Elafibranor for treating previously treated primary biliary cholangitis

For public – confidential information is redacted [redacted]

Technology appraisal committee C [03 September 2024]

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Company: Ipsen

Elafibranor for treating primary biliary cholangitis

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

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Background on primary biliary cholangitis (PBC)

Chronic, progressive autoimmune disease that leads to a build-up of bile in the liver

Causes

- Cause is unknown, thought to be a mix of environmental and genetic triggers

Epidemiology

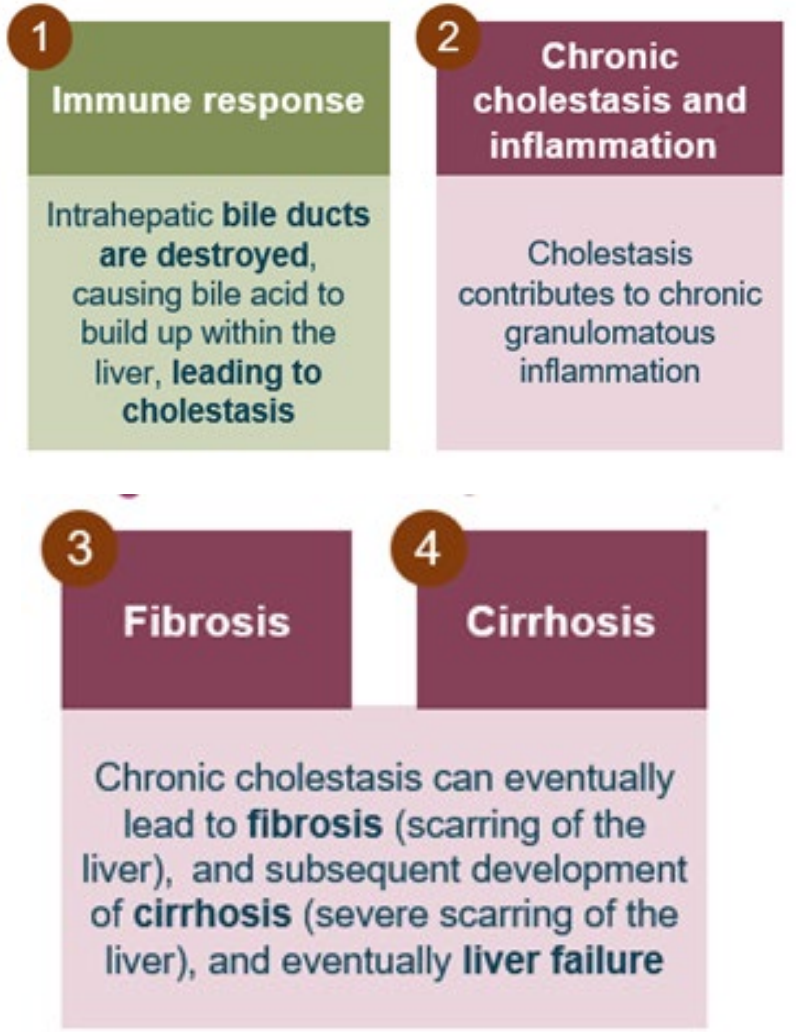
- Around 20,000 people with PBC in UK, annual incidence of 2 to 3 per 100,000
- Approx 90% of people with PBC are women, 25% being under 40 years of age

Diagnosis

- Diagnosis based primarily on biochemical indicators of disease; biopsies rare

Symptoms and prognosis

- Not all people have symptoms, and many have no symptoms until significant liver damage has occurred
- Common symptoms are fatigue and itchy skin (pruritus)
- Early treatment may prevent irreversible liver damage which can lead to liver failure and death



Abbreviations: PBC, primary biliary cholangitis

Patient perspectives

There is an unmet need for people who cannot have UDCA

Submissions from British Liver Trust, Liver4Life, PBC Foundation

- Challenging condition which is rare, has no cure, may have a significant symptom burden and usually requires lifelong medication
- People report feeling very scared following a PBC diagnosis because it is an uncommon condition, but it can be a relief for unexplained symptoms
- Patients report severe fatigue and severe itching as main symptoms
- For most people, a liver transplant is the only treatment option, but PBC can still recur after a liver transplant
- Patient and carers report frustration due to limited access to specialist teams and second-line treatments
- Unmet need for people who cannot have UDCA as OCA has more side effects and there are very limited second-line options

