Seladelpar for previously treated primary biliary cholangitis [ID6429]

Technology appraisal committee D [09 July 2025]

For public – confidential information redacted

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Seladelpar for treating primary biliary cholangitis

- ✓ **Background and key issues**
- ❑ Clinical effectiveness
- ❑ Modelling and cost effectiveness
- ❑ Other considerations
- ❑ Summary

NICE National Institute for Health and Care Excellence

Background on primary biliary cholangitis (1/2)

Progressive autoimmune liver disease causing inflammation (cholangitis) and destruction of bile ducts and toxic bile acid buildup leading to liver damage

Epidemiology

- Around 20,000 people with PBC in UK, annual incidence of 2 to 3 per 100,000
- Occurs predominantly in women (90% of people with PBC are women)
- Most commonly diagnosed between age 40 and 60, with peak prevalence between 60 and 79 years. It rarely occurs in people under 25 years

Abbreviations: PBC, primary biliary cholangitis

Background on primary biliary cholangitis (2/2)

Symptoms and prognosis

- ~ 50-60% of patients are asymptomatic at diagnosis (detected by routine liver blood tests)
- Not all people have symptoms and many have no symptoms until significant liver damage has occurred
- Fatigue and pruritus (itching) are the most common symptoms. Pruritus occurs in about 80% of people and may significantly affect quality of life
- As PBC progresses people may have complications of liver disease and are at higher risk of hepatocellular carcinoma
- People may have non-liver symptoms, including from co-occurring autoimmune conditions. These include bone and joint aches, dry eyes and mouth and abdominal pain
- Early treatment may prevent irreversible liver damage which can lead to liver failure and death

Abbreviations: PBC, primary biliary cholangitis

Patient perspectives (1/2)

Submission from British Liver Trust

- Many people experience delayed diagnosis, leading to feelings of isolation, confusion, and frustration from unexplained symptoms. Although having a diagnosis is a relief, as PBC is relatively rare, people have often not heard about it so can still feel isolated
- Fatigue, itching and gastrological problems are the most common and disruptive symptoms, severely affecting quality of life, sleep, and ability to work or manage daily tasks
- PBC can progress to cirrhosis and liver cancer, with some people requiring liver transplants. The timeline is unpredictable, adding to peoples' anxiety
- Frustrations with variation of care and accessing a specialist team, particularly for ~40% who need 2nd line treatment after UDCA. Variations in access to 2nd line treatments
- OCA has more side effects than UDCA. Colestyramine (treatment for itch) challenging to take
- PBC predominantly affects women over 40, but younger women may face anxiety about fertility and pregnancy

Abbreviations: BASL, The British Association for the Study of the Liver; BHPG, British Hepatology Pharmacy Group; PBC, primary biliary cholangitis; UDCA, ursodeoxycholic acid

Patient perspectives (2/2)

"I am really struggling at work – I can't concentrate when I am constantly itching and scratching"
"I am too embarrassed to go out with my friends – I am constantly scratching and I worry that they think it's contagious"
"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."

"I wish there was a magic pill to take this fatigue away " People… have no idea what this kind of tiredness feels like." " I used to like running now I can't even walk to local shop"

"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."

"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."
"For 10 years my PBC was controlled. Then things got really bad...[before transplant had] hepatic encephalopathy. Some days fine but others nasty and aggressive…and couldn't understand why...sometimes I didn't know who my daughter was. I was unable to drive."

Abbreviations: PBC, primary biliary cholangitis

Clinical perspectives

Submissions from BHPG, BSAL

"The technology would provide a large (positive) step change in the management of patients with PBC"

- Treatment with seladelpar aims to normalise liver biochemistry to slow or stop the progression of liver disease. Also to reduce PBC-related pruritus
- Patients who do not respond to first-line (UDCA) referred to MDT for consideration of 2nd line treatments (OCA, elafibranor, occasionally off-label bezafibrate)
- 2nd line treatments prescribed by 35 hub centres, hubs serve smaller volume 'spoke' sites
- Seladelpar provides an additional 2nd or 3rd line treatment option delivered through specialist centres but should not be restricted to hub centres
- There is a significant unmet need, with around 40% of patients not responding adequately to UDCA and 30–50% not responding to 2nd -line therapies. Although some crossover activity with elafibranor (PPAR delta) allows for another option
- Seladelpar is expected to integrate well into existing care pathways, with a favourable and manageable safety profile

Abbreviations: BHPG, British Hepatology Pharmacy Group; BSAL, British Society for Study of the Liver. OCA: obeticholic acid; PBC, primary biliary cholangitis; UDCA, ursodeoxycholic acid, MDT multidisciplinary team

Equality considerations

Equality issues

Company:	People with PBC face long wait times (3 to 4 months) and have higher mortality whilst on liver transplant lists compared to people with other liver diseases
Stakeholders in TA1016:	**Prevalence in women:** estimated that 90% of people with PBC are women globally, with incidence rates 5 to 6 times higher for women than men **Outcomes by age:** people diagnosed with PBC under the age of 50 experience more severe and progressive disease and poor treatment response compared with patients over the age of 50 at diagnosis **Outcomes by sex:** men are at greater risk for more advanced disease at diagnosis and poor treatment response compared with women
BHPG/ British Liver Trust	**Geography:** recent UK-wide audit highlights geographical disparities in care, with access to specialist teams and second-line treatments varying due to differences in local availability of resources

- EAG did identify any further equality issues
- No equality issues raised at scoping stage

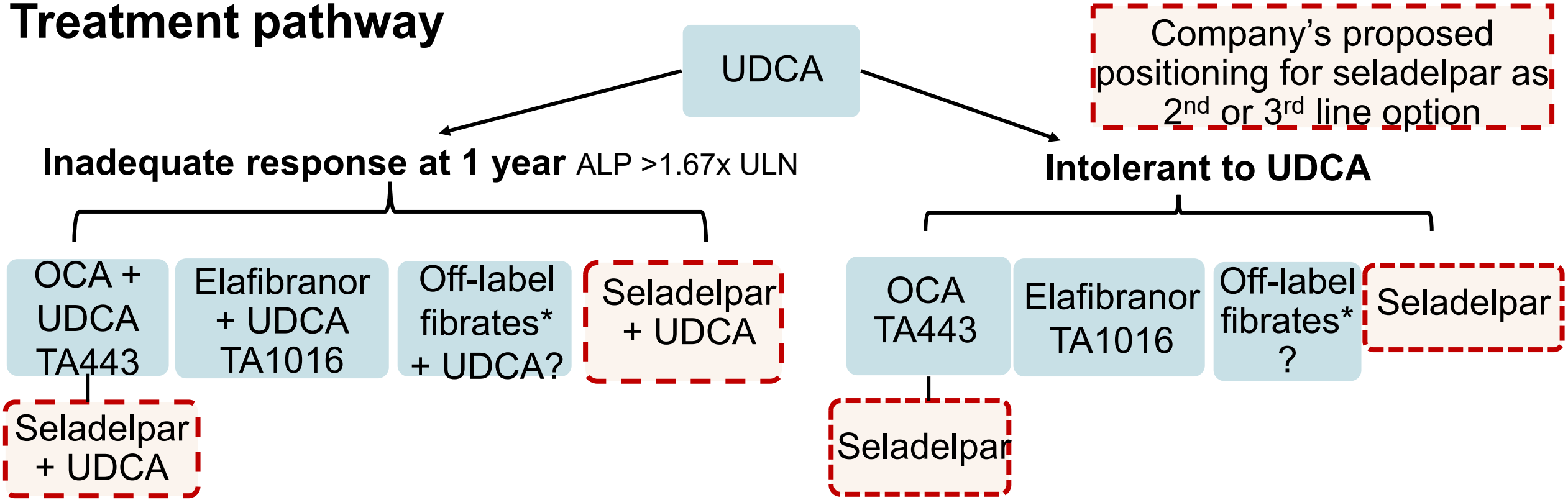
Abbreviations: BHPG, British Hepatology Pharmacy Group; PBC, primary biliary cholangitis; TA, technology appraisal

