatment)** being assessed by NICE rather than sub-groups, as this could distract from the focus of the SIP and the NICE review overall. However, if relevant to the submission please outline why certain sub-groups have been chosen.

2a) The condition – clinical presentation and impact

Please provide a few sentences to describe the condition that is being assessed by NICE and the number of people who are currently living with this condition in England. Please outline in general terms how the condition affects the quality of life of patients and their families/caregivers. Please highlight any mortality/morbidity data relating to the condition if available. If the company is making a case for the impact of the treatment on carers this should be clearly stated and explained.
Response: Primary biliary cholangitis (PBC) is a rare, chronic autoimmune liver disease that can gradually worsen over time. Bile is a liquid that is produced inside the liver, used to help digest fats and absorb certain vitamins, in addition to removing waste products from the body. Bile passes out of the liver through small tubes called bile ducts. In PBC, the immune system (the body's natural defence against infection and illness) mistakenly attacks the bile ducts, leading to them being damaged and injured, resulting in bile building up in the liver. This leads to further liver damage that can lead to scarring (also known as cirrhosis).[1] Presentation of PBC is variable, however all patients experience a substantial clinical burden.[2] PBC does not always cause symptoms, however some patients may experience bone and joint aches, extreme tiredness (fatigue), itchy skin (pruritus), dry eyes and mouth and pain or discomfort in the upper right-hand side of their stomach.[3] As some patients do not exhibit symptoms, delayed diagnosis, which occurs in approximately 25% of PBC cases, negatively impacts PBC prognosis.[4] If PBC is not treated, or reaches an advanced stage, there may be other health problems including osteoporosis (where the bones become weak and brittle), portal hypertension (increased blood pressure in the blood vessels in your abdomen), ascites (a build of fluid in your stomach and around your intestines), vitamin deficiencies and a slightly increased risk of developing liver cancer.[1] Late-stage PBC generally lasts for two to four years before liver-related premature death or the need for a liver transplant.[5]

Although PBC is a rare disease, its prevalence (the measurement of all individuals affected by a disease) and incidence (the measurement of the number of new individuals who contract a disease) have been increasing in recent years.[6] The estimated UK prevalence of PBC is approximately 35 per 100,000 population according to UK-PBC equal to approximately 20,000 PBC patients in the UK.[7,8]

PBC occurs more commonly in females than males, with a ratio of 9:1 females impacted to males.[9] Conversely, male patients tend to have more advanced disease at diagnosis, likely due to delayed presentation. [10,11] Most patients present with PBC between the age of 40 to 60 years, however, cases have been reported in individuals as young as 15 years.[9,12] Age at diagnosis is also associated with PBC severity and prognosis. Patients with PBC symptom onset under the age of 50 are associated with more severe and progressive disease and poorer treatment response compared to patients over the age of 50 at diagnosis.[13]

2b) Diagnosis of the condition (in relation to the medicine being evaluated)

Please briefly explain how the condition is currently diagnosed and how this impacts patients. Are there any additional diagnostic tests required with the new treatment?

Response:

Diagnosis of PBC is confirmed primarily through testing for certain markers in the blood or looking at the liver through a scan or a sample of liver tissue. As more than 50% of patients with PBC are asymptomatic at diagnosis, often, PBC is only identified through a routine laboratory test or upon investigation for an unrelated disorder.[9,14] Delayed diagnosis, which occurs in approximately 25% of PBC cases, negatively impacts PBC prognosis, as patients with a delayed diagnosis are likely to have later-stage PBC that is more difficult to treat.[4] In particular, male patients with PBC are more commonly diagnosed at a later disease stage than female patients, possibly as males appear to experience fewer symptoms compared to females.[15]

2c) Current treatment options:

The purpose of this section is to set the scene on how the condition is currently managed:

- What is the treatment pathway for this condition and where in this pathway the medicine is likely to be used? Please use diagrams to accompany text where possible. Please give emphasis to the specific setting and condition being considered by NICE in this review. For example, by referencing current treatment guidelines. It may be relevant to show the treatments people may have before and after the treatment under consideration in this SIP.
- Please also consider:
    - if there are multiple treatment options, and data suggest that some are more commonly used than others in the setting and condition being considered in this SIP, please report these data.
    - are there any drug–drug interactions and/or contraindications that commonly cause challenges for patient populations? If so, please explain what these are.

Response:

There are international guidelines for PBC, which recommend appropriate treatment or care options for patients, with the European Association for the Study of the Liver (EASL) publishing clinical guidelines for PBC in 2017 and a further publication from Hirschfield et al in 2021 on an

international consensus integrated pathway for patients with PBC.[10,11] Additionally, the British Society of Gastroenterology/UK-PBC treatment and management guidelines were published in 2018, focusing on the efforts to slow down disease progression through efficient diagnosis, the importance of grouping patients by risk, appropriately treating and alleviating (as able) any associated symptoms, whilst also highlighting the remaining unmet needs for new treatments for PBC.[4]

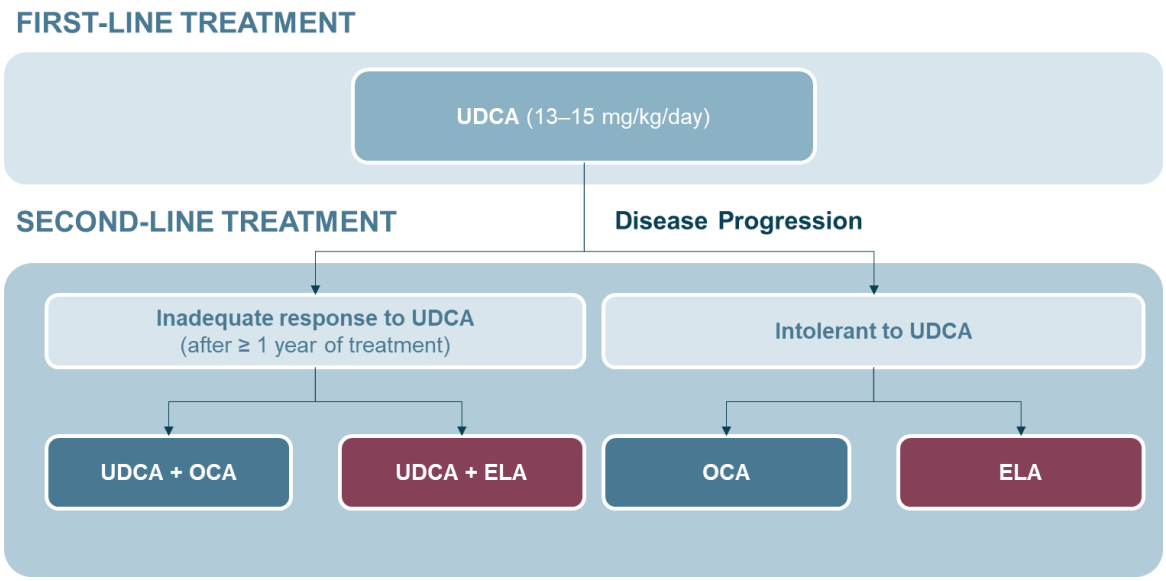
Progression of PBC is driven by a destructive cycle between immune responses (where the body attacks its own cells) and cholestasis. Cholestasis is the slowing or stalling of bile flow through the bile ducts. In terms of treatment response, the bigger the cholestasis response the better the treatment will have worked. Therefore, in clinical trials for PBC treatments, this cholestasis response is used to measure if a treatment has improved disease progression and survival of patients. Cholestasis can be measured through specific biochemical markers in the blood. These biomarkers, ALP and TB can therefore be used to predict the long-term clinical benefit of PBC treatment. ALP is an enzyme that is mostly found in the liver and bones, with high levels in the blood indicating liver damage with the higher the amount of ALP detected in the blood stream the greater the extent of liver damage. Similarly, bilirubin levels increase as PBC progresses, with high levels of bilirubin indicating cholestatic liver disease. More about the endpoints used to measure PBC progression can be found in section B.1.3.1.4 of the company submission.

Treatments for PBC generally aim to slow disease progression and prevent end-stage liver disease complications, whilst also providing symptom management. Liver transplant is the only potentially curative treatment for PBC, but it should be seen as a last resort after treatment to sufficiently reduce biochemical levels of alkaline phosphatase (ALP) and total bilirubin (TB) has failed. In addition it is typically only available for PBC patients with complications of cirrhosis, severe disease, or severe medically-resistant pruritus.[10]

Current treatment options for patients with PBC are limited, with only two therapies approved in Europe by the European Medicines Agency: ursodeoxycholic acid (UDCA) and obeticholic acid (OCA).[16] UDCA is the only licensed first treatment for patients newly diagnosed with PBC.[17] However, although UDCA has a well-understood safety profile and is effective in reducing visible progression of disease in the liver tissue, up to 5% of patients are unable to take the treatment (intolerant) and 25-50% of patients do not respond strongly enough to the treatment (inadequate response) to prevent progressive liver disease.[18,19] The only available licensed therapy for PBC patients who are intolerant or inadequately responding to UDCA is OCA and this was recommended by NICE in 2017.[20]

There remains an unmet need for a well-tolerated treatment for UDCA resistant/intolerant patients, as OCA is not effective at controlling disease symptoms in most patients and is associated with side effects, including dose-associated worsening of itch. Elafibranor offers an alternative mechanism of action to OCA, so presents an alternative option for patients who are intolerant or respond inadequately to UDCA. The proposed positioning of elafibranor in the PBC treatment is outlined in Figure 1.

Figure 1: Proposed positioning of elafibranor in the recommended PBC sequence of treatment options in the UK



Abbreviations: ELA – elafibranor; kg – kilograms; mg – milligrams; OCA – obeticholic acid; PBC – primary biliary cholangitis; UDCA – ursodeoxycholic acid
Source: Adapted from EASL 2017

2d) Patient-based evidence (PBE) about living with the condition

Context:

- **Patient-based evidence (PBE)** is when patients input into scientific research, specifically to provide experiences of their symptoms, needs, perceptions, quality of life issues or experiences of the medicine they are currently taking. PBE might also include carer burden and outputs from patient preference studies, when conducted in order to show what matters most to patients and carers and where their greatest needs are. Such research can inform the selection of patient-relevant endpoints in clinical trials.

In this section, please provide a summary of any PBE that has been collected or published to demonstrate what is understood about **patient needs and disease experiences**. Please include the methods used for collecting this evidence. Any such evidence included in the SIP should be formally referenced wherever possible and references included.

Response:

Patients with PBC experience a substantial clinical burden, with symptoms often impacting their daily life. Throughout clinical trials to investigate a medicines efficacy and safety, patients are able to describe their symptoms and quality of life, both quantitatively and qualitatively. These methods often stem from questionnaires that ask patients to score how they are feeling at certain time points, either of the day or of their treatment cycle. In the UK specifically, there is a research cohort set up by UK-PBC that contains detailed symptom and quality of life data. Patients are recruited into this cohort via the UK-PBC Consortium which is a research group of over 150 NHS trusts across the UK. In 2021, these data were studied and the symptoms of PBC analysed. It was reported that fatigue and bone ache were present in 63.4% and 43.1% of patients with PBC, representing a significant symptom burden.[21] More about the research cohort and health-related quality of life studies can be found in the company submission B.1.3.2.2.

At early-stages, PBC generally may not present symptoms (50% of patients are asymptomatic at diagnosis) but instead the disease will be shown by biochemical markers in the blood, which can be discovered through tests. As the condition mainly affects women, many of these symptoms are experienced around the same time as menopause, therefore some symptoms such as itch and depression may actually be dismissed by the GP. At moderate-stage PBC, patients may start to show symptoms and potentially other related disease conditions. At this stage, the most commonly reported symptoms are pruritus and fatigue, occurring in 29-69% and 25-76% of patients with PBC at diagnosis, respectively.[22,23] Pruritus has a significant negative impact on patients, as it is incredibly damaging to sleep, impacts on patients' social lives, housework and work.[24] Patients with PBC and pruritus are also more likely to have other symptoms and conditions such as fatigue, depression, anxiety and sleep-related issues in comparison to PBC patients that do not experience pruritus. Similarly, fatigue has a significant negative impact on patients, with patients reporting that their fatigue resulted in brain fog, mental confusion, dizziness, memory problems, difficult focussing and attention problems, further leading to sleep problems.[25] Fatigue affects up to 80% of patients with PBC and one in five patients who have fatigue describe it as "significant" or "life altering". During late-stage PBC, patients can develop additional symptoms as their disease progresses which includes progressive jaundice, malnutrition, portal hypertension and liver failure.[11,26] If you would like to read more about the substantial clinical burden of PBC on patients, this can be found in section B.1.3.2.1 in the company submission.

SECTION 3: The treatment

Note to authors: Please complete each section with a concise overview of the key details and data, including plain language explanations of any scientific methods or terminology. Please provide all references at the end of the template. Graphs or images may be used to accompany text if they will help to convey information more clearly.

3a) How does the new treatment work?

What are the important features of this treatment?

Please outline as clearly as possible important details that you consider relevant to patients relating to the mechanism of action and how the medicine interacts with the body

Where possible, please describe how you feel the medicine is innovative or novel, and how this might be important to patients and their communities.

If there are relevant documents which have been produced to support your regulatory submission such as a summary of product characteristics or patient information leaflet, please provide a link to these.

Response:

Elafibranor is a peroxisome proliferator-activated receptor (PPAR) agonist, which activates two different receptors on cells in the liver known as PPAR alpha (α) and PPAR delta (δ), affecting bile acid production, maintenance of glucose levels and inflammation. Elafibranor is the only treatment under development for PBC which targets both PPARα and PPARδ.[27] Through activating PPARα, elafibranor can remove and reduce the amount of bile acid produced. This reduces the build-up of bile in the liver and therefore reducing the amount of damage caused in the liver. Additionally, activation of PPARδ helps to manage glucose levels, liver fat and prevent inflammation in the liver.[27,28] By activating both PPARα and δ, elafibranor is expected to provide additional therapeutic benefits compared with treatments which can activate only a single PPAR, whilst avoiding the side effects associated with activation of another commonly targeted receptor called PPAR (gamma) y including weight gain, fluid retention, and heart failure.[29,30]

3b) Combinations with other medicines

Is the medicine intended to be used in combination with any other medicines?

- Yes / No

If yes, please explain why and how the medicines work together. Please outline the mechanism of action of those other medicines so it is clear to patients why they are used together.

If yes, please also provide information on the availability of the other medicine(s) as well as the main side effects.

If this submission is for a combination treatment, please ensure the sections on efficacy (3e), quality of life (3f) and safety/side effects (3g) focus on data that relate to the combination, rather than the individual treatments.

Response:

Elafibranor will be used as a single treatment (monotherapy) on its own for patient's intolerant to UDCA or can be added to UDCA for patients with an inadequate response.

3c) Administration and dosing

How and where is the treatment given or taken? Please include the dose, how often the treatment should be given/taken, and how long the treatment should be given/taken for.

How will this administration method or dosing potentially affect patients and caregivers? How does this differ to existing treatments?

Response:

Elafibranor will be administered orally, once daily, with or without food as a single 80 mg tablet.[31]

3d) Current clinical trials

Please provide a list of completed or ongoing clinical trials for the treatment. Please provide a brief top-level summary for each trial, such as title/name, location, population, patient group size, comparators, key inclusion and exclusion criteria and completion dates etc. Please provide references to further information about the trials or publications from the trials.

Response:

Study	Study of Elafibranor in Patients With Primary Biliary Cholangitis (PBC) (ELATIVE)[32], NCT04526665
Study design	Kowdley, K.V. et al. Efficacy and Safety of Elafibranor in Primary Biliary Cholangitis. N Engl J Med (2023)[32] doi:10.1056/NEJMoa2306185.
Study design	Phase III, Multinational, multi-centre, randomised, double-blind, placebo-controlled.
Population	Adult patients with primary biliary cholangitis who had an inadequate response to or were unable to tolerate ursodeoxycholic acid.
Settings and locations where the data were collected	Multinational trial including the following study centre locations: United States of America, Argentina, Belgium, Brazil, Canada, Chile, France, Germany, Italy, South Africa, Spain, Switzerland, Turkey, and the United Kingdom.
Completion Date	June 2023
Intervention(s)	Elafibranor 80 mg once daily
Comparator(s)	Placebo (an inactive drug) once daily

Reported outcomes specified in the decision problem	• Cholestasis response (as described in section 2c) defined as alkaline phosphatase (ALP) levels that decreased to a predefined range and bilirubin levels at or under the upper limit of a normal threshold at Week 52 • Mortality • Liver function based on markers of liver biochemistry • Symptoms including pruritus, fatigue and abdominal pain • Adverse effects of treatment • Health-related quality of life
All other reported outcomes	Pharmacokinetics
Key Inclusion Criteria	• Informed consent • Males or females age of 18 to 75 years inclusive • Confirmed diagnosis of PBC • On UDCA for at least 12 months prior and at stable dose for ≥3 months, or unable to tolerate UDCA treatment. • ALP levels ≥1.67 x upper limit of normal (ULN) • Total bilirubin levels ≤2 x ULN • Females must be of non-childbearing potential or must be using highly effective contraception for the full duration of the study and for 1 month after the last drug intake
Key Exclusion Criteria	• History or presence of other concomitant liver disease, including: HAV, HBV, HCV, AIH, PSC, ALD, NASH, Gilbert's syndrome or alpha-1-antitrypsin deficiency • History of: o Liver transplant, or current placement on liver transplant list o Model for end-stage liver disease (MELD)-Na score ≥12 o Signs and symptoms of cirrhosis/portal hypertension o Hepatorenal syndrome • Markers of liver damage, such as: o Alanine aminotransferase and/or aspartate aminotransferase >5 x ULN o Platelet count <150 x 103/µL o Albumin <3.0 g/dL o Known pregnancy or lactating (female patients) o Severely advanced patients according to Rotterdam criteria (TB > upper limit normal and albumin < lower limit normal) • Prohibited medications: o Fibrates and glitazones (2 months prior to screening) o OCA, azathioprine, colchicine, cyclosporine, methotrexate, mycophenolate mofetil, pentoxifylline, budesonide and other systemic corticosteroids (3 months prior to screening) o Immunotherapy directed against interleukins or other cytokines or chemokines (12 months prior to screening)

3e) Efficacy

Efficacy is the measure of how well a treatment works in treating a specific condition.

In this section, please summarise all data that demonstrate how effective the treatment is compared with current treatments at treating the condition outlined in section 2a. Are any of the outcomes more important to patients than others and why? Are there any limitations to the data which may affect how to

interpret the results? Please do not include academic or commercial in confidence information but where necessary reference the section of the company submission where this can be found.

Response:

The primary endpoint of the ELATIVE study was the biochemical (or cholestasis) response to treatment after 52 weeks (a year) on treatment. As described in section 2c above, cholestasis is the slowing or stalling of bile flow through your bile ducts, with the bigger the biochemical response (measured through ALP and TB levels) equating to the better the treatment has worked. In the ELATIVE trial, cholestasis response was defined as ALP level of ≤1.67 times the upper-limit normal (ULN) range (a specified range which defines a normal ALP level), with a reduction of ALP levels of at least 15% from the start of the trial, and normal total bilirubin levels at Week 52. The ELATIVE study met its primary outcome of cholestasis response; after 52 weeks, with a statistically significant response observed in 50.9% (55/108) of patients in the elafibranor group and in 3.8% (2/53) of patients in the placebo (an inactive drug) group.[32] In other words, x13 more patients achieved a biochemical response with elafibranor compared to placebo.

The key secondary endpoint was the response to treatment based on a reduction of ALP levels to a normal range. Normalisation of ALP levels has been associated with improvement in survival and/or the need for a liver transplant. The proportion of people who responded to treatment was greater in people prescribed elafibranor (16/108 [14.8%] patients) than those taking a placebo (0/53 [0.0%] patients), resulting in a statistically significant difference of 14.8% favouring the elafibranor group. The reduction in ALP was seen by the first visit after treatment commencement and was sustained throughout the trial until Week 52.[32]

The second and third key secondary endpoints were the change in pruritus (itch) from the start of the trial through Week 24 and 52, respectively.[32] These data are described in the section below, as these endpoints specifically focus on the quality of life impact that elafibranor could bring.

More key findings from the ELATIVE pivotal trial can be found in section B.2.12.1 of the company submission.

3f) Quality of life impact of the medicine and patient preference information

What is the clinical evidence for a potential impact of this medicine on the quality of life of patients and their families/caregivers? What quality of life instrument was used? If the EuroQol-5D (EQ-5D) was used does it sufficiently capture quality of life for this condition? Are there other disease specific quality of life measures that should also be considered as supplementary information?

Please outline in plain language any quality of life related data such as **patient reported outcomes (PROs).**

Please include any **patient preference information (PPI)** relating to the drug profile, for instance research to understand willingness to accept the risk of side effects given the added benefit of treatment. Please include all references as required.

Response:

Pruritus is one of the most common symptoms in patients with PBC, with an important health-related impact on quality of life (HRQoL).[24,33] The second and third key secondary endpoints of the ELATIVE trial focussed on the change in pruritus over the duration of the trial (52 weeks) and were assessed using the PBC worst itch numeric rating scale (WI-NRS), a system used to score the severity of itch. WI-NRS was measured among the moderate-to-severe pruritus patients of the study. Although the difference between treatments was not shown to be significant based on a statistical analysis, there was a clear trend for greater improvement in pruritus for patients treated with elafibranor compared with placebo. An additional two instruments were used to

measure the impact of elafibranor on pruritus: the itch domain of the PBC-40 (a patient-derived, disease specific quality of life measure that has been developed and validated for use in the PBC patient population) and the 5-D itch score. A marked improvement in pruritus according to the PBC-40 Itch and 5-D patient reported outcome measures was seen. This marked benefit was demonstrated in those with moderate-to-severe pruritus at the start of the trial as well as the broader overall patient population treated with elafibranor.

Fatigue also has a significant negative impact on PBC patients, affecting up to 80% of patients, with 20% of patients saying that their fatigue is "significant"[34]. In the ELATIVE trial, participants with moderate-to-severe pruritus experienced an improvement in fatigue when using elafibranor compared to placebo, according to the PROMIS Fatigue T-score questionnaire. However, this improvement was not statistically significant.

It was also seen in the ELATIVE trial that fewer patients treated with elafibranor experienced pruritus as a side effect of treatment compared to placebo (20% vs 26%), with similar results seen for fatigue as a side effect (9% elafibranor vs 13% placebo). These findings are in contrast to that for OCA, which has been shown to worsen pruritus.

Additionally, within the ELATIVE clinical trial, patients completed the generic quality of life questionnaires, known as EQ-5D-5L questionnaires, at multiple time points across the 52-week study. Overall, HRQoL, as measured by responses to the EQ-5D-5L questionnaire, remained high and stable throughout the study period, with no meaningful differences observed between the elafibranor and placebo groups.[35]

3g) Safety of the medicine and side effects

When NICE appraises a treatment, it will pay close attention to the balance of the benefits of the treatment in relation to its potential risks and any side effects. Therefore, please outline the main side effects (as opposed to a complete list) of this treatment and include details of a benefit/risk assessment where possible. This will support patient reviewers to consider the potential overall benefits and side effects that the medicine can offer.

Based on available data, please outline the most common side effects, how frequently they happen compared with standard treatment, how they could potentially be managed and how many people had treatment adjustments or stopped treatment. Where it will add value or context for patient readers, please include references to the Summary of Product Characteristics from regulatory agencies etc.

Response:

Within the ELATIVE clinical trial, there were similar percentages seen in both the elafibranor and placebo groups for side effects (adverse events). Adverse events (AEs) occurred more frequently in patients receiving elafibranor than in those receiving placebo. AEs that affected more than 10% of patients were mostly gastrointestinal in nature, including abdominal pain (11% vs 6%), diarrhoea (11% vs 9%), nausea (11% vs 6%) and vomiting (11% vs 2%). The majority of AEs were of mild or moderate intensity, and no patients receiving elafibranor had severe pruritus.[32,35] No clinically meaningful changes in kidney function were observed. Adverse events leading to discontinuation of treatment occurred in 10% of elafibranor patients and 9% of patients in the placebo arm of the trial.

Elafibranor can be used for any people diagnosed with PBC according to the MHRA approved indication (if approved), however precaution should be taken for patients with severely reduced liver function. Additional precautionary use should include:

- During pregnancy or in women of childbearing potential not using effective contraception

- During breastfeeding; women who are breastfeeding should not breastfeed for at least three weeks following the termination of elafibranor treatment.

Elafibranor is not known to interact with other medicines.[31] Clinical drug-drug interaction studies showed no clinically significant effects when administering elafibranor with other medications such as cholesterol lowering agents (simvastatin, atorvastatin) and blood thinning agents such as warfarin.

3h) Summary of key benefits of treatment for patients

Issues to consider in your response:

- Please outline what you feel are the key benefits of the treatment for patients, caregivers and their communities when compared with current treatments.
- Please include benefits related to the mode of action, effectiveness, safety and mode of administration

Response:

PBC patients who received elafibranor within the ELATIVE trial demonstrated a clinically meaningful and statistically significant biochemical response as measured by a lowering of ALP and bilirubin levels compared to placebo. These changes are predicted to result in a better long-term outcome for people with PBC by reducing the risk of liver complications, the need for a liver transplant and death. The results also show a trend of improvement for the symptom of pruritus in the WI-NRS measure, however this was not statistically significant. Elafibranor did show a marked improvement for pruritus when the itch domain of the PBC-40 and the 5-D itch questionnaires were used to measure itch. Elafibranor is an oral tablet that is only needed to be taken once a day with no dose changes required. The dose was found to be well tolerated in patients within the ELATIVE trial and similar number of patients discontinued treatment with elafibranor for side effects compared to placebo. Furthermore, the ELATIVE trial showed that the treatment of elafibranor did not impact the HRQoL for patients on treatment.

Currently, OCA is the only licensed and reimbursed treatment option for PBC patients whose disease has an inadequate response to UDCA. OCA is associated with side effects, such as pruritus, therefore elafibranor would provide an alternative treatment that can prevent disease progression and not worsen symptoms (like pruritus) and may improve symptoms in some patients.

3i) Summary of key disadvantages of treatment for patients

Issues to consider in your response:

- Please outline what you feel are the key disadvantages of the treatment for patients, caregivers and their communities when compared with current treatments. Which disadvantages are most important to patients and carers?
- Please include disadvantages related to the mode of action, effectiveness, side effects and mode of administration
- What is the impact of any disadvantages highlighted compared with current treatments

Response:

OCA is currently available through specialised hubs, where patients must travel to ensure they receive this treatment. Ipsen are anticipating that we will have a similar treatment pathway, whereby patients would need to be prescribed elafibranor at specialist centres. This could entail some patients travelling further than their local centre to receive treatment. However, as the treatment is an oral, daily medicine, patients will be able to obtain their prescription and take the treatment at home over the coming months.

Within the ELATIVE clinical trial, there were similar percentages seen in both the elafibranor and placebo groups for side effects (adverse events). Adverse events (AEs) occurred in more than 10% of patients and more frequently in patients receiving elafibranor than in those receiving placebo. The AEs were mostly gastrointestinal in nature, including abdominal pain, diarrhoea, nausea and vomiting. The majority of AEs were of mild or moderate intensity, and no patients receiving elafibranor had severe pruritus.

3i) Value and economic considerations

Introduction for patients:

Health services want to get the most value from their budget and therefore need to decide whether a new treatment provides good value compared with other treatments. To do this they consider the costs of treating patients and how patients' health will improve, from feeling better and/or living longer, compared with the treatments already in use. The drug manufacturer provides this information, often presented using a health economic model.

In completing your input to the NICE appraisal process for the medicine, you may wish to reflect on:

- The extent to which you agree/disagree with the value arguments presented below (e.g., whether you feel these are the relevant health outcomes, addressing the unmet needs and issues faced by patients; were any improvements that would be important to you missed out, not tested or not proven?)
- If you feel the benefits or side effects of the medicine, including how and when it is given or taken, would have positive or negative financial implications for patients or their families (e.g., travel costs, time-off work)?
- How the condition, taking the new treatment compared with current treatments affects your quality of life.

Response:

As part of the NICE submission a cost-effectiveness analysis (CEA) was conducted to show the value for money of the introduction of elafibranor as a treatment option for PBC patients. As part of a CEA, an incremental cost-effectiveness ratio (ICER) is determined. NICE have predetermined ICER thresholds that determine whether a medicine is cost-effective. The results of our CEA show that elafibranor is a cost-effective treatment for PBC patients that are inadequate responders or intolerant to UDCA, with the ICER falling within the NICE threshold.

How the model reflects the condition:

The cost-effectiveness model used in the elafibranor CEA is structured into two main parts; one that captures the improvement or worsening in biochemical response to drug treatment and another part which captures the liver disease related outcomes. These outcomes include liver transplant, liver cancer, complications of cirrhosis in patients who fail to control their biochemical levels of ALP and TB and these patients therefore have a higher risk of liver disease outcomes and complications. The model showed that compared to OCA combined with UDCA or no additional treatment (i.e. UDCA alone), treatment with elafibranor delays disease progression more, reduces

disease severity, the complications of cirrhosis and the need for liver transplants, ultimately prolonging the lives of patients on elafibranor. The model used the results from the ELATIVE trial, specifically the biochemical response (lowering of ALP and TB levels) that was achieved with elafibranor. When these results are applied to the model, the CEA can predict the long-term outcomes of patients with PBC and, when compared to existing treatments, elafibranor could reduce the complications of liver disease and the need for a liver transplant, and ultimately death.

Modelling how much a treatment improved quality of life:

Another key health outcome measured in a CEA is the quality-adjusted life year (QALY). The QALY is derived from a utility* measurement of the quality of life (QoL) for patients, usually measured directly from the clinical trial or derived from external sources e.g. published literature on patients quality of life in the disease area. The utility measurement for different levels of biochemical response used to calculate the QALY in the elafibranor CEA is derived from a combination of published literature which was accepted in the OCA appraisal by NICE. Other values from the literature for QoL were used in the model for the different liver disease states in the model, such as liver cancer and the different stages of liver transplant (also accepted by NICE in the OCA review). Additionally, the QoL benefit of elafibranor has on pruritus compared to UDCA alone or in combination with OCA has attempted to be captured within the model.

Modelling how the costs of current treatment differ with the new treatment:

The model shows how treatment with elafibranor can save the health service on costs of liver transplant and being hospitalised for liver disease related complications compared to OCA and UDCA. Further, the monitoring costs of elafibranor should be the same if not lower compared to existing treatments.

Uncertainty:

The data that has been used in the model was sourced directly from the ELATIVE trial, with the inputs corroborated by clinical experts as being plausible to predict the long-term benefits and outcomes of elafibranor. The CEA of elafibranor applies most of the assumptions that were used in the NICE appraisal of OCA during 2016/2017. These assumptions were accepted, therefore Ipsen has considered a similar approach with their cost-effectiveness model with additional clinical validation from current practicing healthcare practitioners. However, there were some assumptions that NICE queried in their appraisal of OCA and these have been addressed in our submission to NICE, with further input by clinical experts to validate these new assumptions. A range of other, alternative assumptions and data sources have been tested in our model which have been presented in the company submission as scenarios. We found that these generally did not have a significant impact on the results of the CEA.

Additional factors:

We have not made a case for the severity modifier to be applied in our submission, as according to the model results, treatment with elafibranor does not qualify the medicine for the modifier. However, there is an additional benefit that has not been captured within the model as elafibranor may have a benefit on carers in reducing the burden they experience in looking after or supporting a person with PBC. Carers face emotional strain like anxiety and guilt, along with practical challenges like limited time for themselves and frustration with medical care. However, quantifying this burden is difficult due to the lack of research on the topic, hence why it has not been included in the model.

Another benefit of elafibranor that has not been captured in the model is its dosing and administration regimen. Elafibranor is a once-daily oral tablet, with no dosing adjustment required for age or kidney functions and this may minimise trips of the patient to hospitals as well as clinical/health service burden.

*Utility: Health utility is a measure of the preference or value that an individual or society gives a particular health state, with 1 being perfect health and 0 being death.

3j) Innovation

NICE considers how innovative a new treatment is when making its recommendations.
If the company considers the new treatment to be innovative please explain how it represents a 'step change' in treatment and/ or effectiveness compared with current treatments. Are there any QALY benefits that have not been captured in the economic model that also need to be considered (see section 3f)

Response:

Elafibranor is a new technology that has a different mode of action compared to the current second-line reimbursed treatment OCA, providing a clinically and cost-effective alternative for clinicians and patients to choose from.[27,28,36]

As described in section 3i, there are additional benefits that have not been captured within the model. Elafibranor may have a benefit on carers in reducing the burden they experience in looking after or supporting a person with PBC.

Another advantage for elafibranor compared to OCA is that dose-titration is not required. OCA should be started at a dose of 5 mg once daily for the first 6 months and after this, for patients who are tolerating OCA and have not achieved an adequate reduction in ALP or TB, the dose is increased to a maximum dose of 10 mg once daily.[16] Elafibranor's dose is 80 mg once daily as a single tablet and no dose adjustment is required during treatment.

3k) Equalities

Are there any potential equality issues that should be taken into account when considering this condition and this treatment? Please explain if you think any groups of people with this condition are particularly disadvantaged.
Equality legislation includes people of a particular age, disability, gender reassignment, marriage and civil partnership, pregnancy and maternity, race, religion or belief, sex, and sexual orientation or people with any other shared characteristics

More information on how NICE deals with equalities issues can be found in the NICE equality scheme
Find more general information about the Equality Act and equalities issues here

Response:

PBC is much more common in women than men, with recent studies suggesting a 9:1 female to male ratio worldwide. There are more reported UK cases in females than in males, mostly affecting women over 40 years old.[9,10,37] However, men are at greater risk of more advanced disease at diagnosis and poorer treatment response compared with female patients.[10,11,38,39] Though the majority of PBC patients present symptoms between the age of 40 to 60 years, cases

have been reported in individuals as young as 15 years.[9,12] Individuals diagnosed with PBC under the age of 50 experience more severe and progressive disease and poor treatment response compared with patients over the age of 50 at diagnosis. [13]

An additional equality consideration should be access to liver transplant. Webb et al. (2019) found disparities in access of liver transplants across the UK in addition of significant wait times, due to organ availability impacting timing for surgery.[38]

SECTION 4: Further information, glossary and references

4a) Further information

Feedback suggests that patients would appreciate links to other information sources and tools that can help them easily locate relevant background information and facilitate their effective contribution to the NICE assessment process. Therefore, please provide links to any relevant online information that would be useful, for example, published clinical trial data, factual web content, educational materials etc.
Where possible, please provide open access materials or provide copies that patients can access.

Response:

Key clinical trial (ELATIVE) information:

- Published clinical trial data available at: https://www.nejm.org/doi/full/10.1056/NEJMoa2306185
- Further information about the clinical trial available at: https://clinicaltrials.gov/study/NCT04526665

Background information about PBC:

- NHS information: https://www.nhs.uk/conditions/primary-biliary-cholangitis-pbc/
- PBC Foundation: https://www.pbcfoundation.org.uk/what-is-pbc/about-pbc/
- British Liver Trust: https://britishlivertrust.org.uk/information-and-support/liver-conditions/primary-biliary-cholangitis/

Link to the NICE appraisal: https://www.nice.org.uk/guidance/indevelopment/gid-ta11378

Further information on NICE and the role of patients**:**

- Public Involvement at NICE Public involvement | NICE and the public | NICE Communities | About | NICE
- NICE's guides and templates for patient involvement in HTAs Guides to developing our guidance | Help us develop guidance | Support for voluntary and community sector (VCS) organisations | Public involvement | NICE and the public | NICE Communities | About | NICE
- EUPATI guidance on patient involvement in NICE: https://www.eupati.eu/guidance-patient-involvement/
- EFPIA – Working together with patient groups: https://www.efpia.eu/media/288492/working-together-with-patient-groups-23102017.pdf
- National Health Council Value Initiative. https://nationalhealthcouncil.org/issue/value/
- INAHTA: http://www.inahta.org/
- European Observatory on Health Systems and Policies. Health technology assessment - an introduction to objectives, role of evidence, and structure in Europe: http://www.inahta.org/wp-

content/themes/inahta/img/AboutHTA_Policy_brief_on_HTA_Introduction_to_Objectives_Role_of_Evidence_Structure_in_Europe.pdf

4b) Glossary of terms

Response:

Abbreviations:
AE – adverse events
ALP – alkaline phosphatase
CEA – cost-effectiveness analysis
EASL – European Association for the Study of the Liver
Ela – elafibranor
HRQoL – health-related impact on quality of life
ICER – incremental cost-effectiveness ratio
MELD – Model for end-stage liver disease
MHRA – Medicines and Healthcare products Regulatory Agency
OCA – obeticholic acid
PBC – primary biliary cholangitis
PPAR – peroxisome proliferator-activated receptor
QALY – quality-adjusted life year
QOL – quality of life
SIP – Summary of Information for Patients
TB – total bilirubin
UDCA – ursodeoxycholic acid
ULN – upper limit normal
WI-NRS – worst itch numeric rating scale

Definitions:
ICER: An incremental cost effectiveness ratio is calculated by the difference in cost between the new treatment and the standard of care, divided by the difference in health effects (QALYs).

Incidence: the measurement of the number of new individuals who contract a disease

Prevalence: the measurement of all individuals affected by a disease

QALYs: The quality-adjusted life year is a generic measure of disease burden, including both the quality and the quantity of life lived.

Utility: Health utility is a measure of the preference or value that an individual or society gives a particular health state, with 1 being perfect health and 0 being death.

4c) References

Please provide a list of all references in the Vancouver style, numbered and ordered strictly in accordance with their numbering in the text:

Response:

1. Primary biliary cholangitis. *nhs.uk* https://www.nhs.uk/conditions/primary-biliary-cholangitis-pbc/ (2017).
2. Axley, P., Mudumbi, S., Sarker, S., Kuo, Y.-F. & Singal, A. Patients with stage 3 compared to stage 4 liver fibrosis have lower frequency of and longer time to liver disease complications. *PLoS One* **13**, e0197117 (2018).
3. Primary biliary cholangitis (primary biliary cirrhosis) - Symptoms. *nhs.uk* https://www.nhs.uk/conditions/primary-biliary-cholangitis-pbc/symptoms/ (2017).
4. Hirschfield, G. M. *et al.* The British Society of Gastroenterology/UK-PBC primary biliary cholangitis treatment and management guidelines. *Gut* **67**, 1568–1594 (2018).
5. Montano-Loza, A. J. & Corpechot, C. Definition and Management of Patients With Primary Biliary Cholangitis and an Incomplete Response to Therapy. *Clin Gastroenterol Hepatol* **19**, 2241-2251.e1 (2021).
6. Lv, T. *et al.* Regional variation and temporal trend of primary biliary cholangitis epidemiology: A systematic review and meta-analysis. *J Gastroenterol Hepatol* **36**, 1423–1434 (2021).
7. James, O. F. *et al.* Primary biliary cirrhosis once rare, now common in the United Kingdom? *Hepatology* **30**, 390–394 (1999).
8. Epidemiology of PBC – UK-PBC. https://www.uk-pbc.com/about/aboutpbc/epidemiology-of-pbc/.
9. Galoosian, A., Hanlon, C., Zhang, J., Holt, E. W. & Yimam, K. K. Clinical Updates in Primary Biliary Cholangitis: Trends, Epidemiology, Diagnostics, and New Therapeutic Approaches. *J Clin Transl Hepatol* **8**, 49–60 (2020).
10. EASL. EASL Clinical Practice Guidelines: The diagnosis and management of patients with primary biliary cholangitis. *J Hepatol* **67**, 145–172 (2017).

11. Hirschfield, G. M. *et al.* A consensus integrated care pathway for patients with primary biliary cholangitis: a guideline-based approach to clinical care of patients. *Expert Review of Gastroenterology & Hepatology* **15**, 929–939 (2021).
12. Gazda, J., Drazilova, S., Janicko, M. & Jarcuska, P. The Epidemiology of Primary Biliary Cholangitis in European Countries: A Systematic Review and Meta-Analysis. *Can J Gastroenterol Hepatol* **2021**, 9151525 (2021).
13. Carbone, M. *et al.* Sex and age are determinants of the clinical phenotype of primary biliary cirrhosis and response to ursodeoxycholic acid. *Gastroenterology* **144**, 560-569.e7; quiz e13-14 (2013).
14. Lindor, K. D., Bowlus, C. L., Boyer, J., Levy, C. & Mayo, M. Primary Biliary Cholangitis: 2018 Practice Guidance from the American Association for the Study of Liver Diseases. *Hepatology* **69**, 394–419 (2019).
15. Abdulkarim, M. *et al.* Sex differences in clinical presentation and prognosis in patients with primary biliary cholangitis. *Scand J Gastroenterol* **54**, 1391–1396 (2019).
16. EMA. Ocaliva | European Medicines Agency | SmPC. (2023).
17. MHRA. Ursodeoxycholic acid | Medicines and Healthcare Regulatory Agency | SmPC.
18. Kuiper, E. M. M. *et al.* Improved prognosis of patients with primary biliary cirrhosis that have a biochemical response to ursodeoxycholic acid. *Gastroenterology* **136**, 1281–1287 (2009).
19. Zhang, L.-N. *et al.* Early biochemical response to ursodeoxycholic acid and long-term prognosis of primary biliary cirrhosis: results of a 14-year cohort study. *Hepatology* **58**, 264–272 (2013).
20. NICE. Obeticholic acid for treating primary biliary cholangitis (TA443) | Guidance | NICE. (2017).
21. Rice, S. *et al.* Effects of Primary Biliary Cholangitis on Quality of Life and Health Care Costs in the United Kingdom. *Clin Gastroenterol Hepatol* **19**, 768-776.e10 (2021).

22. Jung, H. E. *et al.* Prognostic indicators in primary biliary cirrhosis: significance of revised IAHG (International Autoimmune Hepatitis Group) score. *Clin Mol Hepatol* **18**, 375–382 (2012).
23. Milovanovic, T. *et al.* Quality of Life in Patients with Primary Biliary Cholangitis: A Single-Center Experience in Serbia. *Dig Dis* **38**, 515–521 (2020).
24. Mayo, M. J. *et al.* Impact of Pruritus on Quality of Life and Current Treatment Patterns in Patients with Primary Biliary Cholangitis. *Dig Dis Sci* **68**, 995–1005 (2023).
25. *Understanding the Experience of Patients with Primary Biliary Cholangitis and Pruritus. Poster Number: PCR34. Presented at ISPOR 2023*. (2023).
26. Kim, K.-A. *et al.* Population-based epidemiology of primary biliary cirrhosis in South Korea. *Aliment Pharmacol Ther* **43**, 154–162 (2016).
27. Ratziu, V. *et al.* Elafibranor, an Agonist of the Peroxisome Proliferator-Activated Receptor-alpha and -delta, Induces Resolution of Nonalcoholic Steatohepatitis Without Fibrosis Worsening. *1159.e5* (2016) doi:10.1053/j.gastro.2016.01.038.
28. Ye, X., Zhang, T. & Han, H. PPARα: A potential therapeutic target of cholestasis. *Front. Pharmacol.* **13**, (2022).
29. Cariou, B. & Staels, B. GFT505 for the treatment of nonalcoholic steatohepatitis and type 2 diabetes. *Expert Opin Investig Drugs* **23**, 1441–1448 (2014).
30. Hanf, R. *et al.* The dual peroxisome proliferator-activated receptor alpha/delta agonist GFT505 exerts anti-diabetic effects in db/db mice without peroxisome proliferator-activated receptor gamma-associated adverse cardiac effects. *Diab Vasc Dis Res* **11**, 440–447 (2014).
31. IPSEN. Draft Summary of Product Characteristics (SmPC). (2023).
32. Kowdley, K. V. *et al.* Efficacy and Safety of Elafibranor in Primary Biliary Cholangitis. *N Engl J Med* **390**, 795–805 (2024).
33. Dyson, J. K. *et al.* The inter-relationship of symptom severity and quality of life in 2055 patients with primary biliary cholangitis. *Aliment Pharmacol Ther* **44**, 1039–1050 (2016).

34. Jopson, L. & Jones, D. E. J. Fatigue in Primary Biliary Cirrhosis: Prevalence, Pathogenesis and Management. *Dig Dis* **33 Suppl 2**, 109–114 (2015).
35. IPSEN. Clinical Study Report: A Double-Blind, Randomized, Placebo-Controlled Study and Open-Label Long Term Extension to Evaluate the Efficacy and Safety of Elafibranor 80 Mg in Patients with Primary Biliary Cholangitis with Inadequate Response or Intolerance to Ursodeoxycholic Acid. (2023).
36. Schattenberg, J. M. *et al.* A randomized placebo-controlled trial of elafibranor in patients with primary biliary cholangitis and incomplete response to UDCA. *J Hepatol* **74**, 1344–1354 (2021).
37. Alvaro, D. *et al.* Estrogens and the pathophysiology of the biliary tree. *World J Gastroenterol* **12**, 3537–3545 (2006).
38. Webb, G. J., Ryan, R. P., Marshall, T. P. & Hirschfield, G. M. The Epidemiology of UK Autoimmune Liver Disease Varies With Geographic Latitude. *Clin Gastroenterol Hepatol* **19**, 2587–2596 (2021).
39. French, J. *et al.* Identification of a Latitude Gradient in the Prevalence of Primary Biliary Cholangitis. *Clin Transl Gastroenterol* **12**, e00357 (2021).

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Single Technology Appraisal

Elafibranor for treating primary biliary cholangitis [ID6331]

Clarification questions

29th April 2024

File name	Version	Contains confidential information	Date
ID6331 Elafibranor clarification letter_Company response_redacted	1	Yes	22/05/24

Notes for company

Highlighting in the template

Square brackets and grey highlighting are used in this template to indicate text that should be replaced with your own text or deleted. These are set up as form fields, so to replace the prompt text in [grey highlighting] with your own text, click anywhere within the highlighted text and type. Your text will overwrite the highlighted section.

To delete grey highlighted text, click anywhere within the text and press DELETE.

Section A: Clarification on effectiveness data

Literature searches

A1. Appendix D: Please give the source/citation details for any study design search filters applied to the clinical effectiveness searches in MEDLINE and Embase (Appendix D, Table 1 for MEDLINE, Table 2 for Embase)

These filters were adapted from the validated and commonly used “randomised controlled trials” and “observational studies” filters published by Scottish Intercollegiate Guidelines Network (SIGN), with minor adaptations to reflect contemporary syntax in the Ovid SP platform (e.g. .tw. -> .ti,ab,kf.) and to remove the “letter” design from the study exclusion filter, as these studies occasionally contain novel data.[1]

A2. Appendix D, Tables 1 and 2: Please provide a rationale for searching for other study designs in the MEDLINE and Embase search strategies for clinical effectiveness (interventional studies (RCTs and non-RCTs) and observational studies) when the focus of the review question specifies “Randomised Controlled Trials.”

When the original SLR was conducted in November 2022, the disposition of the PBC literature was unclear (as in, whether there would be sufficient randomised evidence

in support of interventions for PBC, as well as the frequent designation of PBC as a 'rare disease'). To ensure that data originating from studies lower in the hierarchy of evidence (i.e. SLRs of RCTs > RCTs > interventional studies > … etc.) could be resorted to in the event of insufficient data, our initial research question remained broad. Having reviewed records at both title/abstract and full-text review stage, it was ascertained that there were sufficient data in the form of both RCTs and in patients treated "post-UDCA", or in the second line, to focus the research question of the review. These prioritisation criteria are detailed in Table 9 in Appendix D.

A3. Appendix G, p.16: Please give the source/citation for the "best practice guidelines" that were used "for identifying inputs relevant to cost-effectiveness modelling".

NICE PMG6, chapter 7, section 7.2.3: "Two resources for identifying useful sources of utility data for economic modelling are the database of preference weights on the CEA (Cost-Effectiveness Analysis) Registry website and the NICE Decision Support Unit technical support document 'The identification, review and synthesis of health state utility values from the literature'."[2,3]

Systematic literature review

A4. Appendix D.1, p.1; and D.1.1, Table 9 (p. 10-2): The review question is "What randomised control trials (RCTs) have been conducted that evaluate the efficacy and/or safety of elafibranor and other comparators of interest in patients with PBC?" However, within the inclusion criteria for the SLR, non-randomised interventional studies and observational studies are listed as included, as are studies with "any other comparator (or none)." Could the company please clarify why they included non-randomised interventional studies, single arm studies and observational studies in the SLR?

See response to A2. Ultimately, only RCT study designs were included for data extraction; see Table 9, Appendix D for the full prioritisation criteria. The only exception to this was data for studies of elafibranor itself, wherein all study designs containing summary clinical data were eligible for inclusion.

A5. Appendix D.1.1, Table 9 (p.11): The list of eligible comparators in Table 9 mentions “any other comparators”. Could the company please list these comparators and, in doing so, clarify whether studies with a comparator arm including UDCA or OCA (when not part of the intervention) were eligible?

See response to A2. Ultimately, the decision was made to adopt a broad PICO for this review, given the lack of clarity surrounding the literature disposition. It was also anticipated that some interventional studies may look to compare different dosing regimens of the same investigational drug, hence the breadth. Under this definition, both UDCA and OCA would be covered under “any other comparators” (either could also be argued under “standard of care”). In practice, we found the following comparative therapies:

- UDCA (delivered singly or in combination with placebo)
- Placebo alone
- Different doses of the same intervention under investigation, e.g. seladelpar 2/5/10 mg in Bowlus 2022.[4]

A6. Could the company clarify if they contacted study authors for further data when records reporting studies lacked critical information?

This was not conducted, though no instances where this may have been the only option to obtain missing data were noted with the data that were ultimately extracted in this review.

Clinical trial

A7. Please provide a summary of the discussion undertaken with clinicians, as reference 117 only contains questions and not answers.

Please refer to the clinical validation report provided (“Clinician validation findings report merged_v2.0_FINAL_10May2024.docx”). This report includes the collated discussion points from individual meetings with both [redacted].

A8. The subgroups ‘inadequate response’ and ‘unable to tolerate UDCA’ were not considered in the ELATIVE trial subgroup analysis. The company stated that the distribution of patients in the ELATIVE trial is reflective of clinical practice. Can the

company provide additional information on the distribution of participants who had an inadequate response to UDCA or were unable to tolerate UDCA in the trial?

Up to 40% of UDCA-treated patients have an inadequate response and remain at high risk of disease progression. It is estimated that between 3-5% of patients with PBC are intolerant to UDCA.[5] The ELATIVE trial enrolled a population representative of a typical population of patients with PBC in need of second-line therapy, i.e. with an inadequate response and/or intolerance to UDCA. At baseline, 95% (153/161) were on concurrent UDCA treatment and at risk of disease progression due to inadequate response. The trial also enrolled 5% (8/161) of participants who did not receive concurrent UDCA (i.e. were intolerant to UDCA and received elafibranor monotherapy). The distribution of trial participants is also in line with the UK-PBC population-based study, where 96% (7864/8226) patients received UDCA as first-line therapy and 4% (362/8226) patients did not receive UDCA due to intolerance.[6]

A9. Please can the company justify the choice of surrogate composite endpoints as the primary outcome and comment on whether there are other outcomes that could have been used as the primary outcome.

Both ALP and bilirubin levels have been shown to be highly predictive of long-term clinical outcomes, including transplant-free survival.[7,8] Results from the Global PBC Study Group have confirmed a near log-linear correlation of both elevated ALP and bilirubin levels after 1 year of follow up with decreased long-term liver transplant-free survival.[7] Histological progression in the fibrosis stage in paired liver biopsies performed in patients with PBC 10 years after initial histological diagnosis was associated with the absence of biochemical response to UDCA at 2 years: a first stage increase associated with ALP >1.67 x ULN and second stage increase with ALP >1.76 x ULN.[9] In a retrospective study, patients with ALP ≤1.67 x ULN and bilirubin ≤1 mg/dL after 1 year of UDCA treatment had the least likelihood of reaching adverse clinical outcomes with similar results for ALP <1.5 and <x2 ULN for ALP.[10]

Based on these findings, the primary endpoint of cholestasis response, defined as an ALP <1.67 x ULN, TB ≤ULN, and ALP decreased ≥15%, has been recognised as a relevant surrogate marker for the treatment of PBC by the FDA and EMA industry guidance and formed the basis for the conditional marketing approvals of obeticholic

acid (Ocaliva®) in this indication by the FDA and EMA in 2016. Based on these findings, the primary endpoint of cholestasis response, defined as an ALP <1.67 x ULN, TB ≤ULN, and ALP decreased ≥15%, has been recognised as a relevant surrogate marker for the treatment of PBC by the FDA and EMA industry guidance and formed the basis for the conditional marketing approvals of obeticholic acid (Ocaliva®) in this indication by the FDA and EMA in 2016.[11–13] The addition of a minimum ALP reduction of ≥15% from baseline was included as part of the composite endpoint in these trials as a conservative threshold so that patients who only had a small change in ALP from 1.67 x ULN were excluded. This ensured that only subjects with a relevant clinical effect were judged to have a successful response and reduced the natural variation that can occur with biochemistry test results. Recent evidence demonstrated that treatment with OCA resulted in significantly greater transplant-free survival in a clinical trial setting than comparable external controls, which provides additional support for the use of the surrogate primary endpoint as a basis for approval of future second-line therapies in PBC.[14] Collectively, the primary efficacy endpoint is expected to be a clinically relevant endpoint predictive of transplant-free survival, and thus a reliable surrogate endpoint in PBC.

Indirect treatment comparisons

A10. Priority Question: Please can the company explain the rationale behind conducting an NMA when only two trials were considered relevant to the decision problem.

The rationale for the choice of an NMA is provided in Appendix D.1.4.1-D.1.4.3 and briefly summarised in Section B.2.9 of the original company submission. As the ELATIVE and POISE studies included four treatments, a network approach for the indirect treatment comparison was the most appropriate.

Where comparators to an intervention are not compared in head-to-head trials but a network of evidence can be formed between the intervention and comparators, an NMA is the approach recommended by the NICE Guidelines Technical Support Unit when the absence of heterogeneity that may confound comparisons has been confirmed.[15] The method for NMA recommended by the NICE Decision Support Unit adopts a Bayesian approach.[16] Since the network of evidence considered within the

submission connected elafibranor to OCA 5-10 mg, it was appropriate to verify that an NMA was the preferred approach via a feasibility assessment. For a Bayesian NMA to be the most appropriate approach, the assumption that there is no difference in the distribution of trial-level effect modifiers and that included studies are sufficiently homogeneous needs to be verified. If heterogeneity is identified in the feasibility assessment, alternative statistical approaches to make relevant adjustments would have needed to be pursued.

During the feasibility assessment, it was determined and validated with clinical experts that the ELATIVE and POISE trials were similar in both trial design as well as patient populations and outcomes assessed, allowing for the use of NMA methodology.

A11. Please can the company provide the datasets that they used to perform the NMAs.

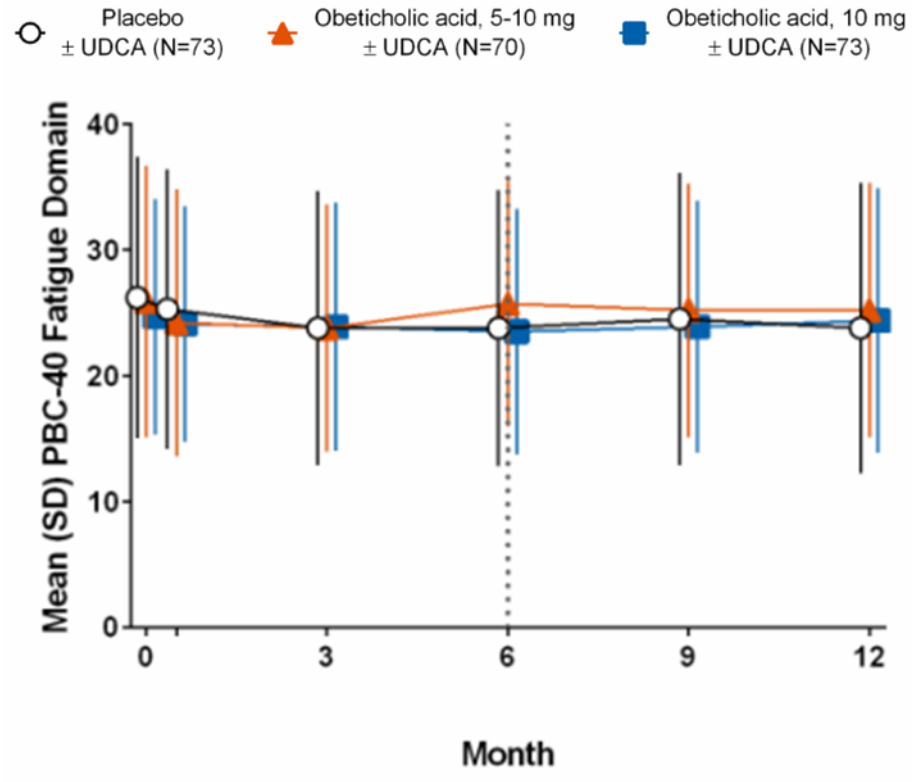
Please find the attached data sets in text file format used for the NMAs.

A12. Priority Question: Fatigue is included as an outcome within the decision problem and has a noted impact on patient quality of life according to patient organisation submissions, yet has not been included in the NMA despite data being available for the outcome in the ELATIVE trial. Please can the company explain the rationale behind not including an NMA for fatigue?

In the ELATIVE and POISE studies, fatigue was measured using the PBC-40 fatigue domain, which may have facilitated comparisons in an NMA. However, despite the reported impact that fatigue has on patient quality of life, there was no evidence from ELATIVE and POISE on a significant impact of treatment on the symptom compared to placebo. Therefore, analysis of the endpoint would not have demonstrated any differences between elafibranor and OCA.

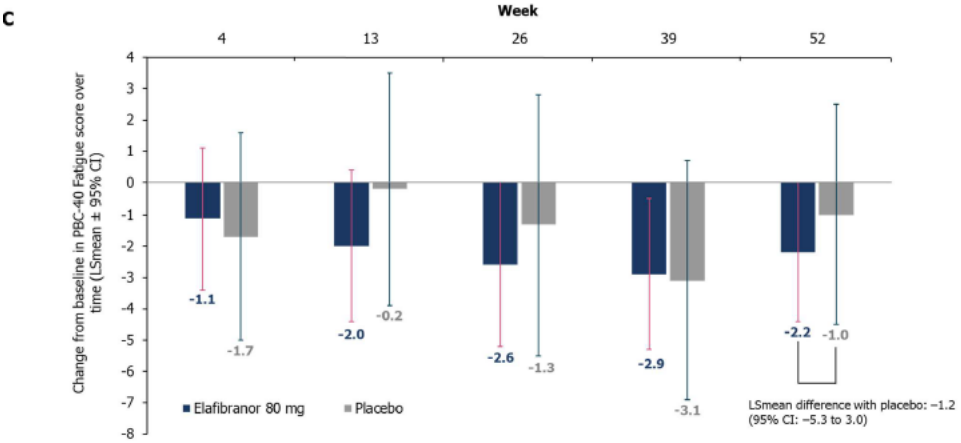
Specifically, in the POISE study, there was no difference detected between either dose of OCA or placebo in the PBC-40 fatigue scores after up to 12 months of exposure to treatment (Figure 1).[18] Similarly, there was no difference detected between elafibranor or placebo in the PBC-40 fatigue scores up to 12 months of exposure.

Figure 1: PBC-40 Fatigue scores in the POISE study[18]



Source: Figure S7C of Nevens *et al.* (2016)[18]

Figure 2: PBC-40 Fatigue scores in the ELATIVE study[19]



No. of Patients					
Elafibranor 80 mg	43	42	43	42	42
Placebo	20	17	15	16	16

Source: Figure S5C of Kowdley *et al.* (2023)[19]

Therefore, inclusion of fatigue as a symptom in the economic model wouldn't significantly influence the results. Consequently, an NMA for fatigue was not pursued since differences between treatments were highly unlikely to be detected. Additional post-hoc analyses of the ELATIVE trial results are being planned to further understand the impact of elafibranor on fatigue.

A13. Appendix D.1.4.2, Table 22 (p.64): The COBALT trial was excluded from the NMA because the study had not been published in full. Did the company attempt to contact the authors of the COBALT trial to obtain the information required to assess its suitability for the NMA?

The reason for the exclusion of the COBALT trial should have been made clearer in the submission. The COBALT trial was designed to collect long term outcome data where participants were expected to have a minimum follow-up time of approximately 6 years.[20] The trial was terminated early due to feasibility challenges where the data monitoring committee (DMC) noted that the objectives of the trial were not feasible given the inherent challenges with enrolling and maintaining patients in a placebo-controlled study in a rare disease when the study drug is commercially available. The trial at the point of termination did not demonstrate a statistically significant difference in clinical endpoints between OCA and placebo. Results were only reported in brief as an abstract.[21] Without a complete set of results, it would be difficult to accurately assess the trial's suitability for inclusion in the NMA. As such, it was deemed appropriate to exclude the COBALT study from the NMA.

A14. Priority Question; Appendix D.1.4.2.1 (p.77): Please provide further rationale for excluding the phase II trial of elafibranor (Schattenberg et al 2021) and Hirschfield et al (2015) within the NMA, given that many of the listed outcomes are measured at the earliest time point available and not 12 months (for example, 'Change from baseline in pruritus according to the 5-D Itch score questionnaire using the earliest reported data after commencement of treatment').

Both Hirschfield et al. (2015) and Schattenberg et al. (2021) were 12-week trials which assessed the efficacy of OCA and elafibranor, respectively.[22,23] As the primary endpoint of ELATIVE was assessed over a 12-month period, trials with a 12-week duration were not considered comparable to ELATIVE.[19] In the NMA, the majority of outcomes were assessed at 12 months, in line with the primary endpoint of ELATIVE.

The only outcomes assessed in the NMA at timepoints sooner than 12 months were pruritus-related, given the exacerbation of pruritus at the onset of treatment

associated with OCA.[18] It was not possible to include Hirschfield et al. (2015) for pruritus at these earlier timepoints as neither PBC-40 Itch nor 5-D Itch were reported. Therefore, the study could not have been included in the aforementioned analyses. Whilst Schattenberg et al. (2021) did report outcomes relating to pruritus, there was insufficient data available to include it in the analyses performed. Data was not reported for 5-D Itch outcomes. Similarly, PBC-40 Itch data were sparce with only median percent change from baseline reported without population size, standard deviation or standard errors given. As such conclusions on the strength of the data could not be made, making the data unreliable for any further analyses.

Moreover, the Hirschfield et al. (2015) study did not assess OCA at its licensed dose of 5-10 mg; the doses assessed were OCA 10 mg, 25 mg, and 50 mg.[22] Therefore, this study would not inform comparisons of elafibranor with the dose of OCA that is used in clinical practice. OCA is currently only licensed at a dose of 5-10 mg where patients initially receive a 5 mg dose before assessment by clinicians where it is determined whether up titration to the higher 10 mg dose is appropriate. Additionally, the exclusion of doses higher than what is intended for use in clinical practice (namely elafibranor 120 mg, OCA 25 mg and OCA 50 mg) was validated by clinical experts.[24]

A15. Can the company please comment further on whether the transitivity assumption within the NMA holds and any potential differences in the distribution of effect modifiers within ELATIVE and POISE.

