Single Technology Appraisal

Seladelpar for previously treated primary biliary cholangitis [ID6429]

Committee Papers

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

SINGLE TECHNOLOGY APPRAISAL

Seladelpar for previously treated primary biliary cholangitis [ID6429]

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 Gilead Sciences

2. **Company summary of information for patients (SIP)** from Gilead Sciences

3. **Clarification questions and company responses**

4. **Patient group, professional group and NHS organisation submissions** from:
   a. British Liver Trust
   b. The British Association for the Study of the Liver
   c. British Hepatology Pharmacy Group

5. **Expert personal perspectives** from:
   a. Dr Palak Trivedi, Consultant Hepatologist – Clinical expert nominated by Gilead Science and the British Association for the Study of the Liver
   b. Robert Mitchell Thain, CEO of PBC Foundation – patient expert nominated by PBC Foundation

6. **External Assessment Report** prepared by Peninsula Technology Assessment Group (PenTAG)
   a. External Assessment Report
   b. Addendum

7. **External Assessment Report – factual accuracy check**

8. **Additional information on indirect comparisons** from Gilead Sciences

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

Seladelpar for previously treated primary biliary cholangitis [ID6429]

Company evidence submission

February 2025

File name	Version	Contains confidential information	Date
ID6249_Seladelpari. Company Evidence Submission [REDACTED] v2	**2.0**	**Yes**	**11/02/2025**

Contents

Tables and figures

Tables

Figures

Abbreviations

Acronym	Definition
AASLD	*American Association for the Study of Liver Diseases*
ALP	*Alkaline phosphatase*
ALT	*Alanine aminotransferase*
AMA	*Antimitochondrial antibody*
ANA	*Antinuclear antibody*
ANCOVA	*Analysis of covariance*
AST	*Aspartate aminotransferase*
BSC	*Best supportive care*
BSG	*British Society of Gastroenterology*
CC	*Compensated cirrhosis*
CEAC	*Cost-effectiveness acceptability curve*
CEM	*Cost-effectiveness model*
CSR	*Clinical study report*
DCC	*Decompensated cirrhosis*
EASL	*European Association for the Study of the Liver*
eGFR	*Estimated glomerular filtration rate*
ELF	*Enhanced liver fibrosis*
ELISA	*Enzyme-linked immunosorbent assay*
EQ-5D	*Euro QoL 5-Dimension*
EOT	*End-of-treatment*
GGT	*Gamma-glutamyl transferase*
HCC	*Hepatocellular carcinoma*
HCRU	*Healthcare resource utilisation*
HRQoL	*Health-related quality of life*
ICER	*Incremental cost-effectiveness ratio*
IL	*Interleukin*
INMB	*Incremental net monetary benefit*
INR	*International normalised ratio*
IPD	*Individual patient data*
ITC	*Indirect treatment comparison*
ITT	*Intent-to-treat*
LFTS	*Liver transplant-free survival*

LLN	*Lower limit of normal*
LOCF	*Last observation carried forward*
LT	*Liver transplant*
LYG	*Life years gained*
MAIC	*Matching-adjusted indirect comparison*
MedDRA	*Medical dictionary for regulatory activities*
MELD	*Model for End-Stage Liver Disease*
mITT	*Modified intent-to-treat*
MHRA	*Medicines and Healthcare products Regulatory Agency*
MMRM	*Mixed model repeated measures*
MSPN	*Moderate-to-severe Pruritus NRS*
NHB	*Net health benefit*
NICE	*National Institute for Health and Care Excellence*
NRS	*Numerical rating scale*
OCA	*Obeticholic acid*
OWSA	*One-way sensitivity analysis*
PAS	*Patient access scheme*
PBC	*Primary biliary cholangitis*
PBC WI-NRS	*PBC Worst Itch-Numeric Rating Scale*
PBC-40 QoL	*Primary biliary cholangitis-40 quality of life*
PPAR	*Peroxisome proliferator activated receptor*
PSA	*Probabilistic sensitivity analysis*
QALY	*Quality adjusted life year*
SAS	*Safety analysis set*
SLR	*Systematic literature review*
SmPC	*Summary of Product Characteristics*
SoC	*Standard of care*
OWSA	*One-way sensitivity analyses*
TEAE	*Treatment-emergent adverse event*
UDCA	*Ursodeoxycholic acid*
UKELD	*United Kingdom Model for End-Stage Liver Disease*
ULN	*Upper limit of normal*
VAS	*Visual analogue scale*
WPAI	*Work Productivity and Impairment*
WTP	*Willingness to pay*

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

1.1 Decision problem

The submission covers the technology's full marketing authorisation for this indication, namely, for the treatment of primary biliary cholangitis (PBC), including pruritus, in adults in combination with ursodeoxycholic acid (UDCA) who have an inadequate response to UDCA alone, or as monotherapy in those unable to tolerate UDCA (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	Not applicable
Intervention	Seladelpar	As per the final scope	Not applicable
Comparator(s)	For people, whose disease has an inadequate response to ursodeoxycholic acid: • Obeticholic acid (OCA) in combination with UDCA • UDCA monotherapy • Elafibranor in combination with UDCA Where UDCA cannot be tolerated: • OCA monotherapy • Best supportive care • Elafibranor monotherapy	For people, whose disease has an inadequate response to ursodeoxycholic acid: • Obeticholic acid (OCA) in combination with UDCA • Elafibranor in combination with UDCA Where UDCA cannot be tolerated: • OCA monotherapy • Elafibranor monotherapy	Seladelpar and UDCA monotherapy are positioned differently in the PBC treatment paradigm. UDCA monotherapy is positioned as a first-line treatment option for PBC by UK and international clinical practice guidelines and does not align with the recommended positioning of seladelpar. Instead, seladelpar is positioned as a second-line treatment option for patients who have demonstrated an inadequate response to UDCA (i.e., have tried UDCA and failed) or cannot tolerate UDCA, and as a third-line treatment for patients who have demonstrated an inadequate response to, or cannot tolerate, OCA. Therefore, seladelpar would not displace patients who are already responding to treatment with UDCA monotherapy. The comparative effectivneness of seladelpar is measured in the pivotal Phase 3 RESPONSE study against placebo ± UDCA. As such, UDCA is included in the clinical trial, but not as a standalone comparator arm, only as a by-product of the trail design, and UDCA monotherapy is therefore not a comparator included in Section 3 of the Company Evidence Submission

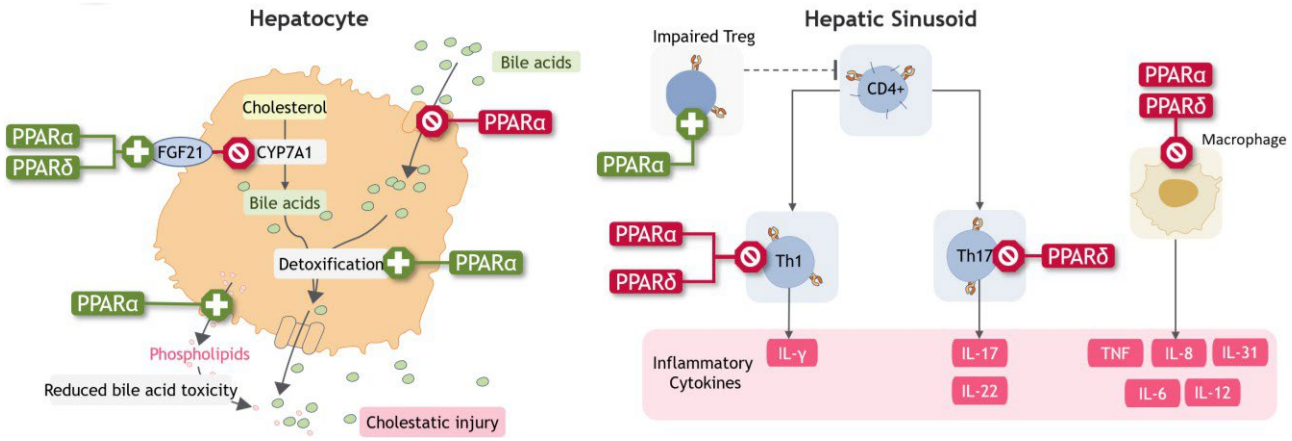
			For patients who cannot tolerate UDCA, best supportive care is not considered a relevant treatment option, given the availability of OCA and elafibranor monotherapies as alternative second-line treatment options.
Outcomes	The outcome measures to be considered include: • Mortality • Liver function based on markers of liver biochemistry • Symptoms including pruritus, fatigue, and abdominal pain • Time to liver transplantation • PBC-related consequences, including ascites, varices, encephalopathy, and hepatic cell carcinoma • Adverse effects of treatment • Health-related quality of life (HRQoL)	As per the final scope	Not applicable
Subgroups to be considered	If the evidence allows the following subgroups will be considered: • Early-moderate stage PBC (minimal / moderate fibrosis) with isolated elevated ALP values above the upper limit of normal • Individuals with pruritus • Those who have inadequately responded to UDCA and/or OCA.	None	Subgroups according to PBC stage, presence/absence of pruritus, and patient response to UDCA and/or tolerability to UDCA are not considered separately in the company submission. The company submission provides clinical- and cost-effectiveness evidence for seladelpar within its full marketing authorisation.

Key: ALP: alkaline phosphatase; HRQoL: health-related quality of life; OCA: obeticholic acid; PBC: primary biliary cholangitis; UDCA: ursodeoxycholic acid;

1.2 Description of the technology being evaluated

Seladelpar is a potent and selective agonist of peroxisome proliferator-activated receptor (PPAR) δ transcription factor distributed across hepatocytes, cholangiocytes, Kupffer cells, and hepatic stellate cells (2). The activation of PPARδ by seladelpar releases fibroblast growth factor 21 (FGF21) from hepatocytes, which in turn reduces the accumulation of bile acids by inhibiting the expression of cholesterol 7α-hydroxylase, the rate-limiting enzyme for bile acid synthesis (3, 4). In Kupffer cells and macrophages, activation of PPARδ promotes the anti-inflammatory M2 phenotype (5). These actions result in reduced bile acid exposure in the liver and circulating bile acid levels, leading to improvement in cholestasis, reduced inflammation, and increased lipid metabolism (6). Further, following activation of the PPARδ receptor, reductions in serum bile acids and interleukin (IL)-31 have been closely correlated with pruritus improvement (Figure 1) (7, 8).

Figure 1: PPARδ activation



Key: CYP7A1: cholesterol 7α-hydroxylase; FGF21: Fibroblast growth factor 21; IL: interleukin; PPARα: PPAR alpha; PPAR delta: PPARδ; Th: T helper.
Sources: Schnabl *et al.* (2024) (9); Hirschfield *et al.* (2024) (5); Al-Aqil *et al.* (2018) (10); Kremer *et al.* (2024) (7).

In September 2017, seladelpar was granted orphan designation (EU/3/17/1930) by the European Commission (EC) due to the seriousness of PBC, the lack of licensed treatment options, and the rarity of the condition. Seladelpar also has Priority Medicine (PRIME) designation in the EU, which is assigned to optimise the development of novel medicines that target conditions with an unmet medical need for which no treatment option exists or where they can offer a major therapeutic advantage over existing treatments. On 12th December 2024, the

Committee for Medicinal Products for Human Use (CHMP) recommended the granting of a conditional marketing authorisation for seladelpar (11). In the UK, the MHRA approved seladelpar to treat adult patients with PBC on 16th January 2024 (PLGB 50729/0001) (1).

Table 2 provides an overview of the technology being evaluated. The Summary of Product Characteristics (SmPC) is included in Appendix A1.1.

Table 2: Technology being evaluated

UK approved name and brand name	Seladelpar (Livdelzi®)
Mechanism of action	Seladelpar selectively activates PPARδ. PPARδ is unique among PPAR isotopes, with broad expression in cells that play a key role in the pathobiology of PBC: hepatocytes, cholangiocytes, Kupffer cells, and stellate cells (2). The activation of PPARδ by seladelpar releases FGF21 from hepatocytes, which in turn reduces the accumulation of bile acids by inhibiting the expression of cholesterol 7α-hydroxylase, the rate-limiting enzyme for bile acid synthesis (3, 4).
Marketing authorisation/CE mark status	Seladelpar received marketing authorisation from the Medicines and Healthcare products Regulatory Agency (MHRA) on 16/01/2025 (PLGB 50729/0001) (1).
Indications and any restriction(s) as described in the summary of product characteristics (SmPC)	Seladelpar is indicated for the treatment of primary biliary cholangitis (PBC), including pruritus, in adults in combination with ursodeoxycholic acid (UDCA) who have an inadequate response to UDCA alone, or as monotherapy in those unable to tolerate UDCA.
Method of administration and dosage	The recommended dose of seladelpar is 10 mg orally once daily. Seladelpar is presented as an oral capsule, with light grey opaque body and a dark blue opaque cap. Seladelpar capsules should be swallowed whole and be taken with or without food.
Additional tests or investigations	Prior to initiation of treatment with seladelpar, the patient's hepatic status must be known. Whether the patient has decompensated cirrhosis (including Child-Pugh Class B and C) or has had a prior decompensation event should be determined prior to initiation of treatment. No additional tests or investigations are anticipated beyond what is already performed in clinical practice to identify patients eligible to receive seladelpar.
List price and average cost of a course of treatment	List price: £3,155.00 per pack of 30 capsules of 10 mg seladelpar
Patient access scheme (if applicable)	A patient access scheme (PAS) has been approved by PASLU for NHSE&I. This PAS involved a simple [redacted]% discount from list price. The confidential net price is [redacted] per pack.

Key: FGF21, fibroblast growth factor 21; MHRA, Medicines and Healthcare products Regulatory Agency; NHSE&I, NHS England and NHS Improvement; PASLU, Patient Access Schemes Liaison Unit; PPAR, peroxisome proliferator activated receptor.

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

1.3.1 Disease overview

PBC is a serious, rare, progressive, and potentially life-limiting chronic autoimmune liver disease characterised by impaired bile flow (cholestasis) and accumulation of toxic bile acids (12, 13). Symptoms such as pruritus (itch) and fatigue associated with the disease pose a burden to patient health-related quality of life (HRQoL). As PBC progresses, liver damage advances from cholestasis to hepatic inflammation, fibrosis, cirrhosis, and end-stage liver disease, which may be characterised by liver failure, hepatocellular carcinoma (HCC), need for liver transplantation, and death (9, 14, 15).

PBC predominantly affects women, with an estimated global prevalence of 1 in 1,000 women over the age of 40. In the UK , data shows a female-to-male ratio of 9:1 (16-19), however, studies on patient cohorts from Denmark, Italy and the US observe less of a female preponderance and are closer to 4:1.(20, 21) The incidence and prevalence of PBC increases with age, with a peak range between 60 and 79 years. PBC is typically identified in middle-aged individuals (40-60 years of age) and is exceptionally rare in individuals under 25 years of age (15).

PBC is a gradually progressive disease whereby the clinical progression from early- to end-stage disease can be highly variable between patients.(14, 22) The diagnosis of PBC often occurs at an early, pre-clinical, asymptomatic phase when following up in abnormal serum liver tests, especially elevated ALP. After excluding extra-hepatic biliary obstruction, the presence of either antimitochondrial antibodies (AMAs), or very rarely, histological confirmation by liver biopsy, establishes the diagnosis. Approximately 50-60% of patients are asymptomatic at diagnosis. Overt symptoms develop within two to four years in most asymptomatic patients, although one-third may remain symptom free for many years (14).

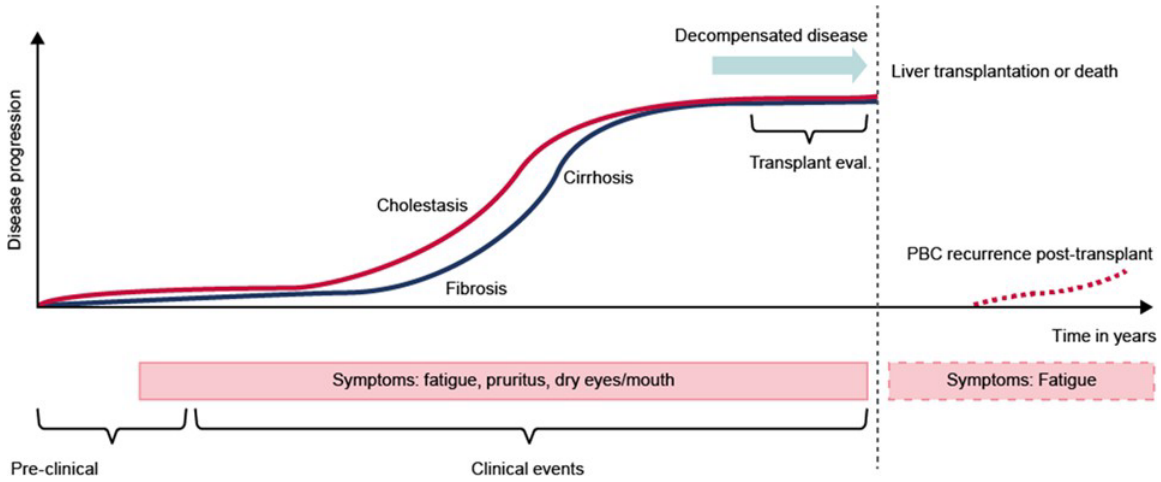
The development of biochemical and clinical features of PBC characterises the intermediate, clinical, symptomatic phase of PBC, which may last for up to 10 years.(22) The hallmark of PBC is cholestasis secondary to hepatobiliary injury and bile acid accumulation, with an accompanying elevation in disease-associated serum biomarkers such as alkaline phosphatase

(ALP). Other disease biomarkers include gamma-glutamyl transferase (GGT), for which increases may be seen earlier in disease, and hyperbilirubinemia as disease progresses. Patients with PBC may also have elevated serum transaminases (alanine aminotransferase [ALT] and aspartate aminotransferase [AST]), as well as increased immunoglobulin concentrations (14).

Fatigue and pruritus are the most common presenting symptoms of PBC. Cholestatic pruritus, the precise cause of which is unknown, occurs in up to 80% of patients with PBC and can be extremely debilitating (see Section 1.3.2.1.1) (23, 24). In addition, fatigue has also been noted in up to 80% of patients and can be a clinically important cause of disability leading to a significant negative impact on HRQoL (see Section 1.3.2.1.2). The severity of fatigue is independent of the severity of liver disease, and there is currently no proven treatment (24, 25). Other features of the disease include coexisting autoimmune disease, hypercholesterolemia, and bone loss, including osteoporosis (see Section 1.3.2.1.3) (26-28).

As PBC progresses, patients enter a terminal, accelerated, two- to four-year phase whereby liver damage advances from cholestasis to hepatic inflammation, fibrosis, and end-stage liver disease, which includes cirrhosis and may necessitate liver transplantation (see Section 1.3.2.1.4) (14, 22). Clinical progression within this stage of PBC varies between individual patients, but is largely characterised by the development of cirrhosis and its sequalae, including worsening portal hypertension, ascites, jaundice, and increased risk of HCC (15, 29).

Figure 2: Disease progression in patients with PBC



Key: PBC, primary biliary cholangitis. Fatigue may persist after liver transplant. The frequency of post-transplant PBC is highly variable among studies 9-61%).
Source: Trivella *et al.* (2023) (15)

PBC is a rare chronic liver disease and is recognised as an orphan disease by the European Medicines Agency (EMA) (30). The prevalence rate of PBC in England is estimated to be 39.6 per 100,000 of the total population, according to a retrospective cohort study by Webb *et al.* (2021) (31), equal to approximately 20,000 patients in England. Other UK-based sources have provided UK prevalence estimates ranging from 7.4 (2017-2020) to 91.0 (2006-2010) per 100,000 population (32-34). The annual incidence of PBC is estimated at 2.5 per 100,000 of the total population in the UK. Epidemiological differences in incidence have been described in the UK, with an association between latitude, deprivation, and smoking status described by Webb *et al*. (2021) (31).

1.3.2 Burden of disease

1.3.2.1 Clinical burden

The progressive nature of PBC imposes substantial clinical burden to patients, largely due to pruritus, fatigue, associated comorbidities and extrahepatic manifestations, and long-term outcomes, such as liver transplantation and shortened survival, for which key biochemical markers in PBC act as prognostic predictors (see Section 1.3.2.2).

The most common manifestations of PBC are elaborated in the following sections.

1.3.2.1.1. Pruritus

As mentioned in Section 1.3.1, cholestatic pruritus is present in up to 80% of patients with PBC and can be severe and disabling (23, 24). Pruritus can be described as a sensation of “bugs crawling under the skin” and a “deep itch”, which at times, can be “relentless” and make those with this sensation want to tear their skin off or scratch until they bleed, suggesting that itch can be incredibly severe (35). Severe pruritus can cause sleep deprivation, social isolation, and trigger suicidal ideation; in extreme cases, it can be an indication for liver transplantation even in the absence of liver failure (14). Patients may experience pruritus all over the body, including the legs, arms, back, sides, abdomen, head, feet, hands, face, chest and groin area (36).

Data on the natural history of pruritus in PBC are limited, with few studies describing the epidemiology of the symptom in the UK. A cross-sectional study of the UK-PBC research cohort, a UK-based group of >5,000 PBC patients established and monitored for population-based research, revealed that 74% of patients experienced pruritus at some point since their development of PBC (n=2,194), with 35% of patients reporting persistent pruritus, defined as itch that occurs frequently or all the time. The PBC-40 itch domain score was used to define severity of pruritus; 26%, 17%, and 12% of patients met the criteria for mild (score: 4-8), moderate (score 9-11), and severe (score ≥12) pruritus, respectively. The study also identified that younger age at diagnosis and higher level of ALP were significantly associated with persistent high pruritus (19).

The patient-reported prevalence of pruritus in the UK-PBC cohort is higher than reported in a population-based evaluation study conducted by Abbas *et al.* (2024), which reported a prevalence of 21% across 8,968 patients with PBC who were under follow-up in 122 NHS centres across the UK. However, the study reported that over one-third of patients (38%) had not been assessed for pruritus in the previous 24 months at the time of analysis. The infrequent evaluation of pruritus in the UK adds to the unmet need for adequate treatment and management of PBC, as more patients may experience pruritus than indicated in available sources, contributing to a substantial clinical burden (16).

Elsewhere, in a longitudinal observational cohort study of 211 PBC patients in the US, pruritus was reported in 81% of patients as assessed by the PBC-40 itch domain. Clinically significant pruritus was reported by 30% of patients. Patients with clinically significant pruritus more frequently had cirrhosis and reported fatigue compared to those with mild pruritus. Approximately 20% of patients with clinically significant pruritus reported experiencing itching for more than 12 hours per day. Clinically significant pruritus involved an average of six to ten body parts, and the most reported body parts were head/scalp (67%), lower legs (63%), back (62%), palms of hands (43%), and soles of feet (35%) (23).

Furthermore, despite a lack of data in UK patient cohorts, it is evident that the comorbidity burden for patients with PBC who experience pruritus is substantially higher than for patients with PBC without pruritus, and these comorbidities worsen with time. In a retrospective analysis of claims

data in the US since 2006, patients with PBC and pruritus experienced greater likelihood of PBC-related comorbidities, including rheumatoid arthritis (hazard ratio [HR] [95% confidence interval [CI]]: 2.77 [1.83, 4.20]), systemic lupus erythematosus (SLE) (HR [95% CI]: 2.69 [1.44, 5.01]), cognitive impairment (HR [95% CI]: 2.64 [1.71, 4.06]), sleep disorders (HR [95% CI]: 2.63 [1.98, 3.49]), and depression (HR [95% CI]: 1.95 [1.58, 2.40]), compared to patients with PBC without pruritus (37).

1.3.2.1.2. Fatigue

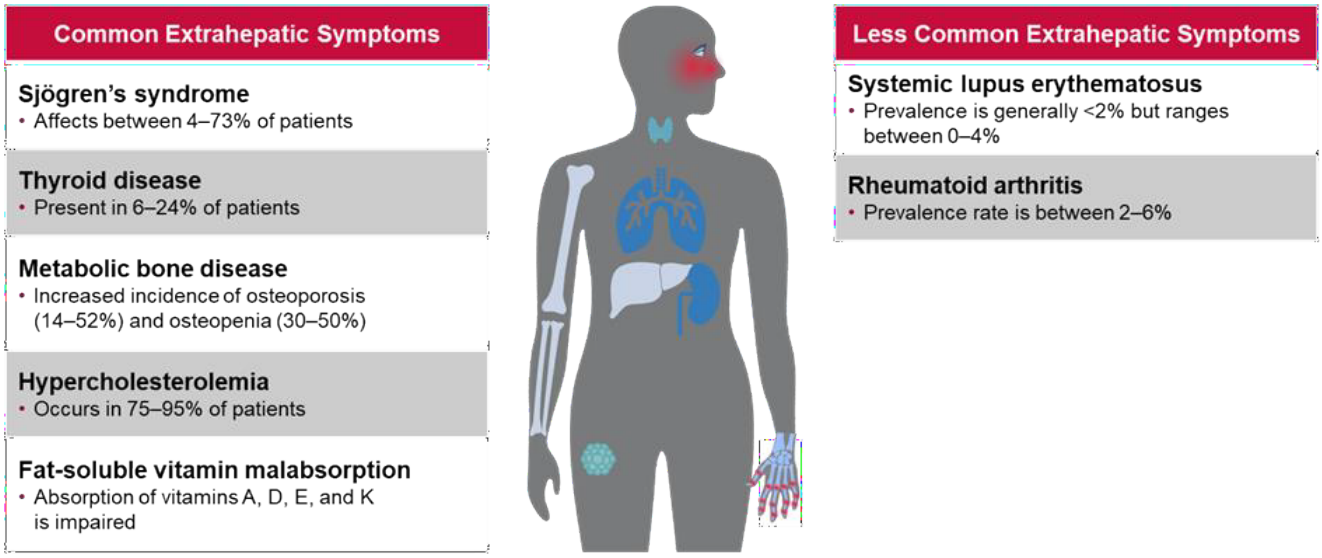
As highlighted in Section 1.3.1, fatigue occurs in up to 80% of PBC patients, with 20% of all patients experiencing significant or life-altering fatigue (24, 25). Fatigue may fluctuate independently of disease activity or stage, indicating that patients with early stages of PBC can still experience severe fatigue, as well as those with more progressed disease (24).

Data on the prevalence of fatigue in PBC patients is limited to studies in the US. In a retrospective, cross-sectional database study of US patients with PBC, fatigue was more frequently reported in the overall PBC population (20%) and PBC-pruritus subpopulation (27%) compared to controls without PBC (10%) (25). In a 2006 US retrospective claims data analysis, patients with PBC and fatigue also experienced greater likelihood of cognitive impairment (HR [95% CI]: 4.00 [2.93, 5.45]), sleep disorders (HR [95% CI]: 2.83 [2.35, 3.41]), depression (HR [95% CI]: 2.39 [2.09, 2.73]), rheumatoid arthritis (HR [95% CI]: 2.24 [1.78, 2.81]), and autoimmune thyroid disease (HR [95% CI]: 2.02 [1.44, 2.82]) compared to patients with PBC without fatigue (24).

1.3.2.1.3. Extrahepatic manifestations and comorbidities

Extrahepatic manifestations, other autoimmune conditions, and comorbidities, are seen in up to 95% of patients with PBC, further adding to the clinical burden of PBC (Figure 3) (26-28).

Figure 3: Extrahepatic symptoms of PBC



Key: PBC, primary biliary cholangitis
Source: Younoussi *et al.* (2019) (26) , Chalifoux *et al.* (2017) (27) , Wah-Suarez *et al.* (2019) (28)

Details on the most common extrahepatic manifestations, autoimmune conditions, and other comorbidities are listed below:

- **Sjögren's syndrome** is a progressive autoimmune disorder that affects 4–70% of patients with PBC. Lymphocytic infiltration of the exocrine glands leads to decreased exocrine secretions, typically manifesting as ocular and oral dryness (27). Patients with Sjögren's syndrome are at risk of complications related to decreased saliva production, which on top of the discomfort of dry mouth, can cause intraoral manifestations such as refractory stomatitis and ulcer (38). Additionally, up to 70% of patients with Sjögren's syndrome report debilitating fatigue (39).

- **Thyroid disorders** are present in 6–24% of patients with PBC. Hashimoto's thyroiditis is the most common subtype seen in patients with PBC, and can lead to the inability to concentrate, memory loss, and depression (27).

- **Metabolic bone disease** affects patients with PBC, with 30–50% experiencing osteopenia and 14–52% experiencing osteoporosis, which can lead to falls and fractures, substantially impacting morbidity and mortality. (14, 40) Major risk factors for osteoporosis in PBC

include severe cholestasis and advanced histological stage, but patients with less advanced disease can also be affected. Post-menopausal women are at particular risk (36).

- **Hypercholesterolemia**, or high levels of cholesterol in the blood, occurs in 75–95% of patients with PBC. While hypercholesterolemia is a well-established modifiable risk factor for cardiovascular disease in the general population, it is not always associated with an increase in cardiovascular events in patients with PBC; however, patients with PBC with cardiovascular risk factors may still warrant cholesterol-lowering therapy (26, 28).

- **Fat-soluble vitamin deficiency**, which has been associated with progression to cirrhosis, liver-related mortality, and need for liver transplantation, may occur when decreased bile acid secretion leads to impaired absorption of vitamins A, D, E, and K (26, 41).

Less common extrahepatic manifestations include SLE and rheumatoid arthritis, with both also adding to the clinical burden of PBC. Due to kidney inflammation being one of the most severe manifestations of SLE, patients who develop SLE are at risk of progressing to end-stage kidney disease, subsequently leading to need for dialysis or kidney transplantation (42). Further, patients who develop rheumatoid arthritis, characterised by chronic inflammation of joint tissue, may experience swelling, pain, and deformation of small joints. As cases advance, this can lead to functional limitations and the involvement of internal organs (43).

1.3.2.1.4. Long-term outcomes

The natural history and prognosis of PBC has changed and improved significantly during the last several decades, owed to ealier diagnosis and earlier treatment initiation. Consequently, the disease has gone from a slow, progressive disease resulting in liver fibrosis and cirrhosis to a disease process with slower rates of progression and fibrosis, and higher rates of clinical remission (44).

A substantial proportion of undertreated patients remain at risk for cirrhosis-associated complications, including esophageal varices, ascites, and hepatic encephalopathy. A study analysing PBC coding through inpatient care data in Germany reported ascites, esophageal varices with or without bleeding, hepatic encephalopathy, and arterial hypertension were coded

in 19%, 24%, 4%, and 33% of cases, respectively (45). Furthermore, an epidemiological study in Sweden found the cumulative risk of liver complications within 10 years, including esophageal varices and/or gastric varices, liver failure, or ascites, was significantly higher in patients with PBC (men: 33%; women: 17%) than in patients without PBC (men and women: 0.3%) (46).

Between 1st April 2022 to 31st March 2023, there were 648 elective liver transplants performed in the UK, of which 7% represented patients with PBC (n=46). The risk-adjusted patient survival rates after liver transplantation in the UK were 95.1% (95% CI: 91.2%, 97.4%) and 89.1% (83.0%, 92.9%) at one and five years, respectively, and align with transplant-free survival rates reported in the US (survival rates of 85-94% and 87% at one and five years, respectively) (47, 48). However, PBC recurrence after transplantation has been reported to be 22% at five years post-transplant and 36% at 10 years post-transplant, which can lead to graft loss, need for re-transplantation, or death (48). In addition, liver transplantation can likely be associated with post-operative complications. The most common of these within the first-year post-transplant are bone pain and fractures, hypertension, and renal failure (49). The development of PBC-related complications significantly contributes to healthcare costs in the UK (see Section 1.3.2.4).

1.3.2.1.5. Mortality

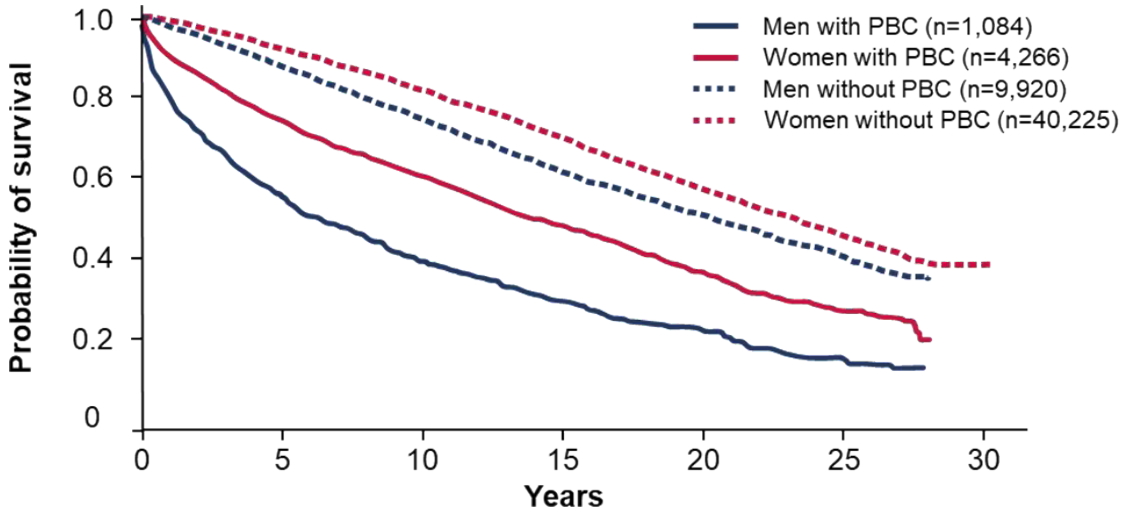
Despite the availability of treatment options, patients with PBC remain at an early risk of death compared to the general population. Patients whose PBC is detected at a sufficiently early time point and who exhibit complete biochemical response to therapy with first-line UDCA monotherapy have a normal life expectancy (50, 51). Otherwise, for patients who do not respond well to treatment, life expectancy is estimated to be 10 years following disease onset (52). In a study by Mendes *et al*. (2008), which analysed 11,860 death certificates issued in the US of patients with PBC, the mean age at death was 65.6 years (53).

Data on the mortality rate of PBC in the UK is limited to a single study by Koop *et al*. (2024), who conducted a UK Biobank cohort stidy from 2006-2010 involving 454 PBC patients. The all-cause mortality rate was reported to be 22.9%, with a diagnosis associated with the digestive system (6.8%) and malignancies of hepatic origin (2.4%) identified as a significant driver of increased mortality (34). Studies by Warnes *et* al. (2023) and Haldar *et* al. (2021) also identified hepatic

venous pressure gradient and anti-gp210 auto-antibody as significant factors behind mortality and liver transplant in UK-based patients with PBC (54, 55).

In addition, data from a more recent Swedish population-based cohort support an increased risk of death in those with PBC compared to those without, and also highlight differences by gender; only 37% of men and 59% of women were alive 10 years after their PBC diagnosis, This study also found that the highest risk of death was observed in the first year after PBC diagnosis, with an HR of 9.04 (95% CI: 8.12, 10.07) for patients with PBC compared to patients without PBC (Figure 4) (46).

Figure 4: Kaplan-Meier plot for survival by gender and PBC



Key: PBC, primary biliary cholangitis
Source: Marschall *et al.* (2019) (46)

1.3.2.2 Correlation of surrogate markers with long-term outcomes

The overall aim of PBC treatment is to prevent progressive liver disease and relieve disease-related symptoms (14). However, the slow, progressive nature of the disease makes it challenging to assess outcomes requiring long-term follow-up in the setting of a clinical trial. As such, surrogate markers can be used in clinical trials to enable the prompt evaluation of therapeutic benefit (56).

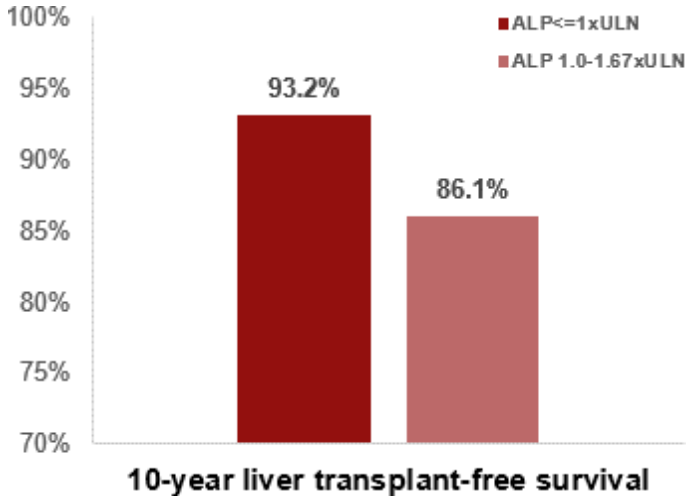
Both ALP and bilirubin are recognised as independent predictors of prognosis in PBC patients (56). Elevated ALP is typical in patients with PBC and is a cholestatic marker associated with

ongoing bile duct destruction and disease progression. Similarly, elevated bilirubin is an indicator of cholestasis, cirrhosis, and poor hepatic function (14). ALP and bilirubin have been established as surrogate endpoints likely to predict clinical benefit in previous clinical studies, which used widely accepted thresholds of 1.67 x upper limit of normal (ULN) and 1 x ULN, respectively (57-59). These surrogate endpoints have been recognised by the US Food and Drug Administration (FDA) and the European Association for the Study of the Liver (EASL) and identified as independent predictors of prognosis in PBC (14, 56, 60).

In clinical practice, there are a number of prognostic models for UDCA non-response described by different groups, which are based on cut-offs of the degree of elevation in ALP, total bilirubin, and in some instances, ALT (see Table 4,Section 1.3.3.1.1). In the UK, the prognostic model most widespread in clinical practice focuses on ALP >1.67 x ULN (15, 79). A study of the UK-PBC cohort by Jones *et al*. (2022) confirmed that the PBC prognostic models have a mechanistic underpinning, with disease activity higher in UDCA non-responders versus UDCA responders. However, ongoing PBC disease activity was observed in all UDCA responder cohorts in the study irrespective of the prognostic model applied, apart from in patients with normal liver blood tests. Therefore, the normalisation of ALP and total bilirubin would be viewed as the optimal goal of treatment. The higher the cut-off for ALP and total bilirubin, the greater the degree of disease inflammatory/immune/metabolic activity seen. This means that in current UK practice, there will remain a proportion of patients labelled as UDCA responders who continue to have ongoing disease activity. Although some patients are therefore mislabelled as UDCA responders, this is not expected to impact the patients treated with seladelpar, other than providing them with a different treatment option. The categorisation of patients based on response criteria as opposed to normal liver tests potentially results in the under-utilisation of second line-treatment and increased adverse outcomes (61).

There are multiple, recent studies that evidence the improved clinical outcomes associated with ALP normalisation (ALP ≤ ULN) in patients with PBC (61-64). Observations from the Global PBC Study Group suggest that an elevation in ALP exceeding 1 x ULN may indicate an ascending linear risk with regards to long-term outcomes, with a benefit from ALP normalisation; 10-year survival rates in patients with normal ALP levels were 93.2% vs 86.1% in patients with ALP between 1 – 1.67 x ULN (Figure 5) (64).

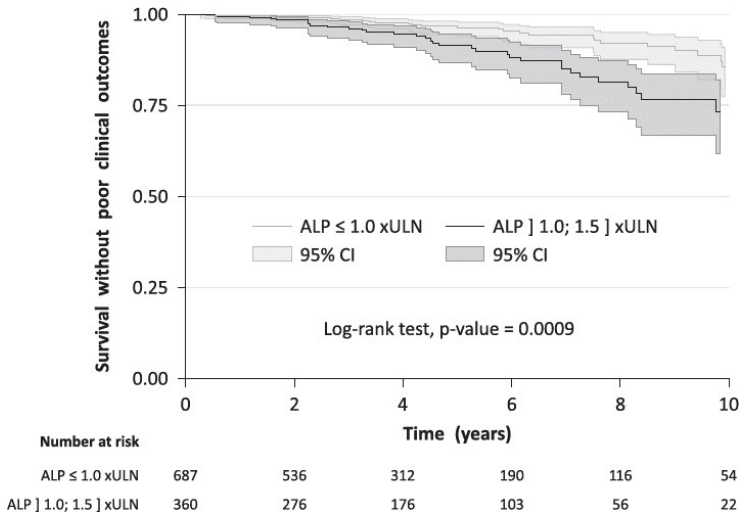
Figure 5: Ten-year liver transplant -free survival of PBC patients stratified by ALP levels (≤1.0 x ULN or 1.0 - 1.67 x ULN).



Key: ALP, alkaline phosphatase; PBC, primary biliary cholangitis; ULN, upper limit of normal
Source: Murillo Perez *et al.* (2020) (64)

In addition, in PBC patients with a normal GLOBE score (model to predict liver transplant-free survival incorporating age, ALP, total bilirubin, albumin and platelet count) (65), elevated ALP levels > 1 x ULN after one year of treatment with UDCA (first-line therapy for PBC, see Section 1.3.3.1.1) were associated with an increased risk of liver transplant or death, adjusted for age, gender and liver enzyme values (HR [95% CI]: 1.31 [1.00, 1,72], p=0.048) (Figure 6) (66). Furthermore, in a large retrospective cohort study 1,047 patients with PBC and adequate response to UDCA followed up for over 15 years, normal ALP levels were associated with significant and absolute relative gains in complication-free survival at 10 years, particularly in patients with advanced fibrosis (defined in the study as a liver stiffness measurement ≥ 10 kPa) and/or younger age (≤62 years) (62).

Figure 6: Complication-free survival curves with or without normal ALP levels at entry



Key: ALP, alkaline phosphatase; CI, confidence interval; PBC, primary biliary cholangitis; ULN, upper limit of normal
Notes: The Kaplan-Meier curve and its 95% CI for the normal ALP group are in grey and light grey, respectively. Thise for the abnormal ALP group are in black and dark grey, respectively. The p-value corresponds to the log-rank test.
Source: Corpechot *et al.* (2024) (62)

In support of the published evidence outlined above, a real-world retrospective evaluation of ALP normalisation in 22,487 US patients with PBC receiving treatment (REAL) conducted by Gilead found ALP normalisation (ALP ≤ ULN) was associated with a reduced risk for mortality, incident liver transplantation decompensated cirrhosis, ascites requiring treatment, hospitalisation, and composite clinical endpoints (Table 3) (63).

Table 3: Association between having normal ALP levels at first ALP test after six months following treatment initiation and subsequent clinical Outcomes

Outcome	Hazard Ratio (95% CI)[a]	p-value
Death	0.59 (0.42-0.83)	.003
Liver transplant	0.30 (0.16-0.55)	<.001
Decompensated cirrhosis	0.36 (0.26-0.50)	<.001
Ascites requiring treatment	0.22 (0.14-0.34)	<.001
Hospitalisation[b]	0.22 (0.06-0.86)	.029
Composite endpoint 1[c]	0.51 (0.37-0.50)	<.001
Composite endpoint 2[d]	0.44 (0.33-0.59)	<.001

Key: ALP, alkaline phosphatase; CI, confidence interval
Notes:

[a]Cox proportional hazard models adjusting for type of treatment at index, age, sex, race/ethnicity, cirrhosis at baseline, presence of select comorbidities at baseline (systemic lupus erythematosus, autoimmune hepatitis,rheumatoid arthritis, autoimmune thyroid disease, Raynaud syndrome, Sjögren syndrome, hypercholesterolemia, urinary tract infection, and pruritus), Charlson Comorbidity Index score, payer type, and days from index to firstALP test after 6 months
[b]With a primary diagnosis of any of the following: oesophageal or gastric variceal bleeding, hepatic encephalopathy, or spontaneous bacterial peritonitis.
[c]Composite endpoint 1: Death or liver transplantation.
[d]Composite endpoint 2: Death, liver transplantation, hospitalisation (with a primary diagnosis of oesophageal/gastric variceal bleeding, hepatic encephalopathy, or spontaneous bacterial peritonitis), or ascites requiring treatment.
Source: Kowdley *et al.* (2024) (63)

In keeping with these emerging data, it has been suggested that the goal of treatment should be to achieve complete biochemical normalisation (62, 66). Feedback from [redacted], and an additional UK clinical expert, highlighted that the clinical community are moving towards ALP normalisation as the key goal of treatment for a select group of patients likely to get the highest incremental gains with treatment (i.e., those diagnosed <62 years with high baseline FibroScan scores) to prevent long-term adverse liver outcomes and death. Both experts believed that clinical guidance would be updated to reflect this.

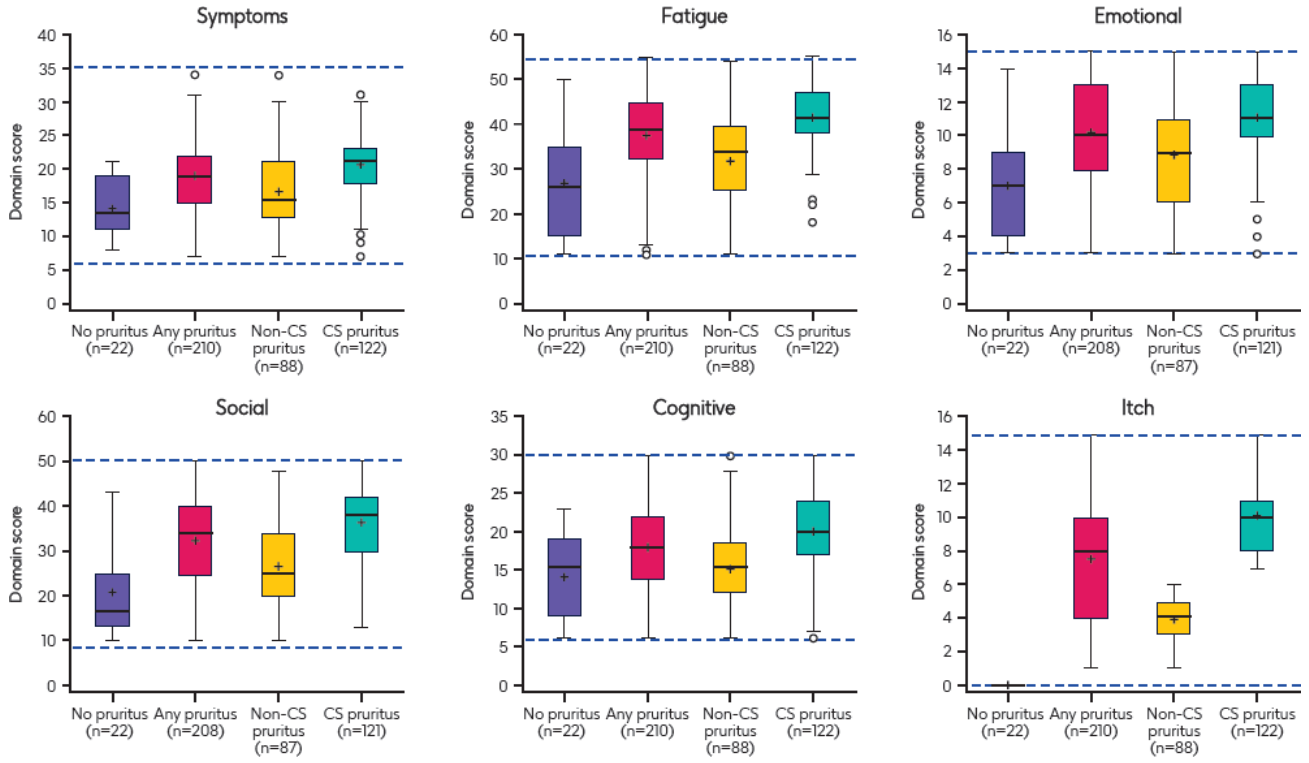
1.3.2.3 Humanistic burden

Many of the clinical symptoms experienced by patients with PBC are associated with humanistic burden, with patients self-reporting depressive symptoms, anxiety, and an overall lower HRQoL compared to the general population (18, 49).

Amongst these symptoms, pruritus has a detrimental impact on HRQoL and limits daily life activities for patients with PBC, and may cause fatigue, depression, and even suicidal tendencies (67). In TARGET-PBC, a longitudinal observational cohort of patients with PBC across the US, patients with clinically significant pruritus (defined as a PBC-40 itch domain score ≥7) scored significantly worse across all PBC-40 domains compared to those with mild pruritus (PBC-40 itch domain score 1–6), indicating a worse HRQoL (all domains $p<0.0001$) (23). These results were recently replicated in an ambispective and cross-sectional analysis of adult PBC patients enrolled in the US PicnicHealth PBC registry by Halliday *et al.* (2024) (68) (Figure 7). Furthermore, the scores for the 5-D Itch scale, a questionnaire that measures the severity of itching across five dimensions (degree, duration, direction, disability, and distribution), in TARGET-PBC were consistent with the PBC-40 itch domain, with respondents with clinically significant pruritus reporting significantly worse scores across all domains. Itch caused

significant disruption to patients' sleep (88%), and also impacted their social life (58%), housework/errands (53%), and work/school (44%) (23).

Figure 7: Median PBC-40 domain scores by itch severity



Key: CS, clinically significant; PBC, primary biliary cholangitis.
Notes: Thresholds for clinical significance (and the minimum and maximum possible score) for each of the domains were: Itch: 7 (0–15), Fatigue: 33 (11–55), Cognitive: 18 (6–30), Symptoms: 18 (6–35), Social: 32 (8–50) and Emotional: 12 (3–15).Dotted blue lines represent the minimum and maximum possible scores for each domain, median is depicted by the black line, upper and lower quartiles by upper/lower box, min/max as error bars. Values that were more than 1.5 times the interquartile range away from the box were considered to be outliers and are shown as circles.
Source: Halliday *et al.* (2024) (68)

Pruritus in PBC patients often worsens at night, and patients frequently report sleep disturbance, contributing to cognitive symptoms and fatigue (68) (Figure 7), the latter constituting a frequent symptom for patients (see Section 1.3.2.1.2). Results from a survey of members of the PBCers organisation, an online and in-person support group for patients with PBC, by Rishe *et al.* (2008) reported up to 74% of patients with pruritus experienced sleep disturbance due to their itch (35). Additionally, a post-hoc analysis of the relationship between pruritus severity and sleep disturbance as part of the Phase 2 GLIMMER study observed a strong correlation between change from baseline in weekly sleep score and change from baseline in weekly itch score

(r=0.88; 95% CI: 0.83, 0.91). This indicates sleep interference was worse in patients with more severe pruritus compared to those with milder pruritus (69).

ITCH-E, a real-world study conducted by Gilead that recruited 90 patients from a PBC advocacy group and physician panels in the US between December 2023 and March 2024, reported that patients with moderate to severe pruritus (50 of 90 patients, 56%) had statistically significantly worse PBC-40 mean scores in Symptom, Itch, Fatigue, Cognitive, and Social domains ($p<0.05$), alongside worse scores on the Functional Assessment of Chronic Illness Therapy (FACIT)-fatigue ($p<0.001$), 5D-itch ($p<0.001$), Chronic Liver Disease Questionnaire (CLDQ)-PBC Total ($p<0.001$) and EuroQol 5-Dimension (EQ-5D) ($p=0.005$) HRQoL tools. Most patients described their pruritus as consistently intense and emphasised that a PBC treatment that can relieve itch would considerably improve their emotional, physical, and social well-being, potentially reducing anxiety, fatigue, and social isolation (70).

Data on the impact of pruritus on HRQoL in the UK is limited. A PBC foundation survey, which sampled 141 patients with PBC in the UK between June and December 2022, reported that pruritus negatively affects patients in their day-to-day activities; 79%, 44%, and 28% of patients highlighted that an improvement or disappearance of pruritus would provide them with an ability to sleep, enjoy relaxation time, and to go out and enjoy social occasions, respectively. In the same survey, 25% of patients highlighted that they would require complete resolution of itch to enable a return to the aforementioned activities, while 67% reported that mild pruritus would be acceptable (71).

1.3.2.4 Societal and economic burden

PBC complications have been shown to significantly contribute to healthcare costs in the UK, with an analysis of 2,240 PBC patients (over 10% of all UK patients) by Rice *et al.* (2021) reporting) esophageal varices (£2,504; 95% CI: £1,311 to £3,696) and hepatic encephalopathy (£823; 95% CI: £148 to £1,498) as the greatest contributors to mean annual costs to the NHS (18).

However, the most significant cost to the NHS is liver transplantation. Although the average cost of a liver transplant for a patient with PBC is not published in the literature, previous appraisals, namely TA443 and more recently TA1016, have utilised the cost of the procedure to estimate

the cost of transplantation for patients diagnosed with hepatitis B and C in the UK (72, 73). Singh and Longworth (2014) estimated the mean total costs for patients with HCV were £18,055 pre-transplantation, £64,452 during the transplant phase, and £36,009 in two years post-transplant. The average cost per transplanted patient with HCV from assessment to two-years post-transplant was £111,810 (74). In the highly specialised technology appraisal of odevixibat for progressive familial intrahepatic cholestasis (HST17), the total costs associated with the pre-transplant phase, transplant procedure, and post-liver transplant follow-up (two years), for patients with PBC were reported at £19,699, £70,320, and £39,287, respectively (75). Considering the above, optimising the treatment of PBC in the earlier stages to reduce disease progression is important to reduce the economic burden of the disease.

Furthermore, the management of PBC is also associated with significant healthcare resource use (HCRU) in the UK. In 2023/2024, PBC was responsible for 482 hospital admissions in England (ICD10 K74.3), accounting for 809 consultant episodes and 286 bed days. For patients admitted to hospital, the average length of stay was 13.4 days (76).

The societal burden of PBC has also been reported in the literature, with negative impacts to daily life, financial security, and emotional well-being for patients and caregivers alike. In a study that surveyed 119 members of the Canadian PBC society, 45% of patients reported that they had to decrease their social interactions with family and friends to accommodate their symptoms. Additionally, current and future financial security was a concern for 19% of patients, as they were forced to take early retirement, reduce their work hours, or go on disability leave. Patients who were still working reported that it was an everyday struggle and that they worried about their performance (77).

Furthermore, the presence of pruritus can also exacerbate the burden of PBC on impaired activity. In the ITCH-E real-world study conducted by Gilead, patients with moderate to severe pruritus reported statistically greater Work Productivity and Impairment (WPAI) activity impairment and lower work status compared to patients with no to mild pruritus ($p<0.001$). Among those employed, patients with moderate to severe pruritus reported more work time missed (9.8% vs 5.8%), greater impairment while working (46.5% vs 32.4%), and overall work impairment due to PBC (49.7% vs 35.2%) (78).

Due to the complications related to PBC, patients may also frequently rely on caregivers for various needs. In a survey of 22 caregivers of patients with cholestasis in France, Germany, the UK, and the US, most caregivers (73%) were employed, and none had formal care support. One-third of caregivers also reported mean productivity loss of 12.9 days over the last three months, and a mean of 2.8 missed years of employment during their career (79), highlighting the full extent of caregiving responsibilities.

1.3.3 Clinical care pathway

Current guidance for the clinical care of adults with PBC in the UK is provided by the British Society of Gastroenterology (BSG) and the UK-PBC , which are reflective of the established guidance provided by the EASL and the American Association for the Study of Liver Diseases (AASLD) (14, 80, 81). Clinical expert feedback provided as part of TA1016 confirmed that BSG/UK-PBC guidance will shortly be updated to reflect recent evolutions in PBC management in the UK (72).

The National Institute for Health and Care Excellence (NICE) has not provided full guidelines on the treatment of PBC, however, they have produced guidance on OCA (TA443) and, more recently, elafibranor (TA1016) for treating PBC (72, 73).

NICE published final guidance on 26th April 2017 recommending 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. NICE also recommended that the response to OCA should be assessed after 12 months, with treatment continued only if there is evidence of clinical benefit (73).

Final guidance for elafibranor was recently published on 13th November 2024. NICE recommended elafibranor, within its marketing authorisation, as an option for treating PBC in adults, when used with UDCA, if the PBC has not responded well-enough to UDCA, or alone, if UDCA cannot be tolerated (72).

NHS England also commissions specialist services for PBC under its policy for liver transplantation services in adults and children. The service provides assessment,

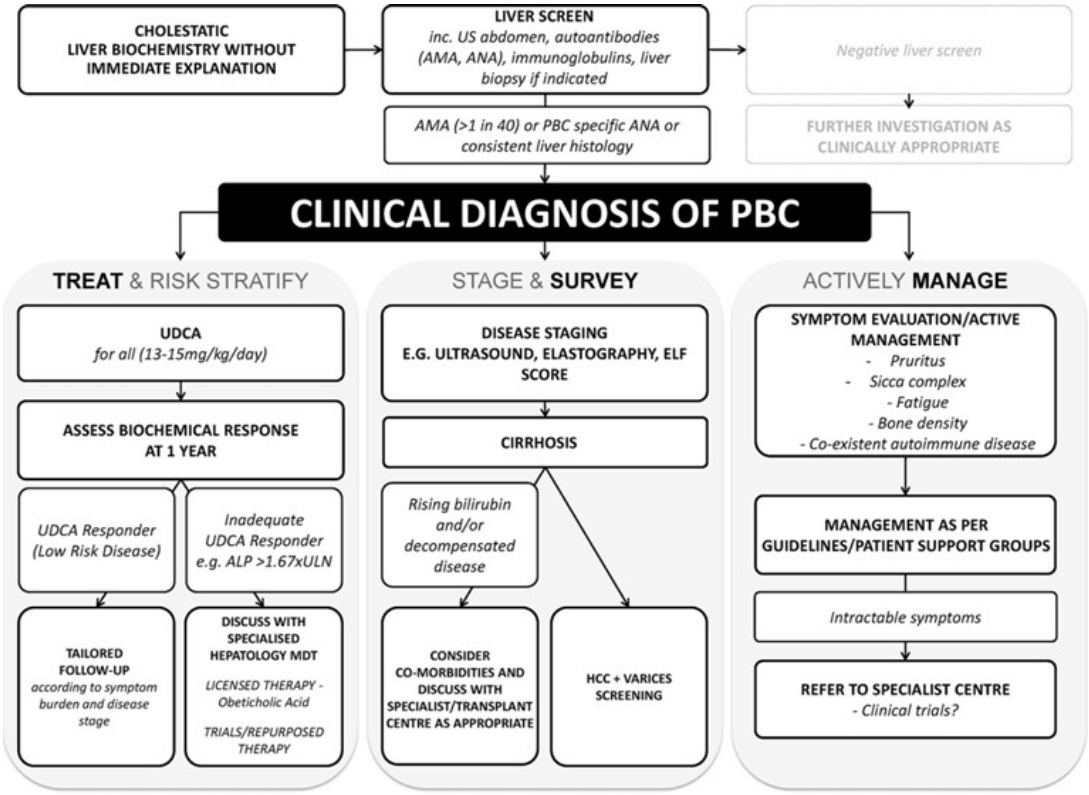
transplantation and lifelong follow-up for patients requiring transplant surgery, including from living donors (82).

1.3.3.1 BSG/UK-PBC guidelines

1.3.3.1.1. Summary of BSG guidelines

The BSG/UK-PBC guidelines highlight that while care always needs to be personalised to the patients, there are consensus pathways that are important for patients with PBC, which encompass the important 'pillars' of care that provide optimal management of the disease and its complications (80). The 'pillars' of care, as described in the current BSG/UK-PBC treatment and management guidelines, are depicted below in Figure 8.

Figure 8: BSG/UK-PBC consensus care pathway for patients with PBC



Key: ALP, alkaline phosphatase; AMA, anti-mitochondrial antibody; ANA, antinuclear antibodies; ELF, enhanced liver fibrosis; PBC, primary biliary cholangitis; UDCA, ursodeoxycholic acid; ULN, upper limit of normal.
Source: Hirschfield *et al.* (2018) (80)

According to guidance from the BSG/UK-PBC and other internationally recognised treatment guidelines, the diagnosis of PBC can be established when two of the following criteria are met (14, 80, 81):

- Biochemical evidence of cholestasis based on ALP elevation
- Presence of AMA, or other PBC-specific autoantibodies if AMA is negative
- Histologic evidence of nonsuppurative destructive cholangitis and destruction of interlobular bile ducts

Most patients with PBC have abnormal liver tests including elevations of ALP, mild elevations of aminotransferase (ALT or AST) activity (which reflect the degree of liver parenchyma inflammation and necrosis), and increased levels of immunoglobulins (mainly immunoglobulin M [IgM]) (14, 80, 81). The serologic hallmark of PBC is AMA, which is positive in 90–95% of individuals with PBC. In rare cases, some patients may exhibit AMA-negative PBC (15). In order to differentiate AMA-negative PBC from other conditions with similar characteristics, liver biopsy may be necessary when AMA or other PBC-specific antibodies are absent (14, 80, 81).

Prior to the proposed positioning of seladelpar, diagnosed PBC patients are recommended by the BSG/UK-PBC guideline and other internationally recognised clinical practice guidelines to receive oral UDCA at 13-15 mg/kg/day as a first-line therapy (14, 80, 81). In a UK population-based evaluation study conducted by Abbas *et al.* (2024), 88% of patients were treated with UDCA monotherapy (n=7,864). However, of the 6,053 patients with weight and dose data available, nearly one-third (n=1,850, 30.6%) received a sub-optimal dose (<13 mg/kg/day), of whom 48% had ALP > ULN and 13% had ALP >1.67 x ULN. In patients who were not treated with UDCA monotherapy (n=998), the most common reason was drug intolerance (n=362) (14). For patients who are tolerant to UDCA monotherapy, treatment is recommended to be life-long (80).

Amongst patients with first-line UDCA monotherapy for at least 12 months in the study by Abbas *et al.* (2024), 2,102 had evidence of an inadequate UDCA response (16), defined by ALP >1.67 x ULN and/or elevated bilirubin <2 x ULN. Although there are varied response criteria for evaluating treatment response to UDCA monotherapy, an expert group consulted by the

BSG/UK-PBC in the production of treatment guidelines noted that the response criteria most widespread in UK clinical practice focused on ALP >1.67 x ULN (16, 80). Reassessment for response is recommended to occur after 12 months of UDCA monotherapy. Table 4 details the commonly referenced criteria for assessing response to UDCA monotherapy in PBC.

Table 4: Commonly referenced criteria for assessing response to UDCA monotherapy in PBC

Global Providers	Biochemical Response Criteria
Barcelona (81)	ALP decrease of 40% or normalisation of ALP
Paris I (81)	ALP 3x ULN; AST 2x ULN; and total bilirubin 1 mg/dL
Paris II (81)	ALP 1.5x ULN; AST 1.5x ULN; and total bilirubin 1 mg/dL
POISE (57)	ALP <1.67x ULN, ALP decrease ≥15%, and total bilirubin ≤1.0x ULN
Rochester (81)	ALP 2x ULN
Rotterdam (81)	Total bilirubin <1x ULN and albumin >1x LLN
Toronto (81)	ALP 1.67x ULN

Key: ALP: alkaline phosphatase; AST: aspartate aminotransferase; PBC: primary biliary cholangitis; POISE: PBC OCA International Study of Efficacy; ULN: upper limit of normal

For patients with an inadequate response to UDCA monotherapy (or UDCA intolerance) after 12 months, the addition of second-line OCA (initial dose 5mg/day, titrating to 10mg/day at six months if tolerated) in combination with UDCA or as a standalone treatment is currently recommended by the BSG/UK-PBC and other internationally recognised guidelines (14, 80, 81). The future of OCA in the UK PBC treatment pathway is considered uncertain following recent regulatory decisions by the EC and US FDA (see Section 1.3.3.3), although at present, there are no changes to the recommendations on the use of OCA in PBC from the MHRA or NICE (83). In the study by Abbas *et al*. (2024), 50% of patients eligible for second-line therapy in UK clinical practice received treatment with OCA.

The remaining 50% of patients in the UK received treatment with fibric acid derivatives (bezafibrate or fenofibrate) (16), which are off-label therapies and are not approved for the treatment of PBC by any regulatory bodies, including the MHRA (80). Discussions with UK clinical experts suggests that fibrates are used as an adjunctive option to UDCA monotherapy in UK clinical practice for patients that do not meet the clinical criteria for second-line therapy (i.e., have ALP between 1 – 1.67 x ULN). As part of the appraisal of elafibranor for the treatment

of PBC (TA1016), clinical experts suggested that fibrates are used in combination with second-line treatment to treat itching. Due to toxicity and limited evidence of efficacy, fibrates were considered not to be widely used in UK clinical practice (72).

The BSG/UK-PBC guideline recommends that patients should be evaluated for symptoms, particularly pruritus and fatigue (80), with a clinical expert in consultation with Gilead confirming that this assessment should typically occur every 12 months. The treatments which are used empirically to manage pruritus in the UK are cholestyramine, rifampicin, and antihistamines. Cholestyramine is recommended as a first-line treatment option for pruritus for patients with PBC (80), and in a UK population-based evaluation study by Abbas *et al.* (2024), was prescribed to 41% of patients who received treatment for pruritus (16). Rifampicin, a second-line treatment option for pruritus, was reported in 17% of PBC patients treated for pruritus (16), while anti-histamines, which are deemed to be useful adjuncts to therapies that manage cholestatic itch and are non-recommended as specific therapy (80), were used to treat 30% of patients (16).

Liver transplantation is an established and successful procedure that may prolong the life of patients with chronic liver disease, and is recommended as an effective treatment option for advanced PBC by the BSG/UK-PBC and other internationally recognised guidelines (14, 80, 81). In the UK, patients should have a clear indication for transplantation as well as, usually a United Kingdom Model for End-Stage Liver Disease (UKELD) score of 49 or greater (i.e., meet minimal listing criteria based on a biochemical marker of disease severity using the latest bilirubin, international normalised ratio [INR], creatinine and sodium). Of note, patients with pruritus refractory to all medical therapy are eligible for listing for transplantation in the absence of an elevated UKELD score (80, 84). Despite this, it is acknowledged that liver transplantation remains a challenging procedure and, in most settings, organ availability has a significant impact on determining the precise timing and indications for surgery (80).

1.3.3.1.2. Disparities in BSG/UK-PBC guidelines and clinical practice

Despite the availability of published guidelines for PBC management in the UK, there are disparities between such guidelines and the care patients receive. A population-based evaluation of clinical care delivery in the UK by Abbas *et al.* (2024), which collected data from 8,968 patients with PBC between 1st January 2021 and 31st March 2022, reported that poor

adherence to guideline standards exists across all domains of PBC care in the NHS. Most strikingly, only 51% of patients who had evidence of an inadequate response to first-line UDCA monotherapy were prescribed a second-line therapy despite the availability of OCA, falling far below the 90% target. Similarly, more than one-third of patients had not been assessed for pruritus (38%) or fatigue (43%) in the previous 24 months prior to the study, falling short of the 90% target set by the BSG/UK-PBC. The audit of PBC-related healthcare in the UK by Abbas *et al.* (2024) underscores the need for NHS centres to maximise their adherence to key guideline standards set by the BSG/UK-PBC and improve the delivery of PBC-related healthcare to a patients (16).

1.3.3.2 NICE guidelines

As highlighted above in Section 1.3.3, NICE have not developed guidelines for the treatment and management of patients with PBC. In July 2016, NICE published guidance on the assessment and management of cirrhosis in people who are 16 years or older [NG50], which was subsequently updated in September 2023 (85). Although non-specific to PBC, they provide recommendations on the diagnosis, monitoring, prevention and early management of complications associated with cirrhosis. As highlighted in 1.3.2, the clinical progression of PBC is largely characterised by the development of cirrhosis and its sequelae (see Figure 2, Section 1.3.1).

Upon PBC diagnosis, transient elastography is recommended to confirm the presence/absence of cirrhosis. For patients with compensated cirrhosis, the Model for End-Stage Liver Disease (MELD) score is recommended to be calculated every 6 months, with an MELD score of 12 or more providing an indicator that the patient is at high risk of complications of cirrhosis (85).

1.3.3.3 Unmet needs with current treatment

The goal of current PBC treatment is to prevent progressive liver disease and ameliorate disease-associated symptoms that reduce patient HRQoL (14, 80, 81). However, as outlined in Sections 1.3.2.1, 1.3.2.3, and 1.3.2.4, there is currently a substantial clinical, humanistic, economic, and societal burden associated with PBC, and there are few approved treatment options that can effectively alleviate these burdens.

First-line UDCA monotherapy is the only drug approved as a first-line treatment for PBC, however, it fails to sufficiently reduce ALP in approximately 40% of PBC patients, and approximately 5% of patients are intolerant to treatment. This places patients at risk of disease progression, liver transplantation, and death. As such, a large proportion of patients require a second-line treatment option that elicits an adequate response and is tolerable (29, 86, 87).

OCA is limited in improving biochemical response. More than half of patients treated with OCA in PBC do not respond adequately, with only moderate decreases in ALP levels observed. In the Phase 3 POISE study, only 46% and 47% of patients in the OCA titrated arm and OCA 10 mg arm demonstrated a composite biochemical response (defined as an ALP <1.67 x ULN, with a reduction of ≥15% from baseline, and normal total bilirubin ≤1.0x ULN) after 12 months, respectively (57), while only 7% of patients normalised their ALP levels (88). The result of the latter corresponds to observations from an analysis a UK cohort of PBC patients by Abbas *et al.* (2023), whereby only 3% of patients who received treatment with OCA normalised their ALP within 12 months (17). As highlighted in Section 1.3.2.2, patients without normalised ALP are at an increased risk of disease progression, liver transplant, and death. Therefore, given the benefits of ALP normalisation in terms of reduced clinical burden and mortality, effective and well-tolerated treatments are urgently needed for patients with PBC.

In addition to greater biochemical improvement, reduction in pruritus remains a prominent clinical unmet need in PBC patients. OCA is associated with a dose-dependent increase in pruritus. In support, high rates of discontinuation have been reported as treatment-induced pruritus (89-91), with prospective, observational multicentre studies reporting OCA discontinuation rates of 12% to 17% with a significant proportion of patients (45% to 71%) discontinuing due to treatment induced pruritus (89). For example, in the analysis by Abbas *et al.* (2023), the exacerbation of pruritus was reported in 34%, 11% and 20% of patients receiving treatment with OCA at 3, 6 and 12 months (17). Furthermore, in the Phase 3 ELATIVE study, elafibranor did not significantly reduce moderate-to-severe pruritus according to the PBC Worst Itch Numeric Rating Scale (PBC WI-NRS) (63). Recommended treatment to manage itch by the BSG/UK-PBC, including cholestyramine and rifampicin, have no established efficacy, while instead they are associated with tolerability issues, including bloating and constipation, and side-effect concerns (80). As highlighted in Section 1.3.3.1, fibrates may also be off-label used in combination with current

second-line treatment options to treat itch, however, these have documented toxicity and efficacy issues that are yet to be addressed in UK clinical practice. Considering the above, there are currently no approved treatment options that significantly improve pruritus as measured by the Pruritus Numerical Rating Scale (NRS).

At the time of writing, the future positioning of OCA in the PBC treatment paradigm in the UK is uncertain, considering recent developments in the EU and the US. In June 2024, the EMA's advisory committee, the Committee for Medicinal Products for Human Use (CHMP), recommended to revoke its conditional approval after readout of the Phase IV COBALT study (92). In November 2024, the ECs revocation decision came into effect, resulting in the conditional marketing authorisation for OCA being revoked in Europe with immediate effect (93). Similarly, in the US, The Gastrointestinal Advisory Committee voted on September 13th 2024 against approval for OCA in PBC, citing that the clinical outcomes in patients with PBC could not be verified with the available data from the Phase IV COBALT study (94). The decision from EC and the US FDA has brought uncertainty to the PBC patient community, and there is now an urgent need for alternative treatment options.

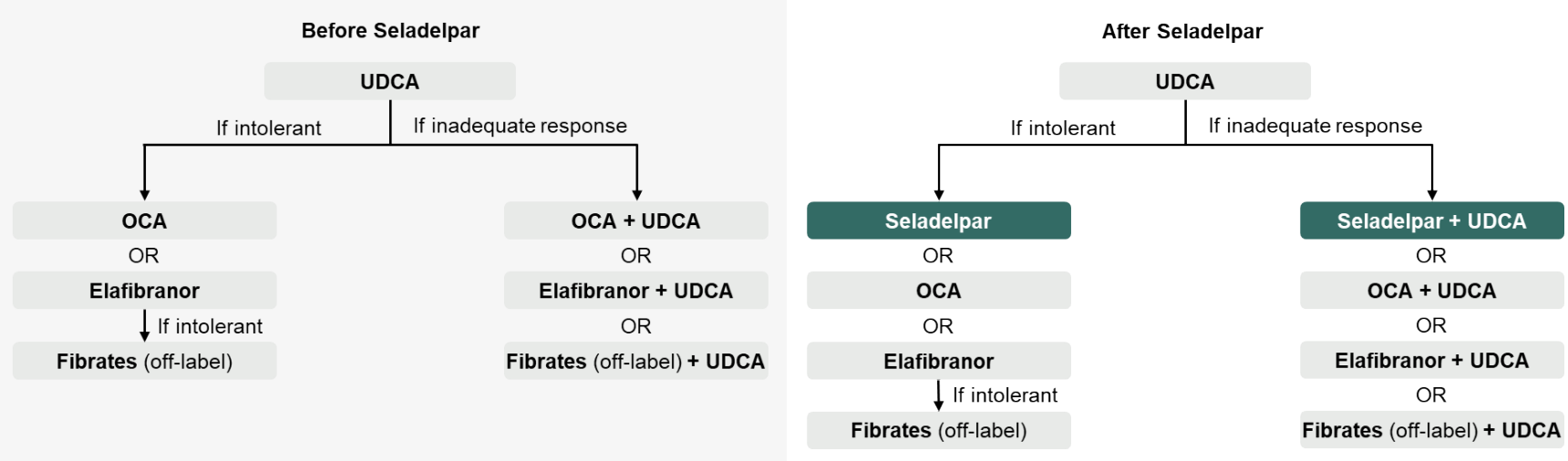
To summarise, despite the availability of first-line UDCA monotherapy and multiple second-line treatment options, many patients with PBC do not respond adequately to therapy, or do not tolerate available therapies, and continue to experience symptoms such as pruritus, disease progression and a deterioration in HRQoL. Hence, additional, more effective treatment options are needed to prevent progressive liver disease and ameliorate disease-associated symptoms that reduce HRQoL.

1.3.3.4 Proposed positioning of seladelpar in the PBC treatment pathway

The proposed positioning of seladelpar in PBC treatment pathway in the UK is displayed schematically below in Figure 9. Seladelpar is positioned as a second-line treatment option for PBC following intolerance or inadequate response to UDCA, or as a third-line option in patients who are intolerant or do not adequately respond to OCA. In the second and third lines of therapy, UDCA monotherapy is not a treatment option for patients with PBC.

Figure 10 presents the epidemiology of the sub-populations of PBC relevant to this appraisal.

Figure 9: Proposed positioning of seladelpar in the UK PBC treatment pathway



Key: OCA: obeticholic acid; PBC: primary biliary cholangitis; UDCA: ursodeoxycholic acid
Notes: UDCA is recommended as the first-line therapy for PBC by internationally recognised clinical practice guidelines. Seladelpar, alongside OCA and elafibranor, are positioned as second-line therapies for PBC in combination with UDCA or as a standalone treatment for UDCA-intolerant patients.
Source: Kowdley *et al.* (2023) (95)

Figure 10: Epidemiological cascade for PBC patients in England and Wales

Key: 1L, first-line; 2L, second-line; BSC, best supportive care; PBC, primary biliary cholangitis; UDCA, ursodeoxycholic acid.
Notes:
[a-f]Based on IQVIA data
[g-h]Based on data published by Abbas *et al.* (2024)
Sources: Abbas *et al.* (2024); Data on File – IQVIA UK PBC Market Sizing & Potential (16, 96)

1.4 Equality considerations

Patients with PBC with cirrhosis-related complications or debilitating symptoms are subjected to significant wait times for liver transplantation; on average, UK patients are required to wait at least 3-4 months for a liver transplant. PBC patients on the liver transplant waiting list are more likely to die compared to patients with other liver diseases. In a study that evaluated waitlist outcomes in patients with PBC using data from the United Network for Organ Sharing, 17% of waitlisted patients with PBC died without receiving a liver transplantation, compared to 12% and 9% in patients with hepatitis C virus (HCV) and primary sclerosing cholangitis (PSC), respectively (97). Furthermore, in a study that compared adults with PBC to those with alcohol-related liver disease (ALD) or non-alcoholic steatohepatitis (NASH) listed for liver transplantation from 2013 to 2019, 24-month cumulative incidence of waitlist mortality for PBC was 23% (95% CI: 20, 27%), compared to 14% (95% CI: 13, 15%) in ALD and 20% (95% CI: 19, 21%) for NASH (98).

In addition, geographic factors may also impact the probability of referral for a transplant assessment. In England, patients eligible for liver transplant are sevenfold more likely to be referred for a liver transplant if they live in a region containing a liver transplant centre compared with regions without a liver transplant centre, highlighting that the national provision of such services is inequitable in terms of access (16).

Considering the above, treatment with seladelpar could allow for liver transplant to be avoided for patients in PBC, and thus address the inequity of access to liver transplant for PBC patients in the UK.

2 Clinical effectiveness

2.1 Identification and selection of relevant studies

A systematic literature review (SLR) was conducted to identify all relevant clinical trial evidence associated with the decision problem outlined in Section 1.1

See Appendix B1.1 for full details of the process and methods used to identify and select the clinical evidence relevant to seladelpar for the treatment of PBC in combination with UDCA in adults who have an inadequate response to UDCA, or as monotherapy in patients unable to tolerate UCDA.

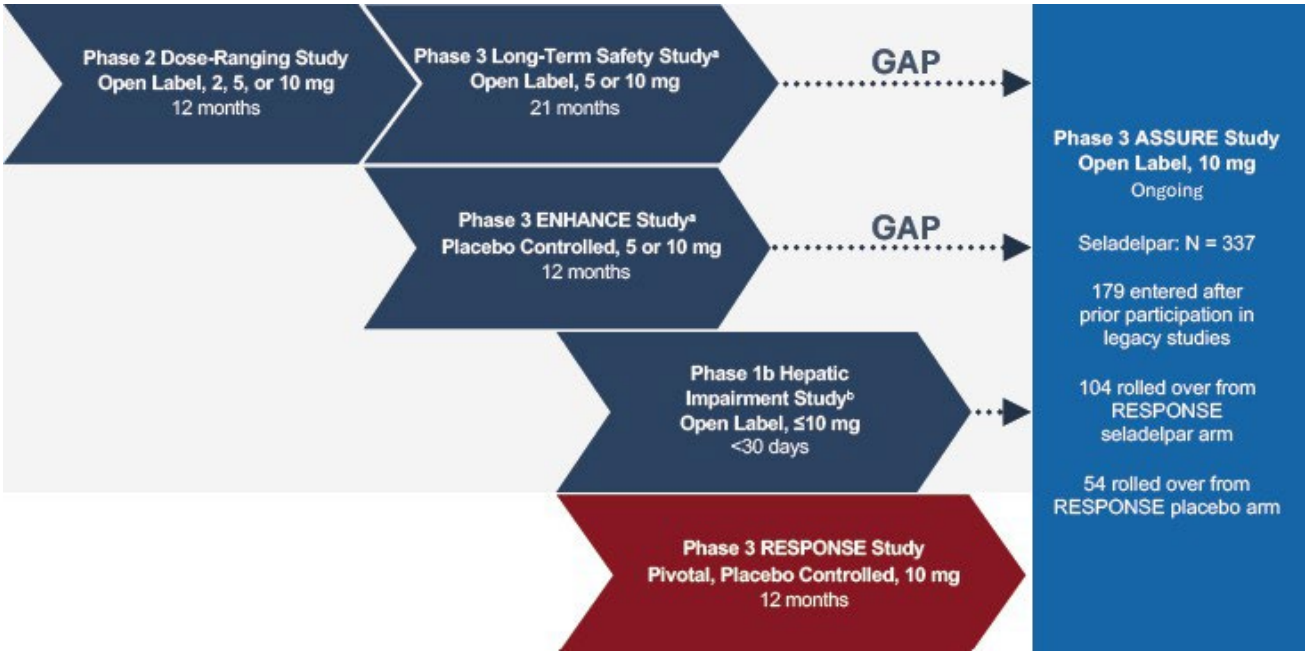
2.2 List of relevant clinical effectiveness evidence

Six trials were identified in the clinical SLR that provide direct clinical evidence for the efficacy and safety of seladelpar for the treatment of PBC in combination with UDCA in adults who have an inadequate response to UDCA, or as monotherapy in patients unable to tolerate UDCA.

The studies identified by the SLR included a Phase 2 proof-of-concept study, a series of 'Legacy studies' of seladelpar, which collectively refers to the dose-ranging Phase 2 study, (CB8025-21629), Phase 3 ENHANCE study (CB8025-31735;) and Phase 3 long-term safety study (CB8025-31731), and the pivotal Phase 3 RESPONSE study (CB8025-32048). Eligible patients who completed an aforementioned PBC study with seladelpar were able to rollover into the ongoing, long-term ASSURE study (CB8025-31731-RE) and continue treatment with seladelpar 10 mg for up to five years. Figure 11 provides a schematic on the relationship between the clinical studies of seladelpar in PBC.

A breakdown of the data from the studies highlighted in Figure 11 included in the Company Evidence Submission is provided below in Sections 2.2.1 to 2.2.3.

Figure 11: Studies investigating the efficacy and safety of seladelpar in PBC



Key: NASH, non-alcoholic steatohepatitis; PBC, primary biliary cholangitis.
Notes: Data cut-off – January 31st 2024
[a]These studies had an early termination due to unexpected findings in a concurrent study for NASH, which were subsequently found to predate treatment.
[b]Patients were eligible to enrol in ASSURE after completing the study, but they had to meet screening criteria and had variable time to entry into ASSURE
Source: Adapted from Trivedi *et al.* (2024) (99)

2.2.1 Data included in the main submission

RESPONSE is the pivotal study informing the economic model in the submission. This was a 12-month, placebo-controlled, randomised, Phase 3 study investigating the efficacy and safety of seladelpar for the treatment of PBC in combination with UDCA in adults who have an inadequate response to UDCA, or as monotherapy in patients unable to tolerate UDCA. The study occurred from April 21st, 2021 (first patient randomised) to August 11th 2023 (last patient last visit) (5, 100). To date, seven records relating to RESPONSE were identified by the SLR. Final data from RESPONSE was recently published by Hirschfield *et al.* (2024) in the New England Journal of Medicine (5), and this publication will be used as the primary source of data underpinning the submission. Where appropriate, data from the final clinical study report (CSR), dated 30th November 2023 (100), will be used to supplement additional information on the RESPONSE study that is not published in the public domain.

ASSURE serves as the long-term, open-label study for patients completing the pivotal RESPONSE study or with prior participation in any 'Legacy' seladelpar trial. As of the most-recent data-cut off on 31st January 2024, 337 patients were enrolled in the study: 54 crossed over from RESPONSE placebo arm, 104 rolled over from RESPONSE seladelpar arm, and 179 enrolled from seladelpar 'Legacy studies'. To date, three conference posters have been presented, reporting interim efficacy and safety results from the 31st January 2024 data cut-off (99, 101, 102). The poster exhibited at the European Association for the Study of the Liver (EASL) 2024 congress by Trivedi *et al.* (2024) presents separate interim two-year efficacy results for patients who directly rolled over from the RESPONSE study and those who participated in a previous 'Legacy' study (99). This poster provides long-term data on patients who received continuous seladelpar treatment, and informs the write-up of the long-term clinical effectiveness and safety data for patients who rolled over from RESPONSE to ASSURE in Sections 2.6.1 and 2.11.1. Given the similarities in the methodology of the RESPONSE and ASSURE studies, we report the study methodology for RESPONSE in Sections 2.3 and 2.4 and provide details on ASSURE when reporting clinical effectiveness and safety data.

Of note, pooled interim efficacy and safety results for up to three and five years, respectively, were recently presented at The Liver Meeting congress by Lawitz *et al.* (2024) and Trivedi *et al.* (2024) (99, 101). Considering the >1 year treatment gap between 'Legacy study' completion and ASSURE enrolment, the pooled long-term data is positioned as supporting evidence in the submission where appropriate. Further details of the ongoing ASSURE study can be found in Section 2.12.

While data from RESPONSE is used to inform the economic model, supporting clinical evidence for the efficacy and safety of seladelpar for the treatment of PBC is available from the 'Legacy studies' (Figure 11). The dose-ranging Phase 2 (CB8025-21629) and Phase 3 long-term safety (CB8025-31731) studies provide supporting clinical evidence for the efficacy and safety of seladelpar relevant to the submission and are described below. Of note, given that a marketing authorisation application has been made for the 10 mg dose, only the efficacy data for seladelpar 10 mg will be reported for these studies in Section 2.6 of the submission.

CB8025-21629 assessed the efficacy and safety of seladelpar at doses of 2, 5 and 10 mg/day for 52 weeks, and occurred from 28th November 2016 to 9th July 2019 (103). Patients who completed either CB8025-21629 or ENHANCE clinical studies could directly roll over to CB8025-31731 and continue to receive the same dose of seladelpar (2, 5, or 10 mg). CB8025-31731 commenced on 11th December 2017 and was open for over 21 months prior to its termination on 20th December 2019, which allowed patients to be treated with seladelpar for up to 33 months. Overall, a total of 106 patients with PBC who completed either of the lead-in studies directly enrolled in CB8025-31731 (treatment interruption less than four weeks); 104 patients were from the dose-ranging Phase 2 study and two patients were from ENHANCE. Considering that >98% of patients directly enrolled in CB8025-31731 from CB8025-21629 (104), we report the study methodology for CB8025-21629 in Sections 2.3 and 2.4, and provide related clinical effectiveness and safety data from CB8025-31731 in Sections 2.6 and 2.11 where applicable.

Table 5: Clinical effectiveness evidence - RESPONSE

Study	**RESPONSE (NCT04620733)**
Study design	*A Placebo-controlled, Randomised, Phase 3 Study to Evaluate the Efficacy and Safety of Seladelpar in Patients with Primary Biliary Cholangitis (PBC) and an Inadequate Response to or an Intolerance to Ursodeoxycholic Acid (UDCA)*
Population	Adults with PBC and an inadequate response to or an intolerance to UDCA
Intervention(s)	Seladelpar ± UDCA
Comparator(s)	Placebo ± UDCA
Indicate if study supports application for marketing authorisation	Yes
Indicate if study used in the economic model	Yes
Rationale if study not used in model	*RESPONSE presents the pivotal, regulatory, clinical evidence in support of seladelpar for the treatment of PBC*
Reported outcomes specified in the decision problem	• Mortality • **Liver function based on markers of liver biochemistry** • **Symptoms including pruritus,** fatigue, and abdominal pain • Time to liver transplantation

	• PBC-related consequences, including ascites, varices, encephalopathy, and hepatic cell carcinoma • **Adverse effects of treatment** • **HRQoL**
All other reported outcomes	• Not applicable

Key: HRQoL, health-related quality of life; PBC: primary biliary cholangitis; UDCA: ursodeoxycholic acid.
Notes: Outcomes in bold are those directly used in the economic modelling.

Table 6: Clinical Effectiveness Evidence – CB8025-21629

Study	**CB8025-21629 (NCT02955602)**
Study design	*An 8-Week, Dose Ranging, Open Label, Randomised, Phase 2 Study with a 44-Week Extension, to Evaluate the Safety and Efficacy of Seladelpar in Patients with Primary Biliary Cholangitis (PBC) and an Inadequate Response to or Intolerance to Ursodeoxycholic Acid (UDCA)*
Population	Adults with PBC and an inadequate response to or an intolerance to UDCA
Intervention(s)	Seladelpar ± UDCA
Comparator(s)	Placebo ± UDCA
Indicate if study supports application for marketing authorisation	Yes
Indicate if study used in the economic model	No
Rationale if study not used in model	*Clinical efficacy of seladelpar will be informed by the results of the pivotal RESPONSE study*
Reported outcomes specified in the decision problem	• Mortality • Liver function based on markers of liver biochemistry • Symptoms including pruritus, fatigue, and abdominal pain • Time to liver transplantation • PBC-related consequences, including ascites, varices, encephalopathy, and hepatic cell carcinoma • Adverse effects of treatment • HRQoL
All other reported outcomes	Not applicable

Key: HRQoL, health-related quality of life; PBC, primary biliary cholangitis; UDCA, ursodeoxycholic acid.

CB8025-21629 analysed patients with adults with PBC at risk of disease progression (ALP >1.67 x ULN) who were receiving or intolerant to UDCA, including a proportion with compensated cirrhosis. Therefore, despite data from either study not being used to populate the economic

model, this study provides an additional source of supporting evidence and are included in Sections 2.2 to 2.6.

2.2.2 Data provided in the appendices

As described above in Section 2.2.1, ASSURE also enrolled eligible patients from 'Legacy studies' of seladelpar. These patients had a >1 year gap off treatment before enrolling into ASSURE, and the study only reported outcomes up to Month 12 in these patients. Consequently, this data is positioned as supporting evidence for the efficacy and safety of seladelpar in PBC, with results briefly summarised in Appendix K.

Furthermore, ENHANCE was a planned 52-week, placebo-controlled, randomised Phase 3 study that evaluated efficacy and safety of seladelpar in patients with PBC with inadequate response or intolerance to UDCA. Although ENHANCE is generalisable to the licensed population of seladelpar, this study only reports on endpoints up to Month 3 (planned primary and key secondary end point times were Month 12) due to early study termination as a result of unexpected histological findings in a concurrent study for non-alcoholic steatohepatitis (NASH; NCT03551522), which were later determined to be unrelated to seladelpar (105). A summary of ENHANCE is provided in Appendix J.

2.2.3 Data not summarised in the Company Evidence Submission

The Phase 2 double-blind, randomised, placebo-controlled, proof-of-concept study evaluated the anti-cholestatic effects and safety of seladelpar in adult PBC patients with an inadequate response to UDCA. Although this study is generalisable to PBC patients, and the licensed population of seladelpar, it enrolled a low number of patients (70 patients), occurred over a short time frame (12 weeks) and evaluated seladelpar outside of the licensed dose (patients were assigned to placebo, seladelpar 50 mg/day, or seladelpar 200 mg/day) (3). Hence, consideration of this study as supporting evidence was not considered appropriate.

2.3 Summary of methodology of the relevant clinical effectiveness evidence

2.3.1 RESPONSE

2.3.1.1 Trial methodology

Table 7: Summary of trial methodology for RESPONSE

Trial Number (Acronym)	**RESPONSE (NCT04620733)**
Location	This study was conducted at 90 sites across 24 countries: Argentina, Australia, Austria, Belgium, Canada, Chile, Czech Republic, France, Germany, Greece, Hungary, Israel, Italy, Republic of Korea, Mexico, New Zealand, Poland, Romania, Russia, Spain, Switzerland, Turkey, United Kingdom, and USA
Trial design	A Placebo-controlled, Randomised, Phase 3 Study to Evaluate the Efficacy and Safety of Seladelpar in Patients with PBC and an Inadequate Response to or an Intolerance to UDCA
Eligibility criteria for participants	Inclusion criteria were treatment with UDCA for at least 12 months or a history of unacceptable side effects with UDCA (last dose, >3 months before screening), an ALP level ≥1.67 x ULN, AST and ALT levels ≤3 x ULN, a total bilirubin level ≤2 x ULN, an eGFR > 45 mL/min/1.73m^2, INR < 1.1 X ULN, and a platelet count ≥ 100×10^3/μL Key exclusion criteria were advanced primary biliary cholangitis (an albumin level below the lower limit of the normal range and a total bilirubin level above 1.0 x ULN), hepatic decompensation, and any other chronic liver disease
Settings and locations where the data were collected	Study visits occurred in clinic, with the assistance of a home health service, or using virtual technologies according to the sites' determination
Study periods and trial drugs	Eligible patients were randomly assigned to two treatment groups (randomisation ratio 2:1) stratified by ALP level (< 350 U/L vs ≥ 350 U/L) and the presence of clinically important pruritus (Pruritus NRS < 4 vs NRS ≥ 4): • Seladelpar arm: Patients received seladelpar 10 mg once daily for up to 12 months • Placebo arm: Patients received placebo corresponding to the seladelpar dosage and schedule for up to 12 months Following the treatment period, patients were invited to participate in the open-label, long-term, ASSURE study in which seladelpar was administered to all patients. Patients who declined to participate had a Safety Follow-up Visit two weeks after last dose of study drug

Prior and concomitant Medication	UDCA was taken as background therapy as part of participation in the study. UDCA was continued in those patients who could tolerate it at their pre-study dose as recommended per the Investigator's clinical judgement
Primary outcome	Proportion of patients who were considered responders at 12 months based on the following composite endpoint of ALP and total bilirubin at 12 months • ALP < 1.67 x ULN • ≥ 15% decrease in ALP • Total bilirubin ≤ 1.0 x ULN
Secondary outcomes used in the model/ specified in the scope	• Proportion of patients with ALP ≤ 1.0 x ULN at 12 months (e.g., normalisation) • Change from baseline in weekly averaged Pruritus NRS in patients with baseline NRS ≥ 4 at 6 months • Absolute and relative changes in ALP at 3, 6 and 12 months • Absolute and relative changes in ALT, AST, GGT, total bilirubin, and 5'-nucleotidase at each visit • Absolute and relative changes in IL-31 • Change from baseline in United Kingdom – Primary Biliary Cirrhosis and Global PBC Study Group risk scores at each visit • Change from baseline in QoL measure for use in PBC-40 questionnaire (PBC-40 QoL) at each visit • Changes from baseline in PBC-40 QoL itch domain and the 5-D Itch scale*
Pre-planned subgroups	• Age categories (age at Screening: <65, ≥65 years; age at PBC diagnosis: <50, ≥50 years) • Sex (female, male) • Race (White, Black, Asian, Other) • Region (North America, Europe, Rest of World) • Baseline ALP (<350 U/L, ≥350 U/L) • Total bilirubin (<0.6x ULN, ≥0.6x ULN) • Pruritus NRS (<4, ≥4) • UDCA use vs UDCA intolerance • Prior use of OCA and/or fibrates (yes, no) • Cirrhosis (yes, no) • Total bilirubin (≤1x ULN, >1x ULN)

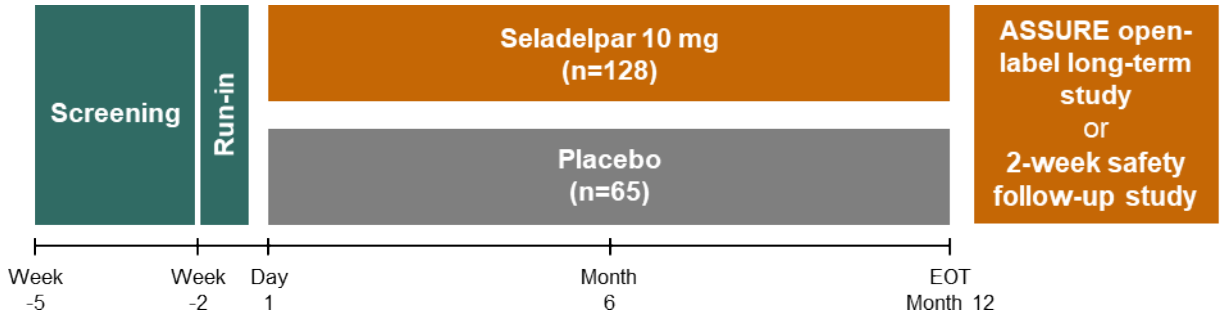
Key: ALP, alkaline phosphatase; AST, aspartate aminotransferase; eGFR, estimated glomerular filtration rate; IL-31, interleukin-31; INR, international normalised ratio; NRS, numerical rating scale; OCA, obeticholic acid; QoL quality of life; PBC, primary biliary cholangitis; UDCA, ursodeoxycholic acid; ULN, upper limit of normal.
Notes: *Exploratory endpoints.

2.3.1.2 Trial design

RESPONSE was a double-blind, placebo-controlled, randomised, Phase 3 study to evaluate the safety and efficacy of seladelpar 10 mg in patients with PBC and an inadequate response

to or an intolerance to UDCA. The study design for RESPONSE is depicted below in Figure 12.

Figure 12: RESPONSE study diagram



Key: EOT, end of treatment; SoC, standard of care; UDCA, ursodeoxycholic acid.
Notes: Seladelpar and placebo were administered with SoC UDCA unless patient had history of unacceptable side effects.
Source: Hirschfield *et al.* (2024); Figure 1, RESPONSE CSR (5, 100)

Approximately 180 patients were to be assessed to evaluate the efficacy and safety of seladelpar, with the proportion of patients achieving a composite biochemical response of ALP and total bilirubin after 12 months as the primary endpoint (5, 100). The composite biochemical response was defined as ALP < 1.67 x ULN, ≥15% decrease in ALP, and total bilirubin ≤1.0x ULN

Patients were randomly assigned to a treatment group in a 2:1 ratio, by means of an interactive online response system, with stratification according to the baseline ALP (<350 or ≥350 U/L) and the Pruritus NRS score (<4 or ≥4, with scores on the NRS ranging from 0 [no itch] to 10 [worst itch imaginable]) (5, 100). The two treatment groups are described below:

- **Seladelpar arm**: Patients received seladelpar 10 mg once daily for up to 12 months
- **Placebo arm**: Patients received placebo corresponding to seladelpar dosage and schedule for up to 12 months

After the completion of RESPONSE, patients were invited to enrol in an open-label, long-term study (ASSURE) wherein each patient was to be administered seladelpar 10 mg, and patients previously randomised on placebo were to initiate seladelpar treatment. Patients who declined

participation in ASSURE had a Safety Follow-up Visit performed 2 weeks after the last dose of study drug (5, 99, 100).

A total of 193 patients underwent randomisation and received either seladelpar (128 patients) or placebo (65 patients). Overall, 174 patients (90.2%) completed the study; 11 (8.6%) who received seladelpar and 8 (12.3%) who received placebo withdrew from the study. Of 166 patients who completed the trial at sites offering enrolment into the ongoing, long-term ASSURE study, 159 (95.8%) enrolled (5, 99, 100).

2.3.1.3 Eligibility criteria

The key inclusion and exclusion criteria for RESPONSE are described in Table 8.

Table 8: Key eligibility criteria for RESPONSE

Key Inclusion Criteria	Key Exclusion Criteria
Aged 18–75 years old (inclusive)	Previous exposure to seladelpar
Confirmed PBC as defined by having any two of the following three diagnostic criteria: • History of ALP >1.0x ULN for at least six months • Positive AMA titters (>1:40 on immunofluorescence or M2 positive by enzyme-linked immunosorbent assay (ELISA) or positive PBC-specific ANAs • Documented liver biopsy results consistent with PBC	A medical condition other than PBC that, in the Investigator's opinion, would preclude full participation in the study (e.g., cancer) or confound its results (e.g., Paget's disease, any active infection)
Treatment with UDCA for ≥12 months or a history of unacceptable side effects with UDCA (last dose >3 months before Screening)	Advanced PBC (defined by the Rotterdam criteria: albumin level <LLN and total bilirubin >1.0x ULN)
ALP ≥1.67x ULN	Hepatic decompensation
AST and ALT ≤3.0x ULN	Any other chronic liver disease
Total bilirubin ≤2.0x ULN	Known history of HIV or positive antibody test at Screening
eGFR >45 mL/min/1.73m^2	Clinically important alcohol consumption

INR <1.1x ULN	History of malignancy
Platelet count ≥100,000/mm^3	Treatment with OCA and fibrates within six weeks prior to Screening
	Treatment with antipruritic drugs must have been on a stable dose within one month prior to Screening
	Pregnancy or breastfeeding

Key: ALP, alkaline phosphatase; ALT, alanine aminotransferase; AMA, antimitochondrial antibody; ANA:,antinuclear antibody; AST, aspartate aminotransferase; eGFR, estimated glomerular filtration rate; ELISA, enzyme-linked immunosirbent assay; HIV, human immunodeficiency virus; INR, international normalised ratio; LLN, lower limit of normal; OCA, obeticholic acid; PBC, primary biliary cholangitis; UDCA, ursodeoxycholic acid; ULN, upper limit of normal

For a full list of eligibility criteria, please refer to the RESPONSE CSR (100).

2.3.1.4 Settings and locations where the data were collected

Patients were randomised and treated across 90 study sites across 24 countries: Argentina, Australia, Austria, Belgium, Canada, Chile, Czech Republic, France, Germany, Greece, Hungary, Israel, Italy, Republic of Korea, Mexico, New Zealand, Poland, Romania, Russia, Spain, Switzerland, Turkey, United Kingdom, and USA (5, 100).

All study visits occurred in clinic, with the assistance of a home health service, or using virtual technologies (e.g., phone calls or video calls) according to sites' determination. Due to the COVID-19 pandemic, home health service or virtual health technologies, if available, were allowed if patients could not visit the clinic to perform study assessments (5, 100).

During the period from randomisation until database lock, the Sponsor study team members responsible for study oversight, patients, Investigators, and all study-site personnel were blinded to treatment assignment. Unblinding of a patient's treatment assignment could only occur in the event of an emergency (5, 100).

2.3.1.5 Trial drugs and concomitant medications

2.3.1.5.1. Seladelpar

Seladelpar 5 and 10 mg capsules were supplied in a blinded manner. Seladelpar was administered orally, once daily, for a duration of up to 12 months. Patients who met specific safety monitoring criteria or had tolerability issues could have a dose down-titration. Patients

who were initially assigned to 10 mg seladelpar were down titrated to 5 mg seladelpar in a blinded manner (5, 100).

Upon entry into ASSURE, patients received seladelpar at a dose of 10 mg daily. Patients with noted tolerability issues received seladelpar 5 mg if deemed an appropriate starting dose by the Investigator. As per the RESPONSE protocol, patients could be up and down-titrated from 10 mg to 5 mg throughout the study for reasons of safety or tolerability (99, 101, 102).

2.3.1.5.2. Placebo

Placebo was supplied as capsules identical in appearance to the 5 mg and 10 mg seladelpar capsules but containing no active medication. Patients initially assigned to placebo had a blinded down titration and remained in the placebo arm (5, 100).

Patients previously randomised to placebo during the RESPONSE study were to initiate seladelpar treatment upon enrolment into ASSURE at Month 12 (end-of-treatment [EOT]) (5, 99, 100).

2.3.1.5.3. Ursodeoxycholic acid (UDCA)

UDCA was taken as a background therapy as part of participation in the study. UDCA therapy was continued in those patients who could tolerate it at their pre-study dose and as recommended per the Investigator's clinical judgment. UDCA was administered orally, one or more times per day. The UDCA dose, compliance with UDCA, and any changes in dose during the study were documented and monitored (5, 100).

2.3.1.5.4. Prior and concomitant medication

The use of concomitant medications and occurrence of concomitant procedures were documented on the patient's electronic case record form (5, 100).

All patients were instructed to remain on their optimal or best possible diet and lifestyle, including drinking habits, specifically alcoholic beverages, throughout the study (5, 100).

Patients were also permitted to receive the required medication to treat new or existing medical conditions on study. Any new treatment for PBC symptoms (eg, antipruritic drugs) was discussed with the Medical Monitor (5, 100).

2.3.1.5.5. Restricted medication

Restricted medications included OCA, fibrates (e.g., bezafibrate, fenofibrate, elafibranor, lanifibranor, pemafibrate, and saroglitazar), immunosuppressant therapies, and any experimental or unapproved treatment for PBC or related autoimmune disease. For a full list of restricted medications, please see the RESPONSE CSR (100).

2.3.1.6 Outcomes used in the economic model or specified in the scope, including primary outcome

The primary efficacy endpoint to evaluate the efficacy of seladelpar was the proportion of patients achieving a composite biochemical response at Month 12 of treatment (5, 100). Composite biochemical response was defined as the fulfilment of ALP < 1.67× ULN, ≥ 15% decrease in ALP, and total bilirubin ≤ 1.0× ULN

The key secondary endpoints were the proportion of patients with ALP normalisation (≤1.0x ULN) at Month 12, and the change from baseline in mean Pruritus NRS at Month 6 among patients with moderate-to-severe pruritus (NRS ≥4) at baseline (5, 100).

Other secondary and exploratory efficacy endpoints used to evaluate the efficacy of seladelpar include:

- Absolute and relative changes in ALP at 3, 6, and 12 months.
- Proportion of patients with a decrease in NRS ≥ 2, NRS ≥ 3, or NRS ≥ 4 in patients with baseline NRS ≥ 4 at each visit
- Absolute and relative changes in ALT, AST, GGT, bilirubin (total, direct, and indirect) and 5’-nucleotidase at each visit
- Absolute and relative change in IL-31 at each visit
- Change from baseline in UK-PBC and Global PBC Study Group risk scores at each visit
- Change from baseline in HRQoL measure for use in PBC questionnaire (PBC-40 QoL) at each visit (total score and domain score)
- Changes from baseline in PBC-40 QoL itch domain and the 5-D Itch scale

Safety evaluations used to assess the safety of seladelpar monitored the frequency and nature of treatment-emergent adverse events (TEAEs), based on the assessment of clinical events, physical examination, vital signs, electrocardiogram (ECG), and laboratory tests (biochemistry and haematology) (5, 100).

2.3.1.7 Patient datasets

The intention-to-treat (ITT) analysis set, defined as patients who were randomised into the study and received at least one dose of study drug, was used as the primary population used for the efficacy analyses, except for the secondary and exploratory endpoints evaluated in patients with moderate-to-severe pruritus. Analyses of these endpoints were performed using the moderate-to-severe Pruritus NRS (MSPN) analysis set, which comprised all patients in the ITT set who had a baseline Pruritus NRS score ≥4 (5, 100) (Table 9).

Table 9: Analysis of efficacy endpoints (RESPONSE & ASSURE)

Efficacy Endpoint	Analysis Set	Location in Submission
Primary endpoint		
Composite endpoint of ALP and total bilirubin at 12 months	ITT	2.6.1.1
Key secondary endpoints		
ALP ≤ 1.0× ULN at 12 months (eg, normalisation)	ITT	2.6.1.2.1
Change from baseline in weekly averaged Pruritus NRS in subjects with baseline NRS ≥ 4 at 6 months	MSPN	2.6.1.2.2
Other secondary and exploratory endpoints		
Absolute and relative changes in ALP at 3, 6, and 12 months	ITT	2.6.1.3.1
Patients with a decrease in NRS ≥ 2, NRS ≥ 3, or NRS ≥ 4 in subjects with baseline NRS ≥ 4 at each visit	MSPN	2.6.1.3.2
Absolute and relative changes in liver biochemistry at each visit	ITT	2.6.1.3.3
Absolute and relative change in IL-31 at each visit	ITT	2.6.1.3.4

UK-PBC and GLOBE risk scores at 12 months	ITT	2.6.1.3.5
PBC-40 QoL at each visit	ITT	2.6.1.3.6
PBC-40 QoL Itch Domain at each visit	MSPN	2.6.1.3.7
5-D Itch scale at each visit	MSPN	2.6.1.3.8

Key: ALP, alkaline phosphatase, IL-31, interleukin-31; ITT, intent-to-treat, MSPN, moderate-to-severe pruritus NRS; NRS, numerical rating scale; PBC, primary biliary cholangitis; QoL, quality of life; ULN, upper limit of normal.

The safety population was the same as the ITT analysis set and is defined as all patients who received at least one dose of study drug. Patients were included in this analysis set based on the actual treatment received (5, 100).

Of the 360 patients who were screened and consented to take part in RESPONSE, 193 were considered eligible and were randomised in a 2:1 ratio to receive either seladelpar or placebo (ITT analysis set). Within the ITT analysis set, 49 patients in the seladelpar arm and 23 patients in the placebo arm had a baseline Pruritus NRS score ≥4 (MSPN Analysis Set). In total, 174 patients completed the study and were invited to participate in the long-term ASSURE study to continue or initiate treatment with seladelpar (5, 100). However, nine patients in Russia were not allowed to rollover onto ASSURE. Excluding these patients, a total of 159 out of 166 eligible patients (95.8%) who completed treatment agreed to participate in ASSURE (see Appendix B1.2) (99, 100).

A summary of the analysis sets is provided below in Table 10.

Table 10: Patient disposition (RESPONSE and ASSURE)

Analysis Sets, (n, %)	**Seladelpar 10 mg (n=128)**	**Placebo (n=65)**	**Total (n=193)**
Intent-to-Treat Analysis Set[a]	128 (100)	65 (100)	193 (100)
MSPN Analysis Set[b]	49 (38.3)	23 (35.4)	72 (37.3)
Safety Analysis Set[c]	128 (100)	65 (100)	193 (100)
Completed RESPONSE	118 (92.2)	57.7 (87.7)	175 (90.7)
Patients Eligible for ASSURE Who Completed Treatment	110 (85.9)	56 (86.2)	166 (86.0)

Patients Who Completed RESPONSE and Enrolled into ASSURE	104 (81.3)	55 (84.6)	159 (82.4)

Key: ALP, alkaline phosphatase; ITT, intent-to-treat; MSPN, moderate-to-severe pruritus NRS; NRS, numerical rating scale.

Notes: The number of all randomised patients was the base for calculating the percentage of patients for other analysis sets.

[a]The ITT Analysis Set was defined as any patients who was randomised into the study and received at least 1 dose of study drug.

[b]The MSPN Analysis Set included patients in the ITT Analysis Set who had a baseline NRS value ≥ 4.

[c]The Safety Analysis Set was defined as any patient who received at least 1 dose of study drug.

Source: Table 17, RESPONSE CSR (100)

2.3.1.8 Baseline characteristics

Table 11 presents key demographics and baseline characteristics for the RESPONSE ITT analysis set. Overall, baseline characteristics were balanced between treatment arms, with a few exceptions. More patients in the seladelpar arm than in the placebo arm were of Hispanic or Latino ethnicity (41.5% and 22.7%, respectively). Additionally, more patients in the seladelpar arm than in the placebo arm had total bilirubin ≤1x ULN (92.3% and 84.4%, respectively), while fewer patients in the seladelpar arm than in the placebo arm had total bilirubin >1 x and ≤2 x ULN (7.7% and 15.6%, respectively) (Table 11) (5, 100).

Table 11: Baseline characteristics (RESPONSE; ITT analysis set)

	Placebo (n=65)	Seladelpar (n=128)	Total (n=193)
Age at Screening, years, mean (SD)	57.0 (9.2)	56.6 (10.0)	56.7 (9.7)
Age at diagnosis, years, mean (SD)	49.3 (10.9)	49.2 (9.9)	49.2 (10.3)
Female sex, n (%)	60 (92.3)	123 (96.1)	183 (94.8)
Race[a]			
American Indian or Alaska Native, n (%)	3 (4.6)	3 (2.3)	6 (3.1)
Asian, n (%)	4 (6.2)	7 (5.5)	11 (5.7)
Black or African American, n (%)	2 (3.1)	2 (1.6)	4 (2.1)
White, n (%)	56 (86.2)	114 (89.1)	170 (88.1)
Ethnicity[a]			
Hispanic or Latino, n (%)	27 (41.5)	29 (22.7)	56 (29.0)
Not Hispanic or Latino, n (%)	38 (58.5)	97 (75.8)	135 (69.9)
Patients with cirrhosis at baseline, n (%)	9 (13.8)	18 (14.1)	27 (14.0)
Duration of disease, years, mean (SD)[b]	8.6 (6.5)	8.2 (6.7)	8.3 (6.6)
Positive for AMA, n (%)[c]	55 (84.6)	106 (82.8)	161 (83.4)
UDCA			
Intolerance, n (%)[d]	4 (6.2)	8 (6.2)	12 (6.2)
Daily dose, mg/kg, mean (SD)[e]	14.9 (3.3)	15.0 (3.1)	15.0 (3.2)
Prior use of OCA and/or fibrates, n (%)	13 (20.0)	20 (15.6)	33 (17.1)

Pruritus NRS, mean (SD)	6.6 (1.4)	6.1 (1.4)	6.3 (1.4)
<4, n (%)	42 (64.6)	79 (61.7)	121 (62.7)
≥4, n (%)	23 (35.4)	49 (38.3)	72 (37.3)
ALP, U/L, mean (SD)f	313.8 (117.7)	314.6 (123.0)	314.3 (120.9)
≥350, n (%)	18 (27.7)	35 (27.3)	53 (27.5)
Total bilirubin, mg/dL, mean (SD)g	0.737 (0.3)	0.769 (0.3)	0.758 (0.3)
≤1x ULN, n (%)	60 (92.3)	108 (84.4)	168 (87.0)
>1 and ≤2x ULN, n (%)	5 (7.7)	20 (15.6)	25 (13.0)
ALT, U/L, mean (SD)[h]	48.2 (22.8)	47.4 (23.5)	47.7 (23.2)
AST, U/L, mean (SD)[i]	41.7 (16.0)	39.6 (16.1)	40.3 (16.1)
GGT, U/L, mean (SD)[j]	287.5 (249.6)	269.0 (240.0)	275.3 (242.8)
Albumin, g/dL, mean (SD)[k]	4.1 (0.2)	4.2 (0.3)	4.1 (0.3)

Key: ALP, alkaline phosphatase; ALT, alanine aminotransferase; AST, aspartate aminotransferase; GGT, gamma-glutamyl transferase; NRS, Numerical Rating Scale; OCA, obeticholic acid; PBC, primary biliary cholangitis; SD, standard deviation; UDCA, ursodeoxycholic acid.
Notes:
[a]Race and ethnicity were not collected for the patients enrolled in France due to prohibition by local regulations; [b]Duration of PBC (time [in years] from diagnosis date to the informed consent date) was defined as (informed consent date – PBC diagnosis date + 1) / 365.2425
[c]Defined as reactivity against the mitochondrial M2 antibody [d]UDCA intolerance was from UDCA usage at baseline; [e]Total daily UDCA dose (mg/kg) = total daily UDCA dose (mg) at baseline/Day 1 weight (kg); [f]ALP reference range: 37–116; [g]Total bilirubin reference range: 0.1–1.10; [h]ALT reference range: 6–41; [i]AST reference range: 9–34; [j]GGT reference range: 7–38; [k]Albumin reference range: 3.50–5.50.
Source: Hirschfield *et al.* (2024); Table 18 & 19, RESPONSE CSR (5, 100)

2.3.2 CB8025-21629

2.3.2.1 Trial methodology

Table 12: Summary of trial methodology for CB8025-21629

Trial Number (Acronym)	**CB8025-21629 (NCT02955602)**
Location	The study was conducted across 32 sites in four countries: Canada, Germany, United Kingdom, and the US
Trial design	An 8-week, Dose-ranging, Open-label, Randomised, Phase 2 Study with a 44-week Extension, to Evaluate the Safety and Efficacy of Seladelpar in Patients with PBC and an Inadequate Response to or Intolerance to UDCA
Eligibility criteria for participants	Eligible patients were 18 to 75 years of age, met established diagnostic criteria for PBC, and were either UDCA intolerant or receiving stable recommended doses of UDCA for the prior 12 months. PBC diagnostic criteria included ≥2 of the following: • History of ALP >ULN for ≥6 months, or • Positive antimitochondrial antibody titers (>1:40 on immunofluorescence or M2 positive by enzyme-linked immunosorbent assay), or • Positive PBC-specific antinuclear antibodies, and liver biopsy histology consistent with PBC. Patients were also required to have ALP levels ≥1.67xULN. Patients with compensated cirrhosis (diagnosed by liver histology, imaging tests, or liver elastography) were eligible.

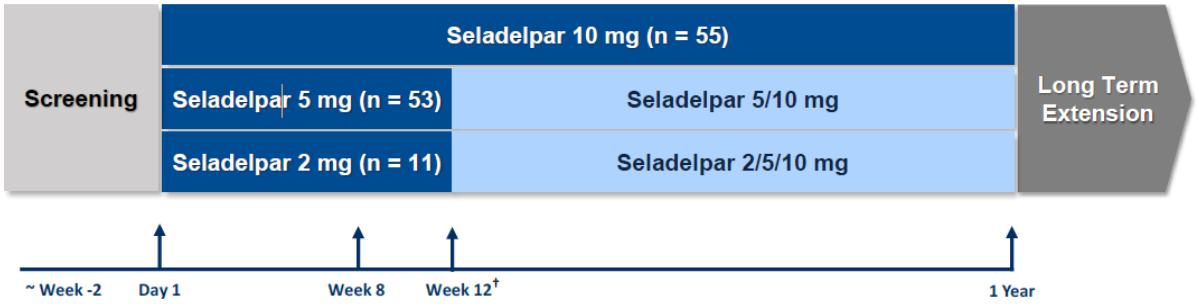
	Patients were excluded if they had AST or ALT levels >3 x ULN; total bilirubin >2.0 mg/dL (34.2 Ul/L); total bilirubin >ULN and albumin <lower limit of normal (Rotterdam advanced stage), except for patients with Gilbert's syndrome or other medical conditions that would preclude full participation or confound study results.
Settings and locations where the data were collected	All study visits occurred in clinic
Study periods and trial drugs	Eligible patients were randomly assigned to three treatment groups (randomisation ration 1:1:1): • Seladelpar 2 mg: Patients received seladelpar 2 mg once daily for 52 weeks • Seladelpar 5 mg: Patients received seladelpar 5 mg once daily for 52 weeks • Seladelpar 10 mg: Patients received seladelpar 10 mg once daily for 52 weeks Doses could be up-titrated to 10 mg once daily after 12 weeks of treatment based on investigator judgement for patients with an inadequate biochemical response.
Prior and concomitant Medication	• UDCA was taken as background therapy as part of participation in the study. UDCA was continued in those patients who could tolerate it at their pre-study dose as recommended per the Investigator's clinical judgement • Concomitant medications with a potential effect on cholestasis markers (e.g., OCA, fibrates, and long-term steroids) were prohibited.
Primary outcome	Mean percent change in ALP from baseline to Week 8.
Secondary outcomes used in the model/ specified in the scope	• Absolute change in ALP and mean percent change in ALP from baseline to 12 weeks and 52 weeks of treatment • Composite responder endpoint of ALP and total bilirubin (ALP < 1.67 x ULN, ≥ 15% decrease in ALP, and total bilirubin ≤ 1.0 x ULN) • Responder rates by published PBC response criteria (Paris I and II; Toronto I and II; Barcelona; Rotterdam) • Change and percent change from baseline to 12 weeks and 52 weeks of treatment in markers of liver biochemistry • Change from baseline to 12 weeks and 52 weeks of treatment in patient reported outcomes (Pruritus VAS score, 5-D Itch scale score, and PBC-40 QoL score)
Pre-planned subgroups	• Cirrhosis (yes, no)

K**ey**: ALP, alkaline phosphatase; ALT, alanine aminotransferase; AST, aspartate aminotransferase; OCA, obeticholic acid; QoL quality of life; PBC, primary biliary cholangitis; UDCA, ursodeoxycholic acid; ULN, upper limit of normal, VAS, visual analogue score.

2.3.2.2 Trial design

CB8025-21629 was an international, multicentre, open-label, randomised, parallel-group, Phase 2 study to evaluate the safety and efficacy of three different doses of seladelpar (2 mg, 5 mg and 10 mg) in patients with PBC and an inadequate response to or intolerance to UDCA. The study design for this trial is depicted in Figure 13.

Figure 13: CB8025-21629 study design



Key: EOT, end of treatment; SoC, standard of care; UDCA, ursodeoxycholic acid.
Notes: Seladelpar and placebo were administered with SoC UDCA unless patient had history of unacceptable side effects.
† After 12 weeks of treatment, doses could be increased up to 10 mg based on patient efficacy response and tolerability
Source: Figure S1B, Bowlus *et al.* (2022); Figure 1, CB8025-21629 CSR (58, 103).

Approximately 128 patients were to be assessed to evaluate the efficacy and safety of seladelpar over eight weeks of treatment as the primary endpoint. Patients were centrally randomly assigned on a 1:1 ratio to the 5 and 10 mg treatment groups. Patients in the 2 mg treatment group entered the study in chronological order, and enrolment was open only in the UK. Patients took seladelpar orally once daily for 8 weeks (58, 103).

After completion of the 8-week initial treatment period, patients entered an open-label extension period for a total of up to 52 weeks of treatment. Patients received the assigned dose of seladelpar for at least 12 weeks. After Week 12, patients assigned to the 2 mg or 5 mg dose treatment could have the dose up-titrated, based on individual patient review including ALP response and evaluation of safety and tolerability. Dose down-titration was performed for safety reasons and was allowed at any time during the study, including during the first eight weeks of treatment (58, 103).

After the completion of CB8025-21629, patients were invited to enrol in an open-label, partially randomised, international, multicentre, Phase 3 long-term extension study (CB8025-31371) (58,

103, 104). Upon enrolment, patients continued to receive the same oral dose of daily seladelpar. During the extension treatment period, the dose could be adjusted for reasons related to safety or efficacy. CB8025-31371 was open for over 21 months prior to its termination (see Section 2.2), which allowed patients to be treated with seladelpar for up to 33 months (104).

A total of 119 patients underwent randomisation and received either seladelpar 2 mg (11 patients), 5 mg (53 patients) or 10 mg (55 patients) in CB8025-21629. Overall, 106 patients (89.1%) completed the study; one (9.1%) who received seladelpar 2 mg, seven (13.2%) who received seladelpar 5 mg and six (10.9%) who received seladelpar 10 mg withdrew from the study. A total of 105 patients (88.2%) completed Week 52, 104 (99.0%) of whom rolled over into CB8025-31371 (46,85). Overall, 98.1% of patients who received treatment in CB8025-31371 were enrolled from CB8025-21629; only two patients had completed the ENHANCE study when it was terminated early along with CB8025-31371 (see Appendix B1.) (104).

2.3.2.3 Eligibility Criteria

The key inclusion and exclusion criteria for CB8025-21629 are described below in Table 13.

Table 13: Key eligibility criteria for CB8025-21629

Key Inclusion Criteria	Key Exclusion Criteria
Aged 18–75 years old (inclusive)	A medical condition other than PBC that, in the Investigator's opinion, would preclude full participation in the study (e.g., cancer)
Confirmed PBC as defined by having any two of the following three diagnostic criteria: • History of ALP >1.0x ULN for at least six months • Positive AMA titers (>1:40 on immunofluorescence or M2 positive by ELISA) or positive PBC-specific ANAs • Documented liver biopsy results consistent with PBC	AST or ALT >3xULN
Treatment with UDCA for ≥12 months or intolerant to UDCA	Total bilirubin > 2.0 mg/dL
ALP ≥1.67x ULN	Presenting any of the following conditions: Autoimmune hepatitis or Primary sclerosing cholangitis

	Known history of alpha-1-antitrypsin deficiency; acute pancreatitis; chronic viral or HIV infection
	Current use of fibrates, simvastatin, OCA or any experimental or unapproved treatment for PBC or immunosuppressant.
	Creatine kinase >ULN
	Serum creatinine > ULN
	Treatment with colchicine, methotrexate, azathioprine or systemic steroid in the 2 months preceding screening.
	Pregnancy or breastfeeding

Key: ALP: alkaline phosphatase; ALT: alanine aminotransferase; AMA: antimitochondrial antibody; ANA: anti-nuclear antibody; AST, aspartate aminotransferase; ELISA, enzyme-linked immunosorbent assay; HIV, human immunodeficiency virus; INR, international normalised ratio; LLN, lower limit of normal; OCA, obeticholic acid; PBC, primary biliary cholangitis; UDCA, ursodeoxycholic acid; ULN, upper limit of normal

For a full list of eligibility criteria, please refer to the CB8025-21629 CSR (103).

2.3.2.4 Settings and location where the data were collected

In CB8025-21629, a total of 32 sites enrolled patients. These centres were located in Canada, Germany, United Kingdom and the US. All study visits occurred in clinic.

2.3.2.5 Trial drugs and concomitant medication

2.3.2.5.1. Seladelpar

Seladelpar 2, 5 and 10 mg capsules were supplied in a blinded manner. Seladelpar was administered orally, once daily, for a duration of up to 52 weeks. Patients who met specific safety monitoring criteria or had tolerability issues could have a dose down-titration. Patients who were initially assigned to 10 mg seladelpar were down titrated to 5 mg seladelpar in a blinded manner (58, 103).

During CB8025-31371, the dose of seladelpar could be adjusted for reasons related to safety or efficacy. Increasing the dose up to 10 mg due to an inadequate biochemical response could be made at any time based on investigator judgement for those patients who were taking 2 or 5 mg seladelpar in CB8025-21629 (104).

2.3.2.5.2. Ursodeoxycholic acid (UDCA)

UDCA was taken as a background therapy as part of participation in the study. UDCA therapy was continued in those patients who could tolerate it at their pre-study dose and as recommended per the Investigator's clinical judgment. The patients were to continue taking UDCA at approximately the same dose during the study. After Week 8, dose adjustment or interruption of UDCA was not recommended, but was acceptable. Any changes in UDCA dosing were to be documented (58, 103).

2.3.2.5.3. Prior and concomitant medication

The use of concomitant medications and occurrence of concomitant procedures were documented on the patient's electronic case record form (58, 103) .

Patients were also permitted to receive the required medication to treat new or existing medical conditions on study. Any patient that required a medication that would have compromised their safety in the trial was withdrawn (58, 103) .

2.3.2.5.4. Restricted medication

Restricted medications included OCA, fibrates (e.g., bezafibrate, fenofibrate), simvastatin, colchicine, methotrexate, azathioprine, or long-term systemic steroids (For >2 weeks), and any experimental or unapproved treatment for PBC or related autoimmune disease. For a full list of restricted medications, please see the CB8025-21629 CSR (103).

2.3.2.6 Outcomes used in the economic model or specified in the scope, including primary outcome

The primary efficacy endpoint to evaluate the efficacy of seladelpar was the mean percent change in ALP from baseline at Week 8 (58, 103).

Key secondary efficacy endpoints included mean absolute and percent changes from baseline at Weeks 12 and 52 in ALP, responder rates for a composite endpoint of ALP and total bilirubin (ALP <1.67 x ULN, ≥15% decrease in ALP from baseline, and normal total bilirubin), and ALP ≤ULN (58, 103).

Additional secondary endpoints included changes from baseline at Weeks 12 and 52 in total and direct (conjugated) bilirubin, AST, ALT, GGT, 5' nucleotidase, and pruritus intensity using a visual analog scale (VAS; 0 to 100; 0 = no itch, 100 = worst itch imaginable) (58, 103).

Safety assessments included TEAEs, laboratory analyses, vital signs, physical examinations, and concomitant medications (58, 103).

2.3.2.7 Patient datasets

Efficacy analyses were conducted using data from the modified ITT (mITT) analysis set, defined any patient diagnosed with PBC who received ≥1 dose of seladelpar with ≥1 post-baseline ALP measurement. The SAS comprised all patients who received ≥1 dose of seladelpar (58, 103).

2.3.2.8 Baseline characteristics

The baseline characteristics of patients in the CB8025-21629 SAS are shown in Table 14.

Table 14: Baseline characteristics (CB8025-21629; SAS)

	Seladelpar			
	2 mg (n=11)	**5 mg (n=53)**	**10 mg (n=55)**	**Total (n=119)**
Sex, female, n (%)	11 (100.0)	51 (96.2)	50 (90.9)	112 (94.1)
Race, White, n (%)	10 (90.9)	50 (94.3)	49 (89.1)	109 (91.6)
Age (years)	55.2 (9.6)	57.5 (8.1)	57.4 (9.7)	57.2 (9.0)
BMI (kg/m2)	29.4 (7.3)	26.6 (5.7)	27.7 (5.3)	27.4 (5.7)
Duration of PBC (years)	9.3 (6.9)	10.0 (7.0)	9.4 (6.2)	9.7 (6.6)
Cirrhosis, n (%)	0	14 (26.4)	11 (20.0)	25 (21.0)
History of pruritus, n (%)	7 (63.6)	38 (71.7)	39 (70.9)	84 (70.6)
ALP (U/L)	300.4 (121.4)	345.4 (188.0)	295.3 (136.0)	318.1 (160.9)
ALT (U/L)	54.1 (24.6)	46.2 (26.1)	45.8 (22.7)	46.7 (24.3)
AST (U/L)	45.0 (19.3)	43.2 (20.3)	43.6 (18.7)	43.5 (19.3)
GGT (U/L)	254.5 (143.3)	234.9 (149.4)	234.3 (192.9)	236.4 (169.2)
INR	1.1 (0.1)	1.0 (0.1)	1.0 (0.1)	1.0 (0.1)
Total bilirubin (mg/dl)[a]	0.6 (0.1)	0.8 (0.4)	0.8 (0.3)	0.8 (0.3)
Albumin (g/L)	0.4 (0.02)	0.4 (0.04)	0.4 (0.04)	0.4 (0.03)

Platelets (×10^3/µl)	242.4 (84.2)	214.9 (88.5)	243.5 (74.1)	230.7 (82.3)
UDCA intolerant, n (%)	0	5 (9.4)	3 (5.5)	8 (6.7)
Concomitant UDCA, n (%)	11 (100)	48 (90.6)	52 (94.5)	111 (93.2)
UDCA dose (mg/kg/day), n Mean (SD)	11 13.6 (4.0)	48 15.1 (3.2)	51 15.1 (4.9)	110 15.0 (4.1)
Previous treatment with OCA, n (%)	0	8 (15.1)	7 (12.7)	15 (12.6)
Pruritus VAS score, n Mean (SD)	11 15 (18)	52 24 (23)	55 31 (29)	118 26 (26)
MELD score[b], n Mean (SD)	11 7.3 (1.3)	49 6.9 (1.2)	52 6.9 (1.1)	NC NC
Rotterdam[c] Early Moderately advanced Advanced	 11 (100.0) 0 0	 43 (81.1) 10 (18.9) 0	 42 (76.4) 11 (20.0) 2 (3.6)	 96 (80.7) 21 (17.6) 2 (1.7)

Key: ALP, alkaline phosphatase; ALT, alanine aminotransferase; AST, aspartate aminotransferase; GGT, gamma-glutamyltransferase; INR, international normalised ratio; MELD, model for end-stage liver disease; mITT, modified intent-to-treat; NC, not calculated; OCA, obeticholic acid; PBC, primary biliary cholangitis; UDCA, ursodeoxycholic acid; VAS, visual analog scale.
Notes: Values are mean (SD) unless otherwise noted.
[a]Multiply by 17.1 to convert to SI units (lmol/L).
[b]MELD score was calculated using the mITT population.
[c]Rotterdam score categories were early (normal total bilirubin and normal albumin), moderately advanced (abnormal albumin OR abnormal total bilirubin), and advanced (abnormal albumin AND abnormal total bilirubin).
Source: Bowlus *et al.* (2022); Tables 6 & 7, CB8025-21629 CSR (58, 103).

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

2.4.1 RESPONSE

2.4.1.1 Analysis population

As highlighted in Section 2.3.1.7, efficacy and safety analyses included data from the ITT analysis set, defined as patients who were randomised in the study and received at least one dose of study drug. Pruritus NRS endpoints were analysed among patients with a baseline NRS score of ≥4 and in the ITT analysis set (5, 100).

2.4.1.2 Sample Size

A sample size of 180 patients was estimated to provide over 90% power to detect a significant difference between treatment groups with a two-sided test of equality of binomial proportions

using Fisher's exact test with a type I error rate of 0.05 (Ph 3 trial) (5, 100). This was based on an estimation that 55% of patients who received seladelpar at a dose of 10 mg and 20% of the patients who received placebo would have a biochemical response, and that 25.5% and 2.5%, respectively would have normalised ALP levels (105). A total of 48 patients with a baseline pruritus NRS score of at least 4 was estimated to provide more than 80% power to detect a clinically important difference of 2 or more points between treatment groups using a two-sample two-sided t-test with a type I error rate of 0.05 (5, 100, 106).

2.4.1.3 Statistical analysis

A summary of statistical analysis for RESPONSE is available below in the Table 15.

Statistical testing was two-sided and performed at a 5% significance level. For all primary and key secondary efficacy endpoints, control of study-wide Type 1 error was maintained at 5% using the hierarchical fixed-sequence methodology in the following order: primary endpoint (composite biochemical response of ALP and total bilirubin), normalisation of ALP at Month 12, change in Pruritus NRS score at Month 6. All other secondary and exploratory efficacy endpoints were described descriptively; p-values for comparing seladelpar with placebo for the other secondary and exploratory endpoints were considered nominal (5, 100).

Table 15: Summary of key statistical analysis used in RESPONSE

Trial number (acronym)	**NCT04620733 (RESPONSE)**
Hypothesis objective	The null hypothesis for response to treatment based on the primary endpoint is that there is no difference in response rates between the seladelpar and placebo groups. The alternative hypothesis is that there is a difference in response rates between both groups
Statistical analysis	Statistical testing was two-sided and performed at the 0.05 alpha level. For the primary and key secondary efficacy end points, we maintained the 0.05 type I error using a hierarchical fixed-sequence method in the following order: the primary end point; normalisation of alkaline phosphatase levels at month 12; and the change in pruritus NRS score from baseline to month 6. Other end points are reported as point estimates and measures of variability that were not adjusted for multiple testing and should not be used to infer definitive benefits of treatment.
Sample size, power calculation	On the basis of estimates that 55% of patients who received seladelpar at a dose of 10 mg daily and 20% of patients who received placebo would have a biochemical response and that 25.5% and

	2.5%, respectively, would have normalised alkaline phosphatase levels, we calculated that a sample size of 180 patients would provide more than 90% power to detect a significant difference between treatment groups with a two-sided test of equality of binomial proportions using Fisher's exact test with a type I error rate of 0.05. We estimated that a total of 48 patients with a baseline pruritus NRS score of at least 4 would provide more than 80% power to detect a clinically important difference of 2 or more points between treatment groups using a two-sample two-sided t-test with a type I error rate of 0.05.
Data management, patient withdrawals	Missing data were not imputed for analysis, unless otherwise stated. For the analysis of the primary endpoint, any patient who did not provide an assessment at or had discontinued treatment prior to the specified timepoint for evaluation or who otherwise had missing data was considered a non-responder. For the key secondary endpoint, change from baseline in weekly averaged Pruritus NRS at 6 months, a missing timepoint was imputed as an average of the two adjacent weekly averages (at most one week apart); otherwise, it was imputed by the adjacent weekly average that was present. For example, if a patient who was involved in the study was missing Week 23 and Week 24 data, Week 23 was imputed based on Week 22 average while Week 24 was imputed based on Week 25 data. Furthermore, a patient who discontinued prior to or during Week 24 did not have an imputed value for Week 26. Data collected after Month 6 were not used for imputation.

Key: CI: confidence interval; NRS: numerical rating scale.
Source: Hirschfield *et al.* (2024); RESPONSE CSR (5, 100)

2.4.1.4 Primary efficacy analysis

As described previously, the primary efficacy endpoint was the proportion of patients achieving the composite biochemical response endpoint evaluated at 12 months (Month 12), which was defined as ALP < 1.67× ULN; ≥ 15% decrease in ALP and total bilirubin ≤ 1.0× ULN (5, 100).

The primary efficacy analysis was conducted using a Cochran-Mantel-Haensel test to evaluate the incidence of response at Month 12. Any patient who did not provide an assessment at or had discontinued treatment prior to the specified timepoint for evaluation or who otherwise had missing data was considered a non-responder. The risk difference and 95% CI using Miettinen and Nurminen were also provided. The statistical significance of the difference between placebo and seladelpar was determined using a two-sided p-value threshold of ≤0.05 (5, 100).

2.4.1.5 Key secondary analyses

The key secondary endpoint efficacy analysis for the proportion of patients with ALP normalisation at Month 12 was analysed using the same approach as the primary efficacy endpoint. Additionally, the key secondary endpoint of change from baseline in weekly averaged Pruritus NRS at six months was analysed using a MMRM for patients in the MSPN analysis set. The model included terms for baseline NRS, randomisation stratum, treatment group, week, and treatment-by-week interaction. The least squares (LS) mean changes (with 95% CIs) according to randomisation group and the LS mean difference between the groups and associated two-sided 95% CIs and two-sided p-values were derived from the model. For Pruritus NRS, data for a missing assessment were imputed as a mean of the adjacent two weeks; missing data were not imputed for other continuous endpoints (5, 100).

2.4.1.6 Other secondary analyses

Postbaseline composite biochemical response endpoints were analysed in a similar manner to that described for the primary efficacy endpoint (5, 100).

Similarly, postbaseline ALP assessments were analysed in the same manner as described for the key secondary efficacy endpoint, namely ALP normalisation at Month 12, while postbaseline Pruritus NRS assessments were evaluated using the methods described for the other key secondary efficacy endpoint, namely change from baseline in weekly averaged Pruritus NRS at 6 months (5, 100).

The remaining secondary endpoints were summarised using descriptive statistics by treatment group by visit (5, 100).

2.4.1.7 Analyses of exploratory efficacy endpoints

Exploratory analyses were summarised using descriptive statistics by treatment group by visit (5, 100).

2.4.1.8 Subgroup analyses

The influence of select baseline and demographic characteristics on the primary and key secondary efficacy endpoints as well as safety was evaluated. Subgroup analyses were not

powered to identify a treatment difference, and all summaries are descriptive, A minimum of five patients in each treatment arm was required to conduct subgroup analyses (5, 100).

2.4.1.9 Safety analysis

Safety data were summarised by actual treatment arm and overall using the safety analysis set (SAS) population (5, 100).

2.4.1.10 Participant flow

Details of participant flow in the RESPONSE and ASSURE clinical studies are provided in Appendix B1.2.

2.4.2 CB8025-21629

2.4.2.1 Analysis population

The primary endpoint was analysed in the modified intention-to-Treat (mITT) set, defined as all randomised patients with confirmed PBC diagnosis who received at least one dose of the study treatment and had at least one post-baseline ALP measurement. Safety evaluation parameters were analysed in the SAS, which was defined as all patients who received at least one dose of seladelpar (58, 103).

2.4.2.2 Sample size

It was assumed that 5 and 10 mg treatment groups would have at least a 10% difference between groups in the mean ALP percent change with a 15% standard deviation (SD). Based on this assumption and on the use of a 2-sided 2-sample t-test at the alpha 0.05 level of significance, a study sample size of 49 patients per group would have 90% power to detect a 10% mean difference between the 5 and 10 mg treatment groups (58, 103).

There was no formal sample size justification for the 2 mg treatment group (58, 103).

2.4.2.3 Statistical analysis

A summary of the statistical analyses for CB8025-21629 is available in Table 16

Table 16: Summary of key statistical analysis used in CB8025-21629

Trial number (acronym)	NCT02955602 (CB8025-21629)
Hypothesis objective	The null hypothesis is that there is no difference in the mean ALP percent change between the seladelpar treatment groups. The alternative hypothesis is that there is a difference in ALP percent change.
Statistical analysis	The primary efficacy analysis compared the mean percent change in ALP from baseline to Week 8 using an analysis of covariance (ANCOVA) model with treatment group as the main effect and the baseline ALP value as a covariate. All secondary analyses were carried out using two-sided tests at the alpha 0.05 level of significance for the mITT population by the initial treatment groups.
Sample size, power calculation	A sample size of 49 patients was required to achieve at least 90% power to detect a 10% mean difference between the 5 and 10 mg treatment groups. There was no formal sample size justification for the 2 mg treatment group.
Data management, patient withdrawals	The last observation carried forward (LOCF) approach was used for the analysis of ALP, responder rates by published PBC response criteria, MELD score, GLOBE score, and the composite endpoint. Missing post-baseline data less than 2 days after end of treatment (EOT) was imputed by carrying forward the last non-missing on treatment post-baseline value (LOCF). For all other analyses no imputation of missing data was applied.

Key: ALP, alkaline phosphatase; ANCOVA, analysis of covariance; EOT, end of treatment; mITT, modified intent-to-treat; MELD, Model for End-Stage Liver Disease; LOCF, last observation carried forward; PBC, primary biliary cholangitis.
Source: Bowlus *et al.* (2022); CB8025-21629 CSR (58, 103)

2.4.2.4 Primary efficacy analysis

The primary efficacy analysis compared the mean percent change in ALP from baseline to Week 8 using an analysis of covariance (ANCOVA) model with treatment group as the main effect and the baseline ALP value as a covariate. Pairwise comparisons between the seladelpar 2, 5, and 10 mg groups were performed (58, 103).

2.4.2.5 Secondary analysis

All secondary analyses were carried out using two-sided tests at the alpha 0.05 level of significance for the mITT population by the initial treatment groups (58, 103).

2.4.2.6 Exploratory analyses

All exploratory analyses were summarised using descriptive statistics by treatment group (58, 103).

2.4.2.7 Safety analysis

Safety data were summarised by actual treatment arm and overall using the SAS analysis population (58, 103).

2.4.2.8 Participant flow

Details of participant flow in the CB8025-21629 and CB8025-31371 clinical studies are provided in Appendix B1.2.

2.5 Critical appraisal of the relevant clinical effectiveness evidence

The critical appraisal of RESPONSE was conducted using the ROB2.0 checklist, while the quality assessments of ASSURE, CB8025-21629, and CB8025-31731 were conducted using the Downs & Black checklist. Complete quality assessments for each study are presented in Appendix B1.3.

2.6 Clinical effectiveness results of the relevant studies

Summary of clinical effectiveness results:

- The efficacy and safety of seladelpar for the treatment of adults with PBC and an inadequate response to or an intolerance to UDCA has been demonstrated in the double-blind, placebo-controlled, randomised, Phase 3 RESPONSE study and the ongoing, open-label, long-term Phase 3 ASSURE study.
- Patients receiving seladelpar were significantly more likely achieve the primary endpoint of composite biochemical response (defined as ALP <1.67x ULN, ≥15% decrease in ALP, and total bilirubin ≤1.0x ULN) vs placebo (61.7% vs 20.0%; p<0.0001)

- Treatment with seladelpar led to a significantly higher percentage of patients achieving ALP normalisation (key secondary endpoint) vs placebo (25.0% vs 0.0%; p<0.0001)
- Among patients with moderate-to-severe pruritus at baseline, seladelpar significantly reduced Pruritus NRS score (key secondary endpoint) from baseline to Month 6 vs placebo (LS mean change from baseline -3.2 vs -1.7, respectively; p=0.0047)
- Results from the long-term extension study, ASSURE, demonstrated that seladelpar has a sustained effect on biochemical markers of cholestasis and liver injury that was maintained for up to two years
- The efficacy and safety of seladelpar was also investigated in a supporting Phase 2, dose-ranging, open-label study (CB8025-21629), where 67% of patients treated with seladelpar 10 mg achieving a composite biochemical response after 52 weeks, and 33% achieved ALP normalisation. These effects were maintained or improved for up to 33 months in the long-term extension study, CB8025-31731.
- The available data from the clinical studies of seladelpar demonstrates that treatment with seladelpar results in a greater proportion of patients achieving ALP normalisation, improvements in pruritus, and improvements in liver function versus placebo.

2.6.1 RESPONSE

As highlighted in Section 2.3.1.7, the ITT analysis set is the primary analysis population for the efficacy analyses, with the exception of the Pruritus NRS evaluations, which were evaluated in the MSPN population (5, 100).

As discussed in Section 2.2, the poster exhibited at the EASL 2024 congress by Trivedi *et al.* (2024) provides long-term data on patients who received continuous seladelpar treatment informs the write-up of the long-term clinical effectiveness and safety data for patients who rolled over from RESPONSE to ASSURE (99). Where data on the outcomes reported in the following sections are available, clinical effectiveness results from ASSURE will be supplemented into the narrative to provide evidence the long-term efficacy of seladelpar for the treatment of PBC.

Due to variable durations of study participation on during ASSURE, the outcomes data at each study timepoint contained a sample of different patients who had data available. Data wasn't censored, hence the sample size at each study timepoint reflects all patients with available data. The absence of responders for study outcomes at each study timepoint may therefore have an effect on the perceived durability of effect of seladelpar in ASSURE. Hence, the results from ASSURE presented below should be interpreted with caution.

2.6.1.1 Results of primary outcome

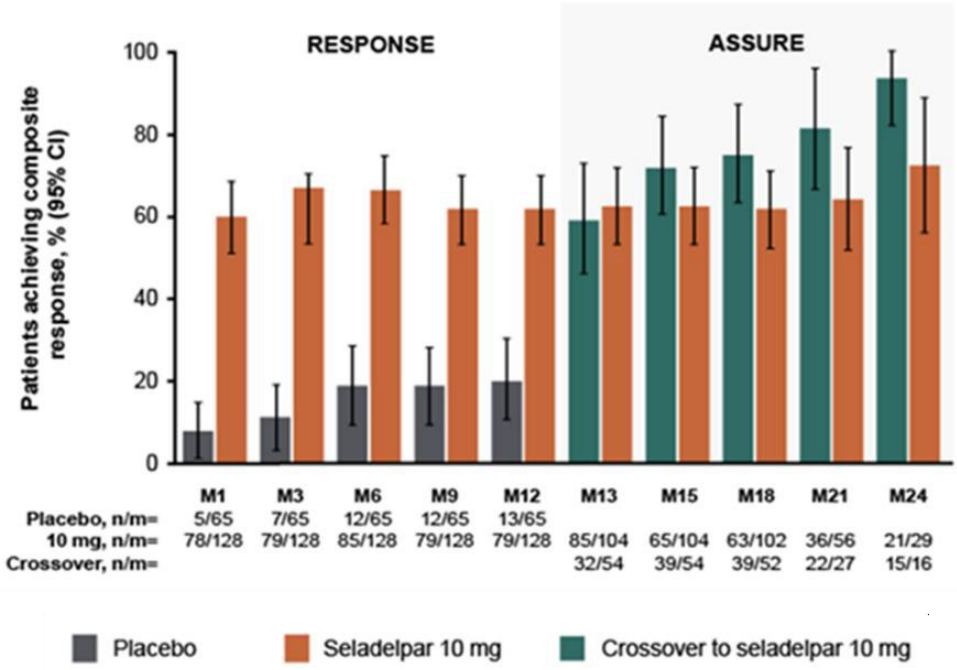
The primary outcome of RESPONSE was a composite biochemical response, as defined in Section 2.3.1.6.

Treatment with seladelpar led to a statistically significantly higher percentage of patients achieving the primary efficacy endpoint of composite biochemical response. At Month 12, the primary endpoint criteria were met in 61.7% of patients (79 of 128 patients) treated with seladelpar, versus 20.0% of patients (13 of 65 patients) receiving placebo (treatment difference, 41.7%; 95% CI, 27.7 to 53.4; p<0.001) (Figure 14; Table 17) (5, 100). The number of patients reaching each criterion at Month 12 are reported in Table 17.

The interim efficacy results of ASSURE were consistent with those observed in RESPONSE. For those patients who continued into the ASSURE study and received continuous seladelpar for a total of 18 months (n=102), 62% achieved a composite biochemical response. For patients who received seladelpar for 24 continuous months (n=29), 72% met the composite biochemical response endpoint (Figure 14) (99).

In addition, patients who crossed over to seladelpar from placebo showed an improvement in the composite biochemical response (Figure 14). Of the 52 patients previously randomised to placebo in RESPONSE, 75% (39 of 52 patients) met the composite biochemical response endpoint following cross-over to six months of treatment with seladelpar. Following 12 months of treatment, this proportion increased to 94% (15 of 16 patients) (99).

Figure 14: Composite biochemical response through Month 24 (RESPONSE & ASSURE; ITT Analysis Set)



Key: CI, confidence interval; M, Month.
Notes: A patient was designated as a responder if all three of the following conditions were met: 1) ALP <1.67x ULN; 2) ALP decrease from baseline of ≥15%; 3) total bilirubin ≤1.0x ULN. Patients with missing data at the specified timepoint for response evaluation were considered non-responders. ULN for ALP = 116 U/L.
Source: Trivedi *et al.* (2024) (99)

Table 17: Analysis of the composite biochemical response at Month 12 (RESPONSE; ITT Analysis Set)

	Placebo (n=65)	Seladelpar 10 mg (n=128)
Patients who achieved composite biochemical response at Month 12[a,b], n (%)	13 (20.0)	79 (61.7)
Response category at Month 12[b]		
ALP <1.67× ULN , n (%)	17 (26.2)	84 (65.6)
≥15% decrease in ALP, n (%)	21 (32.3)	107 (83.6)
Total bilirubin ≤1.0x ULN, n (%)	50 (76.9)	104 (81.3)

Key: ALP, alkaline phosphatase; ITT, intent to treat; ULN, upper limit of normal
Notes: ULN for ALP = 116 U/L.
[a]A patient was designated as a responder if all three of the following conditions were met: 1) ALP <1.67x ULN; 2) ALP decrease from baseline of ≥15%; 3) total bilirubin ≤1.0x ULN
[b]Patients with missing data at the specified timepoint for response evaluation were considered non-responders.
Source: Hirschfield *et al.* (2024); Table 27, RESPONSE CSR (5, 100).

2.6.1.2 Results of key secondary outcomes

2.6.1.2.1. ALP normalisation at Month 12

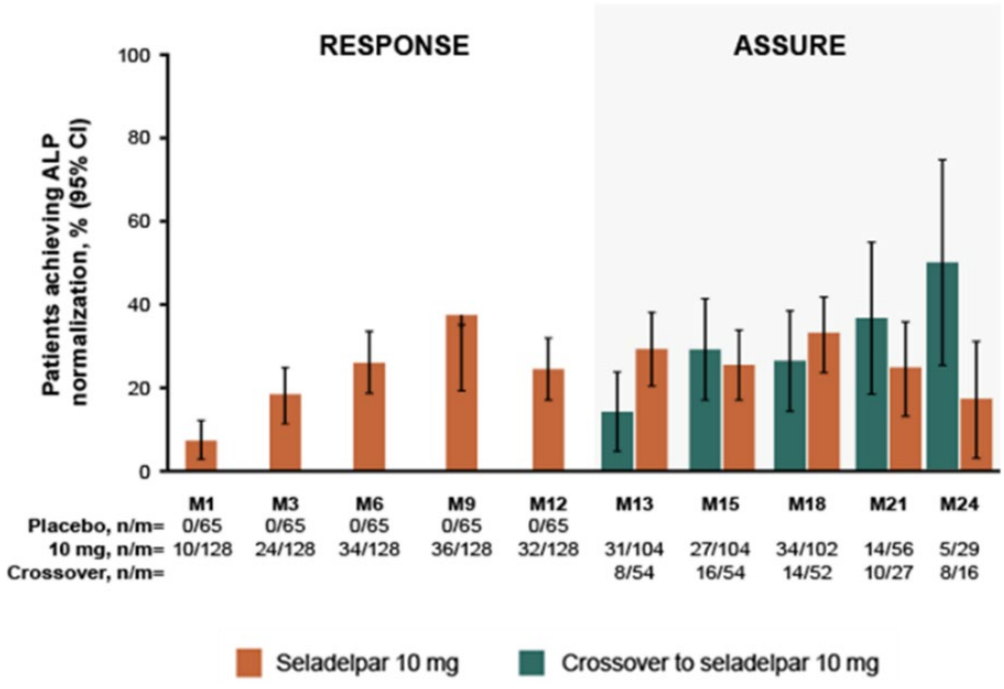
As described in Section 1.3.2.2, ALP normalisation is associated with improved liver-related clinical outcomes amongst patients with PBC, and has emerged as a key treatment goal for the disease (62, 66).

At Month 12, treatment with seladelpar led to a statistically significantly higher percentage of patients achieving ALP normalisation versus placebo (treatment difference, 25.0%; 95% CI, 18.3 to 33.2; p<0.001) (Figure 15) (5, 100). The number of patients reaching each criterion at Month 12 are reported in Table 17.

The interim efficacy results of ASSURE were consistent with those observed in RESPONSE. For those patients who continued into the ASSURE study and received continuous seladelpar for a total of 18 months (n=102), 33% reached ALP normalisation. For patients who received seladelpar for 24 continuous months (n=29), 17% achieved ALP normalisation (Figure 15) (99).

In addition, patients who crossed over to seladelpar from placebo showed an improvement in the composite biochemical response (Figure 15). Of the 52 patients previously randomised to placebo in RESPONSE, 27% (14 of 52 patients) achieved ALP normalisation following cross-over to six months of treatment with seladelpar. Following 12 months of treatment, this proportion increased to 50% (8 of 16 patients) (99).

