NICE National Institute for Health and Care Excellence

Part 1	No confidential information
Public handouts	

Odevixibat for progressive familial intrahepatic cholestasis [ID1570]

1st Evaluation meeting

Lead team presentation

Chair: Paul Arundel

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Evidence Review Group: ScHARR

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Company: Albireo

5th August 2021

Key issues, clinical effectiveness

The company positions odevixibat as a first line therapy. • When would odevixibat be used in the treatment pathway in clinical practice? • Before, after, or at the same point in the pathway as partial external biliary diversion (PEBD)?
The company's main trial evidence is limited to PFIC types 1 & 2. Are results generalisable to: • PFIC types other than 1 and 2? • The population in seen in NHS clinical practice? Should the clinical effectiveness of odevixibat be considered by subtype?
How generalisable are the trial results to anticipated NHS use, given that: • The dose of odevixibat in trials differs from that in the marketing authorisation? • There are no defined criteria for dose escalation following lack of response?
There is no comparative data with the company's comparator, PEBD. • Can committee judge the relative effect of odevixibat? • Will the company's planned indirect analysis resolve this uncertainty?

PEBD, Partial external biliary diversion; PFIC, Progressive familial intrahepatic cholestasis

Key issues, cost effectiveness

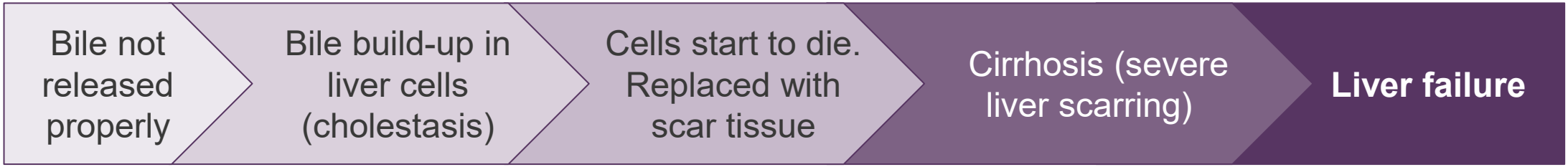
Issue	
To represent loss of response in the model, the company use a proxy outcome (discontinuation rate from PEDFIC2 trial). Is this acceptable?	
The company uses a small cohort to define the proportion taking high dose odevixibat in the model. • What proportion would have high and low dose odevixibat in clinical practice?	
People with odevixibat do not have PEBD in the company model. • Should PEBD be included for odevixibat? • If yes, at a rate equal to standard care?	
The company's probability of requiring liver transplant without prior PEBD is calculated using data that includes both responders and non-responders to standard of care. • For non-responders, is an equal probability of transplant for odevixibat and PEBD expected?	
Different mortality rates are used in the company's and ERG's model. Which are most appropriate?	
The company model uses non-PFIC specific utility values taken from the literature. • Is this acceptable? If not, should utility values from the trial be used?	
Does odevixibat represent a step-change in the treatment of PFIC?	
If routine commissioning cannot be recommended, should managed access be considered? • Does odevixibat have the potential to be cost effective? • Is data collection feasible and will it address the identified uncertainties?	

Key:
Discussion;  Model driver: >£10,000 per QALYS gain change from base case; 
Small/moderate impact: <10,000 per QALY gained change from base case; 

PEBD, Partial external biliary diversion; PFIC, Progressive familial intrahepatic cholestasis

Background (1): Progressive familial intrahepatic cholestasis (PFIC)

Definition: group of hereditary liver disorders that affect the flow of bile from the liver



Common symptoms: Characterised by pruritus (itching) which can be severe and disabling

- Other symptoms: jaundice, vitamin deficiencies, failure to thrive, diarrhoea
- Cirrhosis related: portal hypertension, increased risk of liver cancer, swollen blood vessels in lining of oesophagus, fluid retention in abdomen (ascites)

Multiple subtypes of PFIC: classified by mutant gene

3 main subtypes (PFIC1-3) of which PFIC2 most common

Diagnosis primarily clinical: Pruritus with raised serum bile acid and:

- PFIC 1 or 2: normal gamma GT
- PFIC 3: raised gamma GT, ductular proliferation on liver biopsy

Aim of treatment: No cure: aims to reduce side effects and prevent complications

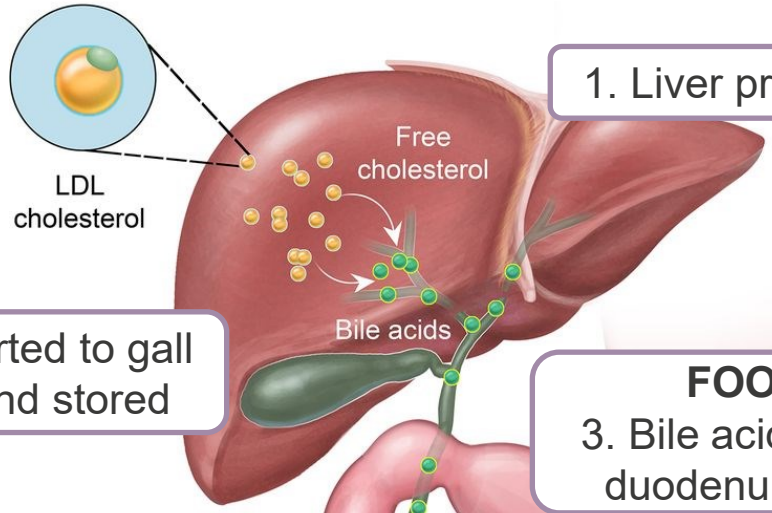
Fatal if untreated: Data limited, higher mortality associated with having PFIC1 or early symptom onset

Prevalence: Uncertain but estimated 1 per 50,000 to 1 per 100,000 PFIC patients worldwide

gamma GT, gamma-glutamyl transferase; PFIC, progressive familial intrahepatic cholestasis

*Source: Srivastava A. 2014.

Background (2): the bile acid cycle

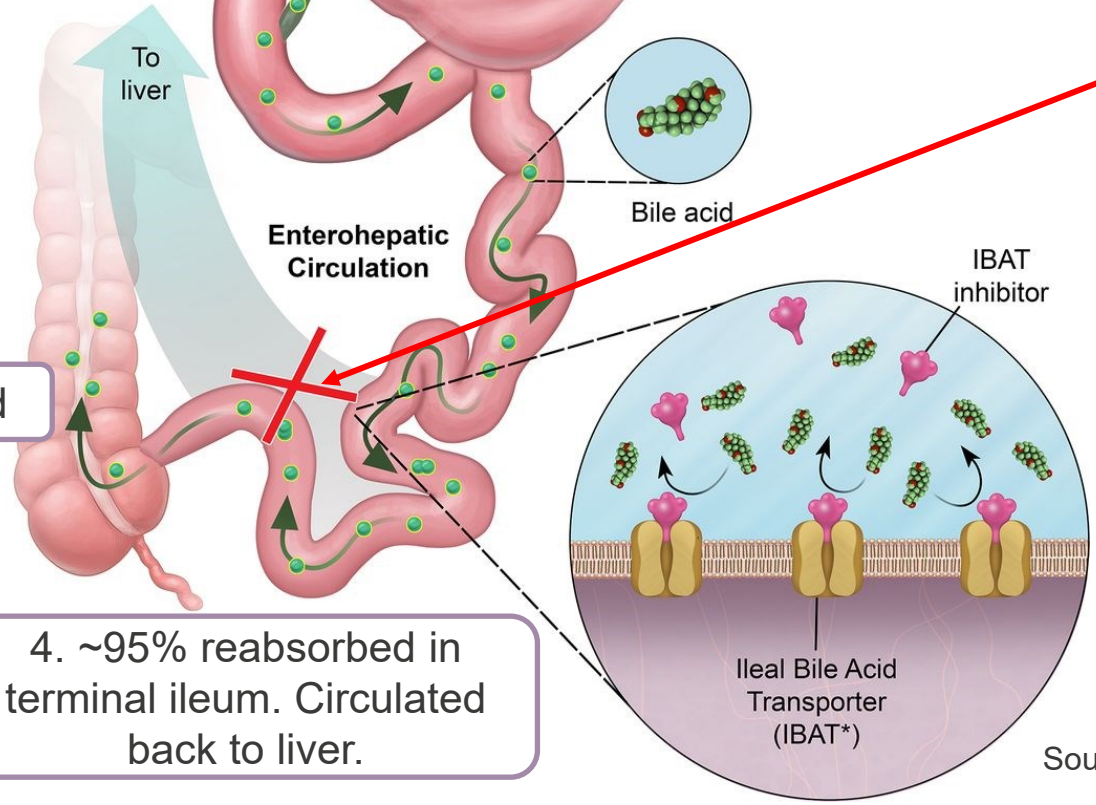


1. Liver produces bile acids

2. Transported to gall bladder and stored

FOOD EATEN

3. Bile acids released into duodenum via bile duct



5. ~5% excreted

4. ~95% reabsorbed in terminal ileum. Circulated back to liver.

Functions of bile

1. Aid digestion by breaking down fats
2. Enable absorption of fat-soluble vitamins
3. Help excrete waste products (e.g. bilirubin and excess cholesterol)

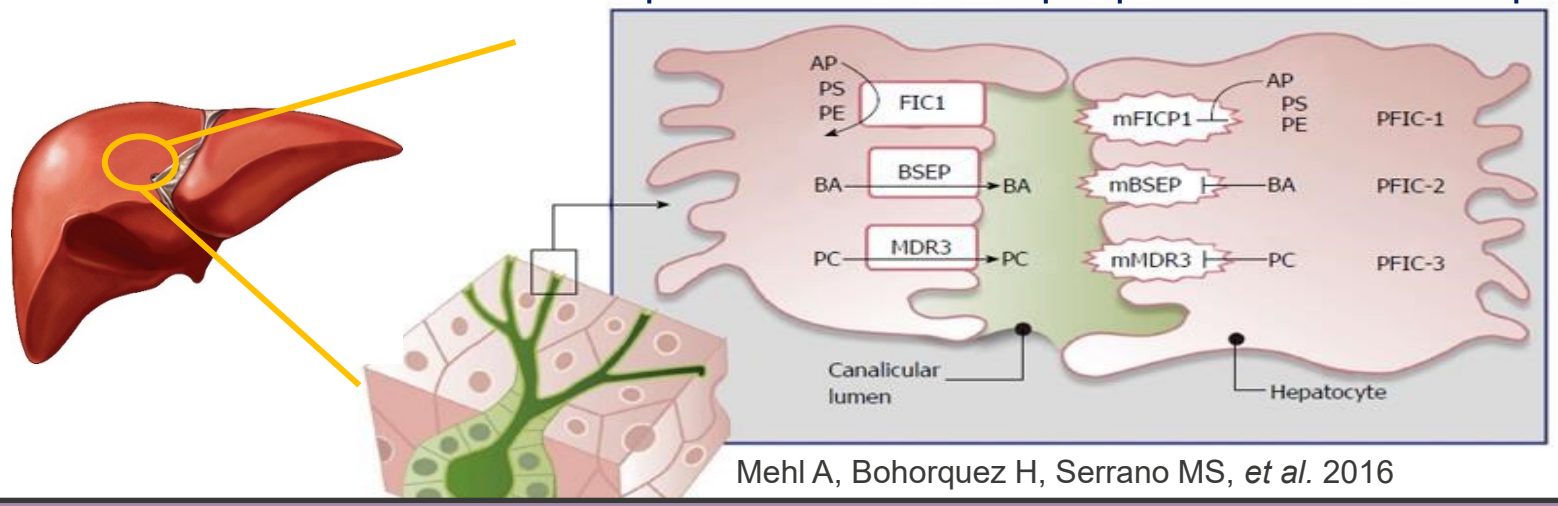
Odevixibat inhibits ileal bile acid transporter (IBAT)

→ Less reabsorption of bile acid

→ Decreased levels in liver

Source: Slavetinsky C, Sturm E. 2020

Background (3): disruption of bile flow in PFIC



Mehl A, Bohorquez H, Serrano MS, *et al.* 2016

AP, Aminophospholipids; BSEP, Bile salt export pump; FIC, Familial intrahepatic cholestasis; PS, Phosphatidylserine; PE: Phosphatidylethinolamine; BA, Bile acids; PC, Phosphatidylcholine; MDR, Multidrug resistance protein; m, Mutant

	PFIC1	PFIC2	PFIC3
Mutant gene	*AT8B1*	*ABCB11*	*ABCB4*
Deficient protein	FIC 1	BSEP	MDR 3
Common genotypes	FIC1-A, FIC1-B, FIC1-C	BSEP1, BSEP2, BSEP3	Multiple
Role	Moves fats across liver cell membrane	Moves bile salts from liver into bile	Moves fats from liver into bile
Cholestasis cause in PFIC	Unclear	Deficient bile salt secretion = build up in liver cells	Low phospholipid in bile = reduced protective function. Bile duct damage.
Included in evidence	Yes	Yes	Limited
Prevalence*	10 – 38%	38 – 91%	28 - 38%