Transitivity can be evaluated by comparing the distribution of effect modifiers across different studies.[25] In the feasibility assessment for the NMA, potential treatment effect modifiers were first identified and validated with clinical experts before their distribution across the ELATIVE and POISE studies was compared.[24] Age at diagnosis, ALP levels at baseline, TB at baseline, cirrhosis, and ANA positive status were all identified as treatment effect modifiers in discussion with clinical experts and, subsequently, homogeneity was confirmed by assessing their distribution in the two studies. The homogeneity of the identified treatment effect modifiers in the ELATIVE and POISE trials was then validated by clinical experts.[24]

Age at diagnosis: It was noted by clinical experts that patients who are diagnosed with PBC at a younger age are less likely to respond to therapy. Whilst ELATIVE did

not directly report this characteristic, both age and time since diagnosis were reported, and clinical validation confirmed that it is appropriate to calculate age at diagnosis using age and time since diagnosis. Mean age at diagnosis was consistent across both ELATIVE and POISE; mean (standard deviation [SD]) age at diagnosis was 48 and 50 for the elafibranor and placebo arms of ELATIVE, respectively, and 47 (11), 48 (12) and 47 (9) for the OCA 10 mg, OCA 5-10 mg and placebo arms of POISE, respectively. As mean age at diagnosis for patients in the ELATIVE study was derived from mean age at baseline and mean time since diagnosis, it was not possible to directly calculate the SD of mean age at diagnosis.

ALP levels: Interviews with clinicians confirmed that ALP level at baseline is a treatment effect modifier and prognostic factor, which must be considered within the feasibility assessment. Since attaining thresholds of ALP levels are included in the definitions of response to treatment in PBC, baseline levels of a study population can dramatically affect the likelihood of attaining response to treatment. ALP levels were consistent between both ELATIVE and POISE. For ELATIVE, the elafibranor and placebo arms had mean (SD) ALP values of 321.3 (121.9) and 323.1 (198.6) U/L respectively. For POISE the OCA 10 mg, OCA 5-10 mg and placebo arms had mean (SD) ALP values of 316.3 (103.9), 325.9 (116.2) and 327.5 (115.0) U/L respectively. SDs for ELATIVE and POISE were similar, demonstrating a similar distribution of this characteristic amongst participants of the two studies.

TB levels: Serum TB has been concluded to be a robustly validated biomarker of long-term outcome in PBC and are used as endpoints in clinical trials.[26] Interviews with clinicians confirmed that TB levels at baseline is a treatment effect modifier and prognostic factor, which must be considered within the feasibility assessment. TB levels were consistent between both ELATIVE and POISE. The was no difference in mean (SD) TB levels in the ELATIVE trial between treatment arms with both reporting values of 0.6 (0.3) mg/dL. In the POISE trial, mean (SD) TB levels were 0.7 (0.4), 0.6 (0.3) and 0.7 (0.4) mg/dL across OCA 10 mg, OCA 5-10 mg and placebo treatment arms respectively.

Cirrhosis: Clinical validation confirmed that cirrhotic patients respond to therapy differently to those who are not cirrhotic and so cirrhosis status should be considered as a treatment effect modifier. It was noted by the clinical expert that cirrhosis could

be defined by a liver stiffness score of approximately 17 kPa or more. This would allow for cirrhosis status to still be considered when direct data is not reported. Whilst the presence of baseline cirrhosis was not directly reported in either ELATIVE or POISE, liver stiffness was. Liver stiffness values across ELATIVE and POISE were deemed similar by clinical experts (mean [SD] values of 9.9 [7.8] and 10.7 [8.9] kPa for the elafibranor and placebo arms of ELATIVE, respectively, and 11.4 [8.2], 10.7 [8.6] and 12.7 [10.7] kPa for the OCA 10 mg, OCA 5-10 mg and placebo arms of POISE, respectively). It was noted by clinical experts that the slight difference seen between the two patient populations is consistent with the margin for error when measuring for liver stiffness and therefore is not significant. Additionally, one clinical expert also confirmed that these ranges fell within the same level of cirrhotic severity (i.e. fibrosis indicating risk but short of cirrhosis [9-12 kPa]). Standard deviations were similar across both trials, demonstrating a similar distribution of the characteristic across the study populations.

ANA positive status: ANA positive status was not reported in either the ELATIVE or POISE data. As such, an assessment of homogeneity could not be conducted.

Given the similarity of the distribution of treatment effect modifiers across the ELATIVE and POISE studies, the transitivity assumption has not been violated.

A16. The Deviance Information Criterion (DIC) has not been presented for the NMA. Please provide the DIC or provide a rationale for why the DIC is not reported within the CS.

In the NMA, the total residual deviance was used to inform the selection of the best fitting model. However, the Deviance Information Criterion (DIC) is a function of the total residual deviance and the effective number of parameters.[27] Often, the DIC may be used to verify the best fitting model, where a DIC of at least three points lower indicates a model to be a better fit to the data than an alternative model.[28] In all cases the difference in DIC between the random and fixed effects models was less than three. Therefore, the conclusions remain the same from the use of the total residual deviance in that random effects models should be maintained in the base case. The DIC values for each outcome assessed in the NMA are presented below in Table 1.

Table 1: DIC values from network meta-analysis (ELATIVE vs. POISE)

Outcome	DIC Value	
	Random effects	Fixed effects
Cholestasis response at Week 52	31.74	30.96
ALP normalisation at Week 52	23.56	22.80
Change from baseline in ALP at Week 52	43.48	42.64
Change from baseline in 5D-Itch at Week 52	14.26	13.95
Change from baseline in 5D-Itch at earliest timepoint (Weeks 2-4)	13.53	13.20
Change from baseline in PBC-40 Itch at Week 52	9.96	9.66
Change from baseline in PBC-40 Itch at earliest timepoint (Weeks 2-4)	8.78	8.46
Odds of occurrence of pruritus as a TEAE within 12 months	33.66	32.92
Odds of discontinuation due to pruritus within 12 months	21.53	21.26
Odds of discontinuation all cause within 12 months	28.76	28.44
Change from baseline in HDL cholesterol at Week 52	28.23	27.47

Abbreviations: ALP – alkaline phosphatase; DIC – deviance information criterion; HDL – high density lipoprotein; TEAE – treatment emergent adverse event

A17. The Surface Under the Cumulative Ranking Area (SUCRA) has not been presented for the NMA. Please provide the SUCRAs or provide a rationale for why the SUCRAs are not reported within the CS.

SUCRAs have not been reported in the company submission as they are not a requirement from the NICE DSU TSD which recommends methodology for performing NMAs.[27] Moreover, they are not needed to inform the model and they will not provide any additional information to differentiate between treatments beyond the summary statistics that have already been presented (median outputs, between-study standard deviation, total residual deviance and posterior probabilities).

Posterior probabilities, in particular, have been developed which report the probability that elafibranor is the preferred treatment in each analysis.[27] In each end point, the posterior probability that elafibranor is preferred compared to either placebo or OCA 5-10 mg (P) was defined as:

$$P = \frac{1}{n} \times \sum_{i=1}^{n} I_i$$

Where n is the number of iterations in the sample that the results of the NMA are calculated from and I_i is the indicator function for whether elafibranor is preferred to the comparator in each iteration i. This gives an analogue to the SUCRAs in that the posterior probabilities report the proportion of iterations in which elafibranor ranks

above the comparator considered. As such, inclusion of SUCRAs would provide similar insights to the posterior probabilities.

A18. Appendix D, Section D.1.5 (p.89): "In order to truncate the priors on the continuous outcomes, different informative priors were identified to enable assessment of the between-study standard deviation on the standardised mean difference scale." Please can the company provide a reference and explain the rationale behind using this specific method.

Use of informative priors is recommended and described by Turner et al. (2015) who outline the standard informative priors for use in Bayesian network-meta analyses.[29] Priors were truncated according to the methodology recommended by Ren et al. (2018) to prevent simulation of excessively large between-study variance and thereby facilitating convergence of the NMAs.[30] Additionally, where the network meta-analyses were of mean differences, priors for between-study standard deviation on the odds ratio scale were converted to the mean difference scale in line with the methodology recommended by the same publication. Specifically, the conversion of priors for between-study standard deviation on the odds ratio scale to the mean difference scale was informed by Ren et al. (2018), whereby it was assumed:

$$\tau = \frac{\sqrt{3}}{\pi}\sigma\tau_{SMD}$$

where τ is the between-study standard deviation, τ_{SMD} is the between-study standard deviation on the standardised mean difference scale and σ is an estimate of an individual level standard deviation.[30] For the analyses, σ was taken as the standard deviation of the outcome of interest across both arms of the ELATIVE study.

A19. Priority Question; Appendix D.1.5 (p.89): Please explain the rationale behind applying the "Subjective outcomes" informative prior as opposed to the "Signs/symptoms reflecting continuation/end of condition" informative prior from Turner et al (2015), given that pruritis can be seen as a sign of PBC continuation.

Even though pruritus is indeed a symptom associated with PBC, the measurement methods used for assessing pruritus are not objective. There are no biomarkers

associated with PBC that directly correlate to presence of or severity of pruritus. As such, to assess pruritus, subjective methods need to be used. In the case of both POISE and ELATIVE, questionnaires were used to assess pruritus. Results from both the 5-D Itch questionnaire and the PBC-40 Itch questionnaire were used for comparisons between ELATIVE and POISE.

The 5-D Itch questionnaire comprises five domains, each accounting for five points, which measure the impact of pruritus from different angles: duration, degree, direction, disability and distribution. Scores can range from five (no pruritus) to 25 (most severe pruritus).[31]

The PBC-40 Itch questionnaire is a patient-reported, disease specific symptom and HRQoL questionnaire consisting of three questions scored on a 5-point scale for a maximum score of 15 (most severe).[32]

Both questionnaires rely on patient reported outcomes which, by their nature, are subjective. As such the use of subjective outcomes informative priors was deemed the appropriate method. Turner et al. (2015) state that 'subjective' outcomes include self-reported outcomes (such as pain or adverse events) and outcomes measured by an assessor.[29] Therefore, use of the 'subjective outcome' prior is appropriate for change in pruritus measured by 5-D Itch and PBC-40 Itch questionnaires, as both are self-reported.

A20. Appendix D.1.5 (p.89): Please provide analyses for the following outcomes using the "Signs/symptoms reflecting continuation/end of condition" informative prior from Turner et al (2015).

- Mean change from baseline in pruritis (5-D Itch) at 12 months
- Mean change from baseline in pruritis (5-D Itch) at 2-4 weeks
- Mean change from baseline in pruritis (PBC-40 Itch domain) at 12 months
- Mean change from baseline in pruritis (PBC-40 Itch domain) at 2-4 weeks

Mean change from baseline in pruritus (5-D Itch) at 12 months

Figure 3: Forest plot - Median difference in mean change in 5-D Itch from baseline at 12 months

Abbreviations: CrI – credible interval; mg – milligram; OCA – obeticholic acid
Analysis details: Burn-in: 200,000; Number of iterations: 100,000; Thinning interval: 10.

When using the 'signs/symptoms reflecting continuation/end of condition' prior in the analysis of 5-D Itch at 12 months, patients treated with elafibranor 80 mg had a greater reduction in pruritus when compared to placebo, OCA 5-10 mg and OCA 10 mg (median difference in mean change from baseline [95% CrI]: [redacted] [redacted], [redacted] [redacted], [redacted] and [redacted] [redacted], respectively; Figure 3). These results are very similar to those calculated using the 'subjective outcomes' informative prior (results replicated from company submission: median difference in mean change from baseline [95% CrI]: [redacted] [redacted], [redacted], [redacted] [redacted], [redacted] and [redacted] [redacted], [redacted], respectively). Posterior probabilities (Table 2) were similar to those previously calculated and continue to demonstrate elafibranor as the treatment most likely to result in a reduction in pruritus. With the 'signs/symptoms reflecting continuation/end of condition' prior, the between study deviation was higher (τ = [redacted] vs τ = [redacted], respectively) and the total residual deviance was slightly lower ([redacted] vs [redacted], respectively) than when the 'subjective outcomes' prior was used. As the total residual deviance was within 3 points of each other for both analyses, the two models are an equally good fit to the data (

Table 3). Overall, results from the analyses produced similar results to the base case with no differences in conclusions.

Table 2: Posterior probabilities using signs/symptoms reflecting continuation/end of condition' prior

Comparisons	Posterior probabilities
Elafibranor 80 mg vs placebo	[redacted]
Elafibranor 80 mg vs OCA 5-10 mg	[redacted]
Elafibranor 80 mg vs OCA 10 mg	[redacted]

Abbreviations: mg – milligram; OCA – obeticholic acid

Table 3: Total residual deviance results according to prior used in analysis

Outcome type	Total residual deviance
Subjective outcomes	[redacted]
Signs/symptoms reflecting continuation/end of condition	[redacted]

Mean change from baseline in pruritus (5-D Itch) at 2-4 weeks

Figure 4: Forest plot - Median difference in mean change in 5-D Itch from baseline at 2-4 weeks

Abbreviations: CrI – credible interval; mg – milligram; OCA – obeticholic acid
Analysis details: Burn-in: 500,000; Number of iterations: 100,000; Thinning interval: 10.

When using the 'signs/symptoms reflecting continuation/end of condition' prior in the analysis of 5-D Itch at 2-4 weeks, patients treated with elafibranor 80 mg had a greater reduction in pruritus, when compared to placebo, OCA 5-10 mg and OCA 10 mg (median difference in mean change from baseline [95% CrI]:]: [redacted] [redacted], [redacted] [redacted], [redacted] [redacted], [redacted] and [redacted] [redacted], [redacted] respectively: Figure 4). These results are very similar to those calculated using the 'subjective outcomes' informative prior (results replicated from company submission: (median difference in mean change from baseline [95% CrI]: [redacted], respectively). Posterior probabilities (Table 4) were similar to those previously calculated and continue to demonstrate elafibranor as the treatment most likely to result in a reduction in pruritus. With the 'signs/symptoms reflecting continuation/end of condition' prior, the between study deviation was higher ([redacted] vs [redacted] , respectively) and the total residual deviance was slightly lower ([redacted] vs [redacted], respectively) than when the 'subjective outcomes' prior was used. As the total residual deviance was within 3 points of each other for both analyses, the two models are an equally good fit to the data (

Table 5). Overall, results from the analyses produced similar results to the base case with no differences in conclusions.

Table 4: Posterior probabilities

Comparisons	Posterior probabilities
Elafibranor 80 mg vs placebo	[redacted]
Elafibranor 80 mg vs OCA 5-10 mg	[redacted]
Elafibranor 80 mg vs OCA 10 mg	[redacted]

Abbreviations: mg – milligram; OCA – obeticholic acid

Table 5: Total residual deviance results according to prior used in analysis

Outcome type	Total residual deviance
Subjective outcomes	[redacted]
Signs/symptoms reflecting continuation/end of condition	[redacted]

Mean change from baseline in pruritis (PBC-40 Itch domain) at 12 months

Figure 5: Forest plot - Median difference in mean change in PBC-40 Itch from baseline at 12 months

Abbreviations: CrI – credible interval; mg – milligram; OCA – obeticholic acid
Analysis details: Burn-in: 500,000; Number of iterations: 100,000; Thinning interval: 10.

When using the 'signs/symptoms reflecting continuation/end of condition' prior in the analysis of PBC-40 Itch at 12 months, patients treated with elafibranor 80 mg had a greater reduction in pruritus, when compared to placebo, OCA 5-10 mg and OCA 10 mg (median difference in mean change from baseline [95% CrI]:]: [redacted] [redacted], [redacted] [redacted], [redacted] and [redacted] [redacted], [redacted] respectively:

Figure 5). These results are very similar to those calculated using the 'subjective outcomes' informative prior (results replicated from company submission: median difference in mean change from baseline [95% CrI]: [redacted] [redacted], [redacted], [redacted] [redacted], [redacted] and [redacted] [redacted], [redacted], respectively). Posterior probabilities (Table 6) were similar to those previously calculated and continue to demonstrate elafibranor as the treatment most likely to result in a reduction in pruritus. With the 'signs/symptoms reflecting continuation/end of condition' prior, the between study deviation was higher ($\tau =$ [redacted] vs $\tau =$ [redacted], respectively) and the total residual

deviance was slightly lower ([redacted] vs [redacted], respectively) than when the 'subjective outcomes' prior was used. As the total residual deviance was within 3 points of each other for both analyses, the two models are an equally good fit to the data (

Table 7). Overall, results from the analyses produced similar results to the base case with no differences in conclusions.

Table 6: Posterior probabilities

Comparisons	Posterior probabilities
Elafibranor 80 mg vs placebo	[redacted]
Elafibranor 80 mg vs OCA 5-10 mg	[redacted]
Elafibranor 80 mg vs OCA 10 mg	[redacted]

Abbreviations: mg – milligram; OCA – obeticholic acid

Table 7: Total residual deviance results according to prior used in analysis

Outcome type	Total residual deviance
Subjective outcomes	[redacted]
Signs/symptoms reflecting continuation/end of condition	[redacted]

Mean change from baseline in pruritis (PBC-40 Itch domain) at 2-4 weeks

Figure 6: Forest plot - Median difference in mean change in PBC-40 Itch from baseline at 2-4 weeks

Abbreviations: CrI – credible interval; mg – milligram; OCA – obeticholic acid
Analysis details: Burn-in: 500,000; Number of iterations: 100,000; Thinning interval: 10.

When using the 'signs/symptoms reflecting continuation/end of condition' prior in the analysis of PBC-40 Itch at 12 months, patients treated with elafibranor 80 mg had a greater reduction in pruritus, when compared to placebo, OCA 5-10 mg and OCA 10 mg (median difference in mean change from baseline [95% CrI]: [redacted] [redacted], [redacted] [redacted], [redacted] and [redacted] [redacted], [redacted] respectively: Figure 6). These results are very similar to those calculated using the 'subjective outcomes'

informative prior (results replicated from company submission: (median difference in mean change from baseline [95% CrI]: [redacted] [redacted], [redacted], [redacted] [redacted], [redacted] and [redacted] [redacted], [redacted], respectively), with the exception that the comparison of elafibranor 80 mg with OCA 10 mg [redacted]. Posterior probabilities (Table 8) were similar to those previously calculated and continue to demonstrate elafibranor as the treatment most likely to result in a reduction in pruritus. With the 'signs/symptoms reflecting continuation/end of condition' prior, the between study deviation was higher (τ = [redacted] vs τ = [redacted], respectively) and the total residual deviance was slightly lower ([redacted] vs [redacted], respectively) than when the 'subjective outcomes' prior was used. As the total residual deviance was within 3 points for both analyses, the two models are an equally good fit to the data (

Table 9). Overall, results from the analyses produced similar results to the base case with no differences in conclusions.

Table 8: Posterior probabilities

Comparisons	Posterior probabilities
Elafibranor 80 mg vs placebo	[redacted]
Elafibranor 80 mg vs OCA 5-10 mg	[redacted]
Elafibranor 80 mg vs OCA 10 mg	[redacted]

Abbreviations: mg – milligram; OCA – obeticholic acid

Table 9: Total residual deviance results according to prior used in analysis

Outcome type	Total residual deviance
Subjective outcomes	[redacted]
Signs/symptoms reflecting continuation/end of condition	[redacted]

A21. Were any subgroup analyses conducted on the NMA? If so, please provide the methods and outcomes of these sensitivity analyses.

No, subgroup analyses were not conducted in the NMA.

A22**.** Were any sensitivity analyses conducted on the NMA? If so, please provide the methods and outcomes of these sensitivity analyses.

In the submission, fixed effect model results are described as sensitivity analyses and the results for these are already provided in Appendix D. No additional sensitivity analyses were conducted.

Section B: Clarification on cost-effectiveness data

Economic analysis

Question from NICE technical team. Priority Question: The commissioning organisation submission from NHSE identifies the use of fibrates in clinical practice, suggesting they are an appropriate comparator for elafibranor. Please explain why fibrates were not included as a comparator in the company submission.

Fibrates were not included in the final scope for the assessment of elafibranor and therefore NICE and the committee cannot consider them.

Even if fibrates had been included in the final scope their use is off-label and they have not been studied to regulatory standards in patients with PBC. Fibrates are stated as being contraindicated in PBC as described in the summary of product characteristics for bezafibrate and fenofibrate.[33,34] Real-world evidence from registry studies in the Netherlands and the UK shows high discontinuation rates for fibrates within the first year of use, ranging from 21.1% to 25.9%. These high rates of discontinuation suggest issues with tolerability and effectiveness with relative contraindications in impaired renal function.[35,36] Furthermore, fibrates can interact with statins, increasing the risk of adverse events and toxicity thus complicating the treatment of patients with concurrent cardiovascular risk factors requiring caution in their use with statins.[33,34]

The NICE Clinical Guideline [NG238] titled “Cardiovascular disease (CVD): risk assessment and reduction, including lipid modification states:

- “Do not routinely offer fibrates to prevent CVD”[37]

This NICE recommendation applies to primary and secondary prevention of CVD, including people with diabetes and chronic kidney disease (CKD). Given PBC patients have co-morbidities of diabetes and hypercholesterolaemia in 10% and 58% of patients respectively, then NICE indirectly considering fibrates in this appraisal causes contradictions and confusion in the alignment of NICE recommendations for treatments.[38] It serves to highlight the nuances and complexity involved in clinical and patient shared decision making of prescribing treatments.

B1. Priority Question: Please provide further details about the consultation process with clinical experts including the elicitation process of model parameters from clinical experts.

Prior to model development, an economic model protocol outlining the company's proposed key economic model inputs and assumptions was verified with a single clinical expert via a consultation meeting. A slide deck was developed in advance of the meeting to guide the discussion, with questions incorporated by the company to the clinician. The clinician could raise a comment or question at any time during the discussion. The purpose of the protocol validation meeting was to gain insight on current clinical practice in the management of PBC and validate the company's proposed key inputs and assumptions in the economic model for elafibranor. The key agenda topics discussed were:

1. Key patient characteristics of the eligible population.
2. Comparator information and market shares of comparator treatments.
3. The proposed model structure and whether it was reflective of PBC disease health states.
4. Clarification on proposed model assumptions and inputs including measurement of changes in pruritus, the treatment discontinuation approach, utility values by health state, and quality of life decrements due to adverse events.

During the model development, two separate consultation meetings with one clinical expert per meeting were conducted with the purpose of validating the economic model parameters and assumptions. Both meetings had the same agenda points,

and the same slides were presented which included content on the meeting objectives, background of the ELATIVE trial and the methods used to parameterise the economic model. The clinicians could intervene in the discussion at any point during the meeting and either provide their input, make any comments or pose a question about the model inputs and assumptions. The company prepared questions for the clinicians on the model parameters and assumptions for discussion during the consultation meetings. To allow the clinical experts to provide their input on the different model parameters, slides were presented in the following order:

1. The demonstration of the model and its structure, the categorisation of the PBC biomarker and liver disease components, and whether the model structure and definition of health states were in line with clinical practice.

2. The presentation of ITC analysis results and their alignment with observations in clinical practice.

3. Discussion around discontinuation assumptions (due to pruritus and all-cause discontinuation) and whether there are more appropriate approaches (i.e. all-cause discontinuation) that could be more reflective of clinical practice.

4. Assumptions around transition probabilities between elafibranor and obeticholic acid and whether the sources informing these transition probabilities are appropriate to use and in line with clinical practice.

5. Sources and potential variation of excess mortality probabilities and assumptions.

6. Validation of ITC-related assumptions, including validity of ELATIVE patient level data and ITC results informing itch severity, and the use of PBC-40 Itch or 5-D Itch score as a more appropriate measure of pruritus to inform changes in pruritus.

7. Accurate identification of TEAEs and health state utility values identified from various sources (either literature or trial data) and if these agree with clinical observations.

After each slide was presented, the clinical expert would provide their view and answer the questions posed. It is important to note that independently getting the perspective of more than one clinical expert on the same ensured validity of all assumptions and inputs before finalising the economic models. To come to an informed conclusion where the two clinicians' opinions differed, all reasonable possibilities were explored.

When it arose in discussion, if the clinician disagreed with a parameter or assumption, they gave their best estimate at the alternative. Notably, this is how the transition probability from the moderate risk of disease progression health state to the liver disease component were derived, in discussion of the transition probabilities available from literature.

B2. Priority Question:

a. **Cholestasis response was defined as ALP ≤1.67 x ULN, TB ≤ULN and ALP decrease ≥15% in the NMA, and the model PBC biomarker state definitions were ALP ≤ 200 u/l for low risk and TB ≤ 20 µmol/l; ALP > 200 u/l and TB ≤ 20 µmol/l for moderate risk; and TB > 20 µmol/l and CC) for severe risk. Is ALP = 200 u/l the same as ALP = 1.67 x ULN? Please convert the ALP and TB response definitions to the units used for ALP and TB in the state definitions.**

As noted in the company submission, ALP and TB levels are routinely used as composite endpoints to assess patients' biochemical response to treatment for PBC, due to their value as prognostic biomarkers.[7] Cholestasis response, defined as ALP < 1.67 x ULN, TB ≤ ULN and ALP decrease from baseline of ≥ 15%, has been recognised as a relevant surrogate marker in PBC clinical trials.[18,19] The addition of a minimum ALP reduction of ≥ 15% from baseline was included as part of the composite endpoint in these trials as a conservative threshold so that patients who only had a small change in ALP from 1.67 x ULN were excluded.

ULN for ALP in the ELATIVE trial was defined as 104 U/L for females and 129 U/L for males.[19] Therefore, 1.67 x ULN of ALP is equal to 174 U/L for females and 215 U/L for males. Using the percentage of females and males from the ELATIVE trial (95.7% females, 4.3% males) gives a net threshold of 1.67 x ULN of ALP in

ELATIVE of 176 U/L. The ULN for TB in ELATIVE was defined as 20.5 µmol/l, aligning with the TB threshold used in the economic model.

According to clinical experts, in the UK, most laboratories have standardised by using an ALP threshold of 130 U/L as the ULN for both females and males, resulting in 217 U/L as the threshold of 1.67 x ULN for ALP. However, a target threshold of 200 U/L is typically used in clinical practice to determine response to treatment which is simple for clinicians and patients to anchor to.[39] Therefore, the ALP threshold of 200 U/L used in the health state definitions in the economic model align with the UK clinical practice threshold for determining response to treatment, broadly being 1.67 x ULN and is consistent with TA443.

Clinical expert opinion suggests that the choice of specific values for these thresholds is somewhat discretionary.[39] While there is a linear increase in disease risk as ALP levels rise, there is not a precise ALP and TB level at which a patient's risk of progression to liver disease significantly changes.[39] Moreover, it has been advised that there is no material difference in the risk between ALP levels of 176 U/L, 200 U/L or 217 U/L; all values correlate with 1.67 x ULN and indicate an elevated ALP level that suggests increased disease progression risk. Indeed a 15% variation from 200 U/L equates to 170 – 230 U/L. As such, aligning the health state definitions to the thresholds used in clinical practice is most relevant for decision making.

b. The company has stated that the model PBC biomarker states definitions are consistent with the definitions in NICE TA443. Please explain the clinical and/or statistical rationale for the model PBC biomarker state definitions.

The PBC biomarker health states were defined as:

- Low risk: ALP ≤ 200 u/L and TB ≤ 20 µmol/L
- Moderate risk: ALP > 200 u/L and TB ≤ 20 µmol/L
- High risk: TB > 20 µmol/L or liver stiffness score > 15 kPa

From a statistical perspective, there is not a drop-change in risk according to singular thresholds of ALP and TB. There is a linear increase in risk of progression as ALP increases.[39] Likewise, there is an exponential increase in the risk of progression as TB increases. Therefore, the choice of ALP and TB thresholds is discretionary, as higher levels of each biomarker indicate higher risk of progression to liver disease.

As noted in the company submission, the PBC biomarker states definitions are supported by reported observations of PBC disease progression in clinical practice.[39] ALP and bilirubin levels are routinely used in composite endpoints to assess patients' biochemical response to treatment for PBC.[18,19,39] Slow progression of PBC has been observed in patients with normal bilirubin and ALP ≤ 1.67x ULN, whereas fast progression of PBC has been observed in patients with abnormal bilirubin and ALP > 1.67x ULN.[40] Furthermore, studies have shown ALP ≤ 1.67 x ULN (and up to 2x ULN) combined with TB ≤ ULN predict lower likelihood of adverse outcomes.[7,9,10]

The use of the PBC biomarker health states was motivated by the model definition in TA443, which as part of the model development and appraisal process, was externally validated as relevant for decision-making.[41]

In adaption of the model from TA443, external validation was sought for the continued relevance of the model structure. Expert clinical advice concluded that the health state definitions remain relevant at this time to current clinical practice, as ALP ≤ 200 u/L is a common target and anchor for the need for treatment. TB exceeding the ULN precedes an increase in risk of disease progression, whilst compensated cirrhosis, identified by elevated FibroScan scores, identified the greatest risk of disease progression.

To address the uncertainty cited in TA443 regarding the lack of data on histological progression among PBC patients for the composite criteria for the high-risk biomarker health state, CC was further defined using a liver stiffness score (as measured by transient elastography) of > 15 kPa. This cut-off value was also validated through consultation with clinical experts and corroborating literature sources.[39,42] To address the uncertainty cited in TA443 regarding the lack of data on histological progression among PBC patients for the composite criteria for the high-

risk biomarker health state, CC was further defined using a liver stiffness score (as measured by transient elastography) of > 15 kPa.

c. **The company evidence submission does not report any evaluation of structural uncertainty in the PBC biomarker states definitions. Does the company think that alternative PBC biomarker states definitions are plausible and could be implemented in the model structure? Would any other definitions be compatible with the available evidence? Does the company think this could have a significant effect on the cost-effectiveness estimates?**

The PBC biomarker states in the model are defined according to risk of disease progression and response to treatment which are commonly used in UK clinical practice. Inadequate response broadly refers to persistently elevated ALP and TB levels despite treatment (see Section B.1.3.1.4 of the NICE submission for further discussion).

There are several different criteria for defining inadequate response to treatment. However, there is no consensus on the most appropriate criteria to apply at a population level (see also Section B.1.3.1.4 of the NICE submission).[43] Choice of criteria in clinical trials often depends on the study eligibility criteria. The existing scoring systems that have been proposed to define the lack of response all have limitations, including that they are dichotomous, as they only define two levels of risk (responder and non-responder), they are not able to provide intermediate levels of risk and they do not measure risk over time. However, in line with cholestasis response (which informs the definition of health states in the PBC biomarker health state), they commonly include thresholds of ALP and TB with some also including alanine transaminase (ALT). Definitions used for response to treatment criteria, as reported in the UK-PBC guidelines,[44] include:

Table 10: Definitions for treatment response criteria reported in UK-PBC guidelines

Criteria	Treatment response criteria	Sample size	Results
Barcelona criteria	Response to treatment defined by ALP decrease >40% of baseline values or normal levels after 1 year of treatment	192 patients (181 women)	8.9% died or fulfilled criteria for liver transplantation Observed survival higher than that predicted by Mayo model and lower than control population (P <0.001) 61% responded to treatment.

			Survival of responders was significantly higher than that predicted by Mayo model and similar to that estimated for control population (P=0.15).
Paris I criteria	Treatment response defined as: ALP <3xULN and AST<2xULN and Bilirubin <1mg/dL	292 patients	10-year transplant-free survival rate of 90% (95% CI 81% to 95%), compared with 51% (95% CI 38% to 64%) for those who did not (P<0.001).
Paris II criteria	Early stage PBC defined by normal bilirubin and albumin at baseline Response treatment criteria: ALP and AST ≤1.5×ULN with normal bilirubin level (defined as 1 mg/L in ELATIVE[19])	165 patients; average follow-up 7 years	All adverse events observed in non-responders (P<0.001).
Mayo	Response defined as ALP<2xULN at 1 year	73 patients; median 2 years follow-up	Patients with ALP≥2×ULN had a 2-fold greater likelihood of developing endpoints compared with patients with lower values (23% vs 11%) (P<0.05). Patients with bilirubin>1mg/dL were four times more likely to develop endpoints compared with those with lower values (33% vs 8%) (P=0.02). Patients with ALP≤1.67×ULN and bilirubin≤1mg/dL had the least likelihood of reaching adverse clinical endpoints.
Toronto criteria	ALP<1.67xULN at 2 years of treatment with UDCA	69 patients with follow-up liver biopsy performed approximately 10 years after initial histological diagnosis	Histological progression in stage of fibrosis observed in paired liver biopsies was associated with absence of biochemical response at 2 years: ALP>1.67xULN, P=0.001, OR 12.14, 95%CI 2.69 to 54.74 when defined as an increase in one stage. ALP>1.76×ULN, P=0.03, OR 5.07, 95%CI 1.17 to 21.95 when defined as an increase in two stages. Ductopenia (>50%loss) predicted histological progression (P=0.012) and biochemical response to UDCA (P=0.002).
Rotterdam criteria	PBC classified as early (pre-treatment bilirubin and albumin values normal), moderately advanced (one level abnormal), or advanced (both values abnormal) Biochemical response defined by normalisation of abnormal bilirubin and/or albumin values	375 patients; median follow-up time 9.7 years	Prognosis for early PBC comparable to Dutch population and better than predicted by Mayo risk score. Survival of responders better than that of non-responders (according to Paris and Rotterdam criteria; P<0.001) Prognosis of early PBC comparable for responders and non-responders. Prognosis of responders significantly better in those with (moderately) advanced disease.

Source: Hirschfield 2008[44]

No single scoring system is likely to fully describe the pathology of PBC.[9,43] ALP treatment response correlates biochemistry and histological progression in the Toronto criteria. The Rotterdam criteria are focused towards liver function/stage, including albumin and bilirubin.[45] Paris-II criteria have been designed specifically to better fit early-stage patients, who represent more than two-thirds of patients in recent cohorts.[45]

Despite the numerous criteria to define response to treatment, they all correlate in that increases in the relevant PBC biomarkers are linearly related to increases in risk of progression to liver disease. Moreover, due to the continuous nature of ALP and TB, it is possible to identify insurmountable permutations of ALP and TB thresholds to define risk status.

To investigate structural uncertainty in the PBC biomarker state definition and understand the impact that an alternative definition of response may have on cost-effectiveness results the following dichotomous scoring systems have been applied:

- Paris II criteria
- ALP Normalisation
- Barcelona criteria

Results for these scoring criteria are available from the ELATIVE and POISE trials so could facilitate an indirect treatment comparison of the likelihood of response for elafibranor versus OCA. A Bucher ITC was performed rather than an NMA for the PARIS II and Barcelona criteria in the interests of time, with the NMA result for ALP normalisation presented in the original submission being applied.

According to clinical expert opinion, the Paris-II criteria reflects earlier stage disease.[39] The Barcelona criteria represents another approach considering the relative percentage decrease in ALP. Finally, ALP normalisation has been more recently purported to be the most desirable goal of treatment but any improvement in ALP and bilirubin would decrease the risk of complications for patients.[8,43] The Rotterdam criteria were not considered because they reflect later stage disease.

Paris II

To apply the Paris-II criteria to the model, the PBC biomarker health states were redefined as:

- Low risk: ALP < 1.5 x ULN, AST < 1.5 x ULN and TB ≤ 1 mg/dl
- Moderate risk: ALP > 1.5 x ULN or AST > 1.5 x ULN, and TB ≤ 1 mg/dl
- High risk: TB > 1mg/dl or liver stiffness score > 15 kPa

The updated health state definitions were used to identify the distribution of patients at baseline and the transitions between health states. A Bucher ITC was also performed to compare the relative likelihood of achieving Paris-II response when treated with OCA 5-10 mg compared to elafibranor.

The Bucher ITC shows that patients treated with OCA 5-10 mg had lower odds of achieving response when compared to elafibranor 80 mg (median OR [95% credible interval (CrI)]: [redacted] under the Paris-II criteria, compared to the NMA analysis median OR [95% CrI] of [redacted]) using the ELATIVE trial definition of cholestasis response. As for the NMA of cholestasis response, the odds of achieving response as defined by the PARIS-II criteria with OCA 5-10 mg were not statistically significantly lower than elafibranor 80 mg. Nonetheless, assessments of the median ORs for cholestasis response indicate a numerical inclination towards elafibranor or OCA 5-10 mg.

The cost-effectiveness results when the PARIS-II response criteria are incorporated into health state definitions are shown in

Table 11 below; this result shows an decrease in incremental QALY gain ([redacted]) and an increase in incremental cost saving ([redacted]) for elafibranor versus OCA, compared to the base case. Within this scenario analysis, elafibranor remains cost-effective.

Table 11: Scenario results for elafibranor vs OCA and elafibranor vs UDCA, using Paris-II criteria definition for PBC biomarker states

Treatment	Total	Incremental	

	Costs (£)	LYG	QAYs	Costs (£)	LYG	QALYs	ICER (£) versus baseline
Elafibranor	[redacted]	[redacted]	[redacted]	-	-	-	-
OCA	245,504	12.543	8.139	[redacted]	[redacted]	[redacted]	Dominating
UDCA	103,639	10.690	6.281	[redacted]	[redacted]	[redacted]	30,982

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

ALP normalisation

To apply ALP normalisation definition of response to the model, the PBC biomarker health states were redefined as:

- Low risk: ALP ≤ ULN, TB ≤ 20 µmol/L and liver stiffness score > 15 kPa
- Moderate risk: ALP > ULN, TB ≤ 20 µmol/L and liver stiffness score > 15 kPa
- High risk: TB > 1mg/dl or liver stiffness score > 15 kPa

The updated health state definitions were used to identify the distribution of patients at baseline and the transitions between health states. The NMA from the original company submission (median OR [95% CrI] of [redacted] [[redacted], [redacted]]) informed relative likelihood of achieving the ALP normalisation when treated with OCA 5-10 mg compared to elafibranor.

The cost-effectiveness results when the ALP normalisation response criteria are incorporated into health state definitions are shown in

Table 12 below; this result shows an decrease in incremental QALY gain ([redacted]) and a slight increase in incremental cost saving ([redacted]) for elafibranor versus OCA, compared to the base case. Within this scenario analysis, elafibranor remains cost-effective.

Table 12: Scenario results for elafibranor vs OCA and elafibranor vs UDCA, using ALP normalisation definition for PBC biomarker states

Treatment	Total	Incremental	

	Costs (£)	LYG	QAYs	Costs (£)	LYG	QALYs	ICER (£) versus baseline
Elafibranor	[redacted]	[redacted]	[redacted]	-	-	-	-
OCA	241,647	12.971	8.578	[redacted]	[redacted]	[redacted]	Dominating
UDCA	101,879	11.079	6.656	[redacted]	[redacted]	[redacted]	31,892

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

Barcelona criteria

As noted in Table 10 above, the Barcelona criteria defines treatment response according ALP decrease > 40% of baseline values. To investigate structural uncertainty the PBC biomarker health states were redefined as:

- Low risk: ALP > 40% reduction from baseline, TB ≤ 20 µmol/L and liver stiffness score > 15 kPa
- Moderate risk: ALP ≤ 40% reduction from baseline, TB ≤ 20 µmol/L and liver stiffness score > 15 kPa
- High risk: TB > 20 µmol/L or liver stiffness score > 15 kPa

The updated health state definitions were used to identify the distribution of patients at baseline and the transitions between health states. A Bucher ITC was also performed to compare the relative likelihood of achieving the Barcelona response criteria when treated with OCA 5-10 mg compared to elafibranor. The Bucher ITC was conducted instead of the NMA in the interests of time to facilitate a timely response to the EAG questions.

The Bucher ITC shows that patients treated with OCA 5-10 mg had lower odds of achieving response when compared to elafibranor 80 mg (median OR [95% credible interval (CrI)]: [redacted] [[redacted], [redacted]] under the Barcelona criteria, compared to the NMA analysis median OR [95% CrI] of [redacted] [[redacted], [redacted]]) using the ELATIVE trial definition of cholestasis response. As for the NMA of cholestasis response, the odds of achieving response as defined by the Barcelona criteria with OCA 5-10 mg were not statistically significantly lower than elafibranor 80 mg. Nonetheless,

assessments of the median ORs for cholestasis response indicate a numerical inclination towards elafibranor or OCA 5-10 mg.

The cost-effectiveness results when the Barcelona response criteria are incorporated into health state definitions are shown in Table 13 below; this result shows an decrease in incremental QALY gain ([redacted]) and a slight decrease in incremental cost saving ([redacted]) for elafibranor versus OCA, compared to the base case. Within this scenario analysis, elafibranor remains cost-effective.

Table 13: Scenario results for elafibranor vs OCA and elafibranor vs UDCA, using Barcelona criteria for PBC biomarker states

Treatment	Total			Incremental			ICER (£) versus baseline
	Costs (£)	LYG	QAYs	Costs (£)	LYG	QALYs	
Elafibranor	[redacted]	[redacted]	[redacted]	-	-	-	-
OCA	241,307	12.949	8.547	[redacted]	[redacted]	[redacted]	Dominating
UDCA	101,879	11.079	6.656	[redacted]	[redacted]	[redacted]	31,001

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

Interpretation of model structural uncertainty using different biomarker state definitions

All the scenarios lead to a decrease in incremental QALY gain compared to using cholestasis response to define treatment response.

For ALP normalisation and Paris-II scenarios, the ALP threshold to distinguish between the low risk and moderate risk health states is reduced. Similarly, for the ALP reduction of > 40% scenario, the ALP reduction required is higher compared to using cholestasis response (> 15% reduction in ALP from baseline). Therefore, the threshold of ALP considered in each of these scenarios is lower than in the base case analysis, which is informed by cholestasis response.

There is a clear trend that stricter criteria on ALP for response leads to lower incremental QALYs for elafibranor. For example, when cholestasis response, which has the least strict ALP criteria, is used to define biomarker states, elafibranor has [redacted] and [redacted] incremental QALYs compared to OCA and UDCA, respectively.

With alternative definitions, in which the criteria on ALP threshold is stricter, the incremental QALYs for elafibranor reduce. When ALP normalisation is used there are [redacted] and [redacted] incremental QALYs for elafibranor compared to OCA and UDCA, respectively. When the Barcelona criteria is used, which requires a 40% reduction in ALP, elafibranor has [redacted] and [redacted] incremental QALYs compared to OCA and UDCA, respectively. For the PARIS II criteria, which requires ALP < 1.5xULN, elafibranor has [redacted] and [redacted] incremental QALYs compared OCA and UDCA, respectively.

With these alternative definition scenarios, the stricter response criteria means that there are fewer patients treated with elafibranor who achieve low risk of disease progression, resulting in smaller gains in quality of life compared to UDCA and OCA.

Moreover, increases in quality of life for stricter criteria for low risk are not captured. The stricter criteria for response means that patients with milder disease are in the low-risk health state in the scenario analysis definitions compared to the low-risk health state defined according to cholestasis response. This means that the utility benefits are underestimated for the low-risk health states defined in these scenario analyses, since if they were defined according to the criteria they would be defined based on patients who are healthier. Therefore, the estimated QALY gain does not capture as much of the benefit of elafibranor in improved treatment response. Indeed, under these stricter criteria there will be proportionally more patients without symptoms or complications, which was demonstrated to have a utility value (0.917) higher than the general population by Rice *et al.* (2021).[46]

The increase in the ICER as the threshold for response is made stricter is explained by the reduced attainment of response under stricter criteria and the resulting underestimation of quality of life associated with the low-risk health state. In all scenarios presented, the quality of life associated with low-risk of disease progression is assumed equal despite stricter criteria on ALP for response means that patients in the low-risk health state in these scenarios are generally healthier than in the base case when cholestasis response is considered. As such, the ICERs for the scenario analyses are all overestimates since quality of life in the low-risk health state is underestimated. If the increases in quality of life associated with

stricter response criteria were available to be parametrised, it is expected that the ICER would remain stable.

B3. The high-risk health state is defined as “TB > 20 µmol/L or compensated cirrhosis (CC) (defined as kPa >15)”. As patients with CC are more likely to progress to decompensated cirrhosis (DCC) than those without:

a. Is there any data from the ELATIVE trial on the progression of CC patients to DCC?

The duration of the ELATIVE study was too short to objectively collect data on patients who developed cirrhosis which then progressed to DCC within the time frame of the trial.

Despite this, in line with the health state definitions used in the economic model, [redacted] (n/N = [redacted]) in the ELATIVE trial was reported to progress to DCC during the study period, having presented with CC (kPa > 15) and with elevated TB levels at baseline. Amongst all patients, [redacted] had CC (kPa > 15) at baseline.

B4. Transitions from the moderate state:

a. Can the company provide any published evidence supporting the transition from the moderate risk health state to DCC without experiencing CC?

There is no identified published evidence supporting the transition from the moderate risk health state to DCC without experiencing CC. In a clinical trial setting, patients are regularly followed up, so it is most likely that patients with DCC were observed with CC prior to progression of their disease. Moreover, as the aetiology of DCC is such that CC precedes it,[47–49] there is limited clinical interest in collecting this data.

b. Were there any qualifying statements by the clinical experts regarding the estimation of the moderate risk to DCC transition probability?

Transitions of patients from the moderate risk health state to the DCC health state without experiencing CC was validated with clinical experts. The clinical expert noted that patients can develop cirrhosis very quickly and the presence of cirrhosis is usually identified as the result of a bleed. This immediately classifies patients as

DCC and therefore results in the CC state not being recognised. It was noted that this only applies to a very small number of patients.[39]

The value used for the transition probability of moderate risk to DCC was given by the clinical experts.

c. Did the clinical experts agree that in the base case the transitions from the moderate risk state to liver states should have a positive probability?

Yes, the clinical experts agreed with this statement.

d. Have the transitions from the moderate risk health state to further liver disease stages been validated with published evidence?

There is no identified published evidence available to validate the probabilities given by clinicians.

A cost-effectiveness study focussing on non-alcoholic fatty liver disease adopted a Markov model in which patients in a significant liver disease health state can transition to further liver disease stages.[50] This model did not have a 'moderate risk' health state but rather 'no/mild disease' from which patients could move into the 'significant liver disease' health states.

Clinical parameters and variables

B5. Priority question: Section B.3.2.1, p.118: "Patients who discontinue elafibranor were assumed to return to their health state at baseline." This is the base case assumption in the company model.

a. Are there any clinical expert statements obtained during expert elicitation/validation that support this 'return-to-baseline after discontinuation' assumption?

The return to baseline assumption presumes that upon discontinuation of treatment, patients return to their starting PBC biomarker risk status and subsequently follow the disease trajectory of UDCA. This assumption is based on the lack of evidence indicating that treatment benefits persist after discontinuation. In other words, there

is no evidence that patients will remain in their current health state at or after discontinuation.

The clinical expert supported the return to baseline discontinuation assumption, with statement from the expert validation interview stating that “after a patient discontinues, patients revert to where they were before commencing the therapy and they continue the same disease progression as before they started treatment.”[39] Additionally, the clinical expert verified that treatments do not modify the underlying disease mechanism, so the treatment effect is not sustained after discontinuation.[39]

b. Is it plausible for risk status to improve immediately after discontinuation?

The return to baseline assumption does not result in improvement of risk status of patients after discontinuation. Instead, patients lose any treatment effect immediately and return to their risk status at baseline. This is a conservative assumption as any improvement in risk status during treatment is immediately reverted when patients discontinue treatment by moving patients back to their baseline risk status. As mentioned above, the ‘return to baseline’ assumption was based on clinical expert opinion during model validation.

c. If it is plausible for risk status to improve immediately after discontinuation, is the aggregate % of patients in the cohort that the model predicts improves risk status immediately after discontinuation clinically plausible?

No patients have improved risk status after discontinuation. On discontinuation, patients revert to their starting risk status before treatment and continue the same disease progression as they would experience with no treatment.

d. Please present the absolute number of patients who improve their risk status immediately after discontinuation by cycle by comparator in the model with reference to the model location in the company PfC response.

No patients have improved risk status after discontinuation.

e. **Does the company have any comments to make to justify the base case discontinuation assumption?**

In the base case, all-cause treatment discontinuation is applied across the entire time horizon for elafibranor and OCA to capture the number of patients remaining on treatment each cycle. The discontinuation assumptions are based on the available data, published literature and clinical expert opinion.

For elafibranor, in the absence of long-term data on treatment discontinuation, parametric distributions were used to extrapolate the all-cause time to discontinuation (TTD) during and beyond the ELATIVE study duration. Choice of parametric distributions were based on best statistical fit, according to Akaike Information Criterion (AIC) and Bayesian Information Criterion (BIC) statistics. The discontinuation assumptions, including the return to baseline option, were validated by clinical expert opinion and are considered to appropriately capture treatment discontinuation in the economic model.[39]

f. **There is an error in the Markov Trace sheets, columns AP, AQ, AR. When the option 'Return to baseline' is selected in the 'Clinical inputs' sheet, the numbers in columns AP, AQ, AR are incorrect. This is reflected in the FALSE statements in column AT. It is also reflected in the implausibly high %s of patients alive in the predicted survival models. The starting population number is inappropriately multiplied by the % of patients in that state at baseline for this scenario. Please correct these errors.**

The error, relating to the stay in state calculation, has been corrected. The stay in state option was included in the model to allow uncertainty to be assessed and providing the option to explore an alternative discontinuation assumption for the purpose of scenario analysis. The error has no impact on the base case results as return to baseline is applied, which is more conservative than the stay in state assumption.

g. **Could the company please present the results of a scenario analysis where patients stay in the health state they are in when they discontinue treatment?**

Results of a scenario of elafibranor and OCA patients staying in state after discontinuation are as follows:

Table 14: Scenario results for elafibranor vs OCA and elafibranor vs UDCA, using the stay in state discontinuation option

Treatment	Total			Incremental			ICER (£) versus baseline
	Costs (£)	LYG	QALYs	Costs (£)	LYG	QALYs	
Elafibranor	[redacted]	[redacted]	[redacted]	-	-	-	-
OCA	241,460	12.784	8.377	[redacted]	[redacted]	[redacted]	Dominating
UDCA	104,283	10.808	6.383	[redacted]	[redacted]	[redacted]	27,654

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

B6. Priority Question; Section B.3.3.2.1, p.118: "To capture the worsening condition of patients who are treated with UDCA only, the LOCF (last observation carried forward) assumption was implemented by continuing to apply to transition probabilities from cycle 3 to cycle 4 (last 3 months of the study) for the remainder of the time horizon." There is no possibility for the risk category to improve while on UDCA only from cycle 4 onwards.

a. **Could you please provide a plot of the model prediction, high-risk-free survival curve for each comparator (alive and either low or medium risk)?**

Plotted below is the high-risk free survival curve (number of patients alive in the mild and moderate risk health states) for each the intervention and comparators included in the economic model (Figure 7). The predicted high-risk free survival at different time points is also presented in Table 15.

Figure 7: Predicted high-risk free survival over time

[redacted]

Abbreviations: OCA – obeticholic acid; UDCA – ursodeoxycholic acid
Footnote: The starting population of patients is 86% and not 100% due to the initial starting distribution containing some patients at severe risk.

Table 15: Predicted high-risk free survival at different time points

	High-risk free survival		
	Elafibranor	OCA	UDCA
1 year	[redacted]	[redacted]	[redacted]
5 years	[redacted]	[redacted]	[redacted]
10 years	[redacted]	[redacted]	[redacted]
20 years	[redacted]	[redacted]	[redacted]
40 years	[redacted]	[redacted]	[redacted]
Median (years)	[redacted]	[redacted]	[redacted]

Abbreviations: OCA – obeticholic acid; UDCA – ursodeoxycholic acid

b. Is there any clinical evidence to validate the high-risk-free survival and LT-free survival model predictions? If so, could you please provide it?

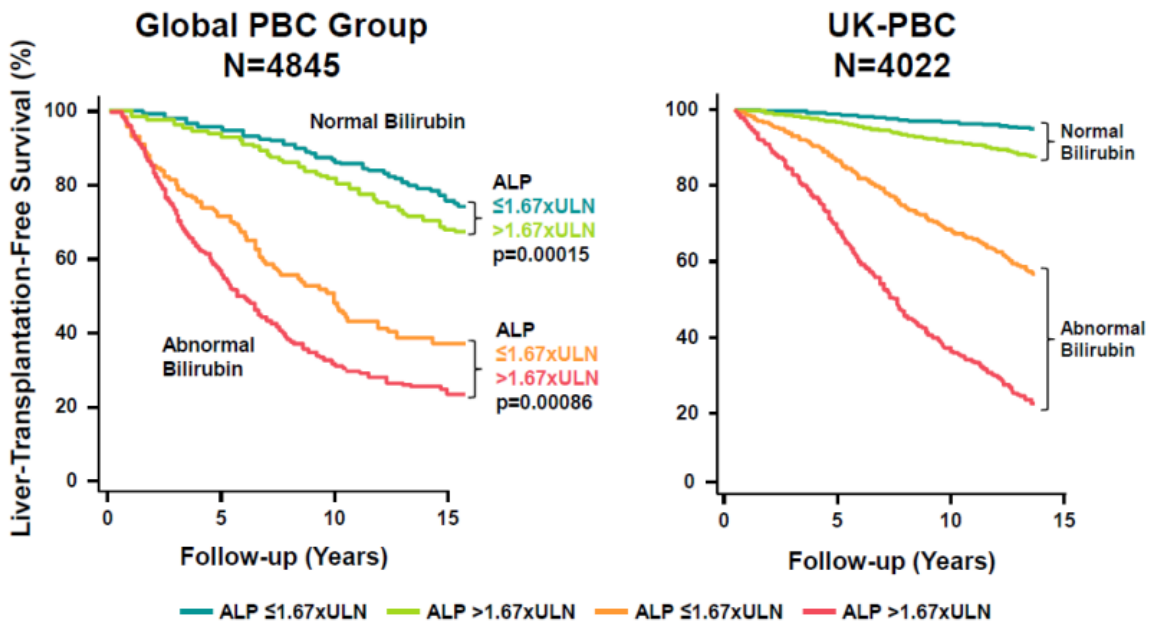
In terms of high-risk free survival, the Montano-Loza and Corpechot 2021 study highlighted that liver function tests which also include the measurement of ALP and serum bilirubin levels, have been evaluated extensively across different cohorts worldwide and are recommended for stratification of patients after one year of UDCA therapy.[51] By this stratification, high-risk patients with shorter survival can be more easily recognised and can be considered for new treatments. However, due to lack of available literature data for comparison of high-risk free survival results, one of the clinical experts interviewed confirmed that ALP and bilirubin biomarkers are major predictors of patient survival in clinical practice. Also, by looking at the 10-year survival of patients and the median difference of curves in the high-risk free survival

plot across comparator treatments (Figure 7), the clinical expert validated that the economic model predictions are in line with observations in clinical practice.

Clinical evidence by the Global PBC group and UK-PBC, which was presented in Section B.1.3.1.4: Surrogate endpoints as biomarkers of disease progression of the NICE submission evidence can validate the LT-free survival model predictions. Shown in

Figure **8** below, data from the Global-PBC and UK-PBC group (sourced from TA443) also illustrate the impact of the relationship between ALP and bilirubin levels and their association with LT-free survival rates over time.[41] The same clinical expert also validated the results presented in the economic model and confirmed that changes in survival rates across treatments are in line with real-life experience. Through comparing the economic model predictions for LT-free survival and the Global and UK-PBC LT-free survival results, the effect of treatment with elafibranor on survival can be evaluated. In the economic model patients treated with elafibranor have a 5-year, 10-year and 15-year survival of [redacted], respectively. In the UK-PBC data set, patients had approximately a 95%, 80% and 70% survival in the normal bilirubin group at 5, 10 and 15 years, respectively, and 80%, 35% and 20% survival in the abnormal bilirubin group at 5, 10 and 15 years, respectively, showing that most patients treated with elafibranor had normal bilirubin.

Figure 8: Global-PBC and UK-PBC data for liver transplant free survival rates based on ALP and bilirubin thresholds



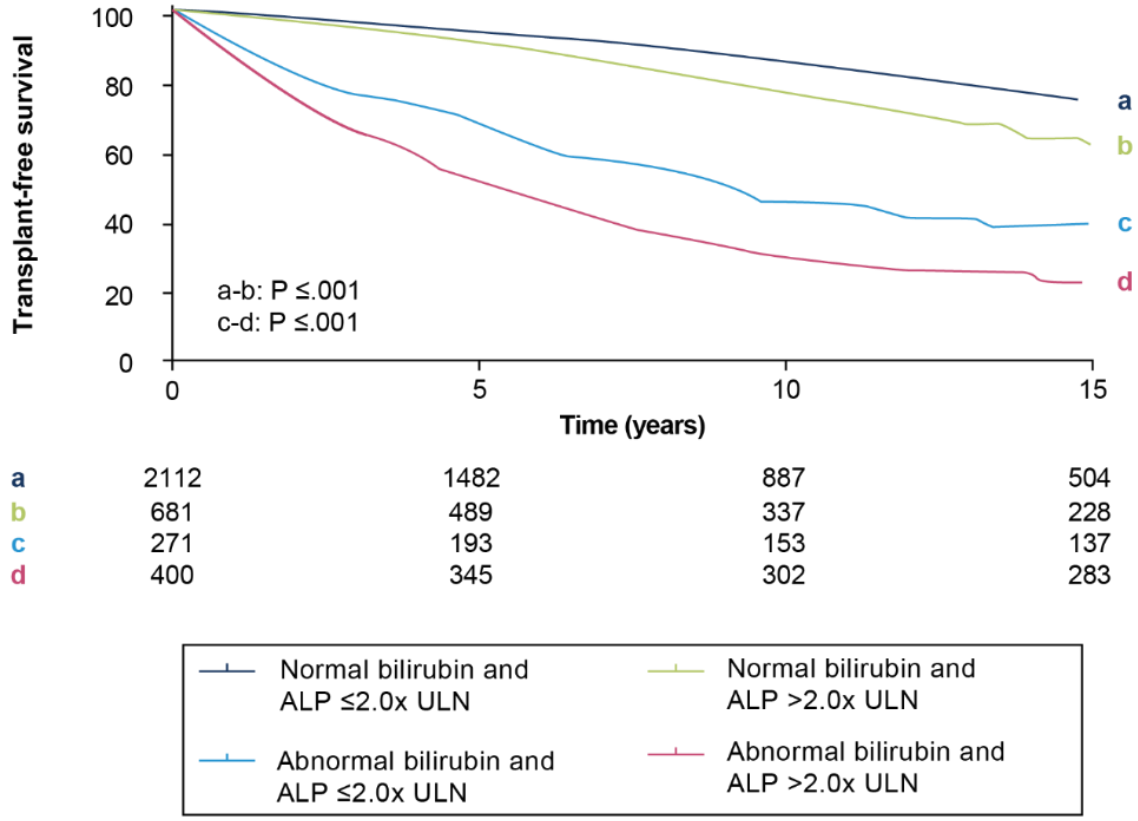
Liver transplant-free survival for Global PBC is based on all-cause mortality or liver transplant and the UKPBC is based on liver-related death or liver transplant. Courtesy of Global PBC Study Group and UK-PBC

Abbreviations: ALP – alkaline phosphatase; PBC – primary biliary cholangitis; ULN – upper limit of normal
Source: NICE TA443[41]

Data from Lammers et al. (2014) (

Figure 9) were also analysed. This study investigated ALP and bilirubin as surrogate endpoints in PBC and their role in predicting transplant-free survival. It demonstrated that, in the normal bilirubin groups, 75-90% of patients with normal bilirubin had approximately 15 year liver transplant free survival, compared to 25%-40% of patients with abnormal bilirubin, underscoring the significance of these biomarkers in long-term survival predictions.[7] Similarly, results from this study demonstrate that the majority of patients treated with elafibranor have normal bilirubin.

Figure 9: ALP and bilirubin levels are predictors of transplant-free survival in PBC



Abbreviations: ALP – alkaline phosphatase; PBC – primary biliary cholangitis; ULN – upper limit of normal
Source: Lammers 2014[51]

c. Did the clinical experts validate the model predictions for UDCA high-risk-free survival and LT-free survival?

Following model development, the outputs of the model were discussed with one clinical expert did validate the model predictions for both UDCA high-risk free survival and LT-free survival as being reasonable and plausible.

B7. Priority question: Economic model file, sheet "Model parameters!" Column J "Probabilistic": for the parameters sampled from the Lognormal distribution, please make sure the mean is on the natural log of the odds ratio scale and that standard errors are also on the natural log scale (derived from upper and lower-limit values transformed to the logistic scale). The formulation used first uses the EXP function and then transforms back using the LN function. Normally, the odds ratio is transformed to the log scale, sampled and then transformed back using EXP. Please check that the formulation used is

correct. The EAG has spotted this as a potential error for the OR of cholestasis response and the OR of pruritus recurrence. If this is identified as an error please provide an edited CEM and update of the probabilistic analysis results.

The company agree that the implementation of the PSA sampling for ORs was incorrect. However, with the suggested correction, varying the ORs on the lognormal scale led to implausible values. Therefore, the distribution applied to ORs has been updated to use the Gamma distribution.

To ensure appropriate variation in sampling within the PSA, the standard error has been taken as the square root of the standard deviation from the NMA results.

The updated PSA is provided in the Appendix.

B8. Priority question: Economic model file, sheet "Model parameters!" Cell J79: The probabilistic value for the OR for treatment discontinuation parameter is coded as a fixed value.

a. **Can the company update their probabilistic analysis results to include parameter uncertainty in the OR for the treatment discontinuation parameter?**

The parameter highlighted has been updated such that it is included in the PSA. The updated PSA is provided in the Appendix.

b. **Can the company provide the source of the upper and lower estimates used to derive the standard error of OR for discontinuation? If the source is the NMA, please clarify how the NMA estimates were transformed into the model inputs.**

The upper and lower estimates for NMA inputs were sourced from the 95% credible intervals of the NMA results. The credible interval was assumed to be derived from a normal distribution in that the upper and lower bounds of the interval were calculated as:

$$95\%\ Credible\ interval = \mu \pm Z_{0.025,0.975} \times se$$

where $Z_{0.025,0.975}$ is the 2.5% and 97.5% percentiles of the standard normal distribution. This formula had been used to calculate the standard error of all odds ratios and transformed these results to fixed values in the “Model parameters!” sheet.

The estimate of standard error in the NMA have been updated to use the variability from the NMA results. It is now assumed that the standard error is the square root of the standard deviation of the relevant result from the NMA. The square root of the standard deviation was taken to prevent excess variation, since the standard deviation reflects the variation in the sample rather than the variation of the mean estimate.

The updated PSA is provided in the Appendix.