Figure 15: ALP normalisation through Month 24 (RESPONSE & ASSURE; ITT Analysis Population)



Key: ALP: alkaline phosphatase; CI: confidence interval; M: Month
Notes: A patient was designated as a responder if the ALP value at Month 12 was ≤ 1.0 × ULN. Patients with missing data at the specified timepoint for response evaluation were considered as non-responders.
Source: Trivedi *et al.* (2024) (99)

2.6.1.2.2. Change from baseline in mean Pruritus NRS score at Month 6

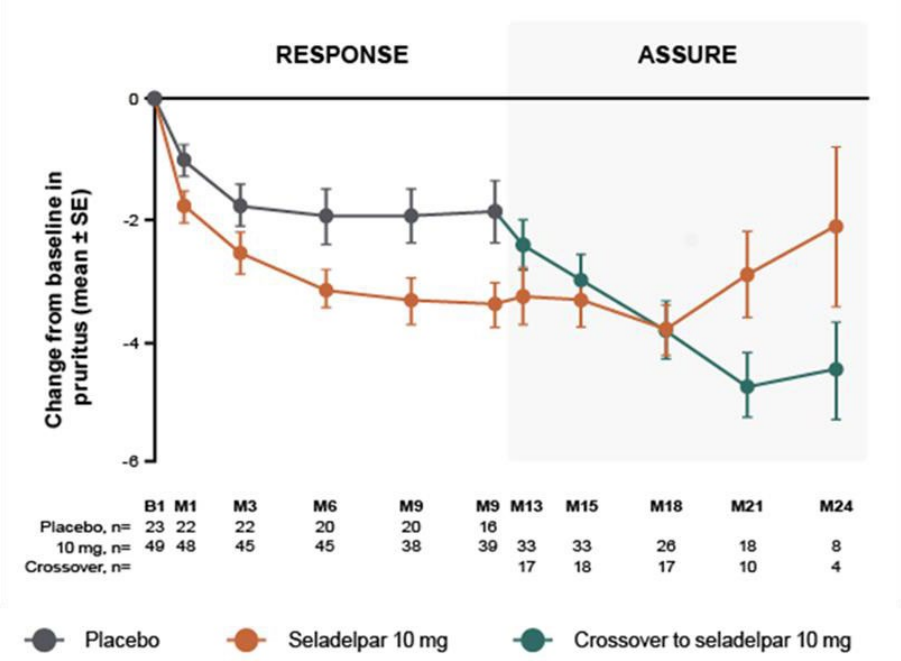
As described in Table 11 (Section 2.3.1.8), a total of 38.3% of patients (49 of 128 patients) in the seladelpar group and 35.4% of patients (23 of 65 patients) in the placebo group had moderate-to-severe pruritus at baseline, defined as a Pruritus NRS score ≥4.

At Month 6, treatment with seladelpar led to a statistically significant improvement in Pruritus NRS score compared with placebo in the MSPN analysis set. The LS mean change from baseline was -3.2 and -1.7 in the seladelpar and placebo arms, respectively (LS mean difference, -1.5, 95% CI, 2.5, -0.5; p=0.0047) (5, 100).

Seladelpar maintained a sustained reduction in pruritus in patients with baseline NRS ≥4 for up to two years for patients who continued to receive seladelpar in ASSURE. For patients who crossed over from placebo to seladelpar at study entry, the reduction in Pruritus NRS was

consistent with the reduction observed for patients initially randomised to receive seladelpar in RESPONSE (Figure 16) (99).

Figure 16: Change from baseline in Pruritus NRS through Month 24 (RESPONSE & ASSURE; MSPN Analysis Set)



Key: BL, baseline; LS, least squares; M, month; MSPN, moderate-to-severe Pruritus NRS; NRS, Numerical Rating Scale; SE, standard error.
Notes: MSPN analysis set included patients with NRS score ≥4 at baseline. A missing assessment at a specific timepoint was imputed as an average of the two adjacent weekly averages (at most one week apart): if only one adjacent weekly average was available, it was imputed by the available adjacent weekly average; if no adjacent weekly average was available, it was not imputed.
Source: Trivedi *et al.* (2024) (99)

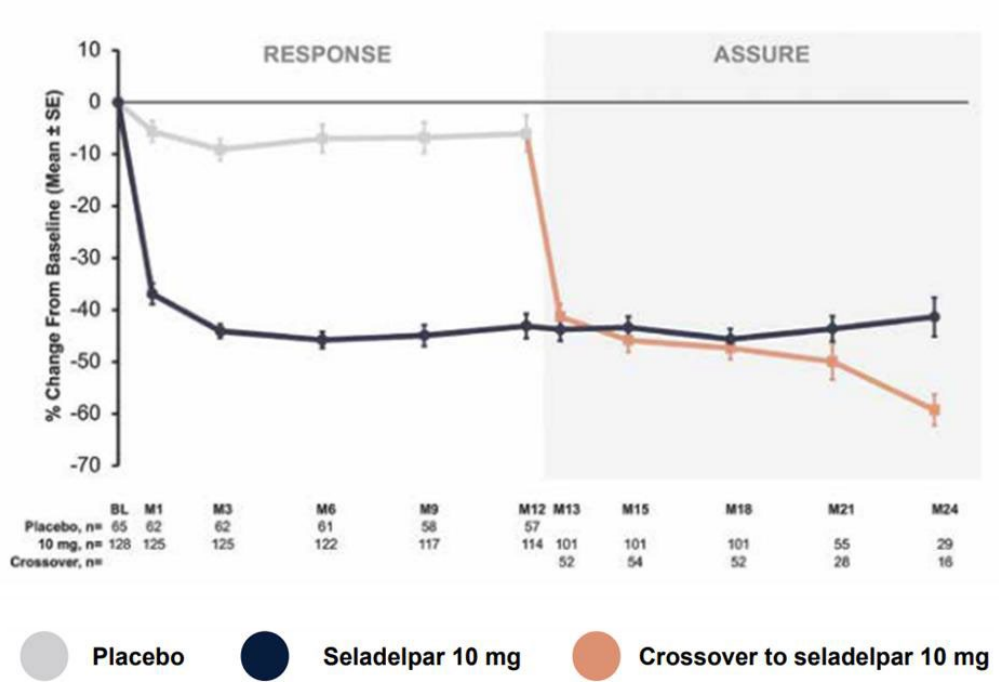
2.6.1.3 Results of other secondary and exploratory outcomes

2.6.1.3.1. Absolute and relative changes in ALP at 3, 6, and 12 months

Greater postbaseline reductions in ALP levels were observed in the seladelpar arm compared with the placebo arm at all RESPONSE study standpoints. The least square (LS) mean percentage changes from baseline in ALP levels at Month 3, 6 and 12 were -43.4%, -44.8%, and -42.4%, respectively, in the seladelpar arm with minimal decreases in the ALP levels observed in the placebo arm at Months 3, 6 and 12 with LS mean percentage changes of -8.0%, -5.9%, and -4.3%, respectively. P-values for the LS mean differences at all study timepoints were < 0.0001 (Figure 17) (5, 100).

Upon enrolment into ASSURE, patients with continuous seladelpar treatment maintained a durable effect on ALP through 24 months, while patients who crossed over to seladelpar from placebo demonstrated post-baseline reductions in ALP consistent with patients initially randomised to seladelpar in RESPONSE (Figure 17) (99).

Figure 17: Percent change from baseline in ALP over time (RESPONSE & ASSURE; ITT Analysis Set)



Key: ALP, alkaline phosphatase; BL, baseline; ITT, intent-to-treat; M, month; SE, standard error.
Sources: Trivedi *et al.* (2024); Figure 9, RESPONSE CSR (99, 100).

2.6.1.3.2. Proportion of patients with a decrease in NRS ≥2, NRS ≥3, NRS ≥4 in patients with baseline NRS ≥4 at each visit

A higher percentage of patients with moderate or severe baseline Pruritus NRS had a decrease in Pruritus NRS ≥ 2 in the seladelpar arm compared with placebo as early as Month 1, and this beneficial effect was sustained through Month 12 (Table 19). The percentage of patients with a decrease in Pruritus NRS ≥ 2, NRS ≥ 3, and NRS ≥ 4 at Month 6 was [redacted] , [redacted] , and [redacted] , respectively, in the seladelpar arm, relative to [redacted] and [redacted], respectively, in the placebo arm. Similarly, at Month 12, the percentage of patients with a decrease in Pruritus NRS

≥ 2, NRS ≥ 3, and NRS ≥ 4 was [redacted] and [redacted] in the seladelpar arm, respectively, relative to [redacted] and [redacted], respectively, in the placebo arm (5, 100).

Outcomes data in the long-term ASSURE study was not presented in the EASL Congress presentation, and hence is not presented in the submission.

Table 18: Analysis of Pruritus NRS Decrease of NRS ≥ 2, NRS ≥ 3, or NRS ≥ 4 (Weekly Averages) Over Time (MSPN Analysis Set)

	Seladelpar 10 mg (n=128)	Placebo (n=65)
Pruritus NRS Decrease ≥ 2 Response Rate[a,b]		
Month 1, n (%) (Wald 95% CI for Response Rate)	[redacted]	[redacted]
Month 3, n (%) (Wald 95% CI for Response Rate)	[redacted]	[redacted]
Month 6, n (%) (Wald 95% CI for Response Rate)	[redacted]	[redacted]
Month 9, n (%) (Wald 95% CI for Response Rate)	[redacted]	[redacted]
Month 12, n (%) (Wald 95% CI for Response Rate)	[redacted]	[redacted]
Pruritus NRS Decrease ≥ 3 Response Rate[b,c]		
Month 1, n (%) (Wald 95% CI for Response Rate)	[redacted]	[redacted]
Month 3, n (%) (Wald 95% CI for Response Rate)	[redacted]	[redacted]
Month 6, n (%) (Wald 95% CI for Response Rate)	[redacted]	[redacted]
Month 9, n (%) (Wald 95% CI for Response Rate)	[redacted]	[redacted]
Month 12, n (%) (Wald 95% CI for Response Rate)	[redacted]	[redacted]
Pruritus NRS Decrease ≥ 4 Response Rate[b,d]		
Month 1, n (%) (Wald 95% CI for Response Rate)	[redacted]	[redacted]
Month 3, n (%) (Wald 95% CI for Response Rate)	[redacted]	[redacted]
Month 6, n (%)	[redacted]	[redacted]

(Wald 95% CI for Response Rate)	[redacted]	[redacted]
Month 9, n (%) (Wald 95% CI for Response Rate)	[redacted]	[redacted]
Month 12, n (%) (Wald 95% CI for Response Rate)	[redacted]	[redacted]

Key: CI = confidence interval; MSPN = moderate to severe Pruritus NRS; NRS = numerical rating scale; N = total number of patients, n = number of patients in the category
Notes:
[a] A patient was designated as a responder if Pruritus NRS decrease was ≥ 2.
[b] Patients with missing data on the specified timepoint(s) for response evaluation were considered non-responders.
[c] A patient was designated as a responder if Pruritus NRS decrease was ≥ 3.
[d] A patient was designated as a responder if Pruritus NRS decrease was ≥ 4.
Source: Table 42, RESPONSE CSR (5, 100).

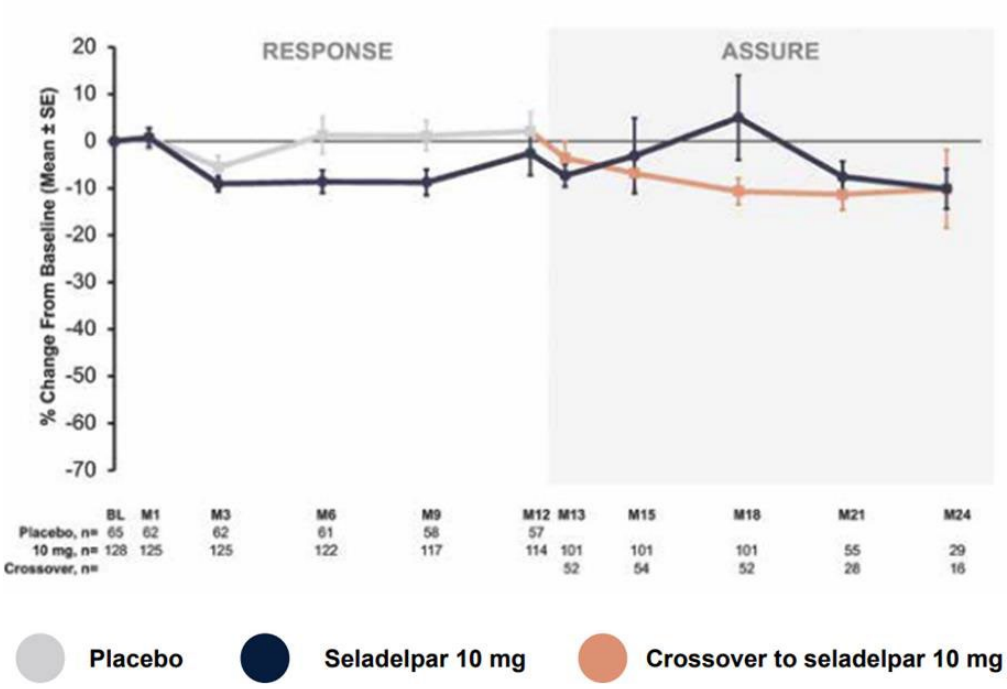
2.6.1.3.3. Absolute and relative changes in markers of liver biochemistry

The hallmark of PBC is cholestasis secondary to hepatobiliary injury and bile acid accumulation, with an accompanying elevation in disease-associated serum biomarkers such as ALP. Other disease biomarkers included GGT, for which an increase may be seen earlier in the disease, and hyperbilirubinemia as the disease progresses, and 5'-nucleotidase, which is an independent marker of cholestasis. Patients with PBC may also have elevated serum transaminases (ALT and AST) (14). The percent and absolute changes from baseline in total bilirubin (Section 2.6.1.3.3.1), GGT (Section 2.6.1.3.3.2), ALT (Section 2.6.1.3.3.3) AST (Section 2.6.1.3.3.4), and 5'-nucleotidase (Section 2.6.1.3.3.5) are provided below.

2.6.1.3.3.1. Total bilirubin

Mean baseline total bilirubin values were comparable between treatment arms (0.769 mg/dL in the seladelpar arm and 0.737 mg/dL in the placebo arm). Overall, there were small numerical decreases in total bilirubin levels in the seladelpar arm at multiple study timepoints compared to baseline, while similar decreases were not observed in the placebo arm. Nevertheless, the total bilirubin levels appeared to remain stable through Month 24 in both treatment groups (5, 100). The LS mean percent changes from baseline in total bilirubin during RESPONSE and ASSURE by treatment arm are presented below in Figure 18.

Figure 18: Percent change from baseline in total bilirubin over time (RESPONSE & ASSURE; ITT Analysis Set)



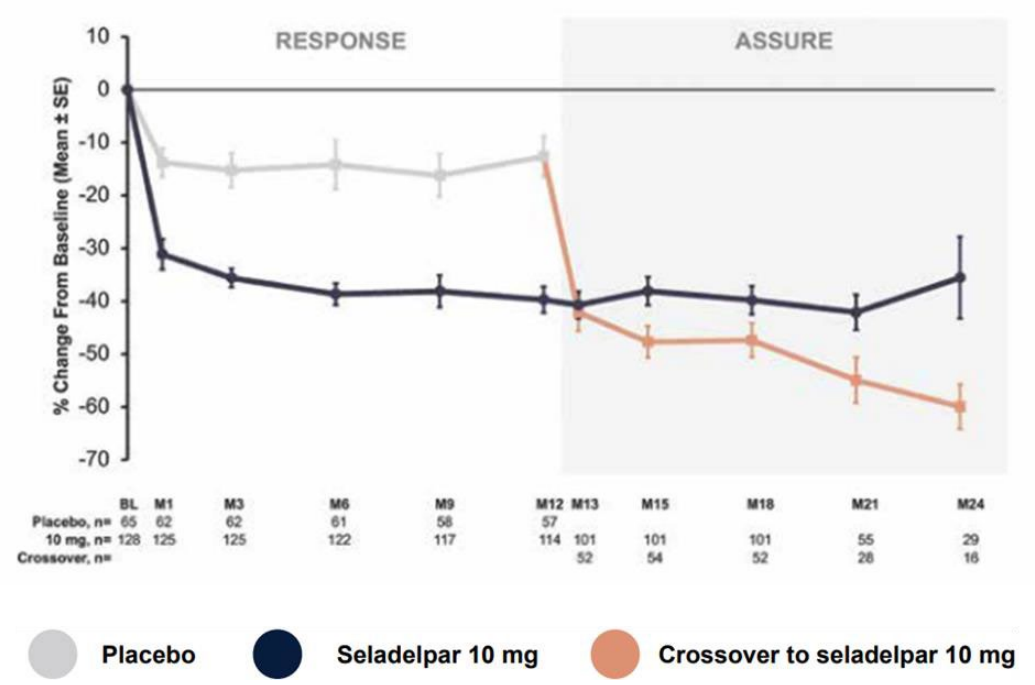
Key: BL, baseline; ITT, intent-to-treat; M, month; SE, standard error.
Sources: Trivedi *et al.* (2024); Figure 9, RESPONSE CSR (99, 100).

2.6.1.3.3.2. GGT

At baseline, mean GGT values were comparable between treatment arms (269.0 U/L in the seladelpar arm and 287.5 U/L in the placebo arm). Overall, there were greater postbaseline reductions in GGT levels (LS mean percent changes) at each timepoint over the course of the study in the seladelpar arm compared with the placebo arm, with larger decreases observed as early as Month 1. LS mean percent changes from baseline in GGT levels at Month 12 were -39.1% in the seladelpar arm compared with -11.4% in the placebo arm. P-values for LS mean differences were p=0.0002 at Month 1 and p < 0.0001 at 3, 6, 9 and 12 months (5, 100).

Upon enrolment into ASSURE, patients with continuous seladelpar treatment maintained a durable effect on GGT through 24 months, while patients who crossed over to seladelpar from placebo demonstrated postbaseline reductions in GGT consistent with patients initially randomised to seladelpar in RESPONSE (99). The LS mean percent changes from baseline in GGT during RESPONSE and ASSURE by treatment arm are presented below in Figure 19.

Figure 19: Percent change from baseline in GGT over time (RESPONSE & ASSURE; ITT Analysis Set)



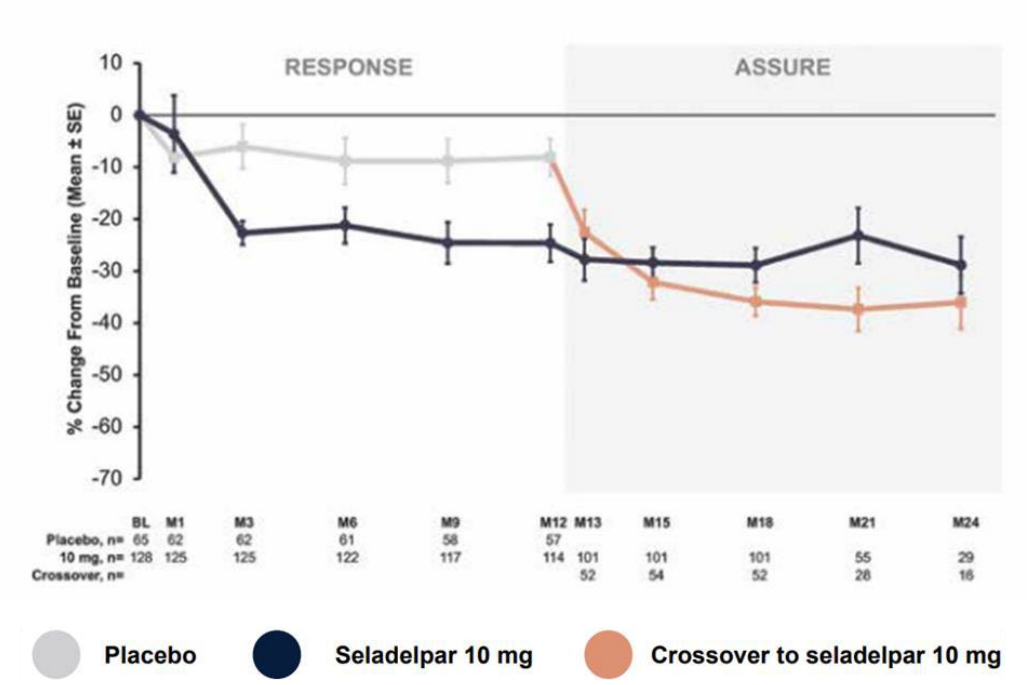
Key: BL, baseline; GGT, gamma-glutamyl transferase; ITT, intent-to-treat; LS, least squares; M, month; SE, standard error
Source: Trivedi *et al.* (2024); Figure 10, RESPONSE CSR (99, 100).

2.6.1.3.3.3. ALT

Postbaseline reductions in ALT levels were greater in the seladelpar arm compared with the placebo arm starting at Month 3 and continuing through Month 12. LS mean percent changes from baseline in ALT levels at Month 12 were -23.5% in the seladelpar arm compared with -6.5% in the placebo arm. P-values for LS mean differences at Months 3, 6, 9 and 12 were < 0.05.

Upon enrolment into ASSURE, patients with continuous seladelpar treatment maintained a durable effect on ALT through 24 months, while patients who crossed over to seladelpar from placebo demonstrated postbaseline reductions in ALT consistent with patients initially randomised to seladelpar in RESPONSE. The LS mean percent changes from baseline in ALT during RESPONSE and ASSURE by treatment arm are presented below in Figure 20.

Figure 20: Percent change from baseline in ALT over time (RESPONSE & ASSURE; ITT Analysis Set)

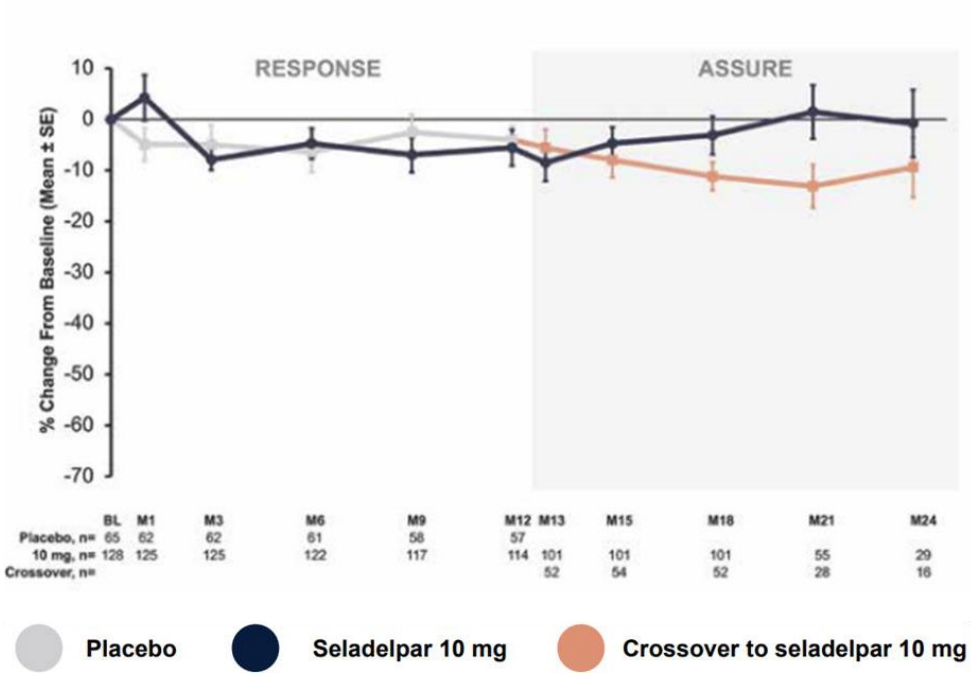


Key: ALT, alanine aminotransferase; BL, baseline; ITT, intent-to-treat; LS, least squares; M, month; SE, standard error
Source: Trivedi *et al.* (2024); Figure 11, RESPONSE CSR (99, 100).

2.6.1.3.3.4. AST

AST values were similar in both treatment arms over the course of RESPONSE and ASSURE and remained unchanged from baseline through Month 24 (5, 99, 100). The LS mean percent changes from baseline in GGT during RESPONSE and ASSURE by treatment arm are presented below in Figure 21.

Figure 21: Percent change from baseline in AST over time (RESPONSE & ASSURE; ITT Analysis Set)



Key: ASP, aspartate transferase; BL, baseline; ITT, intent-to-treat; LS, least squares; M, month; SE, standard error
Source: Trivedi *et al.* (2024); Figure 12, RESPONSE CSR (99, 100).

2.6.1.3.3.5. 5'-nucleotidase

There were greater postbaseline reductions in 5'-nucleotidase levels in the seladelpar arm compared with the placebo arm throughout the course of the study. Levels of 5'-nucleotidase decreased from baseline as early as Month 1 in patients receiving seladelpar with further reductions at Months 3 through 12 (LS mean percent changes at Months 1, 3, 6, 9 and 12: -34.3%, -40.1%, -42.7%, -43.2%, -42.3%, respectively). Smaller decreases in 5'-nucleotidase levels were observed in patients receiving placebo (LS mean percent changes at Months 1, 3, 6, 9 and 12: -10.5%, -12.0%, -14.1%, -17.8% and -20.8%, respectively). P-values for LS mean differences were < 0.05 at all study timepoints (5, 100).

Outcomes data in the long-term ASSURE study was not presented in the EASL Congress presentation, and hence is not presented in the submission.

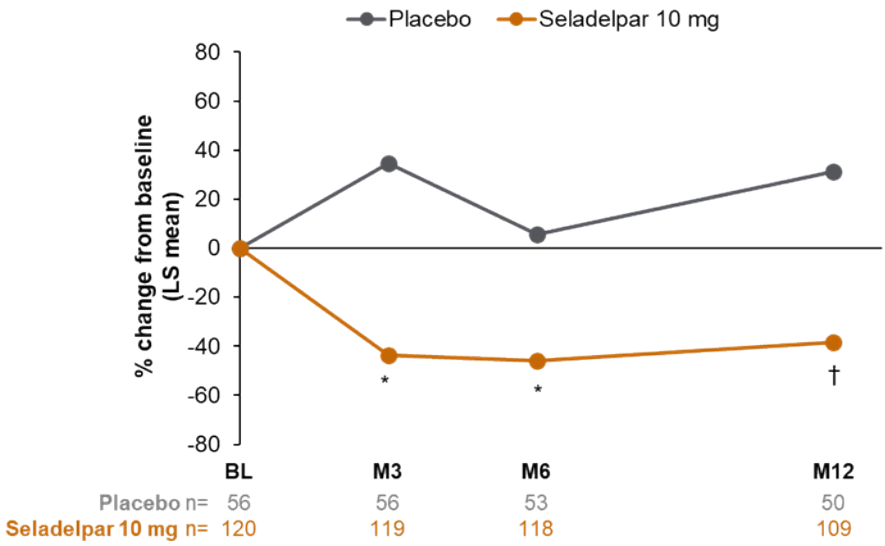
2.6.1.3.4. Change from baseline in interleukin-31 (IL-31) through Month 12

As highlighted in Section 1.2, reductions in IL-31 have been closely correlated with pruritus improvement (7, 8).

Analyses were performed to evaluate serum levels of IL-31. A total of 120 patients in the seladelpar arm and 56 patients in the placebo arm contributed a sample for IL-31 analysis on study (referred to as IL-31 analysis set). In RESPONSE, mean baseline IL-31 values were comparable between the two treatment arms (seladelpar 5.6 pg/mL and placebo 6.0 pg/mL). Decreases in IL-31 levels appeared to be greater than with placebo at Months 3, 6, and 12. Postbaseline decreases in IL-31 levels were observed in the seladelpar arm at all study timepoints, with LS mean percent changes at Months 3, 6, and 12 of -43.7%, -46.1%, and -38.5%, respectively. In contrast, serum IL-31 levels were increased in subjects receiving placebo over the course of the study with LS mean percent changes of 34.8%, 5.5%, and 31.4%, for Months 3, 6 and 12, respectively (p-values < 0.05 for the LS mean differences at all study timepoints) (5, 100).

Outcomes data in the long-term ASSURE study was not presented in the EASL Congress presentation, and hence is not presented in the submission.

Figure 22: Percent change from baseline in serum IL-31 though Month 12 (RESPONSE; IL-31 analysis set)



Key: BL, baseline; IL-31, interleukin-31; LS, least squares; M, month.
Notes: IL-31 analysis set consisted of any patient who was randomized into the study, received at least one dose of study drug, and had both baseline and postbaseline IL-31 measurements; *p<0.0001 vs placebo; †p<0.05 vs placebo.
Source: Figure 21, RESPONSE CSR (100).

2.6.1.3.5. Change from baseline in UK-PBC and GLOBE risk scores at Month 12

Two scoring systems developed by the UK-PBC Consortium (UK-PBC risk scores) and Global-PBC Study Group (GLOBE risk scores) use clinical and biochemical variables to measure the risk of progression of PBC. The UK-PBC score uses information from the UK-PBC Research Cohort to estimate the risk that a patient with PBC established on treatment with UDCA will develop liver failure within 5, 10 or 15 years from diagnosis, with higher UK-PBC scores indicating an increased risk of adverse outcomes compared to lower scores (107). Similarly, the GLOBE score is used to predict transplant-free survival of UDCA-treated patients with PBC (65).

Seladelpar treatment was associated with trends in decreased risk of clinical outcomes as evaluated by the 5-year, 10-year, and 15-year UK PBC risk scores when compared with placebo (15-year UK PBC risk score: nominal p<0.05 for all timepoints except Month 12). Based on the 15-year UK PBC risk score, a greater decrease in the estimated risk of clinical outcomes was observed in the seladelpar arm compared with the placebo arm from Month 1 through Month 12, with a HR of 0.87 (95% CI not reported) at Month 12 (Table 19) (5, 100).

Analysis of GLOBE risk scores showed a greater decrease in the risk of clinical outcomes in the seladelpar arm compared with placebo at all study timepoints evaluated (nominal p<0.0001). Based on the GLOBE risk score, a greater decrease in the estimated risk of clinical outcomes was observed in the seladelpar arm compared with placebo, with a HR of 0.68 (95% CI not reported) at Month 12 (Table 19) (5, 100).

Table 19: Estimated UK-PBC and GLOBE risk scores at baseline and Month 12 in RESPONSE (RESPONSE; ITT Analysis Set)

Measure	Placebo (n=65)	Seladelpar 10 mg (n=128)
5-year UK-PBC risk score		
Baseline, mean (SD)	0.022 (0.018)	0.023 (0.019)
Month 12, mean (SD)	0.019 (0.016)	0.018 (0.023)

HR[a] at Month 12		0.90
10-year UK-PBC risk score		
Baseline, mean (SD)	0.071 (0.056)	0.072 (0.057)
Month 12, mean (SD)	0.062 (0.050)	0.056 (0.066)
HR[a] at Month 12		0.89
15-year UK-PBC risk score		
Baseline, mean (SD)	0.125 (0.093)	0.128 (0.096)
Month 12, mean (SD)	0.111 (0.085)	0.097 (0.106)
HR[a] at Month 12		0.87
GLOBE risk score		
Baseline, mean (SD)	0.33 (0.708)	0.31 (0.660)
Month 12, mean (SD)	0.32 (0.691)	-0.08 (0.699)
HR[a] at Month 12		0.68

Key: HR, hazard ratio; ITT, intent to treat; PBC, primary biliary cholangitis; SD, standard deviation; UK, United Kingdom
Notes:
[a]95% CIs for the HRs were not reported.
Sources: Hirschfield *et al.* (2024); RESPONSE CSR (5, 100).

Outcomes data in the long-term ASSURE study was not presented in the EASL Congress presentation, and hence is not presented in the submission.

2.6.1.3.6. Change from baseline in PBC-40 QoL at each visit

HRQoL data in RESPONSE was collected using the PBC-40 QoL questionnaire. The PBC-40 QoL questionnaire is a disease-specific HRQoL tool developed to specifically measure the psychometric profile of PBC patients. The questionnaire covers 40 items across six domains relevant to PBC, with each item scored on a scale from one to five (higher scores indicating lower QoL). The six domains consist of general symptoms, itch, fatigue, emotional, social, and cognitive function. Patients are assessed using a 4-week recall period. Clinically significant itch is defined as a score of ≥7 points from a maximum of 15 points on the itch domain (108).

Overall, the LS mean change in PBC-40 QoL from baseline to Month 12 was -6.19 in the seladelpar arm versus -5.85 in the placebo arm (nominal p=0.9019) (5, 100).

Outcomes data in the long-term ASSURE study was not presented in the EASL Congress presentation, and hence is not presented in the submission.

Table 20: Change from baseline in PBC-40 QoL (RESPONSE; ITT Analysis Set)

	Placebo (n=65)		Seladelpar 10 mg (n=128)	
	Value	**CfB**	**Value**	**CfB**
Baseline for Month 12 Completers				
n	51	-	94	-
Mean, (SD)	88.3 (28.78)	-	87.4 (28.54)	-
Median	83.5	-	84.5	-
Min, Max	47, 155	-	40, 148	-
Month 12				
n	51	51	94	94
Mean, (SD)	83.7 (26.29)	-4.60 (19.03)	82.0 (28.84)	-5.36 (15.26)
Median	83.0	-2.00	76.5	-3.00
Min, Max	36, 162	-79.0, 35.0	36, 151	-54.0, 25.0
LS Mean (SE)	-	-6.19 (2.23)	-	-5.85 (1.64)
LS Mean of Difference (95% CI)	-	-	-	0.33 (-4.98, 5.64
p-value	-	-	-	0.9019

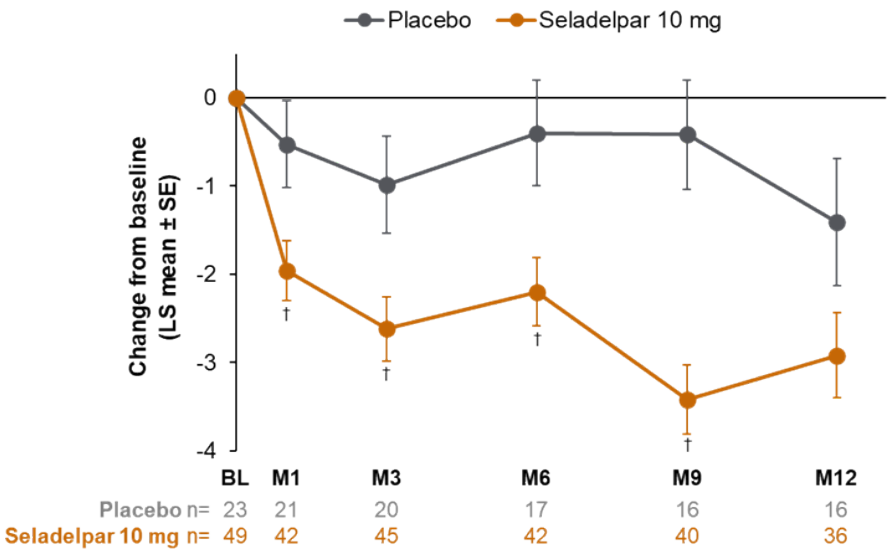
Key: CI, confidence interval; LS, least-squares; Max, maximum, Min, minimum; PBC, primary biliary cholangitis; QoL, quality of life; SE, standard error.
Source: Table 14.2.10.1.1, RESPONSE CSR (100).

2.6.1.3.7. Change from baseline in PBC-40 QoL Itch domain at each visit

Consistent with the results from the analysis of the key secondary efficacy endpoint of changes in Pruritus NRS at Month 6, LS mean changes in the Itch Domain of the PBC-40 QoL from baseline to Month 6 were 2.20 in the seladelpar arm vs 0.40 in the placebo arm (nominal p=0.0131). Notably, greater decreases in the seladelpar vs placebo arm were evident as early as Month 1. Nominal p values for the LS mean differences were <0.05 from Month 1 through Month 9 (5, 100).

Outcomes data in the long-term ASSURE study was not presented in the EASL Congress presentation, and hence is not presented in the submission.

Figure 23: Change from baseline in the Itch Domain of the PBC-40 QoL through Month 12 (RESPONSE; MSPN Analysis Set)



Key: BL, baseline; LS, least squares; M, month; MSPN, moderate-to-severe Pruritus NRS; NRS, Numerical Rating Scale; PBC, primary biliary cholangitis; QoL, quality of life; SE, standard error.
Notes: MSPN analysis set included patients with NRS score ≥4 at baseline; †p<0.05 vs placebo.
Source: Figure 15, RESPONSE CSR (100).

2.6.1.3.8. Change from baseline in 5-D Itch scale at each visit

The 5-D Itch Scale is a 5-domain questionnaire that has been validated in patients with chronic pruritus to detect changes over time. The five dimensions are degree, duration, direction, disability (impact on sleep, leisure/social, housework/errands, and work/school), and distribution, with each domain accounting for five points. The 5-D Itch score can range from five (no pruritus) to 25 (most severe pruritus) (109).

At Month 6, the LS mean change from baseline in the total score of the 5 D Itch scale was [redacted] in the seladelpar arm vs [redacted] in the placebo arm. At Month 12, the LS mean change from baseline in the total score of the 5 D Itch scale was [redacted] in the seladelpar arm vs [redacted] in the placebo arm. Greater decreases in the total score of the 5-D Itch scale in the seladelpar vs placebo arm were observed at all study timepoints (nominal p<[redacted] for the LS mean differences) (5, 100).

Outcomes data in the long-term ASSURE study was not presented in the EASL Congress presentation, and hence is not presented in the submission.

Figure 24: Change from baseline in 5-D Itch Scale total score through Month 12 (RESPONSE; MSPN Analysis Set)

Key: BL, baseline; LS, least squares; M, month; MSPN, moderate-to-severe Pruritus NRS; NRS, Numerical Rating Scale; SE, standard error.
Notes: †p<0.05 vs placebo.
Source: Figure 16, RESPONSE CSR (100).

2.6.2 CB8025-21629

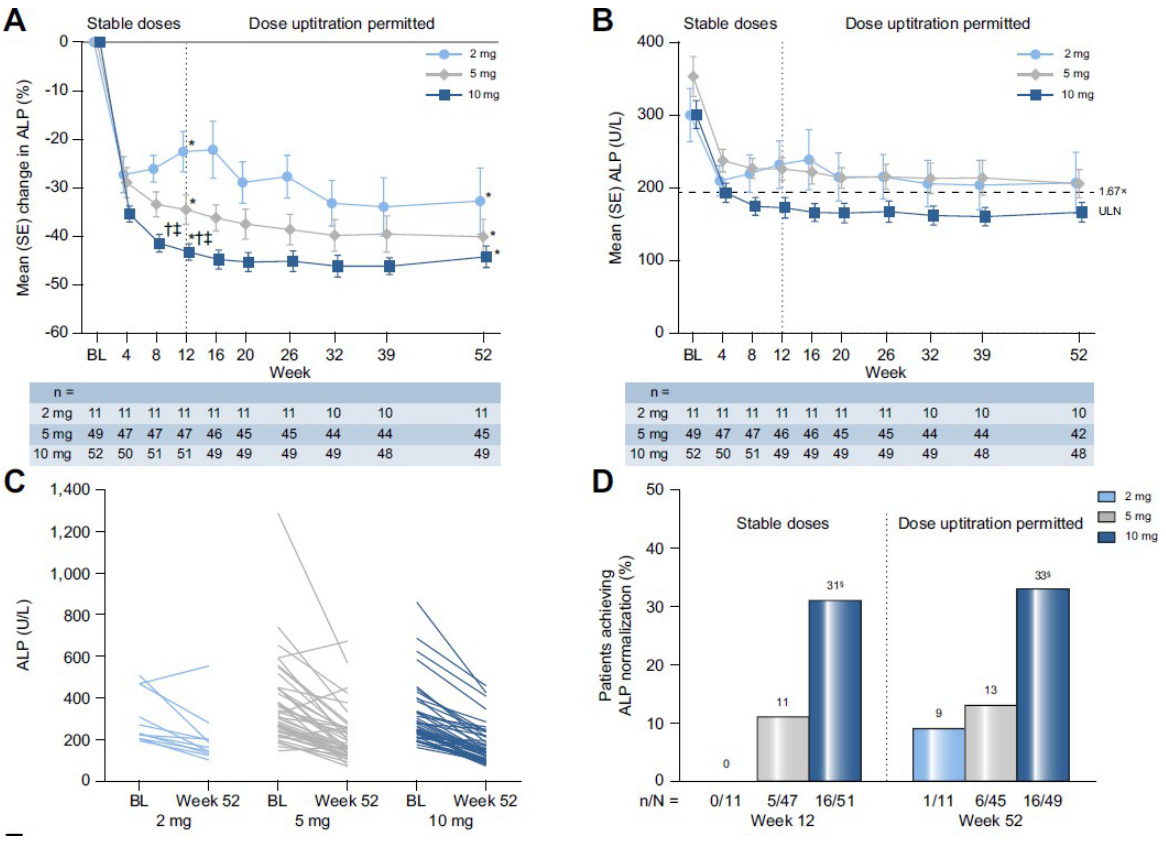
CB8025-21629 was a dose-ranging, Phase 2 study which assessed the efficacy and safety of seladelpar (2, 5, or 10 mg) in patients with PBC and inadequate response to or intolerance to UDCA. As the seladelpar marketing authorisation is for the 10 mg dose, the data for the 2 mg and 5 mg arm are not summarised herein. Efficacy data for the 2 mg and 5 mg doses are published in the Bowlus *et al.* (2022) and Mayo *et al.* (2024) publications (58, 104), as well as the CB8025-21629 CSR (103).

2.6.2.1 Results of primary outcome

At Week 8, the mean reduction in ALP from baseline in the seladelpar 10 mg arm was -41.4% (95% CI, -45.1%, -37.7%). At the end of the dose-ranging period, mean ALP levels were significantly reduced from baseline by 128 U/L (p≤0.005). Reductions were maintained or continued to decline through Week 52 (-133.8 U/L [33%]). Overall, ALP decreased from baseline in the majority of patients at Week 52 (58, 103).

Notably, ALP normalisation was observed in 31% of patients in the 10 mg cohort as early as Week 12 and was maintained at 33% through Week 52 (46,84). The durable effect of seladelpar was demonstrated in the long-term extension study, CB8025-31731, whereby 31.8% of rollover patients (7 of 22 patients) demonstrated ALP normalisation after 24 months of treatment (104).

Figure 25: Effect of seladelpar on ALP through Week 52 (CB8025-21629; mITT Analysis Set)



Key: ALP, alkaline phosphatase; ANCOVA, analysis of covariance; BL, baseline; LOCF, last observation carried forward; LS, least squares; ULN, upper limit of normal.
Notes: (A) Mean percent change in ALP from BL (imputed using LOCF). (B) Mean absolute ALP values (observed). (C) Change in ALP from BL in individual patients (observed). (D) Proportion of patients achieving ALP normalisation (imputed using LOCF).
*p≤0.02 vs. BL (paired t test); †p <−0.01 vs. 2 mg cohort (ANCOVA test of LS means)
‡p≤0.02 vs. 5 mg cohort (ANCOVA test of LS means)
§p≤0.03 vs. 5 mg cohort (Fisher's exact test).
Sources: Bowlus et al (2022); CB8025-21629 CSR (58, 103)

2.6.2.2 Results of relevant secondary outcomes

2.6.2.2.1. Composite biochemical response

At Weeks 12 and 52, the composite biochemical response endpoint was achieved by 67% of the seladelpar 10 mg treatment arm at both timepoints (58, 103). Table 21 highlights the response rates for the different components of the composite biochemical endpoint in CB8025-21629.

The durable effect of seladelpar was demonstrated in the long-term extension CB8025-31731 study, whereby 72.7% (16 of 22 patients) achieved a composite endpoint response (104).

Table 21: Summary of composite biochemical endpoint by visit (CB8025-21629; mITT Analysis Set)

	Seladelpar 10 mg[a] (n=52)
Patients who achieved composite biochemical response at Week 12, n (%)	34 (66.7)
Response category at Week 12	
ALP <1.67× ULN, n (%)	40 (78.4)
≥15% decrease in ALP, n (%)	49 (96.1)
Total bilirubin ≤1.0x ULN, n (%)	42 (82.4)
Patients who achieved composite biochemical response at Week 52, n (%)	33 (67.3)
Response category at Week 52	
ALP <1.67× ULN, n (%)	35 (71.4)
≥15% decrease in ALP, n (%)	47 (95.9)
Total bilirubin ≤1.0x ULN, n (%)	45 (91.8)

Key: ALP, alkaline phosphatase; mITT, modified intent-to-treat; n, number in category; ULN, upper limit of normal.
Notes: [a]The analysis was based on the initial dose; patients were enrolled to 2 mg or randomised to 5 mg or 10 mg. Beginning at the Week 12 visit, patients may have had their initial dose titrated up or down.
Sources: Bowlus et al (2022); Table 13, CB8025-21629 CSR (58, 103).

2.6.2.2.2. Absolute and relative changes in markers of liver biochemistry

2.6.2.2.2.1. Total bilirubin

Mean baseline total bilirubin levels were within the normal range (ULN = 1.1 mg/dL) for the seladelpar 10 mg cohort. At 12- and 52-weeks post-baseline, mean and median percent

changes in total bilirubin levels indicate that total bilirubin remain stable. At Week 52, the mean (SD) percent change at Week 52 was -7.03% (22.3%); corresponding to a relative change from baseline of -0.068 (0.190) mg/dL (58, 103).

2.6.2.2.2.2. GGT

Patients treated with seladelpar 10 mg experienced a decrease in GGT after 12 and 52 weeks of treatment. At 12 weeks, the mean percent change in GGT was -34.3% (49 of 52 patients, 95% CI: -40.6%, -27.9%). The pattern for decline in GGT persisted to 52 weeks, where a 32.5% decrease in GGT was observed (48 of 52 patients, -41.2%, 23.7%), corresponding to a mean change from baseline of -88.1 U/L (58, 103).

2.6.2.2.2.3. ALT

Seladelpar 10 mg reduced ALT, indicating a strong hepatoprotective effect in the liver parenchyma. A decrease in mean ALT is evident within 12 weeks (-21.7%; 49 of 52 patients, 95% CI: -33.1%, -10.24, and persists to Week 52 (-31.3%; 48 of 52 patients, 95% CI: -37.8%, -24.9%). These values correspond to changes in observed results of -10.9 U/L at Week 12 and -15.3 U/L at Week 52 (58, 103).

2.6.2.2.2.4. AST

Patients treated with seladelpar 10 mg experienced a decrease in AST after 12 and 52 weeks of treatment. Mean percent changes in AST decreased at both the Week 12 (-9.35%; 49 of 52 patients, 95% CI: -15.3%, -3.4%) and Week 52 (-14.0%; 48 of 52 patients, 95% CI: -19.7%, -8.3%) visits. These values correspond to mean changes in absolute values of -3.35 U/L at Week 12 and -6.14 U/L at Week 52 (58, 103).

2.6.2.2.2.5. 5’-nucleotidase

Patients treated with seladelpar 10 mg experienced a decrease in 5’nucleotidase after 12 and 52 weeks of treatment. Mean percent changes in 5’nucelotidase decreased at both the Week 12 (-26.02%; 49 of 52 patients, 95% CI: -32.08%, -19.96%) and Week 52 (-22.77%; 48 of 52 patients, 95% CI: -29.76%, -15.78%) visits (103).

2.6.2.2.3. Effects of seladelpar on GLOBE score

The GLOBE score had a pattern of improvement with mean changes of -0.292, and -0.346 at Week 12 and -0.271, and -0.404 at Week 52 for the 5, and 10 mg dose groups, respectively (58, 103).

2.6.2.2.4. Effects of seladelpar on UK-PBC score

A decrease in UK-PBC 5- and 10-year risk scores compared to baseline is demonstrated for all treatment groups at 12 and 52 weeks. Mean risk scores at 15 years demonstrated similar decreases at 12 and 52 weeks (58, 103).

Table 22: UK-PBC Score Baseline Values and Percent Change from Baseline (CB8025-21629; mITT Analysis Set)

	Seladelpar 10 mg[a] (n=52)
Week 1: UK-PBC Score 5 Years	
N	46
Mean	2.0774
SD, SE	1.9391, 0.2859
Min, Max	0.119, 8.999
Week 1: UK-PBC Score 10 Years	
N	46
Mean	6.6487
SD, SE	5.9368, 0.8753
Min, Max	0.397, 27.072
Week 12: UK-PBC Score 5 Years	
N	48
Mean	1.8124
SD, SE	1.7267, 0.2492
Min, Max	0.135, 8.229
Week 12: UK-PBC Score 10 Years	
N	48
Mean	5.8293
SD, SE	5.3605, 0.7737
Min, Max	0.452, 24.988
Week 52: UK-PBC Score 5 Years	
N	47
Mean	1.7244
SD, SE	1.6121, 0.2351
Min, Max	0.058, 7.999
Week 52: UK-PBC Score 10 Years	
N	47
Mean	5.5607

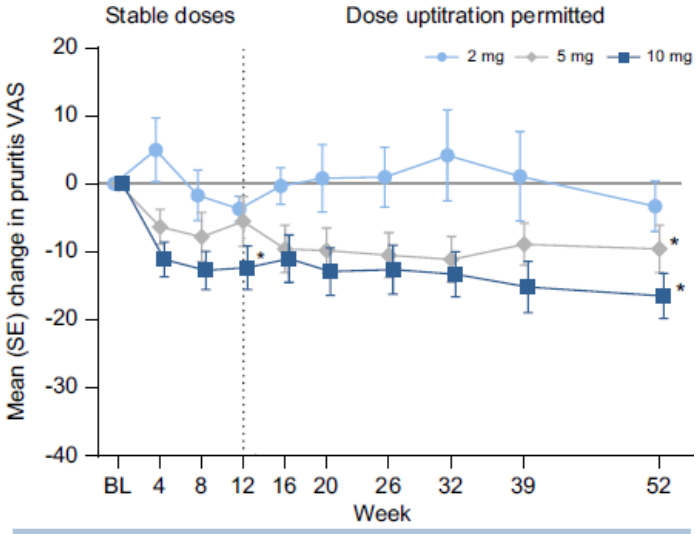
SD, SE	5.0092, 0.7307
Min, Max	0.196, 24.355

Key: ALP, alkaline phosphatase; ALT, alanine aminotransferase; AST, aspartate aminotransferase; BIL, total bilirubin; CI, confidence interval; LN, natural log; max, maximum; min, minimum; mITT, modified intent-to-treat; n, number in category; N, number in treatment group; SD, standard deviation; SE, standard error; TA, transaminases; UK-PBC, United Kingdom – Primary Biliary Cirrhosis score; ULN, upper limit of normal.
Notes:
[a]Analysis is based on initial dose (patients were enrolled to 2 mg or randomised to 5 mg or 10 mg). Beginning at the Week 12 visit, the initial dose could have been up- or down-titrated.
No imputation for missing data was used for this table. Note: Table presents UK-PBC risk score = 100× (1- 0.982 exp(0.0287854× (ALP / ULN-1.722136304) - 0.0422873× ((((TA / ULN)/10)ULN)/10)1) - 8.675729006) + 1.4199× (LN((BIL / ULN) /10)+2.709607778) -1.960303× (Albumin / LLN-1.17673001) - 0.4161954× (Platelet / LLN-1.873564875))). Baseline survivor function will take values of 0.982, 941, and 0.893 for 5 years, 10 years, and 15 years respectively.
ALP, TA, and BIL refers to the AP, transaminases (refers to the ALT, where available, otherwise the AST), and total bilirubin assessments, respectively, at the visit being reported. Albumin and platelet represent their baseline assessment.
Source: Table 33, CB8025-21629 CSR (103).

2.6.2.2.5. Pruritus VAS

Patients with PBC had a wide range of baseline pruritus severity as measured by pruritus VAS. At baseline, the seladelpar 10 mg group reported a medium VAS score of 25.0 mm. Mean pruritus VAS scores decreased by 12.3 mm from baseline at Week 12. At Week 52, mean VAS scores decreased further from baseline by 16.5 mm (58, 103).

Figure 26: Effect of seladelpar on pruritus VAS through Week 52 (CB8025-21629; mITT Analysis Set)



n =										
2 mg	11	11	11	11	11	10	11	10	10	10
5 mg	48	46	45	45	45	45	44	42	43	42
10 mg	52	49	49	49	49	49	49	49	48	48

Key: BL, baseline; mITT, modified intention-to-treat; VAS, visual analogue score.
Notes: 0 = no itch, 100 = worst itch imaginable. *Nominal p ≤0.009 vs. BL (paired t test).

Source: Bowlus *et al.* (2022); CB8025-21629 CSR (58, 103)

2.6.2.2.6. 5-D Itch Scale

Seladelpar treatment was associated with mean reductions in the 5-D Itch scale at Weeks 12 and 52. After 12 weeks of treatment, the 5-D Itch scale total score declined by [redacted] points ([redacted] of 52 patients, 95% CI: [redacted]). At Week 52, patients treated with seladelpar 10 mg reduced the 5-D Itch scale total score by [redacted] points ([redacted] of 52 patients, 95% CI: [redacted]) (58, 103).

2.6.2.2.7. PBC-40 QoL

The PBC-40 QoL tool has been described previously in Section 2.6.1.3.6.

2.6.2.2.7.1. Itch Domain Measure

A consistent pattern of improvement in itch as measured by the PBC-40 QoL questionnaire was observed in 10 mg dose group through Week 52. Seladelpar treatment was associated with mean changes in the PBC-40 QoL Itch domain measure at Week 52 of [redacted] in the 10 mg dose group. Changes in proportions of patients responses on the PBC-40 QoL Itch domain (3 questions) after 52 weeks of seladelpar treatment are presented below in Figure 25. (103)

Figure 27: Changes in proportion of patient's responses on PBC-40 QoL Itch domain after one year of seladelpar treatment (mITT Analysis Set)

Key: BL, baseline; mITT, modified intent-to-treat; PBC, primary biliary cholangitis; Q, question, QoL, quality of life; yr, year.
Source: Figure 17, CB8025-21629 CSR (84).

2.6.2.2.7.2. Fatigue Domain Measure

Seladelpar treatment was associated with a mean change in PBC-40 QoL Fatigue domain of [redacted] in seladelpar 10 mg cohort at 52 weeks. Similar to the results in the itch domain, a consistent pattern of improvement in the fatigue domain was noted (58, 103).

2.6.3 Summary of results

The efficacy and safety of seladelpar for the treatment of seladelpar for the treatment of PBC has been evaluated in the RESPONSE and CB8025-21629 clinical studies.

RESPONSE was a double-blind, placebo-controlled, randomised Phase 3 study to evaluate the efficacy of seladelpar in patients with PBC and an inadequate response to or an intolerance to UDCA.

Overall, seladelpar was effective for the treatment of PBC as demonstrated by a statistically significantly higher percentage of patients achieving the composite biochemical response endpoint with seladelpar vs placebo, reflecting improvement in cholestatic markers associated with clinical outcomes. A statistically significantly higher percentage of patients achieving ALP normalisation, an increasingly recognised treatment goal for PBC, was observed in the seladelpar vs placebo arm.

In addition, a statistically significant decrease in pruritus at Month 6 from baseline, measured with the Pruritus NRS, was observed following treatment with seladelpar vs placebo in patients with moderate-to-severe pruritus at baseline; this effect was observed as early as Month 1 and was also evident from Month 6 through Month 12. Results from the PBC-40 QoL Itch Domain and 5 D Itch scale total score, corroborated with the findings obtained from the Pruritus NRS, illustrating an overall clinically meaningful improvement of pruritus in patients treated with seladelpar across a wide range of assessments. Treatment with seladelpar also led to greater reductions in key liver markers, as well as biomarkers related to pruritus, compared with placebo.

Interim results from the ASSURE long-term extension study of seladelpar demonstrated improvements in and durable effect on markers of cholestasis and liver injury that were maintained for up to two years in RESPONSE rollover patients These results are consistent with the pooled analyses presented at The Liver Meeting Congress by Lawitz *et al.* (2024), whereby

81% of patients (30 of 37 patients) achieved a composite biochemical response and 41% (15 of 37 patients) achieved normalisation of ALP levels (101). Patients with baseline NRS ≥4 from the RESPONSE rollover groups also demonstrated a sustained reduction in pruritus through two years.

The results observed in RESPONSE are consistent with those reported in the supporting CB8025-21629 study, a Phase 2, randomised, open-label, 52-week study of seladepar in patients with PBC with an inadequate response or intolerance to UDCA.

In CB8025-21629, evidence of seladelpar's efficacy, safety, and improvement in patient-reported pruritus was substantial and durable. Significant reductions in mean ALP levels were observed after three months of treatment with seladelpar 10 mg, with a 43% reduction from baseline and normalisation of ALP in 31% of patients. ALP reductions, an evidence-based surrogate for long-term transplant-free outcomes, were maintained through 52 weeks. The clinically significant and durable effects of the seladelpar 10 mg dose on ALP levels, the composite biochemical response endpoint, and ALP normalisation strongly supports the improvement in cholestatic markers associated with clinical outcomes.

In summary, treatment with seladelpar has been observed to have positive impacts on ALP and bilirubin levels, both of which have been established as predictors of clinical benefit. Seladelpar, also addresses the burden of pruritus in patients with PBC; no approved treatments for PBC improve pruritus as measured by the NRS. Hence, seladelpar fulfils an unmet medical need as an efficacious and well tolerated treatment in patients with PBC who have experienced an inadequate response or intolerance to UDCA.

2.7 Subsequent treatments used in the relevant studies

Not applicable.

2.8 Subgroup analysis

Pre-planned subgroup analyses based on baseline disease covariates were prespecified and conducted for the primary and key secondary endpoints. These subgroups were explored to better characterise patient populations for whom seladelpar may provide the most benefit (4,82). The subgroups analysed were as follows: age categories (age at screening: < 65, ≥ 65 years;

age at PBC diagnosis: < 50, ≥ 50 years), Sex (Female, Male), Race (White, Black, Asian, Other), Region (North America, Europe, Rest of World), Baseline ALP (< 350 U/L, ≥ 350 U/L), Total bilirubin (< 0.6× ULN, ≥ 0.6× ULN), Pruritus NRS (< 4, ≥ 4), UDCA use vs UDCA intolerance, Prior use of OCA and/or fibrates (yes, no), Cirrhosis (yes, no), and Total bilirubin (≤ 1 × ULN, > 1× ULN)

A summary of the subgroup analyses for the primary and key secondary endpoints are provided below, with descriptive results for the subgroups specified in the decision problem, namely Pruritus NRS, UCDA use vs UDCA intolerance, and prior use of OCA/fibrates, presented in Appendix C.

2.8.1 Results of subgroup analyses of primary outcome

The effect of seladelpar on the primary efficacy endpoint was observed to be similar across subgroups. One exception to this was in the subgroup of patients with baseline ALP ≥350 U/L, in which the proportion of responders in the seladelpar arm was lower compared with that in patients with baseline ALP <350 U/L (22.9% vs 76.3%, respectively). This finding was not unexpected as greater reductions in ALP levels are required to achieve the ALP <1.67x ULN component of the composite biochemical response endpoint for patients with elevated ALP values at baseline. Furthermore, despite small group sizes, a higher percentage of patients who received seladelpar monotherapy achieved the primary efficacy endpoint compared with those who received placebo (5, 100). A forest plot of the composite biochemical endpoint response rate at Month 12 by subgroup is presented in Appendix C.

2.8.2 Results of subgroup analyses of key secondary outcomes

2.8.2.1 ALP normalisation at Month 12

The effect of seladelpar on the key secondary efficacy endpoint of ALP normalisation at month 12 was observed to be similar across subgroups. One exception to this was in the subgroup of patients with baseline ALP ≥350 U/L, in which no patients achieved ALP normalisation. This finding was not unexpected considering that the number of patients in this subgroup was small, and that patients with markedly elevated ALP values at baseline require greater reductions in ALP levels to achieve normalisation. Furthermore, despite small group sizes, a higher

percentage of patients who received seladelpar monotherapy achieved ALP normalisation compared with those who received placebo (25% vs 0%, respectively) (5, 100). A forest plot of the ALP normalisation endpoint response rate at Month 12 by subgroup is presented in Appendix C.

2.8.2.2 Change from baseline in mean Pruritus NRS score at Month 6

The effect of seladelpar on the key secondary efficacy endpoint of ALP normalisation at month 12 was observed to be similar across subgroups. However, in many of these subgroups the sample sizes were small (5, 100). A forest plot of the change from baseline in mean pruritus NRS score response rate at Month 6 by subgroup is presented in Appendix C.

2.9 Meta-analysis

There was only one relevant Phase 3 trial providing data for the efficacy of seladelpar in PBC at 52 weeks, therefore a meta-analysis was not conducted.

Due to the absence of direct head-to-head data comparing the efficacy of seladelpar, elafibranor, and OCA, an indirect treatment comparison (ITC) was necessary (110). To achieve this objective, an SLR was conducted to identify randomised controlled trials evaluating the relevant treatments in PBC. A total of five studies, conducted globally, assessing the three approved treatments (OCA, elafibranor, and seladelpar) were included in the feasibility assessment and ITC (Table 23) (110). For methods and results of the SLR, please refer to Appendix B1.1.

Table 23: Study characteristics of the included evidence in the ITC

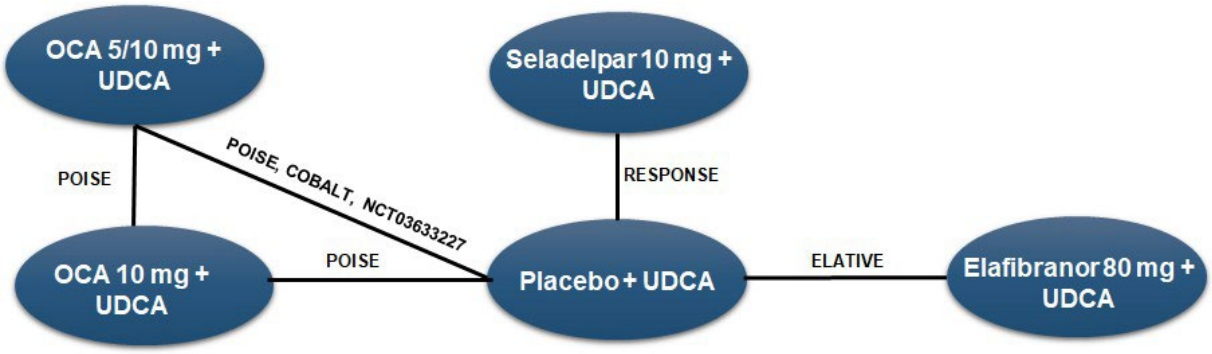
Study Characteristics	Phase	Treatment Duration (months)	Intervention	Comparator
RESPONSE	3	12	SEL 10 mg + UDCA	UDCA
ELATIVE	3	12	ELA 80 mg + UDCA	UDCA
POISE	3	12	OCA 5 mg/10 mg + UDCA	OCA 10 mg + UDCA; UDCA
NCT03633227	4	12	OCA 5 mg/10 mg + UDCA	UDCA
COBALT	4	84*	OCA 5 mg/10 mg + UDCA	UDCA

Key: ELA, elafibranor; OCA, obeticholic Acid; SEL, seladelpar; UDCA, ursodeoxycholic acid
Notes: *Approximately 7 years.
Source: Data on File – Seladelpar ITC Report (110)

2.9.1 Feasibility assessment

A feasibility assessment study for indirect comparisons of seladelpar versus other approved treatments (UDCA, OCA, and elafibranor) was conducted and conclusions are provided in a separate report (111). Figure 28 depicts the network diagram for the approved treatments at 12 months.

Figure 28: Network diagram of the approved interventions at 12 months



Key: ELA, elafibranor; OCA, obeticholic acid; SEL, seladelpar, UDCA, ursodeoxycholic acid.
Source: Data on File – Seladelpar ITC Report (110)

The feasibility assessment evaluated the suitability of the identified trials for inclusion and determined the most appropriate methodology for conducting the ITC. Five assessing the efficacy and safety of seladelpar, elafibranor, and OCA over a 52-week period were selected for feasibility assessment and inclusion in the ITC. Among the five studies, three studies assessed OCA versus placebo (POISE, NCT03633227, and COBALT), while one study each assessed seladelpar (RESPONSE) and elafibranor (ELATIVE) versus placebo (110).

Among the five studies, four were published in peer-reviewed journals (RESPONSE, ELATIVE, POISE, and COBALT), while one (NCT03633227) was unpublished clinical trial. All studies employed a double-blind design and were conducted globally. Three of the studies (RESPONSE, ELATIVE, and POISE) were Phase 3 trials, while COBALT and NCT03633227 were Phase 4 studies. The sample sizes varied across studies, ranging from 22 patients in NCT03633227 to 334 patients in COBALT. The treatment duration was 12 months for all studies except COBALT, which extended to 84 months. ELATIVE, POISE, and RESPONSE were the most comprehensive studies, covering a wide range of efficacy, safety, and quality-of-life

outcomes. COBALT and NCT03633227 provided limited efficacy data. All the included studies were assessed for risk of bias based on the ROB2.0 checklist (110).

To evaluate homogeneity between trials, key factors were assessed, including trial design, study type, interventions of interest, comparators, patient characteristics (including effect modifiers), and outcome measures along with their definitions. The key effect modifiers for PBC (TA1016) include age at diagnosis, baseline ALP and bilirubin levels, cirrhosis status, and ANA positivity, though the latter was not reported in any of the studies (110).

The feasibility assessment indicated that the RESPONSE and ELATIVE trials exhibited notable differences in key effect modifiers, including baseline bilirubin levels and the proportion of patients with cirrhosis. Further, within the ELATIVE trial, the proportion of patients with cirrhosis was notably lower in the elafibranor group (8.3%) compared to the placebo group (13.2%). Whereas the RESPONSE and POISE trials were found to be sufficiently homogeneous in terms of trial and patient characteristics especially effect modifiers (110).

Additionally, the RESPONSE and ELATIVE trials differed significantly in ALP and bilirubin ULN cut-offs, with RESPONSE using uniform thresholds of 116 IU/L for ALP and 18.8 µmol/L for bilirubin, while ELATIVE applied gender-specific cut-offs (ALP: 104 IU/L for females and 129 IU/L for males; bilirubin: 20.5 µmol/L). RESPONSE and POISE trials also used different ULN cut-offs (ALP: 118 IU/L for females and 124 IU/L for males; bilirubin: 19.32 µmol/L for females and 25.48 µmol/L for males). These differences necessitated the recalculations of key efficacy outcomes involving ALP or bilirubin ULN, such as composite response, ALP normalisation, and ALP response based on the Toronto I criteria (110).

Further, the placebo effect sizes varied significantly regarding composite response outcome, with the ELATIVE trial's placebo arm showing the lowest composite response rate (3.8%) compared to the rate observed in other large phase 3 trials (9.6% to 20%) using the same composite response definition, complicating ITC for composite outcome (110).

The observed heterogeneity in effect modifiers and trial designs suggested a potential violation of the transitivity assumption between RESPONSE and ELATIVE, rendering conventional unadjusted methods unsuitable. According to NICE Technical Support Document (TSD) 18,

networks with only one or two trials per treatment are particularly susceptible to systematic variation (bias) due to imbalances in the distribution of effect modifiers, underscoring the importance of robust adjustment methods like MAIC in such scenarios. Hence, an anchored MAIC was performed to compare seladelpar 10 mg and elafibranor 80 mg using RESPONSE and ELATIVE trials. In addition, Bayesian NMA was performed as sensitivity analysis (110)..

Seladelpar 10 mg and OCA 5-10 and OCA 10 mg were compared using Bayesian NMA (random effects model) using RESPONSE and POISE trials. In addition, anchored MAIC was performed as sensitivity analysis (110).

A feasibility assessment and statistical analysis plan was developed to present the data to be used in the ITCs along with the methodology.

2.9.2 Outcomes selected for the analyses

The key outcomes assessed in this NMA are summarised below in Table 24.

Table 24: List of outcomes evaluated in the NMA and their data availability at 12 months

Outcome	Type of data or distribution	ELATIVE	POISE	RESPONSE	COBALT	NCT03633227
Efficacy outcomes						
Composite outcome	Binomial	✓	✓	✓	×	×
ALP ≤ 1.0× ULN	Binomial	✓	✓	✓	×	×
Toronto I	Binomial	✓	✓	✓	×	×
ALP CFB at 12 months	Continuous	✓	✓	✓	✓	×
Safety outcomes						
Pruritus (any grade)	Binomial	✓	✓	✓	×	✓
All-cause discontinuations	Binomial	✓	✓	✓	×	✓
Quality-of-life						
PBC-40 Itch (Overall population)	Binomial	×	✓	✓	×	×
5D-Itch CFB (Overall population)	Continuous	×	✓	✓	×	×
5D-Itch CFB (NRS≥4)	Continuous	✓	×	✓	×	×
PBC-40 Itch (NRS≥4)	Continuous	✓	×	✓	×	×
NRS Itch (NRS≥4)	Continuous	✓	×	✓	×	×

Key: ALP, alkaline phosphatase; CFB, change from baseline; LFT, liver function test; NRS, numerical rating scale; PBC, primary biliary cholangitis; T.Bil: total bilirubin.
Source: Data on File – Seladelpar ITC Report (110)

2.9.3 Results

The results for the comparison of seladelpar 10 mg and OCA (5-10 and 10 mg) using Bayesian NMA are presented below. The results for comparison of seladelpar 10 mg and elafibranor 80 mg using MAIC methodology are presented in Section 2.10.

The results of the Bayesian NMA for the efficacy outcomes utilised in the economic model are presented below. Note that the results of the comparison between seladelpar 10 mg and UDCA monotherapy are not presented in the company submission; as described in Table 1, UDCA is not considered to be a relevant comparator given the different positionings of seladelpar 10 mg and UDCA monotherapy in the PBC treatment paradigm. The results of the comparison versus UDCA can be found in the accompanying seladelpar ITC report, alongside the results for the remaining efficacy outcomes outlined in Table 24 (110).

2.9.3.1 Composite response at 12 months

At 12 months, the biochemical response rate was comparable between OCA 5-10 mg + UDCA and OCA 10 mg + UDCA using Bayesian NMA (Table 25). The statistical significance could not be established due to the wider CIs (110).

Table 25: Bayesian NMA results for composite outcomes (SEL 10 mg vs. OCA)

SEL 10 mg + UDCA vs.	RR (95% CrI), Turner prior
OCA 5-10 mg + UDCA	[redacted]
OCA 10 mg + UDCA	[redacted]

Key: CrI, credible interval; NMA, network meta-analysis; OCA, obeticholic acid; RR, risk ratio; SEL, seladelpar; UDCA, ursodeoxycholic acid
Source: Data on File – Seladelpar ITC Report (110)

2.9.3.2 ALP normalisation (≤1 ULN) at 12 months

Seladelpar 10 mg combined with UDCA exhibited numerically higher, but statistically non-significant ALP normalisation rates compared to OCA 5-10 mg + UDCA and OCA 10 mg + UDCA (Table 26) (110).

Table 26: Bayesian NMA results for ALP normalisation (SEL 10 mg vs. OCA)

SEL 10 mg + UDCA vs.	RR (95% CrI), Turner prior

OCA 5-10 mg + UDCA	[redacted]
OCA 10 mg + UDCA	[redacted]

Key: ALP, alkaline phosphatase; CrI, credible interval; NMA, network meta-analysis; OCA, obeticholic acid; RR, risk ratio; SEL, seladelpar; UDCA, ursodeoxycholic acid
Source: Data on File – Seladelpar ITC Report (110)

2.9.3.3 ALP responders (Toronto I: ALP ≤1.67 × ULN) at 12 months

Seladelpar 10 mg combined with UDCA was numerically better than OCA 5-10 mg + UDCA after 12 months, and comparable with OCA 10 mg + UDCA without attaining statistical significance (Table 27) (110).

Table 27: Bayesian NMA results for ALP responders (Toronto I) (SEL 10 mg vs. OCA)

SEL 10 mg + UDCA vs.	RR (95% CrI), Turner prior
OCA 5-10 mg + UDCA	[redacted]
OCA 10 mg + UDCA	[redacted]

Key: ALP, alkaline phosphatase; CrI, credible interval; NMA, network meta-analysis; OCA, obeticholic acid; RR, risk ratio; SEL, seladelpar; UDCA, ursodeoxycholic acid
Source: Data on File – Seladelpar ITC Report (110)

2.9.3.4 Pruritus

Treatment with seladelpar 10 mg was associated with statistically significant lower odds of developing pruritus at 12 months compared to OCA 5-10 mg and OCA 10 mg. Furthermore, lower odds were also observed in comparison with elafibranor 80 mg however, the wide CrI precluded statistical significance (Table 28) (110).

Table 28: Bayesian NMA results for the development of pruritus at 12 months

SEL 10 mg + UDCA vs.	OR (95% CrI), Turner prior
ELA 80 mg + UDCA	[redacted]
OCA 5-10 mg + UDCA	[redacted]
OCA 10 mg + UDCA	[redacted]

Key: CrI, credible interval; ELA, elafibranor; NMA, network meta-analysis; OCA, obeticholic acid; OR, odds ratio; SEL, seladelpar; UDCA, ursodeoxycholic acid
Source: Data on File – Seladelpar ITC Report (110)

2.10 Indirect and mixed treatment comparisons

As detailed above in Section 2.9, an anchored MAIC was performed to compare seladelpar and elafibranor using a placebo (UDCA) as a common comparator. It should be noted that the placebo behaviour was very different (low) in ELATIVE compared to RESPONSE, POISE, and other trials. The relative treatment effect calculated from each trial is the basis for indirect comparison in conventional and population-adjusted methods like anchored MAIC. Hence, the relative treatment effect from ELATIVE was deemed non-reliable to form the base for indirect comparison for the composite biochemical response outcome. The unanchored MAIC was identified as a potential solution for this limitation but is itself associated with uncertainties. As per the expert guidance, anchored MAIC was considered in the base case for all outcomes, while unanchored MAIC was considered in the sensitivity analysis for the composite biochemical response outcome. Bayesian NMA was also performed as sensitivity analysis (110).

2.10.1 Results of the MAIC

The results of the MAIC for the efficacy outcomes utilised in the economic model are presented below. For reasons described previously, the results of the comparison between seladelpar 10 mg and UDCA monotherapy are not presented in the company submission, and can instead be found in the accompanying seladelpar ITC report alongside results for the remaining efficacy outcomes outlined in Table 24 (110).

2.10.1.1 ALP normalisation (≤1 ULN) at 12 months

Due to the zero events in the placebo arms of the RESPONSE and ELATIVE trials, Stata software (used for analysis) automatically applied a continuity correction of 0.5 to each arm. This adjustment ensured that effect estimates could be accurately generated, particularly when handling instances where zero counts were present (110).

At 12 months, a statistically significant increase in ALP normalisation rate was observed with seladelpar 10 mg compared to UDCA, however, no statistical difference was reported between elafibranor 80 mg and seladelpar 10 mg using anchored MAIC adjusted for all four effect modifiers i.e. cirrhosis, age, ALP, and total bilirubin (Figure 29). Directionally, seladelpar appeared better than elafibranor, suggesting a trend toward improved outcomes with seladelpar. Further, in the sensitivity analysis, similar findings were reported after adjusting for two effect

modifiers i.e. cirrhosis and total bilirubin. For results of the sensitivity analysis, please refer to the accompanying seladelpar ITC report (110).

Figure 29: Forest plot depicting base case anchored MAIC results for ALP normalisation (SEL 10 mg vs. ELA 80 mg) at 12 months

Key: ALP, alkaline phosphatase; CI, confidence interval; ELA, elafibranor; ESS, effective sample size; MAIC, matching-adjusted indirect comparison; RR, risk ratio; SEL, seladelpar.
Source: Data on File – Seladelpar ITC Report (110)

Of note, a sensitivity analysis was also performed using OR model outputs. Further, a sensitivity analysis was also performed by conducting Bayesian NMA with and without outcome recalculations.

The results of the sensitivity analysis are aligned with the base-case results i.e., no statistical difference was reported between elafibranor 80 mg and seladelpar 10 mg (110).

2.10.1.2 Composite response (ALP < 1.67×ULN. ≥15% ALP decrease from baseline, and TB ≤ 1.0× ULN) at 12 months

At 12 months, no evidence of significant difference was reported between seladelpar 10 mg + UDCA and elafibranor 80 mg using anchored MAIC adjusted for four effect modifiers i.e. cirrhosis, age, ALP, and total bilirubin. Directionally, elafibranor appeared better than seladelpar, suggesting a trend toward improved outcomes with elafibranor. However, the wide confidence interval ( ) indicates that these results were not statistically significant (Figure 30). Similar findings were reported using anchored MAIC after adjusting for two effect modifiers. Further, results numerically favoured seladelpar using unanchored MAIC for seladelpar vs elafibranor after adjusting for both two and four effect modifiers. For the results of the sensitivity analysis, please refer to the accompanying seladelpar ITC report (110).

Figure 30: Base case anchored MAIC results (adjusted for 4 effect modifiers) for composite response (SEL 10 mg vs. ELA 80 mg) at 12 months

Key: CI, confidence interval; ELA, elafibranor; ESS, effective sample size; MAIC, matching-adjusted indirect comparison; RR, risk ratio; SEL, seladelpar; UDCA, ursodeoxycholic acid.
Source: Data on File – Seladelpar ITC Report (110)

2.10.1.3 ALP responders (Toronto I: ALP ≤1.67 × ULN) at 12 months

At 12 months, no statistical difference in ALP response rate as per Toronto I criteria was reported between seladelpar 10 mg + UDCA and elafibranor 80 mg using anchored MAIC adjusted for four effect modifiers i.e. cirrhosis, age, ALP, and total bilirubin (Figure 31). Similar findings were reported in the sensitivity analysis of anchored MAIC after adjusting for two heterogenous effect modifiers i.e. cirrhosis and total bilirubin. For the results of the sensitivity analysis, please refer to the accompanying seladelpar ITC report (110).

Figure 31: Forest plot depicting base case anchored MAIC results for ALP responders as per Toronto I criteria (SEL 10 mg vs. ELA 80 mg) at 12 months

Key: ALP, alkaline phosphatase; CI, confidence interval; ELA, elafibranor; ESS, effective sample size; MAIC, matching-adjusted indirect comparison; RR, risk ratio; SEL, seladelpar; UDCA, ursodeoxycholic acid.
Source: Data on File – Seladelpar ITC Report (110)

2.10.2 Conclusions

Seladelpar demonstrated favourable results across most efficacy outcomes, QoL measures (particularly pruritus scales), and safety outcomes, when compared to elafibranor. While statistical significance was not achieved for most outcomes, likely due to the limited number of studies available for comparison, seladelpar's profile remains compelling. Beyond its comparable or numerically better efficacy, seladelpar stands out in addressing patient-centric outcomes, such as improvements in pruritus and a lower incidence of infections, which are crucial for HRQoL. These benefits likely contributed to a lower dropout rate observed with seladelpar compared to elafibranor, further highlighting its potential as a more tolerable and patient-friendly treatment option. Similar findings were also reported in the comparison between seladelpar and OCA, where seladelpar demonstrated favourable results across most efficacy outcomes, HRQoL measures, and safety outcomes including significantly lower rates of pruritus (110).

2.10.2.1 Uncertainties in the indirect and mixed treatment comparisons

As highlighted in Section 2.9, during the evaluation of heterogeneity between the trials, RESPONSE and ELATIVE were considered heterogenous in terms of key effect modifiers like cirrhosis and total bilirubin levels at baseline. Further, RESPONSE and POISE were found be be sufficiently similar in terms of key effect modifiers like ALP levels at baseline, cirrhosis %, total bilirubin levels at baseline, and age. These observations were confirmed by clinical experts (110).

Table 29: Population characteristics reported across the included studies

Population characteristics	ELATIVE	RESPONSE	POISE
Intervention	Elafibranor 80 mg + UDCA	Seladelpar 10 mg + UDCA	OCA 5-10 mg + UDCA
			OCA 10 mg + UDCA
Comparator	UDCA	UDCA	UDCA
Mean age years (SD)	57.1 (8.7)	56.7 (9.79)	56 (10.41)

Background UDCA (%)	95	93.8	93
Female (%)	96	94.2	90.6
Previous UDCA (%)	100	100	100
Baseline ALP mean U/L (SD)	321.9 (150.9)	314.3 (121.88)	323 (112.53)
ALP ULN Definition	Females: 104; Males: 129	116	Females: 118; Males: 124
Total bilirubin level- mg/dl (SD)	0.56 (0.298)	0.76 (0.30)	0.65 (0.38)
Total bilirubin level-µmol/liter (SD)	9.6 (5.1)	12.9 (5.147)	11.1 (6.498)
Cirrhosis (%)	9.94**	14	16
Time (years) since PBC Diagnosis (SD)	8.0 (6.2)	8.33 (6.66)	8.33 (6.10)
Age at diagnosis (SD) [95% CI]	NR	49.23 (10.30)	47.32 (10.79)
Bilirubin >ULN at baseline (%)	3.7	13.0	8.3

Key: ALB, albumin; ALP, alkaline phosphatase; NR, not reported; OCA, obeticholic acid; SD, standard deviation; SEL, seladelpar; UDCA, ursodeoxycholic acid; ULN, upper limit of normal.
Notes: *Median values; **8.3 in elafibranor and 13.2 in UDCA.
Source: Data on File – Seladelpar ITC Report (110)

The trials differed in terms of ULN for ALP and total bilirubin levels, which reflects variations in inclusion criteria and outcome definitions (Table 30).

Table 30: ULN cut-offs for ALP and total bilirubin levels across the included studies

ULN Cut-off	ALP ULN U/L		Bilirubin ULN micromoles/L		ALP normalization (ALP ≤1 ULN)		Composite response (ALP<1.67 ULN & ALP 15% reduction & bilirubin ≤1 ULN)	
	Female	Male	Female	Male	Female	Male	Female	Male
RESPONSE	116		18.8		116		194	
ELATIVE	104	129	20.5		104	129	A 174 B 20.5	A 215 B20.5
POISE	118	124	19.3	25.5	118	124	A 197 B 19.3	A 207 B 25.5

Key: ALP, alkaline phosphatase; ULN, upper limit of normal
Source: Hirschfield *et* al. (2024); Kowdley *et al*. (2024); Nevens *et al*. (2016) (5, 57, 59).

Despite these differences in ALP ULN values, the mean ALP levels at baseline were similar across trials, indicating a homogeneous distribution of patients based on ALP. However, since

the majority (~95%) of participants in these trials were females, the actual ALP ULN cut-off for ELATIVE was lower compared to RESPONSE and POISE.

This difference in outcome definition based on ULN is particularly important for indirect comparisons, as placebo responses are expected to be most influenced by the ULN thresholds applied to define response criteria for key outcomes like composite response. Specifically, in ELATIVE, the placebo (UDCA) group had to achieve a lower ULN cut-off for ALP, compared to placebo arms in RESPONSE and POISE. This likely reduced the placebo response rate in ELATIVE, leading to extremely low composite response rates. Consequently, the relative treatment effects derived using the ELATIVE placebo arm against seladelpar and OCA may be impacted, potentially inflating the estimated treatment effects due to a lower-than-expected placebo response. In POISE and RESPONSE, close to 30% of patients had ALP > 3× ULN at baseline, whereas in ELATIVE, this proportion was higher at 39.1%. When recalculating the ALP > 3× ULN in RESPONSE using ELATIVE's ULN cut-offs, the proportion increased to approximately 37%, further highlighting the similarity in ALP distribution across the trials.

RESPONSE included more severe patients in terms of cirrhosis and bilirubin levels at baseline compared to ELATIVE. ELATIVE trial included lower proportion of patients with cirrhosis at baseline (9.94%) compared to RESPONSE trial (14.0%). It is important to note that in the ELATIVE trial, the proportion of patients with cirrhosis at baseline were lower in elafibranor arm compared to placebo (UDCA) arm (8.3% vs. 13.2%). The differences in cirrhosis are particularly important as cirrhosis has been linked to worse prognosis and negative hard clinical endpoints like liver transplant and death. Mean bilirubin levels (µmol/liter) were higher in RESPONSE compared to ELATIVE trial. Further, more than 96% of patients had bilirubin levels lower than ULN at baseline in ELATIVE trial compared to 87% in RESPONSE trial.

In the RESPONSE, ELATIVE, and POISE trials, zero events were observed in the placebo arms for the ALP normalisation outcome. As per NICE DSU TSD 2 recommendations, a continuity correction was applied to address this issue. Specifically, 1 was added to the total number of patients in the affected arm, and 0.5 was added to the frequency of the given event in the Bayesian NMA. For the MAIC between seladelpar and elafibranor, the continuity correction was applied automatically by Stata software. However, continuity corrections introduce bias in effect

size estimates, as the event frequency is artificially increased. This adjustment can alter the difference between treatment arms, leading to potential discrepancies from uncorrected results.

Since ITCs rely on common comparators, the placebo effect size similarity across trials is crucial. However, as previously highlighted, the composite response rate in the ELATIVE placebo arm was extremely low (3.8%), compared to other Phase 3 trials (ranging from 9.6% to 20.0%) that used a similar composite outcome definition. This raises concerns about the reliability of the ELATIVE trial's placebo response as a basis for indirect comparisons.

One potential approach to address this issue is unanchored MAIC. However, NICE TSD 18 prioritizes anchored comparisons over unanchored ones. Consequently, unanchored MAIC was considered solely as a sensitivity analysis, where the results favoured seladelpar compared to the base-case anchored MAIC. Another potential solution involved exploring a risk difference model as suggested by Spiegelhalter et al., which was assessed as a sensitivity analysis for the composite response outcome.

Ultimately, the decision to conduct two separate analyses was based on differences in key effect modifiers between RESPONSE and ELATIVE, necessitating adjustments in population-adjusted comparisons such as MAIC. The guidance from NICE TSD 18, in consultation with ITC experts, informed the rationale, planning, and execution of MAIC between seladelpar and elafibranor. Additionally, the observed homogeneity in effect modifiers between RESPONSE and POISE, in alignment with ITC expert recommendations, supported the use of Bayesian NMA between seladelpar and OCA as per NICE TSD 2.

2.11 Adverse reactions

2.11.1 RESPONSE

The safety and tolerability of seladelpar for the treatment of PBC was evaluated as a primary outcome in RESPONSE and ASSURE. The SAS included all patients who received at least one dose of study drug (5, 100). TEAEs were coded with the with the Medical Dictionary for Regulatory Activities (MedDRA) version 24.0, and the severity of TEAEs was graded based on the NCI CTCAE Version 5.0.

2.11.1.1 Exposure to seladelpar

The mean duration of exposure in RESPONSE was 50.5 weeks in the seladelpar arm and 48.3 weeks in the placebo arm. The majority of patients (seladelpar arm: 93.8%, placebo arm: 89.2%) in both treatment arms received study drug for ≥39 weeks (Table 31). Due to the protocol allowed study visit window at Week 52, 64.8% and 56.9% of patients in the seladelpar and placebo arms, respectively, received ≥52 weeks of study drug, cumulatively (5, 100).

Table 31: Treatment exposure (RESPONSE, SAS)

	RESPONSE	
	Placebo (n=65)	**Seladelpar 10 mg (n=128)**
Duration of Exposure (Weeks)[a, b]		
N	65	126
Mean (SD)	48.33 (11.573)	50.49 (7.377)
Min, Max	1.3, 55.4	5.4, 54.7
Treatment exposure		
N	65	126
Mean (SD)	3343.2 (822.59)	3470.0 (570.13)
Min, Max	110, 4150	360, 4510

Key: Max, maximum; Min, minimum; n, total number of patients; SD, standard deviation
Notes: Percentages were based on the number of patients in the Safety Analysis Set under each treatment arm.
[a]Exposure (Weeks) in RESPONSE was defined as ([Last exposure date] – [First exposure date] + 1) / 7.
[b]Exposure (Weeks in ASSURE was defined as [the date of the last dose of study drug from long-term study – date of the first dose of study drug from long-term study + 1] /7.
Source: Table 45, RESPONSE CSR (100).

As of the January 31st 2024 data cut-off for the long-term ASSURE study, presented at the EASL 2024 congress by Trivedi *et al*. (2024), a total of 116 patients receiving continuous seladelpar had exposure ≥12 months, 103 had exposure of ≥12 months, and 28 patients had exposure of ≥18 months. For patients previously randomised to placebo in RESPONSE and transitioned to seladelpar 10 mg in ASSURE, 52 patients had exposure of ≥26 weeks, 14 had exposure of ≥12 months, and two patients had exposure of ≥12 months. No patients had exposure of ≥24 months in the crossover seladelpar cohort (99).

2.11.1.2 Summary of adverse events

Overall, 166 patients reported ≥1 TEAE during RESPONSE, corresponding to 86.7% of patients in the seladelpar arm (111 of 128 patients) and 84.6% of patients in the placebo arm (55 of 65 patients). TEAEs related to seladelpar were recorded in 17.2% of patients (22 of 111 patients).

Overall, the majority of TEAEs were Grade 1 (mild) or Grade 2 (moderate) in severity. A similar proportion of patients in each treatment group experienced any Grade ≥3 TEAEs. TEAEs leading to treatment discontinuation were reported for 3.1% of patients in the seladelpar arm and 4.6% of patients in the placebo arm. No deaths were recorded in the study (5, 100).

Overall, the safety profile of seladelpar observed in ASSURE was consistent with that observed in RESPONSE.

Table 32: Summary of TEAEs (RESPONSE & ASSURE, SAS)

TEAE category, n (%)	RESPONSE		ASSURE	
	Placebo (n=65)	Seladelpar 10 mg (n=128)	Crossover Seladelpar (n=54)	Continuous Seladelpar (n=104)
Patients with at least one TEAE	55 (84.6)	111 (86.7)	42 (77.8)	73 (70.02)
Serious TEAE	4 (6.2)	9 (7.0)	7 (13.0)	6 (5.8)
Grade 3 or Higher TEAE	5 (7.7)	14 (10.9)	5 (9.3)	9 (8.7)
Grade 3 or Higher TEAE due to pruritus	1 (1.5)	0	0	0
Treatment-related TEAE	8 (12.3)	22 (17.2)	NR	NR
Treatment-related Serious TEAE	0	0	NR	NR
Treatment-related Grade 3 or Higher TEAE	0	0	NR	NR
TEAE Leading to Dose Interruption	4 (6.2)	7 (5.5)	NR	NR
TEAE Leading to Dose Reduction	0	0	NR	NR
TEAE with Action Taken as Permanent Withdrawal of Study Drug	3 (4.6)	4 (3.1)	1 (1.9)	2 (1.9)
Treatment-related TEAE with Action Taken as Permanent Withdrawal of Study Drug	0	2 (1.6)	NR	NR
TEAE Leading to Study Discontinuation	3 (4.6)	3 (2.3)	1 (1.9)	1 (1.0)
Treatment-related TEAE Leading to Study Discontinuation	0	2 (1.6)		
TEAE with Fatal Outcome	0	0	0	0
Treatment-related TEAE with Fatal Outcome	0	0	0	0

Key: TEAE, treatment-emergent adverse event; n, total number of patients; NR, not reported; SAS: safety analysis set.
Notes: A treatment-related TEAE was defined as an adverse event for which the Investigator's assessment of relationship to study drug was reported as "possible", "probable", or "definite".
Percentages were based on the number of patients in the ASA under each treatment group. One patient ([redacted]) underwent a dose reduction following a study drug interruption due to a TEAE of drug-induced liver injury and is not reflected in the dose reduction row in the table
Source: Hirschfield et al (2024); Table 47, RESPONSE CSR; Trivedi *et al.* (2024) (5, 99, 100).

2.11.1.3 Common adverse events

TEAEs that occurred in ≥ 5% of patients in either treatment arm in RESPONSE and/or ASSURE are summarised below Table 33.

In RESPONSE, the percentage of patients who reported pruritus TEAEs was greater among patients who received placebo than among those who received seladelpar (15.4% vs 4.7%, respectively). TEAEs occurring in ≥5% of patients in either arm that were reported more often in the seladelpar arm that in the placebo arm (≥2% higher incidence) were abdominal pain (7.0% vs 1.5%, respectively), headache (7.8% vs 3.1%), abdominal distension (6.3% vs 3.1%) and COVID-19 (18.0% vs 15.4%) (Table 33) (5, 100). The safety profile observed in ASSURE were consistent with those observed in RESPONSE.

Table 33: Most common TEAEs occurring in ≥ 5% of patients in either treatment arm (RESPONSE & ASSURE, SAS)

TEAE, n (%)	RESPONSE		ASSURE	
	Placebo (n=65)	Seladelpar (n=128)	Crossover Seladelpar (n=54)	Continuous Seladelpar (n=104)
COVID-19	10 (15.4)	23 (18.0)	5 (9.3)	5 (4.8)
Pruritus	10 (15.4)	6 (4.7)	0	10 (9.6)
Upper respiratory tract infection	6 (9.2)	1 (0.8)	NR	NR
Headache	2 (3.1)	10 (7.8)	NR	NR
Nasopharyngitis	5 (7.7)	7 (5.5)	0	5 (4.8)
Pharyngitis	5 (7.7)	4 (3.1)	NR	NR
Abdominal pain	1 (1.5)	9 (7.0)	1 (1.9)	5 (4.8)
Arthralgia	4 (6.2)	8 (6.2)	4 (7.4)	3 (2.9)
Fatigue	4 (6.2)	8 (6.2)	1 (1.9)	5 (4.8)
Nausea	3 (4.6)	8 (6.2)	2 (3.7)	5 (4.8)
Abdominal distention	2 (3.1)	8 (6.2)	NR	NR
Asthenia	4 (6.2)	5 (3.9)	NR	NR
Urinary tract infection	4 (6.2)	4 (3.1)	2 (3.7)	7 (6.7)
Hypertension	4 (6.2)	4 (3.1)	NR	NR
Vertigo positional	4 (6.2)	1 (0.8)	NR	NR
Diarrhoea	0	0	5 (9.3)	2 (1.9)

Key: TEAE, treatment-emergent adverse event; n, total number of patients; n = number of patients in the category; NR, not reported.
Notes: A patient was counted only once for multiple events with the same preferred term. Preferred terms were sorted by the descending order of frequency in the seladelpar arm in RESPONSE.
Source: Hirschfield *et al.* (2024); Table 48, RESPONSE CSR; Trivedi *et al.* (2024) (5, 100).

Across RESPONSE and ASSURE, the majority of TEAEs were Grade 1 (mild) or Grade 2 (moderate) in severity. As displayed in Table 32, Grade 3 TEAEs were reported for 10.2% of patients in the seladelpar arm and 6.2% of patients in the placebo arm in RESPONSE. All Grade 3 TEAEs were reported in only patient each, and none were considered treatment-related by the Investigator. The majority of Grade 3 events resolved by the end of the study; three events were ongoing at the time of RESPONSE completion (hypertension and invasive ductal breast carcinoma in the seladelpar arm, and pruritus in the placebo arm). In addition, there were two Grade 4 TEAEs reported in RESPONSE, within one in each treatment arm. However, both events were considered unrelated to study drug (5, 100).

2.11.1.4 Summary of serious adverse events

A similar proportion of patients experienced a serious TEAE across each treatment group in RESPONSE (Table 34). All treatment-emergent SAEs were individually reported on study, with the exception of COVID-19. There was no pattern in the types of treatment-emergent SAEs observed in either the RESPONSE or ASSURE studies (5, 100).

Table 34: Serious TEAEs (RESPONSE & ASSURE, SAS)

Serious TEAE, n (%)	RESPONSE	
	Placebo (n=65)	Seladelpar 10 mg (n=128)
Patients with at least one serious TEAE	4 (6.2)	9 (7.0)
COVID-19	1 (1.5)	1 (0.8)
Acute respiratory failure	0	1 (0.8)
Chronic obstructive pulmonary disease	0	1 (0.8)
Coagulopathy	0	1 (0.8)
Coronary artery disease	0	1 (0.8)
Duodenal obstruction	0	1 (0.8)
Dyspnoea exertional	0	1 (0.8)
Femur fracture	0	1 (0.8)
Invasive ductal breast carcinoma	0	1 (0.8)
Oesophageal varices haemorrhage	0	1 (0.8)
Papillary thyroid cancer	0	1 (0.8)
Rotator cuff syndrome	0	1 (0.8)
Bladder cancer	1 (1.5)	0
Headache	1 (1.5)	0
Pneumonia	1 (1.5)	0
Presyncope	1 (1.5)	0
Suicide attempt	1 (1.5)	0

Key: TEAE, treatment-emergent adverse event; n; total number of patients.
Notes: A patient with multiple events of the same preferred term was counted only once.

Source: Hirschfield *et al.* (2024); Table 51, RESPONSE CSR; Trivedi *et al.* (2024) (5, 99, 100)

There was no pattern in the types of treatment-emergent SAEs observed in either the RESPONSE or ASSURE studies (5, 100).

2.11.1.5 Adverse events of interest

TEAEs of interest comprised those potentially reflecting liver-related toxicity, muscle-related toxicity, renal-related toxicity, and pancreatic-related toxicity. The preferred terms for the TEAEs of interest were defined by selecting relevant preferred terms based on MedDRA Version 24.0 (5, 100).

2.11.1.5.1. Liver-related toxicity

TEAEs potentially reflecting liver-related toxicity were reported for 6.3% and 9.2% of patients in the seladelpar and placebo arms in RESPONSE, respectively. All TEAEs in this category were Grade 1 (mild) or Grade 2 (moderate) in severity, except for one Grade 3 event of oesophageal varices haemorrhage occurring in a single patient of the seladelpar arm in the setting of known cirrhosis at baseline. Liver function test increase and hyperbilirubinemia were identified as treatment-related TEAEs, occurring in 2% (one patient treated with seladelpar, and one patient treated with placebo) and 0.5% (one patient treated with seladelpar) of patients in RESPONSE. Both events also led to study discontinuation (5, 100).

In ASSURE, as of the January 31st 2024 data-cut off presented at the EASL 2024 congress by Trivedi *et al*. (2024), liver-related TEAEs of hyperbilirubinemia and hepatic cyst were reported for two patients each (1.9%, 2 of 104 patients). Two patients discontinued the study as a result of liver-related TEAEs, specifically an event of hyperbilirubinemia (one patient, 1.0%) and oesophageal varices haemorrhage (one patient, 1.0%) (99).

2.11.1.5.2. Muscle-related toxicity

TEAEs potentially reflecting liver-related toxicity were reported for 6.3% of patients in the seladelpar arm (8 of 128 patients) and 7.7% of patients in the placebo arm (5 of 65 patients) in RESPONSE. All events occurring in the seladelpar arm were Grade 1 (mild) or Grade 2(moderate), and there were no TEAEs in this category leading to treatment discontinuation (4,82). In ASSURE, all muscle-related TEAEs were Grade 1 (mild) or Grade 2 (moderate), and none led to seladelpar discontinuation (99).

2.11.1.5.3. Renal-related toxicity

There were no TEAEs reported reflecting renal-related toxicity in RESPONSE across both treatment arms. In ASSURE, there was one proteinuria renal event reported as Grade 1 (mild) in severity and did not lead to study discontinuation (5, 99, 100).

2.11.1.5.4. Pancreatic-related toxicity

TEAEs potentially reflecting liver-related toxicity were reported for 1.6% of patients in the seladelpar arm (2 of 128 patients) and 1.5% of patients in the placebo arm (1 of 65 patients) in RESPONSE. All events of Grade 1 or 2 in severity, and no pancreatic-related TEAEs led to study discontinuation (5, 100). No pancreatic TEAEs were reported for the ASSURE study (99).

2.11.1.6 Study drug discontinuation

TEAEs leading to treatment discontinuation were reported for 3.1% of patients in the seladelpar arm (3 of 128 patients) and 4.6% of patients in the placebo arm (3 of 65 patients) in RESPONSE. Two patients in the seladelpar arm (1.6%, 2 of 128 patients) experienced a treatment-related TEAE that led to study discontinuation (versus zero in the placebo arm) (5, 100). In ASSURE, one patient in each of the crossover seladelpar (1.9%, 1 of 54 patients) and continuous seladelpar (1.0%, 1 of 104 patients) had a TEAE leading to study discontinuation (99).

2.11.1.7 Deaths

No deaths occurred in the RESPONSE study (5, 100). In ASSURE, one patient death was reported, albeit in the ‘Legacy patient’ arm and not in the continuous and crossover seladelpar treatment arms described in this appraisal. The fatal outcome was due to autoimmune haemolytic anaemia and was assessed to be unrelated to seladelpar by the Investigator.

2.11.2 CB8025-21629

The safety and tolerability of seladelpar for the treatment of PBC was evaluated using the SAS. As highlighted previously in Section B.2.3.2.7, the SAS included all patients who received at least one dose of seladelpar (58, 103). TEAEs were coded with MedDRA version 22.0.

Mayo *et al.* (2024) provides a pooled summary of TEAEs during the CB8025-21629 and CB8025-31731 studies (104). For the sake of brevity, and in the absence of a CSR for CB8025-31731, the pooled analysis from Mayo *et al.* (2024) forms the primary source of information underpinning the analysis of safety data, with evidence from the lead-in CB8025-21629 study provided where necessary (58, 103).

2.11.2.1 Exposure to seladepar

In CB8025-21629, the mean duration of seladelpar exposure was similar between the 2 mg ([redacted] days) and the 10 mg ([redacted] days) initial dose groups and lower for the 5 mg ([redacted] days) initial dose group. Study drug compliance exceeded 90% in all dose groups (58, 103). Furthermore, CB8025-31731 was open for over 21 months prior to its termination (see Section 2.2.1), which allowed patients to be treated with seladelpar for up 33 months in total across CB8025-21629 and CB8025-31731 (104).

2.11.2.2 Summary of adverse events

Overall, 101 patients (95%) reported ≥1 TEAE during the parent CB8025-21629 and the long-term CB8025-31731 studies, with similar incidences reported amongst the different dose cohorts. Overall, the majority of TEAEs were Grade 1 (mild) or Grade 2 (moderate) in severity, with only a single Grade ≥3 TEAE reported in the seladelpar 10 mg arm (1 of 50 patients, 2.0%). TEAEs leading to treatment discontinuation were reported in 10% (1 of 10 patients), 4% (2 of 46 patients) and 2% (1 of 50 patients) of patients in the 2 mg, 5 mg, and 10 mg treatment groups, respectively. One death was reported in the seladelpar 5 mg treatment cohort (104).

Table 35: Summary of TEAEs over 24 months of seladelpar treatment (CB8025-21629 & CB8025-31731; SAS)

	Seladelpar 2 mg (n=10)	Seladelpar 5 mg (n=46)	10 mg (n=50)	Total (n=106)
Any TEAE	10 (100)	42 (91)	49 (98)	101 (95)
Any treatment-related TEAE	6 (60)	17 (37)	16 (32)	39 (37)
Any Grade ≥3 treatment-related TEAE	0	0	1 (2)	1 (1)
Any safety-related discontinuations	1 (10)	2 (4)	1 (2)	4 (4)
Any serious TEAE	1 (10)	9 (20)	11 (22)	21 (20)

Any Grade ≥3 treatment-related serious TEAE	0	0	0	0
Deaths	0	1 (2)	0	1 (1)

Key: SAS, safety analysis set; TEAE, treatment-emergent adverse event.
Notes: Data are expressed as N (%). Adverse events were coded using MedDRA® version 22.0. Patients were counted one time even if they had multiple occurrences. Data presented are for all patients in the safety population during year 1 (parental study) and year 2 (extension study).
Source: Mayo *et al.* (2024) (104).

2.11.2.3 Common adverse events

The most common (≥10%) TEAEs over the 24 month treatment period were pruritus (24.5%), nausea (21.7%), fatigue (18.9%), arthralgia (17.9%), diarrhoea (17.9%), urinary tract infection (17.9%), nasopharyngitis (14.2%), vomiting (13.2%), abdominal pain upper (12.3%), headache (12.3%), abdominal pain (11.3%), back pain (11.3%), dizziness (11.3%), gastro-oesophageal reflux disease (11.3%) and upper respiratory tract infection (11.3%) (104). A breakdown of common adverse events by dose cohort is presented below in Table 36.

During C8025-31731, the frequency of TEAE occurrences tended to decrease, with notable decreases in pruritus (22.6%–2.8%), nausea (15.1%–7.5%) and fatigue (12.3%–9.4%) from study entry to Month 12, respectively (104).

Table 36: Most common TEAEs occurring in ≥10% of patients in either treatment arm (CB8025-21629 & C8025-31731; SAS)

	Seladelpar 2 mg (n=10)	Seladelpar 5 mg (n=46)	Seladelpar 10 mg (n=50)	Total (n=106)
Pruritus	5 (50.0)	11 (23.9)	10 (20.0)	26 (24.5)
Nausea	5 (50.0)	9 (19.6)	9 (18.0)	23 (21.7)
Fatigue	3 (30.0)	12 (26.1)	5 (10.0)	20 (18.9)
Arthralgia	1 (10.0)	8 (17.4)	10 (20.0)	19 (17.9)
Diarrhoea	3 (30.0)	6 (13.0)	10 (20.0)	19 (17.9)
Urinary tract infection	2 (20.0)	8 (17.4)	9 (18.0)	19 (17.9)
Nasopharyngitis	4 (40.0)	4 (8.7)	7 (14.0)	15 (14.2)
Vomiting	4 (40.0)	6 (13.0)	4 (8.0)	14 (13.2)
Abdominal pain upper	3 (30.0)	4 (8.7)	5 (10.0)	12 (11.3)
Back pain	3 (30.0)	4 (8.7)	5 (10.0)	12 (11.3)
Dizziness	1 (10.0)	7 (15.2)	4 (8.0)	12 (11.3)
Gastro-oesophageal reflux disease	1 (10.0)	6 (13.0)	5 (10.0)	12 (11.3)
Upper respiratory tract infection	1 (10.0)	7 (15.2)	4 (8.0)	12 (11.3)

Key: SAS, safety analysis set; TEAE, treatment-emergent adverse event
Notes: Data are expressed as N (%). Adverse events were coded using MedDRA® version 22.0. Patients were counted one time even if they had multiple occurrences. Data presented are for all patients in the safety population during year 1 (parental study) and year 2 (extension study).
Source: Mayo *et al.* (2024) (104)

2.11.2.4 Summary of serious adverse events

Across the CB8025-21629 and CB8025-31731 studies, serious TEAEs were reported in 11 patients (22%) in the seladelpar 10 mg group, 9 (20%) in the seladelpar 5 mg group, and 1 (10%) patient in the 2 mg group, but none were treatment-related. Of note, there were no serious TEAEs that were liver-related (104).

2.11.2.5 Study drug discontinuation

In the initial parent CB8025-21629 study, four patients (three in the 5 mg cohort and one in the 10 mg cohort) discontinued seladelpar due to TEAEs. The TEAEs leading to study drug discontinuation were gastroesophageal reflux (Grade 1 [mild], adjudicated as possibly related to seladelpar), pruritus (Grade 1 [mild], adjudicated as related to underlying PBC and unrelated to seladelpar), pneumonia (Grade 3 [severe], adjudicated as unrelated to seladelpar), and increases in ALT and AST levels (Grade 2 [moderate] and Grade 3 [severe], respectively, concomitant with rifampicin use and adjudicated as possibly related to either seladelpar or rifampicin) (58, 103).

During the second year of the study (CB8025-31731), four patients discontinued the study prior to study closure due to safety-related reasons. The events leading to discontinuation that were unrelated to seladelpar were an elevated total bilirubin level that met the study liver safety monitoring criteria (Grade 2 [moderate], increase >1.5 × baseline value), which was attributed to progression of PBC (severe ductopenia noted on a post-treatment biopsy), a serious TEAE related to systemic scleroderma, which was a pre-existing condition, and a malignant neoplasm. In a fourth patient, a non-SAE of periodic increases in liver function tests (Grade 2 [moderate] total bilirubin, Grade 2 [moderate] AST) with a temporal relationship with rheumatoid arthritis flares and increased use of non-steroidal anti-inflammatory drugs, which resolved upon discontinuation of seladelpar, was considered possibly related to seladelpar (104).

2.11.2.6 Deaths

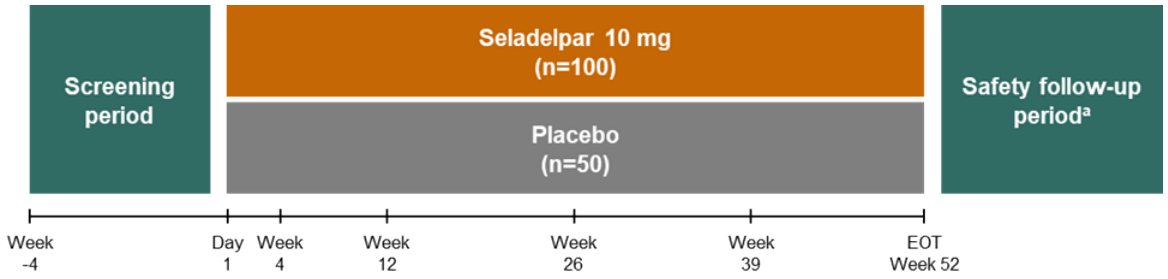
One patient in the seladelpar 5 mg cohort died during the CB8025-31731 study. The patient discontinued from the study due to a malignant neoplasm and subsequently died seven months after discontinuation from the study (104).

2.12 Ongoing studies

The long-term, Phase 3 ASSURE study is ongoing and will provide additional evidence for the efficacy and safety of seladelpar in patient with PBC and an inadequate response or intolerance to UDCA. The most-recent data cut-off was taken on 31st January 2024, and was presented at EASL 2024 by Trivedi *et al.* (2024) (99), and at The Liver Meeting 2024 by Lawitz *et al.* (2024) (101) and Trivedi *et al.* (2024) (102). A data-cut off of efficacy and safety, dated [redacted], is expected to be made available in [redacted]. Depending on the timing of availability, this may be submitted as new evidence to provide further evidence of the continued benefits of treatment with seladelpar over the longer-term.

Furthermore, IDEAL is an ongoing, double-blind, placebo-controlled, randomised, Phase 3 study to determine the effects of seladelpar on normalisation of ALP levels in patients with PBC and an incomplete response or intolerance to UDCA. This study will enrol approximately 150 patients with PBC who have an incomplete response or intolerance to UDCA, in each case with ALP >1.0x ULN and <1.67x ULN and total bilirubin >2.0x ULN. The estimated primary completion date for IDEAL is December 2025 (112). The study schematic for IDEAL is provided below in Figure 32.

Figure 32: IDEAL study diagram



Key: EOT: end of treatment
Notes:
[a]The safety follow-up visit will occur two weeks (+3 days) after the last dose of the study drug, including patients who discontinue treatment early.
Sources: Study NCT06060665. ClinicalTrials.gov (112)

In addition, AFFIRM is an ongoing, double-blind placebo-controlled, randomised, Phase 3b/4 trial to evaluate the effect of seladelpar on clinical outcomes in patients with PBC and compensated cirrhosis. The estimated primary completion for AFFIRM is July 2029, hence

additional evidence from this study is not anticipated to become available during the timelines for this appraisal (113).

2.13 Interpretation of clinical effectiveness and safety evidence

2.13.1 Principal findings from the clinical evidence

PBC is a serious, rare, progressive and potentially life-limiting autoimmune liver disease characterised by cholestasis and accumulation of toxic bile acids (13, 14). Many patients with PBC do not respond adequately to currently available therapies and continue to have ALP elevation and progressive disease. PBC patients may also suffer from debilitating symptoms of pruritus, which can be severe, and for which there are no specifically approved therapies (114). Thus, there remains a high unmet clinical need in PBC, including pruritus.

The efficacy and safety of seladelpar in PBC patients was investigated in the placebo-controlled, randomised, Phase 3 RESPONSE study, and the dose-ranging, open-label, randomised Phase 2 CB8025-21629 study.

RESPONSE was designed as a single pivotal study to evaluate the efficacy and safety of seladelpar in PBC patients with an inadequate response to or an intolerance to UDCA, the mainstay of first-line therapy. The primary efficacy endpoint of the study evaluated the composite biochemical response (ALP < 1.67× ULN, ≥ 15% decrease in ALP, total bilirubin ≤ 1.0× ULN) at Month 12. Key secondary efficacy endpoints included normalisation of ALP at Month 12 (≤ 1.0× ULN) and change from baseline in weekly averaged Pruritus NRS at Month 6 in patients with baseline Pruritus NRS ≥ 4. Safety over 12 months of treatment with seladelpar compared with placebo was also a primary endpoint of the study (5, 100).

In RESPONSE, treatment with seladelpar led to a statistically significantly higher percentage of patients achieving the primary efficacy endpoint of composite biochemical response (defined as ALP <1.67x ULN, with a decrease of 15% or more from baseline, and a normal total bilirubin level) at Month 12 compared with placebo (61.7% vs 20.0%, respectively; treatment difference [95% CI]: 41.7% [27.7, 53.4%]; p<0.0001) (4,82). Consistent results were observed in the long-term ASSURE study, where 72.4%–93.8% of RESPONSE rollover patients receiving seladelpar for up to two years achieved a composite biochemical response at the interim analysis (see

Section 2.6.1.1) (99). When considering all ASSURE patients, including those from 'Legacy studies' of seladelpar, 81% of patients (30 of 37 patients) demonstrate a durable composite biochemical response up to Month 30, with nearly half (15 of 37 patients, 41%) achieving ALP normalisation(101).

Table 37 presents a summary of pivotal efficacy findings for seladelpar versus existing second-line therapies in PBC in the UK.

Table 37: Summary of pivotal efficacy findings for second-line therapies in PBC in the UK

Category, %	Seladelpar	Elafibranor	OCA	
	10 mg (n=128)	80 mg (n=108)	5/10 mg (n=70	10 mg (n=73)
Patients meeting primary endpoint*	62%	51%	46%	47%
Patients achieving ALP normalisation	25%	15%	NR	

Key: ALP, alkaline phosphatase; NR, not reported; OCA, obeticholic acid; PBC, primary biliary cholangitis.
Notes: *Composite endpoint was defined as ALP <1.67x ULN, an ALP decrease ≥15% from baseline, and total bilirubin ≤ULN.
Sources: Hirschfield *et al.* (2024); Kowdley *et al.* (2024); Nevens *et al.* (2016) (5, 57, 59)

In addition, seladelpar significantly decreased pruritus, as measured by the Pruritus NRS, in patients experiencing moderate-to-severe pruritus at baseline (LSM change from baseline of -3.2 in the seladelpar arm vs -1.7 in the placebo arm; p=0.005).The improvements may meet the threshold for a minimally clinically important difference, as a study found that a 2–3 point decrease on the NRS marks the smallest noticeable improvement in chronic itch severity as perceived by patients. Improvements in pruritus from baseline as measured by the Pruritus NRS vs placebo were also observed in the overall study population. In addition, patients with PBC receiving seladelpar showed greater reductions in PBC-40 Itch Domain scores and 5-D Itch Scale assessments compared to placebo (5, 100). In the ASSURE study, a sustained reduction in pruritus was observed for up to three years in patients with baseline NRS ≥4 treated with seladelpar, supporting the findings of RESPONSE.(101, 115).

Table 38 presents a summary of pivotal pruritus findings for second-line therapies in PBC in the UK.

Table 38: Summary of pivotal pruritus findings for second-line therapies in PBC in the UK

Category	Seladelpar	Elafibranor	OCA	
	10 mg (n=128)	80 mg (n=108)	5/10 mg (n=70)	10 mg (n=73)
Mean change in pruritus severity	3.2-point improvement in Pruritus NRS* scores in patients with moderate-to-severe pruritus; significant reductions compared to placebo were observed (p=0.0047)	1.93-point decrease in WI-NRS* scores through Week 52 in patients with moderate-to-severe pruritus; however, did not meet secondary endpoint of change in WI-NRS through Week 52 (p=0.20) and Week 24 (NR)**	~5.75-point worsening in VAS scores at Month 12	~2.5-point worsening in VAS scores at Month 12

Key: NR, not reported; NRS, numerical rating scale; OCA, obeticholic acid; PBC, primary biliary cholangitis; VAS, visual analogue scale; WI-NRS, Worst Itch numerical rating scale
Notes: *The Pruritus NRS used in the RESPONSE trial and WI-NRS used in the ELATIVE trial both range from "0-no itch" to "10-worst itch imaginable"; **There was no significant difference in the mean change on the NRS up to Week 24 between the elafibranor and placebo groups, though the specific p-value was not reported.
Sources: Hirschfield *et al.* (2024); Kowdley *et al.* (2024); Nevens *et al.* (2016) (5, 57, 59)

Based on the data from trials thus far, seladelpar has been generally well-tolerated by patients with PBC. In RESPONSE, the frequency of AEs and SAEs between the seladelpar and placebo arms was largely similar (87% vs 85% and 7% vs 6%, respectively). Only 5% and 6% of patients treated with seladelpar reported pruritus and fatigue as AEs, respectively. Through Month 12, only 3% of patients receiving seladelpar discontinued treatment due to an AE compared to 5% of patients in the placebo group (5, 100). A consistent safety profile was observed in the two-year interim analysis of the ASSURE study, with few SAEs and discontinuations reported in patients treated with seladelpar at the time of the data cut-off (99). Results from pooled analyses of ASSURE patients, including those enrolled from 'Legacy studies', for up to five years further supports the long-term tolerability of treatment, and demonstrates an overall safety profile consistent with that of placebo.(102)

Table 39 presents a summary of pivotal safety and tolerability findings for seladelpar and existing second-line therapies in PBC in the UK.

Table 39: Summary of pivotal safety and tolerability findings for second-line therapies in PBC in the UK

Category, %	Seladelpar	Elafibranor	OCA	
	10 mg (n=128)	80 mg (n=108)	5/10 mg (n=70	10 mg (n=73)
Patients reporting any AE	87	96	Only reported by AE type*	
Patients reporting an SAE	7	11**	16	11
Patients discontinued due to AEs	3	10	6	11
Patients reporting pruritus (as AE)	5	20	56	68
Patients reporting fatigue (as AE)	6	9	16	23

Key: AE, adverse event; OCA, obeticholic acid; PBC, primary biliary cholangitis; SAE, serious adverse event.
Notes: *AEs experienced by at least 10% of patients in at least one treatment group were reported (e.g., 56% of patients in the 5-10 mg group and 68% in the 10 mg group experienced pruritus); **SAEs 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.
Sources: Hirschfield *et al.* (2024); Kowdley *et al.* (2024); Nevens *et al.* (2016) (5, 57, 59)

The randomised, open-label, 52-week, Phase 2 CB8025-21629 study further supports the efficacy and safety of seladelpar in patients with PBC with an inadequate response or intolerance to UDCA. In CB8025-21629, significant reductions in mean ALP levels were observed after three months of treatment with seladelpar 10 mg, with a 43% reduction from baseline and normalisation of ALP in 31% of patients. ALP reductions, an evidence-based surrogate for long-term transplant-free outcomes, were maintained through 52 weeks. The clinically significant and durable effects of the seladelpar 10 mg dose on ALP levels, the composite biochemical response endpoint, and ALP normalisation strongly supports the improvement in cholestatic markers associated with clinical outcomes. Seladelpar was safe and well tolerated, and the safety profile was similar to that observed amongst patients who received seladelpar in the pivotal RESPONSE study (58, 103).

Overall, seladelpar, demonstrated efficacy and a tolerable safety profile in patients with PBC, with consistent results observed in patients with compensated cirrhosis, as well as in those with and without compensated cirrhosis treated for up to two years in the long-term ASSURE study. As such, seladelpar offers a valuable second-line treatment option for patients with PBC who have an inadequate response to or are unable to tolerate first-line UDCA monotherapy, addressing the unmet needs presented by existing PBC treatment options.

2.13.2 Strengths and limitations of the evidence base

Treatment with seladelpar positively impacts ALP normalisation and bilirubin levels, which are established predictors of prognosis in PBC. Reductions of ALP to <1.67x ULN have been reported to reduce the risk of disease progression over 10 years as well as overall survival, with further improvements observed when ALP drops to ≤1.0x ULN (64). Additionally, ALP normalisation has been associated with reduced risk of clinical events such as decompensated cirrhosis and liver transplantation, and greater percentage decreases in ALP levels are associated with better transplant-free survival, a 40% decrease in ALP levels found to be significant in predicting outcome (56). Similarly, normalisation of bilirubin has been associated with improved liver transplant-free survival as well as overall survival (56). Importantly, approximately 40% of PBC patients fail to achieve a biochemical response of reduced ALP levels with first-line UDCA therapy (81). With second-line OCA treatment, more than half of patients treated do not respond adequately, with only moderate decreases in ALP levels (87).

Seladelpar also acts to address the burden of pruritus in patients with PBC. Pruritus can be unbearable, causing sleep deprivation, social isolation, and potentially triggering suicidal ideation, and overall having a negative impact on patient QoL. Despite this, there are no approved treatments for PBC that improve pruritus as measured by the NRS. Specifically, elafibranor did not demonstrate a statistically significant improvement in pruritus in the pivotal ELATIVE trial, and new or worsening pruritus frequently occurs in patients receiving OCA, with up to 10% of patients discontinuing OCA within a year due to pruritus (57, 59). Moreover, patients receiving OCA and UDCA in the ITCH-E study have reported poor effectiveness of current treatments for pruritus and stressed the need for a PBC treatment that can relieve itch (70).

Importantly, seladepar is well-tolerated in patients with PBC. Treatment with OCA has led to notable safety concerns, including reductions in high density lipoprotein (81, 86, 87). Additionally, treatment with elafibranor was observed to lead to a higher frequency of AEs compared to placebo (59).

With regards to study limitations, the pivotal RESPONSE study lacked a head-to-head comparison versus OCA or elafibranor. An active control study with OCA is infeasible, considering that the use of OCA as a comparator would have made it difficult to establish the

effect of seladelpar on pruritus, a key secondary endpoint in the study. A comparison versus elafibranor was also unfeasible, as this therapy had not been commercialised upon the initiation of the RESPONSE study. Furthermore, coadministration with other PBC treatments such as OCA has not been assessed in earlier phase studies and would have confounded the interpretation of the overall safety profile of seladelpar and other important assessments such as liver histopathology.

In addition, owing to the slow, progressive nature of PBC, it is challenging for randomised, placebo-controlled trials to evaluate clinical outcomes requiring long-term follow-up, such as cirrhosis and liver failure. Although the occurrence of PBC clinical outcomes were not captured in RESPONSE, it is hopeful that the ongoing long-term ASSURE and AFFIRM studies can capture the occurrence of these in the future.

2.13.3 Applicability of clinical evidence to practice

2.13.3.1 Patient characteristics

The PBC patient population observed in pivotal RESPONSE study is anticipated to reflect the distribution of patients observed in UK clinical practice. A majority of patients were female (94.8%), with a mean age at diagnosis of 49.2 years (range: 26-68 years) (5, 100), aligning closely to the UK-based cohorts analysed by Abbas *et al.* (2023) (90.4% female; age at PBC diagnosis: 47 years, range: 41-54 years) (17). In total, 93.8% of patients were receiving concurrent UDCA at baseline within the BSG/UK-PBC guideline-recommended 13-15 mg/kg daily dose (80), a figure closely aligned to that reported in a UK-based by Abbas *et al.* (2024), whereby 87.7% of patients (6,864 of 7,690 patients) in England received treatment with UDCA (16). Furthermore, the low incidence of UDCA intolerance in RESPONSE (6.2%) also closely aligns to the 4.2% of patients (320 of 7,690 patients) that did not receive first-line UDCA monotherapy due to intolerance in the Abbas *et al.* (2024) study and is reflective of previous pivotal clinical studies in PBC (5, 16, 57, 59). This highlights that the majority of patients treated with seladelpar in RESPONSE were non-responders to UDCA upon study entry. The population of RESPONSE also highlights the substantial clinical burden of PBC, with 14.0% of patients cirrhotic at baseline and 37.3% reporting moderate-to-severe pruritus (5, 100). The characteristics are reflective of UK practice; in a UK-wide multicentre study by Abbas *et al.*

(2023), 11.2% of patients had compensated cirrhosis (51 of 457 patients, 11.2%) (17), while the proportion of patients reporting moderate-to-severe pruritus at baseline is consistent with the ELATIVE study of elafibranor (41%, 66 of 161 patients) (59), which was deemed generalisable to UK clinical practice (72).

In addition, RESPONSE included eight study sites from the UK, namely Queen Elizabeth Hospital, Hull Royal Infirmary, Kings College Hospital, University Hospitals Plymouth NHS Trust, Portsmouth Hospitals NHS Trust, Royal London Hospital, Queen's Medical Centre, and the Gemini Clinical Trial Unit. In total, six of the eight study sites enrolled and treated patients. Across the six study sites, eight UK patients were enrolled and included in the RESPONSE ITT analysis set (8 of 193 patients, 4.1%), seven (87.5%) of which rolled over into the long-term ASSURE study.

2.13.3.2 Analysis sets

In consideration of the most appropriate analysis set for decision-making, the ITT analysis set in RESPONSE (n=193) is presented and the data is used in the subsequent cost-effectiveness analysis. This analysis set includes all patients who were randomised into the study and received at least one dose of study drug (5, 100).

2.13.3.3 Service provision

No additional infrastructure or personnel is required, and therefore seladelpar would fit in with the current service provisions already set up within NHS England.

Repeat prescriptions of seladelpar are planned to be delivered via homecare medicines services. Homecare provision will be funded by Gilead, with NHS England covering the cost of drug only.

3 Cost effectiveness

3.1 Published cost-effectiveness studies

A systematic literature review (SLR) was conducted, to identify published cost-effectiveness studies and determine economic modelling precedents in PBC.

In brief, the PubMed, Embase, and National Health Service Economic Evaluation Database were searched from inception to 2024. A full description of the SLR is provided in Appendix E: Published cost-effectiveness studies (including search strategy, included, and excluded records with reasons and data extraction tables).

The searches identified 12 studies from 17 publications after de-duplication. The majority of studies were HTA submissions (n=7) followed by peer-reviewed journal articles (n=4), whereas one study was published as a conference poster. These are summarised in Table 40 below. No studies considered the cost-effectiveness of seladelpar in the UK, thus no studies are considered of direct relevance to the NICE decision problem and are purely of interest from the perspective of structural and parameter assumptions.

Table 40: 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)
Baschet (116)	2017	The study uses a Markov state-transition model consisting of two components: the liver disease component defining the PBC risk of progression based on ALP and bilirubin biomarkers; and the clinical endpoint component depicting progression through end stage liver disease, including decompensated cirrhosis, liver transplantations and liver-related mortality.	PBC patients with inadequate response or intolerance to UDCA	Not reported	Not reported	In patients with inadequate response, the ICER is 94,284 gained; in patients intolerant to UDCA, the ICER is 82,818.
Boberg (117)	2013	The study uses a Markov model with three health states: alive without liver transplantation, alive after liver transplantation, and death. The intervention is UDCA, compared with a placebo as the comparator. A lifetime time horizon is applied, with annual transitions between health states.	UDCA-treated adult PBC patients (56 years)	Not reported	(Costs are reported in Euros) The total lifetime costs were 102,912 (discounted) and 115,031 (discounted) for the UDCA and the control group respectively. The cost saving for a patient on UDCA was 12,119 (discounted).	N.A. (UDCA dominating)

CADTH (118)	2017	The study uses a Markov state-transition model with 10 health states: low, moderate, and high-risk PBC-specific disease states; decompensated cirrhosis; HCC; pre-liver transplant; liver transplant; post-liver transplant; PBC re-emergence; and excess mortality. Transitions occur every 3 months, with initial probabilities and natural history data based on the POISE study, and data from the Global and UK-PBC study cohorts used after year 1. For UDCA-tolerant patients, the intervention is UDCA + OCA, compared with UDCA alone, while for UDCA-intolerant patients, the intervention is OCA alone, compared with no treatment. The time horizon is set at a lifetime (50 years) with a 3-month cycle, and no explicit rationale is provided.	Adult PBC patients with an inadequate response to UDCA (UDCA-tolerant) and adult PBC patients who are unable to tolerate UDCA (UDCA-intolerant) (56 years).	The total QALYs from the base-case analysis are as follows: For the UDCA-tolerant population, UDCA alone resulted in 9.95 QALYs, while OCA plus UDCA achieved 17.06 QALYs. For the UDCA-intolerant population, no treatment resulted in 7.72 QALYs, compared with 16.94 QALYs for OCA alone.	(Costs are reported in Canadian dollars) The total costs from the base-case analysis are as follows: For the UDCA-tolerant population, UDCA alone incurred costs of 115,452, while OCA plus UDCA incurred costs of 705,334. For the UDCA-intolerant population, no treatment incurred costs of 116,310, compared with 681,721 for OCA alone.	The ICER results from the base-case analysis are as follows: For the UDCA-tolerant population, the ICER for OCA plus UDCA is 82,921 compared with UDCA alone. For the UDCA-intolerant population, the ICER for OCA alone is 61,365 compared with no treatment.
ICER (119)	2016 2017	The study uses a microsimulation model with an annual cycle length. The health states include PBC 1-3,	Adults with PBC whose disease has not adequately responded to	The total QALYs from the base-case analysis for UDCA alone and OCA plus UDCA were 10.74	(Costs are reported in U.S. dollars) The total costs from the base-case	The ICER for OCA plus UDCA is 473,400 compared

Linked : Samur (120)		compensated cirrhosis, decompensated cirrhosis, hepatocellular carcinoma, liver transplant, liver-related death, and death from other causes. The intervention is UDCA + OCA, compared with UDCA alone	UDCA treatment (56 years).	and 11.78, respectively.	analysis for UDCA alone and OCA plus UDCA were 142,300 and 633,900, respectively (assming an annual cost of 69,350 for OCA)	with UDCA alone in the base-case.
Longworth (121)	2003	A within-trial analysis is conducted. The interventions modelled are liver transplantation and absence of liver transplantation. The time horizon is 27 months, comprising 2 years post-transplantation and 3 months on the transplant waiting list. Treatment sequencing is not reported.	PBC, ALD, and PSC patients aged 16 and older listed for an isolated liver transplant in six liver transplant centres in England	The mean QALYs measured over 27 months from the date of listing for PBC patients are as follows: for patients who underwent transplantation, the observed mean QALYs were 1.30 (95% CI: 1.18–1.43), while for patients in the absence of transplantation, the shadow estimated mean QALYs were 0.76 (95% CI: 0.65–0.91).	(Costs are reported in British pound sterling) The mean cost, measured over 27 months from the date of listing and including the cost of assessment for PBC patients, is as follows: for patients who underwent transplantation, the observed mean cost was 1.30 GBP (95% CI: 1.18–1.43), while for patients in the absence of transplantation, the shadow estimated mean cost was 0.76 GBP (95% CI: 0.65–0.91).	ICER (95% CI): 28,716 (1,000–59,000)
NCPE (122)	2017	The study uses a Markov state-transition model with no explicit rationale provided. The model includes 10 health	Adults with an inadequate response to, or unable to tolerate UDCA	The total QALYs for OCA dose titration therapy are 3.096 for the UDCA inadequate responder population	(Costs are reported in euros) The total costs for OCA dose titration therapy are 454,067	The ICER for OCA dose titration therapy is 146,659 for

		states, with transitions occurring every 3 months. Three health states represent the progression of PBC based on ALP and bilirubin biomarkers, while seven health states represent liver disease clinical outcomes entered once patients progress to decompensated cirrhosis or HCC. The intervention is OCA dose titration (5 mg for the first six months, followed by 10 mg for subsequent months). In the UDCA inadequate responder group, the comparator is oral UDCA at 13–15 mg/kg/day, while in the UDCA-intolerant group, the comparator is placebo (no treatment). The model uses a three-month cycle length and a lifetime time horizon of 50 years, with no explicit rationale for this time horizon provided.		and 3.9 for the UDCA-intolerant population.	for the UDCA inadequate responder population and 108,094 for the UDCA-intolerant population.	the UDCA inadequate responder population and 108,094 for the UDCA-intolerant population.
NICE (73)	2017	The study uses a Markov state-transition model with no explicit rationale provided. The model is divided into two components: biomarkers and liver disease. The	Adults with an inadequate response to, or unable to tolerate UDCA (56 years)	The total QALYs for the UDCA-intolerant population using the PAS price of OCA are 6.61 for no treatment (placebo) and 13.56 for OCA titration. For	(Costs are reported in British pound sterling) The total costs for the UDCA-intolerant population using the PAS price of OCA are 103,233 for no	The ICER results for the UDCA-intolerant population using the PAS price of

		biomarker component includes three health states (low, moderate, and severe), while the liver disease component encompasses significant liver disease states, including decompensated cirrhosis, hepatocellular carcinoma, pre-transplant state, transplantation, re-emergence of PBC, and death. For UDCA-intolerant patients, the intervention is OCA (dose titration starting at 5 mg once daily, increasing to 10 mg once daily after six months based on tolerability) compared to no treatment or fibrates. For UDCA inadequate responders, the intervention is OCA (dose titration as above, combined with UDCA) compared to UDCA monotherapy or UDCA with fibrates. The model uses a four-week cycle length over a 50-year time horizon.		the UDCA inadequate responder population, the total QALYs are 7.85 for no treatment (placebo) and 13.68 for OCA titration.	treatment (placebo) and 251,671 for OCA titration. For the UDCA inadequate responder population, the total costs are 96,977 for no treatment (placebo) and 261,791 for OCA titration.	OCA are 21,351 for OCA titration. For the UDCA inadequate responder population, the ICER is 28,281 for OCA titration.
Pasha (123)	1999	A within-trial analysis is conducted. Major events include ascites, varices, variceal bleeds,	Patients with PBC from the Mayo and	N.A.	N.A.	N.A. (UDCA dominating)

		encephalopathy, liver transplantation, and death. The interventions and comparators modelled are UDCA and placebo. The time horizon is 4 years after the start of the trials.	Canadian UDCA trials (55 years)			
PBAC (124)	2021	The analysis is a cost-utility analysis and cost-effectiveness analysis, with outcomes measured in QALYs and life years gained. A lifetime time horizon of 30 years is used, based on the POISE clinical trial (12 months) and the POISE LTSE study (5 years). The model is a semi-Markov state-transition model with 10 health states, including three biochemical states (low, moderate, and high risk of PBC disease progression) and seven liver disease states (DCC, HCC, Pre-LT, LT, Post-LT, PBC re-emergence, and death). For patients with an inadequate response to UDCA, the intervention is OCA + UDCA compared to UDCA alone, while for patients intolerant to UDCA, the intervention is OCA compared to	Adult PBC patients who are UDCA tolerant or intolerant (56 years)	For patients with an inadequate response to UDCA, the total QALYs are 8.85 for UDCA-monotherapy and 10.88 for OCA titration + UDCA. Results for patients who are UDCA intolerant are not presented.	(Costs are reported in Australian dollars) For patients with an inadequate response to UDCA, the total costs are 139,739 for UDCA monotherapy. The costs for OCA titration + UDCA are redacted. Results for patients who are UDCA intolerant are not presented.	ICERs are redacted

		placebo. The cycle length is 3 months.				
Ratcliffe (125)	2001	The study uses a microsimulation model to simulate patient outcomes with end-stage liver disease, caused by either ALD or PBC. A scenario in which PBC patients are prioritised is reported. Patients enter the model with end stage liver disease and are first assessed for liver transplant suitability. Patients who are suitable for transplant enter onto the waiting list. If patients survive the waiting period, they undergo surgery and are tracked until death. Should the patients require re-transplantation, they are re-assessed and enter the same liver transplant pathway. Patients unsuitable for transplant enter a separate pathway.	Patients with end stage liver disease, caused by either ALD or PBC (46% of the cohort had PBC); Mean age not reported	Only life years (LYs) are reported. Prioritising transplant in the PBC group led to 4.01 life years gained. Under this scenario, patients that did not receive transplant survived for 1.03 years.	(Costs are reported in British pound sterling) In the PBC prioritisation scenario, costs are 59,610 for those that receive transplant and 24,358 for those that do not.	In the PBC prioritisation scenario, ICER is 11,830.
SMC (126)	2017	The study uses a Markov state-transition model. Patients enter the model in either a PBC moderate or high-risk liver disease health state, with the high-risk state also covering compensated	Adults with an inadequate response to, or unable to tolerate UDCA (56 years)	The total QALYs with PAS for OCA are as follows: For OCA (vs UDCA) in UDCA inadequate responders: 5.50.	(Costs are reported in British pound sterling) The total costs for the UDCA-inadequate and UDCA-intolerant patient population using the PAS price of	The ICER results with PAS for OCA are 28,821 for OCA compared to UDCA in UDCA

		cirrhosis. For patients with an inadequate response to UDCA, the intervention is OCA + UDCA compared to UDCA alone, while for patients intolerant to UDCA, the intervention is OCA compared to placebo. The model uses with 3-month cycles. Treatment involves OCA tablets titrated from 5 mg to 10 mg, given daily.		For OCA (vs UDCA) in UDCA-intolerant patients: 6.59.	OCA are 158,000 and 143,000, respectively.	inadequate responders and 21,695 for OCA compared to UDCA in UDCA-intolerant patients.
NICE (72)	2024	The study uses a Markov state-transition model. The model is divided into two components: biomarkers and liver disease. The biomarker component includes three health states (mild, moderate, and high), while the liver disease component encompasses significant liver disease states, including decompensated cirrhosis, hepatocellular carcinoma, pre-transplant state, transplantation, post-transplant, re-emergence of PBC, and death. For UDCA-intolerant patients, the intervention is elafibranor compared to OCA monotherapy.	Adults with an inadequate response to, or unable to tolerate UDCA (57 years)	In the base-case, the total QALYs for OCA and UDCA are 7.56 and 6.38, respectively. The results for elafibranor are redacted.	(Costs are reported in British pound sterling) The total costs for OCA and UDCA are 203,726 and 104,283, respectively. The results for elafibranor are redacted.	In the base-case, elafibranor has an ICER of 31,762 compared to UDCA and dominates OCA.

		For UDCA inadequate responders, the intervention is elafibranor in combination with UDCA compared to UDCA monotherapy or OCA in combination with UDCA. The model uses a three-month cycle length over a 43-year time horizon.				

Key: CADTH, canadian agency for drugs and technologies in health; ICER, incremental cost-effectiveness ratio; QALYs, quality-adjusted life years; OCA, obeticholic acid; PBAC, pharmaceutical benefits advisory committee; PBC, primary biliary cholangitis; UDCA, ursodeoxycholic acid

3.2 Economic analysis

As stated in Section 3.1, no cost-effectiveness studies relevant to the decision problem were identified, thus a de novo model was built to assess the cost-effectiveness of seladelpar vs. its relevant comparators in England.

3.2.1 Patient population

Aligned with the demographics of the RESPONSE trial that are discussed in Section 2.3.1.8 and outlined in Table 41 and the expected license indication, the patient population in the model is defined as adults (≥18 years) with PBC, with an inadequate response to first-line UDCA monotherapy or who are unable to tolerate UDCA treatment, and without cirrhosis or with compensated cirrhosis. To capture differences in treatment practices (See Section 1.3) and treatment and disease outcomes, and in alignment with the NICE scope, UDCA tolerant (i.e., monotherapy inadequate responders) and UDCA intolerant patients are evaluated as independent subgroups in the model.

The RESPONSE baseline characteristics were used to inform key model characteristics as described below. Patient characteristic parameters in the model include baseline age, the percentage of the cohort that is female and mean weight. The baseline age and percentage female parameters are used to estimate background (general population) mortality rates (Section 3.3) and age-related utility decrements (Section 3.4), while the mean body weight parameter is used to derive weight-based dosing levels and associated acquisition costs for UDCA (Section 3.5.1).

Patient demographics at baseline from the Phase III RESPONSE trial were used to inform the characteristics of the population entering the model, as summarised in Table 41. The model used average values across all treatment groups to represent the patient characteristics, based on the total intention to treat (ITT) cohort including the seladelpar and placebo arms. At baseline the inputs were consistent for both UDCA tolerant and intolerant subgroups.

Table 41: RESPONSE trial key demographics and baseline characteristics

Baseline characteristics	Mean (SD)	Reference
Age in years, Mean (SD)	56.7 (9.70)	RESPONSE trial

Female, %	94.82%	RESPONSE trial
Weight in kg, Mean (SD)	71.1 (15.3)	RESPONSE trial

Key: kg, kilograms; mg, milligrams; SD, standard deviation

The distribution of the cohort across the PBC biomarker states at baseline (i.e., model initiation) was based on the complete data only in RESPONSE. This data was estimated from outputs of the conducted IPD transition probability analyses (For details, see Appendix M: IPD transition probability analyses) and is summarised in Table 42.

Table 42: Baseline PBC biomarker health state distribution for the RESPONSE complete data only

Health state	Total % (N); N= 187	Reference
ALP Normalisation, % ALP ≤ 1x ULN / TB Normal (TB ≤ 1x ULN)	0.00% (0)	RESPONSE trial
Mild ALP Elevation, % 1 < ALP ≤ 1.67x ULN / TB Normal (TB ≤ 1x ULN)	5.88% (11)	RESPONSE trial
High ALP Elevation, % ALP > 1.67x ULN / TB Normal (TB ≤ 1x ULN)	71.66% (134)	RESPONSE trial
Compensated Cirrhosis or Elevated Bilirubin, % CC or TB > 1x ULN	22.46% (42)	RESPONSE trial

Key: ALP, alkaline phosphatase; CC, compensated cirrhosis; TB, total bilirubin; ULN, upper limit of normal
Percentages may not sum to 100% due to rounding.

3.2.2 Model structure

A cohort-level Markov state transition model was developed to simulate the natural disease progression of PBC and associated outcomes over a lifetime horizon. The design of the model was informed by published literature on existing economic models, predominantly the models used in the NICE and ICER appraisals for OCA (73),(119) . In addition, the recent NICE appraisal for elafibranor was also reviewed after it became available. Broadly, the modelling approach is consistent with that taken in the NICE technology appraisals for OCA (73) and elafibranor (72). Consultation exercises with clinical experts and health economists were also conducted as part of the design and validation process, to ensure the model appropriately and accurately characterises clinical practice and outcomes.

The model structure is divided into two core components: a PBC biomarker component and a liver disease component. Health states in the PBC biomarker component capture the effects of treatment on key markers of disease status, while the advanced liver disease states reflect the clinical consequences of disease progression. Death is included as an absorbing state.

Four health states are included in the PBC biomarker component, defined by ALP and total bilirubin elevation level ratios and the presence of compensated cirrhosis. The elevation levels are based on the clinically recognised definitions and align with those implemented in other models:

- **ALP normalisation:** ALP ≤ 1x ULN / TB ≤ 1x ULN
- **Mild ALP elevation:** 1 < ALP ≤ 1.67x ULN / TB ≤ 1x ULN
- **High ALP elevation:** ALP > 1.67x ULN/ TB ≤ 1x ULN
- **Compensated Cirrhosis or Elevated Bilirubin:** CC or TB > 1x ULN

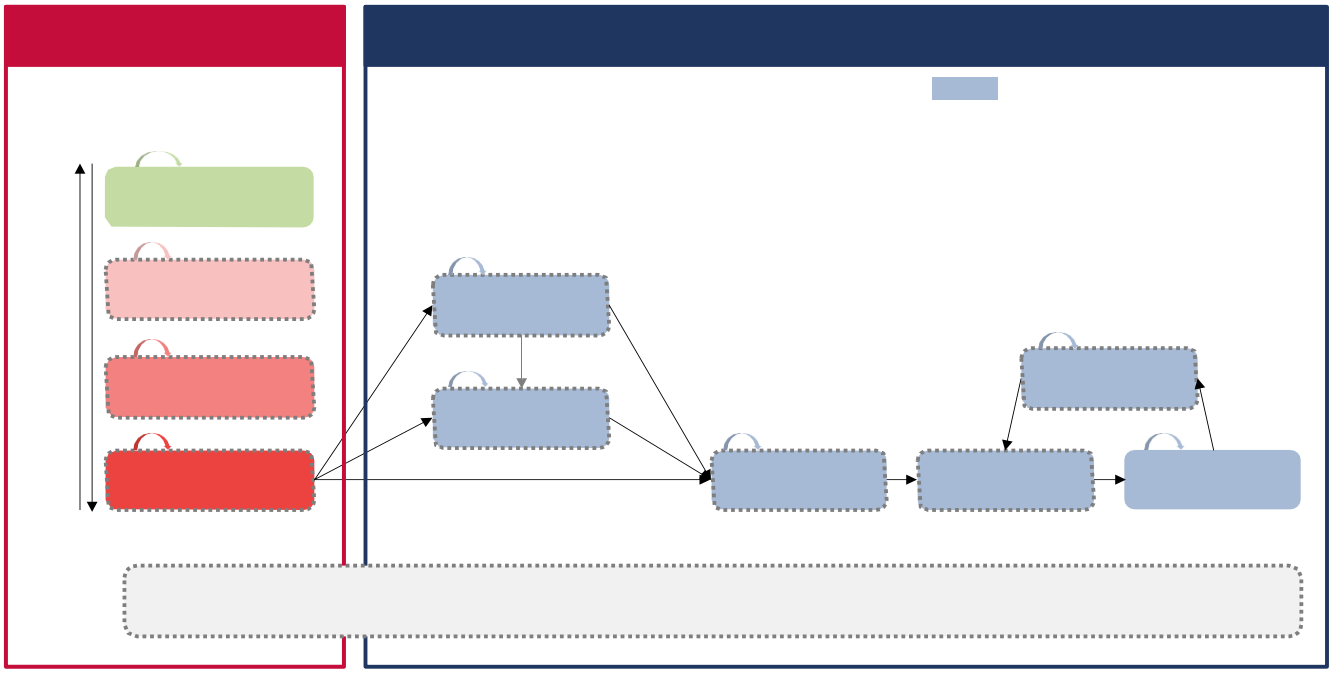
The inclusion of an ALP normalisation state is a notable difference from the approach taken in the OCA and elafibranor NICE appraisals. The previous approach aligned with the composite biochemical response definition, with threshold values of 1.67x ULN for ALP and 1x ULN for total bilirubin (64). The addition of the ALP normalisation health state reflects recent evidence which suggests that ALP normalisation is associated with better long-term outcomes compared to patients with ALP 1-1.67xULN. As previously described in Section 1.3.2.2, a recent analysis of outcomes from the Global PBC Study Group showed that ALP normalisation was associated with higher rates (93.2% vs. 86.1%) of 10 year liver transplant free survival than mild ALP elevation (1 < ALP ≤ 1.67x ULN) (127). Data from the Real-world Evaluation of ALP Normalisation in PBC Patients Receiving Treatment (REAL Study) also suggest increased benefit (i.e., reduction) in progression to advanced liver disease for patients with ALP normalisation vs. ALP 1-1.67xULN (73). Consequently, it has been suggested the goal of treatment should be to achieve complete biochemical normalisation (62, 66).

With a significantly greater proportion of patients achieving normalisation with seladelpar vs. placebo in RESPONSE (25.0% vs. 0.0%, P<0.001), this structure is considered appropriate for capturing the expected benefits of treatment.

Health states included in the advanced liver disease component are consistent with the NICE OCA and elafibranor models: decompensated cirrhosis (DCC), hepatocellular carcinoma (HCC), pre-liver transplant (LT), LT, post-LT (to account for patients waiting for the transplant and recovering from transplant; and the difference in utilities at these different stages) and PBC re-emergence.

A schematic diagram of the model structure is presented in Figure 33.

Figure 33: Schematic diagram of the model structure



Key: ALP: alkaline phosphatase, CC: compensated cirrhosis, PBC: primary biliary cholangitis, TB: total bilirubin, ULN: upper limit of normal

Patients may enter the cost-effectiveness model (CEM) through the four PBC biomarker health states. Based on the RESPONSE trial baseline characteristics, patients only enter the model in the mild and high ALP elevation health states or CC/elevated bilirubin health state. This is outlined in Table 42 in Section 3.2.1. In this component, they can freely transition between the ALP normalisation, mild, high, or CC/elevated bilirubin health states. From the CC/elevated bilirubin state, patients may move to the liver disease component, entering the DCC, HCC, or pre-liver transplant (LT) states.

Patients in the DCC state can stay there or transition to HCC or pre-LT states. Those in the HCC state may remain or move to pre-LT states. In the pre-LT state, patients either stay while awaiting

LT or transition to the LT state. During the LT state, patients undergo a liver transplant and then move to the post-LT state in the next cycle.

In the post-LT state, patients can remain or transition to the PBC re-emergence state. Within the PBC re-emergence state, patients may either stay or receive another liver transplant. From any of these health states, patients can transition to the death state, where they remain for the remainder of the model time horizon. Rates of death from the PBC biomarker states are based on age- and sex-matched general population mortality data (128); in the advanced liver disease states, excess liver-disease-related mortality risks are also considered.

Treatment discontinuation is evaluated in the PBC biomarker component with implications for modelled progression profiles beyond month 12. Patients are also assumed to discontinue treatment upon progression into the advanced liver complication health states, in line with the OCA and elafibranor SmPCs and the anticipated SmPC for seladelpar.

A comparison of the implementation of the key elements of the seladelpar cost-effectiveness model to the OCA and elafibranor NICE appraisal models is provided in Table 43.

Table 44 summarises the main features of the economic analysis.

