Seladelpar for treating primary biliary cholangitis [ID6429]

For projector – all confidential information has been redacted

ACM3, technology appraisal committee D [06 May 2026]

Chair: Megan John

External assessment group: Peninsula Technology Assessment Group (PenTAG)

Technical team: Luke Cowie, Emily Leckenby, Lizzie Bell

Company: Gilead

Seladelpar for treating primary biliary cholangitis [ID6429]

- ✓ **Background and ACM2 summary**
- ❑ Key issues
- ❑ Cost effectiveness results
- ❑ Summary

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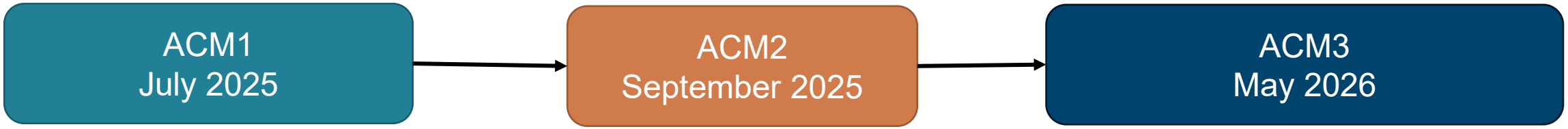
Appraisal history

DG post ACM1 – Seladelpar should not be used within its marketing authorisation to treat primary biliary cholangitis, including pruritus, in adults:

- with ursodeoxycholic acid (UDCA), if the primary biliary cholangitis has not responded well enough to UDCA, or
- alone, if UDCA cannot be tolerated

Post ACM2 – After negative decision at ACM2, company requested opportunity to provide further evidence



Not recommended – uncertainty in:

- Treatment pathway
- Methodology and results of ITCs
- Effect of itching and other aspects of PBC on QoL

Topic paused – company requested third meeting for consideration of additional evidence

Additional evidence:

- Updated base case from company
- EAG critique of new evidence

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Abbreviations: ACM, appraisal committee meeting; DG, draft guidance; ITC, indirect treatment comparison; PBC, primary biliary cholangitis; QoL, quality of life

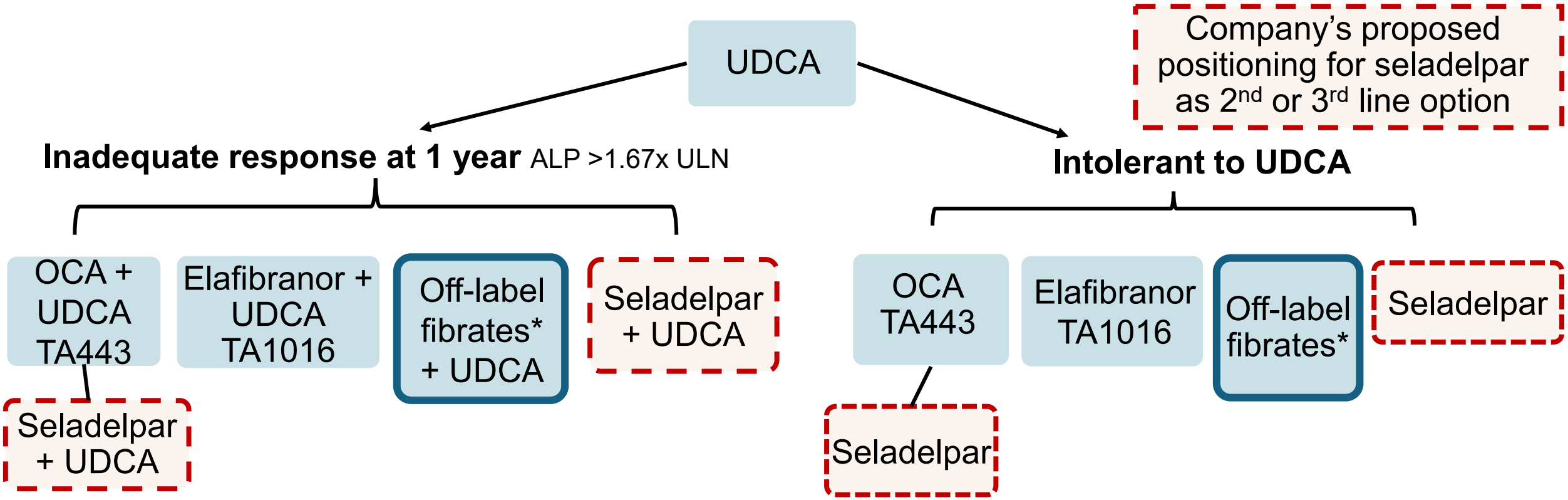
Technology (seladelpar, Livdelzi®, Gilead)