"The itching just got worse and worse…I was scratching so much that I bled"

"I didn't respond to any treatment…I was told I would eventually need a liver transplant"

"[Elafibranor] was a game changer…My itching is now manageable and I am able to go to work"

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

Clinical perspectives

Elafibranor addresses the unmet need for some people having OCA

Submissions from BASL, BHPG

- Treatments aim to slow the progression to end-stage liver disease in PBC and reduce the quality-of-life burden of PBC symptoms
- Disease burden not linked to disease severity, most symptoms in early disease
- Standard of care varies across the country, some reluctant to use 2L treatments
- PBC treatments target two separate drivers of progression, adding complexity
- There is a significant unmet need for this population as a lot of people do not respond to current treatments
  - Approx 40% do not respond to UDCA as first-line treatment
  - Over 30% of people do not respond to second-line treatments
- Elafibranor has a very benign side-effect profile, but no long-term data to confirm
- Elafibranor addresses unmet need for people who have significant itch with OCA

"The benefit [of elafibranor] will be incremental rather than transformative…quality-of-life improvement will be in terms of better itch control and in the avoidance of clinical features in advanced liver disease in people unable to tolerate existing second-line therapy"

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

Equality considerations

Differences in prevalence, outcomes, and access to transplants

Equality issues raised by stakeholders

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

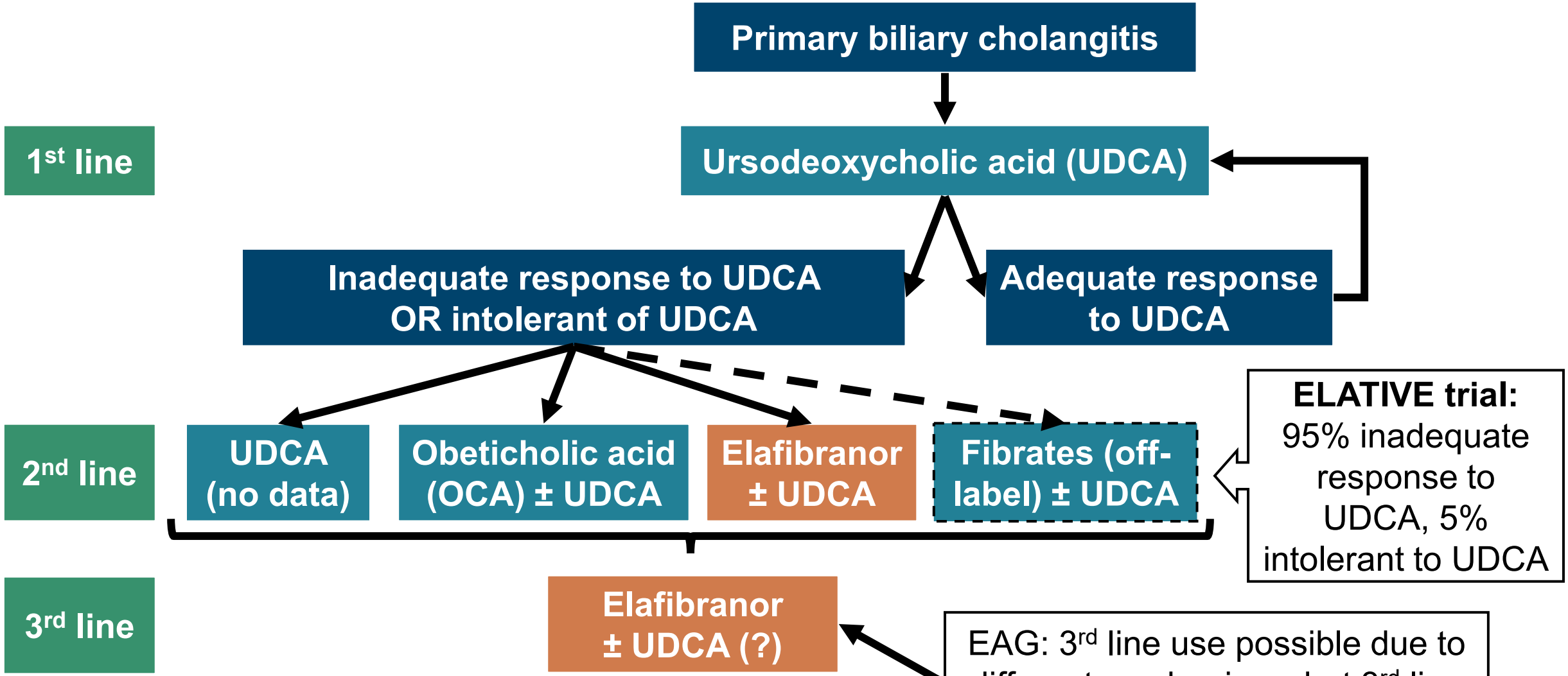
Liver transplants: long waiting lists for transplants with priority given to elderly patients, younger patients most likely to see irreversible liver damage, people with PBC are most likely to die out of all people waiting for a liver transplant