Seladelpar (Livdelzi, Gilead)

Marketing authorisation (MHRA Jan 2025)	Seladelpar is indicated for the treatment of PBC, including pruritus, in adults in combination with ursodexycholic acid (UDCA) who have an inadequate response to UDCA alone, or as monotherapy in those unable to tolerate UDCA
Mechanism of action	Seladelpar is a selective PPARδ agonist. In liver cells PPARδ activation reduces bile acid synthesis and accumulation. In immune cells, it shifts macrophages toward an anti-inflammatory M2 state
Administration	Oral tablets • 10 mg orally once daily, with or without food
Price	• The list price: £3,155.00 per pack of 30 capsules of 10mg seladelpar • Company has a confidential PAS discount in place

Abbreviations: MHRA, Medicines and Healthcare products Regulatory Agency; PAS, patient access scheme; PBC, primary biliary cholangitis; PPAR, peroxisome proliferator-activated receptor; UDCA, ursodeoxycholic acid

Treatment pathway



- UDCA is established 1st line treatment option (BSG/PBC guidelines).
- * Fibrates not a comparator in the NICE scope/company decision problem. Not comparator in TA443 and TA1016 because considered adjunctive treatment for pruritus, not 2nd line comparator (decision problem – comparators, TA443/1016 recs)

Fibrates: 2nd line, or adjunctive treatment? Is there a preferred sequence for OCA + elafibranor (+ seladelpar)? Would seladelpar be used 3rd line?

Abbreviations: ALP, alkaline phosphatase; OCA: obeticholic acid; PBC: primary biliary cholangitis; TA, technology appraisal; UDCA, ursodeoxycholic acid; ULN, upper level of normal

Key issues for discussion

#	Issue	ICER impact
	Decision problem	
1	Exclusion of fibrates as comparators (n.b. not in scope)	Large
2	Uncertainty in the PBC treatment pathway and potential position of seladelpar	Unknown
	Clinical effectiveness	
3	Positive treatment response for people having placebo in seladelpar trials	Unknown
4	Uncertainty in the relative effectiveness of seladelpar in comparison with existing treatment options	Large
	Cost-effectiveness	
5	Treatment discontinuation	Large
6	Source for health state utility data	Moderate

Abbreviations: ICER, Incremental cost-effectiveness ratio; PBC, primary biliary cholangitis

Large ICER impact

Key issue 1: Exclusion of fibrates as comparator (1/2)

Background

- Fibrates were not included final scope (consistent with the elafibranor appraisal scope [TA1016])
- In TA1016 bezafibrate was included in model for treating itching but not as a stand-alone 2nd line treatment

Company

- Fibrates not a comparator- notes not licensed and used in adjunctive role alongside UDCA in people with response to this treatment ALP 1–1.67× ULN (not 2nd line)
- Previously excluded from elafibranor and OCA appraisals, so inclusion here would be inconsistent

Abbreviations: OCA, obeticholic acid; PBC, primary biliary cholangitis; TA, technology appraisal; UDCA, ursodeoxycholic acid; ULN, Upper limit of normal

Key issue 1: Exclusion of fibrates as comparator (2/2)

Large ICER impact

EAG suggest fibrates could be a potential comparator

- Uncertainty that fibrates are used solely to manage itching and are not an active 2nd line treatment
  - UK Audit found that 50% of PBC patients with inadequate UDCA response were treated with fibrates over OCA, likely due to concerns that OCA may worsen pruritus, according to clinical experts
  - NHS England considering fibrates for treating PBC through its medicines repurposing programme (before suspension)
  - One EAG clinical expert stated fibrates are their centre's preferred second-line treatment
- Exploratory analysis by EAG suggests fibrates are a lower-cost but potentially less effective option

Should fibrates be considered as a comparator for seladelpar?

Abbreviations: OCA, obeticholic acid; PBC, primary biliary cholangitis; UDCA, ursodeoxycholic acid

Key issue 2: Uncertainty in the PBC treatment pathway (1/2)

Unknown ICER impact

Background

- No NICE guidelines specific to PBC, the most relevant guidance comes from the BSG/UK-PBC guidelines, Guidelines published (2018) before elafibranor guidance (TA1016 2024)

Company

- Seladelpar is primarily a second-line treatment used after intolerance or inadequate response to UDCA
- It may be a third-line option for people who do not tolerate or respond to OCA

Abbreviations: BSG/UK-PBC, British Society of Gastroenterology/United Kingdom – Primary Biliary Cholangitis; OCA, obeticholic acid; PBC, primary biliary cholangitis; UDCA, ursodeoxycholic acid

Key issue 2: Uncertainty in the PBC treatment pathway (2/2)

Unknown ICER impact

EAG: unclear what treatment sequence is 2nd line and later + limited data on 3rd line clinical effectiveness of elafibranor

- Elafibranor has only recently entered clinical use- its likely positioning in TA1016 was considered 2nd line (3rd line also plausible), but insufficient experience on what treatment displaces in treatment sequence.
- OCA may be less preferred as 2nd line option due to pruritus risk
- Effectiveness of seladelpar may vary in later lines, there is limited data on 3rd line efficacy
- Seladelpar, elafibranor and fibrates are all PPAR agonists, unclear if seladelpar would be used after no response to elafibranor, and also the clinical effectiveness in this group of people
- Clinical expert suggested adding-on therapies may be a possibility for people with very high ALP levels

Where would seladelpar be positioned in the treatment pathway? Is its clinical effectiveness expected to differ if used at 2nd or 3rd line?