Marketing authorisation	Adults with PBC in combination with UDCA who have an inadequate response to UDCA alone, or as monotherapy in those unable to tolerate UDCA
Mechanism of action	• Selective PPARδ agonist • Reduces bile acid synthesis and accumulation • Anti-inflammatory
Administration	10 mg orally once daily
Price	• The list price: £3,155.00 per pack of 30 capsules of 10mg seladelpar • Confidential PAS discount in place (company increased PAS from ACM2)

Abbreviations: ACM, appraisal committee meeting; PAS, patient access scheme; PBC, primary biliary cholangitis; PPAR, peroxisome proliferator-activated receptor; UDCA, Ursodeoxycholic acid;

Treatment pathway

RECAP



- UDCA is established 1st line treatment option (BSG/PBC guidelines).

*At ACM2 committee concluded:

- fibrates are not a relevant comparator for people with PBC and pruritus because they are unlicensed and not consistently used in NHS practice

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

Relevant committee preferred assumptions following ACM2

No	Key issue and committee	Committee preference	Company response	Changes to company base case?
-	Uncertainty in the relative effectiveness of seladelpar in comparison with existing treatment options (DG 3.7 to 3.9)	• Bayesian NMAs should be done and validated for the ITC for seladelpar and all its comparators, without outcome recalculation	• Agree with committee preference	Updated to reflect committee preference at ACM2
1	Treatment discontinuation rate, 0 to 12 months (DG 3.12)	• The treatment discontinuation rates should be derived from their respective ITC	• Disagree, suggest an alternative approach	Yes
2	Source for pruritus disutility values (DG 3.14)	• The same data source (RESPONSE) should be used for utility values for ALP health states and pruritus	• Disagree, suggest an alternative approach	Yes

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Abbreviations: DG, draft guidance; ITC, indirect treatment comparison; NMA, network meta-analysis; ALP, alkaline phosphatase

Equality considerations and ACM3 remit

Equality issues:

- No new equality issues identified since ACM1 and ACM2

ACM3 remit:

- After negative decision at ACM2, company requested ACM3 to provide further evidence for 2 key issues (discontinuation and pruritus disutilities)
- No additional input requested from stakeholders as only new evidence from the company about the 2 key issues

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Key Issue 1: 0 to 12 month treatment discontinuation (1/3)

Large ICER impact

ACM2 RECAP:

- Company preferred discontinuation rates directly from clinical trials, but provided a scenario deriving rates from its ITC anchored to real-world OCA data, assuming identical discontinuation for seladelpar and elafibranor

- EAG:
  - Maintained that discontinuation rates be anchored to the RESPONSE trial and derived from each ITC to maintain internal consistency
  - Disagreed with equal discontinuation for seladelpar and elafibranor due to clinical differences in the treatments

- **Committee conclusion after ACM2**: preferred the EAG approach

Abbreviations: ACM, appraisal committee meeting; ITC, indirect treatment comparison; OCA, obeticholic acid

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Key Issue 1: 0 to 12 month treatment discontinuation (2/3)