Rarer subtypes include: *PFIC4 (TJP2 mutation), PFIC5 (NR1H4 mutation) and PFIC6 (MYO5B mutation). Limited clinical evidence in PFIC6 only. Additional genetic mutations causing PFIC identified but not yet linked to subtype.*

**Source: Baker et al. 2019*

Background (4): Clinical presentation of PFIC

	PFIC1	PFIC2	PFIC3
Age at presentation	Infancy (likely in 1st year)	Neonatal period	Late infancy (30%) to early adulthood
End-stage liver disease	1st decade	Rapid, first few years	1st to 2nd decade of life
Rate of progression	Moderate	Fast	Slow
Pruritus (itching)	Severe	**Very severe**	Moderate
Extrahepatic features	Watery diarrhoea Pancreatitis Hearing loss **Slow growth** Thicker skin	Absent	Absent
Liver tumours	Not reported	**High risk**	Not reported
Serum GGT	Normal	Normal	**Elevated**
Serum bile acids	Raised ++	**Raised +++**	Raised +
Milder episodic forms	BRIC 1	BRIC 2	None (jaundice & itching in carriers during pregnancy)
Special features	- Early-onset jaundice - **Fat-soluble vitamin deficiencies** common	- Responds well to transplant	- Damage to bile ducts common

gamma GT, gamma-glutamyl transferase; BRIC, benign recurrent intrahepatic cholestasis

*__bold__ denotes outcomes of interest specific to each PFIC type

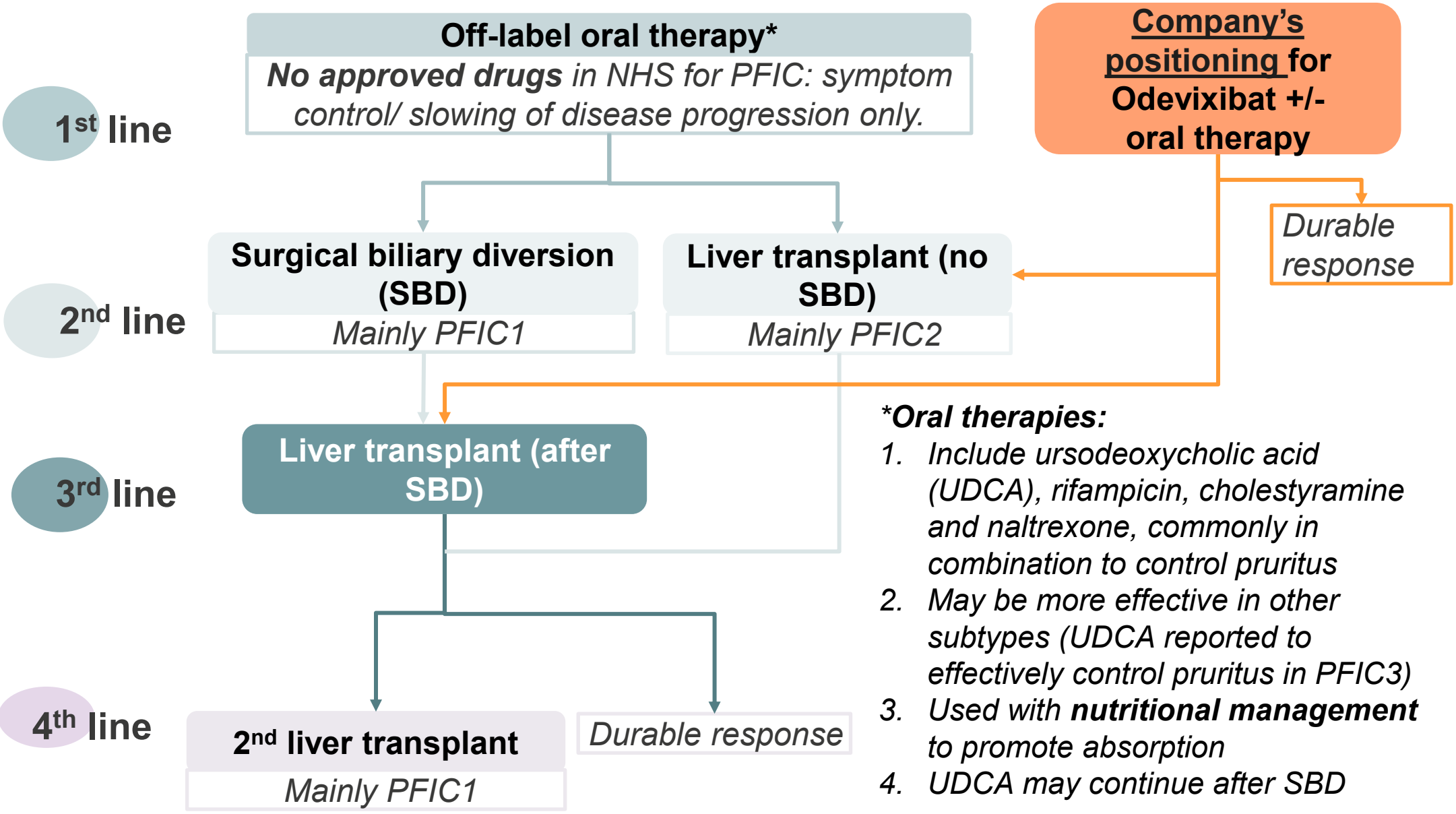
Odevixibat, Bylvay®

Marketing authorisation	*'treatment of progressive familial intrahepatic cholestasis (PFIC) in patients aged 6 months or older.'* • CHMP positive opinion under **exceptional circumstances** (*"unable to provide comprehensive data on the efficacy and safety under normal conditions of use, because the condition to be treated is rare or because collection of full information is not possible or is unethical*")
Mechanism of action	Selective inhibitor of ileal bile acid transporter (IBAT) • Increases bile clearance through colon: less circulates back to liver
Administration	Oral capsules of 200 µg, 400 µg, 600 µg, and 1200 µg
Dosage	40 µg/kg once daily Increase to 120 µg/kg/day if no improvement in pruritus and reduction of serum bile acid levels after 3 months
Duration	Lifelong or until no further benefit. Consider alternative treatment when no treatment benefit after 6 months continuous daily treatment.
Eligible UK population	Estimated [redacted] patients eligible for treatment (plus [redacted] new patients per year)*
List price	Per pack of 30†: 200µg [redacted], 400µg [redacted], 600µg [redacted], 1200µg [redacted] Mean costs of odevixibat anticipated to be [redacted]† per patient per year. A confidential patient access scheme has been proposed.

*Source: Budget impact report, company submission, table 90. †Source: company's budget impact model

Treatment pathway (1): company's suggested positioning

No UK-specific guidelines. European Association for the Study of the Liver recommends:



Oral therapies:

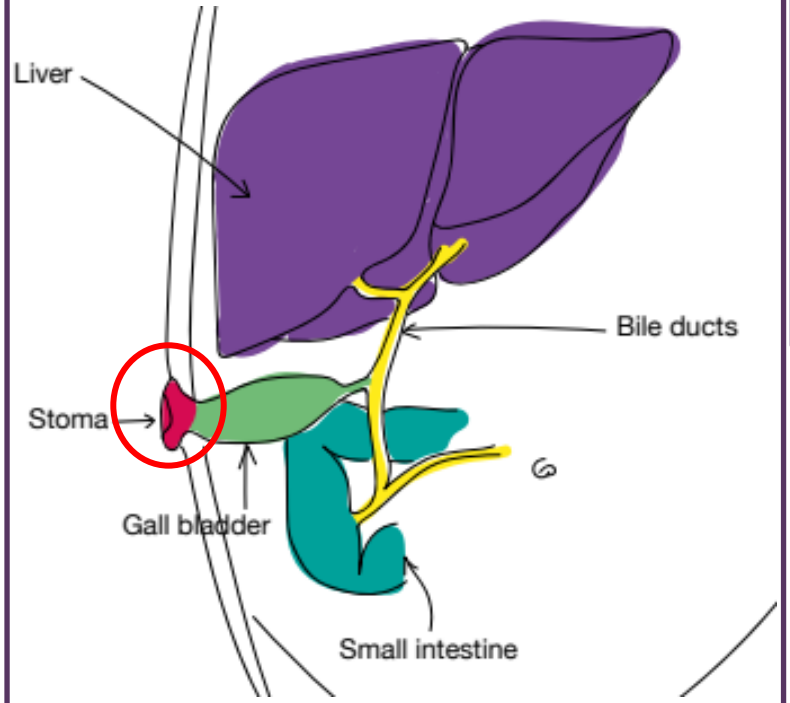
1. *Include ursodeoxycholic acid (UDCA), rifampicin, cholestyramine and naltrexone, commonly in combination to control pruritus*
2. *May be more effective in other subtypes (UDCA reported to effectively control pruritus in PFIC3)*
3. *Used with **nutritional management** to promote absorption*
4. *UDCA may continue after SBD*

◉ *Does this pathway correctly reflect treatment options for PFIC1 and 2 in the NHS?*

Treatment pathway (2): surgical options

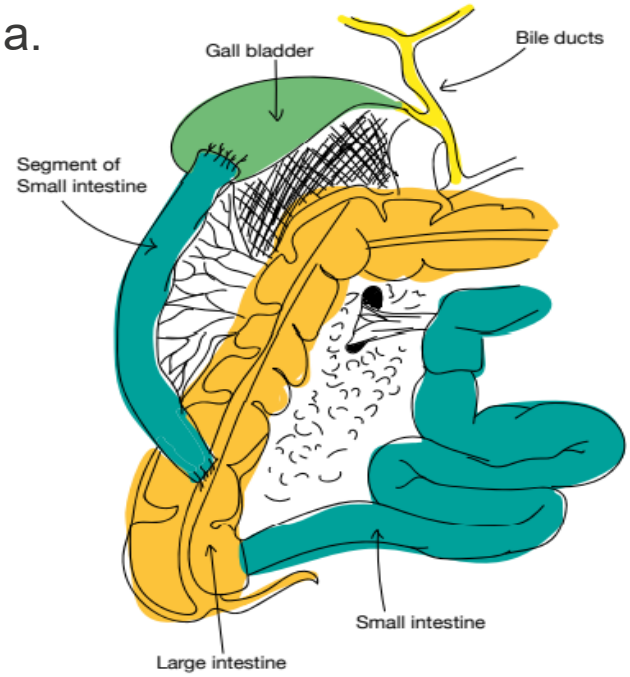
SURGICAL BILIARY DIVERSION (SBD)

Partial external biliary diversion (PEBD): most common SBD
Pros: Rapid sBA reduction, increased native liver survival, can delay transplant
Cons: rarely permanent, complications (including re-operation)

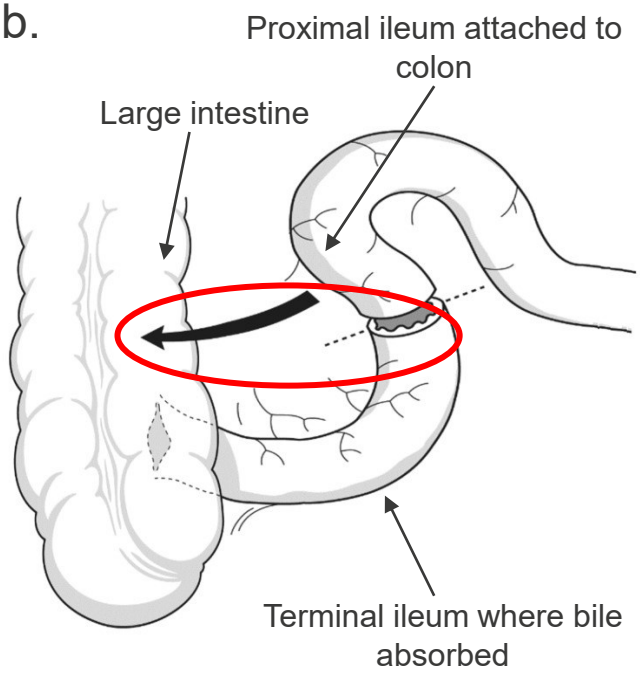


Partial internal biliary drainage (a), internal ileal exclusion (b)
Pros: newer surgeries that avoid stoma & related complications
Cons: Few cases: little evidence

a.



b.



LIVER TRANSPLANT

Eventually required by most PFIC patients (even after SBD)
Pros: replaces defective liver cells, improves pruritus & survival
Cons: morbidity and mortality risks, complications (e.g. graft rejection), lifelong immunosuppression

PEBD, Partial external biliary diversion; sBA, serum bile acid

Source: Children's Liver Disease Foundation. 2019 and adapted from Christensen P, Laurberg S. 2013

Treatment pathway (3): ERG comments

- Odevixibat could be used **before or after PEBD and liver transplant**
  - [redacted] of 62 people in the pivotal trial had prior PEBD surgery

- Company proposes odevixibat as a 1st line therapy in the NHS, but states that the relevant comparator is PEBD for this submission because "odevixibat is the medical equivalent" of PEBD
  - PEBD positioned at 2nd line in the treatment pathway: difficult to determine where odevixibat would be used in the NHS.