Abbreviations: ALP, alkaline phosphatase; OCA, obeticholic acid; PBC, primary biliary cholangitis; UDCA, ursodeoxycholic acid

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Clinical effectiveness evidence for seladelpar (1/2)

	RESPONSE (n=193)- key trial in model
Design	Phase III, double-blind, placebo-controlled, randomised study
Population	People with PBC and an incomplete response or intolerance to UDCA. 17% had prior use of OCA or fibrates.
Intervention	Seladelpar 10mg +/- UDCA (n=128) (5mg seladelpar reduced dose for intolerance)
Comparator(s)	Placebo +/- UDCA (n=65)
Duration	12 months
Primary outcomes	Proportion achieving a composite biochemical response at month 12 (achieving all three of the following endpoints: ALP < 1.67× ULN; ≥ 15% decrease in ALP and total bilirubin ≤ 1.0× ULN)
Key Secondary outcomes outcomes table	• Proportion with normalisation of ALP (≤ 1.0xULN) at 12 months • Change from baseline in weekly averaged pruritus NRS score • UK-PBC risk score (used to determine risk of end stage liver disease)

Abbreviations: ALP, alkaline phosphatase; OCA, obeticholic acid; PBC, primary biliary cholangitis; UDCA, Ursodeoxycholic Acid; ULN, Upper limit of normal

Clinical effectiveness evidence for seladelpar (2/2)

Other clinical evidence for seladelpar

- Clinical development of seladelpar complicated by termination of some studies due to safety concerns in another indication, later found to be unrelated to the drug
- ENHANCE (terminated early → limited data after 3 months) was an RCT similar to RESPONSE
- Phase II dose-ranging study 8-week follow up with 44-week extension (n=119)
- ASSURE: Study participants including terminated studies eligible to enter 24 month ASSURE open-label (seladelpar +/- UDCA)

Abbreviations: ALP, Alkaline phosphatase; NRS, Pruritus numerical rating scale; PBC, primary biliary cholangitis; UDCA, Ursodeoxycholic Acid; ULN, Upper limit of normal

Primary outcome– RESPONSE Composite outcome and ALP response (1/2)

- Participants had a higher response (measured with composite outcome) with seladelpar than placebo
- Composite outcome largely driven by ALP-related measures, specifically, the proportion of participants achieving a ≥15% reduction in ALP and normalization to ≤1.67×ULN
- Minimal differences in bilirubin levels were observed between study arms. EAG noted that baseline bilirubin was low and indicates that people earlier in disease stage, so minimal differences expected
- These findings were generally consistent across other seladelpar studies

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Full composite outcome, ALP response and additional outcome results available in appendix

Abbreviations: ALP, Alkaline phosphatase; ULN, Upper limit of normal

Primary outcome– RESPONSE Composite outcome and ALP response (2/2)

	RESPONSE	
	Seladelpar	**Placebo**
Composite outcome at 12 months	79/128 (61.7%)	13/65 (20.0%)
ALP baseline and response sub-outcomes		
Baseline ALP, U/L, mean (SD)	314.6 (123.0)	313.8 (117.7)
ALP <1.67× ULN, n/N (%)	84/128 (65.6)	17/65 (26.2)
≥ 15% decrease in ALP n/N (%)	107/128 (83.6)	21/65 (32.3)
Bilirubin baseline and response sub-outcome		
Baseline total bilirubin mg/dl, mean (SD)	0.769 (0.3)	0.737 (0.3)
Total bilirubin ≤ 1.0× ULN, n/N (%)	104/128 (81.3)	50/65 (76.9)

NICE

Full composite outcome, ALP response and additional outcome results available in appendix

Abbreviations: ALP, Alkaline phosphatase; PBC: primary biliary cholangitis; SD, standard deviation; UDCA, ursodeoxycholic acid; ULN, Upper limit of normal

Key Issue 3: Positive treatment response for people having placebo in seladelpar trials

Unknown ICER impact

EAG

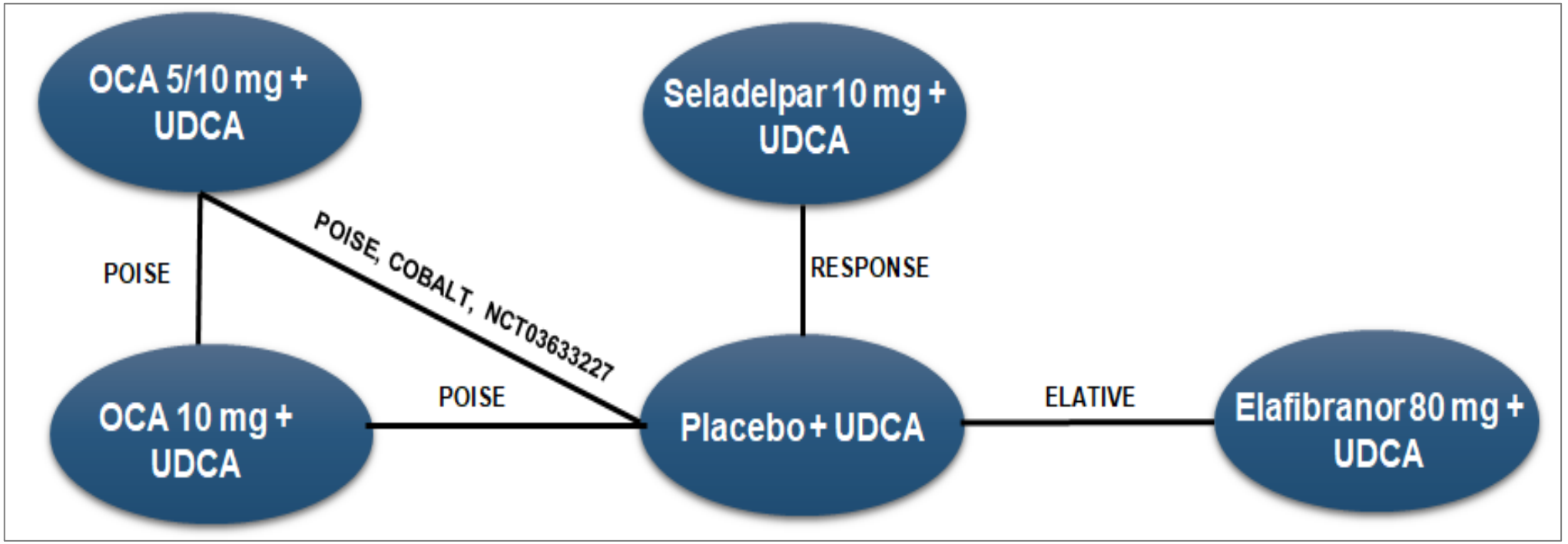
- A significant minority of participants in the RESPONSE trial showed meaningful clinical improvement in ALP response in the placebo arm
- This effect couldn't be attributed to changes in background treatments or UDCA dosing, which remained consistent with prior use
- EAG clinical expert said placebo responses in PBC trials common + may be due to greater adherence to UDCA in clinical trials
- Adherence could reduce treatment costs or lead to higher wastage if costs remain unchanged
- Implications:
  - Absolute rates less reliable and data from single arm studies may be biased
  - Indirect comparisons may be biased if placebo effect differs between trials
  - Uncertainty about real world adherence over time and how well trial results reflect NHS clinical practice

How should this uncertainty be considered in decision making?