Table 43: Changes applied in the elafibranor health economic model compared to NICE OCA and elafibranor models

Model aspect	Seladelpar CEM implementation	Key differences: vs. NICE OCA and elafibranor models	[Significance] Notes
Modelling approach	Cohort-level Markov state transition model	N/A	[None] The overall approach is consistent with that of the OCA and elafibranor NICE submission models.
Time horizon	Lifetime	N/A	
Cycle length	Length of 1st and 2nd cycles is aligned with RESPONSE assessment visit interval i.e., 1 and 2 months, respectively. A 3-month cycle length is used beyond this point. A half-cycle correction is included.	In the OCA and elafibranor models, a 3-month cycle length is used for all cycles.	[Low] The difference in approach is considered appropriate as it allows for a more direct representation of the available trial data. The extra granularity allows for a reduction in uncertainty.
General structure	Core health states are included across a PBC biomarker and an advanced liver disease component. A composite (i.e., all-cause) absorbing 'Dead' state is also included.	N/A	[None] The two-component structure is consistent with that of the OCA and elafibranor NICE submission models.
Health states – PBC biomarker component	Defined by ALP and total bilirubin levels and the presence of CC: • ALP normalisation (≤1xULN & TB ≤1xULN)	ALP normalisation health state added. Health states descriptors in the OCA and elafibranor models are based on disease progression risk levels as opposed to ALP elevation but the underlying biomarker and cirrhosis status definitions are consistent.	[Medium] Data from the REAL study that suggests slower progression to advanced liver disease for normal ALP (≤1xULN) vs. 1xULN<ALP ≤1.67xULN & ALP ≥1.67xULN, and ALP normalisation was observed in 25.0% of patients in the seladelpar arm vs 0.0% in the placebo arm

	• Mild ALP elevation (1xULN<ALP ≤1.67xULN & TB ≤1xULN) • High ALP elevation (>1.67xULN & TB ≤1xULN) • Elevated total bilirubin/CC (CC or TB>1xULN)	Liver stiffness score (≥15 kPA) explicitly used in definition for CC in the elafibranor model.	(p<0.001) of the RESPONSE trial. Therefore, the inclusion of an ALP normalisation state is expected to better capture the demonstrated benefit of seladelpar treatment. An ALP normalisation state was not included in the elafibranor model despite this response being observed in 14.8% of elafibranor treated patients vs. 0.0% in the placebo arm (p=0.002) in the ELATIVE trial. However, a PBC health state structure including an ALP normalisation state was evaluated as a scenario in response to a structural uncertainty clarification question. For this implementation, the other PBC state definitions were also re-defined: • Low risk: ALP <ULN, TB≤1xULN • Moderate risk: ALP >ULN, TB≤1xULN • High risk: TB≥1mg/dL or liver stiffness score >15kPA
Health states – Advanced liver disease component	• Decompensated cirrhosis • HCC • Pre-liver transplant • Liver transplant • Post liver transplant • PBC re-emergence	N/A	[None] The approach is consistent with that of the OCA and elafibranor NICE submission models.
Evaluated transitions/risks – PBC	Progression from the PBC biomarker states to the advanced liver disease	The implementation is consistent with the NICE OCA model but differs from the elafibranor model:	[Low/ Medium] The significance of this depends on rates of progression to advanced liver disease from the

biomarker states to advanced liver disease	component is only evaluated from the 'Elevated total bilirubin/CC' state.	In the elafibranor model, patients can also transition to the advanced liver disease component from the moderate risk (i.e., the high ALP elevation state in the seladelpar CEM) PBC biomarker state.	high ALP state observed in the RESPONSE trial and relevant literature. In response to a related clarification question in the elafibranor appraisal, the Company clarified that: "There is no published evidence supporting transition from the moderate PBC state to DCC without experiencing CC. However, clinical experts elicited confirmed such occurrence was possible in the real-world setting. They noted although this occurs only in a very small number of patients, cirrhosis can develop very quickly and is often identified via a bleed resulting in the classification of DCC." In the elafibranor appraisal, cyclical (3-monthly) from moderate PBC transition probabilities as informed by clinical input: • DCC 0.0002 • HCC: 0.0002 • Pre-LT: 0.0006
Evaluated transition/ risks – Treatment waning i.e., PBC biomarker transitions in month 13+	Beyond 12 months, in the base-case only small transitions from high ALP to the CC/elevated bilirubin state are assumed for seladelpar, OCA, or elafibranor while on	No treatment waning effects are assumed for OCA or elafibranor: In both models, no transitions between the PBC biomarker states after month 12 are assumed for OCA or elafibranor.	[Low] The approach is more realistic than that of the elafibranor NICE submission model as some patients in the high ALP state are assumed to progress.

	treatment, based on hazard ratio adjusted calibrations using global and UK PBC data. UDCA / BSC, transition probabilities are used for modelling of subsequent treatments only. For UDCA / BSC, transitions are assumed based on calibrations using global and UK PBC data. Patients may still transition from the mild or moderate state to the severe state beyond month 12.	However, patients may still progress to the advanced liver disease component (per the implementation detailed above). Patients on UDCA monotherapy may still transition from the mild or moderate state to the severe state beyond month 12. In the elafibranor model, no improvements in biomarker status were also assumed for UDCA monotherapy beyond month 12 for patients who discontinued OCA or elafibranor and moved to UDCA.	
Evaluated transitions/risks – Mortality	Transitions to the 'Dead' state are evaluated from all health states – Age- and sex-matched general population mortality probabilities are considered for the PBC health states, while excess liver-related mortality risks are also considered for the advanced liver disease states.	The implementation is consistent with the NICE OCA model but differs slightly from the elafibranor model: Excess mortality risks were also evaluated for the high-risk (i.e., 'Elevated total bilirubin/CC') PBC health state in the elafibranor model.	[Undetermined/ Low] The significance of this depends primarily on observed death rates in the RESPONSE trial and relevant literature. In the elafibranor appraisal, an annual excess mortality probability of 0.012 was evaluated for the high-risk state. Excess mortality probabilities were applied additively to background general population estimates in the Company's base case, but this approach was queried by the EAG – comparisons with the literature suggest lower rates of liver disease survival than expected in clinical practice for this implementation and an implementation where the excess

			mortality probabilities were treated as effective SMRs was preferred i.e., general population mortality probability * (1+excess mortality probability) vs. general population mortality probability + excess mortality probability.
Evaluated transitions/ risks – Discontinuation	Alternative treatment discontinuation probabilities are evaluated for model period months 0-12 and month 13+. Within these periods, the probability of discontinuation is assumed to be constant over time/ model cycles.	In the elafibranor model, the possibility of discontinuation was also considered across the entire model time horizon. The risk profile implementation differed, however, with parametric survival models fit to the time-to-discontinuation endpoint used here. The Company's initial base case applied an exponential model but the effective assumption of a constant probability of discontinuation in time was challenged by the EAG and the log-normal and Gompertz models were considered as more appropriate alternatives. In the OCA model, discontinuation was only considered in the first three model months due to a lack of data to inform profiles beyond this point. The ERG requested a sensitivity analysis in which discontinuation was evaluated for later months i.e., months 3-6, 6-9, 9-12.	[Undetermined/ Medium] The implicit assumption of a constant rate of discontinuation over time in the elafibranor model was challenged by the EAG and this led to the consideration/ use of parametric models which support time-varying hazards to inform discontinuation.
Evaluated transitions/ risks – post-discontinuation progression	Discontinuers are assumed to remain in their existing PBC biomarker state but subsequently follow the disease progression profile for the selected subsequent treatment. Post discontinuation, patients continue to progress according	In the elafibranor model, discontinuers are assumed to revert to their initial PBC biomarker state and subsequently follow the disease progression profile for UDCA monotherapy. The assumption that patients would revert to their baseline state on discontinuation was queried in detail by the EAG.	[Undetermined/ Medium] The adopted approach is justifiable and makes best use of the available data but may be subject to challenge if the evaluated discontinuation profiles result in considerable changes in the distribution of patients across biomarker health states between

	to the derived seladelpar or active comparator treatment transition profiles. Beyond month 12, alternative PBC transition profiles are considered for patients on- and off-treatment for the seladelpar ± UDCA, elafibranor ± UDCA, and OCA ± UDCA strategies.	UDCA monotherapy disease progression profiles were also assumed for UDCA tolerant discontinuers in the OCA appraisal model, while best supportive care profiles were assumed for UDCA intolerant patients.	those on- and off-treatment in the long run.
Analysis populations	The UDCA intolerant and UDCA tolerant, inadequate responder populations are evaluated as independent subgroups.	Independent evaluation of intolerant patients is consistent with the NICE OCA appraisal, which derived transition profiles from the literature for this subgroup. The use of data from the literature was, however, challenged by the NICE ERG and the Committee noted it would prefer trial data to be used. The elafibranor appraisal did not evaluate the UDCA tolerant and intolerant populations separately – trial data for the overall population were used.	[Medium] The appropriateness of independently evaluating the UDCA tolerant, inadequate responder and UDCA intolerant populations depends on the availability of suitable (i.e., sufficient) data from the RESPONSE trial and literature to inform robust ITC / transition profile analyses. The pooled intolerant and tolerant, inadequate responder population approach adopted in the elafibranor appraisal was considered appropriate by the EAG.
Adverse events – Pruritus	Pruritus is included as a long-term adverse disease symptom, considering its effects on quality of life and costs and any changes in its frequency and severity over time as a result of PBC treatment. Treatment-specific mean per-patient utility decrement and cost profiles are evaluated across the model time horizon.	The implementation approach is consistent with the long-term adverse symptom element of the elafibranor model – here pruritus was included as both a short-term, treatment-related adverse event and a long-term adverse disease symptom based on PBC-questionnaire outcomes. For both, quality of life and costs impacts were considered. The effects of pruritus on quality of life were assumed to be captured in the	[Undetermined/ Low] In the elafibranor appraisal, the EAG queried the inclusion of pruritus as both a treatment-related adverse event and as am adverse symptom (based on PBC-40 questionnaire scores) due to the potential for double counting. Its preferred base case considered differences based on PBC-40 scores alone i.e., the frequency of pruritus as a TEAE was assumed equal between the elafibranor and OCA arms to avoid

	Four alternative options for implementing pruritus utility decrements are included in the model, for flexibility. These are discussed in more detail in Section 3.3.2.	applied health state utility profiles in the OCA submission. Short-term management costs were, however, evaluated.	double counting of the impact on quality of life. The seladelpar model implementation is aligned with the EAGs preferred base case. The elafibranor EAG also raised concerns about the use of the PBC-40 questionnaire outcomes as it is not typically used in clinical practice.
Adverse events – Other (i.e., excl. pruritus)	The cost and quality of life impact of other (i.e., excluding pruritus) adverse events are evaluated once on initiation for each treatment.	N/A	[None] The approach is consistent with that of the OCA and elafibranor NICE submission models.
Costs	Included across the following components: • Drug acquisition • Administration • Background health state costs • Pruritus (incl. long-term treatment) • Other adverse events (i.e., excl. pruritus) • Subsequent line treatment • End-life-care	The set of direct cost components included is consistent with the NICE OCA and elafibranor models.	[None] The approach is generally consistent with that of the OCA and elafibranor NICE submission models.
QALY estimation – Health states and event-related decrements	Utility values are assigned to all core health states with decrements evaluated for events i.e., pruritus (continuous) and other adverse events (one-off).	N/A	[None] The approach is generally consistent with that of the elafibranor NICE submission model.

QALY estimation – General population utility adjustments	The option to adjust applied utilities for general population age-related decrements is included and applied as default.	The implementation is consistent with the NICE elafibranor model. Age-related utility decrements were not evaluated in the company base case for the OCA submission and the face validity of the effective implementation was queried by the ERG – the health state utility value for the mild and moderate PBC risk was higher than that of the age-matched general population.	[None] The approach is consistent with that of the elafibranor NICE submission model and addresses issues raised with the original OCA submission approach.

Key: ALP, alkaline phosphatase; BST, best supportive care; CC, compensated cirrhosis; CEM, Cost-effectiveness model; DCC, disease controlling criteria; EAG, Evidence Assessment Group; ERG, external review group; HCC, Hepatocellular carcinoma; ITC, indirect treatment comparison; kPA, kilopascal; OCA, Obeticholic acid; PBC, primary biliary cholangitis; QALY, quality adjusted life year; TB, total bilirubin; ULN, upper limit of normal

Table 44: Features of the economic analysis

Factor	Previous evaluation, TA1016 (elafibranor)	Previous evaluation, TA443 (obeticholic acid)	Current evaluation, chosen values	Current evaluation, justification
Time horizon	Lifetime	Lifetime	Lifetime	Consistent with the NICE reference case, a lifetime time horizon is chosen to sufficiently capture all relevant costs and outcomes associated with the interventions being compared.
Cycle length	Three months	Three months	Lengths of the first and second cycles are one and two months, respectively. A three-month cycle length is used subsequently.	Lengths of first and second cycles are aligned with RESPONSE assessment visit interval. This approach allows for a more direct representation of the available trial data and reduces uncertainties.
Treatment waning effect?	No	No	No	There is no evidence of a waning of treatment effect for seladelpar.
Discount rate	3.5% discount for utilities and costs	3.5% discount for utilities and costs	3.5% discount for utilities and costs	As per the NICE reference case
Perspective (NHS/PSS)	NHS/PSS	NHS/PSS	NHS/PSS	As per the NICE reference case
Source of utilities	Calculated from literature	Sourced from literature	Utilities for base-case ALP health states and pruritus disutility are obtained from mapping while the rest are sourced from literature	HRQoL evidence was not collected through EQ-5D in the RESPONSE trial. The literature sources are appropriate to define liver disease state 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	BNF, eMIT, literature, assumption, NHS reference costs	These are the most appropriate sources to define costs and resource use in the model.

Key: BNF, British national formulary; EQ-5D, Euro QoI 5-Dimension; eMIT, electronic market information tool, HRQoL, health related QoL; NHS, national health service; PSS, personal social services; QoL, quality of life

3.2.3 Intervention technology and comparators

The intervention modelled is seladelpar at a dose of 10 mg daily, per the dosing schedule in the RESPONSE trial. In line with current practice seladelpar is given in combination with UDCA for the tolerant patients and as monotherapy for the intolerant patients.

As detailed in Section 1.3.3, in England, current second-line disease-modifying options comprise OCA and elafibranor (ELA). The approach to management second-line management depends on UDCA tolerance, with both OCA and ELA given in combination with UDCA for tolerant patients and as monotherapy for intolerant patients. Continuation of UDCA monotherapy is not clinically indicated with the availability of additional treatment options. Therefore, as discussed in section 1.1 we do not consider UDCA monotherapy to be a relevant comparator of interest in England for decision-making. Similarly, for UDCA intolerant patients, best supportive care (BSC) is not a relevant option given the availability of OCA and ELA as treatment options. In summary, the model includes the following comparators:

- OCA +/- UCDA
- ELA +/-UCDA

3.3 Clinical parameters and variables

3.3.1 Transition probabilities

3.3.1.1 PBC transition probabilities

PBC biomarker state transition profiles are based on a combination of RESPONSE trial IPD analysis outputs, ITC findings, and calibrations for published long-term outcome data. Alternative transition profiles are evaluated for months 0-12, corresponding to the RESPONSE trial period, and month 13+.

RESPONSE IPD were analysed to inform profiles for seladelpar ± UDCA, UDCA monotherapy (subsequent treatment only), and BSC (subsequent treatment only) (see Section 3.3.1.1.1). Profiles for elafibranor ± UDCA and OCA ± UDCA are estimated

relative to seladelpar ± UDCA based on ITC findings (see Section 2.9 and Section 3.3.1.1.2).

Table 45: Overview of PBC biomarker state transition profiles in the base case

Model time period	Seladelpar ± UDCA	UDCA monotherapy/ BSC**	OCA ± UDCA	ELA ± UDCA
Month 0-12	RESPONSE IPD analysis - Initial treatment profile	RESPONSE IPD analysis - Initial treatment profile**	Based on ITC findings – Relative to seladelpar	Based on ITC findings – Relative to seladelpar
Beyond Month 12	LTFS calibration using HR-adjusted global & UK PBC data	LTFS calibration using global & UK PBC data	LTFS calibration using HR-adjusted global & UK PBC data	LTFS calibration using HR-adjusted global & UK PBC data

Key: BSC, best supportive care;ELA, elafibranor; HR, hazard ratio; ITC, indirect treatment comparison; IPD, individual patient data; LOCF, last observation carried forward; LTFS, liver transplant-free survival; OCA, obeticholica acid; PBC, primary biliary cholangitis; UDCA, ursodeoxycholic acid;
**Used for modelling of subsequent treatments only; not considered relevant comparators.

3.3.1.1.1. Month 0-12 transition probabilities: seladelpar

For the RESPONSE IPD transition analyses (for details, see Appendix M: IPD transition probability analyses), a complete case analysis definition was used in the base case for 'On treatment' patients. That is, transition probabilities were only generated from patients who had provided an observation at a given timepoint. Furthermore, [redacted] was censored following the treatment discontinuation. Patients in the model who discontinue their initial treatment move from their current 'on-treatment' state to the same state in the 'off-treatment' trace, then are allocated the transition probabilities of a subsequent treatment (in the base case to UDCA monotherapy or BSC for the UDCA tolerant and intolerant populations, respectively).

RESPONSE IPD were analysed to inform month 0-12 PBC biomarker transition profiles for seladelpar ± UDCA, UDCA monotherapy, and BSC (note that the latter two serve only to provide transition probabilities for subsequent treatment). To maximise use of the available data, transition probabilities were estimated for each assessment period in RESPONSE: Month 0-1, Month 1-3, Month 3-6, Month 6-9, and Month 9-12. Initially, data were analysed by UDCA tolerance subgroup. However, due to the small

size (n=11 across the seladelpar and placebo arms) of the UDCA intolerant population, data for all patients were used to inform transition probabilities for both the UDCA tolerant and UDCA intolerant subgroups in the model.

The RESPONSE IPD transition analyses were conducted under two alternative analysis definitions:

- Complete data only i.e., transition data are estimated based only on the observed status of patients
- Missing imputed as CC/Elevated TB i.e., patients with missing observations at a given assessment point are classified as being in the CC/Elevated TB state

Transition data for the complete case definition are used in the base case. The transition probabilities for the first 12 months are outlined in Table 46. Month 0-12 discontinuers follow the transition profile of their defined subsequent treatment. In order to achieve this, data for this state are needed to inform transitions beyond month 1 for patients who discontinue to UDCA monotherapy / BSC. Therefore, transition probabilities from the ALP normalisation state for UDCA monotherapy/ BSC were estimated by re-weighting (normalising) the probabilities of transitioning from this state to the Mild ALP, High ALP, or CC/ Elevated TB states estimated for seladelpar in the corresponding cycle. This ensures that patients who discontinue seladelpar ± UDCA/ elafibranor ± UDCA or OCA ± UDCA from the ALP normalisation state do not maintain this response beyond this point.

In the model, these data are adjusted for general population mortality (See Section 3.3.3.1) and, for the CC / elevated TB state, transitions to the advanced liver disease states (Section 3.3.1.1.3).

A limitation of the transition probability analysis was that cirrhosis status was only collected at baseline. Therefore, its influence on health state occupancy is limited to the baseline observation. The original statistical analysis plan for transition probabilities is provided in Appendix M: IPD transition probability analyses.

Table 46: Transition probabilities estimated using RESPONSE trial data (pooled) – seladelpar & UDCA*

Health State:		0-1 months		1-3 months		3-6 months		6-9 months		9-12 months	
From:	**To:**	**SEL**	**UDCA**	**SEL**	**UDCA**	**SEL**	**UDCA**	**SEL**	**UDCA**	**SEL**	**UDCA**
ALP normalisation: *ALP ≤ 1x ULN / TB Normal*	ALP normalisation	0.250	0.250	0.900	0.000	0.958	0.000	0.818	0.000	0.824	0.000
	Mild ALP elevation	0.250	0.250	0.100	1.000	0.042	1.000	0.121	0.667	0.176	1.000
	High ALP elevation	0.250	0.250	0.000	0.000	0.000	0.000	0.030	0.167	0.000	0.000
	CC or Elevated Bilirubin	0.250	0.250	0.000	0.000	0.000	0.000	0.030	0.167	0.000	0.000
Mild ALP elevation: *1 < ALP ≤ 1.67x ULN / TB Normal*	ALP normalisation	0.250	0.000	0.234	0.000	0.189	0.000	0.180	0.000	0.095	0.000
	Mild ALP elevation	0.625	0.667	0.672	0.600	0.774	0.692	0.700	0.867	0.810	0.875
	High ALP elevation	0.000	0.333	0.047	0.400	0.038	0.308	0.100	0.133	0.071	0.063
	CC or Elevated Bilirubin	0.125	0.000	0.047	0.000	0.000	0.000	0.020	0.000	0.024	0.063
High ALP elevation: *ALP > 1.67x ULN/ TB Normal*	ALP normalisation	0.093	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000
	Mild ALP elevation	0.605	0.125	0.229	0.133	0.167	0.130	0.042	0.054	0.160	0.081
	High ALP elevation	0.279	0.854	0.686	0.822	0.667	0.739	0.792	0.946	0.760	0.838

	CC or Elevated Bilirubin	0.023	0.021	0.086	0.044	0.167	0.130	0.167	0.000	0.080	0.081
CC or Elevated Bilirubin: *CC or TB > 1x ULN*	ALP normalisation	0.000	0.000	0.000	0.000	0.067	0.000	0.000	0.000	0.000	0.000
	Mild ALP elevation	0.290	0.182	0.143	0.167	0.267	0.000	0.222	0.333	0.200	0.000
	High ALP elevation	0.355	0.273	0.214	0.833	0.267	0.500	0.222	0.000	0.100	0.250
	CC or Elevated Bilirubin	0.355	0.545	0.643	0.000	0.400	0.500	0.556	0.667	0.700	0.750

Key: ALP, alkaline phosphatase; CC, compensated cirrhosis; SEL, seladelpar; TB, total bilirubin; UDCA, ursodeoxycholic acid; ULN, upper limit of normal

*UDCA monotherapy used for subsequent treatments and calibration purposes only.

3.3.1.1.2. Month 0-12 transition probabilities: obeticholic acid and elafibranor

Currently, direct comparative efficacy data is not available for seladelpar vs. elafibranor or OCA. Furthermore, data from the ELATIVE (elafibranor) and POISE (OCA) trials is not available in the format required to inform transition profiles equivalent to those derived from RESPONSE IPD for seladelpar (See Section 3.3.1.1.1). This is partly due to redaction in publicly available materials and the inclusion of the ALP normalisation health state.

Therefore, indirect treatment comparison (ITC) analyses were conducted to generate comparative efficacy estimates for seladelpar vs. these external comparators for key biochemical response endpoints. The conducted ITC analyses are described in detail in Section 2.9.

Subsequently, efforts were made to ensure model predictions align with the comparative efficacy estimates generated from ITC. To achieve this, month 0-12 transition probabilities to the ALP normalisation and to the Mild ALP elevation states for seladelpar were adjusted by applying hazard ratios for the external comparator. These hazard ratios can be thought of as calibration factors, as they may be difficult to derive from other analyses or interpret in isolation.

Individual calibration factors (hazard ratios) are applied for transitions to the ALP normalisation state and transitions to the Mild ALP elevation state. Calibration targets were set for these based on month 12 relative outcome estimates from the ITC analyses for the ALP normalisation and the Toronto I criteria (ALP<1.67×ULN) endpoints and corresponding model predictions for seladelpar i.e., the proportion of patients in the ALP normalisation and Mild ALP elevation states, respectively. The calibration factors were adjusted simultaneously until predictions for the proportion of patients in each of these states for the comparator matched the set targets.

Table 47 presents the calibration target input data and resultant calibration factors (hazard ratios) for each comparator treatment used in the base-case. Various ITC analyses were conducted to generate robust comparative efficacy evidence across relevant biomarker response endpoints (for details, see Section 2.9). The ITC analyses were based on data from the products' respective clinical trials, namely RESPONSE (seladelpar), ELATIVE (elafibranor), and POISE (OCA). In the base-

case, relative risk (RRs) and odds ratios (ORs) from the primary ITC analyses for elafibranor (anchored and unanchored MAIC) and OCA (Bayesian NMA) are used in the model as the relative outcome measures; where available, ORs for the respective endpoints are used in the base case to estimate calibration targets with RRs used in all other instances. For OCA, results for the 5-10mg dosing group were selected for the model as this is aligned with clinical practice: the starting dose is 5mg once daily with up-titration to 10mg only recommended if deemed necessary due to sub-optimal response and if tolerated. ITC analyses were for the overall trial populations, and the same ORs / RRs were assumed for the UDCA tolerant and UDCA intolerant populations for calibration purposes. The calibrated transition probabilities for the first 12 months are outlined in Table 48.

Table 47: Calibration factors and resultant HRs for external comparators: obeticholic acid and elafibranor

Comparator (Dosing)	Elafibranor ± UDCA		OCA ± UDCA (5-10mg)	
Endpoint	**ALP normalisation ALP ≤ 1 × ULN**	**Toronto I criteria ALP ≤ 1.67x × ULN**	**ALP normalisation ALP ≤ 1 × ULN**	**Toronto I criteria ALP ≤ 1.67x × ULN**
ITC analysis	Unanchored MAIC	Unanchored MAIC	Bayesian NMA	
Effect modifier	RR	OR	OR	OR
Effect	[redacted]	[redacted]	[redacted]	[redacted]
Model predicted proportion – Seladelpar	[redacted]	[redacted]	[redacted]	[redacted]
Comparator 12-month target based on effect modifier	[redacted]	[redacted]	[redacted]	[redacted]
Calibrated HR vs. seladelpar to be applied on TPs	0.7182	0.9081	0.044	1.162

Key: ALP, alkaline phosphatase; HR, hazard ratio; ITC, indirect treatment comparison, NE, not evaluable; NMA, network meta-analysis, OCA, obeticholic acid; OR, odds ratio; RR, relative risk; TP, transition probability; UDCA, ursodeoxycholic acid.

Table 48: Transition probabilities estimated via calibrated HRs – OCA and elafibranor

Health State:		0-1 months		1-3 months		3-6 months		6-9 months		9-12 months	
From:	**To:**	**OCA**	**ELA**	**OCA**	**ELA**	**OCA**	**ELA**	**OCA**	**ELA**	**OCA**	**ELA**
ALP normalisation : *ALP ≤ 1x ULN / TB Normal*	ALP normalisation	0.250	0.250	0.900	0.900	0.958	0.958	0.818	0.818	0.824	0.824
	Mild ALP elevation	0.250	0.250	0.100	0.100	0.042	0.042	0.121	0.121	0.176	0.176
	High ALP elevation	0.250	0.250	0.000	0.000	0.000	0.000	0.030	0.030	0.000	0.000
	CC or Elevated Bilirubin	0.250	0.250	0.000	0.000	0.000	0.000	0.030	0.030	0.000	0.000

Health State:		0-1 months		1-3 months		3-6 months		6-9 months		9-12 months	
From:	**To:**	**OCA**	**ELA**	**OCA**	**ELA**	**OCA**	**ELA**	**OCA**	**ELA**	**OCA**	**ELA**
Mild ALP elevation: *1 < ALP ≤ 1.67x ULN / TB Normal*	ALP normalisation	0.013	0.182	0.012	0.175	0.009	0.139	0.009	0.129	0.004	0.067
	Mild ALP elevation	0.823	0.682	0.867	0.724	0.945	0.821	0.846	0.743	0.891	0.834
	High ALP elevation	0.000	0.000	0.061	0.051	0.046	0.040	0.121	0.106	0.079	0.074
	CC or Elevated Bilirubin	0.165	0.136	0.061	0.051	0.000	0.000	0.024	0.021	0.026	0.025
High ALP elevation: *ALP > 1.67x ULN/ TB Normal*	ALP normalisation	0.004	0.066	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000
	Mild ALP elevation	0.661	0.570	0.260	0.210	0.191	0.153	0.048	0.038	0.184	0.147
	High ALP elevation	0.309	0.336	0.658	0.702	0.647	0.678	0.786	0.795	0.738	0.772
	CC or Elevated Bilirubin	0.026	0.028	0.082	0.088	0.162	0.169	0.166	0.167	0.078	0.081
CC or Elevated Bilirubin: *CC or TB > 1x ULN*	ALP normalisation	0.000	0.000	0.000	0.000	0.003	0.048	0.000	0.000	0.000	0.000
	Mild ALP elevation	0.329	0.268	0.164	0.131	0.303	0.245	0.254	0.204	0.229	0.184
	High ALP elevation	0.335	0.366	0.209	0.217	0.278	0.282	0.213	0.227	0.096	0.102
	CC or Elevated Bilirubin	0.335	0.366	0.627	0.652	0.417	0.424	0.533	0.568	0.675	0.714

Key: ALP, alkaline phosphatase; CC, compensated cirrhosis; ELA, elafibranor; OCA, obeticholic acid; TB, total bilirubin; UDCA, ursodeoxycholic acid; ULN, upper limit of normal

3.3.1.1.3. Month 13+ transition probabilities

In the base case, transitions past the 12-month RESPONSE observation period are estimated via calibration to 10-year liver-free transplant survival (LTFS) outcome data from the Global PBC and UK PBC registry cohorts (64). The starting point for the calibration requires use of the RESPONSE placebo data, as this reflects outcomes for UDCA-treated and untreated patients. Hazard ratios from Perez et al. (129) are then applied to the outcomes predicted from UDCA monotherapy/BSC to generate outcomes for OCA, elafibranor and seladelpar.

Murillo-Perez *et al*. (2022) reported significantly improved transplant-free survival for patients managed with OCA ± UDCA vs. comparable non-OCA external controls inadequately responding to UDCA (129). Specifically, based on six years of POISE trial and OLE follow-up data for OCA and outcome data for propensity-score matched control cohorts from the Global PBC and the UK PBC registries, reported hazard ratios for the first occurrence of liver transplant or death were 0.29 (95% CI, 0.10–0.83) and 0.30 (95% CI, 0.12–0.75), respectively. Accordingly, Global PBC and UK PBC 10-year LTFS data are adjusted by applying hazard ratios to reflect expected improvements in outcomes for patients receiving active management with seladelpar ± UDCA, elafibranor ± UDCA, and OCA ± UDCA. For patients that have discontinued seladelpar, elafibranor, or OCA, the calibrated transition profiles for UDCA monotherapy or BSC progression are assumed according to their tolerance status. The LTFS calibration process is described below.

The calibration process aims to ensure that the transition probabilities to and within the advanced liver disease health states reflect the expected LTFS outcomes for the respective treatment groups. There are five core steps to adjust transition probabilities to align with clinical outcome data; where relevant, the calibration process is repeated in sub-steps for alternative outcome data to generate independent profiles for the respective treatment groups:

- **Step 1** - Transitions from decompensated cirrhosis (DCC): Probabilities calibrated to reflect 10-year LTFS observed in studies, with liver transplant and liver-related death transitions modelled based on risk ratios.

- **Step 2** - Transitions from "severe risk" (i.e., CC / elevated TB state): Probabilities calibrated to match 10-year LTFS data for patients with abnormal total bilirubin levels from the GLOBE and UK PBC cohorts.

- **Step 3** - Transitions from "moderate risk" (High ALP elevation): Probabilities calibrated

    - [**UDCA/BSC subsequent therapies**] to reflect LTFS estimates based on the mean of the UK and GLOBE risk scores, ensuring alignment with worsening prognosis over time.

    - [**Seladelpar / Elafibranor / OCA**] for LTFS outcomes (a) adjusted for primary treatment benefits using a HR.

- **Step 4** - Transitions from "mild risk" (Mild ALP elevation): Probabilities calibrated

    - [**UDCA/BSC subsequent therapies**] Calibrated to reflect a 10-year LTFS consistent with estimates for patients with normal bilirubin and lower ALP levels.

    - [**Seladelpar / Elafibranor / OCA**] for LTFS outcomes (a) adjusted for primary treatment benefits using a HR.

- **Step 5** - Transitions from "ALP normalisation": Probabilities calibrated

    - [**UDCA/BSC subsequent therapies**] Calibrated to reflect a 10-year LTFS consistent with estimates for patients with normalised ALP.

    - [**Seladelpar / Elafibranor / OCA**] for LTFS outcomes (a) adjusted for primary treatment benefits using a HR.

Background (i.e., age- and sex-matched general population) mortality and half-cycle correction are considered in the calibration process. Inputs used in the calibration process are presented in Table 49 below.

With respect to the HRs used for the adjustment of active therapies from Perez et al., (129), the average of the HRs reported for (OCA) POISE vs Global PBC (non-OCA

controls [HR: 0.29; 95% CI, 0.10–0.83] for POISE vs UK-PBC [HR: 0.30; 95% CI, 0.12–0.75] for the LTFS or death endpoint was used (129). All post-month 12 PBC biomarker state transition profiles estimated through the calibration process are presented in Table 50.

Table 49: Liver calibration inputs

Step	Input	Value	Source
Step 1 - DCC	DCC: LTFS 10-year target	10.0%	NICE TA433, below clarification questions Figure 2
	DCC: ratio of death to LT	2.43	NICE TA433, below clarification questions Figure 2
	Pre-LT to LT	35.0%	NICE TA433, Table 54 (refers to Kim 2016)
	Pre-LT to liver death	9.0%	NICE TA433, Table 54 (refers to Kim 2016)
Step 2 – "Severe"	Severe: LTFS 10-year target	39%	NICE TA433, below clarification questions Figure 3
	Severe to HCC	1.4%	NICE TA433, clarification questions Table 20 (refers to Trivedi 2016)
	Severe to Pre-LT	4.0%	NICE TA433, Table 54 (calibrated)
	HCC to Pre-LT	4.0%	NICE TA433, Table 54 (refers to Wright 2016)
	HCC to liver death	43.0%	NICE TA433, Table 54 (refers to Wright 2016)
Step 3 – "Moderate"	(a) [UDCA/ BSC] Moderate: LTFS 10-year	78.0%	NICE TA433, above clarification questions Table 19
	(b) [Seladelpar / Elafibranor / OCA] Moderate: LTFS 10-year target	92.9%	[UDCA/ BSC] Moderate: LTFS 10-year target adjusted for crude average of HRs from Perez 2020: 0.295
	(c) [Seladelpar / Elafibranor / OCA] Moderate: LTFS 10-year target	82.2%	[UDCA/ BSC] Moderate: LTFS 10-year target adjusted for crude average of HRs upper bounds from Perez 2020: 0.790
Step 4 – "Mild"	(a) [UDCA/BSC] Mild: LTFS 10-year target	86.1%	Murillo Perez 2020 (130)
	(b) [Seladelpar / Elafibranor / OCA] Mild: LTFS 10-year target	95.7%	[UDCA/ BSC] Mild: LTFS 10-year target adjusted for crude average of HRs from Perez 2020: 0.295
	(c) [Seladelpar / Elafibranor / OCA]Mild: LTFS 10-year target	88.8%	[UDCA/ BSC] Mild: LTFS 10-year target adjusted for crude average of HRs upper bounds from Perez 2020: 0.790

Step 5 – "ALP normalisation"	(a) [UDCA/BSC] ALP normalisation: LTFS 10-year target	93.2%	Murillo Perez 2020 (64)
	(b) [Seladelpar / Elafibranor / OCA] ALP normalisation: LTFS 10-year target	97.9%	[UDCA/ BSC] ALP normalisation: LTFS 10-year target adjusted for crude average of HRs from Perez 2020: 0.295
	(c) [Seladelpar / Elafibranor / OCA] ALP normalisation: LTFS 10-year target	94.6%	[UDCA/ BSC] ALP normalisation: LTFS 10-year target adjusted for crude average of HRs upper bounds from Perez 2020 (64): 0.790

Key: ALP, alkaline phosphatase; BSC, best supportive care; DCC, decompensated cirrhosis; HCC, hepatocellular carcinoma; LT, liver transplant; LTFS, liver transplant-free survival; OCA, obeticholic acid; UDCA, ursodeoxycholic acid

Table 50: Post-month 12 PBC biomarker transition profiles estimated through calibration

From	To	Initial treatment (i.e., Seladelpar / Elafibranor / OCA) Biomarker progression HR: 0.295	Subsequent treatment (i.e., UDCA mono/ BSC)
ALP normalisation: **ALP ≤ 1x ULN / TB Normal**	**ALP normalisation**	1.0000	0.9987
	Mild ALP elevation	0.0000	0.0000
	High ALP elevation	0.0000	0.0000
	CC or Elevated Bilirubin	0.0000	0.0013
'Mild ALP elevation: **1 < ALP ≤ 1.67x ULN / TB Normal**	**ALP normalisation**	0.0000	0.0000
	Mild ALP elevation	1.0000	0.9878
	High ALP elevation	0.0000	0.0000
	CC or Elevated Bilirubin	0.0000	0.0122
High ALP elevation: **ALP > 1.67x ULN/ TB Normal**	**ALP normalisation**	0.0000	0.0000
	Mild ALP elevation	0.0000	0.0000
	High ALP elevation	0.9983	0.9719
	CC or Elevated Bilirubin	0.0017	0.0281
CC or Elevated Bilirubin: **CC or TB > 1x ULN**	**ALP normalisation**	0.0000	0.0000
	Mild ALP elevation	0.0000	0.0000
	High ALP elevation	0.0000	0.0000
	CC or Elevated Bilirubin	1.0000	1.0000

Key: ALP, alkaline phosphatase; BSC, best supportive care; CC, compensated cirrhosis;HR, hazard ratio; OCA, obeticholic acid; PBC, primary biliary cholangitis; TB, total bilirubin; UDCA, ursodeoxycholic acid; ULN, upper limit of normal

Beyond month 12, patients that have discontinued their initial PBC treatment follow the progression profile of their defined subsequent treatment i.e., UDCA monotherapy or BSC in the base case, according to their UDCA tolerance status. For patients receiving UDCA monotherapy or BSC as subsequent treatment, the long-term progression uses the calibrated LTFS outcomes as described previously.

Based on various clinical assumptions and data from the final assessment period of RESPONSE, alternative scenarios with different PBC biomarker transition profiles beyond month 12 are explored (See Section 3.11.3). These are summarised in Table 51 below.

Table 51: Summary of the beyond month 12 PBC biomarker transition profile options included in the model

Option	Profile description	Relevant treatment strategies	Basis	Limitations
LTFS calibration - Global & UK-PBC data	Transition profiles are calibrated according to published LTFS outcome data for the respective health states. Published LTFS data reflect outcomes for UDCA-treatment or no treatment. These data are adjusted for active treatment (i.e., Seladelpar, elafibranor, or OCA) such that target outcomes for the calibration are improved.	**[Base-case]**	Leverages published long-term outcome data for the respective health states.	LTFS data are not exclusively for patients who have previously inadequately responded to UDCA monotherapy. The active treatment HR is based on OCA outcome data, and this may not fully capture the benefits of seladelpar.
No further progression	No further transitions occur between the PBC biomarker health states.	Seladelpar ± UDCA / elafibranor ± UDCA / OCA ± UDCA	ASSURE LTE study data for seladelpar show sustained response rates for both ALP normalisation and the composite endpoint through year 2+ of treatment.	RESPONSE LTE data for later time points is based on a limited number of observations, and therefore uncertainties remain regarding sustained response at the 2-year point and beyond.

Month 9-12 last observation carried forward (LOCF) – Improvements possible	The transition profile from the final RESPONSE assessment period is carried forward, including for transitions where patients' status improves.	All treatment strategies	Leverages relevant data from RESPONSE – Serves to demonstrate the impact of limiting on further improvements in status (See profile below)	Outcomes are extrapolated based on a limited amount of data.
Month 9-12 LOCF – No improvements possible	The transition profile from the final RESPONSE assessment period is carried forward, but no further improvements in status are permitted.	UDCA monotherapy/ BSC	Leverages relevant data from RESPONSE – There is not a clear mechanism for continued improvements given the population comprises patients who have previously inadequately responded to UDCA treatment, and that no disease-modifying treatments are given as part of BSC.	

Key: ALP, alkaline phosphatase; BSC, best supportive care, HR, hazard ratio, LTE, long-term extension, LOCF, cost observation carried forward; LTFS, liver transplant-free survival; OCA, obeticholic acid, PBC, primary biliary cholangitis.

3.3.1.2 Liver disease health states

Patients may transition to the DCC, HCC and pre-LT advanced liver disease component health states from the CC/ elevated TB biomarker state. In secondary analyses, Perez et al., reported significantly improved event-free survival for hepatic decompensation, liver transplant or death for patients managed with OCA ± UDCA vs. comparable non-OCA external controls inadequately responding to UDCA (129). However, outcome differences among patients with cirrhosis were non-significant [HR: 0.20; 95% CI, 0.03–1.22]; there is currently not a clear basis for differential risks of progression from the CC/ elevated TB state for patients managed with seladelpar, elafibranor, or OCA, and the same set of transition profiles are assumed for all treatments in the model. These transition probabilities are not treatment-specific, since patients discontinue treatment upon progression into these health states. The same probabilities are used regardless of UDCA tolerance in the base-case.

Table 52 presents annual transition probabilities for progression to and between the advanced liver disease states available in the model. These data were either directly sourced from the NICE OCA appraisal (TA443) and/or estimated via calibration using 10-year LTFS outcome data reported in the NICE OCA appraisal (73). The calibration process is described previously in Section 3.3.1.1.3. It is noted similar calibration process using the same 10-year LTFS data was also carried out in the NICE OCA appraisal, but the scope differs here due to the inclusion of the ALP normalisation state. Where estimated, calibrated values derived in the current appraisal are used in the base case.

Table 52: Transition probabilities for the liver disease component health states

From	To	Value	Source
CC or Elevated Bilirubin ***CC or TB > 1x ULN***	**DCC**	10.79%	Calibrated – Global PBC and UK-PBC outcome data reported in NICE TA443 (Ocaliva in PBC). (73)
	HCC	1.00%	NICE TA443 (Ocaliva in PBC). Committee papers Table 54. (73)
	Pre-LT	4.00%	
Decompensated cirrhosis	**HCC**	1.00%	

	Pre-LT	6.80%	Calibrated – Global PBC and UK-PBC outcome data reported in NICE TA443 (Ocaliva in PBC) (73)
	Liver-related mortality	17.00%	NICE TA443 (Ocaliva in PBC). Committee papers Table 54. (73)
Hepatocellular carcinoma	**Pre-LT**	4.00%	
	Liver-related mortality	43.00%	
Pre-LT	**LT**	35.00%	
	Liver-related mortality	9.00%	
LT	**Liver-related mortality**	21.00%	
Post-LT	**PBC rec.**	2.58%	
	Liver-related mortality	6.00%	
PBC recurrence	**LT**	0.08%	
	Liver-related mortality	0.00%	Assumption: No excess mortality in the PBC recurrence health state.

Key: CC, compensated cirrhosis, HCC, hepatocellular carcinoma; LT, liver transplant; PBC, primary biliary cholangitis; TB, total bilirubin; ULN, upper limit of normal

3.3.2 Pruritus

Pruritus is one of the most important adverse events associated with PBC, often impacting patients' quality-of-life. The RESPONSE clinical trial results demonstrated that treatment with seladelpar led to a greater reduction in pruritus, as measured by the pruritus numerical rating scale (range, 0 [no itch] to 10 [worst itch imaginable]), compared to placebo (5). Specifically, in the trial the least-squares mean change from baseline in the pruritus score was −3.2 with seladelpar, versus −1.7 with placebo. The least-squares mean difference between the two groups was −1.5, with a 95% confidence interval of −2.5 to −0.5, and a statistically significant P-value of 0.005. These findings suggest that seladelpar offers a meaningful improvement in managing pruritus symptoms for patients with PBC. By shifting the distribution of patients experiencing mild / moderate / severe pruritus, seladelpar may be associated with improved HCRU and QoL (5, 73).

As such, pruritus is accounted for as a long-term adverse event in the model. Pruritus was modelled as mild, moderate and severe with the definition based on the national pruritus rating scale (131): mild pruritus: <4 points, moderate pruritus: ≥4 - <7, severe pruritus: ≥7. In the model, the shift in the distribution of patients across these levels of

pruritus with treatment drives the differentiation in outcomes. Pruritus can happen in any health state, except for post-liver transplant.

The proportions of patients with different severities of pruritus at different timepoints are outlined in Table 53. Note that not all patients experience pruritus, therefore values might not add up to 100%. The values are sources from RESPONSE patient level data for seladelpar and have been adjusted to account for differences in the distribution of severity at baseline in RESPONSE. Inputs for each timepoint were calculated as changes from baseline, which were then applied to the pooled RESPONSE baseline value. For external comparators, pruritus severity distribution is estimated based on pruritus AE odds ratios from the ITC (see Section 2.9.3.4) in the base-case. A scenario assuming the same pruritus rates as for seladelpar (pruritus AE odds ratios assuming to be 1) is explored:

In the base-case, proportions after the first year are assumed to be the same as at 12 months and are applied through the entire time horizon.

Table 53: Proportion in pruritus severity categories at different timepoints

Treatment strategy	At month 1			At month 3			At month 6			At month 9			At month 12			After month 12			Source
	Mild	Mod	Sev	Mild	Mod	Sev	Mild	Mod	Sev	Mild	Mod	Sev	Mild	Mod	Sev	Mild	Mod	Sev	
UDCA tolerant																			
Seladelpar + UDCA	[redacted]																		RESPONSE
Obeticholic acid + UDCA	[redacted]																		Calculated based on AE ITC odds ratio – SEL vs. ELA: [redacted]
Elafibranor + UDCA	[redacted]																		Calculated based on AE ITC odds ratio – SEL vs. ELA: [redacted]
UDCA-intolerant																			
Seladelpar	[redacted]																		RESPONSE
Obeticholic acid	[redacted]																		Calculated based on AE ITC odds ratio – SEL vs. ELA: [redacted]
Elafibranor	[redacted]																		Calculated based on AE ITC odds ratio – SEL vs. ELA: [redacted]

Key: AE, adverse event; BSC, best supportive care; ELA, elafibranor; Mod, moderate; SEL, seladelpar; Sev, severe; UDCA, ursodeoxycholic acid

3.3.3 Mortality

3.3.3.1 Background (general population) mortality

Mortality in the PBC biomarker health states is based on age- and sex-matched general population rates reported in 2020-2022 national lifetables by the Office of National Statistics. (128). Liver-specific excess mortality is captured within the advanced liver disease transition probabilities (see Table 52).

3.3.4 Discontinuation

As with the PBC biomarker state transition profiles, alternative treatment discontinuation probability profiles are included for months 0-12, corresponding to the RESPONSE trial period, and beyond month 12. For discontinuation rates both in the 0-12 and beyond month 12 cycles, the overall rate of discontinuation is assumed to be equal across all biochemical health states.

In the base-case, discontinuation rates for months 0-12 in the model are based on all-cause discontinuation events reported in the RESPONSE (seladelpar ± UDCA), ELATIVE (elafibranor), and POISE (OCA) trials. Data on the timing of discontinuation events for seladelpar and elafibranor showed no clear temporal pattern, with events occurring relatively evenly in the early and late trial assessment periods (59, 100). Based on this, a constant rate of discontinuation is assumed across cycles for month 0-12 in the model. Annual discontinuation probabilities used to inform cyclical profiles are presented in Table 54.

Data on long-term discontinuation rates beyond month 12 (month 13+) for seladelpar are not available. However, with the at-risk population comprised of a majority of responders (i.e., patients meeting the ALP normalisation or Toronto I criteria endpoints) and with lower adverse event rates expected from month 12 onwards, discontinuation risks are expected to be lower beyond month 12 than in month 0-12. Between week 52 and week 104 of the ELATIVE long-term extension, premature discontinuation of treatment was only reported for 3.13% (3/96) of patients treated with elafibranor versus 11.11% (12/108) in the double-blinded month 0-12 trial observation period. Based on this, discontinuation probabilities beyond month 12 are assumed to be 0.28 of the month 0-12 values in the base case. On the basis that any differences

in discontinuation between treatments are likely to be driven by the occurrence of pruritus and other adverse events in the early phases of treatment, it is further assumed that there is no difference in discontinuation risk between treatments, with the ratio between 0-12 month and beyond month 12 discontinuation rates equal to that observed for seladelpar.

Given the considerable unknowns for this aspect, a number of alternative assumption-based profiles for discontinuation beyond month 12 were evaluated in scenarios (See Section 3.11.3):

- The full seladelpar month 0-12 probability is assumed for all treatments
- Discontinuation is assumed to be a multiple of 0.5 of the seladelpar month 0-12 probability for all treatments
- Discontinuation is assumed to be a multiple of 0.5 for the month 0-12 individual probability for each treatment
- No discontinuation occurs beyond month 12

Table 54: Annual treatment discontinuation probabilities by treatment and model time-period

Model time period	Treatment	n	N	Annual probability	Source
UDCA-tolerant					
Month 0-12	Seladelpar + UDCA	10	128	0.078	RESPONSE TFL, 14.3.1.1.10 (Subjects who discontinued treatment, seladelpar arm; ITT population) (100)
	OCA + UDCA	16	144	0.111	NICE TA443 (Ocaliva). Committee papers pg. 120; Figure 11. (73)
	Elafibranor + UDCA	12	108	0.111	Knowdley 2024 (ELATIVE, suppl. materials, Figure S1 - Overall population, discontinued treatment) (59)
Month 13+	Seladelpar + UDCA	-	-	0.022	0.28 of SEL month 0-12 prob. for all treatments; based on the ratio of year 1 and year 2 (LTE, ELA) disc. in ELATIVE
	OCA + UDCA	-	-	0.022	
	Elafibranor + UDCA	-	-	0.022	
UDCA-intolerant					

Month 0-12	Seladelpar	10	128	0.078	RESPONSE TFL, 14.3.1.1.10 (Subjects who discontinued treatment, seladelpar arm; ITT population) (100)
	OCA	16	144	0.111	NICE TA443 (Ocaliva). Committee papers pg. 120; Figure 11. (73)
	Elafibranor	12	108	0.111	Knowdley 2024 (ELATIVE, suppl. materials, Figure S1 - Overall population, discontinued treatment) (59)
Month 13+	Seladelpar	-	-	0.022	0.28 of SEL month 0-12 prob. for all treatments; based on the ratio of year 1 and year 2 (LTE, ELA) disc. in ELATIVE.
	OCA	-	-	0.022	
	Elafibranor	-	-	0.022	

Key: BSC, best supportive care; ELA, elafibranor, ITT, intent-to-treat; LTE, long-term extension; N, total number of patients; n, number of patients in the category OCA, obeticholic acid; TFL, tables, figures, and listings; UDCA, ursodeoxycholic acid

3.3.5 Safety

Serious adverse events that occurred ≥1 patient are considered in the model. Adverse events are associated with a one-off cost and disutility, happening after treatment initiation in the first cycle.

In the RESPONSE trial, other adverse events reported were less significant compared to the impact of pruritus (5). Adverse event rates in the model for each treatment are informed by data from the products' respective clinical trials, namely RESPONSE (seladelpar & UDCA), ELATIVE (elafibranor), and POISE (OCA). Adverse event incidence rates are outlined in Table 55 and Table 56.

Disutilities associated with other adverse events are discussed in Section 3.4.4.

Table 55: Adverse event (excluding. pruritus) incidence rates – UDCA tolerant

Adverse event	Seladelpar + UDCA			Obeticholic acid + UDCA			Elafibranor + UDCA		
	n	N	AE rate	n	N	AE rate	n	N	AE rate
Acute kidney injury	0	120	0.00%	0	73	0.00%	3	108	2.78%
Diarrhoea	3	120	2.50%	0	73	0.00%	0	108	0.00%
Headache	4	120	3.33%	0	73	0.00%	0	108	0.00%
Hip fractures	0	120	0.00%	0	73	0.00%	2	108	1.85%
Source	RESPONSE (TFL, Table 14.3.1.7.10), UDCA-use population data			Nevens 2016 (POISE, suppl. materials, Table S8 - reported only for overall population)			Knowdley 2024 (ELATIVE, suppl. materials, Table S6 - reported only for overall population)		

Key: AE, adverse event; N, total number of patients; n = number of patients in the category TFL, table figures and listings; UDCA, ursodeoxycholic acid.

Table 56: Adverse event (excluding. pruritus) incidence rates – UDCA intolerant

Adverse event	Seladelpar			Obeticholic acid			Elafibranor		
	n	N	AE rate	n	N	AE rate	n	N	AE rate
Acute kidney injury	0	8	0.00%	0	73	0.00%	3	108	2.78%
Diarrhoea	0	8	0.00%	0	73	0.00%	0	108	0.00%
Dry eye / dry mouth	0	8	0.00%	0	73	0.00%	0	108	0.00%
Rash erythematous / rash papular, erysipelas	0	8	0.00%	0	73	0.00%	0	108	0.00%
Headache	0	8	0.00%	0	73	0.00%	0	108	0.00%
Hip fractures	0	8	0.00%	0	73	0.00%	2	108	1.85%
Osteoarthritis	0	8	0.00%	2	73	2.74%	0	108	0.00%
Source	RESPONSE (TFL, Table 14.3.1.7.10), UDCA-intolerant data			Nevens 2016 (POISE, suppl. materials, Table S8 - reported only for overall population)			Knowdley 2024 (ELATIVE, suppl. materials, Table S6 - reported only for overall population)		

Key: AE, adverse event; N, total number of patients; n = number of patients in the category; TFL, tables figures and listings UDCA, ursodeoxycholic acid.

3.4 Measurement and valuation of health effects

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

HRQoL evidence was not collected through a generic preference elicitation instrument in the RESPONSE trial. However, a mapping exercise was conducted to derive health state utility values for the biomarker health states from PBC-40 observations collected in RESPONSE (see Section 3.4.2). For the liver disease health states, utility values were obtained from the literature (see section 3.4.3).

3.4.2 Mapping

PBC-40 questionnaire data were collected at baseline and months 1, 3, 6, 9, and 12 and mapping exercises were conducted to generate EQ-5D data from this for consideration in the model. Details of the mapping methodology are described in detail in a separate report (132) and are summarized below.

The PBC-40 questionnaire is a disease-specific patient-reported measure designed to assess the impact of PBC on quality of life across six domains: fatigue, mood, social quality and cognitive state, itch and other symptoms. It is particularly useful to support and guide the management of PBC due to its evidence about the symptom burden and its impact on the lives of patients.

As mentioned in 3.4.1, a generic preference elicitation instrument was not used in the RESPONSE trial. An external dataset from the ITCH-E study was used to develop a mapping algorithm to translate disease-specific PBC-40 responses into EQ-5D utility scores while the GLIMMER trial was used for external validation.

The ITCH-E study was a real-world study with the aim of understanding how patients with PBC characterise itching and its impact, if any, on their daily lives and quality of life. Ninety patients were recruited, and they completed PROs which included the PBC-40 and EQ-5D questionnaires. The GLIMMER trial was a multicentre, double-blind, randomized, placebo-controlled study, following 4 weeks single-blind placebo, patients received linerixibat or placebo till week 16. The PBC-40 questionnaire and 5D itch scale was completed by the participants recruited at the visits. This study assessed the relationship between the pruritus severity and sleep disturbance in participants regardless of treatment group.

The following steps were included in the mapping exercise:

- Step 1: The ITCH-E dataset was divided into a training set (80%) and a test set (20%). The models were trained using the training dataset and tested with the test dataset. Various models were explored to identify the optimal model that best predicted the EQ-5D-5L health utility values from PBC-40 domain scores.

- Step 2: Internal validation was conducted using 10-fold cross-validation, and accuracy metrics such as MAE, RMSE, and R^2 were examined for all models to determine the best fit.

- Step 3: The models were applied to predict EQ-5D-5L utility index scores based on PBC-40 responses collected in the RESPONSE trial.

- Step 4: The mapping algorithm was externally validated using the GLIMMER trial to ensure generalisability.

Predictive models were developed to map RESPONSE PBC-40 data to five-level EQ-5D (EQ-5D-5L) values, using both direct and indirect mapping approaches. Direct mapping regressed EQ-5D utility values against PBC-40 dimensions, while indirect mapping treated each EQ-5D dimension as a dependent variable, utilizing ordinal regression models to predict response probabilities.

For the direct mapping, five alternative statistical models were employed to predict EQ-5D health state utility values based on PBC-40 scores and baseline characteristics such as age and sex:

- Ordinary Least Squares (OLS)
- Tobit Model (around mean)
- Tobit Model (around median)/Censored Least Absolute Deviation (CLAD)
- Beta regression
- Extended Beta Regression (Bias Correction/ Reduction)
    - In cases of small sample size, this method produces the same results as standard beta regression that uses maximum likelihood estimation; hence results are not included here as they were the same.

In addition, two-part OLS and Tobit and log-transformed two-part OLS and Tobit models were fitted.

For the indirect mapping, EQ-5D domain responses were predicted individually based on PBC-40 scores and baseline characteristics such as age and sex using an ordinal logistic regression. The proportional odds assumption was fulfilled as confirmed by a Brant test.

All fitted models were evaluated based on root mean square error (RMSE) and mean absolute error (MAE) value. These are presented in Table 57. R^2, Mean Absolute Percentage Error (MAPE) and concordance correlation coefficient (CCC) values were

also evaluated. With the lowest RMSE and MAE values, the OLS was deemed to be the best predictive model.

Equivalent analyses were conducted for the three-level EQ-5D (EQ-5D-3L).

Table 57: Predictive accuracy of the model using cross-validation

	RESPONSE EQ-5D-5L		RESPONSE EQ-5D-3L	
Model	**RMSE**	**MAE**	**RMSE**	**MAE**
OLS	0.169	0.124	0.169	0.127
Tobit (mean)	1.680	1.254	0.183	0.146
Tobit (median)	0.182	0.142	0.184	0.145
Beta regression	0.176	0.139	0.188	0.149
Two-Part-OLS	0.178	0.135	0.177	0.139
Two-Part (Tobit)	0.180	0.134	0.179	0.140
Long-Transform Two-part with OLS	0.351	0.319	0.510	0.444
Long-Transform Two-part with Tobit	0.355	0.323	0.454	0.393

Key: EQ-5D, Euro QoL 5-Dimension; MAE mean absolute error; OLS, ordinary least squares; RMSE, root mean square error;

The mapped EQ-5D-5L utility data with OLS are presented in Table 58.

Table 58: Mapped EQ-5D utility data

Visit	EQ-5D-5L		EQ-5D-3L	
	Mean	**SE**	**Mean**	**SE**
Baseline	[redacted]	[redacted]	[redacted]	[redacted]
Month 12	[redacted]	[redacted]	[redacted]	[redacted]

Key: EQ-5D-3L, EuroQol-5 Dimension-3 Levels; EQ-5D-5L, EuroQol-5 Dimension-5 Levels; SE, standard error

To estimate PBC biomarker health state utility and pruritus utility decrements values based on RESPONSE data, mixed models for repeated measures (MMRMs) were fitted to the EQ-5D-5L and EQ-5D-3L utility data obtained through mapping. MMRMs are well suited for the analysis of longitudinal clinical trial data for continuous outcomes, such as utility values, and are commonly used for this purpose; the fitted models included a random effect component for patient ID to account for potential correlation due to repeated measurements over time. Separate models were fitted with fixed effects for 1) baseline utility and the PBC biomarker health states and 2) baseline utility, the PBC biomarker health states and PBC-40 itch domain score (Mild: ≥1 to <7; Clinically severe: ≥7). This was done to allow for appropriate exploration of alternative

assumptions regarding pruritus disutility values in the model. The specification of the fitted models for the EQ-5D-5L and ED-5L-3L are presented in Table 59 and Table 60.

Table 59: Specification of the MMRMs fitted to EQ-5D-5L utility data mapped from RESPONSE

Coefficient	Estimate	SE	Pr(>|t|)
MMRM 1 – PBC biomarker states only			
(Intercept)	0.1170	0.0202	0.0000
BASE	0.8790	0.0238	0.0000
Health.StateLow Risk	0.0044	0.0072	0.5368
Health.StateModerate Risk	-0.0112	0.0073	0.1269
Health.StateHigh Risk	-0.0196	0.0090	0.0303
MMRM 2 – PBC Biomarker states and itch score			
(Intercept)	0.1551	0.0224	0.0000
BASE	0.8425	0.0251	0.0000
Health.StateLow Risk	0.0056	0.0071	0.4325
Health.StateModerate Risk	-0.0074	0.0073	0.3071
Health.StateHigh Risk	-0.0150	0.0090	0.0958
ItchMild itch	-0.0051	0.0059	0.3885
ItchCS itch	-0.0323	0.0076	0.0000

Key: MMRM, mixed-effects model for repeated measures; PBC, primary biliary cholangitis; Pr, p-value; SE, standard error.

Table 60: Specification of the MMRMs fitted to EQ-5D-3L utility data mapped from RESPONSE

Coefficient	Estimate	SE	Pr(>|t|)
MMRM 1 – PBC biomarker states only			
(Intercept)	0.1327	0.0205	0.0000
BASE	0.8634	0.0240	0.0000
Health.StateLow Risk	0.0046	0.0079	0.5627
Health.StateModerate Risk	-0.0137	0.0081	0.0891
Health.StateHigh Risk	-0.0237	0.0100	0.0176
MMRM 2 – PBC Biomarker states and itch score			
(Intercept)	0.1703	0.0228	0.0000
BASE	0.8272	0.0252	0.0000
Health.StateLow Risk	0.0058	0.0079	0.4619
Health.StateModerate Risk	-0.0097	0.0080	0.2295
Health.StateHigh Risk	-0.0187	0.0099	0.0592
ItchMild itch	-0.0041	0.0065	0.5238
ItchCS itch	-0.0345	0.0084	0.0000

Key: MMRM, mixed-effects model for repeated measures; PBC, primary biliary cholangitis; Pr, p-value SE, standard error.

The health state utility values (HSUVs) were then derived from the MMRMs. Separate utility values were derived for the RESPONSE MMRMs with and without itch considering a baseline utility value of [redacted] for the EQ-5D-5L models and a baseline utility of [redacted] for the EQ-5D-3L models. This was done to allow for flexible inclusion

of pruritus disutility. When pruritus disutility is included in the CEM, the model applies the utility values for MMRM (3L or 5L) with itch scores. When the CEM does not include pruritus disutility, utility values for MMRM (3L or 5L) without itch scores (No pruritus disutility) are applied.

The utility values for ALP normalisation health state were assumed equal to the Mild ALP elevation value, due to face validity issues i.e., a lower utility value is estimated for the ALP normalisation state. Itch Mild itch was defined by PBC-40 itch domain scores of ≥1 to <7 and the coefficient for this covariate was assumed for both mild (<4 points) and moderate pruritus (moderate: ≥4 - <7), while ItchCS itch was defined by scores ≥7 and the coefficient for this was assumed for severe pruritus (severe: ≥7). The utility values derived from MMRMs are presented in Table 61.

Table 61: HSUVs and pruritus disutility derived from MMRMs

HSUVs				
PBC biomarker health state	**RESPONSE EQ-5D-5L MMRM 1 – No pruritus disutility**	**RESPONSE EQ-5D-5L MMRM 2 – Incl. pruritus disutility**	**RESPONSE EQ-5D-3L MMRM 1 – No pruritus disutility**	**RESPONSE EQ-5D-3L MMRM 2 – Incl. pruritus disutility**
ALP normalisation	[redacted]	[redacted]	[redacted]	[redacted]
Mild ALP Elevation	[redacted]	[redacted]	[redacted]	[redacted]
High ALP Elevation	[redacted]	[redacted]	[redacted]	[redacted]
CC or Elevated Bilirubin	[redacted]	[redacted]	[redacted]	[redacted]

Itch severity disutility value		
Pruritus severity	**RESPONSE EQ-5D-5L MMRM**	**RESPONSE EQ-5D-3L MMRM**
Mild (<4 points)	-0.0051	-0.0041
Moderate (≥4 - <7 points)	-0.0051	-0.0041
Severe (≥7 points)	-0.0323	-0.0345

Key: ALP, alkaline phosphatase; CC, compensated cirrhosis, EQ-5D-5L, EQ-5D-3L; EuroQol-5 Dimension-3 Levels; EuroQol-5 Dimension-5 Levels; HSUVs, health state utility values; MMRM, mixed-effects model for repeated measures; PBC, primary biliary cholangitis; Pr, p-value SE, standard error

3.4.3 Health-related quality-of-life studies

An SLR was conducted in August 2024, to identify studies reporting HRQoL data associated with PBC. Full details of the methodology and results of included studies

are presented in Appendix F. In total, seven studies from 14 publications articles reporting utility data were identified; the seven studies are presented in Table 63. Based on the findings of the SLR, disutility values for pruritus were derived as the difference between utility values reported for the general PBC population (0.870) from Rice et al (18) (Table 63) and utility values reported for each pruritus severity level in the Smith et al. (Table 64) (133-135). As this yields a higher disutility in the mild vs. moderate pruritis states, the average was applied to both mild and moderate health states, aligned with the approach with the mapped disutilities. The disutility values are presented in Table 65.

Table 62: Summary of the results of utility studies included in the economic SLR

Study	Country	Population	Study type	Instrument	Results
Bondini 2007 (136)	US	18 PBC patients	Observational (prospective cohort)	HUI (Mark 2 and Mark 3)	HUI utility value reported as 0.81 (SD=0.1) in PBC population.
Longworth 2003 (121)	UK	122 PBC patients assessed for transplantation and followed up for a maximum of 24 months post-surgery	Observational (prospective cohort)	EQ-5D index	Mean EQ-5D scores of transplantation patients before and after transplantation were reported in a graph. Extracted values are presented in Table 113
Rice 2021 (18)	UK	4,583 participants in the UK-PBC research cohort	Observational (cross-sectional)	EQ-5D-5L index	Full results reported are presented in Table 63.
Skat-Rørdam 2024 (137)	Denmark	69 patients with PBC	Observational (cross-sectional)	EQ-5D-5L index	Mean index value: 0.7945
Cortesi 2020 (138)	Italy	66 patients with PBC	Observational (prospective cohort)	EQ-5D-3L index	Mean index value (SD): 0.872 (0.112) Median index value (IQR):

					0.887 (0.827–0.915)
Wunsch 2023 (139, 140)	Global	386 patients with PBC	Observational (cross-sectional)	EQ-5D-5L index	Mean index value: 0.730
GLIMMER trial (Smith 2023) (133-135)	Global	Patients with PBC from the GLIMMER trial	Randomized-controlled trial	EQ-5D-5L index	Full results are presented in Table 64.

Table 63 Utility values from Rice et al.

Patient Group	EQ-5D index (95% CI)	
	Pre-transplant	Post-transplant
No symptoms/no complications	0.917 (0.901–0.933)	0.838 (0.791–0.886)
Itching/no complications	0.899 (0.880–0.917)	0.897 (0.761–1.034)
Fatigue/no complications	0.842 (0.820–0.865)	0.644 (0.538–0.749)
Bone ache/no complications	0.756 (0.725–0.787)	0.697 (0.591–0.802)
Other symptoms/ no complications	0.832 (0.806–0.858)	0.833 (0.719–0.946)
≥1 symptom/no complications	0.721 (0.708–0.735)	0.600 (0.537–0.664)
≥1 symptom /varices	0.727 (0.686–0.767)	-
≥1 symptom /ascites	0.596 (0.550–0.642)	-
≥1 symptom / hepatic encephalopathy	0.694 (0.658–0.731)	-
≥1 symptom / liver cancer	0.778 (0.689–0.868)	-
≥1 symptom /≥ 1 complications	0.663 (0.638–0.688)	-

Table 64 Utility values from Smith 2023 et al.

Cohort	Baseline utility value, mean (SD)
Severe pruritus	0.490
Mild pruritus	0.750
Moderate pruritus	0.760
Mild sleep impairment	0.830
Severe sleep impairment	0.520
Severe itch + severe sleep disturbance	0.470
Minimal depression	0.780
Severe depression	0.400
Mild depression + severe pruritus	0.280
Moderate depression + severe pruritus	0.290
Severe depression + severe pruritus	0.300

Table 65 Pruritus disutility derived from Smith and Rice et al.

Pruritus severity	General PBC population from Rice et al (18)	Reported utility values from Smith et al. (133-135)	Calculated disutility
Mild (<4 points)	0.870	0.7500	-0.1150 (0.7550 – 0.870)
Moderate (≥4 - <7 points)		0.7600	-0.1150 (0.7550 – 0.870)
Severe (≥7 points)		0.4900	-0.3800 (0.4900 – 0.870)

No other studies identified were collectively sufficient to parametrise HSUVs in the CEM, so alternative sources were sought. Specifically, utility inputs were sourced separately from the NICE elafibranor and OCA appraisals.

For consistency and comparability with previous appraisals, the same set of liver disease utility values were used in the base-case of both the NICE elafibranor and OCA appraisals. However, the elafibranor evidence assessment group (EAG) base case used an alternative value for the high-risk health state (equivalent to CC or Elevated Bilirubin in the seladelpar model): a utility value of 0.550 was used in the company base case, sourced from a 2006 RCT-based study of the health benefits of antiviral therapy among mild chronic hepatitis C conducted by Wright et al., (141). The EAG base case used a value of 0.717 reported in an SLR and meta-analysis of Health utilities in Patients with Chronic Hepatitis C published by Saeed et al., in 2020. The EAG noted that the Wright et al., value of 0.555 was included in the meta-analysis, but that it was the lowest included value. An ALP normalisation state was not included in either the elafibranor and OCA models, and the utility for the mild risk state was assumed as a result.

Additionally, HRQoL following liver transplant is expected to vary with time since transplant. In the current CEM, utility values may be specified for the following post-liver transplant timepoints: 3 months, 6 months, 12 months, and 24 months. However, no time-dependent utility data was identified for post-liver transplant and, as with the approach taken in the NICE OCA and elafibranor appraisals, the same

value was assumed for all time points. Similarly, the same utility value was assumed for the pre-liver transplant and liver transplant health states.

These are summarised in Table 66.

Table 66: Health state utilities from NICE elafibranor and OCA appraisals

Health state	Mean	Source
ALP normalisation	0.8400	Assumed to be the same as mild risk state
Mild ALP Elevation	0.8400	Per TA1016 / TA443 – Company base case
High ALP Elevation	0.8400	Per TA1016 / TA443 – Company base case
CC or Elevated Bilirubin	0.5500	Per TA1016 / TA443 – Company base case
	0.7170	TA1016 / TA443 – EAG preferred implementation
Decompensated cirrhosis*	0.3800	Previously reported value(142), via TA443
Hepatocellular carcinoma	0.4500	Previously reported value(142), via TA443
Pre-liver transplant*	0.3800	Previously reported value(142), via TA443
Liver transplant*	0.3800	Previously reported value(142), via TA443
Post-liver transplant: 3 months*	0.5700	Previously reported value(142), via TA443
Post-liver transplant: 6 months*	0.5700	Previously reported value(142), via TA443
Post-liver transplant: 12 months*	0.5700	Previously reported value(142), via TA443
Post-liver transplant: 24 months*	0.5700	Previously reported value(142), via TA443
PBC recurrence	0.6700	Previously reported value (KOL), via TA443

Key: ALP, alkaline phosphatase; CC, compensated cirrhosis; EAG, external assessment group; OCA, obeticholic acid; PBC, primary biliary cholangitis; TA, technology appraisal

3.4.4 Adverse events

Disutility values for other adverse events were considered in the CEM. As discussed in Section 3.3.5 the model accounts for the most significant adverse events. Disutility values for other adverse events are evaluated once on treatment initiation (i.e., in cycle) according to the specified incidence rates for each preferred term event. Default disutility values were sourced from published literature, including NICE TA688 for selective internal radiation therapies in HCC and the catalogue of EQ-5D scores for the UK publication by Sullivan et al., and are presented in Table 67 below.

Table 67: Adverse event disutility values

Adverse event	Disutilities	Source
Acute kidney injury	-0.0480	NICE TA688 [143]
Diarrhoea	-0.1030	Peasgood 2010 [144] (Diarrhoea and vomiting)
Dry eye / dry mouth	-0.2020	NICE TA688 [143] - assumed same as rash
Rash erythematous / rash papular, erysipelas	-0.2020	NICE TA688 [143]
Headache	-0.0266	Sullivan 2011 [145]
Hip fractures	-0.1480	PHE 2018 (page 22 [0.582-0.73]) [146]
Osteoarthritis	-0.1017	Sullivan 2011 [145]

Key: NICE, National Institute of Health and Care Excellence; PHE, Public Health England; TA, Technology appraisal.

3.4.5 Health-related quality-of-life data used in the cost-effectiveness analysis

3.4.5.1 Health state utility values

In the base case, ALP biomarker health state utility values were based on the mapping exercise of the RESPONSE trial as previously presented in Section 3.4.2. Specifically, ALP biomarker health state utility values (except CC or Elevated Bilirubin state) from RESPONSE EQ-5D-3L-MMRM including pruritus disutility were applied in the base-case. This ensured that regardless of source, any pruritis disutility applied would not already be captured within the core ALP health state values, as this was controlled for in the mapping regression. For CC or Elevated Bilirubin state, utility values from the EAG preferred implementation in TA1016 / TA443 were used (see Section 3.4.3). This is due to the unexpected directional difference in utility between the High ALP Elevation state and CC or Elevated Bilirubin state from the mapping exercise (See Table 61). This is potentially driven by the low sample size in the CC or Elevated Bilirubin state (N =125 observations in the utility analysis, 12% of the overall sample), which reduces the reliability of the utility estimates as lower sample sizes reduces the statistical power of the analyses.

The liver disease health state utility values were based on previous NICE elafibranor and OCA appraisals as presented in Section 3.4.3.

The effects of pruritus on quality of life were accounted for via the application of disutility values for each mild, moderate, and severe pruritus as defined by the PBC-40 measure. Specified disutility values are applied continuously (i.e., across the entire model time horizon) to the proportion of patients estimated within each severity group (See Section 3.3.2) over time. In the base case, literature-based disutilities from Smith et al. (see Table 65) are used as utility was directly elicited from PBC patients with pruritis using the EQ-5D, whereas the values from the RESPONSE trial were mapped from another measure. The Smith et al. utility values therefore sit higher up NICE's hierarchy of preferred utility methods (147). A scenario with the trial-based pruritis disutilities presented in Table 61 is explored.

Table 68 outlines utility values used in the model.

Table 68: Summary of utility values for cost-effectiveness analysis

State	Utility value: mean (standard error)	95% confidence interval	Reference in submission (section and page number)	Justification
ALP normalisation	[redacted]	-	Section 3.4.2, Page 179	3L utility values from the mapping exercise of the RESPONSE trial
Mild ALP Elevation	[redacted]	-	Section 3.4.2, Page 179	3L utility values from the mapping exercise of the RESPONSE trial
High ALP Elevation	[redacted]	-	Section 3.4.2, Page 179	3L utility values from the mapping exercise of the RESPONSE trial
CC or Elevated Bilirubin	0.7170 (0.021)	0.68-0.76	Section 3.4.3, Page 184	EAG preferred implementation in TA1016 / TA443
Decompensated cirrhosis	0.3800 (0.04)	0.31-0.46	Section 3.4.3, Page 184	Previously reported value(142), via TA443
Hepatocellular carcinoma	0.4500 (0.05)	0.36-0.54	Section 3.4.3, Page 184	Previously reported value(142), via TA443
Pre-liver transplant	0.3800 (0.04)	0.31-0.46	Section 3.4.3, Page 184	Previously reported value(142), via TA443
Liver transplant	0.3800 (0.04)	0.31-0.46	Section 3.4.3, Page 184	Previously reported value(142), via TA443

Post-liver transplant: 3 months	0.5700 (0.06)	0.46-0.68	Section 3.4.3, Page 184	Previously reported value(142), via TA443
Post-liver transplant: 6 months	0.5700 (0.06)	0.46-0.68	Section 3.4.3, Page 184	Previously reported value(142), via TA443
Post-liver transplant: 12 months	0.5700 (0.06)	0.46-0.68	Section 3.4.3, Page 184	Previously reported value(142), via TA443
Post-liver transplant: 24 months	0.5700 (0.06)	0.46-0.68	Section 3.4.3, Page 184	Previously reported value(142), via TA443
PBC recurrence	0.6700 (0.07)	0.54-0.79	Section 3.4.3, Page 184	Previously reported value (KOL), via TA443

Key: ALP, alkaline phosphatase; CC, compensated cirrhosis; KOL, key opinion leader; OCA, obeticholic acid; PBC, primary biliary cholangitis; TA, technology appraisal

3.4.5.2 Disutilities

As summarised in Section 3.4.2 and Section 3.4.4, disutilities for pruritus and AEs, respectively, are included in the CEM. In the base-case, values from Smith et al., 2023 are used. The disutilities applied in the model are summarised in Table 69.

Table 69: Disutilties applied in the cost-effectiveness model

Cause	Disutility	Reference in submission (section and page number)
Mild pruritus (<4 points)	-0.115	Section 3.4.3, Page 184
Moderate pruritus (≥4 - <7 points)	-0.115	Section 3.4.3, Page 184
Severe pruritus (≥7 points)	-0.380	Section 3.4.3, Page 184
Acute kidney injury	-0.0480	Section 3.4.4, Page 188
Diarrhoea	-0.1030	Section 3.4.4, Page 188
Dry eye / dry mouth	-0.2020	Section 3.4.4, Page 188
Rash erythematous / rash papular, erysipelas	-0.2020	Section 3.4.4, Page 188
Headache	-0.0266	Section 3.4.4, Page 188
Hip fractures	-0.1480	Section 3.4.4, Page 188
Osteoarthritis	-0.1017	Section 3.4.4, Page 188

3.5 Cost and healthcare resource use identification, measurement and valuation

The model includes the following direct cost categories:

- Treatment acquisition and administration costs
- Health state costs
- AE 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 NHS Cost Inflation Index (NHSCII) (148).

3.5.1 Intervention and comparators' costs and resource use

Drug dosage and acquisition costs are shown in Table 70, and the total monthly costs for each regimen are summarised in Table 71.

The acquisition cost of seladelpar includes a simple PAS discount off list price of and [redacted] the dosage of seladelpar was taken from the RESPONSE trial. Acquisition costs of all other treatments were sourced from British National Formulary (BNF) NHS indicative price and based on the dosing schedule according to their respective product labels.

The model accounts for the titration of obeticholic acid. This was based on the POISE trial where patients received obeticholic acid at 5mg once daily for the initial six-month period. The patients in POISE were only up-titrated to 10 mg once daily if they did not reach the primary endpoint criteria for response. In the model the average daily dose for the first 6 months is 5mg and 10 mg thereafter.(73).

Table 70: Treatment dosages and unit costs

Treatment	Average daily dose		Unit costs (£)			Costs per month (£)		Reference
	Month 0-6	Month 7+	Per unit, mg	Units per pack	Cost per pack	Month 0-6	Month 7+	
Seladelpar	10 mg	10 mg	10	30	[redacted]	[redacted]	[redacted]	NHS PAS price
OCA	5 mg	10 mg	5 10	30 30	2,384.04 2,384.04	2,418.81	2,418.81	OCA; BNF, NHS indicative price
Elafibranor	80 mg	80 mg	80	30	£2,867.00	2,908.81	2,908.81	NHS indicative price

Key: BNF, British national formulary; kg, kilogram; mg, milligram; NHS, national health system; OCA, obeticholic acid; PAS, patient access scheme; UDCA, ursodeoxycholic acid

Table 71: Overall treatment monthly costs

Treatment strategy	Month 0-6	Month 7+
UDCA tolerant		
Seladelpar + UDCA	[redacted]	[redacted]
OCA + UDCA	£2,492.33	£2,492.33
Elafibranor + UDCA	£2,982.33	£2,982.33
UDCA intolerant		
Seladelpar	[redacted]	[redacted]
OCA	£2,418.81	£2,418.81
Elafibranor	£2,908.81	£2,908.81

Key: BSC, best supportive care; OCA, obeticholic acid; UDCA, ursodeoxycholic acid.

The model does not include drug administration costs as seladelpar is orally administered and is delivered through Homecare medicines service.

3.5.2 Health-state unit costs and resource use

An SLR was conducted in August 2024, to identify studies reporting costs and healthcare resource use (HCRU) associated with PBC (149). A total of 31 studies received from 44 publications were included in this review. The majority of studies were conducted in the US (n=19) and only one study (18) in the UK (149). Subsequently, majority of the health-state unit costs and resource use were sourced from previous NICE appraisals for OCA (73) and elafibranor (72). The UK study by Rice et al (2021) (18) identified in the SLR was used to inform the excess HCRU costs in the post-transplant phase.

HCRU for the mild and high ALP elevation health states in the PBC biomarker component were sourced from NICE TA443 submission for OCA (73). HCRU for ALP normalisation is assumed to be the same as mild ALP health state. Similarly, HCRU for compensated cirrhosis or elevated bilirubin, HCC, and decompensated cirrhosis were sourced from Wright 2006 (141). To quantify the costs associated with the identified HCRU, unit costs were obtained from NHS reference costs (150).

To provide a comprehensive breakdown of the costs associated with LT, costs associated with pre-LT, LT, and post-LT health states were sourced from the NICE HST17 submission in the base-case, in line with the approach taken in the NICE

elafibranor submission (72). The costs of liver transplant and pre-liver transplant are one-time costs, whereas the rest of the costs are annual costs.

A list of health states and associated costs in the economic model is presented in Table 72.

Table 72: List of health states and associated costs in the economic model

Health state	Resource	Resource use per time period	Cost per unit (£)	Time period	Source
ALP normalisation	Blood test / liver function test	9.00	2.00	Annual	Assumption; 2022/23 National Cost Collection data (DAPS03 - Clinical biochemistry)(150)
	Total cost per time period (£)	**18.00**			
Mild ALP Elevation	Outpatient appointment	2.00	235.00	Annual	NICE TA443 (73); 2022/23 National Cost Collection data (Weighted average of WF01A - WF01D and WF02A - WF02D codes; Hepatobiliary and Pancreatic)(150)
	Blood test / liver function test	9.00	2.00		NICE TA443 (73); 2022/23 National Cost Collection data (DAPS03 - Clinical biochemistry)(150)
	Total cost per time period (£)	**487.00**			
High ALP Elevation	Outpatient appointment	3.00	235.00	Annual	NICE TA443 (73); 2022/23 National Cost Collection data (Weighted average of WF01A - WF01D and WF02A - WF02D codes; Hepatobiliary and Pancreatic)(150)
	Blood test / liver function test	9.00	2.00		NICE TA443 (73); 2022/23 National Cost Collection data (DAPS03 - Clinical biochemistry)(150)
	Total cost per time period (£)	**722.00**			
Compensated cirrhosis or Elevated Bilirubin	Outpatient appointment	4.62	235.00	Annual	Wright 2006(141); 2022/23 National Cost Collection data (Weighted average of WF01A - WF01D and WF02A - WF02D codes; Hepatobiliary and Pancreatic)(150)
	Inpatient admission	0.57	2,821.00		Wright 2006(141); 2022/23 National Cost Collection data (Weighted average of GC01C-GC01E codes) (150)

	Hepatic angiography	0.13	234.00		Wright 2006(141); 2022/23 National Cost Collection data (GB11Z, Diagnostic Endoscopic Retrograde Cholangiopancreatography; Hepatobiliary and Pancreatic)(150)
	Endoscopy	0.31	2,364.00		Wright 2006(141); 2022/23 National Cost Collection data (GB13Z, Endoscopic Ultrasound Examination, of Hepatobiliary or Pancreatic Duct; Hepatobiliary and Pancreatic)(150)
	Liver biopsy	0.26	940.00		Wright 2006(141); 2022/23 National Cost Collection data (GA04D, Complex, Hepatobiliary or Pancreatic Procedures; Hepatobiliary and Pancreatic)(150)
	Total cost per time period (£)	**3,700.00**			
Decompensated cirrhosis	Outpatient appointment	5.74	235.00	Annual	Wright 2006(141); 2022/23 National Cost Collection data (Weighted average of WF01A - WF01D and WF02A - WF02D codes; Hepatobiliary and Pancreatic)(150)
	Inpatient admission	3.10	2,821.00		Wright 2006(141); 2022/23 National Cost Collection data (Weighted average of GC01C-GC01E codes) (150)
	Hepatic angiography	0.18	234.00		Wright 2006(141); 2022/23 National Cost Collection data (GB11Z, Diagnostic Endoscopic Retrograde Cholangiopancreatography; Hepatobiliary and Pancreatic)(150)
	Endoscopy	2.27	2,364.00		Wright 2006(141); 2022/23 National Cost Collection data (GB13Z, Endoscopic Ultrasound Examination, of Hepatobiliary or Pancreatic Duct; Hepatobiliary and Pancreatic)(150)
	Liver biopsy	0.07	940.00		Wright 2006(141); 2022/23 National Cost Collection data (GA04D, Complex, Hepatobiliary or Pancreatic Procedures; Hepatobiliary and Pancreatic)(150)
	Total cost per time period (£)	**15,566.00**			

Hepatocellular carcinoma	Outpatient appointment	5.74	235.00	Annual	Wright 2006(141); 2022/23 National Cost Collection data (Weighted average of WF01A - WF01D and WF02A - WF02D codes; Hepatobiliary and Pancreatic)(150)
	Inpatient admission	3.10	2,821.00		Wright 2006(141); 2022/23 National Cost Collection data (Weighted average of GC01C-GC01E codes) (150)
	Hepatic angiography	0.65	234.00		Wright 2006(141); 2022/23 National Cost Collection data (GB11Z, Diagnostic Endoscopic Retrograde Cholangiopancreatography; Hepatobiliary and Pancreatic)(150)
	Endoscopy	0.46	2,364.00		Wright 2006(141); 2022/23 National Cost Collection data (GB13Z, Endoscopic Ultrasound Examination, of Hepatobiliary or Pancreatic Duct; Hepatobiliary and Pancreatic)(150)
	Liver biopsy	0.30	940.00		Wright 2006(141); 2022/23 National Cost Collection data (GA04D, Complex, Hepatobiliary or Pancreatic Procedures; Hepatobiliary and Pancreatic)(150)
	Total cost per time period (£)	**11,613.00**			
Pre-LT	-	-	22,164.00	One-off	NICE HST17 (Per NICE TA1016 (ELA) costing approach (Pg. 143))
LT	Procedure-related HCRU	-	79,120	One-off	NICE HST17 (Per NICE TA1016 (ELA) costing approach (Pg. 143))
	Organ cost	-	20,096		NICE HST17 (Per NICE TA1016 (ELA) costing approach (Pg. 143))
	Retrieval of organ	-	27,694		NICE HST17 (Per NICE TA1016 (ELA) costing approach (Pg. 143))
	Post-LT (first 2-years)	-	44,203		NICE HST17 (Per NICE TA1016 (ELA) costing approach (Pg. 143))
	Immunosuppressants (azathioprine, tacrolimus)	-	71.22 (annual cost)		Dosing: BNF (Per NICE TA1016 (ELA) costing approach (Pg. 143))
	Total one-off cost (£)	**171,185.00**			

Post-LT (0-12 months)	Immunosuppressants (azathioprine, tacrolimus)	-	71.22 (annual cost)	Annual	Dosing: BNF (Per NICE TA1016 (ELA) costing approach (Pg. 143))
	Excess HCRU	-	3,854.00		Rice et al., 2021 (Per NICE TA1016 (ELA) costing approach (Pg. 143))
	Total cost per time period (£)	**3,925.00**			
Post-LT (12-24 months)	Immunosuppressants (azathioprine, tacrolimus)	-	71.22 (annual cost)	Annual	Dosing: BNF (Per NICE TA1016 (ELA) costing approach (Pg. 143))
	Excess HCRU	-	3,854.00		Rice et al., 2021 (Per NICE TA1016 (ELA) costing approach (Pg. 143))
	Total cost per time period (£)	**3,925.00**			
PBC recurrence	Outpatient appointment	3.21	235.00	Annual	Assumed average of mild ALP elevation, moderate ALP elevation and CC or elevated bilirubin HCRU; 2022/23 National Cost Collection data (Weighted average of WF01A - WF01D and WF02A - WF02D codes; Hepatobiliary and Pancreatic)(150)
	Inpatient admission	0.57	2,821.00		Assumed average of mild ALP elevation, moderate ALP elevation and CC or elevated bilirubin HCRU; 2022/23 National Cost Collection data (Weighted average of GC01C-GC01E codes) (150)
	Blood test / liver function test	9.00	2.00		Assumed average of mild ALP elevation, moderate ALP elevation and CC or elevated bilirubin HCRU; 2022/23 National Cost Collection data (DAPS03 - Clinical biochemistry)(150)
	Hepatic angiography	0.13	234.00		Assumed average of mild ALP elevation, moderate ALP elevation and CC or elevated bilirubin HCRU; 2022/23 National Cost Collection data (GB11Z, Diagnostic Endoscopic Retrograde Cholangiopancreatography; Hepatobiliary and Pancreatic)(150)

	Endoscopy	0.31	2,364.00		Assumed average of mild ALP elevation, moderate ALP elevation and CC or elevated bilirubin HCRU; 2022/23 National Cost Collection data (GB13Z, Endoscopic Ultrasound Examination, of Hepatobiliary or Pancreatic Duct; Hepatobiliary and Pancreatic)(150)
	Liver biopsy	0.26	940.00		Assumed average of mild ALP elevation, moderate ALP elevation and CC or elevated bilirubin HCRU; 2022/23 National Cost Collection data (GA04D, Complex, Hepatobiliary or Pancreatic Procedures; Hepatobiliary and Pancreatic)(150)
	Total cost per time period (£)	**3,386.00**			

Key: ALP, alkaline phosphatase; HCRU, healthcare resource use, LT, liver transplant; PBC, primary biliary cholangitis

3.5.3 Adverse reaction unit costs and resource use

3.5.3.1 Pruritus costs

Pruritus related cost inputs were calculated in the model based on healthcare utilisation rates of services across different levels of pruritus (mild, moderate, severe), leveraged from the NICE elafibranor submission (72). These are outlined in Table 73. Pruritus treatment costs were included in the model. The pruritus treatment dose and costs are outlined below in Table 74. In case of multiple formulations, the formulation with the cheapest cost per mg was used.

Table 73: Pruritus related cost inputs

Cost element	% use (mild pruritus)	% use (moderate pruritus)	% use (severe pruritus)	Source
Outpatient visit (doctor)	100%	100%	100%	NICE ID6331 (Elafibranor), Committee papers (72)
Outpatient visit follow-up (doctor)	100%	100%	100%	NICE ID6331 (Elafibranor), Committee papers (72)
Blood test monitoring	100%	100%	100%	NICE ID6331 (Elafibranor), Committee papers (72)
Colestyramine	30%	30%	30%	NICE ID6331 (Elafibranor), Committee papers (72) Table 60. *(inputs reported for OCA and UDCA)*
Rifampicin	30%	30%	30%	NICE ID6331 (Elafibranor), Committee papers (72) Table 60. *(inputs reported for OCA and UDCA)*
Naltrexone	5%	5%	5%	NICE ID6331 (Elafibranor), Committee papers (72) Table 60. *(inputs reported for OCA and UDCA)*
Gabapentin	15%	15%	15%	NICE ID6331 (Elafibranor), Committee papers (72) Table 60. *(inputs reported for OCA and UDCA)*
Bezafibrate	20%	20%	20%	NICE ID6331 (Elafibranor), Committee papers (72) Table 60. (inputs reported for OCA and UDCA)

Key: HCRU, healthcare resource utilization; OCA, obeticholic acid; UDCA, ursodeoxycholic acid .

Table 74 Pruritus treatment dose and costs

Pruritus treatment	Dose	Source	Monthly cost	Source
Colestyramine	6g	BNF, Colestyramine	£9.81	Calculation based on Colestyramine NHS indicative price from BNF (151)

Rifampicin	525 mg	Düll 2022 (152)	£22.74	Calculation based on Rifampicin NHS indicative price from BNF (151)
Naltrexone	150 mg	Düll 2022 (152)	£75.01	Calculation based on Naltrexone NHS indicative price from BNF (151)
Gabapentin	-	Monthly cost directly taken from NICE ID6331, Elafibranor (Committee Papers, Table 61.) (72)	£2.32	NICE ID6331, Elafibranor (Committee Papers, Table 61.) (72)
Bezafibrate	-	Monthly cost directly taken from NICE ID6331, Elafibranor (Committee Papers, Table 61.) (72)	£7.74	NICE ID6331, Elafibranor (Committee Papers, Table 61.) (72)

Key: BNF, British national formulary; NHS, national health system

Annual resource usage and unit costs associated with pruritus management was sourced from the elafibranor NICE submission (72) and is reported in Table 75.

Table 75: Pruritus related health care resource use

Cost element	Annual resource use (mild pruritus)	Annual resource use (moderate pruritus)	Annual resource use (severe pruritus)	Unit cost (£)	Source
Outpatient visit (doctor)	1	1	2	£220	NICE ID6331 (Elafibranor), Committee papers (72) Table 59. *(mild and moderate pruritus: inputs reported for mild itch, Severe pruritus: inputs reported for clinically significant itch*) and Table 61. *(unit costs)*
Outpatient visit follow-up (doctor)	2	2	4	£179	
Blood test monitoring	2	2	4	£2	

Key: NICE, national institute for health and care excellence

3.5.3.2 Other adverse event costs

As discussed in Section 3.3.5 and Section 3.4.4 the model accounts for the most significant adverse events. As TEAEs are assumed to occur in the first cycle as a one-off, the costs of these events were assumed to last for the duration of one cycle and are outlined in Table 76.

Table 76: Adverse event unit costs

Adverse event	Mean	Source
Acute kidney injury	£618.72	National Schedule of NHS Costs 2022/23. NES; [LA07H, J, K, L, M, N] Acute Kidney Injury without intervention or with Interventions, all cc scores.
Diarrhoea	£546.08	National Schedule of NHS Costs 2022/23. NES; [FD10A-H, FD10J-M] Non-Malignant Gastrointestinal Tract Disorders without Interventions, with Single Intervention, with Multiple Interventions, all cc scores.
Dry eye / dry mouth	£49.00	PSSRU. Unit Costs of Health and Social care 2023. Unit costs for a GP. Per surgery consultation lasting 10 minutes.
Rash erythematous / rash papular, erysipelas	£483.83	National Schedule of NHS Costs 2022/23. NES; [JD07A-H, FD10J-K] Skin Disorders without Interventions and with Interventions, all cc scores.
Headache	£441.08	National Schedule of NHS Costs 2022/23. NES; [AA31C-E] Headache, Migraine or Cerebrospinal Fluid Leak, all cc scores.
Hip fractures	£1,032.15	National Schedule of NHS Costs 2022/23. NES; [HE11A-H] Hip Fracture without Interventions, with Single Intervention, with Multiple Interventions, all cc scores.
Osteoarthritis	£49.00	PSSRU. Unit Costs of Health and Social care 2023. Unit costs for a GP. Per surgery consultation lasting 10 minutes.

Key: GP, general practitioner; NHS, national health services, PSSRU, Personal Social Services Research Unit

3.5.4 Miscellaneous unit costs and resource use

3.5.4.1 Subsequent treatment costs

The model assumes that upon progression, patients will primarily receive UDCA alone or best supportive care in the next line of treatment, based on on the lack of clear guidelines for later lines of treatment. For UDCA, where multiple formulations are available, the formulation with the least “wastage” (excess mg of active ingredient beyond the weight-based daily dose) was selected. If multiple formulations had the same “wastage,” the formulation with the higher strength was chosen to minimise the number of tablets a patient needs to take. This approach also assumes that only one formulation of UDCA is prescribed per patient.

Table 29 shows the current subsequent treatment selections implemented in the model. In the NICE submission for elafibranor, a similar approach was taken, where

third-line treatment after both elafibranor and OCA consisted of UDCA and best supportive care (72).

Although the EAG acknowledged that this subsequent treatment approach aligned with the original scope developed with NICE, they raised some concern about the actual use of alternative strategies in clinical practice (72). The EAG discussed a treatment approach with elafibranor and OCA in sequence, as a strategy given their different mechanisms of action. They highlighted the current data gap to directly support this approach but had confirmation from clinical experts in the field that this is a viable treatment strategy.

The proposed updated approach would allow a mix of treatments upon second-line discontinuation; for example, after seladelpar discontinuation, 50% of patients could receive elafibranor, 30% obeticholic acid, and the remainder BSC. This would also allow for flexibility to include combination regimens, as discussed by the EAG. Only subsequent treatment costs, not efficacy, would be impacted by this change (72).

Due to data availability, the proposed updated approach was not implemented in the current model.

Table 77: Subsequent treatments in the model

Initial treatment	Subsequent treatment	Source	Cost per month (£)	Source
UDCA-tolerant				
Seladelpar + UDCA	UDCA monotherapy	Assumption	73	Calculated in the model
OCA + UDCA	UDCA monotherapy	Assumption	73	Calculated in the model
Elafibranor + UDCA	UDCA monotherapy	Assumption	73	Calculated in the model
UDCA-intolerant				
Seladelpar	BSC	Assumption	0	Calculated in the model
OCA	BSC	Assumption	0	Calculated in the model
Elafibranor	BSC	Assumption	0	Calculated in the model

Key: BSC, best supportive care; OCA, obeticholic acid; UDCA, ursodeoxycholic acid

3.5.4.2 End-of-life care costs

End-of-life care costs are included to account for additional resource use in the final months of life and are applied in the cycle of death for DCC and HCC patients. This approach and the cost inputs are in line with the elafibranor NICE submission. Cost upon death in DCC is £10,902 (based on Gola et al) and cost upon death in HCC is £8,805 (based on NICE TA666) (153). Gola *et al.*, evaluated 205 hospitalisation costs among end-stage liver disease patients in the UK and reported a mean per patient cost of terminal admission cost, which is used in the model.(154). These costs are outlined below in Table 78.

Table 78: End of life costs

Cost element	Unit cost (£)	Source
Decompensated cirrhosis	£10,902	Gola 2015 (154)
Hepatocellular carcinoma	£8,805	NICE TA666 (153)

3.6 Severity

The QALY shortfall calculations have been assessed for a cohort with an average age of 57 and a female proportion of 95% as per the RESPONSE trial as summarised in Table 79. QALY shortfall from previous evaluations are summarised in Table 80 and health state benefits and utility values for QALY shortfall analysis are presented in Table 81. The results indicate that the seladelpar does not meet the criteria for a QALY weighting and are summarised in Table 82.

Table 79: Summary features of QALY shortfall analysis

Factor	Value (reference to appropriate table or figure in submission)	Reference to section in submission
Sex distribution	94.8% (female)	Section 3.2.1
Starting age	56.7	Section 3.2.1

Key: QALY, quality-adjusted life year

Table 80: Summary list of QALY shortfall from previous evaluations

TA	Expected total QALYs for the general population	Expected total QALYs that people living with a condition would be expected to have with current treatment	QALY shortfall
TA443	Age: 56	UDCA intolerant	UDCA intolerant

	% of females: 91% 14.15	Population: No treatment: 6.61 OCA titration: 13.52 UDCA inadequate responder population: UDCA: 7.85 OCA titration + UDCA: 13.64	Population: No treatment: 7.54 OCA titration: 0.63 UDCA inadequate responder population: UDCA: 6.30 OCA titration + UDCA: 0.51
TA1016	Age: 57 % of females: 97% 13.84	OCA: 7.58 UDCA: 6.49 Elafibranor: redacted	OCA: 6.26 UDCA: 7.35 Elafibranor: N.A.

Key: OCA, obeticholic acid; QALY, quality-adjusted life year; TA, technology appraisal; UDCA, ursodeoxycholic acid

Table 81: Summary of health state benefits and utility values for QALY shortfall analysis

Not applicable; shortfall not achieved.

Table 82: Summary of QALY shortfall analysis

Expected total QALYs for the general population	Total QALYs that people living with a condition would be expected to have with current treatment	QALY shortfall
UDCA-tolerant		
13.46	Seladelpar + UDCA	[redacted]
	OCA + UDCA	4.0311
	Elafibranor + UDCA	3.6060
UDCA-intolerant		
13.46	Seladelpar	[redacted]
	OCA	4.0491
	Elafibranor	3.5607

Key: BSC, best supportive care; OCA, obeticholic acid; QALY, quality-adjusted life years; UDCA, ursodeoxycholic acid

3.7 Uncertainty

In past appraisals, the key areas of uncertainty comprised relative effectiveness in the absence of head-to-head data (elafibranor vs, OCA) and the relationship between biomarkers and long-term clinical outcomes.

Regarding indirect evidence, Gilead has conducted a robust ITC which, unlike in the elafibranor appraisal, has included adjustment for imbalanced effect modifiers. Regarding the relationship between surrogates and long-term outcomes, the clinical inputs for the economic model relied on the 12-month RESPONSE trial outcomes. This limited timeframe means that complications such as cirrhosis and liver failure associated with advanced stages of PBC may not be fully captured in the model due

to the slow and progressive nature of the disease. However, ALP and TB levels are well-established surrogate endpoints to predict long-term clinical benefit (See Section 1.3.2.1.5).

3.8 Managed access proposal

Not applicable.

3.9 Summary of base-case analysis inputs and assumptions

3.9.1 Summary of base-case analysis inputs

A summary of the input parameters of the economic models can be found in Appendix L: Summary of base-case analysis inputs.

3.9.2 Assumptions

Model structure & clinical basis

- The cohort is initially distributed across the 'Mild ALP elevation', 'High ALP elevation' and 'CC/ Elevated bilirubin' PBC biomarker component health states.
- ALP normalisation (ALP<1xULN) and the Toronto I criteria (ALP<1.67xULN) are clinically relevant determinants of patient outcomes.
- All patients with DCC or HCC are candidates for liver transplantation.

Treatment efficacy and Outcomes

- Treatment-specific transition probabilities between PBC biomarker states up to 12 months determine outcomes such as ALP normalisation and Toronto I criteria.
- Indirect treatment comparisons (ITCs) against OCA and ELA on ALP normalisation and Toronto I criteria inform the respective arm transition probabilities.

- Beyond month 12, transition probabilities in the PBC biomarker states can differ between initial therapies (seladelpar/ elafibranor / OCA) and subsequent therapies (UDCA monotherapy / BSC) based on chosen assumptions.
- Discontinuation is assumed to occur at a constant rate in the Month 0-12 period and the Month 12+ period.
- There are no differences in discontinuation between seladelpar ± UDCA/ elafibranor ± UDCA/ and OCA ± UDCA beyond Month 12.
- Month 12: based on data from RESPONSE (seladelpar), ELATIVE (elafibranor), and POISE (OCA).
- Month 12+: based on the ratio of year 1 to year 2 discontinuation risks for elafibranor in ELATIVE and its LTE (0.28) and the month 0-12 discontinuation probability for seladelpar.
- Mortality risks in the PBC biomarker health states are per the age- and sex-matched general population.
- Excess mortality risks apply in the advanced liver disease states, according to published outcome data.
- Transition probabilities in the advanced liver disease component are treatment-independent.

Safety

- Pruritus is a long-term (lifetime) adverse disease outcome and can occur in any living health state, except for 'post-liver transplant'.
- The quality of life and cost implications of pruritus vary by severity: Mild, Moderate, Severe (PBC-40 itch domain (mild: ≥1 - <4 points, moderate pruritus: ≥4 - <7, severe pruritus: ≥7).

- Other adverse events are associated with a one-off cost and utility decrement in the month of treatment imitation.

Costs

- Background health state costs are treatment-independent.

Utility values

- Health state and pruritus utility outcomes are treatment-independent, with differences captured indirectly via modelled transition and pruritus outcome profiles.

3.10 Base-case results

3.10.1 Base-case incremental cost-effectiveness analysis results

The base-case cost-effectiveness analysis results are presented in Table 83 and Table 84. Seladepar +/- UDCA was cost-effective vs. elafibranor +/- UDCA and OCA +/- UDCA within NICE's willingness to pay (WTP) threshold of £20,000-£30,000/QALY.

Table 83: UDCA-tolerant: base-case results, using the PAS price of seladelpar

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER versus baseline (£/QALY)	ICER incremental (£/QALY)
Seladelpar + UDCA	[redacted]	[redacted]	[redacted]	-	-	-	-	-
OCA + UDCA	384,110	15.458	9.432	[redacted]	[redacted]	[redacted]	Strictly Dominated	Strictly Dominated
Elafibranor + UDCA	445,408	15.503	9.857	[redacted]	[redacted]	[redacted]	Strictly Dominated	Strictly Dominated

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

Table 84: UDCA-intolerant: base-case results, using the PAS price of seladelpar

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER versus baseline (£/QALY)	ICER incremental (£/QALY)
Seladelpar	[redacted]	[redacted]	[redacted]	-	-	-	-	-
OCA	369,860	15.458	9.414	[redacted]	[redacted]	[redacted]	Strictly Dominated	Strictly Dominated
Elafibranor	430,967	15.503	9.903	[redacted]	[redacted]	[redacted]	Strictly Dominated	Strictly Dominated

Key::BSC, best supportive care, ICER, incremental cost-effectiveness ratio; LYG, life years gained; OCA, obeticholic acid, QALYs, quality-adjusted life years, UDCA, ursodeoxycholic acid

Table 85: UDCA-tolerant: pairwise net health benefit, using the PAS price of seladelpar

Technologies	Total costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs	NHB at £20,000	NHB at £30,000
Seladelpar + UDCA	[redacted]	[redacted]	-	-	-	-
OCA + UDCA	384,110	9.432	[redacted]	[redacted]	1.051	0.969
Elafibranor + UDCA	445,408	9.857	[redacted]	[redacted]	3.690	2.587

Key: ICER, incremental cost-effectiveness ratio; NHB, net health benefit; OCA, obeticholic acid, QALYs, quality-adjusted life years, UDCA, ursodeoxycholic acid

Table 86: UDCA-intolerant: pairwise net health benefit, using the PAS price of seladelpar

Technologies	Total costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs	NHB at £20,000	NHB at £30,000
Seladelpar	[redacted]	[redacted]	-	-	-	-
OCA	369,860	9.414	[redacted]	[redacted]	1.196	1.105
Elafibranor	430,967	9.903	[redacted]	[redacted]	3.763	2.653

Key: BSC, best supportive care, ICER, incremental cost-effectiveness ratio; NHB, net health benefit; OCA, obeticholic acid, QALYs, quality-adjusted life years, UDCA, ursodeoxycholic acid

3.10.2 Disaggregated results

Disaggregated QALYs and costs by health state are presented in Appendix H: Clinical outcomes and disaggregated results from the model.

3.11 Exploring uncertainty

3.11.1 Probabilistic sensitivity analysis

The probabilistic sensitivity analysis (PSA) quantifies the level of confidence in the output of the analysis, in relation to uncertainty in the model inputs, where input parameters were represented as distributions around the point estimate. Input parameter values were drawn by random sampling from each distribution using Monte Carlo Simulation methods until convergence was reached (250 simulations). The mean PSA results are presented in Table 87 and Table 88, with ICERs representing pairwise results for seladelpar +/- UDCA vs. each comparator. Net Health Benefit (NHB) for seladelpar + UDCA vs each comparator is presented at a WTP threshold of £20,000. The results are aligned with the base case results, with seladepar +/- UDCA remaining cost-effective vs. elafibranor +/- UDCA and OCA +/- UDCA at a WTP threshold of £20,000/QALY.

The cost-effectiveness acceptability curves (CEACs) for the two populations are presented in Figure 34 and Figure 35. Seladelpar +/- UDCA had a 54-51% (UDCA-tolerant) and 54-52% (UDCA-intolerant) probability of being the most cost-effective treatment at NICE's WTP corridor of £20,000-£30,000/QALY. Elafibranor had a zero % probability of being the most cost-effective treatment at these thresholds in both populations.

Table 87: UDCA-tolerant: discounted probabilistic pairwise results, using the PAS price of seladelpar

Technology	Total costs (£)	Total LYs	Total QALYs	Incremental costs (£)	Incremental LYs	Incremental QALYs	ICER incremental (£/QALY)	NHB at £20,000
Seladelpar + UDCA	[redacted]	[redacted]	[redacted]				-	-
OCA + UDCA	384,250	15.462	13.046	[redacted]	[redacted]	[redacted]	37,182	0.080
Elafibranor + UDCA	445,902	15.536	12.838	[redacted]	[redacted]	[redacted]	Dominant	3.371

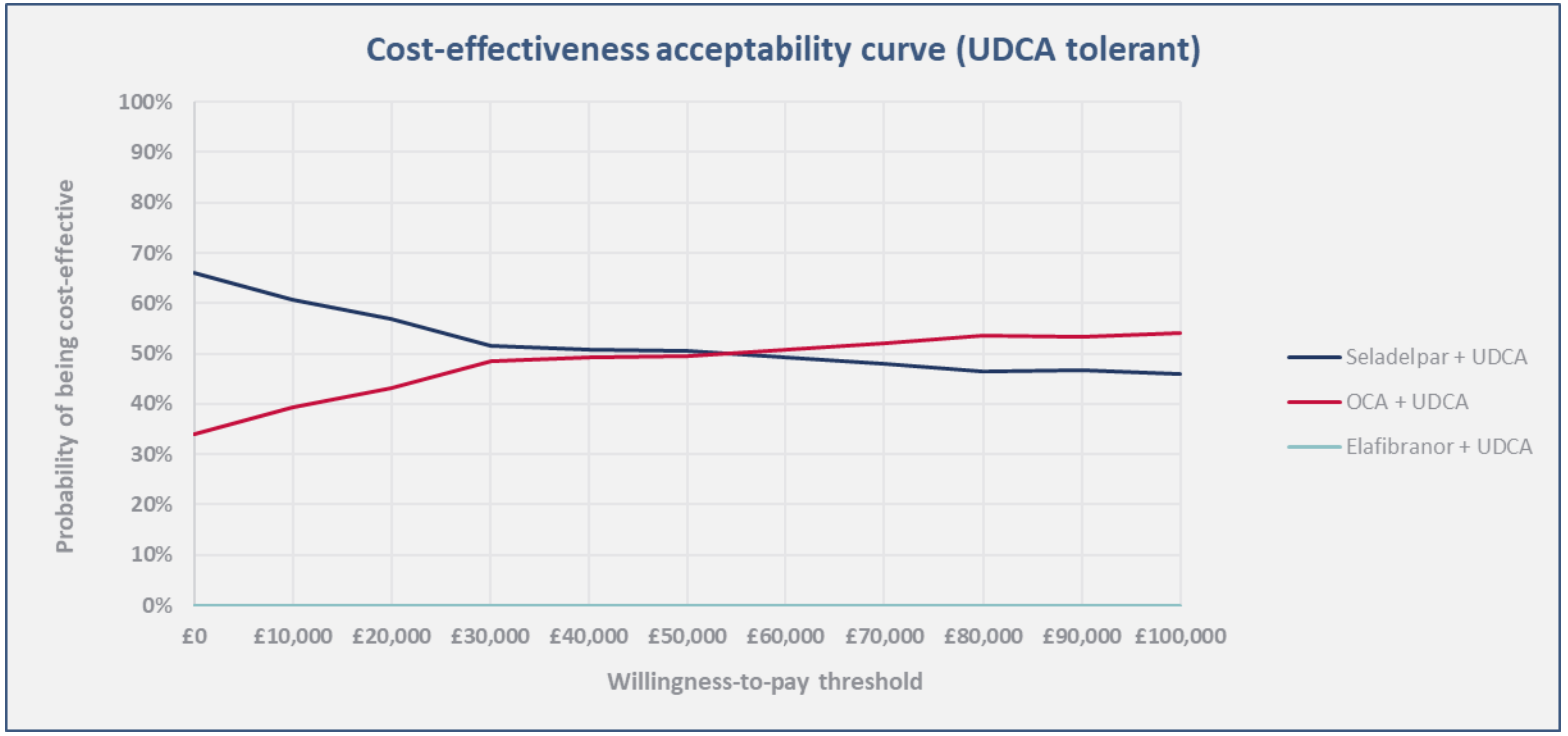
Key: ICER, incremental cost-effectiveness ratio; NHB, net health benefit; OCA, obeticholic acid, QALYs, quality-adjusted life years, UDCA, ursodeoxycholic acid

Table 88: UDCA-intolerant: discounted probabilistic pairwise results, using the PAS price of seladelpar

Technology	Total costs (£)	Total LYs	Total QALYs	Incremental costs (£)	Incremental LYs	Incremental QALYs	ICER incremental (£/QALY)	NHB at £20,000
Seladelpar	[redacted]	[redacted]	[redacted]				-	-
OCA	374,864	15.605	13.212	[redacted]	[redacted]	[redacted]	25,738	0.058
Elafibranor	437,070	15.693	12.946	[redacted]	[redacted]	[redacted]	Dominant	3.434

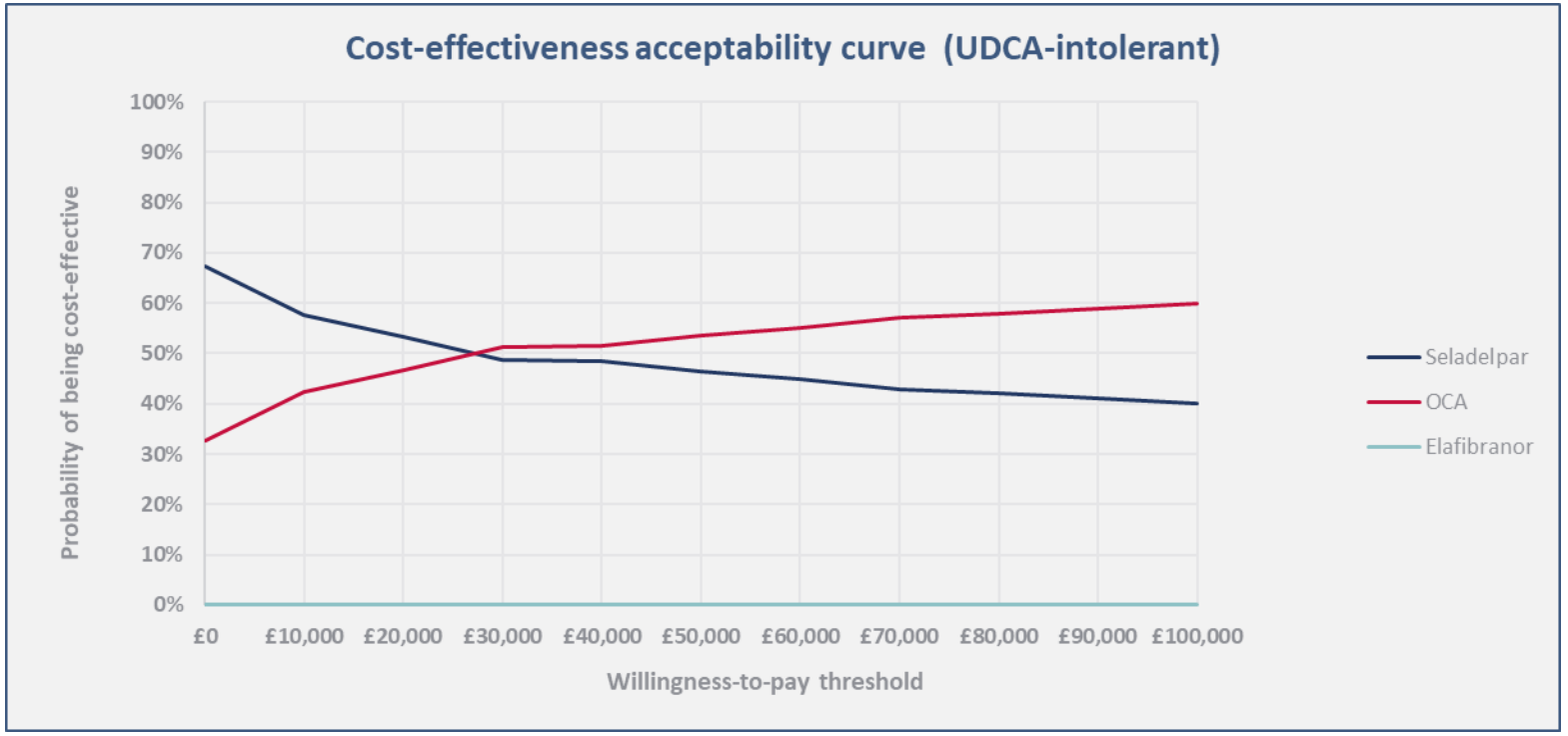
Key: BSC, best supportive care, ICER, incremental cost-effectiveness ratio; NHB, net health benefit; OCA, obeticholic acid, QALYs, quality-adjusted life years

Figure 34: CEAC (UDCA tolerant)



Key: CEAC, cost-effectiveness acceptability curve; OCA, obeticholic acid, UDCA, ursodeoxycholic acid

Figure 35: CEAC (UDCA-intolerant)

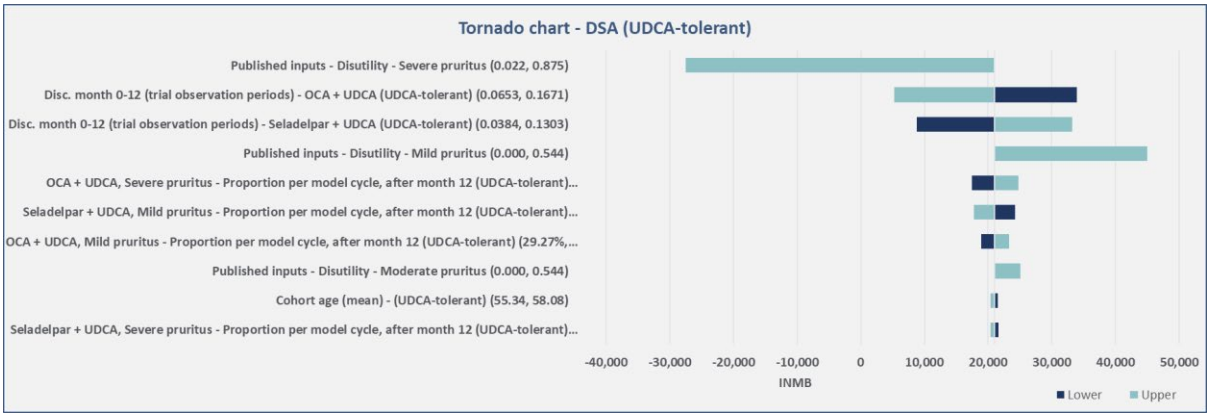


Key: BSC, best supportive care; CEAC, cost-effectiveness acceptability curve; OCA, obeticholic acid

3.11.2 Deterministic sensitivity analysis

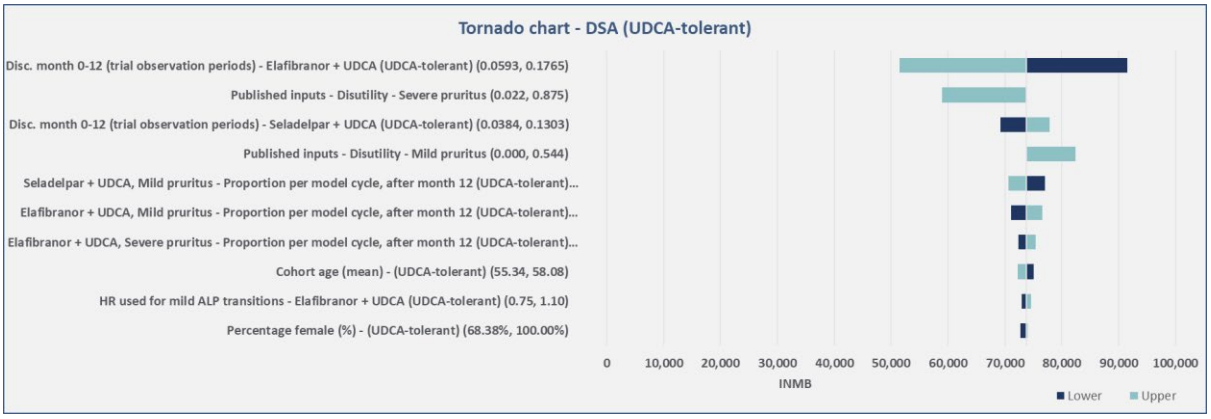
One-way sensitivity analyses (OWSA) were performed on Incremental Net Monetary Benefit (INMB) for seladelpar + UDCA vs each comparator at a conservative WTP threshold of £20,000. Tornado diagrams for each pairwise comparison are presented in Figure 36 to Figure 39.

Figure 36: Tornado vs. OCA, UDCA tolerant population



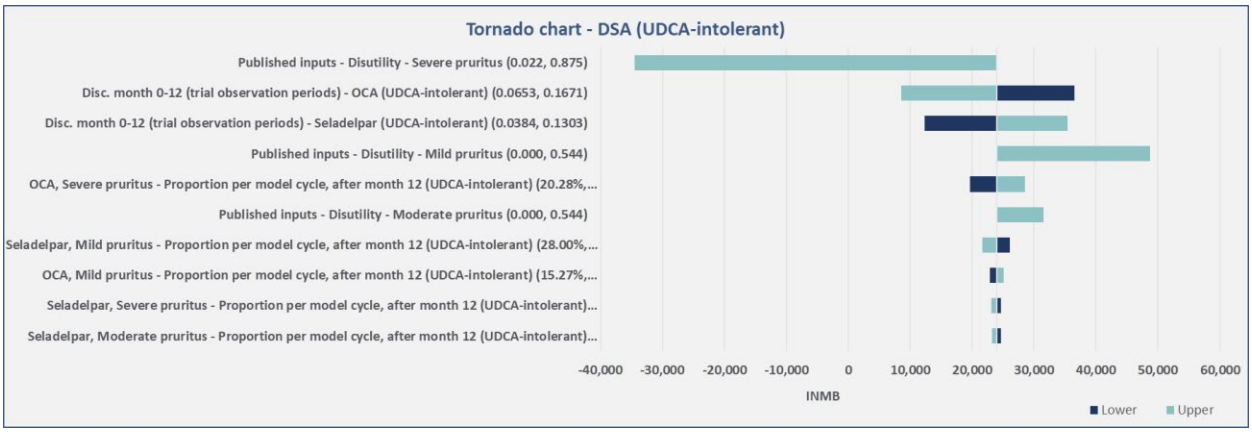
Key: ALP, alkaline phosphatase; DSA, deterministic sensitivity analysis; HCRU, healthcare resource utilisation; INMB, incremental net monetary benefit; OCA, obeticholic acid, UDCA, ursodeoxycholic acid

Figure 37: Tornado vs. elafibranor, UDCA tolerant population



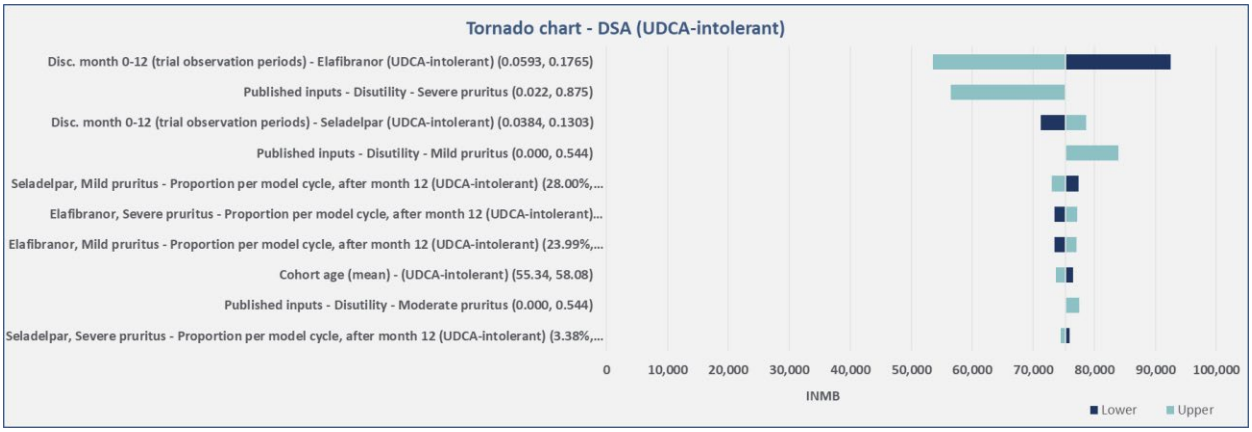
Key: ALP, alkaline phosphatase; DSA, deterministic sensitivity analysis; HCRU, healthcare resource utilisation; INMB, incremental net monetary benefit; OCA, obeticholic acid, UDCA, ursodeoxycholic acid

Figure 38: Tornado vs. OCA, UDCA intolerant population



Key: ALP, alkaline phosphatase; BSC, best supportive care, DCC, decompensated cirrhosis INMB, incremental net monetary benefit; OCA, obeticholic acid, UDCA, ursodeoxycholic acid

Figure 39: Tornado vs. elafibranor, UDCA intolerant population



Key: ALP, alkaline phosphatase; BSC, best supportive care, DCC, decompensated cirrhosis INMB, incremental net monetary benefit; OCA, obeticholic acid, UDCA, ursodeoxycholic acid

3.11.3 Scenario analysis

Scenario analyses were performed on INMB for seladelpar + UDCA vs each comparator at a conservative WTP threshold of £20,000. The results of the top 10 most impactful scenario analyses are presented in Table 89 in order of decreasing impact on the base case NMB. In the interest of brevity, tabulated results are only provided in the UDCA-tolerant population as the most impactful parameters in the UDCA-intolerant population were largely similar in terms of both ordinal and absolute value, as can be seen from the tornado diagrams in the UDCA-intolerant population presented in Figure 40 to Figure 41. Tabulated results in this population can be provided on request.

Cost-effectiveness was highly influenced by long-term discontinuation rates, with higher discontinuation rates generally reducing cost-effectiveness vs. OCA and elafibranor. Pruritis disutility was more influential in comparisons vs. OCA than vs. elafibranor, as can be expected given the poor pruritis outcomes with OCA.

Table 89: Summary of scenario analyses (UDCA-tolerant)

No.	Base case setting	Scenario	Incremental costs	Incremental QALYs	INMB
Results vs. OCA + UCDA					
	Base case results		[redacted]	[redacted]	**21,013**
1	Disc. probs. beyond M12 equal to 0.28 month 0-12 values (all treatments)	Disc. probs. beyond M12 equal to 0.5 month 0-12 values	[redacted]	[redacted]	-6,854
2	Disc. probs. beyond M12 equal to 0.28 month 0-12 values (all treatments)	Disc. probs. beyond M12 equal to 0.28 month 0-12 values	[redacted]	[redacted]	-1,137
3	Comparator ORs for pruritus from ITC	Comparator ORs for pruritus set to 1	[redacted]	[redacted]	9,612
4	Time horizon: 50 years	Time horizon: 10 years	[redacted]	[redacted]	9,981
5	Pruritus disutilities: Smith et al.	Pruritus disutilities: None	[redacted]	[redacted]	10,555
6	Pruritus disutilities: Smith et al.	Pruritus disutilities: RESPONSE - EQ-5D-3L - MMRM	[redacted]	[redacted]	12,378
7	Beyond M12 PBC TPS: M9-12 LOCF – calibrated to LTFS	Beyond M12 PBC TPS: M9-12 LOCF - Improvements possible (all treatments)	[redacted]	[redacted]	12,592
8	Comparator HRs for PBC state TPs from ITC	Comparator HRs for PBC state TPs set to 1	[redacted]	[redacted]	14,467
9	Beyond M12 PBC TPS: M9-12 LOCF – calibrated to LTFS	Beyond M12 PBC TPS: M9-12 LOCF - No improvements (UDCA mono/ BSC) - Improvements (SEL/ ELA/ OCA)	[redacted]	[redacted]	14,569
10	Disc. probs. beyond M12 equal to 0.28 month 0-12 values (all treatments)	Disc. probs. beyond M12 equal to SEL month 0-12 value; (all treatments)	[redacted]	[redacted]	23,054
Results vs. elafibranor + UCDA					
	Base case results		[redacted]	[redacted]	**73,809**
1	Disc. probs. beyond M12 equal to 0.28 month 0-12 values (all treatments)	Disc. probs. beyond M12 equal to 0.5 month 0-12 values	[redacted]	[redacted]	29,433
2	Time horizon: 50 years	Time horizon: 10 years	[redacted]	[redacted]	43,054

3	Disc. probs. beyond M12 equal to 0.28 month 0-12 values (all treatments)	Disc. probs. beyond M12 equal to 0.28 month 0-12 values	[redacted]	[redacted]	46,277
4	Disc. probs. beyond M12 equal to 0.28 month 0-12 values (all treatments)	Disc. probs. beyond M12 equal to SEL month 0-12 value; (all treatments)	[redacted]	[redacted]	51,931
5	Disc. probs. beyond M12 equal to 0.28 month 0-12 values (all treatments)	Disc. probs. beyond M12: None	[redacted]	[redacted]	88,913
6	Disc. probs. beyond M12 equal to 0.28 month 0-12 values (all treatments)	Disc. probs. beyond M12 equal to 0.5 SEL month 0-12 value; (all treatments)	[redacted]	[redacted]	65,155
7	Beyond M12 PBC TPS: M9-12 LOCF – calibrated to LTFS	Beyond M12 PBC TPS: M9-12 LOCF - Improvements possible (all treatments)	[redacted]	[redacted]	66,184
8	Beyond M12 PBC TPS: M9-12 LOCF – calibrated to LTFS	Beyond M12 PBC TPS: M9-12 LOCF - No improvements (UDCA mono/ BSC) - Improvements (SEL/ ELA/ OCA)	[redacted]	[redacted]	68,162
9	Complete case analysis	Missing imputed as CC/ Elevated Bilirubin for RESPONSE TPs	[redacted]	[redacted]	68,506
10	Comparator ORs for pruritus from ITC	Comparator ORs for pruritus set to 1	[redacted]	[redacted]	70,316

Key: BSC, best supportive care; Disc., discontinuation; EQ-5D, EuroQol 5-dimension; ELA, elafibranor; HSUV, health state utility values, ICER, incremental cost-effectiveness ratio; LOCF, last observation carried forward, LYG, life years gained; LTFS, liver transplant free survival; MMRM, mixed-effects model for repeated measures; NMB, net monetary benefit; OCA, obeticholic acid; PBC, primary biliary cholangitis, probs, probabilities; QALYs, quality-adjusted life years, SEL, seladelpar, TPS, transition probabilities, UDCA, ursodeoxycholic acid

Figure 40 Top 10 most influential scenarios vs. OCA (UDCA-intolerant)

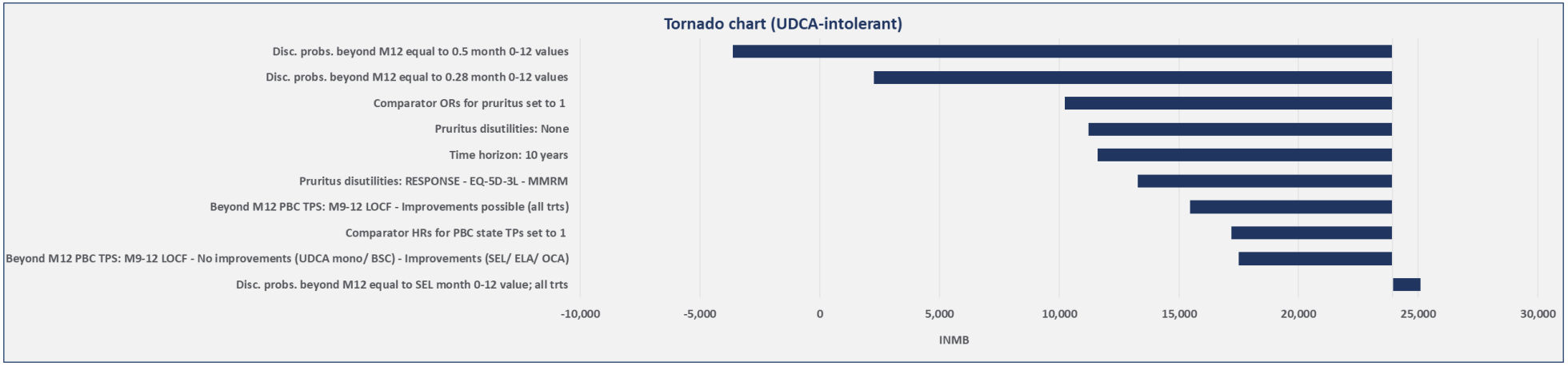
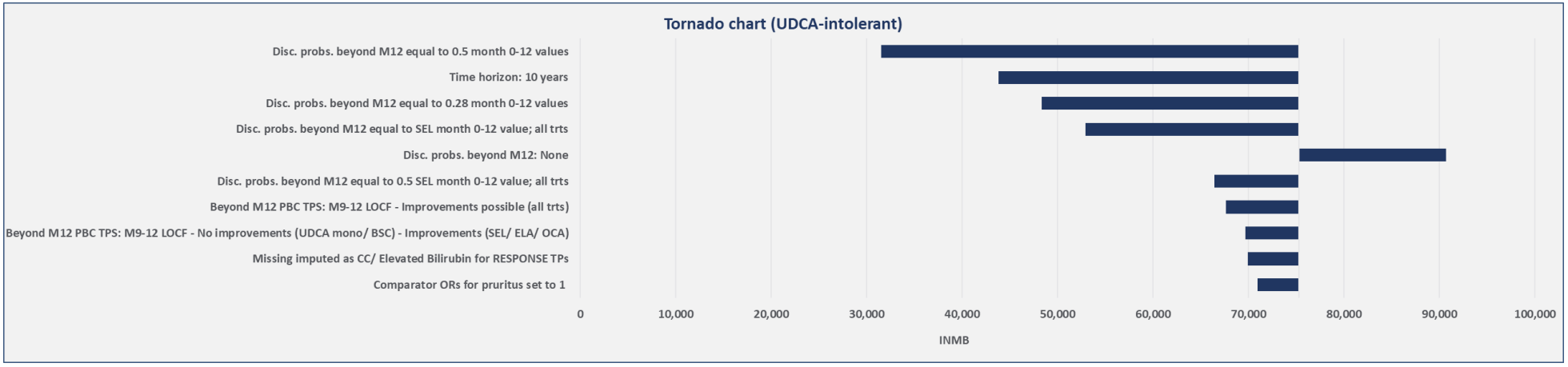


Figure 41 Top 10 most influential scenarios vs. elafibranor (UDCA-intolerant)



Key: BSC, best supportive care, HSUV, health state utility values, ICER, incremental cost-effectiveness ratio; LOCF, last observation carried forward, LYG, life years gained; LTFS, liver transplant free survival, NMB, net monetary benefit; OCA, obeticholic acid, PBC, primary biliary cholangitis, QALYs, quality-adjusted life years, SEL, seladelpar, TPS, transition probabilities, UDCA, ursodeoxycholic acid

3.12 Subgroup analysis

The only subgroups considered to be of relevance are the UCDA-tolerant vs. intolerant populations for which results have already been provided.

3.13 Benefits not captured in the QALY calculation

Carer disutilities are not included in the economic model. However, as previously highlighted in Section 1.3.2.4, caregivers of PBC patients often face significant responsibilities, with many balancing employments alongside caregiving tasks. A survey across four countries reported that a substantial proportion of caregivers experienced productivity losses and career disruptions, emphasising the broader impact of caregiving on their professional and personal lives. In particular, there is substantial burden to caregivers in the liver disease states (155, 156). More patients treated with seladelpar are likely to achieve a biochemical response (see Section 2.6) and thus are less likely to progress to liver disease states. Consequently, excluding caregiver disutility from the analysis will lead to an underestimation of the incremental QALYs associated with seladelpar treatment compared to elafibranor and OCA.

3.14 Validation

3.14.1 Validation of cost-effectiveness analysis

3.14.1.1 Validation of approach

During the conceptualisation phase, the model was validated through a series of three targeted interviews, which included two sessions with clinical experts and one with an economist. These interviews aimed to gather specialised feedback on the model's design and ensure its alignment with both clinical relevance and economic considerations. Overall, the experts were in agreement regarding the model's structure, providing only minor suggestions for improvement. This constructive feedback was promptly incorporated into the model, enhancing its robustness and practical applicability.

3.14.2 Validation of calculations

The model underwent a comprehensive internal quality control (QC) process. This review assessed multiple dimensions, including methodological approach, macro usage, parameterisation, logical flow, and editorial structure. All insights from this rigorous QC process were integrated into the draft. Subsequently, an external review was conducted, during which additional feedback was provided. This feedback was fully incorporated.

3.14.3 Validation of outputs

The key uncertainty in the model relates to the long-term outcomes predicted by the surrogate endpoints collected in the RESPONSE study (see Appendix H for the validation of the biomarker health state occupancy vs. the RESPONSE study). Two clinical predictive scoring scores were collected in the RESPONSE study: the GLOBE score (65) and the UK PBC risk score (107). The GLOBE risk score is a validated prediction of LTFS whereas the UK PBC score is a predictor of end-stage liver disease free survival (ESLDFS) (with liver transplant included as a proxy for ESLD). LTFS is formally estimated as an outcome in the model whereas ESLDFS is not (as a time-to-event curve for the composite of mortality in the DCC and HCC health states and entry to the LT state would need to be generated).

Table 90 presents the relevant clinical scores presented in the CSR for seladelpar at 12 months and Table 91 presents the outcomes predicted from the scores using the published baseline survival curves alongside the model LTFS. Note that for comparability the model survival curve was generated with discontinuation set to zero (thus generating prediction for the 111 patients for which values were available in the CSR complete case analysis).

It can be seen that the predicted LTFS from the model lies within 2% of the mean predicted by the CSR GLOBE scores at year 15. The predicted LTFS from the model is substantially lower than that predicted by the CSR UK PBC risk score, as expected, as the model LTFS includes non-liver-related mortality not included within the UK PBC risk score outcome.

Table 90: Month 12 PBC risk scores from the RESPONSE study

Year	Mean (SD)	Sample size	Lower CI	Upper CI
GLOBE score (LTFS)				
Any year	-0.08 (0,699)	109	-0.211	0.051
UK PBC score (ESLDFS)				
5	0.018	111	0.016	0.020
10	0.056	111	0.044	0.068
15	0.097	111	0.077	0.117

Key: CI, confidence interval; ESLDFS, end-stage liver disease free survival; LTFS, liver transplant free survival; PBC, primary biliary cholangitis.

Table 91: Risk score predictions from RESPONSE vs. model LTFS predictions

Year	Baseline survival	Risk score predicted - Mean	Risk score predicted – Lower CI	Risk score predicted – Upper CI	Model predicted LTFS
GLOBE risk score (LTFS)					
5	93.9%	94.3%	93.5%	95.0%	93.4%
10	84.3%	85.4%	83.5%	87.1%	85.3 %
15	73.6%	75.4%	72.4%	78.0%	76.8%
UK PBC risk score (ESLDFS)					
5	98.2%	98.2%	98.2%	98.2%	93.4%
10	94.1%	93.8%	93.7%	93.8%	85.3 %
15	89.3%	88.3%	88.1%	88.5%	76.8%

Key: CI, confidence interval; ESLDFS, end-stage liver disease free survival, LTFS, liver transplant free survival; PBC, primary biliary cholangitis.
Note: Survival from model calculated as survival at year (y+1)/survival at year 1, as risk scores for the validation were measured at month 12.

3.15 Interpretation and conclusions of economic evidence

A *de novo* model was built to assess the cost-effectiveness of seladelpar +/- UDCA in UDCA tolerant and intolerant populations. The results of the cost-effectiveness analysis demonstrated that seladelpar +/- UDCA was less costly and more effective than OCA +/- UDCA and elafibranor +/- UDCA, generating NHBs that were positive at NICE's lower WTP threshold of £20,000/QALY.

There are some notable differences between the seladelpar model and those in previous appraisals. Firstly, our model structure includes an ALP normalisation state, which was not a feature of the OCA and elafibranor models. We included this health state as it was a key secondary endpoint in the RESPONSE study, in accordance with recent evidence that achieving ALP normalisation may have a more profound impact on long-term liver outcomes than achieving ≤1.67x ULN (64).

Secondly, the different models have different ALP cutoff values defining health state boundaries (see Table 92). Notably, the OCA and ELATIVE studies had different definitions of ALP normalisation to RESPONSE (118 U/L and 124 U/L for females and males, respectively, in POISE, 104 U/L and 129 U/L for females and males, respectively, in ELATIVE and 116 U/L in RESPONSE). The effect of the weaker definition in RESPONSE vs. ELATIVE (noting that the trial populations were predominantly female) was observed in the MAIC conducted as part of the evidence synthesis; reanalysis of the RESPONSE data to fit the cutoff definitions in ELATIVE doubled the composite response effect size (RR [redacted]).

Finally, the seladelpar model does not include UDCA monotherapy or BSC as a comparator. As discussed in section 1.3.3.1, the availability of two disease-modifying treatments renders continued use of UDCA monotherapy or BSC in this population redundant, as this would not be clinically indicated. The only situation in which their use might be envisaged would be where patients had failed or were intolerant to both treatments, which would comprise only a very small fraction of patients.

Although there are always uncertainties associated with the use of surrogate endpoints, NICE is familiar with these within the context of PBC and the evidence supporting the ability of liver biomarkers to predict long-term outcomes is continually strengthening. Furthermore, in contrast with the comparators, seladelpar brings with it strong evidence on its impact on pruritis, which contributed a not insignificant proportion of the QALY gains, particularly vs. OCA.

In conclusion, seladelpar is a clinically effective treatment which would add to the currently limited choice of treatments in this area of unmet need, at a cost-effective price to the NHS.

Table 92: Comparison of biomarker cutoffs for PBC model health states in NICE appraisals

Technology appraisal	Health state	Definition	Comments
Ocaliva - TA443	Low risk	ALP ≤ 1.67 x ULN [ALP ≤ 200 units/L]	Explanation for the threshold: As POISE is a global trial, there were variations in the definition of ULN for ALP. The eligibility criteria state that patients must have ALP >1.67x ULN for inclusion, and the average ALP for women in the trial was 197.561. As a result, 1.67x ULN is assumed to be 200 U/L. The ULN for total bilirubin is commonly defined as 1.2 mg/dL (20 µmol/L), and so was assumed to be 20 µmol/L.
	Moderate risk	ALP > 1.67 x ULN [ALP > 200 units/L] and TB ≤ 1.0 x ULN [TB > 20 µmol/L]	
	Severe risk	TB > 1.0 x ULN [TB > 20 µmol/L] or compensated cirrhosis	
Elafibranor - TA1016	Mild risk	ALP ≤ 200 u/L and TB ≤ 20 µmol/L	Explanation for the threshold: ULN for ALP in the ELATIVE trial was defined as 104 U/L for females and 129 U/L for males. 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. 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.
	Moderate risk	ALP > 200 u/L and TB ≤ 20 µmol/L	
	High risk	TB > 20 µmol/L or compensated cirrhosis (defined as kPa >15)	
Seladelpar	ALP normalisation	ALP ≤ 1x ULN [ALP ≤ 116 units/L] / TB ≤ 1xULN [TB ≤ 18.8 µmol/L]	Per RESPONSE study.
	Mild ALP elevation	1 < ALP ≤ 1.67x ULN [116 units/L ≤ ALP ≤ 194 units/L] / TB ≤ 1xULN [TB ≤ 18.8 µmol/L]	

	High ALP elevation: ALP > 1.67x ULN/ TB Normal	1 < ALP ≤ 1.67x ULN / TB ≤ 1xULN [TB ≤ 18.8 µmol/L]	
	Compensated Cirrhosis or Elevated Bilirubin	CC or TB > 1x ULN [TB > 18.8 µmol/L]	

Key: ALP, alkaline phosphatase, CC, compensated cirrhosis, TB, total bilirubin, ULN, upper limit of normal

4 References

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5 Appendices

Appendix A: Summary of product characteristics (SmPC) and UK public assessment report

Appendix B: Identification, selection and synthesis of clinical evidence

Appendix C: Subgroup analysis

Appendix D: Adverse reactions

Appendix E: Published cost-effectiveness studies

Appendix F: Health-related quality of life studies

Appendix G: Cost and healthcare resource identification, measurement and valuation

Appendix H: Clinical outcomes and disaggregated results from the model

Appendix I: Price details of treatments included in the submission

Appendix J: ENHANCE

Appendix K: ASSURE ‘Legacy’ patients

Appendix L: Summary of base-case analysis inputs

Appendix M: IPD transition probability analyses

Appendix N: Checklist of confidential information

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Single technology appraisal

Seladelpar for previously treated primary biliary cholangitis [ID6429]

Summary of Information for Patients (SIP)

February 2025

File name	Version	Contains confidential information	Date
ID6329 Seladelpar vi. NICE SIP [noCON]_11.02.2025	1.0	No	11/02/2025

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):

Seladelpar (Livdelzi®)

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

Seladelpar is indicated 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.

Seladelpar received marketing authorisation from the Medicines and Healthcare products Regulatory Agency (MHRA) on 16th January 2025 (PLGB 50729/0001) (1). Further details can be found in Section 1.2 of the company evidence submission. https://mhraproducts4853.blob.core.windows.net/docs/db8eda542a05d4cd6075a00680a3a44e103bfea8

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:

Gilead has provided financial support to the PBC foundation in the form of grant funding towards conference organisation, and through compensation towards input into educational material development.

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.
Primary biliary cholangitis (PBC) is a life-long liver disease that occurs when small bile ducts in the liver get inflamed and then eventually destroyed. This leads to bile build-up, causing liver damage, scarring (also known as cirrhosis), and potentially liver cancer, liver failure, and death if left untreated. PBC is an autoimmune disease where the body's immune system mistakenly attacks healthy bile duct cells (2, 3). PBC affects individuals across all genders, ethnicities, and races. As with most autoimmune conditions, PBC shows female predominance with a female-to-male ratio of 9:1 observed in recent UK studies (4-7). The disease is diagnosed predominantly in middle-aged women (40-60 years), with rare occurrences observed under 25 years of age. The prevalence of PBC in the UK was reported to be 39.6 per 100,000 persons in a study by Webb *et al*. (2021) (8), equating to an estimated 21,837 patients currently residing in the UK. PBC progresses slowly, with most patients (approx. 50-60%) showing no symptoms at diagnosis. Consequently, PBC is typically discovered due to abnormal results in routine liver blood tests, typically elevated alkaline phosphatase and/or the presence of antimitochondrial antibodies. In rare cases, a diagnosis of PBC may be confirmed by a liver biopsy (see Section 2b) (9). The onset of symptoms is highly variable amongst patients, with these commonly developing within two to four years in most patients, and may last for up to 10 years (10). Extreme tiredness (fatigue) and itching (pruritus) are the most common symptoms of PBC, and may significantly impact patient health-related quality of life (HRQoL). Up to 80% of patients with PBC experience itching, which can vary in severity between patients (11, 12). The itching can be so severe that it can cause sleep deprivation, social isolation and suicidal ideation (9). As the disease advances,

patients may also experience bone and joint aches, dry eyes and mouth, and abdominal pain (13-15).

Patients progressing towards end-stage liver disease are at risk of its associated complications, including liver failure and hepatocellular carcinoma, a type of liver cancer, which may result in premature death or the need for a liver transplant within two to four years (9, 10). For patients who do not respond well to treatment, life expectancy is expected to be 10 years following disease onset (16). On the other hand, for patients whose disease is detected early and who exhibit an adequate response to treatment, life expectancy is generally aligned with that of the general population (17, 18). A study by Mendes *et al*. (2008) reported an average life expectancy of 65.6 years amongst a sample of death certificates issued in the US for patients with PBC (19).

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?

PBC often goes unnoticed as many patients have no symptoms at diagnosis. It's typically discovered due to abnormal results in routine liver blood tests:

- **Alkaline phosphatase (ALP) levels**: Individuals with PBC usually have high ALP levels in the blood, which could be liver damage
- **Antimitochondrial antibodies (AMA)**: The presence of AMAs in the blood is positive in most PBC cases

A liver biopsy, which involves the removal of a small sample of liver tissues to examine for signs of disease, may also be used to diagnose PBC in UK clinical practice, however, this is used very rarely (20).

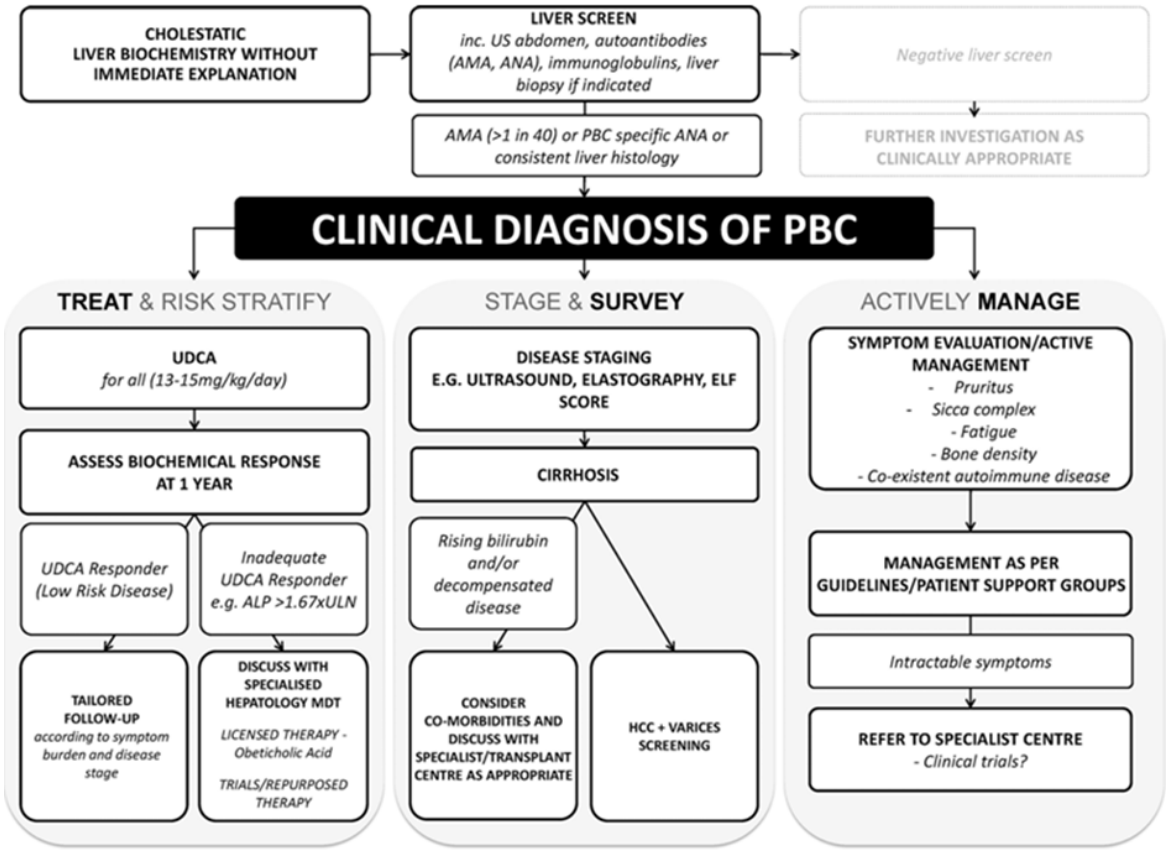
2c) Current treatment options:

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.

The British Society of Gastroenterology/UK-PBC provide guidance on the diagnosis and treatment of people with PBC, which is aligned with international guidance provided in Europe by the European Association for the Study of the Liver (EASL) and the United States by the American Association for the Study of Liver Diseases (AASLD) (9, 20, 21). Figure 1 illustrates the proposed treatment of people with PBC in the UK.

Figure 1: BSG/UK-PBC consensus care pathway for patients



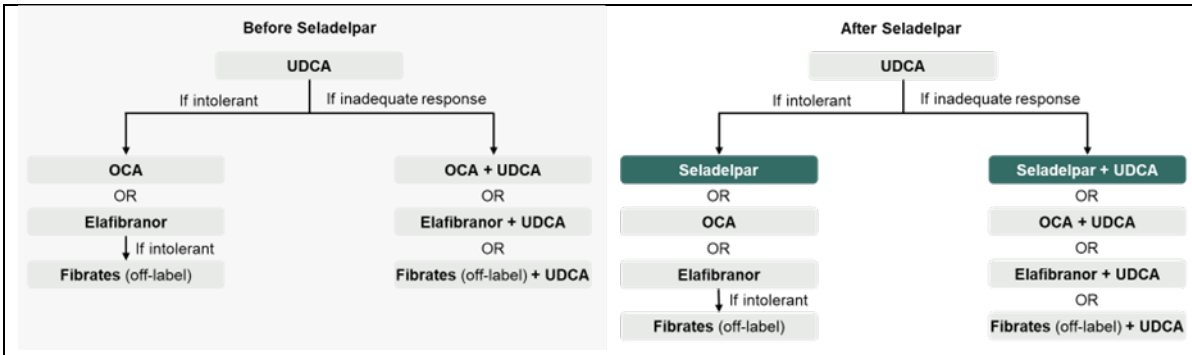
Key: ALP, alkaline phosphatase; AMA, anti-mitochondrial antibody; ANA, antinuclear antibodies; ELF, enhanced liver fibrosis; PBC, primary biliary cholangitis; UDCA, ursodeoxycholic acid; ULN, upper limit of normal.
Source: Hirschfield et al. (2018) (20)

The management of PBC requires a life-long, structured approach due to its long-term and progressive nature. Treatments for PBC generally aim to slow disease progression and prevent end-stage liver disease complications, whilst also providing symptom management (20).

All patients with PBC begin treatment with ursodeoxycholic acid (UDCA) at a dose of 13 – 15mg/kg/day (20). In most people with PBC (~30-40%), UDCA is highly effective at controlling the disease. However, in some people, UDCA is less effective, and these patients may receive treatment with obeticholic acid (OCA) or elafibranor in addition to UDCA if treatment to sufficiently reduce biochemical levels of ALP and total bilirubin (TB) has failed after 12 months. For the minority of people with PBC (~5-10%) unable to tolerate treatment with UDCA, treatment would instead begin with OCA or elafibranor without UDCA (22-24).

Seladelpar presents an additional treatment option for PBC patients following intolerance or inadequate response to UDCA, or as a treatment option for patients who are intolerant or do not respond to OCA. Currently, there are no additional treatment options for those patients with PBC who cannot tolerate OCA.

Figure 2: Proposed positioning of seladelpar in the UK PBC treatment pathway



Key: kg, kilograms; mg, milligrams; OCA, obeticholic acid; PBC, primary biliary cholangitis; UDCA, ursodeoxycholic acid
Source: Kowdley et al. (2023) (25); Zapata et al. (2024) (26)

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.

Patients with PBC often experience itching, which can dramatically impair HRQoL. In a study conducted by Gilead, named ITCH-E, researchers examined how PBC-related itching impacts patient HRQoL, activity, and work productivity. The study recruited patients through either the PBCers Organisation, which is the largest PBC online support group worldwide, or physician panels that included patients with PBC. Patients could participate in the study if they were adults, lived in the United States, agreed to participate, and were currently taking an approved treatment for PBC (either UDCA or OCA) (27).

Patients did the following:

1. Completed a screening survey to determine eligibility
2. Rated their itch symptoms using a numeric rating scale
3. Agreed to participate in the study
4. Completed a questionnaire via their smartphone or computer
5. Called in to an automated voice response system and responded to prompts if they had moderate to severe itching (pruritus)

Patients were categorised based on their answer to the Pruritus Numeric Rating Scale (NRS) assessment tool during screening. Patients with a Pruritus NRS score of 0-3 were placed in the no/mild pruritus (NMP) group, while those with a Pruritus NRS score of 4-10 were placed in the moderate/severe pruritus (MSP) group (27).

The sample included 40 NMP and 50 MSP patients. Overall, patients with MSP reported worse health outcomes. Compared with the NMP group, and after controlling for confounding factors (including age, gender, ethnicity, and UDCA and OCA treatment), the MSP group had statistically worse PBC-40 mean scores in Symptoms, Itch, Fatigue, Cognitive, and Social, but not Emotional, domains (27).

Patients also spoke about how PBC-related itching impacted their lives:

"The itch that you get from PBC versus a bug bite or poison ivy, ***you can't satisfy the itch. Scratching it doesn't satisfy it****. It comes from the inside out, and* ***you can dig and dig and dig and it just doesn't get satisfied.****"*

"Emotionally, it gets you down because of ***what your body looks like****… When you itch so bad, you want to excuse yourself, not being around them [other people]."*

"I'm itching while ***at work****, which makes it* ***very hard to focus****, it's* ***very distracting****, and very hard to get anything done. So, I'm* ***less productive****."*

To conclude, compared with adults with PBC with NMP, those with MSP experience a significant burden on their health-related sense of well-being and impairment in daily activities.

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.

Seladelpar is a medicine that selectively activates a receptor called peroxisome proliferator-activated receptor (PPAR)-delta (δ), which is important for controlling glucose, fat, and cholesterol metabolism. PPARδ is found in many tissues, including the liver (28).

When seladelpar activates PPARδ, it reduces the production of bile acid in the liver by lowering the production of an enzyme called cholesterol 7 alpha-hydroxylase-1 (CYP7A1). This enzyme normally converts cholesterol into bile acid, and the reduction is influenced by a protein called Fibroblast Growth Factor 21 (FGF21). Through reducing the production of bile acid in the liver, treatment with seladelpar may prevent liver damage and reduce circulating bile acid levels (29, 30).

Seladepar has potential to meet the current unmet need of people living with PBC, as the first and only treatment that achieved statistically significant reduction across biochemical response, ALP normalisation, and itch versus placebo. Itch is a common symptom that can significantly impair quality of life in people with PBC (see Section 2d).

Patient Information Leaflet (PIL):
https://mhraproducts4853.blob.core.windows.net/docs/c6ce7a35ce7d51a7ea3059bda94e3d26cfd338e0

Summary of Product Characteristics (SmPC):
https://mhraproducts4853.blob.core.windows.net/docs/db8eda542a05d4cd6075a00680a3a44e103bfea8

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.

Seladelpar 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?