- Mixed clinical advice as to whether PEBD and odevixibat clinically equivalent

- In exploratory analyses, ERG proposes **different populations depending on need for immediate PEBD**, with:
  - 9 potential treatment combinations
  - Odevixibat positioned at 1st, 2nd and 3rd line

◉ *When would odevixibat be used in the treatment pathway?*
◉ *Would it ever be used before or after PEBD in the NHS?*

NHS England and Improvement perspective

Pathway well defined

- Odevixibat, if approved:
  - would provide an additional treatment option
  - would not alter the pathway of care

Administered by highly specialised paediatric liver disease services

- 3 providers in NHS
- Provide family-centred specialist care for children and families with liver disease, including metabolic liver disease, acute liver failure and pre-and post liver transplant management
- Administered under existing arrangements
- No additional investment required

Professional group submission

British Association for the Study of the Liver

Symptoms and presentation

- Considerable heterogeneity within each individual subtype
- Understanding link between genetics and symptoms: poor, but improving
- Benefit from odevixibat will differ depending on PFIC subtype and treatments used

Unmet need for PFIC treatments

- Clinicians "*feel helpless"* to manage intractable pruritus: distressing for families and children
- Odevixibat side effects mild to moderate: no impact on management / patient's quality of life
- If approved, will complement available therapies for PFIC

Implementation

- Likely positive impact on specialised services: improved patient symptoms = less clinical support
- No additional infrastructure, staffing or professional input required
- Genetic testing routine in suspected PFIC cases: no extra clinical requirements or blood tests

Evidence base

- Trials reflect UK practice, are generalisable to UK setting, capture most important outcomes
- Development of liver cancer in children with PFIC2 and need for surgical intervention (transplant or non-transplant) not captured in trials

Patient and carer group submissions

Patient and carer group submissions

Living with PFIC – Impact on patient and carer quality of life

Quality of life may be extremely poor

Debilitating physical effects including pruritus and muscle wastage

- *"My child…broke his leg the day after he started walking due to **lack of absorption of vitamin D**."*
- *"He couldn't eat/drink/sleep properly, his physical development was very delayed, his itching was unbearable. He needed **24/7 care** and attention*."

Considerable psychological impact from living with symptoms

Education disrupted

- Increased sick days due to broken sleep/ hospital appointments
- Impaired social development and peer group interaction
- Lack of concentration in school due to tiredness / itching-related pain
- Need for one-to-one support / part-time schooling to help with movement and toilet needs

Significant impact on family

- Both mental and physical impact on carers and families
  - *"It **takes over the whole family** including our older child. Lots of hospital visits, sleepless nights, lots of washing with sickness and loose stools."*
- Loss of earnings, career repercussions for carers as must give ***"constant care**."*
- Traumatic for siblings to see suffering. Siblings suffer psychologically, have significant time away from home and education suffers.

Patient and carer perspectives

Symptoms of PFIC

Pruritus most common symptom: can be severe

- Most frequent at night: 67% PFIC patients report pruritis associated sleep disturbances
- [redacted] occur because of uncontrolled pruritus*
- *"The itch was a huge issue with significant impact on the family."*

Poor weight gain in PFIC

- Worrying symptom for parents and carers, especially PFIC1

Growth retardation in people with PFIC

	PFIC1 (%)	PFIC2 (%)
Failure to thrive	90	59
Height (<3rd percentile)	85	49
Weight (<3rd percentile)	56	29

Source: company submission, table 5

Other problems of note

- Associated learning disabilities and poor behaviour problematic for families
- Unpredictability of condition, particularly speed of progression, causes anxiety
- Portal hypertension can be distressing
- PFIC so rare that families feel isolated, disease not always understood by local care providers

*Source: NAPPED natural history cohort study of patients with PFIC1 and PFIC2

Patient and carer group submissions

Current treatments for PFIC

Current treatment options poor

- Oral treatments manage symptoms (pruritis, vitamin deficiency, nutrition) with aim to delay transplant:
  - Not PFIC specific so varying levels of success
- Transplant not a cure:
  - Requires lifetime care and long-term immunosuppression associated with risks and anxiety that transplant will fail

PFIC specific treatments welcomed

No treatment currently available specifically for PFIC patients

- *"Anything that could help with symptoms, e.g. itching, slowing the progression of the condition would be a miracle and a* ***huge relief for all families*** *with a PFIC child."*
- *"The new treatment being discussed for PFIC with it being* ***available to all types of the condition*** *sounds great."*
- The treatment gives *'hope to patients'*
- There is unmet need for patients with this condition to have better treatment options

Patient and carer perspectives

Liver transplant in PFIC

Associated with significant complications

- Lack of suitable donors: **long waiting list** (as of 31 Mar 2021, 115 people on waiting list for a liver*)
- Reported post-transplant **complications** in PFIC: worsening diarrhoea, no catch-up of stature growth, fatty liver, pancreatitis and deafness.
  - *"My daughter suffered severe, life-threatening post transplant complications. She is now immunosuppressed…with ongoing medical issues which will continue throughout her life"*
- **Rarely used for PFIC1** due to ongoing extrahepatic manifestations post-transplant

Currently required by most PFIC patients

- Odevixibat *"gives hope of avoiding transplant and a better quality of life"*
  - *"Very little option…only treatment option was a liver transplant"*

High rejection rates post-transplant

- Patients and caregivers anxious about transplant and associated complications

Overall and graft survival in paediatric patients receiving a liver transplant for any reason

Time after transplant	6 months	1 year	5 years	10 years	20 years
Patient survival	87%	86%	81%	78%	69%
Graft survival	**76%**	**73%**	**67%**	**63%**	**53%**

Source: company submission Table 8

*Source: NHS Blood and Transplant. Annual Activity Report

Clinical effectiveness evidence

Decision problem

	Final scope NICE	Company deviations	ERG comments
Population	People with progressive familial intrahepatic cholestasis (PFIC)	• Expected licence in people aged ≥6 months • Excludes people with BSEP3 mutation (complete deletion of protein)	Scope population includes all PFIC types: **does not reflect evidence** (which is mainly PFIC1 and 2)
Intervention	Odevixibat (A 4250)	None	None
Comparators	Established clinical management without odevixibat, may include: • off-label drug treatments such as ursodeoxycholic acid (UDCA) • surgical interventions such as partial external biliary diversion (PEBD) or internal ileal exclusion	Odevixibat compared with off-label drug treatments in company model, however company do not consider these relevant comparators in NHS practice because: • Limited symptomatic efficacy • No RCTs to support use • Used alongside odevixibat Costs and resource use for off-label drugs applied for odevixibat and standard care	• Company does not **present comparative clinical evidence** for PEBD • Off label drugs included in both arms of RCT: included in the definition of **'established clinical management'** without odevixibat

BSEP, bile salt export pump; RCT, randomised controlled trial

Clinical evidence summary

Odevixibat

A4250- 003
Phase II, single arm, dose finding study
Chronic cholestasis (not PFIC specific)
N = 24

Primary efficacy data:
PEDFIC1
Phase III, blinded RCT vs. placebo
PFIC1 and 2
N = 62

Expanded access program (EAPs)

PEDFIC2
Phase III, open-label extension study of PEDFIC1
Cohort 1: PEDFIC1 patients
Cohort 2: All PFIC types
N = 71

Planned study: [redacted], Odevixibat vs External Control
Indirect comparison of [redacted]

Natural History

NAPPED
PFIC1 and 2

Key:
- Completed
- Ongoing
- Planned

See slide 26 for further relevant studies

N, number; RCT, randomised controlled trial

Clinical trials (1): Completed

	Phase 2 study (A4250-003) (N=24)	PEDFIC1 (N=62)
Trial design	Phase 2 open-label dose-escalating	Phase 3, double-blind, RCT
Population	Chronic cholestasis (mixed causes)	PFIC1 and 2
Location	7 sites in Europe	33 sites in United States, Canada and Europe ([redacted] patients in UK)
Control arm	None	Placebo
Key inclusion criteria	sBA ≥2 times ULN, VAS itch ≥3 (0-10 scale), aged ≥12 months to <18 years	sBA ≥100 µmol/L, pruritis ≥2 (0-4 scale), aged ≥6 months to ≤18 years, no biliary diversion surgery within prior 6 months
Treatment duration	Single dose, then 4 week treatment period	24 weeks
Dose	10, 30, 60, 100, 200 µg/kg/day	40, 120 µg/kg/day
1º endpoints	• Change in total sBA levels over treatment period • Incidence of treatment-emergent SAEs	• % with ≥70% reduction in sBA from baseline or reaching ≤70 µmol/L by end of treatment (Europe and rest of world) • Proportion +ve pruritus assessments over treatment period (United States).
HRQoL?	No	PedsQL questionnaire (not in model)
In model?	NO	**YES: Primary efficacy data**

HRQoL; health related quality of life; N, number; PedsQL, Pediatric Quality of Life Inventory; RCT, randomised controlled trial; SAE, serious adverse event; sBA, serum bile acid; UK, United Kingdom; ULN, upper limit of normal; VAS, visual analogue scale

Clinical trials (2): Ongoing

	PEDFIC2 (N=71)
Trial design	Phase 3, multi-centre, open-label extension study of PEDFIC1
Population	PFIC 1, 2, 3 and 6
Location	Worldwide ([redacted] patients in UK)
Date of completion	Expected [redacted]
Control arm	None
Key inclusion criteria	Cohort 1: completed PEDFIC1 Cohort 2: Treatment naïve: PFIC, any age, sBA ≥100 µmol/L, pruritis ≥2 (0-4 scale) , no biliary diversion surgery in prior 6 months.
Treatment duration	72 weeks, median treatment duration at data cut [redacted] weeks (range [redacted])
Dose	120 µg/kg/day
1º endpoints	• Change from baseline sBA (≤70 µmol/L or reduction of 70%) at end of treatment period (Europe and rest of world) • Proportion of positive pruritus assessments over treatment period (United States)
Key 2º endpoints	• Number undergoing biliary division surgery or liver transplant • Mortality • Change in growth and end stage liver disease
HRQoL?	PedsQL questionnaire
Used in model	**YES: Discontinuation rates and response rates for up dosing from interim analysis 15th July 20 (week 24)**

HRQoL; health related quality of life; N, number; PedsQL, Pediatric Quality of Life Inventory; sBA, serum bile acid;

PEDFIC1 and 2: trial schema

PEDFIC1
24 week treatment period

PEDFIC2
72 week treatment period

Rx 1:1:1

- **Placebo** N=20
- **Odevixibat 40µg/kg/day** N=23
- **Odevixibat 120 µg/kg/day** N=19

Odevixibat 120 µg/kg/day
Cohort 1: N=56

Odevixibat 120 µg/kg/day
Cohort 2: N=17

Current data cut:
15 July 2020
Week 24
Included data from:

	N
Placebo	**
40µg/kg/day	**
120µg/kg/day	*
Cohort 2	*
Total	**

	Continued to PEDFIC2, N (%)*		Didn't continue to PEDFIC2 N (%)	
	Completed PEDFIC1 treatment period	Early roll over - lack of efficacy/intolerable symptoms of disease	Completed PEDFIC1 treatment period	Didn't complete PEDFIC1 treatment period
Placebo	14 (70)	5 (25)	1 (5)	0 (0)
40µg/kg/day	17 (74)	4 (17)	1 (4)	1 (4)
120µg/kg/day	14 (74)	2 (11)	2 (11)	1 (5)
Total	**45 (73)**	**11 (18)**	**4 (7)**	**2 (3)**

*Includes * patients who entered PEDFIC2 after the data cut off date, not included in PEDFIC2 analysis
Source: adapted from PEDFIC1 clinical study report, table 9. N, number; Rx; randomisation

Other relevant evidence sources

Study	Status	Study design	Population	Key outcomes	In model?
Clinical effectiveness of odevixibat					
Expanded access programme	Ongoing	Expanded access (120 µg/kg/day odevixibat)	PFIC with elevated sBA; not in PEDFIC2	Unknown	No
Odevixibat vs External Control [redacted]	Planned	Indirect treatment comparison vs. standard care with/without PEBD	[redacted]	[redacted]	No
Registry study	Planned	[redacted]	[redacted]	[redacted]	No
Natural history of PFIC					
NAPPED	Ongoing	Observational retrospective, cohort study	PFIC1 and 2	Incidence of LT, PEBD Mortality	**YES: Data for PEBD, probability of LT**
Resource use and utilities					
PICTURE	Complete	Caregiver and clinician resource survey	PFIC1, 2 and 3: caregivers and clinicians	Impact of PFIC on patient and caregiver HRQoL	**YES: Resource use (base case)**
Utilities elicitation study	Complete	Vignette study	General public, PFIC clinicians, stoma bag patients	Utility values for health states in the model	**YES: Utilities (scenario analysis)**

HRQoL; health related quality of life; LT, liver transplant; PEBD, partial external biliary diversion; sBA, serum bile acid

ERG comments on trials (1): Population

1. **Eligibility criteria for PEDFIC1 and PEDFIC2 reasonable and generally representative of routine UK clinical practice**

- **PEDFIC1 and 2:** Some discrepancies between NHS practice and trial population:
  - Patients required **sBA ≥100 µmol/L and average pruritis score ≥2** (scale 1-4, caregiver-observed scratching over 2 weeks)
    - *5 people excluded from PEDFIC1, 3 from PEDFIC2 who met pruritus eligibility criteria but not sBA criteria*
    - *Aim of treatment is to **reduce pruritus-related itching and scratching**: people with sBA <100µmol/L likely treated in clinical practice*
- **PEDFIC1:** does not include people with:
  a) Subtypes other than PFIC1 & 2; b) Previous non-response to IBAT inhibitor; c) Biliary division surgery within 6 months

  These people were not excluded from PEDFIC2 Cohort 2 which is likely more representative of NHS clinical practice than the population in PEDFIC1

  *However, patients enrolled in **PEDFIC1 generally characteristic** of PFIC patients in NHS*
- **Phase 2 study** included multiple cholestatic diseases: PFIC subtypes (potential confounder) grouped in analyses

2. Differences in PEDFIC1 baseline demographics between odevixibat and placebo should not advantage either arm

- Some observed differences in age, growth parameters and use of off-label treatments between PEDFIC1 arms at baseline: not expected to impact how odevixibat would work

◉ *Are the trials generalisable to subtypes other than PFIC1 and 2?*

IBAT, ileal bile acid transporter; sBA, serum bile acid

ERG comments on trials (2): Trial design

1. **Potential biases in PEDFIC2 trial design**

- Open label design: potential attrition bias, natural recovery, regression to the mean

2. **Trial dosing not reflective of marketing authorisation**

Summary of product characteristics: "*The recommended dose of odevixibat is **40 mcg/kg/day**…..If an **adequate clinical response** has not been achieved after 3 months of continuous therapy, the dose may be increased to **120 mcg/kg/day***"

In both PEDFIC1 and 2, dose not dependant on response.