Environmental factors: some evidence suggests smoking, nail polish, hair dyes, hormone replacement and toxic waste linked to linked to PBC

Abbreviations: PBC, primary biliary cholangitis

Treatment pathway

*EMA has recommended revoking the marketing authorisation for OCA, this has no impact on the UK



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

Elafibranor (IQIRVO, Ipsen)

Marketing authorisation	• **Anticipated marketing authorisation wording:** • [redacted] • Marketing authorisation expected in [redacted]
Mechanism of action	• Elafibranor is a peroxisome proliferator-activated receptor (PPAR) agonist, combining the effects of PPAR-alpha and PPAR-delta activation • Combined targeting leads to reduced bile acid concentration in the liver, reduced bile acid synthesis and liver inflammation
Administration	• One 80 mg tablet taken orally daily
Price	• List price for pack of 30 x 80 mg tablets: [redacted] • List price per day: [redacted]; per 12 months of treatment: [redacted] • A patient access scheme is available

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

Key issues

Key Issue raised by EAG	ICER impact
Network meta-analysis results subject to methodological limitations and very wide credible intervals	Unknown
Model survival predictions not validated and possibly under-estimation of people who are liver disease-free	Small – EAG scenario 1
All-cause discontinuation for OCA too high in the model	Large – EAG scenario 2
High-risk biomarker utility values not based on latest data	Moderate – EAG scenario 4
Other key issues raised by NICE team	**ICER impact**
Fibrates might be used off-label and are not modelled	Unknown

Abbreviations: OCA, obeticholic acid

Key issue (NICE team): Use of fibrates

Experts report fibrates are used off-label

Background

- Fibrates not licensed for treating PBC, OCA is NICE recommended second-line treatment for PBC (TA443)

Company

- Model does not include fibrates as a comparator as use is off-label and not recommended by NICE
- Fibrates have not been studied to regulatory standards for PBC patients, there are concerns of tolerability
- Model does include bezafibrate for treating pruritis with OCA and UDCA, but not with elafibranor

EAG comments

- UK audit found over half of people at 2L had fibrates, but can also be used to treat itch
- EAG clinical expert: a small number of people may take a combination of UDCA, OCA and bezafibrate
- [redacted]

Professional organisations

- Fibrates are commonly used as second line treatment off-label, most would also be having UDCA too
- Elafibranor is a PPAR-alpha/PPAR-delta agonist, overlaps activity with bezafibrate (PPAR-alpha agonist)
- Clinical expert: concerns with bezafibrate due to toxicity and lack of supportive evidence

Are fibrates an appropriate comparator for elafibranor that should be included in the model?