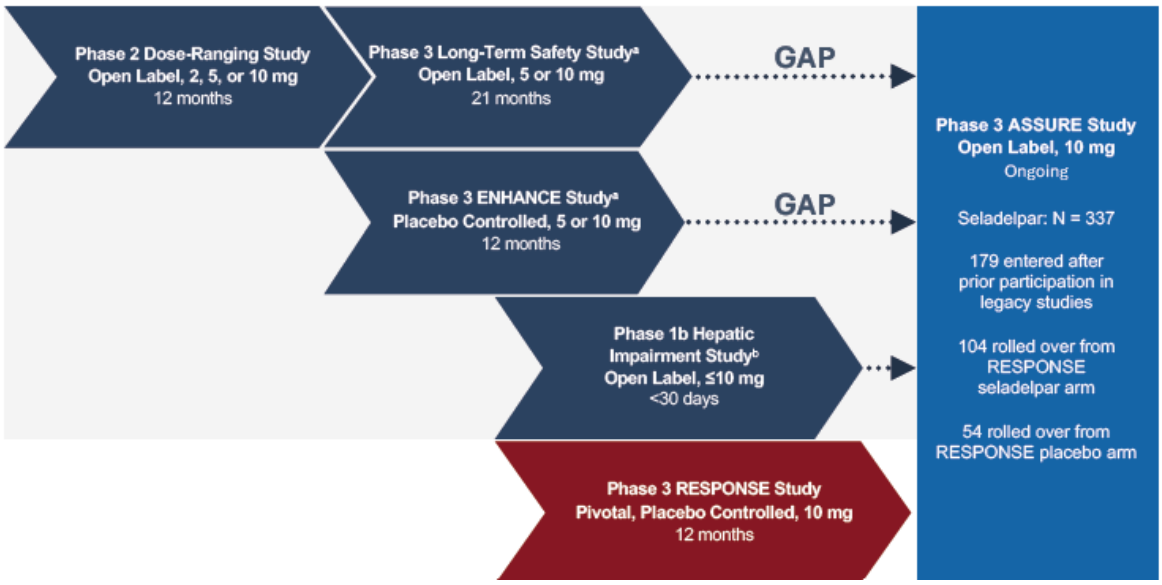
Seladelpar is available as hard capsules with 10mg dosage strength for oral administration.

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.

Six clinical studies have evaluated the efficacy and safety of seladelpar of PBC. These include two placebo-controlled studies, RESPONSE (*completed*) and ENHANCE (*terminated*), and four open-label studies, namely a Phase 2 dose-ranging study (*completed*), a Phase 3 long-term safety study (*terminated*), a Phase 1b hepatic impairment study (*ongoing*), and ASSURE (*ongoing*) (Figure 1).

Figure 3: Studies investigating the efficacy and safety of seladelpar in PBC



Key: NASH, non-alcoholic steatohepatitis; PBC, primary biliary cholangitis.
Notes: Data cut-off – January 31st 2024
[a]These studies had an early termination due to unexpected findings in a concurrent study for NASH, which were subsequently found to predate treatment.
[b]Patients were eligible to enrol in ASSURE after completing the study, but they had to meet screening criteria and had variable time to entry into ASSURE
Source: Adapted from Trivedi *et al.* (2024) (31)

RESPONSE was the pivotal Phase 3, double-blind, placebo-controlled trial designed to evaluate the safety and efficacy of seladelpar in adults with PBC with an inadequate response or intolerance to UDCA. Enrolled patients were to be randomly assigned in a 2:1 ratio to receive oral seladelpar (10mg daily) or placebo (32).

Patients were included in the trial if their ALP was greater than or equal to 1.67-times the upper limit of normal (ULN) and TB was less than or equal to 2 times the ULN. Patients were excluded from the trial if they had other chronic liver diseases, clinically important hepatic decompensation including portal hypertension with complications, or cirrhosis with complications (e.g., Model for End Stage Liver Disease [MELD] score of 12 or greater, known oesophageal varices or history of variceal bleeds, history of hepatorenal syndrome) (32).

The study included 193 patients and took place in 90 study sites across 24 countries: Argentina, Australia, Austria, Belgium, Canada, Chile, Czech Republic, France, Germany, Greece, Hungary, Israel, Italy, Republic of Korea, Mexico, New Zealand, Poland, Romania, Russia, Spain, Switzerland, Turkey, United Kingdom, and USA (32).

The last patient visit was on 11th August 2023. Further information about the RESPONSE study can be accessed here: https://www.nejm.org/doi/full/10.1056/NEJMoa2312100.

Patients who completed RESPONSE were able to rollover into the ongoing Phase 3, open-label ASSURE study, which is investigating the long-term safety and efficacy of seladelpar 10 mg in patients with PBC. This study also includes patients that participated in prior seladelpar trials (Figure 1). As of January 31st 2024, 337 patients with PBC were enrolled in the study (31). Further information on ASSURE can be accessed using the following links:

- Interim 2-year efficacy and safety results: https://www.natap.org/2024/EASL/EASL_128.htm

- Pooled interim 3-year efficacy and safety results: https://www.natap.org/2024/AASLD/AASLD_90.htm

Further information about the supporting seladelpar clinical studies in PBC, namely ENHANCE, the Phase 2 dose-ranging study, the Phase 3 long-term safety study, and the Phase 1b hepatic impairment study, can be accessed using the following links.

- ENHANCE: https://journals.lww.com/hep/fulltext/2023/08000/seladelpar_efficacy_and_safety_at_3_months_in.9.aspx
- Phase 2 dose-ranging study: https://www.journal-of-hepatology.eu/article/S0168-8278(22)00187-8/fulltext
- Phase 3 long-term safety study: https://onlinelibrary.wiley.com/doi/10.1111/apt.17755
- Phase 1b hepatic impairment study: https://clinicaltrials.gov/study/NCT04950764

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.

In the pivotal RESPONSE study, seladelpar was compared with placebo in a study of 193 adults with PBC. The main measure of effectiveness was a biochemical (or cholestasis) response after 12 months (a year) of treatment. In the study, a biochemical response was defined as ALP level of ≤1.67 times the 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 Month 12. The study showed a statistically significant difference in the proportion of patients observing a biochemical response between the seladelpar and placebo treatment groups; a greater proportion of patients (61.7%, 79 of 128 patients) of patients in the seladelpar group achieved a biochemical response compared to the placebo (inactive drug) group (20.0%, 13 of 65 patients) (32).

The key secondary endpoints were normalisation of the ALP level (≤1.0 times the ULN) at Month 12 and a change from baseline in itch among patients with moderate-to-severe itch up to Month 6 of treatment. The results of the latter are described below in Section 3f, as itch can significantly impact the HRQoL of patients with PBC.

ALP normalisation is associated with improved liver-related clinical outcomes (i.e., lower risk of needing a liver transplant or experiencing severe liver damage, complications, or cirrhosis) and mortality. However, despite available treatments, ALP normalisation is uncommon amongst patients with PBC. Treatment with seladelpar led to a significantly higher percentage of patients achieving ALP normalisation (32 of 128 patients, 25.0%) versus placebo (0 of 65 patients, 0.0%) (32). For patients who enrolled into the long-term ASSURE study and received seladelpar treatment for an additional 6 months (totalling 18 months of treatment) and 12 months (totalling 24 months of treatment), 33% (34 of 102 patients) and 17% (5 of 29 patients) achieved ALP normalisation, respectively (31).

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 seladelpar (32/128 [25.0%] patients) than those taking a placebo (0/65 [0.0%] patients), resulting in a statistically significant difference of 25% favouring the seladelpar 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 interim efficacy results of ASSURE were consistent with those observed in RESPONSE. For those patients who continued into the ASSURE study and received continuous seladelpar for a total of 18 months (n=102), 33% reached ALP normalisation. For patients who received seladelpar for 24 continuous months (n=29), 17% achieved ALP normalisation (31).

Further information on the secondary/additional efficacy outcomes can be found in Section 2.6 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.

As highlighted in Section 2d, patients with PBC often experience itching, which can dramatically impair HRQoL. PBC-related itching affects up to 80% of patients, and may be extremely debilitating, causing sleep, fatigue, pain, and social isolation issues.

As highlighted above, a key secondary endpoint in the RESPONSE study was a change from baseline in itch among patients with moderate-to-severe itch up to Month 6 of treatment. The change in itch was measured using the Pruritus NRS, a tool used to score average itch intensity over the past 24 hours on a scale of 0 [no itch] to 10 [worst itch imaginable]. After 6 months of treatment, patients with moderate-to-severe itch who received seladelpar received a statistically significant improvement in Pruritus NRS score compared with placebo (32). The reduction in itch was maintained for up to 24 months in patients with moderate-to-severe itch at study entry who rolled over into the long-term ASSURE study (31).

Additional measurement tools to measure the impact of seladelpar on HRQoL were the PBC-40 QoL questionnaire and the 5-D itch scale. Overall, among patients with moderate-to-severe pruritus at study entry, reduction in itch from study entry to Month 12 as measured by PBC-40 QoL and 5-D itch scale appeared to be greater in patients who were treated with seladelpar versus those who received placebo (32).

In RESPONSE, fewer patients treated with seladelpar in RESPONSE experienced pruritus as a side-effect of treatment versus placebo (4.7% vs 15.4%) (32). By contrast, OCA, a licensed treatment option available in the UK, has been shown to worsen itch in patients with PBC.

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.

Seladelpar demonstrated a well-tolerated safety profile, with a similar incidence of side-effects observed between the seladelpar and placebo treatment groups in the pivotal RESPONSE trial (86.7% vs 84.6%). A majority of side-effects were mild/moderate in severity; and either self-limiting or managed with standard medical care (32).

In RESPONSE, the most frequently reported AEs were COVID-19 (18.0%), headache (7.8%), and abdominal pain (7.0%). By contrast, COVID-19 (15.4%), itch (15.4%), and upper respiratory tract infection (9.2%) were the most frequently reported AEs amongst patients receiving treatment with placebo (32). Overall, a lower incidence of AEs was reported in the long-term ASSURE study up to Month 24 (31).

AEs that resulted in the discontinuation of seladelpar were rare, and only occurred for three patients (4.6%) who received treatment with seladelpar during the RESPONSE study. None of the AEs that led to the discontinuation of seladepar were deemed related to treatment (32).

Seladelpar has no noted severe interactions with other medicines, including statins, which may be used by patients with PBC to control cholesterol levels.

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
-

Treatment with seladelpar positively impacts ALP normalisation, which is an established predictor of prognosis in PBC

ALP normalization has been associated with reduced risk of clinical events such as decompensated cirrhosis and liver transplantation, and greater percentage decreases in ALP levels are associated with better transplant-free survival, a 40% decrease in ALP levels was found to be significant in predicting outcome (33). With second-line treatment with elafibranor, a majority of patients do not normalise their ALP levels; only 15% of patients treated with elafibranor in the pivotal ELATIVE study achieved ALP normalisation (34).

In RESPONSE, treatment with seladelpar led to a statistically significantly higher percentage of patients achieving the key secondary efficacy endpoint of ALP normalisation at Month 12 compared to placebo (25.0% vs 0.0%, respectively, $p<0.0001$) (32). Consistent results were observed in the long-term ASSURE study, where 17.2-50.0% of patients receiving seladelpar for up to two years achieved ALP normalisation at the interim analysis (31).

Seladelpar acts to address the burden of pruritus in patients with PBC

There are no approved treatments for PBC that significantly improve pruritus as measured by the NRS. Specifically, elafibranor did not demonstrate a statistically significant improvement in pruritus in the pivotal ELATIVE trial (34), and new or worsening pruritus frequently occurs in

patients receiving OCA, with up to 10% of patients discontinuing OCA within a year due to pruritus (35).

In RESPONSE, seladelpar significantly decreased pruritus, as measured by the NRS, in patients experiencing moderate-to-severe pruritus at baseline. These improvements meet the threshold for a minimally clinically important difference (32). In the ASSURE study, a sustained reduction in pruritus was observed for up to two years in patients moderate-to-severe pruritus treated with seladelpar (31).

Seladelpar is well tolerated in patients with PBC
Treatment with UDCA and OCA has led to notable safety concerns, including weight gain, hair loss, and gastrointestinal side effects in those treated with UDCA and fatigue and reductions in high density lipoprotein in those treated with OCA. Additionally, treatment with elafibranor was observed to lead to a higher frequency of AEs compared to placebo (34).

Based on the data from trials thus far, seladelpar has been generally well-tolerated by patients with PBC. In RESPONSE, the frequency of AEs and SAEs between the seladelpar and placebo arms was largely similar (87% vs 85% and 7% vs 6%, respectively). Only 5% and 6% of patients treated with seladelpar reported pruritus and fatigue as AEs, respectively. Through Month 12, only 3% of patients receiving seladelpar discontinued treatment due to an AE compared to 5% of patients in the placebo group (32). A consistent safety profile was observed in the long-term ASSURE study, with few SAEs and discontinuations reported in patients treated with seladelpar at the time of the 2-year interim analysis

Seladelpar provides a treatment option for a wide range of patients with PBC, including those both with and without cirrhosis
Current second-line treatments are not recommended for certain patients with PBC, such as OCA, which is not recommended for use in patients with advanced cirrhosis, demonstrating a need for a second-line option in patients who are inadequate responders or intolerant to UDCA, and subsequently, progress to cirrhosis.

Seladelpar offers a wide range of patients with PBC, including those without cirrhosis and those with compensated cirrhosis, an opportunity for biochemical response and improvement in symptoms. In RESPONSE, the biochemical response results in patients with cirrhosis were consistent with those of the overall study population (cirrhosis: 38.9%; overall population: 61.7%) (32).

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

The incidence of AEs was similar between the seladelpar and placebo treatment groups
As outlined in Section 3g, the incidence of AEs between the seladelpar and placebo treatment groups was similar (86.7% vs 84.6%). AEs that were reported more often in the seladelpar group

than in the placebo group included COVID-19, headache, abdominal pain, nausea, and abdominal distension. However, these were mild/moderate in severity and did not results in the discontinuation of seladelpar (or placebo) (32).

Patients may have to travel further distances to obtain their prescription of seladelpar
In England, patients eligible for treatment with OCA or elafibranor are referred to a multi-disciplinary team, located in a specialist centre that is networked to neighbouring, non-specialist hospitals. The specialist centre is anticipated to be responsible for the approval and prescription of seladelpar treatment. Therefore, the prescription of seladelpar at specialist centres could cause patients to travel further than their local centre to receive treatment.

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.

The manufacturer of seladelpar built an economic model in Microsoft Excel to assess the cost-effectiveness of second-line seladelpar for patients with PBC who had an inadequate response or were intolerant to first-line UDCA. The model, informed by outcomes from the pivotal RESPONSE study, simulates the long-term progression of PBC over a lifetime.

How the model reflects the condition:
The economic model structure is divided into two core components; one that captures the effects of treatment of key markers of disease status and another which captures the clinical consequences of disease progression. The purpose of these components is to model the treatment response in the PBC biomarker health states via ALP and TB levels and to capture the long-term effects of biochemical improvements via transitions to liver complication health states. The model aims to capture seladelpar's value through the inclusion of an ALP normalised health state and capture pruritus improvement through pruritus-associated utility and cost inputs.

Modelling how much a treatment improved quality of life:
HRQoL data are incorporated into model via the assignment of health state utility values and disutility values for pruritus and other adverse events. Utility values for the advanced liver disease-related outcomes were sourced from published literature accepted in the OCA appraisal by NICE.

The effects of pruritus on HRQoL were accounted for via the application of disutility values for each mild, moderate, and severe pruritus as defined by the PBC-40 measure. Default disutility values for other adverse events were sourced from published literature.

Modelling how the costs of treatment differ with the new treatment:
The costs associated with each health state in the model are consistent amongst existing treatments available in the UK.

Uncertainty:
In previous NICE appraisals, the key areas of uncertainty concerned the absence of head-to-head data between current second-line treatment options (i.e., elafibranor vs OCA), and the relationship between markers of the disease (i.e., ALP, TB) and long-term clinical outcomes. However, the Company conducted a robust indirect treatment comparison (i.e., estimated the relative effectiveness of seladelpar versus elafibranor and OCA, as these had not been directly compared in the RESPONSE study). Data up to 5 years has also been collected in the long-term ASSURE study, which supports the sustained effect of seladelpar on disease biomarkers and subsequent improvement in long-term clinical outcomes.

Cost-effectiveness results:
The results of the cost-effectiveness analysis showed that seladelpar was associated with increased QALYs versus comparator second-line therapies, albeit with a higher cost.

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)

As demonstrated in the pivotal RESPONSE study, seladelpar is the first and only treatment for PBC that achieved statistically significant reduction across biochemical response, ALP normalisation, and itch versus placebo.

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

Patients with PBC with cirrhosis-related complications or debilitating symptoms are subjected to significant wait times for liver transplantation; on average, UK patients are required to wait at least 3-4 months for a liver transplant. PBC patients on the liver transplant waiting list are more likely to die compared to patients with other liver diseases. In a study that evaluated waitlist outcomes in patients with PBC using data from the United Network for Organ Sharing, 17% of waitlisted patients with PBC died without receiving a liver transplantation (36).

In addition, geographic factors may also impact the probability of referral for a transplant assessment. In England, patients eligible for liver transplant are sevenfold more likely to be referred for a liver transplant if they live in a region containing a liver transplant centre compared with regions without a liver transplant centre, highlighting that the national provision of such services is inequitable in terms of access (4).

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.

Further information on seladelpar:

- Patient Information Leaflet (PIL): https://mhraproducts4853.blob.core.windows.net/docs/c6ce7a35ce7d51a7ea3059bda94e3d26cfd338e0
- Summary of Product Characteristics (SmPC): https://mhraproducts4853.blob.core.windows.net/docs/db8eda542a05d4cd6075a00680a3a44e103bfea8

Further information on the pivotal RESPONSE study:

- Published clinical trial data available at: https://www.nejm.org/doi/full/10.1056/NEJMoa2312100
- Further information about the clinical trial available at: https://clinicaltrials.gov/study/NCT04620733

Further information on the long-term ASSURE study:

- Published clinical trial data available at: https://www.natap.org/2024/EASL/EASL_128.htm, https://www.natap.org/2024/AASLD/AASLD_90.htm
- Further information about the clinical trial available at: https://clinicaltrials.gov/study/NCT03301506

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-ta11540

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

Adverse event (AE): Any unfavourable or unintended side-effects of a drug

Alkaline phosphatase (ALP): A liver enzyme that is a key marker of PBC

Antimitochondrial antibodies (AMAs): Antibodies that form against mitochondria.

Health-related impact on quality of life (HRQoL): An individuals or groups perceived physical and mental health over time.

Incidence: The number of new cases of a disease that develop in a population over a specific time period.

Incremental cost-effectiveness ratio (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).

Model for End-Stage Liver Disease (MELD): A numerical scale that predicts the urgency of a liver transplant for patients aged 12 years and older, ranging from 6 (less sick) to 40 (gravely sick).

Obeticholic acid (OCA): A second-line treatment used to treat adult patients with PBC in combination with UDCA for people whose disease has responded inadequately to UDCA or as monotherapy for people who cannot tolerate UDCA.

Peroxisome proliferator-activated receptor (PPAR): A group of nuclear receptor proteins that regulate gene expression and are involved in many biological processes, including inflammation, carcinogenesis, and metabolic pathways.

Prevalence: A measure of the proportion of the population that has a specific characteristic or condition at a specific time.

Primary biliary cholangitis: A rare, life-long liver disease characterised by impaired bile flow and the accumulation of toxic bile acids in the liver, leading to inflammation and destruction of bile ducts within the liver and causing increased levels of enzymes found primarily in the liver.

Placebo: A substance that has no therapeutic effect.

Quality-adjusted life year (QALY): The quality-adjusted life year is a generic measure of disease burden, including both the quality and the quantity of life lived.

Total bilirubin (TB): A key indicator of disease progression and prognosis in PBC

Ursodeoxycholic acid (UDCA): The main treatment prescribed for patients with PBC.

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.

Upper limit normal (ULN): The highest value that is considered normal for a given set of values.

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:

2. Gulamhusein AF, Hirschfield GM. Primary biliary cholangitis: pathogenesis and therapeutic opportunities. Nat Rev Gastroenterol Hepatol. 2020;17(2):93-110.
3. Lleo A, Wang G-Q, Gershwin ME, Hirschfield GM. Primary biliary cholangitis. Lancet. 2020;396(10266):1915-26.
4. 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 Rep. 2024;6(1):100931.
5. Abbas N, Culver EL, Thorburn D, Halliday N, Crothers H, Dyson JK, et al. UK-Wide Multicenter Evaluation of Second-line Therapies in Primary Biliary Cholangitis. Clin Gastroenterol Hepatol. 2023;21(6):1561-70.e13.
6. 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.
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NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Single Technology Appraisal

Seladelpar for previously treated primary biliary cholangitis [ID6249]

Clarification questions

March 2025

File name	Version	Contains confidential information	Date
ID6429 Seladelpar Clarification Response [CON]_20.03.25	1.0	Yes	20/03/25

Tables and Figures

Figures

Section A: Clarification on effectiveness data

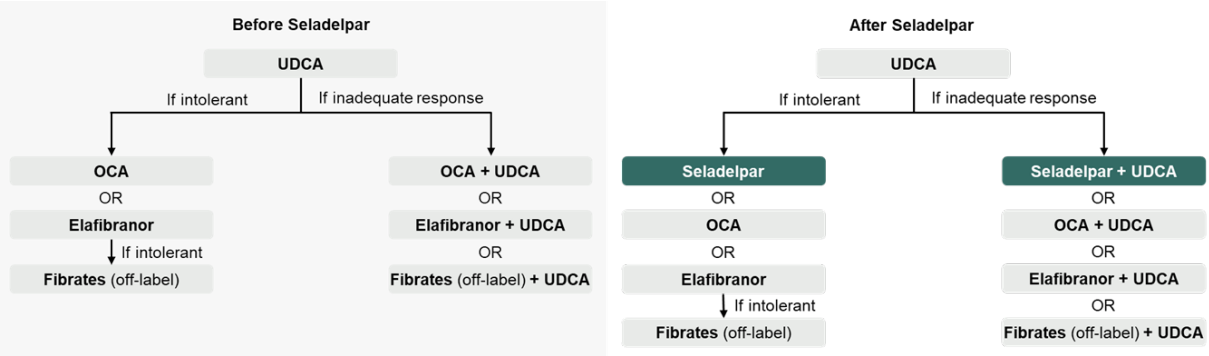
Proposed positioning of the technology

A1. The treatment pathway for PBC in the NHS is currently uncertain, following the recent positive recommendation for elafibrinor. If you have conducted engagement activities with UK clinicians to consider how the treatment pathway may change following the introduction of elafibrinor and how it would change if seladelpar was recommended, it would be useful if you could please provide this? This will be particularly useful if clinicians provide a rationale for why treatments are used at each treatment line.

Company response: Feedback from UK clinicians indicate there is significant variation in clinical practice in both patient referral to PBC treatment centres/ regional or national multi-disciplinary teams (MDTs) for consideration of second-line therapy, and choice of second-line therapy (as demonstrated by the 2024 UK national audit) (1). British Society of Gastroenterology (BSG) and British Association for the Study of the Liver (BASL) have published the PBC Care Bundle (a checklist designed to aid PBC patient management and guide escalation decisions) (2), with the aim of addressing some of these disparities in care provision against auditable standards in guidelines. It is notable the at the BSG/UK-PBC Primary Biliary Cholangitis treatment and management guidelines are currently being updated and will include relevant data and guidance on use of novel second line treatments for PBC (elafibranor and seladelpar).

UK clinicians agree with our proposed positioning of seladelpar in the treatment pathway (Figure 1), namely that seladelpar will provide an alternative second-line treatment option for those who are inadequate responders to, or intolerant of UDCA:

Figure 1: Proposed positioning of seladelpar in the UK PBC treatment pathway (Figure 9, Company Evidence Submission)



Key: OCA: obeticholic acid; PBC: primary biliary cholangitis; UDCA: ursodeoxycholic acid
Notes: UDCA is recommended as the first-line therapy for PBC by internationally recognised clinical practice guidelines. Seladelpar, alongside OCA and elafibranor, are positioned as second-line therapies for PBC in combination with UDCA or as a standalone treatment for UDCA-intolerant patients.
Source: Kowdley *et al.* (2023) (3)

Rationale for Second-Line Treatment Selection

This is dependent on multiple factors, including individual patient characteristics, prescribing clinician level of comfort with and preference for available second line treatments (guided by the licensed indication, contra-indications, potential for side effects, and drug-drug interactions). All second line treatments would typically be used in combination with UDCA, except in the ~5% of patients who are intolerant of UDCA, in whom second line treatment would be prescribed as monotherapy.

Lack of clinical response to first-line UDCA can be ascertained at 12 months or earlier. This should then trigger referral to the regional (England)/ national [Wales and Northern Ireland]) MDT, for consideration of second-line treatment.

The patient's hepatic status should be known prior to initiation of all second line therapies, i.e. whether the patient has decompensated cirrhosis (including Child-Pugh Class B and C) or has had a prior decompensation event (e.g., ascites, jaundice, variceal bleeding, hepatic encephalopathy).

OCALIVA

Due to prescriber's familiarity with Ocaliva (OCA), this is likely to be the first drug considered for second line treatment.

OCA would not be an appropriate second-line treatment option for those with contra-indications: Child-Pugh Class B or C (decompensated cirrhosis); those with a previous hepatic decompensation event, and patients with complete biliary obstruction (4).

Clinician insights suggest OCA would likely not be an appropriate treatment choice for:

- Patients experiencing pruritis
- Patients with cirrhosis, or with clinically significant portal hypertension
- Caution and additional monitoring may be required if OCA selected for use in patients with thyroid disease, or those receiving concomitant treatment with interacting drugs (e.g warfarin, theophylline)

UK clinicians have limited clinical experience with the newer second-line treatments, elafibranor and seladelpar, hence the rationale for treatment selection will largely be based on Phase 3 clinical trial data, and relevant safety information contained in the Summary of Product Characteristics (SmPC) for these products. UK clinicians suggest they may favour seladelpar over elafibranor as second-line treatment in those with osteoporosis, with chronic kidney disease (given the risk of elevated creatinine phosphokinase [CPK] worsening renal injury), in pregnancy, and in those receiving statins.

Key aspects from the SmPCs for elafibranor and seladelpar are detailed below – please see SmPCs for full information.

ELAFIBRANOR

Elafibranor use in patients with severe hepatic impairment (Child-Pugh C) is not recommended (5).

Elafibranor is not recommended during pregnancy and in women of childbearing potential not using effective contraception, due to the potential risk of foetal harm. (Note the US FDA label advises against the use of elafibranor with hormonal contraceptives) (6).

CPK should be evaluated prior to initiation of elafibranor treatment to determine the baseline CPK level and thereafter, according to the routine patient management. Caution should be used in patients with predisposing factors [for muscle injury/ myopathy] including old age (>65 years), hypothyroidism, personal or familial history of hereditary muscular disorders, severe infection, trauma, surgery, disturbances of hormone or electrolyte imbalance or alcohol abuse. Caution should be exercised when co-administering elafibranor with HMG-CoA reductase inhibitors (risk of rhabdomyolysis)

Consider the risk of fracture in the care of patients treated with elafibranor and monitor bone health according to current standards of care.

Concomitant administration with fibrates should be avoided.

SELADELPAR

Seladelpar is not recommended for use in patients who have or develop decompensated cirrhosis and is contra-indicated in patients with complete biliary obstruction (7).

Concomitant administration of seladelpar with probenecid should be avoided.

A2. We're confused about the role of fibrates in the CS. At times, consistent with the final NICE scope, you describe fibrates as an adjunct treatment, used off-label, that is not a direct comparator to existing treatments in the 2nd line position. However, on p.36 you cite evidence that describes fibrates as a treatment option for 50% of people who are eligible for 2nd line treatment (the other 50% receiving OCA). In Figure 9 you also present fibrates as an alternative treatment option in the same position as seladelpar, elafibrinor and OCA for intolerant patients. Can you please clarify whether you consider fibrates to be a true comparator to seladelpar in the 2nd line position? If not, can you please justify this based on data for real-world use of fibrates in the UK?

Company response: The company does not consider fibrates to be a comparator to seladelpar in the 2nd line position indicated in the decision problem.

As highlighted in Section 1.3.3.1.1 of the Company Evidence Submission, clinical experts consulted by Gilead during scoping confirmed that fibrates are used as an adjunctive option to UDCA in patients that do not meet the clinical criteria for second-line therapy; the fibrate cohort discussed would have ALP levels between 1-1.67 times the upper limit of normal (ULN), and would therefore not be considered the same as the cohort for seladelpar (8). In addition, feedback from clinical experts in the recent final draft guidance for elafibranor for previously treated primary biliary cholangitis [TA1016] also noted that, in light of the aforementioned data published by Abbas *et al*. (2024) (1), fibrates may be used as an add-on treatment for itching, rather than to treat PBC(9).

Furthermore, as part of the final draft guidance for TA1016, clinical experts confirmed that fibrates would not be widely used as a second-line treatment for PBC due to toxicity and limited efficacy evidence. Consequently, the committee concluded that fibrates were not used to treat PBC and were not an appropriate comparator for the second-line treatment of PBC (9). The inclusion of fibrates as a comparator within the appraisal for seladelpar would therefore create inequity.

As highlighted in Section 1.3.3.1.1 of the Company Evidence Submission, the use of fibrates alongside UDCA in UK clinical practice has been documented in the UK, albeit these have been used as an adjunctive treatment option for the treatment of itching, rather than PBC itself (as outlined above). Despite this unequivocal lack of recommendation of fibrates in UK-PBC treatment guidelines, the recent UK-wide audit of PBC care delivery by Abbas *et al*. (2024) reported high utilisation of fibrates, with 571 of 1,074 patients with PBC (53.2%) receiving second-line treatment bezafibrate or fenofibrate (1). However, beyond the aforementioned study by Abbas *et al*. (2024), two additional studies that provide data for the real-world use of fibrates in the UK were identified in '*Data on File - Disease Area Review in Primary Biliary* Cholangitis'. These studies report comparatively lower rates of real-world fibrate use in the UK. In an observational study conducted by Shah *et al*. (2019), 60% of patients (46 of 77 patients) began second-line therapy with OCA during a 14-month period, while 34% (26 of 77 patients) commenced treatment with bezafibrate (10). Another nationwide study by Abbas *et al*. (2023) reported similar results; 76.4% of patients (349 of 457

patients) received second-line treatment with OCA, with the remaining 23.6% (108 of 457 patients) treated with either bezafibrate (10%) or fenofibrate (13%) (11).

Considering the above, fibrates may be used as an off-label, adjunctive treatment option alongside UDCA, but they are intended to treat itching rather than PBC. Consequently, fibrates not a relevant comparator to seladelpar in the 2nd line position indicated in the decision problem.

Trials of seladelpar

The clinical effectiveness sections of the CS are poorly reported, which means that appraisal of the evidence is challenging. Key problems are:

- Clinical effectiveness and safety evidence is not presented from all available studies of seladelpar
- Evidence is not clearly presented for all outcomes listed on the NICE scope (or clearly stated where not measured or that there were no events)
- There are gaps in the evidence presented, particularly the presentation of data in figures without accompanying data and continuous outcomes presented with no variance data.

To appraise the clinical effectiveness evidence of seladelpar within the current appraisal timelines, we require you to submit the clinical effectiveness and safety evidence requested in this section in a format that can easily be appraised. This will best be accompanied by:

(a) Evidence for each study reported in the same document or document section

(b) Evidence presented in tables with clear labelling of study arms, timepoints, available sample, and to include all relevant data points, including variance data for continuous outcomes

A3. [PRIORITY] Please provide CSRs for ASSURE and ENHANCE

Company response: Please find the clinical study reports (CSRs) for ASSURE (data cut-off: 29th June 2023) and ENHANCE attached to the clarification response

document and are provided as Data on File. The Integrated Study Report of the ASSURE and RESPONSE data (data cut-off: 29th June 2023) is also attached as Data on File for additional clarification.

A4. The description of the clinical studies you provide in Section 2.2 is unclear. Can you please clarify the following:

(a) That the "Phase 2 proof-of-concept study" you mention on p.44 of the CS is NCT02609048 // CB8025-21528?

(b) That the "Phase 3 long-term safety study (CB8025-31731)" mentioned in the same paragraph is AFFIRM and that the study reference is actually NCT06051617 // CB8025-41837?

(c) What the trial reference is for the Phase 1b hepatic impairment study shown in Figure 11 on p.45? Can you please confirm that this was not identified by your clinical SLR, as it wasn't mentioned in the list of six studies described in the previous paragraph? If so, can you please describe how this was identified?

(d) Figure 11 on p.45 shows six studies including the Phase 1b study mentioned in the previous question. Can you please provide an updated version of this diagram with all studies of seladelpar included?

Company response:

(a) The EAG correctly assumes that the "Phase 2 proof-of-concept study" corresponds to NCT02609048 (12).

(b) As noted in the Company Evidence Submission, the clinical trial programme for seladelpar in PBC included a Phase 3 long-term safety study, which recruited patients from CB8025-21629, CB8025-31735 [ENHANCE], and Study CB8025-21838. This study was placed on hold on 25th November 2019 due to unexpected end of treatment histological findings in a concurrent non-alcoholic steatohepatitis (NASH) study, and was formally terminated on 20th December 2019 (see Figure 1). This study is identified by the reference CB8025-31731 or NCT03301506 (13).

Of note, this study was restarted on 12th February 2021 following a protocol amendment, which changed the protocol number to CB8025-31731-RE (ASSURE). Consequently, both the Phase 3 long-term safety study (CB8025-31731) and ASSURE (CB8025-31731-RE) share the same study reference (14).

AFFIRM is a randomised, double-blind, placebo-controlled study to evaluate the effect of seladelpar on clinical outcomes in patients with PBC and compensated cirrhosis. The study reference for AFFIRM is NCT06051617 / CB8025-41837, and is currently enrolling patients for study participation.

(c) The Phase 1b hepatic impairment study trial reference is NCT04950764 (15). The company can confirm that this study was not identified by the clinical SLR. This study formed part of the clinical materials received following the transfer of the asset to the company, and was included in the study schematic due to its relevance to ASSURE, despite assessing a population outside of the scope of the decision problem (16).

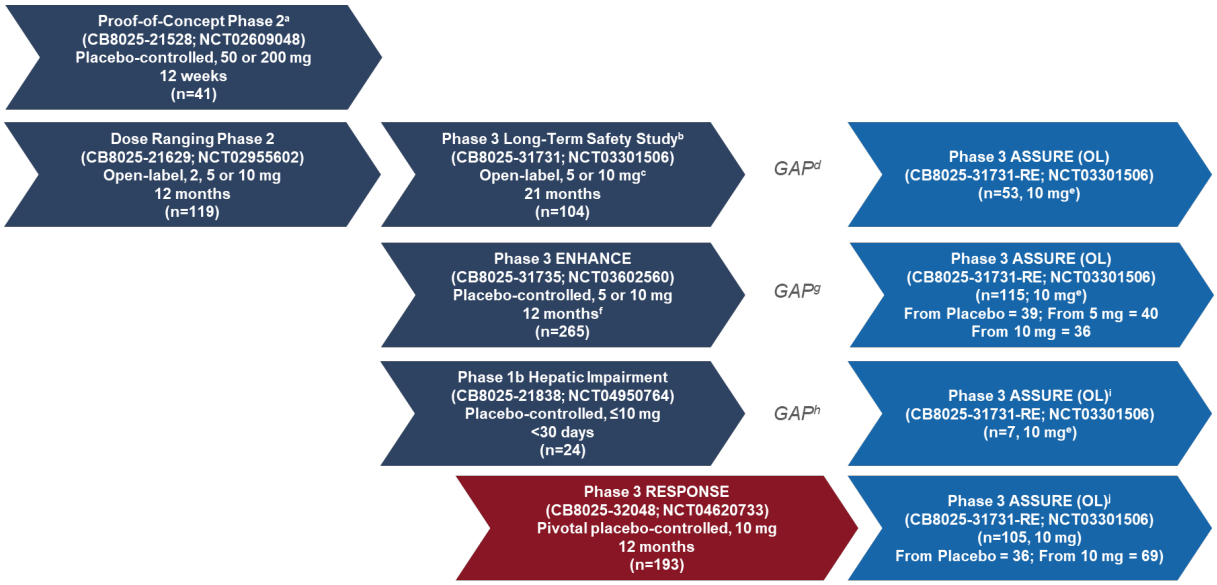
(d) Clinical studies of seladelpar in PBC include a Phase 2 proof-of-concept study (CB8025-21528; early terminated) and a Phase 2 dose-ranging study (CB8025-21629); early terminated Phase 3 study (ENHANCE; CB8025-31735); early terminated long-term open-label Phase 3 long-term safety study (CB8025-31731); pivotal Phase 3 study (RESPONSE; CB8025-32048); and a Phase 1b single and multiple dose pharmacokinetic study (CB8025-21838) in PBC patients with varying degrees of hepatic impairment (16). The seven studies of seladelpar in PBC are depicted in Figure 2.

Patients who had completed CB8025-21629 and CB8025-31735 were given the option to enter the long-term safety study CB8025-31731. Studies CB8025-31735 and CB8025-31731 were terminated early by the Sponsor on 25th November 2019 due to unexpected end of treatment histology findings, in a concurrent Phase 2 study of seladelpar in patients with NASH (CB8025-21730), which were later determined to be unrelated to seladelpar (16).

Subsequently, a new pivotal Phase 3 study, RESPONSE (CB8025-32048), was initiated. The long-term safety study was restarted following a protocol amendment, which changed the protocol number to CB8025-31731-RE (ASSURE). Patients

who were either enrolled in CB8025-31371 at the time of study termination or had completed CB8025-31735 were invited to resume seladelpar treatment (or receive seladelpar for the first time if patients were randomized to placebo in CB8025-31735). Studies CB8025-21629, CB8025-31731, and CB8025-31735 are referred to as legacy studies in Figure 2. Patients completing CB8025-32048 or CB8025-21838 and meeting eligibility criteria per the protocol were also able to enter ASSURE (Figure 2) (16).

Figure 2: ASSURE flow of patients from parent studies as of 29th June 2023 data cut-off



Key: OL, open-label
Notes: Data cut-off – June 29th 2023
[a]Study CB8025-21528 was terminated early due to transaminase elevations. Twelve patients who enrolled in CB8025-21528 subsequently entered study CB8025-21629. In addition, three patients who screen failed in CB8025-21528 were eligible for study CB8025-21629 and subsequently enrolled.
[b]Average time from last seladelpar dose in study CB8025-21629 to enrollment in study CB8025-31731 was 0.3 days (min/max: 0/21).
[c]One patient received 2 mg.
[d]The gap between the last seladelpar dose in study CB8025-31731 and enrollment in study CB8025-31731-RE was an average of 105 weeks (min/max: 65/152).
[e]Seladelpar 5 mg allowed for tolerability issues per Investigator assessment.
[f]The number of patients who reached Month 3, Month 6, and Month 12 in study CB8025-31735 at the time of study termination was 163, 65, and 2, respectively. The two patients who completed study CB8025-31735 rolled into the open-label extension study CB8025-31731 and were treated for 1-4 days. These patients are not depicted in the figure, but their data from CB8025-31731 are included in the final CSR for CB8025-31731 integrated analyses supporting the PBC New Drug Application 217899.
[g]The gap between the last dose of seladelpar or placebo in CB8025-31735 and enrollment in study CB8025-31731-RE was an average of 106 weeks (min/max: 64/158).
[h]Patients enrolled in study CB8025-31731-RE from study CB8025-21838 had limited exposure to seladelpar, with 27-245 days (3.9-35.0 weeks) between study completion and CB8025-31731-RE enrolment.
[i]Patients meeting entry criteria may rollover into study CB8025-31731-RE. As of the data cutoff date for study CB8025-31731-RE, seven patients from study CB8025-21838 entered study CB8025-31731-RE.
[j]Patient numbers reflect patients from study CB8025-32048 who rolled into study CB8025-31731-RE as of the 29th June 2023 data cutoff date. At the Month 12/EOT visit, patients completing CB8025-32048 were invited to roll over into CB8025-31731-RE.
Source: ASSURE Integrated Study Report (14)

A5. [PRIORITY] We're unclear about the flow of participants into ASSURE and the methods and outcomes from the study. Using the guidance on re-

submitting clinical effectiveness evidence provided above, please can you provide the following information in your clarification response?:

- **(a) Baseline characteristics for all participants at the start of ASSURE, including previous treatments at baseline**
- **(b) Baseline characteristics split according to the original study that participants were enrolled in, including previous treatments at baseline**
- **(c) A breakdown of (i) the number of participants from each 'legacy study' that entered ASSURE, (ii) the reasons for non-enrolment in ASSURE for all eligible participants, (iii) the length of time between the legacy studies and baseline of ASSURE**
- **(d) Information on treatments received during the trial, including the dose of seladelpar and background treatments**
- **(e) Tabulated results for all scoped outcomes from this study (i.e. including outcome data with baseline measures for each outcome, measures of variance and the number of participants included for all follow-up timepoints, and safety data).**
- **(f) Please clarify which original study the participant who died participated in**

Company response: As highlighted in Section 2.2 of the Company Evidence Submission, study CB8025-31731-RE (ASSURE) is an ongoing, long-term, open-label, phase 3 study in PBC patients who either completed the pivotal, placebo-controlled phase 3 study CB8025-32048 (RESPONSE) or the ongoing open-label PBC hepatic impairment study CB8025-21838, or in patients who had participated in previous seladelpar PBC studies (phase 3 placebo-controlled study CB8025-31735 or long-term open-label study CB8025-31731, which included patients from the phase 2 open-label study CB8025-21629; these studies are hereinafter referred to as legacy studies) (see Figure 2).

The Company Evidence Submission presents clinical effectiveness results for patients rolling over from RESPONSE using the most recent data cut-off from ASSURE, dated

31st January 2024. To date, three conference posters have been presented reporting interim efficacy and safety results from this data cut-off (16-19). At the time of writing, there is no CSR available for this ASSURE data cut-off, hence the level of detail regarding the efficacy and safety evidence results for the 31st January data cut-off are limited to the information provided in conference posters.

An interim ASSURE CSR, dated 13th November 2023, reporting on an earlier data cut-off (29th June 2023) is available and has been attached to the clarification response document as data on file (16). Of note, the data cutoff date for the interim CSR was before the completion and unblinding of RESPONSE. Therefore, the interim CSR for ASSURE focused only on safety evaluations from Study Day 1 to the June 29th 2023 data cutoff date for the two patient groups – patients from legacy studies, and patients enrolled from RESPONSE. Patients enrolled from RESPONSE were analysed without regard to treatment assignment, hence it is not possible to distinguish which patients have received long-term follow-up with seladelpar in this patient group.

On 30th August 2023, RESPONSE was unblinded. As part of the integrated efficacy and safety statistical analysis plan, unblinded efficacy data from RESPONSE patients who enrolled in ASSURE were analysed in an integrated fashion from baseline in the pivotal study at the time of the data cutoff for the ASSURE study (14).

A focused analysis of ASSURE, separate from the interim CSR, was prepared to summarise these integrated long-term efficacy and safety data. In the integrated report, patients entering ASSURE from RESPONSE were analysed in two groups - those who were continuing seladelpar (continuous seladelpar patients), and those initiating seladelpar (crossover patients) (14).

In the following responses, data from the 29th June 2023 cutoff date taken from the interim CSR and/or the Integrated Study Report will be used as the primary source of information for the following responses, unless otherwise specified, due to the increased level of detail available on the information requested from the EAG.

(a) Baseline characteristics for all participants at the start of ASSURE, including previous treatments at baseline

The baseline characteristics for all participants at the start of ASSURE are presented in Table 1. Baseline characteristics are reported for the Safety Analysis Set (SAS), defined as any patient who was enrolled into the study and received at least one dose of seladelpar through the 29th June 2023 data cutoff date.

Table 1: Baseline characteristics for all participants at the start of ASSURE - (ASSURE, Safety Analysis Set)

	Seladelpar Any Dose in CB8025-31731-RE (n=280)
Age (years)	
Mean (SD)	58.6 (9.76)
Min, Max	33, 79
Sex, n (%)	
Female	264 (94.3)
Male	16 (5.7)
Race, n (%)	
American Indian or Alaska Native	10 (3.6)
Asian	20 (7.1)
Black or African American	5 (1.8)
White	242 (86.4)
Decline to answer	1 (0.4)
Missing	2 (0.7)
Ethnicity, n (%)	
Hispanic or Latino	57 (20.4)
Not Hispanic or Latino	218 (77.9)
Decline to answer	3 (1.1)
Missing	2 (0.7)
Duration of PBC (years)[c]	
n	279
Mean (SD)	10.675 (6.196)
Min, Max	1.270, 27.693
Age at PBC Diagnosis (years)	
n	279
Mean (SD)	48.2 (9.09)
Min, Max	25, 69
Missing	1 (0.4)
Number of Patients with Cirrhosis at Screening, n (%)	46 (16.4)
Child-Pugh A	44 (15.7)
Child-Pugh B	2 (0.7)
Cirrhosis with portal hypertension	9 (3.2)
Liver Stiffness (kPa)[d], n	169
Mean (SD)	10.26 (8.248)

Min, Max	3.0, 74.2
Duration of prior UDCA usage, years[e]	
n	279
Mean (SD)	8.848 (6.114)
Min, Max	0.003, 27.693
Prior Use of OCA and/or Fibrates, n (%)	
Yes	49 (17.5)
UDCA Intolerance, n (%)	
Yes	16 (5.7)
Total Daily UDCA Dose on Day 1 (mg/kg)	
n	266
Mean (SD)	14.700 (3.172)
Min, Max	4.713, 25.635
Pruritus History, n (%)	
Yes	192 (68.6)
No	87 (31.1)
Missing	1 (0.4)
ALP Concentration (U/L) – Normal Range 37-116 U/L	
n	269
Mean (SD)	249.833 (122.780)
Min, Max	68.000, 905.000
ALP Level, n (%)	
< 350 U/L	216 (77.1)
≥ 350 U/L	53 (18.9)
Total Bilirubin Concentration (mg/dL) – Normal Range 0.1-1.1 mg/dL	
n	269
Mean (SD)	0.732 (0.344)
Min, Max	0.220, 2.170
Total Bilirubin Level, n (%)	
≤ 1× ULN	235 (83.9)
> 1 and ≤ 2× ULN	34 (12.1)
> 2× ULN	0 (0)
≤ 0.6× ULN	141 (50.4)
≥ 0.6 and < 1× ULN	94 (33.6)
ALT (U/L) – Normal Range 6-41 U/L	
n	269
Mean (SD)	39.577 (23.299)
Min, Max	5.000, 211.000
AST (U/L) – Normal Range 9-34 U/L	
n	269
Mean (SD)	36.826 (16.935)
Min, Max	12.000, 152.667
GGT (U/L) – Normal Range Female: 7- 38 U/L and Male: 11-52 U/L	
n	269
Mean (SD)	201.511 (180.235)
Min, Max	12.000, 1212.000
Albumin (g/dL) – Normal Range 3.5-5.5 g/dL	
n	269
Mean (SD)	4.137 (0.280)
Min, Max	2.900, 4.950

Previous PBC Treatment	
UDCA	279 (99.6)
OCA	38 (13.6)
Fibrates	16 (5.7)
Steroids	5 (1.8)
Immunosuppressant	1 (0.4)
Methotrexate	1 (0.4)
Systemic Steroids	1 (0.4)
Colchicine	1 (0.4)
Other	15 (5.4)

Key: ALP, alkaline phosphatase; ALT, alanine aminotransferase; AST, aspartate aminotransferase; EOT, end of treatment; GGT, gamma-glutamyl transferase; OCA, obeticholic acid; PBC, primary biliary cholangitis; UDCA, ursodeoxycholic acid.
Notes: Percentages are based on the number of patients in the Safety Analysis Set. Patients in France do not allow race and ethnicity collections, thus have missing race and ethnicity.
[a]Eleven patients from CB8025-32048 had Month 12/EOT laboratory measurements that were not entered into the CB8025-31731-RE database at the time of the data cutoff, including one patient with cirrhosis at baseline.
[b]Note that the "Seladelpar Any Dose in CB8025-31731-RE" included one patient who initiated treatment at 5 mg and was therefore not included in the "Seladelpar 10 mg in CB8025-31731-RE" arm.
[c]Duration of PBC (years) = (informed consent date - diagnosis date +1)/365.25
[d]Only transient elastography results were summarized. For patients rolled over from study CB8025-32048, FibroScan performed at Month 12/EOT of CB8025-32048 could be used for CB8025-31731-RE screening although those data were not entered into study CB8025-31731-RE database.
[e]Duration of Prior UDCA Usage (years) = (UDCA usage end date or informed consent date (whichever is earlier) – UDCA usage start date + 1)/365.25.
[f]One patient did not have UDCA usage entered in the database at the time of the data cutoff.
Source: Tables 13, 14,16 & 19, Interim ASSURE CSR (16)

(b) Baseline characteristics split according to the original study that participants were enrolled in, including previous treatments at baseline

Baseline characteristics are summarised for ASSURE by parent study and RESPONSE treatment for the intent-to-treat (ITT) Analysis Set is presented in Table 2.

Of note, we have requested data on previous treatments at baseline split according to parent study and RESPONSE treatment, but do not currently have access – if this date becomes available, we would be happy to share with the EAG.

Table 2: Baseline characteristics for all participants at the start of ASSURE - (ASSURE, Safety Analysis Set)

	RESPONSE Parent Group		Legacy & CB8025-21838 Parent Group
Category	**Crossover from Placebo[a] (n=36)**	**Continuous Seladelpar[b] (n=69)**	**Seladelpar 10 mg[c] (n=174)**
Age (years)	36	69	174

Mean (SD)	59.4 (8.92)	57.9 (10.70)	58.6 (9.56)
Min, Max	44, 77	33, 77	33, 79
Sex, n (%)			
Female	34 (94.4)	65 (94.2)	164 (94.3)
Male	2 (5.6)	4 (5.8)	10 (5.7)
Race, n (%)[d]			
American Indian or Alaska Native	3 (8.3)	1 (1.4)	6 (3.4)
Asian	3 (8.3)	4 (5.8)	13 (7.5)
Black or African American	0	2 (2.9)	3 (1.7)
White	30 (83.3)	61 (88.4)	150 (86.2)
Decline to answer	0	0	1 (0.6)
Missing	0	1 (1.4)	1 (0.6)
Ethnicity, n (%)[d]			
Hispanic or Latino	15 (41.7)	19 (27.5)	23 (13.2)
Not Hispanic or Latino	21 (58.3)	49 (71.0)	146 (84.5)
Decline to answer	0	0	3 (1.7)
Missing	0	1 (1.4)	1 (0.6)
Duration of PBC (years)[e]			
n	36	68	174
Mean (SD)	9.796 (6.837)	9.699 (6.508)	11.239 (5.915)
Min, Max	1.402, 26.341	1.270, 27.294	2.218, 27.693
Age at PBC Diagnosis (years)			
< 50	18 (50.0)	34 (49.3)	103 (59.2)
≥ 50	18 (50.0)	34 (49.3)	71 (40.8)
Missing	0	1 (1.4)	0
Number of Patients with Cirrhosis at Baseline, n (%)[f,g]	5 (13.9)	8 (11.6)	33 (19.0)
Child-Pugh A	5 (100)	8 (100)	31 (93.9)
Child-Pugh B	0	0	2 (6.1)
Cirrhosis with portal hypertension	1 (20.0)	0	8 (24.2)
Liver stiffness (kPa), n	0	0	168
Mean (SD)	-	-	10.27 (8.271)
Min, Max	-	-	3.0, 74.2
Prior Use of OCA and/or Fibrates, n (%)			

Yes	6 (16.7)	11 (15.9)	32 (18.4)
No	30 (83.3)	58 (84.1)	142 (81.6)
UDCA Intolerance, n (%)[h]			
Yes	0	6 (8.7)	6 (3.4)
No	36 (100)	63 (91.3)	168 (96.6)
Total Daily UDCA Dose at Baseline (mg/kg)			
n	35	63	167
Mean (SD)	15.027 (3.344)	14.407 (2.951)	14.738 (3.234)
Min, Max	9.160, 22.124	8.130, 23.025	4.713, 25.635
Pruritus NRS Level, n (%)			
< 4	28 (77.8)	51 (73.9)	112 (64.4)
≥ 4	7 (19.4)	13 (18.8)	60 (34.5)
Missing	1 (2.8)	5 (7.2)	2 (1.1)
ALP Concentration (U/L) – Normal Range 37-116 U/L			
n	33	61	174
Mean (SD)	272.4 (118.74)	178.6 (92.45)	270.5 (124.35)
Min, Max	143, 666	68, 466	99, 905
ALP Level, n (%)			
< 350 U/L	26 (72.2)	57 (82.6)	132 (75.9)
≥ 350 U/L	7 (19.4)	4 (5.8)	42 (24.1)
Missing	3 (8.3)	8 (11.6)	-
Total Bilirubin Concentration (mg/dL) – Normal Range 0.1-1.1 mg/dL			
n	33	61	174
Mean (SD)	0.652 (0.248)	0.714 (0.404)	0.754 (0.336)
Min, Max	0.30, 1.25	0.29, 2.00	0.220, 2.17
Total Bilirubin Level, n (%)			
≤ 1× ULN	31 (86.1)	53 (76.8)	150 (86.2)
> 1 and ≤ 2× ULN	2 (5.6)	8 (11.6)	24 (13.8)
> 2× ULN	0	0	0
Missing	3 (8.3)	8 (11.6)	0
ALT (U/L) – Normal Range 6-41 U/L			
n	33	61	174
Mean (SD)	39.4 (18.04)	35.9 (25.05)	40.97 (23.57)

Min, Max	12, 81	5, 137	8.5, 211.0
AST (U/L) – Normal Range 9-34 U/L			
n	33	61	174
Mean (SD)	35.6 (12.02)	37.1 (19.12)	37.0 (17.02)
Min, Max	17, 66	14, 111	12.0, 152.7
GGT (U/L) – Normal Range Female: 7- 38 U/L and Male: 11-52 U/L			
n	33	61	174
Mean (SD)	245.2 (226.16)	161.1 (152.89)	208.1 (178.01)
Albumin (g/dL) – Normal Range 3.5-5.5 g/dL			
n	33	61	174
Mean (SD)	4.07 (0.236)	4.18 (0.301)	4.134 (0.280)
Min, Max	3.4, 4.5	2.9, 4.7	3.2, 5.0

Key: ALP, alkaline phosphatase; ALT, alanine aminotransferase; AST, aspartate aminotransferase; EOT, end of treatment; GGT, gamma-glutamyl transferase; OCA, obeticholic acid; PBC, primary biliary cholangitis; UDCA, ursodeoxycholic acid.
Notes: Percentages are based on the number of patients in the Safety Analysis Set.
[a]This group includes patients that were randomized to placebo in CB8025-32048 and received any dose of seladelpar in CB8025-31731-RE. Baseline starts from CB8025-31731-RE.
[b]This group includes patients that were randomized to seladelpar 10 mg in CB8025-32048 and continued on with any dose of seladelpar CB8025-31731-RE. Baseline starts from CB8025-31731-RE.
[c]This group includes patients that came from studies CB8025-21629, CB8025-31735, CB8025-31731, or CB8025-21838 and initiated seladelpar 10 mg in CB8025-31731-RE. Baseline starts from CB8025-31731-RE.
[d]Race and ethnicity are not collected for patients in France due to prohibition by local regulations.
[e]Duration of PBC (time [in years] from diagnosis date to the informed consent date) is defined as (informed consent date – PBC diagnosis date + 1)/365.2425.
[f]Percentages for baseline Child-Pugh class are based on patients with cirrhosis at baseline.
[g]Percentages for portal hypertension are based on patients with cirrhosis at baseline.
[h]UDCA intolerance was derived based on Day 1 UDCA usage.
[i]Total Daily UDCA Dose (mg/kg) = Total Daily UDCA Dose (mg) at Day 1/Day 1 Weight (kg).
Source: Table 14.1.2.3.5, Table 14.1.2.4.1, Table 14.1.3.3.5, and Table 14.1.3.4.1, ASSURE Integrated Study Report (14)

(c) A breakdown of (i) the number of participants from each 'legacy study' that entered ASSURE, (ii) the reasons for non-enrolment in ASSURE for all eligible participants, (iii) the length of time between the legacy studies and baseline of ASSURE

Figure 2 in the response to A4 details the number of patients from each 'legacy study' that entered ASSURE at the time of the 29th June 2023 data cutoff date.

As noted in A3d, the long-term safety study CB8025-31731 was reinitiated following a protocol amendment, which changed the protocol number to CB8025-31731-RE (ASSURE). Patients who had been receiving treatment at the time of the study termination, as well as those who completed study CB8025-21838 were invited to participate in the ASSURE providing they met eligibility requirements.

As of the 29th June 2023 data cut-off, the length of time between the legacy studies and the baseline of ASSURE is described in the bullets below (16):

- The gap between the last seladelpar dose in the Phase 3 long-term safety study (CB8025-31731) and enrolment in ASSURE was an average of 105 weeks (min/max: 65/152).
- The gap between the last dose of seladelpar or placebo in ENHANCE (CB8025-31275) and enrolment in ASSURE was an average of 106 weeks (min/max: 64/158).
- Patients enrolled in ASSURE from the Phase 1b hepatic impairment study (CB8025-21838) had limited exposure to seladelpar, with 27-245 days (3.9-35.0 weeks) between study completion and ASSURE enrolment.

(d) Information on treatments received during the trial, including the dose of seladelpar and background treatments

The average daily dose of seladelpar received through 29th June 2023 is displayed below in Table 3.

We have requested data on the dose of UDCA during the ASSURE study, but do not currently have access – if this data becomes available, we would be happy to share with the EAG.

Table 3: Exposure to seladelpar in ASSURE (Safety Analysis Set)

	RESPONSE Randomised to Placebo		RESPONSE Randomised to Seladelpar	Legacy & CB8025-21838 Parent Group
	RESPONSE Placebo (n=65)	Crossover Seladelpar (n=36)	Continuous Seladelpar (n=128)	Seladelpar 10 mg exposure in CB8025-31731-RE (n=175)
Treatment duration				
N	65	36	128	175
Mean	48.330	20.413	61.479	75.417
SD	11.573	13.535	19.275	25.729
Median	52.000	18.714	55.214	80.143

Q1, Q3	51.143, 52.857	8.714, 29.500	52.143, 72.357	57.286, 92.286
Min, Max	1.286, 55.429	1.000, 50.286	0.143, 114.286	0.143, 124.000
Treatment Exposure (cumulative), n (%)				
≥4 weeks	64 (98.5)	35 (97.2)	127 (99.2)	173 (98.9)
≥8 weeks	63 (96.9)	28 (77.8)	125 (97.7)	172 (98.3)
≥12 weeks	62 (95.4)	24 (66.7)	125 (97.7)	171 (97.7)
≥26 weeks	61 (93.8)	11 (30.6)	123 (96.1)	170 (97.1)
≥39 weeks	58 (89.2)	4 (11.1)	120 (93.8)	160 (91.4)
≥1 year	37 (56.9)	0	102 (79.7)	142 (81.1)
≥1.5 years	0	0	25 (19.5)	90 (51.4)
≥2 years	0	0	3 (2.3)	19 (10.9)
Cumulative dose (mg)				
N	65	36	126	175
Mean	0.0	1423.9	4298.0	5259.0
SD	0.00	941.13	1305.92	1784.10
Median	0.0	1325.0	3890.0	5690.0
Q1, Q3	0.0, 0.0	620.0, 2065.0	3640.0, 5000.0	3910.0, 6400.0
Min, Max	0, 0	80, 3520	360, 9580	10, 8550
Average daily dose (mg/day)				
N	65	36	126	175
Mean	0.0	10.040	9.830	9.974
SD	0.00	0.314	0.624	0.898
Median	0.0	10.000	9.969	9.966
Q1, Q3	0.0, 0.0	9.905, 10.147	9.800, 10.020	9.809, 10.021
Min, Max	0, 0	9.393, 11.429	6.297, 11.975	4.982, 14.494

Key: max, maximum; min, minimum; n, number of patients in the category; N, number of patients; Q, quartile; SD, standard deviation.
Notes: Data for two patients, 143-412 and 635-404, are excluded from cumulative dose and average daily dose descriptive analysis as accurate estimation of dosing could not be done due to large number of unreturned bottles.
[a]Patients who were in CB8025-32048 placebo arm. Only the CB8025-32048 placebo data are included in this column.
[b]Patients who completed treatment with placebo in CB8025-32048 and initiated open-label seladelpar 10 mg in CB8025-31731-RE. Only CB8025-31731-RE data is included.
[c]Patients who were in CB8025-32048 seladelpar arm. For patients who rolled over to CB8025-31731-RE, both CB8025-32048 data and CB8025-31731-RE data are included. For patients who did not enroll in CB8025-31731-RE, only data from CB8025-32048 are included.
[d]Patients who enrolled into CB8025-31731-RE from legacy studies (CB8025-31735, CB8025-21629, CB8025-31731, and CB8025-21838).
Source: Table 37, ASSURE Integrated Study Report (14)

(e) Tabulated results for all scoped outcomes from this study (i.e. including outcome data with baseline measures for each outcome, measures of variance and the number of participants included for all follow-up timepoints, and safety data).

Efficacy

The following efficacy endpoints were analysed for ASSURE and its parent studies:

- Composite biochemical response rates
- ALP normalisation rates
- Efficacy laboratory (ALP/AST/AST/GGT/total bilirubin) changes from baseline
- NRS change from baseline (for patients from legacy and CB8025-21838 studies in ASSURE with baseline NRS ≥4 only)

Composite Biochemical Response Rate

The composite biochemical response rate for all patients in RESPONSE and those who had subsequently enrolled in ASSURE as of the data cutoff date is presented for the ITT analysis set in Table 4.

A responder for the composite biochemical response is defined as a patient who met all 3 of the following criteria: (1) ALP < 1.67× ULN, (2) ALP decreased from baseline ≥ 15% and (3) total bilirubin < ULN.

For patients who were previously enrolled in study RESPONSE, data are presented starting from Day 1 of RESPONSE. Data points through Month 12 were collected in RESPONSE; data points after Month 12 were collected in ASSURE. The number of patients at each time point reflects the number of evaluable patients at that time point.

At Month 12, 13/65 (20.0%) patients who were treated with placebo in RESPONSE achieved a composite biochemical response, compared to 79/128 (61.7%) patients who were treated with seladelpar 10 mg. At Month 13, after one month in RESPONSE, 16/35 (45.7%) crossover patients achieved a composite response and at Month 15, 19/22 (86.4%) crossover patients achieved a composite response. Additionally, the response rate among continuous seladelpar patients was consistent at Month 13 (41/65 [63.1%]) and Month 15 (26/46 [56.5%]) (14)

Table 4: Composite biochemical response rate for patients in RESPONSE and upon rollover to ASSURE (ITT Analysis Set)

	CB8025-32048 and Rollovers to CB8025-31731-RE	
	Placebo (n=65)	Seladelpar 10 mg (n=128)
During RESPONSE		
Patients who achieved response at Month 1, n/m (%)[a,b,c]	5/65 (7.7)	76/128 (59.4)
Patients who achieved response at Month 3, n/m (%)[a,b,c]	7/65 (10.8)	79/128 (61.7)
Patients who achieved response at Month 6, n/m (%)[a,b,c]	12/65 (18.5)	85/128 (66.4)
Patients who achieved response at Month 9, n/m (%)[a,b,c]	12/65 (18.5)	79/128 (61.7)
Patients who achieved response at Month 12, n/m (%)[a,b,c]	13/65 (20.0)	79/128 (61.7)
During ASSURE[d]		
Patients who achieved response at Month 13, n/m (%)[a,b,c]	16/35 (45.7)	41/65 (63.1)
Patients who achieved response at Month 15, n/m (%)[a,b,c]	19/22 (86.4)	26/46 (56.5)
Patients who achieved response at Month 18, n/m (%)[a,b,c]	8/11 (72.7)	15/24 (62.5)
Patients who achieved response at Month 21, n/m (%)[a,b,c]	4/4 (100)	5/8 (62.5)
Patients who achieved response at Month 24, n/m (%)[a,b,c]	0/0	1/3 (33.3)

Notes:
[a]n/m (%) = (number of responders / number of response evaluable patients) × 100%.
[b]A patient was designated as a responder if all 3 of the following conditions were met: (1) ALP < 1.67 × ULN; (2) ALP decrease from baseline ≥ 15%; (3) total bilirubin ≤ ULN.
[c]A patient without an assessment, or who had discontinued treatment before the specified timepoint for response evaluation, or who otherwise had missing data was considered a non-responder.
[d]Data collected during study CB8025-31731-RE as of the data cutoff date of 29 June 2023. Month 13, Month 15, Month 18, Month 21, and 2 years correspond to 1, 3, 6, 9, and 12 months, respectively, of open-label treatment with seladelpar in CB8025-31731-RE.
Source: Table 17, ASSURE Integrated Study Report (14)

The composite biochemical response rate in patients from legacy and CB8025-21838 studies in study ASSURE is summarized for the ITT analysis set in Table 5. For patients who enrolled in CB8025-31731-RE from legacy or CB8025-21838 studies, the response rate at Month 1 was 108/174 patients (62.1%), 121/173 patients (69.9%) at Month 3, 104/148 patients (70.3%) at Month 12, and 69/104 patients (66.3%) at Month 18.

Table 5: Composite biochemical response rate during ASSURE in patients from legacy studies

	Legacy & CB8025-21838 Parent Group
	Seladelpar 10 mg (n=174)
Patients who achieved response at Month 1, n/m (%)[a,b,c]	108/174 (62.1)
Patients who achieved response at Month 3, n/m (%)[a,b,c]	121/173 (69.9)
Patients who achieved response at Month 6, n/m (%)[a,b,c]	131/173 (75.7)
Patients who achieved response at Month 9, n/m (%)[a,b,c]	114/160 (71.3)
Patients who achieved response at Month 12, n/m (%)[a,b,c]	104/148 (70.3)
Patients who achieved response at Month 18, n/m (%)[a,b,c]	69/104 (66.3)
Patients who achieved response at Month 24, n/m (%)[a,b,c]	14/20 (70.0)

Notes: Table presents data collected in open-label study CB8025-31731-RE as of the data cutoff date of 29 June 2023.
[a]n/m (%) = (number of responders / number of response evaluable patients) × 100%.
[b]A patient was designated as a responder if all 3 of the following conditions were met: (1) ALP < 1.67 × ULN; (2) ALP decrease from baseline ≥ 15%; (3) total bilirubin ≤ ULN.
[c]A patient without an assessment, or who had discontinued treatment before the specified timepoint for response evaluation, or who otherwise had missing data was considered a non-responder.
[d]The number of patients reflects the number of evaluable patients at Month 18
Source: ASSURE Integrated Study Report (14)

Normalisation of ALP

The normalization of ALP for all patients in RESPONSE and those who had enrolled in ASSURE is presented for the ITT analysis set in Table 6. Responders for normalization of ALP are defined as patients with levels of ALP < 1× ULN.

Of the 65 patients from the ITT analysis set who received placebo in RESPONSE, none achieved normalization, compared to 32/128 (25%) patients treated with seladelpar at Month 12. Once patients enrolled in ASSURE, 7/35 (20%) crossover patients achieved ALP normalization after 1 month of treatment with seladelpar (Month 13), 7/22 (31.8%) achieved normalization after 3 months (Month 15), 5/11 (45.5%) achieved normalization after 6 months of treatment (Month 18), and 3/4 (75%) achieved normalization after 9 months of treatment (Month 21). This is overall similar to the continuous seladelpar patients, with 16/65 (24.6 %) achieving normalization at Month 13, 8/46 (17.4%) achieving normalization at Month 15, 8/24 (33.3%) achieving normalization at Month 18, and 1/8 (12.5%) achieving normalization at Month 21 (14).

Table 6: Normalisation of ALP levels for patients in RESPONSE and upon rollover to ASSURE (ITT Analysis Set)

	CB8025-32048 and Rollovers to CB8025-31731-RE	
	Placebo (n=65)	Seladelpar 10 mg (n=128)
During RESPONSE		
Patients who achieved ALP response at Month 1, n/m (%)[a,b,c]	0/65	10/128 (7.8)
Patients who achieved ALP response at Month 3, n/m (%)[a,b,c]	0/65	24/128 (18.8)
Patients who achieved ALP response at Month 6, n/m (%)[a,b,c]	0/65	34/128 (26.6)
Patients who achieved ALP response at Month 9, n/m (%)[a,b,c]	0/65	36/128 (28.1)
Patients who achieved ALP response at Month 12, n/m (%)[a,b,c]	0/65	32/128 (25.0)
During ASSURE[d]		
Patients who achieved ALP response at Month 13, n/m (%)[a,b,c]	7/35 (20.0)	16/65 (24.6)
Patients who achieved ALP response at Month 15, n/m (%)[a,b,c]	7/22 (31.8)	8/46 (17.4)
Patients who achieved ALP response at Month 18, n/m (%)[a,b,c]	5/11 (45.5)	8/24 (33.3)
Patients who achieved ALP response at Month 21, n/m (%)[a,b,c]	3/4 (75.0)	1/8 (12.5)
Patients who achieved ALP response at Month 24, n/m (%)[a,b,c]	0/0	0/3

Key: ALP, alkaline phosphatase.
Notes:
[a]n/m (%) = (number of responders / number of response evaluable patients) × 100%.
[b]A patient was designated as a responder if the ALP value at Month 12 was ≤ 1.0× ULN.[c]A patient without an assessment, or who had discontinued treatment before the specified timepoint for response evaluation, or who otherwise had missing data was considered a non-responder.
[d]Data collected during study CB8025-31731-RE as of the data cutoff date of 29 June 2023. Month 13, Month 15, Month 18, Month 21, and 2 years correspond to 1, 3, 6, 9, and 12 months, respectively, of open-label treatment with seladelpar in CB8025-31731-RE.
Source: Table 25, ASSURE Integrated Study Report (14)

The normalization of ALP in ASSURE from patients in the legacy studies is summarized in Table 7. Of the patients who had previously been enrolled in the legacy studies, 44/174 (25.3%) achieved ALP normalization at Month 1, 60/173 (34.7%) at Month 3, 55/148 (37.2%) at Month 12, 35/104 (33.7%) at Month 18, and 5/20 (25%) at 2 years (14).

Table 7: Normalisation of ALP levels for patients in legacy studies

	Legacy & CB8025-21838 Parent Group
	Seladelpar 10 mg (n=174)
Patients who achieved ALP response at Month 1, n/m (%)[a,b,c]	44/174 (25.3)
Patients who achieved ALP response at Month 3, n/m (%)[a,b,c]	60/173 (34.7)
Patients who achieved ALP response at Month 6, n/m (%)[a,b,c]	67/173 (38.7)
Patients who achieved ALP response at Month 9, n/m (%)[a,b,c]	62/160 (38.8)
Patients who achieved ALP response at Month 12, n/m (%)[a,b,c]	55/148 (37.2)
Patients who achieved ALP response at Month 18, n/m (%)[a,b,c]	35/104 (33.7)
Patients who achieved ALP response at Month 24, n/m (%)[a,b,c]	5/20 (25.0)

Key: ALP, alkaline phosphatase
Notes: Table presents data collected in open-label study CB8025-31731-RE as of the data cutoff date of 29 June 2023.
[a]n/m (%) = (number of responders / number of response evaluable patients) × 100%.
[b]A patient was designated as a responder if all 3 of the following conditions were met: (1) ALP < 1.67 × ULN; (2) ALP decrease from baseline ≥ 15%; (3) total bilirubin ≤ ULN.
[c]A patient without an assessment, or who had discontinued treatment before the specified timepoint for response evaluation, or who otherwise had missing data was considered a non-responder.
[d]The number of patients reflects the number of evaluable patients at Month 18
Source: Table 26, ASSURE Integrated Study Report (14)

Changes from Baseline in Efficacy Laboratory Parameters (ALP/AST/ALT/GGT/Total Bilirubin)

Due to the volume of tabulated data, we have provided reference to the appropriate tables summarising laboratory values for ALP, total bilirubin, GGT, ALT, and AST for RESPONSE rollover patients (Table 14.2.4.2.1) and patients enrolled in ASSURE from legacy studies (Table 14.2.4.2.2) in '*Data on File – ASSURE Integrated Study Report'*.

Pruritus NRS Change from Baseline

The weekly change in pruritus NRS score was summarized for the 60 patients in ASSURE who were previously enrolled in the legacy studies and had a baseline Pruritus NRS ≥ 4 in Table 8. Baseline pruritus NRS scores were defined as the mean of all daily scores from 14 days prior to first dose to Day 1.

The mean baseline NRS score for the 60 patients was 6.360. By Month 3, the mean NRS score had decreased to 3.372 (change from baseline -3.041). A similar change from baseline was maintained through Month 18 (mean NRS score of 2.474, change

from baseline -3.336, n=19). At two years, the mean NRS score was 5.250, and the change from baseline was -2.000 (n=4) (14).

Table 8: Change from baseline in weekly Pruritus NRS during ASSURE in legacy patients (Patients with baseline Pruritus NRS ≥ 4)

Timepoint	Legacy Patients in ASSURE (n=60)			
	n	Actual Mean (SD)	n	Change from Baseline Mean (SD)
Baseline[a]	60	6.360 (1.681)	–	–
Month 1	59	4.466 (2.158)	59	-1.934 (2.057)
Month 3	57	3.372 (2.259)	57	-3.041 (2.310)
Month 6	54	2.776 (2.169)	54	-3.484 (2.417)
Month 9	49	3.327 (2.664)	49	-3.073 (2.580)
Month 12	45	2.731 (2.742)	45	-3.766 (2.608)
Month 18	19	2.474 (2.195)	19	-3.336 (2.302)
2 years	4	5.250 (2.062)	4	-2.000 (1.472)

Key: NRS, numerical rating scale; SD, standard deviation.
Notes:
[a]Baseline pruritus NRS was defined as the mean of all daily recorded scores from 14 days prior to first dose up to Day 1 first dose administration.
Source: Table 33, ASSURE Integrated Study Report (14)

Weekly Pruritus NRS Decrease Response Rate for Patients with Baseline NRS ≥ 4

NRS Decrease ≥2

The percentage of patients from the legacy studies who had a decrease in pruritus NRS score of > 2 is presented in Table 9. The percentage of patients with decreases in pruritus NRS score of > 2 was 44.1% (26/59) at Month 1, 81.5% (44/54) at Month 6, 77.8% (35/45) at Month 12, and 75.0% (3/4) at Month 24 (14).

Table 9: Weekly Pruritus NRS decrease ≥ 2 response rate during ASSURE in patients from legacy studies (Patients with baseline Pruritus NRS ≥ 4)

	Legacy Patients in ASSURE (N=60)	
	n/m (%)[a]	95% CI[b]
Patients with weekly pruritus NRS decrease ≥ 2 at Month 1	26/59 (44.1)	31.4, 56.7
Patients with weekly pruritus NRS decrease ≥ 2 at Month 3	41/57 (71.9)	60.3, 83.6

Patients with weekly pruritus NRS decrease ≥ 2 at Month 6	44/54 (81.5)	71.1, 91.8
Patients with weekly pruritus NRS decrease ≥ 2 at Month 9	34/49 (69.4)	56.5, 82.3
Patients with weekly pruritus NRS decrease ≥ 2 at Month 12	35/45 (77.8)	65.6, 89.9
Patients with weekly pruritus NRS decrease ≥ 2 at Month 18	14/19 (73.7)	53.9, 93.5
Patients with weekly pruritus NRS decrease ≥ 2 at Month 24	3/4 (75.0)	32.6, 100.0

Key: CI, confidence interval; NRS, numerical rating scale
Notes:
[a]n/m (%) = (number of responders / number of patients with non-missing assessment) × 100%.
[b]Two-sided 95% Wald confidence interval is provided.
Source: Table 34, ASSURE Integrated Study Report (14)

NRS Decrease ≥3

The percentage of patients from the legacy studies who had a decrease in pruritus NRS score of > 3 is presented in Table 10. The percentage of patients with decreases in pruritus NRS score of > 3 was 28.8% (17/59) at Month 1, 61.1% (33/54) at Month 6, 71.1% (32/45) at Month 12, and 25.0% (1/4) at Month 24 (14).

Table 10: Weekly Pruritus NRS decrease ≥ 3 response rate during ASSURE in patients from legacy studies (Patients with baseline Pruritus NRS ≥ 4)

	Legacy Patients in ASSURE (N=60)	
	n/m (%)[a]	95% CI[b]
Patients with weekly pruritus NRS decrease ≥ 3 at Month 1	17/ 59 (28.8)	17.3, 40.4
Patients with weekly pruritus NRS decrease ≥ 3 at Month 3	31/ 57 (54.4)	41.5, 67.3
Patients with weekly pruritus NRS decrease ≥ 3 at Month 6	33/ 54 (61.1)	48.1, 74.1
Patients with weekly pruritus NRS decrease ≥ 3 at Month 9	29/ 49 (59.2)	45.4, 72.9
Patients with weekly pruritus NRS decrease ≥ 3 at Month 12	32/ 45 (71.1)	57.9, 84.4
Patients with weekly pruritus NRS decrease ≥ 3 at Month 18	13/ 19 (68.4)	47.5, 89.3
Patients with weekly pruritus NRS decrease ≥ 3 at Month 24	1/4 (25.0)	0.0, 67.4

Key: CI, confidence interval; NRS, numerical rating scale
Notes:
[a]n/m (%) = (number of responders / number of patients with non-missing assessment) × 100%.
[b]Two-sided 95% Wald confidence interval is provided.
Source: Table 35, ASSURE Integrated Study Report (14)

NRS Decrease ≥4

The percentage of patients from the legacy studies who had a decrease in pruritus NRS score of > 4 is presented in Table 11. The percentage of patients with decreases in pruritus NRS score of > 4 was 16.9% (10/59) at Month 1, 48.1% (26/54) at Month 6, and 64.4% (29/45) at Month 12. There were no patients who had a decrease in pruritus NRS score of ≥ 4 at Month 24 (14).

Table 11: Weekly Pruritus NRS decrease ≥ 4 response rate during ASSURE in patients from legacy studies (Patients with baseline Pruritus NRS ≥ 4)

	Legacy Patients in ASSURE (N=60)	
	n/m (%)[a]	95% CI[b]
Patients with weekly pruritus NRS decrease ≥ 4 at Month 1	10/59 (16.9)	7.4, 26.5
Patients with weekly pruritus NRS decrease ≥ 4 at Month 3	18/57 (31.6)	19.5, 43.6
Patients with weekly pruritus NRS decrease ≥ 4 at Month 6	26/54 (48.1)	34.8, 61.5
Patients with weekly pruritus NRS decrease ≥ 4 at Month 9	26/49 (53.1)	39.1, 67.0
Patients with weekly pruritus NRS decrease ≥ 4 at Month 12	29/45 (64.4)	50.5, 78.4
Patients with weekly pruritus NRS decrease ≥ 4 at Month 18	9/19 (47.4)	24.9, 69.8
Patients with weekly pruritus NRS decrease ≥ 4 at Month 24	0/4	0.0, 0.0

Key: CI, confidence interval; NRS, numerical rating scale
Notes:
[a]n/m (%) = (number of responders / number of patients with non-missing assessment) × 100%.
[b]Two-sided 95% Wald confidence interval is provided.
Source: Table 36, ASSURE Integrated Study Report (14)

Safety

The following safety endpoints were analysed for ASSURE and its parent studies:

- Number and percentage of patients with TEAEs
- Exposure-adjusted patient incidence of TEAEs
- Clinical laboratories
- Vital signs

- Electrocardiograms (ECGs)

We report on the number and percentage of patients with TEAEs in the clarification response. For the details of the remaining safety endpoints, please refer to '*Data on File - ASSURE Integrated Study Report*' (14).

Summary of Adverse Events

An overview of TEAEs for the 29th June 2023 data cut-off is provided in Table 12.

Table 12: Overall summary of TEAEs in ASSURE by parent study group (ASSURE, Safety Analysis Set)

TEAE Category	Seladelpar 10 mg in CB8025-31731-RE.				Seladelpar Any Dose in CB8025-31731-RE[e] (n=280)
	CB8025-32048 Parent Group		Legacy & CB8025-21838 Parent Group[c] (n=128)	Overall Seladelpar 10 mg[d] (n=279)	
	Crossover[a] (n=36)	Seladelpar Continuous[b] (n=69)			
Patients with ≥ 1 TEAE	12 (33.3)	28 (40.6)	140 (80.5)	180 (64.5)	181 (64.6)
Serious TEAE	0	1 (1.4)	17 (9.8)	18 (6.5)	18 (6.4)
Grade ≥ 3 TEAE	0	1 (1.4)	20 (11.5)	21 (7.5)	21 (7.5)
Treatment-related TEAE	2 (5.6)	3 (4.3)	35 (20.1)	40 (14.3)	40 (14.3)
Treatment-related serious TEAE	0	0	0	0	0
Treatment-related Grade ≥ 3 TEAE	0	0	1 (0.6)	1 (0.4)	1 (0.4)
TEAE with fatal outcome	0	0	0	0	0
Treatment-related TEAE with fatal outcome	0	0	0	0	0
TEAE with action taken as permanent withdrawal of study drug	0	1 (1.4)	8 (4.6)	9 (3.2)	9 (3.2)
Treatment-related TEAE	0	0	3 (1.7)	3 (1.1)	3 (1.1)

with action taken as permanent withdrawal of study drug					
TEAE leading to study discontinuation	0	1 (1.4)	6 (3.4)	7 (2.5)	7 (2.5)
Treatment-related TEAE leading to study discontinuation	0	0	3 (1.7)	3 (1.1)	3 (1.1)
Pruritus TEAEs	0	6 (8.7)	20 (11.5)	26 (9.3)	26 (9.3)
Muscle-related toxicity TEAEs[f]	0	0	12 (6.9)	12 (4.3)	12 (4.3)
Liver-related TEAEs[f]	0	0	11 (6.3)	11 (3.9)	11 (3.9)
Renal-related TEAEs[f]	0	0	0	0	0
Pancreatic-related TEAEs[f]	0	0	2 (1.1)	2 (0.7)	2 (0.7)
Cardiovascular-related TEAEs	0	0	20 (11.5)	20 (7.2)	20 (7.1)

Key: AE, adverse event; TEAE, treatment-emergent adverse event
Notes: Only CB8025-31731-RE patients are included. Adverse events were graded using Medical Dictionary for Regulatory Activities version 24.0
[a]CB8025-31731-RE patients who rolled over from CB8025-32048 placebo arm and received 10 mg seladelpar in CB8025-31731-RE.
[b]CB8025-31731-RE patients who rolled over from CB8025-32048 seladelpar arm, and received 10 mg seladelpar in CB8025-31731-RE.
[c]CB8025-31731-RE patients who rolled over from legacy studies (CB8025-31735, CB8025-21629, CB8025-31731) or CB8025-21838, and received 10 mg seladelpar in CB8025-31731-RE.
[d]All patients in CB8025-31731-RE who received 10 mg seladelpar.
[e]All patients in CB8025-31731-RE who received any dose of seladelpar.
[f]AEs of interest for potential liver-, renal-, pancreatic-, and muscle-related toxicities were identified via predefined search strategy as outlined in the statistical analysis plan.
Source: Table 38, ASSURE Integrated Study Report (14)

Common Adverse Events

The most frequently reported TEAEs (≥ 2%) across cohorts are reported below in Table 13.

Table 13: Common TEAEs by preferred term (incidence >2%) in ASSURE by parent study group (ASSURE, Safety Analysis Set)

Preferred Term	Seladelpar 10 mg in CB8025-31731-RE.				Seladelpar Any Dose in CB8025-31731-RE[e] (n=280)
	CB8025-32048 Parent Group		Legacy & CB8025-21838	Overall Seladelpar 10 mg[d] (n=279)	
	Crossover[a] (n=36)	Seladelpar Continuous[b]			

		(n=69)	Parent Group[c] (n=128)		
Patients with ≥1 TEAE	12 (33.3)	28 (40.6)	140 (80.5)	180 (64.5)	181 (64.6)
COVID-19	2 (5.6)	1 (1.4)	36 (20.7)	39 (14.0)	39 (13.9)
Pruritus	0	6 (8.7)	20 (11.5)	26 (9.3)	26 (9.3)
Nasopharyngitis	0	1 (1.4)	15 (8.6)	16 (5.7)	16 (5.7)
Urinary tract infection	0	2 (2.9)	14 (8.0)	16 (5.7)	16 (5.7)
Nausea	0	1 (1.4)	14 (8.0)	15 (5.4)	15 (5.4)
Diarrhoea	0	1 (1.4)	13 (7.5)	14 (5.0)	14 (5.0)
Fatigue	1 (2.8)	1 (1.4)	9 (5.2)	11 (3.9)	11 (3.9)
Headache	2 (5.6)	1 (1.4)	8 (4.6)	11 (3.9)	11 (3.9)
Abdominal pain	1 (2.8)	1 (1.4)	8 (4.6)	10 (3.6)	10 (3.6)
Abdominal pain upper	1 (2.8)	1 (1.4)	8 (4.6)	10 (3.6)	10 (3.6)
Arthralgia	0	2 (2.9)	8 (4.6)	10 (3.6)	10 (3.6)
Dyspepsia	0	0	6 (3.4)	6 (2.2)	7 (2.5)
Hypertension	0	1 (1.4)	6 (3.4)	7 (2.5)	7 (2.5)
Influenza	0	1 (1.4)	6 (3.4)	7 (2.5)	7 (2.5)
Pyrexia	1 (2.8)	3 (4.3)	3 (1.7)	7 (2.5)	7 (2.5)
Upper respiratory tract infection	0	0	7 (4.0)	7 (2.5)	7 (2.5)
Abdominal distension	0	0	6 (3.4)	6 (2.2)	6 (2.1)

Key: TEAE, treatment-emergent adverse event
Notes: Only CB8025-31731-RE patients are included. Adverse events were graded using Medical Dictionary for Regulatory Activities version 24.0
[a]CB8025-31731-RE patients who rolled over from CB8025-32048 placebo arm and received 10 mg seladelpar in CB8025-31731-RE.
[b]CB8025-31731-RE patients who rolled over from CB8025-32048 seladelpar arm, and received 10 mg seladelpar in CB8025-31731-RE.
[c]CB8025-31731-RE patients who rolled over from legacy studies (CB8025-31735, CB8025-21629, CB8025-31731) or CB8025-21838, and received 10 mg seladelpar in CB8025-31731-RE.
[d]All patients in CB8025-31731-RE who received 10 mg seladelpar.
[e]All patients in CB8025-31731-RE who received any dose of seladelpar.
[f]AEs of interest for potential liver-, renal-, pancreatic-, and muscle-related toxicities were identified via predefined search strategy as outlined in the statistical analysis plan.
Source: Table 39, ASSURE Integrated Study Report (14)

Adverse Events by Severity

TEAEs reported as Grade 3 or higher are summarised by preferred term and system organ class in Table 14. All Grade 3 and higher TEAEs were singularly reported in

patients from the legacy studies, with the exception of Urinary tract infection, which was reported in two patients (14).

Table 14: Patient incidence of treatment-emergent Grade 3 or higher adverse events preferred term (ASSURE, Safety Analysis Set)

Preferred Term	Seladelpar 10 mg in CB8025-31731-RE.				Seladelpar Any Dose in CB8025-31731-RE[e] (n=280)
	CB8025-32048 Parent Group		Legacy & CB8025-21838 Parent Group[c] (n=128)	Overall Seladelpar 10 mg[d] (n=279)	
	Crossover[a] (n=36)	Seladelpar Continuous[b] (n=69)			
Patients with at least one Grade ≥3 TEAE	0	1 (1.4)	20 (11.5)	21 (7.5)	21 (7.5)
Urinary tract infection	0	0	2 (1.1)	2 (0.7)	2 (0.7)
Abdominal pain upper	0	0	1 (0.6)	1 (1.4)	1 (1.4)
Ankle fracture	0	0	1 (0.6)	1 (1.4)	1 (1.4)
Asthenia	0	0	1 (0.6)	1 (1.4)	1 (1.4)
COVID-19 pneumonia	0	0	1 (0.6)	1 (1.4)	1 (1.4)
Cartilage injury	0	0	1 (0.6)	1 (1.4)	1 (1.4)
Cerebral infarction	0	0	1 (0.6)	1 (1.4)	1 (1.4)
Essential hypertension	0	0	1 (0.6)	1 (1.4)	1 (1.4)
Femoral neck fracture	0	0	1 (0.6)	1 (1.4)	1 (1.4)
Gross abscess	0	0	1 (0.6)	1 (1.4)	1 (1.4)
Haemoperitoneum	0	0	1 (0.6)	1 (1.4)	1 (1.4)
Haemorrhoids	0	0	1 (0.6)	1 (1.4)	1 (1.4)
Humerus fracture	0	0	1 (0.6)	1 (1.4)	1 (1.4)
Hydronephrosis	0	0	1 (0.6)	1 (1.4)	1 (1.4)
Hypertension	0	0	1 (0.6)	1 (1.4)	1 (1.4)
Leukocytosis	0	0	1 (0.6)	1 (1.4)	1 (1.4)
Nephrolithiasis	0	0	1 (0.6)	1 (1.4)	1 (1.4)
Non-cardiac chest pain	0	0	1 (0.6)	1 (1.4)	1 (1.4)
Pancreatitis acute	0	0	1 (0.6)	1 (1.4)	1 (1.4)
Pruritus	0	0	1 (0.6)	1 (1.4)	1 (1.4)

Psychotic disorder	0	1 (1.4)	0	1 (1.4)	1 (1.4)
Radius fracture	0	0	1 (0.6)	1 (1.4)	1 (1.4)
Sciatica	0	0	1 (0.6)	1 (1.4)	1 (1.4)
Sepsis	0	0	1 (0.6)	1 (1.4)	1 (1.4)
Squamous cell carcinoma	0	0	1 (0.6)	1 (1.4)	1 (1.4)
Squamous cell carcinoma of skin	0	0	1 (0.6)	1 (1.4)	1 (1.4)

Key: TEAE, treatment-emergent adverse event
Notes: Only CB8025-31731-RE patients are included. Adverse events were graded using Medical Dictionary for Regulatory Activities version 24.0
[a]CB8025-31731-RE patients who rolled over from CB8025-32048 placebo arm and received 10 mg seladelpar in CB8025-31731-RE.
[b]CB8025-31731-RE patients who rolled over from CB8025-32048 seladelpar arm, and received 10 mg seladelpar in CB8025-31731-RE.
[c]CB8025-31731-RE patients who rolled over from legacy studies (CB8025-31735, CB8025-21629, CB8025-31731) or CB8025-21838, and received 10 mg seladelpar in CB8025-31731-RE.
[d]All patients in CB8025-31731-RE who received 10 mg seladelpar.
[e]All patients in CB8025-31731-RE who received any dose of seladelpar.
[f]AEs of interest for potential liver-, renal-, pancreatic-, and muscle-related toxicities were identified via predefined search strategy as outlined in the statistical analysis plan.
Source: Table 14.3.2.4.4.1, ASSURE Integrated Study Report (14)

Treatment-Emergent Adverse Events Leading to Treatment Discontinuation

TEAEs leading to treatment discontinuation in CB8025-31731-RE by parent study group and RESPONSE treatment assignment are summarized by preferred term in Table 15. Overall, nine patients (3.2%) who received seladelpar 10 mg in study ASSURE experienced a TEAE that led to treatment discontinuation. All preferred terms occurred in only one patient each.

Table 15: TEAEs leading to treatment discontinuation by preferred term in ASSURE by parent study group (Safety Analysis Set)

Preferred Term	Seladelpar 10 mg in CB8025-31731-RE.				Seladelpar Any Dose in CB8025-31731-RE[e] (n=280)
	CB8025-32048 Parent Group		Legacy & CB8025-21838 Parent Group[c] (n=128)	Overall Seladelpar 10 mg[d] (n=279)	
	Crossover[a] (n=36)	Seladelpar Continuous[b] (n=69)			
Patients with at least one TEAE leading to treatment discontinuation	0	1 (1.4)	8 (4.6)	9 (3.2)	9 (3.2)
Alopecia	0	0	1 (0.6)	1 (0.4)	1 (0.4)
Blood bilirubin increased	0	0	1 (0.6)	1 (0.4)	1 (0.4)

Chronic myeloid leukaemia	0	0	1 (0.6)	1 (0.4)	1 (0.4)
Diverticulitis	0	0	1 (0.6)	1 (0.4)	1 (0.4)
Galactorrhoea	0	0	1 (0.6)	1 (0.4)	1 (0.4)
Jaundice	0	0	1 (0.6)	1 (0.4)	1 (0.4)
Pancreatitis acute	0	0	1 (0.6)	1 (0.4)	1 (0.4)
Pruritus	0	0	1 (0.6)	1 (0.4)	1 (0.4)
Psychotic disorder	0	1 (1.4)	0	1 (0.4)	1 (0.4)
Renal cancer	0	0	1 (0.6)	1 (0.4)	1 (0.4)

Key: TEAE, treatment-emergent adverse event
Notes: Only CB8025-31731-RE patients are included. Adverse events were graded using Medical Dictionary for Regulatory Activities version 24.0
[a]CB8025-31731-RE patients who rolled over from CB8025-32048 placebo arm and received 10 mg seladelpar in CB8025-31731-RE.
[b]CB8025-31731-RE patients who rolled over from CB8025-32048 seladelpar arm, and received 10 mg seladelpar in CB8025-31731-RE.
[c]CB8025-31731-RE patients who rolled over from legacy studies (CB8025-31735, CB8025-21629, CB8025-31731) or CB8025-21838, and received 10 mg seladelpar in CB8025-31731-RE.
[d]All patients in CB8025-31731-RE who received 10 mg seladelpar.
[e]All patients in CB8025-31731-RE who received any dose of seladelpar.
[f]AEs of interest for potential liver-, renal-, pancreatic-, and muscle-related toxicities were identified via predefined search strategy as outlined in the statistical analysis plan.
Source: Table 41, ASSURE Integrated Study Report (14)

(f) Please clarify which original study the participant who died participated in

The participant who died was enrolled and dosed in the Phase 3 long-term safety study, CB8025-31731. As reported in Section 2.11 of the Company Evidence Submission, the patient discontinued study CB8025-31371 prior to study closure due to a malignant neoplasm, which was deemed unrelated to seladelpar. The patient died seven months after discontinuation from CB8025-31371 (20).

A6. [PRIORITY] Data for ENHANCE are missing from the CS. Please provide:

(a) Baseline characteristics for each arm

(b) Information on treatments received during the trial, including the dose of seladelpar, duration of treatment, and background treatments

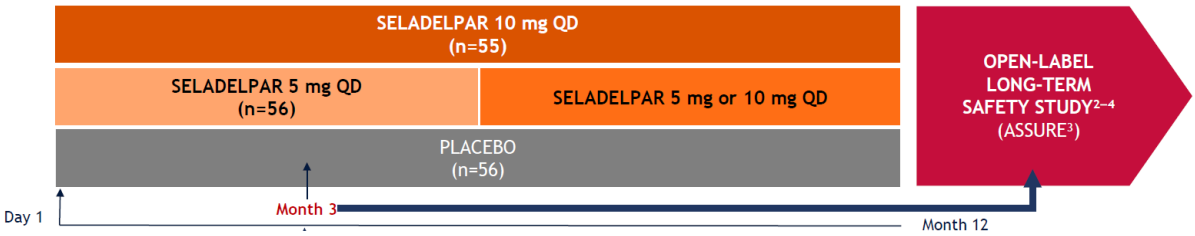
(c) Tabulated data from this study for all scoped outcomes (i.e. including outcome data with baseline measures for each outcome, measures of variance and the number of participants included for all follow-up timepoints, and safety data).

Company response: ENHANCE was designed as a Phase 3, international, double-blind, randomised, placebo-controlled study in adult patients with PBC and an

inadequate response or intolerance to UDCA. The study was initially designed as a 12-month study whereby eligible patients were centrally randomised 1:1:1 to receive seladelpar 5 or 10mg once daily orally or matching placebo following a two-week screening period and subsequent two-week running period (21, 22).

Due to unexpected histological findings in a concurrent Phase 2 study of seladelpar in patients with NASH, dosing in ENHANCE was interrupted on November 25th 2019, and the study was terminated prematurely on December 20th 2019. At the time of termination, ENHANCE was fully enrolled, and patients had a broad range of study drug treatment durations. Patients were requested to discontinue treatment and return to their study site for a safety follow-up visit. While still blinded, all endpoints were amended to Month 3 (previous primary and key secondary endpoints were amended to Month 12 [for biochemical responses] or Month 6 [for pruritus]) (Figure 3) (21, 22).

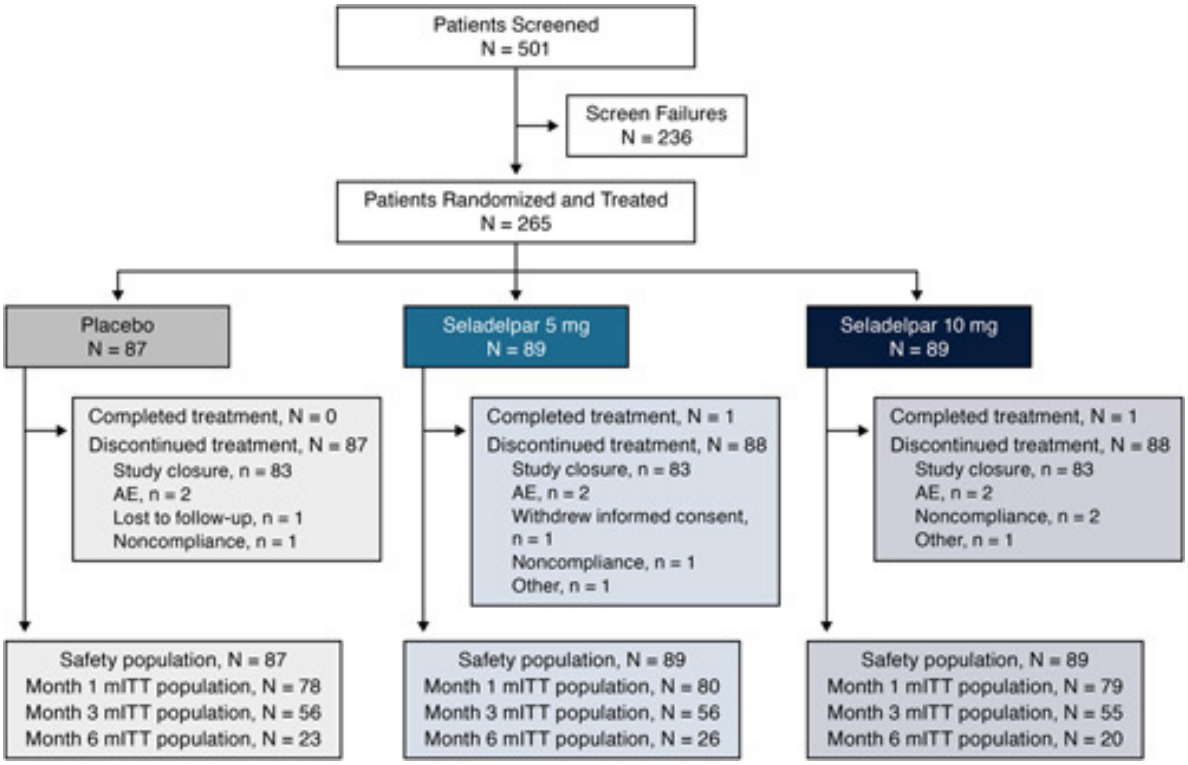
Figure 3: Amended ENHANCE study schematic (Figure 53, Appendix J, Company Evidence Submission)



Key: ALP, alkaline phosphatase; ALT, alanine aminotransferase; AST, aspartate aminotransferase; BL, baseline; NRS, numerical rating scale; PBC, primary biliary cholangitis; QD, once daily; TB, total bilirubin; UDCA, ursodeoxycholic acid; ULN, upper limit of normal.
Source: Hirschfield *et al.* (2023); ENHANCE CSR (21, 22).

Overall, 265 patients were randomised receive placebo (n=87), seladelpar 5 mg (n=89), or seladelpar 10 mg (n=89). Two patients completed study treatment through Month 12; 255 of 265 patients (96.2%) discontinued treatment due to study close, six patients (2.3%) discontinued due to treatment-emergent adverse events (TEAEs), one patient (0.4%) withdrew consent, and one patient (0.4%) was lost to follow-up. A total of 237 patients were analysed for the Month 1 treatment time point (placebo: 78; seladelpar 5 mg: 80; and seladelpar 10 mg: 79), 167 were analysed for the Month 3 treatment time point (placebo: 56; seladelpar 5 mg: 56; and seladelpar 10 mg: 55), and 69 were analysed for the Month 6 treatment time point (placebo: 23; seladelpar 5 mg: 26; and seladelpar 10 mg: 20) (21, 22).

Figure 4: ENHANCE patient disposition



Key: AE, adverse event; mITT, modified intent-to-treat; N, number of patients assigned to the treatment group; n, number of patients in the category.

Notes: Screen failures (a patient may be counted in >1 reason for failure): alkaline phosphatase < 1.67× upper limit of normal (ULN) n=149, estimated glomerular filtration rate <60 mL/min/1.73 m^2 n=27, alanine aminotransferase >3×ULN n=11, total bilirubin > 2.0×ULN n=11, aspartate aminotransferase >3×ULN n=10, did not meet primary biliary cholangitis (PBC) diagnosis criteria n=8, not on a stable and recommended dose of ursodeoxycholic acid (UDCA) for past 12 months OR intolerant to UDCA (last dose >3 months before screening) n=7, creatine kinase >1.0×ULN n=6, platelet count <100×10^3/μL n=6, had advanced PBC per Rotterdam criteria n=4, international normalized ratio >1.0×ULN n=4, presence of clinically significant hepatic decompensation n=4, presence of chronic liver disease n=4, presence of any other condition that would compromise patient safety/clinical trial quality n=4, did not provide written informed consent n=4, evidence of drug abuse n=3, use of fibrates within 30 days before screening n=2, use of simvastatin within 7 days before screening n=2.

Source: Figure 1, Hirschfield *et al.* (2023); ENHANCE CSR (21, 22).

(a) Baseline characteristics for each arm

Baseline demographics and disease characteristics, including markers of cholestasis are presented below in Table 16. Overall, the baseline characteristics were well balanced among treatment groups.

Table 16: Patient baseline demographics and clinical characteristics (ENHANCE; mITT Analysis Set)

	Placebo (n=87)	Seladelpar 5 mg (n=89)	Seladelpar 10 mg (n=89)	Total (n=265)
Age, years	55.9 (8.2)	54.7 (9.7)	55.6 (9.1)	55.4 (9.0)
Female, n (%)	85 (98)	82 (92)	83 (93)	250 (94)
Race				
White, n (%)	80 (92)	83 (93)	77 (87)	240 (91)
Other[a], n (%)	7 (8)	6 (7)	12 (13)	25 (9)
Body mass index (kg/m^2)	28.2 (5.5)	27.7 (6.1)	27.6 (5.9)	27.8 (5.8)
Duration of PBC, years	8.4 (6.2)	8.3 (6.4)	8.4 (6.4)	8.4 (6.3)
UDCA				
Use at baseline, n (%)	85 (98)	83 (93)	81 (91)	249 (94)
Total daily dose (mg/kg)	15.0 (2.6)	15.6 (4.4)	15.3 (3.7)	15.3 (3.6)
Min, Max (mg/kg)	10,0, 23.4	7.3, 36.1	7.5, 26.7	7.3, 36.1
ALP (U/L)	293.4 (106.2)	290.5 (104.2)	290.8 (109.1)	291.5 (106.1)
≥350 U/L (3×ULN), n (%)	19 (22)	22 (25)	23 (26)	64 (24)
Total bilirubin (mg/dL)	0.71 (0.32)	0.76 (0.35)	0.72 (0.32)	0.73 (0.33)
>1×ULN, n (%)	9 (10)	13 (15)	9 (10)	31 (12)
ALT (U/L)	44.4 (20.7)	47.7 (21.0)	46.9 (20.8)	46.4 (20.8)
AST (U/L)	37.5 (16.8)	40.1 (14.5)	40.3 (14.9)	39.3 (15.4)
GGT (U/L)	228.9 (193.0)	231.2 (212.0)	243.1)227.7)	234.5 (210.8)
Pruritus history, n (%)	57 (66)	66 (74)	65 (73)	188 (71)
≥4, n (%)	27 (31)	27 (30)	27 (30)	81 (31)
≥4	6.1 (1.2)	6.1 (1.4)	6.2 (1.4)	6.1 (1.3)
Antimitochondrial antibodies, n (%)				
Positive	75 (86)	79 (89)	81 (91)	235 (89)
Negative	9 (10)	8 (9)	8 (9)	25 (9)
Equivocal	3 (3)	2 (2)	0	5 (2)
Cirrhosis, n (%)	7 (8)	9 (10)	13 (15)	29 (11)
Prior PBC medications[b]				
UDCA	87 (100)	89 (100)	89 (100)	265 (100)
Obeticholic acid	11 (13)	13 (15)	16 (18)	40 (15)
Fibrates	8 (9)	9 (10)	6 (7)	23 (9)
Other[c]	17 (20)	8 (9)	10 (11)	35 (13)

Key: ALP, alkaline phosphatase; ALT, alanine aminotransferase; AST, aspartate aminotransferase; GGT, gamma-glutamyl transferase; n, number of patients in the category; N, number of patients in the treatment group; NRS, numerical rating scale; PBC, primary biliary cholangitis; UDCA, ursodeoxycholic acid; ULN, upper limit of normal.
Notes: All values are mean (SD) unless specified otherwise.
[a]Includes American Indian or Alaska Native, Asian, and Black or African American.
[b]All listed medications except UDCA were discontinued before study entry.
[c]Steroids, immunosuppressants, methotrexate, systemic steroids, and colchicine.
Source: Table 1, Hirschfield *et al*. (2024); Table 5-3 and 5-4, ENHANCE CSR (21, 22).

(b) Information on treatments received during the trial, including the dose of seladelpar, duration of treatment, and background treatments

Overall exposure to seladelpar, is summarised for the Safety Set (SS) in Table 17. The SS included any patient who received at least one dose of study drug (21, 22)..

The mean duration of exposure was similar between the placebo (17.8 weeks), seladelpar 5 mg (17.6 weeks), and seladelpar 10 mg (17.6 weeks) treatment groups. Due to study close and instruction to discontinue study drug on 25th November 2019, duration of exposure decreased from expected 52 weeks to 17 weeks (21, 22).

A total of 54, 53, and 52 patients received treatment in the placebo, seladelpar 5 mg, and seladelpar 10 mg treatment arms, respectively, for a duration of > 12 and ≤ 52 weeks during the study (21).

Median compliance was 100% across all treatment groups (21).

Table 17: Seladelpar exposure and compliance (ENHANCE, Safety Set)

	Placebo (n=87)	Seladelpar 5 mg (n=89)	Seladelpar 10 mg (n=89)	All Seladelpar (n=178)	All Patients (n=265)
Exposure (weeks)[a]					
N	87	89	89	178	265
Mean (SD)	17.826 (11.186)	17.637 (12.145)	17.557 (11.992)	17.597 (12.035)	17.672 (11.742)
Median	17.714	16.571	15.571	16.071	16.571
Q1, Q3	7.286, 26.857`	6.143, 26.143	6.857, 25.571	6.857, 26.000	6.857, 26.000
Min, Max	2.429, 47.857	0.286, 51.000	2.143, 52.000	0.286, 52.000	0.286, 52.000
Treatment exposure, n (%)					
≤4 weeks	13 (14.9)	14 (15.7)	13 (14.6)	27 (15.2)	40 (15.1)
>4 to 8 weeks	9 (10.3)	15 (16.9)	12 (13.5)	27 (15.2)	36 (13.6)
>8 to ≤ 12 weeks	11 (12.6)	7 (7.9)	12 (13.5)	19 (10.7)	30 (11.3)
>12 to ≤ 26 weeks	32 (36.8)	30 (33.7)	31 (34.8)	61 (34.3)	93 (35.1)
>26 to ≤ 39 weeks	20 (23.0)	20 (22.5)	18 (20.2)	38 (21.3)	58 (21.9)
>39 to ≤ 52 weeks	2 (2.3)	3 (3.4)	3 (3.4)	6 (3.4)	8 (3.0)
>52 weeks	0	0	0	0	0
Cumulative dose (mg)[b]					
n	87	89	89	178	265
Mean (SD)	0.0 (0.00)	626.9 (428.81)	1207.2 (846.29)	917.1 (729.49)	616.0 (736.85)
Median	0.0	595.0	1050.0	762.5	340.0
Q1, Q3	0.0, 0.0	235.0, 925.0	430.0, 1800.0	330.0, 1260.0	0.0, 1010.0
Min, max	0, 0	10, 1700	140, 3630	10, 3630	0, 3630
Average daily dose (mg/day)[c]					
n	87	89	89	178	265
Mean (SD)	0.000 (0.000)	5.416 (3.739)	9.792 (1.114)	7.604 (3.518)	5.107 (4.593)
Median	0.000	5.000	10.000	7.100	5.000
Q1, Q3	0.000, 0.000	4.903, 5.093	9.712, 10.000	5.000, 10.000	0.000, 9.754
Min, max	0.000, 0.000	3.000, 39.667	3.945, 15.063	3.000, 39.667	0.000, 39.667
Compliance through last dose date (%)[d]					
n	87	89	89	178	265
Mean (SD)	103.4 (29.98)	107.2 (74.80)	97.6 (11.17)	102.4 (53.55)	102.8 (47.07)

Median	100.0	100.0	100.0	100.0	100.0
Q1, Q3	98.0, 100.0	97.0, 100.0	97.0, 100.0	97.0, 100.0	97.0, 100.0
Min, max	34, 329	60, 793	39, 150	39, 793	34, 793
Compliance through last dose date categories, n (%)[e]					
<80%	1 (1.1)	4 (4.5)	4 (4.5)	8 (4.5)	9 (3.4)
80% to 120%	82 (94.3)	82 (92.1)	83 (93.3)	165 (92.7)	247 (93.2)
>120%	4 (4.6)	3 (3.4)	2 (2.2)	5 (2.8)	9 (3.4)

Key: SD, standard deviation; Q1, first quartile; Q3, third quartile.

Notes:

[a]Exposure (weeks) is defined as [(Treatment end date) – (Day 1 of Treatment) + 1] / 7.

[b]Cumulative dose is calculated as the sum of the actual dose across all study days.

[c]Average daily dose is the cumulative dose divided by total days of exposure.

[d]Overall study drug compliance (%) was calculated as 100 × [(the total number of capsules dispensed – total number of capsules returned) divided by (planned total capsules for treatment duration)].

[e]Percentages were calculated based on the number of patients that received at least 1 dose of study drug.

Source: Table 2, Hirschfield *et al.* (2024; Table 5-5. ENHANCE CSR (21, 22).

Overall, of the 89 patients who were initially dosed with seladelpar 5 mg in the modified Intent-To-Treat Analysis Set (mITT, included any patient who was randomly assigned into the study and received at least one dose of study drug), 24 patients reached Month 6 and were assessed for dose escalation. Of these, five patients (20.8%) met the criteria for up-titration, and four patients (16.7%) were up-titrated to seladepar 10 mg dose. With regards to dose down-titrations, three patients met the down-titration criteria (one [1.1%] in the seladelpar 5 mg group, and two [2.2%] in the seladepar 10 mg group), however, no patient was down-titrated (21).

In the mITT set, 249 patients (96.0%) were tolerant to UDCA usage. Sixteen patients (6.0%) were intolerant to UDCA and received study drug as monotherapy during the study. A total of 243 of 265 patients received at least one dose of UDCA during the study. Mean exposure to UDCA was 23.2 weeks, with a mean (SD) average daily dose of 15.3 mg/kg/day (1,105.7 mg/day), and a mean cumulative dose of 180,510.6 mg. Median compliance for all groups was 98.0% (21).

The most common concomitant medications (≥30% of total patients) by ATC class were vitamins in 135 patients (50.9%), drugs for acid-related disorders in 101 patients (38.1 %), analgesics in 92 patients (34.7%), and lipid-modifying agents in 81 patients (30.6%). The most common concomitant medications (≥15% of total patients) by preferred name were cholecalciferol in 50 patients (18.9%), vitamin D not otherwise specified in 44 patients (16.6%), and paracetamol in 46 patients (17.4%) (21).

(c) Tabulated data from this study for all scoped outcomes (i.e. including outcome data with baseline measures for each outcome, measures of variance and the number of participants included for all follow-up timepoints, and safety data).

As the result of the early termination of the study, while the study was still blinded the primary endpoint was revised to be assessed at Month 3 instead of Month 12 based on the number of patients who reached 3 months of treatment. It became evident that the number of patiens and treatment assumptions at Month 3 afforded the best opportunity to have adequate power for primary and key secondary endpoints. Months 6, 9 and 12 did not have adequate numbers of patients to provide power for the

endpoints (analysis not shown). Nonetheless, Month 6 was intermediate in power estimates and was included as a timepoint for supportive secondary analysis (21).

Results of primary outcome

The primary endpoint was a composite biochemical response defined as ALP <1.67×ULN, ≥15% ALP decrease from baseline, and total bilirubin ≤ ULN at Month 3.

A summary of the responder analysis for the composite endpoint at Month 3, as well as each of its components, is tabulated below in Table 18. For the sake of brevity, we also report a summary of the responder analysis across the remaining study timepoints (Month 1 and Month 6), which were captured as secondary outcomes in the study.

Table 18: Analysis of composite endpoint response at Month 1, Month 3, and Month 6 (ENHANCE, mITT Analysis Set)

	Placebo (n=87)	Seladelpar 5 mg (n=89)	Seladelpar 10 mg (n=89)	All Seladelpar (n=178)
Patients who achieved response at Month 1				
n (%)[ab]	8/78 (10.3)	38/80 (47.5)	51/79 (64.6)	89/159 (56.0)
95% confidence interval[c]	(4.5, 19.2)	(36.2, 59.0)	(53.0, 75.0)	(47.9, 63.8)
Comparison versus placebo				
CMH test P-value[d]	-	<0.0001	<0.0001	<0.0001
Breslow-Day P-Value	-	0.7694	0.1115	0.4412
Comparison versus initial dose of 5 mg				
CMH test P-value[d]	-	-	0.0182	-
Breslow-Day P-Value	-	-	0.0611	-
Response category at Month 1, n (%)				
ALP <1.67 × ULN	11/78 (14.1)	43/80 (53.8)	54/79 (68.4)	97/159 (61.0)
≥15% decrease in ALP	12/78 (15.4)	74/80 (92.5)	76/79 (96.2)	150/159 (94.3)
Total bilirubin ≤ ULN	71/78 (91.0)	68/80 (85.0)	75/79 (94.9)	143/159 (89.9)
Patients who achieved response at Month 3,				
n (%)[ab]	7/56 (12.5)	32/56 (57.1)	43/55 (78.2)	75/111 (67.6)
95% confidence interval[c]	(5.2, 24.1)	(43.2, 70.3)	(65.0, 88.2)	(58.0, 76.1)
Comparison versus placebo				
CMH test P-value[d]	-	<0.0001	<0.0001	<0.0001
Breslow-Day P-Value	-	0.9023	0.6421	0.9184
Comparison versus initial dose of 5 mg				
CMH test P-value[d]	-	-	0.0214	-
Breslow-Day P-Value	-	-	0.0833	-
Response category at Month 3, n (%)				
ALP <1.67 × ULN	10/56 (17.9)	36/56 (64.3)	45/55 (81.8)	81/111 (73.0)
≥15% decrease in ALP	13/56 (23.2)	53/56 (94.6)	52/55 (94.5)	105/111 (94.6)
Total bilirubin ≤ ULN	51/56 (91.1)	48/56 (85.7)	51/55 (92.7)	99/111 (89.2)
Patients who achieved response at Month 6,				

n (%)[ab]	5/23 (21.7)	16/26 (61.5)	14/20 (70.0)	30/46 (65.2)
95% confidence interval[c]	(7.5, 43.7)	(40.6, 79.8)	(45.7, 88.1)	(49.8, 78.6)
Comparison versus placebo				
CMH test P-value[d]	-	0.0006	0.0020	0.0002
Breslow-Day P-Value	-	0.9246	0.2531	0.7042
Comparison versus initial dose of 5 mg				
CMH test P-value[d]	-	-	0.5712	-
Breslow-Day P-Value	-	-	0.0886	-
Response category at Month 6, n (%)				
ALP <1.67 × ULN	8/23 (34.8)	16/26 (61.5)	15/20 (75.0)	31/46 (67.4)
≥15% decrease in ALP	7/23 (30.4)	22/26 (84.6)	17/20 (85.0)	39/46 (84.8)
Total bilirubin ≤ ULN	20/23 (87.0)	23/26 (88.5)	17/20 (85.0)	40/46 (87.0)

Key: ALP, alkaline phosphatase; CMH, Cochran Mantel Haenszel; mITT, modified intent-to-treat; NRS, numerical rating scale; TB, total bilirubin; ULN, upper limit of normal.
Notes: n/m (%) = (number of responders / number of response evaluable patients) × 100%. Patients who did not have an assessment at Month 3 due to treatment discontinuation as a result of study closure were excluded from the analysis.
[a]A patient was designated a responder if all 3 of the following conditions were met: (1) ALP <1.67 × ULN; (2) ALP reduction from baseline ≥15%; (3) TB ≤ ULN.
[b]Patients who discontinued treatment prior to Month 3 assessment due to reasons other than study closure and did not have an assessment at Month 3 for defining response were considered nonresponders.
[c]Two-sided 95% exact (Clopper-Pearson) confidence interval was provided.
[d]Two-sided p-value for each pair-wise comparison was based on the CMH test adjusted for both randomization stratification variables (ALP level: <350 U/L and ≥350 U/L; pruritus NRS: <4 and ≥4). Breslow-Day test was used to check the homogeneity of treatment effects across stratum.
Source: Tables 6-1 and 6-2, ENHANCE CSR (21)

Results of key secondary outcomes

Normalisation of ALP Response Rate at Month 3

ALP normalisation rates at Month 1, Month 3, and Month 6 , are shown below in Table 19.

Table 19: Analysis of Normalisation of ALP Response Rate at Months 1, Month 3, and Month 6 (ENHANCE, mITT set)

	Placebo (n=87)	Seladelpar 5 mg (n=89)	Seladelpar 10 mg (n=89)	All Seladelpar (n=178)
Patients with ALP ≤ 1.0 x ULN at Month 1				
n/m (%)[ab]	0/78 (0)	4/80 (5.0)	10/79 (12.7)	14/159 (8.8)
95% confidence interval[c]	(0, 4.6)	(1.4, 12.3)	(6.2, 22.0)	(4.9, 14.3)
Comparison versus placebo				
CMH test P-value[d]	-	0.0441	0.0013	0.0067
Breslow-Day P-Value	-	-	-	-
Comparison versus initial dose of 5 mg				
CMH test P-value[d]	-		0.0991	
Breslow-Day P-Value	-		0.4523	
Patients with ALP ≤ 1.0 x ULN at Month 3,				
n/m (%)[ab]	0/56 (0)	3/56 (5.4)	15/55 (27.3)	18/111 (16.2)
95% confidence interval[c]	(0, 6.4)	(1.1, 14.9)	(16.1, 41.0)	(9.9, 24.4)
Comparison versus placebo				
CMH test P-value[d]	-	0.0839	<0.0001	0.0014
Breslow-Day P-Value	-	-	-	-
Comparison versus initial dose of 5 mg				
CMH test P-value[d]	-	-	0.0018	

Breslow-Day P-Value	-	-	0.9928	-
Patients with ALP ≤ 1.0 x ULN at Month 6,				
n/m (%)[ab]	0/23 (0)	3/26 (11.5)	6/20 (30.0)	9/46 (19.6)
95% confidence interval[c]	(0, 14.8)	(2.4, 30.2)	(11.9, 54.3)	(9.4, 33.9)
Comparison versus placebo				
CMH test P-value[d]	-	0.0799	0.0023	0.0146
Breslow-Day P-Value	-	-	-	-
Comparison versus initial dose of 5 mg				
CMH test P-value[d]	-	-	0.0958	-
Breslow-Day P-Value	-	-	0.6210	-

Key: ALP, alkaline phosphatase; CMH, Cochran Mantel Haenszel; mITT, modified intent-to-treat; NRS, numerical rating scale; ULN, upper limit of normal.
Notes: n/m (%) = (number of responders/number of response evaluable patients) × 100%. Patients who did not have an assessment at Month 3 due to treatment discontinuation as a result of study closure are excluded from the analysis.
[a]A patient was designated a responder if the following condition was met: ALP ≤1.0 × ULN.
[b]Patients who discontinued treatment prior to Month 3 assessment due to reasons other than study closure and did not have an assessment at Month 3 for defining response were considered non-responders.
[c]Two-sided 95% exact (Clopper-Pearson) confidence interval was provided.
[d]Two-sided p-value for each pair-wise comparison was based on the CMH test adjusted for both randomization stratification variables (ALP level: <350 U/L and ≥350 U/L; pruritus NRS: <4 and ≥4). Breslow-Day test was used to check the homogeneity of treatment effects across stratum.
Source: Tables 6-6 and 6-9, ENHANCE CSR (21)

Pruritus NRS Change from Baseline

Pruritus NRS change from baseline at Month 1, Month 3, Month 6, and Month 9, are shown below in Table 20.

Table 20: Analysis of Pruritus NRS Change from Baseline at Month 3 for Patients with Baseline NRS 2:4 (ENHANCE, mITT Set)

	Placebo (n=87)	Seladelpar 5 mg (n=89)	Seladelpar 10 mg (n=89)	All Seladelpar (n=178)
Baseline pruritus ≥ 4 patients, n (%)	27 (31.0)	27 (30.3)	27 (30.3)	54 (30.3)
Baseline				
N	27	27	27	54
Mean (SD)	6.08 (1.234)	6.07 (1.366)	6.19 (1.441)	6.13 (1.392)
Median	6.29	5.73	5.86	5.82
Q1, Q3	5.00, 6.93	5.00, 7.00	5.00, 7.29	5.00, 7.25
Min, max	4.0, 9.1	4.3, 8.7	4.4, 9.1	4.3, 9.1
Baseline for Month 1 completers				
N	26	26	27	53
Mean (SD)	6.15 (1.204)	6.14 (1.356)	6.19 (1.441)	6.16 (1.386)
Median	6.30	5.87	5.86	5.86
Q1, Q3	5.00, 6.93	5.00, 7.00	5.00, 7.29	5.00, 7.25
Min, max	4.0, 9.1	4.3, 8.7	4.4, 9.1	4.3, 9.1
Month 1 change from baseline				
N	26	26	27	53
Mean (SD)	-1.12 (1.507)	-1.19 (1.769)	-2.37 (1.990)	-1.79 (1.960)
Median	-0.67	-0.86	-1.79	-1.45
Q1, Q3	-2.27, -0.05	-2.33, -0.14	-3.17, -0.69	-2.45, -0.57
Min, max	-4.4, 1.8	-5.1, 3.3	-6.3, 0.0	-6.3, 3.3
LS mean (SE) – Model 1[a]	-1.14 (0.340)	-1.22 (0.342)	-2.38 (0.335)	-

LS mean (SE) – Model 2[b]	-1.14 (0.351)	-	-	-1.81 (0.249)
Comparison versus placebo				
LS mean of difference (95% confidence interval)	-	-0.08 (-1.03, 0.88)	-1.24 (-2.18, -0.29)	-0.67 (-1.52, 0.18)
P-value	-	0.8737	0.0111	0.1223
Comparison versus initial dose of 5mg				
LS mean of difference (95% confidence interval)	-1.16 (-2.11, -0.21)			
P-value	0.0170			
Baseline for Month 3 completers				
N	18	17	18	35
Mean (SD)	6.21 (1.281)	6.26 (1.409)	6.15 (1.249)	6.20 (1.310)
Median	6.24	6.00	5.82	5.87
Q1, Q3	5.00, 7.08	5.08, 6.53	5.17, 7.25	5.08, 7.25
Min, max	4.3, 9.1	4.3, 8.7	4.7, 9.1	4.3, 9.1
Month 3 change from baseline				
N	18	17	18	35
Mean (SD)	-1.44 (1.831)	-1.95 (2.226)	-3.01 (1.952)	-2.49 (2.128)
Median	-1.50	-2.00	-2.72	-2.53
Q1, Q3	-2.30, -0.50	-3.96, -0.10	-4.73, -1.69	-4.45, -0.67
Min, max	-5.6, 2.8	-4.7, 2.2	-5.9, 0.4	-5.9, 2.2
LS mean (SE) – Model 1[a]	-1.55 (0.455)	-2.01 (0.467)	-3.14 (0.455)	-
LS mean (SE) – Model 2[b]	-1.55 (0.464)	-	-	-2.59 (0.335)
Comparison versus placebo				
LS mean of difference (95% confidence interval)	-	-0.46 (-1.77, 0.84)	-1.59 (-2.87, -0.30)	-1.04 (-2.18, 0.10)
P-value	-	0.4781	0.0164	0.0722
Comparison versus initial dose of 5mg				
LS mean of difference (95% confidence interval)	-1.12 (-2.43, 0.18)			
P-value	0.0893			
Baseline for Month 6 completers				
N	6	9	7	16
Mean (SD)	6.37 (1.771)	6.34 (1.681)	5.46 (0.855)	5.96 (1.415)
Median	5.80	5.73	5.23	5.37
Q1, Q3	5.36, 7.87	5.00, 7.73	4.80, 5.78	4.90, 6.89
Min, max	4.3, 9.1	4.3, 8.7	4.8, 7.3	4.3, 8.7
Month 6 change from baseline				
N	6	9	7	16
Mean (SD)	-2.68 (3.244)	-2.55 (2.724)	-3.71 (1.446)	-3.06 (2.269)
Median	-3.43	-2.25	-4.23	-3.11
Q1, Q3	-5.36, -0.97	-5.30, -0.71	-5.17, -2.23	-5.24, -1.82
Min, max	-5.7, 2.8	-5.7, 1.8	-5.5, -1.8	-5.7, 1.8
LS mean (SE) – Model 1[a]	-2.47 (0.941)	-2.46 (0.772)	-4.24 (0.895)	

LS mean (SE) – Model 2[b]	-2.51 (0.972)	-	-	-3.22 (0.597)
Comparison versus placebo				
LS mean of difference (95% confidence interval)	-	0.01 (-2.54, 2.56)	-1.77 (-4.54, 1.01)	-0.71 (-3.11, 1.69)
P-value		0.9924	0.1966	0.5427
Comparison versus initial dose of 5mg				
LS mean of difference (95% confidence interval)	-1.78 (-4.30, 0.74)			
P-value	0.1547			

Key: ALP, alkaline phosphatase; ANCOVA, analysis of covariance; mITT, modified intent-to-treat; NRS, numerical rating scale.

[a]Change from baseline was estimated by an ANCOVA model with treatment group (including 3 levels: Placebo, initial dose 5 mg, and initial dose 10 mg) and randomization ALP stratification as factors, and baseline as a covariate. The p-value for the interaction between treatment and stratum was 0.7595, hence the interaction was dropped from the model.

[b]Change from baseline was estimated by an ANCOVA model with treatment group (including 2 levels: Placebo, All Seladelpar) and randomization ALP stratification as factors, and baseline pruritus score as a covariate.

Source: Table 6-7 and 6-13, ENHANCE CSR (21)

Results of other secondary outcomes

Proportion of Patients with ALP <1.67 x ULN and ALP <1.5 x ULN at Months 1, 3, and 6

A summary of the proportion of patients with ALP <1.67 x ULN and ALP <1.5 x ULN at Months 1, 3 and 6 is tabulated in Table 21 below.

Table 21: Analysis of proportion of patients with ALP<1.67 x ULN (ENHANCE, mITT Set)

	Placebo (n=87)	Seladelpar 5 mg (n=89)	Seladelpar 10 mg (n=89)	All Seladelpar (n=178)
Patients with ALP < 1.67 x ULN at Month 1				
n/m (%)[ab]	11/78 (14.1)	43/80 (53.8)	54/79 (68.4)	97/159 (61.0)
95% confidence interval[c]	(7.3, 23.8)	(42.2, 65.0)	(56.9, 78.4)	(53.0, 68.6)
Comparison versus placebo				
CMH test P-value[d]	-	<0.0001	<0.0001	<0.0001
Breslow-Day P-Value	-	0.7671	0.0841	0.3836
Comparison versus initial dose of 5 mg				
CMH test P-value[d]	-	-	0.0335	-
Breslow-Day P-Value	-	-	0.0639	-
Patients with ALP < 1.67 x ULN at Month 3,				
n/m (%)[ab]	10/56 (17.9)	36/56 (64.3)	45/55 (81.8)	81/111 (73.0)
95% confidence interval[c]	(8.9, 30.4)	(50.4, 76.6)	(69.1, 90.9)	(63.7, 81.0)
Comparison versus placebo				
CMH test P-value[d]	-	<0.0001	<0.0001	<0.0001
Breslow-Day P-Value	-	0.7649	0.4555	0.6562
Comparison versus initial dose of 5 mg				
CMH test P-value[d]	-	-	0.0414	-
Breslow-Day P-Value	-	-	0.1551	-

Patients with ALP < 1.67 x ULN at Month 6,				
n/m (%)[ab]	8/23 (34.8)	16/26 (61.5)	15/20 (75.0)	31/46 (67.4)
95% confidence interval[c]	(16.4, 57.3)	(40.6, 79.8)	(50.9, 91.3)	(52.0, 80.5)
Comparison versus placebo				
CMH test P-value[d]	-	0.0095	0.0088	0.0032
Breslow-Day P-Value	-	0.8534	0.0420	0.4262
Comparison versus initial dose of 5 mg				
CMH test P-value[d]	-	-	0.3327	-
Breslow-Day P-Value	-	-	0.0266	-

Key: ALP, alkaline phosphatase; CMH, Cochran Mantel Haenszel; mITT, modified intent-to-treat; NRS, numerical rating scale; ULN, upper limit of normal.
Notes: n/m (%) = (number of responders / number of response evaluable patients) × 100%. Patients who did not have an assessment at specific timepoints due to treatment discontinuation as a result of study closure were excluded from the analysis.
[a]Two-sided 95% exact (Clopper-Pearson) confidence interval was provided.
[b]Two-sided p-value for each pair-wise comparison was based on the CMH test adjusted for both randomization stratification variables (ALP level: <350 U/L and ≥350 U/L; pruritus NRS: <4 and ≥4). Breslow-Day test was used to check the homogeneity of treatment effects across stratum.
Source: Table 6-8, ENHANCE CSR (21)

Absolute and Relative Changes in ALP

The mean and mean percent change from baseline in ALP for all groups at the Month 1, Month 3 and Month 6 visits are presented below in Table 22 and Table 23.

Table 22: Analysis of ALP – change from baseline (ENHANCE, mITT Set)

Visit	Placebo (N=87)		Seladelpar 5 mg (N=89)		Seladelpar 10 mg (N=89)		All Seladelpar (N=178)	
	Actual Value	Change from Baseline[a]	Actual Value	Change from Baseline[a]	Actual Value	Change from Baseline[a]	Actual Value	Change from Baseline[a]
Baseline								
n	87	89	89	178	87	89	89	178
Mean (SD)	293.392 (106.151)	290.463 (104.206)	290.796 (109.053)	290.629 (106.355)	293.392	290.463 (104.206)	290.796 (109.053)	290.629 (106.355)
Median	254.000	257.670	255.670	256.665	254.000	257.670	255.670	256.665
Q1, Q3	219.000, 337.330	217.000, 339.000	213.000, 351.330	214.000, 350.330	219.000,	217.000, 339.000	213.000, 351.330	214.000, 350.330
Min, max	167.00, 730.67	168.00, 722.67	177.67, 718.33	168.00, 722.67	167.00, 730.67	168.00, 722.67	177.67, 718.33	168.00, 722.67
Baseline for Month 1 completers								
n	78	-	78	-	78	-	156	-
Mean (SD)	296.993 (108.094)	-	291.391 (106.494)	-	289.212 (112.288)	-	290.301 (109.081)	-
Median	257.335	-	257.000	-	251.670	-	256.000	-
Q1, Q3	222.000, 342.670	-	214.670, 339.000	-	206.670, 345.330	-	213.670, 342.165	-
Min, max	167.00, 730.67	-	168.00, 722.67	-	177.67, 718.33	-	168.00, 722.67	-
Month 1								
n	78	78	78	78	78	78	156	156
Mean (SD)	290.333 (117.635)	-6.660 (62.636)	201.526 (71.696)	-89.866 (53.341)	175.359 (68.101)	-113.853 (62.288)	188.442 (70.921)	-101.859 (59.039)
Median	243.500	-14.165	181.500	-80.330	157.000	-100.830	166.500	-88.170
Q1, Q3	208.000, 332.000	-33.670, 2.000	151.000, 241.000	-110.000, -58.330	128.000, 201.000	-143.330, -70.330	143.500, 217.500	-126.665, -62.670
Min, max	118.00, 657.00	-149.67, 381.00	86.00, 415.00	-376.67, 22.67	79.00, 493.00	-376.67, -12.67	79.00, 493.00	-376.67, 22.67
LS mean (SE) - Model 1[b]	-	-1.593 (6.481)	-	-86.663 (6.409)	-	-111.097 (6.400)	-	-
LS mean (SE) – Model 2[c]	-	-1.612 (6.608)	-	-	-	-	-	-98.904 (5.213)

Comparison versus placebo								
LS mean of difference (95% confidence interval)	-	-	-	-85.071 (-100.278, -69.863)	-	-109.505 (-124.710, -94.300)	-	-97.292 (-110.721, -83.863)
P-value	-	-	-	<0.0001	-	<0.0001	-	<0.0001
Comparison versus initial dose of 5 mg								
LS mean of difference (95% confidence interval)	-	-	-	-24.434 (-39.633, -9.235)				
P-value	-	-	-	0.0017				
Baseline for Month 3 completers								
n	56	-	54	-	53	-	107	-
Mean (SD)	294.196 (108.104)	-	284.504 (102.754)	-	269.840 (98.075)	-	277.240 (100.260)	-
Median	255.500	-	255.670	-	240.330	-	252.000	-
Q1, Q3	219.335, 326.000	-	213.670, 292.670	-	203.330, 300.670	-	211.330, 300.670	-
Min, max	167.00, 730.67	-	168.00, 722.67	-	181.67, 718.33	-	168.00, 722.67	-
Month 3								
n	56	56	54	54	53	53	107	107
Mean (SD)	282.000 (114.869	-12.196 (55.138)	178.185 (55.237)	-106.318 (65.962)	148.057 (55.450)	-121.783 (66.405)	163.262 (57.122)	-113.979 (66.326)
Median	234.000	-23.165	163.500	-92.000	134.000	-108.330	152.000	-102.330
Q1, Q3	205.000, 336.500	-42.335, 17.165	142.000, 206.000	-132.670, -65.670	102.000, 170.000	-141.330, -86.670	126.000, 192.000	-138.330, -71.670
Min, max	123.00, 711.00	-208.67, 170.67	105.00, 344.00	-457.67, 2.67	78.00, 306.00	-412.33, -26.67	78.00, 344.00	-457.67, 2.67
LS mean (SE) - Model 1[b]	-	-2.340 (8.090)	-	-101.423 (7.996)	-	-122.188 (7.812)	-	-
LS mean (SE) – Model 2[c]	-	-2.906 (8.185)	-	-	-	-	-	-112.147 (6.432)
Comparison versus placebo								

LS mean of difference (95% confidence interval)	-	-	-	-99.083 (-117.374, -90.792)	-	-119.848 (-138.342, -101.354)	-	-109.241 (-125.312, -93.170)
P-value	-	-	-	<0.0001	-	<0.0001	-	<0.0001
Comparison versus initial dose of 5 mg								
LS mean of difference (95% confidence interval)	-	-	-	-20.765 (-39.332, -2.198)				
P-value	-	-	-	0.0286				
Baseline for Month 6 completers								
n	23	-	24	-	18	-	42	-
Mean (SD)	274.493 (109.129)	-	285.633 (122.120)	-	262.445 (81.899)	-	275.695 (106.217)	-
Median	254.000	-	259.000	-	219.665	-	246.165	-
Q1, Q3	224.000, 290.000	-	201.835, 289.665	-	206.670, 306.330	-	203.330, 291.330	-
Min, max	167.00, 730.67	-	183.33, 722.67	-	190.33, 488.00	-	183.33, 722.67	-
Month 6								
n	23	23	24	24	18	18	42	42
Mean (SD)	260.826 (91.437)	-13.667 (80.773)	177.250 (80.377)	-108.383 (85.988)	142.167 (48.724)	-120.278 (68.427)	162.214 (70.123)	-113.481 (78.261)
Median	255.000	-21.000	156.000	-93.000	131.000	-119.500	147.000	-102.670
Q1, Q3	190.000, 288.000	-49.000, 26.000	126.500, 211.000	-123.000, -67.500	109.000, 178.000	-139.330, -95.330	121.000, 196.000	-134.670, -69.670
Min, max	148.00, 486.00	-244.67, 180.00	90.00, 485.00	-473.67, -30.33	73.00, 243.00	-252.00, 47.33	73.00, 485.00	-473.67, 47.33
LS mean (SE) - Model 1[b]	-	-7.602 (18.489)	-	-97.533 (17.223)	-	-122.960 (16.260)	-	-
LS mean (SE) – Model 2[c]	-	-11.532 (18.385)	-	-	-	-	-	-111.400 (13.915)
Comparison versus placebo								
LS mean of difference (95%	-	-	-	-89.931 (-124.520, -55.343)	-	-115.359 (-154.181, -76.536)	-	-99.869 (-131.362, -68.375)

confidence interval)								
P-value	-	-	-	<0.0001	-	<0.0001	-	<0.0001
Comparison versus initial dose of 5 mg								
LS mean of difference (95% confidence interval)	-	-	-	-25.427 (-63.155, 12.301)				
P-value	-	-	-	0.1826				

Key: ANCOVA, analysis of covariance; LS, least squares; mITT, modified intent-to-treat.
[a]Change from baseline: post baseline value– baseline value.
[b]Change from baseline was estimated by ANCOVA model with change from baseline as the dependent variable, treatment group (including 3 levels: Placebo, initial dose 5 mg, and initial dose 10 mg) and randomization stratification factors as fixed effects, and baseline as a covariate.
[c]Change from baseline was estimated by ANCOVA model with change from baseline as the dependent variable, treatment group (including 2 levels: Placebo, All Seladelpar) and randomization stratification factors as fixed effects, and baseline as a covariate.
Source: Table 6-10, ENHANCE CSR (21)

Table 23: Analysis of ALP – Percentage (%) change from baseline (ENHANCE, mITT Set)

Visit	Placebo (N=87)		Seladelpar 5 mg (N=89)		Seladelpar 10 mg (N=89)		All Seladelpar (N=178)	
	Actual Value	Change from Baseline[a]	Actual Value	Change from Baseline[a]	Actual Value	Change from Baseline[a]	Actual Value	Change from Baseline[a]
Baseline								
n	87	-	89	-	89	-	178	-
Mean (SD)	293.392 (106.151)	-	290.463 (104.206)	-	290.796 (109.053)	-	290.629 (106.355)	-
Median	254.000	-	257.670	-	255.670	-	256.665	-
Q1, Q3	219.000, 337.330	-	217.000, 339.000	-	213.000, 351.330	-	214.000, 350.330	-
Min, max	167.00, 730.67	-	168.00, 722.67	-	177.67, 718.33	-	168.00, 722.67	-
Baseline for Month 1 completers								
n	78	-	78	-	78	-	156	-
Mean (SD)	296.993 (108.094)	-	291.391 (106.494)	-	289.212 (112.288)	-	290.301 (109.081)	-
Median	257.335	-	257.000	-	251.670	-	256.000	-
Q1, Q3	222.000, 342.670	-	214.670, 339.000	-	206.670, 345.330	-	213.670, 342.165	-

Min, max	167.00, 730.67	-	168.00, 722.67	-	177.67, 718.33	-	168.00, 722.67	-
Month 1								
n	78	78	78	78	78	78	156	156
Mean (SD)	290.333 (117.635)	-2.05 (23.426)	201.526 (71.696)	-30.25 (10.531)	175.359 (68.101)	-38.55 (11.778)	188.442 (70.921)	-34.40 (11.889)
Median	243.500	-4.80	181.500	-30.80	157.000	-39.30	166.500	-34.00
Q1, Q3	208.000, 332.000	-11.60, 0.80	151.000, 241.000	-35.20, -24.40	128.000, 201.000	-47.00, -30.00	143.500, 217.500	-43.30, -26.80
Min, max	118.00, 657.00	-33.5, 164.2	86.00, 415.00	-56.1, 8.8	79.00, 493.00	-64.5, -6.4	79.00, 493.00	-64.5, 8.8
LS mean (SE) - Model 1[b]	-	-1.911 (2.184)	-	-30.202 (2.160)	-	-38.436 (2.157)	-	-
LS mean (SE) – Model 2[c]	-	-1.918 (2.227)	-	-	-	-	-	-34.327 (1.757)
Comparison versus placebo								
LS mean of difference (95% confidence interval)	-	-	-	-28.290 (-33.417, -23.164)	-	-36.524 (-41.650, -31.399)	-	-32.409 (-36.935. -27.882)
P-value	-	-	-	<0.0001	-	<0.0001	-	<0.0001
Comparison versus initial dose of 5 mg								
LS mean of difference (95% confidence interval)	-	-	-	-8.234 (-13.357, -3.111)				
P-value	-	-	-	0.0018				
Baseline for Month 3 completers								
n	56	-	54	-	53	-	107	-
Mean (SD)	294.196 (108.104)	-	284.504 (102.754)	-	269.840 (98.075)	-	277.240 (100.260)	-
Median	255.500	-	255.670	-	240.330	-	252.000	-
Q1, Q3	219.335, 326.000	-	213.670, 292.670	-	203.330, 300.670	-	211.330, 300.670	-
Min, max	167.00, 730.67	-	168.00, 722.67	-	181.67, 718.33	-	168.00, 722.67	-
Month 3								
n	56	56	54	54	53	53	107	107

Mean (SD)	282.000 (114.869)	-4.34 (15.798)	178.185 (55.237)	-35.92 (10.896)	148.057 (55.450)	-44.32 (13.379)	163.262 (57.122)	-40.08 (12.845)
Median	234.000	-7.70	163.500	-36.55	134.000	-47.80	152.000	-40.70
Q1, Q3	205.000, 336.500	-14.60, 5.40	142.000, 206.000	-43.60, -31.40	102.000, 170.000	-54.00, -34.10	126.000, 192.000	-48.8, -31.70
Min, max	123.00, 711.00	-28.6, 36.0	105.00, 344.00	-63.3, 1.2	78.00, 306.00	-67.3, -13.5	78.00, 344.00	-67.3, 1.2
LS mean (SE) - Model 1[b]	-	-3.715 (2.236)	-	-35.679 (2.210)	-	-44.207 (2.159)	-	-
LS mean (SE) – Model 2[c]	-	-3.947 (2.303)	-	-	-	-	-	-40.083 (1.810)
Comparison versus placebo								
LS mean of difference (95% confidence interval)	-	-	-	-31.965 (-37.020, -26.909)	-	-40.492 (-45.604, -35.381)	-	-36.136 (-40.659, -31.614)
P-value	-	-	-	<0.0001	-	<0.0001	-	<0.0001
Comparison versus initial dose of 5 mg								
LS mean of difference (95% confidence interval)	-	-	-	-8.528 (-13.660, -3.396)				
P-value	-	-	-	0.0013				
Baseline for Month 6 completers								
n	23	-	24	-	18	-	42	-
Mean (SD)	274.493 (109.129)	-	285.633 (122.120)	-	262.445 (81.899)	-	275.695 (106.217)	-
Median	254.000	-	259.000	-	219.665	-	246.165	-
Q1, Q3	224.000, 290.000	-	201.835, 289.665	-	206.670, 306.330	-	203.330, 291.330	-
Min, max	167.00, 730.67	-	183.33, 722.67	-	190.33, 488.00	-	183.33, 722.67	-
Month 6								
n	23	23	24	24	18	18	42	42
Mean (SD)	260.826 (91.437)	-2.55 (27.086)	177.250 (80.377)	-37.18 (13.114)	142.167 (48.724)	-44.09 (20.223)	162.214 (70.123)	-40.14 (16.675)
Median	255.000	-8.40	156.000	-38.50	131.000	-47.40	147.000	-42.45
Q1, Q3	190.000, 288.000	-21.30, 9.40	126.500, 211.000	-45.65, -31.35	109.000, 178.000	-52.70, -42.70	121.000, 196.000	-48.70, -34.80

Min, max	148.00, 486.00	-42.7, 84.9	90.00, 485.00	-65.5, -6.9	73.00, 243.00	-65.0, 24.2	73.00, 485.00	-65.5, 24.2
LS mean (SE) - Model 1[b]	-	-0.720 (6.605)	-	-35.313 (6.153)	-	-43.705 (5.809)	-	-39.890 (4.960)
LS mean (SE) – Model 2[c]	-	-2.017 (6.553)	-	-	-	-	-	-
Comparison versus placebo								
LS mean of difference (95% confidence interval)	-	-	-	-34.593 (-46.949, -22.236)	-	-42.985 (-56.854, -29.116)	-	-37.872 (-49.098, -26.647)
P-value	-	-	-	<0.0001	-	<0.0001	-	<0.0001
Comparison versus initial dose of 5 mg								
LS mean of difference (95% confidence interval)	-	-	-	-8.392 (-21.870, 5.086)				
P-value	-	-	-	0.2176				

Key: ANCOVA, analysis of covariance; LS, least squares; mITT, modified intent-to-treat.
[a]Percent (%) change from baseline: (post baseline value – baseline value)/baseline value × 100%.
[b]Percent (%) change from baseline was estimated by ANCOVA model with percent (%) change from baseline as the dependent variable, treatment group (including 3 levels: Placebo, initial dose 5 mg, and initial dose 10 mg) and randomization stratification factors as fixed effects, and baseline as a covariate.
[c]Percent (%) change from baseline was estimated by ANCOVA model with percent (%) change from baseline as the dependent variable, treatment group (including 2 levels: Placebo, All Seladelpar) and randomization stratification factors as fixed effects, and baseline as a covariate.
Source: Table 6-11, ENHANCE CSR (21)

Proportion of Patients with ALP Decreased by at least 10%, 20%, 30%, and 40%.

A summary of the proportion of patients with ALP decreased from baseline by ~10%, 20%, 30%, and 40% is tabulated in Table 24

Table 24: Analysis of proportion of patients with ALP decreased by 10%, 20%, 30%, 40% (ENHANCE, mITT Set)

	Placebo (n=87)	Seladelpar 5 mg (n=89)	Seladelpar 10 mg (n=89)	All Seladelpar (n=178)
Month 1				
Patients with ALP decrease by 10% points				
n/m (%)	27/78 (34.6)	77/80 (96.3)	77/79 (97.5)	154/159 (96.9)
95% confidence interval[a]	(24.2, 46.2)	(89.4, 99.2)	(91.2, 99.7)	(92.8, 99.0)
Comparison versus placebo				
CMH test P-value[b]	-	<0.0001	<0.0001	<0.0001
Breslow-Day P-Value	-	0.4118	0.8519	0.7830
Comparison versus initial dose of 5 mg				
CMH test P-value[b]	-	-	0.6629	-
Breslow-Day P-Value	-	-	0.3196	-
Patients with ALP decrease by 20% points				
n/m (%)	7/78 (9.0)	66/80 (82.5)	72/79 (91.1)	138/159 (86.8)
95% confidence interval[a]	(3.7, 17.6)	(72.4, 90.1)	(82.6, 96.4)	(80.5, 91.6)
Comparison versus placebo				
CMH test P-value[b]	-	<0.0001	<0.0001	<0.0001
Breslow-Day P-Value	-	0.5935	0.5833	0.5362
Comparison versus initial dose of 5 mg				
CMH test P-value[b]	-	-	0.1099	-
Breslow-Day P-Value	-	-	0.8067	-
Patients with ALP decrease by 30% points				
n/m (%)	2/78 (2.6)	44/80 (55.0)	59/79 (74.7)	103/159 (64.8)
95% confidence interval[a]	(0.3, 9.0)	(43.5, 66.2)	(63.6, 83.8)	(56.8, 72.2)
Comparison versus placebo				
CMH test P-value[b]	-	<0.0001	<0.0001	<0.0001
Breslow-Day P-Value	-	0.8250	0.6917	0.7543
Comparison versus initial dose of 5 mg				
CMH test P-value[b]	-	-	0.0106	-
Breslow-Day P-Value	-	-	0.9039	-
Patients with ALP decrease by 40% points				
n/m (%)	0/78 (0)	11/80 (13.8)	38/79 (48.1)	49/159 (30.8)
95% confidence interval[a]	(0, 4.6)	(7.1, 23.3)	(36.7, 59.6)	(23.7, 38.6)
Comparison versus placebo				
CMH test P-value[b]	-	0.0008	<0.0001	<0.0001
Breslow-Day P-Value	-	-	-	-
Comparison versus initial dose of 5 mg				
CMH test P-value[b]	-	-	<0.0001	-
Breslow-Day P-Value	-	-	0.9321	-
Month 3				
Patients with ALP decrease by 10% points				
n/m (%)	25/56 (44.6)	53/56 (94.6)	53/55 (96.4)	106/111 (95.5)

95% confidence interval[a]	(31.3, 58.5)	(85.1, 98.9)	(87.5, 99.6)	(89.8, 98.5)
Comparison versus placebo				
CMH test P-value[b]	-	<0.0001	<0.0001	<0.0001
Breslow-Day P-Value	-	0.1878	0.7214	0.6584
Comparison versus initial dose of 5 mg				
CMH test P-value[b]	-	-	0.7201	-
Breslow-Day P-Value	-	-	0.0933	-
Patients with ALP decrease by 20% points				
n/m (%)	9/56 (16.1)	50/56 (89.3)	51/55 (92.7)	101/111 (91.0)
95% confidence interval[a]	(7.6, 28.3)	(78.1, 96.0)	(82.4, 98.0)	(84.1, 95.6)
Comparison versus placebo				
CMH test P-value[b]	-	<0.0001	<0.0001	<0.0001
Breslow-Day P-Value	-	0.5820	0.2773	0.5030
Comparison versus initial dose of 5 mg				
CMH test P-value[b]	-	-	0.5410	-
Breslow-Day P-Value	-	-	0.1111	-
Patients with ALP decrease by 30% points				
n/m (%)	0/56 (0)	41/56 (73.2)	43/55 (78.2)	84/111 (75.7)
95% confidence interval[a]	(0, 6.4)	(59.7, 84.2)	(65.0, 88.2)	(66.6, 83.3)
Comparison versus placebo				
CMH test P-value[b]	-	<0.0001	<0.0001	<0.0001
Breslow-Day P-Value	-	-	-	-
Comparison versus initial dose of 5 mg				
CMH test P-value[b]	-	-	0.5559	-
Breslow-Day P-Value	-	-	0.9878	-
Patients with ALP decrease by 40% points				
n/m (%)	0/56 (0)	20/56 (35.7)	36/55 (65.5)	56/111 (50.5)
95% confidence interval[a]	(0, 6.4)	(23.4, 49.6)	(51.4, 77.8)	(40.8, 60.1)
Comparison versus placebo				
CMH test P-value[b]	-	<0.0001	<0.0001	<0.0001
Breslow-Day P-Value	-	-	-	-
Comparison versus initial dose of 5 mg				
CMH test P-value[b]	-	-	0.0016	-
Breslow-Day P-Value	-	-	0.9108	-
Month 6				
Patients with ALP decrease by 10% points				
n/m (%)	10/23 (43.5)	23/26 (88.5)	17/20 (85.0)	40/46 (87.0)
95% confidence interval[a]	(23.2, 65.5)	(69.8, 97.6)	(62.1, 96.8)	(73.7, 95.1)
Comparison versus placebo				
CMH test P-value[b]	-	0.0004	0.0135	0.0002
Breslow-Day P-Value	-	0.2859	0.3301	0.6881
Comparison versus initial dose of 5 mg				
CMH test P-value[b]	-	-	0.7491	-
Breslow-Day P-Value	-	-	0.0791	-
Patients with ALP decrease by 20% points				
n/m (%)	6/23 (26.1)	22/26 (84.6)	17/20 (85.0)	39/46 (84.8)
95% confidence interval[a]	(10.2, 48.4)	(65.1, 95.6)	(62.1, 96.8)	(71.1, 93.7)
Comparison versus placebo				
CMH test P-value[b]	-	<0.0001	0.0004	<0.0001
Breslow-Day P-Value	-	0.3400	0.6001	0.6731
Comparison versus initial dose of 5 mg				
CMH test P-value[b]	-	-	0.9572	-
Breslow-Day P-Value	-	-	0.2058	-

Patients with ALP decrease by 30% points				
n/m (%)	2/23 (8.7)	18/26 (69.2)	16/20 (80.0)	34/46 (73.9)
95% confidence interval[a]	(1.1, 28.0)	(48.2, 85.7)	(56.3, 94.3)	(58.9, 85.7)
Comparison versus placebo				
CMH test P-value[b]	-	<0.0001	<0.0001	<0.0001
Breslow-Day P-Value	-	0.1760	0.5366	0.3752
Comparison versus initial dose of 5 mg				
CMH test P-value[b]	-	-	0.4670	-
Breslow-Day P-Value	-	-	0.0438	-
Patients with ALP decrease by 40% points				
n/m (%)	1/23 (4.3)	9/26 (34.6)	14/20 (70.0)	23/46 (50.0)
95% confidence interval[a]	(0.1, 21.9)	(17.2, 55.7)	(45.7, 88.1)	(34.9, 65.1)
Comparison versus placebo				
CMH test P-value[b]	-	0.0075	<0.0001	0.0003
Breslow-Day P-Value	-	0.7834	0.4810	0.7717
Comparison versus initial dose of 5 mg				
CMH test P-value[b]	-	-	0.0219	-
Breslow-Day P-Value	-	-	0.1352	-

Key: ALP, alkaline phosphatase; CMH, Cochran Mantel Haenszel; mITT, modified intent-to-treat; NRS, numerical rating scale.
Notes: n/m (%) = (number of responders/number of response evaluable patients) × 100%. Patients who did not have an assessment at specific timepoints due to treatment discontinuation as a result of study closure were excluded from the analysis.
[a] Two-sided 95% exact (Clopper-Pearson) confidence interval was provided.
[b] Two-sided p-value for each pair-wise comparison was based on the CMH test, adjusted for both randomization stratification variables (ALP level: <350 U/L and ≥ 350 U/L; pruritus NRS: <4 and ≥ 4. Breslow-Day test was used to check the homogeneity of treatment effects across stratum.
Source: Table 6-12, ENHANCE CSR (21)

Changes from baseline in Total Bilirubin

Seladelpar at both the 5 mg and 10 mg doses reduced total bilirubin. The mean percent change in total bilirubin for all groups at the Month 3 and Month 6 visits is presented in Table 25.