- PEDFIC2 cohort 2 (treatment naïve) started directly on higher dose
- Responders to 40 µg/kg/day in PEDFIC1 had high dose in PEDFIC2.

3. **Short follow-up period**

- Only 24 weeks comparative data with standard care (placebo), maximum [redacted] week follow up (patients receiving odevixibat in PEDFIC1 who rolled over to PEDFIC2)
- Difficult to assess longer-term outcomes (e.g. survival, transplant-free survival) and long-term impact on sBA levels and pruritus

◉ *How does trial dosing impact trial generalisability to NHS practice?*

sBA, serum bile acid

ERG comments on clinical trials (3): Outcomes

1. **<u>Of trial outcomes, sBA, pruritus reduction and growth most clinically important</u>**

- Vitamin absorption also clinically relevant: not captured in trials
- Many trial outcomes conceptualise sBA response and pruritus in different ways

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2. **<u>No definition of '*adequate clinical response*' for dose escalation</u>**

Company: real-life definition not currently possible. Liaising with clinical experts to define:

a) Specific <u>dose escalation criteria</u>:
   - clinicians consider multiple factors (age, liver disease severity, imminent surgery)

b) <u>Clinically meaningful changes</u> in sBA and pruritus:
   - sBA improvement with no reduction in pruritus might not be useful

ERG: without a definition of response, **generalisability of the trials to NHS unknown**

Clinical experts:

- Most clinically significant outcome is pruritus alleviation: not always associated with sBA reduction, difficult to determine an absolute threshold significant of response
- sBA reduction also important as associated with improved native liver survival

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◉ *Which outcomes are the most important in PFIC?*
◉ *How should an adequate clinical response to odevixibat be defined?*

sBA, serum bile acid

Clinical effectiveness results

Summary of outcomes used in the clinical trials

Definitions of serum bile acid and pruritus response used in clinical trials

Definition	Phase 2 study	PEDFIC1 (used in model)	PEDFIC2 (used in model)
Serum bile acid response (sBA)	None used: • 1° outcome: change in total sBA levels	**≥70% reduction** from baseline or reaching a level **≤70 µmol/L**	None used: • 1° outcome: change from baseline in sBA
Pruritus response	None used: • 2° outcome: change in visual analogue scale (VAS)-itch score	A **positive pruritus assessment**: • A scratching score of **≤1** or **≥1 point drop** from baseline on company's own observer-reported instrument.	

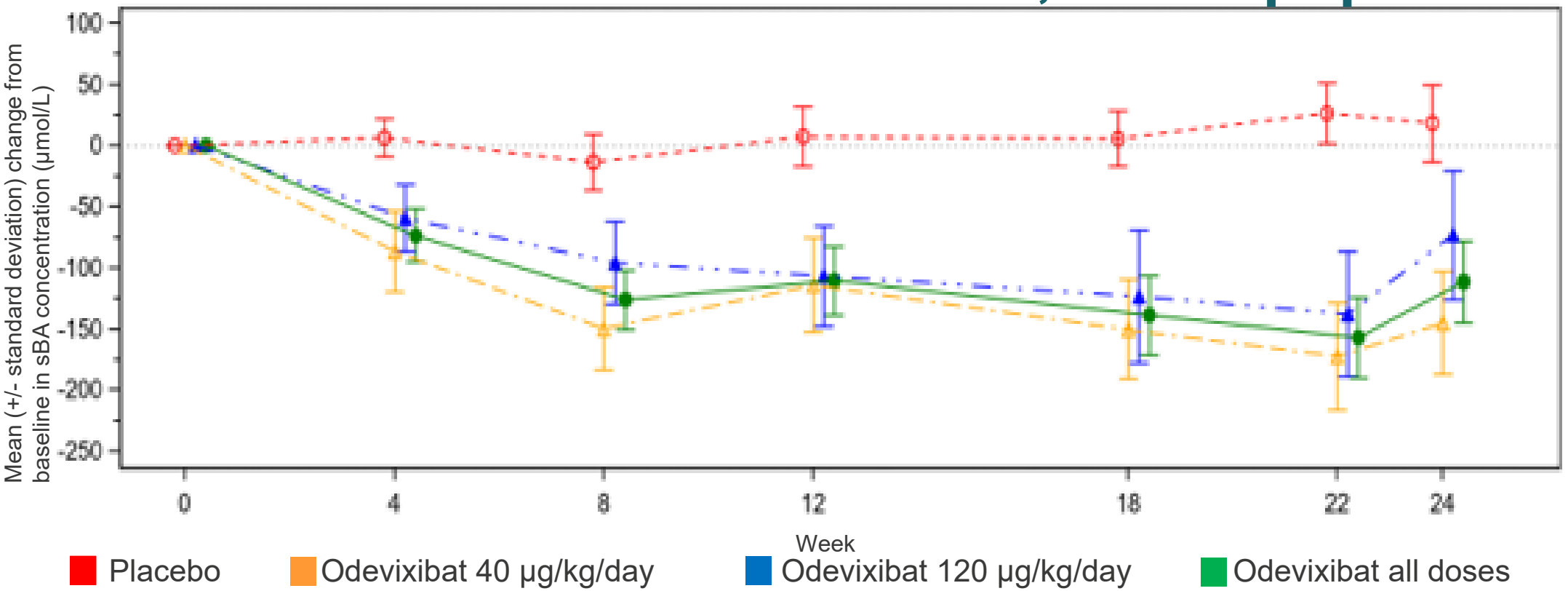
Measuring pruritus

- No publicly available instruments to asses pruritus from PFIC patient/ caregiver perspective
- Company developed new instrument to capture effect of pruritis on quality of life
  - Twice daily pruritus data on a scale of 0 to 4 collected via e-diary from:
    - **Caregivers (ObsRO)**: recorded observed scratching using [redacted]
    - **Patients > 8 years old (PRO):** self-reported itching using [redacted]

ERG comments:

- ObsRO validated by blinded psychometric analyses by independent group: valid, reliable and sensitive to change.
- Validation occurred during PEDFIC1 using [redacted] patients: validity **not known at start of trial**

Serum bile acid reduction: PEDFIC1, whole population



Proportion of patients with sBA response at 24 weeks

	Placebo N=20	Odevixibat 40 µg/kg/day N=23	Odevixibat 120 µg/kg/day N=19	Odevixibat all doses N=42
Responders, N (%) **95% Confidence interval**	0 (0 to 17)	[redacted]	[redacted]	14 (33) (20 to 50)
Adjusted *P* value vs. placebo	-	[redacted]	[redacted]	-

*sBA response defined as at least a 70% reduction from baseline or reaching a level ≤70 µmol/L

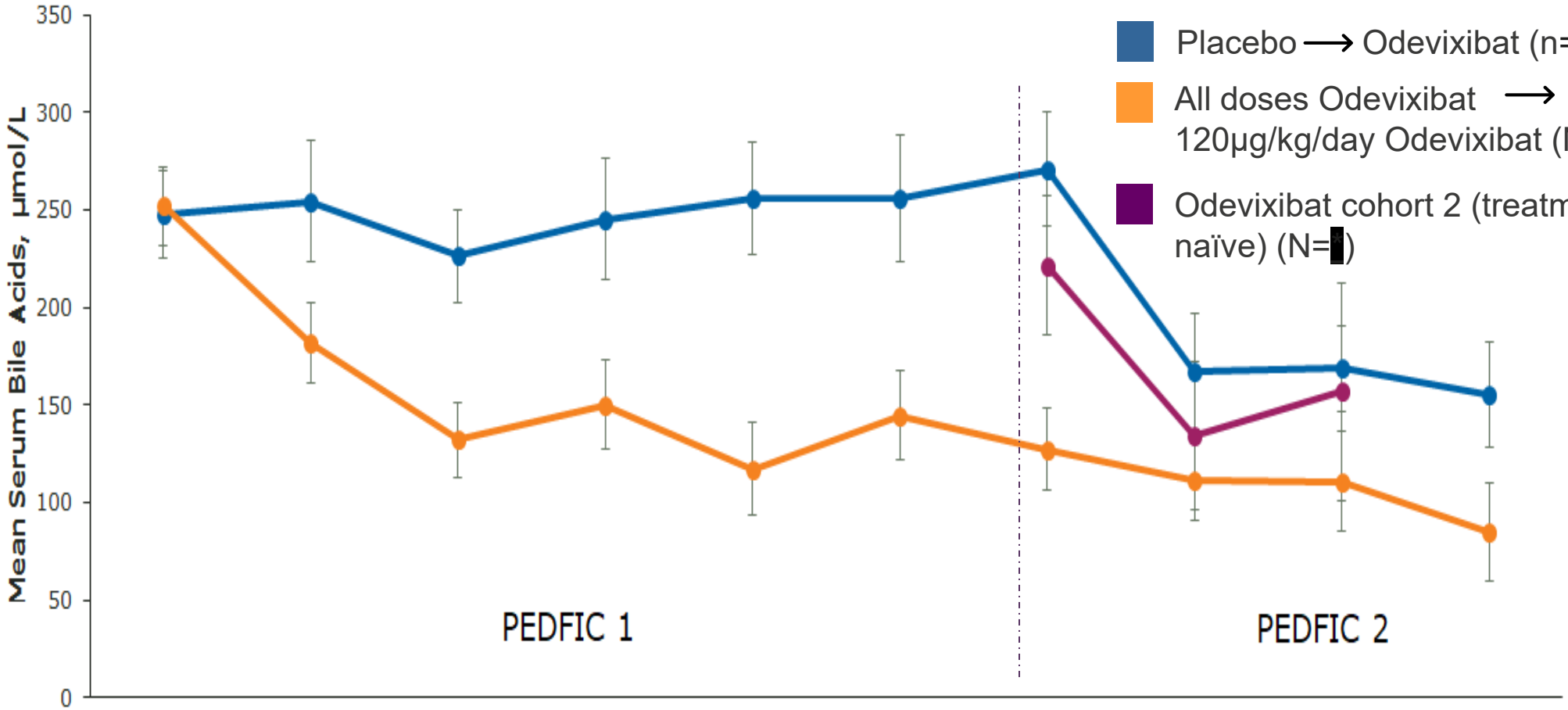
P value for interaction between 40 and 120 µg/kg/day dose [redacted] **Red results used in company base case**

N, number; sBA, Serum Bile Acid. Source: adapted from company submission, Figure 18

Serum bile acid reduction: PEDFIC2, whole population

ERG: Ongoing sBA response for people who received odevixibat in PEDFIC1

- **Greatest reductions in treatment naive patients**, either from Cohort 2, or rolled over from placebo
- 1 of 4* people who didn't respond to 40 µg/kg/day in PEDFIC1 responded to higher PEDFIC2 dose



	PEDFIC 1 Baseline	PEDFIC 1 Week 4	PEDFIC 1 Week 8	PEDFIC 1 Week 12	PEDFIC 1 Week 18	PEDFIC1 Weeks 22–24	PEDFIC 2 Baseline	PEDFIC 2 Week 4	PEDFIC 2 Week 12	PEDFIC 2 Week 22–24
Pbo→Odevix	20	20	18	17	16	15	19	16	15	11
AllOdevix→Odevix	42	40	37	36	26	34	34	31	26	21
Odevix Cohort 2	-	-	-	-	-	-	16	13	12	-