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

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Key clinical trials

Two placebo-controlled trials form the main evidence sources

Clinical trial designs and outcomes

	ELATIVE (N=161)	POISE (N=216)
Design	Double-blind, placebo-controlled, phase 3 trial	Double-blind, placebo-controlled, phase 3 trial
Population	People with PBC and inadequate response or intolerant of UDCA	People with PBC and inadequate response or intolerant of UDCA
Intervention	Elafibranor (N=108) with or without UDCA	OCA (N=70; N=73 for unlicensed dose in UK)
Comparator	Placebo (N=53) with or without UDCA	Placebo (N=73)
Duration	52 weeks	52 weeks
Primary outcome	Cholestasis response at Week 52	Cholestasis response at Week 52
Secondary outcomes	Change from baseline in ALP, TB, liver stiffness, pruritis; adverse events	Change from baseline in ALP, TB, liver stiffness, pruritis; adverse events
Locations	Multinational including UK	Multinational including UK
Used in model?	Yes – for intervention arm data	Yes – used as comparator arm in NMA

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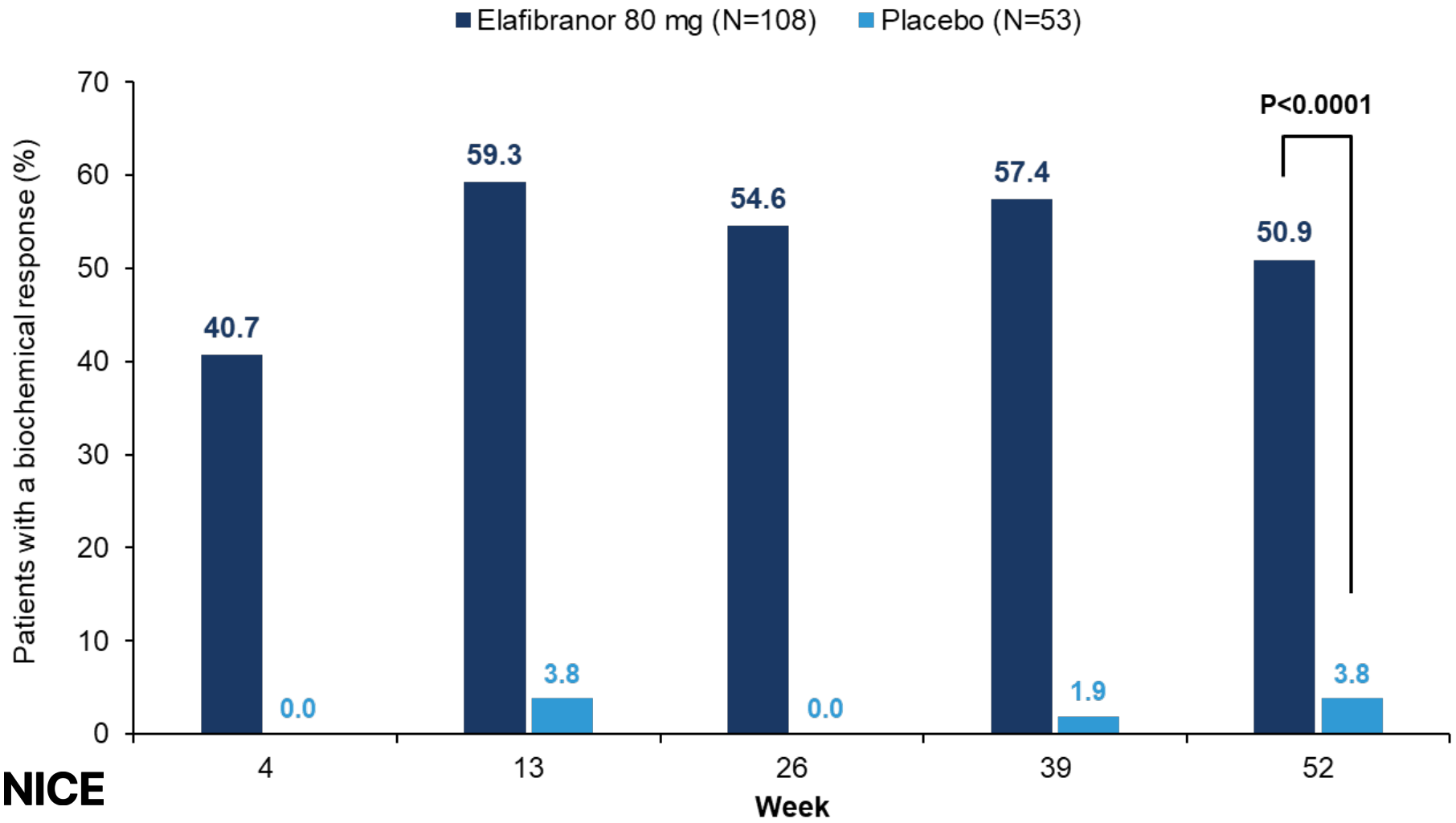
Abbreviations: ALP, Alkaline Phosphatase; NMA, network meta-analysis OCA, obeticholic acid; PBC, primary biliary cholangitis; TB, Total Bilirubin; UDCA, ursodeoxycholic acid