Table 25: Changes from baseline in total bilirubin (ENHANCE, mITT Set)

Visit	Placebo (N=87)		Seladelpar 5 mg (N=89)		Seladelpar 10 mg (N=89)		All Seladelpar (N=178)	
	Actual Value	Change from Baseline[a]	Actual Value	Change from Baseline[a]	Actual Value	Change from Baseline[a]	Actual Value	Change from Baseline[a]
Baseline								
n	87	-	89	-	89	-	178	-
Mean (SD)	0.712 (0.318)	-	0.757 (0.351)	-	0.722 (0.317)	-	0.739 (0.334)	-
Median	0.640	-	0.660	-	0.630	-	0.640	-
Q1, Q3	0.480, 0.860	-	0.530, 0.870	-	0.510, 0.810	-	0.520, 0.860	-
Min, max	0.26, 2.28	-	0.27, 2.11	-	0.25, 1.82	-	0.25, 2.11	-
Baseline for Month 1 completers								
n	78	-	78	-	78	-	156	-
Mean (SD)	0.716 (0.325)	-	0.769 (0.371)	-	0.731 (0.332)	-	0.750 (0.351)	-
Median	0.630	-	0.665	-	0.620	-	0.635	-
Q1, Q3	0.480, 0.850	-	0.520, 0.900	-	0.510, 0.850	-	0.515, 0.900	-
Min, max	0.26, 2.28	-	0.27, 2.11	-	0.25, 1.82	-	0.25, 2.11	-
Month 1								
n	78	78	78	78	78	78	156	156
Mean (SD)	0.704 (0.313)	0.13 (19.396)	0.735 (0.360)	-2.17 (19.321)	0.643 (0.284)	-8.72 (18.528)	0.689 (0.327)	-5.45 (19.152)
Median	0.630	-2.80	0.610	-1.70	0.580	-8.75	0.590	-6.80
Q1, Q3	0.510, 0.820	-12.20, 11.90	0.500, 0.820	-17.30, 7.00	0.470, 0.750	-21.90, 4.00	0.480, 0.780	-19.30, 5.10
Min, max	0.28, 1.93	-36.5, 58.5	0.32, 2.17	-36.1, 55.8	0.23, 2.15	-60.0, 51.1	0.23, 2.17	-60.0, 55.8
LS mean (SE) - Model 1[b]	-	-1.259 (2.261)	-	-2.841 (2.294)	-	-9.883 (2.275)	-	-
LS mean (SE) – Model 2[c]	-	-1.280 (2.284)	-	-	-	-	-	-6.397 (1.761)
Comparison versus placebo								
LS mean of difference (95% confidence interval)	-	-	-	-1.581 (-7.404, 4.241)	-	-8.623 (-14.433, -2.813)	-	-5.117 (-10.206, -0.029)
P-value	-	-	-	0.5931	-	0.0038	-	0.0487
Comparison versus initial dose of 5 mg								
LS mean of difference (95% confidence interval)	-	-	-	-7.042 (-12.859, -1.225)				

P-value	-	-	-	0.0179				
Baseline for Month 3 completers								
n	56	-	54	-	53	-	107	-
Mean (SD)	0.686 (0.264)	-	0.739 (0.318)	-	0.678 (0.291)	-	0.709 (0.305)	-
Median	0.630	-	0.640	-	0.600	-	0.620	-
Q1, Q3	0.485, 0.845	-	0.520, 0.820	-	0.510, 0.730	-	0.520, 0.810	-
Min, max	0.26, 1.54	-	0.27, 1.84	-	0.25, 1.82	-	0.25, 1.84	-
Month 3								
n	56	56	54	54	53	53	107	107
Mean (SD)	0.673 (0.269)	0.06 (22.144)	0.664 (0.272)	-8.02 (16.477)	0.630 (0.253)	-4.89 (17.568)	0.647 (0.262)	-6.47 (17.018)
Median	0.590	2.50	0.595	-11.55	0.580	-6.80	0.580	-9.10
Q1, Q3	0.475, 0.835	-15.20, 12.50	0.490, 0.760	-19.00, 5.80	0.480, 0.690	-14.50, 8.10	0.480, 0.740	-17.40, 7.30
Min, max	0.23, 1.44	-50.0, 67.2	0.24, 1.37	-54.4, 22.2	0.23, 1.60	-56.4, 38.5	0.23, 1.60	-56.4, 38.5
LS mean (SE) - Model 1[b]	-	0.937 (2.694)	-	-6.093 (2.771)	-	-4.011 (2.775)	-	-
LS mean (SE) – Model 2[c]	-	0.935 (2.688)	-	-	-	-	-	-5.054 (2.126)
Comparison versus placebo								
LS mean of difference (95% confidence interval)	-	-	-	-7.030 (-13.954, -0.106)	-	-4.948 (-11.874, 1.978)	-	-5.989 (-11.948, -0.030)
P-value	-	-	-	0.0466	-	0.1602	-	0.0489
Comparison versus initial dose of 5 mg								
LS mean of difference (95% confidence interval)	-	-	-	2.082 (-4.930, 9.094)				
P-value	-	-	-	0.5584				
Baseline for Month 6 completers								
n	23	-	24	-	18	-	42	-
Mean (SD)	0.711 (0.259)	-	0.703 (0.275)	-	0.695 (0.369)	-	0.700 (0.314)	-
Median	0.660	-	0.635	-	0.595	-	0.600	-
Q1, Q3	0.560, 0.900	-	0.495, 0.845	-	0.470, 0.690	-	0.490, 0.820	-
Min, max	0.26, 1.20	-	0.29, 1.41	-	0.34, 1.82	-	0.29, 1.82	-
Month 6								
n	23	23	24	24	18	18	42	42
Mean (SD)	0.723 (0.316)	4.37 (30.446)	0.688 (0.315)	-1.74 (23.097)	0.567 (0.241)	-14.54 (18.167)	0.636 (0.289)	-7.22 (21.845)
Median	0.660	1.20	0.605	0.00	0.485	-19.15	0.570	-7.10

Q1, Q3	0.520, 0.830	-16.20, 21.80	0.495, 0.830	-16.85, 6.15	0.440, 0.600	-25.60, 3.60	0.460, 0.710	-22.80, 4.30
Min, max	0.23, 1.50	-37.8, 81.5	0.21, 1.76	-35.5, 70.9	0.29, 1.23	-52.5, 20.3	0.21, 1.76	-52.5, 70.9
LS mean (SE) - Model 1[b]	-	3.085 (6.977)	-	-2.649 (6.444)	-	-14.831 (6.600)	-	-
LS mean (SE) – Model 2[c]	-	2.169 (7.035)	-	-	-	-	-	-8.538 (5.281)
Comparison versus placebo								
LS mean of difference (95% confidence interval)	-	-	-	-5.734 (-20.334, 8.866)	-	-17.916 (-33.984, -1.848)	-	-10.707 (-23.987, 2.573)
P-value	-	-	-	0.4350	-	0.0295	-	0.1120
Comparison versus initial dose of 5 mg								
LS mean of difference (95% confidence interval)	-	-	-	-12.182 (-27.839, 3.475)				
P-value	-	-	-	0.1248				

Abbreviations: ANCOVA, analysis of covariance; LS, least squares; mITT, modified intent-to-treat.
[a]Percent (%) change from baseline: (post baseline value – baseline value)/baseline value × 100%.
[b]Percent (%) change from baseline was estimated by ANCOVA model with percent (%) change from baseline as the dependent variable, treatment group (including 3 levels: Placebo, initial dose 5 mg, and initial dose 10 mg) and randomization stratification factors as fixed effects, and baseline as a covariate.
[c]Percent (%) change from baseline was estimated by ANCOVA model with percent (%) change from baseline as the dependent variable, treatment group (including 2 levels: Placebo, All Seladelpar) and randomization stratification factors as fixed effects, and baseline as a covariate.
Source: Table 6-15, ENHANCE CSR (21)

Changes in GGT

Seladelpar at both the 5 mg and 10 mg doses reduced GGT. The mean percent change from baseline in GGT for all groups at the Month 3 and Month 6 visits are presented in Table 26.

Table 26: Change from baseline in Gamma Glutamyl Transferase (GGT) (ALT) (U/L) (ENHANCE, mITT Set)

Visit	Placebo (N=87)		Seladelpar 5 mg (N=89)		Seladelpar 10 mg (N=89)		All Seladelpar (N=178)	
	Actual Value	Percent (%) Change from Baseline[a]	Actual Value	Percent (%) Change from Baseline[a]	Actual Value	Percent (%) Change from Baseline[a]	Actual Value	Percent (%) Change from Baseline[a]
Baseline								
n	87	-	89	-	89	-	178	-
Mean (SD)	228.857 (192.978)	-	231.317 (211.987)	-	243.066 (227.747)	-	237.192 (219.465)	-
Median	180.670	-	159.000	-	205.670	-	180.165	-
Q1, Q3	99.670, 290.670	-	112.670, 259.000	-	110.000, 288.670	-	110.670, 274.330	-
Min, max	35.67, 1337.33	-	26.33, 1187.33	-	27.33, 1730.67	-	26.33, 1730.67	-
Baseline for Month 1 completers								
n	78	-	78	-	78	-	156	-
Mean (SD)	231.874 (198.040)	-	240.396 (223.835)	-	250.896 (239.558)	-	245.646 (231.141)	-
Median	178.670	-	158.665	-	214.835	-	182.165	-
Q1, Q3	102.330, 290.670	-	110.670, 265.670	-	110.000, 293.330	-	110.335, 286.170	-
Min, max	51.33, 1337.33	-	26.33, 1187.33	-	27.33, 1730.67	-	26.33, 1730.67	-
Month 1								
n	78	78	78	78	78	78	156	156
Mean (SD)	216.590 (192.483)	-6.95 (27.038)	166.128 (150.571)	-28.52 (15.806)	165.538 (164.201)	-34.03 (17.739)	165.833 (157.025)	-31.28 (16.973)
Median	145.000	-7.55	122.500	-27.75	118.000	-35.35	118.500	-31.50

Q1, Q3	95.000, 264.000	-23.30, 2.20	76.000, 204.000	-35.20, -19.90	72.000, 202.000	-46.10, -21.80	72.000, 203.000	-42.20, -20.10
Min, max	39.00, 1141.00	-56.6, 115.4	19.00, 877.00	-72.5, 16.7	21.00, 974.00	-73.0, 6.0	19.00, 974.00	-73.0, 16.7
LS mean (SE) - Model 1[b]	-	-6.657 (2.573)	-	-28.194 (2.598)		-33.563 (2.602)		
LS mean (SE) – Model 2[c]	-	-6.655 (2.582)	-	-				-30.873 (2.001)
Comparison versus placebo								
LS mean of difference (95% confidence interval)	-	-	-	-21.536 (-28.114, -14.959)	-	-26.906 (-33.487, -20.325)	-	-24.219 (-29.936, -18.501)
P-value	-	-	-	<0.0001	-	<0.0001	-	<0.0001
Comparison versus initial dose of 5 mg								
LS mean of difference (95% confidence interval)	-	-	-	-5.370 (-11.948, 1.209)				
P-value	-	-	-	0.1092				
Baseline for Month 3 completers								
n	56	-	54	-	53	-	107	-
Mean (SD)	216.735 (161.028)	-	214.628 (167.035)	-	217.778 (157.085)	-	216.188 (161.424)	-
Median	167.000	-	173.830	-	205.670	-	179.330	-
Q1, Q3	99.500, 296.330	-	112.670, 248.330	-	85.330, 288.670	-	103.330, 270.000	-
Min, max	51.33, 685.67	-	26.33, 979.00	-	27.33, 729.00	-	26.33, 979.00	-
Month 3								
n	56	56	54	54	53	53	107	107
Mean (SD)	203.750 (175.349)	-8.88 (23.851)	142.333 (111.835)	-32.40 (16.954)	134.094 (111.427)	-38.73 (18.276)	138.252 (111.182)	-35.53 (17.824)
Median	134.500	-9.10	112.000	-34.30	111.000	-37.10	111.000	-35.90
Q1, Q3	85.500, 255.500	-22.90, 4.45	75.000, 175.000	-42.10, -23.10	54.000, 173.000	-51.50, -28.90	65.000, 175.000	-47.10, -23.10
Min, max	27.00, 713.00	-67.2, 77.2	19.00, 617.00	-76.3, 9.6	18.00, 573.00	-88.8, -4.9	18.00, 617.00	-88.8, 9.6
LS mean (SE) - Model 1[b]	-	-6.546 (2.962)	-	-30.319 (3.003)	-	-36.449 (3.057)	-	-
LS mean (SE) – Model 2[c]	-	-6.504 (2.977)	-	-	-	-		-33.315 (2.352)
Comparison versus placebo								

LS mean of difference (95% confidence interval)	-	-	-	-23.773 (-31.275, -16.270)	-	-29.903 (-37.439, -22.367)	-	-26.811 (-33.331, -20.292)
P-value	-	-	-	<0.0001	-	<0.0001	-	<0.0001
Comparison versus initial dose of 5 mg								
LS mean of difference (95% confidence interval)	-	-	-	-6.130 (-13.730, 1.470)				
P-value	-	-	-	0.1132				
Baseline for Month 6 completers								
n	23	-	24	-	18	-	42	-
Mean (SD)	202.233 (139.672)	-	203.343 (195.304)	-	140.796 (84.872)	-	176.537 (159.266)	-
Median	185.670	-	146.335	-	146.165	-	146.165	-
Q1, Q3	85.000, 290.670	-	96.500, 237.330	-	64.670, 205.670	-	77.670, 229.670	-
Min, max	51.33, 568.33	-	26.33, 979.00	-	27.33, 311.00	-	26.33, 979.00	-
Month 6								
n	23	23	24	24	18	18	42	42
Mean (SD)	193.696 (151.158)	-3.94 (35.015)	139.000 (158.230)	-27.85 (28.964)	90.944 (84.952)	-38.90 (27.259)	118.405 (132.728)	-32.59 (28.448)
Median	126.000	-12.40	92.500	-32.40	51.000	-43.25	74.500	-36.55
Q1, Q3	87.000, 271.000	-33.20, 22.80	67.000, 149.500	-42.85, -23.65	33.000, 128.000	-56.80, -34.10	49.000, 149.000	-46.40, -24.30
Min, max	34.00, 550.00	-60.6, 78.1	34.00, 802.00	-78.6, 67.7	18.00, 332.00	-73.8, 50.9	18.00, 802.00	-78.6, 67.7
LS mean (SE) - Model 1[b]	-	0.128 (9.723)	-	-24.077 (8.893)	-	-37.336 (8.359)	-	-
LS mean (SE) – Model 2[c]	-	-2.248 (9.597)	-	-	-	-	-	-31.278 (6.933)
Comparison versus placebo								
LS mean of difference (95% confidence interval)	-	-	-24.206 (-42.825, -5.586)	-	-	-37.464 (-58.991, -15.938)	-	-29.030 (-46.145, -11.914)
P-value	-	-	0.0117	-	-	0.0009	-	0.0012
Comparison versus initial dose of 5 mg								
LS mean of difference (95% confidence interval)	-	-	-	-13.259 (-33.959, 7.441)				
P-value	-	-	-	0.2049				

Key: ANCOVA, analysis of covariance; LS, least squares; mITT, modified intent-to-treat.

Percent (%) change from baseline: (post baseline value – baseline value) / baseline value × 100%.
Percent (%) change from baseline was estimated by an ANCOVA model with percent (%) change from baseline as the dependent variable,treatment group (including 3 levels: Placebo, initial dose 5 mg, and initial dose 10 mg) and randomization stratification factors as fixed effects, and baseline as a covariate.
Percent (%) change from baseline was estimated by an ANCOVA model with percent (%) change from baseline as the dependent variable, treatment group (including 2 levels: Placebo, All Seladelpar) and randomization stratification factors as fixed effects, and baseline as a covariate.
Source: Table 6-20, ENHANCE CSR (21)

Changes in ALT

Seladelpar at both the 5 mg and 10 mg doses reduced ALT. The mean percent change in ALT for all groups at the Month 1, Month 3 and Month 6 visits are presented in Table 27.

Table 27: Percentage (%) change from baseline in Alanine Aminotransferase (ALT) (U/L) (ENHANCE, mITT Set)

Visit	Placebo (N=87)		Seladelpar 5 mg (N=89)		Seladelpar 10 mg (N=89)		All Seladelpar (N=178)	
	Actual Value	Percent (%) Change from Baseline[a]	Actual Value	Percent (%) Change from Baseline[a]	Actual Value	Percent (%) Change from Baseline[a]	Actual Value	Percent (%) Change from Baseline[a]
Baseline								
n	87	-	89	-	89	-	178	-
Mean (SD)	44.422 (20.721)	-	47.662 (20.975)	-	46.931 (20.832)	-	47.296 (20.848)	-
Median	39.000	-	46.330	-	46.000	-	46.165	-
Q1, Q3	28.670, 58.000	-	31.670, 59.000	-	29.000, 58.000	-	29.670, 59.000	-
Min, max	11.67, 109.33	-	9.33, 105.00	-	8.33, 95.67	-	8.33, 105.00	-
Baseline for Month 1 completers								
n	78	-	78	-	78	-	156	-
Mean (SD)	44.770 (21.078)	-	49.627 (21.190)	-	47.336 (19.878)	-	48.481 (20.510)	-
Median	39.000	-	50.000	-	47.170	-	47.835	-
Q1, Q3	28.670, 56.330	-	33.670, 61.670	-	30.670, 61.670	-	32.500, 61.670	-
Min, max	11.67, 109.33	-	9.33, 105.00	-	8.33, 95.00	-	8.33, 105.00	-
Month 1								
n	78	78	78	78	78	78	156	156
Mean (SD)	44.795 (28.752)	-0.68 (35.060)	42.590 (23.492)	-13.38 (30.936)	43.564 (27.286)	-5.23 (49.875)	43.077 (25.382)	-9.30 (41.568)
Median	39.000	-8.55	36.500	-18.90	36.000	-19.25	36.000	-19.00
Q1, Q3	26.000, 55.000	-18.10, 4.50	25.000, 54.000	-33.20, -2.30	26.000, 56.000	-28.60, 2.40	25.000, 54.500	-28.95, -0.95
Min, max	12.00, 182.00	-40.0, 201.7	9.00, 120.00	-63.9, 112.9	9.00, 177.00	-63.6, 282.0	9.00, 177.00	-63.9, 282.0
LS mean (SE) - Model 1[b]	-	-1.850 (4.836)	-	-14.148 (4.951)	-	-5.937 (4.894)	-	-
LS mean (SE) – Model 2[c]	-	-1.823 (4.843)	-	-	-	-	-	-9.984 (3.785)

Comparison versus placebo								
LS mean of difference (95% confidence interval)	-	-	-	-12.298 (-24.777, 0.181)	-	-4.087 (-16.520, 8.346)	-	-8.162 (-18.973, 2.650)
P-value	-	-	-	0.0534	-	0.5178	-	0.1383
Comparison versus initial dose of 5 mg								
LS mean of difference (95% confidence interval)	-	-	-	8.211 (-4.216, 20.638)				
P-value	-	-	-	0.1943				
Baseline for Month 3 completers								
n	56	-	54	-	53	-	107	-
Mean (SD)	44.009 (20.396)	47.594 (21.674)	44.733 (20.521)	46.177 (21.060)	44.009 (20.396)	47.594 (21.674)	44.733 (20.521)	46.177 (21.060)
Median	40.500	-	46.165	-	42.000	-	44.000	-
Q1, Q3	27.670, 55.165	-	29.330, 59.000	-	28.330, 55.670	-	29.000, 58.000	-
Min, max	11.67, 103.00	-	15.33, 105.00	-	8.33, 95.00	-	8.33, 105.00	-
Month 3								
n	56	56	54	54	53	53	107	107
Mean (SD)	43.161 (23.412)	-2.93 (21.388)	35.111 (17.835)	-22.66 (23.489)	37.604 (25.988)	-15.64 (40.221)	36.346 (22.179)	-19.18 (32.893)
Median	36.500	-2.95	29.500	-24.25	29.000	-28.30	29.000	-26.90
Q1, Q3	25.500, 55.000	-17.50, 9.05	22.000, 43.000	-37.00, -12.50	19.000, 53.000	-41.50, -1.50	21.000, 46.000	-39.70, -9.00
Min, max	12.00, 114.00	-45.5, 46.8	14.00, 113.00	-69.0, 66.2	6.00, 148.00	-68.6, 111.9	-	-
LS mean (SE) - Model 1[b]	-	-3.964 (4.375)	-	-23.416 (4.498)	-	-16.674 (4.520)	-	-
LS mean (SE) – Model 2[c]	-	-3.978 (4.380)	-		-	-	-	-20.066 (3.477)
Comparison versus placebo								
LS mean of difference (95% confidence interval)	-	-	-	-19.452 (-30.690, -8.214)	-	-12.710 (-23.959, -1.461)	-	-16.088 (-25.802, -6.373)
P-value	-	-	-	0.0008	-	0.0271	-	0.0013
Comparison versus initial dose of 5 mg								

LS mean of difference (95% confidence interval)	-	-	-	6.743 (-4.617, 18.102)				
P-value	-	-	-	0.2428				
Baseline for Month 6 completers								
n	23	-	24	-	18	-	42	-
Mean (SD)	39.754 (18.945)	-	45.462 (23.257)	-	38.389 (13.533)	-	42.431 (19.797)	-
Median	33.000	-	36.665	-	35.830	-	36.165	-
Q1, Q3	26.330, 54.000	-	29.835, 58.040	-	28.330, 49.000	-	28.330, 54.670	-
Min, max	11.67, 87.00	-	16.33, 105.00	-	18.67, 65.00	-	16.33, 105.00	-
Month 6								
n	23	23	24	24	18	18	42	42
Mean (SD)	38.783 (18.295)	2.32 (27.780)	32.833 (18.047)	-25.02 (23.933)	25.111 (10.346)	-33.38 (18.307)	29.524 (15.558)	-28.60 (21.858)
Median	35.000	4.60	25.500	-29.55	22.000	-33.55	24.500	-30.55
Q1, Q3	26.000, 47.000	-24.10, 15.60	20.500, 42.500	-42.45, -16.90	18.000, 34.000	-46.40, -21.50	20.000, 34.000	-45.50, -18.40
Min, max	18.00, 92.00	-42.0, 67.4	7.00, 87.00	-61.1, 34.7	10.00, 51.00	-67.7, 13.0	7.00, 87.00	-67.7, 34.7
LS mean (SE) - Model 1[b]	-	1.949 (6.581)	-	-23.611 (6.319)	-	-34.872 (6.230)	-	-
LS mean (SE) – Model 2[c]	-	0.858 (6.607)	-	-	-	-	-	-29.351 (5.048)
Comparison versus placebo								
LS mean of difference (95% confidence interval)	-	-	-	-25.560 (-39.528, -11.592)		-36.820 (-52.159, -21.482)		-30.209 (-42.813, -17.605)
P-value	-	-	-	0.0005		<0.0001		<0.0001
Comparison versus initial dose of 5 mg								
LS mean of difference (95% confidence interval)	-	-	-	-11.260 (-26.445, 3.924)				
P-value	-	-	-	0.1431				

Key: ANCOVA, analysis of covariance; LS, least squares; mITT, modified intent-to-treat.
[a]Percent (%) change from baseline: (post baseline value – baseline value) / baseline value × 100%.
[b]Percent (%) change from baseline was estimated by ANCOVA model with percent (%) change from baseline as the dependent variable, treatment group (including 3 levels: Placebo, initial dose 5 mg, and initial dose 10 mg) and randomization stratification factors as fixed effects, and baseline as a covariate.

[c]Percent (%) change from baseline was estimated by ANCOVA model with percent (%) change from baseline as the dependent variable, treatment group (including 2 levels: Placebo, All Seladelpar) and randomization stratification factors as fixed effects, and baseline as a covariate.
Source: Table 6-18, ENHANCE CSR (21)

Changes in AST

Seladelpar at both the 5 mg and 10 mg doses reduced aspartate aminotransferase (AST). There was a decrease from baseline in mean AST values at Month 1 in the seladelpar 5 mg group (mean percent change of -6.48%; p=0.1027) compared to mean percent changes of 1.88% in the placebo group and 3.47% in the seladelpar 10 mg group (p=0.6108). The mean percent change in AST for all groups at the Month 3 and Month 6 visits are presented in Table 28.

Table 28: Percentage (%) change from baseline in aspartate aminotransferase (AST) (U/L) (ENHANCE, mITT Set)

Visit	Placebo (N=87)		Seladelpar 5 mg (N=89)		Seladelpar 10 mg (N=89)		All Seladelpar (N=178)	
	Actual Value	Percent (%) Change from Baseline[a]	Actual Value	Percent (%) Change from Baseline[a]	Actual Value	Percent (%) Change from Baseline[a]	Actual Value	Percent (%) Change from Baseline[a]
Baseline								
n	87	-	89	-	89	-	178	-
Mean (SD)	37.479 (16.817)	-	40.051 (14.454)	-	40.287 (14.875)	-	40.169 (14.625)	-
Median	33.330	-	36.330	-	37.670	-	36.875	-
Q1, Q3	26.670, 45.670	-	29.000, 49.670	-	30.330, 49.000	-	30.000, 49.500	-
Min, max	11.67, 119.33	-	17.67, 85.33	-	12.00, 79.33	-	12.00, 85.33	-
Baseline for Month 1 completers								
n	78	-	78	-	78	-	156	-
Mean (SD)	37.710 (16.698)	-	40.764 (15.041)	-	41.013 (14.737)	-	40.889 (14.842)	-
Median	33.835	-	36.875	-	37.835	-	37.670	-
Q1, Q3	26.670, 45.670	-	28.670, 50.670	-	32.000, 50.000	-	30.330, 50.165	-
Min, max	11.67, 119.33	-	17.67, 85.33	-	12.00, 79.33	-	12.00, 85.33	-

Month 1								
n	78	78	78	78	78	78	156	156
Mean (SD)	37.808 (18.265)	1.88 (31.321)	37.731 (16.734)	-6.48 (22.833)	42.192 (21.675)	3.47 (35.070)	39.962 (19.430)	-1.51 (29.915)
Median	32.500	-5.05	33.000	-8.25	36.000	-3.90	35.000	-5.35
Q1, Q3	25.000, 46.000	-13.90, 9.60	27.000, 45.000	-21.70, 6.90	28.000, 48.000	-16.00, 10.30	27.000, 48.000	-18.85, 9.75
Min, max	14.00, 108.00	-39.1, 173.3	15.00, 98.00	-55.4, 58.8	14.00, 129.00	-45.9, 177.3	14.00, 129.00	-55.4, 177.3
LS mean (SE) - Model 1[b]	-	1.318 (3.686)	-	-6.572 (3.771)	-	3.774 (3.773)	-	-
LS mean (SE) – Model 2[c]	-	1.324 (3.716)	-	-	-	-	-	-1.402 (2.934)
Comparison versus placebo								
LS mean of difference (95% confidence interval)	-	-	-	-7.889 (-17.378, 1.599)	-	2.457 (-7.040, 11.954)	-	-2.726 (-11.024, 5.573)
P-value	-	-	-	0.1027	-	0.6108	-	0.5181
Comparison versus initial dose of 5 mg								
LS mean of difference (95% confidence interval)	-	-	-	10.346 (0.894, 19.798)				
P-value	-	-	-	0.0321				
Baseline for Month 3 completers								
n	56	-	54	-	53	-	107	-
Mean (SD)	36.111 (13.990)	-	39.208 (14.922)	-	39.542 (14.122)	-	39.373 (14.464)	-
Median	33.500	-	34.170	-	37.670	-	36.000	-
Q1, Q3	26.670, 44.835	-	27.330, 49.670	-	30.330, 49.500	-	28.330, 49.670	-
Min, max	11.67, 75.33	-	18.67, 85.33	-	12.00, 77.00	-	12.00, 85.33	-
Month 3								
n	56	56	54	54	53	53	107	107
Mean (SD)	36.089 (15.991)	-0.74 (16.516)	35.259 (15.369)	-8.96 (20.452)	37.623 (19.084)	-5.36 (27.155)	36.430 (17.268)	-7.17 (23.961)
Median	35.000	-2.70	30.500	-10.30	30.000	-10.30	30.000	-10.30
Q1, Q3	24.500, 45.000	-11.50, 5.75	25.000, 38.000	-21.70, 1.80	23.000, 49.000	-21.10, 6.00	24.000, 44.000	-21.70, 5.30
Min, max	11.00, 88.00	-31.5, 40.2	15.00, 86.00	-49.1, 58.9	10.00, 105.00	-60.6, 93.3	10.00, 105.00	-60.6, 93.3
LS mean (SE) - Model 1[b]	-	-0.230 (3.239)	-	-8.493 (3.344)	-	-4.837 (3.407)	-	-
LS mean (SE) – Model 2[c]	-	-0.251 (3.237)	-		-	-	-	-6.708 (2.620)

Comparison versus placebo								
LS mean of difference (95% confidence interval)	-	-	-	-8.264 (-16.598, 0.071)	-	-4.607 (-12.992, 3.778)	-	-6.457 (-13.679, 0.765)
P-value	-	-	-	0.0520	-	0.2794	-	0.0793
Comparison versus initial dose of 5 mg								
LS mean of difference (95% confidence interval)	-	-	-	3.656 (-4.742, 12.055)				
P-value	-	-	-	0.3911				
Baseline for Month 6 completers								
n	23	-	24	-	18	-	42	-
Mean (SD)	33.624 (14.104)	-	35.858 (13.069)	-	36.110 (10.815)	-	35.966 (12.014)	-
Median	27.670	-	32.500	-	36.000	-	33.000	-
Q1, Q3	26.000, 45.670	-	26.500, 43.165	-	27.330, 44.330	-	26.670, 44.000	-
Min, max	14.67, 63.67	-	18.67, 69.67	-	22.00, 58.33	-	18.67, 69.67	-
Month 6								
n	23	23	24	24	18	18	42	42
Mean (SD)	34.304 (16.061)	3.42 (21.611)	31.208 (13.197)	-13.50 (15.682)	29.833 (10.799)	-15.67 (22.755)	30.619 (12.105)	-14.43 (18.811)
Median	29.000	4.00	27.000	-15.70	26.500	-20.95	26.500	-17.10
Q1, Q3	23.000, 38.000	-10.90, 11.50	22.000, 39.000	-21.05, -3.10	22.000, 36.000	-31.30, -1.50	22.000, 36.000	-25.50, -1.50
Min, max	19.00, 76.00	-35.3, 50.0	10.00, 70.00	-46.4, 11.7	19.00, 60.00	-44.3, 45.7	10.00, 70.00	-46.4, 45.7
LS mean (SE) - Model 1[b]	-	1.996 (5.648)	-	-14.751 (5.320)	-	-16.586 (5.467)	-	-15.633 (4.301)
LS mean (SE) – Model 2[c]	-	1.840 (5.587)	-		-		-	
Comparison versus placebo								
LS mean of difference (95% confidence interval)	-	-	-	-16.717 (-28.705, -4.729)	-	-18.552 (-31.697, -5.406)	-	-17.472 (-28.144, -6.801)
P-value	-	-	-	0.0071	-	0.0065	-	0.0018
Comparison versus initial dose of 5 mg								
LS mean of difference (95% confidence interval)	-	-	-	-1.835 (-14.675, 11.006)				
P-value	-	-	-	0.7759				

Key: ANCOVA, analysis of covariance; LS, least squares; mITT, modified intent-to-treat.
Percent (%) change from baseline: (post baseline value – baseline value) / baseline value × 100%.
[a]Percent (%) change from baseline was estimated by ANCOVA model with percent (%) change from baseline as the dependent variable, treatment group (including 3 levels:
[b]Placebo, initial dose 5 mg, and initial dose 10 mg) and randomization stratification factors as fixed effects, and baseline as a covariate.

[c]Percent (%) change from baseline was estimated by ANCOVA model with percent (%) change from baseline as the dependent variable, treatment group (including 2 levels: Placebo, All Seladelpar) and randomization stratification factors as fixed effects, and baseline as a covariate.
Source: Table 6-19, ENHANCE CSR (21)

UK-PBC & GLOBE score

A summary of the change from baseline in the 5-year and 10-year UK-PBC risk scores is tabulated in Table 29 and Table 30.

Table 29: Change from baseline in 5-year UK-PBC risk score (ENHANCE, mITT Set)

Visit	Placebo (N=87)		Seladelpar 5 mg (N=89)		Seladelpar 10 mg (N=89)	
	Actual Value	Percent (%) Change from Baseline[a]	Actual Value	Percent (%) Change from Baseline[a]	Actual Value	Percent (%) Change from Baseline[a]
Baseline						
n	86	-	89	-	89	-
Mean (SD)	0.017 (0.014)	-	0.022 (0.021)	-	0.021 (0.020)	-
Median	0.013	-	0.016	-	0.015	-
Q1, Q3	0.008, 0.023	-	0.010, 0.027	-	0.009, 0.025	-
Min, max	0.001, 0.064	-	0.002, 0.118	-	0.001, 0.145	-
Month 1						
n	86	86	89	89	89	89
Mean (SD)	0.016 (0.012)	-0.001 (0.005)	0.019 (0.018)	-0.003 (0.007)	0.017 (0.021)	-0.004 (0.010)
Median	0.013	0.000	0.012	-0.001	0.011	-0.001
Q1, Q3	0.007, 0.022	-0.003, 0.001	0.009, 0.022	-0.006, 0.000	0.008, 0.020	-0.006, 0.000
Min, max	0.001, 0.058	-0.022, 0.011	0.001, 0.099	-0.030, 0.010	0.001, 0.193	-0.043, 0.048
LS mean (SE) - Model 1[b]	-	-0.002 (0.001)	-	-0.004 (0.001)	-	-0.005 (0.001)
LS mean (SE) – Model 2[c]	-	-0.002 (0.001)	-	-	-	-
Comparison versus placebo						
LS mean of difference (95% confidence interval)	-	-	-	-0.002 (-0.004, 0.000)	-	-0.003 (-0.005, -0.001)
P-value	-	-	-	0.0980	-	0.0146
Comparison versus initial dose of 5 mg						
LS mean of difference (95% confidence interval)	-	-	-	-	-	-0.001 (-0.003, 0.001)
P-value	-	-	-	-	-	0.4236
Month 3						

n	86	86	89	89	89	89
Mean (SD)	0.016 (0.013)	-0.001 (0.006)	0.018 (0.017)	-0.004 (0.008)	0.016 (0.022)	-0.004 (0.010)
Median	0.012	0.000	0.011	-0.002	0.011	-0.002
Q1, Q3	0.007, 0.021	-0.003, 0.001	0.008, 0.019	-0.006, 0.000	0.007, 0.020	-0.007, 0.000
Min, max	0.001, 0.058	-0.021, 0.012	0.001, 0.094	-0.051, 0.010	0.000, 0.193	-0.043, 0.048
LS mean (SE) - Model 1[b]	-	-0.002 (0.001)	-	-0.005 (0.001)	-	-0.005 (0.001)
LS mean (SE) – Model 2[c]	-	-0.002 (0.001)	-	-	-	-
Comparison versus placebo						
LS mean of difference (95% confidence interval)	-	-	-	-0.002 (-0.005, 0.000)	-	-0.002 (-0.005, 0.000)
P-value	-	-	-	0.0436	-	0.0411
Comparison versus initial dose of 5 mg						
LS mean of difference (95% confidence interval)	-	-	-	-	-	0.000 (-0.002, 0.002)
P-value	-	-	-	-	-	0.9845
Month 6						
n	86	86	89	89	89	89
Mean (SD)	0.016 (0.013)	-0.001 (0.006)	0.019 (0.018)	-0.004 (0.008)	0.016 (0.022)	-0.004 (0.010)
Median	0.013	0.000	0.011	-0.002	0.010	-0.002
Q1, Q3	0.007, 0.020	-0.003, 0.001	0.008, 0.020	-0.005, 0.000	0.007, 0.020	-0.007, 0.000
Min, max	0.002, 0.058	-0.017, 0.022	0.000, 0.094	-0.051, 0.023	0.000, 0.193	-0.043, 0.048
LS mean (SE) - Model 1[b]	-	-0.002 (0.001)	-	-0.004 (0.001)	-	-0.005 (0.001)
LS mean (SE) – Model 2[c]	-	-0.002 (0.001)	-	-	-	-
Comparison versus placebo						
LS mean of difference (95% confidence interval)	-	-	-	-0.002 (-0.004, 0.000)	-	-0.003 (-0.005, -0.001)
P-value	-	-	-	0.1056	-	0.0111
Comparison versus initial dose of 5 mg						
LS mean of difference (95% confidence interval)	-	-	-	-	-	-0.001 (-0.003, 0.001)
P-value	-	-	-	-	-	0.3494

Key: ANCOVA, analysis of covariance; LS, least squares; mITT, modified intent-to-treat.
Percent (%) change from baseline: (post baseline value – baseline value) / baseline value × 100%.
[a]Percent (%) change from baseline was estimated by ANCOVA model with percent (%) change from baseline as the dependent variable, treatment group (including 3 levels:
[b]Placebo, initial dose 5 mg, and initial dose 10 mg) and randomization stratification factors as fixed effects, and baseline as a covariate.
[c]Percent (%) change from baseline was estimated by ANCOVA model with percent (%) change from baseline as the dependent variable, treatment group (including 2 levels: Placebo, All Seladelpar) and randomization stratification factors as fixed effects, and baseline as a covariate.
Source: Table 6-22, ENHANCE CSR (21)

Table 30: Change from baseline in 10-year UK-PBC risk score (ENHANCE, mITT Set)

Visit	Placebo (N=87)		Seladelpar 5 mg (N=89)		Seladelpar 10 mg (N=89)	
	Actual Value	Percent (%) Change from Baseline[a]	Actual Value	Percent (%) Change from Baseline[a]	Actual Value	Percent (%) Change from Baseline[a]
Baseline						
n	86	-	89	-	89	-
Mean (SD)	0.057 (0.043)	-	0.070 (0.062)	-	0.066 (0.059)	-
Median	0.044	-	0.052	-	0.049	-
Q1, Q3	0.027, 0.073	-	0.033, 0.088	-	0.029, 0.080	-
Min, max	0.003, 0.199	-	0.006, 0.344	-	0.003, 0.409	-
Month 1						
n	86	86	89	89	89	89
Mean (SD)	0.054 (0.039)	-0.003 (0.017)	0.060 (0.054)	-0.010 (0.021)	0.053 (0.059)	-0.013 (0.029)
Median	0.044	-0.001	0.039	-0.004	0.037	-0.005
Q1, Q3	0.025, 0.071	-0.008, 0.005	0.029, 0.071	-0.019, 0.000	0.025, 0.066	-0.019, 0.000
Min, max	0.004, 0.181	-0.068, 0.036	0.005, 0.296	-0.086, 0.032	0.003, 0.512	-0.129, 0.103
LS mean (SE) - Model 1[b]	-	-0.006 (0.002)	-	-0.012 (0.002)	-	-0.015 (0.002)
LS mean (SE) – Model 2[c]	-	-0.006 (0.002)	-	-	-	-
Comparison versus placebo						
LS mean of difference (95% confidence interval)	-	-	-	-0.005 (-0.012, 0.001)	-	-0.009 (-0.015, -0.003)
P-value	-	-	-	0.0919	-	0.0054
Comparison versus initial dose of 5 mg						
LS mean of difference (95% confidence interval)	-	-	-	-	-	-0.003 (-0.010, 0.003)
P-value	-	-	-	-	-	0.2638
Month 3						
n	86	86	89	89	89	89
Mean (SD)	0.052 (0.040)	-0.004 (0.018)	0.057 (0.053)	-0.013 (0.023)	0.052 (0.060)	-0.013 (0.028)
Median	0.039	0.000	0.036	-0.008	0.035	-0.007
Q1, Q3	0.023, 0.068	-0.009, 0.003	0.026, 0.063	-0.019, 0.000	0.024, 0.066	-0.021, 0.000
Min, max	0.004, 0.183	-0.067, 0.037	0.005, 0.280	-0.137, 0.031	0.001, 0.512	-0.129, 0.103
LS mean (SE) - Model 1[b]	-	-0.007 (0.003)	-	-0.014 (0.003)	-	-0.014 (0.003)
LS mean (SE) – Model 2[c]	-	-0.007 (0.003)	-	-	-	-
Comparison versus placebo						

LS mean of difference (95% confidence interval)	-	-	-	-0.007 (-0.013, 0.000)	-	-0.008 (-0.014, -0.001)
P-value	-	-	-	0.0354	-	0.0180
Comparison versus initial dose of 5 mg						
LS mean of difference (95% confidence interval)	-	-	-	-	-	-0.001 (-0.007, 0.006)
P-value	-	-	-	-	-	0.7945
Month 6						
n	86	86	89	89	89	89
Mean (SD)	0.053 (0.040)	-0.003 (0.019)	0.060 (0.054)	-0.011 (0.024)	0.051 (0.060)	-0.015 (0.029)
Median	0.042	-0.001	0.038	-0.007	0.035	-0.008
Q1, Q3	0.025, 0.064	-0.010, 0.004	0.027, 0.067	-0.017, 0.000	0.023, 0.064	-0.021, 0.000
Min, max	0.006, 0.183	-0.050, 0.069	0.001, 0.280	-0.137, 0.070	0.001, 0.512	-0.129, 0.103
LS mean (SE) - Model 1[b]	-	-0.006 (0.003)	-	-0.011 (0.003)	-	-0.016 (0.003)
LS mean (SE) – Model 2[c]	-	-0.006 (0.003)	-	-	-	-
Comparison versus placebo						
LS mean of difference (95% confidence interval)	-	-	-	-0.006 (-0.013, 0.001)	-	-0.010 (-0.017, -0.003)
P-value	-	-	-	0.0949	-	0.0036
Comparison versus initial dose of 5 mg						
LS mean of difference (95% confidence interval)	-	-	-	-	-	-0.004 (-0.011, 0.002)
P-value	-	-	-	-	-	0.2060

Key: ANCOVA, analysis of covariance; LS, least squares; mITT, modified intent-to-treat.
Percent (%) change from baseline: (post baseline value – baseline value) / baseline value × 100%.
[a]Percent (%) change from baseline was estimated by ANCOVA model with percent (%) change from baseline as the dependent variable, treatment group (including 3 levels:
[b]Placebo, initial dose 5 mg, and initial dose 10 mg) and randomization stratification factors as fixed effects, and baseline as a covariate.
[c]Percent (%) change from baseline was estimated by ANCOVA model with percent (%) change from baseline as the dependent variable, treatment group (including 2 levels: Placebo, All Seladelpar) and randomization stratification factors as fixed effects, and baseline as a covariate.
Source: Table 6-22, ENHANCE CSR (21)

A summary of the change from baseline in the GLOBE risk scores is tabulated in Table 31

Table 31: Change from baseline of GLOBE Risk Score (ENHANCE, mITT Set)

Visit	Placebo (N=87)	Seladelpar 5 mg (N=89)	Seladelpar 10 mg (N=89)

	Actual Value	Percent (%) Change from Baseline[a]	Actual Value	Percent (%) Change from Baseline[a]	Actual Value	Percent (%) Change from Baseline[a]
Baseline						
n	86	-	89	-	89	-
Mean (SD)	0.107 (0.619)	-	0.190 (0.638)	-	0.185 (0.657)	-
Median	0.047	-	0.214	-	0.051	-
Q1, Q3	-0.290, 0.550	-	-0.123, 0.593	-	-0.215, 0.574	-
Min, max	-1.300, 2.130	-	-1.406, 1.958	-	-1.389, 2.074	-
Month 1						
n	77	76	76	76	77	77
Mean (SD)	0.084 (0.632)	-0.018 (0.218)	-0.019 (0.688)	-0.180 (0.207)	-0.122 (0.667)	-0.338 (0.276)
Median	0.027	-0.005	0.024	-0.205	-0.284	-0.335
Q1, Q3	-0.251, 0.455	-0.181, 0.129	-0.340, 0.394	-0.338, -0.045	-0.525, 0.310	-0.492, -0.163
Min, max	-1.416, 2.036	-0.468, 0.626	-1.767, 1.699	-0.587, 0.413	-1.578, 1.578	-1.516, 0.452
LS mean (SE) - Model 1[b]	-	-0.041 (0.029)	-	-0.199 (0.029)	-	-0.355 (0.029)
LS mean (SE) – Model 2[c]	-	-0.041 (0.030)	-	-	-	-
Comparison versus placebo						
LS mean of difference (95% confidence interval)	-	-	-	-0.158 (-0.232, -0.083)	-	-0.314 (-0.388, -0.240)
P-value	-	-	-	<0.0001	-	<0.0001
Comparison versus initial dose of 5 mg						
LS mean of difference (95% confidence interval)	-	-	-	-	-	-0.156 (-0.230, -0.082)
P-value	-	-	-	-	-	<0.0001
Month 3						
n	53	53	53	53	53	53
Mean (SD)	0.103 (0.634)	0.015 (0.242)	-0.078 (0.620)	-0.296 (0.195)	-0.243 (0.604)	-0.374 (0.312)
Median	0.015	0.016	-0.063	-0.286	-0.247	-0.340
Q1, Q3	-0.285, 0.526	-0.136, 0.122	-0.381, 0.337	-0.444, -0.191	-0.617, 0.177	-0.529, -0.197
Min, max	-1.386, 1.490	-0.519, 0.795	-1.469, 1.514	-0.787, 0.205	-1.840, 0.961	-1.854, 0.133
LS mean (SE) - Model 1[b]	-	-0.006 (0.038)	-	-0.317 (0.039)	-	-0.395 (0.039)
LS mean (SE) – Model 2[c]	-	-0.005 (0.039)	-	-	-	
Comparison versus placebo						

LS mean of difference (95% confidence interval)	-	-	-	-0.311 (-0.409, -0.214)	-	-0.389 (-0.487, -0.292)
P-value	-	-	-	<0.0001	-	<0.0001
Comparison versus initial dose of 5 mg						
LS mean of difference (95% confidence interval)	-	-	-	-	-	-0.078 (-0.175, 0.020)
P-value	-	-	-	-	-	0.1172
Month 6						
n	23	23	24	24	17	17
Mean (SD)	0.194 (0.628)	0.043 (0.313)	-0.121 (0.637)	-0.282 (0.320)	-0.120 (0.585)	-0.397 (0.288)
Median	0.223	-0.017	-0.166	-0.297	-0.246	-0.352
Q1, Q3	-0.093, 0.684	-0.108, 0.173	-0.517, 0.250	-0.481, -0.118	-0.494, 0.346	-0.462, -0.157
Min, max	-1.320, 1.361	-0.457, 0.818	-1.249, 1.184	-0.809, 0.728	-0.976, 0.926	-1.059, -0.037
LS mean (SE) - Model 1[b]	-	0.039 (0.084)	-	-0.281 (0.078)	-	-0.373 (0.083)
LS mean (SE) – Model 2[c]	-	0.033 (0.083)	-	-	-	-
Comparison versus placebo						
LS mean of difference (95% confidence interval)	-	-	-	-0.320 (-0.500, -0.140)	-	-0.412 (-0.614, -0.210)
P-value	-	-	-	0.0008	-	0.0001
Comparison versus initial dose of 5 mg						
LS mean of difference (95% confidence interval)	-	-	-	-	-	-0.092 (-0.289, 0.105)
P-value	-	-	-	-	-	0.3534

Key: ANCOVA, analysis of covariance; GLOBE, global primary biliary cholangitis group; LS, least squares; mITT, modified intent-to-treat.
Percent (%) change from baseline: (post baseline value – baseline value) / baseline value × 100%.
[a]Percent (%) change from baseline was estimated by ANCOVA model with percent (%) change from baseline as the dependent variable, treatment group (including 3 levels:
[b]Placebo, initial dose 5 mg, and initial dose 10 mg) and randomization stratification factors as fixed effects, and baseline as a covariate.
[c]Percent (%) change from baseline was estimated by ANCOVA model with percent (%) change from baseline as the dependent variable, treatment group (including 2 levels: Placebo, All Seladelpar) and randomization stratification factors as fixed effects, and baseline as a covariate.
Source: Table 6-23, ENHANCE CSR (21)

PBC 40 QoL

We have requested the data but do not currently have access – if this data becomes available, we would be happy to share with the EAG.

5-D Itch Scale

A summary of the 5-D Itch scale total scores is tabulated in Table 32.

Table 32: Summary of 5-D Itch scale – Total Score (ENHANCE, mITT Set)

Visit	Placebo (N=87)		Seladelpar 5 mg (N=89)		Seladelpar 10 mg (N=89)		All Seladelpar (N=178)	
	Actual Value	Change from Baseline[a]	Actual Value	Change from Baseline[a]	Actual Value	Change from Baseline[a]	Actual Value	Change from Baseline[a]
Baseline								
n	87	-	87	-	89	-	176	-
Mean (SD)	11.3 (4.47)	-	11.6 (4.66)	-	11.2 (4.06)	-	11.4 (4.36)	-
Median	11.0	-	11.0	-	10.0	-	10.5	-
Q1, Q3	8.0, 14.0	-	8.0, 14.0	-	8.0, 14.0	-	8.0, 14.0	-
Min, max	5, 23	-	5, 24	-	5, 25	-	5, 25	-
Month 3								
n	61	61	59	59	60	60	119	119
Mean (SD)	10.5 (3.92)	-0.8 (3.30)	10.1 (3.96)	-1.8 (3.98)	10.3 (3.74)	-1.1 (4.28)	10.2 (3.84)	-1.4 (4.13)
Median	9.0	0.0	9.0	-1.0	10.0	0.0	9.0	0.0
Q1, Q3	8.0, 12.0	-3.0, 1.0	8.0, 12.0	-4.0, 1.0	8.0, 12.5	-4.0, 2.0	8.0, 12.0	-4.0, 1.0
Min, max	5, 25	-9, 6	5, 23	-11, 9	5, 24	-15, 8	5, 24	-15, 9
Month 6								
n	38	38	39	39	38	38	77	77
Mean (SD)	10.0 (4.10)	-1.6 (3.76)	9.9 (4.52)	-1.8 (3.82)	10.4 (3.93)	-0.8 (4.40)	10.1 (4.22)	-1.3 (4.12)
Median	8.0	0.0	8.0	0.0	9.0	0.0	9.0	0.0
Q1, Q3	8.0, 13.0	-3.0, 0.0	7.0, 12.0	-3.0, 0.0	8.0, 12.0	-3.0, 1.0	8.0, 12.0	-3.0, 1.0
Min, max	5, 24	-13, 7	5, 23	-12, 5	5, 23	-11, 10	5,23	-12,10

Key: mITT, modified intent-to-treat.
[a]Change from baseline: post baseline value – baseline value.
Source: Table 6-24, ENHANCE CSR (21)

Safety

Overview of Adverse Events

Overall treatment-emergent adverse events are summarised below in Table 33.

Table 33: Summary of Treatment-Emergent Adverse Events (Safety Set)

	Placebo (n=87) n (%)	Seladelpar 5 mg (n=89) n (%)	Seladelpar 10 mg (n=89) n (%)	All Seladelpar (n=178) n (%)	All Patients (n=265) n (%)
Patients with at least 1 TEAE	64 (73.6)	56 (62.9)	58 (65.2)	114 (64.0)	178 (67.2)
Serious TEAE	3 (3.4)	3 (3.4)	1 (1.1)	4 (2.2)	7 (2.6)
Grade 3 or higher TEAE	6 (6.9)	3 (3.4)	5 (5.6)	8 (4.5)	14 (5.3)
Treatment-related TEAE	16 (18.4)	25 (28.1)	15 (16.9)	40 (22.5)	56 (21.1)
Treatment-related serious TEAE	0	0	0	0	0
Treatment-related Grade 3 or higher TEAE	0	0	0	0	0
TEAE with action taken as permanent withdrawal of study drug	2 (2.3)	2 (2.2)	2 (2.2)	4 (2.2)	6 (2.3)
Treatment-related TEAE with action taken as permanent withdrawal of study drug	2 (2.3)	1 (1.1)	1 (1.1)	2 (1.1)	4 (1.5)
TEAE leading to study discontinuation	0	0	2 (2.2)	2 (1.1)	2 (0.8)
Treatment-related TEAE leading to study discontinuation	0	0	1 (1.1)	1 (0.6)	1 (0.4)
TEAE leading to dose interruption	4 (4.6)	1 (1.1)	1 (1.1)	2 (1.1)	6 (2.3)
TEAE leading to dose interruption - restarted same dose	4 (4.6)	1 (1.1)	1 (1.1)	2 (1.1)	6 (2.3)
TEAE leading to dose interruption - Restarted lower dose	0	0	0	0	0
TEAE with fatal outcome	0	0	0	0	0
Treatment-related TEAE with fatal outcome	0	0	0	0	0

Key: MedDRA, Medical Dictionary for Regulatory Activities, TEAE, treatment-emergent adverse event.
Notes: A TEAE was defined as any AE that newly appeared, increased in frequency, or worsened in severity after initiation of the study drug and up to 30 days after the last study drug administration.
Adverse events were graded using MedDRA Version 21.0.
Source: Table 7-1, ENHANCE CSR (21)

Most Common Adverse Events

The incidence of TEAEs by SOC, preferred term, and group in >5% of patients in the "All Seladelpar" or "All Patients" groups is summarised below in Table 34.

Table 34: Summary of Adverse Events by System Organ Class and Preferred Term in >5% of patients (Safety Set)

	Placebo (n=87) n (%)	Seladelpar 5 mg (n=89) n (%)	Seladelpar 10 mg (n=89) n (%)	All Seladelpar (n=178) n (%)	All Patients (n=265) n (%)
Patients with at least 1 TEAE	64 (73.6)	56 (62.9)	58 (65.2)	114 (64.0)	178 (67.2)
Gastrointestinal disorders	21 (24.1)	25 (28.1)	26 (29.2)	51 (28.7)	72 (27.2)
Abdominal pain upper	3 (3.4)	8 (9.0)	6 (6.7)	14 (7.9)	17 (6.4)
Nausea	4 (4.6)	5 (5.6)	7 (7.9)	12 (6.7)	16 (6.0)
Infections and infestations	23 (26.4)	21 (23.6)	24 (27.0)	45 (25.3)	68 (25.7)
Upper respiratory tract infection	2 (2.3)	6 (6.7)	4 (4.5)	10 (5.6)	12 (4.5)
Skin and subcutaneous tissue disorders	19 (21.8)	11 (12.4)	19 (21.3)	30 (16.9)	49 (18.5)
Pruritus	11 (12.6)	3 (3.4)	10 (11.2)	13 (7.3)	24 (9.1)
Musculoskeletal and connective tissue disorders	12 (13.8)	15 (16.9)	15 (16.9)	30 (16.9)	42 (15.8)
Arthralgia	5 (5.7)	5 (5.6)	4 (4.5)	9 (5.1)	14 (5.3)
Nervous system disorders	8 (9.2)	11 (12.4)	12 (13.5)	23 (12.9)	31 (11.7)
Headache	1 (1.1)	5 (5.6)	7 (7.9)	12 (6.7)	13 (4.9)
General disorders and administration site conditions	16 (18.4)	5 (5.6)	7 (7.9)	12 (6.7)	28 (10.6)
Fatigue	8 (9.2)	2 (2.2)	4 (4.5)	6 (3.4)	14 (5.3)

Key: MedDRA, Medical Dictionary for Regulatory Activities; TEAE, treatment-emergent adverse event.
Notes: A TEAE was defined as any AE that newly appeared, increased in frequency, or worsened in severity after initiation of the study drug and up to 30 days after the last study drug administration. A patient was counted only once for multiple events within preferred term/system organ class. Adverse events were sorted by descending frequency in system organ class, then descending frequency of preferred term within system organ class, first in the All Seladelpar group, then the initial dose Seladelpar 10 mg group, the initial dose Seladelpar 5 mg group, and Placebo group, if applicable. Adverse events were coded using MedDRA Version 21.0.
Source: Table 7-2, ENHANCE CSR (21)

Adverse Events by Maximum Severity

TEAEs with a severity of Grade 3 (based on Grades 1 to 5 according to the CTCAE Version 5.0) are summarised below in Table 35.

Table 35: Treatment-emergent CTCAE Grade 3 or Higher Adverse Events by Treatment, System Organ Class, Preferred Term and CTCAE Grade (Safety Set)

	Placebo (n=87) n (%)	Seladelpar 5 mg (n=89) n (%)	Seladelpar 10 mg (n=89) n (%)	All Seladelpar (n=178) n (%)	All Patients (n=265) n (%)
Patients with at least 1 Grade 3 or higher TEAE	6 (6.9)	3 (3.4)	5 (5.6)	8 (4.5)	14 (5.3)
Abscess oral	0	0	1 (1.1)	1 (0.6)	1 (0.4)
Cellulitis[a]	0	0	1 (1.1)	1 (0.6)	1 (0.4)
Pyelonephritis acute[a]	1 (1.1)	0	0	0	1 (0.4)
Tendonitis	0	0	1 (1.1)	1 (0.6)	1 (0.4)
Flank pain	0	1 (1.1)	0	1 (0.6)	1 (0.4)
Diarrhoea	0	0	1 (1.1)	1 (0.6)	1 (0.4)
Vulvovaginal pruritus	0	0	1 (1.1)	1 (0.6)	1 (0.4)
Adenoid cystic carcinoma[a]	0	1 (1.1)	0	1 (0.6)	1 (0.4)
Uterine leiomyoma	1 (1.1)	0	0	0	1 (0.4)
Leukocytosis[a]	0	1 (1.1)	0	1 (0.6)	1 (0.4)
Headache	1 (1.1)	0	0	0	1 (0.4)
Partial seizures[a]	1 (1.1)	0	0	0	1 (0.4)
Pruritus	1 (1.1)	0	0	0	1 (0.4)
Pruritus generalised	1 (1.1)	0	0	0	1 (0.4)

Key: MedDRA, Medical Dictionary for Regulatory Activities; TEAE, treatment-emergent adverse event.
Notes: A TEAE was defined as any AE that newly appeared, increased in frequency, or worsened in severity after initiation of the study drug and up to 30 days after the last study drug administration. A patient was counted only once for multiple events within preferred term/system organ class according to the worst grade. Adverse events were sorted by descending frequency in system organ class, then descending frequency of preferred term within system organ class, first in the All Seladelpar group, then the initial dose Seladelpar 10 mg group, the initial dose Seladelpar 5 mg group, and Placebo group, if applicable. Adverse events were coded using MedDRA Version 21.0 and graded using CTCAE Version 5.0.
[a]Grade 3 serious adverse events
Sources: Table 7-3, ENHANCE CSR (21)

A7. [PRIORITY] Data for RESPONSE for some outcomes are not completely reported in the CS. Please provide tabulated results for the following outcomes, including measures of variance, where relevant:

(a) The dose of seladelpar and UDCA received in each arm, including the number of people who were down-titrated to seladelpar 5mg

(b) Percent change from baseline in ALP over time, the proportion of participants who achieved ALP < 1.67 x ULN at months 1, 3, 6, 9 and the

proportion of participants who achieved a ≥decrease in ALP at months 1, 3, 6, 9

(c) Change from baseline in pruritus

(d) Change in total bilirubin and the proportion of participants who achieved total bilirubin ≤1.0 x ULN at months 1, 3, 6, 9

(e) Results for the fatigue domain of the PBC-40

Company response: Tabulated outcomes for the requested outcomes are provided below.

(a) The dose of seladelpar and UDCA received in each arm, including the number of people who were down-titrated to seladelpar 5mg

Study drug exposure is summarised below in Table 36, while exposure to UDCA is summarised in Table 37.

For the purpose of reporting study drug exposure, 10 mg of placebo was used for calculating the placebo arm's dose. The mean duration of exposure was 50.5 weeks in the seladelpar arm and 48.3 weeks in the placebo arm. The mean average daily dose of study drug was 9.8 mg in the seladelpar arm and 9.9 mg in the placebo arm. The majority of patients (seladelpar 93.8%; placebo 89.2%) in both treatment arms received study drug for ≥ 39 weeks. Due to the protocol allowed study visit window at Week 52 (± 7 days), 64.8% and 56.9% of patients in the seladelpar and placebo arms, respectively, received ≥ 52 weeks of study drug, cumulatively (23).

Table 36: Study drug treatment exposure (RESPONSE, Safety Analysis Set)

	Placebo (n=65)	Seladelpar 10 mg (n=128)
Duration of Exposure[a] (Weeks)		
N (%)	65 (100)	126 (100)
Mean (SD)	48.33 (11.573)	50.49 (7.377)
Min, Max	1.3, 55.4	5.4, 54.7
Treatment Exposure (by Duration in Categories), n (%)		
≤ 4 Weeks	1 (1.5)	0
> 4 to ≤ 8 Weeks	1 (1.5)	2 (1.6)
> 8 to ≤ 12 Weeks	1 (1.5)	0
> 12 to ≤ 26 Weeks	1 (1.5)	1 (0.8)
> 26 to ≤ 39 Weeks	3 (4.6)	3 (2.3)

> 39 to ≤ 52 Weeks	27 (41.5)	44 (34.4)
> 52 Weeks	31 (47.7)	76 (59.4)
Treatment Exposure (cumulative), n (%)		
≥ 4 Weeks	64 (98.5)	126 (98.4)
≥ 8 Weeks	63 (96.9)	124 (96.9)
≥ 12 Weeks	62 (95.4)	124 (96.9)
≥ 26 Weeks	61 (93.8)	123 (96.1)
≥ 39 Weeks	58 (89.2)	120 (93.8)
≥ 52 Weeks	37 (56.9)	83 (64.8)
Cumulative Dose[b] (mg)		
N	65	126
Mean (SD)	3343.2 (822.59)	3470.0 (570.13)
Min, Max	110, 4150	360, 4510
Average Daily Dose[c] (mg/Day)		
N	65	126
Mean (SD)	9.90 (0.714)	9.81 (0.676)
Min, Max	8.0, 12.7	5.8, 12.5

Abbreviations: SD, standard deviation.
Notes: Percentages were based on the number of patients in the Safety Analysis Set under each treatment arm.
[a] Exposure (Weeks) was defined as ([Last exposure date] – [First exposure date] + 1) / 7.
[b] Cumulative dose was calculated as the sum of {[(dispensed number of capsules – maximum number of (returned capsules, missed doses)) *dispensed dose amount per capsule] for each occurrence of drug dispensed visit}. If no information on returned or missed doses was available, it was assumed that the patient had taken all planned doses. Data for two patients 143-412 and 635-404 were excluded from this summary table as accurate estimation of dosing could not be performed due to a large number of unreturned bottles.
[c] Average daily dose was defined as the cumulative dose divided by total days of exposure.
Source: Table 45, RESPONSE CSR (23)

Table 37: Treatment exposure of UDCA (RESPONSE, Safety Analysis Set)

	Placebo (n=65)	Seladelpar 10 mg (n=128)
Duration of Exposure[a] (Weeks)		
N (%)	62 (95.4)	120 (93.8)
Mean (SD)	48.27 (11.378)	50.29 (8.999)
Min, Max	6.3, 55.4	5.0, 59.0
Treatment Exposure (by Duration in Categories), n (%)		
≤ 4 Weeks	0	0
> 4 to ≤ 8 Weeks	1 (1.6)	3 (2.5)
> 8 to ≤ 12 Weeks	1 (1.6)	1 (0.8)
> 12 to ≤ 26 Weeks	2 (3.2)	1 (0.8)
> 26 to ≤ 39 Weeks	3 (4.8)	2 (1.7)
> 39 to ≤ 52 Weeks	23 (37.1)	38 (31.7)
> 52 Weeks	32 (51.6)	75 (62.5)
Treatment duration, n (%)		
≥ 4 Weeks	62 (100.0)	120 (100.0)
≥ 8 Weeks	61 (98.4)	117 (97.5)
≥ 12 Weeks	60 (96.8)	117 (97.5)
≥ 26 Weeks	58 (93.5)	115 (95.8)
≥ 39 Weeks	55 (88.7)	113 (94.2)
≥ 52 Weeks	38 (61.3)	80 (66.7)
Cumulative Dose[b] (mg)		
N	62	120
Mean (SD)	341906.5 (123826.73)	367715.8 (107963.16)
Min, Max	35100, 732000	26250, 745000

Average Daily Dose[c] (mg/Day)		
N	62	120
Mean (SD	1009.15 (280.913)	1043.27 (243.203)
Min, Max	600.0, 2000.0	585.8, 1997.3

Key: SD, standard deviation; UDCA, ursodeoxycholic acid.
Notes: Percentages were based on the number of patients in the Safety Analysis Set under each treatment arm.
[a] Exposure (Weeks) was defined as ([Last exposure date] – [First exposure date] + 1) / 7.
[b] Cumulative dose was calculated as the sum of {[(dispensed number of capsules – maximum number of (returned capsules, missed doses)) *dispensed dose amount per capsule] for each occurrence of drug dispensed visit}. If no information on returned or missed doses was available, it was assumed that the patient had taken all planned doses. Data for two patients 143-412 and 635-404 were excluded from this summary table as accurate estimation of dosing could not be performed due to a large number of unreturned bottles.
[c] Average daily dose was defined as the cumulative dose divided by total days of exposure.
Source: Table 14.1.9.2.1, RESPONSE CSR (23)

One patient (0.8%) in the seladelpar arm underwent a dose reduction in the study (Table 38). The patient had a dose reduction from 10 mg to 5 mg following a study drug interruption attributed to a Grade 2 TEAE of drug-induced liver injury. The event was assessed as unlikely related to seladelpar, and the dose level was subsequently up-titrated to 10 mg approximately two months after the event was resolved (23).

Table 38: Dose interruptions and reduction (RESPONSE, Safety Analysis Set)

	Placebo (n=65) n (%)	Seladelpar 10 mg (n=128) n (%)	Total (n = 193) n (%)
Patients with at least One Dose Interruption	5 (7.7)	12 (9.4)	17 (8.8)
One Interruption	5 (7.7)	11 (8.6)	16 (8.3)
Two Interruptions	0 (0.0)	1 (0.8)	1 (0.5)
Reason for Dose Interruption			
Adverse Event	4 (6.2)	8 (6.3)	12 (6.2)
AEs related to Safety Monitoring Criteria	1 (1.5)	1 (0.8)	2 (1.0)
Other	1 (1.5)	4 (3.1)	5 (2.6)
Patients with at least one dose reduction	0 (0.0)	1 (0.8)	1 (0.5)
Patients with dose up-titration after dose reduction	0 (0.0)	1 (0.8)	1 (0.5)

Key: AE, adverse event.
Notes: A dose interruption was an interruption in the assigned dose due to an AE, non-compliance, or other reasons. Percentages were based on the number of patients in the Safety Analysis Set under each treatment arm.
Source: Table 46, RESPONSE CSR (23)

(b) Percent change from baseline in ALP over time, the proportion of participants who achieved ALP < 1.67 x ULN at months 1, 3, 6, 9 and the proportion of participants who achieved a ≥decrease in ALP at months 1, 3, 6, 9

The least-squares mean percent changes from in ALP over the course of the study by treatment arm are summarised in Table 39.

Table 39: Percent change from baseline in ALP over time (RESPONSE, ITT Analysis Set)

	Placebo (N=65)	Seladelpar 10 mg (N=128)	LS Mean of Difference (95% CI)	p-value
Visit				
Baseline, n	65	128		
Mean (SD)	313.8 (117.68)	314.6 (122.96)		
Month 1, n	62	125		
LS Mean (SE)[a]	-4.8 (2.72)	-36.2 (2.03)	-31.4 (-37.6, -25.2)	< 0.0001
Month 3, n	62	125		
LS Mean (SE)[a]	-8.0 (2.09)	-43.4 (1.62)	-35.4 (-39.9, -30.8)	< 0.0001
Month 6, n	61	122		
LS Mean (SE)[a]	-5.9 (2.51)	-44.8 (1.89)	-38.9 (-44.6, -33.2)	< 0.0001
Month 9, n	58	117		
LS Mean (SE)[a]	-4.5 (3.29)	-42.8 (2.40)	-38.3 (-45.9, -30.6)	< 0.0001
Month 12, n	57	114		
LS Mean (SE)[a]	-4.3 (3.48)	-42.4 (2.54)	-38.2 (-46.3, -30.1)	< 0.0001

Key: ALP, alkaline phosphatase; CI, confidence interval; ITT, intent-to-treat; LS, least squares; M, Month; MMRM, mixed-effect model repeated measure; NRS, numerical rating scale
Notes: Baseline measurement for chemistry and hematology measures, and other laboratory quantitative measures were defined as the arithmetic mean of applicable measurements at Screening, Run-in, Day 1, and unscheduled assessments prior to or on Day 1.
[a]Percent change from baseline was estimated by the MMRM model including terms for baseline ALP, stratification variables (baseline ALP level: < 350 U/L and ≥ 350 U/L; baseline Pruritus NRS: < 4 and ≥ 4), treatment arm, visit, and treatment- by visit interaction. Unstructured covariance was applied for the repeated measure.
Source: Table 37, RESPONSE CSR (23)

The proportion of participants who achieved ALP < 1.67 x ULN at months 1, 3, 6, 9 and the proportion of participants who achieved a ≥15% decrease in ALP at months 1, 3, 6, 9 are presented below in Table 40. Analyses of the composite biochemical response endpoint at Months 1, 3, 6, and 9 revealed similar results to those of Month 12, with higher percentages of responders in the seladelpar arm compared with the placebo arm starting as early as Month 1. The beneficial effect of seladelpar was maintained throughout the course of the study. P-value at all study timepoints were <0.0001.

Table 40: Analysis of composite endpoint response rate at Month 1, Month 3, Month 6, and Month 9 (RESPONSE, ITT Analysis Set)

	Placebo (N=65)	Seladelpar 10 mg (N=128)
Patients who achieved response at Month 1, n (%)[ab]	5 (7.7)	76 (59.4)
Wald 95% CI for Response Rate	(1.2, 14.2)	(50.9, 67.9)
CHM test p-value[c]		< 0.0001
Response category at Month 1, n (%)[b]		
ALP < 1.67 x ULN	10 (15.4)	82 (64.1)
≥15% decrease in ALP	16 (24.6)	121 (94.5)

Total bilirubin ≤ ULN	55 (84.6)	111 (86.7)
Patients who achieved response at Month 3, n (%)[ab]	7 (10.8)	79 (61.7)
Wald 95% CI for Response Rate	(3.2, 18.3)	(53.3, 70.1)
CHM test p-value[c]		< 0.0001
Response category at Month 3, n (%)[b]		
ALP < 1.67 x ULN	13 (20.0)	90 (70.3)
≥15% decrease in ALP	20 (30.8)	120 (93.8)
Total bilirubin ≤ ULN	60 (92.3)	110 (85.9)
Patients who achieved response at Month 6, n (%)[ab]	12 (18.5)	85 (66.4)
Wald 95% CI for Response Rate	(9.0, 27.9)	(58.2, 74.6)
CHM test p-value[c]		< 0.0001
Response category at Month 6, n (%)[b]		
ALP < 1.67 x ULN	15 (23.1)	89 (69.5)
≥15% decrease in ALP	26 (40.0)	118 (92.2)
Total bilirubin ≤ ULN	54 (83.1)	111 (86.7)
Patients who achieved response at Month 9, n (%)[ab]	12 (18.5)	79 (61.7)
Wald 95% CI for Response Rate	(9.0, 27.9)	(53.3, 70.1)
CHM test p-value[c]		< 0.0001
Response category at Month 9, n (%)[b]		
ALP < 1.67 x ULN	17 (26.2)	85 (66.4)
≥15% decrease in ALP	23 (35.4)	109 (85.2)
Total bilirubin ≤ ULN	54 (83.1)	106 (82.8)

Key: ALP, alkaline phosphatase; TB, total bilirubin; ULN, upper limit of normal; CMH, Cochran Mantel Haenszel,
Notes:
[a]A patient is designated a responder if all three of the following conditions were met: (1) ALP < 1.67 x ULN; (2) ALP decrease from baseline >= 15%; (3) TB <= ULN.
[b]Patients with missing data at the specified time point for response evaluation are considered non-responders.
[c]Two-sided p-value for pair-wise comparison is based on the Cochran Mantel Haenszel test adjusted for both stratification variables (baseline ALP level: < 350 U/L and >= 350 U/L; baseline pruritus NRS: < 4 and >= 4).
Source: Table 14.2.8.1, RESPONSE CSR (23)

(c) Change from baseline in pruritus

The total change from baseline in pruritus throughout the RESPONSE trial is presented in Table 41 and Table 42. Table 41 presents the overall pruritus change from baseline in the moderate-to-severe Pruritus Numerical Rating Scale (NRS) Analysis Set, while Table 42 presents the proportion og patients with a decrease in Pruritus NRS ≥ 2, NRS ≥ 3, or NRS ≥ 4 in patienrs with baseline Pruritus NRS ≥ 4 at each study timepoint.

Table 41: MMRM Analysis of Pruritus NRS Change from baseline at Month 1, Month 3, Month 9 and Month 12 (weekly averages) (RESPOSNSE; MSPN AnalysisSet)

	Placebo	Seladelpar 10 mg

	(n=23)	(n=49)
Baseline		
n	23	49
Mean (SD)	6.6 (1.44)	6.1 (1.42)
Median	7.1	5.9
Q1, Q3	5.6, 7.7	4.9, 7.4
Min, Max	4,9	4,9
Month 1 Change from Baseline[a]		
n	22	48
Mean (SD)	-1.0 (1.24)	-1.8 (1.76)
Median	-0.8	-1.5
Q1, Q3	-1.8, -0.3	-3.1, -0.7
Min, Max	-4, 2	-6, 1
LS Mean (SE)[b]	-0.8 (0.34)	-1.8 (0.23)
LS Mean of Difference (95% CI)		-1.0 (-1.8, -0.2)
p-value		0.0171
Month 3 Change from Baseline[a]		
n	22	46
Mean (SD)	-1.8 (1.64)	-2.5 (2.22)
Median	-1.8	-2.2
Q1, Q3	-3.0, -0.1	-3.9, -1.2
Min, Max	-5, 1	-8, 3
LS Mean (SE)[b]	-1.6 (0.43)	-2.6 (0.30)
LS Mean of Difference (95% CI)		-1.0 (-2.1, 0.0)
p-value		0.0519
Month 9 Change from Baseline[a]		
n	20	36
Mean (SD)	-1.9 (1.93)	-3.3 (2.35)
Median	-1.8	-3.4
Q1, Q3	-3.6, -0.2	-4.9, -1.9
Min, Max	-6, 2	-8, 2
LS Mean (SE)[b]	-1.7 (0.46)	-3.4 (0.32)
LS Mean of Difference (95% CI)		-1.8 (-2.9, -0.6)
p-value		0.0026
Month 12 Change from Baseline[a]		
n	16	39
Mean (SD)	-1.8 (2.01)	-3.4 (2.33)
Median	-2.6	-3.4
Q1, Q3	-3.1, 0.2	-4.8, -2.0
Min, Max	-6, 1	-8,2
LS Mean (SE)[b]	-1.5 (0.50)	-3.3 (0.33)
LS Mean of Difference (95% CI)		-1.8 (-3.0, -0.6)
p-value		0.0036

Key: NRS, numerical rating scale; MMRM, Mixed-Effect Model Repeated Measure; CI, confidence interval.
Notes: Baseline pruritus NRS is defined as the mean of all daily recorded scores during the Run-in Period and on Day 1.
[a]Missing assessment at specific timepoint is imputed as an average of the two adjacent weekly averages (at most one week apart); if only one adjacent weekly average is available it is imputed by the available adjacent weekly average; if no adjacent weekly average is available it is not imputed.
[b]Change from baseline is estimated by Mixed-Effect Model Repeated Measure (MMRM) model including terms for baseline NRS, stratification variable (baseline ALP level <350 U/L versus ALP level >= 350 U/L), treatment group, week, and treatment-by-week interaction. Unstructured structure is applied for the repeated measure and Kenward-Roger correction is applied for the denominator degrees of freedom.
Source: Table 14.2.9.2, RESPONSE CSR (23)

Table 42: Analysis of Pruritus NRS Decrease of NRS ≥ 2, NRS ≥3, or NRS ≥4 (weekly averages) over time (MSPN Analysis Set)

	Placebo (n=23)	Seladelpar 10 mg (n=49)
Pruritus NRS Decrease ≥ 2 Response Rate[a,b]		
Month 1, n (%) (Wald 95% CI for Response Rate)	5 (21.7) (4.9, 38.6)	18 (36.7) (23.2, 50.2)
Month 3, n (%) (Wald 95% CI for Response Rate)	11 (47.8) (27.4, 68.2)	26 (53.1) (39.1, 67.0)
Month 6, n (%) (Wald 95% CI for Response Rate)	7 (30.4) (11.6, 49.2)	34 (69.4) (56.5, 82.3)
Month 9, n (%) (Wald 95% CI for Response Rate)	10 (43.5) (23.2, 63.7)	27 (55.1) (41.2, 69.0)
Month 12, n (%) (Wald 95% CI for Response Rate)	10 (43.5) (23.2, 63.7)	30 (61.2) (47.6, 74.9)
Pruritus NRS Decrease ≥ 3 Response Rate[b,c]		
Month 1, n (%) (Wald 95% CI for Response Rate)	1 (4.3) (0.0, 12.7)	12 (24.5) (12.4, 36.5)
Month 3, n (%) (Wald 95% CI for Response Rate)	4 (17.4) (1.9, 32.9)	17 (34.7) (21.4, 48.0)
Month 6, n (%) (Wald 95% CI for Response Rate)	5 (21.7) (4.9, 38.6)	22 (44.9) (31.0, 58.8)
Month 9, n (%) (Wald 95% CI for Response Rate)	7 (30.4) (11.6, 49.2)	21 (42.9) (29.0, 56.7)
Month 12, n (%) (Wald 95% CI for Response Rate)	5 (21.7) (4.9, 38.6)	23 (46.9) (33.0, 60.9)
Pruritus NRS Decrease ≥ 4 Response Rate[b,d]		
Month 1, n (%) (Wald 95% CI for Response Rate)	0 (0.0, 0.0)	5 (10.2) (1.7, 18.7)
Month 3, n (%) (Wald 95% CI for Response Rate)	2 (8.7) (0.0, 20.2)	11 (22.4) (10.8, 34.1)
Month 6, n (%) (Wald 95% CI for Response Rate)	4 (17.4) (1.9, 32.9)	14 (28.6) (15.9, 41.2)
Month 9, n (%) (Wald 95% CI for Response Rate)	2 (8.7) (0.0, 20.2)	15 (30.6) (17.7, 43.5)
Month 12, n (%) (Wald 95% CI for Response Rate)	2 (8.7) (0.0, 20.2)	15 (30.6) (17.7, 43.5)

Abbreviations: CI, confidence interval; MSPN, moderate to severe Pruritus NRS; NRS, numerical rating scale
[a]A patient was designated as a responder if Pruritus NRS decrease was ≥ 2.
[b]Patients with missing data on the specified timepoint(s) for response evaluation were considered nonresponders.
[c]A patient was designated as a responder if Pruritus NRS decrease was ≥ 3.
[d]A patient was designated as a responder if Pruritus NRS decrease was ≥ 4.
Source: Table 42, RESPONSE CSR (23)

(d) Change in total bilirubin and the proportion of participants who achieved total bilirubin ≤1.0 x ULN at months 1, 3, 6, 9

The LS mean percent changes from baseline in total bilirubin during the course of the study by treatment arm are summarised below in Table 43.

Table 43: Percent changes from baseline in total bilirubin over time (RESPONSE, ITT Analysis Set)

	Placebo (n=65)	Seladelpar 10 mg (n=128)	LS Mean of Difference (95% CI)	p-value
Visit				
Baseline, n	65	128		
Mean (SD)	0.737 (0.3099)	0.769 (0.3141)		
Month 1, n	62	125		
LS Mean (SE)[a]	-0.745 (2.7487)	-6.073 (1.9896)	-5.328 (-11.816, 1.160)	0.1069
Month 3, n	62	125		
LS Mean (SE)[a]	-5.771 (2.3980)	-8.802 (1.7498)	-3.031 (-8.653, 2.591)	0.2889
Month 6, n	61	122		
LS Mean (SE)[a]	1.200 (3.6635)	-8.245 (2.6263)	-9.445 (-18.189, -0.702)	0.0344
Month 9, n	58	117		
LS Mean (SE)[a]	2.522 (3.9601)	-6.749 (2.8164)	-9.270 (-18.743, 0.202)	0.0550
Month 12, n	57	114		
LS Mean (SE)[a]	3.552 (6.0026)	-0.376 (4.2373)	-3.928 (-18.360, 10.504)	0.5914

Key: ALP, alkaline phosphatase; CI, confidence interval; ITT, intent-to-treat; LS, least squares; MMRM, mixed-effect model repeated measure; NRS, numerical rating scale
Notes: Baseline measurement for chemistry and hematology measures, and other laboratory quantitative measures were defined as the arithmetic mean of applicable measurements at Screening, Run-in, Day 1, and unscheduled assessments prior to or on Day 1.
[a]Percent change from baseline was estimated by the MMRM model including terms for baseline ALP, stratification variable (baseline ALP level: < 350 U/L and ≥ 350 U/L; baseline Pruritus NRS: < 4 and ≥ 4), treatment arm, visit, and treatment-by visit interaction. Unstructured covariance was applied for the repeated measure.
Source: Table 38, RESPONSE CSR (23)

The proportion of participants who achieved total bilirubin ≤ 1.0 x ULN at months 1, 3, 6, 9 is presented in Table 40.

(e) Results for the fatigue domain of the PBC-40

Changes from baseline in the Fatigue Domain of the PBC-40 QoL questionnaire in the ITT Analysis Set are summarised below in Table 44. In general, there were no between arm differences in the fatigue domain across the study.

Table 44: Analysis of the fatigue domain of the PBC-40 QoL (RESPONSE, ITT Analysis Set)

	Placebo (n=65)		Seladelpar 10 mg (n=128)	
	Value	Change from Baseline	Value	Change from Baseline
Baseline				
n	65	-	128	-
Mean (SD)	27.4 (10.64)	-	27.6 (10.01)	-

Median	26.5	-	27.0	-
Q1, Q3	19.5, 36.5	-	18.8, 35.0	-
Min, Max	11, 49	-	11, 51	-
Baseline for Month 1 Completers				
n[a]	62	-	-	-
Mean (SD)	26.9 (10.50)	-	-	-
Median	25.5	-	-	-
Q1, Q3	17.5, 36.5	-	-	-
Min, Max	11, 49	-	-	-
Month 1				
n[a]	62	62	118	118
Mean (SD)	24.6 (10.36)	-2.33 (5.876)	25.9 (9.91)	-1.31 (5.664)
Median	22.5	-2.00	27.0	-1.00
Q1, Q3	16.0, 32.0	-5.50, 1.00	16.0, 34.0	-3.50, 2.00
Min, Max	11, 47	-18.5, 12.5	11, 46	-20.0, 23.0
LS Mean (SE)[b]	-	-2.42 (0.727)	-	-1.44 (0.541)
LS Mean of Difference (95% CI)	-	-	-	0.98 (-0.73, 2.69)
p-value	-	-	-	0.2587
Baseline for Month 3 Completers				
n[a]	59	-	121	-
Mean (SD)	26.8 (10.23)	-	27.6 (10.04	-
Median	26.0	-	27.0	-
Q1, Q3	17.5, 36.5	-	18.5, 35.0	-
Min, Max	11, 49	-	11, 51	-
Month 3-2.39 (0.747)				
n[a]	59	59	121	121
Mean (SD)	24.5 (10.22)	-2.28 (7.068)	25.8 (10.37)	-1.88 (4.976)
Median	25.0	-2.5-	26.0	-1.00
Q1, Q3	14.0, 33.0	-6.50, 1.50	17.0, 33.0	-4.50, 0.50
Min, Max	11, 46	-19.0, 14.0	11, 50	-22.0, 9.0
LS Mean (SE)[b]	-	-2.39 (0.747)	-	-1.88 (0.540)
LS Mean of Difference (95% CI)	-	-	-	0.52 (-1.22, 2.26)
p-value	-	-	-	0.5573
Baseline for Month 6 Completers				
n[a]	53	-	113	-
Mean (SD)	26.2 (9.96)	-	26.9 (9.77)	-
Median	24.5	-	27.0	-
Q1, Q3	17.5, 36.0	-	18.0, 35.0	-
Min, Max	11, 49	-	11, 51	-
Month 6				
n[a]	53	53	113	113
Mean (SD)	25.8 (10.12)	-0.42 (6.756)	25.0 (9.90)	-1.90 (5.528)
Median	26.0	-1.50	25.0	-1.00
Q1, Q3	16.0, 33.0	-4.50, 2.50	17.0, 32.0	-5.50, 1.00

Min, Max	11, 44	-18.0, 18.0	11, 47	-17.0, 14.0
LS Mean (SE)[b]	-	-0.78 (0.806)	-	-1.97 (0.575)
LS Mean of Difference (95% CI)	-	-	-	-1.19 (-3.07, 0.69)
p-value	-	-	-	0.2131
Baseline for Month 9 Completers				
n[a]	55	-	112	-
Mean (SD)	26.7 (10.95)	-	27.1 (10.02)	-
Median	25.0	-	27.0	-
Q1, Q3	16.5, 37.0	-	17.0, 35.0	-
Min, Max	11, 49	-	11, 51	-
Month 9				
n[a]	55	55	112	112
Mean (SD)	25.2 (10.15)	-1.50 (6.907)	24.5 (10.65)	-2.62 (6.461)
Median	26.0	-1.50	23.0	-1.00
Q1, Q3	15.0, 33.0	-6.00, 3.00	15.0, 32.5	-5.00, 1.25
Min, Max	11, 49	-15.0, 14.0	11, 54	-23.0, 9.0
LS Mean (SE)[b]	-	-1.49 (0.856)	-	-2.69 (0.616)
LS Mean of Difference (95% CI)	-	-	-	-1.20 (-3.21, 0.81)
p-value	-	-	-	0.2415
Baseline for Month 12 Completers				
n[a]	51	-	94	-
Mean (SD)	26.0 (9.95)	-	25.7 (9.45)	-
Median	24.5	-	26.3	-
Q1, Q3	17.0, 36.0	-	17.0, 34.0	-
Min, Max	12, 49	-	11, 44	-
Month 12				
n[a]	51	51	94	94
Mean (SD)	24.9 (9.81)	-1.17 (8.239)	23.8 (9.88)	-1.92 (6.087)
Median	25.0	-0.50	22.5	-1.50
Q1, Q3	16.0, 33.0	-5.00, 2.50	15.0, 31.0	-4.00, 2.00
Min, Max	11, 48	-24.5, 15.0	11, 53	-21.0, 15.0
LS Mean (SE)[b]	-	-1.5 (0.916)	-	-1.97 (0.675)
LS Mean of Difference (95% CI)	-	-	-	-0.47 (-2.66, 1.71)
p-value	-	-	-	0.6692

Abbreviations: CI, confidence interval; PBC, primary biliary cholangitis; QoL, quality of life; SD, standard deviation; SE, standard error.
Notes: The baseline measurement is the arithmetic mean of applicable measurements at Screening, Run-in, Day 1, and unscheduled assessments prior to or on Day 1.
High scores represent high impact and low scores represent low impact of PBC on quality of life.
[a]At each scheduled timepoint, n represents the number of patients who had both a baseline value and a value at that timepoint.
[b]Change from baseline is estimated by Mixed-Effect Model Repeated Measure (MMRM) model including terms for baseline PBC-40 QoL score, stratification variables (baseline ALP level: < 350 U/L and >= 350 U/L; baseline pruritus NRS: < 4 and >= 4), treatment group, visit, and treatment-by-visit interaction. Unstructured covariance structure is applied for the repeated measure and Kenward-Roger correction is applied for the denominator degrees of freedom. Treatment by baseline PBC-40 QoL score value interaction was explored and added as a term in model analysis for Domain: Social due to its significant effect (p-value < .05).
Source: Table 14.2.10.1.1, RESPONSE CSR (23)

A8. [PRIORITY] For CB8025-21629, please provide:

(a) The actual dose of seladelpar and UDCA received in the trial, including the proportion of participants who were received a reduced dose of seladelpar

(b) Tabulated data for PBC-40, including variance data, and with separate results for the fatigue domain

(c) Tabulated data for the primary outcome (mean reduction in ALP from baseline) including variance data

(d) Tabulated data for pruritus measures including variance data

Company response: CB8025-21629 was an international, multi-centre, open-label, dose-ranging Phase 2 study of seladelpar at doses of 2, 5, and 10 mg in patients with PBC and an inadequate response or intolerance to UDCA. Details of the study methodology and outcomes are presented in Section 2.6 of the Company Evidence Submission.

(a) The actual dose of seladelpar and UDCA received in the trial, including the proportion of participants who were received a reduced dose of seladelpar

After completion of an 8-week initial treatment period, patients entered an open-label extension period for a total of up to 52 weeks of treatment. During the extension period, patients took seladelpar once orally once daily for up to 52 weeks. Due to practical constraints, dose adjustments based on assessment results began at the Week 12 visit. Thus, patients received the randomised dose of seladelpar for at least 12 weeks. After Week 12, patients assigned to the 2 mg or 5 mg dose treatment could have the dose up-titrated, based on individual patient review including ALP response and evaluation of safety and tolerability. During the extension period, a patient's dose could be readjusted for safety or efficacy reasons; for example, patients receiving 2 mg could have their dose increased to 5 mg and subsequently to 10 mg. Each patient's safety and efficacy reviews were performed by the Investigator in collaboration with the Medical Monitor and were based on their clinical judgment, taking into account the safety and tolerability of seladelpar and the biochemical response to seladelpar (e.g,

achieving the goal for ALP decrease). Dose down-titration was performed for safety reasons and was allowed at any time during the study, including during the first 8 weeks of treatment (24).

Data on the actual dose of seladelpar and UDCA received in the trial has been requested, but we do not currently have access – if this data becomes available, we would be happy to share with the EAG.

Table 45 summarises the number of patients whose seladelpar dose was up- or -down-titrated after Week 12 and the number of patients receiving each dose after Week 12. After 12 weeks of treatment, 10 patients (90.9%) in the 2 mg dose group and 31 patients (58.5%) in the 5 mg dose group had up-titrated. At Week 52, 0 patients (0%), 14 patients (26.4%), and 48 patients (87.3%) in the 2, 5, and 10 mg dose groups were receiving their original dose (24).

Table 45: Seladelpar dose titration summary by treatment group (CB8025-21629, Safety Analysis Set)

	Initial Dose		
	2 mg (N = 11)	**5 mg (N = 53)**	**10 mg (n = 55)**
Patients at baseline	11	53	55
Patients who completed 12 weeks of treatment	11	48	52
Dose titrated after Week 12 (n [%])			
No	1 (9.1)	16 (30.2)	52 (94.5)
Up-titrated	10 (90.9)	31 (58.5)	0
Down-titrated	0	6 (11.3)	3 (5.5)
Dose at Week 52 (n [%])			
2 mg	0	1 (1.9)	0
5 mg	5 (45.5)	14 (26.4)	0
10 mg	5 (45.5)	30 (56.6)	48 (87.3)
Final Dose (n [%])[a]			
2 mg	1 (9.1)	2 (3.8)	0
5 mg	5 (45.5)	20 (37.7)	1 (1.8)
10 mg	5 (45.5)	31 (58.5)	54 (98.2)

Abbreviations: n = number in category; N = number in treatment group.
[a] Final dose indicates patient at dose at time of study completion or early discontinuation.
Note: Column headers are the initial dose at baseline. Denominator for percentages is the number of patients who completed the visit being reported.
Source: Table 9, CB8025-21629 CSR (24)

(b) Tabulated data for PBC-40, including variance data, and with separate results for the fatigue domain

The PBC-40 QoL questionnaire was used as a secondary efficacy measure to evaluate HRQoL. As highlighted in Section 2.6 of the Company Evidence Submission,

the PBC-40 QoL questionnaire is a disease-specific HRQoL tool developed to specifically measure the psychometric profile of PBC patients. The questionnaire covers 40 items across six domains relevant to PBC, with each item scored on a scale from one to five (higher scores indicating lower QoL). The six domains consist of general symptoms, itch, fatigue, emotional, social, and cognitive function. Patients are assessed using a 4-week recall period (25).

For the sake of brevity, we report tabulated data for the PBC-40 QoL Itch and Fatigue domains, which are reported below in Table 46 and Table 47, respectively.

A consistent pattern of improvement in itch as measured by the PBC-40 QoL questionnaire was observed in the 5/10 mg cohort and 10 mg dose group. Seladelpar treatment was associated with mean changes in the PBC-40 QoL Itch domain measure at Week 52 of -1.4 in the 10 mg dose group, and - 1.2 in the 5/10 mg cohort (Table 46) (24).

In addition, seladelpar treatment was associated with mean changes in PBC-40 QoL Fatigue domain: -3.4 in the 10 mg group, respectively, and -2.5 in the 5/10 mg cohort at 52 weeks (24).

Table 46: PBC-40 QoL Itch Domain Measure Baseline Values and Change from Baseline (CB8025-21629, mITT Analysis Set)

	Initial Dose[a]			5 mg Cohort	
	2 mg (N = 11)	5 mg (N = 49)	10 mg (n = 52)	5/5 mg[b] (N = 14)	5/10 mg[c] (N = 35)
Baseline PBC-40 QoL Score					
n	11	48	52	14	34
Mean	4.6	5.3	5.6	4.6	5.6
SD, SE	4.0, 1.2	3.9, 0.6	4.4, 0.6	4.1, 1.1	3.9, 0.7
95% CI of mean	(2.0, 7.3)	(4.2, 6.5)	(4.4, 6.8)	(2.3, 7.0)	(4.3, 7.0)
Median	4.0	5.0	5.0	3.0	5.5
Min, Max	0, 11	0, 14	0, 15	0, 14	0, 12
Change from Baseline to Week 12					
n	11	45	49	11	34
Mean	-0.4	-0.5	-0.8	0.6	-0.9
SD, SE	2.0, 0.6	3.4, 0.5	3.1, 0.4	4.3, 1.3	3.1, 0.5
95% CI of mean	(-1.7, 1.0)	(-1.6, 0.5)	(-1.7, 0.1)	(-2.3, 3.5)	(-2.0, 0.2)
Median	0.0	0.0	0.0	0.0	0.0
Min, Max	-5, 3	-7, 9	-11, 7	-5, 9	-7, 6
Within group difference p-value[d]	0.5625	0.3033	0.0709	0.6356	0.0935
LS Mean (SE)	-0.68 (0.77)	-0.51 (0.38)	-0.77 (0.36)	-	-
95% CI of LS Mean	(-2.21, 0.85)	(-1.26, 0.25)	(-1.49, -0.05)	-	-
LS Means Difference (SE)[e]	-	0.17 (0.86)	-0.09 (0.85)	-	-
95% CI of LS Mean Difference[e]	-	(-1.53, 1.88)	(-1.78, 1.60)	-	-
ANCOVA p-value[e]	-	0.8401	0.9187	-	-
LS Means Difference (SE)[f]	-	-	-0.26 (0.53)	-	-
95% CI of LS Mean Difference[f]	-	-	(-1.31, 0.78)	-	-
ANCOVA p-value[f]	-	-	0.6213	-	-
Change from Baseline to Week 52					
n	10	42	48	9	33
Mean	0.4	-1.3	-1.4	-1.7	-1.2
SD, SE	2.7, 0.8	3.2, 0.5	3.7, 0.5	2.2, 0.7	3.5, 0.6
95% CI of mean	(-1.6, 2.3)	(-2.3, -0.3)	(-2.4, -0.3)	(-3.3, 0.0)	(-2.4, 0.1)

Median	0.0	-0.5	-1.0	0.0	-1.0
Min, Max	-3, 6	-7, 6	-12, 7	-5, 0	-7, 6
Within group difference p-value[d]	0.6879	0.0141	0.0127	0.0509	0.0616
LS Mean (SE)	-0.10 (0.79)	-1.22 (0.38)	-1.34 (0.36)	-	-
95% CI of LS Mean	(-1.67, 1.47)	(-1.98, -0.46)	(-2.05, -0.63)	-	-
LS Means Difference (SE)[e]	-	-1.12 (0.88)	-1.24 (0.87)	-	-
Within group difference p-value[d]	-	(-2.86, 0.62)	(-2.96, 0.48)	-	-
ANCOVA p-value[e]	-	0.2050	0.1565	-	-
LS Means Difference (SE)[f]	-	-	-0.12 (0.53)	-	-
95% CI of LS Mean Difference[f]	-	-	(-1.16, 0.93)	-	-
ANCOVA p-value[f]	-	-	0.8229	-	-

Key: ANCOVA, analysis of covariance; CI, confidence interval; LS, least squares; max, maximum; min, minimum; mITT, modified intent-to-treat; PBC, primary biliary cholangitis; SD, standard deviation; SE, standard error.

Notes: No imputation for missing data was used for this table.

[a]Analysis is based on initial dose (patients were enrolled to 2 mg or randomized to 5 mg or 10 mg). Beginning at the Week 12 visit, the initial dose could have been up- or down-titrated.

[b]Analysis consists of patients who had Initial Dose 5 mg and did not up-titrate during the remainder of the study.

[c]Analysis consists of patients who had Initial Dose 5 mg and up-titrated to 10 mg.

[d]P-value is based on a paired t-test of within patient difference between baseline value and post-baseline visit, for each treatment group.

[e]Difference between LS means, p-values, and CIs are estimated by comparing each seladelpar level in a pairwise manner to the 2 mg dose group using the ANCOVA model with treatment group as factor, baseline assessment as a covariate, and percent change from baseline as response variable.

[f]Difference between LS means, p-values, and CIs are estimated by comparing the seladelpar 5 mg dose group to the 10 mg dose group using the ANCOVA model with treatment group as factor, baseline assessment as a covariate, and percent change from baseline as response variable.

Source: Table 29, CB8025-12629 CSR (24)

Table 47: PBC-40 QoL Fatigue Domain Measure Baseline Values and Change from Baseline (CB8025-21629, mITT Analysis Set)

	Initial Dose[a]			5 mg Cohort	
	2 mg (N = 11)	5 mg (N = 49)	10 mg (n = 52)	5/5 mg[b] (N = 14)	5/10 mg[c] (N = 35)
Baseline PBC-40 QoL Score					
n	11	48	52	14	34
Mean	34.5	32.1	30.4	28.4	33.6
SD, SE	12.4, 3.7	10.6, 1.5	11.3, 1.6	9.5, 2.5	10.8, 1.8
95% CI of mean	(26.2, 42.9)	(29.0, 35.1)	(27.3, 33.6)	(23.0, 33.9)	(29.8, 37.3)
Median	36.0	30.0	30.5	28.5	35.5
Min, Max	13, 55	11, 52	11, 54	15, 47	11, 52
Change from Baseline to Week 12					
n	11	45	49	11	34
Mean	-1.5	-2.1	-3.0	-0.4	-2.7
SD, SE	6.1, 1.8	10.4, 1.5	5.2, 0.7	14.7, 4.4	8.7, 1.5
95% CI of mean	(-5.5, 2.6)	(-5.2, 1.0)	(-4.5, -1.5)	(-10.2, 9.5)	(-5.8, 0.3)
Median	-1.0	-3.0	-2.0	-4.0	-3.0
Min, Max	-13, 8	-21, 40	-21, 6	-14, 40	-21, 25
Within group difference p-value[d]	0.4466	0.1739	0.0002	0.9361	0.0802
LS Mean (SE)	-0.89 (2.32)	-2.02 (1.14)	-3.27 (1.10)	-	-
95% CI of LS Mean	(-5.50, 3.71)	(-4.29, 0.25)	(-5.45, -1.09)	-	-
LS Means Difference (SE)[e]	-	-1.13 (2.58)	-2.37 (2.57)	-	-
95% CI of LS Mean Difference[e]	-	(-6.25, 4.00)	(-7.48, 2.73)	-	-
ANCOVA p-value[e]	-	0.6636	0.3586	-	-
LS Means Difference (SE)[f]	-	-	-1.25 (1.59)	-	-
95% CI of LS Mean Difference[f]	-	-	(-4.40, 1.90)	-	-
ANCOVA p-value[f]	-	-	0.4342	-	-
Change from Baseline to Week 52					
n	10	42	48	9	33
Mean	-1.2	-3.0	-3.4	-4.7	-2.5
SD, SE	7.8, 2.5	8.5, 1.3	6.3, 0.9	6.4, 2.1	9.0, 1.6
95% CI of mean	(-6.7, 4.3)	(-5.6, -0.3)	(-5.2, -1.6)	(-9.6, 0.2)	(-5.7, 0.7)

Median	-1.5	-2.0	-3.5	-2.0	0.0
Min, Max	-14, 12	-25, 13	-13, 12	-15, 3	-25, 13
Within group difference p-value[d]	0.6364	0.0290	0.0005	0.0590	0.1212
LS Mean (SE)	-0.63 (2.29)	-2.84 (1.11)	-3.61 (1.05)	-	-
95% CI of LS Mean	(-5.18, 3.92)	(-5.05, -0.63)	(-5.69, -1.54)	-	-
LS Means Difference (SE)[e]	-	-2.21 (2.55)	-2.98 (2.53)	-	-
Within group difference p-value[d]	-	(-7.26, 2.85)	(-8.00, 2.04)	-	-
ANCOVA p-value[e]	-	0.3883	0.2411	-	-
LS Means Difference (SE)[f]	-	-	-0.78 (1.53)	-	-
95% CI of LS Mean Difference[f]	-	-	(-3.81, 2.26)	-	-
ANCOVA p-value[f]	-	-	0.6134	-	-

Key: ANCOVA, analysis of covariance; CI, confidence interval; LS, least squares; max, maximum; min, minimum; mITT, modified intent-to-treat; PBC, primary biliary cholangitis; SD, standard deviation; SE, standard error.
Notes: No imputation for missing data was used for this table.
[a]Analysis is based on initial dose (patients were enrolled to 2 mg or randomized to 5 mg or 10 mg). Beginning at the Week 12 visit, the initial dose could have been up- or down-titrated.
[b]Analysis consists of patients who had Initial Dose 5 mg and did not up-titrate during the remainder of the study.
[c]Analysis consists of patients who had Initial Dose 5 mg and up-titrated to 10 mg.
[d]P-value is based on a paired t-test of within patient difference between baseline value and post-baseline visit, for each treatment group.
[e]Difference between LS means, p-values, and CIs are estimated by comparing each seladelpar level in a pairwise manner to the 2 mg dose group using the ANCOVA model with treatment group as factor, baseline assessment as a covariate, and percent change from baseline as response variable.
[f]Difference between LS means, p-values, and CIs are estimated by comparing the seladelpar 5 mg dose group to the 10 mg dose group using the ANCOVA model with treatment group as factor, baseline assessment as a covariate, and percent change from baseline as response variable.
Source: Table 30, CB8025-21629 CSR (24)

(c) Tabulated data for the primary outcome (mean reduction in ALP from baseline) including variance data

The primary efficacy endpoint of mean (95% confidence intervals [CIs]) percent change in ALP from baseline to Week 8 was -41.4% (-45.1%, -37.7%) in the seladelpar 10 mg dose group. The change in the 10 mg dose group was significantly different from the change in the 2 mg dose group (p = 0.0021) and the 5 mg dose group (p = 0.0024) (24).

The absolute and mean percent change from baseline to 12 weeks and 52 weeks of treatment in ALP was a secondary efficacy endpoint in CB8025021629. Overall, patients receiving 10 mg of seladelpar over 12 weeks exhibited a pronounced decrease in ALP that was evident after the first two weeks of dosing and continued to progressively decrease through Week 12. Mean changes from baseline to the end of Week 12 were -43.2% 10 mg dose group (Table 48), corresponding to a mean change from baseline in ALP of -127.9 U/L (24).

After 12 weeks of dosing, patients initially randomised to the 5 mg dose group and not achieving a satisfactory ALP response (e.g, an ALP level that remains ≥1.67×ULN) could increase their dose to 10 mg (5/10 mg cohort). As shown in Table 48, at Week 52, the mean (95% CI) percent change in ALP for the 10 mg dose group was -44.2% (-48.7%, -39.7%). Patients in the 5/10 mg cohort (who were up-titrated from 5 to 10 mg) demonstrated a mean (95% CIs) percent change in ALP of -37.4% (-46.1%, -28.7%). These values correspond to mean changes from baseline in ALP of -133.8 U/L for the 10 mg dose group, and -146.5 U/L for the 5/10 mg cohorts (24).

Table 48: ALP baseline values and percent change from baseline to Week 12 and Week 52 (CB8025-21629, mITT Analysis Set)

	Initial Dose[a]			5 mg Cohort	
	2 mg (N = 11)	5 mg (N = 49)	10 mg (n = 52)	5/5 mg[b] (N = 14)	5/10 mg[c] (N = 35)
Baseline ALP (U/L, normal range 37-116 U/L)					
n	11	49	52	14	35
Mean	300.409	353.296	301.000	330.000	362.614
SD, SE	121.383, 36.598	192.823, 27.546	137.533, 19.072	286.706, 76.626	144.042, 24.348
95% CI of mean	(218.863, 381.955)	(297.911, 408.681)	(262.711, 339.289)	(164.461, 495.539)	(313.134, 412.094)
Median	229.500	286.500	249.500	251.500	322.500
Min, Max	194.50, 508.00	146.50, 1287.00	161.50, 861.00	167.00, 1287.00	146.50, 740.50
Change from Baseline to Week 12					
n	11	47	51	12	35
Mean	-22.56	-34.49	-43.20	-43.24	-31.49
SD, SE	13.92, 4.20	20.62, 3.01	12.39, 1.74	22.21, 6.41	19.47, 3.29
95% CI of mean	(-31.91, -13.20)	(-40.54, -28.43)	(-46.69, -39.72)	(-57.36, -29.13)	(-38.17, -24.80)
Median	-21.26	-35.85	-43.23	-46.11	-33.61
Min, Max	-47.5, 3.1	-72.6, 35.5	-67.9, -9.1	-72.6, 2.1	-60.4, 35.5
Within group difference p-value[d]	0.0050	<0.0001	<0.0001	0.0361	<0.0001
LS Mean (SE)	-22.94 (4.97)	-33.97 (2.43)	-43.60 (2.32)	-	-
95% CI of LS Mean	(-32.80, -13.07)	(-38.78, -29.16)	(-48.20, -38.99)	-	-
LS Means Difference (SE)[e]	-	-11.04 (5.55)	-20.66 (5.48)	-	-
95% CI of LS Mean Difference[e]	-	(-22.04, -0.03)	(-31.52, -9.80)	-	-
ANCOVA p-value[e]	-	0.0493	0.0003	-	-
LS Means Difference (SE)[f]	-	-	-9.63 (3.38)	-	-
95% CI of LS Mean Difference[f]	-	-	(-16.33, -2.92)	-	-
ANCOVA p-value[f]	-	-	0.0053	-	-
Change from Baseline to Week 52					
n	11	45	49	10	35
Mean	-32.72	-40.09	-44.19	-49.45	-37.41
SD, SE	22.48, 6.78	24.23, 3.61	15.52, 2.22	17.91, 5.66	25.33, 4.28
95% CI of mean	(-47.82, -17.61)	(-47.37, -32.81)	(-48.65, -39.73)	(-62.27, -36.64)	(-46.11, -28.71)
Median	-35.73	-46.33	-46.72	-50.89	-45.55
Min, Max	-63.2, 18.1	-80.0, 39.2	-69.8, -4.4	-80.0, -16.5	-70.3, 39.2
Within group difference p-value[d]	0.0105	<0.0001	<0.0001	0.0149	<0.0001

LS Mean (SE)	-33.08 (6.15)	-39.61 (3.07)	-44.55 (2.93)	-	-
95% CI of LS Mean	(-45.29, -20.87)	(-45.70, -33.52)	(-50.36, -38.73)	-	-
LS Means Difference (SE)[e]	-	-6.52 (6.90)	-11.46 (6.80)	-	-
Within group difference p-value[d]	-	(-20.21, 7.16)	(-24.95, 2.03)	-	-
ANCOVA p-value[e]	-	0.3466	0.0949	-	-
LS Means Difference (SE)[f]	-	-	-4.94 (4.28)	-	-
95% CI of LS Mean Difference[f]	-	-	(-13.43, 3.55)	-	-
ANCOVA p-value[f]	-	-	0.2510	-	-

Key: ALP, alkaline phosphatase; ANCOVA, analysis of covariance; CI, confidence interval; LOCF, last observation carried forward; LS, least squares; max, maximum; min, minimum; mITT, modified intent-to-treat; SD, standard deviation; SE, standard error.

Notes:

[a]Analysis is based on initial dose (patients were enrolled to 2 mg or randomized to 5 mg or 10 mg). Beginning at the Week 12 visit, the initial dose could have been up- or down-titrated.

[b]Analysis consists of patients who had Initial Dose 5 mg and did not up-titrate during the remainder of the study.

[c]Analysis consists of patients who had Initial Dose 5 mg and up-titrated to 10 mg.

[d]LOCF imputation is applied.

[e]P-value is based on a paired t-test of within patient difference between baseline value and post-baseline visit, for each treatment group.

[f]Difference between LS means, p-values and CIs are estimated by comparing each seladelpar level in a pairwise manner to the 2 mg dose group using the ANCOVA model with treatment group as factor, baseline assessment as a covariate, and percent change from baseline as response variable.

[g]Difference between LS means, p-values, and CIs are estimated by comparing the seladelpar 5 mg dose group to the 10 mg dose group using the ANCOVA model with treatment group as factor, baseline assessment as a covariate, and percent change from baseline as response variable.

Source: Table 10 and 11, CB8025-12629 CSR (24)

(d) Tabulated data for pruritus measures including variance data

In CB8025-21629, the pruritus visual analogue scale (VAS), 5-dimension (5-D) Itch scale, and PBC-40 QoL Questionnaire, were secondary efficacy outcomes used to evaluate the effects of seladelpar on pruritus. Results for the pruritus VAS and 5-D Itch scale are reported below. Results from the PBC-40 QoL Questionnaire have been described previously in (c) (24).

Visual Analogue Scale

Patients with PBC had a wide range of baseline pruritus severity as measured by pruritus VAS. Table 49 presents the baseline values and mean changes from baseline in the pruritus VAS after 12 and 52 weeks of dosing. At baseline, the seladelpar 10 mg group reported a median VAS score of 25.0 mm, respectively. Mean changes from baseline for the VAS score were -12.3 mm at Week 12 and -16.5 mm at Week 52 for the seladelpar 10 mg group. Mean changes from baseline in the 5/10 mg cohort was -11.1 mm at Week 12 and -11.8 mm at Week 52. At Week 52, a large proportion of patients in the seladelpar 5/10 mg 10 mg dose groups showed a marked reduction from baseline for the pruritus VAS (p = 0.0098 and p < 0.0001 in the 5/10 mg cohort and 10 mg dose group, respectively) (24).

5-D Itch Scale

As shown in Table 50, baseline total 5-D Itch Scale scores were similar at baseline. Seladelpar treatment was associated with mean reductions in the 5-D Itch Scale in all treatment groups at Week 12 and Week 52 (24).

Table 49: Pruritus Visual Analog Scale Baseline Observed Values and Change from Baseline (CB8025-21629, mITT Analysis Set)

	Initial Dose[a]			5 mg Cohort	
	2 mg (N = 11)	5 mg (N = 49)	10 mg (n = 52)	5/5 mg[b] (N = 14)	5/10 mg[c] (N = 35)
Baseline VAS Score (mm)					
n	11	48	52	14	34
Mean	15.3	23.3	30.1	17.8	25.5
SD, SE	18.3, 5.5	23.9, 3.4	28.4, 3.9	21.5, 5.7	24.7, 4.2
95% CI of mean	(3.0, 27.6)	(16.3, 30.2)	(22.2, 38.0)	(5.4, 30.2)	(16.9, 34.1)
Median	10.0	14.0	25.0	10.0	17.5
Min, Max	0, 57	0, 85	0, 90	0, 80	0, 85
Change from Baseline to Week 12 (mm)					
n	11	45	49	11	34
Mean	-3.7	-5.5	-12.3	12.0	-11.1
SD, SE	6.4, 1.9	25.0, 3.7	22.3, 3.2	24.0, 7.2	22.8, 3.9
95% CI of mean	(-8.0, 0.6)	(-13.0, 2.0)	(-18.7, -5.9)	(-4.1, 28.1)	(-19.1, -3.2)
Median	-5.0	0.0	-5.0	5.0	-3.0
Min, Max	-14, 8	-70, 70	-57, 62	-20, 70	-70, 32
Within group difference p-value[d]	0.0811	0.1473	0.0003	0.1282	0.0075
LS Mean (SE)	-8.7 (5.6)	-6.3 (2.8)	-10.4 (2.7)	-	-
95% CI of LS Mean	(-19.9, 2.4)	(-11.8, -0.8)	(-15.7, -5.2)	-	-
LS Means Difference (SE)[e]	-	2.5 (6.2)	-1.7 (6.2)	-	-
95% CI of LS Mean Difference[e]	-	(-9.9, 14.8)	(-14.1, 10.7)	-	-
ANCOVA p-value[e]	-	0.6952	0.7885	-	-
LS Means Difference (SE)[e]	-	-	-4.1 (3.8)	-	-
95% CI of LS Mean Difference	-	-	(-11.7, 3.5)	-	-
ANCOVA p-value[f]	-	-	0.2837	-	-
Change from Baseline to Week 52 (mm)					
n	10	42	48	9	33
Mean	-3.3	-9.6	-16.5	-1.6	-11.8
SD, SE	11.7, 3.7	22.5, 3.5	23.0, 3.3	8.8, 2.9	24.7, 4.3
95% CI of mean	(-11.7, 5.1)	(-16.6, -2.6)	(-23.1, -9.8)	(-8.3, 5.2)	(-20.5, -3.0)

Median	-1.5	-3.0	-6.0	-2.0	-5.0
Min, Max	-22, 20	-70, 40	-73, 35	-20, 13	-70, 40
Within group difference p-value[d]	0.3964	0.0086	<0.0001	0.6088	0.0098
LS Mean (SE)	-9.2 (4.9)	-10.0 (2.4)	-14.9 (2.2)	-	-
95% CI of LS Mean	(-18.9, 0.5)	(-14.7, -5.3)	(-19.3, -10.4)	-	-
LS Means Difference (SE)[e]	-	-0.8 (5.4)	-5.7 (5.4)	-	-
Within group difference p-value[d]	-	(-11.6, 10.0)	(-16.4, 5.1)	-	-
ANCOVA p-value[e]	-	0.8798	0.2966	-	-
LS Means Difference (SE)[f]	-	-	-4.8 (3.3)	-	-
95% CI of LS Mean Difference[f]	-	-	(-11.3, 1.6)	-	-
ANCOVA p-value[f]	-	-	0.1404	-	-

Key: ANCOVA, analysis of covariance; CI, confidence interval; LS, least squares; max, maximum; min, minimum; mITT, modified intent-to-treat; SD; standard deviation; SE; standard error; VAS; visual analog scale

Notes: No imputation for missing data was used for this table

[a]Analysis is based on initial dose (patients were enrolled to 2 mg or randomized to 5 mg or 10 mg). Beginning at the Week 12 visit, the initial dose could have been up- or down-titrated.

[b]Analysis consists of patients who had Initial Dose 5 mg and did not up-titrate during the remainder of the study.

[c]Analysis consists of patients who had Initial Dose 5 mg and up-titrated to 10 mg.

[d]P-value is based on a paired t-test of within patient difference between baseline value and post-baseline visit, for each treatment group.

[e]Difference between LS means, p-values, and CIs are estimated by comparing each seladelpar level in a pairwise manner to the 2 mg dose group using the ANCOVA model with treatment group as factor, baseline assessment as a covariate, and percent change from baseline as response variable.

[f]Difference between LS means, p-values, and CIs are estimated by comparing the seladelpar 5 mg dose group to the 10 mg dose group using the ANCOVA model with treatment group as factor, baseline assessment as a covariate, and percent change from baseline as response variable.

Source: Table 26, CB8025-21629 CSR (24)

Table 50: Total 5-D Itch Scale baseline values and change from baseline (CB8025-21629, mITT Analysis Set)

	Initial Dose[a]			5 mg Cohort	
	2 mg (N = 11)	**5 mg (N = 49)**	**10 mg (n = 52)**	**5/5 mg[b] (N = 14)**	**5/10 mg[c] (N = 35)**
Baseline					
n	8	36	39	9	27
Mean	12.6	12.1	13.3	11.0	12.4
SD, SE	4.8, 1.7	3.9, 0.6	4.4, 0.7	4.2, 1.4	3.7, 0.7
95% CI of mean	(8.6, 16.6)	(10.8, 13.4)	(11.9, 14.8)	(7.7, 14.3)	(11.0, 13.9)
Median	11.5	11.5	14.0	9.0	12.0
Min, Max	6, 21	6, 21	5, 23	7, 20	6, 21

Change from Baseline to Week 12					
n	6	27	27	5	22
Mean	-1.8	-0.9	-1.6	-1.0	-0.9
SD, SE	2.1, 0.9	3.5, 0.7	3.8, 0.7	3.9, 1.8	3.5, 0.7
95% CI of mean	(-4.1, 0.4)	(-2.3, 0.5)	(-3.0, -0.1)	(-5.9, 3.9)	(-2.4, 0.7)
Median	-2.0	0.0	-2.0	1.0	-1.0
Min, Max	-4, 1	-8, 7	-8, 10	-8, 1	-8, 7
Within group difference p-value[d]	0.0896	0.1972	0.0418	0.6004	0.2577
LS Mean (SE)	-1.4 (1.2)	-1.3 (0.6)	-1.3 (0.6)	-	-
95% CI of LS Mean	(-3.9, 1.0	(-2.4, -0.1)	(-2.4, -0.1)	-	-
LS Means Difference (SE)[e]	-	0.2 (1.4)	0.2 (1.3)	-	-
95% CI of LS Mean Diference[e]	-	(-2.6, 2.9)	(-2.5, 2.9)	-	-
ANCOVA p-value[e]	-	0.9035	0.8966	-	-
LS Means Difference (SE)[e]	-	-	0.0 (0.8)	-	-
95% CI of LS Mean Difference	-	-	(-1.6, 1.7)	-	-
ANCOVA p-value[f]	-	-	0.9897	-	-
Change from Baseline to Week 52					
n	7	27	24	4	23
Mean	-1.6	-2.3	-3.3	-4.5	-2.0
SD, SE	2.8, 1.1	4.2, 0.8	3.8, 0.8	4.9, 2.5	4.1, 0.8
95% CI of mean	(-4.2, 1.0)	(-4.0, -0.7)	(-5.0, -1.7)	(-12.3, 3.3)	(-3.7, -0.2)
Median	-2.0	-1.0	-3.0	-4.0	-1.0
Min, Max	-6, 2	-12, 4	-11, 3	-11.1	-12, 4
Within group difference p-value[d]	0.1908	0.0078	0.0003	0.1656	0.0311
LS Mean (SE)	-2.1 (1.2)	-2.6 (0.6)	-2.8 (0.6)	-	-
95% CI of LS Mean	(-4.5, 0.2)	(-3.9, -1.4)	(-4.1, -1.5)	-	-
LS Means Difference (SE)[e]	-	-0.5 (1.3)	-0.7 (1.4)	-	-
Within group difference p-value[d]	-	(-3.2, 2.1)	(-3.4, 2.0)	-	-
ANCOVA p-value[e]	-	0.6992	0.6076	-	-
LS Means Difference (SE)[f]	-	-	-0.2 (0.9)	-	-
95% CI of LS Mean Difference[f]	-	-	(-2.0, 1.6)	-	-
ANCOVA p-value[f]	-	-	0.8360	-	-

Key: 5-D = 5-Dimension; ANCOVA, analysis of covariance; CI, confidence interval; LS, least squares; max, maximum; min, minimum; mITT, modified intent-to-treat; n = number in category; N = number in treatment group; SD; standard deviation; SE; standard error; - = no value

Notes: No imputation for missing data was used for this table
[a]Analysis is based on initial dose (patients were enrolled to 2 mg or randomized to 5 mg or 10 mg). Beginning at the Week 12 visit, the initial dose could have been up- or down-titrated.
[b]Analysis consists of patients who had Initial Dose 5 mg and did not up-titrate during the remainder of the study.
[c]Analysis consists of patients who had Initial Dose 5 mg and up-titrated to 10 mg.
[d]P-value is based on a paired t-test of within patient difference between baseline value and post-baseline visit, for each treatment group.
[e]Difference between LS means, p-values, and CIs are estimated by comparing each seladelpar level in a pairwise manner to the 2 mg dose group using the ANCOVA model with treatment group as factor, baseline assessment as a covariate, and percent change from baseline as response variable.
[f]Difference between LS means, p-values, and CIs are estimated by comparing the seladelpar 5 mg dose group to the 10 mg dose group using the ANCOVA model with treatment group as factor, baseline assessment as a covariate, and percent change from baseline as response variable.
Source: Table 28, CB8025-21629 CSR (24)

A9. [PRIORITY] No evidence has been provided for the Phase 1b study mentioned in the CS on p.44. We have enquired above whether this is the NCT04950764 // CB8025-21838 study. If so, we believe there is safety data available from this study in people with PBC at the licensed dose of seladelpar. Please can you provide this in clear tables for our appraisal.

Company response: Study CB8025-21838 is an ongoing Phase 1b, 2-part, open-label, non-randomised study evaluating single (Part A) and multiple (Part B) oral doses of seladelpar 10 mg or less in patients with cirrhosis due to PBC and varying degrees of hepatic impairment. Hepatic impairment was assessed based on Child-Pugh (CP) classification at screening, with patients assigned into four cohorts corresponding to each CP class (CP-A without portal hypertension [PHT], CP-A with PHT, CP-B, or CP-C). At least 24 patients were intended to receive seladelpar treatment, with at least six patients in each cohort. In Part A, Cohorts 1 to 4 were designed to use staggered enrollment for dosing with a single oral dose of seladelpar 10 mg. Participation in Part B was limited to Cohort 2 (CP-A with PHT) and Cohort 3 (CP-B) patients who had completed Part A. The patients in Part B received multiple oral doses of seladelpar for 28 days. Each patient's individualised dosing was based on their respective seladelpar exposure in Part A, with the potential to range from 1 to 10 mg once daily or 1 to 5 mg once every other day.

The company did not provide evidence for the Phase 1b study in the Company Evidence Submission. This study was not identified in the clinical SLR, and does not fully align with the scope of the decision problem for this appraisal. The restricted study population (PBC patients with hepatic impairment), low number of patients (24 patients in total), short time frame of the trial (28 days), and the limited additional insights on safety versus the pivotal studies, meant that inclusion of the evidence in the Company Evidence Submission was not appropriate.

Safety data from this study in patients with PBC at the 10 mg dose of seladelpar is currently not available in the public domain. The *'Data on File – Integrated Study Report'* provides a summary of safety data based on an interim cut-off date of 13th October 2023. As detailed in the report, single doses of seladelpar 10 mg and multiple doses of 5 mg (n=2) or 10 mg (n=10) for 28 days once daily appeared safe and well tolerated by patients with PBC and varying degrees of hepatic impairment in this study.

There were no deaths or TEAEs that led to discontinuation of study treatment or withdrawal of the study. Two treatment-emergent SAEs of bronchitis and generalised oedema were assessed as unrelated to study drug by the Investigator. There were no safety concerns based on changes in laboratory values , vital signs, ECG, or physical examination.

A10. How did you determine that people receiving UDCA at the start of RESPONSE and NCT02955602 were experiencing an inadequate response?

Company response: There is no international consensus definition for an inadequate response to UDCA. As highlighted in Table 4 of the Company Evidence Submission (see Table 51 below), several definitions of biochemical response to UDCA have been proposed to define an inadequate response to treatment.

Table 51: Commonly referenced criteria for assessing response to UDCA monotherapy in PBC (Table 4, Company Evidence Submission)

Global Providers	Biochemical Response Criteria
Barcelona (26)	ALP decrease of 40% or normalization of ALP
Paris I (26)	ALP 3x ULN; AST 2x ULN; and total bilirubin 1 mg/dL
Paris II (26)	ALP 1.5x ULN; AST 1.5x ULN; and total bilirubin 1 mg/dL
POISE (27)	ALP <1.67x ULN, ALP decrease ≥15%, and total bilirubin ≤1.0x ULN
Rochester (26)	ALP 2x ULN
Rotterdam (26)	Total bilirubin <1x ULN and albumin >1x LLN
Toronto (26)	ALP 1.67x ULN

Key: ALP: alkaline phosphatase; AST: aspartate aminotransferase; LLN, lower limit of normal; PBC: primary biliary cholangitis; POISE: PBC OCA International Study of Efficacy; ULN: upper limit of normal

While there is no agreement on the international definition of an inadequate response to UDCA, there is consensus that the two most important parameters in evaluating response to UDCA are ALP and total bilirubin (28). In RESPONSE and NCT02955602, ALP ≥ 1.67× ULN and total bilirubin ≤ 2× ULN were key eligibility criteria used to determine that patients entering the studies were experiencing an inadequate response to UDCA (23, 24, 29, 30). This is in alignment with the key eligibility criteria used in the POISE and ELATIVE studies of ocaliva (OCA) and elafibranor, respectively (27, 31), and the current definition of an inadequate response to UDCA referred to in the BSG/UK-PBC primary biliary cholangitis treatment and management guidelines (32).

A11. Can we please have outcome data for the following subgroup analyses in RESPONSE (i.e. we note that these are presented in forest plots in Appendix C but we would like outcome data for each subgroup category): baseline ALP and cirrhosis.

Company response: A summary of the subgroup analyses in RESPONSE for the primary and key secondary endpoints for the baseline ALP (< 350 U/L vs. ≥ 350 U/L) and cirrhosis status (yes vs no) subgroups are provided below in Table 52 - Table 57.

Of note, for study purposes, cirrhosis was defined using the following criteria (one or more):

- Historical liver biopsy demonstrating cirrhosis (e.g., Ludwig Stage 4 or Ishak Stage 5)
- Current or prior history of decompensated liver disease, including ascites, hepatic encephalopathy, esophageal varices, or other clinical conditions consistent with liver cirrhosis and/or PHT,
- • Liver stiffness > 16.9 kPa by FibroScan at Screening
- • Combination of platelets < 140× 10^3/μL with the following:
    - Serum albumin < 3.5 g/dL
    - INR > 1.3 (not due to antithrombotic agent use)
    - Total bilirubin > 1.0× ULN
- The presence of radiological evidence of cirrhosis (nodular liver) with concurrent splenomegaly
- Clinical determination by the Investigator

Results of subgroup analyses of the primary outcome

As highlighted in Section 2.8 of the Company Evidence Submission, the effect of seladelpar on the primary efficacy endpoint was observed to be similar across subgroups. One exception to this was in the subgroup of patients with baseline ALP ≥350 U/L, in which the proportion of responders in the seladelpar arm was lower compared with that in patients with baseline ALP <350 U/L (22.9% vs 76.3%, respectively) (Table 52). This finding was not unexpected as greater reductions in ALP

levels are required to achieve the ALP < 1.67x ULN component of the composite biochemical response endpoint for patients with elevated ALP values at baseline (23).

Table 52: Subgroup analysis of composite endpoint response rate at Month 12 by baseline ALP group (RESPONSE, ITT Analysis Set)

	Baseline ALP (< 350 U/L)		Baseline ALP (≥ 350 U/L)	
	Placebo (n=65)	Seladelpar 10 mg (n=128)	Placebo (n=65)	Seladelpar 10 mg (n=128)
N	47	93	18	35
Patients who achieved response at Month 12, n (%)[ab]	11 (23.4)	71 (76.3)	2 (11.1)	8 (22.9)
Wald 95% CI for Response Rate	11.3, 35.5	67.7, 85.0	(0.0, 25.6)	(8.9, 36.8)
Risk Difference (%) (Miettinen-Nurminen 95% CI)	-	52.9 (36.4, 66.0)	-	11.7 (-12.9, 31.0)
CMH test p-value[c]	-	< 0.0001	-	0.3192
Mantel-Fleiss Criterion	-	19.5	-	3.4
Breslow-Day p-value	-	0.2754	-	0.0613
Response Category at Month 12, n (%)				
ALP < 1.67 x ULN	15 (31.9)	76 (81.7)	2 (11.1)	8 (22.9)
≥15% decrease in ALP	14 (29.8)	80 (86.0)	7 (38.9)	27 (77.1)
Total bilirubin ≤ ULN	34 (72.3)	78 (83.9)	16 (88.9)	26 (74.3)

Abbreviations: ALP = alkaline phosphatase, TB = total bilirubin, ULN = upper limit of normal, CMH = Cochran Mantel Haenszel, CI = confidence interval.
N=total number of patients. n=number of patients in the category.
Subgroup analyses are only performed when there are at least 5 patients in each treatment group.
Percentages are based on the number of patients in the subgroup.
[a] A patient is designated a responder if the following condition was met: ALP <= 1.0 x ULN.
[b] Patients with missing data at the specified time point for response evaluation are considered non-responders.
[c] Two-sided p-value for pair-wise comparison is based on the Cochran Mantel Haenszel test adjusted for the stratification variable (baseline pruritus NRS: < 4 and >= 4). Breslow-Day test is used to check the homogeneity of treatment effects across stratum. Mantel-Fleiss criterion is used to assess the validity of the chi-square approximation for the distribution of the Mantel-Haenszel statistic.
Source: Tables 14.2.2.3, RESPONSE CSR (23)

Table 53: Subgroup analysis of composite response endpoint rate at Month 12 by cirrhosis status (RESPONSE, ITT Analysis Set)

	Cirrhosis (Yes)		Cirrhosis (No)	
	Placebo (n=65)	Seladelpar 10 mg (n=128)	Placebo (n=65)	Seladelpar 10 mg (n=128)
N	9	18	56	110
Patients who achieved response at Month 12, n (%)[ab]	2 (22.2)	7 (38.9)	11 (19.6)	72 (65.5)
Wald 95% CI for Response Rate	(0.0, 49.4)	(16.4, 61.4)	(9.2, 30.0)	(56.6, 74.3)

Risk Difference (%) (Miettinen-Nurminen 95% CI)	-	16.7 (-22.7, 47.1)	-	45.8 (30.8, 58.1)
CMH test p-value[c]		0.5202		< 0.0001
Mantel-Fleiss Criterion	-	2.7	-	22.2
Breslow-Day p-value	-	0.0047	-	0.3667
Response Category at Month 12, n (%)				
ALP < 1.67 x ULN	2 (22.2)	10 (55.6)	15 (26.8)	74 (67.3)
≥15% decrease in ALP	2 (22.2)	14 (77.8)	19 (33.9)	93 (84.5)
Total bilirubin ≤ ULN	3 (33.3)	11 (61.1)	47 (83.9)	93 (84.5)

Abbreviations: ALP = alkaline phosphatase, TB = total bilirubin, ULN = upper limit of normal, CMH = Cochran Mantel Haenszel, CI= confidence interval. N=total number of patients. n=number of patients in the category. Subgroup analyses are only performed when there are at least 5 patients in each treatment group. Percentages are based on the number of patients in the subgroup.
[a] A patient is designated a responder if the following condition was met: ALP <= 1.0 x ULN.
[b] Patients with missing data at the specified time point for response evaluation are considered non-responders.
[c] Two-sided p-value for pair-wise comparison is based on the Cochran Mantel Haenszel test adjusted for the stratification variable (baseline pruritus NRS: < 4 and >= 4). Breslow-Day test is used to check the homogeneity of treatment effects across stratum. Mantel-Fleiss criterion is used to assess the validity of the chi-square approximation for the distribution of the Mantel-Haenszel statistic.
Source: Tables 14.2.2.6, RESPONSE CSR (23)

Results of subgroup analyses of key secondary outcomes

ALP normalisation at Month 12

As highlighted in Section 2.8 of the Company Evidence Submission, the effect of seladelpar on the key secondary efficacy endpoint of ALP normalisation at month 12 was observed to be similar across subgroups. One exception to this was in the subgroup of patients with baseline ALP ≥350 U/L, in which no patients achieved ALP normalisation. This finding was not unexpected considering that the number of patients in this subgroup was small, and that patients with markedly elevated ALP values at baseline require greater reductions in ALP levels to achieve normalisation (23).

Table 54: Subgroup analysis of normalisation of ALP response rate at Month 12 by baseline ALP group (RESPONSE, ITT Analysis Set)

	Baseline ALP (< 350 U/L)		Baseline ALP (≥ 350 U/L)	
	Placebo (n=65)	Seladelpar 10 mg (n=128)	Placebo (n=65)	Seladelpar 10 mg (n=128)
N	47	93	18	35
Patients who achieved response at Month 12, n (%)[ab]	0	32 (34.4)	0	0
Wald 95% CI for Response Rate	0.0, 0.0	24.8, 44.1	0.0, 0.0	0.0, 0.0
Risk Difference (%) (Miettinen-Nurminen 95% CI)	-	34.4 (25.5, 44.5)	-	0
CMH test p-value[c]	-	<0.0001	-	NE

Mantel-Fleiss Criterion	-	10.8	-	NE
Breslow-Day p-value	-	NE	-	NE

Key: ALP, alkaline phosphatase; ULN, upper limit of normal; CMH, Cochran Mantel Haenszel; CI, confidence interval.
Notes: Subgroup analyses are only performed when there are at least five patients in each treatment group. Percentages are based on the number of patients in the subgroup.
[a]A patient is designated a responder if the following condition was met: ALP <= 1.0 x ULN.
[b]patients with missing data at the specified time point for response evaluation are considered non-responders.
[c]Two-sided p-value for pair-wise comparison is based on the Cochran Mantel Haenszel test adjusted for the stratification variable (baseline pruritus NRS: < 4 and >= 4). Breslow-Day test is used to check the homogeneity of treatment effects across stratum. Mantel-Fleiss criterion is used to assess the validity of the chi-square approximation for the distribution of the Mantel-Haenszel statistic.
Source: Table 14.2.4.3, RESPONSE CSR (23)

Table 55: Subgroup analysis of normalisation of ALP response rate at Month 12 by cirrhosis status (RESPONSE, ITT Analysis Set)

	Cirrhosis (Yes)		Cirrhosis (No)	
	Placebo (N=65)	Seladelpar 10 mg (N=128)	Placebo (N=65)	Seladelpar 10 mg (N=128)
N	9	18	56	110
Patients who achieved response at Month 12, n (%)[ab]	0	1 (5.6)	0	31 (28.2)
Wald 95% CI for Response Rate	0.0, 0.0	0.0, 16.1	0.0, 0.0	19.8, 36.6
Risk Difference (%) (Miettinen-Nurminen 95% CI)	-	5.6 (-25.8, 26.3)	-	28.2 (20.6, 37.2)
CMH test p-value[c]	-	0.5403	-	<0.0001
Mantel-Fleiss Criterion	-	0.3	-	10.5
Breslow-Day p-value	-	NE	-	NE

Key: ALP, alkaline phosphatase; ULN, upper limit of normal; CMH, Cochran Mantel Haenszel; CI, confidence interval.
Notes: Subgroup analyses are only performed when there are at least five patients in each treatment group. Percentages are based on the number of patients in the subgroup.
[a]A patient is designated a responder if the following condition was met: ALP <= 1.0 x ULN.
[b]patients with missing data at the specified time point for response evaluation are considered non-responders.
[c]Two-sided p-value for pair-wise comparison is based on the Cochran Mantel Haenszel test adjusted for the stratification variable (baseline pruritus NRS: < 4 and >= 4). Breslow-Day test is used to check the homogeneity of treatment effects across stratum. Mantel-Fleiss criterion is used to assess the validity of the chi-square approximation for the distribution of the Mantel-Haenszel statistic.
Source: Table 14.2.6.3, RESPONSE CSR (23)

Change from baseline in mean Pruritus NRS score at Month 6

As highlighted in Section 2.8, the effect of seladelpar on the key secondary efficacy endpoint of change from baseline in mean Pruritus NRS score at Month 6 was observed to be similar across subgroups. However, in many of these subgroups the sample sizes were small (23).

Table 56: Subgroup MMRM analysis of Pruritus NRS change at Month 6 by baseline ALP group (RESPONSE, MSPN Analysis Set)

	Baseline ALP (< 350 U/L)		Baseline ALP (≥ 350 U/L)	
	Placebo (n=65)	Seladelpar 10 mg (n=128)	Placebo (n=65)	Seladelpar 10 mg (n=128)

Baseline				
N	14	29	9	20
Mean (SD)	6.7 (1.51)	5.8 (1.36)	6.6 (1.42)	6.6 (1.40)
Median	7.1	5.6	6.5	6.7
Q1, Q3	5.6, 7.7	4.7, 7.1	5.6, 7.6	5.5, 7.8
Min, Max	4, 9	4, 8	5, 9	4, 9
Month 6 Change from Baseline[a]				
N	12	26	8	19
Mean (SD)	-2.0 (2.14)	-3.1 (1.94)	-1.8 (1.77)	-3.2 (2.29)
Median	-1.6	-3.1	-1.9	-2.6
Q1, Q3	-3.6, -0.6	-4.2, -2.3	-2.8, -0.3	-5.3, -1.9
Min, Max	-6, 1	-8, 2	-5, 1	-7, 1
LS Mean (SE)[b]	-1.6 (0.53)	-3.2 (0.36)	-1.8 (0.68)	-3.2 (0.46)
LS Mean of Difference (95% CI)	-	-1.5 (-2.8, -0.2)	-	-1.4 (-3.1, 0.3)
p-value	-	0.0234	-	0.0977

Key: ALP, alkaline phosphatase; CI, confidence interval; MMRM, Mixed-Effect Model Repeated Measure; MSPN, moderate-to-severe Pruritus NRS; NRS, numerical rating scale.
Notes: Baseline pruritus NRS is defined as the mean of all daily recorded scores during the Run-in Period and on Day 1. Subgroup analyses are only performed when there are at least five patients in each treatment group.
[a]Missing assessment at specific timepoint is imputed as an average of the two adjacent weekly averages (at most one week apart); if only one adjacent weekly average is available it is imputed by the available adjacent weekly average; if no adjacent weekly average is available it is not imputed. Data collected after Month 6 are not used for imputation.
[b]Change from baseline is estimated by Mixed-Effect Model Repeated Measure (MMRM) model including terms for baseline NRS, treatment group, week, and treatment-by-week interaction. Unstructured covariance structure is applied for the repeated measure and Kenward-Roger correction is applied for the denominator degrees of freedom.
Source: Table 14.2.6.3, RESPONSE CSR (23)

Table 57: Subgroup MMRM analysis of Pruritus NRS change from baseline at Month 6 by cirrhosis status (RESPONSE, MSPN Analysis Set)

	Cirrhosis (Yes)		Cirrhosis (No)	
	Placebo (N=65)	**Seladelpar 10 mg (N=128)**	**Placebo (N=65)**	**Seladelpar 10 mg (N=128)**
Baseline				
N	5	6	18	43
Mean (SD)	6.0 (1.20)	7.1 (1.58)	6.8 (1.49)	6.0 (1.36)
Median	6.1	7.4	7.1	5.7
Q1, Q3	4.9, 7.1	5.9, 8.5	5.6, 8.0	4.9, 7.1
Min, Max	5, 7	5, 9	4, 9	4, 9
Month 6 Change from Baseline[a]				
N	4	5	16	40
Mean (SD)	-1.9 (1.73)	-1.9 (2.60)	-1.9 (2.06)	-3.3 (1.99)
Median	-1.6	-1.7	-1.9	-3.1
Q1, Q3	-3.1, -0.7	-3.6, -1.2	-3.3, -0.3	-4.5, -2.1
Min, Max	-4, 0	-5, 2	-6, 1	-8, 1
LS Mean (SE)[b]	-1.9, (1.07)	-2.3 (1.00)	-1.4 (0.45)	-3.4 (0.29)
LS Mean of Difference (95% CI)	-	-0.4 (-3.8, 3.0)	-	-2.0 (-3.1, -0.9)
p-value	-	0.7946	-	0.0005

Key: ALP, alkaline phosphatase; CI, confidence interval; MMRM, Mixed-Effect Model Repeated Measure; MSPN, moderate-to-severe Pruritus NRS; NRS, numerical rating scale.
Notes: Baseline pruritus NRS is defined as the mean of all daily recorded scores during the Run-in Period and on Day 1. Subgroup analyses are only performed when there are at least five patients in each treatment group.

[a]Missing assessment at specific timepoint is imputed as an average of the two adjacent weekly averages (at most one week apart); if only one adjacent weekly average is available it is imputed by the available adjacent weekly average; if no adjacent weekly average is available it is not imputed. Data collected after Month 6 are not used for imputation.
[b]Change from baseline is estimated by Mixed-Effect Model Repeated Measure (MMRM) model including terms for baseline NRS, treatment group, week, and treatment-by-week interaction. Unstructured covariance structure is applied for the repeated measure and Kenward-Roger correction is applied for the denominator degrees of freedom.
Source: Table 14.2.6.5, RESPONSE CSR (23)

A12. Were subgroup analyses conducted as part of ASSURE? If so, please report these data.

Company response: Efficacy and safety analyses for subpopulations of ASSURE and its parent studies, as of the June 29th 2023 data cut-off, are provided in the *'Data on File – Integrated Study Report'*. Efficacy and safety analyses of ASSURE and its parent studies are presented for the following key subpopulations:

- **Monotherapy**: For patients from RESPONSE, this was defined as patients not receiving UDCA at the time of enrolment into RESPONSE. For patients from legacy studies, this was defined as patients who were considered intolerant to UDCA upon entry into ASSURE.

- **Cirrhosis**: For patients from RESPONSE, this was defined as patients with confirmed cirrhosis at the time of enrolment into RESPONSE. For patients from legacy studies, this was defined as patients with confirmed cirrhosis upon entry to ASSURE.

- **Total bilirubin > 1x ULN**: For patients from study RESPONSE this was defined as patients with total bilirubin > 1× ULN at the time of enrolment into RESPONSE. For patients from legacy studies, this was defined as patients with total bilirubin > 1× ULN upon entry to ASSURE.

Given the high volume of tabulated information provided in *'Data on File – Integrated Study Report'*, we have provided a written summary of the efficacy results from the key subpopulations below, supplemented with references to the appropriate tables in the report. We have done this to ensure the EAG can find the appropriate information without diluting the key points. Of note, the interpretation of some of these data is limited by small sample sizes.

- Among monotherapy patients enrolled in RESPONSE, only seven (one crossover and six continuous patients) had enrolled in ASSURE at the time of

the data cutoff date. An additional six patients from legacy studies were also analysed as a monotherapy subpopulation. While interpretation of efficacy is limited by the small number of patients, there were patients from both RESPONSE (Table 19) and legacy studies (Table 20) who were composite biochemical responders, and there were patients that achieved ALP normalisation while receiving seladelpar (Table 27 and Table 28). Changes in biochemical parameters followed a similar pattern to what was observed in the overall population with decreases from baseline values in ALP, GGT, and ALT for the monotherapy patients from the legacy studies (Table 14.2.4.3.1 and Table 14.2.4.4.1).

- Among cirrhosis patients enrolled in RESPONSE, 11 (four crossover and seven continuous patients) had enrolled in ASSURE at the time of the data cutoff date. Thirty-three patients from the legacy studies enrolled in ASSURE. While the number of crossover and continuous patients from RESPONSE is too small to make a meaningful comparison for the composite biochemical response rate (Table 21), the trend of crossover patients only achieving ALP normalization once they started receiving seladelpar was consistent with the overall population (Table 29). The proportion of responders in the seladelpar arm was lower compared with that in the overall population. This finding was not unexpected as baseline ALP levels were higher in the cirrhosis subpopulation compared with those in the overall RESPONSE population. Among patients with cirrhosis enrolled in ASSURE from the legacy studies, 65.6% of patients achieved the composite biochemical response (Table 22) and 50.0% of patients achieved ALP normalization after three months of treatment (Table 30). This is similar to what was observed both in RESPONSE and in the overall study population of legacy patients in ASSURE. For all patients, laboratory parameters showed decreases from baseline for ALP, GGT, and ALT, with bilirubin levels being stable over time (Table 14.2.4.3.2 and Table 14.2.4.4.2).

- Of the 25 patients with total bilirubin > 1× ULN enrolled in RESPONSE, 12 patients (two crossover and 10 continuous) had enrolled in ASSURE at the time of the data cutoff date. Fifty percent of crossover patients and 30.0% of continuous seladelpar patients after one month of seladelpar treatment in

ASSURE achieved the composite biochemical response (Table 23), and only one continuous seladelpar patient achieved ALP normalization in ASSURE (Table 31). A total of 24 patients with total bilirubin > 1× ULN had enrolled from the legacy studies. After three months of seladelpar treatment in ASSURE, 21.7% of patients in this subpopulation from the legacy studies achieved a composite biochemical response (Table 24) and 17.4% achieved ALP normalization (Table 32). The proportion of responders in this subpopulation was lower than that in the overall population for both parent study groups, which was not unexpected as baseline ALP levels were higher, and patients with higher baseline ALP require greater reductions to achieve the 1.67× ULN component of the composite endpoint or ALP normalization. Total bilirubin was also higher in this subpopulation in RESPONSE and legacy parent study groups, which may have played a role in the composite biochemical response results. Generally, patients in this subpopulation showed decreases from baseline for ALP, GGT, total bilirubin, and ALT, consistent with the overall population (Table 14.2.4.3.3 and Table 14.2.4.4.3).

Exposure-adjusted patient incidence of TEAEs was examined for the aforementioned key subpopulations by parent study and year of treatment. Patient incidence for each subpopulation was generally comparable to the overall exposure-adjusted AE profile in years 1 and 2 of seladelpar treatment; however, due to small sample sizes, intepretation was limited.

Of note, a baseline pruritus NRS ≥ 4 subpopulation was analysed only for patients from legacy studies in ASSURE. Baseline pruritus NRS was defined as the mean of all daily recorded scores from 14 days prior to first dose up to Day 1. Results can be accessed in '*Data on File – Integrated Study Report*'.

Data on the interim efficacy and safety results in PBC patients with compensated cirrhosis enrolled in the ASSURE study for the most recent data cut-off (January 31st 2024) was presented as an oral presentation at the European Association for the Study of the Liver (EASL) Congress in Milan, Italy, on June 5th-8th 2024 (33). However, the level of evidence is restricted to the cirrhosis subpopulation for legacy patients only, and the level of evidence reported in the presentation is limited; there is no associated publication for this source.

A13. On p.73 of the CS, you state that "Complete quality assessments for each study are presented in Appendix B1.3". In the appendix, no assessment is presented for RESPONSE. Moreover, checklists provided are yes/no/UTD responses only, without (a) details of the rationale for the decision and (b) detail regarding variation in response across outcomes (as per best practice, critical appraisal should always be conducted at the outcome-level, but we will accept some discussion of any variation in response across outcome and follow-up timepoint).

(a) [PRIORITY] Please submit a complete critical appraisal checklist for RESPONSE including the details specified in (a) and (b)

(b) Please (re-)submit critical appraisal checklists for the remaining studies of seladelpar and include the details specified in (a) and (b).

Company response:

(a) The complete risk of bias assessment for RESPONSE using Cochrane ROB 2.0 is provided below in Table 58.

Table 58: Risk of bias assessment - RESPONSE

Randomization process	1.1 Was allocation sequence random?	Yes; A random component was used in the sequence generation process. The randomization procedure will be performed centrally via an interactive web response system (IWRS)
	1.2 Was allocation concealed?	Yes; The interactive web response system (IWRS) was utilized to allocate interventions to participants, where the process of allocation is controlled by an external unit or organization, independent of the enrolment personnel (e.g. independent central pharmacy, telephone or internet-based randomization service providers).
	1.3 Did baseline differences between groups suggest a problem?	PN; Demographics were generally balanced between the two treatment arms, with differences observed in region (North America and Latin

		America) and ethnicity (Hispanic/Latino)
	Assesor's Judgement	Low risk
Deviations from intended interventions	2.1 Were participants aware of assigned intervention?	No; This was a double-blind trial; the Sponsor study team members responsible for oversight, study patients, Investigators, and all site personnel were blinded to treatment assignment
	2.2 Were carers aware of assigned intervention?	No; This was a double-blind trial; the Sponsor study team members responsible for oversight, study patients, Investigators, and all site personnel were blinded to treatment assignment
	2.3 If Y/PY/NI to 2.1 or 2.2: Were there deviations from the intended intervention?	NA
	2.4 If Y/PY to 2.3: Were these deviations likely to have affected the outcome?	NA
	2.5 If Y/PY/NI to 2.4: Were these deviations balanced between groups?	NA
	2.6 Was an appropriate analysis used to estimate the effect of assignment to intervention?	Yes; Both ITT and modified ITT were used to estimate the effect of assignment to intervention
	2.7 If N/PN/NI to 2.6: Was there potential for a substantial impact (on the result) of the failure to analyze participants in the group to which they were randomized?	NA
	Assessor's Judgement	Low risk
Missing outcome data	3.1 Were data for this outcome available for all, or nearly all, participants randomized?	Yes; ITT analysis was used for binary or dichotomous outcomes i.e., composite response, ALP normalization, and Toronto-I; Continuous outcomes (ALP change from baseline) used the ITT analysis set for completers
	3.2 If N/PN/NI to 3.1: Is there evidence that the result was	NA

	not biased by missing outcome data?	
	3.3 If N/PN to 3.2: Could missingness in the outcome depend on its value?	NA
	3.4 If Y/PY/NI to 3.3: Is it likely that missingness in the outcome depended on its true value?	NA
	Assessor's Judgement	Low risk
Measurement of the outcome	4.1 Was the method of measuring the outcome inappropriate?	No; All outcomes along with the method of assessment are pre-specified in the protocol
	4.2 Could measurement or ascertainment of the outcome have differed between intervention groups?	No; In all outcomes, similar measurement methods and thresholds were used at comparable time points
	4.3 If N/PN/NI to 4.1 and 4.2: Were outcome assessors aware of the intervention received by study participants?	No; This was a double-blind trial; the Sponsor study team members responsible for oversight, study patients, Investigators, and all site personnel were blinded to treatment assignment
	4.4 If Y/PY/NI to 4.3: Could assessment of the outcome have been influenced by knowledge of intervention received?	NA
	4.5 If Y/PY/NI to 4.4: Is it likely that assessment of the outcome was influenced by knowledge of intervention received?	NA
	Assessor's Judgement	Low risk
Selection of the reported result	5.1 Were the data that produced this result analysed in accordance with a pre-specified analysis plan that was finalized before unblinded outcome data were available for analysis?	Yes; All outcomes were pre-specified in the statistical analysis plan or protocol

	5.2 Is the numerical result being assessed likely to have been selected, on the basis of the results, from outcome measurements (e.g. scales, definitions, time points) within the outcome domain?	No; The numerical result was derived from pre-specified outcome measurements, with no evidence of selective reporting based on scale, definition, or time point, as outlined in the trial protocol and statistical analysis plan
	5.3 Is the numerical result being assessed likely to have been selected, on the basis of the results, from multiple eligible analyses of the data?	No; The numerical result was generated from a pre-specified analysis method, with no indication that it was selected from multiple eligible analyses based on the results
	Assessor's Judgement	Low risk
	Assessor's overall Judgement	Low risk

(b) Updated critical appraisals for ASSURE, CB8025-21629, and CB8025-31731 are provided below. For each study, two reviewers conducted the critical appraisal. The reviewers worked independently before coming together to discuss and agree the assessment findings. Differing opinions of the reviewers were solved through discussion, with a senior team member casting a deciding vote on any discrepancies. No disagreements occurred during screening.