Abbreviations: ALP, Alkaline phosphatase; UDCA, Ursodeoxycholic Acid

Indirect treatment comparisons- company uses different approaches for each comparator (1/2)

- No head-to-head trials of seladelpar compared with OCA, or elafibranor. Key trials were:
  - Seladelpar + UDCA vs. UDCA + placebo (RESPONSE)
  - Elafibranor + UDCA vs. UDCA + placebo (ELATIVE)
  - OCA + UDCA vs. UDCA + placebo (POISE, COBALT, NCT03633227)



Link to results from these studies

Abbreviations: OCA, obeticholic acid; UDCA, Ursodeoxycholic Acid

Indirect treatment comparisons- company uses different approaches for each comparator (2/2)

Company's base case used:

- Seladelpar with OCA comparison: Bayesian Network meta-analysis
- Seladelpar with elafbrinor comparison: Anchored Matching Adjusted Indirect Comparison (MAIC)
  - 4 treatment effect modifiers (age, baseline ALP, bilirubin, cirrhosis), aligned with TA1016 and validated by literature and expert opinion
  - Company considered Bayesian NMA unsuitable (for comparison with elafibranor) because of differences in baseline bilirubin and cirrhosis rates between RESPONSE and ELATIVE making transitivity assumption violated (i.e. there were systemic differences between the comparisons other than the treatments being compared)
- PROM itch outcomes: NMA (including all comparator trials)
- In NMA + MAIC matched RESPONSE data to for sex-specific cut-offs of ULN "with outcome recalculation"

Abbreviations: ALP, Alkaline phosphatase; NMA, Network Meta-analysis; OCA, obeticholic acid; PROM, patient-reported outcome measure; TA, technology appraisal; UDCA, Ursodeoxycholic Acid; ULN, Upper limit of normal

Key issue 4: uncertainty in indirect comparisons

Large ICER impact

EAG noted uncertainty associated with using different methods for each comparison. Also, estimates using each approach had uncertainty (wide credible intervals). Overall preferred Bayesian NMA because fewer concerns with transitivity than the low ESS with MAIC

Overall Bayesian NMA approach	MAIC approach
• Idiosyncratic reporting of priors • Adjusting for age upholds transitivity assumption but does not reflect NHS clinical practice (minor impact on results) • No clear differences between seladelpar and OCA (wide credible intervals) • Results for seladelpar vs. OCA changed when included ELATIVE trial • In NMA (including ELATIVE) seladelpar statistically significantly reduced risk of pruritus vs. OCA and upper tract respiratory infection vs elafibranor	• Clinical experts considered differences in trials unlikely clinically meaningful • Resulted in a low ESS (70, 36% of original sample) suggesting that baseline differences were difficult to reconcile through matching • No clear evidence that seladelpar more effective than elafibranor (wide credible intervals)

- What is most appropriate approach?
- How much uncertainty is there around the results?

Abbreviations: ESS, effective sample size; MAIC, Matching-Adjusted Indirect Comparison; NMA, Network Meta-analysis; OCA, obeticholic acid

Company NMA results seladelpar vs. OCA

- Seladelpar statistically significantly improved ALP outcomes vs placebo . No clear difference vs OCA especially vs 10mg OCA
- Credible intervals were extremely wide for all comparisons

RR >1	Favours seladelpar
RR <1	Favours OCA
-ve mean diff	Value favours seladelpar
*	Statistically significant

Comparison	Seladelpar vs placebo	Seladelpar vs OCA (5-10mg)	Seladelpar vs OCA (10mg)
ALP normalisation (≤1 ULN) at 12 months			
RR (95% CrI)	[redacted]	[redacted]	[redacted]
ALP response (Toronto I: ALP ≤1.67 × ULN) at 12 months			
RR (95% CrI)	[redacted]	[redacted]	[redacted]
ALP change from baseline			
Mean difference	[redacted]	[redacted]	[redacted]

Link to EAG NMA results (ALP change from baseline)

Abbreviations: ALP, Alkaline phosphatase; CrI, credible intervals; OCA, Obeticholic Acid; PBC: primary biliary cholangitis; ULN, Upper limit of normal

Company MAIC results seladelpar vs elafibranor

- In MAIC (and NMA) no statistically significant difference vs elafibranor in ALP outcomes
- Wide credible intervals

RR >1	Favours seladelpar
RR <1	Favours comparator
*	Statistically significant

	Anchored MAIC (company base case)		Bayesian NMA (EAG preferred)	
	vs. placebo	vs. elafibranor	vs. placebo	vs. elafibranor
ALP normalisation at 12 months				
RR (95% CrI)	[redacted]	[redacted]	[redacted]	[redacted]
ALP response (Toronto I) at 12 months				
RR (95% CrI)	[redacted]	[redacted]	[redacted]	[redacted]
ALP change from baseline at 12 months				
Mean difference (95% CrI)	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: ALP, Alkaline phosphatase; CrI, credible intervals; MAIC, Matching-Adjusted Indirect Comparison; NMA, Network Meta-analysis; RR, risk ratio

Company NMA results: Safety outcomes

- Less pruritus at 12 months with seladelpar than OCA (both doses) and placebo*
- Lower odds of upper tract respiratory infection with seladelpar vs placebo or elafibranor*

* Statistically significant

	vs placebo	vs elafibranor	vs OCA (5-10mg)	vs OCA (10mg)
	ALP Any adverse event at 12 months			
Odds ratio (95% CrI)	[redacted]	[redacted]	[redacted]	[redacted]
	All cause discontinuation at 12 months			
Odds ratio (95% CrI)	[redacted]	[redacted]	[redacted]	[redacted]
	Upper tract respiratory infection at 12 months			
Odds ratio (95% CrI)	[redacted]	[redacted]	[redacted]	[redacted]
	Development of pruritus at 12 months			
Odds ratio (95% CrI)	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: ALP, Alkaline phosphatase; CrI, credible intervals; NMA, network meta-analysis; OCA, Obeticholic Acid

Company NMA results: Patient reported outcome measures

- Seladelpar showed a numerical reduction in pruritus at 12 months versus placebo and OCA, with statistical significance only on the 5-D Itch scale