Key clinical trial results – ELATIVE

Elafibranor (n=108) improves cholestasis response compared to placebo (n=53)

Percentage of patients with cholestasis response at Week 52 (Intention-to-treat population)



Cholestasis response was defined as alkaline phosphatase (ALP) <1.67 x upper limit of normal (ULN), total bilirubin ≤ULN, and ALP decrease ≥15%

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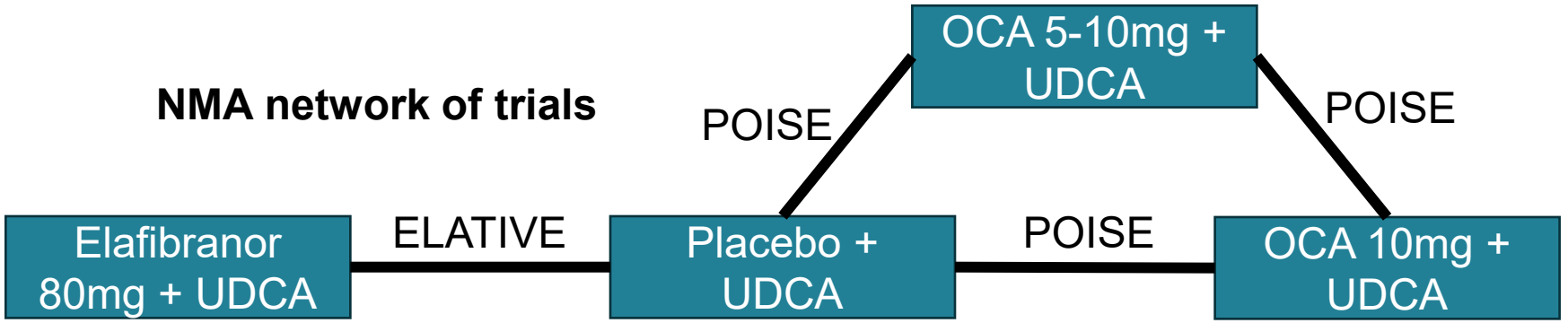
Network meta-analysis overview and results

Cholestasis response not statistically significantly different between elafibranor and OCA

NMA network of trials



Random effects model used in base case

Fixed effects model used in sensitivity analyses

Forest plot – OR of achieving cholestasis response at 12 months in random effects NMA

[redacted]

Abbreviations: NMA, network meta-analysis; OCA, obeticholic acid; OR, odds ratio; UDCA, ursodeoxycholic acid

Key issue: Network meta-analysis results

Wide credible intervals suggest considerable uncertainty in results

Table: NMA results for the random-effects model with credible intervals (CrIs) used in economic modelling

NMA result for elafibranor versus OCA 5-10mg	Figures for the random-effects model
Odds of cholestasis response at 12 months	Median OR: [redacted]
Mean change in pruritis from baseline at 12 months	Median change: [redacted]
Mean change in PBC-40 Itch using earliest data	Median change: [redacted]
Odds of pruritis TEAE (any severity) in 12 months	Median OR: [redacted]
Odds of discontinuation (all-cause) in 12 months	Median OR: [redacted]

EAG uncertainty	EAG comments	Company comments
Credible intervals	• Very wide intervals, all outcomes lack statistical significance • Results are similar for the fixed-effects model	Noted lack of convergence in random effects NMA
Odds ratios	• ORs tend to overestimate effects with a link between exposure and outcome, if interpreted as RRs • EAG analysis does not change NMA conclusions, suggesting uncertainty with elafibranor effectiveness	No rationale given for using ORs instead of RRs
Other issues	• Issues with statistical methods used, excluded studies, transitivity	Responded at clarification

Is the NMA suitable for decision-making? What is the treatment effect of elafibranor versus OCA?