Large ICER impact

Company argument summary	Company rationale	EAG response
OCA discontinuation rate is overestimated	• High relative OCA discontinuation rate based on ITC results driven by low discontinuation in UDCA/placebo arm of POISE; potentially due to exclusion of people with severe pruritus (see ITC results and descriptive statistics here)	• No clear reason for POISE UCDA/placebo discontinuation being lower than in RESPONSE or ELATIVE, would expect equal discontinuation across all 3 trials. Highlighted uncertainty due to low event counts
RWE and clinical studies are unreliable inputs	• RWE suggests discontinuation rates in clinical practice vary substantially from those in clinical studies and predicted by ITC, suggesting both are unreliable inputs for model (see RWE sources here)	• RWE consistently shows much higher discontinuation than in clinical trials • 6-month IQVIA data for ELA and SEL, but not for OCA
Methodological differences between seladelpar and other models generate counter-intuitive results	• When seladelpar is substantially discounted and parity priced to OCA, reducing seladelpar's discontinuation rate reduces its cost-effectiveness (see further detail here)	• This can occur for high-cost drugs when incremental costs accrue faster than incremental benefits

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Abbreviations: ITC, indirect treatment comparison; UDCA, ursodeoxycholic acid; OCA, obeticholic acid; RWE, real-world evidence

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Key Issue 1: 0 to 12 month treatment discontinuation (3/3)

Large ICER impact

Company base case:

- Prefer to apply the same 0 to 12m discontinuation rate to all three comparators; 15.6% (average of ITC results)

EAG suggested base case:

- Equal discontinuation rates may be reasonable, given no differences in baseline characteristics of control arms for pivotal RCTs, but recommends exploring higher rates (20%, 30%, 40%)
  - Prefers 40% for its base case (informed by IQVIA RWE)
- Notes that if discontinuation with OCA is higher than for seladelpar then seladelpar is less likely to be cost-effective

Which approach for treatment discontinuation is most appropriate?

Abbreviations: ITC, indirect treatment comparison; RWE, real-world evidence; RCT, randomised controlled trial; OCA, obeticholic acid

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Key Issue 2: Source for pruritus disutility values (1/5)

Medium ICER impact

ACM2 RECAP:

- Company:
  - Base case: Smith et al. 2022
  - Proposed 2 alternative approaches: alternative application of the Smith et al. 2022 disutilities, and a different literature source for pruritus disutility (Hussain et al. 2023)

- EAG
  - Preferred utilities based solely on RESPONSE EQ-5D-3L data (mapped via ITCH-E study), ensuring internal consistency and avoiding reliance on small external studies that may overestimate pruritus burden

- **Committee conclusion after ACM2:** preferred EAG approach because it used data from the same trial population as the effectiveness evidence and avoided potential double counting

Abbreviations: ACM, appraisal committee meeting

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Key Issue 2: Source for pruritus disutility values (2/5)

Medium ICER impact

Company:

- Fundamental methodological limitations in the mapping study used in the committee base case:
  - RESPONSE data shows little overlap between PBC-40 Clinically Severe and NRS Severe scores
  - So disutilities for Severe pruritus from ITCH-E mapping study almost certainly under-represent magnitude of disutility of Severe pruritus on the NRS scale (values sampled from patients with mild and moderate pruritus on the NRS scale)
  - Further stratification of PBC-40 pruritis scores to generate separate Moderate and Severe scores from the aggregate Clinically Severe score would not be appropriate (because of poor correlation with NRS severity)
- Company commissioned a survey by the PBC foundation (n=152)
  - 55% described feeling frustrated by their itch, with many also reporting embarrassment, low mood, and anxiety
  - 47% reported itch-disturbed sleep, and a third had scratched their skin raw
  - Itch remains deprioritised in routine care: only 36% reported that itch was discussed at clinic appointments

Company collated quotes from people living with chronic pruritus:

"[I] struggle to do ordinary things because I couldn't stop itching"

"I would sometimes scratch them [my arms] so much, particularly during the night, I would draw blood"

"I used to be driving and wanted to pull over to scratch [my feet] – I even took a knife to them a few times"

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Abbreviations: PBC, primary biliary cholangitis; NRS, numerical rating scale

Key Issue 2: Source for pruritus disutility values (3/5)

Medium ICER impact

Company presented new evidence:

Adelphi DSP data

Obtained Adelphi DSP data for PBC (global EQ-5D, PBC-40 and NRS data)

EQ-5D utility differences estimated using multivariable linear regression model, with pruritus severity as the key explanatory variable (NRS score)

Used resulting EQ-5D-based disutilities in its updated base case

Argues these values more robust than RESPONSE values that require mapping from PBC-40

Company base case:

- To apply the pruritus disutility values from the DSP study

Abbreviations: PBC, primary biliary cholangitis; DSP, Disease Specific Programmes; NRS, numerical rating scale

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Key Issue 2: Source for pruritus disutility values (4/5)

Medium ICER impact

EAG:

- PBC survey shows high itch prevalence but does not quantify disutility; does not justify rejecting ITCH-E study
- Company used NRS instead of PBC-40 to classify itch severity, most patients classified mild/moderate:
  - Possible to correct by using PBC-40 in the model. But EAG cannot implement without access to IPD

- Acknowledges severe pruritus disutility may be underestimated in ITCH-E (-0.0345) but has concerns about the validity and coding of the Adelphi DSP analysis:
  - Notes that unadjusted and adjusted incremental disutilities were substantially different for both mild and severe pruritus
  - Reviewing coefficients and standard errors of all explanatory variables, results suggest that ethnicity is a much bigger determinant of health state utility (with white respondents experiencing a disutility of [redacted]) than severe pruritus ([redacted])
  - So EAG considers Adelphi DSP analysis lacks face validity, suggesting that model may be mis-specified

- **EAG suggested base case:**
  - Due to uncertainty in disutility values, performed sensitivity analyses using disutilities of -0.05, -0.1, and -0.15 for severe pruritus; prefers a disutility of -0.15 for its base case
    - Notes that other evidence of pruritus, e.g., for chronic kidney disease, estimates a disutility of -0.2
    - Therefore, EAGs preference may be conservative

Abbreviations: PBC, primary biliary cholangitis; NRS, numerical rating scale; DSP, Disease Specific Programmes; IPD, individual patient data

Key Issue 2: Source for pruritus disutility values (5/5)

Medium ICER impact

Pruritus severity	Company base case		EAG base case	
	ACM2 (Smith et al.)	**ACM3** (Adelphi DSP data)	**ACM2*** (RESPONSE EQ-5D-3L data mapped via ITCH-E study)	**ACM3** (ACM2, except value from sensitivity analysis for severe pruritus)
Mild	-0.1150	[redacted]	-0.0041	-0.0041
Moderate	-0.1150	[redacted]	-0.0041	-0.0041
Severe	-0.3800	[redacted]	-0.0345	-0.1500

* Committee's preferred health state utilities at ACM2

Which source provides the most appropriate disutility values for pruritus?

Abbreviations: ACM, appraisal committee meeting; DSP, Disease Specific Programmes

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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 lower than £25,000 per QALY gained
- EAG suggested base case* is lower than the company's base case

* The EAG highlight its base case is not explicitly preferred, due to the uncertainties in the two relevant parameters

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Abbreviations: ICER, incremental cost-effectiveness ratio, UDCA, ursodeoxycholic acid; QALY, quality-adjusted life-years

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Committee decision making slide

Issue	Committee preference at ACM2	Company base case at ACM3	EAG base case at ACM3
Treatment discontinuation rate (0 to 12 months)	• Treatment discontinuation rates should be derived from their respective ITC	• Same 0 to 12m discontinuation rate to all 3 comparators (15.6%, average of ITC results)	• Same 0 to 12m discontinuation rate to all 3 comparators (40%, based on RWE)
Source for pruritus disutility values	• Same data source (RESPONSE EQ-5D-3L data) should be used for utility values for ALP health states and pruritus	• EQ-5D-based disutilities from its DSP analysis	• RESPONSE EQ-5D-3L data, but with -0.15 disutility for severe pruritus

Which approach for treatment discontinuation is most appropriate?

Which source provides the most appropriate disutility values for pruritus?