Source: company submission, Figure 25 * based on people previously enrolled in PEDFIC1 with PEDFIC2 week 24 data available at data cut-off

Reduction in pruritis: PEDFIC1, whole population

Source: company submission, figure 20

Key pruritus outcomes, PEDFIC1

	Placebo	40 µg/kg/day	120 µg/kg/day	All doses
Proportion of positive pruritus assessments at patient level over 24 weeks* (1° US endpoint)				
Mean % positive assessments (standard error)	29 (5)	[redacted]	[redacted]	54 (5)
Patients Achieving a Positive Pruritus Assessment for More Than 50% of the Time (2° endpoint)				
Responders*, % (95% confidence interval)	[redacted]	[redacted]	[redacted]	[redacted]

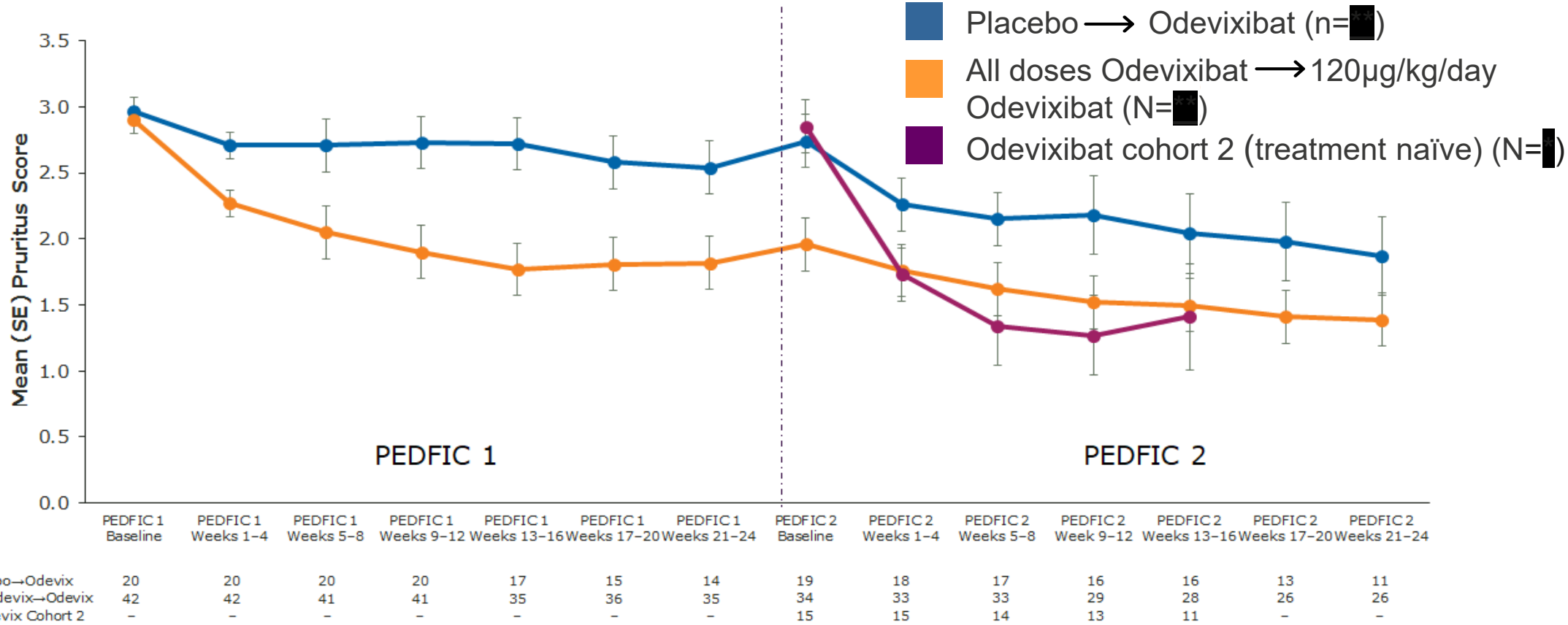
*Defined as scratching score of ≤1 or ≥1 point drop from baseline on observer-reported instrument.

P value for interaction between 40 and 120 µg/kg/day dose [redacted]

Green results used in company scenario analyses (could not use 1° endpoint in model)

Source: company submission, table 16 and 19

Reduction in pruritis: PEDFIC2, whole population



Pbo→Odevix	20	20	20	20	17	15	14	19	18	17	16	16	13	11
AllOdevix→Odevix	42	42	41	41	35	36	35	34	33	33	29	28	26	26
Odevix Cohort 2	–	–	–	–	–	–	–	15	15	14	13	11	–	–

Proportion of positive pruritus assessments to week 24, PEDFIC2

	Cohort 1				Cohort 2	Cohort 2 + placebo
	40 µg/kg	120 µg/kg	All doses	Placebo		
Mean % positive pruritus assessment (standard error)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

◉ *Do the clinical effectiveness results support: a) a benefit with odevixibat compared with standard care, b) a starting dose of 40 µg/kg/day, c) improved response with dose elevation to 120 µg/kg/day ?*

Source: company submission, Figure 26 and table 17

PFIC subtypes: size of the evidence base

PFIC type	Odevixibat, N			Natural history, N
	Phase 2 study (not in model)	PEDFIC1	PEDFIC2†	NAPPED
PFIC1	1 + 1 re-enrolled at different dose	17	3	130
	Total: 22			
PFIC 2	7 + 2 re-enrolled at different dose	45	7	264 (56 with BSEP3 mutations*)
	Total: 61			
PFIC3	2	0	5	0
	Total: 7			
PFIC6	0	0	1	0
	Total: 1			

*odevixibat not suitable for people with BSEP3 mutations (complete absence of BSEP protein)
† Excluding people who participated in PEDFIC1. NB: only [redacted] patients in cohort 2 had week 24 data available at the data cut.

ERG comments

Lack of evidence in subtypes other than PFIC1 and PFIC2

- Lack of robust, comparative evidence in PFIC3, almost no data in rarer subtypes (PFIC4-6)
- Data collection challenges for rarer subgroups but still included in the proposed licence

Clinical experts: In subtypes other than PFIC1 and 2, may see improvement of pruritus **not associated** with fall in sBA

◉ *Would treatment effect be expected to differ by PFIC subtype?*
◉ *Is there enough evidence to recommend odevixibat in rarer subtypes?*

Clinical effectiveness of odevixibat by PFIC subtype

Response endpoint	Subtype	40 µg/kg	120 µg/kg	Combined doses	Response with 120 µg/kg when no response to 40 µg/kg, % (N/N1)
sBA response	**Overall**	44%	21%	33%	[redacted]
	PFIC1	NA	NA	[redacted]	[redacted]
	PFIC2	NA	NA	[redacted]	[redacted]

Bold: denotes highest score in category. **Red** results in company base case

Source: company response to clarification, table 3

PEDFIC2

- **PFIC1 and 2:** differing effects seen in by PFIC subtype at week 24, but subgroups small
- **PFIC3:** 4 of 5 (80%) patients met sBA responder definition at last data cut-off (mean exposure [redacted])

ERG comments

- Impact of PFIC subtype (1 or 2) on effectiveness of odevixibat for key outcomes uncertain
- Data suggest potential interaction by subtype and dose, but analyses not powered to detect differences and no statistical comparisons

◉ *Should the clinical effectiveness of odevixibat be considered by subtype?*

N, number; N1, total number; sBA, Serum Bile Acid

Other key endpoints from PEDFIC1 and 2

1. Growth:

- PEDFIC1: Mean change in z score to week 24 suggest [redacted] **with odevixibat vs. placebo** in weight and BMI
- PEDFIC2: Week 24 results suggest [redacted] **with 120µg/kg/day odevixibat**
  - Mean height z-scores [redacted] in the placebo group during PEDFIC1 [redacted] during PEDFIC2

2. Change in caregiver reported PedsQL* baseline to week 24:

PEDFIC1: Larger changes from baseline in people who had odevixibat compared with placebo

3. [redacted] in both scratching and sleep, Caregiver Global Impression of Change scale:

PEDFIC2: [redacted] at week 24

4. Number listed for liver transplant PEDFIC1 and 2:

0 patients

ERG comments

Growth: **Interpret with caution** due to low patient numbers

- PEDFIC1: no significance testing, confidence intervals overlap and [redacted]
- PEDFIC2: hard to interpret growth results from people who changed doses when rolled over

Other outcomes: Did not critique based on 3 clinical expert's advice that outcomes not relevant in PFIC

◉ *Are these outcomes clinically important?*
◉ *Should they be included in the modelling?*

*PedsQL, Pediatric Quality of Life Inventory

Summary of adverse events

- Majority of adverse events mild to moderate in severity and assessed **unrelated** to study drug
- **Long-term PEDFIC2 data ([redacted])**: adverse event profile [redacted]

Adverse event	Phase 2	PEDFIC1		PEDFIC2	Comments
	Odevixibat (all doses) %	Odevixibat (all doses) %	Placebo %	Odevixibat (all cohorts) %	
Patients with ≥1 TEAE	[redacted]	83	85	73	- PEDFIC1: TEAEs lower in 40 µg/kg than 120 µg/kg and placebo cohorts - Fewer TEAEs in Cohort 2 (treatment naive) during PEDFIC2
TEAEs related to study drug	[redacted]	33	15	29	- Most common: [redacted]
Serious TEAEs	[redacted]	7	25	6	- All SAEs in PEDFIC2 were in people who had not received odevixibat in PEDFIC1
Serious TEAEs related to study drug	[redacted]	0	0	0	
TEAE causing discontinuation	[redacted]	2	0	4	
Total discontinuations	[redacted]	[redacted]	[redacted]	[redacted]	

INR, international normalized ratio; SAE, serious adverse event; TEAE, treatment emergent adverse event.

Source: adapted from ERG report, Tables 16 and 17

◉ *How tolerable is odevixibat compared with standard care?*

Sources of comparative evidence

STANDARD CARE WITH SURGICAL BILIARY DIVERSION

No direct comparative evidence

Phase 2 study: 1 patient (aged 15 months) had odevixibat then PEBD: sBA level, itch and sleep disturbance score improvements following both interventions

Planned study: Odevixibat vs External Control

Will compare odevixibat ([redacted]) with standard care ([redacted]):

- Part A: without prior PEBD, Part B: with prior PEBD

1° endpoint: Part A: [redacted]

2° endpoints: [redacted]

Exploratory endpoints: [redacted]

Results expected: [redacted]

ERG comments

- [redacted] study should address uncertainty about clinical effectiveness of odevixibat vs. PEBD

OFF-LABEL ORAL THERAPIES

Company: **not a comparator,** likely short term supportive care alongside odevixibat

- **PEDFIC1** provides data for odevixibat + off-label therapy vs. off-label therapy alone
  - UDCA (placebo 90%, odevixibat 76%), rifampicin (placebo 85%, odevixibat 57%)

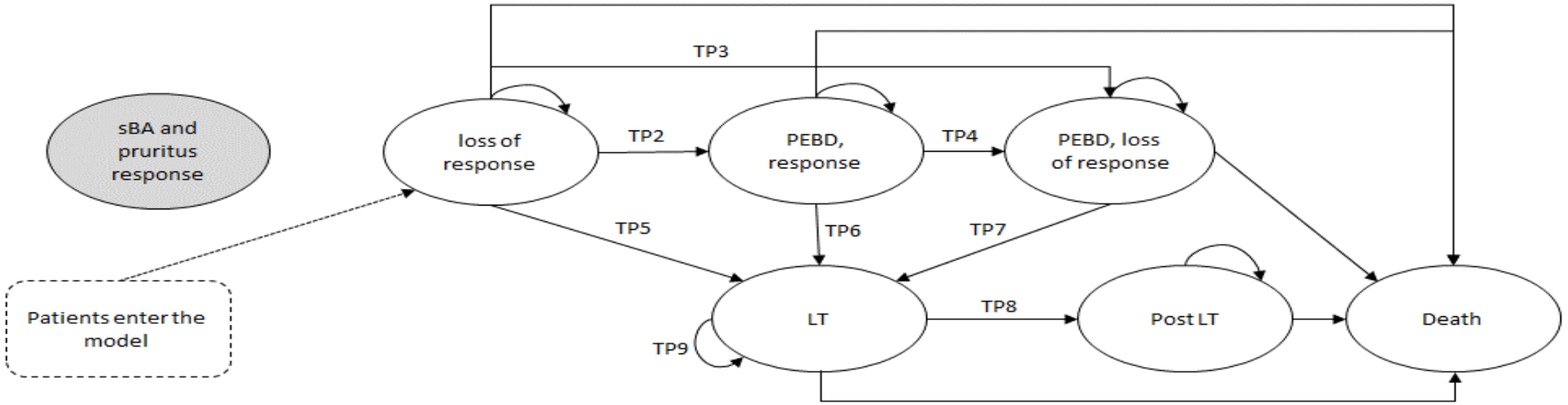
◉ *Can committee judge the relative effect of odevixibat?*
◉ *Will the [redacted] study resolve uncertainties in the long-term clinical effectiveness evidence?*

PEBD, partial external biliary diversion; sBA, serum bile acid; UDCA, ursodeoxycholic acid