B9. In the ‘Data Store’ sheet of the Excel model, the discontinuation risk for OCA is calculated by: calculating the 12-month RR ($\boldsymbol{RR_{12}}$) from the 12-month OR ($\boldsymbol{OR_{12}}$) and the 12-month elafibranor risk, and then multiplying by the 3-month elafibranor risk ($\boldsymbol{E\_R_3}$) for each cycle. Two alternative equivalent approaches are (1) calculate the 3-month OCA odds for each cycle from the elafibranor 3-month odds for each cycle (derived from elafibranor 3-month risk for each cycle) and the 12-month OR, and then derive the OCA 3-month risk by cycle (similar to the step-by-step approach taken in the company model); (2) calculate the 3-month RR for each cycle using

$$\boldsymbol{RR_3} = \left(\frac{\boldsymbol{OR_{12}}}{\boldsymbol{1 - E\_R_3 + E\_R_3 \times OR_{12}}}\right)$$

and then multiplying by the 3-month risk for each cycle. The RR is more sensitive to the baseline risk than the OR (see Doi et al, 2022), so we recommend using one of the equivalent methods.

a. Could the company please implement one of those alternative methods for discontinuation?

The second alternative method in calculating the RR was implemented in the economic model. A switch in the “Settings” sheet has been added to allow the user to change the anchor for the derivation of RRs from ORs for discontinuation from 12 months to 3-monthly. The results from using the 3-month duration to anchor derivation of RRs from ORs for discontinuation are shown in Table 16.

It should be highlighted that as the NMA assesses discontinuation over a 12-month duration, it is most appropriate to convert the OR to a RR using data at the 12-month period that informed the NMA. As such, the conversion of the RR anchoring from 3-monthly probabilities is not deemed to be appropriate.

Table 16: Scenario results for elafibranor vs OCA and elafibranor vs UDCA, using the 3-month duration to anchor derivation of RRs from ORs for discontinuation

Treatment	Total			Incremental			ICER (£) versus baseline
	Costs (£)	LYG	QALYs	Costs (£)	LYG	QALYs	
Elafibranor	[redacted]	[redacted]	[redacted]	-	-	-	-
OCA	255,181	12.848	8.457	[redacted]	[redacted]	[redacted]	Dominating
UDCA	104,283	10.808	6.383	[redacted]	[redacted]	[redacted]	29,350

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

b. Could the company please implement one of those alternative methods for determining the transition probabilities for OCA?

The second alternative method in calculating the RR was implemented in the economic model. A switch in the "Settings" sheet has been added to allow the user to change the anchor for the derivation of RRs from ORs for cholestasis response from 12 months to 3-monthly. The results from using 3-month duration to anchor derivation of RRs from ORs for cholestasis response are shown in Table 17.

It should be highlighted that as the NMA assesses cholestasis response over a 12-month duration, it is most appropriate to convert the OR to a RR using data at the 12-month period that informed the NMA. As such, the conversion of the RR anchoring from 3-monthly probabilities is not deemed to be appropriate.

Table *17*: Scenario results for elafibranor vs OCA and elafibranor vs UDCA, using the 3-month duration to anchor derivation of RRs from ORs for cholestasis response:

Treatment	Total			Incremental			ICER (£) versus baseline
	Costs (£)	LYG	QALYs	Costs (£)	LYG	QALYs	
Elafibranor	[redacted]	[redacted]	[redacted]	-	-	-	-
OCA	242,811	12.686	8.279	[redacted]	[redacted]	[redacted]	Dominating
UDCA	104,283	10.808	6.383	[redacted]	[redacted]	[redacted]	29,350

B10. Section B.3.3.2.2, p.119: "The transitions from the low-risk health state were assumed equivalent to elafibranor as there was no evidence to suggesting a difference in the maintenance of cholestasis response for patients treated with elafibranor or OCA." Is there any published evidence or clinical expert statements to support this assumption?

This assumption avoids biasing the clinical effectiveness results in favour of elafibranor. If the OR of cholestasis response with OCA relative to elafibranor were applied to the patients who are in the mild health state, it would reflect a reduced probability of maintaining response to treatment for which there is no clinical evidence. The ELATIVE and POISE trials had eligibility criteria requiring patients to have ALP ≥1.67 x ULN at baseline.[18,19] Therefore, the application of the OR to the moderate and severe health states only reflects the clinical data included in the NMA, i.e., the proportion of patients achieving cholestasis response in both trials is amongst patients with moderate or severe risk of progression at baseline.

The application of the OR to patients in the moderate and severe health states only was validated by observing that the proportion of patients in the low-risk health state after 1 year in the CEM for the OCA arm closely mirrored the findings of the POISE trial as reported in the literature.[18]

B11. Priority Question: Please can the company answer the following queries regarding the time to discontinuation assumptions.

a. **How were time to discontinuation predictions in the OCA arm validated? Is there time to event data for all-cause discontinuation of OCA 5-10mg treatment to validate the model predictions?**

Time to discontinuation predictions for OCA were derived by applying the odds ratio of all-cause discontinuation within a 12-month period for patients treated with OCA relative to elafibranor to the selected TTD curve for elafibranor. The resulting discontinuation curve was validated with clinical experts and checked for consistency with published literature and available data sources.

The model estimates that the proportion of patients who have discontinued OCA treatment at 1 year and 2 years is [redacted] % and [redacted] %, respectively. These extrapolation estimates and the discontinuation curves were confirmed to be approximately correct by clinical experts.[39] Additionally, a UK study of second-line treatments in PBC by Abbas et al. (2022) found similar results to these estimates, with 25.7% of patients having discontinued OCA treatment at 1 year.[36]

Since the submission, Ipsen has obtained real-world evidence data from UK-PBC registry which also approximately agrees with the estimates in the model, with [redacted] %, [redacted] % and [redacted] % of UK PBC patients reported to have discontinued treatment at 1,2 and 5 years, respectively.[52] Further evidence from a UK prescription data from one centre shows that 22% and 31% of patients have discontinued OCA since receiving their first order at 1 year and 2 years, respectively, which approximately aligns with the estimates in the economic model.[53]

The discontinuation predictions for OCA were validated with clinicians, who agreed that the difference between discontinuation of elafibranor and OCA would remain constant with elafibranor having a lower discontinuation rate due to better tolerability than OCA.[39] However the long-term discontinuation predictions for elafibranor remain unclear due to the lack of extended data on its use over patients' lifetimes.

b. Were the clinical experts asked if the result that patients are more than twice as likely to discontinue treatment with OCA 5-10mg compared to elafibranor was plausible given their knowledge of the drugs? If so, what were their views?

Yes, clinicians were consulted as to whether the OR of all-cause discontinuation with OCA 5-10mg relative to elafibranor is reflective of the likelihood of discontinuation seen in clinical practice.[39] One clinician agreed with the OR presented, stating that discontinuation for OCA being at least double that of elafibranor was plausible and seems correct. The second clinician was unable to comment on the appropriateness of the OR for discontinuation, citing a lack of real-world evidence for elafibranor to compare to the estimated discontinuation predictions.

c. Is it realistic to assume a constant risk of time to discontinuation over the long term or are patients who discontinue treatment more likely to

discontinue early during treatment than at latter stages for both OCA and elafibranor?

It is probable that patients who discontinue treatment are more likely to discontinue early during treatment, however there is limited long-term data available with which to derive long-term discontinuation predictions. Clinical experts consulted during the model validation reached consensus that in practice discontinuation mostly occurs at the start of treatment and is often due to tolerability issues, primarily pruritus. It was agreed that at 1 or 2 years, discontinuation usually occurs due to disease progression or lack of efficacy. Despite this, the clinicians were unable to definitively predict the shape of the discontinuation curve, especially in the long-term.

Since the submission, data from UK-PBC and UK prescription data have been sourced which support the discontinuation predictions in the economic model (as detailed in B11a).

d. Why are the discontinuation projections from the Gompertz function considered implausible?

The Gompertz curve predicts unrealistically high retention to treatment over the long-term, predicting no discontinuation after approximately 15 years. For this reason, the Gompertz curve is considered to be clinically implausible and so was not selected as the discontinuation projection.

The Gompertz distribution projects that approximately [redacted]%, [redacted]% and [redacted]% of patients will remain on OCA at 5, 10 and 20 years, respectively. Whilst the 5-year timepoint reasonably reflects the data from the UK-PBC registry, which reports [redacted]% of OCA patients remain on treatment at 5 years, the long-term predictions are clinically implausible. The lognormal curve, which projects the second highest retention to treatment, projects that [redacted]% of patients will remain on OCA at 5 years, which is slightly less close than the Gompertz curve. However, it's long-term projections appear more plausible with [redacted]% and [redacted]% of patients remaining on treatment at 10 and 20 years, respectively. This is believed to be a more representative discontinuation prediction of clinical practice. As such, the base case assumption has been updated in the economic model for the lognormal curve to be used. Updated cost-effectiveness results are presented in the Appendix.

B12. KM data for time to discontinuation for elafibranor:

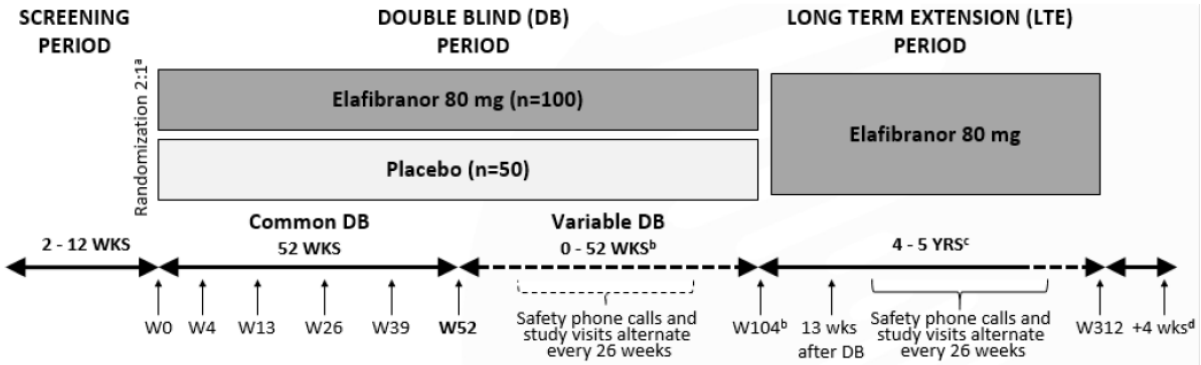
a. Could you please provide the numbers at risk used to derive the Kaplan-Meier curve for discontinuation up to 24 months?

You can find the numbers at risk for discontinuation up to 24 months in the file provided named 'KM_data_Elafibranor_TTD_ITT'.

b. Could you please provide the reasons for discontinuation for patients in the 12 months beyond the end of the 12-month trial follow-up period that was used for the Kaplan-Meier analysis.

Discontinuations were observed in patients beyond 12 months as the analysis included data in the overall double-blind (DB) period of the ELATIVE trial, across both the common and variable DB periods. The common DB treatment period is defined as the first 52 weeks while the overall DB period included a treatment period of variable length beyond Week 52 during which participants continued to receive elafibranor or placebo until all participants completed their Week 52 visit or until a maximum blinded treatment duration of 104 weeks, whichever came first (see Figure 10).

Figure 10: ELATIVE study design

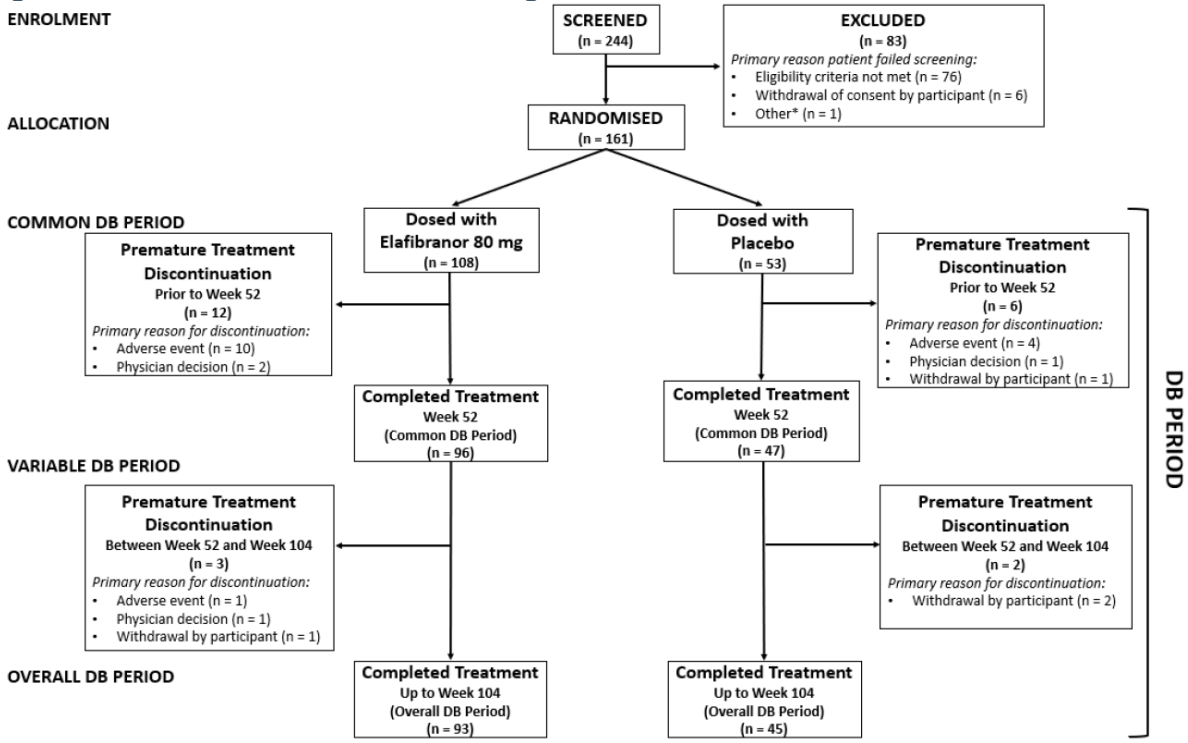


Abbreviations: DB – double-blind; LTE – long-term extension, mg – milligram; wks – weeks
Footnotes: [a] If receiving UDCA at randomisation, it was continued throughout study participation.
[b] The variable double-blind period was an additional 52 weeks after the end of the common double-blind period (Week 104) or until the last completed Visit 6 (Week 52), whichever occurred first. [c] The LTE duration will be up to 5 years after end of the double-blind period or until the subject's total treatment duration is 6 years, whichever occurs first. [d] The safety follow-up period will continue for 4 weeks after last dose of study drug.

The CONSORT diagram (Figure 11) shows a detailed disposition of participants in the study across the overall DB period.[54] Due to the timing of the data cut, one

additional patient who discontinued elafibranor during the variable DB period was included in the Kaplan-Meier analysis.[54]

Figure 11: ELATIVE trial CONSORT diagram



Abbreviations: DB – double-blind

B13. In the company Excel model, under the clinical effectiveness tab, a Hazard Ratio (HR) is reported for each health state which is equal to 1. How were differences in survival between OCA and elafibranor explored and what evidence was used?

Differences in survival between OCA and elafibranor were explored using the probability per cycle of mortality in excess of the general population, which were applied in addition to mortality occurring in the general population. The hazard ratios of 1 for all PBC biomarker and liver disease health states are placeholders for alternative data. They are not in use as inclusion of HRs for each health state in addition to the excess mortality to the general population would lead to double counting.

The excess mortality probabilities were informed using transition probability values from the NICE OCA appraisal (TA443).[41] In addition to the probability values sourced from TA443, one clinical expert noted that in the low risk there is no excess mortality compared to the general population, and additionally if patients remain in the

moderate risk health state they likely have no excess mortality compared to the general population. Therefore, for both health states excess mortality was assumed to be zero in the economic model (in line with TA443 model assumptions as well). The clinical expert advised that patients in the high risk health state do have an increased risk of mortality compared to the general population, as reflected in the model.[55]

B14. Section B.3.3.6, p.125: “It was assumed that the occurrence of pruritus would vary across treatments while other AEs were assumed to occur at the same rate as for elafibranor”. Is there any published evidence or clinical expert statements to support this assumption?

It is assumed that pruritus occurs at varying rates across treatments due to evidence suggesting that the occurrence of pruritus increases with dose in patients treated with OCA. A post hoc analysis performed in the POISE trial showed that increases in doses of OCA (from 5 to 10mg) increases the incidence and severity of pruritus, and therefore pruritus occurs at a different rate between doses.[18] In contrast, the ELATIVE study did not find a difference between elafibranor and placebo in the frequency of pruritus.[19]

The NMA performed by the company supported conclusions on difference in pruritus AEs across treatments. This was demonstrated in the analysis of pruritus occurrence of any severity as a treatment emergent adverse event (TEAE) within 52 weeks between elafibranor and both OCA doses, validating the difference in frequency of pruritus occurrence across treatments.

In the economic model, only AEs of grade 2 or higher occurring in ≥5% in one arm of the ELATIVE study were included. Therefore, comparisons across ELATIVE and POISE would need to be performed in AEs of grade 2 or higher. However, the severity of AEs in the POISE trial was not reported. Consequently, it is not possible to compare the frequency of specific AEs of grade 2 or higher. Therefore, to avoid adding uncertainty to the economic model, it was deemed that there was no significant difference in the rate of AEs other than pruritus.

This conclusion is generally supported by trial data. There was not a significant difference between elafibranor and placebo in ELATIVE in the frequency of AEs of

grade 2 or higher. Similarly, with the exception of pruritus, there was not a significant difference between OCA and placebo in the frequency of AEs.

Measurement and valuation of health outcomes

B15. Priority Question: Can the company provide further details of EQ-5D scores mapped to the 3L version, including:

a. **time points of data collection; mean EQ-5D-3L index scores (not VAS), SD and number of observations by treatment arm, across each time point; and**

Presented in Table 18Table 18 are the descriptive health state utility scores by given health states and various time points throughout the clinical trial. The descriptive results demonstrate inconsistencies in the relationship between disease severity and health state utility value, further supporting the invalidity of the trial data for informing health state utility values.

Table 18: Average utility values by health state and timepoint from the ELATIVE clinical trial

Treatment and timepoint (weeks)	Health state utility values by health state		
	Low	Moderate	Severe
Elafibranor 80 mg, mean (SD, n)			
Baseline	[redacted]	[redacted]	[redacted]
Week 13	[redacted]	[redacted]	[redacted]
Week 26	[redacted]	[redacted]	[redacted]
Week 39	[redacted]	[redacted]	[redacted]
Week 52	[redacted]	[redacted]	[redacted]
Overall	[redacted]	[redacted]	[redacted]
Placebo, mean (SD, n)			
Baseline	[redacted]	[redacted]	[redacted]
Week 13	[redacted]	[redacted]	[redacted]
Week 26	[redacted]	[redacted]	[redacted]
Week 39	[redacted]	[redacted]	[redacted]
Week 52	[redacted]	[redacted]	[redacted]
Overall	[redacted]	[redacted]	[redacted]
Grand total	[redacted]	[redacted]	[redacted]

Abbreviations: n – count of utility weights; SD – standard deviation

b. **(adjusted or unadjusted) differences in EQ-5D-3L scores between treatment arms.**

Differences in descriptive utility scores by treatment arm throughout the trial duration are presented in Table 19 and

Table 20Table 19
Table 20. Consistently, there is no statistical difference detected between elafibranor and placebo, though the utility values tend to be lower for elafibranor than placebo over time.

Table 19: Health state utility values by treatment arm

Treatment and timepoint (weeks)	Average utility weights
Elafibranor 80 mg, mean (SD, n)	
Baseline	[redacted]
Week 13	[redacted]
Week 26	[redacted]
Week 39	[redacted]
Week 52	[redacted]
Overall	[redacted]
Placebo, mean (SD, n)	
Baseline	[redacted]
Week 13	[redacted]
Week 26	[redacted]
Week 39	[redacted]
Week 52	[redacted]
Overall	[redacted]
Grand total	[redacted]

Abbreviations: n – count of utility weights; SD – standard deviation

Table 20: Difference between treatment arms for given time points throughout the trial duration

	Difference:	SE for difference	CI 95%
Overall	[redacted]	[redacted]	[redacted]
Baseline	[redacted]	[redacted]	[redacted]
Week 13	[redacted]	[redacted]	[redacted]
Week 26	[redacted]	[redacted]	[redacted]
Week 39	[redacted]	[redacted]	[redacted]
Week 52	[redacted]	[redacted]	[redacted]

Abbreviations: CI – confidence interval; SE – standard error

B16. Priority Question: There was a large difference in the health state utility values (HSUV) for high-risk patients estimated from the ELATIVE trial compared to the values sourced from the literature.

a. **Could the company please explain the reasons for the selection of value from the literature instead of the ELATIVE trial estimate, and what may explain the difference?**

As mentioned in the company submission, the utility estimate for the high-risk state derived from the ELATIVE trial data of [redacted] was deemed unreliable, because the incremental difference in utility between the moderate and high-risk states was lower than expected. This is hypothesised to be driven by the low sample size in the high-risk state (N=78 observations in the utility analysis, 10.3% of the overall sample), which reduces the reliability of the estimates as lower sample sizes reduce the statistical power of the analyses.

Clinical trials often have strict eligibility criteria that exclude patients with very severe disease stages or significant comorbidities. This pre-selection of relatively healthier patients could result in higher average utility values among trial participants compared to the broader patient population. Therefore, it may be that patients included in the ELATIVE trial had less severe disease compared to the general patient population, due to natural selection bias and eligibility criteria of clinical trials, which excludes patients with severe disease stages or significant comorbidities.[54] Self-selection bias can occur in clinical trials as patients who volunteer to participate are often more motivated, have higher expectations, and/or are in a better health state than the broader patient population with the same disease.[56] Patients participating in a clinical trial may also have improved disease education that could cause a 'response shift', where participants re-evaluate and re-calibrate their perception of their health state.[57] These factors could contribute to a higher reported utility by patients in the ELATIVE trial.

The Rice *et al.* (2021) study was identified in the SLR and reported utility values according to symptoms and complications amongst patients who have and have not had liver transplant, which is not compatible with the structure of our model as the distribution of complications and symptoms across health states is unknown.[46] However, it reports a utility value of 0.917 for patients who have not had a liver

transplant and are free of symptoms and complications, which is higher than the general population utility value. This suggests that the utility value for patients at low risk of disease progression could be higher. However, a higher utility value would result in reduced ICERs for elafibranor, thus the utility values in use remain conservative.

Collectively, the studies identified in the SLR were insufficient to parametrise HSUVs in the CEM, so alternative sources were sought. The utility estimate for the high-risk state from TA443 of 0.55 was chosen as the most reliable utility estimate available. This utility estimate in TA443 was derived from a publication by Wright *et al.* (2006) that used data from a UK randomised control trial of patients with chronic, mild Hepatitis C to derive health-related quality of life estimates.[58] Given the precedence and previous validation with a UK clinical expert in TA443, this utility value is considered appropriate utility estimate for high-risk PBC patients. This assumption has been validated with the UK clinical experts during development of the company submission, who confirm its continued relevance.[39]

b. Did the clinical experts validate the utility estimates, and did they consider the ELATIVE trial utility estimate to be implausible? If not, could the company please provide a scenario analysis using the high-risk utility values from the ELATIVE trial?

Yes, the clinical experts validated the utility estimates and considered the ELATIVE trial high-risk state utility to be implausible.[39] The clinicians advised that patient utility is primarily regulated by their symptoms. PBC is a cholestatic disease, that is relatively stable in terms of symptoms during early stages before an exponential deterioration in health as disease progresses. In particular, the onset of cirrhosis is associated with a significant decline in patients' HRQoL.

Based on the clinical expert statements, the expectation is for a drop-off in utility from the moderate state to high-risk state, which includes CC, as patients become cirrhotic. However, only a slight decrement was found in the incremental difference in utility between the moderate and high-risk states derived from ELATIVE trial. Therefore, the ELATIVE trial utility estimate for high-risk state was considered implausible.

A scenario analysis where the utility value for the high-risk state is assumed to be the ELATIVE trial estimate has been provided below in Table 21; this result shows a decrease in the incremental QALY gain ([redacted]). Within this scenario analysis, elafibranor remains cost-effective compared to OCA at its list price. However, the results of this analysis should be interpreted with caution as the HRQoL of patients at severe risk of progression is overestimated.

Table 21: Scenario results for elafibranor vs OCA and elafibranor vs UDCA, using the ELATIVE trial high-risk state utility estimate

Treatment	Total			Incremental			ICER (£) versus baseline
	Costs (£)	LYG	QALYs	Costs (£)	LYG	QALYs	
Elafibranor	[redacted]	[redacted]	[redacted]	-	-	-	-
OCA	242,656	12.672	9.203	[redacted]	[redacted]	[redacted]	Dominating
UDCA	104,283	10.808	7.639	[redacted]	[redacted]	[redacted]	35,578

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

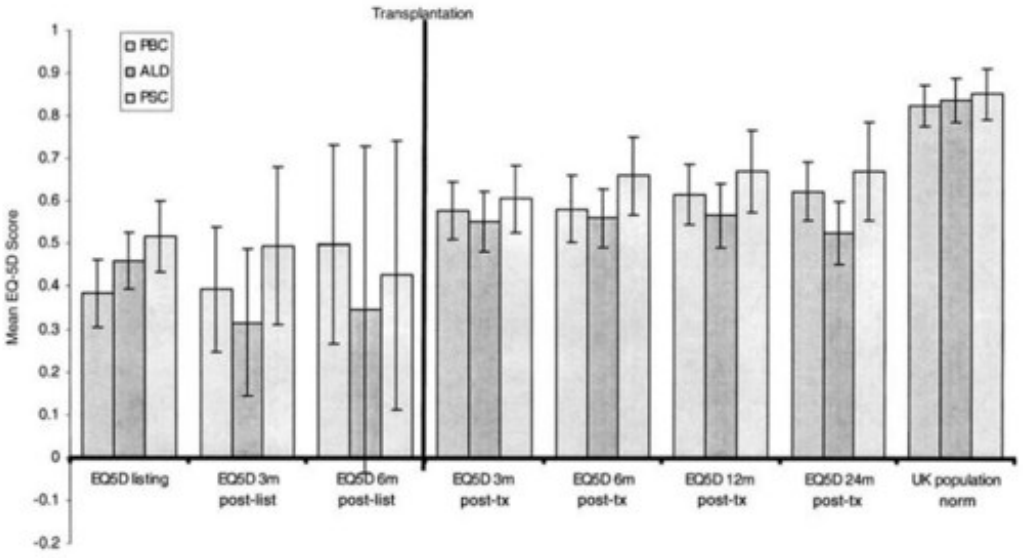
B17. The utility value for the Pre-LT state in the CEM (i.e. 0.38) is quite different from the utility values from Rice et al (2021), a recently published study documented in Appendix H, and other studies reported:

a. Can the company please comment on the reasons for selecting the Pre-LT utility used in the study; for instance, the applicability of the states for which utility estimates were obtained in the studies to the states in the CEM?

The utility value for pre-LT state of 0.38 was sourced from TA443, which applies a decrement to the utility values from Wright *et al.* (2006), as explained further in the response to B18.a below.[41,58] This utility value was deemed to be a reliable source of utility estimates for the pre-LT state in the CEM given it has been previously validated and its relevance was confirmed during the clinical expert validation.

Furthermore, the utility value of 0.38 from TA443 aligns with the pre-LT utility reported by Longworth *et al.* (2003) in an observational study of patients in England and Wales waiting for a transplant and using published prognostic models.[59] The graph in Figure 12 is extracted from Longworth et al. (2003), and shows the EQ-5D of pre-LT PBC patients ("EQ5D listing") of 0.38.[59]

Figure 12: Mean EQ-5D scores of transplantation patients before and after transplantation, including UK population norms EQ-5D scores



Error bars depicts 95% bootstrap confidence intervals. Values of zero are included for patients who died post-transplantation
Source: Longworth 2003[59]
Abbreviations: EQ5D – EuroQol 5-dimensional; PBC – primary biliary cholangitis

Other sources of utility estimates were considered, including Rice *et al.* (2021).[46] However, no studies, except for Rice *et al.* (2021), reporting relevant utility estimates were found to use for the pre-LT state. Specifically with Rice *et al.* (2021), while health state utility values are reported for pre-liver transplant, these appear to relate to patients who have not had a liver transplant, and not necessarily patients who are waiting for a liver transplant. This differs from the CEM as the pre-LT state consists of patients waiting for a liver transplant.

Additionally, utility estimates presented in Rice *et al.* (2021) are grouped according to symptoms and complications and are adjusted for symptoms and/or complications one at a time. It is not possible to determine which symptoms are incurred in the CEM health states and groups of complications may be present in multiple health states, so the transferability of the utility values in Rice *et al.* (2021) to the CEM is challenging. Furthermore, some of the reported utility values are counterintuitive, such as ≥1 symptom/ascites (HRQoL = 0.596) having a lower utility value than ≥1 symptom/≥1 complication (HRQoL = 0.663) despite ≥1 symptom/ascites being a subset of ≥1 symptom/≥1 complication group.

Finally, patients in the pre-LT health state are listed and waiting for a LT; they were previously in the DCC or HCC health states, indicating that their condition has

worsened to the extent that they require LT. Therefore, it follows that their utility value should be lower than patients who have HCC or DCC. To explore the sensitivity of results to this assumption, a scenario analysis with the utility value associated with Pre-LT is instead assumed to be the maximum of HCC (0.45) and DCC (0.38) health states has been provided below (Table 22); this result shows a marginally smaller incremental QALY gain (0.008) compared to the base-case assumptions. Within this scenario analysis, elafibranor remains cost-effective.

Table 22: Scenario results for elafibranor vs OCA and elafibranor vs UDCA, assuming pre-LT is the maximum of HCC or DCC utility values

Treatment	Total			Incremental			ICER (£) versus baseline
	Costs (£)	LYG	QAYs	Costs (£)	LYG	QALYs	
Elafibranor	[redacted]	[redacted]	[redacted]	-	-	-	-
OCA	242,656	12.672	8.290	[redacted]	[redacted]	[redacted]	Dominating
UDCA	104,283	10.808	6.415	[redacted]	[redacted]	[redacted]	29,476

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

B18. Section B.3.4.6.1, p.133-4: Can the company clarify the statement: “It was noted that utility values associated with DCC, pre-LT, LT, and post-LT were given a redacted decrement in TA443 to ensure the HSUVs were reflective of someone with PBC. Therefore, the utility values used in this submission have no decrement applied.”

a. The EAG noticed that some health states (i.e. DCC, pre-LT and LT) in the economic model may be using utility values with a decrement applied from the previous submission TA443 (i.e. 0.38, 0.38 and 0.57), and utility values without a decrement for the post-LT state (i.e. 0.67).

The utility values for the liver disease component were sourced from TA443, in which a decrement was applied for certain states. This decrement was deemed necessary for all hepatitis C virus (HCV) specific utility values sourced from literature based on clinical expert opinion. The decrement reflects the worse outcomes and accelerated disease progression of patients with PBC compared to HCV. The decrement was not applied to states for which PBC specific utility values were identified or for HCC as,

according to clinical expert opinion, in HCC the utility value is driven by treatment of HCC itself instead of due to the disease state.

The appropriateness of the decrement has been validated by a clinical expert during development of the company submission. The clinician confirmed that the decrement is required for the DCC, pre-LT and LT given the utility values from TA443 were derived from Wright et al. (2006) for HCV patients, and worse outcomes and more severe symptoms in PBC compared to HCV, including the impact of pruritus. As symptoms are a key driver of utility, the decrement to HCV utilities for PBC patients is deemed suitable.

The utility decrement has not been applied to the post-LT state based on clinical expert opinion. Patients are expected to experience improved utility following a liver transplant compared to patients in the LT health state. Thus, the utility decrement has not been applied for post-LT patients.

A summary of the utility values for the liver disease component is shown in Table 23:

Table 23: Summary of liver disease component utility values for cost-effectiveness analysis

State	Utility value: mean (SE)	Justification
DCC	0.38 (0.08)	Previously reported value for DCC (TA330)[60]; utility decrement applied based on clinical expert opinion[39]
HCC	0.45 (0.09)	Previously reported value for HCC (TA330)[60]; utility decrement not applied based on clinical expert opinion[39]
Pre-LT	0.38 (0.08)	Previously reported value for pre-LT (TA330)[60]; utility decrement applied based on clinical expert opinion[39]
LT	0.57 (0.11)	Previously reported value for LT (TA330)[60]; utility decrement applied based on clinical expert opinion[39]
Post-LT	0.67 (0.13)	Previously reported value for post-LT (TA330)[60]; utility decrement not applied based on clinical expert opinion[39]
Re-emergence of PBC	0.67 (0.13)	Assumed equivalent to post-LT based on clinical expert opinion[39]

Abbreviation: DCC – decompensated cirrhosis; HCC – hepatocellular carcinoma; LT – liver transplant; PBC – primary biliary cholangitis

b. Was the initial statement a typo as the second part doesn't seem to follow from the first part? Could the company please clarify the approach taken to derive the utility values for DCC, pre-LT and LT?

The second statement is a typographical error. The utility decrement has been applied for the DCC, pre-LT and LT states. The approach taken to derive utility values for the liver disease component has been explained in the response to B18.a above.

B19. Section B.3.4.4, p.133: "As AEs are assumed to occur in the first cycle as a one-off, the disutility of these events was assumed to last for the duration of one cycle." For AEs incorporated into the model, is there a clinical justification for these AEs to be assumed as one-off and have a three-month duration?

Typically, NICE appraisals (as per the NICE TA443 appraisal), include grade 3+ adverse events (AEs) due to the management cost associated with the severity of AEs. However, as no grade 3+ AEs occurred in ≥5% of one arm of the study population in the ELATIVE trial, the threshold has been reduced such that the economic model has only considered grade 2+ AEs reported in ≥5% of patients. Therefore, treatment-related grade 2+ AEs were incorporated as one-off events and the impact was attributed to the first cycle of treatment for patients entering the model, assuming that AEs are likely to occur close to treatment initiation and require acute care. Since the majority of events considered are Grade 2, and Grade 2 events by definition 'introduce a low level of inconvenience or concern to the subject and may interfere with daily activities, but are usually improved by simple therapeutic measures and may cause some interference with functioning',[61] it was assumed that the duration of AEs was acute in nature and quickly resolved. For example, an UTI would not be expected to last a lifetime if treated.

One of the clinical experts interviewed validated the duration AEs, as well as the disutilities associated with them to be assumed equivalent to one model cycle. The economic model already allows for the duration of disutility due to adverse events to be changed to 1 month, 2 months or 3 months (base-case). Through testing both scenarios for AE disutility duration to 1 month and 2 months (scenario #1 and #2, respectively), no significant impact to the results was observed; there were very minor changes in QALYs and thus very minor changes to the ICER (Table 24).

Table 24: Scenario results for elafibranor vs OCA and elafibranor vs UDCA, using the AE disutility duration of one month or two months

Scenario	Total costs of elafibranor (GBP)	Total QALYs of elafibranor	Incremental costs to OCA (GBP)	Incremental QALYs to OCA	Incremental costs to UDCA (GBP)	Incremental QALYs to UDCA	ICER of elafibranor vs OCA	ICER of elafibranor vs UDCA
Base case	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	Dominating	29,350
#1	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	Dominating	29,355
#2	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	Dominating	29,353

Abbreviations: GBP – Great British Pound; ICER – incremental cost-effectiveness ratio; OCA – obeticholic acid; QALY – quality adjusted life-year; UDCA – ursodeoxycholic acid

Cost and healthcare resource use

B20. Priority Question: The EAG has identified different proportions of patients having OCA and receiving medicines for pruritus in this submission from the previous NICE submission (TA443). For example, 30% of the patients treated with OCA or UDCA received cholestyramine for pruritus in this submission, but this figure was 85% in the previous submission. Can the company comment on why there is a large difference between the treatment proportions of pruritus from the previous submission?

In model development, the company engaged with clinical experts to validate the management of pruritus. Based on their up-to-date clinical experience, the resource use reported in TA443 was revised to reflect current practice. A clinical expert advised that currently 30% of patients treated with OCA or UDCA receive cholestyramine for pruritus, compared to the 85% previously reported.[39]

B21. End of life costs are included in the CEM for DCC and HCC. Could the company please clarify how the cost estimates for DCC and HCC in the CEM were estimated, and specifically whether end of life costs were part of these costs?

The health state costs associated with DCC and HCC were identified from TA443 whereas the end of life costs were informed from published literature. In TA443, the health state costs were cited as Wright et al. (2006).[58]

The resources consumed for DCC and HCC as health state costs included inpatient days, outpatient days and tests and procedures. From the source, it is reported that resource use was measured for the maximum time for which information was available for each health state. The date of entry into a health state was defined as the date when the patient first attended the study hospital and there was evidence

that the patient had reached the health state stage in question. The date of exit from a health state was defined as the date when the patient moved to the next health state, died or was lost to follow-up.[58] Therefore, for patients who died within the DCC or HCC health states, the costs of death were included. However, patients may have been censored prior to death or progressed to another health state; in this case, the costs of death were not included in the health state costs. It is not reported which proportion of patients died within the health state, nor the duration of their observation for those who died during the observational period. Therefore, it is not possible to conclude whether the resource use described accurately captures the resource use consumed within the final three months of their life. For this reason, and as DCC and HCC are associated with burdensome care at end of life, the costs associated with end of life were sought from published literature.

The Gola et al. (2015) study evaluated the costs of hospital admissions for patients with end-stage liver disease over the 12 months prior to death obtained from hospital records and case-note audit.[62] The analysis included costs incurred during admission, including bed and board, nursing, specialist consultations, medications, investigations and surgery.[62] In our economic model, the mean cost for individual admissions which resulted in the patient's death (terminal admission) of £9,615 that was inflated to 2022 costs (using PSSRU inflation indices) informed the DCC end of life costs.

For the HCC end of life costs, a previous NICE appraisal from 2019 of atezolizumab with bevacizumab for untreated unresectable or advanced hepatocellular carcinoma (TA666), provided costs of terminal care, including services like hospital care, local authority funded social care, district-nursing costs and the cost of GP visits, similarly to Gola et al. 2015.[62,63] In the appraisal a standard cost for palliative care before death is assumed to be assigned to all patients.[63] Therefore, in our economic model we used the total cost of terminal care estimated at £8,186 from the appraisal which was then inflated to 2022 costs (using PSSRU inflation indices) to inform the HCC end of life costs.

In comparison of the health state and end of life costs in the DCC and HCC health states, the mean health state costs were £4,161 and £3,053, respectively, whilst end of life costs were £10,902 and £8,805, respectively. This demonstrates that costs at

end of life are considerably greater than the average costs accrued whilst living within the health state. Therefore, it is prudent to include these costs to ensure the full costs associated with liver disease are realised.

B22. Could the company please provide a clinical explanation for why average costs may be lower in the HCC state than the DCC state?

The resource use for the DCC and HCC health states were identified from TA443, which cited Wright et al. (2006) as the original source.[41,58] From the source, it was noted that the mean annual total costs for HCC were slightly lower than for DCC as some patients in the HCC health state had cirrhosis (n = 7) rather than DCC (n = 13). For DCC and HCC, it was reported that the principal cost component for both the health states was inpatient days which, on average, accounted for over 70% of the total costs. Therefore, whilst HCC has worse prognosis than DCC, the symptoms of liver disease for patients with HCC may be less severe than for patients with DCC, necessitating fewer resources to manage the condition.

Moreover, in one of the validation meetings, a clinical expert noted that it requires a secondary evaluation using a FibroScan to decide whether a patient is considered high-risk or DCC, as most PBC patients remain in the compensated cirrhosis state.[55] The same clinical expert confirmed that the patients that do move into a DCC state can incur significantly high costs. Additionally, the Rice *et al*. 2021 study states that varices, which are part of DCC, incur greater incremental costs than liver cancer.[46] No other relevant sources have been identified which contradict the difference between HCC and DCC average costs.

B23. Can the company clarify the rationale for the compliance rate used in treatment acquisition calculations for elafibranor and OCA, particularly given that trials tend to overestimate compliance rates among patients? Moreover, can the company comment on why is it justifiable to assume an equivalent compliance rate between elafibranor and OCA?

Table 11 in the Clinical Study Report (CSR) for elafibranor in the ELATIVE trial states the compliance in the trial was [redacted] % and at the time of submission despite best efforts we had not been able to find a compliance rate reported for obeticholic acid (OCA) in the literature and neither was one reported nor applied in TA443.[54]

Therefore a simplified assumption that OCA compliance would be the same as elafibranor was made.[54]

We have now managed to find an adherence rate in the POISE trial for OCA that was reported in the Pharmaceutical Benefits Advisory Committee (PBAC) review of the drug.[64] This was stated to be 93.55%.[64] It appears to have been calculated from the OCA titration arm from the study drug exposure which was 341.7 days as reported in the Canadian Agency for Drugs and Technologies in Health (CADTH) OCA submission i.e. 341.7/365.25 = 93.55%.[65] PBAC thought this value was overestimated and should be 80% but there was no rationale provided on this assumption by PBAC. One report based on prescription refills by AllianceRx Walgreens in the USA reported adherence (described as the proportion of days covered – PPDC) as being 77.1 for OCA.[66] The challenge in applying an adherence rate of 77.1% would be to assume that the efficacy with this adherence rate would be the same as that seen in the POISE trial.

It is possible to apply the methodology used from OCA in the PBAC review to elafibranor. In the ELATIVE trial the study exposure in the elafibranor arm (Table 12 in the CSR) was [redacted] weeks x 7 = [redacted] days. Therefore, the adherence rate would be [redacted] /365.25 = [redacted] % for elafibranor.

Finally, and possibly the most accurate method to calculate drug consumption should be based on the mean cumulative dose elafibranor in the ELATIVE trial which was [redacted] mg (table 14.1.20 in the ELATIVE CSR) out of a theoretical 29,220 mg (80 mg x 365.25) over the 52-week study period. This would give a mean dose intensity of [redacted] /29,220 = [redacted] % for elafibranor. Data for the mean cumulative dose for OCA in POISE trial could not be found. Longer term follow-up data and real-life use of elafibranor once licensed and available on the market would provide additional data on adherence to treatment.

For the purposes of this NICE submission, we would recommend that the most accurate and consistent application of compliance/adherence in the health economic model would be to apply a figure of either [redacted] % or [redacted] % for elafibranor and a figure of 93.55% for obeticholic acid. In our revised base case, we have applied figures of [redacted] % for elafibranor and 93.55% for OCA as these are calculated using

the same methodology, with the alternative figure of [redacted] % for elafibranor presented as a scenario. The updated economic model results, including the updated compliance rates, are provided in the Appendix.

Section C: Textual clarification and additional points

C1. Section B.2, p 43: Please confirm if the following statement in the summary section of the clinical effectiveness, part of the key inclusion criteria for adult patients in the ELATIVE trial, is accurate or if there is a typographical error: “(ALP ≤1.67 x ULN and TB ≤2 x ULN)”.

There is a typographical error in the statement. The correct statement should be: “(ALP ≥ 1.67 x ULN and TB ≤ 2 x ULN)".

C2. Section B.1.1, Table 1: “Any best supportive care treatment other than OCA 5-10 mg has not been recommended by NICE and therefore will not be considered in the submission”. Please can the company clarify whether they consider OCA a supportive treatment and for excluding supportive treatment as one of the comparators, as the current wording in this table suggests this. If so, please state if there was any evidence from clinical experts to justify this.

The current wording of this statement is incorrect as it does imply that OCA 5-10mg is considered a supportive treatment which the company does not agree with. The statement should be amended to: “OCA 5-10 mg as a second-line treatment is the standard of care for patients with PBC. Any treatment used in best supportive care has not been recommended by NICE nor does it provide the standard of care; therefore, any best supportive care will not be considered in the submission”.

C3. Section B.3.3.4, p.123: “Results from the NMA showed that patients treated with elafibranor had a lower likelihood of discontinuation for any reason within 12 months compared with OCA (OR [95% CI]: [redacted] [[redacted], [redacted]]).” Can the company rectify that the OR estimate in this statement is for OCA rather than elafibranor?

Correct, the OR estimate refers to OCA rather than elafibranor. New paragraph would be: “Results from the NMA showed that patients treated with OCA had a higher likelihood of discontinuation for any reason within 12 months compared with elafibranor (OR [95% CI]: [redacted] [[redacted], [redacted]]).” We have double-checked the model and can confirm it is only a textual error; it is inputted correctly in the model.

C4. Appendix D, Table 15: The reported ALP least-squares mean change from baseline (SE) U/L at month 12 for the placebo group in POISE trial is -7.7 (14.7),

whereas in the supplementary appendix of Nevens et al (2016) the figure is -14.4 ± 14.7.

a. Could the company please clarify this?

Correct, the value described in the Appendix D has been misreported. The ALP least-squares mean change from baseline (SE) U/L at month 12 for the placebo group in POISE trial is -14.4 ± 14.7.

b. Can the company please confirm that the correct figures are used within the NMA for ALP?

The NMA did not use LS mean values for change from baseline in ALP but rather the mean change from baseline. The values used in the NMA have been checked and are correct.

C5. Appendix D (p.2): Please could the company confirm that 8 December 2023 was the date on which the updated searches were conducted. Appendix D states “For the SLR update, searches were conducted on 8th December 2022,” whereas in Appendix D in Tables 1, 2 and 3 the date of the updated search is given as “08.12.2023”.

There is a typographical error in the statement. The date of the searches for the SLR update was 8 December 2023. Statement should be “For the SLR update, searches were conducted on 8th December 2023”.

C6. Appendix D (p.1 and p.7): Please could the company clarify which year’s conference proceedings were the first year’s to be searched for the original SLR. Appendix D page 1 states “conference proceedings... (2020 –2022 during the original SLR...)”, however, Appendix D page 7 states that the conference proceedings were searched “...occurring between 2021-2022..." for the original SLR (in Appendix D, Table 5 the earliest year’s conference proceedings listed are for 2021).

There is a typographical error in the statement. Conference proceedings were searched on 13th December 2022 during the original SLR for proceedings occurring between 2021–2022.

References

Doi SA, Furuya-Kanamori L, Xu C, Chivese T, Lin L, Musa OAH, et al. The Odds Ratio is "portable" across baseline risk but not the Relative Risk: Time to do away with the log link in binomial regression. J Clin Epidemiol. 2022;142:288-93. Available from: https://doi.org/10.1016/j.jclinepi.2021.08.003

Hirschfield GM, Mason A, Luketic V, Lindor K, Gordon SC, Mayo M, et al. Efficacy of obeticholic acid in patients with primary biliary cirrhosis and inadequate response to ursodeoxycholic acid. Gastroenterology. 2015;148(4):751-61.e8. Available from: https://doi.org/10.1053/j.gastro.2014.12.005

National Institute for Health and Care Excellence (NICE). Obeticholic acid for treating primary biliary cholangitis [TA443]. Technology appraisal guidance. London: National Institute for Health and Care Excellence (NICE); 2017. Available from: https://www.nice.org.uk/guidance/ta443 [Date accessed: 18/04/2024].

Nevens F, Andreone P, Mazzella G, Strasser SI, Bowlus C, Invernizzi P, et al. A placebo-controlled trial of obeticholic acid in primary biliary cholangitis. N Engl J Med. 2016;375(7):631-43. Available from: https://doi.org/10.1056/NEJMoa1509840.

Rice S, Albani V, Minos D, Fattakhova G, Mells GF, Carbone M, et al. Effects of primary biliary cholangitis on quality of life and health care costs in the United Kingdom. Clin Gastroenterol Hepatol. 2021;19(4):768-76.e10. Available from: https://doi.org/10.1016/j.cgh.2020.06.025 .

Schattenberg JM, Pares A, Kowdley KV, Heneghan MA, Caldwell S, Pratt D, et al. A randomized placebo-controlled trial of elafibranor in patients with primary biliary cholangitis and incomplete response to UDCA. Journal of Hepatology. 2021;74(6):1344-54. Available from: https://doi.org/10.1016/j.jhep.2021.01.013.

Turner RM, Jackson D, Wei Y, Thompson SG, Higgins JPT. Predictive distributions for between-study heterogeneity and simple methods for their application in Bayesian meta-analysis. Statistics in Medicine. 2015;34(6):984-98. Available from: https://doi.org/10.1002/sim.6381 .

Company References

1. Search filters. SIGN. Accessed May 22, 2024. https://testing36.scot.nhs.uk

2. 7 Assessing cost effectiveness | The guidelines manual | Guidance | NICE. Published November 30, 2012. Accessed May 22, 2024. https://www.nice.org.uk/process/pmg6/chapter/assessing-cost-effectiveness

3. Papaioannou D, Brazier J, Paisley S. NICE DSU Technical Support Document 9: The Identification, Review and Synthesis of Health State Utility Values from the Literature. National Institute for Health and Care Excellence (NICE); 2010. Accessed May 22, 2024. http://www.ncbi.nlm.nih.gov/books/NBK425822/

4. Bowlus CL, Galambos MR, Aspinall RJ, et al. A phase II, randomized, open-label, 52-week study of seladelpar in patients with primary biliary cholangitis. J Hepatol. 2022;77(2):353-364. doi:10.1016/j.jhep.2022.02.033

5. Invernizzi P, Floreani A, Carbone M, et al. Primary Biliary Cholangitis: advances in management and treatment of the disease. Dig Liver Dis. 2017;49(8):841-846. doi:10.1016/j.dld.2017.05.001

6. Abbas N, Smith R, Flack S, et al. Critical shortfalls in the management of PBC: Results of a UK-wide, population-based evaluation of care delivery. JHEP Rep. 2024;6(1):100931. doi:10.1016/j.jhepr.2023.100931

7. Lammers WJ, van Buuren HR, Hirschfield GM, et al. Levels of alkaline phosphatase and bilirubin are surrogate end points of outcomes of patients with primary biliary cirrhosis: an international follow-up study. Gastroenterology. 2014;147(6):1338-1349.e5; quiz e15. doi:10.1053/j.gastro.2014.08.029

8. Murillo Perez CF, Harms MH, Lindor KD, et al. Goals of Treatment for Improved Survival in Primary Biliary Cholangitis: Treatment Target Should Be Bilirubin Within the Normal Range and Normalization of Alkaline Phosphatase. Am J Gastroenterol. 2020;115(7):1066-1074. doi:10.14309/ajg.0000000000000557

9. Kumagi T, Guindi M, Fischer SE, et al. Baseline ductopenia and treatment response predict long-term histological progression in primary biliary cirrhosis. Am J Gastroenterol. 2010;105(10):2186-2194. doi:10.1038/ajg.2010.216

10. Momah N, Silveira MG, Jorgensen R, Sinakos E, Lindor KD. Optimizing biochemical markers as endpoints for clinical trials in primary biliary cirrhosis. Liver Int. 2012;32(5):790-795. doi:10.1111/j.1478-3231.2011.02678.x

11. Reflection papers on regulatory requirements for the development of medicinal products for chronic non-infectious liver diseases (PBC, PSC, NASH) - Scientific guideline | European Medicines Agency. Accessed May 22, 2024. https://www.ema.europa.eu/en/reflection-papers-regulatory-requirements-development-medicinal-products-chronic-non-infectious-liver-diseases-pbc-psc-nash-scientific-guideline

12. FDA C for DE and R and. Expedited Programs for Serious Conditions | Drugs and Biologics. Published December 14, 2023. Accessed May 22, 2024. https://www.fda.gov/regulatory-information/search-fda-guidance-documents/expedited-programs-serious-conditions-drugs-and-biologics

13. FDA O of the C. Demonstrating Substantial Evidence of Effectiveness for Human Drug and Biological Products. Published January 27, 2020. Accessed May 22, 2024. https://www.fda.gov/regulatory-information/search-fda-guidance-documents/demonstrating-substantial-evidence-effectiveness-human-drug-and-biological-products

14. Murillo Perez CF, Fisher H, Hiu S, et al. Greater Transplant-Free Survival in Patients Receiving Obeticholic Acid for Primary Biliary Cholangitis in a Clinical Trial Setting Compared to Real-World External Controls. Gastroenterology. 2022;163(6):1630-1642.e3. doi:10.1053/j.gastro.2022.08.054

15. Daly C, Dias S, Welton NJ, Anwer S, Ades AE. Meta-Analysis: Guideline Methodology Document 1. NICE Guidelines Technical Support Unit; 2021.

16. Dias S., Welton N.J., Sutton A.J., Aeds A.E. NICE DSU Technical Support Document 2: A generalised linear modelling framework for pairwise and network

meta-analysis of randomised controlled trials (September 2016). http://scharr.dept.shef.ac.uk/nicedsu/wp-content/uploads/sites/7/2017/05/TSD2-General-meta-analysis-corrected-2Sep2016v2.pdf (accessed 2017 July 78).

17. Bucher HC, Guyatt GH, Griffith LE, Walter SD. The results of direct and indirect treatment comparisons in meta-analysis of randomized controlled trials. Journal of clinical epidemiology. 1997;50(6):683-691.

18. Nevens F, Andreone P, Mazzella G, et al. A Placebo-Controlled Trial of Obeticholic Acid in Primary Biliary Cholangitis. N Engl J Med. 2016;375(7):631-643. doi:10.1056/NEJMoa1509840

19. Kowdley KV, Bowlus CL, Levy C, et al. Efficacy and Safety of Elafibranor in Primary Biliary Cholangitis. N Engl J Med. Published online November 13, 2023. doi:10.1056/NEJMoa2306185

20. Clinicaltrials.gov. A Phase 4, Double-Blind, Randomized, Placebo-Controlled, Multicenter Study Evaluating the Effect of Obeticholic Acid on Clinical Outcomes in Patients With Primary Biliary Cholangitis. Published February 13, 2023. Accessed May 19, 2024. https://clinicaltrials.gov/study/NCT02308111

21. Kowdley KV, Brookhart MA, Hirschfield GM. Efficacy of Obeticholic Acid (OCA) vs Placebo and External Control (EC) on Clinical Outcomes in Primary Biliary Cholangitis (PBC). AASLD Meeting 2022; Abstract 5032. Hepatology. 2023;77(5):E116. doi:10.1097/HEP.0000000000000347

22. Hirschfield GM, Mason A, Luketic V, et al. Efficacy of obeticholic acid in patients with primary biliary cirrhosis and inadequate response to ursodeoxycholic acid. Gastroenterology. 2015;148:751-61.e8.

23. Schattenberg JM, Pares A, Kowdley KV, et al. A randomized placebo-controlled trial of elafibranor in patients with primary biliary cholangitis and incomplete response to UDCA. J Hepatol. 2021;74(6):1344-1354. doi:10.1016/j.jhep.2021.01.013

24. IPSEN. ITC Feasibility Assessment Clinical validation summary slides 2023 (data on file).

25. Chaimani A, Caldwell D, Li T, Higgins JPT, Salanti G. Chapter 11: Undertaking Network Meta-Analyses. In: Higgins JPT, Thomas J, Chandler J, Cumpston M, Li T, Page MJ, Welch VA (Editors). Cochrane Handbook for Systematic Reviews of Interventions Version 6.4 (Updated August 2023). Cochrane, 2023. Available from Www.Training.Cochrane.Org/Handbook. Vol 6.4.; 2023.

26. Goet JC, Harms MH, Carbone M, Hansen BE. Risk stratification and prognostic modelling in primary biliary cholangitis. Best Practice & Research Clinical Gastroenterology. 2018;34-35:95-106. doi:10.1016/j.bpg.2018.06.006

27. Decision Support Unit, NICE DSU Technical Support Document 2: A generalised linear modelling framework for pairwise and network meta-analysis of randomised controlled trials. (2016). http://scharr.dept.shef.ac.uk/nicedsu/wp-content/uploads/sites/7/2017/05/TSD2-General-meta-analysis-corrected-2Sep2016v2.pdf.

28. Spiegelhalter DJ, Best NG, Carlin BP, Van Der Linde A. Bayesian measures of model complexity and fit. Journal of the Royal Statistical Society: Series B (Statistical Methodology). 2002;64(4):583-639.

29. Turner RM, Jackson D, Wei Y, Thompson SG, Higgins JPT. Predictive distributions for between-study heterogeneity and simple methods for their application in Bayesian meta-analysis. Statistics in Medicine. 2015;34(6):984-998. doi:10.1002/sim.6381

30. Ren S, Oakley JE, Stevens JW. Incorporating Genuine Prior Information about Between-Study Heterogeneity in Random Effects Pairwise and Network Meta-analyses. Med Decis Making. 2018;38(4):531-542. doi:10.1177/0272989X18759488

31. Elman S, Hynan LS, Gabriel V, Mayo MJ. The 5-D itch scale: a new measure of pruritus. British Journal of Dermatology. 2010;162(3):587-593. doi:10.1111/j.1365-2133.2009.09586.x

32. Jacoby A, Rannard A, Buck D, et al. Development, validation, and evaluation of the PBC-40, a disease specific health related quality of life measure for primary biliary cirrhosis. Gut. 2005;54(11):1622-1629. doi:10.1136/gut.2005.065862

33. MHRA. Bezafibrate SPC. Accessed May 19, 2024. https://mhraproducts4853.blob.core.windows.net/docs/d528369024eadd4bc354ab260c8243ddef381b70

34. MHRA. Fenofibrate SPC. Accessed May 19, 2024. https://mhraproducts4853.blob.core.windows.net/docs/9896a81a79ceb55a1c03f78518b0e823eb973caa Accessed 19/05/24

35. Van Hooff MC, De Veer RC, Van de Meer AJ, Werner E, Beuers UHW, Drenth JPH. Real-world experience with fibrates in patients with primary biliary cholangitis. Presented at NVGE 2023. Published online 2023. https://mdl-congressen.nl/sites/mdlcongressen.productie.medonline.nl/files/bijlagen-congres/Programmaboekje%20DDD%20najaar%2023%20incl.%20abstracts.pdf.

36. Abbas N, Culver EL, Thorburn D, et al. UK-Wide Multicenter Evaluation of Second-line Therapies in Primary Biliary Cholangitis. Clin Gastroenterol Hepatol. 2023;21(6):1561-1570.e13. doi:10.1016/j.cgh.2022.07.038

37. Overview | Cardiovascular disease: risk assessment and reduction, including lipid modification | Guidance | NICE. Published December 14, 2023. Accessed May 22, 2024. https://www.nice.org.uk/guidance/ng238

38. Gershwin ME, Selmi C, Worman HJ, et al. Risk factors and comorbidities in primary biliary cirrhosis: a controlled interview-based study of 1032 patients. Hepatology. 2005;42(5):1194-1202. doi:10.1002/hep.20907

39. IPSEN. Clinical expert opinion | Ipsen data on file. Published online April 2024.

40. Samur S, Klebanoff M, Banken R, et al. Long-term clinical impact and cost-effectiveness of obeticholic acid for the treatment of primary biliary cholangitis. Hepatology. 2017;65(3):920-928. doi:10.1002/hep.28932

41. NICE. Obeticholic acid for treating primary biliary cholangitis (TA443) Committee Papers. Technology appraisal guidance [TA443]. Published online 2017. https://www.nice.org.uk/guidance/ta443

42. Corpechot C, F C, F G, et al. Liver stiffness measurement by vibration-controlled transient elastography improves outcome prediction in primary biliary cholangitis. J Hepatol. 2022;77(6):1545-1553. doi:10.1016/j.jhep.2022.06.017

43. Jones DEJ, Wetten A, Barron-Millar B, et al. The relationship between disease activity and UDCA response criteria in primary biliary cholangitis: A cohort study. eBioMedicine. 2022;80:104068. doi:10.1016/j.ebiom.2022.104068

44. Hirschfield GM, Dyson JK, Alexander GJM, et al. The British Society of Gastroenterology/UK-PBC primary biliary cholangitis treatment and management guidelines. Gut. 2018;67(9):1568-1594. doi:10.1136/gutjnl-2017-315259

45. Kuiper EMM, Hansen BE, de Vries RA, et al. Improved prognosis of patients with primary biliary cirrhosis that have a biochemical response to ursodeoxycholic acid. Gastroenterology. 2009;136(4):1281-1287. doi:10.1053/j.gastro.2009.01.003

46. Rice S, Albani V, Minos D, et al. Effects of Primary Biliary Cholangitis on Quality of Life and Health Care Costs in the United Kingdom. Clin Gastroenterol Hepatol. 2021;19(4):768-776.e10. doi:10.1016/j.cgh.2020.06.025

47. Engelmann C, Clària J, Szabo G, Bosch J, Bernardi M. Pathophysiology of decompensated cirrhosis: Portal hypertension, circulatory dysfunction, inflammation, metabolism and mitochondrial dysfunction. Journal of Hepatology. 2021;75:S49-S66. doi:10.1016/j.jhep.2021.01.002

48. D'Amico G, Bernardi M, Angeli P. Towards a new definition of decompensated cirrhosis. Journal of Hepatology. 2022;76(1):202-207. doi:10.1016/j.jhep.2021.06.018

49. Kumar R, Kumar S, Prakash SS. Compensated liver cirrhosis: Natural course and disease-modifying strategies. World Journal of Methodology. 2023;13(4):179. doi:10.5662/wjm.v13.i4.179

50. Tanajewski L, Harris R, Harman DJ, et al. Economic evaluation of a community-based diagnostic pathway to stratify adults for non-alcoholic fatty liver disease: a Markov model informed by a feasibility study. BMJ Open. 2017;7(6):e015659. doi:10.1136/bmjopen-2016-015659

51. Montano-Loza AJ, Corpechot C. Definition and Management of Patients With Primary Biliary Cholangitis and an Incomplete Response to Therapy. Clin Gastroenterol Hepatol. 2021;19(11):2241-2251.e1. doi:10.1016/j.cgh.2020.06.062

52. IPSEN. UK-PBC Registry. Personal communication. Data on file.

53. Gibbons C, Srinavasan S, Bodhani J, Li J, Chen L, Trivedi P. Analyses of obeticholic acid treatment retention in UK patients based on medicine delivery data. Journal of Hepatology. 2022;77:S310. doi:10.1016/S0168-8278(22)00987-4

54. IPSEN. Clinical Study Report: A Double-Blind, Randomized, Placebo-Controlled Study and Open-Label Long Term Extension to Evaluate the Efficacy and Safety of Elafibranor 80 Mg in Patients with Primary Biliary Cholangitis with Inadequate Response or Intolerance to Ursodeoxycholic Acid.

55. FIECON. Clinical consultation meeting report (economic model validation) - (Clinician validation findings report merged_v2.0_FINAL_10May2024). Published online 2024.

56. Tripepi G, Jager KJ, Dekker FW, Zoccali C. Selection Bias and Information Bias in Clinical Research. Nephron Clinical Practice. 2010;115(2):c94-c99. doi:10.1159/000312871

57. Schwartz CE, Huang IC, Rohde G, Skolasky RL. Listening to the elephant in the room: response-shift effects in clinical trials research. Journal of Patient-Reported Outcomes. 2022;6(1):105. doi:10.1186/s41687-022-00510-6

58. Wright M, Grieve R, Roberts J, Main J, Thomas HC, Investigators UMHCT. Health benefits of antiviral therapy for mild chronic hepatitis C: randomised controlled trial and economic evaluation. Health technology assessment (Winchester, England). 2006;10(21):1-iii.