Abbreviations: ITC, indirect treatment comparison; ALP, alkaline phosphatase; DSP, Disease Specific Programmes; RWE, real world evidence

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Supplementary appendix

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Treatment discontinuation: Descriptive Statistics and ITC

Large ICER impact

Discontinuation at 12 Months (ITC Results)

SEL vs.	OR (95% CI)	Discontinuation rate
SEL	-	7.8%
ELA	0.58 (0.11, 2.92)	12.7%
OCA 5-10 mg	0.24 (0.03, 1.38)	26.1%
OCA 10 mg	0.19 (0.03, 1.04)	30.8%

Discontinuation at 12 Months (Descriptive Statistics)

Intervention	Active			Control (UDCA / Placebo)			RR
	n	N	Rate	n	N	Rate	
SEL	10	128	7.81%	8	65	12.31%	0.63
ELA	12	108	11.11%	6	53	11.31%	0.98
OCA	16	144	11.11%	3	73	4.11%	2.70

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NICE Abbreviations: ITC, indirect treatment comparison; SEL, seladelpar; ELA, elafibranor; OCA, obeticholic acid; UDCA, ursodeoxycholic acid; RR, rate ratio

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Treatment discontinuation: RWE sources

Large ICER impact

Source	Treatment	Discontinuation rate
Ronca et al., 2025	OCA	33% (retrospective study; no period specified)
Roberts et al., 2020	OCA	17% (retrospective study; no period specified)
Abbas et al. 2023	OCA	22.1% (annual)
Jones et al., 2025	Elafibranor	42% (no period specified)
IQVIA Longitudinal Access and Adjudication Data	Elafibranor	34% (6-month)
	Seladelpar	46% (6-month)

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Abbreviations: OCA, obeticholic acid; RWE, real-world evidence.

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Treatment discontinuation: Counter-intuitive results

Large ICER impact

Company:

- When SEL's discontinuation rate doubles (to 16%), both incremental costs and QALYs fall, but costs fall disproportionately more, lowering the ICER
- This contradicts clinical evidence accepted by NICE showing SEL is clinically superior to OCA (better liver biomarker control and pruritus outcomes). The model suggests SEL becomes less cost-effective when adherence is better
- The issue arises from differences in model structures and assumptions, especially that OCA + UDCA generates far fewer QALYs here than in the original OCA appraisal
- In the current model, no comparator is cost-effective vs. UDCA, meaning treatments with higher discontinuation (reflecting worse clinical profiles) appear more cost-effective regardless of efficacy

Equal Discontinuation for SEL & OCA: Cost-effectiveness results assuming 40% discount off OCA list price

Intervention	Costs (£)	QALYs	Inc. costs (£)	Inc. QALYs	ICER
Committee base case post-ACM2, but with equal drug costs (annual cost: £ 1,451.28), assumed 40% discount for OCA					
SEL + UDCA	[redacted]	[redacted]	[redacted]	[redacted]	48,311
OCA + UDCA	[redacted]	[redacted]			
As above, but doubling the SEL discontinuation rate from 8% to 16%					
SEL + UDCA	[redacted]	[redacted]	[redacted]	[redacted]	35,211
OCA + UDCA	[redacted]	[redacted]			

Abbreviations: OCA, obeticholic acid; UDCA, ursodeoxycholic acid; SEL, seladelpar; QALY, quality-adjusted life-year; ICER, incremental cost-effectiveness ratio.

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Source for health state utility data: Adelphi DSP

Analysis of Adelphi DSP data, with stratification of pruritus severity on NRS scale

Pruritus category	Mean	Adjusted disutility	95% CI		P - Value
			Lower	Upper	
No Pruritus	0.86				
Mild Pruritus (NRS ≥1-<4)	0.796	[redacted]	[redacted]	[redacted]	0.8538
Moderate Pruritus (NRS ≥4–<7)	0.778	[redacted]	[redacted]	[redacted]	0.0573
Severe Pruritus (NRS ≥7)	0.707	[redacted]	[redacted]	[redacted]	<0.0001*