Comparison	Seladelpar vs placebo	Seladelpar vs OCA (5 to 10mg)	Seladelpar vs OCA (10mg)
	Patient reported outcomes PBC-40 itch		
Mean difference (95% CrI)	[redacted]	[redacted]	[redacted]
	Patient reported outcomes 5-D itch		
Mean difference (95% CrI)	[redacted]	[redacted]	[redacted]

EAG could not identify a MCID for either scale, limiting interpretation of clinical relevance. Using a crude 20% reduction threshold, this would equate to 2.4 points on the PBC-40 and 4 points on the 5-D Itch

Abbreviations: ALP, Alkaline phosphatase; CI, confidence intervals; CrI, credible intervals; MCID, minimum clinically important difference; NMA, network meta-analysis; OCA, Obeticholic Acid; PBC: primary biliary cholangitis; UDCA, ursodeoxycholic acid; ULN, Upper limit of normal; 5-D, 5-dimension

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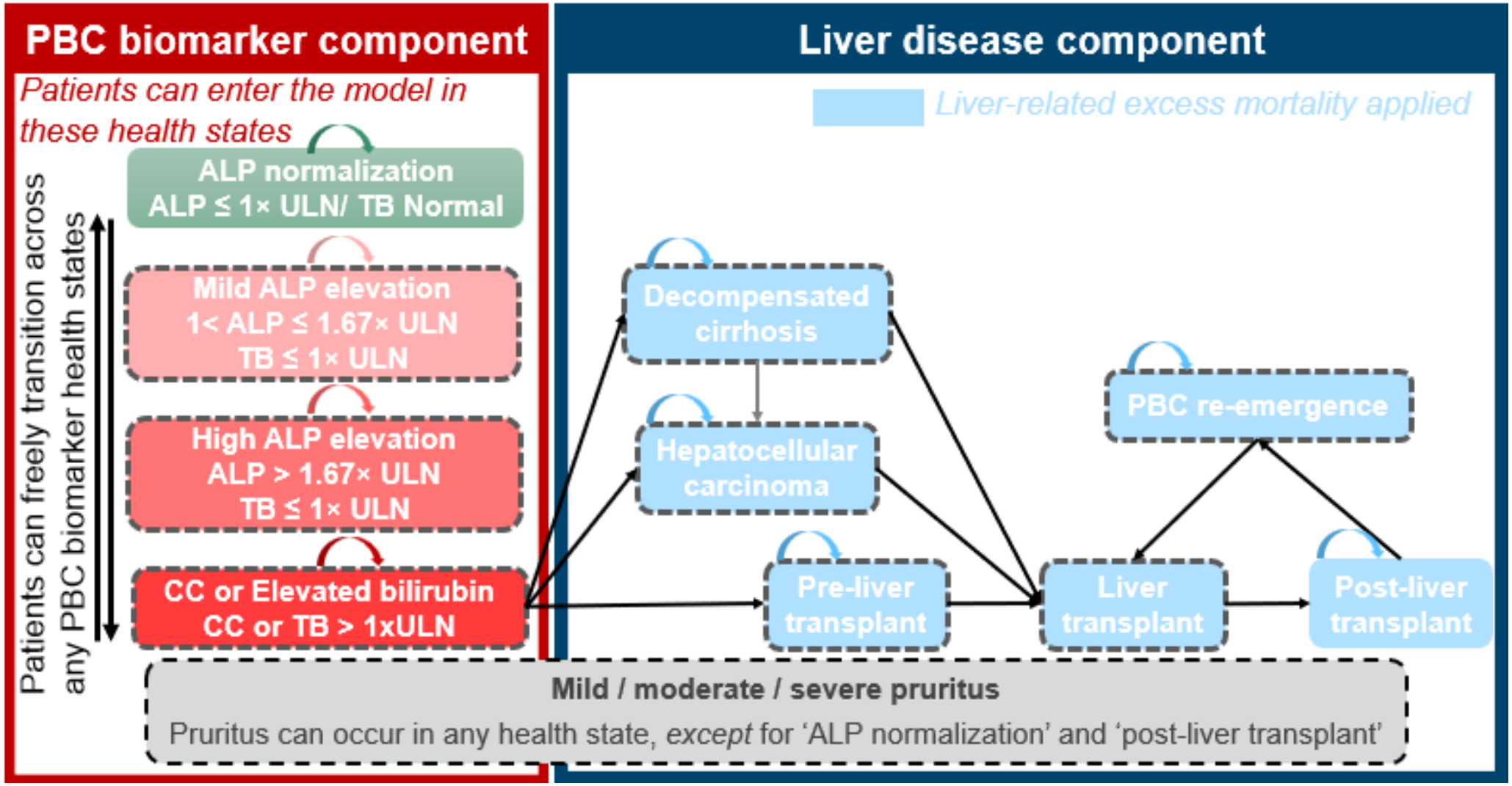
Company's model overview (1/2)

Seladelpar is modelled to increase time spent with normal ALP, reducing both costs and quality-of-life burden associated with liver failure. It also lessens the quality-of-life burden linked to pruritus.

- Cohort-level Markov state transition model with 2 components
- Health states based on ALP levels and liver disease
- ALP used to model transition to liver disease
- Utility and costs were accounted for in people in ALP and liver disease health states and for pruritus of varying severity within these health states
- Modelled cohorts
  - 1) inadequate response to UDCA and
  - 2) intolerant to UDCA (used same data because only 11 (5.2% of) people were intolerant to UDCA in RESPONSE)
- Comparators:
  - OCA (5 to 10 mg) +/- UDCA;
  - Elafibranor +/- UDCA
- Life-time horizon (up to 50 years)

Abbreviations: ALP, alkaline phosphatase; OCA, Obeticholic Acid; UDCA, ursodeoxycholic acid; QALY, Quality-adjusted life year

Company's model overview (2/2)



Note: same approach as TA443 and TA1016, but separate ALP normalisation health-state new (in previous appraisals mild/low risk health states could include people with normal ALP levels)

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

Company's model: transition probabilities Calibrated HRs , transition probabilities

TPs	Source and approach
0 to 12 months	Transitions between ALP states and compensated cirrhosis (CC) • Seladelpar +/- UDCA: calculated from individual patient data in RESPONSE • For OCA and elafibranor: data only available at 12 months. So, estimated calibration targets for the proportion of people expected in ALP normalization and mild elevation health states for each comparator (applied ITC relative risks to the proportion modelled to be in these health states over time in the seladelpar arm) • HRs (for comparators vs seladelpar) were adjusted simultaneously until the model-predicted proportion in each state for each comparator matched the calibration targets
Month 13+	Transitions estimated through calibration to long term Global and UK PBC registry (as in TA443) so that the simulated cohort remaining transplant-free at 10 year (adjusted for general population OS) was aligned with published estimates of 10 year liver-transplant free survival estimates from the registry