59. Longworth L, Young T, Buxton MJ, et al. Midterm cost-effectiveness of the liver transplantation program of England and Wales for three disease groups. Liver Transpl. 2003;9(12):1295-1307. doi:10.1016/j.lts.2003.09.012

60. NICE. Sofosbuvir for treating chronic hepatitis C. NICE technology appraisal guidance [TA330]. Published online February 25, 2015. Accessed July 31, 2023. https://www.nice.org.uk/guidance/ta330

61. IPSEN. Clinical Protocol - A double-blind, randomized, placebo-controlled study and open-label long-term extension to evaluate the efficacy and safety of elafibranor 80 mg in patients with primary biliary cholangitis with inadequate response or intolerance to ursodeoxycholic acid.Version 5.0; Published online December 20, 2022.

62. Gola A, Davis S, Greenslade L, et al. Economic Analysis of Costs for Patients with End Stage Liver Disease Over the Last Year of Life. BMJ Supportive & Palliative Care. 2015;5(1):110-110. doi:10.1136/bmjspcare-2014-000838.23

63. NICE. Atezolizumab with bevacizumab for treating advanced or unresectable hepatocellular carcinoma - Committee papers. Published online 2020. Accessed March 8, 2024. https://www.nice.org.uk/guidance/ta666/evidence/committee-papers-pdf-8954415181

64. Care AGD of H and A. Pharmaceutical Benefits Scheme (PBS) | Obeticholic acid: Tablet 5 mg, Tablet 10 mg; Ocaliva®. Accessed May 16, 2024. https://www.pbs.gov.au/info/industry/listing/elements/pbac-meetings/psd/2020-11/obeticholic-acid-tablet-5-mg-tablet-10-mg-ocaliva

65. Clinical Review Report: Obeticholic Acid (Ocaliva): (Intercept Pharmaceuticals Canada, Inc.): Indication: For the Treatment of Primary Biliary Cholangitis (PBC) in Combination with Ursodeoxycholic Acid (UDCA) in Adults with an Inadequate Response to UDCA or as Monotherapy in Adults Unable to Tolerate UDCA. Canadian Agency for Drugs and Technologies in Health; 2017. Accessed May 16, 2024. http://www.ncbi.nlm.nih.gov/books/NBK534942/

66. Prime AW. AllianceRx Walgreens Prime Studies Use of Ocaliva® in the Treatment of Primary Biliary Cholangitis. Accessed May 16, 2024. https://www.prnewswire.com/news-releases/alliancerx-walgreens-prime-studies-use-of-ocaliva-in-the-treatment-of-primary-biliary-cholangitis-301512791.html

Appendix – updated cost-effectiveness results

I. Base-case results

a. Base-case incremental cost-effectiveness analysis results

The updated base-case cost-effectiveness analysis results are presented in Table 25. The base-case results are based on the price of elafibranor offered under the PAS.

Table 25: Base-case results (deterministic), using the PAS price of elafibranor

Treatment	Total			Incremental			ICER (£) versus baseline
	Costs (£)	LYG	QALYs	Costs (£)	LYG	QALYs	
Elafibranor	[redacted]	[redacted]	[redacted]	-	-	-	-
OCA	242,656	12.672	8.266	[redacted]	[redacted]	[redacted]	Dominating
UDCA	104,283	10.808	6.383	[redacted]	[redacted]	[redacted]	29,350

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

b. Disaggregated results

Disaggregated life years, QALYs and costs by health state are presented in Table 26, Table 27 and Table 28 respectively.

Table 26: LY gain by health state

Health state	LYG elafibranor	LYG OCA	LYG UDCA	Increment elafibranor vs OCA	Increment elafibranor vs UDCA
Mild	[redacted]	2.385	0.356	[redacted]	[redacted]
Moderate	[redacted]	4.558	2.864	[redacted]	[redacted]
High	[redacted]	4.196	5.558	[redacted]	[redacted]
DCC	[redacted]	0.158	0.206	[redacted]	[redacted]
HCC	[redacted]	0.095	0.123	[redacted]	[redacted]
Pre-LT	[redacted]	0.367	0.475	[redacted]	[redacted]
LT	[redacted]	0.036	0.047	[redacted]	[redacted]
Post-LT	[redacted]	0.776	1.040	[redacted]	[redacted]
Re-emergence of PBC	[redacted]	0.101	0.139	[redacted]	[redacted]
Total LYs	[redacted]	12.672	10.808	[redacted]	[redacted]

Abbreviations: DCC – decompensated cirrhosis; HCC – hepatocellular carcinoma; LT – liver transplant; LYG – life years gained; OCA – obeticholic acid; PBC – primary biliary cholangitis; UDCA – ursodeoxycholic acid

Table 27: QALY gain by health state

Health state	QALY elafibranor	QALY OCA	QALY UDCA	Increment elafibranor vs OCA	Increment elafibranor vs UDCA
Mild	[redacted]	1.862	0.287	[redacted]	[redacted]
Moderate	[redacted]	3.563	2.288	[redacted]	[redacted]
High	[redacted]	2.063	2.765	[redacted]	[redacted]
DCC	[redacted]	0.056	0.074	[redacted]	[redacted]
HCC	[redacted]	0.040	0.053	[redacted]	[redacted]
Pre-LT	[redacted]	0.131	0.171	[redacted]	[redacted]
LT	[redacted]	0.019	0.025	[redacted]	[redacted]
Post-LT	[redacted]	0.472	0.638	[redacted]	[redacted]
Re-emergence of PBC	[redacted]	0.060	0.083	[redacted]	[redacted]
Total QALYs	[redacted]	8.266	6.383	[redacted]	[redacted]

Abbreviations: DCC – decompensated cirrhosis; HCC – hepatocellular carcinoma; LT – liver transplant; OCA – obeticholic acid; PBC – primary biliary cholangitis; QALYs – quality-adjusted life years; UDCA – ursodeoxycholic acid

Table 28: Costs by health state, using the PAS price of elafibranor

Health state	Cost elafibranor (£)	Cost OCA (£)	Cost UDCA (£)	Increment elafibranor vs OCA (£)	Increment elafibranor vs UDCA (£)
Mild	[redacted]	65,254	312	[redacted]	[redacted]
Moderate	[redacted]	84,889	3,037	[redacted]	[redacted]
High	[redacted]	52,273	48,745	[redacted]	[redacted]
DCC	[redacted]	2,637	3,434	[redacted]	[redacted]
HCC	[redacted]	1,166	1,509	[redacted]	[redacted]
Pre-LT	[redacted]	7,797	10,080	[redacted]	[redacted]
LT	[redacted]	23,836	30,858	[redacted]	[redacted]
Post-LT	[redacted]	2,860	3,835	[redacted]	[redacted]
Re-emergence of PBC	[redacted]	841	1,162	[redacted]	[redacted]
Death	[redacted]	1,103	1,310	[redacted]	[redacted]
Total costs	[redacted]	242,656	104,283	[redacted]	[redacted]

Abbreviations: DCC – decompensated cirrhosis; HCC – hepatocellular carcinoma; LT – liver transplant; OCA – obeticholic acid; PAS – patient access scheme; PBC – primary biliary cholangitis; UDCA – ursodeoxycholic acid

II. Exploring uncertainty

a. Probabilistic sensitivity analysis

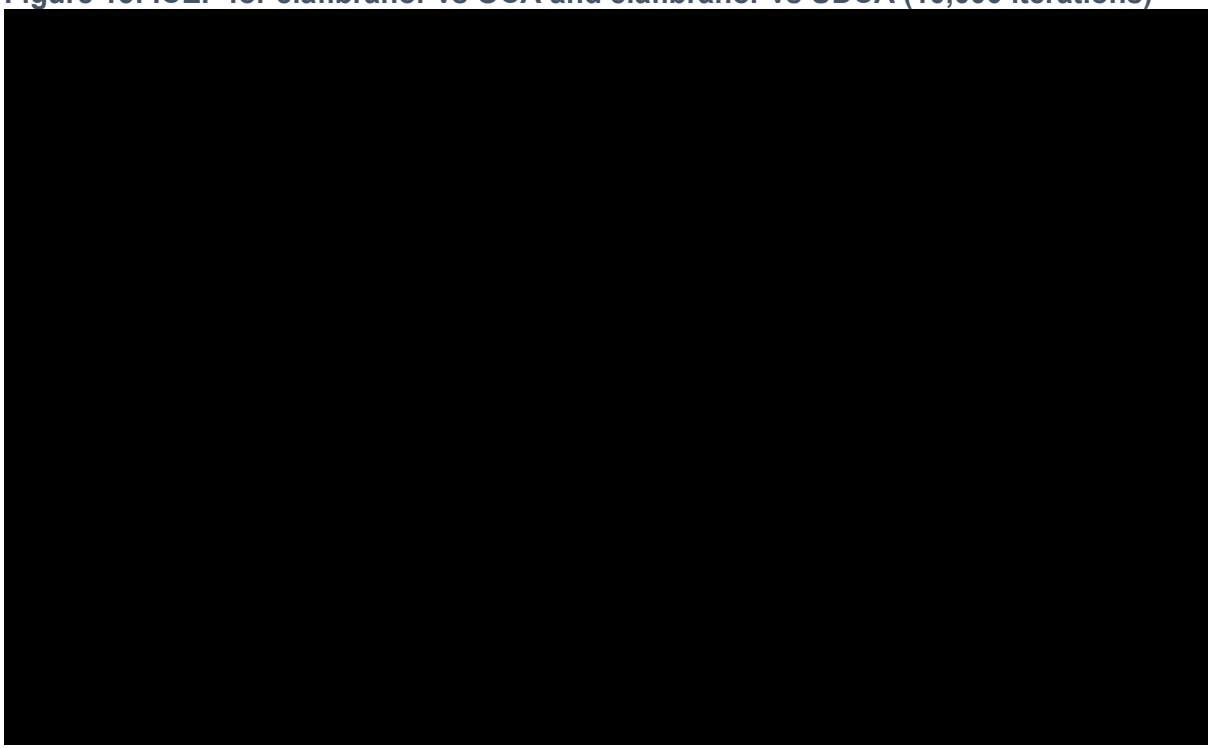
The updated mean probabilistic sensitivity analysis (PSA) results are presented in Table 29. The updated incremental cost-effectiveness plane (ICEP), cost-effectiveness acceptability curve (CEAC), and cost-effectiveness acceptability frontier (CEAF) are presented in Figure 13, Figure 14, and Figure 15. The PSA results are based on the price of elafibranor offered under the PAS.

Table 29: PSA results for elafibranor vs OCA and elafibranor vs UDCA, using the PAS price of elafibranor

Treatment	Total Costs (£)	Total QALYs	Incremental Costs (£)	Incremental QALYs	ICER of elafibranor (£)
Elafibranor	[redacted]	[redacted]	-	-	-
OCA	243,132	7.997	[redacted]	[redacted]	Dominating
UDCA	102,898	6.499	[redacted]	[redacted]	35,611

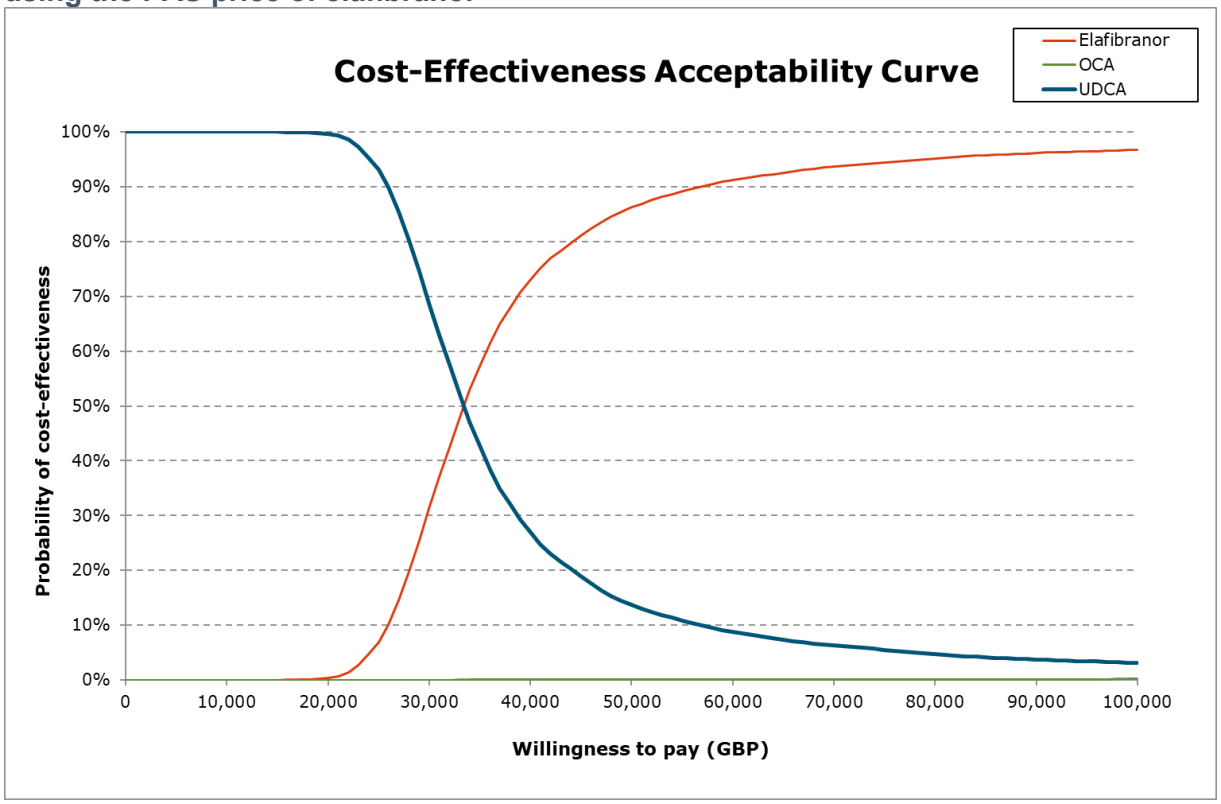
Abbreviations: ICER – incremental cost-effectiveness ratio; OCA - obeticholic acid; QALY – quality-adjusted life year; UDCA – ursodeoxycholic acid

Figure 13: ICEP for elafibranor vs OCA and elafibranor vs UDCA (10,000 iterations)



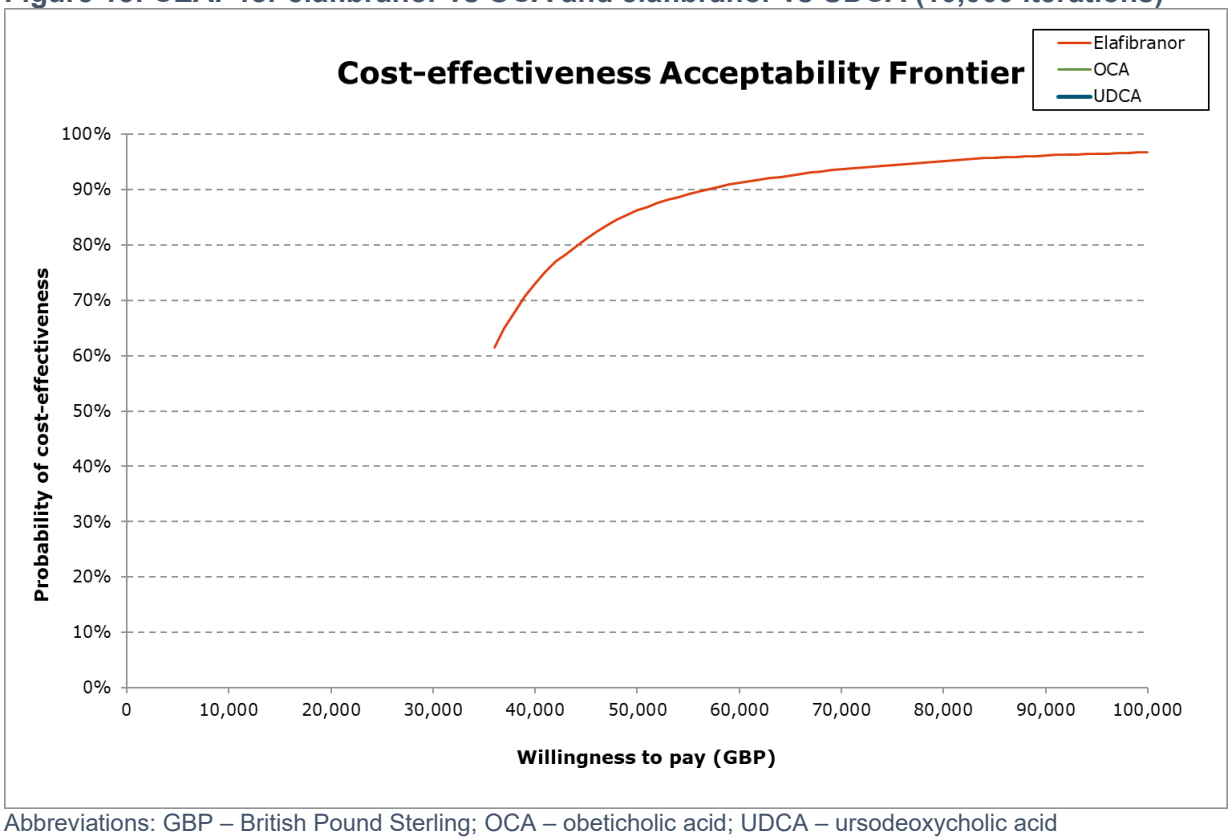
Abbreviations: GBP – Great British Pound: ICEP – incremental cost effectiveness plane; OCA – obeticholic acid; QALY – quality adjusted life year; UDCA – ursodeoxycholic acid

Figure 14: CEAC for elafibranor vs OCA and elafibranor vs UDCA (10,000 iterations) , using the PAS price of elafibranor



Abbreviations: GBP – British Pound Sterling; OCA – obeticholic acid; UDCA – ursodeoxycholic acid

Figure 15: CEAF for elafibranor vs OCA and elafibranor vs UDCA (10,000 iterations)



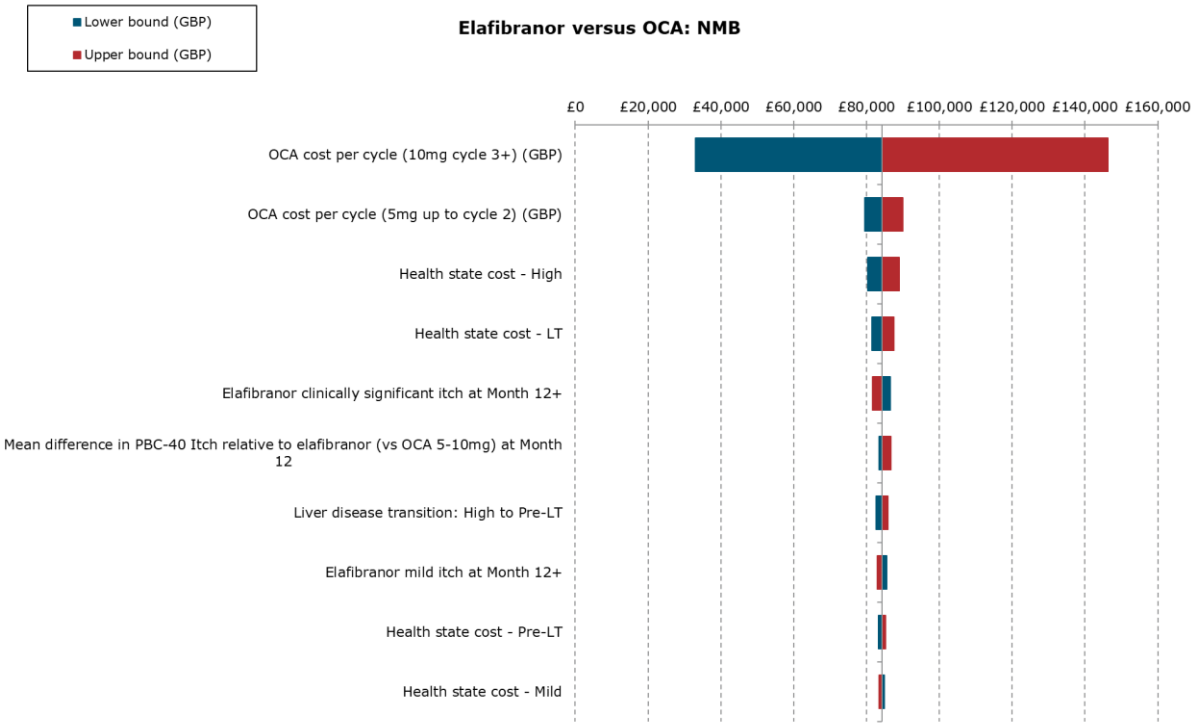
Abbreviations: GBP – British Pound Sterling; OCA – obeticholic acid; UDCA – ursodeoxycholic acid

b. *One-way sensitivity analysis*

Updated tornado plots of the one-way sensitivity analysis (OWSA) is presented in Figure 14 elafibranor versus OCA and in

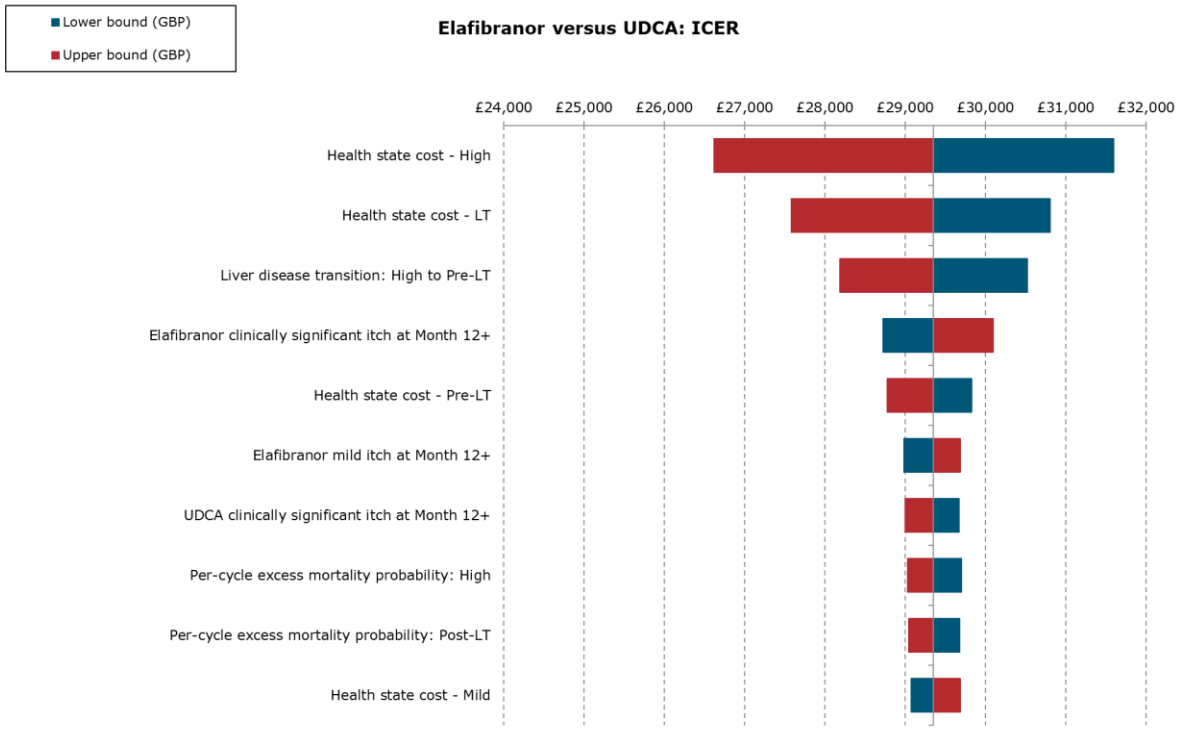
Figure 17 elafibranor versus UDCA.

Figure 16: OWSA tornado diagram for elafibranor versus OCA



Abbreviations: GBP – Great British Pound; LT – liver transplant; NMB – net monetary benefit; OCA – obeticholic acid

Figure 17: OWSA tornado diagram for elafibranor versus UDCA



Abbreviations: GBP – Great British Pound; ICER – incremental cost-effectiveness ratio; LT – liver transplant; NMB – net monetary benefit; UDCA – ursodeoxycholic acid

c. Scenario analysis

The scenario analyses performed are summarised in Table 30 and results presented in Table 31.

Table 30: Summary of scenario analyses

#	Model aspect	Base-case	Scenario analysis
1	Time horizon	Lifetime	20 years
2	Discount rate	3.5% for costs and outcomes	0% for costs and outcomes
3			5% for costs and outcomes
4	OCA price per pack discount	0%	10%
5			20%
6			30%
7			40%
8			50%
9			[redacted]%
10	Source for LT costs	HST17	Singh and Longworth

11	AEs	Include	Exclude
12	Costs of pruritus	Mild and CS are different	Mild and CS are the same
13	Definition of treatment response	Cholestasis response	ALP normalisation
14			Reduction in ALP of ≥40%
15			PARIS-II
16	UDCA extrapolations	Improvements not possible	Improvements possible
17	UDCA transition matrix extrapolation	Last observation carried forwards	Average of all transition matrices
18	Moderate risk to liver disease transitions	Include	Exclude
19	Duration of treatment effect of elafibranor relative to OCA on discontinuation	Lifetime	1 year
20	Treatment discontinuation distribution	Lognormal	Exponential
21			Weibull
22			Log-logistic
23			Gompertz
24	Disutility due to pruritus source	ELATIVE	Clinical opinion
25	Mild and moderate risk biomarker health states utilities	Younossi, 2000	ELATIVE
26	Utility values for DCC health state	0.38 (TA330)	0.62 (McPhail et al, 2021)
27	Compliance	Drug exposure (94.83% vs. 93.55%)	Mean cumulative (93.24% vs. 93.55%)
28	Discontinuation	Return to baseline	Stay in state

Abbreviations: AE – adverse event; CS – clinically significant; DCC – decompensated cirrhosis; HST – Highly Specialised Technologies; LT – liver transplant; OCA – obeticholic acid; TA – technology appraisal; UDCA – ursodeoxycholic acid

Table 31: Scenario analysis results

Scenario	Total costs of elafibranor (GBP)	Total QALYs of elafibranor	Incremental costs to OCA (GBP)	Incremental QALYs to OCA	Incremental costs to UDCA (GBP)	Incremental QALYs to UDCA	ICER of elafibranor vs OCA	ICER of elafibranor vs UDCA
Base-case	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	Dominating	29,350
#1	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	Dominating	£31,450
#2	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	Dominating	26,157
#3	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	Dominating	31,095
#4	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	Dominating	29,350
#5	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	Dominating	29,350

#6	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	29,350
#7	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	29,350
#8	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	29,350
#9	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	29,350
#10	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	Dominating	29,730
#11	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	Dominating	29,358
#12	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	Dominating	29,238
#13	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	Dominating	31,892
#14	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	Dominating	31,001
#15	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	Dominating	30,982
#16	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	Dominating	31,531
#17	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	Dominating	31,844
#18	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	Dominating	29,248
#19	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	Dominating	29,350
#20	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	Dominating	30,245
#21	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	Dominating	30,073
#22	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	Dominating	29,726
#23	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	Dominating	29,202
#24	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	Dominating	31,668
#25	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	Dominating	31,385
#26	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	Dominating	29,539
#27	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	Dominating	28,667
#28	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	Dominating	27,654

NICE National Institute for Health and Care Excellence

Spoken to Single Technology Appraisal

Elafibranor for treating primary biliary cholangitis [ID6331]

Patient Organisation Submission

Thank you for agreeing to give us your organisation's views on this technology and its possible use in the NHS.

You can provide a unique perspective on conditions and their treatment that is not typically available from other sources.

To help you give your views, please use this questionnaire with our guide for patient submissions.

You do not have to answer every question – they are prompts to guide you. The text boxes will expand as you type. [Please note that declarations of interests relevant to this topic are compulsory].

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- Your response should not be longer than 10 pages.

About you

1.Your name	[redacted]
2. Name of organisation	British Liver Trust
3. Job title or position	[redacted]
4a. Brief description of the organisation (including who funds it). How many members does it have?	The British Liver Trust is the UK's leading liver health charity, working to improve liver health for all and supporting all adults and children affected by liver disease or liver cancer. We are funded by voluntary donations, including community and event fundraising, individual donors, gifts in wills, corporate supporters and trust and foundation grants. We have recently merged with the Children's Liver Disease Foundation. We operate throughout the UK, reaching more than two million people each year. Our website has over 1.6 million unique visitors annually, our online forum has over 35,000 patient members, our nurse-led Helpline handles over 500 enquiries a month, regular newsletter goes to circa 23,000 people with liver disease and liver cancer, we run around 350 support groups each year (a mix of virtual and face to face); and connect with around 45,000 people via social media.
4b. Has the organisation received any funding from the company bringing the treatment to NICE for evaluation or any of the comparator treatment companies in the last 12 months? If so, please state the name of the company, amount, and purpose of funding.	**Yes - £5,000 grant from Ipsen to support the co production, writing and publish of patient information materials for people with PBC.** **Not related to the product.**

4c. Do you have any direct or indirect links with, or funding from, the tobacco industry?	No
5. How did you gather information about the experiences of patients and carers to include in your submission?	The British Liver Trust have collated information for this submission via a variety of different sources and channels; 1. Direct feedback and communication from patient and carers via our nurse-led specialist helpline. The British Liver Trust nurse led helpline has reviewed 114 enquires from patients or carers with PBC for this submission. This accounts for over 30 hours of helpline time. The callers were predominantly female (over 90%) which would fit with the epidemiology. 2. Feedback and comments via threads and a specific ask on our liver community forum (35K members) 3. Insight gained from patients attending support groups 4. Insight gained from a focus group held in February 2024 5. Individual telephone interviews with patients 6. Feedback from one clinician who has been involved with a trial for the treatment 7. Literature search and review of current guidelines

6. What is it like to live with the condition? What do carers experience when caring for someone with the condition?	Estimates for the UK suggest that PBC has a prevalence of c35/100,000 with the implication that there are about 20,000 patients in the UK. Although a more recent study (Abbas N, Smith R, Flack S et al Critical shortfalls in the management of PBC: Results of a UK-wide, population-based evaluation of care delivery JHEP Reports, vol 6, issue 1, 100931 published January 2024.) suggests it could be higher -around 25,000. PBC most often starts in middle age, although occasionally it can develop in people as early as their 20s. It can have very few symptoms early on. So some people have had PBC for a few years before they are diagnosed. Research studies show that, out of women over 40 years old, at least 1 in every 1,000 has PBC. Patients and carers report that living with PBC can be challenging. They are living with a condition which is rare, has no cure, may have a significant symptom burden and usually requires lifelong medication. As the disease can also (although less commonly) affect younger women, they may be concerned about having a family and whether becoming pregnant and having a baby is even possible. Patients often take a while to come to terms with a diagnosis of Primary biliary cholangitis (PBC). It is relatively uncommon so they often have not heard about it. They report feeling very scared – however many have also spent some time before being diagnosed trying to cope with unexplained symptoms. It can therefore be a relief to finally have a reason for them. Symptoms can impact on daily tasks for example it may be difficult to work due to fatigue or brain fog. Patients also comment on. difficulties with shopping or household chores if they are struggling with painful joints. The two most common issues facing people living with PBC are fatigue and itching. Patients and carers tell us that these particularly symptoms of fatigue and itch (pruritis) can significantly affect their quality of life. More than half of all those with PBC have fatigue and 1 in 5 people have it severely. Fatigue caused by a disease isn't just feeling a bit tired. Of course, sleeping and eating well can help to minimise it. But patients report not being able to 'fight your way through it'. It's more a case of learning how to manage it. Some quotes from patients: "I wish there was just a magic pill to take this fatigue away" "Nobody understands that when you look ok that you can be feeling so terrible inside" "On a good day I can make food for myself – I then batch cook because I know there will be other days when I cannot get out of bed"

	"You just have to learn to live with the stress and the symptoms. People who tell you they are tired too, have no idea what this kind of tiredness feels like." Patients with fatigue often say that they have difficulty asking for help as others think "everyone feels tired". Around 4 out of 5 people with PBC suffer from itching at some point. It isn't related to how bad a person's PBC is and may actually improve in more advanced PBC. As well as driving people mad, itching can affect your sleep quality, increasing fatigue and making it harder to cope. Some quotes: "My skin is so raw as the itch is so unbearable, I have used a hairbrush to scratch myself." "The itching just got worse and worse until it was starting to affect my sleep and my confidence - I was scratching so much that I bled." When itching is severely affecting quality of life, doctors will now consider a liver transplant. This can effectively provide a cure for some people with PBC – however for some people, sadly the PBC recurs after transplant. Living with a lifelong condition can be isolating and exhausting and if the condition progresses can have a significant impact on the person and anyone caring for them. In some patients, PBC may lead to them developing cirrhosis, decompensated cirrhosis and hepatocellular carcinoma. In PBC, cirrhosis is caused by damage to the bile ducts over many years – often called stage 4 PBC. It's very difficult to put a time frame on this. As PBC may not have symptoms in the earlier stages, we don't necessarily know how long someone has had it when they are diagnosed. In one patient study, around 1 in 6 people (17%) diagnosed with early stage PBC had advanced disease 10 years later. Cirrhosis has serious complications including ascites, hepatic encephalopathy. Some patients with PBC will require a liver transplant . One patient said: "For 10 years my PBC was controlled. Then things got really bad. For the last eight to 10 months before my transplant, I suffered from hepatic encephalopathy. Some days I was fine, but on others I was nasty and aggressive to my husband, and I couldn't understand why. I would also ring him at work several times a day to ask what day it was and leave taps running and the cooker on. Sometimes I didn't know who my daughter was. I was unable to drive."

7. What do patients or carers think of current treatments and care available on the NHS?	**What do patients or carers think of current treatments and care available on the NHS?** Patients and carers express frustration. Care and treatments do vary across the UK , in particular some patients have difficulties in accessing a specialist team with knowledge of treatments, particularly if they require second line treatment if they are a non-responder or intolerant of ursodeoxycholic acid. The first line treatment for PBC is ursodeoxycholic acid (UDCA) which is recommended for use in all patients. It can reduce risk and rate of progression to cirrhosis, however not all patients respond to it and the importance of second-line treatments in high risk patients is now appreciated. In the UK c60% of patients respond to UDCA and have normal or near-normal life expectancy. UDCA occurs naturally in the body so patients generally report few side effects. The most common side effect reported is diarrhoea or gastro intestinal disturbance – which for some is not tolerable and leads them to stopping treatment. Some people also report, weight gain, hair loss and flatulence. There is a pill burden associated with UDCA. Around 6 out of every 10 people find that UDCA controls their PBC. It is less likely to work well in people diagnosed before the age of 50. “I didn’t respond to any treatment. It was around that time, I was told I would eventually need a liver transplant. I had this but now my PBC has recurred.” If blood tests show that UDCA isn’t working well enough for you, patients are often prescribed another medicine called obeticholic acid. This medicine works by reducing high levels of bile salts within the liver. Sometimes if patients are intolerant of UDCA this is prescribed on its own. This has more side effects than UDCA. The commonest are itching and tiredness. Less often, patients report it can also cause dizziness, palpitations, mouth pain, constipation, joint pain and abdominal pain. For some patients these treatments cannot control PBC. There are also some treatments for itch. Patients are often prescribed colestyramine. This helps to get rid of the bile acids that are causing the itching. Colestyramine comes as a powder that you mix with water. It can taste very bitter and lots of patients report finding it difficult to take. Colestyramine, can stop other medicines from being absorbed properly so needs to be taken at least 4 hours before or after any other medicines.

	If colestyramine doesn't help other medicines for itching include rifampicin - a type of antibiotic, naltrexone – a type of drug called an opioid antagonist, an SSRI - medicines usually used for depression, such as Prozac and some body moisturising. Many patients report that they have tried everything and that "nothing works for the itch". Care pathways that patients describe can also vary widely with patients reporting huge variation in how often they are monitored , and who is responsible for the follow up and monitoring . The UK PBC audit group showed poor adherence to guidelines exists across all domains of PBC care in the NHS. Although specialist PBC treatment centres had greater adherence to guidelines, no single centre met all quality standards. Nationwide improvement in the delivery of PBC-related healthcare is required. More than a third of patients had not been assessed for fatigue (n = 3,885; 43%) or pruritus (n = 3,415; 38%) in the previous 24 months. JHEP Reports 2024. https://doi.org/10.1016/j.jhepr.2023.100931
8. Is there an unmet need for patients with this condition?	Yes. In the UK c60% of patients respond to UDCA and have normal or near-normal life expectancy. This leaves around 40% of patients who do not respond to UDCA – and therefore rely on second line treatments. For many of these patients they then struggle with second line treatments and new treatments are urgently needed. For some patients the only option is a liver transpant and sadly for some of these patients their PBC recurs.

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Advantages of the technology

9. What do patients or carers think are the advantages of the technology?	The British Liver Trust has spoken to one patient who has been involved in the clinical trial for this treatment. They said "for me it was a game changer and I hope that I will be able to continue with this treatment. My itching is now manageable and I am able to go to work." We have spoken to two clinicians who conducted trials – both of whom said that they had seen positive results and patients had not experienced side effects. One clinician stated: "Elafibranor is a novel, effective, new treatment for PBC. The ELATIVE phase III randomised placebo-controlled trial demonstrated significant improvement in both ALP values and markers of disease progression. Patient reported outcomes suggested possible improvement in itching, a bothersome symptom of PBC that is frequently exacerbated by obeticholic acid (OCA), which is currently the only licenced second-line therapy. Elafibranor was generally well tolerated with well documented safety profile demonstrated across this and previous trials." We have also read the Knowdely et al paper in the NEJM. As stated above there is a definite unmet – particularly for those patients who do not respond to UDCA.

Disadvantages of the technology

10. What do patients or carers think are the disadvantages of the technology?	Not aware of any.

Patient population

11. Are there any groups of patients who might benefit more or less from the technology than others? If so, please describe them and explain why.	PBC is up to 10 times more common in women than men. It can affect people from all ethnic backgrounds.

Equality

12. Are there any potential equality issues that should be taken into account when considering this condition and the technology?	

Other issues

13. Are there any other issues that you would like the committee to consider?	

Key messages

24. In up to 5 bullet points, please summarise the key messages of your submission.	• Living with PBC is challenging – with many patients reporting itch and fatigue as severely impacting quality of life. • PBC can lead to cirrhosis, decompensated cirrhosis and hepatocellular carcinoma • There is variation in care across the UK and poor adherence to guidelines across all domains for PBC care. • 40% of patients don't respond to first line treatments and some patients don't respond to any treatments and need transplantation. • There is a clear unmet need.

Thank you for your time.

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NICE National Institute for Health and Care Excellence

Single Technology Appraisal
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- Your response should not be longer than 10 pages.

About you

1.Your name	[redacted]
2. Name of organisation	Liver4Life
3. Job title or position	[redacted]
4a. Brief description of the organisation (including who funds it). How many members does it have?	UK charity providing support to people affected by Liver disease. We are funded by individual fundraising, grants from associations, support from Pharma companies and project activities
4b. Has the organisation received any funding from the company bringing the treatment to NICE for evaluation or any of the comparator treatment companies in the last 12 months? [Relevant companies are listed in the appraisal stakeholder list.] **If so, please state the name of the company, amount, and purpose of funding.**	£595, for [redacted] to take part in roundtable
4c. Do you have any direct or indirect links	NO

with, or funding from, the tobacco industry?	
5. How did you gather information about the experiences of patients and carers to include in your submission?	Liver4Life run patient support groups for people affected by Auto-immune conditions including PBC. At our last patient support group we took this document to the group and worked through the questions individually.

Living with the condition

6. What is it like to live with the condition? What do carers experience when caring for someone with the condition?	PBC is a difficult to diagnose auto-immune condition that is rarely looked for in primary or secondary care. Patients report physical issues with tiredness, itching, and achy joints as common issues. There is also a stigma attached to liver disease, with most people assuming that even though this condition is completely unrelated to alcohol, it must have a link somewhere as it is a liver disease. It is also difficult for patients to understand why they have PBC, and may have psychological issues about their diagnosis. Carers can also find it difficult to understand the levels of tiredness and itchiness that people with PBC live with, and it can put pressure on relationships if these effects are not understood. There is also a carer stigma regarding the liver and alcohol as well, with people talking 'behind' the patients back about the 'real' reason for the liver condition.

Current treatment of the condition in the NHS

7. What do patients or carers think of current treatments and care available on the NHS?	**Patients are generally pleased with the overall service they receive within the NHS. There has been an increased focus on 'rare' liver in the past few years as new treatments are being developed. PBC patients are now less likely to feel as if they have been managed in a holding pattern. There are still very few treatments available to PBC patients.**
8. Is there an unmet need for patients with this condition?	There is still no known cure for PBC, and therefore any therapy that can ease the trauma and suffering of living with this condition, and increasing and extending the quality of life of people affected is very welcome.

Advantages of the technology

9. What do patients or carers think are the advantages of the technology?	The ability to reduce the speed at which PBC progresses is really important to patients without a cure, and if this treatment also offers a reduction in side effects (itching, achiness) then that would be very welcomed. It is important that NHS patients have access to as many potential treatments as possible, so that they can be managed in a bespoke way, and this treatment will add another option to their lifelong care pathway.

Disadvantages of the technology

10. What do patients or carers think are the disadvantages of the technology?	The Patients we spoke to developing this response were unaware of any disadvantages, although early adopters of any new treatment would like a closer eye kept on them.

Patient population

11. Are there any groups of patients who might benefit more or less from the technology than others? If so, please describe them and explain why.	Patients who are not near a specialist centre will be disadvantaged. There are centres of excellence within the NHS where you will receive better, more nuanced care, than a small District General Hospital 9normally known as the postcode lottery)

Equality

12. Are there any potential equality issues that should be taken into account when considering this condition and the technology?	NO

Other issues

13. Are there any other issues that you would like the committee to consider?	

Key messages

24. In up to 5 bullet points, please summarise the key messages of your submission.	• PBC Patients have previously been left with few options upon diagnosis, and no cure • Itching, tiredness and aching can be debilitating and stop people live a normal life • Rollout and implementation of new technologies is not uniform • PBC patients are very keen to see a range of treatments available to them for their care. •

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About you

1.Your name	[redacted]
2. Name of organisation	PBC Foundation
3. Job title or position	[redacted]
4a. Brief description of the organisation (including who funds it). How many members does it have?	PBC Foundation is a registered charity that works in PBC. Its three main aims are patient support, advocacy, and facilitating research and education. PBC Foundation has over 16,000 patients registered but it serves over 20,000 patients in 85 countries around the world. Funding is from multiple sources including governmentt, private individuals' donations, corporate grants and industry.
4b. Has the organisation received any funding from the company bringing the treatment to NICE for evaluation or any of the comparator treatment companies in the last 12 months? [Relevant companies are listed in the appraisal stakeholder list.] **If so, please state the name of the company, amount, and purpose of funding.**	Ipsen are one of over ten different industry companies that part fund the Foundation's work. **Ipsen** **£27,000** Summit 2023 (25k plus £2k additional attendee) paid July 2023 **£11,000** Patient Conference 2023 (10k plus £1k additional attendee) paid sept 2023 **£5,000** Volunteer Conference 2023 paid march 2024 **Total £43,000** **Advanz** £5,000 Summit 2023 – paid june 23 £30,000 core 2023 – paid Nov 23 £5,000 Patient conf 2023 – paid dec 23 **Total £40,000** **Falk**

	£10,000 Summit 2023 – paid july23 **£5,000** core 2023 – paid April 23 **£5,000** core 2023 – paid nov 23 **£2,500** patient conf – paid sept23 **£2,000** video project – Paid sept23 **£10,000** bronze corp 2024 – paid feb 24 **Total £34,500**
4c. Do you have any direct or indirect links with, or funding from, the tobacco industry?	None
5. How did you gather information about the experiences of patients and carers to include in your submission?	There are a number of ways we gather patient information: We use surveys in our self-care app We host weekly Q&A sessions online with a prominent PBC clinical expert, and regular online and face-to0face meetings for patients and carers We host an annual 2-day patient conference and an annual 2-day volunteer conference, almost all attendees are patients and/or carers. We take refular helpline calls from patients and crers

Living with the condition

6. What is it like to live with the condition? What do carers experience when caring for someone with the condition?	There are two aspects to PBC in effectual terms: disease progression and symptom burden- the two of which do not correlate in any way. In simple terms, biochemical normalisation can often lead to normal life expectancy, and almost always lead to improved life expectancy. Symptom burden can profoundly affect QoL for both patients and carers. There are physical implications of living with PBC, but also psychological, emotional, social, and economic implications also. The shock of a diagnosis of an incurable condition can have a profound effect, as can untreatable symptoms- principally fatigue and pruritus. There can be hope of treatment, but then loss of hope when treatment does not improve liver biochemistry: all the literature shows this is associated with shorter lifespan and a journey towards liver failure and end stage liver disease. Once a patient reaches the stage of cirrhosis, then the complications and consequences are immeasurably worse for both patients and carers, and avoiding progression to cirrhosis is paramount.

Current treatment of the condition in the NHS

7. What do patients or carers think of current treatments and care available on the NHS?	For those patients in whom current therapies are successful, the thinking is that these therapies are enough. However, there is a small but significant number of patients for whom current therapies do not normalise biochemistry. Patients are aware of the gap, and would like to see this unmet need addressed.
8. Is there an unmet need for patients with this condition?	Absolutely, yes. For a rare condition, PBC still takes a disproportionate number of liver transplants or, with some patients not even making it to transplantation, early death.

Advantages of the technology

9. What do patients or carers think are the advantages of the technology?	1) Normalisation of liver biochemistry in a proportion of patients 2) Improvement, if not normalisation, of liver biochemistry in an underserved patient population 3) Potential combination therapy for patients who may not respond to double therapy 4) Potential improvement in itch, which is an enormously underserved population

Disadvantages of the technology

10. What do patients or carers think are the disadvantages of the technology?	Patients do not perceive there to be any new or additional disadvantages of this therapy, for all it still leaves a significant number of patients without biochemical normalisation.

Patient population

11. Are there any groups of patients who might benefit more or less from the technology than others? If so, please describe them and explain why.	1) Patients who are intolerant to UDCA 2) Patients for whom UDCA has not normalised liver biochemistry 3) Patients who already itch and so OCA is not seen as the best therapeutic solution 4) Patients on UDCA and OCA who still have abnormal liver biochemistry 5) High-risk patients who would not be anticipated to respond to UDCA (e.g. young women, or those with an incredibly high ALP)

Equality

12. Are there any potential equality issues that should be taken into account when considering this condition and the technology?	For many reasons, there is a disparity in black and latinx patients in response to current therapies. Whilst we have not seen any specific data, a new therapy working on a new mechanism may begin to address this inequality in life expectancy improvements.

Other issues

13. Are there any other issues that you would like the committee to consider?	This therapy would benefit a relatively small number of patients, and carers, ut that individual benefit would be genuinely life-changing: not just for length of life, but for quality of life, too. We ”now many patients who drop out of the work force, who disengage from society, even their families, whilst coming to terms with not only an incurable condition, but one which can shorten life expectancy quite dramatically. Many high risk patients are women in their prime years who have so much to give and to live for, yet that is taken beyond their control.

Key messages

24. In up to 5 bullet points, please summarise the key messages of your submission.	• The therapy can be used in multiple ways to address a life-threatening unmet need • By normalising liver biochemistry, and lengthening life expectancy, fewer PBC patients face liver transplantation or early death • Fewer PBC-led transplants free up scarce resources for other patients • The emotional, social, psychological and financial benefits gained by patients who do normalise and anticipate a full life is currently beyond our measure: but is beyond significant • Potential gains in benefit in itch severity could also be life-changing

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NICE National Institute for Health and Care Excellence

Single Technology Appraisal

Elafibranor for treating primary biliary cholangitis [ID6331]

Professional organisation submission

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To help you give your views, please use this questionnaire. You do not have to answer every question – they are prompts to guide you. The text boxes will expand as you type.

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- Your response should not be longer than 13 pages.

About you

1. Your name	[redacted]
2. Name of organisation	The British Association for the Study of the Liver (BASL)
3. Job title or position	[redacted]
4. Are you (please select Yes or No):	An employee or representative of a healthcare professional organisation that represents clinicians? Yes A specialist in the treatment of people with this condition? Yes A specialist in the clinical evidence base for this condition or technology? No Other (please specify): Liver diseases specialist
5a. Brief description of the organisation (including who funds it).	British Association for the Study of the Liver is the National Association for specialists in liver disease (hepatology). BASL is composed of interested individuals from clinical medicine, clinical and basic research and allied professions. BASL is funded through membership fees and organising and hosting an annual meeting and educational events.
5b. Has the organisation received any funding from the manufacturer(s) of the technology and/or comparator products in the last 12 months? [Relevant manufacturers are listed in the appraisal matrix.] **If so, please state the name of manufacturer, amount, and purpose of funding.**	Yes – Ipsen (company). BASL received £24,000 in sponsorship funding towards their Annual Conference and other educational and research events between April 2023 and March 2024. Yes – Dr Falk Pharma UK Ltd (comparator). BASL received £9,700 in sponsorship funding towards their Annual Conference and other educational and research events between April 2023 and March 2024. BASL and Dr Falk run annual quality and service improvement awards and Dr Falk fund the awards at a cost to them of £3,000. Yes – Advanz Pharma (comparator). BASL received £17,450 in sponsorship funding towards their Annual Conference and other educational and research events between April 2023 and March 2024. Yes Norgine Ltd (comparator). BASL received £27,100 in sponsorship funding towards their Annual Conference and another research event between April 2023 and March 2024.
5c. Do you have any direct or indirect links with, or funding from, the tobacco industry?	No

The aim of treatment for this condition

6. What is the main aim of treatment? (For example, to stop progression, to improve mobility, to cure the condition, or prevent progression or disability.)	To stop or slow the progression of liver disease in primary biliary cholangitis.
7. What do you consider a clinically significant treatment response? (For example, a reduction in tumour size by x cm, or a reduction in disease activity by a certain amount.)	Clinically significant treatment response in the long-term is a reduction in liver-related outcomes or liver-related mortality. Short-term and medium-term surrogate markers of a treatment response are a reduction in serum alkaline phosphatase (ALP) to less than 1.67x the upper limit of normal. Additional outcome measure in this condition is meaningful improvement in pruritus.
8. In your view, is there an unmet need for patients and healthcare professionals in this condition?	Yes, as approximately 40% of patients with PBC do not respond biochemically to ursodeoxycholic acid (UDCA), which is first line therapy. Currently available second line therapies are obeticholic acid (OCA) and bezafibrate. There remains some controversy as to which of these two should be used. Biochemical response rates of OCA and bezafibrate vary, but are reported to be >30%. Hence a significant proportion of patients with PBC do not adequately respond to first line treatment or the subsequent addition of second line therapy.

What is the expected place of the technology in current practice?

9. How is the condition currently treated in the NHS?	Treatment of patients with PBC who have abnormal LFTs with UDCA is standard, with assessment of response by agreed criteria. Patients who inadequately respond to UDCA, are referred to a specialist MDT for consideration of second-line therapy, either obeticholic acid or bezafibrate.
9a. Are any clinical guidelines used in the	Yes, the British Society of Gastroenterology/UK-PBC primary biliary cholangitis treatment and management guidelines (https://gut.bmj.com/content/67/9/1568).

treatment of the condition, and if so, which?	
9b. Is the pathway of care well defined? Does it vary or are there differences of opinion between professionals across the NHS? (Please state if your experience is from outside England.)	There are established guidelines with broad agreement of specialists in the field about the structured approach to treating PBC, using UDCA as first-line therapy and assessing response according to validated criteria. It is also agreed that, for UDCA non-responders, second-line therapy should be considered. For patients who inadequately respond to UDCA, access to second line therapy is overseen by specialists through a series of geographical Operational Delivery Networks, with monitoring of response to treatment using standard criteria.
9c. What impact would the technology have on the current pathway of care?	The place of Elafibranor in the algorithm of management of PBC would have to be established. It would likely initially be considered as a potential second-line therapy for patients inadequately responding to UDCA, though where it should sit in relation to current second-line options is unclear.
10. Will the technology be used (or is it already used) in the same way as current care in NHS clinical practice?	This is a new treatment, not currently in use in the NHS. The treatment, if adopted, would need to be incorporated into the current algorithm of care, The published indices of treatment response for this agent are similar to those widely used to assess treatment response in currently used agents.
10a. How does healthcare resource use differ between the technology and current care?	The use of elafibranor would be overseen and monitored by the same infrastructure and staff as currently in place for the management of patients with this condition.
10b. In what clinical setting should the technology be used? (For example, primary or secondary care, specialist clinics.)	This would be used in secondary care as second- or third- line therapy, delivered by via specialist clinics and overseen nationally by a system of regional MDTs (the PBC Operational Delivery Networks).
10c. What investment is needed to introduce the technology? (For example, for facilities, equipment, or training.)	Investment over and above current care would be needed to cover the cost of the medication, Itself. Use of this medication does not require any specific facilities or equipment, although there would need to be training of staff overseeing monitoring of the use of Elafibranor, as it is a new generation of medication.

11. Do you expect the technology to provide clinically meaningful benefits compared with current care?	The therapy will provide a further treatment option for those patients with PBC who are inadequate responders to UDCA and do not respond to or cannot tolerate OCA or fibrates. It is to be noted that Elafibranor is a combined PPAR-alpha and PPAR-delta agonist, and therefore there is overlapping activity with bezafibrate (a PPAR-alpha agonist)
11a. Do you expect the technology to increase length of life more than current care?	There is no current evidence to support that, but if this can change the trajectory of disease in a sub-group of patients with progressive disease, then it may do so for a minority of patients with PBC.
11b. Do you expect the technology to increase health-related quality of life more than current care?	The currently available evidence does not indicate that.
12. Are there any groups of people for whom the technology would be more or less effective (or appropriate) than the general population?	Currently not known.

The use of the technology

13. Will the technology be easier or more difficult to use for patients or healthcare professionals than current care? Are there any practical implications for its use (for example, any concomitant treatments needed, additional clinical requirements, factors	This medication has been used a large number of large-scale clinical trials and its side-effect profile is fairly well-established. Staff can therefore be educated regarding the side-effect profile and monitoring.

affecting patient acceptability or ease of use or additional tests or monitoring needed.)	
14. Will any rules (informal or formal) be used to start or stop treatment with the technology? Do these include any additional testing?	Criteria to start and to define responsiveness/non-response would be the same as those used for current first-line therapy for PBC and established second-line therapies.
15. Do you consider that the use of the technology will result in any substantial health-related benefits that are unlikely to be included in the quality-adjusted life year (QALY) calculation?	Based on currently available information, no.
16. Do you consider the technology to be innovative in its potential to make a significant and substantial impact on health-related benefits and how might it improve the way that current need is met?	Elafibranor has a novel mode of action, though part of its activity overlaps with that of fibrates (PPAR-alpha agonists) and therefore it is innovative. The impact it will make in terms of the proportion of patients with PBC who have a durable response to treatment, which leads to a reduced liver-related mortality or the need for liver transplantation, is currently unclear.
16a. Is the technology a 'step-change' in the management of the condition?	Evidence does not currently suggest this, though is a further agent in the armamentarium of treatment options for this condition.

16b. Does the use of the technology address any particular unmet need of the patient population?	Yes, there is a sub-group of patients with PBC who do not respond to first-line therapy or current second-line therapy, leaving them at increased risk of progression of liver disease to the need for liver transplantation or liver-related mortality.
17. How do any side effects or adverse effects of the technology affect the management of the condition and the patient's quality of life?	The most common side-effects noted in patients taking Elafibranor were abdominal symptoms including abdominal pain, diarrhoea, nausea and vomiting, which resolved on drug cessation. Staff administering the medication would need to be aware of this and inform patients of these potential side-effects.

Sources of evidence

18. Do the clinical trials on the technology reflect current UK clinical practice?	Yes, the published trials assess the effectiveness of elafibranor in patients who have an inadequate response to first-line therapy (UDCA).
18a. If not, how could the results be extrapolated to the UK setting?	
18b. What, in your view, are the most important outcomes, and were they measured in the trials?	The most important outcomes are the published response criteria for PBC treatment as well as symptomatic changes. These were evaluated in the published trials.
18c. If surrogate outcome measures were used, do they adequately predict long-term clinical outcomes?	There is evidence to support the use of biochemical response measures in predicting long-term outcomes in PBC.

18d. Are there any adverse effects that were not apparent in clinical trials but have come to light subsequently?	Almost all published experience has been from clinical trials. This agent is not in current use in the UK.
19. Are you aware of any relevant evidence that might not be found by a systematic review of the trial evidence?	No
20. How do data on real-world experience compare with the trial data?	There is little real-world data out there for Elafibranor so far to inform. The real-world UK. data on other second line therapies for PBC has, though been in line with published trial data for these agents.

Equality

21a. Are there any potential equality issues that should be taken into account when considering this treatment?	There should not be any equality issues in relation to this treatment, as long as all areas have good access to diagnosis of PBC, use of first-line therapy and response to treatment, leading on to access to second- or third-line therapies through specialist delivery networks.
21b. Consider whether these issues are different from issues with current care and why.	These issues are the same as for currently available care.

Key messages

22. In up to 5 bullet points, please summarise the key messages of your submission.	• Elafibranor has a novel mode of action and shows benefit (using accepted response criteria) in a significant proportion of patients with primary biliary cholangitis who do not respond to first-line therapy. • Elafibranor use could be built into the current algorithm of clinical care of patients with PBC, though it is currently unclear where the use of Elafibranor may sit in relation to other currently used second-line therapies. This would be a valid area for future study. • There is an already established national process through regional specialist delivery networks to oversee access to further treatment for patients who do not respond adequately to first-line therapy. Therefore, if elafibranor were to be approved for use in a defined setting, there is a functional mechanism already in place within the NHS to oversee who should receive this treatment and also to evaluate treatment response. •

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NICE National Institute for Health and Care Excellence

Single Technology Appraisal

Elafibranor for treating primary biliary cholangitis [ID6331]

Professional organisation submission

Thank you for agreeing to give us your organisation's views on this technology and its possible use in the NHS.

You can provide a unique perspective on the technology in the context of current clinical practice that is not typically available from the published literature.

To help you give your views, please use this questionnaire. You do not have to answer every question – they are prompts to guide you. The text boxes will expand as you type.

Information on completing this submission

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- Your response should not be longer than 13 pages.

About you

1. Your name	[redacted]
2. Name of organisation	British Hepatology Pharmacy Group (BHPG)
3. Job title or position	[redacted]
4. Are you (please select Yes or No):	An employee or representative of a healthcare professional organisation that represents clinicians? Yes A specialist in the treatment of people with this condition? Yes A specialist in the clinical evidence base for this condition or technology? Yes Other (please specify):
5a. Brief description of the organisation (including who funds it).	BHPG is an affiliated group of the British Association for the Study of the Liver (BASL). It is a professional pharmacy organisation aiming to develop knowledge and understanding of liver disorders.
5b. Has the organisation received any funding from the manufacturer(s) of the technology and/or comparator products in the last 12 months? [Relevant manufacturers are listed in the appraisal matrix.] **If so, please state the name of manufacturer, amount, and purpose of funding.**	Yes: Advanz £2000 Dr Falk £2000 Gilead £2000 All the above have provided sponsorship to run education study days for the British Hepatology Pharmacy Group via BASL.
5c. Do you have any direct or indirect links with, or funding from, the tobacco industry?	No

The aim of treatment for this condition

6. What is the main aim of treatment? (For example, to stop progression, to improve mobility, to cure the condition, or prevent progression or disability.)	To stop progression of disease to cirrhosis and prevent complications.
7. What do you consider a clinically significant treatment response? (For example, a reduction in tumour size by x cm, or a reduction in disease activity by a certain amount.)	Improvement in cholestatic markers and full biochemical response within one year of treatment.
8. In your view, is there an unmet need for patients and healthcare professionals in this condition?	Yes, current therapies are only effective in around 50% of this population and come with side effects which can impact quality of life.

What is the expected place of the technology in current practice?

9. How is the condition currently treated in the NHS?	First line includes ursodeoxycholic acid followed by obeticholic acid as second line treatment. Fibrates are also commonly used as second line treatment off label.
9a. Are any clinical guidelines used in the	bsg.org.uk/clinical-resource/bsg-and-ukpbc-pbc-guidelines PBC-English-report.pdf (easl.eu)

treatment of the condition, and if so, which?	
9b. Is the pathway of care well defined? Does it vary or are there differences of opinion between professionals across the NHS? (Please state if your experience is from outside England.)	Pathway of care is well defined and highlighted in the UK-PBC care pathway and as per BSG guidance. However, a recent UK wide audit has shown variations of care. This could be due to the availability and accessibility of specialist resources at a local level.
9c. What impact would the technology have on the current pathway of care?	This would be a good addition as a second line agent as current therapies are only 50% effective in inducing a complete biochemical response.
10. Will the technology be used (or is it already used) in the same way as current care in NHS clinical practice?	
10a. How does healthcare resource use differ between the technology and current care?	Additional resource will be required to manage prescribing and dispensing of this high cost medication in secondary care.
10b. In what clinical setting should the technology be used? (For example, primary or secondary care, specialist clinics.)	Secondary care/clinics managing patients with PBC.
10c. What investment is needed to introduce the technology? (For example, for facilities, equipment, or training.)	Investment should be considered in developing formal PBC networks as currently there is variation across the country as to how patients access second line treatment.

11. Do you expect the technology to provide clinically meaningful benefits compared with current care?	Yes, should increase the number of patients that achieve biochemical response.
11a. Do you expect the technology to increase length of life more than current care?	Yes as it provides further treatment options when current options have failed to do so.
11b. Do you expect the technology to increase health-related quality of life more than current care?	Yes potential benefits to minimise PBC related symptoms would improve patients' quality of life.
12. Are there any groups of people for whom the technology would be more or less effective (or appropriate) than the general population?	

The use of the technology

13. Will the technology be easier or more difficult to use for patients or healthcare professionals than current care? Are there any practical implications for its use (for example, any concomitant treatments needed, additional clinical requirements, factors	As its another once daily oral tablet, this will not be difficult to use. No additional monitoring would be needed above what is currently standard of care.

affecting patient acceptability or ease of use or additional tests or monitoring needed.)	
14. Will any rules (informal or formal) be used to start or stop treatment with the technology? Do these include any additional testing?	As per current second line therapy, it should be used when patients have failed to achieve biochemical response to ursodeoxycholic acid after a year of optimal dosing. I do think there is sufficient data in regards to stopping rules for this medication, but it would be sensible to keep them the same as current second line treatment rules (obeticholic acid) with a caveat of looking at improvement in fibrosis markers.
15. Do you consider that the use of the technology will result in any substantial health-related benefits that are unlikely to be included in the quality-adjusted life year (QALY) calculation?	
16. Do you consider the technology to be innovative in its potential to make a significant and substantial impact on health-related benefits and how might it improve the way that current need is met?	
16a. Is the technology a 'step-change' in the	No.

management of the condition?	
16b. Does the use of the technology address any particular unmet need of the patient population?	Yes
17. How do any side effects or adverse effects of the technology affect the management of the condition and the patient's quality of life?	The side effect profile reported in the trial is similar to those listed for existing treatment. Close monitoring of any potential adverse events upon treatment initiation is required to avoid negative impact on patients' quality of life.