ASSURE (Interim CSR [dated 13th November 2023])

Description of criteria	Response	Rationale
Is the hypothesis/aim/objective of the study clearly described?	Yes	To evaluate the long-term safety and efficacy of seladelpar 10 mg in patients with PBC.
Are the main outcomes to be measured clearly described in the Introduction or Methods section?	Yes	Main outcomes clearly described in interim CSR
Are the characteristics of the patients included in the study clearly described?	Yes	Baseline characteristics are clearly described in interim CSR
Are the interventions of interest clearly described?	Yes	Single seladelpar 10 mg dose cohort analysed in the Primary Analysis Population
Are the distributions of principal confounders in each group of patients to be compared clearly described?	N/A	Single seladelpar 10 mg dose cohort analysed in the Primary Analysis Population
Are the main findings of the study clearly described?	Yes	Safety results clearly outlined in interim CSR
Does the study provide estimates of the random variability in the data for the main outcomes?	Yes	Descriptive statistics for continuous variables consist of mean, SD, median and range, and include count and proportion for categorical variables
Have all important adverse events that may be a consequence of the intervention been reported?	Yes	The safety and tolerability endpoints were assessed by TEAEs as well as biochemistry and haematology laboratory results.
Have the characteristics of patients lost to follow-up been described?	Yes	Study discontinuations are provided in the interim CSR
Have actual probability values been reported (e.g., 0.035 rather than <0.05) for the main outcomes except where the probability is less than 0.001?	No	Results were characterised by descriptive statistics.
Were the patients asked to participate in the study representative of the entire population from which they were recruited?	Yes	Study recruited adults with primary biliary cholangitis (PBC) at risk of disease progression (ALP ≥1.67 x ULN) who were receiving or intolerant to ursodeoxycholic acid
Were those patients who were prepared to participate	UTD	Disposition of patients according to clinical trial site location not

representative of the entire population from which they were recruited?		disclosed
Were the staff, places, and facilities where the patients were treated, representative of the treatment the majority of patients receive?	UTD	All study visits occurred in clinic; detail of staff, places and facilities not presented
Was an attempt made to blind study patients to the intervention they have received?	No	Open-label study
Was an attempt made to blind those measuring the main outcomes of the intervention?	No	Open-label study
If any of the results of the study were based on “data dredging”, was this made clear?	UTD	Unclear without additional analysis of results
In trials and cohort studies, do the analyses adjust for different lengths of follow-up of patients, or in case control studies, is the time period between the intervention and outcome the same for cases and controls?	Yes	Number of patients with measurements at each timepoint is disclosed alongside the results
Were the statistical tests used to assess the main outcomes appropriate?	Yes	Descriptive statistics for continuous variables consist of mean, SD, median and range, and include count and proportion for categorical variables
Was compliance with the intervention/s reliable?	UTD	Compliance with seladelpar and/or UDCA not disclosed
Were the main outcome measures used accurate (valid and reliable)?	Yes	Aligned with historical clinical studies in PBC
Were the patients in different intervention groups (trials and cohort studies) or were the cases and controls (case-control studies) recruited from the same population?	N/A	Open-label study
Were study patients in different intervention groups (trials and cohort studies) or were the cases and controls (case-control studies) recruited over the same time?	N/A	Open-label study
Were study patients randomised to intervention groups?	N/A	Open-label study
Was the randomised intervention assignment concealed	N/A	Open-label study

from both patients and health care staff until recruitment was complete and irrevocable?		
Was there adequate adjustment for confounding in the analyses from which the main findings were drawn?	No	Adjustments for confounding factors in the analyses were not disclosed
Were losses of patients to follow-up taken into account?	Yes	Results only presented for all patients with outcomes at selected study timepoints
Did the study have sufficient power to detect a clinically important effect where the probability value for a difference being due to chance?	UTD	There was no formal sample size justification for the study, so unclear if study was sufficiently powered.

CB8025-21629 (Bowlus *et al*. [2024])

Description of criteria	Response	Rationale
Is the hypothesis/aim/objective of the study clearly described?	Yes	Examined efficacy and safety of seladelpar in adults with PBC at risk of disease progression who were receiving or intolerant to UDCA
Are the main outcomes to be measured clearly described in the Introduction or Methods section?	Yes	Study endpoints and assessments clearly described in Methods
Are the characteristics of the patients included in the study clearly described?	Yes	Reported in Table 1 of study publication
Are the interventions of interest clearly described?	Yes	Seladelpar treatment cohorts clearly described in Methods
Are the distributions of principal confounders in each group of patients to be compared clearly described?	Yes	Baseline demographics and characteristics similar across dose cohorts. There was an imbalance in baseline ALP levels among cohorts, and this was noted in the Results
Are the main findings of the study clearly described?	Yes	Main findings clearly described in Results and Discussion
Does the study provide estimates of the random variability in the data for the main outcomes?	Yes	Primary and secondary efficacy analyses were carried out using 2-sided tests at the α = 0.05 significance level. For biochemistry

		measures, within-group comparisons with baseline using a paired t test were performed at Weeks 12 and 52, and pairwise comparisons of least squares (LS) means between treatment cohorts using an ANCOVA model were performed at Weeks 8, 12, and 52.
Have all important adverse events that may be a consequence of the intervention been reported?	Yes	Treatment-emergent adverse events (TEAEs) were reported in the Results section
Have the characteristics of patients lost to follow-up been described?	Yes	Details of patients who discontinued the study are described in the Results
Have actual probability values been reported (e.g., 0.035 rather than <0.05) for the main outcomes except where the probability is less than 0.001?	No	Actual probability values have not been reported for all outcomes described in the Results section of the Bowlus *et al*. (2022) publication
Were the patients asked to participate in the study representative of the entire population from which they were recruited?	Yes	Study recruited adults with primary biliary cholangitis (PBC) at risk of disease progression (ALP ≥1.67 x ULN) who were receiving or intolerant to ursodeoxycholic acid
Were those patients who were prepared to participate representative of the entire population from which they were recruited?	UTD	International study conducted at 32 centres in four countries (Canada, Germany, United Kingdom, and US). Unable to determine how patient characteristics aligned to UK clinical practice
Were the staff, places, and facilities where the patients were treated, representative of the treatment the majority of patients receive?	UTD	All study visits occurred in clinic; detail of staff, places and facilities not presented
Was an attempt made to blind study patients to the intervention they have received?	No	Open-label study
Was an attempt made to blind those measuring the main outcomes of the intervention?	No	Open-label study
If any of the results of the study were based on “data dredging”, was this made clear?	UTD	Unclear without additional analysis of results
In trials and cohort studies, do the analyses adjust for different lengths of follow-up of patients, or in case control studies, is the time period between the intervention and	Yes	Number of patients with measurements at each timepoint is disclosed alongside the results for each study outcome

outcome the same for cases and controls?		
Were the statistical tests used to assess the main outcomes appropriate?	Yes	Primary and secondary efficacy analyses were carried out using 2-sided tests at the α = 0.05 significance level. For biochemistry measures, within-group comparisons with baseline using a paired t test were performed at Weeks 12 and 52, and pairwise comparisons of least squares (LS) means between treatment cohorts using an ANCOVA model were performed at Weeks 8, 12, and 52.
Was compliance with the intervention/s reliable?	Yes	Median compliance to seladelpar for the duration of the study was ≥96% in all groups.
Were the main outcome measures used accurate (valid and reliable)?	Yes	Aligned with historical clinical studies in PBC
Were the patients in different intervention groups (trials and cohort studies) or were the cases and controls (case-control studies) recruited from the same population?	N/A	Open-label study
Were study patients in different intervention groups (trials and cohort studies) or were the cases and controls (case-control studies) recruited over the same time?	N/A	Open-label study. All patients received seladelpar at a 2 mg, 5 mg, or 10 mg dose
Were study patients randomised to intervention groups?	N/A	Open-label study
Was the randomised intervention assignment concealed from both patients and health care staff until recruitment was complete and irrevocable?	N/A	Open-label study
Was there adequate adjustment for confounding in the analyses from which the main findings were drawn?	No	Adjustments for confounding factors in the analyses were not disclosed
Were losses of patients to follow-up taken into account?	Yes	Where specified, the last observation carried forward was used for missing laboratory data; other missing data were not imputed.
Did the study have sufficient power to detect a clinically important effect where the probability value for a difference being due to chance?	Yes	The final planned sample size was 49 patients each in the 10 mg and 5 mg cohorts (increased from 12), and up to 18 in the 2 mg cohort, allowing for detection of at least a 10% mean difference in ALP percent change between the 5 mg and 10 mg cohorts with a

		15% SD at 90% power using a 2-sided, 2-sample t test at a α = 0.05 significance level.

CB8025-31731 (Mayo *et al*. [2024])

Description of criteria	Response	Rationale
Is the hypothesis/aim/objective of the study clearly described?	Yes	To evaluate the long-term safety and efficacy of seladelpar in patients with PBC.
Are the main outcomes to be measured clearly described in the Introduction or Methods section?	Yes	Study outcomes clearly described in the Results section
Are the characteristics of the patients included in the study clearly described?	Yes	Reported in Table 1 of study publication
Are the interventions of interest clearly described?	Yes	Seladelpar treatment cohorts clearly described in Methods
Are the distributions of principal confounders in each group of patients to be compared clearly described?	Yes	Baseline demographics and characteristics similar across dose cohorts
Are the main findings of the study clearly described?	Yes	Main findings clearly described in Results and Discussion
Does the study provide estimates of the random variability in the data for the main outcomes?	Yes	Descriptive statistics for continuous variables consist of mean, SD, median and range, and include count and proportion for categorical variables
Have all important adverse events that may be a consequence of the intervention been reported?	Yes	The safety and tolerability endpoints were assessed by TEAEs as well as biochemistry and haematology laboratory results.
Have the characteristics of patients lost to follow-up been described?	Yes	Study discontinuations (other than due to study termination) are provided in the Supplementary Materials of Mayo *et al*. (2024)
Have actual probability values been reported (e.g., 0.035 rather than <0.05) for the main outcomes except where the probability is less than 0.001?	No	Results were characterised by descriptive statistics.

Were the patients asked to participate in the study representative of the entire population from which they were recruited?	Yes	Study recruited adults with primary biliary cholangitis (PBC) at risk of disease progression (ALP ≥1.67 x ULN) who were receiving or intolerant to ursodeoxycholic acid
Were those patients who were prepared to participate representative of the entire population from which they were recruited?	UTD	Disposition of patients according to clinical trial site location not disclosed
Were the staff, places, and facilities where the patients were treated, representative of the treatment the majority of patients receive?	UTD	All study visits occurred in clinic; detail of staff, places and facilities not presented
Was an attempt made to blind study patients to the intervention they have received?	No	Open-label study
Was an attempt made to blind those measuring the main outcomes of the intervention?	No	Open-label study
If any of the results of the study were based on “data dredging”, was this made clear?	UTD	Unclear without additional analysis of results
In trials and cohort studies, do the analyses adjust for different lengths of follow-up of patients, or in case control studies, is the time period between the intervention and outcome the same for cases and controls?	Yes	Number of patients with measurements at each timepoint is disclosed alongside the results
Were the statistical tests used to assess the main outcomes appropriate?	Yes	Descriptive statistics for continuous variables consist of mean, SD, median and range, and include count and proportion for categorical variables
Was compliance with the intervention/s reliable?	UTD	Compliance with seladelpar and/or UDCA not disclosed
Were the main outcome measures used accurate (valid and reliable)?	Yes	Aligned with historical clinical studies in PBC
Were the patients in different intervention groups (trials and cohort studies) or were the cases and controls (case-control studies) recruited from the same population?	N/A	Open-label study
Were study patients in different intervention groups (trials	N/A	Open-label study

and cohort studies) or were the cases and controls (case-control studies) recruited over the same time?		
Were study patients randomised to intervention groups?	N/A	Open-label study
Was the randomised intervention assignment concealed from both patients and health care staff until recruitment was complete and irrevocable?	N/A	Open-label study
Was there adequate adjustment for confounding in the analyses from which the main findings were drawn?	No	Adjustments for confounding factors in the analyses were not disclosed
Were losses of patients to follow-up taken into account?	Yes	Results only presented for all patients with outcomes at selected study timepoints
Did the study have sufficient power to detect a clinically important effect where the probability value for a difference being due to chance?	UTD	There was no formal sample size justification for the study, so unclear if study was sufficiently powered.

Network meta-analysis and MAIC

A14. In the feasibility assessment for the NMA, studies evaluating fibrates were included in the SLR but excluded from the NMA due to 'intervention not of interest'. The rationale given for this was that fibrates are used off-label, concerns about the standard of the evidence base, and variations in eligibility criteria and outcome definitions in comparison with RESPONSE. As interventions used off-label may be appraised within a NICE assessment if they are used routinely in practice, and these studies provide evidence for UDCA that may have been useful for the network, please can you provide clear explanation for why each study was excluded from the NMA for (a) eligibility criteria and/or (b) outcome definitions.

Company response: Fibrates were not included in the NICE UK-specific ITC because they are not approved in the UK and are used off-label. Additionally, they have not been studied to regulatory standards in patients with PBC, and their inclusion criteria, as well as outcome definitions (e.g., composite response), do not align with those of the RESPONSE trial.

We explored the feasibility of conducting an ITC that includes studies assessing fibrates. However, the feasibility report concluded that such an analysis is not possible due to significant heterogeneity among studies in terms of patient characteristics and inclusion criteria. Furthermore, the outcome definitions and timepoints differ between studies assessing fibrates and the RESPONSE trial (34).

A15. In the feasibility assessment for the NMA, it is stated that all treatment durations were relevant for inclusion in the SLR but that a 12-month treatment duration only was selected for the NMA. While the NMA was feasible at 12-months and longer follow-up is useful, we would have expected to see a 6-month analysis as well, given that this would have included a broader range of studies (including ENHANCE). Please can you provide a rationale for why the 6-month treatment duration was not considered relevant?

Company response: In the NMA/MAIC, the outcomes were assessed at 12 months, which was in line with the primary endpoint of RESPONSE, POISE, and ELATIVE

trials. The 12-month duration is also aligned with the previous PBC NICE UK submission (9).

Furthermore, PBC is a long-term liver disease, and complications associated with PBC progression, such as cirrhosis and liver failure, may take a long time to develop. Hence, the analysis was conducted at the longest follow-up time possible for the included trials

In terms of EAG's request for inclusion of the ENHANCE trial, please note ENHANCE was originally intended to be a 52 week, double-blind, placebo-controlled Phase 3 study in patients with PBC having a design and endpoints similar to the pivotal study. However, this study was terminated early due to unexpected end of treatment histology findings noted in a separate Livdelzi study in non-alcoholic steatohepatitis (Study CB8025-21730). It is important to note that this potential safety signal was subsequently refuted by an independent external panel who determined that the findings were not related to Livdelzi. At the time of study termination, only a small number of patients (N=3; Livdelzi n=2, placebo n=1) had reached the 52-week timepoint; the primary and key secondary efficacy endpoints originally planned for 12 months were therefore amended to a shorter 3-month timepoint prior to database lock and unblinding.

We understand from this request that EAG wants to understand the outcome trend at earlier timepoints; hence, we have performed the Bayesian NMA by including all trials reporting 6 months of data for the key outcomes:

Seladelpar vs Elafibranor at 6 Months

ALP normalisation results at 6 months

Outcome	Turner prior	Turner prior Biological markers	Vague prior	
	RR (95% CrI)		RR (95% CrI)	RR (95% CrI)
ALP normalization	1.98 (0.03, 82.33)		2.23 (0.04, 89.14)	1.99 (0.03, 136.2)

Note: Studies included in the analysis: ELATIVE (Elafibranor 80 mg vs UDCA), RESPONSE (Seladelpar 10 mg vs UDCA), ENHANCE (Seladelpar 10 mg vs UDCA)

ALP change from baseline at 6 months

Outcome	Rhodes prior Biological markers	Rhodes generic prior	Vague prior
	MD (95% CrI)	**MD (95% CrI)**	**MD (95% CrI)**
ALP change from baseline	-32.21 (-84.15, 44.18)	-17.81 (-102.6, 64.83)	-15.27 (-93.7, 56.21)

Note: Studies included in the analysis: ELATIVE (Elafibranor 80 mg vs UDCA), RESPONSE (Seladelpar 10 mg vs UDCA), ENHANCE (Seladelpar 10 mg vs UDCA)

Seladelpar vs OCA at 6 months

ALP change from baseline results at 6 months

Outcome	Rhodes prior Biological markers	Rhodes generic prior	Vague prior
	MD (95% CrI)	**MD (95% CrI)**	**MD (95% CrI)**
Seladelpar vs OCA 5-10mg	-53.35 (-81.95, -21.91)	-54.58 (-86.09, -21.05)	-53.69 (-85.22, -21.54)
Seladelpar vs OCA 10mg	-26.72 (-53.55, 4.44)	-29.28 (-61.2, 3.21)	-29.68 (-61.04, 2.28)

Statistically significantly favorable for seladelpar

Note: Studies included in the analysis: RESPONSE (Seladelpar 10 mg vs UDCA), ENHANCE (Seladelpar 10 mg vs UDCA) and POISE (OCA 5 mg, OCA 5-10 mg vs UDCA); POISE trial did not report ALP normalization results at 6 months

A16. In "Data on File – Seladelpar ITC Report" Appendix C presents absolute probabilities for ALP change from baseline at 12 months.

a) **Please explain how you have reached absolute probability values of negative 120?**

b) **Please also present the ALP change from baseline at 12 months with and without outcome recalculation.**

Company response:

(a) The ALP change from baseline is a continuous outcome. The absolute probability values were derived based on the mean changes observed for seladelpar (-133.9) and elafibranor (-117). The absolute treatment effect values obtained from the model are consistent with the trial-level results.

(b) The ALP change from baseline is a continuous outcome and has not been recalculated. We believe the EAG may be misinterpreting this as a binary outcome, and we need to confirm this with them

A17. In "Data on File – Seladelpar ITC Report" the following details are needed for the MAIC:

a) **Please confirm which data were IPD and which data were aggregated in the MAIC?**

b) Which software and package(s) were used in the conduct of the MAIC(s)?

Company response:

(a) The data used from the RESPONSE trial were IPD, whereas the data used from the ELATIVE trial were aggregated in the MAIC

(b) The MAIC analysis was conducted using R, version 4.4.1, with the sandwich package used for the analysis, as per NICE TSD 18 guidelines

A.18. [PRIORITY] Please justify your choice of effect modifiers in the NMA.

Company response: The selection of effect modifiers was based on a comprehensive approach, incorporating:

- Previous NICE Technology Appraisal Review – The effect modifiers identified in prior NICE Technology Appraisals for PBC, including TA1016, were reviewed
- Targeted Literature Review – An assessment of published studies was conducted to ensure alignment with the broader evidence base
- Clinical Expert Validation – Input from clinical experts was sought to confirm the clinical relevance and validity of the selected effect modifiers

The following effect modifiers were identified in NICE TA1016 and validated against the literature and expert opinion (9):

- Age

- ALP levels at baseline
- Total bilirubin at baseline
- Cirrhosis (%)
- ANA-positive status

As noted in NICE TA1016, ANA-positive status was not reported in any of the included studies, despite being identified as a potential effect modifier (9). As a result, the studies were compared based on the four other effect modifiers, ensuring consistency with both the literature and expert clinical judgment

This structured approach ensured that the chosen effect modifiers were clinically relevant, evidence-based, and aligned with NICE methodological guidance, enhancing the robustness of the analysis

A.19. [PRIORITY] There are a number of details missing from various tables in Data on File – Seladelpar ITC Report. Please provide units of measurement for Bilirubin in ELATIVE, and ALP in ELATIVE and RESPONSE; and please include the units used to describe the spread of the data for age, bilirubin, and ALP (are these mean and SD) in Tables 9 and 11.

Company response: Please see below the details of all measurement units:

- Age/mean age at diagnosis was reported in years as Mean (SD)
- Background UDCA/previous UDCA/prior OCA use data was reported as proportion of patients (%)
- Proportion of females was reported as %
- Baseline ALP values were reported as mean (SD) with U/L units
- ALP ULN definition was reported as U/L
- Total bilirubin level data was provided as mean (SD) using units µmol/L and mg/dl

- The data for patients with cirrhosis was presented as %
- Albumin levels were depicted as mean (SD) in g/L
- Time since PBC diagnosis was reported in years as mean (SD)
- The proportion of patients with bilirubin >ULN at baseline was depicted as %

The report has been updated, and the missing details for all the tables have been added. Please see below the updated tables (Table 59 - Table 61 changes are highlighted in red).

Table 59: Population characteristics reported across the included studies (Table 4, ITC Report)

Population characteristics	ELATIVE	RESPONSE	POISE	NCT03633227	COBALT
Intervention	Elafibranor 80 mg + UDCA	Seladelpar 10 mg + UDCA	OCA 5-10 mg + UDCA OCA 10 mg + UDCA	OCA 5-10 mg + UDCA	OCA 5-10 mg + UDCA
Comparator	UDCA	UDCA	UDCA	UDCA	UDCA
Mean age, years (SD)	57.1 (8.7)	56.7 (9.79)	56 (10.41)	61.6 (9.43)	53.65 (10.38)
Background UDCA (%)	95	93.8	93	--	147 (88.31)
Female (%)	96	94.2	90.6	72.7	89.85
Previous UDCA (%)	100	100	100	NR	161.99 (97.29)
Baseline ALP mean U/L (SD)	321.9 (150.9)	314.3 (121.88)	323 (112.53)	241.75*	490.25 (286.55)
ALP ULN Definition U/L	Females: 104; Males: 129	116	Females: 118; Males: 124	NR	NR
Mean total bilirubin level-mg/dl (SD)	0.56 (0.298)	0.76 (0.30)	0.65 (0.38)	43.44*	1.65 (0.80)
Mean total bilirubin level-µmol/liter (SD)	9.6 (5.1)	12.9 (5.147)	11.1 (6.498)	NR	NR
Cirrhosis (%)	9.94 (8.3 in elafibranor	14	16.7	NR	NR

Population characteristics	ELATIVE	RESPONSE	POISE	NCT03633227	COBALT
	and 13.2 in UDCA)				
Mean ALB (g/L) (SD)	43.8 (3.0)	41.6 (2.0)	43.17 (2.99)	33.75*	3.98 (0.41)
Mean time (years) since PBC Diagnosis (SD)	8.0 (6.2)	8.33 (6.66)	8.33 (6.10)	NR	NR
Mean age at diagnosis, years (SD)	NR	49.23 (10.30)	47.32 (10.79)	NR	NR
Bilirubin >ULN at baseline (%)	3.7	13.0 (15.6 in elafibranor and 7.7 in UDCA)	8.3	NR	NR
Prior OCA use (%)	8.1	17.1	0	NR	NR

Table 60: Baseline covariates prior and post matching; primary matching set [Binary outcomes] (Table 9, ITC Report)

	ELATIVE	RESPONSE	
Variable		Raw	Adjusted
N	161	193	193
Age, years (Mean±SD)	57.1 ± 8.7	56.73±9.79	57.1 ± 8.72
Cirrhosis (%)	10	14	10
Bilirubin, µmol/L (Mean±SD)	9.6 ± 5.1	12.83 ± 5.13 µmol/L	9.6±5.11
ALP, U/L (Mean±SD)	321.9±150.9	314.3±121.9	321.90 ± 151.29

Table 61: Baseline covariates prior and post matching; primary matching set [Continuous outcomes] (Table 11, ITC Report)

	ELATIVE	RESPONSE	
Variable		Raw	Adjusted
N	161	193	171 (Evaluable)
Age, years (Mean±SD)	57.1 ± 8.7	56.73±9.79	57.1 ± 8.73
Cirrhosis (%)	10	14	10

Bilirubin, µmol/L (Mean±SD)	9.6 ± 5.1	0.75 ± 0.30 mg/dL 12.83 ± 5.13 µmol/L	9.6±5.12
ALP, U/L (Mean±SD)	321.9±150.9	314.3±121.9	321.90 ± 151.35

A20. [PRIORITY] Please give further detail on the units of measurement that the key effect modifiers were matched on, e.g. was this mean, proportion, SD?

Company response: Please see below the details of measurement units for key effect modifiers:

- Age/mean age at diagnosis was reported in years as Mean (SD)
- The data for patients with cirrhosis was presented as %
- Total bilirubin level data was provided as mean (SD) using units µmol/L and mg/dl
- Baseline ALP values were reported as mean (SD) with U/L units

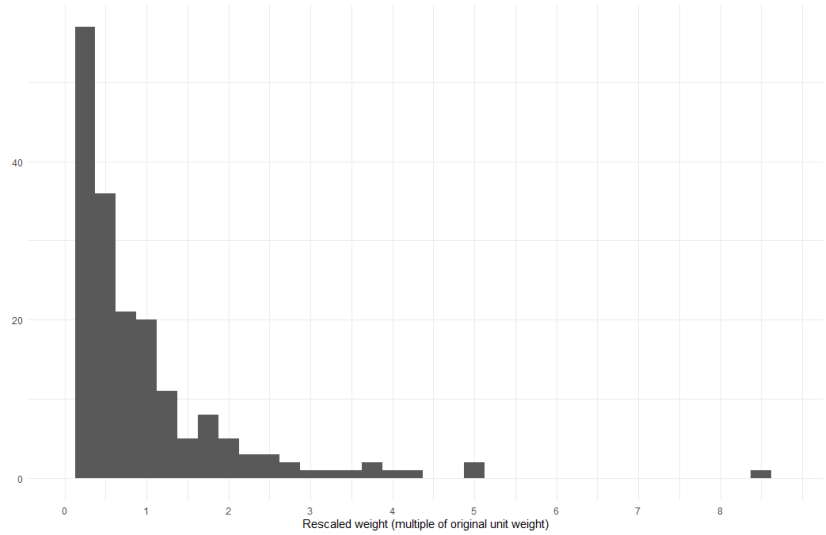
Please see Tables 9 and 11 for updated unit details (Response to question A.19).

A21. Please present Figures 4 and 5 including "1" on the x axis.

Company response: Please see below the figure including "1" on the x-axis. Please note that we have added the figures for both rescaled weights (as per NICE TSD 18, working example) and actual weights.

Figure 5: Distribution of primary matching weights (A) Rescaled weights (B) Actual weights (Figure 4, ITC Report)

(A) Rescaled weights



(B) Actual weights

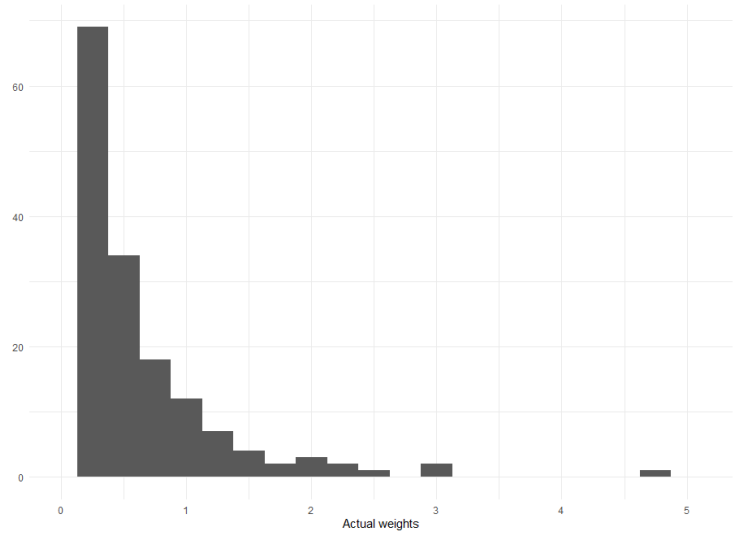
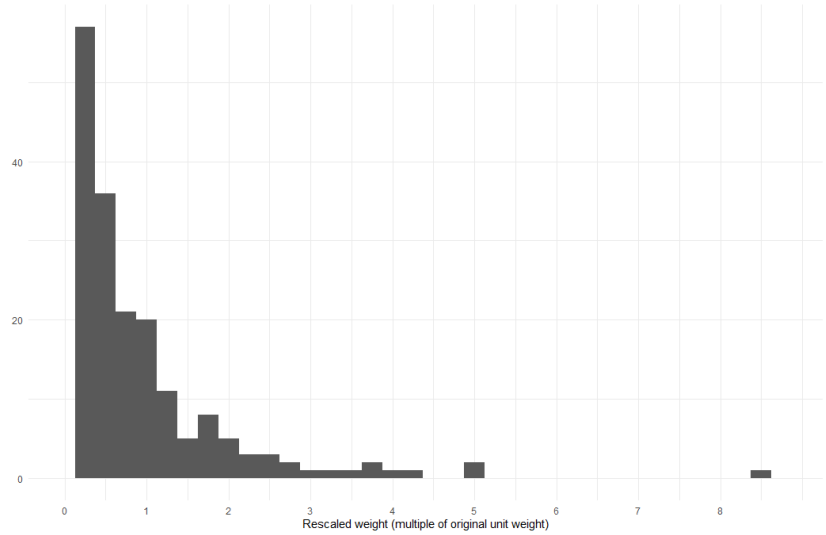
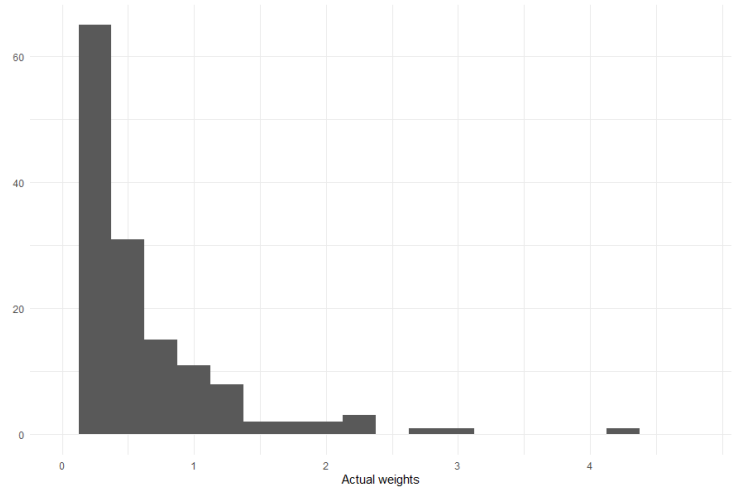


Figure 6: Distribution of primary matching weights (A) Rescaled weights (B) Actual weights

(A) Rescaled weights



(B) Actual weights



A22. Please present the ESS as a % of the total original sample sizes in Tables 10 and 12.

Company response: Please see below the updated tables 10 and 12 with ESS as a % of the total original sample size.

Table 62: Extreme patient weights within the primary matching set (Table 10, ITC Report)

	Anchored MAIC (Weights)
ESS	70
ESS as a % of the total original sample size	36.27
Patients with weight > 5	2
% of ESS concentrated in patients with	2.86

weight>5	
Patients with weight >1	31
% of ESS concentrated in patients with weight>1	44.29

Key: ESS, effective sample size.

Table 63: Extreme patient weights within the primary matching set (Table 12, ITC Report)

	RESPONSE Elafibranor cut-off matched (Anchored)
ESS	65
ESS as a % of the total original sample size	38.01
Patients with weight > 5	0
% of ESS concentrated in patients with weight>5	0
Patients with weight >1	30
% of ESS concentrated in patients with weight>1	46.15

Key: ESS, effective sample size.

A23. [PRIORITY] Please can you explain how outliers evident in Table 10 were handled in the analysis? Please can you provide this analysis without outliers?

Company response: The analysis presented in the report was conducted without excluding any outliers, in accordance with guidance from NICE DSU TSD 18 on MAIC. However, as requested, we have also conducted an additional sensitivity analysis excluding outliers with weights >5 to assess the impact on results.

Table 62 shows that 2.86% of the ESS was concentrated in patients with weights >5, indicating that a small proportion of patients had a disproportionately high influence on the adjusted estimates

The sensitivity analysis results after excluding extreme weights (>5) were aligned with the base case, i.e., no evidence of a statistical difference between the treatments

	ELATIVE cut-off matched population at 12 months	MAIC results Base case	MAIC results removing outlier weights >5
		RR (95% CI)	RR (95% CI)

ALP normalization	Seladelpar vs UDCA	27.12 (1.68, 437.99)	26.3 (1.63, 424.58)
	Seladelpar vs Elafibranor	1.66 (0.03, 85.54)	1.61 (0.03, 82.95)
Composite response	Seladelpar vs UDCA	9.39 (3.50, 24.23)	7.24 (2.81, 18.69)
	Seladelpar vs Elafibranor	0.70 (0.13, 3.78)	0.54 (0.101, 2.84)
Toronto I	Seladelpar vs UDCA	5.36 (2.26, 12.73)	4.13 (1.83, 9.31)
	Seladelpar vs Elafibranor	0.98 (0.29, 3.29)	0.75 (0.23, 2.44)
ALP CFB at 12 months		**MAIC results Base case**	**MAIC results removing outlier weights >5**
		MD (95% CI)	**MD (95% CI)**
ALP CFB	Seladelpar vs UDCA	-142.13 (-202.68, -81.58)	NA
	Seladelpar vs Elafibranor	-30.43 (-97.84, 36.99)	NA

Further, the sensitivity analysis results after excluding extreme weights (>2) were also aligned with the base case, i.e., no evidence of a statistical difference between the treatments

A24. [PRIORITY] Please explain the finding in Table 12 that patients with weight >5 was 0 (Figure 5 suggests otherwise). Please also explain how these outliers were handled in the analysis. Please provide this analysis without outliers.

Company response: The observed weights did not include any extreme weight i.e., >5. The Figure 5 presents rescaled weights, while the table displays the actual observed weights.

The figures presented in the report were based on rescaled weights, following the NICE TSD 18 worked example. While the analysis used the actual weights. The rescaling makes it easier to see how the weights are distributed. See *Worked Example of MAIC and STC* attached.

Figures using the actual and rescaled weights are added below.

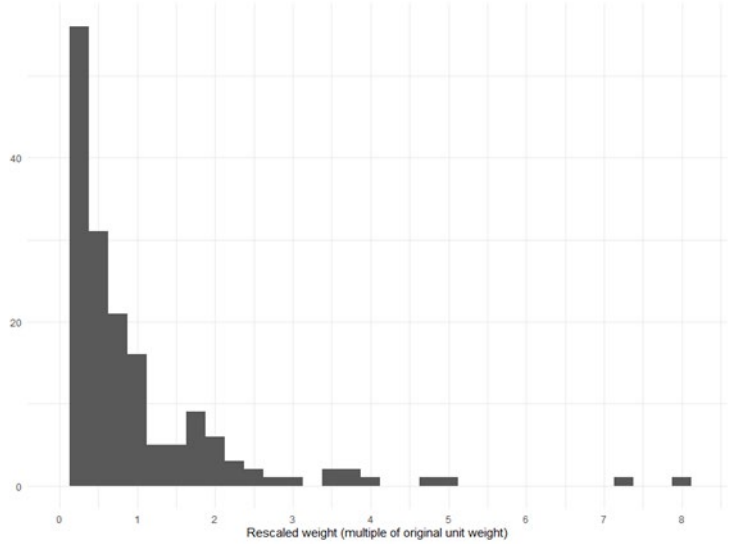
The sensitivity analysis after excluding extreme weights (>5) was not feasible for this outcome (ALP change from baseline) as none of the patients actually had a weight of >5 points.

Table 64: Extreme patient weights with primary matching set (Table 12, ITC Report)

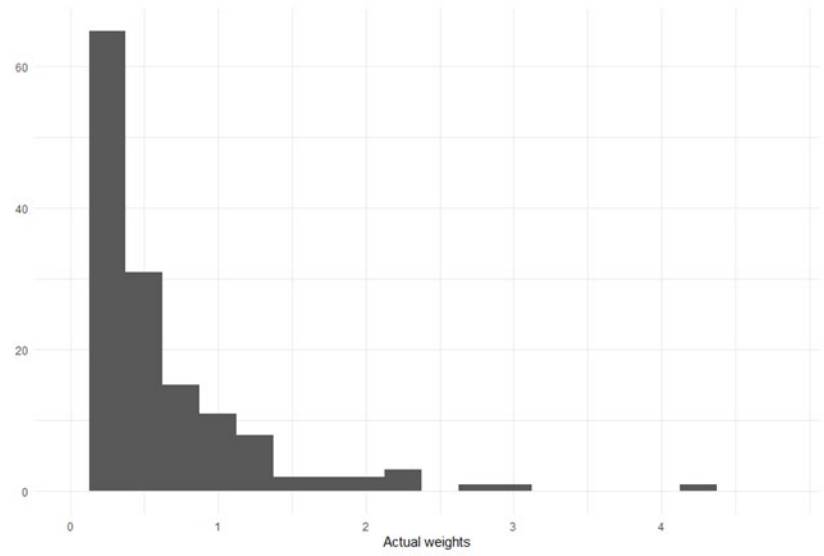
	RESPONSE Elafibranor cut-off matched (Anchored)
ESS	65
ESS as a % of the total original sample size	65/171 (38.01)
Patients with weight > 5	0
% of ESS concentrated in patients with weight>5	0
Patients with weight >1	30
% of ESS concentrated in patients with weight>1	46.15

Figure 7: Distribution of primary matching weights (A) Rescaled weights (B) Actual weights (Figure 5, ITC Report)

(A) Rescaled weights (Available to NICE)



(B) Actual weights (newly added)



A25. [PRIORITY] Please present adjusted and unadjusted *p* values for the effect modifiers in Tables 9 and 11.

Company response: Please see below the updated tables with unadjusted and adjusted p-values

Binary outcomes (e.g. ALP normalization, composite response, etc.)

Variable	ELATIVE	RESPONSE		P-value	
		Raw	Adjusted	Unadjusted	Adjusted
N	161	193	193		
Age	57.1 ± 8.7	56.73±9.79	57.1 ± 8.72	0.7099	1.0000
Cirrhosis (%)	10	14	10	0.6976	0.6760
Bilirubin	9.6 ± 5.1	0.75 ± 0.30 mg/dL 12.83 ± 5.13 µmol/L	9.6±5.11	0.0001	1.0000
ALP: Alkaline phosphatase	321.9±150.9	314.3±121.9	321.90 ± 151.29	0.4325	1.0000

Continuous outcomes (e.g., ALP change from baseline)

Variable	ELATIVE	RESPONSE	P-value

		Raw	Adjusted	Unadjusted	Adjusted
N	161	171	171		
Age	57.1 ± 8.7	56.73±9.79	57.1 ± 8.72	0.7167	1.0000
Cirrhosis (%)	10	14	10	0.4872	0.8894
Bilirubin	9.6 ± 5.1	0.75 ± 0.30 mg/dL 12.83 ± 5.13 µmol/L	9.6±5.11	0.0001	1.0000
ALP: Alkaline phosphatase	321.9±150.9	314.3±121.9	321.90 ± 151.29	0.4328	1.0000

A26. Please can you explain what '(Evaluable)' is referring to in Table 11?

Company response: Table 11 refers to the ALP change from the baseline outcome (continuous outcome). Evaluable (sample size or population) refers to the number of participants for whom the outcome was measured in each intervention group (Chapter 6: Choosing effect measures and computing estimates of effect | Cochrane Training**).** We have used the ALP change from baseline data as reported in the respective trials.

A27. [PRIORITY] Please outline the methodology used for re-calculation of the ALP from RESPONSE using ELATIVE ALP and total bilirubin ULN cut-offs. Please present these data before and after re-calculation. Please justify the favoured use of ELATIVE ALP cut-offs as opposed to POISE or RESPONSE.

Company response: The re-calculation of ALP responder status from the RESPONSE trial was performed using individual patient data. For comparisons of Seladelpar with Elafibranor, ALP and total bilirubin cut-off definitions from the ELATIVE trial were applied; for comparisons with Obeticholic Acid, cut-off values from the POISE trial were applied. Specifically, patients whose ALP and bilirubin values met the respective trial-specific ULN thresholds were reclassified as responders.

ULN Cut-off	ALP ULN U/L		Bilirubin ULN micromoles/L		ALP normalization (ALP ≤1 ULN)		Composite response (ALP<1.67 ULN & ALP 15% reduction & bilirubin ≤1 ULN)	
	Female	Male	Female	Male	Female	Male	Female	Male
RESPONSE	116		18.8		116		194	
ELATIVE	104	129	20.5		104	129	A 174 B 20.5	A 215 B20.5
POISE	118	124	19.3	25.5	118	124	A 197 B 19.3	A 207 B 25.5

This trial-specific approach ensures methodological consistency and clinical relevance when comparing Seladelpar against different comparators. By aligning outcome definitions precisely with the comparator trials (ELATIVE and POISE), the indirect treatment comparison results are more robust, clinically meaningful, and directly comparable. The chosen strategy has been validated by ITC and clinical experts, supporting the appropriateness and reliability of these comparisons. Further, a sensitivity analysis without outcome recalculation was also conducted for each outcome to check the base case robustness. The results for this sensitivity analysis were aligned with the base case.

Please see below the data demonstrating ALP responder status both before and after re-calculation to transparently illustrate the impact of aligning definitions with comparator trial criteria.

Table 65: Outcomes data recalculated using ELATIVE cut-offs

Outcome	Seladelpar Arm (Original)	Seladelpar Arm (Recalculated – ELATIVE Cut-off)	Placebo Arm (Original)	Placebo Arm (Recalculated – ELATIVE Cut-off)
ALP Normalization	32/128 responders	23/128 responders	0/65 responders	0/65 responders
Composite Response	79/128 responders	73/128 responders	13/65 responders	6/65 responders
Toronto I	84/128 responders	77/128 responders	17/65 responders	8/65 responders

Table 66: Outcomes data recalculated using POISE cut-offs

Outcome	Seladelpar Arm (Original)	Seladelpar Arm (Recalculated – POISE Cut-off)	Placebo Arm (Original)	Placebo Arm (Recalculated – POISE Cut-off)
ALP Normalization	32/128 responders	33/128 responders	0/65 responders	0/65 responders

Composite Response	79/128 responders	81/128 responders	13/65 responders	13/65 responders
Toronto I	84/128 responders	86/128 responders	17/65 responders	17/65 responders

Please note that the data before and after recalculation is also available in *'Data on File – Seladelpar ITC Feasibility Assessment'*.

A28. Please justify why in Section 6.1.1 of the ITC report, Seladelpar vs Elafibranor sensitivity analyses are not presented for Seladelpar vs. Placebo?

Company response: The sensitivity analyses presented in Section 6.1.1 of the ITC report specifically focus on the Seladelpar vs. Elafibranor comparison. Although sensitivity analyses involving Seladelpar vs. Placebo were indeed conducted (since placebo acts as the common comparator for the indirect treatment comparison), these results were intentionally not included in detail within this section.

The primary rationale for excluding detailed sensitivity analyses of the Seladelpar vs. Placebo comparison was to facilitate a clearer and more straightforward interpretation of the critical indirect comparison between Seladelpar and Elafibranor. Given the extensive array of sensitivity scenarios explored, focusing explicitly on the Seladelpar–Elafibranor results helps to avoid overwhelming the reader with excessive data.

However, it is important to highlight that the full range of Seladelpar vs. Placebo sensitivity analyses have been performed and are consistent with the direct evidence from the RESPONSE trial, further supporting the robustness and validity of the indirect comparison conclusions. The updated tables provided now explicitly include these Seladelpar vs. Placebo results, reinforcing transparency and completeness of evidence.

ALP normalization (≤1 ULN) at 12 months

Table 67: Sensitivity analysis results for ALP normalisation at 12 months

ALP normalization at 12 months	
Risk Difference (RD) - Anchored MAIC (adjusted for 4 effect modifiers*; with outcome recalculation)	**RD (95%CI)**
Seladelpar 10 mg vs. placebo (ESS=70)	0.2 (0.13, 0.27)
Seladelpar vs. Elafibranor (ESS=70)	0.05 (-0.04, 0.15)

ALP normalization at 12 months	
Odds Ratio (OR) - Anchored MAIC (adjusted for 4 effect modifiers*; with outcome recalculation)	**OR (95%CI)**
Seladelpar 10 mg vs. placebo (ESS=70)	33.87 (2.03, 565.35)
Seladelpar vs. Elafibranor (ESS=70)	1.77 (0.03, 96.33)
Anchored MAIC (adjusted for 2 heterogenous effect modifiers; with outcome recalculation)**	**RR (95%CI)**
Seladelpar 10 mg vs. placebo (ESS=82)	27.12 (1.68, 437.99)
Seladelpar vs. Elafibranor (ESS=82)	1.66 (0.03, 85.54)
Bayesian NMA (with outcome recalculation)	**RR (95%CrI)**
Seladelpar vs. placebo (Vague prior)	50.94 (1.99, 4956.0)
Seladelpar vs. Elafibranor (Vague prior)	1.37 (0.01, 222.4)
Seladelpar vs. placebo (Informative prior: Turner et al.)	45.56 (4.78, 5216.0)
Seladelpar vs. Elafibranor (Informative prior: Turner et al.)	1.37 (0.02, 159.9)
Seladelpar vs. placebo (Informative prior: Specific for Biological markers Turner et al.)	52.61 (3.816, 6315.0)
Seladelpar vs. Elafibranor (Informative prior: Specific for Biological markers Turner et al.)	1.53 (0.01, 204.6)
Bayesian NMA (without outcome recalculation)	**RR (95%CrI)**
Seladelpar vs. placebo (Vague prior)	69.34 (2.82, 7638.0)
Seladelpar vs. Elafibranor (Vague prior)	1.83 (0.01, 241.5)
Seladelpar vs. placebo (Informative prior: Turner et al.)	65.87 (7.33, 6462.0)
Seladelpar vs. Elafibranor (Informative prior: Turner et al.)	2.00 (0.02, 152.1)
Seladelpar vs. placebo (Informative prior: Specific for Biological markers Turner et al.)	66.56 (5.24, 4147.0)
Seladelpar vs. Elafibranor (Informative prior: Specific for Biological markers Turner et al. (35)	1.86 (0.02, 137.1)

*Age, alkaline phosphatase and bilirubin levels at baseline, cirrhosis %

** bilirubin and cirrhosis

ALP: Alkaline phosphatase; CI: Confidence interval; CrI: Credible interval; ESS: Effective sample size; MAIC: Matching-Adjusted Indirect Comparison; NMA: Network meta-analysis; OR: Odds ratio; RD: Risk difference; RR: Risk ratio

Composite response (ALP <1.67x ULN, ≥15% ALP decrease from baseline, total bilirubin ≤1.0 ULN) at 12 months

Table 68: Sensitivity analysis results for composite response at 12 months

Composite response at 12 months	
Risk Difference (RD) - Anchored MAIC (adjusted for 4 effect modifiers*; with outcome recalculation)	**RD (95%CI)**
Seladelpar vs. placebo (ESS=70)	0.48 (0.34, 0.63)
Seladelpar vs. Elafibranor (ESS=70)	-0.01 (-0.19,

Composite response at 12 months	
	0.17)
Odds Ratio (OR) - Anchored MAIC (adjusted for 4 effect modifiers*; with outcome recalculation)	**OR (95%CI)**
Seladelpar vs. placebo (ESS=70)	19.35 (6.08, 61.56)
Seladelpar vs. Elafibranor (ESS=70)	0.73 (0.11, 4.72)
Anchored MAIC (adjusted for 2 heterogenous effect modifiers; with outcome recalculation)**	**RR (95%CI)**
Seladelpar vs. placebo (ESS=82)	9.33 (3.61, 24.07)
Seladelpar vs. Elafibranor (ESS=82)	0.69 (0.13, 3.66)
Unanchored MAIC (with outcome recalculation)	**RR (95%CI)**
Seladelpar vs. Elafibranor (adjusted for 2 effect modifiers**, ESS=51)	1.15 (0.88,1.49)
Seladelpar vs. Elafibranor (adjusted for 4 effect modifiers*, ESS=47)	1.02 (0.76,1.36)
Bayesian NMA (with outcome recalculation)	**RR (95%CrI)**
Seladelpar vs. placebo (Vague prior)	8.04 (0.95, 24.85)
Seladelpar vs. Elafibranor (Vague prior)	0.71 (0.07, 4.39)
Seladelpar vs. placebo (Informative prior: Turner et al.)	8.13 (4.08, 18.64)
Seladelpar vs. Elafibranor (Informative prior: Turner et al.)	0.68 (0.24, 1.51)
Seladelpar vs. placebo (Informative prior: Specific for Biological markers Turner et al.)	8.07 (2.54, 20.98)
Seladelpar vs. Elafibranor (Informative prior: Specific for Biological markers Turner et al.)	0.68 (0.16, 2.15)
Bayesian NMA (without outcome recalculation)	**RR (95%CrI)**
Seladelpar vs. placebo (Vague prior)	4.44 (0.52, 13.27)
Seladelpar vs. Elafibranor (Vague prior)	0.52 (0.05, 2.85)
Seladelpar vs. placebo (Informative prior: Turner et al.)	4.46 (2.62, 7.80)
Seladelpar vs. Elafibranor (Informative prior: Turner et al.)	0.51 (0.22, 1.01)
Seladelpar vs. placebo (Informative prior: Specific for Biological markers Turner et al.)	4.45 (1.38, 10.49)
Seladelpar vs. Elafibranor (Informative prior: Specific for Biological markers	0.51 (0.12

Composite response at 12 months	
Turner et al.)	,1.41)

*Age, alkaline phosphatase and bilirubin levels at baseline, and cirrhosis %
** bilirubin and cirrhosis
CI: Confidence interval; CrI: Credible interval; ESS: Effective sample size; MAIC: Matching-Adjusted Indirect Comparison; NMA: Network meta-analysis; OR: Odds ratio; RD: Risk difference; RR: Risk ratio

ALP response (Toronto I: ALP ≤1.67 × ULN) at 12 months

Table 69: Sensitivity analysis results for ALP response Toronto I at 12 months

ALP response (Toronto I) at 12 months	
Risk Difference (RD) - Anchored MAIC (adjusted for 4 effect modifiers*; with outcome recalculation)	**RD (95%CI)**
Seladelpar vs. placebo (ESS=70)	0.45 (0.29, 0.62)
Seladelpar vs. Elafibranor (ESS=70)	0.03 (-0.18, 0.23)
Anchored MAIC (adjusted for 2 heterogenous effect modifiers; with outcome recalculation)**	**RR (95%CI)**
Seladelpar vs. placebo (ESS=82)	5.66 (2.49, 12.85)
Seladelpar vs. Elafibranor (ESS=82)	1.03 (0.31, 3.36)
Bayesian NMA (with outcome recalculation)	**RR (95%CrI)**
Seladelpar vs. placebo (Vague prior)	5.39 (0.86, 12.07)
Seladelpar vs. Elafibranor (Vague prior)	1.02 (0.15, 6.8)
Seladelpar vs. placebo (Informative prior: Turner et al.)	5.5 (3.15, 10.21)
Seladelpar vs. Elafibranor (Informative prior: Turner et al.)	1.01 (0.54, 1.84)
Seladelpar vs. placebo (Informative prior: Specific for Biological markers Turner et al.)	5.38 (2.14, 10.93)
Seladelpar vs. Elafibranor (Informative prior: Specific for Biological markers Turner et al.)	1.00 (0.37, 2.81)
Bayesian NMA (without outcome recalculation)	**RR (95%CrI)**
Seladelpar vs. placebo (Vague prior)	3.19 (0.48, 7.02)
Seladelpar vs. Elafibranor (Vague prior)	0.77 (0.11, 4.12)
Seladelpar vs. placebo (Informative prior: Turner et al.)	3.22 (2.05, 5.21)
Seladelpar vs. Elafibranor (Informative prior: Turner et al.)	0.75 (0.42, 1.25)
Seladelpar vs. placebo (Informative prior: Specific for Biological markers Turner et al.)	3.22 (1.23, 5.97)
Seladelpar vs. Elafibranor (Informative prior: Specific for Biological markers Turner et al.)	0.76 (0.27, 1.88)

*Age, alkaline phosphatase and bilirubin levels at baseline, cirrhosis
** bilirubin and cirrhosis
CI: Confidence interval; CrI: Credible interval; ESS: Effective sample size; MAIC: Matching-Adjusted Indirect Comparison; NMA: Network meta-analysis; OR: Odds ratio; RD: Risk difference; RR: Risk ratio

ALP change from baseline at 12 months

Table 70: Sensitivity analysis results for ALP CFB at 12 months

ALP CFB at 12 months	
Anchored MAIC (adjusted for 2 heterogenous effect modifiers)*	**MD (95%CI)**
Seladelpar vs. placebo (ESS=74)	-122.03 (-171.05, -73)
Seladelpar vs. Elafibranor (ESS=74)	-10.33 (-68.07, 47.42)
Bayesian NMA	**MD (95%CrI)**
Seladelpar vs. placebo (Vague prior)	-115.1 (-142.7, -87.13)
Seladelpar vs. Elafibranor (Vague prior)	-5.7 (-46.07, 36.2)
Seladelpar vs. placebo (Rhodes prior)	-115.2 (-143.3, -87.62)
Seladelpar vs. Elafibranor (Rhodes prior)	-5.72 (-48.91, 32.25)
Seladelpar vs. placebo (Rhodes prior specific for Biological marker)	-115.0 (-142.2, -91.7)
Seladelpar vs. Elafibranor (Rhodes prior specific for Biological marker)	-7.94 (-47.64, 38.01)

* Bilirubin and cirrhosis
ALP: Alkaline phosphatase; CFB: Change from baseline; CI: Confidence interval; CrI: Credible interval; ESS: Effective sample size; MAIC: Matching-Adjusted Indirect Comparison; MD: Mean difference; NMA: Network meta-analysis

A29. In the NMA, can you please justify the use of Toronto I as the ALP cut-off criteria in the ALP responders at 12 months analysis over the alternative criteria (Paris I and II, Toronto II, or Barcelona) (Data on File – Seladelpar ITC Report)

Company response: Toronto I was used as the ALP cut-off criterion in the ALP responders at 12 months analysis based on the inclusion criteria of the RESPONSE trial, which required patients to have an ALP level of ≥1.67× ULN at baseline. This selection ensures consistency between the trial population and the responder definition used in the analysis, thereby maintaining alignment with the patient characteristics that informed the efficacy outcomes of Seladelpar. Further, Toronto I was also deemed important from an economic modeling perspective.

Additionally, for the alternative criteria (Paris I and II, Toronto II, or Barcelona), please see the results for key analyses below.

In general, the results for these outcomes were aligned with the prioritized outcomes i.e., no evidence of statistical differences between the trials.

Seladelpar vs Elafibranor	MAIC results	Bayesian NMA (REM)
	RR (95% CI)	RR (95% CrI)
PARIS I	0.84 (0.51, 1.38)	0.93 (0.67, 1.29)
PARIS II	2.68 (0.32, 22.22)	1.6 (0.54, 5.44)

REM: Random effects model

Paris I Criteria: ALP < 3× upper limit of normal (ULN) and AST < 2× ULN and Normal bilirubin level (≤ 1 mg/dL or ≤ 17 µmol/L)

Paris II Criteria: ALP ≤ 1.5× ULN and AST ≤ 1.5× ULN and Normal bilirubin level (≤ 1 mg/dL or ≤ 17 µmol/L)

Seladelpar vs OCA Bayesian NMA (REM)	OCA 5-10 mg	OCA 10 mg
	RR (95% CrI)	RR (95% CrI)
PARIS I	0.55 (0.29, 1)	0.61 (0.31, 1.16)
PARIS II	0.7 (0.24, 1.9)	0.73 (0.24, 1.99)

REM: Random effects model

Paris I Criteria: ALP < 3× upper limit of normal (ULN) and AST < 2× ULN and Normal bilirubin level (≤ 1 mg/dL or ≤ 17 µmol/L)

Paris II Criteria: ALP ≤ 1.5× ULN and AST ≤ 1.5× ULN and Normal bilirubin level (≤ 1 mg/dL or ≤ 17 µmol/L)

A30. The EAG notes that the estimates of changes in pruritus severity measured in the RESPONSE trial was based on those with a score of 4+ at baseline. As the numbers used in the model apply to all patients, please confirm whether the data were reanalysed to take this into account. Please also provide a breakdown of how the numbers were calculated from the raw data, sufficient for the EAG to trace and replicate the proportions

Company response: Pruritus outcome inputs were based on additional analyses of RESPONSE IPD considering the complete ITT population, i.e., irrespective of baseline pruritus severity scores. Specifically, for SEL+UDCA/SEL (initial treatments) and UDCA monotherapy/ BSC (subsequent treatments), pruritus severity proportions inputs were estimated based on relative changes from baseline in the number of patients with each severity grade:

- RESPONSE IPD were analyzed to determine the number of patients with Mild, Moderate, or Severe pruritus at baseline and the Month 1, 2, 3, 6, 9, and 12 assessment points.
    - Pruritus severity grades were defined by PBC-40 itch domain scores: Mild: ≥1 - <4 points; Moderate: ≥4 - <7; Severe: ≥7.

- To avoid potential bias due to differences in the initial severity distribution between arms, percentage changes from baseline in the number of patients with each severity classification were estimated for each assessment point using these data, and these treatment-specific values were then applied to a common baseline distribution to give the modelled severity proportions inputs.
    - The common baseline distribution was specific to the UDCA tolerant subgroup population, considering patients across both trial arms.
    - Due to the low number (n=11) of intolerant patients in RESPONSE, overall population data (i.e., for SEL±UDCA and UDCA monotherapy or BSC, respectively) were used to derive percentage change estimates for the UDCA intolerant population treatments.

The data and input calculation set outlined in the bullets above are included in the 'RESPONSE pruritus dist. data and input calculations' workbook submitted alongside this letter. The raw data and input calculations are also added to the updated model post clarification in the 'pruritus' worksheet.

Following further review, an error was identified in the original input calculation set and this has since been corrected. The impact of this on model results is minor, as shown in Table 71. We have also re-run the sensitivity analysis (OWSA, PSA, and scenario analysis) with results provided in Appendix A: Updated sensitivity analysis results with corrected pruritus distribution.

Pruritus severity proportion inputs for OCA ± UDCA and ELA ± UDCA are estimated relative to the SEL ± UDCA profiles according to findings from the ITC analyses. These data and calculations are contained within the model.

Table 71: UDCA tolerant population incremental summary results

Technologies	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER versus baseline (£/QALY)	NHB at £20,000/QALY
Original submission base case					
Seladelpar + UDCA	-	-	-	-	-

OCA + UDCA	4,910	-0.270	-0.805	Strictly Dominated	1.051
Elafibranor + UDCA	66,208	-0.225	-0.380	Strictly Dominated	3.690
Updated base case with corrected pruritus inputs					
Seladelpar + UDCA	-	-	-	-	-
OCA + UDCA	4,980	-0.270	-0.836	Strictly Dominated	1.085
Elafibranor + UDCA	66,235	-0.225	-0.391	Strictly Dominated	3.703

Section B: Clarification on cost-effectiveness data

B1. [PRIORITY] In your base case, the model assumes that UDCA-tolerant patients (who have taken UDCA monotherapy as the first line) will re-take UDCA monotherapy if they fail any treatments. For UDCA-intolerant patients, the model assumes they will receive BSC even though other treatments with different mechanisms of action are available. Can you please explain the reasoning behind these assumptions for both groups (especially the reasoning for reverting to UDCA monotherapy for the former group). Why wasn't the updated approach of using a basket of treatments after treatment discontinuation implemented?

Company response: We acknowledge that other treatments with different mechanisms of action such as seladelpar, elafibranor and OCA could have been included as third-line treatments after discontinuation of second-line treatment. However, this approach was not implemented in the model due to lack of evidence of the clinical effectiveness of such treatments at third line, as acknowledged previously by the EAG of elafibranor NICE submission. This approach is aligned with numerous NICE appraisals for chronic treatments in which multiple sequences of treatments are possible, whereby despite the availability of subsequent treatments, committee decision-making was based on discontinuation to best supportive care (e.g. atopic dermatitis, psoriasis, Crohn's disease, etc.).

B2. [PRIORITY] Health state utilities by ALP level were taken from RESPONSE, these utilities were then adjusted for AEs sourced from other studies, with incidence based on those observed RESPONSE study. The EAG is concerned this may be double counting of the utility decrements as within-trial HRQoL responses will already take into account the AEs patients are experiencing. Please justify the choice of analytic approach.

Company response: The trial did not specifically assess health-related quality of life (HRQoL) at the time of adverse event (AE) occurrence and, therefore, did not capture the associated utility decrement. To account for utility decrements associated with AEs, we applied literature-based estimates on a one-off basis. We would like to draw the EAG's attention to the fact that the model is not sensitive to the AE disutilities, as can be observed when these disutilities are set to 0, that is, removed from the model (Table 72). Please note as previously explained in our response to clarification question A30, an error was identified in the original input calculation of pruritus distribution and was subsequently corrected. We therefore present the side-by-side comparison of the updated base case with corrected pruritus inputs and scenario with AE disutilities excluded and corrected pruritus inputs in Table 72.

Table 72 Cost-effectiveness results for scenario where AE utility decrements are removed (UDCA-tolerant)

Technologies	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER versus baseline (£/QALY)	NHB at £20,000/QALY
Updated base case with corrected pruritus inputs					
Seladelpar + UDCA	-	-	-	-	-
OCA + UDCA	4,980	-0.270	-0.836	Strictly Dominated	1.085
Elafibranor + UDCA	66,235	-0.225	-0.391	Strictly Dominated	3.703
Scenario with AE disutilities excluded and corrected pruritus inputs					
Seladelpar + UDCA	-	-	-	-	-
OCA + UDCA	4,980	-0.270	-0.839	Strictly Dominated	1.088
Elafibranor + UDCA	66,235	-0.225	-0.391	Strictly Dominated	3.703

B3. On page 33 of the submission, it states that response to OCA should be assessed after 12 months, following NICE recommendations. Please confirm how was this applied in the economic model: it appears just to modify costs without modifying effects.

Company response: No formal stopping rules were applied at 12 months for any of the comparators in the economic model, consistent with the approach in previous appraisals in PBC. Notably, although the recommendation for OCA includes the wording "*Assess the response to obeticholic acid after 12 months. Only continue if there is evidence of clinical benefit*"; no detail is available in the recommendation regarding what defines "clinical benefit".

B4. In the economic case, UDCA-intolerant and UDCA-inadequate responders appear to have the same effectiveness. However, a clinical expert consulted by the EAG suggested that there would be a difference in effectiveness between these subgroups. Can you please justify the assumption?

Company response: The RESPONSE study only had 11 UDCA intolerant patients across the seladelpar and placebo arms. The small sample size was deemed insufficient to inform robust ITC / transition profile analyses. Instead, data for all patients from the RESPONSE trial were used to inform transition probabilities for both the UDCA tolerant and UDCA intolerant subgroups in the model. In the ITC analysis, data from ELATIVE (elafibranor) and POISE (OCA) were used. To note, trial populations from all three trials are deemed sufficiently representative of the distribution of patients treated with and without UDCA in clinical practice, which is estimated at around 5% (See Table 73). This pooled intolerant and tolerant, inadequate responder population approach adopted in the elafibranor appraisal was considered appropriate by the EAG. An alternative of using literature to derive transition profiles was used in the OCA NICE submission but was deemed inappropriate by the NICE ERG and the Committee noted it would prefer trial data to be used.

Given that the small numbers of UDCA intolerant patients in trials are too small to facilitate stratified analysis and that the trial populations from RESPONSE (saledelpar), ELATIVE (elafibranor) and POISE (OCA) are sufficiently representative of the distribution of patients treated with and without UDCA in clinical practice, we

concluded the pooled intolerant and tolerant, inadequate responder population approach is the most appropriate approach while acknowledging there is uncertainty of the effectiveness in UDCA intolerant patients.

Table 73 Distribution of UDCA-intolerant patients

Trial name	Number of UDCA-intolerant patients (Total trial population)	Percentage of the total trial population
RESPONSE (saledelpar)	11 (193)	5.7%
ELATIVE (elafibranor)	8 (161)	5.0%
POISE (OCA)	11 (216)	5.1%

B5. On page 193, it is stated that the model accounts for the titration of OCA (essentially doubling the dose) if patients did not reach the primary endpoint criteria for response, with this titration occurring at month 6. However, the transition probabilities for ALP-normal patients remaining in that health state seem to peak between months 3 and 6. Can you justify why the effectiveness of OCA appears to worsen beyond month 6, even though inadequate responders should have shown improvement due to titration? Furthermore, it appears that all patients on OCA are assumed to take the 10mg dosage beyond the 6th month, implying they were all inadequate responders. Can you please justify this assumption?

Company response: The model transition probabilities for ALP-normal patients for OCA and elafibranor are assumed equal to those in the seladelpar arm. Consequently, the pattern highlighted by the EAG—where ALP-normal patients remain in that health state, peaking between months 3 and 6—is attributed to observations from the RESPONSE trial for seladelpar. Further, the efficacy outcomes from the ITC analyses used in the cost-effectiveness model (CEM) are the ALP normalisation and the Toronto I criteria (ALP<1.67×ULN) endpoints at month 12 (single time point). The same calibration factors applied to transitions into the ALP normalisation state and the Mild ALP elevation state are consistently applied across each model cycle period up to 12 months for OCA. Consequently, the derived transition profiles for OCA in the first 12 months followed the same pattern as seladelpar.

We acknowledge that in practice only a portion of the patients receiving OCA would be titrated to up to 10mg depending on tolerability and response status. However, due to the same package price for OCA 5mg and 10mg (30 units per package), the monthly cost of OCA remains the same for both 5mg and 10mg dosage group. The percentage distribution of patients who remained at 5mg and who are titrated to 10mg at month 6 would not have changed the model result. Consequently, the model adopted a simpler approach assuming all patients were titrated to 10mg when calculating monthly costs for OCA.

B6. In the economic model, BSC is used as a second-line treatment for patients who are intolerant to UDCA. The EAG notes that there is zero additional cost for this. Please confirm / justify this (e.g. confirm that patients receive no treatments other than the routine investigations listed in table 72 of CS)?

Company response: We confirm that patients who are intolerant to UDCA receive no treatments other than the routine investigations listed in Table 73 of the CS.

B7. The BSG guidelines highlight the necessity for hepatocellular carcinoma surveillance in patients with cirrhosis. Can you confirm if Table 72 of the submission and the model includes this resource use?

Company response: We confirm that the model does implicitly include the resource use of hepatocellular carcinoma (HCC) surveillance for patients with cirrhosis. The healthcare resource use for patients with cirrhosis (i.e. Compensated cirrhosis or Elevated Bilirubin and Decompensated cirrhosis) was sourced from Wright 2006 (36), based on a randomised controlled trial. The resource use of HCC surveillance would therefore have been inherently included in the reported healthcare resource use, as seen in the resource use of hepatic angiography and liver biopsy procedures.

B8. Can you please clarify why individual trial data are used for adverse events instead of data from an indirect treatment comparison?

Company response: Other than pruritis, the ITC did not consider individual AEs thus could not be used to inform the model. However, the model results are not sensitive to AEs, as shown in Table 74 below. Please note as previously explained in our response to clarification question A30, an error was identified in the original input

calculation of pruritus distribution and was subsequently corrected. We therefore present the side-by-side comparison of the updated base case with corrected pruritus inputs and scenario with AEs excluded and corrected pruritus inputs in Table 74.

Table 74 Cost-effectiveness results for scenario where AEs are removed (UDCA-tolerant)

Technologies	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER versus baseline (£/QALY)	NHB at £20,000/QALY
Updated base case with corrected pruritus inputs					
Seladelpar + UDCA	-	-	-	-	-
OCA + UDCA	4,980	-0.270	-0.836	Strictly Dominated	1.085
Elafibranor + UDCA	66,235	-0.225	-0.391	Strictly Dominated	3.703
Scenario with AEs excluded and corrected pruritus inputs					
Seladelpar + UDCA	-	-	-	-	-
OCA + UDCA	5,008	-0.270	-0.839	Strictly Dominated	1.089
Elafibranor + UDCA	66,228	-0.225	-0.391	Strictly Dominated	3.702

Section C: Textual clarification and additional points

C1. You describe in Appendix E that the "Pharmacoevidence® Artificial Intelligence/Machine Learning (AI/ML) tool" was used as a second reviewer. NICE is supportive of AI use in HTA, but is aware of its potential risks (Use of AI in evidence generation: NICE position statement | Our research work | What we do | About | NICE). Did you first engage with NICE before using the AI tool (as requested in the linked position statement)? Also, as per the position statement, could you provide a rationale for its use in this instance (e.g. what is the "demonstrable value" of doing so)? Finally, could you provide published evidence of the validation/effectiveness of the tool itself?

Company response: We acknowledge NICE's position statement regarding AI use in HTA. Due to time constraints during the systematic review process, we did not engage with NICE in advance of utilizing the Pharmacoevidence® AI/ML tool; however, its use fully aligned with NICE's methodological standards outlined in the Technical Support Documents. Specifically, our review followed guidance from NICE TSD 9 and 13 (Identification, selection, and synthesis of clinical evidence), which explicitly

recommends a rigorous two-reviewer screening process and robust quality control to minimize bias and errors in study selection.

The rationale for integrating the AI tool was driven by the substantial volume of citations retrieved during literature searches, presenting significant timeline challenges for submission. The AI tool effectively performed initial screening by rapidly prioritizing and filtering citations, significantly reducing manual effort while maintaining a high standard of methodological rigor. Crucially, the AI-assisted screening process was explicitly employed as a complementary second reviewer, thereby ensuring adherence to NICE's and Cochrane's two-reviewer recommendation.

To ensure robust quality control, we implemented additional QC measures including:

- Manual verification: Human reviewers independently verified citations excluded by the AI, ensuring no relevant studies were mistakenly omitted. Citations excluded by the AI were checked at two distinct levels:
- QC Level: Applied when there was disagreement between the human reviewer and AI tool (e.g., human included vs. AI excluded, or vice versa). An independent human reviewer resolved Disagreements at this stage
- QA Level: Applied when both the human and AI reviewers agreed to exclude the citation, ensuring that exclusion decisions were consistently accurate
- Bibliographic validation: The final included study list was cross-referenced against published systematic literature reviews and technology appraisals, confirming comprehensiveness.
- Benchmarking: AI-assisted results were internally benchmarked against traditional manual screening, confirming consistent performance and sensitivity.

Overall, the AI tool demonstrated clear efficiency gains by reducing manual workload without compromising the comprehensiveness or accuracy of our review (see agreement/disagreement levels between humans and AI in response to the next question). Our process successfully captured all relevant references identified in prior authoritative SLRs and TAs, confirming reliability and robustness.

We recognize NICE's emphasis on transparency and rigor regarding the use of AI methods in evidence generation. We remain fully committed to engaging proactively with NICE in future discussions related to the validation, appropriate implementation, and best practices for AI methodologies. If required, we are prepared to provide additional details about the AI tool, including underlying code, algorithms, and validation data. Our experience demonstrates that AI-assisted screening can significantly enhance the efficiency of systematic reviews while maintaining methodological robustness, provided appropriate human oversight and rigorous quality control measures are in place, consistent with NICE TSD guidance.

Publications for the AI tool:

- Kaur R., Rai P., Attri S., Kaur G., Singh B. MSR15 Revolutionizing Systematic Literature Reviews: Harnessing the Power of Large Language Model (GPT-4) for Enhanced Research Synthesis. Value in Health 2024 27:6 Supplement (S262-) (https://doi.org/10.1016/j.jval.2024.03.1448)

- Attri S., Kaur R., Singh B., Rai P. MSR57 Transforming Systematic Literature Reviews: Unleashing the Potential of GPT-4: A Cutting-Edge Large Language Model, to Elevate Research Synthesis. Value in Health 2024 27:6 Supplement (S270-) (https://doi.org/10.1016/j.jval.2024.03.1490)

- Rai P., Pandey S., Attri S., Singh B., Kaur R. MSR78 Advancing Systematic Literature Reviews: A Comparative Analysis of Large Language Models (Claude Sonnet 3.5, Gemini Flash 1.5, and GPT-4) in the Automation Era of Generative AI. Value in Health 2024 27:12 Supplement (S453-) (https://doi.org/10.1016/j.jval.2024.10.2312)

- Singh B., Kaur R., Rai P. MSR140 Empowering Systematic Literature Reviews: Utilizing Generative AI for Comprehensive Literature Screening From Titles and Abstracts to Full-Text. Value in Health 2024 27:12 Supplement (S465-) (https://doi.org/10.1016/j.jval.2024.10.2374)

- Kaur R., Singh B., Pandey S., Soni V., Dubey R. MSR51 Advanced Kaplan-Meier Curve Analysis With Generative AI: Leveraging the Capabilities of GPT-

4o. Value in Health 2024 27:12 Supplement (S447-S448) (https://doi.org/10.1016/j.jval.2024.10.2285)

- Kaur R., Attri S., Soni V., Singh B. MSR125 AI-Powered Search Strategy Development and Optimization for Systematic Literature Reviews. Value in Health 2024 27:12 Supplement (S462-) (https://doi.org/10.1016/j.jval.2024.10.2359)

- Kaur R., Soni V., Waddell N., Pandey S., Kaur G., Singh B. MSR167 Transforming Query and Data Retrieval Systems With the Advanced Power of GPT-4o: Generative AI at the Forefront of Extracting Data. Value in Health 2024 27:12 Supplement (S471-) (https://doi.org/10.1016/j.jval.2024.10.2401)

- Kaur R., Singh B., Pandey S. MSR94 Leveraging Python Dash and R Shiny for Advanced Health Economic Model Development. Value in Health 2024 27:12 Supplement (S456-) (https://doi.org/10.1016/j.jval.2024.10.2328)

- Pandey S., Kaur R., Teitsson S., Malcolm B., Rai P., Singh B., Klijn S. EE494 AI-Driven Virtual Assistance Interface for Excel-Based Economic Model. Value in Health 2024 27:12 Supplement (S153-) (https://doi.org/10.1016/j.jval.2024.10.775)

C2. After use of the AI tool, it was reported that all studies excluded by the AI/ML tool underwent manual re-screening by an independent human reviewer 2 for quality assurance. Could you please report what level of agreement there was between the tool and the human reviewer.

Company response: The quality assurance process for excluded publications by the AI tool led to the complete agreement between the AI tool and human reviewers (no disagreements), as it served as a second layer after the initial quality control check as part of the two-review and QC process.

Just like the human-two-review and QC process, disagreements existed between the human reviewer (reviewer 1) and the AI tool (reviewer 2), which were resolved by an independent patient matter expert (Human). Please see below the process:

Reviewer 1 (Human)	Reviewer 2 (AI)	QC (Human)	QA (Human) for excluded citation only

Included	Included	Proceed to the next stage	-
Excluded	Included	Final decision by QC	If excluded, checked during QA (no disagreements)
Included	Excluded	Final decision by QC	If excluded, checked during QA (no disagreements)
Excluded	Excluded	-	Checked during QA (no disagreements)

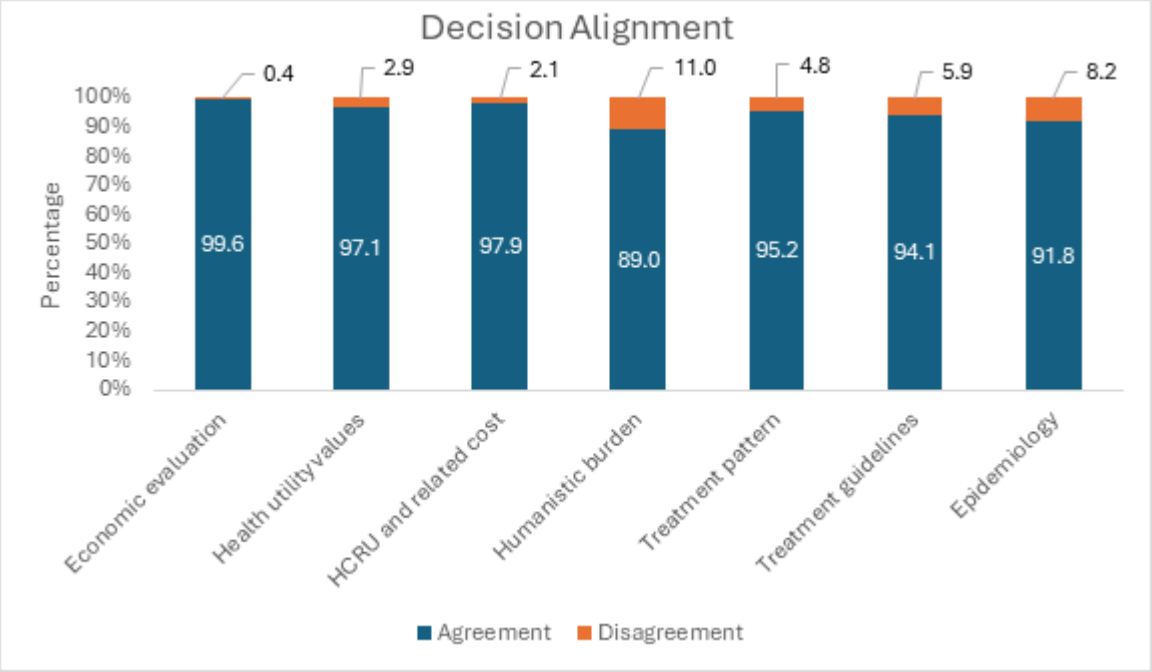
Citations excluded by the AI were checked at two distinct levels:

- **QC Level:** Applied when there was disagreement between the human reviewer and AI tool (e.g., human included vs. AI excluded, or vice versa). An independent human reviewer resolved Disagreements at this stage
- **QA Level:** Applied when both the human and AI reviewers agreed to exclude the citation, ensuring that exclusion decisions were consistently accurate

In standard practice for systematic literature reviews (SLRs), an ideal agreement between two human reviewers is approximately 95%. However, real-world experience typically demonstrates around or below 90% agreement, mainly due to reviewer expertise and judgment variations.

In our AI-assisted review process, the overall average agreement between AI and human reviewers was 94.97% (median: 95.24%), ranging from 89.01% (Humanistic Burden Review) to 99.59% (Economic Evaluation Review), as detailed in the graph below. This demonstrates that the AI-assisted process meets or exceeds expected human reviewer agreement levels, reinforcing the reliability and validity of our screening approach.

Figure 8: Decision alignment between human and AI reviewers at the QC stage



C3. Could you please explain why you used SIGN search filters (which are pragmatic and unverified filters) rather than other available validated filters for the clinical and economic searches? Also, the EAG could not identify the SIGN filters used (when comparing the searches to the search filters listed on SIGN's webpage [Search filters]). SIGN does not have, for example, a "humanistic burden" filter, and the filters SIGN do have are for OVID and are separate for Medline and Embase, whereas the company ran their searches in Embase.com (which incorporates a single search for both Medline and Embase). Could you please refer to the specific filters used.

Company response: For the clinical and economic review, SIGN filters were not directly used to design the searches. Instead, they were used as a reference along with published systematic literature reviews (SLRs), Cochrane reviews, and meta-analyses to identify relevant keywords according to the PICOS criteria, with appropriate truncations applied based on the type of biomedical database. This is the most latest evidence search conducted up to date, the results of which were validated from the existing SLRs and snowballing.

We acknowledge that SIGN does not offer filters for reviews, such as humanistic burden, epidemiology, health utility values, treatment patterns, treatment guidelines,

and healthcare resource utilization. Therefore, filters were developed and validated using published SLRs & Cochrane reviews and relevant truncations.

We agree that the Embase.com platform was used to search both Embase and Medline. However, to mitigate the possibility of missing citations indexed explicitly in Medline, separate searches were also conducted in PubMed.com using the MeSH terms for the relevant keywords for disease, study design, and outcomes identified from SIGN as well as published SLRs and meta-analyses.

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Appendix A: Updated sensitivity analysis results with corrected pruritus distribution

Updated PSA results with corrected pruritus distribution:

Table 75: UDCA-tolerant: discounted probabilistic pairwise results, using the PAS price of seladelpar

Technology	Total costs (£)	Total LYs	Total QALYs	Incremental costs (£)	Incremental LYs	Incremental QALYs	ICER incremental (£/QALY)	NHB at £20,000
Seladelpar + UDCA	380,523	15.752	13.052					-
OCA + UDCA	384,463	15.461	13.267	-3,939	0.291	-0.215	18,312	-0.018
Elafibranor + UDCA	446,891	15.526	12.958	-66,367	0.225	0.093	Dominated	3.412

Key: ICER, incremental cost-effectiveness ratio; NHB, net health benefit; OCA, obeticholic acid, QALYs, quality-adjusted life years, UDCA, ursodeoxycholic acid

Table 76: UDCA-intolerant: discounted probabilistic pairwise results, using the PAS price of seladelpar

Technology	Total costs (£)	Total LYs	Total QALYs	Incremental costs (£)	Incremental LYs	Incremental QALYs	ICER incremental (£/QALY)	NHB at £20,000
Seladelpar	365,322	15.888	13.035				-	-
OCA	370,849	15.579	13.280	-5,527	0.309	-0.244	22,636	0.032
Elafibranor	434,258	15.671	12.985	-68,936	0.217	0.050	Dominant	3.497

Key: BSC, best supportive care, ICER, incremental cost-effectiveness ratio; NHB, net health benefit; OCA, obeticholic acid, QALYs, quality-adjusted life years

Figure 9 CEAC (UDCA tolerant)

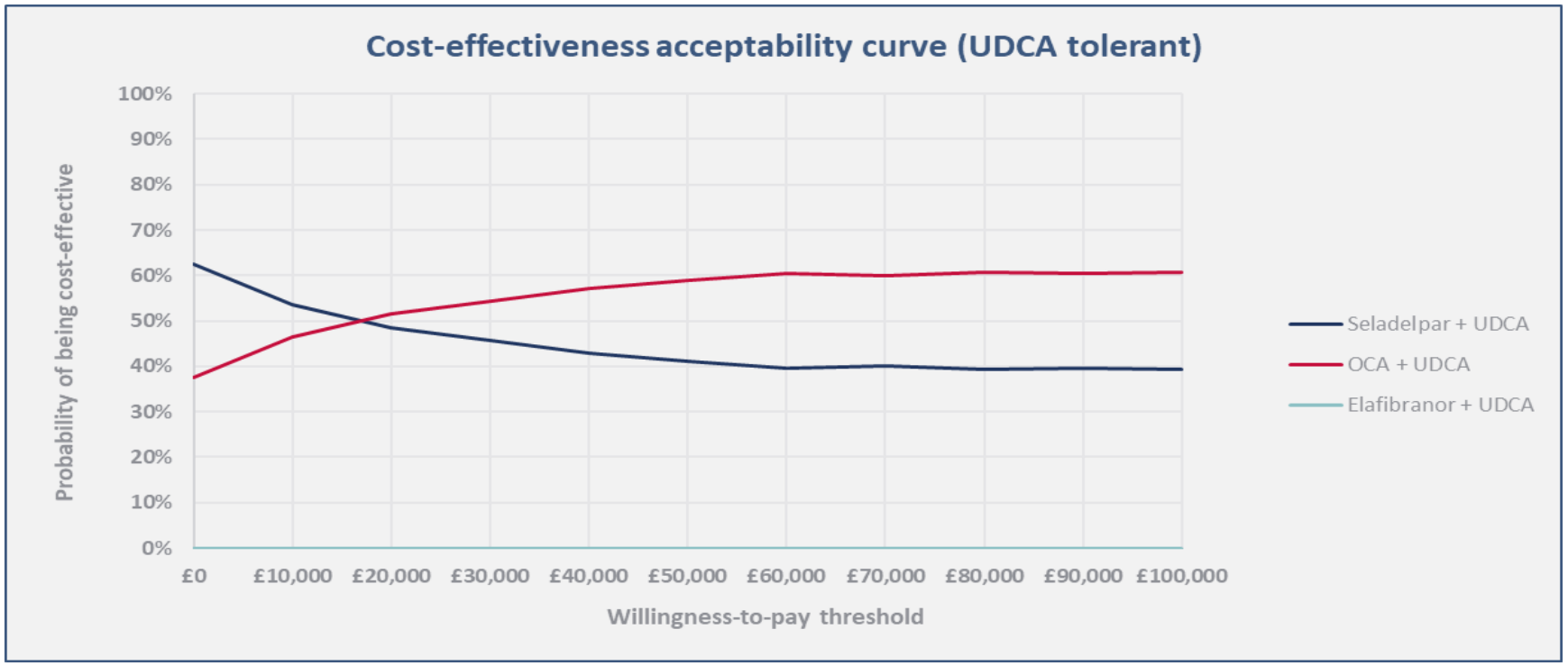
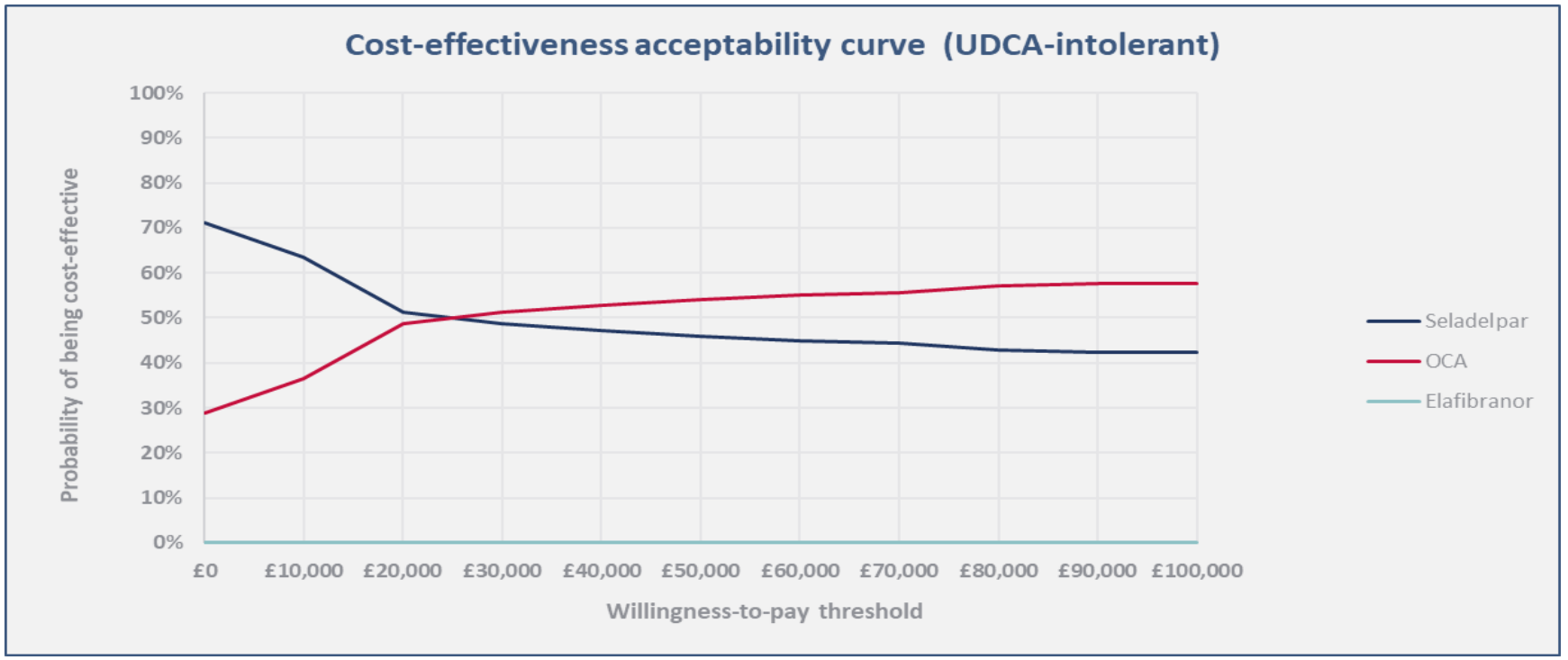


Figure 10 CEAC (UDCA intolerant)



Updated OWSA results with corrected pruritus distribution:

Figure 11 Tornado vs. OCA, UDCA tolerant population

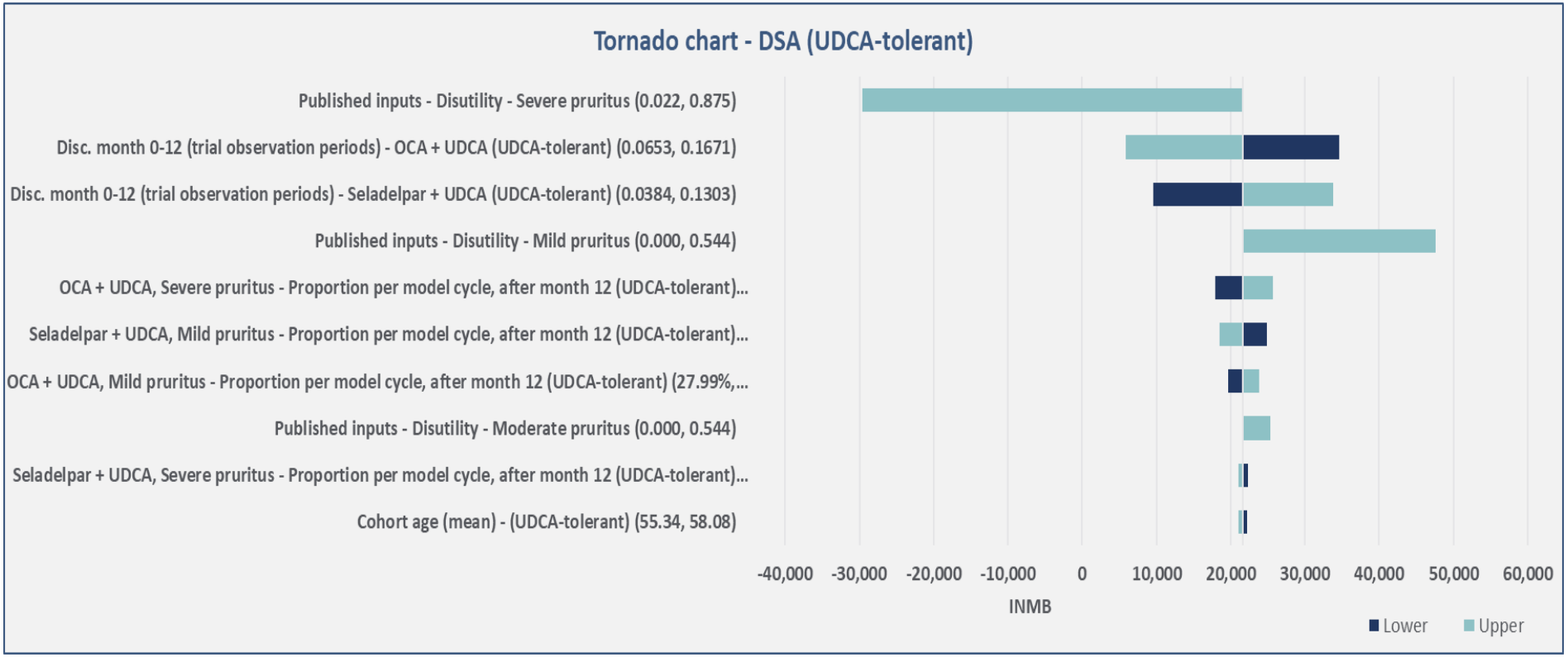


Figure 12 Tornado vs. elafibranor, UDCA tolerant population

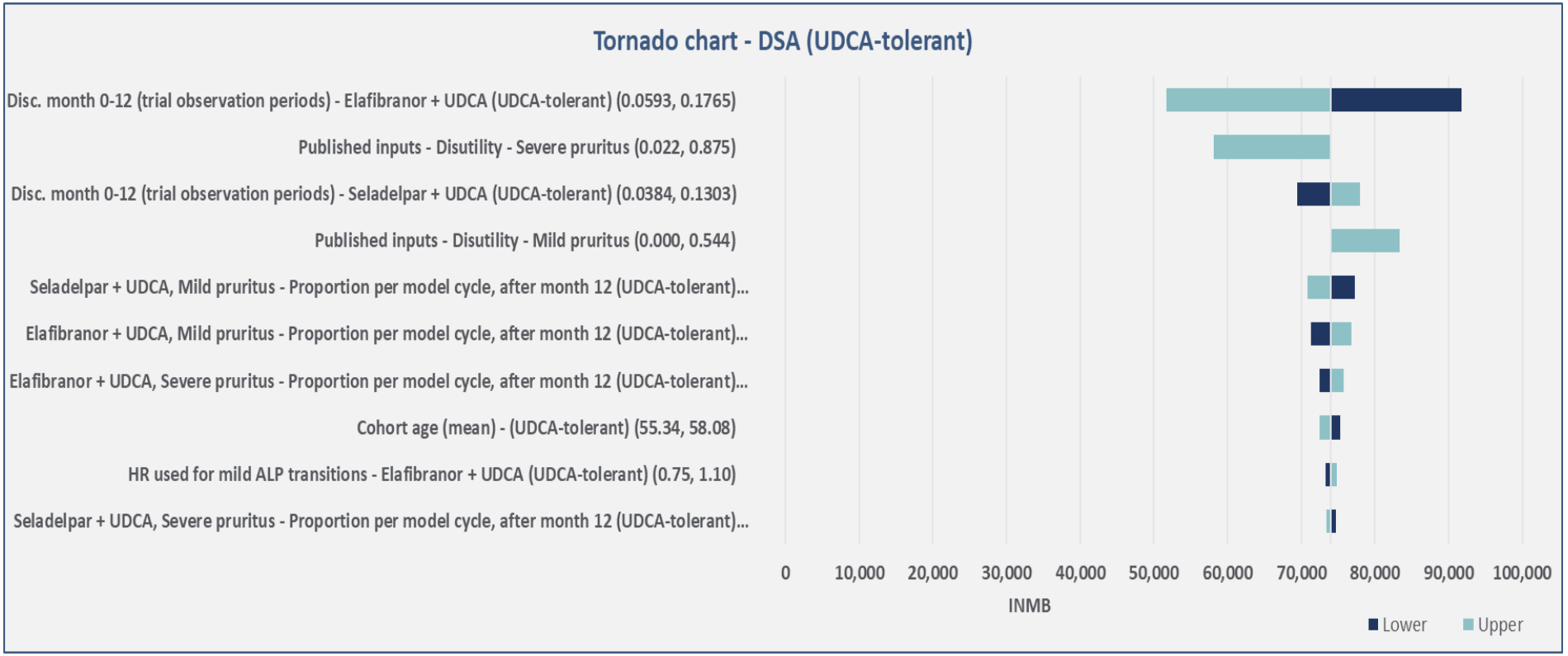


Figure 13 Tornado vs. OCA, UDCA intolerant population

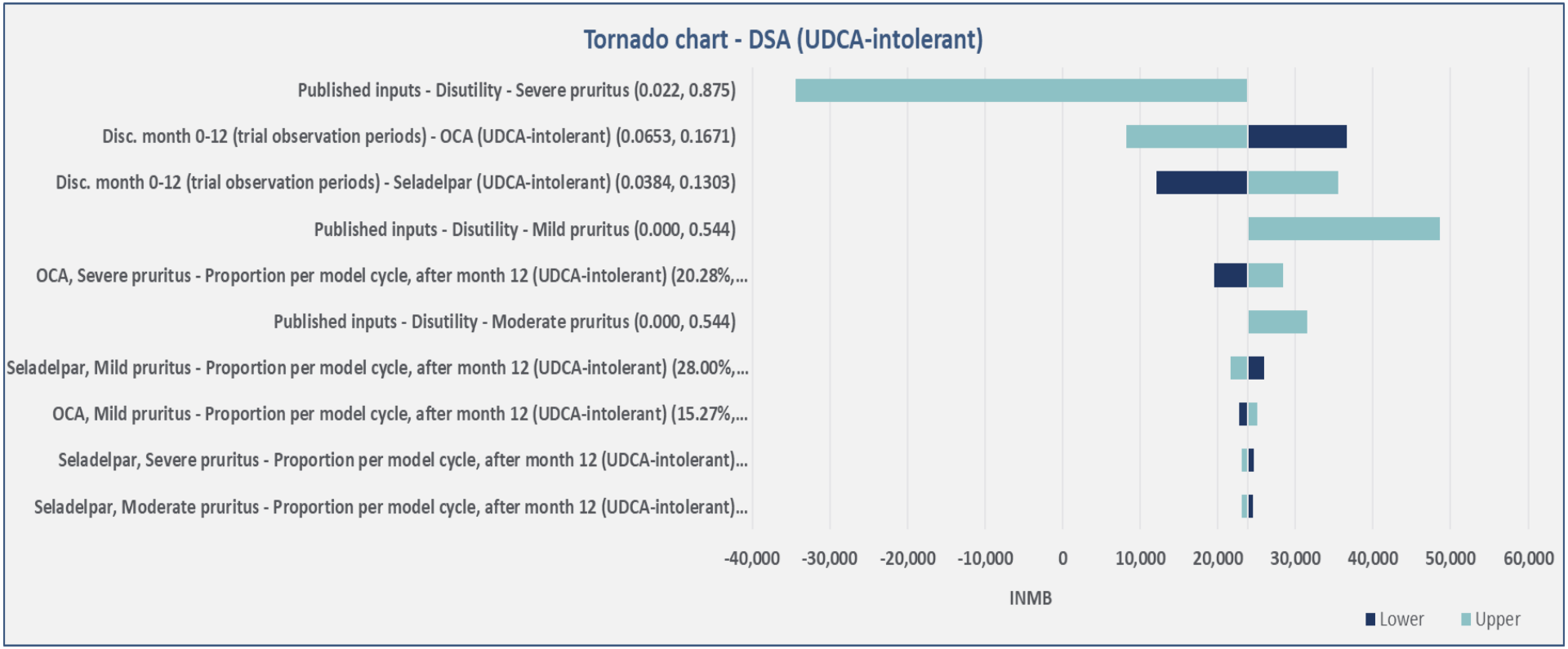
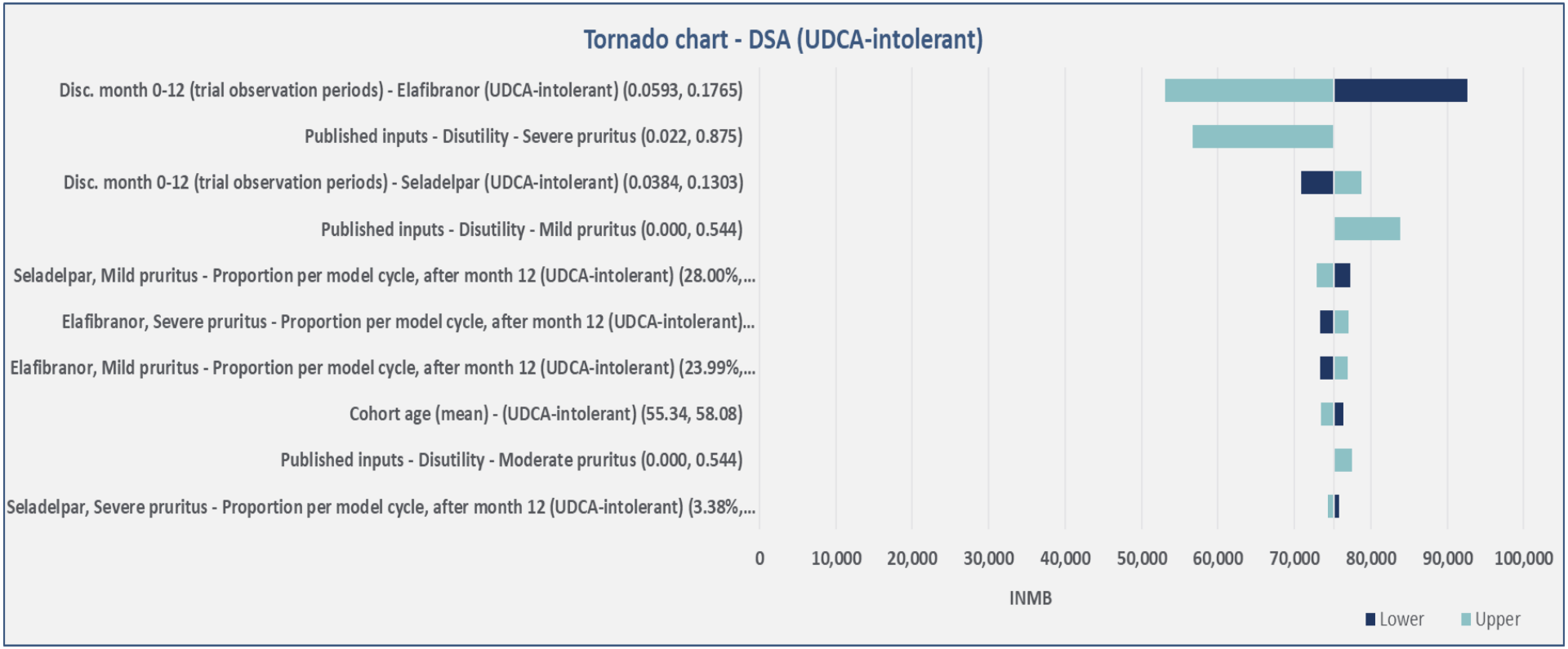


Figure 14 Tornado vs. elafibranor, UDCA intolerant population



Updated scenario analysis results with corrected pruritus distribution:

Table 77 Summary of updated scenario analyses with corrected pruritus distribution (UDCA-tolerant)

No.	Base case setting	Scenario	Incremental costs	Incremental QALYs	INMB
Results vs. OCA + UCDA					
	Base case results		**-4,980**	**0.836**	**21,691**
1	Disc. probs. beyond M12 equal to 0.28 month 0-12 values (all treatments)	Disc. probs. beyond M12 equal to 0.5 month 0-12 values	24,573	0.913	-6,317
2	Disc. probs. beyond M12 equal to 0.28 month 0-12 values (all treatments)	Disc. probs. beyond M12 equal to 0.28 month 0-12 values	18,801	0.916	-487
3	Comparator ORs for pruritus from ITC	Comparator ORs for pruritus set to 1	-3,788	0.292	9,631
4	Time horizon: 50 years	Time horizon: 10 years	-2,698	0.383	10,349
5	Pruritus disutilities: Smith et al.	Pruritus disutilities: None	-4,980	0.282	10,624
6	Pruritus disutilities: Smith et al.	Pruritus disutilities: RESPONSE - EQ-5D-3L - MMRM	-4,980	0.377	12,516
7	Beyond M12 PBC TPS: M9-12 LOCF – calibrated to LTFS	Beyond M12 PBC TPS: M9-12 LOCF - Improvements possible (all treatments)	2,607	0.792	13,225
8	Comparator HRs for PBC state TPs from ITC	Comparator HRs for PBC state TPs set to 1	-2,786	0.618	15,148
9	Beyond M12 PBC TPS: M9-12 LOCF – calibrated to LTFS	Beyond M12 PBC TPS: M9-12 LOCF - No improvements (UDCA mono/ BSC) - Improvements (SEL/ ELA/ OCA)	1,886	0.854	15,201
10	Disc. probs. beyond M12 equal to 0.28 month 0-12 values (all treatments)	Disc. probs. beyond M12 equal to SEL month 0-12 value; (all treatments)	-8,525	0.747	23,467
Results vs. elafibranor + UCDA					
	Base case results		**-66,235**	**0.391**	**74,065**
1	Disc. probs. beyond M12 equal to 0.28 month 0-12 values (all treatments)	Disc. probs. beyond M12 equal to 0.5 month 0-12 values	-19,687	0.499	29,662

2	Time horizon: 50 years	Time horizon: 10 years	-40,005	0.159	43,193
3	Disc. probs. beyond M12 equal to 0.28 month 0-12 values (all treatments)	Disc. probs. beyond M12 equal to 0.28 month 0-12 values	-36,898	0.482	46,542
4	Disc. probs. beyond M12 equal to 0.28 month 0-12 values (all treatments)	Disc. probs. beyond M12 equal to SEL month 0-12 value; (all treatments)	-45,208	0.344	52,088
5	Disc. probs. beyond M12 equal to 0.28 month 0-12 values (all treatments)	Disc. probs. beyond M12: None	-80,723	0.426	89,238
6	Disc. probs. beyond M12 equal to 0.28 month 0-12 values (all treatments)	Disc. probs. beyond M12 equal to 0.5 SEL month 0-12 value; (all treatments)	-57,926	0.372	65,372
7	Beyond M12 PBC TPS: M9-12 LOCF – calibrated to LTFS	Beyond M12 PBC TPS: M9-12 LOCF - Improvements possible (all treatments)	-59,029	0.370	66,426
8	Beyond M12 PBC TPS: M9-12 LOCF – calibrated to LTFS	Beyond M12 PBC TPS: M9-12 LOCF - No improvements (UDCA mono/ BSC) - Improvements (SEL/ ELA/ OCA)	-59,768	0.432	68,405
9	Complete case analysis	Missing imputed as CC/ Elevated Bilirubin for RESPONSE TPs	-60,699	0.402	68,745
10	Comparator ORs for pruritus from ITC	Comparator ORs for pruritus set to 1	-65,867	0.223	70,335

NICE National Institute for Health and Care Excellence

Single Technology Appraisal

Seladelpar for previously treated primary biliary cholangitis [ID6429]

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].

Information on completing this submission

- 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
- We are committed to meeting the requirements of copyright legislation. If you intend to include **journal articles** in your submission you must have copyright clearance for these articles. We can accept journal articles in NICE Docs.
- Your response should not be longer than 10 pages.

NICE National Institute for Health and Care Excellence

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 c 40,000 patient members, our nurse-led Helpline handles c 500 enquiries a month, regular newsletter goes to circa 27,000 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? [Relevant companies are listed in the appraisal stakeholder list.]	The British Liver Trust has received the following grants in the last **12 months**: Ipsen: £5000 to support our Yellow Alert campaign which aims to raise awareness of the quick and simple early signs of liver disease in newborn babies. £5000 for a survey of parents of children and young people with liver disease Gilead: Three separate grants(£3,320, £4,980, and £8,300) all to support our hepatitis B programme of work Advanz Pharmaceuticals: £15,000 for patient support – our helpline and support groups

If so, please state the name of the company, amount, and purpose of funding.	**All grants are arm's length, and the company has no input into any content. The activities are not related to any 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 208 enquires from patients or carers with PBC for this submission. This accounts for over 40 hours of helpline time. The callers were predominantly female (over 85%) which would fit with the epidemiology. 2. Feedback and comments via threads and a specific ask on our liver community forum (40K members) 3. Insight gained from patients attending British Liver Trust support groups 4. Insight gained from a focus group held in February 2024 5. Individual telephone interviews with patients 6. Literature search and review of current guidelines 7. We were unable to speak to either a patient or a clinician who had been involved in trials on this occasion due to time constraint

NICE National Institute for Health and Care Excellence

Patient organisation submission
British Liver Trust

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 many 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. This leads to feelings of isolation and not being able to discuss it with anyone, and they feel no one understands – however many have also spent some time before being diagnosed trying to cope with unexplained symptoms. 'I felt like I was going mad, and it was all in my head – I am quite a young woman, why am I feeling this way' It can therefore be a relief to finally have a diagnosis to explain their ongoing symptoms. 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 itching and fatigue. Patients and carers tell us that these particularly symptoms of itch (pruritis) and fatigue can significantly affect their quality of life. 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:

	"I am really struggling at work – I can't concentrate when I am constantly itching and scratching" " My husband gets so upset to see me scratching myself with a coat hanger- its the only relief I get" "I am too embarrassed to go out with my friends – I am constantly scratching and I worry that they think its contagious" "Because I scratch so much there is always blood on my clothes where I have broken the skin – it really gets me down" "I feel like I don't know what normal life is like anymore – I am constantly distracted by the itch – I can't concentrate on the TV or family conversations" "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. 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. Patients with fatigue often say that they have difficulty asking for help as others think "everyone feels tired". Some quotes from patients with PBC about fatigue: "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." "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." "I used to like running now I can't even walk to the local shop" Some patients also experience issues with digestion such as feeling bloated, nauseas or having diarrhoea. One patient said: "Nobody warned me about the digestive problems. Some days, I feel like I can't eat anything without paying for it later—bloating, discomfort, unpredictable bowel issues. It's exhausting and also embarrassing. I don't like talking about it."

	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."

NICE National Institute for Health and Care Excellence

Current treatment of the condition in the NHS

Patient organisation submission
British Liver Trust

7. 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 gastro intestinal disturbance – including bloating, diarrhoea and nausea 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 of the available treatments. It was around that time, I was told I would eventually need a liver transplant. I had a transplant 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. Some patients tell us that their itch worsens when they are on obeticholic acid. For some patients these treatments cannot control PBC. In November 2024, NICE approve Elafibranor as a second line treatment. If a patient has been taking ursodeoxycholic acid (UDCA) and it is shown not to be fully effective, elafibranor can be given together with UDCA. If they were taking UDCA but were experiencing intolerable side effects, elafibranor can be taken instead of UDCA. Feedback from patients suggests that many patients are still not being given the opportunity for this second line treatment and there is variation in access depending on whether they are being treated in a specialist centre. There is a need for more treatment options for these patients so that they have a choice and also for new second line treatments to be provided equitably across England.

	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 is not very palatable and has a very unusual texture which means patients often really struggle to take it . Colestyramine, can stop other medicines from being absorbed properly so needs to be taken at least 4 hours before or after any other medicines, which can also mean it is challenging to fit in with other prescribed medications. 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. The impact on quality of life, living with persistent, unresolved symptoms is intolerable for many patients. Patients also express their frustration at accessing second line treatments if there are inadequate pathways to access specialist hepatology care. For some patients the only option is a liver transplant and sadly for some of these patients their PBC recurs

Advantages of the technology

9. What do patients or carers think are the advantages of the technology?	Seladelpar is particularly good at addressing a lower incidence of pruritus. Some PBC patients may also respond better to a treatment other than Elafibranor and it's important that there is a choice of second line treatments.

Disadvantages of the technology

10. What do patients or carers think are the disadvantages of the technology?	

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.	

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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

14. In up to 5 bullet points, please summarise the key messages of your submission.	• Living with PBC is challenging – with many patients reporting itch, fatigue and gastro problems as severely impacting quality of life. • PBC can lead to cirrhosis, decompensated cirrhosis, hepatocellular carcinoma and liver transplantation • 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 for additional second line treatments

Thank you for your time.

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Your privacy

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NICE National Institute for Health and Care Excellence

Single Technology Appraisal

Seladelpar for previously treated primary biliary cholangitis [ID6429]

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

- 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
- We are committed to meeting the requirements of copyright legislation. If you intend to include **journal articles** in your submission you must have copyright clearance for these articles. We can accept journal articles in NICE Docs.
- Your response should not be longer than 13 pages.

About you

1. Your name	[redacted]
2. Name of organisation	1) The British Association for the Study of the Liver (BASL) [redacted]
3. Job title or position	1) Chair of the BASL Special Interest Groups (BASL SIG) for Immune-Mediated and Cholestatic Liver Diseases 2) Associate Professor of Cholestatic and Immune-Mediated Liver Diseases 3) Consultant Hepatologist
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).	1) 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. 2) The Centre for Liver and Gastrointestinal Research focuses on the basic, translational and clinical aspects of human liver disease. It is funded through the National Institute of Health Research (NIHR) Birmingham Biomedical Research Centre (BRC) at the University of Birmingham (a public research university, which received its royal charter in 1900). 3) The Liver Unit is one of the largest in the UK, providing a comprehensive range of secondary and tertiary services (hepatology, hepatopancreatobiliary, and transplantation). The unit serves a population of >17.1 million people, and houses UK's dedicated autoimmune and cholestatic liver disease programme.

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.**	1) BASL Gilead (company) - BASL received £56,194 in sponsorship funding towards their Annual Conference and other educational events between November 2023 and November 2024. Ipsen Ltd (comparator) - BASL received £61,800 in sponsorship funding towards their Annual Conference and other educational events between November 2023 and November 2024. Advanz Pharma (comparator) – BASL received £44,898.73 in sponsorship funding towards their Annual Conference and other educational events between November 2023 and November 2024. Dr. Falk Pharma UK Ltd (comparator) - BASL received £15,600 in sponsorship funding towards their Annual Conference and other educational events between November 2023 and November 2024. 2) Centre for Liver and Gastrointestinal Research, University of Birmingham (UK)- peer-reviewed research grant funding for specific research groups with the Centre for Liver and Gastrointestinal Research. 3) Liver Unit, University Hospitals Birmingham (UK) - none
5c. Do you have any direct or indirect links with, or funding from, the tobacco industry?	1) NO 2) NO 3) 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.)	1) Improve and normalise liver biochemistry; a marker associated with reduced risk of liver disease progression (lower risks of needing a liver transplant / dying from liver disease in the future). 2) Improve symptoms related to liver disease (itching), which is associated with better quality of life for patients.
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.)	**Essential**: Reduction in liver biochemistry (termed biochemical response; determined after a minimum of 12-months therapy). These criteria are associated with a significantly lower risk of liver disease progression compared to biochemical non-responders. - Serum ALP values below 1.67x the upper limit of normal and/or a reduction by 15% from pre-treatment values; - Maintenance/reduction of serum bilirubin values below the upper limit of normal. **Desirable** Normalisation in liver biochemistry (determined after a minimum 12 months of therapy). Attaining this target is associated with the lowest probability of liver disease progression, and a survival gain beyond biochemical non-response alone, specifically in patients aged less than 62 years at diagnosis and those with evidence of advanced liver fibrosis on non-invasive testing (transient elastography readings above 10 kPa). - Normalisation in serum ALP values - Normalisation in serum ALT and/or AST values - Reduction in pruritus (itch) intensity
8. In your view, is there an unmet need for patients and healthcare professionals in this condition?	Yes, absolutely.

What is the expected place of the technology in current practice?

9. How is the condition currently treated in the NHS?	1) Attenuating disease progression: first-line treatment (at diagnosis) consists of ursodeoxycholic acid. Approximately 60% of patients lower liver biochemistry to below the biochemical response threshold with ursodeoxycholic acid alone. However, 40% do not; and a larger proportion maintain biochemical values above the upper limit of normal. These individuals are candidates for second-line therapies. Currently, the licensed second-line therapies consist of either (a) Obeticholic acid; and (b) Elafibranor. Both these therapies have been shown to improve liver biochemistry amongst people who are either intolerant of, or incompletely respond to Ursodeoxycholic acid. However, the proportion of people who normalise ALP values under Obeticholic acid (4% at 12 months) and Elafibranor treatment (≤15% at 12 months) are low, and neither drug convincingly attenuates pruritus symptoms. Moreover, Obeticholic acid has been shown to exacerbate pruritus in small numbers of patients, limiting use in those with active itch symptoms from their PBC. Off-label / non-licensed therapies are occasionally prescribed as second-line therapy; specifically oral bezafibrate. 2) Symptom control: At present, there is only one licensed medication for the treatment of pruritus in PBC (Colestyramine). This drug is effective in approximately 30% of patients. However, it cannot be taken with other oral medicines, is unpalatable, and leads to gastrointestinal side effects (constipation). Other anti-pruritic medications are available but off-license / off-label; such as rifampicin, sertraline, bezafibrate and naltrexone. The other principal symptoms of PBC, such as fatigue and cognitive impairment (brain fog) do not have any licensed medical therapies. 3) Extrahepatic manifestations: (a) Assessment and treatment of low bone mineral density; and (B) PBC-related Sicca syndrome, a condition associated with dry eyes and mouth, that's is treated conservatively through topical lubricants and/or pilocarpine (muscarinic receptor agonist). 4) Screening and surveillance for complications: as disease progresses, the condition progresses to cirrhosis, warranting surveillance for the development of (a) hepatocellular carcinoma, (b) gastroesophageal varices, and (c) ascites. 5) Timely assessment for liver transplantation: organ transplantation is reserved for those individuals who have not responded to current first and second-line therapies, who develop persistent jaundice, hepatic

	decompensation refractory to medical therapy (ascites, gastrointestinal bleeding from portosystemic varices, or hepatic encephalopathy), or cirrhosis-related hepatocellular carcinoma.
9a. Are any clinical guidelines used in the treatment of the condition, and if so, which?	Joint UK-PBC and BSG PBC guidelines (published in 2018; currently in the process of being updated).
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 is currently well-defined. Differences in clinical practice do exist (as reflected in national audit data), but these are largely due to deviations / inadequate adoption of guideline recommendations (Abbas et al. JHep. Reports 2023).
9c. What impact would the technology have on the current pathway of care?	The technology would provide a large (positive) step change in the management of patients with PBC, as it would be the first licensed medicine proven to (a) normalise liver biochemistry in one / 4 patients who inadequately respond to first-line therapy; (b) induce liver biochemical reductions in patient groups who inadequately responded to ursodeoxycholic acid, off-label bezafibrate and obeticholic acid; and (c) attenuate PBC-related pruritus symptoms.
10. Will the technology be used (or is it already used) in the same way as current care in NHS clinical practice?	Similar. The technology would be used in PBC patients with an inadequate biochemical response (or intolerance) to first-line therapy in ursodeoxycholic acid, and/or in patients with abnormal biochemistry and persistent itch/pruritus symptoms despite colestyramine.
10a. How does healthcare resource use differ between the technology and current care?	The technology would be administered as a once daily, fixed dose oral medication. This differs to Obeticholic acid (which requires dose titration according to duration of treatment and liver disease stage). The technology does not differ, in terms of resource use, from Obeticholic acid or Elafibranor, from an NHS standpoint.
10b. In what clinical setting should the technology be used? (For example,	Specialist secondary and tertiary care services: currently, prescription of any/all second-line treatments in PBC are the responsibilities of large volume PBC “hub” centres (approximately 35 in England), that serve geographically defined operational delivery networks comprising smaller volume “spoke” sites.

primary or secondary care, specialist clinics.)	
10c. What investment is needed to introduce the technology? (For example, for facilities, equipment, or training.)	No additional investment. The technology will use existing infrastructure in the NHS (hospital pharmacies, homecare medicines providers for medicine delivery, etc.)
11. Do you expect the technology to provide clinically meaningful benefits compared with current care?	Yes. The medicine provides PBC patients with another treatment option; the first to lower (normalise) liver biochemistry AND improve pruritus-related symptoms. This is despite (in addition to) existing medical therapies to treat PBC.
11a. Do you expect the technology to increase length of life more than current care?	Yes. Robust population-based data, alongside several multicentre (international) cohort studies have shown that biochemical response, and in particular normalisation in ALP values, associates with long-term transplant-free survival rates akin to that of an age- and sex-matched population without PBC. The ability of Seladelpar to induce these biochemical changes, which are durable over time, is therefore expected to prolong life-expectancy in PBC patients.
11b. Do you expect the technology to increase health-related quality of life more than current care?	Yes. Seladelpar has been shown to attenuate PBC-related pruritis symptoms in a durable manner (over at least 18 months), which has not been demonstrated by any other licensed therapy before.
12. Are there any groups of people for whom the technology would be more or less effective (or appropriate) than the general population?	Individuals with PBC and normal liver biochemistry / near normal liver biochemistry whilst taking ursodeoxycholic acid, who do not have pruritus. Individuals with serum ALP values between 1.0x to 1.67x the upper limit of normal, who have a normal serum bilirubin, a transient elastography reading <10 kPa, and an age >62 years at first presentation/diagnosis.

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 affecting patient acceptability or ease of use or additional tests or monitoring needed.)	Not envisaged to be more difficult for patients or healthcare professionals to use than current therapies. Seladelpar will be initiated alongside ursodeoxycholic acid (unless there is documentary evidence of drug intolerance to the later). Monitoring will be conducted through dedicated PBC ODN hub centres.
14. Will any rules (informal or formal) be used to start or stop treatment with the technology? Do these include any additional testing?	Seladelpar will be administered (and treatment responses monitored) by hub centres as part of dedicated PBC ODNs, for individuals with ANY of the following: - Persistently elevated ALP values (>1.67x ULN) despite first-line therapy in ursodeoxycholic acid; - Intolerance to ursodeoxycholic acid - Elevated bilirubin values above the upper limit of normal, but below 50 micromol/L - Elevated ALP values and persistent cholestatic pruritus despite colestyramine Stopping rules will be set as: - Development of hepatic decompensation on therapy

	- Development of abnormal renal function - Intolerance of Seladelpar - No reduction is serum ALP values (<15% pre-treatment readings) after 12 months of therapy.
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?	The technology has the ability to lower serum lipid levels (total cholesterol, LDL-C and triglycerides), and thus may lower the risks of cardiovascular / cerebrovascular events when taken long-term.
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?	Please see above (sections 11 and 12)
16a. Is the technology a 'step-change' in the management of the condition?	Please see above (section 9c)
16b. Does the use of the technology address any particular unmet need of the patient population?	Yes: - Persistent biochemical non-response despite currently available first and second-line therapy - Pruritus-related to PBC

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?	No major side effects / adverse events have been documented in the clinical trials of Seladelpar. However, the compound is a focussed peroxisome proliferator activated receptor delta agonist. There is potential for myalgia and the development of elevated creatinine values (from other, less specific pan- or dual PPAR agonists). Therefore monitoring of renal function and myalgia symptoms will be undertaken, for patients on Seladelpar, and any such side effects documented and reported using the yellow card system should they occur (not expected though).

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?	N/A
18b. What, in your view, are the most important outcomes, and were they measured in the trials?	All the following outcomes (which are considered important) were captured in the clinical trials: - Reduction in serum ALP, ALT and AST values - Normalisation in serum ALP values - Maintenance of serum bilirubin and albumin values - Maintenance of transient elastography readings - Attenuation in pruritus symptoms The following were not captured in the clinical trials, given the variable and often slowly progressive clinical course of PBC as a disease (i.e., taking years/decades for patients to reach a major liver-related clinical event).

	- Rates of liver transplantation - Mortality rate - Incidence of hepatocellular carcinoma - Incidence of hepatic decompensation
18c. If surrogate outcome measures were used, do they adequately predict long-term clinical outcomes?	Yes (Ref. Lammers et al. Gastro. 2014).
18d. Are there any adverse effects that were not apparent in clinical trials but have come to light subsequently?	No.
19. Are you aware of any relevant evidence that might not be found by a systematic review of the trial evidence?	No dedicated systematic reviews on the topic so far.
20. Are you aware of any new evidence for the comparator treatment since the publication of NICE technology appraisal guidance on obeticholic acid in combination with ursodeoxycholic acid for treating primary biliary cholangitis [TA443]?	No

21. How do data on real-world experience compare with the trial data?	No real world experience of this technology so far.

Equality

22a. Are there any potential equality issues that should be taken into account when considering this treatment?	No
22b. Consider whether these issues are different from issues with current care and why.	N/A

Key messages

23. In up to 5 bullet points, please summarise the key messages of your submission.	• Seladelpar is a first-in class PPAR-delta agonist, which is able to induce biochemical response in patients with PBC who inadequately respond to first-line therapy (ursodeoxycholic acid). Biochemical response is a consistently validated metric associated with transplant-free survival rates that mirror an age- and sex-matched control population. • One in 4 patients treated with Seladelpar normalise serum ALP values, which for those aged below 62 years and/or having advanced liver fibrosis, is associated with at least four extra years of life gained beyond meeting biochemical response criteria alone. • Seladelpar is the first compound that has been shown to attenuate pruritus in PBC long-term (>1 year) in clinical trials. • Side effects from Seladelpar are few and far between, with no major adverse events related to study drug demonstrated in clinical trials to date. • Alongside the above, Seladelpar has been shown to lower serum lipid levels (total cholesterol, LDL-C and triglycerides), which may associate with lower rates of cardiovascular and cerebrovascular events amongst treated patients.

Thank you for your time.

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Your privacy

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Single Technology Appraisal

Seladelpar for previously treated primary biliary cholangitis [ID6429]

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- Your response should not be longer than 13 pages.

NICE National Institute for Health and Care Excellence

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 or No A specialist in the treatment of people with this condition? Yes or No A specialist in the clinical evidence base for this condition or technology? Yes or No Other (please specify):
5a. Brief description of the organisation (including who funds it).	We are the pharmacy affiliate Group for the British Association for the Study of the Liver. This is the National Association for specialists in liver disease (hepatology). 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.**	**Sponsor** / **Amount** Norgine — £2000 +vat Ipsen — £2500 +vat Dr Falk — £2500 +vat Advanz Pharma — £2500 +vat Gilead — £2500 +vat
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 and symptom relief.
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) which is licensed, elafibranor (newly licensed) and bezafibrate which is unlicensed. Biochemical response rates of OCA, elafibranor and bezafibrate vary, but are reported to be between 30-50%. 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, elafibranor 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.)	Pathway of care is well defined and highlighted in the UK-PBC care pathway and as per BSG guidance. Second line therapies are being developed in a ODN Hub and spoke type fashion. 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?	It was sit in the second line treatment category and would compete with obeticholic acid, elafibranor and bezafibrate.
10. Will the technology be used (or is it already used) in the same way as current care in NHS clinical practice?	It is not currently used but if approved it would need to be incorporated into the current algorithm of care. The published measures 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 seladelpar would be overseen and monitored by the same infrastructure and staff. However there was no additional funding for this and as the number of high cost medications increase, additional funding for prescribing and dispensing this would increase availability for patients.
10b. In what clinical setting should the technology be used? (For example, primary or secondary care, specialist clinics.)	Should be used in secondary care as second or third line therapy. It should be delivered through specialist clinics overseen by hub centres but ideally prescribing should not be restricted to just the hub centres.
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. PBC network/ODN was never funded but rather became an extension of HCV ODN model which may not be appropriate in all centres with high volumes of patients. With growing awareness and increasing number of patients diagnosed with PBC and requiring second line treatment investment is needed in terms of clinic space and trained HCPs to safely manage this.

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 current second line treatment options.
11a. Do you expect the technology to increase length of life more than current care?	We do not think there is current evidence of this but in theory if it can reduce progression of disease then it should increase length and quality of life.
11b. Do you expect the technology to increase health-related quality of life more than current care?	No head to head comparison with this and other second line agents.
12. Are there any groups of people for whom the technology would be more or less effective (or appropriate) than the general population?	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	It's a simple tablet formulation with a minimal side effect profile. Staff would easily be able to be educated around this and monitoring requirements.

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 and second therapy for PBC(Obeticholic acid and elafibranor).
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?	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?	Although it has some crossover activity (PPAR delta) with elafibranor, trials have shown benefit and allows for another option for the treatment of PBC in those who have failed other agents.
16a. Is the technology a 'step-change' in the management of the condition?	No, but it is another second line agent.

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 seladelpar were abdominal symptoms including abdominal pain, diarrhoea, nausea and vomiting as well as headaches which did not require cessation of drug. 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 seladelpar 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?	Biochemical response and symptom improvement including pruritus.
18c. If surrogate outcome measures were used, do they adequately predict long-term clinical outcomes?	Yes

18d. Are there any adverse effects that were not apparent in clinical trials but have come to light subsequently?	All data is from clinical trials at the moment.
19. Are you aware of any relevant evidence that might not be found by a systematic review of the trial evidence?	No
20. Are you aware of any new evidence for the comparator treatment since the publication of NICE technology appraisal guidance on obeticholic acid in combination with ursodeoxycholic acid for treating primary biliary cholangitis [TA443]?	Elafibranor is another comparator but no head to head data.
21. How do data on real-world experience compare with the trial data?	No real world data.

Equality

22a. Are there any potential equality issues that should be taken into account when considering this treatment?	We need to ensure that there are strong referral links in place so patients who are usually seen at spoke centres are not disadvantaged in timely access to second-line therapies. I think opening up prescribing with shared care in place would limit this.
22b. 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

23. In up to 5 bullet points, please summarise the key messages of your submission.	• Seladelpar is another agent that could be offered to patient who have not responded to first or current second line treatment. • It will fit in to the existing model of care and medication delivery pathways that have been already established • It has a good and manageable safety profile. • Some investment should be considered in developing formal PBC networks to promote less variation in care and access to this new treatment •

Thank you for your time.

Please log in to your NICE Docs account to upload your completed submission.

Your privacy

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NICE National Institute for Health and Care Excellence

Single Technology Appraisal

Seladelpar for previously treated primary biliary cholangitis [ID6429]

Clinical expert statement and technical engagement response form

Thank you for agreeing to comment on the external assessment report (EAR) for this evaluation, and for providing 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. The EAR and stakeholder responses are used by the committee to help it make decisions at the committee meeting. Usually, only unresolved or uncertain key issues will be discussed at the meeting.

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.

We are committed to meeting the requirements of copyright legislation. If you want to include **journal articles** in your submission you must have copyright clearance for these articles. We can accept journal articles in NICE Docs. For copyright reasons, we will

have to return forms that have attachments without reading them. You can resubmit your form without attachments, but it must be sent by the deadline.

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.

Please note, part 1 can be completed at any time. We advise that **part 2** is completed after the expert engagement teleconference (if you are attending or have attended). At this teleconference we will discuss some of the key issues, answer any specific questions you may have about the form, and explain the type of information the committee would find useful.

The deadline for your response is **5pm** on **Wednesday 17th June.** 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 during engagement, 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 during engagement 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.

Clinical expert statement

Seladelpar for previously treated primary biliary cholangitis [ID6429]

NICE National Institute for Health and Care Excellence

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	Palak Trivedi
2. Name of organisation	1) The British Association for the Study of the Liver (BASL) 2) Centre for Liver and Gastrointestinal Research, University of Birmingham (UK) 3) Liver Unit, University Hospitals Birmingham (UK)
3. Job title or position	1) Chair of the BASL Special Interest Groups (BASL SIG) for Immune-Mediated and Cholestatic Liver Diseases 2) Associate Professor of Cholestatic and Immune-Mediated Liver Diseases 3) 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 PBC? ☒ A specialist in the clinical evidence base for PBC 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.	☐ Yes

(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
8. What is the main aim of treatment for PBC? (For example, to stop progression, to improve mobility, to cure the condition, or prevent progression or disability)	1) Improve (normalise) liver biochemistry; a marker associated with reduced risk of liver disease progression (lower risks of needing a liver transplant / dying from liver disease in the future). 2) Improve symptoms related to liver disease (itching), which is associated with better quality of life for patients.
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)	**Essential**: - Reduction in liver biochemistry (termed biochemical response; determined after a minimum of 12-months therapy). These criteria are associated with a significantly lower risk of liver disease progression compared to biochemical non-responders. - Serum ALP values below 1.67x the upper limit of normal and/or a reduction by 15% from pre-treatment values; - Maintenance/reduction of serum bilirubin values below the upper limit of normal. **Desirable** - Normalisation in liver biochemistry (determined after a minimum 12 months of therapy). Attaining this target is associated with the lowest probability of liver disease progression, and a survival gain beyond biochemical non-response alone, specifically in patients aged less than 62 years at diagnosis and those with evidence of advanced liver fibrosis on non-invasive testing (transient elastography readings above 10 kPa). - Normalisation in serum ALP values - Normalisation in serum ALT and/or AST values - Reduction in pruritus (itch) intensity

10. In your view, is there an unmet need for patients and healthcare professionals in PBC?	Yes, absolutely.
11. How is PBC 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?	Overview of PBC treatment in the UK / NHS 1) Attenuating disease progression: first-line treatment (at diagnosis) consists of ursodeoxycholic acid. Approximately 60% of patients lower liver biochemistry to below the biochemical response threshold with ursodeoxycholic acid alone. However, 40% do not; and a larger proportion maintain biochemical values above the upper limit of normal. These individuals are candidates for second-line therapies. Currently, the licensed second-line therapies consist of either (a) Obeticholic acid; and (b) Elafibranor. Both these therapies have been shown to improve liver biochemistry amongst people who are either intolerant of, or incompletely respond to Ursodeoxycholic acid. However, the proportion of people who normalise ALP values under Obeticholic acid (4% at 12 months) and Elafibranor treatment (≤15% at 12 months) are low, and neither drug convincingly attenuates pruritus symptoms. Moreover, Obeticholic acid has been shown to exacerbate pruritus in small numbers of patients, limiting use in those with active itch symptoms from their PBC. Off-label / non-licensed therapies are occasionally prescribed as second-line therapy; specifically oral bezafibrate. 2) Symptom control: At present, there is only one licensed medication for the treatment of pruritus in PBC (Colestyramine). This drug is effective in approximately 30% of patients. However, it cannot be taken with other oral medicines, is unpalatable, and leads to gastrointestinal side effects (constipation). Other anti-pruritic medications are available but off-license / off-label; such as rifampicin, sertraline, bezafibrate and naltrexone. The other principal symptoms of PBC, such as fatigue and cognitive impairment (brain fog) do not have any licensed medical therapies.

	3) Extrahepatic manifestations: (a) Assessment and treatment of low bone mineral density; and (B) PBC-related Sicca syndrome, a condition associated with dry eyes and mouth, that's is treated conservatively through topical lubricants and/or pilocarpine (muscarinic receptor agonist). 4) Screening and surveillance for complications: as disease progresses, the condition progresses to cirrhosis, warranting surveillance for the development of (a) hepatocellular carcinoma, (b) gastroesophageal varices, and (c) ascites. 5) Timely assessment for liver transplantation: organ transplantation is reserved for those individuals who have not responded to current first and second-line therapies, who develop persistent jaundice, hepatic decompensation refractory to medical therapy (ascites, gastrointestinal bleeding from portosystemic varices, or hepatic encephalopathy), or cirrhosis-related hepatocellular carcinoma. PBC treatment pathways are generally well-defined. Differences in clinical practice do exist (as reflected in national audit data), but these are largely due to deviations / inadequate adoption of guideline recommendations (Abbas et al. JHep. Reports 2023). With regards guidelines, there are joint UK-PBC and BSG PBC guidelines (published in 2018) which are currently in the process of being updated.
12. What is the current order of treatments for PBC in the pathway?	Seladelpar would provide a large (positive) step change in the management of patients with PBC, as it would be the first licensed medicine proven to (a) normalise liver biochemistry in one out of 4 patients who inadequately respond to first-line therapy; (b) induce liver biochemical reductions in patient groups who

• Would seladelpar be used after OCA or elafibranor? And if so, would its clinical effectiveness be expected to differ at later lines? • Are any treatments ever used in combination? • Are fibrates used to treat primary biliary cholangitis? And if so, where are they used in the treatment pathway? • Would clinicians ever choose fibrates over OCA or elafibranor as a treatment option? • Is there a preferred treatment sequence for current treatments for PBC?	inadequately responded to ursodeoxycholic acid, off-label bezafibrate and obeticholic acid; and (c) attenuate PBC-related pruritus symptoms.
13. 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? • 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)	Similar. The technology would be used in PBC patients with an inadequate biochemical response (or intolerance) to first-line therapy in ursodeoxycholic acid (including, but not limited to those who lack responses / are intolerant to other currently available second-line agents), and/or in patients with abnormal biochemistry and persistent itch/pruritus symptoms despite colestyramine. Seladelpar would be administered as a once daily, fixed dose oral medication. This differs to Obeticholic acid (which requires dose titration according to duration of treatment and liver disease stage). The technology does not differ, in terms of resource use, from Obeticholic acid or Elafibranor, from an NHS standpoint. It is envisaged that the decision to initiate Seladelpar (and prescription of such) will be by specialist secondary and tertiary care services (i.e. hubs of existing operational delivery networks; ODNs). Currently, prescription of any/all second-line treatments in PBC are the responsibilities of these large volume PBC “hub”

	centres (approximately 35 in England), that serve geographically defined operational delivery networks comprising smaller volume “spoke” sites. No additional investment is needed as such. As a technology, Seladelpar will use existing infrastructure in the NHS (hospital pharmacies, homecare medicines providers for medicine delivery, etc.).
14. 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?	Seladelpar provides PBC patients with another treatment option; the first to lower (normalise) liver biochemistry AND improve pruritus-related symptoms. This is despite (in addition to) existing medical therapies to treat PBC. Additionally, robust population-based data, alongside several multicentre (international) cohort studies have shown that biochemical response, and in particular normalisation in ALP values, associates with long-term transplant-free survival rates akin to that of an age- and sex-matched population without PBC. The ability of Seladelpar to induce these biochemical changes, which are durable over time, is therefore expected to prolong life-expectancy in PBC patients. Additionally, seladelpar has been shown to attenuate PBC-related pruritis symptoms in a durable manner (over at least 18 months), which has not been demonstrated by any other licensed therapy before.
15. Are there any groups of people for whom the technology would be more or less effective (or appropriate) than the general population?	Individuals with PBC and normal liver biochemistry / near normal liver biochemistry whilst taking ursodeoxycholic acid, who do not have pruritus. Individuals with serum ALP values between 1.0x to 1.67x the upper limit of normal, who have a normal serum bilirubin, a transient elastography reading <10 kPa, and an age >62 years at first presentation/diagnosis.

16. 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)	Not envisaged to be more difficult for patients or healthcare professionals to use than current therapies. Seladelpar will be initiated alongside ursodeoxycholic acid (unless there is documentary evidence of drug intolerance to the later). Monitoring will be conducted through dedicated PBC ODN hub centres.
17. Will any rules (informal or formal) be used to start or stop treatment with the technology? Do these include any additional testing?	Seladelpar will be administered (and treatment responses monitored) by hub centres as part of dedicated PBC ODNs, for individuals with ANY of the following: - Persistently elevated ALP values (>1.67x ULN) despite first-line therapy in ursodeoxycholic acid; - Intolerance to ursodeoxycholic acid - Elevated bilirubin values above the upper limit of normal, but below 50 micromol/L - Elevated ALP values and persistent cholestatic pruritus despite colestyramine Stopping rules will be set as: - Development of hepatic decompensation on therapy - Development of abnormal renal function

	- Intolerance of Seladelpar - No reduction is serum ALP values (<15% pre-treatment readings) after 12 months of therapy.
18. 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	The technology has the ability to lower serum lipid levels (total cholesterol, LDL-C and triglycerides), and thus may lower the risks of cardiovascular / cerebrovascular events when taken long-term. Currently used instruments that measure quality of life in PBC (e.g. the PBC-40, PBC-10) capture most elements, aside from hyperlipidaemia and bone health (the positive effects on bone health with Seladelpar have not yet been fully studied.)
19. 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?	Yes, please see above. In particular, Seladelpar address two critical unmet needs: - Persistent biochemical non-response despite currently available first and second-line therapy - Pruritus-related to PBC
20. How do any side effects or adverse effects of the technology affect the management of the condition and the patient's quality of life?	No major side effects / adverse events have been documented in the clinical trials of Seladelpar. However, the compound is a focussed peroxisome proliferator activated receptor delta agonist. There is potential for myalgia and the development of elevated creatinine values (from other, less specific pan- or dual PPAR agonists). Therefore monitoring of renal function and myalgia symptoms will be undertaken,

	for patients on Seladelpar, and any such side effects documented and reported using the yellow card system should they occur (not expected though).
21. 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. All the following surrogate outcomes (which are considered important) were captured in the clinical trials, and adequately predict clinical outcomes (e.g. Ref. Trivedi et al. J. Hepatol. 2014; Lammers et al. Gastro 2014; Murillo-Perez et al. Am. J. Gastro. 2020; Corpechot et al. J. Hepatol. 2022 and Hepatology 2024). - Reduction in serum ALP, ALT and AST values - Normalisation in serum ALP values - Maintenance of serum bilirubin and albumin values - Maintenance of transient elastography readings This is in addition to an attenuation in pruritus symptoms. The following were not captured in the clinical trials, given the variable and often slowly progressive clinical course of PBC as a disease (i.e., taking years/decades for patients to reach a major liver-related clinical event). These will take decades to observe: - Rates of liver transplantation - Mortality rate - Incidence of hepatocellular carcinoma - Incidence of hepatic decompensation No new adverse events have come to light since publication of clinical trial results to my knowledge.

22. Are you aware of any relevant evidence that might not be found by a systematic review of the trial evidence?	No dedicated systematic reviews on the topic so far.
23. Are you aware of any new evidence for the comparator treatment(s) since the publication of NICE technology appraisal guidance [TA1016]?	No.
24. How do data on real-world experience compare with the trial data?	No real world experience of this technology so far.
25. 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 • lead to recommendations that have a different impact on people protected by the equality legislation than on the wider population	No equality issues have been identified.

• 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 2Key messages

In up to 5 sentences, please summarise the key messages of your statement:

- Seladelpar is a first-in class PPAR-delta agonist, which is able to induce biochemical response in patients with PBC who inadequately respond to first-line therapy (ursodeoxycholic acid). Biochemical response is a consistently validated metric associated with transplant-free survival rates that mirror an age- and sex-matched control population.
- One in 4 patients treated with Seladelpar normalise serum ALP values, which for those aged below 62 years and/or having advanced liver fibrosis, is associated with at least four extra years of life gained beyond meeting biochemical response criteria alone.
- Seladelpar is the first compound that has been shown to attenuate pruritus in PBC long-term (>1 year) in clinical trials.
- Side effects from Seladelpar are few and far between, with no major adverse events related to study drug demonstrated in clinical trials to date.
- Alongside the above, Seladelpar has been shown to lower serum lipid levels (total cholesterol, LDL-C and triglycerides), which may associate with lower rates of cardiovascular and cerebrovascular events amongst treated patients.

Thank you for your time.

Your privacy

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NICE National Institute for Health and Care Excellence

Single Technology Appraisal

Seladelpar for previously treated primary biliary cholangitis [ID6429]

Patient expert statement

Thank you for agreeing to give us your views on this treatment and its possible use in the NHS.

Your comments are really valued. You can provide a unique perspective on conditions and their treatment that is not typically available from other sources

Information on completing this form

In part 1 we are asking you about living with previously treated primary biliary cholangitis or caring for a patient with previously treated primary biliary cholangitis. 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.

Help with completing this form

If you have any questions or need help with completing this form please email the public involvement (PIP) team at pip@nice.org.uk (please include the ID number of your appraisal in any correspondence to the PIP team).

Please use this questionnaire with our hints and tips for patient experts. You can also refer to the Patient Organisation submission guide. **You do not have to answer every question** – they are prompts to guide you. There is also an opportunity to raise issues that are important to patients that you think have been missed and want to bring to the attention of the committee.

NICE National Institute for Health and Care Excellence

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.

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Your response should not be longer than 15 pages.

The deadline for your response is **noon on Friday 4 July 2025.** 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, 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.

Patient expert statement

Part 1: Living with this condition or caring for a patient with previously treated primary biliary cholangitis

Table 1 About you, previously treated primary biliary cholangitis, current treatments and equality

1. Your name	Robert Mitchell-Thain
2. Are you (please tick all that apply)	☐ A patient with previously treated primary biliary cholangitis? ☐ A patient with experience of the treatment being evaluated? ☒ A carer of a patient with previously treated primary biliary cholangitis? ☒ A patient organisation employee or volunteer? ☐ Other (please specify):
3. Name of your nominating organisation	PBC Foundation (UK) Ltd
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:

Patient expert statement

	☐ 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 previously treated primary biliary cholangitis? **If you are a carer (for someone with previously treated primary biliary cholangitis) please share your experience of caring for them**	My mother was diagnosed in 1994. I have been part of her support network in that time, witnessing her journey, biochemical response, symptom burden and the emotional roller coaster of living with an incurable disease. In my professional capacity, I have also met, and learned from, over 3000 individual patients living with previously diagnosed PBC, which informs my opinions.
7a. What do you think of the current treatments and care available for previously treated 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?**	**a)** A number of treatments are available, all of which have limited success in biochemical normalisation in PBC. They all have a range of side effects and bring different challenges to patients. The current range of treatments fall some way short of addressing the needs of many PBC patients. **b)** These views are consistently held within the PBC patient population, as well as the wider PBC community
8. If there are disadvantages for patients of current NHS treatments for previously treated primary biliary cholangitis (for example, how they are given or taken, side effects of treatment, and any others) please describe these	There are a number of side effects from current treatments: from itch, through to kidney and liver toxicity, bone issues are also talked about by patients. As an aside, waiting for patients to be 1.67xULN of ALP before a second-line therapy is clinical madness. The data shows clearly risk is very similar if a patient is 1.1 times ULN or 2xULN. Second-line therapies need to be given as soon as a patient is seen not to be a responder, irrespective of how abnormal ALP is.
9a. If there are advantages of previously treated primary biliary cholangitis 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?	**A)** ALP normalisation has a number of life advantages: 1) prognosis 2) emotional burden of same prognosis 3) symptom burden of disease progression 4) financial and home insecurity around early death or need for liver transplant. These all have an impact on home life, work life, family and emotional and psychological journeys through a patient's lifetime. **B)** Prognosis is the most important as that influences everything else

9b. If you have stated more than one advantage, which one(s) do you consider to be the most important, and why? **9c. Does previously treated primary biliary cholangitis 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**	**C)** In some patients previously available treatments to PBC can help, but not in all patients. There are still currently approximately 20-30% of all PBC patients who do not respond to current treatments. (Not taking into account those who are eligible for second-line therapy and not gaining access to it)
10. If there are disadvantages of previously treated primary biliary cholangitis over current treatments on the NHS please describe these. For example, are there any risks with previously treated primary biliary cholangitis? If you are concerned about any potential side effects you have heard about, please describe them and explain why	The most pertinent disadvantage is that there are still patients who do not respond or normalise biochemically with current treatments available. This is a threat to life length and quality. Current treatments also carry a list of side effects as noted above.
11. Are there any groups of patients who might benefit more from previously treated primary biliary cholangitis 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	Data shows us that men and younger ladies tend to fare less well with PBC. Also, the higher the ALP (and bilirubin) at baseline, the more challenging it is to successfully treat PBC. Older patients, e.g. in 70s and 80s who have mild disease but have not normalised biochemically may benefit less than others but this is still open to debate: it comes down to a case by case determination of risk Vs benefit
12. Are there any potential equality issues that should be taken into account when considering previously treated primary biliary cholangitis and previously treated primary biliary cholangitis? Please explain if you think any groups of people with this condition are particularly disadvantage	In short, there are a significant number of patients who are not being adequately treated. Statistically, there may be challenges for patients of colour who tend to receive care later in their journey and, hence, often respond to treatment to a lesser degree.

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.	
13. Are there any other issues that you would like the committee to consider?	In the textbook, PBC is a disease that is easy to manage. In the real world, it still causes untold misery, enormous burden to quality of life and, all too often, early death. Data tells us that a normal liver biochemistry in the main leads to a normal life expectancy. We need more patients to be able to have access to that biochemical normalisation: this means a wider range of treatments, as well as better use of treatments. We still do not understand why some patients respond at all, or to certain types of medications and not others. Until we do, the PBC community needs all the help it can get: and seladelpar is one very important tool in the PBC clinician's tool box.

Part 2: Key messages

In up to 5 sentences, please summarise the key messages of your statement:

- Abnormal liver biochemistry is a clear risk to life expectancy
- Current treatments help, but not everyone
- There is an unmet need this treatment can address
- Improved treatment leads to improved outcomes for patients, families, and society
- No PBC patient should need a liver transplant, and improved treatments can free up a scarce resource for another patient in need.

Thank you for your time.

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Robert J Mitchell-Thain

Patient expert statement

Seladelpar for previously treated primary biliary cholangitis [ID6429]:
A Single Technology Appraisal

Produced by	Peninsula Technology Assessment Group (PenTAG) University of Exeter Medical School
Authors	Caroline Farmer[1] Jemma Perks[1] Alan Lovell[1] Maxwell S. Barnish[1] Valdemar Santo[1] Ahmed Abdelsabour[1] Dawn Lee[1] Taha Khan[2] Rebecca Jones[3] Gwilym Webb[4] Edward CF Wilson[1] [1] Peninsula Technology Assessment Group (PenTAG), University of Exeter Medical School, Exeter [2] St Leonard's Practice, Exeter [3] Leeds Teaching Hospital NHS Trust [4] Cambridge University Hospitals NHS Foundation Trust
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Declared competing interests of the authors	None
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Author contributions

Caroline Farmer	Lead for the EAG's appraisal of the clinical evidence, project management, writing and editorial input
Jemma Perks	Critical appraisal of the company's statistical analyses, including the indirect treatment comparisons, and drafting sections of the report.
Alan Lovell	Critical appraisal of the literature search strategies, conducted additional evidence searches, and editorial input
Maxwell S. Barnish	Critical appraisal of the clinical evidence and drafted sections of the report
Valdemar Santo	Critical appraisal of the economic evidence and drafted sections of the report
Ahmed Abdelsabour	Quality assurance of the EAG's economic analyses
Dawn Lee	Guidance on the company's indirect treatment comparison
Taka Khan	Clinical advice to the EAG
Rebecca Jones	Clinical advice to the EAG
Gwilym Webb	Clinical advice to the EAG
Edward CF Wilson	Critical appraisal of the company submission and economic analyses, conduct of economic analyses, writing and editorial input. Guarantor of the report

This report should be referenced as follows: Farmer, Perks, Lovell, Barnish, Santo, Abdelsabour, Lee, Khan, Jones, Webb, Wilson. Seladelpar for previously treated primary biliary cholangitis [ID6429]: A Single Technology Appraisal. Peninsula Technology Assessment Group (PenTAG), 2025.

Confidential information

Confidential information contained within this report is shown in Table 1.

Table 1: Confidential information included in the report

Brief description	AIC/CIC	Page number(s)	Source
Unpublished baseline characteristics of clinical trial data	CON	50 – 52	Company
Unpublished intervention and comparator characteristics of clinical trial data	CON	54, 56	Company
Unpublished analysis of clinical trial data	CON	63 – 75	Company
Composite response by sub-group	CON	80	Company
Overview of adverse event data	CON	82	Company
Primary network results	CON	93 - 98	Company
Sensitivity network results	CON	100 - 105101	Company
Bayesian NMA sensitivity analyses (efficacy outcomes)	CON	107 - 109	Company
Calibration factors and resultant HRs	CON	126 - 127	Company
Utilities and disutilities for ALP and pruritus	CON	132131	Company
Company results	CON	141 - 142	Company
EAG corrected base case	CON	145 - 146	EAG
EAG preferred model assumptions	CON	148 - 150	EAG
EAG's Scenarios	CON	151 - 153	EAG

Abbreviations: AIC, academic in confidence; ALP, Alkaline phosphatase; CIC, commercial in confidence; EAG, External Assessment Group; HR, hazard ratio; NA, not applicable; NMA, network meta-analysis

Table of Contents

List of key issues

List of tables

List of Figures

Abbreviations

Term	Definition
AASLD	American Association for the study of Liver Diseases
ACG	American College of Gastroenterology
AE	Adverse event
AIC	Academic in confidence
ALB	Albumin
ALP	Alkaline phosphatase
ALT	Alanine aminotransferase
AMA	Antimitochondrial antibodies
ANA	Antinuclear antibodies
AST	Aspartate transferase
BNF	British National Formulary
BSC	Best supportive care
BSG	British Society of Gastroenterology
CASP	Critical Appraisal Skills Programme
CEM	Cost effectiveness model
CI	Confidence interval
CIC	Commercial in confidence
CrI	Credible interval
CS	Company submission
DCC	Decompensated cirrhosis
DDW	Digestive Disease Week
DHSC	Department of Health and Social Care
DIC	Deviance Information Criterion
disc	Discontinued
EAG	External Assessment Group
EASL	European Association for the Study of the Liver
GP	General practitioner
HCC	Hepatocellular carcinoma
HCP	Healthcare professional
HR	Hazard ratio
HRQoL	Health Related Quality of Life
ICER	Incremental cost-effectiveness ratio
inc	Incremental
ITC	Indirect treatment comparison
IU/L	International units per litre
LLN	Lower limit of normal

Term	Definition
LS	Least squared
LT	Liver transplant
LYG	Life years gained
MAIC	Matching adjusted indirect comparison
MD	Mean difference
MHRA	Medicines & Healthcare products Regulatory Agency
MMRM	Mixed model for repeated measures
NA	Not applicable
NE	Not evaluable
NHB	Net health benefit
NHS	National Health Service
NHSCII	NHS Cost Inflation Index
NICE	National Institute for Health and Care Excellence
NMA	Network meta-analysis
NR	Not reported
NRS	Numerical rating scale
NS	Non-significant
OCA	Obeticholic acid
ODN	Operational delivery network
OR	Odds ratio
PBC	Primary biliary cholangitis
PICO	Population intervention comparator outcome
POISE	PBC OCA International Study of Efficacy
PPAR	Peroxisome proliferator-activated receptor
PRISMA	Preferred Reporting Items for Systematic Reviews and Meta-Analyses
PSA	Probabilistic Sensitivity Analysis
PSS	Personal Social Services
PSSRU	Personal Social Services Research Unit
QALY	Quality-adjusted life year
QoL	Quality of life
RCT	Randomised controlled trial
RFI	Request for Information
RoB	Risk of bias
RR	Relative risk
RWE	Real-world evidence
SCM	Specialist committee member
SD	Standard deviation
SE	Standard error
SLR	Systematic literature review

Term	Definition
TA	Technology appraisal
TEAE	Treatment-emergent adverse event
TP	Transition probability
UDCA	Ursodeoxycholic acid
UEG	United European Gastroenterology
UK	United Kingdom
ULN	Upper limit of normal
USA	United States of America
UTI	Urinary tract infection

1. EXECUTIVE SUMMARY

This summary provides a brief overview of the key issues identified by the External 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. Section 1.2 provides an overview of key model outcomes and the modelling assumptions that have the greatest effect on the ICER. Sections 1.3 to 1.6 explain the key issues in more detail. Background information on the condition, technology and evidence and information on non-key issues are in the main EAG report.

All issues identified represent the EAG's view, not the opinion of NICE.

1.1. Overview of the EAG's key issues

A brief overview of the key issues identified by the EAG in their appraisal of the company submission (CS) is provided in Table 2. Further detail of the issues is provided in Sections 1.3, 1.4, 1.5, and 1.6. Broadly speaking, the key clinical issues related to the unanchored MAIC and Bayesian NMA. In terms of cost effectiveness issues, the EAG was unable to ascertain the source of the odds ratios used for the relative effectiveness estimates, and preferred alternative sources for treatment discontinuation and health state utility data compared to the company base case. Finally, the EAG noted the company's estimates of uncertainty for some parameters did not reflect uncertainty in the underlying data.