The liver disease component transition probabilities are from TA443 apart from CC/EB to decompensated cirrhosis (used Global PBC and UK -PBC data). Assumed no excess mortality with PBC recurrence

Abbreviations: ALP, alkaline phosphatase; CC, compensated cirrhosis; EB, Elevated bilirubin; HRs, hazard ratios; ITC, indirect treatment comparison; LTFS, liver transplant-free survival; MAIC, Matching-Adjusted Indirect Comparison; NMA, network meta-analysis; OCA, Obeticholic Acid; PBC, primary biliary cholangitis; TA, technology appraisal; TPs, transition probabilities; UDCA, ursodeoxycholic acid

Key issue 5: Treatment discontinuation (1/2)

Large ICER impact

Company approach:

Treatment discontinuation rates company base case	
0 to 12 months	For seladelpar rates were obtained from RESPONSE, while the rates for the comparators were naively sourced from their respective studies (rather than from ITC)

EAG (Discontinuation at 12-months)

- Discontinuation rates were notably higher when using ITC-derived values for comparators vs naïve trial-based rates, resulting in more patients discontinuing by month 12
- Prefers ITC results to inform discontinuation because it may account for differences in trial populations and aligns with methods for other model parameters

Cumulative discontinuation at 12 months (UDCA tolerant and intolerant)	Seladelpar	Elafibranor	OCA
Company base case	6.73%	9.59%	9.59%
ITC (EAG preference)	6.73%	11.02%	26.95%

Abbreviations: ITC, indirect treatment comparison; OCA, Obeticholic acid, OLE, open-label extension; UDCA, Ursodeoxycholic acid

Key issue 5: Treatment discontinuation (2/2)

Large ICER impact

Company approach:

Treatment discontinuation rates company base case	
12 months +	Discontinuation rate ratio of 0.28 was calculated from ELATIVE and ELATIVE OLE (weeks 0 to 52 vs. 53 to 104) for elafibranor and applied to estimate post-12-month discontinuation rates for seladelpar and OCA

EAG (Discontinuation 12 months +)

- Prefers to use RESPONSE and ASSURE (seladelpar trials) to calculate the 12 month + discontinuation rate ratio (0.12 rather than 0.28)
- Additional scenario assumes discontinuation rate of 22.1% across all comparators based on UK audit rates

Which source for treatment discontinuation is most appropriate?

Abbreviations: ITC, indirect treatment comparison; OCA, Obeticholic acid, OLE, open-label extension; UDCA, Ursodeoxycholic acid

Moderate ICER impact

Key issue 6: Source for health state utility data (1/2)

- RESPONSE collected disease-specific PBC-40 data but not EQ-5D data
- The company derived a mapping algorithm from the ITCH-E study (90 participants in real world study) and used to map PBC-40 (RESPONSE) to EQ-5D-5L. Further mapped to EQ-5D-3L utilities, then MMRM model applied to utility values
- Disutility for pruritus from Smith et al. 2022 based on EQ-5D-5L data from GLIMMER study (RCT of linerixibat in people with moderate to severe pruritus over 16 weeks)
- Assumed a baseline utility of 0.87 for PBC without pruritus, based on Cortesi et al. (2020) Italian cohort

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; PBC, primary biliary cholangitis; EQ-5D-5L, EuroQol-5 Dimensions-5 Levels; MMRM, Mixed model for repeated measures

Key issue 6: Source for health state utility data (2/2)

Moderate ICER impact

EAG:

- Disutilities for pruritus derived from RESPONSE give smaller disutility than those sourced from Smith et al.
- Company's disutilities are the difference between 2 estimates from different sources with different approaches
- Considered the MMRM pruritus disutilities from RESPONSE more appropriate due to internal consistency, alignment with UK cohort data, and use of RESPONSE trial data

Which source for health state utility data is most appropriate?

Abbreviations: ALP, Alkaline phosphatase; EQ-5D-3L, EuroQol-5 Dimensions-3 Levels; EQ-5D-5L, EuroQol-5 Dimensions-5 Levels; MMRM, Mixed model for repeated measures

Seladelpar for treating primary biliary cholangitis

- ❑ Background and key issues
- ❑ Clinical effectiveness
- ❑ Modelling and cost effectiveness
- ❑ Other considerations
- ✓ **Summary**

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Summary of company and EAG base case assumptions (1/2)

Assumption	Company base case	EAG base case
Modelled baseline distribution	Baseline distribution across ALP health states based on RESPONSE (5.88% people had mild ALP elevation ≤ 1.67 x ULN)	No patients enter the model in the ALP normalisation or mild elevation states (would not be eligible for 2nd line treatment)
ITC informing treatment effect	• Vs. elafibranor (MAIC) • Vs OCA (Bayesian NMA excluding elafibranor trial)	Bayesian NMA including elafibranor trial using Turner prior (ALP normalisation and Mild ALP elevation)
Pruritus disutility	ALP health states: MMRM2 model Pruritus: Smith et al	MMRM2 model for ALP health states and pruritus severity disutility values
Treatment discontinua-tion	• 0 to 12 m: individual trial data from RESPONSE, ELATIVE and POISE • 12m+: rate ratio based on ELATIVE trials	• 0 to 12m: based on ITC • 12m+: rate ratio based on RESPONSE & ASSURE

Abbreviations: ALP, alkaline phosphatase; CC, compensated cirrhosis; EQ-5D, EuroQol-5 Dimensions-5 Levels; ITC, indirect treatment comparison; MAIC, Matching-Adjusted Indirect Comparison; MMRM, Mixed model for repeated measures; NMA, network meta-analysis; PBC, primary biliary cholangitis; UDCA, ursodeoxycholic acid

Cost-effectiveness results

Confidential discounts for comparators – ICERs in Part 2 slides

ICER ranges presented below

Summary – in both the UDCA tolerant and intolerant cohorts:

- Company base case is much higher than £30,000 per QALY gained
- EAG base case higher than company's
- Seladelpar +/- UDCA has highest total costs and total QALYs. The QALY difference between seladelpar and elafibranor is small

Scenario analyses:

- No scenario gives cost-effectiveness estimates within £20,000 to £30,000 per QALY
- Discontinuation scenario using UK estimates from UK audit (Abbas et al.) results in large increases in the ICER

Committee decision making slide

Issue	Questions for committee
Comparators	• Should fibrates be considered a comparator for seladelpar?
Treatment pathway	• Where would seladelpar be positioned in the treatment pathway? • Is its clinical effectiveness expected to differ if used at 2nd or 3rd line?
Positive treatment response for people having placebo	• How should this uncertainty be considered in decision making?
Treatment comparison	• What is the most appropriate approach for the treatment comparison? • How much uncertainty is there around the results?
Treatment discontinuation	• Which source for treatment discontinuation rate is most appropriate?
Utilities	• Which source for health state utility data is most appropriate?