Sources of evidence

18. Do the clinical trials on the technology reflect current UK clinical practice?	Yes.
18a. If not, how could the results be extrapolated to the UK setting?	
18b. What, in your view, are the most important outcomes, and were they measured in the trials?	Biochemical response without serious adverse effects which was measured as a primary and secondary outcome in the study. Particularly, biochemical response is a good surrogate marker of long term clinical outcomes.
18c. If surrogate outcome measures were used, do they adequately predict	As above

long-term clinical outcomes?	
18d. Are there any adverse effects that were not apparent in clinical trials but have come to light subsequently?	
19. Are you aware of any relevant evidence that might not be found by a systematic review of the trial evidence?	
20. How do data on real-world experience compare with the trial data?	

Equality

21a. Are there any potential equality issues that should be taken into account when considering this treatment?	All patients should be given access to the drug through an established PBC MDT Network, in the same way that obeticholic acid is prescribed, regardless of the location of their PBC clinic (DGH or specialist centre).
21b. Consider whether these issues are different from issues with current care and why.	Same issue with current care.

Key messages

22. In up to 5 bullet points, please summarise the key messages of your submission.	• Good addition to second line treatment options for PBC which is considered a rare disease • Good safety profile • Some investment should be considered in developing PBC networks to promote less variation in care and access to this new treatment • •

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NICE National Institute for Health and Care Excellence

Single Technology Appraisal

Elafibranor for treating primary biliary cholangitis [ID6331]

NHS organisation submission (ICBs and NHS England)

Thank you for agreeing to give us your organisation's views on this technology and its possible use in the NHS.

You can provide a unique perspective on the technology in the context of current clinical practice that is not typically available from the published literature.

To help you give your views, please use this questionnaire. You do not have to answer every question – they are prompts to guide you. The text boxes will expand as you type.

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- Your response should not be longer than 10 pages.

About you

1. Your name	Yasmin Stammers
2. Name of organisation	NHS England
3. Job title or position	Head of Internal Medicine (Lead commissioner for specialised hepatobiliary and pancreas services)

4. Are you (please select Yes or No):	Commissioning services for an ICB or NHS England in general? Yes ~~or No~~ Commissioning services for an ICB or NHS England for the condition for which NICE is considering this technology? Yes ~~or No~~ Responsible for quality of service delivery in an ICB (for example, medical director, public health director, director of nursing)? ~~Yes or~~ No An expert in treating the condition for which NICE is considering this technology? ~~Yes or~~ No An expert in the clinical evidence base supporting the technology (for example, an investigator in clinical trials for the technology)? ~~Yes or~~ No Other (please specify):
5a. Brief description of the organisation (including who funds it).	The clinical reference group (CRG) is a group of clinicians, commissioners, public health experts, patients and carers who provide advice to NHS England based on their specific knowledge and expertise. CRGs provide advice on various areas such as service specification development, commissioning policies, innovation and quality of services. This CRG specifically advises the NHS on matters regarding Hepatobiliary & Pancreas services.
5b. Do you have any direct or indirect links with, or funding from, the tobacco industry?	No

Current treatment of the condition in the NHS

6. Are any clinical guidelines used in the treatment of the condition, and if so, which?	1. British Society of Gastroenterology and UK-PBC guideline (published in Gut 2018) 2. European Association for the Study of Liver Disease guideline (published in Journal of Hepatology 2017)
7. Is the pathway of care well defined? Does it vary or are there differences of opinion between professionals across the NHS? (Please state if your experience is from outside England.)	The current pathway of care for people with PBC is largely delivered within secondary care. Ursodeoxycholic acid (UDCA) is the first line treatment and we would expect approximately 70% of patients to have achieved a biochemical response (defined as a serum alkaline phosphatase level of below 1.67x the upper limit of normal) after 12 months of appropriate weight-based UDCA. Patients who are either intolerant of UDCA or who do not sufficiently lower their alkaline phosphatase can be considered for second line therapy with obeticholic acid (OCA) delivered through centres specially commissioned by NHS England. Patients with decompensated (Child's B or C grade) cirrhosis should not receive OCA. The recent UK-wide audit of over 9,000 patients with PBC (Abbas N et al. JHEP Reports 2023) found underutilisation of second line therapy with only around 50% of potentially eligible patents receiving either OCA or the unlicensed fibric acid derivatives (bezafibrate or fenofibrate). The reasons for this disparity are being explored and we anticipate local and regional initiatives to identify and appropriately refer more "high risk" PBC patients for consideration of second line therapies including elafibranor when available.
8. What impact would the technology have on the current pathway of care?	We currently do not have plans to change the arrangements for delivering second line PBC therapies in England but this area is under regular review. At the time of writing, we would anticipate elafibranor could be delivered using the existing structures. To avoid inappropriate prescribing, we would support the use of a PBC MDT discussion prior to initiation.

The use of the technology

9. To what extent and in which population(s) is the technology being used in your local health economy?	Elafibranor is not currently available, outside of clinical trial settings, in NHS England. The nearest comparable technology would be the bile acid FXR agonist obeticholic acid which is the currently licensed and NICE-approved second line therapy for PBC.

10. Will the technology be used (or is it already used) in the same way as current care in NHS clinical practice?	We would envisage incorporating elafibranor into the existing specialist pathways for managing PBC in people who are either intolerant of or incompletely responsive to first line therapies. An additional use may be in people who have failed to optimally respond to second line therapies (fibrates or OCA), as these patients were included in the recent ELATIVE phase 3 trial of elafibranor.
10a. How does healthcare resource use differ between the technology and current care?	We are not aware of any significant differences in terms of monitoring. It would be important to agree stopping rules, for example where there is an inadequate response to a defined duration of elafibranor treatment.
10b. In what clinical setting should the technology be used? (For example, primary or secondary care, specialist clinics.)	We would favour secondary and tertiary care centres but with a proviso that patients are discussed in an MDT prior to initiating therapy.
10c. What investment is needed to introduce the technology? (For example, for facilities, equipment, or training.)	None.
10d. If there are any rules (informal or formal) for starting and stopping treatment with the technology, does this include any additional testing?	Stopping rules will need to be clarified. In addition, there needs to be clear guidance on patients deemed unsuited for elafibranor such as advanced or decompensated cirrhosis.
11. What is the outcome of any evaluations or audits of the use of the technology?	We are not aware of widespread use of elafibranor for the treatment of PBC in the UK, outside of registered clinical trials. It was not included in the recent UK-wide national audit of PBC management.

Equality

12a. Are there any potential equality issues that should be taken into account when considering this treatment?	PBC prevalence is asymmetrical within the population with a 10-fold higher incidence in women compared to men. That said, UK data shows PBC is typically diagnosed at a later stage in men, potentially reflecting perception bias among clinicians. Generally, PBC is usually a disease of older patients with the median age at diagnosis being 65 years. There are some key differences in the clinical manifestations of PBC between men and women and between older and younger patients, although the basic approach to management is the same in all demographic groups. The impact of ethnicity on presentation is not well described, but there are reports internationally of how ethnicity affects the presentation of autoimmune liver disease, and it should be borne in mind that most of the classical descriptions of PBC in the literature were mainly derived from Caucasian-only populations.
12b. Consider whether these issues are different from issues with current care and why.	The phase 3 ELATIVE trial of Elafibranor in PBC recruited from centres in North America, South America, Europe and South Africa. There were no recruiting centres in Asia or Australasia. The trial data showed 93.5% of people treated with elafibranor were Caucasian.

Thank you for your time.

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NICE National Institute for Health and Care Excellence

Single Technology Appraisal

Elafibranor for treating primary biliary cholangitis [ID6331]

Clinical expert statement

Information on completing this form

In part 1 we are asking for your views on this technology. The text boxes will expand as you type.

In part 2 we are asking you to provide 5 summary sentences on the main points contained in this document.

Please do not embed documents (such as a PDF) in a submission because this may lead to the information being mislaid or make the submission unreadable. Please type information directly into the form.

Do not include medical information about yourself or another person that could identify you or the other person.

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Combine all comments from your organisation (if applicable) into 1 response. We cannot accept more than 1 set of comments from each organisation.

Please underline all confidential information, and separately highlight information that is submitted as 'confidential [CON]' in turquoise, and all information submitted as 'depersonalised data [DPD]' in pink. If confidential information is submitted, please also

send a second version of your comments with that information redacted. See Health technology evaluations: interim methods and process guide for the proportionate approach to technology appraisals (section 3.2) for more information.

The deadline for your response is **5pm** on **Monday 19 August 2024.** Please log in to your NICE Docs account to upload your completed form, as a Word document (not a PDF).

Thank you for your time.

We reserve the right to summarise and edit comments received, or not to publish them at all, if we consider the comments are too long, or publication would be unlawful or otherwise inappropriate.

Comments received are published in the interests of openness and transparency, and to promote understanding of how recommendations are developed. The comments are published as a record of the comments we received, and are not endorsed by NICE, its officers or advisory committees.

Part 1: Treating primary biliary cholangitis and current treatment options

Table 1 About you, aim of treatment, place and use of technology, sources of evidence and equality

1. Your name	Professor David Emrys Jeffreys Jones OBE
2. Name of organisation	Newcastle University & Newcastle upon Tyne Hospitals Trust
3. Job title or position	Professor of Liver Immunology & Hon Consultant Hepatologist
4. Are you (please tick all that apply)	☐ An employee or representative of a healthcare professional organisation that represents clinicians? ☒ A specialist in the treatment of people with primary biliary cholangitis? ☒ A specialist in the clinical evidence base for primary biliary cholangitis or technology? ☐ Other (please specify):
5. Do you wish to agree with your nominating organisation's submission? (We would encourage you to complete this form even if you agree with your nominating organisation's submission)	☒ Yes, I agree with it ☐ No, I disagree with it ☐ I agree with some of it, but disagree with some of it ☐ Other (they did not submit one, I do not know if they submitted one etc.)
6. If you wrote the organisation submission and/or do not have anything to add, tick here. (If you tick this box, the rest of this form will be deleted after submission)	☐ Yes
7. Please disclose any past or current, direct or indirect links to, or funding from, the tobacco industry.	Nil
8. What is the main aim of treatment for primary biliary cholangitis? (For example, to stop progression, to improve mobility, to cure the condition, or prevent progression or disability)	There are two aims of treatment that are largely independent of each other 1) Prevention of progression of the disease to end-stage liver disease (through a combination of cirrhosis development and advanced ductopenia (loss of the intra-hepatic bile ducts) with risk of death or need

	for transplantation as a salvage therapy. Note that there are two drivers of disease progression and risk to life, progression to cirrhosis and advanced ductopenia. This is in contrast to hepatocellular liver disease (eg HCV or MASLD) where there is a single driver in the form of progression to cirrhosis. This adds an important extra dimension to the treatment needs in PBC. 2) Reduction of the quality-of-life burden associated with PBC-related symptoms (especially chronic itch and fatigue). There is no connection between the severity of disease and degree of symptoms. Many of the most symptomatic patients have clinically early disease. The conventional clinical focus has been on reducing risk but for most patients this is an abstract concept of reducing something, albeit undesirable, that might happen in the future). Symptoms and their impact on life quality are a more immediate, "here and now" concern.
9. What do you consider a clinically significant treatment response? (For example, a reduction in tumour size by x cm, or a reduction in disease activity by a certain amount)	In terms of risk reduction, lowering of serum alkaline phosphatase to below 1.67 times the upper limit of normal, and bilirubin in the normal range is the standard response criterion used at present. It is likely that there will be a tightening of this over the next few years with normalisation of tests being the desirable target. In terms of symptoms, significant treatment responses have not been well defined. In terms of itch, we use a 10-point Likert scale with a 4 point improvement (or a reduction to below 2/10 severity) as being clear improvement. This is quite stringent and in clinical practice a 2-point reduction would give meaningful quality of life improvement. Fatigue is even less well defined but similar values would probably apply.
10. In your view, is there an unmet need for patients and healthcare professionals in primary biliary cholangitis?	Yes

11. How is primary biliary cholangitis currently treated in the NHS? • Are any clinical guidelines used in the treatment of the condition, and if so, which? • Is the pathway of care well defined? Does it vary or are there differences of opinion between professionals across the NHS? (Please state if your experience is from outside England.) • What impact would the technology have on the current pathway of care?	NHS management in the UK follows the BSG/UK-PBC guidelines *Hirschfield GM, Dyson JK, Alexander GJM, Chapman MH, Collier J, Hübscher S, Patanwala I, Pereira SP, Thain C, Thorburn D, Tiniakos D, Walmsley M, Webster G, Jones DEJ. The British Society of gastroenterology/UK-PBC primary biliary cholangitis treatment and management guidelines.* ***Gut*** *2018; 67:1568-1594.* These will be updated shortly to reflect recent evolutions in management. Most care for PBC is delivered by gastroenterologists supported by specialised hepatology centres with an ODN model guiding second-line therapy (22 ODNs covering England). Very advanced disease is managed by one of the 6 English liver transplant units. Therapy would typically not be initiated or changed in primary care. The approach is standard across England but there are recent audit data to suggest that the reach and effectiveness of implementation of the current therapy model is highly variable. Elafibranor would not change the current pathway but would add an extra treatment option for use within that pathway. It may well be that elafibranor represents an easier drug to use in practice (better tolerability than obeticholic acid regarding itch although tolerability issues of its own (say around muscle and renal issues) may emerge in clinical practice. An easier drug to use (if that is the case) may well help to improve apparent reluctance in some centres to use second-line therapy.
12. Will the technology be used (or is it already used) in the same way as current care in NHS clinical practice? • How does healthcare resource use differ between the technology and current care?	See above comment. I would foresee elafibranor being used within the current system, providing further treatment options within the pathway, rather than requiring a different approach.

• In what clinical setting should the technology be used? (for example, primary or secondary care, specialist clinic) • What investment is needed to introduce the technology? (for example, for facilities, equipment, or training)	Use would entirely be initiated in secondary care or specialist clinics, with decision support through the current ODN model. There would be no additional investment requirement
13. Do you expect the technology to provide clinically meaningful benefits compared with current care? • Do you expect the technology to increase length of life more than current care? • Do you expect the technology to increase health-related quality of life more than current care?	Yes, although the benefit will be incremental rather than transformative. The benefit is likely to come through better tolerability (and thus greater treatment reach in practice) rather than better outcomes per se. There will be specific benefit in the group of PBC patients needing second-line therapy who also experience itch. This is a group in whom current care in the form of obeticholic acid can be a particular challenge. The quality-of-life improvement will be in terms of better itch control and in the avoidance of the clinical features in advanced liver disease in people unable to tolerate existing second-line therapy.
14. Are there any groups of people for whom the technology would be more or less effective (or appropriate) than the general population?	No
15. Will the technology be easier or more difficult to use for patients or healthcare professionals than current care? Are there any practical implications for its use? (For example, any concomitant treatments needed, additional clinical requirements, factors affecting patient acceptability or ease of use or additional tests or monitoring needed)	Probably easier to use and that will be a factor in terms of clinical value. The caveat is that this will be, as obeticholic acid is, a lifelong treatment and tolerability over the longer term will be the key issue. Tolerability issues for therapies in PBC have, in the past, typically only emerged over longer term use.

16. Will any rules (informal or formal) be used to start or stop treatment with the technology? Do these include any additional testing?	No additional testing. Starting rules will be as for existing therapy with decisions made through the existing system. At present there are no stopping rules (formal or informal) for obeticholic acid. The emergence of additional therapy options meaning that there are alternative therapy approaches will accelerate the development of stopping/swapping rules
17. Do you consider that the use of the technology will result in any substantial health-related benefits that are unlikely to be included in the quality-adjusted life year (QALY) calculation? • Do the instruments that measure quality of life fully capture all the benefits of the technology or have some been missed? For example, the treatment regimen may be more easily administered (such as an oral tablet or home treatment) than current standard of care	No, with the caveat that prediction of long-term hard endpoint change is difficult to predict in PBC at an individual level. The symptom benefit around itch is very well quantified using the existing tools. The treatment is easier to use through the reduced risk of itch, but this improvement will be fully quantified using the standard symptom impact tools. The systemic impacts of PBC itch are particularly well captured by EQ-5D.
18. Do you consider the technology to be innovative in its potential to make a significant and substantial impact on health-related benefits and how might it improve the way that current need is met? • Is the technology a 'step-change' in the management of the condition? • Does the use of the technology address any particular unmet need of the patient population?	Elafibranor will, in my view, be an important addition to the therapeutic option that we have for PBC. This will, however, be an incremental advance over obeticholic acid rather than a step-change (the advent of the first second-line therapy obeticholic acid was indeed a step change). The unmet need that is addressed is a second-line therapy option for PBC patients with significant itch, where use of obeticholic acid might be regarded us undesirable, and as an alternative second-line therapy in patients who develop significant itch with obeticholic acid that is not responsive to standard management approaches. The extent to which elafibranor will be useful as a therapy specifically for itch treatment (i.e. patients who need itch controlling therapy but in whom second-line therapy is not indicated; an area with limited licensed therapies but not, as far as I understand, a proposed labelled indication for elafibranor) will become clear if and when we have clinical access.
19. How do any side effects or adverse effects of the technology affect the management of the condition and the patient's quality of life?	The trial experience to date (which is up to 18 months; long term safety assessment is awaited) suggests a very benign side-effect profile. There is some evidence of muscle pain (a class effect) and there will be keen interest in any

	longer term renal signal (renal impairment is a major issue with bezafibrate when it is used off-license as a second-line therapy in PBC). With the caveat that long-term data are needed the side-effect profile and drug tolerability represent major advantages of the drug. Given the lack of significant side-effects, and the positive effect on itch, elafibranor is a net improver of PBC patient quality life. This is important in a condition where quality of life issues are frequently an important factor.
20. Do the clinical trials on the technology reflect current UK clinical practice? • If not, how could the results be extrapolated to the UK setting? • What, in your view, are the most important outcomes, and were they measured in the trials? • If surrogate outcome measures were used, do they adequately predict long-term clinical outcomes? • Are there any adverse effects that were not apparent in clinical trials but have come to light subsequently?	Yes. The trials were conducted in part in the UK in typical UK patients. The outcomes assessed were standard for early phase PBC trials (biochemical primary endpoint with a robust PRO panel, together with some mechanistic data). Clearly hard endpoint data are highly desirable but are a major challenge to derive in a rare, chronic condition such as PBC.
21. Are you aware of any relevant evidence that might not be found by a systematic review of the trial evidence?	No
22. Are you aware of any new evidence for the comparator treatment since the publication of NICE technology appraisal guidance [TA443]?	Yes. There are three relevant additional datasets 1) Multiple real world evidence data sets on obeticholic acid, including form the UK and utilising synthetic control methodology, to suggest that improvement in liver biochemistry with OCA is matched by a significant reduction in risk of death or need for liver transplant in PBC. This gives confidence that the similar biochemical improvement seen with elafibranor is also likely to be clinically meaningful.

	2) The confirmatory trial COBALT has reported. In contrast to the real-world evidence this failed to show any reduction in rate of death or need for transplant with the OCA treated group. However, the progression to end stage disease was, in both groups, significantly lower than predicted. There is evidence that awareness of alkaline phosphatase values (which rapidly improve with obeticholic acid) resulted in a significant proportion of the placebo grove moving to commercially available obeticholic acid or bezafibrate confounding the trial. 3) Emerging data suggest the combination of an FXR agonist and a PPAR agonist (in the trials to date OCA and bezafibrate) gives a significantly greater biochemical signal than any single drug (elafibranor included) with normalisation of all liver function tests in over 50%. This suggests that optimal treatment in the future will be a combination approach (especially in the highest risk patient). This requires availability of properly evaluated drugs in both categories and is a strong argument for availability of elafibranor in addition to obeticholic acid rather than as an alternative.
23. How do data on real-world experience compare with the trial data?	We don't have real world experience of elafibranor use yet. The real-world experience of obeticholic (both anecdotally and in formal real world evidence studies) mirrors clinical trial experience fully.
24. What percentage of people are intolerant to ursodeoxycholic acid in NHS clinical practice? What treatment options are available for people who are intolerant to ursodeoxycholic acid?	No more than 5% if UDCA is re-introduced in a staged way in people who initially have problems tolerating it. We currently treat them with obeticholic acid which is theoretically an issue in UDCA intolerant people with itch. This is a vanishingly small group in my experience, however.
25. What proportion of people have fibrates? Would you expect usage of fibrates to be different in people having different treatments (e.g. elafibranor monotherapy, elafibranor with UDCA, obeticholic acid monotherapy, obeticholic acid with UDCA, no other active treatment)?	Currently around 10% of UK PBC patients take fibrates (and around another 10% obeticholic acid). Concerns about the safety of bezafibrate (renal and liver toxicity) have led to reductions in its use. The vast majority of both these groups would be people also taking UDCA. We only very rarely use bezafibrate monotherapy as there, contrasts with obeticholic where there is a published clinical trial, no evidence to it works as monotherapy.

	Elafibranor availability as a properly evaluated PPAR agonist would, in my view, largely lead to bezafibrate disappearing as an off-label therapy.
26. If obeticholic acid is not available, what treatment options would be used for people whose disease has an inadequate response to, or who are unable to tolerate, ursodeoxycholic acid?	The options would be limited to elafibranor (if supported) and off-label bezafibrate. I have highlighted my concerns about bezafibrate, its potential toxicity and the lack of evidence to support it. As outlined above, the combination of FXR agonist and PPAR agonist appears to be the optimal approach to treatment. If obeticholic acid (the only approved FXR agonist) were no longer available this would preclude this approach which would be disadvantageous for patients.
27. NICE considers whether there are any equalities issues at each stage of an evaluation. Are there any potential equality issues that should be taken into account when considering this condition and this treatment? Please explain if you think any groups of people with this condition are particularly disadvantaged. Equality legislation includes people of a particular age, disability, gender reassignment, marriage and civil partnership, pregnancy and maternity, race, religion or belief, sex, and sexual orientation or people with any other shared characteristics. Please state if you think this evaluation could • exclude any people for which this treatment is or will be licensed but who are protected by the equality legislation	None

• lead to recommendations that have a different impact on people protected by the equality legislation than on the wider population • lead to recommendations that have an adverse impact on disabled people. Please consider whether these issues are different from issues with current care and why. More information on how NICE deals with equalities issues can be found in the NICE equality scheme. Find more general information about the Equality Act and equalities issues here.	

Part 2: Key messages

In up to 5 sentences, please summarise the key messages of your statement:

1) There is unmet need in PBC and elafibranor would help us to meet that need.

2) Its action in improving itch in PBC (as opposed the existing second-line agent obeticholic acid which can worsen itch) would particularly help in the management of people who need both second-line therapy and improved itch management

3) Its likely simplicity of use will bring benefit in terms of simplifying treatment will improve the reach of treatment

4) It would be applied within an existing optimised care delivery network

5) Elafibranor has a different, complementary mode of action to obeticholic acid. It shouldn't be thought of as a like for like replacement. Rather it is an additional treatment option. Access to it would improve PBC management in England

Thank you for your time.

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NICE National Institute for Health and Care Excellence

Single Technology Appraisal

Elafibranor for treating primary biliary cholangitis [ID6331]

Patient expert statement

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Your comments are really valued. You can provide a unique perspective on conditions and their treatment that is not typically available from other sources

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Your response should not be longer than 15 pages.

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Thank you for your time.

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Comments received are published in the interests of openness and transparency, and to promote understanding of how recommendations are developed. The comments are published as a record of the comments we received, and are not endorsed by NICE, its officers or advisory committees.

Patient expert statement

Part 1: Living with this condition or caring for a patient with primary biliary cholangitis

Table 1 About you, primary biliary cholangitis, current treatments and equality

1. Your name	Mo Christie
2. Are you (please tick all that apply)	☒ A patient with primary biliary cholangitis? ☐ A patient with experience of the treatment being evaluated? ☐ A carer of a patient with primary biliary cholangitis? ☒ A patient organisation employee or volunteer? ☐ Other (please specify):
3. Name of your nominating organisation	PBC Foundation
4. Has your nominating organisation provided a submission? (please tick all options that apply)	☐ No (please review all the questions and provide answers when possible) ☒ Yes, my nominating organisation has provided a submission ☐ I agree with it and **do not wish to** complete a patient expert statement ☐ Yes, I authored / was a contributor to my nominating organisations submission ☐ I agree with it and **do not wish to** complete this statement ☒ I agree with it and **will be** completing
5. How did you gather the information included in your statement? (please tick all that apply)	☒ I am drawing from personal experience ☒ I have other relevant knowledge or experience (for example, I am drawing on others' experiences). Please specify what other experience: ☐ I have completed part 2 of the statement **after attending** the expert engagement teleconference

	☐ I have completed part 2 of the statement **but was not able to attend** the expert engagement teleconference ☐ I have not completed part 2 of the statement
6. What is your experience of living with primary biliary cholangitis? **If you are a carer (for someone with primary biliary cholangitis) please share your experience of caring for them**	I was diagnosed with PBC in 2007 at the age of 36, my daughter was a year old at the time. I didn't respond to Urso and my symptoms, in particular fatigue and itch, had a serious impact on my quality of life. I couldn't sleep due to the itch so that was compounding my fatigue and I struggled both physically and mentally. I tried my best to keep my job going so I could contribute financially to the family but that resulted in spending the majority of my free time in bed resting, I also had to take, sometimes lengthy, periods of sick leave, particularly when I had a hospital admission for treatment or an infection. My husband also had to take leave from work to take me to clinic and for treatments. My husband took over the household chores and cooking, our daughter was still very young and her early years totally passed me by. For a number of years I didn't recognise myself, I barely left the house other than for clinic visits, I really didn't know how long I could go on living like that. There were no other options at that time for 2nd line therapy. I tried multiple off licence treatments to help with the itch but none were successful, some of which had really awful side effects including vomiting, diarrhoea, severe headaches and flu like symptoms but the itch was so bad I was willing to try anything. I also tried light therapy and plasmapheresis and although the plasmapheresis did take the edge off the itching it required 2 weeks intensive treatment as an in-patient and then treatment as an outpatient 3 times per week. The hospital was a 100 mile round trip from home, treatment took a few hours and I couldn't drive afterwards as I felt so unwell so my husband had to take time off work to take me. Over time my veins gave up and I had a permcath fitted a few times but these were susceptible to infection and a further stay in hospital for IV antibiotics. In 2013 due to the impact on my quality of life I was referred for transplant.

	There were serious complications during my transplant resulting in a further emergency surgery and then the need for a second transplant. I was on the emergency list just 36 hours when another match was found for me and I received my second liver transplant, 17 days after my first. There were further complications and my family were called to be with me as I wasn't expected to make it through the night. The wait for my second transplant was very difficult, the decision I'd made to try to improve my quality of life was potentially resulting in my life ending leaving my husband and our then 7 year old daughter. I continued to struggle both physically and mentally, my recovery was very difficult but being free from the itch has truly changed my life.
7a. What do you think of the current treatments and care available for primary biliary cholangitis on the NHS? **7b. How do your views on these current treatments compare to those of other people that you may be aware of?**	Urso was the only 1st line treatment available at this time and there were no 2nd line options. We now have Oca licensed but there is currently a risk to that licence. My understanding is that this new treatment works in a different way to Urso and Oca so it gives a new way of managing PBC whether that be as a 2nd line treatment or part of a triple therapy for disease progression. The additional benefit of a treatment for itch is a huge unmet need within the patient community. I think there is a lack of understanding in just how much the itch can impact quality of life. There are a number of off licence medications that can be tried for itch but they have limited success and can have side effects. A fellow patient once told me that her itch was so bad she just wanted to walk out to the ocean and keep going and I can totally understand that.
8. If there are disadvantages for patients of current NHS treatments for primary biliary cholangitis (for example, how they are given or taken, side effects of treatment, and any others) please describe these	Patients know there is a gap if current therapies don't normalise biochemistry, also a lack of itch treatments and would like the unmet need addressed. Cholesytramine can be prescribed for itch but its difficult and unpleasant to take, can interact with other medication and often doesn't improve the itch.
9a. If there are advantages of elafibranor over current treatments on the NHS please describe these. For example, the effect on your quality of life, your ability to continue work, education, self-care, and care for others?	Elafibranor works differently to what is currently available. Improving patient's quality of life enables them to live their best life possible with PBC feeling that they are contributing to their family life and society. I felt huge guilt when I had to take sick leave from work or spend weekends resting especially with a very young daughter.

9b. If you have stated more than one advantage, which one(s) do you consider to be the most important, and why? **9c. Does elafibranor help to overcome or address any of the listed disadvantages of current treatment that you have described in question 8? If so, please describe these**	I think the most important advantage is that it works differently to what is currently available and could potentially help many patients live a longer and better quality of life. Elafibranor is easier to take than Cholestyramine for itch.
10. If there are disadvantages of elafibranor over current treatments on the NHS please describe these. For example, are there any risks with elafibranor? If you are concerned about any potential side effects you have heard about, please describe them and explain why	I don't see any potential disadvantages.
11. Are there any groups of patients who might benefit more from elafibranor or any who may benefit less? If so, please describe them and explain why Consider, for example, if patients also have other health conditions (for example difficulties with mobility, dexterity or cognitive impairments) that affect the suitability of different treatments	Patients who do not respond to current therapies could benefit massively from this new medication. The additional benefit of itch therapy could make a significant improvement in patient's quality of life. High risk patients could benefit from the additional of this therapy from an early stage to prevent the need for transplant or early death.
12. Are there any potential equality issues that should be taken into account when considering primary biliary cholangitis and elafibranor? Please explain if you think any groups of people with this condition are particularly disadvantage Equality legislation includes people of a particular age, disability, gender reassignment, marriage and civil partnership, pregnancy and maternity, race, religion or belief, sex, and sexual orientation or people with any other shared characteristics	I'm aware of a disparity in black and latin patients responding to current therapies. A therapy with a new mechanism could be the difference.

More information on how NICE deals with equalities issues can be found in the NICE equality scheme Find more general information about the Equality Act and equalities issues here.	
13. Are there any other issues that you would like the committee to consider?	

Part 2: Key messages

In up to 5 sentences, please summarise the key messages of your statement:

- This therapy can be used in many ways to address a life threatening unmet need.
- Normalise liver biochemistry to extend life expectancy resulting in less transplants or early deaths.
- Please don’t underestimate the effect of itch on quality of life, improvement in this could be life changing for patients.
- The move to normalising biochemistry has many benefits for patients in terms of life expectancy and quality of life, with the addition of emotional, social, physiological and financial benefits.
- Click or tap here to enter text.

Thank you for your time.

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NICE National Institute for Health and Care Excellence

Single Technology Appraisal

Elafibranor for treating primary biliary cholangitis [ID6331]

Patient expert statement

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Patient expert statement

Part 1: Living with this condition or caring for a patient with primary biliary cholangitis

Table 1 About you, primary biliary cholangitis, current treatments and equality

1. Your name	Lisa Woodcock
2. Are you (please tick all that apply)	☒ A patient with primary biliary cholangitis? ☐ A patient with experience of the treatment being evaluated? ☐ A carer of a patient with primary biliary cholangitis? ☐ A patient organisation employee or volunteer? ☐ Other (please specify):
3. Name of your nominating organisation	British Liver Trust
4. Has your nominating organisation provided a submission? (please tick all options that apply)	☐ No (please review all the questions and provide answers when possible) ☒ Yes, my nominating organisation has provided a submission ☐ I agree with it and **do not wish to** complete a patient expert statement ☒ Yes, I authored / was a contributor to my nominating organisations submission ☐ I agree with it and **do not wish to** complete this statement ☒ I agree with it and **will be** completing
5. How did you gather the information included in your statement? (please tick all that apply)	☒ I am drawing from personal experience ☐ I have other relevant knowledge or experience (for example, I am drawing on others' experiences). Please specify what other experience: ☐ I have completed part 2 of the statement **after attending** the expert engagement teleconference

	☐ I have completed part 2 of the statement **but was not able to attend** the expert engagement teleconference ☐ I have not completed part 2 of the statement
6. What is your experience of living with primary biliary cholangitis? **If you are a carer (for someone with primary biliary cholangitis) please share your experience of caring for them**	Pre transplant it was very hard, my main symptom was itch – till my skin bleed, daily. I had insomnia, and was getting by on 2-3 hours sleep a day, I was losing weight rapidly and my skin was getting damaged to scaring. Brain fog was extremely difficult to deal with also and financially I had to work. My mum also has PBC and for her the worst symptoms are brain fog and fatigue. Post transplant I now have recurring PBC – Confirmed by multiple biopsies, and the itch is starting to return, the liver pain is daily ad the fatigue is very bad, daily.
7a. What do you think of the current treatments and care available for primary biliary cholangitis on the NHS? **7b. How do your views on these current treatments compare to those of other people that you may be aware of?**	**Very little knowledge within the system, especially at GP practices. Only 2 licensed medications – one which causes itch.** **Overall very poor, sadly.** **My mum wh is responsive to Urso (unlike myself) agrees, because she see's what I have had to go through and continue to go through.**
8. If there are disadvantages for patients of current NHS treatments for primary biliary cholangitis (for example, how they are given or taken, side effects of treatment, and any others) please describe these	I don't think there are disadvantages, Urso is based on weight and myself nor my mum have had side effects from Uro. I am unresponsive to it. The other licensed drug can cause itch, and treats a disease that has a common symptom of itch.
9a. If there are advantages of elafibranor over current treatments on the NHS please describe these. For example, the effect on your quality of life, your ability to continue work, education, self-care, and care for others? **9b. If you have stated more than one advantage, which one(s) do you consider to be the most important, and why?** **9c. Does elafibranor help to overcome or address any of the listed disadvantages of current treatment that**	**Not knowing what the side effects may be, it is hard to say. But it will be good to have another licensed option for those that are unresponsive and suffer from chronic pruritis.**

you have described in question 8? If so, please describe these	
10. If there are disadvantages of elafibranor over current treatments on the NHS please describe these. For example, are there any risks with elafibranor? If you are concerned about any potential side effects you have heard about, please describe them and explain why	N/A
11. Are there any groups of patients who might benefit more from elafibranor or any who may benefit less? If so, please describe them and explain why Consider, for example, if patients also have other health conditions (for example difficulties with mobility, dexterity or cognitive impairments) that affect the suitability of different treatments	Those unresponsive to the other options and or those that suffer with chronic pruritis
12. Are there any potential equality issues that should be taken into account when considering primary biliary cholangitis and elafibranor? Please explain if you think any groups of people with this condition are particularly disadvantage Equality legislation includes people of a particular age, disability, gender reassignment, marriage and civil partnership, pregnancy and maternity, race, religion or belief, sex, and sexual orientation or people with any other shared characteristics More information on how NICE deals with equalities issues can be found in the NICE equality scheme	N/A

Find more general information about the Equality Act and equalities issues here.	
13. Are there any other issues that you would like the committee to consider?	N/A

Part 2: Key messages

In up to 5 sentences, please summarise the key messages of your statement:

- PBC needs more education and awareness raised
- GP have a lack of knowledge
- Not enough licensed options for PBC sufferers
- Click or tap here to enter text.
- Click or tap here to enter text.

Thank you for your time.

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NICE National Institute for Health and Care Excellence

NHS commissioning expert statement

Elafibranor for treating primary biliary cholangitis [ID6331]

Thank you for agreeing to give us your views on this technology and its possible use in the NHS.

You can provide a unique perspective on the technology in the context of current clinical practice that is not typically available from the published literature.

To help you give your views, please use this questionnaire. You do not have to answer every question – they are prompts to guide you. The text boxes will expand as you type. Your response should not be longer than 10 pages.

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- Your response should not be longer than 10 pages.

About you	
1. Your name	**Yasmin Stammers**
2. Name of organisation	**NHS England**

3. Job title or position	**Head of Internal Medicine, Specialised Commissioning.** **Senior Commissioner, Hepatobiliary and Pancreas Clinical Reference Group**
4. Are you (please tick all that apply):	✓ ☐ commissioning services for a CCG or NHS England in general? ✓ ☐ commissioning services for a CCG or NHS England for the condition for which NICE is considering this technology? ☐ responsible for quality of service delivery in a CCG (for example, medical director, public health director, director of nursing)? ☐ an expert in treating the condition for which NICE is considering this technology? ☐ an expert in the clinical evidence base supporting the technology (for example, an investigator in clinical trials for the technology)? ☐ other (please specify):
5. Do you wish to agree with your nominating organisation's submission? (We would encourage you to complete this form even if you agree with your nominating organisation's submission)	✓ ☐ yes, I agree with it ☐ no, I disagree with it ☐ I agree with some of it, but disagree with some of it ☐ other (they didn't submit one, I don't know if they submitted one etc.)
6. If you wrote the organisation submission and/ or do not have anything to add, tick	☐ yes

here. (If you tick this box, the rest of this form will be deleted after submission.)	
7. Please disclose any past or current, direct or indirect links to, or funding from, the tobacco industry.	**None**
Current treatment of the condition in the NHS	
8. Are any clinical guidelines used in the treatment of the condition, and if so, which?	1. British Society of Gastroenterology and UK-PBC guideline (published in Gut 2018) 2. European Association for the Study of Liver Disease guideline (published in Journal of Hepatology 2017)
9. Is the pathway of care well defined? Does it vary or are there differences of opinion between professionals across the NHS? (Please state if your experience is from outside England.)	The current pathway of care for people with PBC is largely delivered within secondary care. Ursodeoxycholic acid (UDCA) is the first line treatment and we would expect approximately 70% of patients to have achieved a biochemical response (defined as a serum alkaline phosphatase level of below 1.67x the upper limit of normal) after 12 months of appropriate weight-based UDCA. Patients who are either intolerant of UDCA or who do not sufficiently lower their alkaline phosphatase can be considered for second line therapy with obeticholic acid (OCA) delivered through centres specially commissioned by NHS England. Patients with decompensated (Child's B or C grade) cirrhosis should not receive OCA. The recent UK-wide audit of over 9,000 patients with PBC (Abbas N et al. JHEP Reports 2023) found under-utilisation of second line therapy with only around 50% of potentially eligible patients receiving either OCA or the unlicensed fibric acid derivatives (bezafibrate or fenofibrate). The reasons for this disparity are

	being explored and we anticipate local and regional initiatives to identify and appropriately refer more "high risk" PBC patients for consideration of second line therapies including elafibranor when available. For example, the UK-PBC collaboration are currently piloting a "PBC Care Bundle" in Yorkshire and East England regions to see if this improves uptake of second line therapies.
10. What impact would the technology have on the current pathway of care?	We have no plans to change the arrangements for delivering second line PBC therapies in England but this area is under regular review. At the time of writing, we would anticipate elafibranor could be delivered using the existing structures. To avoid inappropriate prescribing, we would support the use of a PBC MDT discussion prior to initiation.
The use of the technology	
11. To what extent and in which population(s) is the technology being used in your local health economy?	Elafibranor is not currently available outside of clinical trial settings in NHS England. The nearest comparable technology would be obeticholic acid which is the currently licensed and NICE-approved second line therapy for PBC.
12. Will the technology be used (or is it already used) in the same way as current care in NHS clinical practice?	We would envisage incorporating elafibranor into the existing specialist pathways for managing PBC in people who are either intolerant of or incompletely responsive to first line therapies. An additional use may be in people who have failed to optimally respond to second line therapies (fibrates or OCA), as these patients were also included in the recent ELATIVE phase 3 trial of elafibranor.
• How does healthcare resource use differ between the technology and current care?	We are not aware of any significant differences in terms of monitoring. It would be important to agree stopping rules, for example where there is an inadequate response following a defined duration of elafibranor treatment.

• In what clinical setting should the technology be used? (For example, primary or secondary care, specialist clinics.)	We would favour secondary and tertiary care centres but with a proviso that patients are discussed in an MDT prior to initiating therapy.
• What investment is needed to introduce the technology? (For example, for facilities, equipment, or training.)	None identified at this time.
• If there are any rules (informal or formal) for starting and stopping treatment with the technology, does this include any additional testing?	Stopping rules will need to be clarified. In addition, there needs to be clear guidance on patients deemed unsuited for elafibranor such as advanced or decompensated cirrhosis.
13. What is the outcome of any evaluations or audits of the use of the technology?	We are not aware of widespread use of elafibranor for the treatment of PBC in the UK, outside of registered clinical trials. It's use was not recorded in the recent UK-wide national audit of PBC management.
Equality	
14a. Are there any potential equality issues that should be	PBC prevalence is asymmetrical within the population with a 10-fold higher incidence in women compared to men. That said, UK data shows PBC is typically diagnosed at a later stage in men, potentially reflecting perception bias among clinicians.

taken into account when considering this treatment?	Generally, PBC is usually a disease of older patients with the median age at diagnosis being 65 years. There are some key differences in the clinical manifestations of PBC between men and women and between older and younger patients, although the basic approach to management is the same in all demographic groups. The impact of ethnicity on presentation is not well described, but there are reports internationally of how ethnicity affects the presentation of autoimmune liver disease, and it should be borne in mind that most of the classical descriptions of PBC in the literature were mainly derived from Caucasian-only populations.
14b. Consider whether these issues are different from issues with current care and why.	The phase 3 ELATIVE trial of elafibranor in PBC recruited from centres in North America, South America, Europe and South Africa. There were no recruiting centres in Asia or Australasia. The trial data showed 93.5% of people treated with elafibranor were Caucasian.
Topic-specific questions	
15. What percentage of people are intolerant to ursodeoxycholic acid in NHS clinical practice? What treatment options are available for people who are intolerant to ursodeoxycholic acid?	UDCA therapy is generally well tolerated. The recent UK-wide audit of PBC management found approximately 5% of patients had documented intolerance to UDCA (Abbas N et al *JHEP Rep* 2023). The current treatment options for people who are intolerant to UDCA would be to consider either obeticholic acid or a fibrate (usually bezafibrate or fenofibrate).
16. What proportion of people have fibrates? Would you expect usage of fibrates to be different in people having different treatments (e.g. elafibranor monotherapy, elafibranor with UDCA, obeticholic acid monotherapy,	In the recent UK audit (Abbas N et al JHEP Rep 2023) the proportion of people given second line therapies was split almost exactly equally between obeticholic acid and fibric acid derivatives (bezafibrate or fenofibrate). Only 8% of people on second line therapy were receiving a combination of both obeticholic acid plus a fibrate and we would expect similar proportions with elafibranor.

obeticholic acid with UDCA, no other active treatment)?	
17. If obeticholic acid is not available, what treatment options would be used for people whose disease has an inadequate response to, or who are unable to tolerate, ursodeoxycholic acid?	Currently, the only other option would be a fibric acid derivative such as bezafibrate or fenofibrate, neither of which is currently licensed for the treatment of PBC.

Thank you for your time.

Please log in to your NICE Docs account to upload your completed statement, declaration of interest form and consent form.

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Elafibranor for treating primary biliary cholangitis [ID6331]

Evidence Assessment Group Report

Produced by Newcastle University

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Report key: Commercial in confidence (CiC) data are highlighted in blue throughout the report.

Any de-personalised data are highlighted in pink throughout the report.

Abbreviations

AE	Adverse events
AIC	Akaike's Information Criterion
ALP	Alkaline phosphate
ANA	Antinuclear antibodies
BIC	Bayesian information criterion
BSC	Best supportive care
CE	Cost-effectiveness
CEM	Cost-effectiveness model
CI	Confidence interval
CRD	Centre for Reviews and Dissemination
CrI	Credible interval
CS	Company's submission
DCC	Decompensated cirrhosis
DSU	Decision Support Unit
EAG	Evidence Assessment Group
EQ-5D	European Quality of Life-5 Dimensions
HCC	Hepatocellular carcinoma
HRQoL	Health-related quality of life
HR	Hazard ratio
HST	Highly Specialised Technology
HTA	Health technology assessment
HUI	Health utility index
ICEP	Incremental cost-effectiveness plane
ICER	Incremental cost-effectiveness ratio
INAHTA	International Network of Agencies for Health Technology Assessment
ITT	Intention-to-treat
LT	Liver transplant
LYG	Life years gained
MeSH	Medical subject headings
N/A	Not applicable
NHS	National Health Service
NICE	National Institute for Health and Care Excellence
NIHR	National Institute for Health Research
NMA	Network meta-analysis
NMB	Net monetary benefit
OCA	Obeticholic acid
OR	Odds ratio
OWSA	One-way sensitivity analysis
PAS	Patient access scheme
PBC	Primary biliary cholangitis
PBC-40	Primary biliary cholangitis-40 questionnaire
PSA	Probabilistic sensitivity analysis
PSS	Personal Social Services
QALY	Quality adjusted life year
QoL	Quality of life
RCT	Randomised controlled trial
RR	Risk ratio
SD	Standard deviation
SE	Standard error
SIGN	Scottish Intercollegiate Guidelines Network
SLR	Systematic literature review
SUCRA	Surface Under the Cumulative RAnking curve

TA	Technology Assessment
TB	Total bilirubin
TEAE	Treatment-emergent adverse event
U/L	Units per litre
UDCA	Ursodeoxycholic acid
UK	United Kingdom
UK-PBC	United Kingdom Primary Biliary Cholangitis
ULN	Upper limit of normal
VAS	Visual analogue scale

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1 EXECUTIVE SUMMARY

This summary provides a brief overview of the key issues identified by the Evidence Assessment Group (EAG) as being potentially important for decision making. It also includes the EAG's preferred assumptions and the resulting incremental cost-effectiveness ratios (ICERs).

Section 1.1 provides an overview of the key issues identified by the EAG. Section 1.2 presents the model outcomes. Section 1.3 summarises all key issues identified by the EAG relating to clinical effectiveness and cost-effectiveness. Section 1.4 summarises the EAG's preferred assumptions and ICERs.

Further detail regarding key and non-key issues are described in the main EAG Report (Sections 2 to 6).

All issues identified represent the EAG's view, not the opinion of the National Institute for Health and Care Excellence (NICE).

1.1 Overview of the EAG's key issues

Table 1.1: Summary of EAG's key issues

Issue number	Brief summary of issue	Report section(s)
1	Uncertainty in the results of the network meta-analysis (NMA)	Section 3.3.4, 3.5
2	Uncertainty and lack of validation in the economic model's survival predictions	Section 4.3.3
3	All-cause discontinuation predictions for OCA determining cost-effectiveness in the economic model.	Section 4.3.4.2
4	Appropriate utility value for the high-risk biomarker health state in the economic model.	Section 4.3.5.1
Abbreviations: EAG = Evidence Assessment Group; NMA = network meta-analysis; OCA = obeticholic acid		

1.2 Overview of key model outcomes

NICE technology appraisals compare how much a new technology improves length (overall survival) and quality of life in a quality-adjusted life year (QALY). An ICER is the ratio of the extra cost for every QALY gained. A technology is considered absolutely dominant when it improves quality of life (measured in QALYs gained) and reduces costs (measured in £GBP) relative to its best alternative treatment.

Overall, the technology is modelled to affect QALYs by:

- Improving the primary biliary cholangitis (PBC) biomarker risk category (i.e. reducing the risk of liver disease): There were no treatment-specific differences in quality of life. Instead, reducing the PBC biomarker risk of liver disease improved quality of life, then treatment response differences led to differences in quality of life across treatment arms.

- Treatment discontinuation leading to a deterioration in the PBC biomarker risk categories (i.e. increased risk of liver disease): After one year on treatment elafibranor and OCA patients are assumed to stay on their risk category unless they discontinue and move to UDCA and best supportive care. Patients receiving UDCA are assumed to not have PBC biomarker risk improvements after the first year of treatment. Therefore, differences in treatment discontinuation are an important driver of quality of life differences.

Overall, the technology is modelled to affect costs by:

- [redacted]Improving the PBC biomarker risk category: Patients categorised at high-risk of liver disease are assumed to receive more intensive care than patients at mild or moderate risk. Patients as high risk of disease can transition to more severe disease stages such as liver failure leading to transplant (LT), decompensated cirrhosis (DCC), and hepatocellular cancer (HCC) at a higher rate than moderate-risk of disease patients.
- Treatment maintenance: Discontinuation of elafibranor or OCA leads to an increase in the risk of liver disease, and it only continues to increase under UDCA with best available care. Due to the lifelong duration of treatment, assumptions around long-term maintenance differences also affect differences in total treatment costs.
- Compliance differences: There are small differences in treatment compliance between OCA and elafibranor. This has an impact on treatment costs but there is a lack of evidence on the impact of compliance in effectiveness, so this only affects cost differences.

The modelling assumptions that have the greatest effect on the ICER are:

- Duration of the treatment differences in discontinuation: Data is only available comparing all-cause discontinuation between elafibranor and OCA over the first year. The economic model assumes this difference is sustained over the lifelong duration of treatment.
- Relative effectiveness parameters to model treatment with OCA in the economic model: To derive cholestasis response, occurrence of pruritus as an adverse event, and all-cause discontinuation for OCA, the model uses 12-month odds ratios from the network meta-analysis anchored to 12-month elafibranor baseline risks to derive 12-month risk ratios. A constant risk ratio is assumed and applied to 3-month elafibranor probabilities to generate 3-month probabilities for OCA. An alternative approach suggested by the EAG is to assume a constant hazard ratio calculated from the 12-months odds ratio.
- Treatment effectiveness definition: The company's base-case analysis follows the cholestasis response definition from the POISE and ELATIVE trials, and the PBC biomarker risk definitions from NICE TA443. More strict treatment response definitions such as alkaline phosphate (ALP) normalisation, the Barcelona criteria, or the PARIS II criteria require low risk-of-progression patients to achieve lower ALP thresholds. These thresholds are more difficult to attain and lead to reduced treatment effectiveness estimates.
- Utility values in the high-risk PBC biomarker health-state: The economic model used utility values from the published literature to calculate quality of life. Utility values collected from patients in the ELATIVE trial covered all the PBC biomarker risk

categories; however, only the mild and moderate-risk utility values from the trial were explored in a scenario analysis. There was a noticeable discrepancy between the PBC high risk value elicited from the ELATIVE trial ([redacted]) and the published utility value used in the economic model (0.55) from NICE TA330. [1,2] The company considers that selection bias and a small sample size make the trial utilities less reliable; however, the omission of this scenario many not accurately represent the parameter uncertainty in the economic model.

- UDCA after the first year: Patients discontinuing second-line treatment are assumed to move to UDCA and best supportive care. At this stage their risk level is assumed to continue deteriorating and is assumed not to improve (unlike elafibranor and OCA patients who stay in their risk category after the first year) less severe assumptions of risk progression at third-line UDCA treatment reduce the effectiveness estimates.
- Pruritus: Pruritus differences play a minor role in the cost-effectiveness results from the economic model compared to all-cause discontinuation, cholestasis response, and treatment cost differences. The difference in pruritus between elafibranor and OCA is assumed to remain constant over the lifelong duration of treatment, impacting both quality of life and total costs.

1.3 Description of the EAG's key clinical and economic issues

Table 1.2: Key issue 1: Uncertainty in the results of the network meta-analysis (NMA)

Report section	Sections 3.3.4, 3.5
Description of issue and why the EAG has identified it as important	The company state in their submission that the NMA results show elafibranor 80 mg to be superior to the comparators from the POISE trial, including OCA 5-10 mg. However, the EAG note that the NMA, used as the company's base case for dichotomous outcomes, is subject to methodological limitations and that the 95% CrIs are substantially wide. As a result, the EAG considers the outcome estimates obtained from NMAs to be highly uncertain.
What alternative approach has the EAG suggested?	The EAG undertook sensitivity analyses exploring alternative methodological approaches and assumptions for both dichotomous and continuous NMA outcomes included within the company's economic model (see Section 3.5). These sensitivity analyses included conducting both random-effects and fixed-effect frequentist analyses instead of using a Bayesian approach, as well as conducting a fixed-effect Bayesian approach with RR as the summary statistic instead of an OR for dichotomous outcomes. The EAG were unable to satisfactorily run a random-effects Bayesian model with RR as the summary statistic. The EAG's sensitivity analyses did not change the NMAs findings; rather they highlighted the 95% CIs were still substantially wide and that the estimates are highly uncertain.
What is the expected effect on the cost effectiveness estimates?	Due to the uncertainties and lack of additional available data, the EAG are unable to comment on whether more evidence would either increase or reduce the ICERs.

Report section	Sections 3.3.4, 3.5
What additional evidence or analyses might help to resolve this key issue?	Further comparable evidence between elafibranor and OCA 5-10 mg or UDCA monotherapy, either within direct head-to-head comparisons or to add to indirect treatment comparisons, may potentially increase the certainty of the clinical effectiveness of elafibranor.
Abbreviations: CI = confidence interval; CrI = credible interval; EAG = Evidence Assessment Group; ICER = incremental cost-effectiveness ratio; NMA = network meta-analysis; OCA = obeticholic acid; UDCA = ursodeoxycholic acid	

Table 1.3: Key issue 2: Uncertainty and lack of validation in the economic model's survival predictions

Report section	Section 4.3.3
Description of issue and why the EAG has identified it as important	The EAG is concerned that survival predictions from the economic model, whether it is liver-disease free, transplant free, or overall survival were not validated with clinical experts during the company submission. Moreover, there was little validation of survival with published evidence. The EAG is concerned the model is under-predicting the proportion of patients who are free of liver disease.
What alternative approach has the EAG suggested?	The EAG has suggested changing the approach to including the excess mortality risk for high-risk patients and testing scenario analyses removing transitions from moderate risk to liver disease or reducing the treatment effect on discontinuation (which is a primary factor in the transitions towards high-risk of liver disease).
What is the expected effect on the cost effectiveness estimates?	If the proportion of patients who develop liver disease is lower than the predictions from the model, the potential QALY gain and costs saved associated with the treatment may be lower than those currently predicted.
What additional evidence or analyses might help to resolve this key issue?	The model predictions could be validated with clinical experts and published literature.
Abbreviations: EAG = Evidence Assessment Group	

Table 1.4: Key issue 3: All-cause discontinuation predictions for OCA determining cost-effectiveness in the economic model

Report section	Section 4.3.4.2
Description of issue and why the EAG has identified it as important	Treatment discontinuation is the primary driver of cost and QALY outcomes in the economic model. The proportion of patients stopping OCA treatment predicted by the model were considered high when compared to clinical expert opinion and external data. The EAG believes the cause of this could partly be down to the assumption that the difference in discontinuation rates between elafibranor and OCA continues indefinitely.

Report section	Section 4.3.4.2
What alternative approach has the EAG suggested?	Opting for a one-year duration in the difference in discontinuation rates between OCA and elafibranor rather than a lifetime duration led to better discontinuation predictions for OCA. The EAG also evaluated a scenario with different outcomes for third-line UDCA after discontinuation of second-line treatment.
What is the expected effect on the cost effectiveness estimates?	Assuming a 1-year duration of a difference in discontinuation rates would increase the cost of OCA treatment, decrease the cost of liver disease in the OCA arm, and increase the discounted QALYs of OCA because patients would remain on OCA for longer.
What additional evidence or analyses might help to resolve this key issue?	Observational evidence on treatment discontinuation for both elafibranor and OCA.
Abbreviations: EAG = Evidence Assessment Group; OCA = obeticholic acid; UDCA = ursodeoxycholic acid	

Table 1.5: Key issue 4: Appropriate utility value for the high-risk biomarker health state in the economic model

Report section	Section 4.3.5.1
Description of issue and why the EAG has identified it as important	A utility value was elicited using the EQ-5D questionnaire in the ELATIVE trial for the high risk biomarker state, while the company base-case analysis used a value from the published literature. There was a noticeable difference between the values obtained in the trial compared to the literature for the high-risk of liver disease state in the model. There was also considerable variation in utility estimates for compensated cirrhosis in the literature. The EAG is concerned that trial utility values were only explored for the mild-risk and moderate-risk patients as a scenario analysis, particularly when utility values at the high-risk had an impact on overall results while being highly uncertain. Therefore, exploring the full parametric uncertainty for the high-risk utility value may be informative for decision-making.
What alternative approach has the EAG suggested?	The EAG has presented a scenario analysis using trial values across all the PBC biomarker risk of liver disease states. Moreover, the EAG adopted a high-risk utility value from a more recent published source, a systematic review with a meta-analysis that includes the study referenced for the estimate used in the CS.
What is the expected effect on the cost effectiveness estimates?	A higher utility for the high risk biomarker state would increase discounted QALYs more in the OCA arm than in the elafibranor arm, thus decreasing the cost-effectiveness of elafibranor.

Report section	Section 4.3.5.1
What additional evidence or analyses might help to resolve this key issue?	Observational evidence for the utility of patients in the high risk biomarker state.
Abbreviations: EAG = Evidence Assessment Group; PBC = primary biliary cholangitis; QALY = quality-adjusted life year	

1.4 Summary of the EAG's preferred assumptions and ICER

Table 1.6: Summary of EAG's preferred assumptions and ICER

Technologies	Total costs	Total QALYs	Incremental costs	Incremental QALYs	ICER (£/QALY)
CS base-case – Probabilistic					
Elafibranor	[redacted]	[redacted]	[redacted]	[redacted]	Elafibranor dominating
OCA	[redacted]	[redacted]	[redacted]	[redacted]	
Fixing errors (1-8) – Probabilistic					
Elafibranor	[redacted]	[redacted]	[redacted]	[redacted]	Elafibranor dominating
OCA	[redacted]	[redacted]	[redacted]	[redacted]	
EAG base-case – Probabilistic					
Elafibranor	[redacted]	[redacted]	[redacted]	[redacted]	Elafibranor dominating
OCA	[redacted]	[redacted]	[redacted]	[redacted]	
Abbreviations: CS = company submission; EAG = Evidence Assessment Group; ICER = incremental cost-effectiveness ratio; QALY = quality-adjusted life year; OCA = obeticholic acid					

Table 1.7: Summary of key EAG scenario analysis results – deterministic analysis: elafibranor versus OCA

Scenario #	EAG base-case input	Alternative input	Incremental costs (£)	Incremental QALYs	ICER (£/QALY)
	EAG base-case	N/A	[redacted]	[redacted]	Elafibranor Dominating
2	Treatment difference on discontinuation for 1 year	No treatment difference on discontinuation	[redacted]	[redacted]	Elafibranor Dominating
4	Literature values for PBC biomarker state utilities	Trial values for PBC biomarker state utilities	[redacted]	[redacted]	Elafibranor Dominating
7	All-cause discontinuation risk function: lognormal	All-cause discontinuation risk function: Gompertz	[redacted]	[redacted]	Elafibranor Dominating
9		All-cause discontinuation risk function: Exponential	[redacted]	[redacted]	Elafibranor Dominating
12	UDCA probabilities after one year	UDCA probabilities after one year	[redacted]	[redacted]	Elafibranor Dominating

Scenario #	EAG base-case input	Alternative input	Incremental costs (£)	Incremental QALYs	ICER (£/QALY)
	follow the probabilities seen in months 9-12	follow the average probabilities of the first 12 months including probabilities to improve PBC risk			
13	Treatment effectiveness definition: Cholestasis response	Treatment effectiveness definition: ALP normalisation	[redacted]	[redacted]	Elafibranor Dominating
14		Treatment effectiveness definition: Barcelona criteria	[redacted]	[redacted]	Elafibranor Dominating
15		Treatment effectiveness definition: Paris II	[redacted]	[redacted]	Elafibranor Dominating

Abbreviations: EAG = Evidence Assessment Group; ICER = incremental cost-effectiveness ratio; QALY = quality-adjusted life year; OCA = obeticholic acid

2 CRITIQUE OF COMPANY'S DEFINITION OF DECISION PROBLEM

Table 2.1: Statement of the decision problem (as presented by the company)

	Final scope issued by NICE	Decision problem addressed in the company submission	Rationale if different from the final NICE scope	EAG comment
Population	Adults with primary biliary cholangitis (PBC) whose disease has an inadequate response to, or who are unable to tolerate, ursodeoxycholic acid (UDCA).	As per the final scope	N/A	**Some concerns** The inclusion criteria of the ELATIVE trial does not prohibit participants who have received prior treatments other than UDCA, although prior OCA treatment is unlikely. This means some participants may have been receiving elafibranor as a third-line treatment in the trial; e.g. if they have potentially previously used OCA. Furthermore, clinical advice to the EAG noted that it may not be appropriate to combine those who are intolerant to UDCA and those who do not respond to UDCA in a single analysis, as these are two clinically heterogenous populations, though almost all data are for the non-response population. See Section 2.1 for further details.
Intervention	Elafibranor alone or in combination with UDCA.	As per the final scope	Elafibranor treatment with and without UDCA (determined according to tolerability to UDCA) are not considered separately in the company submission as the ELATIVE trial population is representative of the distribution of patients treated with and without UDCA in clinical practice.	**Appropriate** The EAG's concerns surrounding the stratification of those who do not respond to UDCA and those intolerant to UDCA are described in Section 2.1. The EAG find the intervention in the ELATIVE trial to be in line with the NICE scope.