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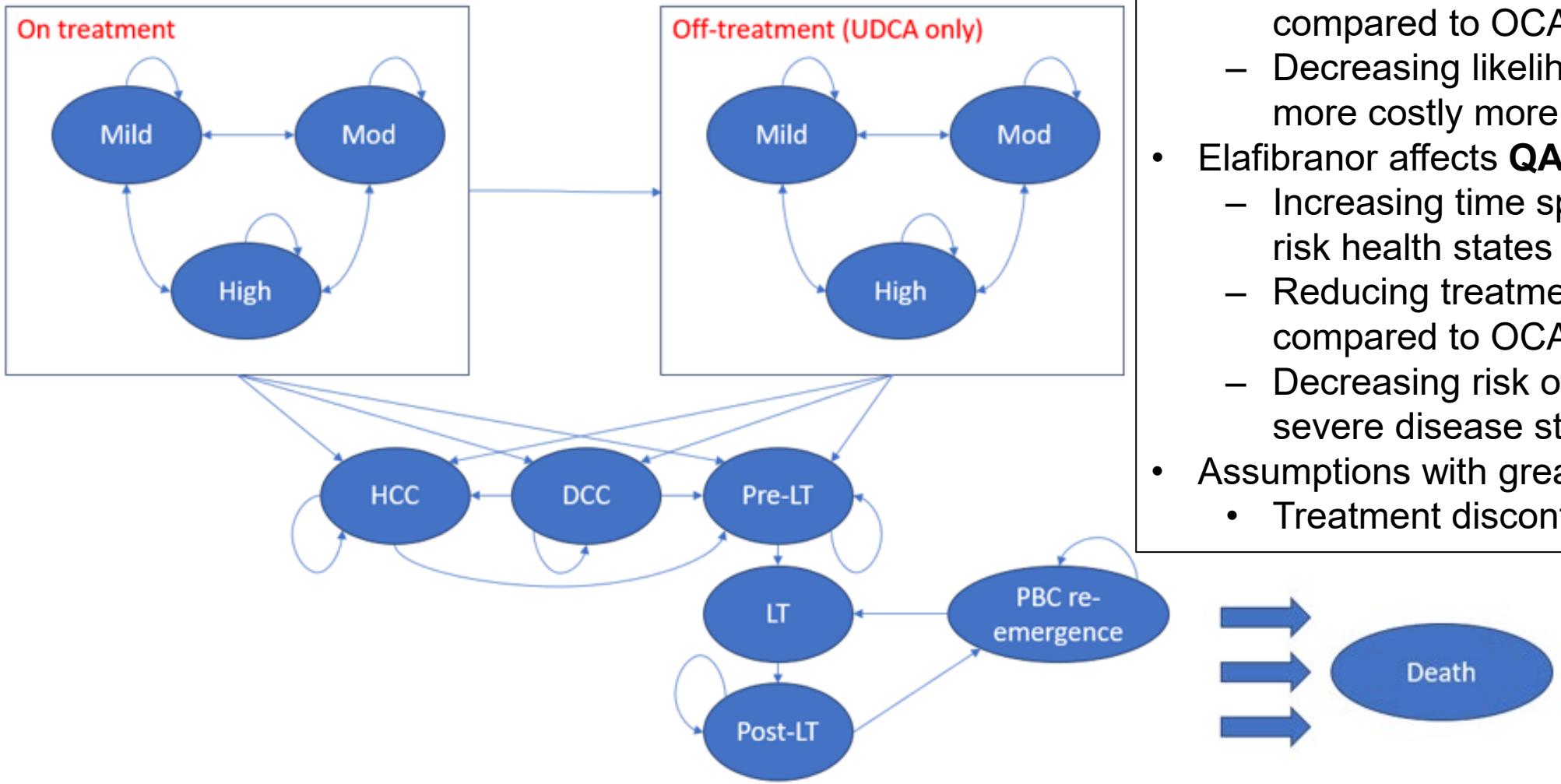
Company's model overview