NMA, network meta-analysis; PFS, progression-free survival; PSM, partitioned survival model; STM, state transition model.

Seladelpar for treating primary biliary cholangitis

Supplementary appendix

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Decision problem - Comparators

Final scope issued by NICE	Decision problem addressed in the company submission
For people, whose disease has an inadequate response to ursodeoxycholic 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: • OCA in combination with UDCA • Elafibranor in combination with UDCA Where UDCA cannot be tolerated: • OCA monotherapy • Elafibranor monotherapy

Link back to treatment pathway, key issue 1

Abbreviations: OCA: obeticholic acid; PBC: primary biliary cholangitis; UDCA, ursodeoxycholic acid

Key clinical trial results – Change in UK-PBC score (RESPONSE, ENHANCE, ASSURE and CB8025-21629)

	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)*

Link back to Clinical effectiveness evidence

Primary outcomes– Composite outcome and ALP response (1/2)

- Composite outcomes in seladelpar studies were largely driven by ALP-related measures, specifically, the proportion of participants achieving a ≥15% reduction in ALP and normalization to ≤1.67×ULN.
- Minimal differences in bilirubin levels were observed between study arms, consistent with expectations based on disease stage. These findings were generally consistent across studies.

	RESPONSE (NCT04620733 // CB8025-32048)		ENHANCE (NCT03602560 // CB8025-31735)		ASSURE (NCT03301506 // CB8025-31731-RE)				Phase II dose-ranging study (NCT02955602 // CB8025-21629)	
	Composite outcome									
	Seladelpar	Placebo	Seladelpar 5mg	Seladelpar 10mg	Placebo	RESPONSE Seladelpar/ Seladelpar	RESPONSE Placebo/ Seladelpar	Legacy seladelpar	5mg	10mg
Composite outcome at12 months	79/128 (61.7%)	13/65 (20.0%)	NA	NA	NA	NA	[redacted]	[redacted]	NR	33/52 (67.3%)
	ALP response									
	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 (%)	6m: 89/128 (69.5%) 12m: 84/128 (65.6%)	6m: 15/65 (23.1%) 12m: 17/65 (26.2%)	6m: 16/26 (61.5%)	6m: 15/20 (75.0%)	6m: 8/23 (34.8%)	NR			NR	40/52 (78.4%)

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Link to Primary outcome

Abbreviations: ALP, Alkaline phosphatase; PBC: primary biliary cholangitis; UDCA, ursodeoxycholic acid; ULN, Upper limit of normal

Key clinical trial results –ALP response (1/2)

Seladelpar demonstrated a notable improvement in ALP response compared to placebo after one month of treatment, with response rates remaining relatively stable at subsequent follow-up assessments

	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]3 m: 0/56 (0%) 6m: [redacted]	13m: [redacted] 15m: [redacted] 18m: [redacted] 21m: [redacted] 24m: [redacted]	3m: [redacted] 12m: [redacted]	3m: [redacted] 12m: [redacted]

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Link to Primary outcome

Key clinical trial results –ALP response (2/2)

- Majority of people who received seladelpar experienced a 15% reduction in ALP from baseliner; no increase in the number of people who experienced a 15% reduction after 1 month
- Approximately two thirds of people who received treatment with seladelpar achieved ALP levels <1.67 x ULN

	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
≥ 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: [redacted] 6m: [redacted]	1m: [redacted] 3m: [redacted] 6m: [redacted]	1m: [redacted] 3m: [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: NR 9m: NR 12m: [redacted]

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Link to Primary outcome

Key clinical trial results – Bilirubin outcomes (RESPONSE, ENHANCE, ASSURE and CB8025-21629)

	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) 12m: -0.38 (4.24)	1m: -0.745 (2.75) 3m: -5.77 (2.40) 6m: 1.20 (3.66) 9m: 2.52 (3.96) 12m: 3.56 (6.00)	NR	NR	NR	NR	NR	NR
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

Link to Primary outcome

Other outcomes

Fatigue	• Complete data from the fatigue domain of the PBC-40 questionnaire were presented at clarification, covering timepoints at 1, 3, 6, 9, and 12 months in the RESPONSE study, as well as from the Phase II dose-ranging study. • No differences in fatigue scores were observed between treatment arms at any timepoint in RESPONSE, and the Phase II dose-ranging study also showed no clear evidence of a treatment-related effect on fatigue. • Based on the available evidence, the Evidence Assessment Group (EAG) concluded that seladelpar does not appear to have an impact on fatigue in people with PBC.
Mortality	• There were no reported deaths in either the RESPONSE or ENHANCE trials. • One death occurred in the long-term safety study (CB8025-31731) prior to its termination. The participant was receiving 5 mg seladelpar and died from a malignant neoplasm. The event was judged by investigators to be unrelated to treatment. • Another death was reported in the ASSURE study involving a participant who had previously taken part in a legacy seladelpar study. The cause of death was autoimmune haemolytic anaemia, and it was also deemed unrelated to treatment by investigators.

Link to Primary outcome

Health-related quality of life (PBC-40)

- Only quality of life data reported by the company was from the RESPONSE study
- PBC-40 is a disease-specific quality of life measure for PBC that addressed six domains: fatigue, mood, social quality, cognitive state, itch, and other symptoms
- Minimum and maximum score of the PBC-40 is 40 to 200, with higher scores representing poorer overall QoL
- After 12 months in RESPONSE, PBC-40 scores showed no difference between arms. Both groups had numerical reductions, but without a defined MCID, the clinical relevance was unclear. The 5.85-point drop in the seladelpar arm equated to just a 3.7% change on the 160-point scale.

	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

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Link back to Primary outcome

Abbreviations: HRQoL, heart-related quality of life); LS, least squared; NR, not reported; SD, standard deviation; SE, standard error; 12m, 12 months

Subgroup analyses

Link to Primary outcome

- Not included in the company decision problem
- Subgroup results from the RESPONSE trial were available

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

[redacted]

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

Adverse Events

	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]

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Link to Primary outcome

Abbreviations: TEAE, treatment-emergent adverse event

Key clinical trial results – Composite outcome (1/2)

Minimal differences in bilirubin levels were observed between study arms, consistent with expectations based on disease stage. As a result, composite outcomes in seladelpar studies were largely driven by ALP-related measures, specifically, the proportion of participants achieving a ≥15% reduction in ALP and normalization to ≤1.67×ULN. These findings were generally consistent across studies.

	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

Link to Primary outcome

Key clinical trial results – Composite outcome (2/2)

	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
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

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Link to Primary outcome

Key clinical trial results – Pruritus outcomes in people with baseline pruritus NRS ≥4 (1/2)

- Reasonable pruritus response in the placebo arm of RESPONSE (likely due to improved UDCA adherence under trial conditions)
- Treatment with seladelpar in RESPONSE did not result in a clinically meaningful reduction (MCID: 2.7 ±1.7) in mean pruritus NRS scores compared to placebo.