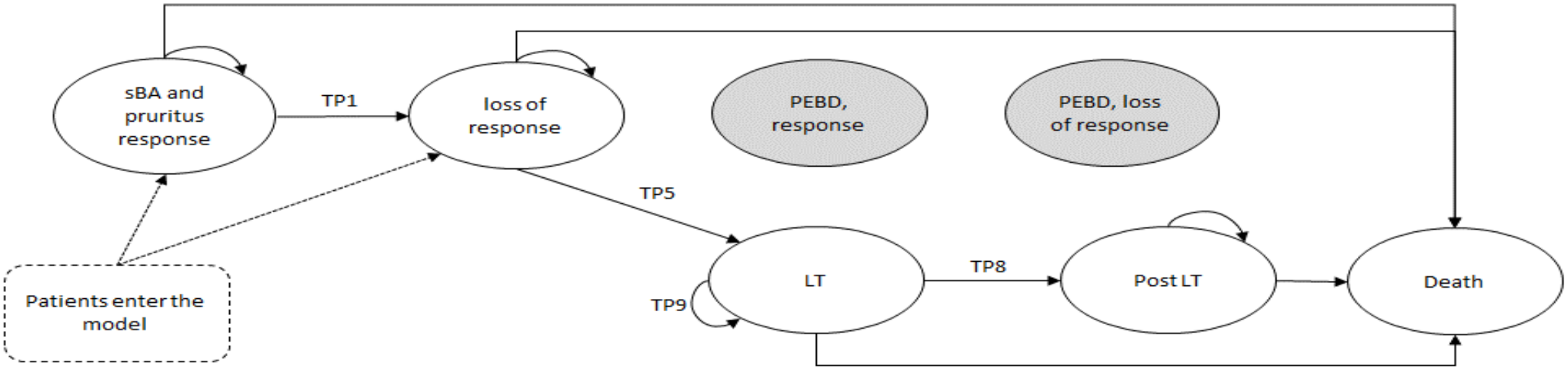
Cost effectiveness

Company's economic model

Standard of care arm



Treatment arm



Health states shaded in grey not used in that arm of the model.
Abbreviations: LT, liver transplant; PEBD, partial external biliary diversion; sBA, serum bile acid; TP, transition probability. Source: ERG report, Figure 9

Clinical evidence inputs in the company's model

Input	Evidence Source	ERG comments
Population	PFIC1 and 2 Baseline characteristics from PEDFIC1 whole population	Doesn't capture **treatment differences for other subtypes**: e.g. PFIC 3 more likely to respond to UDCA - > less have surgery
Intervention	40 µg/kg/day escalated to 120 µg/kg/day if no response at 6 months	
Comparator	Standard care (including off-label therapies, PEBD and liver transplant)	Standard UK practice is to manage symptoms **without PEBD** then progress straight to transplant.
Treatment response	Odevixibat: - 40 µg/kg/day: sBA reduction in PEDFIC1 trial - 120 µg/kg/day: PEDFIC1 non-responders to 40 µg/kg who subsequently switched to 120 µg/kg in PEDFIC2 Oral therapies: 0% response, symptom management only PEBD: NAPPED study	
Adverse events	No treatment-related AE costs or disutilities applied	AE, adverse event; PEBD, partial external biliary diversion; PedsQL, Pediatric Quality of Life Inventory; sBA, serum bile acid
HRQoL data	Literature PedsQL scores from similar diseases mapped to EQ-5D using algorithm by Khan et al.	
Discontinuation rate	Proportion of patients discontinuing treatment in PEDFIC2 (who had odevixibat in PEDFIC1)	

Key assumptions in the company model

Model structure

- Lifetime horizon (max age 100 years)
- Baseline age: 4.25 years (mean age in PEDFIC1), 50% female
- Discount rate 3.5%, cycle length 1 year with ½ cycle correction

Transition probabilities

- Progression to PEBD driven by pruritis exacerbation and elevation of bile acids
- Rate of progression to PEBD, liver transplant and outcomes post-transplant (including re-transplant) differ by PFIC subtype
- Re-transplantation has same risk of death and outcomes as initial transplant

Response assumptions

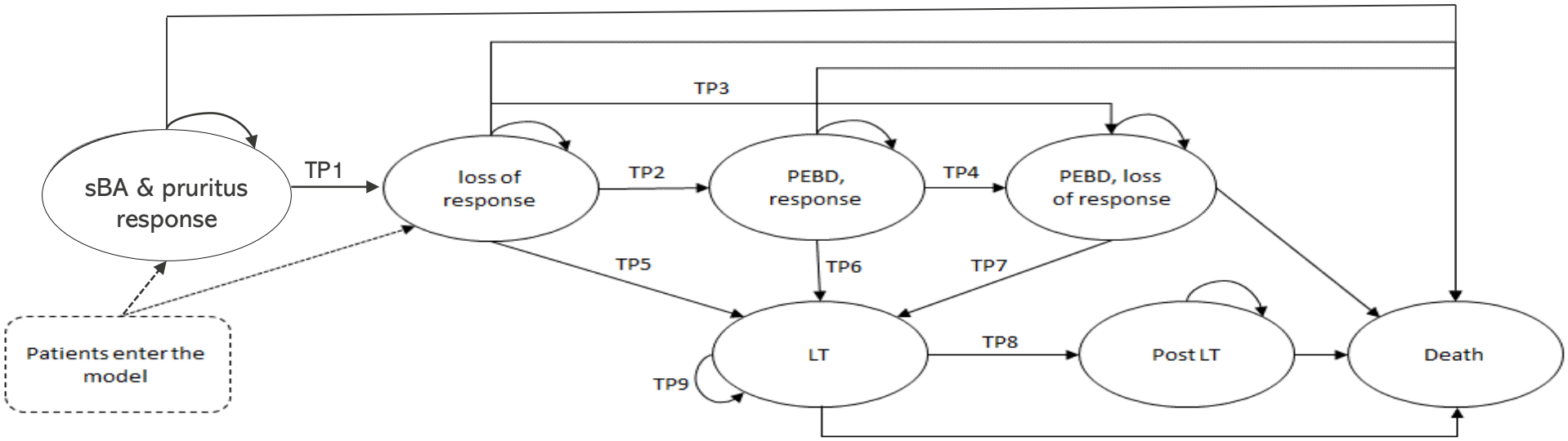
- sBA response is always associated with a pruritus response
- Patients maintaining an sBA response do not require liver transplant
- If no response to odevixibat, progress as per natural history excluding PEBD
- Patients do not have an sBA response to oral off-label therapy (symptom management only)
- 5% annual probability of losing response to PEBD surgery
- 67% have repeated surgery after PEBD due to complications: same costs as initial PEBD surgery

Utilities

- Caregiver costs and disutilities apply until age 18

PEBD, partial external biliary diversion; sBA, serum bile acid

Data informing the health state transitions



TP	Transition	Odevixibat	Standard of care
1	Loss of sBA/pruritus response	Assumed [redacted]% per year	100% at baseline
2	PEBD, response	0%	NAPPED study*
3	PEBD, no response	0%	NAPPED study*
4	Loss of response to PEBD	0%	Assumed 5% per year
5	LT without PEBD	NAPPED study	
6	LT after PEBD response	Assumed 0%	
7	LT after PEBD non-response	NAPPED study	
8	LT to post-LT	General population	
9	Re-transplant	Bull et al	
-	Mortality	Meta-analysed/pooled life years mortality sourced	

*includes all types of SBD: company assumes equal outcomes, costs and QALYs for PEBD to other SBD methods.
LT, liver transplant; PEBD, partial external biliary diversion; sBA, serum bile acid; SBD, surgical biliary diversion; TP, transition probability

sBA & pruritus response

Modelling serum bile acid response

	Phase 2 study	PEDFIC1 (used in model)	PEDFIC2 (used in model)
Definition of sBA response	None used: • 1° outcome: change in total sBA levels	**≥70% reduction** from baseline or reaching a level **≤70 µmol/L**	None used: • 1° outcome: change from baseline in sBA

PEDFIC1 definition of sBA used in model differs from that in NAPPED

- Company states that threshold was chosen based on NAPPED natural history study curves in which prolonged native liver survival was observed with
  - PFIC1: an sBA reduction **<65 µmol/L** following SBD
  - PFIC2: an sBA reduction of **75% or to <102 µmol/L** following SBD
- But, threshold in model (**≥70% reduction** from baseline or reaching a level **≤70 µmol/L**) differs from the NAPPED cut-off's above

ERG comments

Limited data on sBA response when dose increased to 120 µg/kg/day

- Only [redacted] of the 4 patients who did not meet sBA responder definition in PEDFIC1 responded in PEDFIC2*: company assumes [redacted]% respond to high dose
- **Substantial uncertainty** in parameter due to small patient numbers

NICE *based on people with week 24 data available for PEDFIC2
sBA, serum bile acid; SBD, surgical biliary diversion

sBA and pruritus, loss of response

Modelling loss of response to odevixibat

Company: Assumes odevixibat given until loss of response

- **Discontinuation rate from PEDFIC2** (after receiving odevixibat in PEDFIC1) used as proxy for loss of response in model
- Annual probability of discontinuing odevixibat ([redacted]%) based on [redacted] discontinuation event among [redacted] patients, with a mean exposure time of [redacted] weeks

ERG comments:

1. **Loss of response to odevixibat modelled by proxy**
   - Company assumes people only stop odevixibat due to AEs or withdrawal of consent
   - Long-term loss of response rates likely higher rate than modelled

2. **Data informing discontinuation rates ambiguous**
   - [redacted] patients discontinued due to AEs in PEDFIC2 in the prior placebo and treatment naïve cohorts: not included in company's discontinuation rate calculations

◉ *Is the discontinuation rate a suitable (reliable) proxy for loss of response?*
◉ *How uncertain is this discontinuation rate?*

AE, adverse event; sBA, serum bile acid

PEBD, Response

Transition probabilities for PEBD
ERG comments

1. <u>Model assumes standard of care arm has PEBD and odevixibat arm does not, however sequential treatment with odevixibat and PEBD possible</u>

- [redacted] patients ([redacted] in odevixibat, [redacted] in placebo arms) previously received PEBD surgery in PEDFIC1
- Clinical advice suggests PEBD could be offered to people who do not respond to odevixibat, especially considering the long waiting list for transplant
- Use of different treatment pathways for each arm results in more QALYs for odevixibat as it bypasses PEBD state
- **ERG** performed scenario analyses that:
  - include PEBD for non-responders on odevixibat with equal annual probability of PEBD in both arms: [redacted] ICER vs. base case
  - Position odevixibat before and after PEBD in the pathway

2. <u>Uncertainty surrounding long-term probability of PEBD</u>

- Exponential distribution chosen for simplicity: more complex models have better fit to data.
- Company did not present ICERs using other distributions to extrapolate long-term effects

◉ *Would PEBD ever be used for people who have had odevixibat?*
◉ *If yes, is it acceptable to assume equal rates of PEBD with and without odevixibat?*

ICER, incremental cost-effectiveness ratio; PEBD, partial external biliary diversion; QALY, quality adjusted life year; sBA, serum bile acid

Liver transplant

Transition probabilities for liver transplant

ERG comments

Assumption	ERG comment
Transplant rates for people with loss of response prior to PEBD is likely to be underestimated	• NAPPED native liver survival curves used to determine probability of transplant without prior PEBD: do not consider sBA response i.e. include both responders and non-responders • Transition probability underestimates people who have LT due to a lack of sBA response -> likely **more people without response need LT** in clinical practice than observed in NAPPED • **Preferred scenario:** Assume probability of transplant pre PEBD loss of response = probability for PEBD loss of response: [redacted] ICER from base case
0% probability of liver transplant in sBA responders	• Data from NAPPED: <100% native liver survival in sBA responders, suggests some have transplant • **Company:** this data reflects the people who lose response to PEBD or odevixibat and go on to have transplant • **ERG** unclear whether data from NAPPED aligns with the company's assumed loss of response rate

◉ *Is it acceptable to assume equal probability of transplant for people with and without prior PEBD?*
◉ *Would people responding to treatment ever require a liver transplant? If yes, how should this be modelled?*

ICER, incremental cost-effectiveness ratio; LT, liver transplant; PEBD, partial external biliary diversion; sBA, serum bile acid

Transition probabilities: Mortality

Pre-transplant mortality

‘sBA and PEBD, response’ health states

- General population mortality from ONS life tables

‘Loss of response’ health states

- **Company** calibrated model to match pre-transplant mortality for PFIC1 and PFIC2 patients in NAPPED (9% PFIC1, 4% PFIC2)

Post-transplant mortality

Acute: year of transplant

Variation in mortality rates reported in literature

Meta analysis of 10 global studies:

- rate of acute post-LT mortality converted to annual probability in model

Long-term: 2nd year onwards

- Pooled data analysis of digitised Kaplan Meier curves from 4 studies reporting long-term survival data and fitted exponential curve

Company’s post -LT annual mortality rate	**Acute = 11.31%**	**Long-term = 1.94%**