Table 2: Summary of key issues

ID	Summary of issue	Report sections
#1	Exclusion of fibrates as comparators in the appraisal scope and the CS	2.5, 4.2.4, 6.4.1
#2	Uncertainty in the treatment pathway for PBC and the potential role of seladelpar	2.2, 2.3, 2.4
#3	Positive treatment response for participants in trials of seladelpar who received placebo	3.2.3
#4	Uncertainty in the relative effectiveness of seladelpar in comparison with existing treatment options	3.3, 0, 3.5
#5	Unclear provenance of odds ratios for relative effectiveness estimates	4.2.6.1

ID	Summary of issue	Report sections
#6	Treatment discontinuation	4.2.6.4
#7	Source for health state utility data	4.2.7.1
#8	Analysis of uncertainty	4.2.9

Abbreviations: CS, company submission; PBC, Primary biliary cholangitis

The key differences between the company's preferred assumptions and the EAG's preferred assumptions are outlined in Table 3.

Table 3: Key differences between the company's preferred assumptions and EAG's preferred assumptions

	Company's preferred assumption	EAG preferred assumption	Report Sections
Population	Starting state of patients as per RESPONSE baseline	No patients in ALP normalisation or mild states	4.2.3
Comparator	Exclusion of fibrates	Inclusion of fibrates	4.2.4, 6.4.1
Treatment effectiveness (0-12m)	RESPONSE + unanchored MAIC + Bayesian NMA	RESPONSE + Bayesian NMA (Turner prior)	4.2.6.1
Discontinuation (0-12m)	RESPONSE, ELATIVE & NICE TA443 (OCA appraisal), raw data	RESPONSE + Bayesian NMA (Turner Prior)	4.2.6.4
Discontinuation (12m+)	Rate ratio based on ELATIVE trials	Rate ratio based on RESPONSE and ASSURE trials	4.2.6.4
ALP level health state utilities and disutility from pruritus	MMRM2 + Smith et al. 2022	MMRM2	4.2.7.1
Uncertainty in calibration HRs	10% of mean	100% of mean	4.2.9

Abbreviations: ALP, Alkaline phosphatase; MAIC, Matching adjusted indirect comparison; MMRM, Mixed model for repeated measures; NICE, National Institute for Health and Care Excellence; 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.

Overall, the technology was modelled to affect QALYs by:

- Increasing time spent in ALP normalisation health state and subsequent reductions in progression to liver failure.
- Reducing the QALY burden associated with pruritus.

Overall, the technology was modelled to affect costs by:

- Reduced background health care resource use through increased time spent in the ALP normalisation state
- Reduced end of life care costs through reduced progression to liver failure.

The modelling assumptions that had the greatest effect on the ICER were:

- Exclusion of fibrates as a comparator
- Choice of discontinuation rates from 0-12m
- Choice of source for disutility associated with pruritus.

1.3. The decision problem: summary of the EAG's key issues

The EAG identified one key issue related to the decision problem for this appraisal, which was about the removal of fibrates from the scope of the appraisal and their subsequent omission from the company submission (CS).

Key Issue 1: Exclusion of fibrates as comparators in the appraisal scope and the CS

Report sections	**2.5, 4.2.4, 6.4.1**
Description of issue and why the EAG has identified it as important	Fibrates were included on the draft NICE scope for this appraisal but were removed in the final scope, which was consistent with the appraisal of elafibranor (TA1016). The company and other stakeholders to both this appraisal and TA1016 suggested that fibrates were not an active comparator and were considered to be background or adjunctive treatment. However, fibrates and seladelpar have a similar mechanism of action and therefore would be expected to influence PBC outcomes in a similar way. Moreover, some centres in the UK used fibrates as a 2nd line treatment option as an alternative to OCA. Finally, the EAG received advice that a licence was being sought for the use of fibrates to treat PBC (as they were used off-label), suggesting that there was sufficient grounds to consider fibrates as an active treatment for PBC. However, the EAG understood that this application would no longer proceed following the suspension of the Medicines Repurposing programme in NHS England. Overall, the EAG considered that there was significant uncertainty in the claim that fibrates were only used as an adjunctive

Report sections	2.5, 4.2.4, 6.4.1
	treatment to treat itching and would not influence disease processes. If fibrates were to be considered as an alternative treatment for PBC, this would require substantial changes to the company's indirect treatment comparisons (although evidence for fibrates was included in the SLR for this analysis) and cost-effectiveness analysis.
What alternative approach has the EAG suggested?	The EAG was aware that NICE previously considered the role of fibrates in TA1016 and in scoping for this appraisal and concluded that fibrates were not an active comparator to seladelpar. However, given the treatment mechanism, licence extension activities, and feedback from the EAG's clinical expert, the EAG considered that further discussion of this issue by the committee may be relevant to resolve this uncertainty. The treatment pathway used for PBC varied across NHS settings, and the EAG considered it possible that further engagement with clinicians who treat PBC may identify views about the role of fibrates that were not previously available to NICE. If there was agreement that fibrates should be considered an active comparator to seladelpar, the EAG would wish to appraise the company's NMA including evidence for fibrates, and for fibrates to be considered a comparator in the company's economic analysis.
What is the expected effect on the cost-effectiveness estimates?	Major. Clinical experts to the EAG advised that fibrates may be expected to be less clinically effective than newer treatments (such as elafibranor and seladelpar) but were substantially cheaper (approximately 60,000% to 100,000% difference in list prices). Observational data suggests superior effectiveness of fibrates to OCA (Abbas 2023).[1] The EAG estimates that fibrates are likely to be a highly cost-effective second line treatment with more expensive therapies (OCA, seladelpar and elafibranor) representing better value for taxpayers only as 3rd, 4th and 5th line therapies respectively.
What additional evidence or analyses might help to resolve this key issue?	Formal inclusion of fibrates as a comparator.

Abbreviations: EAG, External Assessment Group; MAIC, matching-adjusted indirect comparison; NMA, Network meta-analysis; OCA, Obeticholic acid; PBC, Primary biliary cholangitis; SLR, systematic literature review; TA, Technology Appraisal

Key Issue 2: Uncertainty in the treatment pathway for PBC and the potential role of seladelpar

Report sections	2.2, 2.3, 2.4
Description of issue and why the EAG has identified it as important	The treatment pathway for PBC varies across NHS settings, with differences in the preferred order of treatments and the criteria and timing used to assess continuation with treatment. Elafibranor was recently recommended as a treatment for PBC (TA1016) though the committee noted uncertainty in its likely positioning in the treatment pathway – it was considered most likely to be used as a 2nd line treatment option, which is where the evidence base was, though a 3rd line position was also considered plausible. To date, there has been insufficient experience with elafibranor in clinical practice to form a

Report sections	2.2, 2.3, 2.4
	clear understanding of the treatment pathway and the treatments that seladelpar would displace. The company considered that seladelpar would be a 2nd line treatment option, which again was consistent with the evidence base. This means that OCA and elafibranor (and potentially fibrates – Key Issue 1) were direct comparators to seladelpar. There was limited evidence for seladelpar at subsequent treatment lines. Clinical expert advice was that PBC is a slow progressing disease and therefore receiving seladelpar at later lines of treatment should not mean that seladelpar is being received by people with notably more progressed disease. However, as later treatment positions are populated by a subsection of the population (i.,e. those who do not respond or are intolerant to earlier treatments), the clinical effectiveness of seladelpar may differ at subsequent treatment lines. This may be particularly the case if seladelpar is preceded by treatment with elafibranor. Clinical expert advice also suggested the possibility of adding therapies, where another treatment could be introduced if the initial clinical benefit is observed but it does not meet the POISE criteria (e.g. patients with a very high ALP level).
What alternative approach has the EAG suggested?	The EAG was unable to resolve this uncertainty during the appraisal as further evidence for seladelpar at alternative treatment lines would be required. Moreover, the model does not allow either the introduction of active subsequent treatments or add-ons to subsequent lines of treatment.
What is the expected effect on the cost-effectiveness estimates?	Unclear in relation to add-ons because it would increase the costs of each treatment pathway, but also potentially increase QALYs and life years. This is because patients would not switch to UDCA monotherapy, which had shown inadequate response on 1st line, or to BSC for those who are intolerant to UDCA.
What additional evidence or analyses might help to resolve this key issue?	Clinical expert opinion on the likely positioning of seladelpar following the introduction of elafibranor and on the extent to which the clinical effectiveness of seladelpar may vary between the available evidence and a population who had previously received elafibranor. The model would require considerable re-engineering to incorporate the full treatment pathway

Abbreviations: ALP, Alkaline Phosphatase; BSC, best supportive care; EAG, External Assessment Group; NHS, National Health Service; PBC, Primary biliary cholangitis; POISE, PBC OCA International Study of Efficacy; QALY, Quality-adjusted life year; UDCA, Ursodeoxycholic acid.

1.4. The clinical effectiveness evidence: summary of the EAG's key issues

The EAG identified two key issues related to the clinical effectiveness evidence: about the unanchored MAIC and comparing relative effectiveness across two ITCs respectively.

Key Issue 3: Positive treatment response for participants in trials of seladelpar who received placebo

Report sections	3.2.3
Description of issue and why the EAG has identified it as important	A significant minority of participants who received placebo and UDCA in the company's pivotal trial, RESPONSE, exhibited a clinically meaningful response to treatment. Based on information about the clinical trial provided by the company, this effect was not explained by the addition of background treatments within the trial and the dose of UDCA received by participants should have been consistent with the dose they were receiving previously. Clinical expert advice to the EAG was that placebo-responses in trials of treatments for PBC are common, though may vary in their magnitude. While the EAG was unaware of evidence to explain the cause of the placebo response, and this issue was not addressed by the company in its submission, the EAG's clinical expert suggested that the placebo response may be due to participants' increasing their adherence to UDCA within trial conditions. PBC is a chronic, long-term condition and some people with PBC have a high quality of life and limited symptoms until their disease progresses. It may be that in this context, real-world adherence to UDCA may be under the intended dose but that people will increase their adherence when participating in a clinical trial with clear dosing requirements. This may mean that those who have mildly elevated ALP may exhibit a clinically meaningful response to the intended dose of UDCA within the trial. A placebo response has implications for appraising the evidence for seladelpar: 1. Absolute rates of response in both arms of the trial may be unreliable, as an unknown number of treatment responses may be due to the cause of the placebo response. This means that relative treatment effects in comparative studies will be the most reliable source of evidence and single-arm studies may be at a high risk of bias. 2. Variation in placebo response across studies may have implications for the transitivity of ITCs. 3. As the cause of the placebo response was uncertain, it was unclear how this may behave across trial follow-up timepoints. For example, if the cause was due to increased adherence to treatment during the trial, this may not persist throughout the full duration of the trial if participants become more relaxed about adhering to the protocol over time 4. If the placebo response is due to trial conditions, then this presents a risk for the generalisability of evidence from studies to real-world practice. If adherence to treatments for PBC is lower in practice than might be seen in clinical trials, then treatment outcomes may be reduced as compared to the trial evidence. 5. If adherence to treatments for PBC is lower in clinical practice than in the trial evidence, then either treatment costs may be lower in practice than would be suggested by trials or costs may be the same but there may be a high degree of wastage.

Report sections	3.2.3
What alternative approach has the EAG suggested?	Consideration of the clinical effectiveness of seladelpar should take into account the potential impact of the placebo response. The EAG has focused its appraisal on the most robust evidence available, including relative treatment effects in blinded, comparative studies. Potential variation between placebo outcomes in the company ITCs are also discussed.
What is the expected effect on the cost-effectiveness estimates?	Uncertain.
What additional evidence or analyses might help to resolve this key issue?	Real-world data on treatment uptake of treatments for PBC would provide evidence about the potential for non-adherence patterns and treatment wastage.

Abbreviations: ALP, Alkaline Phosphatase; EAG, External Assessment Group; ITC, indirect treatment comparison; PBC, Primary biliary cholangitis; UDCA, Ursodeoxycholic acid.

Key Issue 4: Uncertainty in the relative effectiveness of seladelpar in comparison with existing treatment options

Report sections	3.3, 0, 3.5
Description of issue and why the EAG has identified it as important	The available studies of seladelpar compared treatment outcomes either with placebo or were comparisons of outcomes between different doses of seladelpar. There was no direct evidence comparing seladelpar with alternative active treatment options for people who are intolerant or have an inadequate response to UDCA. The company conducted a SLR to identify evidence to inform an ITC comparing seladelpar with OCA, elafibranor and fibrates (though fibrates were not included in the economic analysis). The feasibility assessment identified inconsistencies in the study designs across the network and the company therefore conducted a MAIC to compare seladelpar and elafibranor for composite response and an NMA to compare seladelpar and OCA The EAG had a number of concerns with the split MAIC and NMA approach as this could generate inconsistent results across all three comparators.
What alternative approach has the EAG suggested?	The EAG prefers the Bayesian NMA as the base case for all efficacy outcomes.
What is the expected effect on the cost-effectiveness estimates?	Minor. This is because the calibration HRs generated by the various analyses are similar.
What additional evidence or analyses might help to resolve this key issue?	Despite issues with transitivity across the network, the EAG nevertheless would prefer to see an ITC that included all relevant comparators to seladelpar with meaningful consideration of how transitivity may influence outcome data. This should include outcome recalculation, and with the company's preferred priors for the following key outcomes: ALP normalisation, composite response, or ALP response (Toronto I).

Abbreviations: ALP, Alkaline Phosphatase; EAG, External Assessment Group; ITC, indirect treatment comparison; MAIC, Matching adjusted indirect comparison; OCA, Obeticholic acid; PBC, Primary biliary cholangitis; SLR, systematic literature review; UDCA, Ursodeoxycholic acid.

1.5. The cost effectiveness evidence: summary of the EAG's key issues

The EAG identified a number of issues related to the company's economic model. This included:

- Unclear provenance of odds ratios used in the company base case for the comparison of seladelpar and elafibranor for both ALP normalisation and mild ALP elevation.
- Concerns about the choice of discontinuation rates used in the model, with discrepancies in discontinuation rates between sources that could have a meaningful impact on the ICER for seladelpar
- Potential overestimation of health-related quality of life (HRQoL) impacts of pruritus in the model
- Insufficient simulations to generate stable results in the probabilistic analysis and uncertainty in a number of parameters not reflecting uncertainty in the underlying data

Key Issue 5: Unclear provenance of odds ratios for relative effectiveness estimates

Report sections	4.2.6.1
Description of issue and why the EAG has identified it as important	The company used ORs to calculate the calibration HRs in its base case with one exception where RR was used. The EAG could not identify how the ORs were calculated for the company's base case for the comparison between seladelpar vs elafibranor for mild ALP elevation (Toronto 1 criteria), and for seladelpar vs OCA for both ALP normalisation and mild ALP elevation (CS, Table 47). Only RRs were presented for these comparisons in the ITC and the numbers reported do not appear in either the CS or ITC report submitted by the company. The EAG further noted that uncertainty in the ORs is not captured in the probabilistic analysis with the 'calibration HR's only varied by +/- 10%. Credibility intervals are not provided around the ORs, whereas credibility intervals around RRs are much wider than the uncertainty assigned to the calibration HRs.
What alternative approach has the EAG suggested?	The EAG prefers to use ITC results from a single analysis. The EAG calculated calibration HRs on the basis of these RRs. The EAG was not able to calculate credibility intervals for the calibration HRs from the RR data as this generated probabilities outside [0,1] (ORs are required for this purpose). Instead, the EAG set the SE of the calibration HR equal to the mean rather than 10% of the mean to more closely approximate the wide CrIs in the RRs.
What is the expected effect on the cost-effectiveness estimates?	Minor

Report sections	4.2.6.1
What additional evidence or analyses might help to resolve this key issue?	Confirmation of the provenance of the Odds Ratios from the Company.

Abbreviations: ALP, Alkaline Phosphatase; CrI, Credible interval; CS, company submission; EAG, External Assessment Group; HR, hazard ratio; ITC, indirect treatment comparison; OR, odds ratio; PBC, Primary biliary cholangitis; RR, relative risk; SE, standard error; SLR, systematic literature review; UDCA, Ursodeoxycholic acid.

Key Issue 6: Treatment Discontinuation

Report sections	4.2.6.4
Description of issue and why the EAG has identified it as important	The company conducted an ITC on discontinuation rates yet used naïve values from the respective source studies in its base case. The company did not justify this decision.
What alternative approach has the EAG suggested?	The EAG considered use of the ITC results to inform discontinuation theoretically preferable as it takes into account differences in trial populations. It is also more consistent with the estimation methods used for other model parameters.
What is the expected effect on the cost-effectiveness estimates?	Large
What additional evidence or analyses might help to resolve this key issue?	None.

Abbreviations: EAG, External Assessment Group; ITC, Indirect treatment comparison

Key Issue 7: Source of health state utility data

Report sections	4.2.7.1
Description of issue and why the EAG has identified it as important	The company used the MMRM2 mapping algorithm to estimate health state utilities drawn from RESPONSE trial data. This included a covariate for pruritus but the company chose a different source from the literature for the disutility associated with pruritus. The EAG noted that treatment costs for pruritus were included in the company's model, but not a treatment effect from these. The EAG therefore considered that the company had overestimated the disutility from (treated) pruritus. Furthermore, introducing additional external data increases the risk of inconsistencies between sources (eg yielding a health state for ALP normalisation that is higher than that of the general population).
What alternative approach has the EAG suggested?	The MMRM2 analysis, including covariates for pruritus is more internally consistent than the company's base case.
What is the expected effect on the cost-effectiveness estimates?	Moderate

Report sections	4.2.7.1
What additional evidence or analyses might help to resolve this key issue?	None.

Abbreviations: ALP, Alkaline phosphatase; EAG, External Assessment Group; MMRM, Mixed model for repeated measures

Key Issue 8: Analysis of uncertainty

Report sections	4.2.9
Description of issue and why the EAG has identified it as important	The company's probabilistic analysis comprised only 250 simulations which the EAG noted did not generate stable results. The uncertainty in a number of parameters (notably the calibration hazard ratios) did not reflect the uncertainty in the underlying data.
What alternative approach has the EAG suggested?	The EAG increased the PSA to 2000 simulations and set relevant standard errors equal to the mean values rather than 10% of the mean.
What is the expected effect on the cost-effectiveness estimates?	Minor
What additional evidence or analyses might help to resolve this key issue?	None.

Abbreviations: EAG, External Assessment Group; PSA, Probabilistic Sensitivity Analysis.

1.6. Other key issues: summary of the EAG's views

The EAG did not identify any other key issues not covered by the headings above.

1.7. Summary of EAG's preferred assumptions and resulting ICER

Table 4: Summary of EAG's preferred assumptions and ICER (UDCA-tolerant subgroup)

Section in EAG report	Preferred Assumption	Treatment	Total costs (£)	Total QALYs	Incremental ICER	NHB	+/- corrected base case
	Company Base Case	Seladelpar + UDCA	[redacted]	[redacted]	-	-8.72	-
		OCA + UDCA	£384,110	9.432	Dominated	-9.77	-
		Elafibranor + UDCA	£445,408	9.857	Dominated	-12.41	-

Section in EAG report	Preferred Assumption	Treatment	Total costs (£)	Total QALYs	Incremental ICER	NHB	+/- corrected base case
	EAG Corrected Company Base Case	Seladelpar + UDCA	[redacted]	[redacted]	-	-8.72	-
		OCA + UDCA	£384,110	9.432	Dominated	-9.77	-
		Elafibranor + UDCA	£445,408	9.857	Dominated	-12.41	-
4.2.3	No patients in the normal or mild state at model start	Seladelpar + UDCA	[redacted]	[redacted]	-	-8.73	0.01
		OCA + UDCA	£383,750	9.416	Dominated	-9.77	0.00
		Elafibranor + UDCA	£444,687	9.825	Dominated	-12.41	0.00
4.2.6.1	Bayesian NMA for calibration HRs	Seladelpar + UDCA	[redacted]	[redacted]	-	-8.72	0.00
		OCA + UDCA	£383,493	9.405	Dominated	-9.77	0.00
		Elafibranor + UDCA	£448,871	9.976	Dominated	-12.47	-0.05
4.2.6.4	Discontinuation 0-12m	OCA + UDCA	£322,082	9.117	-	-6.99	-2.79
		Seladelpar + UDCA	[redacted]	[redacted]	£50,975	-8.72	0.00
		Elafibranor + UDCA	£439,170	9.825	Dominated	-12.13	-0.28
4.2.6.4	Discontinuation 12m+	Seladelpar + UDCA	[redacted]	[redacted]	-	-10.52	1.79
		OCA + UDCA	£421,730	9.554	Dominated	-11.53	1.76
		Elafibranor + UDCA	£491,809	9.995	Dominated	-14.60	2.18
4.2.7.1	Pruritus disutilities from MMRM2	Seladelpar + UDCA	[redacted]	[redacted]	-	-7.46	1.27
		OCA + UDCA	£384,110	11.131	Dominated	-8.07	1.70
		Elafibranor + UDCA	£445,408	11.247	Dominated	-11.02	1.39
4.2.9	set the SE of the calibration HRs equal to the mean HR from RR	Seladelpar + UDCA	[redacted]	[redacted]	-	-8.72	0.00
		OCA + UDCA	£384,110	9.432	Dominated	-9.77	0.00
		Elafibranor + UDCA	£445,408	9.857	Dominated	-12.41	0.00
		OCA + UDCA	£350,432	10.797		-6.72	3.05

Section in EAG report	Preferred Assumption	Treatment	Total costs (£)	Total QALYs	Incremental ICER	NHB	+/- corrected base case
Cumulative impact of EAG base case		Seladelpar + UDCA	[redacted]	[redacted]	£81,847	-9.26	-0.54
		Elafibranor + UDCA	£488,310	11.464	Dominated	-12.95	-0.54
Cumulative impact of EAG base case (probabilistic analysis)		OCA + UDCA	£328,796	10.134		-6.31	3.46
		Seladelpar + UDCA	[redacted]	[redacted]	£76,925	-8.72	0.00
		Elafibranor + UDCA	£458,147	10.766	Dominated	-12.14	0.27

Abbreviations: disc, discounted; EAG, external assessment group; HR, hazard ratio; ICER, incremental cost-effectiveness analysis; inc, incremental; MMRM, Mixed model for repeated measures; NMA, network meta-analysis; OCA, Obeticholic acid; QALYs, quality adjusted life years. NHB, Net health benefit; RR, relative risk; SE, standard error; UDCA, Ursodeoxycholic acid.

NHB calculated at £20,000 per QALY.

Table 5: Summary of EAG's preferred assumptions and ICER (UDCA-intolerant subgroup)

Section in EAG report	Preferred Assumption	Treatment	Total costs (£)	Total QALYs	Incremental ICER	NHB	+/- corrected base case
	Company Base Case	Seladelpar	[redacted]	[redacted]		-7.88	-
		OCA	£369,860	9.414	Dominated	-9.08	-
		Elafibranor	£430,967	9.903	Dominated	-11.65	-
	EAG Corrected Company Base Case	Seladelpar	[redacted]	[redacted]		-7.88	-
		OCA	£369,860	9.414	Dominated	-9.08	-
		Elafibranor	£430,967	9.903	Dominated	-11.65	-
4.2.3	No patients in the normal or mild state at model start	Seladelpar	[redacted]	[redacted]		-7.89	0.01
		OCA	£369,521	9.398	Dominated	-9.08	0.00
		Elafibranor	£430,287	9.870	Dominated	-11.64	0.00
4.2.6.1	Bayesian NMA for calibration HRs	Seladelpar	[redacted]	[redacted]		-7.88	0.00
		OCA	£369,279	9.387	Dominated	-9.08	0.00
		Elafibranor	£434,275	10.023	Dominated	-11.69	-0.05
4.2.6.4	Discontinuation 0-12m	OCA	£308,522	9.064		-6.36	2.72
		Seladelpar	[redacted]	[redacted]	£43,923	-7.88	0.00

Section in EAG report	Preferred Assumption	Treatment	Total costs (£)	Total QALYs	Incremental ICER	NHB	+/- corrected base case
		Elafibranor	£424,789	9.866	Dominated	-11.37	0.28
4.2.6.4	Discontinuation 12m+	Seladelpar	[redacted]	[redacted]		-9.62	-1.74
		OCA	£407,151	9.559	Dominated	-10.80	-1.72
		Elafibranor	£477,058	10.072	Dominated	-13.78	-2.14
4.2.7.1	Pruritus disutilities from MMRM2	Seladelpar	[redacted]	[redacted]		-6.71	1.17
		OCA	£369,860	11.115	Dominated	-7.38	1.70
		Elafibranor	£430,967	11.238	Dominated	-10.31	1.34
4.2.9	set the SE of the calibration HRs equal to the mean HR from RR	Seladelpar	[redacted]	[redacted]		-7.88	0.00
		OCA	£369,860	9.414	Dominated	-9.08	0.00
		Elafibranor	£430,967	9.903	Dominated	-11.65	0.00
Cumulative impact of EAG base case		OCA	£336,673	10.780		-6.05	3.03
		Seladelpar	[redacted]	[redacted]	£78,324	-8.50	-0.62
		Elafibranor	£473,495	11.457	Dominated	-12.22	-0.57
Cumulative impact of EAG base case (probabilistic analysis)		OCA	£339,063	10.901		-6.05	3.03
		Seladelpar	[redacted]	[redacted]	£74,833	-8.53	-0.65
		Elafibranor	£478,279	11.615	Dominated	-12.30	-0.65

Abbreviations: disc, discounted; EAG, external assessment group; HR, hazard ratio; ICER, incremental cost-effectiveness analysis; inc, incremental; MMRM, Mixed model for repeated measures; NMA, network meta-analysis; OCA, Obeticholic acid; QALYs, quality adjusted life years. NHB, Net health benefit; RR, relative risk; SE, standard error; UDCA, Ursodeoxycholic acid.

NHB calculated at £20,000 per QALY.

Modelling errors identified and corrected by the EAG are described in section 6.1. The errors pertained only to the probabilistic results therefore the deterministic 'EAG corrected' base case is the same as the Company base case. For further details of the exploratory and sensitivity analyses done by the EAG, see section 6.4. The EAG estimated that exclusion of fibrates as a comparator will have had a large impact on the cost-effectiveness results, with fibrates highly likely to be the most cost-effective second line therapy, before OCA, seladelpar or elafibranor. Due to data limitations this was not modelled formally but is considered qualitatively in section 6.4.1.

2. INTRODUCTION AND BACKGROUND

2.1. Introduction

In this report, the External Assessment Group (EAG) provides a review of the evidence submitted by Gilead in support of seladelpar for treating previously treated primary biliary cholangitis.

2.2. Critique of the company's description of the underlying health problem

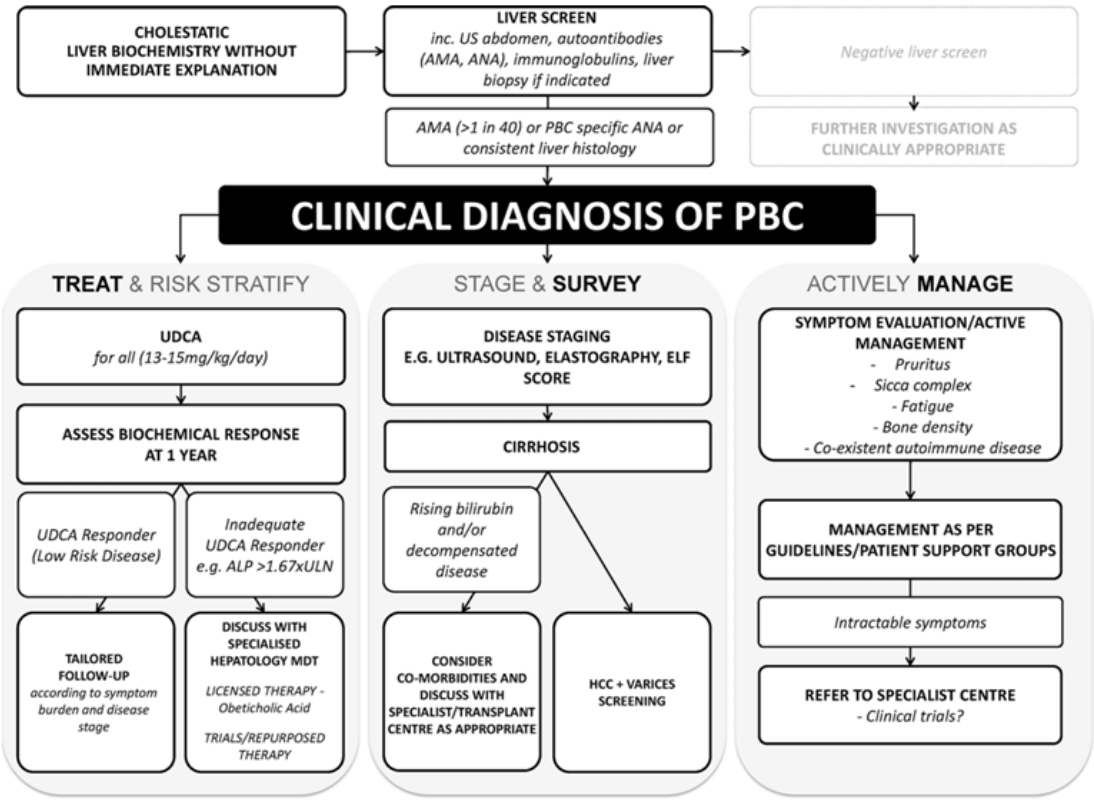
The company's description of the underlying health problem was presented in Sections 1.3.1 and 1.3.2 of the CS. Primary biliary cholangitis (PBC) is a rare, progressive, autoimmune liver disease characterised by cholestasis (impaired bile flow) and accumulation of toxic bile acids.[2] With disease progression, liver symptoms can progress from cholestasis to hepatic inflammation, fibrosis, cirrhosis, and ultimately end-stage liver disease.[3] PBC is typically identified in people aged 40 to 60,[3] with a female predominance of around 1:9 in UK studies.[1,4-6] In the UK, the prevalence of PBC is 39.6 per 100,000 of the total population, suggesting there are around 20,000 people in the UK with PBC. The most common presenting symptoms of PBC are fatigue and pruritus (itching).[8,9] Up to 95% of people with PBC also have extrahepatic manifestations.[10-12] Although progression has been improved by the availability of targeted treatment options, people with PBC remain at increased risk of mortality compared to the general population – for those who do not respond well to treatment, life expectancy is estimated at 10 years following disease onset.[13] A UK Biobank study from 2006-2010 found a 22.9% all-cause mortality rate in people with PBC, with hepatic and digestive conditions being key drivers of mortality.[14] Reduced quality of life has been shown in PBC,[6,15] with pruritus identified as a key limiting factor for quality of life.[16,17] The EAG received clinical expert advice that the clinical and demographic profile presented above appears appropriate, and that many though not all people with PBC will experience pruritus, although the severity of symptoms may fluctuate over time. It is unknown why autoimmune conditions are so much more common in women.

2.3. Critique of the company's overview of current service provision

The company's overview of current service provision was presented in Section 1.3.3 of the CS. There were no NICE guidelines specifically for the treatment of PBC. Therefore, the most relevant available guidelines were the British Society of Gastroenterology/United Kingdom –

Primary Biliary Cholangitis (BSG/UK – PBC) guidelines.[18] The treatment pathway presented by these guidelines is depicted in Figure 1. In short, the guideline suggests that all people diagnosed with PBC are first treated with ursodeoxycholic acid (UDCA) and assessed for their response at one year. Those who experience an inadequate response, as defined as ALP >1.67x the upper level of normal (ULN) may receive obeticholic acid (OCA), off-label therapy (i.e. fibrates), or may be considered for clinical trials. This is also the case for people who are intolerant to UDCA. People with PBC will also receive treatment to manage their symptoms and additional health needs, including following onset of cirrhosis.

Figure 1: BSG/UK-PBC consensus care pathway for patients with PBC



Abbreviations: AMA, antimitochondrial antibodies; ANA, Antinuclear antibodies; HCC, Hepatocellular carcinoma; OCA: obeticholic acid; PBC: primary biliary cholangitis; UDCA: ursodeoxycholic acid

Source: British Society of Gastroenterology/United Kingdom – Primary Biliary Cholangitis (BSG/UK – PBC) guidelines. [18]

Clinical advice to the EAG was that the treatments received by people with PBC will be tailored to their needs, including consideration of the magnitude and speed of their response to treatment and the side effect profile that they experience. NHS centres may have different

procedures for assessing response to treatment, for example, there is variation in treatment duration before people with PBC are switched to a different treatment following signs of inadequate response. Different centres also take different approaches to the order of treatments that they administer to people with PBC. A UK-based evaluation of routine service delivery[4] found that 2nd line treatment for 50% of people with PBC who had an inadequate response to UDCA was fibrates, which are an off-label treatment, as opposed to OCA. The decision to use fibrates as opposed to OCA may be guided by severity of pruritus in each person with PBC, as OCA is known to exacerbate symptoms of pruritus. However, the EAG understood that there was also variation in practice across centres in terms of their willingness to try OCA rather than fibrates.

Figure 1 does not show that combination treatments are also common for PBC, and so people who experience an inadequate response to treatment may receive an additional treatment in combination. People may also experience dose reductions to manage side effects. Finally, the Figure above was created prior to the positive NICE recommendation for elafibranor (TA1016, November 2024), which is another option for people who had an inadequate response to UDCA or were intolerant to it.

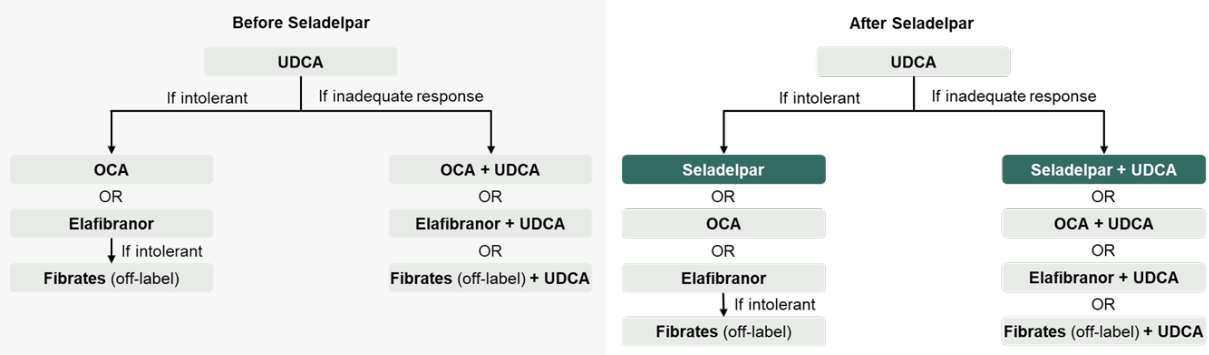
2.4. Proposed position of seladelpar

Seladelpar is a selective agonist of peroxisome proliferator-activated receptor (PPAR) δ transcription factor distributed across hepatocytes, cholangiocytes, Kupffer cells, and hepatic stellate cells.[19] PPARδ activation releases fibroblast growth factor 21 (FGF21) from hepatocytes, inhibiting the expression of cholesterol 7α-hydroxylase[20,21] and as such reducing bile acid accumulation. PPARδ activation in Kupffer cells and macrophages promotes the anti-inflammatory M2 phenotype.[22] These activations result in reductions in liver bile acid exposure and circulating levels of bile acid, leading to improvement in cholestasis, reduced inflammation, and increased lipid metabolism.[23]

Seladelpar was indicated for the treatment of PBC, including pruritus, in adults in combination with UDCA who have an inadequate response to UDCA alone, or as monotherapy in those unable to tolerate UDCA. The recommended dose of seladelpar was 10 mg orally once daily. Seladelpar received EMA (December 2024) and MHRA (January 2024) approvals in this indication. Seladelpar was classified as an orphan drug by the EMA.

The company's proposed positioning of seladelpar in the treatment pathway is shown below in Figure 2. The company positioned seladelpar as primarily a second-line treatment option for PBC, following intolerance or inadequate response to UDCA, as either a monotherapy or combination therapy with UDCA. The company stated that seladelpar could also be a third-line option in people who are intolerant or do not adequately respond to OCA (CS p.40), although they did not state whether they considered seladelpar to be an option for people who have previously received 2nd line treatment with either fibrates or elafibranor. Currently there is very limited evidence for the role of seladelpar in a third line position.

Figure 2. Proposed positioning of seladelpar in the UK PBC treatment pathway



Abbreviations: OCA: obeticholic acid; PBC: primary biliary cholangitis; UDCA: ursodeoxycholic acid

Notes: UDCA is recommended as the first-line therapy for PBC by internationally recognised clinical practice guidelines. Seladelpar, alongside OCA and elafibranor, are positioned as second-line therapies for PBC in combination with UDCA or as a standalone treatment for UDCA-intolerant patients.

Clinical expert advice to the EAG was that, on face value, seladelpar would be a reasonable 2nd line treatment option for PBC; OCA was not a preferred option due to the increased risk of pruritus, and fibrates were being used off-label and there were uncertainties about relative effectiveness. However, as elafibranor has only recently entered routine clinical practice, there was a lack of experience using it to treat people with PBC and experts were unclear how they may order elafibranor and seladelpar in practice. Moreover, elafibranor, seladelpar and fibrates are all PPAR agonists, and the EAG considered it plausible that inadequate response to treatment with one may preclude treatment with another. The EAG was unable to resolve this uncertainty during the appraisal and this is discussed further in Key Issue 2.

2.5. Critique of company's definition of decision problem

The company's decision problem was presented in Section 1.1 of the CS. The submission covered the full marketing authorisation for seladelpar in this indication, namely for the treatment of primary biliary cholangitis (PBC), including with pruritus, in adults in combination with ursodeoxycholic acid (UDCA) who have an inadequate response to UDCA alone, or as monotherapy in those unable to tolerate UDCA. The EAG considered that the company's decision problem is generally well-aligned to the final scope issued by NICE for this appraisal. However, the EAG noted some limitations in the evidence available to address the company's decision problem. While the company suggested that seladelpar could be used in second- or third-line positioning, the evidence base was largely in the second line setting. As discussed in Section 2.4, the recent NICE recommendation for elafibranor in this indication (TA1016) resulted in uncertainty in the potential position of seladelpar in the treatment pathway. The EAG considered it plausible that the clinical effectiveness of treatments would vary according to their positioning, as people later in the treatment pathway will be a subset of people from the overall population who have shown a lack of tolerance or response to earlier treatments.

The company excluded fibrates as a comparator from its submission, which was consistent with the final scope issued by NICE and the approach used in the appraisal of elafibranor. The company stated that fibrates were used as an adjunctive treatment primarily to treat pruritus, and that they would only be prescribed as a second line treatment option for people not eligible for OCA (see company response to clarification, A2). Nevertheless, the EAG considered there to be some uncertainty about the role of fibrates in treating PBC. This was based on the following considerations:

- An audit of UK practice suggested that 50% of people with PBC who have an inadequate response to UDCA receive treatment with fibrates rather than OCA, which clinical experts to the EAG advised may be due to concerns that OCA exacerbates pruritus (as opposed to a concern that fibrates would not be an appropriate treatment option)
- A clinical expert to the EAG advised that fibrates are the preferred second line treatment option in their centre and noted that they were very surprised that fibrates were not being considered as a comparator to seladelpar

- The EAG received advice that a licence extension application for using fibrates to treat PBC was underway by NHS England, though the EAG was unable to verify this during its appraisal.

Despite the fact that fibrates were not included on the NICE scope and that the NICE committee had already discussed this issue in its appraisal of elafibranor, the EAG nevertheless considered the above evidence to raise uncertainty about this issue, which is discussed further in Key Issue 1. The EAG understood that fibrates were a cheaper but potentially less clinically effective treatment for PBC, though comparative evidence for their clinical and cost effectiveness would be needed to understand the potential impact on this appraisal of fibrates being considered a true comparator to seladelpar. The EAG further noted that a recent cohort study[1] found fibrates to be more effective than OCA at reducing ALP levels.

Table 6: Summary of decision problem

	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	Not applicable	The CS was consistent with the final scope, though the EAG noted that outcomes from studies of seladelpar typically pooled the two populations (people intolerant to UDCA and people who had an inadequate response).
Intervention	Seladelpar	As per the final scope	Not applicable	The intervention evaluated was consistent with the licence, which was seladelpar monotherapy in people who were intolerant to UDCA or seladelpar plus UDCA in people who had an inadequate response to UDCA. There was no evidence for combining seladelpar with other available treatments for PBC.
Comparator(s)	For people, whose disease has an inadequate response to ursodeoxycholic acid: • Obeticholic acid (OCA) in combination with UDCA • UDCA monotherapy • Elafibranor in combination with UDCA Where UDCA cannot be tolerated: • OCA monotherapy	For people, whose disease has an inadequate response to ursodeoxycholic acid: • Obeticholic acid (OCA) in combination with UDCA • Elafibranor in combination with UDCA Where UDCA cannot be tolerated: • OCA monotherapy	Seladelpar and UDCA monotherapy are positioned differently in the PBC treatment paradigm. UDCA monotherapy is positioned as a first-line treatment option for PBC by UK and international clinical practice guidelines and does not align with the recommended positioning of seladelpar. Instead, seladelpar is positioned as a second-line treatment option for patients who have demonstrated an	Overall, the EAG agreed that UDCA monotherapy would not be a comparator to seladelpar, given that those who respond to UDCA would not be eligible for seladelpar. Clinical advice to the EAG was that UDCA monotherapy may be administered to people who have an inadequate response to UDCA if other available treatments were not considered to be appropriate, however the EAG considered that this may be relevant to fewer people following the recent introduction of elafibranor.

	Final scope issued by NICE	Decision problem addressed in the company submission	Rationale if different from the final NICE scope	EAG comment
	• Best supportive care • Elafibranor monotherapy	• Elafibranor monotherapy	inadequate response to UDCA (i.e., have tried UDCA and failed) or cannot tolerate UDCA, and as a third-line treatment for patients who have demonstrated an inadequate response to, or cannot tolerate, OCA. Therefore, seladelpar would not displace patients who are already responding to treatment with UDCA monotherapy. The comparative effectiveness of seladelpar is measured in the pivotal Phase 3 RESPONSE study against placebo ± UDCA. As such, UDCA is included in the clinical trial, but not as a standalone comparator arm, only as a by-product of the trial design, and UDCA monotherapy is therefore not a comparator included in Section 3 of the Company Evidence Submission For patients who cannot tolerate UDCA, best supportive care is not considered a relevant treatment option, given the	Key Issue 1 describes uncertainty in the role of fibrates in the treatment of PBC and the possibility that fibrates may be considered an additional comparator to seladelpar.

	Final scope issued by NICE	Decision problem addressed in the company submission	Rationale if different from the final NICE scope	EAG comment
			availability of OCA and elafibranor monotherapies as alternative second-line treatment options.	
Outcomes	The outcome measures to be considered include: • Mortality • Liver function based on markers of liver biochemistry • Symptoms including pruritus, fatigue, and abdominal pain • Time to liver transplantation • PBC-related consequences, including ascites, varices, encephalopathy, and hepatic cell carcinoma • Adverse effects of treatment • Health-related quality of life (HRQoL)	As per the final scope	Not applicable	Evidence for the effectiveness of seladelpar was available for most of the scoped outcomes, though within the available follow-up, limited evidence was available for mortality and time to liver transplantation. Moreover, key PBC-related consequences were not consistently reported as outcomes in their own right, and safety data from the studies were not universally informative, and therefore differences in these outcomes could not be assessed.
Economic analysis	NICE reference case	As per scope	NA	The cost effectiveness of treatments was expressed in terms of incremental cost per quality-adjusted life year. The time horizon for estimating clinical and cost effectiveness was sufficiently long to reflect any differences in costs or outcomes

	Final scope issued by NICE	Decision problem addressed in the company submission	Rationale if different from the final NICE scope	EAG comment
				between the technologies being compared. Costs were considered from an NHS and Personal Social Services perspective
Subgroups	If the evidence allows the following subgroups will be considered: • Early-moderate stage PBC (minimal / moderate fibrosis) with isolated elevated ALP values above the upper limit of normal • Individuals with pruritus • Those who have inadequately responded to ursodeoxycholic acid and/or obeticholic acid.	None	Subgroups according to PBC stage, presence/absence of pruritus, and patient response to UDCA and/or tolerability to UDCA are not considered separately in the company submission. The company submission provides clinical- and cost-effectiveness evidence for seladelpar within its full marketing authorisation.	Subgroup data were not available to compare outcomes according to disease stage, except some limited evidence comparing treatment outcomes according to presence of cirrhosis at baseline. In general, people participating in studies evaluating seladelpar were earlier in their disease, consistent with a 2nd line treatment position. Some evidence was available comparing outcomes between people with/without moderate pruritus and according to response to UDCA. In the latter case, there was a small sample of people who had been intolerant to UDCA, meaning that the results were highly uncertain. The company did not pool data across studies of seladelpar to explore variation in treatment effect, including according to subgroup.
Special considerations including issues related to equity or equality	None	NA	NA	No equality considerations were identified during appraisal.

Abbreviations ALP, Alkaline phosphatase; CS, company submission; EAG, External Assessment Group; OCA, Obeticholic acid; NA, not applicable; NICE, National Institute for Health and Care Excellence; NR, not reported; PBC, primary biliary cholangitis; UDCA, ursodeoxycholic acid

Source: CS, NICE scope, Company decision problem form

3. CLINICAL EFFECTIVENESS

3.1. Critique of the methods of review(s)

The EAG considered the company's systematic literature review (SLR) to be broadly appropriate. Details are provided in Table 7 below.

The company undertook a SLR to identify randomised controlled trials (RCTs) of seladelpar for the treatment of PBC in combination with UDCA in adults who have an inadequate response to UDCA, or as monotherapy in patients unable to tolerate UCDA, as well as other relevant pharmacological therapies to inform indirect treatment comparisons. There are a number of RCTs available that have evaluated seladelpar, and therefore the restriction to RCTs was able to retrieve a reasonable body of evidence for seladelpar. However, as other treatments for PBC may have been evaluated in fewer RCTs, the restriction may have limited the evidence base available for comparator treatments.

No date limits were used. The company searched Embase, Medline (via PubMed – although in response to clarification, the company clarified that Medline was searched both via PubMed and Embase.com) and the Cochrane Central Register of Controlled Trials (CENTRAL) and the Cochrane Database of Systematic Reviews (CDSR) (both via the Cochrane Library). Given the search was for RCTs only, searching the CDSR was unnecessary, and indeed retrieved no records. Nevertheless, the EAG considered the remaining databases a suitable range of sources, given the decision problem.

Search terms for the population and intervention were appropriate. The company initially claimed to use SIGN study type filters – although the company clarified during clarification that filters were developed for the searches. The EAG would have preferred to see a validated filter used for the searches performed. Nevertheless, the RCT filter used looked reasonable, although perhaps overly sensitive (i.e. it would have retrieved many non-RCTs).

Conference abstracts were included via the Embase search. Additional conferences were also searched for by hand. These included the American Association for the Study of Liver Diseases (AASLD), European Association for the Study of the Liver (EASL), Digestive Disease Week (DDW), United European Gastroenterology Week (UEG), The International Liver Congress, and the American College of Gastroenterology (ACG). The company also searched the International Clinical Trials Register Search Portal (ICTRP), and clinicalTrials.gov of the US National Institute

of Health. Finally, the company stated that, supplemental to the above-described searches, they also searched systematic reviews and used citation snowballing for the identification of any missing studies – although details of this process were not provided.

In summary, the EAG considered that the RCT search described was suitable for the decision problem. However, the lack of a formal part of the search for cohort or longitudinal studies, and for real-world evidence (RWE) in general, meant that some evidence with regards to safety may have been missed.

Table 7: Summary of EAG's critique of the methods implemented by the company to identify evidence relevant to the decision problem

Systematic review step	Section of CS in which methods are reported	EAG assessment of robustness of methods
Searches	Appendix B.1.1	The company conducted an SLR for clinical evidence in Embase, MEDLINE and Cochrane (CENTRAL and the Database of Systematic Reviews), and searched for abstracts and posters from five conference series (AASLD, EASL, DDW, UEG, and ACG). Trial registries and supplemental searches were also used, although the details of these searches remained unclear. The EAG considered the sources searched and the search strategies used to be appropriate to identify RCTs.
Inclusion criteria	Appendix B.1.1	The EAG considered the SLR inclusion criteria to be broadly appropriate. The SLR criteria only included RCTs. However, the company submission includes non-RCT evidence, including ASSURE, for seladelpar. The EAG was satisfied, following a search of clinicaltrials.gov, that no studies of seladelpar were missed. The EAG had concerns, however, that the focus on RCTs may have led to the exclusion of studies for other comparators in the network. Seladelpar is unusual having so many RCTs, while other drugs may be more likely to have Phase 2 non-randomised studies as well as long-term follow-up studies. The EAG considered there was a potential bias of including seladelpar long-term non-randomised data from ASSURE in the submission and not searching for studies with the same design of other comparators. The SLR was broader than the NICE scope in terms of comparators, including fibrates, setanaxib, budesonide, linerixibat, and saroglitazar. However, the EAG noted that fibrate studies were excluded from the ITC (Clarification response A14) because they are used off-label in the UK.
Screening	Appendix B.1.1	Screening was conducted by two independent reviewers with disagreements resolved by a third reviewer.
Data extraction	Appendix B.1.1	Data extraction was conducted by two independent reviewers with disagreements resolved by a third reviewer.

Systematic review step	Section of CS in which methods are reported	EAG assessment of robustness of methods
Tool for quality assessment of included study or studies	Appendix B.1.1	Critical appraisal was conducted using the Cochrane Risk of Bias 2 (RoB 2) tool, which is suitable for the assessment of RCTs.
Evidence synthesis	CS Section 2.9	The company stated that no pairwise meta-analysis was conducted as only one phase 3 trial was conducted that had follow-up data at 12 months. The EAG considered this to be overly restrictive an approach, given that earlier follow-up timepoints were available from multiple studies and the results seem to suggest that response to treatment with seladelpar happens rapidly and remains constant up to 12-months. Indirect treatment comparisons were used due to the lack of head-to-head data comparing seladelpar, OCA and elafibranor. These are critiqued in section 3.4.

Abbreviations: AASLD, American Association for the study of Liver Diseases; ACG, American College of Gastroenterology; CS, Company submission; DDW, Digestive Disease Week; EAG, External Assessment Group; EASL, European Association for the Study of the Liver; OCA, Obeticholic acid; RCT, randomised controlled trial; RoB, Risk of bias; SLR, systematic review; UEG, United European Gastroenterology; UK, United Kingdom.

3.2. Critique of trials of the technology of interest, the company's analysis and interpretation (and any standard meta-analyses of these)

3.2.1. Studies included in the clinical effectiveness review

The clinical SLR conducted by the company identified six studies that evaluated the effectiveness of seladelpar for the treatment of PBC. In addition, the EAG identified a Phase I, open-label single-arm pharmacokinetic study that reported safety data for seladelpar in people with PBC (N = 24; NCT04950764), though this study was conducted in people with existing liver damage and therefore was not considered relevant to the decision problem for this appraisal.

The clinical development of seladelpar was complicated by the termination of studies due to safety concerns related to seladelpar in another indication, which were ultimately determined to be unrelated to the study drug. In addition, participants from several different studies, including terminated studies, were eligible to enter ASSURE, albeit with different lead-in times. Participants recruited from earlier studies were recruited as part of protocol number CB8025-31731, which the company refers to as the 'Phase 3 long-term safety study. This study was terminated and then restarted under protocol number CB8025-31731-RE, otherwise known as ASSURE, and participants from RESPONSE were then eligible to join. For simplicity, throughout the report the EAG refers to both phases of the study as ASSURE and notes where

data is from the 'legacy' participants (i.e. participants recruited in the earlier studies) and/or from RESPONSE participants.

The company focussed the CS on two studies (RESPONSE and the Phase II dose-ranging study (NCT02955602) with some limited data available for the ASSURE extension study. Additional data from ASSURE and ENHANCE were provided at clarification. During the clarification call (10th March 2025), the company stated that there were limitations with data from ASSURE, which meant that limited data were available. In the clarification response, the company said that data limitations arose from the acquisition of seladelpar from another company.

For the purposes of the assessment, the EAG considered that the key evidence for seladelpar came from the four studies highlighted (as shaded rows) at the top of Table 8 below: Phase III studies RESPONSE, ENHANCE and ASSURE and the Phase II dose-ranging study NCT02955602 // CB8025-21629. No data were available from the other four studies, either because these were ongoing or because they were considered not relevant to the decision problem.

Table 8: Clinical evidence for seladelpar for the treatment of PBC and the evidence included in the CS

Study name and acronym	Study design	Population	Intervention	Comparator	Evidence presented in the CS
RESPONSE (NCT04620733 // CB8025-32048)	Phase III, double-blind, placebo-controlled, randomised study with 1-year follow-up Study complete	People with PBC and an incomplete response or intolerance to UDCA N = 193	Seladelpar 10mg or 5mg	Placebo	Yes Used in the model
ENHANCE (NCT03602560 // CB8025-31735)	Phase III, double-blind, placebo-controlled, randomised study Intended 1-year follow-up, but terminated early so we have 3- and 6-month follow-up. Significant attrition noted at 6 months. Study complete	People with PBC and an incomplete response or intolerance to UDCA N = 265	Seladelpar 10mg or 5mg	Placebo	Partially Limited results are presented in Appendix J with additional results at clarification.
ASSURE (NCT03301506 // CB8025-31731 // CB8025-31731-RE)	Phase III long-term continuation, single-arm, open-label study with 5-year follow-up Study ongoing	People with PBC who participated in one of the previous trials of seladelpar N = 500	Seladelpar 10mg or 5mg	None	Partially Limited results are presented in Appendix K with additional results at clarification.
Phase II dose-ranging study (NCT02955602 // CB8025-21629)	Phase II, open-label randomised dose-ranging study with 8 -week follow-up followed by a 44-week extension Study complete	People with PBC and an incomplete response or intolerance to UDCA N = 119	Seladelpar 10mg, 5mg or 2mg	None	Yes

Study name and acronym	Study design	Population	Intervention	Comparator	Evidence presented in the CS
AFFIRM (NCT06051617 // CB8025-41837)	Phase III, double-blind, placebo-controlled, randomised study with 2.5 years follow-up Study ongoing	People with PBC and compensated cirrhosis N = 192	Seladelpar 10mg (people with CP-A cirrhosis) or 5mg (people with CP-B cirrhosis)	Placebo	No – the company stated that no interim data are available. Primary completion date will be July 2029
Phase II 2xdose study (NCT02609048 // CB8025-21528)	Phase II, double-blind, randomised, placebo-controlled study Study complete	People with PBC and an incomplete response or intolerance to UDCA N = 41 (terminated early)	Seladelpar 50mg or 200mg	Placebo	No – company stated that dose was not relevant to the marketing authorisation for seladelpar, which the EAG agreed with
Phase I pharmacokinetic study (NCT04950764 // CB8025-21838)	Phase I, single-arm, open-label with 17-week follow-up Study complete	People with PBC and evidence of liver damage who have previously received treatment with UDCA N = 24	Seladelpar 10mg or less	None	No – company stated at clarification that the population was not relevant to the appraisal, which the EAG agreed with
IDEAL (NCT06060665 // CB8025-32251)	Phase III, double-blind, placebo-controlled, randomised study with 52-week follow-up Study ongoing	People with PBC and an incomplete response or intolerance to UDCA N=150	Seladelpar 10mg	Placebo	No – company stated that no interim results available. Primary completion date will be December 2025

Abbreviations: CS, company submission; EAG, External Assessment Group; PBC, primary biliary cholangitis; RCT, randomised controlled trial; UDCA, ursodeoxycholic acid

Note: Shaded rows: the studies the EAG considered were the key evidence for seladelpar

3.2.2. Description and critique of the design of the studies

3.2.2.1. Design of the studies

An overview of the four key studies that evaluated seladelpar is provided in this section and Table 9 below. CB8025-21629 was an open-label, phase II dose-ranging study evaluating three different doses of seladelpar, including the licensed dose (10mg) and the dose that people with PBC may receive if a dose-reduction is needed (5mg). RESPONSE and ENHANCE were blinded, placebo-controlled phase III RCTs that assessed the efficacy and safety of seladelpar compared to placebo over 12 months, however limited data was available from ENHANCE after 3 months follow-up due to termination. ASSURE was an open label extension study assessing the long-term safety of seladelpar. There were multiple recruitment routes into ASSURE, with participants entering from multiple previous studies of seladelpar, and these are outlined in Table 10. Of note, those who previously participated in RESPONSE entered ASSURE immediately at trial end, while those entering after participation in other trials of seladelpar had a gap in treatment before entering ASSURE.

Overall, the EAG considered that the available studies for seladelpar, all of which were RCTs, provided a good evidence base from which to evaluate seladelpar. While high attrition in ENHANCE posed some challenges for treatment duration >3 months, the EAG nevertheless considered that this study offered value to the overall evidence base.

Table 9. Overview of key studies evaluating seladelpar

Study name and acronym	Location	Aims	Trial arms	Follow-up timepoints	Design considerations	Applicability to decision problem
RESPONSE (NCT04620733 // CB8025-32048)	90 sites across 24 countries in Europe, North America, South America, Asia and Australasia	To evaluate efficacy and safety of seladelpar for PBC over 12 months	Seladelpar + UDCA / seladelpar monotherapy (n=128) Vs Placebo + UDCA / placebo (n=65)	1, 3, 6, 9, 12 months	Large, multi-site RCT with robust follow-up procedures. Possible concerns about external validity, given high rate of exclusions during screening. Randomisation stratified by baseline ALP and pruritus score. Outcome assessments were available in clinic or remotely at home (the trial was ongoing during the COVID pandemic. Participants were randomised 2:1 to seladelpar (as monotherapy [6.2%[22]] or in combination with UDCA [93.8%[22]]) or placebo (monotherapy or in combination with UDCA)	Relevant for seladelpar as a 2nd line treatment option in people with an inadequate response to UDCA; limited evidence in 3rd line and for seladelpar monotherapy in people intolerant to UDCA. Unclear how many participants were based in UK.
ENHANCE (NCT03602560 // CB8025-31735)	140 sites across Europe, North America, South America, Asia and Australasia	To evaluate efficacy and safety of seladelpar for PBC over 12 months	Seladelpar + UDCA / Seladelpar monotherapy (5mg n= 89; 10mg n = 89) Vs Placebo + UDCA / placebo (n=87)	1, 3, 6 months, however high attrition at 3 and 6 months due to trial termination	Stated that randomisation was 1:1:1 but substantially fewer patients were in 5mg then 10mg arm, which was unexplained in CS.	Short follow-up available compared to RESPONSE, however 3-month data would be useful comparison with RESPONSE and may provide additional safety data. Unclear how many participants were based in UK.
ASSURE (NCT03301506 //	Multiple sites across	To evaluate the safety and	Seladelpar + UDCA /	1, 3, 6, 9, 12, 18, 24 months	Participants entered from multiple previous trials (as	Useful long-term safety data. Efficacy outcomes

Study name and acronym	Location	Aims	Trial arms	Follow-up timepoints	Design considerations	Applicability to decision problem
CB8025-31731-RE)	Europe, North America, South America, Asia and Australasia	tolerability of Seladelpar	Seladelpar monotherapy (crossover from RESPONSE placebo n=36, RESPONSE continuous seladelpar n=69, the legacy & CB8025-21838 group (i.e. those who had come from trials other than RESPONSE, i.e. CB8025-31731 (the previous version of ASSURE before it was paused), Phase II dose-ranging study, ENHANCE, or Phase 1 pharmacokinetic study) n=174, RESPONSE placebo group n=65)		profiled below under eligibility criteria in Table 10), however there were typically delays of >1 year between previous studies and the baseline of ASSURE. There was uncertainty about how potential differences in participant characteristics between parent study groups upon entry to ASSURE were handled in the analysis and what treatments participants had in the interim.	were also measured. Unclear how many participants were based in UK.
Phase II dose-ranging study (NCT02955602 // CB8025-21629)	32 sites across Canada, Germany, USA and UK	To evaluate efficacy and safety of several doses of seladelpar for PBC	Seladelpar + UDCA / Seladelpar monotherapy (10mg n=55;	8 weeks, 12 weeks, 1 year		10mg arm relevant to licence. Unclear how many participants were based in UK.

Study name and acronym	Location	Aims	Trial arms	Follow-up timepoints	Design considerations	Applicability to decision problem
			5mg n=53; 2mg n=11)			

Abbreviations: ALP, Alkaline phosphatase; PBC, Primary biliary cholangitis; RCT, Randomised controlled trial; UDCA, Ursodeoxycholic acid; UK, United Kingdom; USA, United States of America.

3.2.2.2. Population

Trial eligibility criteria

Key eligibility criteria for studies evaluating seladelpar are shown in Table 10. The population targeted in the NICE final scope was 'adults with primary biliary cholangitis whose disease has an inadequate response to, or who are unable to tolerate, ursodeoxycholic acid'. The EAG considered that the participants recruited within the studies fitted within the NICE scope for the appraisal. However, some participants who fit within the NICE scope were excluded from the trials, through for example the application of age cut offs (for example 18-75 in RESPONSE), platelet count requirements (for example ≥100,000/mm3 in RESPONSE), and bilirubin cutoffs (for example ≤2.0x ULN in RESPONSE). As higher bilirubin levels indicate likely worse prognosis, this meant that participants in the trials may on average have milder disease than the overall population with PBC that would be seen in clinical practice. However, clinical expert advice to the EAG was that this population would be relevant for the use of seladelpar as a 2nd or 3rd line treatment, as the disease is slow progressing and bilirubin levels will increase slowly over time for most people.

The EAG identified that a high proportion of people who were screened for participation in RESPONSE were identified as not being eligible, which raised an uncertainty in the external validity of the trial.

Table 10: Key eligibility criteria for studies evaluating seladelpar

	Study arms	Inclusion	Exclusion
RESPONSE (NCT04620733 // CB8025-32048)	Seladelpar + UDCA / Seladelpar monotherapy (n=128) Vs Placebo + UDCA / placebo (n=65)	Aged 18–75 years old with PBC who have been treated with UDCA for ≥12 months or a history of unacceptable side effects with UDCA (last dose >3 months before screening. Stable treatment with antipruritic drugs if required. ALP ≥1.67x ULN AST and ALT ≤3.0x ULN Total bilirubin ≤2.0x ULN	Advanced PBC (albumin level <LLN and total bilirubin >1.0x ULN) Hepatic decompensation Another chronic liver disease or comorbid condition that the investigator considered would confound the trial results History of malignancy Treatment with OCA and fibrates within 6 weeks prior to screening.

	Study arms	Inclusion	Exclusion
		eGFR >45 mL/min/1.73m2 Platelet count ≥100,000/mm3	
ENHANCE (NCT03602560 // CB8025-31735)	Seladelpar + UDCA / Seladelpar monotherapy (5mg n= 89; 10mg n = 89) Vs Placebo + UDCA / placebo (n=87)	Aged 18-75 years old with PBC Stable and recommended UDCA dose for at least 12 months or intolerant to UDCA. ALP ≥1.67 x ULN	Advanced PBC as defined by the Rotterdam criteria (albumin below LLN AND total bilirubin above 1 x ULN) A medical condition, other than PBC, that in the investigator's opinion would confound the results Presence of clinically significant hepatic decompensation Other chronic liver diseases Inadequate response to OCA or intolerance to OCA: obeticholic acid had to be discontinued 30 days prior to screening
ASSURE (NCT03301506 // CB8025-31731-RE)	Seladelpar + UDCA / Seladelpar monotherapy (crossover from placebo n=36, continuous seladelpar n=69, legacy & CB8025-21838 group n=174, RESPONSE placebo group n=65)	No new inclusion criteria. All participants had previously participated in RESPONSE, CB8025-31731 (the previous version of ASSURE before it was paused), CB8025-21629 dose-ranging study, ENHANCE, or the CB8025-21838 pharmacokinetic study. Those from studies besides RESPONSE are called the 'Legacy & CB8025-21838' group.	No new exclusion criteria
Phase II dose-ranging study (NCT02955602 // CB8025-21629)	Seladelpar + UDCA / Seladelpar monotherapy (10mg n=55; 5mg n=53; 2mg n=11)	Aged 18–75 years old with PBC who have been treated with UDCA for ≥12 months or are intolerant	AST or ALT >3xULN Total bilirubin > 2.0 mg/dL Creatine kinase >ULN

	Study arms	Inclusion	Exclusion
		ALP ≥1.67x ULN	Serum creatinine > ULN Current use of fibrates or OCA

Abbreviations: ALT, Alanine aminotransferase; AST, Aspartate transferase; LLN, lower limit of normal; OCA, Obeticholic acid; PBC, Primary biliary cholangitis; UDCA, Ursodeoxycholic acid; ULN, upper limit of normal.

Baseline characteristics

An overview of key baseline characteristics from the studies evaluating seladelpar are shown in Table 11. The EAG agreed that generally the population was fairly consistent across studies and between arms. No study reported [redacted] participants intolerant to UDCA, so typically data represent seladelpar in combination with UDCA, although monotherapy would be used in a minority of participants. This was considered fairly consistent across the trials. Furthermore, the proportion treated with UDCA was considered consistent with UK RWE studies where Abbas et al. (2023)[1] found 88.3% of participants were treated with UDCA and Abbas et al. (2024)[4] found this to be 90%.

In all studies, [redacted] of participants were female, which was consistent with clinical advice to the EAG that the clinical population for PBC was predominantly female. Between [redacted] and [redacted] of participants across study arms had cirrhosis at baseline, reflecting more progressed disease. Decompensated cirrhosis was an exclusion criterion in the trials and the SmPC stated that seladelpar was not indicated in these patients.

Bilirubin status was fairly consistent across study arms – bilirubin levels were considered a prognostic marker for disease progression and prognosis, with higher levels indicating likely worse clinical outcomes. The British Society of Gastroenterology/UK-PBC primary biliary cholangitis treatment and management guidelines[18] see UDCA treated patients with an alkaline phosphatase (ALP) >1.67x ULN and/or elevated bilirubin <2x ULN as a group of high-risk patients. However, some clinical advice to the EAG did not agree that these would be seen as particularly high-risk patients in a routine clinical practice setting. Elevated bilirubin can be a marker of advanced bilirubin. Between [redacted] and [redacted] of participants across study arms had results indicating elevated bilirubin levels.

Mean duration of disease ranged between [redacted] and [redacted] years across study arms. Seladelpar is intended for second line positioning an alternative second-line treatment option for those who are inadequate responders to, or intolerant of UDCA. Figure 2 shows the proposed change in the treatment pathway following introduction of seladelpar. The EAG had concerns in the context of the trials that previous non-response or intolerance to previous line of treatment could influence the treatment efficacy of seladelpar observed in the trials. The most common prior treatments were UDCA and OCA.

Table 11: Baseline characteristics of studies evaluating seladelpar

	RESPONSE (NCT04620733 // CB8025-32048)	ENHANCE (NCT03602560 // CB8025-31735)			ASSURE (NCT03301506 // CB8025-31731-RE)			Phase II dose-ranging study (NCT02955602 // CB8025-21629)
	All participants	Seladelpar 5mg	Seladelpar 10mg	Placebo	RESPONSE, crossover from placebo	RESPONSE, continuous seladelpar	Legacy & CB8025-21838	All participants
Age, years, mean (SD)	56.7 (9.7)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	57.2 (9.0)
Female sex, n (%)	183/193 (94.8)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	112/119 (94.1)
Duration of disease, years, mean (SD)	8.3 (6.6)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	9.7 (6.6)
Intolerant to UDCA, n (%)	12/193 (6.2)	NR	NR	NR	[redacted]	[redacted]	[redacted]	8/119 (6.7)
Prior use of OCA and/or fibrates, n (%)	33/193 (17.1)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	NR
Pruritus ≥4, n (%)	72/193 (37.3)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	NR; history of pruritus 84/119 (70.6%)
Cirrhosis at baseline, n (%)	27/193 (14.0)	NR	NR	NR	[redacted]	[redacted]	[redacted]	25/119 (21.0)
ALP, U/L, mean (SD)	314.3 (120.9)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	318.1 (160.9)
Total bilirubin >1 and ≤2x ULN, n (%)	25/193 (13.0)	NR	NR	NR	[redacted]	[redacted]	[redacted]	NR; mean (SD) 0.8 (0.3)
ALT, U/L, mean (SD)	47.7 (23.2)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	46.7 (24.3)
AST, U/L, mean (SD)	40.3 (16.1)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	43.5 (19.3)

Abbreviations: ALP, Alkaline phosphatase; ALT, Alanine aminotransferase; AST, Aspartate transferase; LLN, lower limit of normal; NR, not reported; OCA, Obeticholic acid; SD, standard deviation; UDCA, Ursodeoxycholic acid; U/L, units per litre; ULN, upper limit of normal.

3.2.2.3. Intervention

All key studies evaluated seladelpar in accordance with the licensed dose. Intervention characteristics of seladelpar as evaluated in the included studies are summarised in Table 12. Seladelpar was either administered in combination with UDCA or as monotherapy for those who were intolerant to UDCA. Intervention characteristics were not available separately for those on combination and monotherapy. Information on background treatment was not available separated by treatment arm for any of the key trials, meaning that the EAG was unable to assess whether there was a change in the use of background treatment according to the treatment received in the study. This was particularly important for understanding the effect of treatment on pruritus, since any different in pruritus between treatment arms may be masked if there was a difference in the use of treatments for itching. Fibrates were not permitted for use during the studies.

Table 12: Characteristics of seladelpar as evaluated in the included studies

	Titration phase?	Planned dose	Actual dose	Dose reduction n/N (%) and when	Duration of treatment, mean weeks (SD)	Background treatment
RESPONSE (NCT04620733 // CB8025-32048)	NR	Seladelpar 10mg (and 5mg where dose reductions needed for tolerance) UDCA participants' usual dose	Average daily dose mean (SD) [redacted] mg/day	[redacted]	50.5 (7.4)	Information on background treatment received during the trial was not reported. Fibrates were not permitted in the trial.
ENHANCE (NCT03602560 // CB8025-31735)	Yes – in one arm (5mg then 10mg); NR in other arm	Seladelpar 5mg then 10mg or 10mg UDCA participants' usual dose	Average daily dose 5mg group mean (SD) [redacted] mg/day; 10mg group [redacted], all seladelpar [redacted]	NR	5mg group 17.637 (12.145), 10mg group 17.557 (11.992), all seladelpar 17.597 (12.035)	Information on background treatment received during the trial was not reported. Fibrates were not permitted in the trial.
ASSURE (NCT03301506 // CB8025-31731-RE)	NR	Seladelpar 5mg or 10mg participants' usual dose	Average daily dose RESPONSE placebo, crossover to seladelp[redacted] ar mean (SD) [redacted] mg/day, RESPONSE seladelpar, continuous seladelpar [redacted], legacy & CB8025-21838 group [redacted]	NR	RESPONSE placebo, crossover to seladelpar [redacted], RESPONSE seladelpar, continuous seladelpar [redacted], legacy & CB8025-21838 group [redacted]	Information on background treatment received during the trial was not reported. Fibrates were not permitted in the trial.

	Titration phase?	Planned dose	Actual dose	Dose reduction n/N (%) and when	Duration of treatment, mean weeks (SD)	Background treatment
Phase II dose-ranging study (NCT02955602 // CB8025-21629)	Yes – after 12 weeks participants could have their dose titrated	Seladelpar (10mg, 5mg or 2mg) UDCA participants' usual dose	NR – company says doesn't have access	0% on 2mg. 11.3% on 5mg. 5.5% on 10mg.	8 weeks initial treatment period then extension up to 52 weeks	Information on background treatment received during the trial was not reported. Fibrates were not permitted in the trial.

Abbreviations: NR, not reported; OCA, Obeticholic acid; SD, standard deviation; UDCA, Ursodeoxycholic acid; U/L, units per litre; ULN, upper limit of normal.

3.2.2.4. Comparators

RESPONSE and ENHANCE included a comparator arm of placebo, taken either in combination with UDCA or as monotherapy in people who were intolerant to UDCA. Characteristics of placebo in these two studies are shown in Table 13. None of the studies that evaluated seladelpar included a direct comparison with any of the other treatments available for PBC in the proposed position in the treatment pathway. In order to provide a comparison to elafibranor and OCA, an indirect treatment comparison was conducted by the company, which is critiqued in Section 3.4. A direct comparison between seladelpar doses was available from ENHANCE and the Phase 2 dose-ranging study.

Table 13. Profile of comparators

	Placebo monotherapy or in combination with UDCA		
	Dose reduction n/N (%) and when	Duration of treatment, mean weeks (SD)	Background treatment
RESPONSE (NCT04620733 // CB8025-32048)	[redacted]	48.3 (11.6)	As per Table 12*
ENHANCE (NCT03602560 // CB8025-31735)	NR	17.8 (NR)	As per Table 12*

Abbreviations: NR, not reported; SD, standard deviation; UDCA, ursodeoxycholic acid

* Not reported separately for placebo.

3.2.2.5. Outcomes

The outcomes reported in studies evaluating seladelpar are summarised in Table 8. The CS was focussed primarily on RESPONSE and the Phase II dose-ranging study, with limited outcome data from ASSURE and ENHANCE provided in appendices. At clarification, the EAG asked the company to provide data for scoped outcomes not reported in the CS and to complete data for outcomes partially reported in the CS (e.g. to provide variance data for continuous outcomes or provide data at additional follow-up timepoints). As this was a large amount of data presented at clarification, the EAG was unable to verify data presented in the trial CSRs or to identify data from the CSRs that were not reported in the CS. To allow easy review of the submitted data by the committee, data for scoped outcomes are reported in full in Section 3.2.3.1.

All four studies evaluated a composite outcome for treatment response, which was defined as achieving all three of the following endpoints: ALP < 1.67× ULN; ≥ 15% decrease in ALP and total bilirubin ≤ 1.0× ULN. A clinical expert to the EAG advised that this endpoint was useful for decision-making, though noted that bilirubin may be less sensitive to treatment response in the study cohorts as baseline bilirubin was relatively low and participants were earlier in the disease course. In order to understand the potential effect of seladelpar, results for each of the endpoints in the composite outcome were also presented separately.

None of the available studies reported data for the time to liver transplant. While the EAG agreed that this was an important outcome for understanding the potential value of treatments for PBC, the available follow-up of studies evaluating seladelpar was too short to allow for meaningful assessment of this outcome. As those eligible for initiating treatment with seladelpar would likely be early in the disease course, the EAG understood that it may be many years before a significant number were considered in need of a transplant. Instead, the company assessed change in the risk of end-stage liver disease (ESLD) requiring transplant as assessed using the UK-PBC risk score. Data for this outcome was reported for RESPONSE, ENHANCE and, for one arm, the Phase II dose-ranging study. The UK-PBC Risk score[24] was a multivariate prognostic risk model comprising measures of albumin, platelet count, bilirubin, transaminases and ALP. The model was developed to predict ESLD requiring a liver transplant in a cohort of UK participants who had received ≥ 12 months of treatment with UDCA, of whom 9.2% experienced an event. ESLD was defined as death from a liver-related cause, liver transplant, or serum bilirubin measuring ≥100 µmol/L for the first time. In a separate cohort of participants from the UK with PBC (the validation cohort), scores on the UK-PBC risk score were strongly associated with ESLD requiring transplant at five years (AUC 0.96, 95%CI 0.93, 0.99), ten years (AUC 0.95, 95%CI 0.93, 0.98) and 15 years (AUC 0.94, 95%CI 0.91, 0.97). No specific thresholds had been reported for determining levels of risk, as the authors suggest that the level of risk that is meaningful needs to be considered for each individual patient. While reasonable, this does present limitations for interpreting the data from the tool in this context, since there was no threshold through which to interpret whether differences in risk score between study arms were clinically ‘meaningful’. Nevertheless, a reduction in risk score following treatment would be correlated with a reduced risk of ESLD requiring liver transplant, which was a meaningful outcome for this appraisal that is not otherwise captured in the clinical data.

The EAG noted that the company also assessed the risk of ESLD using the Global-PBC risk score, which was another multivariate risk tool developed in a population outside of the UK. For

the purposes of assessing clinical effectiveness, the EAG focussed its appraisal on the UK-PBC risk score as it considered it more relevant to UK patients.

The NICE scope included abdominal pain, ascites, varices, encephalopathy, and hepatic cell carcinoma as PBC-related outcomes of interest. While the EAG assumed that these outcomes were assessed as part of the study procedures for assessing the safety of treatments, the company did not specifically report data for these outcomes in the CS. It's possible that the company would have highlighted where there were meaningful differences in these outcomes, but the EAG considered this to be uncertain.

Table 14: Scope outcomes reported in the included trials of seladelpar

	RESPONSE		ENHANCE (NCT03602560)		Phase II dose-ranging		ASSURE	
	Measured	**Reported in CS**	**Measured**	**Reported in CS**	**Measured**	**Reported in CS**	**Measured**	**Reported in CS**
Mortality	✓	✓	✓	✓	✓	✓	✓	✓
Liver function (liver biochemistry)	✓	✓	✓	✓	✓	✓	✓	✓
Pruritus	✓	✓	✓	✓	✓	✓	✓	✓
Fatigue	✓	✓	✓	✓	✓	✓	×	×
Abdominal pain	✓	×	✓	×	✓	×	✓	×
Time to liver transplant	×	×	×	×	×	×	×	×
Ascites	✓	×	✓	×	✓	×	✓	×
Varices	✓	×	✓	×	✓	×	✓	×
Encephalopathy	✓	×	✓	×	✓	×	✓	×
Hepatic cell carcinoma	✓	×	✓	×	✓	×	✓	×
Adverse events of treatment	✓	✓	✓	✓	✓	✓	✓	✓
Health-related quality of life	✓	✓	✓	✓	✓	×	×	×

Source: CS, company clarification response, study clinical trial records.

3.2.2.6. Critical appraisal of the design of the studies

The company conducted critical appraisal using the Cochrane RoB 2 tool, which was a well-regarded and appropriate tool for the evaluation of randomised trials. Full risk of bias tables for RESPONSE, ASSURE, CB8025-21629 (dose-ranging study), and CB8025-31731 (the previous version of ASSURE before it was paused) with justification for the decisions reached were provided in the clarification response (Table 58 and following un-numbered tables).

With regards to RESPONSE, the one issue ('partial no') that the company noted was an imbalance in geographic region between the treatment arms. The EAG considered the overall demographic profile to be well-balanced.

With regards to ASSURE, the company noted the open label nature of the trial, which could lead to performance bias as well as inability to determine a few items of the checklist, including the lack of a formal sample size determination.

With regards to the Phase II dose-ranging trial, the company noted the open label nature of the trial, as well a lack of reporting exact probability values for all the outcomes, lack of information about covariate adjustment in the analysis, and inability to determine a few items of the checklist.

With regards to CB8025-31731, the company noted the open label nature of the trial, as well as that only descriptive statistics were available, lack of information about covariate adjustment in the analysis, and inability to determine a few items of the checklist.

The EAG generally agreed with the company's assessment that the trials were high-quality, although high levels of attrition in ENHANCE (at following up timepoints ≥3 months) and in ASSURE should be noted as there is a high risk of bias that data would not be representative of the full trial populations. The EAG noted a placebo-response in the placebo-controlled studies evaluating seladelpar, which is discussed in Key Issue 3. This was not noted in the company's quality appraisal. As clinical expert advice to the EAG was that this may be due to improved adherence to treatments during the study duration, this has implications for the generalisability of evidence from the studies to clinical practice.

3.2.3. Description and critique of the results of the studies

3.2.3.1. Clinical effectiveness results

Liver function

ALP response

The effect of treatment on ALP across studies is show in Table 15.

The EAG observed that there was a notable response in ALP in people treated with placebo in both RESPONSE and ENHANCE. While background treatment was not reported separately for trial arms, other treatments that would affect ALP (OCA, elafibranor, fibrates) were not permitted during the studies, and the EAG was unable to identify a reason based on the study design that would cause the placebo-effect on ALP outcomes. The consulted one of its clinical experts about this, who stated that a placebo response was common trials of treatments for PBC. While they stated that there was no evidence that had determined the cause of the placebo response, they suggested that adherence to treatments may increase within trial conditions as compared to everyday life. This would provide an explanation for the placebo-response, as people may increase their adherence to UDCA within the trial and therefore show a response in ALP, particularly if their ALP was mildly elevated at baseline. As increased adherence to treatment within the clinical trial would affect both treatment arms, the EAG considered that relative differences in ALP normalisation between seladelpar and placebo were the most robust approach to understanding the treatment effectiveness of seladelpar. Trials without a placebo arm (ASSURE and the Phase II dose-ranging study) should therefore be interpreted with caution on the basis that absolute rates may be artificially inflated due to trial conditions. This issue is considered in Key Issue 3.

The data for ALP response showed a relative improvement in ALP response with seladelpar as compared to placebo after only one month of treatment. The response rate was then reasonably consistent at subsequent follow-up timepoints. The vast majority of people who received seladelpar experienced a 15% reduction in ALP from baseline, which was evident at 1 month follow-up. Graphs provided by the company (e.g. CS Figures 17 and 25) showed that further 15% reductions did not occur and ALP levels remained approximately at the level they were at when assessed at month 1. There was no increase in the number of people who experienced a 15% reduction after 1 month. Overall, the EAG considered that a short duration of treatment

with seladelpar may be needed to determine whether a person may experience a response in ALP and whether that response was adequate to remain on treatment.

Within trial conditions, approximately two thirds of people who received treatment with seladelpar achieved ALP levels <1.67 x ULN, which the EAG noted was predictive of improved long-term disease outcomes. However, due to the potential for increased treatment adherence in the trials as compared to clinical practice (Key Issue 3, as discussed above), this effect may be in part explained by improved adherence to UDCA in those receiving combination treatment.

Due to high levels of attrition in ASSURE after ≥15 months, it was not possible for the EAG to determine whether rates of ALP response declined over longer-term follow-up, though there was no evidence of this from the limited data available.

Overall, the EAG considered that the effect of treatment with seladelpar on ALP response was reasonably consistent across studies and indicated a positive benefit of treatment in comparison with placebo.

Table 15: Response in ALP in studies evaluating seladelpar

	RESPONSE (NCT04620733 // CB8025-32048)		ENHANCE (NCT03602560 // CB8025-31735)			ASSURE (NCT03301506 // CB8025-31731-RE)	Phase II dose-ranging study (NCT02955602 // CB8025-21629)	
	Seladelpar	**Placebo**	**Seladelpar 5mg**	**Seladelpar 10mg**	**Placebo**	**Seladelpar**	**5mg**	**10mg**
Baseline ALP, U/L, mean (SD)	314.6 (123.0)	313.8 (117.7)	[redacted]	[redacted]	[redacted]	[redacted]	345.4 (188.0)	295.3 (136.0)
ALP <1.67× ULN, n/N (%)	1m: 82/128 (64.1%) 3m: 90/128 (70.3%) 6m: 89/128 (69.5%) 9m: 85/128 (66.4%) 12m: 84/128 (65.6%)	1m: 10/65 (15.4%) 3m: 13/65 (20.0%) 6m: 15/65 (23.1%) 9m: 17/65 (26.2%) 12m: 17/65 (26.2%)	1m: 43/80 (53.8%) 3m: 36/56 (64.3%) 6m: 16/26 (61.5%)	1m: 54/79 (68.4%) 3m: 45/55 (81.8%) 6m: 15/20 (75.0%)	1m: 11/78 (14.1%) 3m: 10/56 (17.9%) 6m: 8/23 (34.8%)	NR	NR	40/52 (78.4%)
ALP <1.0× ULN, n/N (%)	1m: 10/128 (7.8%) 3m: 24/128 (18.8%) 6m: 34/128 (26.6%) 9m: 36/128 (28.1%) 12m: 32/128 (25.0%)	1m: 0/65 (0%) 3m: 0/65 (0%) 6m: 0/65 (0%) 9m: 0/65 (0%) 12m: 0/65 (0%)	1m: [redacted] 3m: 3/56 (5.4%) 6m: [redacted]	1m: [redacted] 3m: 15/55 (27.3%) 6m: [redacted]	1m: [redacted] 3m: 0/56 (0%) 6m: [redacted]	13m: [redacted] * 15m: [redacted] * 18m: [redacted] * 21m: [redacted] * 24m: [redacted] *	3m: [redacted] 12m: [redacted]	3m: [redacted] 12m: [redacted]

	RESPONSE (NCT04620733 // CB8025-32048)		**ENHANCE (NCT03602560 // CB8025-31735)**			**ASSURE (NCT03301506 // CB8025-31731-RE)**	**Phase II dose-ranging study (NCT02955602 // CB8025-21629)**	
≥ 15% decrease in ALP n/N (%)	1m: 121/128 (94.5%) 3m: 120/128 (93.8%) 6m: 118/128 (92.2%) 9m: 109/128 (85.2%) 12m: 107/128 (83.6%)	1m: 16/65 (24.6%) 3m: 20/65 (30.8%) 6m: 26/65 (40.0%) 9m: 23/65 (35.4%) 12m: 21/65 (32.3%)	1m: 74/80 (92.5%) 3m: 53/56 (94.6%) 6m: 22/26 (84.6%)	1m: 76/79 (96.2%) 3m: 52/55 (94.5%) 6m: 17/20 (85.0%)	1m: 12/78 (15.4%) 3m: 13/56 (23.2%) 6m: 7/23 (30.4%)	NR	NR	49/52 (96.1%)
% change in ALP from baseline, U/L, LS mean % (SE)**	1m: -36.2 (2.03) 3m: -43.4 (1.62) 6m: -44.8 (1.89) 9m: -42.8 (2.40) 12m: -42.4 (2.54)	1m: -4.8 (2.72) 3m: -8.0 (2.09) 6m: -5.9 (2.51) 9m: -4.5 (3.29) 12m: -4.3 (3.48)	1m: [redacted] 3m: -35.68 [redacted] 6m: [redacted]	1m: [redacted] 3m: -44.21 [redacted] 6m: [redacted]	1m[redacted] 3m: -3.72 [redacted] 6m: [redacted]	NR	1m: NR 3m: -33.97 (2.43) 6m: NR 9m: NR 12m: [redacted]	1m: NR 3m: -43.60 (2.32) 6m: 9m: NR 12m: [redacted]

Abbreviations: ALP, Alkaline phosphatase; NR, not reported; SD, standard deviation; SE, standard error; ULN, upper limit of normal.

Source: CS, company clarification response, Phase II dose-ranging study CSR

Notes: *Participants who received continuous seladelpar in RESPONSE and ASSURE, ** change values in completers only.

Bilirubin

Outcomes evaluated change in bilirubin are shown in Table 16. As discussed previously (Section 3.2.2.2), bilirubin levels were relatively low in the trial samples, which would be expected given trial populations represented those earlier in the disease course who would be eligible for seladelpar. Accordingly, the evidence showed limited change in bilirubin following treatment with seladelpar in RESPONSE and ENHANCE – there was no difference in the proportion of people with total bilirubin ≤1.0xULN between participants receiving seladepar or placebo, and while there was a higher percentage change in total bilirubin following seladelpar than placebo, these changes were minute in comparison with the standard deviation of baseline bilirubin levels.

Table 16: Bilirubin outcomes in studies evaluating seladelpar

	RESPONSE (NCT04620733 // CB8025-32048)		ENHANCE (NCT03602560 // CB8025-31735)			ASSURE (NCT03301506 // CB8025-31731-RE)	Phase II dose-ranging study (NCT02955602 // CB8025-21629)	
	Seladelpar	**Placebo**	**Seladelpar 5mg**	**Seladelpar 10mg**	**Placebo**	**Seladelpar**	**5mg**	**10mg**
Baseline total bilirubin, mg/dl, mean (SD)	0.769 (0.3)	0.737 (0.3)	[redacted]	[redacted]	[redacted]	[redacted]	0.8 (0.4)	0.8 (0.3)
Total bilirubin ≤ 1.0× ULN, n/N (%)	1m: 111/128 (86.7%) 3m: 110/128 (85.9% 6m: 111/128 (86.7%) 9m: 106/128 (82.8%) 12m: 104/128 (81.3%)	1m: 55/65 (84.6%) 3m: 60/65 (92.3%) 6m: 54/65 (83.1%) 9m: 54/65 (83.1%) 12m: 50/65 (76.9%)	1m: 68/80 (85.0%) 3m: 48/56 (85.7%) 6m: 23/26 (88.5%)	1m: 75/79 (94.9%) 3m: 51/55 (92.7%) 6m: 17/20 (85.0%)	1m: 71/78 (91.0%) 3m: 51/56 (91.1%) 6m: 20/23 (87.0%)	NR	NR	NR
% change total bilirubin, mg/dl, LS mean (SE)	1m: -6.07 (1.99) 3m: -8.80 (1.75) 6m: -8.25 (2.63) 9m: -6.75 (2.82)	1m: -0.745 (2.75) 3m: -5.77 (2.40) 6m: 1.20 (3.66) 9m: 2.52 (3.96)	NR	NR	NR	NR	NR	NR

	RESPONSE (NCT04620733 // CB8025-32048)		**ENHANCE (NCT03602560 // CB8025-31735)**			**ASSURE (NCT03301506 // CB8025-31731-RE)**	**Phase II dose-ranging study (NCT02955602 // CB8025-21629)**	
	12m: -0.38 (4.24)	12m: 3.56 (6.00)						
Change total bilirubin, mg/dl, LS mean (SE)	NR	NR	1m: [redacted] 3m: [redacted] 6m: [redacted]	1m: [redacted] 3m: [redacted] 6m: [redacted]	1m: [redacted] 3m: [redacted] 6m: [redacted]	NR	NR	NR

Abbreviations: ALP, Alkaline phosphatase; NR, not reported; SD, standard deviation; SE, standard error; ULN, upper limit of normal.

Composite response

Data for composite response are shown in Table 17. As discussed above, there was minimal change in bilirubin levels between study arms, which would be expected given the disease stage of trial participants. Accordingly, any differences in composite outcomes reported in studies of seladelpar were driven by differences in the outcomes related to ALP; i.e. the proportion of participants who experienced a 15% reduction in ALP and normalisation of ALP levels ≤1.67xULN.

As with ALP, findings were relatively consistent across studies. Separate results were presented for the reduced dose of seladelpar (5mg) in ENHANCE and showed that participants experienced a reduced treatment effect, although half of all participants on this dose nevertheless achieved the composite response following treatment.

Attrition was notable for later follow-up timepoints in ENHANCE and for data from ASSURE in those participants who continued from RESPONSE, meaning that longer-term composite response was uncertain.

Table 17: Composite outcome across studies evaluating seladelpar

	RESPONSE (NCT04620733 // CB8025-32048)		ENHANCE (NCT03602560 // CB8025-31735)			ASSURE (NCT03301506 // CB8025-31731-RE)			Phase II dose-ranging study (NCT02955602 // CB8025-21629)	
	Seladelpar	**Placebo**	**Seladelpar 5mg**	**Seladelpar 10mg**	**Placebo**	**RESPONSE Seladelpar/Seladelpar**	**RESPONSE Placebo/ Seladelpar**	**Legacy seladelpar**	**5mg**	**10mg**
1 month	76/128 (59.4%)	5/65 (7.7%)	38/80 (47.5%)	51/79 (64.6%)	8/78 (10.3%)	NA	[redacted]	[redacted]	NR	NR
3 months	79/128 (61.7%)	7/65 (10.8%)	32/56 (57.1%)	43/55 (78.2%)	7/56 (12.5%)	NA	[redacted]	[redacted]	NR	34/52 (66.7%)
6 months	85/128 (66.4%)	12/65 (18.5%)	16/26 (61.5%)	14/20 (70.0%)	5/23 (21.7%)	NA	[redacted]	[redacted]	NR	NR
9 months	79/128 (61.7%)	12/65 (18.5%)	NA	NA	NA	NA	[redacted]	[redacted]	NR	NR
12 months	79/128 (61.7%)	13/65 (20.0%)	NA	NA	NA	NA	[redacted]	[redacted]	NR	33/52 (67.3%)
13 months	NA	NA	NA	NA	NA	[redacted]	NA	NR	NA	NA
15 months	NA	NA	NA	NA	NA	[redacted]	NA	NR	NA	NA
18 months	NA	NA	NA	NA	NA	[redacted]	NA	[redacted]	NA	NA
21 months	NA	NA	NA	NA	NA	[redacted]	NA	NR	NA	NA
24 months	NA	NA	NA	NA	NA	[redacted]	NA	[redacted]	NA	NA

Abbreviations: NA, not applicable; NR, not reported.

Pruritus

The results for pruritus are shown in Table 18. A variety of measures were used to assess pruritus in studies evaluating seladelpar, of which the EAG prioritised the pruritus NRS scale and the pruritus subscale of the PBC-40, as this was where the majority of evidence was available.

As with ALP levels, the EAG noted a reasonable response in pruritus in the placebo arm of RESPONSE, which as discussed previously may be associated with increased adherence to UDCA within trial conditions. As a consequence, relative differences in pruritus should be used as opposed to the absolute mean change and response rates.

The company stated that a change of 2 points on the pruritus NRS scale was indicative of a minimally clinically meaningful important difference (MCID) in pruritus. They cited a study by Reich et al (2016)[25] in support of this, though the EAG noted that the MCID identified in the study was 2.7 ±1.7 and the authors concluded that the MCID should lie between 2 and 3. There was no clinically meaningful reduction in mean pruritus NRS scores following treatment with seladelpar in RESPONSE in comparison to the placebo arm. A higher proportion of people who received seladelpar in RESPONSE experienced a clinically meaningful reduction in pruritus (either a reduction of 2 or 3 points), suggesting that a minority of people who receive seladelpar may experience a meaningful reduction in pruritus compared to receiving UDCA alone.

The EAG was unable to identify a MCID for the itch scale of the PBC-40 questionnaire, though a threshold of ≥7 (on a scale of 3 – 15) had been considered to be clinically significant levels of itch.[26] There was no difference in response on the PBC-40 questionnaire between 5mg and 10mg seladelpar in the phase II dose-ranging study. Absolute change in itch on the PBC-40 in the phase II study appeared relatively small in comparison with the range of the scale.

Overall, the EAG considered that seladelpar did not increase the risk of pruritus across the study samples, which may make it a preferred alternative to OCA for people with PBC who experience pruritus. A minority of people may also experience a meaningful reduction in pruritus with seladelpar, while others may find that their pruritus remains the same.

Table 18: Pruritus outcomes in people with baseline pruritus NRS ≥4 across studies evaluating seladelpar

	RESPONSE (NCT04620733 // CB8025-32048)		**ENHANCE (NCT03602560 // CB8025-31735)**			**ASSURE (NCT03301506 // CB8025-31731-RE)**		**Phase II dose-ranging study (NCT02955602 // CB8025-21629)**	
	Seladelpar	**Placebo**	**Seladelpar 5mg**	**Seladelpar 10mg**	**Placebo**	**Seladelpar (RESPONSE)**	**Seladelpar (Legacy)**	**5mg**	**10mg**
Pruritus NRS									
Baseline score Pruritus NRS, mean (SD)	6.1 (1.42)	6.6 (1.44)	[redacted]	[redacted]	[redacted]	NR	[redacted]	NA	NA
Change in Pruritus NRS, LS mean (SE) [mean and SD for ASSURE]	1m: -1.8 (0.23) 3m: -2.6 (0.30) 6m: NR 9m: -3.4 (0.32) 12m: -3.3 (0.33)	1m: -0.8 (0.34) 3m: -1.6 (0.43) 6m: NR 9m: -1.7 (0.46) 12m: -1.5 (0.50)	1m: NR 3m: [redacted] 6m: NR	1m: NR 3m: [redacted] 6m: NR	1m: NR 3m: [redacted] 6m: NR	NR	1m: [redacted] 3m: [redacted] 6m: [redacted] 9m: [redacted] 12m: [redacted] 18m: [redacted]	NA	NA
Reduction of ≥2 on pruritus NRS, n/N (%)	1m: [redacted] 3m: [redacted] 6m: [redacted] 9m: [redacted] 12m: [redacted]	1m: [redacted] 3m: [redacted] 6m: [redacted]	NR	NR	NR	NR	1m: [redacted] 3m: [redacted] 6m: [redacted]	NA	NA

	RESPONSE (NCT04620733 // CB8025-32048)		**ENHANCE (NCT03602560 // CB8025-31735)**			**ASSURE (NCT03301506 // CB8025-31731-RE)**		**Phase II dose-ranging study (NCT02955602 // CB8025-21629)**	
		9m: [redacted] 12m: [redacted]					9m: [redacted] 12m: [redacted] 18m: [redacted]		
Reduction of ≥3 on pruritus NRS, n/N (%)	1m: [redacted] 3m: [redacted] 6m: [redacted] 9m: [redacted] 12m: [redacted]	1m: [redacted] 3m: [redacted] 6m: [redacted] 9m: [redacted] 12m: [redacted]	NR	NR	NR	NR	1m: [redacted] 3m: [redacted] 6m: [redacted] 9m: [redacted] 12m: [redacted] 18m: [redacted]	NA	NA
Reduction of ≥4 on pruritus NRS, n/N (%)	1m: [redacted] 3m: [redacted] 6m: [redacted] 9m: [redacted] 12m: [redacted]	1m: [redacted] 3m: [redacted] 6m: [redacted] 9m: [redacted] 12m: [redacted]	NR	NR	NR	NR	1m: [redacted] 3m: [redacted] 6m: [redacted] 9m: [redacted] 12m: [redacted]	NA	NA

	RESPONSE (NCT04620733 // CB8025-32048)		**ENHANCE (NCT03602560 // CB8025-31735)**			**ASSURE (NCT03301506 // CB8025-31731-RE)**		**Phase II dose-ranging study (NCT02955602 // CB8025-21629)**	
							18m: [redacted]		
PBC-40									
Baseline PBC-40 Itch domain, mean (SD)	[redacted]	[redacted]	Assessed but company does not have access to the data	Assessed but company does not have access to the data	Assessed but company does not have access to the data	NA	NA	[redacted]	[redacted]
Change from baseline, LS mean (SE)	3m: [redacted] 6m: [redacted] 12m: [redacted]	3m: [redacted] 6m: [redacted] 12m: [redacted]	Assessed but company does not have access to the data	Assessed but company does not have access to the data	Assessed but company does not have access to the data	NA	NA	3m: [redacted] 12m: [redacted]	3m: [redacted] 12m: [redacted]

Abbreviations: NA, not applicable; NR, not reported; NRS, numerical rating scale; SD, standard deviation; SE, standard error.

*Not restricted to participants with clinically significant itch at baseline

Source: CS, company clarification response, ENHANCE CSR, RESPONSE CSR

Fatigue

Complete data from the fatigue domain of the PBC-40 from RESPONSE at 1, 3, 6, 9 and 12 months and from the Phase II dose-ranging study were presented by the company at clarification. There was no difference between arms at any timepoint in RESPONSE and no clear evidence of a difference in fatigue from the Phase II dose-ranging study. Overall, the EAG considered that there was no evidence that treatment with seladelpar would affect fatigue in people with PBC.

Risk of ESRD requiring liver transplant

Data for the UK-PBC score, indicating change in the risk of ESLD requiring transplant, are shown in Table 19. As stated in Section 3.2.2.5, there was no MCID to determine what change in risk would be clinically meaningful at the population level, and the authors of the risk tool suggest that a change in risk should be interpreted for each individual patient. The EAG also noted that, as risk of 5- and 10-year ESLD requiring transplant was low for the trial samples, given their early disease stage, it would be very difficult to detect a change in risk. Overall, the EAG was unable to identify reliable evidence of a change in risk of ESLD at 5- or 10-years from the available data.

Table 19: Change in UK-PBC score in studies evaluating seladelpar

	RESPONSE (NCT04620733 // CB8025-32048)		**ENHANCE (NCT03602560 // CB8025-31735)**			**ASSURE (NCT03301506 // CB8025-31731-RE)**	**Phase II dose-ranging study (NCT02955602 // CB8025-21629)**	
	Seladelpar 10mg	**Placebo**	**Seladelpar 5mg**	**Seladelpar 10mg**	**Placebo**	**Seladelpar**	**5mg**	**10mg**
Baseline score UK-PBC, mean (SD)	5-year: 0.02 (0.02) 10-year: 0.07 (0.06)	5-year: 0.02 (0.02) 10-year: 0.07 (0.06)	5-year [redacted] 10-year [redacted]	5-year [redacted] 10-year [redacted]	5-year [redacted] 10-year [redacted]	NR	NR	NR
5-year UK-PBC risk score	12m: 0.02 (0.02)	12m: 0.02 (0.02)	1m: [redacted] 3m: [redacted] 6m: [redacted]	1m: [redacted] 3m: [redacted] 6m: [redacted]	1m: [redacted] 3m: [redacted] 6m: [redacted]	NR	NR	NR
Change in 5-year UK-PBC, LS mean (SE)	NR	NR	1m: [redacted] 3m: [redacted] 6m: [redacted]	1m: [redacted] 3m: [redacted] 6m: [redacted]	1m: [redacted] 3m: [redacted] 6m: [redacted]	NR	NR	1m: NR 3m: 1.81% (0.24)* 12m: 1.72% (0.23)*
10-year UK-PBC risk score	12m: 0.06 (0.07)	12m: 0.06 (0.05)	1m: [redacted] 3m: [redacted] 6m: [redacted]	1m: [redacted] 3m: [redacted] 6m: [redacted]	1m: [redacted] 3m: [redacted] 6m: [redacted]	NR	NR	NR
Change in 10-year UK-PBC, LS mean (SE)	NR	NR	1m: [redacted] 3m: [redacted] 6m: [redacted]	1m: [redacted] 3m: [redacted] 6m: [redacted]	1m: [redacted] 3m: [redacted] 6m: [redacted]	NR	NR	1m: NR 3m: 5.82% (0.77)* 12m: 5.56% (0.73)*

Abbreviations:

Note: *LS mean (SE) was not reported, data are % change.

Mortality

There were no reported deaths in RESPONSE or ENHANCE. One death was reported in the long-term safety study prior to termination (CB8025-31731) and another in ASSURE: both participants who were receiving seladelpar, although the deaths were judged by the investigators to be unrelated to treatment. The death in CB8025-31731 was in a participant receiving 5mg seladelpar and due to a malignant neoplasm. The death in ASSURE was in a participant who had previously participated in a 'legacy study' of seladelpar and was due to autoimmune haemolytic anaemia.

Health-related quality of life

Health-related quality of life (HRQoL) data are reported in Table 20. The only quality of life data reported by the company was from the RESPONSE study: the company did not report data for HRQoL from the Phase II dose-ranging study (they reported pruritus and fatigue subscales only and data were not available from the trial CSR) or ASSURE (data also not available from the CSR), and data for HRQoL from ENHANCE were not accessible to the company during the appraisal.

HRQoL data available were from the PBC-40, [27] which was a disease-specific quality of life measure for PBC that addressed six domains: fatigue, mood, social quality, cognitive state, itch, and other symptoms. Validation data[27] showed that scores on the social and fatigue subscales were strongly correlated with the social functioning and energy/vitality domains, respectively, of the SF-36 and there were moderate correlations between the symptoms and emotional subscales with physical functioning (former), mental health and role emotional domains (latter). The minimum and maximum score of the PBC-40 is 40 to 200, with higher scores representing poorer overall quality of life.

Data from RESPONSE showed no difference between study arms in PBC-40 scores after 12-months. Both arms showed a numerical reduction in scores, but the EAG was unable to identify a MCID for the PBC-40 from which to interpret whether the reductions were clinically meaningful. Given the size of the scale (a range of 160 points), a reduction of 5.85 shown in the seladelpar arm at 12-months was equivalent to a 3.7% change in score. The EAG also noted that due to concerns about the placebo response in RESPONSE (Key Issue 3) relative difference in HRQoL would be the most robust evidence for this outcome.

Overall, the EAG did not consider there to be evidence that treatment with seladelpar resulted in meaningful differences in disease-specific HRQoL compared to placebo.

Table 20: HRQoL data (PBC-40) from studies evaluating seladelpar

	RESPONSE (NCT04620733 // CB8025-32048)		**ENHANCE (NCT03602560 // CB8025-31735)**			**ASSURE (NCT03301506 // CB8025-31731-RE)**	**Phase II dose-ranging study (NCT02955602 // CB8025-21629)**	
	Seladelpar 10mg	**Placebo**	**Seladelpar 5mg**	**Seladelpar 10mg**	**Placebo**	**Seladelpar**	**5mg**	**10mg**
Baseline mean (SD)	87.4 (28.54)	88.3 (28.78)	Not available to company	Not available to company	Not available to company	NR	NR	NR
Change from baseline, LS mean (SE)	12m: -5.85 (1.64)	12m: -6.19 (2.23)	Not available to company	Not available to company	Not available to company	NR	NR	NR

Abbreviations: HRQoL, heart-related quality of life); LS, least squared; NR, not reported; SD, standard deviation; SE, standard error; 12m, 12 months

Subgroup analyses

Although subgroups were specified in the NICE scope, these were not included in the company decision problem. However, subgroup results from the RESPONSE trial were available (CS Appendix C). Subgroup analyses were not powered to detect a treatment difference and, as such, the company stated that all results were descriptive. The primary endpoint of RESPONSE was the proportion of participants achieving a composite biochemical response at Month 12 of treatment (see Figure 3). Therefore, subgroup results for this outcome were presented. The company considered the results to be consistent across subgroups. The EAG generally agreed with this assessment and noted that all subgroups exhibited a beneficial treatment effect in composite outcome for seladelpar as compared to placebo. However, it was noted that there was a difference in response between participants with baseline ALP < and ≥350 U/L, with those with ALP ≥350 at baseline showing a smaller response to treatment (this was statistically significant). As subgroup data were not presented across other scoped outcomes, it was not possible for the EAG to determine whether this was a reliable finding evident across multiple outcomes.

Figure 3: Analysis of the composite biochemical response endpoint by subgroup at Month 12 (RESPONSE; ITT Analysis Set)

Abbreviations: ALP, alkaline phosphatase; CI: confidence interval; ITT, intent to treat; NRS, Numerical Rating Scale; OCA, obeticholic acid; PBC, primary biliary cholangitis; UDCA, ursodeoxycholic acid; ULN, upper limit of normal.

Notes: Baseline ALP in patients with cirrhosis was 345.8 compared to 314.3 U/L for the ITT analysis set, translating to a higher threshold to achieve an ALP decrease below of 1.67x ULN.

Source: CS Appendix C, Figure 47.

Adverse effects

An overview of adverse events from across studies evaluating seladelpar is shown in Table 21. The data suggested that treatment with seladelpar did not result in a notable increase in adverse events. The most common side effects associated with seladelpar were mild in nature and not considered to be associated with major health or resource implications (headache, nausea, abdominal pain, abdominal distension). The EAG reviewed evidence provided by the company on specific AEs of interest (including acute kidney injury, muscle pain, carcinoma) and found zero or low event rates with no conclusive differences between study.

Table 21: Overview of adverse event data from studies evaluating seladelpar

	RESPONSE (NCT04620733 // CB8025-32048)		**ENHANCE (NCT03602560 // CB8025-31735)**			**ASSURE (NCT03301506 // CB8025-31731-RE)**	**Phase II dose-ranging study (NCT02955602 // CB8025-21629)**	
	Seladelpar 10mg	**Placebo**	**Seladelpar 5mg**	**Seladelpar 10mg**	**Placebo**	**Seladelpar**	**5mg**	**10mg**
≥1 TEAE	111/128 (86.7%)	55/65 (84.6%)	56/89 (62.9%)	58/89 (65.2%)	64/87 (73.6%)	[redacted]	42/46 (91%)	49/50 (98%)
Serious TEAE	9/128 (7.0%)	4/65 (6.2%)	3/89 (3.4%)	1/89 (1.1%)	3/87 (3.4%)	[redacted]	9/46 (20%)	11/50 (22%)
≥Grade 3 TEAE	14/128 (10.9%)	5/65 (7.7%)	3/89 (3.4%)	5/89 (5.6%)	6/87 (6.9%)	[redacted]	[redacted]	[redacted]
Treatment-related TEAE	22/128 (17.2%)	8/65 (12.3%)	25/89 (28.1%)	15/89 (16.9%)	16/87 (18.4%)	[redacted]	17/46 (37%)	16/50 (32%)
Treatment-related ≥Grade 3 TEAE	0/128 (0%)	0/65 (0%)	0/89 (0%)	0/89 (0%)	0/87 (0%)	[redacted]	[redacted]	[redacted]
TEAE leading to discontinuation	3/128 (2.3%)	3/65 (4.6%)	0/89 (0%)	2/89 (2.2%)	0/87 (0%)	[redacted]	[redacted]	[redacted]

Abbreviations: TEAE, treatment-emergent adverse event

Source: CS, company clarification response, Phase II dose ranging study CSR

3.3. Critique of trials identified and included in the indirect comparison and/or multiple treatment comparison

The company provided a report with the CS that summarised the assessment conducted to determine whether an indirect treatment comparison (ITC) between seladelpar and (a) OCA and (b) elafibranor was feasible. Key methodology used in the SLR conducted by the company to inform the analysis is described in Section 3.1.

While the SLR conducted by the company identified 24 studies and was inclusive with respect to treatments (RCTs that evaluated seladelpar, OCA, elafibranor, bezafibrate, fenofibrate, setanaxib, budesonide, linerixibat, and saroglitazar), the feasibility assessment focussed on only those studies that evaluated interventions that the company considered relevant to the decision problem; i.e. seladelpar, OCA, and elafibranor. In principle, it is not necessary to exclude studies from a network meta-analysis because the treatments they evaluate are not relevant to the decision problem if they include data for a common comparator (e.g. UDCA). In that case, they can strengthen the network and lend towards a stronger analysis. In its response to clarification, the company stated that they considered including fibrates in the analysis but that the study designs were heterogeneous with respect to patient characteristics. As the company did not report the feasibility assessment for the analysis including fibrates, it was not possible for the EAG to validate this claim.

The company also restricted the analysis to studies with a 12-month follow-up, which led to the exclusion of several otherwise relevant studies. At clarification, the company stated that this was because PBC is “a long-term liver disease, and complications associated with PBC progression, such as cirrhosis and liver failure, may take a long time to develop” (CQ A15). However, the EAG noted that long-term outcomes such as cirrhosis and liver failure were not considered in the company’s ITC, and it considered that outcomes such as ALP response, pruritus and safety could all have been assessed meaningfully at earlier timepoints. While, in general, longer follow-up data may be most insightful into the potential benefit of treatments, the decision to restrict the analysis to a 12-month follow-up also led to the exclusion of studies from the ITC, thus weakening the network. The EAG was not able to determine if a stronger network may have been feasible at earlier timepoints.

In the end, five studies from the company’s clinical effectiveness SLR were used across the company base case(s) and sensitivity analyses for the ITC, comparing:

- seladelpar + UDCA to UDCA + placebo (RESPONSE)

- elafibranor + UDCA to UDCA + placebo (ELATIVE)
- OCA + UDCA to UDCA + placebo (POISE, COBALT, and NCT03633227).

Key study design and population characteristics for these studies are presented in Table 22 and discussed in detail in Section 3.2.1. Shaded rows represent key treatment effect modifiers, as stated by the company.

Table 22: Population and trial characteristics

Population and trial characteristics	ELATIVE	RESPONSE	POISE	NCT03633227	COBALT
Intervention	Elafibranor 80 mg + UDCA	Seladelpar 10 mg + UDCA	OCA 5 mg/10 mg + UDCA OCA 10 mg + UDCA	OCA 5 mg/10 mg + UDCA	OCA 5 mg/10 mg + UDCA
Trial phase	Phase 3	Phase 3	Phase 3	Phase 4	Phase 3b/4
Sample size	161	193	216	22	334
Comparator	UDCA	UDCA	UDCA	UDCA	UDCA
Mean age years (SD)	57.1 (8.7)	56.7 (9.79)	56 (10.41)	61.6 (9.43)	53.65 (10.38)
Background UDCA (%)	95	93.8	93	--	88.31
Female (%)	96	94.2	90.6	72.7	89.85
Previous UDCA (%)	100	100	100	NR	97.29
Baseline ALP mean U/L (SD)	321.9 (150.9)	314.3 (121.88)	323 (112.53)	241.75*	490.25 (286.55)
ALP ULN Definition	Females: 104; Males: 129	116	Females: 118; Males: 124	NR	NR
Total bilirubin level-mg/dl (SD)	0.56 (0.30)	0.76 (0.30)	0.65 (0.38)	43.44*	1.65 (0.80)
Total bilirubin level-µmol/liter (SD)	9.6 (5.1)	12.9 (5.15)	11.1 (6.50)	NR	NR
Cirrhosis (%)	9.94 (8.3 in Elafibranor and 13.2 in UDCA)	14	16	NR	NR
ALB (g/L) (SD)	43.8 (3.0)	41.6 (2.0)	43.17 (2.99)	33.75*	3.98 (0.41)
Time (years) since PBC Diagnosis (SD)	8.0 (6.2)	8.33 (6.66)	8.33 (6.10)	NR	NR
Age at diagnosis (SD) [95% CI]	NR	49.23 (10.30)	47.32 (10.79)	NR	NR

Population and trial characteristics	ELATIVE	RESPONSE	POISE	NCT03633227	COBALT
Bilirubin >ULN at baseline (%)	3.7	13.0 (15.6 in seladelpar¥ and 7.7 in UDCA)	8.3	NR	NR
Prior OCA use (%)	8.1	17.1	0	NR	NR

*Median values. ALB, Albumin; ALP, Alkaline phosphatase; CS, company submission; NR, not reported; OCA, Obeticholic acid; SD, Standard deviation; UDCA, Ursodeoxycholic Acid; ULN, Upper limit of normal.

¥Bilirubin at baseline (%) corrected in RESPONSE trial.

Shaded rows: key treatment effect modifiers according to CS.

A brief summary of the included study methods is provided in Box 1.

Box 1: Brief description of studies included in the company's ITC

RESPONSE

Only one study evaluating seladelpar, RESPONSE, was included in the ITC. Details of RESPONSE are described in Section 3.2. In brief, RESPONSE was a double-blind RCT (Phase 3) comparing seladelpar + UDCA to placebo + UDCA in 193 patients with PBC. Most participants were female, White or non-Hispanic/ Latino and the mean (SD) age was 56.7 (9.79) years. The primary efficacy endpoint was the proportion of participants achieving a composite biochemical response, defined as an alkaline phosphatase (ALP) level less than 1.67 times the upper limit of the normal range, with a decrease of 15% or more from baseline, and a normal total bilirubin level at month 12. The proportion of subjects with normalisation of ALP (≤ 1.0xULN) at 12 months and change from baseline in weekly averaged Pruritus numerical rating scale (NRS) score in subjects with baseline NRS ≥ 4 from baseline to month 6, were key secondary endpoints. Most subjects (93.8%) received seladelpar or placebo in addition to UDCA, while 12 (6.2%) subjects were intolerant to UDCA and received seladelpar as monotherapy (in comparison with placebo only). Subjects with at least one treatment-emergent adverse event were more likely in the seladelpar combination arm (88.3%) vs. seladelpar monotherapy (62.5%), although these were not notably different to placebo. The EAG noted that no subgroup analysis was available comparing seladelpar monotherapy to seladelpar + UDCA to explore differences in the primary efficacy endpoint, though as so few participants received seladelpar monotherapy, this would have likely been highly uncertain.

ELATIVE

One study evaluating the effectiveness of elafibranor, ELATIVE, was included in the ITC. ELATIVE was a double-blind RCT (Phase 3) comparing elafibranor + UDCA to placebo + UDCA in 161 patients

with PBC. Most subjects were female, and the mean (SD) age was 57.1 (8.7) years. The primary efficacy endpoint was biochemical response using the same general definition as in RESPONSE (i.e. an alkaline phosphatase level of <1.67 times the up- per limit of the normal range, with a reduction of ≥15% from baseline, and normal total bilirubin levels) at week 52. Key secondary endpoints were also reasonably consistent with RESPONSE: normalisation of the alkaline phosphatase level at week 52 and a change in pruritus intensity from baseline through week 52 and through week 24, as measured on the Worst Itch Numeric Rating Scale (WI-NRS; scores range from 0 [no itch] to 10 [worst itch imaginable]). The EAG note that the proportion of patients with cirrhosis at baseline differed between study arms (13.2% placebo vs. 8.3% elafibranor). As a treatment effect modifier, cirrhosis patients may experience different treatment outcomes, exaggerating the observed effects of the intervention as cirrhosis is related to worse treatment outcomes, this adds a level of uncertainty to the ITC.

POISE

POISE was a double-blind RCT (Phase 3) comparing OCA + UDCA to UDCA + placebo in 216 patients with PBC. Most subjects were female, and the mean (SD) age was 56 (10.41). The primary efficacy endpoint was an ALP level of less than 1.67 times the upper limit of the normal range, with a reduction of at least 15% from baseline, and a normal total bilirubin level at 12 months.

NCT03633227

NCT03633227 was an unpublished double-blind Phase 4 trial comparing OCA + UDCA to UDCA in 22 patients with PBC, initially over a 48-week period. It was not stated clearly in the CS how the company obtained the data for this unpublished study. Most subjects were female, and the mean (SD) age was 61.6 (9.43). The primary efficacy endpoints, as well as secondary endpoints, were numerous and available in detail in public record,27 briefly these included Maximum Observed Concentration (Cmax) of Total OCA at week 12, week 18, week 24, week 30, and week 48. Amongst key secondary endpoints were change from baseline in total bilirubin at weeks 3, 6, 12, 18, 24, 30, 36, 42, and 48; and extension months 3, 6, 9, 12, and 15. As well as change from baseline in ALP at weeks 3, 6, 12, 18, 24, 30, 36, 42, and 48; and extension months 3, 6, 9, 12, and 15.

COBALT

COBALT was a double-blind Phase 3b/4 trial comparing OCA + UDCA to UDCA + placebo in 334 patients with PBC. Most subjects were female, and the mean (SD) age was 53.65 (10.38). The primary efficacy endpoint was time to first occurrence of any of the following events: death (all-cause); liver transplant; model for end-stage liver disease score ≥15; hospitalization ≥24 hours for new onset or recurrence of variceal bleed, hepatic encephalopathy (West Haven score ≥2), or spontaneous bacterial peritonitis (confirmed by diagnostic paracentesis); or uncontrolled ascites requiring therapeutic

paracentesis ≥2 times in a month. The following can be considered key secondary endpoints: mean ALP change from baseline over time among patients who discontinued study visits or started commercial therapy; and the relationship between investigational product discontinuation and initiation of commercial PBC therapies by comparing mean ALP by treatment arm up to 6 months before vs up to 12 months after initiation of commercial therapy. Table 22 suggests that ALP was measured in all participants, while the trial publications suggest it was only measured in those who discontinued or switched treatment.

3.4. Critique of the indirect comparison and/or multiple treatment comparison

The company presented evidence to suggest that the transitivity assumption was violated between the RESPONSE and ELATIVE trials, with differences in baseline bilirubin levels, and the proportion of patients with cirrhosis, thus preventing the use of the Bayesian NMA. The company identified four treatment effect modifiers that aligned with those used in TA1016 (age, baseline ALP and bilirubin levels, cirrhosis status; Table 22). At clarification, the EAG asked the company to justify the choice of key effect modifiers beyond precedence. The company clarified that these were validated against the literature and expert opinion, which the EAG accepted. The EAG did, however, note that baseline differences in population characteristics were quite small and clinical advice was that these were unlikely to be meaningful. Nevertheless, the company conducted separate analyses to compare seladelpar vs. OCA (NMA) and seladelpar vs. elafibranor (an anchored matched adjusted indirect comparison; MAIC).

The company presented two base-case ITC options for efficacy outcomes (composite response, ALP normalisation, ALP response, and ALP change from baseline:

- Bayesian network meta-analysis (NMA) for the comparison of seladelpar vs OCA, and
- Anchored MAIC for the comparison of seladelpar vs elafibranor.

The company presented two base-case ITC options for safety outcomes (≥1 adverse event, all-cause discontinuation, upper respiratory tract infection) and the proportion of participants with pruritus:

- Bayesian network meta-analysis (NMA) for the comparison of seladelpar vs OCA and elafibranor, and

- anchored MAIC for the comparison of seladelpar vs elafibranor.

The company presented one base-case ITC option for PBC-40 Itch, 5-D Itch, and NRS Itch:

- Bayesian network meta-analysis (NMA) for the comparison of seladelpar vs OCA, and seladelpar vs elafibranor.

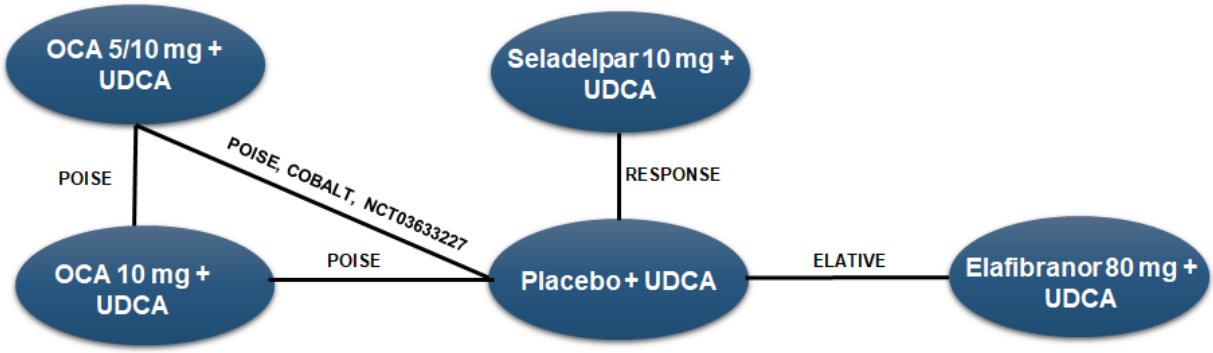
The company's justification of the model choice is available in section 3.4.1.2 (NMA) and 3.4.2.2 (MAIC). While the EAG supported the ambition to adjust for treatment effect modifiers to produce a more robust comparison using an anchored MAIC, this meant that within the presented base case(s), no ITC included seladelpar, OCA, and elafibranor. Furthermore, the EAG considered that the differences in baseline population differences between the RESPONSE and ELATIVE trials were relatively small and clinical expert advice was that these were unlikely to be clinically meaningful. Overall, the EAG considered that comparing the relative effectiveness of the treatments using two separate ITCs in this way was not robust and introduced significant bias, which is discussed later in section 3.4.2.5.

3.4.1. Bayesian NMA

3.4.1.1 Network of included studies

The company presented the following overall network (Figure 4). The base case included RESPONSE and POISE for the indirect comparison of seladelpar + UDCA and OCA + UDCA, using UDCA + placebo as the common comparator. The base case was presented *with* outcome recalculation using the POISE ALP and total bilirubin ULN cut-offs. The company excluded ELATIVE, COBALT, and NCT03633227 from their base case networks for efficacy outcomes and scaled measures of pruritus (this is explained in section 3.4.1.2).

Figure 4: Network diagram of the approved interventions at 12 months



OCA: Obeticholic acid; UDCA: Ursodeoxycholic Acid

3.4.1.2 Feasibility and transitivity

In order to select studies for inclusion in any NMA, studies must meet assumptions of transitivity, consistency, and homogeneity. The company did not present formal tests of consistency and heterogeneity as the network contained singular closed loops and single evidence sources, respectively. The EAG agreed with this.

Transitivity of the network relies on the generalisability of evidence across the trials. Overall, the company considered there to be key differences in study design characteristics across trials that presented a threat to transitivity. While they considered that RESPONSE and POISE reported similar trial and participant characteristics, they stated that participants in RESPONSE and ELATIVE differed in two key effect modifiers: baseline bilirubin and baseline proportions of cirrhosis. In addition, the company noted that the RESPONSE, ELATIVE, and POISE trials differed in the definition of ULN used to calculate efficacy outcomes involving ALP or bilirubin ULN, including: composite response (ALP <1.67x ULN, ≥15% ALP decrease from baseline, total bilirubin ≤1.0 ULN), ALP normalisation (≤1 ULN), and ALP response (Toronto I criteria: ALP ≤1.67 × ULN). The ALP and bilirubin ULN cut-offs used in each study are shown in Table 23. NCT03633227 and COBALT did not report outcomes requiring the definition of ULN.

Table 23: ALP and bilirubin ULN cut-offs (Phase 3 trials)

Comparison	RR (95% Credible Interval)
RESPONSE	ALP 116 IU/L and 18.8 µmol/L for bilirubin
POISE	ALP: 118 IU/L for females and 124 IU/L for males; bilirubin: 19.32 µmol/L for females and 25.48 µmol/L for males*
ELATIVE	ALP: 104 IU/L for females and 129 IU/L for males; bilirubin: 20.5 µmol/L*

Abbreviations: ALP, Alkaline phosphatase; IU/L, International units per litre; RR, relative risk; ULN, upper limit of normal

*sex-specific cut off(s) used for efficacy outcomes recalculations (composite response, ALP normalisation, and ALP response (Toronto I criteria)) and referred to as “with outcome recalculation” in the company submission

To maintain the assumption of transitivity across the included studies, and support interpretation, the company recalculated RESPONSE data using individual patient data (IPD) to match the sex-specific cut-offs for ULN for relevant outcomes. The company presented these efficacy outcomes (composite response, ALP normalisation, and ALP response (Toronto I

criteria)) as "*with* outcome recalculation" using the sex specific cut-off values from POISE (NMA base case) and ELATIVE (MAIC base case). The EAG noted that whilst this was not in line with UK practice, as the clinical expert confirmed sex-specific cut-offs are not used in the NHS, this was necessary to uphold the assumption of transitivity in the network and helps to minimise discrepancies in outcome interpretation. The company presented a sensitivity analysis *without* outcome recalculation to assess robustness, which also supports the translation into UK practice. This is discussed further in 3.4.1.7.

The company further determined that COBALT and NCT03633227 differed from RESPONSE and POISE in participant characteristics, including effect modifiers.

The company presented a base case NMA for the efficacy outcomes and scaled pruritus measures (PBC-40 Itch, 5-D Itch, and NRS Itch) that included the RESPONSE and POISE trials, which the EAG considered to be similar and comparable following a number of efficacy outcome recalculations described next and outlined in Table 22.

The company noted that the inclusion of the phase 3 ELATIVE trial in the network would violate the assumption of transitivity on account of differences in key effect modifiers: baseline mean bilirubin levels and proportion of participants with cirrhosis (Table 23). The EAG agreed with the company's ambition to adjust for imbalances in treatment effect modifiers. The company adjusted by using an anchored MAIC for efficacy and safety outcomes in their base cases (see section 3.4.2). However, the company presented a base case that included the ELATIVE trial for the patient reported outcomes. The company did not justify the decision to only adjust for treatment effect modifiers when looking at efficacy and safety outcomes, but not patient reported outcomes, in their base case.

In the safety analyses and the proportion of participants with pruritus, the EAG did not have the data for number of events for each outcome that were used in the company's ITCs except for studies evaluating seladelpar. This led to uncertainty about how different the studies included in ITCs actually were and therefore the extent to which the requisite assumptions for ITCs, such as transivitity, actually held.

3.4.1.3 Statistical methods

For the efficacy outcomes, the company presented the following base case and sensitivity scenarios using various prior distributions, which were assigned to key parameters (e.g., treatment effects; Table 24).

Table 24: Efficacy outcomes seladelpar vs OCA

Model	Base-case Priors	Sensitivity priors	Efficacy Outcomes
Bayesian NMA (using POISE and RESPONSE trials)	Turner priors[28]	Vague priors[29] Turner prior specific for Biological markers (with and without outcome recalculation) Turner prior specific for Biological markers (with addition of ELATIVE trial)	ALP normalization (ALP ≤ 1.0× ULN) at 12 months Composite response (ALP <1.67x ULN, ≥15% ALP decrease from baseline, total bilirubin ≤1.0 ULN) at 12 months ALP response (Toronto I: ALP ≤1.67 × ULN) at 12 months
Bayesian NMA (using POISE and RESPONSE trials)	Rhodes priors specific for biological markers.[30]	Vague priors[29] Rhodes prior specific for biological markers (with addition of ELATIVE trial; and with addition of COBALT trial, respectively)	ALP change from baseline at 12 months

Abbreviations: ALP, Alkaline phosphatase; NMA, network meta-analysis; RR, relative risk; ULN, upper limit of normal

For the scaled pruritus outcomes (PBC-40 Itch, 5-D Itch, and NRS Itch), the company presented the following base case and sensitivity scenarios using various prior distributions, which were assigned to key parameters (Table 25).

Table 25: Patient reported outcomes seladelpar vs OCA

Model	Base-case Priors	Sensitivity priors	Efficacy Outcomes
Bayesian NMA (using POISE and RESPONSE trials)	Rhodes priors[30] specific for signs/symptoms reflecting continuation/end of condition and infection/onset of new acute/chronic disease.	Vague priors[29] Turner priors specific for signs/symptoms reflecting continuation/end of condition	PBC-40 itch 5-D itch

Abbreviations: NMA, network meta-analysis; OCA, Obeticholic acid.

For safety (≥1 adverse event and all-cause discontinuation) and the proportion of participants with pruritus, the company presented the following base case and sensitivity scenarios using various prior distributions, which were assigned to key parameters (Table 26).

Table 26: Safety outcomes seladelpar vs OCA and elafibranor

Model	Base-case Priors	Sensitivity priors	Efficacy Outcomes
Bayesian NMA (using POISE, ELATIVE and RESPONSE trials)	Turner prior[28]	Turner prior: specific for adverse events	Any adverse event Pruritus All cause discontinuation Upper respiratory tract infection

Abbreviations: NMA, network meta-analysis; OCA, Obeticholic acid.

The Rhodes and Turner priors were established, widely used distributions for between-study variance, often employed to stabilise estimation in cases of sparse networks. Vague priors are appropriate choices in situations where sparse data could contribute to poor estimation of between-study variance; the EAG believed the use of these was justified given how sparse the analyses were.

The Bayesian NMA Markov Chain Monte Carlo (MCMC) approach is a robust method in the presence of zero count data (TSD2), although in sparse networks, a continuity correction may still be required to enable model convergence and reduce bias in the estimation of treatment effects.

The informative priors are updated with data from the studies through three separate Markov Chain Monte Carlo (MCMC) sampling simulations, each starting from different initial values for the unknown parameters. To ensure independence between simulations, the thinning parameter was adjusted (thin ≥10). All chains ran for 200,000 iterations following a burn-in period of 20,000 iterations, until satisfactory convergence of the posterior distributions. The EAG considered these methods to be appropriate. Additionally, the company used the Deviance Information Criterion (DIC) to evaluate model fit and complexity, which was consistent with standard practice. The company reported a risk ratio as the primary effect measure.

3.4.1.4 Primary network results (efficacy outcomes)

ITC results for the company's primary network comparing seladelpar with OCA and with placebo are summarised in this section, by outcome, and including model fit (which the EAG found acceptable (DIC)).

For ALP normalisation (≤1 ULN) at 12 months (Table 27), seladelpar was associated with a higher chance of response overall as compared to both placebo and OCA. However, the credible intervals were extremely wide for all comparisons, suggesting a high degree of

uncertainty in the magnitude of benefit offered by seladelpar in comparison with OCA and placebo. Furthermore, in comparison with OCA, [redacted]. The uncertainty may, in part, reflect the Bayesian NMA MCMC handling of zero count data discussed in section 3.4.1.3, which can introduce bias into the model. For example, the placebo arm in the RESPONSE trial had 0% ALP normalisation. The EAG noted that TSD2 recommends addressing such scenarios, where the model faces a lot of uncertainty, by either placing a distribution on the baseline model or adding a continuity correction.

Table 27: ALP normalisation (≤1 ULN) at 12 months

Comparison	RR (95% Credible Interval)	Favours	DIC
Seladelpar vs placebo	[redacted]	[redacted]	23.860
Seladelpar vs OCA (5-10mg)	[redacted]	[redacted]	
Seladelpar vs OCA (10mg)	[redacted]	[redacted]	

Abbreviations: ALP, Alkaline phosphatase; DIC, Deviance Information Criteria; OCA, Obeticholic acid; RR, risk ratio; ULN, upper limit of normal.

*statistically significant

For composite response at 12months (Table 28), seladelpar was associated with an increased chance of response compared to placebo. There was no clear difference in effect between seladelpar and OCA.

Table 28: Composite response (ALP <1.67x ULN, ≥15% ALP decrease from baseline, total bilirubin ≤1.0 ULN) at 12 months

Comparison	RR (95% Credible Interval)	Favours	DIC
Seladelpar vs placebo	[redacted]	[redacted]	32.667
Seladelpar vs OCA (5-10mg)	[redacted]	[redacted]	
Seladelpar vs OCA (10mg)	[redacted]	[redacted]	

Abbreviations: ALP, Alkaline phosphatase; DIC, Deviance Information Criteria; OCA, Obeticholic acid; RR, risk ratio; ULN, upper limit of normal.

*statistically significant

For ALP response using the Toronto I criteria (Table 29), seladelpar was associated with a treatment benefit as compared with placebo, however there was no clear difference between seladelpar and OCA.

Table 29: ALP response (Toronto I: ALP ≤1.67 × ULN) at 12 months

Comparison	RR (95% Credible Interval)	Favours	DIC
Seladelpar vs placebo	[redacted]	[redacted]	33.246
Seladelpar vs OCA (5-10mg)	[redacted]	[redacted]	
Seladelpar vs OCA (10mg)	[redacted]	[redacted]	

Abbreviations: ALP, Alkaline phosphatase; DIC, Deviance Information Criteria; OCA, Obeticholic acid; RR, risk ratio; ULN, upper limit of normal.

*statistically significant

In terms of the change in ALP levels from baseline at 12-months (Table 30), seladelpar was associated with a large reduction in ALP as compared to placebo. There was no clear difference in ALP change between seladelpar and OCA.

Table 30: ALP change from baseline at 12 months

Comparison	Mean difference (95% Credible Interval)	Favours	DIC
Seladelpar vs placebo	[redacted]	[redacted]	43.858
Seladelpar vs OCA (5-10mg)	[redacted]	[redacted]	
Seladelpar vs OCA (10mg)	[redacted]	[redacted]	

Abbreviations: ALP, Alkaline phosphatase; DIC, Deviance Information Criteria; OCA, Obeticholic acid; RR, risk ratio.

*statistically significant

Overall, for ALP response, the analysis suggested that seladelpar was more effective are reducing ALP levels than placebo; all analyses were consistent with this and, while there was some uncertainty in the magnitude of the effect, credible intervals were consistent with a clinical benefit for seladelpar.

In comparison with OCA, the evidence for seladelpar was less conclusive: any differences in effect were smaller, were not statistically significant and, particularly in comparison with OCA 10mg, approached the line of null effect.

3.4.1.5 Primary network results (safety)

In the company's base case comparing seladelpar vs elafibranor vs. OCA vs. placebo for the risk of ≥1 adverse event at 12-months, seladelpar was associated with a numerical increased risk as compared to placebo and a numerical reduction in the risk of adverse events in comparison with both elafibranor and OCA (Table 31). In all cases, the credible intervals were wide and crossed the line of null effect, suggesting uncertainty with both the direction and the magnitude of the effect. Moreover, as this analysis considered any adverse event, the EAG did not consider the results to be particularly meaningful with respect to understanding the potential impact of any difference in adverse effects on participants' health or treatment continuation. The EAG considered the model fit (DIC) to be acceptable.

Table 31: Any adverse event at 12 months

Comparison	Odds ratio (95% Credible Interval)	Favours	DIC
Seladelpar vs placebo	[redacted]	[redacted]	39.579
Seladelpar vs elafibranor	[redacted]	[redacted]	
Seladelpar vs OCA (5-10mg)	[redacted]	[redacted]	
Seladelpar vs OCA (10mg)	[redacted]	[redacted]	

Abbreviations: DIC, Deviance Information Criteria; OCA, Obeticholic acid.

*statistically significant

In the company's base case scenario for the comparison of seladelpar vs elafibranor vs. OCA vs. placebo, the point estimates favoured seladelpar for all comparisons, including placebo for all-cause discontinuation at 12-months (Table 34). However, credible intervals all crossed the line of null effect, suggesting significant uncertainty in both the direction and magnitude of the effects. The EAG considered the model fit (DIC) to be acceptable.

Table 32: All cause discontinuation at 12 months

Comparison	Odds ratio (95% Credible Interval)	Favours	DIC
Seladelpar vs placebo	[redacted]	[redacted]	39.969
Seladelpar vs elafibranor	[redacted]	[redacted]	
Seladelpar vs OCA (5-10mg)	[redacted]	[redacted]	
Seladelpar vs OCA (10mg)	[redacted]	[redacted]	

Abbreviations: DIC, Deviance Information Criteria; ITC, indirect treatment comparison; OCA, Obeticholic acid.

*statistically significant

Note: the company's ITC report did not define clearly whether this analysis could include discontinuation due to poor efficacy as well as due to adverse events.

In the company's base case scenario for the comparison of seladelpar vs elafibranor vs. OCA vs placebo for upper tract respiratory infection, the point estimates favoured seladelpar for all comparisons, with lower odds of developing upper tract respiratory infection at 12 months (Table 33). The width of the credible intervals indicated that these effects were statistically significant versus placebo and elafibranor. The credible interval for seladelpar versus both doses of OCA crossed the line of no effect, suggesting there was no statistically significant difference in upper tract respiratory infection at 12 months.

Table 33: Upper tract respiratory infection at 12 months

Comparison	Odds ratio (95% Credible Interval)	Favours	DIC
Seladelpar vs placebo	[redacted]	[redacted]	36.329
Seladelpar vs elafibranor	[redacted]	[redacted]	
Seladelpar vs OCA (5-10mg)	[redacted]	[redacted]	
Seladelpar vs OCA (10mg)	[redacted]	[redacted]	

Abbreviations: DIC, Deviance Information Criteria; OCA, Obeticholic acid.

*statistically significant

In the company's base case scenario for the comparison of seladelpar vs elafibranor vs. OCA vs placebo, seladelpar was associated with a lower risk of developing pruritus in comparison with placebo and OCA (Table 34). Seladelpar had a numerically lower risk of developing pruritus in comparison with elafibranor, though the credible interval crossed the line of null effect. The EAG considered the model fit (DIC) to be acceptable.

Table 34: Development of pruritus at 12 months

Comparison	Odds ratio (95% Credible Interval)	Favours	DIC
Seladelpar vs placebo	[redacted]	[redacted]	44.596
Seladelpar vs elafibranor	[redacted]	[redacted]	
Seladelpar vs OCA (5-10mg)	[redacted]	[redacted]	
Seladelpar vs OCA (10mg)	[redacted]	[redacted]	

Abbreviations: DIC, Deviance Information Criteria; ITC, indirect treatment comparison; OCA, Obeticholic acid.

*statistically significant

Note: the company's ITC report does not state whether this analysis was conducted in all participants, those who did not have pruritis at baseline, or assessed worsening of pruritis in people who already had pruritis at baseline.

Overall, the evidence for the relative safety of seladepar vs comparator treatments was primarily based on all-cause discontinuation and the rate of any adverse event. Both analyses resulted in highly uncertain results, with wide credible intervals that crossed the line of null effect. Overall there was a trend for seladelpar to have a more favourable risk profile than the active treatments, though the EAG considered these results to be highly speculative due to the choice of outcomes and the significant uncertainty around the point estimates.

There was evidence to suggest that seladelpar was more effective than OCA (both doses) and placebo at preventing the development of pruritus at 12 months. Given that OCA was known for the risk of worsening pruritus, these findings were as expected. While there was a lower risk of developing pruritus associated with seladelpar than elafibranor, this finding was more uncertain.

3.4.1.6 Primary network results (patient reported outcome measures)

The company presented a Bayesian NMA for the assessment of PBC-40 Itch, the 5-D Itch scale, and NRS Itch between seladepar and elafibranor. However, data from the ELATIVE trial was limited to participants with moderate or severe pruritus at baseline (NRS≥4), for whom the company stated that they were unable to identify baseline characteristics. This meant that it was not possible to compare population characteristics across the trials to determine transitivity, and this may be a risk given concerns about the comparability of the overall study populations.

The company presented a Bayesian NMA for the assessment of the PBC-40 itch (Table 35) and the 5-D Itch scale (Table 36), between seladepar, placebo and OCA (both doses) using Rhodes priors. Seladelpar was associated with a numerical reduction in pruritus at 12-months in comparison with placebo and OCA using both the PBC-40 and 5D-Itch scales, though the differences were only statistically significant on the 5D-itch. As stated in Section 3.2.3.1, the EAG was unable to identify a MCID for interpreting differences in the PBC-40 itch (which is on a scale ranging from 3 to 15 with higher scores indicating worse pruritus) or the 5D-itch (which is on a scale of 5 to 25, with higher scores indicating worse pruritus). The EAG was therefore unable to determine if the differences between treatments for each outcome were clinically meaningful. If using an arbitrary and crude threshold of a 20% reduction in score on either scale, this would be equivalent to a difference of 2.4 points on the PBC-40 and 4 points on the 5D-Itch.

Table 35: Patient reported outcomes PBC-40 itch

Comparison	Mean difference (95% Credible Interval)	Favours	DIC
Seladelpar vs placebo	[redacted]	[redacted]	10.038
Seladelpar vs OCA (5-10mg)	[redacted]	[redacted]	
Seladelpar vs OCA (10mg)	[redacted]	[redacted]	

Abbreviations: DIC, Deviance Information Criteria; ITC, indirect treatment comparison; OCA, Obeticholic acid.

*statistically significant

Note: it was not stated in the company's ITC report what timepoint was used for this assessment.

Table 36: Patient reported outcomes 5-D itch

Comparison	Mean difference (95% Credible Interval)	Favours	DIC
Seladelpar vs placebo	[redacted]	[redacted]	13.273
Seladelpar vs OCA (5-10mg)	[redacted]	[redacted]	
Seladelpar vs OCA (10mg)	[redacted]	[redacted]	

Abbreviations: DIC, Deviance Information Criteria; ITC, indirect treatment comparison; OCA, Obeticholic acid.

*statistically significant

Note: it was not stated in the company's ITC report what timepoint was used for this assessment.

3.4.1.7 Sensitivity network results (efficacy outcomes)

The company presented a number of sensitivity analyses for ALP normalisation, composite response, and ALP response (Toronto I) with differing priors and outcome recalculation (Table 37). Overall, there was no meaningful difference in model fit using the same network for any scenario. Without other diagnostics available to the EAG to check for agreement, this suggested that there was no clear advantage of one model over the others in terms of predictive performance or parsimony. This strengthened confidence in the analysis findings.

Table 37: Model DIC for sensitivity analyses ALP normalisation, composite response and ALP response (Toronto I)

Model	**DIC** (*ALP normalisation)*	**DIC** (*Composite response)*	**DIC** (*ALP response – Toronto I)*
Bayesian NMA (Vague prior; with outcome recalculation) using POISE and RESPONSE trials	23.804	32.652	33.230
Bayesian NMA (Turner prior specific for biological markers; with outcome recalculation) using POISE and RESPONSE trials	23.889	32.636	33.213
Bayesian NMA (Turner prior; without outcome recalculation) using POISE and RESPONSE trials	23.892	44.529	33.257
Bayesian NMA (Turner prior specific for biological markers; without outcome recalculation) using POISE and RESPONSE trials	23.778	32.667	33.277
Bayesian NMA (Turner prior specific for biological markers; without outcome recalculation using RESPONSE, POISE and ELATIVE trials)	33.768	44.435	45.803

Abbreviation: ALP, Alkaline phosphatase; DIC, Deviance Information Criteria; NMA, Network meta-analysis.

Note: Shaded rows: scenarios looked at by the EAG (others were excluded for reasons stated in the text)

Analyses *with* and *without* outcome recalculation for ALP and bilirubin ULN cut-offs gave some indication as to the sensitivity of the treatment effect to these differing cut-offs. The findings were largely consistent between models in terms of the direction of effect and statistical significance using the Turner prior *with* (Table 27; Table 28; and Table 29) and *without* outcome recalculation (Table 38). This indicated that the outcome was not sensitive to recalculations for ALP and bilirubin ULN cut-offs, meaning that recalculation was unlikely to add additional uncertainty to the treatment effect for these outcomes. It also suggested that the analyses may retain generalisability to the UK population (without sex-specific cut offs). However, the EAG noted the wide credible intervals for seladelpar vs placebo for ALP normalisation and considered the importance of exploring adjustments for the zero-event rate in the RESPONSE placebo arm to improve the estimate discussed in (section 3.4.1.4).

Table 38: Bayesian NMA (Turner prior; without outcome recalculation)

Comparison	*ALP normalisation* **RR (95% CrI)**	*Composite response* **RR (95% CrI)**	*ALP response – Toronto I* **RR (95% CrI)**
Seladelpar vs OCA (5-10 mg)	[redacted]	[redacted]	[redacted]
Seladelpar vs OCA (10 mg)	[redacted]	[redacted]	[redacted]
Seladelpar vs placebo	[redacted]	[redacted]	[redacted]

Abbrevations: ALP, Alkaline phosphatase; CrI, Credible Interval; OCA, Obeticholic acid; RR: Risk Ratio

*statistically significant

The EAG noted that the treatment effect of seladelpar, relative to placebo, was particularly sensitive to the use of vague priors within the sensitivity ITC (Table 39). The non-significant RR with wider 95% CrIs vs placebo for composite and ALP response (Toronto I) were at odds with both the base case and with the head-to-head RESPONSE trial results. The latter showed a statistically significant difference and a larger proportion of participants achieving composite response as compared to placebo. The EAG noted that using vague priors can lead to wider credible intervals as the prior provides less information to constrain the parameter (represented by the credible interval) which is evident in the data. Although it was encouraging to note that the DIC was still adequately capturing the underlying data patterns without overfitting (Table 37). The EAG recommended that both odds ratios and risk ratios be presented to assess the extent to which the choice of effect measure might influence this result, this would help to quantify any uncertainty. The use of a risk ratio instead of an odds ratio in the presence of low or zero counts (such as in the placebo arm for ALP normalisation) may account for some of the unexpected differences between the models, although generally speaking the EAG noted the Bayesian NMA MCMC approach is a robust method in the presence of zero count data (TSD2).

Table 39: Bayesian NMA (Vague prior; with outcome recalculation)

Comparison	*ALP normalisation* **RR (95% CrI)**	*Composite response* **RR (95% CrI)**	*ALP response – Toronto I* **RR (95% CrI)**
Seladelpar vs OCA (5-10 mg)	[redacted]	[redacted]	[redacted]
Seladelpar vs OCA (10 mg)	[redacted]	[redacted]	[redacted]
Seladelpar vs placebo	[redacted]	[redacted]	[redacted]

Abbrevations: ALP, Alkaline phosphatase; CrI, Credible Interval; NMA, network meta-analysis; OCA, Obeticholic acid; RR: Risk Ratio

*statistically significant

The EAG did not interpret the remaining sensitivity analyses listed in Table 37 (without highlighting) as it was difficult to determine the effect of the difference in priors and the effect of outcome recalculation in isolation, as both were changed in a single model for comparison to the base case.

The company presented several sensitivity analysis for ALP change from baseline (Table 40):

Table 40: Sensitivity analyses ALP change from baseline

Model	DIC
Bayesian NMA (Vague prior) (using POISE and RESPONSE trials)	44.224
Bayesian NMA (Informative prior, using RESPONSE, COBALT, and POISE trials: Rhodes prior specific for biological markers)	60.523
Bayesian NMA (Informative prior, using RESPONSE, POISE, and ELATIVE trials: Rhodes prior specific for biological markers).	62.602

Abbreviations: ALP, Alkaline phosphatase; DIC, Deviance Information Criteria; NMA, network meta-analysis.

Note: Shaded rows: scenarios interpreted by the EAG

The findings for the Bayesian NMA using a vague prior and the POISE and RESPONSE trials were consistent with the primary network. The EAG did not consider the sensitivity analysis including the COBALT trial to be appropriate due to violation of the transitivity assumption (explained in section 3.4.1.2). The EAG noted that the addition of the ELATIVE trial in the Bayesian NMA using the Rhodes prior and the RESPONSE, POISE, and ELATIVE trials also presented some uncertainty around the assumption of transitivity across the network. Despite this, the EAG interpreted this analysis, because it was the only model that included the three treatments (OCA, elafibranor, and seladelpar) in a single analysis; with the caveat that this estimate had a level of uncertainty. The results of this sensitivity analysis are presented in Table 41.

The results for placebo and OCA were inconsistent with the primary network, the differences in the estimate for seladelpar vs OCA were unaccounted for and discussed in section 3.4.2.5, alongside the estimate for seladelpar vs elafibranor.

Table 41: Sensitivity analysis Bayesian NMA (Informative prior, using RESPONSE, POISE, and ELATIVE trials: Rhodes prior specific for biological markers)

Comparison	*ALP change from baseline* **MD (95% Credible Interval)**
Seladelpar vs OCA (5-10 mg)	[redacted]
Seladelpar vs OCA (10 mg)	[redacted]
Seladelpar vs elafibranor	[redacted]
Seladelpar vs placebo	[redacted]

Abbreviations: ALP, Alkaline phosphatase; MD, mean difference; NMA, network meta-analysis; OCA, Obeticholic acid

*statistically significant

3.4.1.8 Sensitivity network results (safety outcomes)

The sensitivity analyses were consistent with the primary network using Turner priors specific to adverse events.

3.4.1.9 Sensitivity network results (PBC-40 itch and 5-D itch)

The sensitivity analyses for both PBC-40 itch and 5-D itch for seladelpar vs. placebo and OCA (both doses) were consistent with the primary network using Turner priors, however the use of vague priors in sensitivity analyses resulted in a non-statistically significant finding versus placebo and OCA (both doses) for 5-D itch. The EAG noted that using vague priors can lead to wider credible intervals as the prior provides less information to constrain the parameter (represented by the credible interval), which was evident in the data.

3.4.2. Anchored MAIC

3.4.2.1. Definition

Anchored Matching-Adjusted Indirect Comparison (MAIC) is a method of indirect comparison used to compare individual patient level data from one study (RESPONSE) to aggregate data from another (ELATIVE), adjusting for differences in treatment effect modifiers between studies. The company presented scenarios comparing seladelpar and elafibranor using UDCA + placebo as a common comparator.

3.4.2.2. Transitivity and feasibility

The anchored MAIC was presented as the company's base case for all comparisons of seladelpar (RESPONSE) to elafibranor (ELATIVE) for the efficacy outcomes. The company also presented an unanchored MAIC as a sensitivity analysis for the composite biochemical response outcome (defined as ALP < 1.67× ULN; ≥ 15% decrease in ALP and total bilirubin ≤ 1.0× ULN) to overcome issues of transitivity between the placebo response in ELATIVE vs RESPONSE (there was a larger treatment benefit of placebo in RESPONSE compared to ELATIVE). The company noted that the placebo group in ELATIVE had to achieve a lower ULN cut-off to achieve ALP response, compared to the placebo arm in RESPONSE, which may have led to the differential placebo response rate. The relative treatment effect calculated from each trial was the basis for indirect comparison in conventional and population-adjusted methods like anchored MAIC. The use of an unanchored MAIC offered a more flexible comparison between the trials, as it did not rely on baseline data from the comparator trial and instead compared treatment arms directly by adjusting for the baseline characteristics of participants in each trial. However, the EAG noted that this was not necessary as the company had already recalculated response data so that the cut-offs matched between trials (see section 3.3), and so the EAG considered the unanchored MAIC not to be of additional value.

3.4.2.3. Statistical methods

The company presented the effective sample size (ESS) calculation and distribution of matching weights plots but omitted the covariate balance plots, which would also be expected for this analysis. Covariate balance plots would have been a useful addition to this submission to be clear about how successful matching was. Post-matching the distribution of weights were not evenly distributed around 1, indicating that the baseline characteristics of the RESPONSE trial population were somewhat dissimilar from ELATIVE. The uneven distribution of weights pointed to potential differences between the groups that could still influence the results, even after matching, and this raised concerns about the robustness of the comparison. The extreme weights (>5) made up 2.86% of the ESS, which was acceptably low, however this must be interpreted alongside the ESS which, upon matching, was 70 (36.27% of the original sample). The small ESS suggested that the treatment arms had substantial baseline differences that were difficult to reconcile through matching.

The company reported a risk ratio as the primary effect measure and applied a continuity correction of 0.5 to each arm to handle zero counts among placebo arms. The EAG noted this

method is referenced as a solution to handling zero count data and sparse networks when using a frequentist model, in TSD2.[29] The EAG noted that adding an arbitrary correction may over- or underestimate the treatment. The EAG suggested that it would have added value to this submission had the company presented both ORs and RRs to assess the extent to which the choice of effect measure, particularly in this scenario of zero or low event rates, influenced the results and overall conclusions.

The results for ALP normalisation at 12-months for seladelpar vs. placebo and vs. elafibranor are shown in Table 42. Seladelpar was associated with an improved rate of ALP normalisation compared to placebo, though the confidence interval was wide, suggesting significant uncertainty in the magnitude of the effect. There was a small, numerical benefit for seladelpar over elafibranor, though this was not statistically significant. The EAG noted that this may have been related to the use a continuity correction to adjust for zero counts which may have added a level of bias to this estimate (discussed in Section 3.4.2.3).

The comparison between seladelpar was broadly comparable with the NMA results for ALP normalisation (see Table 27), in the sense that seladelpar was associated with a large clinical benefit as compared to placebo, though the magnitude of effect was highly uncertain.