	Final scope issued by NICE	Decision problem addressed in the company submission	Rationale if different from the final NICE scope	EAG comment
Comparator(s)	For people whose disease has an inadequate response to UDCA: Obeticholic acid (OCA) in combination with UDCA UDCA monotherapy For people who are unable to tolerate UDCA: OCA monotherapy Best supportive care	As per the final scope	As stated above, subgroups according to patient response to UDCA and/or tolerability to UDCA are not considered separately in the company submission as the ELATIVE trial population is representative of the distribution of patients treated with and without UDCA in clinical practice. Thus, the comparators presented are UDCA and OCA 5-10mg dose with UDCA (where a proportion of both arms do not receive UDCA, which represents the cohorts receiving OCA only and no treatment). To note, only approximately 5% of patients are unable to tolerate UDCA, as reflected in the proportions of patients in the elafibranor and OCA trials. [3-6] Any best supportive care treatment other than OCA 5-10 mg has not been recommended by NICE and therefore will not be considered in the submission.	**Some concerns** The EAG asked the company to clarify the meaning behind "*best supportive care treatment other than OCA 5-10 mg*" and has concerns that relevant comparators used within clinical practice may have been missed from the submission as a result. See Section 2.3 for further details.
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	As per the final scope	All outcomes have been addressed throughout the company submission, as follows: As outcomes of the ELATIVE trial, including outcomes based on liver function biomarkers, occurrence of pruritus symptoms and adverse events, and health-related quality-of-life (Section **Error! Reference**	**Appropriate** The company further clarified the reasoning for a composite of surrogate outcomes to measure the primary outcome in the ELATIVE trial in their response to the points for clarification (PfCs); the EAG were satisfied with their response. Furthermore, although mortality was not measured as an outcome measure in the ELATIVE trial,

	Final scope issued by NICE	Decision problem addressed in the company submission	Rationale if different from the final NICE scope	EAG comment
	PBC-related events, including ascites, varices, encephalopathy, and hepatic cell carcinoma adverse effects of treatment health-related quality-of-life		**source not found.** and **Error! Reference source not found.**). As outcomes of the cost-effectiveness model, which captures patient mortality, outcomes according to liver function biomarkers, pruritus, adverse events, liver transplantation, health-related quality-of-life, and PBC disease-specific health states, including hepatocellular carcinoma and decompensated cirrhosis [including PBC-related events such as ascites, varices, encephalopathy] (Section **Error! Reference source not found.**).	deaths were reported as an adverse event and mortality was considered in the economic model by using life years and QALYs.
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. If the technology is likely to provide similar or greater health benefits at similar or lower cost than technologies recommended in published NICE technology appraisal guidance for the same indication, a cost comparison may be carried out. The reference case stipulates that the time horizon for estimating clinical and cost-	As per the final scope	N/A	**Some concerns** The company presented an incremental cost-utility analysis using QALYs in accordance with the reference case and the final scope. The population in the scope is limited to patients who have not responded to UDCA or are intolerant to UDCA. The company's economic analysis was consistent with this population. The EAG assumes that cost-effectiveness of elafibranor was not evaluated at third-line treatment as it was outside the scope and there was no effectiveness evidence at third-line. Elafibranor and OCA could

	Final scope issued by NICE	Decision problem addressed in the company submission	Rationale if different from the final NICE scope	EAG comment
	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.			have been included as third-line treatments in the evaluation of cost-effectiveness of elafibranor at second-line, but the same evidence issues apply.
Subgroups to be considered	None	None	As stated above, subgroups according to patient response to UDCA and/or tolerability to UDCA are not considered separately in the company submission as the ELATIVE trial population is representative of the distribution of patients treated with and without UDCA in clinical practice.	None
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.	As per the final scope	N/A	**Appropriate** As per the NICE scope.

Source: CS Section B.1.1, Table 1, p.12-3[1]; PfC response[7]

Abbreviations: CS = company submission; EAG = Evidence Assessment Group; N/A = not applicable; NHS = National Health Service; NICE = National Institute for Health and Care Excellence; OCA = obeticholic acid; PBC = primary biliary cholangitis; PfC = points for clarification; QALY = quality-adjusted life year; UDCA = ursodeoxycholic acid

2.1 Population

2.1.1 Lines of therapy

The clinical advisor to the EAG indicated that elafibranor could plausibly be positioned as a third-line treatment. The company are positioning elafibranor as a second-line treatment for PBC in people who do not respond to or are intolerant to UDCA see company submission (CS) Section B.1.3.5, Figure 14, p.41.[1] However, the inclusion criteria of the ELATIVE trial does not prohibit participants from receipt of prior second-line therapy, such as OCA (CS Section B.2.3.1, Table 6, p.48-9). As such, the EAG cannot be certain that the participants in the ELATIVE trial are all receiving either elafibranor or placebo with or without UDCA as a second-line treatment, as opposed to third-line treatment, although prior OCA treatment seems unlikely.

2.1.2 Handling of participants who do not respond to, or are intolerant to, UDCA

The EAG asked the company to provide additional information on the distribution of participants who had an inadequate response to UDCA or who were intolerant to UDCA (PfC A8). The company responded that the population enrolled in ELATIVE trial was representative of a typical population of patients with PBC who have inadequate response and/or intolerance to UDCA and that, at baseline, 95% of participants in the trial were on concurrent UDCA and the remaining 5% were intolerant to UDCA.[7] As clinical advice to the EAG suggested that around 3-5% of patients with PBC are intolerant to UDCA, the EAG are satisfied that the proportion of participants intolerant to UDCA in ELATIVE is representative of clinical practice.

The clinical advisor to the EAG agreed that the trial population seemed reflective of the population seen within UK clinical practice. However, the participants unresponsive to UDCA and participants intolerant to UDCA can be considered two clinically different populations. The company did not stratify analyses of the ELATIVE trial by whether participants respond to treatment with UDCA or whether they could not tolerate UDCA. The majority of participants in the ELATIVE trial were taking UDCA at baseline (95.0%; CS Section B.2.3.2, p.50).[1] Although both the EAG and the clinical advisor appreciate that the overall sample size in ELATIVE may have prohibited stratification, pooling both populations means the effect of elafibranor on those intolerant to UDCA compared with those who do not respond to UDCA is uncertain.

2.2 Comparators

In the CS, the company stated: "*Any best supportive care treatment other than OCA 5-10 mg has not been recommended by NICE and therefore will not be considered in the submission*" (CS Section B.1.1, Table 1, p.12).[1] Clinical advice to the EAG noted that the term "best supportive care" (BSC) was not usually used in reference to PBC patients and, if used, that it is likely done in the context of end of life care (for example, when treating people with decompensated cirrhosis). The EAG asked the company to clarify their statement from the decision problem (PfC C2). The company responded: *"The current wording of this statement is incorrect as it does imply that OCA 5-10mg is considered a supportive treatment which the company does not agree with. The statement should be amended to: "OCA 5-10 mg as a second-line treatment is the standard of care for patients with PBC. Any treatment used in best supportive care has not been recommended by NICE nor does it provide the standard of care; therefore, any best supportive care will not be considered in the submission"."*[7] The EAG are satisfied that this clarification confirms that OCA was not considered BSC in the submission.

Following the NICE scope, the company did not include alternate fibrates within their submission (CS Section B.1.1, Table 1, p.13).[1] However, in terms of use of fibrates, a recent UK-wide audit suggested that, of the 1074 participants with PBC who received second-line treatment, 571 received either bezafibrate or fenofibrate.[8] Clinical advice to the EAG suggested that fibrates can be used to treat people with PBC who also experience itch, meaning a small number of people may take a combination of UDCA, OCA and bezafibrate within specialist centres.

3 CLINICAL EFFECTIVENESS

3.1 Critique of the methods of review(s)

The CS describes a systematic literature review (SLR) conducted to identify evidence on the effectiveness and safety of elafibranor and relevant comparators for treating PBC. A summary of the EAG's critique is presented in Table 3.1 below. The EAG's assessments (detailed in bold) are on a three-point Likert scale (key issue, some concerns or appropriate).

Table 3.1: Summary of the EAG's critique of the clinical effectiveness systematic literature review

Systematic review stage	Section in CS where methods are reported	EAG's assessment of the robustness of methods
Data sources	Appendix D 1.1, p. 1-10	**Some concerns** The range of sources searched by the company was appropriate but the reason given for restricting the years for which conference proceedings were searched was unconvincing. The ClinicalTrials.gov results were restricted to those with results and conference proceedings were excluded from Embase searches which could have missed relevant studies. See Section 3.1.1.1 for further details.
Search strategies	Appendix D 1.1, p. 1-10	**Some concerns** The search strategies were appropriate but focusing thesaurus headings increases specificity to the detriment of sensitivity. See Section 3.1.1.2 for further details.
Search filters	Appendix D 1.1, p. 1-10	**Appropriate** Search filters adequately captured the decision problem. (In response to the clarification letter the company stated that the search filters used were those designed by the Scottish Intercollegiate Guidelines Network (SIGN)).
Eligibility criteria	Appendix D.1, p.1; D.1.1, Table 9 (p. 10-2)	**Some concerns** The EAG has some concerns about the review question, the eligible study designs, and other eligibility criteria listed in Appendix D, Table 9. The EAG also note that the protocol for the SLR was not provided within the company submission and asked the company to clarify this. See Section 3.1.2 below for further details.
Screening	Appendix D1.2, p.12; D1.3, p.14	**Some concerns** The EAG have some concerns regarding the company's screening process, particularly surrounding the handling of studies that lacked available information and RCTs with mixed lines of treatment. Please see Section 3.1.3 for further details.
Data extraction	Appendix D1.2, p.12-3	**Some concerns** It is unclear from the CS whether the data extraction form was piloted. Furthermore, the EAG have some concerns about the data extraction process and the

Systematic review stage	Section in CS where methods are reported	EAG's assessment of the robustness of methods
		company did not provide a copy of the data extraction form. See Section 3.1.4 for further details.
Quality appraisal	Appendix D1.2, p.13	**Some concerns** The EAG have concerns about the appropriateness of the chosen quality appraisal tool in the review for all types of study designs. Moreover, the EAG have some concerns surrounding how the quality appraisal was performed. See Section 3.1.5 for further details.
Abbreviations: CS = company submission; EAG = Evidence Assessment Group; RCT = randomised controlled trial; SIGN = Scottish Intercollegiate Guidelines Network; SLR = systematic literature review		

3.1.1 Search methods for the clinical effectiveness SLR

The company conducted separate searches for clinical effectiveness studies (presented in the CS Appendix D),[9] and cost effectiveness, HRQoL and cost and resource use studies (CS Appendix G).[10] The EAG used the PRESS checklist to appraise the search strategies.[11] In this section, we present the critique of the search methods for clinical effectiveness studies. The critique of searches for cost effectiveness studies, HRQoL studies and cost and resource use is presented in Section 4.1. As some of the issues were the same for all the searches there are cross references to the relevant section to avoid repetition. The searches were based on terms related to the condition with the application of a study design (or research type) search filter(s) in some of the electronic bibliographic databases. The searches were first run in November 2022 and were updated in December 2023, so are considered up to date.

3.1.1.1 Data Sources

The company excluded conference proceedings in Embase, which could have led to the exclusion of relevant records. However, the EAG's clinical advisor confirmed that the two main conferences in the area had been covered by the company's hand searches. The company stated that: "*the exclusion of abstracts from conferences prior to 2021 was justified under the assumption that high-quality research would since have been published in a peer-reviewed journal*" (Appendix D.1.1, p.10).[9] This may not have been the case, as there may be other reasons for non- or slow-publication (such as results not being perceived as 'positive', direction of effect of result(s), lack of statistical significance of results and non-English language) as well as the potential effect of the COVID-19 pandemic on speed of publication of non-COVID-19 related results. However, conference searching could have been more expansive in this respect.[12,13] The ClinicalTrials.gov search was limited to those records with study results posted, which may have resulted in the exclusion of some relevant studies.

3.1.1.2 Search strategies

Bibliographic searches typically focussed on five terms related to the condition: biliary liver cirrhosis; primary biliary cholangitis; primary biliary cholestasis; primary biliary cirrhosis; and PBC. The EAG have some concerns regarding this, as search terms were not as broad as they could have been, resulting in a search strategy that was more specific than sensitive. Search terms need to be as comprehensive as possible to avoid missing potentially relevant

studies. Truncation could have been used when searching to capture plurals. The company did not always include MeSH terms as free-text terms (e.g. the MeSH heading 'Liver Cirrhosis, Biliary' was not translated into free-text terms). Focused MeSH (MEDLINE) and Emtree (Embase) terms were used in the search string. For example, in MEDLINE there was a focus on the heading 'Liver Cirrhosis, biliary.' Focusing this heading could lead to the exclusion of any studies that discuss liver cirrhosis but where this heading was not identified as the focus of the paper. The five terms used for bibliographic database searching were not used consistently when searching conference abstracts and health technology assessment (HTA) websites. The term 'primary biliary cholestasis' was not included in conference and HTA search strings, which could have resulted in these searches missing key reports.

3.1.2 Eligibility criteria

3.1.2.1 SLR protocol

The EAG have concerns about whether a pre-defined eligibility criteria within the SLR were adhered to. Firstly, the company state: "*The SLR was performed in accordance with a pre-specified protocol*" (CS Appendix D.1, p.1).[9] However, the company did not provide a copy of the protocol and it is not stated within the CS whether the protocol was published or registered on a database (e.g. PROSPERO). Having sight of an a-priori published review protocol is usually the only possible way to assess whether pre-defined eligibility criteria have been adhered to.[14] As such, it is difficult for the EAG to assess whether predefined eligibility criteria were adhered to during the review process and therefore, there is possibility of selection bias in the SLR.[15]

3.1.2.2 Included study designs

In Appendix D (Section D.1, p.1), the review question is stated as: "What randomised control trials (RCTs) have been conducted that evaluate the efficacy and/or safety of elafibranor and other comparators of interest in patients with PBC?"[9] However, within the inclusion criteria for the SLR, non-randomised interventional studies and observational studies are listed as included (Appendix D, Table 9, p.11).[9] As a well-formulated review question guides all aspects of the SLR, including setting the eligibility criteria,[16] the EAG asked the company to clarify this point (PfC A4). The company responded: "*Ultimately, only RCT study designs were included for data extraction; […] The only exception to this was data for studies of elafibranor itself, wherein all study designs containing summary clinical data were eligible for inclusion*." [7] The EAG have concerns regarding this, as the review questions and eligibility criteria should be clearly defined before starting the review and adhered to throughout the review process unless there is a justifiable reason to deviate from these criteria, which should be transparently stated.

3.1.2.3 Interventions and comparators

The list of comparators in Appendix D (Table 9) describes "*any other comparators (or none)*" as eligible.[9] As it was unclear to the EAG what these other comparators were, the EAG asked the company to clarify this point (PfC A5). The company responded: "*It was also anticipated that some interventional studies may look to compare different dosing regimens of the same investigational drug, hence the breadth. Under this definition, both UDCA and OCA would be covered under "any other comparators" (either could also be argued under "standard of care")."*[7] As these treatments are the current standard of care for PBC, [6,17] the EAG are satisfied with this response. However, it is unclear to the EAG what other interventions were

eligible for the SLR and whether the listed interventions were eligible to be included in the broader SLR only, or only in the SLR submitted for NICE.

3.1.2.4 Other limitations in the eligibility criteria

Eligible studies in the company's SLR were those published in English (Appendix D, Table 9, p.12).[9] As it has been suggested that studies conducted in non-English speaking countries are more likely to be published in English journals if they have statistically significant results than studies with insignificant results,[18] it is possible that potentially eligible studies may have been excluded from the SLR.

Furthermore, the company limited the included RCTs identified on ClinicalTrials.gov to trials with results only (Appendix D, Tables 7 and 8, p.10).[9] The Cochrane Handbook states: "*Searches for studies should be as extensive as possible in order to reduce the risk of publication bias and to identify as much relevant evidence as possible*." [19] Therefore, there is a chance of publication bias in the SLR if relevant RCTs were excluded.

3.1.3 Screening

In Appendix D (Section D.1.2, p.12), it is stated that: "*In cases where the article did not give enough information to be sure it met the inclusion criteria; it was excluded to ensure that only relevant articles were ultimately included in the SLR*".[9] It was unclear to the EAG whether the company attempted to contact authors of studies that lacked enough information; therefore, the EAG asked the company to clarify this point (PfC A6). The company responded: "*This was not conducted, though no instances where this may have been the only option to obtain missing data were noted with the data that were ultimately extracted in this review."*[7] However, this is not consistent with what is reported in Appendix D (Section D.1.2, p.12). Not including some studies that might be relevant due to limited information in the publication may lead to reporting bias in an SLR. Contacting authors of the primary studies is, therefore, important to enhance the precision and completeness of the review and decrease the chance of missing information and the consequential impact of reporting bias.[20]

In Appendix D (Section D.1.3, p.14), it is stated that: "*181 records reporting on observational studies in a first-line or mixed treatment line setting being deprioritised*."[9] Furthermore, in Appendix D (Table 9, p.12) it is stated that: "*Any studies of elafibranor, and RCTs in the second-line or later treatment setting were then prioritised for extraction".*[9] It is unclear to the EAG whether the company included RCTs with mixed lines of treatments where results of eligible treatment lines were reported separately. If the results of any such studies were not considered in the SLR, this may have led to potentially eligible studies being excluded from the SLR and consequently, this could possibly have impacted the NMA and subsequently the economic model.

3.1.4 Data extraction

It is unclear if the data extraction form was piloted; moreover, the company did not provide a copy of the data extraction form (Appendix D, section D.1.2, p.12-13).[9] It is mentioned in Appendix D (Section D.1.2, p.12) that a single individual extracted the data and a second individual verified the extracted data independently and checked that no relevant information was missing. Although this is considered an acceptable minimum, this approach could lead to significantly higher chance of error than two researchers extracting the data independently.[18]

3.1.5 Quality appraisal

Eligible studies in the company's SLR included both observational studies and RCTs (Appendix D, Table 9, p.11). However, the company's quality appraisal of included studies focused on the Centre for Reviews and Dissemination's (CRD's) quality assessment tool, which is mainly used for interventional studies. It is therefore unclear how the quality of observational studies would have been assessed. Furthermore, it is unclear whether the quality assessment tool was piloted and it is reported that the quality assessment was performed by one individual and verified by another reviewer independently.[9] As critical appraisal can be open to subjectivity, the CRD's guidance recommends piloting the use of the quality appraisal tool and by having two researchers perform the process independently.[18] This helps minimise the error in quality assessment and the influence of individual preconceptions.[21] As such, the EAG believes the quality appraisal process may have been open to greater subjectivity or error and, consequently, the judgements regarding the included studies and the interpretations of findings might be inaccurate or inappropriate.[22]

3.2 Critique of trials of the technology of interest, their analysis and interpretation (and any standard meta-analyses of these)

A summary of the EAG's critique of the design, conduct and analysis of the ELATIVE trial is presented in Table 3.2.

Table 3.2: Summary of EAG's critique on the design, conduct and analysis of the ELATIVE trial

Trial design or conduct concept	Section in CS where methods are reported	EAG's assessment
Intervention	B.2.3.1, Table 6, p.49	**Appropriate** The intervention in the ELATIVE trial was elafibranor 80 mg with or without concomitant UDCA therapy. The EAG agrees this is in line with the NICE decision problem.
Comparator	B.2.2.1, Table 6, p.48; B.1.1, Table 1, p.8; PfC A8	**Appropriate** According to the CS, the comparator in the trial was a placebo, with or without UDCA; as 95% of participants were taking UDCA, the EAG is satisfied that the ELATIVE trial adequately matches the NICE decision problem.
Randomisation	B.2.3.1, Table 6, p. 48	**Appropriate** The CS reported that the ELATIVE trial was randomised but did not report on the method of randomisation. However, a journal article associated with the ELATIVE trial describes the randomisation method.[4] As such, the EAG is satisfied that randomisation in the ELATIVE trial was appropriate.
Allocation concealment	B.2.3.1, Table 6, p.177	**Some concerns** There was limited information on the method or process of allocation concealment in the trial; allocation method but not concealment method was reported in

Trial design or conduct concept	Section in CS where methods are reported	EAG's assessment
		the protocol within an associated article.[4] The EAG have concerns that inadequate allocation concealment can introduce selection bias and a possible overestimation of effects. See section 3.2.1 for further details
Eligibility criteria	B.2.3.1, Table 6, p.48-9	**Appropriate** Eligible participants were adults aged 18 to 75 years with PBC who had an inadequate response to, or were unable to tolerate, UDCA. The demographic variables are similar to the UK population and key prognostic factors were captured. The EAG believes the eligibility criteria for the trial was in line with the NICE decision problem.
Blinding	B.2.3.1, Table 6, p.48-9	**Appropriate** The CS notes that the trial was double blinded but there were no details of the approach used. However, an article associated with the ELATIVE trial reported that the investigator, participants and study personnel were blinded to treatment.[4] Accordingly, the EAG is satisfied that blinding in the ELATIVE trial was adequate.
Baseline characteristics	B.2.3.2, Table 7, p.50-1	**Appropriate** The company stated that: "*Treatment arms were well balanced for each key demographic and baseline variable*." The clinical advisor agreed that the population characteristics were well balanced across the treatment groups. The EAG therefore considers that this is appropriate.
Dropout rate	B.2.3.3.1, Figure 17, p.52	**Appropriate** Across both arms of the ELATIVE trial, the discontinuation rate was under 20%. As such, the EAG has no concerns about the dropout rate.
Statistical analyses	B.2.4.2, p.53-6	**Appropriate** The statistical analyses were appropriate to detect effects.
Outcome measures	B.2.3.1, Table 6, p. 48-9; PfC A9	**Appropriate** The company used surrogate composite endpoints (ALP ≤ 1.67 x ULN, TB ≤ ULN, and ALP decrease ≥15%) indicative of cholestatic response as the primary outcome. The EAG asked the company to justify this choice of primary outcome and comment on whether alternative measures could have been used. The company clarified the reasoning for a composite of surrogate outcomes to measure the primary outcome in the ELATIVE trial in the PfCs; the EAG were satisfied with their response. Furthermore, although mortality was not measured as an outcome measure in the ELATIVE trial, deaths were reported as an adverse event and mortality was considered in the economic model by using life years and QALYs.

Trial design or conduct concept	Section in CS where methods are reported	EAG's assessment
Results: Efficacy outcomes	B.2.6, p.56-61	**Appropriate** The EAG has no concerns about the reporting of efficacy outcomes in the ELATIVE trial.
Results: Adverse events	B.2.10, Tables 25-26, p.90-92	**Appropriate** The EAG has no concerns about the reporting of adverse events in the ELATIVE trial.
Results: Subgroup analyses	B.2.7, p.66-9. PfC A8	**Some concerns** The subgroups 'inadequate response' and 'unable to tolerate UDCA' were not considered in the ELATIVE trial subgroup analysis. The EAG asked the company to provide additional information on the distribution of participants who had an inadequate response to UDCA or were unable to tolerate UDCA in the trial. See section 3.2.5 for further details.
Abbreviations: ALP = alkaline phosphatase; CS = company submission; EAG = Evidence Assessment Group; NICE = National Institute for Health and Care Excellence; OCA = obeticholic acid; PBC = primary biliary cholangitis; PfC = points for clarification; TB = total bilirubin; UDCA = ursodeoxycholic acid; ULN = upper limit of normal		

3.2.1 Allocation concealment

The process and methods for concealing allocation was not reported in the CS, though the protocol provided as supplementary material to an associated article describes how allocation took place (protocol section 7.4).[44] However, the method of concealing allocation is unclear.[4] The EAG is concerned whether treatment allocation was adequately concealed, as this is important in preventing any potential bias in the reporting of subjective outcomes, such as for the PBC-40 questionnaire.[23]

3.2.2 Results: Subgroup analyses

Subgroups stratifying the population between those who had an inadequate response to UDCA and those who were unable to tolerate UDCA were not considered in the ELATIVE trial as the company stated that trial population was representative of the distribution of patients treated with and without UDCA in clinical practice (CS Section B.1.1, Table 1, p.12) The EAG asked the company to provide additional information on the distribution of participants who had an inadequate response to UDCA or were unable to tolerate UDCA in the trial (PfC A8). The company responded that the ELATIVE trial enrolled a population representative of a typical population of patients with PBC in need of second-line therapy, reporting that 95% of participants in the trial (153/161) were using UDCA concurrently, while the 5% (8/161) of participants who were intolerant to UDCA received elafibranor monotherapy or placebo.[7] Clinical advice to the EAG noted those who are intolerant to UDCA and those who do not respond to UDCA are two clinically different populations, but appreciated that numbers in these subgroups may have been too small to facilitate stratified analysis. The EAG agrees that, although such subgroup analyses may have facilitated understanding of the effectiveness of elafibranor for these two population groups, the overall numbers of participants who were unable to tolerate UDCA was too low to be able to facilitate this stratification.

3.3 Critique of trials identified and included in the indirect comparison and/or multiple treatment comparison

The company conducted an network meta-analysis (NMA) between the ELATIVE and POISE trials to indirectly compare the effectiveness of elafibranor against obeticholic acid (OCA). A summary of the EAG's critique of the NMA is provided in **Error! Reference source not found.**.

Table 3.3: Summary of the EAG's critique of the company's indirect comparisons

Aspect of NMA design or conduct	Section in CS where methods are reported	EAG's assessment
Statistical methods	B.2.9.1, p.70-1; Appendix D.1.5, p.87-101; PfCs A10, A16, A17, A18	**Some concerns** The company conducted an NMA to assess the effectiveness of elafibranor and OCA. The EAG have concerns with regards the appropriateness of conducting an NMA when only two studies were included. Furthermore, the EAG asked the company to clarify multiple points surrounding the statistical methods, including the choice of priors, the presentation of the DICs and SUCRAs, and the methods used to assess heterogeneity. See Section 3.3.1 for further details.
Included and excluded studies	Appendix D.1.4.2 and Appendix D.1.4.2.1, p.63-82; PfC A13 and A14	**Some concerns** The EAG questioned why the COBALT trial had been excluded from the NMA and whether the company had contacted the study authors to obtain information to ascertain eligibility. Furthermore, the EAG also questioned whether data from the phase II trial of elafibranor and of OCA could have been used to inform analyses where the time-point used was the earliest measured within the trials.[24,25] See Section 3.3.2 for further details.
Included study characteristics and demographics	Appendix D.1.4.2.2, Table 27, p.86	**Appropriate** Clinical advice to the EAG considered that the baseline demographics of both trials were balanced enough to feasibly permit pooling.
Transitivity assumption	PfC A15	**Some concerns** The EAG asked the company to comment on the transitivity assumption within the NMA in the PfCs. The company stated that the distribution of treatment effect modifiers within ELATIVE and POISE were similar, meaning the transitivity assumption was not violated. However, the EAG note that data were not available for a key effect modifier ANA positive status. See Section 3.3.3 for further details.
Results	B.2.9.1.1 to B.2.9.1.11, p.72-86	**Key issue 1** Results of the NMAs feeding into the company's economic model were highly uncertain due to wide CrIs and the EAG have some concerns that the use of ORs

Aspect of NMA design or conduct	Section in CS where methods are reported	EAG's assessment
		to assess dichotomous outcomes instead of RRs may have overestimated effectiveness. See Section 3.3.4 for further details. **Some concerns** Although included in the decision problem, fatigue was not included as an outcome within the company's NMAs. See Section 3.3.4 for further details.
Subgroup analyses	PfC A21	**Appropriate** The EAG asked the company to clarify whether subgroup analyses were planned or performed, the company confirmed that no subgroup analyses were performed for the NMAs. Given that the decision problem did not specify any subgroups, the EAG considers this appropriate.
Sensitivity analyses	Appendix D, PfC A22	**Some concerns** Only a sensitivity analysis changing the NMA structure from random effects to fixed effects was undertaken in the CS. The EAG asked the company to clarify whether any other sensitivity analyses were planned or performed. The company noted that no further sensitivity analyses were performed, therefore the EAG conducted their own sensitivity analyses by changing dichotomous outcomes from ORs to RRs. See Sections 3.3.4.3 and 3.4 for further details.
Abbreviations: ANA = antinuclear antibodies; CrI = credible interval; CS = company submission; DIC = Deviance Information Criterion; EAG = Evidence Assessment Group; NMA = network meta-analysis; OCA = obeticholic acid; OR = odds ratio; PfC = points for clarification; RR = risk ratio; SUCRA = Surface Under the Cumulative RAnking curve		

3.3.1 Statistical methods

3.3.1.1 Rationale for conducting an NMA

In the absence of head-to-head evidence between elafibranor and OCA, the company conducted an NMA between the ELATIVE and POISE trials. The EAG asked the company to clarify the rationale behind conducting an NMA when only two studies were considered relevant to the decision problem (PfCs, A10). The company responded that the rationale for choosing an NMA was provided in Appendix D (Sections D.1.4.1 to D.1.4.3) and briefly summarised in the CS (Section B.2.9).[1,7,9] The company noted that the NICE Decision Support Unit (DSU) recommends a Bayesian approach to NMA and, because the network connected elafibranor to OCA 5-10 mg and ELATIVE and POISE were considered sufficiently homogenous by the company's clinical experts, an NMA was permissible.[26]

The EAG acknowledge that a Bayesian NMA is an appropriate methodology recommended by the NICE DSU.[26] Additionally, the EAG's clinical advisor confirmed that the POISE and

ELATIVE trials seemed sufficiently homogenous to pool. However, the company noted that there were issues with convergence in the random-effects NMA (Appendix D, Section D.1.5, p.89).[9] This is exemplified by the substantial number of burn-ins and iterations reported for each random-effects Bayesian NMA conducted. For example, the NMA for the primary outcome of 'Odds of achieving cholestasis response at 12 months' had a burn-in of [redacted], followed by [redacted] iterations with a thinning interval of [redacted] (CS Section B.2.9.1.1, Figure 30, p.72).[1] Furthermore, there is also a large amount of uncertainty in the results of the NMA (see Section 3.3.3). Given this, the EAG believe that the company could have explored other methodologies to compare the clinical effectiveness of elafibranor versus OCA 5-10 mg (such as an anchored matching-adjusted indirect comparison).

3.3.1.2 Choice of informative priors for pruritis outcomes

The company derived their choice of informed priors for the NMA from Turner et al (2015).[27] For the outcomes surrounding pruritis, the company chose to use the "Subjective outcomes" informative prior for the following outcomes (Appendix D.1.5, p.89).[9]

- Mean change from baseline in pruritis (5-D Itch) at 12 months
- Mean change from baseline in pruritis (5-D Itch) at 2-4 weeks
- Mean change from baseline in pruritis (PBC-40 Itch domain) at 12 months
- Mean change from baseline in pruritis (PBC-40 Itch domain) at 2-4 weeks

The EAG asked the company to explain the rationale behind applying this informative prior as opposed to the "Signs/symptoms reflecting continuation/end of condition" informative prior, given that pruritis can be seen as a symptom of PBC continuation (PfC A19).[28] The company responded that the measurement methods for assessing pruritis are not objective and that there are no biomarkers associated with PBC that directly correlate to the presence or severity or pruritis and, as such, subjective measurements (the PBC-40 Itch and 5-D Itch questionnaires) were used in both ELATIVE in POISE.[7] However, the EAG note that the paper by Turner et al (2015) lists "Signs/symptoms reflecting continuation/end of condition" as a subjective outcome (Table 3).[27] As such, the EAG believe that conducting a sensitivity analysis on these four outcomes using the alternative informative prior may have been justifiable.

As such, the EAG requested that the company re-run the NMAs for the pruritis outcomes listed above using the "Signs/symptoms reflecting continuation/end of condition" informative prior from Turner et al (2015; PfC A20).[27] The company responded by providing new analyses for these outcome measures using the "Signs/symptoms reflecting continuation/end of condition" informative prior from Turner et al (2015).[7,27] The EAG present a comparison of the results for elafibranor versus OCA 5-10 mg between the different priors in Table 3.4 below. The EAG are satisfied that there is little to no difference between results dependent on the choice of priors for the pruritis outcomes.

Table 3.4: Comparison of results for pruritis outcomes using company and alternative choice of priors

Outcome measure	Company prior: Subjective outcomes	Alternative prior: Signs/symptoms reflecting continuation/end of condition
Mean change from baseline in pruritis (5-D Itch) at 12 months	[redacted]	[redacted]

Mean change from baseline in pruritis (5-D Itch) at 2-4 weeks	[redacted]	[redacted]
Mean change from baseline in pruritis (PBC-40 Itch domain) at 12 months	[redacted]	[redacted]
Mean change from baseline in pruritis (PBC-40 Itch domain) at 2-4 weeks	[redacted]	[redacted]

Source: created by the EAG using data from CS Sections B.2.9.1.4, B.2.9.1.5, B.2.9.1.6 and B.2.9.1.7; and PfC A20.[1,7]
Abbreviations: CS = company submission; EAG = Evidence Assessment Group; PBC-40 = primary biliary cholangitis-40; PfC = points for clarification

3.3.1.3 Reporting of Deviance Information Criterion and Surface Under the Cumulative Ranking curve

The company did not report the Deviance Information Criterion (DIC) or Surface Under the Cumulative Ranking (SUCRA) curves for the NMAs in the original CS. The EAG asked the company to clarify why the DIC or SURCRA had not been presented (PfCs A16 and A17). For the query regarding the DICs (PfC A16), the company responded by providing a table outlining the DIC values for all NMAs, comparing the fit of the random effects model with the fixed effects model.[7] As also noted by the company in their response, a difference of less than three points suggests there is little difference between the models.[29] The EAG are satisfied that the DICs presented by the company suggest there is little difference in fit between the random and fixed effect models.

Regarding the SUCRAs (PfC A17), the company stated that they did not report these within the CS as it is not a requirement of the NICE DSU and they would not provide any additional information to differentiate beyond the summary statistics already presented.[7] The EAG acknowledge that SUCRAs are not mentioned in NICE DSU Technical Support Document 2 and appreciate that, in light of the small amount of treatments being compared within the NMAs, presenting SUCRAs may not have had any further benefit to presenting the summary statistics and posterior probabilities.[26]

3.3.1.4 Methods used to assess heterogeneity

In Appendix D (Section D.1.5, p.89), the company state: "*In order to truncate the priors on the continuous outcomes, different informative priors were identified to enable assessment of the between-study standard deviation on the standardised mean difference scale*." Given that this is not a standard method for assessing heterogeneity within NMAs, the EAG asked the company to provide a reference and explain the rationale behind using this method (PfC A18). The company responded by stating that the priors were truncated according to methodology recommended by Ren et al (2018) to prevent simulation of excessively large between-study variance and aid convergence in the NMAs.[7,30] The EAG believe that the use of the Ren et al (2018) methodology was appropriate.[30]

3.3.2 Included and excluded studies

3.3.2.1 Exclusion of the COBALT trial

Although most of the reasons for studies' exclusion from the NMAs given within Appendix D were deemed appropriate (Section D.1.4.2, Table 22), the company noted that the COBALT trial was excluded and stated: "*Study not published in full to facilitate balanced evaluation in the feasibility assessment*" (p.64).[9] As such, the EAG asked the company to clarify whether they had attempted to contact the authors of the COBALT trial to obtain the information required to ascertain its suitability for the NMA (PfC A13). The company responded that the COBALT trial was terminated early due to feasibility challenges where the data monitoring committee noted that the objectives of the trial were not feasible; the trial did not demonstrate a statistically significant difference in clinical endpoints between OCA and placebo and results were only reported as an abstract.[7,31]

The EAG acknowledge that the limited detail in the abstract would have made assessing the similarity of COBALT with ELATIVE and POISE difficult. However, the EAG asked the company to clarify whether they had asked the authors of the COBALT study for further information to be able to assess the suitability of the trial for NMA. The company did not provide this information for this question and, in a previous PfC response (A6), noted that contacting authors for information was not conducted.[7] As such, the EAG believe that the company could have contacted the authors of the COBALT study to ask about key effect modifiers, which may have allowed assessment of suitability for the NMA. In not doing so, it is possible that the company excluded a potentially eligible study from the NMA.

3.3.2.2 Exclusion of Schattenberg et al (2021) and Hirschfield et al (2015)

A phase II trial of elafibranor (Schattenberg et al 2021) and a trial of OCA (Hirschfield et al 2015) were also excluded from the company's NMAs.[24,25] The company excluded both studies because the ELATIVE trial was "*designed to evaluate efficacy after 12 months of treatment, studies which provide only 12 weeks of treatment would not be comparable in their outcomes*" (Section D.1.4.2.1, p.77).[9] However, the EAG asked the company to provide further rationale (PfC A14), given that some outcomes used within the NMAs were measured at earlier time-points than 12 months (e.g. 'Change from baseline in pruritus according to the 5-D Itch score questionnaire using the earliest reported data after commencement of treatment').

For Hirschfield et al 2015, the company responded that neither PBC-40 Itch nor 5-D Itch were reported and did not assess OCA at its licensed dose of 5-10 mg; therefore, the study could not have been included in the relevant analyses.[7] The EAG are satisfied with this rationale. For Schattenberg et al (2021), the company noted that 5-D Itch was not reported and PBC-40 Itch data were only reported as a median percentage change from baseline without population size, SDs or standard errors (SEs) provided. The EAG acknowledge that the data regarding pruritis measured using PBC-40 was limited within Schattenberg et al (2021), with data not shown within the paper.[24] However, as with the COBALT study (see section 3.3.2.1), it may have been possible for the company to contact the authors of the Schattenberg et al (2021) trial in order to obtain further information needed to fully assess its suitability for NMA.

3.3.3 Transitivity assumption

Following details of the feasibility assessment for the NMA presented in Appendix D, the EAG asked the company to provide further comment on the transitivity assumption (PfC A15). The company responded that five key effect modifiers were considered as part of their feasibility assessment: age at diagnosis, ALP levels, TB level, cirrhosis and antinuclear antibody (ANA) positive status. ALP levels and TB levels were deemed sufficiently similar in ELATIVE and POISE. Age at diagnosis was not directly reported by ELATIVE but was calculated using participants' age and time since diagnosis to compare with POISE, which was also found to be sufficiently homogenous. Cirrhosis was not directly reported in either ELATIVE or POISE, though the company noted that their clinical experts stated that liver stiffness of 17 kPa or more could be used as a proxy; the difference between the two trials in terms of liver stiffness was deemed to be within a reasonable margin of error.[7]

However, ANA positive status was not reported in either ELATIVE nor POISE, and so an assessment of homogeneity could not be conducted.[7] Given that the company have noted that ANA positive status was a key effect modifier, it is not possible to know whether the participants in POISE and ELATIVE were sufficiently similar for this variable. As such, it is not known whether the transitivity assumption has been violated in terms of ANA positive status, which may threaten the validity of the indirect estimates.[32]

3.3.4 Results

3.3.4.1 Exclusion of fatigue as an outcome measure in the NMA

The final NICE scope listed fatigue as an outcome of interest for the submission.[33] Furthermore, information provided by patient organisations to NICE noted that fatigue was a key symptom of PBC that impacts on quality of life,[34,35] while the British Society of Gastroenterology/UK-PBC guidelines state: "*Fatigue is a significant problem in up to half of patients and is complex in nature. Social isolation is an important factor in poor QoL in fatigued patients with PBC*."[17] As such, the EAG asked the company to justify why fatigue had not been considered for an NMA, given that data from the ELATIVE trial on the PROMIS Fatigue Short Form 7a Score was available (CS Section B.2.6.1.3.7, p. 66; PfC A12).[1]

The company responded that fatigue was measured by both ELATIVE and POISE using the PBC-40 fatigue domain but that there was no evidence from either trial that there was a significant impact of treatment on the symptoms compared with placebo. Therefore, the company concluded that including fatigue in the economic model would not significantly influence the results and, as such, did not pursue an NMA for this outcome.[7] However, further post-hoc ELATIVE trial results are being planned to understand the impact of elafibranor on fatigue. The EAG believe that a lack of evidence of effect in individual trials does not preclude pooling within an NMA. In not pooling the data on fatigue from ELATIVE and POISE, it is not possible to determine the indirect treatment effect of elafibranor compared with OCA 5-10 mg for this outcome.

3.3.4.2 Uncertainty in NMA results used within the economic model

Results for 'Odds of achieving cholestasis response at 12 months' (CS Section B.2.9.1.1, p.72-3), 'Mean change in pruritis (PBC-40 Itch) from baseline at 12 months' (CS Section B.2.9.1.6, p.78-9), 'Mean change in PBC-40 Itch from baseline using the earliest reported data after commencement of treatment' (CS Section B.2.9.1.7, p.80-1), 'Odds of occurrence of pruritis

TEAE of any severity within 12 months' (CS Section B.2.9.1.8, p.81-2) and 'Odds of discontinuation (all-case) within 12 months' (CS Section B.2.9.1.10, p.84-5) against OCA 5-10 mg were all used within the economic model. The results were as follows.

[redacted]

[redacted]

[redacted]The company noted that there were issues with convergence in the random-effects NMA (Appendix D, Section D.1.5, p.89), and with less than five studies used within the NMA, a fixed-effects model may have been preferable. However, the lack of any significant change in the results for the fixed-effects models compared with the random-effects models suggests this choice would not change the uncertainty in the NMA results for outcomes used to inform the cost-effectiveness.

3.3.4.3 Use of odds ratios as opposed to risk ratios for dichotomous outcome measures

The EAG note that the company used ORs instead of RRs to assess the effectiveness of elafibranor within the NMA. When there is an association between the exposure and outcome, ORs tend to overestimate the effects of interventions if misinterpreted as RRs, which could present an issue; however, the qualitative direction of effect will not be changed.[23,36] Furthermore, NICE DSU Technical Document 1 states: "*A clear discussion of the underlying statistical and clinical assumptions implied by the model, and their impact on the final decision should also be provided. In particular, reasons for choosing to model the outcomes on a particular scale (e.g. odds ratio, hazard ratio, risk difference etc) and the assumptions implied in any transformation from the relative to the absolute effects should be clearly presented*" (p.17-8). This rationale was not provided in the CS. As such, the EAG conducted their own analyses to estimate the relative effect of elafibranor versus OCA 5-10 mg for the dichotomous outcomes 'Odds of achieving cholestasis response at 12 months', 'Odds of occurrence of pruritis TEAE of any severity within 12 months' and 'Odds of discontinuation (all-case) within 12 months' using RRs (see Section 3.4 below).

3.4 Additional work on clinical effectiveness undertaken by the EAG

The EAG asked the company to provide the datasets used to perform the NMAs within the CS (PfC A11), which the company provided.[7] The EAG used data already provided in the CS (Document B) and data from the POISE trial, obtained via TA443,[1,6] as well as the data provided by the company in response to the PfCs, to perform additional analyses.

Given the potential issues of using ORs, as noted in Section 3.3.3 above, the EAG aimed to conduct sensitivity analyses for the outcomes 'Odds of achieving cholestasis response at 12 months,' 'Odds of occurrence of pruritis TEAE of any severity within 12 months' and 'Odds of discontinuation (all-case) within 12 months' by conducting NMAs where the effects were presented as RRs with associated 95% CrIs. However, the EAG were unable to satisfactorily run these analyses using OpenBUGS or the gemtc R package.

Frequentist NMAs using both random and fixed effects models using both RRs and ORs were run by the EAG for all binary outcome measures used within the economic model, listed above. This was done to check that the results were plausible given the difficulty in achieving convergence using the Bayesian approach. To run the frequentist NMAs, the EAG used the online application MetaInsight, which uses code from the netmeta R package to generate results.[37,38] To facilitate running the NMAs for continuous outcomes, the EAG transformed the standard errors (SEs) provided by the company in their datasets into standard deviations (SDs) using the following formula in Microsoft Excel: SD=SE*sqrt(n).

3.4.1 Dichotomous outcomes

3.4.1.1 Random-effects analyses

Results comparing the company's random-effects NMA results with the EAG's alternative results for dichotomous outcomes used in the economic model are presented in Table 3.5. As noted in Section 3.4 above, the EAG were not able to satisfactorily run a random-effects Bayesian NMA using RR for dichotomous outcomes. When using a fixed-effects frequentist model with OR, the result for the odds of pruritis TEAE of any severity at 12 months became statistically significant. However, the remaining confidence intervals derived from the frequentist analyses were wide and still not statistically significant, suggesting uncertainty in the underlying data and the overall effectiveness of elafibranor.

Table 3.5: NMA results comparing elafibranor 80 mg versus OCA 5-10 mg using different approaches (dichotomous outcomes, random-effects models)

Outcome measure	Company base-case (Bayesian OR, random-effects)	Frequentist OR, random-effects	Frequentist RR, random-effects
Cholestasis response at 12 months			
Odds of pruritis TEAE of any severity at 12 months			
All-cause discontinuatio			

Outcome measure	Company base-case (Bayesian OR, random-effects)	Frequentist OR, random-effects	Frequentist RR, random-effects
n at 12 months			

Source: created by the EAG and using data from CS Sections B.2.9.1.1 (p.72-3), B.2.9.1.6 (p.78-9), B.2.9.1.7 (p.80-1), and B.2.9.1.10 (p.84-5)[1]
Abbreviations: CI = confidence interval; CrI = credible interval; CS = company submission; EAG = Evidence Assessment Group; NMA = network meta-analysis; OCA = obeticholic acid; OR = odds ratio; RR = risk ratio; TEAE = treatment-emergent adverse event

3.4.1.2 Fixed-effects analyses

Results comparing the company's fixed-effects NMA results with the EAG's alternative results for dichotomous outcomes used in the economic model are presented in Table 3.6. When using a fixed-effects frequentist model with RR, the result for the odds of pruritis TEAE of any severity at 12 months was no longer statistically significant compared with the company's approach. However, the remaining confidence intervals derived from the frequentist analyses were wide and still not statistically significant, suggesting uncertainty in the overall effectiveness of elafibranor.

Table 3.6: NMA results comparing elafibranor 80 mg versus OCA 5-10 mg using different methodologies (dichotomous outcomes, fixed-effects models)

Outcome measure	Company base-case (Bayesian OR, fixed-effects)	Bayesian RR, fixed-effects	Frequentist OR, fixed-effects	Frequentist RR, fixed-effects
Cholestasis response at 12 months	[redacted]	[redacted]	[redacted]	[redacted]
Odds of pruritis TEAE of any severity at 12 months	[redacted]	[redacted]	[redacted]	[redacted]
All-cause discontinuation at 12 months	[redacted]	[redacted]	[redacted]	[redacted]

Source: created by the EAG and data from CS Appendix D (Sections D.1.6.1, D.1.6.6, D.1.6.8 and D.1.6.11)[9]
Abbreviations: CI = confidence interval; CrI = credible interval; CS = company submission; EAG = Evidence Assessment Group; NMA = network meta-analysis; OCA = obeticholic acid; OR = odds ratio; RR = risk ratio; TEAE = treatment-emergent adverse event

3.4.2 Continuous outcomes

Results comparing the company's random and fixed-effects frequentist NMA results with the EAG's alternative results for continuous outcomes used in the economic model are presented in Table 3.7. When the EAG used a frequentist, random-effects approach, the NMA result for the change in the PBC-40 Itch domain at 12 months became statistically significant in favour of elafibranor. However, there was little difference between the company's and EAG's analyses for the remaining analyses surrounding change in PBC-40 Itch domain score at 12 months and at 2-4 weeks.

Table 3.7: NMA results comparing elafibranor 80 mg versus OCA 5-10 mg using different approaches (continuous outcomes)

Outcome measure	Company NMAs		EAG analyses	
	Bayesian, median difference in mean change, random-effects	Bayesian, median difference in mean change, fixed-effects	Frequentist MD, random-effects	Frequentist MD, fixed-effects
Change in PBC-40 Itch domain at 12 months	[redacted]	[redacted]	[redacted]	[redacted]
Change in PBC-40 Itch domain at 2-4 weeks	[redacted]	[redacted]	[redacted]	[redacted]

Source: created by the EAG and data from: CS Sections B.2.9.1.6 and B.2.9.1.7 (p.78-81); CS Appendix D, Sections D.1.6.6 and D.1.6.7; and PfC A11.[1,9]
Abbreviations: CI = confidence interval; CrI = credible interval; CS = company submission; EAG = Evidence Assessment Group; MD = mean difference; NMA = network meta-analysis; OCA = obeticholic acid;

3.5 Conclusions of the clinical effectiveness section

An SLR was conducted to identify evidence on the effectiveness and safety of elafibranor and relevant comparators for treating PBC. The EAG have some concerns surrounding multiple aspects of the SLR process, such as the literature search, eligibility criteria, screening, data extraction, and quality appraisal. The review question suggests that the aim of the review is to identify RCTs that evaluate the efficacy and/or safety of elafibranor and other comparators of interest whereas the inclusion criteria list observational studies among the eligible study designs to be included in the review. No protocol nor a reference to a published or registered protocol was provided. Therefore, it was not possible to judge if prespecified eligibility criteria were adhered to throughout the process. The company did not attempt to contact study authors regarding missing or unclear information, which could have led to excluding eligible studies from the SLR. Moreover, RCTs of mixed-line treatments were excluded, which could have resulted in excluding RCTs where results of eligible treatment lines were reported separately. If the results of any such studies were not considered in the SLR, this may have led to potentially eligible studies being excluded from the SLR and, consequently, this could possibly have impacted the NMA and subsequently the economic model.

The main clinical evidence was based on the ELATIVE trial, a multinational RCT investigating the efficacy and safety of elafibranor 80 mg with or without UDCA versus placebo with or without UDCA in 161 adult patients with PBC who have had an inadequate response to or

were unable to tolerate UDCA, followed up over a 52-week period. The EAG believe the ELATIVE trial was mainly conducted appropriately, though the process for allocation concealment was unclear. Moreover, the subgroup analyses performed did not include the subgroups “inadequate response” and “unable to tolerate UDCA.” Though clinical advice to the EAG noted that these are two clinically different populations, the EAG appreciates that the overall numbers of participants who did not tolerate UDCA was too low to be able to facilitate this stratification. No data were reported from the trial on long-term outcomes listed in the scope, such as mortality and liver transplantation, but the EAG appreciate that these are considered in the economic analyses.

To compare the relative efficacy of elafibranor with OCA, the company performed a series of indirect treatment comparisons in the form of NMAs. The EAG had several concerns surrounding the choice of methodology and presentation of the methods, though the company provided additional information and rationale for many of these queries during the points for clarification process. However, the EAG noted that the width of the 95% CrIs, including when elafibranor is compared against OCA 5-10 mg, were substantially wide and the company noted that there was difficulty in achieving convergence within the model. As such, the EAG performed multiple additional NMA analyses to explore the effect of changing the model on the results for outcomes used within the economic model. In general, the results of these analyses would not change the overall conclusions of the NMAs. Although the results of the EAG analyses mostly aligned with those of the company’s base case and fixed-effect sensitivity analyses, it should be noted that the results were still open to substantial uncertainty and it is therefore difficult to draw any conclusions regarding the clinical effectiveness of elafibranor versus OCA 5-10 mg.

4 COST EFFECTIVENESS

4.1 EAG comment on company's review of cost-effectiveness evidence

This section pertains mainly to the review of cost-effectiveness analysis studies. However, the search section also contains summaries and critiques of other searches related to cost-effectiveness presented in the company submission. Therefore, 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.

Table 4.1 presents an overview of the EAG's critique of the methods used to identify studies for the review of cost-effectiveness.

Table 4.1: Summary of the EAG's critique of the methods for the review of cost-effectiveness

Aspect of cost-effectiveness SLR	Section in CS where methods are reported	EAG's assessment
Data sources for cost-effectiveness analysis review	Appendix G.1, p. 1	**Some concerns** A systematic review was carried out by the company in November 2022 with a December 2023 update. Searches were conducted simultaneously for cost-effectiveness studies, HRQoL, and cost and resource use. An appropriate range of electronic bibliographic databases, HTA websites and conference proceedings were searched alongside hand-searching bibliographies to identify additional relevant studies, but the reason given for restricting the years for which conference proceedings were searched was unconvincing. Conference proceedings were excluded from Embase searches, which could have missed relevant studies. See Section 4.1.1 for further details.
Search strategies	Appendix G.1.1, p. 2; Appendix H.1.1, p. 1; Appendix I.1.1, p. 1	**Some concerns** The search strategy used to find cost-effectiveness studies is generally fit for purpose; however, the use of focussed MeSH headings may have increased specificity to the detriment of sensitivity. See Section 4.1.2 for further details.
Search filters	Appendix G.1.1, p. 2	**Appropriate** The search filters adequately captured the decision problem.
Data sources for model input	Appendix G.1.3, p. 21; Appendix I.1.3, p. 4; Appendix H.1.3, p. 3	**Appropriate** Eight cost-effectiveness studies were identified, of which four were health technology appraisal submissions for OCA using the same model structure.
Eligibility criteria for inclusion of	Appendix G.1.2, p. 19	**Appropriate** The eligibility criteria were appropriate to capture cost-effectiveness studies in this area.

Aspect of cost-effectiveness SLR	Section in CS where methods are reported	EAG's assessment
economic evaluations		
Eligibility criteria for inclusion of health state utility value studies	Appendix H.1.2, p. 2	**Appropriate** The eligibility criteria were appropriate to capture quality of life data in this area.
Eligibility criteria for inclusion of resource use and cost studies	Appendix I.1.2, p. 2	**Appropriate** The eligibility criteria were appropriate to capture resource use and costs in this area.
Abbreviations: CS = company submission; EAG = Evidence Assessment Group; HRQoL = health-related quality of life; HTA = health technology assessment; OCA = obeticholic acid		

4.1.1 Data sources for cost-effectiveness analysis review

The range of sources searched by the company for the cost-effectiveness, health-related quality of life (HRQoL), and cost and resource SLR was appropriate: electronic bibliographic databases (MEDLINE, Embase, INAHTA); conference proceedings and hand searching of reference lists. The company excluded conference proceedings in Embase, which could have led to the exclusion of relevant records. However, clinical advice to the EAG confirmed that the two main conferences in the area had been covered by the company's hand searches.

4.1.2 Search strategies

The company's search included filters to identify cost-effectiveness studies, cost and resource use (direct and indirect), HRQoL and utilities developed by SIGN. This was amended to include additional search terms which may have increased the scope of the search. Whilst these adaptations may have increased the sensitivity of the search, the use of focussed MeSH and Emtree headings within the search strategy have the opposite effect and may have limited the sensitivity of the search. Please see section 3.1.1.2 where this issue is discussed further along with the restriction of conference abstracts searched to 2021 onwards.

4.2 Conclusions of the cost effectiveness review

The SLR was unable to find previously published economic evaluations assessing the cost-effectiveness of elafibranor as a treatment for PBC. A total of eight economic evaluations were identified by the company, four of which were HTAs for OCA using the same model structure, one published micro-simulation for OCA, two publications focused on UDCA, and one publication on liver transplantation (CS Section B.3.1, Table 29).[1] The structure used to evaluate OCA across the four health technology appraisals [6,39-41] informed the structure in the clinical pathway for the current submission.

4.3 Summary and critique of company's submitted economic evaluation by the EAG

4.3.1 NICE reference case checklist

Table 4.2 summarises the NICE reference case checklist and the EAG's assessment on the company's submission in relation to their base-case analysis.

Table 4.2: NICE reference case checklist

Element of health technology assessment	Reference case	EAG comment on company's submission
Defining the decision problem	From the scope: Adults with PBC whose disease has an inadequate response to, or who are unable to tolerate UDCA.	**Appropriate** The population included patients who are unable to tolerate UDCA and patients with an inadequate response to UDCA. There were a small number of patients unable to tolerate UDCA. The EAG considered this approach appropriate.
Comparators	For people whose disease has an inadequate response to UDCA: • OCA in combination with UDCA • UDCA monotherapy For people who are unable to tolerate UDCA: • OCA monotherapy • Best supportive care	**Some concerns** OCA and UDCA are presented as the second-line treatment alternatives to elafibranor, in line with the scope developed together with NICE. As patients who discontinue move to UDCA as third-line treatment, the EAG is concerned that elafibranor could be used with OCA in sequence as an alternative treatment strategy to the elafibranor to UDCA sequence. Consultations with a clinical expert indicated this is a possibility given the different mechanisms of action between elafibranor and OCA but clinical effectiveness data may be scarce. The scope also omits the use of fibrates in second-line treatment. These are typically used off-label and could make up a sizeable share of second-line treatment, even if they do not have regulatory approval. See sections 2.1.1 and 4.3.2.1 for further details.
Perspective on outcomes	Outcome measures from the final scope considered to be included: • Mortality	**Some concerns** Outcomes included in the cost-effectiveness model were: • Mortality (life years gained)

Element of health technology assessment	Reference case	EAG comment on company's submission
	• Liver function based on markers of liver biochemistry • PBC symptoms including pruritus, fatigue, and abdominal pain • Time to liver transplantation • PBC related events including ascites, varices, encephalopathy, and hepatic cell carcinoma (HCC) • Adverse effects of treatment • Health-related quality of life (HRQoL).	• Liver function biomarkers • Pruritus • Time to liver transplantation • PBC-related events included HCC and decompensated cirrhosis (DCC) • Adverse events: pruritus, fatigue, and urinary tract infections • HRQoL measured in QALYs The economic model does not explicitly parametrise the impact of ascites, varices, encephalopathy or abdominal pain from PBC onto each health state. See section 4.3.5.2 for further details.
Perspective on costs	NHS and personal social services (PSS)	**Appropriate** The EAG considers the perspective on costs was adequately captured.
Type of economic evaluation	Cost-utility analysis with a fully incremental analysis	**Appropriate** The company presented a full cost-utility analysis using QALYs over an ICER for OCA.
Time horizon	Long enough to reflect all important differences in costs and outcomes between the technologies being compared	**Appropriate** A lifetime horizon was used for the cost-effectiveness analysis.
Synthesis of evidence on health effects	Based on a systematic review	**Appropriate** An NMA was performed including the ELATIVE and POISE trials. A systematic review was used to search for quality-of-life data.
Measuring and valuing health effects	Quality of life to be presented in QALYs. The EQ-5D is the preferred measure of health-related quality of life in adults.	**Appropriate** As per the NICE reference case.
Source of data for	Reported directly by the patients or carers or both.	**Key issue 4**

Element of health technology assessment	Reference case	EAG comment on company's submission
measurement of health-related quality of life		EQ-5D-5L patient data were collected from the pivotal ELATIVE trial, but not used in the model. Utility values from NICE TA443 for the target population were used in the economic model instead. See section 4.3.5.1 for further details.
Source of preference data for valuation of changes in health-related quality of life	Representative sample of the UK population.	**Appropriate** EQ-5D values were scored in accordance with NICE guidelines.
Equity considerations	An additional QALY has the same weight regardless of the other characteristics of the individuals receiving the health benefit.	**Appropriate** No decision modifiers were applied on the results.
Evidence on resource use and costs	Costs should relate to NHS and PSS resources and should be valued using the prices relevant to the NHS and PSS.	**Some concerns** Costs and resource use mostly sourced from NHS reference costs, PSS and the established trials, which largely consistent with NICE perspective, although a few costs were extracted from the literature based on their systematic review. Evidence from the NHS cost tariffs were not clearly referenced, posing a transparency concern to the EAG. See section 4.3.6 for further details.
Discounting	The same annual rate for both costs and health effects (3.5%)	**Appropriate** Discounting of costs and outcomes was in line with NICE guidelines

Source: Company submission document B, Table 1[1]
Abbreviation: EAG = Evidence Assessment Group; DCC = decompensated cirrhosis; HCC = hepatocellular carcinoma; HUI = health utility index; NHS = National Health Service; NICE = National Institute for Health and Care Excellence; NMA = network meta-analysis; OCA= obeticholic acid; PBC = primary biliary cholangitis; PSS = Personal Social Services; QALY = quality adjusted life-year; UDCA = ursodeoxycholic acid; VAS = visual analogue scale

4.3.2 Decision problem

Table 4.3: Summary of EAG's critique on the design of the decision problem

Analysis feature	Section in CS where methods are reported	EAG's assessment
Population	Document B.3.2.1, p. 110	**Appropriate** Patient baseline characteristics were based on the ELATIVE trial intention-to-treat (ITT) population.
Interventions	Document B.3.2.3, p. 116	**Appropriate** The intervention was elafibranor 80 mg, which is in line with the NICE decision problem.
Comparators	Document B.3.2.3, p. 116	**Some concerns** Elafibranor is compared to OCA and UDCA alone as alternatives for second-line treatment, while third-line treatment after both elafibranor and OCA consists of UDCA and best supportive care. This is consistent with the initial scope developed together with NICE. Beyond this, the EAG considers it may be possible to use elafibranor and OCA together in sequence as an alternative treatment strategy considering the different mechanisms of action from each. This was further confirmed after consultation with a clinical expert in the field, even though there is an evidence gap in the clinical effectiveness of any sequence strategy combining elafibranor and OCA. The use of fibrates was also not considered part of the initial scope since they are typically used off-label. However, fibrates may make an important share of the second-line treatment in this patient population. See sections 2.1.1 and 4.3.2.1 for further details
Perspective	Document B.3.2.2, p. 115	**Appropriate** The company used NHS and PSS perspective in costs and all direct health effects for patients, which is appropriate for the submission.
Time horizon	Document B.3.2.2, p. 116	**Appropriate** The company used a lifetime horizon, which the EAG finds appropriate.
Discounting	Document B.3.2.2, p. 116	**Appropriate** The company used a 3.5% annual discount for cost and health outcomes, which the EAG finds appropriate.
Severity modifier	Document B.3.6, p. 144	**Appropriate** The company concluded that the population did not meet the severity modifier criteria.

Source: EAG outputs
Abbreviations: CS = company submission; EAG = Evidence Assessment Group; ITT = intention-to-treat; OCA= obeticholic acid; NICE = National Institute for Health and Care Excellence; NHS = National Health Service; OCA= obeticholic acid; PSS = personal social services

4.3.2.1 Comparators

- **Potential use of OCA in sequence from elafibranor**

The model assumes a clinical pathway where both second-line elafibranor and OCA are followed by UDCA and best available care after second-line discontinuation. After consultation with an expert clinician, the EAG would like to highlight the fact that, due to the different mechanisms of actions of elafibranor or OCA, sequential treatment strategies can be proposed where OCA is offered to patients discontinuing elafibranor, and vice versa.

The EAG further considers that the positioning of OCA or elafibranor as third-line treatments could affect their cost-effectiveness but acknowledges that more evidence on the effectiveness of OCA or elafibranor as sequential treatments would be required to obtain more concrete results.

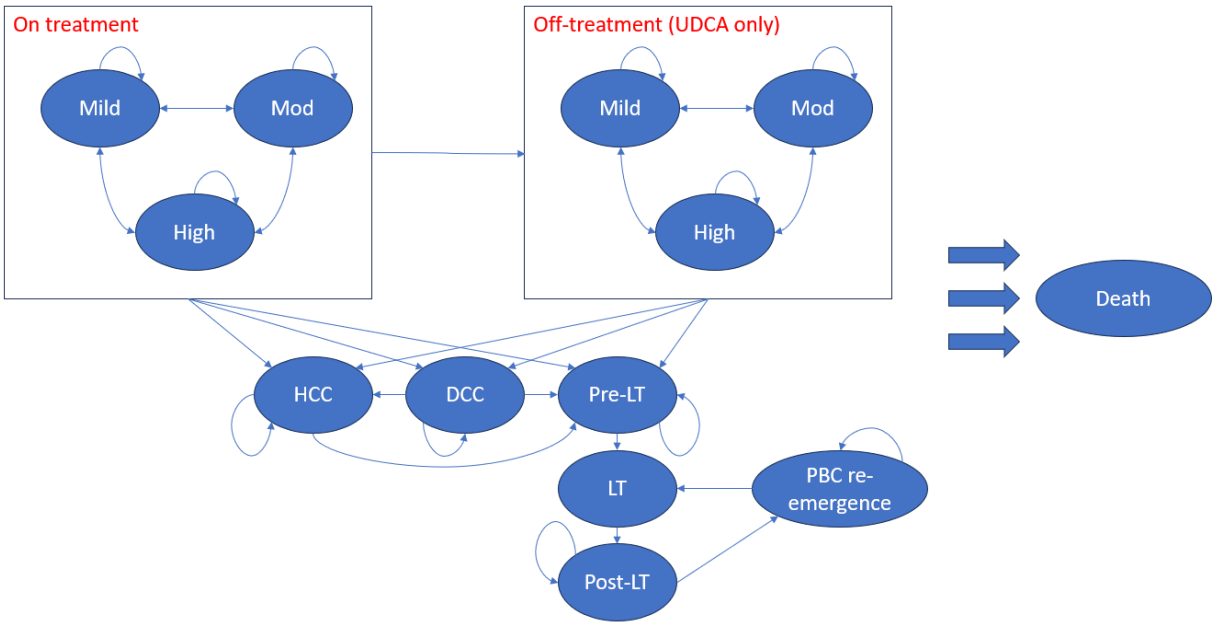
- **Use of fibrates as third-line treatment**

The company was asked about the use of fibrates as a potential treatment within elafibranor's anticipated positioning.[7] In their response, the company highlighted that: fibrates were not included in the NICE scope, since their use is off-label; they have not been studied to regulatory standards for PBC patients; and there are concerns of tolerability issues for patients with cardiovascular disease. [redacted]

4.3.3 Model structure and assumptions

The company model diagram is reproduced in Figure 4.1. The company used a cohort Markov model, with the model structure based on the model developed in NICE TA443.[6] In this model, patients transition between mild, moderate and high risk biomarker states. Responders to treatment, while they are on treatment, have a higher probability of being in a lower risk biomarker state. When a patient discontinues treatment, they effectively return to their initial state pre-second-line treatment, implemented in a manner appropriate to a cohort analysis. There is a probability of transitioning from moderate and high biomarker states to liver disease states. Once a patient has transitioned to a liver disease state, they may progress to other liver disease states, pre/undergoing/post liver transplant (pre-LT/LT/post-LT), liver disease states, PBC re-emergence, and death.[1]

Figure 4.1: Model structure



Source: CS Document B, Section 3.2.2, Figure 41[1]
Abbreviations: CS = company submission; DCC = decompensated cirrhosis; HCC = hepatocellular carcinoma; LT = liver transplant, PBC = primary biliary cholangitis; UDCA = ursodeoxycholic acid

Table 4.4: Summary of EAG's critique on the design of the economic modelTable 4.4 summarises the EAG's critique on the model structure adopted by the company.