	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]	6m: NR 12m: -3.3 (0.33)	6m: NR 12m: -1.5 (0.50)	6m: NR	6m: NR	6m: NR	NR	6m: [redacted] 12m: [redacted]	NA	NA
Reduction of ≥2 on pruritus NRS, n/N (%)	6m: [redacted] 12m: [redacted]	6m: [redacted] 12m: [redacted]	NR	NR	NR	NR	6m: [redacted] 12m: [redacted]	NA	NA

Key clinical trial results – Pruritus outcomes in people with baseline pruritus NRS ≥4 (1/2)

- Reasonable pruritus response in the placebo arm of RESPONSE (likely due to improved UDCA adherence under trial conditions)
- Treatment with seladelpar in RESPONSE did not result in a clinically meaningful reduction (MCID: 2.7 ±1.7) in mean pruritus NRS scores compared to placebo.

	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] 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

Key clinical trial results – Pruritus outcomes in people with baseline pruritus NRS ≥4 (2/2)

	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
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] 18m: [redacted]	NA	NA
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]

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- umol/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
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

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*Median values.

¥Bilirubin at baseline (%) corrected in RESPONSE trial.

Shaded rows: key treatment effect modifiers according to CS.

Abbreviations: 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.

Statistical methods (NMA and Anchored MAIC approach)

- For the efficacy outcomes, scaled pruritus outcomes (PBC-40 Itch, 5-D Itch, and NRS Itch), the 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

Model	Base-case Priors	Sensitivity priors	Efficacy Outcomes
Efficacy outcomes seladelpar vs OCA			
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
Patient reported outcomes seladelpar vs OCA			
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
Safety outcomes seladelpar vs OCA and elafibranor			
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

EAG NMA results: ALP change from baseline

*statistically significant
¥priors are unclear

- The Bayesian NMA (POISE, RESPONSE, ELATIVE with Rhodes priors) captured trends for seladelpar vs elafibranor and placebo reasonably well, despite concerns about transitivity and priors
- However, adding ELATIVE unexpectedly reversed the direction of effect for seladelpar vs OCA (10 mg), raising concerns about the consistency and robustness of the NMA

Model	Bayesian NMA (POISE, RESPONSE, and ELATIVE: Rhodes prior specific for biological markers)	BASE CASE: Anchored MAIC (adjusted for 4 effect modifiers)	BASE CASE: Bayesian NMA (POISE and RESPONSE: Rhodes priors specific for biological markers)
	MD (95% CrI)	MD (95% CrI)	MD (95% CrI)
Seladelpar vs elafibranor	[redacted]	[redacted]	N/A
Seladelpar vs placebo	[redacted]	[redacted]	[redacted]
Seladelpar vs OCA (5-10mg)	[redacted]	N/A	[redacted]
Seladelpar vs OCA (10mg)	[redacted]	N/A	[redacted]

Link back to Company NMA results

Abbreviations: CI, confidence interval; CrI, Credible Interval; MAIC, Matching adjusted indirect comparison; MD, Mean Difference; N/A, not applicable; NMA, network meta-analysis.

Health state definitions in PBC appraisals

Seladelpar	**ALP normalisation**	**ALP mild elevation**	**ALP high elevation**	**CC or Elevated bilirubin**
	ALP ≤ 1× ULN/ TB Normal	• 1< ALP ≤ 1.67× ULN • TB ≤ 1× ULN	• ALP > 1.67× ULN • TB ≤ 1× ULN	CC or TB > 1xULN
OCA (TA443)	**ALP normalisation**	**Low risk**	**Moderate risk**	**Severe risk**
	NA	ALP ≤ 1.67 x ULN	ALP > 1.67 x ULN and total bilirubin (TB) ≤ 1.0 x ULN	TB > 1.0 x ULN or compensated cirrhosis
Elafibranor (TA1016)	**ALP normalisation**	**Mild risk**	**Moderate risk**	**High risk**
	NA	ALP ≤ 200 u/L and TB ≤ 20 µmol/L	ALP > 200 u/L and TB ≤ 20 µmol/L	TB > 20 µmol/L or compensated cirrhosis (defined as kPa >15)

TB: total bilirubin

Link to model overview slide

Naïve results from trials included in indirect comparisons

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)

Treatment	Source links
OCA 5-10 mg and 10mg	POISE trial: NCT01473524 (Nevens et al 2016)
Elafibranor	ELATIVE trial: NCT04526665 (Kowdley et al 2024)
Seladelpar	RESPONSE trial: NCT04620733 (Hirschfield et al 2024)

Link back to ITC slide

Note: 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

Abbreviations: ALP: Alkaline Phosphatase; OR: Odds Ratio; RD: Risk Difference; RR: Risk Ratio; UDCA: Ursodeoxycholic Acid; ULN: Upper Limit of Normal

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

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Link to transition probabilities slide

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
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

Link to transition probabilities slide

Recent NICE appraisals for PBC

Link back to treatment pathway, key issue 1, Company's model: data informing transition probabilities

Technology appraisal	Drug	Recommendation
NICE TA1016 (14 November 2024)	Elafibranor for previously treated primary biliary cholangitis	• Elafibranor is recommended, within its marketing authorisation, as an option for treating primary biliary cholangitis in adults, when used: • with ursodeoxycholic acid (UDCA), if the primary biliary cholangitis has not responded well enough to UDCA, or • alone, if UDCA cannot be tolerated.
NICE TA443 (26 April 2017)	Obeticholic acid for treating primary biliary cholangitis	• Obeticholic acid is recommended, within its marketing authorisation, as an option for treating primary biliary cholangitis in combination with ursodeoxycholic acid for people whose disease has responded inadequately to ursodeoxycholic acid or as monotherapy for people who cannot tolerate ursodeoxycholic acid. Obeticholic acid is recommended only if the company provides it with the discount agreed in the patient access scheme. • Assess the response to obeticholic acid after 12 months. Only continue if there is evidence of clinical benefit.

Abbreviations: TA, technology appraisal; UDCA, Ursodeoxycholic Acid

Managed access

- **Company has not made a managed access proposal for this topic**
- **Committee cannot make a managed access recommendation until the company has submitted a proposal and this has been reviewed by NICE.**

Criteria for a managed access recommendation:

- The technology cannot be recommended for use because the evidence is too uncertain
- The technology has the **plausible potential** to be cost effective at the **currently agreed price**
- New evidence that could **sufficiently support the case for recommendation** is expected from ongoing or planned clinical trials, or could be collected from people having the technology in clinical practice
- Data could feasibly be collected within a reasonable timeframe (up to a **maximum of 5 years**) without **undue burden**.