Table 42: ALP normalisation at 12 months

Comparison	RR (95% Confidence Interval)	Favours
Seladelpar vs placebo	[redacted]	[redacted]
Seladelpar vs elafibranor	[redacted]	[redacted]

Abbreviations: ALP, Alkaline phosphatase; RR, relative risk.

*statistically significant

The results for the composite response at 12-months are shown in Table 43. Seladelpar was associated with an increased rate of composite response compared with placebo, though while confidence intervals were narrower than for ALP normalisation, they were still wide and suggested uncertainty in the magnitude of the effect. Seladelpar was associated with a slight decreased chance of composite response compared to elafibranor, though this was not statistically significant.

Comparison	RR (95% Confidence Interval)	Favours
Seladelpar vs placebo	[redacted]	[redacted]

Comparison	RR (95% Confidence Interval)	Favours
Seladelpar vs elafibranor	[redacted]	[redacted]

Table 43: Composite response at 12 months

Abbreviation: RR, relative risk.

*statistically significant

The results for ALP response (Toronto I) at 12 months are shown in Table 44. Seladelpar was associated with a large increased chance of ALP response compared to placebo, though with wide confidence intervals. There was no difference in effect between seladelpar and elafibranor.

Table 44: ALP response (Toronto I) at 12 months

Comparison	RR (95% Confidence Interval)	Favours
Seladelpar vs placebo	[redacted]	[redacted]
Seladelpar vs elafibranor	[redacted]	[redacted]

Abbreviations: ALP, Alkaline phosphatase; RR, relative risk.

*statistically significant

The results for mean ALP change from baseline at 12-months are shown in Table 45. Seladelpar was associated a large mean reduction in ALP compared to placebo. There was no difference between seladelpar and elafibranor.

Table 45: ALP change from baseline at 12 months

Comparison	Mean difference (95% Confidence Interval)	Favours
Seladelpar vs placebo	[redacted]	[redacted]
Seladelpar vs elafibranor	[redacted]	[redacted]

Abbreviation: ALP, Alkaline phosphatase.

*statistically significant

Overall, the EAG considered the results to suggest that treatment with seladepar was more effective for ALP response outcomes compared to placebo, though consistently wide confidence intervals were shown, reflective of uncertainty in the model. There was no clear evidence to suggest that seladelpar was superior to elafibranor for these efficacy outcomes.

3.4.2.4. Primary analysis results (safety outcomes)

In addition to the NMA which was presented as the base case for the safety outcomes, the company also presented an anchored MAIC for seladelpar vs elafibranor. However, the EAG

favoured the NMA base case presented in section 3.4.1.5, which included this comparison in a single model.

3.4.2.5. Sensitivity analysis results (efficacy outcomes)

3.4.2.6. Bayesian NMA sensitivity analyses (efficacy outcomes)

The company presented several Bayesian NMA sensitivity analyses using differing priors and outcome recalculation, for ALP normalisation, composite response, and ALP response (Toronto I) listed in Table 46.

Table 46: Sensitivity analyses with DIC for ALP normalisation, composite response, and ALP response (Toronto I) using ELATIVE and RESPONSE trials

Model	**DIC** (*ALP normalisation)*	**DIC** (*Composite response)*	**DIC** (*ALP response – Toronto I)*
Bayesian NMA (Vague prior; with outcome recalculation) using ELATIVE and RESPONSE trials	20.131	24.679	25.657
Bayesian NMA (Turner prior; with outcome recalculation) using ELATIVE and RESPONSE trials	20.074	24.669	25.66
Bayesian NMA (Turner prior specific for Biological markers; with outcome recalculation) using ELATIVE and RESPONSE trials	20.143	24.637	25.66
Bayesian NMA (Vague prior; without outcome recalculation) using ELATIVE and RESPONSE trials	20.577	25.235	26.166
Bayesian NMA (Turner prior; without outcome recalculation) using ELATIVE and RESPONSE trials	20.364	25.203	26.168
Bayesian NMA (Turner prior specific for Biological markers; without outcome recalculation) using ELATIVE and RESPONSE trials	20.346	25.224	26.185

Abbreviations: ALP, Alkaline phosphatase; DIC, Deviance Information Criteria; NMA, Network meta-analysis.

Note: Shaded row: scenario interpreted by the EAG

As noted at the beginning of Section 3.4, the company determined that the transitivity assumption was violated between the RESPONSE and ELATIVE trials, due to differences in baseline bilirubin levels and the proportion of participants with cirrhosis. Despite this, the EAG considered the Bayesian NMA sensitivity analysis *with* outcome recalculation (using Turner prior) as this:

1 was most aligned to the company's choice of NMA base-case for seladelpar vs OCA, with the caveat that this estimate was somewhat uncertain due to issues with transitivity;

2 would help to isolate the unique benefit of accounting for treatment effect modifiers through a MAIC approach, something that was not feasible within the standard framework of a Bayesian NMA.

The EAG did not consider the other sensitivity analyses in Table 46 to be pertinent to decision-making as they did not align with the NMA base case.

The results of the sensitivity analyses are presented in Table 47. The findings suggested that adjusting for population differences via the MAIC did not have the desired effect, in that the results did not show more precise point estimates with narrower confidence intervals via the MAIC vs the NMA, as would be expected. Moreover, based on the more advanced symptoms of bilirubin and cirrhosis at baseline in the RESPONSE trial (Table 22), the EAG would have anticipated a more favourable treatment effect for seladelpar after adjusting for treatment effect modifiers through the MAIC. The EAG noted that this discrepancy was likely attributable to the low ESS, which resulted in an insufficiently robust analysis. This was similar for the comparison of seladelpar to placebo. Overall, this led to increased uncertainty in the MAIC.

Table 47: Sensitivity analysis Bayesian NMA (Turner prior; with outcome recalculation)

Comparison	*ALP normalisation* **RR (95% CrI)**	*Composite response* **RR (95% CrI)**	*ALP response – Toronto I* **RR (95% CrI)**
Seladelpar vs elafibranor	[redacted]	[redacted]	[redacted]
Seladelpar vs placebo	[redacted]	[redacted]	[redacted]

Abbreviations: ALP, Alkaline phosphatase; CrI, credible interval; NMA, network meta-analysis; RR, relative risk.
*statistically significant

The company presented sensitivity analysis for ALP change from baseline shown in Table 48. The EAG considered that Bayesian NMA ¥ sensitivity analysis was most pertinent as this was most aligned to the base case (using similar priors as in the base case), with the caveat that clarity was needed on the prior used. In the company's DIC document, the priors for this model were defined as "Rhodes prior specific for signs/symptoms reflecting continuation/end of condition and infection/onset of new acute/chronic disease" and in the ITC report these were defined as "informative priors specific for biological markers".

Table 48: Sensitivity analyses with DIC for ALP change from baseline

Model	DIC
Bayesian NMA (Vague prior)	44.224
Bayesian NMA (Rhodes prior)	33.974
Bayesian NMA ¥	34.119

Abbreviations: ALP, Alkaline phosphatase; DIC, Deviance Information Criteria; NMA, Network meta-analysis.

Note: Shaded row: scenario interpreted by the EAG

¥ priors are unclear

The EAG interpreted these findings alongside the sensitivity analysis presented in Table 41, in which the Bayesian NMA (including RESPONSE, POISE, and ELATIVE trials, using Rhodes prior specific for biological markers) included all three Phase 3 trials in a single model (with acknowledgement of the issues with transitivity). Interpreting these analyses side by side was useful to determine the effect of including the POISE trial in the same network as the RESPONSE and ELATIVE trials. The results of these analyses are combined in Table 49.

Despite the caveats in transitivity and idiosyncratic priors, the Bayesian NMA (POISE, RESPONSE, and ELATIVE: Rhodes prior specific for biological markers) model appeared to be capturing the trends in the data between seladelpar vs elafibranor and seladelpar vs placebo with a similar level of accuracy. However, it was concerning that, in the same model, the comparison between seladelpar vs OCA differed when compared to the Bayesian NMA (POISE and RESPONSE: Rhodes priors specific for biological markers) without the inclusion of the ELATIVE trial. Most notably the effect for seladelpar vs OCA (10mg) changed direction, although this was not statistically significant. This would not be expected as the additional data was for elafibranor vs placebo and did not form part of a loop. Therefore, the direction and magnitude of the effects would have been expected to be consistent. This highlighted additional uncertainty regarding the robustness of the NMA presented.

Table 49: ALP change from baseline

Model	Bayesian NMA (ELATIVE and RESPONSE)¥ MD (95% CrI)	Bayesian NMA (POISE, RESPONSE, and ELATIVE: Rhodes prior specific for biological markers) MD (95% CrI)	BASE CASE: Anchored MAIC (adjusted for 4 effect modifiers) MD (95% CrI)	BASE CASE: Bayesian NMA (POISE and RESPONSE: Rhodes priors specific for biological markers) MD (95% CrI)
Seladelpar vs elafibranor	[redacted]	[redacted]	[redacted]	N/A
Seladelpar vs placebo	[redacted]	[redacted]	[redacted]	[redacted]
Seladelpar vs OCA (5-10mg)	N/A	[redacted]	N/A	[redacted]
Seladelpar vs OCA (10mg)	N/A	[redacted]	N/A	[redacted]

Abbreviations: CI, confidence interval; CrI, Credible Interval; MAIC, Matching adjusted indirect comparison; MD, Mean Difference; N/A, not applicable; NMA, network meta-analysis.

*statistically significant

¥priors are unclear

3.4.3. Anchored MAIC sensitivity analyses (efficacy outcomes)

The company set out to conduct additional sensitivity analyses for ALP normalisation, composite response, and ALP response (Toronto I) using an anchored MAIC with different effect measures and treatment effect modifiers:

- Anchored MAIC using risk difference rather than risk ratio (adjusted for 4 effect modifiers, with outcome recalculation)
- Anchored MAIC using odds ratio rather than risk ratio (adjusted for 4 effect modifiers, with outcome recalculation)
- Anchored MAIC (adjusted for bilirubin and cirrhosis, with outcome recalculation)

However, the anchored MAIC using an odds ratio was not presented in the CS for ALP response (Toronto I), which the EAG believed would have been valuable to the submission and was likely an oversight on behalf of the company.

The EAG noted that adjusting only for bilirubin and cirrhosis led to an improved ESS (ESS = 82) compared to the primary outcome and helped to isolate the effect of adjusting for bilirubin and cirrhosis, which were imbalanced at baseline between trials. The direction of the effect in these sensitivity analyses was consistent with the primary effect. This suggested that adjusting for bilirubin and cirrhosis may be most influential to the analysis; as supported by the notable baseline differences in these characteristics between the trials (Table 22).

3.4.3.1. Sensitivity analysis results (safety outcomes)

No sensitivity analysis for the safety outcomes was presented. The potential risk for decision-making was that it was unknown whether the most appropriate method to determine the comparative safety profile of available treatment options had been used.

3.5. Conclusions of the clinical effectiveness section

In this section, the EAG summarise their conclusions for the clinical effectiveness of seladelpar.

Considerations related to the company's SLR and the presentation of evidence

- The SLR conducted by the company had some limitations. The EAG considered that the key evidence for seladelpar that was relevant for decision-making had been identified, but highlighted a concern that some evidence may have been missed for comparator treatments.

- The presentation of the clinical effectiveness evidence for seladelpar in the CS was poor and the vast majority of information and evidence that was appraised by the EAG was considered after receipt of the clarification response. While the company provided a comprehensive response to all of the EAG requests, the consequences were that (a) the EAG did not ask some clarification queries of interest in order to allow the company to focus their response on providing the necessary information, (b) the EAG did not have another opportunity to ask clarification questions on the newly submitted information and data. While NICE amended the timelines of the appraisal to allow the EAG to appraise the additional information provided at clarification, the delay nevertheless created pressure on the EAG in appraising the information provided. Overall, the EAG considered that it was able to conduct a reasonable appraisal of the evidence base, but highlighted this point as there is a risk that key evidence was missed.

Methodological considerations for the company's clinical trials of seladelpar

- The studies evaluating seladepar were considered to be representative of those earlier in the disease course (mean duration of disease at baseline of RESPONSE, ENHANCE and the Phase II dose-ranging study ranged between 8.3 and 9.7 years), before the onset of significant liver damage, which is consistent with the target population for seladelpar. A significant minority of participants in the trials had previously received OCA and/or fibrates, meaning that they received seladelpar as a 3rd+ line of treatment. The EAG considered it plausible that those receiving seladelpar at a later line of treatment may respond differently than those who had not, since those receiving seladelpar at a later treatment line would have shown an inadequate response or intolerance to more treatments. Subgroup analysis for the composite response in RESPONSE showed no difference in outcome according to treatment line, though given the small sample and the lack of analyses across other studies and outcomes, the EAG considered this to be uncertain. As elafibrinor, a treatment using an overlapping mechanism of action to seladelpar, was only recently available to people with PBC, there was no evidence for the effectiveness of seladelpar after treatment with elafibrinor.

- A minority of participants in the trials had discontinued UDCA due to intolerance, as opposed to a lack of response, and received seladelpar as monotherapy rather than in combination with UDCA. While the proportion of participants who were intolerant to UDCA was generally consistent with the proportion in the target population, the company often merged the two populations in their clinical effectiveness results, and it was not possible to appraise the potential for variation in treatment effect between the groups.

- The company did not report the background treatments used by participants during the studies, meaning that the EAG was unable to assess whether variation in treatments for the symptoms of PBC (e.g. treatments for itching) influenced the findings. Fibrates were not permitted during the study.

- There was a notable placebo effect in the placebo-controlled trials of seladelpar, particularly in RESPONSE, the pivotal trial. The EAG was advised by a clinical expert that this is common in trials of interventions for PBC that may be due to increased adherence to treatments in trial conditions than in everyday life, though the EAG was unable to identify evidence to substantiate this. The key implication of this for interpreting the clinical effectiveness evidence for seladelpar is that the treatment effect may be augmented by increased adherence to UDCA in those who received it in combination with seladelpar, and

therefore relative effect estimates (i.e. the difference between the seladelpar vs placebo arms) will be most pertinent for understanding the clinical benefit of seladelpar. In clinical practice, the EAG considered it plausible that adherence of both seladelpar and UDCA may reduce as compared to the clinical trial.

- While the company sought to collect long-term evidence for the effectiveness of seladelpar, the actual follow-up was still relatively short (up to 24 months though with very high attrition after 15 months). The EAG considered this sufficient time to be able to determine the relative effect of seladelpar for liver function, pruritus, fatigue and health-related quality of life. However, the EAG did not consider this sufficient time to understand the potential the effect of treatment on medium- and long-term clinical outcomes for people with PBC, including impact on the need for a liver transplant and overall survival.

The clinical effectiveness data for seladelpar

- The clinical trials showed that there was a meaningful clinical benefit of treatment with seladelpar as compared to placebo for reductions in ALP, as shown across all ALP outcomes. ALP levels are a diagnostic indicator of PBC and reductions in ALP are used to determine treatment response in clinical practice.

- The benefit of seladelpar for ALP levels as compared to placebo occurred rapidly in the trials, with participants showing a clinical benefit after only one month of treatment. Throughout the available follow-up of the trials (12 months with more robust follow-up or 15-months with high attrition), the relative treatment effect of seladelpar remained stable over time. Based on the data provided, it was perceived that notable reductions in ALP did not occur after one month, and so the EAG considered it reasonable that people with PBC could receive seladelpar for a short duration to determine their likely response.

- There was no reliable evidence to determine whether benefits in ALP were associated with improvements in long-term disease progression, including the risk of liver transplant or survival. The potential for seladelpar to offer long-term benefits for patients' wellbeing therefore relied on the strength of ALP levels as a surrogate outcome. ALP levels were considered to be predictive of long-term disease outcomes and were one of the factors included in the UK-PBC risk score, used to predict long-term liver outcomes.[24] Reducing ALP levels was therefore expected to be beneficial to patient wellbeing, though other factors in the risk model were equally important or stronger predictors (e.g. bilirubin levels).

- There was no meaningful difference in bilirubin levels between seladelpar and placebo, though the EAG considered it was likely that this was due to the overall low levels of bilirubin in trial participants (expected given the earlier disease stage of people with PBC at the anticipated positioning of seladelpar).
- In terms of pruritus, the evidence suggested that seladelpar did not increase the risk of pruritus, which may therefore make it a preferred alternative treatment to OCA. A minority of people who received seladelpar may have experienced a meaningful reduction in their pruritus, while others may not have noticed a difference.
- The EAG did not consider that the trials of seladelpar had reported a meaningful benefit of seladelpar for participants' health-related quality of life. A key factor for affecting the quality of life of people with PBC is fatigue, which was not affected by treatment with seladelpar. This finding was consistent with findings for other treatments that have reported that fatigue is notoriously impervious to treatment for PBC.
- Safety evidence for seladelpar did not identify major concerns for adverse events, though the evidence base for key events included as outcomes in the NICE scope (abdominal pain, ascites, varices, encephalopathy, and hepatic cell carcinoma) were not reported in a way that the EAG could appraise. Given the short follow-up of the trials, the long-term safety of seladelpar is unclear.

Considerations related to the company's ITC and MAIC

The EAG identified the following limitations with the company's analyses:

- The low ESS in the MAIC compared to elafibranor
- The uncertainty in the base-case NMA for ALP normalisation
- Transitivity concerns in the NMA due to baseline differences in treatment effect modifiers in the comparison to elafibranor
- Counterintuitive results in the MAIC compared to elafibranor
- Omission of sensitivity analyses including ORs alongside RR

- Unexpected inconsistent NMA outcomes in the comparison to OCA in the network with and without the inclusion of the ELATIVE trial
- Idiosyncratic reporting of priors

Overall, the EAG considered that the Bayesian NMA be adopted as the base case for all efficacy outcomes, rather than relying on the MAIC(s). This recommendation was based on the fact that the low ESS in the MAIC, and counterintuitive results which appear to stem from this, are considered more detrimental to the model than the transitivity concerns in the NMA. The EAG consider that the most reliable comparison between seladelpar, OCA, and elafibranor is achieved within a single model, rather than through separate models i.e. OCA vs. seladelpar and separately elafibranor vs. seladelpar, which the Bayesian NMA can afford. Therefore, when possible, the NMA that incorporates all three trials (POISE, ELATIVE, and RESPONSE) should be prioritised.

Uncertainty in the relative treatment effect could be reduced through the presentation of additional Bayesian NMA models to align with these findings for the following outcomes which are used in the economic analysis: ALP normalisation and ALP response (Toronto I). These models should use the following principles:

- Use all phase 3 trials (RESPONSE, ELATIVE, and POISE) in a single analysis
- Report results w*ith* outcome recalculation (present analyses adjusting the RESPONSE IPD data for both the POISE and ELATIVE cut offs, respectively)
- Report ALP normalisation with and without adjustments for zero events
- Use the same priors as listed in the base case(s) (Table 24)
- Present both odds ratios and RR for the effect measure where low event numbers are an issue
- Present absolute probabilities versus placebo, elafibranor and OCA (both doses)

Without these analyses being available the EAG considers that there is considerable uncertainty in the relative effectiveness of seladelpar in the comparison to elafibranor and OCA.

4. COST-EFFECTIVENESS

4.1. EAG comment on company's review of cost-effectiveness evidence

The company conducted an SLR to identify evidence on the burden of PBC (humanistic, economic, and healthcare resource use), health utility values, economic evaluations, treatment patterns, and treatment guidelines. The EAG considered the approach to be broadly appropriate. Details are reported in Table 50 below. As the EAG had additional comments to make on the search, these are provided here.

The review focused on studies for which full-text publications were available in English, although no geographic restrictions were applied. Searches were performed in a relatively narrow range of sources: Embase® (via Embase.com), MEDLINE (via PubMed – although at clarification the company stated that Medline was searched both via PubMed and Embase.com) and NHS EED (via the University of York CRD interface).

As with the clinical effectiveness search, the company initially claimed to use SIGN study type filters – although the company clarified during clarification that filters were developed for the searches. The EAG would have preferred to see validated filters used for the searches performed – such filters are available for humanistic burden, epidemiology, health utility values, treatment patterns, treatment guidelines, and healthcare resource utilisation. Nevertheless, the filters used appeared broadly appropriate.

Conference abstracts were included via the Embase search. Additional conferences were also searched for by hand. These included the American Association for the Study of Liver Diseases (AASLD), European Association for the Study of the Liver (EASL), Digestive Disease Week (DDW), United European Gastroenterology Week (UEG), The International Liver Congress, the American College of Gastroenterology (ACG), and the Professional Society for Health Economics and Outcomes Research (ISPOR). The company stated that, supplemental to the above-described searches, they also searched HTA assessment reports and systematic reviews and used citation snowballing for the identification of any missing studies. However, as with the equivalent step in the clinical effectiveness SLR, details of this process were not provided. Nevertheless, and in summary, the EAG considered that the economic searches described were suitable for the decision problem.

The company used the Pharmacoevidence® Artificial Intelligence/Machine Learning (AI/ML) tool as a second screener of identified records.[31-33] The company stated that citations were screened based on prompts designed using the inclusion/exclusion criteria, which were then optimised based on the results obtained from a small subset of the citations. The EAG requested more details about the AI process at clarification. The company reported that all disagreements between the human reviewer (reviewer 1) and the AI tool (reviewer 2) were resolved by an independent topic expert (Human), and that the level of disagreement between the human reviewer and the AI tool was within the range of agreement expected if both reviewers were human. Given the QA processes described by the company, the EAG believed that the use of the AI/ML tool was appropriate.

Table 50. Summary of EAG's critique of the methods implemented by the company to identify evidence on cost-effectiveness, utilities and health resource use and costs

Systematic review step	Section of CS in which methods are reported	EAG assessment of robustness of methods
Searches	Appendix E	The company conducted an SLR for cost effectiveness evidence as part of a broad review to cover all economic data. The databases searched were Embase, MEDLINE, and NHS EED, plus hand-searching for abstracts and posters from six conference series (AASLD, EASL, DDW, UEG, ACG, and ISPOR). Supplemental searches were also used, although the details of these searches remained unclear. The search terms used for the population and intervention were reasonable, as were the study filters (albeit unvalidated filters were used). However, other databases/sources could have been searched – such as INAHTA, the CEA Registry from Tufts, and guideline providers such as NICE. The EAG considered that the economic searches described were broadly suitable for the decision problem.
Inclusion criteria	Appendix E	The SLR for evidence on cost-effectiveness, utilities, and health resource use and costs was focused on adults with PBC and did not consider sources from broader populations.
Screening	Appendix E	Two independent reviewers (the second reviewer being AI) screened all records and disagreements were resolved by a third reviewer. Clarification response C1 indicated that AI was only used for this review, not for the clinical effectiveness review, for which its use was not mentioned in the CS.
Data extraction	Appendix E	Two independent human reviewers conducted data extraction and disagreements were resolved by a third reviewer.
QA of included studies	Appendix E	Risk of bias assessment was performed using Drummond's checklist for economic evaluations and the Philips checklist for

Systematic review step	Section of CS in which methods are reported	EAG assessment of robustness of methods
		model studies. It was not stated how many reviewers were involved.

Abbreviations: AASLD, American Association for the study of Liver Diseases; ACG, American College of Gastroenterology; CS, Company submission; DDW, Digestive Disease Week; EAG, External Assessment Group; EASL, European Association for the Study of the Liver; HRQoL, health-related quality of life; OCA, Obeticholic acid; QA, quality assessment; RCT, randomised controlled trial; RoB, Risk of bias; SLR, systematic review; UEG, United European Gastroenterology; UK, United Kingdom.

4.2. Summary and critique of company's submitted economic evaluation by the EAG

4.2.1. NICE reference case checklists

Table 51: NICE reference case checklist

Attribute	Reference case	EAG comment on company's submission
Perspective on outcomes	All direct health effects, whether for patients or, when relevant, carers	Per the NICE reference case
Perspective on costs	NHS and PSS	Per the NICE reference case
Type of economic evaluation	Cost–utility analysis with fully incremental analysis	Cost–utility analysis. A fully incremental analysis was conducted although the company also provided pairwise analyses.
Time horizon	Long enough to reflect all important differences in costs or outcomes between the technologies being compared	50 years. This was long enough for the patient population (mean age of 56.5 years) with <0.1% remaining alive in the model's final cycle
Synthesis of evidence on health effects	Based on systematic review	The 0-12 month transition probabilities for seladelpar and subsequent treatments were based on RESPONSE IPD data, while the comparators were derived from calibration factors (hazard ratios) obtained through an indirect treatment comparison. Beyond the first 12 months, TPs were estimated by calibrating to 10-year liver transplant-free survival outcome data by ALP levels from both the

Attribute	Reference case	EAG comment on company's submission
		Global PBC and UK PBC registry cohorts.
Measuring and valuing health effects	Health effects should be expressed in QALYs. The EQ-5D is the preferred measure of health-related quality of life in adults.	Expressed in QALYs derived through a mapping exercise from PBC-40 QoL data and from the literature.
Source of data for measurement of health-related quality of life	Reported directly by patients and/or carers	Reported directly by patients through the PBC-40 questionnaire. Carer HRQoL data were not included.
Source of preference data for valuation of changes in health-related quality of life	Representative sample of the UK population	The RESPONSE trial used the PBC-40 questionnaire to collect QoL data, which was then converted into EQ-5D through a mapping exercise. This informed the PBC biomarker component in the company's base case model. Pruritus-related disutilities were adjustable based on user selection and model specifications. Liver disease component utilities were sourced from Wright et al 2006 as used in TA443
Equity considerations	An additional QALY has the same weight regardless of the other characteristics of the individuals receiving the health benefit	Per the NICE reference case
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	Per the NICE reference case. Price year was 2022-23. Costs sourced from other price years were inflated to 2022-23 using the NHS Cost Inflation Index (NHSCII).
Discounting	The same annual rate for both costs and health effects (currently 3.5%)	Per the NICE reference case

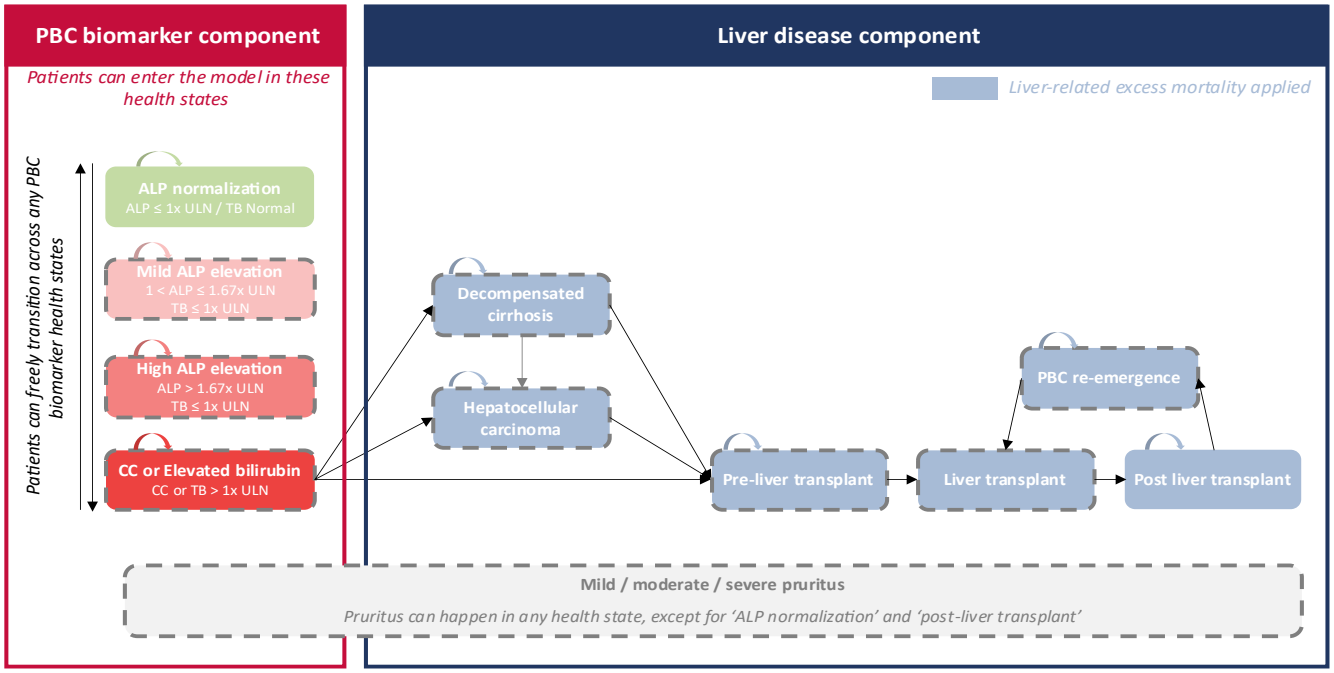
Abbreviations: EQ-5D, EuroQol 5 dimension; HRQoL, health-related quality of life; NHS, National Health Service; NICE, National Institute for Health and Care Excellence; PSS, Personal Social Services; QALY, quality-adjusted life year; QoL, quality of life; TA, technology appraisal

4.2.2. Model structure

A cohort-level Markov state transition model with two components was developed to simulate disease progression (shown in Figure 5). The first component (hereafter "PBC biomarker component") included three health states related to ALP levels (normal, mild elevation, high elevation) and a fourth health state for compensated cirrhosis or elevated bilirubin (hereafter "CC/EB"). Based on the RESPONSE trial, patients could enter the model in any of these health states except for the ALP normalisation health state. Once patients reached CC/EB, they could either transition to other health states in the PBC biomarker component or progress to the Liver disease component, comprising two health states: decompensated cirrhosis and HCC and three relating to liver transplant (pre-transplant, liver transplant, post-transplant) and a final health state allowing for re-emergence of PBC following transplant. Death was possible from any health state and mild/moderate/severe pruritus could occur alongside any health state other than post-liver transplant and death. The model structure (see Figure 5) generally aligned with those used in TA1016 (elafibranor) and TA443 (OCA), except for the inclusion of the ALP normalisation health state in the PBC biomarker component (model diagrams from TA1016 and TA443 are available in Appendix A).

The inclusion of the ALP normalisation health state was justified with evidence from the Global PBC Study Group,[34] which showed that ALP normalisation was associated with higher 10-year liver transplant-free survival rates (93.2% vs. 86.1%) compared to mild ALP elevation (1 < ALP ≤ 1.67x ULN). This finding is further supported by the REAL study[35] (RWE) and one EAG clinical expert input and therefore the EAG accepted this approach. However, the EAG noted that the ALP normalisation state was also assigned a higher utility and lower cost than the mild elevation state. The EAG explored the impact of this in a scenario by setting the utility and cost of the ALP normalisation state equal to that of the mild elevation, to more closely match the model structure in previous appraisals.

Figure 5 Schematic diagram of the model structure



Abbreviations: ALP, alkaline phosphatase; CC, compensated cirrhosis; PBC, primary biliary cholangitis; TB, total bilirubin; ULN, upper limit of normal.

Source: CS

A trivial difference from previous TAs was the cycle length. While previous TAs used a constant three-month cycle length, the first two cycles of the Company's model were one month's and two month's duration respectively, representing follow-up points in the RESPONSE trial. The EAG considered this appropriate.

4.2.3. Population

The company modelled two populations comprising adults aged 18 and older who have PBC who either (1) do not respond adequately to first-line treatment with UDCA monotherapy or (2) cannot tolerate UDCA.

The EAG noted that the RESPONSE trial included both populations within its entry criteria, but the data were not analysed separately for the purposes of the decision model, assuming the same transition probabilities for both. The company justified this by stating that only 11 (5.2%) UDCA-intolerant patients were included across the seladelpar and placebo arms and this was insufficient for a robust analysis. The company noted that the proportion of patients intolerant to UDCA were similar in the ELATIVE (ELA) and POISE (OCA) trials (between 5% and 5.7%) as

to the RESPONSE trial (which formed the key studies in the ITC). For these reasons, the EAG considered this approach acceptable but noted the implicit assumption that both patient populations responded to treatments in an identical manner, which may not necessarily be the case.

The EAG noted that 5.88% of patients had insufficiently elevated ALP levels at baseline in the RESPONSE study (≤1.67xULN, Table 52). The EAG understood this was due to the two-week run-in period for the trial, during which some patients had experienced positive changes in ALP levels. In the UK, patients eligible for second-line treatment for PBC must have an ALP level of at least 1.67 × ULN. The EAG therefore modified the starting population allocating patients to the high and CC states, as per Table 52, for its preferred base case.

Table 52 Baseline PBC biomarker health state distribution

Health state	Company base case* % (N); N= 187	EAG base case
ALP Normalisation, % ALP ≤ 1x ULN / TB Normal (TB ≤ 1x ULN)	0.00%	0
Mild ALP Elevation, % 1 < ALP ≤ 1.67x ULN / TB Normal (TB ≤ 1x ULN)	5.88%	0
High ALP Elevation, % ALP > 1.67x ULN / TB Normal (TB ≤ 1x ULN)	71.66%	74.9%
Compensated Cirrhosis or Elevated Bilirubin, % CC or TB > 1x ULN	22.46%	25.1%

Abbreviations**:** ALP, alkaline phosphatase; CC, compensated cirrhosis; TB, total bilirubin; PBC, Primary biliary cholangitis; ULN, upper limit of normal

Note: Percentages may not sum to 100% due to rounding.

Source CS table 42. *From RESPONSE complete case data.

4.2.4. Interventions and comparators

Seladelpar was administered at 10 mg daily, as per the RESPONSE trial. It was combined with UDCA for those who are tolerant to UDCA and used as monotherapy for those who were intolerant to UDCA. Other second-line disease-modifying options comprised OCA and elafibranor (ELA). All treatments were positioned as second line treatment following intolerance or inadequate response with UDCA monotherapy. The company also suggested using

seladelpar as a third-line treatment for patients who did not respond adequately to or cannot tolerate OCA.

Fibrates were excluded as a comparator to seladelpar in the final NICE scope because:

- Off label use: Fibrates are used off-label and have undocumented efficacy and toxicity issues
- Adjunctive use: Fibrates are mainly used as an adjunctive treatment alongside with UDCA and not as the main treatment
- Different target population: Fibrates are mainly used in the cohort of patients with ALP levels between 1 and 1.67 while seladelpar can only be used in the patients with ALP levels $\geq$ 1.67
- Appraisal exclusion: Fibrates were excluded in ELA and OCA appraisals and therefore its inclusion here would be inequitable to the manufacturer of seladelpar

As discussed in section 2.5, the EAG considers fibrates a valid comparator: two of the three clinical experts contacted by the EAG agreed with the company's position based on the points mentioned above. However, the third expert used fibrates as a substitute for OCA when appropriate and therefore considered them a treatment option. He also noted that fibrates were currently undergoing a licensing process for PBC, led by NHS England. A publication by Abbas et al. (2023) supported the view of the third clinical expert:

The study analysed a cohort of UK patients with PBC who were referred for second-line treatment. Data from 14 Operational Delivery Networks (ODNs) showed that 23.6% of patients (108 out of 457) used fibrates between 2017 and 2021. These patients had a mean ALP level of 2.27 × ULN, and 8.3% had cirrhosis. The study found that ALP and ALT reductions at month 12 were greater in the fibrate group compared to the OCA group. These data conflict with the opinions of the first two experts and the NICE scope. The EAG further noted that the NICE manual permits the use of 'off-label' comparators (Section 6.2.4, NICE manual[36]).

Based on the Abbas study, the EAG considers fibrates to be a legitimate comparator in the decision problem. Inclusion of an additional comparator would have required considerable re-engineering of the company's model which the EAG was unable to undertake within the time available. However, an informal estimate of the impact on the cost-effectiveness of seladelpar is presented in Section 6.4.1.

With respect to third line use, the company did not enable a third-line comparison in the decision model, and the CS lacks evidence for both those who are tolerant and those who are intolerant OCA.

4.2.4.1. Subsequent treatments

The subsequent treatments proposed by the company in the treatment pathway only included UDCA monotherapy or best supportive care (BSC). While this treatment pathway was supported in previous appraisals, the EAG noted that elafibranor (ELA) and OCA were also treatment options and may be used as subsequent therapies, alone or in combination, before reverting to BSC / UDCA monotherapy. Clinical advice to the EAG suggested that patients could switch from ELA or seladelpar to OCA if they did not experience significant itching.

Addressing full sequencing of the treatments would require substantial re-engineering of the company's model, as well as data on treatment effects in subsequent lines. In the absence of such analyses or data, the EAG adopted this approach in its own base case but urged caution in interpreting the results.

4.2.5. Perspective, time horizon and discounting

The analysis was performed from the viewpoint of the NHS and PSS, considering both costs and QALYs over a lifetime (up to 50 years). These outcomes were discounted at an annual rate of 3.5%. The EAG noted that discounting was initiated from the first cycle (month 1) rather than from year 1 (the second year of analysis). Conventionally discounting has been 'lumped' into annualised rates. However, the company's approach was theoretically preferable and was broadly consistent with the NICE reference case.

4.2.6. Treatment effectiveness and extrapolation

For the first 12 months, RESPONSE individual patient data (IPD) were used to estimate transition probabilities for seladelpar and subsequent treatments (UDCA monotherapy and BSC). Transition probabilities (TPs) for comparators (OCA and elafibranor) were drawn from relative risks and odds ratios estimated from the ITC (see section 3.4 for more information on the ITC).

Beyond the first 12 months, TPs were estimated by calibrating to 10-year liver transplant-free survival (hereafter "LTFS") outcome data from both the Global PBC (Murillo-Perez et al., 2020)

and from UK PBC registry cohorts based on ALP levels at 12m. A summary of the sources for TPs is provided in table 45 of the CS.

Calculations are detailed in sections 4.2.6.1 and 4.2.6.2:

4.2.6.1. Month 0-12 transition probabilities

Seladelpar

For seladelpar +/- UDCA, transitions between ALP states and CC were estimated at 1, 3, 6, 9 and 12 months directly from the RESPONSE data. The company's base case drew on complete case analysis, with a scenario ("Missing imputation method") classifying missing observations as being in the CC/Elevated TB state. The EAG noted that the scenario was a pessimistic analysis but may be a reasonable lower bound as a measure of effect. The EAG considered that the company's approach to estimating transition probabilities was reasonable, however noted that as data were drawn directly from RESPONSE, without fitting statistical models, transitions for which there were zero observed events were assigned a zero probability of occurring, with absolute certainty. The impact of this on decision uncertainty is considered in section 4.2.9.

The EAG observed that transition probabilities from month 0 to 1 from ALP normalisation to normal, mild, high and cc were set to an arbitrary 25% each. However, the EAG noted that these were purely holding values and there were zero observations informing them (entry requirement for the trial was elevated ALP) and this therefore had no impact on the analysis as no patients made this transition.

OCA and elafibranor

The company conducted an ITC to generate relative treatment effect estimates (RR and OR) of ALP normalisation and mild ALP elevation for OCA (at two dosing regimens: (a) 10mg and (b) 5mg titrated up to 10mg) and elafibranor at 12 months (*inter alia*, see Section 0). As its base case, the company chose RRs and ORs from the primary ITC analyses for elafibranor (anchored and unanchored MAICs) and OCA (Bayesian NMA).

This was used to generate a 'calibration hazard ratio (HR)' which is best explained by example, as shown in Box 2. Note the numbers in the example are purely for illustration and do not reflect real data. Figures used in the company base case are in Table 53.

Box 2: Example of the calibration hazard ratio used for OCA and elafibranor at 12 months

Suppose the model predicted 20% of the cohort on treatment A to be in state 1 at 12m, and the RR for A vs B was 1.25.

The target percentage of the B cohort in state 1 was therefore 0.2/1.25 = 16%.

The transition probabilities for the B cohort were set equal to those for A multiplied by a constant, which the EAG assumed was given a value of 1 in the first instance.

A search algorithm was employed to find a value for the constant yielding the target 16% of the B cohort in state 1 at 12m. The constant is the calibration HR.

This was repeated for both health states (ALP normalisation and mild elevation) and for both treatments: OCA and elafibranor.

The EAG considered that, in the absence of direct comparative evidence, the method used by the company was an appropriate approach to calculating transition probabilities. However, the EAG noted the following methodological concerns and cautions:

1 It was possible that the search algorithm may have more than one solution, which may be associated with different costs and QALYs for the comparator arms.

2 The EAG was concerned that the uncertainty in the calibration HR was not carried through into the PSA, with values being varied by +/-10% of the mean rather than reflecting the credibility intervals of the underlying RR or OR.

With respect to issue one, the EAG repeated the search algorithm with different starting values for the calibration HR. This resulted in similar HRs each time (+/- 0.0001) and the EAG was therefore satisfied that the calibration approach was plausible.

With respect to issue two, the EAG explored estimating calibration HRs at the reported lower and upper 95% credibility limits for the ALP normalisation RR for elafibranor and implied 95% credibility limits for the ORs for the other comparisons. However, these were not calculable, leading to errors or non-sensical results from the search algorithms. As an approximation in consideration of the very wide CrIs from the ITCs, the EAG set the SE equal to the point estimate ratios rather than to 10% of the point estimate.

As described in section 3.5, the EAG considered that the Bayesian NMA should be adopted as the base case for relative treatment effects, and assumed a SE as described in the paragraph above (equal to the mean rather than 10% of the mean).

The company clarified that the ORs used in the original CEM were not derived by calibrating to RRs, as initially suspected by the EAG. Instead, the ORs and RRs were from a prior indirect comparison used to inform the original CEM. unanchored MAIC estimates were used for ALP normalisation, while anchored MAIC estimates adjusted for four effect modifiers were used in the primary analysis comparing the original CEM with the updated ITC, based on the Toronto I criteria. The company subsequently provided an updated base case incorporating these revised ITC inputs directly into the model

Table 53: Calibration factors and resultant HRs for external comparators: obeticholic acid and elafibranor

Comparator (Dosing)	**Elafibranor ± UDCA**		**OCA ± UDCA (5-10mg)**	
Endpoint	ALP normalisation ALP ≤ 1 × ULN	Toronto I criteria ALP ≤ 1.67x × ULN	ALP normalisation ALP ≤ 1 × ULN	Toronto I criteria ALP ≤ 1.67x × ULN
Company Base Case				
ITC analysis	Unanchored MAIC	Unanchored MAIC	Bayesian NMA	
Effect modifier	RR	OR	OR	OR
Effect	[redacted]	[redacted]	[redacted]	[redacted]
Model predicted proportion – Seladelpar	[redacted]	[redacted]	[redacted]	[redacted]
Comparator 12-month **target based on effect modifier**	[redacted]	[redacted]	[redacted]	[redacted]
Calibration HR (SE)	0.7182 (0.072)	0.9081 (0.091)	0.044 (0.004)	1.162 (1.12)
EAG preferred Base Case				
ITC analysis	Bayesian NMA			
Effect modifier	RR	RR	RR	RR
Effect	[redacted]	[redacted]	[redacted]	[redacted]

Comparator (Dosing)	Elafibranor ± UDCA		OCA ± UDCA (5-10mg)	
Model predicted proportion – Seladelpar	[redacted]	[redacted]	[redacted]	[redacted]
Comparator 12-month target based on effect modifier	[redacted]	[redacted]	[redacted]	[redacted]
Calibration HR (SE)	0.6500 (0.6500)	1.1081 (1.1081)	0.044 (0.044)	1.1116 (1.1116)

Abbreviations: ALP, alkaline phosphatase; EAG, External Assessment Group; HR, hazard ratio; ITC, indirect treatment comparison, NE, not evaluable; NMA, network meta-analysis, OCA, obeticholic acid; OR, odds ratio; RR, relative risk; TP, transition probability; UDCA, ursodeoxycholic acid.

Source: Adapted from Company submission, Table 47

4.2.6.2. Month 13+ transition probabilities

Consistent with the appraisal of OCA (TA443), transitions beyond month 12 were estimated through calibration to 10-year liver transplant-free survival (LTFS) outcome data from the Global PBC and UK PBC registry cohorts. For the CC/elevated bilirubin and decompensated cirrhosis health states, the model initially constructed a transition probability matrix based on the probabilities outlined in TA443. This matrix was then calibrated using Solver, with the objective that the proportion of the simulated cohort remaining liver-transplant-free at 10 years (adjusted for general population OS) aligned with published estimates of 10-year liver-transplant-free survival (LTFS). This was the same for all treatment arms. For mild, moderate and ALP normalisation states, the matrix was then calibrated using Solver, with the objective that the proportion of the simulated cohort remaining liver-transplant-free at 10 years (adjusted for general population OS) aligned with published estimates of 10-year liver-transplant-free survival from Murillo-Perez et al. 2022.

The EAG considered that the company could have made use of the longer-term data from ASSURE to predict disease progression. However, given the increased attrition post 12 months and in the absence of comparative data between the treatments, the EAG considered the company's approach reasonable.

4.2.6.3. Liver disease

Patients in the liver disease component of the model (Figure 5) could only transition to these health states from the CC/EB health state, which was part of the PBC biomarker component of

the model. The company did not find any relationship between the treatments administered and the progression rates to the liver disease component of the model. Therefore, the transition probabilities were the same for all treatments, as shown in Table 52 of the CS.

The TPs were primarily derived from the appraisal of OCA (TA443), with the exception of the transition from CC/EB to decompensated cirrhosis, which was sourced from Global PBC and UK-PBC outcome data. Additionally, the excess PBC recurrence mortality, compared to the general population, was assumed to be zero. The EAG was uncertain whether assuming zero increased mortality in the PBC recurrent health state was overly optimistic. Therefore, the EAG conducted a scenario using the mortality rate from the Pre-LT health state.

4.2.6.4. Treatment discontinuation

0-12 months

All cause discontinuation rates from months 0-12 for seladelpar were obtained from RESPONSE, while the rates for the comparators were naively sourced from their respective studies. However, the company had access to comparative data from an ITC on all-cause discontinuation for elafibranor 80 mg, as provided in Tables 45 and 46 of the ITC report submitted by the company. Although the information was available, it was not utilised and the company did not explain this decision.

The EAG compared the implied 12-month discontinuation rates generated by the model under the company's base case and noted that the discontinuation rates derived from the ITC were significantly higher for the comparators than those based on individual trials, leading to substantially higher percentages of patients discontinuing at month 12 (Table 54). The EAG considered that the ITC was more suitable for the economic analysis because the ITC took into account the differences between trial populations and would have been more consistent with the approach used to calculate other model inputs. The EAG therefore adopted this in its base case.

Table 54: Cumulative discontinuation at 12m (UDCA tolerant and intolerant)

	Seladelpar	Elafibranor	OCA
Company base case	6.73%	9.59%	9.59%
ITC	6.73%	11.02%	26.95%

Abbreviations: ITC, indirect treatment comparison; OCA, Obeticholic acid, UDCA, Ursodeoxycholic acid.

12months +

Discontinuation rates beyond month 12 required several assumptions. The company argued that, since the at-risk population mostly comprised responders and lower adverse event rates would be expected from month 12 onwards, discontinuation rates would be anticipated to be lower after month 12 compared to the period from month 0 to 12. The EAG agreed with this argument.

The company calculated a discontinuation rate ratio from the ELATIVE and ELATIVE OLE studies for elafibranor between weeks 0-52 and 53-104 of 0.28 (Table 55). This rate ratio was then applied to calculate discontinuation rates for seladelpar and OCA post 12m.

The EAG noted that the company used ELATIVE as the source for rate ratios rather than rooting the analysis in studies of seladelpar (and hence a combination of RESPONSE and ASSURE). The EAG preferred to use data relating to seladelpar as the source in its base case, generating a rate ratio of 0.12 rather than 0.28 (Table 55).

Table 55 Discontinuation rate calculations from elafibranor trials vs. seladelpar trials

Company base case		
Trials	ELATIVE	ELATIVE OLE
Patients that discontinued	12	3
Total number of patients	108	96
Discontinuation rate	= (3/96)/(12/108)= 0.28	
EAG Scenario		
Trials	RESPONSE	ASSURE
Patients that discontinued	10	1
Total number of patients	128	104
Discontinuation rate	= (1/104)/(10/128)= 0.12	

Abbreviations: EAG, External Assessment Group; OLE, Open Label Extension

4.2.6.5. Subsequent treatments

As previously stated (section 4.2.4.1), the EAG considered that the exclusion of active treatments at third line was a limitation of the model.

Data to inform the effectiveness of third line (3L) BSC/UDCA monotherapy were extracted from the placebo arm of the RESPONSE study. This assumed equal effect of BSC and UDCA. Clinical advice to the EAG was that where first line UDCA monotherapy had already failed (i.e. first line), response to repeated monotherapy was unlikely, and therefore there was unlikely to

be any additional benefit of UDCA over and above BSC. The EAG therefore considered the company's approach reasonable, notwithstanding concerns regarding the exclusion of active 3L treatments.

The model assumed that once progression to the liver disease component occurred, all treatments were discontinued. Clinical advice to the EAG was that OCA would continue to be used to treat patients following a liver transplant. However, the EAG believed that excluding this would have a limited impact on the model results, as there were few patients in the PBC recurrence health state.

4.2.6.6. Pruritus

As noted in section 4.2.2, incidence of pruritus was estimated using the RESPONSE IPD data for seladelpar and from an ITC for the comparators. The outcome measure used was the pruritus numerical rating scale, a simple rating scale from 0-10.[37] Pruritus was defined as mild (<4), moderate (≥4 to <7) or severe (≥7). Pruritus can occur in any health state, regardless of its severity, except for post-liver transplant.

The company used the Bayesian NMA (with Turner prior) to inform the odds ratios for OCA and elafibranor (Table 28 of the CS), which the EAG agrees is the most appropriate analysis.

4.2.6.7. Safety / Adverse events (excluding pruritus)

Serious adverse events that occurred in one or more patients were included in the model. Data were extracted from individual trials rather than from the ITC, which the EAG broadly agrees with as an ITC on each possible AE would not generate meaningful results due to small numbers of observations (Table 56 and Table 57).

Table 56 Adverse event (excluding. pruritus) incidence rates – UDCA tolerant

Adverse event	Seladelpar + UDCA			Obeticholic acid + UDCA			Elafibranor + UDCA		
	n	N	AE rate	n	N	AE rate	n	N	AE rate
Acute kidney injury	0	120	0.00%	0	73	0.00%	3	108	2.78%
Diarrhoea	3	120	2.50%	0	73	0.00%	0	108	0.00%
Headache	4	120	3.33%	0	73	0.00%	0	108	0.00%
Hip fractures	0	120	0.00%	0	73	0.00%	2	108	1.85%

Adverse event	Seladelpar + UDCA			Obeticholic acid + UDCA			Elafibranor + UDCA		
	n	N	AE rate	n	N	AE rate	n	N	AE rate
Source	RESPONSE (TFL, Table 14.3.1.7.10), UDCA-use population data			Nevens 2016 (POISE, suppl. materials, Table S8 - reported only for overall population)			Knowdley 2024 (ELATIVE, suppl. materials, Table S6 - reported only for overall population)		

Abbreviations: AE, adverse event; N, total number of patients; n, number of patients in the category; TFL, table figures and listings; UDCA, ursodeoxycholic acid.

Source table 55 of the CS

Table 57 Adverse event (excluding. pruritus) incidence rates – UDCA intolerant

Adverse event	Seladelpar			Obeticholic acid			Elafibranor		
	n	N	AE rate	n	N	AE rate	n	N	AE rate
Acute kidney injury	0	8	0.00%	0	73	0.00%	3	108	2.78%
Diarrhoea	0	8	0.00%	0	73	0.00%	0	108	0.00%
Dry eye / dry mouth	0	8	0.00%	0	73	0.00%	0	108	0.00%
Rash erythematous / rash papular, erysipelas	0	8	0.00%	0	73	0.00%	0	108	0.00%
Headache	0	8	0.00%	0	73	0.00%	0	108	0.00%
Hip fractures	0	8	0.00%	0	73	0.00%	2	108	1.85%
Osteoarthritis	0	8	0.00%	2	73	2.74%	0	108	0.00%
Source	RESPONSE (TFL, Table 14.3.1.7.10), UDCA-intolerant data			Nevens 2016 (POISE, suppl. materials, Table S8 - reported only for overall population)			Knowdley 2024 (ELATIVE, suppl. materials, Table S6 - reported only for overall population)		

Abbreviations: AE, adverse event; N, total number of patients; n, number of patients in the category; TFL, table figures and listings; UDCA, ursodeoxycholic acid.

Source table 56 of the CS

The EAG was unconvinced of the value of dividing AEs into UDCA-tolerant and UDCA-intolerant patient groups due to the small numbers of observations in the UDCA-intolerant data. The EAG therefore conducted a scenario assigning the UDCA tolerant population AE rates to both populations.

The EAG also noted that TA1016 (elafibranor) included several grade two AEs (reported in ≥ 5% of patients) excluded from this analysis, namely urinary tract infections and fatigue (Table

58). The EAG therefore conducted a scenario including the impact of these, with data drawn from the safety analysis set in the RESPONSE CSR (associated disutilities and costs are discussed in sections 4.2.7.3 and 4.2.8.3 respectively).

Table 58 AEs included for elafibranor, UDCA and OCA

Adverse events	Seladelpar[2]	Elafibranor[1]	UDCA[1]	OCA[1]
Urinary tract infections	3.1%	5.8%	1.9%	5.8%
Fatigue	6.3%	4.7%	5.9%	4.7%

Abbreviations: AE, adverse event; CEM, cost-effectiveness model; OCA, obeticholic acid, UDCA, ursodeoxycholic acid.

[1] Grade 2+ AEs, Source: table 41 and 42 of TA1016 Committee papers

[2] TEAEs in ≥ 5% of Subjects in Either Treatment Arm by Preferred Term (Safety Analysis Set), source RESPONSE CSR table 48

4.2.7. Health-related quality of life

4.2.7.1. PBC biomarker component & pruritus disutility

EQ-5D data were not collected as part of the RESPONSE study. Instead, the disease-specific PBC-40 was used. The Company converted these data to EQ-5D-3L utilities by ALP level using a mapping algorithm (algorithm 'MMRM2'). This included covariates for pruritus, and thus provided a disutility estimate for this too. However, the company opted not to use the disutility estimates for pruritus from the mapping algorithm, substituting them for alternate estimates derived from Smith et al. 2022 (Table 59). The company justified this on the basis that the Smith study used EQ-5D measures directly, which is generally preferred by NICE, although the company conducted a scenario analysis using the MMRM2 disutilities.

Table 59: Utility and disutility estimates for ALP level and pruritus

Parameter	MMRM2-based (dis)utilities	Company base case
ALP Normalisation	[redacted]	[redacted]
Mild ALP elevation	[redacted]	[redacted]
High ALP elevation	[redacted]	[redacted]
Mild pruritus	-0.0041	-0.115
Moderate pruritus	-0.0041	-0.115
Severe pruritus	-0.0345	-0.380

Abbreviations: ALP, Alkaline phosphatase; MMRM, Mixed model for repeated measures

Source: Company base case disutilities for pruritus sourced from Smith et al. 2022[38]

The EAG noted that the disutilities for pruritus used in the Company base case were an order of magnitude higher than those calculated in the MMRM2 analysis. The EAG's critique follows:

As stated, the disease-specific PBC-40 health related quality of life questionnaire was administered alongside the RESPONSE study. A mapping algorithm was generated from the ITCH-E study,[39] a real-world study focused on the impact of pruritus in PBC. In this study 90 participants with PBC completed both the PBC-40 and EQ-5D-5L questionnaires. The analysis was further mapped to EQ-5D-3L responses. A mixed model for repeated measures (MMRM) approach was applied to estimate utility values by health state (ALP level) based on the mapped algorithm between PBC-40 and EQ-5D-5L and between PBC-40 and EQ-5D-3L. In both cases algorithms with and without itching as covariates were calculated (named MMRM1 and MMRM2 respectively).

The company also conducted a systematic review of the literature of HRQoL in PBC, yielding seven studies from 14 publications reporting utility data. Of these, the company selected those from Smith 2022a, b and c. These are one abstract presented at three conferences, estimating EQ-5D-5L-based health related quality of life as a function itch severity from the baseline results of the GLIMMER study (Levy 2022).[40]

In GLIMMER, 147 participants with PBC and moderate-severe pruritus (>4 on 0-10 NRS-numerical rating scale) were enrolled and randomised to various doses of linerixibat over 16 weeks. Smith stated that at baseline 76 had moderate pruritus, 36 had severe and 35 mild. Inclusion of mild pruritus appears to contradict the inclusion criteria for the GLIMMER study. However, the EAG noted that there was a run-in period for the GLIMMER study of 4 weeks before baseline measurement.

At baseline, patients' mean (SD) utility is as per Table 60 below. The abstract noted that the utility value for mild/moderate pruritus (0.75 to 0.76) was "marginally lower than the general UK population (mean at age 55-64: 0.804)". The source for this is not stated but appears consistent with the HSE 2014 cohort recommended by NICE.[41] For comparison the study also cites a health state utility of 0.87 (SD 0.11) for the PBC population. This was from a study[42] of 66 Italian participants with PBC from a cohort of 2962 with different chronic liver diseases, whose HRQoL was measured with EQ-5D-3L, using Italian-specific preference weights.

The EAG noted the inconsistency between the HRQoL of the general population (0.804) and that of the PBC population (0.87): the health utility of the PBC population was higher than the

general population, which lacked face validity. This could be due to differences in populations and/or differences in preference weights between Italian and UK algorithms for calculating health state utilities. (The EAG noted the conference abstract did not state which mapping algorithm was used to translate EQ-5D health profiles to utilities, but assumed it was a UK-relevant one).

Table 60: Health state utility values by pruritus severity as reported by Smith in the GLIMMER study

Health state	Mean (SD) EQ-5D-5L utility
PBC + Mild pruritus	0.75 (0.17)
PBC + Moderate pruritus	0.76 (0.17)
PBC + Severe pruritus	0.49 (0.28)

Abbreviations: PBC, Primary biliary cholangitis; SD, standard deviation.

Source: Levy et al. 2022[40] as reported in Smith et al. 2022[38]

The company assumed a utility for PBC without pruritus of 0.87, equal to that observed in the Italian cohort (Cortesi et al 2020[42]), but the company cites Rice et al 2021.[6] The EAG was not able to identify this figure in the Rice study and therefore believes this to be an error, as the Smith abstract cites the Cortesi paper. The Company subtracted 0.87 from the utilities in Table 60 above to estimate disutilities of -0.11 for mild/moderate and -0.38 for severe pruritus.

The EAG noted that the Rice paper was a study of 2240 UK participants with PBC from the UK-PBC research cohort measuring health related quality of life with the EQ-5D-5L instrument. In this study the utility for asymptomatic PBC was 0.917, whilst that for all itching was 0.899, a reduction of 0.018. The EAG noted that the study did not differentiate by itch severity but observed the Rice et al comment that "…itch was not [statistically significantly] associated with HRQoL impairment, probably reflecting the impact (albeit incomplete) of treatment".[6]

The EAG noted the two sources used for estimation of the disutility of pruritus in the company's base case, and the lack of face validity of the utility of asymptomatic PBC being higher than that of the general population. It also noted that the Rice study (a large UK-cohort) found a minimal impact of pruritus on quality of life, due to the 'incomplete impact of treatment'. The EAG further noted that the company included the cost of treatments for pruritus but not any reduction in disutility to represent a treatment effect of the antipruritics. Therefore, the EAG considered that the company overestimated the impact of (treated) pruritus on health-related quality of life and considered the company's MMRM2 model based on EQ-5D-3L to be more appropriate. This is

because it draws on data with greater internal consistency, is consistent with observations from the UK-PBC cohort, is based on the observed data from the pivotal trial of seladelpar (RESPONSE), and the NICE manual states a preference for EQ-5D-3L over 5L.[36]

Finally, the EAG also noted that the standard deviation of estimates had been entered into the model as standard error, overestimating uncertainty in the utility values (see Section 6.1).

4.2.7.2. Liver disease component

The company assigned health state utilities from committee and EAG preferred values from TA443 (OCA NICE appraisal). The EAG agrees with the values assigned.

4.2.7.3. Other AEs (excluding pruritus)

Disutilities for adverse events were sourced from values used in previous appraisals and the literature (Table 61).

Table 61 Adverse event disutility values

Adverse event	Disutilities	Source
Acute kidney injury	-0.0480	NICE TA688
Diarrhoea	-0.1030	Peasgood 2010 (Diarrhoea and vomiting)
Dry eye / dry mouth	-0.2020	NICE TA688 - assumed same as rash
Rash erythematous / rash papular, erysipelas	-0.2020	NICE TA688
Headache	-0.0266	Sullivan 2011
Hip fractures	-0.1480	PHE 2018 (page 22 [0.582-0.73])
Osteoarthritis	-0.1017	Sullivan 2011

Abbreviations: NICE, National Institute of Health and Care Excellence; PHE, Public Health England; TA, Technology appraisal.

Source: CS

The quality of life impact of AEs was applied as a one off 'QALY penalty', with the stated disutilities equating to a reduction in QALYs gained. This confuses health state utilities with the time spent in a particular health state. Acute conditions such as diarrhoea and headache may only occur at commencement of treatment, be relatively self-limiting and wear off within a few weeks. The company's implementation of the QALY burden associated with these may therefore be reasonable. However, the chronic sequelae from acute kidney injury, hip fracture and osteoarthritis may not be adequately captured. The EAG noted that these events only occur

in the OCA and elafibranor arms (Table 56 and Table 57, section 4.2.6.7), and thus underestimation of the QALY burden of these is likely to be a conservative analysis.

As noted in section 4.2.7.3, the EAG conducted two scenarios including UTIs and fatigue as adverse events. The disutilities for these scenarios were retrieved from TA1016 (Table 62).

Table 62 Disutilities included in EAG scenarios

Adverse event	Disutility value	Source
Urinary tract infections	-0.06	TA1016
Fatigue	-0.07	

Abbreviations: EAG, External Assessment Group; TA, technology appraisal

4.2.7.4. Age and weight adjustments

General population utilities and mortality were adjusted by age as appropriate.

The starting age and weight in the economic model were 56.70 years (SD 9.7) and 71.1 kg (SD 15.3) respectively, based on the mean figures observed in the RESPONSE trial. The model did not account for the increasing weight of the population as it ages. This underestimated the cost of seladelpar in patients tolerant to UDCA as they remain longer in the PBC biomarker component of the model while on treatment.. To explore the impact of this on the ICER, the EAG conducted sensitivity analyses with starting weight at +/- 1 SD (55.8 and 86.4kg respectively)

4.2.8. Resources and costs

4.2.8.1. Drug and administration costs

In the company base case list prices were used for all treatments except seladelpar which has a confidential PAS discount. PAS discounts for comparator products are provided in the confidential appendix to this report.

The company implemented a titration of OCA dosing, doubling the dose for patients not responding adequately. UDCA dosage is weight-dependent (14 mg/kg). To minimize wastage, the company assumed use of formulations that more closely aligned with specific weights. If multiple formulations resulted in the same amount of wastage, the higher strength formulation was chosen to minimize the number of tablets a patient needs to take. All treatments are oral

therefore administration costs were excluded. The EAG agrees with the approach to costing drugs.

4.2.8.2. Health state costs

The company conducted an SLR to identify studies reporting costs associated with PBC. As only 1 of 31 studies was UK based, the company drew most resource use estimates from the previous NICE appraisals for elafibranor and OCA (TA1016[43] & TA443[35]). In the ALP health states, resource use over and above drug costs comprised blood and liver function tests, outpatient and inpatient appointments. For liver disease health states, resource use included various diagnostics, transplant, immunosuppressants and follow-up care. Quantities and costs were estimated on an annual basis except for pre-LT and LT where the costs are one-off before being recalculated to the cycle length (3 months except for cycles 1 and 2 of the model). The EAG considered the company's approach reasonable.

4.2.8.3. Adverse event resource use and costs

Pruritus

Patients experiencing pruritus were assumed to incur outpatient contacts and blood test monitoring, plus treatment with either colestyramine, rifampicin, naltrexone, gabapentin or bezafibrate. Proportions were based on those used in the NICE appraisal for elafibranor.[43] The EAG noted that treatments for pruritus were assumed the same irrespective of severity, the only resource use difference was an increased frequency of outpatient contacts and blood tests for severe pruritus. In the absence of data to the contrary, the EAG considered this approach reasonable.

Other AEs

Costs for adverse events were sourced from the National Schedule of Reference costs 2022/23.[44] The EAG considered the costs applied to be appropriate.

As mentioned in Section 4.2.7.3, the EAG included a scenario including urinary tract infections and fatigue as adverse events. For UTI the EAG included a one-off GP consultation and a 3-day course of trimethoprim. For fatigue the EAG assumed a GP consultation.

Table 63 Adverse event unit costs

Adverse event	Mean	Source
Urinary tract infections	£49 + £0.78 = £49.78	PSSRU. Unit Costs of Health and Social care 2023. Unit costs for a GP. Per surgery consultation lasting 10 minutes. BNF, 28x100mg trimethoprim, representative cost
Fatigue	£49	PSSRU. Unit Costs of Health and Social care 2023. Unit costs for a GP. Per surgery consultation lasting 10 minutes.

Abbreviations: BNF, British National Formulary; GP, general practitioner; NHS, national health services, PSSRU, Personal Social Services Research Unit

4.2.8.4. End of life costs

End-of-life care costs for DCC and HCC patients are included to account for additional resource use in the final months of life. The cost upon death is £10,902 for DCC and £8,805 for HCC, based on studies by Gola et al. [45] (in which costs reflect hospitalisation expenses for end-stage liver disease patients in the UK) and NICE TA666.[46] Both the approach and the costs are in line with TA1016. The EAG agrees with the approach.

4.2.9. Uncertainty

The company conducted a Probabilistic Sensitivity Analysis (PSA) and Deterministic Sensitivity Analyses (DSA) on most variables.

In the PSA, where available the company assigned standard errors and other hyperparameters to relevant distributions appropriately from source studies. In cases where such data were not available, 10% of the base input was used as the standard error.

Overall, the EAG considered this approach to be appropriate but noted that as described in section 4.2.6.1, uncertainty in the network meta-analyses was not carried through into uncertainty in the decision model. The EAG observed that this would not be straightforward due to the method used to estimate the calibration HRs. However, the EAG considered an SE of 10% of the mean assigned to the calibration HRs did not reflect the uncertainty in the credibility intervals around the underlying RR and OR distributions, preferring a SE equal to the mean.

The company's PSA comprised 250 simulations, stating this was sufficient to achieve convergence (Section 3.11.1 of CS). The EAG re-ran the PSA three times and noted the pairwise ICER between seladelpar+UDCA and OCA+UDCA varied by around 20%, which the EAG did not consider represented stable results (i.e. insufficient simulations to minimise Monte

Carlo error). Exploratory analyses undertaken by the EAG found that 2000 iterations reduced the range to around 5% and therefore increased the simulations to 2000.

5. COST-EFFECTIVENESS RESULTS

5.1. Company's cost-effectiveness results

The results presented in this report incorporate a PAS discount for the technology of interest and list prices for all comparator treatments. This report is accompanied by a confidential appendix that reports the results of the analyses when confidential prices for comparator treatments are included.

5.1.1. Base case results

The results reported by the company are in Table 64 and Table 65 below. In the deterministic results seladelpar dominated other treatments for both the UDCA tolerant and UDCA intolerant populations. In the probabilistic analyses, seladelpar also dominated elafibranor in both populations and was of borderline cost-effectiveness versus OCA. The EAG noted a small number of errors in coding for the probabilistic analyses and refers readers to the EAG corrected company base case (section 6.1) for further discussion of these.

Table 64: Company base case results (UDCA tolerant population)

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER incremental (£/QALY)	INHB at £20,000
Deterministic results								
Seladelpar + UDCA	[redacted]	[redacted]	[redacted]	-	-	-	-	
OCA + UDCA	384,110	15.458	9.432	[redacted]	[redacted]	[redacted]	Dominated	
Elafibranor + UDCA	445,408	15.503	9.857	[redacted]	[redacted]	[redacted]	Dominated	
Probabilistic results*								
Seladelpar + UDCA	[redacted]	[redacted]	[redacted]	-	-	-	-	
OCA + UDCA	385,485	15.459	13.03	[redacted]	[redacted]	[redacted]	17,714	-0.018
Elafibranor + UDCA	447,750	15.532	12.76	[redacted]	[redacted]	[redacted]	Dominated	3.361

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

Source: tables 83 and 87 of the CS. *Error in company probabilistic results. See section 6.1.

Table 65 Company base case results (UDCA intolerant population)

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER incremental (£/QALY)	INHB at £20,000
Deterministic results								
Seladelpar	[redacted]	[redacted]	[redacted]					

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER incremental (£/QALY)	INHB at £20,000
OCA	369,860	15.5	9.414	[redacted]	[redacted]	[redacted]	Dominated	1.196
Elafibranor	430,967	15.5	9.903	[redacted]	[redacted]	[redacted]	Dominated	3.763
Probabilistic results*								
Seladelpar	[redacted]	[redacted]	[redacted]	-	-	-	-	-
OCA	373,664	15.582	13.203	[redacted]	[redacted]	[redacted]	18,949	-0.014
Elafibranor	435,496	15.654	12.878	[redacted]	[redacted]	[redacted]	Dominated	3.403

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

Source: tables 84 and 88 of the CS.

*Error in company probabilistic results. See section 6.1.

5.2. Company's sensitivity analyses

5.2.1. Deterministic sensitivity analyses

One-way sensitivity analyses were conducted on a wide range of variables as well as a number of scenario analyses. Overall, the results were most sensitive to assumptions around the disutility and incidence of pruritus (mild, moderate and severe), and discontinuation rates for each treatment.

5.2.2. Probabilistic sensitivity analysis

The company submitted a fully incremental probabilistic cost-effectiveness analysis, covering both the population tolerant to UDCA and the population intolerant to UDCA. The company stated that the analysis was conducted over 250 iterations. The EAG noted a substantial difference between the probabilistic and deterministic results. This was due to a coding error (see section 6.1).

Figure 34 and 35 of the CS show seladelpar ± UDCA had a 54-51% probability (UDCA-tolerant) and a 54-52% probability (UDCA-intolerant) of being the most cost-effective treatment at NICE's willingness-to-pay (WTP) corridor of £20K-£30K per QALY. Elafibranor had a 0% probability of being the most cost-effective treatment at these thresholds in both populations.

5.3. Model validation and face validity check

According to the company, the model was validated through targeted interviews with clinical experts and one economist at the conceptualisation, calculation and output phases. The EAG considered the approaches to be valid, however disagreed with some of the company's modelling decisions and noted a few small errors in the coding as explored in section 6 below.

6. EXTERNAL ASSESSMENT GROUP'S ADDITIONAL ANALYSES

The EAG identified a number of limitations within the company's base case and explored the impact of parameter values, and assumptions, which the EAG believed were more plausible.

This section is organised as follows: Section 6.1 details the impact of errors identified in the EAG's validation of the executable model. Section 6.2 provides a summary of the alternative assumptions explored by the EAG to test the robustness of the cost-effectiveness results to specific assumptions and additional uncertainties identified by the EAG. Section 6.3 presents the EAGs base case, which represents what the EAG consider to be the most plausible and methodologically sound approach to assessing cost-effectiveness, based on NICE's reference case. Section 6.4 presents the impact of scenario analyses conducted to explore uncertainty within the EAG base case.

6.1. EAG corrections and adjustments to the company's base case model

The EAG identified a small number of errors in the company's model. These were all related to the probabilistic analysis and so do not affect the deterministic base case:

- Literature-based pruritus disutilty profiles (i.e., the Smith et al., profile) were coded as positive rather than negative numbers
- Standard deviations were used in place of standard error to estimate the uncertainty in disutility associated with pruritus in the Smith et al. 2022 disutilities.
- The Company's PSA comprised only 250 iterations and stated that this was sufficient to reach convergence. However, the EAG's explorations disagreed with this and increased the simulations to 2000.
- The Company's model used a VBA coded function for sampling from the Dirichlet distribution. This created errors when the EAG attempted to replicate the analysis. The EAG therefore substituted this for the dirich() function from the SimTools addin from the University of Chicago.[47] This code also substantially increased the speed of probabilistic analysis (due to the nature of the issue it was not possible to apply this as a reversible edit to the Company's model).

Table 66: EAG-corrected company base case results: UDCA-tolerant population

Scenario	Treatment	Disc costs	Disc QALYs	Inc costs	Inc QALYs	ICER £/QALY	+/- company base case
Deterministic analysis							
Company base case	Seladelpar + UDCA	[redacted]	[redacted]	-	-	-	
	OCA + UDCA	384,110	9.432	[redacted]	[redacted]	Dominated	
	Elafibranor + UDCA	445,408	9.857	[redacted]	[redacted]	Dominated	
EAG corrected company base case	Seladelpar + UDCA	[redacted]	[redacted]	-	-	-	
	OCA + UDCA	384,110	9.432	[redacted]	[redacted]	Dominated	0%
	Elafibranor + UDCA	445,408	9.857	[redacted]	[redacted]	Dominated	0%
Probabilistic analysis							
Company base case	Seladelpar + UDCA	[redacted]	[redacted]				
	OCA + UDCA	384,250	13.046	[redacted]	[redacted]	37,182	
	Elafibranor + UDCA	445,902	12.838	[redacted]	[redacted]	Dominated	
EAG corrected company base case	Seladelpar + UDCA	[redacted]	[redacted]		-	-	
	OCA + UDCA	386,285	9.476	[redacted]	[redacted]	Dominated	Switch to Dom'd
	Elafibranor + UDCA	448,673	9.922	[redacted]	[redacted]	Dominated	NA

Abbreviations: disc, discounted; EAG, external assessment group; inc, incremental; QALYs, quality adjusted life years

Table 67: EAG-corrected company base case results: UDCA-intolerant population

Scenario	Treatment	Disc costs	Disc QALYs	Inc costs	Inc QALYs	ICER £/QALY	+/- company base case
Deterministic analysis							
Company base case	Seladelpar	[redacted]	[redacted]	-			
	OCA	369,860	9.414	[redacted]	[redacted]	Dominated	

	Elafibranor	430,967	9.903	[redacted]	[redacted]	Dominated	
EAG corrected company base case	Seladelpar	[redacted]	[redacted]	-			
	OCA	369,860	9.414	[redacted]	[redacted]	Dominated	0%
	Elafibranor	430,967	9.903	[redacted]	[redacted]	Dominated	0%
Probabilistic analysis							
Company base case	Seladelpar	[redacted]	[redacted]				
	OCA	374,864	13.212	[redacted]	[redacted]	25,738	
	Elafibranor	437,070	12.946	[redacted]	[redacted]	Dominated	
EAG corrected company base case	Seladelpar	[redacted]	[redacted]				
	OCA	373,347	9.504	[redacted]	[redacted]	Dominated	Change to Dom'd
	Elafibranor	435,819	10.037	[redacted]	[redacted]	Dominated	NA

Abbreviations: disc, discounted; EAG, external assessment group; inc, incremental; QALYs, quality adjusted life years

6.2. Exploratory and sensitivity analyses undertaken by the EAG

The EAG identified several limitations within the company's base case and explored the impact of parameter values and assumptions which the EAG believed were more plausible. These analyses were conducted within the company corrected base-case analysis (section 6.1), with the exception of inclusion of fibrates as a comparator. The EAG was not able to formally include fibrates within the company's model. Instead the likely impact of inclusion is discussed in section 6.4.1.

Results are presented first for the patient population tolerant to UDCA, then for the UDCA-intolerant population. A summary of the EAG changes and the corresponding sections in the report where they were discussed is provided in Table 68.

Table 68 EAG changes and corresponding sections

Change	Section
ALP normalisation £ and utility set equal to mild ALP elevation	4.2.2
Patients enter model only in high ALP levels or CC/elevated bilirubin*	4.2.3
Bayesian NMA as source of relative treatment effect for all comparators*	4.2.6.1
Increased mortality post liver transplant	4.2.6.3
Discontinuation 0-12m based on ITC*	4.2.6.4

Change	Section
Use RESPONSE and ASSURE data for seladelpar discontinuation at 12m+*	4.2.6.4
Same incidence of AEs in UDCA tolerant and intolerant populations	4.2.6.7
Inclusion of UTI and fatigue as adverse events	4.2.6.7, 4.2.7.3, 4.2.8.3
Use of MMRM2 model for pruritus disutility*	4.2.7.1
Starting weight +/- 1 SD	4.2.7.4
Uncertainty in calibration HRs set equal to mean, not 10%*	4.2.9
Transitions for which zero observed data	4.2.9

Abbreviations: AE, adverse event; ALP, Alkaline phosphatase; EAG, External Assessment Group; MMRM, Mixed model for repeated measures; SD, standard deviation; UDCA, Ursodeoxycholic acid; UTI, urinary tract infection.

* denotes EAG base case

6.3. EAG's preferred assumptions

The EAG's preferred assumptions for the analysis are:

- No patients enter the model in the ALP normalisation or mild elevation states.
- Use of calibration HRs drawn from the Bayesian NMA with outcome recalculation and with Turner prior for relative treatment effect (ALP normalisation and Mild ALP elevation) of seladelpar vs elafibranor and vs OCA
- Discontinuation 0-12m based on ITC
- Discontinuation 12m+ based on RESPONSE & ASSURE
- Use of MMRM2 mapping algorithm to map from RESPONSE PBC-40 data to EQ-5D-3L for ALP health states and pruritus severity.

6.3.1. Population of those tolerant to UDCA

The EAG preferred base case (probabilistic) ICER is £76,925 (Table 69).

Key drivers of the results were the use of the ITC results to estimate discontinuation and the use of disutilities for pruritus from the MMRM2 mapping algorithm rather than Smith et al. 2022.[38]

Table 69: EAG's preferred model assumptions, UDCA-tolerant

Section in EAG report	Preferred Assumption	Treatment	Total costs (£)	Total QALYs	Incremental ICER	NHB	+/- corrected base case
	EAG Corrected Company Base Case	Seladelpar + UDCA	[redacted]	[redacted]	-	-8.72	0.00
		OCA + UDCA	£384,110	9.43	Dominated	-9.77	0.00
		Elafibranor + UDCA	£445,408	9.86	Dominated	-12.41	0.00
4.2.3	No patients in the normal or mild state at model start	Seladelpar + UDCA	[redacted]	[redacted]	-	-8.73	0.01
		OCA + UDCA	£383,750	9.42	Dominated	-9.77	0.00
		Elafibranor + UDCA	£444,687	9.82	Dominated	-12.41	0.00
4.2.6.1	Bayesian NMA for calibration HRs	Seladelpar + UDCA	[redacted]	[redacted]	-	-8.72	0.00
		OCA + UDCA	£383,493	9.40	Dominated	-9.77	0.00
		Elafibranor + UDCA	£448,801	9.98	Dominated	-12.46	0.05
4.2.6.4	Discontinuation 0-12m	OCA + UDCA	£322,082	9.12	-	-6.99	-2.79
		Seladelpar + UDCA	[redacted]	[redacted]	£50,975	-8.72	0.00
		Elafibranor + UDCA	£439,170	9.83	Dominated	-12.13	-0.28
4.2.6.4	Discontinuation 12m+	Seladelpar + UDCA	[redacted]	[redacted]	-	-10.52	1.79
		OCA + UDCA	£421,730	9.55	Dominated	-11.53	1.76
		Elafibranor + UDCA	£491,809	9.99	Dominated	-14.60	2.18
4.2.7.1	Pruritus disutilities from MMRM2	Seladelpar + UDCA	[redacted]	[redacted]	-	-7.46	-1.27
		OCA + UDCA	£384,110	11.13	Dominated	-8.07	-1.70
		Elafibranor + UDCA	£445,408	11.25	Dominated	-11.02	-1.39
4.2.9	set the SE of the calibration HRs	Seladelpar + UDCA	[redacted]	[redacted]	-	-8.72	0.00

Section in EAG report	Preferred Assumption	Treatment	Total costs (£)	Total QALYs	Incremental ICER	NHB	+/- corrected base case
	equal to the mean HR from RR	OCA + UDCA	£384,110	9.43	Dominated	-9.77	0.00
		Elafibranor + UDCA	£445,408	9.86	Dominated	-12.41	0.00
Cumulative impact of EAG base case		OCA + UDCA	£351,028	10.83	-	-6.72	-3.05
		Seladelpar + UDCA	[redacted]	[redacted]	£84,574	-9.26	0.54
		Elafibranor + UDCA	£488,235	11.46	Dominated	-12.95	0.54
Cumulative impact of EAG base case (probabilistic analysis)		OCA + UDCA	328,900	10.14	-	-6.30	3.47
		Seladelpar + UDCA	[redacted]	[redacted]	77,783	-8.71	0.01
		Elafibranor + UDCA	458,258	10.78	Dominated	-12.13	0.28

Abbreviations: disc, discounted; EAG, external assessment group; inc, incremental; QALYs, quality adjusted life years. NHB, net health benefit.

Note: NHB calculated at £20,000 per QALY.

6.3.2. Population of those intolerant to UDCA

The EAG preferred base case (probabilistic) ICER is £74,833 (Table 70).

Key drivers of the results were the same as for the UDCA-tolerant population: the use of the ITC results to estimate discontinuation and the use of disutilities for pruritus from the MMRM2 mapping algorithm rather than Smith et al. 2022.

Table 70: EAG's preferred model assumptions, UDCA-intolerant

Section in EAG report	Preferred Assumption	Treatment	Total costs (£)	Total QALYs	Incremental ICER	NHB	+/- corrected base case
	EAG Corrected Company Base Case	Seladelpar	[redacted]	[redacted]	-	-7.88	0.00
		OCA	£369,860	9.41	Dominated	-9.08	0.00
		Elafibranor	£430,967	9.90	Dominated	-11.65	0.00
4.2.3	No patients in the normal or	Seladelpar	[redacted]	[redacted]	-	-7.89	0.01
		OCA	£369,521	9.40	Dominated	-9.08	0.00

Section in EAG report	Preferred Assumption	Treatment	Total costs (£)	Total QALYs	Incremental ICER	NHB	+/- corrected base case
	mild state at model start	Elafibranor	£430,287	9.87	Dominated	-11.64	0.00
4.2.6.1	Bayesian NMA for calibration HRs	Seladelpar	[redacted]	[redacted]	-	-7.88	0.00
		OCA	£369,279	9.39	Dominated	-9.08	0.00
		Elafibranor	£434,205	10.02	Dominated	-11.69	0.04
4.2.6.4	Discontinuation 0-12m	OCA	£308,522	9.06	-	-6.36	-2.72
		Seladelpar	[redacted]	[redacted]	£43,923	-7.88	0.00
		Elafibranor	£424,789	9.87	Dominated	-11.37	-0.27
4.2.6.4	Discontinuation 12m+	Seladelpar	[redacted]	[redacted]	-	-9.62	1.74
		OCA	£407,151	9.56	Dominated	-10.80	1.72
		Elafibranor	£477,058	10.07	Dominated	-13.78	2.14
4.2.7.1	Pruritus disutilities from MMRM2	Seladelpar	[redacted]	[redacted]	-	-6.71	-1.17
		OCA	£369,860	11.12	Dominated	-7.38	-1.70
		Elafibranor	£430,967	11.24	Strictly Dominated	-10.31	-1.34
4.2.9	set the SE of the calibration HRs equal to the mean HR from RR	Seladelpar	[redacted]	[redacted]	-	-7.88	0.00
		OCA	£369,860	9.41	Dominated	-9.08	0.00
		Elafibranor	£430,967	9.90	Dominated	-11.65	0.00
Cumulative impact of EAG base case		OCA	£337,231	10.81	-	-6.05	-3.03
		Seladelpar	[redacted]	[redacted]	£80,883	-8.50	0.62
		Elafibranor	£473,422	11.46	Strictly Dominated	-12.21	0.57
Cumulative impact of EAG base case (probabilistic analysis)		OCA	339,592	10.936	-	-6.04	3.04
		Seladelpar	[redacted]	[redacted]	76,937	-8.52	-0.64
		Elafibranor	478,137	11.615	Dominated	-12.29	-0.65

Abbreviations: EAG, External Assessment Group; ICER, incremental cost-effectiveness ratio; QALY, quality adjusted life year

6.4. EAG scenario analyses

Exploratory analyses (Table 71 & Table 72) were conducted individually on top of the EAG base case. The model was insensitive to all scenarios considered.

Table 71: EAG's scenarios, UDCA-tolerant (deterministic, except for unobserved transitions)

Section in EAG report	Preferred Assumption	Treatment	Total costs (£)	Total QALYs	Incremental ICER	NHB	+/- EAG base case
	EAG Base Case	OCA + UDCA	£351,028	10.83	-	-6.72	0.00
		Seladelpar + UDCA	[redacted]	[redacted]	£84,574	-9.26	0.00
		Elafibranor + UDCA	£488,235	11.46	Dominated	-12.95	0.00
4.2.2	ALP normalisation Cost and Utility set to same as mild	OCA + UDCA	£351,149	10.83	-	-6.73	-0.01
		Seladelpar + UDCA	[redacted]	[redacted]	£91,356	-9.40	-0.14
		Elafibranor + UDCA	£489,732	11.43	Dominated	-13.05	-0.10
4.2.6.3	Mortality for PBC recurrence	OCA + UDCA	£345,916	10.68	-	-6.61	0.11
		Seladelpar + UDCA	[redacted]	[redacted]	£85,898	-9.12	0.14
		Elafibranor + UDCA	£481,023	11.30	Dominated	-12.75	0.19
4.2.6.7	same AEs for tolerant and intolerant group	OCA + UDCA	£351,028	10.83	-	-6.72	0.00
		Seladelpar + UDCA	[redacted]	[redacted]	£84,574	-9.26	0.00
		Elafibranor + UDCA	£488,235	11.46	Dominated	-12.95	0.00
4.2.6.7 & 4.2.7.3 & 4.2.8.3	Include AEs for urinary tract infection	OCA + UDCA	£351,031	10.83	-	-6.72	0.00
		Seladelpar + UDCA	[redacted]	[redacted]	£84,514	-9.26	0.00
		Elafibranor + UDCA	£488,238	11.46	Dominated	-12.95	0.00
4.2.6.7 & 4.2.7.3 & 4.2.8.3	Include AEs for fatigue	OCA + UDCA	£351,028	10.83	-	-6.72	0.00
		Seladelpar + UDCA	[redacted]	[redacted]	£84,736	-9.26	0.00
		Elafibranor + UDCA	£488,237	11.46	Dominated	-12.95	0.00
4.2.7.4	Starting weight 55.8kg	OCA + UDCA	£348,260	10.83	-	-6.58	0.14
		Seladelpar + UDCA	[redacted]	[redacted]	£84,376	-9.11	0.15
		Elafibranor + UDCA	£485,338	11.46	Dominated	-12.80	0.14
4.2.7.4		OCA + UDCA	£350,819	10.83	-	-6.71	0.01

Section in EAG report	Preferred Assumption	Treatment	Total costs (£)	Total QALYs	Incremental ICER	NHB	+/- EAG base case
	Starting weight 86.4kg	Seladelpar + UDCA	[redacted]	[redacted]	£84,554	-9.25	0.01
		Elafibranor + UDCA	£488,014	11.46	Dominated	-12.94	0.01

Abbreviations: EAG, External Assessment Group; ICER, incremental cost-effectiveness ratio; QALY, quality adjusted life year

Table 72: EAG's scenarios, UDCA-intolerant (deterministic, except for unobserved transitions)

Section in EAG report	Preferred Assumption	Treatment	Total costs (£)	Total QALYs	Incremental ICER	NHB	+/- EAG base case
	EAG Base Case	OCA	£337,231	10.81	-	-6.05	0.00
		Seladelpar	[redacted]	[redacted]	£80,883	-8.50	0.00
		Elafibranor	£473,422	11.46	Dominated	-12.21	0.00
4.2.2	ALP normalisation Cost and Utility set to same as mild	OCA	£337,352	10.81	-	-6.06	-0.01
		Seladelpar	[redacted]	[redacted]	£87,316	-8.64	-0.14
		Elafibranor	£474,919	11.43	Dominated	-12.32	-0.10
4.2.6.3	Mortality for PBC recurrence	OCA	£332,318	10.67	-	-5.95	0.10
		Seladelpar	[redacted]	[redacted]	£82,128	-8.37	0.13
		Elafibranor	£466,440	11.29	Dominated	-12.03	0.18
4.2.6.7	same AEs for tolerant and intolerant group	OCA	£337,987	10.82	-	-6.08	-0.03
		Seladelpar	[redacted]	[redacted]	£82,690	-8.57	-0.07
		Elafibranor	£474,536	11.46	Dominated	-12.27	-0.05
4.2.6.7 & 4.2.7.3 & 4.2.8.3	Include AEs for urinary tract infection	OCA	£337,234	10.81	-	-6.05	0.00
		Seladelpar	[redacted]	[redacted]	£80,827	-8.50	0.00
		Elafibranor	£473,424	11.45	Dominated	-12.22	0.00
4.2.6.7 & 4.2.7.3 & 4.2.8.3	Include AEs for fatigue	OCA	£337,233	10.81	-	-6.05	0.00
		Seladelpar	[redacted]	[redacted]	£80,921	-8.50	0.00
		Elafibranor	£473,424	11.46	Dominated	-12.22	0.00
4.2.7.4	Starting weight 55.8kg	OCA	£337,223	10.81	-	-6.05	0.00
		Seladelpar	[redacted]	[redacted]	£80,887	-8.50	0.00
		Elafibranor	£473,416	11.46	Dominated	-12.21	0.00

Section in EAG report	Preferred Assumption	Treatment	Total costs (£)	Total QALYs	Incremental ICER	NHB	+/- EAG base case
4.2.7.4	Starting weight 86.4kg	OCA	£337,239	10.81	-	-6.05	0.00
		Seladelpar	[redacted]	[redacted]	£80,879	-8.50	0.00
		Elafibranor	£473,427	11.46	Dominated	-12.22	0.00

Abbreviations: EAG, External Assessment Group; ICER, incremental cost-effectiveness ratio; QALY, quality adjusted life year

6.4.1. Likely impact of including fibrates as a comparator

Abbas et al.[1] reported the results of a prospective cohort study of patients referred for second line therapy within operational delivery networks (ODNs) in England. The findings were that ALP reductions in those taking fibrates were higher than those taking OCA. These results must be interpreted with caution as it is a prospective cohort study rather than a randomised controlled trial.

However, if fibrates are assumed of at least equal effectiveness to OCA, then they are likely to represent a much more cost-effective treatment for PBC than either OCA, elafibranor or seladelpar, given the list price for 100x200mg bezafibrate is approximately £8.63 (BNF 2025) and fenofibrate 28x160mg is £2.87 (Drug Tariff), whereas list prices for the OCA (30x5mg), elafibranor (30x80mg) and seladelpar (30x10mg) are £2,384, £2,867 and £3,155 respectively (BNF 2025), a 600 to 1,000 fold difference in list price.

Given this, and the EAGs base case preferred assumptions, seladelpar is likely to be cost-effective as a 4th line treatment only after failure of UDCA, fibrates and OCA.

6.5. Conclusions of the cost-effectiveness section

Under the EAG's preferred assumptions, the most plausible ICER for seladelpar + UDCA compared with OCA + UDCA was £84,574 per QALY gained in patients able to tolerate UDCA. The ICER in those unable to tolerate UDCA was similar at £80,883.

However, the EAG considers the exclusion of fibrates as a comparator to be a major limitation in the analysis. There is weak evidence to suggest fibrates are at least as effective as OCA. If this it considered to be true then neither OCA, elafibranor nor seladelpar will be cost-effective as second line options. Seladelpar is most likely cost-effective as a 4th line treatment only, after fibrates and OCA.

The key drivers of the differences between the EAG's and company's preferred ICERs are the use of the ITC to estimate discontinuation rates and the use of the MMRM2 model to estimate disutilities associated with pruritus.

7. QALY MODIFIER

The EAG agrees with the company assessment that seladelpar did not qualify for a QALY modifier due to the shortfall analysis.

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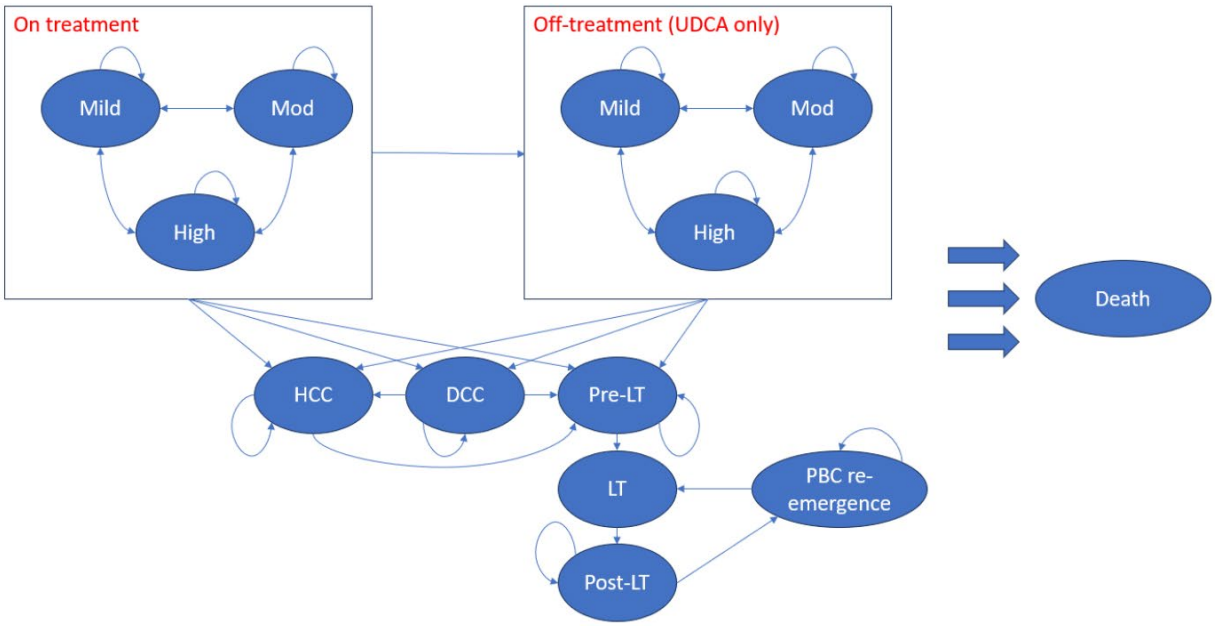
Appendix A: Model Diagrams for elafibranor and OCA

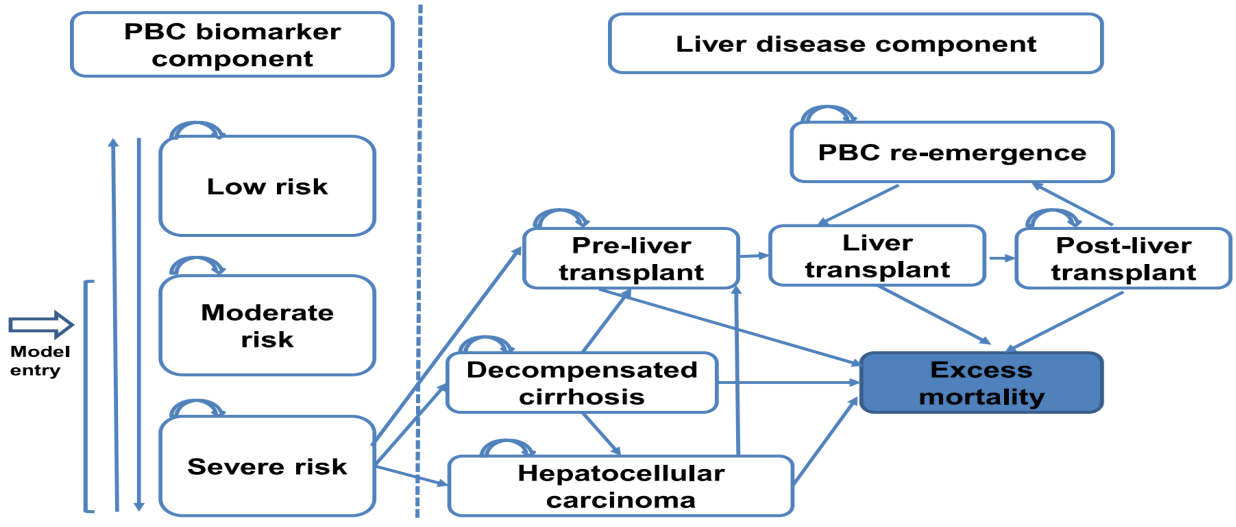
Figure 6 Elafibranor model diagram



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

Source: TA1016 committee papers

Figure 7 OCA model diagram



Source: TA443 committee papers

Seladelpar for previously treated primary biliary cholangitis [ID6429]
A Single Technology Appraisal

Addendum #1

May, 2025

Produced by	Peninsula Technology Assessment Group (PenTAG) University of Exeter Medical School
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1. INTRODUCTION

In its report, the EAG noted that discontinuation rates had a large impact on the cost effectiveness of seladelpar for the treatment of primary biliary cholangitis. This was explored in the EAG's scenario analysis and following submission of the EAG report, the EAG proposed to NICE an additional scenario analysis to draw upon real world discontinuation rates derived from a UK audit (Abbas et al. 2023).[1] This addendum presents the results of that additional scenario analysis, which assumed that all treatments were associated with the same discontinuation rate of 22.1% at 12-months.

This appendix to addendum #1 presents the results including confidential discounts for all comparator products.

2. EAG SCENARIO ANALYSIS RESULTS

The results of the scenario analysis are shown in Table 1 for the subgroup of participants who were tolerant to UDCA but did not exhibit an adequate response and Table 2 for the subgroup of participants who were intolerant to UDCA.

Table 1: UDCA tolerant subgroup

Preferred Assumption	Treatment	Total costs (£)	Total QALYs	Inc. costs (£)	Inc QALYs	ICER	NHB	+/- EAG base case
EAG Base Case	OCA + UDCA	£351,028	10.83	-	-	-	-6.72	0.00
	Seladelpar + UDCA	[redacted]	[redacted]	[redacted]	[redacted]	£84,574	-9.26	0.00
	Elafibranor + UDCA	£488,235	11.46	-	-	Dominated	-12.95	0.00
Discontinuation from Abbas (2023)	Seladelpar + UDCA	[redacted]	[redacted]	-	-	-	-5.07	1.65
	OCA + UDCA	£336,929	10.82	-	-	Dominated	-6.03	3.23
	Elafibranor + UDCA	£390,403	11.05	-	-	Dominated	-8.47	4.48

Abbreviations: EAG, External Appraisal Group; ICER, incremental cost effectiveness ratio; Inc, Incremental; QALYs, quality adjusted life years

Table 2: UDCA intolerant subgroup

Preferred Assumption	Treatment	Total costs (£)	Total QALYs	Inc. costs (£)	Inc QALYs	ICER	NHB	+/- EAG base case
EAG Base Case	OCA + UDCA	£337`231	10.81	-	-	-	-6.05	0.00
	Seladelpar + UDCA	[redacted]	[redacted]	[redacted]	[redacted]	£80,883	-8.50	0.00
	Elafibranor + UDCA	£473,422	11.46	-	-	Dominated	-12.21	0.00
Discontinuation from Abbas (2023)	Seladelpar + UDCA	[redacted]	[redacted]	-	-	-	-4.37	1.68
	OCA + UDCA	£323,190	10.80	-	-	Dominated	-5.36	3.14
	Elafibranor + UDCA	£376,349	11.04	-	-	Dominated	-7.77	4.44

Abbreviations: EAG, External Appraisal Group; ICER, incremental cost effectiveness ratio; Inc, Incremental; QALYs, quality adjusted life years

3. REFERENCES

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Single Technology Appraisal

Seladelpar for previously treated primary biliary cholangitis [ID6429]

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 **5:00pm on Monday 12 May 2025** 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 ’confidential’ should be highlighted in turquoise and all information submitted as ‘depersonalised data’ in pink.

Issue 1 Status of licence extension application for fibrates to treat PBC

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
Key Issue 1, Section 1.3 (page 16), the EAG highlights 'Finally, the EAG received advice that a licence was being sought for the use of fibrates to treat PBC (as they are currently used off-label)'. Section 2.5 (page 31), the EAG notes that 'The EAG received advice that a licence extension application for using fibrates to treat PBC was underway by NHS England, though the EAG was unable to verify this during its appraisal'.	Please update the narrative in the report to confirm that the licence extension application for using fibrates to treat PBC has been terminated due to the suspension of the Medicines Repurposing work programme, so this treatment will remain off-label.	Gilead understands that NHS England were seeking a licence variation for bezafibrate to treat PBC via the Medicines Repurposing work programme. However, in April 2025, a decision was made to suspend this programme due to a lack of repurposing opportunities, the evidence challenges of supporting licence variations, and the planned integration of NHS England into the Department of Health and Social Care (1). As a result of the suspension of the Medicines Repurposing work programme, the licence extension application for bezafibrate for PBC was terminated. Hence, the use of fibrates to treat PBC will remain off-label.	Thanks for this comment. We received the same advice about the suspension of the Medicines Repurposing programme and that the licence extension would no longer be sought, but we received this information too late to be able to amend the original report. We have now amended the text accordingly. p.16

Section 2.3 (page 28), the EAG highlights 'Those who experience an inadequate response, as defined as ALP >1.67x the upper level of normal (ULN) may receive obeticholic acid (OCA), a re-purposed therapy (i.e. fibrates), or may be considered for clinical trials.'	We propose the text should be updated to the following: 'Those who experience an inadequate response, as defined as ALP >1.67x the upper level of normal (ULN) may receive obeticholic acid (OCA), off-label therapy (i.e. fibrates), or may be considered for clinical trials	Fibrates are not officially a re-purposed therapy. As highlighted above, the licence extension for bezafibrate to treat PBC was terminated, therefore fibrates are still to be considered off-label.	Thank you for your comment. The EAG don't consider this to be a factual inaccuracy but agree that the proposed change adds clarity. p.28
Section 4.2.4 (page 117), the EAG states 'Appraisal exclusion: Fibrates were excluded in ELA and OCA appraisals and therefore its inclusion here would be inequitable to the manufacturer of seladelpar.'	No action required. Gilead appreciates the EAG's interpretation of NICE's rationale for excluding fibrates as a comparator, including that to do otherwise would be inequitable. However, the EAG then goes on to state that "the EAG considers fibrates a valid comparator". Gilead wishes to further reiterate that fibrates were not included as comparators in the appraisals of OCA and, most recently, elafibranor. NICE is obliged to follow a fair process throughout the appraisal, and applicants have a legitimate expectation that NICE will follow precedent where similar circumstances apply. As such, it would be	n/a	Thank you for this comment. As you state, this is not a factual inaccuracy. No change made.

	unreasonable for NICE follow the EAG recommendation to include fibrates as a comparator.		

Issue 2 Outdated citation used for PBC prevalence estimates in the UK

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
Section 2.2 (page 27), the EAG highlights 'In the UK, the prevalence of PBC is 25 per 100,000 of the total population, suggesting there are around 17,000 people in the UK with PBC'.	We propose that the text should be amended to the following: 'In the UK, the prevalence of PBC is 39.6 per 100,000 of the total population, suggesting there are around 20,000 people in the UK with PBC'.	The publication referenced by the EAG (Burke *et al*. [2022]) cites an outdated prevalence rate that was originally published in 1999 by James *et al*. (2). Gilead believes it would be more appropriate to utilise the most recent prevalence rate of 39.6 per 100,000 of the total population, estimated by Webb *et al*. (2021), which was provided in the company submission (3). Utilising the prevalence estimates from Webb *et al*. (2021), Gilead estimates there are around 20,000 people in the UK with PBC.	Thank you for this comment, the updated reference is much appreciated and we have edited the text as proposed. p. 27

Issue 3 Inaccurate interpretation of data from Abbas *et al*. (2024)

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
Section 2.3 (page 29), the EAG highlights 'A UK-based evaluation of routine service delivery4 found that 2nd line treatment for 50% of people with PBC was fibrates, which are an off-label treatment, as opposed to OCA.'	We propose that the text should be amended to the following: A UK-based evaluation of routine service delivery found that 50% of people with PBC with inadequate UDCA response who were prescribed 2nd line therapy received treatment with fibrates, which are an off-label treatment, as opposed to OCA.	Clarification that the proportion of patients receiving fibrates in Abbas *et* al. (2024) is in relation to patients with inadequate UDCA response who were prescribed second-line treatment	Thanks for your comment. The EAG has amended the text to clarify that those considered in this statement are those with an inadequate response to treatment, though do not consider it necessary to explain that the use of 2nd line treatment is only in those who are prescribed 2nd line treatment. p.29
Section 2.5 (page 31), the EAG states 'An audit of UK practice suggested that 50% of people with PBC receive treatment with fibrates rather than OCA, which clinical experts to the EAG advised may be due to concerns that OCA	We propose that the text should be amended to the following: An audit of UK practice suggested that 50% of people with PBC with inadequate UDCA response who were prescribed 2nd line therapy received treatment with fibrates, which clinical experts to the EAG advised may be	Clarification that the proportion of patients receiving fibrates in Abbas *et* al. (2024) is in relation to patients with inadequate UDCA response who were prescribed second-line treatment	Thanks for your comment. We have clarified that the statistic applies to those with PBC who had an inadequate response to treatment p.31

exacerbates pruritus (as opposed to a concern that fibrates would not be an appropriate treatment option)'	due to concerns that OCA exacerbates pruritus (as opposed to a concern that fibrates would not be an appropriate treatment option)		

Issue 4 Grouping of ASSURE and Phase 3 Long-Term Safety Study (CB8025-31731)

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
Section 3.2.1 (page 40), the EAG notes 'The company focussed the CS on two studies (RESPONSE and the Phase II dose-ranging study (NCT02955602) with some limited data available for the ASSURE extension study.'	The text should be amended to clarify that the Phase 3 Long-Term Safety Study (CB8025-31731) and ASSURE (CB8025-31731-RE) are considered by Gilead to be two separate studies. We propose that the text should be amended to the following: The company focussed the CS on two studies (RESPONSE and the Phase II dose-ranging study (NCT02955602) with some limited data available for the Phase 3 Long-Term Safety Study (CB8025-31731) and the ASSURE extension study.	Clarification regarding the studies included in the clinical effectiveness review	Thank you for your comment. As the Phase 3 Long-Term Safety Study (CB8025-31731) was terminated and then became ASSURE (CB8025-31731-RE) following restart, for simplicity we have referred to the whole as ASSURE and noted where data is available for the 'legacy' participants and/or the participants from RESPONSE. However, we have added a note in Section 3.2.1 to explain

			that this was our approach. p.40-41
Table 8, Section 3.2.1 (page 42), the EAG does not include the Phase 3 Long-Term Safety Study (CB8025-31731) in the table of clinical evidence for seladelpar for the treatment of PBC and evidence included in the CS	As above, the Phase 3 Long-Term Safety Study (CB8025-31731) and ASSURE (CB8025-31731-RE) are considered by Gilead to be two separate studies. Therefore, we propose that Table 8 should be updated to incorporate the Phase 3 Long-Term Safety Study.	The Phase 3 Long-Term Safety Study was identified by the clinical SLR, and evidence on efficacy and safety was provided in Sections 2.6.2 and 2.11.2.	As above, we have amended the text in Section 3.2.1 to clarify that we have merged these linked phases for simplicity. However, we have included the original trial reference in column 1 of the table entry. Table 8, p.42

Issue 5 Data availability from studies not included in the company submission

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
Section 3.2.1 (page 41), the EAG highlights 'No data were available from the other four studies, either because these were ongoing or because they were considered not	We propose the text should be amended to the following: No data were available from the other four studies for the licensed dose of seladelpar (10mg), either because these were ongoing or because they	Data is available for the Phase 2 high dose study (NCT04950764 // CB8025-21838), albeit this focused on seladelpar 50mg and 200mg. Therefore, clarification that no data was available from the other studies at the licenced	The EAG do not consider this to be a factual inaccuracy – as stated in the EAG report, data were not available from the other four studies either because they were ongoing or because they

relevant to the decision problem.'	were considered not relevant to the decision problem	dose of seladelpar is more accurate.	were not relevant to the decision problem. No change made.

Issue 6 Clarification regarding evidence from ASSURE presented in the company submission

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
Table 8, Section 3.2.1 (page 42) Row 4, Column 6, the EAG highlights 'Partially. Limited results are presented in Appendix K with additional results at clarification'	We propose the text should be amended to the following: Yes. Limited results for RESPONSE rollover patients are presented in Section 2.6.1 of the company submission. Limited results for legacy patients are presented in Appendix K. Additional results were provided at clarification.	Potentially misleading reporting of the evidence provided in the company submission	The EAG do not consider this to be a factual inaccuracy – the statement is correct as reported. No change made.
Section 3.2.2.5 (page 56), the EAG highlights 'The CS was focussed primarily on RESPONSE and the Phase II dose-ranging study, with limited outcome data from ASSURE and ENHANCE provided in appendices.'	We propose that the text should be amended to the following: The CS was focussed primarily on RESPONSE and the Phase II dose-ranging study, supplemented with limited outcome data from ASSURE (RESPONSE rollover patients). Limited outcomes data from ASSURE (legacy	Potentially misleading reporting of the evidence provided in the company submission	The EAG do not consider this to be a factual inaccuracy – the statement in the report is correct. No change made.

	patients) and ENHANCE were provided in the appendices.		

Issue 7 Reporting inaccuracies in Table 9

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
Table 9, Section 3.2.2.1 (page 45), Row 3, Column 6, the EAG note '[The company] stated that randomisation was 1:1:1 but substantially fewer patients in 5mg then 10mg arm, which was unexplained in CS.'	We propose that the text should be amended to the following: Randomisation was 1:1:1 but substantially fewer patients in 5mg then 10mg arm, which was unexplained in CS.	The clinical study report and published literature for ENHANCE confirms a 1:1:1 randomisation ratio across seladelpar treatment arms. This is also implied in Row 3, Column 4 of Table 9.	The EAG do not consider this to be a factual inaccuracy – the statement is correct. However, we have made a minor edit to improve the grammar. Table 9, p.45
Table 9, Section 3.2.2.1 (page 45), Row 3, Column 7, the EAG highlight 'Short follow-up available compared to RESPONSE, however 3-month data would be useful comparison with RESPONSE and may provide additional safety data.'	We propose that the text should be amended to the following: Short follow-up available compared to RESPONSE due to early study termination, however 3-month data would be useful comparison with RESPONSE and may provide additional safety data.	Clarification that ENHANCE was terminated early, hence follow-up was amended to Month 3 as opposed to Month 12 (as per RESPONSE).	The EAG do not consider this to be a factual inaccuracy – the statement is correct. It is stated elsewhere in the EAG report that the ENHANCE trial was terminated early. No change made.

Table 9, Section 3.2.2.1 (page 45), Row 5, Column 6, the EAG note 'Seladelpar + UDCA / Seladelpar monotherapy (crossover from RESPONSE placebo n=36, RESPONSE continuous seladelpar n=69, the legacy & CB8025-21838 group (i.e. those who had come from trials other than response, i.e. CB8025-31731 (the previous version of ASSURE before it was paused), Phase II dose-ranging study, ENHANCE, or Phase 1 pharmacokinetic study) n=174, RESPONSE placebo group n=65).'	We propose that the text should be amended throughout the report to the following: Seladelpar + UDCA / Seladelpar monotherapy (crossover from RESPONSE placebo n=36, RESPONSE continuous seladelpar n=69, the legacy & CB8025-21838 group (i.e. those who had come from trials other than response, i.e. CB8025-31731 (the previous version of ASSURE before it was paused), Phase II dose-ranging study, ENHANCE, or Phase 1 pharmacokinetic study) n=174	Incorrect reporting of parent group sample sizes	Thank you for your comment although we see no corrections in your suggested response. As stated in the EAG clarification questions, we found the CS unclear about the flow of participants through the legacy studies and into the long-term/ASSURE studies. The numbers reported in this table in the EAG report reflect the number of participants in those arms with baseline demographic data and/or exposure to seladelpar (Clarification response A5). No change made.
Table 9, Section 3.2.2.1 (page 45), Row 5, Column 6, the EAG note 'Participants entered from multiple previous trials (as profiled	We propose that the text should be amended to the following: Participants entered from multiple previous trials (as profiled below under eligibility criteria in Table 10), however	Clarification that only patients from legacy studies enrolling into ASSURE were subjected to delays of >1 year. This statement is not applicable to	The EAG do not consider this to be a factual inaccuracy – the statement is correct that 'typically' there was a

below under eligibility criteria in Table 10), however there were typically delays of >1 year between previous studies and the baseline of ASSURE.'	there were typically delays of >1 year between legacy studies and the baseline of ASSURE.	RESPONSE rollover patients.	delay of >1 year for participants entering the study. No change made.
Table 9, Section 3.2.2.1 (page 46), Row 6, Column 7, the EAG highlights '10mg and 5mg arms relevant to licence.'	We propose that the text should be amended to the following: 10mg arm relevant to licence	Clarification that seladelpar is only licenced in the 10 mg dose	Thank you for your comment, we have amended the text. p.46

Issue 8 Inaccurate reporting of clarification data request

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
Section 3.2.2.2 (page 42), the EAG highlights 'The EAG identified that a high proportion of people who were screened for participation in RESPONSE were identified as not being eligible. At clarification, the EAG asked the company to provide information on why these participants were excluded to understand	We propose that the EAG remove this statement from the report. In the set of clarification question statements received by Gilead, the company was not asked to comment on the exclusion of patients from RESPONSE at screening. It is possible that the EAG were referring to the request for information on the reasons for non-enrolment in ASSURE for all eligible participants (A5c, which was responded to in the clarification	Question was not asked by the EAG during clarification questions	Thank you for your comment. You're correct that this statement referred to ASSURE and not RESPONSE. We have amended the text. p. 47

whether the trial population would be representative of the population who would receive seladelpar in clinical practice. The company did not respond to the request for this information and this therefore is an uncertainty in the external validity of the trial.	response), in which case this statement should be amended as appropriate to highlight the request and subsequent response provided.		

Issue 9 Inaccurate reporting of baseline characteristics for ASSURE

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
Table 11, Section 3.2.2.2, Row 4, Column 6, the EAG highlights the female sex, n (%) for RESPONSE crossover patients as [redacted]	This should be correct to [redacted]	Inaccurate reporting of data	The data reported in the EAG report were correct based on the demographic data provided by the company at clarification (A5, Table 2). We have not amended the data as requested by the company as we're unclear from the request whether the data they provided at clarification was incorrect or whether

			they are providing data for a different analysis set. No change made.
Table 11, Section 3.2.2.2, Row 9, Column 6, the EAG highlights cirrhosis at baseline, n (%) for RESPONSE crossover patients as [redacted]	This should be corrected to [redacted]	Inaccurate reporting of data	Thanks for your comment. We had calculated the number of participants with cirrhosis as 6 based on those reported in Table 2 of the company's clarification response (A2) with Child-Pugh A (n=5) and cirrhosis with portal hypertension (n=1), however we assume that a participant is counted in both categories and the total is therefore 5. We have amended the numerator and also the percentage (i.e. to 5/36 (13.8%). p.51
Table 11, Section 3.2.2.2, Row 9, Column 8, the EAG highlights cirrhosis at baseline, n (%) for legacy	This should be corrected to [redacted]	Inaccurate reporting of data	Thank you for this comment. As per our response above, we had calculated this figure

and CB8025-21838 patients as 40/174 (23.0)			based on the total of the sub-categories of cirrhosis. We have edited the number and percentage. p.51

Issue 10 Inaccurate reporting of mortality across seladelpar PBC studies

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
Section 3.2.3.1 (page 77), the EAG states 'There were no reported deaths in RESPONSE or ENHANCE. One death was reported in the Phase II dose-ranging study and another in ASSURE: both participants who were receiving seladelpar, although the deaths were judged by the investigators to be unrelated to treatment. The death in the phase II dose-ranging study was in a participant receiving 5mg seladelpar and due to a malignant	We propose that the text should be amended to the following: There were no reported deaths in RESPONSE or ENHANCE. One death was reported in the Phase 3 Long-Term Safety Study (CB8025-31731) and another in ASSURE: both participants who were receiving seladelpar, although the deaths were judged by the investigators to be unrelated to treatment. The death in the Phase 3 Long-Term Safety Study was in a participant receiving 5mg seladelpar and due to a malignant neoplasm. The death in ASSURE was in a participant who had previously participated in a 'legacy study' of	Correction of the studies that had reported deaths	Thank you for this comment. We have amended the study reference. P.76

neoplasm. The death in ASSURE was in a participant who had previously participated in a 'legacy study' of seladelpar and was due to autoimmune haemolytic anaemia.'	seladelpar and was due to autoimmune haemolytic anaemia.		

Issue 11 Inaccurate reporting of the availability of data for the indirect treatment comparison

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
Section 3.4.1.2 (page 89), the EAG states 'The company did not justify the decision to only adjust for treatment effect modifiers when looking at efficacy and not safety.'	We propose the text should be amended to the following: The company submission did not justify the decision to only adjust for treatment effect modifiers when looking at efficacy and not safety	Safety MAIC was submitted alongside the company submission pack as part of the *Data on File – Seladelpar ITC Report* (Section 6.3.1)	Thank you for this comment. We agree that the text is potentially misleading, although do not consider that the proposed text resolves this. We have edited the text to address the issue raised. p.89

Issue 12 Incorrect characterisation of how pruritus was modelled

Description of problem	Description of proposed amendment	Justification for amendment	EAG response

Section 4.2.2 (page 115), the EAG states 'Death was possible from any health state and mild/moderate/severe pruritus could occur alongside any health state other than post-liver transplant, ALP normalisation and death.'	We propose the text should be amended to the following: Death was possible from any health state and mild/moderate/severe pruritus could occur alongside any health state other than post-liver transplant and death.	Pruritus cannot occur in the post-liver transplant state and implicitly the death state, but can occur in ALP normalisation state. Please refer to page 174 of the CS for the original statement.	Thank you for the correction. The EAG has edited the report to reflect this. p. 120

Issue 13 Clarification on model structure comparison with previous appraisals

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
Section 4.2.2 (page 115), the EAG states 'The model structure (see Figure 5) generally aligned with those used in TA1016 (elafibranor) and TA443 (OCA), except for the inclusion of the CC/EB and ALP normalisation health states in the PBC biomarker component (model diagrams from TA1016 and TA443 are available in Appendix A).'	We propose the text should be amended to the following: The model structure (see Figure 5) generally aligned with those used in TA1016 (elafibranor) and TA443 (OCA), except for the inclusion of ALP normalisation health states in the PBC biomarker component (model diagrams from TA1016 and TA443 are available in Appendix A).	The CC/EB health state is not a new addition compared to previous appraisals (TA1016 and TA443); rather, it corresponds to the high-risk health state defined in TA1016 and the severe-risk health state in TA443.	Thank you for the correction. The EAG has edited the report to reflect this. p. 120

Issue 14 Definition of insufficiently elevated ALP levels

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
Section 4.2.3 (page 117), the EAG states 'The EAG noted that 5.88% of patients had insufficiently elevated ALP levels at baseline in the RESPONSE study (>1.67xULN, Table 52).'	We propose the text should be amended to the following: The EAG noted that 5.88% of patients had insufficiently elevated ALP levels at baseline in the RESPONSE study (≤ 1.67 × ULN, Table 52).	Insufficiently elevated ALP levels should be defined as ≤ 1.67 × ULN.	Thank you for the correction. The EAG has edited the report to reflect this. p. 122

Issue 15 ITC calibration

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
Section 4.2.6.1 (page 121), the EAG states ' 2 The EAG was unable to match the RR and ORs used in the decision model (row "effect", Table 47 of the CS) to results presented in the ITC.' And 'With respect to issue two, the EAG considered it possible that the ORs were calculated by calibrating to the RRs. That is, the	Gilead highlights that the ORs were not calibrated from RRs as speculated by the EAG, Instead, in the original Company CEM, the model used the OR and RR from a previous analysis for elafibranor. Specifically: • **ALP normalisation**: Unanchored MAIC estimates used in the original CEM vs. the anchored MAIC (four effect modifiers)	An updated company base-case with updated ITC inputs has been provided in Appendix A and additional results from the ITC in an ITC report addendum. We have provided a correction directly in the EAG model.	Thank you for the correction. The text has been updated accordingly, and results now reflect the company base case with the updated data. p. 126

company may have calculated a calibration HR using the RR, then back calculated ORs that generate (approximately) the same calibration HR. The advantage of odds over risks (probabilities) is that relative risks may generate probabilities outside the range [0-1]. Converting probabilities to odds and working with odds ratios before reconverting to probabilities always generates logically possible values. Nevertheless, confirmation of the provenance of the ORs would be required from the company.'	being presented as the primary analysis in the clinical section / ITC report • **Toronto I criteria**: Anchored MAIC with adjustment for two effect modifiers used in original CEM vs. anchored MAIC with adjustment for four effect modifiers being presented as the primary analysis in the clinical section / ITC report		

Issue 16 Inaccuracies in the quoted discontinuation values

<table>
<tr><th>Description of problem</th><th>Description of proposed amendment</th><th>Justification for amendment</th><th>EAG response</th></tr>
<tr>
<td>Section 4.2.6.4 (page 124), the EAG presents the following table of discontinuation at 12m (UDCA tolerant and intolerant) from the company base-case and updated results based on ITC analysis (table 54):</td>
<td>We propose that the numbers in the table should be amended to:
<table>
<tr><th></th><th>Seladelpar</th><th>Elafibranor</th><th>OCA</th></tr>
<tr><td>Company base case</td><td>6.73%</td><td>9.59%</td><td>9.59%</td></tr>
</table>
</td>
<td>We noted several inaccuracies in the quoted discontinuation values in table 54 from both the company base-case and updated results</td>
<td>Thank you for the correction. The EAG has edited the report to reflect this. It</td>
</tr>
</table>

	Seladelpar	Elafibranor	OCA
Company base case	6.73%	18.34%	9.59%
ITC	6.73%	26.97%	19.37%

ITC	6.73%	11.02%	26.95%

based on ITC analysis. Specifically, the percentage of discontinuation at month 12 for elafibranor in the company base-case and results using ITC for elafibranor and OCA. These numbers could not be replicated with the original Company model submitted (for company base-case) and the updated EAG model (for updated results with ITC). We therefore believe the misquoted numbers in the table to be errors and propose the updated numbers for correction.

should be noted that the EAG economic results were not affected by this error.

p. 130

Issue 17 Clarification on discontinuation table

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
Section 4.2.6.4 (page 124), the EAG states 'The EAG compared the implied discontinuation rates at 12 months generated by the model under the company's base case and noted that the discontinuation rates from the ITC were significantly higher for the comparators than those calculated from the individual trials (Table 54) .'	We propose that the text should be amended to the following: The EAG compared the implied 12-month discontinuation rates generated by the model under the company's base case and noted that the discontinuation rates derived from the ITC were significantly higher for the comparators than those based on individual trials, leading to substantially higher percentages of patients discontinuing at month 12 (Table 54).	Further clarification is needed, as Table 54 does not present the discontinuation rates from the company's base case or the ITC analysis. Instead, it shows the percentage of patients who discontinue at month 12, conditional on survival.	Thank you for the correction. The EAG has edited the report to reflect this p.129
Table 54, Section 4.2.6.4 (page 124), the table is titled as ' Discontinuation at 12m (UDCA tolerant and intolerant)'	We propose that table 54 should be re-titled to: Cumulative discontinuation at 12m (UDCA tolerant and intolerant)	As above.	Thank you for the correction. The EAG has edited the report to reflect this. p. 130

Issue 18 Further clarification on underestimates of the cost of seladelpar

Description of problem	Description of proposed amendment	Justification for amendment	EAG response

Section 4.2.7.4 (page 132), the EAG states 'This underestimates the cost of seladelpar in patients tolerant to UDCA as they remain longer in the PBC biomarker component of the model'	We propose that the text should be amended to the following: This underestimates the cost of seladelpar in patients tolerant to UDCA as they remain longer in the PBC biomarker component of the model **while on treatment**.	Further clarification is needed, we propose to add 'while on treatment' to the sentence to make the statement more accurate.	Thank you for your comment. Whilst the EAG does not consider this a factual inaccuracy we have implemented the suggested change as it may provide further clarity. p.137

Issue 19 Incorrect characterisation of liver disease health states

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
Section 4.2.8.2 (page 133), the EAG notes 'For liver failure health states, resource use included various diagnostics, transplant, immunosuppressants and follow-up care.'	We propose that the text should be amended to the following: For liver disease health states, resource use included various diagnostics, transplant, immunosuppressants and follow-up care.	Incorrect characterisation of liver disease health states	Thank you for the correction. The EAG has edited the report to reflect this. p.138

Issue 20 Clarification on the Company's costing approach

Description of problem	Description of proposed amendment	Justification for amendment	EAG response

Section 4.2.8.2 (page 133), the EAG notes 'Quantities and costs were estimated on an annual basis, before being recalculated to the cycle length (3 months except for cycles 1 and 2 of the model).'	We propose that the text should be amended to the following: Quantities and costs were estimated on an annual basis except for pre-LT and LT where the costs are one-off, before being recalculated to the cycle length (3 months except for cycles 1 and 2 of the model).	Proposed text more accurately reflects the Company's costing approach.	Thank you for your comment, whilst the EAG does not consider this to be a factual inaccuracy, we made the suggested amendment to the text as this may provide additional clarity. p.138

Issue 21 Inadequate specificity on how disutilities are coded in the PSA

Description of problem	**Description of proposed amendment**	**Justification for amendment**	**EAG response**
Section 6.1 (page 140), the EAG notes 'Disutilities due to pruritus were coded as positive rather than negative numbers.'	We propose that the text should be amended to the following: 'Literature-based pruritus disutilty profiles (i.e., the Smith et al., profile) were coded as positive rather than negative numbers'	There are several options of pruritus disutilty profiles (including literature-based profiles and MMRM-based profiles) in the model. The EAG's statement only applies to the literature-based pruritus disutilty profiles (i.e., the Smith et al., profile) and this should be clarified.	Thank you for the correction. The EAG has edited the report to include the suggested wording. p.145

Issue 22 Incorrect interpretation of the MMRM pruritus disutility sampling implementation and incorrect sampling method in the EAG model

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
Section 6.1 (page 140), the EAG notes 'Disutilities for pruritus from the MMRM analyses were not varied in the PSA'	We propose to remove the statement.	The statement is incorrect. The original model varied the coefficients of the mapping models, thereby implicitly varying the disutilities for pruritus in the PSA. In addition, we would like to highlight the original approach is more appropriate than the approach implemented in the EAG model, which varies disutilities for pruritus from MMRM independently with an assumed 10% SE.	Thank you for your comment. The EAG accepts the company's clarification and have removed this correction from the EAG's analysis. p.145

Issue 23 Modelling error in EAG base-case results

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
Section 6.3.1, table 69 (page 145), the EAG presented the results of cumulative impact of EAG base case (UDCA-tolerant):	We propose to amend the table to:	We identified an issue with the EAG model detailed as	Thank you for the correction.

OCA + UDCA	£350,432	10.797	
Seladelpar + UDCA	[redacted]	[redacted]	£81,847
Elafibranor + UDCA	£488,310	11.464	Dominated

OCA + UDCA	351,028	10.831	
Seladelpar + UDCA	[redacted]	[redacted]	£84,573
Elafibranor + UDCA	488,600	11.476	Dominated

follows: In the EAG model, the calibration factors were hard coded in EAG's preferred scenario (Bayesian NMA for both ELA and OCA) [Q12 to Q15 in the *EAG parameter* sheet]. After several iterations of the calibration process, we believe these calibration factors were obtained prior to the implementations of other changes aligned with EAG's base-case preferences—such as adjustments to baseline patient distribution and discontinuation rates—which would affect the calibration outcomes. These inconsistencies can

The company's description of the error is accurate. The EAG has rerun the analysis and the results approximately matched those provided by the company. The report has been updated to reflect these changes. The EAG would like to note that this calibration method yields slightly different results each time it is conducted, but the

		be observed in the *ITC_calibration* sheet in EAG's model: the 'Current values' and 'Targets' in the ITC calibration worksheet do not match. Consequently, we believe the results of the EAG base case are incorrect, as the calibration factors should have been updated to reflect all model changes. We have therefore attempted to implement EAG's preferred ITC assumptions (Bayesian NMA for both ELA and OCA) with updated calibration factors. We have provided a correction directly in the EAG model.	change in results is small and has a small impact on the overall results of the economic model.

<table>
<tr>
<td>Section 6.3.1, table 70 (page 146), the EAG presented the results of cumulative impact of EAG base case (UDCA-intolerant):
<table>
<tr><td>OCA</td><td>£336,673</td><td>10.780</td><td></td></tr>
<tr><td>Seladelpar</td><td>[redacted]</td><td>[redacted]</td><td>£78,324</td></tr>
<tr><td>Elafibranor</td><td>£473,495</td><td>11.457</td><td>Dominated</td></tr>
</table>
</td>
<td>We propose to amend the table to:
<table>
<tr><td>OCA</td><td>337,231</td><td>10.814</td><td></td></tr>
<tr><td>Seladelpar</td><td>[redacted]</td><td>[redacted]</td><td>£80,883</td></tr>
<tr><td>Elafibranor</td><td>473,422</td><td>11.456</td><td>Dominated</td></tr>
</table>
</td>
<td>As above.</td>
<td>Thank you for the correction. The EAG has rerun the analysis and the results matched those proposed by the company. The report has been updated to reflect these changes.</td>
</tr>
</table>

Issue 24 Incorrect cross-references within the report

Description of problem	**Description of proposed amendment**	**Justification for amendment**	**EAG response**
Table 7, Section 3.1 (page 40), the EAG notes 'Indirect treatment comparisons were used due to the lack of head-to-head data comparing seladelpar, OCA	We propose that the text should be amended to the following: Indirect treatment comparisons were used due to the lack of head-to-head data comparing seladelpar, OCA and elafibranor. These are critiqued in section 3.4	Incorrect cross-reference.	Text updated (on page 40) with correct cross-reference.

and elafibranor. These are critiqued in section 0.’			
Section 3.2.2.4 (page 56), the EAG highlights ‘None of the studies that evaluated seladelpar included a direct comparison with any of the other treatments available for PBC in the proposed position in the treatment pathway. In order to provide a comparison to elafibranor and OCA, an indirect treatment comparison was conducted by the company, which is critiqued in Section 0.’	We propose that the text should be amended to the following: None of the studies that evaluated seladelpar included a direct comparison with any of the other treatments available for PBC in the proposed position in the treatment pathway. In order to provide a comparison to elafibranor and OCA, an indirect treatment comparison was conducted by the company, which is critiqued in Section 3.4	Incorrect cross-reference.	Text updated (on page 56) with correct cross-reference.
Section 3.4.2.6 (page 105), the EAG highlights ‘As noted at the beginning of Section 0, the company determined that the transitivity assumption was violated between the RESPONSE and ELATIVE trials, due to differences in baseline bilirubin levels and	We proposed the text should be amended to the following: As noted at the beginning of Section 3.4, the company determined that the transitivity assumption was violated between the RESPONSE and ELATIVE trials, due to differences in baseline bilirubin levels and the proportion of participants with cirrhosis.	Incorrect cross-reference.	Text updated (on page 105) with correct cross-reference.

the proportion of participants with cirrhosis.'			
Section 4.2.6 (page 119), the EAG states 'Transition probabilities (TPs) for comparators (OCA and elafibranor) were drawn from relative risks and odds ratios estimated from the ITC (see section 0 for more information on the ITC).'	We propose the text should be amended to the following: Transition probabilities (TPs) for comparators (OCA and elafibranor) were drawn from relative risks and odds ratios estimated from the ITC (see section 3.4 for more information on the ITC).	Incorrect cross-reference.	Text updated (on page 119) with correct cross-reference.

Issue 25 Typographical errors

Description of problem	**Description of proposed amendment**	**Justification for amendment**	**EAG response**
Table 8, Section 3.2.1 (page 42), Row 2, Column 4	Suggested to correct to: Seladelpar 10mg or 5mg	Typographical error	Typographical error in Table 8 corrected
Table 8, Section 3.2.1 (page 42), Row 3, Column 4	Suggested to correct to: Seladelpar 10mg or 5mg	Typographical error	Typographical error in Table 8 corrected
Table 8, Section 3.2.1 (page 42), Row 4, Column 4	Suggested to correct to: Seladelpar 10mg or 5mg	Typographical error	Typographical error in Table 8 corrected

Table 8, Section 3.2.1 (page 43), Row 8, Column 3	Suggested to correct to: N = 41 (terminated early)	Typographical error	Typographical error in Table 8 corrected
Table 9, Section 3.2.2.1 (page 45), Row 2, Column 4	Suggested to correct to: (n=65)	Typographical error	Typographical error in Table 9 corrected
Table 9, Section 3.2.2.1 (page 46), Row 5, Column 4, the EAG highlights '(i.e. those who had come from trials other than response, i.e. CB8025-31731 (the previous version of ASSURE before it was paused), Phase II dose-ranging study, ENHANCE, or Phase 1 pharmacokinetic study)	Suggested to correct to: (i.e. those who had come from trials other than RESPONSE, i.e. CB8025-31731 (the previous version of ASSURE before it was paused), Phase II dose-ranging study, ENHANCE, or Phase 1 pharmacokinetic study)	Typographical error	Typographical error in Table 9 corrected
Table 10, Section 3.2.2.2 (page 49), Row 4, Column 3, the EAG highlights 'ALP 2:1.67 x ULN'.	Suggested to correct to: ALP ≥1.67 x ULN	Typographical error	Typographical error in Table 10 corrected
Section 3.2.3.1 (page 74), the EAG highlights 'Complete data from the fatigue domain of the PBC-	Suggested to correct to: Complete data from the fatigue domain of the PBC-40 from RESPONSE at 1, 3, 6, 9 and 12 months and from the Phase II dose-	Typographical error	Typographical error on page 73 corrected

40 from RESPONSE at 1, 3, 6, 9 and 12months and from the Phase II dose-ranging study were presented by the company at clarification.'	ranging study were presented by the company at clarification		
Section 3.2.3.1 (page 74), the EAG states 'As stated in Section 3.2.2.5, there was no MCID to determine what change in risk would be clinically meaningful at the population level, and the authoes of the risk tool suggest that a change in risk should be interpreted for each individual patient.'	Suggested to correct to: As stated in Section 3.2.2.5, there was no MCID to determine what change in risk would be clinically meaningful at the population level, and the authors of the risk tool suggest that a change in risk should be interpreted for each individual patient	Typographical error	Typographical error on page 73 corrected
Section 4.1 (page 111), the EAG states 'The company conducted a SLR to identify evidence….'	Suggested to correct to: an SLR	Typographical error	Typographical error on page 110 corrected
Section 4.1 (page 111), the EAG states 'The EAG the approach to be broadly appropriate'	Suggested to correct to: The EAG considers the approach to be broadly appropriate	Typographical error	Typographical error on page 110 corrected
Section 4.2.8.2 (page 133), the EAG states 'The company conducted a SLR	Suggested to correct to: The company conducted ~~a~~ an SLR to identify studies reporting costs associated with PBC.	Typographical error	Typographical error on page 132 corrected

to identify studies reporting costs associated with PBC.'			

Issue 26 Incorrect marking

Location of incorrect marking	Description of incorrect marking	Amended marking	EAG response
We have identified some instances where information has been marked-up when it should not be. These are described in the rows below.			
Table 9, Section 3.2.2.1 (page 46), Row 5, Column 4	Seladelpar + UDCA / Seladelpar monotherapy (crossover from RESPONSE placebo n=36, RESPONSE continuous seladelpar n=69, the legacy & CB8025-21838 group ([redacted] n=174, RESPONSE placebo group n=65)	Seladelpar + UDCA / Seladelpar monotherapy (crossover from RESPONSE placebo n=36, RESPONSE continuous seladelpar n=69, the legacy & CB8025-21838 group (i.e. those who had come from trials other than RESPONSE, i.e. CB8025-31731 (the previous version of ASSURE before it was paused), Phase II dose-ranging study, ENHANCE, or Phase 1 pharmacokinetic study)	Thank you for this comment. We have removed this mark-up. p.46

Table 10, Section 3.2.2.2 (page 48), Row 4, Column 3	[redacted]	Aged 18-75 years old with PBC Stable and recommended UDCA dose for at least 12 months or intolerant to UDCA. ALP ≥1.67 x ULN	Thank you for this comment. We have removed this mark-up.
Table 10, Section 3.2.2.2 (page 48), Row 4, Column 4	[redacted]	Advanced PBC as defined by the Rotterdam criteria (albumin below LLN AND total bilirubin above 1 x ULN) A medical condition, other than PBC, that in the investigator's opinion would confound the results Presence of clinically significant hepatic decompensation Other chronic liver diseases Inadequate response to OCA or intolerance to OCA: obeticholic acid had to be discontinued 30 days prior to screening	Thank you for this comment. We have removed this mark-up.

Table 10, Section 3.2.2.2 (page 48), Row 4, Column 4	[redacted]	No new inclusion criteria. All participants had previously participated in RESPONSE, CB8025-31731 (the previous version of ASSURE before it was paused), CB8025-21629 dose-ranging study, ENHANCE, or the CB8025-21838 pharmacokinetic study. Those from studies besides RESPONSE are called the 'Legacy & CB8025-21838' group.	Thank you for this comment. We have removed this mark-up.
Table 21, Section 3.2.3.1 (page 80), Row 8, Columns 4-6	[redacted]	0/89 (0%) | 2/89 (2.2%) | 0/87 (0%)	Thank you for this comment. We have removed this mark-up.
Table 59, Section 4.2.7.1 (page 128, Row 5-7, Column 2	[redacted]	-0.0041 -0.0041 -0.0345	Thank you for this comment. We have removed this mark-up.

Section 6.4.1 (page 149)	whereas list prices for the OCA (30x5mg), elafibranor (30x80mg) and seladelpar (30x10mg) are £2,384, £2,867 and [redacted] respectively (BNF 2025), a 600 to 1,000 fold difference in list price.	whereas list prices for the OCA (30x5mg), elafibranor (30x80mg) and seladelpar (30x10mg) are £2,384, £2,867 and £3,155 respectively (BNF 2025), a 600 to 1,000 fold difference in list price.	Thank you for this comment. We have removed this mark-up.

References

1. NHS England. Repurposing medicines in the NHS in England 2025 [Available from: https://www.england.nhs.uk/medicines-2/medicines-repurposing-programme/.
2. James OF, Bhopal R, Howel D, Gray J, Burt AD, Metcalf JV. Primary biliary cirrhosis once rare, now common in the United Kingdom? Hepatology. 1999;30(2):390-4.
3. Webb GJ, Ryan RP, Marshall TP, Hirschfield GM. The Epidemiology of UK Autoimmune Liver Disease Varies With Geographic Latitude. Clin Gastroenterol Hepatol. 2021;19(12):2587-96.

Appendix A

Original company base-case vs. updated company base-case with updated ITC inputs for elafibranor:

Treatment	Total costs (£)	Total LYs	Total QALYs	Incremental costs (£)	Incremental LYs	Incremental QALYs	ICER			
Updated company base-case										
Seladelpar + UDCA	[redacted]	[redacted]	[redacted]				-	-	-	-
OCA + UDCA	384,110	15.458	9.432				[redacted]	[redacted]	[redacted]	Dominates
Elafibranor + UDCA	451,540	15.703	10.029				[redacted]	[redacted]	[redacted]	Dominates
Original company base-case										
Seladelpar + UDCA	[redacted]	[redacted]	[redacted]				-	-	-	-

OCA + UDCA	384,110	15.458	9.432	[redacted]	[redacted]	[redacted]	Dominates
Elafibranor + UDCA	445,408	15.503	9.857	[redacted]	[redacted]	[redacted]	Dominates

Original ITC inputs in company base-case vs. updated ITC inputs (with yellow highlighting the original company base-case inputs and green indicating the updated inputs):

Endpoint/ Outcome	**ITC analysis**	**Effect Measure**	**Value**
ALP normalization	Unanchored MAIC	RR	1.37
	Anchored MAIC - Adjusted for four effect modifiers		1.66
	Unanchored MAIC	OR	-
	Anchored MAIC - Adjusted for four effect modifiers		1.77
Toronto I criteria	Anchored MAIC - Adjusted for two effect modifiers	RR	1.03

	Anchored MAIC - Adjusted for four effect modifiers		0.975
	Anchored MAIC - Adjusted for two effect modifiers	OR	1.24
	Anchored MAIC - Adjusted for four effect modifiers		1.046

ID6429 Additional information on indirect comparisons
27-06-2025

Table of Contents

Q1. Confirm the source publication from which the estimates were obtained for OCA and elafibranor

Table 1: List of studies

Treatment	Title
OCA 5-10 mg and 10mg	POISE trial: NCT01473524 [1]
Elafibranor	ELATIVE trial: NCT04526665 [2]
Seladelpar	RESPONSE trial: NCT04620733 [3]

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Q2. Provide the baseline characteristics from these publications for OCA and elafibranor, and the equivalent information for the RESPONSE population informing the indirect comparison

Table 2: Baseline characteristics

Population characteristics	ELATIVE		RESPONSE		POISE		
Group	Elafibranor 80 mg (N=108)	Placebo (N=53)	Seladelpar 10 mg (N=128)	Placebo (N=65)	OCA 5-10 mg (N=70)	OCA 10 mg (N=73)	Placebo (N=73)
Mean age, years (SD)	57.5 (8.4)	56.4 (9.3)	56.6 (10)	57 (9.2)	56 (11)	56 (11)	56 (10)
Background UDCA no. (%)	102 (94)	51 (96)	120 (93.7)	61 (93.8)	65 (93)	67 (92)	68 (93)
Female no. (%)	102 (94)	52 (98)	123 (96.1)	60 (92.3)	65 (93)	63 (86)	68 (93)
Race or ethnic group (White) no. (%)	101 (94)	46 (87)	114 (89.1)	56 (86.2)	67 (96)	70 (96)	66 (90)
Previous UDCA no. (%)	108 (100)	53 (100)	128 (100)	65 (100)	70 (100)	73 (100)	73 (100)
Baseline ALP mean U/L (SD)	321.3 (121.9)	323.1 (198.6)	314.6 (123)	313.8 (117.7)	326 (116)	316 (104)	327 (115)
Mean total bilirubin level- mg/dl (SD) ~	0.57 (0.30)	0.55 (0.29)	0.77 (0.3)	0.74 (0.3)	0.6 (0.33)	0.66 (0.39)	0.69 (0.42)
Mean total bilirubin level-µmol/liter (SD)	9.7 (5.1)	9.4 (5.0)	13.17 (5.13)	12.65 (5.13)	10.26 (5.64)	11.29 (6.67)	11.80 (7.18)
Patients with Total bilirubin level — mg/dl <ULN at baseline — no. (%)	104 (96.29)	51 (96.22)	108 (84.38)	60 (92.31)	66 (94.29)	66 (90.41)	66 (90.41)
Cirrhosis at baseline— no. (%)	9 (8.33)	7 (13.21)	18 (14.1)	9 (13.8)	13 (18.5)`	10 (13.6)`	13 (17.8)`
Mean total aspartate aminotransferase — U/liter (SD)	45.0 (24.2)	47.2 (32.8)	39.6 (16.1)	41.7 (16)	52.3 (25.3)	50.5 (31.1)	48.8 (22.4)
Mean total alanine aminotransferase — U/liter (SD)	49.3 (29.4)	50.3 (38.7)	47.4 (23.5)	48.2 (22.8)	61.6 (39)	56.3 (39.7)	56 (30.3)
Mean total γ-Glutamyltransferase — U/liter (SD)	213.3 (186.1)	220.0 (220.3)	269 (240)	287.5 (249.6)	252.8 (167)	261.1 (207.4)	309.6 (449.4)
Mean total WI-NRS/ Pruritus NRS* score (SD)	3.3 (2.8)	3.2 (2.9)	3 (2.8)*	3 (3)*	--	--	--
Mean total Liver stiffness Mean — kPa (SD)	9.9 (7.8)	10.7 (8.9)	9.8 (6.2)	8.7 (4.2)	10.7 (8.6)	11.4 (8.2)	12.7 (10.7)

~: Total bilirubin converted from µmol/liter to mg/dl or vice versa using conversion factor 17.1 as reported in the trial publications; `: Data reported in Vierling 2017 (Vierling J, Hirschfield G, Jones D, et alPTU-100 Efficacy of obeticholic acid treatment in patients with primary biliary cholangitis with cirrhosis Gut 2017;66:A100); ALP: Alkaline Phosphatase; kPa: Kilopascal; no.: Number; UDCA: Ursodeoxycholic Acid; ULN: Upper Limit of Normal; U/L: Units per Liter; WI-NRS: Worst Itch Numeric Rating Scale. ALP, bilirubin cut-offs in appendix

Q3. Provide the naïve comparison vs placebo for OCA, elafibranor showing absolute and relative effect results for the following outcomes (it would be incredibly helpful to present these data in a table alongside the equivalent data for seladelpar vs placebo from RESPONSE)

- ALP normalisation (≤ 1 ULN @ 12 months)
- ALP response (Toronto 1) at 12 months
- Composite response at 12 months
- ALP change from baseline at 12 months (and baseline values)

ALP normalisation (≤ 1 ULN @ 12 months)

Table 3: Trial level data for ALP normalisation (≤ 1 ULN @ 12 months)

ALP normalization trial level data	Active Treatment	N treatment vs PBO	Treatment response	Placebo response	Treatment vs placebo RR (95% CI)	Treatment vs placebo OR (95% CI)	RD (95% CI)
ELATIVE	Elafibranor 80 mg	108 vs 53	15%	0%	16.35 (1, 267.38)	19.09 (1.12, 324.58)	0.15 (0.08, 0.22)
POISE	OCA 5-10 mg	70 vs 73	1.4%	0%	3.13 (0.13, 75.49)	3.17 (0.13, 79.2)	0.01 (-0.01, 0.04)
	OCA 10 mg	73 vs 73	6.9%	0%	11 (0.62, 195.38)	11.8 (0.64, 217.47)	0.07 (0.01, 0.13)
RESPONSE	Seladelpar 10 mg	128 vs 65	25%	0%	33.26 (2.07, 534.58)	44.12 (2.65, 733.27)	0.25 (0.17, 0.33)
RESPONSE (ELATIVE matched ALP ULN cut-off)	Seladelpar 10 mg	128 vs 65	18%	0%	24.05 (1.48, 389.7)	29.18 (1.74, 488.6)	0.18 (0.11, 0.25)
RESPONSE (POISE matched ALP ULN cut-off)	Seladelpar 10 mg	128 vs 65	33%	0%	34.28 (2.13, 550.68)	45.95 (2.77, 763.32)	0.26 (0.18, 0.33)

ALP: Alkaline Phosphatase; OCA: Obeticholic Acid; OR: Odds Ratio; RD: Risk Difference; RR: Risk Ratio; SD: Standard Deviation; UDCA: Ursodeoxycholic Acid; ULN: Upper Limit of Normal; RESPONSE (ELATIVE matched ALP ULN cut-off): Response rates were calculated using ALP ULN cut-offs consistent with those reported in the ELATIVE and POISE trials, respectively. ALP, bilirubin cut-offs in appendix

ALP response (Toronto 1) at 12 months

Table 4: Trial level data for ALP response (Toronto 1) at 12 months

ALP response (Toronto 1)	Active treatment	N Treatment vs PBO	Treatment response	Placebo response	Treatment vs placebo RR (95% CI)	Treatment vs placebo OR (95% CI)	RD (95% CI)
ELATIVE	Elafibranor 80 mg	108 vs 53	51.9%	9.4%	5.5 (2.34, 12.91)	10.34 (3.82, 27.97)	0.42 (0.3, 0.55)
POISE	OCA 5-10 mg	70 vs 73	47.1%	16.4%	2.87 (1.62, 5.09)	4.53 (2.09, 9.86)	0.31 (0.16, 0.45)
	OCA 10 mg	73 vs 73	54.8%	16.4%	3.33 (1.91, 5.82)	6.16 (2.85, 13.33)	0.38 (0.24, 0.53)
RESPONSE	Seladelpar 10 mg	128 vs 65	65.6%	26.2%	2.51 (1.64, 3.85)	5.39 (2.78, 10.46)	0.39 (0.26, 0.53)
RESPONSE (ELATIVE matched ALP and total bilirubin ULN cut-off)	Seladelpar 10 mg	128 vs 65	77%	12.3%	4.89 (2.52, 9.5)	10.76 (4.74, 24.43)	0.48 (0.36, 0.59)
RESPONSE (POISE matched ALP and total bilirubin ULN cut-off)	Seladelpar 10 mg	128 vs 65	67.2%	26.2%	2.57 (1.68, 3.93)	5.78 (2.97, 11.24)	0.41 (0.28, 0.54)

ALP: Alkaline Phosphatase; OCA: Obeticholic Acid; OR: Odds Ratio; RD: Risk Difference; RR: Risk Ratio; SD: Standard Deviation; UDCA: Ursodeoxycholic Acid; ULN: Upper Limit of Normal; RESPONSE (ELATIVE/POISE matched ALP and total bilirubin ULN cut-off): Response (relative to matched ALP and bilirubin ULN cut-offs):

Response rates were calculated using ALP and total bilirubin ULN cut-offs consistent with those reported in the ELATIVE and POISE trials, respectively; ALP, bilirubin cut-offs in appendix

Composite response at 12 months

Table 5: Trial level data for Composite response at 12 months

Composite response	Active Treatment	N treatment vs PBO	Treatment response	Placebo response	Treatment vs placebo RR (95% CI)	Treatment vs placebo OR (95% CI)	RD (95% CI)
ELATIVE	Elafibranor 80 mg	108 vs 53	50.9%	3.8%	13.5 (3.42, 53.22)	26.46 (6.13, 114.21)	0.47 (0.36, 0.58)
POISE	OCA 5-10 mg	70 vs 73	45.7%	9.6%	4.77 (2.25, 10.08)	7.94 (3.2, 19.73)	0.36 (0.23, 0.5)
	OCA 10 mg	73 vs 73	46.6%	9.6%	4.86 (2.3, 10.24)	8.22 (3.33, 20.31)	0.37 (0.24, 0.5)
RESPONSE	Seladelpar 10 mg	128 vs 65	61.7%	20%	3.09 (1.86, 5.11)	6.45 (3.19, 13.05)	0.42 (0.29, 0.55)
RESPONSE (ELATIVE matched ALP and total bilirubin ULN cut-off)	Seladelpar 10 mg	128 vs 65	73%	6%	6.18 (2.84, 13.44)	13.05 (5.25, 32.42)	0.48 (0.37, 0.59)
RESPONSE (POISE matched ALP and total bilirubin ULN cut-off)	Seladelpar 10 mg	128 vs 65	81%	13%	3.16 (1.91, 5.24)	6.89 (3.4, 13.97)	0.43 (0.3, 0.56)

ALP: Alkaline Phosphatase; OR: Odds Ratio; RD: Risk Difference; RR: Risk Ratio; UDCA: Ursodeoxycholic Acid; ULN: Upper Limit of Normal; RESPONSE (ELATIVE/POISE matched ALP and total bilirubin ULN cut-off): Response rates were calculated using ALP and total bilirubin ULN cut-offs consistent with those reported in the ELATIVE and POISE trials, respectively ALP, bilirubin cut-offs in appendix

ALP change from baseline at 12 months (and baseline values)

Table 6: ALP levels trial data and comparison vs placebo (ALP change from baseline at 12 months (and baseline values)

Study level data	RESPONSE~		ELATIVE		POISE		
	Seladelpar 10 mg	placebo	Elafibranor 80 mg	placebo	OCA 5-10 mg	OCA 10 mg	placebo
N	128	65	108	53	70	73	73
ALP baseline score means (SD)	314.6 (123.0)	313.8 (117.7)	321.3 (121.9)	323.1 (198.6)	326 (116)	316 (104)	327 (115)
Evaluable N	114	57	94	47	64	62	70
ALP CFB at 12 months means (SD)	-133.9 (90.86)	-16.9 (88.11)	-117 (92.26)	-5.3 (93.05)	-112.5 (115.2)	-129.9 (114.96)	-14.4 (122.99)
MD (LCI, UCI) vs placebo	-117 (-145.31, -88.69)		-111.7 (-142.2, -81.2)		-98.1 (-138.43, -57.77)	-115.5 (-156.11, -74.89)	--

ALP: Alkaline Phosphatase; CFB: Change from Baseline; MD: Mean Difference; OCA: Obeticholic Acid; SD: Standard Deviation; UDCA: Ursodeoxycholic Acid; ULN: Upper Limit of Normal; ~: Matched data for ALP were not evaluated, as ALP cut-off had no impact on the change-from-baseline (CFB) in ALP levels. ALP, bilirubin cut-offs in appendix

Appendix

ALP and Bilirubin ULN cut-offs between RESPONSE, ELATIVE, and POISE trials

Table 7: ALP and Bilirubin ULN cut-offs between RESPONSE, ELATIVE, and POISE trials

ULN Cut-off	ALP ULN U/L		Bilirubin ULN micromoles/L		ALP normalization (ALP ≤1 ULN)		Composite response (ALP<1.67 ULN & ALP 15% reduction & bilirubin ≤1 ULN)	
	Female	Male	Female	Male	Female	Male	Female	Male
RESPONSE	116		18.8		116		194	
ELATIVE	104	129	20.5		104	129	A 174 B 20.5	A 215 B20.5
POISE	118	124	19.3	25.5	118	124	A 197 B 19.3	A 207 B 25.5

ULN: Upper Limit of Normal