Table 4.4: Summary of EAG's critique on the design of the economic model

Analysis feature	Section in CS where methods are reported	EAG's assessment
Type of model	Document B.3.2.2, p.110	**Appropriate** A Markov state-transition model was used. The structure aligned with NICE TA443 assessing OCA treatment for PBC.
Health states/events and transitions	Document B.3.2.2, p.110	**Some concerns** Moderate-risk patients are assumed to progress directly to the liver disease health state without moving through the high-risk. The EAG expects this is likely to be a very small risk, however there was a lack of clarity in the methods used to calculate this parameter. Although this assumption was validated with clinical experts, the EAG is concerned the model predictions were not and are likely to present a scenario where fewer than expected patients remain free from liver disease in the long-term. It was not clear to the EAG how the excess mortality risk at high-risk parameter was obtained, and although this assumption was agreed with clinicians, the EAG

Analysis feature	Section in CS where methods are reported	EAG's assessment
		saw no evidence that the survival predictions were validated by clinicians. The model structure includes a pre-LT state capturing patients with moderate risk, high risk, DCC, and HCC and allows them to stay in this state over their lifetime. The EAG believes there is structural uncertainty around whether transitions direct to LT or through pre-LT should be modelled from each disease state. The EAG is also concerned about the parameters and approach to calculate excess mortality. Although different approaches led to similar survival predictions, comparisons with the literature suggest that model predictions of survival for HCC and DCC may be lower than the survival expected in clinical practice. See section 4.3.3.1 for further details.
UDCA transitions		**Some concerns** The EAG considers it is still a matter of uncertainty what happens to the biomarker risk distribution after patients discontinue second-line treatment. The company's base-case approach was considered appropriate, but the EAG has explored an alternative scenario. The model also makes a strong assumption that after the first year, there are no transitions from moderate risk to mild risk for patients receiving UDCA. [redacted] The model only used the 9-12 month transitions from the placebo arm of ELATIVE to predict the long-term transitions for third-line treatment with UDCA. The EAG questions that the full 12 month transitions during the trial duration were only used as a scenario analysis. See section 4.3.3.2 for further details.
Model predictions		**Key issue 2** The EAG is concerned that the survival predictions made in the model (from liver disease-free, liver transplant-free, and overall survival), were not validated with expert clinicians or the published literature. A point of concern is the potential

Analysis feature	Section in CS where methods are reported	EAG's assessment
		overprediction of patients moving from the PBC biomarker risk states to liver disease in the model. See section 4.3.3.3 for further details.

Source: EAG output
Abbreviations: CS = company submission; DCC = decompensated cirrhosis; EAG = Evidence Assessment Group; HCC = hepatocellular carcinoma; LT = liver transplant; OCA = obeticholic acid; NICE = National Institute for Health and Care Excellence; PBC = primary biliary cholangitis; TA = technology appraisal; UDCA = ursodeoxycholic acid

4.3.3.1 Health states/events and transitions

- **Transitions from the moderate risk category to liver disease**

A deviation from the model structure in NICE TA443 was the possibility of moderate risk patients to transition directly to the liver disease health-states (CS Section B.3.3.2.3, Table 35).[1,6] The company in the current submission argued that the assumption that moderate-risk patients would remain in the moderate-risk health state for the rest of their life in NICE TA443 was criticised by the EAG that reviewed TA443 (CS Section B.3.3.2.3).[1] Therefore, the company assumes that moderate-risk patients can transition directly to liver disease without moving through the high-risk of progression stage.

The EAG Report from NICE TA443,[6] made a critique about the PBC biomarker risk stage in the model, where after 12 months OCA patients are assumed to stay in the moderate or high-risk stage and not move to other risk stages. The current model makes this assumption for both elafibranor and OCA. However, we found no mention of the transitions from moderate-risk to the liver-disease stage of the model in the EAG Report for TA443.[6,43]

The base-case model submitted assumes that moderate-risk patients develop decompensated cirrhosis (DCC) without developing compensated cirrhosis (CC) which is part of the definition of the high-risk level. [redacted]. The EAG acknowledges there can be a minority of patients with a missed CC diagnosis developing DCC. However, this risk is expected to be small compared the risk of CC for moderate risk category patients in the model.

From the information provided in Document B from the company submission[1] it was unclear to the EAG how the cycle probabilities from moderate risk to liver disease were derived. At the factual accuracy check, the company clarified that during the clinical validation of inputs meeting one of the clinicians noted that 6% of the moderate to high-risk health state patients are rapid progressors.[44] This estimate is used to derive the transition probability of being a rapid progressor using a method presented in the FAC the EAG has not yet critiqued. [redacted] Therefore, while it is plausible that a small number of patients in a moderate risk group develop liver

disease either directly or after progressing to a high risk biomarker state first, yet the risk of this transition is still uncertain and may not have been fully explored, hence the EAG has run a scenario excluding this assumption, see scenario 10, section 6.1.2.

- **Excess mortality for high-risk patients**

A difference in the model structure in this submission compared to NICE TA443 was the application of disease-related excess mortality on the cohort of patients categorised as at high-risk of PBC progression (CS Section B.3.2.2, Table 32; Section B.3.3.5, Table 40).[1,6] The company stated that an assumption of a 1.2% excess from the general population mortality was applied upon the advice of clinical experts. During the factual accuracy check, the company indicated that a 5% annual excess mortality risk was provided by the clinicians in the clinical validation of inputs meeting, slide 23 (FIECON 2024, page 16[44]). The EAG was not able to find the quoted estimate but found that one clinician estimated annual excess mortality to be 10% to 15% for high-risk patients, and 2% to 3% for moderate-risk (FIECON 2024, page 16[44]). These inputs were not discussed or assessed on the base-case analysis presented by the company, but more importantly, the survival predictions resulting from these inputs were not validated by neither published evidence nor expert opinion.

The EAG has confirmed with a clinical expert that the primary reason of excess mortality is progression to liver disease. Other than disease progression, fatigue and cardiovascular conditions may lead to a higher risk of mortality relative to the general population. From the perspective of the company, no other clinical explanation for excess mortality was offered other than liver disease progression. The EAG investigates the impact of assuming excess mortality on the cost-effectiveness estimates in a scenario analysis with no excess mortality, see scenario 1, section 6.1.2.

The model prediction for the proportion of patients free from liver disease over time may be too low when compared to GLOBE and UK-PBC predictions. Excess mortality for patients in the high-risk PBC biomarker health state is a key parameter determining the survival predictions in the model. To illustrate, Table 4.5 presents survival at different time points with and without excess mortality in the high-risk PBC biomarker health state. Removing excess mortality assumption in this health state increases the median overall survival of OCA by two years as shown in Table 4.5. No excess mortality risks were applied in low and moderate-risk health states.

Table 4.5: Overall survival for OCA in the company base-case model after correcting for errors 1-12: different approaches to excess mortality at high-risk PBC

	Mortality excess in high-risk (absolute approach)	Mortality excess in high-risk (proportional approach)	No mortality excess in high-risk
Timepoints	**OCA**	**OCA**	**OCA**
1 year	[redacted]	[redacted]	[redacted]
5 years	[redacted]	[redacted]	[redacted]
10 years	[redacted]	[redacted]	[redacted]
20 years	[redacted]	[redacted]	[redacted]
40 years	[redacted]	[redacted]	[redacted]
Median (years)	[redacted]	[redacted]	[redacted]
Source: CS economic model, EAG output			

Abbreviations: CS = company submission; EAG = Evidence Assessment Group; OCA = obeticholic acid

- **Calculations used for excess mortality in high risk state**

The company implemented excess mortality in the economic model by adding the values reported in Table 4.6 to the cycle-adjusted mortality risk for the general population. It is unclear to the EAG whether this is an appropriate interpretation of the methodology used in NICE TA443 (which is where excess mortality parameters are sourced from), as excess mortality is additive to (independent of) the general population mortality risk.[6]

Table 4.6: Calculations used for excess mortality by the company

Health state	Excess mortality	Source
High-risk PBC	1.20%	Expert opinion
DCC	4.20%	TA443, 2017[6]
HCC	10.20%	TA443, 2017[6]
Pre-LT	2.20%	TA443, 2017[6]
LT	18.90%	TA443, 2017[6]
Post-LT	1.50%	TA443, 2017[6]
Re-emergence of PBC	2.20%	TA443, 2017[6]

Source: CS Document B, Table 40, p. 124[1]
Abbreviations: CS = company submission; DCC = decompensated cirrhosis; HCC = hepatocellular carcinoma; LT = liver transplant; PBC = primary biliary cholangitis; TA = technology appraisal

However, further comparisons with the published literature suggest that liver disease survival, as predicted using the model parameters, is potentially lower than what would be expected in clinical practice both for HCC[45,46] and DCC.[47]

One of the reasons that excess mortality for high-risk of liver disease has a large impact on the results is because the company opted for an additive approach increasing the per-cycle mortality risk by 1.2% (e.g. 2% in general population + 1.2% excess). The EAG opted for an approach that reinterprets the 1.2% excess mortality as a percentage of the age-specific general population mortality probability (0.02*1.012 rather than 0.02+0.012) because of uncertainty in excess mortality in the high-risk group, and to increase the survival predictions of the model. The survival predictions using this approach are reported in Table 4.5.

- **The presence of the pre-liver transplant as an absorbing state**

The EAG acknowledges that the model structure was based on a previous submission accepted by NICE following the clinical pathway of PBC patients.[6] In this regard, one of the criticisms raised by the EAG assessing TA443 was the use of a pre-liver transplantation health state that a patient must enter before subsequently making the transition to the liver transplant state or dead state.[43]

As the current submission followed a similar model structure. The EAG thinks there is structural uncertainty associated with the inclusion of this pre-LT state. The cost of the pre-LT state (£5297) is significantly higher than the high-risk biomarker state (£2081), DCC state (£4161), and the HCC state (£3053), while the utility is equal to the DCC state (0.38) and lower than the HCC state (0.45) and the high-risk biomarker state (0.55). Patients may transition to the pre-liver disease state from each of these states, and the three-month probability of a liver

transplant from the pre-LT state was 0.1, meaning that patients can remain in the state for a long time. It is unclear whether the higher average cost and lower average utility is representative for a long period of time.

The EAG reiterates the concern from TA443 that patients in different biomarker risk and liver disease stages of liver disease are captured in the same health state and can stay there for the duration of their lifetime, sharing the same HRQoL, costs, and time to liver transplant probability.[43] The company did not discuss these implications in the company submission.

The EAG base-case excluded the pre-LT state from the model structure, allowing patients to transition directly to liver-transplantation from their liver disease state following the EAG critique for TA443 (see Section 6.1.1).[43]

4.3.3.2 UDCA transitions

- **Uncertainty around biomarker risk categories after treatment discontinuation**

The company state that patients who discontinue elafibranor were assumed to return to their biomarker risk level state at baseline (CS Section B.3.3.2.1, p. 166).[1] Within the model file, patients in the PBC biomarker stage who discontinue second-line treatment (elafibranor or OCA) are distributed across the biomarker risk categories based on the biomarker risk distribution from ELATIVE at baseline.[1] The EAG is concerned that this approach does not account for changes in the risk distribution within the cohort over time, and whether the biomarker risk distribution from the ELATIVE baseline population was representative of the risk distribution after discontinuation of second-line treatment. The EAG has therefore tested a scenario (provided as an option in the model submitted by the company), where patients remain in their risk stage after discontinuation, which is a stronger and less likely assumption where moving to third-line treatment does not immediately make the cohort's risk distribution more severe (see scenario 6, Section 6.1.2). This alternative implicitly assumes that the initial benefit if treatment is maintained.

- **Uncertainty around moderate to mild risk transitions after 12 months**

The change in PBC risk status for patients receiving third-line UDCA after 12 months is assumed to only deteriorate (progress to higher risk) without the possibility of improving, which implies changes in PBC biomarkers are permanent and only deteriorate after this stage. The probability of risk progression is taken from the placebo arm of the ELATIVE trial,[4] if the probabilities from months 9 to 12 in the trial stay the same over the patient lifetime.

[redacted]

The EAG considers this is a strong assumption based on highly uncertain evidence, especially since allowing for risk improvements still means an overall risk progression from mild to

moderate, only at a lower rate. Therefore, the EAG explored a scenario relaxing this assumption by using a scenario set up in the CS, allowing for temporary improvements or progression across risk of progression stages after 12 months (see Section 6.1.2).

- **Uncertainty around the use of 9 to 12 month probabilities from the placebo arm to predict long-term transitions for UDCA**

For patients treated with UDCA only, the transition probabilities from mild risk to medium risk, and from medium risk to high risk, are assumed to be the same over the patient lifetime from month 12 (with no chance of risk improvement, see above). These probabilities were assumed to be the same as the probabilities of the placebo arm of ELATIVE between months 9 and 12.

The company did not provide any clinical justification for this assumption, neither from published evidence nor expert opinion. Therefore, the EAG is concerned that the model might be making inefficient use of the dataset by ignoring the first nine months of data. Patients in the placebo arm had an inadequate response or no response to UDCA at entry to the trial.

The EAG has tested different scenario analyses with different approaches to obtain long-term data using the 12-month data (see scenario 12 in Section 6.1.2).

4.3.3.3 Model predictions

- **Uncertainty around the lack of validation in the model survival predictions**

[redacted]

Overall, the EAG is concerned the model is potentially under-predicting liver disease-free survival. There are many assumptions that the company makes that could potentially contribute to this, including: the transitions from moderate risk to liver disease; the increase in mortality for high-risk patients; the immediate deterioration of biomarker risk stage after discontinuation; the assumption that UDCA patients cannot transition from moderate to low risk; and the uncertainty around long-term transitions. The latter three assumptions also increase the weight of treatment discontinuation assumptions relative to cholestasis response in being the determinant factor of outcomes in the economic model.

Moreover, the EAG was concerned that the overall survival predictions were not further validated by clinical experts or the use of published literature. Communications between the company and clinical experts requested by the EAG provided insights into how some of the parameters of survival for the HCC and DCC states might not be fully reflective of advances in clinical care. This was partially corroborated by the EAG when comparing both survival predictions (median HCC survival of 1.5 years, and median DCC survival of four years) with the literature (e.g. HCC overall survival estimates after five years varied between 43% and 69%).[45-47] The EAG conducted scenario analyses adapting some of the scenarios proposed in the company submission to assess the structural uncertainty from assumption around treatment discontinuation.

4.3.4 Treatment effectiveness, adverse effects and outcome probabilities

Table 4.4: Summary of EAG's critique on the design of the economic modelTable 4.7 summarises the EAG's critique on the treatment effectiveness, adverse effects and outcome probabilities within the economic model.

Table 4.7: Summary of EAG's critique on the design of the economic model

Analysis feature	Section in CS where methods are reported	EAG's assessment
Treatment effectiveness and extrapolation	Document B.3.3.2, p. 117	**Some concerns** The EAG is concerned that the ALP thresholds in the definition of cholestasis response used for the NMA does not match the ALP thresholds used for the effectiveness in the economic model, especially since the NMA has a stricter definition it is unclear whether ALP threshold differences are clinically meaningful. The implementation of NMA data for cholestasis response, pruritus occurrence as a TEAE, and all-cause discontinuation relied on deriving a 12-month RR and assuming a constant RR across different time periods was considered suboptimal. The EAG preferred to assume a constant hazard ratio (HR) across time periods. There is a potential for using elafibranor and OCA in sequence, as suggested in Sections 2.1.1 and 4.3.2.1. However, although the clinical expert consulted by the EAG suggested this is feasible, there is a lack of effectiveness data at third line. Suboptimal modelling of treatment effectiveness in the economic model. Inappropriate parametric distribution for the OR. The assumption of constant RRs across widely varying baseline risks and different time periods. See Section 4.3.4.1 for further details.
Time-to-event analysis and extrapolation methods	Document B.3.3.4, p.177	**Key issue 3** The EAG has concerns that the approach used by the company to model treatment discontinuation overpredicts the proportion of OCA patients stopping treatment. The EAG prefers the conservative assumption that the difference in treatment discontinuation rates has a 1-year duration. This is of particular concern as differences in discontinuation are the primary factor driving the incremental QALY gain of elafibranor in the economic model. See Section 4.3.4.2 for further details
Conceptualisation of pruritus in the economic model	B.3.3.6, p. 124	**Some concerns** The EAG is concerned about the conceptualisation of pruritus outcomes in the economic model. The

Analysis feature	Section in CS where methods are reported	EAG's assessment
		company used outcomes from the PBC-40 to calculate clinically significant pruritus, which is a questionnaire that is not typically used in clinical practice to assess pruritus. Moreover, the economic model included pruritus identified as a Grade ≥ 2 AE, and pruritus identified from the PBC-40 questionnaire. It is not clear to the EAG whether the definition of both pruritus outcomes was mutually exclusive or how the company accounted for potentially double-counting the impact of pruritus. See Section 4.3.4.3 for further details.
Source: CS Document B[1] Abbreviations: CS = company submission; EAG = Evidence Assessment Group; NMA = network meta-analysis; OCA= obeticholic acid; OR = odds ratio; PBC = primary biliary cholangitis; TEAE = treatment-emergent adverse events		

4.3.4.1 Treatment effectiveness and extrapolations

- **Definitions of effectiveness between the NMA and the economic model**

The primary outcome in the ELATIVE and POISE trials used for the NMA was cholestasis response, defined as ALP ≤ 1.67x ULN, with a reduction of ≥ 15% from baseline, and total bilirubin ≤ ULN.[1,4,5] In the economic model, relative treatment effectiveness was presented as an increase in the transition probabilities from moderate risk or high risk to mild risk biomarker states, where the risk categories were stratified as follows.

- Mild risk: ALP ≤ 200 u/L and TB ≤ 20 µmol/L
- Moderate risk: ALP > 200 u/L and TB ≤ 20 µmol/L
- High risk: TB > 20 µmol/L or compensated cirrhosis (defined as kPa > 15)

It is unclear to the EAG what the impact on cost-effectiveness of using different ALP thresholds to define mild and moderate risk in the economic model compared to the cholestasis response definition used in ELATIVE and POISE is.[1,4,5]

In the points for clarification letter, the EAG asked the company to provide the cholestasis treatment response thresholds used.[7] In the response, the company specified that the 1.6x ULN ALP threshold for women was 174 U/L for and for men was 215 U/L, while the ULN for TB was defined as 20.5 µmol/l for all the population.[7]

The mild to moderate risk threshold in the economic model (defined by ALP levels), diverges from the more conservative cholestasis definition used in the ELATIVE trial. Although the 200 U/L in the economic model may align more with clinical practice in the UK,[7] the EAG considers that applying a less conservative threshold on ELATIVE data could translate into a larger proportion of moderate-risk patients returning to mild-risk. However, it is not clear to the EAG whether a narrower ALP threshold (e.g. ALP > 174 U/L) would make a significant difference on patients transitioning between moderate and mild risk states.

The EAG acknowledges that using the cholestasis response definition from ELATIVE is appropriate to have consistent definitions of response in estimating the odds ratio of response for OCA versus elafibranor. However, there is an inconsistency in the response definitions used to estimate the OR and to estimate the baseline risks.

After consultation with an expert clinician, the EAG is concerned that the risk categories presented for the economic model are not typically used in clinical practice. Although ALP and TB are strongly related to progression to liver disease, response is usually seen as a dichotomous variable while the risk is usually assessed using the UK-PBC risk score or the GLOBE scoring system, which includes more variables related to progression.

The EAG asked the company to assess structural uncertainty through assessing alternative definitions for the mild, moderate and high-risk health states.[7] The company provided scenario analyses using different definitions of treatment response showing that stricter definitions of uncertainty lead to reduced incremental QALY estimates, these analyses were replicated for the EAG base-case in Section 6.1.2.

The EAG was not able to produce a scenario analysis changing the ALP thresholds between the moderate and mild risk health states in the economic model. Therefore, the EAG considers the company base-case to be a potentially favourable scenario towards the intervention, as stricter treatment response criteria tended to reduce the incremental benefit of elafibranor.[7] However, the EAG considers it unlikely that narrower thresholds will change the results.

- **Sampling distributions of OR for the probabilistic analysis**

The EAG requested the company to review and correct the formula for the lognormal distribution sampling the OR from the NMA for: cholestasis response; all-cause discontinuation; and occurrence of pruritus as a TEAE. The lognormal distribution was incorrectly specified in the CS Excel model for the OR of response and the OR of likelihood of pruritus as a TEAE, and no parametric distribution was specified for the OR of treatment discontinuation. In the response to the EAG's request, the company updated the economic model by changing the sampling distribution of the OR parameters mentioned from the lognormal to the gamma distribution.[7]

For the OR of cholestasis response, the mean, median, lower limit and upper limit of the 95% CrI for the gamma distribution (α = [redacted], β = [redacted]) used in the company submission and the lognormal distribution (μ=[redacted][ln(median)], SD = [redacted]) are presented in Table 4.8 along with the NMA results presented in the CS.[1] The mean OR for cholestasis response was not reported in the CS and the EAG could not replicate the Bayesian random-effects NMA results due to difficulties in convergence. As such, the comparison of the mean estimate from a lognormal distribution to the mean estimate from the NMA for the fixed effect analysis is also presented in Table 4.8. After the factual accuracy check, the company provided the mean NMA OR for OCA cholestasis response, Table 4.8 has been updated to reflect this.

It appears that the gamma distribution was specified so that the gamma mean value was the NMA median value. Given the discrepancy between median values from the NMA and the median values from the gamma distribution, the EAG considers it an error to opt for the gamma distribution over the lognormal distribution, which provides a much better fit to the NMA results, even though the mean is slightly closer to 1 than the likely NMA mean estimate. This was

addressed by sampling OR parameters using the lognormal distribution in the EAG's base-case analysis cholestasis response, all-cause discontinuation, and occurrence of pruritus as a TEAE (see Section 6.1.1).

Moreover, the median OR NMA values (e.g. [redacted] for response) were used in the deterministic analysis in the CS. The EAG considers mean values should be used where possible in deterministic analysis. As the mean values from the NMA for the OR of cholestasis response, all-cause discontinuation, and pruritus occurrence as a TEAE were not reported in the CS (and the EAG could not replicate the Bayesian random-effects NMA), the EAG initially used the mean values associated with the lognormal distribution (e.g. [redacted] for response). After the factual accuracy check, the company provided the mean estimates from the NMA for: OCA odds of cholestasis response, OCA odds of pruritus occurrence as a TEAE, and OCA odds of all-cause discontinuation, therefore, the inputs of the EAG's base-case deterministic analysis have been updated to include the mean estimates from the company's NMA. The mean and CI results from the NMA and the mean and CI results used in the EAG analyses for each outcome are presented in Table 4.9.

Table 4.8: The fit of gamma and lognormal distributions for OCA OR cholestasis response

	Random effects			Fixed effect	
Statistic	**NMA results**	**Gamma distribution**	**Lognormal distribution**	**NMA results**	**Lognormal distribution**
Mean	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Median	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
CI lower limit	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
CI upper limit	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Source: CS economic model, EAG output
Abbreviations: CI = confidence interval; CS = company submission; EAG = Evidence Assessment Group; NMA = network meta-analysis; OCA = obeticholic acid
*From the EAG running the fixed effect NMA using the company code

Table 4.9: Median and 95% CI for the OR parameters from the NMA (random effects) versus lognormal parameters used by the EAG in the economic model

	NMA - random effects results			Lognormal distribution values for the EAG analyses		
OCA OR	**Mean**	**LL (95% CI)**	**UL (95% CI)**	**Expected value**	**LL (95% CI)**	**UL (95% CI)**
Cholestasis response	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Pruritus occurrence as an AE	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
All-cause discontinuation	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Source: CS economic model, EAG output
Abbreviations: AE= adverse event; CI = confidence interval; CS = company submission; EAG = Evidence Assessment Group; LL = lower limit; NMA = network meta-analysis; OCA =obeticholic acid; OR = odds ratio; UL = upper limit

- **How OR was used to determine OCA probabilities of response, pruritus and discontinuation**

The OR of response and discontinuation for OCA versus elafibranor were estimated using evidence after 12 months' follow-up. The model cycle length was three months. Transition probabilities to the low-risk biomarker state in the first four cycles were based on trial data where non-zero probabilities ranged from [redacted]. The elafibranor probability of response at 12 months was [redacted]. There was considerable uncertainty in the OR estimates.

Either a constant RR, OR, or hazard ratio (HR) can be assumed across time periods and baseline risks. While each of these may vary empirically with baseline risk due to various factors, the OR and HR are mathematically independent of the baseline risk. The mathematical dependence of RR on baseline risk makes certain RR estimates less plausible than associated HRs and ORs at different baseline risks.

The company chose to assume a constant RR. There was no apparent method in the model to ensure that the OCA probability of transitioning to mild risk would always be ≤ 1 when sampling from a lognormal or Gamma distribution for the OR parameter; and values > 1 would have occurred for moderate to mild risk in the first cycle when running the PSA.

There is no risk of deriving impossible probabilities when assuming a constant OR, or HR. For OR, this requires first deriving a RR from the OR using the transition probability in the model (see equation below[49]) before multiplying the same transition probability by that RR. For HR, this requires calculating the HR at 12 months and multiplying this with the elafibranor rate at three months derived from transition probability at three months.

$$RR_3 = \left(\frac{OR_{12}}{1 - E\_R_3 + E\_R_3 \times OR_{12}}\right)$$

Considering the different time periods (3 and 12 months) and repeated time periods, the EAG chose to assume a constant HR.

- **Effectiveness of elfibranor used in sequence, either as second-line followed by OCA or as third-line after OCA**

Elafibranor and OCA could have been included as third-line treatments in the evaluation of cost-effectiveness of elafibranor at second-line, but there was no effectiveness evidence at third-line. Treatment following discontinuation of second-line treatment is potentially not representative of what may occur in clinical practice given the use of these drugs as second-line.

4.3.4.2 Time-to-event analysis and extrapolation

- **All-cause discontinuation predictions for OCA**

The company's model took a different approach to including all-cause discontinuation compared with TA443.[6] As patients undergo treatment for the duration of their life, treatment discontinuation was also included over the long term. The company used time-to-event data for all-cause discontinuation of treatment from the elafibranor arm of ELATIVE,[4] applying a

12-month RR (derived from the OR estimate in the NMA) across each cycle to predict all-cause discontinuation for OCA.

The model selection to predict long-term discontinuation for elafibranor was chosen on the grounds of statistical fit to trial data. The company reported that clinical opinion recommended "*the flattest curve compared to other distributions*" (CS Section B.3.3.4, p. 122).[1] However, the Gompertz curve (having a flat tail) was deemed as having an unrealistically high retention rate over the long term and was therefore excluded from the base-case analysis.[1] An exponential distribution was selected in the CS as it was a good fit to the data. The exponential distribution assumes that the discontinuation rate is constant over time.

[redacted]. Furthermore, the EAG's clinical expert criticised the assumption that the risk of discontinuation is constant over time, as many patients who need to discontinue OCA due to pruritus or drug-induced liver damage will do so early in their treatment. It was considered that this is also likely to be the case with elafibranor. As such, this means that difference in discontinuation rates between elafibranor and OCA may change over time.

After the points for clarification, the company updated their base-case scenario to use the lognormal distribution function to model the long-term risk of all-cause discontinuation.[7] Previous communications between the company and clinical experts provided in the response to the EAG's points for clarification letter suggest that all-cause discontinuation occurs primarily early-on during treatment and, in the case of OCA, pruritus is a major cause for discontinuation (although other fibrates may present renal toxicity issues leading to discontinuation).[7] After the first couple of years, discontinuation occurs due to disease progression or lack of efficacy. For the long-term predictions, one of the clinicians suggested somewhere between the lognormal and the Gompertz models would be appropriate.

[redacted] This indicates to the EAG that the company base-case assumptions in the economic model are potentially overpredicting the proportion of patients who discontinue OCA. Figure 4.2 compares the discontinuation predictions for OCA from the company's base-case, the company's base-case after corrections, and the EAG's proposed analysis.

Figure 4.2: OCA all-cause treatment discontinuation predictions CS and EAG base-case

*CS base-case using the lognormal mean OR for discontinuation

Abbreviations: CS = company submission; EAG = evidence assessment group; OR = odds ratio

The EAG explored the impact on cost-effectiveness of alternative assumptions of all-cause discontinuation, particularly assessing the Gompertz function where treatment retention predictions align more closely to expert opinion, and the assumption that the treatment effect on discontinuation only lasts for the first year to represent patients who discontinue early on.

A summary of the EAG's view on the company's choice of each parametric survival model is summarised in Table 4.10 below.

Table 4.10: Comparison of the company and EAG's preferred choices of extrapolations

Survival measure	CS Section	Company choice of extrapolation	EAG's preferred choice of extrapolation
All-cause discontinuation: OCA versus elafibranor	B.3.3.4, p.121	Initial submission: Exponential with lifelong treatment effect After PfC response: Lognormal with lifelong treatment effect	Lognormal with 1-year treatment effect (Gompertz with 1-year treatment difference in the scenario analysis)

Source: EAG output

Abbreviations: CS = company submission; EAG = Evidence Assessment Group; OCA = obeticholic acid; PfC = points for clarification

4.3.4.3 Conceptualisation of pruritus in the economic model

- **Inclusion of pruritus as a TEAE and pruritus measured by the PBC-40**

The economic model includes ELATIVE data on Grade ≥ 2 TEAE occurring in ≥ 5% of participants during the trial, which includes pruritus for both the elafibranor and placebo arms.[4] The company used the OR from the NMA on pruritus recurrence as a TEAE to calculate the proportion of pruritus as a TEAE for OCA.

Independently from the analysis above, the company includes the impact of pruritus on costs and quality of life using the PBC-40, in particular for patients with PBC-40 scoring ≥ 7, classified as clinically significant pruritus.[50] The company uses NMA results for median PBC-40 score differences from baseline to 12 months to generate the proportion of OCA patients expected to have a clinically significant pruritus (PBC-40 score ≥ 7).

It is not clear to the EAG whether the definitions of pruritus as a Grade ≥ 2 TEAE and pruritus captured by the PBC-40 are mutually exclusive and, if not, what measures the company took to avoid double-counting the impact of pruritus. The EAG has applied a conservative assumption to the EAG base-case analysis where all pruritus AE differences between treatments are being captured by the PBC-40 scores, see section 6.1.1.

- **Use of the PBC-40 to generate proportions of patients with clinically significant pruritus**

After consultation with a clinical expert, the EAG is concerned that the use of the PBC-40 questionnaire to calculate the proportion of patients with clinically significant pruritus may not be an accurate approach, as clinicians in the NHS use different methods to assess whether a patient requires treatment for pruritus, including rating pruritus on 1-10 scales or using the 5D-Itch questionnaire. Uncertainty surrounding clinically significant pruritus calculated was compounded by clinical advice suggesting the proportion of OCA-treated patients presenting mild pruritus was too high. Therefore, the EAG ran a sensitivity analysis around the threshold value of clinically significant pruritus from the PBC-40 and its impact on cost-effectiveness, see scenario 3 in section 6.1.2.

4.3.5 Health-related quality of life

Table 4.11 summarises the EAG's critique on HRQoL within the economic model.

Table 4.11: Summary of EAG's critique on HRQoL

Analysis feature	Section in CS where methods are reported	EAG's assessment
HRQoL evidence used for Markov states	B.3.4.1; B.3.4.2, p.125-129. B.3.4.6.1, p.133-134;	**Some concerns** The EAG have concerns around the applicability of quality of life values for the pre-liver transplant state (capturing patients with multiple liver disease stages), across the sources gathered by the company, particularly with respect to Rice et al, 2021.[51] **Key issue 4** Utility values were elicited using the EQ-5D questionnaire in the ELATIVE trial, while the company

Analysis feature	Section in CS where methods are reported	EAG's assessment
		base-case analysis uses values from the published literature. The EAG is concerned that trial utility values were only included in scenario analysis for the mild-risk and moderate-risk patients, especially when there seems to be a large discrepancy between trial values and the parameters used for utility at the high-risk state. See section 4.3.5.1 for further comment.
Disutility for adverse effects	B.3.4.4, p.133.	**Some concerns** The EAG is uncertain whether the pruritus utility decrements adequately represent the difference in pruritus included in the model as a TEAE and as an adverse event. See section 4.3.4.3 for further comment.
Abbreviations: AE = adverse events; CEM = cost-effectiveness model; CS = company submission; EAG = Evidence Assessment Group; EQ-5D = European Quality of Life-5 Dimensions; HRQoL = health-related quality of life; LT = liver transplant; PBC = primary biliary cholangitis; SLR = systematic literature review; TEAE = treatment-emergent adverse event		

4.3.5.1 HRQoL evidence used in the cost-effectiveness model:

The utility values for each PBC biomarker risk state calculated using trial data are presented in Table 4.12. The utility values included in the CS economic model are reported in Table 4.13.

Table 4.12: Utility values for the biomarker states elicited from the ELATIVE trial

Health states	Utility values
Low-risk state	[redacted]
Moderate-risk state	[redacted]
High-risk state	[redacted]
Source: CS Document B, Table 45, p.128[1] Abbreviations: CS = company submission	

Table 4.13: Health state utility values in the CS economic model

	Utility value	Reference	Justification
Mild	0.84 (0.17)	Table 61, p. 157	Cholestatic disease utility reported in Younossi et al (2000)[52]
Moderate	0.84 (0.17)	Table 61, p. 157	Cholestatic disease utility reported in Younossi et al (2000)[52]
High	0.55 (0.11)	Table 61, p. 157	Previously reported value for compensated cirrhosis[2]
DCC	0.38 (0.08)	Table 83, p. 194	Previously reported value for DCC;[2] redacted utility decrement not applied
HCC	0.45 (0.09)	Table 61, p. 157	Previously reported value for HCC[2]
Pre-LT	0.38 (0.08)	Table 83, p. 194	Previously reported value for

	Utility value	Reference	Justification
			pre-LT;[2] redacted utility decrement not applied
LT	0.57 (0.11)	Table 83, p. 194	Previously reported value for LT;[2] redacted utility decrement not applied
Post-LT	0.67 (0.13)	Table 83, p. 194	Previously reported value for post-LT[2]
Re-emergence of PBC	0.67 (0.13)	Table 61, p. 157	Assumed equivalent to post-LT, without utility decrement provided according to KOL feedback[2]

Source: CS Section B.3.4.6.1, Table 49, p.134[1]
Abbreviations: AR = adverse reaction; CS = company submission; DCC = decompensated cirrhosis; HCC = hepatocellular carcinoma; HS = health state; KOL = key opinion leader; LT = liver transplant; PBC = primary biliary cholangitis; SE = standard error; TA = technology appraisal

- **Applicability of utility values**

There is a question around the applicability of the utility values in Table 4.13. There is significant variation in utility values in the literature referenced by the company. This CS draws upon utility estimates for similar states in hepatitis C patients. In a systematic review (6 studies, N=162) of chronic hepatitis C studies of utility values by Saeed et al (2020),[53] which was not reported in the CS, statistical heterogeneity was high (I^2 = 88%). The mean estimate 0.595 (SE = 0.062,) was higher than that reported in the CS (0.38).

- **Utility values for the high-risk health state in the trial versus the economic model**

HRQoL evidence was collected through the EQ-5D-5L in the ELATIVE trial, but utility values obtained from the literature (consistent with NICE TA443 for OCA) were used in the economic model due to concerns of small sample sizes for patients in the high-risk (biomarker) health state.[1,6] EQ-5D-5L scores from the trial were mapped to the EQ-5D-3L version using the mapping algorithm from Hernandez-Alava et al (2020).[54] A linear mixed effects model was then used to calculate the utility values of each PBC biomarker risk health state from the economic model.[1] The utility values for each PBC biomarker risk state calculated using trial data are presented in **Error! Reference source not found.**.

The company claimed that: "*the incremental difference in utility between the moderate and high risk health states is lower than expected from the regression analysis,*" which might be "*driven by the low sample size in the high risk state*" (CS Section B.3.4.2, p.128).[1] The company decided to use utility values obtained from the literature based on the above judgement, and conducted a scenario analysis using the utility values for the mild and moderate biomarker risk state using utility values from ELATIVE.[4] The EAG considers that the company could have explored a scenario using all the patient-reported data collected from the trial for all the health states covered in the model, including the high-risk of liver disease state.

The EAG acknowledges that the size of the high-risk sample was small but considers the data collected to still be informative for the analysis. The analysis relied on a sample of 78 observations at high-risk, which was only 10% of the overall sample of observations and was therefore considered unreliable.[7] Adding to this uncertainty, the company mentioned the

possibility that trial recruitment tends to favour representation from patients with better health than what would be expected for a particular health condition (PfC B16a).[7]

The utility values included in the CS economic model are reported in Table 4.13. The EAG notes that the use of utility values derived from Younossi et al (2000) for the low and moderate risk states, based on a hepatitis C population, was criticised by the EAG appraising NICE TA443.[6,52] The utility value of 0.55 for the high risk state (compensated cirrhosis) was for a chronic hepatitis C population.[55]

The EAG notes that the utility for the high-risk state used in the economic model (0.55) [redacted]. The EAG requested the company to comment on this difference in the points for clarification letter, to which the company reiterated that the decrement in utility scores observed between the moderate and the high-risk health states was lower than they expected and, therefore, was considered unreliable (PfC B16a).[7]

The EAG agrees with the company that disease symptoms are likely to be the drivers of quality of life in PBC and, particularly at the early stages, PBC displays relatively stable symptoms. The EQ-5D score analysis presented by the company in their response to the EAG's points for clarification reflects this through the small, non-statistically significant differences across biomarker health states (PfC B15b).[7]

Because the EAG considers patient-reported utility data to have value,[56] the EAG ran a scenario analysis using utilities elicited from the ELATIVE trial for all the biomarker health states.[4] Moreover, the EAG base-case adopted an alternative published EQ-5D-3L utility value (mean = 0.717, SE = 0.021, I^2 = 62%, 8 studies, N = 414) for the high risk state from a more recent source,[53] based on compensated cirrhosis for a chronic hepatitis C population (see Section 6.1.1). The value used for the high-risk state in the CS comes from Wright et al,[55] which was included in the meta-analysis in Saeed et al,[53] and which was the lowest value in the meta-analysis.

- **Utility value used for the pre-liver transplant health state**

Patients can move to the pre-LT state from the high-risk biomarker state, the DCC state and the HCC state with similar transition probabilities (1.02%, 1.53%, 1.02%) and there are significantly more patients in the high-risk state over time than in the DCC and HCC states. Utility values in these states were 0.55, 0.38, 0.45, respectively. As explained in Section 4.3.3.1, patients may stay in the pre-LT for a long time. It is not clear to the EAG that a utility of 0.38 is representative of the utility in this state. There is also the aforementioned issue of uncertainty in the applicability of several of the utility values to the PBC population. The EAG has removed the pre-LT state in its base-case analysis (see Sections 4.3.3.1 and 6.1.1).

4.3.5.2 Disutility values for adverse events

- **Disutility values for pruritus**

Pruritus was treated as a TEAE and a symptom of interest in the company's submission. The associated disutility values are presented in Table 4.14. It was not clear to the EAG how the company separated pruritus caused by TEAEs (and thus the disutility from pruritus) from pruritis as a symptom of PBC, so it is unclear to the EAG whether the differences in the pruritis

disutility values adequately represent the differences in pruritus as a TEAE and as an adverse event.

Table 4.14 Disutility values for pruritus

	Utility value	Justification
As an adverse event	0.11	Clinical expert opinion[42]
As a long-term disutility applied in the model	[redacted]	ELATIVE trial[4]
Source: CS Section B.3.4.6.2, Table 50, p.135[1] Abbreviations: CS = company submission		

4.3.6 Resources and costs

Table 4.15 summarises the EAG's critique on resources and costs within the economic model.

Table 4.15 Summary of EAG's critique on resources and costs

Analysis feature	Section in CS where methods are reported	EAG's assessment
Adverse event costs	B.3.5.3, p.142	**Appropriate** The EAG noticed there was divergence from NICE TA443[6] regarding the resources used to treat pruritus. The EAG checked with the company and an external clinical expert to ensure this reflected changes in current practice from the time of the previous submission. See Section 4.3.6.1 for further comment.
Treatment acquisition costs	B.3.5.1, p.136	**Some concerns** The company did not sufficiently justify the compliance rate used in treatment acquisition calculations for elafibranor and OCA. In response to the points of clarification, the company provided multiple estimates based on different calculation methods. See Sections 4.3.6.2 and 4.3.6.3 for further comment.
Health states costs	B.3.5.2, Table 56, P.138-41	**Some concerns** The company did not clearly reference the evidence regarding the NHS costs. See Section 4.3.6.3 for further comment.
End-of-life costs (terminal care costs)	B.3.5.5, p.143-44	**Some concerns** The company included end of life costs in the economic model for DCC and HCC, which the EAG believes may be a potential issue of double counting. See Section 4.3.6.4 for further comment.
Abbreviations: CS = company submission; EAG = Evidence Assessment Group; DCC = decompensated cirrhosis; HCC = hepatocellular carcinoma; NHS = National Health Service; OCA = obeticholic acid; PBC = primary biliary cholangitis; TA = technology appraisal; UDCA = ursodeoxycholic acid		

4.3.6.1 Adverse event costs

The EAG noted a difference in the proportions of patients having OCA and receiving medicines for pruritus in the company's current submission compared with NICE TA443;[6] these proportions are presented in Table 4.16. For example, 30% of patients treated with OCA or UDCA received colestyramine for pruritus in the current submission, yet this figure was 85% in the previous submission.[6] Colestyramine is the drug of choice for treating cholestatic pruritus recommended by NICE (see the BNF recommendation for colestyramine),[57] yet its prevalence and alternative options are not clearly stated. Clinical advice to the EAG suggested that the proportions presented for OCA/UDCA are appropriate. Moreover, after a request for comment in the EAG's points for clarification, the company confirmed that clinicians validated the resource use of managing pruritus and confirmed it reflects current practice.

Table 4.16: Percentage of patients who receive medicines for pruritus in the current and previous company submission

Drug	Percentage of patients cost applies to for patients treated with OCA or UDCA (current submission) [a]	Percentage of patients cost applies to for patients treated with OCA or UDCA (previous submission) [b]
Colestyramine	30%	85%
Rifampicin	30%	15%
Bezafibrate	20%	N/A
Gabapentin	15%	N/A
Naltrexone	5%	5%

Source: (a) CS Section B.3.5.4, Table 58, p.142;[1] (b) TA443, Section 5.5.4[6]
Abbreviations: CS = company submission; OCA = obeticholic acid; UDCA = ursodeoxycholic acid

4.3.6.2 Compliance rates

The compliance rate used in treatment acquisition calculations for elafibranor and OCA is [redacted], which was sourced from the ELATIVE study. The EAG believes that trials tend to overestimate compliance rates among patients and therefore asked the company to provide further clarification regarding the rationale for using this compliance rate.[7] In response, the company provided further estimates of treatment compliance for elafibranor ([redacted] depending on the method used to estimate compliance) and for OCA (93.55%). The company updated its base-case to have a [redacted] compliance rate for elafibranor and a 93.55% rate for OCA. The EAG base-case adopted a conservative scenario where compliance rates are 93.55% for both treatments, see section 6.1.1.

4.3.6.3 Health state costs

The costs for the health states are presented in Table 4.17. The EAG note that the costs for the HCC state are lower than the one for the DCC in the economic model. This may be because not everyone with HCC has DCC, and so some people with HCC do not incur the cost of treating complications associated with DCC. The company later corroborated this using expert views and published studies that this cost difference may occur due to less symptom severity for HCC patients relative to DCC patients.[44,51,55]

The EAG noticed that the NHS reference costs used in the economic model were not properly referenced (i.e. the service code and name of clinical procedure were not provided). As such, it is not possible for the EAG to check the consistency and appropriateness of the type of NHS costs used in the model. Hence, there is a lack of transparency in the evidence presented by the company submission.

Table 4.17: List of health states and associated costs in the economic model

Health state	Cost per cycle (GBP)	Source
Mild	106.67	National tariffs NHS England 2021/22; NICE TA443[6,58]
Moderate	154.72	National tariffs NHS England 2021/22; NICE TA443[6,58]
High	2080.52	National tariffs NHS England 2021/22; NICE TA443[6,58]
DCC	4161.05	National tariffs NHS England 2021/22; Wright et al (2006)[55,58]
HCC	3053.32	National tariffs NHS England 2021/22; Wright et al (2006)[55,58]
Pre-LT	5296.66	HST17[59]
LT	163,638.57	HST17; BNF records on azathioprine, tacrolimus and prednisolone[59-62]
Post-LT	919.57	BNF records on azathioprine, tacrolimus and prednisolone; Rice et al (2020)[51,60-62]
Re-emergence of PBC	2080.52	Assumption

Source: CS Section B.3.5.2, Table 56, p.138-41[1]
Abbreviations: BNF = British National Formulary; CS = company submission; DCC = decompensated cirrhosis; GBP = pounds sterling; HCC = hepatocellular carcinoma; HST = highly specialised technology; LT = liver transplant; NHS = National Health Service; PBC = primary biliary cholangitis; TA= technology appraisal

4.3.6.4 End of life costs

End of life costs were included in the economic model for DCC and HCC in the current submission as presented in Table 4.18. The EAG is concerned that there is potentially a double counting issue if no distinctive estimation was made between these end-of-life costs and the aforementioned health state costs for the DCC and HCC states especially since the cost values used cover a 12-month period, which is longer than the 3-month model cycle.[7] The EAG explored an alternative scenario testing the impact of removing end-of-life costs from the analysis, see scenario 5, section 6.1.2.

Table 4.18: End of life costs considered in the model

	End of life cost	Source
DCC	£10,902	Gola et al (2015)[63]
HCC	£8805	NICE TA666[64]

Source: CS Section B.3.5.5, Table 63, p.144 [1]
Abbreviations: CS = company submission; DCC = decompensated cirrhosis; HCC = hepatocellular carcinoma; TA = technology appraisal

5 COST EFFECTIVENESS RESULTS

5.1 Company's cost effectiveness results

The company's base-case deterministic cost-effectiveness results using the PAS discount for elafibranor are shown in Table 5.1 and **Error! Reference source not found.**. Table 5.1 shows the deterministic analysis for the combined PBC population of second-line patients that have inadequate response or that cannot tolerate UDCA. The analysis compares elafibranor, OCA and UDCA alone for this population and shows elafibranor dominating OCA by increasing health outcomes by [redacted] QALYs and decreasing costs by [redacted] per patient; and being more costly and more effective than UDCA alone (ICER = [redacted]). The incremental net monetary benefit of elafibranor versus OCA for a willingness to pay threshold of £30,000 was [redacted] (see Table 5.2).

Table 5.1: Company base-case deterministic results for elafibranor versus OCA and elafibranor versus UDCA, using the PAS price of elafibranor

Technology	Total costs (£)	Total LYs	Total QALYs	Incremental costs (£)	Incremental LYs	Incremental QALY	ICER (£)
Elafibranor	[redacted]	[redacted]	[redacted]	-	-	-	-
OCA	£242,656	12.67	8.27	[redacted]	[redacted]	[redacted]	Dominating
UDCA	£104,283	10.81	6.38	[redacted]	[redacted]	[redacted]	[redacted]

Source: CS Document B, Section 3.9.1

Abbreviations: CS = company submission; ICER = incremental cost-effectiveness ratio; LYs = life years gained; OCA = obeticholic acid; PAS = Patient Access Scheme; QALY = quality-adjusted life year; UDCA = ursodeoxycholic acid

Table 5.2: Company base-case deterministic results for net monetary benefit

Technology	Incremental costs (£)	Incremental QALY	ICER (£)	NMB at £20,000	NMB at £30,000
OCA	[redacted]	[redacted]	Dominating	[redacted]	[redacted]

Source: EAG outputs

Abbreviations: EAG = Evidence Assessment Group; ICER = incremental cost-effectiveness ratio; NMB = net monetary benefit; OCA = obeticholic acid

5.2 Company's sensitivity analyses

To explore uncertainty within their cost-effectiveness analysis, the company conducted a probabilistic sensitivity analysis over 10,000 iterations using the PAS price for elafibranor. After updating the model following the points for clarification process, the company reported the following probabilistic sensitivity analysis (PSA) results showing elafibranor as the dominant intervention over OCA, increasing QALYs by [redacted] and decreasing costs by [redacted]. Table 5.3 and Figure 5.1: ICEP for elafibranor versus OCA and elafibranor versus UDCA (10,000 iterations), using the PAS price of elafibranor show the probabilistic results reported by the company after the response to the EAG's points for clarification.

The EAG considers that the parametric distributions used to model uncertainty in the mean estimate were inappropriate (see section 4.3.4.1). These were corrected as errors in Section 6. The EAG also considers that arbitrary uncertainty has been introduced in the model by

specifying a gamma distribution for the cost of OCA using variance based on an arbitrary 20% of the cost of OCA. The EAG has not corrected for this, but is should not introduce much uncertainty relative to the uncertainty elsewhere in the model.

Table 5.3: PSA results for elafibranor versus OCA and elafibranor versus UDCA, using the PAS price of elafibranor

Technology	Total costs (£)	Total QALYs	Incremental costs (£)	Incremental QALY	ICER (£)
Elafibranor	[redacted]	[redacted]	-	-	-
OCA	£243,132	7.997	[redacted]	[redacted]	Dominating
UDCA	£102,898	6.499	[redacted]	[redacted]	[redacted]

Source: CS Document B, Section B.3.10.1[1]
Abbreviations: CS = company submission; ICER = incremental cost-effectiveness ratio; OCA = obeticholic acid; PAS = Patient Access Scheme; PSA = probabilistic sensitivity analysis; QALY = quality-adjusted life year; UDCA = ursodeoxycholic acid

Figure 5.1: ICEP for elafibranor versus OCA and elafibranor versus UDCA (10,000 iterations), using the PAS price of elafibranor

[redacted]

Source: PfCs[7]
Abbreviations: GBP = pounds sterling; OCA = obeticholic acid; PfC = points for clarification; PSA = probabilistic sensitivity analysis; QALY = quality-adjusted life-year; UDCA = ursodeoxycholic acid

The EAG re-ran the PSA analysis in the same model file and obtained markedly different results, with marked differences in the CrIs as well. In the EAG's run, elafibranor was dominant over OCA, presenting an increment in QALYs of [redacted] and a change in costs of [redacted] Results obtained by the EAG are reported in Table 5.4 and Figure 5.2.

Table 5.4 PSA results for elafibranor versus OCA and elafibranor versus UDCA, using the PAS price of elafibranor

Technology	Total costs (£)	Total QALYs	Incremental costs (£)	Incremental QALY	ICER (£)
Elafibranor	[redacted]	[redacted]	-	-	-
OCA	£286,862	8.80	[redacted]	[redacted]	Dominating
UDCA	£103,017	6.50	[redacted]	[redacted]	[redacted]

Source: CS Document B, Section B.3.10.1[7]
Abbreviations: CS = company submission; ICER = incremental cost-effectiveness ratio; OCA = obeticholic acid; PAS = Patient Access Scheme; PSA = probabilistic sensitivity analysis; QALY = quality-adjusted life year; UDCA = ursodeoxycholic acid

Figure 5.2: EAG re-run of ICEP for elafibranor versus OCA (10,000 iterations), using the PAS price of elafibranor

Source: CS model, EAG analysis
Abbreviations: EAG = Evidence Assessment Group; GBP = pounds sterling; ICEP = incremental cost-effectiveness plane; OCA = obeticholic acid; PAS = Patient Access Scheme; PSA = probabilistic sensitivity analysis; QALY =quality-adjusted life year

The base-case one-way sensitivity analysis (OWSA) presented by the company excluded the deterministic analysis of the OR parameters for cholestasis response, occurrence of pruritus, and all-cause discontinuation, as well as treatment compliance for elafibranor and OCA. The EAG considered these parameters to be an informative part of the analysis. Therefore, these were included and reported subsequently in Table 5.5 and **Error! Reference source not found.**.

Table 5.5: OWSA results for elafibranor versus OCA (top 10 most sensitive parameters only)

Parameter name	Lower bound NMB (£)	Upper bound NMB (£)	Difference (£)
OCA odds ratio of all-cause discontinuation	[redacted]	[redacted]	[redacted]
OCA cost per cycle (10 mg cycle 3+) (GBP)	[redacted]	[redacted]	[redacted]
OCA compliance	[redacted]	[redacted]	[redacted]
Elafibranor compliance	[redacted]	[redacted]	[redacted]
OCA cost per cycle (5 mg up to cycle 2) (GBP)	[redacted]	[redacted]	[redacted]
Health state cost – High	[redacted]	[redacted]	[redacted]
OCA odds of cholestasis response	[redacted]	[redacted]	[redacted]
Health state cost – LT	[redacted]	[redacted]	[redacted]
Elafibranor clinically significant itch at month 12+	[redacted]	[redacted]	[redacted]
Mean difference in PBC-40 Itch relative to elafibranor (versus OCA 5-10 mg) at month 12	[redacted]	[redacted]	[redacted]

Source: CS Document B, Section B.10.2[1]
Abbreviations: CS = company submission; GBP = pounds sterling; LT = liver transplant; NMB = net monetary benefit; OCA = obeticholic acid; OWSA = one-way sensitivity analysis

Figure 5.3: OWSA results for elafibranor versus OCA in net monetary benefit (top 10 most sensitive parameters only)

Source: CS economic model
Abbreviations: CS = company submission; GBP = pounds sterling; LT = liver transplant; NMB = net monetary benefit; OCA = obeticholic acid; OWSA = one-way sensitivity analysis; PBC = primary biliary cholangitis

The OWSA suggests the OR parameter of discontinuation is the largest determinant of cost-effectiveness, as well as an important source of uncertainty. Other parameters included the cost of OCA, the impact of compliance differences on drug costs, the health state cost for high-risk of liver disease patients, and the OR of cholestasis response.

From the scenario analyses conducted by the company, changing the price of OCA had the potential to make it a less costly and less effective alternative to elafibranor. Scenario results of particular relevance to the EAG are reported in Table 5.6, full results are reported in the company response to the EAG's points for clarification (Appendix C).[7] Changing the assumption around discontinuation had the largest impact on relative efficacy, although elafibranor remained dominant over OCA. Excluding AEs had little impact on cost-effectiveness, while the use of more strict treatment effectiveness definition decreased the incremental effectiveness of elafibranor but this remained positive.

Table 5.6: Deterministic scenario analysis results for the company base-case submitted after the points for clarification (selection of scenarios considered relevant to the EAG analysis)

#	Model aspect	Base-case	Scenario analysis	Incremental costs OCA (£)	Incremental QALYs OCA	ICER versus OCA (£)
	Company base-case	**N/A**	**N/A**	[redacted]	[redacted]	**Dominating**
1	Time horizon	Lifetime	20 years	[redacted]	[redacted]	Dominating
4	OCA price per pack discount	0%	10%	[redacted]	[redacted]	Dominating
5			20%	[redacted]	[redacted]	Dominating
6			30%	[redacted]	[redacted]	[redacted]
7			40%	[redacted]	[redacted]	[redacted]
8			50%	[redacted]	[redacted]	[redacted]
9			[redacted]	[redacted]	[redacted]	[redacted]
11	AEs	Include	Exclude	[redacted]	[redacted]	Dominating
13	Definition of treatment response	Cholestasis response	ALP normalisation	[redacted]	[redacted]	Dominating
14			Reduction in ALP of ≥ 40%	[redacted]	[redacted]	Dominating
15			PARIS-II	[redacted]	[redacted]	Dominating
16	UDCA extrapolations	Improvements not possible	Improvements possible	[redacted]	[redacted]	Dominating
17	UDCA transition matrix extrapolation	Last observation carried forwards	Average of all transition matrices	[redacted]	[redacted]	Dominating
18	Moderate risk to liver disease transitions	Include	Exclude	[redacted]	[redacted]	Dominating
19	Duration of treatment effect of elafibranor relative to OCA on discontinuation	Lifetime	1 year	[redacted]	[redacted]	Dominating
20		Lognormal	Exponential	[redacted]	[redacted]	Dominating
21			Weibull	[redacted]	[redacted]	Dominating

#	Model aspect	Base-case	Scenario analysis	Incremental costs OCA (£)	Incremental QALYs OCA	ICER versus OCA (£)
22	Treatment discontinuation distribution		Log-logistic	[redacted]	[redacted]	Dominating
23			Gompertz	[redacted]	[redacted]	Dominating
25	Mild and moderate risk biomarker health states utilities	Younossi et al 2000 [52]	ELATIVE	[redacted]	[redacted]	Dominating
27	Compliance	Drug exposure ([redacted] versus 93.55%)	Mean cumulative ([redacted] versus 93.55%)	[redacted]	[redacted]	Dominating
28	Discontinuation	Return to baseline	Stay in state	[redacted]	[redacted]	Dominating

Source: response to the EAG's points for clarification, appendix c[7]
Abbreviations: AE = adverse event; ALP = alkaline phosphatase; ICER; = incremental cost-effectiveness ratio; N/A = not applicable; OCA = obeticholic acid; QALY = quality adjusted life years; UDCA= ursodeoxycholic acid

5.3 Model validation and face validity check

5.3.1 Face validity assessment and technical verification

The EAG has found multiple errors in the excel file calculating the model, these are listed in Section 6.1.1.

5.3.2 Comparison with external data

No expert opinion was elicited to validate overall survival predictions from the model (see Section 4.3.3.3). UK-PBC data and expert opinion were used to validate OCA discontinuation data.

6 EVIDENCE ASSESSMENT GROUP'S ADDITIONAL ANALYSES

6.1 Exploratory and sensitivity analyses undertaken by the EAG

Based on the considerations in the preceding sections of this EAG report, the EAG defined an EAG base-case. This EAG base-case included several adjustments to the company base-case presented in Section **Error! Reference source not found.**. These adjustments have been subdivided into three categories (derived from Kaltenthaler 2016).[65]

- Fixing errors (correcting the model where the company's submitted model was unequivocally wrong)
- Fixing violations (correcting the model where the EAG considered that the NICE reference case, scope or best practice had not been adhered to)
- Matters of judgement (amending the model where the EAG considers that reasonable alternative assumptions are preferred)

6.1.1 EAG base-case

Adjustments made by the EAG to derive the EAG base-case (using the CS base-case as starting point) are listed below.

Fixing errors

1. High-risk to DCC risk parameter, Excel file: the company stated that the source of the annual transition probability between high risk and DCC of 1% was NICE TA443.[6] The value in NICE TA443 was actually 10%. "Data Store!" Sheet, Cell E127, changed value 1% for 10%.

2. Distribution sampling the OR parameters (see section 4.3.4.1), Excel file: The EAG changed the distribution sampling the OR parameters for cholestasis response, all-cause discontinuation, and pruritus recurrences as a TEAE for the probabilistic analysis to the lognormal distribution. "Model Parameters!" Sheet, Cell F33 update formula to "=(LN(M33)-LN(L33))/3.92", Cell J33 update formula to "=IFERROR(EXP(NORM.INV(RAND(),LN('Clinical Inputs'!D20),F33)),E33)". Cell F34 update formula to "=(LN(M34)-LN(L34))/3.92", Cell J34 update formula to "=IFERROR(EXP(NORM.INV(RAND(),LN('Clinical Inputs'!D127),F34)),E34)". Cell F79 update formula to "=(LN(M79)-LN(L79))/3.92", Cell J79 update formula to "=IFERROR(EXP(NORM.INV(RAND(),LN('Clinical Inputs'!D143),F79)),E79)"

3. Mean and median OR parameters (see section 4.3.4.1), Excel file: the company's base-case analysis uses the median parameters from the NMA for the OR of OCA on cholestasis response, all-cause discontinuation, and pruritus recurrence as TEAE, as the mean value in the deterministic analysis. Initially the EAG used the mean values from the distributions sampling each OR parameter in the model, after the factual accuracy check, the company provided the mean estimates from the NMA results. "Model Parameters!" Sheet, Cells E33, E34, E79 values were replaced by the mean values in Table 4.9, respectively.

4. The discounting is implemented from cycle 0 rather than 1: The EAG reconstructed the Markov trace to make it easier for the EAG to remove the pre-LT state in a scenario analysis described below, and initial cycle for discounting became apparent. See "EAG elafibranor engine!" Sheet, and "EAG OCA engine!" Sheet.

5. Excel file: The upper and lower values for the OR of all-cause discontinuation are not consistent with the credible intervals reported in the submission:[1] Model parameters! Sheet, Cells L79 and M79, changed values to [redacted]

6. Excel file: The OR parameter for ALP normalisation is 0.07 in the economic model rather than [redacted] stated in the company's response to the EAG's points for clarification, question B2.c, page 31[7]: "Data Store!" sheet, cell P65, changed value 0.07 to [redacted].

7. Excel file and CS Document B (Section B.3.10.2):[1] The submitted model did not include the NMA parameters for OCA odds of cholestasis response, odds of pruritus occurrence, and odds of discontinuation in the OWSA: "Model Parameters!" sheet, column K, cells K33, K34, and K79, replaced value with "0".

8. Excel file: The model does not include OCA and elafibranor compliance rates in the OWSA: "Model Parameters!" sheet, column K, K86 and K89 replaced value with "0".