Figure: Company's model structure



- Elafibranor affects **costs** by:
  - Increasing time spent in lower and less costly PBC biomarker risk health states
  - Reducing treatment discontinuation compared to OCA
  - Decreasing likelihood of progressing to more costly more severe disease stages
- Elafibranor affects **QALYs** by:
  - Increasing time spent in PBC biomarker risk health states which have better QoL
  - Reducing treatment discontinuation compared to OCA
  - Decreasing risk of progressing to more severe disease stages with worse QoL
- Assumptions with greatest ICER effect:
  - Treatment discontinuation

Abbreviations: DCC, decompensated cirrhosis; HCC, hepatocellular carcinoma; LT, liver transplant, OCA, obeticholic acid; PBC, primary biliary cholangitis; QoL, quality of life

How company incorporated evidence into base case model

Table: Inputs, assumptions and evidence source for company base case model

Input	Assumption and evidence source
Baseline characteristics	ELATIVE trial ITT population
Intervention efficacy	ELATIVE trial
Comparator efficacy	NMA results used to adjust ELATIVE trial efficacy for OCA
Discontinuation	ELATIVE data extrapolated for the full time horizon, NMA results for OCA used to adjusted elafibranor discontinuation (see slide 20)
Utilities	TA330; literature (see slide 21)
Costs	BNF; eMIT
Resource use	NHS reference costs 2021/22 inflated to 2022/23 values; NICE TA443; NICE HST17; literature

Abbreviations: BNF, British National Formulary; eMIT, electronic market information tool; ITT, intention-to-treat; OCA, obeticholic acid; NMA, network meta-analysis;

Key issue: Modelled survival predictions

Liver disease progression in trial much lower than model, estimates not validated

Liver disease-free survival

EAG comments:

Model potentially under-predicts liver disease-free survival due to:

- Transitions from moderate risk to liver disease
- Increase in mortality for high-risk patients (reduced increase used in EAG base case, see slide 23)
- Immediate deterioration of risk stage after discontinuation
- UDCA patients cannot move from moderate to low risk
- Uncertain long-term transitions

Liver disease risk predictions far lower in trial than in model for elafibranor at all time points:

Transplant-free survival	5 years	10 years	15 years
Company model	[redacted]	[redacted]	[redacted]
ELATIVE (GLOBE score)	[redacted]	[redacted]	[redacted]

Overall survival

EAG comments:

- Predictions not validated by clinical experts or literature
- Company's experts suggested some aspects of HCC and DCC survival might not fully reflect current care
- Comparison of survival predictions:
  - Model, median HCC survival: 1.5 years
  - Model, median DCC survival: 4 years
  - Literature, HCC overall survival after five years: 43% to 69%
- EAG scenario analyses assess structural uncertainty

Is the company's model suitable for decision-making?

Abbreviations: DCC, decompensated cirrhosis; HCC, hepatocellular carcinoma; UDCA, ursodeoxycholic acid

Key issue: All-cause discontinuation for OCA (1)

The company model used a different approach to TA443

Background

- OCA can be given for a person's lifetime, so company included treatment discontinuation for the long term
- Estimated OCA discontinuation by applying 12-month RR (from NMA) to elafibranor discontinuation (ELATIVE)
- This is different to TA443, where discontinuation was only considered in the first year of treatment

Company

- Originally used an exponential distribution to model discontinuation which assumed constant discontinuation
- Experts agree that discontinuation mostly occurs early in treatment with OCA
- Updated base case uses a lognormal distribution for all-cause discontinuation and lifetime difference in discontinuation between elafibranor and OCA

EAG comments

- UK-PBC data shows at 5 years, [redacted] still on OCA; company's updated model predicted [redacted] by comparison
- Company's model overpredicts OCA discontinuation so EAG base case also uses a lognormal distribution but assumes only a 1-year difference in treatment discontinuation between elafibranor and OCA

Which distribution should be used to model OCA treatment discontinuation?