ERG comments, post-transplant mortality

- Methods for literature search unclear: unsure all relevant studies included in analyses
- Heterogeneity in meta analyses studies: PFIC subtype, geography and follow-up period
- Repeated company’s post-transplant mortality analyses with following changes:
  1. Correction of errors
  2. No rate-to-probability adjustment: output already proportion of deaths per year

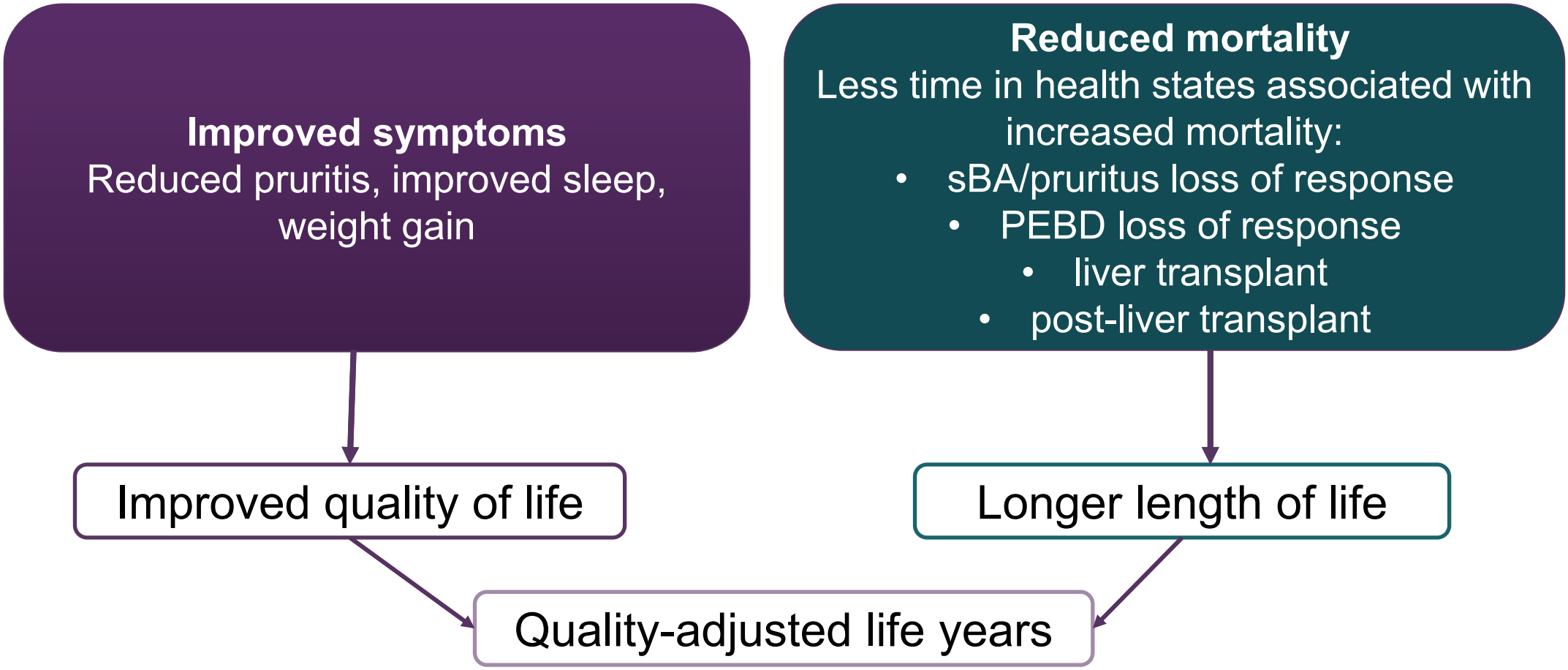
ERG’s post-LT annual mortality rate	**Acute = 10.92%**	**Long-term = 1.42%**

◉ *Should company or ERG post-transplant mortality rates be used in the model?*

LT, liver transplant; PEBD, partial external biliary diversion; sBA, serum bile acid

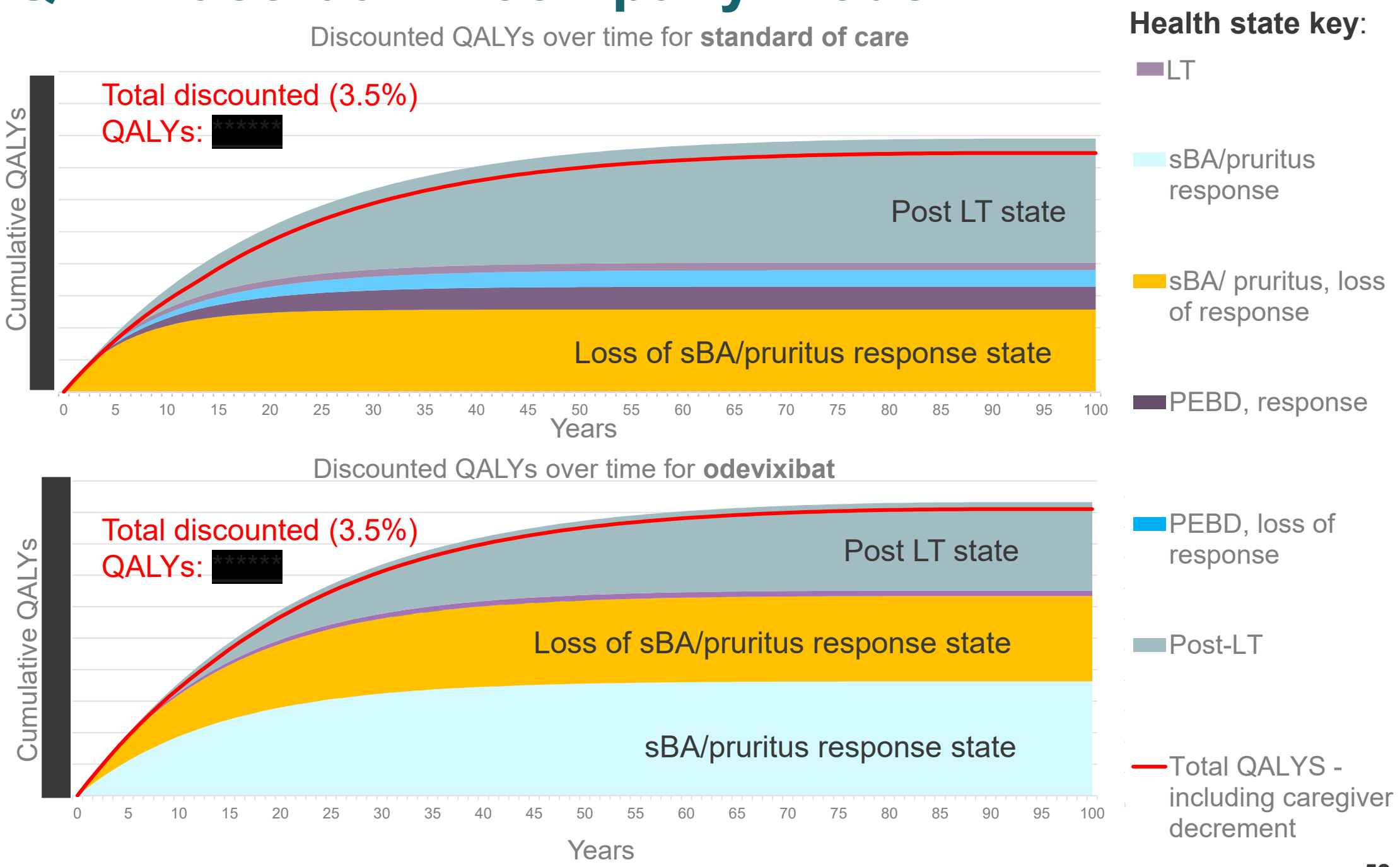
Health-related quality of life

Overview: how quality-adjusted life years accrue for odevixibat versus standard of care



PEBD, partial external biliary diversion; sBA, serum bile acid

QALY accrual in company model



LT, liver transplant; PEBD, partial external biliary diversion; QALY, quality adjusted life years; sBA, serum bile acid

Utility values: sources in the company base case

Company collected caregivers and patients PedsQL data in PEDFIC1

- Mapped to EQ-5D but not used in company base case: small patient numbers, low statistical power

Utility values from the literature in base case:

Health state	Utility	Justification
Without PEBD		
sBA & pruritus response	0.914	No literature utility values in responders Utility in "Healthy" children: Kamath et al*
Loss of response	0.830	Utility in children with chronic intrahepatic cholestasis: Kamath et al.* Short stature disutility in children with chronic kidney disease: Al-Uzri et al.
After PEBD		
sBA & pruritus response	0.659	Utility in "healthy" children: Kamath et al.* Stoma bag disutility in adults with ulcerative colitis: Arseneau et al
Loss of response	0.599	Utility in "healthy" children: Kamath et al.* Stoma bag disutility in adults with ulcerative colitis: Arseneau et al. Short stature disutility in children with chronic kidney disease: Al-Uzri et al.
LT	0.710	Utility for severe pruritus: Kini et al.
Post LT	0.850	Utility mapped from PedsQL in systematic review of children undergoing LT: Parmar et al.
Caregiver disutility applied until age 18 according to TA534 (spinal muscular atrophy): loss of response, PEBD response and post LT states: -0.05. Loss of PEBD response: -0.10		

N.B Multiplier for age from Ara and Brazier applied to all utility values

* Also reported parent-proxy reported utilities but only patient reported utilities included in base case

LT, liver transplant; PEBD, partial external biliary diversion; PedsQL, Pediatric Quality of Life Inventory; sBA, serum bile acid

Utility values: sources used in scenario analyses

1. **Change from baseline EQ-5D mapped from PEDFIC1**
2. **Vignette study** to elicit utilities for health states in PFIC

- **Time trade-off** interviews with 95 members of public to estimate health-state specific utilities
  - Health state descriptions used PEDFIC1 PedsQL and itch diary data, validated by 4 clinical experts
  - Utilities calculated using: visual analogue scales, time trade off weights and EQ-5D weights (mapped from time trade off values)
- **Follow-up vignette study for PEBD stoma bag disutility** conducted in 3 carers of patients with PFIC and one clinical expert. Value of [redacted] used in company scenario analyses (based on data from 2 carers).

Utility values in the company's model and estimated from the mapping and vignette studies

Health state	Company model	Company's mapping study	Company's vignette study
Odevixibat response	0.914	0.858	[redacted]
Odevixibat loss of response	0.830	0.697	[redacted]
PEBD response	0.659	-	[redacted]
PEBD loss of response	0.599	-	[redacted]
LT	0.710	-	[redacted]
Post LT	0.850	-	[redacted]

Blue results used in the ERG base case

Source: ERG report, Table 29

LT, liver transplant; PEBD, partial external biliary diversion; PedsQL, Pediatric Quality of Life Inventory

Utility values, ERG comments

	Preferred source
1. <u>High utility values for odevixibat responders and non-responders</u> Due to ongoing complications and symptoms of disease: • Responders unlikely to have same utility as healthy child (0.91) • Non-responders likely to have a utility value lower than 0.83	Common baseline EQ-5D utility mapped from PedsQL data (odevixibat responders **0.858**, non-responders **0.697**) with observed change from baseline applied by response
2. <u>Utilities mapped from PEDFIC1 PedsQL data most appropriate</u> • Company base case did not use mapped utilities due to small sample size and marginal difference in absolute scores.	
3. <u>Disutility for stoma bag uncertain</u> • Unclear justification for using disutility from ulcerative colitis study (0.722) as opposed to colorectal cancer (0.945). • Literature disutilities higher than that from company's vignette: company's disutility multiplier may overestimate disutility of stoma bag • **ERG prefers** average of ulcerative colitis and colorectal cancer utilities	Disutility multiplier of **0.833** for stoma bag. Utility values of **0.715** for PEBD responders, **0.581** for PEBD non-responders
4. <u>Utility for post-liver transplant health state overestimated</u> Company's utility of 0.850 for post-LT high compared to literature (0.70-0.73) especially considering: • The need for immunosuppression/risk of complications post-transplant • It includes re-transplant (QoL may differ from 1st transplant) **ERG prefers**: ratio of post-LT (0.850) and odevixibat response utility (0.914) applied to odevixibat response utility (0.858) from mapping study	Disutility multiplier of **0.798** (0.858*0.850/ 0.914) for post LT health state.

◉ *Which sources for utility values are preferred for decision making?*

LT, liver transplant; PEBD, partial external biliary diversion; PedsQL, Pediatric Quality of Life Inventory

Costs and resource use

Drug costs in the model

Odevixibat dosing based on average weight by age applied in modelling.