9. Excel file: Compliance parameters sampled from a normal distribution can go above 100% in the sensitivity analyses. The sampling distribution was changed to the Beta distribution: "Model Parameters!" sheet; changed formula in G86 to "=IFERROR(E86*((E86*(1-E86)/F86^2)-1),"")"; changed formula in H86 to "=IFERROR((1-E86)*((E86*(1-E86)/F86^2)-1),"")"; changed formula in J86 to "=IFERROR(BETA.INV(RAND(),G86,H86),E86)"; updated lower and upper distribution values. In row 89 changed formula in G89 to "=IFERROR(E89*((E89*(1-E89)/F89^2)-1),"")"; changed formula in H89 to "=IFERROR((1-E89)*((E89*(1-E89)/F89^2)-1),"")"; changed formula in J89 to "=IFERROR(BETA.INV(RAND(),G89,H89),E89)".

10. The model does not include UDCA cost parameters in the OWSA: "Model Parameters!" sheet, cell K90, replaced value with "0".

11. Although the analysis in the company submission tests multiple risk distributions for the baseline risk of elafibranor, the model does not include the uncertainty around the parameter inputs for the probabilistic distribution of the baseline risk of all-cause discontinuation of elafibranor. The EAG used the Gompertz, log-logistic, and exponential distributions in the scenario analysis to account for this.

12. The model cycle length was three months. The cycle treatment discontinuation probabilities were calculated from 84-day time periods rather than 91.25 day time periods from the parametric time to discontinuation curves. The EAG changed the cells in: Data Store! D624:D924 to '=C625*cycle_length_days' from '=C625*(12*7)'.

13. Upper interval level of the Odds of cholestasis response parameter: after the factual accuracy check the company corrected that the upper interval levels of the OR parameter for OCA cholestasis response had been erroneously reported in the company submission document B and the response to the points for clarification. The value in sheet "Model Parameters!" cell M33 was updated to [redacted].

Fixing violations

The EAG did not identify a clear violation of the NICE guidelines, or the scope agreed between NICE and the company. There are questions surrounding the potential omission of fibrates

from the scope, as well as the potential inclusion of elafibranor and OCA in sequence as an alternative strategy (see section 4.3.2.1).

Matters of judgement

1. *Assumption of constant 12-month hazard ratios*

The OR of response and discontinuation for OCA versus elafibranor were estimated using evidence after 12 months follow-up (see Section 4.3.4.1). The model cycle length was three months. Transition probabilities to the low-risk biomarker state in the first four cycles were based on trial data where non-zero probabilities ranged from [redacted]. The elafibranor probability of response at 12 months was [redacted]. There was considerable uncertainty in the OR estimates.

As explained in Section 4.3.4.1, the EAG preferred to assume a constant HR over different time periods and baseline risks rather than a constant RR that the company assumed.

2. The pre-liver transplant health state in the model

The economic model structure proposed by the company included a pre-LT state through which a patient must pass before transitioning to the LT state. The three-month probability of a LT from the pre-LT state was 0.1, and the patient can die before a transplant. Patients can move to the pre-LT state from: the PBC biomarker states of moderate risk and high risk; the DCC state; or the HCC state (see Section 4.3.3.1). There is structural uncertainty associated with the inclusion of this state.

The approach taken by the EAG to address this issue is borrowed from the appraisal of NICE TA443, where the then EAG decided towards eliminating the pre-liver transplant state to allow the cohort to transition from health states at risk of liver failure directly to the liver transplant state.[6,43] Moreover, although changing this assumption is expected to reduce the survival predictions of PBC patients in the short-term, the change in transplant-free survival was very small, Table 6.1 compares the transplant-free survival predictions for the company base-case model (after fixing for errors 1 to 12) between including the pre-LT state versus allowing direct transitions to LT.

Table 6.1 Transplant-free survival predictions for OCA in the company base-case model after errors 1-12

	Including pre-LT	Direct transitions to LT
Timepoints	**OCA**	**OCA**
1 year	[redacted]	[redacted]
5 years	[redacted]	[redacted]
10 years	[redacted]	[redacted]
20 years	[redacted]	[redacted]
40 years	[redacted]	[redacted]
Median (years)	[redacted]	[redacted]

Source: CS economic model, EAG output
Abbreviations: CS = company submission; EAG = Evidence Assessment Group; LT = liver transplant; OCA = obeticholic acid

3. Discontinuation assumptions

After considering the opinion of clinicians consulted by the EAG and by the company, the EAG considers that the primary driver of outcomes in the model is the difference in all-cause discontinuation between elafibranor and OCA. The results of the NMA suggest elafibranor offers an improvement in all-cause discontinuation over OCA and the model assumes this difference is maintained during the complete lifetime duration of treatment (see Section 4.3.4.2).

Pruritus is a primary factor driving differences in discontinuation rates between OCA and elafibranor; it is expected that patients are more likely to discontinue treatment early on if pruritus is the primary cause, based on the clinical opinion received by the company.[42] Therefore, the EAG base-case model assumes that the difference between elafibranor and OCA in discontinuation rates is only maintained over the first year. This is likely to be a conservative assumption, based on the 12-month data informing the NMA.

The EAG has explored the use of a Gompertz function to model long-term treatment discontinuation in the scenario analysis (see Sections 4.3.4.2 and 6.1.2).

4. High risk state excess mortality as a percentage of general population mortality

One of the reasons that excess mortality for high-risk of liver disease has a large impact on the results is because the company opted for an additive approach increasing the per-cycle mortality risk by 1.2% (e.g. 2% in general population + 1.2% excess). The company reported that a clinical expert stated that the excess mortality for the high-risk state could be between 0% and 4%. Considering the uncertainty around an excess mortality risk in the high-risk biomarker state and the lower than expected survival estimates in the model, the EAG opted for an approach that reinterprets the 1.2% excess mortality as a percentage of the age-specific general population mortality probability (0.02*1.012 rather than 0.02+0.012; see Section 4.3.3.1).

5. Alternative utility values for the high-risk state

The scenarios presented by the company only include ELATIVE trial data for the mild and moderate PBC biomarker states, as pointed out in Section 4.3.5.1. The EAG has included a scenario analysis using ELATIVE data for all biomarkers (see Section 6.1.2). Moreover, the EAG has adopted utility values for the high-risk state from a more up-to-date study in its base-case equivalent to 0.72,[53] which is in-between the trial data estimate and the utility value proposed by the company based on published evidence.

6. Pruritus as a symptom or as a TEAE

It remained unclear to the EAG how patients with pruritus as a Grade ≥ 2 AE were differentiated from pruritus patients identified using the PBC-40 scale. Therefore, the EAG base-case makes the conservative assumption that pruritus differences (both as a symptom and treatment expected AE - TEAE) are being captured by PBC-40 score differences. Hence, the frequency of pruritus as a TEAE was assumed to be equal between elafibranor and OCA. This was done to avoid double-counting in the calculation of the impact of pruritus on quality of life, as highlighted in Sections 4.3.4.3 and 4.3.5.2.

7. Compliance rates

Differences in compliance rates between elafibranor and OCA can vary according to the method used to calculate them (see the company's response to the points for clarification and Section 4.3.6).[7] As described in Section 4.3.6.2, since the administration methods of elafibranor and OCA are similar the EAG base-case makes the conservative assumption that both treatments follow the OCA compliance rate provided by the company of 93.6%.

6.1.2 EAG exploratory scenario analyses

The EAG performed the following scenario analyses to explore the impact of alternative assumptions conditional on the EAG base-case.

EAG scenarios

1. Reduce the excess mortality risk in the high-risk biomarker state by changing the excess mortality at high-risk from 1.2% to 0% (see Section 4.3.3.1).
2. Extrapolation of discontinuation: Assume no difference in discontinuation (set all-cause discontinuation OR for OCA versus elafibranor to 1; see Section 4.3.4.1).
3. Adverse events: Change the PBC-40 threshold for clinically significant pruritus from scores ≥ 7 to scores ≥ 8 (see Sections 4.3.4.3 and 4.3.5.2).
4. HRQoL: Use ELATIVE trial health-utility values for all biomarker states (see Section 4.3.5.1 and Table 4.12).
5. Resources and costs: Remove the palliative care costs from the HCC and DCC states (see Section 4.3.6.4).

Scenarios from the CS

6. Assume patients do not change biomarker risk after moving to third-line (see Section **Error! Reference source not found.**).
7. Change the discontinuation distribution to the Gompertz function from the lognormal function (see Section 4.3.4.1).
8. Change the discontinuation distribution to the log-logistic function from the lognormal function (see Section 4.3.4.1).
9. Change the discontinuation distribution to the exponential function from the lognormal function (see Section 4.3.4.1).
10. Remove the moderate risk transitions to liver disease (see Section 4.3.3.1).
11. Remove the restriction that UDCA patients cannot improve (see Section **Error! Reference source not found.**).
12. Use average biomarker risk transition probabilities for UDCA after 12 months rather than only 9-12 month probabilities and remove the restriction that UDCA patients cannot improve (see Section **Error! Reference source not found.**).
13. Other definitions of treatment response: ALP normalisation (see Section 4.3.4.1).
14. Other definitions of treatment response: 40% reduction in ALP (see Section 4.3.4.1).

15. Other definitions of treatment response: PARIS-II (see Section 4.3.4.1).

16. OCA unit price reduced by 20%

17. OCA unit price reduced by 50%

6.1.3 EAG subgroup analyses

No additional subgroup analyses were conducted by the EAG.

6.2 Impact on the ICER of additional clinical and economic analyses undertaken by the EAG

6.2.1 The EAG base-case, scenario and sensitivity analyses

The EAG base-case was described in Section 6.1.1. Table 6.2 reports the cost-effectiveness results of updating the company base-case model correcting for errors found by the EAG, and the individual impact of the matters of judgement by the EAG to generate the EAG base-case results.

Treatment discontinuation has the biggest impact on the cost-effectiveness results. Increasing treatment discontinuation rates decreases treatment cost, increases liver disease cost, and decreases total QALYs. Treatment costs dwarf liver disease costs. When fixing errors in the company model, the mean OR for discontinuation was used instead of the median value. That increased the discontinuation rate for OCA, significantly reducing the total cost of the OCA arm. OCA is not cost-effective compared to UDCA at a threshold of £30,000 with an ICER of £67,707/QALY. This indicates that the reduction in OCA cost is more significant than the reduction in OCA QALYs. The deterministic ICER for elafibranor increased from elafibranor dominating to an ICER of £1,528 after fixing errors.

The cost-effectiveness of elafibranor + UDCA versus OCA + UDCA with UDCA as third-line treatment is a combination of the cost-effectiveness of OCA + UDCA and the cost-effectiveness of UDCA. The ICER for elafibranor versus OCA is £1,528, while the ICER for elafibranor versus UDCA was £25,643. Hence, the greater percentage of patients in the OCA arm receiving UDCA only, the less cost-effective elafibranor is. In a full incremental analysis, OCA is dominated by extension, and would be eliminated from the analysis. However, given that OCA is recommended for use in the NHS, the pairwise results for elafibranor versus OCA are presented in this section.

Likewise, when the difference in discontinuation rates between OCA and elafibranor was assumed to only last for 1 year, more patients continued receiving OCA, and this increased the ICER for elafibranor from £1,528 to elafibranor dominating after making that assumption. OCA cost increases significantly.

Making the assumption of a constant hazard ratio has the next biggest impact, followed by a higher utility value for the high risk biomarker; while the other preferred assumptions in the EAG base case have little impact on cost-effectiveness outcomes.

Table 6.2: Deterministic and probabilistic EAG base-case

Technologies	Total costs	Total QALYs	Incremental costs	Incremental QALYs	ICER (£/QALY)
CS base-case – deterministic					
Elafibranor	[redacted]	[redacted]	[redacted]	[redacted]	
OCA	[redacted]	[redacted]	[redacted]	[redacted]	Elafibranor Dominating
CS base-case – probabilistic					
Elafibranor	[redacted]	[redacted]	[redacted]	[redacted]	
OCA	[redacted]	[redacted]	[redacted]	[redacted]	Elafibranor Dominating
Fixing errors (1-12) – deterministic					

Technologies	Total costs	Total QALYs	Incremental costs	Incremental QALYs	ICER (£/QALY)
Elafibranor	[redacted]	[redacted]	[redacted]	[redacted]	
OCA	[redacted]	[redacted]	[redacted]	[redacted]	£1,528
Fixing errors (1-12) – probabilistic					
Elafibranor	[redacted]	[redacted]	[redacted]	[redacted]	
OCA	[redacted]	[redacted]	[redacted]	[redacted]	Elafibranor Dominating
Constant hazard ratio for response and discontinuation					
Elafibranor	[redacted]	[redacted]	[redacted]	[redacted]	
OCA	[redacted]	[redacted]	[redacted]	[redacted]	£6391
Removing the pre-liver transplant state					
Elafibranor	[redacted]	[redacted]	[redacted]	[redacted]	
OCA	[redacted]	[redacted]	[redacted]	[redacted]	£1295
Reducing the difference in discontinuation rates to 1 year					
Elafibranor	[redacted]	[redacted]	[redacted]	[redacted]	
OCA	[redacted]	[redacted]	[redacted]	[redacted]	Elafibranor Dominating
Changing the formula of excess mortality at high-risk					
Elafibranor	[redacted]	[redacted]	[redacted]	[redacted]	
OCA	[redacted]	[redacted]	[redacted]	[redacted]	£1524
Alternative utility at high-risk					
Elafibranor	[redacted]	[redacted]	[redacted]	[redacted]	
OCA	[redacted]	[redacted]	[redacted]	[redacted]	£1657
Pruritus differences using PBC-40 scores only					
Elafibranor	[redacted]	[redacted]	[redacted]	[redacted]	
OCA	[redacted]	[redacted]	[redacted]	[redacted]	£1553
Equivalent compliance rates					
Elafibranor	[redacted]	[redacted]	[redacted]	[redacted]	
OCA	[redacted]	[redacted]	[redacted]	[redacted]	£748
EAG base-case (errors 1-12, matters of judgment 1-7) – deterministic*					
Elafibranor	[redacted]	[redacted]	[redacted]	[redacted]	
OCA	[redacted]	[redacted]	[redacted]	[redacted]	Elafibranor Dominating
EAG base-case (errors 1-12, matters of judgment 1-7) – probabilistic*					
Elafibranor	[redacted]	[redacted]	[redacted]	[redacted]	
OCA	[redacted]	[redacted]	[redacted]	[redacted]	Elafibranor Dominating

*EAG results updated after the FAC, see fixing errors 3 and 13
Abbreviations: CS = company submission; EAG = Evidence Assessment Group; ICER = incremental cost-effectiveness ratio; QALY = quality-adjusted life year

6.3 Overall conclusions of the EAG's cost-effectiveness analysis

The estimated probabilistic results from the EAG base-case suggest that elafibranor dominates OCA using the PAS price for elafibranor. Incremental QALYs for elafibranor versus OCA were [redacted] and incremental costs were [redacted]. The probabilistic EAG base-case analyses indicated cost effectiveness probabilities of [redacted]% and [redacted]% at willingness to pay thresholds of £20,000 and £30,000 per QALY gained, respectively.

The incremental cost-effectiveness plane showing the incremental costs and QALYs for elafibranor compared to OCA is presented in Figure 6.1. The cost-effectiveness acceptability curves for elafibranor and OCA is presented in Figure 6.2.

Figure 6.1 Incremental cost-effectiveness plane elafibranor versus OCA (EAG base-case)

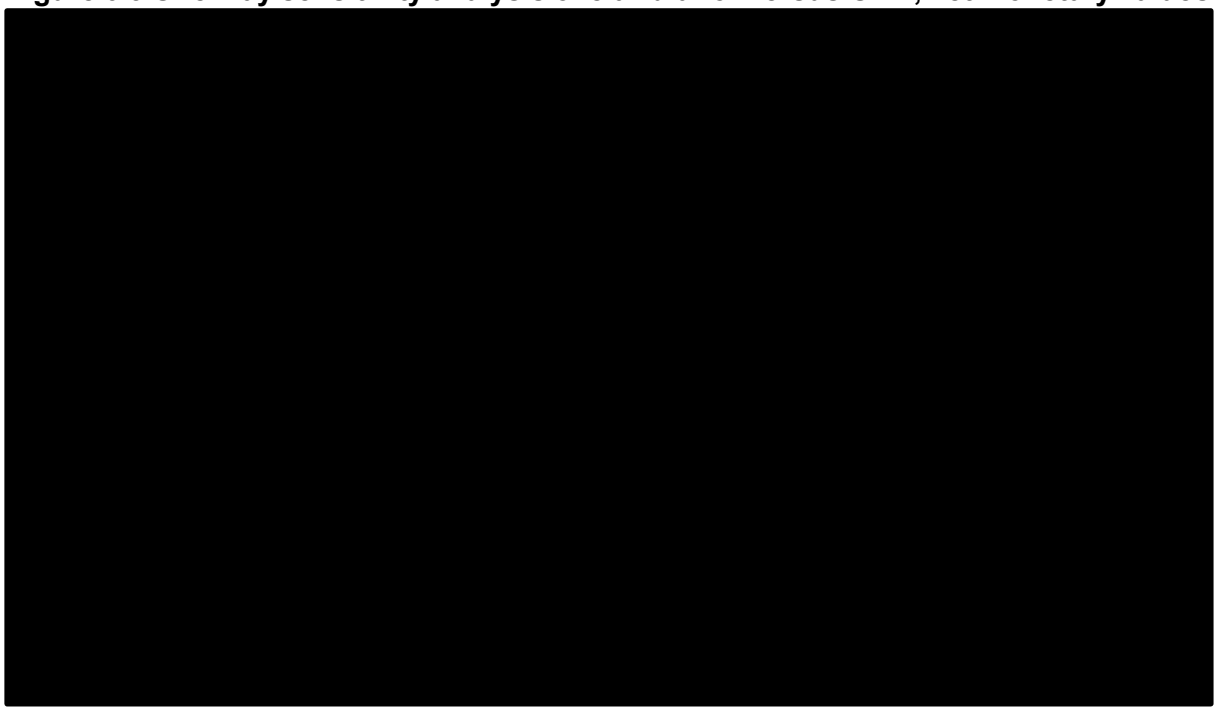
Source: CS model, EAG's base-case
Abbreviations: CS = company submission; EAG = Evidence Assessment Group; GBP = pounds sterling; OCA = obeticholic acid; PSA = probabilistic sensitivity analysis; QALY = quality-adjusted life year

Figure 6.2 Cost-effectiveness acceptability curve (CEACs) elafibranor versus OCA (EAG base-case)

Source: CS model, EAG's base-case
Abbreviations: CEAC = cost-effectiveness acceptability curve; CS = company submission; EAG = Evidence Assessment Group; GBP = pounds sterling; OCA = obeticholic acid

The most influential parameters in the deterministic OWSA were: the unit cost of OCA; the odds ratio of all-cause discontinuation; differences in compliance rates; and differences in clinically significant pruritus. Treatment response had a minor impact relative to these parameters in the cost-effectiveness results. Results using net monetary values are illustrated in Figure 6.3 and reported in Table 6.3.

Figure 6.3 One-way sensitivity analysis of elafibranor versus OCA, net monetary values



Source: CS model, EAG's base-case
Abbreviations: CS = company submission; EAG = Evidence Assessment Group; GBP = pounds sterling; LT = liver transplant; NMB = net monetary benefit; OCA = obeticholic acid

Table 6.3 One-way sensitivity analysis of elafibranor versus OCA, net monetary values

Parameter name	Lower bound NMB (£)	Upper bound NMB (£)	Difference (£)
OCA cost per cycle (10 mg cycle 3+) (GBP)	[redacted]	[redacted]	[redacted]
OCA odds ratio of all-cause discontinuation	[redacted]	[redacted]	[redacted]
OCA compliance	[redacted]	[redacted]	[redacted]
Elafibranor compliance	[redacted]	[redacted]	[redacted]
OCA cost per cycle (5 mg up to cycle 2) (GBP)	[redacted]	[redacted]	[redacted]
Elafibranor clinically significant itch at Month 12+	[redacted]	[redacted]	[redacted]
Mean difference in PBC-40 Itch relative to elafibranor (vs OCA 5-10 mg) at Month 12	[redacted]	[redacted]	[redacted]
Health state cost – LT	[redacted]	[redacted]	[redacted]

Parameter name	Lower bound NMB (£)	Upper bound NMB (£)	Difference (£)
OCA odds of cholestasis response	[redacted]	[redacted]	[redacted]
Health state cost – High	[redacted]	[redacted]	[redacted]

Source: CS Document B, Section B.10.2[1]
Abbreviations: CS = company submission; GBP = pounds sterling; LT = liver transplant; NMB = net monetary benefit; OCA = obeticholic acid

The results of the EAG scenario analyses are reported in Table 6.4. The scenarios with the largest impact on the cost-effectiveness of elafibranor versus OCA assessed by the EAG were: assuming no treatment difference in discontinuation (more cost-savings but less incremental QALYs), changing the risk function of treatment discontinuation (higher risks led to lower cost-savings and lower incremental QALYs), changing the assumptions around third-line treatment with UDCA (less severe disease progression meant less cost-savings and fewer incremental QALYs), and using more strict definitions of treatment effectiveness (leading to less cost-savings and fewer incremental QALYs).

Table 6.4: EAG scenario analysis

Scenario #	EAG base-case input	Alternative input	Incremental costs (£)	Incremental QALYs	ICER (£/QALY)
	EAG base-case	N/A	[redacted]	[redacted]	Elafibranor Dominating
1	1.2% excess mortality at high-risk	No excess mortality at high-risk	[redacted]	[redacted]	Elafibranor Dominating
2	Treatment difference on discontinuation for 1 year	No treatment difference on discontinuation	[redacted]	[redacted]	Elafibranor Dominating
3	Clinically significant itch if PBC-40 ≥ 7	Clinically significant itch if PBC-40 ≥ 8	[redacted]	[redacted]	Elafibranor Dominating
4	Literature values for PBC biomarker state utilities	Trial values for PBC biomarker state utilities	[redacted]	[redacted]	Elafibranor Dominating
5	Palliate care costs for HCC and DCC	Removing palliative care costs for HCC and DCC	[redacted]	[redacted]	Elafibranor Dominating
6	Risk distribution after discontinuation based on ELATIVE baseline	Risk distribution after discontinuation does not change	[redacted]	[redacted]	Elafibranor Dominating
7	All-cause discontinuation	All-cause discontinuation	[redacted]	[redacted]	Elafibranor Dominating

Scenario #	EAG base-case input	Alternative input	Incremental costs (£)	Incremental QALYs	ICER (£/QALY)
	risk function: lognormal	risk function: Gompertz			
8		All-cause discontinuation risk function: Log-logistic	[redacted]	[redacted]	Elafibranor Dominating
9		All-cause discontinuation risk function: Exponential	[redacted]	[redacted]	Elafibranor Dominating
10	Risk of progression from moderate risk to liver disease	No risk of progression from moderate risk to liver disease	[redacted]	[redacted]	Elafibranor Dominating
11	UDCA treated patients cannot improve their risk category after year 1	UDCA treated patients can improve their risk category	[redacted]	[redacted]	Elafibranor Dominating
12	UDCA probabilities after one year follow the probabilities seen in months 9-12	UDCA probabilities after one year follow the average probabilities of the first 12 months including probabilities to improve PBC risk	[redacted]	[redacted]	Elafibranor Dominating
13	Treatment effectiveness definition: Cholestasis response	Treatment effectiveness definition: ALP normalisation	[redacted]	[redacted]	Elafibranor Dominating
14		Treatment effectiveness definition: Barcelona criteria	[redacted]	[redacted]	Elafibranor Dominating
15		Treatment effectiveness definition: PARIS-II	[redacted]	[redacted]	Elafibranor Dominating
16	List price for OCA 5-10 mg	20% price reduction for OCA 5-10 mg	[redacted]	[redacted]	Elafibranor Dominating

Scenario #	EAG base-case input	Alternative input	Incremental costs (£)	Incremental QALYs	ICER (£/QALY)
17		50% price reduction for OCA 5-10 mg	[redacted]	[redacted]	[redacted]

Source: EAG outputs
Abbreviations: ALP = alkaline phosphate; DCC = decompensated cirrhosis; EAG = Evidence Assessment Group; HCC = hepatocellular carcinoma; ICER = incremental cost-effectiveness ratio; N/A = not applicable; OCA = obeticholic acid; PBC = primary biliary cholangitis; QALY = quality-adjusted life year; UDCA = ursodeoxycholic acid

6.4 Overall conclusions of the EAG's critique

The EAG consider that the CS met the NICE scope to an appropriate degree. The EAG had comments regarding the positioning of elafibranor and OCA as the third-line treatment after discontinuation of elafibranor or OCA as second-line treatment. It is plausible for OCA to follow discontinuation of elafibranor in sequence and vice versa, due to the different mechanisms of action in each. The assumption that UDCA is the only possible third-line treatment may not accurately reflect the clinical pathway in either the OCA or elafibranor arms of the decision model. However, treatment effectiveness at third-line is uncertain due to a lack of evidence.

The company conducted an SLR to identify evidence surrounding the effectiveness and safety of elafibranor and relevant comparators for treating PBC. The EAG have some concerns surrounding multiple aspects of the SLR methodology, including: the literature search; eligibility criteria; screening; data extraction; and quality appraisal. The main clinical evidence was based on the ELATIVE trial. In general, the EAG believes that the ELATIVE trial was well-conducted and relevant to the decision problem but the method of allocation concealment was not reported and there was a lack of subgrouping by participants intolerant to and those non-responsive to UDCA. However, the EAG appreciate that the numbers of participants who were intolerant to UDCA in the ELATIVE trial was low and is reflective of clinical practice.

To compare the relative efficacy of elafibranor with OCA, the company performed a series of NMAs. Although the company provided additional information and a rationale for many of the EAG's queries regarding the NMA methodology during the points for clarification process, the EAG still have concerns about the substantial width of the 95% CrIs, including when compared against OCA 5-10 mg. Additionally, it was noted by the company that there was difficulty in achieving convergence within the model. The EAG performed multiple additional NMA analyses for outcomes used within the economic model; the results of these analyses did not change the overall conclusions. The results of the EAG analyses were still open to substantial uncertainty and it is therefore difficult to draw any conclusions regarding the clinical effectiveness of elafibranor versus OCA 5-10 mg.

The company conducted SLRs with searches aimed at identifying cost-effectiveness studies, HRQoL and cost and resource use data to inform the economic model. The search strategy used was considered fit for purpose but the use of focused MESH headings may have increased the specificity of the search to the detriment of specificity. Moreover, conference proceedings were excluded from Embase searches, which may have missed relevant studies.

Regarding the economic model, the posterior distributions of the ORs estimated in the NMA were skewed with considerable variance and the company inadequately specified the parametric distributions for the ORs in their base-case. Median values were used in the CS, which the EAG replaced these with mean values. The company assumed a constant RR, while the EAG preferred to assume a constant HR.

The lack of external validation, whether from clinical experts or from the published literature, of the survival predictions in the model for OCA or elafibranor (liver-disease free, LT-free, OS, etc.) was noted as a key issue by the EAG due to concerns that the model was underpredicting liver disease-free survival for elafibranor compared to the predictions from UK-PBC scores and GLOBE scores from ELATIVE.[48] The EAG thinks this may partly be a consequence of strong assumptions in the model structure including: the risks of progression from moderate risk to liver disease; the excess mortality at high risk parameter; the assumption that biomarker

risk categories continue to deteriorate in third-line after elafibranor or OCA; and the assumption that biomarker risk cannot improve in third-line, accelerating its deterioration. The use of elafibranor trial data as the baseline in the economic model, with current practice (OCA) response and discontinuation derived by multiplying baseline risks with the effectiveness statistics, makes the development of a model with plausible predictions harder. The EAG was also concerned about whether the mortality parameters for liver disease were reflective of advances in clinical practice.

Another key issue the EAG raised regarding the economic analysis is the uncertainty around treatment discontinuation, particularly since the difference in treatment discontinuation rates between elafibranor and OCA is the primary driver of cost-effectiveness estimates. Consultation with a clinical expert and additional data from UK-PBC provided by the company suggested that treatment discontinuation predictions for OCA in the model may be too high.[66] The economic model assumes that the difference in treatment discontinuation rates between OCA and elafibranor are maintained over a lifelong treatment duration. However, the patterns of discontinuation can shift after the first year or two with OCA, as patients appear to discontinue at a higher rate early on (in part due to the effect of OCA on pruritus). Furthermore, uncertainty surrounding the risk of treatment discontinuation over the long term for OCA and elafibranor is a key cause of uncertainty in the cost-effectiveness results. The EAG has suggested limiting the difference in treatment discontinuation rates between OCA and elafibranor to one year, which leads to better predictions for OCA. Nevertheless, uncertainty in treatment discontinuation rates continued to have a significant impact on outcomes.

The next key issue highlighted by the EAG was the use of utility values from the published literature for the PBC biomarker risk states in the economic model, rather than using the patient-reported values elicited from the ELATIVE trial.[1] The most impactful quality of life parameter was utility at the PBC high-risk of liver disease biomarker state, where the utility values selected for the base-case were noticeably lower than the moderate-risk health state, and lower than the value elicited for this population from the ELATIVE trial data.[1] The EAG explored an alternative utility value for the high-risk state from the published literature in between the trial value and the company's base-case value informed by NICE TA443.[6,53]

On the subject of how the economic model calculated quality of life, the EAG was concerned about the applicability of utilities from NICE TA443, since they include a confidential decrement based on expert opinion; the implications of this assumption were not discussed in the CS.[1,6] Furthermore, the model included different disutility values from different sources for pruritus: as a TEAE; and as a symptom of PBC. It was not clear how each definition of pruritus was mutually exclusive, or how any potential overlap was accounted for.

The company considered that this condition did not meet the severity modifier criteria.

The approach taken to calculate costs and resource use was considered fit for purpose. The EAG only raised concerns on two issues. Firstly, the EAG were concerned with transparency in the use of NHS tariffs from a previous NICE submission,[6] as the current submission lacked clarity around the specific cost codes being used. The second issue surrounded the differences in treatment compliance rates between elafibranor and OCA, which is an area of uncertainty feeding directly into the total cost differences, as different approaches to calculating compliance rates led to different estimates.[7]

The EAG base-case assumed a constant HR for cholestasis response and discontinuation, removed the pre-LT state, reduced the duration of the difference in discontinuation risk rates between OCA and elafibranor to one year, updated the high-risk utility value, changed the approach to high-risk mortality, and assumed PBC-40 differences in pruritus also capture treatment-emergent exacerbations.

After updating for errors found by the EAG, the company base-case suggested that, after applying the PAS discount to the unit cost of elafibranor, elafibranor was the dominant strategy over OCA by increasing QALYs by [redacted] and decreasing costs by [redacted] with credible intervals showing substantial uncertainty around the cost-effectiveness estimates. After applying the PAS discount to the unit cost of elafibranor, the EAG base-case also suggested that elafibranor was the dominant intervention over OCA by increasing QALYs by [redacted] and decreasing costs by [redacted] with a [redacted]% probability of being cost-effective at a £20,000 willingness to pay threshold.

The cost of OCA, the difference in treatment discontinuation rates, the assumption of a constant HR, treatment compliance differences, and differences in pruritus were found by the EAG to be the parameters with the largest impact on the cost-effectiveness results. Further structural assumptions were tested using scenario analyses proposed by the EAG and recreating scenarios from the CS. Assuming no difference in treatment discontinuation rates, changing the parametric time-to-discontinuation model, and changing the treatment effect definitions had the largest impact on cost-effectiveness estimates. Nonetheless, elafibranor remained dominant over OCA across most of the scenarios after the PSA discount for elafibranor was applied. Although the dominance of elafibranor over OCA remained robust after the analyses proposed by the EAG, large uncertainties from the NMA results were translated into large uncertainties in the incremental costs and benefits of elafibranor. Moreover, the model structure strongly emphasises the impact of differences on treatment discontinuation over differences in treatment effectiveness[redacted]The EAG would be interested to see how alternative treatment strategies, such as the use of elafibranor and OCA in sequence, could affect the treatment landscape for this cohort of PBC patients and how this could be further explored.

7 REFERENCES

1 Ipsen. *Elafibranor for treating primary biliary cholangitis [ID6331]. Single technology appraisal. Company evidence submission: Document B*. Paris, France: Ipsen; 2024.

2 NICE. *Sofosbuvir for treating chronic hepatitis C [TA330]. Technology appraisal guidance.* London: National Institute for Health and Care Excellence (NICE); 2015. Available from: https://www.nice.org.uk/guidance/ta330.

3 Invernizzi P, Floreani A, Carbone M, Marzioni M, Craxi A, Muratori L, et al. Primary Biliary Cholangitis: advances in management and treatment of the disease. *Digestive and Liver Disease*. 2017;49(8):841-6. Available from: https://doi.org/https://doi.org/10.1016/j.dld.2017.05.001.

4 Kowdley K, V., Bowlus C, L., Levy C, Akarca U, S., Alvares-da-Silva M, Reis., Andreone P, et al. Efficacy and Safety of Elafibranor in Primary Biliary Cholangitis. *New England Journal of Medicine*. 2024;390(9):795-805. Available from: https://doi.org/10.1056/NEJMoa2306185.

5 Nevens F, Andreone P, Mazzella G, Strasser SI, Bowlus C, Invernizzi P, et al. A placebo-controlled trial of obeticholic acid in primary biliary cholangitis. *N Engl J Med*. 2016;375(7):631-43. Available from: https://doi.org/10.1056/NEJMoa1509840.

6 NICE. *Obeticholic acid for treating primary biliary cholangitis [TA443]. Technology appraisal guidance*. London: National Institute for Health and Care Excellence (NICE); 2017. Available from: https://www.nice.org.uk/guidance/ta443 [Date accessed: 18/04/2024].

7 Ipsen. *Elafibranor for treating primary biliary cholangitis [ID6331]. Single technology appraisal. Company evidence submission: Points for Clarification Response*. Paris, France: Ipsen; 2024.

8 Abbas N, Smith R, Flack S, Bains V, Aspinall RJ, Jones RL, et al. Critical shortfalls in the management of PBC: Results of a UK-wide, population-based evaluation of care delivery. *JHEP Reports*. 2024;6(1):100931. Available from: https://doi.org/https://doi.org/10.1016/j.jhepr.2023.100931.

9 Ipsen. *Elafibranor for treating primary biliary cholangitis [ID6331]. Single technology appraisal. Company evidence submission: Appendix D*. Paris, France: Ipsen; 2024.

10 Ipsen. *Elafibranor for treating primary biliary cholangitis [ID6331]. Single technology appraisal. Company evidence submission: Appendix G*. Paris, France: Ipsen; 2024.

11 McGowan J, Sampson M, Salzwedel DM, Cogo E, Foerster V, Lefebvre C. PRESS peer review of electronic search strategies: 2015 guideline statement. *Journal of Clinical Epidemiology*. 2016;75:40-6. Available from: https://doi.org/10.1016/j.jclinepi.2016.01.021.

12 Scherer RW, Meerpohl JJ, Pfeifer N, Schmucker C, Schwarzer G, von Elm E. Full publication of results initially presented in abstracts. *Cochrane Database of Systematic Reviews*. 2018;(11). Available from: https://doi.org/10.1002/14651858.MR000005.pub4.

13 Hopewell S, Loudon K, Clarke MJ, Oxman AD, Dickersin K. Publication bias in clinical trials due to statistical significance or direction of trial results. *Cochrane Database of Systematic Reviews*. 2009;(1). Available from: https://doi.org/10.1002/14651858.MR000006.pub3.

14 Whiting P, Savović J, Higgins JP, Caldwell DM, Reeves BC, Shea B, et al. ROBIS: A new tool to assess risk of bias in systematic reviews was developed. *J Clin Epidemiol*. 2016;69:225-34. Available from: https://doi.org/10.1016/j.jclinepi.2015.06.005.

15 Drucker AM, Fleming P, Chan A-W. Research Techniques Made Simple: Assessing Risk of Bias in Systematic Reviews. *Journal of Investigative Dermatology*.

2016;136(11):e109-e14. Available from: https://doi.org/https://doi.org/10.1016/j.jid.2016.08.021.

16 Thomas J, Kneale D, McKenzie JE, Brennan SE, Bhaumik S. Chapter 2: Determining the scope of the review and the questions it will address. In: Higgins JPT, Thomas J, Chandler J, Cumpston M, Li T, Page MJ, Welch VA, eds. *Cochrane Handbook for Systematic Reviews of Interventions version 6.4 (updated August 2023). Cochrane*. 2023.

17 Hirschfield GM, Dyson JK, Alexander GJM, Chapman MH, Collier J, Hubscher S, et al. The British Society of Gastroenterology/UK-PBC primary biliary cholangitis treatment and management guidelines. *Gut*. 2018;67(9):1568-94. Available from: https://doi.org/10.1136/gutjnl-2017-315259.

18 CRD. *Systematic Reviews: CRD's guidance for undertaking reviews in health care*. York: Centre for Reviews and Dissemination (CRD), University of York; 2009. Available from: https://www.york.ac.uk/media/crd/Systematic_Reviews.

19 Lefebvre C, Glanville J, Briscoe S, Featherstone R, Littlewood A, Metzendorf M-I, et al. Chapter 4: Searching for and selecting studies. In: Higgins JPT, Thomas J, Chandler J, Cumpston M, Li T, Page MJ, Welch VA, eds. *Cochrane Handbook for Systematic Reviews of Interventions version 6.4 (updated October 2023) Cochrane*. 2023.

20 Li T, Higgins JPT, Deeks JJ, eds. Chapter 5: Collecting data. In: Higgins JPT, Thomas J, Chandler J, Cumpston M, Li T, Page MJ, Welch VA, eds. *Cochrane Handbook for Systematic Reviews of Interventions version 6.4 (updated August 2023). Cochrane*. 2023.

21 Boutron I, Page MJ, Higgins JPT, Altman DG, Lundh A, Hróbjartsson A. Considering bias and conflicts of interest among the included studies. In: Higgins JPT, Thomas J, Chandler J, Cumpston M, Li T, Page MJ, Welch VA, eds. *Cochrane Handbook for Systematic Reviews of Interventions, Version 6.4 (updated August 2023)*. The Cochrane Collaboration; 2023.

22 Tod D, Booth A, Smith B. Critical appraisal. *International Review of Sport and Exercise Psychology*. 2022;15(1):52-72. Available from: https://doi.org/10.1080/1750984X.2021.1952471.

23 Higgins JPT, Savović J, Page MJ, Elbers RG, Sterne JAC. Assessing risk of bias in a randomized trial. In: Higgins JPT, Thomas J, Chandler J, Cumpston M, Li T, Page MJ, Welch VA, eds. *Cochrane Handbook for Systematic Reviews of Interventions, Version 6.4*. The Cochrane Collaboration; 2023.

24 Schattenberg JM, Pares A, Kowdley KV, Heneghan MA, Caldwell S, Pratt D, et al. A randomized placebo-controlled trial of elafibranor in patients with primary biliary cholangitis and incomplete response to UDCA. *J Hepatol*. 2021;74(6):1344-54. Available from: https://doi.org/10.1016/j.jhep.2021.01.013.

25 Hirschfield GM, Mason A, Luketic V, Lindor K, Gordon SC, Mayo M, et al. Efficacy of obeticholic acid in patients with primary biliary cirrhosis and inadequate response to ursodeoxycholic acid. *Gastroenterology*. 2015;148(4):751-61.e8. Available from: https://doi.org/10.1053/j.gastro.2014.12.005.

26 Dias S, Welton NJ, Sutton AJ, Ades AE. *NICE DSU Technical Support Document 2: A generalised linear modelling framework for pairwise and network meta-analysis of randomised controlled trials; last updated September 2016*. Sheffield: NICE Decision Support Unit (DSU); 2011. Available from: https://www.sheffield.ac.uk/nice-dsu/tsds/full-list [accessed 26 April 2024].

27 Turner RM, Jackson D, Wei Y, Thompson SG, Higgins JPT. Predictive distributions for between-study heterogeneity and simple methods for their application in Bayesian meta-analysis. *Statistics in Medicine*. 2015;34(6):984-98. Available from: https://doi.org/https://doi.org/10.1002/sim.6381.

28 NHS. *Primary biliary cholangitis (primary biliary cirrhosis): Symptoms (Page last reviewed: 02 February 2024;*

Next review due: 02 February 2027). London: National Health Service (NHS). Available from: https://www.nhs.uk/conditions/primary-biliary-cholangitis-pbc/symptoms/ [accessed 15 May 2024].

29 Spiegelhalter DJ, Best NG, Carlin BP, Van Der Linde A. Bayesian measures of model complexity and fit. *Journal of the Royal Statistical Society: Series B (Statistical Methodology)*. 2002;64(4):583-639. Available from: https://doi.org/https://doi.org/10.1111/1467-9868.00353.

30 Ren S, Oakley JE, Stevens JW. Incorporating Genuine Prior Information about Between-Study Heterogeneity in Random Effects Pairwise and Network Meta-analyses. *Medical Decision Making*. 2018;38(4):531-42. Available from: https://doi.org/10.1177/0272989X18759488.

31 Kowdley KV, Brookhart MA, Hirschfield GM. Efficacy of Obeticholic Acid (OCA) vs Placebo and External Control (EC) on Clinical Outcomes in Primary Biliary Cholangitis (PBC). *Hepatology*. 2022;77(Abstract 5032. AASLD Meeting):E116. Available from: https://doi.org/10.1097/HEP.0000000000000347.

32 Chaimani A, Caldwell DM, Li T, Higgins JPT, Salanti G. Chapter 11: Undertaking network meta-analyses. In: Higgins JPT, Thomas J, Chandler J, Cumpston M, Li T, Page MJ, Welch VA, eds. *Cochrane Handbook for Systematic Reviews of Interventions version 6.4 (updated August 2023). Cochrane, 2023. Available from www.training.cochrane.org/handbook*. 2023.

33 NICE. *Elafibranor for treating primary biliary cholangitis [ID6331]. Final scope. Health technology evaluation*. London: National Institute for Health and Care Excellence (NICE); 2024. Available from: https://www.nice.org.uk/guidance/gid-ta11378/documents/final-scope [Date accessed: 8 April 2024].

34 Ipsen. *Elafibranor for treating primary biliary cholangitis [ID6331]. Patient organisation submission - British Liver Trust.* Single Technology Appraisal (STA). Ipsen; 2024.

35 Ipsen. *Elafibranor for treating primary biliary cholangitis [ID6331]. Patient organisation submission - Liver4Life*. Single Technology Appraisal (STA). Ipsen; 2024.

36 Balasubramanian H, Ananthan A, Rao S, Patole S. Odds ratio vs risk ratio in randomized controlled trials. *Postgrad Med*. 2015;127(4):359-67. Available from: https://doi.org/10.1080/00325481.2015.1022494.

37 Owen RK, Bradbury N, Xin Y, Cooper N, Sutton A. MetaInsight: An interactive web-based tool for analyzing, interrogating, and visualizing network meta-analyses using R-shiny and netmeta. *Research Synthesis Methods*. 2019;10(4):569-81. Available from: https://doi.org/https://doi.org/10.1002/jrsm.1373.

38 Balduzzi S, Rücker G, Nikolakopoulou A, Papakonstantinou T, Salanti G, Efthimiou O, Schwarzer G. netmeta: An R Package for Network Meta-Analysis Using Frequentist Methods. *Journal of Statistical Software*. 2023;106(2):1 - 40. Available from: https://doi.org/10.18637/jss.v106.i02.

39 CADTH. *Pharmacoeconomic Review Report: Obeticholic Acid (Ocaliva): Intercept Pharma Canada, Inc.: Indication: For the treatment of primary biliary cholangitis.* Ottawa: Canadian Agency for Drugs and Technologies in Health (CADTH); 2017. Available from: https://pubmed.ncbi.nlm.nih.gov/30525351/.

40 NCPE. *Cost-effectiveness of obeticholic acid (Ocaliva®) for the treatment of primary biliary cholangitis in combination with ursodeoxycholic acid (UDCA) in adults with an inadequate response to UDCA or as monotherapy in adults unable to tolerate UDCA*. Dublin: National Centre for Pharmacoeconomics, Ireland (NCPE); 2017. Available from: https://www.ncpe.ie/drugs/obeticholic-acid-ocaliva/.

41 SMC. *Obeticholic acid (Ocaliva®). SMC No: 1232/17*. Glasgow: Scottish Medicines Consortium (SMC); 2017. Available from: https://www.scottishmedicines.org.uk/medicines-advice/obeticholic-acid-ocaliva-fullsubmission-123217/.

42 Ipsen. *Elafibranor for treating primary biliary cholangitis [ID6331]. Clinical expert opinion. Single Technology Appraisal (STA)*. 2024.

43 Fayter D, Ramaekers BLT, Grimm S, Pouwels X, Armstrong N, Ryder S, et al. *Obeticholic acid for treating primary biliary cirrhosis: a Single Technology Assessment [TA443]. Evidence Assessment Group Report*. York: Kleijnen Systematic Reviews Ltd; 2016.

44 Ipsen, FIECON. *Clinical consultation meeting report: economic model validation (Clinician validation findings report merged_v2.0_FINAL_10May2024)*. France, Paris: Ipsen; 2024.

45 Drefs M, Schoenberg MB, Börner N, Koliogiannis D, Koch DT, Schirren MJ, et al. Changes of long-term survival of resection and liver transplantation in hepatocellular carcinoma throughout the years: A meta-analysis. *European Journal of Surgical Oncology*. 2024;50(3). Available from: https://doi.org/10.1016/j.ejso.2024.107952.

46 Sun Q, Zhang X, Gong X, Hu Z, Zhang Q, He W, et al. Survival analysis between laparoscopic and open hepatectomy for hepatocellular carcinoma: a meta-analysis based on reconstructed time-to-event data. *Hepatology International*. 2021;Oct(5):1215-35. Available from: https://doi.org/10.1007/s12072-021-10219-1.

47 Tantai X, Liu Y, Yeo YH, Praktiknjo M, Mauro E, Hamaguchi Y, et al. Effect of sarcopenia on survival in patients with cirrhosis: A meta-analysis. *Journal of Hepatology*. 2022;76(3):588-99. Available from: https://doi.org/https://doi.org/10.1016/j.jhep.2021.11.006.

48 Ipsen. *Clinical Study Report: A Double-Blind, Randomized, Placebo-Controlled Study and Open-Label Long Term Extension to Evaluate the Efficacy and Safety of Elafibranor 80 Mg in Patients with Primary Biliary Cholangitis with Inadequate Response or Intolerance to Ursodeoxycholic Acid*. Paris, France: Ipsen Pharma; 2023.

49 Holger J, Schünemann GEV, Higgins JPT, Santesso N, Deeks JJ, Glasziou P, et al. Interpreting results and drawing conclusions In: Higgins JPT, Thomas J, Chandler J, Cumpston M, Li T, Page MJ, Welch VA, eds. *Cochrane Handbook for Systematic Reviews of Interventions, Version 6.4 (updated August 2023)*. The Cochrane Collaboration; 2023.

50 Mayo MJ, Carey E, Smith HT, Mospan AR, McLaughlin M, Thompson A, et al. Impact of Pruritus on Quality of Life and Current Treatment Patterns in Patients with Primary Biliary Cholangitis. *Digestive Diseases and Sciences*. 2023;68(10):995-1005. Available from: https://doi.org/10.1007/s10620-022-07581-x.

51 Rice S, Albani V, Minos D, Fattakhova G, Mells GF, Carbone M, et al. Effects of primary biliary cholangitis on quality of life and health care costs in the United Kingdom. *Clin Gastroenterol Hepatol*. 2021;19(4):768-76.e10. Available from: https://doi.org/10.1016/j.cgh.2020.06.025.

52 Younossi ZM, Kiwi ML, Boparai N, Price LL, Guyatt G. Cholestatic Liver Diseases and Health-Related Quality of Life. *Official journal of the American College of Gastroenterology | ACG*. 2000;95(2). https://journals.lww.com/ajg/fulltext/2000/02000/cholestatic_liver_diseases_and_health_related.28.aspx.

53 Saeed YA, Phoon A, Bielecki JM, Mitsakakis N, Bremner KE, Abrahamyan L, et al. A Systematic Review and Meta-Analysis of Health Utilities in Patients With Chronic Hepatitis C. *Value in Health*. 2020;23(1):127-37. Available from: https://doi.org/10.1016/j.jval.2019.07.005.

54 Hernandez Alava M, Pudney S, Wailoo A. The EQ-5D-5L Value Set for England: Findings of a Quality Assurance Program. *Value in Health*. 2020;23(5):642-8. Available from: https://doi.org/https://doi.org/10.1016/j.jval.2019.10.017.

55 Wright M, Grieve R, Roberts J, Main J, Thomas HC, U.K. Mild Hepatitis C Trial Investigators. Health benefits of antiviral therapy for mild chronic hepatitis C: randomised controlled trial and economic evaluation. *Health technology assessment (Winchester, England)*. 2006;10(21):1-113, iii. Available from: https://doi.org/10.3310/hta10210.

56 NICE. *NICE health technology evaluations: the manual. Process and methods [PMG36]. Published: 31 January 2022. Last Update Date: 31 October 2023.* London: National Institute for Health and Care Excellence (NICE); 2022. Available from: https://www.nice.org.uk/process/pmg36/chapter/introduction-to-health-technology-evaluation [Date accessed: 08/04/2024].

57 BNF. *Treatment summaries: Cholestasis*. National Institute for Health and Care Excellence; 2023. Available from: https://bnf.nice.org.uk/treatment-summaries/cholestasis/.

58 NHS England. *2021/22 National Cost Collection Data Publication*. 2023. Available from: https://www.england.nhs.uk/publication/2021-22-national-cost-collection-data-publication/.

59 NICE. *Odevixibat for treating progressive familian intrahepatic cholestasis [ID1570, HST17]: Committee papers.*; 2021. Available from: https://www.nice.org.uk/guidance/hst17/documents/committee-papers.

60 BNF. *Medicinal forms : Azathioprine*. British National Formulary (BNF). Available from: https://bnf.nice.org.uk/drugs/azathioprine/medicinal-forms/.

61 BNF. *Medicinal forms: Tacrolimus* British National Formulary (BNF). Report No.: 23/05/2024. Available from: https://bnf.nice.org.uk/drugs/tacrolimus/medicinal-forms/.

62 BNF. *Medicinal forms: Prednisolone*. British National Formulary (BNF). Available from: https://bnf.nice.org.uk/drugs/prednisolone/medicinal-forms/.

63 Gola A, Davis S, Greenslade L, Hopkins K, Low J, Marshall A, et al. Economic analysis of costs for patients with end stage liver disease over the last year of life. *BMJ Supportive & Palliative Care*. 2015;5(1):110. Available from: https://doi.org/10.1136/bmjspcare-2014-000838.23.

64 NICE. *Atezolizumab with bevacizumab for treating advanced or unresectable hepatocellular carcinoma [TA666]. Technology appraisal guidance*. London: National Institute for Health and Care Excellence (NICE); 2020. Available from: https://www.nice.org.uk/guidance/ta666?fromsource=mas.

65 Kaltenthaler E, Carroll C, Hill-Mcmanus D, Scope A, Holmes M, Rice S, et al. The use of exploratory analyses within the National Institute for Health and Care Excellence single technology appraisal process: an evaluation and qualitative analysis. *Health Technology Assessment*. 2016;20(26):1-48. Available from: https://doi.org/10.3310/hta20260.

66 Ipsen. Ipsen UK-PBC Data Requests. Paris, France: Ipsen Pharma; 2024.

Single Technology Appraisal

Elafibranor for treating primary biliary cholangitis [ID6331]

EAG report – factual accuracy check and confidential information check

"Data owners may be asked to check that confidential information is correctly marked in documents created by others in the evaluation before release." (Section 5.4.9, NICE health technology evaluations: the manual).

You are asked to check the EAG report to ensure there are no factual inaccuracies or errors in the marking of confidential information contained within it. The document should act as a method of detailing any inaccuracies found and how they should be corrected.

If you do identify any factual inaccuracies or errors in the marking of confidential information, you must inform NICE by **the end of the day on Wednesday 17 July 2024** using the below 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 committee papers.

Please underline all confidential information, and information that is submitted as [redacted] should be highlighted in turquoise and all information submitted as '[redacted]' in pink.

Issue 1 Confidentiality markings

Location of incorrect marking	Description of incorrect marking	Amended marking	EAG Response
Section 3.3.4.2, Page 37: ‘[redacted]’	This text does not contain any information that is CIC and should not be marked up.	‘However, the lack of any significant change in the results for the fixed-effects models compared with the random-effects models suggests this choice would not change the uncertainty in the NMA results for outcomes used to inform the cost-effectiveness.’	The EAG has removed the CiC marking from this section as per the company’s request.
Section 3.4.1.1, Table 3.5, Page 39: ‘Frequentist OR, random-effects’ and ‘Frequentist RR, random-effects’	Results from the EAG frequentist OR and RR approaches are closely aligned with the results presented for ‘Company base-case’ and therefore discloses information on the efficacy and safety of elafibranor relative to OCA which has not been published.	The company propose that the data presented for ‘Frequentist OR, random-effects’ and ‘Frequentist RR, random-effects’ be marked as CIC (see Table 1).	The EAG has added CiC marking to all results in Table 3.5 (p.40) as per the company’s request.
Section 3.4.1.2, Table 3.6, Page 39: ‘Bayesian RR, fixed-effects’, ‘Frequentist OR, fixed-effects’ and Frequentist RR, fixed-effects’	Results from the EAG Bayesian RR, frequentist OR and frequentist RR approaches are closely aligned with the results presented for the Company’ Bayesian approach and therefore discloses information on	The company propose that the data presented for ‘Bayesian RR, fixed-effects’, ‘Frequentist OR, fixed-effects’ and ‘Frequentist RR, fixed-	The EAG has added CiC marking to all results in Table 3.6 (p.40) as per the company’s request.

Location of incorrect marking	Description of incorrect marking	Amended marking	EAG Response
	the efficacy and safety of elafibranor relative to OCA which has not been published.	effects' be marked as CIC (see Table 2).	
Section 3.4.2, Table 3.7, Page 40: 'Frequentist MD, random-effects' and 'Frequentist MD, fixed-effects'	Results from the EAG analyses frequentist approach are closely aligned with the results presented for the Company base-case Bayesian approach and therefore discloses information on the efficacy and safety of elafibranor relative to OCA which has not been published.	The company propose that data presented for the EAG analyses, namely the 'Frequentist MD, random-effects' and the 'Frequentist MD, fixed-effects' be marked as CIC (see Table 3).	The EAG has added CiC marking to all results in Table 3.7 (p.41) as per the company's request.
Section 4.3.3.1, Page 53: "The cost of the pre-LT state (£5297) is significantly higher than the high-risk biomarker state (£2081), DCC state (£4161), and the HCC state (£3053), while the utility is equal to the DCC state (0.38) and lower than the HCC state (0.45) and the high-risk biomarker state ([redacted])."	The utility value for the high-risk health state was sourced from published literature and is not CIC. It is inconsistently marked up as CIC throughout the document. In section 4.3.3.1 (Page 53) the value is marked up, however in the following four instances it is not: • Table 4.13, Section 4.3.5.1, Page 64 • Section 4.3.5.1, Page 65 (twice)	The company propose that the utility value for the high-risk health state should not be marked as CIC: "The cost of the pre-LT state (£5297) is significantly higher than the high-risk biomarker state (£2081), DCC state (£4161), and the HCC state (£3053), while the utility is equal to the DCC state (0.38) and lower than the HCC state	The EAG has removed the CiC marking to the utility value for the high-risk health state in Section 4.3.31, Page 53.

Location of incorrect marking	Description of incorrect marking	Amended marking	EAG Response
	• Section 4.3.5.1, Page 66	(0.45) and the high-risk biomarker state (0.55).”	
Section 4.3.4.1, Page 58: ‘For the OR of cholestasis response, the mean, median, lower limit and upper limit of the 95% CrI for the gamma distribution (α = 0.12, β = 2.13) used in the company submission and the lognormal distribution (μ=-1.347[ln(median)], SD = 1.08) are presented in Table 4.8 along with the NMA results presented in the CS.’	The parameters used in the gamma distribution (i.e. α, μ, and SD) can be used to calculate the 95% CI of the OR of cholestasis response. The 95% CI of the OR of cholestasis response was also marked as CIC in the submission evidence.	The company propose that the following information be marked as CIC: ‘For the OR of cholestasis response, the mean, median, lower limit and upper limit of the 95% CrI for the gamma distribution (α = [redacted], β = [redacted]) used in the company submission and the lognormal distribution (μ=[redacted][ln(median)], SD = [redacted]) are presented in Table 4.8 along with the NMA results presented in the CS.’	The EAG has updated the CiC markings in Section 4.3.4.1, Page 60, as requested here by the company.
Section 4.3.4.1, Page 58: ‘Moreover, the median OR NMA values (e.g. 0.26 for response) were used in the deterministic analysis in the CS.’	The median OR for cholestasis response has not been published.	The company propose that the median OR value for cholestasis response (0.26) be marked as CIC. ‘Moreover, the median OR NMA values (e.g. [redacted] for response) were used in the	The EAG has added a CiC markings to the text in Section 4.3.4.1, Page 60, as requested by the company.

Location of incorrect marking	Description of incorrect marking	Amended marking	EAG Response
		deterministic analysis in the CS.'	
Section 4.3.4.1, Page 58: '…the EAG has used the mean values associated with the lognormal distribution (e.g. 0.45 for response).'	The mean OR is based on the median OR for cholestasis response, neither of which have been published. Marking up as CIC will ensure consistency as the same value was marked as CIC in Table 4.8. and Table 4.9.	The company propose that the mean OR value associated with the lognormal distribution for cholestasis response (0.45) be marked as CIC: '…the EAG has used the mean values associated with the lognormal distribution (e.g. [redacted] for response).'	The EAG has added a CiC markings to the text in Section 4.3.4.1, Page 60, as requested by the company.
Section 5.2, Table 5.6, Page 76 Scenario #27, Base case: Drug exposure (94.83% versus 93.55%), scenario analysis: Mean cumulative (93.24% versus 93.55%)	The company propose that the compliance rate for elafibranor (using drug exposure days or mean cumulative dose) were sourced from the ELATIVE CSR and have not been published.	The company propose that the compliance rate for elafibranor (using drug exposure days or mean cumulative dose) be marked as CIC (see Table 4).	The EAG has added a CiC markings to the text in Table 5.6, Page 78, as requested by the company: Drug exposure ([redacted] versus 93.55%) Mean cumulative ([redacted] versus 93.55%)

Location of incorrect marking	Description of incorrect marking	Amended marking	EAG Response
Section 6.1.1, Page 80 'The elafibranor probability of response at 12 months was 0.509. There was considerable uncertainty in the OR estimates.'	The probability of response at 12 months (0.509) has not been published.	The company propose that the probability of response at 12 months (0.509) be marked as CIC: 'The elafibranor probability of response at 12 months was [redacted]. There was considerable uncertainty in the OR estimates.'	The EAG has added a CiC markings to the text in Section 6.1.1, Page 82, as requested by the company.

Proposed markup changes to EAG report tables

Table 1: NMA results comparing elafibranor 80 mg versus OCA 5-10 mg using different approaches (dichotomous outcomes, random-effects models), EAG Report section 3.4.1.1, Table 3.5, Page 39

Outcome measure	Company base-case (Bayesian OR, random-effects)	Frequentist OR, random-effects	Frequentist RR, random-effects
Cholestasis response at 12 months	[redacted]	[redacted]	[redacted]
Odds of pruritis TEAE of any severity at 12 months	[redacted]	[redacted]	[redacted]
All-cause discontinuation at 12 months	[redacted]	[redacted]	[redacted]

Source: created by the EAG and using data from CS Sections B.2.9.1.1 (p.72-3), B.2.9.1.6 (p.78-9), B.2.9.1.7 (p.80-1), and B.2.9.1.10 (p.84-5)[5]
Abbreviations: CI = confidence interval; CrI = credible interval; CS = company submission; EAG = Evidence Assessment Group; NMA = network meta-analysis; OCA = obeticholic acid; OR = odds ratio; RR = risk ratio; TEAE = treatment-emergent adverse event

Table 2: NMA results comparing elafibranor 80 mg versus OCA 5-10 mg using different methodologies (dichotomous outcomes, fixed-effects models), EAG Report section 3.4.1.2, Table 3.6, Page 39

Outcome measure	Company base-case (Bayesian OR, fixed-effects)	Bayesian RR, fixed-effects	Frequentist OR, fixed-effects	Frequentist RR, fixed-effects
Cholestasis response at 12 months	[redacted]	[redacted]	[redacted]	[redacted]
Odds of pruritis TEAE of any severity at 12 months	[redacted]	[redacted]	[redacted]	[redacted]

All-cause discontinuation at 12 months	[redacted]	[redacted]	[redacted]	[redacted]

Source: created by the EAG and data from CS Appendix D (Sections D.1.6.1, D.1.6.6, D.1.6.8 and D.1.6.11)[8]
Abbreviations: CI = confidence interval; CrI = credible interval; CS = company submission; EAG = Evidence Assessment Group; NMA = network meta-analysis; OCA = obeticholic acid; OR = odds ratio; RR = risk ratio; TEAE = treatment-emergent adverse event

Table 3: NMA results comparing elafibranor 80 mg versus OCA 5-10 mg using different approaches (continuous outcomes), EAG Report section 3.4.2, Table 3.7, Page 40

Outcome measure	Company NMAs		EAG analyses	
	Bayesian, median difference in mean change, random-effects	Bayesian, median difference in mean change, fixed-effects	Frequentist MD, random-effects	Frequentist MD, fixed-effects
Change in PBC-40 Itch domain at 12 months	[redacted]	[redacted]	[redacted]	[redacted]
Change in PBC-40 Itch domain at 2-4 weeks	[redacted]	[redacted]	[redacted]	[redacted]

Source: created by the EAG and data from: CS Sections B.2.9.1.6 and B.2.9.1.7 (p.78-81); CS Appendix D, Sections D.1.6.6 and D.1.6.7; and PfC A11.[5,8]
Abbreviations: CI = confidence interval; CrI = credible interval; CS = company submission; EAG = Evidence Assessment Group; MD = mean difference; NMA = network meta-analysis; OCA = obeticholic acid;

Table 4: Deterministic scenario analysis results for the company base-case submitted after the points for clarification (selection of scenarios considered relevant to the EAG analysis), EAG Report section 3.4.2, Table 5.2, Page 76 (scenario 27 only)

#	Model aspect	Base-case	Scenario analysis	Incremental costs OCA (£)	Incremental QALYs OCA	ICER versus OCA (£)
27	Compliance	Drug exposure ([redacted]% versus 93.55%)	Mean cumulative ([redacted]% versus 93.55%)	[redacted]	[redacted]	Dominating
Source: response to the EAG's points for clarification, appendix c[6] Abbreviations: ICER; = incremental cost-effectiveness ratio; OCA = obeticholic acid; QALY = quality adjusted life years;						