Abbreviations: NMA, network meta-analysis; OCA, obeticholic acid; PBC, primary biliary cholangitis; RR, relative risk

Key issue: All-cause discontinuation for OCA (2)

Figure 4.2: OCA all-cause treatment discontinuation predictions CS and EAG base-case

*deterministic,
errors fixed by EAG

Abbreviations: CS, company submission; OCA, obeticholic acid

Key issue: High-risk biomarker utility values

EAG raises concerns with utility values used for high-risk health state

Background

- EQ-5D-5L was collected in ELATIVE trial but not used by company due to small sample size in high-risk
- Company opted to use utility values from literature instead

Company

- Linear mixed effects model that calculated utility values of PBC biomarker risk health states led to a decrement in utility between moderate and high-risk health states lower than expected
- Company considered results unreliable, likely due to small sample sizes, and used values from literature

EAG comments

- EAG agrees small sample adds uncertainty, but still considers the data informative
- Utility value for high-risk state in ELATIVE trial is [redacted] than value used in model
- EAG uses more recent utility value from literature for high-risk state (0.717) and uses ELATIVE trial data for all health states in scenario analyses

Table: Utility values in trial and company model

Health state	ELATIVE	Model (SE)	Source
Mild risk	[redacted]	0.84 (0.17)	Cholestatic disease; Younossi (2000)
Moderate risk	[redacted]	0.84 (0.17)	
High risk	[redacted]	0.55 (0.11)	Compensated cirrhosis; TA330

What utility values should be used for the high-risk health state?

EAG base case changes

Changes made to company base case in EAG base case

	Assumption	Company base case	EAG base case
	Model errors	-	Fixed 13 errors in company model
	Probabilities for OCA outcomes	OCA response, pruritus, discontinuation captured via a constant RR	Use constant HR instead
	Pre-liver transplant health state	Include health state in model	Exclude health state in model
Key Issue	Discontinuation	Difference maintained for lifetime	Difference maintained for first year
Key Issue	High risk excess mortality	1.2% excess mortality added to 2% general population mortality (3.2%)	2% general population mortality increased by 1.2% (2.02%)
Key Issue	High risk utility values	0.55 used in model	0.717 used based on recent paper
	Pruritis as a TEAE	Captured via PBC-40 scores and additionally as a Grade ≥ 2 AE	Occurrence assumed to be captured via PBC-40, avoid double counting
	Compliance rates	[redacted] for elafibranor and 93.55% OCA	93.55% for elafibranor and OCA

Abbreviations: AE, adverse event; HR, hazard ratio; OCA, obeticholic acid; PBC, primary biliary cholangitis; RR, relative risk; TEAE, treatment emergent adverse event

To be discussed by committee in Part 2

Cost-effectiveness results

- **Company base case**
  - ICER above £20k
- **EAG base case**
  - ICER above £20k
- **Scenario analyses for:**
  - High-risk mortality
  - Treatment discontinuation
  - Utility values
  - Palliative care costs
  - Progression risks
  - Treatment effectiveness
- **Cost-effectiveness plane:**
  - Shows substantial uncertainty

Key questions for committee

- What are the most appropriate comparators for elafibranor?
- Is the company's NMA suitable for decision-making?
- Is the company's model suitable for decision-making?
- Which distribution should be used to model OCA treatment discontinuation?
- What utility values should be used for the high-risk health state?

All ICERs are reported in PART 2 slides because they include confidential comparator PAS discounts

PAS, patient access scheme

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Key issues

Key Issue	ICER impact	Slide
Network meta-analysis results subject to methodological limitations and very wide credible intervals	Unknown	15
Model survival predictions not validated and possibly under-estimation of people who are liver disease-free	Small – EAG scenario 1	19
All-cause discontinuation for OCA too high in the model	Large – EAG scenario 2	20
High-risk biomarker utility values not based on latest data	Moderate – EAG scenario 4	22

Other key issues raised by the NICE team	Slide
Fibrates might be used off-label and are not modelled	10

Abbreviations: OCA, obeticholic acid

Thank you

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