- PFIC patients start underweight but gain weight with odevixibat: assumed to reach average for UK population by year 3. No further dose increases once reach 55.5kg.
- % in each weight category: normal distribution applied to mean weight from growth curve

No administration or wastage costs for odevixibat: self-administered with no capsule splitting

Daily odevixibat acquisition costs applied for each age group in the company's model

Weight (kg)	Daily dose (µg)		Capsules/day†		Daily cost (list price)	
	Low dose	High dose	Sprinkle	Swallow	Low dose	High dose
4 - <7.5	200	600	1		[redacted]	[redacted]
7.5 - <12.5	400	1200	2		[redacted]	[redacted]
12.5 - <17.5	600	1800	3		[redacted]	[redacted]
17.5 - <25.5	800	2400	4	2	[redacted]	[redacted]
25.5 - <35.5	1200	3600		3	[redacted]	[redacted]
35.5 - <45.5	1600	4800		4	[redacted]	[redacted]
45.5 - <55.5	2000	6000		5	[redacted]	[redacted]
≥55.5	2400	7200		6	[redacted]	[redacted]

† Number of capsules when sprinkled based on 200 µg capsules, when swallowed based on 1200 µg capsules

Pharmacological treatments (list prices, apply to **both arms** in the 'loss of response' states)

Therapy	% patients	Dose per day	Cost/cycle	Source for usage data
UDCA*	95%	12mg/kg	£7.05/kg	PEDFIC1
Rifampicin	66%	10mg	£4.46	PEDFIC1
Cholestyramine	37.5%	4,000mg	£78.60	PICTURE (burden of illness study)
Naltrexone*	10%	2mg/kg	£12.00/kg	TA443

*confidential commercial medicines unit price: available to NHS at discount. UDCA, ursodeoxycholic acid

Source: ERG report, Table 22 and company submission, table 63

Health state costs: company base case

ERG: Counterintuitive relationship between odevixibat efficacy and cost-effectiveness

- Scenarios with **lower response rates or increased loss of response** to odevixibat lowers ICER.
- Moving patients off odevixibat to LT creates a more favourable cost profile which in turn reduces the incremental costs between the model arms and lowers the ICER

Cost accrual by health state in the company submission after clarification

PEBD, partial external biliary diversion; sBA, serum bile acid

Costs, ERG comments

1. Proportion of people of high and low dose odevixibat uncertain

- In the company's model, approximately **% of patients are on high dose odevixibat: costs 3x that of low dose
- Small patient numbers – significant uncertainty on proportion on high dose

2. Costs for PEBD may be overestimated (standard care only)

- Company assumptions may be overestimates:
  - Repeated surgery in 67% patients
  - Prior PEBD with same cost as initial surgery
- Bowel prolapse applied as separate cost but included in data for post-operative complications: already captured in infections cost
- Company's cost for infections may overestimate real cost to NHS if minor complications only

◉ *What proportion of people are expected to be on high and low dose odevixibat in clinical practice?*
◉ *Are the company's assumptions about PEBD valid?*

PEBD, partial external biliary diversion; SmPC, summary of product characteristics

Cost effectiveness results

Assumptions summary: company and ERG base case

Assumption	Company base case	ERG base case
Probability of LT in no prior PEBD non-responders	NAPPED data for 'no SBD' transplant rates	Same as probability of LT in PEBD non-responders
Utility values	Literature values	• Responders and non-responders: mapped from PEDFIC1 • Stoma bag disutility multiplier: average of colorectal and ulcerative colitis values • Post LT: ratio of post-LT and odevixibat response utilities in company's model applied to odevixibat response utility from mapping study
Mortality rates for acute and post LT	Company meta-analyses	ERG meta-analyses
Costs of adverse events	Excluded	Included
Productivity costs	Included	Excluded

NICE

LT, liver transplant; PEBD, partial external biliary diversion; SBD, surgical biliary diversion

Scenario analyses: company and ERG base case

	Company scenarios	ERG scenarios
Treatment pathway	• Patients treated with odevixibat until surgery	• Including PEBD in odevixibat arm
Utility values	• Utility values from: ○ Company vignette study (EQ-5D and time trade off) +/- stoma bag disutility ○ PEDFIC1 trial values with change from baseline analysis ○ Stoma bag disutility from colorectal cancer study (0.945)	• Excluding caregiver disutility
Response rates	• Include pruritus only response rates	• Odevixibat = PEBD annual loss of response (5%)
	• PEBD = Odevixibat annual loss of response ([redacted])	• Varying proportion receiving high dose odevixibat
	• Odevixibat = PEBD annual loss of response (5%)	
Other	• LT mortality from NHS transplant data	• General population mortality for non-responders
		• Start age of 3 years
		• Lower costs of PEBD

* EQ-5D - EuroQol 5 dimension; ICER - incremental cost-effectiveness ratio; LT - liver transplant; PEBD - partial external biliary diversion; PAS, patient access scheme; QALY - quality-adjusted life year

QALY weighting

- For ICERs above £100,000 per QALY, recommendations must take into account the magnitude of the QALY gain and the additional QALY weight that would be needed to fall below £100,000 per QALY
- To apply the QALY weight, there must be compelling evidence that the treatment offers significant QALY gains

Life incremental QALY gained	
Less than or equal to 10	1
11 to 29	Between 1 to 3 (equal increments)
Greater than or equal to 30	3

Incremental QALYs versus standard of care (deterministic ICERs):

- Company base case (and ERG's most optimistic scenario): [redacted] QALYs (undiscounted [redacted] QALYs)
- ERG base case: [redacted] QALYs (undiscounted [redacted] QALYs)

No QALY weighting applied in company or ERG base case.

ICER, incremental cost-effectiveness ratio; QALY, quality-adjusted life year

Service design and delivery

Company

- Treatment must be initiated and supervised by physicians, including paediatricians, **experienced in the management of PFIC**
- In England, odevixibat will be initiated and monitored in **3 highly specialised centres**
- No additional monitoring requirements other than for adequate response
- No special warnings or precautions for use
- No additional infrastructure requirements identified
- Potential to provide via homecare service

Clinical experts:

- Initiate odevixibat in specialist centres
- Potential for ongoing monitoring and supply through secondary or primary care, if not, may require funding to support homecare delivery (large geographical areas covered by each tertiary centre)
- Similar resource use (monitoring and follow up) to current standard of care but may reduce burden on NHS by delaying need for surgery

Innovation

Company:

- **1st licenced pharmacological treatment** for PFIC
- **Easy to administer**: Once daily medication, can be sprinkled for younger children
- **Unmet need**:
  - Currently no effective or approved pharmacological treatments for PFIC
  - Existing treatments have high failure rate and can be invasive
  - Shortage of suitable organs for transplant: few patients alive with native liver by age 20
- **Efficacious**: Improves sBA and pruritus, delays transplant and removes need for SBD
- **Improves social aspects** of disease: e.g. educational attainment, ability to work, ability to contribute to society

Clinical expert:

- **Step-change** in treatment as new drug with novel mechanism.
- Addresses large **unmet need** in population: current therapies have limited effectiveness, associated with adverse effects and tolerability concerns
- Odevixibat is easy to administer with no drug interactions and minimal side effects

Patient organisation: families **calling out** for ways to manage symptoms

◉ *Does odevixibat represent a step-change in the treatment of PFIC?*

sBA, serum bile acid; SBD, surgical biliary diversion

Equalities

Odevixibat is indicated for use in children (aged 6 months and older) and adults.

Company: the use of odevixibat is not expected to raise any equality issues.

Clinical and patient experts: no inequalities issues flagged in submission

◉ *Are there any potential equalities issues that should be considered for odevixibat?*

Managed access: company's proposal for data collection

- The MAA team consider the following sources are feasible to collect within an MAA:
  - More mature data from PEDFIC2, single-arm open-label extension of PEDFIC1 to provide data on:
    - Survival outcomes, liver transplantation rates, alternative utility values for patients
  - [redacted] Indirect comparison of [redacted] to provide data on the efficacy of odevixibat vs PEBD
- Whilst [redacted] registry study data may become available, this source cannot be adapted to collect data in clinical practice as part of a MAA
- The MAA team highlight the following key considerations:
  - Odevixibat needs to be plausibly cost-effective for MAA entry
  - PEDFIC2 and [redacted] will provide evidence for high-dose odevixibat only
    - Anticipated data availability would be [redacted]
- MAA could collect data in clinical practice on proportion on high-dose odevixibat and previous PEBD usage
  - Low assumed discontinuation rate and potential subsequent PEBD usage mean it is unlikely that meaningful data could be collected in clinical practice

◉ *Does odevixibat have the potential to be cost effective?*
◉ *Is data collection feasible and will it address the identified uncertainties?*
◉ *If yes, is a managed access agreement plausible?*

Key issues, clinical effectiveness

The company positions odevixibat as a first line therapy. • When would odevixibat be used in the treatment pathway in clinical practice? • Before, after, or at the same point in the pathway as partial external biliary diversion (PEBD)?
The company's main trial evidence is limited to PFIC types 1 & 2. Are results generalisable to: • PFIC types other than 1 and 2? • The population in seen in NHS clinical practice? Should the clinical effectiveness of odevixibat be considered by subtype?
How generalisable are the trial results to anticipated NHS use, given that: • The dose of odevixibat in trials differs from that in the marketing authorisation? • There are no defined criteria for dose escalation following lack of response?
There is no comparative data with the company's comparator, PEBD. • Can committee judge the relative effect of odevixibat? • Will the company's planned indirect analysis resolve this uncertainty?

PEBD, Partial external biliary diversion; PFIC, Progressive familial intrahepatic cholestasis

Key issues, cost effectiveness

Issue	
To represent loss of response in the model, the company use a proxy outcome (discontinuation rate from PEDFIC2 trial). Is this acceptable?	
The company uses a small cohort to define the proportion taking high dose odevixibat in the model. • What proportion would have high and low dose odevixibat in clinical practice?	
People with odevixibat do not have PEBD in the company model. • Should PEBD be included for odevixibat? • If yes, at a rate equal to standard care?	
The company's probability of requiring liver transplant without prior PEBD is calculated using data that includes both responders and non-responders to standard of care. • For non-responders, is an equal probability of transplant for odevixibat and PEBD expected?	
Different mortality rates are used in the company's and ERG's model. Which are most appropriate?	
The company model uses non-PFIC specific utility values taken from the literature. • Is this acceptable? If not, should utility values from the trial be used?	
Does odevixibat represent a step-change in the treatment of PFIC?	
If routine commissioning cannot be recommended, should managed access be considered? • Does odevixibat have the potential to be cost effective? • Is data collection feasible and will it address the identified uncertainties?	

Key:
Discussion;  Model driver: >£10,000 per QALYS gain change from base case; 
Small/moderate impact: <10,000 per QALY gained change from base case; 

PEBD, Partial external biliary diversion; PFIC, Progressive familial intrahepatic cholestasis

Back up slides

Odevixibat, 'exceptional circumstances' marketing authorisation

Positive CHMP opinion received based on:

- High unmet need with limited treatment options
- ongoing sBA and pruritus response in PEDFIC1 and 2
- Insufficient data to determine if odevixibat can delay disease progression and need for liver transplantation.

CHMP requested a **registry-based efficacy study** as follow-up: protocol to be submitted to the EMA [redacted]

Objectives:

a. [redacted]

b. [redacted]

c. [redacted]

d. [redacted]

Number of Patients: [redacted]

Diagnosis and Main Criteria for Inclusion: [redacted]

AE, adverse event; SAE, serious adverse event; CHMP, Committee for Medicinal Products for Human Use; sBA, serum bile acid

Factors affecting the guidance

- In forming the guidance, committee will take account of the following factors:

Nature of the condition	Clinical effectiveness
• Extent of disease morbidity and patient clinical disability with current care • Impact of disease on carers' QoL • Extent and nature of current treatment options	• Magnitude of health benefits to patients and carers • Heterogeneity of health benefits • Robustness of the evidence and the how the guidance might strengthen it • Treatment continuation rules
Value for money	**Impact beyond direct health benefits**
• Cost effectiveness using incremental cost per QALY • Patient access schemes and other commercial agreements • The nature and extent of the resources needed to enable the new technology to be used	• Non-health benefits • Costs (savings) or benefits incurred outside of the NHS and personal and social services • Long-term benefits to the NHS of research and innovation • The impact of the technology on the delivery of the specialised service • Staffing and infrastructure requirements, including training and planning for expertise

QALY, quality-adjusted life year; QoL, quality of life

Analyses by PFIC subtype

Recap: PEDFIC1 data suggest potential interaction by subtype and dose, but:

- Small patient numbers: analyses not powered to detect differences
- No statistical comparisons
- Did not include subtypes other than PFIC1 and 2

ERG comments

- Transition probabilities estimated as weighted average of PFIC subtypes, but response rates combined patients with PFIC1 and PFIC2
- **Lack of data on response rates** of odevixibat separately for patients with PFIC1 and PFIC2: ERG could not explore the cost-effectiveness separately for subtypes.

◉ *Is any difference in treatment effect by PFIC subtype captured in the company's modelling?*
◉ *Should cost-effectiveness analyses by PFIC subtype be available for decision making?*

Changes made to company model post clarification

- 3.5% discount rate for costs and outcomes
- Final data from the PICTURE study incorporated for health state resource use and carer costs
- Utilities correctly age-adjusted
- Drug costs based on weight distributions as opposed to mean weight
- Cholestyramine and rifampicin doses corrected to account for varying dosage with age
- Post-liver transplant costs applied to all patients in the post liver transplant health state
- Updated data used to estimate post-liver transplant mortality